Tetrahedron Letters No.33, pp. 3913-3918, 1966. Pergamon Press Ltd.
Printed in Great Britain.

REACTIONS OF EPOXIDES, XII[1]: BORON TRIFLUORIDE CATALYSED REARRANGEMENTS OF 5,6-EPOXIDES IN THE 4,4-DIMETHYLCHOLESTANE SERIES.

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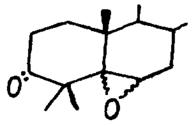
(Received 21 June 1966)

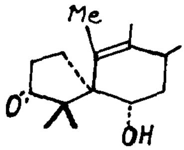
We have examined the reactions between boron trifluoride and 5α,6α-epoxy- and 5β,6β-epoxy-4,4-dimethylcholestan-3-ones (Ia and Ib).[2] While this work was in progress we learned that Professor Sir Ewart Jones and Dr. T.G. Halsall[2] had examined the same reactions, and we gratefully acknowledge their generosity in sending us a copy of their first draft manuscript in January 1965.

We agree with the Oxford group in assigning the C-5 spiran structure (II) to the sole product from the α-epoxyketone (Ia). In January 1965 we also agreed that the major product (A) from the β-epoxyketone (Ib) had the 5β-methyl-19-nor-9(10)-olefinic structure (IIIa). This structure for (A) was based upon spectroscopic evidence, which revealed the presence of hydroxyl- and 6-membered ring ketonic functions ($\nu_{max.}$3610, 1705 cm^{-1}) and a tetrasubstituted double bond [λ_{max}197.5mμ, (ϵ =14,000); no olefinic proton in NMR spectrum]. The optical rotation of the hydroxy-ketone (A) ($[\alpha]_D$+25°) and of the derived 3,6-diol ($[\alpha]_D$+26°) were considered abnormal for a compound structurally analogous to Westphalen's diol, but we ascribed the absence of a large positive rotation^3 to some subtle conformational change concerned with the

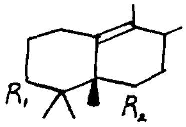


I

(a) α-epoxide
(b) β-epoxide

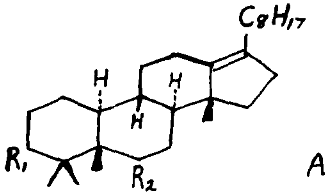


II



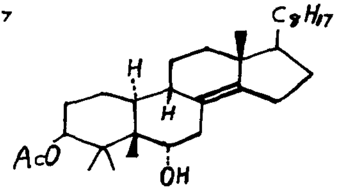
III

(a) R_1 = :O; R_2 = β-OH
(b) R_1 = β-OAc; R_2 = α-O
(c) R_1 = β-OAc; R_2 = :O



IV

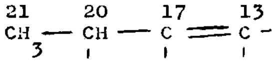
(a) R_1 = :O; R_2 = β-OH
(b) R_1 = β-OAc; R_2 = α-OH
(c) R_1 = R_2 = :O



V

4,4-dimethyl system.

Fresh evidence, which we have communicated to the Oxford workers, compels us to alter our views concerning the hydroxy-ketone (A), and to formulate it as (IVa) the product of "backbone rearrangement".[4] The NMR spectrum (determined at 100mc. in CCl_4 solution, relative to tetramethylsilane) included a three-proton doublet (0.935 p.p.m; J=7c/s) and a one-proton multiplet (2.42 p.p.m.) assigned to the 21-methyl and 20-methine protons respectively in the partial structure:-



$$\overset{21}{CH_3}-\underset{|}{\overset{20}{CH}}-\underset{|}{\overset{17}{C}}=\underset{|}{\overset{13}{C}}-$$

Spin-decoupling experiments showed that the 21-methyl signal could be reduced to a singlet by simultaneous irradiation at the frequency corresponding to the 20-proton.[4] These findings, which remove the apparent anomaly in the optical rotation of the hydroxy-ketone (A), are supported by ORD data and a further study of NMR spectra, which will be reported in our full paper.[5]

This instance of the "backbone rearrangement" is peculiar in being initiated by cleavage of a 5β-carbon-oxygen bond. Migration of the C-10 angular methyl group cannot be concerted with C-O cleavage, which is even more remarkable in view of the high yield (ca.80%) of (IVa) The mechanistic significance of this reaction will be discussed later.[5]

3β-Acetoxy-5α,6α-epoxy-4,4-dimethylcholestane reacted with BF_3 in benzene for 5 min. to give three hydroxy-olefins. The major product (45%) was the 5β-methyl-19-nor-9(10)-olefin (IIIb) [m.p. 155-156°, $[\alpha]_D$+13°, $\lambda_{max.}$ 199mμ (ϵ =16,700), tetrasubstituted C=C confirmed by NMR] derived by angular methyl migration from C-10, in a "Westphalen" type of reaction.[3] Oxidation of (IIIb) with chromic acid-acetone gave the 6-ketone (IIIc) [m.p. 90-92°, $\nu_{max.}$ 1710 cm^{-1}, negative Cotton effect, a = -179]. Another product (18%) was found to be the 13(17)-olefin (IVb) [m.p. 102-103°, $[\alpha]_D$+44°, $\lambda_{max.}$ 199mμ (ϵ =10,800)] derived from a complete "backbone rearrangement". The structure (IVb) was established by NMR spin-decoupling experiments similar to those described above, and by conversion of the compound, through vigorous alkaline hydrolysis, followed by oxidation, into the non-crystalline 3,6-diketone (IVc), identical with a sample prepared by oxidation of the hydroxy-ketone (IVa).

The third isomeric product (ca. 18%) [an oil, $[\alpha]_D$+60°, $\lambda_{max.}$ 199mμ (ϵ =15,800)], had properties consistent with the 8(14)-olefinic structure (V). The NMR spectrum confirmed the absence of olefinic protons. Oxidation with chromic acid-acetone gave a crude ketone, $\lambda_{max.}$ 244mμ (ϵ =4140), the extinction of which increased on chromatography on alumina (ϵ =12,600) although the product could not be obtained pure. These observations, and the stability of the hydroxy-olefin to 2,3-dichloro-5,6-dicyano-benzoquinone,[6] argue in favour of initial oxidation to give the non-conjugated $\Delta^{8(14)}$-6-ketone, which readily isomerises to a Δ^{7}-6-ketone. The compound (V ?) underwent auto-oxidation in a few days to give a highly polar mixture of products, so that its study could not be continued.

Extended treatment of the 3β-acetoxy-5α, 6α-epoxide with BF_3 gave decreasing yields of the 9(10)-olefin, and much non-polar material. Further experiments confirmed that the 9(10)-olefin is converted by BF_3 into a mixture of products containing isomers (IVb) and (V), and that (V) can in turn be converted by BF_3 into a mixture containing (IVb). These results suggest a slow sequential shift of the double bond (or of the site of the related carbonium ion) from the C-10 position towards 13(17) as an irreversible process, with further reactions, involving loss of the C-6 oxygen function, ultimately leading to non-polar material. ORD data, to be reported later,[5] support the concept of the "backbone rearrangement" as a series of stereospecific migration processes leading to inversion at every ring junction involved.

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