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REACTIONS OF 5α-HYDROXY STEROIDS IX.* THE ACID CATALYSED REARRANGEMENT OF 4β-ACETOXY-5α-OXYGENATED CHOLESTANES.

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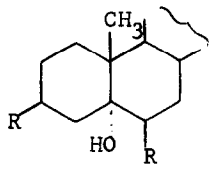
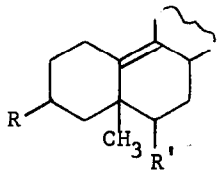
The Westphalen rearrangement[1] of 3β,6β-substituted-cholestan-5α-ols (1) to give 5β-methyl-Δ^9-compounds (2) has received considerable study[2]. No rearrangement products are obtained from 5β-hydroxy-[3], 6α-substituted-[4], 6β-methyl-[5] or 6-keto-derivatives[6]. Recently Davies and Summers[7] reported the rearrangement of 4β,7β-diacetoxycholestan-5α-ol (3a) to give the corresponding 5β-methyl-Δ^9-compound (4a). The rearrangement products from the treatment of 5α-hydroxy steroids under the Westphalen rearrangement conditions have been limited to Δ^9- and $\Delta^{1(10)}$-5β-methyl derivatives[8].

We now report the reaction of 4β-acetoxycholestan-5α-ol (3b) under the Westphalen rearrangement conditions (H_2SO_4-Ac_2O-AcOH)[2(b)] to give, in addition to the 5β-methyl-Δ^9-compound (4b; 60%), the more extensively rearranged 5β-methyl-$\Delta^{8(14)}$-(5a; 14%) and 5β-methyl-$\Delta^{13(17)}$-(6a; 3%) products.

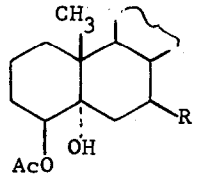
The assignment of the 5β-methyl-Δ^9-structure (4b) to the major product, m.p. 95-96°, $[\alpha]_D$ + 54°, ν_{max} 1735 and 1235 cm^{-1}; δ0.78**($C^{18}H_3$), δ0.82 and 0.92 (side chain CH_3), δ1.06 (5β-CH_3), δ2.03 (OAc), and δ4.77 (axial 4α-H, J apparent 9.0 and 5.5 cps), was based on the following evidence. The location of the tetrasubstituted double bond ($\varepsilon_{202\ m\mu}$ 11,250) was established by conversion of (4b) via the alcohol (4c), δ0.99 (5β-CH_3) δ3.47 (axial 4α-H, J apparent 9.0 and 5.5 cps), into the β,γ-unsaturated ketone (4α), ν_{max} 1713 cm^{-1}, λ_{max}^{9} 290 mμ (ε290), 300 mμ (ε312) 308 mμ (ε273) and 321 mμ (ε152), δ1.25 (5β-CH_3). The inversion at C-5 in (4b) is confirmed by the appearance of the 4α-proton in the NMR spectra of (4b) and (4c), and by the marked shift (+ 0.26 ppm) in the signal due to the 5β-methyl group[10] on oxidation of the alcohol (4c) to give (4d).



(1)

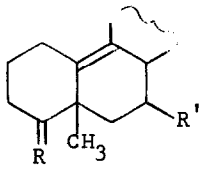


(2)



(3) (a) R = OAc

(b) R = H

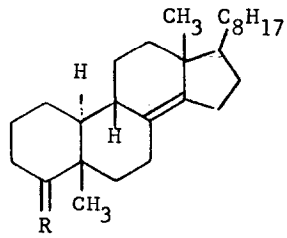


(4) (a) R, βOAc, H; R' OAc

(b) R, βOAc, H; R' H

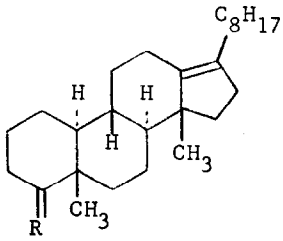
(c) R, βOOH, H; R' H

(d) R, O; R' H.



(5) (a) R, βOAc, H

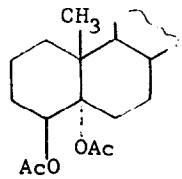
(b) R, βOH, H.



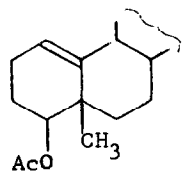
(6) (a) R, βOAc, H.

(b) R, βOH, H.

(c) R, O.



(7)



(8)

The second product, m.p. 104-105°, $[\alpha]_D$ + 81.5°, ν_{max} 1735 and 1235 cm^{-1}, δ0.84 ($C^{18}H_3$), δ0.84 and 0.92 (side chain CH_3), δ1.01 (5β-CH_3), δ2.01 (OAc), δ4.57 (axial 4α-H, $W_{\frac{1}{2}}$ 17 cps), was assigned the 5β-methyl-$\Delta^{8(14)}$- structure (5a). The location of the tetrasubstituted double bond ($\varepsilon_{200\ m\mu}$ 11,040) was established by ozonolysis of the alcohol (5b) to give an oil, ν_{max} 3450 (OH), 1742 and 1719 cm^{-1} (5- and 6-membered ring carbonyl functions).

A minor product (6a) from the reaction of (3b) under Westphalen rearrangement conditions was shown (IR, UV, NMR, tlc) to be identical with the major product (ca. 80%) from the reaction of 4β,5α-diacetoxycholestane (7) with BF_3-acetic anhydride at 80° for 1 min. The tetrasubstituted double bond ($\varepsilon_{199.5\ m\mu}$ 9,800) in (6a), $[\alpha]_D$ + 21°, ν_{max} 1735 and 1240 cm^{-1}, was located at the 13,17-position, with a backbone rearranged skeleton by analysis of the NMR spectrum. The NMR spectrum of (6a) exhibited signals, δ0.79 and 0.90 ($C^{26}H_3$ and $C^{27}H_3$), δ0.90 (5β-CH_3, 14β-CH_3), δ0.90 and 1.00 ($C^{21}H_3$), δ2.01 (OAc) and δ4.47 (axial 4α-H, $W_{\frac{1}{2}}$ 15 cps) consistent with the assigned structure. The location of the double bond at the 13,17-position followed from the collapse of the $C^{21}H_3$ doublet to a singlet at δ0.95 ppm on double irradiation with -88 cps, thus defining the 20-H at δ2.41 ppm as a proton in an allylic position.

Oxidation of the alcohol (6b), $[\alpha]_D$ + 27°, ν_{max} 3450(OH), δ0.91 ppm (5β-CH_3) obtained by hydrolysis of (6a), gave the corresponding ketone (6c), $[\alpha]_D$ - 8.5°, ν_{max} 1710 cm^{-1}, δ1.11 ppm (5β-CH_3). The shift (+ 0.20 ppm) in the signal due to the 5β-methyl group on oxidation of the C-4 hydroxyl group provides further support[10] for the proposed structure.

A further unidentified minor product (3%), m.p. 117-120°, $[\alpha]_D$ + 19°, ν_{max} 1735 and 1235 cm^{-1}, δ0.67 ($C^{18}H_3$), δ0.82 and 0.91 (side chain CH_3), δ0.94 ($C^{19}H_3$ or 5β-CH_3), δ4.57 (4α-H; $W_{\frac{1}{2}}$ 15 cps), δ5.37 (olefinic proton; $W_{\frac{1}{2}}$ 7 cps) was isolated from the reaction of (3b) under Westphalen rearrangement conditions. It seems probable that this compound has the 4β-acetoxy-5β-methyl-$\Delta^{1(10)}$-structure (8).

The notable feature of the rearrangements of the 4β-acetoxy-5α-oxygenated steroids reported above is the marked increase in the proportion of products produced by partial or complete backbone rearrangement. We

consider that in the absence of an electron withdrawing substituent in ring B (normally-OAc at C-6 or C-7) the 8,9-hydride shift to form a transient C-8 carbonium ion would be a significantly less energetic process.

A full account of this and other related work will be published later.

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** Determined at 60 Mc for $CDCl_3$ solutions.

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