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).

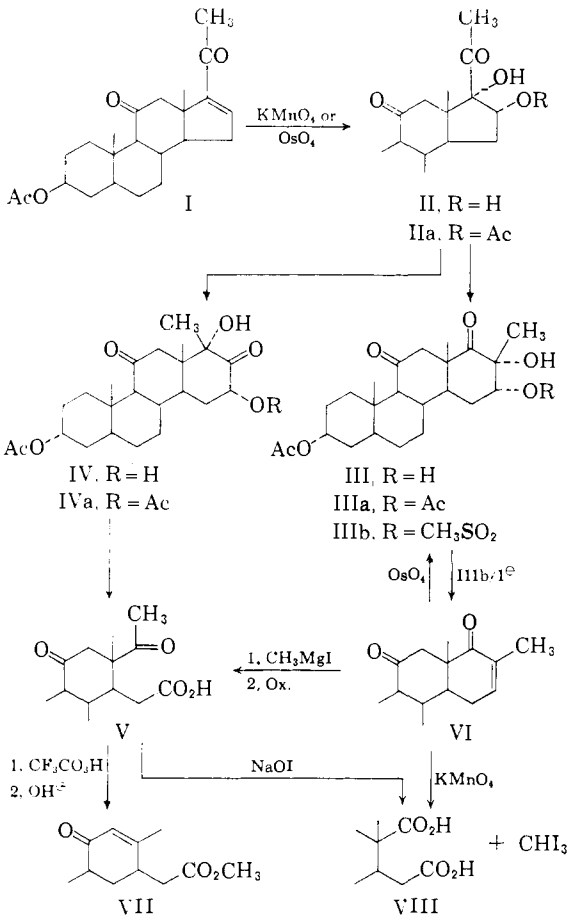
(5) Decomposition of the osmate ester by the method of W. S. Allen and S. Bernstein, THIS JOURNAL, **78**, 1909 (1956), on the other hand, proceeds to give high yields of the normal product II (private communication from Drs. J. Fried and P. Diassi).

(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).

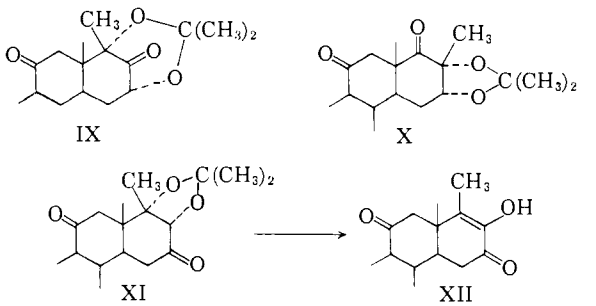
(7) N. L. Wendler, D. Taub, S. Dobriner and D. K. Fukushima, THIS JOURNAL, **78**, 5027 (1956).

oxidation is cleaved to the known etiobilianic acid (VIII)[7] in the same manner that the $\Delta^{\alpha\beta}$-ketone VI as well as the unrearranged diolone II are converted to this acid.

The minor product from the D-homoannulation of II was established to have structure IV in the following way: Oxidation with permanganate converted IV to the methyl ketonic acid V found to be identical by infrared comparison with the oxidation product of the methylcarbinol derived from the $\Delta^{\alpha\beta}$-ketone VI and methylmagnesium iodide. The structure of the methyl ketonic acid (V) was further substantiated by sodium hypoiodite oxidation to give iodoform and the etiobilianic acid. By another sequence, oxidation of V *via* oxygen interpolation at C-13/C-17 with peroxytrifluoroacetic acid followed by β-elimination with base provided the non-crystalline $\Delta^{\alpha\beta}$-ketonic ester VII,[8] λ_{max} 233 mμ (ε 9,000). Like the 17a-ketone III, its isomer IV also formed an acetonide derivative which was stable to the prolonged action



of refluxing alkali. The latter fact requires the formulation of this acetonide to be IX since the remaining structural possibility as its acetonide XI should readily undergo base-catalyzed β-elimination of its oxygen functionality with ensuing formation of the diosphenol XII (compare the transformation of III and IV with alkali below). Further, since the original configuration at C-16 of any rearrangement product of II must be 16α,[9] the subsequent formation of another isomeric species would require mediation by an ene-diol XIII or its equivalent which should correspondingly collapse to the diosphenol XII. Therefore, assuming the α-configuration of the 16-hydroxyl group in IV to be secure on this basis, then the fact of acetonide formation by IV requires a *cis* relationship of the two hydroxyl functions thereby defining the α-orientation of the hydroxyl group at 17a and consequently establishing structure IV for the minor product of D-homoannulation of II. The retro-rearrangement of IV as its mesylate derivative (R = CH_3SO_2) to a normal steroid ring



system[10] independently defines in an unique manner the structure and stereochemistry of IV. The details of this and related transformations will be dealt with elsewhere.

Both D-homo steroids III and IV afforded their respective 3,16-diacetate derivatives IIIa and IVa on acetylation with acetic anhydride in pyridine at room temperature. There was no evidence of the formation of a triacetate derivative under these conditions as reported elsewhere in other series.[3,6] The acetylation products were single spot by paper chromatography, showed strong OH absorption in their infrared spectra and gave acetyl group analyses corresponding to two acetyl functions per molecule.

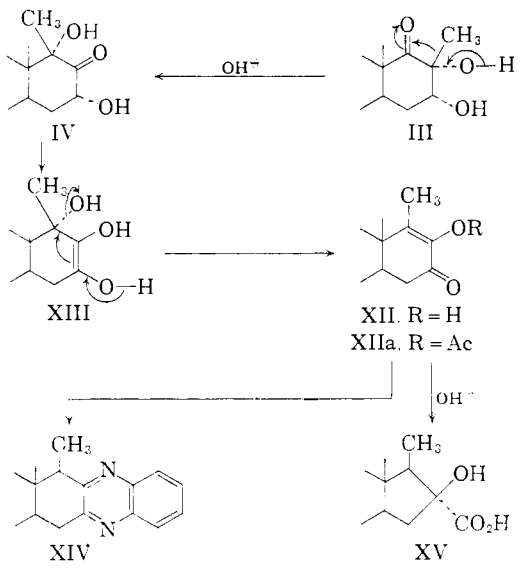
Treatment of the minor isomer IV with hot alkali converted it smoothly into the base-soluble diosphenol XII, $\lambda_{max}^{CH_3OH}$ 279 mμ (ε 9,450). The latter afforded a 3,17-diacetate derivative, m.p. 198.5–199.5°, with $\lambda_{max}^{CH_3OH}$ 241 mμ, (ε 10,750), that in turn yielded the methyl ketonic acid V on permanganate oxidation. The major D-homo isomer III likewise gave the diosphenol XII on treatment with hot alkali and, ostensibly, as a consequence of an initial methyl migration from C-17 → C-17a wherein IV is involved as a transitory intermediate.[11] The latter transformation would be in

(8) Compare N. L. Wendler, D. Taub and H. L. Slates, THIS JOURNAL, **77**, 3559 (1955).

(9) The configuration of the hydroxyl at C-16 in II is established as 16α by the method of its formation as well as by degradation to the 16α-acetoxy-17-ketone (unpublished observation; compare ref. 2 in another series). A configurational change at that position seems unlikely until ring expansion has occurred to place it adjacent to a carbonyl function whereupon it would be capable, in theory at least, of epimerization. See, however, S. Bernstein, N. Heller and S. Stolar, THIS JOURNAL, **81**, 1256 (1959); H. Kuo, D. Taub and N. L. Wendler, *Chemistry & Industry*, 1128 (1959).

(10) N. L. Wendler, *ibid.*, 20 (1959).

(11) In view of recent findings [I. Elphimoff-Felkin and Skrobek, *Bull. soc. chim.*, 742 (1959); D. Taub and N. L. Wendler, *Chemistry & Industry*, 902, 903 (1959)] that certain D-homo systems can equilibrate in virtue of a reversible relationship with parent steroid, this possibility though highly improbable cannot be excluded for the conversion III → IV, namely *via* II or its 16-epimer.



effect comparable to the D-homoannulation process itself wherein methyl rather than a ring bond migration is involved. The driving force for this change can be visualized to arise in the eventual collapse of the system to a stable enolate. The reverse methyl migration C-17a → C-17 (IV → III) has also been observed[10] and will be considered at greater length elsewhere in conjunction with other related phenomena.

The diosphenol XII readily forms a quinoxaline derivative XIV, a reaction observed earlier in another series by Cooley, Ellis, Hartley and Petrow.[3] Prolonged refluxing of XII with concentrated alkali invokes benzilic acid contraction to the 16-etianic acid derivative XV. This type of contraction phenomena has already been observed in other closely related instances.[12] The stereochemistry of XV has not been established independently, but is assigned by analogy with the established course of base-catalyzed ring contraction of isomeric diosphenols.[13]

Experimental[14]

3α-Acetoxy-16α,17α-dihydroxypregnane-11,20-dione (II).—(A) A solution of 3.64 g. of the Δ^{16}-ketone I in 100 cc. of acetone was oxidized, according to the method of Cooley, Ellis, Hartley and Petrow,[3] by dropwise addition over a period of 1 hour of a solution of 1.49 g. of potassium permanganate in 140 cc. of 90% acetone at 0–5°. The reaction mixture was decolorized with sulfur dioxide gas, filtered and evaporated. The residue was dissolved in ether and washed with dilute aqueous potassium bicarbonate solution. Acidification of the latter deposited acidic material. The neutral residue from evaporation of the ether solution, 3 g., was crystallized from aqueous methanol to give 1 g. of II. The latter was recrystallized from methanol as balls of needles, m.p. 153–157°. This product exhibited polymorphism and could be recrystallized from chloroform–ether to give prisms, m.p. 186–188°, having an infrared spectrum identical with the 153–157° melting material; λ_{max}^{chf} 2.95–3μ (OH), 5.81 μ (OAc), 5.87 μ (C=O); $[\alpha]^{chf}$ D +98°.

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.98; H, 8.37. Found: C, 68.11; H, 8.23.

Acetylation of a sample of the diol II with acetic anhydride in pyridine at room temperature provided the **3,16-diacetate derivative (IIa)**, m.p. 198–201; λ_{max}^{chf} 2.82 μ (OH) 5.8 μ (OAc), 5.87 μ (C=O).

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.96; H, 8.04. Found: C, 67.09; H, 8.17.

Treatment of a 100-mg. sample of II in 10 cc. of acetone with 1 drop of concentrated hydrochloric acid for 18 hours gave the **acetonide derivative of II**, m.p. 166–169°; no OH in infrared.

Anal. Calcd. for $C_{26}H_{38}O_6$: C, 69.95; H, 8.52. Found: 70.17; H, 8.60.

(B) A solution of 1.86 g. of the unsaturated ketone I in 10 cc. of dioxane was treated with 1.6 g. of osmium tetroxide in 10 cc. of dioxane and allowed to stand for 3 days. At the conclusion of this time the black osmate ester was decomposed with a stream of hydrogen sulfide in the cold according to Barton and Elad.[3] The product was filtered and the filtrate concentrated at low temperature *in vacuo* to give 1.8–1.9 g. of product. The latter on crystallization from methanol afforded II as elongated prisms, m.p. 184–186°, identical by mixed melting point and infrared comparison with material obtained by permanganate oxidation of I (method A).

Acetylation of the mother liquors from the separation of II afforded the D-homo isomer diacetate IIIa, m.p. 214–216° (see below).

Rearrangement of 3α-Acetoxy-16α,17α-dihydroxypregnane-11,20-dione (II) on Alumina.—The product from hydroxylation of 20 g. of I with 19 g. of osmium tetroxide in 250 cc. of dioxane (method B above) was chromatographed on 600 g. of neutral alumina. Fractions eluted with 5% ether in benzene through 50% ether in benzene[15] provided 10.6 g. (80% of isomer total) of **3α-acetoxy-16α,17α-dihydroxy-17β-methyl-5β-D-homoandrostane-11,17a-dione (III)** as dimorphic crystals from methanol–hexane or from ether; m.p. 172–175° and 196–198°, $[\alpha]^{chf}$ D +70°. Both forms exhibited identical infrared spectra.

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.98; H, 8.37. Found: C, 68.22; H, 8.37.

Acetylation of the diol III with acetic anhydride in pyridine at room temperature afforded the **3,16-diacetate derivative IIIa**, m.p. 215.5–217°; λ_{max}^{Nujol} 2.94 μ (OH), 5.90 μ (C=O), 5.77 μ (OAc).

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.96; H, 8.04; CH_3CO, 19.2. Found: C, 66.90; H, 7.83; CH_3CO, 18.5.

Treatment of a 100-mg. sample of III in 10 cc. of acetone with 1 drop of concentrated hydrochloric acid for 15 hours provided the **acetonide derivative X** from ether–pentane; m.p. 201–204°; no OH in infrared. The n.m.r. spectrum exhibited six methyl peaks.

Anal. Calcd. for $C_{26}H_{38}O_6$: C, 69.95; H, 8.52. Found: C, 70.19; H, 8.59.

The fractions from the original chromatography eluted with ether[15] gave 2.8 g. (20% of isomer total) of **3α-acetoxy-16α,17aα-dihydroxy-17aβ-methyl-5β-D-homoandrostane-11,17-dione (IV)** as needles from ether; m.p. 203–205°, $[\alpha]^{chf}$ D +72°.

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.98; H, 8.37. Found: C, 67.84; H, 8.57.

Acetylation of IV with acetic anhydride in pyridine at room temperature gave the **3,16-diacetate derivative IVa**, m.p. 243–245°; λ_{max}^{Nujol} 2.92 μ (OH), 5.86 μ (C=O), 5.75 μ (OAc).

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.96; H, 8.04; CH_3CO, 19.2. Found: C, 66.92; H, 7.98; CH_3CO, 19.5.

Treatment of 100 mg. of IV in 10 cc. of acetone with 1 drop of concentrated hydrochloric acid afforded the acetonide derivative IX, m.p. 224–226°; no OH in infrared. The n.m.r. spectrum exhibited six methyl peaks.

Anal. Calcd. for $C_{26}H_{38}O_6$: C, 69.95; H, 8.52. Found: C, 69.60; H, 8.47.

3α-Acetoxy-16α-methanesulfonyloxy-17α-hydroxy-17β-methyl-5β-D-homandrostane-11,17a-dione (IIIb).—A solution of 870 mg. of III in 5 cc. of pyridine was treated with

(12) (a) N. L. Wendler and D. Taub, *Chemistry & Industry*, 415 (1958); see also (b) V. Georgian and N. Kundu, *ibid.*, 1322 (1958).

(13) N. L. Wendler, D. Taub and R. P. Graber, *Tetrahedron*, **7**, 173 (1959).

(14) All melting points were taken on a micro-hot-stage and are corrected.

(15) In later separations employing more active alumina similar percentage compositions of chloroform–benzene and chloroform were employed for elution.

0.5 cc. of methanesulfonyl chloride at 0–5° and allowed to stand at this temperature for 15–18 hours. The reaction product was treated with ice-water and the organic material extracted into ethyl acetate. The ethyl acetate extract was washed free of pyridine with 5% aqueous hydrochloric acid and finally with aqueous potassium bicarbonate solution. Evaporation of the solvent and crystallization of the residue from acetone–ether afforded IIIb, m.p. 185–186°; λ_{max}^{chf} 2.84 μ (OH), 5.78 and 7.96 μ (OAc), 5.84 μ (C=O), 7.42 and 8.5 μ (CH_3SO_2O).

Anal. Calcd. for $C_{24}H_{36}O_8S$: C, 59.50; H, 7.44; S, 6.61. Found: C, 59.29; H, 7.32; S, 6.98.

Conversion of the Mesylate Derivative IIIb to the Δ^{αβ}-Ketone VI.—A solution of 500 mg. of IIIb in 20 cc. of acetone was treated with 1.5 g. of sodium iodide and heated 18 hours at 110–115° in a sealed tube. The reaction product was worked up by evaporation of the acetone, discharging the iodine formed with sodium thiosulfate and extracting the organic material with ether. The ether solution was evaporated and the residue acetylated with acetic anhydride in pyridine at room temperature and the product chromatographed to yield the Δ^{αβ}-ketone VI, m.p. and mixed m.p. with authentic VI 206–212°. The infrared spectra of the two samples were identical.

Conversion of the Δ^{αβ}-Ketone VI to III by Osmium Tetroxide Hydroxylation.—A solution of 250 mg. of the Δ^{αβ}-ketone VI in 10 cc. of dioxane was treated with 250 mg. of osmium tetroxide in 10 cc. of dioxane and allowed to react at room temperature for 3 days. At the end of this period the osmate ester was decomposed with hydrogen sulfide and the product worked-up as already described. Crystallization from ether afforded III, m.p. 172–175°; mixed m.p. with III prepared by D-homoannulation of II was not depressed. The two samples showed identical infrared spectra.

Acetylation of a sample of III obtained above from the hydroxylation of VI gave material melting at 212–214.5° which was identical with the 3,16-diacetate of the major product of D-homoannulation of II both by melting point and infrared comparison.

Oxidation of II and III to 3α-Acetoxy-11-keto-etiobilianic Acid (VIII).—A solution of 200 mg. of the pertinent compound (II or III) in 20 cc. of acetone was treated with 260 mg. of potassium permanganate and stirred for 2.5 hours. The reaction product was concentrated at room temperature by blowing the acetone down in a stream of nitrogen. The residue was suspended in 20 cc. of water, acidified with sulfuric acid and decolorized with sodium bisulfite. Extraction of the organic material with ether and purification of the acidic component by extraction with bicarbonate afforded the etiobilianic acid VIII from ether; m.p. 228–236° identical with an authentic specimen.[7]

Acetylation of the above acid in pyridine with acetic anhydride provided the known anhydride,[7] m.p. 212–215°.

Formation of the Methyl Ketonic Acid V from the Minor Isomer IVa, the Δ^{αβ}-Ketone VI and the Diosphenol Diacetate XIIa.—The oxidation of IVa and XIIa was carried out in the same manner as described above for the formation of the etiobilianic acid VIII. In each case the methyl ketonic acid V was purified through bicarbonate extraction and subsequent acidification. This acid was obtained in an amorphous state and was identical as obtained from both IVa and XIIa by infrared comparison. Treatment of V in sodium hydroxide solution with a solution of iodine in potassium iodide resulted in immediate precipitation of iodoform, m.p. 120–121°.

The formation of V from the Δ^{αβ}-ketone VI was effected by first allowing the latter to react with an excess of methylmagnesium iodide in ether followed by acetylation at C-3 to provide the corresponding 17a-methylcarbinol, λ_{max} 2.92–2.97 μ (OH), 5.78 and 8.03 μ (OAc) and 5.84 μ (C=O). Oxidation of the crude methylcarbinol with permanganate in the manner described afforded V identical with previously obtained samples.

Conversion of the Methyl Ketonic Acid V to the Δ^{αβ}-Ketonic Ester VII.—The methyl ketonic acid 3α-acetate (I, 600 mg.) was converted to the corresponding methyl ester by treatment with diazomethane in ether–methanol; infrared spectrum: $\lambda_{max}^{CHCl_3}$ 5.75 μ, (-OAc, -COOMe), 5.80–5.83 μ (11.20 -C=O), 7.97 μ (-OAc), 8.55 μ (-COOMe).

A solution of peroxytrifluoroacetic acid in methylene chloride was prepared by dropwise addition of 2.50 cc. of trifluoroacetic anhydride to a stirred solution of 0.40 cc. of 90% hydrogen peroxide in 2.50 cc. of methylene chloride maintained at 0°.[16] After 15 minutes this solution was added dropwise to a cold (0°) stirred slurry of 382 mg. of the above methyl ester of V in 7.5 cc. of methylene chloride and 6.5 g. of disodium hydrogen phosphate.[16] The stirred mixture was kept at 25° for 2 hours, 20 cc. of methylene chloride was added and the mixture was refluxed 30 minutes. It was then cooled, water was added and the mixture was extracted with methylene chloride. The amorphous oxidation product was transparent in the ultraviolet. The latter was partly saponified by refluxing for 30 minutes in 10 cc. of methanol and 2.6 cc. of 1.0 *N* aqueous sodium hydroxide. The solution was cooled, acidified with dilute hydrochloric acid and extracted with chloroform. Extraction of the chloroform phase with 5% sodium carbonate solution, acidification of the latter extract followed by chloroform extraction gave some amorphous Δ^{αβ}-ketonic acid VII, $\lambda_{max}^{CH_3OH}$ 233 mμ. From the chloroform layer was obtained the methyl ester of VII, $\lambda_{max}^{CH_3OH}$ 233 mμ, ε, 9,000; infrared spectrum: λ_{max}^{chl} 2.90 (3α-OH); 5.76, 8.56 μ (-COOMe), 5.99 (conj. 11—C=O). The absence of saturated carbonyl absorption in the 5.80–5.85 μ region (compare the methyl ester of V) shows that the 20-carbonyl function as well as the saturated 11-carbonyl function are no longer present. Acetate functionality is also absent as evidenced by the lack of absorption at 8.0 μ.

An initial attempt to perform this sequence utilizing perbenzoic acid as the oxidant failed.[17]

3α,17-Dihydroxy-17a-methyl-5β-D-homo-Δ^{17}-androstene-11,16-dione (XII).—A solution of 250 mg. of the major isomer III in 25 cc. of 10% methanolic potassium hydroxide was refluxed for 2 hours. At the end of this period the reaction mixture was concentrated to dryness *in vacuo*. The residue was completely water soluble and on acidification precipitated solid material. The latter was dissolved in ethyl acetate and the ethyl acetate solution extracted thoroughly with potassium bicarbonate solution. The dried ethyl acetate solution on concentration deposited crystalline XII, m.p. 271–277°. Recrystallization from ethyl acetate–hexane gave needles, m.p. 276.5–278°; $\lambda_{max}^{CH_3OH}$ 279 mμ, ε 9,450; λ_{max}^{chf} 2.78 and 2.92 μ (OH), 5.85 μ (C=O) 5.99 and 6.08 μ (conj. C=O).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.83; H, 8.67. Found: C, 73.14; H, 8.58.

Acetylation of a sample of the diosphenol XII with acetic anhydride in pyridine at room temperature provided the corresponding **3,17-diacetate derivative XIIa**, m.p. 198.5–199.5°; $\lambda_{max}^{CH_3OH}$ 241 mμ, ε 10,750.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.77; H, 7.91. Found: C, 69.84; H, 8.07.

In a similar manner a 200-mg. sample of the minor isomer IV was converted essentially quantitatively to the diosphenol XII identical in every respect with material obtained from III.

A solution of 89 mg. of the diosphenol XII in 2 cc. of ethanol was treated with 100 mg. of *o*-phenylenediamine and 2 drops of acetic acid and refluxed for 2 hours. The reaction mixture was evaporated to dryness, the residue extracted with ether and the ether solution washed with potassium bicarbonate solution. Evaporation of the ether solution deposited the **quinoxaline derivative XIV**, m.p. 234–239°, recrystallized from acetone–ether as buff-colored plates, m.p. 236–240°; $\lambda_{max}^{CH_3OH}$ 321 mμ (10,800), 238 mμ (32,300), 311 mμ infl. (8,360).

Anal. Calcd. for $C_{27}H_{34}O_2N_2$: C, 77.51; H, 8.13; N, 6.70. Found: C, 77.41; H, 7.95; N, 7.12.

3α,16β-Dihydroxy-11-keto-17β-methyl-16-isoetianic Acid (XV).—A solution of 1.5 g. of the diosphenol diacetate XIIc in 50 cc. of methanol was treated with 15 g. of potassium hydroxide in 15 cc. of water and refluxed 16–18 hours. The reaction mixture was concentrated to near dryness and the residue dissolved in water and precipitated by acidification with hydrochloric acid. The precipitate was dissolved in ethyl acetate and the organic acid extracted with potassium bicarbonate solution. Acidification of the latter caused the acid XV to deposit in a crystalline state. Filtration fol-

(16) Procedure of W. D. Emmons and G. B. Lucas, THIS JOURNAL, **77**, 2287 (1955), and earlier references cited therein.

(17) Compare ref. 7.

lowed by recrystallization from acetone afforded the 16-isoetianic acid XV, m.p. 264–268°.

Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.23; H, 8.79. Found: C, 68.89; H, 8.67.

D-Homoannulation of IIa.—A solution of 500 mg. of IIa in 20 cc. of toluene was refluxed with 500 mg. of aluminum *t*-butoxide for 3 hours. At the end of this period the toluene was evaporated *in vacuo* and the residue decomposed with 10% aqueous hydrochloric acid. The organic material was extracted with ethyl acetate and ethyl acetate extract, washed with potassium bicarbonate solution and brine. Evaporation of the dry ethyl acetate solution and crystallization of the residue from ether afforded 260 mg. of the 17a-D-homo ketone derivative IIIa, m.p. 210.5–213°; mixed m.p. with an authentic sample of IIIa was not depressed.

RAHWAY, N. J.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

The Ethoxalylation of 16α,17α-Isopropylidenedioxyprogesterone

BY GEORGE R. ALLEN, JR., AND MARTIN J. WEISS[1]

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Reaction of 16α,17α-isopropylidenedioxyprogesterone (II) with ethyl oxalate under mono-acylation conditions is described. Treatment of the product with one or two molar equivalents of bromine gave 2α-bromo- (III) or 2α,4-dibromo-16α,17α-isopropylidenedioxyprogesterone (VI), respectively, in 60–65% yields. Condensation of II at C-21 could not be effected. The 16α,17α-isopropylidenedioxy group inhibits ethoxalylation at C-21. A method for the hydrolytic deacetonation of 16α,17α-isopropylidenedioxysteroids is described.

Recently we reported[2a] that 16α,17α- isopropylidendioxy - 4,9(11) - pregnadiene - 3,20 - dione (I) condenses with ethyl oxalate in the presence of one molar equivalent of sodium methoxide exclusively at C-2.[2b] This preferential acylation at C-2 is not the result of an inability of C-21 to undergo acylation, for a 2,21-bis-ethoxalyl derivative is formed on reaction of I with excess ethyl oxalate in the presence of two molar equivalents of sodium methoxide.[2a] Since progesterone appears to undergo ethoxalylation at C-2 and at C-21 in a relatively indiscriminate manner,[3,4] the very real selectivity (at least 90%) for C-2 observed with I is presumably the result of steric hindrance exerted by the 16α,17α-isopropylidenedioxy function on the acetyl side-chain[8] or, as is less likely, an activating effect of the $\Delta^{9(11)}$-moiety on the Δ^4-3-ketone system. In order to evaluate the influence of these groups on the course of the ethoxalylation reaction, we undertook an investigation of this acylation with 16α,17α-isopropylidenedioxyprogesterone (II).

Reaction of the known 16α,17α-isopropylidenedioxyprogesterone (II)[9] with 1.1 molar equivalents of sodium methoxide and 1.7 molar equivalents of ethyl oxalate[5] for 24 hours gave a sodioethoxalyl derivative and an 8% recovery of II. The free ethoxalyl derivative, for which satisfactory analytical values could not be obtained, resulted on acidification of an aqueous solution of the sodium salt. When the condensation time was decreased to three hours, the ethoxalyl derivative was formed in lower yield, and II was recovered to the extent of 35–47%.

A solution of this ethoxalyl derivative in methanolic potassium acetate was treated with one molar equivalent of bromine. Subsequent deacylation *in situ* of the presumed bromoethoxalyl intermediate by addition of methanolic sodium methoxide gave, in 64% yield, a crystalline monobromo - 16α,17α - isopropylidenedioxyprogesterone. It may be noted that this monobromide was formed in equally good yield when the addition of the sodium methoxide was eliminated. The monobromo derivative of II was formulated as 2α - bromo - 16α,17α - isopropylidenedioxyprogesterone (III), since infrared spectral evidence indicated the presence of a 2α-bromo-Δ^4-3-keto moiety (see below and Table I).[10,11] Confirmation of the 2-bromo structure was obtained on treatment with refluxing collidine to give, in 70% yield, 16α,17α - isopropylidenedioxy - 1,4 - pregnadiene-3,20-dione (VII). The structure of this latter product was established by infrared spectral evidence,[12] polarographic assays and the ultraviolet absorption maxima of its dinitrophenylhydrazone.[13]

(1) To whom inquiries concerning this paper should be directed.

(2) (a) G. R. Allen, Jr., and M. J. Weiss, THIS JOURNAL, **81**, 4968 (1959). (b) Apparent preferential ethoxalylation at C-2 has also been observed with 9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxyprogesterone [S. Bernstein, J. J. Brown, L. Feldman and N. E. Rigler, *ibid.*, **81**, 4956 (1959)].

(3) G. R. Allen, Jr., and M. J. Weiss, *ibid.*, **82**, 1709 (1960).

(4) Apparent selectivity for C-21 has been reported for 11α-hydroxy-, 11β-hydroxy- and 11-keto-progesterone[6] and in the patent literature for 4,16-pregnadiene-3,20-dione.[6] However, in our laboratory attempts to effect preferential ethoxalylation of 11α-hydroxy-Δ^{16}-progesterone and of $\Delta^{9(11),16}$-progesterone were essentially unsuccessful.[3] With the latter compound, under monoethoxalylation conditions, the bulk of the product was the 2,21-bis-ethoxalyl derivative.[7]

(5) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze and R. W. Jackson, THIS JOURNAL, **77**, 4436 (1955).

(6) A. H. Nathan and J. A. Hogg, U. S. Patent 2,719,855 (1955); *C. A.*, **50**, 7889b (1956).

(7) R. E. Schaub, G. R. Allen, Jr., and M. J. Weiss, THIS JOURNAL, **81**, 4962 (1959).

(8) For a discussion of the steric effect of a 16α,17α-isopropylidenedioxy group on the acetyl side-chain see footnotes 26 and 38 in ref. 2a.

(9) G. Cooley, B. Ellis, F. Hartley and V. Petrow, *J. Chem. Soc.*, 3373 (1955).

(10) (a) M. Fieser, M. A. Romero and L. F. Fieser, THIS JOURNAL, **77**, 3305 (1955); (b) E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957).

(11) In addition to the spectral evidence for the α-orientation of the bromo substituent in III, it may be noted that the introduction of a 2-bromo substituent *via* an ethoxyalylation procedure makes it probable that this group is so oriented.[2a] Similar considerations have led to the postulation of an α-orientation for certain 2-methyl steroids also prepared *via* a 2-ethoxalyl derivative [J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, THIS JOURNAL, **77**, 6401 (1955)].

(12) *Inter alia* see (a) J. Fried, R. W. Thoma and A. Klingsberg, *ibid.*, **75**, 5764 (1953); (b) H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro, E. P. Oliveto and E. B. Hershberg, *ibid.*, **77**, 4781 (1955); (c) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).