Synthetic Steroids. Part I. The Preparation of 3β,16α-Dihydroxyandrost-5-ene-11,17-dione and 3β,11β,16α-Trihydroxyandrost-5-en-17-one

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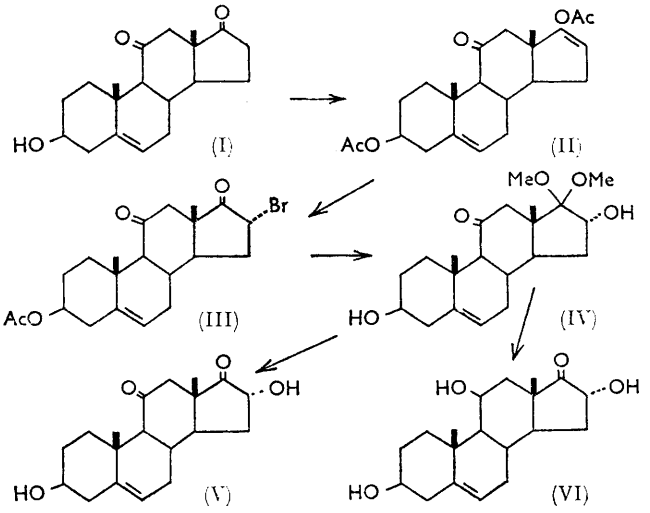
The preparation of 3β,16α-dihydroxyandrost-5-ene-11,17-dione (V) and 3β,11β,16α-trihydroxyandrost-5-en-17-one (VI) from 3β-hydroxyandrost-5-ene-11,17-dione (I) is described. A single absorption band of medium intensity in the region 800—820 cm.$^{-1}$ has been observed in the infrared spectra of four 3β-acetoxy-11-oxo-Δ^5-steroids.

WORK currently in progress [1] on the metabolism of C_{19} and C_{21} steroids in the foetus and new-born infant has required, for chromatographic and spectral standards, a range of 3β-hydroxy-Δ^5-steroids oxygenated at C-11, -16, and -17. In view of the general lack of availability



of these steroids and the importance which this type is currently assuming, we report the synthesis of 3β,16α-dihydroxyandrost-5-ene-11,17-dione (V) and 3β,11β,16α-trihydroxyandrost-5-en-17-one (II) from 3β-hydroxyandrost-5-ene-11,17-dione (I). These steroids are the 11-oxygenated counterparts of 3β,16α-dihydroxyandrost-5-en-17-one, which, together with 3β,16α-dihydroxypregn-5-en-20-one, forms the most abundant steroid isolated from the urine of new-born infants.[2] The method of Aoki *et al.*[3] for the introduction of a 16α-hydroxy-group into 3β-hydroxyandrost-5-en-17-one by way of 3β,17β-diacetoxy-5α,6β-dichloro-16α,17α-epoxyandrost-5-ene is not applicable to the preparation of compound (VI) since at no stage in this reaction sequence can the 11-ketone be conveniently reduced to the 11β-hydroxy-compound. The recently reported method [4] for the introduction of a 16α-hydroxy-group into the steroid nucleus provides a more convenient route to a higher yield of 3β,16α-dihydroxyandrost-5-en-17-one. This method proceeds *via* the intermediate 3β,16α-dihydroxy-17,17-dimethoxyandrost-5-ene. For 11-oxygenated steroids the 16α-hydroxy-17-acetal allows the ready reduction of the 11-carbonyl group.

3β-Hydroxyandrost-5-ene-11,17-dione (I) was treated with isopropenyl acetate and toluene-*p*-sulphonic acid to give 3β,17β-diacetoxyandrosta-5,16-dien-11-one (II) which on treatment with bromine by the method of Fajkos and Sorm,[5] gave 3β-acetoxy-16α-bromoandrost-5-ene-11,17-dione (III). This bromination procedure yields a purer bromo-ketone than does bromination of the enedione (I) followed by removal of the two bromine atoms which add at Δ^5. Treatment of the bromo-ketone (III) with sodium methoxide and methanol [4] resulted in 3β,16α-dihydroxy-17,17-dimethoxyandrost-5-en-11-one (IV), from which the protecting group at C-17 can be removed by hydrolysis with toluene-*p*-sulphonic acid in aqueous acetone to give 3β,16α-dihydroxyandrost-5-ene-11,17-dione (V) [17% yield from (I)].

Reduction of the acetal (IV) with lithium aluminium hydride in ether followed by acid hydrolysis gave 3β,11β,16α-trihydroxyandrost-5-en-17-one (VI) [7% yield from (I)].

The infrared spectra of 3β-hydroxy-Δ^5-steroids have previously been reported both by Hirschmann [6] and Jones and Herling [7] to contain two absorption bands between 800 and 807 cm.$^{-1}$ of varying relative intensity, due to the out-of-plane deformation of the C-6 hydrogen. Similar bands near 800 and 812 cm.$^{-1}$ are also present in the spectra of the corresponding 3β-acetoxy-Δ^5-steroids. We have observed that the introduction of the 11β-hydroxy-group into the steroid nucleus does not fundamentally alter those absorption bands due to the 6-hydrogen in the 800—820 cm.$^{-1}$ region; nor does the introduction of 11-carbonyl group when associated with a 3β-hydroxy-group. However, when the 11-ketone is present together with a Δ^5-3β-acetate, only one medium intensity band is observed in the 800—820 cm.$^{-1}$ region. This single absorption band is observed both for spectra taken in carbon disulphide and Nujol (see Table).

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. Rotations were determined in chloroform at

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[3] T. Aoki, H. Yamamura, K. Takei, and H. Mori, *Chem. Pharm. Bull.*, 1964, **12**, 808.
[4] A. Hassner and P. Catsoulacos, *J. Org. Chem.*, 1966, **31**, 3149.
[5] J. Fajkos and F. Sorm, *Coll. Czech. Chem. Comm.*, 1959, **24**, 766.
[6] H. Hirschmann, *J. Amer. Chem. Soc.*, 1952, **74**, 5357.
[7] R. N. Jones and F. Herling, *J. Amer. Chem. Soc.*, 1956, **78**, 1152.

20° with a Bendix-Ericcson automatic polarimeter. Ultraviolet spectra were determined in ethanol solutions using a Perkin-Elmer model 137 spectrometer, and infrared spectra were recorded in carbon disulphide solutions with a Perkin-Elmer 237 or Unicam SP 200 spectrometer. Proton magnetic resonance spectra were recorded for deuteriochloroform or pyridine solutions using a Perkin-Elmer 60 Mc./sec. spectrometer, and were calibrated using tetramethylsilane as an internal standard. Alumina refers to Spence grade H, activity II. All solvents were evaporated using a Büchi rotary evaporator. Gas-liquid chromatography was carried out on a Perkin-Elmer model 801 instrument using 6 ft. × $\frac{1}{16}$ in. internal diameter glass columns packed with E 301 on 'Chromosorb G.' The purity of all intermediates was checked by examination on 'unbaked' silica chromoplates.

Infrared spectra

Steroid	Absorption ($cm.^{-1}$) In Nujol	In CS_2
3β,11β,17β-Trihydroxyandrost-5-ene ...	814, 800	
3β,11β-Dihydroxyandrost-5-en-17-one ...	808, 792	
3β,11β,16α-Trihydroxyandrost-5-en-17-one ...	812, 800	
3β,16α-Dihydroxyandrost-5-ene-11,17-dione ...	812, 800	
3β,17β-Diacetoxy-11β-hydroxyandrost-5-ene ...		798, 814
3β-Acetoxy-11β,17β-dihydroxyandrost-5-ene ...		800, 816
3β-Acetoxyandrost-5-ene-11,17-dione ...	817	819
3β,17-Diacetoxyandrost-5,16-dien-11-one	820(i), 811	820
3β-Acetoxy-16α-bromoandrost-5-ene-11,17-dione ...	818	817
3β,17β-Diacetoxyandrost-5-en-11-one ...	817	811

3β,17-*Diacetoxyandrosta*-5,16-*dien*-11-*one* (II).—3β-Hydroxyandrost-5-ene-11,17-dione (2·5 g.) and toluene-*p*-sulphonic acid (200 mg.) were dissolved in isopropenyl acetate (30 ml.). The solution was heated under reflux through a short fractionating column so that the vapours were on the point of distilling over into a receiving condenser. With this arrangement any acetone formed was removed from the reaction flask. The constant slow distillation was continued for 8 hr. The volume in the reaction flask was kept constant by the addition of fresh isopropenyl acetate (total of 30 ml. during 8 hr.). When the reaction was complete the solution was evaporated to 15 ml. and poured into aqueous sodium carbonate; the steroid was extracted into ether. The ethereal solution was washed with further aqueous sodium carbonate and with saturated salt solution. The ethereal solution was dried ($MgSO_4$) and evaporated to dryness. The residue was recrystallised from ether–petroleum to give 3β,17-*diacetoxyandrosta*-5,16-*dien*-11-*one* (2·25 g.), m. p. 155—161°, $[\alpha]_D$ −13° (*c* 0·1); $\bar{\nu}_{max.}$ 1757, 1734, 1706, 1245, 1204, and 820 $cm.^{-1}$; ^1H n.m.r. ($CDCl_3$) τ 9·13 (C-18 methyl), 8·78 (C-19 methyl), 7·98 (acetate), 7·85 (enol acetate), 4·57 multiplet (6-H), and 4·42 multiplet (16-H). An analytical sample was recrystallised from hexane, m. p. 159—161° (Found: C, 71·2; H, 7·5. $C_{23}H_{30}O_5$ requires C, 71·5; H, 7·8%).

3β-*Acetoxy*-16α-*bromoandrost*-5-*ene*-11,17-*dione* (III).—3β,17-Diacetoxyandrosta-5,16-dien-11-one (II) (2·5 g.) was dissolved in dry carbon tetrachloride (100 ml.) and the solution was cooled to −10°. The solution was stirred while a solution of bromine (1·06 g., 1·02 mol.) in carbon tetrachloride (13 ml.) was added during 2 min. The solution was stirred for a further 2 min. and then an aqueous solution of sodium hydrogen sulphite was added. The steroid was extracted into chloroform (100 ml.) and the chloroform solution was washed with sodium carbonate and saturated salt solution. The solution was dried ($MgSO_4$) and evaporated to dryness. The residue was recrystallised from ethanol to give 3β-*acetoxy*-16α-*bromoandrost*-5-*ene*-11,17-*dione* (2·1 g.), m. p. 182—185°; $[\alpha]_D$ +37°, (*c* 0·1); $\bar{\nu}_{max.}$ 1760, 1738, 1714, 1671, 1241, and 817 $cm.^{-1}$; ^1H n.m.r. ($CDCl_3$) τ 9·10 (C-18 methyl), 8·77 (C-19 methyl), 7·97 (acetate), 4·55 multiplet (6-H), and 5·37 multiplet (16β-H). An analytical sample was recrystallised from ethanol, m. p. 183—185° (Found: C, 60·1; H, 6·0; Br, 18·5. $C_{21}H_{27}BrO_4$ requires C, 59·7; H, 6·4; Br, 18·9%).

3β,16α-*Dihydroxy*-17,17-*dimethoxyandrost*-5-*en*-11-*one* (IV).—3β-Acetoxy-16α-bromoandrost-5-ene-11,17-dione (1·9 g.) in hot methanol (80 ml.) was added to a hot solution of sodium methoxide [methanol (50 ml.) and sodium (2 g.)]. The solution was heated under reflux for 1 hr. and then poured into cold water (300 ml.). The steroid was extracted with ether and the ethereal solution was washed successively with dilute hydrochloric acid, sodium carbonate solution, and saturated salt solution. The ethereal solution was dried ($MgSO_4$) and evaporated to dryness. The residue was recrystallised from ether to give 3β,16α-*dihydroxy*-17,17-*dimethoxyandrost*-5-*en*-11-*one* (0·6 g.) m. p. 168—174°; $[\alpha]_D$ −68° (*c* 0·1); $\bar{\nu}_{max.}$ ($CDCl_3$) 1704, 1170, 1112, and 1055 $cm.^{-1}$; ^1H n.m.r. ($CDCl_3$) τ 9·26 (C-18 methyl), 8·81 (C-19 methyl), 6·65, 6·59 (methoxy-protons), and 4·66 multiplet (6-H). An analytical sample was recrystallised from ether, m. p. 172—176° (Found: C, 68·7; H, 9·1. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·9%). Chromatography of the mother-liquors on alumina gave crystalline material which was recrystallised from ether to give 3β-hydroxyandrost-5-ene-11,17-dione (I) (45 mg.), identified by i.r. and ^1H n.m.r. spectroscopy and an undepressed mixed m. p.

3β,16α-*Dihydroxyandrost*-5-*ene*-11,17-*dione* (V).—3β,16α-Dihydroxy-17,17-dimethoxyandrost-5-en-11-one (IV) (240 mg.) was dissolved in acetone (50 ml.) and a solution of toluene-*p*-sulphonic acid (200 mg.) in water (5 ml.) was added. The solution was kept at 40° for 12 hr. and then water (10 ml.) was added and the solution evaporated under reduced pressure to half its volume. The steroid was extracted with chloroform and the extract was washed with aqueous sodium carbonate and saturated salt solution, dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallised from acetone–petroleum to give 3β,16α-*dihydroxyandrost*-5-*ene*-11,17-*dione* (170 mg.), m. p. 204—210°. A further recrystallisation from aqueous acetone gave material, m. p. 209—212°, $[\alpha]_D$ +81° (*c* 0·1), $\bar{\nu}_{max.}$ (Nujol) 1755 and 1690 $cm.^{-1}$; ^1H n.m.r. (pyridine) τ 9·12 (C-18 methyl), 8·66 (C-19 methyl), 5·30 multiplet (16β-H), and 4·63 multiplet (6-H). An analytical sample was recrystallised from aqueous acetone, m. p. 209—212° (Found: C, 70·2; H, 8·3. $C_{19}H_{26}O_4,C_3H_6O$ requires C, 70·2; H, 8·6%).

3β,11β,16α-*Trihydroxyandrost*-5-*en*-17-*one* (VI).—3β,16α-Dihydroxy-17,17-dimethoxyandrost-5-en-11-one (IV) (320 mg.) was dissolved in ether (100 ml.), lithium aluminium hydride (500 mg.) was added, and the solution was heated under reflux for 2 hr. The excess of lithium aluminium hydride was decomposed with ethyl acetate and then dilute hydrochloric acid was added. The acidified material was set aside for 2 hr. Fresh ether (300 ml.) was added and the ethereal solution was washed with sodium carbonate solution followed by saturated salt

solution. The solution was dried ($MgSO_4$) and evaporated to dryness. The residue was recrystallised from acetone–petroleum and again from aqueous acetone to give 3β,11β,16α-*trihydroxyandrost-5-en-17-one* (VI) (100 mg.), m. p. 209—210°; $[\alpha]_D$ +8° (*c* 0·1), $\bar{\nu}_{max.}$ (Nujol) 1745 $cm.^{-1}$; ^1H n.m.r. (pyridine) τ 8·56 (C-18 methyl), 8·38 (C-19 methyl), 6·05 broad multiplet (3α-H), 5·31 multiplet (16β-H), 4·66 multiplet (6-H), and 4·5 doublet (11α-H). An analytical sample was recrystallised from aqueous methanol, m. p. 209—212° (Found: C, 68·1; H, 9·1. $C_{19}H_{28}O_4,CH_4O$ requires C, 68·15; H, 9·15%).

We thank the M.R.C. for a grant (to R. W. K.).

[7/533 *Received, May 2nd,* 1967]