[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES OF BROWN UNIVERSITY]

Synthesis of 5β,6β-Oxidosteroids from 5α,6β-Diol Diacetates

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5β,6β-Oxidopregnane-3β,20β-diol was obtained in 73% yield by treatment of pregnane-3β,5α,6β,20β-tetraol tetraacetate with Claisen alkali. 5β,6β-Oxidocholestan-3β-ol was obtained in 73% yield by treatment of cholestan-3β,5α,6β-triol triacetate with sodium ethoxide in ethanol.

In 1949, Davis and Petrow[2] observed, *inter alia*, that alkaline hydrolysis (potassium hydroxide in ethanol) of 3β,5α,6β-triacetoxyandrostan-17-one gave, in unstated yield, 5β,6β-oxidoetiocholan-3β-ol-17-one. This result is surprising in view of the observation that 3β,5α,6β-triacetoxycholestane, when refluxed in methanol with a little aqueous potassium hydroxide, affords cholestane-3β,5α,6β-triol 5-monoacetate[3a] in 79% yield.[3b]

Using the observations of Davis and Petrow[2] as a basis, a series of reactions has been developed which leads to steroid 5β,6β-oxides in good overall yield from Δ^5-steroids or the corresponding α-oxides as shown in Fig. 1. After this work had been completed, Fieser and Fieser[4] reported that treatment of the triacetoxycholestane with potassium hydroxide in absolute ethanol gave cholesterol β-oxide in 85% yield. This observation is discussed further below.

Treatment of Δ^5-pregnene-3β,20β-diol diacetate (I) with perbenzoic acid gave a mixture of products, and the amounts of the various compounds isolated depended on the method of working up the reaction mixture. Chromatography on ethyl acetate-washed alumina gave 20% of 5β,6β-oxidopregnane-3β,20β-diol diacetate II and 46% of pregnane-3β,5α,6β,20β-tetraol 3,20-diacetate (VII). Chromatography on unwashed alumina (see Experimental) gave 20% of the β-oxide II and 28% of 5α,6α-oxidopregnane-3β,20β-diol diacetate VI, previously reported,[5] without mention of the isolation of the isomeric β-oxide II. Direct crystallization of the crude oxidation product gave 30% of the α-oxide VI only.

Further support for the structural assignments for the two oxides is derived from molecular rotation differences. The ΔM_D between Δ^5-pregnane-3β,20β-diol diacetate I and the α-oxide diacetate VI is 0°; and the β-oxide diacetate II is +172°. The ΔM_D between cholesterol and the α-oxide is −34°; the β-oxide + 195°; and between cholesteryl acetate and the α-oxide acetate is −18°; the β-oxide acetate + 182°.

The *trans*-tetraol diacetate VII was also produced in 54% yield by placing the α-oxide on the ethyl acetate-washed alumina and allowing the column to stand for a period before elution. This result indicates that the *trans*-tetraol diacetate is an artifact of the peroxidation reaction and is formed by hydrolysis of the α-oxide on the alumina. The β-oxide was not opened under these conditions.

This epoxidation thus parallels the results of those with other Δ^5-steroids, in that mixtures of the α- and β-oxide are formed,[6] with the α-oxide predominating.

The α-oxide diacetate VI was readily hydrolyzed in the presence of periodic acid[7] to give, in 73% yield, pregnane-3β,5α,6β,20β-tetraol 3,20-diacetate (VII). The *trans*-tetraol diacetate was also obtained in much poorer yield (20%) by hydrolysis in the presence of sulfuric acid. Since 5α,6α-oxides are known to give 5α,6β-diols by acid-catalyzed hydrolysis,[8] the structure of the *trans*-tetraol 3,20-diacetate VII from the peroxidation reaction is thus established.

For comparison, Δ^5-pregnene-3β,20β-diol diacetate (I) was treated with osmium tetroxide, and a new glycol, pregnane-3β,5α,6α,20β-tetraol 3,20-diacetate (XII), was obtained in 36% yield. The structural assignment for the 5- and 6-hydroxyls in the oxidation product was made on the basis of the usual course of reaction of Δ^5-steroids with osmium tetroxide.[9]

The *trans*-tetraol diacetate VII was converted to pregnane-3β,5α,6β,20β-tetraol tetraacetate X in 65% yield by treatment with acetic acid–acetic anhydride in the presence of *p*-toluenesulfonic acid.

The *trans*-tetraol diacetate VII was readily hydrolyzed to pregnane-3β,5α,6β,20β-tetraol (VIII) in 95% yield by potassium hydroxide in aqueous methanol (Claisen alkali). The same tetraol VIII was also obtained in 64% yield from the α-oxide diacetate VI by treatment with aqueous acid followed by aqueous base to saponify the acetates.

When saponification of the *trans*-tetraol tetraacetate X was attempted with Claisen alkali, instead of the expected tetraol VIII, a 73% yield of 5β,6β-oxidopregnane 3β,20β-diol (III) was obtained. The diacetate II, prepared from the diol III with acetic anhydride and pyridine, was identical with a sample obtained as described above by direct peroxidation of Δ^5-pregnene-3β,20β-diol diacetate (I).

The same reaction was then attempted with cholestane-3β,5α,6β-triol triacetate (XI). Using Claisen alkali, the results were quite variable, although in one experiment, a 46% yield of 5β,6β-oxidocholestan-3β-ol (IV) was obtained, accom-

(1) Abstracted from the Ph.D. Thesis of Alex T. Rowland, Brown University, 1958. Jesse Metcalf Fellow, 1955–1956; Allied Chemical and Dye Corporation Fellow, 1956–1957.

(2) M. Davis and V. Petrow, *J. Chem. Soc.*, 2536 (1945).

(3) (a) J. Hattori, *J. Pharm. Soc. Japan*, **69**, 129 (1939); *C. A.*, **33**, 8622 (1939); (b) E. J. Tarlton, M. Fieser and L. F. Fieser, THIS JOURNAL, **75**, 4423 (1953).

(4) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 198.

(5) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

(6) A. J. Bowers and H. J. Ringold, THIS JOURNAL, **80**, 3091 (1958), and ref. 24 cited therein.

(7) L. F. Fieser and S. Rajagopalan, *ibid.*, **71**, 3938 (1949).

(8) Reference 4, p. 196.

(9) Reference 4, p. 189.

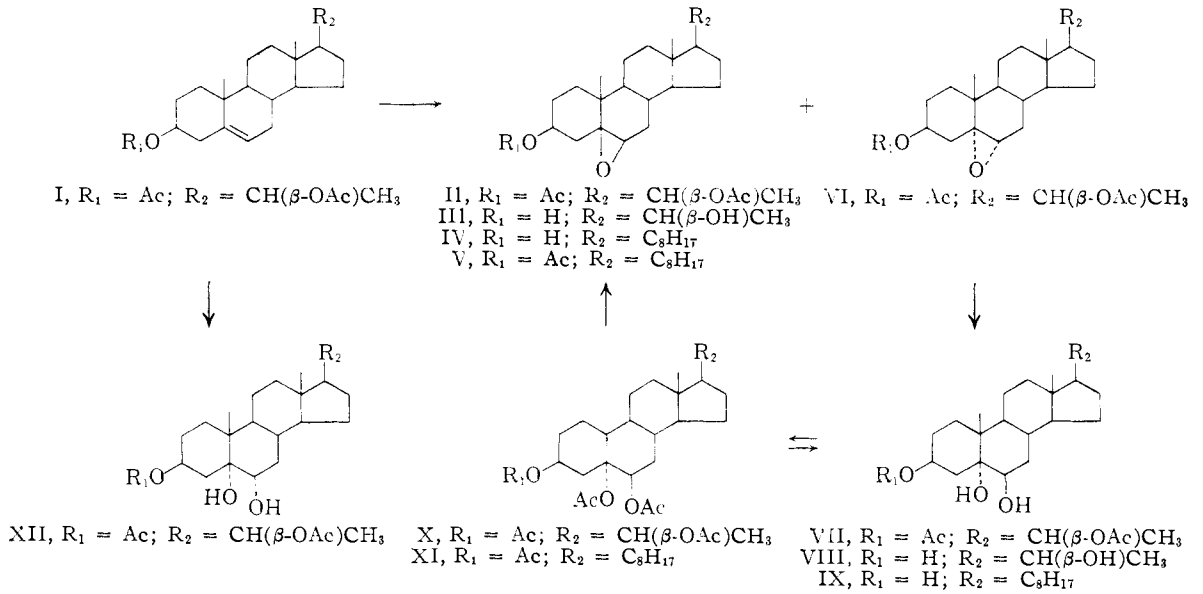
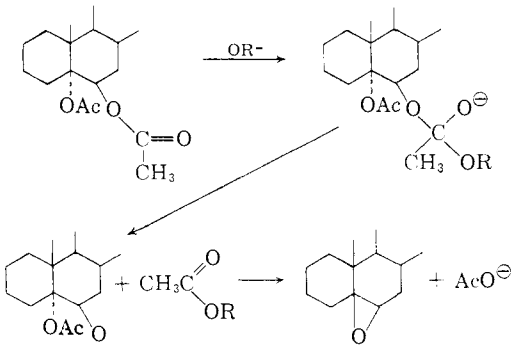


Fig. 1.—Conversion of Δ^5-steroids to 5β,6β-oxides.

panied by 11% of cholestane-3β,5α,6β-triol (IX). Davis and Petrow,[2] and Tarlton, Fieser and Fieser,[3] reported 5α-acetoxycholestane-3β,6β-diol from the same reaction. In other experiments no β-oxide could be isolated, and the product melted over a wide range, indicating that a mixture of compounds had been formed.

When sodium ethoxide in ethanol was substituted for the Claisen alkali, however, a 73% yield of 5β,6β-oxidocholestan-3β-ol (IV) was obtained, identical with the reported product.[10] The acetate, prepared with acetic anhydride and pyridine, also corresponded in properties with the previously reported 5β,6β - oxidocholestan - 3β - ol acetate (V).[10a,11]

The formation of the oxido-compounds is readily explainable on the basis of initial attack by the anion (–OH or $-OC_2H_5$) on the 6-acetate carbonyl carbon to give an axial 6-oxyanion, which then attacks the *trans*-5α-axial acetoxy group from the backside, displacing acetate and forming the β-oxide.



This reaction path is supported by the fact that 3β,5α - diacetoxyandrostan - 6β - ol - 17 - one also gave the β-oxide with potassium hydroxide in ethanol[2] but the *trans*-tetraol diacetate VII did not. Presumably a 5α-hydroxyl group is not a good enough leaving group to be displaced by backside attack of the oxy-anion.

When hydroxide is present in the reaction mixture, ordinary saponification of the acetates, due to the water present (Claisen alkali) or formed from the alcohol and hydroxide ion, competes with the oxide-forming reactions, and the products will depend on the over-all rates of the two competing reactions. If the rates are similar, then the formation of the cholestan-β-oxide would be quite dependent on slight changes in reaction conditions, and the apparently conflicting reports are explainable.[12] The use of alkoxides in alcohol eliminates the presence of water, the competing saponification reaction is avoided, and oxide formation then takes place.

The formation of oxides from *trans*-diaxial diol diacetates is generally attractive since *trans*-diols are readily available, either from other oxides, or by treatment of olefins with performic acid[13] and hydrolysis of the resulting ester mixture.

Experimental[14]

Reaction of Δ^5-Pregnene-3β,20β-diol Diacetate I with Perbenzoic Acid.—To a solution of 7.80 g. (19.4 millimoles) of Δ^5-pregnene-3β,20β-diol diacetate I in 15 ml. of phosgene-free chloroform was added a solution of 3.90 g. (28.3 millimoles) of perbenzoic acid in 71 ml. of chloroform. The solution was kept at 5° for 68 hours, and then at room tem-

(10) (a) Reference 4, p. 197; (b) R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, 613 (1943).

(11) D. R. James and C. W. Shoppee, *ibid.*, 4224 (1954).

(12) After this work had been completed, and submitted for publication, our attention was called, by the publication of ref. 4, p. 198, to the work of E. J. Tarlton, Ph.D. Dissertation, Harvard, 1953. Tarlton found that treatment of cholestane-3β,5α,6β-triol triacetate or 5α-acetoxycholestane-3β,6β-diol with potassium hydroxide in *ethanol* rather than *methanol* gave the β-oxide IV in 85% yield. His interpretation of the reaction is essentially the same as the one given here.

(13) Reference 4, p. 189.

(14) All melting points were determined by the capillary method and are corrected. Optical rotations were determined at room temperature in approximately 1% chloroform solutions unless specified otherwise. Microanalyses by Dr. S. M. Nagy and associates, Microchemical Laboratory, The Massachusetts Institute of Technology. Merck and Co., Inc., Alumina (Suitable for Chromatographic Adsorption) was used unless specified otherwise.

perature for 30 minutes. After the addition of 50 ml. of chloroform, the solution was washed successively with two 70-ml. portions of 10% sodium bicarbonate solution and 100 ml. of water. The solution was then dried over anhydrous magnesium sulfate, concentrated to dryness at 45° under reduced pressure and the residue was chromatographed on 310 g. of ethyl acetate-washed alumina.

The column was eluted with 35% benzene–65% hexane, and 2.1 g. of material was obtained, which on recrystallization from ether gave 1.6 g. (20%) of 5β,6β-oxidopregnane-3β,20β-diol diacetate II, m.p. 174–175°, $[\alpha]_D$ + 3°, $\lambda_{max}^{CCl_4}$ 1754 cm.$^{-1}$. The analytical sample was prepared by recrystallization from ether–petroleum ether, and had m.p. 175.5–176° after drying 20 hours at 100° (0.5 mm.).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.73; H, 9.15. Found: C, 71.65; H, 9.09.

The column was then eluted with 10% ether–90% benzene, and a second fraction was obtained which was recrystallized from carbon tetrachloride containing a little chloroform, to give 3.26 g. of pregnane-3β,5α,6β,20β-tetraol 3,20-diacetate (VII) ("*trans*-tetraol diacetate"), m.p. 236–238°, $[\alpha]_D$ −15°; $\lambda_{max}^{CHCl_3}$ 3703, 1731 cm.$^{-1}$. The mother liquors were reworked to give an additional 437 mg., m.p. 235.5–238°, of the *trans*-tetraol diacetate VII. The column was then eluted with 40% ether–60% benzene to given an additional 163 mg., m.p. 236-238°, after recrystallization; total yield 3.85 g. (46%) of *trans*-tetraol diacetate VII.

The analytical sample was prepared by further recrystallization from the same solvent and had m.p. 231–234° after drying at 25° (12 mm.) for 20 hours.

Anal. Calcd. for $C_{25}H_{40}O_6$: C, 68.78; H, 9.24. Found: C, 68.80; H, 9.46.

If the reaction product was chromatographed on alumina, elution with the benzene–hexane mixture gave 20% of the β-oxide II, m.p. 172–173° after recrystallization. When the column was then eluted with the ether–benzene mixture, instead of the *trans*-tetraol diacetate VII, the α-oxide, 5α,6α-oxidopregnane-3β,20β-diol diacetate VI, m.p. 182–183.5° after recrystallization from acetone–methanol, was obtained in 28% yield. A sample from another run had m.p. 180.5–182°, $[\alpha]_D$ −37°; reported[5] m.p. 180–181°, $[\alpha]_D$ −39°.

If the crude reaction product was recrystallized from methanol, the α-oxide VI, m.p. 180.5–182.5°, $[\alpha]_D$ −35°, could be obtained in 30% yield.

In some runs using ethyl acetate-washed alumina, up to 19% of the α-oxide was obtained from the fractions eluted with 1:1 benzene–hexane, after removal of the β-oxide, and before elution of the *trans*-tetraol diacetate (yield 19%).

Action of Alumina on 5α,6α-Oxidopregnane-3β,20β-diol Diacetate (VI).—A 0.300-g. (0.717 millimole) sample of the α-oxide VI was dissolved in approximately 3 ml. of 1:1 benzene–hexane, and the solution was placed on a column of 9.0 g. of ethyl acetate-washed alumina. The column was allowed to stand for 14 hours and was then eluted with 1:1 benzene–hexane, which yielded 35 mg. of impure α-oxide VI, m.p. 182–186.5°. The column was then eluted with 30% ether–70% benzene, and, after recrystallization from chloroform–petroleum ether, 149 mg. (54%) of the *trans*-tetraol diacetate VII, m.p. 232.5–235.5°, $[\alpha]_D$ −15°, was obtained.

Pregnane-3β,5α,6β,20β-tetraol 3,20-Diacetate (VII). (a) **From α-Oxide VI and Periodic Acid.**—To a solution of 200 mg. (0.478 millimole) of the α-oxide VI in 6 ml. of hot acetone was added a solution of 125 mg. (0.549 millimole) of periodic acid dihydrate in 2 ml. of acetone and 2 ml. of water. The reaction mixture was concentrated to 5 ml., allowed to stand at room temperature for 15 minutes, and then boiled for 30 minutes, with the concurrent dropwise addition of water, whereupon a white crystalline solid formed. The mixture was cooled, the solid collected and air-dried, and recrystallized from carbon tetrachloride containing a little petroleum ether to yield 152 mg. (73%) of pregnane-3β,5α,6β,20β-tetraol 3,20-diacetate (VII), m.p. 235–237°, mixture m.p. with an authentic sample, 236.5–239°. The infrared spectrum was identical with that of an authentic sample.

(b) **From α-Oxide VI and Aqueous Acid.**—To a solution of 100 mg. (0.239 millimole) of the α-oxide VI in 5 ml. of acetone were added 1 ml. of water and 3 drops of concentrated sulfuric acid, and the resulting solution was allowed to stand at room temperature for 24 hours. The solution was then concentrated, diluted with water, and cooled, and the crystals which formed were recrystallized from acetone–methanol–water to give 21 mg. (20%) of the *trans*-tetraol diacetate VII, m.p. 225–232°, $[\alpha]_D$ −10°.

Pregnane-3β,5α,6α,20β-tetraol 3,20-Diacetate (XII).—A solution of 700 mg. (1.74 millimoles) of Δ^5-pregnene-3β,20β-diol diacetate I, 500 mg. (1.96 millimoles) of osmium tetroxide and 0.5 ml. of anhydrous pyridine in 55 ml. of absolute ether was allowed to stand in the dark at room temperature for 48 hours. Then several more milliliters of pyridine was added and the solution allowed to stand an additional 21 hours. It was then concentrated to half-volume under an air jet, allowed to stand an additional 23 hours, and then evaporated to dryness under an air jet.

The black residue was dissolved in 45 ml. of 95% ethanol, 3.5 g. of ascorbic acid[15] and 20 ml. of water were added, the solution was boiled under reflux for 45 minutes, concentrated, and cooled in an ice-bath. The black viscous mass was extracted twice with ether, and the ether extract was washed successively with 10% sodium sulfite solution, 10% sodium bicarbonate solution, and water, dried over anhydrous magnesium sulfate, and then the ether was evaporated. Recrystallization of the residue from ether gave 198 mg. of the *cis*-tetraol diacetate II, m.p. 258–264°. Two further recrystallizations from methanol–acetone gave II, m.p. 263.5–265.5°, $[\alpha]_D$ +11.7°.

The analytical sample was prepared by an additional recrystallization from methanol–acetone, followed by drying at 100° (5 mm.) for 24 hours, and had m.p. 265–267°.

Anal. Calcd. for $C_{25}H_{40}O_6$: C, 68.77; H, 9.23. Found: C, 68.34; H, 9.14.

The original etner mother liquor yielded an additional 45 mg. of impure *cis*-tetraol diacetate II, and continuous ether extraction of the black residue for 3 days gave a further 31 mg. The total yield of crude material was 274 mg. (36%).

Pregnane-3β,5α,6β,20β-tetraol Tetraacetate X.—A mixture of 0.447 g. (1.02 millimoles) of *trans*-tetraol diacetate VII, 0.535 g. of *p*-toluenesulfonic acid monohydrate, 20 ml. of acetic acid and 7 ml. of acetic anhydride was allowed to stand at room temperature for 41 hours, and then poured into an ice–dilute sodium carbonate mixture. The resulting mixture was extracted with ether, the ether extract was washed with sodium carbonate solution, and then with saturated brine, and dried over anhydrous magnesium sulfate. The ether was evaporated and the residue was recrystallized from petroleum ether to give 0.413 g., m.p. 162–168.5°. Recrystallization from methanol–water gave 345 mg., (65%), m.p. 167.5–169°, $[\alpha]_D$ −34.7°, of pregnane-3β,5α,6β,20β-tetraol tetraacetate (X).

A sample was recrystallized from petroleum ether, dried at 100° (5 mm.) for 27 hours, and then had m.p. 168–170°.

Anal. Calcd. for $C_{29}H_{44}O_8$: C, 66.89; H, 8.51. Found: C, 66.98; H, 8.47.

Pregnane-3β,5α,6β,20β-tetraol VIII.—A solution of 1.0 g. (2.3 millimoles) of the *trans*-tetraol diacetate VII and 1.25 g. of potassium hydroxide in 10 ml. of water and 45 ml. of methanol was boiled under reflux for 5.75 hours. The solution was then concentrated to about one-half of the original volume and allowed to cool to room temperature and stand overnight. The first crop of tetraol VIII (283 mg. of fine needles, m.p. 280–286°) was removed and the mother liquor was evaporated slowly to yield an additional 485 mg., m.p. 284.5–286.5°, total yield 95%.

Two recrystallizations from methanol–acetone gave an analytical sample, m.p. 285–287.5°, $[\alpha]_D$ −18° (1% in pyridine), λ_{max}^{Nujol} 3753 cm.$^{-1}$, after drying 23 hours at 100° (1 mm.).

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.54; H, 10.29. Found: C, 70.81; H, 9.96.

The tetraol VIII was also obtained directly from the α-oxide VI. A solution of 310 mg. (0.742 millimole) of the α-oxide VI in 10 ml. of glacial acetic acid was boiled under reflux for 45 minutes, then diluted with water, and the precipitate dissolved in 10 ml. of methanol, to which was added 300 mg. of potassium hydroxide and 3 ml. of water. This solution was stirred at room temperature for 12 hours and then boiled under reflux for 3 hours. The solution was then concentrated and allowed to cool, and 166 mg. (64%) of the tetraol VIII, m.p. 278.5-286°, was obtained. Recrystallization from methanol–acetone–water gave m.p. 283.5–

(15) H. Reich, M. Suter and T. Reichstein, *Helv. Chim. Acta*, **23**, 170 (1940).

286.5°, $[\alpha]_D$ −19° (1% in pyridine); mixture m.p. with tetraol prepared from *trans*-tetraol diacetate VII, 280–282.5°.

5β,6β-Oxidopregnane-3β,20β-diol (III).—A solution of 150 mg. (0.288 millimole) of pregnane-3β,5α,6β,20β-tetraol tetraacetate X and 300 mg. of potassium hydroxide in 7 ml. of methanol and 2 ml. of water was boiled under reflux for 5.75 hours, and allowed to stand at room temperature for 3.75 hours. A few drops of water was added, the solution was concentrated until it became turbid, methanol was added to clear the solution, and it was cooled overnight. The yield of 5β,6β-oxidopregnane-3β,20β-diol (III), was 70 mg. (73%), m.p. 213–217°. One recrystallization from chloroform–acetone gave 60 mg., m.p. 216–217.5°, $[\alpha]_D$ −8.5°; $\lambda_{max}^{CHCl_3}$ 3420, 3520 cm.$^{-1}$. A sample for analysis was recrystallized from chloroform–petroleum ether, dried at 100° (1 mm.) for 6.5 hours, and then had m.p. 211–213°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.24. Found: C, 75.63; H, 10.38.

5β,6β-Oxidopregnane-3β,20β-diol Diacetate II.—A solution of 40.0 mg. (0.12 millimole) of the oxidodiol III in 1 ml. of pyridine and 1 ml. of acetic anhydride was allowed to stand for 5.5 hours at room temperature, and then heated on a steam-bath for 1.75 hours. The solution was then cooled, diluted with water and extracted three times with ether. The ether extract was washed successively with dilute hydrochloric acid (twice), 10% sodium bicarbonate solution (twice), and with saturated brine, and then dried with anhydrous magnesium sulfate and the ether was removed. The residue was crystallized from ether–petroleum ether to give 40 mg. (80%) of 5β,6β-oxidopregnane-3β,20β-diol diacetate II, m.p. 171–173°. One recrystallization gave 30 mg., m.p. 170–171°, mixture m.p. 170.5–172° with an authentic sample.

Cholestane-3β,5α,6β-triol Triacetate XI.—Cholestane-3β,5α,6β-triol[3] (IX) (1.0 g.) was treated as described above for the *trans*-tetraol diacetate VII and 943 mg. (73%) of cholestane-3β,5α,6β-triol triacetate XI was obtained, m.p. 151.2–151.8°, $[\alpha]_D$ −32°; reported m.p. 148–149°[2]; m.p. 149–150°, $[\alpha]_D$ −35°.[3]

5β,6β-Oxidocholestan-3β-ol (IV).—To a solution of 1.7 g. (0.074 g. atom) of sodium in 90 ml. of absolute ethanol was added 2.20 g. (4.03 millimoles) of cholestane-3β,5α,6β-triol triacetate XI. The solution was boiled under reflux for 3.5 hours, and then, after the addition of a few ml. of water, concentrated nearly to dryness under reduced pressure. The residue was extracted with three portions of ether, the ether extract was washed with saturated brine, dried with anhydrous sodium sulfate, and the ether was evaporated. The residue was crystallized from acetone–methanol to give 1.18 g. (73%) of 5β,6β-oxidocholestan-3β-ol (IV), m.p. 130.5–133°, $[\alpha]_D$ +9°, $\lambda_{max}^{CCl_4}$ 3360 cm.$^{-1}$. One recrystallization gave 1.02 g., m.p. 130–133.5°; reported[10b] m.p. 131–132°, $[\alpha]_D$ +11.5°, + 10.7°.

5β,6β-Oxidocholestan-3β-ol Acetate V.—A solution of 200 mg. (0.498 millimole) of the β-oxide IV in 4 ml. of pyridine and 4 ml. of acetic anhydride was heated on a steam-bath for 4 hours and worked up as above for the β-oxide diacetate II. Recrystallization of the product from aqueous methanol gave 153 mg. (69%) of 5β,6β-oxidocholestan-3β-ol acetate (V), m.p. 100–102.5°, $[\alpha]_D$ −1.7°, $\lambda_{max}^{CCl_4}$ 1736 cm.$^{-1}$. Two additional recrystallizations gave m.p. 107–109°; reported[11] m.p. 112–113°, $[\alpha]_D$ −1°.

PROVIDENCE 12, R. I.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

D-Homoannulation of 16α,17α-Dihydroxy-20-keto Steroids.[1] I

BY N. L. WENDLER AND D. TAUB

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The D-homoannulation of a 16α,17α-dihydroxy 20-ketopregnane with Lewis acids produces a 16α,17α-dihydroxy 17β-methyl 17a-ketone (III) as the major product together with a 16α,17aα-dihydroxy 17aβ-methyl 17-ketone (IV) as the minor component. These systems are quite labile to alkali even under mild conditions giving in both instances a diosphenol. The formation of the latter from the major D-homo isomer III proceeds ostensibly by methyl migration C-17 → C-17a.

The introduction of an hydroxyl function at C-16, and in particular 16α, destabilizes the resultant system and makes it more prone to D-homoannulation. Whereas 16α-hydroxy derivatives of cortical systems can be isolated without difficulty,[2] the 21-desoxy analogs are much more labile and their isolation must be effected in the absence of chromatographic procedures employing alumina.

Hydroxylation of 3α-acetoxy-Δ^{16}-pregnene-11,20-dione (I) with potassium permanganate according to the method of Cooley, Ellis, Hartley and Petrow[3] yielded the 16α,17α-diol II, m.p. 186–188°, in moderate yield by fractional crystallization. The latter forms an acetonide derivative, m.p. 166–169°. Passage of the diolone II through a column of alumina resulted in essentially complete D-homoannulation. Hydroxylation of I, on the other hand, with osmium tetroxide and work-up according to the method of Barton and Elad[4] produced to a major extent the same D-homoannulation product; some of the unrearranged diolone II could be isolated, nonetheless, by fractional crystallization.[5] The 16-acetate of II, on the other hand, was stable to alumina chromatography although readily converted to the D-homo derivative IIIa on refluxing with aluminum *t*-butylate in toluene. The composition of the D-homoannulated product was found to consist of *ca.* 80% of the 17α-ketone III and 20% of the 17-ketone IV.[6]

The structure of the major isomer III was established by its identification with the product of osmium tetroxide hydroxylation of the $\Delta^{\alpha\beta}$-ketone VI.[7] Conversely, the diolone III as its 16-mesylate IIIb was converted to the $\Delta^{\alpha\beta}$-ketone VI on heating with sodium iodide in acetone solution at 110°. The diolone III readily forms an acetonide derivative X and on permanganate

(1) For a preliminary communication of this work see: N. L. Wendler and D. Taub, *Chemistry & Industry*, 1237 (1957).

(2) See for example: B. Ellis, F. Hartley, V. Petrow and D. Wedlake, *J. Chem. Soc.*, 4383 (1955); W. S. Allen and S. Bernstein, THIS JOURNAL, **77**, 1028 (1955); **78**, 1909 (1956).

(3) G. Cooley, B. Ellis, F. Hartley and V. Petrow, *J. Chem. Soc.*, 4377 (1955).

(4) D. H. R. Barton and D. Elad, *ibid.*, 2085 (1956).

(5) Decomposition of the osmate ester by the method of W. S. Allen and S. Bernstein, THIS JOURNAL, **78**, 1909 (1956), on the other hand, proceeds to give high yields of the normal product II (private communication from Drs. J. Fried and P. Diassi).

(6) The structures of the products of D-homoannulation of 16α,17α-dihydroxy 20-keto systems have been incorrectly assigned previously. See Cooley, Ellis, Hartley and Petrow, ref. 3; also: K. Heusler and A. Wettstein, *Chem. Ber.*, **87**, 1301 (1954); H. H. Inhoffen, F. Blomeyer and K. Bruckner, *ibid.*, **87**, 593 (1954); J. Romo and A. DeVivar, *J. Org. Chem.*, **21**, 902 (1956).

(7) N. L. Wendler, D. Taub, S. Dobriner and D. K. Fukushima, THIS JOURNAL, **78**, 5027 (1956).