836. *Studies in the Synthesis of Cortisone. Part XVI.** *A New Method of Preparing* 11-*Oxotigogenin.*†

By J. H. Chapman, J. Elks, G. H. Phillipps, and L. J. Wyman.

Attempts to prepare 11-oxotigogenin by the action of zinc upon 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one ‡ or its carboxylic or sulphonic esters failed. However, the esters were readily reduced to the required ketone by alkali or alkaline-earth metals in liquid ammonia, particularly good results attending the use of calcium. Under the same conditions, reduction of the unesterified ketol yields 5α : 25*D*-spirostan-3β : 11α : 12β-triol.

The behaviour of 3β : 12α-dihydroxy-5α : 25*D*-spirostan-11-one and its diacetate towards these reducing agents parallels, for the most part, that of the 12β-epimers.

The method that has been used in the bile-acid series to convert a 12β-hydroxy-11-ketone into the 11-ketone itself, namely, replacement of the hydroxyl group by bromine and

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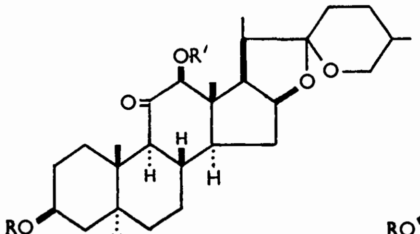
* Part XV, preceding paper.

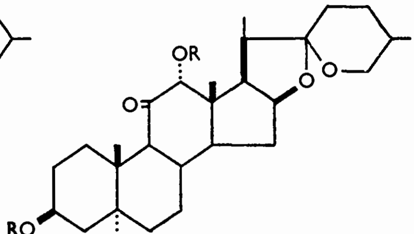
† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

‡ See footnote † on p. 4330.

subsequent debromination,[1,2] is inapplicable to the spirostan series because of the instability of the spiroketal side-chain to acid reagents (see preceding paper). Mueller *et al.*[3] attempted, without success, to reduce 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one (I; R = R′ = H)



(I)



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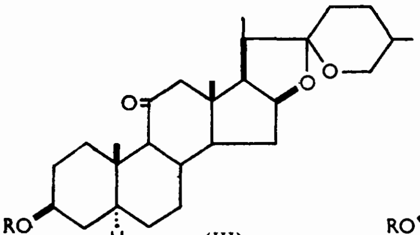

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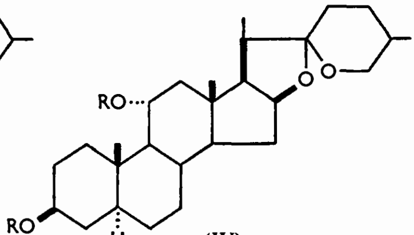

(IV)

with sodium amalgam; moreover, both the free ketol and its diacetate were resistant to the action of zinc. Rosenfeld and Gallagher[4] recently reported that in the 11 : 12-ketols of the cholanic acid series the axial 11β- and 12α-acetoxy-groups can be removed by prolonged treatment with zinc and acetic acid; the equatorial 11α- and 12β-acetoxy-groups were much more resistant, though not wholly inert. In a number of experiments with 3β : 12β- (I; R = R′ = Ac) and 3β : 12α-diacetoxy-5α : 25*D*-spirostan-11-one (II; R = Ac) and the corresponding free alcohols (I; R = R′ = H) and (II; R = H), we obtained no evidence that zinc was causing removal of the substituent from $C_{(12)}$ to a significant degree. With very drastic conditions (100 parts of zinc in boiling acetic acid for 24 hours), the diacetates underwent some reaction, probably the desired one, as indicated by the infrared spectra of the crude products, but even then 50% or more of the ketol derivative remained.

The readiness of sulphonic esters to undergo fission of the C–O bond has suggested their use in this problem. However, in both the cholanic acid[1] and the spirostan series[3,5] a 12β-methanesulphonyloxy- or 12β-toluene-*p*-sulphonyloxy-group proved extraordinarily resistant both to replacement by iodine and to reductive removal. We attempted to reduce 3β-acetoxy-12β-methanesulphonyloxy-5α : 25*D*-spirostan-11-one (I; R = Ac, R′ = $Me{\cdot}SO_2$) with zinc, zinc–copper, or zinc–copper–nickel, with chromous chloride, and with hydriodic acid, but the ketol derivative was unaffected by any of them. In agreement with the work of Djerassi *et al.*[5] on the corresponding toluene-*p*-sulphonate, the methanesulphonate was reduced by lithium aluminium hydride to 5α : 25*D*-spirostan-3β : 11β : 12β-triol, the S–O bond rather than the $C_{(12)}$–O bond having been split. A slow reaction occurred between the methanesulphonate and lithium chloride in boiling dimethylformamide, but the yield of crystalline product was too low to permit identification.

3β : 12β-Diacetoxy-5α : 25*D*-spirostan-11-one (I; R = R′ = Ac) was finally converted into 11-oxotigogenin (III; R = H) by means of metal and liquid ammonia systems. This

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[1] Borgstrom and Gallagher, *J. Biol. Chem.*, 1949, **177**, 951.

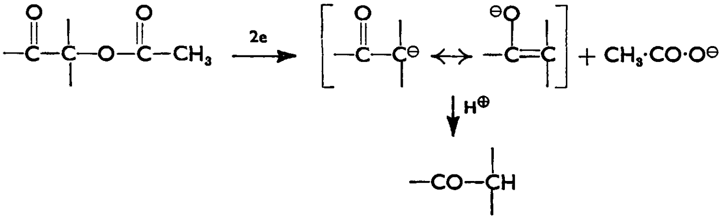
[2] Hershberg, Herzog, Coan, Weber, and Jevnik, *J. Amer. Chem. Soc.*, 1952, **74**, 2585.

[3] Mueller, Norton, Stobaugh, Lin Tsai, and Winniford, *ibid.*, 1953, **75**, 4892.

[4] Rosenfeld and Gallagher, *ibid.*, 1955, **77**, 4367.

[5] Djerassi, Ringold, and Rosenkranz, *ibid.*, 1954, **76**, 5533.

reduction of an α-acetoxy-ketone may, by analogy with the fission of allyl and benzyl alcohols and their derivatives, be represented as follows: [6]



In the absence of a source of protons, the initially formed carbanion will be protected by its negative charge from further attack by the metal. However, a proton source of sufficient strength will discharge the carbanion, and the resulting neutral ketone molecule will then be liable to further reduction by excess of metal.[7] We attempted to avoid such over-reduction by adding a solution of the ketol diacetate (I; R = R′ = Ac) in tetrahydrofuran to one of lithium in liquid ammonia until the disappearance of the blue colour indicated that the metal had all been used; at this stage ammonium chloride or an alcohol was added to liberate the neutral steroid. The products of such experiments, after hydrolysis of the 3-acetoxy-group had been completed by means of alkali, were always mixtures, which were shown by paper chromatography to contain 11-oxotigogenin (III; R = H), 11α-hydroxytigogenin (IV; R = H), and, in some instances, the ketol (I; R = R′ = H) derived from the starting material by hydrolysis only; there was no indication of a much more polar compound, such as a triol, which could arise by simple reduction of the 11-oxo-group of the ketol (I; R = R′ = Ac). From these mixtures the required ketone (III; R = H) was isolated in only about 20% yield.

Attention was then turned to metals other than lithium. Neither sodium nor potassium was satisfactory, for the products obtained by the titration technique contained much ketol (I; R = R′ = H). Calcium, on the other hand, gave a product that appeared, from paper-chromatographic studies, to contain neither the ketol (I; R = R′ = H) nor the diol (IV; R = H), and, from it, nearly pure 11-oxotigogenin was isolated in *ca.* 70% yield. Barium was found to be as good as calcium, but had no advantage.

The titration technique was not particularly convenient, and variations in the purity of the calcium, as well as uncertainties about the stoicheiometry of the reaction (see below), ruled out the possibility of using the exact amount of metal required. A more suitable method was found in the use of an excess of calcium and later removal of the final excess by addition of bromobenzene; this compound, unlike the more conventional reagents, caused no over-reduction. An additional practical improvement was the replacement of tetrahydrofuran by toluene which was more readily purified and which, in spite of its immiscibility with liquid ammonia, was satisfactory as long as stirring was effective. By these means, the yield of 11-oxotigogenin (isolated as its benzoate) from the ketol diacetate (I; R = R′ = Ac) was raised to 80—84%.

Calcium–ammonia reduction of the free ketol (I; R = R′ = H) gave a completely different result; the major product had the composition of a spirostan-triol [a minor product was 11α-hydroxytigogenin (IV; R = H)]. By analogy with the reduction of 11-oxo-steroids to 11α-hydroxy-steroids by lithium in liquid ammonia in presence of a source of protons [7] (the unprotected hydroxyl groups could act as such a source in this instance), this compound was assigned the structure, 5α : 25*D*-spirostan-3β : 11α : 12β-triol (V; R = R′ = R″ = H), which was confirmed when Wendler *et al.*[8] described the production of the triol (V; R = R′ = R″ = H) along with the diol (IV; R = H) from the ketol (I; R = R′ = H) by reduction with sodium and butan-1-ol.

The difference in behaviour between the free ketol (I; R = R′ = H) and its diacetate might be ascribed to initial salt formation by the 12β-hydroxy-group in the former, with

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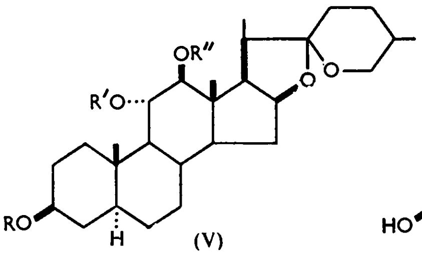
[6] Birch, *Quart. Rev.*, 1950, **4**, 69.

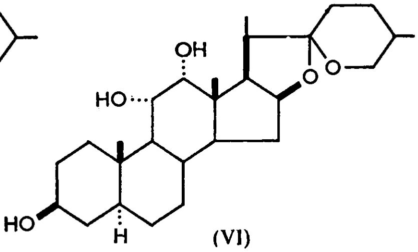
[7] Cf. Sondheimer, Mancera, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1953, **75**, 1282.

[8] Wendler, Hirschmann, Slates, and Walker, *ibid.*, 1955, **77**, 1632.

consequent protection of the $\mathrm{C_{(12)}}$–O bond from fission by further electron attack. This, is made less probable, however, by the fact that the course of reduction of the ketol was the same in the presence or the absence of methanol (cf. ref. 6). The possibility that the presence of a proton source, as such, was responsible for preferential attack on the carbonyl group in the free ketol was ruled out by an experiment in which the ketol diacetate (I; R = R′ = Ac) was reduced with calcium in ammonia in presence of methanol; the product was almost entirely 11α-hydroxytigogenin (IV; R = H), the triol (V; R = R′ = R″ = H) being present only in minute amounts.



(V)



(VI)

Since a likely reason for the different behaviour of the free ketol and its diacetate lies in the electron-withdrawal effect provided by the carbonyl of the 12β-acetoxy-group in the latter, the effect of varying the 12-acyloxy-group was investigated. A more powerful electron-withdrawal effect was provided in 3β-acetoxy-12β-methanesulphonyloxy-5α : 25*D*-spirostan-11-one (I; R = Ac, R′ = Me·SO$_2$), but reduction of this ester under the usual conditions gave 11-oxotigogenin in yield somewhat inferior to that obtained from the diacetate; the same was true of the dibenzoate (I; R = R′ = Bz). With the di*iso*butyrate (I; R = R′ = Pr^{i}·CO) steric hindrance apparently reduced the reactivity of the $\mathrm{C_{(12)}}$–O bond, the product being a mixture of 11-oxotigogenin (III; R = H) and the ketol (I; R = R′ = H); there was, however, no indication from paper chromatography that the triol was being formed in significant amount. As would be expected from the experiments described above, the 3-monoesters (I; R = Ac or Bu^{t}·CO, R′ = H) gave none of the 11-oxo-compound, the products of reduction being mixtures of the triol (V; R = R′ = R″ = H) with the original ketol (I; R = R′ = H).

Reduction of 3β : 12α-diacetoxy-5α : 25*D*-spirostan-11-one (II; R = Ac) with calcium and liquid ammonia again gave 11-oxotigogenin (III; R = H) in high yield. The corresponding ketol (II; R = H) might, by analogy with its 12β-epimer, have been expected to yield predominantly 5α : 25*D*-spirostan-3β : 11α : 12α-triol (VI), but it gave a mixture that appeared, from paper chromatography and rotation measurements, to consist of roughly equal amounts of the triol (VI) and 11α-hydroxytigogenin (IV; R = H). The greater ease of cleavage of the axial $\mathrm{C_{(12\alpha)}}$–O bond, compared with that of the equatorial $\mathrm{C_{(12\beta)}}$–O bond invites comparison with Rosenfeld and Gallagher's work on the relative ease of reduction of axial and equatorial α-acetoxy-ketones by zinc [4] (see above).

The stoicheiometry of the reduction is somewhat obscure. In rough titration experiments, the ketol diacetate (I; R = R′ = Ac) was found to react with 2·8—3·2 g.-atoms of calcium or 6—8 g.-atoms of lithium. On the basis of the reaction scheme suggested above, cleavage of the 12β-acetoxy-group would require only 1 g.-atom of the former, or 2 g.-atoms of the latter metal. However, reaction is certainly not confined to that centre, for the crude product, before alkaline hydrolysis, exists largely as the free 3-hydroxy-compound. It has been shown by Kharasch *et al.*[9] that the ethyl esters of various carboxylic acids will react with 2 g.-atoms of sodium in liquid ammonia to give rather complex mixtures, containing the acyloin and, in some instances, the aldehyde corresponding to the acid fragment of the ester. We have obtained evidence for the formation of acetaldehyde in our experiments, for the toluene recovered from reductions in this solvent was found to be contaminated by crotonaldehyde. Nevertheless, both of these reactions would account for the

[9] Kharasch, Sternfeld, and Mayo, *J. Org. Chem.*, 1940, **5**, 362.

consumption of only 2 g.-atoms of calcium per mole of steroid, and it must be assumed that further reduction occurs of one or both of the two carbon residues split from the molecule.

There have been two references in the recent literature to reactions similar to those described in this paper. Treatment of 6β-hydroxytestosterone (the vinylogue of an α-ketol) with lithium in liquid ammonia gives testosterone,[10] and the same reagent reduces 3β : 5α-dihydroxyergosta-7 : 9(11) : 22-trien-6-one to ergost-22-ene-3β : 6α-diol.[11] The removal, in both instances, of a free hydroxy-group stands in contrast with our experience; it is, however, not clear whether the difference is related to the situation of the hydroxy-group in the steroid nucleus or to the presence or absence of double bonds in conjugation with the ketone group.

EXPERIMENTAL

For general experimental information see Part XIII of this series.[12] Chromatography on paper was carried out as described elsewhere.[13]

Metal–ammonia reductions were carried out in uninsulated 3-necked flasks, fitted with a dropping funnel, a glass stirrer passing through a fibre-washer, and a short air-condenser, plugged at the top with cotton-wool. Liquid ammonia was run rapidly from a cylinder into the flask, and sufficient of the metal was added to impart a permanent blue colour to the liquid. The stated weight of metal was then added during about 5 min. and the solution was stirred gently for 10 min. (except for lithium, for which the time was reduced to 1 min.) before the solution of steroid was added.

Action of Lithium Aluminium Hydride on 3β-*Acetoxy*-12β-*methanesulphonyloxy*-5α : 25D-*spirostan*-11-*one*.—The methanesulphonate[14] (2·0 g.) in tetrahydrofuran (80 ml.) was added to a suspension of lithium aluminium hydride (2·0 g.) in tetrahydrofuran (20 ml.). The suspension was boiled under reflux for 2 hr. and the excess of hydride was decomposed by addition of ethyl acetate. After acidification the product was extracted with ether, precipitated from methanol by means of water, and chromatographed on alumina. Benzene, ether, and mixtures thereof eluted gums that could not be purified, but 1 : 4 methanol–ether gave a solid which, on crystallisation from aqueous methanol, yielded 5α : 25*D*-spirostan-3β : 11β : 12β-triol (0·17 g.), m. p. 253—256°, $[\alpha]_D$ −67°. This material was identified by its m. p. and infrared spectrum with an authentic sample prepared as described by Djerassi *et al.*,[15] who give m. p. 262—263° and $[\alpha]_D$ −64°.

Reduction of 3β : 12β-*Diacetoxy*-5α : 25D-*spirostan*-11-*one*.—(a) *With calcium and liquid ammonia in absence of an alcohol.* A solution of the ketol diacetate (15 g.) in toluene (200 ml.) was dried by concentration to 150 ml. at normal pressure. The solution was cooled to room temperature and was then added with vigorous stirring to a solution of calcium turnings (4·2 g.) in liquid ammonia (500 ml.). The addition was made in 5 min., the mixture was stirred for a further 3 min., and excess of calcium was then destroyed by the dropwise addition of bromobenzene (*ca.* 4 ml.). Water (5 ml.) was added cautiously and the ammonia was allowed to evaporate. The toluene was removed by distillation on the steam-bath under reduced pressure and methanol (200 ml.) was added to the residue, followed by a solution of potassium hydroxide (5 g.) in water (10 ml.). The mixture was boiled for 1 hr., water (50 ml.) was added, and the mixture was warmed for 30 min. on the steam-bath in order to coagulate the product. Water (250 ml.) and acetic acid (15 ml.) were added, the mixture was cooled, and the product was filtered off, washed thoroughly with water, and dried. The crude 11-oxotigogenin so obtained weighed 12·3 g. and had m. p. 209—218° and $[\alpha]_D$ —31°.

This material in pyridine (120 ml.) was benzoylated by addition of benzoyl chloride (12 ml.). After 2 hr., water (20 ml.) was added to destroy excess of reagent, and the product was precipitated after a further 2 hr. by addition of more water (200 ml.). Addition of boiling methanol (135 ml.) to a solution of the substance in boiling chloroform (45 ml.) gave 11-*oxotigogenin benzoate* as lances (11·5 g.), m. p. 228—232°, $[\alpha]_D$ −32° (*c*, 2). A further 1·05 g. were obtained

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[10] Amendolla, Rosenkranz, and Sondheimer, *J.*, 1954, 1226.

[11] Zürcher, Heusser, Jeger, and Geistlich, *Helv. Chim. Acta*, 1954, **37**, 1562.

[12] Elks and Phillipps, *J.*, 1956, 4320.

[13] Brooks, Hunt, Long, and Mooney, *J.*, in the press.

[14] Elks, Phillipps, Walker, and Wyman, preceding paper.

[15] Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 1278.

from the mother-liquors by evaporation and repeated crystallisation. The total yield was 12·55 g., 83%.

A sample of 11-oxotigogenin benzoate, prepared in a similar way from authentic 11-oxotigogenin, melted at 231—233° and had $[\alpha]_D$ −32° (*c* 1·0) (Found: C, 76·5; H, 8·6. $C_{34}H_{46}O_5$ requires C, 76·4; H, 8·7%), $\nu_{max.}$ (in CS_2) 3100, 1715, 1272, 1171, 706 (OBz), 1715 (CO), 981, 920, and 895 cm.$^{-1}$ (25*D*-spirostan).

If the toluene recovered from such an experiment was shaken with a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, a precipitate appeared in the aqueous layer and, on further shaking, redissolved in the toluene layer. Evaporation of the toluene and chromatography of the residue gave crotonaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 189° after crystallisation from ethanol. It was identified by mixed m. p. and infrared spectroscopy with an authentic sample.

In a similar reduction to the above, on 50 g. of the ketol diacetate, and with tetrahydrofuran in place of toluene, the yield of 11-oxotigogenin benzoate was 83·5%.

(b) *With calcium and liquid ammonia in the presence of methanol.* A solution of calcium (7·0 g.) in liquid ammonia (1400 ml.) was stirred while a 2·08% solution of 3β : 12β-diacetoxy-5α : 25*D*-spirostan-11-one in 4 : 1 dioxan–methanol was added slowly. The blue colour of the liquid ammonia solution was discharged when 70 ml. of the solution (equiv. to 1·46 g. of ketol diacetate) had been added. The addition was stopped at this point and methanol (20 ml.) was added carefully. The ammonia was removed and water was added, followed by sufficient concentrated hydrochloric acid to bring the pH to about 2. The solid (1·16 g.) was filtered off and washed with water and was then boiled for 2 hr. with a mixture of 40% aqueous sodium hydroxide (8 ml.) and ethanol (90 ml.). Most of the solvent was distilled off and the residue was diluted with water, to precipitate a solid (1·13 g.), m. p. 214—218°, $[\alpha]_D$ −76°.

Paper chromatography of this material showed one main spot with the R_F of 11α-hydroxytigogenin; very faint spots corresponded to 5α : 25*D*-spirostan-3β : 11α : 12β-triol and to 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one.

Crystallisation of the solid (1·04 g.) from acetonitrile gave 0·70 g. (64%) of 11α-hydroxytigogenin, m. p. 212—217°. The infrared spectrum was identical with that of an authentic sample.

Acetylation of the diol (250 mg.) with acetic anhydride and pyridine on the steam-bath for 90 min. gave the diacetate as needles (0·21 g.), m. p. 172—174°, $[\alpha]_D$ −83°, after crystallisation from methanol. The material was identified by mixed m. p. and infrared spectrum with an authentic specimen.

Sondheimer *et al.*[7] give m. p. 218—220°, $[\alpha]_D$ −78°, for 11α-hydroxytigogenin and m. p. 174—176°, $[\alpha]_D$ −79°, for the diacetate.

Reduction of 3β : 12β-*Dihydroxy*-5α : 25D-*spirostan*-11-*one with Calcium and Liquid Ammonia*.—A solution of the ketol (20 g.) in tetrahydrofuran (sodium-dried; 200 ml.) was added, during about 20 min., to a solution of calcium (4 g.) in liquid ammonia (400 ml.). The mixture was stirred for a further 30 min. and an excess of ethanol was added carefully. The ammonia was allowed to evaporate, and water was added, followed by sufficient concentrated hydrochloric acid to bring the pH to about 2. The mixture was stirred vigorously during these additions and until a granular solid separated. After being left for some hours in the refrigerator, the solid (19 g.) was filtered off. Crystallisation from ethyl acetate gave 12·7 g. of 5α : 25*D*-spirostan-3β : 11α : 12β-triol, m. p. 248—250°, $[\alpha]_D$ −65°, and a further crop (1·45 g.) of slightly lower m. p. This material was impure; the presence of unchanged ketol and of 11α-hydroxytigogenin was indicated by infrared spectroscopy and by chromatography of the acetylated material (see below). Wendler *et al.*[8] give m. p. 256—258°, $[\alpha]_D$ −65·4°.

The crude triol was acetylated with pyridine (80 ml.) and acetic anhydride (80 ml.) overnight at room temperature. The product (16·0 g.) was chromatographed on alumina (Peter Spence, Grade O : 450 g.), to give the following, in order of decreasing ease of elution :

3β : 11α-Diacetoxy-5α : 25*D*-spirostan (0·42 g.), m. p. 173—175°, after recrystallisation from methanol.

3β : 12β-Diacetoxy-5α : 25*D*-spirostan-11-one (1·05 g.), m. p. 227—229° after crystallisation from ethanol.

3β : 11α-Diacetoxy-5α : 25*D*-spirostan-12β-ol (0·15 g.), m. p. 204—209°, $[\alpha]_D$ −61·5° (from methanol), $\nu_{max.}$ (in CS_2) 3550 (OH), 1735 and 1238 (OAc), 978, 918, and 896 cm.$^{-1}$ (25*D*-spirostan). Wendler *et al.*[8] give m. p. 206—208°, $[\alpha]_D$ −64·4°.

3β : 12β-Diacetoxy-5α : 25*D*-spirostan-11α-ol (3·8 g.), m. p. 232—233·5°, $[\alpha]_D$ −61·5° (from methanol), $\nu_{max.}$ (in CS_2) 3620 (OH), 1732 and 1240 (OAc), 980, 920, and 898 cm.$^{-1}$ (25*D*-spirostan). Wendler *et al.*[8] give m. p. 231—232°, $[\alpha]_D$ −55·5°.

Acetylation of the triol (1 g.) with boiling acetic anhydride (15 ml.) containing fused sodium acetate (1 g.) for 2½ hr. gave, after chromatography on alumina and crystallisation from methanol, 3β : 11α : 12β-triacetoxy-5α : 25*D*-spirostan (0·31 g.), m. p. 198—200°, $[\alpha]_D$ −58°, $\nu_{max.}$ (in CS_2) 1738 and 1238 (OAc), 978, 918, and 898 cm.$^{-1}$ (25*D*-spirostan). Wendler *et al.*[8] give m. p. 197—198°, $[\alpha]_D$ −53·3°.

When the reduction of 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one was carried out in presence of methanol by the method used for the corresponding diacetate, the major product was, again, 5α : 25*D*-spirostan-3β : 11α : 12β-triol, m. p. 248—250°. Paper chromatography of the crude material showed it to be free from the starting ketol (this was confirmed by the infrared spectrum) but revealed a trace of 11α-hydroxytigogenin. On crystallisation from ethyl acetate the triol separated in polymorphic forms—needles and rosettes—which could be partially separated by hand. The needles melted at 250—253°; the rosettes changed to needles at *ca.* 230° and then melted at 249—250°. The infrared spectra of Nujol mulls showed differences of detail which, however, disappeared in the spectra of bromoform solutions.

Reduction of Other Esters of 3β : 12β-*Dihydroxy*-5α : 25D-*spirostan*-11-*one.*—(a) *Dibenzoate.* A solution of the ketol dibenzoate[14] in pure, dry tetrahydrofuran (3·27% w/v) was added dropwise to a stirred solution of calcium (120 mg.) in liquid ammonia (50 ml.). The colour of this solution was discharged after 15·9 ml. of the solution (equiv. to 0·52 g. of the steroid) had been added. Ammonium chloride (1 g.) and ethanol were added, the ammonia was evaporated off and water was added, followed by excess of hydrochloric acid. The solid was filtered off and boiled with 5% methanolic potassium hydroxide for 1 hr. The product was isolated by means of chloroform and, after crystallisation from ethyl methyl ketone, gave 11-oxotigogenin (0·21 g., 62%), m. p. 219—223°, $[\alpha]_D$ −30°. A second crop (26 mg.) melted at 210—216°. Sondheimer *et al.*[7] give m. p. 223—225°, $[\alpha]_D$ −29°.

(b) 3-*Acetate* 12-*methanesulphonate.* Addition of this ester[14] (1·13 g.) in tetrahydrofuran (10 ml.) to calcium (300 mg.) in liquid ammonia (100 ml.), and subsequent decomposition of excess of calcium with bromobenzene, hydrolysis of the product with methanolic potassium hydroxide, and benzoylation as already described, gave 11-oxotigogenin benzoate (0·703 g., 66%) as rods, m. p. 228—232°, $[\alpha]_D$ −32°.

(c) *Di*iso*butyrate.* Reduction of the di*iso*butyrate[14] by the titration method as described in (a) gave a crude product, m. p. 195—210°, $[\alpha]_D$ −36°. It was shown by its infrared spectrum and by paper chromatography to be a mixture of 11-oxotigogenin with 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one. The acetate obtained from this mixture melted between 160° and 180° and had $[\alpha]_D$ −52°.

(d) 3-*Monoacetate.* Reduction of the ketol monoacetate[14] in tetrahydrofuran with excess of calcium in liquid ammonia as descibed in (b) gave a crude product having m. p. 223—234°, $[\alpha]_D$ −58°. Paper chromatography suggested the presence of 5α : 25*D*-spirostan-3β : 11α : 12β-triol and 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one.

(e) 3-*Monopivalate.* Reduction of this ester,[14] by the titration technique as in (a) above, gave a product having m. p. 207—223°, $[\alpha]_D$ −52°; paper chromatography suggested that it was a mixture of 5α : 25*D*-spirostan-3β : 11α : 12β-triol and 3β : 12β-dihydroxy-5α : 25*D*-spirostan-11-one.

Reduction of 3β : 12α-*Diacetoxy*-5α : 25D-*spirostan*-11-*one.*—A solution of the ketol diacetate[14] (0·5 g.) in tetrahydrofuran (10 ml.) was reduced in the usual way with calcium (0·14 g.) in liquid ammonia (50 ml.). Excess of calcium was destroyed with bromobenzene, and the crude product was hydrolysed with methanolic potassium hydroxide. The 11-oxotigogenin (355 mg.), so obtained, melted at 206—213° and had $[\alpha]_D$ −31°. Benzoylation and subsequent crystallisation from chloroform–methanol gave 11-oxotigogenin benzoate (363 mg., 72%), m. p. 228—232°, $[\alpha]_D$ −32°.

Reduction of 3β : 12α-*Dihydroxy*-5α : 25D-*spirostan*-11-*one.*—Reduction of the ketol[14] (250 mg.) in tetrahydrofuran (5 ml.) with excess of calcium in liquid ammonia and removal of excess with bromobenzene gave, after crystallisation of the resulting gum from chloroform–methanol, an impure product (154 mg.), m. p. 211—229°, $[\alpha]_D$ −69°. Paper chromatography suggested the presence of 5α : 25*D*-spirostan-3β : 11α : 12α-triol[14] and 5α : 25*D*-spirostan-3β : 11α-diol; the rotation is consistent with the presence of these compounds in equal proportions.

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