## 335. *The 11-Oxo- and 12-Oxo-derivatives of Cholest-4-en-3-one.*

By David N. Kirk and Vladimir Petrow.

The compounds named in the title have been prepared by using deoxycholic acid as starting material.

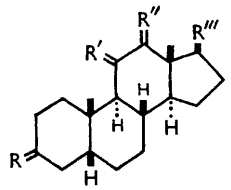
The 11-oxo- (II; R = O, R′ = $H_2$) and 12-oxo-derivative (II; R = $H_2$, R′ = O) of cholest-4-en-3-one were required for studies dealing with biogenesis. For their preparation deoxycholic acid was chosen as raw material, attention being first directed to cholestene-3 : 12-dione, as the intermediates therefrom seemed likely to prove of value in the production of the 11-oxygenated isomer.

Deoxycholic acid diformate [1] was converted into the acid chloride and thence by reaction with di*iso*propylcadmium [2] into 3α : 12α-dihydroxycoprostan-24-one (I; R = R″ = ···OH, ⁻H; R′ = $H_2$), isolated as the crystalline 3-(hydrogen succinate). The constitution assigned to this ester was established by oxidation of the 12α-hydroxy-group followed by Huang-Minlon reduction [3] of the resulting dione; coprostan-3α-ol [4] was obtained.

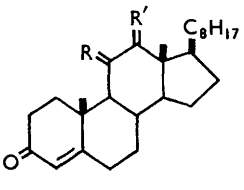
Huang-Minlon reduction of the parent 3α : 12α-dihydroxycoprostan-24-one 3-(hydrogen succinate) gave coprostane-3α : 12α-diol (Ia; R = R″ = ···OH, ⁻H; R′ = $H_2$), isolated as its crystalline 3α-(hydrogen succinate). Oxidation of the free diol with chromic acid furnished coprostane-3 : 12-dione (Ia; R = R″ = O, R′ = $H_2$), which passed readily on careful monobromination, followed by dehydrobromination, into the required cholest-4-ene-3 : 12-dione (II; R = $H_2$, R′ = O) [$\lambda_{max.}$ 240 mμ in $CHCl_3$; $\nu_{max.}$ 1710 (12-ketone), 1678 and 1620 cm.$^{-1}$ (4-en-3-one) [5]].

[1] Cortese and Bauman, *J. Biol. Chem.*, 1936, **113**, 779; Hoehn and Moffett, *J. Amer. Chem. Soc.*, 1945, **67**, 740.
[2] Riegel and Kaye, *J. Amer. Chem. Soc.*, 1944, **66**, 723; Kuwada and Yogo, *J. Pharm. Soc.* (*Japan*), 1937, **57**, 963.
[3] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487; 1949, **71**, 3301.
[4] Dorée and Gardner, *J.*, 1908, **93**, 1630; Dutcher and Wintersteiner, *J. Amer. Chem. Soc.*, 1939, **61**, 1992; Bridgewater and Shoppee, *J.*, 1953, 1709.
[5] Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252.

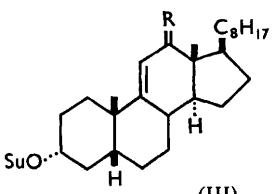
Conversion of coprostane-3α : 12α-diol 3-(hydrogen succinate) into an 11-oxygenated intermediate was unexpectedly difficult. Oxidation gave the 12-oxo-derivative, characterised by hydrolysis to amorphous 3α-hydroxycoprostan-12-one (Ia; R = ···OH, -H; R′ = $H_2$; R″ = O), which formed a crystalline acetate. Bromination of 12-oxocoprostan-3α-yl hydrogen succinate proceeded slowly in acetic acid at 70° to give two isomeric 11-bromo-derivatives. The major product, m. p. 149—152°, was shown to be the 11α-bromo-isomer (Ia; R = ···O·CO·$[CH_2]_2$·$CO_2H$, -H; R′ = ···Br, -H; R″ = O) by its stability




(I) R‴ = CHMe·$CH_2$·$CH_2$·COPr$^i$
(Ia) R‴ = $C_8H_{17}$




(II)




(III)
(Su = $HO_2C$·$[CH_2]_2$·CO-)

to boiling pyridine and by its ultraviolet absorption maximum at 287 mμ (equatorial bromine).[6] The minor product of the bromination, m. p. 214—215°, exhibited maximum ultraviolet absorption at 311 mμ and was dehydrobrominated by boiling pyridine to 12-oxocoprost-9(11)-en-3α-yl hydrogen succinate (III; R = O) ($\lambda_{max.}$ 239·5 mμ). It was therefore assigned the 11β-(axial)formulation[6] (I*a*; R = ···O·CO·$[CH_2]_2$·$CO_2H$, -H; R′ = ···H, -Br; R″ = O). Attempts to convert these isomeric bromo-derivatives, or the mixture resulting from the bromination, into 3α : 12β-dihydroxycoprostan-11-one (Ia; R = ···OH, -H; R′ = O, R″ = ···H, -OH) (cf. Gallagher[7]) by vigorous alkaline hydrolysis, led to amorphous products from which a crystalline hydrogen succinate was ultimately obtained. This derivative, though not analytically pure, was probably the required 3α : 12β-dihydroxycoprostan-11-one 3-(hydrogen succinate). Its transformation into a 12-bromo-derivative by phosphorus tribromide under the conditions recommended by Hershberg *et al.*[8] led in very low yield to a product deficient in bromine which was not studied further.

No better results attended an attempt to extend to the 11-bromo-ketone the elegant procedure of Cornforth *et al.*[9] for converting hecogenin into 11-oxotigogenin. Thus reduction of the 11α-bromo-12-one with sodium borohydride led to a bromohydrin, but conversion of the latter into a crystalline 11β : 12β-epoxide could not be achieved with such reagents as alcoholic alkali[9] or silver oxide in pyridine.[10] Reduction of the bromohydrin with zinc dust[9] gave coprost-11-en-3-α-yl hydrogen succinate in very low yield, which was characterised as the dibromide.

One further route to the 11-ketone was examined. 12-Oxocoprostan-3α-yl hydrogen succinate (Ia; R = ···O·CO·$[CH_2]_2$·$CO_2H$, -H; R′ = $H_2$, R″ = O) was dehydrogenated with selenium dioxide in propionic acid to the 9(11)-dehydro-derivative (III; R = O), previously obtained from the 11β-bromo-12-one (cf. above). Huang-Minlon reduction followed by succinoylation furnished a very low yield of coprost-9(11)-en-3α-yl hydrogen succinate (III; R = $H_2$). Attempted addition of the elements of hypobromous acid to this compound employing *N*-bromoacetamide,[11] with or without added perchloric acid, failed to give a satisfactory product.

These discouraging results led us to examine an alternative route from deoxycholic acid

[6] Cookson, *J.*, 1954, 282.
[7] Gallagher, *J. Biol. Chem.*, 1946, **162**, 539; Borgstrom and Gallagher, *ibid.*, 1949, **177**, 951.
[8] Hershberg, Herzog, Coan, Weber, and Jevnik, *J. Amer. Chem. Soc.*, 1952, **74**, 2585.
[9] Cornforth, Osbond, and Phillipps, *J.*, 1954, 907.
[10] Schmidlin and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 1241.
[11] Hicks and Wallis, *J. Biol. Chem.*, 1946, **162**, 641; Callow and James, *J.*, 1956, 4739.

to cholest-4-ene-3 : 11-dione *via* 3α-hydroxy-11-oxocholan-24-oic acid.[7] The latter, after acetylation or formylation of the 3α-hydroxy-group, was treated with thionyl chloride. The resulting acid chloride with di*iso*propylcadmium gave 3α-hydroxycoprostane-11 : 24-dione (I; R = ···OH, -H; R′ = O; R″ = $H_2$). The 24-oxo-group was selectively eliminated therefrom by Huang-Minlon reduction, whch does not normally attack 11-ketones,[3] to give 3α-hydroxycoprostan-11-one (Ia; R = ···OH, -H; R′ = O; R″ = $H_2$). Mild oxidation furnished coprostane-3 : 11-dione (Ia; R = R′ = O, R″ = $H_2$), which passed into the 4-monobromo-derivative on careful bromination.[12] Reaction with ethoxycarbonylhydrazine,[13] followed by cleavage of the derived hydrazone with acetone and hydrochloric acid,[13] furnished the required cholest-4-ene-3 : 11-dione (II; R = O, R′ = $H_2$), which was characterised by its ultraviolet absorption maximum at 238·5 mμ, and by infrared absorption bands at 1706 (11-one) and 1676 cm.$^{-1}$ (4-en-3-one [5]).

## Experimental

Optical rotations were measured in a 1 dm. tube in chloroform solution unless otherwise stated. Ultraviolet and infrared absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc. B.D.H. chromatographic alumina was used.

3α : 12α-*Dihydroxycoprostan*-24-*one* 3-(*Hydrogen Succinate*) (I; R = ···O·CO·$[CH_2]_2$·$CO_2H$, -H; R′ = $H_2$, R″ = ···OH, -H).—A solution of *iso*propylmagnesium bromide prepared from magnesium (27 g.), *iso*propyl bromide (106 ml.), and ether (300 ml.) was diluted with dry benzene (800 ml.), cooled to −10°, and treated under nitrogen with cadmium bromide (160 g.; freshly dried at 120°) in small portions during 45 min., at <5°. After a further 2 hours' stirring at −5° to 0° the solution was free from *iso*propylmagnesium bromide (Michler's ketone test [14]).

Deoxycholic acid diformate (50 g.) was treated with purified thionyl chloride (400 ml.) for 2 hr. at room temperature, then excess of thionyl chloride was removed under reduced pressure at 60°. Dry toluene (400 ml.) was added and distilled off under the same conditions, and the solid residue, dissolved in dry benzene (400 ml.), was added to the stirred solution of di*iso*propylcadmium at 0°. Next morning the mixture was poured into water (4 l.), concentrated hydrochloric acid (150 ml.), and crushed ice (1 kg.). The organic layer was washed, dried, and distilled to dryness, and the residue treated with potassium hydroxide (16 g.) in methanol (500 ml.) and water (30 ml.). The crude product, in benzene solution, was passed through a column of alumina (600 g.). Elution with ether and chloroform gave material (28·9 g.) which was treated with succinic anhydride (72 g.) in pyridine (300 ml.) for 1·5 hr. at 90°. The mixture was then stirred into water and after 2 hr. the product was extracted with ethyl acetate–benzene. Purification from ethyl acetate–hexane gave the *half-ester* as flakes, m. p. 136—137°, $[\alpha]_D^{24}$ +49° (*c* 0·5) (Found: C, 71·9; H, 9·8. $C_{31}H_{50}O_6$ requires C, 71·8; H, 9·7%).

*Coprostan*-3α-*ol*.—The foregoing compound (500 mg.) in acetic acid (20 ml.) was treated with potassium chromate (250 mg.) in water (5 ml.) at room temperature for 20 hr., to give the 12 : 24-dione 3-half-ester, leaflets (from ethyl acetate–hexane), m. p. 167—169°. This compound (400 mg.) and hydrazine hydrate (1 ml.) in diethylene glycol (20 ml.) were heated at 100° for ½ hr., then treated with hydrazine hydrate (0·5 ml.) and potassium hydroxide (2 g.) and the mixture was heated at 200° for 2 hr. in a stream of nitrogen, in an open flask. After the mixture had been poured into water, the product was isolated with ether–benzene, percolated through alumina (10 g.) in ether solution, and purified from methanol. Coprostan-3α-ol formed flakes, m. p. 117°, $[\alpha]_D^{22}$ +30° (*c* 0·18) (lit.,[4] m. p. 116—118°, $[\alpha]_D$ +30°).

The acetate separated from methanol as prisms, m. p. 86—87°, $[\alpha]_D^{22}$ +38° (*c*, 0·21) (lit.,[4] m. p. 83—84°).

*Coprostane*-3α : 12α-*diol* 3-(*Hydrogen Succinate*) (Ia; R = ···O·CO·$[CH_2]_2$·$CO_2H$, -H; R′ = $H_2$; R″ = ···OH, -H).—3α : 12α-Dihydroxycoprostan-24-one 3-(hydrogen succinate) (5·18 g.) and hydrazine hydrate (2·5 ml.) in diethylene glycol (50 ml.) were heated at 100° for ½ hr., then potassium hydroxide (6 g.) was added, and the mixture heated slowly to 200° in a stream of nitrogen in an open flask. After 2 hr. at 200° ± 5° the mixture was poured into dilute

[12] Koechlin, Kritchevsky, and Gallagher, *J. Biol. Chem.*, 1950, **184**, 393; Djerassi and Rosenkranz, *Experientia*, 1951, **7**, 93.
[13] Joly and Nominé, *Bull. Soc. chim. France*, 1956, 1381.
[14] Gilman and Schulze, *J. Amer. Chem. Soc.*, 1925, **47**, 2002.

hydrochloric acid and the product isolated by means of chloroform as a gum. This was treated with succinic anhydride (10 g.) in pyridine (40 ml.) at 90—100° for 1 hr. *Coprostane-3α : 12α-diol 3-(hydrogen succinate)*, isolated with chloroform and purified from ether–hexane, formed flakes, m. p. 150—151°, $[\alpha]_D^{22}$ +48° (*c* 0·51) (Found: C, 73·6; H, 10·3. $C_{31}H_{52}O_5$ requires C, 73·7; H, 10·4%).

The free 3α : 12α-diol, obtained by hydrolysis of the ester, was isolated only as a powder, m. p. 80—100° with frothing (from aqueous acetone).

*Coprostane-3 : 12-dione* (Ia; R = R″ = O, R′ = $H_2$).—The foregoing crude diol (1·4 g.) in acetic acid (20 ml.) was treated with chromium trioxide (0·7 g.) in water (2 ml.) for 20 hr. at room temperature. Dilution with water gave a crystalline product which was purified from ethanol. *Coprostane-3 : 12-dione* formed plates, m. p. 138—138·5°, $[\alpha]_D^{23}$ +99° (*c* 0·22) (Found: C, 80·8; H, 11·0. $C_{27}H_{44}O_2$ requires C, 80·9; H, 11·1%).

*4-Bromocoprostane-3 : 12-dione*.—The dione (720 mg.) in acetic acid (15 ml.) was treated dropwise with bromine in acetic acid (1·0 mol.), then poured into water. Extraction with ether–benzene and purification from ethanol gave the *4-bromo-dione* as flakes, m. p. 191—193°, $[\alpha]_D^{23}$ +135° (*c* 0·13) (Found: C, 67·8; H, 9·1; Br, 16·7. $C_{27}H_{43}O_2Br$ requires C, 67·6; H, 9·0; Br, 16·7%).

*Cholest-4-ene-3 : 12-dione* (II; R = $H_2$, R′ = O).—The 4-bromo-dione (480 mg.) in acetic acid (10 ml.) was treated with semicarbazide hydrochloride (390 mg.) and sodium acetate (300 mg.) in water (1 ml.) and acetic acid (10 ml.) under nitrogen, at 50° for 3 hr. *p*-Hydroxybenzaldehyde (3·9 g.) and sodium acetate (300 mg.) in 50% aqueous acetic acid (20 ml.) were added. After a further 3 hr. at 50° the mixture was poured into water, and the product extracted with ether, which was washed with sodium hydroxide solution until colourless, then with water, dried, and evaporated. Purification of the residue from methanol gave *cholest-4-ene-3 : 12-dione* as prisms, m. p. 117—118°, $[\alpha]_D^{23}$ +119° (*c* 0·28), $\lambda_{max.}$ 240 mμ (ε 15,150) in ethanol, $\nu_{max.}$ 1710, 1678, and 1620 $cm.^{-1}$ in carbon tetrachloride (Found: C, 81·2; H, 10·7. $C_{27}H_{42}O_2$ requires C, 81·3; H, 10·6%). The 3-(2 : 4-*dinitrophenylhydrazone*) separated from ethanol–chloroform in orange-red leaflets, m. p. 244—246°, $\lambda_{max.}$ 389 mμ (ε = 33,200) in chloroform (Found: N, 9·9. $C_{33}H_{46}O_5N_4$ requires N, 9·7%).

*12-Oxocoprostan-3α-yl Hydrogen Succinate* (Ia; R = ···O·CO·$[CH_2]_2$·$CO_2H$, $^-$H; R′ = $H_2$, R″ = O).—Coprostane-3α : 12α-diol 3-(hydrogen succinate) (4·4 g.) in acetic acid (220 ml.) was treated with potassium chromate (2·2 g.) in water (22 ml.) at room temperature for 16 hr. The solids which separated proved difficult to filter, so water and chloroform were added, and the chloroform layer was washed neutral, dried and evaporated. The *12-ketone* crystallised from methanol in flakes, m. p. 200—201°, $[\alpha]_D^{25}$ +92° (*c*, 0·37) (Found: C, 73·9; H, 10·0. $C_{31}H_{50}O_5$ requires C, 74·1; H, 10·0%).

The *3α-acetate* was obtained after hydrolysis of the foregoing compound with aqueous methanolic potassium carbonate, and acetylation of the resulting amorphous hydroxy-ketone with acetic anhydride and pyridine. It separated from methanol in plates, m. p. 144—145°, $[\alpha]_D^{17}$ +117° (*c*, 0·45) (Found: C, 78·6; H, 10·8. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%).

*Bromination of 12-Oxocoprostan-3α-yl Hydrogen Succinate*.—The 12-ketone (10 g.) in acetic acid (100 ml.) at 70° was treated with bromine in acetic acid (19·0 ml. of 1·06M-solution). Decolorisation was completed in 1·5 hr.; then the solution was poured into water and the product isolated with chloroform. Crystallisation of the resulting material from acetone–hexane gave pale yellow crystals (2·25 g.), m. p. 183—192° (decomp.), which after purification from methanol gave *11β-bromo-12-oxocoprostan-3α-yl hydrogen succinate* as flakes, m. p. 214—215° (decomp.), $[\alpha]_D^{16}$ +45° (*c*, 0·28), $\lambda_{max.}$ 311 mμ (ε 105) in ethanol (Found: C, 63·9; H, 8·4; Br, 14·1. $C_{31}H_{49}O_5Br$ requires C, 64·0; H, 8·5; Br, 13·7%).

The mother-liquors after crystallisation of the 11β-bromo-compound were evaporated to dryness, and the residue dissolved in aqueous methanol. The crystals which separated (7·94 g.; m. p. 138—147°) were purified from the same solvent to give the *11α-bromo-ketone* in flakes, m. p. 150—154° (decomp.), $[\alpha]_D^{16}$ +59° (*c* 0·34), $\lambda_{max.}$ 287 mμ (ε 76) in ethanol (Found: C, 64·5; H, 8·7; Br, 13·1. $C_{31}H_{49}O_5Br$ requires C, 64·0; H, 8·5; Br, 13·7%).

*Dehydrobromination of the 11β-Bromo-ketone*.—The 11β-bromo-ketone (780 mg.) in pyridine (10 ml.) was heated under reflux for 2 hr. The product was isolated with chloroform and purified from methanol, giving *12-oxocoprost-9(11)-en-3α-yl hydrogen succinate* (III; R = :O) as plates, m. p. 211—212°, $[\alpha]_D^{24}$ +50° (*c* 0·27), $\lambda_{max.}$ 239·5 mμ (ε 9460) in ethanol (Found: C, 74·4; H, 9·8. $C_{31}H_{48}O_5$ requires C, 74·3; H, 9·8%).

The 11α-bromo-ketone was unaffected under the above conditions.

*Alkaline Hydrolysis of* 11(α + β)-*Bromo-12-oxocoprostan-3α-yl Hydrogen Succinate.*—The total product obtained by bromination of the 12-ketone (10 g.) as described above was heated under reflux in ethanol (200 ml.) with potassium hydroxide (23 g.) and water (25 ml.), under nitrogen for 6 hr. The product, isolated with chloroform, was a bromine-free oil. Esterification with succinic anhydride (10 g.) in pyridine (50 ml.) at 90° for ½ hr., isolation with chloroform, and crystallisation from aqueous methanol gave a product, m. p. 157—160°, $[\alpha]_D^{20}$ +31° (*c*, 0·31), which was probably impure 3α : 12β-dihydroxycoprostan-11-one 3-(hydrogen succinate) (Found: C, 73·0; H, 9·6. Calc. for $C_{31}H_{50}O_6$: C, 71·8; H, 9·7%).

11α-*Bromocoprostane-3α* : 12β-*diol* 3-(*Hydrogen Succinate*) (Ia; R = ···O·CO·$[CH_2]_2$·$CO_2H$, −H; R′ = ···Br, −H; R″ = ···H, −OH).—The 11α-bromo-ketone (5·81 g.) in methanol (400 ml.) was treated successively with sodium hydrogen carbonate (1·5 g.) in water (10 ml.), and sodium borohydride (1 g.) in ice-water (20 ml.). After 20 hr. at room temperature the solution was diluted with water. Extraction with ether and purification from aqueous methanol gave the *bromohydrin* in flakes, m. p. 135—138°, $[\alpha]_D^{17}$ +18° (*c* 0·33) (Found: C, 64·1; H, 8·9; Br, 13·5. $C_{31}H_{51}O_5Br$ requires C, 63·8; H, 8·8; Br, 13·7%).

*Coprost-11-en-3α-yl Hydrogen Succinate.*—The foregoing bromohydrin (2 g.) was stirred in boiling acetic acid (50 ml.) with zinc dust (4 g.) for 2 hr. The decanted solution was poured into water, and the product isolated with ether and purified from methanol. The 11-*enyl ester* formed needles, m. p. 159—160°, $[\alpha]_D^{22}$ +125° (*c* 0·04) (Found: C, 76·3; H, 10·4. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·4%).

When this product (66 mg.) in carbon tetrachloride (10 ml.) was treated with an excess of bromine in carbon tetrachloride, the 11 : 12-*dibromide* was formed. After purification from methylene chloride–methanol it was obtained as a powder, m. p. 184—188° (decomp.), $[\alpha]_D^{25}$ +50° (*c* 0·23) (Found: C, 57·8; H, 7·6; Br, 24·9. $C_{31}H_{50}O_4Br_2$ requires C, 57·6; H, 7·8; Br, 24·7%).

*Dehydrogenation of* 12-*Oxocoprostan-3-yl Hydrogen Succinate with Selenium Dioxide.*—The 12-ketone (10 g.), selenium dioxide (2·6 g.), propionic acid (60 ml.), and 2N-hydrochloric acid (1 drop) were heated under reflux for 15 hr. The flakes which separated on cooling were purified from methanol–methylene chloride (selenium being removed by filtration). The keto-ester (III; R = O) formed plates, m. p. 211—212·5°, $[\alpha]_D^{25}$ +52° (*c* 0·24), $\lambda_{max.}$ 239·5 mμ (ε 9200) in ethanol, identical with the sample prepared from the 11β-bromo-ketone (above).

The propionic acid mother-liquors, after dilution with benzene, stirring for 1 hr. with a 25% aqueous solution of chromic acid to remove colloidal selenium,[15] evaporation, and crystallisation from methanol, yielded a further quantity of the same material.

*Coprost-9(11)-en-3-yl Hydrogen Succinate* (III; R = $H_2$).—Reduction of the last compound (7·5 g.) with hydrazine hydrate (4 ml.) in diethylene glycol (75 ml.) and potassium hydroxide (8 g.) by the general procedure described above, followed by re-succinoylation with succinic anhydride (10 g.) in pyridine (50 ml.) and purification from methanol, gave this *ester* (III; R = $H_2$) in fibrous needles, m. p. 149—151°, $[\alpha]_D^{23}$ +55° (*c* 0·27) (Found: C, 76·3; H, 10·2. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·4%).

3α-*Formyloxy-11-oxocholan-24-oic Acid.*—The 3α-hydroxy-acid (4·67 g.) in 98—99% formic acid (15 ml.) was heated at 75° for 3½ hr., then the formic acid was removed under reduced pressure, and the residue heated to 90° at 12—15 mm. pressure for ½ hr. Purification from 70% aqueous ethanol gave the 3-*formate*, needles, m. p. 206°, $[\alpha]_D^{23}$ +68° (*c* 0·22 in methanol) (Found: C, 71·6; H, 9·2. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·2%).

3α-*Hydroxycoprostane-11* : 24-*dione* (I; R = ···OH, −H; R′ = O; R″ = $H_2$).—A solution of di*iso*propylcadmium was prepared as described above from magnesium (2·95 g.), *iso*propyl bromide (12 ml.), ether (50 ml.), anhydrous benzene (100 ml.), and cadmium bromide (17 g.).

3α-Formyloxy-11-oxocholan-24-oic acid (3·2 g.) was treated with pure thionyl chloride (25 ml.) for 2 hr. at room temperature, then excess of thionyl chloride was removed under reduced pressure at 60°. Dry toluene (50 ml.) was added and distilled off under the same conditions, and the solid residue, dissolved in dry benzene (25 ml.), was added to the stirred solution of di*iso*propylcadmium at 0°. The mixture was left at room temperature overnight and poured into water (2 l.) containing acetic acid (150 ml.). The organic phase was washed, the solvent removed, and the residue treated with potassium hydroxide (0·5 g.) in 90% methanol (40 ml.) at 60° for ½ hr. The product was isolated by means of ether and benzene, the solvents

[15] McKenzie, Mattox, Engel, and Kendall, *J. Biol. Chem.*, 1948, **173**, 271.

were removed, and the residue (2·6 g.) in light petroleum (b. p. 40—60°) was chromatographed on to alumina (60 g.). Elution with benzene and purification from hexane gave 3α-*hydroxycoprostane*-11 : 24-*dione* in needles, m. p. 114—116°, $[\alpha]_D^{22}$ +61° (*c* 0·50) (Found: C, 77·7; H, 10·9. $C_{27}H_{44}O_3$ requires C, 77·8; H, 10·7%).

The same product was obtained when the 3-acetate [16] was used in place of the formate.

3α-*Benzoyloxycoprostane*-11 : 24-*dione* formed flakes, m. p. 148—149°, $[\alpha]_D^{27}$ +70° (*c* 0·17) (Found: C, 78·7; H, 9·3. $C_{34}H_{48}O_4$ requires C, 78·5; H, 9·2%).

3α-*Hydroxycoprostan*-11-*one* (Ia; R = ···OH, ⁻H; R′ = O; R″ = $H_2$).—3α-Hydroxycoprostane-11 : 24-dione (1·5 g.) in diethylene glycol (30 ml.) containing 100% hydrazine hydrate (1 ml.) was heated at 100° for ½ hr., then solid potassium hydroxide (3 g.) was added. The mixture was heated in an open flask in a stream of nitrogen for 2 hr. at 200—205°, then cooled and poured into dilute hydrochloric acid. The product, isolated by means of ether, failed to crystallise even after percolation through alumina. Esterification with *p*-nitrobenzoyl chloride in pyridine gave 3α-p-*nitrobenzoyloxycoprostane*-11-*one* which crystallised from ethanol–acetone in leaflets, m. p. 121°, $[\alpha]_D^{20}$ +74° (*c* 0·10) (Found: C, 73·9; H, 8·9; N, 2·8. $C_{34}H_{49}O_5N$ requires C, 74·0; H, 8·9; N, 2·5%).

Hydrolysis of the *p*-nitrobenzoate with aqueous-methanolic potassium hydroxide (2 hr. under reflux) gave 3α-*hydroxycoprostan*-11-*one*, leaflets (from aqueous methanol), m. p. 115—116°, $[\alpha]_D^{23}$ +62° (*c* 0·21) (Found: C, 80·2; H, 11·4. $C_{27}H_{46}O_2$ requires C, 80·4; H, 11·5%).

*Coprostane*-3 : 11-*dione* (Ia; R = R′ = O, R″ = H).—The foregoing compound (435 mg.) in acetic acid (20 ml.) was treated with chromium trioxide (200 mg.) in water (1 ml.) and acetic acid (3 ml.) for 16 hr. at room temperature, then poured into water. *Coprostane*-3 : 11-*dione*, isolated with ether, separated from hexane in prisms, m. p. 118°, $[\alpha]_D^{23}$ +57·5° (*c* 0·18) (Found: C, 80·6; H, 11·4. $C_{27}H_{44}O_2$ requires C, 80·9; H, 11·1%).

The 3-(*mono*-2 : 4-*dinitrophenylhydrazone*) separated from ethyl acetate in yellow plates, m. p. 187—188° (Found: N, 10·1. $C_{33}H_{48}O_5N_4$ requires N, 9·6%).

4-*Bromocoprostane*-3 : 11-*dione*.—Coprostane-3 : 11-dione (670 mg.) in acetic acid (10 ml.) was treated dropwise with bromine in acetic acid (9·0 ml. of 0·187M-solution). After 20 min. the solution was diluted with water to turbidity, and the solids which separated were purified from hexane. The 4-*bromo-dione* formed prisms, m. p. 143—144°, $[\alpha]_D^{24}$ +123° (*c* 0·07) (Found: C, 67·1; H, 9·3; Br, 16·2. $C_{27}H_{43}O_2Br$ requires C, 67·6; H, 9·0; Br, 16·7%).

*Cholest*-4-*ene*-3 : 11-*dione* (II; R = O, R′ = $H_2$).—The 4-bromo-dione (400 mg.) and ethoxycarbonylhydrazine (240 mg.) in acetic acid (5 ml.) were heated on the steam-bath for 15 min., then acetone (35 ml.) and concentrated hydrochloric acid (10 ml.) were added and the mixture was allowed to cool. The solids which separated on dilution of the solution with water were purified from aqueous methanol, then from hexane. *Cholest*-4-*ene*-3 : 11-*dione* formed rectangular prisms, m. p. 107—109°, $[\alpha]_D^{29}$ +173° (*c* 0·10), $\lambda_{max.}$ 238·5 mμ (ε 13,630) in ethanol, $\nu_{max.}$ 1706 (satd. C=O), 1676 (αβ-unsatd. C=O), and 1616 cm.$^{-1}$ (conjugated C=C) in carbon disulphide (Found: C, 81·0; H, 10·4. $C_{27}H_{42}O_2$ requires C, 81·3; H, 10·6%).

The 2 : 4-*dinitrophenylhydrazone* separated from ethanol as an orange-red powder, m. p. 198—200°, $\lambda_{max.}$ 386·5 mμ (ε 29,800) in chloroform (Found: N, 10·1. $C_{33}H_{46}O_5N_4$ requires N, 9·7%).

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The British Drug Houses Ltd.,
Graham Street, London, N.1.

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[16] Turner, Mattox, Engel, McKenzie, and Kendall, *J. Biol. Chem.*, 1946, **166**, 345.