The Conversion of Hecogenin Acetate into 11-*Oxotigogenin Acetate.*

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A process is described for replacing the 12-keto-group in hecogenin acetate by an 11-keto- or 11β-hydroxy-group. Translocation of the oxygen atom is effected by formation of an 11β : 12β-epoxide; the reaction of this with hydrogen bromide yields a 12α-bromo-11β-alcohol.

DEOXYCHOLIC ACID was the raw material initially used for partial synthesis of 11-oxygenated steroids, and several elegant procedures have been reported for substituting an oxygen atom at $C_{(11)}$ for the existing one at $C_{(12)}$. The sapogenin hecogenin (3β-hydroxy-5α : 22a-spirostan-12-one) is another readily accessible $C_{(12)}$-substituted steroid: it is a by-product in the manufacture of sisal fibre (Callow, Cornforth, and Spensley, *Chem. and Ind.*, 1951, 699; Spensley, *ibid.*, 1952, 426). The *trans*-relation of rings A and B and the presence of heterocyclic rings E and F limit the application to hecogenin of experience gained with deoxycholic acid. Preferential elimination of the 12-keto-group in an 11 : 12-diketone, discovered in the bile acid series by Wintersteiner and Moore (*J. Biol. Chem.*, 1946, **162**, 725), was applied, with improvements, by Djerassi, Ringold, and Rosenkranz (*J. Amer. Chem. Soc.*, 1951, **73**, 5513) in the preparation of 11-oxo-5α-22a-spirostan-3β-yl acetate (VII) from hecogenin acetate (I). Another conversion of (I) into (VII) is less direct, proceeding by way of a 7 : 9(11)-diene (Hirschmann, Snoddy, and Wendler, *ibid.*, 1953, **75**, 3252).

The present work has already been briefly reported (Cornforth and Osbond, *Chem. and Ind.*, 1953, 919). We are indebted to Dr. A. Wettstein for letting us see in advance of publication a detailed paper (Schmidlin and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 1241) which describes similar experiments. The plan for the work was based on the following considerations:

(1) Hecogenin acetate can be brominated in the 11(presumably the 11α)-position (Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 303; Mueller, Stobaugh, and Winniford, *J. Amer. Chem. Soc.*, 1951, **73**, 2400).

(2) The carbonyl group in ω-bromoacetophenone can be reduced by sodium borohydride without loss of halogen (Chaikin and Brown, *ibid.*, 1949, **71**, 122).

(3) Reduction of the 12-keto-group in hecogenin by lithium aluminium hydride gives the 12β-alcohol along with its 12α-epimer (Hirschmann, Snoddy, and Wendler, *ibid.*, 1952, **74**, 2694).

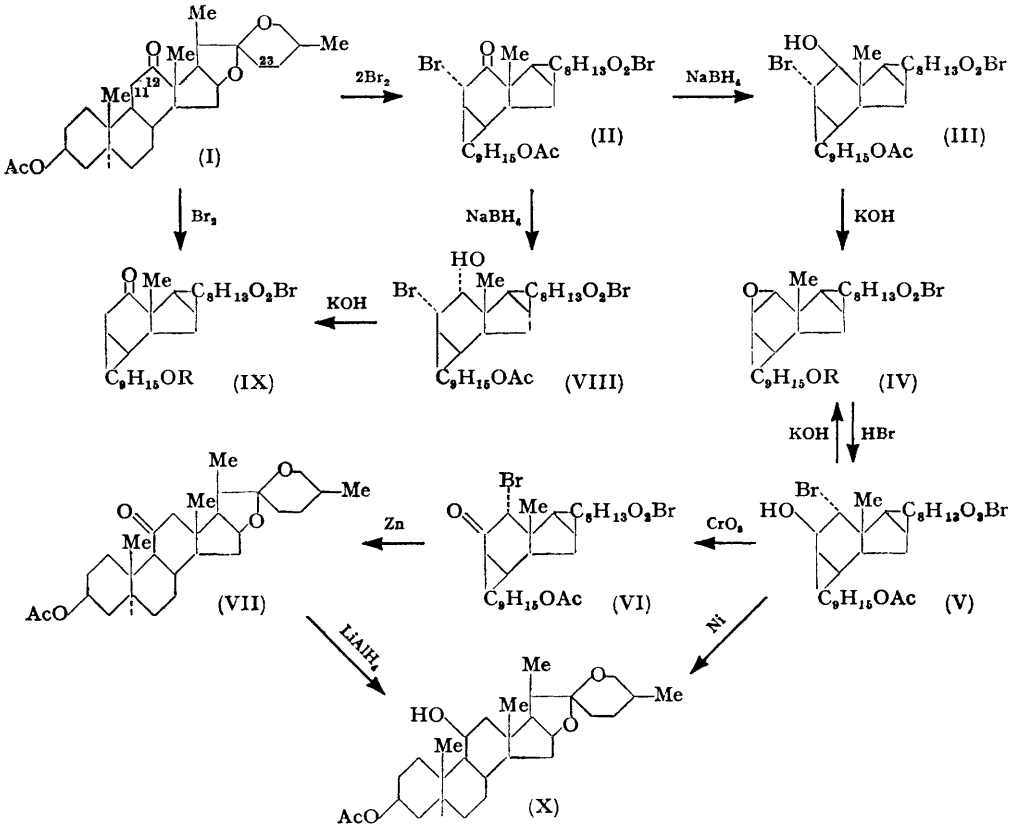
(4) Methyl 3α-acetoxy-11α : 12α-epoxycholanate on hydrogenolysis yields a 12α-alcohol (Press and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 878), whereas the corresponding 11β : 12β-epoxide gives an 11β-alcohol (Ott and Reichstein, *ibid.*, 1943, **26**, 1799). If the difference between these α- and β-epoxides persists in the mode of addition of hydrogen bromide, the 11β : 12β-epoxide should give a 12α-bromo-11β-alcohol, since the 11α : 12α-

epoxide with hydrogen bromide affords an 11β-bromo-12α-alcohol (Gallagher and Long, *J. Biol. Chem.*, 1946, **162**, 495).

(5) Methyl 3α-acetoxy-12α-bromo-11β-hydroxycholanate (obtained by addition of hypobromous acid to the 11-ene) can be oxidized by chromic acid to the 12α-bromo-11-ketone, which is reduced by zinc to methyl 3α-acetoxy-11-oxocholanate (Ott and Reichstein, *loc. cit.*).

From these analogies it appeared that the transformation (I) ⟶ (II) ⟶ (III) ⟶ (IV) ⟶ (V) ⟶ (VI) ⟶ (VII), shown in the diagrams, would be feasible; and so it proved in practice.

Reduction of 11α : 23ξ-dibromo-12-oxo-5α : 22a-spirostan-3β-yl acetate (II) with sodium borohydride was conveniently carried out in aqueous-alcoholic suspension containing sodium hydrogen carbonate (which inhibits, presumably by buffer action, the formation of bromide ion). The product could be separated by chromatography into two isomeric bromohydrins, 11α : 23ξ-dibromo-12β-hydroxy-5α : 22a-spirostan-3β-yl acetate (III) and 11α : 23ξ-dibromo-12α-hydroxy-5α : 22a-spirostan-3β-yl acetate (VIII), the former (III) predominating. An observation of interest is the reluctance of the 12β-hydroxyl group in (III) to undergo acetylation (see Experimental section). On treatment with cold aqueous-alcoholic alkali the bromohydrin (III) was converted smoothly into 23ξ-bromo-11β : 12β-epoxy-5α : 22a-spirostan-3β-ol (IV; R = H). Under the same conditions, the isomer (VIII) yielded no epoxide, 23ξ-bromo-3β-hydroxy-5α : 22a-spirostan-12-one (23-bromohecogenin) (IX; R = H) being formed in good yield.



When either the 3β-hydroxy-epoxide or its 3-acetate (IV) was treated in acetic acid with hydrogen bromide, 12α : 23ξ-dibromo-11β-hydroxy-5α : 22a-spirostan-3β-yl acetate (V) was formed. The sparing solubility of this compound rendered unnecessary the separation of

the bromohydrins (III) and (VIII) and the purification of the epoxide (IV), for the new bromohydrin (V) could be freed from 23-bromohecogenin acetate (arising from the unwanted isomer VIII) by washing with benzene.

Oxidation of the bromohydrin (V) proceeded smoothly; the resulting 12α : 23ξ-dibromo-11-oxo-5α : 22a-spirostan-3β-yl acetate (VI) was easily reduced by zinc dust in acetic acid–sodium acetate to 11-oxo-5α : 22a-spirostan-3β-yl acetate (11-oxotigogenin acetate) (VII). The properties of this substance were in good agreement with earlier data (Chamberlin *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 2396; Djerassi, Ringold, and Rosenkranz, *loc. cit.*).

Reduction of the ketone (VII) with lithium aluminium hydride, followed by acetylation, gave 11β-hydroxy-5α : 22a-spirostan-3β-yl acetate (X) which also had the expected properties (cf. Djerassi, Batres, Velasco, and Rosenkranz, *J. Amer. Chem. Soc.*, 1952, **74**, 1712). The same substance (X) was obtained directly from the bromohydrin (V) and Raney nickel. This conversion (V ⟶ X) is of value in assigning configurations at the 11- and 12-positions to the substances (II), (III), (IV), (V), (VI), and (VIII). It is clear that the 11-hydroxy-group in (V) must be β-oriented. Hence the epoxide (IV) from which (V) originated is the 11β : 12β-epimer. The *trans*-mode of addition of acids to epoxides is well established; thus the 12-bromine atom in (V) and (VI) is 12α.

The bromohydrin (III) from which the β-epoxide (IV) originated is necessarily a 12β-alcohol and its epimer (VIII) is therefore a 12α-alcohol. Finally, Bartlett's work (*ibid.*, 1935, **57**, 224) on the behaviour of *cis*- and *trans*-2-chloro*cyclo*hexanol with alkali—the *cis*-epimer yields a ketone and the *trans* an epoxide—indicates that (III) is a *trans*-bromohydrin and (VIII) a *cis*-bromohydrin, and that the 11-bromine atom in (II), (III), and (VIII) has the expected α-orientation.

An observation from early exploratory work may be added. Reduction of the dibromide (II) by lithium aluminium hydride in ether gave a mixture which, after acetylation, was warmed with zinc in acetic acid. A bromine-containing product was isolated which from its composition and properties appeared to be 23ξ-bromo-5α : 22a-spirost-11-en-3β-yl acetate. Fieser *et al.* (*ibid.*, 1953, **75**, 1700, 1704) have reported similar eliminations from ring A.

Experimental

M. p.s were determined in the Kofler apparatus, and optical rotations in 1% chloroform solution at 20°, except where otherwise stated.

11α : 23ξ-*Dibromo*-12-*oxo*-5α : 22*a*-*spirostan*-3β-*yl Acetate* (II).—Hecogenin acetate (10 g.) in chloroform (80 c.c.; ethanol-free) was stirred at 10° during addition of bromine (2·5 c.c.) in chloroform (20 c.c.) during 15 min. After a further 15 min. the pressure in the reaction vessel was reduced to about 30 mm. and the chloroform was distilled through a condenser cooled with solid carbon dioxide. The residue was stirred with a little ethyl acetate until crystallization set in; ethanol (50 c.c.) was then added slowly. The product (7·2 g.) was collected and washed with ethanol; it had m. p. 188—190° and gave 0·98 equivalent of bromide ion on hydrolysis with alcoholic alkali. Recrystallization from chloroform–ethanol gave material, m. p. 189—191° (decomp.), $[\alpha]_D$ −38°, assaying 100% in the same test.

Sodium Borohydride Reduction of the Dibromide (II).—The above dibromide (25 g.), suspended in ethanol (250 c.c.), was stirred during the addition of 7% sodium hydrogen carbonate solution (37·5 c.c.). Sodium borohydride (0·90 g.) in water (12·5 c.c.) was then added and the paste was efficiently stirred for 2½ hr. The product (25·7 g.) was collected after dilution with water (750 c.c.). Assay of the filtrate showed that 0·03 equiv. of bromide ion had been liberated. The crude product (20 g.) in 1 : 1 benzene–light petroleum (40—60°) was chromatographed on alumina (600 g.; acetic acid-washed grade " O," Brockmann II—III).

	Eluates	Volume (ml.)	Residue (g.)	M. p. (decomp.)
I	Benzene–light petroleum 1 : 1	1000	5·50	180°
II	,, ,, ...	1250	4·20	188
III	,, ,, ...	1250	1·15	192
IV	Benzene	1250	1·70	192
V	,, ...	1250	0·95	*ca.* 180
VI	,, ...	1250	0·50	*ca.* 180
VII	Ether–benzene 1 : 4	2500	2·70	193

Infra-red analysis showed that fraction I contained unchanged ketone. Fractions II—IV were almost identical; fractions V and VI were essentially the same as II—IV but of lower purity. Fraction VII differed in the " fingerprint " region from II—IV.

Fractions II—IV were combined and crystallized from aqueous acetone, to give 11α : 23ξ-*dibromo*-12β-*hydroxy*-5α : 22*a*-*spirostan*-3β-*yl acetate* (III) as needles, m. p. 197° (decomp.) to 202° (decomp.) according to the rate of heating, $[\alpha]_D$ −56° (Found: C, 55·1; H, 7·0; Br, 25·6. $C_{29}H_{44}O_5Br_2$ requires C, 55·1; H, 7·0; Br, 25·3%). The infra-red spectrum in carbon disulphide showed bands at 3620 (hydroxyl), 1731 and 1238 (acetate); 1010, 944, 914, and 860 (23-bromo-22a-sapogenin); and 724 cm.$^{-1}$ (C–Br).

Fraction VII on crystallization from aqueous methanol gave 11α : 23ξ-*dibromo*-12α-*hydroxy*-5α : 22*a*-*spirostan*-3β-*yl acetate* (VIII), needles, m. p. 198° (decomp.), $[\alpha]_D$ −62° (Found: C, 55·3; H, 7·0; Br, 25·6%). The infra-red spectrum in carbon disulphide showed bands at 3620 (hydroxyl); 1738 and 1242 (acetate); 1016, 948, 917, and 860 (23-bromo-22a-sapogenin) and 723 cm.$^{-1}$ (C–Br). A mixture of the 12α- and the 12β-alcohol melted at *ca.* 190°.

The pure 12β-alcohol (III) could also be separated without chromatography. The crude sodium borohydride reduction product was recrystallized from *iso*propanol, from which it separated in a solvated form, m. p. 128—140°; this product (1 g.) was dissolved in acetic anhydride on a steam-bath, and a few drops of pyridine were added. On cooling, after 1 hr., the 12β-alcohol (III) (0·63 g.) separated, having m. p. 196—201° (decomp.), $[\alpha]_D$ −54° (Found: C, 55·1; H, 7·0%). The infra-red spectrum confirmed that acetylation of the 12β-hydroxyl group had not occurred.

Action of Alkali on the Bromohydrin (III).—The bromohydrin (III) (from chromatography; 500 mg.) and potassium hydroxide (250 mg.) were shaken in ethanol (25 ml.) at room temperature for 4 hr. The resulting solution was left for 20 hr., then concentrated at low pressure and diluted with water; 23ξ-*bromo*-11β : 12β-*epoxy*-5α : 22*a*-*spirostan*-3β-*ol* (IV; R = H) (390 mg.) separated in needles, m. p. 207—209°, $[\alpha]_D$ −26° (Found: C, 63·5; H, 8·1; Br, 15·8. $C_{27}H_{41}O_4Br$ requires C, 63·6; H, 8·1; Br, 15·7%). Infra-red spectrum in Nujol: bands at 3420 (hydroxyl), and 1012, 946, 918, and 868 cm.$^{-1}$ (23-bromo-22a-sapogenin), with only a minute band at 1708 (unconjugated carbonyl). Assay of the aqueous filtrate showed 99% of the theoretical amount of bromide ion. The bromohydrin (III), purified by the acetic anhydride method (above), gave the same epoxide and the infra-red spectrum of the total product showed no carbonyl absorption.

The epoxide (IV; R = H) (300 mg.) was warmed on a steam-bath for 20 min. with acetic anhydride (4 c.c.) and pyridine (4 c.c.). After evaporation at low pressure the residue was triturated with methanol (5 c.c.), giving 23ξ-*bromo*-11β : 12β-*epoxy*-5α : 22*a*-*spirostan*-3β-*yl acetate* (314 mg.), m. p. 233—235°, $[\alpha]_D$ −30°. A sample crystallized from ethanol had m. p. 238—239°, $[\alpha]_D$ −30° (Found: C, 62·8, 63·1; H, 7·9, 7·9; Br, 14·3. $C_{29}H_{43}O_5Br$ requires C, 63·2; H, 7·8; Br, 14·5%). Infra-red spectrum in carbon disulphide: bands at 1735 and 1240 (acetate); 1012, 945, 918, 860 (23-bromo-22a-sapogenin); and 732 cm.$^{-1}$ (C–Br). On hydrolysis the hydroxy-epoxide was regenerated, as felted needles [from light petroleum (b. p. 60—80°)], m. p. 204—206°, $[\alpha]_D$ −28° (Found: C, 63·3; H, 8·1; Br, 15·9%).

Action of Alkali on the Bromohydrin (VIII).—The bromohydrin (VIII) (500 mg.) was treated with alcoholic potassium hydroxide exactly as described for the isomer (III). The crystalline product (400 mg.) had m. p. 206—210° (decomp.) and $[\alpha]_D$ −14°, and gave an acetate, m. p. 225—227°, $[\alpha]_D$ −15°.

For comparison, 23ξ-bromo-12-oxo-5α : 22a-spirostan-3β-yl acetate, prepared by partial debromination of dibromo-compounds, was available, and some of this was converted by methanolysis into the 3β-alcohol which had m. p. 205° (decomp.), $[\alpha]_D$ −14°, after two crystallizations from ethanol (Found: C, 63·6; H, 8·1; Br, 15·6. Calc. for $C_{27}H_{41}O_4Br$: C, 63·6; H, 8·1; Br, 15·7%). Mueller, Stobaugh, and Winniford (*loc. cit.*) gave m. p. 210° (decomp.) and $[\alpha]_D^{26}$ −3° (in dioxan). Mixed m. p.s of this substance, and its acetate, with the corresponding products from the bromohydrin (VIII) were undepressed. The infra-red spectra were also compared and were almost identical: the spectrum of the 3β-alcohol in Nujol showed bands at 3650 (hydroxyl); 1702 (unconjugated carbonyl); 1008, 944, 918, 862 (23-bromo-22a-sapogenin); and 722 cm.$^{-1}$ (C–Br). Spectrum of the acetate in carbon disulphide: bands at 1735 and 1240 (acetate); 1710 (unconjugated carbonyl); 1010, 945, 920, 860 (23-bromo-22a-sapogenin); and 728 cm.$^{-1}$ (C–Br).

12α : 23ξ-*Dibromo*-11β-*hydroxy*-5α : 22*a*-*spirostan*-3β-*yl Acetate* (V).—The following was a general procedure. The acetoxy-epoxide (IV) (5 g.) was ground in a glass mortar with acetic acid (23 c.c.), and hydrogen bromide in acetic acid (2 c.c. of 4·6N) was added dropwise, with

continuous stirring with a pestle, during 10—15 min. After a further 10 min. the crystalline product was collected, washed with acetic acid, dried, and stirred twice on a filter with a little benzene. The residue had m. p. 230—231° (decomp.). When pure acetoxy-epoxide was used the yield was 94% of the theoretical, but it was often convenient to treat the crude sodium borohydride reduction product with alcoholic potassium hydroxide, to acetylate the resulting mixture, and to add hydrogen bromide as above. The contaminating 23-bromohecogenin acetate [arising from the bromohydrin (VIII)] then remained in the acetic acid filtrate and the benzene washings and could be recovered therefrom.

Crystallization of the acetic acid-insoluble product from toluene gave 12α : 23ξ-*dibromo*-11β-*hydroxy*-5α : 22*a*-*spirostan*-3β-*yl acetate* (V) in well-formed needles, m. p. 233—236° (decomp.), $[\alpha]_D$ −23° (Found : C, 55·4; H, 7·2; Br, 25·2. $C_{29}H_{44}O_5Br_2$ requires C, 55·1; H, 7·0; Br, 25·3%). Infra-red spectrum in Nujol : bands at 3560 (hydroxyl); 1717 and 1267 (acetate); 1005, 952, 921, 865 (23-bromo-22a-sapogenin); and 732 cm.$^{-1}$ ($C_{(23)}$–Br).

The same substance (V) separated slowly from a cold solution of the hydroxy-epoxide (IV; R = H) in acetic acid containing hydrogen bromide. When the bromohydrin (V) (315 mg.) was boiled with methanolic potassium hydroxide (10 c.c. of 1%) for 0·5 hr. and the product crystallized from light petroleum (b. p. 60—80°), the hydroxy-epoxide (230 mg.) was obtained, m. p. 202—205°, showing no ketonic absorption in the infra-red.

Oxidation of the Bromohydrin (V).—A solution of 12α : 23ξ-dibromo-11β-hydroxy-5α : 22a-spirostan-3β-yl acetate (600 mg.) in chloroform (10 c.c.; ethanol-free) was shaken with chromium trioxide (0·3 g.) in water (1 c.c.) and acetic acid (4 c.c.) for 1½ hr. at 25°. Water was added; the chloroform layer was shaken with aqueous sodium chloride, then with sodium hydrogen carbonate solution containing sodium chloride, dried ($MgSO_4$) and evaporated. The residue was treated with hot ethyl acetate (3 c.c.). After cooling, the product (448 mg.) was collected; the mother-liquors yielded further crops (total 58 mg.) of identical m. p. and rotation. 12α : 23ξ-*Dibromo*-11-*oxo*-5α : 22*a*-*spirostan*-3β-*yl acetate* (VI) was thus obtained in well-formed prisms, m. p. 229—232° (decomp.), $[\alpha]_D^{24}$ −78° (Found : C, 55·0; H, 6·9; Br, 25·4. $C_{29}H_{42}O_5Br_2$ requires C, 55·2; H, 6·7; Br, 25·3%). Infra-red spectrum in Nujol : bands at 1723 and 1253 (acetate); 1702 (unconjugated carbonyl); 1005, 950, 917, 865 (23-bromo-22a-sapogenin); and 730 cm.$^{-1}$ (C–Br).

11-*Oxo*-5α : 22*a*-*spirostan*-3β-*yl Acetate* (VII).—The dibromo-ketone (VI) (500 mg.) was added to a mixture of zinc powder (2 g.), sodium acetate (1 g.; anhydrous), and acetic acid (5 c.c.). After 1 hour's boiling the product, now halogen-free, was isolated by means of ether. Trituration with methanol gave a nearly pure product (350 mg.), m. p. 215—220° (capillary). Recrystallization from acetone gave pure 11-oxotigogenin acetate (VII), m. p. 229—232°, $[\alpha]_D$ −39° (Found : C, 73·6; H, 9·6. Calc. for $C_{29}H_{44}O_5$: C, 73·7; H, 9·3%). The infra-red spectrum showed the usual acetate, carbonyl, and sapogenin bands. A sample kept for a week with 2 : 4-dinitrophenylhydrazine sulphate in ethanol failed to form a hydrazone; under the same conditions reaction of the hydrazine with hecogenin acetate was complete in a few minutes.

11β-*Hydroxy*-5α : 22*a*-*spirostan*-3β-*yl Acetate* (X).—(i) A concentrated solution of 11-oxotigogenin acetate (VII) in dry ether was treated with lithium aluminium hydride in ether (3 c.c. of 0·21M) and refluxed for 3 hr. Ice and dilute nitric acid were added; the product after recovery from the ether was acetylated with acetic anhydride (0·3 c.c.) and pyridine (0·3 c.c.) on a steam-bath for 0·5 hr. After isolation in the usual way the product was crystallized from acetone. The 11β-hydroxytigogenin acetate separated in rods, m. p. 225—228°, $[\alpha]_D$ −45° (*c* 2 in dioxan) (Found : C, 73·2; H, 9·8. Calc. for $C_{29}H_{46}O_5$: C, 73·4; H 9·7%). The infra-red spectrum showed hydroxy-, acetate, and sapogenin bands; no carbonyl band was detectable.

(ii) 12α : 23ξ-Dibromo-11β-hydroxy-5α : 22a-spirostan-3β-yl acetate (0·75 g.) was added to a refluxing suspension of Raney nickel (~2 g.) in ethyl acetate (30 c.c.). Ethanol (10 c.c.) was then added and heating continued overnight. After removal of catalyst and solvent the product was acetylated with pyridine–acetic anhydride, recovered in the normal manner, and crystallized from acetone. The product (0·1 g.; m. p. 219—225°) was identified by mixed m. p. with the specimen prepared as above; the infra-red spectra of the two samples were identical.

23ξ-*Bromo*-5α : 22*a*-*spirost*-11-*en*-3β-*yl Acetate*.—11α : 23ξ-Dibromo-12-oxo-5α : 22a-spirostan-3β-yl acetate (4·5 g.) was powdered finely, suspended in dry ether (11 c.c.), cooled in ice, and treated with a solution (added all at once) of lithium aluminium hydride in ether (25·5 c.c. of 0·28M). After 0·5 hour's swirling at 0° the mixture was left at 0° overnight and at room temperature for 3 hr.; it was then poured on a mixture of ice and dilute nitric acid. The

product recovered from the ether was dried by being boiled with benzene and was left with pyridine (5 c.c.) and acetic anhydride (10 c.c.) at 37° overnight. After the usual isolation procedure the product was dissolved in acetic acid (10 c.c.), zinc powder (10 g.) was added, and the mixture was warmed for 1 hr. on a steam-bath. Water and chloroform were added; the filtered chloroform extract after being washed with sodium hydrogen carbonate solution was evaporated. The residue was crystallized once from methanol (which yielded 0·97 g. of m. p. 215°), and then from ethyl acetate. 23ξ-*Bromo*-5α : 22*a*-*spirost*-11-*en*-3β-*yl acetate* separated in four-sided tabular crystals, m. p. 226—228° (decomp.), $[\alpha]_D$ −38° (*c* 2 in dioxan) (Found : C, 65·5; H, 8·1. $C_{29}H_{43}O_4Br$ requires C, 65·1; H, 8·0%). This substance was shown to contain bromine and this was not ionized by a boiling solution of sodium in *n*-propanol. The substance gave a yellow colour with tetranitromethane.

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