0.5 ml. of 0.1 *N* ethanolic potassium hydroxide. The solution was mixed and the optical density at 550 mμ measured in a Coleman Model 11 Universal Spectrophotometer. The extent of conversion of the pyridine to the pyridinium compound was calculated with the aid of the molar extinction coefficient determined by measurements made in the same way on pure 4-(*p*-nitrobenzyl)-N-β-dibenzylaminoethyl pyridinium chloride.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroidal Sapogenins. XX.[1a] Synthesis and Reactions of the Epimeric Δ^5-22-Isospirosten-3β,7-diols[1b]

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Alkaline hydrolysis with alumina of 7α-bromo-Δ^5-22-isospirosten-3β-ol acetate (Ia) produced Δ^5-22-isospirosten-3β,7α-diol 3-monoacetate (IIa), which upon chromium trioxide oxidation afforded Δ^5-22-isospirosten-3β-ol-7-one 3-acetate (IIIa). **The latter** could also be obtained by oxidation of Ia or most advantageously from Δ^5-22-isospirosten-3β-ol acetate (diosgenin **acetate)** by N-bromosuccinimide bromination–alumina hydrolysis–chromium trioxide oxidation without purification of **intermediates.** Lithium aluminum hydride reduction of the 7-ketone IIIa led to Δ^5-22-isospirosten-3β,7β-diol (IVa). The **configuration of the** epimeric diols II and IV was established by a comparison of the molecular rotation differences with **analogous derivatives** in the cholesterol series and by the course of pyrolysis experiments of the respective dibenzoates. **The 3β,7α-dibenzoate** IId led predominantly to $\Delta^{2,4,6}$-22-isospirostatriene (VI), while the epimeric 3β,7β-dibenzoate IVb **afforded** $\Delta^{6,7}$-22-isospirostadien-3β-ol benzoate (V).

Two methods have been recorded[1,3] for the synthesis of $\Delta^{5,7}$-22-isospirostadien-3β-ol (7-dehydrodiosgenin) (V). Since this substance represents the starting material in the synthesis[4,5] of the adrenal hormone cortisone from the plant sapogenin diosgenin it appeared of interest to study the applicability of the classical Windaus 7-dehydrocholesterol synthesis[6] to the sapogenin series and to characterize the intermediates.

Δ^5-22-Isospirosten-3β-ol-7-one acetate (IIIa), the key intermediate in such a synthesis has previously been prepared[7] in poor yield by direct chromium trioxide oxidation of Δ^5-22-isospirosten-3β-ol acetate or its 23-bromo derivative. In the present work it has been possible to increase the yield in this reaction to over 40%[8] by employing two alternate procedures. In either instance, the starting material was 7α-bromo-Δ^5-22-isospirosten-3β-ol acetate (Ia)[3] which without purification could be oxidized directly to IIIa with chromium trioxide in aqueous acetic acid. Alternately, the bromo derivative Ia was hydrolyzed in carbon tetrachloride solution (directly from the Wohl–Ziegler bromination[3]) with aluminum oxide to yield in *ca.* 50% over-all yield (based on Δ^5-22-isospirosten-3β-ol acetate) pure Δ^5-22-isospirosten-3β,7α-diol 3-monoacetate (IIa) which could then be oxidized to the ketone IIIa. A similar reaction sequence could be carried out with the 3-benzoate leading to Δ^5-22-isospirosten-3β,7α-diol 3-monobenzoate (IIc); for further characterization the free diol IIb and the dibenzoate IId were prepared. A small amount of the 7β-hydroxy epimer (IV) was also produced in the hydrolysis reaction.

In agreement with the observation of Fieser, *et al.*,[6] in the cholesterol and stigmasterol series lithium aluminum hydride reduction of the 7-keto derivative IIIa afforded predominantly the 7β-hydroxy isomer IVa, further characterized by its 3,7-dibenzoate IVb. The molecular rotation differences (Table I) both with respect to the differences between the two pairs of epimers (ΔM_D epimers) or the C-7 unsubstituted parent compound (ΔM_D parent compound) are in excellent agreement with the corresponding cholesterol derivatives. This coincidence in the rotation measurements automatically correlates the configuration of the presently described epimeric Δ^5-22-isospirosten-3β,-7-diols (II, IV) with the Δ^5-cholestene-3β,7-diols. The present assignments of configurations are based on the conclusions of Fieser and Fieser,[6,9] and of Barton[10] in the cholesterol series employing as additional chemical evidence the now generally accepted concept of thermal *cis*-elimination,[10] rather than on the proposed revision of configurational assignments made by Schaltegger and Müllner.[11] Thus in agreement with the results in

(1a) Paper XIX, H. J. Ringold, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 3441 (1952).

(1b) Presented on the program of the Division of Organic Chemistry, A. C. S. meeting, Milwaukee, Wis., April, 1952.

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(3) G. Rosenkranz, J. Romo and J. Berlin, *J. Org. Chem.*, **16**, 290 (1951).

(4) J. M. Chemerda, E. M. Chamberlain, E. H. Wilson and M. Tishler, THIS JOURNAL, **73**, 4052 (1951).

(5) G. Rosenkranz, J. Pataki and C. Djerassi, *ibid.*, **73**, 4055 (1951).

(6) For leading references on the original procedure and subsequent improvements see L. F. Fieser, M. Fieser and R. N. Chakravarti, *ibid.*, **71**, 2226 (1949).

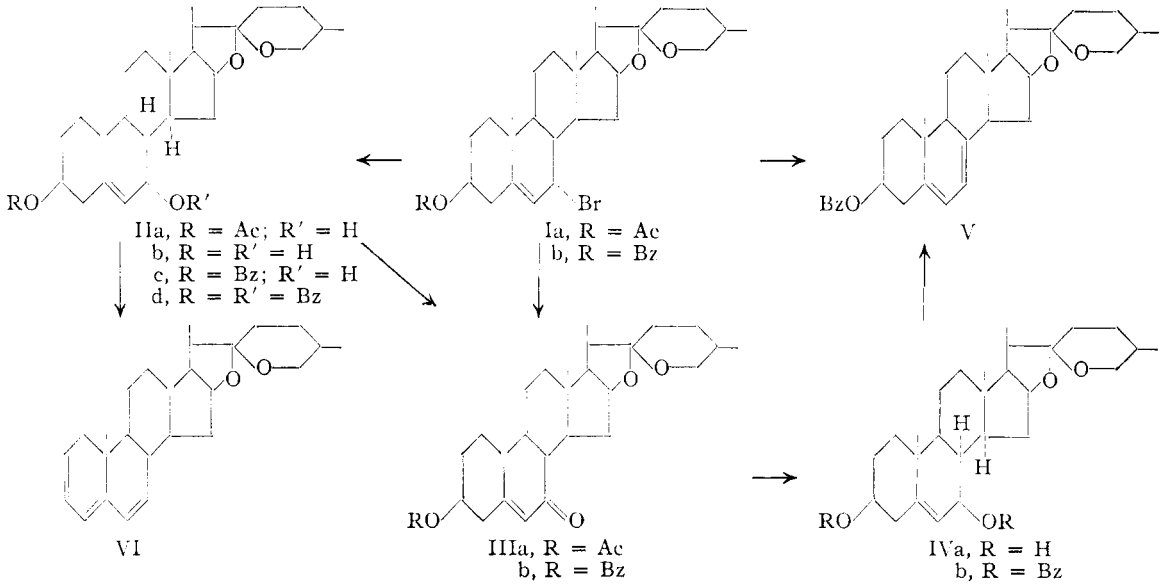
(7) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, *ibid.*, **69**, 2178 (1949); R. E. Marker and D. W. Turner, *ibid.*, **63**, 767 (1941).

(8) The best yield reported in the cholesterol series (ref. 6), is 33%.

(9) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 181.

(10) D. H. R. Barton, *J. Chem. Soc.*, 2174 (1949).

(11) H. Schaltegger and F. X. Müllner, *Helv. Chim. Acta*, **34**, 1096 (1951). These authors revise the configuration of the epimeric 7-hydroxycholesterols on quite insufficient evidence without taking into account the thermal elimination data of the dibenzoates (refs. 6, 9, 10). The incorrectness of their view has been established recently by H. Heymann and L. F. Fieser, *ibid.*, **35**, 631 (1952).



the cholesterol series,[6,9,10] thermal treatment of the 3β,7α-dibenzoate IId led to $\Delta^{2,4,6}$-22-isospirostatriene (VI)[12] while similar treatment of the 3β,7β-dibenzoate IVb afforded the known[3] $\Delta^{5,7}$-22-isospirostadien-3β-ol benzoate (V).

TABLE I

MOLECULAR ROTATION DIFFERENCES OF THE EPIMERIC Δ^5-22-ISOSPIROSTEN-3β,7-DIOLS AND Δ^5-CHOLESTENE-3β,7-DIOLS

Substances	$[M]_D$	ΔM_D (Parent compound)	ΔM_D (Epimers)
Cholesterol[a]	−154		
Δ^5-Cholestene-3β,7α-diol[c,d]	−334	−180	+362
Δ^5-Cholestene-3β,7β-diol[b]	+28	+182	
Δ^5-22-Isospirosten-3β-ol (diosgenin)	−534		
Δ^5-22-Isospirosten-3β,7α-diol	−690	−156	+367
Δ^5-22-Isospirosten-3β,7β-diol	−323	+211	
Cholesterol acetate[a]	−188		
Δ^5-Cholestene-3β,7α-diol 3-monoacetate[b,c]	−374	−186	
Δ^5-22-Isospirosten-3β-ol acetate	−578		
Δ^5-22-Isospirosten-3β,7α-diol 3-monoacetate	−755	−177	
Cholesterol benzoate[a]	−74		
Δ^5-Cholestene-3β,7α-diol 3-monobenzoate[b]	−258	−184	
Δ^5-Cholestene-3β,7α-diol dibenzoate[d]	−653	−579	+1227
Δ^5-Cholestene-3β,7β-diol dibenzoate[b]	+574	+648	
Δ^5-22-Isospirosten-3β-ol benzoate	−472		
Δ^5-22-Isospirosten-3β,7α-diol 3-monobenzoate	−642	−170	
Δ^5-22-Isospirosten-3β,7α-diol dibenzoate	−1068	−596	+1234
Δ^5-22-Isospirosten-3β,7β-diol dibenzoate	+166	+638	

[a] D. H. R. Barton, *J. Chem. Soc.*, 783 (1948). [b] H. B. Henbest and E. R. H. Jones, *ibid.*, 1792, 1798 (1948). [c] Reference 14. [d] O. Wintersteiner and W. L. Ruigh, THIS JOURNAL, **64**, 2453 (1942).

(12) J. Romo, H. J. Ringold, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **16**, 1873 (1951).

In a recent patent Lowenbein[13] claimed extremely high yields (86%) of 7-dehydrocholesterol by reaction of 7-bromocholesteryl acetate with calcium hydroxide in xylene–nitrobenzene solution. These results could not be confirmed by Schmutz, *et al.*,[14] and in spite of numerous attempts in this Laboratory to apply Lowenbein's[13] conditions (using calcium oxide, magnesium oxide, barium hydroxide or calcium hydroxide) to the 7-bromo derivatives (I) in the sapogenin series only discouraging results were realized; the best run is described in the Experimental section.

Experimental[15]

Δ^5-22-Isospirosten-3β-ol-7-one Acetate (IIIa) (a) From Δ^5-22-Isospirosten-3β-ol Acetate without Isolation of Intermediates.—Δ^5-22-Isospirosten-3β-ol acetate (diosgenin acetate) (19.0 g.) was brominated in carbon tetrachloride solution (140 cc.) with 8.8 g. of N-bromosuccinimide (Arapahoe Chemicals, Boulder, Col.) for 9 minutes in the previously described manner.[3] The filtered solution was stirred for two hours at room temperature with 150 g. of ethyl acetate-washed alumina, filtered, the alumina stirred for 15 minutes with acetone and the combined carbon tetrachloride and acetone extracts were evaporated to dryness. The residue, dissolved in 520 cc. of acetic acid, was allowed to stand at room temperature for 3 days with a solution of 3.0 g. of chromium trioxide in 90 cc. of water and then poured into a large excess of water. The collected precipitate was recrystallized twice from methanol affording 8.5 g. (43%) of the ketone IIIa with m.p. 190–194°, λ_{max}^{EtOH} 234 mμ, log ϵ 4.24. Further recrystallization produced the analytical sample with m.p. 197–198°, $[\alpha]^{20}D$ −163°, λ_{max}^{EtOH} 234 mμ, log ϵ 4.28. Marker, *et al.*,[7] obtained this substance in poor yield and reported m.p. 198°; no rotation or spectrum was given.

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 74.19; H, 9.12.

(b) From 7α-Bromo-Δ^5-22-isospirosten-3β-ol Acetate (Ia).—A solution of 5.0 g. of the pure 7-bromo derivative Ia[3] in a mixture of 67 cc. of acetic acid and 7.0 cc. of water was oxidized with 0.63 g. of chromium trioxide in 6.5 cc. of water for 3 days. After working up as in (a) there was obtained

(13) A. Lowenbein, U. S. Patent 2,476,424 (July 19, 1949).

(14) J. Schmutz, H. Schaltegger and M. Sanz, *Helv. Chim. Acta*, **34**, 1111 (1951).

(15) Melting points are uncorrected. We are indebted to Srta. Paquita Revaque for determining the optical rotations (chloroform solution) and ultraviolet absorption spectra (95% ethanol solution). Thanks are due to Srta. Amparo Barba for the microanalyses.

2.1 g. (48%) of the 7-keto compound IIIa. The benzoate IIIb was isolated in essentially the same yield when the reaction was carried out with the 7-bromobenzoate Ib.[3]

(c) From Δ^5-22-Isospirosten-3β,7α-diol 3-Monoacetate (IIa).—Twenty-one grams of the pure 7α-hydroxy compound IIa in 500 cc. of acetic acid upon oxidation with 3.3 g. of chromium trioxide in 100 cc. of water in the above described manner furnished 13.1 g. (62%) of the 7-ketoacetate IIIa with m.p. 195–198°.

Δ^5-22-Isospirosten-3β-ol-7-one Benzoate (IIIb).—A solution of 3.0 g. of Δ^5-22-isospirosten-3β,7α-diol 3-monobenzoate (IIc) in 50 cc. of acetic acid was oxidized at room temperature for 60 hours with 0.41 g. of chromium trioxide in 9 cc. of water. Dilution with water and recrystallization from chloroform–methanol afforded 2.26 g. (75%) of the 7-ketobenzoate IIIb with m.p. 230–232°, $[\alpha]^{20}D$ −111°, λ_{max}^{EtOH} 234, 272 and 280 mμ, log ϵ 4.55, 3.06, 2.81.

Anal. Calcd. for $C_{34}H_{44}O_5$: C, 76.65; H, 8.33. Found: C, 76.91; H, 8.52.

Δ^5-22-Isospirosten-3β,7α-diol (II) and Derivatives.—Δ^5-22-Isospirosten-3β-ol acetate (19.0 g.) was brominated and hydrolyzed with alumina as described above in the preparation of IIIa and the residue after evaporation of the pooled acetone and carbon tetrachloride eluates was recrystallized from hexane–benzene yielding 9.4 g. (48%) of **Δ^5-22-isospirosten-3β,7α-diol 3-monoacetate (IIa)** with m.p. 188–191°, $[\alpha]^{20}D$ −153°. The analytical sample was obtained from the solvent and showed m.p. 195–196°, $[\alpha]^{20}D$ −160°.

Anal. Calcd. for $C_{29}H_{44}O_3$: C, 73.69; H, 9.38. Found: C, 73.87; H, 9.28.

Chromatography of the mother liquors followed by saponification gave 5–10% of the 3β,7β-diol IVa, further characterized by its dibenzoate (IVb).

When the combined NBS bromination–alumina hydrolysis was applied to Δ^5-22-isospirosten-3β-ol benzoate, there was isolated in 59% yield **Δ^5-22-isospirosten-3β,7α-diol 3-monobenzoate (IIc)** with m.p. 188–190°, $[\alpha]^{20}D$ −120°, λ_{max}^{EtOH} 228, 272 and 280 mμ, log ϵ 4.22, 3.01, 2.90.

Anal. Calcd. for $C_{34}H_{46}O_5$: C, 76.37; H, 8.67. Found: C, 76.33; H, 8.75.

Alkaline saponification (90 minutes refluxing) of either IIa or IIc produced in nearly quantitative yield **Δ^5-22-isospirosten-3β,7α-diol (IIb)**, which after recrystallization from acetone possessed m.p. 223–224°, $[\alpha]^{20}D$ −159°.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83. Found: C, 75.07; H, 10.12.

Benzoylation of either the diol IIb or the 3-monobenzoate IIc with pyridine–benzoyl chloride at 0° for 3 days followed by recrystallization from hexane–benzene afforded in *ca.* 80% yield **Δ^5-22-isospirosten-3β,7α-diol dibenzoate (IId)** with m.p. 196–198°, $[\alpha]^{20}D$ −167°, λ_{max}^{EtOH} 230, 272 and 280 mμ, log ϵ 4.63, 3.24, 3.19.

Anal. Calcd. for $C_{41}H_{50}O_6$: C, 77.08; H, 7.89. Found: C, 76.95; H, 7.65.

Δ^5-22-Isospirosten-3β,7β-diol (IVa).—To a mixture of 1 g. of lithium aluminum hydride in 125 cc. of dry ether was added dropwise a solution of 4.0 g. of Δ^5-22-isospirosten-3β-ol-7-one acetate (IIIa) in 175 cc. of ether. After refluxing for 2 hours acetone was added to decompose the excess reagent followed by addition of dilute sulfuric acid. The product was extracted with chloroform, washed with dilute bicarbonate solution, water, dried and evaporated. Recrystallization from hexane–acetone gave 3.85 g. of the desired diol IVa which retained solvent very tenaciously. After drying for 8 hours at 100° in a high vacuum, the m.p. was 216–219°, $[\alpha]^{20}D$ −75°.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83. Found: C, 75.37; H, 10.06.

The 3β,7β-dibenzoate IVb was prepared as described above for IId and after recrystallization from benzene–hexane it exhibited m.p. 252–253°, $[\alpha]^{20}D$ + 26°, λ_{max}^{EtOH} 230, 272 and 280 mμ, log ϵ 4.65, 3.25, 3.18.

Anal. Calcd. for $C_{41}H_{50}O_6$: C, 77.08; H, 7.89. Found: C, 77.36; H, 8.05.

Thermal Treatment of Δ^5-22-Isospirosten-3β,7α-diol Dibenzoate (IId).—One-half gram of the dibenzoate IId was heated in a sublimation tube at 200° and 0.01 mm. for 3 hours, whereupon all but a small amount of oil had sublimed. The entire sublimate was dissolved in ether, washed with sodium carbonate solution to remove the benzoic acid and evaporated to yield a semisolid with λ_{max}^{EtOH} 294 and 306 mμ, log ϵ 3.96, 3.98. Crystallization from acetone gave 0.13 g. (42%) of colorless crystals of **$\Delta^{2,4,6}$-22-isospirostatriene (VI)** with m.p. 183–185°, $[\alpha]^{20}D$ −104°, λ_{max}^{EtOH} 294 and 306 mμ, log ϵ 4.23, 4.28; the infrared spectrum was identical with that of an authentic specimen (reported[12]: m.p. 186–188°, $[\alpha]^{20}D$ −107°).

When 2.0 g. of the dibenzoate IId was refluxed for 22 hours with 25 cc. of diethylaniline, there was isolated after chromatography 0.42 g. (34%) of the triene VI.

Thermal Treatment of Δ^5-22-Isospirosten-3β,7β-diol Dibenzoate (IVb).—A solution of 2.0 g. of the 3β,7β-dibenzoate IVb in 25 cc. of diethylaniline was refluxed in an atmosphere of nitrogen for 16 hours and the solvent was then removed by distillation with steam. The resulting black residue was extracted with ether, washed with dilute hydrochloric acid, sodium bicarbonate solution, water, dried and evaporated leaving 1.7 g. of a black oil with λ_{max}^{EtOH} 230, 270, 280, 292 mμ, log ϵ 4.14, 4.09, 3.90, and 3.73. Crystallization from ethyl acetate afforded 0.565 g. (35%) of **$\Delta^{5,7}$-22-isospirostadien-3β-ol benzoate (V)** with m.p. 208–210°, $[\alpha]^{20}D$ −92°, λ_{max}^{EtOH} 230, 270, 282, 292 mμ, log ϵ 4.18, 4.11, 4.13, 3.97; the substance proved to be identical (mixed melting point, infrared spectrum) with an authentic specimen.[3]

The loss of benzoic acid to produce the $\Delta^{5,7}$-dien moiety appeared to be nearly quantitative and the low yield of pure product seemed to be due to extensive decomposition of the side chain. A reduced reaction time or the substitution of dimethyl- for diethylaniline reduced the yield to *ca.* 25%. Pyrolysis of the dibenzoate IVb by heating at 225° and 0.01 mm. gave as the only pure product 23% of the $\Delta^{5,7}$-dien-3β-ol benzoate (V).

Dehydrobromination of 7α-Bromo-Δ^5-22-isospirosten-3β-ol Benzoate (Ib) with Calcium Hydroxide.—After trying a wide variety of experimental conditions with several alkaline earths oxides and hydroxides in an attempt to apply Lowenbein's[13] conditions to the sapogenin series, the following conditions were found to give the best and most reproducible results:

A mixture of 20 g. of calcium hydroxide, 50 cc. of xylene and 15 cc. of nitrobenzene was stirred and heated to 125° and a small amount of solvent was allowed to distil to remove moisture. After cooling, 5.0 g. of the 7-bromobenzoate Ib was added in one portion and the mixture was stirred for 2 hours at 125°. The cooled solution was filtered, the precipitate was washed with hot benzene, 5.0 g. of sodium bicarbonate in 50 cc. of water was added and the volatile material was removed by steam distillation. The residue was extracted with ethyl acetate, washed with water, dried, concentrated and chilled; 0.86 g. of benzoate V with m.p. 205–207° crystallized. Chromatography of the mother liquors furnished an additional 0.3 g. of V of equal purity totalling 27%.

In the case of the acetate Ia, the optimum yield (22%) was realized when barium hydroxide and a reaction time of 30 minutes were employed.

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