667. *Compounds Related to the Steroid Hormones. Part I. The Preparation and Reactions of Some* 11-*Methyl-steroids.*

By J. Elks.

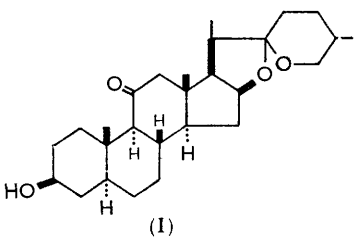
The preparation of some 11β-hydroxy-11α-methyl-steroids by the action of methyl-lithium on the corresponding 11-ketones is described. Some dihydroxy-11-ketones failed to undergo the reaction.

3β-Acetoxy-11α-methyl-5α,25D-spirostan-11β-ol is dehydrated by perchloric acid–acetic acid to a mixture of the 11-methylene- and 11-methyl-$\Delta^{9(11)}$-compounds; only the latter results from the action of thionyl chloride–pyridine on the 11α-methyl-11β-hydroxy-compound. The two olefins are interconvertible under acid conditions, the exocyclic olefin being the more stable.

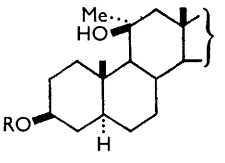
Both olefins can be hydrogenated to a compound formulated as 11β-methyltigogenin acetate.

Several recent papers [1] have described the reaction of 11-oxo-steroids with methyl-lithium and with methylmagnesium halides, to give the 11β-hydroxy-11α-methyl compounds. We now report some similar observations and the results of some dehydration experiments.

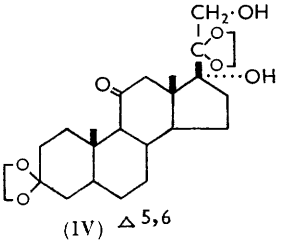
11-Oxotigogenin (I), with methyl-lithium in ether–dioxan, ether–benzene, or ether–tetrahydrofuran, gave in high yield a single compound, formulated as 11α-methyl-5α,25D-spirostan-3β,11β-diol (II; R = H). This configuration is assigned to the 11-substituents on the assumption that methyl-lithium, like lithium aluminium hydride,[2a] will attack this carbon atom from the less hindered α-side; at $C_{(17)}$, where a somewhat similar steric situation prevails, both reagents are known to behave in this way.[2b,3] Some additional evidence for formula (II) comes from dehydration and is presented below.



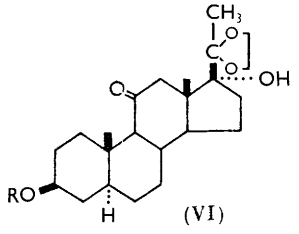
(I)



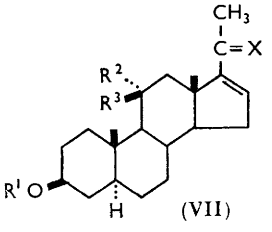
sidechain
(II) 25D-spirostan
(III) ergost-22-ene



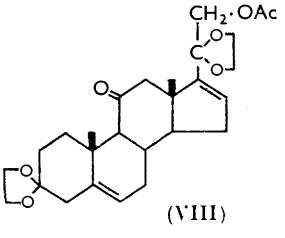
(IV) Δ 5,6
(V) 5α-H



(VI)



(VII)



(VIII)

An attempt to replace methyl-lithium by methylmagnesium iodide in the preparation of the diol (II) was unsuccessful, the starting ketone being recovered; this may be

[1] (*a*) Ringold, Batres, and Zderic, *Tetrahedron*, 1958, **2**, 164; (*b*) Fonken and Hogg, *ibid.*, p. 365; (*c*) Wendler, Graber, and Hazen, *ibid.*, 1958, **3**, 144; (*d*) Fonken, *J. Org. Chem.*, 1958, **23**, 1075; (*e*) Fonken, Hogg, and McIntosh, *ibid.*, 1959, **24**, 1600.

[2] Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publ. Inc., New York, 1956, pp. (*a*) 250, 254; (*b*) 257—268.

[3] Kharasch and Reinmuth, "Grignard Reactions of Nonmetallic Substances," Constable, London, 1954, p. 511; Greenhalgh, Henbest, and Jones, *J.*, 1951, 1190.

attributable to the greater liability of the Grignard reagent to steric hindrance.[4] Simple androstan-11-one derivatives have been reported to be reactive to Grignard reagents, but even then yields seem to be poor.[1a,b,c]

3β-Hydroxy-5α-ergost-22-en-11-one reacted similarly with methyl-lithium, to give the methylcarbinol (III), but when, in the hope of obtaining 11α-methyl derivatives of hydrocortisone and related compounds, the 3,20-bis(ethylene ketals) (IV and V, respectively) of cortisone and 4,5α-dihydrocortisone were treated with the reagent, the 11-oxo-groups were almost wholly unaffected, even under much more vigorous conditions than were required with compound (I). The possibility that the 21-hydroxy-group was responsible for these failures [cf.1b,1e] was excluded by the observation that 3β,17α-dihydroxy-5α-pregnane-11,20-dione 20-ethylene ketal (VI; R = H) was similarly unreactive to methyl-lithium. However, 3β-hydroxy-5α-pregn-16-ene-11,20-dione 20-ethylene ketal (VII; R^1 = H, R^2R^3 = :O, X = ·O·CH_2·CH_2·O·) [conveniently prepared by dehydration of the 17α-hydroxy-20-ketal (VI; R = Ac) with thionyl chloride [5] and subsequent alkaline hydrolysis] reacted normally with methyl-lithium to give the 11β-hydroxy-11α-methyl-compound (VII; R^1 = H, R^2 = Me, R^3 = OH, X = O·CH_2·CH_2·O·), which was converted by deketalisation and acetylation into 3β-acetoxy-11β-hydroxy-11α-methyl-5α-pregn-16-en-20-one (VII; R^1 = Ac, R^2 = Me, R^3 = OH, X = :O). Again, 21-acetoxypregna-5,16-diene-3,11,20-trione 3,20-bis(ethylene ketal) (VIII) underwent the reaction, as judged by the infrared spectrum of the crude product, although a pure compound was not isolated in this instance.

It is not clear whether the failure of compounds (IV), (V), and (VI) to undergo reaction is related specifically to the presence, in them, of the 17α-hydroxy-group or rather to the fact that, unlike the reactive compounds, they each have two hydroxy(or acetoxy)-groups. Both the Syntex [1a] and the Upjohn [1e] workers have reported that certain 11-ketones fail to react with methyl-lithium: the latter group have related this to ease of enolisation of the 11-oxo-group, but the structural factors involved remain undefined.

The stability of the 11α-methyl-11β-alcohols seemed to us of some interest, and a study of 3β-acetoxy-11α-methyl-5α,25D-spirostan-11β-ol (II; R = Ac) was accordingly undertaken. This was stable to acetic acid even at 100°,* but addition of a trace of perchloric acid caused dehydration, rapid at 100°, slow at room temperature, with formation of 11-methylenetigogenin acetate (IX) as major product. This dehydration is described in greater detail below.

The presence of an exocyclic methylene group was shown by infrared bands at 3100, 1640, and 898 $cm.^{-1}$ and by the formation of formaldehyde on ozonolysis. Proof that there had been no re-arrangement of the carbon skeleton came from the conversion of the product (IX) into 11-oxotigogenin acetate (X) by the successive action of osmium tetroxide and periodic acid.

Catalytic hydrogenation of the 11-methylene compound with Adams catalyst in ethyl acetate–acetic acid gave a compound that we formulate as 11β-methyltigogenin acetate (XI) on the grounds (*a*) of analogy with catalytic hydrogenation of 11-oxo-steroids, which leads, by rear-side attack, to 11β-hydroxy-compounds,[6] and (*b*) that the same compound is obtained by catalytic hydrogenation of the 11-methyl-$\Delta^{9(11)}$-compound (XII) (see below). *cis*-Hydrogenation of the double bond being assumed, the compound must then be 11β-methyltigogenin acetate (XI) or 11α-methyl-9β-tigogenin acetate. The

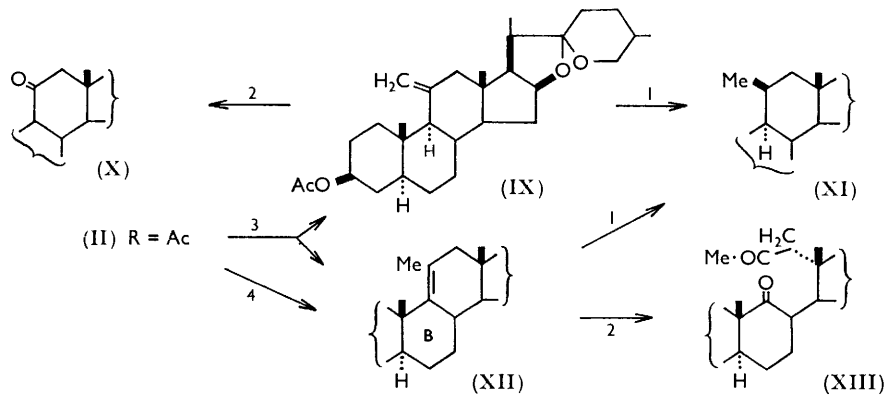
* Beyler, Hoffman, and Sarett (*J. Amer. Chem. Soc.*, 1960, **82**, 178) reported that some dehydration occurs during regeneration of 11α-methylhydrocortisone from its 17,20:20,21-bismethylenedioxy-derivative by prolonged treatment with 50% acetic acid at 100°. They tentatively ascribe the 11-methyl-$\Delta^{9(11)}$-structure to the product, apparently by analogy with the course of acid-catalysed dehydration of secondary 11β-alcohols.

[4] Newman, " Steric Effects in Organic Chemistry," Wiley, New York, 1956, p. 396.
[5] Allen and Bernstein, *J. Amer. Chem. Soc.*, 1955, **77**, 1028.
[6] Reichstein and his co-workers, *Helv. Chim. Acta*, 1943, **26**, 586, 598; 1944, **27**, 821; 1945, **28**, 1420; 1947, **30**, 205. Herzog, Jevnik, and Hershberg, *J. Amer. Chem. Soc.*, 1953, **75**, 269.

latter is excluded by the formation of the compound from the 11-methylene-9α-compound (IX).

A Catalin model of 11β-methyltigogenin acetate (XI) suggests a remarkable degree of crowding of the 11-methyl by the angular methyl groups. An unusual splitting of the CH_3 band (1388 and 1378 cm.$^{-1}$) in the infrared spectrum of this compound may perhaps be a consequence of this.

At room temperature, 3β-acetoxy-11α-methyl-5α,25D-spirostan-11β-ol (II; R = Ac) was stable to phosphorus oxychloride in pyridine, even in the presence of a trace of phosphoric acid,[7] but it was rapidly dehydrated by thionyl chloride in pyridine to an olefin isomeric with compound (IX). Hydrogenation of this compound was slow, and reduction of the double bond was accompanied by some reduction of the sapogenin side-chain; however, conditions were found under which a modest yield of 11β-methyltigogenin acetate (XI) could be isolated. Hence, the olefin is a 3β-acetoxy-11-methyl-5α,25D-spirosten, and, since the product of successive treatment with osmium tetroxide, alkali, and periodic acid showed ketone bands at 1720 and 1703 cm.$^{-1}$ consistent with the diketone (XIII), but no aldehyde bands, the double bond can be placed with some confidence at position 9,11 as in (XII), rather than at 11,12.



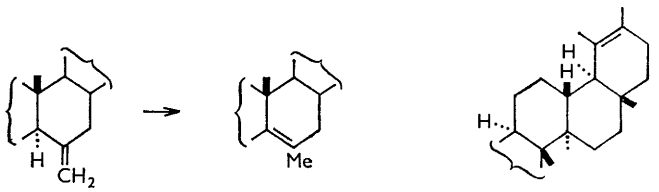
Reagents: 1, H_2–Pt; 2, OsO_4, then HIO_4; 3, $HClO_4$; 4, $SOCl_2$–pyridine.

To return to the perchloric acid-catalysed dehydration of the methylcarbinol (II; R = Ac), examination, by infrared spectroscopy and rotation, of samples withdrawn at intervals, suggested that the first-formed olefin mixture consisted of the exocyclic olefin (IX) and the endocyclic olefin (XII) in the ratio *ca.* 1 : 1, but that this ratio changed during several hours at room temperature to 4 : 1. This somewhat unexpected observation was confirmed by experiments in which the pure olefins (IX) and (XII) were subjected at room temperature to the action of (*a*) perchloric acid–acetic acid, (*b*) hydrogen chloride in chloroform, or (*c*) formic acid–benzene. In each instance there resulted an equilibrium mixture, containing 75—80% of the exocyclic methylene compound (IX). (Prolonged treatment with perchloric acid at 100° led to the gradual disappearance of the exocyclic methylene band from the infrared spectrum: this may have been due to a more deep-seated re-arrangement, but it was accompanied by destruction of the sapogenin side-chain, and therefore no attempt was made to isolate a pure product.)

The stability of the exocyclic olefin (IX) relative to that of the endocyclic olefin (XII) is at first sight surprising, since the reverse is true of monocyclic cyclohexane derivatives,[8] as also of 3-methylene-5α-cholestanes in relation to 3-methyl-5α-cholestenes.[9] Further,

[7] Elks, Phillipps, and Wall, *J.*, 1958, 4001.
[8] Brown, Brewster, and Shechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467; Turner and Garner, *ibid.*, 1958, **80**, 1424; Cope, Ambros, Ciganek, Howell, and Jacura, *ibid.*, 1959, **81**, 3153.
[9] Beton, Halsall, Jones, and Phillips, *J.*, 1957, 753.

a recent paper [10] has described the isomerisation, by acid, of a 6-methylene-5α-steroid (XIV) to the 6-methyl-Δ^5-isomer (XV). The immediate environment of the olefinic system in compounds (XIV) and (XV) is closely similar to that in (IX) and (XII), yet the former pair, unlike the latter, behaves normally in that the endocyclic olefin is the more stable. Part, at least, of the explanation of this difference may lie in the strong



(XIV) (XV) (XVI)

interaction between the 11-methyl group and the $C_{(1)}$-methylene group in the endocyclic olefin (XII): a similar explanation has been given for the instability of the system (XVI) in pentacyclic triterpene derivatives.[9]

In 1-methylcyclohexanol derivatives of fixed conformation, the direction of elimination of the hydroxyl group with phosphorus oxychloride–pyridine depends upon its configuration: an axial hydroxyl group is eliminated exclusively with an axial hydrogen attached to a neighbouring ring carbon atom, to give the endocyclic olefin. On the other hand, equatorial hydroxy-groups cannot achieve the necessary co-planarity with the other reacting centres to yield the endocyclic compound, and they are instead eliminated with a methyl-hydrogen atom, to give the methylene compound.[9,11,12] The endocyclic olefin (XII) is formed by the action of thionyl chloride–pyridine on our 11-hydroxy-11-methyl-compound; if thionyl chloride can be equated with phosphorus oxychloride in this context, the reaction can be taken as support for the structure (II), with its axial 11β-hydroxy-group.

Experimental

M. p.s were measured on a Kofler block. Unless otherwise stated, chloroform was used as solvent for rotation measurements, and ethanol for ultraviolet spectra. Infrared spectra were recorded on a Perkin–Elmer Model 21 spectrophotometer with rock-salt optics.

3β-*Acetoxy*-11α-*methyl*-5α,25D-*spirostan*-11β-*ol* (II; R = Ac).—(a) *Preparation in ether–dioxan.* Methyl-lithium was prepared from lithium (0·84 g., 0·12 g.-atom) in ether (80 ml.) with methyl iodide (8·52 g., 0·06 mole) in ether (60 ml.).[13] This and all other operations with methyl-lithium were carried out under nitrogen. A solution of 11-oxotigogenin (4·30 g., 0·01 mole) in pure dry dioxan (200 ml.) was added, with stirring, during 5—10 min.; a white solid separated during the addition. Ether was distilled off until the internal temperature reached 63°, and the mixture was kept at 60—65° and stirred for a further 5 hr. After being left overnight at room temperature, the mixture was treated cautiously with water and then, after the unchanged lithium had dissolved, with a large volume of water. The precipitated solid (4·41 g.) was filtered off, washed with water, and dried; its infrared spectrum showed that it contained only a trace of ketonic material. Crystallisation from aqueous ethanol gave 11α-*methyl*-5α,25D-*spirostan*-3β,11β-*diol* (II; R = H) as fine needles, m. p. 218—221°. For analysis it was dried at 100°/0·05 mm. (Found: C, 75·7; H, 10·3. $C_{28}H_{46}O_4$ requires C, 75·3; H, 10·4%). It had $[\alpha]_D$ −58° (*c* 0·86), $\nu_{max.}$ (in Nujol) 3620 and 3440 (OH), 980, 920, and 896 cm.$^{-1}$ (25D-spirostan).

The crude diol (4·4 g.) was acetylated by treatment overnight at room temperature with pyridine (25 ml.) and acetic anhydride (25 ml.). The mixture, which contained crystals, was poured on ice and the solid was filtered off, washed with water, and dried. Crystallisation from acetone gave 3β-*acetoxy*-11α-*methyl*-5α,25D-*spirostan*-11β-*ol* (II; R = Ac) as an acetone solvate

[10] Beal, Rebenstorf, and Pike, *J. Amer. Chem. Soc.*, 1959, **81**, 1231.
[11] Barton, Campos-Neves, and Cookson, *J.*, 1956, 3500.
[12] Clinton, Christiansen, Neumann, and Laskowski, *J. Amer. Chem. Soc.*, 1958, **80**, 3389; Corey and Sauers, *ibid.*, 1957, **79**, 3925.
[13] Gilman, Zoellner and Selby, *J. Amer. Chem. Soc.*, 1933, **55**, 1252.

(3·67 g.), which lost solvent at *ca.* 140° and melted at 201°. A second crop (0·87 g., total yield, 83%) had similar properties; the analytical specimen of the solvate, m. p. 197—200° after loss of solvent at 140°, was dried *in vacuo* over silica gel (Found: C, 72·35; H, 9·8. $C_{30}H_{48}O_5,C_3H_6O$ requires C, 72·5; H, 10·0%) and had $\nu_{max.}$ (in CS_2) 3620 (OH), 1734 and 1240 (OAc), 1720, 1360, and 1214 (acetone), 980, 920, and 898 cm.$^{-1}$ (25D-spirostan). In CCl_4 the band at 1380 cm.$^{-1}$ was enhanced, consonantly with the presence of a new methyl group.

The solvate was unchanged after being heated at 100°/0·05 mm. for 90 minutes, but it lost its solvent at 130—140°/0·05 mm. in 4 hr. It then melted at 197—200° without preliminary change and had $[\alpha]_D$ −61° (*c* 0·83) (Found: C, 73·9; H, 9·7. $C_{30}H_{48}O_5$ requires C, 73·7; H, 9·9%).

(b) *Preparation in ether–benzene.* Methyl-lithium was prepared from lithium (3·1 g., 0·44 g.-atom) and methyl iodide (28·4 g., 0·2 mole) in ether (150 ml.). 11-Oxotigogenin (21·5 g., 0·05 mole) in benzene (550 ml.) was added and the mixture was stirred and boiled under reflux for 5 hr., left overnight at room temperature, and treated with water. Addition of ethyl acetate gave a clear upper layer, which was separated, washed with very dilute hydrochloric acid and water, and dried. The solution was evaporated to dryness and the residue was acetylated as in (a) and crystallised from acetone. The desolvated product (18·5 g., 76%) melted at 196—198°.

(c) *Preparation in ether–tetrahydrofuran.* Methyl-lithium was prepared from lithium (0·14 g., 0·02 g.-atom) in ether (15 ml.) with methyl iodide (1·42 g., 0·01 mole) in ether (10 ml.). A solution of 11-oxotigogenin (0·86 g., 0·002 mole) in tetrahydrofuran (freshly distilled from phenylmagnesium bromide; 50 ml.) was added and the mixture was stirred and boiled under reflux for 5 hr. The solution remained clear, apart from the separation of a little gelatinous material; the internal temperature rose gradually from 54° to 70°. After being left overnight at room temperature, the mixture was worked up as in (a), to give 0·89 g. of crude diol. Acetylation and crystallisation from acetone gave the monoacetate acetone solvate (0·77 g., 70·5%).

3β-*Acetoxy*-11α-*methylergost*-22-*en*-11β-*ol* (III; R = Ac).—3β-Hydroxyergost-22-en-11-one (0·41 g., 0·001 mole) in benzene (50 ml.) was added to a 0·95N-solution of methyl-lithium in ether (6 ml.), and the mixture was stirred and refluxed for 5 hr. The mixture was left overnight at room temperature and was then worked up in the usual way. The crude product was a gum, whose infrared spectrum showed the absence of ketone. Acetylation overnight at room temperature with acetic anhydride (3 ml.) and pyridine (3 ml.), and isolation with ether, gave a solid, m. p. 174—189°, which was crystallised from ethanol to give 3β-*acetoxy*-11α-*methylergost*-22-*en*-11β-*ol* as prisms, m. p. 195—201°, which effloresced on being dried at 120°/0·1 mm. for 4 hr. (Found: C, 78·9; H, 10·9. $C_{31}H_{52}O_3$ requires C, 78·8; H, 11·1%), and had $[\alpha]_D$ −15·1° (*c* 1·1), $\nu_{max.}$ (in CS_2) 3620 (OH), 1734 and 1242 (OAc) and 970 cm.$^{-1}$ (*trans*-·CH=CH·).

3β-*Hydroxy*-5α-*pregn*-16-*ene*-11,20-*dione* 20-*Ethylene Ketal* (VII; R^1 = H, R^2R^3 = :O, X = ·O·CH_2·CH_2·O·).—3β-Acetoxy-17α-hydroxy-5α-pregnane-11,20-dione 20-ethylene ketal[7] (5·05 g.) in pyridine (100 ml.) was cooled to −20° and treated with thionyl chloride (20 ml.), added gradually with swirling. The mixture was allowed to come to 0° and then left overnight in the refrigerator. The dark liquid was poured on ice and an excess of 2N-sodium hydroxide. The mixture was extracted with ether, and the extract was washed with water, dried, and evaporated. The residue was boiled under reflux for 1 hr. with sodium hydroxide (5 g.) in water (5 ml.) and methanol (150 ml.). Most of the solvent was distilled off and the residue was diluted with water. The precipitated solid crystallised from aqueous methanol containing a trace of sodium hydroxide to give the ketal (2·96 g.), as a solvate, m. p. *ca.* 100°, then, after resolidification, 148—154°. Crystallisation from aqueous acetone gave material with m. p. 113—115° and 154—156°. After being dried at 130°/0·05 mm. for 6 hr., the compound had m. p. 154—155°, $[\alpha]_D$ +50° (*c* 0·87).

This substance has previously been reported as having m. p. 112—115° for the solvate and m. p. 150—155° for the anhydrous material.[7]

Reaction of 3β-*Hydroxy*-5α-*pregn*-16-*ene*-11,20-*dione* 20-*Ethylene Ketal with Methyl-lithium.*—Methyl-lithium was prepared from lithium (0·14 g., 0·02 g.-atom) in ether (10 ml.) with methyl iodide (1·42 g., 0·01 mole) in ether (10 ml.). A solution of the steroid (0·37 g., 0·001 mole) in benzene (40 ml.) was added and the cloudy mixture was stirred and refluxed for 5 hr. (internal temperature 70°) and then left at room temperature overnight. The usual isolation procedure gave a white froth (0·44 g.) whose infrared spectrum showed only traces of ketone.

The product was refluxed with methanol (20 ml.), acetic acid (5 ml.), and water (5 ml.) for

1 hr. Most of the solvent was removed *in vacuo* and the product was isolated with ether. The crude residue was treated overnight at room temperature with acetic anhydride (3 ml.) and pyridine (3 ml.), and the acetate (0·29 g.) was isolated with ether. Crystallisation from aqueous methanol gave 3β-*acetoxy*-11β-*hydroxy*-11α-*methyl*-5α-*pregn*-16-*en*-20-*one* (VII; R^1 = Ac, R^2 = Me, R^3 = OH, X = :O) (0·16 g., 42%) as needles, m. p. 189—197°. Further crystallisation from methanol gave cubes, m. p. 197·5—201°, $[\alpha]_D$ +38·6° (*c* 1·04) (Found: C, 73·85; H, 9·4. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%), $\lambda_{max.}$ 239 mμ (ε 8800), $\nu_{max.}$ (in CS_2) 3620 (OH), 1732 and 1242 (OAc), 1668 and 820 cm.$^{-1}$ (conjugated C=O).

When the proportion of methyl-lithium was increased by 50%, and the reaction time was extended to 6 hr. the product of this reaction, crystallised from aqueous methanol containing a trace of sodium hydroxide, gave 3β,11β-*dihydroxy*-11α-*methyl*-5α-*pregn*-16-*en*-20-*one ethylene ketal* (VII; R^1 = H, R^2 = Me, R^3 = OH, X = ·O·CH_2·CH_2·O·) as needles, m. p. 178—182·5°, in 69% yield. Further crystallisation gave material melting constantly at 186—187°, $[\alpha]_D$ +8° (*c* 0·95) (Found: C, 74·3; H, 9·8. $C_{24}H_{38}O_4$ requires C, 73·8; H, 9·8%), $\nu_{max.}$ (in Nujol) 3400 (OH), 1614 (trisubstituted C=C) and 1195, 1110, and 1048 cm.$^{-1}$ (ketal).

Reaction of 21-*Acetoxypregna*-5,16-*diene*-3,11,20-*trione* 3,20-*Bis*(*ethylene Ketal*) (VIII) *with Methyl-lithium*.—The steroid [5] (0·236 g., 5 × 10^{-4} mole) in benzene (40 ml.) was added to an ethereal solution of methyl-lithium prepared from lithium (0·14 g.) and methyl iodide (1·42 g.) in ether (20 ml.). The mixture was stirred and refluxed for 5 hr. and left overnight at room temperature. The product, worked up in the usual way, was a gum (0·24 g.), whose infrared spectrum indicated about 25% of unchanged 11-ketone. The material was acetylated at room temperature to give a gum, which resisted crystallisation.

11-*Methylenetigogenin Acetate* (IX).—(a) *Dehydration at* 100°. 3β-Acetoxy-11α-methyl-5α,25D-spirostan-11β-ol (2·0 g.) in acetic acid (180 ml.) was heated to *ca.* 100° on the water-bath. A solution of 60% aqueous perchloric acid (1·0 ml.) in acetic acid (20 ml.), also at 100°, was added, the mixture was left on the water-bath for 3 min., then poured into water (*ca.* 1 l.), and the solid was filtered off, washed with water, and dried. Crystallisation from methanol gave the 11-*methylene compound* (1·0 g., 52%) as needles, m. p. 177—180°. A second crop appeared to be a mixture of the 11-methylene compound and the 11-methyl-Δ^9-isomer. Further crystallisation of the first crop from methanol gave needles, m. p. 178·5—181°, $[\alpha]_D$ −66° (*c* 0·69), $[\alpha]_D$ −55° (*c* 1·13 in acetic acid) (Found: C, 76·6; H, 10·0. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%), $\nu_{max.}$ (in CS_2) 3100, 1640, and 898 (=CH_2), 1735 and 1242 (OAc), 980, 920, and 898 cm.$^{-1}$ (25D-spirostan). The intensity of the band at 898 cm.$^{-1}$ was consistent with its being contributed by both the methylene and the spirostan group. The olefin gave a very pale yellow colour with tetranitromethane in chloroform.

(b) *Dehydration at room temperature*. 3β-Acetoxy-11α-methyl-5α,25D-spirostan-11β-ol (2·0 g.) was dissolved in warm acetic acid (200 ml.), the solution was cooled to room temperature, and 60% aqueous perchloric acid (1 ml.) was added. A portion was transferred to a 1 dm. polarimeter tube and readings were taken at intervals, as shown in the Table. After 29 hours, the solution was poured into water and the product was worked up as in (a), to give 1·10 g. (57%) of needles, m. p. 181—184°, $[\alpha]_D$ −67·5° (*c* 1·16).

Time (hr.)	0	0·08	0·17	0·25	0·33	0·58 *	1·08
α	−0·49°	−0·40°	−0·34°	−0·32°	−0·32°	−0·33°	−0·34°
% of (IX) †						57	59
Time (hr.)	2	3·5	5·25	7·75	23	29	
α	−0·36°	−0·38°	−0·39°	−0·42°	−0·45°	−0·45°	
% of (IX) †	63	67·5	70	77·5	84	84	

* Dehydration was complete about this time, according to infrared spectra. † Based on assumption that product was simple mixture of (IX) and (XII) (see below).

Concentration of the mother-liquors gave 0·37 g. of material, m. p. 120—165°. Equilibration of this material with 60% perchloric acid (0·175 ml.) in acetic acid (35 ml.) at room temperature for 24 hr. and subsequent crystallisation gave a further 0·23 g. (12%) of 11-methylenetigogenin acetate, m. p. 180·5—183°.

Ozonolysis of 11-*Methylenetigogenin Acetate* (*With* Dr. P. J. May).—The steroid (196 mg.) in methylene chloride (20 ml.) was treated for 15 min. between −15° and −10°, with ozonised oxygen (0·55 mmol. of ozone per min.). The water (10 ml.) in the outlet trap was added, and after 1 hr., the mixture was slowly distilled into methanol (5 ml.) containing dimedone (123 mg.). The mixture was shaken for 2 days, the organic solvents were boiled off on the water-bath, and

the aqueous residue was cooled to 0°. Formaldehyde dimedone derivative, m. p. 189—190°, was collected in 46·8% yield; a second crop brought the yield to 48·5%.

Conversion of 11-*Methylenetigogenin Acetate into* 11-*Oxotigogenin Acetate.*—A solution of 11-methylenetigogenin acetate (0·5 g.) in dioxan (10 ml.) was treated with osmium tetroxide [14] (0·45 g.) in dioxan (9 ml.) and the mixture was left in the dark at room temperature for 4½ days. Hydrogen sulphide was passed through the mixture until precipitation was complete and the solid was filtered off and washed with dioxan. The combined filtrate and washings were evaporated to small bulk and diluted with water. The precipitated crude 3β-acetoxy-11β-hydroxymethyl-5α,25D-spirostan-11α-ol (0·33 g.) was dried. This material (100 mg.) in dioxan (15 ml.) was treated with periodic acid (125 mg.) in water (1 ml.). The solution was left at room temperature for 48 hr., then diluted with water and extracted with ether. The extract was washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated. The residue, in 1 : 1 hexane–benzene, was chromatographed on alumina (B.D.H. Brockmann I; 5 g.). Benzene and 19 : 1 benzene–ether eluted crystalline fractions which, on crystallisation from aqueous methanol and then from hexane, gave 11-oxotigogenin acetate (16·5 mg.) as needles, m. p. 221—223°, $[\alpha]_D$ −39·1° (*c* 0·82), identified by mixed m. p. and infrared spectra.

Hydrogenation of 11-*Methylenetigogenin Acetate.*—Adams catalyst (50 mg.) in ethyl acetate (10 ml.) was reduced in hydrogen at room temperature and pressure. A solution of 11-methylenetigogenin acetate (0·47 g.) in ethyl acetate (30 ml.) and acetic acid (5 ml.) was added and the mixture was shaken in hydrogen. Uptake was complete in *ca.* 80 min. The catalyst was filtered off and the filtrate was evaporated to dryness. Crystallisation of the residue from ethanol gave 11β-*methyltigogenin acetate* (XI) as needles (0·34 g., 72%), m. p. 187—190°. After further crystallisation from ethanol, the compound had m. p. 193—195°, $[\alpha]_D$ −64° (*c* 0·79) (Found: C, 76·3; H, 10·3. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·2%), $\nu_{max.}$ (in CS_2) 1734 and 1240 (OAc), 980, 920, and 898 cm.$^{-1}$ (25D-spirostan). In CCl_4 there were also bands at 1388, 1378, and 1367 cm.$^{-1}$.

With palladised charcoal or Adams catalyst in pure ethyl acetate, the hydrogenation was slow and incomplete.

3β-*Acetoxy*-11-*methyl*-5α,25D-*spirost*-9(11)-*en* (XII).—A solution of 3β-acetoxy-11α-methyl-5α,25D-spirostan-11β-ol (3·6 g.) in pyridine (180 ml.) was cooled to −20° and treated gradually with thionyl chloride (3·6 ml.). The solution was allowed to come to 0°, then left at this temperature for 75 min. The dark solution was poured into water (1800 ml.) and the solid was filtered off, washed with water, dried, and crystallised from methanol. After being dried at 100°/0·1 mm. the 11-*methyl*-Δ^9-*compound* (2·58 g., 74%) had m. p. 140—143°. The compound behaved erratically on crystallisation, probably owing to polymorphism: the m. p. alternated between *ca.* 142° and 147°, and the crystal form between prisms and needles, although there was no apparent correspondence between crystal form and m. p. The crystals were solvated and melted partly at *ca.* 80° before losing solvent, resolidifying and remelting at the higher temperature. An analytical specimen, dried at 100—110°/0·05 mm., melted almost completely at 141—142°, a few crystals remaining to 147°; it had $[\alpha]_D$ −11° (*c* 0·93), −6° (*c* 0·92 in acetic acid) (Found: C, 76·7; H, 9·8. $C_{30}H_{46}O_4$ requires C, 76·55; H, 9·85%), $\nu_{max.}$ (in CS_2) 1735 and 1242 (OAc), 980, 920, and 898 cm.$^{-1}$ (25D-spirostan). It gave a strong yellow-brown colour with tetranitromethane in chloroform.

Hydrogenation of 3β-*Acetoxy*-11-*methyl*-5α,25D-*spirost*-9(11)-*en.*—Adams catalyst (300 mg.) in ethyl acetate (15 ml.) and acetic acid (15 ml.) was reduced in hydrogen. The steroid (0·705 g.) in ethyl acetate (22·5 ml.) and acetic acid (22·5 ml.) was added and the hydrogenation was continued. After 55 min., 54·8 ml. of hydrogen had been taken up (calc. for 1 mol.: 36·6 ml.) and reduction had become slow. The catalyst was filtered off, the filtrate was evaporated to dryness, and the residue was chromatographed in 1 : 1 hexane–benzene on alumina (neutral; Brockmann Grade I; 20 g.). Hexane–benzene (1 : 1) and benzene eluted 410 mg. of material which was crystallised from methanol to give 11β-methyltigogenin acetate (XI) as needles (300 mg., 43%), m. p. 184—186°. Further crystallisation from ethanol gave material with m. p. 192—195·5°, $[\alpha]_D$ −63° (*c* 1·01), identified by mixed m. p. and infrared spectrum with material prepared as described above.

In another experiment, the hydrogenation was taken slightly further (20·3 ml. uptake; calc. 12·1 ml.). Chromatography gave, in addition to 11β-methyltigogenin acetate, a fraction

[14] Barton and Elad, *J.*, 1956, 2085.

eluted by benzene–ether, which was not crystalline but whose infrared spectrum suggested that it was probably essentially dihydro-11β-methyltigogenin 3-acetate.

Treatment of 3β-*Acetoxy*-11-*methyl*-5α,25D-*spirost*-9(11)-*en successively with Osmium Tetroxide and Periodic Acid.*—The steroid (0·5 g.) was treated with osmium tetroxide (0·5 g.) in dioxan as described above for the 11-methylene isomer. The crude 3β-acetoxy-11β-methyl-5α,25D-spirostan-9α,11α-diol (0·14 g.), isolated with methylene chloride, was a gum. This crude material was refluxed for 2 hr. with 40% aqueous sodium hydroxide (1 ml.) and ethanol (10 ml.). The crude triol, isolated with ether, was dissolved in dioxan (15 ml.) and treated with periodic acid (125 mg.) in water (1 ml.) After 2 days, the product was isolated with ether as a gum (129 mg.). The infrared spectrum in carbon disulphide showed bands at 3620 (OH) and at 1720 and 1703 cm.$^{-1}$ (ketone). There was no indication of an aldehyde band, but a weak band at 1356 cm.$^{-1}$ may have been associated with a methyl ketone grouping.

Acid-catalysed Equilibrium between 11-*Methylenetigogenin Acetate* (IX) *and* 3β-*Acetoxy*-11-*methyl*-5α,25D-*spirost*-9(11)-*en* (XII).—(a) *With hydrogen chloride in chloroform.* The steroid (100 mg.) was dissolved in chloroform (10 ml.) and a slow stream of dry hydrogen chloride was passed in for 6 hr. The solution was left for a further 16 hr. and then washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated to dryness. The infrared spectra of the products from both of the isomers were similar and indicated the presence of *ca.* 80% of exocyclic methylene.

Reacetylation of the mixture originating from the 11-methyl-Δ^9-compound with acetic anhydride–pyridine at room temperature, and crystallisation from methanol, gave the pure 11-methylenetigogenin acetate, m. p. 181—183°, $[\alpha]_D$ −67° (*c* 1·16).

(b) *With formic acid.* The steroid (100 mg.) in benzene (6 ml.) was shaken with 98—100% formic acid (10 ml.) for 7 days. Water was added, the benzene layer was separated, the aqueous layer was extracted with benzene, and the combined benzene solutions were washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated. The products from the two materials were virtually identical in infrared spectra and in rotation ($[\alpha]_D$ −52·5° and −54°), both indicating the presence of *ca.* 75% exocyclic methylene compound.

Crystallisation of the product from the 11-methyl-Δ^9-isomer gave the pure 11-methyl-enetigogenin acetate, m. p. 180—181·5°.

(c) *With perchloric acid.* 3β-Acetoxy-11-methyl-5α,25D-spirost-9(11)-en (100 mg.) in acetic acid (10 ml.) was treated with 60% perchloric acid (0·05 ml.). The specific rotation dropped from −6° to −46° (equiv. to 81·5% of 11-methylenetigogenin acetate) within 21·5 hr. The solution was poured into water, and the precipitated solid was crystallised from methanol, to give 11-methylenetigogenin acetate (44% yield), m. p. 179—182°.

The author is indebted to Dr. J. E. Page for interpreting the infrared spectra.

GLAXO LABORATORIES LTD., GREENFORD, MIDDLESEX. [*Received, February 22nd,* 1960.]