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THE REARRANGEMENT OF 12α-METHANESULFONYLOXYCHOLANE

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A 12α-mesyloxy derivative of 12-epi-rockogenin has low reactivity under conditions which produce ready elimination with its 12β-epimer (1,2). In contrast, 12α-mesylates in the bile acid group undergo facile dehydromesylation (3). When the latter mesylates are refluxed in collidine solution, elimination takes place to give high yields of sulfur-free mixtures consisting of crystalline Δ^{11}-derivatives and uncrystallized oils[a], the latter being the major products.

Preliminary studies suggested that these oils were rearrangement products resulting from a shift of the C-18 angular methyl group. Investigation of this rearrangement has been carried out employing the simpler 12α-cholanol mesylate[b] (I), in order to avoid complications involving the 24-acid (or ester) function.

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[a] In reference 3, only the example of methyl 3β-chloro-12α-mesyloxycholanate was reported. Other compounds behaving similarly are methyl 12α-mesyloxycholanate, methyl 12α-mesyloxy-3-cholenate, and methyl desoxycholate dimesylate. J. von Euw and T. Reichstein [Helv. Chim. Acta, 29, 654 (1946)], in a comprehensive paper dealing with the preparation of Δ^{11}-steroids from tosylate esters, reported several cases in which oil of undetermined structure was found in the products. Ch. R. Engel, K. F. Jennings and G. Just [J. Am. Chem. Soc., 78, 6153 (1956)] have recorded other cases. We are not aware of any further investigation of these oils.

[b] In reference 3, footnote 16, the specific rotation is given erroneously; it should read +64.7° (chf).

Collidine reflux of I gives, after processing, a clean colorless oil (93% yield, as olefin) which, on standing in i-propyl ether (or petroleum ether), affords crystalline 11-cholene (4), 22%, that can be separated free of residual oil. 11-Cholene, $(\alpha)_D$ +36.6°, shows a moderately strong absorption band at 724 cm.$^{-1}$ characteristic of cis olefins. The chromatographically homogeneous oil, $(\alpha)_D$ +1.6°(chf), is isomeric[c] with 11-cholene and gives a strong positive tetranitromethane test, but shows no identifiable infrared double-bond absorption, indicating that it is tetra-substituted. Its NMR spectrum, reproduced in Figure 1 with that of 11-cholene for comparison, supports this conclusion, and further, indicates that it has a rearranged nucleus.

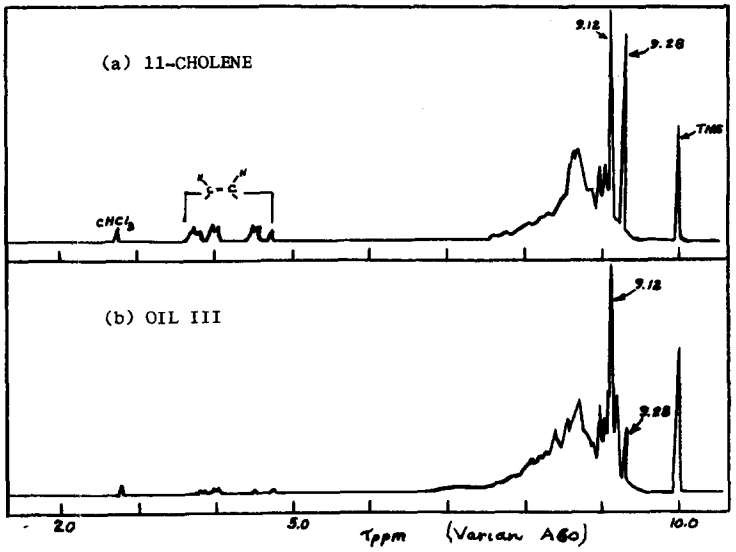
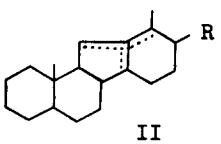


FIG. 1. NMR SPECTRA OF (a) 11-CHOLENE AND (b) OIL III

[c] Anal. calculated for $C_{24}H_{40}$: C, 87.73; H, 12.27. Found: C, 87.63; H, 12.26.

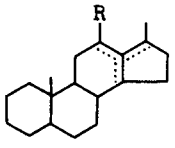
The 11-cholene spectrum (a) has the expected two sharp singlets at 9.28 and 9.12 τ characteristic of steroids with 18- and 19-angular methyl groups, and a multiplet (3.8 to 4.7 τ) assigned to the cis 11- and 12-vinyl protons (5). The spectrum of the oil (b) shows a much diminished line at 9.28 τ, barely perceptible absorption at the exact positions of the olefin lines of 11-cholene, and a group of signals in the region of 9.12 τ. The weak 9.28 τ line and the still weaker group centered near 4.3 τ can be attributed to traces of 11-cholene remaining in the oil, and the multiplet near the C-19 methyl absorption probably arises from mixed olefinic material having a shifted methyl group[d].

Although more deep-seated rearrangements are known, the skeletal structures resulting from a single Wagner type carbon to carbon shift represented by II and III seem to be the most reasonable ones. In fact, the products of the rearrangement of the 12β-mesylate derivatives of rockogenin are C-nor-D-homo compounds of the II type (1), recently confirmed by the work of Mitsuhashi and Shimizu (7). In these 12β-mesylate structures, the mesyloxy group is coplanar with the shifting



II

R=—CHCH$_2$CH$_2$CH$_3$
|
CH$_3$



III

[d] A double bond in the vicinity of C-13 would be expected to affect the chemical shift of the protons of a methyl at C-12, and probably also of the 19-methyl protons. [J. N. Shoolery and M. T. Rogers, J. Am. Chem. Soc. 80, 5121 (1958); G. Slomp and F. A. MacKellar, ibid., 84, 204 (1962)].

13-14 bond. However, in the epimeric compounds, the leaving mesyloxy group is trans-antiparallel to the 18-angular methyl group, and the arguments advanced by Hirschmann et al (1) to support their choice of the II type structure for the 12β-mesylates rearrangement products apply with equal force to favor structure III for products from 12α-mesylates.

Further evidence that the oil is indeed a mixture comes from chemical work. Efforts to separate the mixture were unavailing[e], but osmium tetroxide hydroxylation yielded several (at least six) crystalline diols, two of which were isolated and characterized. The first, present in minor concentration, was 11α,12α-dihydroxycholane[f] (IV), identical with a product prepared from 11-cholene, corroborating the NMR indications that the oil contained traces of 11-cholene. The second, Compound V[g], the predominant diol in the mixture, is isomeric with IV, and does not form an acetate under mild acetylation conditions. On oxidation with lead tetra acetate, it yields a dicarbonyl product with IR absorption bands at 1709 and 1736 $cm.^{-1}$, corresponding to absorptions of an aliphatic carbonyl group and a cyclopentanone, respectively (8).

An NMR spectrum of V, Figure 2, shows no line near 9.28 τ

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[e] Equilibration studies on this mixture are in progress.

[f] m.p., 111-112°; $[\alpha]_D$ +7.2°(chf). Compound IV was assigned the cis-α-configuration by analogy with the known methyl 11α,12α-dihydroxycholanate [H. B. Alther and T. Reichstein, Helv. Chim. Acta 25, 805 (1942)]; the latter compound and IV have nearly identical IR spectra in the 900 to 1100 $cm.^{-1}$ region, both having maxima at 955, 1031, and 1096 $cm.^{-1}$.
New compounds reported in this paper gave correct elemental analyses.

[g] m.p., 161-162°; $[\alpha]_D$ +41.1°(chf), $\lambda_{max}^{CS_2}$ 3330(s); 923, 943, 980, 1015, 1066, 1107, 1176 $cm.^{-1}$.

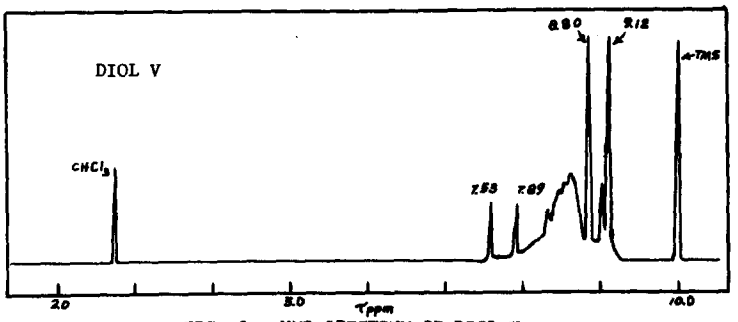

FIG. 2. NMR SPECTRUM OF DIOL V.

(18-methyl protons), but has the 19-methyl signal at 9.12 τ and a new singlet at 8.80 τ, assigned to the protons of the shifted methyl now at C-12[h]. The lines at 7.53 and 7.89 τ are evidently from the two hydroxyl protons, as the lines disappear when the sample is shaken with deuterium oxide. Structure V, derived from olefin III (Δ^{12}), is consistent with the physical and chemical evidence presented above.[i]

Only tentative assignment of stereochemistry at C-12 and C-13 is justified on present evidence. Assuming no other shifts of skeletal hydrogens, the requirements of a cis relationship of the hydroxyl groups and the chair conformation for ring C offer only two stereochemical alternatives, VII and VIII.

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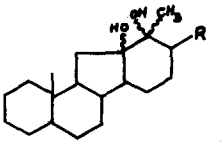
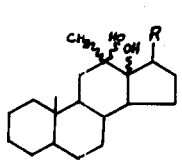
[h] A methyl group attached to the same carbon atom as a hydroxyl group would have a shift in this region (reference 6, p.53; N. S. Bhacca, L. F. Johnson and J. N. Shoolery, "NMR Spectra Catalog", Varian Associates, Palo Alto, California, 1962).

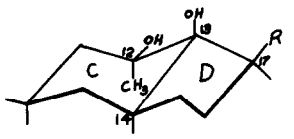
[i] The alternative structure VI derived from II would also satisfy the present experimental evidence. 12β-mesyloxycholane, which would by analogy (1) be more likely to yield this structure, does undergo extremely facile rearrangement, and diols have been obtained similarly from the olefinic product. However, preliminary comparisons by thin-layer chromatography show that these diols are all different from diol V.



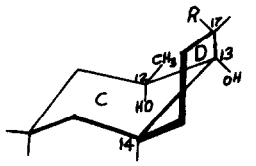
VI



V



VII



VIII

Our tentative preference is structure VII for the diol V[j].

12-Epi-rockogenin 3-methylsuccinate-12(α)-mesylate (1), survives reflux in collidine unchanged[k]. A satisfactory explanation of the difference in reactivity between 12α-derivatives of spirostanes and of cholanes in the collidine reaction hinges on elucidation of the mechanism(s) of the dehydromesylation reaction, but the problem is probably related to some seemingly anomalous chemistry of 12-substituted steroids; some aspects of which are discussed controversially in two recent communications (11), and others of which encountered in this laboratory will be reported in the future.

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[j] VII would result from the attack of osmium tetroxide from the β-side, VIII from the α-side. A Dreiding model of the starting olefin (III,Δ^{12}) shows about the same accessibility to attack by the reagent from either side. The activation energies of the two transition states (from α or β attack) thus being approximately equal, the favored isomer would come from the more stable osmate ester formed. VII has the C/D trans configuration of the natural steroids which presumably is more stable than the cis form (9).

Since the correct configurational assignment of one of the three substituents at C-12 and C-13 will inferentially fix the others, we had hoped to achieve the assignment by comparisons with a known 12-methyl-12-hydroxy steroid. Dr. S. G. Levine (Research Triangle Institute) very kindly provided NMR spectra of the 12-methyl-12-hydroxy tigogenin acetate epimeric pair (10) and a sample of the 12β-hydroxy-12α-methyl compound; unfortunately, neither NMR nor IR comparisons yielded a satisfactory answer.

[k] Experiments performed by Mr. John Jacobus, National Science Foundation Undergraduate Research Program, 1962.

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