

STEREOCHEMISTRY OF WIDDROL

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In the previous paper (1), we assigned the absolute configuration A for widdrol (2). However, after submitting our paper, we became aware of Enzell's publication (3) in which the different structure (Ia) is described for this alcohol. Additional work, described briefly in this letter, now leads us to acceptance of Enzell's structure, and at the same time brings to light some interesting reactions which occur during cleavage of the epoxides of widdrol and its ethyl ether.

One observation, on which our previous conclusion was based, is appearance of one of the methyl signals in abnormally low field in the NMR spectra of the bromoether IIa and the hydroxyether IIb, the sole product of the acid isomerization of the trans-epoxyalcohol IIIa. Recently we prepared the acetate IIc, liq., ν_{\max} 1742 cm^{-1} , the chloroether IID, m.p. 94°, and the ether IIe, b.p.₁ 55-70°, n_D^{15} 1.4913. In the NMR spectra of these compounds and that of the ketoether IIf (1) (see Table I), the four methyl groups show little variation in chemical shift from compound to compound, thus showing the absence of any appreciable steric effect (6) from the various substituents

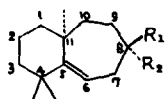
Table I. NMR Signals in various Widdrol Derivatives (5)

Compound	No.	Methyl Signals			
Ether	IIf	0.92	1.06	1.18	1.22
Hydroxyether	IIf	0.93	1.06	1.19	1.19
Acetoxyether	IIf	0.98	1.05	1.22	1.22
Ketoether	IIf	0.76	0.97	1.20	1.41
Bromoether	IIf	0.97	1.08	1.27	1.27
Chloroether	IIf	1.01	1.07	1.23	1.23

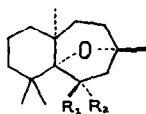
at C-6 in compounds IIf-f. This constancy of chemical shift for each methyl group could not be the case if widdrol had structure A.

The second point on which structure A was based, is the stereochemical requirement for the methyl migration which occurred during acid treatment of the cis-epoxide IVa and which always led to formation of the three diols, Va, VIa and VII. This reaction has now extended to widdrol ethyl ether Ib (1,7). Epoxidation of Ib afforded the cis-epoxy ethyl ether IVb, $[\alpha]_D +5.71(\text{CHCl}_3)$, in 6% yield, besides the trans-epoxy ethyl ether IIIb (1) in 90% yield. The structure of each compound was established by comparison of its IR and NMR spectra and $[\alpha]_D$ with those of the corresponding epoxyalcohols IIIa and IVa (1).

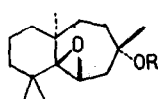
Acid treatment of IIIb afforded a complicated mixture from which were isolated two isomeric hydroxy ethyl ethers, VIII, m.p. 57.5°, δ : 3.72 (1H, broad singlet), 5.38 (1H, triplet, $J=3$), in 9% yield, and IX, liq., δ : 4.24 (1H, doublet, $J=8$), 5.37 (1H, broad singlet),



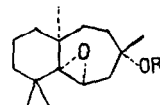
A: $R_1 = \text{OH}$, $R_2 = \text{Me}$
 Ia: $R_1 = \text{Me}$, $R_2 = \text{OH}$
 Ib: $R_1 = \text{Me}$, $R_2 = \text{OEt}$



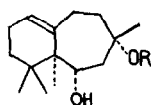
IIa: $R_1 = \text{Br}$, $R_2 = \text{H}$
 IIb: $R_1 = \text{OH}$, $R_2 = \text{H}$
 IIc: $R_1 = \text{OAc}$, $R_2 = \text{H}$
 IId: $R_1 = \text{Cl}$, $R_2 = \text{H}$
 IIe: $R_1 = R_2 = \text{H}$
 II f: $R_1 = R_2 = \text{O}$



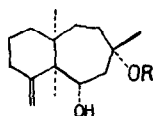
IIIa: $R = \text{H}$
 IIIb: $R = \text{Et}$



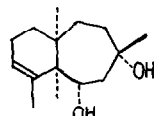
IVa: $R = \text{H}$
 IVb: $R = \text{Et}$



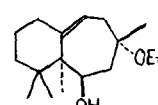
Va: $R = \text{H}$
 Vb: $R = \text{Et}$



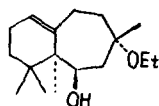
VIa: $R = \text{H}$
 VIb: $R = \text{Et}$



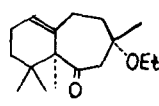
VII



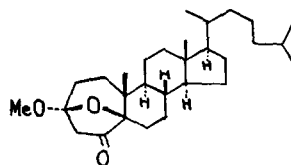
VIII



IX



X



XI

in 17% yield, and an unsaturated ether, m.p. 94° , of unknown structure, in 20% yield. Under the same conditions, IVb afforded two isomeric hydroxy ethyl ethers, Vb, liq., δ : 3.81 (1H, singlet), 5.33 (1H, triplet, $J=3$), and VIb, m.p. 70° , $\nu_{\text{max}}^{\text{KBr}}$ 1634, 891 cm^{-1} , in 50% and 45% yield respectively. Vb and IX were converted by chromic acid to the same ketone X, m.p. 64° , $\nu_{\text{max}}^{\text{KBr}}$ 1695 cm^{-1} , which on lithium aluminumhydride reduction afforded 35% of IX and 65% of Vb. These

experiments clearly indicate that the migration of the angular methyl group is independent of configuration of the epoxide ring in the starting materials IIIb and IVb.

Although the entire course of the acid-catalized isomerization in the trans-epoxides IIIa and IIIb can be visualized as occurring by a concerted mechanism (8), that in the cis-epoxides IVa and IVb deserves some comment. A solvated intermediate was suggested by Enzell (3) to explain the occurrence of cis methyl migration in the case of IVa. Such an intermediate, assuming it to be formed at all, normally leads to a triol, but, in the present case, the resulting triaxial interactions between the C-4 and C-11 methyls and the newly formed 6 α -hydroxyl, would preclude the formation of the triol. The fact that attack of the C-8 hydroxyl on the carbonium ion at C-5 does not occur in the case of the cis-epoxide, can be attributed to approach of these two centers being inhibited by (i) increased non-bonded interaction between the C-4 methyl and C-6 α -hydroxyl groups and (ii) formation of intramolecular hydrogen bonding between the C-6 and C-8 hydroxyl groups. Removal of non-bonded interaction between C-4 and C-11 methyl groups is considered to be the driving force for the methyl migrations.

We have now found (9) that Johnson's 3-oxacyclopentanone XI has the stereochemistry shown, contrary to the previous formulation (10), and have observed a negative Cotton effect ($[\text{M}]_{285}^{\text{peak}} +4116$, $[\text{M}]_{333}^{\text{trough}} -2946$), thus proving the correctness of Enzell's assumption (3), based on the sign of Cotton effect of IIIf.

REFERENCES

- (1) S. Itô, K. Endo, T. Nozoe: Chem. Pharm. Bull. Japan, 11, 132 (1963).
- (2) First isolated by Erdtman and Thomas. See Acta Chem. Scand., 12, 267(1958).
- (3) C. Enzell: Ibid., 16, 1553(1962).
- (4) Correct analytical figures were obtained for all new compounds. IR spectra were measured for a liquid film unless otherwise stated.
- (5) NMR spectra were measured at 60 Mc/s for CCl₄ solution. Chemical shift (δ) is expressed in ppm from internal tetramethylsilane, and coupling constant (J) in cps.
- (6) Inter al. R.F. Zürcher: Helv. Chim. Acta, 44, 1380(1961), 46, 2054(1963), and the references cited therein. K. Tori, K. Kuriyama: Chem. Ind., 1962, 1525.
- (7) S. Itô, K. Endo, M. Kodama, T. Nozoe: To be published.
- (8) cf. V. Sykora, L. Novotný, F. Sorm: Tetrahedron Letters, No. 14, 24(1959).
- (9) Evidence will be provided in a forthcoming paper by S. Itô, T. Ogino, T. Watanabe, and K. Endo.
- (10) W.S. Johnson, M. Neeman, S.P. Birkeland, N.A. Fedoruk: J. Amer. Chem. Soc., 84, 989(1962).