The Backbone Rearrangement of 10β-Hydroxy-steroids

By J. G. LL. JONES and B. A. MARPLES*

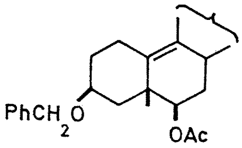
(*Department of Chemistry, University of Technology, Loughborough, Leicestershire*)

Summary Dehydration of a $6\beta,10\beta$-dihydroxy-5β-methyl-19-nor-steroid and a 10β-hydroxy-6-oxo-5β-methyl-19-nor-steroid gives backbone-rearranged products.

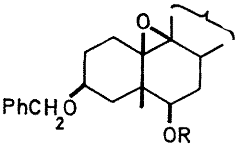
THE Westphalen rearrangement[1] of 5α-hydroxy-steroids to give mainly 5β-methyl-$\Delta^{9(10)}$-compounds has been studied.[2] Also, the boron trifluoride-catalysed cleavage of 4,5- and 5,6-epoxides to give the more extensively rearranged 5β-methyl-$\Delta^{8(14)}$- and 5β-methyl-$\Delta^{13(17)}$-compounds is now well known.[3] Both reactions nominally involve C-5 and C-10 carbonium ions, but the factors which determine the extent of rearrangement are not clear. In an attempt to elucidate the detailed mechanisms, we have studied the dehydration of the $6\beta,10\beta$-diol (**6**) and the 10β-hydroxy-6-ketone (**8**).

Treatment of the $6\beta,10\beta$-diol (**5**) with toluene-*p*-sulphonic acid in acetic anhydride at 100° gave a high yield (77%) of the backbone rearranged product (**7**)[†] $[\alpha]_D + 27°$ (*c*,[‡] 1·3). The ^1H n.m.r. spectrum[§] of (**7**) is typical of compounds in this series[3] and shows peaks at τ 2·76 (s, Ph), 5·4—5·8 (m, AcOCH), 5·58 (s, Ph.CH_2.O), 6·2—6·5 (m,OCH), 8·02 (s,AcO), 8·88 (s,5β-Me), 9·02 (lower branch of 21-Me doublet), 9·11 (upper branch of 21-Me doublet, 14β-Me, and lower branch of 26- and 27-Me doublets), and 9·21 (upper branch of 26- and 27-Me doublets). Double irradiation at 88 Hz. downfield from the 21-Me doublet caused its collapse to a singlet (τ 9·07) and confirmed the presence of the $\Delta^{13(17)}$-double bond.[3]

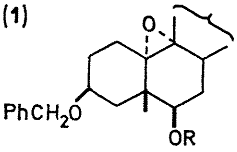
The $6\beta,10\beta$-diol(**6**)[¶] was prepared from the 5β-methyl-$\Delta^{9(10)}$- compound (**1**)[4] by the indicated route. Oxidation of (**1**) with monoperphthalic acid gave a mixture of the β-epoxide (**2**)[¶] $[\alpha]_D + 43°$ (*c* 0·6) and the α-epoxide (**3**)[¶] m.p. 88—90° $[\alpha]_D + 13°$ (*c* 0·4). Hydrolysis of the mixture and preparative t.l.c.[**] gave the β-epoxide (**4**) $[\alpha]_D + 38·5°$ (*c* 0·9) and the α-epoxide (**5**) m.p. 126—127° $[\alpha]_D + 25°$ (*c* 1·0). Reduction of the β-epoxide with lithium aluminium hydride in tetrahydrofuran gave the $6\beta,10\beta$-diol (**6**)



(1)



(2) R=Ac
(4) R=H



(3) R=Ac
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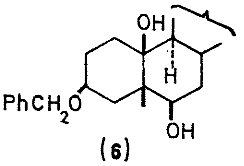
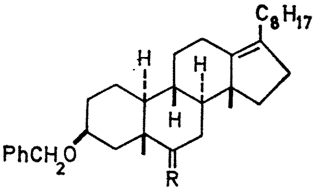
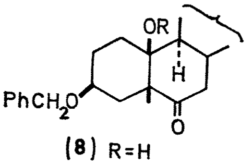


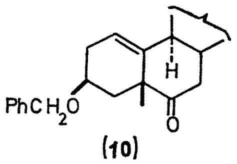
(6)



(7) R=β-OAc,α-H
(9) R=O
(12) R=β-OH,α-H



(8) R=H
(11) R=Ac



(10)

[†] Where no m.p. is quoted the compound is a gum.

[‡] All rotations for $CHCl_3$ solutions.

[§] All spectra are for CCl_4 solutions.

[**] The separation of the alcohols is easier than that of the acetates.

[¶] Satisfactory spectroscopic data are available and will be reported later. Similar compounds to (2) and (3) have been reported: J.-C. Guilleux and M. Mousseron-Canet, *Bull. Soc. chim. France*, 1967, 24.

$[\alpha]_D$ + 12° *c* 2·2). Jones oxidation[5] of (6) gave the 10β-hydroxy-6-ketone (**8**) m.p. 111—112° $[\alpha]_D$ − 36° (*c* 2·2).

Treatment of the ketone (8) with toluene-*p*-sulphonic acid in acetic anhydride at 100° gave the backbone-rearranged product (**9**) (20%), the $\Delta^{1(10)}$-compound (**10**) (25%) and the acetate (**11**) (13%) which were separated by preparative t.l.c. The ^{1}H n.m.r. spectrum of (**9**) shows peaks at τ 2·75 (s, Ph), 5·55 (s, Ph.CH_2.O), 6·1—6·4 (m, OCH), 8·67 (s, 5β-Me), 9·03 (shoulder, lower branch of 21-Me doublet), 9·04 (s, 14β-Me), 9·12 (upper branch of 21-Me doublet and lower branch of 26- and 27-Me doublets), and 9·21 (upper branch of 26- and 27-Me doublets). These data are only consistent with the structure shown (9) and the failure of the ketone to isomerise with base to a Δ^7-6-ketone excludes the alternative $\Delta^{8(9)}$- and $\Delta^{8(14)}$-structures. Final confirmation of the structure of (9) was obtained by its preparation by Jones oxidation[5] of the alcohol (**12**) which was obtained by hydrolysis of (7). The ^{1}H n.m.r. spectrum of (**10**) shows a vinyl proton signal (τ 4·4—4·7) and the chemical shifts of the 5β-methyl and 18-methyl groups (τ 8·78 and 9·33) suggest the $\Delta^{1(10)}$-structure for (**10**) rather than the possible alternative $\Delta^{9(11)}$-structure.

The low yield of backbone-rearranged product obtained from the 6-ketone (8) compared to that from the 6β,10β-diol (6) is probably due to the greater electron-withdrawing properties of the 6-carbonyl- as compared with the 6-hydroxy- (or OAc) group. The migration of a hydride ion from C-8 to C-9 will be more difficult in the ketone (8). It has recently been suggested[2d] that in the dehydration of 5α-hydroxy-steroids a 6β-acetoxy-group similarly inhibits the backbone rearrangement to a small extent. The marked difference in the course of rearrangement of the 6β,10β-diol (**6**) and 5α-hydroxy-6β-substituted compounds suggests that the two reactions do not involve the same C-10 carbonium ion-like intermediate. Since the 10β-hydroxy-group and the 1α- and 9α-hydrogen atoms are in the *anti*-periplanar conformation, it seems likely that a discrete C-10 carbonium ion is not involved in the dehydration of (6) and (8), and that the hydride ion shift from C-9, and in (8) the loss of a proton from C-1, is concerted with the breakage of the C-10–oxygen bond. In the Westphalen rearrangement, the migrating methyl group and the 9α-hydrogen atom cannot be in a truly *anti*-periplanar conformation, and it is possible that a more C-10 carbonium ion-like intermediate is formed with subsequent loss of a proton from C-9 (or C-1). It is unlikely that a discrete C-10 carbonium ion is usually involved in the cleavage of 4,5- and 5,6-epoxides since the products are generally the more extensively rearranged $\Delta^{8(14)}$- and $\Delta^{13(17)}$-compounds. It is not yet clear why the methyl group and hydride ion migrations should be more readily concerted in the reaction of the epoxides than in the dehydration of 5α-hydroxy-compounds. Differences in solvent and reagents may be significant.

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[2] (a) J. S. Mihina, *J. Org. Chem.*, 1962, **27**, 2807; (*b*) G. Snatzke and H.-W. Fehlhaber, *Annalen*, 1964, **676**, 188; (c) A. Fischer, M. J. Hardman, M. P. Hartshorn, D. N. Kirk, and A. R. Thawley, *Tetrahedron*, 1967, **23**, 159; (d) J. M. Coxon and M. P. Hartshorn, *Tetrahedron Letters*, 1969, 105.

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