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ABNORMAL OPTICAL ROTATORY DISPERSION OF STEROIDAL TETRAHYDROFURANONES

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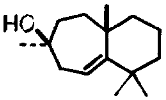
In the course of the structural study of widdrol I, a sesquiterpene alcohol from various conifers, we have prepared the keto-ether II having a unique tetrahydrofuran-3-one part-structure. Although the structures I and II were eventually established (1,2), the negative Cotton effect ($[\Phi]_{289}^{peak}$ +3200, $[\Phi]_{332}^{trough}$ -4400) (3,4) in the ORD curve of II seemed to deserve further investigation with respect to the applicability of current concepts of ORD to five-membered ring ketones (5). In the meantime, Johnson and his coworkers (6) have synthesized a steroidal compound III, with a very similar but mirror-image part-structure (Cf. II), from A-homocholest-4a-en-3-one and assigned the structure IIIa to it. The fact that the ORD curve of III also exhibited a negative Cotton effect ($[\Phi]_{285}^{peak}$ +4100, $[\Phi]_{333}^{trough}$ -2900) (7), prompted us to reinvestigate the stereochemistry of III by synthesizing pairs of diastereoisomers of similar structures. We now wish to present the result of our study which shows that the stereochemistry of compound III is in fact represented by the formula III and that the Cotton effect of the tetrahydrofuran-3-ones can not be interpreted in terms of a 'first order' effect in the cyclopentanone ring system (5).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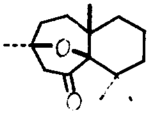
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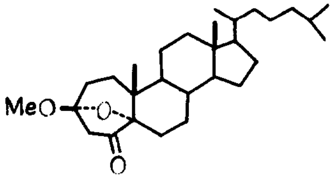
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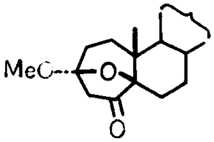
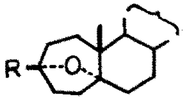
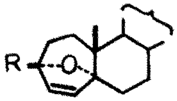
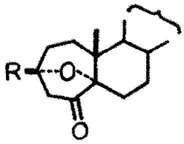
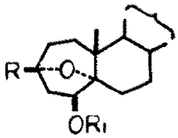
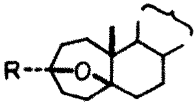
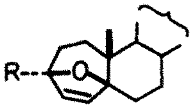
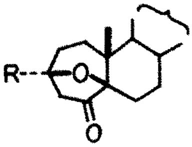
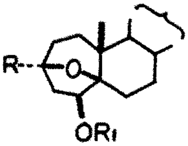
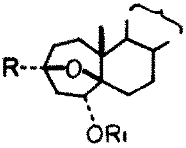
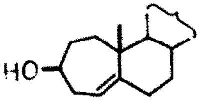

III

A-Homocholest-4a-en-3β-ol IV, m.p. 103-103.5° (8), and the corresponding 3α-ol V, m.p. 145-146°, were obtained by lithium aluminumhydride reduction of A-homocholest-4a-en-3-one VI (6) and chromatographic separation of the benzoates of the products (benzoate of IV, amorphous, benzoate of V, m.p. 134-135°) and subsequent lithium aluminumhydride

Partial formula	Compds	No.	δ_{19-Me}
	R=OH R=OMe	XIII XIV	0.81 0.80
	R=OH R=OMe	XI XII	0.73 0.73
	R=H R=OH R=OMe	X XXVI XXVII	0.85 0.85 0.84
	R=R_1=H R=H R_1=Ac R=OMe R_1=H	VIII IX XXVIII	1.09 1.00 1.10

Partial formula	Compds	No.	δ_{19-Me}
	R=OH R=OMe	XIX XX	1.06 1.06
	R=OH R=OMe	XVII XVIII	1.10 1.10
	R=H R=OH R=OMe	XXI XXIV III	1.11 1.10 1.09
	R=R_1=H R=OMe R_1=H R=OMe R_1=Ac	XXV XXXI XXXII	1.09 1.08 1.08
	R=R_1=H R=OMe R_1=H R=OMe R_1=Ac	XVI XXXIII XXXIV	1.10 1.08 1.11



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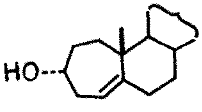

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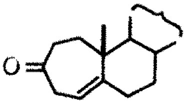

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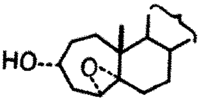

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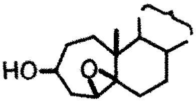

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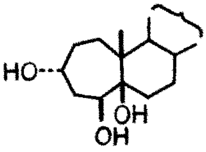
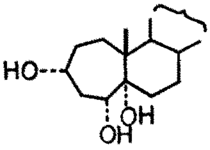
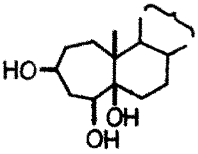


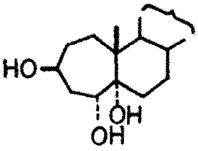
XXII



XXIII



XXIX



XXX

FIG. I

reduction to remove the benzoate grouping (9).

Perbenzoic acid oxidation of V yielded the corresponding 3α-hydroxy-4aα,5α-oxide VII, m.p. 149-154.5° (65% yield), and 4aβ-hydroxy-3α,5α-oxide VIII, m.p. 168-170° (15% yield), which gave amorphous acetate IX. Chromic acid oxidation of VIII gave 4a-keto-3α,5α-oxide X, m.p. 83-84°, ν 1748 cm^{-1}, $\delta_{4\alpha}$2.61, $\delta_{4\beta}$2.19, δ_{3}4.63 (ABX), $J_{4\alpha,4\beta}$18, $J_{3,4\alpha}$7, $J_{3,4\beta}$1 (10). On sodium borohydride reduction, X reverted back to VIII quantitatively. Chromic acid oxidation of VII, followed by alumina chromatography, afforded 3β-hydroxy-4-en-3α,5α-oxide XI, m.p. 164-166°, δ_{4}6.08, δ_{4a}5.92 ($J_{4,4a}$ 6cps), which, with methanolic hydrochloric acid, yielded the corresponding methyl ether XII, m.p. 132.5-134°, and, on hydrogenation (Pd-C), gave 3β-hydroxy-3α,5α-oxide XIII, m.p. 123-125°. With acid in methanol, XIII gave the corresponding methyl ether XIV, m.p. 102.5-103.5°.

Perbenzoic acid oxidation of IV proceeded similarly and gave the products with the inverted partial stereochemistry; the 3β-hydroxy-4aβ,5β-oxide XV, amorphous (33% yield), and 4aα-hydroxy-3β,5β-oxide XVI, m.p. 165.5° (35% yield). When the same reaction sequences as in the cases of VII and VIII were applied to XV and XVI, respectively, they afforded 3α-hydroxy-4-en-3β,5β-oxide XVII, m.p. 176-176.5°, δ_{4}6.36, δ_{4a}5.89 ($J_{4,4a}$ 6 cps), 3α-methoxy-4-en-3β,5β-oxide XVIII, m.p. 95.5-97°, 3α-hydroxy-3β,5β-oxide XIX, m.p. 177-178°, and 3α-methoxy-3β,5β-oxide XX, m.p. 83-83.5°, and 4a-keto-3β,5β-oxide XXI, m.p. 129-131.5°, ν 1741 cm^{-1}, $\delta_{4\beta}$2.65, $\delta_{4\alpha}$2.14, δ_{3}4.55, $J_{4\alpha,4\beta}$17.5, $J_{3,4\beta}$7, $J_{3,4\alpha}$1. XXI reverted back to XVI on sodium borohydride reduction.

In order to obtain the 4a-keto-3,5-oxides with the oxygen functions at 3- and 4a-position, osmium tetroxide oxidation of the epimeric alcohols IV and V was carried out. The products obtained from V were the epimeric glycols; 3α,4aβ,5β-triol XXII, m.p. 186-187°, and 3α,4aα,5α-triol XXIII, m.p. 183-184° (83% and 13% yield, respectively). Chromic acid oxidation of the former afforded the 3α-hydroxy-4a-keto-3β,5β-oxide XXIV, m.p. 179-180°, ν 1749 cm^{-1}, which on methylation furnished 3α-methoxy-4a-keto-3β,5β-oxide III obtained earlier by Johnson (6). Acid treatment of XXII gave the 4aβ-hydroxy-3β,5β-oxide XXV, m.p. 169-169.5°, chromic acid oxidation of which afforded XXI. Chromic acid oxidation of the triol XXIII gave 3β-hydroxy-4a-keto-3α,5α-oxide XXVI, m.p. 201.5-202.5°, ν 1747 cm^{-1}, methylation of which afforded 3β-methoxy-4a-keto-3α,5α-oxide XXVII, m.p. 126-127°, ν 1749 cm^{-1}, and sodium borohydride reduction of XXVII, in turn, afforded the corresponding 3β-methoxy-4aβ-hydroxy-3α,5α-oxide XXVIII, m.p. 200-202°. The products obtained by the osmium tetroxide oxidation of IV were the corresponding epimeric 1,2-glycols; 3β,4aβ,5β-triol XXIX, m.p. 196-197° (55% yield), and 3β,4aα,5α-triol XXX, m.p. 238-239° (13% yield). Chromic acid oxidation of triols XXIX and XXX afforded XXIV and XXVI, respectively.

The keto-oxide III, which was originally obtained from A-homocholest-4a-en-3-one VI through 4aβ-hydroxy-3α-methoxy-3β,5β-oxide XXXI (6), acetate XXXII, m.p. 109-110°, was reduced with sodium borohydride to give the epimeric alcohol, 4aα-hydroxy-3α-methoxy-3β,5β-oxide XXXIII, m.p. 174.5-176°, which gave amorphous acetate XXXIV. The hydroxy-oxide XXXI was also converted to XVIII via its xanthate, thus interrelating the products of perbenzoic acid oxidation and osmium tetroxide oxidation.

Many of these compounds form stereoisomeric pairs with regard to the configuration of the oxide bridge and/or hydroxyl group at the 4a-position as shown in Fig. I. The configuration of the oxide bridge in the two series of compounds was established from the chemical shifts of 19-methyl signal (listed in Fig. I): In the 3β,5β-oxide series, the methyl signals always appear at 1.05-1.11 ppm irrespective of the nature of the substituents in the five-membered ring, whereas in the 3α,5α-oxide series, the chemical shifts of the methyl signals are very dependent on the nature of the substituents present in the five-membered ring (11). These assignments are also in accord with modern concepts of the stereospecificity of the reaction sequences used (12).

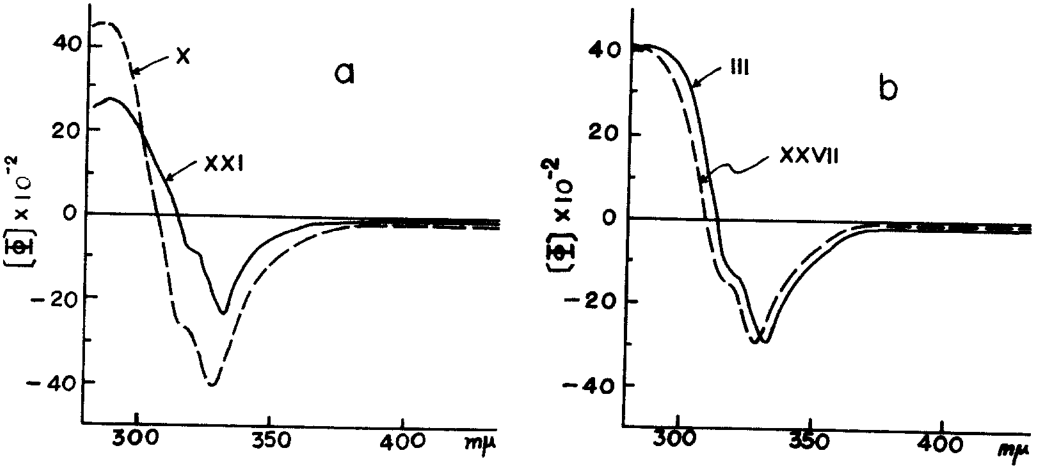


FIG. II. ORD curves of a) 4a-keto-A-homocholestan-3α,5α-oxide X and 4a-keto-A-homocholestan-3β,5β-oxide XXI and b) 3α-methoxy-4a-keto-A-homocholestan-3β,5β-oxide III and 3β-methoxy-4a-keto-A-homocholestan-3α,5α-oxide XXVII.

Molecular models of the two pairs of 3-oxacyclopentanones with diastereoisomeric part-structure, X and XXI, and XXVII and III, clearly show that their oxacyclopentanone rings are fixed in a twisted conformation, and on grounds of previous findings (5) this would result in the appearance of Cotton effects of opposite sign, *i.e.*, positive for X and XXVII and negative for XXI and III. However, *all the ORD curves of these 3-oxacyclopentanones exhibited unexpectedly negative Cotton effects* as shown in Fig. II, indicating that, in the case of twisted oxacyclopentanones, the sign of the Cotton effect is not solely governed by the ring chiralities. Although the reason for this abnormality is not as yet clear, the present result might serve as a warning against using the sign of Cotton effect to deduce the absolute configuration of an oxacyclopentanone.

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1) C. Enzell, *Acta Chem. Scand.*, **16**, 1553 (1962).

2) S. Itô, K. Endo and T. Nozoe, *Chem. Pharm. Bull. Japan*, **11**, 132 (1963). *Idem.*, *Tetrahedron Letters*, 3375 (1964).

3) Enzell reported the values as $[\Phi]_{292}^{peak}$ +3200, $[\Phi]_{323}^{trough}$ -4000 (1).

4) All ORD curves described in this paper were measured in methanol.

5) W. Klyne, *Tetrahedron*, **13**, 29 (1961).

6) W.S. Johnson, M. Neeman, S.P. Birkeland and N.A. Fedoruk, *J. Am. Chem. Soc.*, **84**, 989 (1962).

7) We thank Professor W.S. Johnson, Stanford University, for informing us in a personal communication that the ORD curve of this compound shows a negative Cotton effect (a -70).

8) Correct analytical figures were obtained for all compounds described.

9) Structures IV and V were assigned to these epimeric alcohols on the basis of the stereochemical requirements of the reactions described. The assignment is supported by the "benzoate sector rule" developed by Professor Nakanishi, Tohoku University, and his coworkers. Cf. N. Harada, K. Nakanishi and M. Ohashi, Abstracts of the papers at the 20th Annual Meeting of the Chemical Society of Japan, Vol. III, p. 636 (1967).

10) NMR spectra were measured in $CDCl_3$. Chemical shifts (δ) are expressed in ppm from internal TMS and coupling constants (J) in c/s.

11) Proximity effect of ethylenic linkage, carbonyl group, hydroxyl and acetoxyl groups is well known. Cf. N.S. Bhacca and D.H. Williams, *Application of NMR Spectroscopy in Organic Chemistry*, Holden-Day, San Francisco (1964).

12) Cf. E.L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York (1962).