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32-OXYGENATED LANOSTANE DERIVATIVES FROM 3β-ACETOXY-Δ^7-LANOSTENE VIA 7α,8α-EPOXIDES[1]

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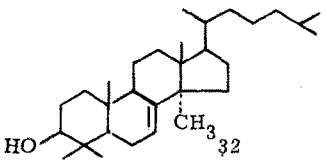
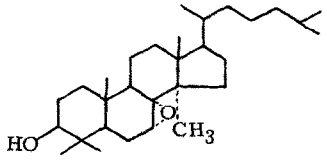
Lanostane derivatives, in which the angular methyl carbon attached to C-14 (32-methyl) bears an oxygen function are of considerable interest as probable intermediates in the enzymatic conversion of lanosterol to cholesterol,[2] and as intermediates for non-enzymatic demethylation reactions as well. Both 7α- and 9α-hydroxylanostanes would appear to be suitable precursors for the functionalization of the 32-methyl group since they possess the proper 1,3-diaxial relationship of their respective hydroxyl groups and the 32-methyl group to undergo intramolecular hydrogen abstraction reactions.[3] In a previous communication[4] we have shown that 9α-hydroxylanostanes suffer fragmentation with the formation of 9,10-seco-derivatives to the exclusion of intramolecular functionalization. We now wish to report the successful introduction of an oxygen function at C-32 using 7α-hydroxylanostane derivatives.[5]

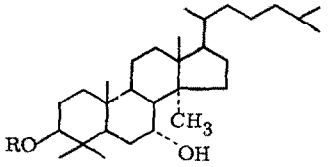
The required 3β-acetoxy-7α-hydroxylanostane (IIIb), originally described by Barton and Thomas,[6] was prepared by a new method from Δ^7-lanostene-3β-ol (I).[7] Epoxidation of the latter with m-chloroperbenzoic acid under the



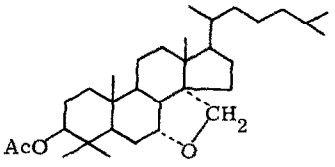
I



II



IIIa R = H
IIIb R = Ac



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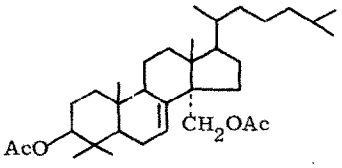

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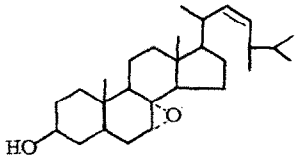
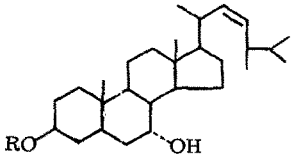
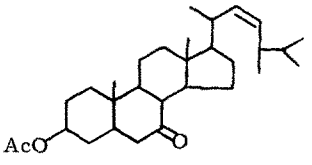


VI



VIIa R = H
VIIb R = Ac



VIII

precautions stated previously[4] afforded the 7α,8α-epoxide II, m.p. 152-153°; $[\alpha]_D$ +24°;[8] n.m.r. 6.53τ (7β-H), 8.96τ (32-CH_3),[9] which was reduced with lithium in ethylamine by a modification of the procedure of Hallsworth and Henbest[10] requiring the presence of t-butanol as a proton source, to a mixture of I and lanostane-3β,7α-diol (IIIa),[6] m.p. 163-166°; $[\alpha]_D$ +3.2°; the latter substances readily separated by preparative thin layer chromatography in 25% and 43% yield, respectively. Acetylation of IIIa with acetic anhydride-pyridine at room temperature for three hours gave mainly the 3β-monoacetate (IIIb),[6] m.p. 209-210.5°; $[\alpha]_D$ +14°, and a small amount of the 3β,7α-diacetate (IIIc),[6] m.p. 171-171.5°; $[\alpha]_D$ -16°. That the reduction of the epoxide II had furnished the 7α-ol IIIa and not an 8β-ol, as reported by Hallsworth and Henbest[10] for 7α,8α-oxido-Δ^{22}-ergostenyl acetate, followed from the identity of the physical constants for IIIa, IIIb and IIIc, with those reported by Barton and Thomas[6] and from the oxidation of IIIb with CrO_3 in acetone to 3β-acetoxylanostan-7-one.[6] The n.m.r.[11] spectra of IIIa and IIIb exhibited signals for single protons at 6.70 and 5.46τ, respectively (3α-H) and 5.92τ (7β-H) and showed the expected deshielding of the 32-methyl protons by the axial 7α-hydroxyl group by 0.29 p.p.m.[12]

Reaction of IIIb with 7 mole equivalents of lead tetraacetate[13] in benzene-cyclohexane for 18 hours furnished in 75% yield[14] the oxide IV, m.p. 202-204°; $[\alpha]_D$ +25°; g.l.c.[15] single peak, ret. time 9.2 min; λ_{max}^{KBr} no OH, 5.78 and 12.14μ, the latter band reported[13d] to be characteristic also of 6β,19-oxidosteroids. The n.m.r. spectrum of IV showed four protons in the region characteristic of protons attached to carbon bearing oxygen at 5.50τ (m. 3α-H), 5.84τ (m. 7β-H), 6.03τ (d. J, 8 cps, 32-H) and 6.67τ (d. J, 8 cps, 32-H),[13c] and no longer

exhibited the signal for the 32-methyl group found at 8.91τ in III and IIIa. Acetolytic cleavage of the tetrahydrofuran ring in IV was effected most satisfactorily by reaction with pyridine hydrochloride[16] in boiling acetic anhydride, which afforded in 75% yield the Δ^7-32-acetoxy compound V, m.p. 115-116°; $[\alpha]_D$ +11°; λ_{max}^{KBr} 5.75, 6.12 and 8.02μ; n.m.r. 4.76τ (d. J, 5 cps, 7-H), 5.50τ (m. 3α-H), 5.45τ (d. J, 12 cps, 32-H), 6.11τ (d. J, 12 cps, 32-H),[13c] 7.96τ (3β-acetyl), 8.04τ (32-acetyl), 9.04τ (19-CH_3), 9.12τ (30 and 31-CH_3) and 9.29τ (18-CH_3) g.l.c.[15] single peak time 9.4 min.

The finding that reductive opening of the 7α,8α-epoxide ring in II had proceeded entirely with the formation of the 7α-ol IIIa rather than of an 8α-ol as reported[10] by Hallsworth and Henbest for 7α,8α-oxido-Δ^{22}-ergostene-3β-ol acetate,[17] raised the question as to why such differences should exist in the opening of the epoxide ring between 14α-CH_3 and 14α-H-steroids. Reinvestigation of the lithium-ethylamine reduction in the 7α,8α-oxidoergostene series has indeed shown that in this case, too, opening occurs with the formation of the 7α-hydroxy compound. 7α,8α-Oxido-Δ^{22}-ergostene-3β-ol (VI), m.p. 153-156°; $[\alpha]_D$-10.5°;[18] n.m.r. 4.80τ (m. 22 and 23-H), 6.42τ (m. 3α-H), 6.67τ (7β-H), prepared in 80% yield from 5,6-dihydroergosterol with 1.5 equivalents of m-chloroperbenzoic acid at 5°, on reduction with Li in ethylamine exactly as described by Hallsworth and Henbest[10] afforded 5,6-dihydroergosterol and Δ^{22}-ergostene-3β,7α-diol (VIIa),[18] m.p. 200-201°; $[\alpha]_D$ -24°. The latter on acetylation with pyridine-acetic anhydride for 18 hours gave equal amounts of the 3β-monoacetate VIIb, m.p. 131-133°; $[\alpha]_D$-37°; λ_{max}^{KBr} 2.82, 5.74, 5.82 and 10.33μ; essentially identical in properties

with those reported[10] for Δ^{22}-ergostene-3β,8α-diol 3-monoacetate, and the 3β,7α-diacetate, m.p. 121-123°; $[\alpha]_D$ -49°; λ_{max}^{KBr} 5.75 and 10.36μ. Conclusive evidence for the presence of a 7α-rather than an 8α-hydroxyl group in the reduction product was obtained by inspection of the n.m.r. spectra of VIIa and VIIb, which showed signals for equatorial (7β) protons at 6.17τ in addition to those for the 3α-proton, and from the oxidation of VIIb with CrO_3 in acetone to the known 3β-acetoxy-Δ^{22}-ergostene-7-one (VIII), m.p. 198-199°; $[\alpha]_D$ -66°.[17] The resistance of the 7α-hydroxyl group in conventional sterols to acetylation under "standard" conditions is unexpected and has not been reported previously.[19] It undoubtedly contributed to the erroneous identification of VIIb as possessing a tertiary (8α-) hydroxyl group.

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1. This investigation was supported by Public Health Service Research Grant CA 07445, General Research Support Grant 1-SO1-FR-05367 and by research career program award 5-K6-AM-21846 from the National Institute of Arthritis and Metabolic Diseases.

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8. Rotations in chloroform at 25-30° (c, 0.5-1.0). Correct analytical figures were obtained for all products. Analyses by J. Alicino, Metuchen, N. J.

9. The 32-methyl group in II is deshielded to the extent of 0.24 p.p.m. as compared to saturated lanostane derivatives. For comparison substance cf. A. I. Cohen, D. Rosenthal, G. W. Krakower and J. Fried, Tetrahedron, 21 (1965) in press. For data on other steroid epoxides see K. Tori, T. Komeno and T. Nakagawa, J. Org. Chem., 29, 1136 (1964).

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11. Taken on Varian A-60 instrument in $CDCl_3$. m = multiplet, d = doublet.

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15. These results were obtained with an F and M gas chromatograph Model 400 equipped with a 4 ft. glass column containing 3.8% SE-30 on 80/100 mesh Diatoports at a column temperature of 250° using helium as carrier gas at a flow rate of 100 m./min. Samples IV and V were run in sequence.

16. Cf. the use of this reagent for the conversion of sapogenins to pseudosapogenins (W. G. Dauben and G. Fonken, J. Am. Chem. Soc., 76, 4618 (1954) and M. E. Wall, H. E. Kenney and E. S. Rothman, J. Am. Chem. Soc., 77, 5665 (1955)). Reaction with p-toluensulfonic acid at room temperature (cf. K. Heusler, J. Kalvoda, Ch. Meystre, G. Anner and A. Wettstein, Helv. Chim. Acta, 44, 2161 (1962 and references 13c, d) gave a complex mixture which contained V, as ascertained by g.l.c.

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