

The C-8 Epimers of 7-Oxo-5 α -lanost-9(11)-en-3 β -yl Acetate

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Oxidation of 5 α -lanost-8-en-3 β -yl acetate under controlled conditions gives 7,11-dioxo-5 α -lanost-8-en-3 β -yl acetate and 7-oxo-5 α -lanost-9(11)-en-3 β -yl acetate in approximately equal amounts. Reaction of 5 α -lanosta-7,9(11)-dien-3 β -yl acetate with acetic acid-hydrogen peroxide gives 7-oxo-5 α ,8 α -lanost-9(11)-en-3 β -yl acetate. Evidence is presented for the constitution and stereochemistry of each product.

IN 1937 Marker and his co-workers¹ reported the oxidation of 5 α -lanost-8-en-3 β -yl acetate (I) with chromium trioxide under relatively mild conditions to yield two products, α - and β -ketodihydrolanosteryl acetate. The β -isomer was later identified as 7-oxo-5 α -lanost-8-en-3 β -yl acetate (II).² Subsequent attempts to repeat the isolation of the α -isomer in the manner described by Marker (fractional crystallisation) were unsuccessful.³ Recently, Briggs and his co-workers⁴ have reinvestigated this oxidation employing column chromatography to separate the total product. They isolated three compounds, 7-oxo-5 α -lanost-8-en-3 β -yl acetate (II), 7,11-dioxo-5 α -lanost-8-en-3 β -yl acetate (III), and 7-oxo-5 α -lanost-9(11)-en-3 β -yl acetate (IV). From a comparison of m.p.s they tentatively suggested the identity of the last mentioned compound with Marker's α -ketodihydrolanosteryl acetate.

¹ R. E. Marker, E. L. Wittle, and L. A. Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1368.

² D. H. R. Barton, J. S. Fawcett, and B. R. Thomas, *J. Chem. Soc.*, 1951, 3147.

We have independently re-examined the original experiment of Marker.¹ G.l.c. analysis shows that there are only two true products formed in the oxidation, namely the 7,11-dioxo-8-ene (III) and the 7-oxo-9(11)-ene (IV). The 7-oxo-8-ene (II) isolated by Marker¹ and by subsequent workers²⁻⁴ is an artefact formed by rearrangement of the β,γ -unsaturated ketone (IV). Its formation is avoided if the crude product is rapidly separated by preparative layer chromatography on silica gel. An analogous situation has been noted previously for the oxidation of the 7,9(11)-diene (V) and related compounds with sodium dichromate.⁵ Support for the structure of the β,γ -unsaturated ketone (IV) came from spectral data. The i.r. spectrum showed a carb-

³ M. J. Birchenough and J. F. McGhie, *J. Chem. Soc.*, 1950, 1249; J. F. Cavalla and J. F. McGhie, *ibid.*, 1951, 744 and references therein.

⁴ L. H. Briggs, J. P. Bartley, and P. S. Rutledge, *J.C.S. Perkin I*, 1972, 581.

⁵ J. Elks, R. M. Evans, A. G. Long, and G. H. Thomas, *J. Chem. Soc.*, 1954, 451.

onyl absorption at 1705 cm^{-1} , and the n.m.r. spectrum had signals for an olefinic proton ($\tau\ 4.60$) coupled to a methine proton ($\tau\ 7.10$) flanked by both a ketone group and a double bond. Also, treatment with boron trifluoride-ether in benzene gave the α,β -unsaturated

material crystallises as plates (as does Marker's α -keto-dihydrolanosteryl acetate¹) in contrast to the silky needles reported by the latter workers.

This finding prompted us to reinvestigate the reaction of 5α -lanosta-7,9(11)-dien-3 β -yl acetate (VI) with acetic acid-hydrogen peroxide, a reaction from which Jeger and his co-workers⁶ isolated a compound (m.p. $153\text{--}154^\circ$, $[\alpha]_D +119^\circ$) to which they assigned structure (IV). We obtained the same compound as the major product of this oxidation (m.p. $160\text{--}164^\circ$, $[\alpha]_D +115^\circ$). Examination of the i.r. spectrum (1720 cm^{-1}) and the n.m.r. spectrum [$\tau\ 4.44$ (1H, m) and 6.82 (1H, m)] established

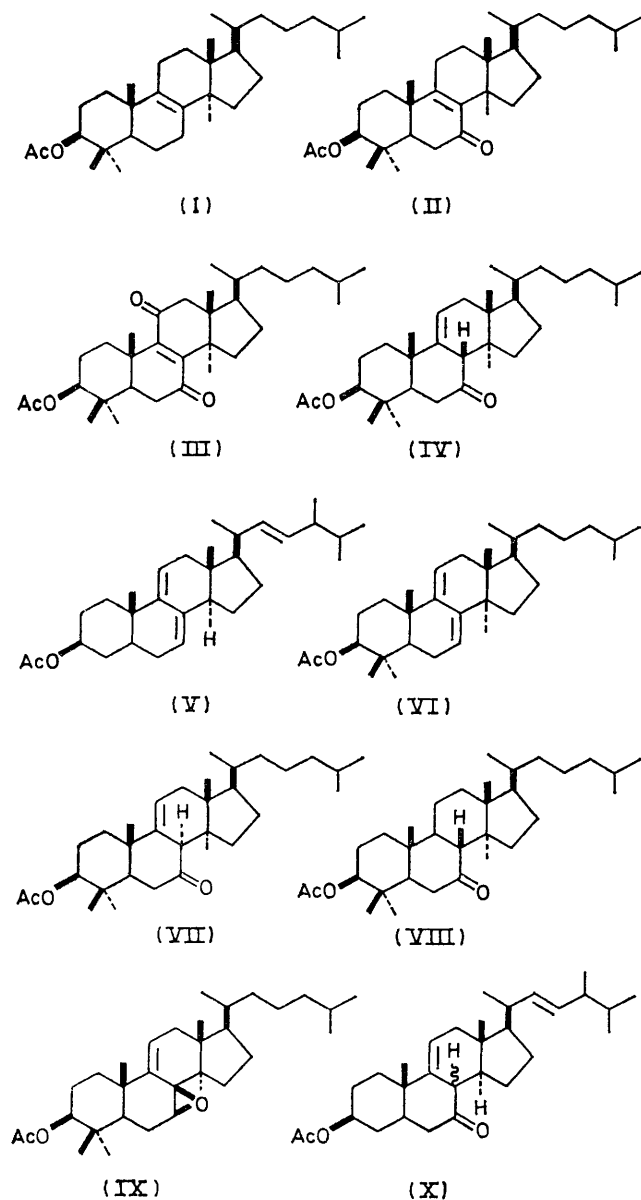
the presence of the partial structure $-\text{C}(\text{O})-\overset{\text{H}}{\text{C}}=\overset{\text{H}}{\text{C}}-\text{CH}-$. The keto-group was located at C-7 since treatment with boron trifluoride-ether in benzene gave the α,β -unsaturated ketone (II). Interestingly, this reaction proceeded some 20 times faster than the corresponding isomerisation of the ketone (IV), thus precluding the possibility that preliminary interconversion was occurring. It follows that the above product and the β,γ -unsaturated ketone (IV) from the oxidation of 5α -lanost-8-en-3 β -yl acetate are epimeric at C-8. From the evidence cited below we formulate the former compound as the 8α -isomer (VII).

In the first place a comparison of the o.r.d. spectra of the isomers (IV) and (VII) (see Experimental section) and 7-oxo- 5α -lanostan-3 β -yl acetate (VIII)⁷ showed the greatest similarity to be between the first and last mentioned curves, as would be expected if these are the two compounds with 8β -stereochemistry. Secondly, the isomer, m.p. $160\text{--}164^\circ$, $[\alpha]_D +115^\circ$, may also be obtained by rearrangement of $7\beta,8\beta$ -epoxylanost-9(11)-en-3 β -yl acetate (IX) on a column of silica gel.⁸ If, as would be expected,⁹ this process involves a suprafacial 1,2-shift of a hydride ion from C-7 α , the isomer formed must be the one with 8α -stereochemistry. It was independently established that no interconversion occurs between isomers (IV) and (VII) during chromatography on silica gel. Finally, it was recognised that isomer (VII), in which ring B is held in a rigid boat conformation, must be thermodynamically the less stable one by a significant amount,¹⁰ and conditions were sought that would permit this compound to equilibrate to the more stable isomer (IV). The isomer, m.p. $160\text{--}164^\circ$, $[\alpha]_D +115^\circ$, (VII) was recovered unchanged (optical rotation) after being heated at 10° above its m.p. for 5 min, as was the case when it was allowed to stand in chloroform solution for one week (optical rotation and n.m.r. spectroscopy). Chromatography on neutral alumina gave only the α,β -unsaturated ketone (II) together with a more polar compound. However, chromatography on alumina that had been previously treated with acetic acid¹¹ achieved the required equilibration of (VII) to (IV) with a minimum of isomerisation to the α,β -unsaturated ketone (II).

⁶ R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry,' Academic Press, New York, 1970.

¹⁰ M. Hanack, 'Conformation Theory,' Academic Press, New York, 1965.

¹¹ P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovell, G. W. Wood, G. F. Woods, J. Elks, R. M. Evans, D. E. Hathway, J. F. Oughton, and G. H. Thomas, *J. Chem. Soc.*, 1953, 2921.



ketone (II), identical with an authentic sample. Presumably our compound (IV) is the same as that obtained by Briggs *et al.*⁴ although we have consistently obtained a considerably lower value for the rotation ($[\alpha]_D +56.7^\circ$ as compared to $+78^\circ$). Furthermore, our

⁶ M. V. Mijovic, W. Voser, H. Heusser, and O. Jeger, *Helv. Chim. Acta*, 1952, **35**, 964.

⁷ C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 4001.

⁸ J. E. Fox, A. I. Scott, and D. W. Young, *J.C.S. Perkin I*, 1972, 799.

This completed our investigation of the stereochemistry of the two isomers.

The above work lends support to previous investigations on the existence of C-8 epimers of the β,γ -unsaturated ketone (X).¹²

Further work to utilise to synthetic advantage the unnatural stereochemistry of 7-oxo-5 α ,8 α -lanost-9(11)-en-3 β -yl acetate (VII) is in progress, and will be reported in a subsequent communication.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. N.m.r. data refer to solutions in deuteriochloroform with tetramethylsilane as internal standard; they were recorded with a Perkin-Elmer R10 instrument. Rotations and u.v. spectra refer to solutions in chloroform and ethanol respectively, and i.r. spectra to Nujol mulls. T.l.c. and preparative layer chromatography (p.l.c.) were performed with plates prepared from Merck Silica Gel GF₂₅₄. G.l.c. data are for a column of 1% SE 30 at 251° with nitrogen carrier gas at a flow rate of 40 ml min⁻¹. Retention times are reported relative to 1.00 for cholestane (actual retention time ca. 4.1 min). O.r.d. data were obtained using a Bellingham and Stanley Polaramatic 62 instrument.

Oxidation of 5 α -Lanost-8-en-3 β -yl Acetate (I) under Marker's Conditions.—Chromium trioxide (548 mg) was dissolved in 90% acetic acid (20 ml) and the solution was heated to 80°. A solution of 5 α -lanost-8-en-3 β -yl acetate (1.0 g) in glacial acetic acid (30 ml) also at 80° was then added. After 10 min at the same temperature the mixture was cooled on an ice-bath, then poured into water (250 ml) and extracted with ether. The combined extracts were washed with water only, dried (Na₂SO₄), and evaporated. Examination of the product (which still contained traces of acetic acid) by g.l.c. showed a single peak of relative retention time 5.2, indicating the absence of 7-oxo-5 α -lanost-8-en-3 β -yl acetate (relative retention time 5.6). T.l.c. showed two spots of approximately equal intensity. These were separated preparatively to afford 7,11-dioxo-5 α -lanost-8-en-3 β -yl acetate, identical with an authentic sample, and 7-oxo-5 α -lanost-9(11)-en-3 β -yl acetate (330 mg), crystallised from ethyl acetate-methanol as plates, m.p. 152–154°, $[\alpha]_D +56.7^\circ$ (*c* 1.19) (lit.,⁴ m.p. 150–152°, $[\alpha]_D +78^\circ$), ν_{\max} 1735, 1705, 1640, and 1250 cm⁻¹, λ_{\max} 295 and 325 (shoulder) nm (ϵ 97 and 47), τ 4.60 (1H, m, 11-H), 5.50 (1H, m, 3 α -H), 7.10 (1H, m, 8 β -H), 7.92 (3H, s, acetate), and 8.88, 9.08, 9.19, 9.25, and 9.33 (5 \times Me, s), g.l.c. relative retention time 5.2, o.r.d. (*c* 0.1, MeOH) $[\alpha]_{370} +133^\circ$ (broad), $[\alpha]_{317} -58^\circ$, and $[\alpha]_{263} +1320^\circ$ (*c* 0.1, dioxan) $[\alpha]_{370} +174^\circ$, $[\alpha]_{328} +69^\circ$, and $[\alpha]_{303} +414^\circ$.

Rearrangement of the β,γ -Unsaturated Ketone (IV).—A solution of the ketone (60 mg) in dry benzene (10 ml) was treated with boron trifluoride-ether (10 drops). After 6 h

at room temperature (t.l.c. control) the solution was washed with 2N-sodium carbonate, then with water, and evaporated. Crystallisation of the residue from methanol afforded needles of 7-oxo-5 α -lanost-8-en-3 β -yl acetate (54 mg, 90%), m.p. and mixed m.p. with an authentic sample 147.5–149.5°, $[\alpha]_D +18.3^\circ$ (*c* 1.05), ν_{\max} 1735, 1650, 1580, and 1245 cm⁻¹ (lit.,¹³ m.p. 151.5–152.5°, $[\alpha]_D +18.2^\circ$).

7-Oxo-5 α ,8 α -lanost-9(11)-en-3 β -yl Acetate (VII).—A suspension of 5 α -lanosta-7,9(11)-dien-3 β -yl acetate (1.8 g) in glacial acetic acid (400 ml) was treated with 30% hydrogen peroxide (6 ml) and shaken at room temperature for 72 h (the solution became clear after 36 h). The solution was poured into water (4 l), and the precipitate was filtered off, washed thoroughly with water, and dissolved in ether. The ether layer was dried and evaporated. The oily residue was crystallised from methanol to give the 7-oxo-8 α -isomer (VII) (840 mg, 45%), as rods, m.p. 160–164°, $[\alpha]_D +115.0^\circ$ (*c* 1.08) (lit.,⁶ m.p. 153–154°, $[\alpha]_D +119^\circ$), ν_{\max} 1735, 1720, and 1240 cm⁻¹, λ_{\max} 295 nm (ϵ 80), τ 4.44 (1H, m, 11-H), 5.40 (1H, m, 3 α -H), 6.82 (1H, m, 8 α -H), 7.92 (3H, s, acetate), and 8.86, 9.02, 9.06, 9.15, and 9.34 (5 \times Me, s), g.l.c. relative retention time 5.2, o.r.d. (*c* 0.1, MeOH) $[\alpha]_{364} +376^\circ$, $[\alpha]_{323} -245^\circ$, $[\alpha]_{263} +3630^\circ$ (*c* 0.1, dioxan) $[\alpha]_{370} +323^\circ$, $[\alpha]_{328} -423^\circ$, $[\alpha]_{294} +2375^\circ$ (Found: C, 79.3; H, 10.7. C₃₂H₅₂O₃ requires C, 79.3; H, 10.8%). Examination by t.l.c. of the mother liquors from the methanol crystallisation showed the presence of significant amounts of at least six other products. These were not further investigated.

Rearrangement of the β,γ -Unsaturated Ketone (VII).—(a) *With boron trifluoride.* A solution of the ketone (100 mg) in dry benzene (10 ml) was treated with boron trifluoride-ether (12 drops). After 20 min at room temperature (t.l.c. control) the solution was worked up as previously described to give 7-oxo-5 α -lanost-8-en-3 β -yl acetate (78 mg, 78%), m.p. and mixed m.p. 149–151°, $[\alpha]_D +18.5^\circ$ (*c* 1.02), ν_{\max} 1735, 1650, 1580, and 1245 cm⁻¹ (lit.,¹³ m.p. 151.5–152.5°, $[\alpha]_D +18.2^\circ$).

(b) *With treated alumina.* Laporte type 0 alumina (50 g) was shaken with 10% acetic acid (100 ml) for 10 min. The alumina was filtered off, washed thoroughly with methanol, air dried, and then left in an oven at 140° overnight. A column was prepared using this alumina (10 g) and light petroleum. The ketone (VII) (50 mg) was dissolved in benzene-light petroleum (1:1, 1 ml) and adsorbed onto the column. The column was then immediately eluted with benzene (100 ml) to give a product that t.l.c. showed to contain ca. 15% of the α,β -unsaturated ketone (II). Fractionation of this material by p.l.c. on silica gel and crystallisation of the less polar component from ethyl acetate-methanol afforded 7-oxo-5 α ,8 β -lanost-9(11)-en-3 β -yl acetate (28 mg), m.p. 150–151°, $[\alpha]_D +57.9^\circ$ (*c* 0.54), identical (mixed m.p., i.r., n.m.r.) with material from the oxidation of lanostenyl acetate under Marker's conditions.

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¹² R. Budziarek, G. T. Newbold, R. Stevenson, and F. S. Spring, *J. Chem. Soc.*, 1952, 2892; R. Budziarek, R. Stevenson, and F. S. Spring, *J. Chem. Soc.*, 1952, 4874; D. Maclean and F. S. Spring, *J. Chem. Soc.*, 1954, 328; ref. 5.

¹³ L. Ruzicka, E. Rey, and A. C. Muhr, *Helv. Chim. Acta*, 1944, 27, 472.