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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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RE.: SOLICITUD DE PATENTE EN COLOMBIA
EXPEDIENTE N° 03-055750
TITULO: PROCESO PARA PREPARAR CLOPIDOGREL.
SOLICITANTE: CADILA HEALTHCARE LIMITED
FECHA SOLICITUD: 02 de julio de 2003

ASUNTO: RESPUESTA A OPOSICIÓN PRESENTADA POR PROCAPS S.A.

DILIA RODRIGUEZ D'ALEMAN, en mi condición de apoderada de la sociedad solicitante, por el presente escrito doy respuesta a su auto notificado por estado de 18 de febrero de 2005, para el cual se presentó solicitud de prórroga y vence el 18 de agosto de 2005 y me permito presentar las siguientes aclaraciones:

La solicitud de patentes en cuestión se dirige a un proceso de obtención de un producto y se titula "PROCESO PARA PREPARAR CLOPIDOGREL". El objetivo de un proceso químico es siempre desarrollar un proceso mejor o más eficiente, con una alta productividad, una mayor simplicidad operacional (por ejemplo, cristalizando el isómero deseado en el primer paso), lo cual se logra reduciendo el número de pasos incluso alterando la secuencia de los pasos ya conocidos, incrementando la producción global al igual que mejorando la producción de cada paso individual, superando los inconvenientes del proceso existente, diseñando condiciones de reacción moderadas, proporcionando productos limpios con menos productos colaterales e impurezas, suministrando un producto óptimamente puro sin ninguna contaminación, reciclando los isómeros indeseables y por ende reduciendo la generación de residuos lo que se traduce en un proceso amigable al medio ambiente, evitando tediosas cromatografías de columna, diseñando condiciones de reacción para reducir el tiempo de reacción, diseñando una combinación de reacción más segura que usen menos reactivos al azar

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e igualmente las condiciones de reacción sean menos severas, etc.

Cada uno de los objetivos mencionados anteriormente contribuye a una mejor efectividad en los costos y hacen que el proceso químico sea comercialmente viable. Por consiguiente, el éxito en uno o más de los anteriores objetivos son considerados mejoras significativas sobre cualquier proceso existente. Si uno o más de los objetivos citados son logrados por un proceso no obvio se considera que el proceso tiene un merito inventivo y por tanto se convertirían en materia sujeto de patente. Así las cosas, a continuación suministramos nuestros argumentos para establecer la no obviedad del proceso inventado y reivindicado en la solicitud 03-055750.

El opositor PROCAPS afirma que la presente invención carece de nivel inventivo y debería ser considerada obvia basándose en los documentos:

D1: Burgos et al.. Journal of Labelled Compounds and Radiopharmaceuticals. Volumen 43, No 9, August 2000, Pages: 891-898.

D2: Patente US4.529.596.

El artículo D1 describe un método para preparar [benceno -U-13C]-rac-clopidrogrel por orto-metalación/clorinación de derivados ácido benzoico usando la síntesis de Strecker.

Aunque podría parecer que el documento D1, enseña la invención reivindicada, lo que se plantea a continuación deja en claro que dicho documento se encuentra lejos de enseñar las características novedosas de la invención reclamada.

Si bien es cierto que en la solicitud en análisis, los inventores han utilizado la síntesis de Strecker como base para preparar el compuesto de fórmula (IV), lo que hace que aparentemente tal proceso parezca haber sido enseñado por el documento D1, concluir que el documentos D1 preveía la invención solicitada, como lo establece PROCAPS resulta un juicio a priori e incorrecto como se demuestra a continuación.

Basándose en dicha similitud, PROCAPS argumenta que dicho documento describe un método para producir Clopidrogel por reacción de un aldehído con tienopiridona en la

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presencia de acetona cianohidrina para formar el compuesto que es hidrolizado y esterificado con MeOH, y que D1 menciona que la acetona cianohidrina está en equilibrio con acetona y el HCN. De acuerdo con lo expuesto, PROCAPS establece que la diferencia de D1 con la presente solicitud es el paso extra de resolución (paso 4), y al respecto señala que ese paso no hace que la invención sea inventiva toda vez que según PROCAPS éste es un método general en el estado de la técnica para separar enantiómeros por resolución.

Contrario a lo expuesto por PROCAPS, consideramos que tal correlación no es correcta y el nivel inventivo de la presente invención se vincula a algunas modificaciones únicas y no obvias en el proceso de preparación y no en el paso de resolución como lo establece el opositor. En este orden de ideas, centraremos nuestra discusión en las modificaciones relacionadas con la síntesis de Strecker, la conversión de nitrilo a ester vía amida y el paso de resolución.

1. Síntesis de Strecker

La reacción de Strecker es una reacción ampliamente conocida como se puede apreciar en los escritos:

1. Strecker, Ann, 75, 27 (1850)
2. Strecker, Ann, 91, 349 (1854)
3. Liebigs Ann. Chem., 155, 177 (1870)

Ver Anexo I.

Una primera diferencia entre el documento citado y la invención es que en el proceso reportado en D1 la acetona cianohidrina ha sido usada como fuente de cianuro mientras la invención reivindicada se refiere a un proceso que usa NaCN o KCN como fuente de cianuro. El uso de NaCN y KCN como fuente de cianuro también es conocido desde hace mucho tiempo. Incluso, el uso de NaHSO₃ en tales reacciones es también conocido desde hace algunas décadas en el estado de la técnica.

Sin embargo, el citado estado de la técnica D1 presenta algunos serios inconvenientes como son:

- A. Baja productividad. 31%

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- B. Presencia de impurezas formadas a partir de amina cíclica y acetona cianohidrina (paginas 894-895)
- C. Uso de columna de cromatografía por separación
- D. Escalamiento de la síntesis. El producto aislado es solo 744 mg.

Por el contrario, la invención reivindicada supera estos problemas y tiene las siguientes ventajas:

- A. Muy alta productividad. 97% como se observa en el ejemplo 1.
- B. No hay formación de impurezas partir la fuente de cianuro.
- C. No requiere columnas de cromatografía.
- D. Escalamiento de la síntesis. 24g de producto aislado (ver el ejemplo 1). De hecho la síntesis ha sido hecha a nivel de kilogramos.

El solicitante igualmente ha empleado variaciones de la síntesis de Strecker (ver ejemplos 1 a 9) con reactivos, solventes y cada una de ellos reportaron una producción diferente pero todos coinciden en que dicha productividad es mucho mayor que la reportada en el estado de la técnica. Por consiguiente, es posible afirmar que el solicitante ha usado de manera ventajosa ideas y conceptos ya conocidos para desarrollar un mejor proceso, el cual de manera sorprendente, inesperada y no obvia tiene una mayor productividad, no presenta impurezas y reduce los pasos necesarios para la obtención del producto ya que no requiere que se realice la etapa de una cromatografía en columna como necesita el proceso reportado en D1.

Teniendo en cuenta lo expuesto la invención reivindicada muestra propiedades mejoradas inesperadas que no están presentes en el estado de la técnica. (Patent Law Basic. Rosenberg. West Group, páginas 6 a 7; **Anexo II**) Claramente se puede apreciar que las propiedades mejoradas del proceso de la invención reclamada son, mejor producción, reacciones más limpias sin impurezas y simplicidad operacional.

Partiendo de lo expuesto subrayamos que el hecho que un proceso mejore considerablemente la productividad o reduzca la presencia de impurezas en el producto deseado mediante modificaciones menores de sus reactivos, condiciones de reacción, etc es un motivo suficiente para que el proceso reclamado sea considerado no obvio y por tanto, patentable como se puede corroborar en los siguientes ejemplos de patentes

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concedidas para procesos que con una pequeña variación mejoran su productividad y/o sus propiedades.

Anexo III. US 6.355.827, Komoschinski et al, describe un proceso mejorado para la preparación de 2-cianoindan-1-onas donde el solvente MeOH ha sido reemplazado por DMF:H₂O y la producción fue mejoradas de 70% a 95%.

En la presente invención, la producción ha sido mejorada de 31% a 97%.

Anexo IV. US 6.201.135, Maywald et al, describe un proceso de separación de impurezas a partir de 3(2'-acetoxi-etil-dihidro-2(3H)-furanona, basado en un proceso conocido pero que usa un proceso de purificación distinto para obtener el producto puro.

De manera similar, a través de la presente invención, se obtiene un producto puro sin que el proceso incluya un paso adicional de purificación.

Anexo V. US 6.037.503, Oren et al, describe un proceso para la preparación de p-fluorofenol, donde la fuente del ión hidroxil ha sido cambiada de Ca(OH)₂ a NaOH con miras a minimizar impurezas, y de manera inesperada se logro una alta conversión y una reacción limpia.

La invención reivindicada también basa su aporte en el cambio de la fuente de CN de acetona cianohidrina como reporta el estado de la técnica más cercano a NaCN o KCN con el fin de eliminar impurezas y el resultado logrado de manera inesperada es que se alcanza una alta conversión y por ende, una mejor productividad y una reacción limpia.

Anexo VI. US 6.107.490, Murthy et al., describe un proceso para prepara 4-metil-5-hidroximetil imidazole, donde el medio de reacción ha sido cambiado de base/agua a K₂CO₃/isopropanol y de este modo se mejora la producción.

El opositor cita los comentarios del autor del documento D1 sobre el hecho que la acetona cianohidrina permanece en equilibrio la acetona con HCN, con este comentario el opositor probablemente trata de establecer que es el grupo CN⁽⁻⁾ el grupo reactivo y

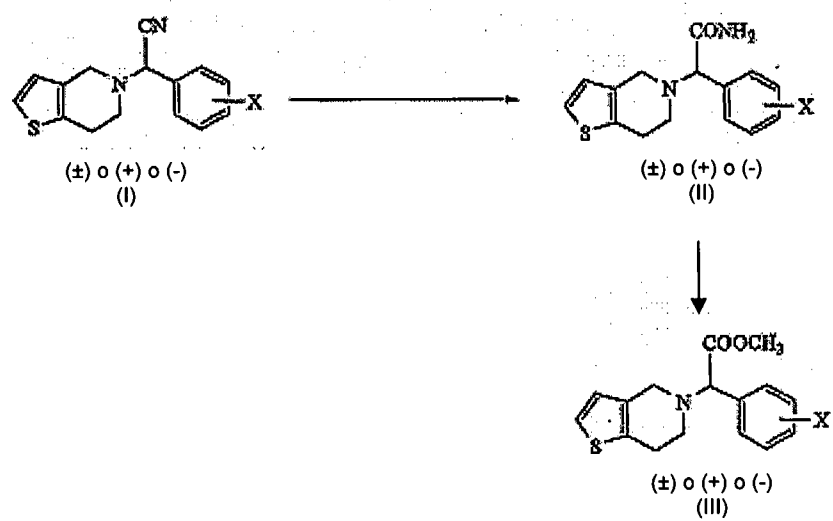
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como dicho grupo está presente tanto en la anterioridad como en la solicitud en análisis, la invención resulta obvia.

Nuevamente, el solicitante desea enfatizar en la obviedad y el conocimiento de que en la reacción Strecker es bien sabido que el grupo reactivo es $\text{CN}^{(-)}$. Pero este no es el conocimiento que reivindica la solicitud 03-055750. La diferencia entre estos procesos no está dada por $\text{CN}^{(-)}$ que es el grupo reactivo, la diferencia la marca una apropiada selección de la fuente del ión $\text{CN}^{(-)}$, que al utilizar como fuente NaCN o KCN proporciona efectivamente resultados inesperados como los que se mencionaron anteriormente.

2. Conversión de nitrilo a ester vía amida



De acuerdo con Burgos (documento D1), la conversión no fue llevada a cabo a través de la saponificación del nitrilo a amida, ya que el autor de dicho artículo plantea que esta ruta tiene problemas de reacción retro-Strecker (ver página 895 del documento D1). De ahí que Burgos realiza una hidrólisis promovida por HCl a amida en orden de evitar la reacción retro-Strecker y finalmente produce una menor cantidad de producto.

De manera contraria, la invención reivindicada define un proceso modificado donde la saponificación del nitrilo (I) con KOH-t-BuOH produce amida (II) y aumenta la productividad (94%) y sin ninguna reacción retro-Strecker (ejemplo 10 de la solicitud colombiana). La alta productividad y la limpieza de la reacción es un hecho

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sobresaliente. También, el ejemplo 18 (con KOH/isopropanol) de la solicitud en análisis describe un proceso donde el producto precipita puro a partir de la mezcla de reacción sin extracción, simplemente adicionando agua, lo cual ofrece una ventaja de simplicidad operacional.

Además, el problema que plantea el proceso de Burgos es que requiere de largo tiempo (48 horas) y secado azeotrópico de la masa de reacción (ver página 497), mientras el presente proceso de reacción **requiere tan solo de 3 horas** (ejemplo 10 de la descripción) y ofrece considerables ventajas de simplicidad operacional, donde el producto deseado **precipita por simple adición de agua y sin necesidad de ninguna etapa de extracción**. Todos estos temas: tiempo, simplicidad operacional, pureza y eliminación de etapas de extracción indudablemente marcan un factor importante en relación con la productividad y la viabilidad comercial. Como se puede apreciar tales ventajas de simplicidad operacional no fueron divulgadas en ninguna referencia del estado de la técnica.

En este orden de ideas, nos gustaría llamar la atención sobre el hecho que la invención reivindicada en la solicitud 03-055750 soluciona los problemas visualizados en el estado del arte y mejora significativamente el proceso mediante modificaciones a las reacciones que en el estado de la técnica había sido establecidas como no viables, y por ende, dicho estado de la técnica había tratado de evitar. Esto claramente es la antítesis de lo obvio, pues no obvio seguir el camino que el estado de la técnica había declarado no viable y mediante dicha vía mejorar el procedimiento. Además, para que la presente invención sea obvia debe haber indicios razonables para esperar o prever el resultado, y a partir del estado de la técnica descrito lo que preveía es que no funcionaba utilizar este procedimiento. Es decir, en el presente caso el estado de la técnica desanima el uso de saponificación para obtener la amida.

3. Resolución:

PROCAPS sostiene que el paso de resolución (paso 4) es obvio y puede ser llevado a cabo por cualquier persona versada en la materia. Dicha afirmación es errada como se aprecia a partir de los siguientes argumentos:

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Un principio químico bien conocido por cualquier experto en el estado de la técnica es que una mezcla racémica puede ser resuelta en sus antípodos ópticos. Así que no hay novedad en el hecho que la mezcla sea resuelta. La novedad se liga al establecimiento del agente de resolución adecuado.

Además, las técnicas de resolución son bien conocidas en el estado de la técnica. Sin embargo, predecir cual isómero será resuelto con cual agente y las condiciones de reacción es una tarea ardua, como se expresa en las páginas 201-202 del anexo VII que establece que el diseño de agentes que resuelvan estas mezclas representa una mayor complejidad comparada con el diseño de medicamentos desde que el diseño de agentes de resolución debe predecir el cristal, algunas veces es más complejo que el diseños de interacciones medicamento/receptor. Respecto a la predicción para escoger el agente de resolución correcto, Sheldon concluye que un análisis objetivo del estado actual de la técnica lleva a la inevitable conclusión que aunque hay considerables progresos en este sentido, falta un largo camino para lograr racionalizar los diseños de resoluciones, por ahora todo se limita a una cuestión de intuición.

La resolución como ciencia no ha sido perfeccionada a un nivel donde uno pueda extrapolar o predecir el resultado de una u otro. Aunque uno podría estar motivado a tratar algún agente de resolución estándar para la resolución, basado en el estado de la técnica, porque "es obvio" ensayarlo, pero el estado de la técnica también sugiere que no hay garantías de éxito en tales ensayos. Además, el estado de la técnica no da ninguna indicación sobre cuales son los parámetros (solventes), con o sin agua, temperatura y duración del calentamiento, rata de enfriamiento, etc, y finalmente, cuales agentes de resolución son críticos.

En el mundo de los compuestos activos opticamente/quiralidad, la probabilidad de no poder predecir es tan alta, que es imposible predecir cual antípoda quiral de la pareja nitrilo (dextrogiro o levogiro) o cual antípoda quiral de la pareja amina (dextrogiro o levogiro) podría resultar en S (+)-Clopidrogel dextrógira, porque no hay una conexión directa entre la orientación espacial de los grupos y la dirección de la rotación óptica. Entonces, fue necesario resolver la amida racémica en isómeros dextrógiros puros (+) (ejemplo 31 de la descripción) e isómeros levógiros puros (-) (ejemplo 34 de la descripción) e idear que la amida destrógira (+) produzca clopidrogel (+) (ejemplo 35 de

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la descripción)

Este aspecto de la invención no tiene precedentes y es impredecible basado en el estado del arte.

A continuación hacemos referencia a literatura que soporta nuestros argumentos relativos a la extrapolación debida a la naturaleza análoga de los sustratos:

En el libro de Sheldon, **anexo VII**, página 190, donde la fenil glicina es resuelta con el ácido alcanfor sulfónico (CSA) en el famoso proceso Andeco para D-fenil glicina, pero una simple sustitución de p-hidroxi en la fenil glicina (página 200), la resolución requirió de un nuevo y único agente de resolución (+) ácido fenil etano sulfónico (PES), además inventando un medio de reacción de resolución totalmente diferente (solvente, concentración, temperatura, etc). Esto claramente soporta el argumento que uno no puede extrapolar o predecir la resolución mediante la naturaleza análoga de los sustratos.

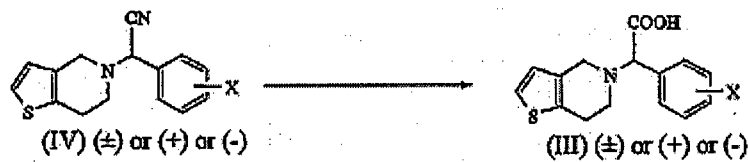
Similarmente, la estrategia de resolución de compuestos de cadena abierta no puede ser extrapolada a partir de sus análogos de cadenas cerradas. Entonces, en el caso de resolución de varios intermediarios de Dilitazem, resoluciones exitosas son reportadas para los compuestos de cadena abierta, por ejemplo con Lisina y α -metil benzil amina respectivamente, mientras ninguna resolución es reportada para productos cíclicos (**Anexo VIII**).

Nuevamente se encuentra que aun cuando haya sido reportada la resolución para análogos de cadena abierta en el estado de la técnica, no es posible extrapolar que la resolución de sus análogos cíclicos será exitosa.

De otra parte, PROCAPS establece que la reivindicación 4 de la presente invención carece de novedad por la información del ejemplo 5 de la patente US 4.529.596. Sin embargo, el citado ejemplo describe un proceso para preparar el ácido α -[4, 5, 6, 7-tetrahidro-tieno-[3,2-c]-5-pirridil]-o-clorfenilacético a partir del correspondiente compuesto éster usando hidrólisis alcalina. Sin embargo, nuestro método de preparar el ácido (III) como se reivindicó en la reivindicación 5 de la descripción, es por hidrólisis

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del correspondiente ciano compuesto (IV) en presencia de un apropiado catalizador ácido/básico, en un adecuado solvente.



Como se obra en las reivindicaciones, la solicitud no reivindica propiedad sobre el compuesto de fórmula (III), que por cierto es ampliamente conocido como el primer metabolito del Clopidrogrel. El proceso de preparación del (III) de acuerdo con la presente solicitud no es en ninguna forma enseñado por el ejemplo del estado de la técnica. Así que ninguno de los documentos citados afectan la novedad del proceso reclamado, el cual es único.

PROCAPS sostiene que la hidrólisis de ciano a ácido es enseñada por dicho ejemplo que muestra la hidrólisis del correspondiente acetato, tornándolo en obvio para cualquier persona versada en la materia. En efecto PROCAPS sostiene que los grupos acetato y ciano son intercambiables y reemplazables, y un experto en la materia podría lógicamente reemplazar uno con el otro para obtener los mismos resultados.

El solicitante se opone rotundamente a dichos argumentos puesto que el procedimiento puede parecer un mero reemplazo, cuando cualquier persona experta en síntesis química respondería que es todo lo contrario, como se puede establecer a continuación:

El grupo ciano y el grupo éster son de clases totalmente diferentes aunque ambos experimenten hidrólisis para producir un ácido, ellos difieren significativamente en su mecanismo de hidrólisis, su cinética de hidrólisis, sus selectividad y especificidad y en su habilidad para sufrir hidrólisis en una condición particular.

Así las cosas, discutiremos a continuación cada uno de estos puntos:

- Mecanismo de hidrólisis.

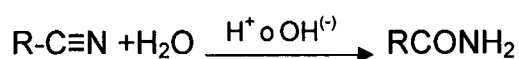
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Es bien conocido que un grupo éster hidroliza directamente a un ácido, por ejemplo
 $\text{RCOOME} + \text{OH}^{(-)} \rightarrow \text{RCOO}^{(-)}$ (**Anexo IX, página 378**)

De otra parte, la hidrólisis del grupo ciano ocurre a través de la formación de un intermediario de una amida:



Que subsecuentemente es hidrolizado al correspondiente ácido carboxílico. (**Anexo X**)

Entonces, es claramente evidente que el mecanismo de hidrólisis es diferente para un éster que para un grupo ciano, incluyendo diferente intermediario. En realidad, es posible controlar la hidrólisis y obtener una amida, que es lo discutido a continuación.

Adicionalmente, también es conocido que el equilibrio de hidrólisis éster es hacia el producto mientras el equilibrio de hidrólisis ciano es hacia el reactivo.

▪ Cinética de la hidrólisis.

Ya que la hidrólisis del grupo ciano ocurre a través de la formación de un intermediario de la amida se apreciará que la rata de hidrólisis de la mida determinará inicialmente la rata de hidrólisis del grupo ciano.

Se encuentra bien establecido que la reactividad relativa del grupo amida es casi 100 veces mesón que la correspondiente al grupo éster. (**Página 472-473 del Anexo XI**) Entonces, la facilidad y reactividad de ciano hacia la hidrólisis son menores comparadas a la del grupo éster. Por lo tanto, la afirmación de que si un sustrato particular experimenta hidrólisis por su grupo éster y por tanto, deberá tener una hidrólisis similar en correspondiente grupo ciano no es correcta desde el punto de vista de la cinética de la reacción. De hecho, cualquier persona experta en química orgánica confirmaría que en la mayoría de los casos la hidrólisis del grupo ciano es difícil y presenta problemas, y si el grupo ciano es hidrolizado, esto requiere de condiciones drásticas.

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Nuevamente, la reacción de hidrólisis está caracterizado cinéticamente por valores p_p , p_m , p_i y p^o_R . Los valores para el grupo ciano son sustancialmente diferentes a los valores del grupo éster (**Anexo XI**). Esto también soporta nuestra afirmación que los dos grupos actúan diferente durante la hidrólisis y el mero hecho que el grupo éster de un sustrato particular sufra hidrólisis no permite extrapolar que un derivado ciano del correspondiente sustrato también sufra hidrólisis.

- Selectividad y especificidad.

En general, un grupo ciano no puede ser remplazado por un grupo éster. En un solo sustrato donde ambos grupos están presentes, el grupo éster reaccionará preferiblemente en muchas circunstancias. Entonces, en un sustrato donde estén presentes tanto el grupo ciano como el grupo éster, el éster puede ser removido preferencialmente (**Anexo XII**). Esto soporta nuestro argumento que el grupo ciano y el grupo éster son dos únicos y específicos sustitos, que reaccionan con diferentes reactivos de manera diferente y normalmente la reactividad de los grupos éster es más alta que la del grupo ciano.

- Habilidad para sufrir hidrólisis en una condición particular.

Una prueba adicional de que un grupo éster y un grupo ciano no hidrolizan similarmente y que uno no puede remplazar el uno por el otro sobre el mismo sustrato es suministrada por la síntesis clásica de vitamina B12 (**Anexo XIII**). En la página 132 el esquema de síntesis para la preparación de la vitamina B₁₂ (-) es descrito. Al inicio el material es ácido cobirínico abcdeg hexametiléster f nitrilo (96), que contiene 6 grupos éster (CO₂Me) y un grupo ciano sobre la parte externa del esqueleto alquilo. Sin embargo, como puede observarse en este sustrato, una hidrólisis ácida usando H₂SO₄ concentrado lleva a que solo el grupo ciano consiga hidrolizarse al correspondiente ácido a través de la formación del intermediario amida (97), manteniendo todos los seis grupos éster intactos.

Entonces es claro que un grupo ciano y un grupo éster cuando están presentes en el mismo sustrato sufren hidrólisis diferentes y uno no puede sustituir un grupo con otro para obtener el mismo resultado.

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En este orden de ideas y sin ánimo de instruir sobre como debe realizarse el examen de patentabilidad, nos gustaría establecer que muchas de las invenciones parecen ser obvias una vez han sido hechas. Sin embargo, si se miran los problemas que existían antes de su desarrollo y la solución ingeniosa que permitió superarlos es evidente que se encuentran lejos de resultar obvios. Estudiosos de este aspecto, como Lord Russel (**Anexo XIV**) dicen que "No hay nada más fácil que decir, luego del hecho, que la cosa era obvia y no incluía invención".

En el presente caso es claro que en circunstancias normales, la hidrólisis del grupo ciano no es muy superficial y requiere de condiciones drásticas. Sin embargo, el presente invento ha mostrado un método superficial y fácil de hidrolizar un sustrato, que tiene algunos efectos benéficos para la totalidad del proceso para la preparación del Clopidrogel como se describió anteriormente.

Así las cosas, qué tan fácil hubiera sido mejorar el proceso sin las modificaciones que se reivindican en esta solicitud? Posiblemente se hubiera podido lograr pero seguramente de otra manera pues para empezar el estado de la técnica más próximo lo que enseñaba era que la vía saponificación usada por el solicitante no era la ideal. Siendo así, como podría resultar obvio modificar una reacción que no era la más conveniente, justo con los cambios que investigó y desarrolló el solicitante y que dichos cambios permitirían potencializar la productividad del proceso. Claramente no era posible dicha predicción. Por consiguiente, el proceso no es obvio y la solicitud cumple con la totalidad de los requisitos de patentabilidad, incluso el tener altura inventiva.

También nos gustaría destacar algunas otras características mejoradas de la presente invención:

Nuestro proceso de resolución de ($\pm$) amina (VII), con S (+) CSA es no solo impredecible sino que es tecnológicamente más deseable desde la perspectiva del proceso, ya que el deseado isómero dextrógiro de amida (+) precipita cuantitativamente en el primer intento como diastereoisómero, sin ninguna contaminación de isómeros no deseados como isómeros (-) o ($\pm$). (Ejemplo 31 de la descripción). La pureza óptica del producto logrado mediante el proceso reivindicado es de 99.5%. No se requiere de

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etapas para la remoción de impurezas.

Llamamos la atención sobre el hecho que las patentes US 4.546.201, US4.515.811, GB 1.426.186 y GB1.422.015 (Anexos XV, XVI, XVII y XVIII) se relacionan con procesos de resolución óptica de ácido ($\pm$) 2-(6'-metoxi-2'-naptil) propanoico (NAPROXEN). El objetivo de todas estas patentes ha sido establecer los agentes de resolución e identificar los parámetros críticos del proceso que eviten múltiples cristalizaciones y permita obtener una mayor proporción de los deseados d-isómeros en un solo paso de cristalización con una mejorada calidad (es decir sin contaminaciones de isómeros indeseables).

Una vez más, la resolución de la mezcla racémica de ($\pm$) Naproxen en cuatro patente confirma nuestra tesis que aunque conceptualmente uno puede argumentar que basado en el estado de la técnica es "obvio ensayar", la experiencia sugiere que nadie podría garantizar que tal experimento podría haberse esperado que suceda.

Finalmente hay otras características no obvias del proceso reivindicado como son:

- El agente de resolución para amida (VII) es (+)CSA, que no ha sido reportado para esta síntesis.
- La resolución de dicha amida no tiene precedentes y sus propiedades por ejemplo, SOR (especifica rotación óptica) del diastereoisómero de VII con S (+) CSA=+51° (C=1, MeOH) y SOR de (+) amida (VII)=+41° (C=1, MeOH) son hasta el momento desconocidas. (ver ejemplo 31).
- La invención en donde (+) nitrilo (IV) produce solo (+) amida (V) y (+) amida solo produce (+) éster es nueva y no obvia. Ningún documento del estado de la técnica puede predecir esto.
- El proceso para convertir (+) amida a (+) éster es tanto altamente productivo como sin racemización.

En este contexto, es notorio que en el estado de la técnica reportado por Burgos (D1)

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para la conversión de amida racémica a éster racémico donde se requiere una drástica condición de reflujo por 144 horas para llevar a cabo tan solo la conversión parcial del material inicial y con una baja productividad (7% según la página 895) de éster, con 26% de amida que no reacciona y es aislada por cromatografía de columna.

- El proceso de conversión de sal diastereoisomérica de (+)amida/(+)CSA a (+) ester sin ninguna racemización en 97% del producto en 26 horas (ejemplo 37) es efectivamente único e impredecible. Incluso el mismo proceso de convertir una sal diastereoisomérica a un compuesto deseado es nuevo, novedosos e inventivo.

Basándonos en las razones técnicas expuestas nos permitimos citar los apartes de la Interpretación Prejudicial correspondiente al PROCESO 15-IP-2004 donde se realizan las siguientes consideraciones en relación con el nivel inventivo: "Según el tratadista Gómez Segade, el inventor debe acreditar los méritos que le tornen al invento susceptible de ser amparado por una patente; en tal sentido, sólo si la invención fruto de su investigación y desarrollo creativo constituye "un salto cualitativo en la elaboración de la regla técnica" -actividad intelectual mínima que le permitirá que su invención no sea evidente (no obvia)- le posibilitará alcanzar tal propósito. Es decir que con el requisito del nivel inventivo, lo que se pretende es dotarle al examinador técnico, de un elemento que le permita concluir que a la invención objeto de estudio no se habría podido llegar a partir de los conocimientos técnicos existentes en ese momento dentro del estado de la técnica, con lo cual la invención se constituye en un "paso" más allá de lo existente."

Como se puede observar, los argumentos técnicos expuestos por el solicitante en relación a las diferencias que existen entre el proceso reivindicado y aquellos que se encuentran en el estado de la técnica acreditan los méritos de la invención para que ella sea amparada por una patente, ya que ellos son claros en evidenciar que dichos procesos no solo son distintos en el paso de resolución como lo afirma el opositor, sino que el proceso reclamado en la solicitud 03055750 presenta otros puntos que lo distinguen de del proceso empleado en el artículo de Burgos, como son las modificaciones relacionadas con la síntesis de Strecker y la conversión de nitrilo a ester vía amida.

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Las modificaciones realiza al proceso son el fruto de investigación y desarrollo creativo constituye y sin lugar a duda, ellas no son variaciones menores que el solicitante ha planteado para separar el proceso reivindicado del existente en el estado de la técnica, sino que marcan la diferencia entre una muy alta productividad (97%) no formación de impurezas partir la fuente de cianuro, no requiere columnas de cromatografía y un escalamiento de la síntesis a 24g de producto aislado, donde de hecho la síntesis ha sido hecha a nivel de kilogramos; constituyéndose en un salto cualitativo y cuantitativo en el proceso.

Adicional a los efectos inesperados, dichos cambios no eran evidentes puesto que las reglas existentes en el estado de la técnica enseñaban que la saponificación del nitrilo a amida, vía tomada por el inventor, no era la óptima ya que Burgos explícitamente indica que dicha ruta tiene problemas de reacción retro-Strecker. De ahí que Burgos realiza una hidrólisis promovida por HCl a amida en orden de evitar la reacción retro-Strecker y finalmente produce una menor cantidad de producto. Contrario a los lineamientos dados por D1, el inventor modifica justamente la saponificación del nitrilo a amida que Burgos había establecido que no funcionaba, de tal manera que potencia el proceso llevándolo a una mayor productividad, lo cual sin duda constituye un "paso" más allá de lo existente."

Retomando la información de la Interpretación Prejudicial 15-IP-2004, el mismo autor antes citado ha dicho:

"Se reconoce que hay invento cuando se utilizan medios ya conocidos, pero combinados por primera vez en forma tal, que de su combinación deriva un resultado distinto del dado por cada uno de los medios, o por otras combinaciones conocidas... También existe la posibilidad de que el resultado sea conocido, pero se llegue a él a través de nuevos medios. El titular de una patente no tiene el derecho de evitar que un tercero obtenga el mismo resultado por medios distintos" [5].

En concordancia con lo expuesto por el señor Gómez Segade el proceso que se reivindica en la solicitud 03055750 parte de una reacción ya conocida, a la cual se le han efectuado algunas modificaciones para que su novedosa combinación de reactivos

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y etapas se derive en un resultado distinto en cuanto a productividad y calidad del producto del que ha sido reportado para la reacción de Strecker y para la reacción que divulgó Burgos.

Tal como lo precisa Gómez Segade, el alcance de la invención está dado por las reivindicaciones y ellas claramente limitan dicha invención al proceso modificado y al Clopidrogel producido mediante dicho proceso. En ningún momento es la intención del solicitante extender su solicitud a procesos ya conocidos en el estado de la técnica como el revelado por Burgos ni a moléculas de Clopidrogel sintetizadas mediante dichos procesos.

Ante estos hechos es evidente que la solución planteada en la invención reclamada en la totalidad de las reivindicaciones de la solicitud CO 03-055750 no solo cumple con el requisito de novedad, sino que no es evidentemente derivada del estado de la técnica y por ende, cumple con el requisito de nivel inventivo requerido en virtud del artículo 14 y definido en el artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina.

Por lo tanto, se solicita respetuosamente a la Oficina de Patentes Colombiana declarar infundada la oposición presentada por PROCAPS y conceder el privilegio de patente.

Agradezco continuar con el presente trámite.

Señor Jefe,

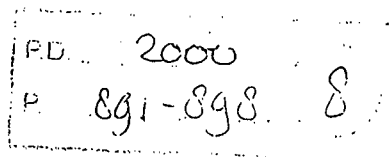


DILIA RODRIGUEZ D'ALEMAN

MRO/srch

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XP008008850



ortho-Metalation/Chlorination of Benzoic Acid Derivatives:
Preparation of [*benzene*-U-¹³C]-*rac*-Clopidogrel
([*benzene*-U-¹³C]-*rac*-SR25990C).

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SUMMARY

Directed *ortho*-lithiation is used to form [*benzene*-U-¹³C]-2-chlorobenzaldehyde, the key building block for preparation of labelled racemic Clopidogrel ([*benzene*-U-¹³C]-*rac*-SR25990C). Some practical observations are reported concerning the metalation of some derivatives of benzoic acid.

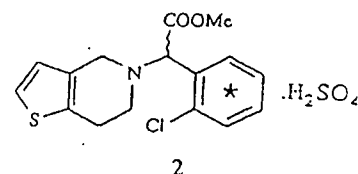
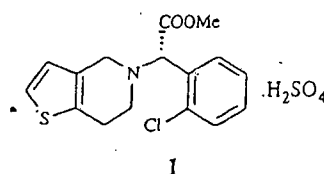
Keywords: 2-Chlorobenzaldehyde, *ortho*-Metalation, Strecker-Synthesis, Plavix, Clopidogrel, SR25990

INTRODUCTION

Clopidogrel sulfate (PlavixTM, SR25990C, 1) is an orally active inhibitor of platelet aggregation, now marketed as an antithrombotic agent.^{1,2} As part of studies of the metabolism of SR25990, a synthesis of stable isotopically-labelled SR25990 for use as a mass spectroscopic standard was required. Although Clopidogrel is a single enantiomer, the labelled racemate (2) would suffice as a standard; this was therefore the synthetic target, and was approached by means of a Strecker reaction, with [*benzene*-U-¹³C]-2-chlorobenzaldehyde (3) as the pivotal intermediate. In turn, the obvious approach to 3 was by directed *ortho*-metalation and chlorination of a derivative of commercially available [*benzene*-U-¹³C]-benzoic acid, and subsequent reduction.

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RESULTS AND DISCUSSION

The *ortho*-metalation of benzoic acid³ and of a number of amides,⁴ and subsequent chlorination with hexachloroethane is known. However, following the method described by Snieckus⁴ for *ortho*-metalation of diethylbenzamide, no metalation was observed (Table 1). In view of this, the stability of *s*-butyllithium in the medium was examined; when *s*-butyllithium was added to one equivalent quantity of TMEDA in THF, 1,2-dimethoxyethane, or *tert*-butyl methyl ether and the base concentration checked by double titration, it was found that *s*-butyllithium was consumed within 15 minutes at -78°C .

Table 1. *ortho*-Metalation Reactions of Diethyl- and Diisopropylbenzamides^a

R	Conditions	E ⁺ (E)	a (%)	b (%)	c (%)	d (%)	e (%)
Et	THF, -78°C	C ₂ Cl ₆ (Cl)	-	78 ^b	17 ^b	-	-
Et	Toluene, -78°C	D ₂ O (D)	48	12	27	13	-
<i>i</i> -Pr	Toluene, -78°C	D ₂ O (D)	ca. 70	ca. 20	-	-	ca. 10
<i>i</i> -Pr	Toluene, -78°C	C ₂ Cl ₆ (Cl)	68 ^c	19	-	-	13

a. Yields and product identification by GC-MS.

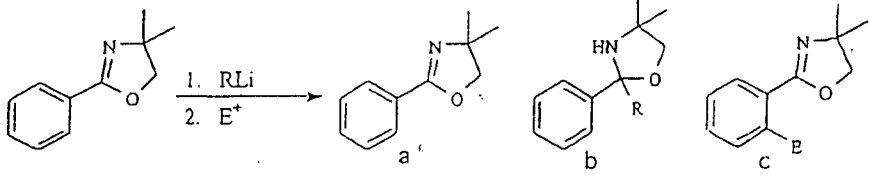
b. isolated yield.

c. 40% isolated.

Similar observations have been reported by Stanetty and Mihovilovic,⁵ and the base-induced cleavage of tetrahydrofuran to give acetaldehyde enolate and ethylene,⁶ and of 1,2-dimethoxyethane to give methyl vinyl ether and methoxide,⁷ are well known. A similar process can reasonably be postulated for cleavage of TBME. This process was avoided by using toluene as the reaction solvent. Under these conditions,

metalation occurred but was both slow and incomplete, with the result that significant amounts of starting material remained, with which a proportion of lithiated species reacted to give a benzophenone. Moreover, the process was complicated by nucleophilic addition of *s*-butyllithium to the amide and by bis-metalation (Table 1). Side-reactions were suppressed effectively by using diisopropylbenzamide as the substrate (Table 1). However, metalation still did not proceed to completion and attempts to separation of the product from starting material were unsuccessful. Better results were obtained using the oxazoline 4 (in unlabelled form, Table 2),⁸ in which case the efficiency of metalation was sufficient that it was not necessary to complex the base with TMEDA.

Table 2. *ortho*-Metalation of unlabelled 4.^a

					
RLi	conditions	E ⁺ (E)	a (%)	b (%)	c (%)
BuLi	Et ₂ O, 0°C	D ₂ O (D)	-	34	66
<i>i</i> -Pr ₂ NLi	THF, -78°C	D ₂ O (D)	100	0	0
<i>s</i> -BuLi	Toluene, -78°C	D ₂ O (D)	0	3	97
		C ₂ Cl ₆ (Cl)	43	3	54

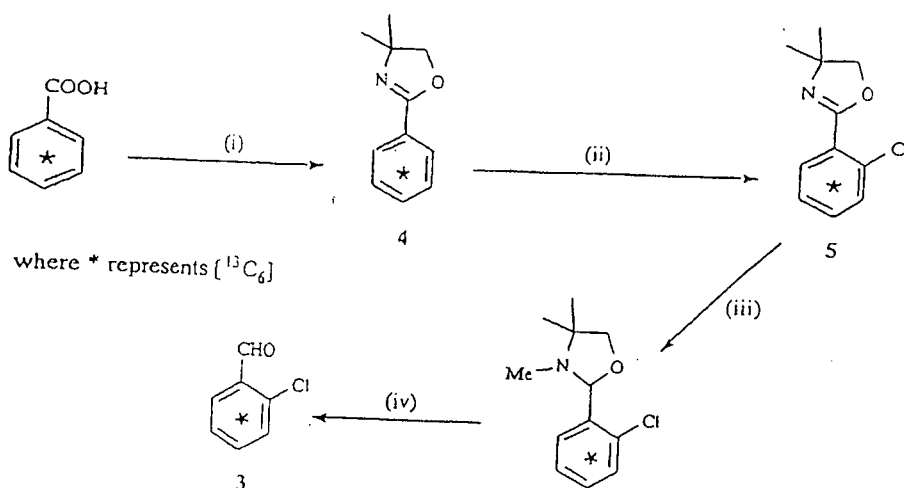
^a Yields and product identification by GC-MS.

Given the efficiency of the metalation of 4, the yield of chlorinated product was disappointing. In the absence of any other proton source, it can only be surmised that excess *s*-butyllithium reacts with hexachloroethane more rapidly than does the *ortho*-metalated intermediate, and that the resulting 2-chlorobutane is a better electrophile (as a proton source) than is hexachloroethane. Suppression of this process was, however, difficult since the addition of a smaller amount of base resulted in incomplete lithiation and, where the reaction time was extended, a

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significantly increased level of the undesired addition product. Nevertheless, this appeared to be the best method available.

The route used to prepare [*benzene*-U- ^{13}C]-2-chlorobenzaldehyde (3) is shown in Scheme 1. [*benzene*-U- ^{13}C]-Benzoic acid was converted to the oxazoline 4 using the literature method.⁹ Lithiation and chlorination of 4 gave 5 in 60% yield after separation from unreacted starting material. An advantage of the chosen approach was that 5 could be reduced,¹⁰ and the resulting oxazolidine hydrolysed readily to give 3 directly. This product, although isolated, was not purified since chromatographic losses were significant and better overall results were obtained by carrying out the Strecker synthesis directly using the crude material.



Scheme 1. Preparation of [*benzene*-U- ^{13}C]-2-Chlorobenzaldehyde (3)

Reagents: (i) a. SOCl_2 ; b. $\text{H}_2\text{NCMe}_2\text{CH}_2\text{OH}$; c. SOCl_2 .

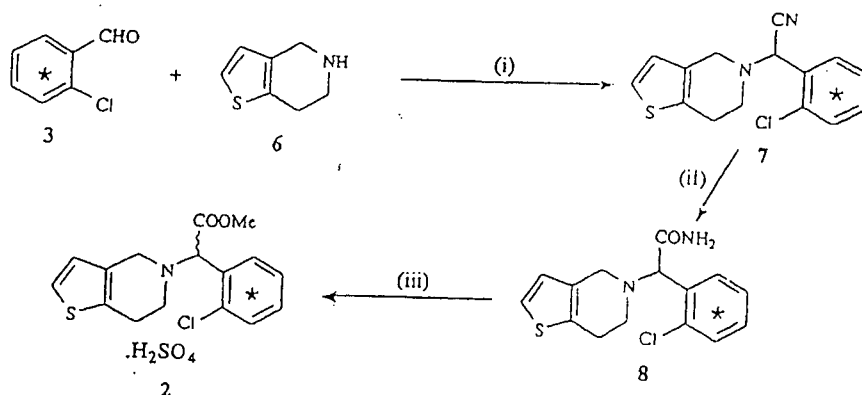
(ii) a. *s*-BuLi, toluene, -78°C . b. C_2Cl_6 , -40°C to R.T.

(iii) a. MeI, R.T.; b. NaBH_4 , EtOH, R.T. (iv) 2N HCl, R.T.

Assembly of the desired material was carried out using Strecker methodology as planned: treatment of labelled aldehyde 3 with the thienopyridine 6 and acetone cyanohydrin gave the nitrile 7 in 31% overall yield from 5. Despite the poor overall yield, the last process appeared relatively clean, with the only impurities detected by

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GC-MS of the crude product being small quantities of adducts formed from 6 and acetone cyanohydrin which were not isolated. Conversion of the resulting nitrile 7 to the final product 2 required a two-step process; saponification of 7 was not an option, since a retro-Strecker reaction occurred in preference to hydrolysis, but hydrochloric acid-promoted hydrolysis gave the amide 8 in quantitative yield. Methanolysis of 8 proceeded directly to the ester 2, which was isolated as its sulfate. This step required strongly acidic conditions and the yield was only modest (although most of the unreacted starting material was recovered); alternative methods, using Meerwein's reagent¹¹ and dimethylformamide dimethyl acetal¹² were examined but these represented no improvement upon the method used. The process as described provides [*benzene-U-¹³C]-*rac*-SR25990 (2) in an overall 7% yield from labelled benzoic acid.*



Scheme 2. Elaboration of [*benzene-U-¹³C]-2-Chlorobenzaldehyde to 2*

Reagents: (i) acetone cyanohydrin, MgSO_4 , 45°C , toluene.

(ii) HCl , MeOH , R.T. (iii) a. 2 eq. H_2SO_4 , MeOH , reflux; b. H_2SO_4 , Et_2O , R.T.

EXPERIMENTAL

^1H n.m.r. spectra were recorded using a Jeol GSX-270 instrument. Gas chromatography and mass spectrometry were performed using a Hewlett-Packard chromatograph (HP 5890) fitted with a mass-selective detector (HP 5970MSD) on a capillary column (HP-1, 23 m x 0.2 mm x 0.33 μm), using decane as an internal

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standard for quantitative measurements. High-resolution mass spectra were recorded using a VG Autospec magnetic sector instrument at the University of York. Reagents were obtained commercially, [benzene- U - ^{13}C]-benzoic acid in particular being obtained from Cambridge Isotope Laboratories.

[benzene- U - ^{13}C]-2-(2-Chlorophenyl)-4,4-dimethyl-4,5-dihydrooxazole (5). Oxazole 4 (prepared using the method of Shono *et al.*⁹ from [benzene- U - ^{13}C]-benzoic acid in 82% yield; 2.19 g, 12 mmol) in anhydrous toluene (10 ml) was added during 15 min under nitrogen at $-78^{\circ}C$ to a solution of *sec*-butyllithium (1.3M in hexanes; 11.1 ml, 14 mmol). After 30 min, hexachloroethane (8.6 g, 36 mmol) in toluene (20 ml) was added by means of a cannula following which the mixture was allowed to warm to room temperature during 40 min. The reaction was quenched with aqueous ammonium chloride and re-extracted with toluene (3 x 50 ml), and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give an oil. The crude material was purified by chromatography on silica gel in hexane - ethyl acetate (85:15) followed by preparative HPLC of the mixed fractions in the same system to give 5 (1.5 g, 58%). $\delta_H(CDCl_3)$ 1.39 (6H, s), 4.12 (2H, s), 7.0-7.2 (2H, m), 7.5-7.75 (2H, m), 8.1-8.4 (1H, m).

[benzene- U - ^{13}C]-rac-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)acetonitrile (7). A solution of 5 (1.50 g, 8.3 mmol) in methyl iodide (3.1 ml) was heated at reflux for 16 h. Upon cooling, excess methyl iodide was removed under vacuum and the pale yellow solid was redissolved in anhydrous ethanol (15 ml). Sodium borohydride (461 mg, 12 mmol) was added in portions during 10 min, and the mixture stirred for 2 h. Ethanol was removed under reduced pressure, water (25 ml) was added followed, after 30 min, by 2N hydrochloric acid (50 ml). After a further 30 min, the mixture was extracted with toluene (3 x 25 ml), and the combined extracts were washed with aqueous sodium hydrogencarbonate (40 ml) and dried ($MgSO_4$). To this solution of 3 were added 6 (1.40 g, 10 mmol),² anhydrous magnesium sulfate (1.4 g) and, after 5 minutes, acetone cyanohydrin (850 mg, 10 mmol). The suspension was stirred under nitrogen at $45^{\circ}C$ for 48 h, following which volatile materials were removed under vacuum, and the residue purified by

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column chromatography on silica gel in hexane - ethyl acetate (85:15) followed by crystallisation from hexane to give 7 (744 mg, 31%). $\delta_{\text{H}}(\text{CDCl}_3)$ 2.75-3.05 (4H, m), 3.64 (1H, d), 3.79 (1H, d), 5.29 (1H, m), 6.79 (1H, d), 7.07 (1H, d), 6.95-8.1 (4H, m); m/z (EI) 294/296 (M^+), 156, 110 (100%).

[benzene- U - ^{13}C]-rac-2-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)acetamide (8): A solution of 7 (729 mg, 2.5 mmol) in anhydrous methanol (10 ml) saturated with hydrogen chloride was stirred for 48 h. Volatile material was removed under vacuum and the residue was azeotropically dried with dichloromethane. The residue was partitioned between aqueous sodium hydrogencarbonate and dichloromethane. The aqueous phase was re-extracted with dichloromethane and the combined organic fractions were dried (MgSO_4) and concentrated to give 8 (729 mg, 94%). $\delta_{\text{H}}(\text{CDCl}_3)$ 2.8-3.0 (4H, m), 3.59 (1H, d), 3.69 (1H, d), 4.91 (1H, m), 6.07 (1H, m), 7.06 (1H, m), 6.8-8.0 (4H, m); m/z (EI) 312/314 (M^+), 268/270 (100%), 138.

Methyl [benzene- U - ^{13}C]-rac-(2-Chlorophenyl)-(6,7-dihydro-4H-thieno[3,2-*c*]pyridin-5-yl)acetate Sulfate (2). A solution of 8 (729 mg, 2.3 mmol) in methanol containing sulfuric acid (1 ml) was heated at reflux for 144 h. The solvent volume was reduced under vacuum, and the mixture partitioned between ethyl acetate and aqueous sodium hydrogencarbonate. The aqueous phase was re-extracted with ethyl acetate and the combined organic phases were dried (MgSO_4) and concentrated under reduced pressure. Column chromatography of the residue in hexane - ether (85:15) on silica gel gave the free base of 2 (366 g, 50%) followed by 8 (190 mg, 26%). Addition of a 1 g/l solution of sulfuric acid in ether to a stirred solution of the free base of 2 in ether, followed by filtration after 10 min gave 2. $\delta_{\text{H}}(\text{CD}_3\text{OD})$ 3.7-3.85 (2H, m), 2.87 (3H, s), 4.1-4.55 (2H, m), 5.87 (1H, q), 6.80 (1H, d), 7.2-7.45 (2H, m), 7.40 (1H, d), 7.8-8.05 (2H, m); m/z (FAB $^+$) 328, 330 ($[\text{MH}]^+$), 286, 154 (100%), 137, 136. HRMS 328.0869; calc. for $\text{C}_{10}^{13}\text{C}_6\text{H}_{17}\text{ClNO}_2\text{S}$ 328.0870

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ANNEXURE-I

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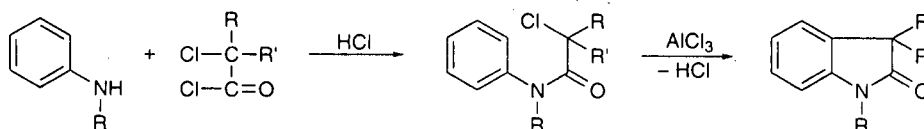
Organic Name Reactions

Reviews: W. S. Johnson, G. H. Daub, *Org. React.* **6**, 1 (1951); H. O. House, *Modern Synthetic Reactions* (W. A. Benjamin, Menlo Park, California, 2nd ed., 1972) pp 663-666; R. J. Hart, H. G. Heller, *Perkin Trans. I* **1972**, 1321; N. R. El-Rayyes, *J. Prakt. Chem.* **315**, 295 (1973); V. B. Bagos *et al.*, *Helv. Chim. Acta* **62**, 90 (1979). Cf. Perkin Reaction.

363. Stollé Synthesis

R. Stollé, *Ber.* **46**, 3915 (1913); **47**, 2120 (1914); *J. Prakt. Chem.* **105**, 137 (1923); **128**, 1 (1930).

Formation of indole derivatives by the reaction of arylamines with α -haloacid chlorides or oxalyl chloride, followed by cyclization of the resulting amides with aluminum chloride:

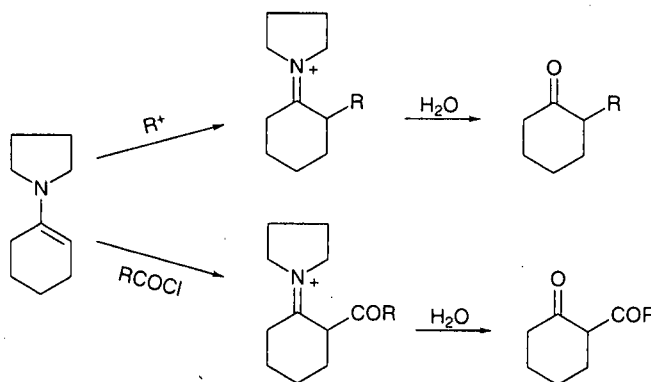


W. C. Sumpter, *Chem. Rev.* **34**, 396 (1944); **37**, 446 (1945); P. L. Julian *et al.*, *Heterocyclic Compounds* **3**, 142, 209 (1952); A. H. Beckett *et al.*, *Tetrahedron* **24**, 6093 (1968). Cf. Hinsberg Oxindole Synthesis.

364. Stork Enamine Reaction

G. Stork *et al.*, *J. Am. Chem. Soc.* **76**, 2029 (1954); G. Stork, H. Landesman, *ibid.* **78**, 5128 (1956).

Synthesis of α -alkyl or α -acyl carbonyl compounds from enamines and alkyl or acyl halides:

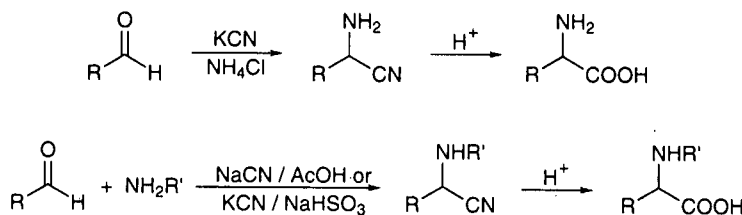


Reviews: J. Szmuszkowicz, *Adv. Org. Chem.* **4**, 1 (1963); A. G. Cook, Ed., *Enamines* (Marcel Dekker, New York, 1969); H. O. House, *Modern Synthetic Reactions* (W. A. Benjamin, Menlo Park, California, 2nd ed., 1972) pp 570-580, 766-772; S. F. Dyke, *Chemistry of Enamines* (Cambridge University Press, New York, 1973); P. W. Hickmott, *Tetrahedron* **38**, 1975 (1982).

Strecker Amino Acid Synthesis

Strecker, *Ann.* **75**, 27 (1850); **91**, 349 (1854).

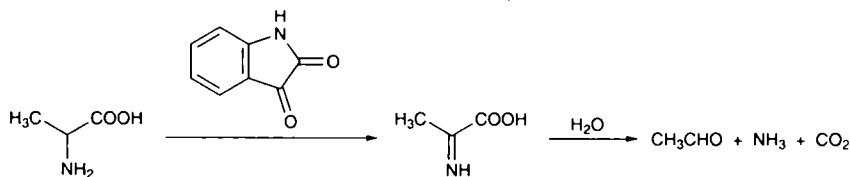
Synthesis of α -amino acids by reaction of aldehydes with ammonia and hydrogen cyanide followed by hydrolysis of the resulting α -aminonitriles. Safer, milder, and more selective reaction conditions have been developed, especially in regard to asymmetric synthesis. The scope of the reaction has been extended to include primary and secondary amines:



Reviews: J. P. Greenstein, M. Winitz, *Chemistry of the Amino Acids* vol. **3** (New York, 1961) pp 698-700; G. C. Barrett, *Chemistry and Biochemistry of the Amino Acids* (Chapman and Hall, New York, 1985) pp 251, 261. Asymmetric synthesis using enantiopure sulfinimines: F. A. Davis *et al.*, *Tetrahedron Letters* **35**, 9351 (1994). Review of stereoselective synthesis: R. O. Duthaler, *Tetrahedron* **50**, 1539-1650 *passim* (1994). Cf. Bucherer-Bergs Reaction.

366. Strecker DegradationA. Strecker, *Ann.* **123**, 363 (1862).

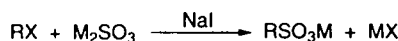
Reaction of an α -amino acid with a carbonyl compound in aqueous solution or suspension to give carbon dioxide and an aldehyde or ketone containing one less carbon atom. Inorganic oxidizing agents can also be used to bring about the transformation:



Mechanism: Schönberg *et al.*, *J. Chem. Soc.* **1948**, 176. Reviews: Schönberg, Moubacher, *Chem. Rev.* **50**, 261 (1952); N. van Chuyen *et al.*, *Agr. Biol. Chem.* **36**, 1199 (1972), *C.A.* **77**, 114855e (1972) Photo-promoted hypochlorite oxidation: Y. Ogata *et al.*, *Bull. Chem. Soc. Japan* **54**, 2057 (1981).

367. Strecker Sulfite AlkylationA. Strecker, *Ann.* **148**, 90 (1868).

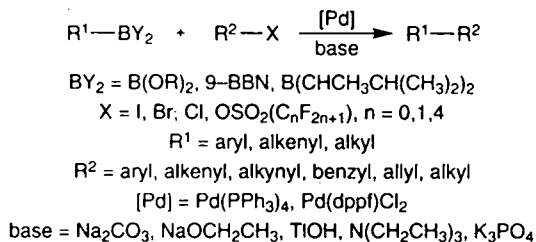
Formation of alkyl sulfonates by reaction of alkyl halides with alkali or ammonium sulfites in aqueous solution in the presence of iodide:



A. Collmann, *ibid.* 101; W. Hemilian, *ibid.* **168**, 145 (1873); *Ber.* **6**, 562 (1873); *Swiss. pats.* **105,845**; **104** (1925); F. C. Wagner, E. E. Reid, *J. Am. Chem. Soc.* **53**, 3409 (1931); C. Weygand, *Organic Preparations* (New York, 1945) p 306; M. Quaedvlieg, *Houben-Weyl* **9**, 372 (1955).

368. Suzuki CouplingN. Miyaura *et al.*, *Tetrahedron Letters* **1979**, 3437; N. Miyaura, A. Suzuki, *Chem. Commun.* **1979**, 866.

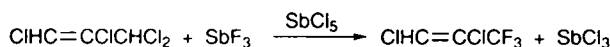
Palladium-catalyzed cross coupling of organic halides or perfluorinated sulfonates with organoboron derivatives proceeding with high stereo- and regioselectivity:



Competition with Heck reaction, *q.v.*, when using an alkenyl boronate ester: A. R. Hunt *et al.*, *Tetrahedron Letters* **34**, 3599 (1993). Alternative palladium catalysts: G. Marck *et al.*, *ibid.* **35**, 3277 (1994); T. I. Wallow, B. M. Novak, *J. Org. Chem.* **59**, 5034 (1994). Reviews: A. Suzuki, *Pure Appl. Chem.* **63**, 419-422 (1991); A. R. Martin, Y. Yang, *Acta Chem. Scand.* **47**, 221-230 (1993). Cf. Hydroboration Reaction; Stille Coupling.

369. Swarts ReactionF. Swarts, *Bull. Acad. Roy. Belg.* **24**, 309 (1892).

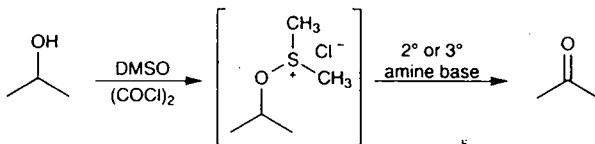
Fluorination of organic polyhalides with antimony trifluoride (or zinc and mercury fluorides) in the presence of trace of a pentavalent antimony salt:



A. L. Henne, *Org. React.* **2**, 49 (1944); M. Hudlicky, *Chemistry of Organic Fluorine Compounds* (MacMillan, New York, 1962) pp 93-98.

370. Swern Oxidation (Moffatt-Swern Oxidation)K. Omura, D. Swern, *Tetrahedron* **34**, 1651 (1978).

Mild oxidation of primary and secondary alcohols, promoted by oxalyl chloride activation of dimethyl sulfoxide, evidently involving the dimethyl alkoxysulfonium salts. Upon the addition of base, the intermediates rearrange intramolecularly to generate aldehydes or ketones, respectively:



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Patent Law Basics

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This work is affectionately dedicated to the memory of my parents, Frederick and Martha Rosenberg, whose constant encouragement and unfaltering confidence in me—even during the darkest hours—were in no small measure responsible for making it a reality.

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§ 6.01(1)

SUBSTANTIVE REQUISITES

Where a process consists of more than a single step, the arrangement, order, or sequence in which these component steps are to be performed may itself be of patentable significance. Thus, the patentability of a multi-step process may reside solely in the arrangement of its constituent steps—each of the individual steps being old, the particular order constituting a new combination. On the other hand, the patentability of a process may reside in the materials being employed, the physical manipulative steps being old.¹⁸ Weight must be accorded to the particular ingredients that are combined with each other in a claimed method, even though they are analogous to those of the prior art.¹⁹ Method claims need not recite all of the operating details.²⁰

The patentability of a process may reside in a particular step or in the order in which the constituent steps are performed.²¹ Any difference in magnitude in any process parameter (e.g., time, temperature, pressure) between what is claimed and the prior art should be deemed to render the process technically novel, though not unobvious unless the difference is somehow critical and/or the result unexpected. Nevertheless, a lower court was of the opinion that a method of applying a composition to hair that differed from the prior art only in the time the composition was left in contact with the hair was not even novel.²² It is conceivable that sufficient novelty and nonobviousness may reside in a starting material as to sustain the patentability of a process claim, the steps themselves being old. While the materials employed in a process cannot be ignored in resolving the question of the patentability of process claims,²³

¹⁸ *In re Coleman*, 621 F.2d 1141, 205 U.S.P.Q. 1172 (C.C.P.A. 1980); *Ex parte MacAdams*, 206 U.S.P.Q. 445 (P.O. Bd. App. 1980). *Contra*, *Ludlow Corp. v. Textile Rubber & Chem. Co.*, 636 F.2d 1057, 1061, 209 U.S.P.Q. 281, 284 (C.C.P.A. 1981).

¹⁹ *Ex parte Glaister*, 201 U.S.P.Q. 255 (P.O. Bd. App. 1976).

²⁰ *Ex parte Erlich*, 3 U.S.P.Q.2d 1011, 1017 (P.T.O. Bd. Pat. App. & Int. 1987).

²¹ *William Gold Refining Co. v. Semi-Alloys, Inc.*, 434 F. Supp. 453, 454, 198 U.S.P.Q. 37, 39 (W.D.N.Y. 1977).

²² *Revlon, Inc. v. Carson Prods. Co.*, 602 F. Supp. 1071, 226 U.S.P.Q. 51, 61 (S.D.N.Y. 1985).

²³ *Ex parte Klioze*, 220 U.S.P.Q. 91 (P.O. Bd. App. 1983); *Ex parte MacAdams*, 206 U.S.P.Q. 445 (P.O. Bd. App. 1978); *Ex parte Macy*, 132 U.S.P.Q. 545 (P.O. Bd. App. 1960).

where a process differs from the prior art solely in that a different but related or analogous starting material is employed, that process, though novel, may be deemed *prima facie* obvious,²⁴ unless it is a biotechnological process within the purview of the Biotechnological Process Patents Act of 1995, Pub. L. 104-41.^{24.1} Moreover, to be considered *prima facie* obvious, the prior art apparently must define a fairly narrow class of compounds that would render obvious the use of a member of such narrow class as a starting material in the prior art process.^{24.2} The novelty of such a process resides in the fact that the materials are not identical with those employed by the prior art. [Failure of the prior art to teach the analogy between the materials should tend] to establish unobviousness, as would the existence of a different (and unexpected result.) In chemical cases, the starting materials are often spoken of as reactants or reagents; and in mechanical cases as the workpiece.

The materials subjected to treatment by the steps of a process and the steps themselves are the parameters which define a process. The nature and composition of the product are defined by and necessarily flow from the foregoing parameters. Two processes which treat the same starting material in the same manner are identical and must of necessity give rise to the same product.

The steps of a method or process claim are analogous to the components of an apparatus claim. Both are "combination" claims. It should be noted that many of the so-called one-step processes actually involve several steps, the single step being performed at a particular stage in a conventional series of steps.

Formerly, the nature of the steps themselves was of significance in determining whether a process fell within the realm of statutory subject matter. At an early date, the courts distinguished between processes involving the use of machines and those involving the application of more fundamental forces, holding that only processes involving the latter type of forces fell

²⁴ *In re Durden*, 763 F.2d 1406, 1410, 226 U.S.P.Q. 359, 362 (C.A.F.C. 1985).

^{24.1} See §§ 9.03, 9.05[8][c], *infra*.

^{24.2} *In re Ochiai*, 71 F.3d 1565 (C.A.F.C. 1995), *rev'g* 24 U.S.P.Q.2d 1265 (P.T.O. Bd. Pat. App. & Int. 1992). See § 9.05[8][c], *infra*.

patent owner has been deemed not determinative of what constitutes relevant prior art.¹³ The amount of time and effort devoted to development do not contribute to patentability.¹⁴ The slow but inevitable progress of an industry through trial and error and the persistent and intelligent search for improvement are insufficient to support a patent.¹⁵ Nevertheless, it is reversible error for a court, in determining whether there has been compliance with 35 U.S.C. § 103, to give any weight to the fact that the claimed subject matter was arrived at by experimentation.¹⁶

[2] Proper Application of 35 U.S.C. § 103

Section 103 makes patentability depend upon, in addition to novelty and utility, the nonobvious nature of the "subject matter sought to be patented." The first sentence of this section requires that: (1) the scope and content of the prior art be determined; (2) the differences between the prior art and the claims in issue be ascertained; and (3) the level of ordinary skill in the pertinent art be resolved. Against this background, the obviousness or nonobviousness of the subject matter is to be determined.¹⁷

The Federal Circuit has added evidence of "secondary considerations" as a fourth factual inquiry.^{17.1} According to the Federal Circuit, the term "secondary considerations" includes evidence of unexpected results and objective evidence of nonobviousness and synergy.^{17.2}

¹³ *Mannesmann Demag Corp. v. Engineered Metal Prods. Co.*, 605 F. Supp. 1362, 1383, 226 U.S.P.Q. 466, 482 (S.D.N.Y. 1985).

¹⁴ *Kalkowski v. Ronco, Inc.*, 424 F. Supp. 343, 351, 194 U.S.P.Q. 563, 569 (N.D. Ill. 1976).

¹⁵ *Picard v. United Aircraft Corp.*, 128 F.2d 632, 636, 53 U.S.P.Q. 563, 566-67 (2d Cir. 1942).

¹⁶ *Carter-Wallace, Inc. v. Gillette Co.*, 675 F.2d 10, 13-14, 214 U.S.P.Q. 497, 499 (1st Cir. 1982).

¹⁷ *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 U.S.P.Q. 459, 467 (1966); M.P.E.P. 706, Rev. 49 (July 1976).

^{17.1} *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1582, 37 U.S.P.Q.2d 1314, 1318 (C.A.F.C. 1996).

^{17.2} *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1183, 41 U.S.P.Q.2d 1181, 1187 (C.A.F.C. 1997).

[a] Making Antecedent Factual Determinations Under 35 U.S.C. § 103

Questions of obviousness are not resolved in a vacuum but in the perspective of the prior art.

[i] What Constitutes "Prior Art" Under 35 U.S.C. § 103

Art applicable to a particular inquiry under 35 U.S.C. § 103 must satisfy two conditions: (1) it must be deemed *pertinent* or relevant to the claimed subject matter and (2) it must be deemed *prior* in time to the date the claimed invention was made.

The *scope* of art pertinent or relevant to a 35 U.S.C. § 103 determination includes within its purview not only subject matter falling into the same category of technology as that claimed but extends to subject matter "analogous" thereto. What constitutes analogous art is discussed in § 9.04, *infra*.

The *content* of prior art under 35 U.S.C. § 103 encompasses, but is not limited to, all statutory prior art material named in 35 U.S.C. § 102 that would be considered in determining novelty.¹⁸ This includes prior invention under 35 U.S.C. § 102(g).¹⁹ Evidence adduced in support of a 35 U.S.C. § 102 defense can be probative on the issue of level of skill in the pertinent art.²⁰ Circumstances that have preceded, attended, and succeeded an alleged invention have been said to be strong evidence of the level of ordinary skill in the art.²¹

¹⁸ National Rolled Thread Die Co. v. E.W. Ferry Screw Prods., Inc., 541 F.2d 593, 596, 192 U.S.P.Q. 358, 361 (6th Cir. 1976).

¹⁹ Norris Indus., Inc. v. Tappan Co., 193 U.S.P.Q. 521, 527 (C.D. Cal. 1976).

²⁰ Orthopedic Equip. Co. v. United States, 702 F.2d 1005, 1012, 217 U.S.P.Q. 193, 199 (C.A.F.C. 1983).

²¹ General Monitors, Inc. v. Mine Safety Appliances Co., 211 U.S.P.Q. 1127, 1141 (C.D. Cal. 1981).

[ii] What Constitutes a "Difference" Under 35 U.S.C. § 103

In determining obviousness, the invention must be considered "as a whole," i.e., in its entirety rather than piecemeal.²² Therefore, the process of determining obviousness has been characterized as not one of merely comparing the claims and the accused embodiment detail for detail to see if they match, but rather one of examining the claimed subject matter as a whole to see if, in light of the prior art, it would have been obvious to one skilled in the art.²³

Determinations of unobviousness are to be predicated not only upon what is literally recited in the claims, but also upon those properties of the claimed subject matter that are inherent in what is claimed and are disclosed in the specification.²⁴

While determinations of the obviousness or unobviousness of a claimed invention are to be based upon "the subject matter as a whole," where unobviousness is predicated upon an unusual or surprising result or advantage, such result or advantage must at least be mentioned in the specification.²⁵ Accordingly, a prima facie obvious product could not be rendered nonobvious by resorting to product advantages not disclosed in the specification.²⁶ Similarly, it was held that the patentee could not support the patent by the fact that the actual device, as made and sold, was superior in ways neither related to nor shown on the record to follow from the patent claims.²⁷ Discovery of the source of the problem is part of the "subject matter as a whole" inquiry.²⁸

²² *W.L. Gore & Assocs. v. Garlock, Inc.*, 721 F.2d 1540, 1547-48, 220 U.S.P.Q. 303, 308-09 (C.A.F.C. 1983), *cert. denied*, 469 U.S. 851 (1984); *Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 721 F.2d 1563, 1567, 220 U.S.P.Q. 97, 101 (C.A.F.C. 1983).

²³ *Kirkland v. Western Fiberglass, Inc.*, 16 U.S.P.Q.2d 1892, 1893 (C.A.F.C. 1990).

²⁴ *In re Antonie*, 559 F.2d 618, 619, 195 U.S.P.Q. 6, 8 (C.C.P.A. 1977).

²⁵ *Graham v. John Deere Co.*, 383 U.S. 1, 23, 148 U.S.P.Q. 459, 469 (1966); *United States v. Adams*, 383 U.S. 39, 48-49, 148 U.S.P.Q. 479, 482 (1966).

²⁶ *General Tire & Rubber Co. v. Jefferson Chem. Co.*, 497 F.2d 1283, 1289, 182 U.S.P.Q. 70, 74 (2d Cir. 1974), *rev'g* 363 F. Supp. 871, 183 U.S.P.Q. 513 (S.D.N.Y. 1973), *cert. denied*, 419 U.S. 968 (1974).

²⁷ *Julie Labs., Inc. v. Guideline Instruments, Inc.*, 501 F.2d 1131, 1135, 185 U.S.P.Q. 1, 4 (2d Cir. 1974).

²⁸ *In re Kaslow*, 707 F.2d 1366, 1373, 217 U.S.P.Q. 1089, 1094 (C.A.F.C. 1983).

Patentability may not be based on an undisclosed "inherent" feature that could be discovered only by building the assembly described in the patent specification and testing it.²⁹ To be entitled to consideration, the existence of a synergistic effect apparently must be mentioned in the patent application. Putting such forward for the first time when validity of the patent is being tested in court will not suffice.³⁰ Where the inventor asserts nonobviousness based upon an unusual or surprising result, such result must at least be mentioned in the specification.³¹ At least one court has gone so far as to strongly suggest that the advantage or unexpected result upon which unobviousness is based must not only be adverted to in the specification but must also be mentioned in the claims,³² although another court has suggested that it will suffice if the advantage upon which patentability is predicated is merely brought to the attention of the examiner during the course of prosecuting the application before the Patent & Trademark Office.³³

To illustrate how the scope and content of the prior art are to be determined and any differences between such prior art and the claims in issue are to be ascertained, it is instructive to consider the technology involved in the first Supreme Court interpretation of 35 U.S.C. § 103,³⁴ which is considered definitive by the Federal Circuit,³⁵ by a majority of other federal courts,³⁶ and by the Patent & Trademark Office.³⁷

²⁹ *Maclaren v. B-I-W Group*, 535 F.2d 1367, 1374, 190 U.S.P.Q. 513, 518 (2d Cir. 1976).

³⁰ *Universal Elec. Co. v. A.O. Smith Corp.*, 643 F.2d 1240, 1248, 209 U.S.P.Q. 1077, 1083 (6th Cir. 1981).

³¹ *C. Van der Lely N.V. v. F. Ili Maschio S.n.c.*, 222 U.S.P.Q. 399, 423 (S.D. Ohio 1984).

³² *Koppers Co. v. S & S Corrugated Paper Mach. Co.*, 517 F.2d 1182, 1188, 185 U.S.P.Q. 705, 710 (2d Cir. 1975).

³³ *Weather Eng'g Corp. of Am. v. United States*, 204 U.S.P.Q. 41, 44 (Ct. Cl. 1979).

³⁴ *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966).

³⁵ *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1547, 220 U.S.P.Q. 193, 197 (C.C.P.A. 1983).

³⁶ *Aluminum Co. of Am. v. Amerola Prods. Corp.*, 552 F.2d 1020, 1026, 194 U.S.P.Q. 1, 6 (3d Cir. 1977).

³⁷ Notice, "Examination of Claims for Patentability Under 35 U.S.C. § 103" 949 O.G. 3 (1976); M.P.E.P. 706.

The case involved an agricultural implement, specifically a plow. Material to the issue of obviousness were three components of the plow: (1) the shank with an attached chisel; (2) the hinge plate; (3) the plow frame. See Figure 9-1. The prior art taught the use of these components, but arranged such that the hinge plate was below the shank, the shank being disposed between the hinge plate and the plow frame. The claims in issue called for the disposition of the hinge plate between the shank and plow frame, the shank being disposed below the hinge plate. Although plows embodying the claimed combination of components had improved flexing qualities over the aforementioned prior art, the Supreme Court held the claims obvious and invalid, perhaps because the greater flexing qualities of the claimed invention had not been urged in the course of the prosecution of the application before the Patent Office.³⁸

The foregoing conclusion is reinforced by language in another Supreme Court opinion that was handed down on the same day, in which claims to a battery were held valid and infringed. In that case, the court decided that what in effect amounted to the substitution of magnesium for zinc and cuprous chloride for silver chloride, as the battery's electrodes, satisfied the nonobvious standard because such substitution resulted in a battery having a number of operating advantages which could not be predicted by resort to the prior art and because such advantages had been recognized and argued at the patent application stage and thus were said not to be "the afterthought of an astute patent trial lawyer."³⁹

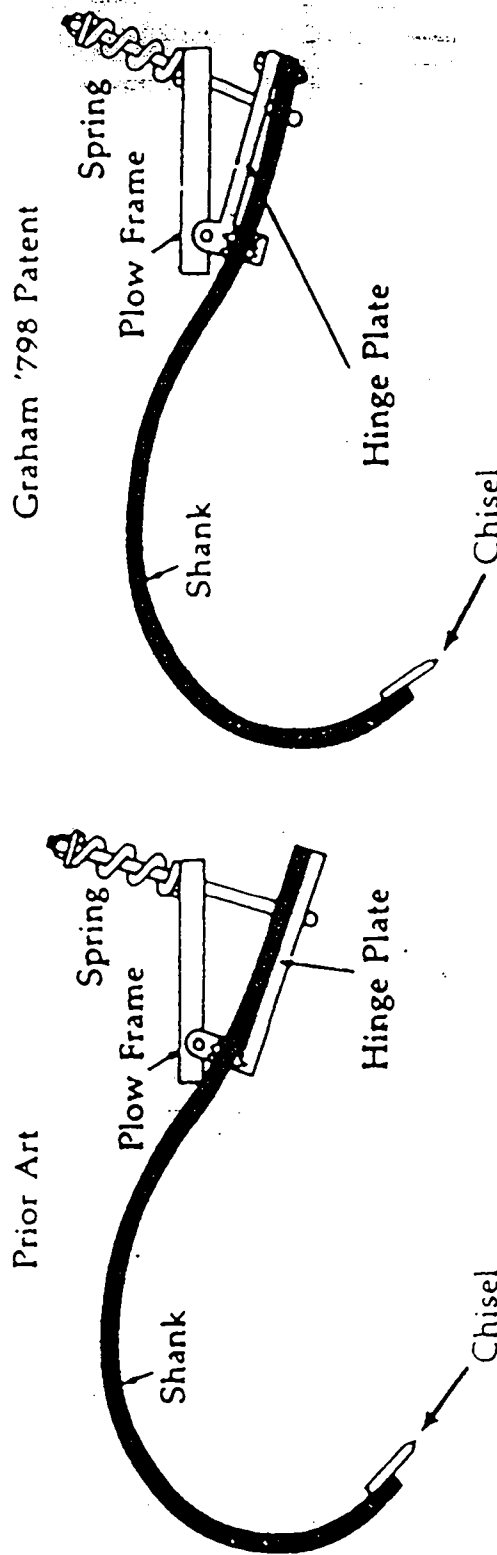
³⁸ *Graham v. John Deere Co.*, 383 U.S. 1, 23, 148 U.S.P.Q. 459, 469 (1966).

³⁹ *United States v. Adams*, 383 U.S. 39, 49, 148 U.S.P.Q. 479, 482 (1966).

Figure 9-1

Graham v. John Deere Co.

Side-by-Side Comparison of Elements



Components
Hinge Plate
Plow Frame
Spring
Shank
Chisel

[a] Patent Application Prosecution before the Patent & Trademark Office

[i] Prima Facie Obviousness and its Rebuttal

That an applicant is prima facie entitled to a patent is established by the prefatory language of 35 U.S.C. § 102. The Federal Circuit, and its predecessor court, the Court of Customs & Patent Appeals, have reconciled the prefatory language of 35 U.S.C. § 102, "A person shall be entitled to a patent unless—" with the requirement of nonobviousness expressed in 35 U.S.C. § 103 by holding that an applicant for a patent has no obligation to submit evidence of nonobviousness unless and until the Patent & Trademark Office establishes a prima facie case of obviousness.

Evaluation of obviousness/nonobviousness in the examination process may be viewed as a two-step process:⁸⁹

Step One—Whether a prima facie case of obviousness has been established; and, if so,

Step Two —Whether affidavits or declarations presented are sufficient to overcome the prima facie case of obviousness.

Thus, the principal significance of the prima facie case with respect to obviousness is that, unless the examiner establishes a prima facie case, the applicant is not obliged to proffer any evidence of nonobviousness.

The examiner bears the initial burden of presenting a prima facie case of unpatentability, based on review of the prior art or any other ground. If that burden is met, the burden of coming forward with evidence or argument shifts to the applicant.^{89.1} After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence, with due consideration to the persuasiveness of the argument.^{89.2}

⁸⁹ In re Surrey, 319 F.2d 233, 235, 138 U.S.P.Q. 67, 69 (C.C.P.A. 1963).

^{89.1} In re Piasecki, 745 F.2d 1468, 1472, 223 U.S.P.Q. 785, 788 (C.A.F.C. 1984).

^{89.2} In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (C.A.F.C. 1992).

NONOBVIOUSNESS

§ 9.03[3][a][i]

When is a *prima facie* case of obviousness established? According to 37 C.F.R. § 1.56(a):^{89.3}

A *prima facie* case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

According to the *Manual of Patent Examining Procedure*, to establish a *prima facie* case of obviousness, three basic criteria must be met:^{89.4}

First, there must be some suggestion or motivation, either in the prior art references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.^{89.5}

Second, there must be a reasonable expectation of success.^{89.6}

Third, the prior art reference (or references when combined) must teach or suggest all the claimed limitations.^{89.7}

A *prima facie* case of obviousness requires supporting objective evidence to be sustained.^{89.8} An examiner must substantiate his or her "suspicions" or "hunches" on the basis of facts drawn from paper prior art.^{89.9} A *prima facie* case of unpatentability is not established merely by speculation that claim limitations are "probably satisfied" by the prior art.^{89.10}

Evidence in rebuttal of prima facie obviousness. Once a *prima facie*

1992).

^{89.3} 57 Fed. Reg. 2021 (Jan. 17, 1992, March 16, 1992).

^{89.4} M.P.E.P. 2142 (Rev. 3, July 1997).

^{89.5} In re Jones, 958 F.2d 347, 350, 21 U.S.P.Q.2d 1941 (C.A.F.C. 1992); In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1599 (C.A.F.C. 1988).

^{89.6} In re Merck & Co., 800 F.2d 1091, 1096, 231 U.S.P.Q. 375, 378 (C.A.F.C. 1986).

^{89.7} In re Royka, 490 F.2d 981, 984, 180 U.S.P.Q. 580, 582 (C.C.P.A. 1974); In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

^{89.8} Ex parte Chopra, 229 U.S.P.Q. 230 (P.T.O. Bd. Pat. App. & Int. 1985).

^{89.9} In re Lunsford, 357 F.2d 385, 391, 148 U.S.P.Q. 721, 725 (C.C.P.A. 1966).

^{89.10} In re Rijckaert, 9 F.3d 1531, 1533, 28 U.S.P.Q.2d 1955, 1957 (C.A.F.C. 1993).

(Release #7, 8/99)

case of obviousness is established, it is incumbent upon the applicant to go forward with objective evidence of nonobviousness.^{89.11} Rebuttal evidence may include evidence that the claimed invention yields unexpectedly improved properties,^{89.12} or properties not present in the prior art,^{89.13} or evidence of secondary considerations.^{89.14}

A showing of unexpected results must be based on evidence, not merely argument or speculation.^{89.15} Such evidence may be present in the specification,^{89.16} or be presented by way of affidavit or declaration.^{89.17} To overcome a prima facie case of obviousness on the basis of unexpected results, the applicant must establish not only that the differences in results achieved in fact are unexpected, but also that the differences are of practical significance.^{89.18} The claimed invention must be compared with the closest prior art.^{89.19}

Rebuttal is merely "a showing of facts supporting the opposite conclusion."^{89.20}

Evaluation of rebuttal evidence. The evidence of obviousness upon which a prima facie conclusion of obviousness is based must be weighed against the rebuttal evidence of nonobviousness.^{89.21} After a prima facie case of obviousness has been made and rebuttal evidence submitted, all the evidence must be considered anew.^{89.22} Facts established by rebuttal evidence must be

^{89.11} *In re Ball Corp.*, 925 F.2d 1480, 18 U.S.P.Q.2d 1491, 1492 (C.A.F.C. 1991); *In re Keller*, 642 F.2d 413, 425, 208 U.S.P.Q. 871, 882 (C.C.P.A. 1981).

^{89.12} *In re Murch*, 464 F.2d 1051, 1054, 175 U.S.P.Q. 89, 91 (C.C.P.A. 1972).

^{89.13} *In re Dillon*, 919 F.2d 688, 692-93, 16 U.S.P.Q.2d 1897, 1901 (C.A.F.C. 1990) (in banc), *cert. denied*, 500 U.S. 904 (1991).

^{89.14} *In re Piasecki*, 745 F.2d 1468, 1473, 223 U.S.P.Q. 785, 788 (C.A.F.C. 1984).

^{89.15} *In re Mayne*, 104 F.3d 1339, 1343-44, 41 U.S.P.Q.2d 1451, 1455 (C.A.F.C. 1997); *In re Huang*, 100 F.3d 135, 139-40, 40 U.S.P.Q.2d 1685, 1689 (C.A.F.C. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 U.S.P.Q. 191, 196 (C.A.F.C. 1984).

^{89.16} *In re Soni*, 54 F.3d 746, 750, 34 U.S.P.Q.2d 1684, 1687 (C.A.F.C. 1995).

^{89.17} *In re Soni*, 54 F.3d 746, 750, 34 U.S.P.Q.2d 1684, 1687 (C.A.F.C. 1995); *In re Piasecki*, 745 F.2d 1468, 1474, 223 U.S.P.Q. 788, 789-90 (C.A.F.C. 1984).

^{89.18} *Ex parte C*, 27 U.S.P.Q.2d 1492, 1497 (P.T.O. Bd. Pat. App. & Int. 1993).

^{89.19} *In re Merchant*, 575 F.2d 865, 869, 197 U.S.P.Q. 785, 788 (C.C.P.A. 1978).

^{89.20} *In re Heldt*, 433 F.2d 808, 811, 167 U.S.P.Q. 676, 678 (C.C.P.A. 1970).

^{89.21} *Ex parte Anderson*, 21 U.S.P.Q.2d 1241, 1258 (P.T.O. Bd. Pat. App. & Int. 1991).

^{89.22} *In re Eli Lilly & Co.*, 902 F.2d 943, 14 U.S.P.Q.2d 1741, 1743 (C.A.F.C. 1991).

that patentability determinations based on that as a test would not only be contrary to the statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of "research."

An invention is merely "obvious to try" where the prior art gives no indication of which parameters are critical or no direction as to which of many possible choices is likely to be successful.⁷⁰ It appears to be unsettled whether to constitute obviousness the prior art must merely suggest which parameters are critical⁷¹ or in addition must indicate an expectation of success.⁷²

The mere fact that a prior art structure *might possibly* function as claimed or be modified in a way that would render the claims obvious does not render such claims obvious within the meaning of 35 U.S.C. § 103.⁷³ "Ought to be tried" is not the standard by which obviousness is determined.⁷⁴ ~~The governing standard is not whether a particular approach leading to an invention would be "obvious to try," but whether such an experiment would have been expected to succeed.~~⁷⁵

-Extrapolation
Reasoning-

Whether prior art renders an invention obvious depends upon the specificity of its teachings.⁷⁶ Generally speaking, there is nothing unobvious in choosing "some" among "many" indiscriminately.⁷⁷ This is particularly applicable where the class of possible alternatives is small.⁷⁸

⁷⁰ Merck & Co. v. Biocraft Labs., Inc., 874 F.2d 804, 10 U.S.P.Q.2d 1843, 1845 (C.A.F.C. 1989); In re O'Farrell, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1681 (C.A.F.C. 1988).

⁷¹ In re O'Farrell, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1681 (C.A.F.C. 1988).

⁷² In re Dow Chem. Co., 837 F.2d 469, 5 U.S.P.Q.2d 1529, 1532 (C.A.F.C. 1988).

⁷³ Ex parte Seiler, 215 U.S.P.Q. 742 (P.O. Bd. App. 1982).

⁷⁴ McDermott v. Omid Int'l, Inc., 723 F. Supp. 1221, 13 U.S.P.Q.2d 1141, 1146 (S.D. Ohio 1988).

⁷⁵ In re Merck & Co., 800 F.2d 1091, 1097, 231 U.S.P.Q. 375, 379-80 (C.A.F.C. 1986).

⁷⁶ In re O'Farrell, 853 F.2d 844, 7 U.S.P.Q.2d 1673, 1681 (C.A.F.C. 1988).

⁷⁷ In re Lemin, 322 F.2d 839, 841, 141 U.S.P.Q. 814, 815 (C.C.P.A. 1964). See also In re Rosicky, 276 F.2d 656, 659, 125 U.S.P.Q. 341, 344 (C.C.P.A. 1960).

⁷⁸ See In re Morin, 405 F.2d 1313, 160 U.S.P.Q. 548 (C.C.P.A. 1969) (thermo-setting vs. thermoplastic).

[5] Superiority, Criticality, and Optimization

Superiority and unobviousness are not synonymous.⁷⁹ Superiority, however, can be evidence of unobviousness.⁸⁰ The mere fact that results attained are unexpectedly good is not controlling.⁸¹ A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use.^{81.1} A refusal to consider superior results is no more warranted by 35 U.S.C. § 103 than a total preoccupation with them.⁸² Making something stronger than the prior art is not the type of innovation for which the patent monopoly is granted.⁸³ Making a known product adjustable or merely adding a plurality of units to it is not patentable invention.⁸⁴ Improvement resulting from changes in size, proportion, or degree of an element contained in the prior art, no matter how desirable or useful, does not constitute patentable invention.⁸⁵ A mere change in material cannot give rise to a patentable invention if the properties of the materials are already known and the result obtained was the one expected.⁸⁶ More than a mere change of the form or rearrangement of parts is necessary for patentability.⁸⁷ Even if better results are achieved, invention does not necessarily occur when the better results arise

⁷⁹ *Brunswick Corp. v. Champion Spark Plug Co.*, 689 F.2d 740, 750, 216 U.S.P.Q. 1, 9 (7th Cir. 1982); *Sargent-Welch Scientific Co. v. J/B Indus.*, 496 F.Supp. 972, 978, 210 U.S.P.Q. 948, 954 (N.D. Ill. 1980).

⁸⁰ *In re Hoffmann*, 556 F.2d 539, 541, 194 U.S.P.Q. 126, 128 (C.C.P.A. 1977); *Harig Prods., Inc. v. K.O. Lee Co.*, 195 U.S.P.Q. 292, 295 (N.D. Ill. 1976).

⁸¹ *In re Szumski*, 302 F.2d 753, 756, 133 U.S.P.Q. 551, 553 (C.C.P.A. 1962).

^{81.1} *In re Gurley*, 27 F.3d 551, 553, 31 U.S.P.Q.2d 1130, 1132 (C.A.F.C. 1994).

⁸² *In re Lindell*, 385 F.2d 453, 455, 155 U.S.P.Q. 521, 523 (C.C.P.A. 1967).

⁸³ *Brunswick Corp. v. Champion Spark Plug Co.*, 689 F.2d 740, 750, 216 U.S.P.Q. 1, 9 (7th Cir. 1982); *St. Regis Paper Co. v. Bemis Co.*, 549 F.2d 833, 839, 193 U.S.P.Q. 8, 11-12 (7th Cir.), *cert. denied*, 434 U.S. 833 (1977).

⁸⁴ *Trans-World Display Corp. v. Mechtronics Corp.*, 437 F. Supp. 692, 698, 195 U.S.P.Q. 588, 593 (S.D.N.Y. 1977).

⁸⁵ *Ward Mach. Co. v. Wm. C. Staley Mach. Corp.*, 192 U.S.P.Q. 505, 512 (D Md. 1975).

⁸⁶ *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 U.S.P.Q. 297 (1945); *Hotchkiss v. Greenwood*, 52 U.S. (11 How.) 248 (1850); *Brunswick Corp. v. Champion Spark Plug Co.*, 689 F.2d 740, 750, 216 U.S.P.Q. 1, 9 (7th Cir. 1982).

⁸⁷ *Span-Deck, Inc. v. Fab-Con, Inc.*, 677 F.2d 1237, 1244, 215 U.S.P.Q. 835, 841 (8th Cir. 1982).

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significantly different from these elements when they are combined in other than the claimed proportions.⁹⁹

Not infrequently the prior art will teach that a certain general result can be attained by doing something in a certain general way. Someone then comes along asserting that by carrying out such prior art process employing the specific values of the operative parameters being claimed, results demonstrably superior to those indicated by the prior art will be attained. Such improved results standing alone are insufficient to establish unobviousness.¹⁰⁰

The prior art having taught generally the functional relationship described it does not rise to the dignity of invention to teach optimization of the function by making quantitative adjustments to achieve the most desirable or effective result, there being involved in such process no discovery but only the exercise of prudence and skill.

Thus, the discovery of the optimum dimensions in a method of separating cheese slices was deemed obvious.¹⁰¹

The fact that the optimum conditions were arrived at by routine experimentation does not in and of itself negate unobviousness.¹⁰² An exception to the rule that the discovery of the optimum value of a variable in a known process is normally obvious¹⁰³ occurs when the parameter optimized was not recognized to be a result-effective variable.¹⁰⁴ Another exception occurs where the results were unexpectedly good.¹⁰⁵

⁹⁹ *In re Waymouth*, 499 F.2d 1273, 182 U.S.P.Q. 290 (C.C.P.A. 1974); *In re Russell*, 439 F.2d 1228, 169 U.S.P.Q. 426 (C.C.P.A. 1971); *Becket v. Coe*, 98 F.2d 332, 38 U.S.P.Q. 26 (D.C. Cir. 1938).

¹⁰⁰ *A.R., Inc. v. Electro-Voice, Inc.*, 311 F.2d 508, 512, 136 U.S.P.Q. 46, 50 (7th Cir. 1962).

¹⁰¹ *L.D. Schreiber Cheese Co. v. Clearfield Cheese Co.*, 540 F. Supp. 1128, 214 U.S.P.Q. 285 (W.D. Pa. 1982).

¹⁰² *In re Fay*, 347 F.2d 597, 602, 146 U.S.P.Q. 47, 51 (C.C.P.A. 1965).

¹⁰³ *In re Aller*, 220 F.2d 454, 456, 105 U.S.P.Q. 233, 235 (C.C.P.A. 1955). Compare *In re Yates*, 663 F.2d 1054, 1057, 211 U.S.P.Q. 1149, 1151 (7th Cir. 1981).

¹⁰⁴ *In re Antonie*, 559 F.2d 618, 620, 195 U.S.P.Q. 6, 8 (C.C.P.A. 1977).

¹⁰⁵ *In re Waymouth*, 499 F.2d 1273, 1276, 182 U.S.P.Q. 290, 293 (C.C.P.A. 1974).

[6] "Teaching Away From"

That the prior art teaches away from what is claimed militates against a finding of obviousness.¹⁰⁶ The Federal Circuit has indicated that one important indicium of nonobviousness is "teaching away from" the claimed invention by the prior art.¹⁰⁷ Although prior art that teaches away is a significant factor to be considered in determining unobviousness, the nature of the teaching is highly relevant, and must be weighed in substance.^{107.1} Doing what the prior art references try to avoid is the very antithesis of obviousness.¹⁰⁸ Prior art that suggests the method or means claimed would produce unacceptable results is the very antithesis of obviousness.¹⁰⁹ Proceeding contrary to the accepted wisdom is strong evidence of unobviousness.¹¹⁰

"Teaching away from" is not dispositive, however, particularly where there is no evidence that the inventor was aware of any of the purported obstacles standing in the way of his invention.¹¹¹ Where the prior art taught the use of a base to effect the desired chemical reaction, the substitution of an acid therefor, was characterized as the epitome of unobviousness.¹¹² However, a prior art warning to "be careful" was not deemed equivalent to uniform prior art teaching that any investigation would be purposeless.¹¹³

The skepticism of an alleged infringer as to the success of a patented device, which proves to be successful, has been taken as an indication of nonobviousness.¹¹⁴ Closely related to—and even

¹⁰⁶ *W.L. Gore & Assocs. v. Garlock, Inc.*, 721 F.2d 1540, 1551-53, 220 U.S.P.Q. 303, 311-13 (C.A.F.C. 1983), *cert. denied*, 469 U.S. 851 (1984).

¹⁰⁷ *In re Braat*, 918 F.2d 185, 16 U.S.P.Q.2d 1812, 1814 (C.A.F.C. 1990); *In re Dow Chem. Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1532 (C.A.F.C. 1988).

^{107.1} *In re Gurley*, 27 F.3d 551, 553, 31 U.S.P.Q.2d 1130, 1132 (C.A.F.C. 1994).

¹⁰⁸ *In re Buehler*, 515 F.2d 1134, 1141, 185 U.S.P.Q. 781, 787 (C.C.P.A. 1975).

¹⁰⁹ *In re Rosenberger*, 386 F.2d 1015, 1018, 156 U.S.P.Q. 24, 26 (C.C.P.A. 1967).

¹¹⁰ *In re Hedges*, 783 F.2d 1038, 228 U.S.P.Q. 685, 687 (C.A.F.C. 1986).

¹¹¹ *Brunswick Corp. v. Champion Spark Plug Co.*, 689 F.2d 740, 750, 216 U.S.P.Q. 1, 8 (7th Cir. 1982).

¹¹² *In re Hughes*, 550 F.2d 1273, 1277, 193 U.S.P.Q. 141 (C.C.P.A. 1977).

¹¹³ *Airtex Corp. v. Shelley Radiant Ceiling Co.*, 536 F.2d 145, 153, 190 U.S.P.Q. 6, 13 (7th Cir. 1976).

¹¹⁴ *Kaiser Indus. Corp. v. Jones & Laughlin Steel Corp.*, 181 U.S.P.Q. 214



US006355827B1

(12) **United States Patent**
Komoschinski et al.

(10) Patent No.: **US 6,355,827 B1**
(45) Date of Patent: **Mar. 12, 2002**

(54) **PROCESS FOR PREPARING 2-CYANOINDAN-1-ONES**

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(73) Assignee: **Bayer Aktiengesellschaft, Leverkusen (DE)**

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/485,957**

(22) PCT Filed: **Aug. 13, 1998**

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(51) Int. Cl.⁷ **C07C 253/14**

(52) U.S. Cl. **558/342**

(58) Field of Search **558/342**

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Journal of the American Chemical Society, vol. 67, Jul.-Dec. 1945, pp. 1745-1754 (see page 1751) Johnson et al, A Plan for distinguishing between Some Five- and Six-membered Ring Ketones.

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(74) *Attorney, Agent, or Firm*—Joseph C. Gil; Didcrico van Eyl

(57) **ABSTRACT**

In a particularly advantageous process for producing 2-cyanoindan-1-ones from 2-halogenated indan-1-ones by reaction with a cyanide salt, the cyanide salt is dissolved in a dipolar aprotic solvent or in a water-miscible ether and 2-halogenated indan-1-one is metered into this solution.

10 Claims, No Drawings

PROCESS FOR PREPARING 2-CYANOINDAN-1-ONES

This application is a 371 of PCT/EP/98/05142 filed Aug. 13, 1998.

BACKGROUND OF THE INVENTION

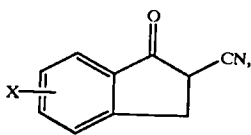
The present invention relates to an improved process for preparing 2-cyanoindan-1-ones from corresponding 2-halogenoindan-1-ones by reaction with cyanide salts.

2-cyanoindan-1-ones are precursors for active compounds as described, for example in WO 96/20151 and WO 95/29171.

It is already known that 2-cyanoindan-1-one and 2-cyano-5-methoxyindan-1-one can be obtained by reacting the corresponding 2-bromoindan-1-ones with the aid of cyanide salts. Thus, J. Am. Chem. Soc. 66, 220 (1944) and 67, 1751 (1945) describe the preparation of these cyanoindan-1-ones by admixing 2-bromoindan-1-one and 2-bromo-5-methoxyindan-1-one, respectively, sodium cyanide or potassium cyanide, ethanol and water, and boiling this mixture at reflux. The yields obtained here are at best 52 and 73%, respectively. Moreover, a 10-fold molar excess of cyanide is employed, involving considerable work-hygienic expense during work-up.

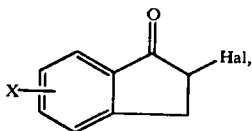
DESCRIPTION OF THE INVENTION

We have now found a process for preparing 2-cyanoindan-1-ones of the formula



in which

X represents hydrogen, halogen, methyl, trifluoromethyl or methoxy,
from 2-halogenoindan-1-ones of the formula



in which

X is as defined under formula (I) and

Hal represents chlorine or bromine,
by reaction with a cyanide salt, characterized in that the cyanide salt is initially charged dissolved in a dipolar aprotic solvent or in a water-miscible ether and the 2-halogenoindan-1-one of the formula (II) is metered into this solution.

Halogen is preferably fluorine, chlorine or bromine.

In the formulae (I) and (II), X preferably represents chlorine, in particular chlorine in the 5 or 6 position. Hal in formula (II) preferably represents chlorine.

Suitable cyanide salts are, for example, alkali metal cyanides and tetraalkylammonium cyanides. Examples

include sodium cyanide, potassium cyanide, lithium cyanide, rubidium cyanide, tetrabutylammonium cyanide and tetrabutylammonium cyanide. The cyanide salt in question can be employed, for example, in an amount of from 1.5 to 6 mol, based on 1 mole of the compound of the formula (II). This amount is preferably from 1.6 to 5 mol, in particular from 1.8 to 3 mol.

Suitable dipolar aprotic solvents are, for example, N-methylpyrrolidone, dimethylformamide, dimethylacetamide, dimethyl sulfoxide, hexamethylphosphoric triamide, sulfolane and acetonitrile, and suitable water-miscible ethers are, for example, tetrahydrofuran and diglycol dimethyl ether. Preference is given to dimethylformamide, dimethylacetamide, N-methylpyrrolidone and dimethyl sulfoxide.

Based on 1 mole of cyanide salt, for example from 200 to 2500 ml of dipolar aprotic solvent or water-miscible ether can be employed. This amount is preferably from 300 to 1500 ml.

The 2-halogenoindan-1-one of the formula (II) is preferably metered in such that it is added in the dissolved form and a little at a time to the cyanide salt solution which has been initially charged. Suitable solvents for the 2-halogenoindan-1-one are likewise dipolar aprotic solvents and water-miscible ethers, as described in more detail above. Preference is given to using the same solvent for dissolving the cyanide salt and for preparing the solution of the 2-halogenoindan-1-one.

Preference is furthermore given to employing the 2-halogenoindan-1-one as a 10 to 30% by weight strength, in particular as a 15 to 25% by weight strength, solution.

The cyanide salt solution and/or the 2-halogenoindan-1-one solution may, if appropriate, contain water. For example, based on the solvent, up to 30% by weight of water may be present. This amount is preferably from 2 to 10% by weight.

The process according to the invention can, if appropriate, be carried out with addition of acids to control the pH. At a high pH, there is the risk that, in addition to the exchange of halogen for cyano, an elimination of hydrogen halide takes place. Accordingly, it is advantageous to control the pH, if appropriate, by addition of a strong acid, and to keep it, for example, in the range from 4 to 11, preferably from 5 to 10. Excessive acidification should be avoided, since this leads to the formation of hydrogen cyanide from the cyanide salt.

The acid can be added to the reaction mixture in any amount as such, but also, for example, together with the 2-halogenoindan-1-one or its solution.

Suitable acids are, in particular, aqueous acids of moderate to high strength, such as aqueous hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, formic acid and acetic acid.

The process according to the invention can be carried out, for example, at temperatures in the range from 10 to 70° C. Preference is given to temperatures in the range from 20 to 60° C.

The reaction mixture that is present after the process according to the invention has been carried out can be worked up, for example, in that it is cooled, any solvents present are stripped off under reduced pressure, the crystal slurry that remains is mixed with water and acidified slightly and the solid which is then present is filtered off and washed with water. If appropriate, the resulting 2-cyanoindan-1-one of the formula (I) can be purified further, for example by recrystallization from an organic solvent.

Using the process according to the invention, it is possible to obtain 2-cyanoindan-1-ones of the formula (I) in surprisingly high yields of 95% and more, employing considerably lower amounts of cyanide than in the prior-art process.

The invention is further described in the following illustrative examples in which all parts and percentages are by weight unless otherwise indicated.

EXAMPLES

Example 1

10.4 g of sodium cyanide were dissolved in a mixture of 100 ml of dimethylformamide and 6 ml of water and initially charged. This solution was heated with stirring to 50° C., and 20.4 g of 2,5-dichloroindan-1-one, dissolved in 100 ml of dimethylformamide, were then added dropwise over a period of 60 minutes. After the addition had ended, stirring was continued at 50° C. for 1 hour. The mixture was then allowed to cool to room temperature and the solvent was stripped off using a rotary evaporator. The resulting crystal slurry was mixed with 200 ml of water and acidified to pH 4.5 using 10% by weight strength aqueous hydrochloric acid. The precipitated solid was filtered off with suction, washed with water, recrystallized from toluene and dried in a vacuum drying cabinet. This gave 18.5 g of 2-cyano-5-chloroindan-1-one (yield: 97% of theory).

Example 2

Example 1 was repeated using 2,6-dichloroindan-1-one instead of 2,5-dichloroindan-1-one. This gave 2-cyano-6-chloroindan-1-one in a yield of 95.5% of theory.

Example 3

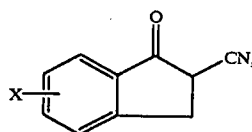
(For Comparison)

A solution of 4.2 g of 2,5-dichloroindan-1-one in 140 ml of methanol was admixed first with 9.6 g of sodium cyanide and then with sufficient water to give a homogeneous solution. This mixture was boiled under reflux on a water bath for 45 minutes and then cooled to room temperature. After dilution with more water, the mixture was extracted twice with diethyl ether. The aqueous solution that remained was acidified with cold hydrochloric acid. The crude 2-cyano-5-chloroindan-1-one was separated off and taken up in chloroform. This solution was then clarified using Norit and subsequently extracted with small portions of a 5% by weight strength aqueous sodium hydroxide solution until no more precipitation was observed on acidification of a sample. Acidification of the combined aqueous phases gave 2.85 g of product which, after recrystallization from toluene, afforded 2.7 g of 2-cyano-5-chloroindan-1-one (yield: 70% of theory).

Although the present invention has been described in detail with reference to certain preferred versions thereof, other variations are possible. Therefore, the spirit and scope of the appended claims should not be limited to the description of the versions contained therein.

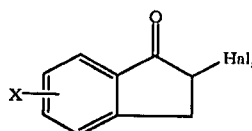
What is claimed is:

1. Process for preparing a 2-cyaniondan-1-one of the formula (I)



wherein X represents hydrogen, halogen, methyl, trifluoromethyl or methoxy, comprising reacting

A) a 2-halogenoindan-1-one of the formula (II)



wherein

X is as defined under formula (I) and Hal represents chlorine or bromine, with

B) a cyanide salt, wherein the cyanide salt is initially charged and dissolved in a dipolar aprotic solvent or in a water-miscible ether and the 2-halogenoindan-1-one of the formula (II) is metered into this solution.

2. Process according to claim 1, wherein in the formulae X and Hal each represent chlorine.

3. Process according to claim 1, wherein from 1.6 to 6 mol of cyanide salt are employed per mole of a compound of the formula (II).

4. Process according to claim 1, wherein the dipolar aprotic solvent or water-miscible ether used is selected from the group consisting of N-methylpyrrolidone, dimethylformamide, dimethylacetamide, dimethyl sulfoxide, hexamethylphosphoric triamide, sulfolane, acetonitrile, tetrahydrofuran and diglycol dimethyl ether.

5. Process according to claim 1, wherein the 2-halogenoindan-1-one of the formula (II) is added in the dissolved form and a little at a time to the cyanide salt solution which has been initially charged.

6. Process according to claim 1, wherein the 2-halogenoindan-1-one of the formula (II) is employed as a 10 to 30% by weight strength solution.

7. Process according to claim 1, wherein based on the solvent, up to 30% by weight of water are present.

8. Process according to claim 1, wherein the pH is kept in the range from 4 to 11 by addition of a strong acid.

9. Process according to claim 1, wherein the process is carried out at from 10 to 70° C.

10. Process according to claim 1, wherein the reaction mixture which is present after the reaction is worked up in that it is cooled, and any solvents present are stripped off under reduced pressure, and the crystal slurry that remains is mixed with water and acidified slightly and the solid is filtered off and washed with water.

* * * * *



US006201135B1

750

(12) **United States Patent**
Maywald et al.

(10) Patent No.: **US 6,201,135 B1**
(45) Date of Patent: **Mar. 13, 2001**

(54) **METHOD FOR SEPARATING
CONTAMINANTS FROM 3-(2'-ACETOXY-
ETHYL-DIHYDRO-2(3H)-FURANONE**

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/530,132**

(22) PCT Filed: **Dec. 2, 1998**

(86) PCT No.: **PCT/EP98/07832**

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§ 102(e) Date: **Apr. 27, 2000**

(87) PCT Pub. No.: **WO99/29680**

PCT Pub. Date: **Jun. 17, 1999**

(30) **Foreign Application Priority Data**

Dec. 8, 1997 (DE) 197 54 302

(51) Int. Cl.⁷ **C07D 307/58**

(52) U.S. Cl. **549/323**

(58) Field of Search **549/323**

(56) **References Cited**

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Malonester Mit Athylenoxyd Entstehenden Nebenprodukte"
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Primary Examiner—Bernard Dentz

(74) *Attorney, Agent, or Firm*—Keil & Weinkauff

(57)

ABSTRACT

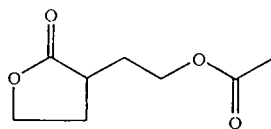
A process for removing impurities from 3-(2'-acetoxyethyl)-
dihydro-2(3H)-furanone (I), which comprises initially pre-
paring the 3-(2'-acetoxyethyl)-dihydro-2(3H)-furanone con-
taining the undesirable impurities in a manner known per se
by acetylating 3-(2'-hydroxyethyl)-dihydro-2(3H)-
furanone, subsequently treating it with strong mineral acids
and finally removing the decomposition products of the
undesirable impurities from I.

6 Claims, No Drawings

1

METHOD FOR SEPARATING CONTAMINANTS FROM 3-(2'-ACETOXY- ETHYL-DIHYDRO-2(3H)-FURANONE

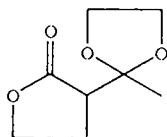
The present invention relates to a process for removing undesirable impurities from 3-(2'-acetoxyethyl)dihydro-2(3H)-furanone of the formula I



3-(2'-acetoxyethyl)dihydro-2(3H)-furanone is a starting material for preparing methyl tetrahydropyran-4-carboxylate, which for its part is an intermediate in the preparation of crop protection agents.

3-(2'-Acetoxyethyl)dihydro-2(3H)-furanone is prepared, for example, by processes that are known per se and described, for example, in U.S. Pat. No. 5,350,863, starting from methyl acetoacetate and ethylene oxide. Another process variant by which 3-(2'-acetoxyethyl)dihydro-2(3H)-furanone is obtainable is described in Dokl. Akad. Nauk SSSR 27 (1940), 956-959 and U.S. Pat. No. 5,283,326.

In both variants, the desired 3-(2'-acetoxyethyl)dihydro-2(3H)-furanone is formed as a mixture with a number of undesirable byproducts, in particular the isomeric dihydro-3-(2-methyl-1,3-dioxolan-2-yl)-2(3H)-furanone II



If I contaminated in this manner is reacted in a continuous gas phase reaction with methanol in the presence of acidic catalysts to give methyl tetrahydropyran-4-carboxylate, considerably lower yields and shorter catalyst onstream times are obtained than when a product of high purity without the byproducts is used. This is probably due to the fact that most byproducts contain sensitive acetal groups which decompose on the surface of the catalyst to oligomeric and polymeric products.

The removal by distillation in particular of II from mixtures comprising I and II can be realized only with difficulties and at high cost, owing to the boiling points, which are very close.

It is an object of the present invention to provide a process by which undesirable byproducts, in particular II, can be removed from mixtures with I without changing I in the process.

We have found that this object is achieved by a process for removing impurities from 3-(2'-acetoxyethyl)dihydro-2(3H)-furanone (I), which comprises initially preparing the 3-(2'-acetoxyethyl)dihydro-2(3H)-furanone containing the undesirable impurities in a manner known per se by acetylating 3-(2'-hydroxyethyl)-dihydro-2-(3H)-furanone, subsequently treating it with strong mineral acids and finally removing the decomposition products of the undesirable impurities from I.

Surprisingly, the desired I is not degraded during treatment with mineral acids and can therefore be obtained in good yield and high purity.

Preferred embodiments of the process according to the invention are disclosed in the subclaims and the description below.

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The process according to the invention starts with the mixture of 3-(2'-hydroxyethyl)dihydro-2(3H)-furanone and undesirable impurities which can be obtained by known processes which were described in the introduction.

This mixture is initially acetylated as completely as possible. Preferred acetylating agents are acetic anhydride or acetic acid itself; in principle, however, all acetylating agents known to the person skilled in the art for corresponding acylations are suitable. The acetylation is generally carried out at temperatures in the range from 40° C. to 200° C., preferably from 60 to 140° C., over a period of from 0.5 to 10, preferably from 0.8 to 5 and in particular from 1 to 3, h.

To ensure complete acetylation, the acetylating agent is generally employed in a molar excess of from 5 to 50%, preferably from 5 to 20%, based on 3-(2'-hydroxyethyl)dihydro-2(3H)-furanone present in the mixture.

In the subsequent step, the acetylation product is treated with strong mineral acids. Preferred mineral acids are hydrochloric acid, nitric acid and, particularly preferably, sulfuric acid. This is employed preferably at at least 80% strength and in particular in the form of concentrated sulfuric acid.

The amount of sulfuric acid used can be varied within wide ranges; in some cases, it was found to be advantageous to use a molar ratio of strong mineral acid, based on the amount of acetylating agent used in the preceding step, in the range of from 1:20 to 1:3, preferably from 1:15 to 1:7 and in particular from 1:8 to 1:12.

For the treatment with the mineral acid, the temperature is generally in the range of from 10 to 80, preferably from 20 to 60 and in particular from 30 to 50° C. The duration of the treatment is generally in the range of from 0.3 to 10, in particular from 1 to 5, h, but can, in principle, be varied within wide limits.

After the treatment with strong mineral acids, the decomposition products of the undesirable impurities, in particular of dihydro-3-(2-methyl-1,3-dioxolan-2-yl)-2(3H)-furanone II, can be removed in a simple manner.

According to a preferred variant, the mineral acid is initially neutralized by addition of base, preferably aqueous alkali metal hydroxide, and the acetic acid formed as coproduct in the acetylation is subsequently, if appropriate, distilled off. Phase separation is subsequently carried out by addition of a suitable organic solvent and water, and the organic phase is then extracted. Suitable organic solvents are in particular aromatic hydrocarbons and especially alkylated benzene derivatives, such as xylene or toluene. The organic extracts are combined and the solvent is removed, and the residue can then be rectified under reduced pressure, giving, in good yield and high purity, the desired product, which may subsequently be processed further. The degree of purity of I can be increased even further by carrying out more than one rectifications in succession. The conditions for the rectification are known per se to the person skilled in the art and described in the literature, so that further details are not required here.

After the process according to the invention has been carried out, the purity of I is generally at least 98, preferably at least 98.5 and particularly preferably at least 99% by weight.

The I obtainable by the process according to the invention can be reacted in a manner known per se in high yield and with good catalyst onstream times to give methyl tetrahydropyran-4-carboxylate. This is an important intermediate in the preparation of crop protection agents.

EXAMPLE 1

Comparison

In a 3.5 l pressure vessel, a mixture of 1009 g (8.7 mol) of methyl acetoacetate, 1218 ml (969 g) of methanol and 110

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g (0.61 mol) of a 30% strength solution of sodium methoxide in methanol was initially charged, and 765.6 g (17.4 mol) of ethylene oxide were subsequently pumped in at 60° C. with stirring over a period of 8 hours. The mixture was then stirred at 60° C. for 24 h. The reaction discharge was repeatedly flushed with nitrogen and subsequently transferred into a stirred apparatus having an attached column. The catalyst was then neutralized by addition of 29.6 g (0.3 mol) of sulfuric acid (96%). The low-boiling components, essentially methanol, methyl acetate and methyl glycol, were distilled off at 10 mbar (1013 Pa) up to a bottom temperature of 100° C. At 100° C., 806 g (7.9 mol) of acetic anhydride were added over a period of one hour with stirring to the distillation residue, and the mixture was then stirred at 100° C. for 2 h. The excess acetic anhydride and the acetic acid, which is formed as coproduct during the acetylation, were subsequently distilled off, and the crude discharge was cooled. After addition of 726 g of toluene and 300 g of water, the phases were separated and the aqueous phase was extracted twice with 200 ml of toluene each time. The organic extracts were combined and the solvent was stripped off under reduced pressure using a rotary evaporator. The residue was rectified batchwise under reduced pressure at 10 mbar (b.p. 161° C./10 mbar). This gave 1077 g (72%) of 3-(2'-acetoxyethyl)dihydro-2(3H)-furanone (calculated 100%).

Composition:

3-(2'-acetoxyethyl)dihydro-2(3H)-furanone	95.0%
dihydro-3-(2-methyl-1,3-dioxolan-2-yl)-2(3H)-furanone	3.5%
3-(2'-hydroxyethyl)dihydro-2(3H)-furanone	0.50%
others	1.0%

EXAMPLE 2

Single Batchwise Rectification

In a 3.5 l pressure vessel, a mixture of 1009 g (8.7 mol) of methyl acetoacetate, 1218 ml (969 g) of methanol and 110 g (0.61 mol) of a 30% strength solution of sodium methoxide in methanol was initially charged, and 765.6 g (17.4 mol) of ethylene oxide were subsequently pumped in at 60° C. with stirring over a period of 8 hours. The mixture was then stirred at 60° C. for 24 h. The reaction discharge was repeatedly flushed with nitrogen and subsequently transferred into a stirred apparatus having an attached column. The catalyst was then neutralized by addition of 29.6 g (0.3 mol) of sulfuric acid (96%). The low-boiling components, essentially methanol, methyl acetate and methyl glycol, were distilled off at 10 mbar up to a bottom temperature of 100° C. At 100° C., 806 g (7.9 mol) of acetic anhydride were added over a period of one hour to the distillation residue, and the mixture was then stirred at 100° C. for 2 h. To decompose the dihydro-3-(2-methyl-1,3-dioxolan-2-yl)-2(3H)-furanone, the reaction mixture was cooled to 40° C., 72.5 g (0.73 mol) of sulfuric acid (96%) were added and the mixture was then stirred at this temperature for 2 hours. To neutralize the sulfuric acid, 127.5 g (1.59 mol) of 50% strength NaOH were subsequently added at 40–45° C. The acetic acid which was formed as coproduct during the acetylation was distilled off and the crude discharge was cooled. After addition of 726 g of toluene and 850 g of water, the phases were separated and the aqueous phase was extracted twice with 200 ml of toluene each time. The organic extracts were combined and the solvent was stripped off under reduced pressure using a rotary evaporator. The residue was rectified batchwise under reduced pressure at 10 mbar (b.p. 161° C./10 mbar). This gave 1056 g (71%) of 3-(2'-acetoxyethyl)dihydro-2(3H)-furanone (calculated 100%).

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Composition:

3-(2'-acetoxyethyl)dihydro-2(3H)-furanone	98.5%
dihydro-3-(2-methyl-1,3-dioxolan-2-yl)-2(3H)-furanone	0.3%
3-(2'-hydroxyethyl)dihydro-2(3H)-furanone	0.3%
others	0.9%

EXAMPLE 3

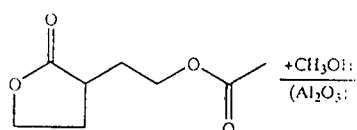
Three-Fold Continuous Rectification

In a 1 m³ pressure vessel, a mixture of 348 kg (3.0 kmol) of methyl acetoacetate, 420.1 l (334.2 kg) of methanol and 37.9 kg (210.3 mol) of a 30% strength solution of sodium methoxide in methanol was initially charged and 264.1 kg (6.0 kmol) of ethylene oxide were subsequently pumped in with stirring at 60° C. over a period of 8 hours. The mixture was then stirred at 60° C. for 24 h. The reaction discharge was repeatedly flushed with nitrogen and subsequently transferred into a 1 m³ [sic] stirred apparatus having an attached column. The catalyst was then neutralized by addition of 10.2 kg (103.5 mol) of sulfuric acid (96%). The low-boiling components, essentially methanol, methyl acetate and methyl glycol, were distilled off at 10 mbar (1013 Pa) up to a bottom temperature of 100° C. At 100° C., 278 kg (2.7 kmol) of acetic anhydride were added with stirring over a period of one hour to the distillation residue, and the mixture was then stirred at 100° C. for 2 h. To decompose the dihydro-3-(2-methyl-1,3-dioxolan-2-yl)-2(3H)-furanone, the reaction mixture was cooled to 40° C., 25.0 kg (251.8 mol) of sulfuric acid (96%) were added and the mixture was then stirred at this temperature for two hours. To neutralize the sulfuric acid, 439.7 kg (548 mol) of 50% strength NaOH were subsequently added at 40–45° C. The acetic acid formed as coproduct during the acetylation was distilled off and the crude discharge was cooled. After addition of 250.4 kg of toluene and 293.2 kg of water, the phases were separated and the aqueous phase was extracted twice with 100 kg of toluene each time. The organic extracts were combined and processed further. This gave 375.3 kg (73%) of 3-(2'-acetoxyethyl)dihydro-2(3H)-furanone (calculated 100%).

Composition:

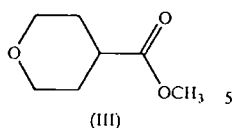
3-(2'-acetoxyethyl)dihydro-2(3H)-furanone	99.5%
dihydro-3-(2-methyl-1,3-dioxolan-2-yl)-2(3H)-furanone	<0.1%
3-(2'-hydroxyethyl)dihydro-2(3H)-furanone	0.3%
others	0.1%

To investigate the effects of the degree of purity of 1 on the subsequent reaction, the products obtained by Examples 1 to 3 were converted into methyl tetrahydropyran-4-carboxylate according to the following general equation:



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-continued



Per hour, a solution consisting of 172 g of 3-(2'-acetoxyethyl)dihydro-2(3H)-furanone and 192 g of methanol was evaporated and passed in a tubular reactor at 250° C. over 2000 g of a γ -aluminum oxide catalyst (Pural SB™, formed into 2 mm strands, dried for 16 h at 120° C. and calcined for 3 h at 520° C.). The gaseous reaction discharge was condensed and the resulting tetrahydropyran-4-carboxylate ester was purified by batchwise distillation (b.p. 117° C./30 mbar).

The results of the reactions of 3-(2'-acetoxyethyl)dihydro-2(3H)-furanone I with different proportions of dihydro-3-(2-methyl-1,3-dioxolan-2-yl)-2(3H)-furanone II are summarized in Table 1:

TABLE 1

Proportion of II in %	Conversion (%)	Yield of III, at the start	Yield of III, after 60 h	Yield of III, after 1200 h	Yield of III, after 1440 h
3.5 (Ex.1)	100	55%	39%	—	—
0.3 (Ex.2)	100	68%	68%	68%	57%
<0.1 (Ex.3)	100	68%	68%	68%	68%

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The results of the table above show the strong effect of the content of impurities, in particular II, on the further processing of I.

We claim:

1. A process for removing impurities from 3-(2'-acetoxyethyl)dihydro-2(3H)-furanone (I), which comprises initially preparing the 3-(2'-acetoxyethyl)dihydro-2(3H)-furanone containing the undesirable impurities in a manner known per se by acetylating 3-(2'-hydroxyethyl)dihydro-2-(3H)-furanone, subsequently treating it with strong mineral acids and finally removing the decomposition products of the undesirable impurities from I.

2. A process as defined in claim 1, wherein the acetylating agent used is acetic anhydride or acetic acid.

3. A process as defined in claim 1, wherein the strong mineral acid used is sulfuric acid.

4. A process as defined in claim 1, wherein the treatment with sulfuric acid is carried out at temperatures of from 20 to 70° C.

5. A process as defined in claim 1, wherein the decomposition products are removed by phase separation, subsequent extraction and distillation or rectification.

6. A process as defined in claim 5, wherein a multi-step distillation or rectification is carried out.

* * * * *



US006037503A

United States Patent [19]

Oren et al.

[11] Patent Number: 6,037,503

[45] Date of Patent: Mar. 14, 2000

[54] PROCESS FOR THE PREPARATION OF
PARA-FLUOROPHENOL2,950,325 8/1960 Britton et al. 260/623
4,940,821 7/1990 Pews et al. 568/775[75] Inventors: Jakob Oren, Nesher; Michel Adda,
Kfar-Saba, both of Israel

FOREIGN PATENT DOCUMENTS

34 30 554 A1 2/1986 Germany
850888 10/1960 United Kingdom

[73] Assignee: Bromine Compounds Ltd., Israel

[21] Appl. No.: 09/101,631

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[22] PCT Filed: Jan. 14, 1997

[86] PCT No.: PCT/IL97/00019

§ 371 Date: Jul. 14, 1998

§ 102(e) Date: Jul. 14, 1998

[87] PCT Pub. No.: WO97/26235

PCT Pub. Date: Jul. 24, 1997

Journal of Organic Chemistry, vol. 26, No. 11, Nov. 1961,
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Boudakian et al., Aromatic Fluorine Compounds. II. Syn-
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bus, Ohio; abstract No. 9744b, XP002030173 & SU 143 404
A, N.N. Vorontsony, Jr., et al.

[30] Foreign Application Priority Data

Jan. 15, 1996 [IL] Israel 116759

[51] Int. Cl.⁷ C07C 39/30; C07C 39/32[52] U.S. Cl. 568/777; 568/774; 568/775;
568/778[58] Field of Search 568/775, 774,
568/778; 570/127, 143, 190

Primary Examiner—Gary Geist

Assistant Examiner—Sreeni Padmanabhan

Attorney, Agent, or Firm—Lerner, David, Littenberg,
Krumholz & Mentlik, LLP

[57]

ABSTRACT

A process for the preparation of p-fluorophenol, which
comprises hydrolyzing p-bromofluorobenzene with a mix-
ture of NaOH and Na₂CO₃ in the presence of a copper
catalyst.

[56] References Cited

U.S. PATENT DOCUMENTS

2,934,369 4/1960 Kuchlewind, Jr. 260/623

17 Claims, No Drawings

PROCESS FOR THE PREPARATION OF PARA-FLUOROPHENOL

This is the U.S. National Stage Application of PCT/IL97/00019 filed Jan. 14, 1997 now WO97/26235 published Jul. 24, 1997.

1. Field of the Invention

This invention relates to a process for the preparation of p-fluorophenol by the hydrolysis of p-bromofluorobenzene. It particularly refers to a process which yields highly pure p-fluorophenol, obtained from a crude p-fluorophenol reaction product, which has an extremely low content of phenol and a low content of heavy by-products.

2. Background of the Invention

Aromatic fluorine compounds based on fluorobenzene are important intermediates for the manufacture of agrochemicals, pharmaceuticals and speciality polymers. One such fluorine compound is p-fluorophenol (hereinafter PFP). Various processes for the preparation of PFP are known in the art. Among them the following may be cited: direct fluorination of phenol, fluorination of p-aminophenol, hydroxylation of fluorobenzene, diazotization of p-fluoroaniline followed by hydrolysis of the diazonium salt, dealkylation of fluoroanisole or fluorophenetole, and hydrolysis of p-chlorofluorobenzene. A process which has received considerable attention in the art is the hydrolysis of p-bromofluorobenzene (hereinafter PBFB). Said hydrolysis has been carried out under basic conditions, under pressure, with or without a catalyst. The problems inherent in the preparation of PFP by the hydrolysis of PBFB are the low selectivity regarding PFP and the formation of phenol by-product. Phenol is not the only by-product formed; other by-products are, for instance, 4,4'-difluorodiphenyl ether (hereinafter DFDPE) and 4-fluoro-4'-hydroxydiphenyl ether (hereinafter FHDPE). Phenol, however, is a particularly undesirable by-product, because it is practically impossible to remove by distillation, and other methods known for its removal, such as melt crystallization or treatment with phthalic anhydride/ H_2SO_4 , require an extra process step, which is detrimental to the economics of the process. Therefore considerable attention has been devoted in the art to the reduction of the amount of phenol formed, but the results have not been completely satisfactory.

Thus, U.S. Pat. No. 2,934,569 and GB 850888 disclose the hydrolysis of PBFB with $Ca(OH)_2$ as a base, and in the presence of a catalyst, whereby it is attempted to reduce the formation of phenol, but PFP is obtained in yields of only 50–70% and large amounts of DFDPE (10–15%) are formed.

Russian Patent 143404 describes the hydrolysis of PBFB using an alkali fluoride, such as $NaHF_2$ or KOAc, as a base and Cu_2O as the catalyst. The reaction takes place at 250° C. for 4 hours with a PFP yield of 73%.

DE 3430554 discloses the hydrolysis of PBFB in the presence of $Ba(OH)_2$ with Cu powder as a catalyst and a quaternary ammonium cocatalyst. Yields of up to 94.6% are mentioned.

U.S. Pat. No. 2,950,325 describes the basic hydrolysis of PBFB with alkaline earth metal oxides or hydroxides, which are said to avoid the formation of by-products such as phenol, "which are frequently formed when the stronger alkaline agent, e.g., potassium hydroxide or sodium hydroxide, is employed in the reaction".

In conclusion, the prior art teaches that the best way of carrying out the basic hydrolysis of PBFB comprises using a copper compound catalyst, and calcium or barium hydroxide as a base. Stronger bases, such as in particular sodium hydroxide, are said to produce bad results. The combined use of calcium hydroxide and copper catalysts, according to prior art, provides yields that may reach 70–75%.

It is a purpose of this invention to provide a process for the production of PFP which gives this product in high yields and a very low amount of phenol by-product.

It is a particular purpose of this invention to provide such a process which comprises the hydrolysis of PBFB and permits a reduction in the formation of phenol to amounts in the order of 0.1% and even below that amount.

It is a further purpose of this invention to provide such a process which does not involve the production of large amounts of heavy by-products, such as DFDPE and FHDPE. Any such heavy by-products are easily removed during the work-up, which includes extraction with an organic solvent, followed by fractional distillation.

It is a still further purpose of this invention to achieve the aforesaid purposes by a simple and economical process, which does not involve the use of expensive reagents.

It is a still further purpose of this invention to provide a process for the production of PFP having increased productivity together with high selectivity.

Other purposes and advantages of this invention will appear as the description proceeds.

SUMMARY OF THE INVENTION

The process according to the invention is characterized in that PBFB is hydrolyzed with a mixture of NaOH and Na_2CO_3 as the base, and using a copper catalyst.

It is known that the use of NaOH alone as base produces PFP with a phenol content of ~0.7%. We have found that under the preferred conditions, the hydrolysis with NaOH together with Na_2CO_3 as the base, succeeded in producing PFP with a lower amount of phenol and a relatively low amount of heavy by-products relative to the prior art processes.

The hydrolysis is carried out on pure PBFB at temperatures from 180 to 240° C., and preferably at a temperature of 200–210° C. An increase in the temperature leads to an increase in the rate of the reaction, but also to an increase in the amount of phenol formed and the amount of F^- in the reaction mixture. A lower temperature increases the reaction time.

The molar ratio NaOH/PBFB is comprised between 0.8 and 2.6, and preferably between 1.4 and 2.4. The Na_2CO_3 /PBFB molar ratio is comprised between 0.25 and 1.6, and preferably between 0.25 and 1.2. The copper catalyst is chosen from among Cu_2O , CuO and $CuSO_4 \cdot 5H_2O$, and is preferably an oxide, Cu_2O or CuO. The molar ratio of PBFB to Cu_2O is from 4 to 16 and the molar ratio of PBFB to CuO is from 2 to 8.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

When the reaction is carried out in a batch process, the NaOH and Na_2CO_3 are used in aqueous solution and the

total base concentration ($\text{NaOH} + \text{Na}_2\text{CO}_3$) in said solution varies from 10 to 30% and preferably from 20 to 25% w/w. The preferred molar ratio NaOH/PBFB is comprised between 1.4 and 1.6. The preferred $\text{Na}_2\text{CO}_3/\text{PBFB}$ molar ratio is comprised between 1.1 and 1.2. The bases are charged together with the PBFB and the catalyst into a reactor, which is sealed and heated to reaction temperature for the required period of time. The use of a higher concentration of base raises the efficiency of the reactor, but as the base concentration increases, more phenol and heavy by-products (DFDPE and FHDPE) are formed. Thus, NaOH/PBFB in a molar ratio of ~ 1.4 , together with $\text{Na}_2\text{CO}_3/\text{PBFB}$ in a molar ratio of ~ 1.1 , gave a product with a low amount of phenol ($\sim 0.1\%$) and relatively low amounts of heavy by-products ($\sim 6-8\%$).

The preferred molar ratio of PBFB to Cu_2O is between 6 and 12, and the preferred molar ratio of PBFB to CuO is between 3 and 6. The larger amounts of catalyst accelerate the reaction and reduce the formation of phenol by-product.

The reaction time is about four hours at $205 \pm 5^\circ \text{C}$. Under the aforesaid conditions, low amounts of phenol and heavy by-products are obtained, with high conversions of PBFB ($>99.5\%$). PFP yields of 85-90%, before distillation, are achieved.

The reaction product is subjected to work-up, comprising filtration of the reaction mixture, acidification to pH 3-7 with concentrated aqueous HCl , then extraction with an organic solvent. The solvent is chosen from among toluene, *n*-butyl acetate (*n*-BuAc) and methyl isobutyl ketone (MIBK).

The organic phases from the extraction are combined and subjected to fractional distillation. The fractional distillation is carried out with about 5-10 theoretical stages and the pure PFP comes off at $123-125^\circ \text{C}$. at 100 mm Hg.

The foregoing advantages of the invention may be better understood through the following illustrative and non-limitative examples.

Examples 1 to 23 illustrate embodiments in which the invention is carried out in a batch process.

EXAMPLE 1

Preparation of PFP using a mixture of Na_2CO_3 and NaOH as the base

A one liter autoclave was charged with 620 g water, 50.6 g NaOH (1.26 mol), 105.2 g Na_2CO_3 (0.99 mol), 157.5 g pure PBFB (0.9 mol) and 11 g Cu_2O (0.076 mol). The autoclave was sealed and heated to 205°C . over 45 minutes, then maintained at 205°C . for 4 hrs. The contents of the autoclave were cooled to room temperature and filtered. The composition of the reaction mixture was determined by GC and GC/MS.

The conversion of the PBFB, determined by titrating the filtrate for Br^- , was $>99.5\%$. The filtrate was carefully acidified with 188 g 32% HCl to pH 3-7 and extracted with 2×250 g toluene.

Four experiments were carried out under these conditions. The extraction was performed counter-current, i.e. organic phase from the second extraction served as the extractant for the first extraction of the following batch.

All the organic phases were combined and then distilled in a laboratory column, 1" diameter, about 5 theoretical stages. The solvent was distilled at atmospheric pressure, and can be recycled. Fractional distillation was then per-

formed. The pure PFP was obtained at $123-125^\circ \text{C}$. at 100 mm Hg. The main fraction contained 320 g PFP in a purity of 99.5% and a phenol content of 0.1%. Off-spec fractions containing ~ 25 g PFP can be transferred to the next distillation.

Based on these results, the yield of PFP is $\sim 85\%$, based on starting PBFB.

EXAMPLES 2 AND 3

The preparation of PFP was carried out as described in Example 1, but under the following conditions and with the results shown in Table I:

aq. ($\text{NaOH} + \text{Na}_2\text{CO}_3$)—20%
 NaOH/PBFB molar ratio—1.4
 $\text{Na}_2\text{CO}_3/\text{PBFB}$ molar ratio—1.1
 $\text{PBFB}/\text{Cu}_2\text{O}$ molar ratio—6.0
 Temperature— $205 \pm 5^\circ \text{C}$.
 Time—4 hours

TABLE I

Example No.	Composition (GC, area %)*					F ⁻ in aq. reaction mixture	
	FB	PBFB	PFP	DFDPE	FHDPE	ppm	mole %
2	1.1	0.1	94.0	2.9	1.7	770	4.2
3	1.6	0.2	92.8	3.0	1.6	700	3.8

*PhOH n.d. < 0.1%

It should be pointed out that under said conditions, the level of F^- in the reaction mixture is $\sim 700-800$ ppm, which is lower than obtained with the use of NaOH alone. The yield of PFP in the crude reaction mixture is 85% or more.

Pure PFP is obtained by filtration of the reaction mixture, acidification to pH 3-7 by aqueous HCl , followed by extraction with one of the following solvents: *n*BuAc, MIBK, toluene, then fractional distillation.

EXAMPLES 4 AND 5

The preparation of PFP was carried out as described in Example 1, but using CuO as catalyst and under the following conditions and with the results shown in Table II:

aq. ($\text{NaOH} + \text{Na}_2\text{CO}_3$)—20%
 NaOH/PBFB molar ratio—1.4
 $\text{Na}_2\text{CO}_3/\text{PBFB}$ molar ratio—1.1
 PBFB/CuO molar ratio—3.2
 Temperature— $205 \pm 5^\circ \text{C}$.
 Time—4 hours

TABLE II

Example No.	Composition (GC, area %)					F ⁻ in aq. reaction mixture	
	FB	PBFB	PFP	DFDPE	FHDPE	ppm	mole %
4	1.3	0.1	93.3	3.4	1.8	880	4.8
5	0.8	0.3	93.8	3.5	1.4	860	4.7

*PhOH n.d. < 0.1%

5
EXAMPLES 6 TO 11

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The comparative behavior of different catalysts is illustrated by the following hydrolyses shown in Table III:

aq. (NaOH+Na₂CO₃)—23%

Temperature—205±5° C.

Time—4 hours

5

TABLE III

Ex. No.	Molar Ratio			Catalyst used	Composition (GC, area %)					
	NaOH/ PBFB	Na ₂ CO ₃ / PBFB	PBFB/ Cat.		FB	PBFB	PhOH	PFP	DFDPE	FHDPE
6	1.5	1.16	6.5	Cu ₂ O	1.4	1.4	0.11	90.3	5.0	1.6
7	1.5	1.16	6.5		1.1	0.6	0.12	91.7	3.2	1.4
8	1.5	1.16	3.6	CuO	1.4	0.2	0.09	91.2	3.9	2.0
9	1.5	1.16	3.6		1.7	0.3	0.09	90.8	3.9	2.0
10	1.6	1.20	6.0	CuSO ₄ ·5H ₂ O	1.6	0.3	0.06	89.7	4.1	3.8
11	1.6	1.00	6.0		2.9	0.3	0.06	87.9	5.1	3.4

EXAMPLES 12, 13 AND 14

The following examples, carried out under the following conditions and with the results shown in Table IV, illustrate the effect of temperature variations within the range 205±5° C.

aq. (NaOH+Na₂CO₃)—20% w/w

NaOH/PBFB molar ratio—1.5

Na₂CO₃/PBFB molar ratio—1.2

PBFB/CuO molar ratio—13

25

30

TABLE IV

Ex. No.	Temp. ° C.	Time hr	Conv. by Br ⁻ %	Composition (GC, area %)						
				FB	PBFB	PhOH	PFP	DFDPE	FHDPE	
12	200	4.5	96.0	1.8	2.9	0.11	93.4	1.6	0.2	
13	205	4.0	97.6	1.0	0.9	0.15	95.1	2.0	0.6	
14	210	3.0	98.5	—	0.1	0.17	97.2	1.9	0.5	

The reaction can be carried out at lower and higher temperatures, e.g. from 180 to 220° C. However, as the temperature is lowered, the reaction proceeds more slowly, and as it is increased, more phenol by-product tends to form.

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EXAMPLES 15 AND 16

The amounts of bases used can vary within relatively wide limits and still produce satisfactory results, as shown by the following examples in Table V:

aq. (NaOH+Na₂CO₃)—20% w/w

PBFB/Cu₂O molar ratio—13

Temperature—205±5° C.

50

TABLE V

Example No.	Molar Ratio		Conv. by Br ⁻ %	Time hr	Main Impurities		
	NaOH/ PBFB	Na ₂ CO ₃ / PBFB			PhOH	DFDPE	FHDPE
15	1.5	1.2	96.0	4.5	0.11	1.6	0.2
16	0.8	1.6	98.9	3.7	0.05	3.7	4.4

The use of Na_2CO_3 alone would give small amounts of phenol, but at the expense of large amounts of DFDPE and FHDPE.

EXAMPLES 17 TO 20

The total concentration of the bases in their aqueous solution can also be varied considerably. Non-limitative examples are given in the following shown in Table VI:

NaOH/PBFB molar ratio—1.4

Na_2CO_3 /PBFB molar ratio—1.1

Temperature— $205 \pm 5^\circ \text{C}$.

Time—4 hours

TABLE VI

Example No.	Type	Catalyst		Conc. of base %	Main Impurities			
		Molar Ratio PBFB/cat			FB	PhOH	DFDPE	FHDPE
17	Cu_2O	6.5		25	2.4	0.13	6.1	3.4
18	CuO	6.5		20	2.3	0.09	4.4	2.9
19	CuO	3.6		25	1.5	0.11	6.2	2.5
20	CuO	3.6		20	1.3	0.08	3.2	1.0

The use of a higher concentration of base raises the efficiency of the reactor, but the results show that the higher the base concentration, the lower the selectivity of the hydrolysis for PFP. Higher base concentrations led to the formation of more phenol and heavies (DFDPE and FHDPE).

EXAMPLES 21 TO 23

The ratio of PBFB to catalyst has an influence on the results of the reaction. Examples 21 to 23, shown in Table VII, relate to hydrolyses carried out under the following conditions:

aq. ($\text{NaOH} + \text{Na}_2\text{CO}_3$)—20%

NaOH/PBFB molar ratio—1.5

Na_2CO_3 /PBFB molar ratio—1.2

Temperature— $205 \pm 5^\circ \text{C}$.

Time—4 hours

TABLE VII

Example No.	PBFB/ Cu_2O	Conv. by Br^- %	Composition (GC area %)					
			FB	PBFB	PhOH	PFP	DFDPE	FHDPE
21	20	85.3	1.5	13.9	0.18	83.0	1.0	0.1
22	13	97.6	1.0	0.9	0.15	95.1	2.0	0.6
23	6	99.1	0.7	0.5	0.09	95.4	2.0	1.1

A large amount of catalyst produces a faster reaction and less phenol by-product, as shown by the tabulated results.

The following examples illustrate embodiments wherein the invention is carried out in a semi-batch process. By semi-batch process is meant a process in which the NaOH is slowly added to the reaction mass during the course of the reaction.

In the semi-batch process, the water, the Na_2CO_3 , the PBFB and the catalyst are charged into a reactor, which is sealed and heated to reaction temperature. NaOH solution is then added at a constant flow rate over a few, preferably 3 to 5, hours, whereafter the temperature is maintained for an additional time, e.g. about one hour, to permit the reaction to be completed. When the reaction is carried out in this manner, the preferred catalyst is Cu_2O and the preferred molar ratio of PBFB to Cu_2O is from 4 to 6.3. The reaction temperature is from 200° to 220°C , preferably about 210°C . The preferred molar ratio Na_2CO_3 /PBFB is 0.25–0.50 and the preferred molar ratio NaOH/PBFB is 1.8–2.2.

EXAMPLE 24

An 8-litre reactor was loaded with 1919 g H_2O , 283 g Na_2CO_3 , 1847 g PBFB and 369 g Cu_2O . The mixture was heated to 210°C . 1738 g of 48% NaOH was then slowly added to the reactor by means of a diaphragm pump, the temperature in the reactor being maintained at 210°C . The NaOH was added at a constant flow rate over 5 hours. The temperature was maintained for an additional hour. During

this hour, a drop in the pressure of about 1 atm from -20 to 19 atm was observed, which indicated elimination of the vapor pressure of the PBFB and completion of the reaction.

The mixture was then cooled to 70° C. The mixture was filtered to remove the catalyst and the filtration line washed with 1000 g water. The mixture was acidified to pH=6.5 and cooled to ambient temperature. The product was extracted with 1850 g butyl-acetate. A second extraction was then done with 927 g butyl-acetate. The two extracts were mixed together. The total weight of the two extracts was 4017 g.

3941 g of this extract was distilled in two fractions, in a water-heated rotavapor and then in an oil-heated rotavapor. The first distilled fraction weighed 3680 g and had the following composition (GC area %): BuAc: 72.2%, PFP: 27.4%, DFDPE: 0.4%. The PFP assay as detered by acid titration was

26.0%. 85 g of a two-phase mixture of BuAc and water was collected in the trap.

The second distilled fraction weighed 28.6 and had the following concentration: BuAc: 1.3%, PFP: 81.4%, DFDPE: 16%. The PFP assay was of 84.5%.

The recovered PFP in the two distillation fractions gave a yield of 83%, relative to the PBFB feed. The residue of distillation represents 85.3 g. The balance on the distillation was 98%.

EXAMPLES 25-29

The same operations of Example 24 were carried out in the following Examples, but with the amount of reagents and catalyst and the composition of the final product set forth in the following Table VIII.

TABLE VIII

Detailed results of semi-batch reaction in the 81 reactor														
Example	PBFB	Feed				Cu ₂ O (wt %)	Temp. (deg. C)	Composition (GC area %)						
		Molar ratio			FB			OFF	PBFB	PhOH	PFP	PFPAc	DFDPE	FDHPE
		PBFB	NaOH	Na ₂ CO ₃										
No.	(moles)													
25	9.59	1	2.4	0.25	20	210	0.7	0.06	0.01	0.088	97.6	0.1	0.8	0.6
26	9.59	1	2.3	0.25	20	220	0.5	0.06	0.07	0.120	87.3	0.3	7.8	3.5
27	9.59	1	2.4	0.5	20	210	0.1	1.44	nd	0.240	96.6	0.1	0.0	1.3
28	10.55	1	2	0.25	20	210	n.d.	0.05	n.d.	0.082	97.9	0.2	0.5	1.0
29	13.4	1	2.2	0.25	13	210	0.2	0.08	n.d.	0.126	97.9	0.1	0.1	1.4

The productivity of the process is increased by the semi-batch operation. In Examples 24 to 29 the PBFB loading of the reactor, calculated on the basis of its final content, after NaOH addition, free of catalyst, varied from 16 to 38 wt %.

The process can be carried out, if desired, in a continuous manner.

While embodiments of the invention have been described by way of illustration, it will be apparent that the invention may be carried out by persons skilled in the art with many modifications, variations and adaptations, without departing from its spirit or exceeding the scope of the claims.

We claim:

1. Process for the preparation of p-fluorophenol, which comprises hydrolyzing p-bromofluorobenzene with a mixture of NaOH and Na₂CO₃ in the presence of a copper catalyst.

2. Process according to claim 1, wherein the copper catalyst is chosen from among Cu₂O, CuO and CuSO₄·5H₂O.

3. Process according to claim 1, wherein the hydrolysis is carried out at temperatures from 180 to 240° C.

4. Process according to claim 1, wherein the hydrolysis is carried out at temperatures of 200-210° C.

5. Process according to claim 1, wherein the molar ratio of sodium hydroxide to p-bromofluorobenzene is comprised between 0.8 and 2.6.

6. Process according to claim 1, wherein the molar ratio of sodium hydroxide to p-bromofluorobenzene is comprised between 1.4 and 2.4.

7. Process according to claim 1, wherein the molar ratio of sodium carbonate to p-bromofluorobenzene is comprised between 0.25 and 1.6.

8. Process according to claim 1, wherein the molar ratio of sodium carbonate to p-bromofluorobenzene is comprised between 0.25 and 1.2.

9. Process according to claim 1, wherein the sodium hydroxide and the sodium carbonate are used in aqueous solution with a total concentration from 10 to 30%.

10. Process according to claim 9, wherein the sodium hydroxide and the sodium carbonate are used in aqueous solution with a total concentration of 20 to 25% w/w.

11. Process according to claim 2, carried out in batch, wherein the copper catalyst is used in such an amount that the molar ratio of p-bromofluorobenzene to Cu₂O is from 6 to 12 and the molar ratio of p-bromofluorobenzene to CuO is from 3 to 6.

12. Process according to claim 2, carried out in semi-batch, wherein the copper catalyst is Cu₂O and is used in such an amount that the molar ratio of p-bromofluorobenzene to Cu₂O is from 4 to 6.3.

13. Process according to claim 1, carried out in semi-batch, wherein the molar ratio of sodium hydroxide to

p-bromofluorobenzene is comprised between 1.8 and 2.2 and the molar ratio of sodium carbonate to p-bromofluorobenzene is comprised between 0.25 and 0.5.

14. Process according to claim 1, carried out in semi-batch, wherein the sodium hydroxide is slowly added to a mixture of p-bromofluorobenzene, sodium carbonate and catalyst, at the reaction temperature and at such a flow rate that the addition lasts from 3 to 5 hours.

15. Process according to claim 14, wherein the reaction mixture is kept at the reaction temperature, after the addition of sodium hydroxide, until the reaction is completed.

16. Process according to claim 1, further comprising subjecting the reaction product to work-up, extraction with a suitable solvent and distillation.

17. Process according to claim 16, wherein the solvent for extraction is chosen from among toluene, n-butyl acetate and methyl isobutyl ketone.

* * * * *

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,037,503
DATED : March 14, 2000
INVENTOR(S) : Oren et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 7, line 11, " Na^2CO^3 " should read -- Na_2CO_3 --.

Col. 7, in Table VI, line 23, "CuO" should read -- Cu_2O --.

Col. 9, line 15, "detered" should read --determined--.

Col. 9, line 20, after "28.6" insert --g--.

Cols. 9 and 10, in Table VIII, under Example No. 27, "nd" should read --n.d.--

Signed and Sealed this

Twenty-seventh Day of February, 2001

Attest:

Nicholas P. Godici

NICHOLAS P. GODICI

Attesting Officer

Acting Director of the United States Patent and Trademark Office



US006107490A

United States Patent [19]

[11] Patent Number: 6,107,490

Murthy et al.

[45] Date of Patent: Aug. 22, 2000

[54] PROCESS FOR THE MANUFACTURE OF 4-METHYL-5-HYDROXYMETHYL-IMIDAZOLE

[75] Inventors: K. S. Keshava Murthy; Gamini Weeratunga; Derek John Norris, all of Brantford, Canada

[73] Assignee: Brantford Chemicals Inc., Brantford, Canada

[21] Appl. No.: 08/571,779

[22] Filed: Dec. 13, 1995

[51] Int. Cl.⁷ C07D 233/64

[52] U.S. Cl. 548/341.1

[58] Field of Search 548/341.1

[56] References Cited

U.S. PATENT DOCUMENTS

4,189,591 2/1980 Mueller et al. 548/342

4,275,216 6/1981 Hubert-Brierre 542/342

Primary Examiner—Patricia L. Morris

Attorney, Agent, or Firm—Ivor M. Hughes; Neil H. Hughes; Marcelo K. Sarkis

[57] ABSTRACT

A process is provided for the manufacture of 4-lower-alkyl-5-hydroxymethyl-imidazole comprising reacting (4)-lower-alkyl imidazole with formaldehyde in an alkanol solvent having from 2 to 5 carbon atoms in the presence of a solid mild base suspended in the solvent.

9 Claims, No Drawings

PROCESS FOR THE MANUFACTURE OF 4-METHYL-5-HYDROXYMETHYL-IMIDAZOLE

FIELD OF THE INVENTION

This invention relates to the manufacture of 4-methyl-5-hydroxymethylimidazole.

BACKGROUND OF THE INVENTION

As indicated in U.S. Pat. No. 4,189,591, 4-methyl-5-hydroxymethylimidazole was discovered by WINDAUS in 1909 and was made by the reaction of formaldehyde with 4-methylimidazole. This product is a suitable intermediate for making Cimetidine.

U.S. Pat. No. 4,189,591 was purportedly directed to making this product by an improved process. The improved process was purportedly carried out in aqueous reaction media. The Patent specifies the reaction must be carried out under closely controlled conditions (column 1, lines 31-32). The patent also specifies that when the water is replaced by methanol, only trace amounts of 4-methyl-5-hydroxymethylimidazole was found in the reaction mixture (column 2, line 67-column 3, line 1). According to the patent, "the other common solvents are no better . . ." (column 3, lines 1-2).

With each of the processes, there are deficiencies relating to reactants, conditions of reactions and yields.

In U.S. Pat. No. 4,275,216, a process is provided by which 4(5)-hydroxymethyl- 5(4)-lower- alkyl imidazoles may be manufactured. The process reacts 5(4)-lower alkyl imidazole with formaldehyde in the presence of a strong base (for example, a mineral base such as sodium hydroxide, tertiary amine, quaternary ammonium hydroxide and alkaline metal alcoholates) and at a reaction temperature of 60-95° C.

It is therefore an object of this invention to provide an improved process which is easier to use and more environmentally friendly providing the ability to separate easily and recover non-reactant materials (such as the solvent and mild base) used in the process.

Further and other objects of the invention will be realized by those skilled in the art from the following Summary of Invention and Detailed Description of Embodiments Thereof.

SUMMARY OF INVENTION

Unexpectedly, we have found that by carrying out the reaction of the 4-methylimidazole with formaldehyde in an alkanol (other than methanol) and preferably isopropanol, good yields are achieved in the manufacture of 4-methyl-5-hydroxymethylimidazole. Preferably anhydrous potassium carbonate (K_2CO_3) or other such mild base is added in solid form and suspended in the reaction mixture to catalyze the reaction.

After the reaction is completed the suspended potassium carbonate when used is removed by filtration.

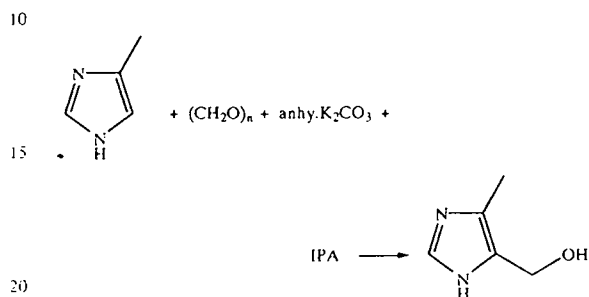
Therefore according to one aspect of the invention, a process for the manufacture of 4-lower-alkyl-5-hydroxymethylimidazoles such as 4-methyl-5-hydroxymethylimidazole is provided comprising reactive formaldehyde (whose source may be paraformaldehyde which when heated degrades into formaldehyde) with 4-methyl-imidazole in an alkanol solvent (other than methanol) (for example having 2-5 carbon atoms) for example isopropanol in the presence of a solid mild base (for

example, a base of a weak acid such as potassium carbonate) suspended in the solvent.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

EXAMPLE 1

Preparation of 4-methyl-5-hydroxymethylimidazole hydrochloride



A mixture containing 4-methylimidazole (30 g, 365 mmol), paraformaldehyde (12 g, 402 mmol), potassium carbonate (55 g, 402 mmol) and industrial isopropanol (150 mL) is heated to 50° C. for 20 h. The reaction mixture is cooled to room temperature and filtered. Hydrogen chloride gas is bubbled through the filtrate at 25° C. until the solution becomes acidic. Acetone (200 mL) was added and cooled to 15° C. for ½ h. The precipitate was filtered, washed with Acetone/IPA (1:1) mixture (30 mL) and dried to give 32.4 g of the hydrochloride salt of the aimed product (60%).

EXAMPLE 2

A mixture containing 4-methylimidazole (100 g), paraformaldehyde (40 g), potassium carbonate (193 g) and isopropanol (500 ml) is heated to 50° C. for 20h. The reaction mixture is cooled to room temperature and filtered to remove the potassium carbonate. Concentrated HCl (35% HCl in water) (230 ml) is added to the filtrate (solution) with cooling (below room temperature—for example, less than 20° C.). The solution was stirred at room temperature for 1 hour and the solvent removed to give 258 g of the crude product.

The recovered product is recrystallized from n-butanol acetone mixture (2:4) to yield the hydrochloride salt of the pure product (50% yield after purification).

EXAMPLE 3

A mixture containing 4-methylimidazole (10 g, 122 mmol), paraformaldehyde (4 g, 134 mmol), potassium carbonate (1.7 g, 12.2 mmol) (catalytic amount of mild base) and isopropanol (20 mL) is heated to 50-55° for 20 hours. The reaction mixture is cooled to room temperature and filtered. Concentrated Hydrochloric acid is added to the filtrate with cooling until the solution becomes acidic. The mixture was stirred at room temperature for 1 hour and the solvent was removed under reduced pressure. The product was crystallized from an acetone: MeOH (6:1) mixture (70 mL) to give 8.9 g of the expected product (49%).

As many changes may be made to the embodiments without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

The embodiments of the invention in which an exclusive property or privilege is claimed are as follows:

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1. A process for the manufacture of 4-lower-alkyl-5-hydroxymethylimidazole comprising reacting (4)-lower-alkyl imidazole with formaldehyde in an alkanol solvent having from 2 to 5 carbon atoms in the presence of a solid mild base suspended in the solvent.

2. The process of claim 1 wherein the alkanol is isopropanol.

3. The process of claims 1 or 2 wherein the solid mild base suspended in the solvent is potassium carbonate.

4. The process of claims 1 or 2 wherein the process further comprises recovering the 4-lower-alkyl-5-hydroxymethylimidazole.

5. The process of claim 3 wherein the process further comprises recovering the 4-lower-alkyl-5-hydroxymethylimidazole.

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6. The process of claims 1 or 2 wherein the process for the production of the 4-lower-alkyl-5-hydroxymethyl-imidazole produces 4-methyl-5-hydroxymethylimidazole.

7. The process of claim 3 wherein the process for the production of the 4-lower-alkyl-5-hydroxymethyl-imidazole produces 4-methyl-5-hydroxymethylimidazole.

8. The process of claim 4 wherein the process for the production of the 4-lower-alkyl-5-hydroxymethyl-imidazole produces 4-methyl-5-hydroxymethylimidazole.

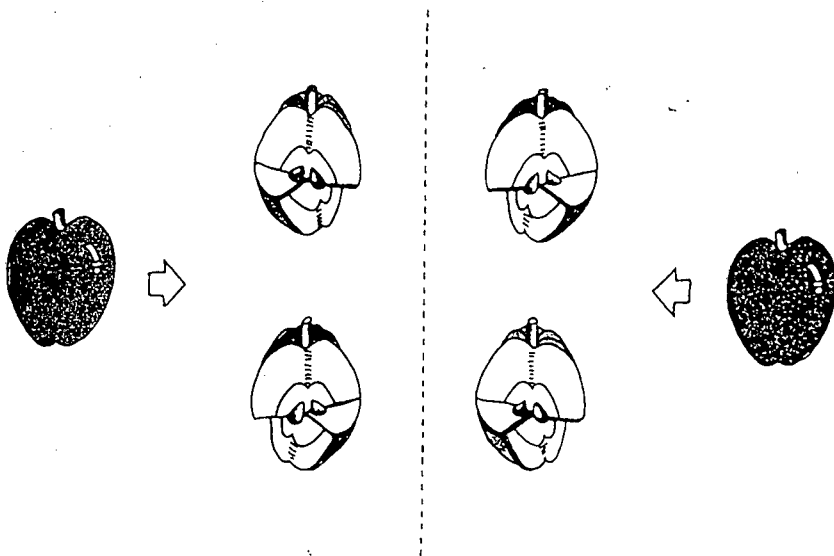
9. The process of claim 5 wherein the process of recovering the 4-lower-alkyl-5-hydroxymethyl-imidazole recovers 4-methyl-5-hydroxymethylimidazole.

* * * * *

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Chirotechnology

INDUSTRIAL SYNTHESIS OF
OPTICALLY ACTIVE COMPOUNDS



Roger A. Sheldon

319
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INDUSTRIAL SYNTHESIS OF
OPTICALLY ACTIVE COMPOUNDS

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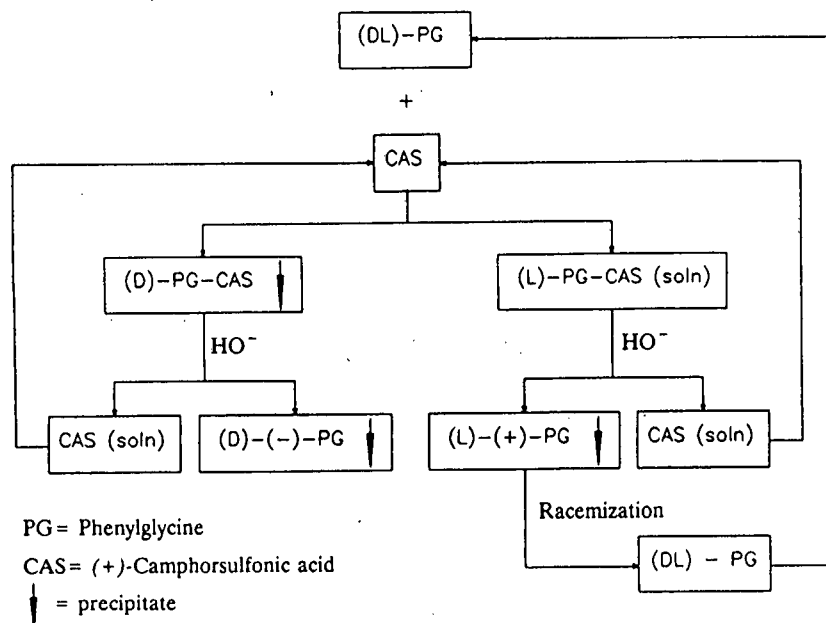
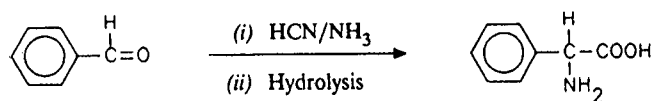


Figure 6-17. Andeno process for D-phenylglycine (D-PG).

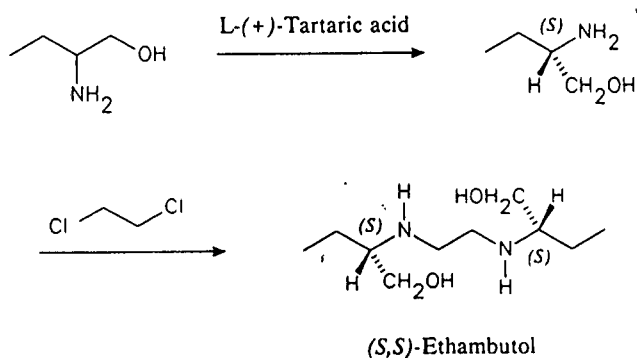


Figure 6-18. Industrial route to (S,S)-ethambutol.

RACEMATE RESOLUTION VIA CRYSTALLIZATION

191

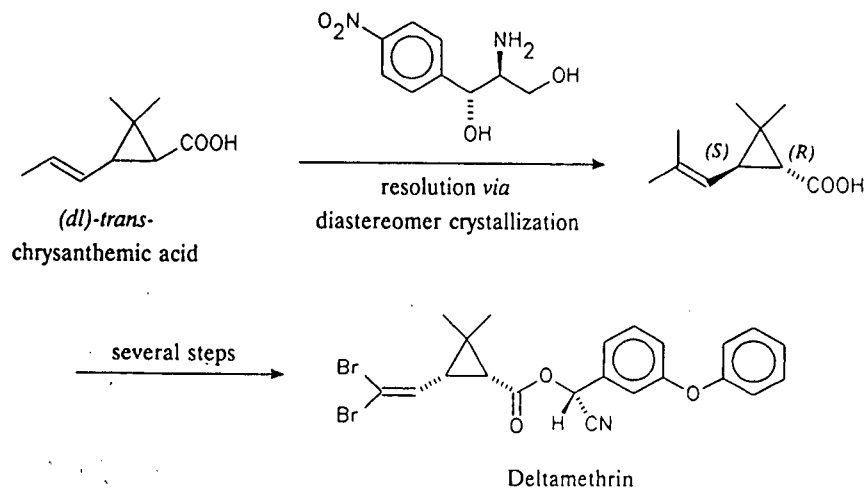


Figure 6-19. Roussel-Uclaf synthesis of deltamethrin.

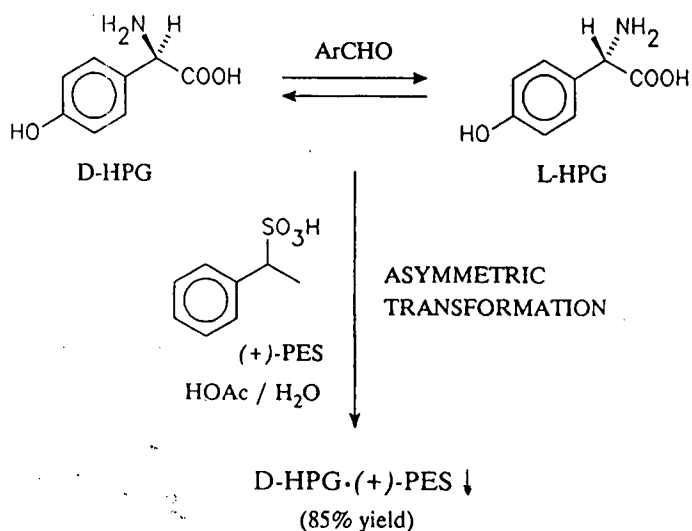
A good example of an industrial process employing classical resolution is the manufacture of the important antibiotic intermediate D-phenylglycine. The latter is produced on more than a thousand tons per annum scale [25] by Andeno using optically pure camphor sulfonic acid in aqueous medium as the resolving agent (Figure 6-17); the L-isomer is racemized in a separate step.

In another example, (*S*)-2-aminobutanol, the key intermediate in the manufacture of the tuberculostatic drug ethambutol, is resolved with L-tartaric acid in methanol as solvent (Figure 6-18) [26]. Similarly, processes have been described for the resolution of naproxen using cinchonidine [27], dehydroabietylamine [28], and *N*-methyl-D-glucamine [29]. Which of these resolving agents is actually used by Syntex for the industrial production of naproxen is not clear.

Optically pure intermediates in existing large-scale industrial processes often constitute a good source of synthetic resolving agents. Sometimes a particular company may use an intermediate from one process as a resolving agent in another. A good example of this is the use of the chloramphenicol intermediate as the resolving agent in the Roussel-Uclaf synthesis [30] of the optically active pyrethroid insecticide deltamethrin (Figure 6-19).

C. Criteria for Good Resolving Agents

Although classical resolutions are not predictable there are certain empirical guidelines, based largely on experience, that can be used as criteria for selecting existing or developing new resolving agents [31]. These are:

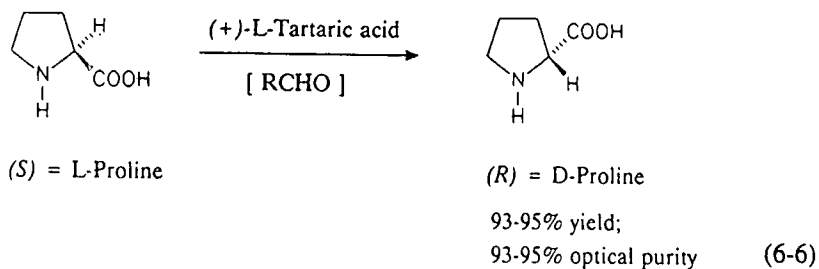


ArCHO = Salicylaldehyde

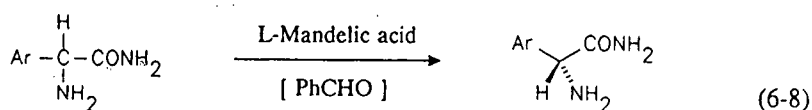
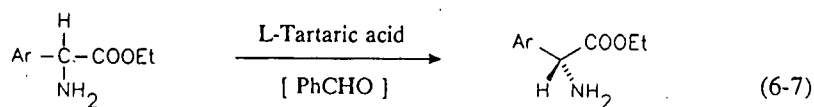
Figure 6-28. Crystallization-induced asymmetric transformation of *p*-hydroxyphenylglycine (HPG) salts with (+)-phenylethanesulfonic acid (PES).

diastereomer interconversion can be used to convert the readily available L-isomer to the D-isomer. A case in point is the synthesis of (*R*)= D-proline from the readily available (*S*)= L-proline [42]. Independent experiments showed that the L=(*2S,3S*)-tartaric acid salt of D-proline is less soluble than the corresponding salt of L-proline.

Consequently, heating equimolar amounts of L-tartaric acid and L-proline at 85°C in the presence of 10% *m*-butyraldehyde in *n*-butyric acid, followed by cooling in an ice-bath, deposited crystals of the D-proline-L-tartaric acid salt in 93–95% yield and 93–95% optical purity (Reaction 6-6). Subsequent recrystallization from aqueous ethanol afforded optically pure D-proline in 85% overall yield.



Similarly, asymmetric transformations have been reported for diastereomeric salts of amino acid amides [43] and amino acid esters [44] in the presence of a catalytic amount of a carbonyl compound (Reactions 6-7 and 6-8, respectively). The efficient synthesis of the commercially important antibiotic intermediates, D-phenylglycine and D-*p*-hydroxyphenylglycine, by asymmetric transformation of the diastereomeric salts of the corresponding amino amides with, for example, L-mandelic acid appears to be economically attractive [43].



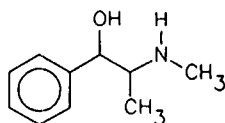
Ar = Phenyl, *p*-Hydroxyphenyl

V. THE FUTURE: RATIONAL DESIGN OF RESOLUTIONS

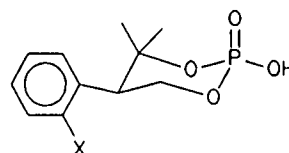
The chiral phosphoric acid resolving agents were designed on the basis of intuition and empirical guidelines derived from years of resolution experience. The ultimate goal is, of course, the rational design of resolution processes. In other words, being able to correlate resolving capability with molecular structure. Bearing in mind the considerable progress that has been made in the rational design of drugs and enzyme inhibitors with the aid of computer assisted modeling (CAMP) of drug-receptor interactions and enzyme inhibition, one might expect analogous studies of pairs of diastereomeric salts to provide the necessary clues. However, the design of resolving agents represents a higher order of complexity compared to drug design since the modelling of resolving agents must predict the crystal packing pattern, something that is far more complex than the modelling of drug-receptor interactions. Several studies have attempted to correlate the crystal structures of pairs of diastereomeric salts with the outcome of resolutions [35,45-49]. The overall conclusion appears to be that the insoluble diastereomer has a dramatically different crystal packing arrangement to the soluble one. For example, the crystal structures of the two pairs of diastereomeric salts formed from ephedrine and the chiral phosphoric acids (XII) and (XIII) were analyzed [48] in detail with the aim of providing an answer to the questions:

Can the observed resolution behavior be rationalized from the observed crystal structures?

Can any relationship between resolving capability and crystal structure be expressed in a quantitative model?



Ephedrine



(XII); X = H

(XIII); X = Cl

Of the four salts, only the diastereomer formed from (*1R,2S*)-ephedrine and (*R*)-(XIII) was insoluble. Interestingly, the (*R*)-(XIII) salt did not exhibit the isostructural crystal packing pattern shown by the other three salts. The insoluble salt showed far more favorable van der Waals interactions as a result of more efficient packing. Apparently, the presence of the *ortho*-chloro substituent in (XIII) triggers, upon crystallization, a completely different hydrophobic packing pattern with the (*1R,2S*)-base than with (*1S,2R*)-base.

Furthermore, it was concluded that the observed [49] correlation between solubility and heat of fusion data, on the one hand, and lattice energy differences on the other, opens the way to predicting resolution efficiency (by simulation, modelling, and lattice energy calculations) in a series of related compounds. However, one cannot help feeling that these studies merely confirm, in hindsight, what was intuitively recognized, namely that the less soluble salt is the one with the higher heat of fusion and that the latter correlates with a larger number of nonbonded interactions in the crystalline state. This still does not provide the answer to the crucial question: how can the number of nonbonded interactions be predicted from a knowledge of molecular structures. Thus, an objective analysis of the current state of the art leads to the inevitable conclusion that although considerable progress has been made we are still a long way from the goal of rational design of resolutions. For the time being we shall still have to rely on our old friends, intuition and experience.

REFERENCES

1. Jacques, J., Collet, A., and Wilen, S., *Enantiomers, Racemates and Resolutions*, Wiley, New York, 1981.
2. Collet, A., in *Chiral Separations by HPLC*, Krstulovic, A.M., (Ed.), Ellis Horwood, Chichester, 1989, pp 81-104.
3. Wilen, S.H., Collet, A., and Jacques, J., *Tetrahedron*, **38**, 1-12 (1978)
4. Reinhold, D.F., Firestone, R.A., Gaines, W.A., Chmerda, J.M., and Sletzing, M., *J. Org. Chem.*, **33**, 1209-1213 (1968).

A potentially attractive route to (*R*)-carnitine would appear to be the Ru-BINAP-catalyzed asymmetric hydrogenation (see chapter 7) of 4-chloroacetoacetate ester (XVIII) which yields the (*R*)-hydroxy compound (XIX) in 97% *ee* [45]. However, to our knowledge, this route has not (yet) been commercialized. 4-Chloroacetoacetate esters can also be reduced to the corresponding (*R*)-hydroxy compound using baker's yeast [46] but enantioselectivities and productivities are substantially lower. Yet another approach is through the (*R*)-epoxy acid (XX) which has been prepared by Sharpless epoxidation of homoallyl alcohol [47] or via enzymatic resolution of the racemic acid [48]. However, both routes suffer from being too long and/or relatively low optical yields and productivities.

As mentioned earlier, many C₃ chirons, such as (*R*)-epichlorohydrin, (*S*)-glycidol, and (*R*)-isopropylidene glycerol ((*R*)-IPG), are suitable precursors for (*R*)-carnitine (Figure 9-25). However, none of these routes can compete with the Sigma Tau or Lonza routes due to the high price of the chiral synthons and/or lengthy procedure. In conclusion, (*R*)-carnitine production is dominated by routes involving classical resolution or precursor fermentation with catalytic asymmetric synthesis as a possible future contender.

VIII. CALCIUM ANTAGONIST: DILTIAZEM

The calcium antagonists are another group of highly successful antihypertensive agents having largely unrelated structures. One of these drugs, diltiazem, is included in the 'chiral top ten.' (See chapter 2, Table 2-2.) The original synthetic route, developed by Tanabe, involved late resolution by diastereomeric salt crystallization. (See chapter 7, Figure 7-30.) This route is gradually being displaced by one developed by Andeno that involves an early resolution of a common intermediate, the glycidate ester, (XXI) (Figure 9-26). The early resolution route is more economically attractive despite the fact that the maximum theoretical yield of the key step is 50%. This is more than compensated for by the overall route being 2-3 steps shorter and by avoiding the transport of isomeric ballast through the process.

ICI scientists [49] have reported an asymmetric synthesis of diltiazem in which the key step employs the osmium-catalyzed enantioselective olefin dihydroxylation pioneered by Sharpless and coworkers. (See chapter 8.) However, this route is unlikely to be competitive as it involves two additional steps starting from anisaldehyde, compared to the enzymatic route and gives material of lower optical purity (88% versus 100%) (Figure 9-27). It also suffers from the fact that it does not 'connect' very well with the established route.

A potentially attractive asymmetric synthesis route is one comprising enantioselective catalysis of Darzen's condensation. If successful, this would give the key optically active glycidate ester in 100% theoretical yield and would connect well with the established routes. Unfortunately, reported examples [50] employ stoichiometric quantities of expensive chiral auxiliaries or chiral bases and give mediocre

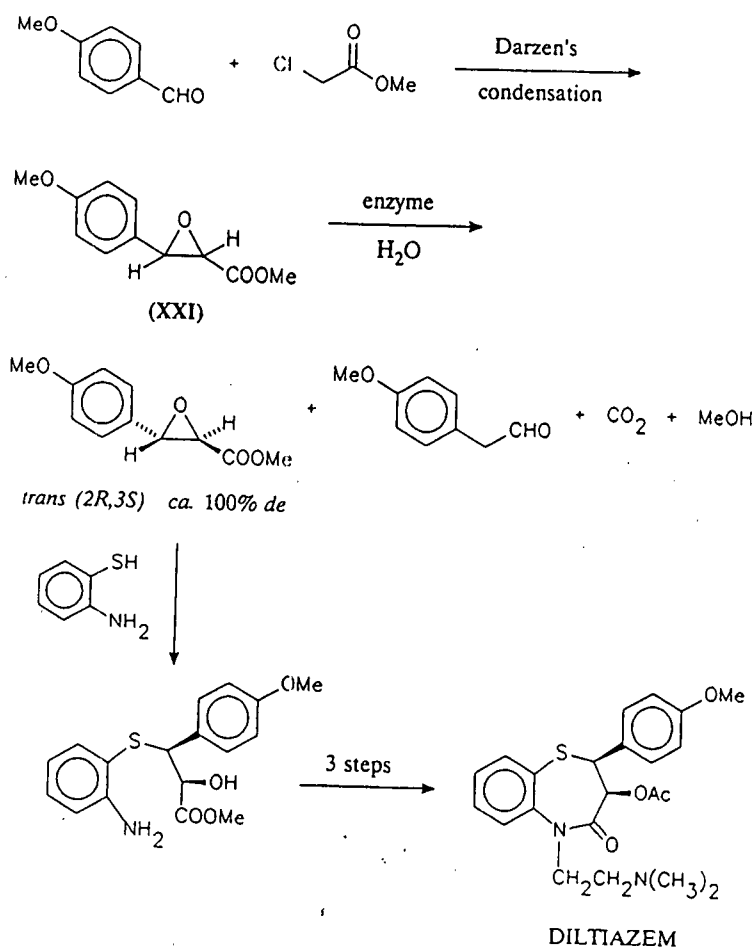


Figure 9-26. Enzymatic resolution route to diltiazem.

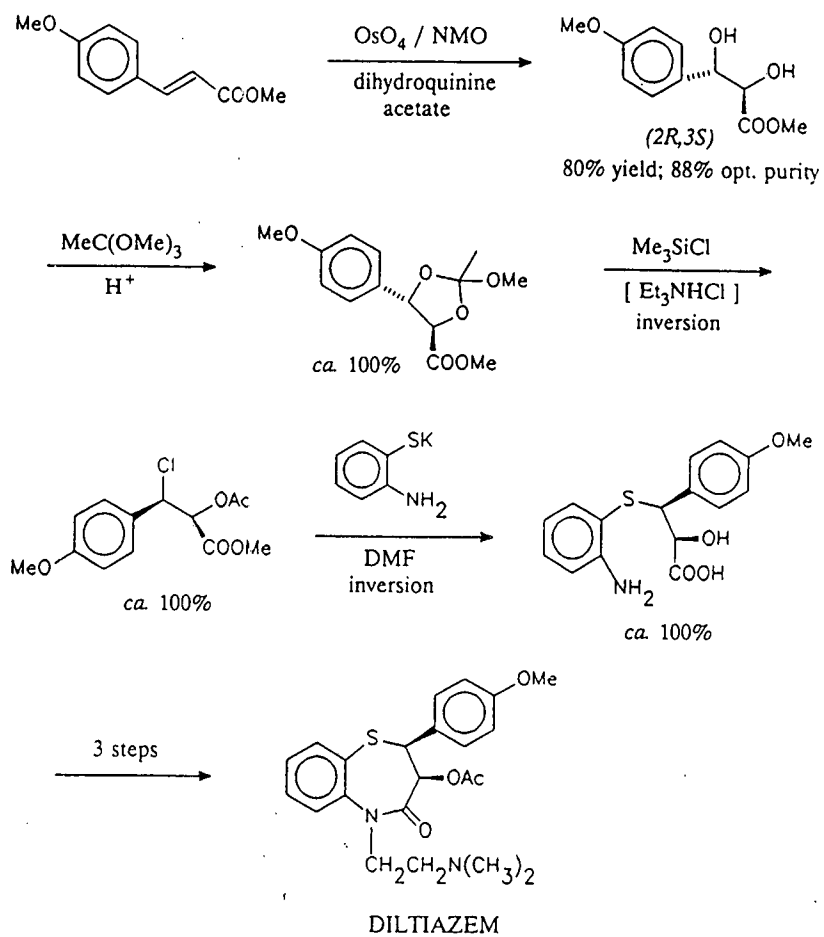


Figure 9-27. Asymmetric synthesis of diltiazem.

enantioselectivities. Nevertheless, a catalytic asymmetric Darzen's condensation remains an important synthetic challenge.

IX. BETA-LACTAM ANTIBIOTICS

The beta-lactam antibiotics account for five of the top ten drugs and are probably the single most important group of drugs. They comprise the penicillins, cephalosporins and, more recently, the penems, carbapenems, and monobactams (Figure 9-28). Penicillin G and cephalosporin C, the key raw materials for the synthesis of penicillins and cephalosporins, are produced by de novo fermentation. (See chapter 4.) They are converted by enzymatic and/or chemical transformations to 6-amino-penicillanic acid (6-APA), 7-aminocephalosporanic acid (7-ACA), and 7-amino-deacetoxycephalosporanic acid (7-ADCA). (See chapter 4).

Several of the commercially more important penicillins and cephalosporins contain D-phenylglycine or D-*p*-hydroxyphenylglycine as the acyl side-chain. (See chapter 4, Figure 4-14.) Since they are unnatural amino acids, they are not available from de novo fermentation. Interestingly, two processes compete for the manufacture of these commercially important chiral intermediates: classical resolution and enzymatic kinetic resolution. As noted in chapter 7, the hydantoinase process—a subtractive, precursor process with in situ racemization—is more economical than other enzymatic resolution methods.

In the production of D-phenylglycine (Figure 9-29) most manufacturers, such as DSM-Andeno, employ a classical resolution of the racemate which is readily available from a Strecker reaction on benzaldehyde. Kanegafuchi probably uses enzymatic resolution of the DL-hydantoin that is also prepared from benzaldehyde.

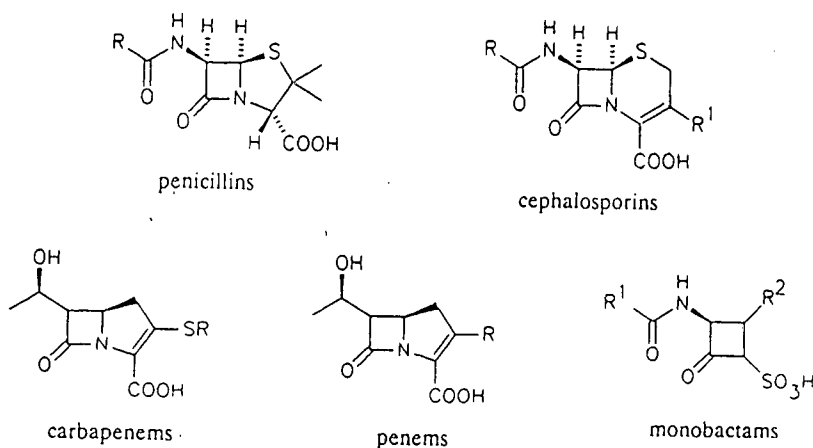


Figure 9-28. Structures of beta-lactam antibiotics.

Trade Name(s):

J: Entamide (Boots)

769

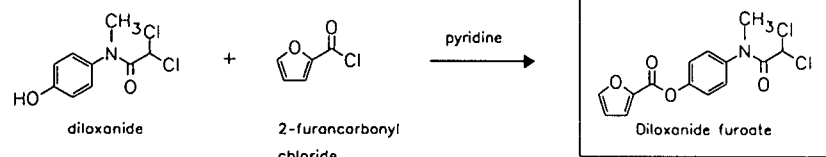
Diloxanide furoate

ATC: P01AX

Use: antiamoebic, antiprotozoal

RN: 3736-81-0 MF: $C_{14}H_{11}Cl_2NO_4$ MW: 328.15 EINECS: 223-108-1

CN: 2-furancarboxylic acid 4-[(dichloroacetyl)methylamino]phenyl ester



Reference(s):

GB 855 556 (Boots; prior. 6.5.1958, 4.6.1958, 14.4.1959).

Formulation(s): tabl. 500 mg

Trade Name(s):

GB: Furamide (Knoll)

Diltiazem

ATC: C08DB01

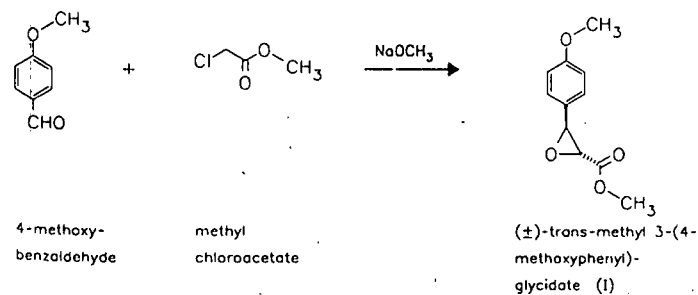
Use: coronary therapeutic (calcium antagonist)

RN: 42399-41-7 MF: $C_{22}H_{26}N_2O_4S$ MW: 414.53 EINECS: 255-796-4LD₅₀: 61 mg/kg (M, i.v.); 740 mg/kg (M, p.o.)CN: (2*S*-*cis*)-3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one

monohydrochloride

RN: 33286-22-5 MF: $C_{22}H_{26}N_2O_4S \cdot HCl$ MW: 450.99 EINECS: 251-443-3LD₅₀: 58 mg/kg (M, i.v.); 508 mg/kg (M, p.o.);

38 mg/kg (R, i.v.); 560 mg/kg (R, p.o.)



Dilevalon (Shionogi; 1989
as hydrochloride); wfm
Levadiril (Schering Corp.;
1990 as hydrochloride);
wfm

01
b: antiprotozoal

I + Oc1ccc(S)cc1[N+](=O)[O-] $\longrightarrow$ COc1ccc(cc1)C(O)C(Sc2ccccc2[N+](=O)[O-])C(=O)OC $\xrightarrow[2. \text{ L-lysine (resolution)}]{1. \text{ NaOH}}$ COc1ccc(cc1)C(O)C(Sc2ccccc2[N+](=O)[O-])C(=O)O

2-nitro-thiophenol (±)-threo form (2S,3S)- (II)

1. H_2 , Pd
2. Δ , xylene

(2S,3S)-2,3-dihydro-3-hydroxy-
2-(4-methoxyphenyl)-1,5-
benzothiazepin-4(SH)-one (III)

1. NaOH

2. 

V $\xrightarrow{\hspace{2cm}}$

2. 2-(dimethylamino)-ethyl chloride (VI)

CN(C)CCN1C(=O)OC2C(Sc3ccccc13)C(OC(=O)C)C2c4ccc(OC)cc4

Diltiozem

(b)

NC1=CC=C(S1) + COC(=O)C(O)(Cc2ccc(OC)cc2)Sc3ccccc3 $\xrightarrow{\text{NaOH}}$ NC1=CC=C(S1)C(O)(Cc2ccc(OC)cc2)C(=O)O

2-amino-
thiophenol (VII)

(±)-threo-methyl 2-hydroxy-
3-(2-aminophenylthio)-
3-(4-methoxyphenyl)-
propionate (VIII)

(±)-threo-form (IX)

IX $\xrightarrow{\alpha\text{-methylbenzylamine or cinchonidine}}$ 
(2S,3S) (X)

X $\xrightarrow{\Delta, \text{ xylene}}$ III $\xrightarrow{\begin{matrix} 1. \text{ IV, pyridine} \\ 2. \text{ NaOH} \\ 3. \text{ VI} \end{matrix}}$ Diltiazem

$$I + VII \longrightarrow VII$$

Δ, xylene, Tos-O-

lipose or protease

$\text{H}_3\text{C}-\text{O}-\text{C}_6\text{H}_4-\text{CH}_2-\text{C}-$
 $-\text{CO}_2, -\text{CH}_2\text{OH}$

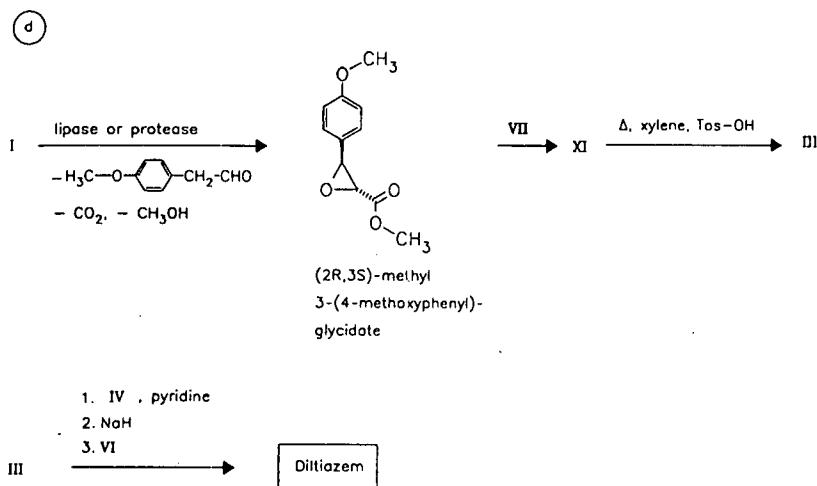
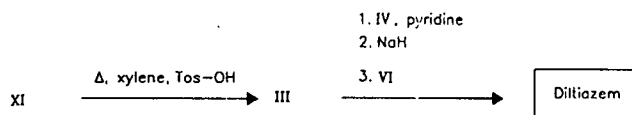
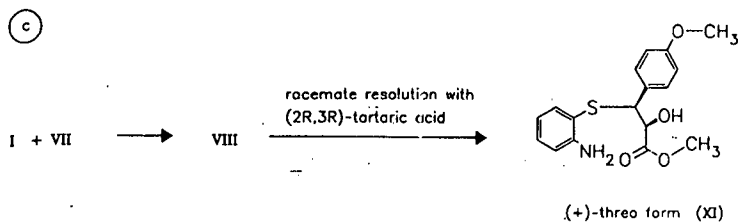
1. IV
2. NaOH
3. VI

Klugitā, H. et al.: Chem
DE 1 805 714 (Tanabe
US 3 562 257 (Tanabe
a) US 4 420 628 (Tanabe
Inoue, H. et al.: J. Ch
Inoue, H. et al.: J. Ch
b) US 4 416 819 (Tanabe
US 4 438 035 (Tanabe
c) US 5 144 025 (Zamb
EP 669 327 (Zamb
d) US 5 274 300 (Tanabe
US 5 240 000 (Tanabe
Gentile, A., Giordani
Rossy, G. et al.: P

alternative synthesis
glycidic ester via chloro-
US 5 081 240 (Sanofi-Sintabo)

enantioselective Darzens
Schwartz, A. et al.: J. C.

condensation of cyclic β .
Lohray, B.B. et al.: J. O.



Reference(s):

- Kugita, H. et al.: Chem. Pharm. Bull. (CIPBTAL) (Tokyo) **18**, 2028, 2284 (1970); **19**, 595 (1971).
 DE 1 805 714 (Tanabe; appl. 28.10.1968; J-prior. 28.10.1967, 17.6.1968).
 US 3 562 257 (Tanabe; 9.2.1971; J-prior. 28.10.1967, 17.6.1968).
 a US 4 420 628 (Tanabe Seiaiku; appl. 13.12.1983; J-prior. 27.2.1981, 22.5.1981).
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 Inoue, H. et al.: J. Chem. Soc., Perkin Trans. I (JCPRB4), **1985**, 421.
 b US 4 416 819 (Tanabe; 22.11.1983; appl. 9.7.1982).
 US 4 438 035 (Tanabe; 20.3.1984; appl. 1.12.1982; J-prior. 7.12.1981).
 c US 5 144 025 (Zambon Group S.p.A.; 1.9.1992; I-prior. 2.4.1990).
 EP 669 327 (Zambon Group A.p.A.; appl. 12.4.1990; I-prior. 13.4.1989).
 d US 5 274 300 (Sepracor; 28.12.1993; appl. 10.2.1989; prior. 26.10.1988).
 US 5 244 803 (Tanabe; 14.9.1993; appl. 7.9.1990; J-prior. 13.9.1989).
 Gentile, A.; Giordano, C.: J. Org. Chem. (JOCEAH) **57**, 6635 (1992).
 Rossy, G. et al. (Synthelabo): Manuf. Chem. (MCHMDI) **1993** (4), 20.

alternative synthesis:

glycidic ester via chlorohydrin route:

US 5 081 240 (Sanofi; 14.1.1992; F-prior. 18.7.1989).

enantioselective Darzens condensation:

Schwartz, A. et al.: J. Org. Chem. (JOCEAH) **57**, 851 (1992).

condensation of cyclic sulfite with 2-aminothiophenol:

Lohray, B.B. et al.: J. Org. Chem. (JOCEAH) **60**, 5983 (1995).

further routes:

DOS 3 337 176 (Ist Lusofarmaco; appl. 12.10.1983; I-prior. 15.10.1982).

DOS 3 415 035 (Shionogi; appl. 19.4.1984; J-prior. 21.4.1983).

EP 158 303 (Abic; appl. 5.4.1985; IL-prior. 13.4.1984).

combination with dihydropyridines:

US 4 504 476 (A. Schwartz et al.; 12.3.1985; appl. 16.9.1983).

inhalative formulation:

EP 133 252 (Gödecke AG; appl. 19.7.1984; D-prior. 20.7.1983).

slow and controlled release formulations:

EP 315 197 (Gödecke AG; appl. 4.11.1988; D-prior. 6.11.1987).

EP 318 398 (Ethypharm; appl. 25.11.1988; F-prior. 26.11.1987).

EP 320 097 (Elan Corp.; appl. 14.10.1988; IE-prior. 16.10.1987, 20.11.1987, 18.3.1988).

EP 340 105 (Sanofi; appl. 25.4.1989; F-prior. 27.4.1988).

US 4 859 470 (Alza Corp.; 22.8.1989; appl. 2.6.1988).

US 5 000 962 (Schering Corp.; 19.3.1991; appl. 25.8.1989).

Formulation(s): amp. 10 mg, 100 mg; cps. 60 mg, 90 mg, 120 mg, 180 mg, 240 mg; lyo. 25 mg; s. r. cps. 90 mg, 120 mg, 180 mg, 240 mg; s. r. tabl. 120 mg, 180 mg; tabl. 30 mg, 60 mg, 90 mg

Trade Name(s):

D:	Corazet (Mundipharma)	Mono-Tildiem (Labs. Synthélabo)	Diladel (Delalande Isnardi)
	Dilicardin (Azupharma)	Synthélabo	Dilem (Ist. Chim. Inter.)
	Dilsal (TAD)	Tildiem (Labs. Synthélabo; 1980)	Dilzené (Sigma-Tau)
	Dil-Sanorania (Sanorania)		Tildiem (Synthelabo)
	Dilta (AbZ-Pharma)	GB: Adizem XL (Napp)	Zilden (Schiapparelli)
	Diltahexal (Hexal)	Angitil SR (Trinity)	J: Clarute (Santen)
	Diltaretard (betapharm)	Britiazim (Thames)	Gadoserin (Toho)
	Dilti (ct-Arzneimittel)	Dilzem SR (Elan)	Helsibon (Tobishi)
	Diltiuc (durachemie)	Slozem (Lipha)	Herbesser (Tanabe; 1987)
	Dilzem (Gödecke; 1981)	Tildiem (Lorex; 1984)	Pazeadin (Taiyo)
	dilzereal (realpharma)	Viazem XL (Du Pont)	Tiaves (Rorer)
F:	Bi-Tildiem (Labs. Synthélabo)	I: Altiazem (Lusofarmaco; 1984)	USA: Cardizem (Hoechst Marion Roussel; 1982)
	Deltrazen (Pharmacia & Upjohn SA)	Angizem (Inverni della Beffa)	Dilacor XR (Watson)
	Diacor (Labs. Houdé)	Carzem (Rottapharm)	Tiazec (Forest)
	Dilrène (Dakota)	Citizem (CT)	

Dimazole

(Diamthazole)

ATC: D01AE17

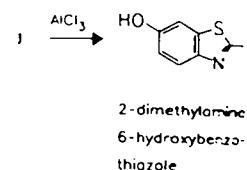
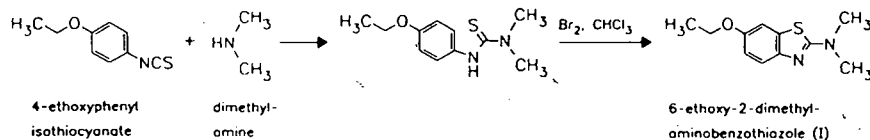
Use: antifungal

RN: 95-27-2 MF: C₁₅H₂₃N₃OS MW: 293.44 EINECS: 202-406-5

CN: 6-[2-(diethylamino)ethoxy]-N,N-dimethyl-2-benzothiazolamine

dihydrochlorideRN: 136-96-9 MF: C₁₅H₂₃N₃OS · 2HCl MW: 366.36 EINECS: 205-270-5LD₅₀: 98 mg/kg (M, i.v.); 430 mg/kg (M, p.o.);

880 mg/kg (R, p.o.)

*Reference(s):*

US 2 578 757 (Hoffman)

Formulation(s): topic*Trade Name(s):*

GB: Asterol (Roche)

I: Asterol (Roche)

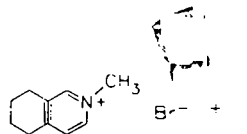
Dimemorfan

RN: 36309-01-0 MF

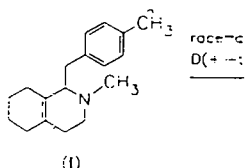
CN: (9α,13α,14α)-3.1

phosphate

RN: 40678-32-9 MF



2-methyl-5,6,7,8-tetrahydroisoquinolinium bromide

*Reference(s):*

DOS 2 128 607 (Yamaza)

Formulation(s): drops*Trade Name(s):*

I: Gentus (Gentil)

ADVANCED ORGANIC CHEMISTRY

REACTIONS,
MECHANISMS, AND
STRUCTURE

FOURTH EDITION

Jerry March

Professor of Chemistry
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This book is dedicated to the nearly 20,000 scientists whose names are listed in the Author Index, and to my wife, Beverly, and our children, Gale, David, and June

the carbonyl group, and the rate increases because moving the double bond from the 7 to the 6 position causes a change in conformation at the carbonyl group (this difference in the side chain at C-17 does not affect the rate).

Quantitative Treatments of the Effect of Structure on Reactivity¹⁵

Suppose a reaction is performed on a substrate molecule that can be represented as XGY, where Y is the site of the reaction, X a variable substituent, and G a skeleton group to which X and Y are attached, and we find that changing X from H to CH₃ results in a rate increase by a factor, say, 10. We would like to know just what part of the increase is due to each of the effects previously mentioned. The obvious way to approach such a problem is to try to find compounds in which one or two of the factors are absent or at least negligible. This is not easy to do acceptably because factors that seem negligible to one investigator do not always appear so to another. The first attempt to give numerical values was that of Hammett.¹⁶ For the cases of *m*- and *p*-XC₆H₄Y, Hammett set up the equation

$$\log \frac{k}{k_0} = \sigma \rho$$

where *k*₀ is the rate constant or equilibrium constant for X = H, *k* is the constant for the group X, *p* is a constant for a given reaction under a given set of conditions, and *σ* is a constant characteristic of the group X. The equation is called the *Hammett equation*.

The value of *p* was set at 1.00 for ionization of XC₆H₄COOH in water at 25°C. *σ_m* and *σ_p* values were then calculated for each group (for a group X, *σ* is different for the meta and para positions). Once a set of *σ* values was obtained, *p* values could be obtained for other reactions from the rates of just two X-substituted compounds, if the *σ* values of the X groups were known (in practice, at least four well-spaced values are used to calculate *p* because of experimental error and because the treatment is not exact). With the *p* value thus calculated and the known *σ* values for other groups, rates can be predicted for reactions that have not yet been run.

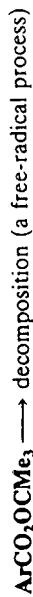
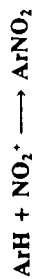
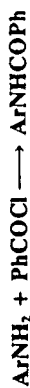
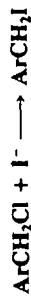
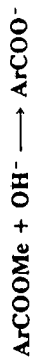
The *σ* values are numbers that sum up the total electrical effects (resonance plus field) of a group X when attached to a benzene ring. The treatment usually fails for the ortho position. The Hammett treatment has been applied to many reactions and to many functional groups and correlates quite well an enormous amount of data. Jaffé's review article¹⁶ lists *p* values for 204 reactions,¹⁷ many of which have different *p* values for different conditions.

¹⁵For monographs, see Exner *Correlation Analysis of Chemical Data*; Plenum: New York, 1968; Johnson *The Hammett Equation*; Cambridge University Press: Cambridge, 1973; Shorter *Correlation Analysis of Organic Reactivity*; Wiley: New York, 1982. *Correlation Analysis in Organic Chemistry*; Clarendon Press: Oxford, 1973; Chapman; Shorter *Correlation Analysis in Chemistry: Recent Advances*; Plenum: New York, 1978. *Advances in Linear Free Energy Relationships*; Plenum: New York, 1972; Wells *Linear Free Energy Relationships*; Academic Press: New York, 1968. For reviews, see Connors *Chemical Kinetics*; VCH: New York, 1990, pp. 311-383; Lewis, in *Bernasconi Investigation of Rates and Mechanisms of Reactions* (vol. 6 of *Weissberger Techniques of Chemistry*), 4th ed.; Wiley: New York, 1986, pp. 871-901; Hammett, Ref. 2, pp. 347-390; Jones, *Physical and Mechanistic Organic Chemistry*, 2nd ed.; Cambridge University Press: Cambridge, 1984, pp. 38-68; Charton, *CHEMTECH* 1974, 502-511, 1975, 245-255; Hine *Structural Effects in Organic Chemistry*; Wiley: New York, 1975, pp. 55-107; Alanav *ev Russ. Chem. Rev.* 1971, 40, 216-232; Laurence, Wojtkowiak *Ann. Chim. (Paris)* 1970, [14] 5, 163-191. For a historical perspective, see Grunwald *CHEMTECH* 1984, 698.

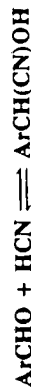
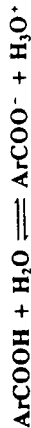
¹⁶For a review, see Jaffé *Chem. Rev.* 1953, 53, 191.

¹⁷Additional *p* values are given in Wells *Chem. Rev.* 1963, 63, 171-218 and van Bekkum; Verkade; Wepster *Recl. Trav. Chim. Pays-Bas* 1959, 78, 821-827.

Among them are reaction separate following:
Rate constants for



Equilibrium constants for



The Hammett equation has also been shown to apply to many physical measurements, including ir frequencies and nmr chemical shifts.¹⁸ The treatment is reasonably successful whether the substrates are attacked by electrophilic, nucleophilic, or free-radical reagents, the important thing being that the mechanism be the same *within* a given reaction series.

However, there are many reactions that do not fit the treatment. These are mostly reactions where the attack is directly on the ring and where the X group can enter into direct resonance interaction with the reaction site in the transition state (that is, the substrate is XY rather than XGY). For these cases, two new sets of *σ* values have been devised: *σ** values (proposed by H. C. Brown) for cases in which an electron-donating group interacts with a developing positive charge in the transition state (this includes the important case of electrophilic aromatic substitutions; see Chapter 11), and *σ⁻* values, where electron-withdrawing groups interact with a developing negative charge. Table 9.4 gives *σ*, *σ**, and *σ⁻* values for some common X groups.¹⁹ As shown in the table, *σ* is not very different from *σ** for most electron-withdrawing groups. *σ⁻* values are not shown in the table, since they are essentially the same as the *σ^m* values.

A positive value of *σ* indicates an electron-withdrawing group and a negative value an electron-donating group. The constant *p* measures the susceptibility of the reaction to electrical effects.²⁰ Reactions with a positive *p* are helped by electron-withdrawing groups and vice versa. The following *p* values for the ionization of some carboxylic acids illustrate this:²¹



¹⁸For a review of Hammett treatment of nmr chemical shifts, see Ewing, in Chapman; Shorter *Correlation Analysis in Chemistry: Recent Advances*; Plenum, New York, 1978, pp. 357-396.

¹⁹Unless otherwise noted, *σ* values are from Exner, in Chapman; Shorter, Ref. 18, pp. 439-540, and *σ** values from Okamoto; Inukai; Brown *J. Am. Chem. Soc.* 1958, 80, 4969 and Brown; Okamoto *J. Am. Chem. Soc.* 1958, 80, 4979. *σ⁻* values, except as noted, are from Jaffe, Ref. 16. Exner, pp. 439-540, has extensive tables giving values for more than 500 groups, as well as *σ*, *σ**, *σ⁻*, and *E*, values for many of these groups. Other large tables of the various sigma values are found in Hansch; Leo; Taft *Chem. Rev.* 1991, 91, 165-195. For tables of *σ*, *σ^m*, *σ⁻*, and *σ^p* values of many groups containing Si, Ge, Sn, and Pb atoms, see Egorochkin; Razuvaev *Russ. Chem. Rev.* 1987, 56, 846-858. For values for heteroaromatic groups, see Mamaev; Shkurko; Baran *Adv. Heterocycl. Chem.* 1987, 42, 1-82.

²⁰For discussions of the precise significance of *p*, see Dubois; Ruasse; Argile *J. Am. Chem. Soc.* 1984, 106, 4840; Ruasse; Argile; Dubois *J. Am. Chem. Soc.* 1984, 106, 4846; Lee; Shim; Chung; Kim; Lee *J. Chem. Soc., Perkin Trans. 2* 1988, 1919.

²¹Jones, Ref. 15, p. 42.

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TABLE 9.4 σ , σ^+ , and σ^- values for some common groups^{a,b}

Group	σ	σ^+	σ^-
O ⁻	-0.81 ³¹	-4.27 ³²	-1.15 ³²
NMe ₂	-0.63	-0.10	-1.7
NH ₂	-0.57	-0.09	-1.3
OH	-0.38 ²²	-0.13 ²²	-0.92 ²³
OMe	-0.28 ²²	0.10	-0.78
OMe ₂	-0.15	-0.09	-0.26
Me	-0.14	-0.06	-0.31
H	0	0	0
Ph	0.05 ²³	0.05	-0.18
COO-	0.11 ³¹	0.02 ³¹	-0.41 ³²
F	0.15	0.34	-0.07
Cl	0.24	0.37	0.11
Br	0.26	0.37	0.15
I	0.28 ²³	0.34	0.14
N=NPh ²⁶	0.34	0.28	0.17
COOH	0.44	0.35	0.42
COOR	0.44	0.35	0.48
COMe	0.47	0.36	0.37
CF ₃	0.53	0.46	0.57 ²⁴
NH ₃ ⁺	0.60 ³¹	0.86 ³¹	
CN ²⁷	0.70	0.62	0.66
SO ₂ Me	0.73	0.64	0.56
NO ₂	0.81	0.71	0.73 ²⁴
NMe ₂ ⁺	0.82 ²⁸	0.88 ²⁸	0.41
N ₃ ⁺	1.93 ²⁹	1.65 ²⁹	1.88 ²⁹
			1.00
			1.27
			0.36
			3 ³⁰

This example shows that the insertion of a CH₃ or a CH=CH group diminishes electrical effects to about the same extent, while a CH₂CH₂ group diminishes them much more. A ρ greater than 1 would mean that the reaction is more sensitive to electrical effects than is the ionization of XC₆H₄COOH ($\rho = 1.00$).

Similar calculations have been made for compounds with two groups X and X' on one ring, where the σ values are sometimes additive and sometimes not,³³ for other ring systems such as naphthalene³⁴ and heterocyclic rings,³⁵ and for ethylenic and acetylenic systems.³⁶

^aMasui; *Koi: Hepler Can. J. Chem.* 1974, 52, 2906.

^bDe la Mare; *Newman Tetrahedron Lett.* 1982, 1305 give this value as -1.6.

³¹Amis; *Taylor Tetrahedron Lett.* 1978, 267.

³²Sjöström; *Wold Chem. Scr.* 1976, 9, 200.

³³Byrne; *Happer; Hartshorn; Powell J. Chem. Soc., Perkin Trans. 2* 1981, 1649.

³⁴For a review of directing and activating effects of C=O, C=N, and C=S groups, see Charton, in *Paai The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 1; Wiley: New York, 1989, pp. 239-298.

³⁵For a review of directing and activating effects of CN and C≡C groups, see Charton, in *Paai: Rappoport The Chemistry of Functional Groups, Supplement C*, pt. 1; Wiley: New York, 1993, pp. 269-323.

³⁶McDaniel; *Brown J. Org. Chem.* 1958, 23, 420.

³⁷Ustyuyuk; *Subbotin; Buchnev; Gruzdeva; Kazisyna Doklady Akad. Nauk SSSR* 1976, 227, 175.

³⁸Lewis; *Johnson J. Am. Chem. Soc.* 1959, 81, 2070.

³⁹Hine; *J. Am. Chem. Soc.* 1960, 82, 4877.

⁴⁰Binev; *Kuzmanova; Kaneti; Juchovski J. Chem. Soc., Perkin Trans. 2* 1982, 1533.

⁴¹Stone; *Pearson J. Org. Chem.* 1961, 26, 257.

⁴²Bertner; *Winitov J. Am. Chem. Soc.* 1959, 81, 1630; see also Wells; *Ehrenson; Taft, Ref. 48*.

⁴³For reviews, see Charton, in *Chapman; Shorter, Ref. 18*, pp. 175-268; *To-nasik; Johnson Adv. Heterocycl. Chem.* 1976, 20, 1-64.

⁴⁴For reviews of the application of the Hammett treatment to unsaturated systems, see Ford; *Katritzky; Topson, in Chapman; Shorter, Ref. 18*, pp. 269-311; *Charton Prog. Phys. Org. Chem.* 1973, 10, 81-204.

The Hammett equation is a linear free-energy relationship (LFER). This can be demonstrated as follows for a case of equilibrium constants (for rate constants a similar demonstration can be made with $\Delta G^\ddagger$ instead of ΔG). For each reaction, where X is any group,

$$\Delta G = -RT \ln K$$

For the unsubstituted case,

$$\Delta G_0 = -RT \ln K_0$$

The Hammett equation can be rewritten

$$\log K - \log K_0 = \sigma \rho$$

so that

$$-\frac{\Delta G}{2.3RT} + \frac{\Delta G_0}{2.3RT} = \sigma \rho$$

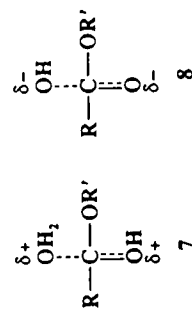
and

$$-\Delta G = \sigma \rho 2.3RT - \Delta G_0$$

For a given reaction under a given set of conditions, σ , R , T , and ΔG_0 are all constant, so that σ is linear with ΔG .

The Hammett equation is not the only LFER.³⁷ Some, like the Hammett equation, correlate structural changes in reactants, but the Grunwald-Winstein relationship (see p. 360) correlates changes in solvent and the Brønsted relation (see p. 258) relates acidity to catalysis. The Taft equation is a structure-reactivity equation that correlates only field effects.³⁸

Taft, following Ingold,³⁹ assumed that for the hydrolysis of carboxylic esters, steric and resonance effects will be the same whether the hydrolysis is catalyzed by acid or base (see the discussion of ester-hydrolysis mechanisms, reaction 0-10). Rate differences would therefore be caused only by the field effects of R and R' in RCOOR'. This is presumably a good system to use for this purpose because the transition state for acid-catalyzed hydrolysis (7) has a greater positive charge (and is hence destabilized by -I and stabilized by +I substituents) than the starting ester, while the transition state for base-catalyzed hydrolysis (8)



³⁷For a discussion of physicochemical preconditions for LFERs, see Exner *Prog. Phys. Org. Chem.* 1990, 18, 129-161.

³⁸For reviews of the separation of resonance and field effects, see Charton *Prog. Phys. Org. Chem.* 1981, 13, 119-251; *Shorter Q. Rev., Chem. Soc.* 1970, 24, 433-453; *Chem. Br.* 1969, 5, 269-274. For a review of field and inductive effects, see Reynolds *Prog. Phys. Org. Chem.* 1983, 14, 165-203. For a review of field effects on reactivity, see Grob *Angew. Chem. Int. Ed. Engl.* 1976, 15, 569-575 [*Angew. Chem.* 88, 621-627].

³⁹Ingold *J. Chem. Soc.* 1930, 1032.

⁴⁰For another set of field-effect constants, based on a different premise, see Draffehn; *Ponsold J. Prakt. Chem.* 1978, 320, 249.

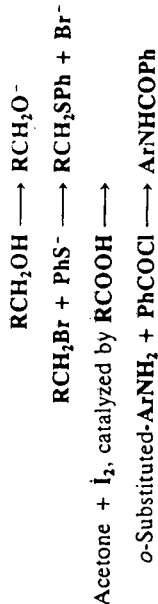
has a greater negative charge than the starting ester. Field effects of substituents X could therefore be determined by measuring the rates of acid- and base-catalyzed hydrolysis of a series 'XCH₂COOR', where R' is held constant.⁴⁵ From these rate constants, a value σ_I could be determined by the equation⁴¹

$$\sigma_I \equiv 0.181 \left[\log \left(\frac{k}{k_0} \right)_B - \log \left(\frac{k}{k_0} \right)_A \right]$$

In this equation (k/k_0)_B is the rate constant for basic hydrolysis of XCH₂COOR' divided by the rate constant for basic hydrolysis of CH₃COOR', (k/k_0)_A is the similar rate-constant ratio for acid catalysis, and 0.181 is an arbitrary constant. σ_I is a substituent constant for a group X, substituted at a saturated carbon, that reflects only field effects.⁴² Once a set of σ_I values was obtained, it was found that the equation

$$\log \frac{k}{k_0} = \rho \sigma_I$$

holds for a number of reactions, among them:⁴³



As with the Hammett equation, σ_I is constant for a given reaction under a given set of conditions. For very large groups the relationship may fail because of the presence of steric effects, which are not constant. The equation also fails when X enters into resonance with the reaction center to different extents in the initial and transition states. A list of some σ_I values is given in Table 9.5.⁴⁴ The σ_I values are about what we would expect for pure field-effect values (see p. 18) and are additive, as field effects (but not resonance or steric effects) would be expected to be. Thus, in moving a group one carbon down the chain, there is a decrease by a factor of 2.8 ± 0.5 (compare the values of R and RCH₂ in Table 9.5 for R = Ph and CH₃CO). An inspection of Table 9.5 shows that σ_I values for most groups are fairly close to the σ_m values (Table 9.4) for the same groups. This is not surprising, since σ_m values would be expected to arise almost entirely from field effects, with little contribution from resonance.

Since σ_p values represent the sum of resonance and field effects, these values can be divided into resonance and field contributions if σ_I is taken to represent the field-effect

⁴¹The symbol σ_I is also used in the literature; sometimes in place of σ_I , and sometimes to indicate only the field (not the inductive) portion of the total effect (p. 17).
⁴²There is another set of values (called σ^+ values) that are also used to correlate field effects. These are related to σ_I values by $\sigma^+ = \sigma_{\text{ArX}} = 0.45\sigma_{\text{ArX}} - \sigma_I$. We discuss only σ_I , and not σ^+ values.
⁴³Wells, Ref. 17, p. 196.
⁴⁴These values are from Bromilow; Brownlee; Lopez; Taft, Ref. 52, except that the values for NHAc, OH, and I are from Wells; Ehrenson; Taft, Ref. 48, the values for Ph and NMe₂ are from Ref. 51 and Taft; Deno; Skell, Ref. 47, and the value for CMe₃ is from Seib-Paul; de Meyer-van Duyse; Tollenaar; J. Mol. Struct. 1973, 19, 811. The values for the CH₂Ph and CH₂COCH₃ groups were calculated from σ^+ values by the formula given in footnote 42. For much larger tables of σ_I and σ_R values, see Charton, Ref. 38. See also Ref. 19 and Taylor; Wait J. Chem. Soc., Perkin Trans. 2 1966, 1765.

TABLE 9.5 σ_I and σ_R values for various groups^{a,b}

Group	σ_I	σ_R	Group	σ_I	σ_R
CMe ₃	-0.07	-0.17	OMe	0.27	-0.42
Me	-0.05	-0.13	OH	0.27	-0.44
H	0	0	I	0.39	-0.12
PhCH ₂	0.04	-0.55	CF ₃	0.42	0.08
NMe ₂ ^c	0.06	-0.10	Br	0.44	-0.16
Ph	0.10	-0.50	Cl	0.46	-0.18
CH ₂ COCH ₃	0.12	-0.50	F	0.50	-0.31
NH ₂	0.20	-0.16	CN	0.56	-0.08 ^d
CH ₃ CO	0.20	-0.16	SO ₂ Me	0.60	0.12
<COOEt>	0.20	-0.16	NO ₂	0.65	0.15
NHAc	0.26	-0.22	NMe ₃ ^e	0.86	

portion.⁴⁷ The resonance contribution σ_R ⁴⁸ is defined as

$$\sigma_R = \sigma_p - \sigma_I$$

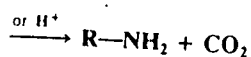
As it stands, however, this equation is not very useful because the σ_R value for a given group, which should be constant if the equation is to have any meaning, is actually not constant but depends on the nature of the reaction.⁴⁹ In this respect, the σ_I values are much better. Although they vary with solvent in some cases, σ_I values are essentially invariant throughout a wide variety of reaction series. However, it is possible to overcome⁵⁰ the problem of varying σ_R values by using a special set of σ_R values, called σ_R^0 , that measure the ability to delocalize π electrons into or out of an unperturbed or "neutral" benzene ring. Several σ_R^0 scales have been reported; the most satisfactory values are obtained from ¹³C chemical shifts of substituted benzenes.⁵¹ Table 9.5 lists some values of σ_R^0 , most of which were obtained in this way.⁵²

An equation such as

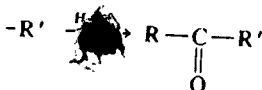
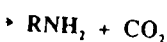
$$\log \frac{k}{k_0} = \rho_I \sigma_I + \rho_R \sigma_R^0$$

^aFor σ_R^0 values for some other NR₂ groups, see Korzhenevskaya; Titov; Chotii; Chikhuta J. Org. Chem. USSR 1987, 28, 1109.
^bAlthough we give a σ_I value for NMe₂, (and F values for three charged groups in Table 9.6), it has been shown that charged groups (called polar substituents) cannot be included with uncharged groups (dipolar substituents) in one general scale of electrical substituent effects: Marriot; Reynolds; Topson J. Org. Chem. 1985, 50, 741.
^cRoberts; Moreland J. Am. Chem. Soc. 1953, 75, 2167; Taft J. Am. Chem. Soc. 1957, 79, 1045; J. Phys. Chem. 1960, 64, 1805; Taft; Lewis J. Am. Chem. Soc. 1958, 80, 2436; Taft; Deno; Skell Annu. Rev. Phys. Chem. 1958, 9, 287-314, pp. 290-293.
^dFor reviews of the σ_I and σ_R concept as applied to benzenes and naphthalenes, respectively, see Ehrenson; Brownlee; Taft Prog. Phys. Org. Chem. 1973, 10, 1-80; Wells; Ehrenson; Taft Prog. Phys. Org. Chem. 1968, 6, 147-322. See also Taft; Topson Prog. Phys. Org. Chem. 1987, 16, 1-83; Charton Prog. Phys. Org. Chem. 1987, 16, 287-315.
^eTaft; Lewis J. Am. Chem. Soc. 1959, 81, 5343; Reynolds; Dais; MacIntyre; Topson; Marriot; von Nagy-Felsobuki; Taft J. Am. Chem. Soc. 1983, 105, 378.
^fFor a different way of overcoming this problem, see Happer; Wright J. Chem. Soc., Perkin Trans. 2 1979, 694.
^gTaft; Ehrenson; Lewis; Glick J. Am. Chem. Soc. 1959, 81, 5352.
^hBromilow; Brownlee; Lopez; Taft J. Org. Chem. 1979, 44, 4766. See also Marriot; Topson J. Chem. Soc., Perkin Trans. 2 1985, 1045.
ⁱFor a set of σ_R values for use in XY⁺ systems, see Charton Mol. Struct. Energ. 1987, 4, 271-317.

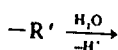
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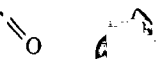
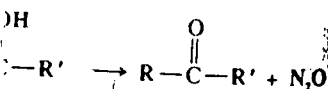
ary amines involves the hydrolysis of iso
more slowly and more vigorous conditions
or base. In this case simple addition of
d-give an N-substituted carbamic acid (3)
to carbon dioxide (or COS in the case of



can be hydrolyzed, respectively, to
bases with sulfuric acid. This is called
is do not give the reaction because
e 6-2, this reaction involves hydrolysis



OH



cases

J. Chem. Soc., Perkin Trans. 2 1985, 1111
nucleophiles, see Satchell; Satchell, C.

Methods for the Oxidation of Organic Compounds

mechanism, but with some slight differences
24, 2615. See also Sun; Folliard *Tetrahedron*

REACTION 6-5

From Jerry March

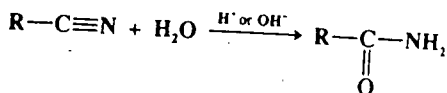
REACTIONS 1887

The conversion of nitro compounds to aldehydes or ketones has been carried out with better yields and fewer side reactions by several alternative methods. Among these are treatment of the nitro compound with aqueous $TiCl_3$,⁵⁰ cetyltrimethylammonium permanganate,⁵¹ tin complexes and $NaHSO_3$,⁵² activated dry silica gel,⁵³ or 30% $H_2O_2-K_2CO_3$,⁵⁴ and treatment of the conjugate base⁵⁵ of the nitro compound with $KMnO_4$,⁵⁶ $t-BuOOH$ and a catalyst,⁵⁷ ceric ammonium nitrate (CAN),⁵⁸ MoO_5 -pyridine-HMPA,⁵⁹ or ozone.⁶⁰

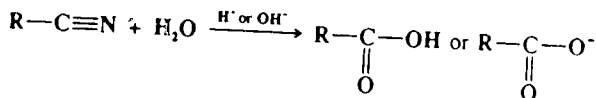
When primary nitro compounds are treated with sulfuric acid without previous conversion to the conjugate bases, they give carboxylic acids. Hydroxamic acids are intermediates and can be isolated, so that this is also a method for preparing them.⁶¹ Both the Nef reaction and the hydroxamic acid process involve the aci form; the difference in products arises from the higher acidity, e.g., a difference in sulfuric acid concentration from 2 M to 15.5 M changes the product from the aldehyde to the hydroxamic acid.⁶² The mechanism of the hydroxamic acid reaction is not known with certainty, but if higher acidity is required, it may be that the protonated aci form of the nitro compound is further protonated.

OS VI, 648; VII, 414. See also OS IV, 573.

6-5 Hydrolysis of Nitriles



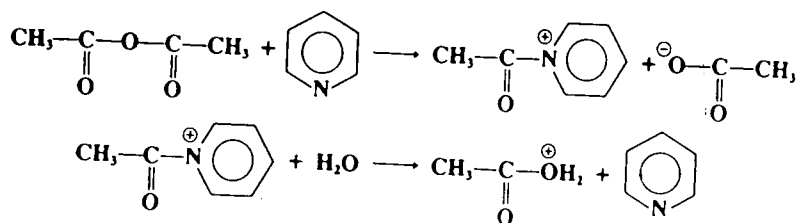
NH-Dihydro-C-oxo-biaddition



Hydroxy,oxo-de-nitrilo-tersubstitution

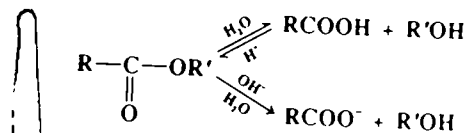
Nitriles can be hydrolyzed to give either amides or carboxylic acids.⁶³ The amide is formed initially, but since amides are also hydrolyzed with acid or basic treatment, the carboxylic acid is the more common product. When the acid is desired,⁶⁴ the reagent of choice is

- ⁶³McMurry; Melton *J. Org. Chem.* 1973, 38, 4367; McMurry *Acc. Chem. Res.* 1974, 7, 281-286, pp. 282-284. See also Kirchhoff *Tetrahedron Lett.* 1976, 2533.
- ⁶⁴Vankar; Rathore; Chandrasekaran *Synth. Commun.* 1987, 17, 195.
- ⁶⁵Upp; Villarrasa *Tetrahedron Lett.* 1970, 31, 7499.
- ⁶⁶Kobayashi; Mazur *J. Am. Chem. Soc.* 1977, 99, 3861.
- ⁶⁷Olsh; Arvanaghi; Vankar; Prakash *Synthesis* 1980, 662.
- ⁶⁸For other methods, see Barton; Motherwell; Zard *Tetrahedron Lett.* 1983, 24, 5227; Yano; Ohshima; Sutoh *J. Chem. Soc., Chem. Commun.* 1984, 695.
- ⁶⁹Schlechter; Williams *J. Org. Chem.* 1962, 27, 3699; Freeman; Yeramyan *J. Org. Chem.* 1970, 35, 2061; Freeman; Lin *J. Org. Chem.* 1971, 36, 1335; Kornblum; Erickson; Kelly; Hengeler *J. Org. Chem.* 1982, 47, 4534; Steliou; Pinnick *J. Org. Chem.* 1985, 50, 4971.
- ⁷⁰Bardet; Oreen; Webb *Tetrahedron Lett.* 1977, 331.
- ⁷¹Olsh; Gupta *Synthesis* 1980, 44.
- ⁷²Olsh; Gupta *Tetrahedron Lett.* 1981, 22, 5235.
- ⁷³McMurry; Melton; Padgett *J. Org. Chem.* 1974, 39, 259. See Williams; Unger; Moore *J. Org. Chem.* 1978, 43, 1171, for the use of singlet oxygen instead of ozone.
- ⁷⁴Hydroxamic acids can also be prepared from primary nitro compounds with SeO_2 and Et_3N ; Sosnovsky; Krogh *Synthesis* 1980, 654.
- ⁷⁵Kornblum; Brown *J. Am. Chem. Soc.* 1965, 87, 1742. See also Cundall; Locke *J. Chem. Soc. B* 1968, 98; Edward; Edwards *Can. J. Chem.* 1971, 49, 3483, 3489, 3493.
- ⁷⁶For reviews, see Zil'berman *Russ. Chem. Rev.* 1984, 53, 900-912; Compagnon; Mueque *Ann. Chim. (Paris)* 1976, [14] 5, 11-22, 23-37.
- ⁷⁷For a list of reagents, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, p. 973.



Many other nucleophiles similarly catalyze the reaction.
OS I, 408; II, 140, 368, 382; IV, 766; V, 8, 813.

0-10 Hydrolysis of Carboxylic Esters (Hydroxy-de-alkoxylation)



Ester hydrolysis is usually catalyzed by acids or bases. Since OR is a much poorer leaving group than halide or OCOR, water alone does not hydrolyze most esters. When H^+ catalyzes the reaction, the attacking species is the more powerful nucleophile OH^- . This reaction is called *saponification* and gives the salt of the acid. Acids catalyze the reaction by making the carbonyl carbon more positive and therefore more susceptible to attack by the nucleophile. Both reactions are equilibrium reactions, so they are practicable only when there is a way of shifting the equilibrium to the right. Since formation of the salt does just this, ester hydrolysis is almost always done for preparative purposes in basic solution, unless the compound is base-sensitive. Ester hydrolysis can also be catalyzed⁵⁰⁸ by metal ions, by cyclodextrins,⁵⁰⁹ by enzymes,⁵¹⁰ and by nucleophiles (see 0-9).¹⁹⁷ Among other compounds used to cleave carboxylic esters have been methanesulfonic acid,⁵¹¹ guanidine,⁵¹² Dowex-50,⁵¹³ Me_3SiI ,⁵¹⁴ $\text{MeSiCl}_2\text{-NaI}$,⁵¹⁵ and KOSiMe_3 .⁵¹⁶ Phenolic esters can be similarly cleaved; in fact the reaction is usually faster for these compounds.⁵¹⁷ Lactones also undergo the reaction⁵¹⁸ (though if the lactone is five- or six-membered, the hydroxy acid often spontaneously relactonizes) and thiol esters (RCOSR') give thiols $\text{R}'\text{SH}$. Sterically hindered esters are hydrolyzed with difficulty (p. 340), though this can be accomplished at room temperature with "anhydrous hydroxide," generated via the reaction of 2 moles of *t*-BuOK with 1 mole

⁵⁰⁸For a list of catalysts and reagents that have been used to convert carboxylic esters to acids, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 981-985.

⁵⁰⁹See Bender; Komiyama *Cyclodextrin Chemistry*; Springer: New York, 1978, pp. 34-41. The mechanism is shown in Saenger *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 344-362 [*Angew. Chem.* **92**, 343-361].

⁵¹⁰For reviews of ester hydrolysis catalyzed by pig liver esterase, see Zhu; Tedford *Tetrahedron* **1990**, *46*, 655-661; Ohno; Otsuka *Org. React.* **1989**, *37*, 1-55. For reviews of enzymes as catalysts in synthetic organic chemistry, see Wong *Chemtrics: Org. Chem.* **1990**, *3*, 91-111, *Science* **1989**, *244*, 1145-1152. Whitesides; Wong *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 617-638 [*Angew. Chem.* **97**, 617-638].

⁵¹¹Loevy *Chem. Ind. (London)* **1964**, 193.

⁵¹²Kunesch; Miet; Poisson *Tetrahedron Lett.* **1987**, *28*, 3569.

⁵¹³Basu; Sarkar; Ranu *Synth. Commun.* **1989**, *19*, 627.

⁵¹⁴Ho; Olah *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 774 [*Angew. Chem.* **88**, 847]; Jung; Lyster *J. Am. Chem. Soc.* **1977**, *99*, 968. For a review of this reagent, see Olah; Narang *Tetrahedron* **1982**, *38*, 2225-2277.

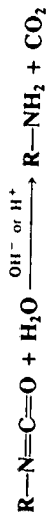
⁵¹⁵Olah; Husain; Singh; Mehrotra *J. Org. Chem.* **1983**, *48*, 3667.

⁵¹⁶Laganis; Chenard *Tetrahedron Lett.* **1984**, *25*, 5831.

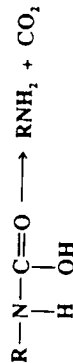
⁵¹⁷For a method of hydrolyzing phenolic esters in the presence of other esters, see Blay; Cardona; Garcia; Pedro *Synthesis* **1989**, 438.

⁵¹⁸For a review of the mechanisms of lactone hydrolysis, see Kaiser; Kozdy *Prog. Bioorg. Chem.* **1976**, *2*, 239-267, pp. 254-265.

6-3 Hydrolysis of Isocyanates and Isothiocyanates Oxo-de-alkylimino-bisubstitution

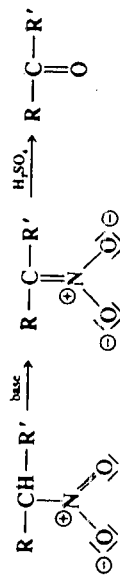


A common method for the preparation of primary amines involves the hydrolysis of isocyanates or isothiocyanates.⁴⁶ The latter react more slowly and more vigorous conditions are required. The reaction is catalyzed by acids or bases. In this case simple addition of water to the carbon-nitrogen double bond would give an N-substituted carbamic acid (3). Such compounds are unstable and break down to carbon dioxide (or COS in the case of isothiocyanates) and the amine:

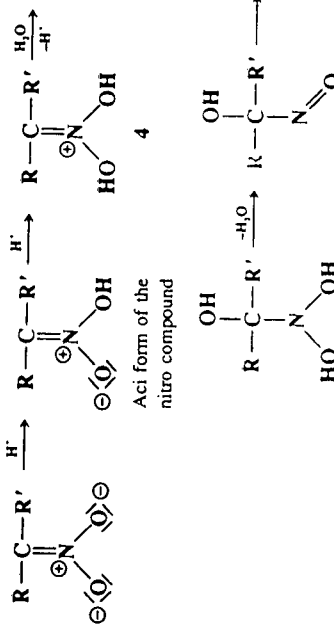


OS II, 24; IV, 819; V, 273; VI, 910.

6-4 Hydrolysis of Aliphatic Nitro Compounds Oxo-de-hydro,nitro-bisubstitution



Primary or secondary aliphatic nitro compounds can be hydrolyzed, respectively, to aldehydes or ketones, by treatment of their conjugate bases with sulfuric acid. This is called the *Nef reaction*.⁴⁷ Tertiary aliphatic nitro compounds do not give the reaction because they cannot be converted to their conjugate bases. Like 6-2, this reaction involves hydrolysis of a C=N double bond. A possible mechanism is:⁴⁸



Intermediates of type 4 have been isolated in some cases.⁴⁹

⁴⁶For a study of the mechanism, see Castro; Moodie; Sansom *J. Chem. Soc., Perkin Trans. 2* 1965, 737. For a review of the mechanisms of reactions of isocyanates with various nucleophiles, see Satchell; Satchell *Chem. Soc. Rev.* 1975, 4, 231-250.

⁴⁷For reviews, see Pinnick *Org. React.* 1990, 38, 655-792; Haines *Methods for the Oxidation of Organic Compounds*; Academic Press: New York, 1980, pp. 220-231, 416-419.

⁴⁸Hawthorne *J. Am. Chem. Soc.* 1957, 79, 2510. A similar mechanism, but with some slight differences, was suggested earlier by van Tamelen; Thiede *J. Am. Chem. Soc.* 1952, 74, 2615. See also Sun; Fullard *Tetrahedron* 1971, 27, 323.

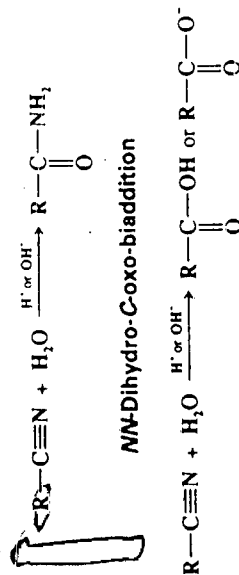
⁴⁹Fuerr; Spinicelli *J. Org. Chem.* 1977, 42, 2191.

The conversion of nitro compounds to aldehydes or ketones has been carried out with better yields and fewer side reactions than several alternative methods. Among these are treatment of the nitro compound with aqueous TiCl_3 ,⁵⁰ cetyltrimethylammonium permanganate,⁵¹ tin complexes and NaHSO_3 ,⁵² activated dry silica gel,⁵³ or 30% H_2O_2 - K_2CO_3 ,⁵⁴ and treatment of the conjugate base⁵⁵ of the nitro compound with KMnO_4 ,⁵⁶ *t*-BuOOH and a catalyst,⁵⁷ ceric ammonium nitrate (CAN),⁵⁸ MoO_5 -pyridine-HMPA,⁵⁹ or ozone.⁶⁰

When primary nitro compounds are treated with sulfuric acid without previous conversion to the conjugate bases, they give carboxylic acids. Hydroxamic acids are intermediates and can be isolated, so that this is also a method for preparing them.⁶¹ Both the Nef reaction and the hydroxamic acid process involve the aci form; the difference in products arises from higher acidity, e.g., a difference in sulfuric acid concentration from 2 *M* to 15.5 *M* changes the product from the aldehyde to the hydroxamic acid.⁶² The mechanism of the hydroxamic acid reaction is not known with certainty, but if higher acidity is required, it may be that the protonated aci form of the nitro compound is further protonated.

OS VI, 648; VII, 414. See also OS IV, 573.

6-5 Hydrolysis of Nitriles



Hydroxy,oxo-de-nitrilo-tersubstitution

Nitriles can be hydrolyzed to give either amides or carboxylic acids.⁶³ The amide is formed initially, but since amides are also hydrolyzed with acid or basic treatment, the carboxylic acid is the more common product. When the acid is desired,⁶⁴ the reagent of choice is

⁵⁰McMurry; Melton *J. Org. Chem.* 1973, 38, 4367; McMurry *Acc. Chem. Res.* 1974, 7, 281-286, pp. 282-284. See also Kirchhoff *Tetrahedron Lett.* 1976, 2533.

⁵¹Vankar; Rathore; Chandrasekaran *Synth. Commun.* 1987, 17, 195.

⁵²Uppil; Villarrasa *Tetrahedron Lett.* 1990, 31, 7499.

⁵³Keenan; Mazur *J. Am. Chem. Soc.* 1977, 99, 3861.

⁵⁴Olah; Arvanaghi; Vankar; Prakash *Synthesis* 1980, 662.

⁵⁵For other methods, see Barton; Motherwell; Zard *Tetrahedron Lett.* 1983, 24, 5227; Yano; Ohshima; Sutoh *J. Chem. Soc., Chem. Commun.* 1984, 695.

⁵⁶Spechter; Williams *J. Org. Chem.* 1962, 27, 3699; Freeman; Yeramyam *J. Org. Chem.* 1970, 35, 2061; Freeman; Lin *J. Org. Chem.* 1971, 36, 1335; Kornblum; Erickson; Kelly; Hengeler *J. Org. Chem.* 1982, 47, 4534; Steliou; Poupard *J. Org. Chem.* 1985, 50, 4971.

⁵⁷Bartlett; Green; Webb *Tetrahedron Lett.* 1977, 331.

⁵⁸Olah; Gupta *Synthesis* 1980, 44.

⁵⁹Galabardes; Pinnick *Tetrahedron Lett.* 1981, 22, 5235.

⁶⁰McMurry; Melton; Padgett *J. Org. Chem.* 1974, 39, 259. See Williams; Unger; Moore *J. Org. Chem.* 1978, 43, 1271, for the use of singlet oxygen instead of ozone.

⁶¹Hydroxamic acids can also be prepared from primary nitro compounds with SeO_2 and Et_3N ; Sosnovsky; Krogh *Synthesis* 1980, 654.

⁶²Kornblum; Brown *J. Am. Chem. Soc.* 1965, 87, 1742. See also Cundall; Locke *J. Chem. Soc. B* 1968, 98; Edward; Tremaine *Can. J. Chem.* 1971, 49, 3483, 3489, 3493.

⁶³For reviews, see Zilberman *Russ. Chem. Rev.* 1984, 53, 900-912; Compagnon; Miocque *Ann. Chim. (Paris)* 1979, [14] 5, 11-22, 23-37.

⁶⁴For a list of reagents, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, p. 993.

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l to a 1-l. beaker. After aqueous phase is acidified, the layers are separated and the 75-ml. portions of ether. washed with 100 ml. of cesium sulfate. The low-pressure at atmospheric pressure produced through a 1-5 g. forerun, the product (Note 4). The yield is 66-

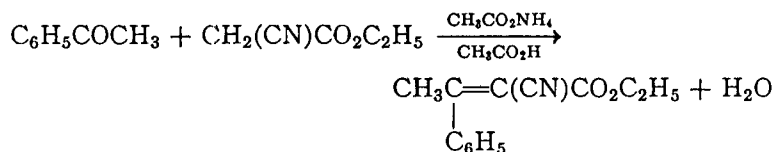
¹ University of Pennsylvania, Philadelphia, Pennsylvania.

² *Org. Syn. Coll. Vol. 2*, 1955 (1943).

³ Wallingford, Jones, and Homeyer, *J. Am. Chem. Soc.*, **64**, 576 (1942); Testa, Fontanella, Christiani, and Fava, *Ann.*, **614**, 158 (1958).

ETHYL (1-PHENYLETHYLIDENE)CYANOACETATE

(Cinnamic acid, α -cyano- β -methyl-, ethyl ester)



Submitted by S. M. McELVAIN and DAVID H. CLEMENS.¹

Checked by W. E. PARHAM, PERRY W. KIRKLIN, JR., and WAYLAND E. NOLAND.

1. Procedure

In a 1-l. three-necked round-bottomed flask fitted with a Hershberg stirrer and a constant water separator (Note 1) surmounted by a reflux condenser are placed 120 g. (1 mole) of acetophenone, 113 g. (1 mole) of ethyl cyanoacetate (Note 2), 15.4 g. (0.2 mole) of ammonium acetate, 48.0 g. (0.8 mole) of glacial acetic acid, and 200 ml. of benzene. The reaction mixture is stirred and heated under reflux for 9 hours during which time 28-33 ml. of lower layer is collected in the water separator (Note 3). To the cooled reaction mixture is added 100 ml. of benzene, and the whole is extracted with three 100-ml. portions of water. The combined aqueous layers are extracted with 30 ml. of benzene, which is then added to the organic layer from the previous extraction. Anhydrous magnesium sulfate (15 g.) is added, and, after swirling occasionally for 10 minutes, the mixture is filtered by suction and the magnesium sulfate washed with two 25-ml. portions of benzene. The benzene is removed by distillation at reduced pressure and the residual oil distilled rapidly through a 15-cm. column. The yield of ester is 113-125 g. (52-58%), b.p. 135-160° (0.35 mm.) (Note 4).

dependent upon the quality could be dried before use,² heated to a temperature at which it can be transferred, but in the flask in which it is

should be distilled before use. tried by distillation.

dium oxide, together with reaction, is removed during the oxylation reaction can. During the first half of the reaction, the temperature rises at a vapor temperature of completion and the ethyl 110-115°. Near the end of the reaction, ethyl phenylcyanoacetate ap-

129-131°/3 mm., 145-147°/0.5 mm., colorless liquid, n_D^{25} 1.5012.

ration

method of Wallingford, et al. for the preparation of ethyl phenylacetate. This compound.

2. Notes

1. A typical water separator has been described by Cope et al.²

2. Eastman Kodak white label grade acetophenone and ethyl cyanoacetate are used without further purification. The checkers used Matheson, Coleman, and Bell acetophenone and ethyl cyanoacetate without further purification.

3. The checkers used ammonium acetate which was slightly moist; consequently 33.5–34.5 ml. of lower layer was collected.

4. The checkers report the refractive index of the product to be $n_D^{25.1}$ 1.5468–1.5469.

3. Methods of Preparation

The above procedure is essentially that described by Cope et al.² Ethyl (1-phenylethylidene)cyanoacetate has been prepared also by condensing acetophenone with ethyl cyanoacetate in the presence of zinc chloride and aniline,³ and other catalysts.⁴ Additional aralkylidenecyano esters have been prepared by the present procedure.⁵

¹ University of Wisconsin, Madison, Wisconsin.

² Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

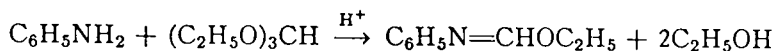
³ Scheiber and Meisel, *Ber.*, **48**, 238 (1915).

⁴ Cragoe, Robb, and Sprague, *J. Org. Chem.*, **15**, 381 (1950).

⁵ McElvain and Clemens, *J. Am. Chem. Soc.*, **80**, 3915 (1958).

ETHYL N-PHENYLFORMIMIDATE

(Formimidic acid, N-phenyl-, ethyl ester)



Submitted by ROYSTON M. ROBERTS and PAUL J. VOGT.¹

Checked by T. L. CAIRNS and J. J. DRYSDALE.

1. Procedure

A 500-ml. flask is equipped with a capillary through a side opening, and 94 g. (1.01 moles) of aniline and 1 ml. of concen-

trated hydrochloric acid column is attached (N acid is removed by boiling the water has distilled cooled to room temperature formate is added. The 2) is distilled as it is 116 ml.) is obtained in

The reaction mixture is lowered to 40 formate is distilled at a fraction of about 4 g., at 117–118°/40 mm. (1 is 118–127 g. (78–84%) and is mainly N,N'-dip

1. A Vigreux column to separate the volatile components was used. Heat was applied with a glass of excess ethyl orth

2. A small amount (5 comes over before the produced by hydrolysis

3. A pressure regulator with a water aspirator.

4. If several runs are used as starting material initial formation of subsequent reaction with e

3. M

Ethyl N-phenylformimidate and ethyl formate.³ This

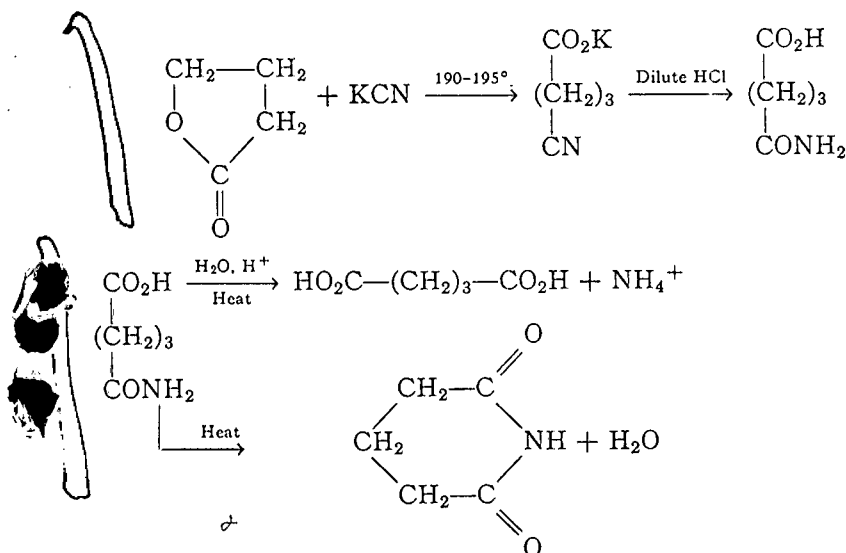
⁵ Farbenfabriken Bayer A.-G., Ger. pat. 908,023 [C. A., 52, 10201 (1958)]; Arita and Odawara (to Asahi Chemical Industries Co.), Jap. pat. 1130 (1950) [C. A., 47, 2214 (1953)].

⁶ Kuwada et al. (to Nippon Petroleum Oil Co.), Jap. pat. 3730 (1951) [C. A., 47, 8096 (1953)].

⁷ Terai et al. (to Noguchi Research Institute, Inc.), Jap. pat. 1111 (1951) [C. A., 47, 3883 (1953)].

GLUTARIC ACID* AND GLUTARIMIDE

1. FROM γ -BUTYROLACTONE



Submitted by G. PARIS, L. BERLINGUET, and R. GAUDRY.¹

Checked by JAMES CASON and EDWIN R. HARRIS.

1. Procedure

Caution! This preparation should be carried out in a good hood since poisonous hydrogen cyanide may be evolved.

In a 500-ml. three-necked flask fitted with a sealed mechanical stirrer and a reflux condenser are placed 86 g. (1 mole) of γ -butyrolactone (Note 1) and 72 g. (1.1 moles) of potassium cyanide (Note 2). As the contents of the flask are stirred, the mixture is heated in an oil bath for 2 hours at a temperature of 190–195° (Note 3). There is an initial

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Q
GLUT/

vigorous reaction which during the heating period the mixture of the salt of the cyano acid in a warm solution is cautiously added about 90 ml. of concentrated hydrochloric acid, which contains glutaric acid. This mixture is used to prepare glutaric acid.

A. *Glutaric acid.* The mixture is concentrated by distilling off the excess of concentrated hydrochloric acid in the hood for 1 hour. The solid is broken up, ground to dryness under reduced pressure, and then portions of boiling chloroform are added by gravity through a filter. The filtrate is treated to about 400 ml. of concentrated hydrochloric acid for effect crystallization, then washed with cold chloroform. The colored glutaric acid, 83.5%, m.p. 95–97°.

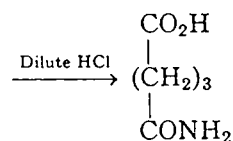
If a pure grade of glutaric acid for about 1 hour with charcoal is removed by filtration under reduced pressure, and then dried. The yield of white glutaric acid is 83.5%.

B. *Glutarimide.* The mixture is concentrated by distilling off the excess of concentrated hydrochloric acid in the hood for 1 hour. The solid is broken up, ground to dryness under reduced pressure, and then portions of boiling chloroform are added by gravity through a filter. The filtrate is treated to about 400 ml. of concentrated hydrochloric acid for effect crystallization, then washed with cold chloroform. The colored glutaric acid, 83.5%, m.p. 95–97°.

. A., 52, 10201 (1958)); Arita
 ap. pat. 1130 (1950) [C. A.,
 . pat. 3730 (1951) [C. A., 47,
 Jap. pat. 1111 (1951) [C. A.,

GLUTARIMIDE

GLUTARIC ACID



NH₄⁺

H₂O

BERLINGUET, and R. GAUDRY.¹
 and EDWIN R. HARRIS.

ried out in a good hood since

a sealed mechanical stirrer
 mole) of γ -butyrolactone
 cyanide (Note 2). As the
 re is heated in an oil bath
 Note 3). There is an initial

vigorous reaction which soon subsides. After the completion of the heating period the mixture is cooled to about 100°, and the potassium salt of the cyano acid is dissolved in about 200 ml. of hot water. The warm solution is cautiously acidified to Congo red by the addition of about 90 ml. of concentrated hydrochloric acid. The resultant solution, which contains glutaric acid monoamide and potassium chloride, is used to prepare glutaric acid or glutarimide.

A. *Glutaric acid*. To the solution of monoamide is added 200 ml. of concentrated hydrochloric acid, and the mixture is heated under reflux in the hood for 1 hour. The reaction mixture is evaporated to dryness under reduced pressure, and the residue is dried by brief heating on a steam bath at reduced pressure. The residual crystalline solid is broken up, ground in a mortar, and extracted with four 200-ml. portions of boiling chloroform. The combined hot extracts are filtered by gravity through a fluted paper on a heated funnel and then concentrated to about 400 ml. After the solution has been cooled in water to effect crystallization, the glutaric acid is collected by suction filtration, washed with cold chloroform, and dried. The yield of slightly discolored glutaric acid, suitable for many purposes, is 105–110 g. (79.5–83.5%), m.p. 95–97°.

If a pure grade of glutaric acid is desired, it is decolorized by boiling for about 1 hour with 10 g. of charcoal in water solution. The charcoal is removed by filtration (Note 4), the water is evaporated under reduced pressure, and the dry residue is recrystallized from chloroform. The yield of white glutaric acid, m.p. 98–99°, is 94–99 g. (71–75%).

B. *Glutarimide*. The solution containing the monoamide is extracted with six 50-ml. portions of ether. The ether solution is dried over anhydrous sodium sulfate (or by filtering by gravity through a layer of the drying agent), and then the ether is evaporated by heating on a steam bath; the last portion is removed at reduced pressure. The oily residue of glutaric acid monoamide is placed in a 300-ml. round-bottomed flask which is fitted with a bent tube attached to a short condenser, and the flask is immersed in a bath (Note 5) held at 220–225°. Heating is continued until water no longer distills (3–4 hours). The cooled glutarimide is dissolved in about 200 ml. of water, and the solution is boiled for about 30 minutes with about 2 g. of charcoal. The charcoal is removed by filtration, water is removed by distillation at reduced pressure, and the dry residue is crystallized from about 125 ml. of 95% ethanol, with final cooling in an ice bath. The

yield of glittering white crystals of glutarimide, m.p. 152–154°, is 65.5–73.5 g. (58–65%) (Note 6).

2. Notes

1. Butyrolactone from Eastern Chemical Corporation, 34 Spring Street, Newark 2, New Jersey, was used without purification.

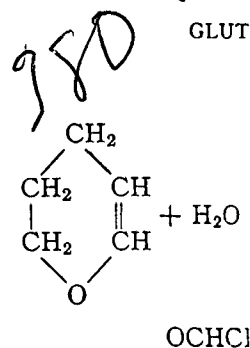
2. Satisfactory results were obtained with potassium cyanide, 96–98% purity, from General Chemical Company or with material indicated as of 95% minimum purity, from Merck & Co., Inc. If potassium cyanide pellets are employed, they should be pulverized before use.

3. Since the reaction mixture is acidified after the heating period, it is most convenient to carry out the reaction in a forced-draft hood in order to provide protection against hydrogen cyanide. If higher temperatures than those specified are used, the reaction may get out of control during the initial vigorous reaction.

4. If filtration by gravity through a fluted paper fails to remove the last traces of charcoal, the filtrate should be refiltered by suction through a thin mat of filter aid such as Supercel.

5. The submitters used an oil bath. The checkers used a salt bath consisting of an equimolar mixture of potassium nitrate and sodium nitrite (Heat Transfer Salt). A salt bath should be handled only with proper precautions, which include wearing goggles and gloves and supporting the bath on a stand bolted to the bench.

6. This material is suitable for preparation of N-bromoglutarimide, as follows. In a 1-l. beaker, provided with a mechanical stirrer, 65 g. of potassium hydroxide is dissolved in 200 ml. of water. The vigorously stirred solution is cooled to about -5° , and as the temperature is maintained below 0° there is added gradually 113 g. (1 mole) of glutarimide and cracked ice. To this mixture is added in one portion 160 g. (1 mole) of bromine; then stirring is continued for 1 minute. The mixture is filtered by suction, and the precipitate is dissolved in hot water. On cooling, there crystallizes about 94 g. (49%) of N-bromoglutarimide which melts at about 165° . This product is usually suitable for use as a brominating agent. Pure N-bromoglutarimide, m.p. 180–185°, is obtained only after several recrystallizations from water.



In a 1-l. round-bottom flask are placed 400 ml. of acid, sp. gr. 1.42, and dihydropyran (Note 1) or a boiling water bath. After 25 to 40 minutes the dissolution is complete for an additional 10 minutes.

While the hydrolysis is in progress, 575 ml., 9.25 m. is placed in a 2-l. flask in a well-ventilated hood with an efficient stirrer, separator, and thermometer. When the g. of sodium nitrite of it has dissolved;

The solution obtained is placed in the separator. A nitric acid solution (10% solution of brown nitric acid), the addition of water to be held below 3 hours (Notes 3 and 4) a blue-green solution.

Pharmaceutical Substances

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A-M

Axel Kleemann and
Jürgen Engel

Bernhard Kutscher and
Dietmar Reichert

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Advanced Organic Chemistry

FOURTH
EDITION

Part A: Structure and Mechanisms

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and RICHARD J. SUNDBERG

*University of Virginia
Charlottesville, Virginia*

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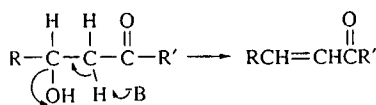
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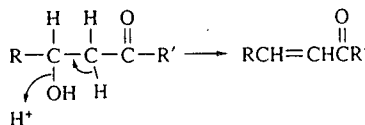
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Under both basic and acidic conditions, the aldol adduct can proceed to dehydrated product.

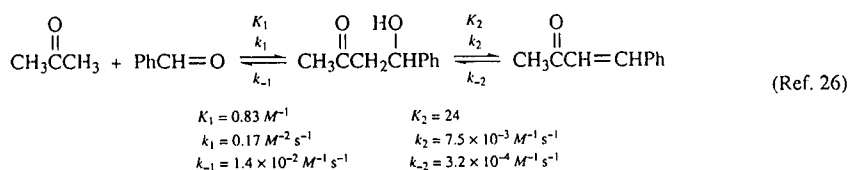


base-catalyzed dehydration



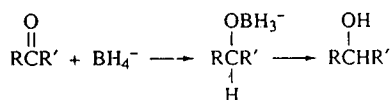
acid-catalyzed dehydration

The dehydration reactions have somewhat higher activation energies than the addition step and are not usually observed under strictly controlled kinetic conditions. Detailed kinetic studies have provided rate and equilibrium constants for the individual steps in some cases. The results for the acetone-benzaldehyde system in the presence of hydroxide ion are given below. Note that K_2 is sufficiently large to drive the first equilibrium forward.



8.4. Reactivity of Carbonyl Compounds toward Addition

We would like at this point to consider some general relationships concerning the reactivity of carbonyl compounds toward addition of nucleophiles. The discussion in Sections 8.2 and 8.3 indicates that many factors influence the overall rate of a reaction under typical conditions. Among the crucial factors are (1) the role of protons or other Lewis acids in activating the carbonyl group toward nucleophilic attack, (2) the reactivity of the nucleophilic species and its influence on the mechanism which is followed, and (3) the stability of the tetrahedral intermediate and the extent to which it proceeds to product rather than reverting to starting material. Because consideration of all of these factors complicates the interpretation of the inherent reactivity of the carbonyl compound itself, examination of an irreversible process where the addition product is stable is the most direct means of comparing the reactivity of carbonyl compounds. Under these conditions, the relative rates of reaction of different carbonyl compounds can be directly compared. One such reaction is hydride reduction. In particular, reduction by sodium borohydride in alcohol solvents is a fast, irreversible reaction that has provided a convenient basis for comparing the reactivity of different carbonyl compounds.²⁷



26. J. P. Guthrie, J. Cossar, and K. F. Taylor, *Can. J. Chem.* **62**:1958 (1984).

27. H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron* **1**:214 (1957); H. C. Brown and K. Ichikawa, *Tetrahedron* **1**:221 (1957).

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**Table 8.3. Rates of Reduction of Aldehydes and Ketones
by Sodium Borohydride**

Carbonyl compound	$k_2 \times 10^4 (M^{-1} s^{-1})^a$
Benzaldehyde	12,400 ^b
Benzophenone	1.9
Acetophenone	2.0
Acetone	15.1
Cyclobutanone	264
Cyclopentanone	7
Cyclohexanone	161

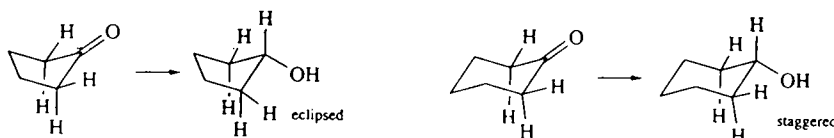
a. In isopropyl alcohol at 0°C.

b. Extrapolated from data at lower temperatures.

The reaction is second-order overall, with the rate given by $k[R_2C=O][NaBH_4]$. The interpretation of the rate data is complicated slightly by the fact that the alkoxyborohydrides produced by the first addition can also function as reducing agents, but this has little apparent effect on the relative reactivity of the carbonyl compounds. Table 8.3 presents some of the rate data obtained from these studies.

Reductions by $NaBH_4$ are characterized by low enthalpies of activation (8–13 kcal/mol) and large negative entropies of activation (–28 to –40 eu). Aldehydes are substantially more reactive than ketones, as can be seen by comparison of the rate data for benzaldehyde and acetophenone. This relative reactivity is characteristic of nearly all carbonyl addition reactions. The reduced reactivity of ketones is attributed primarily to steric effects. Not only does the additional substituent increase the steric restrictions to approach of the nucleophile, but it also causes larger steric interaction in the tetrahedral product as the hybridization changes from trigonal to tetrahedral.

Among the cyclic ketones, the reactivity of cyclobutanone is enhanced because the strain of the four-membered ring is decreased in going from sp^2 to sp^3 hybridization. The higher reactivity of cyclohexanone as compared to cyclopentanone is quite general for carbonyl addition reactions. The major factor responsible for the difference in this case is the change in torsional strain as addition occurs. As the hybridization goes from sp^2 to sp^3 , the torsional strain is increased in cyclopentanone. The opposite is true for cyclohexanone. The equatorial hydrogens are nearly eclipsed with the carbonyl oxygen in cyclohexanone, but the chair structure of the addition product allows all bonds to attain staggered arrangements.



The borohydride reduction rate data are paralleled by the rate data for many other carbonyl addition reactions. In fact, for a series of ketones, most of which are cyclic, a linear free-energy correlation of the form

$$\log k = A \log k_0 + B$$

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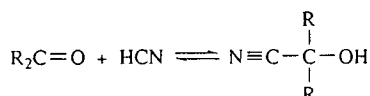
K. Ichikawa,

exists for nucleophiles such as NH_2OH , CN^- , $\text{HOCH}_2\text{CH}_2\text{S}^-$, and SO_3^- .²⁸ These nucleophiles span a wide range of reactivity and represent nitrogen, carbon, and sulfur atoms acting as the nucleophile. The free-energy relationship implies that in this series of ketones the same structural features govern reactivity toward each of the nucleophiles. To a good approximation, the parameter A is equal to 1, which reduces the correlation to

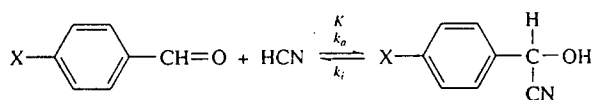
$$\log(k/k_0) = B$$

This equation implies that the relative reactivity is independent of the specific nucleophile and that relative reactivity is insensitive to changes in position of the transition state. Table 8.4 lists the B values for some representative ketones. The parameter B indicates relative reactivity on a log scale. Cyclohexanone is seen to be a particularly reactive ketone, being almost as reactive as cyclobutanone and more than 10 times as reactive as acetone.

The same structural factors come into play in determining the position of equilibria in reversible additions to carbonyl compounds. The best studied of such equilibrium processes is probably addition of cyanide to give cyanohydrins.



For cyclopentanone, cyclohexanone, and cycloheptanone, the K values for addition are 48, 1000, and 8 M^{-1} , respectively.²⁹ For aromatic aldehydes, the equilibria are affected by the electronic nature of the aryl substituent. Electron donors disfavor addition by stabilizing the aldehyde whereas electron-accepting substituents have the opposite effect.



(Ref. 30)

K is correlated by Hammett equation with σ^+ , $\rho = 1.01$

k_a is correlated by Hammett equation with σ^+ , $\rho = 1.18$

Table 8.4. Relative Reactivity of Some Ketones toward Addition of Nucleophiles

Ketone	$B = \log \text{ relative reactivity}^a$
Cyclobutanone	0.09
Cyclohexanone	0.00
4- <i>t</i> -Butylcyclohexanone	-0.008
Adamantanone	-0.46
Cycloheptanone	-0.95
Cyclopentanone	-1.18
Acetone	-1.19
Bicyclo[2.2.1]heptan-2-one	-1.48
3,3,5,5-Tetramethylcyclohexanone	-1.92

a. A. Finiels and P. Geneste, *J. Org. Chem.* 44:1577 (1979); reactivity relative to cyclohexanone as a standard.

28. A. Finiels and P. Geneste, *J. Org. Chem.* 44:1577 (1979).

29. V. Prelog and M. Kobelt, *Helv. Chim. Acta* 32:1187 (1949).

30. W. M. Ching and R. G. Kallen, *J. Am. Chem. Soc.* 100:6119 (1978).

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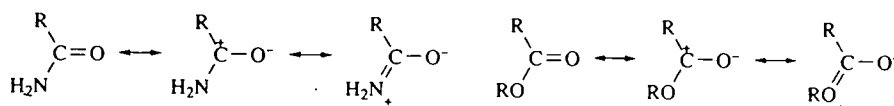
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There are large differences in reactivity among the various carboxylic acid derivatives, such as amides, esters, and acyl chlorides. One important factor is the resonance stabilization provided by the heteroatom. This decreases in the order $N > O > Cl$. Electron donation reduces the electrophilicity of the carbonyl group, and the corresponding stabilization is lost in the tetrahedral intermediate.



The high reactivity of the acyl chlorides also reflects the polar electron-withdrawing effect of the chlorine, which more than outweighs the small π -donor effect.

Another factor which strongly affects the reactivity of these carboxylic acid derivatives is the leaving-group ability of the substituents. The order is $Cl > OAr > OR > NR_2 > O^-$ so that not only does the ease of forming the tetrahedral intermediate decrease in the order $Cl > OAr > OR > NR_2 > O^-$, but the tendency for subsequent elimination to occur is also in the same order. Because the two factors work together, there are large differences in reactivity toward the nucleophiles.

Approximate relative reactivity toward hydrolysis	
RCOCl	10^{11}
RCO ₂ R'	1
RCONR' ₂	10^{-2}
RCO ₂ ⁻	$\ll 1$

Table 8.5 lists the enthalpies for a series of isodesmic reactions involving conversion of carbonyl derivatives to the methyl ketones. The ΔH of the reactions is given both from thermodynamic data (ΔH_{obs}) and as calculated at the MP3/6-31++G* level. These values show that NH_2 , OH , and F all provide significant stabilization to carbonyl groups. A major component of this stabilization is π donation of a lone pair from the substituent. This effect is diminished for $X = \text{Cl}$ and is absent for $X = \text{CN}$. The cyano substituent is destabilizing because of a Coulombic repulsion of the adjacent positively charged carbons. The trifluoromethyl group has a similar effect.³¹ Figure 8.5 shows bond orders and charge densities for a number of carbonyl derivatives.

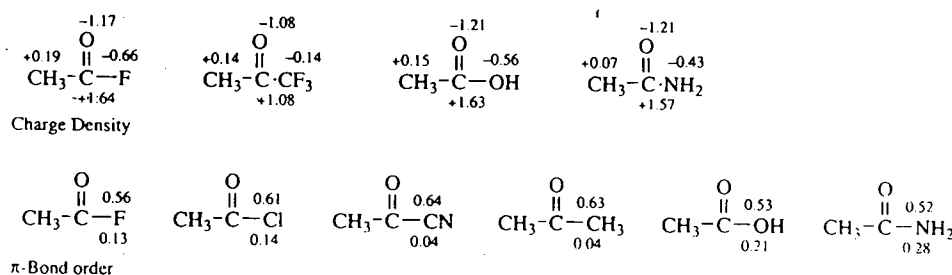


Fig. 8.5. Charge density and bond orders for carbonyl derivatives.

31. K. B. Wiberg, C. M. Hadad, P. R. Rablen, and J. Cioslowski, *J. Am. Chem. Soc.* **114**:8644 (1992)

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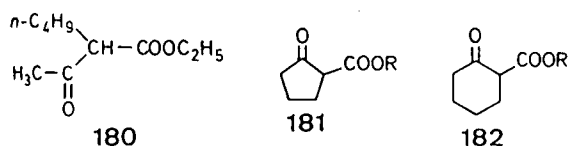
A. Paul KRAPCHO

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5. β -Keto Esters

In our original publication it was reported that the β -keto esters **180**, **181** (mixture of methyl and ethyl esters), and **182** (mixture of methyl and ethyl esters) underwent dealkoxycarbonylations on being heated in wet DMSO containing sodium chloride (130–150 °C, 2–4 h) to yield the respective ketones in excellent yields⁹.

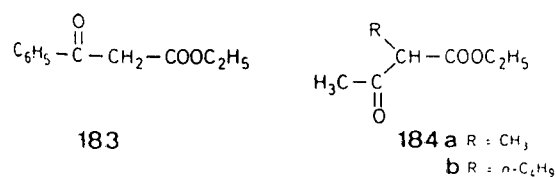


It was then shown that some β -keto esters undergo dealkoxycarbonylations on being heated in aqueous DMSO without added salts^{3,7,8}. On the other hand, β -keto esters with no α -hydrogens require the presence of a salt to effect dealkoxycarbonylations.

5.1. Monosubstituted Substrates

5.1.1. Mono-dealkoxycarbonylations

The acyclic substrates **180**, **183**, **184a**, and **184b** undergo deethoxycarbonylations to the respective ketones (70–80% yields) on being heated in aqueous DMSO^{3, 48}

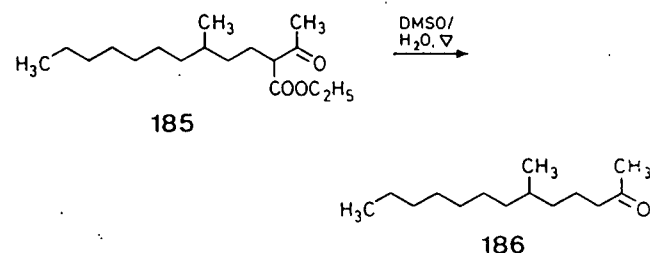


2-Heptanone^{3, 18}:

Ethyl 2-acetylhexanoate (**184b**; 6.12 g, 0.03 mol) and water (1.08 g, 0.06 mol) are dissolved in DMSO (25 ml) in a 2-necked round bottom flask fitted with a condenser and magnetic stirrer. The reaction vessel is placed in a pre-heated oil bath at 210 °C and the mixture heated for

4 h. The reaction mixture is cooled and the product distilled; yield: 3.62 g ($^1\text{H-N.M.R.}$ analysis shows the presence of $\sim 33\%$ ethanol: overall yield of ketone: 70%); b.p. $150\text{--}153^\circ\text{C}$.

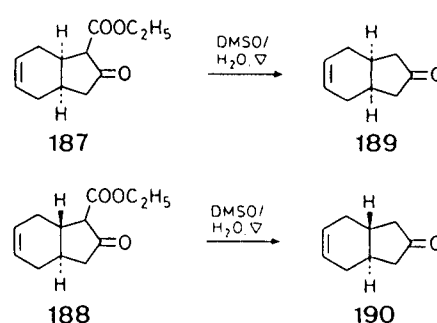
The β -keto ester **185** on heating in DMSO containing a little water (165 °C for 6 h) yields ketone **186** (75%)¹¹³.



6-Methyl-2-tridecanone (186)¹¹³:

The keto ester **185** (980 mg, 3.4 mmol) is heated in DMSO (10 ml) containing water (1 g, 56 mmol) for 6 h. After cooling, the mixture is poured into water (40 ml) and the product extracted with pentane (4 x 10 ml). Evaporation of the pentane and distillation under reduced pressure gives the ketone **186**; yield: 550 mg (75%); b.p. 110 °C. (13 torr (bath temperature)).

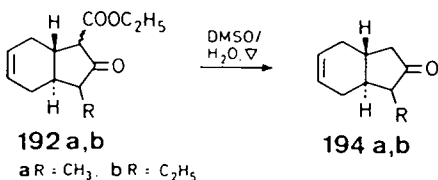
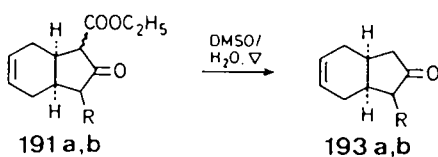
Deethoxycarbonylations of the β -keto esters **187** and **188** can readily be accomplished by heating in wet DMSO (155 °C for 4 h) to give **189** (95%) and **190** (96%), respectively¹¹⁴.



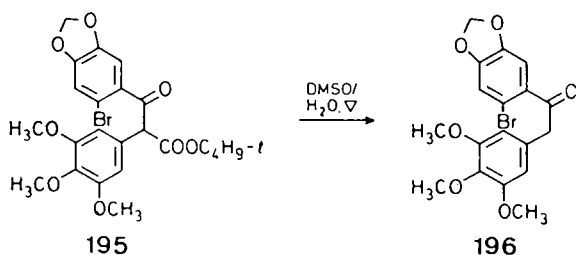
cis-Bicyclo[4.3.0]-nonen-8-one (189)¹¹¹:

The *cis*- β -keto ester **187** (10.4 g, 50 mmol) is heated at 155 °C for 4 h with water (2 g, 111 mmol) in DMSO (45 ml) under an argon atmosphere. After cooling, the mixture is poured into water (150 ml), extracted with light petroleum (4 $\times$ 25 ml), the extracts are dried, and concentrated. The product is obtained by distillation under reduced pressure; yield: 6.2 g (95%); b.p. 50–53 °C/0.3 torr.

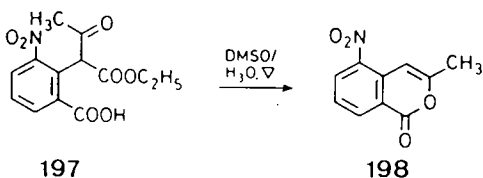
In a similar manner, *cis*-**191a** on heating in wet DMSO yields *cis*-**193a** (49%, based on keto ester **187** which was methylated to prepare **191a**). This product was contaminated with **189** (12%). *trans*-**192a** reacts similarly to yield **194a** [50%, contaminated with **190** (4%)]. The deethoxycarbonylation of *cis*-**191b** gives **193b** (50%), containing **190** (12%) from unethylated **188**. *trans*-**192b** reacts to give **193b** (79%)¹¹⁵.



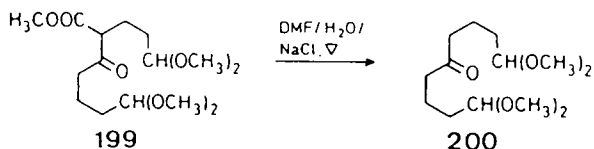
Heating **195** in aqueous DMSO yields ketone **196** (74%, based on acid chloride derived from **195**)¹¹⁶.



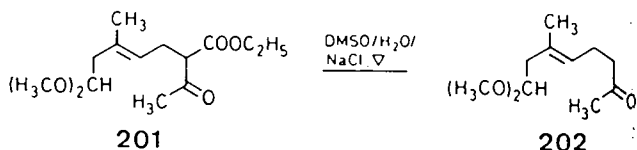
The deethoxycarbonylation of **197** on heating with DMSO containing water (170 °C, reflux, 4 h) and quenching with water gives the isocoumarin **198** (58%)¹¹⁷. This is the enol lactone of the keto acid formed on deethoxycarbonylation.



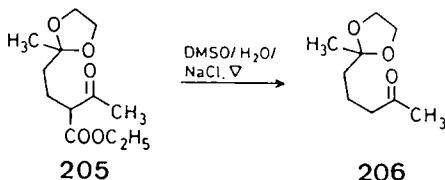
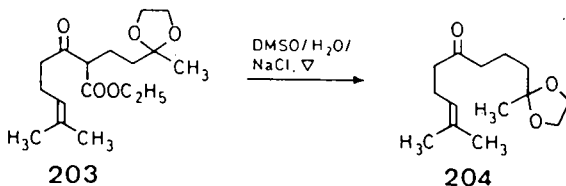
Demethoxycarbonylation of **199** (DMF/water/sodium chloride, reflux, 4 h) yields **200** (~70%)⁵⁹.



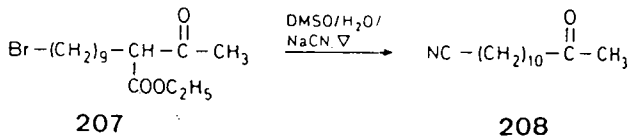
Treatment of the β -keto ester **201** with sodium chloride in wet DMSO (160 °C, 9 h) yields **202** (56%)¹¹⁸.



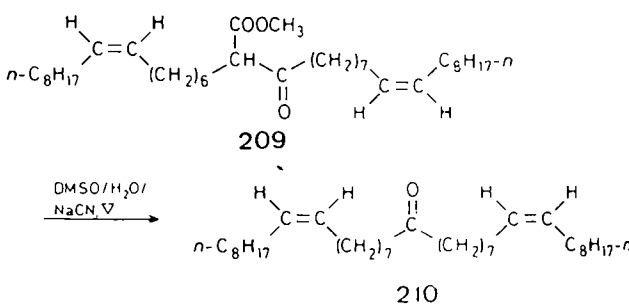
The ethoxycarbonyl group in **203** can readily be removed by heating in wet DMSO containing some sodium chloride (170 °C, 8 h) to yield **204** (70%)¹¹⁹. In a similar manner, **205** can be converted into **206** (60%)¹²⁰.



Treatment of **207** with wet DMSO containing sodium cyanide (160–165 °C, 3 h) not only effects the deethoxycarbonylation but displaces bromide to yield the cyano ketone **208** (28%)¹²¹.



The deethoxycarbonylation of **209** (prepared from methyl oleate by condensation in the presence of sodium hydride) with sodium chloride in wet DMSO (145 °C, 8 h) leads to **210** (95%). Intermediate **210** was utilized in the preparation of civetone (as a mixture of *Z*- and *E*-isomers)¹²².

**18-Oxopentatriaconta-8,26-diene (210)¹²²:**

The crude β -keto ester **209** (22.3 g, 40 mmol) is added to a solution of sodium chloride (2.3 g, 40 mmol) and water (2.1 g, 116 mmol) in DMSO (30 ml). The solution is heated at 145 °C under an inert atmosphere for 8 h and then cooled. Workup by quenching and extraction gives the ketone **210**; yield: 19 g (95%); homogeneous by T.L.C.

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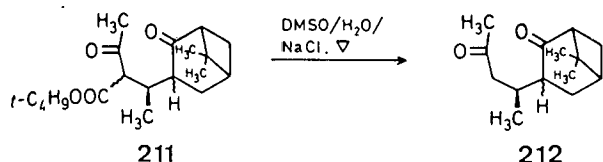
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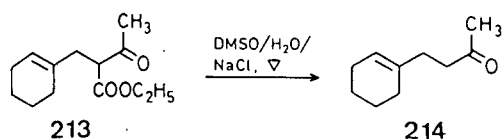
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Demet
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Treatment of diketo ester **211** with sodium chloride in DMSO (no water added, 160 °C, 20 h) led to **212** (88%)¹²³.



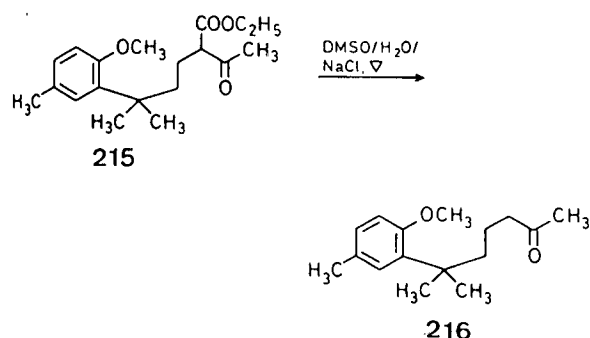
The deethoxycarbonylation of **213** to yield **214** (92%) can be accomplished by heating in wet DMSO containing sodium chloride¹²⁴.



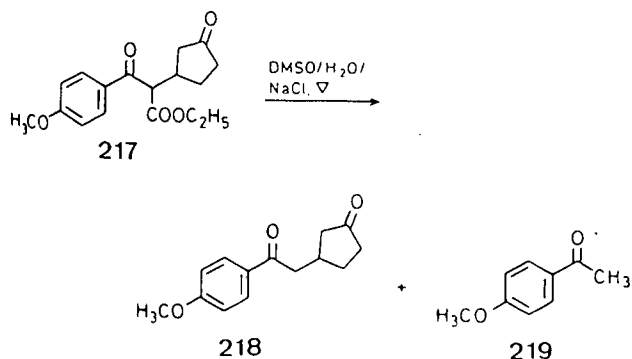
4-(1-Cyclohexenyl)-2-butanone (**214**)¹²⁴:

A mixture of **213** (44.8 g, 0.2 mol), sodium chloride (14.6 g, 0.25 mol), water (11 g, 0.6 mol), and DMSO (150 ml) is heated with stirring for 10 h at 140–150 °C. The mixture is cooled, poured into water (500 ml), and the product extracted into pentane (5 × 100 ml). The pentane extract is washed with saturated aqueous sodium hydrogen carbonate and sodium chloride solutions. Concentration and distillation under reduced pressure gives **214**; yield: 28 g (92%); b.p. 81–83 °C/6 torr.

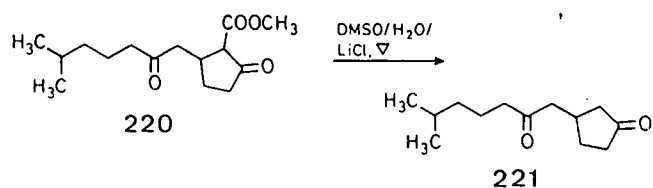
The methoxyketone **215** on treatment with DMSO containing water and sodium chloride (6 h at reflux) led to **216** in a poor yield¹²⁵.



deethoxycarbonylation of β -keto ester **217** (wet DMSO/sodium chloride) gives **218** (no yield listed) and **219** (from a retro-Michael reaction)¹²⁶.



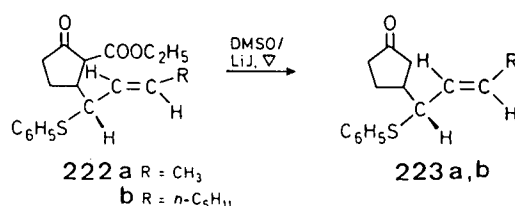
Demethoxycarbonylation of **220** with lithium chloride in wet DMSO gives the cyclopentanone **221** (70%)¹²⁷.



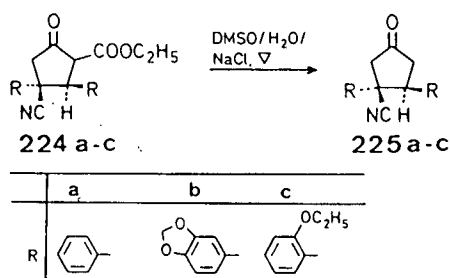
3-(6-Methyl-2-oxoheptyl)-cyclopentanone (**221**)¹²⁷:

The crude 2-methoxycarbonylcyclopentanone **220** (118 mg, 0.46 mmol) is dissolved in DMSO (2 ml) containing water (10 μ l) and lithium chloride (58 mg, 1.4 mmol). The mixture is placed in a pre-heated oil bath at 120 °C for 1.5 h, cooled, and ether and water added. The ether phase is washed with water, and dried with magnesium sulfate, and the solvent removed by distillation through a 15-cm glass-packed column. The product is Kugelrohr distilled; yield: 64 mg (70%); b.p. 60 °C/0.3 torr (bath temperature).

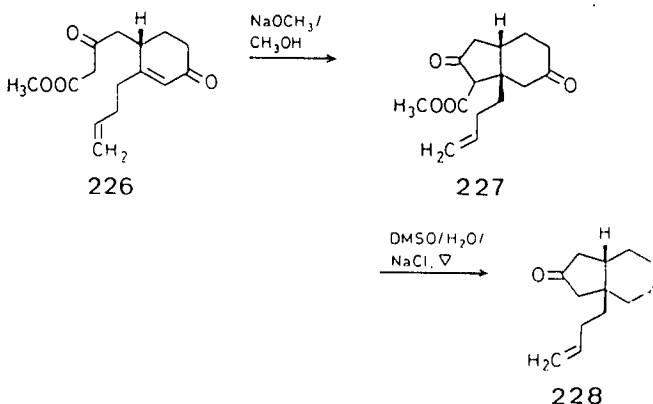
The demethoxycarbonylations of the β -keto esters **222a**¹²⁸ and **222b**¹²⁹ on heating in DMSO and lithium iodide yield the cyclopentanones **223a** (76%) and **223b** (61%), respectively.



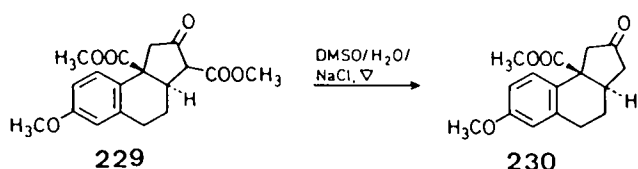
Deethoxycarbonylations of **224a**, **b**, and **c** with sodium chloride in DMSO (120 °C, 1.5–2.5 h) lead to the ketones **225a**, **b**, and **c** in 90%, 70%, and 90% yields, respectively¹³⁰.



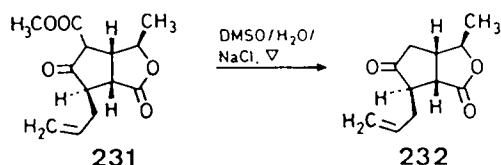
Intramolecular Michael addition of **226** (sodium methoxide in methanol) leads to **227** which can be demethoxycarbonylated (sodium chloride in wet DMSO) to give the *cis*-2,6-indandione **228** (~45% overall yield)¹³¹.



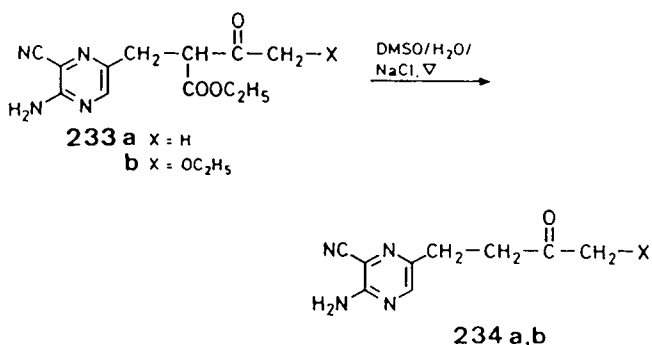
The β -keto ester **229** was deethoxycarbonylated by refluxing with a mixture of wet DMSO and sodium chloride to yield **230** (40%)¹³².



Demethoxycarbonylation of **231** can readily be accomplished by heating with sodium chloride in DMF/water (10:1, 120 °C, 3 h) to yield **232** (94%)¹³³.



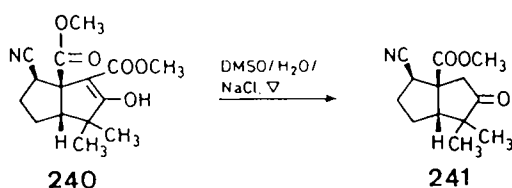
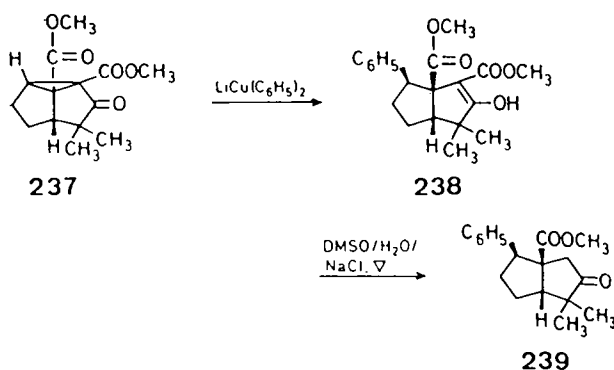
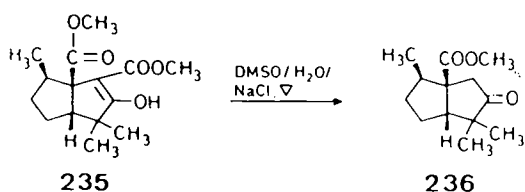
Deethoxycarbonylation of **233a** with wet DMSO containing some sodium chloride yields ketone **234a** (72%). In a similar experimental manner, **233b** was converted to **234b** (19%)²⁹.



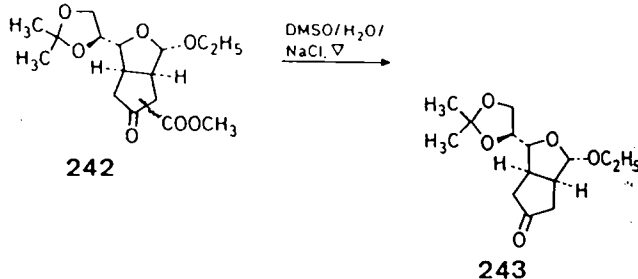
2-Amino-3-cyano-5-(2-ethoxycarbonyl)ethyl-pyrazine (**234a**)²⁹:

The β -keto ester **233a** (10.2 g, 0.039 mol), sodium chloride (2.8 g, 0.048 mol), and water (2.8 g, 0.156 mol) in DMSO (~300 ml) are placed in a three-necked 50-ml round bottom flask fitted with a thermometer, condenser, and magnetic stirrer. The mixture is heated at 155–170 °C for 6 h, cooled, and poured into water (50 ml). The aqueous solution is extracted with chloroform (4 $\times$ 10 ml). The extracts are dried with sodium sulfate, filtered, and evaporated. Crystallization from benzene gives a white crystalline solid; yield: 5.3 g (72%); m.p. 130–131 °C.

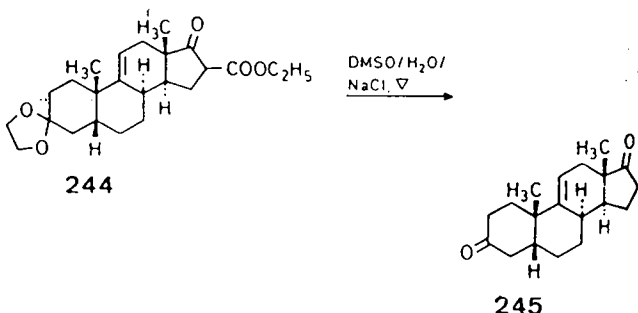
Demethoxycarbonylation of **235** with sodium chloride in hot, wet DMSO gives **236** (74%)¹³⁴. Treatment of **237** with lithium diphenylcuprate gives **238** which on being subjected to demethoxycarbonylation (sodium chloride, hot, wet DMSO) gives **239** (65% overall conversion). Reaction of **237** with diethylaluminum cyanide in toluene gives **240** which on demethoxycarbonylation as above gives **241** (69%)¹³⁴.



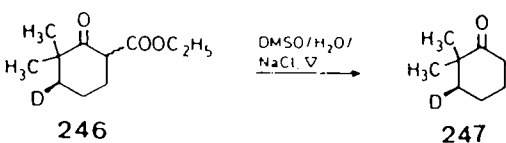
Treatment of **242** (unspecified regio- and stereochemistry) with sodium chloride in wet DMSO gives **243** (85%)¹³⁵.



The deethoxycarbonylation of the steroid β -keto ester **244** has been effected by heating in wet DMSO containing sodium chloride to give **245** (unspecified yield)¹³⁶.



Reaction of **246** with wet DMSO containing sodium chloride (180–185 °C, 3.5 h) leads to (3*R*)-2,2-dimethyl-3-deuteriocyclohexanone (**247**) in ~50% yield¹³⁷.

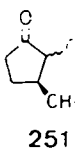
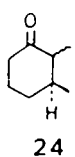


In a synthesis leading to chiral 3-substituted cyclopentanones and cyclohexanones following a cyclization,

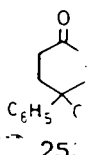
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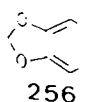
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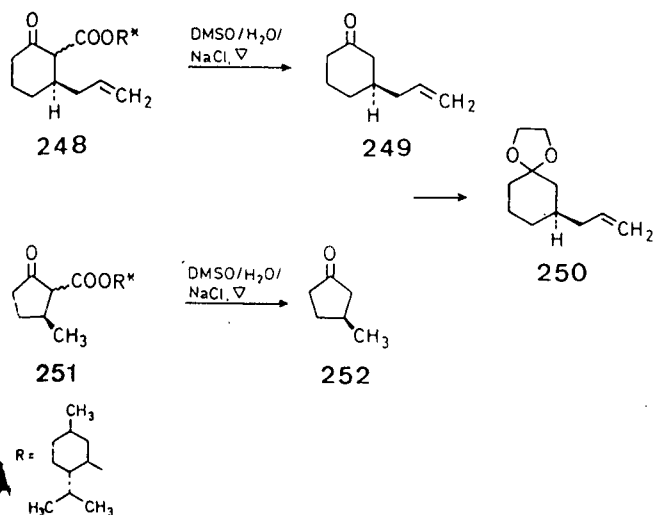
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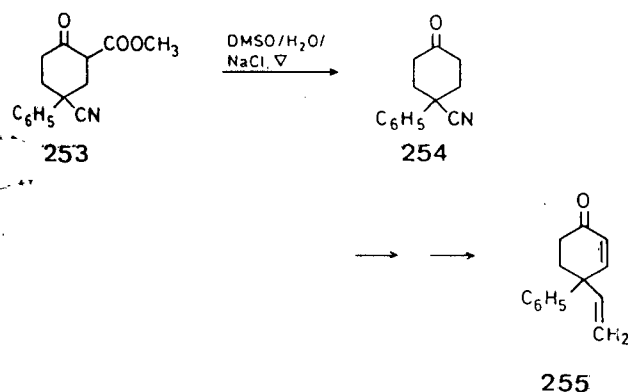
route, the dealkoxycarbonylation of β -keto esters was effected with sodium chloride in wet DMSO. The demethoxycarbonylation of chiral **248** in this manner led to crude **249** which was converted into acetal **250** (67% yield from **248**). In a similar fashion chiral **251** was converted into **252**.¹³⁸



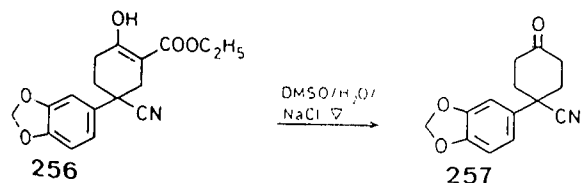
The demethoxycarbonylation of **253** (wet DMSO with sodium chloride present) yields **254** (68%). This compound was converted into **255** which was used in a photochemical study.¹³⁹

4-Cyano-4-phenylcyclohexanone (**254**)¹³⁹:

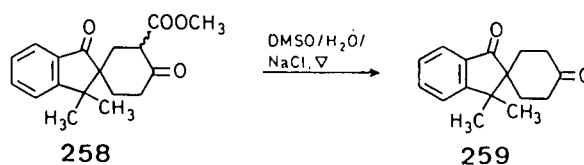
A solution of **253** (85.5 g, 0.333 mol), water (18.5 g, 1.02 mol), and sodium chloride (20.97 g, 0.36 mol) in DMSO (300 ml) is heated to 130 °C in an oil bath at 160 °C for 2 h. The cooled reaction mixture is poured into water (500 ml) and extracted with benzene (5 $\times$ 100 ml). The combined extracts are washed with water (100 ml) and saturated sodium chloride solution (100 ml) and dried with calcium sulfate. The solvent is removed in vacuo and the ketone recrystallized from ethanol; yield: 45.2 g (68%); m.p. 115–117 °C.



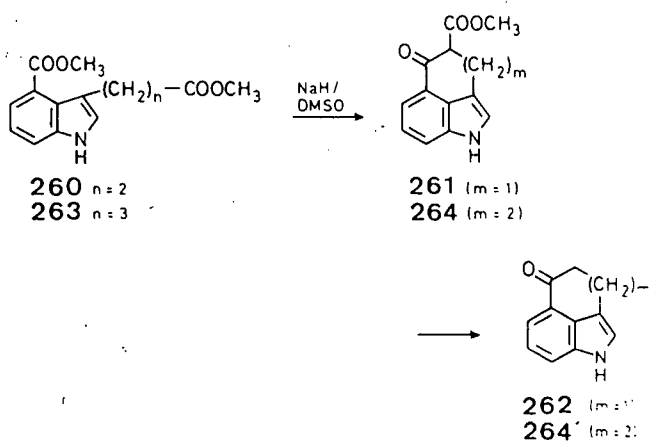
Compound **256** can be deethoxycarbonylated with sodium chloride in wet DMSO to yield cyclohexanone **257** (95%)¹⁴⁰.



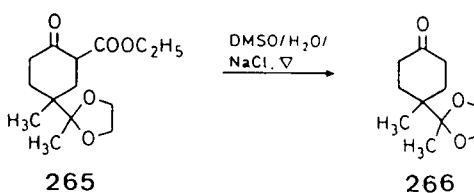
Treatment of **258** with sodium chloride in wet DMSO at 165 °C yields diketone **259** (no yield listed)¹⁴¹.



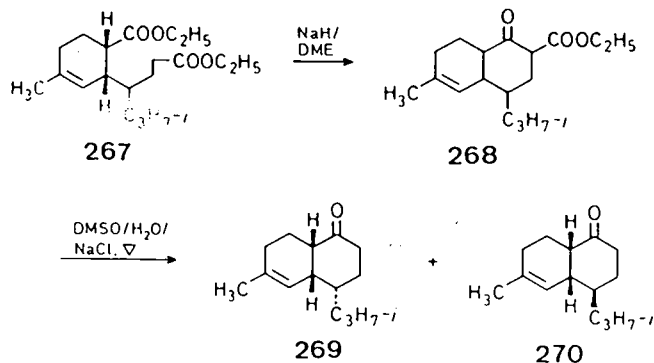
The Dieckmann cyclization of **260** to **261** can be accomplished by use of sodium hydride in DMSO and the resulting sodium salt of the β -keto ester **261** was neutralized with concentrated hydrochloric acid. The DMSO reaction mixture was degassed with nitrogen and heated at 150 °C for 3–6 h. After workup, 65–88% yields of **262** could be obtained¹⁴². The addition of potassium cyanide also effected demethoxycarbonylation while other inorganic salts (lithium chloride or sodium acetate) had a deleterious effect on the demethoxycarbonylation. In DMF, however, lower yields were obtained. Similarly, the one-pot procedure to **264'** from **263**, via intermediate **264**, was also reported¹⁴².



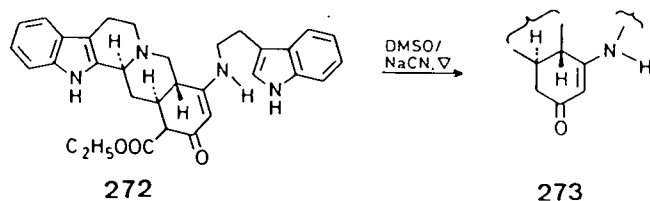
The β -keto ester **265** on refluxing with DMSO containing a little water (170–180 °C for 6 h) and sodium chloride undergoes a smooth deethoxycarbonylation to give **266** (85%)¹⁴³.



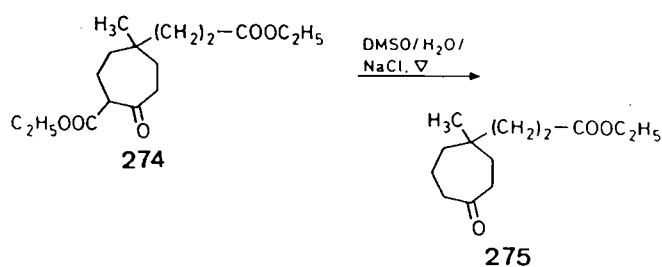
Treatment of **267** with sodium hydride in dimethoxyethane leads to the annelated product **268**. This latter compound on heating with sodium chloride in wet DMSO yields a crude product which consists of **269**, **270**, and **271** in 56%, 23%, and 21% yields, respectively.¹⁴⁴



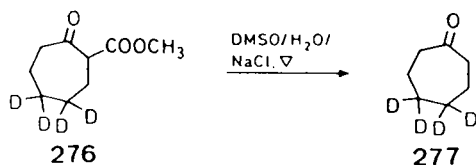
The demethoxycarbonylation of **272** with dry sodium cyanide in dry DMSO (107 °C, 40 h) leads to **273** (58%)¹⁴⁵.



Treatment of **274** with sodium chloride in wet DMSO (160 °C) affords **275** (no yield given)¹⁴⁶.

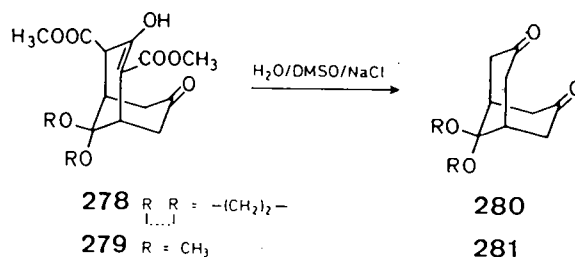


In the preparation of deuterated cycloheptanones, dealkoxycarbonylations have played a significant role. The β -keto ester **276** on heating in wet DMSO containing sodium chloride leads to **277** (85%)¹⁴⁷. The 3,3,6,6-²H₄ system corresponding to **277** could be prepared in a similar manner in 75% yield.

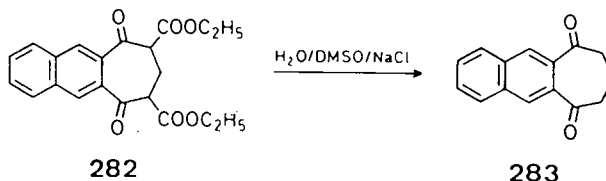


5.1.2. Bis-dealkoxycarbonylations

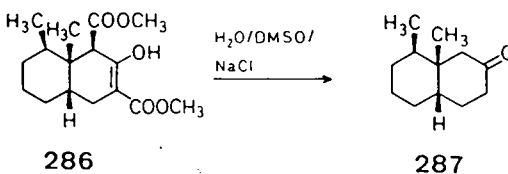
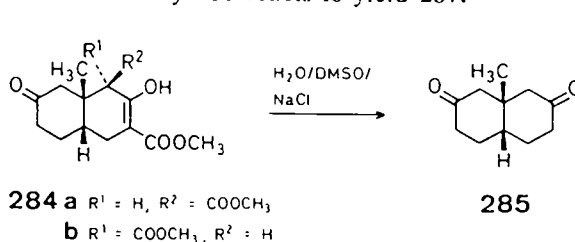
The bis-demethoxycarbonylation of **278** and **279** (sodium chloride in wet DMSO) leads to **280** and **281** in 79% and 67% yields, respectively¹⁴⁸. This is a useful synthetic route to bicyclo[3.3.1]nonan-3,7,9-triones and their acetals.



The bis-deethoxycarbonylation of **282** with sodium chloride in wet DMSO yields **283** (54%)¹⁴⁹.

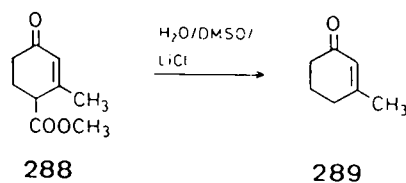


The stereoisomeric diketo diesters **284a** and **284b** yield the diketones **285** on heating in DMSO containing water¹⁵⁰. Similarly **286** reacts to yield **287**.

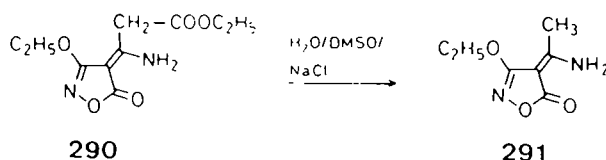


5.1.3. Vinylogous β -Keto Esters

The deethoxycarbonylation of Hagemann's ester (**288**) can be effected with lithium chloride in wet DMSO to prepare 3-methyl-2-cyclohexenone (**289**, 70%)¹⁵¹.

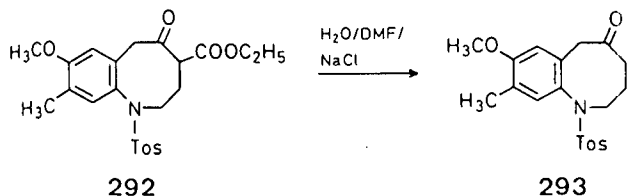


Reaction of **290** with wet DMSO containing sodium chloride at 150 °C until the evolution of carbon dioxide stops leads to **291** (36%)¹⁵².

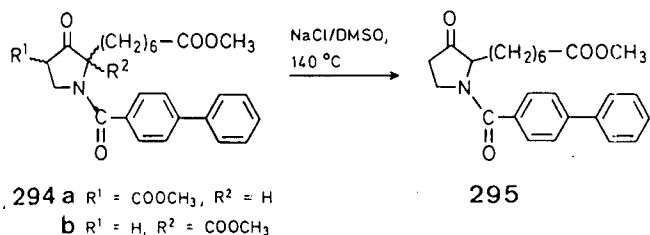


5.1.4. Heterocyclic Substrates

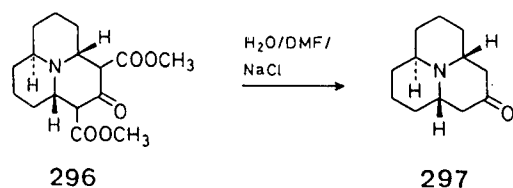
Compound **292** can be quantitatively converted into **293** by heating in DMF containing some water and sodium chloride¹⁵³.



Treatment of a mixture of the methoxycarbonylpyrrolidones **294** with sodium chloride in DMSO at 140 °C gives the pyrrolidine **295** (65%)¹⁵⁴.

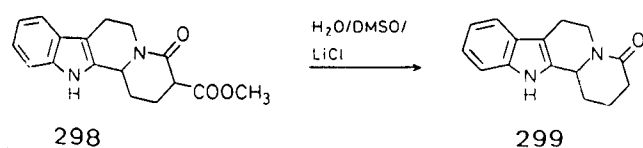


The bis-demethoxycarbonylation of **296** (sodium chloride/water/DMF) yields ketone **297** (56%)⁵⁹. The facile synthesis of **296** and the conversion of **297** into two ladybug defensive alkaloids coccinelline and precoccinelline make this an attractive synthetic route.

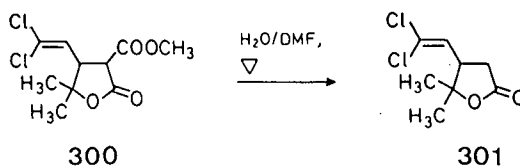
2-Oxoperhydro-9b-azaphenalene (**297**)⁵⁹:

The keto ester **296** (1 g, 3.23 mmol), sodium chloride (0.2 g, 3.42 mmol), and water (2 ml, 11.1 mmol) are dissolved in DMF (15 ml) and heated at reflux under nitrogen for 4 h. The solvent is removed in vacuo and the residue taken up in dichloromethane (10 ml) and filtered through a short column of neutral alumina. Purification is accomplished by chromatography on neutral alumina by eluting with ethyl acetate/hexane (1:1) to give **297**; yield: 0.35 g (65%); m.p. 83 °C.

In syntheses of indoloquinolizines, the deethoxycarbonylations of lactams have been important. Deethoxycarbonylation of **298** (an epimeric mixture) by heating in wet DMSO containing water and lithium chloride leads to **299** (89%)¹⁵⁵.

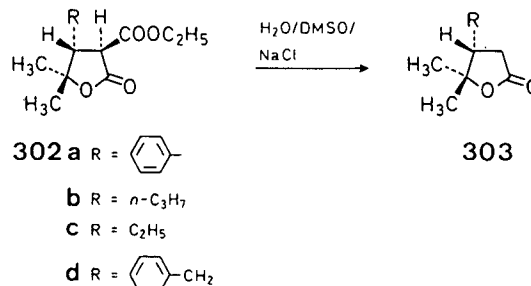


Deethoxycarbonylation of **300** occurs on heating in wet DMF to give **301** (95%)¹⁵⁶.

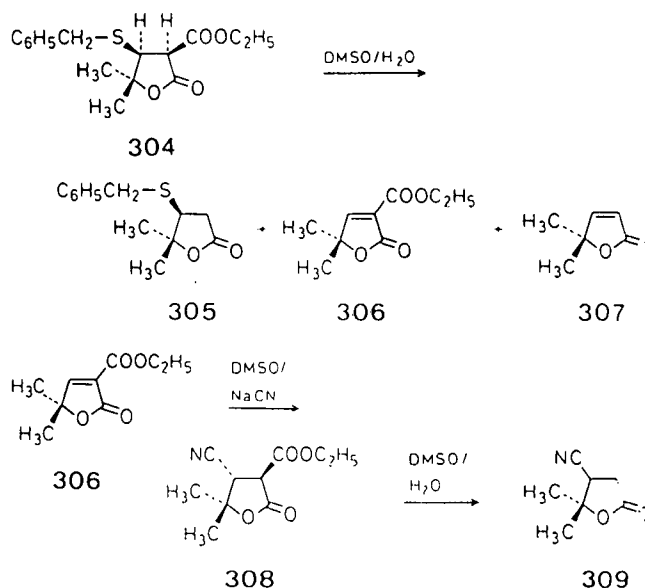
4-(2,2-Dichloroethenyl)-5,5-dimethyltetrahydrofuran-2-one (**301**)¹⁵⁶:

A suspension of lactone **300** (267 g, 1 mol) in dimethylformamide (600 ml) and water (27 ml, 1.5 mol) is heated under reflux for 4–12 h. When the reaction is complete, the water and DMF are removed under reduced pressure. Methanol (500 ml) is added to the residual lactone and then water (100 ml). Cooling induces crystallization to occur. The crystals are filtered and a second crop is collected from the filtrate: yield: 198 g (95%); m.p. 116–119 °C [crystallized from hexane/ethanol (2:1)].

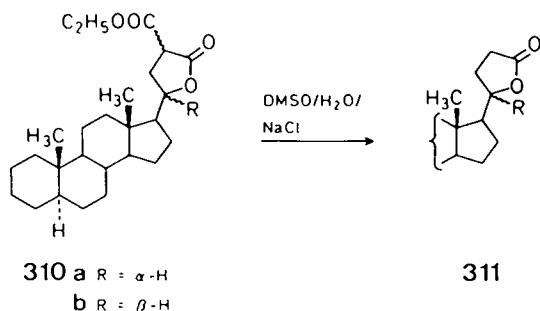
Treatment of butyrolactone **302a** (as the methyl ester) with sodium chloride in wet DMSO (170–210 °C, 3 h) gives **303a** (87%)¹⁵⁷. Deethoxycarbonylations of lactones **302a**, **302b**, and **302c** can also be effected by heating in wet DMSO for 40 h at 140 °C to yield **303a**, **b**, and **c** (73–90% yields)⁹⁴. When **302d** was heated with sodium chloride and wet DMSO at 170 °C, no **303d** could be obtained. However, the use of potassium cyanide in wet HMPT yielded **303d** (60%).



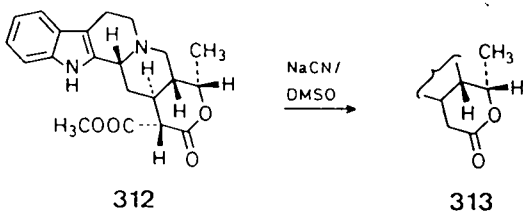
On heating **304** in wet DMSO, the products **305** (63%), **306** (14%), and the unsaturated lactone **307** (17.5%) were isolated⁹⁴. Treatment of **306** with sodium cyanide in DMSO at room temperature leads to **308** and elimination of the ethoxycarbonyl group by reaction with wet DMSO gives **309** (98%)⁹⁴.



Deethoxycarbonylations of the α -ethoxycarbonyl- γ -lactones **310a** or **310b** with sodium chloride in wet DMSO (170 °C, 6 h) lead to **311a** and **311b**, respectively, in 30–40% yields¹⁵⁸.



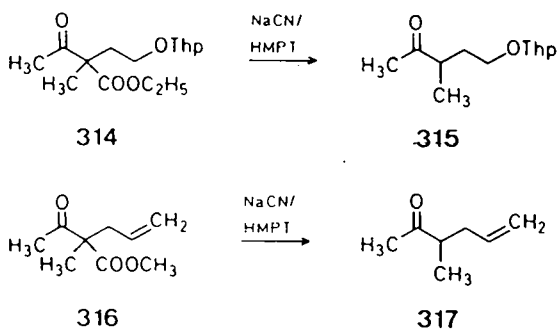
Reaction of the heterocyclic lactone **312** with sodium cyanide in DMSO (80 °C, 48 h) leads to the demethoxycarbonylated lactone **313** (80%)¹⁵⁹.



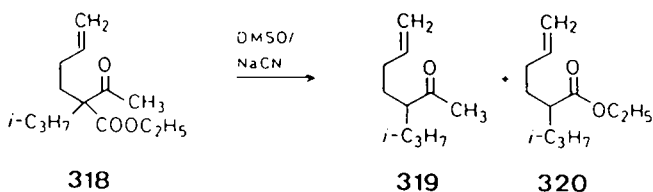
5.2. Disubstituted Substrates

In order to effect dealkoxycarbonylations of disubstituted β -keto esters the use of a salt such as lithium chloride or sodium cyanide is necessary in the dipolar aprotic media.

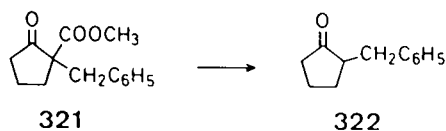
The demethoxycarbonylation of **314** with sodium cyanide in HMPT (110 °C, 4 h) yields **315** (56%). Under similar experimental conditions **316** can be converted into **317** (43%)¹⁶⁰.



On heating **318** with sodium cyanide in DMSO (160 °C, 4 h) a mixture of products was formed which consisted of the deethoxycarbonylated product **319** (80%) and the deacylated product **320** (20%). The mixture can be separated by G.L.C. to give pure **319** (70%)¹⁶¹.



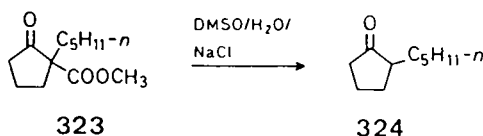
The demethoxycarbonylation of **321** has been effected by lithium iodide dihydrate in dry 2,4,6-collidine (reflux 19 h) to yield **322** (72–76%)¹⁶¹.



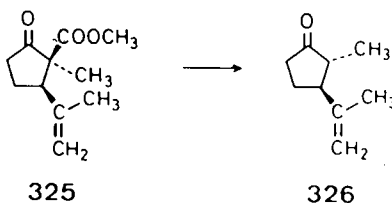
It was then shown that treatment of **321** with lithium chloride (2-fold excess) in HMPT (75 °C, 24 h) leads to **322** (90%). With sodium cyanide (2 fold excess) in HMPT (75 °C, 1 h), **322** could be obtained in an 80% yield¹⁶².

In an experiment in which 2-methyl-2-methoxycarbonylcyclopentanone was reacted with sodium cyanide in HMPT, acetonitrile was isolated (70% yield). In HMPT, it was shown that the reactivity of the salts sodium cyanide, lithium chloride, or lithium bromide towards **321** are 65, 2.45 and 1.0, respectively. Sodium cyanide in DMF is about 1/30 as reactive as sodium cyanide in HMPT towards **321**. The methyl ester **321** is about 72 times more reactive than the corresponding ethyl ester (sodium cyanide/HMPT)¹⁶².

The substituted cyclopentanone **323** on being heated in a sealed tube with sodium chloride in wet DMSO at 180 °C for 3 h leads to 2-*n*-pentyl-1-cyclopentanone (**324**, 35%)¹⁶³.



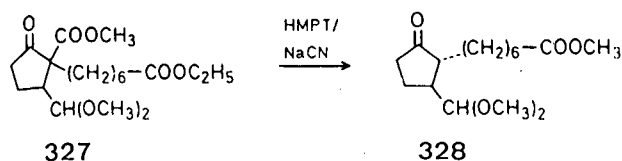
Attempts to demethoxycarbonylate **325** in acidic media lead to extensive decomposition. However, on heating a solution of **325** in HMPT with tetramethylammonium acetate (2 equivalents) at 100 °C (12 h), the demethoxycarbonylated product **326** can be obtained in a 72% yield¹⁶⁴.



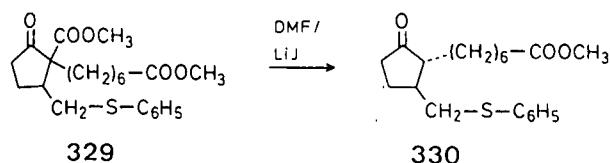
3-Isopropenyl-2-methylcyclopentanone (**326**)¹⁶⁴:

A solution of **325** (1.05 g, 5.37 mmol), tetramethylammonium acetate (2.66 g, 20.0 mmol) and anhydrous HMPT (5 ml) is heated to 100 °C for 12 h. The cooled reaction mixture is exhaustively extracted with ether, the ether extracts are washed with water, saturated aqueous sodium carbonate solution, dried with sodium sulfate, and concentrated by distillation through a 10-cm Vigreux column. The residual oil is distilled at reduced pressure; yield: 0.53 g (72%), b.p. 75–77 °C/7.5 torr.

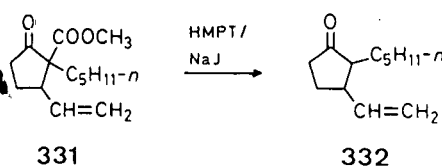
Deethoxycarbonylation of **327** was effected with sodium cyanide in HMPT (70 °C, 1 h, dry argon) to yield **328** (90%)¹⁶⁵. This keto ester is the thermodynamically more stable product and may be the result of equilibration under the experimental conditions.



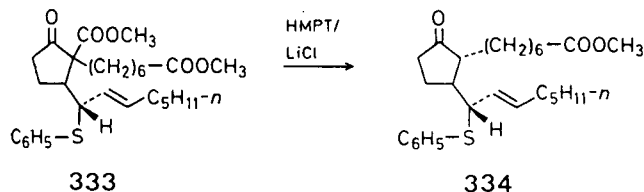
The demethoxycarbonylation of the β -keto ester 329 was effected in refluxing DMF in the presence of lithium iodide to yield 330 (70%)¹⁶⁶.



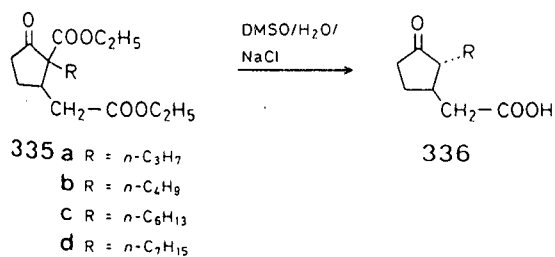
Demethoxycarbonylation of 331 with sodium iodide in HMPT yields 332 (88%)¹⁶⁷.



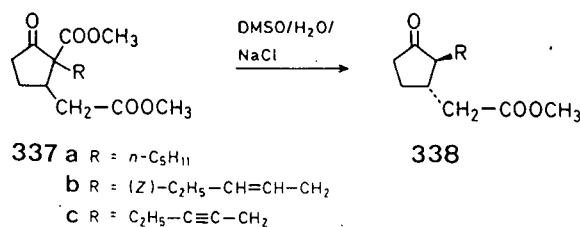
Reaction of 333 with lithium chloride in HMPT (100 °C, 6 h) yields the demethoxycarbonylated product 334 in a 92% conversion¹⁶⁸.



In a study dealing with the structure-activity relationship on rice seedling growth, jasmonic acid and related compounds have been prepared for inhibitory evaluation¹⁶³. Compounds 335 (a, b, c, or d) on heating in wet DMSO containing sodium chloride (180 °C, 4 h) led to the acids 336 (a, b, c, or d) in yields of 28% to 60% (workup involved a saponification procedure).



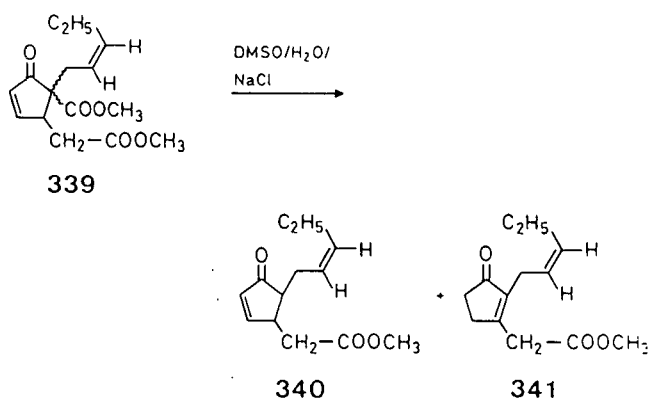
Demethoxycarbonylation of 337a with sodium chloride in wet DMSO (180 °C, 3–4 h, sealed tube) yields methyl dihydrojasmonate (338a; 70%)¹⁶⁹. In a similar experimental fashion 337b and 338c lead to 338b (56–86%) and 338c (86%), respectively¹⁶⁹.



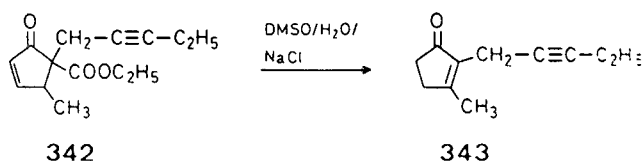
Methyl *dl*-Dehydrojasmonate (338c)¹⁶⁹:

A solution of 337c (24 mg, 0.086 mmol) and sodium chloride (10 mg) is mixed with DMSO (1.5 ml) and water (20 mg) and heated in a sealed tube at 180 °C for 3–4 h. The cooled mixture is poured into ice-cold brine and extracted with hexane. The hexane extracts are washed with saturated sodium chloride solution, dried with sodium sulfate, and the solvent removed under vacuo. The product is distilled: yield: 16.3 mg (86%); b.p. 102–103 °C/3 torr.

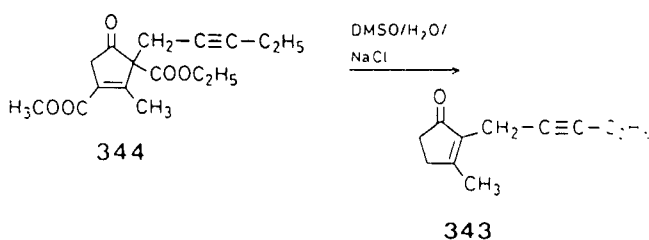
The demethoxycarbonylation of 339 in wet DMSO containing sodium chloride in a sealed tube (170–175 °C, 4 h) affords a mixture of 340 and 341 in a 2:1 ratio, respectively, in an overall 46% yield^{169b}. Isomerization of the double bond also partially occurs under the demethoxycarbonylation conditions used.



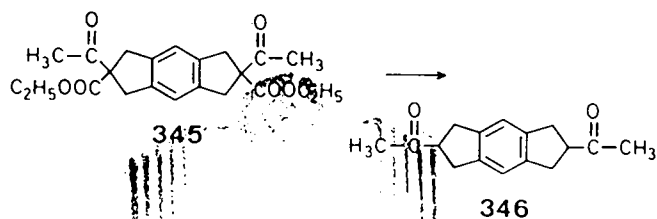
It had previously been reported that 342 on treatment with sodium chloride in wet DMSO at 160 °C leads to 343 (32%)¹⁷⁰.



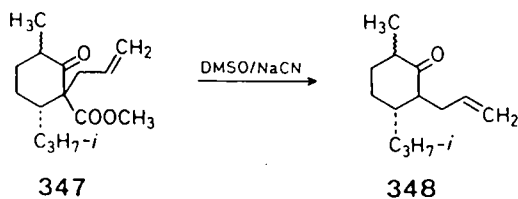
In another synthetic procedure to *cis*-jasmonate, it has been shown that 344 on being heated in aqueous DMSO containing sodium chloride (180 °C, 8 h, sealed tube) also leads to 343 (33%)¹⁷¹. Catalytic hydrogenation of the triple bond of 343 (palladium on barium carbonate/hydrogen) gives *cis*-jasmonate (65%).



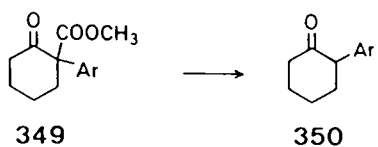
When **345** was heated in wet DMSO containing sodium chloride an incomplete reaction occurred. This β -keto ester was converted into **346** by heating in a mixture of acetic acid and concentrated hydrochloric acid¹⁷².



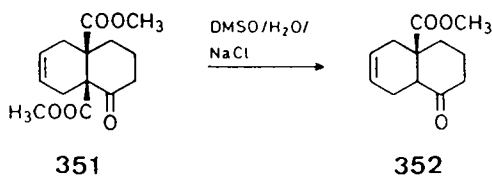
The demethoxycarbonylation of **347** can be readily accomplished by heating in DMSO in the presence of sodium cyanide to produce **348** (92%)¹⁷³. Attempts to effect this transformation under the usual alkaline conditions were unsatisfactory as ring-opening occurred.



The application of the sodium chloride/wet DMSO procedure for the preparation of α -arylcyclohexanones **350** from the readily available α -arylated β -keto esters **349** is suggested but no specific experiments are given¹⁷⁴.

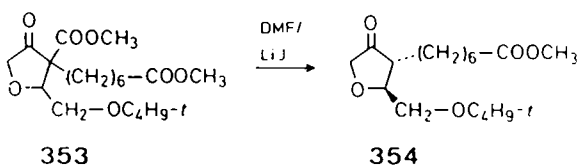


Treatment of **351** with sodium chloride in DMSO and water under nitrogen gives **352** (*trans*:*cis* isomeric mixture of 2:1), the product from the chemoselective removal of the methoxycarbonyl group adjacent to the carbonyl group¹⁷⁵.

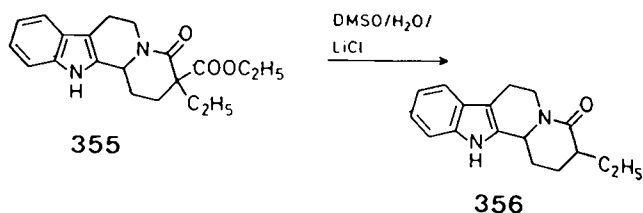


5.2.1. Heterocyclic Substrates

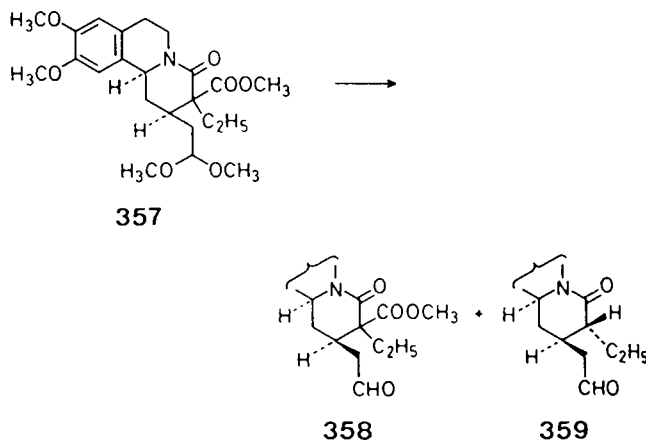
Demethoxycarbonylation of **353** with lithium iodide in DMF yields **354** (45%)¹⁷⁶.



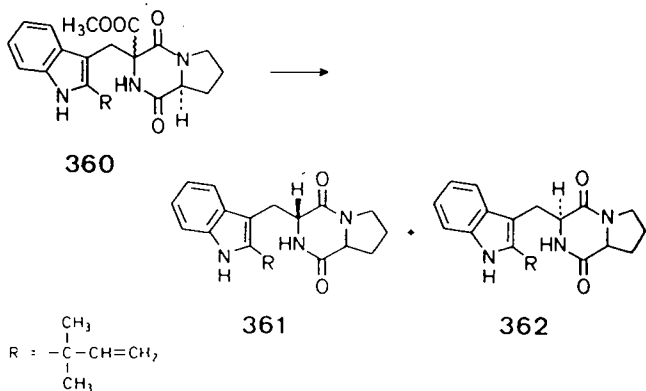
Deethoxycarbonylation of **355** using lithium chloride in wet DMSO (reflux, 4 h) leads to two lactams **356** (major product in 51% yield and a minor lactam)¹⁷⁷.



The demethoxycarbonylation of **357** was attempted by heating in DMSO/water at 180–190 °C in the presence of sodium chloride. The products were the aldehyde **358** (~70%, major) and a small amount of ($\pm$)-4-oxo-protoemine (**359**, ~10%). It was also shown that deacetalization of **357** occurred on heating in DMSO in the absence of water and the salt¹⁷⁷.

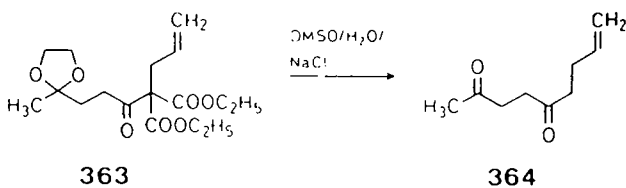


Deoxybrevianamide E (**361**) can be obtained in a 59% yield from **360** by heating at 130–140 °C (2.5 h) in the presence of magnesium chloride hexahydrate in DMSO along with the C-9 epimer **362** (38%)¹⁷⁸. It is noted that the use of sodium chloride in wet DMSO was unsatisfactory for this conversion.

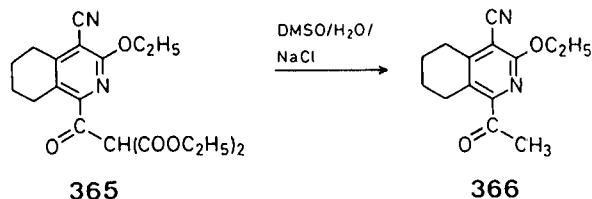


5.2.2. Bis-dealkoxycarbonylations

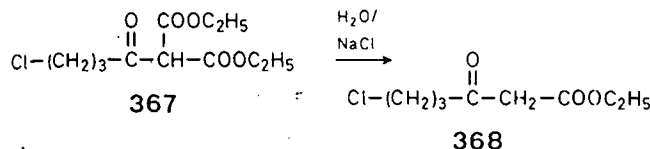
Reaction of **363** with sodium chloride in hot, wet DMSO followed by a methanolic hydrogen chloride workup leads to **364** (no yield listed)¹⁷⁹.



The bis-deethoxycarbonylation of **365** with sodium chloride in wet DMSO at 165–170 °C for 4 h yields the methyl ketone **366** (50%)¹⁸⁰.

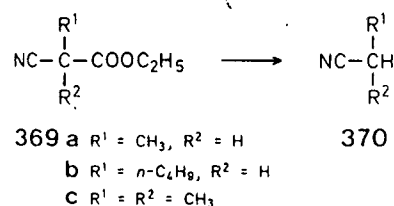


It is of interest to note that when **367** was heated for 3 h at reflux with a saturated aqueous solution of sodium chloride, **368** (53%) was produced, the product of a monodeethoxycarbonylation¹⁸¹.



6. α -Cyano-Esters

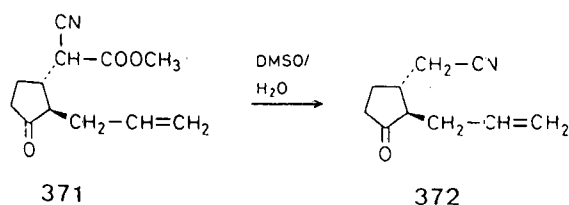
The deethoxycarbonylation of ethyl cyanoacetate in DMSO containing a little water (2 molar equivalents) at 135–165 °C leads to acetonitrile (75–80%)^{9,18}. It has also been shown that the monosubstituted cyanoacetates **369a** and **369b** on heating in DMSO containing some water (4 h) yield the corresponding nitriles **370a** and **370b**, respectively, in 70–80% yields. In these cases, the presence of a salt such as sodium chloride is unnecessary⁹.



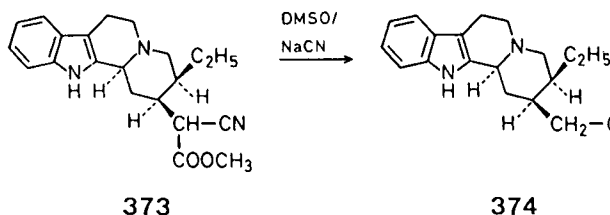
On the other hand, **369c** on being refluxed with DMSO containing 2 molar equivalents of water (4 h) leads only to recovered starting material. In the disubstituted substrate, the presence of a salt is necessary to effect a dealkoxycarbonylation.

6.1. Monosubstituted Substrates

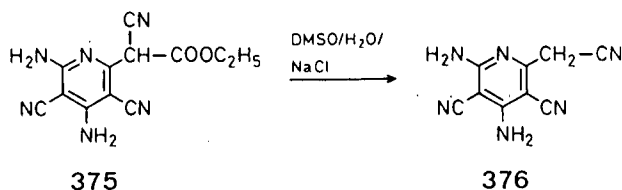
The demethoxycarbonylation of **371** by heating in DMSO/water (9:1) at 140–180 °C yields the *trans*-keto nitrile **372** (80%)¹⁸².



The α -cyano ester **373** on treatment with sodium cyanide in DMSO (145 °C for 1.5 h) leads to the demethoxycarbonylated product **374** (89%)¹⁸³.



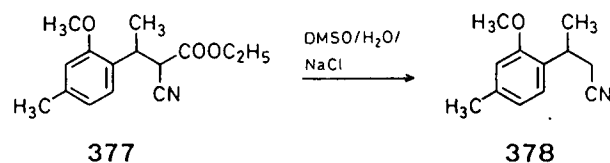
The deethoxycarbonylation of **375** with sodium chloride in aqueous DMSO yields **376** (67%)¹⁸⁴.



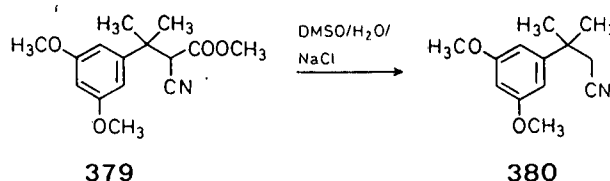
4',6'-Diamino-3',5'-dicyano-2'-pyridylacetone nitrile (**376**)¹⁸⁴:

A solution of **375** (0.081 g, 0.3 mmol), sodium chloride (0.006 g, 0.1 mmol), water (0.011 g, 0.6 mmol), and DMSO (1 ml) is heated at 130–150 °C for 2.5 h. The solution is cooled, poured into water (5 ml), and the solid which precipitates is filtered. Recrystallization from aqueous DMF gives the pure product; yield: 0.04 g (67%); m.p. > 300 °C.

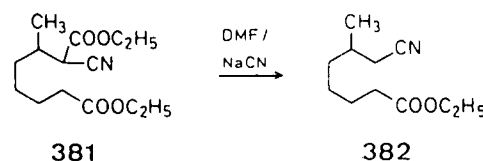
The ethoxycarbonyl group in the α -cyano ester **377** was removed by heating with wet DMSO containing some sodium chloride (3 h, 160–180 °C) to yield **378** (84%)¹⁸⁵.



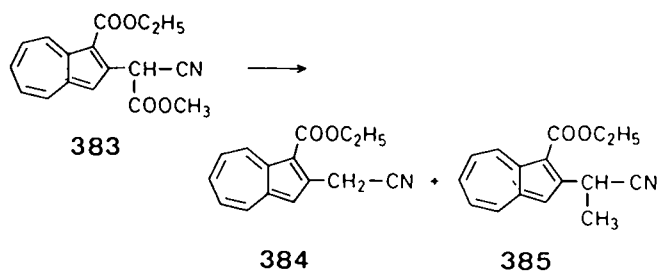
The deethoxycarbonylation of **379** to yield **380** (63%) can be accomplished in a similar manner¹⁸⁶.



The α -cyano ester **381** can be deethoxycarbonylated by heating with sodium cyanide in DMSO (6 h, 160–170 °C) to give **382** (68%)¹⁸⁷.



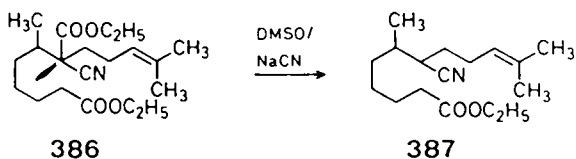
When **383** is heated under reflux in DMF containing lithium iodide dihydrate for 1.5 h, a mixture of **384** and **385** in a 1:1.6 ratio is produced. Compound **385** arises via methylation by iodomethane which is formed during the dealkoxycarbonylation¹⁸⁸.



If a little acetic acid is added to the lithium iodide dihydrate/DMF demethoxycarbonylation medium, **383** gives the desired product **384** in a 75% yield.

6.2. Disubstituted Substrates

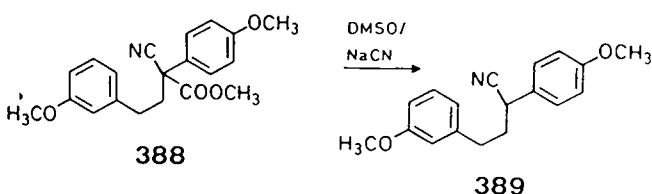
The α -cyano ester **386** can be demethoxycarbonylated by heating with sodium cyanide in DMSO to yield **387** (54%)¹⁸⁷.



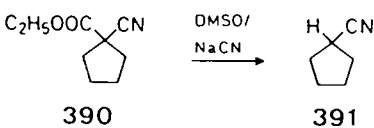
Ethyl 6,11-Dimethyl-7-cyano-dodec-10-enoate (**387**)¹⁸⁷:

A mixture of **386** (20 g, 0.057 mol), dry DMSO (25 ml), and dry sodium cyanide (3.3 g, 0.067 mol) is heated at 160–170 °C in an oil bath for 6 h. The mixture is cooled, poured into cold water (100 ml), and extracted with petroleum ether (b.p. 60–80 °C). The extract is washed with water and 10% aqueous sodium carbonate solution. The product is distilled under reduced pressure; yield: 12 g (54%); b.p. 160–165 °C/2 torr.

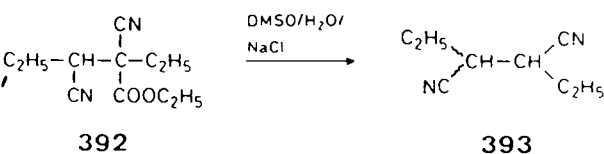
Demethoxycarbonylation of **388** by refluxing in DMSO containing sodium cyanide gives the nitrile **389** (91%)¹⁸⁹.



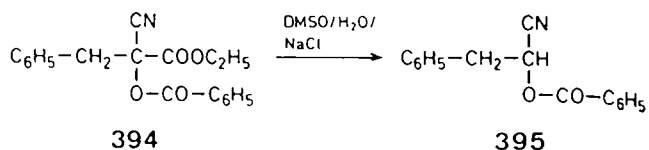
Cyclopentanecarbonitrile (**391**, 75% yield) can be prepared by reaction of **390** with sodium cyanide in DMSO under reflux (2 h). The use of sodium chloride in wet DMSO is reported as being unsuccessful in the attempted conversion of **390** to **391**¹⁹⁰.



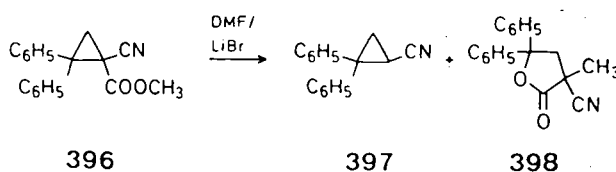
The 2,3-dicyano ester **392** can be demethoxycarbonylated by heating in wet DMSO containing some sodium chloride to yield *meso*- and *racemic*-**393** (55%, based on the preparation of **392** from ethyl cyanoacetate)¹⁹¹.



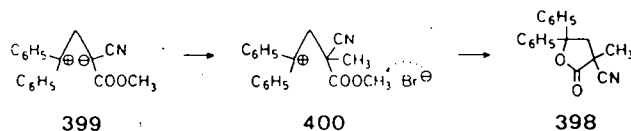
Reaction of **394** in wet DMSO containing sodium chloride (175–200 °C, 0.5 h) gives poor yields of **395** (1–6%) and many unidentified products¹⁹². A 6% yield of **395** is reported upon heating **394** at 175 °C in anhydrous DMSO for 2 h.



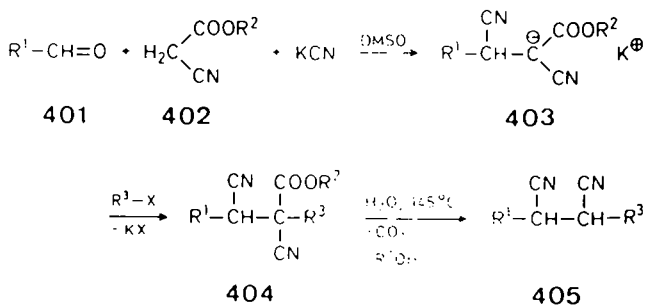
The demethoxycarbonylation of the cyclopropyl cyano ester **396** with lithium bromide in undried DMF (sealed tube, 24 h, 126 °C) leads to **397** (53%) and lactone **398** (23%)¹⁹². If the reaction is performed in an open flask (bromomethane can escape) only **397** and recovered **396** can be isolated. The product **397** probably arises via an attack of the bromide ion on the methyl group of ester **396** ($B_{AL}2$) to yield the carboxylate anion which then decarboxylates (a concerted mechanism is also possible).



The ring-opened intermediates such as **399** and **400** are proposed to rationalize the formation of lactone **398** and also the facile racemization of chiral starting materials. The formation of **397** was much faster in the presence of moisture and much faster relative to racemization of (+)-**396** in the absence of moisture.



The dealkoxycarbonylation of α -cyano esters in wet DMSO in the presence of potassium cyanide has been adapted to the synthesis of 2,3-disubstituted and 2-substituted succinodinitriles. Using DMSO as the solvent, the entire synthesis sequence can be performed in a one-pot reaction as outlined in Scheme E¹⁹¹. The yields of six dinitriles which were prepared by this route are summarized in Table 8.



Scheme E

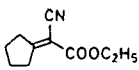
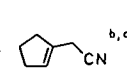
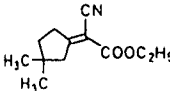
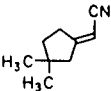
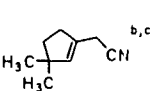
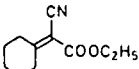
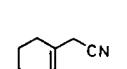
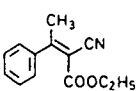
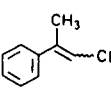
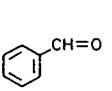
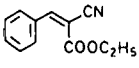
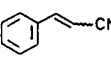
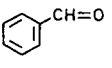
Table 8. Succinodinitriles **405** prepared via Scheme E¹⁹¹

R ¹	R ³ -X	Yield [%] ^a
H ₃ C	H ₃ C-J	23 ^b
C ₂ H ₅	C ₂ H ₅ -J	62 ^c
<i>i</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇ -J	61 ^c
	H ₃ C-J	17 ^d
<i>i</i> -C ₃ H ₇	 -CH ₂ -Cl	53 ^e
<i>i</i> -C ₃ H ₇	HCl	70

^a Yields based on ethyl cyanoacetate.^b Mixture of *meso* and *racemic* forms.^c Racemate only (m.p. data).^d Mixture of *erythro* and *threo* forms.^e *threo* form only.

The dealkoxycarbonylations of 2-cyano-2-alkenoates with wet DMSO containing sodium chloride lead to reasonable yields of unsaturated nitriles¹⁹³. Examples and products are tabulated in Table 9.

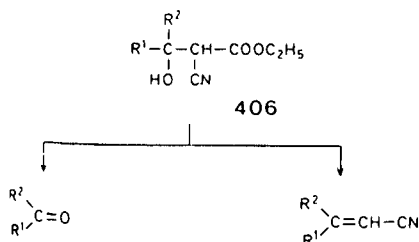
Table 9. Deethoxycarbonylations of 2-cyano-2-alkenoates¹⁹³

Substrate	Products ^a
	 +  ^{b,c}
	 +  ^{b,c}
	 +  +  ^d
	 + 
	 + 

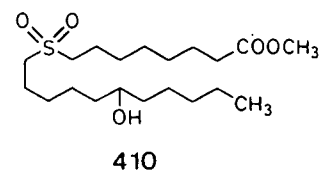
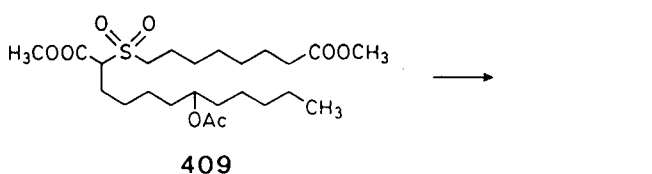
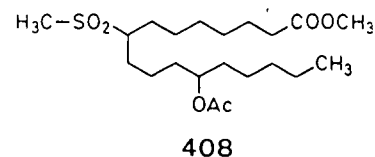
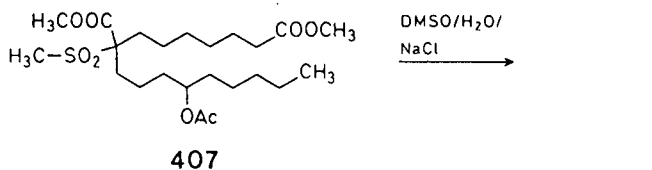
55-66% yields excluding 20% of the corresponding carbonyl compounds.

^b Ketone detected by formation of 2,4-DNP derivative.^c $\alpha:\beta:\gamma$ ratio of 3-4:1.^d $\alpha:\beta:\gamma$ ratio of 1:2.

It is also noted that in the case of entry 4 (Table 9) the sodium chloride is unnecessary. The conjugate addition of water leads to **406** which deethoxycarbonylates with elimination of hydroxide ion to yield the α,β -unsaturated nitrile or it can undergo a retro-aldol reaction to yield some carbonyl product which is isolated as a by-product.

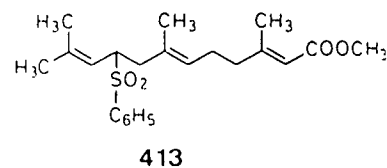
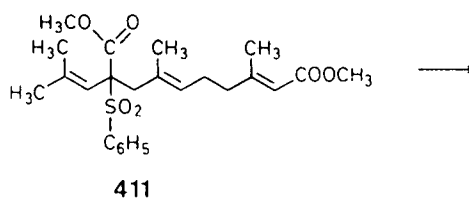
7. α -Alkyl- or -Arylsulfonyl Esters

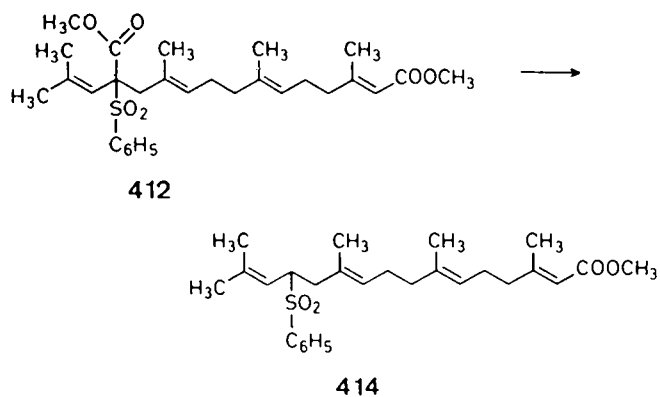
Demethoxycarbonylation of **407** (sodium chloride in wet DMSO) yields the sulfone **408** (95%)¹⁹⁴. In a similar fashion, **409** can be converted into **410** (48%), the acid being formed by hydrolysis of the crude product with methanolic potassium hydroxide solution.

Methyl 8-Methylsulfonyl-12-acetoxyheptadecanoate (**408**)¹⁹⁴:

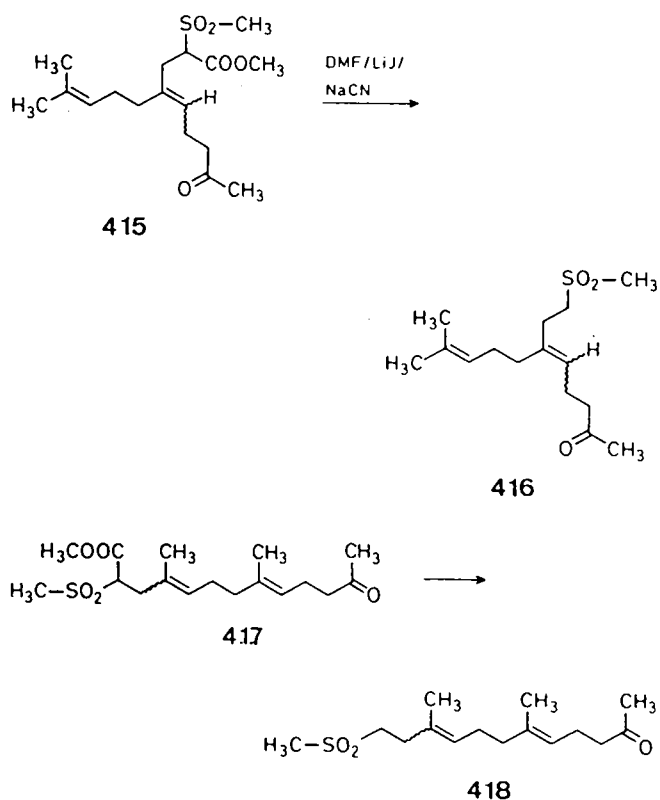
A stirred mixture of the ester **407** (36.7 g, 0.077 mol), sodium chloride (4.68 g, 0.08 mol), and DMSO (60 ml containing 1.6% water) is heated under a nitrogen blanket in an oil bath (185 °C) for 5 h. The mixture is concentrated in vacuo at 100 °C to yield an oily mixture which is diluted with water. This is acidified with 6 normal hydrochloric acid and then extracted with ether. The ether extract is washed with water, dried with sodium sulfate, and concentrated in vacuo to give **408**: yield 31 g (95%).

The α -phenylsulfonyl esters **411** and **412** on treatment with lithium iodide trihydrate or sodium cyanide in DMF at 120 °C for 17 h yield **413** and **414** in 59% and 44% yields, respectively¹⁹⁵.

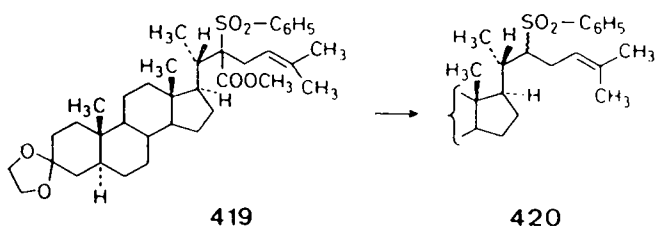




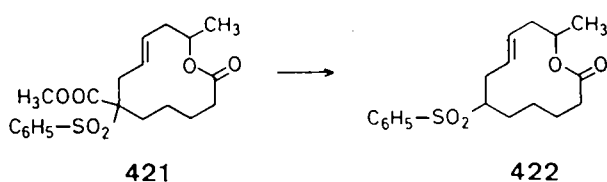
Demethoxycarbonylation of **415** with lithium iodide trihydrate and sodium cyanide in DMF yields **416** (78%)^{4,196}. In a similar procedure **417** can be converted into **418** (78%)¹⁹⁷.



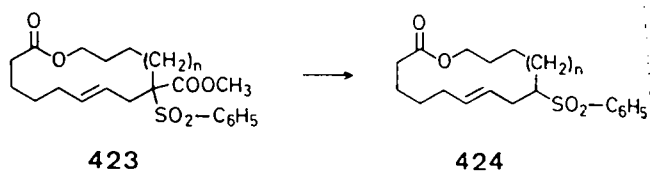
Demethoxycarbonylation of the α -methoxycarbonyl phenyl sulfone **419** with tetramethylammonium acetate in HMPT (100–105 °C, 15 h) yields **420** (78%)¹⁹⁸.



Demethoxycarbonylation of **421** with tetramethylammonium acetate in HMPT at 95 °C yields **422** (86%)¹⁹⁹.

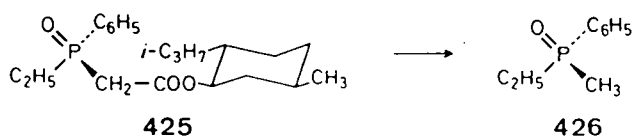


Lactone **424** ($n=1$) can be prepared by heating **423** ($n=1$) with tetramethylammonium acetate in HMPT (90–95 °C, 76%). Similarly, **424** ($n=3$) could be prepared from **423** ($n=3$, 82%)²⁰⁰.



8. Phosphine Oxides

One example of the use of a dealkoxycarbonylation which leads to an optically active phosphine oxide is reported²⁰¹. The demethoxycarbonylation of (–)-ethyl-(menthoxy carbonylmethyl)-phenyl-phosphine (**425**; a single diastereoisomer and enantiomeric at both the menthyl and phosphorus residues) can be effected by heating with lithium chloride in wet DMSO to give **426** (60%). The reaction proceeds without racemization at phosphorus. Attempted demethoxycarbonylation of **425** using chlorotrimethylsilane and sodium iodide or alumina in dioxan and water were unsuccessful. The use of 48% hydrobromic acid is also effective in bringing about this type of cleavage but in this case has to be avoided since optically active phosphines are known to undergo extensive racemization under acidic conditions.

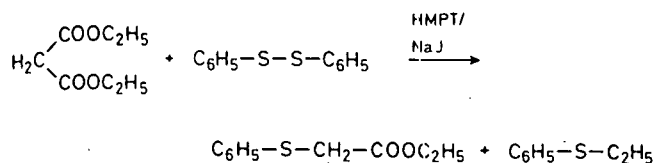


9. Dealkoxycarbonylations in the Presence of Other Electrophiles

The dealkoxycarbonylations of substrates such as geminal diesters, β -keto esters, and α -cyano esters involve carbanionic intermediates which are protonated by water in aqueous dipolar aprotic media to yield esters, ketones, and nitriles, respectively. In the presence of other electrophiles in anhydrous dipolar aprotic media, the carbanions can be trapped and lead to other products.

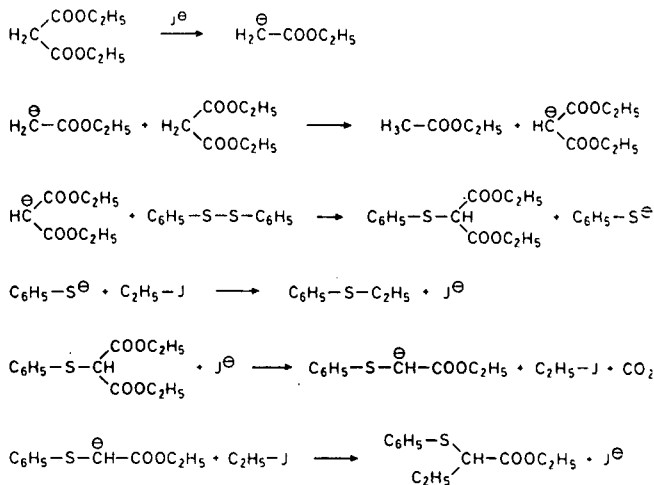
9.1. α -Sulfonylations

The dealkoxycarbonylative sulfonylations of geminal diesters, β -keto esters, and α -cyano esters in HMPT in the presence of sodium iodide at 150–160 °C yield α -phenylthio esters, α -phenylthio ketones, and α -phenylthio nitriles, respectively²⁰². For example, on heating a solution of diethyl malonate, diphenyl disulfide, and sodium iodide in HMPT, ethyl phenylthioacetate and ethyl phenyl sulfide can be isolated in 46% and 40% yields, respectively.



A variety of salts and solvents were investigated and the highest yields of α -sulfonylated esters were obtained with molar ratios of diester : disulfide : sodium iodide of 2 : 1 : 1–2 (82–84% yields based on diphenyl disulfide). The use of DMSO or sulfolane as solvents with sodium iodide led to poorer yields of the α -sulfonylated esters.

Some ethyl 2-phenylthiobutanoate was also formed as a by-product (8–9%). The formation of this product in those cases where excess diethyl malonate is present has been rationalized by the following mechanistic pathway (Scheme F). Other examples of α -sulfonylations are listed in Table 10.



Scheme F

Table 10. Sulfonylations of Geminal Diesters, β -Keto Esters, and Ethyl Cyanoacetate²⁰²

Reactant ^a	Product	Yield [%]
$n\text{-C}_4\text{H}_9\text{--CH}(\text{COOC}_2\text{H}_5)_2$	$n\text{-C}_4\text{H}_9\text{--CH}(\text{COOC}_2\text{H}_5)\text{--S--C}_6\text{H}_5$	40
$\text{C}_6\text{H}_5\text{--CH}_2\text{--CH}(\text{COOC}_2\text{H}_5)_2$	$\text{C}_6\text{H}_5\text{--CH}_2\text{--CH}(\text{COOC}_2\text{H}_5)\text{--S--C}_6\text{H}_5$	46
$n\text{-C}_3\text{H}_7\text{--C}(\text{COOC}_2\text{H}_5)_2$	$n\text{-C}_3\text{H}_7\text{--C}(\text{COOC}_2\text{H}_5)\text{--S--C}_6\text{H}_5$	60
$\text{H}_3\text{C--C}(\text{COOCH}_3)_2$	$\text{H}_3\text{C--C}(\text{COOCH}_3)\text{--S--C}_6\text{H}_5$	71
$\text{C}_6\text{H}_5\text{--CH}_2\text{--C}(\text{COOC}_2\text{H}_5)_2$	$\text{C}_6\text{H}_5\text{--CH}_2\text{--C}(\text{COOC}_2\text{H}_5)\text{--S--C}_6\text{H}_5$	66
$\text{H}_3\text{C--C}(=\text{O})\text{--CH}_2\text{--COOC}_2\text{H}_5$	$\text{H}_3\text{C--C}(=\text{O})\text{--CH}_2\text{--S--C}_6\text{H}_5$ + $\text{H}_3\text{C--C}(=\text{O})\text{--CH(S--C}_6\text{H}_5)\text{--COOC}_2\text{H}_5$	47 + 8
$\text{C}_6\text{H}_5\text{--C}(=\text{O})\text{--CH}_2\text{--COOC}_2\text{H}_5$	$\text{C}_6\text{H}_5\text{--C}(=\text{O})\text{--CH}_2\text{--S--C}_6\text{H}_5$ + $\text{C}_6\text{H}_5\text{--C}(=\text{O})\text{--CH(S--C}_6\text{H}_5)\text{--COOC}_2\text{H}_5$	36 + 30
$\text{Cyclopent-2-en-1-one--COOCH}_3$	$\text{Cyclopent-2-en-1-one--S--C}_6\text{H}_5$ + $\text{Cyclopent-2-en-1-one--S--C}_6\text{H}_5$	47 + 5
$\text{Cyclopent-2-en-1-one--CH}_3\text{--COOCH}_3$	$\text{Cyclopent-2-en-1-one--CH}_3\text{--S--C}_6\text{H}_5$	49
$\text{NC--CH}_2\text{--COOC}_2\text{H}_5$	$\text{NC--CH}_2\text{--S--C}_6\text{H}_5$ + $\text{NC--CH(S--C}_6\text{H}_5)\text{--COOC}_2\text{H}_5$ + $\text{NC--CH(S--C}_6\text{H}_5)\text{--C}_2\text{H}_5$	23 + 3 + 15

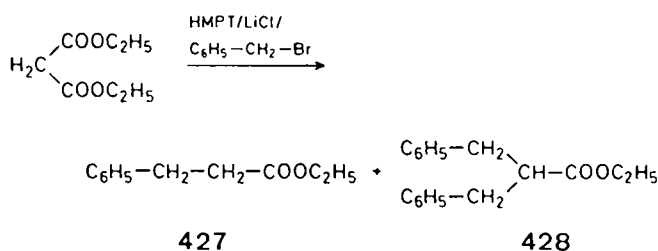
^a 2 mmol each of substrate, diphenyl disulfide, and sodium iodide in HMPT (2 ml) heated at 160–170 °C for 1 h.

Methyl 2-Phenylthio-2-methylpropanoate²⁰²:

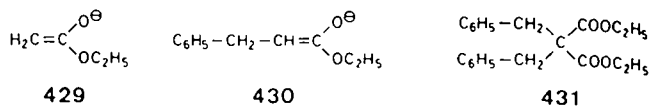
A mixture of dimethyl dimethylmalonate (320 mg, 2 mmol), diphenyl disulfide (436 mg, 2 mmol), sodium iodide (360 mg, 2 mmol) and HMPT (2 ml, distilled from sodium hydride) is heated for 1 h at 165–170 °C. The mixture is cooled to room temperature and poured into water (50 ml). The product is extracted with ether (2 × 50 ml), and the organic extract is washed with water, and dried with anhydrous sodium sulfate. The solvent is removed under reduced pressure and the residue is separated by silica gel T.L.C. (hexane/ether, 6:1) to yield the product; yield: 298 mg (71%); m.p. 41–43 °C.

9.2. α -Alkylations**9.2.1. Intermolecular Alkylations**

In the presence of lithium chloride and benzyl bromide or *n*-octyl bromide, β -keto esters, geminal diesters, and ethyl cyanoacetate in HMPT react to yield α -alkylated ketones, esters and nitriles, respectively²⁰³. Diethyl malonate in HMPT in the presence of lithium chloride and benzyl bromide (160 °C, 1 h) yields **427** (51%) and **428** (26%).

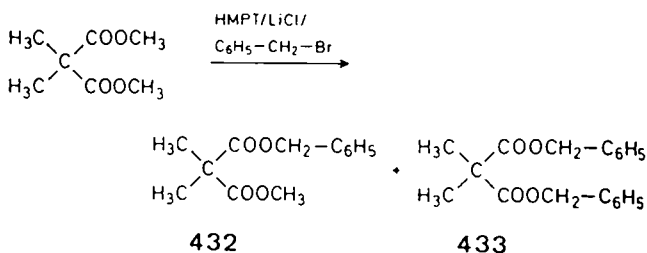


The ester **427** arises from C-benylation of the intermediate carbanionic intermediate **429**. The bis-alkylated ester **428** could arise from benzylation of carbanion **430** (formed from alkylation of the anion of diethyl malonate followed by deethoxycarbonylation) or from **431** (bis-benylation of diethyl malonate) via a dealkoxycarbonylation.



It is also noted that use of DMSO or sulfolane as solvents led to decreased deethoxycarbonylation rates. The salts lithium bromide, sodium chloride, potassium chloride, and tetramethylammonium bromide gave poor yields of **427** and **428**.

Dimethyl diethylmalonate on reaction with lithium chloride in HMPT in the presence of benzyl bromide (155 °C, 1 h) gives **432** (30%) and **433** (18%). In this case the carboxylate anion (formed from B_{AL}2 cleavage of Cl[−]) is trapped before it decarboxylates. Additional examples of the synthetic utility of this alkylative dealkoxycarbonylation procedure are listed in Table 11.

**Table 11.** Alkylative Dealkoxycarbonylations²⁰³

Substrate ^a	Alkyl Halide	Product	Yield [%]
$n\text{-C}_4\text{H}_9-\text{CH}(\text{COOC}_2\text{H}_5)_2$	$\text{C}_6\text{H}_5-\text{CH}_2-\text{Br}$	$n\text{-C}_4\text{H}_9-\text{CH}(\text{C}_6\text{H}_5-\text{CH}_2)-\text{COOC}_2\text{H}_5 + n\text{-C}_4\text{H}_9-\text{C}(\text{C}_6\text{H}_5-\text{CH}_2)_2-\text{COOC}_2\text{H}_5$	71 + 10
$\text{H}_3\text{C}-\text{C}(=\text{O})-\text{NH}-\text{CH}(\text{COOC}_2\text{H}_5)_2$	$\text{C}_6\text{H}_5-\text{CH}_2-\text{Br}$	$\text{H}_3\text{C}-\text{C}(=\text{O})-\text{NH}-\text{CH}(\text{C}_6\text{H}_5-\text{CH}_2)-\text{COOC}_2\text{H}_5$	52
$\text{H}_3\text{C}-\text{C}(=\text{O})-\text{NH}-\text{CH}(\text{COOC}_2\text{H}_5)_2$	$n\text{-C}_8\text{H}_{17}-\text{Br}$	$\text{H}_3\text{C}-\text{C}(=\text{O})-\text{NH}-\text{CH}(n\text{-C}_8\text{H}_{17})-\text{COOC}_2\text{H}_5$	22
$\text{H}_3\text{C}-\text{C}(=\text{O})-\text{CH}_2-\text{COOC}_2\text{H}_5$	$\text{C}_6\text{H}_5-\text{CH}_2-\text{Br}$	$\text{C}_6\text{H}_5-\text{CH}_2-\text{CH}_2-\text{C}(=\text{O})-\text{CH}_3$	24
$\text{Cyclopent-2-en-1-one}-\text{COOCH}_3$	$\text{C}_6\text{H}_5-\text{CH}_2-\text{Br}$	$\text{Cyclopent-2-en-1-one}-\text{CH}_2-\text{C}_6\text{H}_5 + \text{Cyclopent-2-en-1-one}-\text{CH}_2-\text{C}_6\text{H}_5$	47 + 10
$\text{Cyclopent-2-en-1-one}-\text{C}(=\text{O})\text{CH}_3$	$\text{C}_6\text{H}_5-\text{CH}_2-\text{Br}$	$\text{Cyclopent-2-en-1-one}-\text{C}(=\text{O})\text{CH}_2-\text{C}_6\text{H}_5$	35
$\text{NC}-\text{CH}_2-\text{COOC}_2\text{H}_5$	$\text{C}_6\text{H}_5-\text{CH}_2-\text{Br}$	$\text{C}_6\text{H}_5-\text{CH}_2-\text{CH}_2-\text{CN} + \text{C}_6\text{H}_5-\text{CH}_2-\text{CH}(\text{C}_6\text{H}_5)-\text{CN}$	15 + 52
$\text{NC}-\text{CH}_2-\text{COOC}_2\text{H}_5$	$\text{C}_6\text{H}_5-\text{CH}_2-\text{Br}$	$\text{C}_6\text{H}_5-\text{CH}_2-\text{CH}_2-\text{CN} + \text{C}_6\text{H}_5-\text{CH}_2-\text{CH}(\text{C}_6\text{H}_5)-\text{CN}$	30 + 64
$\text{NC}-\text{CH}_2-\text{COOC}_2\text{H}_5$	$n\text{-C}_8\text{H}_{17}-\text{Br}$	$n\text{-C}_8\text{H}_{17}-\text{CH}_2-\text{CN} + n\text{-C}_8\text{H}_{17}-\text{CH}(\text{C}_8\text{H}_{17})-\text{CN}$	15 + 4

^a Mol ratio of ester:alkyl halide:lithium chloride = 1:2:1:1 with HMPT as solvent

^b 150–160 °C for 1–1.5 h.

^c 160 °C for 0.3 h.

^d 140 °C for 2 h.

9.2.2. Intramolecular Alkylations

A synthesis of cyclopropyl ketones **435** has been developed via intramolecular alkylations of α -acyl- γ -butyrolactones effected by halide anions in dipolar aprotic media (**434** $\rightarrow$ **435**)²⁰³. For example, heating **434a** in the presence of one molar equivalent of sodium bromide in DMSO (160 °C for 6 h) leads to ketone **435a** (92%). The use of sodium chloride, sodium iodide, potassium chloride, or tetramethylammonium bromide in DMSO gave **435a** in 50–76% yields, respectively. In refluxing DMF and in the presence of sodium bromide (6 h), **434a** led to **435a** in a 73% yield.



434 a $R^1 = C_6H_5$, $R^2 = H$

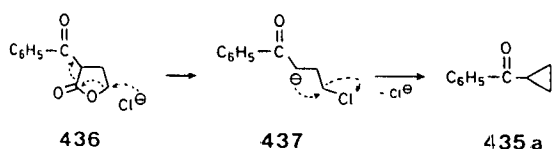
b $R^1 = CH_3$, $R^2 = H$

c $R^1 = CH_3$, $R^2 = CH_3$

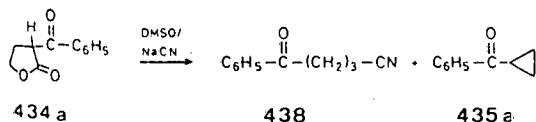
435

The conversion of **434b** to **435b** can be accomplished by heating at 170 °C for 1.5 h in HMPT (5 ml) in the presence of sodium iodide (10 mmol)²⁰⁴. The product **435b** distilled from the reaction mixture in an 86% yield. Using lithium chloride in HMPT at 160–170 °C for 2.5 h, **435b** was obtained in a 42% yield. In a similar manner, **434c** and sodium iodide in HMPT at 180 °C for 1.5 h gives **435c** (81%).

The following mechanism was proposed for the overall reaction:



Consistent with this mechanism is the observation that on treatment of **434a** with sodium cyanide in DMSO, **438** (17%) and a small amount of **435a** (3.6%) are formed.



Examples of other substrates which were converted into cyclopropyl ketones are tabulated in Table 12.

Cyclopropyl Phenyl Ketone (**435a**)²⁰³:

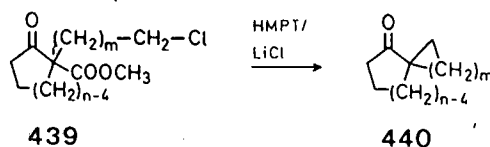
A mixture of **434a** (10 mmol) and alkali metal halide (11 mmol) in DMSO (10 ml) is heated at 160 °C under a nitrogen atmosphere. After cooling the mixture, water is added and the product is extracted into chloroform. The extract is washed with water, dried, and then concentrated. The residue is chromatographed over silica gel to yield pure **435a**.

Table 12. Conversion^a of Lactones **434** to Cyclopropyl Ketones **435**^{203, 204}

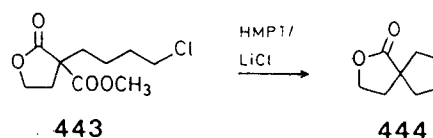
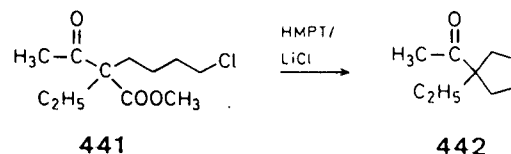
R^1	R^2	Yield [%] of 435
	H	69
	H	69
	H	74
	CH ₃	82
		100
	H	65
H ₃ C	H	52
	H	70

^a Performed in DMSO (160 °C, 6–12 h) except for the last two entries which were done in DMF (reflux, 55–59 h). The salt was sodium chloride except in the last three entries which used sodium bromide.

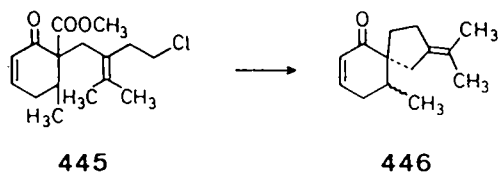
The regiospecific intramolecular alkylation of enolates generated by halide-induced dealkoxycarbonylations of ω -halo- β -keto esters is a useful preparative route to spirocyclic ketones²⁰⁵. Reaction of the cycloalkanone carboxylates **439** ($n=5$, $m=1$; $n=5-7$, 12 , $m=3$) with lithium chloride in HMPT (125–140 °C, 1–1.5 h) leads to the corresponding ketones **440** in 64–75% yields. The use of *N*-methyl-2-pyrrolidone as a solvent leads to similar results but DMF was less satisfactory.



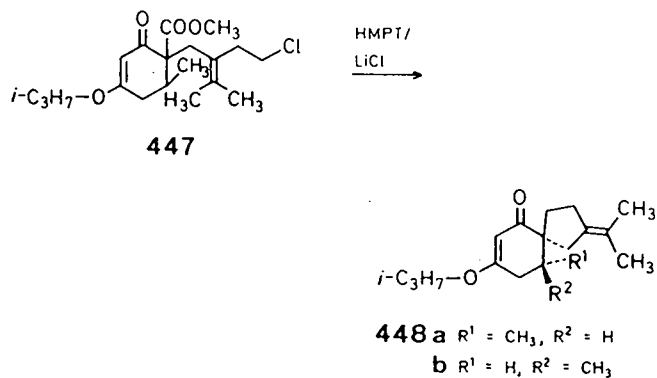
In similar procedures, annelation of the β -keto ester **441** leads to the acetylcyclopentane **442** (80%) while the methyl lactone-carboxylate **443** gives the spirolactone **444** (69%).



Demethoxycarbonylation of the β -keto ester **445** yields ketone **446** (86%) as a 9:1 epimeric mixture. This ketone can be converted into a mixture of β -vetivone and *epi*- β -vetivone, or β -vetispirene (and its epimer).



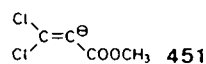
The keto ester **447** on treatment with lithium chloride/HMPT leads to the spiroketones **448** (98%, 9:1 epimeric mixture). Ketone **448a** can be converted into *racemic* β -vetivone in an excellent yield.



9.3. Chlorodemethoxycarbonylations

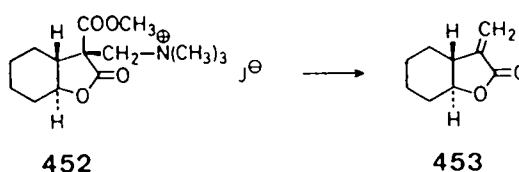
Dimethyl dichloromethylenemalonate (**449**) on reaction with potassium fluoride in sulfolane at 150 °C in the presence of dicyclohexyl-18-crown-6 yields **450** (70% based on 2 mol of **449**)²⁰⁶. The use of potassium chloride in place of potassium fluoride yields the same product.

A mechanistic route to **450** involves a demethoxycarbonylation of **449** to yield the vinyl carbanion **451** which then reacts with $\text{Cl}^\oplus$ to give **450**.



10. Dealkoxycarbonylations of Substrates with β -Elimination

On heating the salt **452** (DMF, 80 °C), the methylenelactone **453** is produced in high yield²⁰⁷, a deaminodemethoxycarbonylation process.



In a general synthetic route to α -substituted acrylonitriles, the quaternary ammonium salts **454** on being heated in DMF for 48 h at 80 °C yield **455**²⁰⁸. The results are tabulated in Table 13.

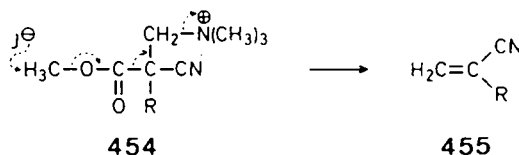
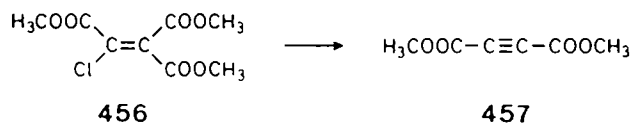


Table 13. α -Acrylonitriles **455** Prepared from **454**²⁰⁸

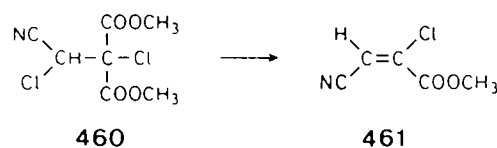
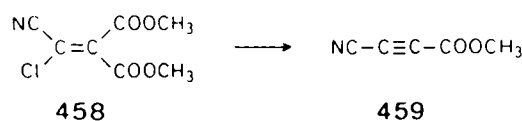
R	Yield [%] of 455
C_2H_5	41
$n\text{-C}_6\text{H}_{13}$	68
$i\text{-C}_3\text{H}_7$	41
$\text{H}_2\text{C}=\text{CH}-\text{CH}_2$	66
$\text{C}_6\text{H}_5-\text{CH}_2-$	71

Several heterocyclic substituted malonate esters which were previously discussed have been shown to undergo competitive ring-openings on dealkoxycarbonylations³³.

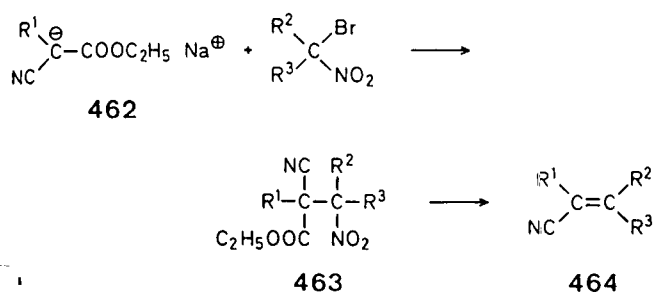
Dechlorodemethoxycarbonylation of **456** on heating in potassium chloride in sulfolane in the presence of dicyclohexyl-18-crown-6 (160 °C, 30 min) yields **457** (7%)²⁰⁶.



In a similar fashion, **458** leads to **459** (16%). Several other examples of saturated esters were also reported as, for example, vacuum distillation of **460** in the presence of tetraethylammonium chloride gives **461** (36%, mixture of isomers).



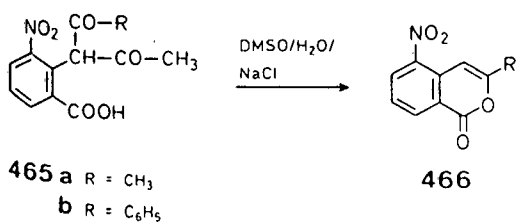
A procedure for the preparation of α,β -unsaturated nitriles has been developed which involves a denitrodealkoxycarbonylation effected in hot dipolar aprotic solvents. The sodium salts of ethyl α -alkylcyanoacetates **462** are treated with α -bromonitroalkanes in HMPT at room temperature to give the coupled products **463**. The resulting solution is heated at 120 °C for 1 h to effect the denitrodeethoxycarbonylation to yield **464** in good yields (Table 14)²⁰⁹. Other dipolar aprotic solvents such as DMF or DMSO were also used but higher temperatures (150 °C) and longer times (6 h) were needed.

Table 14. α,β -Unsaturated Nitriles **464**²⁰⁹.

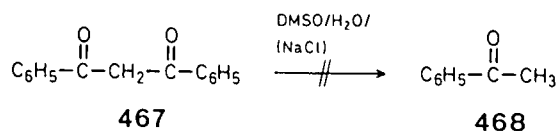
R ¹	R ²	R ³	Yield [%]
<i>i</i> -C ₃ H ₇	CH ₃	CH ₃	70
<i>i</i> -C ₃ H ₇	CH ₃	C ₂ H ₅	62 (E/Z = 1:3)
<i>i</i> -C ₃ H ₇	-(CH ₂) ₅ -		63
<i>n</i> -C ₄ H ₉	CH ₃	CH ₃	72
<i>n</i> -C ₈ H ₁₇	CH ₃	CH ₃	72
 -CH ₂	CH ₃	CH ₃	75
 -CH ₂	CH ₃	C ₂ H ₅	75 (E/Z = 1:2)
 -CH ₂	-(CH ₂) ₅ -		70

1. Related Reactions

The 1,3-dione **465a** was deacylated to yield the isocoumarin **466a** (67%) by heating in wet DMSO (170 °C, 4 h) containing some sodium chloride¹¹⁷. This product was also obtained in the absence of added sodium chloride. Similarly **465b** on refluxing in wet DMSO for 4 h gives **466b** (57%).

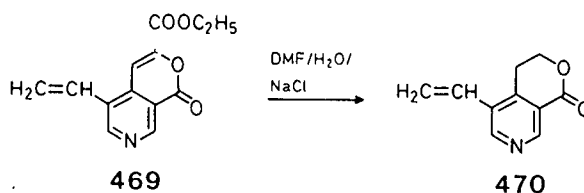


The conversions of **465a** and **465b** to **466a** and **466b** by water in DMSO represent a novel process for hydrolytic cleavage of 1,3-diones. On the other hand, it was also reported that **467** on being heated in wet DMSO (160–170 °C for 4 h) did not yield **468** in the presence or absence of sodium chloride. The use of wet HMPT was also unsuccessful.

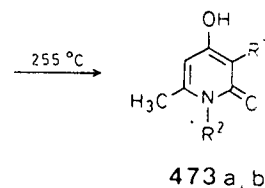
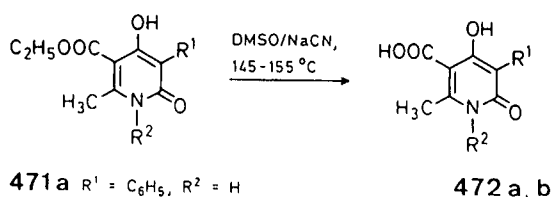


The cleavages of **465a** and **465b** are probably due to the strong electron-withdrawing character of the nitroaryl system which stabilizes the intermediate carbanion. Compound **318** on deethoxycarbonylation with sodium cyanide in DMSO yields some deacylated product **320** (20%)⁵⁴.

On heating the lactone **469** with sodium chloride in wet DMF for 3 days, a product identified as gentianine (**470**, 12%) was isolated²¹⁰.

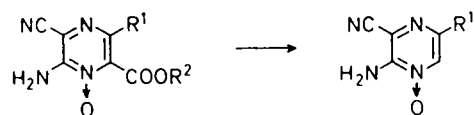


Treatment of the 4-hydroxy-2-pyridones **471a** or **471b** with sodium cyanide in DMSO (145–155 °C, 4 h) yields the acids **472a** (50%) or **472b** (44%), respectively²¹¹. Heating these acids to 255 °C leads to decarboxylations to afford the pyridones **473a** and **473b**, respectively.



The dealkoxycarbonylations of pyrazine *N*-oxides were investigated as a route to 2-amino-3-cyano-5-substituted pyrazines²¹². The pyrazine *N*-oxides **474a** and **474b** on reaction with sodium chloride in wet DMSO (170–185 °C) lead to loss of carbon dioxide but none of the expected pyrazines **475a** or **475b** could be detected.

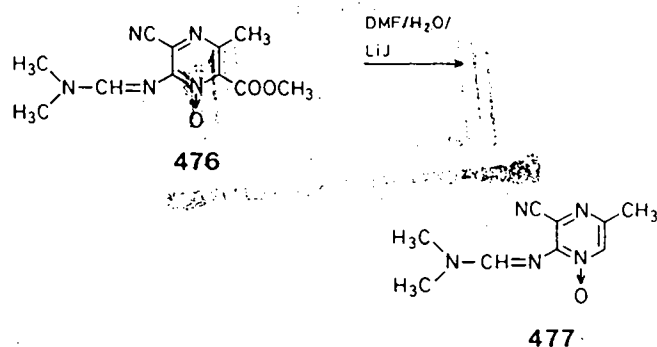
On the other hand, on heating **474a** or **474c** with lithium iodide in wet pyridine, the pyrazine *N*-oxides **475a** or **475b** could be isolated in yields of up to 21%.



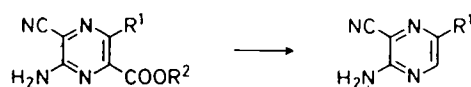
474 a $R^1 = (H_3CO)_2CH$, $R^2 = CH_3$
b $R^1 = (H_3CO)_2CH$, $R^2 = t-C_4H_9$
c $R^1 = R^2 = CH_3$

475

Pyrazine *N*-oxide **476** on being refluxed with lithium iodide in wet DMF for 1 h gives **477** (82%).

**476****477**

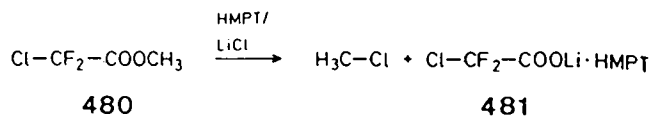
The dealkoxycarbonylations of the pyrazines **478a**, **b**, and **c** were also studied. Attempted deethoxycarbonylation of **478a** to prepare **479a** by heating with lithium iodide in wet DMF led only to products of apparent decomposition. However, the reaction of **478b** with lithium iodide in wet DMF (22 h) gives **479b**. The more sterically hindered ethyl ester **478c** required more vigorous conditions and only gave a small amount of **479c** (15%).



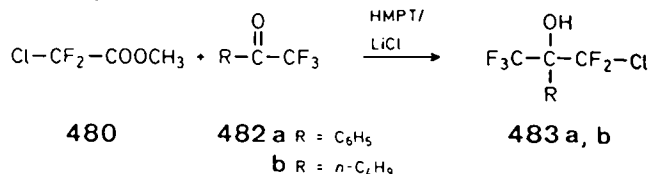
478 a $R^1 = (H_3CO)_2CH$, $R^2 = CH_3$
b $R^1 = R^2 = CH_3$
c $R^1 = CH_3$, $R^2 = C_2H_5$

479

Treatment of **480**, formed *in situ* at 40 °C in tetrahydrofuran, with lithium chloride/HMPT for 2 h leads to the unstable solid **481**. On refluxing the solution of **481** in tetrahydrofuran for 4 h, a quantitative evolution of carbon dioxide occurs. Decomposition of **480** by lithium chloride/HMPT in the presence of 2,2,2-trifluoroethanol yields chlorodifluoromethane. Reaction of **480** with lithium chloride/HMPT in the presence of polyfluoromethyl ketones in tetrahydrofuran results in the formation of tertiary alcohols.

**480****481**

Addition of **480** to a refluxing solution of lithium chloride/HMPT and trifluoromethyl ketones **482** in tetrahydrofuran results in the formation of alcohols **483a** and **483b** in yields of 63% and 38%, respectively²¹³.

**480**

482 a $R = C_6H_5$
b $R = n-C_4H_9$

483 a, b

12. Conclusions

The dealkoxycarbonylation procedures detailed here should continue to find new applications in synthetic chemistry. The reactions are easily performed and the isolation of products can readily be accomplished. Many functionalities survive the reaction conditions and isomerizations of multiple bonds generally do not occur. The choice of experimental conditions is dictated by the substrate structure. The use of lithium chloride in DMSO is recommended as an excellent salt-solvent combination for effecting dealkoxycarbonylations. The sodium cyanide/HMPT combination, while perhaps kinetically more rapid, is partially negated by the hazardous nature of these reagents.

It is with pleasure that I acknowledge the contributions of my coworkers who performed research on various projects related to dealkoxycarbonylations. The undergraduate students were B. J. Grenon, G. A. Glynn, J. M. Eldridge, J. Seastrom, and M. Marusa and the graduate students were A. J. Lovey, E. G. E. Jahngen, Jr., W. P. Stephens, and J. F. Westminster. I also wish to acknowledge the financial support of the Humphrey Chemical Company of North Haven, CT. In particular I wish to express my appreciation to Dr. B. J. Humphrey for his interest in this area of research.

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²¹³ See *Synthesis* 1982 (10), 821-822.

²¹⁴ F. Tureček, O. Turečková, J. Julák, *Collect. Czech. Chem. Commun.* **44**, 3111 (1979).

ANNEXURE - XIII

87

Classics in Total Synthesis

K. C. Nicolaou and
E. J. Sorensen

798

Targets, Strategies, Methods



With a Foreword by
E. J. Corey



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Front cover: A red-tide incident that occurred on 8th May 1976, off Matsushima Island, in Hyogo Prefecture, Japan. The structure shown is that of brevetoxin B, a neurotoxin produced by algae that proliferate during red-tide incidents. Brevetoxin B is believed to have been responsible for massive fish killings and poisoning of humans who ate affected seafood. The total synthesis of brevetoxin B is described in Chapter 37 of this book.

Back cover: Structure of vitamin B₁₂.

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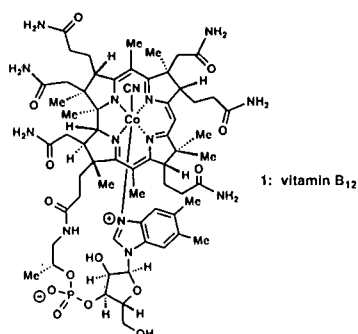
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797

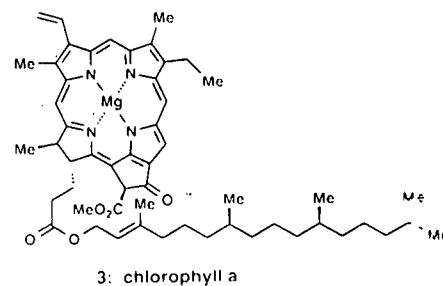
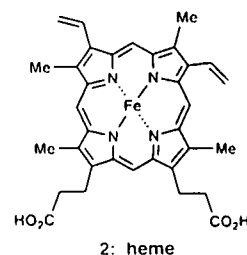
R. B. Woodward and A. Eschenmoser (1973)

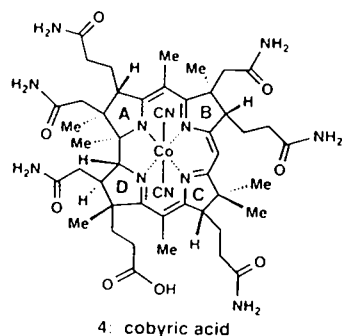
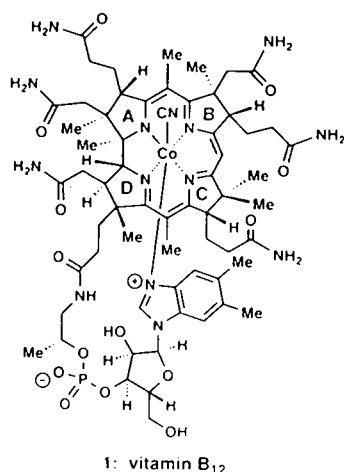
Vitamin B₁₂

8.1 Introduction

The total synthesis of vitamin B₁₂, the result of a close collaboration between the late Professor R. B. Woodward and his group at Harvard and Professor Albert Eschenmoser and his group at ETH Zürich, stands as one of the greatest achievements of synthetic organic chemistry.^{1a-d} Few natural product syntheses can match the pervasive impact that the total synthesis of vitamin B₁₂ has had on the science of organic chemistry. Novel bond-forming strategies, ingenious solutions to formidable synthetic problems, elegant applications of organic synthesis methodology, intriguing hypotheses about the biogenesis of vitamin B₁₂,² and the principles of orbital symmetry conservation³ all issued from this landmark achievement.

The vitamin B₁₂ story began in 1956 with the impressive X-ray crystallographic studies of Dorothy Crowfoot-Hodgkin and her collaborators which culminated in the elucidation of the complete structure of vitamin B₁₂ (1).⁴ By virtue of the stereochemical and constitutional complexity of the structure of vitamin B₁₂, these studies constituted, at the time, a great achievement in X-ray crystallography, and they provided a firm footing for serious synthetic studies. There is an interesting homology between the structures of vitamin B₁₂ (1), the blood pigment heme (2), and the leaf pigment chlorophyll a (3). Each molecule possesses a macrocyclic nucleus comprising four five-membered heterocyclic rings A, B, C, and D, and organized around a central metal atom. As we shall see later, the binding of a metal atom by the corrin nucleus of vitamin B₁₂ is a very useful property shared by precorrinoid structures (i.e. uncyclized corrin precursors). The binding of a metal atom by linear precorrinoid intermediates pre-organizes their structure and facilitates cyclization reactions.



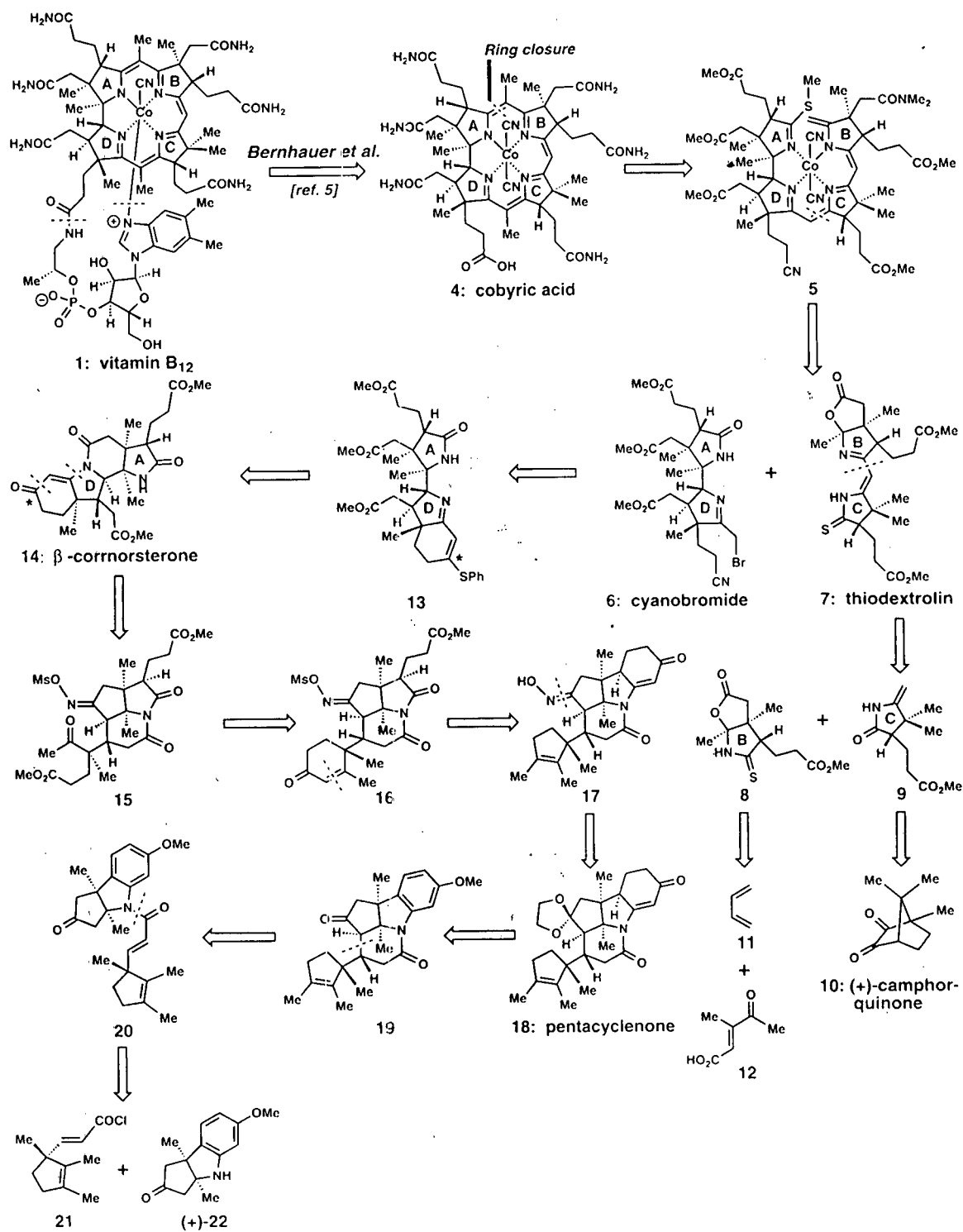


Although there are gross structural similarities between these three molecules, there is an important difference. Unlike the more modestly functionalized relatives heme and chlorophyll a, vitamin B₁₂ is rich in stereochemical detail. Organized around the periphery of the nucleus of vitamin B₁₂ (**1**) are nine asymmetric carbon atoms. Six of these are contiguous and are concentrated in the left wing, or A-D sector, of the molecule, while the remaining three are distributed between rings B and C. The spatial relationships among the various sectors of vitamin B₁₂ are such that it would be very difficult to use preexisting stereocenters in one sector to direct the stereochemical course of reactions that create new stereocenters in any of the other sectors. This situation mandates the adoption of a synthetic strategy wherein each sector or building block is prepared in enantiomerically pure form first and then joined with neighboring sectors. This convergent approach to the synthesis of vitamin B₁₂ could be highly efficient, and it could secure correct relative stereochemical relationships. Another point of interest is the observation that six out of seven side chains attached to the periphery of the vitamin B₁₂ nucleus terminate in a simple amide group, while the seventh accommodates a sequence of isopropanolamine, phosphate, ribose, and dimethylbenzimidazole groups. The last of these groups is also coordinated to the central cobalt atom.

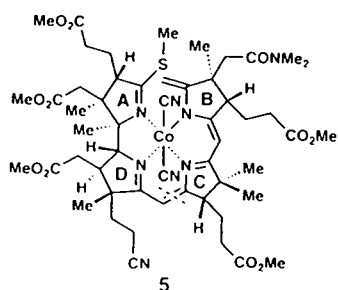
When the Woodward-Eschenmoser synthesis began, it was known from the work of Bernhauer *et al.*⁵ that cobyric acid (**4**), a naturally occurring substance, could be converted directly into vitamin B₁₂. Thus, the synthetic problem was reduced to the preparation of cobyric acid, a molecule whose seventh side chain terminates in a carboxylic acid group and is different from the other side chains. Two strategically distinct and elegant syntheses of the cobyric acid molecule evolved from the combined efforts of the Woodward and Eschenmoser groups and both will be presented. Although there is naturally some overlap, the two variants differ principally in the way in which the corrin nucleus is assembled.

8.2 Retrosynthetic Analysis and Strategy

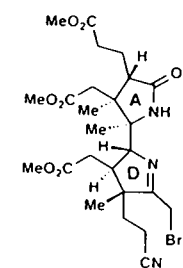
Scheme 1 outlines the retrosynthetic analysis of the Woodward-Eschenmoser A-B variant of the vitamin B₁₂ (**1**) synthesis. The analysis begins with cobyric acid (**4**) because it was demonstrated in 1960 that this compound can be smoothly converted to vitamin B₁₂.⁵ In two exploratory corrin model syntheses to both approaches to the synthesis of cobyric acid,⁶ the ability of secocorrinoid structures (e.g. **5**) to bind metal atoms was found to be central to the success of the macrocyclization reaction to give intact corrinoid structures. In the Woodward-Eschenmoser synthesis of cobyric acid, the cobalt atom situated in the center of intermediate **5** organizes the structure of the secocorrin, and promotes the cyclization



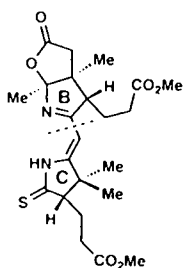
Scheme 1. Retrosynthetic analysis of the Woodward-Eschenmoser synthesis of cobyrinic acid (4).



reaction by bringing into spatial proximity the reactive functional groups contained within rings A and B of intermediate **5**. Retrosynthetic disconnection of **5** is most productive, for it furnishes two fragments of comparable complexity representing the left and right wings of the molecule. Fragment **6**, the left wing or A-D sector, is referred to as cyanobromide, and it contains the six contiguous asymmetric carbon atoms. This intermediate was the conquest of Woodward's group at Harvard. The bromine atom in this intermediate is to serve as a leaving group in a reaction that will allow the two halves of the molecule to be joined. In addition, it is interesting to note that the side chain that is destined to terminate in a carboxylic acid group is differentiated from the others. It is historically significant that important observations were made during the course of the synthesis of compound **6** that provided the impetus for the development of the Woodward-Hoffmann rules for orbital symmetry conservation.³

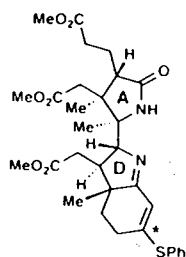


6: cyanobromide

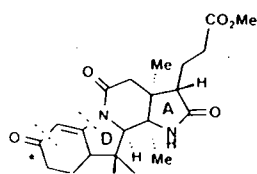


7: thiodextrolin

Thiodextrolin (**7**), an intermediate that was prepared by the Eschenmoser group at ETH, represents the right-wing portion of cobyrinic acid, and it contains rings B and C. An interesting structural feature of thiodextrolin is the thioamide grouping; this conspicuous function imparts nucleophilic character to intermediate **7**. In the synthetic direction (*vide infra*), the electrophilic cyanobromide **6** and the nucleophilic thiodextrolin (**7**) are joined by an alkylative Eschenmoser sulfide contraction reaction.⁷ Retrosynthetic simplification of thiodextrolin (**7**) is rather straightforward furnishing rings B (**8**) and C (**9**). In contrast to the nucleophilic thioamide in thiodextrolin, the thioamide present in B-ring intermediate **8** is to be used as an electrophile in an interesting oxidative Eschenmoser coupling reaction⁷ with the nucleophilic enamide present in C-ring intermediate **9**. A clever sequence of reactions commencing with a Diels-Alder reaction⁸ between butadiene (**11**) and β -methyl- β -acetylacrylic acid (**12**) could potentially furnish intermediate **8**, and a concise sequence starting from (+)-camphorquinone (**10**) could give intermediate **9**.



13

14 β -cornnorsterone

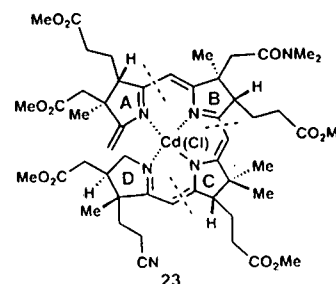
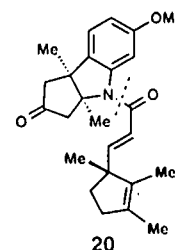
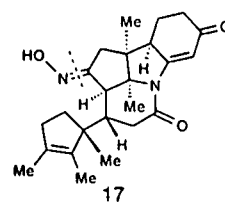
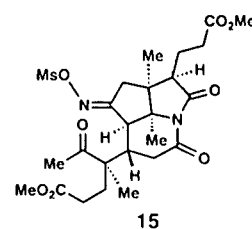
A retrosynthetic analysis of cyanobromide **6** is much less straightforward. The structural relationship between cyanobromide **6** and its predecessor, intermediate **13**, is close. An oxidative scission of the thioether double bond in **13** would furnish an *S*-phenyl thioate at one terminus and an aldehyde at the other. A straightforward sequence of functional group interconversions could then complete the synthesis of cyanobromide **6**. β -Cornnorsterone (**14**), a key intermediate which derives its name from its structural relationship to corrins and steroids, carries the six contiguous stereogenic centers present in the corresponding part of vitamin B₁₂. Although the homology between intermediate **13** and β -cornnorsterone may seem vague, compound **13** could conceivably be formed in one step from **14**. In the event that methanol and thio-phenol could be induced to react with **14** in a completely chemoselective fashion, then **13** would form after loss of a water molecule. By far the most productive single-step transformation in the synthe-

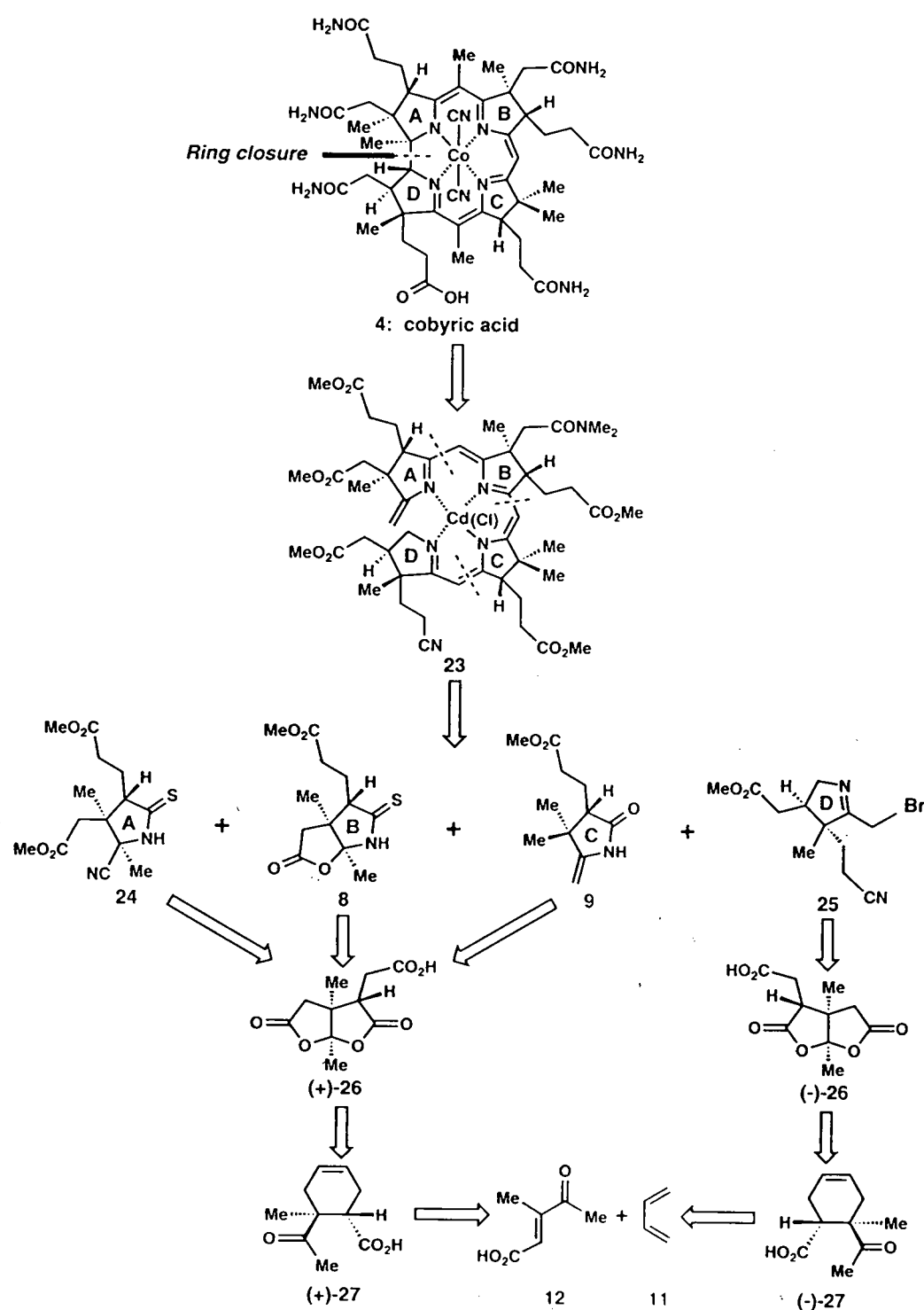
90

sis of cyanobromide **6** is the conversion of oxime mesylate **15** into a stereoisomeric mixture of α - and β -cornorsterones. These two diastereomeric substances are epimeric at the stereocenter adjacent to the ring A lactam carbonyl and, for clarity, only the desired isomer **14** is indicated. In this amazing transformation, the five-membered ring that bears the oxime mesylate is converted into a six-membered lactam ring through a Beckmann rearrangement.⁹ It is important to note that the stereochemistry of the oxime mesylate in **15** would ensure that the carbon-carbon bond *trans* to the mesylate will migrate during the Beckmann rearrangement. Once the six-membered lactam ring is formed, its nitrogen atom would find itself in proximity to the ketone carbonyl group. This nitrogen atom could then attack the ketone carbonyl group, and, at some point, the active methyl group of the ketone could attack the methoxycarbonyl group. Three new rings could potentially be formed in this very productive transformation. Ozonolytic scission of both carbon-carbon double bonds in intermediate **17**, followed sequentially by esterification, intramolecular cyclodehydration, and mesylation reactions could conceivably furnish intermediate **16**. Cleavage of the carbon-carbon double bond in **16**, again with ozone, followed by treatment with diazomethane, was projected to give intermediate **15**.

A sequence of straightforward functional group interconversions leads from **17** back to compound **20** via **18** and **19**. In the synthetic direction, a base-induced intramolecular Michael addition reaction could create a new six-membered ring and two stereogenic centers. The transformation of intermediate **20** to **19** would likely be stereoselective; substrate structural features inherent in **20** should control the stereochemical course of the intramolecular Michael addition reaction. Retrosynthetic disassembly of **20** by cleavage of the indicated bond provides precursors **21** and **22**. In the forward sense, acylation of the nitrogen atom in **22** with the acid chloride **21** could afford amide **20**.

Scheme 2 outlines the retrosynthetic analysis of the Eschenmoser variant of the synthesis of cobyrinic acid (**4**). The approach outlined in Scheme 1 represents the A-B variant; it accomplishes the assembly of the macrocyclic corrin nucleus of cobyrinic acid by a cyclization reaction that creates a carbon-carbon bond between rings A and B. An unconventional and equally elegant approach, the A-D variant, was developed in Zürich by the Eschenmoser group. The distinguishing feature of the A-D variant is the ring closure joining rings A and D via a metal template assisted, photo-induced cycloisomerization of secocorrin-metal complex **23**.^{1d} It is noteworthy that this reaction is quite facile and it creates the natural configuration at the A-D junction with 95% stereoselectivity. Since the Eschenmoser strategy solves both the *trans* A-D junction and the macrocyclization problems in one impressive step, the synthetic problem is reduced to the synthesis of the four heterocyclic rings A (**24**), B (**8**), C (**9**), and D (**25**), each one in enantiomerically pure form, and the development of





Scheme 2. Retrosynthetic analysis of the Eschenmoser synthesis of cobyrinic acid (4).

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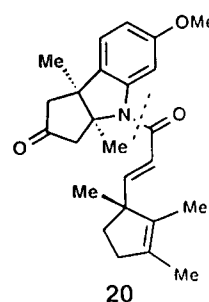
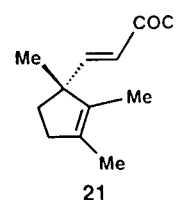
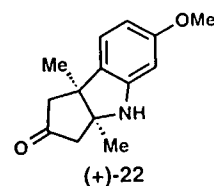
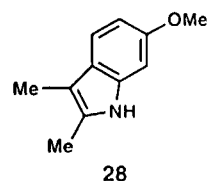
efficient coupling strategies. An elegant feature of the A-D variant is the recognition that all four heterocyclic rings could be elaborated from a single racemic precursor! Rings A (24), B (8), and C (9) could potentially be synthesized from dextrorotatory dilactone (+)-26, while ring D (25) could be obtained from levorotatory dilactone (-)-26. Compound 27, the projected product of a Diels-Alder reaction between butadiene (11) and β -methyl- β -acetylacrylic acid (12), is to be prepared in racemic form. The enantiomers of 27 could then be obtained, in pure form, through a classical resolution. Incidentally, the absolute configuration of (+)-27 was established by the Eschenmoser group through correlation of a derivative with a degradation fragment obtained from vitamin B₁₂.^{1a} Independent treatment of both antipodes of 27 with chromic acid could then furnish both enantiomers of dilactone 26. As we will see later in the synthesis, both groups adopted the same strategy for the synthesis of the B-ring of cobyrinic acid (4).

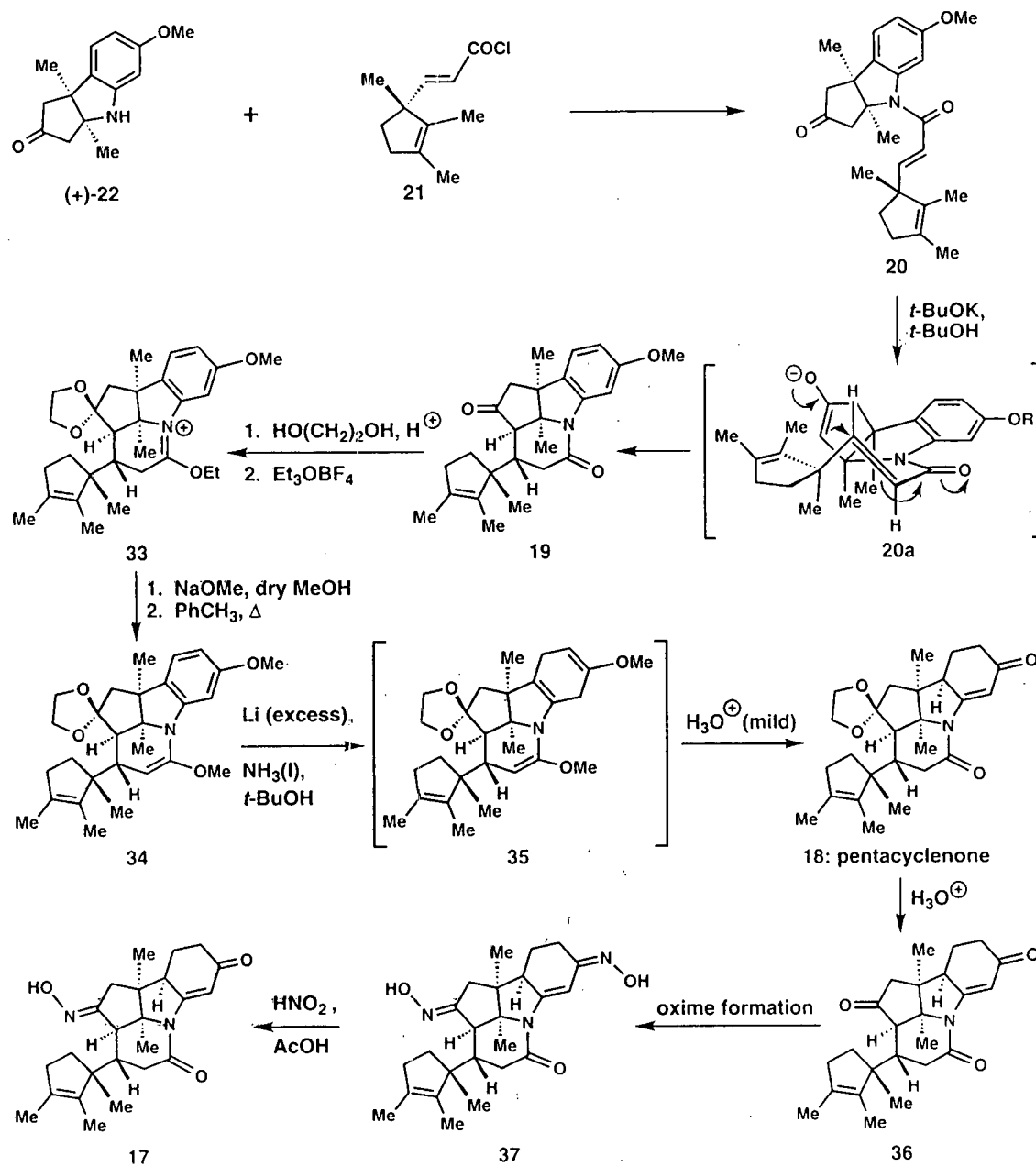
8.3 Total Synthesis

8.3.1 The Woodward Synthesis of Cyanobromide 6

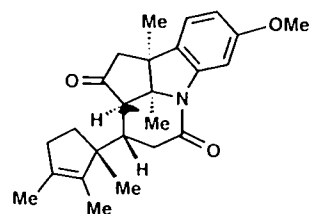
Schemes 3-7 describe the synthesis of cyanobromide 6, the A-D sector of vitamin B₁₂. The synthesis commences with an alkylation of the magnesium salt of methoxydimethylindole 28 to give intermediate 29 (see Scheme 3a). The stereocenter created in this step plays a central role in directing the stereochemical course of the next reaction. Thus, exposure of 29 to methanol in the presence of BF₃ and HgO results in the formation of tricyclic ketone 22 presumably through the intermediacy of the derived methyl enol ether 30. It is instructive to point out that the five-membered nitrogen-containing ring in 22, with its two adjacent methyl-bearing stereocenters, is destined to become ring A of vitamin B₁₂. A classical resolution of racemic 22 with α -phenylethylisocyanate (31) furnishes tricyclic ketone 22 in enantiomerically pure form via diastereomer 32.

Intermediate 22 possesses several nucleophilic sites. Acylation of the nitrogen atom in 22 with acid chloride 21, a substance that can be prepared in enantiomerically pure form from (-)-camphor according to Scheme 3b, furnishes ketone amide 20, and sets the stage for an intramolecular Michael addition reaction (Scheme 4). Treatment of 20 with potassium *tert*-butoxide affords a ketone enolate which reacts intramolecularly with the α,β -unsaturated amide to give intermediate 19 as a single diastereomer. The diastereoselection exhibited in this reaction is thought to be a consequence of the concave nature of intermediate 20a, and the minimization of nonbonding interactions in the transition state for the carbon-carbon bond forming reaction.

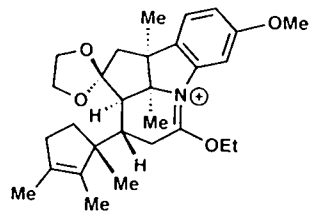




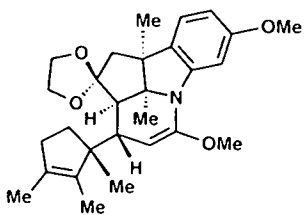
Scheme 4. The Woodward synthesis of intermediate 17.



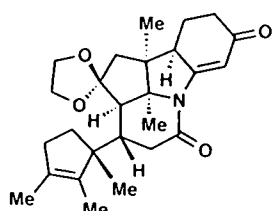
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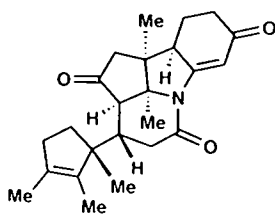
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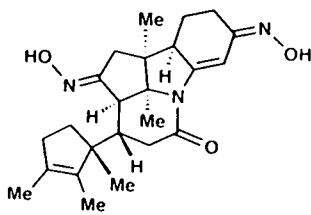
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18: pentacyclenone



36



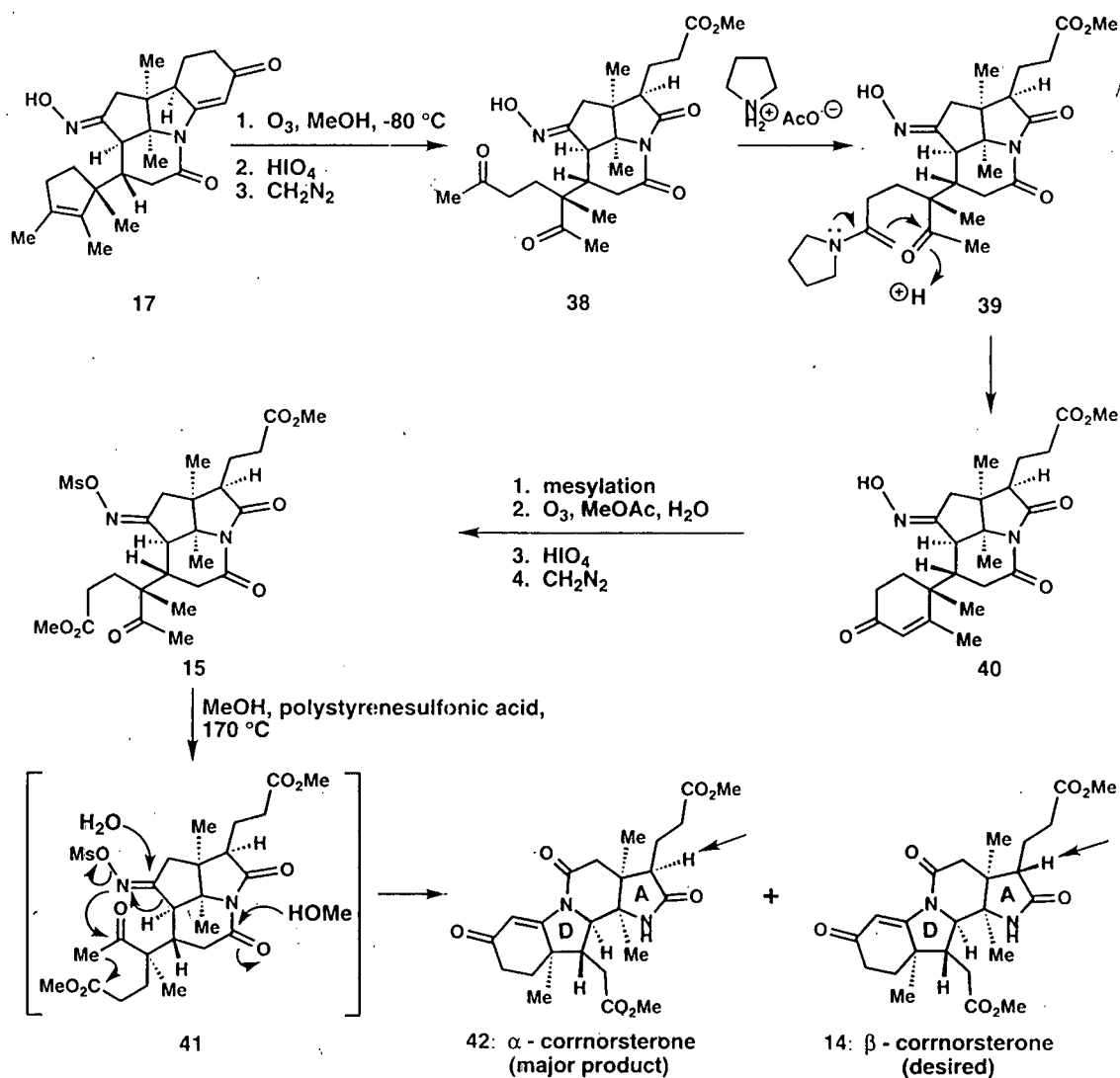
37

When stable substitutes for sensitive functional groups are used in a synthesis, it is certainly advantageous to modify them in a useful way rather than destroy them. Up to this point, the electron-rich aromatic ring has served as a stable surrogate for a carbonyl group and a propionate ester side chain. In order to make use of the carbon atoms that constitute the stable aromatic ring, it is obvious that a reduction needs to be performed. A dissolving-metal or Birch reduction⁹ can accomplish this task, but intermediate **19** is not a suitable substrate for such a reduction because it possesses other easily reducible functional groups. After a conventional ketalization of the ketone in **19**, the oxygen atom of the amide carbonyl is alkylated selectively with Meerwein's salt (Et_3OBF_4) to give iminoester **33**. A simple two-step sequence of reactions then gives intermediate **34**, a suitably protected molecule which is now a viable substrate for a Birch reduction. In the event, the aromatic ring in **34** is reduced to the dihydro level (see **35**) with lithium metal in a solution of liquid ammonia and *tert*-butanol. Interestingly, the hydrolysis of two of the three acid-labile functional groups in **35** with mild aqueous acid is attended by migration of the tetrasubstituted C-C double bond into conjugation with the carbonyl (see intermediate **18**). Note also that a new stereogenic center is created in this step.

Pentacyclenone, the trivial name given to intermediate **18**, contains a single nitrogen atom which will eventually be expressed in the A-ring of vitamin B₁₂. The synthesis of the targeted A-D sector requires incorporation of one more nitrogen atom which is introduced, in the form of an oxime, through a straightforward three-step sequence of reactions. Not surprisingly, the action of aqueous acid on pentacyclenone (**18**) induces cleavage of the dioxolane ring and provides ketone **36**. At this stage in the synthesis, it was hoped that **36** could be converted directly into the desired monoxime **17**. Although oximation of **36** unavoidably leads to the formation of dioxime **37**, the unwanted oximino group can be readily and selectively cleaved with nitrous acid in acetic acid under mild conditions to give the desired monoxime **17**.

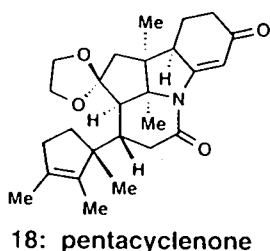
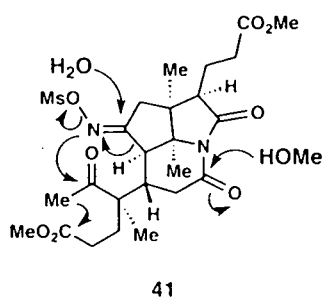
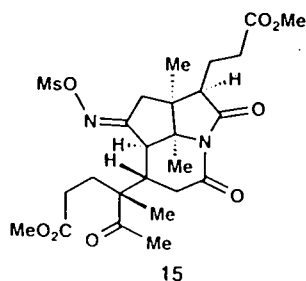
An important stereochemical issue requires comment at this time. It was anticipated that the oxime nitrogen in compound **17**, which is destined to become the D-ring nitrogen of vitamin B₁₂, could be introduced in proper relation to the A-ring nitrogen through a Beckmann rearrangement.⁹ As such is the case, the exclusive formation of the indicated oxime stereoisomer in the oximation reaction is significant because it ensures that migration of the desired carbon-carbon bond situated *trans* to the leaving group will occur during the Beckmann rearrangement.

Scheme 5 details the synthesis of β -cornorsterone (**14**) from **17**. Oxidative scission of both carbon-carbon double bonds in **17** with ozone, followed by two straightforward operations, furnishes intermediate **38**. The stability of the oxime in these systems is noteworthy, and is attributed to its hindered nature. At this juncture, it is instructive to note that substituted cyclopentene rings, like the



Scheme 5. The Woodward synthesis of β -cornnorsterone (14).

one present in 17, can be regarded as latent cyclohexenones; the application of oxidative cleavage and aldol cyclodehydration reactions can accomplish the conversion of a substituted cyclopentene nucleus into a cyclohexenone. Although oxidative scission of the cyclopentene ring in 17 provides a methyl ketone at both ends of the point of cleavage, it is possible to selectively convert the less hindered of the two methyl ketones in 38 into an enamine with pyrrolidinium acetate. The close spatial relationship between the nucleophilic enamine grouping and the electrophilic, but hindered, methyl ketone function in 39 favors the desired cyclodehydration reaction leading to 40. Mesylation of the oxime hydroxyl in 40.

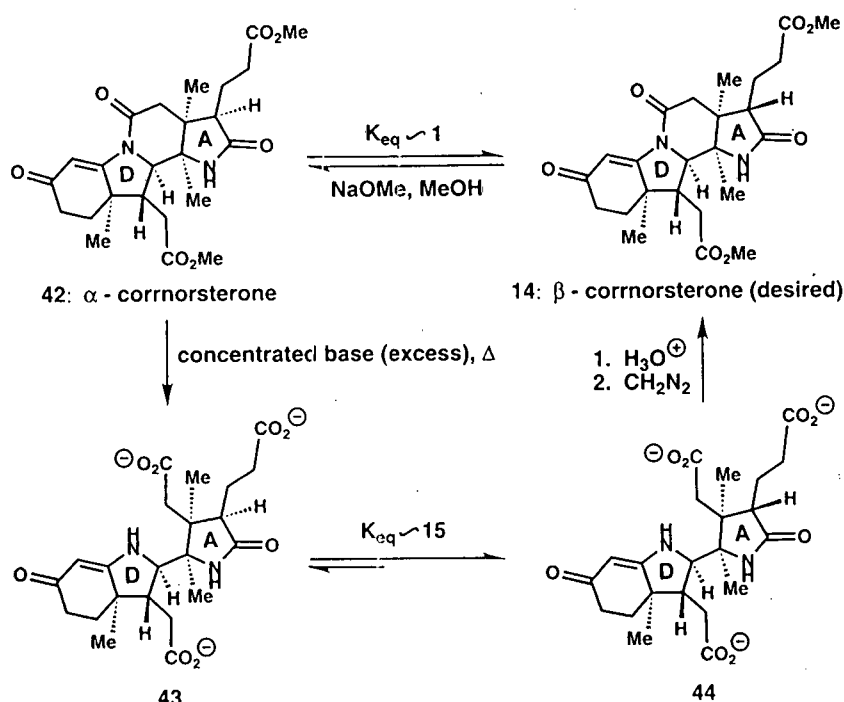


followed sequentially by ozonolysis of the enone double bond, treatment with periodic acid, and esterification with diazomethane, provides compound **15**.

Although it was anticipated all along that the latent reactivity of the oxime could be unveiled in a Beckmann rearrangement, the dramatic productivity of the next reaction was not. When a solution of **15** and polystyrenesulfonic acid in methanol is heated to 170°C, several useful transformations take place (see intermediate **41**). As expected, the Beckmann rearrangement proceeds in the desired way to give a six-membered lactam ring. Located only five atoms away from the lactam nitrogen atom is the electrophilic carbonyl group of the methyl ketone, and only four atoms intervene between the ketone methyl group and the electrophilic ester carbonyl. Under these conditions, and owing to the proximity of these reactive groups, the lactam nitrogen cannot resist attacking the neighboring carbonyl group (the aldol reaction may precede the Beckmann rearrangement). Methanol and water are expelled during this remarkable transformation giving α - and β -cornnorsterone, compounds **42** and **14**, respectively.

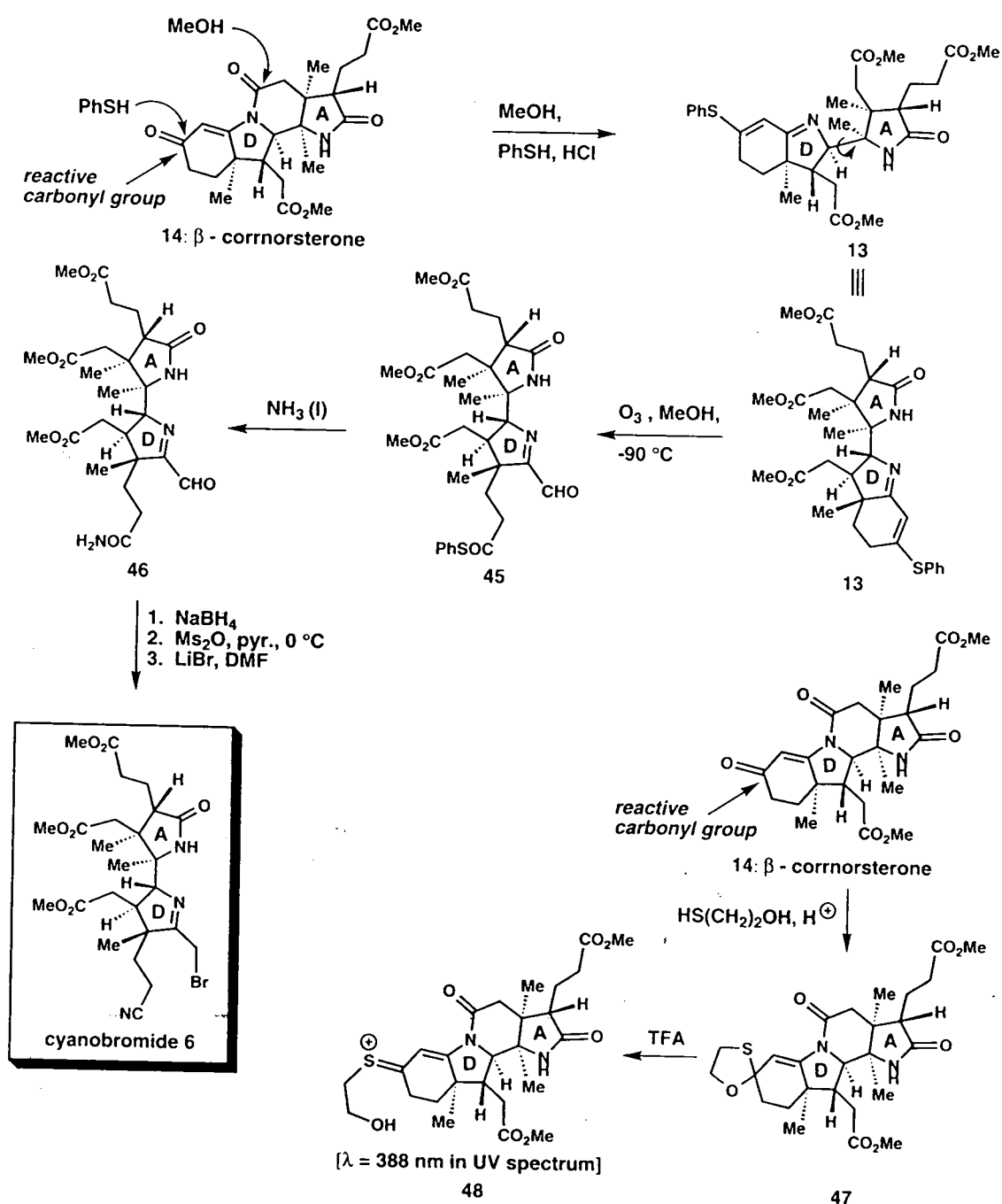
α -Cornnorsterone (**42**), the undesired diastereoisomer, is by far the major product formed in the acid-catalyzed transformation of oxime mesylate **15**. The configuration of the methyl propionate-bearing stereocenter constitutes the only difference between **42** and **14**. It was observed at an earlier stage in the synthesis that the action of alkaline reagents on pentacyclenone (**18**) results in facile cleavage of its six-membered lactam ring. Under the same conditions, however, a very similar six-membered lactam in **42** was found to resist hydrolysis. It was reasoned that if α -cornnorsterone's lactam ring were to be opened, then the resultant acetate chain would occupy a much larger volume of space relative to the lactam ring. This would introduce significant destabilizing steric interactions with the proximal propionate chain. Thus, to avoid such interactions, α -cornnorsterone need only resist hydrolysis. An important breakthrough in the synthesis was achieved when α -cornnorsterone (**42**) was treated with a large excess of concentrated base (Scheme 6). Under these conditions, the six-membered lactam ring in **42** is cleaved, and the stereogenic center next to the A-ring amide carbonyl is epimerized. The equilibrium between compounds **43** and **44** in Scheme 6 is shifted strongly in favor of **44**. Acidification of the reaction mixture, followed by treatment with diazomethane furnishes pure β -cornnorsterone (**14**) in 90% yield together with 6% of recyclable α -cornnorsterone. Interestingly, direct equilibration of the stereoisomeric cornnorsterones using methoxide ion in dry methanol provides a 1:1 mixture of the two substances (Scheme 6).

In β -cornnorsterone (**14**), we have an intermediate that possesses all six contiguous stereogenic centers occupying the left-hand portion of vitamin B₁₂. Scheme 7 presents the straightforward and elegant sequence of reactions that led to the synthesis of cyanobromide **6**, and the observations that formed the basis for this



Scheme 6. Base-induced conversion of 42 to 14.

expedient route. The carbonyl group highlighted by the arrow is part of an unusual β -acylamino α,β -unsaturated system and is, therefore, rather reactive. During the course of studies relevant to the chemistry of β -cornnorsterone (14), it was observed that this reactive carbonyl group can be readily converted into hemithioketal 47 (see lower right-hand portion of Scheme 7). What is very interesting is that in the presence of trace quantities of trifluoroacetic acid, a strikingly intense long-wavelength absorption at 388 nm is observed in the UV spectrum. Such an absorption is characteristic of the unusual acylamino α,β -unsaturated thioketoné onium salt present in 48. This experiment demonstrates that the carbon-oxygen bond of the hemithioketal moiety is cleaved selectively in the presence of acid. An oxonium ion intermediate, which would have formed in the event that the carbon-sulfur bond had cleaved, could not be detected spectroscopically; its presence would have been revealed by a characteristic absorption at 325 nm. The implication of this experiment is that it should be possible to maintain a carbon-sulfur bond at that position while creating a carbon-oxygen bond in another position. In a most impressive transformation, treatment of β -cornnorsterone (14) with HCl and a mixture of methanol and thiophenol results in the completely selective attack upon the δ -lactam carbonyl by a molecule of methanol, and the completely selective addition of the thiophenol to the reactive car-



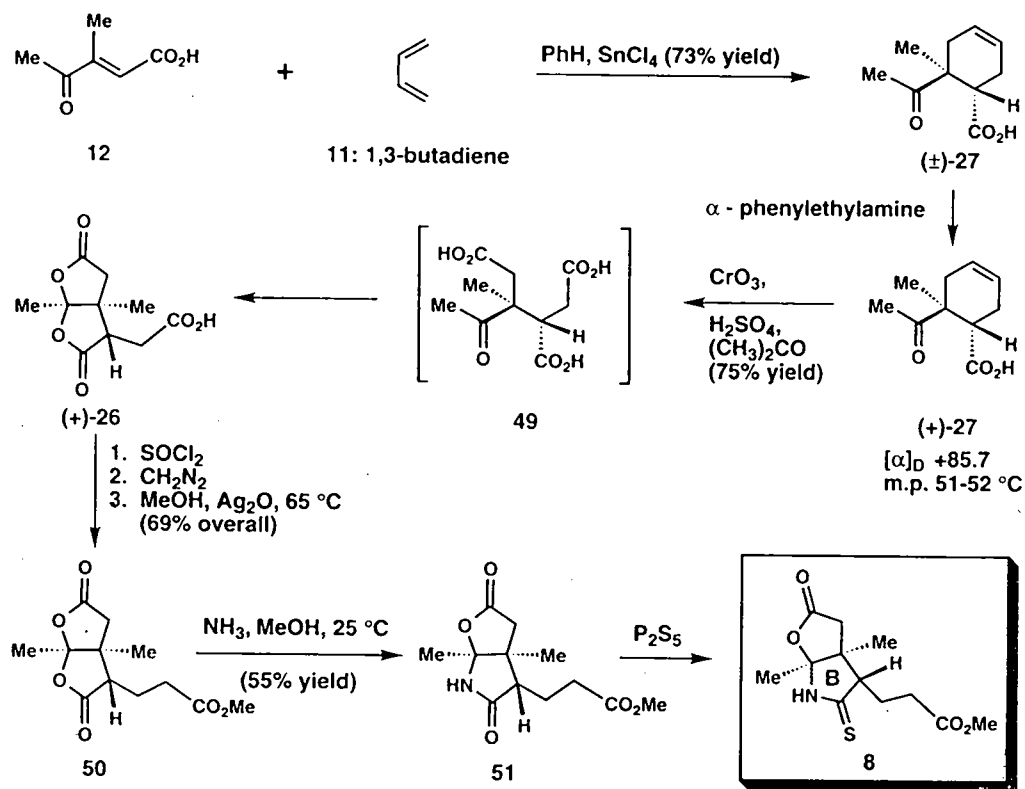
Scheme 7. The Woodward synthesis of cyanobromide 6.

bonyl group to give **13** (Scheme 7). When redrawn, the homology between intermediate **13** and the left wing of vitamin B₁₂ is obvious. Although the ozonolytic cleavage of the vinyl sulfide function in **13** proceeds efficiently and gives **45**, this reaction deserves comment. A step earlier, we learned that, under acidic conditions, the combined action of methanol and thiophenol on β -cornnorsterone (**14**) results in the smooth formation of compound **13**. This reaction is, as it turns out, very general; a variety of thiols can be substituted for thiophenol to produce compounds very similar to **13**. Unfortunately, however, when ethane-, methane-, 2-methyl-2-propane-, or phenylmethanethiol is used, the subsequent ozonolysis reaction produces significant quantities of a sulfur oxidation by-product. Only in the case of thiophenol does the ozonolysis reaction proceed cleanly and in the desired way to give the formyl thioester (i.e. **45**).

Contained within **45** is one side chain that terminates in a phenylthioester group. It was known, at the time, that whereas oxygen-based nucleophiles react with esters and thioesters with roughly equal facility, nitrogen-based nucleophiles react more readily with thioesters. Thus, treatment of **45** with liquid ammonia results in the completely selective replacement of the thiophenol grouping by ammonia to give formyl amide **46** in nearly quantitative yield. Although the inherently reactive aldehyde grouping in **45** is remarkably impervious to the action of liquid ammonia, it is readily reduced by sodium borohydride to the corresponding primary alcohol. Treatment of this substance with methanesulfonic anhydride and pyridine, followed by displacement of the resulting mesylate with bromide ion, completes the synthesis of cyanobromide **6**, a suitably differentiated left-wing building block. It is important to note that the employment of methanesulfonic anhydride in this sequence is not arbitrary; the use of the more conventional methanesulfonyl chloride or bromide to achieve the desired mesylation is attended by the production of significant amounts of a halide by-product. This complicating path can be easily circumvented through the use of methanesulfonic anhydride. It will also be noted that the terminal nitrile function in **6** is formed through dehydration of the primary amide grouping with methanesulfonic anhydride.

8.3.2 The Eschenmoser Synthesis of B-Ring Intermediate 8

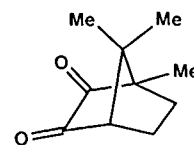
Scheme 8 presents the sequence of reactions that led to the synthesis of the B-ring of vitamin B₁₂ by the Eschenmoser group. An important virtue of the Diels-Alder reaction is that it is a stereospecific process wherein relative stereochemical relationships present in the diene and/or the dienophile are preserved throughout the course of the reaction.⁸ Thus, when the doubly activated dienophile **12** (Scheme 8) is exposed to butadiene **11** in the presence of stannic chloride, a stereospecific reaction takes place to give compound **27** in racemic form. As expected, the *trans* relationship between



Scheme 8. The Eschenmoser synthesis of B-ring intermediate 8.

the keto and carboxyl groups in **12** is reflected in Diels-Alder adduct **27**. The carboxyl group in **27** is an important feature because it provides a simple means whereby this compound can be resolved. Treatment of racemic (±)-**27** with optically active α -phenylethylamine gives a readily separable mixture of diastereomeric ammonium salts. Reconstitution of the enantiomeric carboxylic acids furnishes both in enantiomerically pure form. To reach vitamin B₁₂, it is the dextrorotatory carboxylic acid (+)-**27** which is required. Oxidative cleavage of the carbon-carbon double bond in (+)-**27** with chromic acid produces an intermediate with a carboxyl group on both sides of the point of cleavage (see **49**). The spatial proximity of two of the three carboxyl groups and the ketonic carbonyl group results in a facile intramolecular reaction to give dilactone (+)-**26**. Arndt-Eistert homologation¹¹ of the acetic acid side chain in (+)-**26** furnishes the dilactone propionic ester **50**. The selective formation of lactam **51** when dilactone **50** is treated with ammonia is very interesting. Although ammonia reacts with both lactonic carbonyl groups indiscriminately, it is possible to achieve the selective formation of the desired lactam **51** through a simple

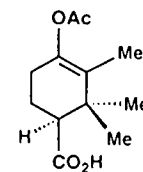
equilibration process. The selective action of phosphorus pentasulfide (P_2S_5) on lactam **51** affords enantiomerically pure thiolactam **8**, a latent electrophile representing the B-ring of vitamin B_{12} .



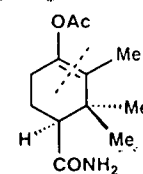
10: (+)-camphorquinone

8.3.3 The Woodward Synthesis of C-Ring Intermediate 9

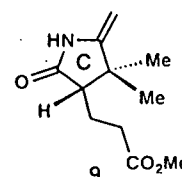
It was known from the work of Manasse and Samuel that a trimethylcyclohexanone carboxylic acid is formed when camphorquinone (**10**, Scheme 9) is exposed to acidic reagents. Subsequent studies by Simonsen and Chakravarti revealed the structure of the trimethylcyclohexanone carboxylic acid, and it was Cornforth¹² who recognized the structural relationship between this substance and ring C of vitamin B_{12} . In the face of such precedent, the approach to the C-ring building block logically begins with an acid-induced conversion of (+)-camphorquinone (**10**) into enantiomerically pure carboxylic acid **52** (Scheme 9). This interesting BF_3 -induced skeletal reorganization presumably proceeds through the cascade of reactions illustrated in Scheme 9. Sequential treatment of carboxylic acid **52** with oxalyl chloride and ammonia furnishes amide **53** and sets the stage for an unusual ozonolysis reaction. Oxidative cleavage of the enol acetate in **53** (dotted line) with ozone affords a mixed anhydride at one terminus and a ketone oxide at the other. This mixed anhydride is, of course, quite electrophilic, and it suffers attack by the primary amide nitrogen to give a succinimide. One of the carbonyl groups of the succinimide is suitably disposed with respect to the ketone oxide, and an intramolecular cycloaddition reaction takes place to give the observed product **54** (see presumed mechanism in Scheme 9). Reduction of **54** with zinc in methanol gives keto succinimide **55**. Treatment of **55** with methanolic hydrogen chloride results in the formation of **56**, which, when pyrolyzed, gives unsaturated lactam **9**, a latent nucleophile representing ring C of vitamin B_{12} .



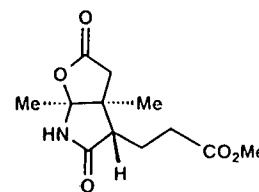
52



53



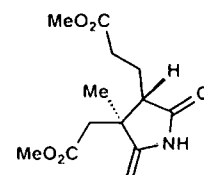
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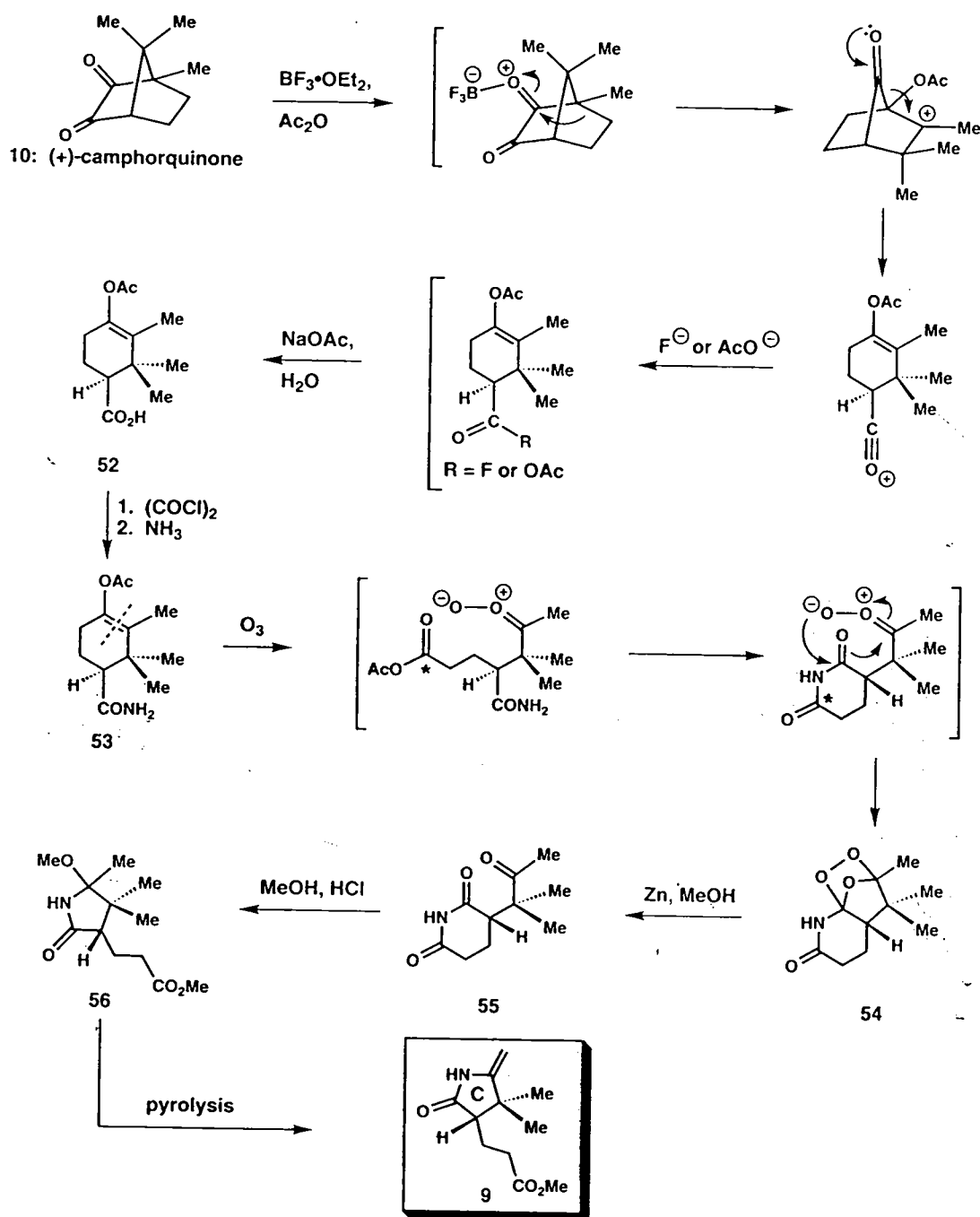
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8.3.4 The Eschenmoser Synthesis of C-Ring Intermediate 9

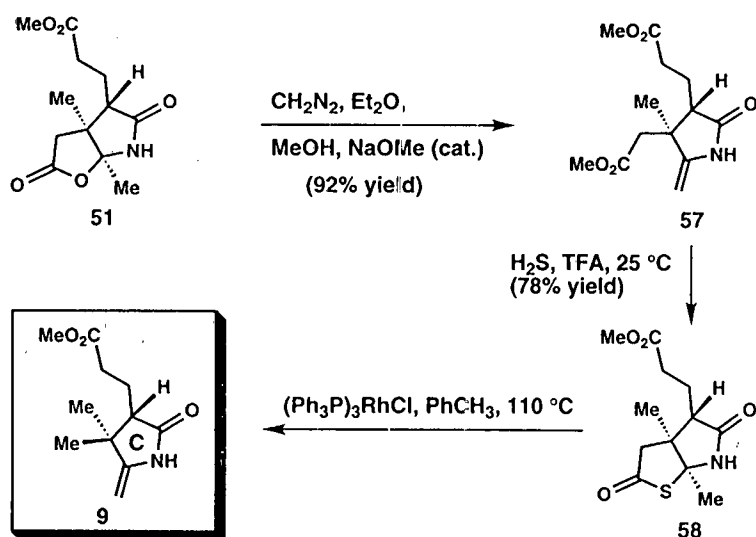
From intermediate **51** (Scheme 10), the precursor of B-ring intermediate **8**, the Eschenmoser synthesis of the C-ring building block requires only three synthetic steps. Treatment of **51** with diazomethane and a catalytic amount of sodium methoxide in a mixture of ether and methanol leads to the formation of intermediate **57**. In the presence of sodium methoxide, the amide hydrogen in **51** is removed as a proton, and the delocalized anion thus formed initiates opening of the γ -lactone ring. Esterification of the liberated acetic acid side chain with diazomethane and simple enamide tautomerization then gives intermediate **57**. When **57** is treated with hydrogen sulfide and trifluoroacetic acid, a new thiolactone ring is formed, and the bicyclo[3.3.0]octane



57



Scheme 9. The Woodward synthesis of C-ring intermediate 9.

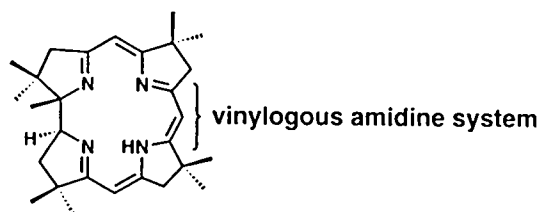


Scheme 10. The Eschenmoser synthesis of C-ring intermediate 9.

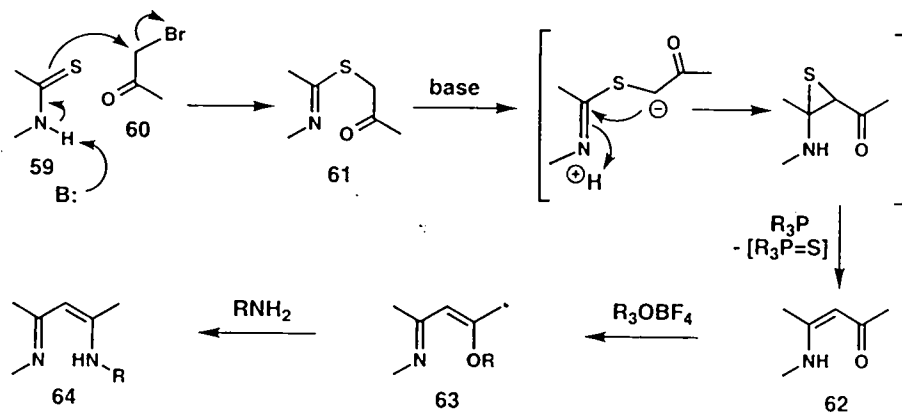
framework is reconstituted, giving intermediate 58. In refluxing toluene solution and in the presence of Wilkinson's catalyst, 58 is transformed into C-ring intermediate 9. Although the Eschenmoser synthesis of the C-ring building block is only three steps from an intermediate already being used for the preparation of the B-ring of vitamin B₁₂, both groups found the camphor-based route summarized in Scheme 9 to be more preparatively useful.

8.3.5 The Eschenmoser Synthesis of Thiodextrolin (7)

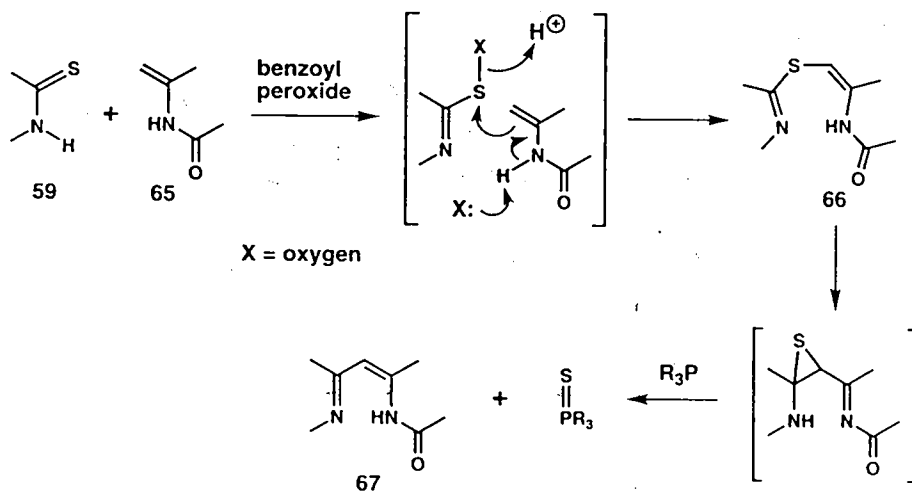
It is instructive to digress at this point. Inherent in any venture with the synthesis of a corrin as its objective is the challenge of constructing the vinylogous amidine system, the characteristic structural unit of the corrin chromophore (see Scheme 11). On its own, the vinylogous amidine system is simply the diaza analogue of the β -keto enol system, a grouping that is very familiar and very accessible. However, in the context of a corrin chromophore, the vinylogous amidine system can present a significant synthetic challenge. During the course of extensive model studies relevant to the synthesis of vitamin B₁₂, Eschenmoser and his group at ETH developed a very elegant and general method for the synthesis of vinylogous amidines which has had a lasting influence on the corrin field. The method is known as the Eschenmoser sulfide contraction reaction,⁷ and its development was motivated by a very important principle in organic synthesis which is enunciated in the following quotation by Eschenmoser: "Whenever in the synthesis of complex organic molecules one is confronted with a situation where the suc-



The sulfide contraction method via alkylative precoupling



The sulfide contraction method via oxidative precoupling



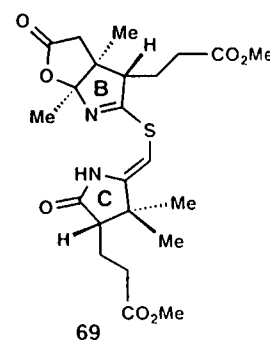
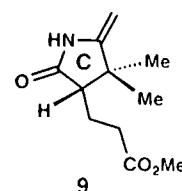
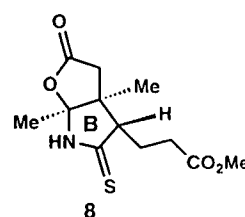
Scheme 11. The Eschenmoser sulfide contraction.

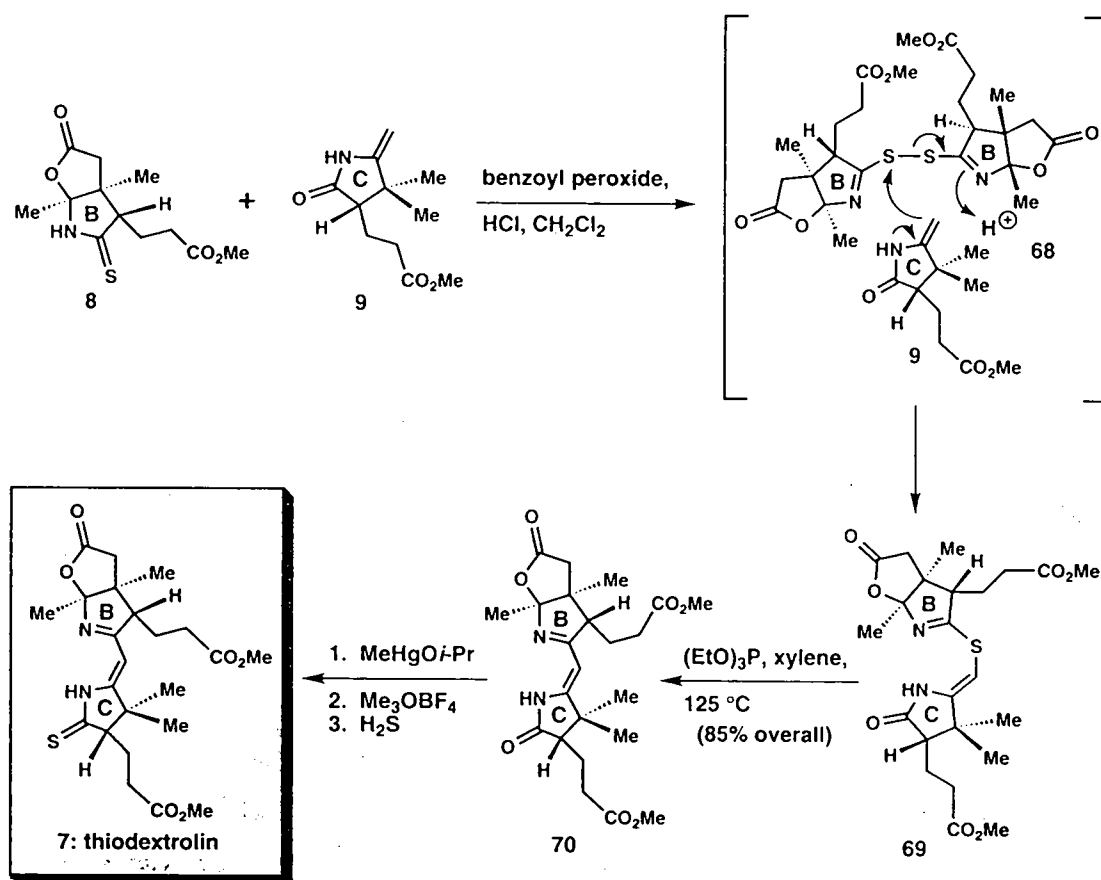
cess of an intermolecular synthetic process is thwarted by any type of kinetically controlled lack of reactivity, one should look out for opportunities of altering the structural stage in such a way that the critical synthetic step can proceed intramolecularly rather than intermolecularly."^{7d}

The key features of both alkylative and oxidative versions of the Eschenmoser sulfide contraction are presented in Scheme 11. In both versions, one of the two coupling partners is a thioamide. In the alkylative Eschenmoser sulfide contraction, the nucleophilic sulfur atom of generic thioamide **59** initiates an S_N2 displacement of a suitable leaving group (i.e. the bromide in intermediate **60**) to give thioiminoester **61**. In the presence of an enolizing base, the nucleophilic character of the carbon atom situated between the sulfur atom and the carbonyl group in **61** is unveiled, and it obligingly attacks the proximal electrophilic thioiminoester carbon (see arrows). It is presumed that this event leads to the formation of an episulfide which subsequently collapses in the presence of a phosphine or a phosphite thiophile to give vinylogous amide **62**. O-Alkylation of **62** with a trialkyloxonium salt (Meerwein's salt), followed by treatment with an amine, leads to the formation of vinylogous amidine system **64**. The latter transformation (**63** $\rightarrow$ **64**) can be formulated as a Michael addition/elimination reaction.

In the oxidative Eschenmoser sulfide contraction (Scheme 11), thioamide **59** is oxidized by benzoyl peroxide to give either a symmetrical disulfide or the *O*-benzoate of the thiolactam-*S*-oxide. In any event, the once-nucleophilic thioamide sulfur atom is now forced to adopt the role of electrophile; a reactivity umpolung has, in effect, been achieved.¹³ The nucleophilic enamide **65** attacks the sulfur atom leading to the formation of sulfur-bridged intermediate **66**. The action of a phosphine or a phosphite thiophile on the putative episulfide then gives vinylogous amidine **67**.

Schemes 8 through 10 describe the syntheses of two key intermediates representing rings B and C. We now have the good fortune to witness the elegant means by which these intermediates were combined to give the entire right-wing portion of vitamin B₁₂ (see Scheme 12). When a solution of the thiolactam **8** and the enamide **9** in CH₂Cl₂ is treated with benzoyl peroxide and a catalytic amount of hydrogen chloride, the sulfur-bridged compound **69** is formed. In this most interesting reaction, the thiolactam moiety in **8** is oxidized with benzoyl peroxide to give bisimidoyl disulfide **68** which reacts with enamide **9**, in the expected way, to give **69**. In this reaction, a new carbon-sulfur bond is created at the expense of a weak sulfur-sulfur bond, while an equivalent of thiolactam **8** is returned to the reaction. The carbon-sulfur bond contained within intermediate **69** is a valuable structural feature. Its existence is transient but nevertheless crucial to the success of the synthesis of thio-dextralin (**7**); it permits the union of rings B and C of vitamin B₁₂ by bringing into proximity the two carbon atoms between which a bond must be formed. When a solution of **69** in xylene is heated in the presence of the thiophile triethylphosphite, the sulfur atom,





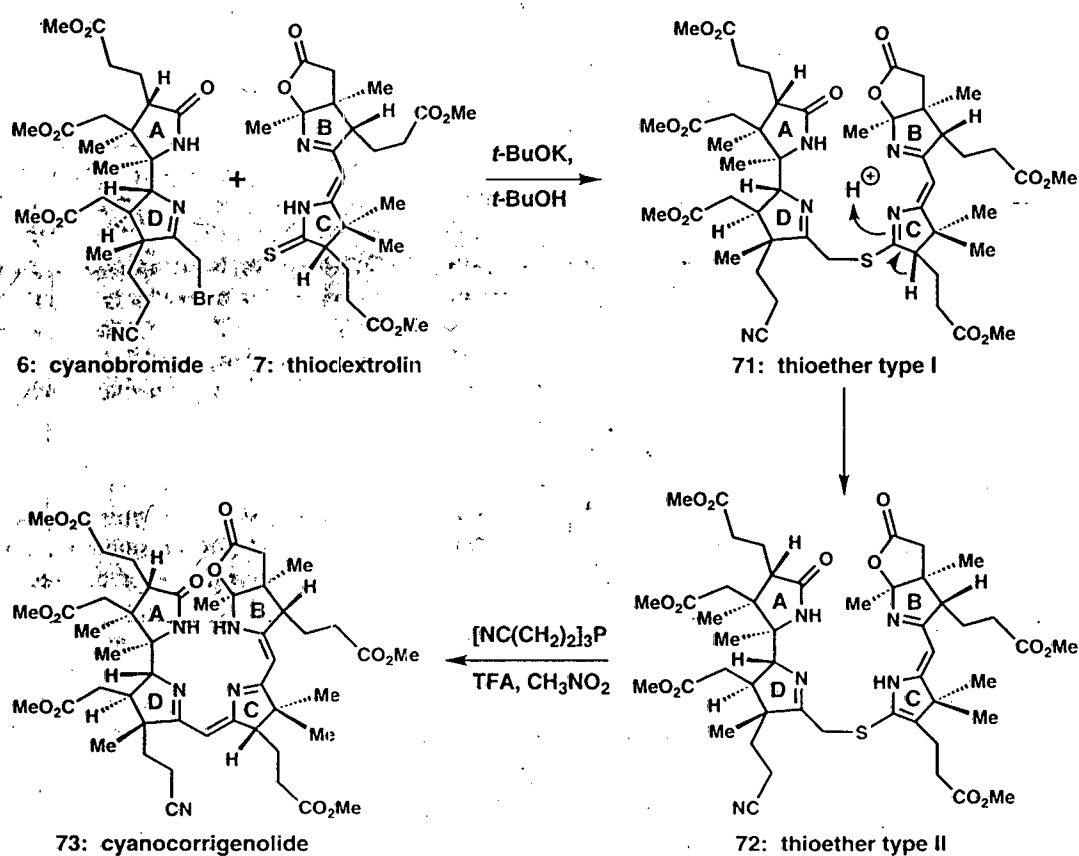
Scheme 12. The Eschenmoser synthesis of thiodextrolin (7).

which facilitates the carbon-carbon bond forming event by making it intramolecular, is removed to give intermediate **70**. Although the mechanistic details of this reaction were not examined, the formation of a transitory episulfide which is subsequently collapsed by triethylphosphite is presumed. The completion of the synthesis of thiodextrolin (**7**) only requires the selective conversion of the amide function in **70** into a thioamide. To accomplish this task, the methylmercury complex of the free amide in **70** is prepared first. This provides sufficient activation of the amide grouping, and allows a smooth and specific O-alkylation with Meerwein's salt. Exposure of the resulting iminomethylester to hydrogen sulfide then gives thiodextrolin (**7**). The synthesis of the right-wing portion, the B-C sector, of vitamin B₁₂ is now complete.

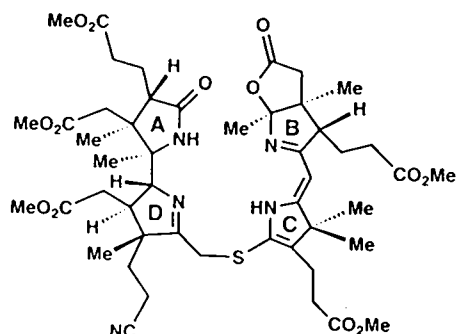
258 99

8.3.6 The Woodward–Eschenmoser Macrocyclization Strategy

We have now reached a pivotal stage in the synthesis. We have retraced the elegant sequences of reactions that have led to syntheses of both the left- and right-wings of vitamin B₁₂ in their correct absolute stereochemical forms. We are now in a position to address the union of cyanobromide **6** and thiodextrolin (**7**) (see Scheme 13). The reactivity potential of these two molecules complement each other. Cyanobromide **6** is, in its most basic form, an alkylating agent, albeit a very elaborate one. Thiodextrolin (**7**), on the other hand, is a nucleophile by virtue of the presence within its structure of the thioamide group. Under carefully controlled conditions and in the presence of potassium *tert*-butoxide, it is possible to bring about a quantitative union of intermediates **6** and **7** through the formation of a carbon–sulfur bond. In the event, the thioamide proton in **7** is removed by a base to give a nucleophilic thiolate ion which subsequently attacks the bromine-bearing carbon in **6** in an intermolecular S_N2-type reaction. The product formed from the direct



Scheme 13. The Woodward–Eschenmoser A–B cyclization strategy.



72: thioether type II

union of **6** and **7** is referred to as thioether type I, intermediate **71**. Upon purification and under a variety of conditions, it was found that this substance undergoes ready conversion to a closely related substance, thioether type II, intermediate **72**. This facile and seemingly sinister transformation destroys the stereocenter in ring C, and it presented a formidable stumbling block on the road to vitamin B₁₂. Although many attempts to join the A-D and B-C sectors in **72** through a carbon-carbon bond were completely unsuccessful, it was discovered that the combined action of tris- β -cyanoethylphosphine and trifluoroacetic acid (TFA) on **72** effects a smooth conversion to cyanocorrigenolide (**73**). In this reaction, it is presumed that the C-ring iminothioether is reconstituted, thereby setting the stage for the Eschenmoser sulfide contraction. As in the synthesis of thiodextrin (**7**), the sulfur atom in **72** serves as a temporary bridge between the A-D and B-C sectors; it brings the two relevant carbon atoms together in space and allows the bond-forming process to proceed intramolecularly. After sulfur extrusion, cyanocorrigenolide (**73**) is obtained.

In **73**, we have an intermediate that contains both halves of vitamin B₁₂. Before the synthesis of the corrin nucleus can be addressed, **73** must be converted into a form amenable to cyclization. The conversion of the lactam carbonyl in ring A into a thiocarbonyl and the concomitant conversion of the lactone attached to ring B into a thiolactone can be achieved with phosphorus pentasulfide (see Scheme 14). Selective alkylation of the thiolactam sulfur atom in ring A with trimethyldithiocyanoxonium tetrafluoroborate then furnishes S-methyldithiocyanocorrigenolide (**74**). Exposure of **74** to dimethylamine in methanol results in smooth cleavage of the thiolactone ring to give a dimethylamide at one terminus and a carbon atom which is now part of an exocyclic methylene group at the other terminus. Direct treatment of this labile intermediate with cobalt chloride in THF then furnishes intermediate **5**.

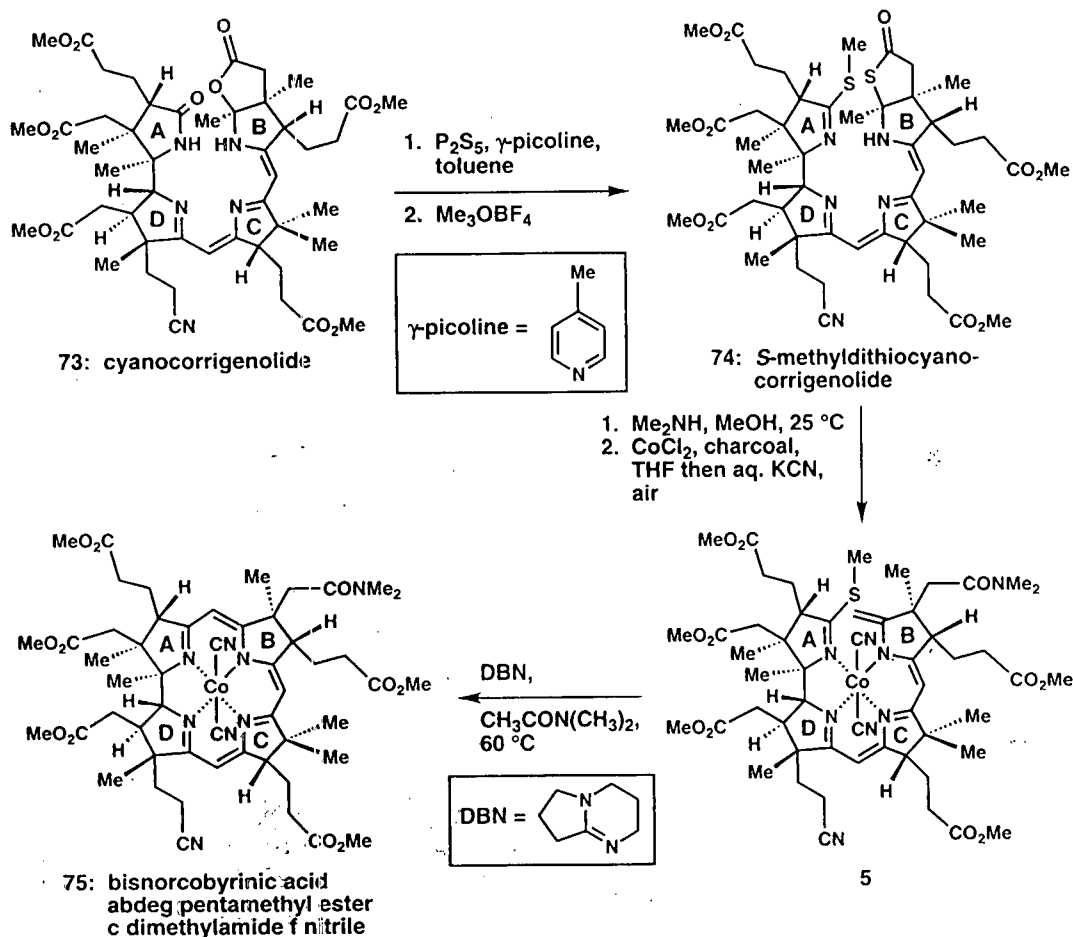
The stage is now set for the crucial cyclization event. There are three structural features contained within **5** that are vital to this transformation. First, the exocyclic methylene in ring B is special because it is expressed in the form of an enamine, and it is therefore nucleophilic. Second, the iminothioester in ring A possesses electrophilic potential that compliments the B-ring enamine. Third, the central cobalt atom preorganizes the structure of the secocorrin in a way that should facilitate the cyclization event. When a solution of **5** in dimethylacetamide is treated with diazabicyclononane (DBN) at 60°C, the key intramolecular cyclization reaction takes place and furnishes compound **75** in high yield (Scheme 14). In this reaction, a new carbon-carbon bond linking rings A and B is formed and the methylthio group is displaced.

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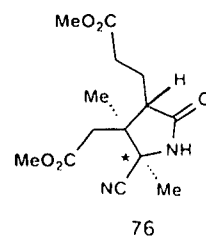
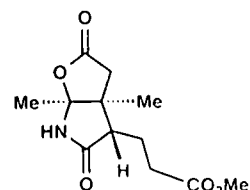
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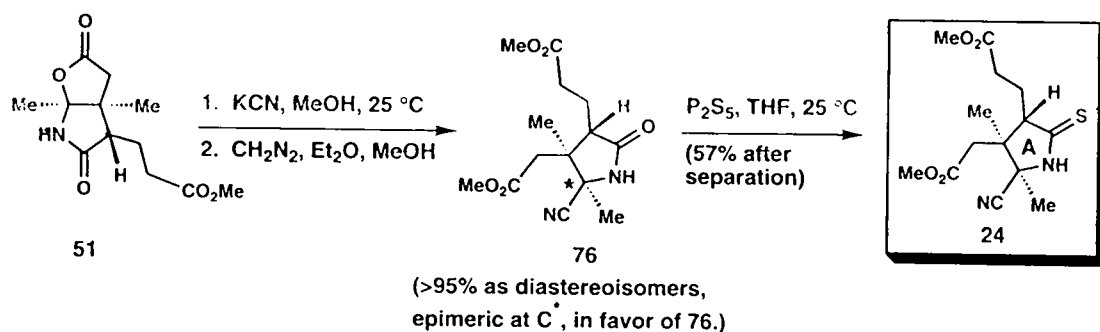


Scheme 14. The Woodward synthesis of intermediate 75.

8.3.7 The Eschenmoser Synthesis of A-Ring Intermediate 24 and D-Ring Intermediate 25

Schemes 15 and 16 summarize the syntheses of intermediates that represent rings A and D of vitamin B_{12} by the Eschenmoser group. Treatment of lactam/lactone **51**, the precursor to B-ring intermediate **8** (whose synthesis has already been described, see Scheme 8), with potassium cyanide in methanol induces cleavage of the γ -lactone ring and furnishes intermediate **76** after esterification of the newly formed acetic acid chain with diazomethane. Intermediate **76** is produced as a mixture of diastereomers, epimeric at the newly formed stereocenter, in a yield exceeding 95%. Selective conversion of the lactam carbonyl in **76** into the corresponding thiolactam



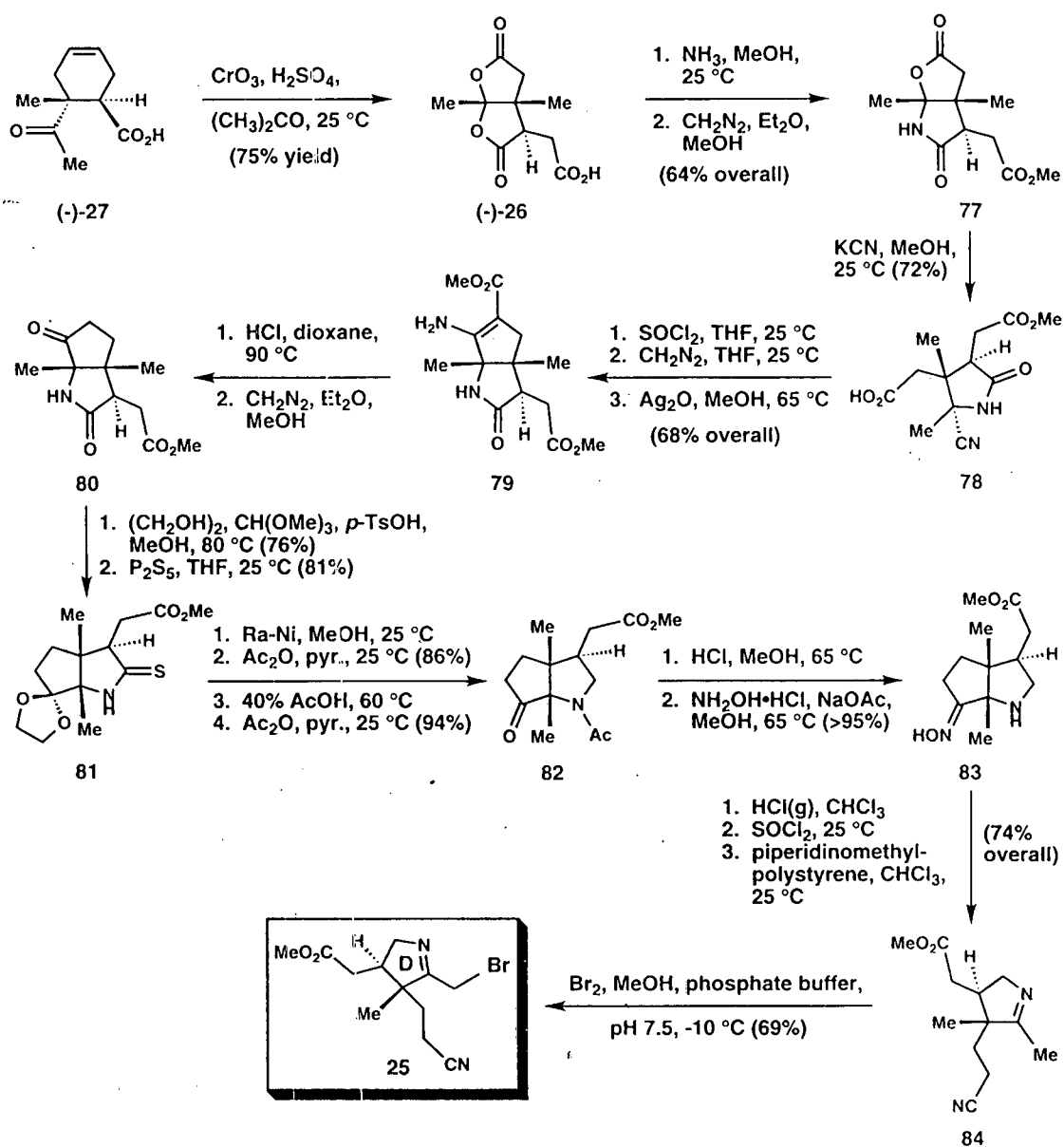


Scheme 15. The Eschenmoser synthesis of A-ring intermediate 24.

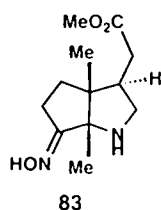
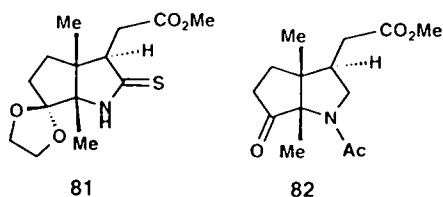
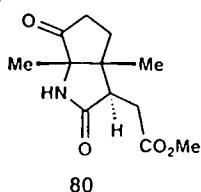
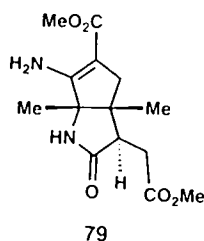
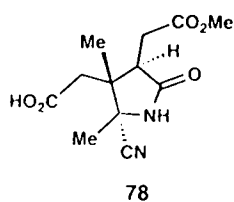
with P₂S₅ completes the synthesis of intermediate 24, an appropriately functionalized representative of the A-ring of vitamin B₁₂.

The path to D-ring intermediate 25 starts with levorotatory carboxylic acid (–)-27 (see Scheme 16). This molecule is one enantiomer of a substance readily assembled in racemic form from a Diels–Alder reaction between butadiene (11) and β-methyl-β-acetylacrylic acid (12), and it is easily obtained in stereochemically pure form through a resolution of the racemate with enantiomerically pure α-phenylethylamine (see Scheme 8). At this juncture, a digression is in order. Those engaged in the synthesis of complex organic molecules are frequently presented with situations requiring only one enantiomer of a compound that can be prepared easily in racemic form. Once the desired stereoisomer is obtained through resolution, it is common practice to discard the unwanted enantiomer. Although wasteful, this practice is certainly acceptable. Nevertheless, it is most gratifying when a carefully planned synthesis utilizes both enantiomers of a racemic starting material. Here, in the Eschenmoser approach to the synthesis of vitamin B₁₂, the two-mirror-image forms of a simple racemic starting material are used to assemble all four rings of the natural product, each in its correct absolute stereochemical form (see Scheme 2). It should also be noted that in the Woodward synthesis of cyanobromide 6, the availability of the “unnatural” enantiomer of key intermediate 19 (Scheme 4) permitted the exploration of a number of alternative synthetic pathways for further advance. In fact, almost all of the transformations that were employed in the synthesis of the left-wing sector were first discovered using substances that belong to the enantiomeric or “unnatural” series. Thus, even though only one enantiomer of intermediate 19 was ultimately incorporated into the vitamin B₁₂ synthesis, the “unnatural” enantiomer of 19 was not really wasted!¹⁴

As in the synthesis of (+)-26 (Scheme 8), treatment of (–)-27 with chromic acid accomplishes oxidative scission of the carbon–carbon double bond, and provides (–)-26 after an intramolecular bislactonization reaction (Scheme 16). By analogy to the conversion of 50 into 51 (see Scheme 8), treatment of (–)-26 with ammo-



Scheme 16. The Eschenmoser synthesis of D-ring intermediate 25.



nia leads, through an equilibration process, to the formation of intermediate **77** after esterification of the acetic acid side chain with diazomethane. When a solution of **77** in methanol is treated with potassium cyanide, the γ -lactone ring is opened, and a molecule of hydrogen cyanide is incorporated giving intermediate **78**. The next three-step sequence of reactions is very interesting. After Arndt-Eistert homologation¹¹ of the acetic acid side chain in **78**, the active methylene group of the newly formed methyl propionate side chain condenses intramolecularly onto the cyano group. To be more precise, the propionate ester, in its enolic form, attacks the electrophilic carbon of the nitrile group intramolecularly to give intermediate **79**. The action of acid on **79** accomplishes the hydrolysis of the vinylogous amide and methyl ester groupings, and induces a decarboxylation reaction. Intermediate **80** is produced after reesterification of the acetic acid side chain adjacent to the lactam-carbonyl with diazomethane. After protection of the ketone carbonyl in **80** in the form of a 1,3-dioxolane, the lactam carbonyl is smoothly and selectively converted into the corresponding thiocarbonyl group with P₂S₅ to give **81**. Complete reduction of the thiocarbonyl moiety in **81** with Raney nickel, followed sequentially by acetylation of the nitrogen atom, hydrolysis of the 1,3-dioxolane, and reacetylation of the nitrogen atom, results in the formation of ketone **82**. Assembly of oxime **83** in two steps from **82** sets the stage for an interesting variant of the Beckmann fragmentation reaction.⁹ Treatment of **83** with gaseous hydrogen chloride, followed successively by thionyl chloride and piperidinomethylpolystyrene induces a Beckmann fragmentation and furnishes intermediate **84** in 74% yield. Bromination of the allylic methyl group in **84** using bromine in buffered methanol solution completes the synthesis of D-ring intermediate **25**.

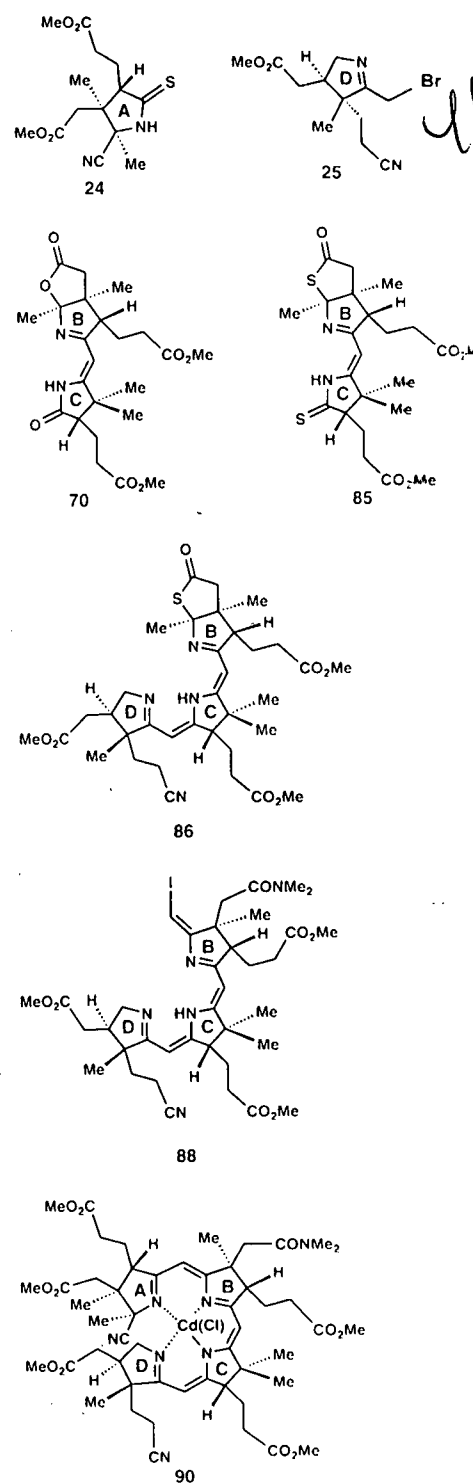
8.3.8 The Eschenmoser Cyclization Strategy

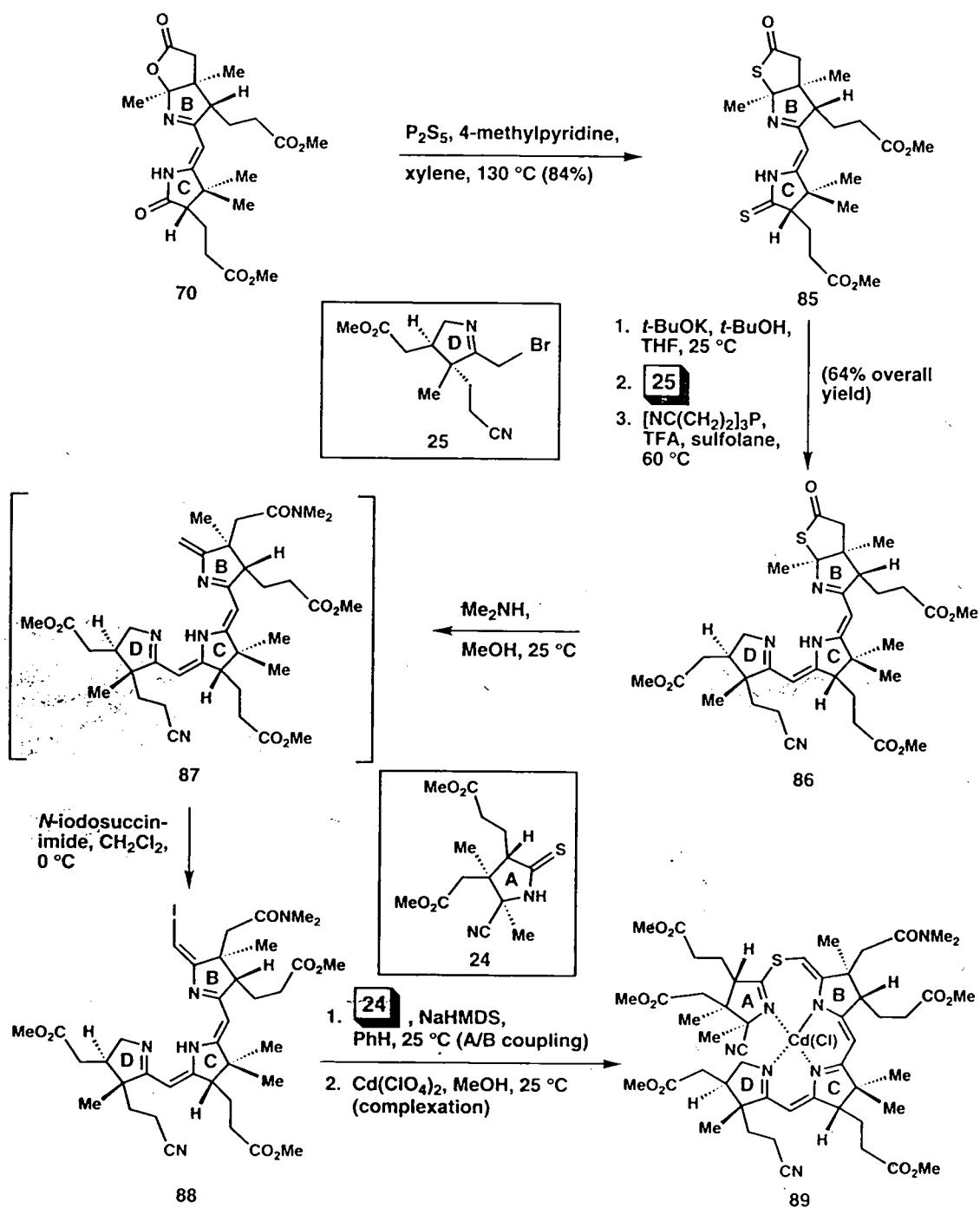
One of the crowning achievements that emanated from the total synthesis of vitamin B₁₂ was the development of the principles of orbital symmetry conservation by R. B. Woodward and R. Hoffmann.³ In Cambridge, MA, it was the observations made during the synthesis of the left-wing of vitamin B₁₂ that provided the seeds for this new theoretical advance, and, in Zürich, it was the recognition by Eschenmoser that a new approach to the synthesis of the macrocyclic corrin nucleus of vitamin B₁₂ could provide a stringent test of a theoretical prediction made by the Woodward-Hoffmann rules. It was under these circumstances that the A-D variant, the efficient and elegant contribution of the Eschenmoser group, was born.^{1d,6b,7d} The A-D variant subjects a secocorrin structure, which is organized in a helical fashion around a central metal atom, to visible light and accomplishes both the crucial macrocyclization reaction and the creation of the natural *trans* configuration at the junction between rings A and D (see Scheme 2). The recognition

that the four optically active building blocks representing rings A (24), B (8), C (9), and D (25) can be synthesized from the two enantiomers of a single starting compound is most impressive, and it seems to reflect underlying regularities in the biosynthesis of the natural corrinoids.^{7d} Schemes 17 and 18 present the synthetic details of this approach.

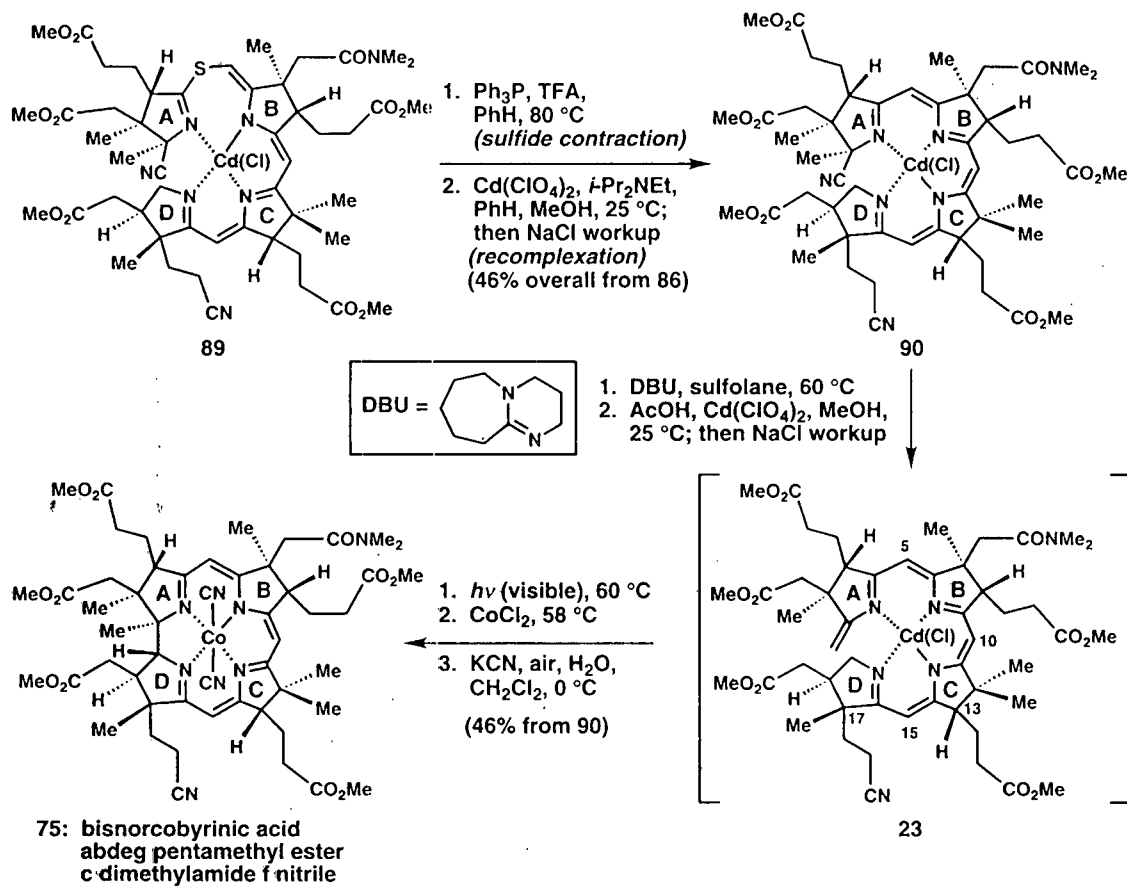
The Eschenmoser A-D variant begins with the conversion of intermediate 70, the precursor of thiodextrolin (7), into the corresponding thiolactam thiolactone 85 with P_2S_5 . The sulfur atom of the thiolactam in 85 is to serve as a nucleophile in a coupling reaction with D-ring building block 25. This reaction is analogous to the coupling of cyanobromide 6 with thiodextrolin (7) (see Scheme 13), a key operation in the Woodward/Eschenmoser A-B variant. Treatment of 85 with *tert*-butoxide produces a thiolate ion which subsequently displaces the ring D-bromide to give a sulfur-bridged intermediate. As we have already seen in analogous systems, the sulfur atom serves as a disposable tether; it forces rings C and D into neighboring regions of space and facilitates the key carbon-carbon bond forming event by making it intramolecular. After it has served its purpose, the sulfur atom is smoothly excised by the phosphine thiophile. In the presence of dimethylamine, intermediate 86 is converted into exocyclic enamine 87. This intermediate is not isolated; it is treated directly with *N*-iodosuccinimide to give vinyl iodide 88. By employing a modified sulfide contraction procedure,^{7c} the iodinated enamine 88 is coupled with the A-ring building block 24 to give, after complexation with cadmium, the sulfur-bridged complex 89. On the basis of observations made during the synthesis of metal-free corphin derivatives,¹⁵ it is likely that metal complexation assists the subsequent sulfide contraction. Treatment of intermediate 89 (Scheme 18) with triphenylphosphine and trifluoroacetic acid induces sulfide contraction, giving intermediate 90 after recomplexation with cadmium.

In the Eschenmoser synthesis of A-ring intermediate 24 (see Scheme 15), a cyano substituent was introduced as a means of masking the strongly nucleophilic enamide double bond so that the thioamide function could adopt the role as nucleophile in the coupling reaction with intermediate 88. Having served its purpose as a protecting group, the cyano substituent in intermediate 90 is eliminated in the presence of DBU giving, after recomplexation with cadmium, key intermediate 23. The stage is now set for the crucial macrocyclization event. Secocorrin complex 23, with its newly formed exocyclic methylene group, is not isolated; upon irradiation with visible light, it readily participates in an antarafacial sigmatropic 1,16-hydrogen shift from the methylene group in ring D to the exocyclic methylenidene group in ring A, followed by an antarafacial electrocyclic 1,15 $\pi \rightarrow \sigma$ isomerization to corrin 75. This reaction was studied in detail in the context of a simpler model system,^{6b,7d} and it is presumed that the path presented in Scheme 19 is taken. The rate-limiting step in this process is the photo-induced shift of a hydrogen atom from the D-ring methylene in 91 to the A-ring

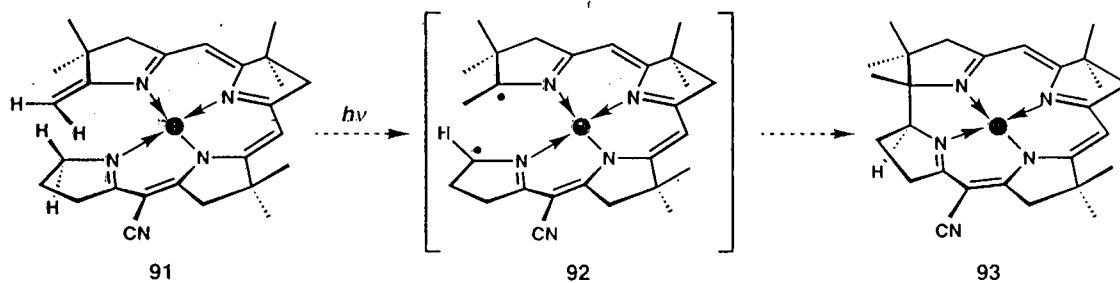




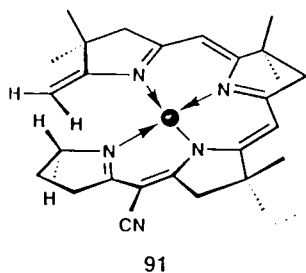
Scheme 17. The Eschenmoser A-D cyclization strategy.



Scheme 18. The Eschenmoser synthesis of intermediate 75.



Scheme 19. Photochemical A-D cycloisomerization: presumed reaction path.



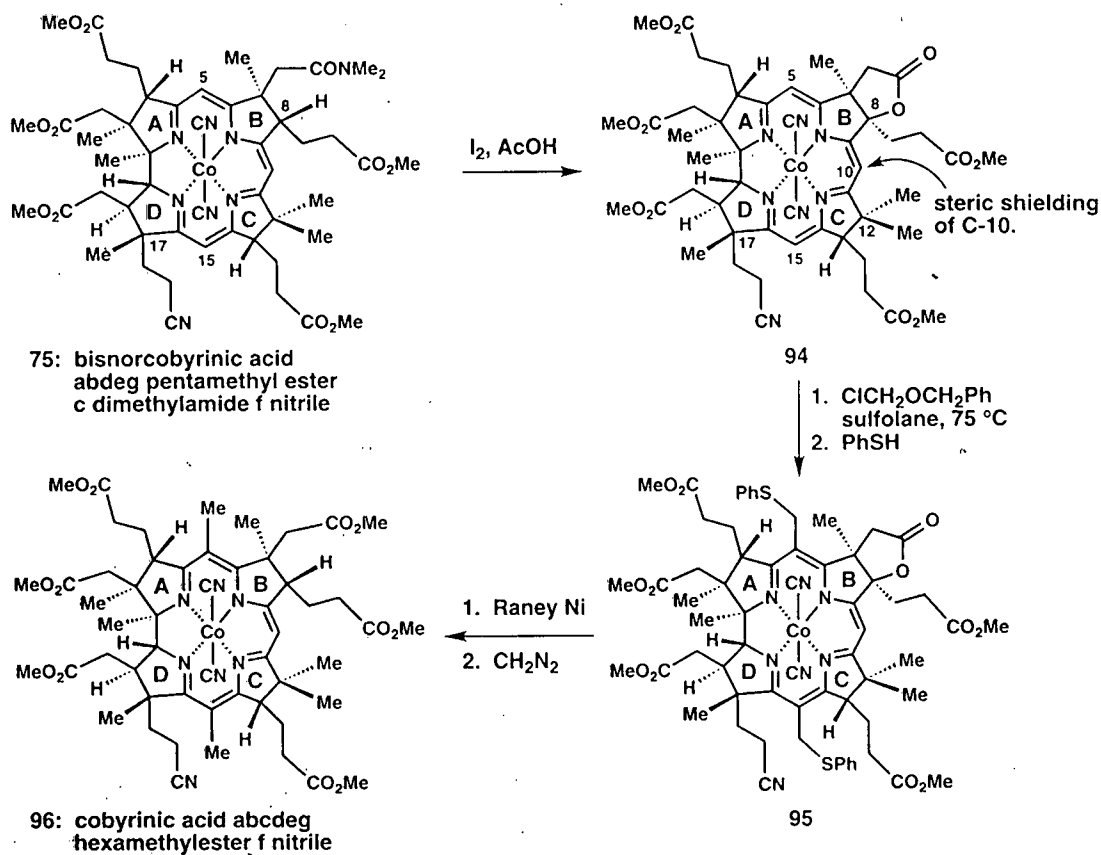
methylidene carbon sixteen atoms away. Studies carried out on the secocorrin palladium complex (**91**; $\bullet = M = \text{Pd}$) revealed that the cyclization displays an isotope effect of about 7 when the D-ring methylene hydrogens in **91** are replaced with deuteriums. Dunitz and his group at ETH contributed X-ray crystallographic results which revealed that the secocorrin structure (**91**; $\bullet = M = \text{CdCl}$) is coiled around the central metal atom in a helical manner.^{1d} The juxtaposition of the D-ring methylene group and the A-ring methylidene is a most gratifying consequence of such an arrangement; the helical arrangement of the secocorrin structure around the metal places the D-ring methylene group beneath (or above) the A-ring methylidene π system and guides the stereochemical course of the cycloisomerization event. Provided that the central metal ion is inert with respect to the quenching of the excitation of the chromophore, the photo-induced cycloisomerization proceeds very smoothly and provides corrin complexes possessing the necessary *trans* configuration between rings A and D. The *trans* A-D configuration found in cobyrinic acid (**4**) is thermodynamically more stable than the alternative *trans* configuration. The macrocyclization event described in Scheme 18 provides the natural stereochemical arrangement almost exclusively. You will note that both paths to cobyrinic acid (**4**) have now converged on a common intermediate. From bisnorcobyrinic acid abdeg pentamethylester c dimethylamide f nitrile (**75**), the journey to cobyrinic acid (**4**) was completed collaboratively by both groups.

8.3.9 Completion of the Woodward–Eschenmoser Total Synthesis of Cobyrinic Acid and Vitamin B₁₂

To complete the synthesis of cobyrinic acid (**4**) and therefore vitamin B₁₂ (**1**) from **75**, three significant challenges remain: two methyl groups, one at position 5 and the other at position 15, must somehow be introduced; the three-carbon side chain attached to position 17 in ring D must eventually terminate in a carboxyl group; and the remaining side chains must be made to terminate in primary amide groups. Scheme 20 presents the solution to the first of these three problems. By taking advantage of the nucleophilic character of an amide oxygen atom, intermediate **75** is readily transformed into lactone **94** on treatment with iodine and acetic acid, presumably through the intermediacy of a C-8 allylic iodide. At this juncture, it was anticipated that the fully substituted carbon atoms at positions 8 and 12 would shield position 10 from attack by alkylating agents. Treatment of **94** with chloromethyl benzyl ether in sulfolane at 75 °C, followed by exposure to thiophenol, results in the completely selective incorporation of phenylthiomethyl groups at carbons 5 and 15; no attack on the hindered C-10 position is observed. It is thought that this reaction affords a bis(benzyloxymethyl) ether which is subsequently converted into a bis(chloromethylated) intermediate by hydrogen chloride. Displacement of both chloride substi-

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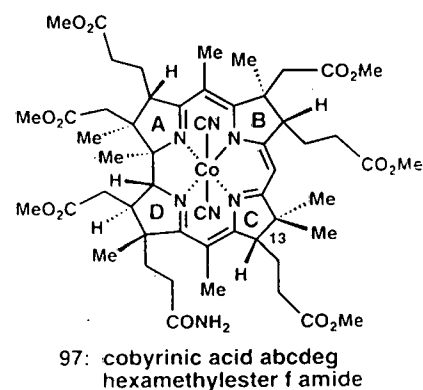
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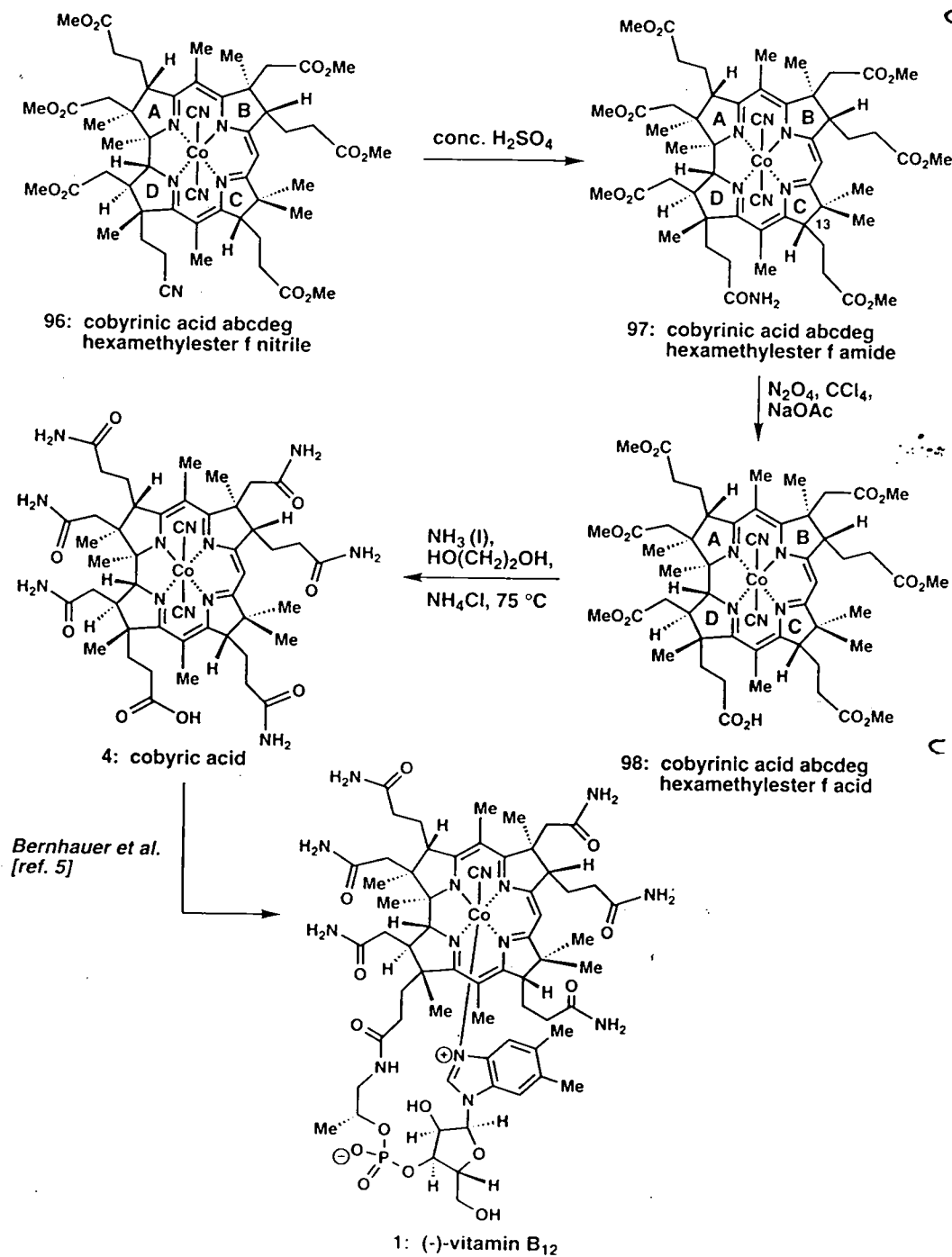


Scheme 20. Synthesis of cobyrinic acid abcdg hexamethylester f nitrile **96**.

tients by thiophenol then furnishes intermediate **95**. Reductive removal of both phenylthio groups with Raney nickel is accompanied by reduction of the lactone ring. Finally, esterification of the free carboxyl group with diazomethane affords cobyrinic acid abcdg hexamethylester f nitrile (**96**). The task of introducing the requisite methyl groups at positions 5 and 15 has now been accomplished.

Scheme 21 presents the successful sequence of reactions that solved the remaining two problems and led to the completion of the synthesis of cobyrinic acid. Exposure of **96** to concentrated sulfuric acid for one hour brings about a clean conversion of the nitrile grouping to the corresponding primary amide grouping. The stability of the corrin nucleus under these rather severe conditions is noteworthy. This new substance, intermediate **97**, is identified as cobyrinic acid abcdg hexamethylester f amide and it is produced along with a very similar substance which is epimeric to **97** at C-13. The action of sulfuric acid on **96** produces a diastereomeric



Scheme 21. Synthesis of (-)-vitamin B₁₂ (1).

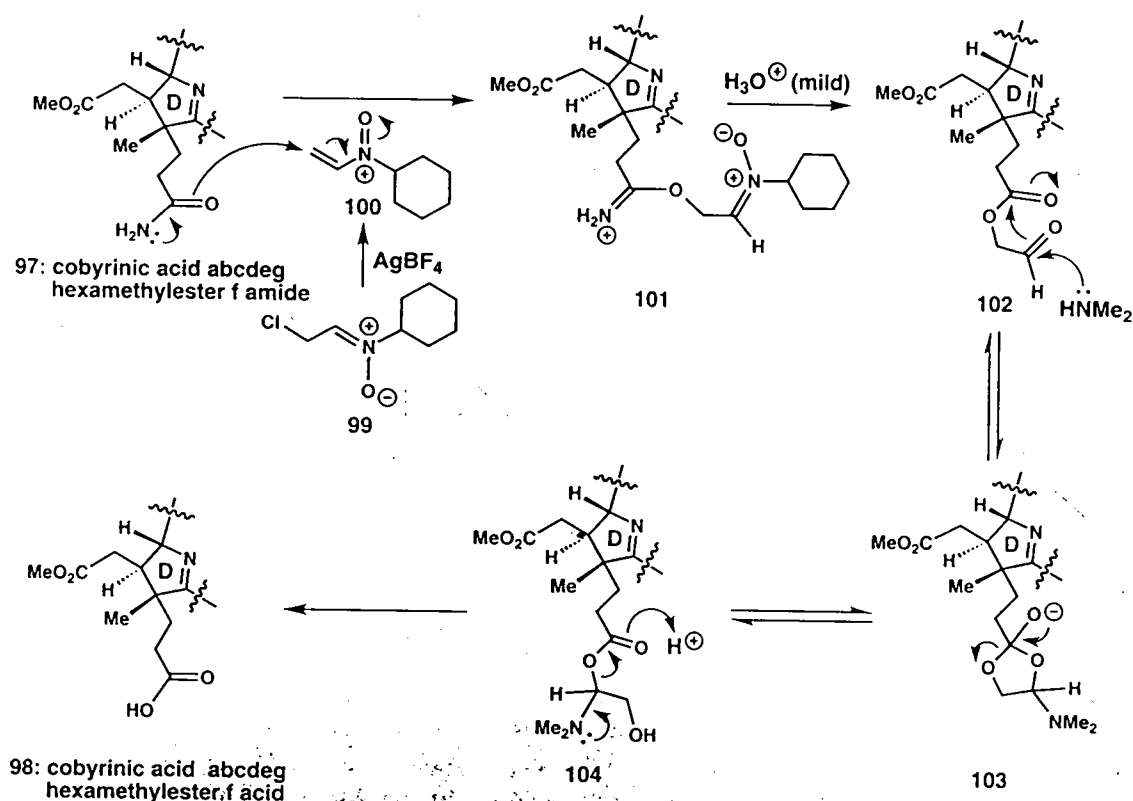
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mixture of primary amides in a ratio of 72:28 in favor of the undesired isomer. These stereoisomeric substances are, however, very readily separable by high-pressure liquid chromatography and it is possible to obtain the desired isomer (compound **97**) in pure form.

Two problems stand between intermediate **97** and the target cobyric acid (**4**). It is instructive at this point to closely examine the structure of **97**. Arranged around its periphery are six side chains which terminate in methoxycarbonyl groups and one side chain which terminates in a primary amide group. One problem requiring a solution is the selective hydrolysis of the primary amide grouping in this compound. At first glance, this problem may seem insurmountable by virtue of the fact that an amide is inherently less electrophilic and, therefore, less susceptible to attack by nucleophilic reagents than esters. Nevertheless, deaminations of amides using nitrous acid or some other nitrous derivative were well known, and both the Woodward and Eschenmoser camps were certainly mindful of these precedents. Although initial model experiments were uniformly unsuccessful, the Cambridge group eventually discovered that when a solution of **97** in carbon tetrachloride is treated with dinitrogen tetroxide, in the presence of sodium acetate, the primary amide can be smoothly deaminated to cobyric acid abcdg hexamethylester **f** acid (**98**). This is one solution to the amide hydrolysis problem.

In Zürich, however, Eschenmoser and his group developed an alternative method that permits the selective hydrolysis of the primary amide function in **97** – a method that, in our opinion, is among the most brilliant in this synthesis. Scheme 22 presents the elegant series of transformations that constitute Eschenmoser's solution to the amide hydrolysis problem. For clarity, only the relevant portion of intermediate **97** is illustrated. In the Eschenmoser method, the cyclohexylnitrone **99** derived from chloroacetaldehyde is treated, in the presence of amide **97**, with silver tetrafluoroborate. This reaction produces the highly electrophilic species **100** which reacts rapidly and selectively with the oxygen atom of the primary amide to give **101**. Mild acid hydrolysis of both carbon–nitrogen double bonds then furnishes formyl ester **102**. The desired carboxylic acid **98** is produced in good yield when this formyl ester is treated with dimethylamine in isopropanol. Dimethylamine attacks the more electrophilic aldehyde carbonyl and then, after an equilibrium transfer of the acyl group, a situation is created that can result in an irreversible release of carboxylic acid **98** (see **104** → **98**). The six methoxycarbonyl groups are impervious to these conditions.

To complete the arduous journey to cobyric acid (**4**), all that remains is the conversion of all six ester groups in **98** into primary amide groups (Scheme 21). Although this functional group transformation is seemingly straightforward, it required a good deal of careful experimentation. When a solution of **98** in liquid ammonia and ethylene glycol is heated to 75 °C in the presence of a catalytic amount of ammonium chloride, cobyric acid (**4**) is obtained in



Scheme 22. Eschenmoser's method for amide hydrolysis.

nearly quantitative yield. You will recall that, in 1960, Bernhauer *et al.* demonstrated that cobyrinic acid (**4**) is readily transformed into vitamin B₁₂ (**1**).⁵ The formal total synthesis of vitamin B₁₂ (**1**) is now, therefore, complete.^{1,16}

8.4 Conclusion

In this chapter, we have attempted to address one of the most significant achievements in organic chemistry. Indeed, the total synthesis of vitamin B₁₂, the culmination of 12 years of extensive research by two groups, has profoundly influenced the science of organic chemistry. Although we have presented the salient accomplishments recorded during the course of this remarkable synthesis, we strongly encourage students of organic synthesis to consult the original writings of Professors Woodward^{1a-c} and Eschenmoser^{1d,1 e,7d} for more detailed and certainly more pedagogical accounts.

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From the perspective of the vitamin B₁₂ synthesis, it would be appropriate to contrast the traditional and contemporary roles of organic synthesis.^{1d} Before the advent of sophisticated physical methods, X-ray crystallography in particular, organic synthesis assumed the important role of confirming a constitutional hypothesis which originated from a degradative assault on a natural product. Indeed, during the classical period of natural products chemistry, an unambiguous synthesis played a decisive role in the elucidation of a natural product's structure. In addition, knowledge about the chemical properties of new structures was obtained, in many instances, as a result of chemical degradative studies. As physical methods matured, the importance of degradative work as a means of elucidating new structures faded. Contemporary natural products and synthetic organic chemists are the beneficiaries of powerful spectroscopic, crystallographic, and other physical methods. As impressive and necessary as these technological developments have been, we have had to pay a substantial price. By disposing of the archaic endeavor of chemical degradation, we have sacrificed an important source of information. Today, studies in natural product total synthesis most often commence with an established structure, but with an ignorance of its chemical properties. This fact confers much importance to synthetic work because it is through synthesis that we are able to achieve an intimate familiarity with the chemical properties of new molecules;^{1d} synthesis must shoulder the burden of acquiring the information that was once a fortuitous by-product of chemical degradation studies. Of course, even greater importance is conferred upon synthetic work in those cases where a new substance is not amenable to chemical degradation; vitamin B₁₂ is a conspicuous example. We contend that target-directed studies in organic synthesis are as important and perhaps even more so today than they have been in the past.¹⁷

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Since it is now well over 20 years in force, this edition focuses solely upon We have therefore re-written the material of all the old cases cited elsewhere. All the new cases are of continuing relevance under the 1977 Act. A practitioner having the misfortune that the Patents Act 1949 will have to have to work.

The jurisprudence or, at any rate, the Office play an ever increasing role in the referred to the important relevant in the Chapters of this edition.

The new Civil Procedure Rules will be and those Chapters concerned with will be re-written accordingly. In general the the court although, in view of the the Court over the last decade the increased powers will have a major impact on Court business is conducted

We would like to thank Douglas Hinchliffe for their invaluable assistance. For the first time in recent history a index in-house and we are grateful for this.

The law is stated as at 1st January

3, New Square
Lincoln's Inn.
February 2000.

they have been made known it was difficult ... not to believe that they must have been obvious to everybody."⁹³

There may be invention in what is merely simplification⁹⁴ or in recognising that the entire industry was going in the wrong direction.⁹⁵ But matters of ordinary skilled designing or mere workshop improvements cannot be considered as requiring the exercise of invention.⁹⁶

Ex post facto analysis

7.28 In *Non-Drip Measure Co. Ltd v. Strangers Ltd*,⁹⁷ Lord Russell said:

"Whether there has or has not been an inventive step in constructing a device for giving effect to an idea which when given effect to seems a simple idea which ought to or might have occurred to anyone, is often a matter of dispute. More especially is this the case when many integers of the new device are already known. Nothing is easier than to say, after the event, that the thing was obvious and involved no invention. The words of Moulton L.J. in *British Westinghouse v. Braulick*⁹⁸ may well be called to mind in this connection: 'I confess' (he said) 'that I view with suspicion arguments to the effect that a new combination, bringing with it new and important consequences in the shape of practical machines, is not an invention, because, when it has once been established, it is easy to show how it might be arrived at by starting from something known, and taking a series of apparently easy steps. This *ex post facto* analysis of invention is unfair to the inventors and, in my opinion, it is not countenanced by English patent law ..."

In *Technograph Printed Circuits Ltd v. Mills & Rockley (Electronics) Ltd*,⁹⁹ Lord Diplock said:

"The cross-examination of the respondents' expert followed with customary skill the familiar 'step by step' course. I do not find it persuasive. Once an invention has been made it is generally possible to postulate a combination of steps by which the inventor might have arrived at the invention that he claims in his specification if he started from something that was already known. But it is only because the invention has been made and has proved successful that it is possible to postulate from what starting point and by what

⁹³ See also *Thierry v. Riekman* (1897) 14 R.P.C. 105.

⁹⁴ *Pope Appliance Corp. v. Spanish River, etc. Mills Ltd* (1929) 46 R.P.C. 23 at 55.

⁹⁵ *Beloit Technologies Inc. v. Valmet Paper Machinery Inc.* (No. 2) [1995] R.P.C. 705 at 750.

⁹⁶ See *Safveans Aktie Bolag v. Ford Motor Co. (Eng.) Ltd* (1927) 44 R.P.C. 49 at 61; *Curtis & Son v. Howard & Co.* (1923) 40 R.P.C. 53 at 183; *Shaw v. Burnet & Co.* (1924) 41 R.P.C. 432.

⁹⁷ (1943) 60 R.P.C. 135 at 142.

⁹⁸ (1910) 27 R.P.C. 209 at 230.

⁹⁹ [1972] R.P.C. 346 at 362.

particular combination of steps in invention. It may be that taken it is now possible to postulate any inventive ingenuity. It is *a posteriori* represents the mental arrived at his invention, but, even in perceiving that the final re inventor to achieve was attained and in his selection of the pa would lead to that result."

Technical not commercial obviousness

Patents are granted for technical, technically obvious development can *Company v. Brabantine (U.K.) Ltd*,¹ A.C.

"The word 'obvious' in section not an advance is technically whether it is commercially obvious in section 3 of the Patent goes back many hundreds of years public are entitled to manufacture the sense of made available to the art. Such a skilled man should not be covered by any monopoly which is part of the state of the workshop modifications or other obvious alterations. He does not and consider whether the step he is taking for special reasons. The prize for a good head start on the competition years."

Obvious to try

In some cases, the final decision of obvious will depend upon whether a prior suggestion into practice which. The classic formulation of this is *Johns Mansville Corporation's Patent*:

¹ [1989] R.P.C. 307 at 327 upheld at [1991] R.P.C. 888.

² [1967] R.P.C. 479 at 493.

s difficult ... not to believe that everybody."⁹³

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y Inc. (No. 2) [1995] R.P.C. 705 at 750.
Ltd (1927) 44 R.P.C. 49 at 61; *Curtis & Son*
aw v. Burnet & Co. (1924) 41 R.P.C. 432.

particular combination of steps the inventor could have arrived at his invention. It may be that taken in isolation none of the steps which it is now possible to postulate, if taken in isolation, appears to call for any inventive ingenuity. It is improbable that this reconstruction *a posteriori* represents the mental process by which the inventor in fact arrived at his invention, but, even if it were, inventive ingenuity lay in perceiving that the final result which it was the object of the inventor to achieve was attainable from the particular starting point and in his selection of the particular combination of steps which would lead to that result."

Technical not commercial obviousness

Patents are granted for technical advances, not for appreciating that a technically obvious development can be exploited commercially. In *Hallen Company v. Brabantia (U.K.) Ltd*,¹ Aldous J. stated:

"The word 'obvious' in section 3 is, I believe, directed to whether or not an advance is technically or practically obvious and not to whether it is commercially obvious. Although the law is encapsulated in section 3 of the Patents Act 1977, the law on obviousness goes back many hundreds of years. The basis of the law is that the public are entitled to manufacture that which has been published, in the sense of made available to the public, with obvious modifications. By 'obvious modifications' are meant that which technically or practically would be obvious to the unimaginative skilled addressee in the art. Such a skilled man should be assured that his actions will not be covered by any monopoly granted to another if he does that which is part of the state of the art with modifications which are workshop modifications or otherwise technically or practically obvious alterations. He does not and should not have to look further and consider whether the step he is taking is obvious or not for commercial reasons. The prize for a good commercial decision or idea is a head start on the competition, and not a monopoly for twenty years."

Obvious to try

In some cases, the final decision on whether or not an invention was obvious will depend upon whether it was obvious to put the teaching of a prior suggestion into practice which would, if done, reveal the invention. The classic formulation of this aspect of the law is by Diplock L.J. in *Johns Mansville Corporation's Patent*²

¹[1989] R.P.C. 307 at 327 upheld at [1991] R.P.C. 195, and see *Richardson-Vicks Inc.'s Patent* [1997] R.P.C. 888.
²[1967] R.P.C. 479 at 493

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United States Patent [19]

[11] Patent Number: **4,546,201**

Piccolo et al.

[45] Date of Patent: **Oct. 8, 1985**

[54] **PROCESS FOR THE OPTICAL
RESOLUTION OF
(±)2-(6'METHOXY-2'-NAPHTHYL)-PRO-
PIONIC ACID**

[75] Inventors: **Oreste Piccolo, Leghorn; Giovanni
Villa, Monticello; Enrico Zen,
Macherio, all of Italy**

[73] Assignee: **Blaschim S.p.A., Milan, Italy**

[21] Appl. No.: **602,744**

[22] Filed: **Apr. 23, 1984**

[30] **Foreign Application Priority Data**

Jul. 27, 1983 [IT] Italy 22261 A/83

[51] Int. Cl.⁴ **C07B 19/00**

[52] U.S. Cl. **562/401; 562/466**

[58] Field of Search **562/401, 466**

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Primary Examiner—Natalie Trousof

Assistant Examiner—Vera C. Clarke

Attorney, Agent, or Firm—Cushman, Darby & Cushman

[57] **ABSTRACT**

Process for the optical resolution of (±)2-(6'methoxy-2'-naphthyl)-propionic acid by adding from 0.45 to 0.65 mole of (S)-alpha-phenylethylamine to each mole of said acid in chloroform.

4 Claims, No Drawings

PROCESS FOR THE OPTICAL RESOLUTION OF (±)2-(6'-METHOXY-2'-NAPHTHYL)-PROPIONIC ACID

This invention relates to a process for the optical resolution of (±) 2-(6'-methoxy-2'-naphthyl)-propionic acid, hereinafter indicated conventionally as (±) AMNP, by means of (S)-alpha-phenylethylamine, hereinafter indicated conventionally as PEA.

More particularly this invention relates to a process which comprises (a) the addition of from 0.45 to 0.65 mole of (S)-alpha-phenylethylamine to each mole of the acid in 3 parts ± 15%, with regard to the acid, of chloroform at from 0° to 58° C., (b) the subsequent cooling of the reaction mixture to 0° C., (c) the filtration of the thus obtained precipitate, (d) the suspension of the filtrate into chloroform at 15°-58° C., (e) the subsequent cooling of the reaction mixture, (f) the filtration of the thus obtained precipitate, (g) the further suspension of the precipitate into chloroform and its treatment with an aqueous alkaline solution, (h) the separation of the chloroform phase from the aqueous phase, (i) the treatment of the latter with acid to afford (+) 2-(6'-methoxy-2'-naphthyl)-propionic acid and its recovery by usual techniques.

(+) AMNP, whose non-proprietary name is Naproxen, is a known drug endowed with anti-inflammatory, anti-pyretic and analgesic activity.

BACKGROUND OF THE INVENTION

The separation of the enantiomers of an acid or a base or the formation of a salt with an optically active base or acid respectively is an elementary knowledge in the art.

On the contrary, there are no further generally applicable pieces of information which allow the chemist to anticipate what are the critical conditions which allow one to separate the enantiomers of a given acid or of a given base on an industrial scale in the most economical way. The finding of these conditions is a largely empirical science which involves overcoming technical prejudices and the original solution of specific technical problems.

The parameters which must be taken into consideration for evaluating if a process of optical resolution is economical on industrial scale are the following:

1. optical purity of the obtained product;
2. yield of the optically active product;
3. productivity (employed volume/amount of treated product ratio);
4. cost of the resolving agent which is used;
5. recoverability of the resolving agent which is used;
6. cost of the recovery of the resolving agent which is used;
7. cost of the solvent or of the solvents mixture which is used;
8. recoverability of the solvent(s) which is (are) used;
9. cost of the recovery of the solvent(s) which is (are) used.

Because of the large therapeutic importance of Naproxen, many methods have been suggested until now for separating the optical isomers of (±) AMNP with optically active bases.

Phenylethylamine or PEA is indicated in some known publications as one of the optically active bases which may be used for separating (±) AMNP.

Among these publications, those which do not indicate the experimental conditions represent information devoid of any value to the artisan.

On the contrary, those which indicate specific operative conditions do not offer such an advantage as to encourage further investigations.

In U.K. Patent Specification No. 1,296,493, PEA is mentioned in generic terms as one of the many optical active bases which may be used for separating (±) AMNP but there is no suggestion concerning the proper solvent, the specific operative conditions, the optical purity of the thus obtained product, the productivity of the process or the recoverability of the solvent and/or of PEA.

U.S. Pat. No. 4,209,638 discloses a process for increasing the amount of a desired enantiomer in a racemic mixture of an arylpropionic acid. (±) AMNP and PEA are mentioned among the possible acids and bases, respectively. The solvent used is a petroleum fraction which begins to boil at 112° C. In accordance with the aim of the patent, an AMNP is obtained which is only slightly enriched with respect to (±) enantiomer and the specification does not mention what kind of and how many further treatments are necessary to obtain a product having the desired optical purity.

European Patent Application No. 82200512.0 discloses a process wherein the resolution with PEA is carried out in water. This process has an unfavourable low productivity (solvent/substrate ratio about 17) and requires repeated crystallizations before obtaining a product having the required optical purity.

Japanese non-examined application No. 50/55,135 conjectures the use of many solvents, inclusive of chloroform, and of a quantity of PEA from 0.5 to 1 mole with respect to one mole of (±) AMNP but it indicates as preferred conditions the use of a mixture of methyl alcohol and ethyl acetate, as solvent, and of one mole of PEA for each mole of (±) AMNP. With this conditions the productivity is about 13 and the yield of (+) AMNP having an optical rotatory power of +66.0 (c=1%, chloroform) is only 48% whereas the yield of AMNP having an optical rotatory power of +63.4 is only 56%.

Furthermore, the artisan appreciates immediately the disadvantages connected with the recovery of the solvents. PEA and (-) AMNP. In fact, (-) AMNP and PEA can not be recovered from the mother liquors by simple addition of acids or bases until they contain methanol; on the other hand the removal of the latter, by distillation, from the mother liquors involves also the removal of ethyl acetate because their boiling points are very close and they form an azeotropic mixture. It is therefore self-evident that the low productivity, low yield and high recovery costs do not make this process economical on an industrial scale. Furthermore, the fact that in this patent application is pointing out these conditions as the best ones discourages the technician from investigating all the other innumerable conditions which are mentioned in generic terms in the Japanese Patent Application No. 50/55,135.

Finally, it is known in the art that the maximum resolving power is usually reached when 1 mole of optical active base is used for each mole of racemic acid or, when using a less optically active base, by completing the salt formation by adding another base.

DETAILED DESCRIPTION OF THE INVENTION

It has been now surprisingly found that the behaviour of PEA in chloroform and in the presence of ($\pm$) AMNP shows an anomaly that has not yet been reported. It is consisting in the fact that, by keeping the volume of the solvent constant, the resolution capacity increases as the amount of PEA decreases from 1 mole to 0.45-0.65 mole for each mole of ($\pm$) AMNP without requiring any adjustment of the missing quantity by addition of another base.

This finding allowed us to develop the process of the instant invention which offers the following advantages:

high yield (70-80%) of (+) AMNP having a rotatory power between +63.0 and +66.0 ($c=1\%$; chloroform); high productivity (solvent/($\pm$) AMNP ratio = 3 l/kg $\pm 15\%$);

use of one base that at the end of the process is easily recovered (Yield $\geq 90\%$) in chloroform solution ready to recycle;

use of a single organic solvent which may be easily recovered and recycled;

easy recovery of the remaining mixture of AMNP enriched in (-) AMNP from the mother liquors by treatment with alkalis; after removal of the organic phase, an aqueous alkaline solution is obtained which affords, simply by heating, ($\pm$) AMNP which is recycled.

Hereinafter are given some Examples which intend to illustrate this invention without limiting it. In addition are given other Examples concerning different experimental conditions in order to show the advantages of the process according to this invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

More particularly Examples 1 and 2 show some typical procedures according to this invention.

Examples from 3 to 5 show the effect of the variation of the PEA/($\pm$)AMNP ratio on the resolution capability when the solvent/($\pm$)AMNP ratio is maintained constant. Using a ratio (PEA/($\pm$)AMNP) equal to 0.45 (Example 3) the resolution capability remains high but the yield of (+) AMNP is drastically reduced; whereas using a ratio equal to 0.75 (Example 4) and 1 (Example 5) the resolution capability tends to zero.

Example 6 shows that when the ratio is 1 increasing of the resolution capability causes a reduction of the productivity.

Finally, Example 7 shows a process which corresponds to that indicated as the preferred one by the Japanese non-examined application No. 50/55,135, excepting that the PEA/($\pm$) AMNP ratio is 0.6 instead of 1. The yield and the optical purity are definitely lower than those obtained with a ratio equal to 1, therefore this behaviour is sharply different from that observed when chloroform is used.

EXAMPLE 1

To a mixture of 460 g (2 moles) of ($\pm$) AMNP in 1.4 l of chloroform at 40° C., 152.8 ml (1.2 moles) of PEA were added in 30 minutes. The mixture was refluxed for 30 minutes, then cooled slowly to 0° C., filtered and washed with 400 ml of chloroform. The humid salt (which gives an acid having $[\alpha]_D^{25} + 54.4$ ($c=1\%$; chloroform)) was treated at 40° C. with 900 ml of chloroform and then cooled to room temperature. After filtration, the salt was suspended in 400 ml of chloroform and 1.3 l of water and treated with 60 ml of a solution of 30% sodium hydroxide up to pH 13-14. The chloroform layer containing PEA was separated and combined with the chloroform extracts obtained from the aqueous phase. The latter was made acid up to pH 5-6 and, after filtration, 180 g (yield, 78%) of (+) AMNP having $[\alpha]_D^{25} + 64.1$ ($c=1\%$; chloroform) were obtained. The racemization of the antipode was made according to well known techniques, by heating the aqueous/alkaline solution from which the remaining PEA has been extracted with chloroform; 270 g $[\alpha]_D^{25} - 1.8$ ($c=1\%$; chloroform) ($\pm$) AMNP have been thus recovered. PEA has been recovered in chloroform solution with a yield of 90%.

reformed and then cooled to room temperature. After filtration, the salt was suspended in 400 ml of chloroform and 1.3 l of water and treated with 60 ml of a solution of 30% sodium hydroxide up to pH 13-14. The chloroform layer containing PEA was separated and combined with the chloroform extracts obtained from the aqueous phase. The latter was made acid up to pH 5-6 and, after filtration, 180 g (yield, 78%) of (+) AMNP having $[\alpha]_D^{25} + 64.1$ ($c=1\%$; chloroform) were obtained. The racemization of the antipode was made according to well known techniques, by heating the aqueous/alkaline solution from which the remaining PEA has been extracted with chloroform; 270 g $[\alpha]_D^{25} - 1.8$ ($c=1\%$; chloroform) ($\pm$) AMNP have been thus recovered. PEA has been recovered in chloroform solution with a yield of 90%.

EXAMPLE 2

To a mixture of 115 g (0.5 mole) of ($\pm$) AMNP in 340 ml of chloroform, cooled to 0° C., 38.2 ml (0.3 mole) of PEA were added in 45 minutes maintaining the temperature of the reaction mixture at 0° C. After 30 minutes, the mixture was filtered and washed with 100 ml of chloroform. The humid salt (which gives an acid having $[\alpha]_D^{25} + 45.5$ ($c=1\%$; chloroform)) was treated with 350 ml of chloroform at the refluxing temperature of the mixture. After cooling to room temperature, the salt was filtered and yielded, after hydrolysis and usual treatment, 40.3 g (yield, 70%) of (+) AMNP $[\alpha]_D^{25} + 65.7$ ($c=1\%$; chloroform).

EXAMPLE 3

Following the procedure of Example 1, but using 114.6 ml (0.9 mole) of PEA, 92.3 g (yield, 40%) of (+) AMNP having $[\alpha]_D^{25} + 65.1$ ($c=1\%$; chloroform) were obtained.

EXAMPLE 4

To a mixture of 115 g (0.5 mole) of ($\pm$) AMNP in 340 ml of chloroform at 40° C., 47.8 ml (0.375 mole) of PEA were added in 30 minutes. The mixture was refluxed for 30 minutes and then cooled slowly to 0° C., filtered and washed with 100 ml of chloroform. The thus obtained salt was hydrolyzed and afforded 74.7 g of (+) AMNP having $[\alpha]_D^{25} + 26.5$ ($c=1\%$; chloroform).

EXAMPLE 5

Following the procedure of Example 4, but using 63.8 ml (0.5 mole) of PEA, 108 g of ($\pm$) AMNP (rotatory power practically equal to zero) were obtained after hydrolysis.

EXAMPLE 6

To a mixture of 100 g (0.438 mole) of ($\pm$) AMNP in 850 ml of chloroform at 40° C., 57 ml (0.448 mole) of PEA were added in 30 minutes. Afterwards, following the procedure of Example 1, 37.1 g (yield, 74%) of (+) AMNP having $[\alpha]_D^{25} + 65.5$ ($c=1\%$; chloroform) were obtained.

EXAMPLE 7

To a mixture of 57.5 g (0.25 mole) of ($\pm$) AMNP in 250 ml of methanol, 19.1 ml (0.15 mole) of PEA dissolved into 800 ml of ethyl acetate were added in 15 minutes at 25° C. The mixture was left overnight at 20°-25° C., the salt was filtered and washed with 100 ml of a (2/1 w/w) mixture of ethyl acetate/methanol. 16.5 g of salt (which gives an acid having $[\alpha]_D^{25} + 58.1$

(c=1%; chloroform) were obtained, which recrystallized from a mixture (6/1) of ethyl acetate/methanol afforded, after hydrolysis, 9.5 g (yield, 33%) of (+) AMNP having $[\alpha]_D^{25} + 62.5$ (C=1%; chloroform).

We claim:

1. A process for the optical resolution of ($\pm$) 2-(6'-methoxy-2'-naphthyl)-propionic acid which comprises:
 - (a) adding from 0.45 to 0.65 mole of (S)-alpha-phenylethylamine to each mole of the acid in 3 parts $\pm 15\%$, with regard to the acid, of chloroform at from 0° to 58° C.,
 - (b) cooling of the reaction mixture to 0° C.,
 - (c) filtering the thus obtained precipitate,
 - (d) suspending the filtrate in chloroform at 15°-58° C.,
 - (e) cooling of the reaction mixture,
 - (f) filtering the thus obtained precipitate,
 - (g) again suspending the precipitate in chloroform and treating this suspension with an aqueous alkaline solution,
 - (h) separating the chloroform phase from the aqueous phase, and

- (i) treating the aqueous phase with acid to yield (+) 2-(6'-methoxy-2'-naphthyl)-propionic acid and recovering same.
2. The process according to claim 1 including the additional steps of:
 - (j) treating the chloroform solution of preceding step (c) with an aqueous/alkaline solution,
 - (k) separating the chloroform phase from the aqueous phase, and
 - (l) heating the aqueous phase of step (k) to yield ($\pm$) 2-(6'-methoxy-2'-naphthyl)-propionic acid which is recycled.
3. The process according to claim 2 including the additional step of:
 - (m) recycling the chloroform solution of preceding step (f), without treatment, to carry out step (a).
4. The process according to claim 2 including the further step of:
 - (n) recycling the chloroform solution of (S)-alpha-phenylethylamine obtained in preceding steps (h) and (k) optionally after evaporation to the desired concentration.

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United States Patent [19]
Holton**[11] Patent Number:** 4,515,811
[45] Date of Patent: May 7, 1985**[54] PROCESS FOR THE RESOLUTION OF D,1
2-(6-METHOXY-2-NAPHTHYL)PROPIONIC
ACID****[75] Inventor:** Percy G. Holton, Menlo Park, Calif.**[73] Assignee:** Syntex Corporation, Panama,
Panama**[21] Appl. No.:** 156,250**[22] Filed:** Jun. 4, 1980**Related U.S. Application Data****[63]** Continuation-in-part of Ser. No. 55,258, Jul. 6, 1979,
abandoned, and a continuation-in-part of Ser. No.
97,118, Nov. 26, 1979, Pat. No. 4,246,193.**[51] Int. Cl.** C07C 91/00; A61K 31/19**[52] U.S. Cl.** 514/554; 260/501.17**[58] Field of Search** 260/501.17; 424/316**[56] References Cited****U.S. PATENT DOCUMENTS**

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Primary Examiner—James H. Reamer**Attorney, Agent, or Firm**—John A. Dhuey; Joseph I.
Hirsch**[57]****ABSTRACT**

Mixtures of d 2-(6-methoxy-2-naphthyl)propionic acid and 1 2-(6-methoxy-2-naphthyl)propionic acid or soluble salts thereof are resolved with N-R-D-glucamine or salts thereof, where R is alkyl having 2 to 36 carbon atoms or cycloalkyl having 3 to 8 carbon atoms, to yield a product substantially enriched in d 2-(6-methoxy-2-naphthyl)propionic acid.

9 Claims, No Drawings

PROCESS FOR THE RESOLUTION OF D,1 2-(6-METHOXY-2-NAPHTHYL)PROPIONIC ACID

CROSS-REFERENCE TO PARENT APPLICATION

This application is a continuation-in-part of applications Ser. Nos. 55,258, filed July 6, 1979, now abandoned and 97,118, filed Nov. 26, 1979, now U.S. Pat. No. 4,246,193.

FIELD OF THE INVENTION

This invention relates to a process for resolving mixtures of d 2-(6-methoxy-2-naphthyl)propionic acid and l 2-(6-methoxy-2-naphthyl)propionic acid to yield a product substantially enriched in d 2-(6-methoxy-2-naphthyl)propionic acid.

d 2-(6-Methoxy-2-naphthyl)propionic acid is a well-known anti-inflammatory, analgesic and anti-pyretic agent which is described and claimed in U.S. Pat. No. 3,904,682. Processes for the preparation of d 2-(6-methoxy-2-naphthyl)propionic acid are described in U.S. Pat. Nos. 3,651,106; 3,652,683; 3,658,858; 3,658,863; 3,663,584; 3,904,682; 3,904,683; and 3,975,432.

BRIEF SUMMARY OF THE INVENTION

In summary, the process of this invention comprises resolving mixtures of d 2-(6-methoxy-2-naphthyl)propionic acid and l 2-(6-methoxy-2-naphthyl)propionic acid or soluble salts thereof with N-R-D-glucamine or a salt thereof, where R is alkyl having 2 to 36 carbon atoms, preferably 2 to 18 carbon atoms, or cycloalkyl having 3 to 8 carbon atoms to yield a product substantially enriched in d 2-(6-methoxy-2-naphthyl)propionic acid, the pharmaceutically active agent. Racemic mixtures of d and l 2-(6-methoxy-2-naphthyl)propionic acid as they occur after known chemical synthesis are the presently preferred starting material for the resolution method of this invention.

The term "alkyl" as used herein refers to and includes straight and branched chain hydrocarbon groups having 2 to 36 carbon atoms. Typical alkyl groups include ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-hexyl, n-octyl, n-dodecyl, n-octadecyl, n-docosanyl, n-hexatriacontanyl, and the like.

The term "cycloalkyl" as used herein refers to and includes cycloaliphatic hydrocarbon groups having 3 to 8 carbon atoms. Typical cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylcyclohexyl, cycloheptyl and cyclooctyl. Of the cycloalkyl groups, cyclohexyl is presently preferred.

Presently preferred resolving agents within the scope of this invention are N-n-propyl-D-glucamine, N-n-butyl-D-glucamine, and N-n-octyl-D-glucamine.

The resolution contemplated by this invention is conducted in an inert organic solvent having a pronounced difference between the solubilities of the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with the resolving agent and the salt of l 2-(6-methoxy-2-naphthyl)propionic acid with the resolving agent, generally at temperatures between room or ambient temperature and an elevated temperature generally up to the reflux temperature of the solvent utilized. The salt of d 2-(6-methoxy-2-naphthyl)propionic acid with the resolving agent (for example, N-n-propyl-D-glucamine, N-n-butyl-D-glucamine or N-n-octyl-D-glucamine) should be significantly less soluble in the solvent than is the salt of l 2-(6-

methoxy-2-naphthyl)propionic acid with the resolving agent and, accordingly, upon the cooling of a heated solution thereof, generally to or about ambient or room temperature, such salt of d 2-(6-methoxy-2-naphthyl)propionic acid with the resolving agent will be preferentially crystallized therefrom. Suitable solvents include water, C₁ to C₁₀ monohydric alcohols, such as, for example, methanol, ethanol, n-propanol, isopropanol, butanol, pentanol, hexanol, cyclohexanol, 2-ethylhexanol, benzyl alcohol, furfuryl alcohol, and the like, C₂ to C₆ dihydric alcohols, such as, for example, ethylene glycol, 1,2-propylene glycol, 1,3-propylene glycol, and the like, C₃ to C₄ trihydric alcohols, such as for example, glycerol, and the like, C₃ to C₁₁ ketones, such as, for example, acetone, acetylacetone, ethyl methyl ketone, diethyl ketone, di-n-propyl ketone, diisopropyl ketone, diisobutyl ketone, and the like. Other solvents include mono- and di(lower)alkyl ether of ethylene glycol and diethylene glycol, dimethylsulfoxide, sulfolanes, formamide, dimethylformamide, N-methyl pyrrolidone, pyridine, dioxane, dimethylacetamide, and the like. The C₁ to C₃ alcohols, e.g. methanol and isopropanol, particularly methanol, are the presently preferred solvents. Sufficient water can be added to the solvent if needed to solubilize all of the materials which have been added thereto.

The starting material [i.e., the mixture of d 2-(6-methoxy-2-naphthyl)propionic acid and l 2-(6-methoxy-2-naphthyl)propionic acid or soluble salts thereof] is heated to an elevated temperature, generally to a temperature in the range from about 60° C. to about 100° C. or the reflux temperature of the solvent, in the presence of the resolving agent to solubilize all of the materials which have been added to the solvent. If desired, the solvent can be held at the elevated temperature until all of the materials have gone into solution. After the solution has been held at the elevated temperature for the desired length of time, it is slowly cooled to ambient temperature. During the cooling process, the solution is preferably seeded with a salt of d 2-(6-methoxy-2-naphthyl)propionic acid and the resolving agent [e.g., the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-propyl-D-glucamine]. The crystalline precipitate which results is enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with the resolving agent. The final temperature to which the solution is taken is chosen by practical considerations but generally is selected so that the temperature difference will be sufficient to provide a high yield of crystals. The crystallizing mixture can be maintained at the lower temperature until crystallization is complete, or nearly so, usually for about 30 minutes to about several hours or so. The crystalline precipitate which results is removed by filtration and washed.

The crystalline material which is obtained at this stage in the process [i.e., a material which is enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with the resolving agent], after separation by filtration and washing, can be charged to water and heated, if necessary, to redissolve the crystalline material. For those N-R-D-glucamines which are soluble in water, the resulting solution is acidified for example with a mineral acid, such as sulphuric acid or hydrochloric acid, or an organic acid such as acetic acid, and the crystalline precipitate so obtained is separated by filtration, washed and dried. There results a white crystalline product substantially enriched in d 2-(6-methoxy-2-

naphthyl)propionic acid. Alternatively, for those N-R-D-glucamines which are insoluble in water, the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with such a resolving agent can be treated with a strong base, such as, for example, potassium hydroxide or other strong base having a pKa value greater than 10, to cleave the salt, followed by filtration to remove the resolving agent and acidification of the filtrate with, for example, a mineral acid such as hydrochloric acid or sulfuric acid, or an organic acid such as acetic acid, to give, after filtration, washing and drying, a white crystalline product substantially enriched in d 2-(6-methoxy-2-naphthyl)propionic acid.

Prior to the cleavage of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with the resolving agent to obtain d 2-(6-methoxy-2-naphthyl)propionic acid, it is generally desirable to redissolve the enriched salt material in further solvent material, heat the solvent to the desired (normally elevated) temperature, seed the resultant solution with the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with the resolving agent, and cool the resultant solution to effect one or more further recrystallizations. Each such recrystallization further increases the proportion of the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with the resolving agent in the recrystallized material. N-n-propyl-D-glucamine, N-n-butyl-D-glucamine, and N-n-hexyl-D-glucamine are particularly suitable resolving agents within the scope of this invention because, with merely one recrystallization step prior to the redissolution of the resultant crystalline product and subsequent acidification, a product having a purity on the order of about 97-99% d 2-(6-methoxy-2-naphthyl)propionic acid can be obtained.

N-n-octyl-D-glucamine, however, is the presently preferred resolving agent because, with use of N-n-octyl-D-glucamine, the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine is readily recoverable by filtration, d 2-(6-methoxy-2-naphthyl)propionic acid of acceptably high optical purity can be obtained without need for one or more recrystallizations prior to the cleaving step, and the resolving agent can be recovered directly and in high yield (on the order of about 97-98%) by filtration. Additionally, the cleavage can be conducted under either alkaline or acidic conditions. Alkaline cleavage results in a precipitate of N-n-octyl-D-glucamine while the d 2-(6-methoxy-2-naphthyl)propionic acid remains in solution in the alkaline medium. Acidic cleavage results in a precipitate of d 2-(6-methoxy-2-naphthyl)propionic acid while the N-n-octyl-D-glucamine remains in solution in the acidic medium.

The N-n-octyl-D-glucamine is substantially insoluble in water, thus permitting recovery thereof in high yields from aqueous systems. This is also true for other resolving agents of this invention where R is alkyl having at least 6 carbon atoms, e.g., those resolving agents where R is alkyl having from 6 to 18 carbon atoms.

The material enriched in l 2-(6-methoxy-2-naphthyl)propionic acid or the N-R-D-glucamine salt thereof (where R is as defined above) can be processed to recover l 2-(6-methoxy-2-naphthyl)propionic acid which can then be racemized according to known techniques to give a material having a higher content of d 2-(6-methoxy-2-naphthyl)propionic acid. See, for example, Dyson U.S. Pat. No. 3,686,183. This material can be recycled, either alone or in combination with other d,l 2-(6-methoxy-2-naphthyl)propionic acid, to provide

additional starting material for the resolution process of this invention.

The amount of resolving agent employed [on a molar basis relative to the d,l 2-(6-methoxy-2-naphthyl)propionic acid being resolved] in accordance with the present invention ranges from between about 50% and 100%. However, as only about 50% [on a molar basis relative to the d,l 2-(6-methoxy-2-naphthyl)propionic acid being resolved] of the resolving agent is needed to form the more insoluble salt thereof with the d 2-(6-methoxy-2-naphthyl)propionic acid, the remainder of the resolving agent (generally on the order of up to about 40-50 molar %) can be replaced, if desired, with a more inexpensive base, including, for example, an inorganic base such as an alkali metal hydroxide, such as sodium hydroxide or potassium hydroxide, or an organic tertiary amine such as triethylamine, triethanolamine, tributylamine, etc.

The aqueous mother liquors resulting from the isolation of d 2-(6-methoxy-2-naphthyl)propionic acid and l 2-(6-methoxy-2-naphthyl)propionic acid contain, for example, salts of the resolving agent with the acid utilized in the acidification step. Such mother liquors can be treated with an inorganic base to form the corresponding insoluble salt with the N-R-D-glucamine, such as, for example, treatment with a suspension of calcium hydroxide to precipitate the corresponding calcium salt, which is removed by filtration. The filtrate is concentrated under vacuum at elevated temperatures to dryness, first removing any further salt, e.g. the calcium salt, which is formed during the early stages of the concentration process. The residue is dissolved in a suitable solvent at an elevated temperature up to the reflux temperature of the solvent, and then cooled to room temperature, to thereby afford the resolving agent as a crystalline precipitate which can be reused, either alone or in combination with new material, in the resolution process of this invention. Alternatively, the resolving agent can be recovered through use of an anion exchange resin and recycled for reuse.

The terms "mixture of d 2-(6-methoxy-2-naphthyl)propionic acid and d 2-(6-methoxy-3-naphthyl)propionic acid" is also intended to include those salts thereof which are soluble in the solvent utilized in the resolution process of this invention. Such salts include, for example, the corresponding sodium salts, potassium salts, lithium salts, and the like. Such salts can be prepared by the addition of base, such as an alkali metal hydroxide, for example, sodium or potassium hydroxide, to a solution of the mixture of the d and l 2-(6-methoxy-2-naphthyl)propionic acid. The resulting mixture of d 2-(6-methoxy-2-naphthyl)propionic acid and l 2-(6-methoxy-2-naphthyl)propionic acid salts can be resolved according to the present invention by use of a salt of the resolving agent which will react to form a salt of d 2-(6-methoxy-2-naphthyl)propionic acid with the N-R-D-glucamine. Suitable glucamine salts include, for example, the hydrochloride salt and the acetate salt. Other salts include the propionate salt, butyrate salt, isobutyrate salt, sulfate salt, nitrate salt, and the like. Accordingly, the term "N-R-D-glucamine" (where R is as defined above) is intended to include those salts thereof which, when used with an appropriate salt of the mixture of d and l 2-(6-methoxy-2-naphthyl)propionic acid, will afford the resolution contemplated hereby.

The N-R-D-glucamine salts of d 2-(6-methoxy-2-naphthyl)propionic acid are useful as anti-inflamma-

tory, analgesic, and/or antipyretic agents, platelet aggregation inhibitors, fibrinolytic agents and as smooth muscle relaxants. The aforesaid salts are also useful in the treatment of dysmenorrhoea and are agents for alleviating post-menopausal symptoms.

Accordingly, such salts would be useful in the treatment and elimination of inflammation such as inflammatory conditions of the muscular skeletal system, skeletal joints and other tissues, for example, in the treatment of inflammatory conditions such as rheumatism, concussion, laceration, arthritis, bone fractures, post-traumatic conditions, and gout. In those cases in which the above conditions include pain and pyrexia coupled with inflammation, such salts would be useful for the relief of these conditions as well as the inflammation.

Administration of the aforesaid salts in an appropriate pharmaceutical composition can be via any of the accepted modes of administration of agents for the treatment of inflammation, pain, or pyrexia. Thus, administration can be, for example, orally, parenterally (as by, e.g., injection), or topically, in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquid solutions, suspensions, creams, lotions, ointments, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. Such pharmaceutical compositions will include a conventional pharmaceutical carrier or excipient and a salt of N-R-D-glucamine with d 2-(6-methoxy-2-naphthyl)propionic acid, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc.

The preferred manner of administration is oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction. Generally, a daily dose of from 2 mg. to 20 mg. of the aforesaid salt per kilogram of body weight is used. For such oral administration, a pharmaceutically acceptable non-toxic composition is formed by an incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like.

A suppository using, for example, polyalkylene glycols, such as polypropylene glycol, as the carrier can be formulated. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. the aforesaid salt and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's *Pharmaceutical Sciences*, Mack Publishing Company, Easton, Pa., 14th Edition, 1970. The composition to be administered will, in any event, contain a quantity of the aforesaid salt(s) in a pharmaceutically effective amount for relief of the particular condition being treated in accordance with the teachings hereof.

The aforesaid salts are also uterine smooth muscle relaxants and thus are useful as agents for maintaining the pregnancy of pregnant mammals, for the benefit of the mother and/or the fetus, until termination of the pregnancy is considered, from a medical point of view, to be favorable, or more favorable, for the mother and/or the fetus. It should be understood, however, that in certain instances, for example where parturition has already begun (i.e., the mother is experiencing uterine contractions, especially near full term), that administration of the aforesaid salts may not maintain the pregnant state for an indefinite period of time. Rather, in such instances, the pregnancy will, most probably, be slightly "prolonged", a factor which may be advantageous to either the mother and/or the fetus.

The aforesaid salts are also used as agents for delaying the onset of, or for postponing, parturition. As used in this application, the phrase "to delay the onset of parturition" is intended to cover that delay in parturition caused by the administration of one of the aforesaid salts at any time before uterine muscle contractions have begun. Thus, it is intended that the aforementioned phrase cover abortion prevention early in pregnancy (i.e., before the fetus is "viable") as well as delaying premature parturition, a term which sometimes is used with reference to that premature labor experienced later in the pregnancy which the fetus is considered to be "viable". In either case, the agents are administered as prophylactic agents in that such administration tends to prevent the onset of parturition. This administration is particularly useful in the treatment of women having a history of spontaneous abortion, miscarriage or premature delivery (i.e., delivery prior to full term). Such administration is also useful where there are clinical indications that the pregnancy might be terminated prior to that time considered favorable to the mother and/or fetus.

As used in this application, the phrase "postponing parturition" is intended to cover that delay in parturition caused by the administration of one of the aforesaid salts after uterine muscle contraction have begun. The condition of the patient, including the time within the gestation period when the contractions have begun, the severity of the contractions and how long the contractions have taken place will affect the results achieved. For example, the effect can be to reduce the intensity and/or the duration of the contractions (the actual act of parturition being "prolonged"), or to stop the contractions altogether. In either case, the effect will be to prolong the gestation period although, depending upon the condition of the patient as described above, the effect may either be slight or, under appropriate circumstances, somewhat greater. Such administration may be to prevent spontaneous abortion, to cause the delivery to be more easily accomplished and/or less painful to the mother, or to occur at a more appropriate time and/or place.

With respect to animals, this treatment can also be utilized to synchronize the deliveries from a group of pregnant animals to happen at or about the same time, or to happen at or about a desired time and/or place, when the births can be handled with greater facility.

In all cases, administration should be consistent with best and/or accepted medical (or veterinary) practices so as to maximize the benefits to the mother and the fetus. For example, administration should not be continued so long past full term that the fetus dies in utero.

In the practice of this aspect of the present invention, a therapeutically effective amount of one of the aforesaid salts or a pharmaceutical composition containing an aforesaid salt is administered to the pregnant animal via any of the usual and acceptable methods known in the art. The salt can be administered either singly or in combination with another compound or compounds, as defined above, or other pharmaceutical agents, carriers, adjuvants, etc. Such salt(s) or compositions can be administered orally or parenterally in the doses and in the forms (including oral, vaginal or uterine tablets or suppositories, etc.) as set forth above regarding anti-inflammatory, etc. activities. Administration can be a single daily dose or up to 3 or 4 smaller doses regularly given throughout the day. The actual amount of the salt administered will, of course, depend on its relative activity for this particular utility.

DESCRIPTION OF SPECIFIC EMBODIMENTS

The following specific description is given to enable those skilled in this art to more clearly understand and practice the present invention. It should not be considered as a limitation upon the scope of the invention but merely as being illustrative and representative thereof.

PREPARATION 1

18 G. of D-glucose, 20 ml. of 70% ethylamine in water and 1 g. of Raney Nickel in 140 ml. of methanol and 30 ml. of water are treated with hydrogen at 160 psi for 2 hours at 60° C. The solution is filtered to remove the catalyst, the solvent concentrated at low pressure, the precipitate dissolved in 50 ml. of methanol, and the resultant solution filtered and cooled to give 15.5 g. of N-ethyl-D-glucamine [m.p. 132°-134° C.; $[\alpha]_D - 15.4^\circ$ (water)] as a precipitate.

PREPARATION 2

18 G. of D-glucose, 20 ml. of n-propylamine and 1 g. of Raney Nickel in 140 ml. of methanol and 40 ml. of water are treated with hydrogen at 160 psi for 2 hours at 60° C. 40 ml. of water is added to dissolve the precipitate, the solution is filtered to remove the catalyst, the solvent concentrated at low pressure, the residue dissolved in 100 ml. of methanol, and the resultant solution cooled to give 14.6 g. of N-n-propyl-D-glucamine [m.p. 141°-143° C.; $[\alpha]_D - 15.2^\circ$ (water)] as a precipitate.

PREPARATION 3

18 G. of D-glucose is mixed with 9 g. of iso-propylamine for 2 hours, 5 ml. of ethanol is added and the mixture stirred overnight. The excess isopropylamine and the ethanol are removed at low pressure, the residue is dissolved in 180 ml. of methanol and treated overnight at 50° C. with 1 g. of 5% Palladium on charcoal and hydrogen (176 psi). The methanol solution is filtered to remove the catalyst, concentrated at low pressure, and the resultant residue recrystallized from ethanol to give 5.7 g. of N-isopropyl-D-glucamine [m.p. 134°-136° C.; $[\alpha]_D - 13.15^\circ$ (water)].

PREPARATION 4

18 G. of D-glucose is mixed with 21.9 g. of n-butylamine and 180 ml. of methanol at reflux for one hour, the excess n-butylamine and the methanol are removed at low pressure, and the residue is dissolved in 180 ml. of methanol and treated overnight at 60° C. with 1.5 g. of 5% Palladium on charcoal and hydrogen (180 psi). The solution is filtered to remove the catalyst, concentrated

at low pressure, and the resultant residue recrystallized from ethanol to give 13.3 g. of N-n-butyl-D-glucamine [m.p. 129°-131° C.; $[\alpha]_D - 14.30^\circ$ (water)].

PREPARATION 5

18 G. of D-glucose, 22 g. of iso-butylamine and 1 g. of Raney Nickel in 140 ml. of methanol and 40 ml. of water are treated with hydrogen at 160 psi for 2 hours at 60° C. The solution is filtered to remove the catalyst, and stored overnight at -10° C. to give a precipitate which is recovered by filtration. 6.6 G. of N-iso-butyl-D-glucamine [m.p. 138°-143° C.; $[\alpha]_D - 18.8^\circ$ (dimethylsulfoxide)] is obtained.

PREPARATION 6

18 G. of D-glucose, 9.9 g. of cyclohexylamine and 1 g. of Raney Nickel in 140 ml. of methanol and 40 ml. of water are treated with hydrogen at 160 psi for 2 hours at 60° C. The solution is filtered to remove the catalyst, and stored overnight at -10° C. to give a precipitate which is recovered by filtration. 2.35 G. of N-cyclohexyl-D-glucamine [m.p. 144°-146° C.; $[\alpha]_D - 20.4^\circ$ (dimethylsulfoxide)] is obtained.

PREPARATION 7

18 G. of D-glucose, 25 ml. of n-octylamine and 1 g. of Raney Nickel in 140 ml. of methanol and 40 ml. of water are treated with hydrogen at 160 psi for 3 hours at 60° C. The reaction mixture is slurried with 300 ml. of dichloromethane to dissolve most of the resultant precipitate, filtered to remove the catalyst, and concentrated at low pressure to give 9.2 g. of N-n-octyl-D-glucamine [m.p. 120°-122° C.; $[\alpha]_D - 16.6^\circ$ (dimethylsulfoxide)].

PREPARATION 8

18 G. of D-glucose, 18.5 g. of n-dodecylamine and 1 g. of Raney nickel in 140 ml. of methanol and 40 ml. of water are treated with hydrogen at 160 psi for 2 hours at 60° C. The solution is filtered to remove the catalyst, and stored overnight at -10° C. The precipitate (20.35 g.) which results is recovered by filtration. 10 G. of the latter and 1 g. of Raney Nickel in 200 ml. of methanol are treated overnight with hydrogen at 180 psi at 60° C. The reduction with hydrogen is then continued for an additional 3.5 hours at 180 psi and 105° C. The reaction mixture is heated to dissolve a precipitate which results, and filtered to remove the catalyst. The reaction mixture is cooled to room temperature, held at that temperature for 2 hours, then filtered to give 4.59 g. of N-n-dodecyl-D-glucamine [m.p. 122°-125° C.; $[\alpha]_D - 14.0^\circ$ (dimethylsulfoxide)].

PREPARATION 9

18.0 G. of glucose and 27.0 g. of n-octadecylamine are stirred in 500 ml. of methanol for approximately 60 hours. The precipitate which forms is collected, washed with about 250 ml. of methanol and then dried under vacuum (with a slight nitrogen bleed) at about 53° C. to thereby afford 39.5 g. of collected material. 2.0 G. of the latter is mixed with 0.5 g. of 5% palladium on charcoal in 200 ml. of isopropanol and treated with hydrogen (300 psi) overnight at 50° C. The precipitate which results is dissolved by heating the solvent. The reaction mixture is filtered through celite to remove the catalyst and cooled to give 1.5 g. of N-n-octadecyl-D-glucamine (m.p. 124°-126° C.). 0.4 G. of the latter is dissolved in 20 ml. of heated isopropanol, filtered and cooled to give

0.36 g. of purified N-n-octadecyl-D-glucamine [m.p. 123°-126° C., $[\alpha]_D - 10.6^\circ$ (pyridine)].

PREPARATION 10

18.0 G. of glucose and 10.1 g. of n-hexylamine are stirred at room temperature in 145 ml. of methanol for approximately 60 hours. The reaction mixture is mixed with 1.0 g. of 5% palladium on charcoal and treated with hydrogen (100 psi) overnight at 45°-50° C. The precipitate which forms is collected and redissolved in 200 ml. of methanol, filtered through celite to remove the catalyst, and cooled to give 15.03 g. of N-n-hexyl-D-glucamine [m.p. 125°-126° C.; $[\alpha]_D - 18.6^\circ$ (dimethylsulfoxide)] as a precipitate.

EXAMPLE 1

4.60 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 1.01 g. of triethylamine (0.5 equivalent) in 35 ml. of isopropanol to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 2.09 G. of N-ethyl-D-glucamine (0.5 equivalent) are added and the solution is cooled to room temperature (i.e. about 20°-23° C.) to give 4.42 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-ethyl-D-glucamine (m.p. 153°-161° C.). A sample of the latter is dissolved in about 25 ml. of water heated to about 80° C., treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 27.7^\circ$ (chloroform)).

1.00 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-ethyl-D-glucamine is dissolved in 19.5 ml. of isopropanol and 1.5 ml. of water at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.65 g. of a recrystallized salt (m.p. 167°-169° C.). This material is treated with hydrochloric acid as set forth above in the preceding paragraph to give a material further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 56.0^\circ$ (chloroform)).

EXAMPLE 2

4.60 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 1.01 g. of triethylamine (0.5 equivalent) in 30 ml. of isopropanol and 1.5 ml. of water to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 2.09 G. of N-ethyl-D-glucamine are added and the solution is cooled to room temperature to give 4.32 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-ethyl-D-glucamine (m.p. 149°-156° C.). A sample of the latter is dissolved in about 25 ml. of water heated to about 80° C., treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 35.9^\circ$).

1.00 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-ethyl-D-glucamine is dissolved in 20 ml. of 5% aqueous isopropanol and 1.0 ml. of water at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.70 g. of a first recrystallized material (m.p. 167°-168° C.). A sample of the latter is treated with hydrochloric acid as set forth in the preceding paragraph to give a material further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 55.4^\circ$).

0.50 G. of the first recrystallized material from the preceding paragraph [i.e. the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-ethyl-D-glucamine] is dissolved in 10 ml. of 5% aqueous isopropanol and 0.5 ml. of water at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.43 g. of a second recrystallized material (m.p. 169°-170° C.). A sample of the latter is treated with hydrochloric acid as set forth in the first paragraph of this Example to give a material even further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 62.0^\circ$).

0.33 G. of the second recrystallized material from the preceding paragraph [i.e., the material further enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-ethyl-D-glucamine] is dissolved in 12 ml. of 5% aqueous isopropanol and 1.0 ml. of water at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.27 g. of a third recrystallized material. The latter is treated with hydrochloric acid as set forth in the first paragraph of this Example to give substantially pure d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 67.1^\circ$).

EXAMPLE 3

2.30 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 0.5 g. of triethylamine in 23 ml. of denatured ethanol to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 1.05 G. of N-ethyl-D-glucamine are added, and the solution is seeded with a small amount of the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-ethyl-D-glucamine and then cooled to room temperature to give 1.95 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-ethyl-D-glucamine (m.p. 157°-160° C.). A sample of the latter is dissolved in about 25 ml. of water heated to about 80° C., treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 38.1^\circ$).

1.0 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-ethyl-D-glucamine is dissolved in 15 ml. of the denatured ethanol at about the reflux temperature of the solvent. The solution is slowly cooled, seeded with a small amount of the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-ethyl-D-glucamine, and then further cooled to room temperature to give, after recovery by filtration, 0.65 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-ethyl-D-glucamine (m.p. 167°-168° C.). A sample of the latter is dissolved in about 25 ml. of water heated to about 80° C., treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 61.6^\circ$).

EXAMPLE 4

4.60 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 1.01 g. of triethylamine (0.5 equivalent) in 35 ml. of isopropanol to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 2.23 G. of N-n-propyl-D-glucamine (0.5 equivalent) are added and the solution is cooled to room temperature to give 4.68 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-propyl-D-glucamine (m.p.

173°-175° C.). A sample of the latter is dissolved in about 25 ml. of water heated to about 80° C.; treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 46.4^\circ$).

1.00 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-propyl-D-glucamine is dissolved in 19.5 ml. of isopropanol and 2.5 ml. of water at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.82 g. of a recrystallized salt (m.p. 180°-181° C.). This material is treated with hydrochloric acid as set forth in the preceding paragraph to give substantially pure 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 68.0^\circ$).

EXAMPLE 5

4.60 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 1.01 g. of triethylamine (0.5 equivalent) in 35 ml. of isopropanol to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 2.23 G. of N-iso-propyl-D-glucamine (0.5 equivalent) are added and the solution is cooled to room temperature give 4.43 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-iso-propyl-D-glucamine. A sample of the latter is dissolved in about 25 ml. of water heated to about 80° C., treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 28.8^\circ$).

1.00 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-iso-propyl-D-glucamine is dissolved in 21 ml. of 5% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.85 g. of a recrystallized salt. The latter is treated with hydrochloric acid as set forth in the preceding paragraph to give a material further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 42.7^\circ$).

EXAMPLE 6

4.60 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 1.01 g. of triethylamine (0.5 equivalent) in 30 ml. of isopropanol and 1.5 ml. of water to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 2.23 G. of N-iso-propyl-D-glucamine are added and the solution is cooled to room temperature to give 4.38 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-iso-propyl-D-glucamine (m.p. 146°-148° C.). A sample of the latter is dissolved in about 25 ml. of water heated to about 80° C., treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 26.9^\circ$).

1.00 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-iso-propyl-D-glucamine is dissolved in 20 ml. of 5% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.76 g. of a first recrystallized material (m.p. 151°-152° C.). A sample of the latter is treated with hydrochloric acid as set forth in the preceding paragraph to give a material further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 43.0^\circ$).

0.50 G. of the first recrystallized material from the preceding paragraph [i.e. the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-iso-propyl-D-glucamine] is dissolved in 10 ml. of 5% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.43 g. of a second recrystallized material (m.p. 153°-154° C.). A sample of the latter is treated with hydrochloric acid as set forth in the first paragraph of this Example to give a material even further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 53.2^\circ$).

0.32 G. of the second recrystallized material from the preceding paragraph [i.e. the material further enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-iso-propyl-D-glucamine] is dissolved in 10 ml. of 5% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.29 g. of a third recrystallized material (m.p. 153°-154° C.). The latter is treated with hydrochloric acid as set forth in the first paragraph of this Example to give a material yet further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 57.9^\circ$).

EXAMPLE 7

4.60 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 1.01 g. of triethylamine (0.5 equivalent) in 18 ml. of ethanol to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 2.37 G. of N-n-butyl-D-glucamine and an additional 18 ml. of ethanol are added and the solution is cooled to room temperature to give 4.28 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-butyl-D-glucamine (m.p. 155°-156° C.). 1.0 G. of the latter is dissolved in about 25 ml. of water heated to about 80° C., treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 27.4^\circ$).

3.0 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-butyl-D-glucamine is dissolved in 48 ml. of ethanol and 1 ml. of water at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 2.64 g. of a recrystallized salt (m.p. 157.5°-158° C.). 1.0 G. of the latter is treated with hydrochloric acid as set forth in the preceding paragraph to give substantially pure d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 65.8^\circ$).

EXAMPLE 8

0.28 G. of potassium hydroxide is dissolved in 18 ml. of methanol, then 2.30 g. of d,l 2-(6-methoxy-2-naphthyl)propionic acid and 1.18 g. of N-n-butyl-D-glucamine are added and the methanolic solution heated to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. The solution is slowly cooled, seeded with a small amount of the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-butyl-D-glucamine, and then further cooled to room temperature to give, after recovery by filtration and washing, 1.18 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-butyl-D-glucamine. The latter is dissolved in 15 ml. of water heated to about 80° C., treated with hydrochloric acid until acidic at which time 0.56 g. of a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid

precipitates out of solution and is recovered by filtration ($[\alpha]_D + 56.8^\circ$).

EXAMPLE 9

2.30 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid and 0.50 g. of triethylamine (0.5 equivalent) are dissolved in 25 ml. of acetone. 1.19 G. of N-n-butyl-D-glucamine is heated in an additional 25 ml. of acetone to 50°C . 3.5 ml. of water in 0.5 ml. increments is added to solubilize the N-n-butyl-D-glucamine. The N-n-butyl-D-glucamine solution is added to the solution of d,l 2-(6-methoxy-2-naphthyl)propionic acid at 50°C . with stirring, then cooled to room temperature to give 1.83 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-butyl-D-glucamine (m.p. $157^\circ\text{--}158^\circ\text{C}$). A sample of the latter is dissolved in about 25 ml. of water heated to about 80°C ., treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 61.1^\circ$).

EXAMPLE 10

4.60 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 1.01 g. of triethylamine (0.5 equivalent) in 40 ml. of isopropanol and 2.0 ml. of water to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 2.37 G. of N-iso-butyl-D-glucamine are added and the solution is cooled to room temperature to give 4.53 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-iso-butyl-D-glucamine (m.p. $150^\circ\text{--}152^\circ\text{C}$). A sample of the latter is dissolved in about 25 ml. of water heated to about 80°C ., treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 30.2^\circ$).

1.00 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-iso-butyl-D-glucamine is dissolved in 20 ml. of 5% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.85 g. of a first recrystallized material (m.p. $154^\circ\text{--}156^\circ\text{C}$). A sample of the latter is treated with hydrochloric acid as set forth in the preceding paragraph to give a material further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 40.3^\circ$).

0.80 G. of the first recrystallized material from the preceding paragraph [i.e., the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-iso-butyl-D-glucamine] is dissolved in 16 ml. of 5% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.77 g. of a second recrystallized material (m.p. $156^\circ\text{--}157^\circ\text{C}$). A sample of the latter is treated with hydrochloric acid as set forth in the first paragraph of this Example to give a material even further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 47.9^\circ$).

0.67 G. of the second recrystallized material from the preceding paragraph [i.e., the material further enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-iso-butyl-D-glucamine] is dissolved in 16 ml. of 5% aqueous isopropanol and 1.0 ml. of water at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.39 g. of a third recrystallized material (m.p. $157^\circ\text{--}158^\circ\text{C}$). The latter is

treated with hydrochloric acid as set forth in the first paragraph of this Example to give a material yet further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 54.3^\circ$).

EXAMPLE 11

2.60 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 0.50 g. of triethylamine (0.5 equivalent) in 15 ml. of isopropanol and 0.5 ml. of water to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. There is an immediate precipitate when 1.32 g. of N-cyclohexyl-D-glucamine (0.5 equivalent) is added to the heated solution. An additional 15 ml. of isopropanol and 1.5 ml. of water are added and the mixture is heated to about the reflux temperature of the solvent to dissolve the precipitate. The solution is cooled to room temperature to give 2.24 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-cyclohexyl-D-glucamine (m.p. $157^\circ\text{--}158^\circ\text{C}$). A sample of the latter is dissolved in about 25 ml. of water heated to about 80°C ., treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 38.7^\circ$).

1.00 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-cyclohexyl-D-glucamine is dissolved in 20 ml. of 5% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.79 g. of a first recrystallized material (m.p. $159^\circ\text{--}160^\circ\text{C}$). A sample of the latter is treated with hydrochloric acid as set forth in the preceding paragraph to give a material further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 51.7^\circ$).

0.20 G. of the first recrystallized material from the preceding paragraph [i.e. the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-cyclohexyl-D-glucamine] is dissolved in 4 ml. of 5% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.18 g. of a second recrystallized material (m.p. $160^\circ\text{--}161^\circ\text{C}$). A sample of the latter is treated with hydrochloric acid as set forth in the first paragraph of this Example to give a material even further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 60.3^\circ$).

0.15 G. of the second recrystallized material from the preceding paragraph [i.e. the material further enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-cyclohexyl-D-glucamine] is dissolved in 5 ml. of 5% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.13 g. of a third recrystallized material (m.p. $161^\circ\text{--}162^\circ\text{C}$). The latter is treated with hydrochloric acid as set forth in the first paragraph of this Example to give substantially pure d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 65.5^\circ$).

EXAMPLE 12

4.60 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 1.01 g. of triethylamine (0.5 equivalent) in 30 ml. of isopropanol and 1.5 ml. of water to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 2.93 G. of N-n-octyl-D-glucamine (0.5 equivalent) are added and the solution is cooled to room temperature to give 4.42 g. of a material enriched in the salt of d 2-(6-

methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine (m.p. 138°-140° C.). A sample of the latter is dissolved in about 25 ml. of water heated to about 80° C., treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 54.8^\circ$).

1.00 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine is dissolved in 9.5 ml. of isopropanol and 0.5 ml. of water at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.85 g. of a recrystallized salt (m.p. 140°-141° C.). This material is treated with hydrochloric acid as set forth in the preceding paragraph to give substantially pure d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 65.8^\circ$).

EXAMPLE 13

0.10 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine from the first paragraph of Example 12 and 0.3 g. of potassium hydroxide in 25 ml. of water are stirred for one hour at room temperature. The precipitate is removed by filtration. The filtrate is treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 55.3^\circ$).

EXAMPLE 14

2.30 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 0.50 g. of triethylamine (0.5 equivalent) in 30 ml. of ethylene glycol to 90° C. to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 1.47 G. of N-n-octyl-D-glucamine are added and the solution is cooled to 40° C. and seeded with crystals of the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine. The reaction mixture is stirred overnight at room temperature to give 1.47 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine (m.p. 115°-122° C.). A sample of the latter is dissolved in about 25 ml. of water heated to about 80° C., treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 65.5^\circ$).

EXAMPLE 15

2.30 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 0.50 g. of triethylamine (0.5 equivalent) in 15 ml. of isopropanol and 0.75 ml. of water to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 1.75 G. of N-n-dodecyl-D-glucamine (0.5 equivalent) are added and the solution is cooled to room temperature to give 2.50 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-dodecyl-D-glucamine (m.p. 133°-135° C.). A sample of the latter is suspended in about 25 ml. of water at room temperature in the presence of 300 mg. of potassium hydroxide and held at that temperature for 60 minutes. The precipitate is removed by filtration. The filtrate is treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 56.1^\circ$).

1.00 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-dodecyl-D-glucamine is dissolved in 20 ml. of 5% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.88 g. of a first recrystallized material (m.p. 135°-137° C.). A sample of the latter is treated with potassium hydroxide then hydrochloric acid as set forth in the preceding paragraph to give a material also enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 58.9^\circ$).

0.62 G. of the first recrystallized material from the preceding paragraph [i.e. the material also enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-dodecyl-D-glucamine] is dissolved in 15 ml. of 5% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.59 g. of a second recrystallized material (m.p. 135°-137° C.).

0.51 G. of the second recrystallized material from the preceding paragraph [i.e., the material further enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-dodecyl-D-glucamine] is dissolved in 10 ml. of 5% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.43 g. of a third recrystallized material (m.p. 135°-137° C.). The latter is treated with potassium hydroxide then hydrochloric acid as set forth in the first paragraph of this Example to give a material yet further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 67.6^\circ$).

EXAMPLE 16

1.15 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 0.25 g. of triethylamine (0.5 equivalent) in 10 ml. of isopropanol to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 1.09 G. of N-n-octadecyl-D-glucamine (0.5 equivalent) are added, and the solution filtered while hot to remove some turbidity, cooled slightly, then seeded with a small amount of the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octadecyl-D-glucamine, and then cooled to room temperature to give 1.55 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octadecyl-D-glucamine (m.p. 123°-127° C.). A sample of the latter is suspended in about 25 ml. of water at room temperature in the presence of 300 mg. of potassium hydroxide and held at that temperature for 60 minutes. The precipitate is removed by filtration. The filtrate is treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 57.9^\circ$).

1.0 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octadecyl-D-glucamine is stirred in 10 ml. of isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature over two hours to give 0.95 g. of a first recrystallized material (m.p. 129°-130° C.). A sample of the latter is treated with potassium hydroxide then hydrochloric acid as set forth in the preceding paragraph to give a material further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 68.1^\circ$).

EXAMPLE 17

100 Mg. of the sodium of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 100 mg. of the hydro-

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chloride salt of N-n-butyl-D-glucamine in 2 ml. of 5% aqueous isopropanol to about the reflux temperature of the solvent. The reaction mixture is slowly cooled, seeded with a small amount of the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-butyl-D-glucamine, and then further cooled to room temperature to give, after recovery by filtration and washing, 1.10 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-butyl-D-glucamine (m.p. 143°-145° C.). A sample of the latter is dissolved in water, and treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 54.9^\circ$).

EXAMPLE 18

The solubilities of the diastereoisomeric salt pairs of d 2-(6-methoxy-2-naphthyl)propionic acid and l 2-(6-methoxy-2-naphthyl)propionic acid with various N-R-D-glucamines in methanol at room temperature and at reflux are given in the following Table:

TABLE I

R	SOLUBILITY IN MeOH (g/100 ml. of solvent)			
	d 2-(6-methoxy-2-naphthyl)propionic acid with N-R-D-glucamine		l 2-(6-methoxy-2-naphthyl)propionic acid with N-R-D-glucamine	
	23° C.	reflux	23° C.	reflux
ethyl	0.83		5.1	
n-propyl	0.31	1.7	6.8	
iso-propyl	2.3	6.4	6.7	95
n-butyl	1.3	9.2	5.0	90
iso-butyl	1.2		10.8	
cyclohexyl	2.1		23.1	
n-octyl	1.8	21.1	21.7	
n-dodecyl	0.32		8.7	

EXAMPLE 19

2.30 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 0.45 g. of triethylamine (0.45 equivalent) in 40 ml. of isopropanol and 1.0 ml. of water to about 80° C. to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 1.46 G. of N-n-hexyl-D-glucamine (0.55 equivalent) is added and the solution is cooled to room temperature to give 2.48 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-hexyl-D-glucamine (m.p. 131°-132° C.). A sample of the latter is suspended in about 25 ml. of water at room temperature, acidified with hydrochloric acid and stirred at that temperature for about 60 minutes. The resultant precipitate, a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid, is recovered by filtration ($[\alpha]_D + 37.2^\circ$).

1.00 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-hexyl-D-glucamine is dissolved in 10 ml. of 5% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.75 g. of a first recrystallized salt (m.p. 130°-131° C.). This material is treated with hydrochloric acid as set forth in the preceding paragraph to give substantially pure d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 66.2^\circ$).

EXAMPLE 20

1.00 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-hexyl-D-glucamine from the first paragraph of Example 19 is

suspended in 10 ml. of water. 0.15 G. of potassium hydroxide are added and the mixture stirred at room temperature for 1.5 hours. The resultant precipitate is collected, washed with 5 ml. of water, and dried to give 0.38 g. of N-n-hexyl-D-glucamine (m.p. 124°-126° C.). D 2-(6-methoxy-2-naphthyl)propionic acid is recovered from the filtrate by treatment with hydrochloric acid as set forth in the first paragraph of Example 19.

EXAMPLE 21

1.00 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-hexyl-D-glucamine from the first paragraph of Example 19 is suspended in 8 ml. of water. 0.15 G. of potassium hydroxide are added and the mixture stirred at room temperature for 45 minutes. The resultant precipitate is collected, washed with 2 ml. of water, and dried under vacuum (with a slight nitrogen bleed) at 45° C. to give 0.47 g. of N-n-hexyl-D-glucamine (m.p. 122°-124° C.). D 2-(6-methoxy-2-naphthyl)propionic acid is recovered from the filtrate by treatment with hydrochloric acid as set in the first paragraph of Example 19.

EXAMPLE 22

2.30 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 1.46 g. of N-n-hexyl-D-glucamine (0.55 equivalent) in 15 ml. of water to about 80° C. 0.17 G. of potassium hydroxide (0.45 equivalent) are added and the pH of the solution adjusted to 8 with potassium carbonate. The solution is seeded with a small amount of the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-hexyl-D-glucamine and cooled to give 1.25 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-hexyl-D-glucamine (m.p. 125°-127° C.).

EXAMPLE 23

4.60 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 0.91 g. of triethylamine (0.45 equivalent) in 60 ml. of isopropanol to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 3.22 G. of N-n-octyl-D-glucamine (0.55 equivalent) are added, the solution is cooled slightly and then seeded with a small amount of the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine to give a precipitate. The reaction mixture is aged at 60° C. for 1.5 hours, then cooled overnight to room temperature to give, after washing with 20 ml. of isopropanol, 4.9 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine (m.p. 138°-139° C.). A sample of the latter is suspended in about 25 ml. of water at room temperature in the presence of 300 mg. of potassium hydroxide and held at that temperature for about 60 minutes. The resultant precipitate is removed by filtration. The filtrate is treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 64.3^\circ$).

EXAMPLE 24

4.60 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is slurried with 25 ml. of water and 0.60 g. of potassium hydroxide (0.45 equivalent) at 70° C. for 10 minutes. 3.22 G. of N-n-octyl-D-glucamine (0.55 equivalent) are added and the solution is cooled slowly to 50° C. A small amount of the salt of d 2-(6-methoxy-2-naph-

thyl)propionic acid with N-n-octyl-D-glucamine is added and the solution cooled overnight, with stirring, to room temperature to give, after recovery by filtration, 4.0 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine (m.p. 138°-140° C.). A sample of the latter is suspended in about 25 ml. of water at room temperature in the presence of 300 mg. of potassium hydroxide and held at that temperature for about 60 minutes. The resultant precipitate is removed by filtration. The filtrate is treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 62.9^\circ$).

EXAMPLE 25

The procedure of Example 24 is repeated using 20 ml. of water to yield 4.05 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine (m.p. 138°-140° C.). The latter is treated with potassium hydroxide then hydrochloric acid as set forth in Example 24 to give a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 65.1^\circ$).

EXAMPLE 26

The procedure of Example 24 is repeated using 15 ml. of water to yield 4.45 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine (m.p. 138°-140° C.). The latter is treated with potassium hydroxide then hydrochloric acid as set forth in Example 24 to give a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ($[\alpha]_D + 63.5^\circ$).

EXAMPLE 27

44.5 G. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine is treated with 6.2 g. of potassium hydroxide in 445 ml. of water. The reaction mixture is stirred at 46° C. for 2 hours, then cooled slowly to 36° C., with stirring, over one additional hour. The reaction mixture is held at room temperature for about 60 hours.

The resultant precipitate is collected by filtration and washed with 150 ml. of water to give 24.6 g. (99% of theory) of N-n-octyl-D-glucamine (m.p. 121°-123° C.).

The filtrate is treated with 12 ml. of concentrated hydrochloric acid to give a fine, thick precipitate. This precipitate is aged, with stirring, with an additional 350 ml. of water, then filtered, washed with water and dried at 45° C. to give 19.4 g. (99% of theory) of d 2-(6-methoxy-2-naphthyl)propionic acid (m.p. 147°-150° C.).

EXAMPLE 28

2.30 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated in 27.3 ml. of isopropanol and 2.7 ml. of water to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 2.93 G. of N-n-octyl-D-glucamine (1.0 equivalent) are added and the solution is cooled to room temperature to give, after washing with 2 ml. of aqueous isopropanol, 2.57 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine (m.p. 138.5°-140° C.). A sample of the latter is suspended in about 25 ml. of water at room temperature in the presence of 300 mg. of potassium hydroxide and held at that temperature for about 60

minutes. The resultant precipitate is removed by filtration. The filtrate is treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ($[\alpha]_D + 61.7^\circ$).

EXAMPLE 29

2.0 Kg of d,l 2-(6-methoxy-2-naphthyl)propionic acid is added to a mixture of 9.08 l. of methanol and 0.92 l. of toluene. This mixture is heated to 55° C. and 2.54 kg of N-n-octyl-D-glucamine is added. The slurry is heated to reflux, at which temperature all solids are in solution. The mixture is cooled to 56° C. and 2.5 g. of the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine is added. After aging at 55°-56° C. for one hour, the slurry is cooled to 25° C. at a rate of 10° C./hour. 3.0 Kg. of a wet cake of the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-n-octyl-D-glucamine is recovered by filtration and washed with 6.0 l. of methanol.

The wet cake from the preceding step is charged to a mixture of 11.0 l. of water and 0.25 l. of hexane and heated to 50° C. 300 G. of potassium hydroxide is added and the mixture is held for one hour at 50° C. The slurry is cooled to 25° C. at a rate of 10° C./hour. The precipitated N-n-octyl-D-glucamine is filtered, washed with 3 l. of water and dried (yield: 1.11 kg.).

The combined filtrate and washes from the preceding step are added to 100 ml. of toluene and 420 ml. of concentrated hydrochloric acid (to a pH of less than 1.0). The slurry is heated to 70° C., aged for one hour and cooled to 25° C. at a rate of 10° C./hour. The precipitated 2-(6-methoxy-2-naphthyl)propionic acid is recovered by filtration and washed with 2.0 l. of water. This material is of sufficient purity that further recrystallizations to increase the optical purity thereof are not necessary.

The d 2-(6-methoxy-2-naphthyl)propionic acid is dissolved in 4.40 l. of acetone and 22.5 g. of carbon are added. The solution is stirred for one hour, then filtered. The filter is washed with 2.0 l. of acetone. The combined filtrate and washes are concentrated under vacuum to a volume of about 1.0 l. and a solution of 60 ml. of concentrated hydrochloric acid in 400 ml. of water is added, followed by a further addition of 5.3 l. of water. The slurry is aged for one hour at 20° C. and the precipitated d 2-(6-methoxy-2-naphthyl)propionic acid recovered by filtration, washed with 5.0 l. of water and dried (yield 838.0 grams; 41.9% w/w based on d,l 2-(6-methoxy-2-naphthyl)propionic acid charged; m.p. 153.5°-156.0° C.; $[\alpha]_D + 66.6^\circ$). This recrystallization is solely for the purposes of removing extraneous insoluble material, if any, and improving the color of the precipitated product.

The filtrates and washes from the preceding step are combined and distilled to a volume of 5.5 l. Distillation is continued, with water being added to maintain the volume at 5.5 l. When all the methanol had distilled off, 1 l. of water is added, followed by the addition of 334 g. of potassium hydroxide. The mixture is cooled to 60° C., seeded with a small amount of N-n-octyl-D-glucamine and cooled to 25° C. The precipitated N-n-octyl-D-glucamine is recovered by filtration, washed with one l. of water, followed by a second wash with 4 l. of water, and then dried (yield: 1.31 kg). Overall N-n-octyl-D-glucamine recovery (i.e., in this step and from the step in the second paragraph of this Example) is 2.42 kg. (95.2%).

431 G. of potassium hydroxide is charged to the combined filtrates and first wash from the preceding step and the mixture is heated to 130° C. The solution is cooled to 50° C. under 30 psi over three hours and 130 ml. of toluene are added, followed by the addition of 1.4 l. of concentrated hydrochloric acid. The slurry is heated to 80° C., aged for one hour at that temperature, and cooled to 25° C. at a rate of 10° C./hour. The precipitated d,l 2-(6-methoxy-2-naphthyl)propionic acid is recovered by filtration, washed with 10 l. of water and dried [yield: 1122 g. (56.1%)].

PREPARATION 11

A mixture of 9.0 g. of D-glucose and 6.0 g. of cyclopropylamine in 200 ml. of methanol is stirred at 35° C. under nitrogen for about 24 hours. An additional 6.0 g. of cyclopropylamine is added to the mixture which is then stirred for an additional 2½ days. The methanol is stripped out and the resultant precipitate is slurried with 50 ml. of ethylacetate. The precipitate is collected and washed with an additional 50 ml. of ethylacetate.

1.0 G. of the latter is dissolved in 25 ml. of methanol and treated for about 18 hours with 2.00 g. of platinum on charcoal and hydrogen (30 psi) at room temperature. The solution is filtered to remove the catalyst, concentrated to a low volume, and stored at -10° C. The methanol is replaced with isopropanol and the solution stored at -10° C. to give 0.2 g. of a material which includes N-cyclopropyl-D-glucamine (m.p. 125°-140° C.).

The latter is dissolved in 5 ml. of isopropanol, heated and filtered to remove insoluble material. The solution is concentrated to about 1-2 ml. and seeded with a very minor amount of the material prepared in the preceding paragraph to give 0.13 g. of a recrystallized material containing N-cyclopropyl-D-glucamine (m.p. 127°-145° C.; nmr spectrum in dimethylsulfoxide relative to tetramethylsilane [ppm(Δ)]: 0.2-0.4 (multiplet, cyclopropyl), 0.75-0.95 (triplet, -CH₃), 1.25-1.6 (multiplet, -CH₂-), 2.0-2.1 (multiplet, cyclopropyl proton α to N atom), 2.35-2.7 (multiplet, methylene protons α to N atom), 3.1-3.6 (multiplet, protons on glucose side chain) and 4.0-4.6 (broad absorption band, 5 OH); [α]_D-15.7° (in water).

PREPARATION 12

1.0 G. of the material prepared according to the first paragraph of Preparation 11 is dissolved in 20 ml. of methanol and treated for about 24 hours with 1 g. of 5% platinum on charcoal and hydrogen (1 atm.). An additional 1.0 g. of 5% platinum on charcoal is added and the reaction continued for about 24 hours more. The solution is filtered to remove the catalyst, and 1.0 g. of d 2-(6-methoxy-2-naphthyl)propionic acid is added to give 0.72 g. of an insoluble salt which is recrystallized from 7 ml. of isopropanol and 1 ml. of water. 0.61 G. of a recrystallized material is collected and washed with 3 ml. of isopropanol to give the N-cyclopropyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid (m.p. 157°-158° C.).

PREPARATION 13

9.0 G. of D-glucose and 6.36 g. of cyclooctylamine in 3 ml. of acetic acid and 200 ml. of methanol is treated for about 24 hours at 30° C. with 1.0 g. of 5% platinum on charcoal and hydrogen (120 psi). The temperature is raised to 50°-60° C. and the reaction continued for 8 additional hours. After standing overnight, the solution

is filtered to remove the catalyst and washed with 100 ml. of methanol. 300 ml. of water and 4 g. of potassium hydroxide is added and the solution concentrated to give a precipitate which is collected and washed with water.

The precipitate is dissolved in 50 ml. of methanol, filtered with charcoal and washed with 50 ml. of methanol. 100 ml. of ethylacetate is added and the solution concentrated to a low volume and cooled to give, after collection and washing with 50 ml. of ethyl acetate, 4.66 g. of N-cyclooctyl-D-glucamine [m.p. 133°-135° C.; [α]_D-18.4° (dimethylsulfoxide)].

EXAMPLE 30

0.16 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated with 0.08 g. of the N-cyclopropyl-D-glucamine from Preparation 11 in 1.6 ml. of 5% aqueous isopropanol to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. The solution is cooled to room temperature to give a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-cyclopropyl-D-glucamine (m.p. 155°-165° C.). A sample of the latter is dissolved in about 25 ml. of water and treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ([α]_D+42.9°).

EXAMPLE 31

2.30 G. of d,l 2-(6-methoxy-2-naphthyl)propionic acid is heated in 31.5 ml. of isopropanol and 3.0 ml. of water to about the reflux temperature of the solvent to dissolve the d,l 2-(6-methoxy-2-naphthyl)propionic acid. 1.46 G. of N-cyclooctyl-D-glucamine is added and the solution is cooled to room temperature to give 1.98 g. of a material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-cyclooctyl-D-glucamine (m.p. 162°-163° C.). A sample of the latter is dissolved in about 25 ml. of aqueous potassium hydroxide and treated with hydrochloric acid until acidic at which time a material enriched in d 2-(6-methoxy-2-naphthyl)propionic acid precipitates out of solution and is recovered by filtration ([α]_D+32.5°).

1.86 G. of the material enriched in the salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-cyclooctyl-D-glucamine is dissolved in 40 ml. of 10% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 1.19 g. of a first recrystallized material (m.p. 165°-168° C.). A sample of the latter is treated with hydrochloric acid as set forth in the preceding paragraph to give a material further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ([α]_D+47.0°).

1.11 G. of the first recrystallized material from the preceding paragraph is dissolved in 25 ml. of 10% aqueous isopropanol at about the reflux temperature of the solvent. The solution is cooled to room temperature to give 0.89 g. of a second recrystallized material (m.p. 167°-169° C.). A sample of the latter is treated with hydrochloric acid as set forth in the first paragraph of this Example to give a material even further enriched in d 2-(6-methoxy-2-naphthyl)propionic acid ([α]_D+53.2°).

EXAMPLE 32

The anti-inflammatory activity of each of the compounds listed below is compared with the activity of

phenylbutazone by means of the carrageenin-induced rat paw inflammation test described below.

TEST FOR ANTI-INFLAMMATORY ACTIVITY UTILIZING CARRAGEENIN-INDUCED PAW INFLAMMATION IN THE RAT

Materials and Methods—Female rats weighing 80–90 grams are used. The test materials are given at hour 0 orally by gavage in 1 ml. aqueous vehicle. At hour 1, 0.05 ml. of a 1% solution (in 0.9% NaCl) of carrageenin is injected into the right hind paw. This injection causes an inflammation of the paw. The rats are sacrificed at hour 4, at which time both hind paws are removed and weighed separately.

End point: % increase in paw size calculated as follows:

$$\frac{\text{Wt. of Right Paw} - \text{Wt. of Left Paw}}{\text{Wt. of Left Paw}} \times 100$$

The results of these tests are summarized in the following table:

Compound	Oral Anti-Inflammatory Activity (on a molar equivalent basis) (Phenylbutazone = 1)
The N-ethyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid	17
The N-n-propyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid	20
The N-n-butyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid	5
The N-n-octyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid	17
The N-n-octadecyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid	7
The N-cyclohexyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid	11

EXAMPLE 33

The carrageenin-induced rat paw inflammation test described in Example 32 above is repeated using the N-cyclopropyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid and the N-cyclooctyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid as the test materials. The results of this test are summarized in the following table:

Compound	Oral Anti-Inflammatory Activity (on a molar equivalent basis) (Phenylbutazone = 1)
N-cyclopropyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid	9
N-cyclooctyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid	20

EXAMPLE 34

Protocol: The test material is suspended in an aqueous carboxymethyl cellulose suspending vehicle. Concentrations are adjusted so that doses can be given in volumes of 20 ml./kg. of body weight. Four groups

(comprising six Swiss-Webster male mice in each group) of mice are used. A single oral dose, by stomach tube, per kilogram of body weight, of either 750 mg., 1500 mg., or 3000 mg. of N-cyclohexyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid is administered to the mice. (The fourth group is used as a control.) After administration the mice are observed daily for 21 days.

Using the above protocol, it is determined that the acute oral LD₅₀ of the N-cyclohexyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid is greater than 3000 mg./kg.

EXAMPLE 35

The protocol described in Example 34 is repeated using the N-n-octyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid as the test material. It is determined that the acute oral LD₅₀ of the above material is greater than 3000 mg./kg.

EXAMPLE 36

Ingredients	Quantity per tablet, mgs.
N-n-octyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid	100
cornstarch (paste)	20
magnesium stearate	0.5
lactose	to 300

The above ingredients are thoroughly mixed and pressed into single scored tablets.

EXAMPLE 27

Ingredients	Quantity per tablet, mgs.
N-n-octyl-D-glucamine salt of d 2-(6-methoxy-2-naphthyl)propionic acid	125
cornstarch	30
magnesium stearate	0.5
polyvinylpyrrolidone	25
lactose	to 350

The above ingredients are thoroughly mixed and pressed into single scored tablets.

What is claimed is:

1. A diastereomeric mixture of the salts of d and l 2-(6-methoxy-2-naphthyl)propionic acid with N-R-D-glucamine, wherein R is cycloalkyl having 3 to 8 carbon atoms.

2. A pharmaceutical composition for the treatment of inflammation, pain or pyrexia comprising a pharmaceutically acceptable excipient and a pharmaceutically effective amount of a salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-R-D-glucamine where R is cycloalkyl having 3 to 8 carbon atoms.

3. A method of treating inflammation, pain or pyrexia in mammals which comprises administering to a mammal suffering therefrom a therapeutically effective amount of a salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-R-D-glucamine, where R is cycloalkyl having 3 to 8 carbon atoms.

4. A method of maintaining the pregnancy of a pregnant mammal comprising administering to a pregnant mammal a therapeutically effective amount of a salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-R-D-

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glucamine, where R is cycloalkyl having 3 to 8 carbon atoms.

5. A salt of d 2-(6-methoxy-2-naphthyl)propionic acid with N-R-D glucamine where R is cycloalkyl having 3 to 8 carbon atoms.

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6. The mixture of claim 1 wherein R is cyclohexyl.
 7. The composition of claim 2 wherein R is cyclohexyl.
 8. The method of claim 3 wherein R is cyclohexyl.
 9. The salt of claim 5 wherein R is cyclohexyl.
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PATENT SPECIFICATION (11)

1 426 186

1 426 186

- (21) Application No. 30268/73 (22) Filed 26 June 1973 (19)
 (31) Convention Application No. 279 329 (32) Filed 10 Aug. 1972 in
 (33) United States of America (US)
 (44) Complete Specification published 25 Feb. 1976
 (51) INT. CL.² C07C 65/14
 (52) Index at acceptance
 C2C 1233 222 227 22X 22Y 292 29X 29Y 302 30Y 321
 32Y 364 366 367 36Y 618 620 624 628 658 660
 662 790 79Y BU NK



(54) PROCESS FOR THE RESOLUTION OF D,L 2-(6-METHOXY-2-NAPHTHYL)-
 PROPIONIC ACID

ERRATA

SPECIFICATION NO 1426186

Page 1, Heading (54) *delete D, L insert d, l*

Page 1, line 42, *delete provided insert providing*

Page 2, line 92, *for dehydroabientylamine read dehydroabietylamine*

Page 3, line 109, *for dehydrobietyl- read dehydroabietyl-*

THE PATENT OFFICE
 23 June 1976

Bas 28320/13

- 20 have been resolved with an organic amine or an inorganic base, via procedures requiring multiple crystallizations in a lower alcohol, such as methanol.
- 25 It is the object of this invention to provide a process for resolving mixtures of d- and l- 2-(6-methoxy-2-naphthyl)propionic acid to yield a composition containing substantially pure d-isomer, which has anti-inflammatory, antipyretic and analgesic activities, such process requiring a single crystallization to remove the salt of the l-isomer produced and a single crystallization to obtain a salt of the d-isomer, which can then be followed by cleaving of the salt moiety with an inorganic acid, whereupon the d-isomer precipitates in its substantially pure form.
- 30 A process for separating d- 2-(6-methoxy-2-naphthyl)propionic acid from a mixture of d- and l- 2-(6-methoxy-2-naphthyl)propionic acid comprises provided a heated two-phase system having water as an aqueous phase and a water-immiscible, inert non-polar organic solvent as an organic phase, a salt of d- 2-(6-methoxy-2-naphthyl)propionic acid and a salt of l- 2-(6-methoxy-2-naphthyl)propionic acid being in said two-phase
- naphthyl)propionic acid and crystallizing the least water-soluble salt of d- 2-(6-methoxy-2-naphthyl)propionic acid from said aqueous phase, and optionally dissolving said crystalline salt of d- 2-(6-methoxy-2-naphthyl)propionic acid in a solvent, acidifying said solution with a mineral acid to yield d- 2-(6-methoxy-2-naphthyl)propionic acid, and crystallizing substantially pure d- 2-(6-methoxy-2-naphthyl)propionic acid therefrom. If desired, this procedure can be followed by one or more additional recrystallizations to further increase the purity of the d-isomer.
- 70 The 2-(6-methoxy-2-naphthyl)propionic acid and methods for its preparation are described in British Patents Nos. 1,211,134 and 1,228,656, as briefly described hereinafter. One such method involves the reaction of a 1-halo-2-methoxy-naphthalene with acetyl chloride in nitrobenzene in the presence of 3 molar equivalents of aluminium chloride to yield the corresponding 2-acetyl-5-halo-6-methoxynaphthalene derivative. The resulting derivative is heated with morpholine in the presence of sulfur at 150°C, and the resulting product is refluxed with concentrated hydrochloric acid to furnish the cor-
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PATENT SPECIFICATION (11)

1 426 186

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- (21) Application No. 30268/73 (22) Filed 26 June 1973 (19)
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C2C 1233 222 227 22X 22Y 292 29X 29Y 302 30Y 321
 32Y 364 366 367 36Y 618 620 624 628 658 660
 662 790 79Y BU NK



(54) PROCESS FOR THE RESOLUTION OF D,L 2-(6-METHOXY-2-NAPHTHYL)-PROPIONIC ACID

(71) We, SYNTAX CORPORATION, a Panamanian Corporation, of Apartado Postal 7386, Panama, Panama, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a method for resolving mixtures of d- and l- 2-(6-methoxy-2-naphthyl)propionic acid to yield a composition containing substantially pure d-isomer.

Prior to this invention, it was heretofore known to use dehydroabietylamine as an agent to resolve monocarboxylic acids (for example, see United States Patent No. 3,454,626). In addition, mixtures of d- and l- 2-(6-methoxy-2-naphthyl)propionic acid have been resolved with cinchonidine, either alone or in combination with an organic amine or an inorganic base, via procedures requiring multiple crystallizations in a lower alcohol, such as methanol.

It is the object of this invention to provide a process for resolving mixtures of d- and l- 2-(6-methoxy-2-naphthyl)propionic acid to yield a composition containing substantially pure d-isomer, which has anti-inflammatory, antipyretic and analgesic activities, such process requiring a single crystallization to remove the salt of the l-isomer produced and a single crystallization to obtain a salt of the d-isomer, which can then be followed by cleaving of the salt moiety with an inorganic acid, whereupon the d-isomer precipitates in its substantially pure form.

A process for separating d- 2-(6-methoxy-2-naphthyl)propionic acid from a mixture of d- and l- 2-(6-methoxy-2-naphthyl)propionic acid comprises provided a heated two-phase system having water as an aqueous phase and a water-immiscible, inert non-polar organic solvent as an organic phase, a salt of d- 2-(6-methoxy-2-naphthyl)propionic acid and a salt of l- 2-(6-methoxy-2-naphthyl)propionic acid being in said two-phase

system, and a salt of dehydroabietylamine which is soluble in said organic phase but is essentially insoluble in said aqueous phase; holding said two-phase system at a temperature from 40—100°C to promote the formation of the dehydroabietylamine salt of l- 2-(6-methoxy-2-naphthyl)propionic acid; crystallizing said dehydroabietylamine salt of l- 2-(6-methoxy-2-naphthyl)propionic acid; separating said crystallised salt from said two-phase system to thereby provide a mother liquor which is enriched in the water soluble salt of d- 2-(6-methoxy-2-naphthyl)propionic acid; separating said aqueous phase from said organic phase; and salting out a salt of d- 2-(6-methoxy-2-naphthyl)propionic acid by adding to said aqueous phase an inorganic salt which is more soluble in said aqueous phase than is said water-soluble salt of d- 2-(6-methoxy-2-naphthyl)propionic acid and crystallizing the least water-soluble salt of d- 2-(6-methoxy-2-naphthyl)propionic acid from said aqueous phase, and optionally dissolving said crystalline salt of d- 2-(6-methoxy-2-naphthyl)propionic acid in a solvent, acidifying said solution with a mineral acid to yield d- 2-(6-methoxy-2-naphthyl)propionic acid, and crystallizing substantially pure d- 2-(6-methoxy-2-naphthyl)propionic acid therefrom. If desired, this procedure can be followed by one or more additional recrystallizations to further increase the purity of the d-isomer.

The 2-(6-methoxy-2-naphthyl)propionic acid and methods for its preparation are described in British Patents Nos. 1,211,134 and 1,228,656, as briefly described hereinafter. One such method involves the reaction of a 1-halo-2-methoxy-naphthalene with acetyl chloride in nitrobenzene in the presence of 3 molar equivalents of aluminium chloride to yield the corresponding 2-acetyl-5-halo-6-methoxynaphthalene derivative. The resulting derivative is heated with morpholine in the presence of sulfur at 150°C, and the resulting product is refluxed with concentrated hydrochloric acid to furnish the cor-

SEE ERRATA SLIP ATTACHED

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responding 2-naphthylacetic acid derivative. The latter compound is then esterified such as by reacting it with an alkanol in the presence of boron trifluoride, and the ester is treated with an alkali metal hydride in an ether solvent and then with an alkyl halide such as methyl iodide to yield the corresponding 2-(6-methoxy-2-naphthyl)-propionate. The latter is hydrolyzed, for example in an aqueous basic solution, to yield the corresponding 2-(6-methoxy-2-naphthyl)propionic acid. Other procedures for the preparation of 2-(6-methoxy-2-naphthyl)propionic acid are shown, for example, by U.S. Patents Nos. 3,651,106; 3,652,633; 3,658,858; 3,658,863; and 3,663,584.

Considering a typical process of the invention in more detail, resolution by crystallization (i.e., removal of a major proportion of the l-isomer by crystallization) is achieved by mixing d- and l- 2-(6-methoxy-2-naphthyl)propionic acid in sufficient water to at least partially solubilize the components. The mixture of the d- and l- isomer will generally be a racemic mixture, although this is not required. Thus, mixtures resulting from prior treatments, where the ratio of d- and l- isomers has been altered from a racemic mix, may be used, if desired. The addition of base, for example, sodium hydroxide, yields a solution of the sodium salts of the d- and l- isomers. Other bases include the hydroxides of the alkali metals and alkaline earth metals, such as, for example, potassium, calcium, and magnesium. A water-immiscible, inert organic solvent, such as toluene, benzene, xylene, or other non-polar solvent, is added and the solution is heated to a temperature in the range from about 40°C to about 100°C., preferably from about 75°C. to about 85°C. While the solution is held at the elevated temperature, a solution of a salt of dehydroabietylamine is added dropwise with vigorous stirring while the elevated temperature is maintained. The reaction mixture is maintained at the elevated temperature for about ½ to about 4 hours, generally for about 1 to about 2 hours, to promote the interchange of the salt of dehydroabietylamine from the d-isomer to the l-isomer. That is, as the salt of the dehydroabietylamine is added to the solution of the salts of the d- and l- isomers, it will react to form a dehydroabietylamine salt of the isomers, desirably the l-isomer. To the extent that a dehydroabietylamine salt of a d-isomer is formed, however, a corresponding molecule of the l-isomer will not have been bound, as desired, to the dehydroabietylamine salt. By holding the reaction mixture at an elevated temperature, the selective solubilization of the dehydroabietylamine salt of the d-isomer in the aqueous phase is enhanced with the corresponding liberation of the salt of de-

hydroabietylamine. Upon liberation, the dehydroabietylamine salt is free to react with an l-isomer as is desired. Suitable salts of dehydroabietylamine include the acetate salt and the hydrochloride salt. Other typical salts include the propionate salt, butyrate salt, sulfate salt, nitrate salt, and the like. The salt selected should be soluble in the water-immiscible, inert organic solvent selected, but should be insoluble or only slightly soluble in water. This not only enables recovery of these materials in subsequent processing, but insures that the dehydroabietylamine salt will be in the appropriate phase for bonding to the l-isomer. Since it is desired that the salt of dehydroabietylamine be preferentially bound to the l-isomer during this first crystallization, it is necessary to limit the amount of the dehydroabietylamine salt added to the solution so as to achieve that objective. Generally about 1.0 to about 1.3 mole, preferably about 1.2 mole, of the salt of dehydroabietylamine is utilized per mole of the l-isomer. Accordingly, for a racemic mixture of d and l isomers, about 0.6 mole of the salt of dehydroabietylamine will be used per mole of the racemic mixture.

After the reaction mixture is held at the elevated temperature for the desired length of time, it is slowly cooled to ambient temperature. The white crystalline precipitate which results is principally the dehydroabietylamine salt of l- 2-(6-methoxy-2-naphthyl)propionic acid. The final temperature to which the solution is taken is chosen by practical considerations, but generally is selected so the temperature difference will be sufficient to provide a high yield of crystals. The crystallizing mixture can be maintained at the lower temperatures until crystallization is complete, or nearly so, usually for about 30 to about 60 minutes. The crystalline precipitate which results is removed by filtration, washed with water, and the washings combined with the original filtrate to provide a mother liquor enriched in the d-isomer. At this point the mother liquor will generally contain about 70—80% d-isomer and about 30—20% l-isomer.

The l-isomer which has been removed from the two-phase system can be racemized by known techniques to give a material having greater d-isomer content. This material can be recycled, either alone or in combination with other d,l-isomer containing material, to provide additional starting material for the process of the present invention.

The aqueous phase of the mother liquor is treated with a basic material, such as sodium hydroxide, to cleave any residual dehydroabietylamine salts which may be present. The organic phase, containing residual dehydroabietylamine, is separated from the aqueous layer. The aqueous phase remain-

ing is washed with portions of the water-immiscible, inert organic solvent and the washings combined with the original solvent material. If desired, the combined organic phase can be discarded; however, since this phase contains residual dehydroabietylamine, it is preferable to regenerate such materials in suitable form for use in further resolution procedures.

The aqueous layer, is now saturated with an inorganic salt. The salt selected must be more water soluble than the salt of the d-isomer present in the aqueous layer. Additionally, it should not be excessively soluble so as to require the use of relatively large quantities in saturating the solution. Preferably, the salt should have a reasonably flat solubility curve between the temperature limits to be encountered (i.e., about 10°C. and 40°C.) so, as the solution thereof is cooled, undue, and undesirable precipitation of the inorganic salt will not occur. The presently preferred salt is sodium chloride. Other salts includes the halides, nitrates and sulfates, for example, calcium chloride, potassium chloride, lithium chloride and magnesium chloride.

The solution is heated to a temperature somewhat above room temperature, for example, to a temperature in the range from about 25°C to about 40°C, for example 35°C, at which point it should be ensured that the solution is saturated with the inorganic salt previously added. Excessively high temperatures should be avoided to ensure that the inorganic salt does not also crystallize during the subsequent cooling step. The solution is then gradually cooled until a temperature somewhat above room temperature, for example about 30°C, is reached, whereupon a seed crystal of the pure salt of the d-isomer is desirably added. Since the addition of the more water soluble inorganic salt reduces the solubility of the less soluble material (i.e., the salt of the d-isomer), further cooling will cause the d-isomer to preferentially crystallize from the aqueous mother liquor. Accordingly, gradual cooling is continued to a temperature in the range of about 10°C to about 15°C. Once again, the crystallizing mixture is maintained at the lower temperature until crystallization is complete, or nearly so, usually for about 15 to about 60 minutes. The crystalline solid obtained, essentially the sodium salt of d 2-(6-methoxy-2-naphthyl)propionic acid is separated by filtration and redissolved in water. The resulting solution is acidified with a mineral acid, such as hydrochloric acid, and the crystalline precipitate so obtained separated by filtration, washed with water and dried. There results a white crystalline product comprising substantially pure d 2-(6-methoxy-2-naphthyl)propionic acid.

As will be seen from the Examples below, this procedure, as described above and without further recrystallization of the d-isomer, yields a product having a purity of about 98-99%. If desired, this purity may be further increased by one or more additional recrystallizations from water solutions thereof, or other solvents as found suitable. Nonetheless, the process of this invention, including, in combination, the use of a resolving agent, such as the salt of dehydroabietylamine, which yields a less soluble salt of the undesired l-isomer, to enrich the concentration of the d-isomer in the mother liquor and the use of an inorganic salt to cause the preferential crystallization of the d-isomer from the mother liquor, yields a product of high purity without the need for tedious, time-consuming steps or numerous multiple recrystallations to obtain the level of purity obtained, in the first instance, by this process.

The following specific description is given to enable those skilled in this art to more clearly understand and practice the present invention. It should not be considered as a limitation upon the scope of the invention but merely as being illustrative and representative thereof.

EXAMPLE I

100 milliliters of water and 23 grams (0.1 mole) of racemic 2-(6-methoxy-2-naphthyl)propionic acid are added to a one-liter flask. The mixture is agitated and neutralized to a pH of 9.5 by the addition of a 50% (weight/weight) aqueous solution of sodium hydroxide, to give a solution of the sodium salt of d, l 2-(6-methoxy-2-naphthyl)propionic acid. After 200 grams of toluene are added to the solution, the reaction mixture is heated to 80°C. and an aqueous solution of 21.1 grams (0.06 mole) of dehydroabietylamine acetate in 100 ml. of water is added with vigorous stirring during a 30 minute period while the temperature of 80°C. is maintained. After the addition of the dehydroabietylamine acetate is completed, the reaction mixture is held at 80°C for one hour and then cooled to ambient temperature over a period of 2 hours. The crystalline precipitate consisting of the dehydroabietylamine salt of the l 2-(6-methoxy-2-naphthyl)propionic acid is removed by filtration and washed with 25 milliliters of water. The washings are combined with the original filtrate and transferred to a 1-liter separatory funnel. The aqueous phase is adjusted to a pH of 10 with dilute sodium hydroxide solution. The aqueous phase is separated from the upper toluene layer, and washed twice with 50 milliliter portions of toluene which are combined with the original toluene layer. 15 grams of sodium chloride are

added to the aqueous layer which is then warmed to 35°C. The aqueous layer is cooled slowly over a 2 hour period. When the temperature reaches 30°C the aqueous layer is seeded with a pure crystal of the sodium salt of d-2-(6-methoxy-2-naphthyl)propionic acid, after which cooling is continued with agitation to a temperature of 13°C. The solution is stirred at this temperature for 15 minutes. The crystalline solid which results is removed by filtration and redissolved in 200 milliliters of water. The resulting solution is acidified with hydrochloric acid to a pH of 2. The white crystalline precipitate which results is separated by filtration, washed with water at 0°C, until the washings are essentially neutral, and dried *in vacuo* at 50°C. for 2 hours to yield 4 grams of d-2-(6-methoxy-2-naphthyl)propionic acid [m.pt. 154°-155°C; $[\alpha]_D^{25} = 64.6$ (1% in chloroform)]. This optical rotation represents a purity of about 98.9%.

EXAMPLE II

The procedure of Example I is repeated, except 19.3 grams (0.06 mole) of dehydroabietylamine hydrochloride are substituted for the 21.1 grams of dehydroabietylamine acetate utilized in Example I. d-2-(6-Methoxy-2-naphthyl)propionic acid in the same yield and of the same quality is obtained.

In the presently preferred embodiment, the inorganic salt utilized to saturate the aqueous phase, after separation of the dehydroabietylamine salt of the 1-isomer from the two-phase system, has the same cation as the cation of the alkali metal or alkaline earth metal salt of the d-isomer in the aqueous phase. The use of the common ion decreases the solubility of the salt of the d-isomer whereby, as the solution is cooled, and optionally seeded with a pure crystal of the salt of the d-isomer being crystallized, the salt of the d-isomer, which is more abundant in the solution than the corresponding salt of the 1-isomer, will preferentially crystallize from the solution thereby yielding d-isomer crystals of high purity. However, it is contemplated that a salt not having such a common cation may be used in the process of the present invention, whereby the crystallization which occurs will be a result of a difference in the solubilities of the various salts in solution.

WHAT WE CLAIM IS:—

1. A process for separating d-2-(6-methoxy-2-naphthyl) propionic acid from a mixture of d- and 1-2-(6-methoxy-2-naphthyl) propionic acid comprising providing a heated two-phase system having water as an

aqueous phase and a water-immiscible, inert non-polar organic solvent as an organic phase, a salt of d-2-(6-methoxy-2-naphthyl) propionic acid and a salt of 1-2-(6-methoxy-2-naphthyl) propionic acid being in said two-phase system, and a salt of dehydroabietylamine which is soluble in said organic phase but is essentially insoluble in said aqueous phase; holding said two-phase system at a temperature from 40—100°C to promote the formation of the dehydroabietylamine salt of 1-2-(6-methoxy-2-naphthyl)-propionic acid; crystallizing said dehydroabietylamine salt of 1-2-(6-methoxy-2-naphthyl) propionic acid; separating said crystallized salt from said two-phase system to thereby provide a mother liquor which is enriched in the water soluble salt of d-2-(6-methoxy-2-naphthyl) propionic acid; separating said aqueous phase from said organic phase; and salting out a salt of d-2-(6-methoxy-2-naphthyl) propionic acid by adding to said aqueous phase an inorganic salt which is more soluble in said aqueous phase than is said water-soluble salt of d-2-(6-methoxy-2-naphthyl) propionic acid and crystallizing the least water-soluble salt of d-2-(6-methoxy-2-naphthyl) propionic acid from said aqueous phase, and optionally dissolving said crystalline salt of d-2-(6-methoxy-2-naphthyl) propionic acid in a solvent, acidifying said solution with a mineral acid to yield d-2-(6-methoxy-2-naphthyl) propionic acid, and crystallizing substantially pure d-2-(6-methoxy-2-naphthyl) propionic acid therefrom.

2. The process of Claim 1 wherein said water-immiscible, inert, non-polar solvent is selected from benzene, toluene and xylene.

3. The process of Claim 1 wherein the two-phase system is kept at a temperature from about 75°C to about 85°C.

4. The process of Claim 1 wherein said salt of dehydroabietylamine is selected from dehydroabietylamine acetate and dehydroabietylamine hydrochloride.

5. The process of Claim 1 wherein about 1.0 to about 1.3 mole of said salt of dehydroabietylamine is added per mole of 1-2-(6-methoxy-2-naphthyl) propionic acid in said mixture.

6. The process of Claim 1 wherein said inorganic salt is selected from halides, nitrates, and sulfates of the alkali metals and alkaline earth metals.

7. The process of Claim 1 wherein said inorganic salt has a relatively flat solubility curve between about 10°C and about 40°C.

8. The process of Claim 1 wherein said inorganic salt is sodium chloride.

9. The process according to claim 1, as described herein.

10. d-2-(6-Methoxy-2-naphthyl)propionic acid or a salt thereof, whenever prepared by

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a process according to any one of the preceding claims.

- 5 11. A pharmaceutical composition comprising a compound of claim 10 with a suitable excipient.

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PATENT SPECIFICATION

(11) 1422015

- 1422015 (21) Application No. 18815/73 (22) Filed 18 April 1973
 (31) Convention Application No. 246461 (32) Filed 21 April 1972
 (31) Convention Application No. 350193 (32) Filed 11 April 1973 in
 (33) United States of America (US)
 (44) Complete Specification published 21 Jan. 1976
 (51) INT CL⁸ C07C 65/14 A61K 31/19
 (52) Index at acceptance
 C2C 222 227 22Y 302 30Y 364 366 367 36Y 624 628 658
 662 790 79Y BU



(54) RESOLUTION OF 2-(6-METHOXY-2-NAPHTHYL)-PROPIONIC ACID

- (71) We, SYNTEX CORPORATION, a Panamanian Corporation of Apartado Postal 7386, Panama, Panama, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—
- This invention relates to an improved method for resolving mixtures of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid to yield mixtures containing a higher proportion of the d-isomer.
- Prior to this invention, 2 - (6 - methoxy - 2 - naphthyl)propionic acid had been resolved with cinchonidine by a procedure requiring multiple crystallizations in a lower alcohol such as methanol. Because of the time and expense required for this tedious procedure, process improvements in both quality and quantity were desired. It is the object of this invention to provide an improved process for resolving mixtures of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid to yield mixtures containing higher proportion of the d-isomer, which process in a single crystallization step provides improved quality
- of the salts of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid and said inorganic base being more soluble than the cinchonidine salts of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid; and
- (b) crystallizing the cinchonidine salts of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid from the mixture to yield a salt mixture enriched in the salt of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid.
- This procedure can be followed by one or more recrystallizations to increase the purity of the d - isomer. Finally, the salt is cleaved to yield the d 2 - (6 - methoxy - 2 - naphthyl)propionic acid.
- The 2 - (6 - methoxy - 2 - naphthyl)propionic acid and methods for its preparation are described, for example, in U.S. Patents Nos. 3,651,106; 3,652,683; 3,658,858; 3,658,863; 3,663,584; and 3,686,238. One such method involves the reaction of a 1 - halo - 2 - methoxynaphthalene with acetyl chloride in nitrobenzene in the presence of 3 molar equivalents of aluminum chloride to yield the corresponding 2 - acetyl - 5 - halo - 6 - methoxynaphthalene derivative. The resulting derivative is heated with morpholine in the presence of sulfur at 150°C. and the resulting

ERRATA

SPECIFICATION No. 1,422,015

- Page 1, line 35, for mixtures read mixture
 Page 1, line 84, after 2- (second occurrence) insert naphthyl)
 Page 2, line 49, for cinchoidine read cinchonidine
 Page 2, line 50, delete acid insert base
 Page 2, lines 53 and 55, for quantity read quantity
 Page 3, line 36, for therof read thereof
 Page 3, line 49, for washetd read washed
 Page 3, line 74, after methoxy delete 1 insert -
 Page 4, line 54, for crystalizing read crystallizing

THE PATENT OFFICE
 21st June, 1976

SEE ERRATA SLIP ATTACHED

PATENT SPECIFICATION

(11) 1422015

1422015

- (21) Application No. 18815/73 (22) Filed 18 April 1973
 (31) Convention Application No. 246461 (32) Filed 21 April 1972
 (31) Convention Application No. 350193 (32) Filed 11 April 1973 in
 (33) United States of America (US)
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C2C 222 227 22Y 302 30Y 364 366 367 36Y 624 628 658
 662 790 79Y BU



(54) RESOLUTION OF 2-(6-METHOXY-2-NAPHTHYL)- PROPIONIC ACID

- (71) We, SYNTEX CORPORATION, a Panamanian Corporation of Apartado Postal 7386, Panama, Panama, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—
- This invention relates to an improved method for resolving mixtures of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid to yield mixtures containing a higher proportion of the d-isomer.
- Prior to this invention, 2 - (6 - methoxy - 2 - naphthyl)propionic acid had been resolved with cinchonidine by a procedure requiring multiple crystallizations in a lower alcohol such as methanol. Because of the time and expense required for this tedious procedure, process improvements in both quality and quantity were desired. It is the object of this invention to provide an improved process for resolving mixtures of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid to yield mixtures containing higher proportion of the d-isomer, which process in a single crystallization step provides improved quality (greater enrichment) and improved throughput.
- In summary, the process of this invention for resolving mixtures of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid comprises the steps of:
- (a) preparing a mixture of cinchonidine, a mixtures of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid, an inert organic solvent in which the cinchonidine salt of 1 2 - (6 - methoxy - 2 - naphthyl) - propionic acid and inorganic base salts of d and l 2 - (6 - methoxy - 2 - naphthyl) - propionic acid are soluble, and in which the cinchonidine salt of 1 2 - (6 - methoxy - 2 - naphthyl)propionic acid is more soluble than the cinchonidine salt of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid, and an inorganic base having a basicity, pK_a, greater than 8, the solubility in the inert organic solvent
- of the salts of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid and said inorganic base being more soluble than the cinchonidine salts of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid; and
- (b) crystallizing the cinchonidine salts of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid from the mixture to yield a salt mixture enriched in the salt of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid.
- This procedure can be followed by one or more recrystallizations to increase the purity of the d - isomer. Finally, the salt is cleaved to yield the d 2 - (6 - methoxy - 2 - naphthyl)propionic acid.
- The 2 - (6 - methoxy - 2 - naphthyl)propionic acid and methods for its preparation are described, for example, in U.S. Patents Nos. 3,651,106; 3,652,683; 3,658,858; 3,658,863; 3,663,584; and 3,686,238. One such method involves the reaction of a 1 - halo - 2 - methoxynaphthalene with acetyl chloride in nitrobenzene in the presence of 3 molar equivalents of aluminum chloride to yield the corresponding 2 - acetyl - 5 - halo - 6 - methoxynaphthalene derivative. The resulting derivative is heated with morpholine in the presence of sulfur at 150°C, and the resulting product is refluxed with concentrated hydrochloric acid to furnish the corresponding 2 - naphthylacetic acid derivative. The latter compound is then esterified such as by reacting it with an alkanol in the presence of boron trifluoride, and the ester is treated with an alkali metal hydride in an ether solvent and then with an alkyl halide such as methyl iodide to yield the corresponding 2 - (6 - methoxy - 2 - propionate. The latter is hydrolyzed, for example, in an aqueous basic solution, to yield a mixture of the d- and l - isomers of 2 - (6 - methoxy - 2 - naphthyl)propionic acid.
- The inorganic base used in the process of this invention has a basicity of pK_a greater than 8. The solubility in the inert organic solvent of the salts of the inorganic base and d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid must be greater than the solu-

SEE ERRATA SLIP ATTACHED

bility of the cinchonidine salts of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid. Suitable inorganic bases include alkali metal hydroxides and carbonates such as potassium, sodium and lithium hydroxides and carbonates, alkaline earth metal hydroxides such as calcium and magnesium hydroxides, and ammonia. The particular choice of inorganic base will depend upon the particular inert organic solvent system used for the crystallization. The selection of the best inorganic base in the process can be routinely determined by applying the above criterion. In methanol solvents, potassium hydroxide is the presently preferred inorganic base.

The inert organic solvent system for the process of this invention can use any inert organic solvent in which the cinchonidine salt of l 2 - (6 - methoxy - 2 - naphthyl)propionic acid and inorganic base salts of 2 - (6 - methoxy - 2 - naphthyl)propionic acid are soluble. Examples of such solvents include acetone, acetylacetone, adiponitrile, benzonitrile, benzylalcohol, benzyl mercaptan, butyl alcohol, capryl alcohol, diacetone alcohol, mono- and di(lower)alkyl ethers of ethylene glycol and diethylene glycol, ethanol, methanol, n - propanol, i - propanol, ethylene glycol, 1,2 - propylene glycol, 1,3 - propylene glycol, 2 - ethylhexanol, dimethylsulfoxide, sulfolanes, dimethylformamide, N - methylpyrrolidinone, formamide, furfuryl alcohol, glycerol, isoamyl alcohol, isoamyl sulfide, isobutyl mercaptan, dibutoxytetraethylene glycol, pyridine, trimethylene glycol, dioxane and dimethylacetamide. The presently preferred solvents are polar and are not acidic or strongly basic.

The mixture should preferably contain about equal molar amounts of the 2 - (6 - methoxy - 2 - naphthyl)propionic acid and bases, including both cinchonidine and the inorganic base. The molar ratio of cinchonidine to inorganic base is not critical for resolution to occur. Cinchonidine to inorganic base molar ratios of 2:3—3:2 are operable, for example. For optimum quality and quantity yields of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid, the molar ratio of cinchonidine and inorganic acid should be about 1:1. At lower cinchonidine to inorganic base molar ratios, the quality of the product is not impaired but the quantity or yield rapidly decreases. With higher cinchonidine to inorganic base molar ratios, the quantity or yield is satisfactory, but the quality is impaired.

In general, resolution by crystallization is achieved by mixing the d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acids, cinchonidine, inorganic base and sufficient solvent to solubilize the components, yielding a suspension of predominately cinchonidine salt of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid in nearly saturated solution of the other components, cooling the mixture, and

separating the crystallized salts. Continued cooling causes continued further crystallization of the dissolved salts. Preferably, the solution is seeded with small quantities of the cinchonidine salt of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid during the cooling since this insures good resolution and high yields of the desired d acid salt. The initial and final temperatures of the solvent are chosen primarily by practical considerations as long as the temperature will not significantly degrade the other components. For example, the mixture can have an initial temperature of from 50° to 100°C and can be cooled to a final temperature lower than the initial temperature, e.g. less than 40°C, preferably about 35°C, the temperature difference being sufficient to provide a high yield of crystals. The crystallizing mixture is maintained at the lower temperatures until crystallization is complete or nearly so, usually for longer than 15 minutes and preferably over 0.5 hours. The crystals are separated from the resultant mixture, for example, by filtration.

The quality or percentage of the d-isomer in the product can be increased, if desired, by recrystallization of the above-obtained crystals using the same solvents used in the initial crystallization or with different solvents as found desirable, the recrystallization being generally carried out as described above.

The combined mother liquors from each of the crystallization steps can be reprocessed. Either one or several recrystallizations can be carried out, depending upon the product purity required.

The salt product is cleaved with any organic or inorganic acid not destructive to the product to yield the d - isomer enriched 2 - (6 - methoxy - 2 - naphthyl)propionic acid. Alternatively, according to the presently preferred technique, the cleavage of the cinchonidine salt product can be effected by treating the salt product with a strong base, such as potassium hydroxide or other strong base having a pKa value greater than 10, followed by acidification, such as with hydrochloric acid, to give d 2 - (6 - methoxy - 2 - naphthyl)propionic acid. When this cleavage is performed, for example, in a 3:1 (w/w) water-methanol mixture, at room temperature, foaming of the reaction mixture, which occurs when the alkaline suspension of cinchonidine is heated to 83°—86°C, is avoided and the product is easy to filter.

The present invention is considered to be an improvement over the resolution technique described in U.S. Patent No. 3,683,015. The present technique, using potassium hydroxide, allows a significant increase in the concentration of the mixture of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid charged to the reaction vessel (for example, this enables an increase from the 78 g of dl mixture per liter of methanol—as shown in the afore-

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mentioned patent—to 320–370 g of dl mixture per liter of methanol as shown in the Examples below). This higher input results in greater throughput for a given size reaction vessel, which is translated into lower production cost per quantity of product obtained. Additionally, the use of potassium hydroxide requires only one slurry of the mixture of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid in methanol to obtain a cinchonidine salt product having a satisfactory optical rotation value (of the liberated acid), that is, a salt mixture suitably enriched in the cinchonidine salt of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid. Generally this is on the order of a product (expressed as the liberated acid) which has an optical rotation value of about 58°, with only one additional recrystallization with methanol being required to attain an essentially pure salt having an optical rotation value of about 66° (of the liberated acid). This feature of the present invention is also translatable into reduction in the production cost per unit quantity of the product obtained. All this is obtained while achieving better resolution in slightly higher yield. The present invention, therefore, is an overall improvement in the process described in U.S. Patent No. 3,683,015.

The following specific description is given to enable those skilled in this art to more clearly understand and practice the present invention. It should not be considered as a limitation upon the scope of the invention but merely as being illustrative and representative thereof.

EXAMPLE 1

A mixture is prepared by adding, to a one liter flask, 70 g (0.305 g mole) of dl 2 - (6 - methoxy - 2 - naphthyl)propionic acid, 44 g (0.150 g mole) of cinchonidine, 8.67 g (0.155 g mole) of potassium hydroxide and 220 ml of methanol. These ingredients are stirred, and the mixture is refluxed for 4 hours. The mixture is then gradually cooled to 25°C over five hours and maintained at that temperature for a further 12 hours. The resultant suspension is then filtered, and the solids are washed with 100 ml of methanol and dried at 50–55°C. The yield of the cinchonidine salt of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid is about 90% (w/w). $[\alpha]_D = 57-58^\circ$ (of the liberated acid).

EXAMPLE 2

Repeating the procedure of Example 1 but replacing 8.67 g of potassium hydroxide with 7.6 g (0.136 g moles) of potassium hydroxide also yields an improved yield of cinchonidine salt of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid compared with that obtainable using 100 percent cinchonidine.

EXAMPLE 3

Repeating the procedure of Example 1 but replacing potassium hydroxide with sodium hydroxide, potassium carbonate, sodium carbonate, calcium hydroxide and ammonia yields, in each case, an improved yield of cinchonidine salt of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid compared with that obtainable using 100 percent cinchonidine.

EXAMPLE 4

A 65 g portion of the cinchonidine salt of d 2 - (6 - methoxy 1 2 - naphthyl)propionic acid ($[\alpha]_D = 58.8^\circ$; of the liberated acid) is mixed with 195 ml methanol, and the mixture is stirred and refluxed for 4 hours. The solution is cooled to 25°C over five hours and filtered. The filtrate is washed with 30 ml of methanol having a temperature of 25°C and dried at 45–50°C. The yield of the cinchonidine salt of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid is about 95.2% (w/w). $[\alpha]_D = 66.1^\circ$ (of the liberated acid).

EXAMPLE 5

The product of Example 4 (61.8 g) is mixed with 450 ml of ethyl acetate and 300 ml of dilute hydrochloric acid (5:1 v/v water to acid). The ethyl acetate layer is then filtered, and the ethyl acetate is replaced with isopropanol by distilling while adding incremental amounts of isopropanol. The product is mixed with water, cooled to 20°C, filtered, and the residue is washed with water to yield d 2 - (6 - methoxy - 2 - naphthyl)propionic acid. $[\alpha]_D = 66.1^\circ$.

EXAMPLE 6

To a suitably sized vessel containing potassium hydroxide (61.8 kg) dissolved in methanol (1557 l) there is charged dl 2 - (6 - methoxy - 2 - naphthyl)propionic acid (500 kg) with constant stirring. Cinchonidine (315 kg) is added and the batch heated under reflux for about four hours. After cooling at a rate of 8°C per hour to 25–30°C and aging for five hours the batch is filtered and the filter cake washed with methanol (1418 l). The wet filter cake is charged in methanol (1444 l) to a second suitably sized vessel and heated under reflux for four hours. After cooling at a rate of 8°C per hour to 25–30°C the batch is filtered and the cake (d - cinchonidine salt) washed with methanol (450 l). The yield of the cinchonidine salt of d - 2 - (6 - methoxy - 2 - naphthyl)propionic acid (d - cinchonidine salt) is about 86–92% w/w.

EXAMPLE 7

To a suitably sized vessel containing potassium hydroxide (54 kg) dissolved in methanol (730 l) there is charged d - cinchonidine salt wet cake (455 kg), obtained as described in Example 6. After stirring for twenty minutes

at 20–25°C under nitrogen, water (2080 l) is added and the stirring continued for a further 2 hours. The precipitated cinchonidine is filtered off and the filter cake washed with water. The combined filtrate and wash is extracted with chloroform (3×416 l). The aqueous layer is then charged with hydrochloric acid (125 kg) in water (794 l) and warmed to 35–40°C to remove any chloroform. The batch is cooled to 25°C, aged for one hour, and d 2 - (6 - methoxy - 2 - naphthyl)propionic acid filtered off and washed with water.

EXAMPLE 8

Acetone (2000 l), the wet cake of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid of example 7 and activated carbon (e.g. that supplied under the Trade Mark Darco G-60) are charged to a suitably sized vessel and the mixture stirred for 5 minutes. The batch is filtered and the filter cake washed with acetone. The combined filtrate and washings are vacuum distilled to a volume of 1000 l and cooled to 25–30°C. Water (3000 l) is charged, and the batch aged for 30 minutes at 5–0°C, and the precipitated d 2 - (6 - methoxy - 2 - naphthyl)propionic acid filtered off, washed with water and dried at about 45–50°C. The yield of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid is 34–38% w/w.

WHAT WE CLAIM IS:—

1. A process for resolving 2 - (6 - methoxy - 2 - naphthyl)propionic acid comprising the steps of:
 - (a) preparing a mixture of cinchonidine, an inorganic base having a basicity, pKa of greater than 8, d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid and an inert organic solvent in which the cinchonidine salt of l 2 - (6 - methoxy - 2 - naphthyl)propionic acid and inorganic base salts of d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid are soluble, and in which the cinchonidine salt of l 2 - (6 - methoxy - 2 - naphthyl)propionic acid is more soluble than the cinchonidine salt of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid, the solubility in the inert organic solvent of salts of the d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid and the inorganic base being greater than the solubility of the cinchonidine salts of the d and l 2 - (6 - methoxy - 2 - naphthyl)propionic acid, and
 - (b) crystalizing the cinchonidine salts of d and l 2 - (6 - methoxy - 2 - naphthyl)-

propionic acid from the mixture to yield a salt product enriched in the d 2 - (6 - methoxy - 2 - naphthyl)propionic acid salt.

2. The process of Claim 1 further including the step of subjecting the enriched cinchonidine salt product to at least one further crystallization to increase the percentage of d - isomer in the product.

3. The process of Claim 1 further including the step of subjecting the enriched cinchonidine salt product to only one further crystallization to provide a substantially pure cinchonidine salt of d 2 - (6 - methoxy - 2 - naphthyl)propionic acid.

4. The process of Claim 1 further including the step of cleaving the cinchonidine salt product enriched in the d 2 - (6 - methoxy - 2 - naphthyl)propionic acid salt to yield 2 - (6 - methoxy - 2 - naphthyl)propionic acid enriched in the d - isomer.

5. The process of Claim 4 wherein said cleavage is effected by treating said salt product enriched in the d 2 - (6 - methoxy - 2 - naphthyl)propionic acid salt with a strong base at about room temperature in approximately a 3:1 (w/w) water-methanol mixture, followed by acidification to yield d 2 - (6 - methoxy - 2 - naphthyl)propionic acid.

6. The process of Claim 5 wherein said strong base is potassium hydroxide.

7. The process of Claim 5 wherein said acidification is conducted with hydrochloric acid.

8. The process of Claim 1 wherein the molar ratio of cinchonidine to inorganic base is from 2:3 to 3:2.

9. The process of Claim 1 wherein the inorganic base is potassium hydroxide.

10. The process of Claim 1 wherein the solvent is methanol.

11. A process for resolving 2 - (6 - methoxy - 2 - naphthyl)propionic acid according to Claim 1, substantially as herein described.

12. A resolved optical isomer of 2 - (6 - methoxy - 2 - naphthyl)propionic acid prepared by the process of any one of the preceding claims.

13. A pharmaceutical composition comprising a compound of claim 12 with a suitable excipient.

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United States Patent [19]

[11] Patent Number: 6,114,523

Allegrini et al.

[45] Date of Patent: Sep. 5, 2000

[54] PROCESS FOR THE RECYCLE OF A WASTE PRODUCT OF DILTIAZEM SYNTHESIS

0 617 130 A2 9/1994 European Pat. Off. .
71 08 982 3/1971 Japan .
1236467 6/1971 United Kingdom .
2 130 578 6/1984 United Kingdom .

[75] Inventors: Pietro Allegrini, Lonigo; Gaetano Marchioro, Vicenza; Giuseppe Barreca, Caldiero; Marco Villa; Laura Russo, both of Milan, all of Italy

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MERK Index Citation 3247 Diltiazem, 12TH Ed., 1996.
Yamada et al, Asymmetric Reduction of a 1,5-Benzothiazepine Derivative with Sodium Borohydride-(S)-alphaAmino Acids: An Efficient Synthesis of a Key Intermediate of Diltiazem J. Org Chem 1996, 61 8586-8590.

[73] Assignee: Zamon Group S.p.A., Vicenza, Italy

Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Arent Fox Kintner Plotkin & Kahn

[21] Appl. No.: 09/176,189

[22] Filed: Oct. 21, 1998

[30] Foreign Application Priority Data

Oct. 22, 1997 [IT] Italy MI97A2374

[51] Int. Cl.⁷ C07C 323/62; C07D 281/10

[52] U.S. Cl. 540/491; 560/17; 562/401; 562/431

[58] Field of Search 540/491; 560/17; 561/401, 431

[56] References Cited

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5,102,999 4/1992 Giordano et al. 540/491
5,144,025 9/1992 Tentorio 540/491
5,223,612 6/1993 Giordano et al. 540/491

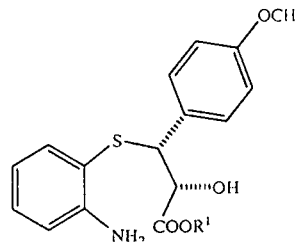
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[57] ABSTRACT

A process which allows the re-use of compounds of formula

III-(2R,3R)



in diltiazem synthesis through a process of conversion to a mixture of enantiomers III-(2R,3R) and III-(2S,3S) is described.

9 Claims, No Drawings

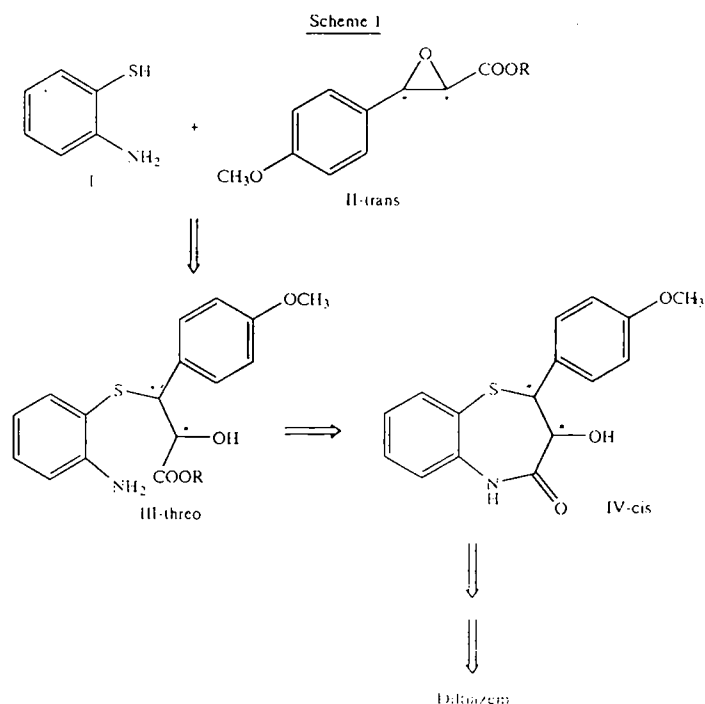
PROCESS FOR THE RECYCLE OF A WASTE PRODUCT OF DILTIAZEM SYNTHESIS

The present invention relates to a method for the recycle of a waste product of diltiazem synthesis and, more particularly, it relates to a method for the preparation of threo-2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)propionic acid esters, intermediates useful for the synthesis of diltiazem, starting from (2R,3R)-2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)propionic acid or derivatives thereof.

Diltiazem, (+)-(2S,3S)-3-acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxy-phenyl)-1,5-benzothiazepin-4(5H)-one (The Merck Index, XII ed., no. 3247, page 541) is a known drug with calcium-antagonist activity described in the U.K. patent 1236467 (Tanabe Seiyaku Co. Ltd.).

Several methods for the preparation of diltiazem such as, for example, those described in the above cited U.K. patent 1236467, in the European patent application 0 059 335 and in the Japanese patent no. 71/8982, all in the name of Tanabe Seiyaku Co. Ltd., are described in the literature.

Most of these methods substantially provide for the following synthetic scheme.



wherein R is a hydrogen atom or a lower alkyl and the asterisks mark the stereogenic carbon atoms

These methods use the compound of formula III-threo in racemic form, as intermediate. However, diltiazem shows stereocenters with S configuration and then, following the above reported scheme, a step for the separation of the (2S,3S) enantiomer from the (2R,3R) one is necessary.

The separation of the two enantiomers can be carried out on the intermediate (III) in the form of an ester (R=alkyl) as well as in the form of acid (R=H).

For example, the separation of the (2S,3S) and (2R,3R) enantiomers at the level of the ester III can be carried out by using an optically active acid as resolving agent (U.S. Pat.

No. 5,144,025—Zambon Group S.p.A.) or by spontaneous resolution (U.S. Pat. No. 5,097,059—Zambon Group S.p.A.).

In case of separation at the level of the acid III, the methods described in the literature provide for, inter alia, the resolution with optically active bases such as α -phenylethylamine (European patent application 0 098 892—Tanabe Seiyaku Co. Ltd) or L-lysine (U.K. patent application 2130578—Istituto Luso Farmaco d'Italia S.p.A.) or the acylation in the presence of a lipase (European patent application 0 617 130—Orion-Yhtymä Oy Fermion).

It is evident that the resolution methods have the disadvantage of giving the desired (2S,3S) isomer with a maximum theoretical yield of 50% on the raceme and of giving also the corresponding (2R,3R) isomer, at the same time.

The isomers with (2R,3R) configuration, unsuitable for diltiazem synthesis, are then a waste product in the industrial synthesis.

As a consequence, a process for the recycle of said compounds in order to recover them for diltiazem synthesis should be useful.

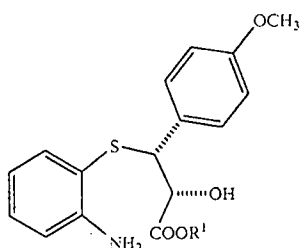
As far as we know, the only method described in the literature for the recycle of an intermediate with (2R,3R) configuration is the process claimed in the U.S. Pat. No.

5,102,999 (Zambon Group S.p.A.) which provides for the racemization of the intermediate IV-cis (2R,3R)

We have now found a process for the conversion of the intermediates III-(2R,3R) to a mixture of enantiomers III-(2R,3R) and III-(2S,3S) which allows to re-use the enantiomers with (2R,3R) configuration of the intermediates of formula III for diltiazem synthesis

Therefore, object of the present invention is a process for the conversion of threo-(2R,3R)-2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)propionic acid derivatives of formula

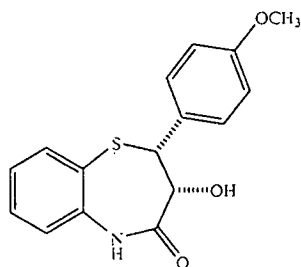
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III-(2R,3R)

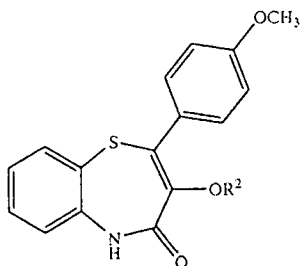
wherein R^1 is a linear or branched $\text{C}_1\text{--C}_3$ alkyl or a hydrogen atom;
into a mixture of enantiomers III-(2R,3R) and III-(2S,3S), comprising:

- (a) the cyclization of the compound III-(2R,3R) to afford the corresponding compound of formula



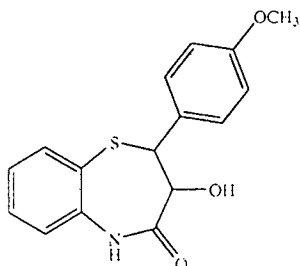
IV-(2R,3R)

- (b) the conversion to the compound of formula



wherein R^2 is a hydrogen atom or a $\text{C}_2\text{--C}_4$ acyl group,

- (c) the reduction to afford the compound of formula



IV-cis

4

- (d) the opening reaction by treating with a strong acid or with a strong base in an alcoholic or aqueous solvent.

The mixture of the two enantiomers III-(2R,3R) and III-(2S,3S) obtained with the process object of the present invention can be resolved according to the already reported methods in order to separate the (2S,3S) enantiomer useful for diltiazem synthesis.

In the present context, if not otherwise specified, the term mixture of enantiomers means a substantially racemic mixture (2R,3R:2S,3S ratio about 1:1) or a mixture wherein the enantiomer 2S,3S prevails.

Analogously, if the absolute configuration of the compounds of formula III or IV is not indicated, it means that said compounds are a substantially racemic mixture (2R,3R:2S,3S ratio about 1:1) or a mixture wherein the enantiomer 2S,3S prevails.

The term linear or branched $\text{C}_1\text{--C}_3$ alkyl means methyl, ethyl, propyl, isopropyl and the term $\text{C}_2\text{--C}_4$ acyl group means acetyl, propionyl, butyryl, isobutyryl.

The intermediates of formula III-(2R,3R) used as starting products in the process object of the present invention are known compounds and they are obtained as waste products in the optical separation processes for diltiazem synthesis.

Generally the compounds of formula III are in the form of acid ($\text{R}^1=\text{H}$) or in the form of methyl ($\text{R}^1=\text{CH}_3$) or ethyl ($\text{R}^1=\text{CH}_2\text{--CH}_3$) ester.

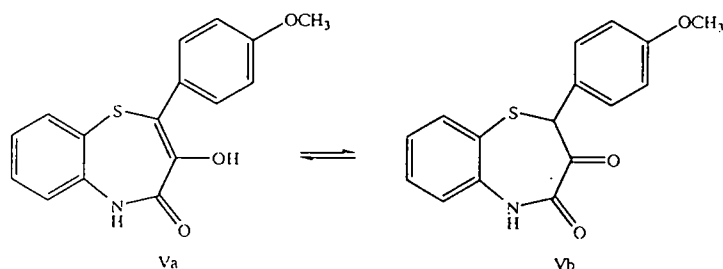
Preferably, in the process object of the present invention the compounds of formula III are methyl esters.

The cyclization of the compound III-(2R,3R) to afford the compound of formula IV-(2R,3R) can be carried out according to the known methods for the cyclization of the corresponding (2S,3S) enantiomer. For example, the cyclization of the esters of formula III-(2R,3R) can be carried out by treating with fosfonic acids (U.S. Pat. No. 5,223,612—Zambon Group S.p.A.) or by treating with sulfonic acids (European patent application 0 447 135—Tanabe Seiyaku Co. Ltd.). Similarly, the cyclization of the acid of formula III-(2R,3R) can be carried out by treating with sulfonic acids (European patent application 0 395 135—Tanabe Seiyaku Co. Ltd.) or with bases (European patent application 0 450 705—Stamicarbon B.V.).

In the process object of the present invention the cyclization reaction is preferably carried out starting from the methyl ester of formula III-(2R,3R) by treating with cis-propenyl-fosfonic acid.

The subsequent conversion reaction of the derivative V can be carried out according to known methods too. For example, the methods described in Org. Chem., 1996, 8586–8590 or in the already cited U.S. Pat. No. 5,102,999 can be used.

Preferably, in the process object of the present invention, the acetyl derivative of formula V ($\text{R}^2=\text{COCH}_3$) is prepared, then hydrolysed to afford the compound Va which will be in equilibrium with its tautomeric form as herein below reported.



The subsequent reduction reaction allows to obtain the compound IV-cis.

Optionally, the hydrolysis and reduction reactions can be carried out one-pot, that is in a unique reaction environment, without isolating the compound Va (or Vb).

The preparation of the acetyl derivative V is preferably carried out by treating with acetic anhydride in dimethylsulfoxide, in the presence of catalytic amounts of pyridine. The optional hydrolysis can be then carried out by treating with bases such as sodium hydroxide or sodium mesylate.

The reduction of the compound of formula V can be carried out with known methods, for example by treating with hydrides according to what reported in the already cited U.S. Pat. No. 5,102,999.

The resultant compound IV-cis can be then converted into the corresponding compound of formula III-threo by treating with a strong acid or with a strong base in an alcoholic or aqueous solvent.

The amount of acid or base is at least equimolar, preferably in excess, with respect to the compound IV-cis.

Generally the reaction is carried out by using an excess of acid or base equal to 10%–30% in moles with respect to the compound IV.

The strong acids used in the process of the invention are inorganic acids such as hydrochloric, hydrobromic, sulfuric and fosforic acid or organic acids such as sulfonic acids, preferably methanesulfonic, p-toluenesulfonic and camphorsulfonic acid.

Sodium hydroxide is preferably used as strong base.

In the process object of the present invention methanesulfonic acid is preferably used.

The reaction is carried out in an alcoholic solvent such as, for example, methanol or ethanol, preferably in methanol, or in water optionally in admixture with a suitable co-solvent such as dimethylsulfoxide.

Dependently on the alcohol used as solvent the corresponding ester of formula III-threo is obtained which can then be used again in the preparation of diltiazem according to the synthetic route illustrated in the previous scheme 1.

When an aqueous solvent is used, the acid ($R^1=H$) of formula III-threo is obtained and used according to the synthetic route illustrated in scheme 1 too.

The opening reaction of the compound of formula IV-cis represents the most characterising feature of the process object of the present invention.

In fact, as far as we know, this reaction has never been described in the literature.

On the contrary, cyclizations of the compound III-threo to afford the compound IV-cis by using acids or bases have widely been described in the literature.

Furthermore, it is evident that the possibility of racemizing the waste products with (2R,3R) configuration of the process for diltiazem preparation at the level of one of the

earliest synthetic intermediates represents a relevant advantage from a practical and economic viewpoint.

A particularly preferred embodiment of the process object of the present invention is the following.

The methyl ester of formula III-(2R,3R), obtained by resolution of the corresponding racemic mixture, is cyclized with cis-propenyl-fosfonic acid and then oxidised by treatment with acetic anhydride/dimethylsulfoxide/pyridine obtaining the acetyl derivative of formula V. After basic hydrolysis and reduction with sodium borohydride the racemic compound IV-cis is obtained and treated with an excess of methanesulfonic acid in methanol up to the obtainment of the racemic methyl ester III-threo.

The resolution of the racemic methyl ester III-threo allows to obtain the compound III-(2S,3S) which is used for diltiazem synthesis and the enantiomer III-(2R,3R) which can undergo a further recycle phase according to the process object of the present invention.

In order to better illustrate the present invention the following examples are now given.

EXAMPLE 1

A mixture of methyl (2R,3R)-2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)-propionate (5 g; 15 mmoles) and cis-propenyl-fosfonic acid (0.183 g; 1.5 mmoles) in xylene (35 ml) was heated under reflux and stirring for 5.5 hours.

After distilling a xylene/methanol mixture (about 3%), the reaction mixture was cooled to 15° C.

The resultant precipitate was filtered under vacuum, washed with xylene (2x5 ml) and then dried in oven at 65° C. obtaining (2R,3R)-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (42 g; 89.6% yield).

EXAMPLE 2

A catalytic amount of pyridine (19.7 g; 0.25 moles) was added to a solution of (2R,3R)-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (500 g; 1.66 moles) in dimethylsulfoxide (1100 g; 14.1 moles) and acetic anhydride (425 g; 4.17 moles). After keeping the solution under stirring at room temperature for 24 hours, water (1000 ml) was slowly added and the mixture was kept under stirring for 30 minutes.

The crystalline precipitate was filtered off, washed with methanol and dried obtaining 3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (481.6 g; 84.7% yield).

EXAMPLE 3

A suspension of 3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (17.1 g; 0.05 mmoles) in metha-

nol (51 ml) was cooled in ice and then a solution of NaOH (5 g; 0.125 mmoles) in water (63 ml) was added.

The solution was then kept under stirring for 2 hours at room temperature.

After neutralisation with HCl 2N (50 ml) and extraction with ethyl acetate, the organic phase was washed twice with water, dried and concentrated obtaining a viscous oil.

The oil was treated with ethyl ether obtaining 2-(4-methoxyphenyl)-1,5-benzothiazepin-3,4(2H,5H)-dione (12.98 g; 86.7% yield) as a crystalline solid.

EXAMPLE 4

Sodium borohydride (0.567 g; 15 mmoles) was added to a solution of 2-(4-methoxyphenyl)-1,5-benzothiazepin-3,4(2H,5H)-dione (4.25 g; 14.2 mmoles) in methanol (65 ml), kept under stirring, at 15° C.

After 1 hour the reaction mixture was poured into a buffer solution (100 ml) at pH 7 and methanol was removed by distillation under vacuum.

The resultant mixture was extracted with methylene chloride (2x30 ml).

After evaporation of the solvent under reduced pressure cis-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (4.15 g; 97% yield) as racemic mixture was obtained.

EXAMPLE 5

In a 500 ml flask, equipped with thermometer and condenser, cis-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (50 g; 165.9 mmoles) was suspended in methanol (200 ml) and methanesulfonic acid (19.2 g; 200 mmoles) was added to the mixture.

The reaction mixture was brought to reflux and the progress of the reaction was followed by TLC (eluent ethylacetate:hexane=6:4). After heating for 7 hours, the content of starting product was about 1%.

The reaction mixture was then cooled at room temperature before adding, with a dropping funnel, a 8% solution of sodium bicarbonate (208 g; final pH=7.0).

The resultant precipitate was filtered off and washed three times with water (3x50 ml). The resultant solid was then dried at 50° C. under vacuum up to constant weight obtaining methyl threo-2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)-propionate (54 g; molar yield 94.2%; HPLC titre 96.5%).

EXAMPLE 6

30% Sodium methylate in methanol (0.1 ml; 0.5 mmoles) and, after 15 minutes, sodium borohydride (54 mg; 1.42 mmoles) were added to a suspension of 3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (1 g; 2.9 mmoles) in methanol (5 ml).

After keeping the mixture under stirring at room temperature for 5 hours, methanesulfonic acid (0.6 ml; 9.3 mmoles) was added and the mixture was heated under reflux for 5 hours. After cooling at room temperature, 8% sodium bicarbonate (9 ml) was added.

After adding toluene, the resultant solid was filtered off, washed with water (3x1 ml) and dried at 50° C. under vacuum obtaining methyl threo-2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)propionate (0.92 g; molar yield 90%; HPLC titre 95%).

EXAMPLE 7

30% Sodium methylate in methanol (0.5 ml; 2.5 mmoles) and, after 15 minutes, sodium borohydride (0.23 g; 7.35

mmoles) were added to a suspension of 3-acetoxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one (5 g; 14.7 mmoles) in methanol (25 ml).

After keeping the mixture under stirring at room temperature for 5 hours, a 6.5M solution of hydrochloric acid in methanol (2.7 ml; 17.6 mmoles) was added and the mixture was heated under reflux for 5 hours.

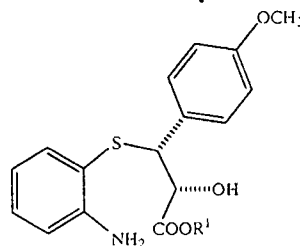
After cooling at room temperature, 8% sodium bicarbonate (16 ml) was added.

The resultant precipitate was filtered off, washed with water (3x5 ml) and dried at 50° C. under vacuum obtaining methyl threo-2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)-propionate (5 g; molar yield 85%; ¹H-NMR titre 75%).

What is claimed is:

1. A process for the conversion of threo-(2R,3R)-2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)propionic acid derivatives of formula

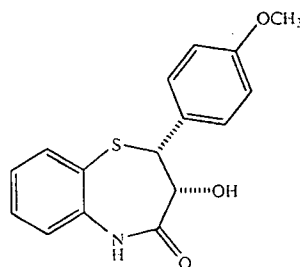
III-(2R,3R)



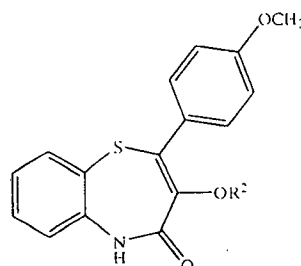
wherein R¹ is a linear or branched C₁-C₃ alkyl or a hydrogen atom; into a mixture of enantiomers III-(2R,3R) and III-(2S,3S), comprising:

(a) the cyclization of the compound III-(2R,3R) to afford the corresponding compound of formula

IV-(2R,3R)

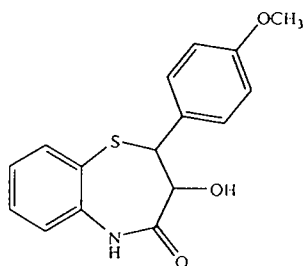


(b) the conversion to the compound of formula



wherein R² is a hydrogen atom or a C₂-C₄ acyl group,

(c) the reduction to afford the compound of formula



IV-cis

(d) the opening reaction by treating with a strong acid or with a strong base in an alcoholic or aqueous solvent.

2. A process according to claim 1 for the conversion of the methyl ester of threo-(2R,3R)-2-hydroxy-3-(2-aminophenylthio)-3-(4-methoxyphenyl)-propionic acid.

3. A process according to claim 1 wherein the compound of formula V wherein R^2 is acetyl is used.

4. A process according to claim 1 wherein the opening reaction is carried out by treating with a strong acid.

5. A process according to claim 4 wherein the strong acid is selected from the group consisting of hydrochloric, hydrobromic, sulfuric, phosphoric, methanesulfonic, p-toluenesulfonic and camphorsulfonic acid.

6. A process according to claim 5 wherein the strong acid is methanesulfonic acid.

7. A process according to claim 4 wherein an alcoholic solvent is used.

8. A process according to claim 7 wherein the solvent is methanol.

9. A method for the preparation of diltiazem, the method comprising conducting the process according to claim 1 and thereafter synthesizing the diltiazem from the III-(2S,3S) enantiomer obtained in the process.



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United States Patent [19]
Braish

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[45] Date of Patent: Jan. 21, 1992

[54] PROCESS FOR RECYCLING AMINE
ISOMER

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[73] Assignee: Pfizer Inc., New York, N.Y.

[21] Appl. No.: 665,506

[22] Filed: Mar. 6, 1991

[51] Int. Cl.⁵ C07C 209/88

[52] U.S. Cl. 564/424; 564/307;
564/308; 564/425; 564/428

[58] Field of Search 564/308, 307, 424, 425,
564/428; 568/308

[56] 0 References Cited

U.S. PATENT DOCUMENTS

3,506,714	4/1970	Hinkley et al.	260/590
4,463,176	7/1984	Dennis et al.	546/208
4,536,518	8/1985	Welch, Jr. et al.	514/647
4,556,676	12/1985	Welch, Jr. et al.	514/554

Primary Examiner—Richard L. Raymond
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Attorney, Agent, or Firm—Peter C. Richardson; Paul H. Ginsburg

[57] ABSTRACT

A novel process for converting trans-isomeric N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine to cis-isomeric N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine is disclosed. The process involves contacting trans-isomeric N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine, or a mixture of same with up to about an equal part by weight of the corresponding cis-isomer, with a basic equilibration agent like potassium tert.-butoxide in a reaction-inert polar organic solvent to ultimately afford a cis/trans-mixture wherein the amount of cis-amine present in said mixture achieves a constant value of about 2:1 on a weight-by-weight basis. The aforesaid resultant mixture is useful as an intermediate product that ultimately leads to pure cis-(1S) (4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine (sertraline), which is a known antidepressant agent.

23 Claims, No Drawings

581
448

PROCESS FOR RECYCLING AMINE ISOMER

TECHNICAL FIELD

This invention relates to a process for recycling a trans-amine to a cis-amine. More particularly, it is concerned with a novel method for converting trans-isomeric N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine to the corresponding cis-isomeric product. The latter material is useful as an intermediate that ultimately leads to the antidepressant agent known as cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine (sertraline).

BACKGROUND ART

There is described in U.S. Pat. Nos. 4,536,518 and 4,556,676 to W. M. Welch, Jr. et al., as well as in the paper of W. M. Welch, Jr. et al., appearing in the *Journal of Medicinal Chemistry*, Vol. 27, No. 11, p. 1508 (1984), a multi-step method for synthesizing pure racemic cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine, starting from the readily available 3,4-dichlorobenzophenone. In the last step of this synthesis, N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]methenamine is reduced by means of catalytic hydrogenation or by the use of a metal hydride complex to N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine, which is actually a mixture of the cis- and trans-isomers in the form of a racemate. The aforesaid isomeric mixture is then separated into its component parts by conventional means, e.g., by fractional crystallization of the hydrochloride salts or by column chromatography on silica gel of the corresponding free base. Resolution of the separated cis-racemate free base compound while in solution with an optically-active selective precipitant acid, such as D-(−)-mandelic acid, in a classical manner then ultimately affords the desired cis-(1S)(4S)-enantiomer (sertraline).

Nevertheless, the above described production of pure cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine is disadvantageous in that large amounts of the unwanted racemic trans-isomer (which ultimately leads to the unwanted trans-(1S)(4R)-enantiomer) are co-produced and must eventually be discarded, thereby lowering the overall yield of the desired cis-(1S)(4S)-enantiomer and increasing the costs of production. Therefore, it is an object of the present invention to utilize the unwanted trans-isomer that is co-produced in the aforesaid synthesis and so lower the total costs of production. Another and more specific object of the present invention is to convert the aforesaid trans-racemate free base to the corresponding cis-isomer and thereby, in effect, recycle the previously unwanted trans-isomer back into the present method of production for the desired cis-isomer. Still another and even more specific object of the present invention is to convert the previously unwanted chiral trans-(1S)(4R)-isomer into the corresponding chiral cis-(1S)(4S)-isomer which is, of course, sertraline.

DISCLOSURE OF THE INVENTION

In accordance with the present invention, there is now provided a process for converting trans-isomeric N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine to cis-isomeric N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-

mine, said process comprising contacting trans-isomeric N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine in the absence or presence of up to about an equal part by weight of the corresponding cis-isomer with a basic equilibration agent, such as 1,3-diazabicyclo[5.4.0]undec-7-ene or an alkali metal lower alkoxide (C₁-C₄) like potassium tert.-butoxide, in a reaction-inert polar organic solvent system at a temperature that is in the range of from about 55° C. up to about 125° C. until the amount of the desired cis-amine in the resultant cis/trans-mixture achieves a constant value of about 2:1 on a weight-by-weight basis. In this connection, it is to be understood that by the use of the term trans-isomeric N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine there is meant to be included not only the racemic trans-compound, but also the corresponding chiral trans-(1S)(4R)-enantiomer which is easily derived from same via resolution with L-(+)-mandelic acid and was first reported by W. M. Welch, Jr. et al. in the aforementioned *Journal of Medicinal Chemistry* reference article.

More specifically, by the use of the process of this invention, a recycled starting material such as pure racemic trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine or a 1:1 by weight mixture of said trans-isomer with the corresponding cis-isomer is converted to about a 2:1 by weight cis/trans-mixture of the isomers in a most facile manner. As previously indicated, the latter 2:1 resultant mixture is useful as an intermediate product that leads to pure cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine (sertraline), which is a known antidepressant agent. In like manner, chiral trans-(1S)(4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine or a 1:1 by weight mixture of said trans-isomer with the corresponding cis-isomer (viz., the chiral cis-(1S)(4S)-enantiomer) is also converted to about a 2:1 by weight cis/trans-mixture of the isomers in a most facile manner. However, in the latter case, the resultant 2:1 cis/trans-mixture of chiral isomers leads directly to sertraline since the resolution step is no longer required.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the process of this invention, the equilibration reaction is generally carried out by using an excess in moles of the basic equilibration agent with respect to the total amount of N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine starting material (i.e., trans-isomer with up to about an equal part by weight of the cis-isomer, etc.) and preferably by using at least about one mole of said starting material per mole of the basic equilibration agent, with the most preferred range being from about 1.0:1.0 to about 1.0:2.0, in order to effect the desired conversion of the trans-isomer to the cis-isomer as previously discussed. The process is normally conducted in a reaction-inert polar organic solvent system at a temperature that is in the range of from about 55° C. up to about 125° C., and preferably one that is in the range of from about 65° C. up to about 90° C., until the desired conversion to the constant 2:1 (by weight) cis/trans-mixture is substantially complete. Generally, the equilibration reaction will require a time period of at least about four hours, although it is preferable in practice to carry out the reaction for a period of about 40 hours. Preferred reac-

tion-inert polar organic solvents for use in this connection include lower dialkyl (C_1 - C_4) ethers having a total of at least five carbon atoms such as di-isopropyl ether, di-n-butyl ether, methyl n-butyl ether and ethyl isopropyl ether, cyclic ethers such as tetrahydrofuran and dioxane, alkylated glycols having a total of from four to eight carbon atoms, like 1,1-diethoxymethane, 1,2-dimethoxyethane, 2-ethoxyethanol, 2-n-butoxyethanol, the dimethyl ether of butylene glycol and the di-n-propyl ether of ethylene glycol, as well as lower N,N-dialkyl lower alkanamides having a total of up to six carbon atoms (with at least one of said atoms always being present in the N,N-unsubstituted alkanamide moiety) like dimethylformamide, diethylformamide, dimethylacetamide, diethylacetamide, dimethylpropionamide and so forth. Preferred basic equilibration agents employed for purposes of the invention process include 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, lithium di-isopropylamide and lithium tetramethylpiperide, as well as various metal lower alkoxides (C_1 - C_4) like the alkali metal lower alkoxides (C_1 - C_4), such as sodium ethoxide and potassium tert-butoxide. Optimum results are generally obtained when dimethylformamide and like alkanamide solvents are employed in conjunction with the first-three named basic equilibration agents, and tetrahydrofuran and the other ether-type solvents are used in conjunction with the remaining basic equilibration agents, such as potassium tert-butoxide and the like. In the latter connection, especially when tetrahydrofuran is employed as the solvent of choice in conjunction with the alkoxide-type equilibration agent, it has often been found most convenient and advantageous in practice to use small amounts of the corresponding lower alkanol in order to "spike" the aforesaid ethereal solvent and so aid in further increasing the solubility of the starting materials and final products that are contained within the selected solvent system. Usually, a minor amount of the alkanol "spike," say, for example, 5% by volume based on the total volume of the ethereal solvent, is sufficient for such purposes.

Upon completion of the equilibration reaction, the desired product, viz., pure racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine or the pure chiral cis-(1S)(4S)-enantiomer thereof (as the case may be), is readily recovered from the reaction mixture by conventional means such as, for example, by first removing the solvent via evaporation under reduced pressure and then dissolving the resultant residue in a chlorinated lower hydrocarbon solvent such as methylene chloride, ethylene dichloride, s-tetrachlorethane, chloroform or carbon tetrachloride, followed by successive washing and drying of the resulting solution and subsequent evaporation of the solvent under reduced pressure to afford the previously discussed 2:1 (by weight) cis/trans-mixture (as detected by such analytical methods as thin layer chromatography, high pressure liquid chromatography, nuclear magnetic resonance spectroscopy, etc.) as the residual oil. When the latter oil is thereafter dissolved in an ethereal solvent such as tetrahydrofuran and treated with a dry hydrohalide gas, like anhydrous hydrogen chloride, the desired cis-amine precipitates from solution as the crystalline hydrohalide salt while the corresponding trans-amine salt remains in solution. In this way, a starting material such as unwanted racemic trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naph-

thaleneamine or a 1:1 (by weight) mixture of same with the desired cis-isomer is conveniently converted to pure crystalline racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride via the aforesaid 2:1 (by weight) cis/trans-mixture. In like manner, the unwanted chiral trans-(1S)(4R)-enantiomer is converted to the desired chiral cis-(1S)(4S)-enantiomer, viz., cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride, as previously discussed.

The pure racemic trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine starting material that may be used for conducting the equilibration process of this invention, as well as the desired pure racemic cis-amine final product are both reported as hydrochloride salts in the paper by W. M. Welch, Jr., as described in the *Journal of Medicinal Chemistry*, Vol. 27, No. 11, p. 1508 (1984), along with the corresponding free base compounds and an approximately 1:1 (by weight) mixture of the racemic cis- and trans-isomers (as the free amine base compounds) in crude form. The pure racemic cis-amine hydrochloride is also reported in U.S. Pat. No. 4,536,518 to W. M. Welch, Jr. et al., along with crude mixtures of the two isomers as hydrochloride salts, while the pure racemic trans-amine hydrochloride is similarly reported in U.S. Pat. No. 4,556,676, also to W. M. Welch, Jr. et al. The pure chiral trans-(1S)(4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine starting material is also reported as a hydrochloride salt in the previously-mentioned paper by W. M. Welch, Jr. et al., along with the corresponding free amine base compound.

As previously indicated, the 2:1 (by weight) cis/trans-mixture of racemic N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine isomers afforded as a final product of the process of this invention is valuable as an intermediate product that leads to the antidepressant agent known as sertraline or cis-(1S)(4S)-N-methyl-1,2,3,4-tetrahydro-1-naphthaleneamine. More specifically, when the aforesaid 2:1 (by weight) resultant cis/trans-mixture of racemic N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine bases is first converted to the corresponding hydrochloride salts in an ethereal solvent system such as pure tetrahydrofuran, the pure crystalline racemic cis-amine salt exclusively separates from solution as a crystalline precipitate to afford pure racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride, which is then recovered and converted back to the pure racemic cis-amine free base compound and subsequently resolved in a classical manner using the methods described by W. M. Welch, Jr. et al. in the aforesaid prior art to ultimately yield the desired pure cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine (sertraline) as the hydrochloride salt. The corresponding 2:1 (by weight) cis/trans-mixture of chiral N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine isomeric bases afforded as a final product of the process of this invention is similarly processed as an intermediate that leads to sertraline, except that the resolution step is not required since the desired pure chiral cis-(1S)(4S)-amine compound (sertraline) is obtained directly after isolation of the crystalline hydrochloride salt.

Hence, the novel process of the present invention now provides a way to convert unwanted trans-isomeric N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-

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dro-1-naphthaleneamine back to the desired pure cis-isomer (racemic or chiral) and thus to effectively recycle the previously unwanted trans-isomer back into the present method of production for obtaining said desired cis-isomer. The latter accomplishment, in turn, represents a major improvement over prior art methods in view of the increased ease and simplicity of operation, and the concomitant decrease in the total costs of production.

EXAMPLE 1

A mixture consisting of 5.0 g. (0.0164 mole) of racemic trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine [W. M. Welch et al., *Journal of Medicinal Chemistry*, Vol. 27, No. 11, p. 1508 (1984)] dissolved in 60 ml. of tetrahydrofuran, which also contained 3.09 ml. of tert.-butanol and 3.68 g. (0.0328 mole) of potassium tert.-butoxide, was heated to reflux for a period of 48 hours. Upon completion of this step, the solvent was removed by means of evaporation under reduced pressure and the resulting residue was thereafter taken up in methylene chloride and washed with three successive 60 ml. portions of water, followed by drying over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was finally obtained a residual oil which proved to be a 2:1 (by weight) mixture of the racemic cis- and trans-amines, as attested to by nuclear magnetic resonance data. When the latter oil was dissolved in tetrahydrofuran and subsequently treated with anhydrous hydrogen chloride gas, the cis-amine precipitated as the hydrochloride salt, while the trans-amine hydrochloride remained in solution. In this manner, there were ultimately obtained 3.5 g. (62%) of pure racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride (m.p. 275°-277° C.) in the form of the recovered crystalline salt. The melting points reported in the literature for the pure racemic cis-amine hydrochloride and pure racemic trans-amine hydrochloride salts were 275°-277° C. and 214°-216° C., respectively, according to W. M. Welch et al. in the *Journal of Medicinal Chemistry*, Vol. 27, No. 11, p. 1508 (1984).

EXAMPLE 2

The procedure described in Example 1 was repeated except that 5.0 g. (0.0164 mole) of a 1:1 (by weight) mixture of pure racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine and pure racemic trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine was the starting material employed in place of the corresponding pure trans-isomer alone, using the same molar proportions as before. In this particular case, the corresponding final product obtained was a residual oil which proved to be a 2:1 (by weight) mixture of the racemic cis- and trans-amines, substantially identical in every respect with the product of Example 1, as attested to by nuclear magnetic resonance data. Pure racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride (m.p. 275°-277° C.) was then isolated from the aforesaid mixture in the same manner as that already described for the same product in Example 1. In this instance, the yield of pure product amounted to 61%, based on the amount of starting material used.

EXAMPLE 3

The procedure described in Example 1 is repeated except that 5.0 g. (0.0164 mole) of a 1:9 (by weight) mixture of pure racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine and pure racemic trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine is the starting material employed in lieu of the corresponding pure trans-isomer alone, using the same molar proportions as before. In this particular case, the corresponding final product obtained is a 2:1 (by weight) mixture of the racemic cis- and trans-amines, substantially identical in every respect with the product of Example 1. Pure racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride is then isolated from the aforesaid mixture in the same manner as that already described for the identical product in Example 1.

EXAMPLE 4

The procedure described in Example 1 is repeated except that 5.0 g. (0.0164 mole) of a 1:4 (by weight) mixture of pure racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine and pure racemic trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine is the starting material employed in lieu of the corresponding pure trans-isomer alone, using the same molar proportions as before. In this particular case, the corresponding final product obtained is again a 2:1 (by weight) mixture of the racemic cis- and trans-amines, substantially identical in every respect with the product of Example 1. Pure racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride is then isolated from the aforesaid mixture in the same manner as that already described for the identical product in Example 1.

EXAMPLE 5

The procedure described in Example 1 is repeated except that 5.0 g. (0.0164 mole) of a 2:3 (by weight) mixture of pure racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine and pure racemic trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine is the starting material employed in lieu of the corresponding pure trans-isomer alone, using the same molar proportions as before. In this particular case, the corresponding final product obtained is again a 2:1 (by weight) mixture of the racemic cis- and trans-amines, substantially identical in every respect with the product of Example 1. Pure racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride is then isolated from the aforesaid mixture in the same manner as that already described for the identical product in Example 1.

EXAMPLE 6

The procedure described in Example 1 is repeated except that 5.0 g. (0.0164 mole) of pure chiral trans-(1S)(4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine [W. M. Welch et al., *Journal of Medicinal Chemistry*, Vol. 27, No. 11, p. 1508 (1984)] is the starting material employed in place of the pure racemic trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine, using the same molar proportions as before. In this particular case, the corre-

sponding final product obtained is a 2:1 (by weight) mixture of chiral cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine (sertraline) and chiral trans-(1S)(4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine. Pure chiral cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride (sertraline hydrochloride) is then isolated from the aforesaid mixture in the same manner as that described previously for the corresponding racemic salt reported in Example 1.

EXAMPLE 7

The procedure described in Example 6 is repeated except that 5.0 g (0.0164 mole) of a 1:1 (by weight) mixture of pure chiral cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine and pure chiral trans-(1S)(4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine is the starting material employed in place of the corresponding pure trans-isomer alone, using the same molar proportions as before. In this particular case, the corresponding final product obtained is a 2:1 (by weight) mixture of the chiral cis-(1S)(4S)- and chiral trans-(1S)(4R)-amines, substantially identical in every respect with the product of Example 6. Pure chiral cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride (sertraline hydrochloride) is then isolated from the aforesaid mixture in the same manner as that described previously for the corresponding racemic salt reported in Example 1.

I claim:

1. A process for converting trans-isomeric N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine to cis-isomeric N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine, which comprises contacting trans-isomeric N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine in the absence or presence of up to about an equal part by weight of the corresponding cis-isomer with a basic equilibration agent in a reaction-inert polar organic solvent system at a temperature that is in the range of from about 55° C. up to about 125° C. until the amount of the desired cis-amine in the resultant cis/trans-mixture achieves a constant value of about 2:1 on a weight-by-weight basis.

2. A process for converting racemic trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine to the corresponding cis-isomeric product, which comprises contacting racemic trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine in the absence or presence of up to about an equal part by weight of the corresponding cis-isomer with a basic equilibration agent in a reaction-inert polar organic solvent system at a temperature that is in the range of from about 55° C. to about 125° C. until the amount of the desired cis-amine in the resultant cis/trans-mixture achieves a constant value of about 2:1 on a weight-by-weight basis.

3. A process for converting chiral trans-(1S)(4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine to the corresponding cis-isomeric product, which comprises contacting chiral trans-(1S)(4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine in the absence or presence of up to about an equal part by weight of the corresponding cis-isomer with a basic equilibration agent in a reaction-inert polar organic solvent system at a temper-

ature of from about 55° C. to up about 125° C. until the amount of the desired cis-amine in the resultant cis/trans-mixture achieves a constant value of about 2:1 on a weight-by-weight basis.

4. A process as claimed in claim 2 wherein racemic trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine is the starting material employed in the absence of any substantial amount of the corresponding cis-isomer.

5. A process as claimed in claim 2 wherein a 1:1 cis/trans-mixture consisting of about equal parts by weight of racemic cis- and racemic trans-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine is the starting material employed.

6. A process as claimed in claim 3 wherein chiral trans-(1S)(4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine is the starting material employed in the absence of any substantial amount of the corresponding cis-isomer.

7. A process as claimed in claim 3 wherein a 1:1 cis/trans-mixture consisting of about equal parts by weight of chiral cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine and chiral trans-(1S)(4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine is the starting material employed.

8. A process as claimed in claim 1 wherein the basic equilibration agent employed is 1,8-diazabicyclo[5.4.0]undec-7-ene.

9. A process as claimed in claim 1 wherein the basic equilibration agent employed is an alkali metal lower alkoxide (C₁-C₄).

10. A process as claimed in claim 9 wherein the alkali metal lower alkoxide is potassium tert.-butoxide.

11. A process as claimed in claim 1 wherein an excess in moles of the equilibration agent is employed with respect to the total amount of N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine starting material.

12. A process as claimed in claim 11 wherein the molar ratio of the N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine starting material to the basic equilibration agent is in the range of from about 1.0:1.0 to about 1.0:3.0, respectively.

13. A process as claimed in claim 12 wherein the molar ratio of N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine starting material to the basic equilibration agent is about 1.0:2.0.

14. A process as claimed in claim 1 wherein the reaction-inert polar organic solvent is a lower N,N-dialkyl lower alkanoamide having a total of up to six carbon atoms with at least one of said atoms always being present in the N,N-unsubstituted alkanoamide moiety.

15. A process as claimed in claim 14 wherein the lower N,N-dialkyl lower alkanoamide is dimethylformamide.

16. A process as claimed in claim 1 wherein the reaction-inert polar organic solvent is tetrahydrofuran or a mixture of same with a minor amount of tert.-butanol.

17. A process as claimed in claim 1 wherein the basic equilibration agent is 1,8-diazabicyclo[5.4.0]undec-7-ene and the reaction-inert polar organic solvent is dimethylformamide.

18. A process as claimed in claim 1 wherein the basic equilibration agent is potassium tert.-butoxide and the reaction-inert polar organic solvent is tetrahydrofuran or a mixture of the same with a minor amount of tert.-butanol.

19. A process as claimed in claim 18 wherein the basic equilibration reaction is conducted at a temperature of from about 65° C. to about 90° C. for a period of at least about four hours.

20. A process as claimed in claim 4 wherein pure racemic cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine is recovered from the resultant 2:1 cis/trans-mixture in the form of a hydrohalide salt.

21. A process as claimed in claim 20 wherein the hydrohalide salt recovered is pure racemic cis-N-meth-

yl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride.

22. A process as claimed in claim 6 wherein pure chiral cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine is recovered from the resultant 2:1 cis/trans-mixture in the form of a hydrohalide salt.

23. A process as claimed in claim 20 wherein the hydrohalide salt recovered is pure chiral cis-(1S)(4S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthaleneamine hydrochloride.

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