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TRANSFORMATIONS OF EBURICOIC ACID VI. 9α-HYDROXYLANOSTANE AND EBURICANE DERIVATIVES AND THEIR PHOTOLYTIC FRAGMENTATION TO 9,10-SECO STEROIDS(1)

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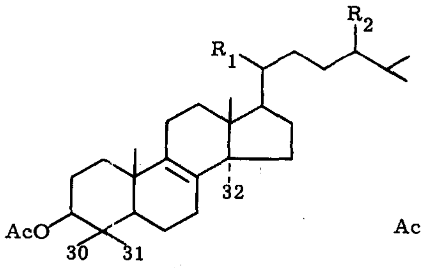
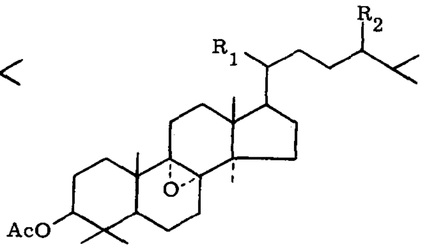
The intramolecular, photochemically initiated hydrogen abstraction reaction (Barton reaction)(2) has been widely employed in the functionalization of unactivated steroid methyl, methylene and methine groups.(3,4) We have been interested in the functionalization of the 32-methyl group of tetracyclic triterpenes of the lanostane type because of the importance that has been ascribed to such 32-oxygenated intermediates in the biogenesis of cholesterol.(5) Both the 7α- and 9α-hydroxyl groups with O-C-32 distances of 2.5 to 2.6 Å, are properly positioned for reaction to occur. We wish to report our results with 9α-hydroxy lanostane and eburicane derivatives.

Whereas "conventional" 9α-hydroxysteroids are available by a variety of procedures no such derivatives are known among the tetracyclic triterpenes. Methyl acetyl dihydroeburicoate (I)(6) on oxidation with m-chloroperbenzoic acid in chloroform afforded in 95% yield the 8α, 9α-oxide (II), m.p. 204-206°, $[\alpha]_D^{25}$ +17°(7) which was completely stable when recrystallized from methanol





I $R_1 = COOCH_3$, $R_2 = CH_3$

Ia $R_1 = CH_3$, R_2 = Ac = H

Ib $R_1 = CH_3$, R_2 = H

Ic $R_1 = CH_2OH$, $R_2 = CH_3$, Ac = H

Id $R_1 = CH_2OAc$, $R_2 = CH_3$

II $R_1 = COOCH_3$, $R_2 = CH_3$

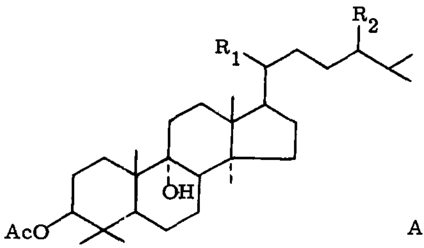
IIa $R_1 = CH_3$, R_2 = Ac = H

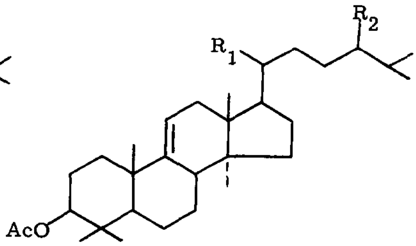
IIb $R_1 = CH_3$, R_2 = H

IIc $R_1 = CH_3$, R_2 = H, 7α,8α-epoxide

IId $R_1 = CH_2OH$, $R_2 = CH_3$, Ac = H

IIe $R_1 = CH_2OAc$, $R_2 = CH_3$





III $R_1 = CH_2OH$, $R_2 = CH_3$, Ac = H

IIIa $R_1 = CH_2OAc$, $R_2 = CH_3$

IIIb $R_1 = CH_3$, R_2 = Ac = H

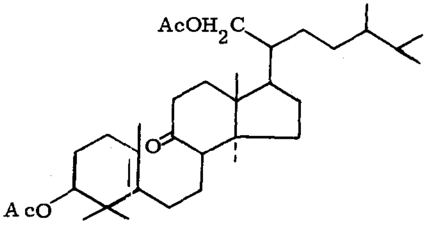
IIIc $R_1 = CH_3$, R_2 = H

IVa $R_1 = CH_2OAc$, $R_2 = CH_3$

IVb $R_1 = CH_3$, R_2 = H

IVc $R_1 = CO_2CH_3$, $R_2 = CH_3$

IVd $R_1 = CH_2OH$, $R_2 = CH_3$, Ac = H



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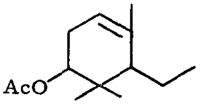

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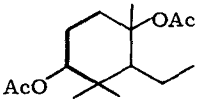

VII

containing a few drops of pyridine.(8) Under the same conditions dihydrolanosterol (Ia) furnished the 8α, 9α-epoxide (IIa) m.p. 158-162°, $[\alpha]_D^{25}$ +7°; (Acetate (IIb), m.p. 140-141°, $[\alpha]_D^{25}$ +15°), and Δ^7-lanostenyl acetate(9) the 7α, 8α-epoxide (IIc) m.p. 156-157°, $[\alpha]_D^{25}$ +37°, in equally high yields. This simple procedure makes these important epoxides available for the first time in pure form. While stable in basic media all the above epoxides are rapidly transformed into the 7,9(11)-dienes by 0.001 M acid. Reduction of II with $LiAlH_4$ in boiling THF or diglyme (100°) gave IId in 85% yield without opening the oxide ring, m.p. 197-198.5°; $[\alpha]_D^{25}$ +12° (diacetate (IIe), m.p. 137-138.5°). Reductive opening of the 8,9-epoxide ring in IId and IIa was achieved by a modification of the procedure of Hallsworth and Henbest(10) using lithium and ethylamine in the presence of t. butanol, to yield the 9α-ols III, m.p. 187-188.5°; $[\alpha]_D^{25}$ +14.5° (diacetate (IIIa), m.p. 141-143°; $[\alpha]_D^{25}$ +18°) and IIIb, m.p. 135-136°, $[\alpha]_D^{25}$ +2.5°(monoacetate IIIc, m.p. 163-164°, $[\alpha]_D^{25}$ +7°) in 50-60% yield, accompanied by the 8,9-dehydro compounds Ic and Ia, respectively.(11) Treatment of IIIa and IIIc with $SOCl_2$ in pyridine gave exclusively (80%) the $\Delta^{9(11)}$-unsaturated substances IVa, m.p. 136.5-138°; $[\alpha]_D^{25}$ +70°, and dihydroparkeol acetate (IVb), m.p. 162-165°; $[\alpha]_D^{25}$ +85°,(12) the latter identified by comparison with a sample kindly provided by Dr. Lawrie. IVa was found to be identical with a sample prepared by reduction of methyl 3β-acetoxy-11-ketoeburicane-21-oate(13) with $LiBH_4$ to the 11β-ol, m.p. 203-204°; $[\alpha]_D^{25}$ +55°,(14) and dehydration to IVc with mesyl chloride in DMF-pyridine, m.p. 153-154°; $[\alpha]_D$ +62°, followed by $LiAlH_4$-reduction to the diol IVd, m.p. 211-212°; $[\alpha]_D^{25}$ +64°, and acetylation to IVa, m.p. 134-135°. The sequence

I$\rightarrow$IV accomplishes the transposition of the 8,9-double bond into the 9(11)-position in better than 50% yield, as compared to ca. 15% by the best previous procedure.(12)

When IIIa was subjected to a I_2-$Pb(OAc)_4$ reaction in cyclohexane benzene for 15 min.(15,16) the sole crystallizable substance was the fragmentation product V (20% yield), m.p. 136-137°; $[\alpha]_D^{25}$ +26°; o.r.d. in MeOH: $[\alpha]_{305}$ +673°, $[\alpha]_{270}$ -148°, similar to that of 4α-methylcholestanone;(17) λ_{max}^{KBr} 5.77μ (CH_3COO) and 5.85μ (9-keto); positive tetranitromethane test; p.m.r.: no vinyl protons, 5.27τ (3α-H), 5.92τ (21-CH_2), 7.95τ (CH_3CO), 8.31τ (19-CH_3), 8.95 and 9.02τ (30,31-CH_3), 8.82τ (18-CH_3) and 9.24τ (32-CH_3). Careful T.L.C. on alumina gave non-polar non-crystalline fractions showing I.R. bands at 5.87μ and p.m.r. signals very similar to those of V but possessing vinyl resonance at 4.78τ and methyl signals at 8.21τ (19-CH_3) instead of 8.31τ, and at 8.72τ, compatible with structures VI and VII, respectively.(18) Photolysis of the 9α-nitrite ester of IIIa, m.p. 105-110°; $[\alpha]_D^{25}$ +63° λ_{max}^{KBr} 5.78, 8.03μ (Acetyl), 6.21, 6.24, 12.27, 12.50, 12.88μ (ONO); $\lambda_{max}^{CHCl_3}$ 338.5 mμ (ϵ = 44), 350.5 (49.5), 363 (58), 377 (61) and 391 (44),(in CCl_4 using an ultraviolet black lamp(20) gave after T.L.C., crystalline V, as well as fractions showing evidence from I.R. and p.m.r. spectra for the presence of VI and VII. Neither the "hypoiodite" nor the nitrite photolysis reaction showed evidence for products resulting from a Barton reaction, in spite of careful fractionation and spectral analysis.

Although fragmentation reactions may occur under the above conditions,(3,4) the dominance if not exclusivity of such a course is unusual in a case involving a 1,3-diaxial relationship between the hydroxyl and methyl groups. It must be ascribed to the stability of the tertiary radical at C_{10} and the relief of the 1,3-diaxial interaction between the 4β- and 19-methyl groups resulting from fission of the 9,10-bond.$^{(21)}$

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(5) Cf. J. H. Richards and J. B. Hendrickson, The Biosynthesis of Steroids, Terpenes and Acetogenins, p. 312, W. A. Benjamin, Inc., New York 1964.

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(7) Rotations in chloroform. Correct analytical figures were obtained for all crystalline products. Analyses by J. Alicino, Metuchen, N. J.

(8) Numerous publications dealing with the perbenzoic acid oxidation of 8,9- and 7,8-unsaturated tetracyclic triterpenes of the lanostane and euphane series describe the formation of 7,9(11)-dienes contaminated with what were considered to be "unstable oxide intermediates". Pertinent papers are those of Lahey and Strasser (ref. 6), and M. J. Birchenough and J. F. McGhie, J. Chem. Soc., 2038 (1949), who isolated mixtures of 8,9-epoxides and 7,9(11)-dienes from I and Ib, respectively, and of J. F. Cavalla, J. F. McGhie and M. K. Pradhan, J. Chem. Soc., 3142 (1951) and D. H. R. Barton, J. S. Fawcett and B. R. Thomas, ibid. 3147 (1951), who encountered complex mixtures devoid of the 7,8-epoxide in the perbenzoic acid oxidation of Δ^7-lanostenyl acetate. The simple expedient described here eliminates all the above difficulties.

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(11) Separation was readily achieved in both the lanostane and eburicane series by first allowing the 8,9-dehydro compounds to crystallize from methanol, acetylating the mother liquors and recovering the pure acetates IIIa and IIIc, respectively. Ic and Ia, which contained some of the 9α-ols could be rè-epoxidized and re-reduced to bring the total yields of 8,9-epoxides to 70%.

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(16) Irradiation was effected with a 300 watt bulb. Longer reaction times reduced the yield of V. Lead tetraacetate alone effected little change of IIIa over an 18 hr. period. Silver acetate-iodine afforded V in 5% yield.

(17) C. Djerassi, O. Halpern, V. Halpern and B. Riniker, J. Am. Chem. Soc., 80, 4001 (1958).

(18) Similar results were obtained when lanostane-3β,9α-diol 3-acetate (IIIc) was subjected to the "hypoiodite" reaction. Although the fragmentation products corresponding to V, VI and VII could not be obtained in crystalline form, I.R. and p.m.r. spectra of chromatographically purified fractions indicated their presence.

(19) Prepared by the standard procedure (cf. D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, J. Am. Chem. Soc., 83, 4076 (1961)), this nitrite ester rapidly reverted to the 9α-ol when treated with methanol or on standing in air.

(20) Model 1910 purchased from the Burton Medi-Quip Co., Van Nuys, Calif. When the reaction was performed in benzene with a Hanovia 250 W-lamp using a Pyrex sleeve, V could not be obtained in crystalline form. Instead, chromatographic fractions of blue-green color ($\lambda_{max}^{benzene}$ 682 mμ) and possessing $E_{1/2}$-.89 volts in the polarograph characteristic of tertiary nitroso compounds could be isolated. There was no evidence for nitroso-dimers or oximes in any of the fractions.

(21) M. Stefanović, M. Gašić, Lj. Lorenc and M. Lj. Mihailović, Tetrahedron 20, 2289 (1964) found that the lead tetraacetate reaction of 1α- and 1β-hydroxycholestanes led exclusively to ring A fission (without attack at C_{11}).