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Transformations in the 16-Acetyl-5β-androstane Series

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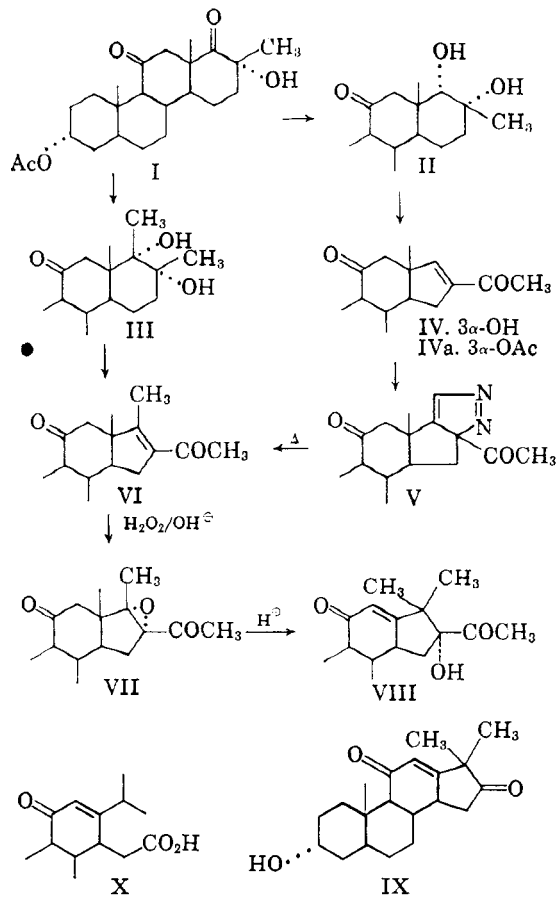
The synthesis of precortical systems in the 16-acetyl-5β-androstane series is described. Rearrangement of the Kägi-Miescher type was observed in one instance of oxide cleavage.

Recently the conversion of the D-homo ketol I to the 16-acetyl-Δ^{16}-5β-androstene IV was reported.[1] In this transformation I was reduced to the diol II by means of aluminum isopropoxide followed by periodate cleavage and cyclization to IV. Correspondingly I was converted to the ditertiary diol III with methylmagnesium iodide. Cleavage oxidation of the diol III and subsequent cyclization with alkali yielded the 17-methyl-16-acetyl-Δ^{16}-5-β-androstene VI.

Our recent experiences with methylations at C-16 of 3α-acetoxy-Δ^{16}-pregnene-11,20-dione by means of diazomethane[2] encouraged the application of this method to the positionally isomeric system IVa. The latter, IVa, was observed to react in a completely parallel fashion with diazomethane to afford the pyrazoline (V). Pyrolysis of the latter gave 3α-acetoxy-17-methyl-16-acetyl-Δ^{16}-5β-androstene-11-one (VI) identical with material obtained by the Grignard sequence. Treatment of the $\Delta^{\alpha,\beta}$-ketone VI with alkaline hydrogen peroxide produced the oxide (VII) and this derivative on acid hydrolysis with dilute perchloric acid suffered oxide opening with methyl migration $C_{13} \rightarrow C_{17}$ to afford the $\Delta^{\alpha,\beta}$-ketone (VIII), m.p. 233–236°, $\lambda_{max}^{CH_3OH}$ 240 mμ (11,200).[3] Recently there have appeared many examples of this rearrangement type,[4a] which was first observed by Cohen, Cook, and Hewett,[4b] in the equilenin series and later studied in detail by Kägi and Miescher.[4c]

The rearranged steroid VIII was reduced at C_{20} with sodium borohydride in dimethylformamide[5] and the intermediate diol cleaved with periodate to provide the enedione IX, m.p. 179–183°, $\lambda_{max}^{CH_3OH}$ 237 mμ (10,900); $\lambda_{max}^{CHCl_3}$ 5.72 μ (five-ring C=O) and 5.99 μ (six-ring C=O). The enedione as a vinylogous β-diketone would be expected to cleave readily with alkali to give the acid X.[6] This, however, did not prove to be the case.

Treatment of IX with alkali produced a complex mixture of neutral, phenolic and acidic components which was not further investigated for lack of material. The sensitivity of IX to air in the presence of alkali was evident from the formation of highly colored solutions under these conditions. The tendency of the hydrindenone system to aromatize has been observed in the jervine alkaloid series.[7]



(1) N. L. Wendler and D. Taub, *J. Org. Chem.*, **23**, 953 (1958).

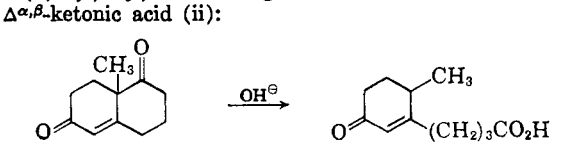
(2) H. L. Slates and N. L. Wendler, *J. Am. Chem. Soc.*, **81**, 5472 (1959).

(3) *Cf.* N. L. Wendler, R. P. Graber, and G. G. Hazen, *Tetrahedron*, **3**, 144 (1958).

(4) (a) L. F. Fieser and M. Fieser, *Steroids*, Reinhold, New York, 1959, p. 529. (b) A. Cohen, J. W. Cook, and C. L. Hewett, *J. Chem. Soc.*, 445 (1935). (c) H. Kägi and K. Miescher, *Helv. Chim. Acta*, **22**, 683 (1939); **32**, 761 (1949).

(5) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Am. Chem. Soc.*, **81**, 3291 (1959).

(6) *Cf., e.g.*, the cleavage of the octalindione (i) to the $\Delta^{\alpha,\beta}$-ketonic acid (ii):

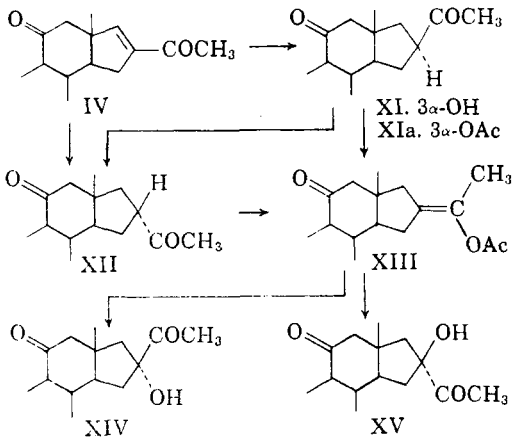


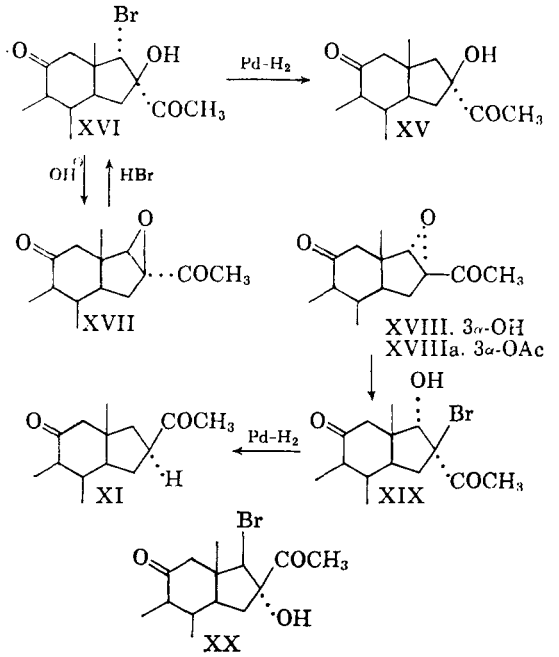
N. L. Wendler, H. L. Slates, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3816 (1951).

Catalytic reduction of 3α-hydroxy-16-acetyl-Δ^{16}-5β-androstene-11-one (IV) over 5% palladium on barium sulfate resulted in the uptake of one mole of hydrogen. Fractional crystallization of the total product gave 3α-hydroxy-16β-acetyl-5β-androstane-11-one (XI), m.p. 206–210°, as the major and 3α - hydroxy - 16α - acetyl - 5β - androstane - 11-one (XII), m.p. 151–154°, as the minor component. The configurations were assigned on the assumption that the predominant mode of addition to the Δ^{16} double bond is from the α-side of ring D.[8] Confirmation of these assignments was obtained by alkaline isomerization of the quasi axial β-isomer XI to an equilibrium mixture in which the quasi equatorial α isomer XII predominated.[9]

Both compounds XI and XII were converted to the same noncrystalline enol acetate (or mixture of geometrical isomers) XIII which, with perbenzoic acid, gave an amorphous oxide mixture. The latter, when cleaved by methanolic sodium hydroxide, gave as the principal products the ketols XIV, m.p. 178–180°, and XV, m.p. 181–184°.[10] The ketol XIV predominated over XV in the ratio 55:45. The $\Delta^{17(20)}$ 20 enol acetates studied by Gallagher and his collaborators[11] react with peracids stereospecifically to give almost exclusively 17α,20α-oxides which in turn lead to 17α-hydroxy-20-keto pregnanes free from the corresponding epimers. This difference in stereospecificity between reaction with 17(20)- and 16(20)-double bonds is noteworthy.

The assigned configurations of the two ketols XIV and XV, based on the assumption that peracid attack from the α side would still predominate, were shown to be correct by the following chemical evidence. Reaction of 3α-acetoxy-Δ^{16}-16-acetyl-5β-androstane-11-one (IVa) with *N*-bromsuccinimide gave a noncrystalline bromohydrin best formulated as XVI, the quasi diaxial product resulting from the 16α,17α-bromonium ion. The bromohydrin XVI was converted by methanolic sodium hydroxide to the β-oxide XVII, m.p. 188–192°, which with hydrogen bromide in acetic was reconverted to XVI. Removal of bromine from XVI by hydrogenation over palladium on calcium carbonate followed by saponification of the 3α-acetate group gave in good yield the 3α-hydroxy ketol, m.p. 181–184° (XV), in conformity with the above structural assignment.





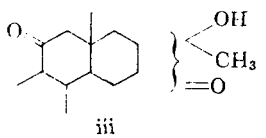
The preparation of the 16α-hydroxy ketol XIV *via* the 16α,17α-oxide XVIII was attempted also. Alkaline hydrogen peroxide treatment of IV gave the 3α-hydroxy-16α,17α-oxide, m.p. 187–193° (XVIII), which was acetylated to the corresponding 3α-acetate, m.p. 166–167° (XVIIIa). Reaction of the latter with hydrogen bromide in acetic acid gave an amorphous bromohydrin XIX which behaved uniquely when treated with hydrogen over palladium on calcium carbonate to give in good

(7) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **75**, 4938 (1953).

(8) The α face of ring D is relatively more accessible to addition reactions than the β face because of the steric bulk of the C_{18} angular methyl group. [See L. F. Fieser, *Experientia*, **6**, 312 (1950).]

(9) Analogous stability relationships at C_{16} in another series (the 16-acetyl-3β-acetoxy-5α-androstanes) were observed by J. Fajkŏs and F. Sŏrm, *Chem. Listy.*, **51**, 579 (1957).

(10) Also obtained were XI and XII and a substance, m.p. 267–271°, apparently isomeric with the ketols XIV and XV (see Experimental). This material, which was not investigated further, could be a 16,17-substituted D-homo compound (iii).



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(11) T. H. Kritchevsky and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 184 (1951); B. A. Koechlin, T. H. Kritchevsky, and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 189 (1951); T. H. Kritchevsky, D. L. Garmaise, and T. F. Gallagher, *J. Am. Chem. Soc.*, **74**, 483 (1952).

yield 3α-acetoxy-16β-acetyl-5β-androstane-11-one (XIa) and the corresponding 3-alcohol XI.[12] This result is compatible with structure XIX for the bromohydrin in which the hydroxyl and bromo substituents are quasi axial with the hydroxyl group β to the 20-carbonyl group in position to be readily eliminated concomitant with reductive loss of bromine.[13] The resulting 16,17-double bond is reduced from the α side to give XIa. The alternate possibility (XX) in which the substituents are *trans* quasi equatorial would be expected to be less prone to loss of its hydroxyl group.[14]

EXPERIMENTAL

Pyrazoline derivative of 3α-acetoxy-16-acetyl-Δ¹⁶-5β-androstene-11-one (V). A 6-g. sample of 3α-hydroxy-16-acetyl-Δ¹⁶-5β-androstene-11-one (IV)[1] was converted to its 3-acetate derivative by room temperature acetylation in 20 cc. of acetic anhydride and 20 cc. of pyridine. The amorphous acetate derivative thus obtained was dissolved in 50 cc. of ether and treated with an excess of diazomethane as described.[2] A total of 5.9 g. of crystalline pyrazoline (V) was obtained which melted after recrystallization from acetone at 190–192°.

Anal. Calcd. for $C_{24}H_{34}O_4N_2$: N, 6.76. Found: N, 6.39.

3α-Hydroxy-17-methyl-16-acetyl-Δ¹⁶-5β-androstene-11-one (VI). The pyrazoline derivative (5 g.) was heated *in vacuo* at 200° for 10–15 min. as described.[2] After the vigorous loss of nitrogen had subsided the product was refluxed with alkali and isolated in the usual manner.[2] The product was crystallized from acetone-hexane (4 g.) m.p. 193–195°; mixed melting point with a sample of VI obtained by another method[1] was not depressed. The infrared spectra of the two samples were the same.

3α-Hydroxy-16α,17α-oxido-16β-acetyl-17β-methyl-5β-androstene-11-one (VII). A solution of 3 g. of Δ^α,β^-ketone (VI) in 100 cc. of methanol was treated at room temperature with 14 cc. of 30% hydrogen peroxide and 14 cc. of 10% sodium hydroxide and allowed to stand for 1.5 hr. at room temperature and 48 hr. at 5–10°. Water was added and the precipitated product was filtered, washed with water, and dried; wt. 2 g. A 200-mg. sample was crystallized from acetone-ether; m.p. 210–214°, no ultraviolet max.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.33; H, 8.89. Found: C, 73.50; H, 8.71.

Rearrangement of the oxide VII *to the Δ^α,β^-ketone* (VIII). A solution of 1 g. of the oxide (VII) in 40 cc. of dioxane was treated with 6 cc. of 70% perchloric acid diluted to 20 cc. with water. The reaction mixture was allowed to stand at room temperature for 72 hr. At the end of this period the solvent was evaporated *in vacuo*, the product extracted with ethyl acetate and the ethyl acetate extract washed with bicarbonate solution. Evaporation of the dried ethyl acetate solution and crystallization of the residue from acetone-ether afforded VIII, m.p. 228–232°; $\lambda_{max}^{CH_3OH}$ 240 mμ (11,200); $\lambda_{max}^{CHCl_3}$ 2.85 (OH), 5.88 (sat. C=O), 6.05 and 6.09 μ (conj. C=O).

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.33; H, 8.89. Found: C, 73.71; H, 8.91.

A sample of VIII (100 mg.) acetylated with acetic anhydride (1 cc.) in pyridine (2 cc.) at room temperature afforded the 3-acetate derivative of VIII, m.p. 244–248°; λ_{max}^{Nujol} 3.03 (OH), 5.78 (OAc), 5.87 (sat. C=O), 6.07 and 6.21 μ (conj. C=O).

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.64; H, 8.46. Found: C, 71.21; H, 8.66.

3α-Hydroxy-17,17-dimethyl-18-nor-Δ¹²-5β-androstene-11,-16-dione (IX). A solution of 200 mg. of the Δ^α,β^ ketone VIII dissolved in 10 cc. of dimethylformamide was treated in the cold (0°) with 50 mg. of sodium borohydride in 2.5–3 cc. of water for 1–2 hr. At the conclusion of this time the excess borohydride was decomposed with glacial acetic acid and the organic product precipitated by addition of saturated salt solution. The precipitate was extracted with ethyl acetate and the ethyl acetate extract washed with water, dried over magnesium sulfate, and evaporated to dryness.

The amorphous residue from the reduction was dissolved in 10 cc. of methanol and oxidized with 250 mg. of sodium metaperiodate in 10 cc. of water for 15 hr. The reaction mixture was evaporated *in vacuo*, the organic product extracted with ether and crystallized from acetone-ether, m.p. 179–183°, $\lambda_{max}^{CH_3CN}$ 237 mμ (10,900); $\lambda_{max}^{CHCl_3}$ 2.74, 2.88–2.9 (OH), 5.72 (five-ring C=O), 5.99 μ (conj. C=O).

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.95; H, 8.86. Found: C, 75.65; H, 8.98.

Catalytic reduction of 3α-hydroxy-16-acetyl-Δ¹⁶-5β-androstene-11-one (IV). A solution of 6 g. of 3α-hydroxy-16-acetyl-Δ¹⁶-5β-androstene-11-one (IV) in 100 ml. of methanol was hydrogenated at 25° and 1 atm. pressure over 5 g. of 5% palladium on barium sulfate catalyst. Hydrogen uptake was complete in 30 min., the catalyst was removed by filtration and the filtrate taken to dryness under vacuum. Crystallization of the solid residue from acetone-hexane gave 4.14 g. 3α-hydroxy-16β-acetyl-5β-androstene-11-one (XI), m.p. 206–210°; $[\alpha]_D^{CHCl_3}$ +41°; $\lambda_{max.}^{CHCl_3}$ 2.80, 2.90–2.95, 5.86 μ.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.70. Found: C, 75.53; H, 9.53.

Acetic anhydride-pyridine acetylation (25° for 18 hr. gave the corresponding *3α-acetate* (XIa) m.p. 120–121°; $\lambda_{max}^{CHCl_3}$ 5.80, 5.86, 8.0 μ.

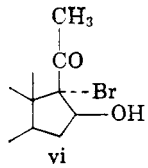
Fractional crystallization of the mother liquors from acetone-hexane gave additional small amounts of XI in two crops followed by two crops of *3α-hydroxy-16α-acetyl-5β-androstane-11-one* (XII), m.p. 150–155°. The analytical sample had m.p. 151–154°; $[\alpha]_D^{CHCl_3}$ +64°; $\lambda_{max}^{CHCl_3}$ 2.80, 2.90–2.95, 5.87 μ different from XI in fingerprint region.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.70. Found: C, 75.66; H, 9.32.

Epimerization of 3α-hydroxy-16β-acetyl-5β-androstene-11-one (XI). A solution of 50 mg. of the 16β-epimer (XI) in 10 ml. of methanol and 2 ml. of water containing 50 mg. of sodium hydroxide was kept at 25° for 2 hr. The alkali was neutralized with acetic acid, water was added, the methanol removed under vacuum, and the product extracted into chloroform. The chloroform extract was washed with water, dried over magnesium sulfate, and concentrated to dryness. The residue (52 mg.) was chromatographed on 3 g. of neutral

(12) Evidently partial hydrolysis of the 3α-acetate function occurred in the aqueous methanolic hydrogenation medium. When 5% palladium on charcoal was used as the catalyst similar results were obtained.

(13) In the case of the bromohydrin (vi) removal of bromine in hydrogen over palladium charcoal in the presence of ammonium acetate occurred without loss of the hydroxyl group [B. Löken, S. Kaufmann, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 1738 (1956)]. See however M. Nishikawa, K. Morita, and S. Naguchi, *J. Pharm. Soc. Japan*, **79**, 1149 (1959).



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(14) Since oxides in general are opened by HX to give predominantly the diaxial product [A. Fürst and Pl. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949); A. Fürst and R. Scotoni, Jr., *Helv. Chim. Acta*, **36**, 1410 (1953)], structure XX might be considered improbable *a priori*. See, however, N. L. Wendler, D. Taub, S. Dobriner, and D. K. Fuku hima, *J. Am. Chem. Soc.*, **78**, 5027 (1956).

alumina. The petroleum ether–benzene, 1:4, to benzene eluates gave 17 mg. of the 16β-acetyl epimer (XI), m.p. 180–200° which on crystallization from ether–petroleum ether had m.p. 207–210°. From the benzene-chloroform eluates was obtained 29 mg. of the 16α-acetyl epimer (XII), m.p. 151–154°.

3α,16α-Dihydroxy-16β-acetyl-5β-androstane-11-one (XIV), *3α,16β - dihydroxy - 16α - acetyl - 5β - androstane - 11 - one* (XV), *and by-products by the peracid sequence.* The catalytic reduction product (XI and XII, 6.02 g.) from 6 g. of IV was converted to the $\Delta^{16(20)}$-enol acetate XIII by the perchloric acid–acetic anhydride procedure of Barton and his collaborators.[15]

A cold (5°–10°) mixture of 0.6 ml. of 60% perchloric acid and 11.4 ml. of acetic anhydride was added dropwise to a stirred slurry of the catalytic reduction product (XI and XII, 6.02 g.) in 20 ml. of chloroform and 100 ml. of carbon tetrachloride maintained at 0°. The mixture was stirred at 25° for 3 hr., cooled to 15°, extracted successively with cold 5% sodium carbonate solution, water, and dried over sodium sulfate. The solvent was removed under vacuum to give crude enol acetate XIII (7.8 g.).The latter was freed from polar impurities by chromatography on 100 g. of neutral alumina. Colorless oils were obtained from the petroleum ether–benzene to benzene eluates. These were combined to give 7.08 g. of material which was dissolved in 9 ml. of benzene. Perbenzoic acid in benzene (49 ml. of 0.38*M*) was added and the mixture kept at 20–25° for 9 hr. Seventy per cent of the calculated amount of peracid was consumed in 4 hr. following which no significant further change in titer occurred. The reaction mixture was extracted with cold sodium carbonate solution, water and sodium chloride solution. The organic layer was dried over sodium sulfate and the solvent removed under vacuum. The residue (7.3 g.) was stirred at 20–25° in a mixture of 275 ml. of ethanol, 145 ml. of water, and 5.5 g. of sodium hydroxide for 2 hr. The alkali was neutralized by acetic acid, the ethanol removed under vacuum, and the product extracted into chloroform. The latter extract was washed with dilute aqueous potassium bicarbonate, water, saturated aqueous sodium chloride, and dried over magnesium sulfate. The residue (5.3 g.) was chromatographed on 200 g. of neutral alumina to give the following results:

Fraction 5: benzene; 101 mg. contained primarily the 16β-acetyl-5β-androstane XI, m.p. 170–190°, raised to 190–200° on crystallization from acetone-ether, identified by mixed melting point and infrared comparison with authentic material.

Fractions 6–8: benzene to 2% chloroform-benzene; ~500 mg. contained largely the 16α-acetyl-5β-androstane XII; m.p. 149–152° on crystallization from acetone-ether; identical with authentic material by mixed melting point and infrared comparison.

Fractions 10–14: 5% chloroform-benzene to 30% chloroform-benzene; 1.30 g. of 16β-hydroxy ketol XV; prisms from acetone-ether, m.p. 181–184°; $[\alpha]_D^{CHCl_3}$ +67°; $\lambda_{max}^{CHCl_3}$ 2.79, 2.90–2.95, 5.86 μ.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.39; H, 9.26. Found: C, 72.37; H, 9.25.

Fractions 16–20: 50% chloroform-benzene to 100% chloroform; 1.83 g. of 16α-hydroxy ketol XIV; prisms from acetone-ether, m.p. 178–180°; $[\alpha]_D^{CHCl_3}$ +62°; $\lambda_{max}^{CHCl_3}$ 2.78, 2.92, 5.87 μ.

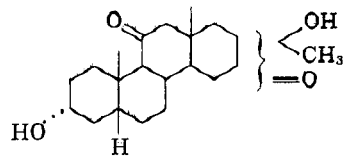
Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.39; H, 9.26. Found: C, 72.21; H, 8.91.

Fraction 23: 2% methanol-chloroform; 205 mg. of needles from acetone-ether m.p. 267–271°; λ_{max}^{Nujol} 2.93, 2.99, 5.85, 5.90 μ.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.39; H, 9.26. Found: C, 72.12; H, 9.11.

(15) D. H. R. Barton, R. M. Evans, J. C. Hamlett, P. G. Jones, and T. Walker, *J. Chem. Soc.*, 747 (1954).

On the basis of its analysis this substance is an isomer of XIV and XV. It could be a 16,17-substituted D-homo compound.



3α-Hydroxy-16β,17β-oxido-16α-acetyl-5β-androstane-11-one (XVII). To a stirred solution of 900 mg. of 3α-acetoxy-16-acetyl-Δ^{16}-5β-androstene-11-one (IVa) in 30 ml. of dioxane cooled to 10° was added 4.8 g. of *N*-bromsuccinimide in 6 ml. of water and 22.5 ml. of 1*N* aqueous perchloric acid. The mixture was stirred at 25° for 3 hr. Aqueous sodium bisulfite solution was added until the yellow color was discharged. Water was added and the mixture extracted with ethyl acetate. The organic extract was dried over magnesium sulfate and concentrated to dryness to give the *bromohydrin* (XVI) as a colorless amorphous solid (1.10 g.); $\lambda_{max}^{CHCl_3}$ 2.95–3.00, 5.82, 5.88, 8.0 μ.

To a solution of 200 mg. of the bromohydrin (XVI) in 10 ml. of methanol at 15° under nitrogen was added 150 mg. of sodium hydroxide in 5 ml. of water. After 45 min. at 25° the mixture was neutralized with acetic acid and concentrated to remove the methanol. Water was added and the mixture extracted with ethyl acetate. Crystallization of the residue (120 mg.) from acetone-ether gave the 16β,17β-oxide (XVII) as prismatic needles, m.p. 188–192°; $[\alpha]_D^{CHCl_3}$ +83°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.75; H, 8.76.

Treatment of 50 mg. of the 16β,17β-oxide (XVII) with hydrogen bromide in acetic acid as described under the preparation of the bromohydrin (XIX) gave bromohydrin (XVI) with infrared spectrum the same as that of authentic material.

Reductive removal of bromine from bromohydrin (XVI). A solution of 400 mg. of the 17α,16β-bromohydrin (XVI) in 20 ml. of methanol was hydrogenated at atmospheric pressure and 25° over 400 mg. of 25% palladium on calcium carbonate. Hydrogen uptake ceased after 20 min. The catalyst was removed by filtration and the filtrate concentrated to dryness. Water was added and the mixture extracted with ethyl acetate. The residue after removal of ethyl acetate was dissolved in 8 ml. of methanol and 150 mg. of sodium hydroxide in 5 ml. of water was added to saponify the 3-acetate function. After 1 hr. at 25° the solution was neutralized with acetic acid, and the methanol removed by concentration under vacuum. Water was added and the mixture was extracted with ethyl acetate. The amorphous residue (215 mg.) was chromatographed on 15 g. of neutral alumina and the crystalline fractions from the 5% chloroform-benzene to 50% chloroform-benzene eluates combined to give 141 mg. of the 16β-hydroxy ketol (XV). Crystallization from ether-acetone gave material with m.p. 175–181°, undepressed with authentic material. The respective infrared spectra and paper chromatographic mobilities were also identical.

3α-Hydroxy-16α,17α-oxido-16β-acetyl-5β-androstane-11-one (XVIII). To a solution of 1.20 g. of 3α-acetoxy-16-acetyl-Δ^{16}-5β-androstene-11-one (IVa) in 75 ml. of methanol kept at 5° was added 4.8 ml. of 30% aqueous hydrogen peroxide followed by 2.4 ml. of 4*N* aqueous sodium hydroxide. After 18 hr. at 5°, most of the methanol was removed under vacuum, additional water added, and the precipitated oxide (XVIII) collected by filtration, washed with water, and dried in air. Crystallization from aqueous methanol gave material (650 mg.) with m.p. 187–193°; $[\alpha]_D^{CHCl_3}$ +46°; $\lambda_{max}^{CHCl_3}$ 2.90, 5.86, 5.90 μ.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.61; H, 9.01.

3α-Acetoxy-16α,17α-oxido-16β-acetyl-5β-androstane-11-one (XVIIIa). Acetylation of 600 mg. of XVIII in 2 ml. of acetic anhydride and 2 ml. of pyridine at 25° for 18 hr., and crystallization of the product from acetone-ether gave 555 mg. of the 3-acetate XVIIIa, m.p. 166–167°; $\lambda_{max}^{CHCl_3}$, 5.80, 5.90, 8.04 μ.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 71.10; H, 8.30. Found: C, 70.72; H, 8.18.

3α-Acetoxy-16β-acetyl-5β-androstane-11-one (XIa) *and 3α-hydroxy-16β-acetyl-5β-androstane-11-one* (*XI*) *from the 16α,17α-oxide* (XVIIIa). To a solution of 350 mg. of the 16α,17α-oxide (XVIIIa) in 14 ml. of acetic acid kept at 12° was added 1.5 ml. of 24% hydrogen bromide in acetic acid. After 30 min. at 12° the solution was concentrated to dryness under vacuum and flushed with benzene several times to give the bromohydrin *3α-acetoxy-16α-hydroxy-17β-bromo-16α-acetyl-5β-androstane-11-one* (XIX) as an amorphous solid; $\lambda_{max}^{CHCl_3}$ 2.90–3.00, 5.80, 5.85, 8.0 μ; negligible ultraviolet absorption in the 220–400 mμ region.

A solution of 370 mg. of the bromohydrin (XIX) in 20 ml. of methanol and 2 ml. of water was treated with hydrogen at atmospheric pressure over 400 mg. of 25% palladium on calcium carbonate catalyst. When hydrogen uptake ceased, the catalyst was removed by filtration and the filtrate concentrated to a small volume. Water was added and the mixture was extracted with ether. The ether extract (260 mg.), which gave a negative Beilstein test, was chromatographed on 8.0 g. of acid washed alumina. From the 50% petroleum ether–benzene to 100% benzene fractions (130 mg.) was obtained 3α-acetoxy-16β-acetyl-5β-androstane-11-one (XIa), m.p. 118–120° identical with an authentic sample by mixed melting and infrared spectra comparisons. The 100% chloroform eluates (78 mg.) on crystallization from acetone-hexane gave the corresponding 3α-ol (XI), m.p. 203–207° undepressed on admixture with an authentic sample. The respective infrared spectra were identical.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION, G. D. SEARLE & Co.]

The Configuration of 7-Hydroxy-Δ⁴-3-oxosteroids[1a]

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The configurations of 7-hydroxy-Δ⁴-3-oxosteroids have been correlated by comparison of the molecular rotations of the corresponding acetates with 7β-acetoxycholestenone and by the analysis of NMR spectra.

In recent years a number of 7-hydroxy-Δ⁴-3-oxosteroids have been reported in the literature.[2] The configurations of these compounds were assigned by various methods, the most popular of which was comparison of molecular rotatory differences. The values obtained were compared to those in the literature for saturated or Δ⁵ unsaturated 7-hydroxysteroids,[3] for which the molecular rotatory contribution [$\Delta M_D = M_D$ (7-OR)-M_D (7-H)] for a 7β-hydroxy group is positive while that for the 7α-group is negative. The data reported by McAleer *et al.*[2e] show, by contrast, that with a Δ⁴-3-ketone grouping in the molecule, both 7α- and 7β-hydroxyls cause negative shifts of about the same magnitude. Thus it appears to be impossible to assign configuration to a 7-hydroxy-Δ⁴-3-oxosteroid on the basis of its molecular rotation.

Some of the acetates of these hydroxy compounds have been reported and here the differences in rotation seemed to offer more chance for differentiating the 7α and 7β isomers. Consequently, when we isolated the isomeric 7-hydroxy-4-androstene-3,17-diones from fermentations, we took the opportunity to prepare their acetates and compare their properties with those reported for the acetate of 7β-hydroxycholestenone.[2a] This is the one 7β-hydroxy-Δ⁴-3-oxosteroid whose structure is unequivocal, as it was prepared from the well-characterized[4] compound, 7β-hydroxycholesterol.[5] This comparison, as seen in Table I, indicated that the

(1) (a) Presented before the 136th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 13–18, 1959, Abstracts, Page 85-P. (b) Present address: University of Minnesota, Minneapolis, Minn.

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