399. *Modified Steroid Hormones. Part XXI.** 17β-*Hydroxy*-11-*methylene and* -11β-*methyl*-5α-*androstan*-3-*one.*

By D. N. Kirk and V. Petrow.

The 11-oxo-group in certain 5α-steroids is found to react with methyl- and ethyl-magnesium halides, giving 11β-hydroxy-11α-alkyl derivatives.

11-Oxotigogenin acetate has been converted into 11β-hydroxy-11α-methyltigogenin acetate and thence by dehydration with thionyl chloride–pyridine or with formic acid into 9,11-dehydro-11-methyl- or 11-methylene-tigogenin acetate. The last compound has been transformed by standard methods into 17β-hydroxy-11-methylene- and -11β-methyl-androstan-3-one.

Some years ago we observed the ready reaction of certain 11-oxo-steroids with methylmagnesium halide to give the corresponding 11-hydroxy-11-methyl derivatives. Extension of these observations was not feasible at the time, but has since become possible. In the meantime other laboratories have reported the smooth reaction of 11-oxo-steroids with methyl-lithium [1] and have commented on the unsatisfactory nature of the corresponding condensation employing the Grignard reagent.

Our initial experiments were directed to the reaction of methylmagnesium halide with such compounds as 3,3:17,17-bisethylenedioxyandrost-5-en-11-one, but no appreciable reaction could be observed. No better results attended the use of 5β-pregnan-11-one derivatives. We finally turned to 11-oxotigogenin acetate,[2] which was of interest at the time as a potential raw material for cortisone production. Treatment of this compound

* Part XX, *J.*, 1960, 4664.

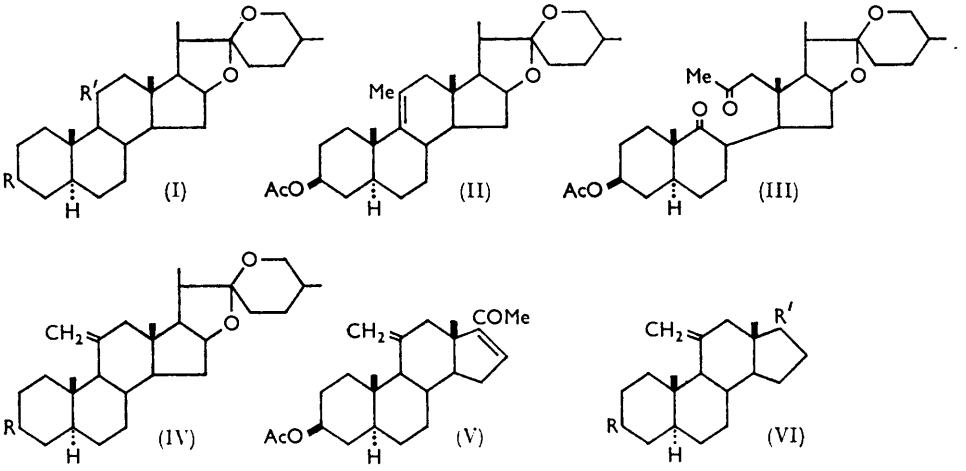
[1] Ringold, Batres, and Zderic, *Tetrahedron*, 1958, **2**, 164; Fonken and Hogg, *ibid.*, p. 365; Fonken, Hogg, and McIntosh, *J. Org. Chem.*, 1959, **24**, 1600; Beyler, Hoffman, and Sarett, *J. Amer. Chem. Soc.*, 1960, **82**, 178; Zderic, Batres, Limón, Cartio, Lisci, Monroy, Necoechea, and Ringold, *ibid.*, p. 3404; Elks, *J.*, 1960, 3333 (published after submission of the present manuscript).

[2] Cornforth, Osbond, and Phillipps, *J.*, 1954, 907; Schmidlin and Wettstein, *Helv. Chim. Acta* 1953, **36**, 1241.

(I; R = –OAc, ··H; R′ = O) with the methyl-Grignard reagent in refluxing ether–benzene gave 11α-methyl-5α,25D-spirostan-3β,11β-diol (I; R = –OH, ··H; R′ = –OH, ··Me) in excellent yield. The last compound was converted into a diol monoacetate and passed into a hydroxy-ketone on oxidation with chromic acid. The hydroxy-ketone was separately obtained from 11-oxotigogenone [3] (I; R = R′ = O) by conversion into the 3,3-dimethoxy-derivative, reaction with methylmagnesium iodide, and regeneration of the 3-oxo-group. It is accordingly formulated as 11β-hydroxy-11α-methyltigogenone (I; R = O; R′ = –OH, ··Me).

Dehydration of 3β-acetoxy-11α-methyl-5α,25D-spirostan-11β-ol with thionyl chloride–pyridine furnished 3β-acetoxy-11-methyl-5α,25D-spirost-9(11)-ene (II), which was converted by osmic acid into 3β-acetoxy-11β-methyl-5α,25D-spirostan-9α,11α-diol. This diol was unaffected by acetic anhydride–pyridine, but was smoothly cleaved by periodic acid to a diketone assigned the constitution of 3β-acetoxy-11-methyl-9,11-seco-5α,25D-spirostan-9,11-dione (III). The infrared spectrum of the last compound showed a shoulder at 1348 cm.$^{-1}$; this is tentatively assigned to the methyl ketone moiety [4] as it was no longer present in the spectrum of the reduction product of the 9,11-dione (III) with sodium borohydride.

Dehydration of 3β-acetoxy-11α-methyl-5α,25D-spirostan-11β-ol with formic acid at 25—50° gave 11-methylenetigogenin acetate (IV; R = –OAc, ··H) which crystallised directly from the solution in excellent yield. On hydroxylation with osmic acid this product (IV) gave 11ξ-hydroxy-11ξ-hydroxymethyl derivative (one acetylatable hydroxyl



group) which was cleaved to 11-oxotigogenin acetate by periodic acid. The 11-methylene derivative (IV; R = –OAc, ··H) was also prepared by dehydration of the 11β-hydroxy-11α-methyl derivative (I; R = –OAc, ··H, R′ = –OH, ··Me) with acetic anhydride–acetic acid–toluene-*p*-sulphonic acid or by direct isomerisation of the 9(11)-ene (II) with formic acid at room temperature.

On catalytic hydrogenation 11-methylenetigogenin acetate (IV; R = –OAc, ··H) absorbed 1 mol. of hydrogen. The product no longer showed the infrared absorption band at 1636 cm.$^{-1}$ characteristic of the exocyclic methylene group and is regarded as 11β-methyltigogenin acetate.

Reaction of 11-oxotigogenin acetate with ethylmagnesium iodide gave the corresponding 11α-ethyl-11β-hydroxy-derivative. Dehydration with thionyl chloride–pyridine or with formic acid then led to the formation of the same product, tentatively regarded as

[3] Djerassi, Ringold, and Rosenkranz, *J. Amer. Chem. Soc.*, 1951, **73**, 5513.
[4] Jones and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 5648; Jones, Cole, and Nolin, *ibid.*, p. 5662.

11-ethylidenetigogenin (acetate) on the basis of physical data (see p. 2095). 3β,20β-Diacetoxy-5α-pregnan-11-one [5] was similarly converted into 11α-methyl-5α-pregnane-3β,11β,20β-triol and thence, by way of the diacetate, into both the 11-methyl-9(11)-ene and the 11-methylene derivative.

Degradation of the side chain of 11-methylenetigogenin acetate with acetic anhydride, pyridine, and methylamine hydrochloride [6] furnished 3β,26-diacetoxy-11-methylene-5α-furost-20(22)-ene, which was converted by oxidation with hydrogen peroxide, followed by refluxing with acetic acid, into 3β-acetoxy-11-methylene-5α-pregn-16-en-20-one (V). The constitution of this product was established by catalytic hydrogenation to 3β-acetoxy-11-methylene-5α-pregnan-20-one, followed by reduction of the carbonyl group with sodium borohydride and acetylation, which afforded 3β,20β-diacetoxy-11-methylene-5α-pregnane identical with material prepared *via* the Grignard reaction on 3β,20β-diacetoxy-5α-pregnan-11-one (above).

3β-Acetoxy-11-methylene-5α-pregn-16-en-20-one (V) was converted by Beckmann rearrangement of its oxime into 3β-acetoxy-11-methylene-5α-androstan-17-one (VI; R = –OAc, ··H; R′ = O), and thence into the 3,17-dione (VI; R = R′ = O). Selective protection of the 3-oxo-group in the last compound by conversion into the 3,3-dimethoxy-derivative, followed by reduction of the 17-oxo-group and regeneration of the carbonyl function at $C_{(3)}$, furnished 17β-hydroxy-11-methyleneandrostan-3-one (VI; R = O; R′ = –OH, ··H), which was required for study as an anabolic agent. Catalytic hydrogenation of the propionate of the last compound followed by oxidation of the newly formed 3-hydroxyl group, gave the corresponding 17β-hydroxy-11β-methylandrostan-3-one (as propionate).

Experimental

Rotations were measured in a 1 dm. tube for chloroform solutions. Ultraviolet absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc., and Miss D. F. Dobson, B.Sc.

11α-Methyl-5α,25D-spirostan-3β,11β-diol (I; R = –OH, ··H; R′ = –OH, ··Me).—11-Oxotigogenin acetate (I; R = –OAc, ··H; R′ = O) (100 g.) in benzene (2 l.) was added to a solution of methylmagnesium iodide prepared from magnesium (100 g.), methyl iodide (260 ml.), and ether (2 l.). The mixture was heated under reflux for 3 hr., cooled, and poured into ammonium chloride solution containing ice. The organic layer was separated and washed, and the solvents were removed under reduced pressure. A portion of the residual gum, purified from acetone–hexane, gave 11α-methyl-5α,25D-spirostan-3β,11β-diol in prisms, m. p. 209—212°, $[\alpha]_D^{23}$ –58° (*c* 0·93) (Found: C, 75·5; H, 10·2. Calc. for $C_{28}H_{46}O_4$: C, 75·3; H, 10·4%).

The main part of the product above was treated on the steam-bath with pyridine (300 ml.) and acetic anhydride (200 ml.) for ½ hr., then poured into water. The precipitated solids were collected after 2 hr., dried, and purified from acetone, followed by ethyl acetate, to give 3β-acetoxy-11α-methyl-5α,25D-spirostan-11β-ol in prisms, m. p. 193—195°, $[\alpha]_D^{23}$ –63° (*c* 0·88) (Found: C, 73·4; H, 10·0. Calc. for $C_{30}H_{48}O_5$: C, 73·7; H, 9·9%).

Similar procedures employing ethylmagnesium iodide led to *11α-ethyl-5α,25D-spirostan-3β,11β-diol*, prisms (from methanol), m. p. 215—218°, $[\alpha]_D^{24}$ –34° (*c* 0·79) (Found: C, 75·7; H, 10·0. $C_{29}H_{48}O_4$ requires C, 75·6; H, 10·5%), and its *3-acetate*, needles (from methylene chloride–methanol), m. p. 177—179°, $[\alpha]_D^{25}$ –39·5 (*c* 0·87) (Found: C, 74·0; H, 9·8. $C_{31}H_{50}O_5$ requires C, 74·05; H, 10·0%).

11β-Hydroxy-11α-methyl-5α,25D-spirostan-3-one (I; R = O; R′ = –OH, ··Me).—(*a*) 11α-Methyl-5α,25D-spirostan-3β,11β-diol (4 g.) in anhydrous pyridine (40 ml.) was treated with the complex prepared from chromium trioxide (4 g.) in pyridine (40 ml.).[8] After 5 hours' stirring the mixture was left overnight, then diluted with benzene and filtered. The filtrate was washed, dried (Na_2SO_4), decolorised (charcoal), and evaporated. Purification from ethanol gave *11β-hydroxy-11α-methyl-5α,25D-spirostan-3-one* in blades, m. p. 210—213°, $[\alpha]_D^{27}$ –52°

[5] Callow and James, *J.*, 1956, 4744.
[6] B.P. 749,697/1956.
[7] Rosenkranz, Mancera, Sondheimer, and Djerassi, *J. Org. Chem.*, 1956, **21**, 520.
[8] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.

(*c* 0·41), $\nu_{max.}$ (in CS_2) 1718 cm.$^{-1}$ (3-ketone) (Found: C, 75·4; H, 9·3. $C_{28}H_{44}O_4$ requires C, 75·6; H, 10·0%).

(*b*) 5α,25D-Spirostan-3,11-dione (I; R = R′ = O) (20 g.) and oxalic acid (1 g.) in anhydrous methanol (800 ml.) were heated under reflux for 2 hr., then cooled, and the crystalline product was purified from methanol–methylene chloride containing a drop of pyridine. The resulting *3,3-dimethoxy-5α,25D-spirostan-11-one* formed prisms, m. p. 192—195° (with evolution of gas), $[\alpha]_D^{22}$ −23° (*c* 1·30), $\nu_{max.}$ (in CCl_4) 1709 cm.$^{-1}$, (in CS_2) 1182, 1103 cm.$^{-1}$ (3,3-dimethoxy) (Found: C, 73·1; H, 9·6. $C_{29}H_{46}O_5$ requires C, 73·4; H, 9·8%).

The ketal was submitted to the Grignard reaction with methylmagnesium iodide. The infrared spectrum of the crude product showed almost complete loss of the 11-carbonyl band, and of the dimethoxy-system, which had apparently been converted into a 2-methoxy-Δ^2-system (bands at 1690 and 1172 cm.$^{-1}$). The total product was dissolved in warm acetic acid (250 ml.), diluted with water (25 ml.), and after ½ hr. poured into water. The precipitated solids were purified from ethanol, to give 11β-hydroxy-11α-methyl-5α,25D-spirostan-3-one identical with the sample prepared as under (*a*).

3β-Acetoxy-11-methyl-5α,25D-spirost-9(11)-ene (II).—3β-Acetoxy-11α-methyl-5α,25D-spirostan-11β-ol (10 g.) in anhydrous pyridine (100 ml.) at −20° was treated with thionyl chloride (5 ml.) and the mixture allowed to warm to room temperature during ½ hr. Precipitation into water gave a light brown solid which was dried at 30—40°, dissolved in boiling hexane, and decolorised with charcoal. The solution was concentrated, and on cooling gave 3β-acetoxy-11-methyl-5α,25D-spirost-9(11)-ene. Purification from hexane or from methanol gave material of variable m. p., between 110° and 126°, but careful chromatography on alumina gave no evidence of heterogeneity. The product formed needles, $[\alpha]_D^{25}$ −13° (*c* 0·84), $\nu_{max.}$ (in CS_2) 1735 cm.$^{-1}$ (OAc) (Found: C, 76·3; H, 9·7. Calc. for $C_{30}H_{46}O_4$: C, 76·55; H, 9·85%).

Saponification of the foregoing 3-acetate (1 g.) with potassium hydroxide (0·5 g.) in 80% methanol (100 ml.) gave the *3β-hydroxy-compound*, which separated from methanol in solvated plates, m. p. 120—130°, transformed by drying at 105° *in vacuo* into an amorphous powder, m. p. 191—194°, $[\alpha]_D^{23}$ −18° (*c* 0·57) (Found: C, 78·2; H, 10·1. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%).

Hydroxylation of the 9(11)-ene (II) *with Osmic Acid.*—3β-Acetoxy-11-methyl-5α,25D-spirost-9(11)-ene (4·1 g.) in pyridine (160 ml.) was treated with osmic acid for 5 days. The solution was saturated with hydrogen sulphide, diluted with benzene, and filtered. The filtrate was washed with dilute acid and water, dried (Na_2SO_4), and evaporated. The solid residue, purified from acetone followed by ethyl acetate, gave *3β-acetoxy-11β-methyl-5α,25D-spirostan-9α,11α-diol* in needles, m. p. 231—233°, $[\alpha]_D^{20}$ −58° (*c* 0·62), $\nu_{max.}$ (in CS_2) 3595, 3535 (*cis*-diol), and 1738 cm.$^{-1}$ (OAc) (Found: C, 70·9; H, 9·8. $C_{30}H_{48}O_6$ requires C, 71·4; H, 9·6%).

Cleavage of the 9α,11α-Diol with Periodic Acid.—The foregoing 9α,11α-diol (2·3 g.) in dioxan (150 ml.) was treated with periodic acid (2·5 g.) in water (25 ml.) for 3 days at room temperature. The solution was poured into water, and the solid product purified from aqueous methanol to give *3β-acetoxy-11-methyl-9,11-seco-5α,25D-spirostan-9,11-dione* (III) in prisms, m. p. 104—106°, $[\alpha]_D^{22}$ −100° (*c* 0·43), $\nu_{max.}$ (in CCl_4) 1734 (OAc), 1719, 1705 (ketones), 1431 (·CO·CH_2·), and 1348 cm.$^{-1}$ (−COMe) [Found: (after drying at 90° *in vacuo*): C, 71·5; H, 9·0. $C_{30}H_{46}O_6$ requires C, 71·7; H, 9·2%]. This gave a *mono-oxime*, m. p. 179—183° (needles from aqueous methanol) (Found: C, 69·6; H, 9·15; N, 2·9. $C_{30}H_{47}NO_6$ requires C, 69·6; H, 9·15; N, 2·7%).

Saponification of a sample of this material in methanolic hydrochloric acid (0·5%) for 24 hr. gave an amorphous product, $\nu_{max.}$ (in CCl_4) 3613 (OH), 1720, 1707 (ketones), 1431 (CO·CH_2), and 1347·5 cm.$^{-1}$ (−COMe).

Reduction of the 9,11-Diketone.—The 9,11-dione (30 mg.) in methanol (6 ml.) was treated with sodium borohydride (50 mg.) and sodium hydroxide (50 mg.) in water (1 ml.) for 6 hr. at room temperature. The solution was diluted with water, and the product extracted with ether. The resulting amorphous 3β,9ξ,11ξ-triol showed no infrared absorption bands near 1348 cm.$^{-1}$.

3β-Acetoxy-11-methylene-5α,25D-spirostan (IV; R = −OAc, ··H).—(*a*) 3β-Acetoxy-11α-methyl-5α,25D-spirostan-11β-ol (20 g.) was dissolved in 98—100% formic acid (400 ml.) at 40°. On cooling, a crystalline product separated, which was collected after 3 hr., washed with methanol, and purified from ethanol, to give 3β-acetoxy-11-methylene-5α,25D-spirostan in needles, m. p. 186—188°, $[\alpha]_D^{21}$ −60° (*c* 0·52), $\nu_{max.}$ (in CCl_4) 3100 (:CH_2), 1737 (OAc), and 1636 cm.$^{-1}$ (:CH_2) [9] (Found: C, 76·6; H, 10·0. Calc. for $C_{30}H_{46}O_4$: C, 76·55; H, 9·85%).

[9] Cf. Sondheimer and Mechoulam, *J. Amer. Chem. Soc.*, 1957, **79**, 5029.

(*b*) 3β-Acetoxy-11-methyl-5α,25D-spirost-9(11)-ene (250 mg.) was stirred with formic acid (10 ml.) for 5 hr., then poured into water. Purification from ethanol gave 3β-acetoxy-11-methylene-5α,25D-spirostan, m. p. 185—187°, not depressed in admixture with the sample prepared as under (*a*).

(*c*) 3β-Acetoxy-11α-methyl-5α,25D-spirostan-11β-ol (0·55 g.) in acetic acid (25 ml.) and acetic anhydride (10 ml.) containing toluene-*p*-sulphonic acid (50 mg.) was left overnight at room temperature. The product was again the 11-methylene compound.

Saponification of the foregoing 3-acetoxy-11-methylene compound (0·6 g.) with potassium hydroxide (400 mg.) in 90% methanol (80 ml.) gave 11-*methylenetigogenin* (IV; R = ⁻OH, ··H), fibrous crystals (from methanol), m. p. 204—207°, $[\alpha]_D^{24}$ −54° (*c* 0·28), $\nu_{max.}$ (in CCl_4) 3610 (OH), 1644 cm.$^{-1}$ (:CH_2) (Found: C, 78·2; H, 10·2. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%).

Dehydration of the 11α-ethyl-11β-hydroxy-compound (I; R = ⁻OAc, ··H; R′ = ⁻OH, ··Et) by any of the above procedures gave what is believed to be 3β-*acetoxy*-11-*ethylidene*-5α,25D-*spirostan* which separated from ethanol in needles, m. p. 193—195°, $[\alpha]_D^{19}$ −53° (*c* 0·53), $\nu_{max.}$ (in CCl_4) 1739 cm.$^{-1}$ (Found: C, 76·5; H, 9·7. $C_{31}H_{48}O_4$ requires C, 76·8; H, 10·0%).

11-*Methylene*-5α,25D-*spirostan*-3-*one* (IV; R = O).—The foregoing 3β-hydroxy-compound (5 g.) in acetone (150 ml.) was treated dropwise with the chromic acid reagent [chromium trioxide (240 g.), sulphuric acid (230 ml.), water to 1 l.] until the presence of excess of oxidant was indicated by the colour of the mixture. The solution was diluted with water to 1 l., and the precipitated solid purified from acetone to give 11-*methylene*-5α,25D-*spirostan*-3-*one* in blades, m. p. 208—212°, $[\alpha]_D^{23}$ −42° (*c* 0·46), $\nu_{max.}$ (in CCl_4) 3105, 1636 (:CH_2), and 1717 cm.$^{-1}$ (C=O) (Found: C, 78·8; H, 9·7. $C_{28}H_{42}O_3$ requires C, 78·8; H, 9·9%).

An attempt to crystallise the 3-ketone from methanol converted it into the 3,3-*dimethoxy-derivative*, m. p. 188—190°, $[\alpha]_D^{23}$ −58° (*c* 0·29), $\nu_{max.}$ (in CCl_4) 3107, 1635 (:CH_2) (no carbonyl absorption) (Found: C, 76·4; H, 9·95. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·2%).

Hydroxylation of 3β-*Acetoxy*-11-*methylene*-5α,25D-*spirostan* (IV; R = ⁻OAc, ··H).—A solution of the 11-methylene compound (4 g.) and osmic acid (2·4 g.) in pyridine (100 ml.) was kept at room temperature for 12 days, then saturated with hydrogen sulphide, diluted with benzene, and filtered. The filtrate was washed with dilute hydrochloric acid and water, and the solvent was removed. The resulting yellow-green solid was decolorised by passage in ether solution through a column of alumina (10 g.) and crystallised from acetone, to give 3β-acetoxy-11-hydroxymethyl-5α,25D-spirostan-11-ol in flakes, m. p. 238—239°, $[\alpha]_D$ −61° (*c* 0·37). Satisfactory analytical results could not be obtained, as the product appeared to be tenaciously solvated [Found: (after drying at 60° *in vacuo*) C, 68·0; H, 9·7; (after drying at 120° *in vacuo*) C, 69·7; H, 9·5. $C_{30}H_{48}O_6$ requires C, 71·4; H, 9·6. $C_{30}H_{48}O_6,H_2O$ requires C, 68·9; H, 9·6%].

Acetylation with acetic anhydride and pyridine (1 : 1) for ½ hr. on the steam-bath gave the 11-*acetoxymethyl*-11-*hydroxy-derivative* which separated from methanol in needles, m. p. 162—163°, $[\alpha]_D^{20}$ −65° (*c* 0·63), $\nu_{max.}$ (in CS_2) 3569, 3490 (associated OH), and 1729 cm.$^{-1}$ (associated OAc) (Found: C, 70·0; H, 8·9. $C_{32}H_{50}O_7$ requires C, 70·3; H, 9·2%).

Cleavage of the 11-hydroxy-11-hydroxymethyl derivative by periodic acid as described for the 9α,11α-diol (above) gave 11-oxotigogenin acetate, identified by mixed m. p. and infrared comparison with an authentic sample.

3β-*Acetoxy*-11β-*methyl*-5α,25D-*spirostan*.—The 11-methylene compound (IV; R = ⁻OAc, ··H) (1 g.) in acetic acid (50 ml.) was hydrogenated over Adams platinum catalyst (100 mg.). After filtration the solvent was evaporated under reduced pressure. Purification of the residue from ethanol gave 3β-acetoxy-11β-methyl-5α,25D-spirostan as needles, m. p. 199—200°, $[\alpha]_D^{21}$ −63° (*c* 1·00), $\nu_{max.}$ (in CCl_4) 1735 cm.$^{-1}$ (Found: C, 75·9; H, 10·2. Calc. for $C_{30}H_{48}O_4$: C, 76·2; H, 10·2%).

11α-*Methyl*-5α-*pregnane*-3β,11β,20β-*triol*.—3β,20β-Diacetoxy-5α-pregnan-11-one (1·8 g.) in benzene (30 ml.) was added to the Grignard reagent prepared from magnesium (2 g.) and methyl iodide (5·5 ml.) in ether (50 ml.). The mixture was heated under reflux for 3 hr., cooled, and poured into aqueous ammonium chloride. The product was extracted with chloroform and purified from aqueous methanol, to give 11α-*methyl*-5α-*pregnane*-3β,11β,20β-*triol* as a powder, m. p. 197—199°, $[\alpha]_D^{23}$ +20° (*c* 0·49) (Found: C, 75·6; H, 10·8. $C_{22}H_{38}O_3$ requires C, 75·4; H, 10·9%).

The 3,20-*diacetate*, prepared by heating the foregoing triol (1 g.) with acetic anhydride (2 ml.) and pyridine (4 ml.) for 4 hr. on the steam-bath, separated from aqueous methanol in

prisms, m. p. 224—227°, $[\alpha]_D^{23}$ +16° (*c* 0·38) (Found: C, 72·2; H, 9·6. $C_{26}H_{42}O_5$ requires C, 71·85; H, 9·7%).

11β-*Hydroxy*-11α-*methyl*-5α-*pregnane*-3,20-*dione*.—The foregoing 3β,11β,20β-triol (1·4 g.) in anhydrous pyridine (16 ml.) was oxidised with the complex prepared from chromium trioxide (2 g.) in pyridine (20 ml.) for 2 days at room temperature. The mixture was diluted with ethyl acetate and filtered, and the filtrate washed with water, dilute sulphuric acid, and water until neutral. After removal of the solvent the residue was purified from acetone–hexane to give 11β-*hydroxy*-11α-*methyl*-5α-*pregnane*-3,20-*dione* in prisms, m. p. 224—226°, $[\alpha]_D^{22}$ +96° (*c* 0·35), $\nu_{max.}$ (in $CHCl_3$) 3603 (OH), and 1702 cm.$^{-1}$ (ketones) (Found: C, 76·3; H, 10·1. $C_{22}H_{34}O_3$ requires C, 76·3; H, 9·9%).

3β,20β-*Diacetoxy*-11-*methyl*-5α-*pregn*-9(11)-*ene*.—A solution of 3β,20β-diacetoxy-11α-methyl-5α-pregnan-11β-ol (2·03 g.) in anhydrous pyridine (50 ml.) was cooled to −20° and treated with thionyl chloride (2 ml.). The mixture was allowed to warm to room temperature during 10 min., then poured into dilute sulphuric acid. Extraction with ether and crystallisation from aqueous methanol gave the 11-*methyl*-9(11)-*ene* in rods, m. p. 126—128°, $[\alpha]_D^{23}$ +88° (*c* 0·34), $\nu_{max.}$ (in CS_2) 1734 cm.$^{-1}$ (acetates) (Found: C, 74·75; H, 9·6. $C_{26}H_{40}O_4$ requires C, 74·95; H, 9·7%).

3β,20β-*Diacetoxy*-11-*methylene*-5α-*pregnane*.—(a) 3β,20β-Diacetoxy-11α-methyl-5α-pregnan-11β-ol (200 mg.) in formic acid (10 ml.) was warmed to 40°, then allowed to cool and set aside for 3 hr. It was poured into water. Extraction with benzene and purification from aqueous methanol gave the 11-*methylene derivative* in leaflets, m. p. 148—150°, $[\alpha]_D^{25}$ +19° (*c* 0·62), $\nu_{max.}$ (in CCl_4) 3095, 1632 (:CH_2), 1729 cm.$^{-1}$ (OAc) (Found: C, 74·85; H, 9·9. $C_{26}H_{40}O_4$ requires C, 74·95; H, 9·7%).

(b) *From* 3β,20β-*diacetoxy*-11-*methyl*-5α-*pregn*-9(11)-*ene*. The 9(11)-ene (100 mg.) in formic acid (2 ml.) was heated on the steam-bath for 20 min. The product, isolated as under (a), proved to be the 11-methylene derivative.

(c) *From* 3β-*acetoxy*-11-*methylene*-5α-*pregn*-16-*en*-20-*one* (V) (see below). Hydrogenation of the 16-en-20-one (0·5 g.) in methanol (100 ml.) over 2% palladium–barium carbonate (50 mg.) led to the uptake of one mol. of hydrogen. The catalyst was removed, and the solution concentrated until crystallisation commenced. Purification from methanol gave 3β-*acetoxy*-11-*methylene*-5α-*pregnan*-20-*one* in prismatic needles, m. p. 137—138°, $[\alpha]_D^{26}$ +85° (*c* 0·32) (Found: C, 77·0; H, 9·7. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·7%).

This 20-one (350 mg.) in 90% methanol (25 ml.) was treated with sodium hydroxide (300 mg.) and sodium borohydride (150 mg.) under reflux for 2 hr., and the solution was then concentrated to small bulk and cooled. The separated solids were purified from aqueous methanol and from acetone, to give 11-*methylene*-5α-*pregnane*-3β,20β-*diol* in needles, m. p. 203—206°, $[\alpha]_D^{29}$ +54° (*c* 0·21), $\nu_{max.}$ (in Nujol) 3580, 3247 (OH), 1632, 895 cm.$^{-1}$ (:CH_2) (Found: C, 79·2; H, 10·6. $C_{22}H_{36}O_2$ requires C, 79·5; H, 10·9%).

The diol (100 mg.) with acetic anhydride (1 ml.) and pyridine (1 ml.) on the steam-bath for 2 hr. gave 3β,20β-diacetoxy-11-methylene-5α-pregnane, identical with the samples prepared as under (a) and (b) above.

Degradation of the Spiro-ketal System in 11-*Methylenetigogenin Acetate* (IV; R = −OAc, ··H).—A mixture of 11-methylenetigogenin acetate (40 g.), pyridine (40 ml.), acetic anhydride (80 ml.), and methylamine hydrochloride (13·4 g.) was heated under reflux for 2·5 hr., cooled, and poured into ice-water. The precipitated product solidified slowly. A sample, crystallised from methanol, gave 3β,26-*diacetoxy*-11-*methylene*-5α-*furost*-20(22)-*ene* in needles, m. p. 94—96°, $[\alpha]_D^{22}$ +30° (*c* 0·61) (Found: C, 75·0; H, 9·3. $C_{32}H_{48}O_5$ requires C, 74·9; H, 9·4%).

The main part of the crude furostene was dissolved in acetic acid (800 ml.) and treated with 30% hydrogen peroxide (350 ml.) for 6 hr. at room temperature. Chloroform (300 ml.) was added, and the mixture was diluted with water. The chloroform was separated, the aqueous phase was re-extracted with chloroform, and the combined extracts were washed and evaporated. A solution of the residue in acetic acid (200 ml.) was heated under reflux for 2 hr., concentrated under reduced pressure, and poured into water. Extraction with chloroform gave a product which, from methanol, gave 3β-*acetoxy*-11-*methylene*-5α-*pregn*-16-*en*-20-*one* in needles, m. p. 184—186°, $[\alpha]_D^{23}$ +34° (*c* 0·42), $\lambda_{max.}$ 238 mμ (ε 8130 in EtOH), $\nu_{max.}$ (in CH_2Cl_2) 1724 (OAc) 1663, 1587 (Δ^{16}-20-one), and 1636 cm.$^{-1}$ (:CH_2) (Found: C, 77·4; H, 9·5. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·25%).

The yield of this product was substantially improved by passing the non-crystalline residues,

in benzene solution, through a column of chromatographic alumina (5 g. per 1 g. of residue), evaporating the benzene, and purifying the product from methanol.

The foregoing compound (10 g.) in ethanol (50 ml.) and pyridine (10 ml.) was treated with hydroxylamine hydrochloride (3·5 g.) under reflux for ½ hr. Water (5 ml.) was added, and the solution was cooled to 0°. The crystalline product was purified from ethanol–chloroform, to give the 20-*oxime* as prisms, m. p. 205—210°, $[\alpha]_D^{23}$ +17° (*c* 0·11), $\lambda_{max.}$ 237 mμ (ε 14,660 in EtOH), $\nu_{max.}$ (in CH_2Cl_2) 1719, 1632, and 1584 cm.$^{-1}$ (Found: N, 3·8. $C_{24}H_{35}NO_3$ requires N, 3·6%).

Beckmann Degradation of the Oxime.—A solution of the oxime (8 g.) in anhydrous pyridine (40 ml.), cooled to −10°, was treated dropwise with phosphorus oxychloride (16 ml.) in pyridine (48 ml.). The mixture was kept at 0° for 3 hr., then poured on ice (120 g.) and concentrated hydrochloric acid (120 ml.) with stirring, the temperature of the mixture being kept below 50°. The product was a paste which hardened on cooling. It was purified from 80% methanol to give 3β-*acetoxy*-11-*methylene*-5α-*androstan*-17-*one* in needles, m. p. 166—167°, $[\alpha]_D^{28}$ +77° (*c* 0·26), $\nu_{max.}$ (in CCl_4) 3110 and 1638 (:CH_2), 1740, 1735sh (17-ketone and OAc), and 1409 cm.$^{-1}$ (17-ketone) (Found: C, 76·4; H, 9·0. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·3%).

3β-*Hydroxy*-11-*methylene*-5α-*androstan*-17-*one* (VI; R = −OH, ··H; R′ = O).—Saponification of the foregoing 3-acetate (4·5 g.) with potassium hydroxide (2 g.) in 80% aqueous methanol (50 ml.) under reflux for ½ hr. and purification from aqueous methanol gave 3β-*hydroxy*-11-*methylene*-5α-*androstan*-17-*one* in rhombic plates, m. p. 166—167°, $[\alpha]_D^{24}$ +89° (*c* 0·69), $\nu_{max.}$ (in CCl_4) 3588 (OH), 3115, 1636 (:CH_2), 1742 (17-ketone), (in CS_2) 905 cm.$^{-1}$ (:CH_2) (Found: C, 79·3; H, 10·7. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%).

11-*Methylene*-5α-*androstane*-3β,17β-*diol* (VI; R = R′ = −OH, ··H).—Reduction of the 17-ketone (VI; R = −OH, ··H; R′ = O) (2 g.) with sodium borohydride (400 mg.) in 80% aqueous methanol (40 ml.) for 1 hr. at room temperature, and purification from acetone–hexane gave the 3β,17β-*diol* in prisms, m. p. 192—194°, $[\alpha]_D^{22}$ +20° (*c* 0·19) (Found: C, 78·4; H, 10·6. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%).

11-*Methylene*-5α-*androstane*-3,17-*dione* (VI; R = R′ = O).—3β-Hydroxy-11-methylene-5α-androstan-17-one (8 g.) in " AnalaR " acetone (100 ml.) was treated dropwise with chromic acid reagent (see above) until the presence of excess of oxidant was indicated by the colour of the solution. Water (700 ml.) containing sodium dithionite (0·5 g.) was added, and the acetone was removed under reduced pressure. The precipitated solids were washed free from chromium salts and purified from aqueous acetone, to give the 3,17-*dione* in square plates, m. p. 193—196°, $[\alpha]_D^{22}$ +115° (*c* 0·73), $\nu_{max.}$ (in CCl_4) 3108 and 1637 (:CH_2), 1741 (17-ketone), and 1719 (3-ketone), (in CS_2) 905 cm.$^{-1}$ (:CH_2) (Found: C, 79·75; H, 9·3. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%).

3,3-*Dimethoxy*-11-*methylene*-5α-*androstan*-17-*one* [VI; R = $(MeO)_2$; R′ = O].—The foregoing dione (6 g.) was stirred in anhydrous methanol (120 ml.) and treated with acetyl chloride (0·5 ml.). The precipitate was collected after ½ hr. and purified from ethanol containing 0·5% of pyridine, to give the 3,3-*dimethoxy-derivative* as needles, m. p. 175—178° (decomp.), $[\alpha]_D^{23}$ +138° (*c* 0·13), $\nu_{max.}$ (in CCl_4) 3109, 1640 (:CH_2), 1745 cm.$^{-1}$ (17-ketone) (Found: C, 76·1; H, 9·8. $C_{22}H_{34}O_3$ requires C, 76·3; H, 9·9%).

3,3-*Dimethoxy*-11-*methylene*-5α-*androstan*-17β-*ol* [VI; R = $(MeO)_2$; R′ = −OH, ··H)].—Reduction of the last compound (4·6 g.) in suspension in methanol (120 ml.) with sodium borohydride (1 g.) and sodium hydroxide (1 g.) in water (15 ml.) for 1·5 hr. at room temperature gave a solution which was diluted with water (300 ml.). The precipitate solids were purified from aqueous methanol, to give the 17β-*alcohol* as blades, m. p. 166—167°, $[\alpha]_D^{26}$ +37° (*c* 0·85), $\nu_{max.}$ (in CCl_4) 3616 (OH), 3110, 1636 (:CH_2), (in CS_2) 899 cm.$^{-1}$ (:CH_2) (Found: C, 76·0; H, 10·3. $C_{22}H_{36}O_3$ requires C, 75·8; H, 10·4%).

The 17-*propionate*, prepared by treating the foregoing compound (1·5 g.) with propionic anhydride (3 ml.) in pyridine (10 ml.) for 20 min. on the steam-bath, separated from methanol in flakes, m. p. 145—148°, $[\alpha]_D^{26}$ +6° (*c* 0·69) (Found: C, 74·5; H, 9·9. $C_{25}H_{40}O_4$ requires C, 74·2; H, 10·0%).

17β-*Hydroxy*-11-*methylene*-5α-*androstan*-3-*one* (VI; R = O; R′ = −OH, ··H).—3,3-Dimethoxy-11-methylene-5α-androstan-17β-ol (1 g.) in 70% acetic acid (20 ml.) was heated to 80° for 20 min. The product was poured into water and the precipitate purified from aqueous methanol, to give 17β-*hydroxy*-11-*methylene*-5α-*androstan*-3-*one* in fibrous crystals, m. p. 207—210°, $[\alpha]_D^{26}$ +33° (*c* 0·78), $\nu_{max.}$ (in CCl_4) 3614 (OH), 3102, 1636 (:CH_2), and 1715 (3-ketone),

(in CS_2) 901 cm.$^{-1}$ (:CH_2) (Found: C, 79·1; H, 9·8. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%). The 17-*acetate* separated from aqueous methanol in plates, m. p. 150—151°, $[\alpha]_D^{23}$ +3° (*c* 0·28) (Found: C, 76·6; H, 9·6. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4%). The 17-*propionate* separated from methanol in flakes, m. p. 169—170°, $[\alpha]_D^{23}$ +18° (*c* 0·48) (Found: C, 77·5; H, 9·7. $C_{23}H_{34}O_3$ requires C, 77·05; H, 9·6%).

11β-*Methyl*-17β-*propionyloxy*-5α-*androstan*-3-*one*.—The foregoing propionate (0·8 g.) was hydrogenated in acetic acid (25 ml.) over Adams platinum catalyst (0·1 g.). The uptake of hydrogen ceased after absorption of about 2 mols., indicating reduction of both the methylene and the 3-keto-group. After removal of the catalyst, and of the solvent under reduced pressure, the residue was treated in acetone (30 ml.) with a slight excess of chromic acid reagent (see above). The solution was diluted with water (100 ml.), and the acetone removed under reduced pressure. The precipitated solid, purified from aqueous methanol, gave the *androstanolone propionate* in prisms, m. p. 136—138°, $[\alpha]_D^{24}$ +26° (*c* 0·34), $\nu_{max.}$ (in CCl_4) 1733 (propionate) and 1717 cm.$^{-1}$ (3-ketone).

CHEMICAL RESEARCH LABORATORIES, THE BRITISH DRUG HOUSES LTD.,
LONDON, N.1.
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