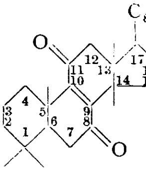
61. *Lanosterol. Part XV.* Some Reactions of Hydrocarbons of the Lanosterol Series.*

By J. F. McGhie, M. K. Pradhan, and W. A. Ross.

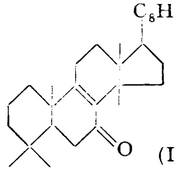
Oxidation of lanostene and γ-lanostadiene with chromic acid, or of γ-lanostadiene with perbenzoic acid, gave lanosten-8-one. Dehydrogenation of this ketone with selenium dioxide yielded lanostatrienone, which on chromic acid oxidation gave lanostadienetrione, also obtained by oxidation of lanostenedione with selenium dioxide. The presence of an α-diketone grouping in lanostadienetrione was shown by oxidation with alkaline hydrogen peroxide to a dicarboxylic acid.

Lanostanedione on oxidation with selenium dioxide gave lanost-6-ene-8 : 11-dione. Lanostanedione when reduced by the modified Wolff–Kishner procedure gave lanostan-11-one, and with lithium aluminium hydride followed by acetylation gave 8-acetoxylanostan-11-ol, dehydrated by phosphorus oxychloride to lanost-10-en-8-yl acetate.

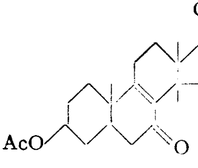
In recent work on lanostadienyl acetate and its derivatives (*J.*, 1952, 3176, and earlier papers) we have reported numerous nuclear oxidation products, such as keto- and diketolanostenyl acetate and triketolanostadienyl acetate, and these compounds have in some cases been reduced further to the corresponding saturated compounds. We now report parallel experiments with the hydrocarbons, lanostadiene (McGhie, Pradhan, and Cavalla, *J.*, 1952, 3176), lanostene (Petrow, Thesis, London, 1935; Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472; Wieland and Joost, *Annalen*, 1941, **546**, 119; Dorée, McGhie, and Kurzer, *J.*, 1947, 1467), and γ-lanostadiene (Ruzicka *et al.*, *loc. cit.*; Dorée, McGhie, and Kurzer, *J.*, 1948, 988). Oxidation of lanostene and γ-lanostadiene with chromic acid to lanost-9-ene-8 : 11-dione (I) has been described by Dorée *et al.* (*loc. cit.*; cf. Roth and Jeger, *Helv. Chim. Acta*, 1949, **32**, 1620); the ultra-violet absorption of this dione shows the system $-CO\cdot\overset{|}{C}\colon\overset{|}{C}\cdot CO-$ to be fully transoid (Campbell and Harris, *J. Amer. Chem. Soc.*, 1941, **63**, 2721; Barton, Fawcett, and Thomas, *J.*, 1951, 3147).



(I)



(II)



(III)

Under the conditions used for conversion of lanostenyl acetate into 8-ketolanost-9-en-2-yl acetate (III) (Marker, Wittle, and Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1368; Ruzicka, Rey, and Muhr, *loc. cit.*; Birchenough and McGhie, *J.*, 1950, 1249) lanostene and chromic acid afford lanost-9-en-8-one (II) in poor yield; the ultra-violet absorption spectrum [max. at 255 mμ (log ε 3·97)] identifies the product as an αβ-unsaturated ketone, which is formulated as (II) by analogy with the corresponding acetoxy-compound (Barton, Fawcett, and Thomas, *loc. cit.*). Similar oxidation of γ-lanostadiene (cf. Cavalla and McGhie, *J.*, 1951, 744) also gave lanost-9-en-8-one, again in poor yield. An alternative route was tried. Birchenough and McGhie (*loc. cit.*) obtained ketolanostenyl acetate (III) by perbenzoic acid oxidation of γ-lanostadienyl acetate, but with the hydrocarbon this method gave only a glass, which was assumed to be an epoxide as it very readily rearranged, in boiling acetic acid containing a drop of sulphuric acid, to lanost-9-en-8-one.

Experiments similar to those described for ketolanostenyl acetate (Cavalla and McGhie, *loc. cit.*) were carried out on lanost-9-en-8-one (II). Dehydrogenation with selenium dioxide gave a trienone, formulated as (IV) since, like the trienyl acetate (Cavalla and McGhie, *loc.*

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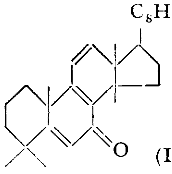
* Part XIV, *J.*, 1952, 3176.

cit.; Barron *et al.*, *loc. cit.*), it is smoothly oxidised to the dienetrione (V). Oxidation of diketolanost-9-ene-8 : 11-dione (I) with selenium dioxide to the same dienetrione lends support to formula (V). The presence of an α-diketone grouping in (V) was confirmed by fission to a dicarboxylic acid, $C_{30}H_{46}O_5$, by alkaline hydrogen peroxide. The absorption maximum at 248 mμ suggests the presence of the system $>C{:}C{\cdot}CO{\cdot}C{:}C{\cdot}CO_2H$. From this, and by analogy with the hydroxyketo-dicarboxylic acid (Cavalla and McGhie, *loc. cit.*; Barton, Fawcett, and Thomas, *loc. cit.*), the acid from (V) may be represented by (VI).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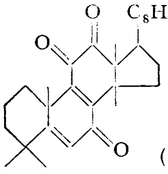
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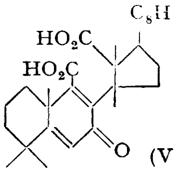
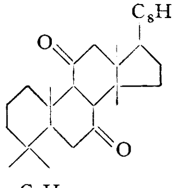

(VI)

Lanost-9-en-8 : 11-diene may be more readily obtained from *iso*cholesterol itself. Oxidation of *iso*cholesterol with Kiliani's chromic acid mixture (McGhie, Thesis, London, 1947) gave a mixture of ketones, reduced by the modified Wolff–Kishner procedure to a mixture of hydrocarbons, which on chromic acid oxidation gave lanostenedione and the trisnor-acid. Voser *et al.* (*Helv. Chim. Acta*, 1951, **34**, 1585) recently reported similar findings.

Lanostane-8 : 11-dione (VII) (Dorée, McGhie, and Kurzer, *loc. cit.*) and selenium dioxide gave a product for which formula (VIII) is suggested on the basis of the ultra-violet absorption spectrum (typical of a disubstituted αβ-unsaturated ketone) and by analogy with acetoxylanost-6-enedione (Cavalla, Thesis, London, 1951; Dorée, McGhie, and Kurzer, *J.*, 1949, 570).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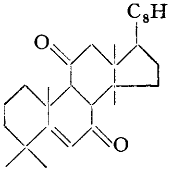
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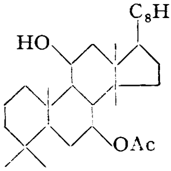
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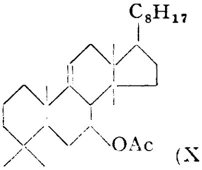
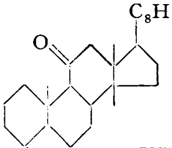

(X)


(XI)

Reduction of lanostanedione with lithium aluminium hydride gave the diol (not isolated) and thence a monoacetate alcohol (IX). According to Shoppee and Sumners (*J.*, 1950, 680), reduction of sterically hindered ketones with lithium aluminium hydride gives the compound with a polar hydroxyl group. Further, Barton and Holness (*J.*, 1952, 78) have shown that polar hydroxyl groups cannot be acetylated under normal conditions. Previous evidence (Barton, Fawcett, and Thomas, and Voser *et al.*, *locc. cit.*) has indicated the more sterically hindered nature of the $C_{(11)}$-ketone group in acetoxylanostanedione and, by analogy supported by some experimental evidence (*e.g.*, formation of a mono-2 : 4-dinitrophenylhydrazone only), the $C_{(11)}$-ketone group in lanostanedione may be considered the more sterically hindered. Reduction of this to give a polar hydroxyl group at $C_{(11)}$ explains the formation of the monoacetate only. The polar nature of the hydroxyl group at $C_{(11)}$ is confirmed by ready dehydration of this compound by phosphorus oxychloride to lanost-10-en-8-yl acetate (X). Lanostanedione (VII) was also reduced by the modified Wolff–Kishner procedure to lanostan-11-one (XI), this providing further evidence for the more sterically hindered nature of the $C_{(11)}$ ketone group.

EXPERIMENTAL

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

Oxidation of γ-Lanostadiene with Chromic Acid.—γ-Lanostadiene (1·0 g.) in glacial acetic acid (40 ml.) was treated at 95° with a solution of chromic acid (0·25 g.) in 90% acetic acid (2·5 ml.) for 2 min. The reaction mixture was poured into water, and the excess of chromic acid was destroyed with dilute sulphurous acid. The precipitated solid was taken up in ether and the solution was washed with water, dilute sodium carbonate solution, and water again, until neutral. Removal of the dried (Na_2SO_4) solvent left a yellow oil, which was adsorbed on alumina (15 × 1·3 cm.) from light petroleum. Elution with light petroleum (300 ml.) and crystallisation from acetone–methanol gave plates (0·05 g.) of *lanosten-*8*-one*, m. p. 120°, $[\alpha]_D$ +31·3° (*c*, 2·24), $\lambda_{max.}$ 255 mμ, log ε 3·97 (Found : C, 84·7; H, 11·7. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). Lanostene was oxidised by the same method to lanosten-8-one.

Oxidation of γ-Lanostadiene with Perbenzoic Acid.—A solution of γ-lanostadiene (4·5 g.) in ice-cold chloroform (50 ml.) was treated at 0° with a chloroform solution of perbenzoic acid (equivalent to 0·28 g. of active oxygen). After 46 hr. the excess of the oxidising agent was destroyed by the addition of a solution of potassium iodide. The mixture was acidified and the iodine removed by shaking with 0·1N-sodium thiosulphate. The chloroform solution was washed twice with 2N-sodium hydroxide, and water until neutral, then dried (Na_2SO_4), and finally the solvent was removed *in vacuo*. The resulting oil was chromatographed in benzene on alumina (5 × 1·3 cm.). The eluates gave a glassy oil, which was heated under reflux with acetic acid (50 ml.) and concentrated sulphuric acid (2 ml.) for 10 minutes and then worked up in the usual way. An oil was obtained, which on crystallisation from acetone–methanol gave a powder (2·7 g.), m. p. 86—90°. Rechromatography, elution with light petroleum (200 ml.) and light petroleum–benzene (1 : 1) (100 ml.), and recrystallisation from acetone–methanol gave plates (1·09 g.) of lanost-9-en-8-one, m. p. (and mixed m. p.) 119—120°, $[\alpha]_D$ +31·0° (*c*, 1·04) (Found : C, 84·5; H, 11·6. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%).

*Action of Selenium Dioxide on Lanosten-*8*-one.*—Lanosten-8-one (500 mg.) in acetic acid (50 ml.) was heated under reflux for 3 hr. with a solution of selenium dioxide (500 mg.) in water (1 ml.). The precipitated selenium was filtered off and the filtrate worked up in the usual way. A solid was obtained which was absorbed on alumina (7 × 1·3 cm.) from light petroleum. Elution with light petroleum–benzene (1 : 1) (300 ml.) and crystallisation from methanol gave needles (300 mg.) of *lanostatrienone*, m. p. 158—159°, $[\alpha]_D$ +106° (*c*, 1·18), $\lambda_{max.}$ 262 and 325 mμ, log ε 3·87 and 3·91 respectively (Found : C, 85·7; H, 10·9. $C_{30}H_{46}O$ requires C, 85·3; H, 11·0%).

Oxidation of Lanostatrienone with Chromic Acid.—Lanostatrienone (600 mg.) in glacial acetic acid (50 ml.) was treated at 95° with a solution of chromic acid (600 mg.) in 90% acetic acid (6 ml.) for 90 minutes, then worked up as in a previous similar oxidation. The orange oil obtained, on crystallisation from methanol, gave orange needles (350 mg.) of *lanostadienetrione*, m. p. 128°, $[\alpha]_D$ −52° (*c*, 3·19), $\lambda_{max.}$ 211—214 and 286 mμ, log ε 3·99 (Found : C, 79·5; H, 9·6. $C_{30}H_{44}O_3$ requires C, 79·6; H, 9·8%).

Action of Selenium Dioxide on Lanostenedione.—The dione (6·0 g.) was added to a suspension of selenium dioxide (6·0 g.) in acetic acid–acetic anhydride (1 : 1) (200 ml.), and the mixture heated under reflux for 3·5 hr. The precipitated selenium was filtered off and the filtrate concentrated *in vacuo* to a red oil. This was adsorbed on alumina (12 × 1·3 cm.) from light petroleum (with difficulty). Elution with light petroleum (200 ml.) gave a red oil, which was dissolved in ethyl acetate and cooled to −30°, whereupon a semi-solid was obtained. This was rechromatographed on alumina and elution gave the following fractions, each recrystallised from methanol : (i) light petroleum (300 ml.), amorphous orange powder (1·2 g.), m. p. 96—100°; (ii) light petroleum–benzene (1 : 1) (200 ml.), orange needles of lanostadienetrione (0·5 g.), m. p. 126—128°. Rechromatography and recrystallisation from methanol of (i) yielded a further crop of lanostadienetrione (0·5 g.), $[\alpha]_D$ −51·4° (*c*, 1·80), $\lambda_{max.}$ 211—214 and 286 mμ (log ε 3·99), mixed m. p. not depressed (Found : C, 79·5; H, 9·7%).

Action of Alkaline Hydrogen Peroxide on Lanostadienetrione.—To a solution of lanostadienetrione (100 mg.) in dioxan (10 ml.) was added 10% aqueous potassium hydroxide (2 ml.). The mixture was warmed to 50° and treated with " Perhydrol " (1·5 ml.) for 15 minutes, the colour of the solution becoming pale. Then a further 0·5 ml. of " Perhydrol " was added and after 10 min. the product was poured into water and extracted with ether. The ethereal layer was further extracted with potassium hydroxide solution (10%), then washed with water, and the solvent removed, to leave a negligible neutral fraction. The alkaline fraction was then acidified and extracted with ether. The ethereal solution was washed with water and evaporation of the dried (Na_2SO_4) solvent and crystallisation from ethyl acetate (3 ml.) gave cubic crystals (60 mg.) of the *keto-dicarboxylic acid*, m. p. 229—230° (decomp.), $[\alpha]_D$ $-67{\cdot}0°$ (*c*, 1·20), $\lambda_{max.}$ 248 mμ, log ε 4·1 (Found : C, 74·0; H, 9·4. $C_{30}H_{46}O_5$ requires C, 74·1; H, 9·5%).

Action of Selenium Dioxide on Lanostanedione.—Lanostanedione (200 mg.) in acetic acid (30 ml.) was heated under reflux for 3·5 hr. with a solution of selenium dioxide (200 mg.) in water (1 ml.). The precipitated selenium was filtered off and the product worked up in the usual way, to give a dark red oil which was adsorbed on alumina (6 × 1·5 cm.) from light petroleum. Elution with light petroleum–benzene (6 : 2) (80 ml.) and recrystallisation from methanol gave plates of *lanost*-6-*ene*-8 : 11-*dione*, m. p. 128°, $[\alpha]_D$ $+10° \pm 5°$ (*c*, 1·28), $\lambda_{max.}$ 239 mμ, log ε 4·05 (Found : C, 81·6; H, 10·9. $C_{30}H_{48}O_2$ requires C, 81·8. H, 10·9%).

Diketolanostane mono-2 : 4-*dinitrophenylhydrazone*, obtained by refluxing the reactants for 25 minutes, had m. p. 190°, $\lambda_{max.}$ 371, ε 17,000 (Found : N, 8·8; $C_{36}H_{54}O_5N_4$ requires N, 9·0%).

8-*Acetoxylanostan*-11-ol.—A solution of lanostanedione (700 mg.) in ether (50 ml.) was added dropwise to a suspension of lithium aluminium hydride (1·2 g.) in ether (100 ml.) with mechanical stirring, under reflux. Stirring was continued for a further 4 hr. and the excess of lithium aluminium hydride was then decomposed by ice-water, followed by dilute sulphuric acid. The mixture was extracted with ether and removal of the solvent gave a gel. Treatment of this with acetic anhydride (20 ml.) and pyridine (5 ml.) on the steam-bath (1 hr.) gave a solid, which after four recrystallisations from acetone–methanol, was 8-*acetoxylanostan*-11-*ol*, needles, m. p. 196—197°, $[\alpha]_D$ $+75°$ (*c*, 0·2) (Found : C, 78·8; H, 11·6. $C_{32}H_{56}O_3$ requires C, 78·6; H, 11·6%).

Dehydration of 8-*Acetoxylanostan*-11-*ol*.—8-Acetoxylanostan-11-ol (100 mg.) in pyridine (10 ml.) was treated with phosphorus oxychloride (2 ml.) on a steam-bath for 1·5 hr., then set aside at room temperature for 20 hr. and worked up in the usual way to give a solid, which on recrystallisation from methanol, gave *lanost*-10-*en*-8-*yl acetate* (80 mg.), m. p. 139—140°, $[\alpha]_D$ $+80{\cdot}0°$ (*c*, 1·02) (Found : C, 81·4; H, 11·5. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·6%). This gave a yellow colour with tetranitromethane.

Modified Wolff–Kishner Reduction of Lanostanedione.—Lanostanedione (900 mg.) in diethylene glycol (20 ml.) was heated under reflux with hydrazine hydrate (0·3 ml., 100%) for 1 hr. at 200°. The mixture was cooled, a solution of sodium (1·0 g.) in diethylene glycol (10 ml.) was added, and the mixture heated under reflux for a further 5 hr. at 230°. The cool solution was diluted with water, acidified, and extracted with ether. The ethereal solution was washed with water and dried (Na_2SO_4). The solvent was removed and the resulting product adsorbed on alumina (6 × 1·5 cm.) from light petroleum. Elution with light petroleum (70 ml.) and crystallisation from chloroform–methanol gave plates (300 mg.) of *lanostan*-11-*one*, m. p. 94—95°, $[\alpha]_D$ $+70°$ (*c*, 3·04) (Found : C, 84·2; H, 12·2. $C_{30}H_{52}O$ requires C, 84·0; H, 12·2%). The product gave no colour with tetranitromethane.

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