900. *Modified Steroid Hormones. Part XIX.* Steroidal 5β-Methyl-A-homo-B-nor-4,4a-unsaturated Ketones. A New Class of Hormone Analogue.*

By David N. Kirk and Vladimir Petrow.

3β-Acetoxy-5α,6α-epoxy-6β-methyl-steroids (I) undergo molecular rearrangement on treatment with boron trifluoride in benzene, to give 3β-acetoxy-5β-methyl-A-homo-B-nor-4a-ketones (II). These novel products can be converted into the 4,4a-unsaturated 3-ketones, which are formally related to 3-oxo-Δ^4-steroids.

Our studies on modified steroid hormones are reported here in so far as they have been extended to the reaction of some 3β-acetoxy-6-methyl-5α,6α-epoxides (I) with boron trifluoride. In place of the expected 3β-acetoxy-6β-fluoro-5α-hydroxy-6α-methyl intermediates,[1] which we had hoped to transform into 6β-fluoro-6α-methyl-Δ^4-3-ketones, fluorine-free acetoxy-ketones were obtained in very high yield. Their transformations establish unequivocally their formulation as 3β-acetoxy-5β-methyl-A-homo-B-nor-4a-ketones (II; R = β-OAc), formed from the epoxides (I) by a hitherto unrecorded structural rearrangement.

5α,6α-Epoxy-6β-methyltigogenin acetate (Ia), employed as a model compound, reacted readily with the boron trifluoride–ether complex in benzene, to give 3β-acetoxy-5β-methyl-A-homo-B-nor-25D-spirostan-4a-one (IIa; R = β-OAc) in *ca.* 90% yield. In accordance with its β-acetoxy-ketone formulation, the last compound lost the elements of acetic acid on percolation through a column of alumina to give 5β-methyl-A-homo-B-nor-25D-spirost-3-en-4a-one (IIIa; R = H) which was characterised by its ultraviolet absorption maximum at 226 mμ and its infrared absorption at 1677 cm.$^{-1}$ (in CCl_4). Hydrogenation of this αβ-unsaturated ketone furnished 5β-methyl-A-homo-B-nor-25D-spirostan-4a-one (IVa). Both the acetoxy-ketone (IIa; R = β-OAc) and the saturated product (IVa) show infrared carbonyl bands at unusually low frequencies (1698 and 1694 cm.$^{-1}$ in CCl_4 respectively), entirely consistent with their formulation as cycloheptanone derivatives.[2]

Alkaline hydrolysis of the acetoxy-ketone (IIa; R = β-OAc) unexpectedly furnished 3β-hydroxy-5β-methyl-A-homo-B-nor-25D-spirostan-4a-one (IIa; R = β-OH) as major product (>70%), very little of the Δ^3-4a-ketone (IIIa; R = H) being formed. Reduction

* Part XVIII, *J.*, 1960, 3872.

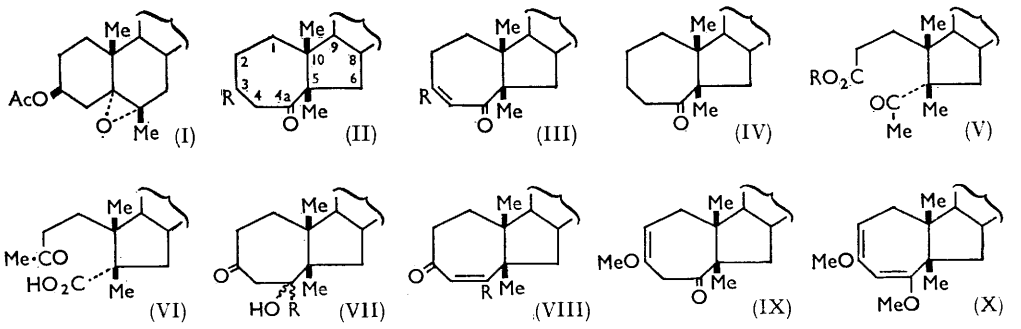
[1] Cf. Henbest and Wrigley, *J.*, 1957, 4765, and Bowers, Cuéllar-Ibáñez, and Ringold, *Tetrahedron*, 1959, **7**, 138, for the analogous reaction in the 6-demethyl series.

[2] Jones and Sandorfy, "Technique of Organic Chemistry. Vol. IX. Chemical Applications of Spectroscopy," Interscience Publ., Inc., New York, 1956, p. 444.

of the β-hydroxy-ketone with sodium borohydride gave 5β-methyl-A-homo-B-nor-25D-spirostane-3β,4aξ-diol. Acetylation of this compound with acetic anhydride–pyridine at room temperature furnished a monoacetate, whilst prolonged heating at 100° led to the formation of the corresponding diacetate. Alternative production of the same monoacetate by reduction of the acetoxy-ketone (IIa; R = β-OAc) with lithium borohydride establishes its constitution as a 3β-acetoxy-5β-methyl-A-homo-B-nor-25D-spirostan-4aξ-ol.

Oxidation of the 3β-hydroxy-4a-ketone (IIa; R = β-OH) with chromic acid and sulphuric acid in acetone gave 5β-methyl-A-homo-B-nor-25D-spirostane-3,4a-dione (IIa; R = :O), which was characterised by its infrared absorption maxima at 1723 and 1698 cm.$^{-1}$. In ethanolic solution the compound appeared to exist in the diketo-form [ultraviolet absorption at 262 (ε 290) and 291 mμ (ε 115)]. Addition of potassium hydroxide led to a shift in the maximum to 299 mμ with a large increase in intensity (ε 20,800), presumably through formation of an enolate ion. Acetylation yielded an enol-acetate which is regarded as 3-acetoxy-5β-methyl-A-homo-B-nor-25D-spirost-3-en-4a-one (IIIa; R = OAc) on the basis of its ultraviolet ($\lambda_{max.}$ 230·5 mμ) and infrared ($\nu_{max.}$ 1760 and 1672 cm.$^{-1}$) absorption spectra. In common with other β-diketones, the compound (IIa; R = :O) was cleaved by ethanolic potassium hydroxide to a keto-carboxylic acid regarded as 4,5β-dimethyl-4-oxo-3,4-seco-B-nor-25D-spirostan-3-oic acid (Va; R = H). Its formulation as the isomeric 3,4-seco-4-oic acid (VIa) is excluded by the observation that the product is readily converted by methanolic hydrogen chloride into a methyl ester (Va; R = Me), which reverts to the original acid on hydrolysis with aqueous-methanolic potassium carbonate at room temperature. This behaviour is consistent with that of primary aliphatic carboxylic acids, tertiary carboxylic acids resisting esterification and subsequent hydrolysis under these conditions.

The β-diketone (IIa; R = :O) was converted by methanolic hydrogen chloride into 3,3-dimethoxy-5β-methyl-A-homo-B-nor-25D-spirostan-4a-one [IIa; R = $(OMe)_2$] and not into the expected enol ether (IIIa; R = OMe). Thermal decomposition of the dimethoxy-ketone in boiling decalin for 2½ hr., followed by crystallisation of the product, led to the isolation of a non-conjugated ketone, $C_{29}H_{44}O_4$, formulated as 3-methoxy-5β-methyl-A-



(*a*) 25D-Spirostane series. (*b*) Androstan-17-one series.
(*c*) 17β-Acetoxyandrostane series. (*d*) 17β-Hydroxy-17α-methylandrostane series.

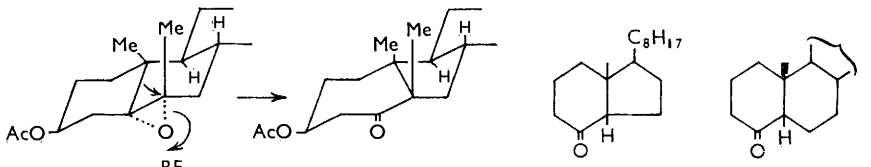
homo-B-nor-25D-spirost-2-en-4a-one (IXa) on the basis of (i) an infrared absorption maximum at 1694 cm.$^{-1}$ (non-conjugated 4a-one), (ii) the absence of ultraviolet absorption between 220 and 300 mμ, and (iii) its reconversion into the 3,4a-dione (IIa; R = :O) by toluene-*p*-sulphonic acid in acetone. Thermal decomposition of the 3,3-dimethoxy-ketone in decalin for 8 hr., in contrast, gave a mixture which could not be separated by crystallisation. Its infrared spectrum revealed the presence of the non-conjugated methoxy-ketone (IXa) and a component possessing a conjugated system ($\nu_{max.}$ 1628 cm.$^{-1}$). The latter component was isolated by chromatography on alumina and was additionally obtained

in somewhat better yield by heating the dimethoxy-ketone [IIa; R = $(OMe)_2$] at 220°. Its ultraviolet spectrum revealed the presence of a homoannular dienic system.[3] This was confirmed by the infrared spectrum which additionally indicated the presence of two non-equivalent methoxy-groups.[4] Acid-hydrolysis regenerated the parent diketone (IIa; R = :O). This product is tentatively formulated as 3,4a-dimethoxy-5β-methyl-A-homo-B-nor-25D-spirosta-2,4(4a)-diene (Xa).

Reduction of the 3,3-dimethoxy-ketone [IIa; R = $(OMe)_2$] with sodium borohydride, followed by regeneration of the oxo-function, furnished 4aξ-hydroxy-5β-methyl-A-homo-B-nor-25D-spirostan-3-one (VIIa; R = H). Methanolic hydrochloric acid dehydrated the last compound to 5β-methyl-A-homo-B-nor-25D-spirost-4(4a)-en-3-one (VIIIa; R = H), characterised by its ultraviolet ($\lambda_{max.}$ 232·5 mμ) and infrared absorption [1670 and 1614 $cm.^{-1}$ (in CCl_4)] spectra. This product differed from the previously described Δ^3-4a-ketone (IIIa; R = H), an observation which establishes not only its constitution but also those of its immediate precursors [IIa; R = $(OMe)_2$ and VIIa; R = H].

The above transformations unequivocally establish structure (IIa; R = β-OAc) for the boron trifluoride-induced rearrangement product of the 6-methylated epoxide (Ia), but give no indication of the stereochemistry of the new system about $C_{(5)}$. If it is assumed that boron trifluoride behaves as a Lewis acid in its attack upon the epoxide ring of (Ia), then cleavage of the epoxide ring to give a 6-carbonium ion can be envisaged. The approximate coplanarity of the participating centres $C_{(10)}$–$C_{(5)}$–$C_{(6)}$-epoxide (cf. XI) [5] would favour migration of the 5,10-linkage with retention of the β-configuration of the 5-methyl group in the product (XII). The rearrangement consequently bears a formal analogy to the C-nor-D-homo-rearrangement of 12β-sulphonoxy-steroids.[6]

Presumptive evidence in favour of the 5β-methyl structure (XII) is provided by optical rotatory dispersion data. The curve of the acetoxy-ketone (IIa; R = β-OAc) shows a rather weak positive Cotton effect superimposed upon the negative plain curve of a 25D-spirostan.[7] The acetoxy-ketone thus resembles the *cis*-8-methylhexahydroindan-4-one (XIII) [8] and 5β-cholestan-4-one (XIV);[9] but differs from the *trans*-isomers (XIII [8] and XIV [10]) which are characterised by strongly negative Cotton effects in their optical rotatory



(XI) (XII) (XIII) (XIV)

dispersions. Supporting evidence follows from application of the octant rule [11] which appears to be valid in the case of cycloheptanones. Analysis of the 5β-methyl structure (IIa; R = β-OAc) and of its 5α-methyl isomer shows that only the former ring system may be expected to shows a positive Cotton effect in its optical rotatory dispersion curve.

The above rearrangement has been applied to the 5α,6α-epoxides [5] derived from 3β-acetoxy-6-methylandrost-5-en-17-one and 3β,17β-diacetoxy-6-methylandrost-5-ene, and the corresponding acetoxy-A-homo-B-nor-ketones (IIb and IIc; R = β-OAc) have been obtained in high yield. The 3β,17β-diacetoxy-4a-ketone (IIc; R = β-OAc) was converted

[3] Dorfman, *Chem. Rev.*, 1953, **53**, 47.
[4] Ref. 2, p. 435.
[5] For the α-configuration of the 5,6-epoxides see Cooley, Ellis, and Petrow, *J.*, 1960, 3676.
[6] Elks, Phillipps, Taylor, and Wyman, *J.*, 1954, 1739; Hirschmann, Snoddy, Hiskey, and Wendler, *J. Amer. Chem. Soc.*, 1954, **76**, 4013.
[7] Djerassi and Ehrlich, *J. Amer. Chem. Soc.*, 1956, **78**, 440.
[8] Djerassi, Marshall, and Nakano, *J. Amer. Chem. Soc.*, 1958, **80**, 4853.
[9] Djerassi, Riniker, and Kiniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6362.
[10] Djerassi, Closson, and Lippman, *J. Amer. Chem. Soc.*, 1956, **78**, 3163.
[11] Djerassi, " Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, 1960, p. 178.

by percolation of its benzene solution through alumina into the Δ^3-4a-ketone (IIIc; R = H). When the 3β-acetoxy-4a,17-diketone (IIb; R = β-OAc) was treated with an excess of methylmagnesium iodide, both keto-groups reacted, to give 4aξ,5β,17α-trimethyl-A-homo-B-norandrostane-3β,4aξ,17β-triol, which was oxidised by chromic acid to the 3-ketone (VIId; R = Me). Dehydration of the last compound with methanolic hydrogen chloride gave 17β-hydroxy-4a,5β,17α-trimethyl-A-homo-B-norandrost-4(4a)-en-3-one (VIIId; R = Me), which exhibited ultraviolet absorption at 246 mμ. The bathochromic shift of 13·5 mμ in the maximum relative to the 4a-demethyl compound (VIIIa; R = H) is compatible with the presence of 4a-methyl substituent.[3]

Experimental

Optical rotations were measured for $CHCl_3$ solutions in a 1 dm. tube. Ultraviolet (in EtOH), infrared, and optical rotatory dispersion measurements were kindly determined by Mr. M. T. Davies, B.Sc., and Miss K. F. Dobson, B.Sc.

3β-*Acetoxy*-5α,6α-*epoxy*-6β-*methyl*-25D-*spirostane* (Ia).—6-Methyldiosgenin acetate (50 g.) in chloroform (200 ml.) was treated with monoperphthalic acid (27 g.) in ether (350 ml.) at 0—5° overnight. The mixture was poured into excess of sodium carbonate solution, the organic layer washed neutral, and the solvent removed. Purification of the residue from acetone and from ethyl acetate gave 3β-*acetoxy*-5α,6α-*epoxy*-6β-*methyl*-25D-*spirostane*, needles, m. p. 251—254°, $[\alpha]_D^{25}$ −114° (*c* 0·44) (Found: C, 73·9; H, 9·2. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%).

3β,17β-*Diacetoxy*-5α,6α-*epoxy*-6β-*methylandrostane* (Ic), similarly prepared from 3β,17β-diacetoxy-6β-methylandrost-5-ene, separated from methanol in plates, m. p. 182—184°, $[\alpha]_D^{23}$ −49° (*c* 0·54) (Found: C, 71·5; H, 9·15. $C_{24}H_{36}O_5$ requires C, 71·25; H, 9·0%).

Rearrangement of 5α,6α-*epoxy*-6β-*methyl-steroids* (I) *by Boron Trifluoride*.—The general procedure was as follows:

The 5α,6α-Epoxide (20 g.) in anhydrous benzene (250 ml.) was treated with redistilled boron trifluoride–ether complex (20 ml.), and the mixture left at room temperature for 5 hr.; it developed a deep blue or purple-blue colour. The solution was poured into saturated sodium hydrogen carbonate solution, and the mixture shaken to decompose the boron trifluoride, the organic layer becoming pale yellow. After being washed with water, the benzene layer was evaporated under reduced pressure, and the solid residue purified by crystallisation.

3β-*Acetoxy*-5β-*methyl*-A-*homo*-B-*nor*-25D-*spirostan*-4a-*one* (IIa; R = β-OAc), prepared from 3β-acetoxy-5α,6α-epoxy-6β-methyl-25D-spirostane, crystallised from acetone in flakes, m. p. 204—205°, $\lambda_{max.}$ 293 mμ (ε 64), $\nu_{max.}$ (in CCl_4) 1739 (OAc), 1698 (4a-C:O), and 1432 cm.$^{-1}$ (CH_2·CO [12]), $[\alpha]_D^{25}$ −76° (*c* 0·47), $[\alpha]_{355}^{25}$ −185° (trough), $[\alpha]_{324}^{25}$ −40° (peak), $[\alpha]_{292}^{25}$ −520° (*c* 1% in dioxan). (Found: C, 74·2; H, 9·7. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%).

3β-*Acetoxy*-5β-*methyl*-A-*homo*-B-*norandrostane*-4a,17-*dione* (IIb; R = β-OAc), prepared from 3β-acetoxy-5α,6α-epoxy-6β-methylandrostan-17-one [5] (Ib), separated from methanol in prisms, m. p. 126—128°, $[\alpha]_D^{25}$ +56° (*c* 0·68), $\lambda_{max.}$ 294 mμ (ε = 86), $\nu_{max.}$ (in CCl_4) 1437, (CO·CH_2, ring A),[12] and 1407 cm.$^{-1}$ (CO·CH_2, ring D),[9] (in CS_2) 1738 (17-C:O and 3-OAc), and 1698 cm.$^{-1}$ (4a-C:O) (Found: C, 73·1; H, 9·0. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·95%).

3β,17β-*Diacetoxy*-5β-*methyl*-A-*homo*-B-*norandrostan*-4a-*one* (IIc; R = β-OAc), prepared from 3β,17β-diacetoxy-5α,6α-epoxy-6β-methylandrostane (Ic), formed prisms (from aqueous methanol), m. p. 156—158°, $[\alpha]_D^{26}$ −8° (*c* 0·61), $[\alpha]_{345}^{25}$ −530° (trough), $[\alpha]_{321}^{25}$ −320° (peak), $[\alpha]_{275}^{25}$ −1800° (*c*, 1% in dioxan), $\nu_{max.}$ (in CCl_4) 1744 (OAc) and 1702 cm.$^{-1}$ (4a-C:O) (Found: C, 71·2; H, 8·9. $C_{24}H_{36}O_5$ requires C, 71·25; H, 9·0%).

5β-*Methyl*-A-*homo*-B-*nor*-25D-*spirost*-3-*en*-4a-*one* (IIIa; R = H).—The corresponding 3β-acetoxy-4a-ketone (IIa; R = OAc) (2 g.) in benzene (20 ml.) was percolated through a column of chromatographic alumina (100 g.) in benzene. Evaporation of the solvent and purification from acetone gave 5β-*methyl*-A-*homo*-B-*nor*-25D-*spirost*-3-*en*-4a-*one* as needles, m. p. 209—211°, $[\alpha]_D^{24}$ −157° (*c* 0·30), $\lambda_{max.}$ 226 mμ (ε 5460), $\nu_{max.}$ (in CCl_4) 1677 cm.$^{-1}$, (in CH_2Cl_2) 1666 and 1641 cm.$^{-1}$ (Found: C, 78·4; H, 9·75. $C_{28}H_{42}O_3$ requires C, 78·8; H, 9·9%).

5β-*Methyl*-A-*homo*-B-*nor*-25D-*spirostan*-4a-*one* (IVa; R = H).—The foregoing compound

[12] Jones and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 5048.

(IIIa; R = H) (340 mg.) in ethanol (100 ml.) was hydrogenated in the presence of a 5% palladium–charcoal (100 mg.). The product was purified from acetone, to give 5β-*methyl*-A-*homo*-B-*nor*-25D-*spirostan*-4a-*one* as needles, m. p. 180—182°, $[\alpha]_D^{24}$ −120° (*c* 0·22), $\nu_{max.}$ (in CCl_4) 1694 cm.$^{-1}$ (Found: C, 78·6; H, 9·9. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%).

Hydrolysis of the 3β-*Acetoxy*-4a-*ketone* (IIa; R = β-OAc).—The acetoxy-ketone (10 g.) and potassium hydroxide (3 g.) in 85% aqueous methanol (180 ml.) were heated under reflux for ½ hr., then the solution was diluted with water (120 ml.) and cooled, and the precipitated solids were purified from acetone–hexane, giving 3β-*hydroxy*-5β-*methyl*-A-*homo*-B-*nor*-25D-*spirostan*-4a-*one* as needles, m. p. 239—241°, $[\alpha]_D^{27}$ −96° (*c* 0·43), $\nu_{max.}$ (in CCl_4) 3578 and 1695 cm.$^{-1}$ (Found: C, 76·0; H, 9·9. $C_{28}H_{44}O_4$ requires C, 75·6; H, 10·0%).

Reduction of the 3β-*Hydroxy*-4a-*ketone* (IIa; R = β-OH).—The hydroxy-ketone (5 g.) in methanol (250 ml.), mixed with a solution of sodium hydroxide (1 g.) and sodium borohydride (2 g.) in water (10 ml.), was kept at 50° for 4 hr. Half the methanol was then removed under reduced pressure and the solution diluted with water to turbidity. The crystalline product was purified from methanol, to give 5β-*methyl*-A-*homo*-B-*nor*-25D-*spirostane*-3β,4aξ-*diol* as flakes, m. p. 248—256°, $[\alpha]_D^{19}$ −91° (*c* 0·63), $\nu_{max.}$ (in CCl_4) 3629 cm.$^{-1}$ (Found: C, 75·1; H, 10·5. $C_{28}H_{46}O_4$ requires C, 75·3; H, 10·4%).

The 3-*monoacetate* was prepared from the above 3β,4aξ-dihydroxy-compound (1 g.) by treatment with acetic anhydride (2 ml.) in pyridine (10 ml.) at room temperature for 18 hr. It separated from methanol as needles, m. p. 181—183°, $[\alpha]_D^{27}$ −138° (*c* 0·75), $\nu_{max.}$ (in CCl_4) 3598, 3456, and 1732 cm.$^{-1}$ (Found: C, 73·8; H, 9·8. $C_{30}H_{48}O_5$ requires C, 73·7; H, 9·9%).

A similar acetylation mixture, when heated on the steam-bath for 6 hr., afforded the diacetate as an amorphous precipitate, m. p. about 100—125°, $\nu_{max.}$ (in CS_2) 1738 cm.$^{-1}$ (no OH absorption).

Reduction of the Acetoxy-ketone (IIa; R = β-OAc) *with Lithium Borohydride.*—A solution of the acetoxy-ketone (5 g.) in anhydrous tetrahydrofuran (150 ml.) was stirred with powdered lithium borohydride (1·8 g.) for 5 hr. at room temperature. The mixture was poured into water, and the precipitated solids were purified from methanol to give the 3β,4aξ-diol 3-monoacetate, identical with the sample prepared as above.

5β-*Methyl*-A-*homo*-B-*nor*-25D-*spirostane*-3,4a-*dione* (IIa; R= :O).—The 3β-hydroxy-4a ketone (IIa; R = β-OH) (5 g.) in "AnalaR" acetone (250 ml.) was treated dropwise with the chromic acid reagent [prepared from chromium trioxide (240 g.), concentrated sulphuric acid (230 ml.) and water (to 1 l.)] until an orange colour persisted. The mixture was poured into water, and the precipitated solid purified from acetone, to give 5β-*methyl*-A-*homo*-B-*nor*-25D-*spirostane*-3,4a-*dione* in plates, m. p. 232—235°, $[\alpha]_D^{21}$ −177° (*c* 0·95), $\lambda_{max.}$ 262 mμ (ε 290), $\lambda_{infl.}$ 291 mμ (ε 115), $\nu_{max.}$ (in CCl_4) 1723, 1698 (3- and 4a-C:O), 1433 and 1417 cm.$^{-1}$ ($CO{\cdot}CH_2$ groups),[12] (in CH_2Cl_2) 1716 and 1693 cm.$^{-1}$ (Found: C, 76·2; H, 9·4. $C_{28}H_{42}O_4$ requires C, 76·0; H, 9·6%).

Cleavage of the 3,4a-*Diketone* (IIa; R = :O) *with Alkali.*—The diketone (2 g.) in ethanol (100 ml.) containing potassium hydroxide (10 g.) was heated under reflux for 5 hr. The mixture was then poured into water. The resulting clear solution, when extracted with ether, afforded only a trace of gum. Acidification of the alkaline liquors with sulphuric acid and extraction with ether gave the *carboxylic acid* (Va; R = H) which was purified from acetone–hexane, giving needles, m. p. 184—187°, $[\alpha]_D^{15}$ −50° (*c* 0·49), $\nu_{max.}$ (in CCl_4) 3400—2400 (broad band due to associated carboxylic acid),[13] 1754 (shoulder: monomeric CO_2H),[13] 1718 (C:O?), 1419 ($CH_2{\cdot}CO_2H$),[13] and 1353 cm.$^{-1}$ (Ac) [13] (Found: C, 72·6; H, 9·7. $C_{28}H_{44}O_5$ requires C, 73·0; H, 9·6%).

Esterification of the Keto-acid (Va; R = H).—The keto-acid (0·52 g.) was dissolved in methanol (26 ml.) to which acetyl chloride (0·25 ml.) had been added. After 20 hr. the solution was poured into dilute sodium hydrogen carbonate solution, and the precipitated material extracted with ether and purified from aqueous methanol. The *methyl ester* (V; R = Me) formed rods, m. p. 142—143°, $[\alpha]_D^{18}$ −65° (*c* 0·51), $\nu_{max.}$ (in CCl_4) 1738 (CO_2Me),[13] 1692 (C:O), 1353 cm.$^{-1}$ (Ac) [13] (Found: C, 73·7; H, 9·7. $C_{29}H_{46}O_5$ requires C, 73·4; H, 9·8%).

Hydrolysis of the Methyl Ester (Va; R = Me).—The methyl ester (100 mg.) in methanol (20 ml.) was treated with potassium carbonate (40 mg.) in water (4 ml.) for 20 hr. at room

[13] Roberts, Gallagher, and Jones, "Infrared Absorption Spectra of Steroids: An Atlas," Interscience Publ. Inc., New York, 1958, Vol. 2, pp. 20—41 and refs. therein.

temperature. Dilution with water and extraction with ether afforded a small quantity of the methyl ester. The alkaline solution was acidified and extracted with ether, giving the keto-acid (Va; R = H) in good yield.

3,3-*Dimethoxy*-5β-*methyl*-A-*homo*-B-*nor*-25D-*spirostan*-4a-*one* [IIa; R = $(MeO)_2$].—The 3,4a-diketone (IIa; R = :O) (2 g.) was stirred in methanol (50 ml.) to which acetyl chloride (0·5 ml.) had been added. It slowly dissolved, with separation of a solid product. After 6 hr. this material was collected and purified from acetone, to give the **3,3-*dimethoxy*-4a-*ketone*** as needles, m. p. 206—209° (decomp.), $[\alpha]_D^{25}$ −83° (*c* 0·35), $\nu_{max.}$ (in CCl_4) 1700 (4a-C:O) and 1434 cm.$^{-1}$ (CH_2·CO),[12] (in CS_2) 1101 cm.$^{-1}$ (3,3-dimethoxy) and the usual 25D-spirostane bands [13] (Found: C, 73·7; H, 9·8. $C_{30}H_{48}O_5$ requires C, 73·7; H, 9·9%).

Thermal Decomposition of the **3,3-*Dimethoxy*-4a-*ketone*** [IIa; R = $(MeO)_2$].—(a) *In boiling decalin.* The dimethoxy-ketone (200 mg.) and decalin (5 ml.) were heated under reflux (short air-condenser) for 2·5 hr. The decalin was removed in steam, and the precipitated solid (m. p. 200—215°) collected and purified from ethanol, to give **3-*methoxy*-5β-*methyl*-A-*homo*-B-*nor*-25D-*spirost*-2-*en*-4a-*one***, as blades, m. p. 231—233°, $[\alpha]_D^{24}$ −172° (*c* 0·49), $\nu_{max.}$ (in CCl_4) 1721 (unassigned weak band), 1694 (4a-C:O) (Found: C, 75·9; H, 9·75. $C_{29}H_{44}O_4$ requires C, 76·3; H, 9·7%).

(b) When the mixture [as in (a)] was heated for 8 hr. and the product, in benzene solution, percolated through a column of chromatographic alumina (5 g.) a compound believed to be **3,4a-*dimethoxy*-5β-*methyl*-A-*homo*-B-*nor*-25D-*spirosta*-2,4(4a)-*diene*** was obtained. It formed needles from acetone, m. p. 197—200°, $[\alpha]_D^{21}$ −206° (*c* 0·17), $\lambda_{max.}$ 253 mμ (ε 10,470), $\nu_{max.}$ (in CCl_4) 1647 (unassigned weak shoulder) and 1628 (conjugated diene), (in CS_2) 1206 (MeO in the conjugated 4a-position at the end of the diene system [4]) and 1162 cm.$^{-1}$ (MeO in the non-terminal 3-position) (Found: C, 76·2; H, 9·7. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%).

(c) *By heat alone.* The dimethoxy-ketone [IIa; R = $(MeO)_2$] was heated in an open test-tube in an oil-bath at 215—220° until gas evolution ceased (45 min.). The cooled melt was purified from acetone to give material identical with the product obtained as under (b).

When either of the foregoing products derived from the dimethoxy-ketone, or the dimethoxy-ketone itself, was dissolved in a 0·2% solution of toluene-*p*-sulphonic acid in acetone at room temperature for 18 hr., and the solution diluted with water to turbidity, the product was the 3,4a-diketone (IIa; R = O).

Reduction of the **3,3-*Dimethoxy*-4a-*ketone*** [IIa; R = $(OMe)_2$].—The dimethoxy-ketone (1·8 g.) in methanol (200 ml.) was treated with sodium hydroxide (360 mg.) and sodium borohydride (1 g.) in water (10 ml.), and the mixture was stirred for 6 hr. at room temperature. Dilution with water gave a crystalline product (m. p. 140—146° after drying at 80° *in vacuo*), the infra-red spectrum of which showed a hydroxyl band but no oxo-groups.

This material (1·7 g.) was dissolved by gentle warming in 90% acetic acid (100 ml.) for 10 min., water was added to turbidity, and the solution was allowed to cool. The crystalline product was purified from acetone–methylene chloride, to give **4aξ-*hydroxy*-5β-*methyl*-A-*homo*-B-*nor*-25D-*spirostan*-3-*one*** (VIIa; R = H) as needles, m. p. 246—249°, $[\alpha]_D^{21}$ −94° (*c* 0·51), $\nu_{max.}$ (in Nujol) 3426 (OH) and 1696 cm.$^{-1}$ (3-C:O) (Found: C, 75·4; H, 9·65. $C_{28}H_{44}O_4$ requires C, 75·6; H, 10·0%).

5β-*Methyl*-A-*homo*-B-*nor*-25D-*spirost*-4(4a)-*en*-3-*one* (VIIIa; R = H).—The 4a-hydroxy-3-ketone (VIIa; R = H) (0·5 g.) was heated under reflux for ½ hr. in methanol (30 ml.) containing 1% of hydrochloric acid. The solution was concentrated to crystallisation, and the product was purified from acetone–methanol. **5β-*Methyl*-A-*homo*-B-*nor*-25D-*spirost*-4(4a)-*en*-3-*one*** formed plates, m. p. 200—203°, $[\alpha]_D^{18}$ −174° (*c* 0·56), $\lambda_{max.}$ 232·5 mμ (ε 10,070), $\nu_{max.}$ (in CCl_4) 1670, 1614 cm.$^{-1}$ (αβ-unsaturated ketone) (Found: C, 78·7; H, 9·9. $C_{28}H_{42}O_3$ requires C, 78·8; H, 9·9%).

Enol-acetylation of the **3,4a-*Diketone*** (IIa; R = O).—The diketone (300 mg.) in acetic anhydride (4 ml.) and pyridine (4 ml.) was heated at 90—100° for 2 hr., then the solution was shaken with ice-water (200 ml.) and the precipitated solid purified from ethanol. **3-*Acetoxy*-5β-*methyl*-A-*homo*-B-*nor*-25D-*spirost*-3-*en*-4a-*one*** formed prisms, m. p. 226—229°, $[\alpha]_D^{21}$ −119° (*c* 0·47), $\lambda_{max.}$ 230·5 mμ (ε 7170), $\nu_{max.}$ (in CCl_4) 1760 (enol acetate), 1716 (sh) and 1672 cm.$^{-1}$ (3-en-4a-one) (Found: C, 74·0; H, 9·0. $C_{30}H_{44}O_5$ requires C, 74·3; H, 9·15%).

17β-*Acetoxy*-5β-*methyl*-A-*homo*-B-*norandrost*-3-*en*-4a-*one* (IIIc; R = H).—3β,17β-Diacetoxy-5β-methyl-A-homo-B-norandrostan-4a-one (5 g.) in benzene (25 ml.) was percolated through a column of alumina (100 g.). Elution with benzene–ether (1 : 1) and purification from aqueous

methanol gave 17β-*acetoxy*-5β-*methyl*-A-*homo*-B-*norandrost*-3-*en*-4a-*one* as needles, m. p. 126—127°, $[\alpha]_D^{27}$ −103° (*c* 0·50), $\lambda_{max.}$ 226·5 mμ (ε 5230) (Found: C, 76·8; H, 9·1. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4%).

The foregoing 17-acetate (2 g.) was heated with potassium carbonate (1 g.) in refluxing 70% aqueous acetone (100 ml.) for 1 hr.; crystallisation of the product from acetone–hexane gave the 17β-*hydroxy-compound* as leaflets, m. p. 166—168°, $[\alpha]_D^{24}$ −97° (*c* 0·12), $\lambda_{max.}$ 226 mμ (ε 5380) and 314 mμ (ε 130), $\nu_{max.}$ (in CCl_4) 3621, 3020, and 1678 cm.$^{-1}$ (Found: C, 78·8; H, 9·8. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%).

This 17β-hydroxy-compound (1·2 g.) was treated with propionic anhydride (2 ml.) in pyridine (5 ml.) for ½ hr. on the steam-bath, to give the 17-*propionate*, which separated from methanol in prisms, m. p. 91—92°, $[\alpha]_D^{26}$ −92° (*c* 0·71), $\lambda_{max.}$ 226 mμ (ε 5340) and 314 mμ (ε 122), $\nu_{max.}$ (in CCl_4) 3025 (ethylenic C–H), 1734 (propionate), and 1675 cm.$^{-1}$ (3-en-4a-one) (Found: C, 77·1; H, 9·65. $C_{23}H_{34}O_3$ requires C, 77·1; H, 9·6%).

5β-*Methyl*-A-*homo*-B-*norandrost*-3-*ene*-4a,17-*dione* (IIIb; R = H), obtained by passing the 3β-acetoxy-4a,17-dione (IIb; R = β-OAc) through alumina as described above, separated from hexane or aqueous methanol in fibrous crystals, m. p. 140—142°, $[\alpha]_D^{17}$ −48° (*c* 0·26), $\lambda_{max.}$ 226 mμ (ε 4627) and 302 mμ (ε 160) (Found: C, 80·05; H, 9·55. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%).

Reaction of 3β-*Acetoxy*-5β-*methyl*-A-*homo*-B-*norandrostane*-4a,17-*dione* (IIb; R = β-OAc) *with Methylmagnesium Iodide*.—The Grignard reagent was prepared from magnesium (5 g.) and methyl iodide (13 ml.) in dibutyl ether (100 ml.). A solution of the 3β-acetoxy-4a,17-diketone (5 g.) in anhydrous tetrahydrofuran (100 ml.) was added, and the mixture was stirred under reflux for 6 hr., cooled, and decomposed in aqueous ammonium chloride containing crushed ice. The product was extracted with the addition of ethyl acetate, and the organic layer was washed and concentrated under reduced pressure to remove tetrahydrofuran and ethyl acetate. The product separated from the residual dibutyl ether on cooling and was purified from ethyl acetate, to give 4aξ,5β,17α-*trimethyl*-A-*homo*-B-*norandrostane*-3β,4aξ,17β-*triol* as prisms, m. p. 231—234°, $[\alpha]_D^{28}$ −38° (*c* 0·89), $\nu_{max.}$ (in Nujol) 3576 and 3406 cm.$^{-1}$ (no C:O absorption) (Found: C, 75·5; H, 10·8. $C_{22}H_{38}O_3$ requires C, 75·4; H, 10·9%).

Treatment of the trihydroxy-compound with acetic anhdride–pyridine at 80—90° for 1 hr. gave the 3-*monoacetate*, which was purified from ethyl acetate to give flakes, m. p. 260—263°, $[\alpha]_D^{25}$ −49° (*c* 0·88), $\nu_{max.}$ (in Nujol) 3454 (associated OH) and 1705 cm.$^{-1}$ (associated OAc) (Found: C, 73·0; H, 9·9. $C_{24}H_{40}O_4$ requires C, 73·4; H, 10·3%).

4aξ,17β-*Dihydroxy*-4aξ,5β,17α-*trimethyl*-A-*homo*-B-*norandrostan*-3-*one* (VIId; R = Me).—The 3,4a,17-trihydroxy-compound (1·7 g.) in " AnalaR " acetone (50 ml.) was oxidised with the chromic acid reagent (see above), and the product purified from ethyl acetate. The 3-*ketone* formed plates, m. p. 200—204°, $[\alpha]_D^{24}$ −50° (*c* 0·53), $\nu_{max.}$ (in Nujol) 3395 (associated OH) and 1670 cm.$^{-1}$ (associated C:O) (Found: C, 75·65; H, 10·4. $C_{22}H_{36}O_3$ requires C, 75·8; H, 10·4%).

17β-*Hydroxy*-4a,5,17α-*trimethyl*-A-*homo*-B-*norandrost*-4(4a)-*en*-3-*one* (VIIId; R = Me).—The foregoing 3-ketone (1 g.) in methanol (20 ml.) and concentrated hydrochloric acid (1 ml.) was heated under reflux for 10 min.; then water was added and the product isolated with ether and purified from acetone–hexane. 17β-*Hydroxy*-4a,5β,17α-*trimethyl*-A-*homo*-B-*norandrost*-4-(4a)-*en*-3-*one* was obtained as prisms, m. p. 170—172°, $[\alpha]_D^{26}$ −180° (*c* 0·23), $\lambda_{max.}$ 246 mμ (ε 7830), $\nu_{max.}$ (in CCl_4) 3613 (OH), 1663 and 1610 ($\Delta^{4(4a)}$-3-ketone), and 1411 cm.$^{-1}$ ($CO{\cdot}CH_2$) (Found: C, 80·0; H, 10·3. $C_{22}H_{34}O_2$ requires C, 79·95; H, 10·4%).

The authors thank the Directors of The British Drug Houses Ltd. for permission to publish this work.

THE BRITISH DRUG HOUSES LTD.,
GRAHAM STREET, LONDON, N.1.

[*Received, May 5th,* 1960.]