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REACTIONS OF EPOXIDES—IV[1]

THE REARRANGEMENTS OF 4α,5α- AND 4β,5β-EPOXY-4-METHYL-CHOLESTANES WITH BORON TRIFLUORIDE, AND A NOVEL KETONE REARRANGEMENT

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Abstract—4β,5β-Epoxy-4α-methylcholestane undergoes rearrangement with boron trifluoride to give mainly 5-methyl-5α-cholestan-4-one. Under similar conditions the 4α,5α-epoxide gives the 5β-methyl-A-nor-B-homo-6-ketone (VI), which rearranges on prolonged treatment with boron trifluoride to give 5-methyl-5β-cholestan-4-one.

IN ORDER to facilitate the interpretation of the complex reactions between 3-substituted 4,5-epoxy-4-methylcholestanes and boron trifluoride, described in Part I,[2] the 3-deoxy analogues (I and II) were prepared and their rearrangements studied.

Reduction of 4-methylcholest-4-en-3-one with sodium borohydride gave a mixture of the epimeric 3-alcohols. The mixture was acetylated, and the mixed acetates were reduced with lithium in ethylamine[3] to give 4-methylcholest-4-ene (III). The epoxidation of this olefin with monoperphthalic acid gave a mixture of the 4α,5α- and 4β,5β-epoxides in approximately 3:2 ratio. The epoxides, imperfectly separated by chromatography, were identified by comparison of their molecular rotations with those reported for 4α,5α- and 4β,5β-epoxy-cholestanes (Table 1). The assumption that the 4-methyl group would not alter significantly the optical rotations of the 4,5-epoxy compounds was confirmed by comparison of data for the isomeric 3-acetoxy-4,5-epoxycholestanes and their 4-methyl derivatives. The 4,5-epoxy-3-ketones, with and without the 4-methyl group, are anomalous in showing a reversal of the contribution of the epoxy group to the molecular rotation.

The rearrangement reactions were carried out in the usual way,[2] by the addition of boron trifluoride etherate to solutions of the epoxides in benzene. The rearrangement of the 4β,5β-epoxide (I) was straight-forward. Chromatography of the product from a 2 min reaction gave non-polar material (47%) of unknown composition, and 5-methyl-5α-cholestan-4-one (IV), together with a trace (6%) of 5β-acetyl-A-nor-cholestane (V). The structure of the 4-ketone (IV) was indicated by its IR absorption (ν_{max} 1708 cm^{-1}) and NMR spectrum, which revealed the presence of a CH_2 group (C-3) adjacent to the ketone (multiplet at ca. τ 7·65). The Cotton curve for the 4-ketone ($a = -18$) is in good agreement with the amplitude calculated from the value for 5α-cholestan-4-one ($a = -91$[4]) and the increment (Δa ca. $+67$[5]) for an axial

[1] Part III, J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Austral. J. Chem.* in press.
[2] Part I, J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* in press.
[3] A. S. Hallsworth, H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 1969 (1957).
[4] [a] C. Djerassi, W. Closson and A. E. Lippman, *J. Amer. Chem. Soc.* **75**, 3163 (1956); [b] C. Djerassi and W. Klyne, *J. Chem. Soc.* 2390 (1963).
[5] C. Beard, C. Djerassi, J. Sicher, F. Šipoš and M. Tichý, *Tetrahedron* **19**, 919 (1963).

methyl group in a positive octant. Confirmation of the structure (IV), including the configuration at C-5, was obtained by the preparation of an identical sample of the compound from 3α-acetoxy-5-methyl-5α-cholestan-4-one,[2] by reduction with calcium in liquid ammonia,[6] followed by re-oxidation of the resulting 4-hydroxy compound with chromic acid.

5β-Acetyl-A-nor-cholestane (V) was identified as a constituent of the first ketonic fractions obtained in the chromatography of the crude reaction product from the epoxide. Although the 5β-acetyl compound could not be obtained pure, its presence

TABLE 1. $[M]_D$ VALUES FOR 4,5-EPOXYCHOLESTANES AND 4,5-EPOXY-4-METHYLCHOLESTANES

Parent compound	$[M]_D$ values α-epoxide	β-epoxide	$\Delta[M]_D(\alpha-\beta)$
Cholest-4-ene	+310°[a]	+14°[b]	+296°
4-Methylcholest-4-ene	+288	+108	+180
3β-AcO-cholest-4-ene	+226,[c] +244[d]	−27[e]	+293, +271
3β-AcO-4-Me-cholest-4-ene	+335[f]	+73[f]	+272
3α-AcO-cholest-4-ene	+224[g]	+130,[h] −139[h]	+94, −85
3α-AcO-4-Me-cholest-4-ene	+258[f]	+53[f]	+205
Cholest-4-en-3-one	−175[d]	+496,[d] +540[h]	−671, −715
4-Methylcholest-4-en-3-one	−75[f]	+414[f]	−489

[a] P. A. Plattner, T. Petrzilka and W. Lang, *Helv. Chim. Acta* **27**, 513 (1944).
[b] C. W. Shoppee, M. E. H. Howden, R. W. Killick and G. H. R. Summers, *J. Chem. Soc.* 630 (1959).
[c] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.* 1958 (1957).
[d] D. J. Collins, *J. Chem. Soc.* 3919 (1959).
[e] Part II, J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* in press.
[f] Part I, J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* in press.
[g] P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta* **32**, 265 (1949).
[h] P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta* **31**, 1822 (1948).

in a mixture with the 5α-methyl-4-ketone was apparent from the NMR spectrum of the sample. This exhibited all the features of the spectrum of the 4-ketone, with additional peaks, especially one at τ 7·83, due to the 5β-acetyl compound. Integration of the main peaks in the spectrum indicated that the acetyl compound accounted for about one-third of the combined fractions in which it was found (28 mg), the remaining two-thirds being the 4-ketone. When the epoxide–boron trifluoride reaction was allowed to proceed for 6·5 hr there was a slight drop in the yield of ketones (IV and V), but without the appearance of any other recognizable product.

The behaviour of the 4α,5α-epoxide with boron trifluoride was quite unusual. A short reaction time led to the isolation (84% yield) of 5-methyl-A-nor-B-homo-5β-cholestan-6-one (VI), characterized by its IR absorption at 1694 cm^{-1},[7] and by the presence in the NMR spectrum of an indistinct multiplet (τ 7·58) due to two protons (7-CH_2) deshielded by the carbonyl group. However, when the reaction time was

[6] J. H. Chapman, J. Elks, G. H. Phillipps and L. J. Wyman, *J. Chem. Soc.* 4344 (1956).
[7] D. N. Kirk and V. Petrow, *J. Chem. Soc.* 4657 (1960).

extended to 56 hr, the product was separated chromatographically into a non-polar fraction (35%) lacking significant IR absorption, and a new ketone (42% yield). Thin layer chromatography showed that none of the original A-nor-B-homo-ketone was present. The new ketone was identified as 5-methyl-5β-cholestan-4-one (VII) from its IR absorption at 1704 cm^{-1}, and by comparison with an authentic sample prepared from 3β-acetoxy-5-methyl-5β-cholestan-4-one,[2] by reduction with calcium in liquid ammonia,[8] and re-oxidation of the resulting 4-hydroxy-compound with chromic acid. The NMR spectrum of the ketone (VII) showed the presence of a deshielded CH_2 group (multiplet, τ 7·68), and the Cotton curve ($a = -75$) had the sign and amplitude predicted from the value for 5β-cholestan-3-one ($a = -3$[4a]), modified by the presence of a methyl group (Δa ca. -67[5]) in the axial α-position in a negative octant. The rearrangement of the A-nor-B-homo-6-ketone under the influence of boron trifluoride was also demonstrated for a purified sample of the ketone, when the product was again a mixture of non-polar material and the 5β-methyl-4-ketone. An attempt to effect a similar rearrangement of 3β-acetoxy-5-methyl-A-nor-B-homo-5β-cholestan-6-one[2] gave no evidence of any reaction having occurred after 48 hr.

DISCUSSION

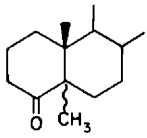
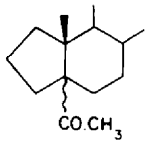
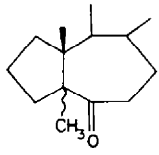
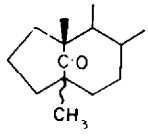
The rearrangements of 4α,5α- and 4β,5β-epoxycholestanes to give 5β- and 5α-cholestan-4-ones respectively are believed[8] to depend upon the facility of rupture of the epoxide linkage to the tertiary C-5 position. The introduction of a 4-methyl group into the epoxides removes this clear preference for cleavage of the epoxide at C-5, and offers a choice between four possible ketonic products, depending upon which of the four C—C bonds attached to C-4 and C-5 migrates during cleavage of the epoxide. The ketonic structures to be considered, together with the hypothetical routes for their formation are indicated in Table 2. The last structure shown in the Table is excluded for each of the ketones actually obtained, by the presence of low-field protons in the NMR spectra. The 5-acetyl-A-nor structure is easily distinguished from the other possible ketones by the characteristic IR and NMR spectral features of the $CO.CH_3$ group. The 5-methyl-4-ketones and 5-methyl-A-nor-B-homo-6-ketones each have a CH_2 group adjacent to the ketonic function, making a structural assignment uncertain on the basis of NMR spectra alone. However, the abnormally low carbonyl stretching frequency of a seven-membered ring ketone[7] allows a distinction to be made. The configurations assigned at C-5 in the ketonic products are in each case based upon the assumption that the migrating C—C bond attacks the site of epoxide cleavage on the side away from the oxygen atom, probably as a concerted process. Although there seems to be no reason for doubting the validity of this assumption in the present instances, it will be shown in the following paper[9] that an exception can arise under special circumstances.

The rearrangement of the A-nor-B-homo-6-ketone (VI) to give the 5β-methyl-4-ketone (VII) seems to be a reaction without precedent in the chemistry of cyclic ketones.

However, a series of acyclic ketones, highly branched at the α,α'-carbon atoms, has been shown[10] to undergo skeletal rearrangement in the presence of concentrated

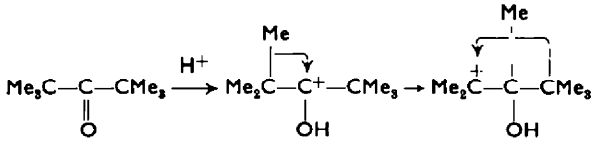
[8] H. B. Henbest and T. I. Wilson, *J. Chem. Soc.* 4596 (1962).
[9] J. W. Blunt, M. P. Hartshorn and D. N. Kirk, Part V, to be published.
[10] S. Barton and C. R. Porter, *J. Chem. Soc.* 2483 (1956).

TABLE 2. POSSIBLE KETONIC PRODUCTS FROM REARRANGEMENTS OF 4,5-EPOXY-4-METHYL CHOLESTANES

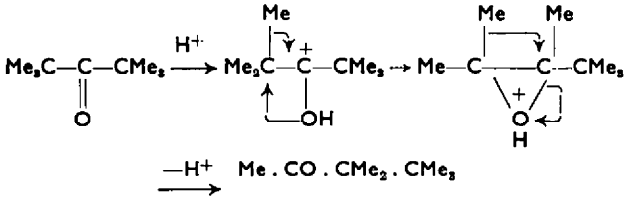
Position of epoxide cleavage	Migrating group	Hypothetical product
C-5	4-CH_3	
C-5	C-3	
C-4	C-10	
C-4	C-6	

sulphuric acid or zinc chloride. Using radio-tracer methods it was shown[10] that the rearrangement of di-t-butyl-ketone (C^{14}:O labelled) using concentrated sulphuric acid gave 3,3,4,4-tetramethylpentan-2-one still labelled at the carbonyl carbon atom. The authors used this evidence to support mechanism (a) and exclude mechanism (b) for this reaction.

(a)

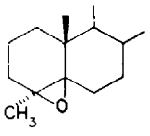


(b)

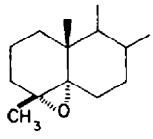


In the present work no decision is possible concerning the reaction path, and examination of Dreiding models shows that both mechanisms (c) and (d) are feasible.

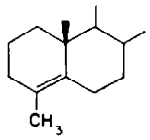
We interpret the initial formation of the A-nor-B-homo-ketone as the result of a



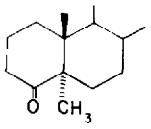
I



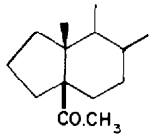
II



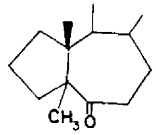
III



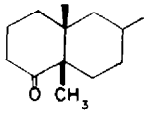
IV



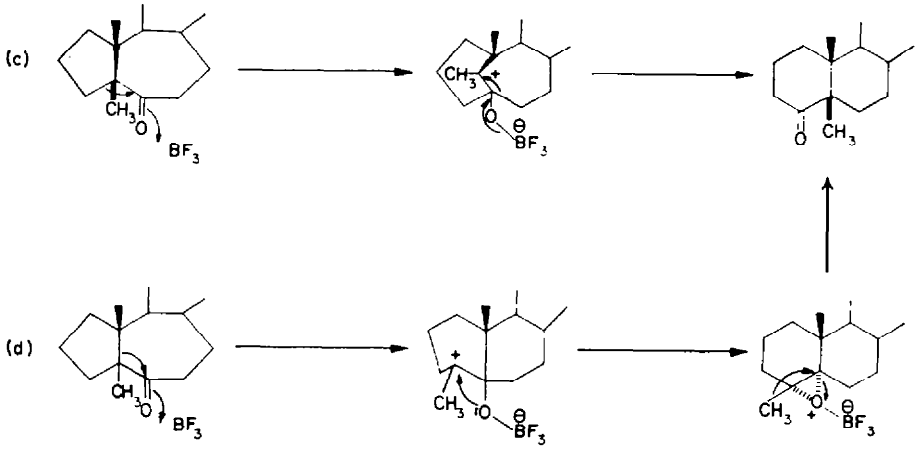
V



VI



VII



kinetic preference for cleavage of the epoxide C-4, with migration of the C_{10}—C_5 bond. It is apparent, however, from an inspection of a Dreiding model of the A-nor-B-homo-ketone, that even in its most favourable conformations the molecule is destabilized by a number of non-bonded and "partially-eclipsed ethane" type interactions[11] in the rings A and B, as well as the near-eclipsed butane-like interaction[11]

[11] E. L. Eliel, *Stereochemistry of carbon compounds* p. 124. McGraw-Hill, New York (1962).

of the *cis*-methyl groups at the ring junction. By comparison it appears that the unfavourable interactions in the 5β-methyl-4-ketone (VII) amount to a considerably smaller total. The difference cannot be evaluated with any precision but seems unlikely to be less than 2 kcal mol^{-1}. It is clear that the isomerization (VI → VII) *must* occur to give the thermodynamically favoured product *if* a mechanism is available. The slow rate observed for this isomerization, compared with the rapid initial formation of the ketone (VI), indicates that the activation energy for the isomerization is relatively high. The failure of the 3β-acetoxy-A-nor-B-homo-6-ketone to undergo isomerization with boron trifluoride can be explained as a result of the −I effect of the acetoxy group, which would be unfavourable to the generation of the neighbouring positive charge required in the transition state.

EXPERIMENTAL

Rotations were measured at room temp for $CHCl_3$ solutions unless otherwise stated. IR spectra, for dilute solutions in CCl_4, were recorded on a Perkin Elmer 421 grating spectrometer calibrated against water-vapour lines in the region 1770–1670 cm^{-1}. Alumina used for chromatography was Spence, Grade H. "Deactivated alumina" refers to Grade H deactivated by the addition of 5% of 10% acetic acid. Light petroleum refers to the fraction of b.p. 50–70°. Boron trifluoride diethyl etherate was freshly distilled before use. O.R.D. curves (in methanol) were kindly determined by Professor W. Klyne.

4-*Methylcholest*-4-*ene* (III)

4-Methylcholest-4-en-3-one (9·5 g) in methanol (500 ml) was heated under reflux for 4 hr with NaOH (2·5 g) and $NaBH_4$ (2·5 g) in water (4·2 ml) and methanol (100 ml). The solution was concentrated (red. press.), diluted with water, and the 3-hydroxy- compounds isolated with the use of ether. The crude product was treated with pyridine (50 ml) and acetic anhydride (20 ml) at 20° for 18 hr, and the crude acetates isolated by use of ether.

The crude acetates (9·5 g) in tetrahydrofuran (50 ml) and ethylamine (100 ml) was stirred and treated with pieces of Li until a permanent blue colour appeared. Solid NH_4Cl was added to destroy the excess Li, and the product was isolated by use of ether. The crude material was dissolved in light petroleum and passed through alumina (100 g), to give 4-*methylcholest*-4-*ene* (5 g) m.p. 62–63° (from ethanol) $[\alpha]_D$ +13° (*c* 1·12), no specific IR absorption. (Found: C, 87·0; H, 12·6. $C_{28}H_{48}$ requires: C, 87·4; H, 12·6%).

Epoxidation of 4-*methylcholest*-4-*ene*

The olefin (3·453 g) was treated with ethereal monoperphthalic acid (ca. 2 moles) at 20° for 12 hr. The solution was then washed with Na_2CO_3 aq and water, and the ether evaporated. The mixture of epoxides was adsorbed onto deactivated alumina (200 g), and eluted with light petroleum. The 4α,5α-*epoxide*, which was eluted first (1·563 g) was a solid, m.p. 104·5–105°, $[\alpha]_D$ +72° (*c* 1·00, dioxan). (Found: C, 83·9; H, 12·4. $C_{28}H_{48}O$ requires: C, 83·9; H, 12·1%).

A mixture of the α- and β-epoxides (574 mg) was eluted next, and was followed by the 4β,5β-*epoxide* (910 mg), which was a waxy solid, m.p. 40–42°, $[\alpha]_D$ +27° (*c* 0·98, dioxan). (Found: C, 84·3; H, 12·1. $C_{28}H_{48}O$ requires: C, 83·9; H, 12·1%).

Final fractions gave a further 327 mg of impure β-epoxide.

Rearrangement of the 4β,5β-*epoxide* (I)

A solution of the β-epoxide (135 mg) in anhydrous benzene (2 ml) was treated with BF_3–etherate (0·13 ml) for 2 min, then the solution was diluted with ether and washed with $NaHCO_3$ aq. Evaporation of the solvents left an oily residue which was adsorbed onto alumina (10 g). Elution with light petroleum gave a non-polar oil (63 mg) having no significant IR absorption. A ketonic fraction (28 mg) eluted by light petroleum–benzene (10:1) solidified but could not be crystallized from a solvent. It had ν_{max} ca. 1700 cm^{-1}, and was shown from its NMR spectrum to be a mixture of 5-acetyl-A-nor-5β-cholestane and 5-methyl-5α-cholestan-4-one. Continued elution with the same

solvent gave *5-methyl-5α-cholestan-4-one*, (36 mg) m.p. 132–133° (needles from methanol), $[\alpha]_D$ +63° (*c* 0·47), ν_{max} 1708 cm^{-1}. O.R.D. $[\phi]_{300}$ +965° (tr.), $[\phi]_{270}$ +2750° (infl.), $[\phi]_{256}$ +3290°! (Found: C, 84·0; H, 12·4. $C_{28}H_{48}O$ requires: C, 83·9; H, 12·1%).

Reduction of 3α-acetoxy-5-methyl-5α-cholestan-4-one

The acetoxy-ketone (35 mg) in anhydrous toluene (5 ml) was added to a solution of Ca (50 mg) in liquid ammonia (10 ml). The mixture was stirred vigorously for 20 min, then treated with solid NH_4Cl to destroy the excess Ca. The ammonia was allowed to evaporate, and the product was isolated by use of ether. The resulting crude solid 4-hydroxy- compound was oxidized in acetone solution with 8 N chromic acid. Dilution with water gave the 5α-methyl-4-ketone (22 mg), m.p. and m.m.p. 132–133°.

Rearrangement of the 4α,5α-epoxide (II)

(a) The epoxide (506 mg) in anhydrous benzene (5 ml) was treated with BF_3–etherate (0·5 ml) for 2 min. The product, isolated as above by use of ether, crystallized from methanol–ether to give *5-methyl-A-nor-B-homo-5β-cholestan-6-one* (420 mg) as needles m.p. 71–72°, $[\alpha]_D$ +31° (*c* 1·00), ν_{max} 1694 cm^{-1}. O.R.D. $[\phi]_{400}$ +350°, $[\phi]_{297}$ +1320, $[\phi]_{264}$ −230°, $[\phi]_{228}$ +855°! (Found: C, 84·3; H, 12·3. $C_{28}H_{48}O$ requires: C, 83·9; H, 12·1%).

(b) A reaction mixture of similar composition (525 mg epoxide) to that under (a) was left at room temp for 56 hr, and became deep purple. The product, isolated by use of ether, was adsorbed from light petroleum onto alumina (50 g). Elution with light petroleum gave an oil (185 mg) having no significant IR absorption. Light petroleum–benzene (10:1) eluted *5-methyl-5β-cholestan-4-one* (220 mg), m.p. 107–108° (plates from methanol–ether), $[\alpha]_D$ −12° (*c* 0·83), ν_{max} 1704 cm^{-1}. O.R.D. $[\phi]_{400}$ −220°, $[\phi]_{313}$ −3040°, $[\phi]_{272}$ +4440°, $[\phi]_{249}$ +3690°. (Found: C, 84·3; H, 12·1. $C_{28}H_{48}O$ requires: C, 83·9; H, 12·1%).

Rearrangement of the 5β-methyl-A-nor-B-homo-6-ketone (VI) *with boron trifluoride*

A solution of the ketone (50 mg) and BF_3–etherate (0·05 ml) in benzene was left at room temp for 56 hr. The product was 5-methyl-5β-cholestan-4-one (22 mg), m.p. 107–108°.

Reduction of 3β-acetoxy-5-methyl-5β-cholestan-4-one

The acetoxy-ketone (30 mg) was reduced with Ca in liquid ammonia as described (above) for the 3α,5α-epimer. Oxidation of the product with chromic acid in acetone gave the 5β-methyl-4-ketone (18 mg) m.p. and m.m.p. 107–108°.

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