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BACKBONE REARRANGEMENT OF A 19-NOR-5-METHYL-5β-CHOLESTANE DERIVATIVE

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The cationic rearrangements of steroids[1/] and terpenoids[2/] which proceed with multicenter shifts of alkyl groups and hydrogen atoms are known as backbone rearrangements. The origin of this rearrangement is not yet fully understood although in early days of conformational theory it was suggested[3/] that methyl group migrations in euphenol are assisted by a conformational driving force. Recently, considerable attention is paid to the conformational analysis of the transition state and to the determination of structural features necessary for the backbone rearrangement[4/]. The present communication deals with the preparation and rearrangement of the highly stericly hindered epoxide (VI).

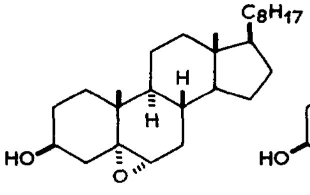
The cholesterol α-oxide[5/] (I) was converted by the known procedure[6/] to chlorodiol (II) which on treatment with potassium hydrogen sulphate in acetic anhydride undergoes the Westphalen-Lettré rearrangement and acetylation to afford the anhydro-compound[7/] (IIIa) m.p. 141-142°. Reduction of (IIIa) with sodium in boiling ethanol gave 5-methyl-19-nor-5β-cholest-9(10)-en-3β-ol[x/] (IIIb) m.p. 130-131°, $[\alpha]_D^{18}=+160^\circ$, ν_{max}(KBr) 3450 cm^{-1}, ^1H n.m.r. (60Mc) δ (p.p.m.) 4.10 (m. 1H, C3-H), 1.23 (s. 3H, $C-CH_3$), 0.77 (s. 3H, C18-H), 0.92 and 0.82 side chain methyl groups.

Transannular oxidation of unsaturated alcohol (IIIb) was carried out by the lead tetraacetate - iodine method[8/] using benzene as solvent. Column chromatography of the complex reaction mixture afforded cyclic ether (IV) m.p. 82-83°, $[\alpha]_D^{16}$=+72°, ^{1}H n.m.r. δ (p.p.m.) 4.41 (m. 1H, C3-H), 3.75 and 3.45 (doublets J_{AB}=8Hz,2H, C5-CH_2-O), 0.73 (s. 3H, C18-H), 0.92 and 0.82 side chain methyl groups. The structure of (IV) was confirmed further by ozonolysis in ethyl acetate at -78° followed by hydrogenation of the ozonide (without isolation) over 5% palladium-on-carbon catalyst giving diketone (V) m.p. 106-107°, $[\alpha]_D^{18}$=-36°, ν_{max}1715 cm^{-1}, ^{1}H n.m.r. δ (p.p.m.) 4.50 (m. 1H, C3-H), 3.96 and 3.78 (doublets J_{AB}=8Hz,2H, C5-CH_2-O), 0.91 and 0.82 side chain methyl groups. Chemical shifts of C5-CH_2-O in the n.m.r. spectrum of (V) and the absorption bands in its ir spectrum are consistent with the presence of the oxo group at the carbon atom C10 and hence with the position of the double bond in (IV).

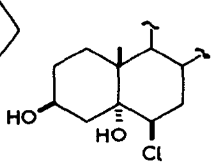
A wide variety of reagents were examined for the opening of the tetrahydrofuran ring in (IV). In spite of the expected liability of the homoallylic ether linkage, (IV) was rather stable in mild acidic conditions; more vigorous treatment gave inseparable mixtures. Boron trifluoride etherate in acetic acid or boron trichloride in methylene chloride[9/] acted on (IV) to give predominantly hydrocarbons.

Oxidation of (IV) with m-chloroperbenzoic acid in methylene chloride gave a mixture of epoxides which were separated by chromatography. The major product was the α-epoxide (VI) m.p. 59-61°, ^{1}H n.m.r. (100Mc) δ p.p.m. 4.41 (m. 1H, C3-H), 3.85 and 3.39 (doublets, 2H,J_{AB}=8Hz), 0.79 (s.3H,C18-H), 0.93 (d.3H,J=6.5Hz,C21-H), 0.89 (d.6H,J=6.5Hz,C26 and C27-H). The second isomer (VII) $[\alpha]_D^{18}$=+6.5° has the cis-orientation of the epoxide oxygen and the 5a -methylene group which follows from its n.m.r. spectrum with one of doublets of the methylene AB system shifted to lower field[10/]: (100Mc) δ (p.p.m.) 4.35 (m.1H,C3-H), 4.05 and 3.36 (doublets, 2H,J_{AB}=8Hz,C5-CH_2-O), 0.93 (d.3H,J=6.5,C21-H), 0.89 (d.6H,J=6.5,C26 and C27-H), 0.86 (s.3H,C18-H, superimposed with one of signals of the previous doublet).

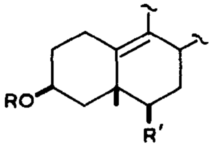
Epoxide (VI) was treated with boron trifluoride etherate in benzene for 10 min. at ambient temperature to give compound (VIII) $[\alpha]_D^{15}$ -21.2° in 66% yield after preparative tlc successively on silica gel and alumina plates. Structure (VIII) was substantiated by the following evidence : a/ in the high resolution mass spectrum the molecular ion at m/e 400.3342 corresponds to the formula $C_{27}H_{44}O_2$, an intense peaks at m/e 287 and 269 are due to characteristic[12/] loss of the side chain and water, b/ the ir spectrum (CCl_4) showed a band at 3600 cm^{-1} for tertiary -OH, c/ ^1H n.m.r. (100Mc) exhibits signals at δ (p.p.m.) 4.32 (m.1H,C3-H), 4.10 and 3.47 (doublets, 2H,J_{AB}=8.5Hz,C5-CH_2-O), 0.97 (d.3H,J=8Hz,C21-H), 0.87 (s.C14-CH_3) superimposed with the doublet centered at 0.85 (J=7.0,C26 and C27-H); on irradiation at -147 Hz, the doublet at 0.97 p.p.m. collapsed to a singlet as expected for the C=C-CH-CH_3 partial structure of the rearranged skeleton[13/].



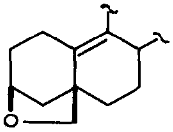
I



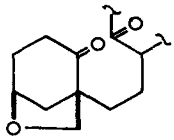
II



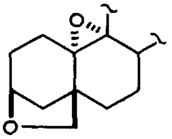
IIIa R=Ac,R'=Cl
b R=R'=H



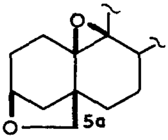
IV



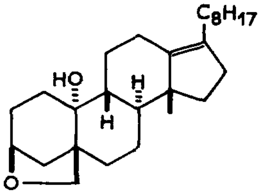
V



VI



VII



VIII

The inspection of molecular models of the possible transition states in the complete backbone rearrangement shows that for ring B with trigonal (or close to trigonal) carbon atom C9 (10α) or C10 (9α) two conformations should be considered : 1 the boat with 5 and 6 β substituents semi-axial and semi-equatorial respectively, 2 the boat with C5 substitutent semi-equatorial and 6β-semi-axial. Both conformations comply with request of anti-coplanar orientation of the vacant orbital of the electron deficient carbon and migrating groups, however it appears that only conformation 1 gives rise to the backbone rearrangement. The reason for this lies in the mutual interactions in the system C18H-C11 H-C5 CH_3-C1 H C11 H-C18H flattening rings B and C and forcing in combination with the interactions of C6 H-C9 H-

C14 H the inversion on C8 and C9. In the conformation 2 a partial relief of the conformational strain due to trans hydrindane ring junction might be achived by twisting the more flexible ring B. Hence the ratio of the backbone rearrangement to other reactions depends on relative stability of the conformer 1. The closing of the tetrahydrofurane ring between 3β-OH and 5β-CH_3 greatly stabilises the conformation 1.

References and Footnotes.

1. J.W. Blunt, M.P. Hartshorn and D.N. Kirk, Chem.Comm., 1966, 160
2. G. Brownlie, F.S. Spring and R. Stevenson, Chem. and Ind., 1955, 1156
3. D.H.R. Barton and R.C. Cookson, Quart. Rev. London, 10, 44 (1956)
4. J.G.Ll. Jones and B.A. Marples, J.Chem.Soc. (Perkin T.1), 1972, 792; J. Bascoul, D. Nikolaidis and A. Crastesdepaulet, Bull.Soc.chim.Fr., 1972, 184
5. G.A. Selter and K.D. McMichael, J.Org.Chem., 32, 2546 (1957)
6. D.H.R. Barton and E. Miller, J.Am.Chem.Soc., 72, 370 (1950)
7. J. Mishina, J.Org.Chem., 27, 2807 (1962)
8. Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner and A. Wettstein, Helv., 45, 1317 (1962)
9. M. Fetizon and P. Foy, Chem.Comm., 1967, 1005
10. For leading references, see K. Tori et al., Tetrahedron Letters, 1966 2921
11. For rearrangement of other 9,10-epoxides, see J.G. Guest and B.A. Marples, Tetrahedron Letters, 1969, 3577
12. G. Snatzke and H.W. Fehlhaber, Ann., 676, 188 (1964); J.W. Blunt, M.P. Hartshorn and D.N. Kirk, Tetrahedron Letters, 1966, 2125
13. M.P. Hartshorn and D.N. Kirk, Tetrahedron Letters, 1966, 3913

x/ All crystalline new compounds gave satisfactory elemental analysis; specific rotatins were determined for ca 1% solutions in $CHCl_3$; all n.m.r. spectra are for $CDCl_3$ solutions.