rat liver extracts at a free dye concentration of 5 × 10^{-6} mole per liter are also listed in Table III. It will be noted that at this particular free dye concentration and in terms of the units used the amount of any one dye bound to the proteins in the rat liver extracts is approximately one third to one half of the amount bound to bovine serum albumin. This observation may be of some significance since it has been found by other investigators that neutral dye molecules do not bind to bovine γ-globulin or pepsin.[4] The composition of these rat liver extracts is currently unknown, but an attempt is being made in this laboratory to isolate and characterize the protein or proteins involved in the formation of these complexes with uncharged dyes.

Acknowledgment.—The authors are indebted to Dr. Holly C. Fryer, Statistical Laboratory, Kansas State College, for advice regarding the statistical analysis of the observed data.

MANHATTAN, KANSAS

[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, ST. LOUIS RESEARCH DEPARTMENT, MONSANTO CHEMICAL CO.]

Studies in Steroid Total Synthesis. V. Abnormal Cleavage of Some Tricyclic Ketone Epoxides

BY WILLIAM S. KNOWLES AND QUENTIN E. THOMPSON

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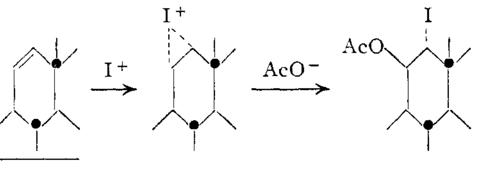
Reductive cleavage of the $5\beta,6\beta$-epoxide function of the tricyclic ketone IIIa does not give the axial 5β-ol (IIc) predicted by conformational theory but gives the equatorial 6β-ol (IId). Both IIIa and the isomeric $5\alpha,6\alpha$-epoxide IIIb are opened abnormally by methoxide and thiophenoxide anions giving products to which we have assigned structure VIIIa,b,c and IXa,b.

In the course of work designed to prepare ring B,C,D-tricyclic intermediates containing a potential C-11 oxygen, the chemistry of the isomeric 5,6-oxides derived from *dl-anti-trans*-1,6a,7,7a,10a,-11,11a,11b - octahydro - 4,6a,9,9 - tetramethylphenanthro[2,3][1,3]dioxol-3(2H)-one (Ic) was investigated. The course of the reactions in most cases was found to be extremely unpredictable. Abnormal cleavage by methoxide and thiophenoxide anions and the abnormal reductive cleavage of the β-oxide form the subject of the present paper.

The readily available tricyclic ketone Ic[1] served as the starting point for the preparation of both oxides. Reaction of Ic with approximately one mole of silver acetate and iodine in glacial acetic acid gave the 5β-acetoxy-6α-iodoketone IIa which upon treatment with aqueous base gave the $5\beta,6\beta$-epoxide IIIa, m.p. 200–201°.[2] The isomeric $5\alpha,6\alpha$-epoxide IIIb, m.p. 214–217°, readily was obtained by treatment of Ic with perbenzoic or monoperphthalic acids. Configurational assignments were made assuming backside attack by peracids would give the α-epoxide, whereas silver acetate–iodine treatment would result in an initial α-oriented attack by I^+ followed by opening with acetate ion to form the 5β-acetoxy-6α-iodo configuration assigned. Base treatment would then yield the β-epoxide.



Catalytic reduction of the α-epoxide IIIb yielded the 6α-alcohol IIb. As expected for an axial hydroxyl located vinylogously beta to a carbonyl group, mild treatment with base caused elimination of water and formation of the dienone Ic. Several attempts to reduce the isomeric epoxide IIIa catalytically did not give clear results. Reduction with zinc and acetic acid proceeded smoothly to yield a new alcohol, m.p. 187–188°, $\lambda_{\max}^{\text{alc}}$ 250, ϵ 15,380. If the reduction had occurred in a normal manner, IIc would be the expected structure for the product. However, ready acetylation at room temperature with pyridine and acetic anhydride indicated the presence of an equatorial hydroxyl function.[3] Attempts to oxidize the alcohol with manganese dioxide[4a,b] or chromic anhydride in pyridine[5] yielded chiefly starting material, again indicative of a non-allylic equatorial hydroxy group.

The rearrangement of Δ^4-cholestenone-6-ol systems to the corresponding 3,6-diones under alkaline conditions has been well established.[6a,b,c] Moreover, it has been shown both in the Δ^4-3-one-6-ol[6b] system and the Δ^8-11-α-ol-7-one[7] system that it is significantly easier to effect rearrangement when the hydroxyl group is axial than when it is equatorial. The axial alcohol represented by

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(1) The ketone Ib was first prepared by R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore (THIS JOURNAL, **74**, 4223 (1952)) as the minor β-*cis*-glycol resulting from osmium tetroxide oxidation of the unsaturated ketone Ia. Subsequently, Woodward and Brutcher (private communication) prepared the same glycol (m.p. 181–182°) by silver acetate–iodine oxidation of Ia.

(2) Compounds IIa and IIIa were first prepared at Harvard by F. V. Brutcher and R. B. Woodward and were disclosed to us by private communication.

(3) The isomeric alcohol IIb acetylated incompletely under the same conditions. This somewhat slower acetylation would be expected for an axial hydroxyl at C-6. The analogous C-12 α- and β-alcohols in the bile acid series show similar behavior [B. Koechlin and T. Reichstein, *Helv. Chim. Acta*, **25**, 918 (1942)].

(4) (a) *Cf.* S. Ball, T. W. Goodwin and R. A. Morton, *Biochem. J.*, **42**, 516 (1948); F. Sondheimer, C. Amendola and G. Rosenkranz, THIS JOURNAL, **75**, 5930, 5932 (1953). (b) Sondheimer, *et al.* [*J. Chem. Soc.*, 1226 (1954)], has used manganese dioxide for the oxidation of 6β-hydroxyprogesterone to the corresponding 6-ketoprogesterone, thus effecting successful oxidation of a system structurally similar to our formula IIc.

(5) *Cf.* G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(6) (a) B. Ellis and V. A. Petrow, *J. Chem. Soc.*, 1078 (1939); (b) P. T. Herzig and M. Ehrenstein, *J. Org. Chem.*, **16**, 1050 (1951), (c) see reference cited in footnote.[4b]

(7) J. Romo, G. Stork, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 2918 (1952).

structure IIc thus would be expected to undergo facile conversion to the corresponding saturated diketone IV. All attempts to effect rearrangement failed. When the product was subjected to hot potassium *t*-butoxide treatment,[7] only dehydration occurred giving the dienone Ic. These facts indicated that in all probability the alcohol was not IIc but rather IId, the isomer obtained by abnormal epoxide opening. This result represents an exception to the general rule that in a polycyclic cyclohexane system an epoxide always opens to give the axial alcohol.[8]

Reduction of IIIa with lithium aluminum hydride to the epimeric diols V followed by oxidation with manganese dioxide likewise yielded IId indicating that abnormal epoxide cleavage was not peculiar to the method of reduction.[8a]

Sulfide anions have been shown to be excellent reagents[9] for opening epoxides, and thus it was of interest to see whether they would behave in a normal manner on IIIa. A base-catalyzed reaction of the β-epoxide IIIa with excess thiophenol in *t*-butyl alcohol at room temperature gave a high yield of crystalline adduct, m.p. 140–142°. Infrared and ultraviolet spectra ($\lambda_{\max}^{\text{alc}}$ 254, ϵ 15,000) and analyses showed clearly that the material was an α,β-unsaturated ketone containing one hydroxyl group and one phenylthioether group. Normal addition of thiophenol to IIIa would be expected to give a 5β-ol-6α-thiophenyl ether, *i.e.*, IIe. However, desulfurization of the adduct with Raney nickel gave the 6β-alcohol IId, m.p. 187–188°, thus indicating again an abnormal epoxide cleavage. Furthermore, treatment of the adduct for ten minutes with hot alcoholic alkali gave a new compound, $C_{25}H_{30}O_3S$, m.p. 128–129°, which arose from the loss of a mole of water and not a mole of thiophenol as would be expected for a structure IIe. These facts would seem to suggest the adduct had the 5-thiophenol-6β-ol structure IIf and the $C_{25}H_{30}O_3S$ dehydration product was VIa. However, examination of the ultraviolet spectrum of the latter product clearly indicated that it could not be VIa. The observed spectrum showed a single peak at 280 mμ, ϵ 17,500, a figure quite inconsistent with structure VIa since the unsubstituted dienone chromophore of Ic has a peak at 289 mμ, ϵ 25,400. An appreciable bathochromic shift would be expected for dienones substituted as in VIa with an electron-rich thiophenyl group. No specific example of a thioenol ether cross-conjugated with a dienone was found in the literature. However, $\Delta^{4,6}$-cholestadien-3-one absorbs at 284 mμ, ϵ 26,300,[10] while the corresponding 6-ethoxy-$\Delta^{4,6}$-cholestadien-3-one absorbs at 295 mμ, ϵ 16,800.[11] In this case, the ethoxyl group causes an 11 mμ bathochromic shift. The greater bathochromic effect of RS-groups as compared to RO-groups has been shown clearly.[12] Therefore, the hypsochromic shift observed in our dienone thioether, m.p. 128–129°, rules out structure VIa. These conclusions are supported by chemical evidence also. Enol thioethers like their oxygen analogs are acid labile.[13]

Solution of our unknown dienone in a small amount of trifluoroacetic acid followed by trituration with water resulted in the quantitative removal of the acetonide groups without affecting the phenyl thioether linkage.

Desulfurization of the dienone acetonide with Raney nickel in ethyl acetate gave the known ketone IIg thus indicating no rearrangement of the carbon skeleton. The dihydroketone IIg had been previously prepared by catalytic hydrogenation of Ic using palladium-on-strontium carbonate.[14] The reduction of the 5,6-double bond during desulfurization was not unexpected since other work in this Laboratory has shown it to be very easily reduced. Attempts to effect desulfurization while preserving the dienone were not completely successful. Use of deactivated nickel at low temperature in ethyl acetate gave what appeared to be a mixture of Ic and IIg since the ultraviolet spectra showed maxima at 289 and 250 mμ the correct positions for the dienone and its dihydro-derivative, respectively.

It can be concluded from the evidence cited that the dienonethioether has the intact carbon skeleton of Ic, and the point of substitution of the thioether linkage cannot be at positions 3, 4, 4a, 5 or 6.[12] However, other points of substitution which would be expected to satisfy the spectral requirements are positions 2 (VIIa), on the methyl group attached to the 4-position (VIIb) and position 11b (IXa). Reasonable mechanisms can be written for the formation of the sulfide linkage at each of these points. However, in work to be cited below, all but the last have been eliminated. Thus, structure VIIIa has been assigned to the adduct of IIIa with thiophenol and IXa for the dehydrated product.

Reaction of the isomeric epoxide IIIb with thiophenol gave an adduct VIIIb apparently differing from VIIIa only in the configuration of the hydroxyl group since dehydration with base yielded IXa.

Because of the unexpected course of base-catalyzed mercaptan opening, the nucleophilic cleavage with methoxide ion was investigated. Treatment of IIIa at reflux with excess sodium methoxide in methanol gave a complex mixture of methoxy tricyclic ketones. The major product, a methoxydienone, m.p. 108–110°, $\lambda_{\max}^{\text{alc}}$ 289 mμ, ϵ 25,200, was obtained in 60–70% yield. Treatment with acid removed the acetonide group without affecting the methoxyl or the ultraviolet spectrum, since the glycol could be converted back to the parent ketone with acetone and copper sulfate. On the basis of these data and the arguments presented below, the ketone and glycol resulting from acid treatment were assigned the structures IXb and Xb, respectively.

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(8) *Cf.* D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953), D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).

(8a) *Cf.* W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954), and P. L. Julian, W. Cole, E. W. Meyer and B. M. Regan, THIS JOURNAL, **77**, 4601 (1955).

(9) F. N. Woodward, *J. Chem. Soc.*, 1892 (1948); C. D. Nenitzescu and N. Scarlatescu, *Ber.*, **68**, 587 (1935); H. Gilman and L. Fullhart, THIS JOURNAL, **71**, 1478 (1949).

(10) A. L. Wilds and C. Djerassi, *ibid.*, **68**, 1712 (1946).

(11) L. Dorfman, *Chem. Revs.*, **53**, 78 (1953).

(12) Bowden Braude and E. R. H. Jones, *J. Chem. Soc.*, 948 (1946).

(13) S. Bernstein and L. Dorfman, THIS JOURNAL, **68**, 1152 (1946), and G. Rosenkranz, St. Kaufmann and J. Romo, *ibid.*, **71**, 3689 (1949).

(14) L. B. Barkley, W. S. Knowles, H. Raffelson and Q. E. Thompson, *ibid.*, **78**, 4111 (1956).

In addition to the major product Xb, three other pure compounds were isolated from the reaction mixture. The first minor product was merely the undehydrated precursor to IXb. Thus its structure was VIIIc, and further treatment with methoxide converted it to IXb. The other compounds, m.p. 142–143° and m.p. 152–153°, were isomeric with IXa. The ultraviolet spectrum of the higher melting compound had a single maximum at 304 mμ, ϵ 15,300, indicating that it was probably VIb, since the observed bathochromic shift of 15 mμ would be expected for this type of substitution on the dienone chromophore.[10] The lower melting isomer had an ultraviolet maximum at 294 mμ, ϵ 24,000. Because of the limited quantity, the structure of this compound remained unknown.

Cleavage of the α-epoxide IIIb with sodium methoxide gave an even more complex mixture of products from which could be isolated the methoxydienone IXb previously obtained from the β-epoxide. Thus, both the mercaptide and methoxide anions cleaved the α- and β-epoxides IIIa and IIIb in a closely analogous and abnormal manner.

The possibility still remained that the methoxyl and the thiophenyl groups could reside on the C-4 methyl group as far as could be deduced from spectral data. This position was ruled out by running Kuhn–Roth C-methyl determinations which conclusively showed the presence of two C-methyl groups in Xa and Xb. Obviously, only one could be present if the thioether or the methoxyl function were located as in VIIc or VIIb.

In addition, it can be argued that the alkoxyl or the thiophenyl group might occupy the 2-position. This alternative has been excluded by synthesis of VIIa. Treatment of the potassium salt of Ic with phenylsulfenyl chloride gave a low yield of an epimeric mixture of the two phenylthioethers VIIa. Extensive crystallization yielded an apparently pure isomer, m.p. 195–197°, $\lambda_{\max}^{\text{alc}}$ 293 mμ, ϵ 19,800. Alkali caused a shift of the maximum to 287 mμ, ϵ 22,400. The infrared spectra of the crude epimers VIIa or of the purified isomer in no way resembled IXa. Moreover, the ultraviolet spectrum of IXa was unaffected by base.

Though deduced from evidence of a negative nature, the structural assignments made appear to be the only ones consistent with the known facts. The mechanism of the reaction can be readily rationalized. Under the influence of base, the α,β-unsaturation in the epoxides III is isomerized to some extent to the β,γ-position. Attack by sulfide or methoxide anion then in essence becomes a 1,4-addition to an unsaturated system. Analogous addition to α,β-unsaturated ketones are of course well known. Subsequent abstraction of a proton from the solvent gives the primary adduct shown. Isomerization of the double bond to the α,β-position followed by loss of water would give IXa.

Acknowledgments.—We thank Dr. Bernart Katlafsky and Mr. O. E. Kinast for their help with the numerous spectra required in this work. We also are indebted to Dr. R. B. Woodward for valuable advice and discussion and to Drs. F. C. Meyer and O. J. Weinkauff whose interest and cooperation made this work possible.

Experimental[15]

***dl-anti-trans*-1,6a,7,7a,10a,11,11a,11b-Octahydro-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxol-3(2H)-one (Ic).**—To a slurry of 30.9 g. of silver acetate in 350 ml. of glacial acetic acid at 25° was added 18.3 g. of *dl-anti-trans*-4,4a,4b,5,8,8a-hexahydro-1,8a-dimethyl-2(3H)phenanthrone (Ia).[16] The mixture was stirred rapidly and 21.5 g. of iodine was added over a period of 15 minutes. When addition of iodine was complete, 3.0 ml. of water was added. The temperature was raised to 90–95° and held for 3 hr. The reaction mixture was then cooled, filtered and the filter cake washed thoroughly with 100 ml. of chloroform and discarded. The filtrate was dried *in vacuo* with the temperature kept below 85°. The thick residue remaining was dissolved in 500 ml. of methanol and filtered to remove a small amount of solid. Strong aqueous base was added dropwise to the methanol solution until just basic to litmus. A solution of 4.8 g. of potassium hydroxide in 100 ml. of methanol was added, and the dark solution was allowed to stand under nitrogen for 16 hr. at room temperature. Following this, the solution was acidified to test paper with a few ml. of acetic acid. Most of the solvents were then removed under reduced pressure at water-bath temperature. The residue was dissolved in 200 ml. of chloroform and washed with 200 ml. of water in two portions. The chloroform layer was then dried with calcium sulfate and the solvent removed under reduced pressure. When about 90% of the chloroform had been removed, the residue was triturated with 75 ml. of hot ethyl acetate. A copious precipitate of glycol Ib separated. The first crop amounted to 14.9 g., m.p. 180–182°. A second crop, 0.60 g., m.p. 170–180° (74%), was obtained from the mother liquors. The infrared spectrum of this glycol was identical with the minor osmium glycol obtained by Woodward.[1]

The glycol was converted to the acetonide (Ic) by dissolving (both crops) in 1 liter of dry acetone and stirred for 48 hr. with 90 g. of anhydrous copper sulfate. The latter was then removed by filtration and the solvent distilled out. The crude acetonide crystallized from the residue and amounted to 13.7 g., m.p. 152–154°. Second and third crops, 1.9 g., m.p. 147–151°, and 0.35 g., m.p. 138–148°, respectively, were obtained by further concentration of the mother liquors. Recrystallization of first crop acetonide once from acetone gave pure material, m.p. 153–154°, $\lambda_{\max}^{\text{alc}}$ 289 mμ, ϵ 25,400.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.18; H, 8.71.

***dl-anti-trans*-1,5,6,6a,7,7a,10a,11,11a,11b-Decahydro-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxole-3(2H)-one (IIg).**—One gram of dienone Ic, dissolved in 30 ml. of isopropyl alcohol and treated with 3 drops of 10% aqueous sodium hydroxide solution, was hydrogenated exactly as described for optically active Ia in a previous paper.[17] The yield of crystalline dihydro-ketone was 1.0 g., m.p. 155–158°. One recrystallization from ether gave pure material, m.p. 157–159°, $\lambda_{\max}^{\text{alc}}$ 250 mμ, ϵ 15,400.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.97; H, 9.31. Found: C, 74.51; H, 9.30.

***dl-anti-trans*-1,5,6,6a,7,7a,10a,11,11a,11b-Decahydro-5β-hydroxy-6α-iodo-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxole-3(2H)-one Acetate (IIa).**[2]—To a suspension of 15 g. of silver acetate in 270 ml. of glacial acetic acid and 90 ml. of chloroform was added 25 g. of crystalline acetonide Ic. The mixture was then stirred rapidly at 25–30° and 22.1 g. of iodine was added over a period of 15 minutes. Stirring was continued for 1.5 hr. after addition of the iodine. The suspension was filtered and the solid washed thoroughly with 300 ml. of chloroform. The filtrate was then quenched with about 400 ml. of ice-water and the chloroform layer was separated and washed twice with 200 ml. of water, once each with 200 ml. of 5% bicarbonate solution and finally once with water. The organic layer was dried with Drierite and the chloroform was removed under slightly reduced

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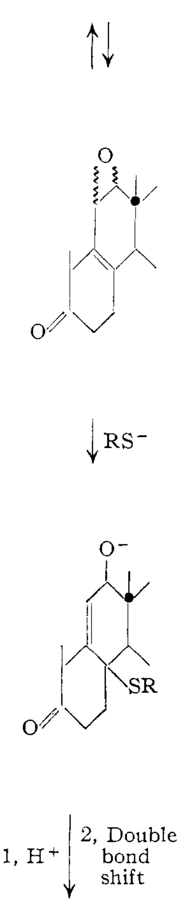
[15] Melting points are uncorrected. Infrared spectra were run in chloroform on a Perkin–Elmer recording spectrophotometer, model 21. Ultraviolet spectra were run on a Cary recording spectrophotometer, model 11. Analyses were done by Mr. A. Bybell of this Laboratory and by Du Good Chemical Laboratory of St. Louis.

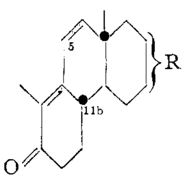
[16] See footnote 1 and reference cited therein.

[17] L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Thompson, THIS JOURNAL, **76**, 5014 (1954).

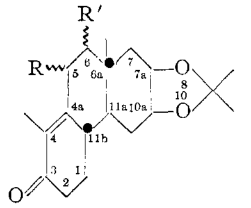
III



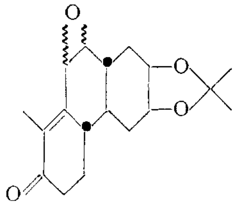
VIIIa or b



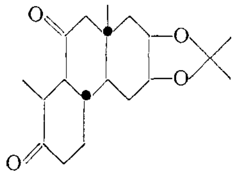
Ia, R = double bond
b, R = β-*cis*-glycol
c, R = β-*cis*-acetonide



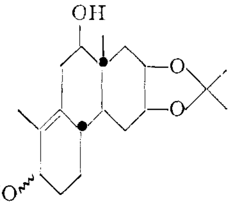
IIa, R = β-OAc, R′ = α-iodo
b, R = H, R′ = α-OH
c, R = β-OH R′ = H
d, R = H, R′ = β-OH
e, R = β-OH, R′ = α-SC$_6$H$_5$
f, R = α-SC$_6$H$_5$, R′ = β-OH
g, R = R′ = H
h, R = H, R′ = β-OAc



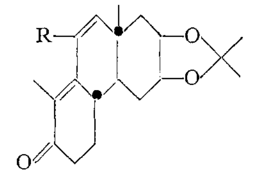
IIIa, β-oxide
b, α-oxide



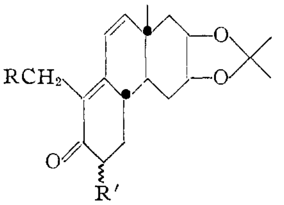
IV



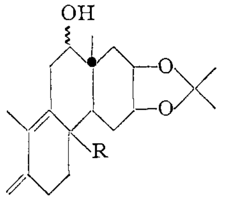
V



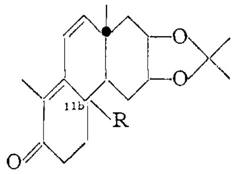
VIa, R = SC$_6$H$_5$
b, R = OCH$_3$



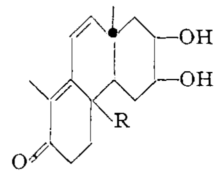
VIIa, R = H, R′ = SC$_6$H$_5$
b, R = OCH$_3$, R′ = H
c, R = SC$_6$H$_5$, R′ = H



VIIIa, β-OH, R = SC$_6$H$_5$
b, α-OH, R = SC$_6$H$_5$
c, β-OH, R = OCH$_3$



IXa, R = SC$_6$H$_5$
b, R = OCH$_3$



Xa, R = SC$_6$H$_5$
b, R = OCH$_3$

pressure. When the first crystalline material had begun to separate, the residue was quenched with 300 ml. of ether. A copious white precipitate of IIa amounting to 34.2 g. (88.5%), m.p. 194–196° dec., was obtained.

Anal. Calcd. for $C_{21}H_{29}O_5I$: C, 51.64; H, 5.98; I, 26.06. Found: C, 51.54; H, 6.08; I, 25.99.

***dl-anti-trans*-5β,6β-Epoxy-1,5,6a,7,7a,10a,11,11a,11b-decahydro-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxole-3(2H)-one (IIIa).**[2]—A suspension of 34 g. of IIa in 300 ml. of benzene was treated with 12.6 g. of potassium hydroxide in 30 ml. of water and 250 ml. of methanol. The three-phase system was stirred vigorously under nitrogen at room temperature until all of the solid had dissolved (3 hr.). Water (200 ml.) was added and the benzene phase was separated. After washing once with water, the benzene was dried and distilled off under slightly reduced pressure. When the volume of solution reached one-third, crystalline epoxide began separating. Evaporation to dryness gave 19.5 g. (87% from Ic) of white crystals, m.p. 198–200°. Recrystallization of a small portion once from benzene gave pure material, m.p. 200–201°, $\lambda_{\max}^{\text{alc}}$ 251.5 mμ, ε 16,270.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.61; H, 8.27.

***dl-anti-trans*-5α,6α-Epoxy-1,5,6,6a,7,7a,10a,11,11a,11b-decahydro-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxole-3(2H)-one (IIIb).**—A solution of 3.02 g. of Ic in about 50 ml. of anhydrous ether was treated with 45.7 ml. of 0.328 *M* ethereal monoperphthalic acid solution[18] and allowed to stand at room temperature for 5 days. During this time, large rice-like crystals of epoxide separated. This crop of essentially pure IIIb amounted to 1.5 g. The filtrate was washed with aqueous base, dried and concentrated to give a second crop of 750 mg., m.p. 212–214°, of good quality epoxide. The total yield was 2.32 g. (73%). One recrystallization of first crop material from acetone gave pure IIIb, m.p. 215–217°, $\lambda_{\max}^{\text{alc}}$ 251 mμ, ε 14,200.

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.71; H, 8.36.

***dl-anti-trans*-1,5,6,6a,7,7a,10a,11,11a,11b-Decahydro-6β-hydroxy-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxole-3(2H)-one (IId). (a). By Zinc–Acetic Acid Reduction of IIIa.**—Four grams of zinc dust was added at room temperature to a solution of 2.85 g. of IIIa in 25 ml. of glacial acetic acid. Vigorous stirring was begun and the temperature kept at 38–40° by cooling until the initial surge of the

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[18] A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1948, p. 768.

reaction had subsided. After the first 15 min., the temperature dropped and stirring was continued at around 30° for another 3.5 hr. before 120 ml. of chloroform was added and the zinc removed by filtration. The filtrate was washed successively with 100-ml. portions of water (twice), 5% bicarbonate solution and finally water. After drying with Drierite, the chloroform was removed and the residual glass triturated with 10 ml. of ether and 10 ml. of hexane. Crystallization occurred immediately. The first crop of IId amounted to 2.0 g. (70%), m.p. 187–188°. No second crop could be obtained. One recrystallization from ether–acetone gave the analytical sample, m.p. 187–188°, λ_{max}^{alc} 250 mμ, ϵ 15,400.

Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 70.93; H, 8.58.

(b) **By Reduction to the Epimeric Glycols V, Followed by Oxidation with Manganese Dioxide.**—To a slurry of 2.0 g. of lithium aluminum hydride in 50 ml. of anhydrous ether was added 2.4 g. of IIIa dissolved in 15 ml. of dioxane and 50 ml. of ether. After stirring at 25° for 2 hr., the mixture was carefully quenched with 5 ml. of methanol. Approximately 100 ml. of an aqueous saturated sodium chloride solution was added and the heterogeneous mixture was filtered to remove solids. The organic layer in the filtrate was separated, washed once with 50 ml. of saturated salt solution, dried and the solvent removed. The residual oil was boiled with 10 ml. of ether causing crystallization. About 1.5 g. of V, m.p. 177–184°, was obtained as a white powder. The infrared spectrum of this material showed strong hydroxyl and no carbonyl absorption. Examination of the mother liquor from the glycol crystallization showed that it was primarily alcoholic but contained some saturated carbonyl.

Oxidation of V was effected by stirring 100 mg. dissolved in 40 ml. of benzene and acetone (about 25%) for 16 hr. with 1 g. of manganese dioxide. The oxidizing agent was separated by filtration and the solvent removed. Addition of a few drops of ether to the clear oily residue gave 85 mg. of crystals, m.p. 185–186°. One recrystallization from ether and acetone gave crystalline IId, m.p. 187–188°. No depression of melting point was observed when taken with the material obtained in part a.

***dl-anti-trans*-1,5,6,6a,7,7a,10a,11,11a,11b-Decahydro-6α-hydroxy-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxole-3(2H)-one (IIb).**—A slurry of 0.100 g. of 2% palladium-on-strontium carbonate catalyst in 50 cc. of isopropyl alcohol was prereduced with hydrogen, and then 0.300 g. of IIIb and 0.05 cc., of 10% aqueous NaOH was added. Hydrogenation was continued at 25° and atmospheric pressure until exactly one equivalent was absorbed. The catalyst was filtered and the solvent was evaporated *in vacuo*. The 300 mg. of crude gummy crystals were crystallized from isopropyl alcohol to give 0.152 g. (50%) of material melting at 205–210°. Further crystallization gave an analytical sample, m.p. 208–211°, λ_{max}^{alc} 250 mμ, ϵ 15,000.

Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.2; H, 8.81. Found: C, 71.7; H, 9.14.

Dehydration of IIb.—A solution of 0.050 g. of IIb in 1 cc. of *t*-butyl alcohol and 1 ml. of 0.95 *N* potassium *t*-butoxide was allowed to stand at 25° 1 hr. After neutralizing the base with acetic acid, the mixture was poured into water and was extracted with chloroform. The extract was washed with bicarbonate and water and dried. Removal of the solvent *in vacuo* followed by trituration with ether gave crystals, m.p. 153–154°, which showed no depression with authentic Ib.

Dehydration of IId.—An identical procedure with the β-alcohol IId at 25° gave back only starting material. However, at boiling temperatures, Ib was obtained in low yield.

***dl-anti-trans*-1,5,6,6a,7,7a,10a,11,11a,11b-Decahydro-6β-hydroxy-4,6a,9,9-tetramethylphenanthro[2,3][1,3]dioxole-3(2H)-one Acetate (IIh).**—A mixture of 160 mg. of IId, 300 mg. of acetic anhydride and 3 ml. of pyridine was allowed to stand at room temperature for 16 hr. Water (5 ml.) was added and crystals began to separate. These were collected and when dry amounted to 100 mg., m.p. 173–175°. Recrystallization from ether–petroleum ether gave pure IIh, m.p. 174–175°, λ_{max}^{alc} 247 mμ, ϵ 15,350.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.55; H, 8.31.

***dl*-1,5,6,6a,7,7a,10a,11,11a,11b-Decahydro-6β-hydroxy-4,6a,9,9-tetramethyl-11b-phenylthiophenanthro[2,3][1,3]-dioxole-3(2H)-one (VIIIa).**—To a suspension of 396 mg. of IIIa in 5 ml. of *t*-butyl alcohol and 3 ml. of thiophenol was added 1 ml. of 0.9 molar potassium *t*-butoxide solution. The mixture was stirred at room temperature under nitrogen for 4 hr. The difficultly soluble epoxide gradually went into solution during this period. Chloroform (50 ml.) was added and this solution was extracted three times with 50-ml. portions of 1 molar sodium hydroxide solution. The chloroform was then washed once with water and dried with Drierite. Removal of solvent left 535 mg. of oily residue which crystallized upon addition of a few drops of ether. Filtration gave 485 mg. of white crystals, m.p. 109–114°. Melting was accompanied by the evolution of a gas. Recrystallization from ether gave sharp melting prisms, m.p. 110–111°, again accompanied by gas evolution. The melts resolidified and melted again at 140–142°. The infrared spectra of the lower melting material and the 140–142° material indicated that the former was very probably an etherate. Loss of ether accompanied the melting process. The analytical sample was obtained by several recrystallizations from ether followed by a final melting under reduced pressure, m.p. 140–142° (pure), λ_{max}^{alc} 254 mμ, ϵ 15,000. The infrared spectrum indicated the presence of an hydroxyl group and an α,β-unsaturated ketone function.

Anal. Calcd. for $C_{25}H_{32}O_4S$: C, 70.06; H, 7.53; S, 7.48. Found: C, 69.94; H, 7.51; S, 7.53.

Desulfurization of VIIIa.—Approximately 500 mg. of alcohol-washed Raney nickel was refluxed for 10 minutes with 20 ml. of ethyl acetate and then cooled. To this suspension was added 74 mg. of VIIIa. After stirring for 6 hr. at room temperature, the nickel was removed by filtration and the solvent distilled off. A clear glass (51 mg.) remained which crystallized on addition of a few drops of ether. The crude material, m.p. 172–177°, was recrystallized from ether–acetone yielding white needles, m.p. 185–187°. The infrared spectrum of this material was found to be identical with that of IId. No depression was observed upon taking a mixed melting point.

***dl*-1,5,6,6a,7,7a,10a,11,11a,11b-Decahydro-6α-hydroxy-4,6a,9,9-tetramethyl-11b-phenylthiophenanthro[2,3][1,3]dioxole-3(2H)-one (VIIIb).**—The α-epoxide IIIb (309 mg.) was treated with thiophenol exactly as described for the preparation of VIIIa. The yield of crystalline VIIIb, m.p. 215–217°, after trituration with ether was 400 mg. (96%). One recrystallization from ether–chloroform gave pure material, m.p. 216–217°, λ_{max}^{alc} 254 mμ, ϵ 14,200.

Anal. Calcd. for $C_{25}H_{32}O_4S$: C, 70.06; H, 7.53; S, 7.48. Found: C, 70.12; H, 7.48; S, 7.50.

***dl*-1,6a,7,7a,10a,11,11a,11b-Octahydro-4,6a,9,9-tetramethyl-11b-phenylthiophenanthro[2,3][1,3]dioxole-3(2H)-one (IXa).**—A mixture of either VIIIa or VIIIb (1.41 g.) and 5 ml. of 95% ethanol was treated with 10 ml. of 1.2 molar ethanolic potassium hydroxide. After refluxing gently under nitrogen for 10 min., the reaction was cooled and quenched with 40 ml. each of saturated sodium chloride solution and chloroform. The chloroform layer was separated, washed again with salt solution, dried and the solvent removed. The residual oil was dissolved in a few ml. of ether and allowed to crystallize in an ice-bath. The yield of first crop crystalline IXa was 875 mg., m.p. 126–128°, second crop 200 mg., m.p. 118–124°. The analytical sample was prepared by recrystallizing first crop material from a small amount of ether, m.p. 128–129°, λ_{max}^{alc} 280 mμ, ϵ 17,500. Careful comparison of material obtained starting with either VIIIa or VIIIb failed to show any difference. Both yielded IXa as evidenced by comparison of ultraviolet and infrared spectra and mixed melting points.

Anal. Calcd. for $C_{25}H_{30}O_3S$: C, 73.14; H, 7.37; S, 7.81. Found: C, 72.87; H, 7.46; S, 7.94.

Desulfurization of IXa.—Approximately 1.0 g. of alcohol-washed Raney nickel was added to a solution of 98 mg. of IXa in 20 ml. of acetone. After the mixture had been stirred overnight at room temperature, the nickel was removed by filtration. After evaporation of solvent, the crystalline residue, m.p. 140–150°, amounting to 50 mg. was dissolved in 20 ml. of ether and filtered through a few grams of alumina to remove hydroxylic materials. The clear oil obtained upon removal of ether yielded 35 mg. of large colorless crystals, m.p. 156–158°. Infrared and mixed m.p. showed this material to be identical with IIg, obtained by hydrogenation of Ic.

***dl*-4,4a,4b,5,6,7,8,8a-Octahydro-6β,7β-dihydroxy-1,8a-dimethyl-4a-phenylthio-2(3H)-phenanthrone (Xa).**—Approximately 350 mg. of IXa was dissolved at room temperature in 2 ml. of glacial trifluoroacetic acid. As soon as the solid had dissolved (5 min.), the mixture was quenched with 15 ml. of saturated sodium chloride solution and 30 ml. of chloroform. The aqueous phase was extracted with another small portion of chloroform and discarded. The chloroform solutions were combined, washed once with salt solution, dried and the solvent removed. The good quality glycol remaining amounted to 271 mg. (86%), m.p. 178–180°. A single recrystallization from ethyl acetate gave pure Xa, m.p. 179–180°, $\lambda_{\max}^{\text{alc}}$ 282 mμ, ϵ 15,000, as colorless needles.

Anal. Calcd. for $C_{22}H_{26}O_3S$: C, 71.31; H, 7.07; S, 8.65. Found: C, 71.19; H, 7.05; S, 8.70.

***dl-anti-trans*-1,6a,7,7a,10a,11,11a,11b-Octahydro-4,6a,-9,9-tetramethyl-2-phenylthiophenanthro[2,3][1,3]dioxole-3(2H)-one (VIIa).**—A suspension of 3.6 meq. of potassium *t*-butoxide in toluene was prepared by adding 3.8 ml. of 0.95 molar potassium *t*-butoxide in *t*-butyl alcohol to 80 ml. of boiling anhydrous toluene. All of the alcohol was fractionated out. The fine suspension of potassium *t*-butoxide at reflux temperature under nitrogen was treated with 1.0 g. of Ic dissolved in 15 ml. of anhydrous toluene. The suspension was then heated and the additional *t*-butyl alcohol formed was distilled out. The potassium salt of the ketone separated as a yellow-white powder. After the alcohol had been removed, the suspension was cooled to −5° and 570 mg. of benzenesulfenyl chloride[19] in 10 ml. of anhydrous toluene was added. A rapid reaction occurred and the heavy suspension was replaced by a fine precipitate of potassium chloride. Water (50 ml.) and ether (50 ml.) were added and the organic layer separated. After washing and drying, the organic solvents were removed under reduced pressure. The residual orange oil which partially crystallized on trituration with ether yielded 600 mg. of impure crystals, m.p. 150–165°. About 200 mg. of diphenyl disulfide was isolated from the mother liquors. Recrystallization of the crude crystalline product 5 times from ethyl acetate and acetone and finally from ethanol gave what appeared to be a pure compound, m.p. 192–194°. Infrared spectra on intermediate fractions had shown the presence of small amounts of saturated carbonyl-containing impurities. The spectrum of the 192–194° material showed only dienone absorption and bands characteristic of an aromatic ring. The ultraviolet spectrum in 95% ethanol showed $\lambda_{\max}^{\text{alc}}$ 293 mμ, ϵ 19,800. When this solution was treated with two drops of sodium hydroxide solution, a shift to $\lambda_{\max}^{\text{alc}}$ 287 mμ, ϵ 22,400, occurred.

Anal. Calcd. for $C_{25}H_{30}O_3S$: C, 73.14; H, 7.37; S, 7.81. Found: C, 73.18; H, 7.15; S, 7.65.

Reaction of IIIa with Sodium Methoxide.—Four grams of IIIa was refluxed under nitrogen for 4 hr. with 40 ml. of 1.2 molar sodium methoxide in methanol. The greenish-yellow solution was cooled and quenched with 150 ml. of aqueous saturated sodium chloride solution. The oil which separated was extracted with 200 ml. of ether in three portions. The ether extracts were washed with salt solution, dried with Drierite and the solvent removed. The yellow glass remaining amounted to 3.75 g. and partially crystallized on standing. The crude mass was boiled with 100 ml. of petroleum ether (b.p. 60–70°). The hot liquor was decanted from some insoluble residue, treated with a little carbon and concentrated. A yellow oil separated on cooling and slowly crystallized on standing. This crop of material amounted to 1.35 g., m.p. 105–108°. Three recrystallizations from petroleum ether gave a pure sample of the methoxy dienone IXb, m.p. 108–110°, $\lambda_{\max}^{\text{alc}}$ 289 mμ, ϵ 25,200. A comparison of the infrared spectrum of this pure ketone with that of the initial reaction product indicated that IXb was present in the crude material roughly to the extent of 70%.

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; CH_3O–, 9.34. Found: C, 72.63; H, 8.75; CH_3O–, 9.35.

Mother liquors from preceding crystallizations were combined and concentrated to about 50 ml. This solution was then placed on a column of 100 g. of alumina and eluted with a mixture of hexane (80%) and ether; 23 fractions of 50 ml. each were collected. Fraction 1 contained 150 mg. of a new methoxy ketone, m.p. 149–151° (crude) and m.p. 152–154°, $\lambda_{\max}^{\text{alc}}$ 304 mμ, ϵ 15,300, shoulder at 256 mμ, after several recrystallizations from ether. On the basis of its spectra, this material was tentatively identified as VIb, since it was undoubtedly isomeric with IXb.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 72.26; H, 8.49; CH_3O–, 9.34. Found: C, 72.18; H, 8.46; CH_3O–, 9.49.

Fractions 2, 3 and 4 and the mother liquors from 1 appeared to contain, in addition to IXb and VIb, another unidentified methoxydienone which was indicated by the presence of several extremely distinct diamond-shaped crystals. These fractions, amounting to about 80 mg., were combined and chromatographed separately on 5 g. of alumina using the same ether–hexane eluent as in the previous chromatogram. Eight fractions were collected. The third fraction, 22 mg., appeared to be relatively pure, m.p. 141.5–143°. These crystals were recrystallized twice from ether and hexane giving 8 mg. of a new C_{20}-methoxy dienone, m.p. still 141.5–143°, $\lambda_{\max}^{\text{alc}}$ 294 mμ, ϵ 24,000. The infrared spectrum closely resembled that of IXb and VIb in the carbonyl region but showed distinct differences in the fingerprint region. The structure of this material is still unknown. Again, however, it is almost certainly isomeric with IXb and VIb. It was an extremely minor product in the methoxide cleavage reaction, however.

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; CH_3O–, 9.34. Found: C, 72.33; H, 8.32; CH_3O–, 9.48.

Still a fourth compound was isolated from the original chromatogram. Fractions 5 to 23 consisted mostly of IXb. The eluent was changed to acetone for fractions 24 to 27. Fraction 24 contained 100 mg. of hard ether-insoluble crystals, m.p. 195–200°, recrystallized from acetone, m.p. 198–202°, $\lambda_{\max}^{\text{alc}}$ 250 mμ, ϵ 12,700. The infrared spectrum showed the presence of one hydroxyl group and an α,β-unsaturated ketone. This material was shown to be VIIIc, the undehydrated precursor to IXb, by its conversion to the latter. Seventy-seven milligrams of VIIIc, refluxed for 3 hr. under nitrogen with 5 ml. of 1.1 molar sodium methoxide solution, yielded upon workup (as previously described) 50 mg. of crude IXb. This was cleaned up by filtration through about 700 mg. of alumina and gave 22 mg. of pure IXb, m.p. 108–110°. Comparison of infrared spectra and a mixed m.p. established their identity.

Reaction of α-Epoxide IIIb with Sodium Methoxide.—To 5 ml. of 1.1 molar sodium methoxide–methanol solution was added 260 mg. of IIIb. The mixture was refluxed under nitrogen for 7 hr. and worked up as described for the reaction of IIIa. The oily product, amounting to 248 mg., was dissolved in 2 ml. of ether, cooled to 0° and seeded with a microcrystal of IXb. After standing at 0° for 60 hr., 77 mg. of crystals, m.p. 113–121°, had formed. These were collected, dissolved in benzene and chromatographed on 15 g. of alumina. In all, 45 fractions were collected. Fractions 22 to 31 contained 20 mg. of crystals, m.p. 105–108°. These were combined and recrystallized twice from petroleum ether giving 10 mg. of pure IXb, m.p. 108–110°. The infrared spectrum of this material was identical with IXb obtained by methoxide cleavage of the β-epoxide IIIa. A mixed m.p. showed no depression. Comparison of the infrared spectrum of the crude product obtained and pure IXb indicated that the latter was present in the crude to the extent of about 30–40%. No other pure material was isolated from the very complex reaction product, although infrared spectra on various fractions suggested that VIb also might be present.

***dl*-4,4a,4b,5,6,7,8,8a-Octahydro-6β,7β-dihydroxy-4a-methoxy-1,4a-dimethyl-2(3H)phenanthrone (Xb).**—Treatment of 480 mg. of purified IXb, m.p. 108–110°, with 3 ml. of trifluoroacetic acid exactly as described previously for the preparation of Xa, gave 350 mg. of crude glycol Xb, m.p. 162–165°. Two melting points, m.p. 165–166° (metastable) and 177–178° (stable), were found for the pure glycol upon several recrystallizations from ethyl acetate. When the melt from the 165–166° material was allowed to resolidify, it remelted at the higher temperature. Furthermore, a solution of the lower melting material seeded with the higher melting form crystallized completely as the latter, $\lambda_{\max}^{\text{alc}}$ 289 mμ, ϵ 25,800.

The acetonide group was also removed with the same results using aqueous mineral acids and dioxane. A number

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[19] H. Lecher and F. Holschneider, *Ber.*, **57**, 755 (1924).

of attempts to remove the methoxyl group by heating with strong aqueous mineral acids either caused general decomposition or failed to change the dienone absorption in the ultraviolet.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27; CH_3O–, 10.61. Found: C, 69.65; H, 8.18; CH_3O–, 10.51.

Treatment of Xb with anhydrous copper sulfate in acetone by standard procedures[1] reconverted the glycol back to its acetonide IXb in essentially quantitative yield.

C-Methyl Determinations.—Compounds of Xa and Xb along with model compounds of established structure (Ia), and the norketone corresponding to Ia but without the methyl group in the 4-position[20], were submitted without structural identification to an independent analyst[21] for Kuhn–Roth C-methyl determination. The observed number of C-methyl groups for Xa, Xb, Ia and the norketone were 1.19, 1.18, 1.31 and 0.58 indicating that both Xa and Xb correspond to Ia in the number of C-methyl groups present.

ST. LOUIS, MISSOURI

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[20] Prepared as outlined in footnote 25 of the Woodward paper cited in reference 1.

[21] Mr. J. F. Alicino, P. O. Box 267, Metuchen, N. J.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

C-22 Isomeric Dihydrosapogenins from Kryptogenin

BY IRVING SCHEER, MALCOLM J. THOMPSON AND ERICH MOSETTIG

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In the reduction of kryptogenin in acidic media three compounds have been obtained: dihydrotigogenin and two new sapogenin derivatives. It is shown that the new compounds are isomeric at C-22 and are 22,26-epoxycholestane-3β,16ξ-diol and 22,26-epoxy-22-isocholestane-3β,16ξ-diol. The preparation of cholestane-3β,22,26-triol and cholestane-3β,26-diol-22-one is described. The latter was converted to 22,26-epoxycholestan-3β-ol and 22,26-epoxy-22-isocholestan-3β-ol.

The reduction of kryptogenin (I) yields a variety of products, depending on the experimental conditions employed. Thus, Marker, *et al.*,[1] obtained diosgenin when reducing I with sodium in ethanol, tigogenin (II) and dihydrotigogenin (III) when using platinum oxide in acid media, and dihydrokryptogenin with the same catalyst in a neutral medium. On the other hand, Kaufmann and Rosenkranz[2] obtained "16-dihydrokryptogenin" (XVII) by hydrogenating I in neutral solution with Raney nickel catalyst. In our hands the hydrogenation of kryptogenin (I) with platinum oxide in glacial acetic acid at 25° gave a mixture of at least three compounds which were separated by chromatography on alumina. The main product was dihydrotigogenin (III) and was obtained in a yield of about 80%. The two other products each being formed in an approximate yield of 10% were unknown derivatives.[3] We could show that these new compounds differ only in their configuration at C-22 and have the structures of a 22,26-epoxycholestane-3β,16ξ-diol (IV) and a 22,26-epoxy-22-isocholestane-3β,16ξ-diol (V).[4] The reduction of kryptogenin diacetate under similar conditions yielded only dihydrotigogenin diacetate as previously reported.[1] The infrared spectra of IV and V exhibited strong hydroxyl absorption at 3571 cm.$^{-1}$ (unassociated) and at 3401 cm.$^{-1}$ (associated), no carbonyl absorption, and differed decidedly in the fingerprint region. The bands characteristic for sapogenins were absent, and there was no resemblance to the infrared spectra of dihydrosapogenins. Elemental analysis established for IV and V the empirical formula $C_{27}H_{46}O_3$, *i.e.*, they are isomeric with dihydrotigogenin. Esterification readily gave diesters, indicating that each, IV and V, contained two hydroxyl groups and a third oxygen in an inert ether-like linkage. Oxidation of IV and V with chromic acid led to the diketo-compounds VI and VII, respectively. The strong bands at 1712 and at 1736 cm.$^{-1}$ suggested a 3-ketone and a 16-ketone. Reduction of VI and VII, either catalytic (with PtO_2 in acetic acid) or with sodium borohydride in methanol, gave nearly quantitatively the dialcohols IV and V, respectively, *i.e.*, in either instance only one isomer.

The deoxylation of 22,26-epoxycholestane-3β,16ξ-diol (IV) and 22,26-epoxy-22-isocholestane-3β,16ξ-diol (V) yielded 22,26-epoxycholestane (VIII) and 22,26-epoxy-22-isocholestane (IX), respectively. Compounds VIII and IX contain only two asymmetric centers (C_5 and C_{22}) not found in the original kryptogenin. The remote possibility that these isomers differ at C_5 was eliminated by showing that 5,6-dihydrokryptogenin (XII) was also reduced to III, IV and V.

In order to confirm the structures of VIII and IX, these compounds were also prepared by a different route. Treatment of 5,6-dihydrokryptogenin diacetate (XIII) with ethane dithiol gave a monoethylenethioketal derivative. Infrared analysis showed that it was not the C-22 carbonyl group that had reacted and that XIV was a C_{16}-ethylenethioketal. Desulfurization with freshly prepared Raney nickel in dioxane yielded a mixture from which after hydrolysis and chromatography on alumina cholestane-3β,22,26-triol (XV) and cholestane-3β,26-diol-22-one (XVI) were obtained in an approximate ratio of 6:1. For the routine preparation of XVI the crude mixture from the desulfurization of XIV was oxidized gently with chromic acid to give XVI as the sole product after saponification. Catalytic reduction (PtO_2, acetic acid) of XVI led to a mixture of the triol XV, 22,26-epoxycholestan-3β-ol (X) and 22,26-epoxy-22-isocholestan-3β-ol (XI). By chromatography and fractional crystallization compounds

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[1] R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. J. P. Goldsmith and C. H. Ruof, THIS JOURNAL, **69**, 2167 (1947).

[2] S. Kaufmann and G. Rosenkranz, *ibid.*, **70**, 3502 (1948).

[3] In one instance when for some reason the reduction did not go to completion a small amount of tigogenin (II) could be isolated.

[4] The configuration at C-22 as shown in the structural formulas V and V is arbitrary. The naming of V as an iso compound is provisional.