930. *The Methylation and Formylation of* 5β-*Lumista*-7,22-*dien*-3-*one*

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Methylation of 5β-lumista-7,22-dien-3-one gives 2,2-dimethyl-5β-lumista-7,22-dien-3-one and 2α-methyl-5β-lumista-7,22-dien-3-one. Chemical evidence indicates that in the latter product ring A is in a boat conformation.

Formylation of 5β-lumista-7,22-dien-3-one gives 2-hydroxymethylene-5β-lumista-7,22-dien-3-one.

It has been shown that 5α-cholest-7-en-3-one with methyl iodide and potassium t-butoxide yields 4α-methyl-5α-cholest-7-en-3-one (lophenone),[1,2] rather than the 2α-methyl isomer which would have been expected by analogy with the methylation of 5α-cholestan-3-one under similar conditions.[3] Similarly, formylation of 5α-cholest-7-en-3-one with sodium

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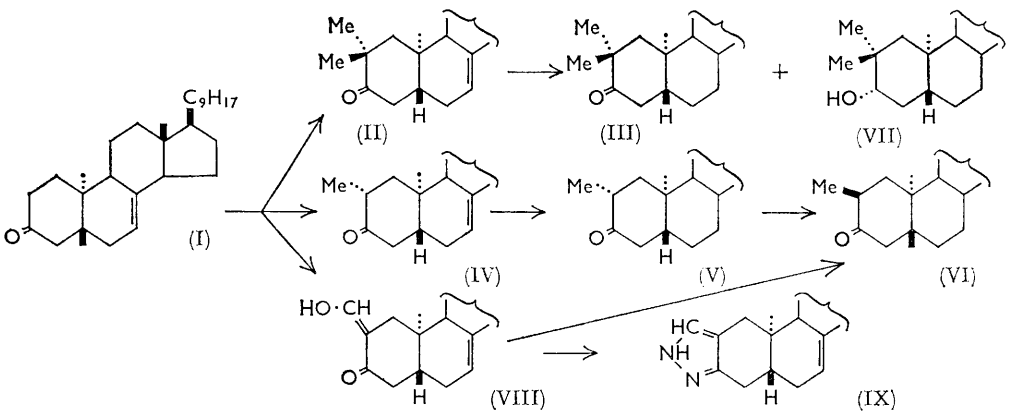
methoxide and ethyl formate has been reported to give 4-hydroxymethylene-5α-cholest-7-en-3-one and not the 2-hydroxymethylene ketone.[4] Recently it has been reported that methylation of ergosta-7,22-dien-3-one gives rise to 4α-methyl-ergosta-7,22-dien-3-one.[5,6] These results must be a reflection of the fact that the Δ^7-double bond causes the 3-keto-group to enolise towards C-4 rather than C-2, and this may be due to the extra strain in ring B caused by the olefinic linkage. It was of interest to study the methylation and formylation of 5β-lumista-7,22-dien-3-one (I) and in this Paper we describe the results obtained.

The ketone [7] (I) was obtained most conveniently by the oxidation of 5β-lumista-7,22-dien-3β-ol [7] with 8N-chromium trioxide–sulphuric acid–acetone.[8] Direct methylation of the ketone with methyl iodide and potassium t-butoxide in t-butyl alcohol under the conditions used previously [2] with 5α-cholest-7-en-3-one, followed by chromatography, led to two new substances. The less polar was shown to be 2,2-dimethyl-5β-lumista-7,22-dien-3-one (II), since hydrogenation in ethyl acetate containing perchloric acid over platinum oxide yielded a compound with an infrared spectrum ($\nu_{max.}$ 1695 cm.$^{-1}$ in CS_2) indicating it to be a dimethylated ketone;[3] this proved to be identical with 2,2-dimethyl-5β-lumistan-



3-one [9] (III). The more polar substance proved to be 2α-methyl-5β-lumista-7,22-dien-3-one (IV). Hydrogenation as before led to a monomethylated ketone ($\nu_{max.}$ 1709 cm.$^{-1}$ in CS_2) which must be 2α-methyl-5β-lumistan-3-one (V) since on acid treatment it was isomerised to 2β-methyl-5β-lumistan-3-one (VI), identical with an authentic sample.[9] 2,2-Dimethyl-5β-lumista-7,22-dien-3-one (II) proved to be the major product when the alkylation was carried out for a longer time with a large excess of potassium t-butoxide and methyl iodide.

The catalytic hydrogenation of ketone (II) in ethyl acetate in the presence of platinum oxide also furnished an alcohol, which was shown to be 2,2-dimethyl-5β-lumistan-3α-ol (VII), since oxidation with Jones's reagent furnished 2,2-dimethyl-5β-lumistan-3-one (III) and since it was obtained by the reduction of the latter with lithium aluminium hydride.

Formylation of 5β-lumista-7,22-dien-3-one (I) with sodium methoxide and ethyl formate under the conditions of Jones *et al.*,[10] gave a hydroxymethylene derivative which was shown to be 2-hydroxymethylene-5β-lumista-7,22-dien-3-one (VIII). The structural assignment for this compound followed from its hydrogenation. Thus, catalytic hydrogenolysis of the ketone (VIII) in ethanol over palladium–charcoal gave an oil which was further

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[9] W. T. Pike, G. H. R. Summers, and W. Klyne, unpublished results.
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hydrogenated in ethyl acetate over platinum oxide. Oxidation of the hydrogenation mixture with Jones's reagent, followed by chromatography, resulted in the isolation of 2β-methyl-5β-lumistan-3-one (VI) in 45% yield.

Condensation of the hydroxymethylene ketone (VIII) with hydrazine hydrate gave a 98% yield of one pure pyrazole (IX).

Thus, unlike the introduction of a Δ^7-double bond into the "normal" steroid nucleus,[1-6] introduction of this double bond into 5β-lumistan-3-one does not influence the course of methylation or of formylation. On the other hand, the fact that one of the methylated products has the 2α-methyl configuration was surprising. Although it has been shown that monomethylation of steroidal ketones may initially give the axial isomer,[10] the 2-methyl group in 2α-methyl-5β-lumista-7,22-dien-3-one (IV) would be expected to epimerise under the strongly basic conditions if it were axially oriented, since enolisation towards position 2 should occur fairly readily. Moreover, the ketone (IV) was unaffected on treatment with ethanolic sulphuric acid, conditions under which, in the saturated cholestane series, the axial (2β-)methyl ketone is readily epimerised to the equatorial (2α-)methyl isomer.[3] Furthermore, 2α-methyl-5β-lumistan-3-one (V) was partly epimerised to the methyl ketone (VI) by this treatment. It therefore appears that the ketone (IV) possesses the stable configuration at position 2, *i.e.*, that the 2α-methyl group is equatorial. To explain the equatorial nature of the methyl group, this compound must adopt a boat conformation in ring A, rather than the more usual chair conformation.

The rotatory dispersion curves of both 2α- and 2β-methyl-5β-lumistan-3-one, when considered in the light of the octant rule,[11] show no abnormal features. The curve for the unsubstituted 5β-lumista-7,22-dien-3-one shows a negative Cotton effect, almost identical with 5β-lumistan-3-one.[12] The amplitude of the Cotton effect for 2α-methyl-5β-lumista-7,22-dien-3-one is similarly almost identical with that of the parent ketone (I), but the uncertainty about the effect of a double bond in ring B and the consequent flexible conformations of ring A do not allow a prediction of the configuration of the methyl group to be made with certainty on the basis of the octant rule.[13]

The curve for 2,2-dimethyl-5β-lumista-7,22-dien-3-one (II) shows a strongly negative Cotton effect, indicative of gross distortion by the *gem*-dimethyl group. It is possible that ring A may have an intermediate conformation, possibly of the twist type.[14-17]

Experimental

The values for $[\alpha]_D$ are for $CHCl_3$ solutions at room temperature. Chromatography was effected on Spence alumina type H. General experimental details for the rotatory dispersion were as described by Jones and Klyne.[18] All curves were measured for methanol solutions (*c*, 0·01) at 18—20°. All values are as molecular rotations.

5β-*Lumista*-7,22-*dien*-3β-*ol*.—The alcohol was prepared by the method of Jones *et al.*[7]

5β-*Lumista*-7,22-*dien*-3-*one* (I).—A solution of 5β-lumista-7,22-dien-3β-ol (3·66 g.) in AnalaR acetone (110 ml.) was titrated with 8N-chromic acid in the usual way to give a crystalline material which was shown by thin-layer chromatography to contain some decomposition product. Filtration of an ethereal solution of the product through alumina (10 g.) gave 5β-lumista-7,22-dien-3-one (3·5 g.) on evaporation of the solvent. Crystallisation from ether–methanol gave plates, m. p. 168—171°, $[\alpha]_D$ +31° (lit.,[7] m. p. 168—172°, $[\alpha]_D$ +34°). Optical rotatory dispersion: trough, −1280 (306 mμ), peak, +4060 (264); $10^{-2}a$ −53.

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Methylation of 5β-Lumista-7,22-dien-3-one.—(*a*) *To give mainly 2α-methyl-5β-lumista-7,22-dien-3-one* (IV). A boiling solution of 5β-lumista-7,22-dien-3-one (1·02 g.) in benzene (10 ml.) and t-butyl alcohol (5 ml.) was treated successively with potassium t-butoxide [prepared from potassium (138 mg.) and t-butyl alcohol (7 ml.)] and methyl iodide (1 ml.) in benzene (1 ml.). After being refluxed for 5 min. the mixture was poured on to ice, extracted with ether, and worked up in the usual way to give a solid, which was chromatographed on alumina (60 g.). Elution with pentane–benzene (17 : 3) gave *2,2-dimethyl-5β-lumista-7,22-dien-3-one* (90 mg.) which crystallised from ether–methanol as fibrous needles, m. p. 138—141°, $[\alpha]_D$ −20° (*c* 1·0), $\nu_{max.}$ (KBr) 1715 cm.$^{-1}$ (Found: C, 84·6; H, 11·4. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). Optical rotatory dispersion: trough, −4680 (313 mμ), peak, +7460 (270); $10^{-2}a$ −121. Further elution with pentane–benzene (17 : 3) gave a solid (300 mg.) which, on crystallisation from ether–methanol, gave *2α-methyl-5β-lumista-7,22-dien-3-one* as furry rods, m. p. 128—131°, $[\alpha]_D$ +51·7° (*c* 0·76), $\nu_{max.}$ 1715 cm.$^{-1}$ (Found: C, 84·5; H, 11·2. $C_{29}H_{46}O$ requires C, 84·8; H, 11·3%). Optical rotatory dispersion: trough, −990 (303 mμ), peak, +4290 (263), $10^{-2}a$ −53. Finally, pentane–benzene (7 : 3) eluted unchanged 5β-lumista-7,22-dien-3-one (500 mg.), m. p. 168—170°, $[\alpha]_D$ +32°.

(*b*) *To give mainly 2,2-dimethyl-5β-lumista-7,22-dien-3-one* (II). A boiling solution of 5β-lumista-7,22-dien-3-one (970 mg.) in benzene (25 ml.) and t-butyl alcohol (14 ml.) was treated successively with potassium t-butoxide [prepared from potassium (1·04 g.) and t-butyl alcohol (35 ml.)] and methyl iodide (9 ml.) in benzene (25 ml.). After being refluxed for 1 hr., the product was isolated as previously and was chromatographed on alumina (60 g.). Elution with pentane–benzene (9 : 1) gave 2,2-dimethyl-5β-lumista-7,22-dien-3-one (450 mg.) which crystallised from ether–methanol as fibrous needles, m. p. 138—141°. Identity with the sample prepared by method (*a*) was established by non-depression in m. p. on admixture and by infrared comparison. Elution with pentane–benzene (9 : 1 and 17 : 3) gave 2α-methyl-5β-lumista-7,22-dien-3-one (300 mg.) which after crystallisation from ether–methanol, showed m. p. 129—132°, undepressed with the previously described sample. Lastly, pentane–benzene (4 : 1) eluted 100 mg. of unchanged 5β-lumista-7,22-dien-3-one, m. p. 168—170°, $[\alpha]_D$ +33°.

2,2-Dimethyl-5β-lumistan-3-one (VII).—2,2-Dimethyl-5β-lumista-7,22-dien-3-one (100 mg.) in ethyl acetate (7 ml.) containing perchloric acid [0·05 ml. of a solution made from 60% aqueous perchloric acid (1 ml.) and ethyl acetate (9 ml.)] was shaken in hydrogen at room temperature over Adams catalyst (23 mg.) until there was no further uptake. The catalyst was removed, and the solvent evaporated to give an oil which was adsorbed from pentane on alumina (5 g.). Elution with pentane–benzene (9 : 1) gave *2,2-dimethyl-5β-lumistan-3-one* (40 mg.) which, on crystallisation from ether–methanol, had m. p. 94—97°, $[\alpha]_D$ −34° (*c* 0·9) (Found: C, 84·4; H, 12·6. $C_{30}H_{52}O$ requires C, 84·05; H, 12·2%). Elution with benzene gave a solid (50 mg.) which, on crystallisation from ether–methanol, gave *2,2-dimethyl-5β-lumistan-3α-ol*, m. p. 139—142°, $[\alpha]_D$ +20° (*c* 0·9) (Found: C, 83·7; H, 12·7. $C_{30}H_{54}O$ requires C, 83·65; H, 12·6%).

The alcohol (30 mg.) was oxidised with Jones's reagent to give 2,2-dimethyl-5β-lumistan-3-one, m. p. 95—97°, $[\alpha]_D$ −33°.

2α-Methyl-5β-lumistan-3-one (V).—The hydrogenation of 2α-methyl-5β-lumista-7,22-dien-3-one (160 mg.) in ethyl acetate over Adams catalyst was carried out as above. Oxidation of the product with Jones's reagent and crystallisation from ether–methanol gave *2α-methyl-5β-lumistan-3-one* (140 mg.) as fibrous needles, m. p. 102—105°, $[\alpha]_D$ +1·7° (*c* 0·96), $\nu_{max.}$ (KBr) 1710 cm.$^{-1}$ (Found: C, 83·8; H, 12·1. $C_{29}H_{50}O$ requires C, 84·0; H, 12·15%). Optical rotatory dispersion: trough, −1940 (303 mμ), peak, +3495 (266), $10^{-2}a$ −54.

Epimerisation of 2α-Methyl-5β-lumistan-3-one.—2α-Methyl-5β-lumistan-3-one (20 mg.) in ethanol (8 ml.) containing 20% sulphuric acid (v/v, 0·2 ml.) was heated under reflux for 4 hr. The product, on crystallisation from ether–methanol, had m. p. 100—128° The infrared spectrum of the product indicated it was a mixture of 2α- and 2β-methyl-5β-lumistan-3-one.

2α-Methyl-5β-lumista-7,22-dien-3-one, on treatment with sulphuric acid in ethanol under the same conditions, was recovered completely unchanged.

2-Hydroxymethylene-5β-lumista-7,22-dien-3-one (VIII).—5β-Lumista-7,22-dien-3-one (1·5 g.) in ether (90 ml.) was treated with sodium methoxide [from sodium (1·3 g.) in methanol (15 ml.)] and ethyl formate (25 ml.) for 5 days at room temperature with occasional shaking. The mixture was then treated with a buffered phosphate solution (pH 8·1; 50 ml.). Ether extraction afforded *2-hydroxymethylene-5β-lumista-7,22-dien-3-one* as a yellow crystalline product. Recrystallisation from ether–methanol gave the analytical sample, m. p. 127—130°, $[\alpha]_D$ +55·1°

(*c* 1·0), $\lambda_{max.}$ (in ethanol) 287 mμ (ε 5800) (Found: C, 81·8; H, 10·5. $C_{29}H_{44}O_2$ requires C, 82·0; H, 10·4%).

Catalytic Hydrogenation of 2-Hydroxymethylene-5β-lumista-7,22-dien-3-one.—The ketone (1·01 g.) in thiophen-free benzene (15 ml.) and ethanol (15 ml.) was shaken in an atmosphere of hydrogen with 10% palladium–charcoal (1·06 g.) until there was no further uptake. Filtration, followed by evaporation under reduced pressure, gave an oil which was rehydrogenated in ethyl acetate (30 ml.) containing 0·2 ml. perchloric acid [from 70% perchloric acid (1 ml.) in ethyl acetate (9 ml.)] with platinum oxide (120 mg.). Oxidation of the product with Jones's reagent gave an oil which was chromatographed on alumina (30 g.). Elution with pentane–benzene (19 : 1) gave 2β-methyl-5β-lumistan-3-one (450 mg.). Crystallisation from ether–methanol gave needles, m. p. and mixed m. p. 128—132°, $[\alpha]_D$ −11°.

5β-*Lumista*-7,22-*dien*[3,2-c]*pyrazole* (IX).—2-Hydroxymethylene-5β-lumista-7,22-dien-3-one (160 mg.) in ethanol (15 ml.) was refluxed with hydrazine hydrate (100%, 200 mg.) for 6 hr. On cooling, crystals (100 mg.) were obtained having m. p. 173—180°. Recrystallisation from ethanol gave 5β-*lumista*-7,22-*dien*[3,2-c]*pyrazole* as fibrous needles, m. p. 174—178° (decomp.) $[\alpha]_D$ +35·3° (*c* 1·09), $\nu_{max.}$ (KBr) 3200 cm.$^{-1}$ (Found: C, 82·6; H, 10·7; N, 6·8. $C_{29}H_{44}N_2$ requires C, 82·8; H, 10·5; N, 6·7%).

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