Tetrahedron. Vol. 26, pp. 1091 to 1094. Pergamon Press 1970. Printed in Great Britain

REACTIONS OF EPOXIDES—XXVI

THE BF_3-CATALYSED REARRANGEMENT OF 5,6α-EPOXY-6β-PHENYL-5α-CHOLESTANE AND A NOVEL KETONE REARRANGEMENT

J. N. Coxon, M. P. Hartshorn and W. J. Rae

Department of Chemistry, University of Canterbury, Christchurch, New Zealand

(*Received in the UK* 20 *October* 1969; *Accepted for publication* 28 *October* 1969)

Abstract—Brief reaction of 5α,6-epoxy-6β-phenyl-5α-cholestane (1) with BF_3-etherate in benzene gives the corresponding A-homo-B-nor-4a-ketone (5), which rearranges on long term reaction to give the 4(5 → 6) *abeo*-5-ketone (6a).

During other studies we had occasion to prepare and examine the reactions of the 6β-phenyl-5α, 6α-epoxide (1). Reaction of 5α-cholestan-6-one with PhMgBr gave the expected 6β-hydroxy compound (2) which on acid catalysed dehydration afforded 6-phenylcholest-5-ene (3). Treatment of the olefin (3) with monoperoxyphthalic acid in ether gave a mixture (ca. 3:1) of the epimeric epoxides which on careful chromatography yielded the pure 5α,6α-epoxide (1) and a sample of the 5β,6β-epoxide (4). The α-configuration was assigned to that epoxide formed in higher yield by analogy with the established[1] stereochemistry of reaction of 6-methylcholest-5-ene with peracids.

Brief treatment (10 sec) of the 6β-phenyl-5α,6α-epoxide (1) with BF_3-etherate in benzene solution gave a high yield (~95%) of the A-homo-B-nor-5β-phenylcholestan-4a-one (5). This structure (5) is assigned to the product as a result of the consideration of spectroscopic and CD data and by analogy with the rearrangement[2] of the 6β-methyl-5α, 6α-epoxide.

Longer term treatment (~1 hr) of either the epoxide (1) or the A-homo-B-nor ketone (5) with BF_3-etherate in benzene solution gave, in addition to some hydrocarbon (~9%), a further ketone (89%) to which structure (**6a***; cf Ref. 2) is assigned on the basis of the following evidence.

The infrared spectrum of **6a** exhibits a band at 1708 cm^{-1}, consistent with the presence of a 6-membered ring carbonyl function. In addition the NMR spectrum of **6a** lacked signals corresponding to protons adjacent to a CO group. The absence of protons on the ring positions immediately adjacent to the keto-group was confirmed by the presence of a sharp singlet ($W_{h/2} = 2{\cdot}4$ cs), assigned to the $>C\underline{\underline{H}}OH$ proton, in the NMR spectrum of the alcohol (**6b**) produced by $LiAlH_4$ reduction of ketone (**6a**). The 6β-phenyl configuration is assigned in part on reaction mechanistic grounds but supported by a consideration of the relative energies of the A-homo-4a-ketone (5), the

---

Part XXV. J. M. Coxon, M. P. Hartshorn and B. L. S. Sutherland, *Tetrahedron Letters* 4029 (1969).

[*] The product of long-term reaction of 5,6α-epoxy-6β-methyl-5α-cholestane with BF_3-etherate in benzene, previously assigned[1] the 5-methyl-5β-cholestan-6-one structure is now believed to be the 4(5 → 6) *abeo*-ketone (cf **6a**) (M. P. Hartshorn, D. N. Kirk and I. R. McDonald, *to be published*).

6β-phenyl-5-ketone (**6a**) and the 6α-phenyl-5-ketone (**8**). Since the ketone formed in the long-term reaction of epoxide (**1**) may be considered to be the product of thermodynamic control, the extremely highly strained 6α-phenyl-5-ketone (**8**) structure may be excluded.

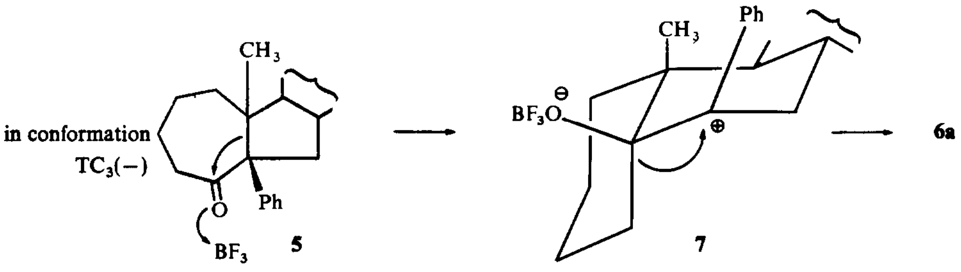
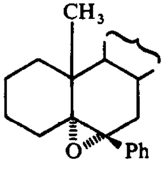
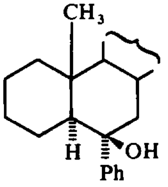


FIG. 1.

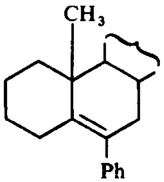
The formation of the 6β-phenyl-5-ketone (**6a**) from the A-homo-B-nor-4a-ketone (**5**) may be rationalised as shown in Fig. 1. The 5β-orientation in the intermediate (**7**) arises as a consequence of the reaction of the ketone (**5**) with ring A in the TC$_3$(−) conformation, one of the two preferred conformations.[3] Reaction of ketone (**5**) with ring A in the other energetically preferred conformation, TC$_3$(+), would give rise



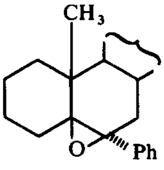
1



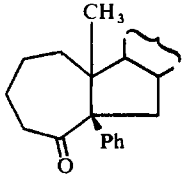
2



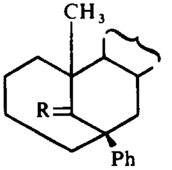
3



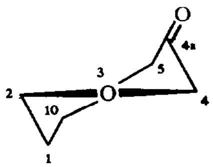
4



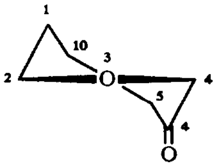
5



6 a: R = O
b: R = H, OH



TC$_3$(−)



TC$_3$(+)

(Fig. 2) to structure **9** as an intermediate. This structure **9** represents the species formed simply by C_6-O heterolysis of the BF_3-coordinated epoxide (**1**). Since the rearrangement (Fig. 2) of structure **9** would, if it occurred, yield the 6α-phenyl-5-ketone (**8**), the mechanism (Fig. 1) of formation of ketone (**6a**) appears secure.

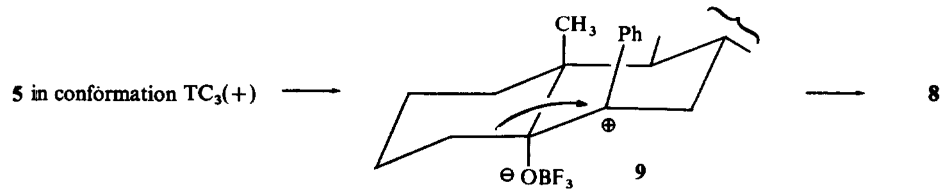


FIG. 2.

EXPERIMENTAL

Rotations were measured for $CHCl_3$ solns at 20°. NMR spectra were determined at 60 Mc in ~10% w/v $CDCl_3$ with $CHCl_3$ and TMS as internal standards. Alumina was P. Spence, Grade H; "deactivated alumina" is Grade H alumina to which 5% of 10% acetic acid has been added. Silica gel used for chromatography was Crosfield Sorbsil grade 60–120. BF_3-etherate was B.D.H. freshly redistilled before use. Light petroleum refers to the fraction b.p. 50–70°.

6α-Phenylcholestan-6β-ol (2)

A soln of cholestan-6-one (9·4 g) in ether was added with stirring over 30 min to an ethereal soln of PhMgBr (90 ml; 1·5M), and the mixture heated under reflux for 12 hr. The steroidal material, isolated by means of ether, was adsorbed onto deactivated alumina. Elution with light petroleum gave diphenyl. Further elution with light petroleum–benzene (3:1) gave the *alcohol* (**2**; 7·5 g) (needles from methanol), m.p. 104–105°, $[\alpha]_D$ −3° (*c* 1·44), ν_{max} (nujol) 3594 cm^{-1}, NMR δ 1·14 ppm ($C^{19}H_3$); 0·72 ppm ($C^{18}H_3$); 0·92, 0·82 ppm (side-chain CH_3). (Found: C, 85·3; H, 11·7. $C_{33}H_{52}O$ requires: C, 85·3; H, 11·3%).

6-Phenylcholest-5-ene (3)

To a soln of **2** (10 g) in dioxan (120 ml) was added perchloric acid (0·4 ml; 60% w/w) and the mixture heated under reflux for 30 min. Isolation by means of ether and crystallization (acetone) gave the *olefin* (**3**; 9 g) as prisms, m.p. 95–96°, $[\alpha]_D$ −81° (*c* 1·24), λ_{max} 244 nm (ε 4250), NMR δ 1·09 ppm ($C^{19}H_3$); 0·72 ppm ($C^{18}H_3$); 0·92, 0·82 ppm (side-chain CH_3). (Found: C, 88·7; H, 11·5. $C_{33}H_{50}$ requires: C, 88·7; H, 11·3%).

Epoxidation of 6-phenylcholest-5-ene (3)

To a soln of **3** (7 g) in ether (100 ml) was added monoperoxyphthalic acid (500 ml; 0·25M) and the soln kept at 20° for 7 days. The steroidal material, isolated by means of ether, was adsorbed onto silica gel (400 g). Elution with pentane gave the *α-epoxide* (**1**; 1 g) as needles (acetone), m.p. 108–109°, $[\alpha]_D$ −12° (*c* 0·92), NMR δ 1·14 ppm ($C^{19}H_3$); 0·65 ppm ($C^{18}H_3$); 0·92, 0·82 ppm (side-chain CH_3). (Found: C, 85·7; H, 10·7. $C_{33}H_{50}O$ requires: C, 85·6; H, 10·9%).

Further elution with pentane gave mixed epoxide fractions (*ca.* 5·5 g) followed by the *β-epoxide* (**4**; 100 mg) as needles (acetone), m.p. 120–121°, $[\alpha]_D$ −25° (*c* 0·70), NMR δ 1·08 ppm ($C^{19}H_3$); 0·68 ppm ($C^{18}H_3$); 0·92, 0·82 ppm (side-chain CH_3). (Found: C, 85·8; H, 10·9. $C_{33}H_{50}O$ requires: C, 85·6; H, 10·9%).

BF_3-*Catalysed rearrangement of epoxide* (1)

(a) *Short term reaction.* A soln of **1** (200 mg) in benzene (20 ml) was treated with BF_3-etherate (0·2 ml) and the soln kept at 20° for 10 sec. The reaction was quenched with $NaHCO_3$ aq. The steroidal material, isolated by means of ether, was an oil (198 mg) pure by TLC identified as the A-*homo*-B-*nor*-4a-*ketone* (**5**), $[\alpha]_D$ 0° (*c* 1·23), ν_{max} (film) 1694 cm^{-1}; NMR δ 2·66 ppm ($C^4\underline{H}_2$); 0·92, 0·82 ppm (side-chain CH_3); 0·67 ppm ($C^{18}H_3$); 0·62 ppm ($C^{19}H_3$); CD: λ_{309} Δε −1·74; λ_{273} Δε +0·312; λ_{265} Δε +0·338; λ_{259} Δε +0·234; λ_{230} Δε +0·78; λ_{218} Δε +0·390; λ_{204} Δε +0·580; M^+ 462·3865, $C_{33}H_{50}O$ requires: 462·3861.

(b) *Long term reaction.* A soln of **1** (1·4 g) in benzene (140 ml) was treated with BF_3-etherate (1·4 ml) and the soln kept at 20° for 1 hr. The reaction was quenched with $NaHCO_3$ aq, and the steroidal material, isolated by means of ether, adsorbed onto alumina (100 g). Elution with light petroleum gave hydrocarbon (120 mg), λ_{max} 232·5 nm (ε 11,200), λ_{max} 245 nm (ε 11,300).

Elution with benzene gave the *rearranged ketone* (**6a**; 1·25 g) as needles (MeOH), m.p. 89–91°, $[\alpha]_D$ −8° (*c* 1·29), ν_{max} (nujol) 1708 cm^{-1}; NMR δ 1·13 ppm ($C^{19}H_3$); 0·67 ppm ($C^{18}H_3$); 0·92, 0·82 ppm (side-chain Me); CD: λ_{300} $\Delta\varepsilon$ −0·352; λ_{268} $\Delta\varepsilon$ −0·0813; λ_{262} $\Delta\varepsilon$ −0·108; λ_{254} $\Delta\varepsilon$ −0·068; λ_{210} $\Delta\varepsilon$ −5·08. (Found: C, 85·7; H, 11·2. $C_{33}H_{50}O$ requires: C, 85·6; H, 10·9%).

Reduction of ketone (**6a**)

LAH (100 mg) was added to a soln of **6a** (200 mg) in ether (20 ml) and the mixture heated under reflux for 2 hr. The product, isolated by means of ether, was an oil (190 mg; pure by TLC), $[\alpha]_D$ +5° (*c* 0·96), ν_{max} (film) 3600, 3560 cm^{-1}; NMR δ 3·70 ppm ($W_{h/2}$ 2·4 cs; $C^5\underline{\underline{H}}OH$), 0·98 ppm ($C^{19}H_3$), 0·71 ppm ($C^{18}H_3$), 0·92, 0·82 ppm (side-chain Me). (Found: C, 83·6; H, 11·2. $C_{33}H_{52}O \cdot \frac{1}{2} H_2O$ requires: C, 83·5; H, 11·2%); M^+ 464·3938 ($C_{33}H_{52}O$ requires: 464·4018).

Acknowledgements—Grants from the Research Committee of the New Zealand Universities Grants Committee are acknowledged. We are grateful to Professor W. Klyne for CD spectra, and Dr. G. J. Wright for accurate mass determinations.

REFERENCES

[1] J. W. Blunt, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* **21**, 559 (1965).

[2] D. J. Collins, J. J. Hobbs and R. J. Rawson, *Chemical Commun.* 135 (1967); *Austral. J. Chem.* **22**, 807 (1969).

[3] J. B. Jones, J. M. Zander and P. Price, *J. Am. Chem. Soc.* **89**, 94 (1967).