Alkyl Group Participation in Wagner–Meerwein Rearrangements of 5α-Hydroxy-steroids

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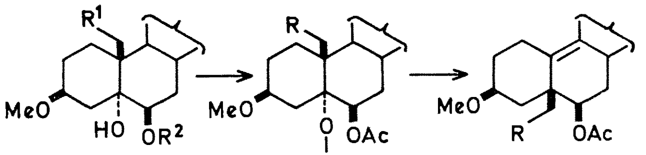
Summary The rearrangement of the 19-methyl-5α-hydroxy-steroid (4) to the 5β-ethyl-$\Delta^{9,10}$-compound (5) occurs at a rate 5·3 times greater than the analogous rearrangement of the 5α-hydroxy-steroid (1) to the 5β-methyl-$\Delta^{9,10}$-compound (2).

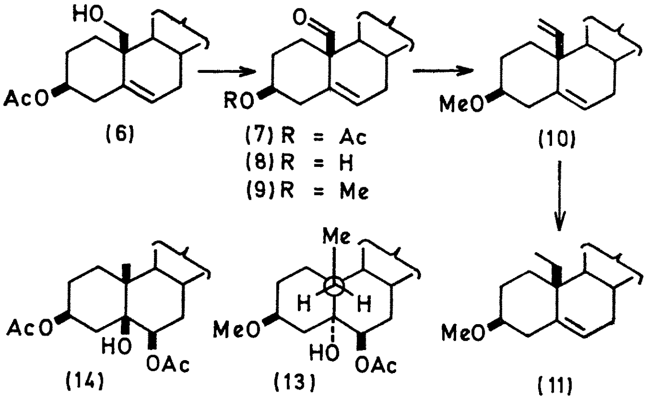
THE Westphalen rearrangement[1] of 6β-substituted-5α-hydroxy-steroids in acetic anhydride–sulphuric acid–acetic acid[2] to give 5β-methyl-19-nor-steroids is well known. For example, 6β-acetoxy-3β-methoxy-5α-cholestan-5-ol (1) gives 6β-acetoxy-3β-methoxy-5-methyl-19-nor-5β-cholest-9-ene (2).[3,4] It has long been assumed that these rearrangements proceed *via* a discrete C-5 carbonium ion† and recent kinetic studies[2,4] have shown that the rate determining step is the heterolysis of the C-5-O-bond of the rapidly formed intermediate acetyl sulphate (3). We now report that the 19-methyl-5α-hydroxy-steroid (4) rearranges to the 5β-ethyl-compound (5) (50%) at a rate 5·3 times greater than the rearrangement of compound (1) to compound (2). We conclude that the alkyl group migration is concerted with heterolysis of the C-5–O bond and that a C-5 carbonium ion is not involved in these reactions.



(1) R¹ = H, R² = Ac
(4) R¹ = Me, R² = Ac
(12) R¹ = Me, R² = H
(3) R = H
(2) R = H
(5) R = Me

The 19-methyl-5α-hydroxy-compound (4), $[\alpha]_D -25°$ (*c*‡ 0·4) was prepared from the 19-hydroxy-compound (6)[5] by the route shown.§ Oxidation of the 19-hydroxy-compound (6) with Jones' reagent gave the aldehyde (7)[6] which was hydrolysed to the alcohol (8).[6] The alcohol (8) was converted *via* the toluene-*p*-sulphonate to the methyl ether (9), m.p. 71—72°, $[\alpha]_D -165°$ (*c* 0·5), which reacted with methylenetriphenylphosphorane to give the diene (10), m.p. 82—84°, $[\alpha]_D -102°$ (*c* 0·4). Selective hydrogenation of the diene (10) using a palladium catalyst gave the 19-methyl compound (11), m.p. 81—82°, $[\alpha]_D -53°$ (*c* 0·4), which after oxidation with performic acid and hydrolysis gave the diol (12) m.p. 203—204°, $[\alpha]_D -3°$ (*c* 0·2). Acetylation of the diol (12) gave the acetate (4) which rearranged under the usual conditions[2] to give the 5β-ethyl compound (5), $[\alpha]_D +47°$ (*c* 0·6), which was separated from the other minor products by preparative t.l.c.

The rearrangements of 0·01M-solutions of compounds (1) and (4) in acetic acid, which were 0·05M in sulphuric acid and 0·5M in acetic anhydride,[2,4] were followed with a recording polarimeter at 22·5°. The first-order rate constants (k_1 = 4·6 × 10^{-3} sec.$^{-1}$ and k_4 = 2·4 × 10^{-2}sec.$^{-1}$) were determined from the slope of a plot of log ($\alpha - \alpha_\infty$¶) against time. Our value of k_1 compares well with that previously determined (5·7 × 10^{-3}sec.$^{-1}$) by this method by Kirk and Hartshorn and their co-workers at 25°.[4] Since the specific rotation of the final mixture from the rearrangement of compound (4) (+43°) is close to that of compound (5) (+47°), we feel this method of following the reaction is satisfactory.



(6)
(7) R = Ac
(8) R = H
(9) R = Me
(10)
(14)
(13)
(11)

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† Snatzke and Fehlhaber alone suggested the possibility of an intermediate nonclassical ion (ref. 7b).

‡ All rotations are for $CHCl_3$ solutions.

§ All new compounds had satisfactory elemental analyses and spectroscopic data.

¶ α_∞ was taken to be the value after at least 10 half-lives.

The most stable conformation of compound (4) is probably close to that represented in (13). The methyl group suffers an interaction with the 11β-hydrogen atom and two skew interactions with the C-1–C-10 and C-9–C-10 bonds. These interactions are thus probably largely responsible for raising the ground-state energy of compound (4) relative to that of compound (1). From models, it is difficult to see how relief of these interactions may occur by the flattening at C-5 necessary in the transition state leading to a C-5 carbonium ion. However, if the alkyl group migration is concerted with the C-5–O bond cleavage such steric relief in the transition state will occur and this would explain the observed rate increase. In the rearrangement of both compounds (1) and (4) this concerted mechanism would also allow relief, in the transition state, of the apparently essential interaction of the angular alkyl group with the 6β-acetoxy-group.** In addition, it readily explains the failure of the 5β-hydroxy-steroid (14) to undergo Westphalen rearrangement.[7]

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** It is well known that 6α-substituted-5α-hydroxy-steroids do not undergo the Westphalen rearrangement (*cf.* ref. 2).

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