1325. *The Methylation of Lumistan-3-ones*

By W. T. Pike, G. H. R. Summers, and W. Klyne

The methylation of 5β-lumistan-3-one and 5α,14α-lumistan-3-one is described. The optical rotatory dispersion measurements of the methylated ketones are recorded and compared with theoretical expectations.

As part of a research programme dealing with ring-A-methylated steroids it became desirable to investigate the methylation of lumistan-3-one derivatives. We have already reported on the methylation of 5β-lumista-7,22-dien-3-one,[1] and we now describe the results obtained with 5β-lumistan-3-one (I) and 5α,14α-lumistan-3-one (II).

The ketone (I) was obtained most conveniently by the method of Jones and his coworkers.[2] Direct methylation of the ketone with methyl iodide and 1·5 molar equivalents of potassium t-butoxide in boiling t-butyl alcohol for 3 minutes yielded mainly 2β-methyl-5β-lumistan-3-one (III). The structural assignment rests on the independent method by which the same substance was subsequently prepared, on its stability towards both acids and bases, and on the finding [2] that the enolisation of the carbonyl group in ketone (I) occurs towards C-2. The reaction also produced smaller amounts of a compound whose infrared spectrum ($\nu_{max.}$ 1695 cm.$^{-1}$ in CS_2) indicated it to be a dimethylated ketone;[3] this must be 2,2-dimethyl-5β-lumistan-3-one (IV). Ketone (IV) 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 monomethylation at C-2 of 5β-lumistan-3-one (I) could alternatively be brought about by the base-catalysed condensation of (I) with ethyl formate to give 2-hydroxymethylene-5β-lumistan-3-one (V) which on catalytic hydrogenolysis yielded the same 2β-methyl-5β-lumistan-3-one (III) as had been obtained previously. Reduction of the ketones (III) and (IV) by lithium aluminium hydride proceeded normally and yielded mainly 2β-methyl-5β-lumistan-3α-ol (VI) and 2,2-dimethyl-5β-lumistan-3α-ol (VII), respectively.

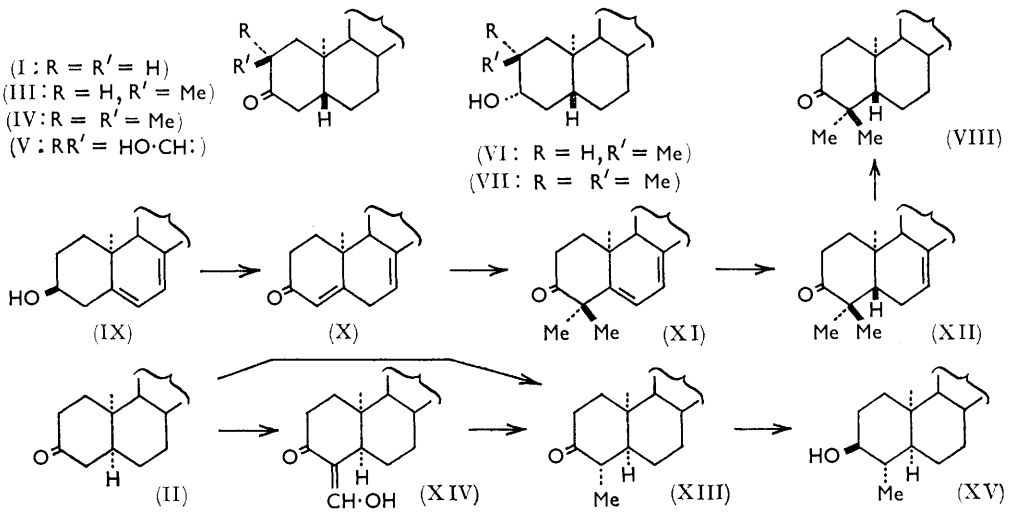
The assignment of ketones (III) and (IV) as being 2-methylated ketones was supported by the fact that ketone (IV) differed from 4,4-dimethyl-5β-lumistan-3-one (VIII) prepared by the following unambiguous method. Oppenauer oxidation of lumisterol (IX) under the conditions of Shepherd *et al.*[4] gave a 45% yield of lumista-4,7,22-trien-3-one (X). Direct methylation of this ketone under the conditions of Woodward *et al.*[5] gave rise to 4,4-dimethyl-lumista-5,7,22-trien-3-one (XI), the constitution of which is defined by the absence of an αβ-unsaturated ketone band in the infrared and ultraviolet spectra. Reduction of 4,4-dimethyl-lumista-5,7,22-trien-3-one (XI) with lithium in liquid ammonia proceeded normally and gave 4,4-dimethyl-5β-lumista-7,22-dien-3-one (XII). Complete hydrogenation of ketone (XII) in ethyl acetate containing a little perchloric acid as promoter, over platinum oxide, gave 4,4-dimethyl-5β-lumistan-3-one (VIII).

Treatment of 5α-lumistan-3-one (II) with methyl iodide and potassium t-butoxide in t-butyl alcohol resulted mainly in methylation at C-4. Chromatography gave 55% of 4α-methyl-5α-lumistan-3-one (XIII). The structural assignment rests on the independent method by which the same substance was subsequently prepared, on its stability towards both acids and bases, and on the finding [2] that the enolisation of the carbonyl group in ketone (II) occurs predominantly towards C-4. The monomethylation at C-4 of 5α-lumistan-3-one could alternatively be brought about by the base-catalysed condensation of (II) with ethyl formate to give 4-hydroxymethylene-5α-lumistan-3-one (XIV) which on

[1] W. T. Pike, G. H. R. Summers, and W. Klyne, *J.*, 1965, 5064.
[2] J. Castells, G. A. Fletcher, E. R. H. Jones, G. D. Meakins, and R. Swindells, *J.*, 1960, 2627.
[3] Y. Mazur and F. Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 5220.
[4] D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, jun., J. E. Stafford, R. L. Pederson, and A. C. Ott, *J. Amer. Chem. Soc.*, 1955, **77**, 1212.
[5] R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J.*, 1957, 1131.

catalytic hydrogenolysis yielded the same 4α-methyl-5α-lumistan-3-one (XIII) as had been obtained previously. Reduction of ketone (XIII) by lithium aluminium hydride proceeded normally and yielded mainly 4α-methyl-5α-lumistan-4β-ol (XV).

The rotatory dispersion curve for 5β-lumistan-3-one (I) has been measured by Djerassi and Klyne;[6] it shows no abnormal features when considered in the light of the octant rule.[7] Similarly, the curve for 5α,14α-lumistan-3-one (II) shows no abnormal features. The curve for 2β-methyl-5β-lumistan-3-one shows a curve similar to that of the parent ketone (I); on the basis of the octant rule, it would be expected that the introduction of an equatorial methyl group would make a negligible change.



The curve for 2,2-dimethyl-5β-lumistan-3-one (IV) is anomalous. The octant rule would predict a more negative Cotton effect for a compound (IV) than for the ketone (I). This seems compatible only with a distorted A-ring in compound (IV).

The 4,4-dimethyl-5β-lumistan-3-one (VIII) shows a negative Cotton effect somewhat weaker than that of the unmethylated ketone (I). This is in complete agreement with theoretical expectation since the octant rule would predict a positive contribution to the Cotton effect by an axial methyl group at C-4. It is pertinent to note that, whereas introduction of a *gem* dimethyl group at C-4 in the " normal " steroid A/B-*trans* series alters the sign of the Cotton effect, the introduction of such a group at C-4 in 5β-lumistan-3-one does not cause inversion of the Cotton effect.

Experimental

$[\alpha]_D$ values are for chloroform solutions. Chromatograms were carried out with Spence alumina type H.

5β-*Lumistan-3-one* (I).—The ketone was prepared by the method of Jones and his co-workers.[2]

Methylation of 5β-*Lumistan-3-one.*—(a) *To give mainly* 2β-*methyl-*5β-*lumistan-3-one* (III). A boiling solution of 5β-lumistan-3-one (1·15 g.) in benzene (12 ml.) and t-butyl alcohol (6 ml.) was treated successively with potassium t-butoxide [prepared from potassium (170 mg.) and t-butyl alcohol (10 ml.)] and methyl iodide (1·2 ml.) in benzene (1·2 ml.). After refluxing for 3 min. the mixture was poured on to ice, extracted with ether, and worked up in the usual way, to give an oil which was adsorbed from pentane on alumina (70 g.). Elution with pentane–

[6] C. Djerassi and W. Klyne, *J.*, 1962, 4929.

[7] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013.

benzene (17 : 3) yielded 2,2-dimethyl-5β-lumistan-3-one (160 mg.) which on crystallisation from ether–methanol gave rods, m. p. 95—97°, $[\alpha]_D$ −35° (*c* 1·4), $\nu_{max.}$ (CS_2) 1695 cm.$^{-1}$ (lit.,[1] m. p. 94—97°, $[\alpha]_D$ −34°) (Found: C, 84·4; H, 12·6. Calc. for $C_{30}H_{52}O$: C, 84·05; H, 12·2%). Further elution with pentane–benzene (17 : 3) yielded oils which crystallised (410 mg.). Recrystallisation of these fractions from ether–methanol gave crystals, m. p. 120—135°, evidently a mixture of monomethyl and dimethyl ketones. Elution with pentane–benzene (17 : 3 up to 7 : 3) gave an oil (210 mg.) which, on recrystallisation from ether–methanol, gave 2β-*methyl*-5β-*lumistan*-3-*one* as rods, m. p. 132—135°, $[\alpha]_D$ −11° (*c* 0·9) $\nu_{max.}$ (KBr) 1709 cm.$^{-1}$ (Found: C, 84·4; H, 12·4. $C_{29}H_{50}O$ requires C, 84·0; H, 12·15%). Finally, benzene eluted 5β-lumistan-3-one (350 mg.), m. p. and mixed m. p. 122—124°, $[\alpha]_D$ −12° (*c* 1·0), after recrystallisation from ether–methanol.

(b) *To give mainly* 2,2-*dimethyl*-5β-*lumistan*-3-*one* (IV). A boiling solution of 5β-lumistan-3-one (970 mg.) in benzene (25 ml.) and t-butyl alcohol (13 ml.) was treated successively with potassium t-butoxide [prepared from potassium (1·08 g.) and t-butyl alcohol (30 ml.)] and methyl iodide (9·0 ml.) in benzene (25 ml.). After refluxing for 1 hr., the product was isolated as previously and was chromatographed on alumina (60 g.). Elution with pentane–benzene (9 : 1) and recrystallisation from ether–methanol afforded 2,2-dimethyl-5β-lumistan-3-one (750 mg.) as rods, m. p. 94—96°, $[\alpha]_D$ −32° (*c* 1·0). Identity with the sample prepared by method (a) was established by mixed m. p. and infrared comparison. Further elution with pentane–benzene (9 : 1 up to 4 : 1) gave 2β-methyl-5β-lumistan-3-one (50 mg.), which crystallised from ether–methanol as rods, m. p. 131—134° undepressed with the previously described sample, $[\alpha]_D$ −12° (*c* 1·0).

2β-*Methyl*-5β-*lumistan*-3-*one* via 2-*Hydroxymethylene*-5β-*lumistan*-3-*one* (V).—5β-Lumistan-3-one (250 mg.) in ether (10 ml.) was treated with sodium methoxide [from sodium (200 mg.) in methanol (3 ml.)] and ethyl formate (4 ml.) for 5 days at room temperature with occasional shaking. Treatment of the mixture with a buffered phosphate solution (pH 8·1) (30 ml.) followed by ether extraction gave the crude hydroxymethylene derivative as a crystalline product, m. p. 150—152°. The crude hydroxymethylene derivative was dissolved in thiophen-free benzene (10 ml.) and ethanol (10 ml.) and shaken in an atmosphere of hydrogen with 10% palladium–charcoal (220 mg.) until there was no further uptake. Filtration, followed by evaporation under reduced pressure, gave an oil which was chromatographed on alumina (12 g.). Elution with pentane–benzene (9 : 1) gave 2β-methyl-5β-lumistan-3-one (150 mg.) which crystallised from ether–methanol as rods, m. p. 133—135°, $[\alpha]_D$ −12° (*c* 0·9). Its identity with the specimen obtained by direct methylation of 5β-lumistan-3-one was established by mixed m. p. and infrared comparison.

2,2-*Dimethyl*-5β-*lumistan*-3α-*ol* (VII).—A solution of lithium aluminium hydride (140 mg.) in ether (10 ml.) was added to a solution of 2,2-dimethyl-5β-lumistan-3-one (150 mg.) in ether (10 ml.). The mixture was refluxed for 1 hr. and the excess reagent decomposed by the addition of ice and dilute hydrochloric acid. Working up in the usual way gave a solid which on recrystallisation from ether–methanol afforded 2,2-dimethyl-5β-lumistan-3α-ol as fibrous needles, m. p. 140—143°, $[\alpha]_D$ +22° (*c* 0·85) (lit.,[1] m. p. 139—142°, $[\alpha]_D$ +20°) (Found: C, 83·7; H, 12·7. Calc. for $C_{30}H_{54}O$: C, 83·65; H, 12·6%).

2β-*Methyl*-5β-*lumistan*-3α-*ol* (VI).—2β-Methyl-5β-lumistan-3-one (180 mg.) in ether (12 ml.) was reduced with lithium aluminium hydride (180 mg.) in ether (10 ml.) as previously. Recrystallisation of the product from ethyl acetate afforded 2β-*methyl*-5β-*lumistan*-3α-*ol* as rods, m. p. 90—93°, $[\alpha]_D$ +30·5° (*c* 0·74) (Found: C, 83·3; H, 12·45. $C_{29}H_{52}O$ requires C, 83·5; H, 12·6%).

Lumista-4,7,22-*trien*-3-*one* (X).—The ketone was prepared by the method of Shepherd *et al.*[4] by the oxidation of lumisterol (IX) with aluminium isopropoxide in toluene and cyclohexanone. The crude oxidation product was recrystallised from ether–methanol, giving rods, m. p. 135—138°, $[\alpha]_D$ +41° (*c* 1·20), $\lambda_{max.}$ 241 mμ (ε 34,200), $\nu_{max.}$ 1667 cm.$^{-1}$ (lit.,[8–10] m. p. 139—140°, $[\alpha]_D$ +48·7°; m. p. 139—140°, $[\alpha]_D$ +48·7°; m. p. 141—142°, $[\alpha]_D$ +39°).

4,4-*Dimethyl*-*lumista*-5,7,22-*trien*-3-*one* (XI).—A boiling solution of lumista-4,7,22-trien-3-one (1·01 g.) in benzene (25 ml.) and t-butyl alcohol (13 ml.) was treated successively with potassium t-butoxide [prepared from potassium (960 mg.) and t-butyl alcohol (35 ml.)] and

[8] I. M. Heilbron, T. Kennedy, F. S. Spring, and G. Swain, *J.*, 1938, 869.
[9] J. Castells, E. R. H. Jones, G. D. Meakins, and R. W. J. Williams, *J.*, 1959, 1159.
[10] P. Westerhof and E. H. Reerink, *Rec. Trav. Chim.*, 1960, **7**, 771.

methyl iodide (7·5 ml.) in benzene (25 ml.). After refluxing for 1 hr., the mixture was poured on to ice, extracted with ether, and worked up in the usual way, to give an oil which was chromatographed on alumina (20 g.). Elution with pentane gave 4,4-dimethyl-lumista-5,7,22-trien-3-one (800 mg.) which crystallised from ether–methanol as plates, m. p. 108—111°, $[\alpha]_D$ +99·5° (*c* 0·97), $\lambda_{max.}$ 287 mμ (ε 9350), $\nu_{max.}$ ($CHCl_3$) 1709 cm.$^{-1}$ (Found: C, 85·0; H, 10·8. $C_{30}H_{46}O$ requires C, 85·2; H, 11·0%).

4,4-*Dimethyl*-5β-*lumista*-7,22-*dien*-3-*one* (XII).—Lithium (160 mg.) was added to a stirred solution of 4,4-dimethyl-lumista-5,7,22-trien-3-one (600 mg.) in anhydrous ether (80 ml.) and liquid ammonia (80 ml.) during 15 min. The solution was stirred for a further 30 min. and ethanol added slowly to discharge the blue colour. The ammonia was evaporated, water added, and the material isolated with ether (containing 10% of chloroform). The ethereal layer was washed with water, dried ($MgSO_4$), and distilled, to give a white crystalline product (580 mg.). Oxidation of the product with 8N-chromic acid in the usual way gave an oil which was filtered through alumina (20 g.) in ether solution. Removal of the solvent gave 4,4-*dimethyl*-5β-*lumista*-7,22-*dien*-3-*one* as an oil which crystallised from ethyl acetate. Recrystallisation from methanol gave the analytical sample, m. p. 122—125°, $[\alpha]_D$ +71° (*c* 0·95), $\nu_{max.}$ (KBr) 1704 cm.$^{-1}$ (Found: C, 84·4; H, 11·3. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%.

4,4-*Dimethyl*-5β-*lumistan*-3-*one* (VIII).—4,4-Dimethyl-5β-lumista-7,22-dien-3-one (350 mg.) in ethyl acetate (30 ml.) containing perchloric acid (0·05 ml. of a solution of 1 ml. of 60% aqueous perchloric acid in 9 ml. of ethyl acetate) was shaken in an atmosphere of hydrogen at room temperature with Adams catalyst (45 mg.) for 2 hr. The catalyst was removed by filtration and the filtrate taken to dryness under reduced pressure, to give an oil (330 mg.). Oxidation with 8N-chromic acid in the usual manner gave an oil which was chromatographed on alumina (15 g.). Elution with pentane–ether (9 : 1) gave 4,4-*dimethyl*-5β-*lumistan*-3-*one* which crystallised from methanol as plates, m. p. 115—118°, $[\alpha]_D$ −3·7° (*c* 0·52), $\nu_{max.}$ (KBr) 1698 cm.$^{-1}$ (Found: C, 84·4; H, 11·9. $C_{30}H_{52}O$ requires C, 84·05; H, 12·2%).

5α,14α-*Lumistan*-3-*one* (II).—The ketone was prepared by the method of Jones and his co-workers.[2]

4α-*Methyl*-5α,14α-*lumistan*-3-*one* (XIII).—(a) *By direct methylation of* 5α,14α-*lumistan*-3-*one*. A boiling solution of 5α,14α-lumistan-3-one (550 mg.) in benzene (15 ml.) and t-butyl alcohol (8 ml.) was treated successively with potassium t-butoxide [prepared from potassium (580 mg.) and t-butyl alcohol (15 ml.)] and methyl iodide (4·5 ml.) in benzene (15 ml.). After refluxing for 1 hr. the mixture was poured on to ice, extracted with ether, and worked up in the usual way, to give an oil which was adsorbed from pentane on alumina (40 g.). Elution with pentane gave an oil (100 mg.; no carbonyl band in the infrared spectrum) which would not crystallise and which was not investigated further. Further elution with pentane gave 4α-*methyl*-5α,14α-*lumistan*-3-*one* (350 mg.) which crystallised from ether–methanol as plates, m. p. 121—124°, $[\alpha]_D$ +36° (*c* 0·81), $\nu_{max.}$ (KBr) 1715 cm.$^{-1}$ (Found: C, 83·9; H, 12·2. $C_{29}H_{50}O$ requires C, 84·0; H, 12·2%). Further elution with pentane–benzene (19 : 1) gave oils (50 mg.) which were shown by thin-layer chromatography to be mixtures of 4α-methyl-5α,14α-lumistan-3-one and starting material.

(b) *By way of* 4-*hydroxymethylene*-5α,14α-*lumistan*-3-*one* (XIV). 5α,14α-Lumistan-3-one (500 mg.) in ether (20 ml.) was treated with sodium methoxide [from sodium (400 mg.) in methanol (5 ml.)] and ethyl formate (7 ml.) for 5 days at room temperature with occasional shaking. Treatment of the mixture with a buffered phosphate solution (pH 8·1) (20 ml.) followed by ether extraction gave a yellow oil (590 mg.) which crystallised. Recrystallisation from ether–methanol gave 4-*hydroxymethylene*-5α,14α-*lumistan*-3-*one* as plates, m. p. 113—116°, $[\alpha]_D$ +9·4° (*c* 1·1), $\lambda_{max.}$ 293 mμ (ε 8800) (Found: C, 81·0; H, 11·3. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%).

4-Hydroxymethylene-5α-lumistan-3-one (500 mg.) in thiophen-free benzene (8 ml.) and ethanol (8 ml.) was shaken with 10% palladium–charcoal (300 mg.) in an atmosphere of hydrogen until there was no further uptake. Filtration, followed by distillation under reduced pressure, gave an oil which was chromatographed on alumina (20 g.). Elution with pentane–benzene (9 : 1) gave 4α-methyl-5α,14α-lumistan-3-one (300 mg.) which crystallised from ether–methanol as plates, m. p. 121—124°, $[\alpha]_D$ +35° (*c* 0·9). Its identity with the specimen obtained by method (a) was established by mixed m. p. and infrared comparison.

4α-*Methyl*-5α,14α-*lumistan*-3β-*ol* (XV).—4α-Methyl-5α,14α-lumistan-3-one (130 mg.) in ether (30 ml.) was refluxed with lithium aluminium hydride (190 mg.) for 1 hr. Decomposition

of the excess reagent with ethyl acetate and working up in the usual way gave 4α-*methyl*-5α,14α-*lumistan*-3β-*ol* which crystallised from methanol, m. p. 131—134°, [α] +27·4° (*c* 0·88) (Found: C, 83·9; H, 12·5. $C_{29}H_{52}O$ requires C, 83·6; H, 12·6%).

Optical Rotatory Dispersion.—General experimental details for the rotatory dispersion were as described by Jones and Klyne.[11] All curves were measured for methanol solutions (*c* 0·01) at 18—20°. All values are as molecular rotations.

2β-Methyl-5β-lumistan-3-one. Trough, −3070 (307·5 mμ), peak, +3240 (272·5). Amplitude $10^{-2}a$, −63. 2,2-Dimethyl-5β-lumistan-3-one. Trough, −1660 (317·5 mμ), peak, +160 (277·5); $10^{-2}a$, −18. 4,4-Dimethyl-5β-lumistan-3-one. Trough, −1260 (303 mμ), peak, +1360 (267); $10^{-2}a$, −26. 5α,14α-Lumistan-3-one. Peak, +1450 (307·5 mμ), trough, −110! (267·5); $10^{-2}a$, +16! 4α-Methyl-5α,14α,-lumistan-3-one. Trough, −110 (303 mμ), peak, +890! (244); $10^{-2}a$, −10! 4,4-Dimethyl-5β-lumista-7,22-dien-3-one. Peak, +1620 (319 mμ), trough, +348 (278); $10^{-2}a$, +19.

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University College of Wales, Swansea.
Westfield College, Hampstead, London N.W.3.

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[11] P. M. Jones and W. Klyne, *J.*, 1960, 871.