

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
RAD: 10-78683- -8	FECHA: 2013-02-06 10:57:35
DEP: 2020 DIRECCION DE NUEVAS CREACIONES	EVE: 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS: 13
ACT: 519 PRESENTACION	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,
Abogado(a)/Señor(a)
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Asunto: Radicación: 10-78683- -8
Trámite: 11
Evento: 378
Actuación: 519
Oficio: 1917
Folios: 13

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/EP2008/011162				
Fecha de Presentación Internacional	23/12/2008				

1. Documentos estudiados

Descripción:	Folios 99 a 181	Junio 29 de 2010
Reivindicaciones	Folios 182 a 199	Junio 29 de 2010
Oposiciones	Folios 246 a 251	Lafrancol Octubre 14 de 2011
Respuesta del solicitante	Folios 273 a 274	Enero 25 de 2012
Prioridad:	DE 10 2007 063 501.1	Diciembre 29 de 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

De acuerdo con lo establecido en el numeral 1.2.2.2 del Capítulo Primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen

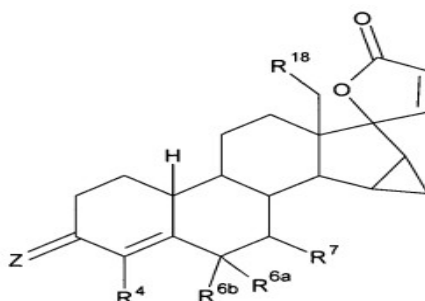
para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada.

Por lo tanto, las reivindicaciones 11 a 24 visibles en los folios 198 y 199 son aceptadas para ser estudiadas, porque se registra el pago por dichas reivindicaciones adicionales, de acuerdo con el recibo presente en el folio 240.

Título de la solicitud: “Derivado de γ – lactona de esteroide de ácido 15, 16 – metilen – 17 – hidroxil – 19 – nor – 21 – carboxílico, su uso y medicamentos que contienen tal derivado”

El problema planteado en esta solicitud consiste en obtención de compuestos análogos de progesterona para el tratamiento de trastornos relacionados con la menopausia y la menstruación.

Para resolver este problema técnico, la solicitud en estudio plantea la obtención de compuestos derivados γ – lactona de esteroide de ácido 15, 16 – metilen – 17 – hidroxil – 19 – nor – 21 – carboxílico con 17, 17 – espirolactona α,β – insaturada, para el tratamiento de trastornos relacionados con la menopausia y la menstruación.



El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K31/58; A61P5/28; A61P5/34; A61P5/42; C07J53/00.

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

El objeto de las reivindicaciones 24 y 24 no es patentable, de acuerdo con el artículo citado.

5. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 11 a 13, 21 y 22, no es patentable, de acuerdo con el artículo 14.

6. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 no es concisa, porque dentro de los sustituyentes se nombran expresiones las cuales a pesar de ser una restricción de una generalidad, no están definidos de manera específica y aun así se pueden obtener muchos posibles compuestos a partir de estos, tales como “alquilo C1-10”, “arilo”, “arilalquilo C7-20”, “alquenilo C2-10”, “alquinilo C2-10”, los cuales no definen de manera precisa que sustituyente puede ser (Por ejemplo, alquilo C1-10 puede ser metil etil, tercbutil, hexil, 2,3 – dimetilheptil; al definir arilo este puede ser fenil, naftil,

fenantril, antranil y sus respectivas sustituciones) y genera una complejidad alta dentro de la solicitud y no se define el alcance certero de lo que se desea proteger. Se solicita hacer una restricción a los sustituyentes específicos, de tal manera que a partir de estos se obtengan los compuestos específicos sintetizados y probados, de real interés para el inventor y que representen la solución al problema técnico objetivo de la invención. Se sugiere realizar dicha restricción a los sustituyentes soportados dentro del capítulo descriptivo y que se muestran en la siguiente tabla:

Sustituyente	Soportado en la descripción
Z	O, =N-OH,
R ⁴	H
R ⁶	H, hidroximetil,
R ^{6a}	H
R ⁶ + R ^{6a}	Doble enlace, ciclopropil,
R ⁷	H, metil, etil, vinil, ciclopropil,
R ^{6a} + R ⁷	Ciclopropil
R ¹⁸	H, metil,

La reivindicación 10 no es concisa, porque en esta se pretende proteger una cantidad amplia de compuestos. Se solicita restringir el alcance de esta reivindicación a una cantidad más reducida de compuestos, es decir, a aquellos que tengan mejor actividad y que representen la solución al problema técnico objetivo de esta invención.

Para las reivindicaciones 14 a 20, se solicita cambiar la expresión “medicamento” por la expresión “composición farmacéutica”, siendo este el término técnico más preciso. Además, para las reivindicaciones 15 a 20, para las cuales se propone una composición farmacéutica de los compuestos de esta solicitud con otros análogos estrogénicos, se solicita definir dichas composiciones en cuanto a su conformación cualitativa y cuantitativa.

7. Análisis de la Oposición

Argumento de Lafrancol

Afirma la sociedad opositora que esta solicitud pretende obtener patente sobre compuestos derivados de y – lactona sus respectivas composiciones farmacéuticas, con efecto gestagénico y antimineralocorticoide para el tratamiento de trastornos relacionados con la menopausia y como contraceptivo, tal cual lo menciona el capítulo reivindicatorio de esta solicitud.

El opositor argumenta que las composiciones farmacéuticas que contienen dichos compuestos y otros compuestos tales como Estradiol y Drospirenona, son eventos y prácticas totalmente conocidos en la industria farmacéutica y por lo tanto carecen de Novedad y de Nivel Inventivo, debido a que se emplean estas moléculas, las cuales ya son plenamente identificadas dentro del sector químico farmacéutico y las cuales cuentan con beneficio patentario.

Como documento soporte, el opositor adjunta las monografías correspondientes a la Drospirenona (The Index Merck, 2006. Página 585) y al Estradiol (The Index Merck, 2006. Página 635)

Respuesta del solicitante

En respuesta a la oposición anteriormente descrita, la sociedad solicitante argumenta que la sociedad opositora solamente cita los compuestos descritos y soportados en las páginas adjuntas del Index Merck que corresponden a la Drospirenona y al Estradiol, pero que no describen a los derivados de γ -lactona del ácido 15, 16 – metileno – 17 – hidroxilo – 19 – nor – 21 – carboxílico, de acuerdo con lo descrito en la reivindicación 1 de la presente solicitud y por lo tanto, la documentación presentada por el opositor no se puede tomar como arte previo relevante que pueda afectar la Novedad ni el Nivel Inventivo de esta solicitud.

La sociedad solicitante afirma que la Drospirenona posee un metilo en el carbono 13, característica técnica que no se describe dentro de la reivindicación 1 de esta solicitud. Además, se relaciona que los compuestos de esta solicitud poseen mejor balance de interacción entre los receptores de progesterona y los receptores mineralocorticoides con respecto a dicha propiedad en el caso de la Drospirenona, de acuerdo a lo descrito en los folios 111 y 112 de esta solicitud.

En consecuencia, los compuestos de esta invención se deben considerar nuevos e inventivos.

Respuesta del examinador Técnico

Se revisan los documentos adjuntados por ambas partes. Se considera que los documentos aportados por la sociedad opositora no son claros ni suficientes porque solamente se limita a mostrar los compuestos ya conocidos dentro del estado de la técnica y con los cuales se pretenden elaborar composiciones farmacéuticas de manera conjunta con los compuestos propuestos en esta solicitud, mas no divulgan compuestos que pertenecen al objeto de esta invención.

Por su parte, la sociedad solicitante menciona las ventajas desde el punto de vista farmacológico que poseen los compuestos de esta solicitud con respecto a lo divulgado en el Estado de la Técnica, en este caso, la Drospirenona. Adicionalmente, argumenta que los soportes presentados por la sociedad opositora no desvirtúan la patentabilidad de esta solicitud.

Al no existir un soporte lógico, claro ni coherente por parte la sociedad opositora y teniendo en cuenta la existencia de una ventaja técnica mejorada de los compuestos de esta solicitud con respecto al arte previo presentado por la oposición, se concluye que la patentabilidad de esta solicitud no es afectada mediante la oposición analizada y por lo tanto, se declara que la oposición carece de fundamentos para ser tomada en cuenta.

Por lo tanto, el documento presentado en esta Oposición no genera un soporte lógico ni suficiente para desvirtuar la Novedad o el Nivel Inventivo de los compuestos de esta invención, por lo cual no se considerará dentro del Examen de Patentabilidad.

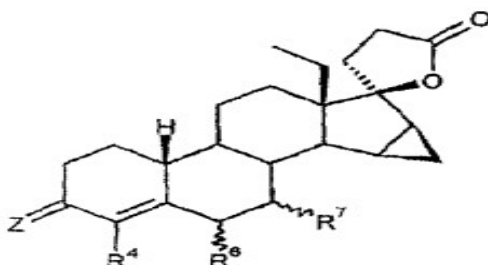
8. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de la cual se invoca prioridad, es decir, el 29 de diciembre de 2008.

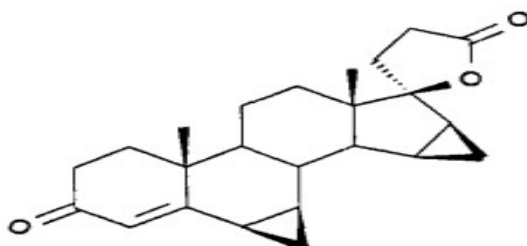
Consultadas las fuentes de información con que se cuenta, se encontraron los siguientes documentos que anticipan el objeto de esta solicitud.

Item	Documento	Título	Fecha de Publicación
D1	ES2331322*	"18 – metil – 19 – nor – 17 – preg – 4 – eno – 21, 17 – carbolactonas, así como sus preparados farmacéuticos que contienen estos compuestos"	Diciembre 29 de 2009
D2	<i>Journal of Medicinal Chemistry</i> . 1991 : 34; 2464 - 2468**	"Aldosterone antagonist 4. Synthesis and Activities of Steroidal 6, 6 – Ethylene – 15, 16 – methylene – 17 – Spirolactones"	Agosto 1 de 1991
D3	US4891365	"17 – substitutes estradienes and estratrienes"	Enero 2 de 1990

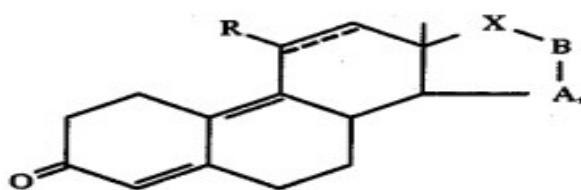
El documento D1¹ divulga compuestos esteroidales derivados de 18 – metil – 19 – nor – 17 – preg – 4 – eno – 21, 17 – carbolactonas, con actividad progestacional y antimineralocorticoide



El documento D2² divulga compuestos esteroidales derivados de 6, 6 – etilen – 15, 16 – metilen – 17 – espirolactonas, con actividad progestacional y antimineralocorticoide.



El documento D3³ divulga compuestos estradienos y estratrienos con actividad progestagénica e inhibidores de aldosterona.



9. Examen de Patentabilidad

Nivel Inventivo (Art 18 D 486)

La reivindicación 1 divulga un derivado de γ – lactona de esteroide de ácido 15, 16 – metilen – 17 – hidroxi – 19 – nor – 21 – carboxílico de la fórmula general I en donde... (Folio 182 a folio 183, línea 1 – 6)

1* Corresponde a un documento perteneciente a la familia de la Publicación WO2006072467 con fecha de Publicación Internacional del Julio 13 de 2006 en alemán.

** Nickisch, K. Beier, N. et al. Aldosterone antagonist 4. Synthesis and Activities of Steroidal 6, 6 – Ethylene – 15, 16 – methylene – 17 – Spirolactones. *Journal of Medicinal Chemistry* 1991:34; 2464 –2468.

[http://worldwide.espacenet.com/publicationDetails/originalDocument?](http://worldwide.espacenet.com/publicationDetails/originalDocument?FT=D&date=20091229&DB=EPODOC&locale=es_LP&CC=ES&NR=2331322T3&KC=T3&ND=4)

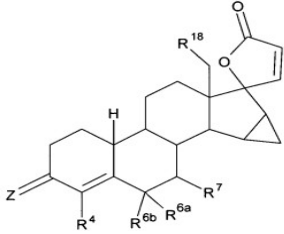
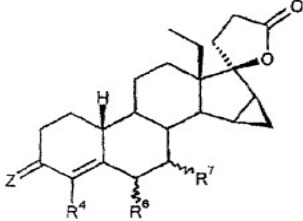
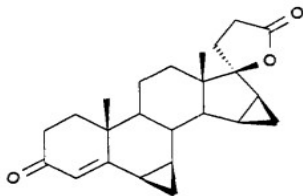
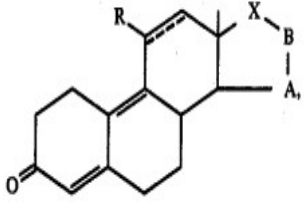
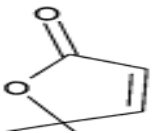
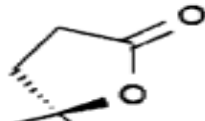
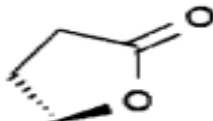
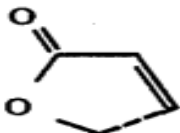
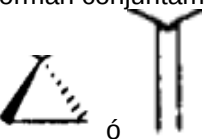
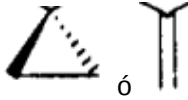
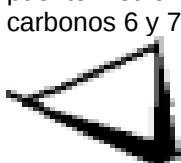
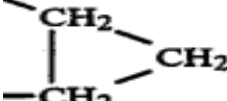
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2 <http://pubs.acs.org/doi/abs/10.1021/jm00112a022>

3 [http://worldwide.espacenet.com/publicationDetails/originalDocument?](http://worldwide.espacenet.com/publicationDetails/originalDocument?FT=D&date=19900102&DB=&locale=en_EP&CC=US&NR=4891365A&KC=A&ND=1)

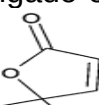
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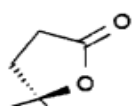
Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	D1	D2	D3
Compuesto de la fórmula I 	Compuesto de la Fórmula 1 	Compuestos de las formulas 5, 6, 7, 8, 9, 10, 13 y 14 	Compuesto de la fórmula I  R es H
Lactona en posición 17 	Lactona en posición 17 	Lactona en posición 17 	X es 
Z es O, 2 átomos de H, NOR' o NNHSO ₂ R'; donde R' es H, alquilo C ₁₋₄	Z es O, 2 átomos de H, NOR o NNHSO ₂ R; donde R' es H, alquilo C ₁₋₄	Grupo oxo en posición 3	Grupo oxo en posición 3
R ⁴ es H o halógeno	R ⁴ es H, halógeno o CF ₃	H	H
R ^{6a} y R ^{6b} son independientemente H, hidroximetil o R ^{6a} y R ^{6b} forman conjuntamente 	R ⁶ es H	En la posición 6, puede estar presente H, hidroximetil o  ó de acuerdo con los compuestos 7, 8, 9, 10, 11, 12, 15 y 16	H en posición 6
R ⁷ es H o alquilo C ₁₋₄	R ⁷ es H o alquilo C ₁₋₄	No se menciona	H es posición 7.
R ^{6a} con R ⁷ forman conjuntamente un puente metileno 	R ⁶ y R ⁷ forman conjuntamente un puente metileno  O R ⁶ y R ⁷ forman un enlace adicional	En posición 7 se sustituye con H o se forma un puente metileno entre los carbonos 6 y 7 	No se menciona
Puente metileno entre los carbonos 15 y 16 	Puente metileno entre los carbonos 15 y 16 	Puente metileno entre los carbonos 15 y 16 	A y B forman conjuntamente 
R ¹⁸ puede ser H o CH ₃ para formar metil o etil respectivamente	Etil en posición 18.	De acuerdo con los compuestos 5, 6, 9, 10, 13 y 14, R es metil o etil	Metil en posición 18.

Los Estados de la Técnica D1, D2 y D3 se consideran los más cercanos a la invención, porque divulgan compuestos esteroideos análogos de progesterona que poseen actividad progestacional y antimineralocorticoide (D1: Página 2, líneas 1 - 55; D2: Páginas 2464 a 2466, compuestos 1 a 16; D3: Página 1, columna 2).

La diferencia entre la invención y lo divulgado en D1 y D2 es que en la invención,

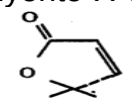
la lactona en posición 17 corresponde a , mientras que para D1 y D2, la

lactona en posición 17 es .

Esta diferencia al parece no conceden ningún efecto técnico inesperado o ventajoso para los compuestos de esta invención, con respecto a lo divulgado en D1 y D2, porque en gran parte de las estructuras se observa que los compuestos de la invención, de D1 y de D2 son similares y no se considera que la ausencia del doble enlace en la lactona sea un factor determinante en la modificación de la actividad de los compuestos de esta invención con respecto a lo divulgado en los Estado de la Técnica D1 y D2.

El Problema Técnico Objetivo que se pretende resolver es el siguiente: ¿Cómo modificar los compuestos divulgados en D1 y D2 para obtener compuestos análogos de progesterona con actividad prostestacional y antimineralocorticoide?

D3 divulga en la página 1, columna 2, que el sustituyente X en la posición 17 del

anillo puede estar sustituida por la siguiente lactona: .

Por lo tanto, una persona versada en la materia y conocedora de los conceptos de D1, D2 y D3, puede sin ningún esfuerzo modificar la lactona sugerida en D3 y cambiarla en los compuestos sugeridos en D1 y D2; además, D1 sugiere la presencia de un halógeno en la posición 4 y de la presencia de los sustituyentes diferentes al oxo en posición 3 divulgada en D1 como Z; también, el hecho de sustituir un H por un alquilo o un cicloalquilo se considera una práctica común, aun mas si la formación del puente metilen entre los carbonos 6 y 7 sugiere que el carbono 7 se une a un grupo alquilo, la cual puede ser aplicada para la posición 7 del anillo, para obtener de esta manera los compuestos propuestos en esta invención de manera obvia o evidente.

En consecuencia, la reivindicación 1, de acuerdo a lo divulgado en D1, D2 y D3, carece de Nivel Inventivo.

Las reivindicaciones 2 a 11 y 14 a 20, dependientes de la reivindicación 1, no aportan características inventivas adicionales a los compuestos de la reivindicación 1. Por lo tanto, estas reivindicaciones carecen de Nivel Inventivo

10. Conclusión

Los requisitos de Patentabilidad de esta solicitud se ven afectados de la siguiente manera:

Item	Documento	Reivindicaciones	Requisitos que afecta
D1	ES2331322	1 a 11 y 14 a 20	Nivel Inventivo
D2	<i>Journal of Medicinal Chemistry.</i> 1991: 34; 2464 - 2468	1 a 11 y 14 a 20	Nivel Inventivo
D3	US4891365	1 a 11 y 14 a 20	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.

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 2013-02-12

Elaboró: Dayron Alexander Ramirez Reyes
Revisó: Gloria Jacqueline Alfonso Roza

Aldosterone Antagonists. 4. Synthesis and Activities of Steroidal 6,6-Ethylene-15,16-methylene 17-Spirolactones

Klaus Nickisch,* Sybille Beier, Dieter Bittler, Walter Elger, Henry Laurent, Wolfgang Losert, Yukishige Nishino, Ekkehard Schillinger, and Rudolf Wiechert

Research Laboratories, Schering AG Berlin and Bergkamen, Müllerstrasse 170-178, D-1000 Berlin 65, Germany.
Received December 28, 1990

Several steroidal 6,6-ethylene-15,16-methylene 17-spirolactones were synthesized to find new progestogens that exhibit both progestational and antimineralocorticoid activities. The influence of substituents in the 10- and 13-position of the steroidal framework on both properties was investigated. It was found that only compound 12, carrying methyl groups at the 10- and 13-positions, possesses high progestational and antimineralocorticoid activity.

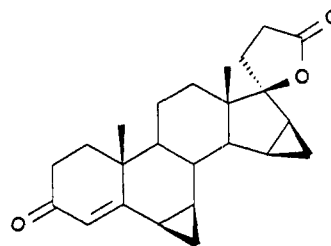
The development of steroidal aldosterone antagonists as potassium-retaining diuretics was initiated by the observation that progesterone acts as a competitive antagonist of the renal action of mineralocorticoid hormones.^{1,2} Extensive molecular modifications led to the synthesis of the antimineralocorticoid spironolactone, a compound that still exhibits weak progestational activity.³⁻⁵ Our research efforts during the past years have been primarily concerned with the development of new potent antialdosterone derivatives and have been culminated in the synthesis of 6 β ,7 β :15 β ,16 β -dimethylene spiro lactones 1 and 2.^{6,7}

Both compounds, when tested in rats, exhibited a 7- to 8-fold higher aldosterone antagonistic potency compared to that of spironolactone.^{8,9} Compound 1 could not be developed as a diuretic because of its progestational activity as measured in the endometrium transformation test and pregnancy maintenance test.^{10,11} Especially in rats 1 showed a progestational potency comparable to cyproterone acetate.¹⁰ These data suggested that aldosterone antagonistic and progestational activity are observed in the same dose range for these compounds.

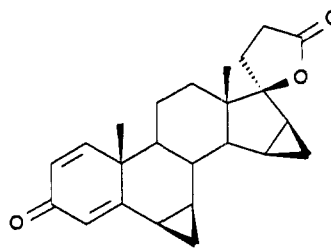
This combination of activities is only found in naturally occurring progesterone, whereas the synthetic derivatives of 17-hydroxyprogesterone and 19-nortestosterone are only potent progestational agents but do not exhibit antimineralocorticoid activity.⁸ The potential advantages of a new progestogen with a profile compared to progesterone have been emphasized^{8,11} especially with respect to the development of a new type of progestogen-estrogen combination for fertility control. Upon taking oral contraceptives, some women exhibit an increasing in blood pressure.¹² Hypertension is generally a contraindication for taking the birth control pill. With a progestogen exhibiting antimineralocorticoid activity, the increase in blood pressure

should be counteracted, therefore allowing predisposed women to choose a hormonal contraceptive as fertility control method for the first time.

The optimal ratio between aldosterone antagonistic and progestational activity has to be carefully evaluated. Probably the most obvious question is how much antimineralocorticoid activity is necessary at fully active progestational doses. To answer this question, we were looking for derivatives of compound 1 exhibiting comparable aldosterone antagonistic potency but higher progestational potency compared to 1.



1



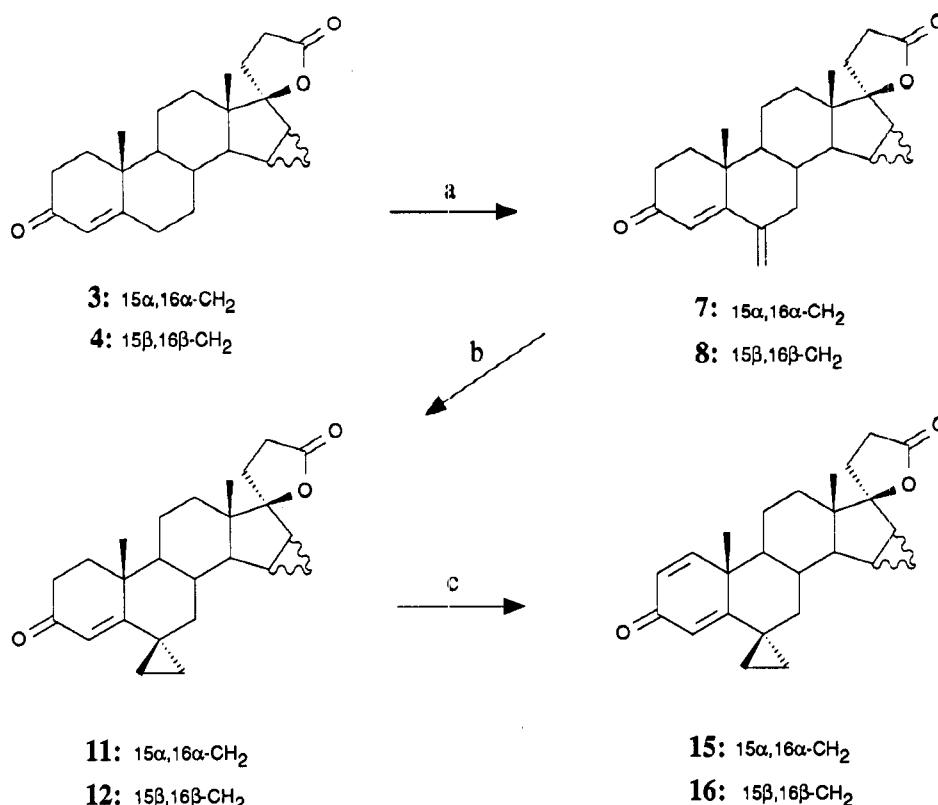
2

Chemistry

The structure-activity relationship of spirorenone analogues has been reported.¹³ Molecular modification of 1 produced only compounds with reduced aldosterone antagonistic potency and reduced binding to the progesterone receptor. We therefore investigated other basic structures showing both activities. For progestational activity the importance of substituents in the 6-position has been emphasized.¹⁴ Optimal activity is found with rather small and moderate lipophilic substituents, such as methyl or chlorine, but aldosterone antagonists with these substitu-

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Scheme I^a

^a (a) 1. pyrrolidine, MeOH, reflux; 2. CH₂O, EtOH, benzene; 3. HCl, dioxane; (b) (CH₃)₃S(O)I, NaH, DMSO; (c) DDQ, toluene, 100 °C.

ents are lacking oral bioavailability. Both requirements are fulfilled by a 6,6-ethylene moiety. Moreover it has been reported that spirolactone derivatives with this moiety exhibit aldosterone antagonistic activity.¹⁵ The progestational activity depends on the nature of substituents at the 17 α -position and to some extent at the 10- and 13-positions of the steroid nucleus.¹⁶ Generally speaking 19-nor derivatives are more potent than 10-methyl compounds. The highest progestational potency is found when the 10-position is substituted by a hydrogen and the 13-position with an ethyl group (e.g., norgestrel).¹⁶ Only a few examples about the systematic comparison of the different series of steroid frameworks on the aldosterone antagonistic activity have been reported.¹⁷ For this reason, we decided to investigate the influence of the substitution pattern in the 10- and 13-position of the steroid framework on the progestational and antimineralocorticoid activity of 6,6-ethylene-15,16-methylene 17-spirolactones.

As starting material for our efforts we chose the 15,16-methylene spirolactones 3–6. The synthesis of 3 and 4 has been reported.¹⁸ Compounds 5 and 6 were prepared under analogous conditions.¹⁹ The transformation of the 13-methyl derivatives 3 and 4 to the 6,6-ethylene compounds 11 and 12 was accomplished in a four-step sequence (Scheme I). Reaction of the unsaturated ketones with pyrrolidine generated enamines, which were reacted with

aqueous formaldehyde to form the hydroxymethyl derivatives. The crude material was transformed to the 6-methylene compounds 7 and 8. The dienes were converted to the 6,6-ethylene derivatives 11 and 12 by reaction with trimethylsulfoxonium iodide and sodium hydride.

For the synthesis of the 19-nor derivatives 13 and 14, a slightly different method of synthesis was applied. The starting materials 5 and 6 were transformed via the enamines to the 6-hydroxymethyl derivatives 9 and 10. The stereochemistry of the 6-substituent was investigated by NMR. The H-4 shows only one allylic coupling of 2 Hz to the H-10, proving that the hydroxymethyl group is in the β -position. All attempts to transform the hydroxymethyl steroids 9 or 10 to the corresponding dienones either under acidic or after transformation to the tosylates under basic conditions were unsuccessful. Only dimeric steroids could be isolated, but their accurate structures were not determined. The desired 6,6-ethylene compounds were finally synthesized by transformation of the hydroxymethyl derivatives 9 and 10 to the tosylates, which were reacted with an excess of trimethylsulfoxonium iodide and sodium hydride in an elimination addition process (Scheme II). The 1,2 double bond was introduced in compounds 11 and 12 by dehydrogenation with DDQ to yield 15 and 16.

Biological Results and Discussion

The most potent antimineralocorticoid compound of this series is clearly the 15 β ,16 β -methylene derivative 12, exhibiting a 5-fold higher potency compared to the standard drug spironolactone (oral administration to adrenalectomized rats infused with aldosterone, Table I). The introduction of a 1,2 double bond to yield 16 diminished the aldosterone antagonistic potency. The 19-nor compound 13 and the 13-ethyl-19-nor derivative 14 both showed reduced antimineralocorticoid activity when compared with 12. The 15 α ,16 α -methylene analogue 11 also

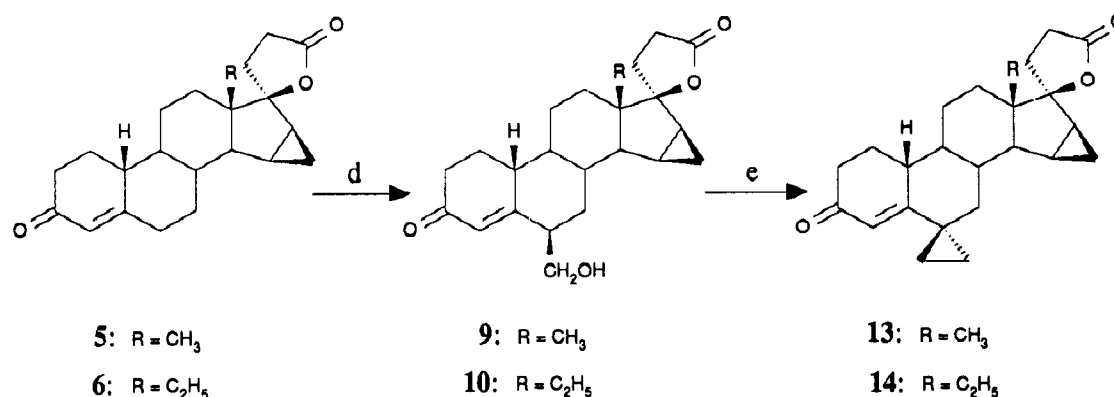
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Scheme II^a

^a (d) 1. pyrrolidine, MeOH, reflux; 2. CH₂O, EtOH, benzene; (e) 1. *p*-TosCl, pyridine; 2. (CH₃)₃S(O)I, NaH, DMSO.

Table I. Biological Activities of Spirolactones

compd	antialdosterone activity maximal relative potency ^a (spironolactone = 100; 95% confidence limits)	progesterone receptor competition factor ^c (progesterone = 1)
11	<100 ^b	2.1
12	507 (393–596)	1.1
13	≈100 ^b	0.5
14	<100 ^b	
15	≈100 ^b	4.0
16	≈100 ^b	2.3
1	685 (549–1095)	2.7

^a Relative potency calculated for the hour of maximal activity after oral administration. ^b <, ≈: lower, not significantly different relative potency estimated from single-dose experiments in which the test compound was administered at a 2-fold higher dose (53.6 mg/kg) than the standard spironolactone (26.8 mg/kg). ^c The competition factor is defined as the ratio of concentration of the test compound to progesterone causing the same specific displacement of the radiolabeled standard from the receptor (measured at 50% displacement).

exhibited decreased antimineralocorticoid activity compared to that of compound 12.

All compounds bind very strongly to the progesterone receptor exhibiting comparable (12) or even higher affinity (13) to the receptor than the naturally occurring progesterone. As it is found with 17 α -ethynyl compounds, the 15 β ,16 β -methylene-19-nor derivative 13 exhibited a stronger binding to the progesterone receptor than the 15 β ,16 β -methylene-10-methyl derivative 12.¹⁶ Unfortunately, the 13-ethyl-19-nor derivative 14 could not be tested *in vitro* because of lack of solubility.

The basic tests clearly showed that only compound 12 exhibits the desired combination of high antimineralocorticoid potency and strong binding to the progesterone receptor. Therefore the progestational activity of the 6,6-ethylene derivative 12 was evaluated in comparison to the 6 β ,7 β -methylene derivative 1 in vivo by using two relevant animal models¹⁰ (endometrium transformation test in estrogen-primed juvenile rabbits and pregnancy maintenance tests in rats, Table II). When tested subcutaneously in rabbits, compound 12 exhibited a progestational activity at least 3-fold higher than that of compound 1, whereas after oral treatment no difference in activity was observed. In the pregnancy maintenance test in rats (sc injection), the progestational activity of the 6,6-ethylene derivative 12 was about 10-fold higher compared to that of compound 1. There is a reasonable correlation between the results of the pregnancy maintenance test and progestational activity in man.¹⁰ Ongoing clinical trials are intended with compound 1 to show if the combination of aldosterone antagonistic with progestational

Table II. Progestational Activity: Endometrium Transformation Test in Rabbits after Subcutaneous and Oral Administration and Pregnancy Maintenance Test in Rats after Subcutaneous Treatment

compd	dose, mg	endometrium transformation test McPhail index		pregnancy maintenance test % inhibition	
		sc	po		
12	3.0			38	
	1.0		2.1	63	
	0.3	2.9	1.6	63	
	0.1	2.6	1.6	58	82
	0.03	1.3	1.5		12
	0.01				0
1	10.0			52	
	3.0		2.4	85	
	1.0	2.7	2.4	74	
	0.3	2.4	1.9	3	
	0.1	1.2	1.6	0	

activity is sufficient to overcome typical progesterone side effects. During the course of these studies it will also become evident whether a substance such as 12, which exhibits reduced antimineralocorticoid activity, would be more suitable for this purpose.

Methods

Antialdosterone Activity in Rats.^{20,21} Adrenalectomized male rats (Wistar strain) with a body weight of 140–160 g were treated with glucocorticoids (1 mg of fluocortolone caproate/kg sc on the day of surgery and 10 mg of fluocortolone/kg sc 1 day before the diuresis experiment, which was performed 5 days after adrenalectomy). These glucocorticoid-substituted rats were infused intravenously with a saline-glucose solution (0.05% NaCl, 5% glucose) containing aldosterone (50 μ g/L) at a rate of 3 mL/h for 15 h. The aldosterone antagonist was administered 1 h before the start of the aldosterone infusion. Urine excretion was measured in fractions of 1 h. Sodium and potassium concentrations in urine were determined by flame photometry. The antialdosterone activity was assessed by the ability of the compounds to reverse the aldosterone effect on the urinary Na/K ratio. The various antialdosterone derivatives and spironolactone were administered at three oral doses of 6.7, 13.4, and 26.8 mg/kg. The dose-response relationship was tested for each fraction

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Table III. 6,6-Ethylene Carbolactones

compd	prep method	yield, %	mp, °C	formula	Anal.	¹ H NMR (100 MHz, CDCl ₃), δ		
						18-CH ₃	19-CH ₃	other
11	A	21	177	C ₂₅ H ₃₂ O ₃	C, H, O	1.20	1.24	5.61 (s, 1, H-4)
12	A	17	184	C ₂₅ H ₃₂ O ₃	C, H, O	1.01	1.22	5.61 (s, 1, H-4)
13	B	21	214	C ₂₄ H ₃₀ O ₃	C, H, O	1.08		5.7 (d, <i>J</i> = 1.5 Hz, 1, H-4)
14	B	17	165	C ₂₅ H ₃₂ O ₃	C, H, O	0.85 (t)		5.7 (s, 1, H-4)
15	C	87		C ₂₅ H ₃₀ O ₃	C, H, O	1.25	1.35	5.98 (d, <i>J</i> = 2 Hz, 1, H-4) 6.17 (dd, <i>J</i> = 10 + 2 Hz, 1, H-2) 7.0 (d, <i>J</i> = 10 Hz, 1, H-1)
16	C	67	200	C ₂₅ H ₃₀ O ₃	C, H, O	1.07	1.33	5.98 (d, <i>J</i> = 2 Hz, 1, H-4) 6.17 (dd, <i>J</i> = 10 + 2 Hz, 1, H-2) 6.97 (d, <i>J</i> = 10 Hz, 1, H-1)

by regression analysis after logarithmic transformation of the doses. The potency of the standard substance, spiro-lactone, was allocated the value of 100.

Binding to Progesterone Receptor.²² For the determination of the affinity of the test substance to the progesterone receptor isolated from the rabbit uterus, tritiated progesterone was used as ligand, and the competition factors are defined as the multiple of the concentration to obtain displacement equivalent to the standard. A high competition factor indicates low binding strength, and a low competition factor indicates high affinity.

Endometrium Transformation Test.¹⁰ Castrated, infantile female rabbits (albino New Zealand) weighing 800–1000 g were administered a daily subcutaneous dose of 0.5 µg of estradiol for 6 days (priming). Thereafter, the animals were treated with varying doses of test compounds (po and sc) for 5 days. On day 12, the animals were sacrificed, and the uteri were excised for histological studies. The rate of the glandular development in endometrium was evaluated by using the McPhail scale (1–4; 1 = inactive, 4 = maximal development of the glands).

Pregnancy Maintenance Test.¹⁰ Pregnant rats were ovariectomized on day of pregnancy. This treatment leads to interruption of pregnancy. The ability of compounds to prevent the loss of pregnancy was used as parameter of gestagenic activity. Daily treatment was performed from day 8 to 21 of pregnancy. At autopsy day 22 the rate of pregnant animals and the rate of surviving fetuses was assessed (10 fetuses/dose = 100 % maintenance). In order to obtain an optimal uterine response to gestagens a dose of 1 µg estrone/day was injected sc in combination with the tested dose of a compound.

Experimental Section

All melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. NMR spectra were taken in CDCl₃ on a Bruker MX 90 or a Varian HA-100 spectrometer, using tetramethylsilane as an internal standard unless otherwise stated. Ultraviolet spectra were obtained in methanol on a Cary 14 UV spectrophotometer. Infrared spectra were obtained in KBr tablets on Perkin-Elmer Model 621 and 580 B infrared spectrophotometer. Optical rotations are specific rotations taken in CHCl₃ (0.5%).

Method A. 6:15β,16β-Dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (8). A solution of 4.1 g (0.0116 mol) of 4 in 31 mL of methanol was heated under reflux with 2.05 mL of pyrrolidine for 15 min. After cooling in an ice bath, the thus-formed precipitate was suctioned off, washed with a small amount of methanol, and dried. This material was dissolved in 90 mL of ethanol, and 45 mL of benzene and 4.5 mL of a 37% strength formalin solution was added dropwise. After a reaction period of 30 min, the reaction solution was evaporated to dryness under vacuum. The residue was chromatographed on silica gel

with hexane/ethyl acetate and the oily residue was agitated for 2 h in 77 mL of dioxane with 9.1 mL of half-concentrated hydrochloric acid. The reaction solution was then combined with an excess of sodium bicarbonate and filtered off from the inorganic salts. The filtrate was diluted with ether and washed with water. After drying and evaporation, the residue was chromatographed on silica gel. Recrystallization from diisopropyl ether/acetone yielded 1.2 g (28%) of 8: mp 173 °C; UV ϵ_{261} = 11 300; IR 1770, 1670, 1620, 1590 cm⁻¹; NMR 1.0 (s, 3, C-18), 1.15 (s, 3, C-19), 5.04 (s (br), 1) and 5.12 (s (br), 1) =CH₂, 5.92 (s, 1, 4-H) ppm. Anal. (C₂₄H₃₀O₃) C, H, O.

6:15α,16α-Dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (7). Under the above-described conditions, 5.9 g (0.0166 mol) of 3 was transformed to 2.26 g (37%) of 7: mp 164 °C; UV ϵ_{262} = 11 300; IR 1765, 1675, 1635, 1600 cm⁻¹; NMR 1.15 (s, 3, C-18), 1.23 (s, 3, C-19), 5.02 (s (br), 1) and 5.13 (s (br), 1) =CH₂, 5.94 (s, 1, 4-H) ppm. Anal. (C₂₄H₃₀O₃) C, H, O.

6,6-Ethylene-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (12). At room temperature, 1.41 g (0.0064 mol) of trimethylsulfoxonium iodide was agitated for 1.5 h with 239 mg (0.0055 mol) of sodium hydride (55% oil suspension) in 21.5 mL of DMSO. Under argon, 1.14 g (0.0031 mol) of 8 was added to the solution and was stirred for 50 min at room temperature. The reaction mixture was then poured into ice water and was weakly acidified with 2 N sulfuric acid. The thus-formed precipitate was filtered off and taken up in methylene chloride. After drying and evaporation, the residue was chromatographed on silica gel. Recrystallization from diisopropyl ether/acetone yielded 725 mg (61%) of 12: mp 184 °C; UV ϵ_{248} = 14 200.

6,6-Ethylene-15α,16α-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (11). Under the described conditions 1.87 g (0.0051 mol) of 7 was transformed to 1.1 g (57%) of 11: mp 177 °C; UV ϵ_{247} = 13 900.

Method B. 6β-(Hydroxymethyl)-15β,16β-methylene-3-oxo-19-nor-17α-pregn-4-ene-21,17-carbolactone (9). A solution of 4.0 g (0.0117 mol) of 5 in 35 mL of methanol was combined with 2 mL of pyrrolidine and heated for 20 min under reflux. After cooling, the thus-formed precipitate was suctioned off and washed with a small amount of cold methanol and dried. This material was dissolved in 43.6 mL of benzene and 87.2 mL of ethanol, and 4.3 mL of a 37% strength formalin solution was added dropwise. The mixture was stirred for 1 h at room temperature and concentrated under vacuum. The resultant crude mixture was chromatographed on silica gel, thus obtaining after recrystallization from diisopropyl ether 1.9 g (44%) of 9: mp 247 °C; IR 3410, 1765, 1670, 1650, 1615 cm⁻¹; NMR 1.07 (s, 3, C-18), 3.75 (m, 2, CH₂OH), 5.94 (s, 1, H-4) ppm. Anal. (C₂₃H₃₀O₄) C, H, O.

6β-(Hydroxymethyl)-18-methyl-15β,16β-methylene-19-nor-17α-pregn-4-ene-21,17-carbolactone (10). Under the above described conditions, 5.0 g (0.0141 mol) of 6 was transformed to 2.33 g (43%) of 10: IR 3450, 1770, 1670, 1610 cm⁻¹; NMR 0.86 (t, *J* = 7 Hz, 3, CH₂CH₃), 2.71 (dt, *J* = 5 + 7 Hz, 1, H-6), 3.76 (m, 2, CH₂OH), 5.95 (d, *J* = 2 Hz, 1, H-4) ppm. Anal. (C₂₄H₃₂O₄) C, H, O.

6,6-Ethylene-15β,16β-methylene-3-oxo-19-nor-17α-pregn-4-ene-21,17-carbolactone (13). A solution of 2.06 g (0.0056 mol) of 9 in 20 mL of pyridine was combined with 3.14 g (0.0165 mol) of *p*-toluenesulfonyl chloride. The mixture was stirred for 3 h at room temperature, combined with 0.2 mL of water, and agitated for another hour, and the reaction mixture was precipitated into ice water. The resultant precipitate was filtered off, washed with

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water, and dried. A solution of 3.84 g (0.0174 mol) of trimethylsulfoxonium iodide in 75 mL of DMSO was combined with 566 mg (0.013 mol) of sodium hydride (55% oil suspension) and agitated for 1 h at room temperature. To this solution was added the dried crude tosylation product dissolved in 2 mL of DMSO dropwise. The reaction mixture was stirred for 30 min and precipitated into ice water. The resultant crude product was chromatographed on silica gel, thus producing 985 mg (48%) of 13: mp 214 °C; UV ϵ_{247} = 13 500.

6,6-Ethylene-18-methyl-15 β ,16 β -methylene-3-oxo-19-nor-17 α -pregn-4-ene-21,17-carbolactone (14). Under the above described conditions 372 mg (0.001 mol) of 10 was transformed to 145 mg (39%) of 14: mp 165 °C; UV ϵ_{247} = 14 700.

Method C. 6,6-Ethylene-15 β ,16 β -methylene-3-oxo-17 α -pregna-1,4-diene-21,17-carbolactone (16). A solution of 670 mg (0.0018 mol) of 12 and 670 mg (0.003 mol) of DDQ in 13.6 mL

of toluene was stirred for 5 h at 100 °C. The reaction solution was then diluted with ether, washed with water sodium bicarbonate solution and water, dried, and evaporated. The residue was then chromatographed on silica gel. After recrystallization from diisopropyl ether/acetone, 445 mg (67%) of 16 was obtained: mp 200 °C; UV ϵ_{243} = 15 200.

6,6-Ethylene-15 α ,16 α -methylene-3-oxo-17 α -pregna-1,4-diene-21,17-carbolactone (15). Under the above-described conditions, 600 mg (0.0016 mol) of 11 was transformed to 520 mg (87%) of 15 as an oil: UV ϵ_{242} = 14 600.

Registry No. 3, 67372-62-7; 4, 67372-68-3; 5, 101765-54-2; 6, 101765-39-3; 7, 101834-16-6; 8, 84529-99-7; 9, 133753-23-8; 10, 133753-24-9; 11, 101834-17-7; 12, 101765-35-9; 13, 101765-58-6; 14, 133753-25-0; 15, 101834-18-8; 16, 101765-36-0; formalin, 50-00-0; aldosterone, 52-39-1.

Synthesis and Evaluation of Antiinflammatory Activities of a Series of Corticosteroid 17 α -Esters Containing a Functional Group

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A series of 21-desoxy-21-chlorocorticosteroids that contain a functionalized ester group at 17 α has been prepared and examined to separate their systemic activity from topical antiinflammatory activity. Introduction of the functionalized ester group at 17 α was carried out by an acid-catalyzed formation of cyclic ortho esters with 17 α ,21-hydroxyl groups of corticosteroids and subsequent acid-catalyzed hydrolysis. As for the functional group, chloro, methoxy, acetoxy, cyano, cyclopropyl, or alkoxycarbonyl group was introduced at the terminal carbon atom of the 17 α -alkanoate group. The topical antiinflammatory activity and systemic activity of these compounds were examined and found to be significantly dependent on the functionalities in the 17 α -esters. Among these derivatives, a series of 17 α -(alkoxycarbonyl)alkanoates (17 α -OCO(CH₂)_nCOOR) showed an excellent separation of the systemic activity from topical activity. The effects of the number of methylene groups (*n*) and of the alkyl groups of the ester (R) on either topical or systemic activity of the corticosteroid derivatives were also investigated.

Introduction

Since hydrocortisone was introduced into dermatological use,¹ many structural modifications of the hydrocortisone molecule have been made with the aim at enhancing antiinflammatory potency. Important structural modifications include halogenation,² methylation,³ and introduction of a double bond at C-1 position of the steroidal skeletons.⁴

Also, it is confirmed that esterification of the 17 α -and/or 21-hydroxyl groups⁵ and replacement of the 21-hydroxyl group with a halogen atom⁶ enhance the topical antiinflammatory activity due to improved penetration of

the skin and to increased affinity for the glucocorticoid receptor.⁷

As a result of these modifications, 21-chloro-9 α -fluoro-11 β ,17 α -dihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 17 α -propionate (clobetasol propionate, CP) is found to have the strongest topical antiinflammatory activity in clinical use.⁸ On the other hand, CP also shows severe adverse effects such as thymolysis and dermal atrophy.⁸

In the field of glucocorticoids, little success has been achieved in completely separating undesired side effects from topical antiinflammatory activity except for 21-carboxylate⁹ and 17 β -carboxylate¹⁰ derivatives. However, the antiinflammatory activity of neither derivatives is as strong as that of CP. Teutsch et al.¹¹ and Kertesz and

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