

REARRANGEMENTS OF 32-OXYGENATED LANOSTANES¹

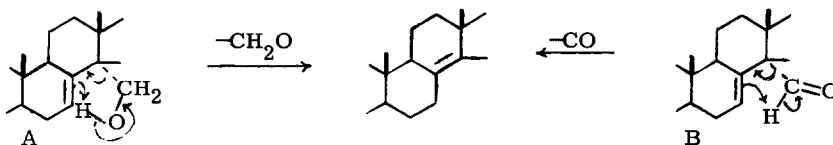
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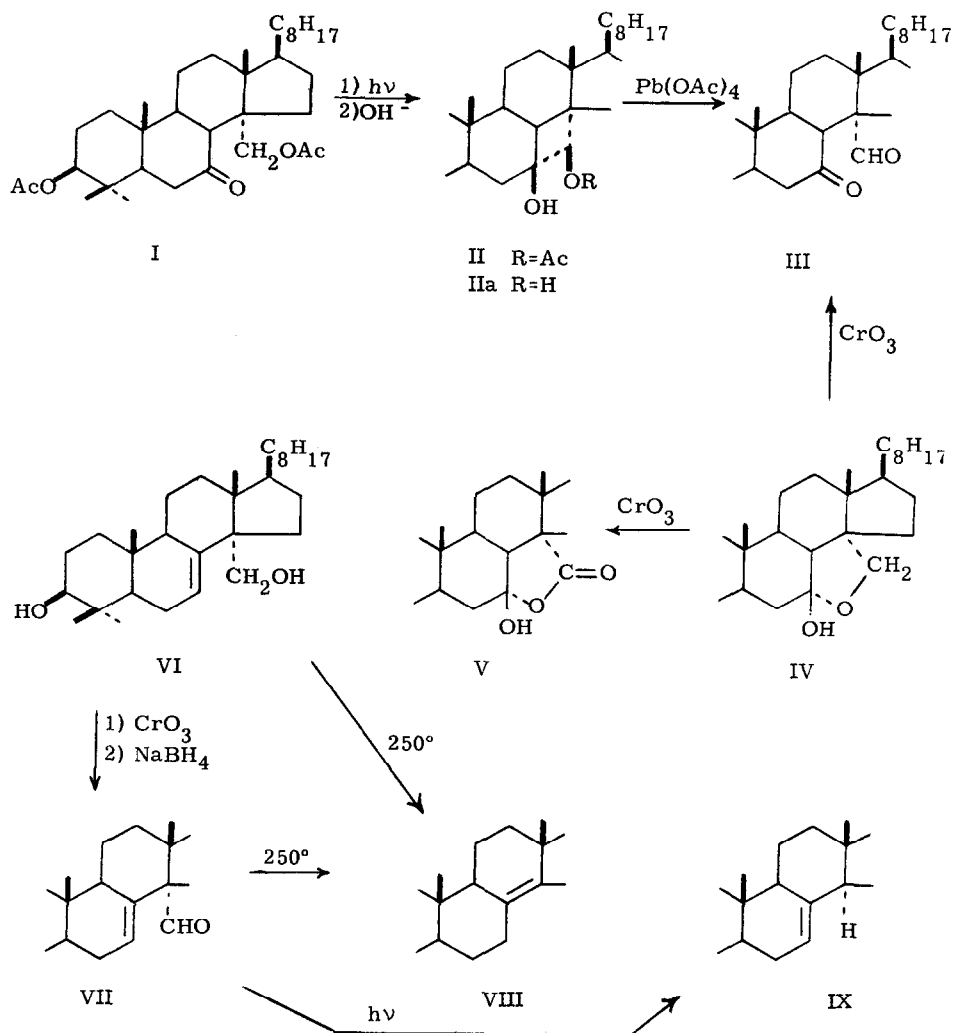
Lanosterol derivatives bearing oxygen on carbon atom 32 have been reported from this^{2,3,4} and other laboratories.^{5,6,7,8} We now wish to describe additional transformations of previously reported compounds with particular emphasis on their conversion into 4,4-dimethylcholestene derivatives.

Δ^7 -Lanostene-3 β ,32-diol (VI)⁴ on pyrolysis in a stream of He for 30 min. at 250-255° furnished in quantitative yield 4,4-dimethyl- $\Delta^{8(14)}$ -cholestene-3 β -ol (VIIIa), m. p. 138-41°; $[\alpha]_D^{34} +14^\circ$;⁹ acetate, m. p. 112-13.5°; $[\alpha]_D^{34} +27.5^\circ$; reported:¹⁰ m. p. 142-43°; $[\alpha]_D +15^\circ$; acetate, m. p. 115-16°; $[\alpha]_D +28^\circ$, identified by i. r. and g. l. c. comparison with an authentic sample.¹¹ The cyclic 6-membered transition state A is sufficiently favored energetically to result in facile Cope rearrangement.^{12,13}



Jones oxidation of VI at -15° ¹⁴ afforded the 3-keto-32-aldehyde VIIb,¹⁵ m. p. 130-30.5°; $[\alpha]_D^{30} +2.3^\circ$; $\lambda_{\max}^{\text{KBr}} 5.82-5.88\mu$; n. m. r., s. 577 cps (CHO), m. 330 cps ($\text{C}=\text{CH}$), which on partial reduction with NaBH_4 in 70% aqueous dioxane at 22° for 40 min. gave the 3 β -ol VIIa, m. p. 131-133°; $[\alpha]_D^{37} +25^\circ$; $\lambda_{\max}^{\text{KBr}} 3.00, 5.85\mu$; n. m. r., s. 577 cps (CHO), m. 327 cps ($\text{C}=\text{CH}$); acetate VII, m. p. 142-44°; $[\alpha]_D^{31} +32^\circ$; reported:⁵ m. p. 144-45°; $[\alpha]_D +24^\circ$.

The aldehydes VII, VIIa and VIIb were decarbonylated by 3 different procedures. Pyrolysis of VIIb at 250° for 75 min. gave the $\Delta^{8(14)}$ -3-ketone VIIIb, m. p. 98-99°; $[\alpha]_D^{32} -5^\circ$;

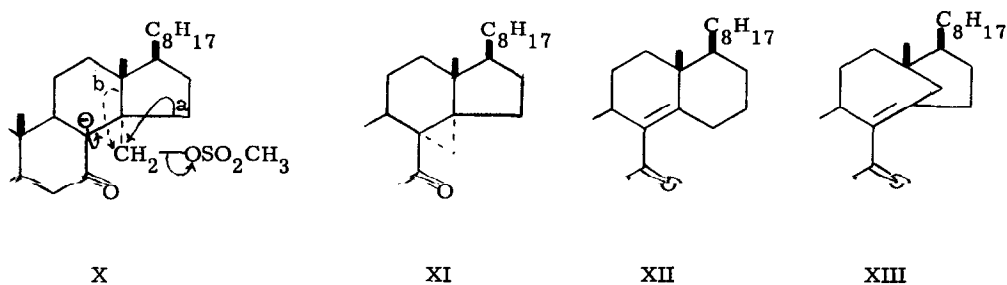


All compounds have 3β -acetoxy substituent except when designated a= 3β -hydroxy or b= 3 -keto.

$\lambda_{\text{max}}^{\text{KBr}}$ 5.88 μ , probably via a cyclic transition state B, also prepared by Jones oxidation of VIIIa. Photolytic decarbonylation,^{14,16} of VIIa for 10 min. furnished IXa, m.p. 142-43°, ¹⁷ acetate IX, m.p. 132-36°; ¹⁷ reported, ¹⁰ m.p. 143-46.5° and 134-36°, respectively, identified by g.l.c. comparison with an authentic specimen. ¹¹ G.l.c. analysis of the crude irradiation product revealed the presence of 5% of the $\Delta^{8(14)}$ -isomer VIIIa, in line with observations by Jeger et al. ¹⁴ in the case of the decarbonylation of 19-formyl- Δ^5 -steroids, to which this reaction is mechanistically analogous. ¹⁸ It should be noted that in a formal sense the photo decarbonylation resembles the biochemical 32-demethylation in that both reactions proceed without double bond shift. ¹⁰ Recent interest has focused on the use of certain transition metal complexes for hydrogenation and decarbonylation reactions. ^{19,20} Refluxing a benzene solution of VII with chloro-tris-(triphenylphosphin)-rhodium for several hours ²¹ furnished after t.l.c. in small yield a 50:50 mixture of VIII and IX as shown by g.l.c.

Application of the 7,32-photocyclization reaction ⁴ to the 7-keto diacetate I afforded in a facile reaction (35 min.) ¹⁴ 40% of the cyclobutanediol derivative II, m.p. 215-17°; $[\alpha]_{\text{D}}^{30}$ +24°; $\lambda_{\text{max}}^{\text{KBr}}$ 2.91, 5.80, 5.85 μ ; n.m.r., s. 341 cps (32- CHOAc), s. 122.5 and 126 cps (3- and 32- CH_3CO), which on hydrolysis furnished the triol IIa, m.p. 202-205°; $[\alpha]_{\text{D}}^{34}$ +13°; $\nu_{\text{max}}^{\text{CCl}_4}$ 3630 and 3570 cm^{-1} ; n.m.r., s. 279 cps (32- CHOH), formulated as the 7 β ,32 β -*cis*-diol because of intramolecular hydrogen bonding indicated by the i.r. band at 3570 cm^{-1} . ²² As a *cis*-glycol, IIa was quantitatively cleaved in 10 min. by lead tetraacetate in acetic acid to form the keto aldehyde IIIa, m.p. 201-203°; $[\alpha]_{\text{D}}^{27}$ -38°; $\lambda_{\text{max}}^{\text{KBr}}$ 3.00, 5.87, sh. 5.93 μ ; n.m.r., s. 592 cps (32- CHO), which was also prepared from the hemiketal IV ⁴ by oxidation with excess Jones reagent to form in 25% yield 3 β -acetoxy-lanostane-7-one-32-al (III), m.p. 216-18°; $[\alpha]_{\text{D}}^{33}$ -27°; $\lambda_{\text{max}}^{\text{KBr}}$ 5.80-5.85 μ ; n.m.r., s. 592 cps (32- CHO), followed by hydrolysis of the latter to the 3 β -ol. Further oxidation of III with Jones reagent furnished the lactol V, m.p. 260-63°; $\lambda_{\text{max}}^{\text{KBr}}$ 2.90, 5.65, 5.79 μ . Attempted selective acetalization of the 32-formyl group of III with ethylene glycol resulted instead in the 7-ethylene ketal-32-aldehyde, m.p. 152-154°; $[\alpha]_{\text{D}}^{34}$ -38°; $\lambda_{\text{max}}^{\text{KBr}}$ 5.79, 5.88; n.m.r., s. 607 cps (32- CHO), m. 232 cps ($(\text{CH}_2)_2$).

The cyclopropane derivative XI appeared of interest because of the possible occurrence of this ring system among natural products. The hemiketal IV was converted into the amorphous 7-keto-32-mesylate X with pyridine and methanesulfonyl chloride at 50°, $\lambda_{\text{max}}^{\text{KBr}} 23$ 5.79, 5.85 (sh.), 7.40, 8.51 μ ; n. m. r., s. 181.5 cps (CH_3SO_2), quart. 249 and 271 cps ($J=10$) ($32-\text{CH}_2\text{O}$). Treatment of X with methylsulfinyl carbanion²⁴ in DMSO at 25°, followed by reacetylation, furnished in 55% yield the cyclopropyl ketone XI,²⁵ m. p. 192-94°;



$[\alpha]_{\text{D}}^{37} -20^\circ$; $\lambda_{\text{max}}^{\text{KBr}} 5.77, 6.00\mu$; $\lambda_{\text{max}}^{\text{alc}} 216\mu$ ($\epsilon 5,500$); M^+ peak at $\underline{m/e} 484$. When the reaction was performed instead in boiling methanolic sodium methoxide there was formed a 1:1 mixture of XI (3-ol), isolated as the acetate, and an α,β -unsaturated ketone, m. p. 167.5-8.5°; $[\alpha]_{\text{D}}^{37} +173^\circ$; $\lambda_{\text{max}}^{\text{alc}} 263\mu$ ($\epsilon 8,500$); $\lambda_{\text{max}}^{\text{KBr}} 3.00, 5.97, 6.20\mu$; n. m. r., no vinyl protons; M^+ peak at $\underline{m/e} 442$. The above spectral²⁶ and analytical data are compatible with structures XII or XIII, which are readily accounted for on mechanistic grounds as well. Rearrangement by path a (structure X) would yield XII, while path b would give rise to XIII. Additional information is required to decide between these alternative structures. The intervention of rearrangement in competition to cyclopropane formation, which is the exclusive reaction in DMSO, may be ascribed to shielding of the enolate anion by methanol (but not by DMSO), thereby favoring rearrangement over internal alkylation.

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9. All rotations in CHCl_3 . N.m.r. spectra in CDCl_3 on a Varian A-60 instrument. G.l.c. analyses were performed on an F and M model 400 instrument using a 3.8% SE 30 on Diatoport S column at a He flow of 100 ml/min, at 250-280°.
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11. We wish to thank Professor K. Bloch of Harvard University for kindly supplying these samples.
12. 62% of the theoretical amount of formaldehyde was isolated as the dimedon derivative.
13. A similarly facile reaction has been observed by J. J. Dugan and P. de Mayo, Can. J. Chem., 43, 2033 (1965) in the conversion of the dimethyl ester of presenegenin to dimethyl polygalate. On the other hand, Δ^5 -androstene-3 β ,19-diol-17-one was converted only to the extent of 25% to $\Delta^{5(10)}$ -19-norandrostene-3 β -ol-17-one in one hour. We wish to thank Dr. J. H. Fried of the Syntex Laboratories for these two compounds.
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15. All new compounds gave correct elemental analyses. Analyses by J. Alicino, Metuchen, New Jersey.
16. Irradiation was effected at 25° with a 200 W Hanovia quartz high pressure mercury lamp without filter in ethanol.
17. Taken on Kofler block. All other m.p.'s in capillaries.
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23. This procedure produced a mixture of the mesylate X and the isomeric cyclic mesylate. Hydrolysis with aqueous dioxane at 25° regenerated IV from the latter leaving X unchanged. The very difficultly soluble IV was removed from the mixture by crystallization. Yield of X, 70%.
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25. The two protons attached to the cyclopropane ring at C-32 are sufficiently deshielded due to the proximity of 7-keto group to be hidden under the methyl peaks, thereby precluding n.m.r. evidence for such a structure. Reduction of the keto group with NaBH₄ in aqueous dioxane for 48 hours at 25° gave a mixture from which the 7β-alcohol could be isolated in small yield. Its n.m.r. spectrum clearly shows the cyclopropyl protons at 23 and 36 cps (J=3,5); 7αH, m. centered at 213 cps.
26. Δ⁸⁽¹⁴⁾-7-ketones absorb at 260-263mμ (ε, 8,000-10,000). Cf. L. Dorfman, Chem. Reviews, 53, 117 (1953).