740. *Steroids. Part VI.* Partial Synthesis of 9 : 11-Dehydroprogesterone.*

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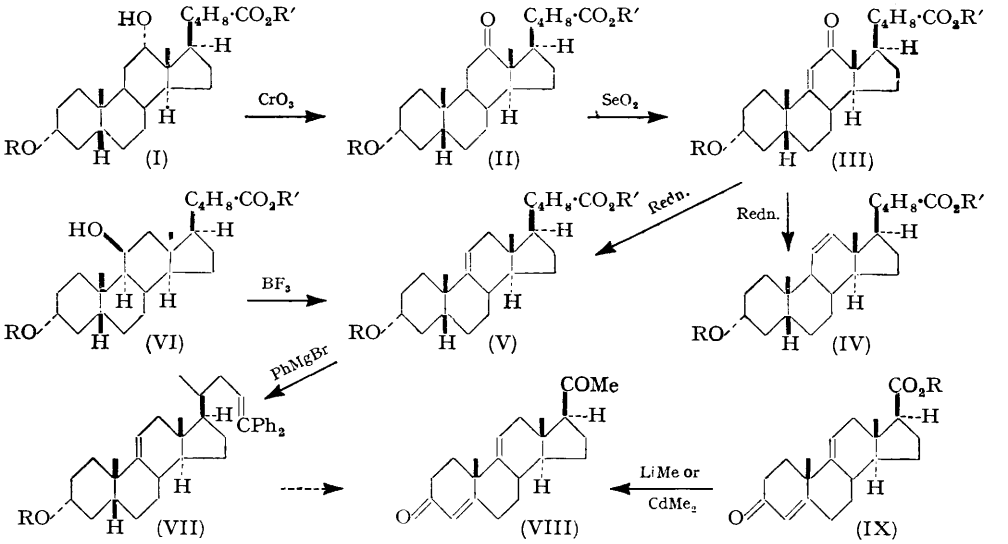
Attempted application of the Miescher–Wettstein degradation to 3α-hydroxychol-9(11)-enoic acid (9 : 11-dehydrolithocholic acid) failed to give 3α-hydroxypregn-9(11)-en-20-one, but by use of 3-oxoetia-4 : 9(11)-dienoic acid the partial synthesis of 9 : 11-dehydroprogesterone has been accomplished.

Progestational activity is a highly specific property; in addition to progesterone (the standard ≡ 1), only seven steroids exhibit comparable activity by subcutaneous application. These are the higher and lower homologues 17α-methylprogesterone (≡ 2) (Plattner, Heusser, and Herzig, *Helv. Chim. Acta*, 1949, **32**, 270; Heusser, Engel, Herzig, and Plattner, *ibid.*, 1950, **33**, 2229, 2237), 19-norprogesterone (≡ 1) (Miramontes, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 3540), 6β-acetoxyprogesterone (≡ $<\frac{1}{3}$) (Ehrenstein and Stevens, *J. Org. Chem.*, 1940, **5**, 318; Balant and Ehrenstein, *ibid.*, 1952, **17**, 1587), 17α-ethynyltestosterone (Inhoffen and Hohlweg, *Naturwiss.*, 1938, **26**, 96; Ruzicka, Hofmann, and Meldahl, *Helv. Chim. Acta*, 1938, **21**, 371), and 6 : 7- (≡ $\frac{1}{2}$) (Wettstein, *ibid.*, 1940, **23**, 388; *Experientia*, 1946, **2**, 408), 9 : 11- (VIII) (≡ $>\frac{1}{2}$) (Shoppee and Reichstein, *Helv. Chim. Acta*, 1941, **24**, 351), and 11 : 12-dehydroprogesterone (≡ 3) (Hegner and Reichstein, *ibid.*, 1943, **26**, 715; von Euw and Reichstein, *ibid.*, 1946, **29**, 669; Meystre, Tschopp, and Wettstein, *ibid.*, 1948, **31**, 1463). Since the position assigned to the double bond in ring C of (VIII) is based on analogy and non-identity with 11 : 12-dehydroprogesterone, it seemed desirable to confirm the structure by partial synthesis.

Steroid 20-ketones are obtainable by degradation of bile acids or sapogenins. When this work was commenced (1949), deoxycholic acid (I*a*) was the only starting material available, and we converted it into 3α-hydroxychol-9(11)-enoic acid (V*a*) for degradation by the Miescher–Wettstein procedure to 3α-hydroxypreg-9(11)-en-20-one. Deoxycholic acid as the 3α-benzoyloxy-methyl ester (I*b*) with chromium trioxide in chlorobenzene–acetic

* Part V, *J.*, 1953, 2983.

acid at 20° (ref. b; references in this form are found in the Table) gave methyl 3α-benzoyloxy-12-oxocholanoate (II*b*) accompanied by the anhydride of the free hydroxy-acid (II*a*), and methyl 3 : 12-dioxocholanoate. By dehydrogenation with selenium dioxide



	M. p.	$[\alpha]_D$	Refs.
I*a*; R = R′ = H	176°	+ 53°E	a, b
I*b*; R = Bz, R′ = Me...	110	—	b
II*a*; R = R′ = H	164	+110E	a, c, e
II*b*; R = Bz, R′ = Me	96/104/128	—	b, e, f
III*a*; R = R′ = H	180	+107M	b, d, e, g
III*b*; R = Ac, R′ = Me	148	+111C	e, g, h, i
III*c*; R = Bz, R′ = Me	125	+126C	f
IV*a*; R = R′ = H	165	+ 43E	j
IV*b*; R = H, R′ = Me	106	+ 46M	k, l
IV*c*; R = Ac, R′ = Me	119	+ 51A	k, l
IV*d*; R = Bz, R′ = Me	Not isolated		f
V*a*; R = R′ = H	190	+47E	c, e, g, h
V*b*; R = H, R′ = Me	105°/113°	+45°A, +46M	g, h
V*c*; R = Ac, R′ = Me	138	+57C, +63A	e, g, h, m
V*d*; R = Bz, R′ = Me	Amorphous		f
VI*a*; R = R′ = H ...	200	+ 55M	m
VI*b*; R = Ac, R′ = Me	147	+ 71A	m, n, o
VII*a*; R = H	Amorphous		f
VII*b*; R = Ac	142	+ 79C	f
VIII	125	+159A	f, p
IX*a*; R = H	240 *	—	q
IX*b*; R = Me	105	+132C	q

A = Acetone; C = chloroform; E = ethanol; M = methanol. * With decomp.

References : a, M. Sorkin and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 797. b, McKenzie, Mattox, Engel, and Kendall, *J. Biol. Chem.*, 1948, **173**, 271. c, Chakravorty and Wallis, *J. Amer. Chem. Soc.*, 1940, **62**, 318. d, Longwell and Wintersteiner, *ibid.*, p. 200. e, Hicks, Berg, and Wallis, *J. Biol. Chem.*, 1946, **162**, 633. f, This paper. g, Seebeck and Reichstein, *Helv. Chim. Acta*, 1943, **23**, 536. h, Mattox, Turner, Engel, McKenzie, McGuckin, and Kendall, *J. Biol. Chem.*, 1946, **164**, 569. i, Turner, Mattox, Engel, McKenzie, and Kendall, *ibid.*, 1946, **162**, 571. j, McKenzie, McGuckin, and Kendall, *ibid.*, 1946, **162**, 555. k, Engel, Mattox, McKenzie, McGuckin, and Kendall, *ibid.*, p. 565. l, Press and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 878. m, Turner, Mattox, Engel, McKenzie, and Kendall, *J. Biol. Chem.*, 1946, **166**, 345. n, Lardon and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 586. o, Ott and Reichstein, *ibid.*, p. 1799. p, Shoppee and Reichstein, *ibid.*, 1941, **24**, 351. q, Casanova, Shoppee, and Summers, *J.*, 1953, 2983.

in chlorobenzene–acetic acid (Schwenk and Stahl, *Arch. Biochem.*, 1947, **14**, 125; ref. b) methyl 3α-benzoyloxy-12-oxocholanoate (II*b*) gave methyl 3α-benzoyloxy-12-oxochol-9(11)-enoate (III*c*), giving no m. p. depression with the saturated 3α-benzoyloxy-methyl ester (II*b*), or, after hydrolysis, 3α-hydroxy-12-oxochol-9(11)-enoic acid (III*a*) (refs. b, d, e, g). Subsequently, Fieser and Rajagopalan (*J. Amer. Chem. Soc.*, 1950, **72**, 5530) have recommended the use of 3α-ethoxycarbonyl derivatives in the reaction sequence (I ⟶ II ⟶ III), whilst a new route from cholic acid to the acid (III*a*) has been described by Fieser, Tishler, *et al.* (*ibid.*, 1951, **73**, 4133).

Methyl 3α-benzoyloxy-12-oxochol-9(11)-enoate (III*c*) was reduced by the Wolff–Kishner reaction, under pressure or at low pressure in triethylene glycol, to a mixture of

3α-hydroxychol-11-enoic acid (IV*a*) and 3α-hydroxychol-9(11)-enoic acid (V*a*). It is known that Wolff–Kishner reduction of $\Delta^{9(11)}$-12-ketones gives mixtures of 11- and 9(11)-unsaturated acids (Alther and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 492); thus, the 3α-hydroxy-acid (III*a*), its 3α-acetoxy-methyl ester (IIIb), and its 3α-ethoxycarbonyl-methyl ester * also afford a mixture of the acids (IV*a*, V*a*). These acids and their 3α-acetoxy-methyl esters are isomorphous with each other and with 3α-hydroxycholanoic [≡ lithocholic] acid and its acetoxy-methyl ester. Reichstein and Seebeck (ref. g., p. 536, footnote 2) noted that the methyl esters (IV*b*, V*b*) are not isomorphous and give a small but definite m. p. depression; we were able to effect a partial separation of these esters by fractional crystallisation from methanol. A similar, nearly complete separation has subsequently been reported by Fieser and Rajagopalan (*loc. cit.*). A previous attempt to separate the 3α-acetoxy-methyl esters (IV*c*, V*c*) by use of bromine (1 mol.) was unsuccessful (ref. g.); we have confirmed this but we have been able completely to remove the 3α-acetoxy-methyl ester (IV*c*) by partial bromination (0·2 mol.). Although (V*c*) reacts with bromine to undergo deep-seated change (cf. ref. h), (IV*c*) undergoes addition to give methyl 3α-acetoxy-11β : 12α-dibromocholanoate (refs. h, o; Kendall *et al.*, *J. Biol. Chem.*, 1948, **172**, 283); this is readily separated chromatographically from the unchanged 3α-acetoxy-methyl ester (V*c*) and by debromination with zinc–acetic acid affords the pure ester (IV*c*). The 3α-benzoyloxy-methyl esters (IV*d* and V*d*) may be separated similarly.

Alternatively, the 3α-benzoyloxy-methyl ester (III*c*) by condensation with ethanedithiol gave a quantitative yield of the 12-mercaptal, desulphurised with Raney nickel in ethanol to a product which was separated chromatographically into an unidentified substance and methyl 3α-benzoyloxychol-9(11)-enoate (V*d*); this was converted by hydrolysis, esterification, and acetylation into the pure 3α-acetoxy-methyl ester (V*c*), identical with a specimen prepared some 10 years ago by dehydration of methyl 3α-acetoxy-11β-hydroxycholanoate (VI) with boron trifluoride in acetic acid–acetic anhydride at 20° (Shoppee, *Helv. Chim. Acta*, 1943, **27**, 543; cf. Heymann and Fieser, *J. Amer. Chem. Soc.*, 1951, **73**, 5252).

By treatment with phenylmagnesium bromide methyl 3α-acetoxychol-9(11)-enoate (V*c*) gave 24 : 24-diphenylchol-9(11)-ene-3α : 24-diol; this was acetylated with acetic anhydride–pyridine, at 20° and the 3α-monoacetate dehydrated by refluxing acetic acid (Morsman, Steiger, and Reichstein, *Helv. Chim. Acta*, 1937, **20**, 1) to 3α-acetoxy-24 : 24-diphenylchola-9(11) : 23-diene (VII).†

The action of *N*-bromosuccinimide in non-polar solvents on allylic systems is catalysed photochemically (Miescher *et al.*, *Helv. Chim. Acta*, 1945, **28**, 1252) and by peroxides (Karrer and Schmid, *ibid.*, 1946, **29**, 573), and appears to involve succinimidoyl radicals for chain-propagation (Dewar, " Electronic Theory of Organic Chemistry," Oxford, 1949, p. 273), since there is attack at the α-methylene group but not at the double bond as would be expected with bromine atoms. Since tertiary hydrogen atoms are not attacked (Ziegler *et al.*, *Annalen*, 1942, **551**, 80; Miescher *et al.*, *loc. cit.*), except in the presence of peroxide (Karrer and Schmid, *loc. cit.*), it was expected that treatment of 3α-acetoxy-24 : 24-diphenylchola-9(11) : 23-diene (VII) with *N*-bromosuccinimide in carbon tetrachloride would lead

* This pure compound, m. p. 158—161°, $\lambda_{max.}$ 239, log ε 4·05—4·10, by Wolff–Kishner reduction gave a product which, after esterification with diazomethane, acetylation, and treatment with perbenzoic acid, was resolved chromatographically into methyl 3α-acetoxycholanoate (30%), the 11α : 12α-epoxide of (IV*c*) (16%), and the 9α : 11α-epoxide of (V*c*) (34—41%). The presence of 30% of 3α-hydroxycholanoic acid in the reduction product seems improbable. We have found that pure methyl 3α-acetoxychol-9(11)-enoate does not react quantitatively with perbenzoic acid at 0°, although Seebeck and Reichstein (ref. g) observed a quantitative reaction at 18°. Fieser and Rajagopalan (*loc. cit.*) do not state their conditions for epoxidation or how their unoxidised product was identified as methyl 3α-acetoxycholanoate; we believe that their unoxidised product was methyl 3α-acetoxychol-9(11)-enoate (V*c*), since the difference in m. p. of these isomorphous compounds is only 4° (ref. g).

† This compound exhibits $\lambda_{max.}$ 206 mμ, log ε 4·51 and $\lambda_{max.}$ 253 mμ, log ε 4·24. The latter maximum arises from the 24 : 24-diphenylethylene grouping (cf. Coles and Braude, *J.*, 1950, 2016); the former is probably due to the two phenyl groups [cf. toluene with $\lambda_{max.}$ 206 mμ, log ε 3·90 (Bowden and Braude, *J.*, 1952, 1068)], whilst the large extinction coefficient appears to be due to a contribution from ethylenic double bond absorption, since a new determination of the ultra-violet spectrum of 1 : 1-diphenylethylene by Dr. Braude shows maxima at 208 mμ, log ε 4·20, 228 mμ, log ε 4·17, and 251 mμ, log ε 4·04. We wish to thank Dr. E. A. Braude for a private discussion and for his kindness in making available his new unpublished results on 1 : 1-diphenylethylene.

to substitution at $C_{(22)}$ in the side-chain under the activating influence of the $C_{(24)}$-phenyl groups rather than at $C_{(12)}$ in the nucleus. In exploratory experiments, the 3α-acetoxymethyl ester (V*c*) was briefly treated with pure *N*-bromosuccinimide (0·75 mol.) in carbon tetrachloride whereby succinimide was formed and 65—70% of the starting material recovered by crystallisation or chromatography; no other crystalline products could be isolated. To determine whether attack at $C_{(12)}$ was taking place, the 3α-hydroxy-methyl ester (V*b*) was similarly treated with *N*-bromosuccinimide; here substitution at $C_{(12)}$ should yield the labile methyl 3α-hydroxy-12α-bromochol-9(11)-enoate, quantitatively converted by treatment in chloroform solution with cold water into the stable methyl 3α : 9α-epoxychol-11-enate, m. p. 53°, $[\alpha]_D$ −58°, which furnishes stable epimeric 11β : 12α- and 11α : 12β-dibromides (Kendall *et al.*, ref. h, *J. Biol. Chem.*, 1948, **173**, 283). Succinimide was again formed, and 60% of the starting material was recovered but methyl 3α : 9α-epoxychol-11-enoate could not be isolated.*

The 3α-acetoxy-9(11) : 23-diene (VII) with *N*-bromosuccinimide in carbon tetrachloride under various conditions gave succinimide, but ~70% of unchanged starting material was the only crystalline product which could be isolated. The residual material consisted of uncrystallisable oils, showing no selective absorption in the 205-mμ region, and taking up only 1·04 mol. of perbenzoic acid to give a non-crystalline 3α-acetoxy-23 : 24-epoxide, reduced by lithium aluminium hydride to a non-crystalline product (probably a 3α : 24-diol). These results suggest disappearance or migration of the 9(11)-double bond. Miescher, Wettstein, *et al.* (*Helv. Chim. Acta*, 1946, **29**, 627; 1947, **30**, 1022) were able to protect a 5(6)-double bond in a 3β-acetoxy-5 : 23-diene, before treatment with *N*-bromosuccinimide, by addition of hydrogen chloride; we find that the 9(11)-double bond in the ester (V*c*) or the diene (VII) fails to add hydrogen chloride (cf. ref. b, p. 278, footnote 8), whilst the attractive alternative of temporary protection by peroxidation: $>\underset{(9)}{C}=\underset{(11)}{CH}- \longrightarrow >C\overset{O}{\diagup\!\diagdown}CH- \longrightarrow >C(OH)\cdot CH_2- \longrightarrow >C{:}CH-$ is precluded by the stability of 9α : 11α-epoxides to lithium aluminium hydride (Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1951, **73**, 118).

It appears then that the Miescher–Wettstein procedure cannot be applied to $\Delta^{9(11)}$-steroids, and it seems improbable that the Barbier–Wieland degradation can be used since it involves oxidation with chromium trioxide, which converts $\Delta^{9(11)}$-steroids into $\Delta^{9(11)}$-12-ketones and 9α : 11α-epoxides (Reichstein *et al.*, *Helv. Chim. Acta*, 1943, **26**, 492, 536; 1945, **28**, 1420; Reich and Lardon, *ibid.*, 1947, **30**, 329; Shoppee, *ibid.*, p. 766).

We were therefore compelled to resort to the alternative route investigated by Casanova, Shoppee, and Summers (*J.*, 1953, 2983), whereby the side-chain of deoxycholic acid is removed before introduction of the 9(11)-double bond. Deoxycholic acid was degraded to 3-oxoetia-4 : 9(11)-dienoic acid (IX), which by treatment with methyl-lithium or, better, as the acid chloride with dimethylcadmium, gave 9 : 11-dehydroprogesterone (VIII), m. p. 125°, $\lambda_{max.}$ 240 (log ε 4·15) (≡ Δ^4-3-oxo-grouping) and 206 mμ (log ε 3·67) (≡ $R_2C_{(9)}{:}CH_{(11)}\cdot$) (cf. Henbest *et al.*, *Chem. and Ind.*, 1951, 866; *J.*, 1952, 2737), exhibiting bands in the infra-red spectrum at 1730 (≡ 20-oxo-group) and 1675 $cm.^{-1}$ (≡ Δ^4-3-oxo-group), which did not depress the m. p. of a specimen prepared by one of us in 1941 by dehydration of 11β-hydroxyprogesterone (Reichstein and Fuchs, *Helv. Chim. Acta*, 1940, **23**, 684; Shoppee and Reichstein, ref. p; Rosenkranz *et al.*, *J. Org. Chem.*, 1952, **17**, 290) with hydrogen chloride–acetic acid.† This partial synthesis establishes the structure originally assigned.

Experimental

For general directions see *J.*, 1953, 243, 540; $[\alpha]_D$ are determined in $CHCl_3$ and ultra-violet spectra in ethanol, a Unicam SP. 500 spectrometer with corrected scale being used. References

* In a German patent U 1313/120 25/05, dated 1.ix.51, it is claimed that treatment of the 5α : 8α-maleic anhydride adduct of 3β-acetoxypregna-5 : 7 : 9(11)-trien-20-one with *N*-bromosuccinimide in irradiated carbon tetrachloride gives a crystalline 12-bromo-drivative.

† Analogy suggests that this preparation, m. p. 121°, may contain traces of 11 : 12-dehydroprogesterone since these isomerides are probably isomorphous. 11α-Hydroxyprogesterone resists dehydration by acetic anhydride at 100° and gives the 11α-acetate (Rosenkranz *et al.*, *J. Org. Chem.*, 1952, **17**, 1066).

denoted by letters are those of the table on p. 3684, where previously recorded constants are also given.

Methyl 3α-*Benzoyloxy*-12-*oxocholanoate* (II*b*).—Methyl 3α : 12α-dihydroxycholanoate (ref. a) was converted into the 3α-benzoate, which was oxidised with chromium trioxide in chlorobenzene at 20—25° according to the directions of Kendall *et al.* (ref. b). Crystallisation of the oxidation product from acetone–methanol led to the separation of a by-product, which was removed by filtration; the filtrate, cooled to 5°, gave methyl 3α-benzoyloxy-12-oxocholanoate (form A) in plates, m. p. 92—96°, after recrystallisation from methanol. Another run furnished form B, needles (from methanol), m. p. 100—104°, which gave no depression (m. p. 92—104°) by admixture with form A. Form A, dissolved in methanol and inoculated with B, gave form B in long needles, m. p. 100—104°; conversely, a methanolic solution of form B seeded with A gave form A in plates, m. p. 92—96°. A solution of form B in methanol inoculated with authentic methyl 3α-benzoyloxy-12-oxocholanoate (form C), m. p. 126—128°, kindly supplied by Professor E. C. Kendall, gave form C in prisms, m. p. 126—128°; conversion of C into A or B was difficult and succeeded only once, when a hot saturated solution of C in methanol was added slowly to crystals of B. Both form A and form B were stable to further oxidation, gave 3α-hydroxycholanoic acid by low-pressure Wolff–Kishner reduction, and furnished by complete hydrolysis and re-esterification with diazomethane methyl 3α-hydroxy-12-oxocholanoate, m. p. 111° [Sawlewicz and Reichstein (*Helv. Chim. Acta*, 1937, **20**, 992) give m. p. 112°]; subsequently, it was found that form A had been encountered incidentally by Hicks, Berg, and Wallis (ref. e, p. 638). Before a specimen of form C was obtained from the U.S.A., repeated recrystallisation of form B always gave form B; from the time that form C was introduced into the laboratories, all further oxidations (I*b* ⟶ II*b*) gave form C.

The by-product, purified by chromatography on aluminium oxide by elution with benzene and ether–benzene (1 : 1) and then by recrystallisation from chloroform–ether, was identified as 3α-*hydroxy*-12-*oxocholanoic anhydride*, m. p. 242—244°, $[\alpha]_D$ +119° ± 1° (*c*, 5·67) (Found, after drying at 90°/0·05 mm. for 2 hr.: C, 75·6; H, 9·7. $C_{48}H_{74}O_7$ requires C, 76·0; H, 9·4%). The united mother-liquors from several oxidations, by chromatography on aluminium oxide, after elution with benzene–pentane (1 : 1) and benzene, gave methyl 3α-benzoyloxy-12-oxocholanoate (II*b*), m. p. 126—128°, by elution with ether–benzene (1 : 3 and 1 : 1), and with ether gave methyl 3 : 12-dioxocholanoate as prisms (from ether–pentane), m. p. 132—133° (Found, after drying at 70°/0·04 mm. for 2 hr.: C, 74·85; H, 9·3. Calc. for $C_{25}H_{38}O_4$: C, 75·1; H, 9·5%), depressed by admixture with (II*b*) to 102°; Reichstein *et al.* (refs. a, n) record m. p. 132—133°.

Methyl 3α-*Benzoyloxy*-12-*oxochol*-9(11)-*enoate* (III*c*).—Oxidation of methyl 3α-benzoyloxy-12-oxocholanoate (II*b*) with selenium dioxide–chlorobenzene–acetic acid by the method of Kendall *et al.* (ref. b) and hydrolysis gave a 72% yield of 3α-hydroxy-12-oxochol-9(11)-enoic acid (III*a*) (m. p. 176—178°; degree of unsaturation, ~85%) after 27 crystallisations from acetone and acetone–methanol–pentane. This material when purified by Kendall's sodium salt method gave 53% of pure 3α-hydroxy-12-oxochol-9(11)-enoic acid, m. p. 180—181°, $[\alpha]_D$ +100°, $\lambda_{max.}$ 240 mμ (log ε 4·07) (cf. Kendall *et al.*, ref. b). Alternatively, by omission of the alkaline hydrolysis stage, the crude 3α-benzoyloxy-methyl ester (III*c*) and the crude 3α-benzoyloxy-acid could be isolated; the crude acid was esterfied with 1% methanolic hydrogen chloride at 20° and the combined 3α-benzoyloxy-methyl esters, dissolved in ether, were passed through a column of aluminium oxide to give by repeated crystallisation from acetone–ether–pentane *methyl* 3α-*benzoyloxy*-12-*oxochol*-9(11)-*enoate* (III*c*), m. p. 123—125°, $[\alpha]_D^{20}$ +126·5° ± 2° (*c*, 1·02), $\lambda_{max.}$ 229 mμ (log ε 4·404) (Found, after drying at 60°/0·04 mm. for 2 hr.: C, 75·75; H, 8·5. $C_{32}H_{42}O_5$ requires C, 75·85; H, 8·35%), showing no m. p. depression on admixture with the saturated 3α-benzoyloxy-ester (II*b*), m. p. 126—128°, and giving no colour with tetranitromethane–chloroform.

Methyl 3α-*Acetoxychol*-9(11)-*enoate* (V*c*).—Methyl 3α-benzoyloxy-12-oxochol-9(11)-enoate (III*c*) by high-pressure Wolff–Kishner reduction gave a mixture of the 3α-hydroxy-acids (IV*a* and V*a*) in crystalline condition and good yield {mixed 3α-acetoxy-methyl esters, m. p. 126—132°, $[\alpha]_D^{18}$ + 62° (*c*, 1·10)}; use of the Huang-Minlon low-pressure procedure in ethylene glycol gave only a 40% yield, because the mixed acids could not be precipitated in crystalline form and extraction was difficult {mixed 3α-acetoxy-methyl esters, m. p. 126—132°, $[\alpha]_D^{20}$ +65° (*c*, 3·03)}, but good results were obtained in triethylene glycol (cf. Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1951, **73**, 118) from which the mixed acids separated readily in crystals {mixed 3α-acetoxy-methyl esters, m. p. 134—136°, $[\alpha]_D$ +62° (*c*, 1·11)}. Similarly, 3α-hydroxy-12-oxochol-9(11)-enoic acid (III*a*) [m. p. 180—181°, $\lambda_{max.}$ 240 mμ (log ε 4·07)] in trimethylene

glycol gave 75—85% yields of the mixed acids (IV*a* and V*a*). Such a mixture (18·6 g.) was esterified in dioxan with ethereal diazomethane, and a sample of the product repeatedly crystallised from ether–pentane to give methyl 3α-hydroxychol-9(11)-enoate (V*b*) as needles, m. p. 105°, $[\alpha]_D$ +44° (*c*, 1·01) (refs. g, h). The greater part of the product was acetylated with acetic anhydride–pyridine at 20° to give, after crystallisation from acetone–methanol, a mixture of the 3α-acetoxy-methyl esters (IV*c* and V*c*) (17 g.), m. p. 134—136°. A specimen (1·18 g.) of the mixture, dissolved in chloroform (5 c.c.), was titrated at 15° with a solution of bromine (0·415 g., 1 mol.) in chloroform (2 c.c.), of which 0·40 c.c. was immediately decolourised. The solution was at once evaporated completely at 15°/10 mm. and 0·05 mm., and the residue chromatographed on aluminium oxide (18 g.) prepared in pentane. Elution with benzene–pentane (1 : 5; 1 : 3) gave the pure 3α-acetoxy-methyl ester (V*c*) (0·72 g.), m. p. 137—139°, $[\alpha]_D$ +63° (*c*, 1·01 in $COMe_2$), after recrystallisation from acetone–methanol. Elution with benzene–pentane (1 : 1) and with benzene gave methyl 3α-acetoxy-11β : 12α-dibromocholanoate (0·20 g.), m. p. 188—195° (decomp.) after recrystallisation from acetone–methanol {Kendall *et al.*, ref. k, give m. p. 195° (decomp.), $[\alpha]_D$ +65°}, debrominated with zinc–sodium acetate in acetic acid for 15 min. at 70° to give the pure 3α-acetoxy-methyl ester (IV*c*), m. p. 116—118°, $[\alpha]_D$ +50° (*c*, 1·04) (refs. k, l), after recrystallisation from acetone–methanol.

The pure ester (V*c*) (270 mg.; m. p. 137—139°) derived from the pure 3α-hydroxy-acid (III*a*) (with $\lambda_{max.}$ 240 mμ, log ε 4·07), dissolved in chloroform (2 c.c.), was treated with a solution of perbenzoic acid (110 mg., 1·3 mol.) in chloroform (1·5 c.c.) at 0° for 17 hr. After removal of chloroform at 30°/10 mm., the product was dissolved in ether, washed with dilute solutions of sodium iodide and sodium thiosulphate, water, 2N-Na_2CO_3, and water, dried, and evaporated. The crystalline residue was chromatographed on aluminium oxide (9 g.) in pentane; elution with benzene–pentane (1 : 3; 2 : 5) gave the unchanged ester (V*c*) (90 mg.), m. p. 136—138°, after recrystallisation from ether–pentane–methanol, giving a yellow colour with tetranitromethane–chloroform. Elution with benzene–pentane (3 : 2) and benzene gave methyl 3α-acetoxy-9α : 11α-epoxycholanoate (138 mg.), m. p. 118° after crystallisation from methanol {Seebeck and Reichstein (ref. g), give m. p. 121°, [α] +44°, whilst Hicks, Berg, and Wallis (*J. Biol. Chem.*, 1946, **162**, 645) give m. p. 118·5°}. The unaltered ester (V*c*) (90 mg.) was re-treated with perbenzoic acid (37 mg.) as above, and by chromatogrphy yielded the unchanged ester (V*c*) (15 mg.), m. p. 135—137°, and methyl 3α-acetoxy-9α : 11α-epoxycholanoate (55 mg.), m. p. 117°.

The pure ester (V*c*) (200 mg.; m. p. 137—139°) in chloroform (1 c.c.) was treated gradually with bromine (74 mg., 1 mol.) in chloroform (2 c.c.) at 18°. The first drop of bromine was not decolorised, and when approximately half of the bromine had been added production of hydrogen bromide could be observed. After addition of ether, the solution was washed with ice-cold N-sodium hydroxide and then water, dried, and evaporated, and the resultant yellow oil chromatographed on aluminium oxide (6 g.) in pentane. Elution with benzene–pentane (1 : 5; 2 : 5) gave the 3α-acetoxy-methyl ester (V*c*) (130 mg.), m. p. and mixed m. p. 136—138° (after recrystallisation from acetone–methanol), giving a yellow colour with tetranitromethane–chloroform. Further elution of the column gave uncrystallisable oils.

Treatment of the 3α-acetoxy-methyl ester (V*c*) (600 mg.; m. p. 136—138°) in chloroform–acetic acid (1 : 1) with dry hydrogen chloride at 0° failed to give a hydrochloride; the product consisted of unchanged ester, m. p. 134—136°, and partly hydrolysed material.

Methyl 3α-Benzoyloxychol-9(11)-enoate (V*d*).—(*a*) Methyl 3α-benzoyloxy-12-oxochol-9(11)-enoate (III*c*) (2 g., m. p. 123—125°; $\lambda_{max.}$ 228, log ε 4·40; dried at 100°/0·01 mm.) was partly dissolved in ethanedithiol (20 c.c.; b. p. 151—154°), and treated at −15° with dry hydrogen chloride (~20 c.c.) with exclusion of moisture. After 3 hr. at 0°, the mixture was neutralised with solid anhydrous sodium carbonate, and the product extracted with ether; the extract was washed with ice-cold 5N-sodium hydroxide and then water, dried, and evaporated. The residual oil was chromatographed on aluminium oxide (100 g.) prepared in pentane; the fractions eluted by benzene–pentane (1 : 1) and benzene furnished positive tests for sulphur and yellow colours with tetranitromethane–chloroform, but did not crystallise and were united. The colourless mercaptal (1·6 g.) in ethanol (250 c.c.) was refluxed for 6 hr. with Raney nickel (prepared from 80 g. of nickel–aluminium alloy according to Mozingo *et al.*, *J. Amer. Chem. Soc.*, 1943, **65**, 1013, except that, after addition of the alloy, the mixture was kept at 20° for 16 hr.); filtration and evaporation in a vacuum gave a colourless oil (1 g.) which was chromatographed on aluminium oxide (30 g.) prepared in pentane. Elution with benzene–pentane (1 : 5 ⟶ 1 : 1) yielded colourless oils, which did not crystallise but gave negative tests for sulphur and yellow colours with tetranitromethane–chloroform; these consisted essentially of the 3α-benzoyloxy-methyl ester (V*d*) (0·5 g.) since complete alkaline hydrolysis, re-esterification with ethereal diazo-

methane, and acetylation afforded the 3α-acetoxy-methyl ester (V*c*), m. p. 132°, $[\alpha]_D^{18}$ +57° (*c*, 2·054). Further elution with ether–benzene gave a colourless oil (0·25 g., negative sulphur, positive tetranitromethane test); this cannot have arisen by partial hydrolysis at $C_{(3)}$ since acetylation failed to give the 3α-acetoxy-methyl ester (V*c*), which crystallises readily.

(*b*) The mixture of 3α-hydroxy-methyl esters (IV*b* and V*b*) (0·46 g.) in pyridine (7 c.c.) was treated with pure benzoyl chloride (0·7 c.c.) at 20° for 2 hr. After working up (cf. Hegner and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 715, 721), chromatography of the product on aluminium oxide by elution with benzene–pentane (1 : 5, 1 : 4, 1 : 3, 1 : 1, 2 : 3) gave a colourless oil (0·42 g.), which was dissolved in chloroform (2 c.c.) and titrated at 18° with bromine (0·16 g., 1 mol.) in chloroform (1 c.c.) until immediate decolorisation ceased. The solution was at once evaporated completely at 18°/10 mm. and 0·05 mm. and the residue chromatographed on aluminium oxide (14 g.) prepared in pentane; elution with benzene–pentane (1 : 5, 3 : 10) gave methyl 3α-benzoyloxychol-9(11)-enoate (V*d*) (146 mg.) as a colourless oil distilling at 170°/0·02 mm. (halogen test negative, tetranitromethane test positive), which did not crystallise. Elution with benzene–pentane (2 : 5, 1 : 1) gave an oil (160 mg.) containing methyl 3α-benzoyloxy-11β : 12α-dibromocholanoate (halogen test positive, tetranitromethane test negative), whilst elution with benzene gave an unidentified substance (12 mg.), m. p. 144—146° after recrystallisation from acetone–methanol.

The non-crystalline 3α-benzoyloxy-methyl ester (V*d*) by complete alkaline hydrolysis, re-esterification with diazomethane, and acetylation gave the 3α-acetoxy-methyl ester (V*c*), m. p. 134—137°.

3α-*Acetoxy*-24 : 24-*diphenylchola*-9(11) : 23-*diene* (VII*b*).—The 3α-acetoxy-methyl ester (V*c*) (1 g.; m. p. 136°) in benzene (6·6 c.c.) was added to a hot solution of phenylmagnesium bromide [from bromobenzene (4·6 c.c.) and magnesium (1·05 g.)], and the mixture refluxed for 3·5 hr. After cooling, the mixture was poured into a saturated solution of ammonium chloride at 0°, and extracted with ether; the product, after hydrolysis with hot methanolic 3% potassium hydroxide, by the usual treatment gave crude 24 : 24-diphenylchol-9(11)-ene-3α : 24-diol. This was treated with acetic anhydride–pyridine at 20° for 15 hr., and the crude 3α-acetoxy-24 : 24-diphenylchol-9(11)-en-24-ol refluxed with acetic acid (15 c.c.) (cf. Morsman, Steiger, and Reichstein, *loc. cit.*) for 6 hr. The product, by recrystallisation from methanol, gave 3α-*acetoxy*-24 : 24-*diphenylchola*-9(11) : 23-*diene* (870 mg.) as colourless needles, m. p. 140—142°, $[\alpha]_D^{17}$ +79° ± 2° (*c*, 1·78), $\lambda_{max.}$ 206 (log ε 4·51) and 253 mμ (log ε 4·24) (Found, after drying at 60°/0·04 mm. for 5 hr.: C, 84·8; H, 9·0. $C_{38}H_{48}O_2$ requires C, 85·0; H, 9·0%). Chromatography of the material from the mother-liquor on aluminium oxide gave by elution with benzene–pentane (1 : 5, 2 : 5) a further quantity (190 mg.) of the diene, m. p. 139° after recrystallisation from ether–methanol. Elution with benzene–pentane (3 : 2) gave an unidentified substance (76 mg.), m. p. 153—155° after crystallisation from acetone–ether. The 3α-acetoxydiene, as expected, gave negative Rosenheim and Tortelli–Jaffé tests, but when the latter was modified by use of trichloroacetic acid in place of acetic acid gave a green colour.

9 : 11-*Dehydroprogesterone* (VIII).—(*a*) 3-Oxoetia-4 : 9(11)-dienic acid [m. p. 240—250° (decomp.); 54 mg.] (Casanova, Shoppee, and Summers, *loc. cit.*), dissolved in dry benzene (2 c.c.), was treated with oxalyl chloride (0·25 c.c.) at 0° and set aside for 1 hr. at 20°. Benzene and excess of oxalyl chloride were removed in a vacuum and the acid chloride subjected to azeotropic distillation with benzene. A solution of methylmagnesium bromide [from magnesium (0·25 g.)] in ether (25 c.c.) was refluxed with dry cadmium chloride (0·5 g.) for 1 hr. with rigorous exclusion of moisture. The above acid chloride was added in benzene (10 c.c.) to the solution of dimethylcadmium, and the mixture stirred under reflux for 1 hr. The mixture was cooled, then decomposed with ice-cold 2N-hydrochloric acid, and the product isolated in the usual way, as an oil (43 mg.) which was chromatographed on neutralised aluminium oxide (2 g.) prepared in pentane. After elution (5 c.c.) with pentane and benzene–pentane (1 : 19, 1 : 9) (fractions 1—13) had given only traces of oil, use of benzene–pentane (1 : 1) gave an oil (10 mg.) which failed to crystallise; use of benzene (fractions 16—20) gave an oil (15 mg.) which crystallised from methanol at 0° and had m. p. 110—117°. This material, by crystallisation from pentane containing a trace of ether, gave needles, m. p. 123°, separated in a centrifuge; recrystallisation gave 9 : 11-dehydroprogesterone (VIII) (7 mg.), m. p. 125°, $[\alpha]_D$ +159° ± 4° (*c*, 0·23 in $COMe_2$), $\lambda_{max.}$ 240 (log ε 4·15) and 206 mμ (log ε 3·67), which did not depress the m. p. of a genuine specimen.

(*b*) 3-Oxoetia-4 : 9(11)-dienic acid (20 mg.) in ether (5 c.c.) was shaken vigorously with ethereal methyl-lithium at 15—20° for 0·5 hr. After being kept at 0° for 1·5 hr., the mixture was poured into ice-cold 2N-hydrochloric acid. The neutral product, isolated in the usual way, was an oil;

the alkaline washings, by acidification, gave only a slight turbidity. Chromatography of the neutral oil on aluminium oxide (250 mg.) and elution with benzene–pentane (2 : 1) and benzene gave fractions which crystallised on inoculation, having m. p. 110—122° and 115—122°; mixed with a genuine specimen of 9 : 11-dehydroprogesterone these preparations had m. p. 110—120°, but were too small for further purification.

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