SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogada
DILIA MARIA RODRIGUEZ D'ALEMAN
info@clarkemodet.com.co
clarkemodet@clarkemodet.com.co

ASUNTO		
	Radicación	10-036274
	Trámite	11
	Evento	378
	Actuación	519
	Oficio	R 15928
	Folios	15

Patente de Invención	☑			Patente de Modelo de Utilidad
Vía Nacional				
Vía PCT (Fase Nacional)	☑	Capítulo I	☑	Capítulo II

No. Solicitud Internacional	PCT/JP2008/066279
Fecha de Presentación Internacional	10/Septiembre/2008

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 12 a 188	26/Marzo/2010
Reivindicaciones:	Folios 189 a 194	26/Marzo/2010
	Folios 228 a 231	15/Febrero/2011
Prioridad:	JP 2007-235580	11/Septiembre/2007

2. Análisis de la Prioridad

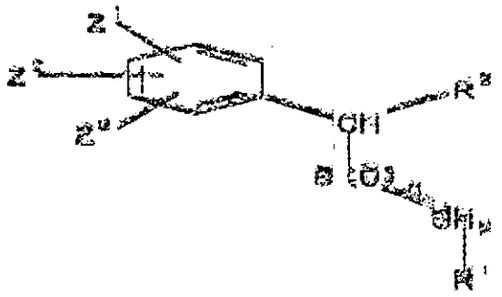
Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "DERIVADO DE ALQUILSULFONA"

El problema planteado en esta solicitud consiste en la necesidad de proporcionar compuestos de fuerte actividad inhibitoria contra la producción y secreción de proteína β-amiloide

Para resolver este problema técnico la solicitud en estudio proporciona un compuesto de la fórmula (I) y composiciones que lo contienen.



(I)

(Ver folio 18)

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C 07 D 219/46

4. De la Solicitud de Patente

Título

El título no corresponde con el objeto de la solicitud porque no define las características técnicas de la invención por cuanto los compuestos derivados de alquilsulfona ya son conocidos en el estado de la técnica, por lo cual se sugiere al Solicitante hacer la corrección necesaria.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

El capítulo reivindicatorio no es conciso porque menciona definiciones genéricas y funcionales, lo cual dificulta determinar la extensión del objeto que se busca proteger. Además menciona la presencia de 1 a 3 sustituyentes sustituyendo el grupo R^2 sin especificar cuales son dichos sustituyentes. Por tal motivo se obtienen un número indefinido de compuestos que no encuentran soporte en la descripción.

Al revisar la descripción en los ejemplos se muestra que R^1 es metilo, etilo, propilo, butilo, etenilo, propenilo, ciclopropilo, ciclobutilo sustituidos por flúor, cloro, hidroxi, tert-butil(dimetil) silil oxil, dioxolan-metil, formil y benciloxi R^2 corresponde a los sustituyentes 4-metil-5-piridin y 5-cloro-4-piridin sustituidos en la posición 2 por sustituyentes bromo, carboxilato de metilo, carboxamida, N-(hidroximetil) carboxamida, N-(hidroxietil) carboxamida, carbaldehído, hidroxiamino y amino, comprende también los sustituyentes 7-cloro-4H-pirido[1,2-a]pirimidin-4-ona sustituido en la posición 2 por hidroxi ó por amino y el sustituyente 6-cloro-[1,2,4]

triazolo [4,3-a] piridin-3(2H-ona) Z^1, Z^2 y Z^3 son flúor. Por lo tanto se sugiere restringir la solicitud a una razonable generalización de tales ejemplos.

5. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de Presentación de la Solicitud de Prioridad: Septiembre 11 de 2007, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	US2682544	Aryl-Pyridylmethyl Alkyl Sulfones and their Preparation	29/Junio/1954
D2	US4148922	3-{8 2-(Dialkylamino)Ethyl{9 -2-(Benzyl)Indoles	10/Abril/1979
D3	Dean F. Bushey, Brenda F. Johnson, and Jamin Huang "Intramolecular Nitrogen-Phosphorus Interactions of Phosphate Esters". *J. Org. Chem.* 1985,50, 2091-2095	Intramolecular Nitrogen-Phosphorus Interactions of Phosphate Esters".	Junio/1985
D4	WO2006109729	Pyridylmethylsulfone Derivative	19/Octubre/2006
D5	EP1466898	Beta-Amyloid Protein Production/Secretion Inhibitors	13/Octubre/2004

D1
http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=2682544A&KC=A&FT=D&ND=3&date=19540629&DB=worldwide.espacenet.com&locale=en_EP divulga (columna 1, líneas 1 a 17, columnas 3 a 9 ejemplos 1 a 15) un compuesto correspondiente a una aril-piridilmetil alquil sulfona.

D2
http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=4148922A&KC=A&FT=D&ND=3&date=19790410&DB=worldwide.espacenet.com&locale=en_EP divulga (columna 1 líneas 10 a 20, columnas 2 a 4, ejemplos 1 a 4) un compuesto correspondiente a un indol bencilsustituido.

D3
http://www.sinab.unal.edu.co:2139/doi/abs/10.1021/jo00212a017 divulga (página 2092 compuesto 15, Ver folios 243 a 247) un compuesto correspondiente a un benzimidazol bencil sustituido.

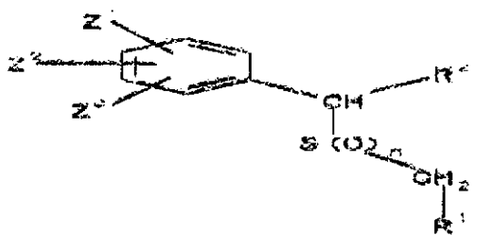
D4
http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2006109729A1&KC=A1&FT=D&ND=3&date=20061019&DB=worldwide.espacenet.com&locale=en_EP
(traducción) divulga (ejemplos 1 a 136) un compuesto derivado de piridina con efecto inhibitorio sobre β-amiloide.

D5
http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=EP&NR=1466898A1&KC=A1&FT=D&ND=3&date=20041013&DB=worldwide.espacenet.com&locale=en_EP divulga (página 2 a página 9, parágrafos 0008 a 0049) un compuesto de la fórmula (1) útil como inhibidor de β-amiloide.

6. **Examen de Patentabilidad** (Art 14 D486)

Novedad (Art 16 D486)

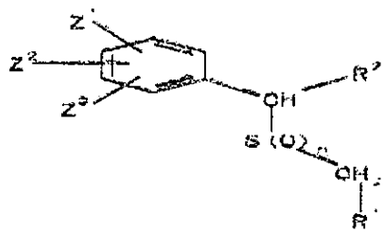
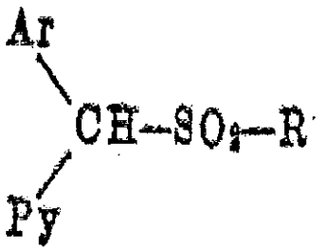
La reivindicación 1 consiste en un compuesto caracterizado porque es representado por la fórmula general (I)



(I)

(Ver folio 228)

Comparación de las características técnicas esenciales, con las del Estado de la Técnica

Características esenciales	D1
 (I)	 (Página 1 líneas 4 a 9)
Anillo de fenilo	Ar Anillo de fenilo
Z^1, Z^2 y Z^3 Cada uno independientemente es hidrógeno, halógeno o un grupo ciano.	Sustituido por 1 a 3 sustituyentes consistentes en alquilo teniendo 1 a 6 átomos de carbono, alcoxi teniendo 1 a 6 átomos de carbono, fenilalquilo teniendo 7 a 10 átomos de carbono, fenoxi, fenilalcoxi teniendo 7 a 10 átomos de carbono, halógeno, amina terciaria y trifluorometilo. (columna 9 reivindicación 1)
CH	**CH**

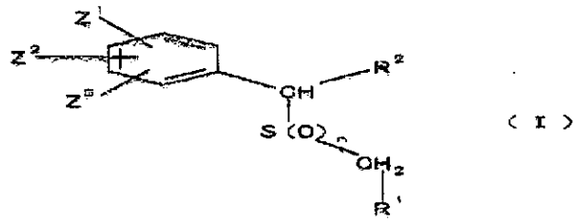
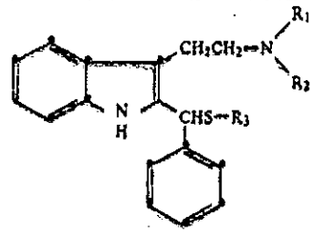
$S(O)_n$ n es 2	SO_2
$CH_2.R_1$ R_1 es C_1-C_6 alquilo	R Radical alquilo inferior
R_2 Grupo heterocíclico aromático monocíclico que contiene nitrógeno de 6 miembros que tiene 1 a 3 grupos sustituyentes	2- Piridilo 5-alcoxi-2- piridilo 5-halo-2- piridilo Alquil-2-piridil. (columna 2 líneas 23 a 26)

Las características esenciales del compuesto de la reivindicación 1 habían sido divulgadas previamente en D1, el cual da a conocer una alquilsulfona aril-piridilmetil sustituida (columna 1, líneas 1 a 17, columnas 3 a 9 ejemplos 1 a 15).

En consecuencia, la reivindicación 1 no es nueva ó carece de novedad, según lo divulgado en el documento D1.

Puesto que las reivindicaciones 2, 3, 7 y 10 no mencionan características nuevas adicionales tampoco se pueden considerar nuevas.

Comparación de las características técnicas esenciales, con las del Estado de la Técnica

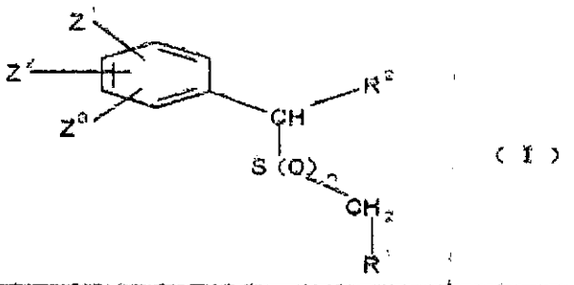
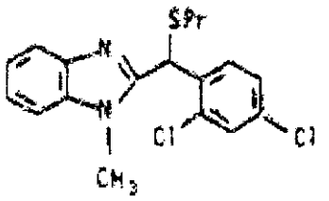
Características esenciales	D2
 (I)	 (columna 1 líneas 10 a 20)
Anillo de fenilo	**Anillo de fenilo**
Z^1, Z^2 y Z^3 Cada uno independientemente es hidrógeno, halógeno o un grupo ciano.	Hidrógeno
CH	CH
$S(O)_n$ n es 0	S
$CH_2.R_1$ R_1 es C_1-C_6 alquilo	R3 Alquilo inferior
R_2 Grupo heterocíclico bicíclico que contiene nitrógeno de 9 o 10 miembros que tiene 1 a 4 grupos sustituyentes	Anillo de indol dialquil etilamino sustituido.

Las características esenciales del compuesto de la reivindicación 1 habían sido divulgadas previamente en D2, el cual da a conocer Un compuesto indol bencil sustituido (columna 1 líneas 10 a 20, columnas 2 a 4, ejemplos 1 a 4)

En consecuencia, la reivindicación 1 no es nueva ó carece de novedad, según lo divulgado en el documento D2.

Puesto que la reivindicación 7 no menciona características nuevas adicionales tampoco se puede considerar nueva.

Comparación de las características técnicas esenciales, con las del Estado de la Técnica

Características esenciales	D3
 (I)	 (página 2092 compuesto 15)
Anillo de fenilo	**Anillo de fenilo**
Z^1, Z^2 y Z^3 Cada uno independientemente es hidrógeno, halógeno o un grupo ciano.	Dos sustituyentes correspondientes a cloro y el otro corresponde a hidrógeno.
CH	**CH**
$S(O)_n$ n es 0	**S**
$CH_2.R_1$ R_1 es C_1-C_6 alquilo	Propilo
R_2 Grupo heterocíclico bicíclico que contiene nitrógeno de 8 o 10 miembros que tiene 1 a 4 grupos sustituyentes	Anillo de benzimidazol metilsustituido

Las características esenciales del compuesto de la reivindicación 1 habían sido divulgadas previamente en D3, el cual da a conocer un compuesto benzimidazol bencil sustituido (página 2092 compuesto 15, Ver folio 244)

En consecuencia, la reivindicación 1 no es nueva ó carece de novedad, según lo divulgado en el documento D3.

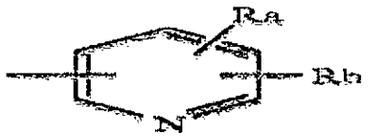
Puesto que la reivindicación 7 no menciona características nuevas adicionales tampoco se puede considerar nueva.

En consecuencia las reivindicaciones 1 – 3, 7 y 10 carecen de novedad.

Nivel Inventivo (Art18 D486)

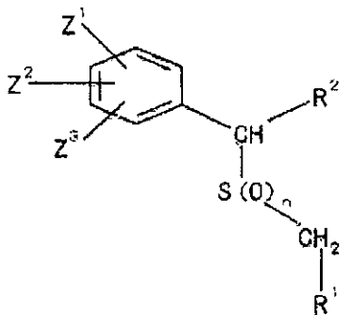
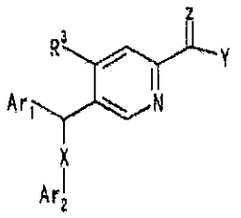
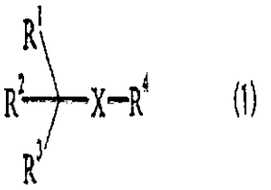
La reivindicación 4 consiste en el compuesto de conformidad con la reivindicación 1, sales del mismo o solvatos del mismo, caracterizado porque R^2 en la fórmula general

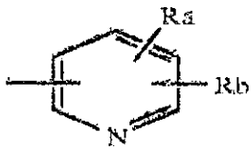
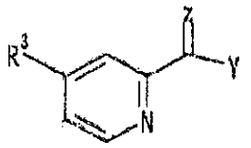
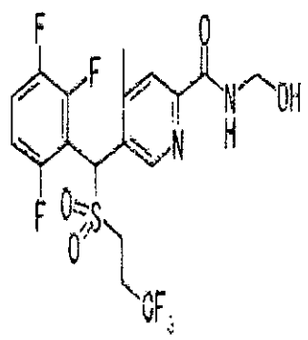
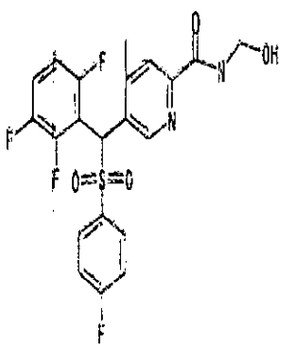
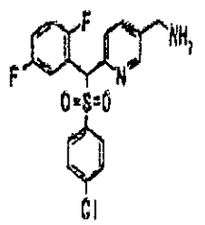
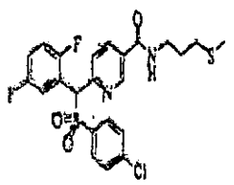
(I) es un grupo representado por la siguiente fórmula (I):



(Ver folio 229)

Comparación de las características técnicas esenciales, con las del Estado de la Técnica

SOLICITUD	D4	D5
		 (I)
Anillo de fenilo	**Ar_1** Grupo fenilo (parágrafo 0010)	**R^3** Q^{31}- Q^{32}- Q^{33}- Q^{34} donde Q^{31},Q^{32} y Q^{33} son un enlace simple y Q^{34} es A^{33} siendo A^{33} un grupo hidrocarbonado (página 4 líneas 27 a 38) siendo este grupo hidrocarbonado un grupo hidrocarbonado cíclico (R^{16}) (página 7 parágrafo 0041)
Z^1, Z^2 y Z^3 Cada uno independientemente es hidrógeno, halógeno o un grupo ciano.	Sustituidos por 1 a 3 sustituyentes seleccionados entre halógeno y alquilo inferior que puede estar sustituido por halógeno o por hidroxilo (parágrafo 0018)	Opcionalmente 1 a 3 sustituyentes seleccionados del grupo que incluye halógeno y grupo ciano (página 8, parágrafo 0048)
CH	**CH**	**C-R^2** R^2 es Q^{21}- Q^{22}- Q^{23}- Q^{24} donde Q^{21},Q^{22} y Q^{23} son un enlace simple y Q^{24} es A^{23} siendo A^{23} un átomo de hidrógeno (página 3 línea 57 a página 4 línea 12) (R^{18}) (página 7 parágrafo 0041)
$S(O)_n$ n es 0	**X** S, SO, SO_2 (parágrafo 0010)	**X** S, SO, SO_2 (página 2 línea 57)

$CH_2.R^1$ R_1 es C_1-C_6 alquilo	Ar_2	R^4 R^4 es Q^{41}-Q^{42}-Q^{43}-Q^{44} donde Q^{41}, Q^{42} y Q^{43} son un enlace simple y Q^{44} es A^{43} siendo A^{43} un grupo hidrocarbonado (página 4 líneas 39 a 53)
R_2  R^a es halógeno o C_1-C_6 alquilo R^b es C_1-C_6 carboxialquilo, carbamoilo, N-alquilcarbamoilo, N,N-di(C_1-C_6 alquilo)carbamoilo N-(C_1-C_6 hidroxialquilo) carbamoilo, carboxi, amino, N-(C_1-C_6 hidroxialquilo) amino o C_1-C_6 alquilsulfonilamino)	 R^3 es hidrógeno, alquilo inferior o halógeno Z es oxígeno o azufre Y es NR^1R^2 donde R^1 es hidrógeno, alquilo inferior o hidroxilo. R^2 es hidrógeno, alquilo inferior que puede estar sustituido, alcanoílo inferior, un grupo alcoxicarbonilo que puede estar sustituido, alcoxi inferior que puede estar sustituido, amino que puede estar sustituido, un grupo fosforo, un grupo fenilo que puede estar sustituido, o un aromático heterocíclico que puede estar sustituido	R^1 R^1 es $(R^5)(R^6)(R^7)$ donde R^5 y R^6 forman un heterociclo insaturado y R^7 corresponde al enlace de insaturación (página 2 línea 58 a página 3 línea 17) (R^{15}) (página 7 parágrafo 0041)
 (ejemplo 4 folio 79)	 (compuesto 13 parágrafo 0131)	 (ejemplo 351 página 226)  (ejemplo 381 página 241)

El documento D4 divulga un compuesto azufrado piridil sustituido (ejemplos 1 a 136)

La diferencia entre la invención, definida en la reivindicación 4 y el compuesto de D4 consiste en el sustituyente Ar^2 de D4 en lugar del grupo CH_2-R^1 reclamado en la solicitud.

El documento D5 divulga un compuesto azufrado trisustituido (página 2 a página 9, parágrafos 0008 a 0049).

La diferencia entre la invención, definida en la reivindicación 4 y el compuesto de D5 consiste en que D5 no divulga específicamente un compuesto que presente el sustituyente CH_2-R^1

El efecto que logra el incluir el sustituyente alquilo correspondiente a CH_2-R^1 es proporcionar nuevos compuestos inhibidores de β-amiloide.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo modificar el compuesto conocido en D4 para proporcionar nuevos compuestos inhibidores de β-amiloide.

Sin embargo, la utilización de un sustituyente alquilo sustituyendo el átomo de azufre para proporcionar nuevos compuestos inhibidores de β-amiloide, ya está divulgada en el documento D5 donde este sustituyente corresponde al grupo R^4 donde R4 es Q41- Q42- Q43- Q44; donde Q41, Q42 y Q43 son un enlace simple y Q44 es A43 siendo A43 un grupo hidrocarbonado (página 4 líneas 39 a 53)

En consecuencia, la persona del oficio normalmente versada en la materia, incluiría el sustituyente alquilo divulgado en D5 como sustituyente del átomo de azufre en el compuesto divulgado en D4 utilizando los sustituyentes carboxi, carboxialquilo, carbamoilo, amino y alquilsulfonilamino sustituyendo el anillo de piridina (Rb en la solicitud) divulgados en D4 y en D5, y el sustituyente halógeno o alquilo (Ra en la solicitud) divulgado en D4 para llegar así al objeto de la reivindicación 4 de la solicitud. Por lo cual se considera obvia.

En conclusión la reivindicación 4 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18).

Puesto que las reivindicaciones 5, 8, 9 y 11 no presentan características inventivas adicionales tampoco se pueden considerar inventivas.

En consecuencia las reivindicaciones 4, 5, 8, 9 y 11 cumplen el requisito de novedad (Art. 16), pero no cumplen con el requisito de nivel inventivo (Art. 18).

7. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US2682544	1 - 3, 7 y 10	Novedad

D2	US4146922	1 y 7	Novedad
D3	Intramolecular Nitrogen-Phosphorus Interactions of Phosphate Esters	1 y 7	Novedad
D4	WO2006109729	4, 5, 8, 9 y 11	Nivel Inventivo
D5	EP1466898	4, 5, 8, 9 y 11	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.

JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
4 OCT. 2012

Elaborado por: Rodolfo Cadena Amaya.
Revisado por: Gloria Jacqueline Alfonso. OKU

intensity) 428 (50, M^+), 412 (99), 411 (100), 396 (75), 381 (85), 365 (80). Anal. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C, 72.79; H, 5.66; N, 6.29.

22,22-Dimethyl-17,27-dioxa-40,41-diazaheptacyclo[27.2.2.2^{12,15}.2^{18,21}.2^{23,26}.1^{2,6}.1^{7,11}]hentetraconta-2,4,6(41),7,9,11(40),12,14,18,20,23,25,29,31,32,34,36,38-octadecaene 40,41-Dioxide (7). Diether dioxide 5 was converted to the dibromide 6 by using the procedure described for 2. The crude product, isolated in 94% yield, was used without purification. The cyclization of 6 to form 7 was carried out in a manner analogous to the preparation of 3, except the dibromide–bis(phenol) solution did not contain $(CH_2)_4O$. Chromatographic purification was accomplished by eluting the product from the silica gel column with 0–10% EtOH in EtOAc. The yield from 225 mg of 6 was 59 mg (23%) of light yellow solid, which was the monohydrate of 7: mp 160–290 °C (gradual decomposition); ^{1}H NMR (50:50 CD_3CN–$CDCl_3$, v/v) δ 1.51 (s, 6, CH_3), 5.18 (s, 4, CH_2O), 6.67 and 7.01 (AB q, 8, J = 8.8 Hz, PhCPh), 7.5 (m, 14, ArH); MS, m/e (relative intensity) 592 (25, M^+), 577 (30), 545 (45), 320 (100), 212 (55), 166 (95). Anal. Calcd for $C_{39}H_{32}N_2O_4 \cdot H_2O$: C, 76.70; H, 5.61; N, 4.59. Found: C, 76.92; H, 5.60; N, 4.62. The ^{1}H NMR spectrum recorded in $CDCl_3$ displayed an AB quartet at 5.12 and 5.20 ppm (J = 14 Hz) for the CH_2 protons.

4,4′-Bis(1,1-dimethylethyl)-2,2′-bipyridine 1,1′-Dioxide (8). A solution of 4,4′-di-*tert*-butyl-2,2′-bipyridine[14] (1.0 g, 3.7 mmol) and *m*-chloroperbenzoic acid (2.6 g, 15 mmol) in 30 mL of CH_2Cl_2 was stirred for 48 h at ambient temperature, diluted to 50 mL with CH_2Cl_2 and washed with 50 mL of aqueous Na_2CO_3. The washings were extracted with 50 mL of CH_2Cl_2, and the combined organic layers were washed with 50 mL of additional Na_2CO_3 solution, dried, filtered, and concentrated to a yellow foam. This foam was chromatographed on 20 g of neutral alumina (Fisher, activity 1, 80–200 mesh), eluting with 0–5% MeOH in CH_2Cl_2, to yield 0.88 g (78%) of 8 as a foam: ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 18, CH_3), 7.29 (d of d, 2, J_1 = 3 Hz, J_2 = 7 Hz, H-5,5′), 7.60 (d, 2, J_1 = 3 Hz, H-3,3′), 8.20 (d, 2, J_2 = 7 Hz, H-6,6′). Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.01; H, 8.03; N, 9.28.

$MeSnCl_3$ Complex Formation with 5, 7, 8, and 9. Stock solutions of 2.00-mL total volume were prepared of each of the ligands and also of $MeSnCl_3$ (handled in an N_2-filled glovebag), in CD_3CN or 50:50 $CDCl_3$–CD_3CN (v/v). Aliquots of the stock solutions were combined to obtain experimental solutions of the compositions listed in Table I. The 90-MHz ^{1}H NMR spectra of the experimental solutions were recorded and were independent of the order in which the component stock solutions were introduced. No solid precipitation was observed.

Dehydrochlorination of 10 in the Presence of 5 and 7. Reactant solutions consisting of 10 (14.0 μL, 12.7 mg, 0.073 mmol), $BuSnCl_3$ (2.7 μL, 4.5 mg, 0.016 mmol), and C_6D_6Cl (0.40 mL) were prepared. Some of the solutions also contained 5 (7.4 mg, 0.017 mmol) or 7 (10.3 mg, 0.017 mmol), and these solutions were made homogeneous by gentle heating before the addition of 10 or $BuSnCl_3$. The reactant solutions were heated to 100 °C as quickly as possible (<5 min) in the probe of the NMR spectrometer, after which spectra were recorded at 10-min intervals. Conversion of the allylic chloride (2 olefinic H, 1 chloroallylic H) to a conjugated diene (4 olefinic H) was monitored by the increase in the ratio of olefinic to chloroallylic protons. Compounds 5 and 7 did not appear to decompose during the experiments.

Acknowledgment. We thank A. M. Mujsce for obtaining the mass spectra and S. L. Haynie for a sample of *trans*-4-chloro-5-decene. Helpful discussions with W. H. Starnes, Jr., are gratefully acknowledged.

Registry No. 1, 95601-80-2; 2, 95601-81-3; 3, 95601-82-4; 4, 95628-38-9; 5, 96259-23-3; 5·$MeSnCl_3$, 96292-57-8; 6, 96259-25-5; 7, 96259-24-4; 7·$MeSnCl_3$, 96292-54-5; 8, 96259-26-6; 8·$MeSnCl_3$, 96292-55-6; 9, 23569-17-7; 9·2$MeSnCl_3$, 96292-56-7; 10, 90370-35-7; $MeOCH_2$-*p*-C_6H_4MgBr, 96259-22-2; *p*-$BrC_6H_4CH_2OMe$, 1515-88-4; $(p\text{-}HOC_6H_4)_2C(CH_3)_2$, 80-05-7; $MeSnCl_3$, 993-16-8; (*E*,*E*)-$CH_3CH_2CH{=}CHCH{=}CH(CH_2)_3CH_3$, 92260-75-8; 6,6′-dibromo-2,2′-bipyridine, 49669-22-9; 2,6-bis(mercaptomethyl)naphthalene, 43012-09-5; 4,4′-di-*tert*-butyl-2,2′-bipyridine, 72914-19-3.

Intramolecular Nitrogen–Phosphorus Interactions of Phosphate Esters

Dean F. Bushey,* Brenda F. Johnson, and Jamin Huang

Union Carbide Agricultural Products Company, Research Triangle Park, North Carolina 27709

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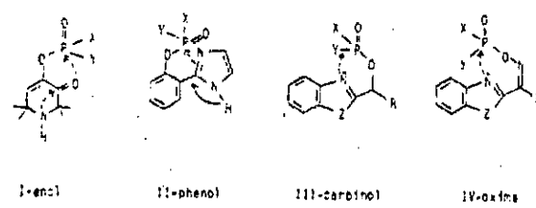
Four different classes of phosphate esters derived from enols, phenols, carbinols, and oximes have been shown to undergo intramolecular rearrangements assisted by a neighboring nitrogen. The unexpected products from these rearrangements have been characterized by spectral methods, especially ^{13}C NMR. Rearrangements involving the *O*-ethyl *S*-propyl thiophosphate group have led to particularly interesting results.

The reaction of phosphate esters with acetylcholinesterase is an important biological process in insect control. In this process, the imidazole group of histidine is assumed to be responsible for activation of the serine hydroxyl, which in turn displaces a ligand of the phosphate insecticide.[1a] An analogous rate acceleration by neighboring amide or amine functionalities in phosphate ester hydrolysis has been documented by several investigators.[1b-f] The implications of this type of intramolecular interaction on the preparation, stability, and biological activity of potential organophosphate insecticides containing a distal nitrogen have not been addressed.

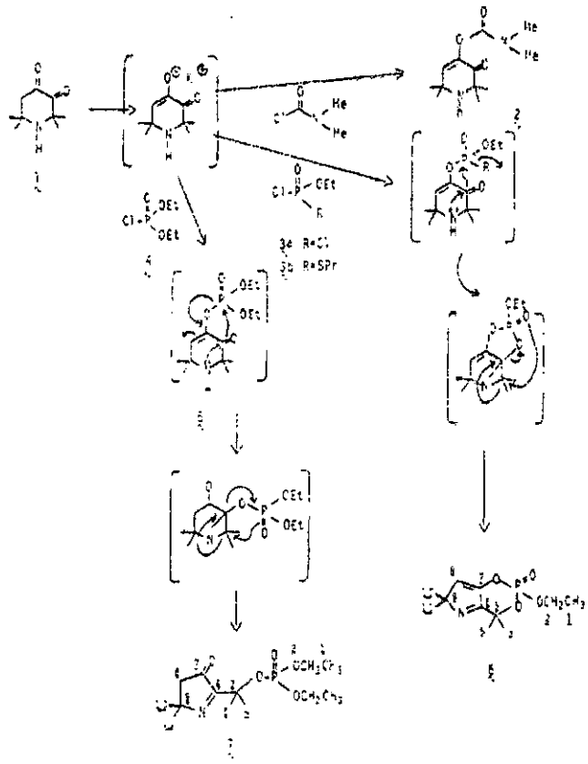
Scheme I



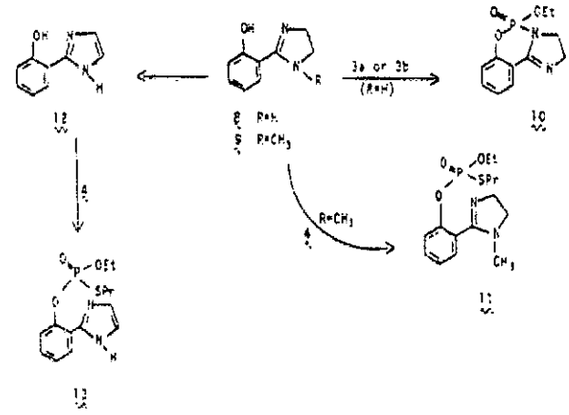
(1) (a) Eto, M. "Organophosphorus Pesticide: Organic and Biological Chemistry", CRC Press: Cleveland, OH 1974; pp 123–144; (b) Sharma, R. K.; Vaidyanathaswamy, R. *J. Org. Chem.* **1982**, *47*, 1741. (c) Naylor, R. A.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1908. (d) Kluger, R.; Chan, J. L. W. *J. Am. Chem. Soc.* **1976**, *98*, 4913. (e) Lazarus, R. A.; Benkovic, P. A.; Benkovic, S. J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 373. (f) Lazarus, R. A.; Benkovic, S. J. *J. Am. Chem. Soc.* **1979**, *101*, 4300.

0022-3263/85/1950-2091$01.50/0

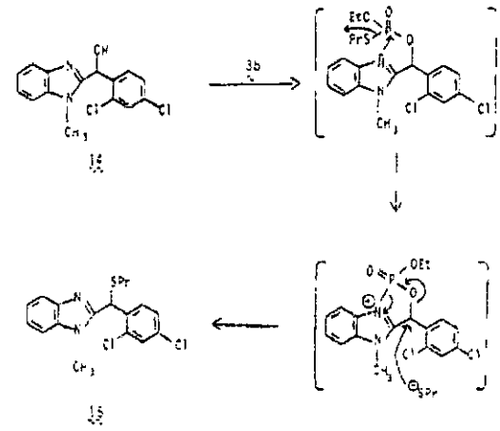
Scheme II



Scheme III



Scheme IV



In the course of studies on novel phosphate esters and thio esters, a number of rearrangements involving a nitrogen atom and having important synthetic consequences have been discovered. These results have also demonstrated some important reactivity differences between the standard diethyl phosphates and the more recently introduced *O*-ethyl *S*-propyl thiophosphates as exemplified by the commercial compound profenfos.

Intramolecular rearrangement promoted by neighboring nitrogen has been observed for phosphate esters and thio esters derived from enols (I), phenols (II), carbinols (III), and oximes (IV) (Scheme I). The extent of interaction is dependent on the nitrogen basicity and the spatial relationship of the involved nitrogen and phosphorus atoms. Although such an effect has been observed in the diethyl phosphate cases (X, Y = OEt), this interaction can be more clearly demonstrated in the thio ester analogues (X = OEt; Y = SPr).

Results

The phosphorylation of the potassium salt of 2,2,6,6-tetramethylpiperi-3,4-dione, 1,[2] in the tetrahydrofuran produced an unexpected result because of an intramolecular nitrogen participation (Scheme II). When the anion of 1 generated by potassium *tert*-butoxide was quenched with dimethylcarbamoyl chloride, the expected carbamate, 2, was isolated. When the same anion was quenched with chlorophosphates **3a** and **3b**, the cyclic phosphate 6 was the only phosphorus–piperidione adduct isolated from column chromatography (18% from **3a**, 10% from **3b**). The only other product isolated in sufficient quantity and purity to establish structural assignments was the starting material 1.

A proposed mechanism for the formation of 6 is shown in Scheme II. The key as to which pathway is followed is determined by the leaving abilities of the phosphate ligands (i.e., Cl ≅ SPr > enol > OEt).

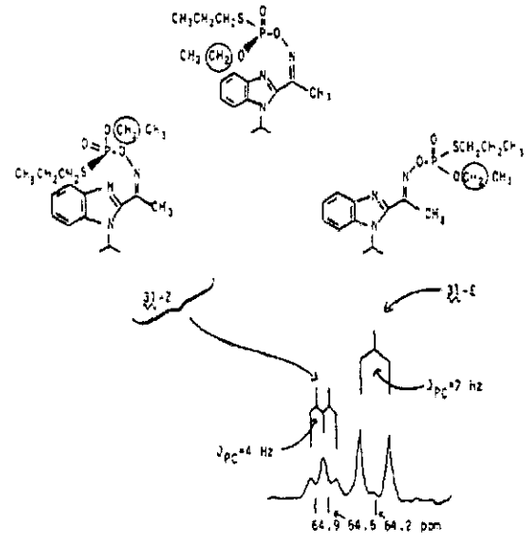
The structural assignment of 6 is based on spectral data. The three unexpected observations which needed to be accommodated by the proposed structure were (1) a lack of an SPr group in the NMR and ^{13}C NMR, (2) a lack of any strong carbonyl stretches in the IR, and (3) an unusually large upfield phosphorus shift in the ^{31}P NMR. Structure 6 addresses these observations and is consistant with all other spectral data, including the extensive phosphorus–carbon and phosphorus–hydrogen coupling, the UV extinction coefficient, and the elemental analysis. Attempts to obtain an X-ray crystal structure on the plate-like crystals which slowly formed in the freezer were unsuccesful.

Quenching of the anion of 1 with diethyl chlorophosphate, 4, followed by column chromatography gave a 17% yield of compound 7. Structure 7 was derived from a similar mechanism as previously presented for compound 6 but with the enol moiety acting as the leaving group. The key as to which pathway is followed is determined by the leaving abilities of the phosphate ligands (i.e., Cl ≅ SPR > enol > OEt). The ^{13}C NMR and IR of 7 were especially useful in assigning the proposed structure.

A direct interaction between the nitrogen and the phosphorus was demonstrated in area II and III (Scheme I). When o-(2-imidazolinyl)phenol 8[3] was reacted with the phosphorochloridate **3b** in the presence of triethylamine, the compound isolated with the tricyclic phosphate 10 (Scheme III). Compound 10 was also prepared from ethyl dichlorophosphate **3a** to confirm the structure. The *N*-methyl analogue 9 was phosphorylated to give the product

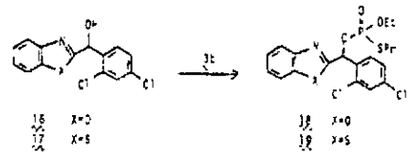
(2) Pilo-Veloso, D.; Rassat, A. *Bull. Chem. Soc. Fr.* **1978**, *11-12*, 621.

Scheme V



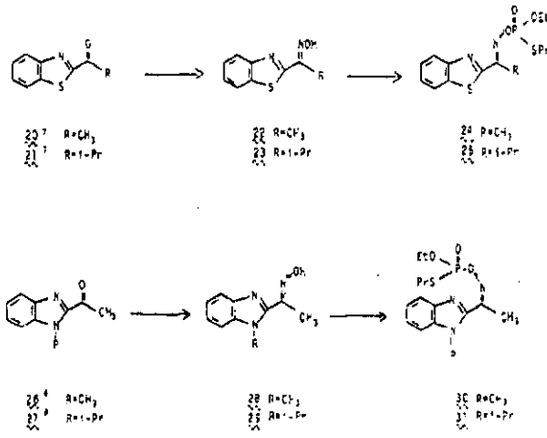
11. Oxidation of 8 to its imidazole analogue 12[3] reduced the nucleophilicity of the nitrogen sufficiently to allow preparation of the phenyl thiophosphate 13.

More surprising is the attempted phosphorylation of the benzimidazolylcarbinol 14 with 3b (Scheme IV). Instead of the expected simple product of alcohol phosphorylation, the product isolated from the reaction mixture was the SPr adduct 15. The postulated mechanism is depicted in Scheme IV. The instability of the carbinol phosphate is unique to the benzimidazole series because the phosphates derived from benzothiazole and benzoxazole 18 and 19,



respectively, were easily formed. Again, as in the case of 8 vs. 12, this is presumably from reduced basicity of the nitrogen interacting with the phosphate.

Finally, a more subtle interaction was observed in the oxime phosphate area IV. The oxime phosphates 24 and 25 were prepared via standard procedures. The phosphate



24 was obtained as a single *E* isomer (i.e., phosphate cis to CH_3; R = CH_3 single peak in NMR (δ 2.63) and ^{13}C NMR is consistent for one isomer). Compound 25 was a mixture of the *E* and *Z* isomers as indicated by the ^{13}C NMR spectrum. Especially diagnostic because of its separation from other peaks is the α-carbon of the POCH_2CH_3 groups (for 25 two doublets; J_{PC} = 7 and 9 Hz). Based on our experience with 24, one would have to expect 30 to be a single *E* isomer, however, ^{13}C NMR analysis indicated both *E* and *Z* isomers to be present. Furthermore, the *Z* isomer was resolved in the ^{13}C NMR spectrum into rotational isomers. The benzimidazole nitrogen apparently exerts sufficient influence on the phosphate to partially stabilize the *Z* isomer, and that interaction is sufficient to hinder rotation presumably around the P–O bond. The same argument holds for 31 as is diagrammed in Scheme V.

Conclusion

Three cases of intramolecular rearrangements of phosphate esters involving neighboring group participation by nitrogen have been presented. In a fourth case, the oxime phosphates, the interaction of nitrogen with the phosphate group, appears to exert a regioselective control over the course of the oxime phosphorylation of *O*-ethyl *S*-propyl chlorothiophosphate. The observed extent of neighboring group participation by nitrogen appears to be dependent on nitrogen basicity, steric strain, spatial relationships, and thermodynamic stability of the possible products. The intramolecular interaction of nitrogen and phosphorus as an influence on biological activity has yet to be demonstrated.

Experimental Section

All melting points are uncorrected. IR spectra were taken on a Perkin-Elmer Model 197 spectrometer. NMR spectra were obtained on a Varian EM-360 spectrometer at 60 MHz with $(CH_3)_4Si$ as an internal standard. ^{13}C NMR and ^{31}P NMR spectra were obtained on a JOEL FX-900 spectrometer with $(CH_3)_4Si$ as an internal standard for the ^{13}C NMR and H_3PO_4 as a standard for the ^{31}P spectra. C, H, and N elemental analyses were performed by either the Technical Center Analytical Group or Galbraith Analytical Laboratories.

General Procedure for the Preparation of Compounds 2, 6 and 7. An equivalent of 2,2,6,6-tetramethylpiperi-3,4-dione, 1, was dissolved in THF under a nitrogen atmosphere. To this was added 1 equiv of potassium *tert*-butoxide. The mixture was refluxed for 2 h and cooled to 25 °C before 1 equiv of the appropriate phosphoryl or carbamoyl chloride was added dropwise as a THF solution. The reaction mixture was stirred at 25 °C overnight and worked up as follows.

Compound 2: The general procedure described above using dimethylcarbamoyl chloride was followed. The final reaction mixture was filtered and concentrated in vacuo to give a yellow solid residue. Trituration with hexane gave a 45% yield of 2 as a white solid: mp 114–116 °C; NMR ($CDCl_3$) δ 7.16 (s, 1, vinyl), 4.33 (br s, 1, NH), 3.07 (s, 6, $N(CH_3)_2$), 1.53 (s, 6, *gem*-dimethyl), 1.35 (s, 6, *gem*-dimethyl); IR ($CHCl_3$) 3700–3200, 2998, 2950, 1735, 1385, 1170 cm^{-1}. Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.97; H, 8.39; N, 11.66. Found: C, 59.89; H, 8.46; N, 11.57.

Compound 6: The general procedure described above using either ethyl dichlorophosphate (3a) or *O*-ethyl *S*-propyl phosphorochloridate (3b) was followed. The reaction mixture was quenched with ether/H_2O and the layers were separated. The ether layer was washed with H_2O (2×) and the original H_2O layer was washed with ether (2×). The combined ether solutions were washed with 0.5 M NaOH (2×), saturated NaCl (1×), dried ($MgSO_4$), and concentrated in vacuo to give a brown liquid residue. This was chromatographed on a Florisil column (10% EtOAc–hexane → 35% EtOAc–hexane) to give compound 6 as a clear oil that slowly solidifies in the freezer (18% from 3a, and 10% from 3b): TLC single Fluorescent spot, R_f 0.17 (50:50 EtOAc/hexane on silica gel); mp 41–43 °C ($CDCl_3$); δ 6.57–6.40 (m, 1, CH, fine splitting), 4.17 (dq, 2, OCH; J_{PH} = 9 Hz), 1.76 (d, 6, $(CH_3)_2CO$, J_{PH} = 1.2 Hz), 1.35 (t, 3, OCH_2CH_3, J = 7 Hz), 1.35 (s, 6, $(CH_3)_2CN$); IR ($CHCl_3$) 3000, 1660, 1580, 1300, 1040, 1020, 1010 cm^{-1}; ^{31}P NMR ($CDCl_3$) δ (H_3PO_4) −12.1 ppm; mass spectrum (70

ev), *m/e* (relative intensity) 259 (18), 232 (13), 216 (36), 151 (56), 140 (14), 136 (15), 134 (15), 133 (35), 123 (100), 99 (40), 83 (46), 69 (72), 55 (74); UV (EtOH) 237 nm (ε 5037); ^{13}C NMR ($CDCl_3$) follows (numbering shown in Scheme II):

carbon	ppm	multiplicity decoupled	J_{PC}	multiplicity, off-resonance
7	165.9	d	9 Hz	d
6	142.7	d	5.5 Hz	d
8	135.2	d	8 Hz	dd
3	55.4	d	9 Hz	d
9	74.3	s		s
2	65.2	d	6 Hz	dt
4	28.7	d	5.5 Hz	dq
5	27.7	d	2.5 Hz	dq
10				
11	16.2	s		q
1	16.0	d	7 Hz	dq

Anal. Calcd for $C_{11}H_{18}NO_4P$: C, 50.96; H, 7.00; N, 5.40. Found: C, 51.41; H, 7.00; N, 5.13.

Compound 7: The general procedure described above using diethyl chlorophosphate (4) was followed. The reaction mixture was simply concentrated and purified by dry column chromatography on silica gel to give compound 7 (17% yield): TLC single spot, R_f 0.43 (80:20 EtOAc/hexane on silica gel); NMR ($CDCl_3$) δ 4.33–3.67 (m, 4, OCH_2), 2.37 (s, 2, CH_2), 1.73 (s, 6, *gem*-dimethyl), 1.57–1.07 (m, 12, OCH_2CH_3 and *gem*-dimethyl singlet at 1.37); IR (neat) 3700–3200, 2998, 1740, 1370, 1020 cm^{-1}; ^{13}C NMR ($CDCl_3$) (numbering shown in Scheme II):

carbon	ppm	multiplicity decoupled	J_{PC}	multiplicity off-resonance
7	201.5	s		s
6	170.1	d	5 Hz	d
3	80.2	d	7 Hz	d
9	64.6	s		s
2	63.7	d	6 Hz	dt
8	49.2	s		t
10				
11	30.9	s		q
4	29.9	s		q
5	26.6	d	5 Hz	dq
1	16.1	d	7 Hz	dq

Anal. Calcd for $C_{13}H_{24}NO_4P$: C, 51.14; H, 7.92; N, 4.59. Found: C, 50.95; H, 8.03; N, 4.48.

Standard Phosphorylation Procedure. The typical procedure for phosphorylation was to dissolve the alcohol, phenol, or oxime in either CH_2Cl_2 or toluene and add 1 equiv of TEA or 4-(dimethylamino)pyridine. To this solution was added, dropwise, 1 equiv of the chlorophosphate. The reaction mixture was stirred at 25 °C overnight, washed with H_2O and aqueous NaOH (if possible), dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified via chromatography.

Preparation of 10: See the above standard phosphorylation procedure starting with the phenol 8[3] (2 equiv of TEA were used with 3a): 44% yield; NMR ($CDCl_3$) δ 8.30–7.87 (m, 1, Ar), 7.83–6.93 (m, 3, Ar), 4.67–3.67 (m, 6), 1.37 (t, 3, OCH_2CH_3, J = 4 Hz); IR (CH_2Cl_2) 3540–2760, 1600, 1405, 1240, 1019 cm^{-1}; ^{13}C NMR ($CDCl_3$) ppm 154.7 (d, J = 5 Hz), 151.7 (d, J = 7 Hz), 133.7 (d, J = 1 Hz), 128.3, 124.7, 118.6 (d, J = 12 Hz), 114.7 (d, J = 3 Hz), 65.0 (d, J = 7 Hz), 54.9 (d, J = 14 Hz), 44.9 (d, J = 4 Hz), 16.1 (d, J = 6 Hz). Anal. Calcd for $C_{11}H_{13}N_2O_3P \cdot H_2O$: C, 48.89; H, 5.60; N, 10.37. Found: C, 48.33; H, 5.56; N, 9.97.

Preparation of 11: The standard phosphorylating procedure described above was used on compound 9. Column chromatography purification gave 11 in 18% yield: NMR ($CDCl_3$) δ 8.00–6.67 (m, 4, Ar), 4.67–3.23 (m, 6), 3.23–2.37 (m, 5, SCH_2, and NCH_3 singlet at 2.73), 2.13–0.67 (m, 8); IR (CH_2Cl_2) 3400–2740, 1585, 1400, 1240, 1030 cm^{-1}; ^{13}C NMR ($CDCl_3$) ppm 164.4, 147.9 (d, J = 8 Hz), 131.0 (d, J = 1 Hz), 130.6, 125.2 (d, J = 1 Hz), 123.4 (d, J = 7 Hz), 120.7 (d, J = 3 Hz), 64.4 (d, J = 7 Hz), 53.3, 52.9, 35.0, 33.1 (d, J = 4 Hz), 24.1 (d, J = 7 Hz), 16.0 (d, J = 7 Hz), 13.1. Anal. Reference 4.

Preparation of 13: The standard phosphorylating procedure described above was used on compound 12.[5] Column chromatography purification gave 13 in 24% yield. NMR ($CDCl_3$) δ 10.0–8.93 (br, 1 NH), 8.40–8.05 (m, 1, Ar), 7.53–7.00 (m, 5, Ar), 4.67–3.90 (m, 2, OCH_2), 3.10–2.40 (m, 2, SCH_2), 2.07–0.67 (m, 8); IR (neat) 3800–1980, 1598, 1420, 1175 cm^{-1}; ^{13}C NMR ($CDCl_3$) ppm 146.3 (d, J = 9 Hz), 142.2 (d, J = 1 Hz), 129.6, 129.3 (d, J = 2 Hz), 125.4 (d, J = 1 Hz), 122.5 (representing two imidazole carbons), 122.1 (d, J = 6 Hz), 120.6 (d, J = 3 Hz), 64.4 (d, J = 7 Hz), 32.8 (d, J = 4 Hz), 23.5 (d, J = 7 Hz), 15.6 (d, J = 7 Hz), 12.5.

General Procedure for the Preparation of 14, 16, and 17.[5] The desired *N*-methylbenzimidazole, benzoxazole, or benzothiazole was dissolved in ether, cooled to −78 °, treated with 1 equiv of *n*-butyllithium, and stirred for 0.5 h before quenching with 1 equiv of 2,4-dichlorobenzaldehyde dissolved in ether. The reaction mixture was allowed to warm to 25 °C overnight and quenched with 10% aqueous NH_4Cl solution. The mixture was extracted with ether (3×) and the combined ether extracts were washed with saturated NaCl, dried ($MgSO_4$), and concentrated in vacuo to give a crude solid residue which was recrystallized from hexane/EtOAc.

Compound 14: 41% yield; mp 189–193 °C; NMR (Me_2SO-d_6) δ 7.93–7.10 (m, 7, Ar), 6.68 (br, 1, OH), 6.25 (s, 1, CH), 3.93 (s, 3, $NHCH_3$). Anal. Calcd for $C_{16}H_{12}Cl_2N_2O$: C, 58.65; H, 3.93; N, 9.12. Found: C, 58.55; H, 4.01; N, 8.91.

Compound 16: 48% yield; mp 123–125 °C; NMR ($CDCl_3$) δ 7.68–7.12 (m, 7, Ar), 6.43 (s, 1, CH), 5.50 (br, 10 H). Anal. Calcd for $C_{14}H_9Cl_2NO_2$: C, 57.16; H, 3.08; N, 4.76. Found: C, 57.07; H, 3.08; N, 4.66.

Compound 17: 71% yield; mp 120–122 °C; NMR ($CDCl_3$) δ 8.00–7.15 (m, 7, Ar), 6.50 (s, 1, CH), 5.05 (br, 1, OH). Anal. Calcd for $C_{14}H_9Cl_2NOS$: C, 54.20; H, 2.92; N, 4.52. Found: C, 54.24; H, 3.07; N, 4.54.

Preparation of 15: The standard phosphorylating procedure described above was used on compound 14. Florisil chromatography followed by recrystallization in hexane/EtOAc gave 15 in 18% yield: mp 66–69 °C; NMR ($CDCl_3$) δ 7.90–7.15 (m, 7, Ar), 5.79 (s, 1, CH), 3.73 (s, 3, NCH_3), 2.52 (t, 2, SCH_2, J = 7 Hz), 1.60 (m, 2), 0.97 (t, 3, $SCH_2CH_2CH_3$, J = 7 Hz); IR (CH_2Cl_2) 2940, 1572, 1481, 1450, 1085 cm^{-1}; ^{13}C NMR ($CDCl_3$) ppm 142.4 (coupled s), 135.8 (s), 134.9 (s), 134.2 (s), 133.5 (s), 132.4 (d), 128.8 (d), 128.1 (d), 122.8 (d), 122.1 (d), 120.1 (d), 109.1 (d), 41.2 (d), 33.9 (t), 29.8 (q), 22.6 (t), 13.5 (q). Anal. Calcd for $C_{19}H_{18}Cl_2N_2S$: C, 59.18; H, 4.98; N, 7.86. Found: C, 59.52; H, 5.05; N, 7.72.

Preparation of 18 and 19.[5] Both compounds prepared by standard phosphorylating procedure described above.

Compound 18: 27% yield from Florisil; NMR ($CDCl_3$) δ 7.95–7.20 (m, 7, Ar), 7.07 (d, 1, J_{PH} = 11 Hz), 4.45–3.90 (m, 2, OCH_2), 3.10–2.55 (m, 2, SCH_2), 1.95–0.75 (m, 8); IR (neat) 2950, 1462, 1438, 1250, 995 cm^{-1}. Anal. Calcd for $C_{19}H_{20}Cl_2NO_4PS$: C, 49.47; H, 4.38; N, 3.04. Found: C, 49.91; H, 4.51; N, 2.96.

Compound 19: 9% yield from Florisil; NMR ($CDCl_3$) δ 8.15–7.10 (m, 8), 4.50–3.90 (m, 2, OCH_2), 3.10–2.50 (m, 2, SCH_2), 1.90–0.75 (m, 8). Anal. Calcd for $C_{19}H_{20}Cl_2NO_4PS$: C, 47.90; H, 4.23. Found: C, 47.50; H, 4.39.

General Procedure for Preparation of Oximes 22, 23, 28, and 29. The ketones were dissolved in ~5% aqueous MeOH or EtOH solution. To this was added 2 equiv of hydroxylamine

(3) (a) Roger, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* (a) 1976, *96*, 2463; (b) 1974, *96*, 2473. (c) Overberger, C. G.; Shen, Chah-Moh *Ibid.* 1971, *93*, 6992. (d) Beger, J.; Wagner, G.; Dinjus, V.; Gorls, H.; Uhlig, E.; Sieler, J. *J Prakt. Chem.* 1983, *325*, 211.

(4) Samples were analyzed by both high resolution mass spectrometry and elemental analysis. Neither method gave satisfactory values because of instability. Reanalysis of the MS sample via ^{13}C NMR indicated decomposition (usually back to the oxime) had occurred. Silica gel chromatography also causes decomposition and loss of sample on the column.

(5) See: (a) Barnard, J.; Metzger, J. *Bull. Soc. Chim. Fr.* 1962, 2072. (b) Gilman, H.; Beel, J. A. *J. Am. Chem. Soc.* 1949, *71*, 2328.

(6) Huang, J. U.S. Patent 4425338 (Union Carbide Co.), 1984.

(7) Compounds 20 and 21 were prepared by reaction of the lithium enolate of benzothiazole with the appropriate esters at −78 °C. Compound 20 previously reported by another procedure: (a) Zubarovsky, V. M. *J. Gen. Chem. USSR* 1951, *21*, 2199; *Chem. Abstr.* 1951, *46*, 8098f. (b) Kendall, J. D.; Duffin, G. F.; Voltz, J. Brit. Pat. 1961, 885520; *Chem. Abstr.* 1961, *57*, 7429b.

(8) Same procedure as ref 7 except using benzimidazole as starting material. Compound 26 reported in ref 7b.

hydrochloride and 2 equiv of potassium carbonate. This mixture is refluxed overnight and allowed to cool and collect precipitate.

Compound **22**: mp 198–200 °C; NMR (Me_2SO-d_6) δ 8.40–7.20 (m, 4, Ar), 3.57–3.07 (m, 1, NOH), 2.37 (s, 3, CH_3); IR (KBr) 3500–2500 (br), 1500, 1322, 921 cm^{-1}. Anal. Calcd for $C_9H_9N_2SO$: C, 56.33; H, 4.19; N, 14.58. Found: C, 56.02; H, 4.11; N, 14.43.

Compound **23**: mp 118–123 °C; NMR ($CDCl_3$) δ 8.30–7.20 (m, 4, Ar), 3.85 (septet, 1, J = 7 Hz), 1.51 (d, 3, J = 7 Hz), 1.40 (d, 3, J = 7 Hz); IR (CH_2Cl_2) 3525, 3260 (br), 2940, 1440, 955 cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: C, 60.00; H, 5.50; N, 12.62.

Compound **28**: mp 215–218 °C; NMR (Me_2SO-d_6) δ 7.83–7.07 (m, 4, Ar), 5.40–3.23 (4, br singlet for NOH and singlet at 4.00 for NCH_3), 2.37 (s, 3, CH_3); IR (KBr) 3700–2100, 1550–1410, 1362, 1325, 1262, 1020, 930 cm^{-1}. Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 62.76; H, 5.64 N, 21.75.

Compound **29**: mp 165–168 °C; NMR ($CDCl_3$/Me_2SO-d_6) δ 8.03–7.00 (m, 4, Ar), 6.03–5.23 (m, 1, CH), 4.03–2.73 (m, 3, (H_2O), s, 3.35 NOH), 2.47 (s, 3, CCH_3), 1.65 (d, 6, dimethyl multi, J = 6): IR (KBr) 3500–2400 (br), 1400, 1362, 1290, 1020, 745 cm^{-1}. Anal. Calcd for $C_{12}H_{16}N_3O{\cdot}H_2O$: C, 61.28; H, 7.29; N, 17.88. Found: C, 61.13; H, 7.29; N, 17.65.

Preparation of Phosphates 24, 25, 30, and 31. These phosphates were prepared by the standard phosphorylating procedure described above. The final organic solutions were not washed with base and were not chromatographed so as not to effect the isomer ratio. The impurities were of a small proportion that it did not interfere with ^{13}C NMR interpretation of the condensed oxime phosphate. Elemental analyses of the crude products were all equally low (2.5%) in carbon, correct for hydrogen, and ~1% low in nitrogen. Subsequent attempts at chromatography led to considerable decomposition on the column.

Compound **24**: NMR ($CDCl_3$) δ 8.33–7.00 (m, 4, Ar), 4.80–3.97 (m, 2, $-POCH_2CH_3$), 3.37–2.67 (m, 2, $SCH_2CH_2CH_3$), 2.63 (s, 3, CH_3), 2.20–1.62 (m, 2, $SCH_2CH_2CH_3$), 1.47 (t, 3, OCH_2CH_3, J = 4 Hz), 1.07 (t, 3, $SCH_2CH_2CH_3$, J = 5 Hz); IR (CH_2Cl_2) 3100–2700 (br), 1370, 1332, 910 cm^{-1}.

Compound **25**: NMR ($CDCl_3$) δ 8.30–7.20 (m, 4, Ar), 4.73–3.60 (m, 2, OCH_2CH_3), 3.47–2.63 (m, 1, CH), 3.96–0.63 (m, 8): IR (neat) 3700–2500 (br), 1798, 1710, 1558, 1462, 1395, 1163, 1100, 660, 620 cm^{-1}.

Compound **30**: NMR ($CDCl_3$) δ 8.00–7.10 (m, 4, Ar), 4.67–3.90 (m, 5, NCH_3 singlet at 4.07), 2.95 (m, 2, SCH_2), 2.63 (s, 3, CH_3), 2.27–1.20 (m, 2), 1.42 (t, 3, OCH_2CH_3, J = 5 Hz), 1.00 (t, 3, $SCH_2CH_2CH_3$, J = 4 Hz); IR (neat) 3700–2000, 2000–1700 (br), 1609 cm^{-1}.

Compound **31**: NMR ($CDCl_3$) δ 8.00–7.00 (m, 4, Ar), 6.00–5.37 (m, 1, CH), 4.67–3.93 (m, 2, $-OCH_2-$), 3.33–2.75 (m, 2, $-SCH_2-$), 2.63 (s, 3, CH_3), 2.17–1.53 (m, 8), 1.38 (t, 3, $-OCH_2CH_3$, J = 6 Hz), 1.00 (t, 3, $-SCH_2CH_2CH_3$, J = 6 Hz); IR (neat) 3600–2200 (br), 1610, 1340, 1200, 1140, 680 cm^{-1}.

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Registry No. 1, 70510-23-5; 2, 96327-78-5; 3a, 1498-51-7; 3b, 7651-98-1; 4, 814-49-3; 6, 96327-79-6; 7, 96327-80-9; 8, 1565-39-5; 9, 96327-81-0; 10, 96327-82-1; 11, 96327-83-2; 12, 52755-90-5; 13, 96327-84-3; 14, 96327-85-4; 15, 96327-86-5; 16, 89204-68-2; 17, 96327-87-6; 18, 89204-57-9; 19, 89204-65-9; 20, 1629-78-3; 21, 96327-88-7; 22, 1629-79-4; 23, 96327-89-8; 24, 96327-90-1; (*E*)-25, 96327-95-6; (*Z*)-25, 96327-91-2; 26, 942-25-6; 27, 31539-67-0; 28, 945-78-8; 29, 96327-92-3; (*E*)-30, 96327-93-4; (*Z*)-30, 96327-96-7; (*E*)-31, 96327-94-5; (*Z*)-31, 96327-97-8; Me_2NCOCl, 79-44-7; 2,4-dichlorobenzaldehyde, 874-42-0; *N*-methylbenzimidazole, 1632-83-3; benzoxazole, 273-53-0; benzothiazole, 95-16-9.

Acyclic Stereoselection. 25. Stereoselective Synthesis of the C-1 to C-7 Moiety of Erythronolide A[1,2]

Clayton H. Heathcock,* Steven D. Young,[3a] James P. Hagen,[3b] Ronaldo Pilli,[3c] and Ulrich Badertscher[3d]

Department of Chemistry, University of California, Berkeley, California 94720

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A stereoselective synthesis of aldehyde ester 1, a synthon for the C-1 to C-7 section of erythronolide A, is reported. The synthesis begins with β,γ-unsaturated aldehyde 12, which is prepared from mesityl oxide as shown in eq 2. Aldehyde 12 reacts with the preformed lithium enolates of reagents 13 and 5 to give, in each case, a 15:1 mixture of two aldols (eq 3 and 4). Reduction of the major isomer 16 from the reaction of 5 with 12 with lithium aluminum hydride followed by periodate cleavage of the resulting vicinal diol provides β-hydroxy aldehyde 20. This material is protected as the triethylsilyl derivative 21, which is treated with the lithium enolate of BHT *O*-benzyllactate (22c). The resulting 5:1 mixture of aldols is converted into acetonides 27c and 28c, which are separated by chromatography. The stereostructure of the major acetonide 27c was elucidated by single-crystal X-ray analysis (Figure 1). Lithium aluminum hydride reduction of 27c gives alcohol 29, which is converted into acetate 34. Ozonolysis of this material gives aldehyde 35, which is oxidized by pyridinium dichromate in DMF. Diazomethane esterification provides diester 36, which is methanolized to hydroxy ester 37. Swern oxidation of 35 provides racemic ester aldehyde 1. Enantiomerically homogeneous 1 is obtained in a similar sequence, via the *O*-methylmandelates 39a and 39b.

In previous papers in this series, we have reported the development of useful strategies and reagents for the stereorational synthesis of complex organic molecules having many stereocenters. In this paper, we report the application of two of these reagents in a synthesis of 1, the

(1) For part 24, see: Heathcock, C. H.; Hagen, J. P.; Young, S. D.; Pilli, R.; Bai, D. L.; Märki, H.-P.; Kees, K.; Badertscher, U. *Chim. Scr.*, in press.

(2) The work reported in this paper was reported in preliminary form at the Fourth International Conference on Organic Synthesis, Tokyo, Japan, August 22–27, 1982. Heathcock, C. H. In "Current Trends in Organic Synthesis"; Nozaki, H., Ed.; Pergamon Press: Oxford and New York, 1983.

(3) Present address: (a) Research Laboratories, Merck Sharp & Dohme, West Point, PA 19486. (b) Department of Chemistry, University of Nebraska, Omaha, NE 68182. (c) Universidade Estandual de Campinas, Barao Geraldo, Campinas S.P., Brasil 13.100. (d) Lonza, Inc., P.O. Box 1400, La Porte, TX 77571.

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