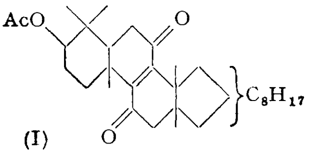
607. *Lanosterol. Part XIV.* Further Experiments on the Reduction of Ketones in the Lanosterol Series.*

By J. F. McGhie, M. K. Pradhan, and (in part) J. F. Cavalla.

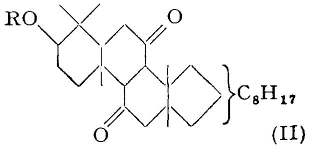
Reduction of acetoxylanostanedione by the modified Wolff–Kishner method (Herr, Whitmore, and Schliessler, *J. Amer. Chem. Soc.*, 1945, **67**, 2061) gave acetoxylanostanone, which on further reduction yielded acetoxylanostanol. This, on dehydration with phosphorus oxychloride followed by hydrogenation, gave acetoxylanostane (Ruzicka *et al.*, *Helv. Chim. Acta*, 1950, **33**, 1893). Similar reduction of acetoxylanostenedione gave acetoxylanostenone, which is isomeric with the " ketolanostenyl acetate " obtained by chromic acid oxidation of lanostenyl or γ-lanostadienyl acetate (Marker, Wittle, and Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1368; Cavalla and McGhie, *J.*, 1951, 744). Lanostadienone on reduction by the modified Wolff–Kishner method, gave lanostadiene.

The investigations now described are a continuation of others (*J.*, 1951, 744, 834, 3142), in which reduction of certain ketones derived from lanostadienol was reported.

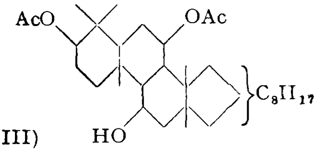
It is known that acetoxylanostenedione (I) is easily reduced under mild conditions to the saturated lanostanedionol (II; R = H) (Dorée McGhie, and Kurzer, *J.*, 1948, 988). Further reduction of (II; R = Ac) with lithium aluminium hydride in anhydrous ether, followed by acetylation, gave diacetoxylanostanol (III) (Cavalla and McGhie, *J.*, 1951, 834; Voser, Montavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893), whereas reduction of acetoxylanostenedione (I) under similar conditions yielded diacetoxylanostanone (IV) (Cavalla and McGhie, *loc. cit.*). The $C_{(8)}$- and the $C_{(11)}$-keto-group therefore differ in reactivity. This has been confirmed by preparation of a monoxime by Voser *et al.* (*loc. cit.*).



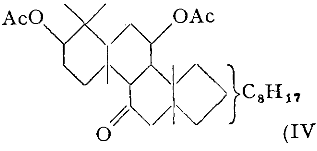
(I)



(II)



(III)



(IV)

Whilst our experiments on the conversion of acetoxylanostanedione into acetoxylanostanone and thence into lanostanol were in progress, the Swiss workers reported such a conversion into acetoxylanostanone (V) (Voser *et al.*, *loc. cit.*). The melting point of (V) reported varied from 140° to 151°, apparently depending on the method of isolation.

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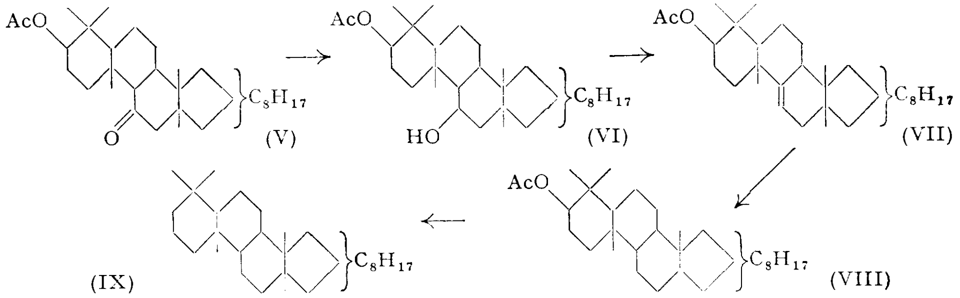
* Part XIII, *J.*, 1951, 3142.

They reduced acetoxylanostanone with lithium aluminium hydride to the corresponding diol, the acetyl derivative (VI) of which was dehydrated with phosphorus oxychloride to acetoxylanostene (VII), whence catalytic reduction gave acetoxylanostane (VIII); from this the fundamental hydrocarbon lanostane (IX) was prepared.

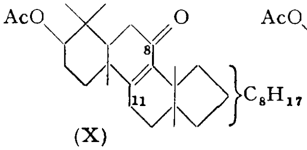
In a previous communication (Cavalla, McGhie, and Pradhan, *loc. cit.*) it was shown that ketolanostenyl acetate (X) is easily reduced by the modified Wolff–Kishner method (Herr, Whitmore, and Schliessler, *loc. cit.*) to *iso*lanostenyl acetate. As the keto-group at $C_{(8)}$ is less hindered than that at $C_{(11)}$ (for a discussion on this point see Barton, Fawcett, and Thomas, *loc. cit.*) and is easily reducible by the Wolff–Kishner method, we subjected acetoxylanostanedione (II; R = Ac) to the modified Wolff–Kishner procedure: Acetoxylanostanedione hydrazone (which was not isolated) was heated with sodium in diethylene glycol at 230°. The product, on acetylation followed by chromatographic purification, gave colourless needles, $C_{32}H_{54}O_3$, m. p. 150—152°, $[\alpha]_D$ +62·9°, identical with acetoxylanostanone (V). Confirmation was obtained by hydrolysis to the corresponding lanostanonol, m. p. 161—162°, $[\alpha]_D$ +60·0°. Reduction of either acetoxylanostanone or lanostanonol with lithium aluminium hydride gave the diol, which, as above, gave (VI) and (VII), m. p. 177—178°, $[\alpha]_D$ +83·0°. After initial difficulties (VII) was hydrogenated to acetoxylanostane (VIII) in glacial acetic acid at 80°, without pre-reduction of the catalyst. The annexed table is a comparison of our products with those of Voser *et al.* (*loc. cit.*).



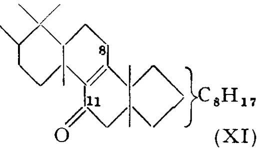
	Voser *et al.*		Present work	
	M. p.	$[\alpha]_D$	M. p.	$[\alpha]_D$
Acetoxylanostanone	143—144°	+60·0°	150—152°	+62·0°
Lanostanonol	160—162	+62·0	161—162	+60·0
Acetoxylanostanol	219—220	+23·0	215—216	+22·8
Acetoxylanostene	170—171	+18·0	177—178	+83·0
Acetoxylanostane	150—151	+41·0	156—157	+45·0

We then turned our attention to the unsaturated diketone, acetoxylanostenedione, where we expected difficulty since it is well known that αβ-unsaturated carbonyl compounds usually give the pyrazolines (Lardelli and Jeger, *Helv. Chim. Acta*, 1949, **32**, 1817) rather than the hydrazones on reaction with hydrazine, the former being converted by hot alkali into *cyclo*propane derivatives. Since, however, carvone, carvenone, and *cyclo*pentenone behave normally (Merejkowsky, *Bull. Soc. chim.*, 1925, **37**, 1174) it has been suggested (Merejkowsky, *loc. cit.*) that *cyclo*propane formation does not take place if it requires the formation of one ring within another. These conditions apply to acetoxylanostenedione, and since the αβ-unsaturated ketone group of ketolanostenyl acetate (X) behaved normally in the Wolff–Kishner reduction, we attempted the reduction of acetoxylanostenedione (I) by the modified Wolff–Kishner process: we isolated a major and a minor component. The former, long white needles, m. p. 119—120°, $[\alpha]_D$ +131·3°, had the formula $C_{32}H_{52}O_3$ of a ketolanostenyl acetate. Its ultra-violet absorption spectrum indicated an αβ-unsaturated ketone by an intense band at 255 mμ (log ε 3·9) and another less intense at 302 mμ (log ε 1·6) (Campbell and Harris, *J. Amer. Chem. Soc.*, 1941, **63**, 2721; Clifford and Woodward, *ibid.*, p. 2727). The αβ-unsaturated ketonic character of the compound was confirmed by infra-red absorption bands at 1736, 1656, 1583, and 1243 cm.$^{-1}$. The 1736- and 1243-cm.$^{-1}$ bands are due to the C═O and C—O vibrations, respectively, of the acetate group, that at 1656-cm.$^{-1}$ to the ketone in conjugation with C═C, and that at 1583 cm.$^{-1}$ to the C═C group. We are indebted to Mr. S. F. D. Orr (Chester Beatty Research Institute) for these measurements. This compound is isomeric with ketolanostenyl acetate (X), m. p. 152—153°, $[\alpha]_D$ +18·5°, which is known to have the keto-group at C$_{(8)}$ (Barton, Fawcett, and Thomas, *loc. cit.*), and arises by the reduction of the unsaturated 8 : 11-diketone (I); it must of necessity be C$_{(11)}$-ketone (XI).

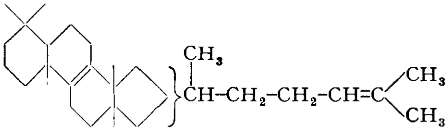
The major component, m. p. 158—160°, $[\alpha]_D$ +78°, had absorption maxima at 235, 243, and 253 mμ (log ε 3·8, 3·9, and 3·8 respectively), indicating that it was impure γ-lanostadienyl acetate. This was obtained by Barton *et al.* as a by-product during the normal Wolff–Kishner reduction of ketolanostenyl acetate, and we think that in this instance it also arises from the isomeric ketolanostenyl acetate (acetoxylanostenone) (XI).



(X)



(XI)



(XII)

Some years ago Ruzicka *et al.* (*Helv. Chim. Acta*, 1944, **27**, 479) reported the preparation of the fundamental hydrocarbons lanostene and γ-lanostadiene (dihydroagnostadiene) from their respective ketones, *via* the semicarbazones which were reduced by the classical Wolff–Kishner procedure (Dorée, McGhie, and Kurzer prepared these hydrocarbons by a modified Clemmensen method; *J.*, 1947, 1467). We have now obtained them in excellent yields by the modified Wolff–Kishner method, in which large quantities can be reduced with comparative ease in a much shorter time. We also report the similar preparation of the hitherto undescribed hydrocarbon, lanostadiene (XII).

EXPERIMENTAL

M. p.s are uncorrected. Specific rotations were determined on chloroform solutions at 20°. The aluminium oxide used in the chromatographic work was from Messrs. Peter Spence Ltd. (Grade " O "). Analyses are by Drs. Weiler and Strauss, Oxford. Light petroleum refers to the fraction of b. p. 60—80°. Ultra-violet absorption spectra were measured with a Unicam S.P. 500 spectrophotometer. Infra-red absorption spectra were determined on carbon disulphide and chloroform solutions. The term " in the usual manner " below refers to dilution with water, extraction with ether, washing successively with aqueous sodium hydroxide solution, aqueous hydrochloric acid, and water, drying of the ethereal solution (Na_2SO_4), and removal of the solvent *in vacuo*.

Modified Wolff–Kishner Reduction of Acetoxylanostanedione.—Acetoxylanostanedione (7·0 g.) in diethylene glycol (250 ml.) was heated under reflux with hydrazine hydrate (3·5 ml.; 100%) at 200° for 1 hour. The mixture was cooled, a solution of sodium (7·0 g.) in diethylene glycol (70 ml.) was added, and the mixture heated under reflux at 220—230° for 6 hours. The solution was allowed to cool, then diluted with cold water, acidified, and extracted with ether. The ethereal solution was washed well with water and dried (Na_2SO_4). Removal of the ether gave a light brown solid (5·0 g.). This was acetylated with pyridine (50 ml.) and acetic anhydride (50 ml.) on a steam-bath for 3 hours. The product was worked up in the usual manner, to give a dark brown oil, which was adsorbed on alumina (14 × 1·3 cm.) from light petroleum; elution with light petroleum (200 ml.) gave a colourless acetate, m. p. 142—145° (from chloroform–methanol). This, on recrystallisation from the same solvent, gave pure acetoxylanostanone as needles (3·3 g.), m. p. 150—152°, $[\alpha]_D^{20}$ +62·9° (*c*, 1·074) (Found: C, 78·9; H, 11·5. Calc. for $C_{32}H_{54}O_3$: C, 78·96; H, 11·2%).

Acetoxylanostanone ⟶ *Acetoxylanostane.*—Acetoxylanostanone was converted, essentially by the methods of Voser *et al.*, into lanostanol, lanostanediol, m. p. 190—191°, $[\alpha]_D^{20}$ +28·4° (*c*, 0·706), acetoxylanostene, and acetoxylanostane (see the Table, p. 3177, for constants).

Modified Wolff–Kishner Reduction of Acetoxylanostenedione.—Acetoxylanostenedione (4·8 g.)

in diethylene glycol (200 ml.) was heated with hydrazine hydrate (4 ml.; 60%) for 1 hour at 200°. The mixture was cooled, a solution of sodium (5·0 g.) in diethylene glycol (80 ml.) was added, and the mixture heated under reflux at 220° for 6 hours. The mixture was then cooled, diluted with water, acidified, and extracted with ether. The ethereal solution was washed well with water and dried (Na_2SO_4). Removal of the ether gave a brown solid. This was acetylated with pyridine (25 ml.) and acetic anhydride (75 ml.) on a steam-bath for 4 hours. The mixture was then worked up in the usual manner, to give a brown oil. This was adsorbed on alumina (18 × 1·3 cm.) from light petroleum; elution with light petroleum (300 ml.), followed by light petroleum–benzene, gave material (A) (2·1 g.) melting between 110° and 116° after crystallisation from chloroform–methanol; further elution by light petroleum–benzene (1 : 1) gave material (B) (0·05 g.), m. p. 142—147° after crystallisation from chloroform–methanol. Further chromatography of (A) gave the following results (m. p.s after crystallisation from methanol) :

Fraction	Eluant	Product, m. p.
1	Light petroleum, 100 ml.	118—136° (0·1 g.)
2	Light petroleum, 200 ml.	150—152° (0·1 g.)
3	Light petroleum–benzene (7 : 3), 100 ml.	110—112° (0·2 g.)
4	Light petroleum–benzene (1 : 1), 100 ml.	112—115° (0·8 g.)
5	Light petroleum–benzene (3 : 7), 100 ml.	112—114° (0·6 g.)
6	Benzene, 100 ml.	114—116° (0·1 g.)

Fraction 2 on recrystallisation from chloroform–methanol gave impure γ-lanostadienyl acetate (0·05 g.), glistening plates, m. p. 158—160°, $[\alpha]_D^{20}$ +78° (*c*, 1·04), $\lambda_{max.}$ 235, 243, and 253 mμ (log ε 3·8, 3·9, and 3·8, respectively, in ethanol). Fractions 4, 5, and 6, on recrystallisation from methanol, gave long colourless needles of pure *acetoxylanostenone* (1·2 g.), m. p. 119—120°, $[\alpha]_D^{20}$ +131·3° (*c*, 1·08), $\lambda_{max.}$ 255 mμ (log ε 3·9, in ethanol) (Found: C, 79·2; H, 10·9. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%).

Lanostene.—Lanostenone (2·0 g.) in diethylene glycol (50 ml.) was heated with hydrazine hydrate (2 ml.; 100%) at 200° for 30 minutes. The mixture was allowed to cool, a solution of sodium (2·0 g.) in diethylene glycol (20 ml.) added, and the whole refluxed for a further 6 hours. The mixture was worked up in the usual manner, to give a yellow glass and on crystallisation from acetic acid pure lanostene (1·8 g.) as plates, m. p. 74—75°, $[\alpha]_D^{20}$ +65·0° (*c*, 1·02) (Found: C, 87·3; H, 12·5. Calc. for $C_{30}H_{52}$: C, 87·4; H, 12·6%), which gave no depression in m. p. on admixture with an authentic specimen.

γ-Lanostadiene.—γ-Lanostadienone (10·0 g.), reduced by the modified Wolff–Kishner method, gave γ-lanostadiene (8·0 g.), plates (from glacial acetic acid), m. p. 93—95°, $[\alpha]_D^{20}$ +75·4° (*c*, 1·02) (Found: C, 87·6; H, 12·2. Calc. for $C_{30}H_{50}$: C, 87·8; H, 12·2%), which gave no depression in m. p. on admixture with an authentic specimen.

Lanostadiene.—Lanostadienone (2·0 g.) in diethylene glycol (25 ml.) was treated with hydrazine hydrate (2 ml.; 100%) and sodium (2·09 g.) in diethylene glycol (25 ml.) as above. The mixture was cooled, poured into water, acidified, and extracted with ether. The ethereal solution was washed with water and dried (Na_2SO_4). Removal of the ether gave a sticky solid. This was adsorbed on alumina (12 × 1·3 cm.) from light petroleum; elution with light petroleum (300 ml.) gave a colourless oil; two crystallisations from chloroform–methanol gave *lanostadiene* as plates (1·8 g.), m. p. 79·5—80°, $[\alpha]_D^{20}$ +65·2° (*c*, 0·981) (Found: C, 87·7; H, 12·2. $C_{30}H_{50}$ requires C, 87·8; H, 12·2%).

One of us (J. F. C.) is indebted to the Department of Scientific and Industrial Research for a maintenance award.

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