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INTRAMOLECULAR CYCLIZATION OF 3β-ACETOXY-5-OXO-7-FORMYL--7α,8-EPOXY-5,6-SECOCHOLESTANE INTO KETAL-ACETALS

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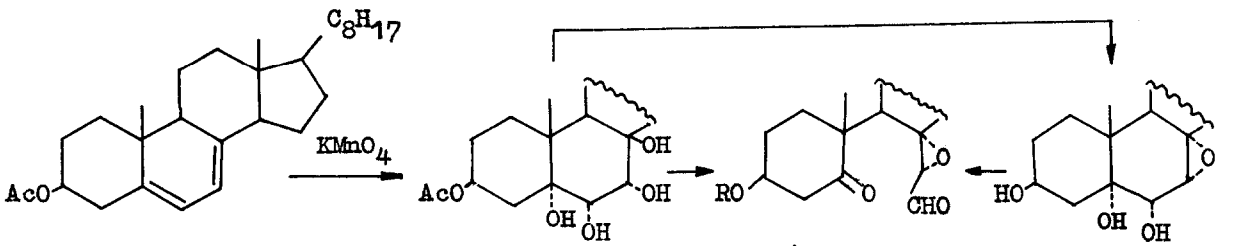
Hydroxylation with potassium permanganate of 3β-acetoxycholesta-5,7-diene 1 gave 3β-acetoxy-5α,6α,7α,8β-tetrahydroxycholestane 2; m.p. 196°C, $[\alpha]_D^{24}$ +9.0° [1]. The compound was unreactive towards HIO_4, but it was transformed (by $Pb(OAc)_4$) into 3β-acetoxy-5-oxo-7-formyl-7α,8-epoxy-5,6-secocholestane 3b, m.p. 126-127°C, $[\alpha]_D^{24}$ +26.2°. The structure of 3b was assigned on the basis of analytical ($C_{29}H_{46}O_5$) and spectral data: IR ($CHCl_3$): 1735, 1718, 1250, 1082, 1025, 850 and 820 cm^{-1}; ^{1}HNMR: δ 0.81 (s, 3H, 18H), 0.89 (s, 3H, 19-H), 2.41 (s, 3H, 3β-OCOCH$_3$) 3.28 (d, 1H, 7-H, J = 3.75 Hz), 5.37 (m, 1H, 3-H$_e$, $\frac{W}{2}$ = 7.5 Hz), 9.65 (d, 1H, CHO, J = 3.75 Hz).



1 2 3 4

However it was not possible to define conclusively either the position or configuration of the epoxide ring on the basis of the above data. The location of the α-epoxide oxygen atom has now been ascertained to involve carbon atoms C-7 and C-8 as follows. Hydrolysis with methanolic-aqueous KOH of pentol 3β-acetate 2 yielded epoxytriol 4 (described previously by us [1]) m.p. 171-172°C, $[\alpha]_D^{24}$ +12.5°, IR ($CHCl_3$): 3610, 3550, 3410, 1050, 985 and 835 cm^{-1}; ^{1}HNMR: δ 0.76

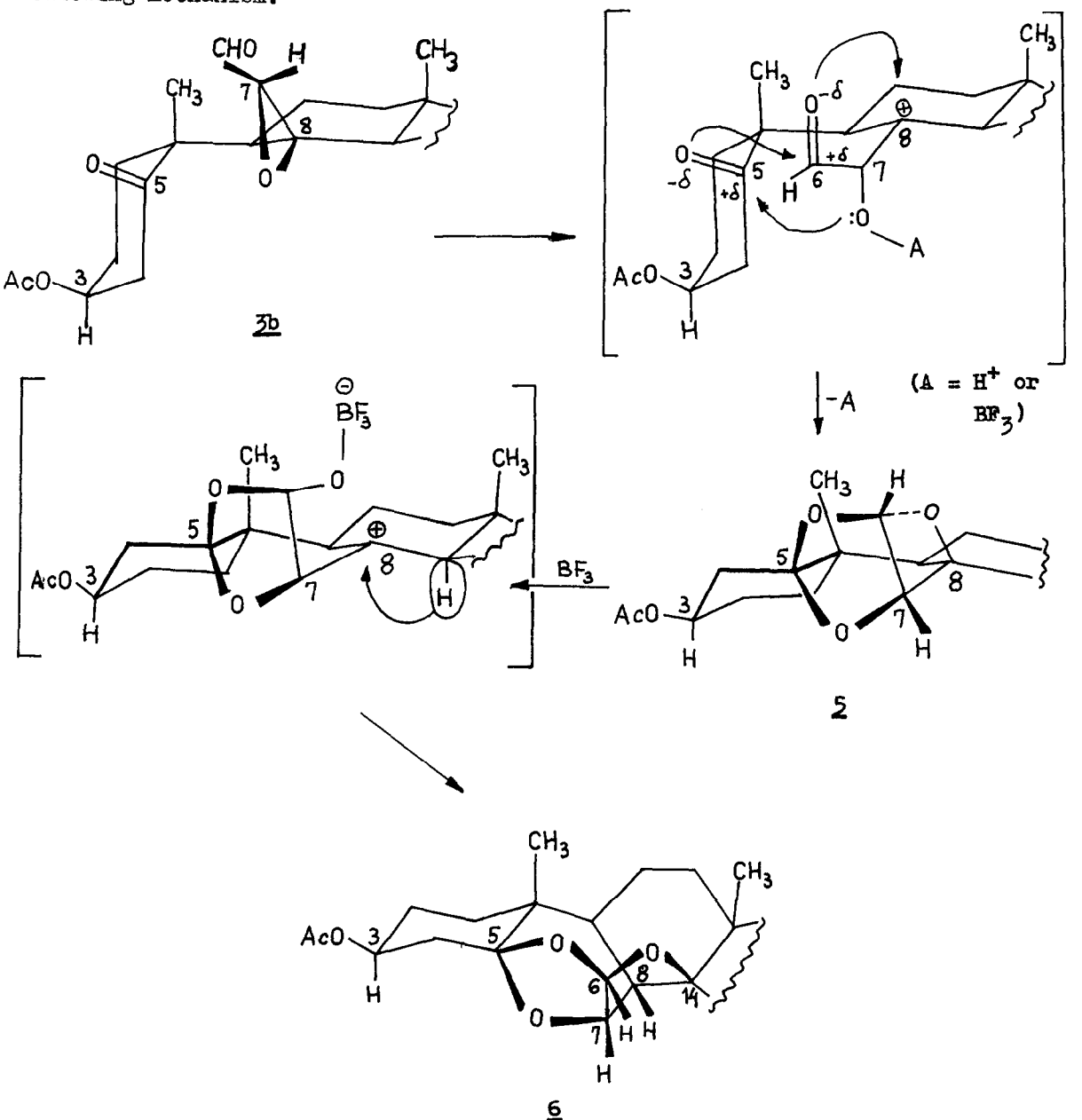
(s, 3H, 18-H) 1.00 (s, 3H, 19-H), 2.95 (m, 1H, OH, J = 10.0 Hz), 3.62 (s, 1H, 7-H), 3.78 (s, 1H, 6-H), 3.97 (m, 1H, 3-H, $\frac{W}{2}$ = 25.0 Hz), 4.45 (s, 1H, OH). Compound 4, treated with $Pb(OAc)_4$, gave an oily 3β-hydroxy-ketoaldehyde 3a, which after esterification with acetic anhydride in pyridine afforded a crystalline product identical with 3β-acetoxy-ketoaldehyde 3b, previously obtained from pentol monoacetate 2. This proved that the configuration and location of the epoxide ring in compound 3b has been the same as in epoxytriol 4.

Epoxy-ketoaldehyde 3b, treated with mineral acids or etheral-BF_3 underwent an intramolecular cyclization to give a crystalline product 5, m.p. 145-146°C, $[\alpha]_D^{24}$ -30.5°, in a quantative yield. It was identified as the cyclic ketal-acetal 5 on the basis of the following evidence. Its elemental analysis and molecular weight (MS) corresponded to the formula $C_{29}H_{46}O_5$. The IR spectrum indicated the presence of the acetoxyl group (1730, 1230 cm^{-1}), cyclic ethers (ketal and acetal rings: 1082, 1062, 1052, 990 and 888 cm^{-1}) and disappearance of the ketone and aldehyde carbonyl groups. The ^{1}HNMR spectrum of 5 showed a broad multiplet corresponding to the H-3 proton (δ 4.70, $\frac{W}{2}$ = 22.5 Hz) characteristic for an axial proton [2]. It indicated that ring A has been interconverted in the course of the reaction, since in compound 3a the H-3 proton occupied the equatorial position. The signals at δ4.78 (d, 1H, J = 2.5 Hz) and 5.56 (d, 1H, J = 2.5 Hz) [3] were assigned to the H-7 and H-6 protons, respectively. The downfield shift of the latter was a consequence of bonding of carbon atom C-6 with two oxygen atoms.

Compound 5, treated with etheral-BF_3 at room temperature, underwent a further intramolecular rearrangement to give isomeric ketal-acetal 6, m.p. 98-100°C, $[\alpha]_D^{24}$ -27.6°. Its structure was deduced as follows. The IR spectrum showed the presence of the acetoxyl group (1730 and 1230 cm^{-1}) and cyclic ketal--acetal (1065, 1040, 1010, 985 and 960 cm^{-1}). The ^{1}HNMR spectrum revealed signals corresponding to the H-6 ~~proton~~ (δ 5.38, d, 1H, $J_{6,7}$ = 4.15 Hz), H-7 (δ 5.08,dd, 1H, $J_{7,8}$ = 7.52, $J_{6,7}$ = 4.15) protons and the axial H-3 proton (δ 4.82, m, 1H, $\frac{W}{2}$ = 22.5 Hz). An alternative structure with the oxygen atom bonded to C-6 and C-9 was rejected because it should lead to values of coupling constants $J_{6,7}$ = = 10 Hz and $J_{7,8}$ = 6 Hz, respectively, which were not in agreement with the experimental data.

The presence of the oxirane ring in ketal-acetals 5 and 6 was excluded by results of LAH reduction of these compounds, which led to the removal of the acetoxy group at C-3 [4].

Cyclization of compound 3 to ketal-acetal 5, as a kinetic product, and its further rearrangement to the thermodynamic product 6 could be explain by the following mechanism:



It should be noted that the formation of compound 6 requires conditions favoring the hydride ion transfer (BF_3-ether), whereas in aqueous-acidic medium, compound 5 is only one product. The higher stability of ketal-acetal 6 relatively to 5 is connected with rearrangement of the 4,5-membered rings into 5,5-membered system.

It appears that reported cyclization of epoxy-ketoaldehyde 4 into ketal-acetals 5 and 6, respectively is not an isolated case since a formation of cyclic acetal derivatives during the oxidation of steroid triols has been previously described [5].

References and Notes

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2. N. S. Bhacca, D. H. Williams, Applications of NMR-Spectroscopy in Organic Chemistry, Holden-Day, 1964, pp. 49-52.
3. The coupling of the H-6 with the H-7 was confirmed by double irradiation experiment.
4. J. Fried, J. W. Brown, L. F. Borkenhagen, Tetrahedron Letters, 29, 2499 (1965).
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