

REACTIONS OF EPOXIDES PART XVI\*

THE BORON TRIFLUORIDE CATALYSED REARRANGEMENT OF

3 $\alpha$ -ACETOXY-5,6 $\alpha$ -EPOXY-5 $\alpha$ -CHOLESTANE.

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The greater yield (61%) of the 6-ketone (2a) from 3 $\alpha$ -acetoxy-5,6 $\alpha$ -epoxy-5 $\alpha$ -cholestane (1a) compared with the yield (34%) of 6-ketone (2b) from the corresponding 3-deoxy compound has been ascribed<sup>1</sup> to the energetically favourable conformational change, involving the 3-acetoxy group, in the formation of the A,B-cis-6-ketone (2a). Reaction of the 3 $\beta$ -acetoxy epoxide (1c) with BF<sub>3</sub>-etherate gave the fluorohydrin (3b; 62%). The non-formation of the 6-ketone (2c) was attributed to the unfavourable conformational change of the 3 $\beta$ -acetoxy group in that reaction path, while the apparent absence of the fluorohydrin (3a) from the 3 $\alpha$ -acetoxy compound (1a) was ascribed to the non-bonded interactions between the 3 $\alpha$ - and 5 $\alpha$ - substituents in the product.

It has been shown<sup>2</sup> that the 3,3-ethylenedioxy-5 $\alpha$ ,6 $\alpha$ -epoxide (1d) gave the fluorohydrin (3c; 62%) on reaction with BF<sub>3</sub>-etherate. In view of the apparently slow rate of reaction<sup>1</sup> of the 3 $\alpha$ -acetoxy compound (1a) we re-examined the rearrangement of (1a) to determine whether the fluorohydrin (3a) was formed rapidly and then underwent further reaction to the observed product(s) (2a) (cf. ref. 3).

In our hands the reaction of the 3 $\alpha$ -acetoxy epoxide (1a) with BF<sub>3</sub>-etherate in dry benzene, using the same concentrations of reagents as Henbest et al.<sup>1</sup> but with a reaction time of 25 sec. (cf. Henbest et al.<sup>1</sup>, 5 min. and 14 hr.), gave a crude product shown (TLC) to contain at least six compounds. This mixture was resolved into its pure components by chromatography on deactivated alumina. The product composition was markedly different from that reported earlier by Henbest et al.<sup>1</sup>

Elution with light petroleum-benzene (9:1) gave the fluorohydrin (3a; 8%), m.p. 114-115<sup>o</sup>,  $\nu_{\max}$  3599, 3575 (OH) and 1735 cm<sup>-1</sup> (OAc). The assigned structure was confirmed by the NMR spectrum\*\*

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\*\* Determined at 60 Mc for CDCl<sub>3</sub> solutions.

which exhibited signals, doublet centred at 4.20 ppm (J 50 cps), 6 $\alpha$ -H; triplet centred at 5.28 ppm (J 3.6 cps), 3 $\beta$ -H; three proton doublet centred at 1.02 ppm (J 5 cps), C<sup>19</sup>H<sub>3</sub>. Further, adsorption of the fluorohydrin (3a) on alumina followed by dilution with ether gave the epoxide (1a).

Further elution with light petroleum-benzene (9:1) gave the 6-ketone (2a; 17%) containing (TLC) a trace of a second compound. Crystallisation of the crude 6-ketone from pentane gave material with physical constants identical with those quoted by Henbest *et al.*<sup>1</sup> The assignment of structure was confirmed by IR, 1734 (OAc) and 1704 cm<sup>-1</sup> (six membered ring ketone), and NMR spectra, multiplet (1H) centred at 4.58 ppm ( $W\frac{1}{2}$  18 cps), 3 $\alpha$ -H.

Further elution with the same solvent gave the backbone rearranged<sup>4</sup> compound (4a; 37%) as an oil. The elemental analysis was consistent with the molecular formula C<sub>29</sub>H<sub>48</sub>O<sub>3</sub>. The presence of a tetrasubstituted double bond was indicated by a positive tetranitromethane test, UV spectrum  $\epsilon_{207}$  7,600 and by the absence of signals due to vinylic protons in the NMR spectrum. The NMR spectrum of this hydroxyacetate (4a) ( $\nu_{\max}$  3500 (OH) and 1734 cm<sup>-1</sup> (OAc)) exhibits signals, multiplet (1 H) centred at 3.38 ppm ( $W\frac{1}{2}$  5 cps), equatorial 6 $\beta$ -H; multiplet (1 H) centred at 4.85 ppm ( $W\frac{1}{2}$  16 cps), axial 3 $\beta$ -H; singlet (3H) at 0.91 ppm, 5 $\beta$ -CH<sub>3</sub>; doublet (3H total) centred at 0.95 ppm (J 6 cps), C<sup>21</sup>H<sub>3</sub> was consistent with the assigned structure. The location of the double bond in the 13,17- position followed from the collapse of the C<sup>21</sup>H<sub>3</sub> doublet to a singlet on double irradiation with -88 cps, thus defining the 20-H at 2.42 ppm as a proton in an allylic position. The presence of an inverted backbone in the hydroxyacetate (4a) is indicated by the character of the signals due to the 3 $\beta$ - and 6 $\beta$ - protons in the NMR spectrum and by the ORD data for the corresponding 6-ketone (4b) obtained by CrO<sub>3</sub>-acetone oxidation of (4a). The ketone (4b), m.p. 108-109°, [ $\alpha$ ]<sub>D</sub> +81.5°,  $\nu_{\max}$  1734 (OAc) and 1704 cm<sup>-1</sup> (six membered ring carbonyl) gave a positive Cotton curve  $\underline{a} + 122$  (in MeOH), consistent with the structure (5). The NMR spectrum of (4b) exhibited a multiplet centred at 4.85 ppm ( $W\frac{1}{2}$  18 cps), 3 $\beta$ -H.

Elution with benzene gave an oil shown (TLC) to be a mixture which was separated by further chromatography into its components, the rearranged 8,14-olefin<sup>5</sup> (6a; 27%) as an oil and a second oil (4%) which was not examined further. The location of the double bond in (6a) at the 8,14-position followed from the physical data reported below. The presence of a tetrasubstituted double bond was indicated by a positive test with tetranitromethane, the lack of signals due to vinylic protons in the NMR spectrum and by the UV spectrum  $\epsilon_{207}$  12,900. The high value for the extinction coefficient for the end absorption in the UV spectrum strongly suggested<sup>6</sup> the presence of an 8,14-olefin system. This supposition was confirmed by ozonolysis of (6b), obtained by hydrolysis of (6a), which yielded the diol-diketone (7) as an oil,  $\nu_{\max}$  1750 (five membered ring carbonyl) and 1704 cm<sup>-1</sup> (six membered ring carbonyl). The 5 $\beta$ 10 $\alpha$ -nature of the A/B-ring

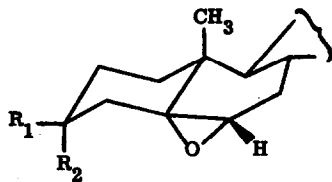
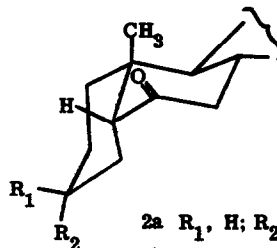
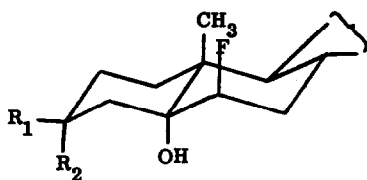
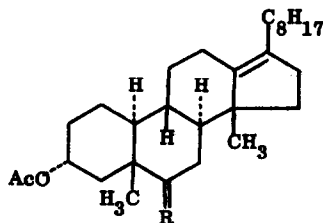
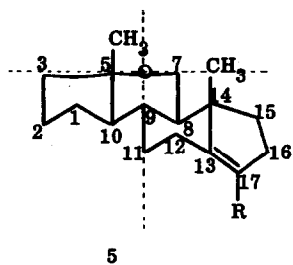
junction in (6a) was further confirmed by the NMR spectrum of (6a) which exhibited a broad multiplet (1H) centred at 5.30 ppm ( $W\frac{1}{2}$  20 cps), axial  $3\beta$ -H.

It is clear that not only does the reaction of the  $3\alpha$ -acetoxy- $5\alpha$ ,  $6\alpha$ -epoxide (1a) with  $\text{BF}_3$ -etherate proceed predominantly (81:8 of known products) by  $\text{C}_5$ -O cleavage but that also subsequent 19-methyl migration is preferred (64:17) to the alternative 6-hydride migration. This pattern of results may be rationalized on the basis of a tendency for the preferred  $\text{C}_5$ -O cleavage of the epoxide to be accompanied by conformational changes leading to a carbonium ion (8) in which ring B adopts a skew form. This mode of reaction allows for maximum orbital overlap between the orbitals of the departing epoxide oxygen atom and C-5, for eclipsing of the  $\text{C}_6$ -H bond and the 4,5-bond (a poor situation for the hydride migration), and for locating the 10,19 bond perpendicular to the plane of the C-5 carbonium ion, favourably disposed for a 1,2-shift of the angular methyl group. The relatively low yield (8%) of fluorohydrin from the  $3\alpha$ -acetate (1a) compared with the  $3\beta$ -epimer (1c) may be accounted for in terms of the dipole-dipole interaction between the  $\text{BF}_3$  coordinated axial  $3\alpha$ -acetate group and the  $5\alpha$ -O $^{\ominus}$ - $\text{BF}_3$  function during fluorohydrin formation from the  $3\alpha$ -acetate (1a); this feature does not arise in the  $3\beta$ -acetate (1c). It should be noted that  $\text{BF}_3$  coordination with the less basic ethylenedioxy ketal oxygen atoms (compared with the carbonyl oxygen atom of an acetate group) is more likely to occur at the less hindered  $3\beta$ -oxygen atom magnifying the  $3\beta$ -O rather than the  $3\alpha$ -O dipole and thus not opposing fluorohydrin formation by dipolar repulsion.

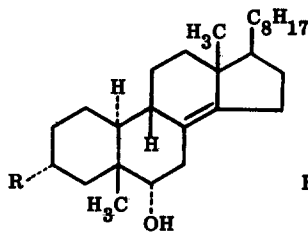
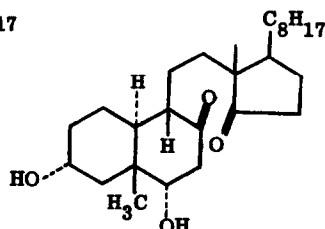
No evidence was obtained which would point to fluorohydrin intermediacy in the formation of the other products.

#### References

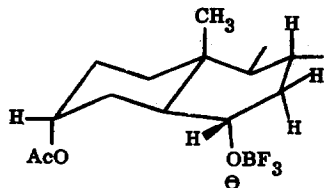
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4. J. W. Blunt, J. M. Coxon, M. P. Hartshorn and D. N. Kirk, Tetrahedron, 23, 1811 (1967); and references cited therein.
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1a  $R_1, H; R_2, OAc$ b  $R_1, R_2, H$ c  $R_1, OAc; R_2, H$ d  $R_1, R_2, \begin{matrix} \diagup O-CH_2 \\ \diagdown O-CH_2 \end{matrix}$ 2a  $R_1, H; R_2, OAc$ b  $R_1, R_2, H$ c  $R_1, OAc; R_2, H$ 3a  $R_1, H; R_2, OAc$ b  $R_1, OAc; R_2, H$ c  $R_1, R_2, \begin{matrix} \diagup O-CH_2 \\ \diagdown O-CH_2 \end{matrix}$ 4a  $R \alpha OH, \beta H$ b  $R = O$ 

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6a  $R, OAc$ b  $R, OH$ 

7



8