

181. Lanosterol. Part XI. Reduction of Ketones in the Lanosterol Series.

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Reduction of acetoxylanostenedione with lithium aluminium hydride gave diacetoxylanostanone, whilst acetoxylanostenedione yielded diacetoxylanostanol. Oxidation of the last with chromic acid gave diacetoxylanostanone, which could be hydrolysed to the corresponding ketolanostanediol.

REDUCTION of the inert double bond in lanostadienol* derivatives was first reported by one of us (J. F. McG.) with Dorée and Kurzer (Part V, *J.*, 1948, 988). It was shown that reduction of acetoxylanostenedione and lanostenedione by zinc and acetic acid, zinc amalgam and hydrochloric acid, sodium and *isopropyl* alcohol, or catalytically, gave the corresponding fully saturated compounds, acetoxylanostanedione and lanostanedione. This work had in view the eventual preparation of the parent hydrocarbon, lanostane, by the further reduction of the products to the corresponding polyalcohols, then dehydration, followed by catalytic reduction, to give lanostane (cf. the degradation of cholic acid to cholane; Wieland *et al.*, *Z. physiol. Chem.*, 1912, **80**, 287).

Whilst this work was in progress Voser, Montavon, Gunthard, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1950, **33**, 1893) reported the preparation of lanostane as follows: Acetoxylanostanedione and ethane-1:2-dithiol gave a monomercaptal, which on reduction with Raney nickel gave the monoketonic derivative, acetoxylanostanone. Hydrolysis and then mild oxidation of the resulting alcohol gave a diketone, isomeric with lanostanedione described above but differing in that both the keto-groups could be reduced by zinc amalgam and hydrochloric acid to yield the hydrocarbon lanostane.

In view of this publication, our own experiments and findings in this field, already briefly recorded elsewhere (*Chem. and Ind.*, 1950, **46**, 744) are summarised below.

Acetoxylanostenedione, prepared by the oxidation of either lanostenyl acetate or γ -lanostadienyl acetate (formerly known as dihydroagnosteryl acetate) with chromic acid (Marker *et al.*, *J. Amer. Chem. Soc.*, 1937, **59**, 1368; Ruzicka *et al.*, *Helv. Chim. Acta*, 1944, **27**, 472), or with ozone (Dorée and McGhie, *Nature*, 1944, **153**, 148), or by hydrogen peroxide (Birchenough, Thesis, London, 1950; Voser *et al.*, *loc. cit.*), was more conveniently prepared by the modified method, from either lanostenyl acetate or γ -lanostadienyl acetate and chromic acid, described in the experimental section. The diketo-acetate formed deep yellow needles (sometimes plates) and gave a curve in the ultra-violet having a well-defined absorption maximum at 275 m μ . ($\log \epsilon$, 3.94), indicating the presence of an unsaturated 1:4-diketone system $\cdot\text{CO}\cdot\overset{\cdot}{\text{C}}\overset{\cdot}{\text{C}}\cdot\text{CO}\cdot$, the inert ethylenic linkage lying between two quaternary carbon atoms. The assumption that no bond migration took place in the formation of acetoxylanostanedione (McGhie, Thesis, London, 1947) received support from recent spectroscopic evidence (Roth and Jeger, *Helv. Chim. Acta*, 1949, **32**, 1620).

The only available information on the reduction of such an unsaturated 1:4-diketone was from the results of Lutz and Gillespie (*J. Amer. Chem. Soc.*, 1950, **72**, 2002), who have shown that either *cis*- or *trans*-dibenzoyl ethylene with lithium aluminium hydride gave, as the principal product, the saturated 4-keto-1:4-diphenylbutanol, together with a small quantity of the unsaturated (*trans*)-1:4-glycol. Reduction beyond the keto-alcohol stage did not take place although an excess of lithium aluminium hydride was present in the reaction mixture. Further reduction of the keto-alcohol with either platinum and hydrogen or lithium aluminium hydride led to a mixture of the saturated stereoisomeric 1:4-diols.

Acetoxylanostenedione, when treated with lithium aluminium hydride, under conditions analogous to those used by Lutz and Gillespie, gave a mixture of stereoisomeric alcohols from which a small yield of a compound, m. p. 215°, $[\alpha]_{\text{D}}^{20} + 53.0^\circ$, could be isolated. Formulation of this compound as a ketodiols appears likely since on treatment with acetic anhydride it afforded a keto-diacetate, m. p. 175—176°, $[\alpha]_{\text{D}}^{20} + 58.4^\circ$.

Subsequently it was found more convenient to acetylate the mixture of alcohols, whereafter two products could be isolated by fractional crystallisation followed by chromatographic purification. The first had m. p. 175—176°, $[\alpha]_{\text{D}}^{20} + 59.0^\circ$, identical with the compound prepared as described above. The second had m. p. 200°, $[\alpha]_{\text{D}}^{20} + 57.5^\circ$, and appears to be an

* See footnote, p. 744.

unsaturated triacetate. Hydrolysis of this compound did not give a crystalline triol; it gives a faint yellow colour with tetranitromethane and may contain the grouping $\text{AcO}\cdot\text{CH}\cdot\text{C}\cdot\text{C}\cdot\text{CH}\cdot\text{OAc}$. These results are in agreement with those of Lutz and Gillespie (*loc. cit.*). Also present in the acetylated mixture of alcohols, although in very small yield, was a saturated alcohol, m. p. 237—238°, identical with the compound obtained by acetylating the product of reduction of acetoxylanostanedione by lithium aluminium hydride.

It was thought that acetoxylanostanedione, being fully saturated, should give less complex results than those found for acetoxylanostenedione. Reduction of this by the same procedure gave a mixture of alcohols which on fractional crystallisation gave a minute yield of a crystalline product, m. p. 219—220°. This, at first, was thought to be unchanged acetoxylanostanedione (m. p. 222—224°) but analysis showed it to be a triol. Further work to confirm such a hypothesis had to be abandoned owing to the paucity of the material available. Acetylation of the mixed alcohols followed by crystallisation gave good yields of a compound, m. p. 239°, $[\alpha]_D^{20} + 70.0^\circ$, analytical figures for which agreed well with those of a hydroxy-diacetate. [Since this work was completed, Voser *et al.* (*loc. cit.*) have reported the preparation of what appears to be the same compound by virtually an identical process.] The presence of an unacetylated hydroxyl group was confirmed by oxidation of the hydroxy-diacetate with chromic acid, a keto-diacetate, m. p. 176—177°, $[\alpha]_D^{20} + 58.4^\circ$, together with an acid fraction which has not yet given crystalline material, being isolated. Hydrolysis of the hydroxy-diacetate, m. p. 239°, gave no crystalline product, though hydrolysis of the keto-diacetate, m. p. 176—177°, gave a keto-diol, m. p. 215—216°, $[\alpha]_D^{20} + 53.6^\circ$. The identity between these two compounds and those obtained by the direct reduction of acetoxylanostenedione was shown by the further reduction of all four with lithium aluminium hydride to an alcohol mixture which on acetylation gave the hydroxy-diacetate, m. p. 239°. Further evidence of the reduction of the inert double bond in acetoxylanostenedione by lithium aluminium hydride was given by the identification of very small amounts of the hydroxy-diacetate, m. p. 239°, in the acetate mixture obtained by acetylating the mixture of alcohols from the reduction.

In a search for alternative methods of isolating the reduction products from acetoxylanostanedione, the mixture of alcohols was boiled with acetic anhydride, a product, m. p. 213—214°, $[\alpha]_D^{20} + 83.4^\circ$, being obtained. This is an unsaturated diacetate giving a yellow colour with tetranitromethane. Attempts to prepare this compound from the hydroxy-diacetate, m. p. 239°, by dehydration with boiling acetic anhydride were unsuccessful. Treatment with phosphorus oxychloride in hot pyridine, however, gave the unsaturated diacetate in good yield.

EXPERIMENTAL.

All m. p.s are uncorrected. Specific rotations were measured in chloroform solution at 20°. Aluminium oxide used in chromatographic work was from Messrs. Peter Spence Ltd. (Grade "0"). All analyses are by Drs. Weiler and Strauss, Oxford.

Acetoxylanostenedione.—Lanostenyl acetate (20 g.) in glacial acetic acid (1 l.) was treated at 95° with excess of chromic acid (12 g.; in 30 ml. of water), in a three-necked flask with mechanical stirring. The chromic acid was added dropwise during 30 minutes with constant stirring and the temperature maintained for a further 1½ hours. The dark green reaction mixture was poured into 4 l. of ice-water, the excess of chromic acid destroyed with dilute sulphurous acid, sodium chloride added to coagulate the oxidation product, and the latter filtered off. This crude yellow material was dissolved in ether (500 ml.) and the solution washed with water till free from chromium salts. Washing with dilute sodium hydroxide solution gave a small acid fraction (1 g.) which could not be obtained crystalline. The ethereal layer was washed till neutral, then dried (Na_2SO_4), and the solvent removed to leave a pale yellow solid. Passage of this material through a short alumina column, using benzene as carrier, followed by crystallisation from methanol, gave glistening yellow plates (12 g.) of acetoxylanostenedione, m. p. 158—159°, $[\alpha]_D^{20} + 91.6^\circ$ (*c* 0.024), identical with an authentic specimen. Reduction of the mother-liquors gave a small quantity (1 g.) of a less pure material.

Acetoxylanostanedione.—This compound was prepared by reducing acetoxylanostenedione with zinc dust and glacial acetate acid (Dorée, McGhie, and Kurzer, *J.*, 1948, 988). Good yields (80%) were obtained of the colourless plates, m. p. 222—224°, $[\alpha]_D^{20} + 55.4^\circ$ (*c* 0.04), identical with an authentic specimen kindly supplied by Dr. F. Kurzer.

Reduction of Acetoxylanostenedione.—In all reductions using lithium aluminium hydride, absolute ether was used. The most satisfactory way of achieving this was found to be drying the ether with calcium hydride.

A solution of acetoxylanostenedione (2 g.) in absolute ether (100 ml.) was added dropwise, with efficient mechanical stirring, to a cooled suspension of lithium aluminium hydride (1.7 g.) in absolute ether (100 ml.) under reflux. As soon as the yellow ketone solution met the hydride the colour disappeared and a white solid was precipitated. The stirring was continued for 1 hour after addition of the diketone. The flask containing the reaction mixture was placed in ice, and ice-water added with great caution to the vigorously stirred suspension; the mixture gelled transitorily and the ether boiled. Once the initial reaction was over cold dilute sulphuric acid was added. Two layers which separated

were transferred to a separatory funnel where the ethereal layer was well washed with water and dried (Na_2SO_4). The solvent was removed, to leave a white amorphous product, very soluble in methanol. Crystallisation from small volumes of methanol gave a mixture of white amorphous powder (which could not be purified further) and hard well-defined crystals, m. p. 211—213°, which were separated by hand. Three further crystallisations from very small volumes of methanol gave large plates of *lanostanonediol*, m. p. 215°, $[\alpha]_D^{20} + 53.0^\circ$ (*c*, 0.038) (Found: C, 78.0; H, 11.3. $\text{C}_{30}\text{H}_{52}\text{O}_3$ requires C, 78.2; H, 11.4%). Mild acetylation of this product with acetic anhydride and pyridine at room temperature for 8 hours gave *diacetoxylanostanone*, m. p. 175—176°, $[\alpha]_D^{20} + 58.4^\circ$ (*c*, 0.018) (Found: C, 75.1; H, 10.3. $\text{C}_{34}\text{H}_{56}\text{O}_5$ requires C, 75.0; H, 10.4%). Attempts at chromatographic separation of the mixed alcohols met with little success and the method of direct crystallisation was adhered to.

A further reduction of acetoxylostanedione (2 g.) with lithium aluminium hydride (1.7 g.) provided a mixture of alcohols which was kept at 100° for 2½ hours with acetic anhydride (25 ml.) and pyridine (5 ml.). The usual working up gave an oily white solid which was crystallised from methanol (20 ml.) to give a white product (1 g.) crystallising in felting needles, m. p. 185—190°. Adsorption on an alumina column (10 × 1.3 cm.) from light petroleum (b. p. 60—80°) followed by elution with benzene-light petroleum (b. p. 60—80°) (1 : 1; 200 ml.) gave a white product, crystallising in felting needles (from methanol), m. p. 198—199°. Two further crystallisations gave *triacetoxylanostene*, m. p. 200°, $[\alpha]_D^{20} + 57.5^\circ$ (*c*, 0.049) (Found: C, 74.1; H, 9.9. $\text{C}_{38}\text{H}_{58}\text{O}_6$ requires C, 73.7; H, 9.9%). With tetranitromethane, this compound gave a pale yellow colour.

Hydrolysis, using 6% alcoholic potassium hydroxide, gave an amorphous product similar to that obtained from the original reduction, from which no crystalline compound could be obtained.

The methanolic mother-liquor from the crude triacetoxylanostene gave a colourless glass on removal of the solvent. This was adsorbed on alumina (15 × 1.3 cm.) from light petroleum (b. p. 60—80°, 200 ml.) and eluted to give the following fractions: (a) light petroleum (b. p. 60—80°; 300 ml.), 0.2 g. of oil; (b) light petroleum (b. p. 60—80°)-benzene (1 : 1; 250 ml.), 0.4 g. of oil; (c) benzene (250 ml.), 0.08 g. of oil; (d) chloroform (250 ml.), trace of oil.

Fraction (a) gave, on crystallisation from methanol, felted needles, m. p. 192—195°, which on two recrystallisations gave triacetoxylanostene, m. p. 199—200°, undepressed on admixture with authentic material.

Fraction (b), crystallised from methanol, gave hard plates, m. p. 172°, raised by two recrystallisations to m. p. 175°. This was identical with diacetoxylanostanone obtained by acetylation of lanostanonediol, m. p. 215—216°.

Fraction (c), recrystallised from methanol gave felted needles, m. p. 217—221°, which on two recrystallisations gave m. p. 237—238°. This was diacetoxylanostanol, identical with that obtained by reduction of acetoxylostanedione with lithium aluminium hydride followed by acetylation.

Hydrolysis of fraction (b) with 5% alcoholic potassium hydroxide gave good yields of lanostanonediol, m. p. 215—216°.

Reduction of Diacetoxylanostanone and Lanostanonediol.—These compounds (0.2 g.) in absolute ether (50 ml.) were severally treated with lithium aluminium hydride (0.5 g.) in absolute ether (50 ml.). In each case the resultant mixed alcohols were acetylated and the product crystallised from acetone-methanol, to give diacetoxylanostanol (0.15 g.), m. p. 238—239°, identical with that obtained by reduction of acetoxylostanedione.

Reduction of Acetoxylostanedione.—A solution of acetoxylostanedione (4 g.) in absolute ether (200 ml.) was treated with a stirred suspension of lithium aluminium hydride (3.4 g.) in absolute ether (100 ml.) in the manner described for the reduction of acetoxylostanedione. More ether was required owing to the smaller solubility of the saturated compound in this solvent. Working up gave a white amorphous solid which was adsorbed from light petroleum (b. p. 60—80°)-benzene (1 : 1; 350 ml.) on alumina (13 × 1.3 cm.). Elution of the column with light petroleum (b. p. 60—80°)-benzene (1 : 1), benzene alone, or benzene-ether (1 : 1) gave products which could not be crystallised. Final elution of the column with ether alone (200 ml.) gave a small quantity (50 mg.) of a white solid which had m. p. 216—217° after crystallisation from methanol. Two further crystallisations gave fine needles of *lanostanetriol*, m. p. 219—220° (Found: C, 78.0; H, 11.6. $\text{C}_{30}\text{H}_{44}\text{O}_3$ requires C, 77.9; H, 11.8%). Mild acetylation of this alcohol (10 mg.) with acetic anhydride-pyridine (1 : 1; 2 ml.) failed to give a solid product.

Acetylation of the Mixed Alcohols.—The product from a further reduction of acetoxylostanedione (4 g.) was kept at 100° for 2 hours with acetic anhydride (40 ml.) and pyridine (10 ml.). The mixture was then poured into water and the white solid precipitated was extracted with ether in the usual manner. Removal of the solvent and crystallisation of the residue from acetone (60 ml.)-methanol (30 ml.) gave long felted needles, m. p. 235—236° (3 g.). Two recrystallisations from the same mixture of solvents gave the pure *diacetoxylanostanol*, m. p. 239°, $[\alpha]_D^{20} + 70.0^\circ$ (*c*, 0.025) (Found: C, 74.7; H, 10.5. $\text{C}_{34}\text{H}_{56}\text{O}_5$ requires C, 74.7; H, 10.7%). Reduction of the mother-liquors from the purification gave a further yield (0.4 g.) of impure material which had m. p. 237° after two crystallisations. No other product could be obtained.

A further reduction of acetoxylostanedione (1.5 g.) gave the typical mixture of alcohols which was boiled for 2 hours with acetic anhydride (35 ml.) and poured into water. Extraction of the white solid with ether and removal of the solvent gave an oily white solid. This was adsorbed from light petroleum (b. p. 60—80°; 300 ml.) on a column of alumina (10 × 1.3 cm.). Elution of the column gave the following fractions: (a) light petroleum (b. p. 60—80°; 600 ml.), trace of oil; (b) light petroleum (b. p. 60—80°)-benzene (1 : 1; 250 ml.), 0.5 g. of colourless oil; (c) benzene (250 ml.), 0.4 g. of white solid; (d) benzene (250 ml.), 0.1 g. of white solid; (e) chloroform (250 ml.), 0.2 g. of white solid.

Fraction (b) gave hard colourless plates, m. p. 208—209°, on crystallisation from acetone-methanol.

Three further crystallisations gave pure *diacetoxylostanene*, m. p. 213—214°, $[\alpha]_D^{20} + 83.4^\circ$ (*c*, 0.020). This compound gave a yellow colour with tetranitromethane and was practically insoluble in methanol (Found : C, 77.4; H, 10.6. $C_{34}H_{56}O_4$ requires C, 77.2; H, 10.7%).

Dehydration of Diacetoxylostanol.—With *acetic anhydride*. Diacetoxylostanol (0.2 g.) was boiled for 1 hour with acetic anhydride (20 ml.) and pyridine (3 ml.). The solution was poured into water and extracted with ether to leave, on removal of the solvent, an oily white solid. Crystallisation from acetone (4 ml.) and methanol (20 ml.) gave fine felting needles (0.15 g.), m. p. 237—238°, undepressed on admixture with diacetoxylostanol. From the mother-liquors only crude starting material could be obtained.

With phosphorus oxychloride. Diacetoxylostanol (0.9 g.) in dry pyridine (50 ml.) was treated at 100° with phosphorus oxychloride (4 ml.) for 1 hour. The mixture was poured into water and extracted with ether, and the ethereal layer washed with dilute hydrochloric acid to remove pyridine. Continued washing with dilute sodium carbonate solution and water till neutral, followed by removal of the solvent, gave a hard white solid. Crystallisation from acetone–methanol gave small rectangular plates (0.65 g.), m. p. 212—214°. Two recrystallisations from the same solvent mixture gave pure diacetoxylostanene, m. p. 213—214°, $[\alpha]_D^{20} + 83.9^\circ$ (*c*, 0.049), identical with the material prepared as above.

Hydrolysis. Diacetoxylostanol (0.25 g.) was refluxed with a solution of potassium hydroxide (2 g.) in alcohol (50 ml.) for 1½ hours, poured into water, and extracted with ether. Removal of the solvent gave an oily white solid from which no crystalline product could be isolated by fractional crystallisation or chromatography.

Oxidation of Diacetoxylostanol.—Diacetoxylostanol (1.8 g.) in glacial acetic acid (100 ml.) was treated, at 45—50° with stirring, with a solution of chromic acid (1.8 g.) in 90% acetic acid (20 ml.). The temperature was maintained for 1 hour and the mixture poured into water; dilute sulphurous acid was added to destroy the excess of chromic acid. The precipitated white solid was extracted with ether, and the ethereal layer washed with water to free it from chromium salts. Extraction of the ether solution with 2*N*-sodium hydroxide gave an acid fraction which has not yet been isolated in the pure state. Methylation, using diazomethane, of the crude acid, followed by chromatography, has given only oils. The neutral fraction was washed, then dried (Na_2SO_4), and the ether removed to leave a colourless glass (1 g.). Crystallisation from acetone (3 ml.) and methanol (15 ml.) gave stout plates, m. p. 181—185°. These were adsorbed from light petroleum (b. p. 60—80°, 200 ml.) on alumina (13×1.3 cm.). Light petroleum (b. p. 60—80°)—benzene (1 : 1, 500 ml.) eluted pure *diacetoxylostanone*, m. p. 176—177°, $[\alpha]_D^{20} + 58.4^\circ$ (*c*, 0.022) (Found : C, 74.9; H, 10.1. $C_{34}H_{56}O_5$ requires C, 75.0; H, 10.4%). Elution of the column with chloroform gave a small quantity of felting needles, m. p. 236°. These were unoxidized diacetoxylostanol. The mixed m. p. of this ketone obtained by the oxidation of diacetoxylostanol with the ketone obtained by acetylation of the alcohol obtained by reduction of acetoxylostanedione was 176°.

Hydrolysis. Diacetoxylostanone (0.25 g.) was refluxed for 2½ hours with a solution of potassium hydroxide (2.5 g.) in alcohol (50 ml.) and poured into water. Extraction with ether, followed by removal of the solvent, gave a coloured solid, which crystallised from aqueous methanol in large plates, m. p. 213—214°. Two further crystallisations from small volumes of methanol gave pure *keto-lostanediol*, m. p. 215—216°, $[\alpha]_D^{20} + 53.6^\circ$ (*c*, 0.030) (Found : C, 77.9; H, 11.2. $C_{30}H_{52}O_3$ requires C, 78.2; H, 11.4%). Reacetylation of this product gave plates of diacetoxylostanone, m. p. 175—177°. The mixed m. p. of the above alcohol obtained by hydrolysis of diacetoxylostanone with the alcohol obtained by the reduction of acetoxylostanedione was 215°.

Reduction of Diacetoxylostanone and Ketolanostanediol.—Diacetoxylostanone and ketolanostanediol (0.25 g.) were severally reduced with lithium aluminium hydride (0.5 g.). Acetylation of the products, followed by crystallisation, gave in each case, diacetoxylostanol, m. p. 237°, alone and on admixture with an authentic specimen.

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