Stereochemistry of Epoxidation of Cholest-5-en-3-one and of the Base-catalysed Rearrangement of the Derived Epoxides

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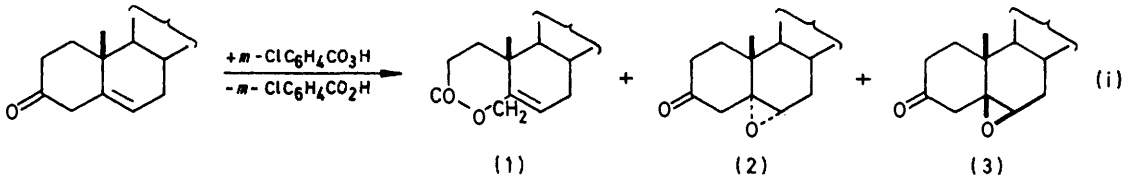
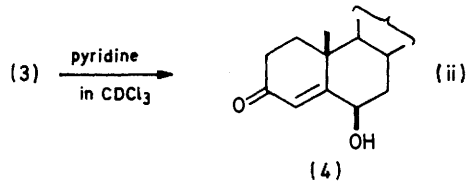
The epoxidation of cholest-5-en-3-one by *m*-chloroperbenzoic acid in deuteriochloroform and in benzene has been investigated by ^{1}H n.m.r. spectroscopy. The product mixtures contain 3,4-secocholest-5-eno-3,4-lactone and the α-epoxide, both recognised by previous workers; the β-epoxide accompanies them, the α : β ratio being *ca.* 2 : 1 in both solvents. Both α- and β-epoxides undergo smooth rearrangement when treated with pyridine in deuteriochloroform, and give the expected 6-hydroxycholest-4-en-3-one. By this treatment the mixed products of epoxidation of 4β-deuteriocholest-5-en-3-one lose exclusively (within experimental error) the 4α-hydrogen atom. The epoxidation of some 3α- and 3β-substituted cholest-5-enes under the same conditions was also carried out to monitor our experimental procedures.

ALTHOUGH there has been much investigation of electrophilic additions to cholest-5-enes and their analogues,[1] the factors that influence the observed orientation and stereochemistry are still not thoroughly understood. Attack by bromine chloride on 3β-substituted cholest-5-enes is known to give nearly exclusively the product formed by initial electrophilic attachment to the α-face of the molecule.[2] Recently, however, we obtained indications that the structurally closely related cholest-5-en-3-one may be attacked by bromine in part on the β-face.[3]

In halogenations, completion of addition to the double bond requires attack also by a nucleophile, which can be supplied separately, either on the same or on the opposite face of the double bond. Epoxidation by peroxy-acids resembles halogenation in having a transition state with substantial carbocationic character;[4,5] but completion of the reaction requires ring closure to give a stable product of *syn*-addition. The stereochemistry of epoxidation of cholest-5-en-3-one was therefore of interest. Its reaction with peroxy-acids in aprotic solvents is known [6] to give 3,4-secocholest-5-eno-3,4-lactone (1), by Baeyer–Villiger oxidation of the carbonyl group, together with the 5α,6α-epoxide (2). By using a method of analysis by ^{1}H n.m.r. spectroscopy similar to that used by Bingham *et al.*[7] for the corresponding 3β- and 3α-substituted cholest-5-enes, we have now shown that the product also includes as a substantial component the 5β,6β-epoxide (3) [reaction (i)], which has been characterised also by its base-catalysed conversion into 6β-hydroxycholest-4-en-3-one (4) [reaction (ii)]. Although a number of analogues of this rearrangement are known,[8,9] its stereochemistry in our example has some unusual features.





EXPERIMENTAL

(a) *Materials and Methods.*—Some of the materials and methods, including the properties of the 4-deuteriated cholest-5-en-3-ones, have been described earlier.[3,10] The methods used to prepare and characterise other known compounds are given in Supplementary Publication No. SUP 21996 (34 pp., 1 microfiche),† which also includes examples of typical ^{1}H n.m.r. spectra.

(b) *Reactions of 5α,6α-Epoxycholestan-3-one.*—This compound underwent the expected ring openings. Thus the epoxide (0.3 g) in acetone (10 cm^3) was treated with hydrogen bromide (45% w/v) in acetic acid (0.2 cm^3). After 10 min the product was filtered off; the resulting *6β-bromo-5α-hydroxycholestan-3-one* after being washed with acetone and dried *in vacuo* had m.p. 178—179° (Found: C, 67.4; H, 9.1; Br, 16.6. $C_{27}H_{45}BrO_2$ requires C, 67.3; H, 9.4; Br, 16.6%),

† For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin II*, 1976, Index issue.

[1] *Cf.* D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968.

[2] D. H. R. Barton, E. Miller, and H. T. Young, *J. Chem. Soc.*, 1951, 2598; J. B. Ziegler and A. C. Shabica, *J. Amer. Chem. Soc.*, 1952, **74**, 4891.

[3] P. B. D. de la Mare and R. D. Wilson, *Tetrahedron Letters*, 1975, 3247.

[4] D. Swern, *Org. Reactions*, 1953, **7**, 378; H. B. Henbest, Chem. Soc. Special Publ. No. 19, 1965, p. 83.

[5] R. P. Hanzlik and G. O. Shearer, *J. Amer. Chem. Soc.*, 1975, **97**, 5231.

[6] S. Mori and F. Mukawa, *Proc. Japan Acad.*, 1955, **31**, 532.

[7] K. D. Bingham, T. M. Blaiklock, R. C. B. Coleman, and G. D. Meakins, *J. Chem. Soc.* (*C*), 1970, 2330.

[8] L. J. Haynes, Sir Ian Heilbron, E. R. H. Jones, and F. Sondheimer, *J. Chem. Soc.*, 1947, 1583.

[9] A. C. Cope and J. K. Heeren, *J. Amer. Chem. Soc.*, 1965, **87**, 3125.

[10] P. B. D. de la Mare and R. D. Wilson, *J.C.S. Perkin II*, 1977, 157.

δ($CDCl_3$) 0.76 (3 H, s, 18-H_3), 1.55 (3 H, s, 19-H_3), 1.6 (1 H, s, OH), 2.17 (1 H, d, $J_{4\alpha,4\beta}$ 16 Hz, $W_{\frac{1}{2}}$ 2.6 Hz, 4α-H), 3.52 (1 H, d, $J_{4\alpha,4\beta}$ 16 Hz, $W_{\frac{1}{2}}$ 1.6 Hz, 4β-H), and 4.00 (1 H, m, $W_{\frac{1}{2}}$ 7 Hz, 6α-H).

Similarly the epoxide (0.05 g) in deuteriochloroform (0.3 cm^3) was treated with pyridine (0.2 cm^3) for 14 days. The solvent and pyridine were removed *in vacuo*; the ^1H n.m.r. spectrum ($CDCl_3$) of the product was the same as that of 6α-hydroxycholest-4-en-3-one,[10] and no signals attributable to the isomer [10] were detected.

(c) *Products of Epoxidation of 3-Substituted Cholest-5-enes.*—Bingham *et al.*[7] have established a method suitable for determining ratios of α- to β-epoxidation of 3-substituted cholest-5-enes, and have examined the influence of structure and of solvent on this ratio for several peroxy-acids. We have extended their measurements for some reference compounds by using *m*-chloroperbenzoic acid, wishing to establish our modification of their method of analysis. We have confirmed that the signals for the 5α,6α- and 5β,6β-epoxides appear as doublets centred, respectively, at δ *ca.* 3 (*J ca.* 3.5 Hz, 6β-H) and 3.2 (*J ca.* 2 Hz, 6α-H), clearly resolved from other signals. The results are given in Table 1; agreement between the two sets of results is quite good.

TABLE 1

Proportions of α-epoxide in product of epoxidation of cholest-5-ene and some of its 3-substituted derivatives with perbenzoic acid and its derivatives

3-Substituent	Peroxy-acid	Solvent	Proportion of 5α,6α-epoxide	Ref.
H	$PhCO_3H$	$CHCl_3$	0.72	7
H	*m*-$ClC_6H_4{\cdot}CO_3H$	$CDCl_3$	0.66	This paper
H	*m*-$ClC_6H_4{\cdot}CO_3H$	C_6D_6	0.70	This paper
H	*p*-$NO_2{\cdot}C_6H_4{\cdot}CO_3H$	C_6H_6	0.80	7
α-MeO	*m*-$ClC_6H_4{\cdot}CO_3H$	$CDCl_3$	0.56	This paper
α-MeO	*m*-$ClC_6H_4{\cdot}CO_3H$	C_6D_6	0.55	This paper
β-MeO	$PhCO_3H$	C_6H_6	0.74	7
β-MeO	*m*-$ClC_6H_4{\cdot}CO_3H$	$CDCl_3$	0.82	This paper
β-MeO	*m*-$ClC_6H_4{\cdot}CO_3H$	C_6D_6	0.82	This paper
α-$PhCO_2$	*m*-$ClC_6H_4{\cdot}CO_3H$	$CDCl_3$	0.46	This paper
α-$PhCO_2$	*m*-$ClC_6H_4{\cdot}CO_3H$	C_6D_6	0.48	This paper
β-$PhCO_2$	*m*-$ClC_6H_4{\cdot}CO_3H$	$CDCl_3$	0.67	This paper
β-$PhCO_2$	*m*-$ClC_6H_4{\cdot}CO_3H$	C_6D_6	0.68	This paper
β-*p*-$NO_2{\cdot}C_6H_4{\cdot}CO_2$	$PhCO_3H$	$CHCl_3$	0.69	7
β-3,5-$(NO_2)_2C_6H_3{\cdot}CO_2$	$PhCO_3H$	$CHCl_3$	0.77	7

(d) *Products of Epoxidation of Cholest-5-en-3-one.*—Analyses of the reaction mixtures from the epoxidation of cholest-5-en-3-one followed the same general method as was applied to the products from the cholest-5-enes, but were a little more complicated. The signals from the product (1) of Baeyer–Villiger oxidation were readily recognisable: δ 4.07 (1 H, d, $J_{4\alpha,4\beta}$ 14 Hz, $W_{\frac{1}{2}}$ 2 Hz, 4α-H), 4.60 (1 H, d, $J_{4\alpha,4\beta}$ 14 Hz, $W_{\frac{1}{2}}$ 4 Hz, 4β-H), and 5.70 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, vinyl 6-H). The ^1H n.m.r. spectrum of 5α,6α-epoxycholestan-3-one has already been described; the doublet for which its 4β-H was responsible lay under one of the signals from the 6α-H of the 5β,6β-epoxide. When allowance was made for this, the presence of 5β,6β-epoxycholestan-3-one was evident in the reaction mixtures from epoxidation in $CDCl_3$ or in C_6D_6; its ^1H n.m.r. spectrum included a doublet, δ 2.94 (1 H, *J* 16 Hz, $W_{\frac{1}{2}}$ *ca.* 2 Hz, 4β-H), resembling the corresponding doublets in the ^1H n.m.r. spectra of the epoxides derived from 3-substituted cholest-5-enes already described; and a doublet at δ 3.0 (1 H, *J ca.* 2 Hz, 6α-H): The product proportions derived from the ^1H n.m.r. spectra of the reaction mixtures are given in Table 2.

The assignments of the signals in the ^1H n.m.r. spectra of these epoxides are confirmed by the spectra of the products of epoxidation of 4β-deuteriocholest-5-en-3-one; details are given in the Supplementary Publication. Furthermore, they confirm that the ground states of these epoxides have ring A in the chair form. Thus the signals for the axial 4β-protons, as compared with those for the equatorial 4α-protons, are both expected and found to be more strongly shifted downfield by the adjacent carbonyl group,[11] so that their signals occur in the same region as those of the 6-proton. Similarly, in the 5α,6α-epoxide the signal for the 4α-proton is both expected and found to be relatively broad, owing to long-range coupling with the 2α-proton signal.

The identification of the signals was further confirmed by examining the products of base-catalysed rearrangement of the epoxide mixtures. Cholest-5-en-3-one (5×10^{-4} mol) was treated with *m*-chloroperbenzoic acid (5.5×10^{-4} mol) in $CDCl_3$ (2 ml) for 11 h at *ca.* 20 °C, and then the solvent was removed *in vacuo*. To the residue were added 2,4-dibromoanisole (9.8×10^{-5} mol), tetramethylsilane (1 drop), and pentadeuteriopyridine (9.3×10^{-3} mol). The mixture was transferred to a stoppered ^1H n.m.r. tube, warmed to 37 °C, and placed in the probe of the ^1H n.m.r. spectrometer (probe temperature 37 °C). The spectrum was scanned at appropriate intervals (initially *ca.* 30 min), and the rearrangement of the two epoxides was followed by monitoring the integrals of the relevant signals, the methoxy-protons of 2,4-dibromoanisole being used as a standard

TABLE 2

Proportions of products from epoxidation of cholest-5-en-3-one (5×10^{-4} mol) with *m*-chloroperbenzoic acid (6×10^{-4} mol) at *ca.* 20 °C for 3 h

Product	Solvent $CDCl_3$ (2 cm^3)	Solvent C_6D_6 (2 cm^3)
Lactone (1)	0.29	0.26
5α,6α-Epoxide (2)	0.49 *	0.52 †
5β,6β-Epoxide (3)	0.22	0.22

* Proportion of total epoxide, 0.69. † Proportion of total epoxide, 0.70.

[11] A. Nickon, M. A. Castle, R. Harada, C. E. Berkoff, and R. O. Williams, *J. Amer. Chem. Soc.*, 1963, **85**, 2185; K. M. Wellman and F. G. Bordwell, *Tetrahedron Letters*, 1963, 1703; G. J. Karabatsos, G. C. Sonnichsen, N. Hsi, and D. J. Fenoglio, *J. Amer. Chem. Soc.*, 1967, **89**, 5067.

when computing absolute concentrations. The signals which had been assigned to the 5β,6β-epoxide disappeared relatively rapidly, and by a process which within experimental error was of the first order in epoxide ($10^5k_1 = 35 \pm 2$ s^{-1}, estimated from three points only). The 5α,6α-epoxide reacted substantially more slowly, and this reaction was also within experimental error of the first order; $10^5k_1 = 2.8 \pm 0.1$ s^{-1}. The final product contained the lactone (1), 6α-hydroxycholest-4-en-3-one,[10] and 6β-hydroxycholest-4-en-3-one (4) [10] in proportions which could be determined by integration of appropriate ^{1}H n.m.r. signals [10] as 0.29 : 0.49 : 0.22, identical with those expected from the results of Table 2.

Under the conditions used here for the rearrangement of the 5,6-epoxycholestan-3-ones, the 5,6-epoxy-3β-methoxycholestanes underwent no significant rearrangement in 25 days.

(e) *Products of Epoxidation of 4β-Deuteriocholest-5-en-3-one.*—A sample of 4β-deuteriocholest-5-en-3-one (15 ± 5% of 4α-^{2}H, 83 ± 3% 4β-^{2}H) [10] was epoxidised similarly, and the mixture was treated with pentadeuteriopyridine. ^{1}H N.m.r. spectroscopy showed that the resulting mixture of epimeric 6-hydroxycholest-4-en-3-ones contained 83 ± 3% ^{2}H at C-4 as estimated by integration of the C-4 and C-6 proton signals. Within experimental error, therefore, no β-deuterium had been removed from either epoxide. The product mixture contained the lactone (1), substantially deuteriated 6α-hydroxycholest-4-en-3-one, and substantially deuteriated 6β-hydroxycholest-4-en-3-one (4), in the proportions 0.24 : 0.54 : 0.22. This estimation was made by using the integrals of the relatively weak signals for the residual 4-protons, and so is subject to more uncertainty than the corresponding analysis for the non-deuteriated material.

DISCUSSION

(a) *Epoxidation of Substituted Cholest-5-enes.*—For the epoxidation of a group of 3β-substituted cholest-5-enes by *m*-chloroperbenzoic acid, in deuteriochloroform or in hexadeuteriobenzene, α- is favoured over β-attack by a factor of a little more than 2. Variations in this ratio with the polar character of the β-substituent [over the range H, MeO, $PhCO_2$, p-$O_2N{\cdot}C_6H_4{\cdot}CO_2$, $3,5(NO_2)_2$-$C_6H_3CO_2$], and in the electrophilicity of the peroxy-acid (over the range $PhCO_3H$, m-$ClC_6H_4{\cdot}CO_3H$, p-$O_2N{\cdot}C_6H_4{\cdot}CO_3H$) seem to be small and show no systematic trends. A substituent at the 3α-, rather than at the 3β-position, however, seems to reduce the proportion of attack on the α-face of the molecule. This result suggests that a bulky axial 3α-substituent can exert steric hindrance of small but significant magnitude to attack by electrophiles, despite the unsymmetrical nature of the transition state established by Hanzlik and Shearer's [5] study of secondary deuterium isotope effects in epoxidation.

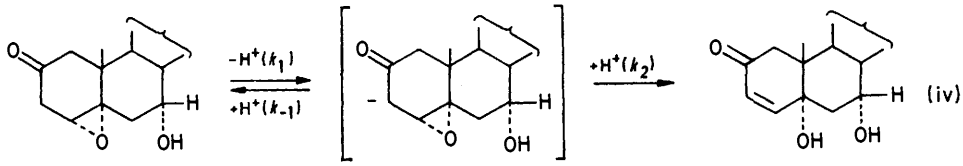
The results now obtained for epoxidation of cholest-5-en-3-one show that the ratio of α- to β-attack by the epoxidising peroxy-acid is very similar to that observed for the series of 3β-substituted cholest-5-enes under similar conditions. No special effect is observed through introduction of the 3-oxo-group, which (since the 3-position now carries no bulky substituent) might have been expected to confer some additional flexibility on ring A and hence to have minimised steric hindrance to attack on the α-face of the molecule. In a later paper, these results will be compared with results obtained in some halogenations currently being studied.

(b) *Base-catalysed Rearrangement of the 5,6-Epoxycholestan-3-ones.*—The isomeric rearrangements of epoxides to allylic alcohols have been studied by a number of groups of workers. Examples given as reaction (iii)

$$RCH_2{\cdot}\underset{\diagdown\,O\,\diagup}{CH}{\cdot}CH_2 \xrightarrow[\text{in } NH_3]{NaNH_2} RCH{:}CH{\cdot}CH_2{\cdot}OH \quad (R = Ph \text{ or } HC{:}C) \quad \text{(iii)}$$

were established by Haynes *et al.*[8] Cope and Heeren illustrated similar reactions of the oct-4-ene oxides, lithium diethylamide in diethylamine being used as the reagent. Rearrangements carried out by using the latter conditions have been studied extensively by Thummel and Rickbourn,[12] who have shown by using *cis*- and *trans*-4-t-butylcyclohexene oxide labelled appropriately with deuterium that the proton *syn* to the epoxy-group is removed preferentially by lithium diethylamide in diethyl ether–hexane. Their work shows also that with cyclic epoxides where alternative sites for proton abstraction are possible, attack by the base is directed away from sites close to bulky substituents.

The corresponding rearrangements of some βγ-epoxyketones, which occur under much milder conditions



(iv)

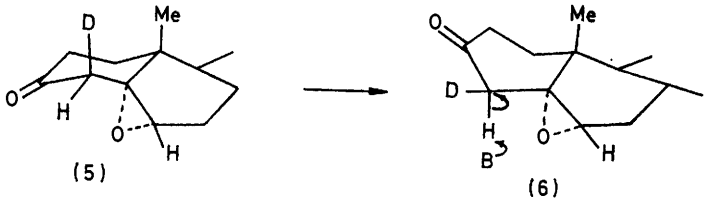
(*e.g.* with diethylamine in ethanol at 30 °C) have been studied by Barton and Houminer.[13] Reaction (iv), for example, was found to be subject to a deuterium isotope effect, $k_{3\text{-}H}/k_{3\text{-}D} = 3$, and to proceed without incorporation of deuterium into the starting material recovered after partial reaction. The removal of a 3-proton was thereby established to be part of the rate-determining process; the two possibilities were considered, (*a*) that the enolate ion was a discrete intermediate, as shown, and (*b*) that the proton removal and reprotonation were synchronous, the two stages shown being telescoped.

[12] B. Rickbourn and R. P. Thummel, *J. Org. Chem.*, 1969, **34**, 3583; 1972, **37**, 3919; R. P. Thummel and B. Rickbourn, *J. Amer. Chem. Soc.*, 1970, **92**, 2064; *J. Org. Chem.*, 1972, **37**, 4250;

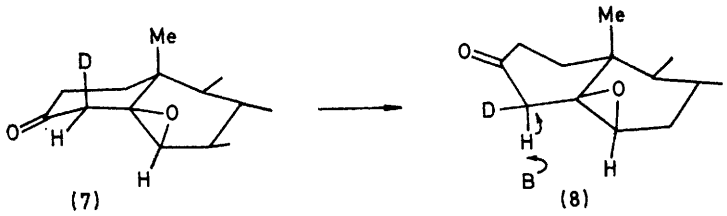
[13] D. H. R. Barton and Y. Houminer, *J.C.S. Perkin I*, 1972, 919.

The results do not provide conclusive evidence on this point.

The rearrangements of the two epoxides examined in the present work resemble in general characteristics those studied by Barton and Houminer,[13] proceeding smoothly



to completion under the influence of a weak base at 37 °C. The slower of these, the reaction of 5α,6α-epoxycholestan-3-one to give 6α-hydroxycholest-4-en-3-one, has stereochemical characteristics which accord also with Thummel and Rickbourn's observations[12] concerning the reactions of epoxides having less ' active ' hydrogen atoms; the 4α-hydrogen atom, *syn*- to the epoxy-group, is removed by base in preference to a



4β-deuterium atom. For the epoxy-ketones, however, the mild conditions required for the transformation establish that the proton loss is powerfully accelerated by the adjacent carbonyl group; and for this to be effective, delocalisation of the developing negative charge over the O=C–$\bar{C}<$ system is needed. This in turn requires adjustment of the conformation of ring A towards an axial location for the departing 4α-hydrogen atom, and this is only possible if this ring becomes boat-like in the transition state [(5) ⟶ (6)]. Ring opening synchronous with proton removal remains here as a possibility.

The corresponding reactions of 5β,6β-epoxycholestan-3-one and its 4β-deuterio-derivative, on the other hand, are more unusual, and appear to provide the first authentic example of a stereoselective *anti*-rearrangement of an epoxide to an allylic alcohol. Again, stereoelectronic factors require the 4α-proton, which is removed preferentially, to adopt an axial conformation, and hence (7) must adopt the boat conformation in the transition state (8).* This reaction is more than ten times faster than that of its isomer, probably because steric hindrance to attack by base adjacent to the epoxide group is less in (8) than in (6). Steric hindrance is also less in (8) than in (7), since in the latter the adjacent 19-methyl group impedes approach to the β-deuterium atom.

It seems likely that the *anti*-stereochemistry found for this epoxide implies that proton removal precedes the opening of the epoxide ring, as in the stepwise mechanism [reaction (iv)] discussed by Barton and Houminer.[13] The results do not establish fully the degree of stereoselectivity of the reactions. A preference for α- over β-removal by a factor of up to eight would be expected for (5) or (7) merely through the primary H/D isotope effect on the base-catalysed rearrangement; and an additional experimental uncertainty arises since we were able to determine the isotopic compositions of the derived 6-hydroxycholest-4-en-3-ones only as a mixture in the products from the 70 : 30 mixture of epoxides. It is certain, however, that for both epoxides removal of the α-hydrogen atom, despite its equatorial disposition in the ground state, is considerably preferred over removal of β-deuterium, and hence that, for the β-epoxide, *anti*-rearrangement is competitive in rate with *syn*-rearrangement.

* This epoxy-ketone formally has a *cis*-AB ring junction. The bonds attached to the three-membered ring, however, are more nearly trigonally than tetrahedrally arranged, and are rather rigidly constrained. The type of chair form adopted by the usual 5β-cholestanes would be very heavily strained and not nearly as accessible as (7) or (8), as shown by Dreiding models.

[6/1630 *Received*, 23*rd August*, 1976]