

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
RAD: 7-137508- -13	FECHA: 2013-09-24 11:42:54
DEP: 2020 DIRECCION DE NUEVAS CREACIONES	EVE: 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS: 6
ACT: 519 PRESENTACION	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
LUIS FELIPE CASTILLO GIBSON

Asunto: Radicación: 7-137508- -13
Trámite: 11
Evento: 378
Actuación: 519
Oficio: 18269
Folios: 6

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/EP2006/005761				
Fecha de Presentación Internacional	14/06/2006				

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:	Radicado N° 07-137508-00000-0000	28/Diciembre/2007
Reivindicaciones:	Radicado N° 07-137508-00000-0000 Radicado N° 07-137508-00007-0000 Radicado N° 07-137508-00010-0000	28/Diciembre/2007 13/Septiembre/2011 21/Agosto/2012.
Prioridad:	US 60/691,361 US 60/726,509	16/junio/2005 12/Octubre/2005

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: "INGREDIENTE FARMACÉUTICO ACTIVO EN BASE A

CANABINOIDE PARA FORMAS DE DOSIS MEJORADAS"

El problema planteado en esta solicitud consiste en proveer un ingrediente mejorado, farmacéuticamente activo de cannabinoide estable, que se puede utilizar para preparar forma de dosis mejoradas de THC para administrar a pacientes.

Para resolver este problema, la solicitud en estudio proporciona una composición que contiene trans-(±)-A-tetrahidrocannabinol cristalino.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K 31/352, A61P 1/08, A61P 29/02.

4. Excepción a la Patentabilidad (Art 20 D 486 literal (d))

El objeto de las reivindicaciones 12-14, 28 y 29,31 no es patentable, de acuerdo con el Art citado, porque aunque se enuncien como una composición se trata de la administración de la composición.

5. De la Solicitud de Patente

Título

El título no es claro, porque no se especifica a que compuesto activo se refiere y si se la invención se trata de este o de sus composiciones.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 2, 6 repite materia innecesariamente, ya que esta reclamada enteramente en la 1.

Las reivindicaciones 3 y 4, mencionan una forma de dosificación farmacéutica pero es la misma materia ya reivindicada en la 1 y 2, como composición, se debe tener en cuenta que una forma farmacéutica es una composición que comprende uno o más fármacos, integrados en una forma farmacéutica (composición físicamente adaptada a la necesidad de los pacientes (ejemplo: capsulas , tabletas, inyectable), presentado para expendio y uso industrial o clínico, y destinado para su utilización en las personas o en los animales"; por lo tanto estas reivindicaciones hacen que el capítulo no sea claro. Se llama la atención que en la reivindicación 27 se menciona composición o forma de dosificación como sinónimos.

La reivindicación 7 no es concisa porque no se especifica con precisión la cantidad de cada isómero en la composición.

La reivindicación 10, no es clara porque primero inicia reclamando el método de preparación de una composición pero enseguida se refiere a un proceso para preparar el compuesto trans-(+/-)-delta⁹-tetrahidrocannabinol cristalino; además menciona dos primeras composiciones (II) y (III), lo cual es confuso; lo mismo que para composiciones orgánicas (primera IV) y (segundas V y VI); además, se observa, como ya se explicó, que estos métodos son para obtener mezclas del compuesto (racematos) o isómeros del trans-(+/-)-delta⁹-tetrahidrocannabinol cristalino y no de composiciones del compuesto con algún excipiente o vehiculo para obtener una composición farmacéutica.

Las reivindicaciones 13 y 14 se refieren a un método para la obtención de una composición (forma de dosificación), por lo tanto se repite la materia reivindicada.

Las Reivindicaciones 15, 16,20 y 23, no son claras en la numeración, porque se presentan 15.15; 16.16; 20.20 y 23.23.

Con respecto a la reivindicación 15 y sus dependientes (16 a 19) , se observa que reivindica una forma de dosificación que comprende una primera composición de cantidad terapéuticamente efectiva del trans-(+/-)-delta⁹-tetrahidrocannabinol cristalino y una segunda composición de un agente adverso a la actividad farmacológica del trans-(+/-)-delta⁹-tetrahidrocannabinol cristalino de preferencia el mencionado agente se selecciona de entre el grupo compuesto por SR141716 y SR 144528 y combinaciones de los mismos, pero lo que se observa es que es una sola composición que puede comprender dos o más principios activos porque el segundo componente no se define de manera concisa ya que se caracteriza como: un agente adverso a la actividad farmacológica del trans-(+/-)-delta⁹-tetrahidrocannabinol cristalino y combinaciones de los mismos; por lo tanto en las reivindicaciones citadas no existe claridad ni concisión.

-La reivindicación 30 dependiente de la 1, que esta caracteriza por parámetros, entre otros, como ángulos teta del compuesto trans-(+/-)-delta⁹-tetrahidrocannabinol cristalino, lo cual no le da Nivel Inventivo a la composición.

El capítulo reivindicatorio no es conciso porque contiene un excesivo número de reivindicaciones independientes (1, 2, 3, 4, 13,15, 20), lo cual hace difícil definir cuál es el objeto que se busca proteger.

Se requiere al Solicitante hacer las aclaraciones y correcciones necesarias.

6. 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: Junio 16 de 2005 .

y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Nº	Documento	Título	Fecha de Publicación*
D1	US2003229027	Stabilized natural cannabinoid formulation	11/12/2003
D2	WO03013538	Oral dosage form comprising a therapeutic agent and adverse effect agent	20/02/2003
D3	Journal of the American Chemical Society	Total synthesis of (±)-delta-9-tetrahydrocannabinol and four of its isomers	8/11/1967

D1¹ enseña una composición farmacéutica que comprende un canabinoide natural como el A9-tetrahidrocannabinol, un cristal de azúcar, alcohol de azúcar.

D2² divulga de forma general una forma de dosificación oral que comprende un agente terapéutico y un agente de efecto adverso.

D3³ divulga el compuesto trans-(±)- A⁹-tetrahidrocannabinol racemato utilizado como agente psicoticomimético.

7. Examen de Patentabilidad (Art 14 D486)

1http://worldwide.espacenet.com/searchResults?compact=false&PN=US2003229027&ST=advanced&locale=en_EP&DB=EPODOC
2http://worldwide.espacenet.com/searchResults?compact=false&PN=WO03013538&ST=advanced&locale=en_EP&DB=EPODOC
3 Anexo al concepto.

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en una composición según radicado N° 07-00010-0000 de 21 de agosto de 2012.

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

Características esenciales	D1	D3
Composición	Composición	Composición
trans-(±)-A-tetrahidrocannabinol (THC) cristalino	trans-(±)-A-tetrahidrocannabinol	Racemato cristalino THC
Vehículo farmacéuticamente aceptable	Cristal de azúcar, alcohol de azúcar	No menciona

El documento D1 es considerado el estado de la técnica más cercano a la invención definida en la reivindicación 1, el cual divulga una composición estable a la oxidación y biodisponibles (resumen párrafo 9, pág. 1) que contiene el compuesto trans-(±)- A⁹-tetrahidrocannabinol (THC); dichas composiciones se pueden presentar en forma de capsulas, tabletas, polvo para administración pulmonar (aerosoles) , enema, administración trans dermal (párrafos 28, 61, 67; pág. 3, 5) y se pueden preparar por métodos como los mencionados en los párrafos (30 a 33, pág 3; reivindicaciones 11 a 13, pág.12) y utilizar en combinaciones terapéuticas (párrafos 74 y 75, pág 7)

La diferencia entre la invención definida en la reivindicación 1 y la composición del documento D1, consiste en que esta especifica que el compuesto se encuentra en estado cristalino.

A pesar de esta diferencia no se logra un efecto técnico sorprendente.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: ¿cómo modificar la composición conocida en el documento D1 para obtener formas farmacéuticas, alternativas estables, frente a las composiciones ya conocidas?

Ahora bien, la utilización de formas cristalinas de un cannabinol para mejorar la estabilidad de una formulación, ya está divulgada en el documento D3 que menciona el racemato cristalino de A⁹-tetrahidrocannabinol (pág 5939).

En consecuencia, es obvio para la persona del oficio normalmente versada en la materia referirse a las enseñanzas divulgadas en el documento D3, partiendo de las composiciones farmacéuticas descritas en el documento D1, para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual la reivindicación 1 no tiene nivel inventivo.

Puesto que las reivindicaciones dependientes 2 a 9, 11, 12, y 23 a 30 no mencionan características adicionales, se considera que tales reivindicaciones tampoco tienen nivel inventivo.

-En cuanto a las reivindicaciones 13, 14 y 25 a 29 que se refieren a un método para la preparación de una composición o forma de dosificación, D1 también menciona métodos de obtención de las composiciones con etapas generales como las reclamadas que son pasos normalmente empleados para este tipo de preparaciones, resultando obvios para una persona del oficio normalmente versada en la materia en donde además no se observa un aporte a la solución al problema técnico planteado en la solicitud.

-La reivindicación 15 y sus dependientes reivindican una forma de dosificación que comprende una primera composición de cantidad terapéuticamente efectiva del trans-(+/-)-delta⁹-tetrahidrocannabinol cristalino y una segunda composición de un agente

adverso a la actividad farmacológica del trans-(+/-)-delta⁹-tetrahidrocannabinol cristalino de preferencia el mencionado agente se selecciona de entre el grupo compuesto por SR141716 y SER 144528 y combinaciones de los mismos.

La diferencia de la reivindicación 15 y el D1 es que es que menciona como compuesto de efecto adverso el Rimonabant (SR141716) ó el SR144528.

No obstante la diferencia no se observa un efecto sorprendente.

Sin embargo D2, menciona que composiciones que pueden contener otro agente adicional entre otros compuestos como (ej. hidrocodona, hidromorfona, oxicodona, codeína, lovorfanol, (D2 pág 8, líneas 3 a 8) al igual que se menciona en la descripción de la solicitud (pág 59 y 60).

De manera que la persona del oficio normalmente versada en la materia incluiría un compuesto se encuentra en estado cristalino de D3 y un compuesto adicional como los divulgados por D2, en la composición de D1 para llegar al objeto de la reivindicación 15. Por lo tanto, se considera que las reivindicaciones 15 a 19 carecen de nivel inventivo.

- La reivindicación 20, reclama un proceso para obtener una forma de dosificación oral sólida de un cannabinoide de liberación controlada que comprende la etapa de incorporar una cantidad terapéuticamente efectiva de trans-(+/-)-delta⁹-tetrahidrocannabinol cristalino dentro de un material de liberación controlada, pero D1 también menciona que se pueden obtener composiciones de entrega controlada (párrafos 47, 48 y 60 pág 4 y 5) utilizando diversos tipos de polímeros; por lo tanto, estarían afectadas por los documentos citados D1 y D3, puesto que el documento D1 describe formas de administración controlada para el compuesto trans-A9-THC y el documento D3 enseña el racemato cristalino de dicho compuesto. Por lo cual la persona del oficio normalmente versada en la materia estaría motivada a referirse a estos dos documentos para lograr obtener una forma de dosificación oral de un cannabinoide de liberación controlada. Por lo tanto, se considera que la reivindicación 20 carece de nivel inventivo al igual que sus dependientes 21 a 22.

8. Conclusión

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

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US2003229027	1-9 y 10-30	Nivel Inventivo
D2	WO03013538	15-19	Nivel Inventivo
D3	Journal of the American Chemical Society	1-14 y 20-30	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 del día siguiente 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.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

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 2013-10-01

Elaboró: Lyna Del Carmen Mordecay Dunoyer
Revisó: Gloria Jacqueline Alfonso Roza

The Total Synthesis of dl - Δ^9 -Tetrahydrocannabinol and Four of Its Isomers¹

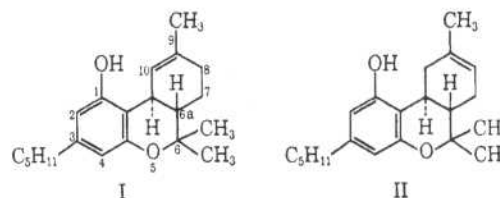
K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead

Contribution from the Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. Received June 2, 1967

Abstract: The total syntheses of the racemic modifications of two psychotomimetically active components of marijuana, Δ^9 -tetrahydrocannabinol (I) and Δ^8 -tetrahydrocannabinol (II), are described. The syntheses of three unnatural isomers, XII, XXI, and XXIII, are also presented. Cyclization of the coumarin V gave the dibenzopyran VII, which was converted by stereochemically controlled reactions to the *trans*-ketone Xa and the *cis*-ketone XI. The *trans*-ketone Xa was converted through the chloride XIV to a mixture rich in the Δ^9 isomer I, from which I was isolated in crystalline form. The *trans*-ketone Xa was also converted via the carbinol XIIIa to the Δ^8 isomer II. The *cis*-ketone XI was converted via the carbinol XXII to the *cis* analog XXIII of Δ^9 -tetrahydrocannabinol. The ketones Xa and XI were converted to the corresponding exocyclic methylene derivatives XII and XXI, respectively. The structure of the key intermediate IX was proven by its alternate synthesis from the chromanone XVII.

The crude resin obtained from the flowering tops of female plants of several *Cannabis sativa* L. varieties has been known and used as a psychotomimetic agent for many years.²⁻⁴ The structure of this material, known variously as marijuana, hashish, etc., had evaded elucidation for many years. Finally, the groups of Cahn,⁵ Todd,⁶ and Adams⁷ elucidated the gross structure of many of the components of the crude resin and several of the natural materials (physiologically inactive) were synthesized. The complete structure of the psychotomimetically active components, however, defied elucidation until more powerful modern physical methods became available. Recently the components of marijuana have received renewed attention. In 1964, Gaoni and Mechoulam,⁸ on the basis of nmr studies, and Santavy,⁹ on the basis of infrared studies and molecular rotation differences, determined the complete structure of the major physiologically active constituent, l - Δ^9 -tetrahydrocannabinol (I).¹⁰ One of these groups has also described^{11a} the first total synthesis of dl -I, the preparation requiring repeated column chromatography to effect purification of an intermediate. Early this year an elegant synthesis of l -cannabidiol was published^{11b} in which this naturally occurring material was prepared in one step from olivetol. In view of the reports^{8,11c} that l -cannabidiol can be con-

verted in unspecified yield to l - Δ^9 -tetrahydrocannabinol, this new synthesis of l -cannabidiol may provide a convenient procedure for the synthesis of l - Δ^9 -tetrahydrocannabinol. Last year the isolation of another psychotomimetically active component, l - Δ^8 -tetrahydrocannabinol (II), from some varieties of Mexican hemp was an-



nounced¹² and a total synthesis of dl -II has also been reported,¹³ the isolation of dl -II requiring column chromatography followed by a preparative vapor phase chromatographic separation.^{13a}

The present paper reports the synthesis of dl - Δ^9 -tetrahydrocannabinol (I), dl - Δ^8 -tetrahydrocannabinol (II), and other tetrahydrocannabinols by procedures amenable to large-scale preparation of these compounds.

The von Pechmann condensation of olivetol¹⁴ (III) and diethyl α -acetoglutarate¹⁵ (IV) in the presence of phosphorus oxychloride gave only one isolated product in spite of the fact that two coumarins and two chromones are possible¹⁶ (Scheme I). That the product isolated was the desired compound V was supported by its spectra and its eventual conversion to IX which was also prepared by another, unambiguous route (see below). The next step in the reaction sequence required an intramolecular condensation involving a methyl group vinylogous to a lactone carbonyl. A few similar intermolecular^{17,18} and intramolecular¹⁹ con-

(1) Part of these results have been reported in a preliminary communication: K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *J. Am. Chem. Soc.*, **88**, 2079 (1966).

(2) (a) D. F. Downing, *Quart. Rev. (London)*, **16**, 133 (1962); (b) D. F. Downing in "Psychopharmacological Agents," Vol. 1, M. Gordon, Ed., Academic Press Inc., New York, N. Y., 1964, pp 585-607.

(3) R. Adams, *Harvey Lectures*, **37**, 168 (1941).

(4) A. R. Todd, *Experientia*, **2**, 55 (1946).

(5) R. S. Cahn, *J. Chem. Soc.*, 1400 (1933), and earlier papers.

(6) F. Bergel, A. L. Morisson, H. Rinderknecht, A. R. Todd, A. D. Macdonald, and G. Woolfe, *ibid.*, 286 (1943), and earlier papers.

(7) R. Adams, M. Harfenist, and S. Loewe, *J. Am. Chem. Soc.*, **71**, 1624 (1949), and earlier papers.

(8) Y. Gaoni and R. Mechoulam, *ibid.*, **86**, 1646 (1964).

(9) F. Santavy, *Acta Univ. Palackianae Olomuc. Fac. Med.*, **35**, 5 (1964); *Chem. Abstr.*, **62**, 4057d (1965).

(10) Compound I has been called Δ^9 -tetrahydrocannabinol by other workers. However, we feel the numbering system used here is preferable, conforming to the *Chemical Abstracts* nomenclature of dibenzopyran compounds.

(11) (a) R. Mechoulam and Y. Gaoni, *J. Am. Chem. Soc.*, **87**, 3273 (1965); (b) T. Petržilka, W. Haefliger, C. Sikemeier, G. Ohloff, and A. Eschenmoser, *Helv. Chim. Acta*, **50**, 719 (1967); (c) Y. Gaoni and R. Mechoulam, *Tetrahedron*, **22**, 1481 (1966).

(12) R. L. Hively, W. A. Mosher, and F. W. Hoffmann, *J. Am. Chem. Soc.*, **88**, 1832 (1966).

(13) E. C. Taylor, K. Lenard, and Y. Shvo, *ibid.*, **88**, 367 (1966).

(13a) NOTE ADDED IN PROOF. After the acceptance of this manuscript, two syntheses of (–)- Δ^8 -tetrahydrocannabinol [(–)-II] appeared in print: T. Y. Jen, G. A. Hughes, and H. Smith, *ibid.*, **89**, 4551 (1967), and R. Mechoulam, P. Braun, and Y. Gaoni, *ibid.*, **89**, 4552 (1967). Both of these groups also prepared (+)-II and in addition the latter group converted (–)-II to (–)-I via (–)-XIV.

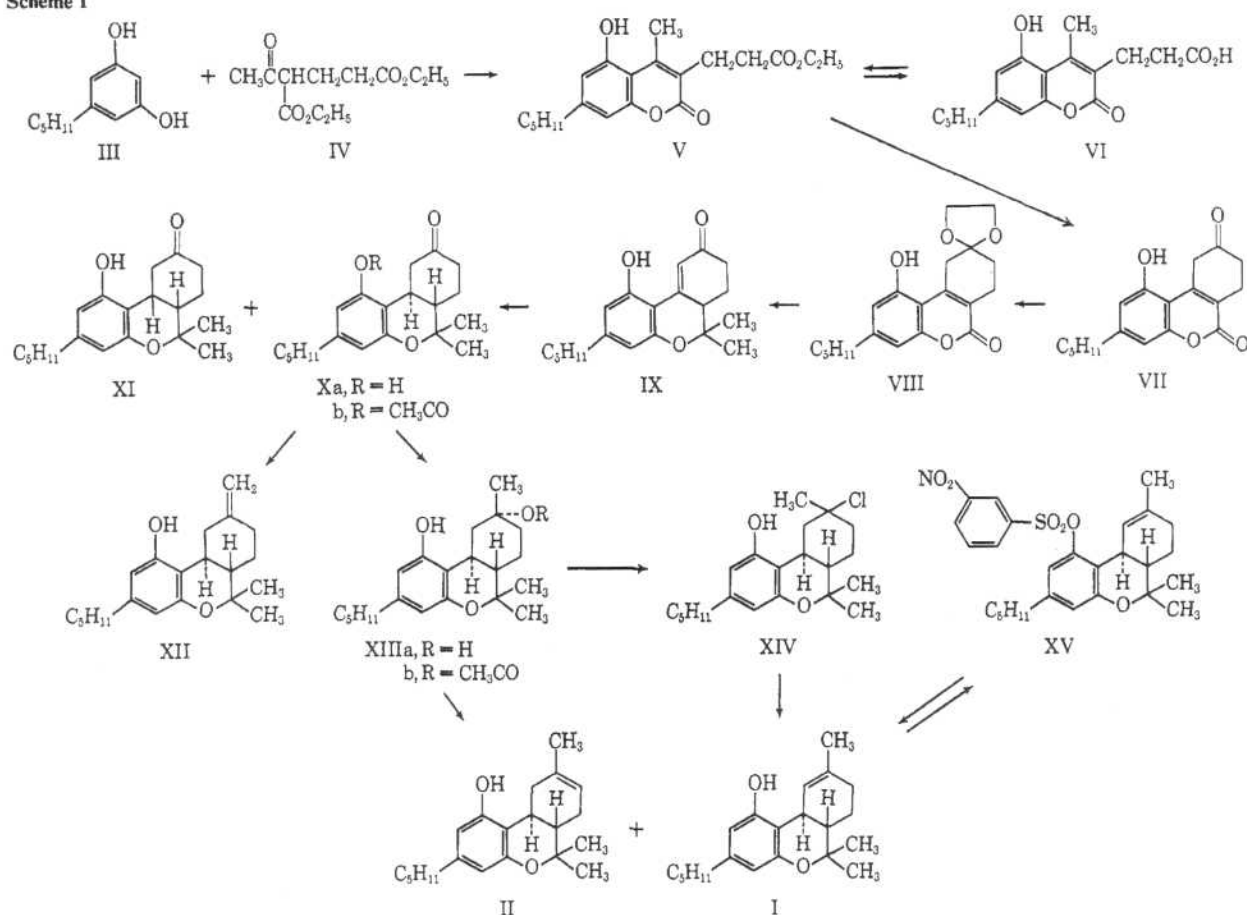
(14) C. M. Suter and A. W. Weston, *ibid.*, **61**, 232 (1939).

(15) H. Henecka, *Ber.*, **81**, 197 (1948).

(16) S. Sethna and R. Phadke, *Org. Reactions*, **7**, 1 (1953).

(17) W. Borscheu and R. Manteuffel, *Ann.*, **505**, 177 (1933).

Scheme I



densations have been reported on compounds where the most acidic protons were on the methyl group. In V, however, the hydroxylic proton and the protons α to the ester group are all probably more acidic than the methyl protons. Treatment of V with sodium hydroxide in ethanol¹⁹ gave the corresponding acid VI rather than the cyclization product VII. The former compound was readily reconverted to V by treatment with the diethyl acetal of dimethylformamide.^{20,21} Treatment of V with sodium hydride in refluxing benzene gave no reaction. The use of potassium *t*-butoxide in dimethyl sulfoxide gave a low yield of cyclized product whereas sodium hydride in dimethyl sulfoxide gave good yields of VII accompanied by small and varying amounts of VI. The spectral properties of VII suggest that the double bond is conjugated with the lactone group forming a coumarin chromophore. In particular the nmr spectrum clearly shows the absence of olefinic protons. Treatment of VII with ethylene glycol gave the corresponding ketal VIII. The reaction of VIII with methylmagnesium iodide²² followed by acid hydrolysis then gave IX²³ which has also been prepared from XVII (see below). The nmr spectrum of IX

indicates the presence of an olefinic proton and the other spectra also confirm the rearranged position of the double bond. The reduction of IX with lithium in liquid ammonia at -70° gave a mixture of two products. The minor product was identical with the *cis*-ketone XI which was also prepared by an alternate and unambiguous route (see below). The major product of this reduction was the desired *trans*-ketone Xa. This ketone was allowed to react with triphenylphosphine-methylene to give the exocyclic analog XII of tetrahydrocannabinol. No deliberate attempts were made to isomerize the double bond to an endocyclic position but it was shown that XII is recovered unchanged under the conditions used for the dehydration of the carbinol XIIIa (see below).

As will be mentioned later the *cis*-ketone XI reacted completely with methylmagnesium iodide. However, when the *trans*-ketone Xa was treated with methylmagnesium iodide, even with a large excess of reagent or at the temperature of refluxing benzene, thin layer chromatography of the reaction mixture showed the presence of a large amount of unreacted starting material. Only small amounts of pure XIIIa could be obtained from these mixtures by crystallization. However, reaction of the corresponding acetate Xb with methylmagnesium iodide gave a product mixture (free of ketone Xa) which could be used directly for subsequent steps. This mixture could also be crystallized to obtain satisfactory yields of the carbinol XIIIa.^{24,25}

(24) The hydroxyl group in XIIIa is assigned the axial configuration because dehydration under conditions not vigorous enough to cause

- (18) R. Kuhn and C. Grundmann, *Ber.*, **69**, 1757 (1936).
 (19) H. Meerwein, *Ann.*, **358**, 71 (1908).
 (20) H. Vorbrüggen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 211 (1963).
 (21) H. Brechbühler, H. Büchi, E. Hatz, J. Schreiber, and A. Eschenmoser, *ibid.*, **2**, 212 (1963); *Helv. Chim. Acta*, **48**, 1746 (1965).
 (22) R. Adams, C. K. Cain, and B. R. Baker, *J. Am. Chem. Soc.*, **62**, 2201 (1940).
 (23) All compounds prepared in this paper which contain centers of asymmetry are racemates and for convenience are represented throughout by one enantiomeric series.

Table I. Nuclear Magnetic Resonance Spectra of Tetrahydrocannabinols^a

Type of proton	dl -I In $CDCl_3^{b,c}$	dl -I In $CCl_4^{b,d}$	dl -II In $CDCl_3^e$	dl -II In CCl_4	dl -XII in $CDCl_3$	dl -XXIII in $CDCl_3^e$	dl -XXI in $CDCl_3$
Aromatic	6.28 (d, $J = 2$) (1)	6.13 (d, $J = 2$) (1)	6.27 (d, $J = 2$) (1)	6.08 (d, $J = 2$) (1)	6.28 (d, $J = 1.5$) (1)	6.27 (br d) (2) ^f	6.25 (d, $J = 1.5$) (1)
Olefinic	6.13 (d, $J = 2$) (1)	5.97 (d, $J = 2$) (1)	6.08 (d, $J = 2$) (1)	5.88 (d, $J = 2$) (1)	6.10 (d, $J =$ 1.5) (1)	6.12 (d, $J = 2$) (1)	6.07 (d, $J =$ 1.5) (1)
C-10	6.32 (br) (1)	6.28 (br) (1)	5.40 (br) (1)	5.32 (br) (1)	4.77 (b) (3) ^g exocyclic	6.27 (br d) (2) ^f C-10	4.65 (br d, $J = 3$) (2) exo- cyclic
C-10a H	3.18 (br d) (1)	3.13 (br d) (1)	3.22 (br d) (1)	3.13 (br d) (1)	and OH	3.58 (br) (1)	
C-9 CH_3	1.68 (s)	1.65 (s)	1.70 (s)	1.65 (s)		1.68 (s)	
C-6 (CH_3) ₂	1.40 (s)	1.37 (s)	1.37 (s)	1.30 (s)	1.38 (s)	1.38 (s)	1.38 (s)
	1.08 (s)	1.05 (s)	1.10 (s)	1.05 (s)	1.05 (s)	1.27 (s)	1.28 (s)
ω - CH_3	0.88 (t) (3)	0.88 (t) (3)	0.88 (t) (3)	0.88 (t) (3)	0.87 (t) (3)	0.87 (t) (3)	0.87 (t) (3)

^a All spectra were determined on a Varian A-60 spectrometer. Values are given in ppm relative to TMS as internal standard. Coupling constants are given in cps. ^b Identical with natural *l*-I.³⁰ ^c Compare ref 13. ^d Compare ref 8. ^e The signal at 6.27 includes one aromatic proton and the C-10 olefinic proton. ^f The signal at 4.77 includes the two exocyclic protons and the phenolic OH which exchanges on addition of D_2O .

This apparent difference in reactivity of Xa and XI toward the Grignard reagent can be readily explained on the basis of steric factors. In the reaction of both Xa and XI with methylmagnesium iodide the initial reaction is probably abstraction of the hydroxylic proton to form the corresponding phenolate anions. Further reaction is then a competition between attack of the Grignard reagent on the carbonyl carbon and enolization of the carbonyl initiated by C-10 proton abstraction by the adjacent phenolate anion. Studies²⁶ by Corey and by Zimmerman have shown that enolization of cyclic ketones proceeds preferentially (but not exclusively) by abstraction of axial protons. Measurements on Dreiding models²⁷ of the ketones with ring C as a chair and ring B as a half-chair (most likely close to the most stable conformation) show that in Xa the hydroxylic oxygen is 1.8 and 2.8 Å distant from the equatorial and axial C-10 protons, respectively. In the *cis*-ketone XI these distances are 1.8 and 3.4 Å, respectively, and in addition the axial proton is sterically shielded from the hydroxylic oxygen by the equatorial hydrogen.

In the reaction of the *cis*-ketone XI, therefore, attack on the carbonyl carbon by the Grignard reagent is preferred over internal abstraction of either the equatorial C-10 proton or the sterically inaccessible axial proton, giving reaction mixtures essentially free of XI. With the *trans*-ketone Xa, however, internal proton abstraction competes favorably with Grignard attack and a large amount of Xa is recovered.

Treatment of the carbinol XIIIa with acetic anhydride in pyridine gave the corresponding diacetate which, upon selective hydrolysis, was converted to the monoacetate XIIIb. Pyrolysis of XIIIb gave impure II while dehydration of XIIIa with a catalytic amount of *p*-toluenesulfonic acid in benzene gave an excellent yield of racemic Δ^8 -tetrahydrocannabinol (II) shown by glpc to be different from and free of either I or XII. This

isomerization of the exocyclic isomer XII gives the endocyclic product II. In an analogous case,²⁸ a 3 β -methyl-3 α -hydroxy steroid (axial hydroxyl) was dehydrated to endocyclic products whereas the isomeric 3 α -methyl-3 β -hydroxy steroid (equatorial hydroxyl) was dehydrated to the exocyclic product.

(25) C. E. Cook, R. C. Corley, and M. E. Wall, *Tetrahedron Letters*, 891 (1965).

(26) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 241.

(27) A. S. Dreiding, *Helv. Chim. Acta*, 42, 1339 (1959).

material had spectra compatible with its structure and the nmr spectrum was identical with that reported for *dl*-II¹² (see Table I).

The reaction of the carbinol XIIIa (or more conveniently the total carbinol mixture from the Grignard reaction on the acetate Xb) with Lucas reagent in acetic acid gave a good yield of the chloride XIV. If the Lucas reaction was carried out on the crude Grignard product from the ketone Xa, the resulting mixture could be separated readily into recovered Xa and the desired chloride XIV.

This chloride, on dehydrohalogenation with potassium hydroxide in ethanol, gave impure racemic Δ^8 -tetrahydrocannabinol (II) identical with the product from dehydration of the carbinol XIIIa. However, dehydrohalogenation of XIV with sodium hydride in tetrahydrofuran gave an excellent yield of a mixture of olefins²⁸ containing 74% I and 26% II. Treatment of this mixture with *m*-nitrobenzenesulfonyl chloride gave pure XV in 23% yield. Hydrolysis of XV gave an excellent yield of crystalline racemic Δ^9 -tetrahydrocannabinol (I),²⁹ shown by glpc to be free of either II or other detectable impurities and identical in all respects (except optical rotation and melting point) with *l*- Δ^9 -tetrahydrocannabinol, isolated from marihuana.³⁰

As a proof for the position of substitution in IX (and therefore also in the von Pechmann product V), we prepared IX by another route which is both unambiguous and which provides an alternate approach to the synthesis of these tetrahydrocannabinol isomers.

The reaction of olivetol (III) with 3-methylcrotonic acid (XVI) in the presence of boron trifluoride etherate at 125°³¹ led to the isolation of two products, XVII (50% yield) and XVIII (22% yield) (Scheme II). The ratio of products could be reversed simply by using boron trifluoride etherate at 25°³² which gives XVII (23% yield) and XVIII (63% yield). Attempted con-

(28) The different behavior of XIV to these basic systems can be explained readily by the assumption that with the sodium hydride-tetrahydrofuran system intramolecular dehydrochlorination is promoted by the initially formed phenolate anion.

(29) Previously obtained as an oil.¹¹

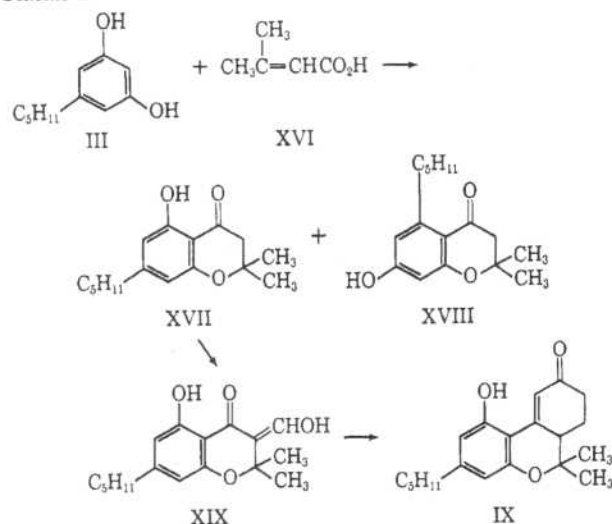
(30) We are indebted to Dr. Nathan B. Eddy of the Department of Health, Education, and Welfare for a sample of *l*- Δ^9 -tetrahydrocannabinol of natural origin.

(31) W. M. McLamore, *J. Am. Chem. Soc.*, 73, 2221 (1951).

(32) H. B. Bhat and K. Venkataraman, *Tetrahedron*, 19, 77 (1963).

condensations with a variety of other systems³³⁻³⁶ were less satisfactory.

Scheme II



Structural assignments of XVII and XVIII were readily made by a study of their spectra. The nmr spectra were most revealing; the hydroxylic proton in XVII appeared at 11.73 ppm while that of XVIII appeared at 8.77 ppm, indicating extensive intramolecular hydrogen bonding in XVII and not in XVIII.³⁷ In addition, the signal associated with the methylene group α to the aromatic ring is shifted downfield by 0.50 ppm in XVIII relative to XVII, indicating extensive deshielding of the methylene protons by the coplanar carbonyl group in XVIII.³⁸ The infrared spectrum of XVII was conspicuous by the absence of absorption characteristic of a free phenol³⁹ while a strong band at 1645 cm^{-1} indicative of strong intramolecular hydrogen bonding⁴⁰ was observed. On the other hand, the infrared spectrum of XVIII exhibited a sharp peak at 3590 cm^{-1} due to an unbonded hydroxyl and the absorption at 1670 cm^{-1} was more normal for an aromatic ketone. Both XVII and XVIII exhibited strong absorption in the ultraviolet region at 280 $\text{m}\mu$ (in ethanol). However, in strong base this band in the spectrum of XVII was shifted to 285 $\text{m}\mu$ and to 328 $\text{m}\mu$ in XVIII, indicative of an *o*-hydroxyaromatic ketone⁴¹ in XVII and a *p*-hydroxyaromatic ketone in XVIII.

The condensation of ethyl formate with XVII in the presence of sodium hydride gave XIX. Ring annulation of XIX with methyl vinyl ketone gave IX, identical in all respects with the material prepared *via* V, thus providing a proof for the position of substitution in V and its subsequent conversion products.

(33) H. R. Snyder and C. T. Elston, *J. Am. Chem. Soc.*, **77**, 364 (1955).

(34) M. Miyano and M. Matsui, *Bull. Chem. Soc. Japan*, **31**, 397 (1958).

(35) L. Smith and V. A. Engelhardt, *J. Am. Chem. Soc.*, **71**, 2671 (1949).

(36) R. D. Desai and M. Ekhlar, *Proc. Indian Acad. Sci.*, **A8**, 194 (1958).

(37) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," The Macmillan Co., New York, N. Y., 1959, p. 69.

(38) See ref 37, p. 122.

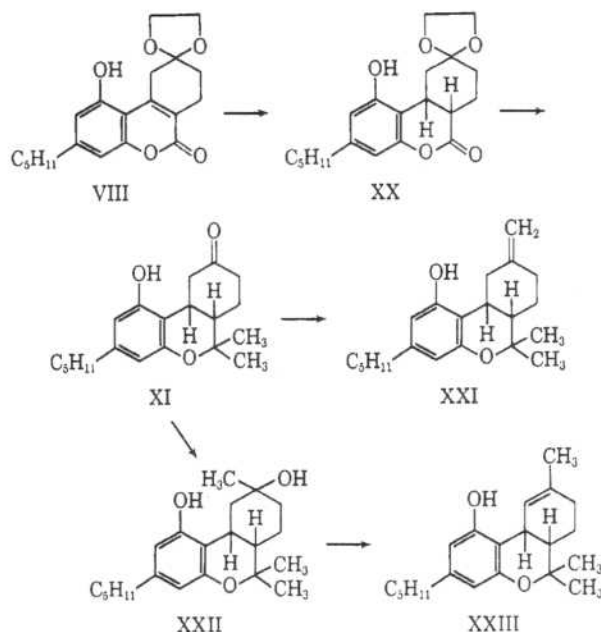
(39) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 90.

(40) See ref 39, p. 124.

(41) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964, p. 109.

The *cis*-ketone XI was prepared by the unambiguous route given in Scheme III. Catalytic hydrogenation of

Scheme III



VIII in the presence of Raney nickel under high pressure and temperature⁴² gave the *cis*-lactone XX. Treatment of the latter compound with methylmagnesium iodide followed by hydrolysis of the protecting group gave the *cis*-ketone XI which was identical with the minor product of the chemical reduction of IX. The reaction of XI with triphenylphosphinemethylene gave the exocyclic *cis* analog XXI of tetrahydrocannabinol. The reaction of XI with methylmagnesium iodide proceeded to completion, unlike the corresponding reaction with the *trans*-ketone Xa, and the methylcarbinol XXII was readily isolated. This latter compound was then dehydrated with *p*-toluenesulfonic acid to give a single product, clearly an endocyclic olefin with an nmr spectrum identical with that reported¹³ for XXIII (the *cis* analog of Δ^9 -tetrahydrocannabinol).

Experimental Section⁴³

Ethyl 5-Hydroxy-4-methyl-7-pentylcoumarin-3-propionate (V). A mixture of 299 g (1.66 moles) of olivetol¹⁴ (III), 420 g (1.84 moles) of diethyl α -acetoglutarate¹⁵ (IV), and 152 ml (254 g, 1.66 moles) of phosphorus oxychloride, protected from atmospheric moisture, was stirred at room temperature until the mixture solidified. The reaction was then allowed to stand for a total of 10 days. The solid was dissolved in chloroform, washed three times with water, dried (Na_2SO_4), and evaporated to an orange solid. This was recrystallized from benzene to give (in several crops) 481 g (84%) of V as colorless crystals, mp 120–122°. Further recrystallization gave the analytical sample: mp 123–124°; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 250 $\text{m}\mu$ (infl) (ϵ 8600), 257 (10,000), 309 (15,000); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1700 cm^{-1} (very broad and strong).

(42) P. L. deBenneville and R. Connor, *J. Am. Chem. Soc.*, **62**, 283 (1940).

(43) All melting points were determined in glass capillaries and are corrected. The infrared spectra were determined using a Beckman IR-9 spectrophotometer. The ultraviolet spectra were determined using a Cary 14 spectrophotometer. The nmr spectra were determined using a Varian A-60 spectrometer and are reported as parts per million relative to TMS as internal standard. All compounds prepared in this section had compatible infrared, ultraviolet, and nuclear magnetic resonance spectra, and spectral data are given only where significant. Florisil (Floridin Co.) is a synthetic magnesium silicate adsorbent.

Anal. Calcd for $C_{20}H_{18}O_5$: C, 69.34; H, 7.57. Found: C, 69.28; H, 7.21.

5-Hydroxy-4-methyl-7-pentylcoumarin-3-propionic Acid (VI). A small sample of V was mixed with an equal weight of potassium carbonate in 50% aqueous ethanol and heated for 10 min under reflux. The solution was diluted with water, acidified with hydrochloric acid, and filtered. Recrystallization from acetonitrile gave the analytical sample as colorless crystals: mp 230–233°; $\nu_{\text{max}}^{\text{CHCl}_3}$ 1660 and 1710 cm^{-1} .

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.70; H, 7.24.

Esterification of VI to V. A mixture of 1.0 g (3.1 mmoles) of VI, 10 ml of benzene, and 1.5 ml of the diethyl acetal of dimethylformamide^{20,21} was heated for 3 hr under reflux. The cooled reaction was diluted with ether, washed with 1 N hydrochloric acid and with water, dried (Na_2SO_4), and concentrated to an orange solid. Recrystallization from benzene gave 790 mg (72%) of V as colorless crystals, mp 121–124°, undepressed upon admixture with an authentic sample.

7,10-Dihydro-1-hydroxy-3-pentyl-6H-dibenzo[b,d]pyran-6,9(8H)-dione (VII). To the sodium hydride obtained by washing 72.0 g (1.5 moles) of 50% sodium hydride in mineral oil dispersion with dry hexane was added 120 g (0.35 mole) of V and the two powders were mixed thoroughly. The reaction flask was cooled to 15–17° and 1.2 l. of dimethyl sulfoxide was distilled from calcium hydride directly into the reaction flask. After stirring for an additional hour at 15–17°, the reaction was kept overnight in the refrigerator. After warming to room temperature the reaction mixture was poured into a rapidly stirred mixture of 4 l. of ice and water and 250 ml of concentrated hydrochloric acid, more ice being added as needed to keep the mixture cold. After stirring for an additional hour the slurry was filtered and the solids were washed well with water. The wet filter cake was then heated on the steam bath with excess concentrated sodium bicarbonate solution and, while still warm, was filtered. The filter cake was washed well with water and recrystallized from acetone to give (in several crops) 81 g (78%) of cyclized product VII as colorless crystals, mp 203–206°. Further recrystallization from acetonitrile gave the analytical sample: mp 205.5–207.5°; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 215 m μ (inf) (ϵ 26,000), 250 (inf) (9750), 258 (10,500), 308 (14,550); $\nu_{\text{max}}^{\text{KBr}}$ 1670 and 1710 cm^{-1} ; nmr (DMSO), no olefinic protons.

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.85; H, 6.85.

The combined sodium bicarbonate filtrates from several reactions were acidified with concentrated hydrochloric acid and filtered. The filter cake was washed well with water and, while still damp, was recrystallized from acetonitrile to give from 3 to 10% yields of the acid VI, mp 228–231°, undepressed upon admixture with an authentic sample.

7,8,9,10-Tetrahydro-1-hydroxy-3-pentylspiro[6H-dibenzo[b,d]pyran-9,2'-[1',3']dioxolan]-6-one (VIII). A solution of 9.22 g (0.031 mole) of VII in 500 ml of benzene containing 10 ml of ethylene glycol and 10 mg of *p*-toluenesulfonic acid was heated overnight under reflux (Dean-Stark trap). The cooled solution was poured into water containing excess sodium bicarbonate. The organic layer was dried (Na_2SO_4) and evaporated to a yellow oil which, upon crystallization from dichloromethane-ether, gave 9.91 g (94%) of VIII as colorless crystals, mp 112–114°. Further recrystallization from ether gave the analytical sample: mp 114.5–116°; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 228 m μ (inf) (ϵ 8400), 250 (inf) (9200), 257 (10,400), 304 (14,200); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1695 cm^{-1} ; nmr (CDCl_3), δ 6.65 (two protons), no other unsaturated protons.

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.61; H, 7.31.

Occasionally on standing, solutions of VIII deposited crystals, mp ~110–140°. This material, on recrystallization from methanol, was reconverted to material with mp 114.5–116°. However, on recrystallization from ether it was also converted to a polymorphic modification of VIII whose analytical sample had mp 145–148°; the infrared, ultraviolet, and nmr spectra were identical with those of the 114.5–116° modification.

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.69; H, 7.40.

dl-6a β ,7,10,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6H-dibenzo[b,d]pyran-9(8H)-one (IX). A slurry of 60.0 g (0.175 mole) of VIII in 1.5 l. of ether was added over 90 min to the Grignard reagent prepared from 44.6 g (1.84 g-atoms) of magnesium and 110 ml (251 g, 1.77 moles) of methyl iodide in 1.8 l. of ether. After refluxing for 2 days the reaction was treated carefully with 200 ml of 1 N hydrochloric acid, the color changing from yellow to red-

brown to green, and then with 740 ml of 6 N hydrochloric acid. The mixture was stirred vigorously for 1 hr and then the ether layer was washed once with water and once with 5% sodium bicarbonate, the color changing from green to yellow-brown. The ether layer was dried (Na_2SO_4) and concentrated with stirring under a nitrogen stream on the steam bath to 500 ml. The resulting precipitate was filtered to give 38.4 g (70%) of IX as pale yellow crystals, mp 193–195°, suitable for the next step. Recrystallization from dichloromethane-ether gave the analytical sample as pale yellow crystals: mp 198–199°; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 231 m μ (ϵ 16,000), 247 (inf) (5000), 325 (26,800); nmr (CDCl_3), δ 6.53 and 6.25 (two one-proton doublets, J = 2 cps, aromatic protons) and 8.07 (one-proton doublet, J = 2 cps, olefinic proton).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.27; H, 8.66.

dl-6a β ,7,10,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6H-dibenzo[b,d]pyran-9(8H)-one (Xa). A solution of 11.5 g (0.0366 mole) of IX in 100 ml of tetrahydrofuran was added slowly to a rapidly stirred solution of 400 mg of lithium in 500 ml of liquid ammonia (distilled through potassium hydroxide pellets) kept at -70° .¹⁴ Whenever the blue color began to fade, addition of IX was stopped and more lithium was added. Addition of IX was then resumed. This process was repeated until a permanent blue color persisted after the complete addition of IX. A total of 1.04 g (0.15 g-atom) of lithium was added. Stirring was continued for an additional 5 min and the blue color was discharged by the addition of ammonium chloride. The ammonia was allowed to evaporate and the residue was diluted with 500 ml of water, acidified with hydrochloric acid solution, and extracted with dichloromethane. The extracts were dried (Na_2SO_4) and concentrated to an oil. Crystallization from dichloromethane-hexane (until the mother liquors were free of either Xa or XI as shown by tlc) gave a total of 9.13 g of colorless crystals (79%) of a mixture of Xa and XI and little else (as shown by tlc). This material was then recrystallized from methanol-water to give 6.09 g (52.7%) of the *trans*-ketone Xa, free of the *cis*-ketone XI (thin layer chromatography), mp 162–164°. Further recrystallization from dichloromethane-hexane gave the analytical sample of Xa as colorless crystals: mp 163–165°; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 230 m μ (inf) (ϵ 9800), 275 (inf) (1375), 283 (1490); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1695 cm^{-1} .

Anal. Calcd for $C_{20}H_{26}O_3$: C, 75.91; H, 8.92. Found: C, 75.87; H, 8.89.

Several times the *trans*-ketone Xa was isolated as a lower melting polymorph whose analytical sample (from dichloromethane-ether) had mp 148–150°.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 75.91; H, 8.92. Found: C, 76.19; H, 9.22.

The two samples had identical infrared, ultraviolet, and nmr spectra and identical behavior on tlc. In addition, the samples could be interconverted by judicious choice of recrystallization solvents and seeds.

The mother liquors from several of these reductions were combined and chromatographed over silica gel. Later benzene fractions contained essentially pure Xa. Recrystallization from methanol-water then gave an amount of Xa, mp 162–165°, corresponding to a total yield of Xa of 59%. Further elution with benzene and with mixtures of benzene and ether gave mixtures of Xa and XI, until 3:1 benzene-ether gave a small amount of solid which upon recrystallization from ether gave the *cis*-ketone XI as colorless crystals, mp 148–150°, undepressed upon admixture with an authentic sample of *cis*-ketone prepared from XX (see below).

dl-6a β ,7,10,10a-Tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6H-dibenzo[b,d]pyran-9(8H)-one Acetate (Xb). A mixture of 1.00 g (3.2 mmoles) of Xa, 5 ml of pyridine, and 5 ml of acetic anhydride was heated for 15 min at 100°, at the end of which time tlc showed the reaction to be complete. The cooled solution was diluted with 100 ml of water, stirred for 30 min, and extracted with ether. The ether layer was extracted four times with water, dried (Na_2SO_4), and evaporated to 1.07 g of a semicrystalline residue. This was crystallized from hexane to give 0.80 g (71%) of Xb as colorless crystals, mp 86–91°. Further recrystallization from hexane gave the analytical sample: mp 88–91°; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 227 m μ (inf) (ϵ 8500), 275 (2000), 282 (2180); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1705 and 1765 cm^{-1} .

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.63; H, 8.35.

dl-6a β ,7,8,9,10,10a-Hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6H-dibenzo[b,d]pyran-1-ol (XII). A slurry of sodium

(44) Thin layer chromatography of the total product mixtures showed that the reductions at -70° were much cleaner than those at -33° .

hydride (obtained by washing 1.52 g (0.032 mole) of 50% sodium hydride in mineral oil dispersion with dry hexane) in 60 ml of dimethyl sulfoxide was heated at 50° until solution took place (about 3 hr). After addition of 11.86 g (0.034 mole) of triphenylmethylphosphonium bromide, the reaction was heated for 3 hr at 70°. A solution of 1.00 g (0.0032 mole) of Xa in 60 ml of dimethyl sulfoxide was added and the reaction was heated overnight at 70°. The cooled reaction was poured into a mixture of ice and water containing 20 g of sodium bicarbonate. This was extracted with benzene and the organic layer was washed with water, dried (Na_2SO_4), and evaporated to 6.15 g of a tan oil containing triphenylphosphine oxide by thin layer chromatography. This oil was passed over silica gel in 1:1 hexane-benzene to give 1.57 g of colorless oil containing an odorous impurity. This oil was absorbed onto silica gel in hexane and the first hexane eluates contained the impurity. Later hexane eluates were evaporated to give 0.59 g (59%) of XII as a colorless oil: $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 230 m μ (infl) (ϵ 9620), 275 (1290), 283 (1300); nmr, see Table I.

Anal. Calcd for $\text{C}_{21}\text{H}_{30}\text{O}_2$: C, 80.21; H, 9.62. Found: C, 79.95; H, 9.91.

Attempted Isomerization of XII. A solution of 40 mg of XII and 3 mg of *p*-toluenesulfonic acid in 3 ml of benzene was heated for 15 min under reflux. The cooled reaction was poured into water containing an excess of sodium bicarbonate. The benzene layer and one benzene wash were combined, dried, and evaporated to an oil. This was evaporatively distilled at 135° (0.05 mm) to give 28 mg of an oil with an nmr spectrum identical with that of XII.

dl-6 α ,7,8,9,10,10 α -Hexahydro-6,6,9 β -trimethyl-3-pentyl-6H-dibenzo[*b,d*]pyran-1,9 α -diol (XIIIa). To a refluxing solution of methylmagnesium iodide prepared from 10.50 g (0.43 g-atom) of magnesium and 27.0 ml (61.5 g, 0.43 mole) of methyl iodide in 650 ml of ether was added a solution of crude Xb prepared from 15.0 g (0.047 mole) of Xa dissolved in 500 ml of ether. The solution was heated for an additional hour under reflux and excess Grignard reagent was decomposed by the cautious addition of water. The reaction mixture was acidified with 3 *N* hydrochloric acid and the ether layer and several ether extracts were washed with water, sodium bicarbonate solution, and finally with water. The ether layer was dried (Na_2SO_4) and evaporated to a semisolid oil which on crystallization from ether-hexane gave 13.93 g (88%) of a mixture of carbinols suitable for conversion to the chloride XIV (see below). Recrystallization from ether-hexane gave 6.82 g (43%) of XIIIa as colorless crystals, mp 159.5–166°. Further recrystallization from ether-hexane gave the analytical sample: mp 162–163°; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 231 m μ (infl) (ϵ 9500), 276 (1220), 282 (1270); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3595 cm^{-1} , no carbonyl absorption.

Anal. Calcd for $\text{C}_{21}\text{H}_{34}\text{O}_2$: C, 75.86; H, 9.70. Found: C, 75.97; H, 9.88.

The same carbinol (XIIIa) could be obtained by the Grignard reaction with the tetrahydropyranyl ether of Xa followed by acid hydrolysis in 31% yield.

dl-9 α -Acetoxy-6 α ,7,8,9,10,10 α -hexahydro-6,6,9 β -trimethyl-3-pentyl-6H-dibenzo[*b,d*]pyran-1-ol (XIIIb). A solution of 100 mg (0.3 mmole) of XIIIa in 1 ml of acetic anhydride and 1 ml of pyridine was heated for 3 hr on the steam bath.⁴⁵ To the cooled reaction was added 5 ml of water and stirring was continued for 15 min. The reaction was diluted with ether, washed four times with water, dried (Na_2SO_4), and evaporated to give the crude diacetate. This was mixed with 300 mg of sodium bicarbonate in 10 ml of methanol and 2 ml of water and heated for 15 min under reflux. The cooled reaction was diluted with 10 ml of water and filtered to give 85 mg (75%) of XIIIb as colorless crystals, mp 130–136°. Recrystallization from hexane gave the analytical sample: mp 137–139.5°; $\nu_{\text{max}}^{\text{CHCl}_3}$ 3600 and 1720 cm^{-1} .

Anal. Calcd for $\text{C}_{25}\text{H}_{38}\text{O}_4$: C, 73.76; H, 9.15. Found: C, 73.66; H, 9.24.

dl-6 α ,7,10,10 α -Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[*b,d*]pyran-1-ol (dl- Δ^8 -Tetrahydrocannabinol) (II). A solution

of 500 mg (1.5 mmoles) of XIIIa and 50 mg of *p*-toluenesulfonic acid in 50 ml of benzene was heated for 30 min under reflux (Dean-Stark trap). The cooled solution was passed through a small column of silica gel and the benzene eluates were evaporated to give 454 mg (96%) of II as a colorless oil (only one isomer by glpc and with spectra identical with those of the analytical sample).

To 35 ml of benzene containing two drops of pyridine was added 350 mg (1.1 mmoles) of II and one-third of the solvent was distilled. The solution was cooled to room temperature under a drying tube and 278 mg (1.3 mmoles) of 3,5-dinitrophenyl isocyanate¹⁶ was added. After stirring overnight a small amount of solid was removed by filtration and the yellow filtrate was adsorbed onto Florisil. Elution with benzene gave a colorless eluate and a light yellow band on the upper portion of the column. Concentration of the eluate gave colorless crystals which, upon one recrystallization from ether-hexane, afforded 330 mg of the 3,5-dinitrophenylurethan of II, mp 208–209.5°. Recrystallization of this material was not successful and gave a product with a lower melting point. Therefore no further attempts were made to characterize II via the 3,5-dinitrophenylurethan and 180 mg of this solid was hydrolyzed by stirring with 1.1 ml of 1 *N* sodium hydroxide solution in 50 ml of methanol overnight. The solution was poured into a mixture of ether and excess dilute hydrochloric acid. The ether layer was washed with water, dried (Na_2SO_4), and concentrated. The residue was dissolved in benzene and passed over Florisil. The upper portion of the column was bright yellow and the colorless benzene eluate was evaporated to give 90 mg of the analytical sample of II as a colorless oil: $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 231 m μ (infl) (ϵ 8820), 275 (1160), 283 (1190); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3600, 1620, and 1575 cm^{-1} ; nmr, see Table I.

Anal. Calcd for $\text{C}_{21}\text{H}_{30}\text{O}_2$: C, 80.27; H, 9.62. Found: C, 80.30; H, 9.73.

dl-9-Chloro-6 α ,7,8,9,10,10 α -hexahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[*b,d*]pyran-1-ol (XIV). To a solution of 7.10 g (0.021 mole) of a mixture of carbinols (see the preparation of XIIIa) in 100 ml of glacial acetic acid was added a solution of 72 g of zinc chloride in 56 ml of concentrated hydrochloric acid. After stirring for 3 hr at room temperature the reaction mixture was poured into a mixture of 2 l. of water and 2 l. of ether. The ether layer was washed five times with 1-l. portions of water, dried (Na_2SO_4), and evaporated to a yellow oil. Crystallization from hexane gave 5.53 g (74%) of XIV as colorless crystals, mp 85–90°. Recrystallization from hexane gave the analytical sample as colorless crystals: mp 87–90°; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 230 m μ (infl) (ϵ 9700), 276 (1200), 277 (1230).

Anal. Calcd for $\text{C}_{21}\text{H}_{31}\text{ClO}_2$: C, 71.88; H, 8.90; Cl, 10.10. Found: C, 71.92; H, 9.02; Cl, 10.06.

Similarly, purified carbinol XIIIa gave XIV in comparable yields.

The Preparation of XIV Directly from Xa. A slurry of 10.00 g (0.0316 mole) of Xa in 100 ml of ether was added over 15 min to a solution of methylmagnesium iodide prepared from 7.0 g (0.29 g-atom) of magnesium and 18.0 ml (41.0 g, 0.29 mole) of methyl iodide in 500 ml of ether. The reaction was heated for 90 min under reflux and cooled in an ice bath. Water was added carefully to decompose the excess Grignard reagent and enough 6 *N* hydrochloric acid was added to give two clear layers. The organic layer was diluted with 600 ml of ether and washed twice with water and finally with brine. The solution was dried (Na_2SO_4) and concentrated. To the residue dissolved in 150 ml of glacial acetic acid was added a solution of 103 g of zinc chloride in 80 ml of concentrated hydrochloric acid. After stirring for 90 min at room temperature the reaction mixture was poured into a mixture of 3 l. of water and 2.4 l. of ether. The ether layer was washed five times with 1.5-l. portions of water, dried (Na_2SO_4), and evaporated. The residue was dissolved in benzene and adsorbed on a column of silica gel. The column was eluted with benzene until thin layer chromatograms showed that no more XIV was being eluted. The column was then eluted with ether and these ether eluates were worked up to give 3.64 g of recovered Xa. The benzene eluates were evaporated and crystallized from hexane to give 3.45 g (49% based on unrecovered Xa) of XIV as light tan crystals, mp 85–88°, identical with the material obtained directly from the carbinol XIIIa.

dl- Δ^8 -Tetrahydrocannabinol (I) and dl- Δ^9 -Tetrahydrocannabinol (II). To a slurry of the sodium hydride from 1.00 g (0.02 mole) of 50% sodium hydride in mineral oil dispersion (washed free of mineral oil with dry hexane) in 200 ml of tetrahydrofuran (distilled from lithium aluminum hydride) was added 1.00 g (0.00285 mole) of XIV. The reaction was heated overnight under reflux with stirring, cooled to room temperature, and poured carefully into a

(45) The acetylation and hydrolysis were both followed by tlc. It had been noted earlier that the carbinol XIIIa had a much lower mobility (silica gel plates, 15% ethyl acetate in benzene solvent) than any of the compounds without the 9 α -hydroxyl. During the acetylation, XIIIa disappeared rapidly and a new spot very similar in mobility to XIIIa appeared. This material is the aromatic acetate. As the acetylation proceeded, this acetate was gradually replaced by a very mobile product, the diacetate. During the hydrolysis, the diacetate was rapidly replaced by another very mobile product XIIIb which, on prolonged hydrolysis, was reconverted into XIIIa. Thus, as to be expected, the phenolic hydroxyl is both acetylated and regenerated faster than the tertiary aliphatic hydroxyl.

(46) C. Naegele and A. Tyabji, *Helv. Chim. Acta*, 16, 349 (1933).

mixture of water and ether. The ether layer was washed four times with 500-ml portions of water, dried (Na_2SO_4), and concentrated to 875 mg (98%) of a yellow oil. Vapor phase chromatographic analysis⁴⁷ of this oil showed the presence of I and II in the ratio 74:26 accompanied by only traces of other components.

***dl*-6 α ,7,8,10 α -Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[*b,d*]pyran-1-ol *m*-Nitrobenzenesulfonate (XV).** To a solution of 500 mg (1.6 mmoles) of the 74:26 mixture of I and II in 10 ml of dry pyridine was added 700 mg (3.2 mmoles) of *m*-nitrobenzenesulfonyl chloride. The solution was heated for 8 hr at 60° and then for 4 hr at 75° at which time tlc indicated the reaction was complete. The cooled reaction was poured into a mixture of ether and dilute hydrochloric acid. The ether layer was washed with dilute hydrochloric acid, water, dilute sodium bicarbonate, and finally with water, dried (Na_2SO_4), and evaporated. The residue was recrystallized repeatedly from methanol to give 180 mg (23%) of XV as very pale yellow crystals, mp 106–107.5°. The analytical sample had mp 105.5–107.5°; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 230 m μ (inf) (ϵ 11,600), 247 (7650), 280 (inf) (ϵ 3950); nmr (CDCl_3), 6.60 (one-proton doublet, $J = 2$ cps), 6.38 (one-proton doublet, $J = 2$ cps), 6.05 (one-proton broad singlet).

Anal. Calcd for $\text{C}_{27}\text{H}_{33}\text{NO}_6\text{S}$: C, 64.91; H, 6.66; N, 2.80; S, 6.42. Found: C, 64.64; H, 6.36; N, 2.70; S, 6.78.

***dl*-6 α ,7,8,10 α -Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[*b,d*]pyran-1-ol (*dl*- Δ^8 -Tetrahydrocannabinol) (I).** A solution of 1.69 g (3.4 mmoles) of XV in 600 ml of methanol containing 25 ml of 1 *N* sodium hydroxide was heated under reflux until tlc indicated the reaction was complete (45 min). The cooled reaction was poured into ether and dilute hydrochloric acid. The organic layer was washed with water, dilute sodium bicarbonate, and finally with water. It was dried and evaporated to a pale tan oil which on crystallization and recrystallization from hexane gave 0.80 g (84%) of I as very light tan crystals, mp (vac) 60–62°. The analytical sample had mp (vac) 64.5–65.5°; the glpc retention time (no detectable impurities) and infrared, ultraviolet, and nmr spectra were identical with natural *l*- Δ^8 -tetrahydrocannabinol; for nmr data, see Table I; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 230 m μ (inf) (ϵ 10,000), 275 (1250), 282 (1280); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3595, 1620, 1575 cm^{-1} .

Anal. Calcd for $\text{C}_{21}\text{H}_{30}\text{O}_2$: C, 80.21; H, 9.62. Found: C, 80.34; H, 9.54.

5-Hydroxy-2,2-dimethyl-7-pentyl-4-chromanone (XVII) and 7-Hydroxy-2,2-dimethyl-5-pentyl-4-chromanone (XVIII). A mixture of 73 g (0.4 mole) of olivetol (III) and 47 g (0.47 mole) of 3-methylcrotonic acid (XVI) was heated in an oil bath to 125°. Through the condenser, 94 ml of boron trifluoride etherate was added and the solution was heated overnight under reflux. The partially cooled reaction was diluted cautiously with 100 ml of water followed by 425 ml of 6 *N* sodium hydroxide and then boiled for 5 min on the steam bath. The solution was cooled, acidified with 6 *N* hydrochloric acid, and extracted with ether. The ether extracts were washed with water, dilute sodium bicarbonate, and water and then dried (Na_2SO_4) and concentrated to 106 g of a tan oil. This was dissolved in ether and extracted repeatedly with 1 *N* sodium hydroxide solution. The ether layer, upon drying and evaporation, gave 53.1 g (50%) of crude XVII as a light tan oil suitable for the next step. Repeated recrystallization from methanol at –70° gave the analytical sample of XVII as tan crystals: mp 23–27°, normally handled as an oil; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 229 m μ (inf) (ϵ 11,780), 280 (13,800), 348 (2980); $\lambda_{\text{max}}^{\text{in ethanolic sodium acetate}}$ 280 (13,450), 348 (2940); $\lambda_{\text{max}}^{0.1\text{ }N\text{ KOH}}$ 242 (14,200), 285 (11,150), 373 (5250); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1645 cm^{-1} ; nmr (CDCl_3), 11.73 (one-proton singlet, hydroxylic proton), 6.33 and 6.25 (two one-proton doublets, $J = \sim 1$ cps, aromatic protons), 2.72 (two-proton singlet, C-3 H's), 2.52 (two-proton triplet, α methylene), 1.45 (six-proton singlet, 2,2-bis CH_3), and 0.88 (three-proton triplet, ω - CH_3).

Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{O}_3$: C, 73.25; H, 8.45. Found: C, 73.02; H, 8.75.

The 1 *N* sodium hydroxide extracts of the total reaction mixture were acidified with hydrochloric acid and extracted with ether. The extracts were dried and concentrated. Crystallization from acetonitrile gave 23.1 g (22%) of crude XVIII as tan crystals, mp 82–86°. Recrystallization from hexane gave the analytical sample of XVIII as colorless crystals: mp 94.5–96°; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 220 m μ

(ϵ 13,640), 233 (9400), 280 (11,300), 315 (4700); $\lambda_{\text{max}}^{\text{in ethanolic sodium acetate}}$, 285 (6250), 328 (13,600); $\lambda_{\text{max}}^{0.1\text{ }N\text{ KOH}}$ 252 (6650) and 328 (19,500); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3590 and 1670 cm^{-1} ; nmr (CDCl_3), 8.77 (one-proton singlet, hydroxylic proton), 6.35 (two protons, pair of doublets, aromatic protons), 2.70 (two-proton singlet, C-3 H's), 3.02 (two-proton triplet, α methylene), 1.42 (six-proton singlet, 2,2-bis CH_3), and 0.87 (three-proton triplet, ω - CH_3).

Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{O}_3$: C, 73.25; H, 8.45. Found: C, 72.98; H, 8.72.

5-Hydroxy-3-hydroxymethylene-2,2-dimethyl-7-pentyl-4-chromanone (XIX). To the sodium hydride obtained by washing 78.5 g (1.64 moles) of 50% sodium hydride in mineral oil dispersion with hexane was added (at room temperature) a solution of 46.1 g (0.175 mole) of XVII in 172 ml (159 g, 2.15 moles) of ethyl formate, utilizing a Dry Ice condenser during the addition. This condenser was then replaced by a water-jacketed condenser. Ether (4.4 l.) was added and after heating overnight under reflux the reaction was cooled and acidified with 1 *N* hydrochloric acid. The ether layer and two ether washes of the aqueous layer were washed with 1 *N* hydrochloric acid and twice with water and then extracted five times with 1 *N* sodium hydroxide. These basic extracts were acidified and extracted with ether. The ether was dried (Na_2SO_4) and concentrated to 27.5 g (54%) of crude XIX as a yellow oil suitable for the next step. Crystallization and recrystallization from hexane gave the analytical sample as yellow crystals: mp 31–32.5°; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 223 m μ (inf) (ϵ 16,400), 274 (4900), 331 (15,650), 366 (inf), (8480), 386 (inf) (4200).

Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_4$: C, 70.32; H, 7.64. Found: C, 70.60; H, 7.89.

The Preparation of IX from XIX. To a solution of 8.33 g (0.029 mole) of crude XIX in 43 ml of methanol and 4.25 ml of methyl vinyl ketone was added 1.0 ml of triethylamine. After standing overnight at room temperature, the solution was diluted with 500 ml of ether and extracted four times with 10% sodium carbonate solution. The ether solution was dried (Na_2SO_4) and concentrated. The residue (8.43 g) was heated overnight under reflux with 84.3 ml of ethanol and 84.3 ml of 2 *N* potassium hydroxide solution. The cooled solution was acidified with 6 *N* hydrochloric acid and extracted with dichloromethane. The extracts were dried (Na_2SO_4) and concentrated, and the residue was crystallized from dichloromethane–ether to give 4.11 g (35%) of IX as yellow crystals, mp 195–198°. Further recrystallization gave pale yellow crystals, mp 197.5–199°, undepressed on admixture with a sample of IX prepared from VIII.

***dl*-6 α ,7,8,9,10,10 α -Hexahydro-1-hydroxy-3-pentylspiro[6H-dibenzo[*b,d*]pyran-9,2'-[1',3']dioxolan]-6-one (XX).** A solution of 5.00 g (0.0145 mole) of VIII in 100 ml of ether was subjected to hydrogenation at 2150-lb pressure and 130° for 2 hr in the presence of 0.5 g of Raney nickel. The catalyst-free solution was evaporated to a crystalline residue which, on recrystallization from ether–hexane, gave 3.53 g (70%) of XX as colorless crystals, mp 142.5–143.5°. A subsequent reduction under apparently identical conditions on a 50-g scale gave a 33% yield of XX. Further recrystallization from ether–hexane gave the analytical sample: mp 143–144°; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 275 m μ (inf) (ϵ 2400), 282 (2790).

Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{O}_3$: C, 69.34; H, 7.57. Found: C, 69.02; H, 7.30.

***dl*-6 α ,7,10,10 α -Tetrahydro-1-hydroxy-6,6-dimethyl-3-pentyl-6H-dibenzo[*b,d*]pyran-9(8H)-one (XI).** A slurry of 3.60 g (0.0104 mole) of XX in 180 ml of ether was added (argon atmosphere) over 30 min to a methylmagnesium iodide solution prepared from 11.1 ml (25.3 g, 0.18 mole) of methyl iodide and 4.32 g (0.18 g-atom) of magnesium in 180 ml of ether. The reaction was heated overnight under reflux and 1 *N* hydrochloric acid was added carefully until two clear layers were obtained. The aqueous layer was washed with dichloromethane, and the combined organic layers were concentrated. The residue was mixed with 80 ml of methanol and 40 ml of 3 *N* hydrochloric acid and heated for 2 hr under reflux. The cooled reaction was diluted with 500 ml of water and extracted with dichloromethane. The extracts were dried (Na_2SO_4) and concentrated to a crystalline residue which on recrystallization from ether gave 1.73 g (53%) of colorless crystals, mp 148–150°. Further recrystallization from ether–hexane gave the analytical sample: mp 149.5–150.5°; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 230 m μ (inf) (ϵ 9800), 277 (1570), 283 (1620).

Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{O}_3$: C, 75.91; H, 8.92. Found: C, 75.01; H, 8.88.

***dl*-6 α ,7,8,9,10,10 α -Hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6H-dibenzo[*b,d*]pyran-1-ol (XXI).** A slurry of sodium hydride (obtained by washing 3.04 g (0.063 mole) of 50% sodium

(47) The vapor phase chromatographic analyses were done on an F & M Model 810R-19 instrument with dual hydrogen flame detectors. The column was 0.25 in. $\times$ 6 ft packed with 0.5% NPGA + 0.5% PEG4000MS on Anakrom ABS (60–70 mesh). The column flow was 100 cc/min of nitrogen, the column temperature was 220°, and the retention time of I was 20 min and that of II was 18 min.

hydride in mineral oil dispersion with dry hexane) in 120 ml of dimethyl sulfoxide was heated at 50° until solution took place (about 30 min). After addition of 22.6 g (0.063 mole) of triphenylmethylphosphonium bromide the reaction was heated for 3 hr at 70°. A solution of 2.00 g (0.0063 mole) of XI in 120 ml of tetrahydrofuran was added and the reaction was heated overnight under reflux. The cooled reaction was poured into a mixture of ice and water containing 40 g of sodium bicarbonate. This was extracted with benzene and the extracts were dried (Na₂SO₄) and concentrated to a semicrystalline residue. Addition of ether and filtration gave two crops of triphenylphosphine oxide which contained no XXI by thin layer chromatography and were discarded. The evaporated mother liquors were passed over silica gel in 1:1 hexane-benzene. The eluates were concentrated and crystallized from hexane at Dry Ice temperature to give 0.94 g (47%) of XXI as tan crystals, mp 35–50°. Further recrystallization gave the analytical sample as colorless crystals: mp 48–52°; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 230 m μ (infl) (ϵ 9500), 277 (1200), 284 (1230); nmr, see Table I.

Anal. Calcd for C₂₁H₃₀O₂: C, 80.21; H, 9.62. Found: C, 80.26; H, 9.21.

*dl-6 α ,7,8,9,10,10 α -Hexahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[*b,d*]pyran-1,9-diol (XXII).* A slurry of 500 mg (1.58 mmoles) of XI in 10 ml of ether was added to a solution of methylmagnesium iodide prepared from 106 mg (4.4 mg-atoms) of magnesium and 0.30 ml (0.68 g, 4.8 mmoles) of methyl iodide in 10 ml of ether to give a clear reaction mixture. After heating for 1 hr under reflux the reaction was cooled in an ice bath and 1 *N* hydrochloric acid was added until two clear layers were formed. The organic layer was diluted with ether and washed twice with water, once with dilute sodium bicarbonate, and again with water. The ether solution was dried (Na₂SO₄) and concentrated to an oil which on crystal-

lization from hexane gave 380 mg (72%) of XXII as colorless crystals, mp 142–145°. Recrystallization from ether-hexane gave the analytical sample: mp 142–145°; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 230 m μ (infl) (ϵ 10,000), 278 (1420), 283 (1450).

Anal. Calcd for C₂₁H₃₂O₃: C, 75.86; H, 9.70. Found: C, 76.07; H, 9.83.

*dl-6 α ,7,8,10 α -Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[*b,d*]pyran-1-ol (XXIII).* A solution of 828 mg (2.5 mmoles) of XXII and 50 mg of *p*-toluenesulfonic acid in 50 ml of benzene was heated for 30 min under reflux. The cooled solution was washed with dilute sodium bicarbonate, dried (Na₂SO₄), and evaporated to give 770 mg (98%) of XXIII as a colorless oil. A small portion of this oil was evaporatively distilled at 135° (0.05 mm) to give the analytical sample: $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 232 m μ (infl) (ϵ 9850), 275 (1470), 282 (1500); nmr, see Table I.

Anal. Calcd for C₂₁H₃₀O₂: C, 80.21; H, 9.62. Found: C, 79.87; H, 9.47.

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Photochemistry of Nucleic Acids. III. The Structure of DNA-Derived Thymine Photodimer¹

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Abstract: The identity of the major thymine photoproduct derived from DNA is established with the *cis-syn* dimer 1 obtained from irradiation of thymine in ice. The ¹⁴C-labeled photoproduct was mixed with unlabeled ice-dimer and the cocrystallized material treated with bromine in alkali. The resulting stereospecific rearrangement reaction gave *cis,cis,cis*-3-carbonamido-1,7-dimethyl-3,5,0-triazatricyclo[5.3.0.0^{2,5}]deca-4,8,10-triene (7) retaining more than 91% of the specific activity of the recrystallized dimer. The mechanism of the rearrangement was investigated by performing the reaction in oxygen-18-enriched solvent. The observed nonincorporation of this isotope into the product 7 is consistent with a mechanism involving isocyanate formation without nucleophilic attack of hydroxide.

Good evidence exists^{3,4} that photoproducts of thymine and of cytosine are responsible for the majority of photobiological effects caused by ultraviolet irradiation of DNA. The formation of pyrimidine dimers is particularly important in this respect and, in principle, they can arise either by photoaddition of adjacent pyrimidines in the same DNA strand-intrastrand dimerization or from bonding between two neighboring

pyrimidines, one in each strand, giving interstrand dimers and thus effecting cross-linking between the complementary DNA chains.

These two modes are expected to lead to dimers of different stereochemistry, and the inspection of molecular models resulted in the prediction⁵ that intrastrand dimers should have *cis-syn* stereochemistry whereas interstrand dimers would give rise to either *cis-anti* or to *trans-anti* products. An alternative opinion⁶ has suggested that such cross-linking should afford *cis-anti* or *trans-syn* interstrand dimers.

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(3) Abbreviations used: DNA, deoxyribonucleic acid; t-RNA, transfer ribonucleic acid; T, thymine; TT, thymine dimer; UT, uracil-thymine dimer.

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