Hydroxy-steroids. Part XV.[1] A Quantitative Study of the Epoxidation of 3-Substituted Cholest-5-enes

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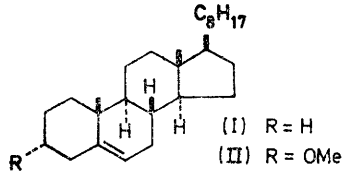
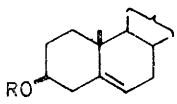
Examination of the conversion of 3-substituted cholest-5-enes into 5α,6α- and 5β,6β-epoxides by various peroxy-acid–solvent combinations gives values for the ratios of isomers produced and the rate constants of the reactions. Peroxylauric acid in benzene forms a high proportion of the α-epoxide (*e.g.* 85% from cholesteryl 3,5-dinitrobenzoate); the use of *p*-nitroperoxybenzoic acid in chloroform leads to fast epoxidation.

THE epoxidation of cyclic olefins, including steroids, has been widely studied, notably by Henbest [2] and by Mousseron-Canet [3] and their collaborators, in work directed mainly towards stereochemical aspects. Recent interest in this reaction [4] has centred on the question of whether the original 'molecular' mechanism [5] should be modified to one involving dipolar addition by the peroxy-acid. Apart from data for a few simple systems (*e.g.* cyclopentenes, cyclohexenes, long-chain olefins, and styrenes [2b,6]) there is little quantitative information about the rates of epoxidations. The present work on a series of 3-substituted cholest-5-ene is concerned with kinetic and geometric features rather than with the detailed mechanism of epoxidation.

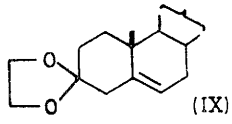
$$\Delta^5\text{-steroid} + \text{peroxy-acid} \longrightarrow 5\alpha,6\alpha\text{-} + 5\beta,6\beta\text{-epoxides}$$

Steroids





(III) R = H
(IV) R = OAc
(V) R = $CH_2Cl\cdot CO$
(VI) R = p-$NO_2\cdot C_6H_4\cdot CO$
(VII) R = 3,5-$(NO_2)_2C_6H_3\cdot CO$
(VIII) R = Me



Peroxy-acids

a, Peroxylauric; b, $PhCO_3H$; c, p-$NO_2\cdot C_6H_4\cdot CO_3H$

Solvents

d, C_6H_6; e, $CHCl_3$; f, EtOAc

Percentages of 5α,6α-epoxides formed.

The letters refer to the peroxy-acids and solvents used. Values are accurate to ±2%.

	(I)	(II)	(IV)	(V)	(VI)	(VII)	(VIII)	(IX)
b, e	72		61	69	69	77	74	35
a, d	80	21	74	79		85	79	37
b, d	80		73					

Rates

The accuracies of the second-order rate constants k (in l mol^{-1} s^{-1} at 12 °C) are estimated to be ±2% (conditions a, d) and ±7% (conditions b, e): the k_{rel} values are based on $k_{rel} = 1$ for cholest-5-ene (I), conditions a, d. Activation energies (E_a) are in kJ mol^{-1} and entropies of activation ($\Delta S^{\ddagger}$) in J K^{-1} mol^{-1}: ΔS_{α} and $\Delta S_{\beta}^{\ddagger}$ refer to formation of the α- and β-epoxides respectively.

	a, d						b, e	
Compd.	k	k_{rel}	E_a	$\Delta S^{\ddagger}$	$\Delta S_{\alpha}^{\ddagger}$	$\Delta S_{\beta}^{\ddagger}$	k	k_{rel}
(I)	17·6 × 10^{-3}	1	46·1	−125	−127	−138	13·2 × 10^{-2}	7·5
(II)	5·63 × 10^{-3}	0·32	47·9	−128	−141	−130		
(III)	9·67 × 10^{-3}	0·55	45·1	−140	−141	−158		
(IV)	2·59 × 10^{-3}	0·15	46·1	−141	−143	−152	13·6 × 10^{-3}	0·77
(V)	2·25 × 10^{-3}	0·13	51·0	−125	−127	−138		
(VII)	2·50 × 10^{-3}	0·18	52·6	−118	−119	−134	14·2 × 10^{-3}	0·81
(VIII)	9·05 × 10^{-3}	0·51	46·1	−130	−132	−143	52·6 × 10^{-3}	3·0

(IV) under conditions	a, e	b, e	c, e	c, f	b, d
k	3·6 × 10^{-3}	13·6 × 10^{-3}	13·0 × 10^{-2}	5·80 × 10^{-3}	14·7 × 10^{-3}
k_{rel}	0·20	0·77	7·4	0·33	0·84

With the exception of 3α-methoxycholest-5-ene (II) the required steroids [(I)—(IX), all known compounds] are readily prepared (see Experimental section for references and constants). The 3α-ether (II) [7] was obtained from epicholesterol, initially prepared in this

[1] Part XIV, J. M. Diggle, M. D. Halliday, A. Kasal, G. D. Meakins, and M. S. Saltmarsh, preceding paper.

[2] (*a*) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1957, 1968; H. B. Henbest, M. Smith, and A. Thomas, *ibid.*, 1958, 3293; H. B. Henbest and B. Nicholls, *ibid.*, 1959, 221; (*b*) H. B. Henbest, *Chem. Soc. Special Publ.*, No. 19, 1965.

[3] M. Mousseron-Canet and J.-C. Guilleux, *Bull. Soc. chim. France*, 1966, 3853, 3858; M. Mousseron-Canet, B. Labeeuw, and J-C. Lanet, *Compt. rend.*, 1966, **262***c*, 1438, and earlier papers.

[4] H. Kwart and D. M. Hoffman, *J. Org. Chem.*, 1966, **31**, 419; K. D. Bingham, G. D. Meakins, and G. H. Whitham, *Chem. Comm.*, 1966, 445; H. Kwart, P. S. Starcher, and S. W. Tinsley, *ibid.*, 1967, 355.

[5] P. D. Bartlett, *Rec. Chem. Progr.*, 1950, **11**, 51; B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1955, 1525.

[6] P. Renolen and J. Ugelstad, *J. Chim. phys.*, 1960, **57**, 634; W. Schneider, *Fette, Seifen, Anstrichm.*, 1967, **69**, 421.

[7] J. R. Lewis and C. W. Shoppee, *J. Chem. Soc.*, 1955, 1365.

work by reduction [8] of 3-oxocholest-5-ene.[9] However, the hydrogenation is very sensitive to the state of the Raney nickel catalyst; careful control is necessary to produce epicholesterol in modest yield (25%). A more reliable, although longer, route is mentioned later.

Preliminary experiments demonstrated that the steroids reacted with the peroxy-acids to give mixtures of the isomeric 5,6-epoxides in high yield. In view of the reported catalysis by trichloroacetic acid of the peroxybenzoic acid–stilbene reaction [10] it was established that the carboxylic acids formed in the present oxidations with peroxybenzoic and peroxylauric acids did not act similarly. The epoxide mixtures were analysed by integrating their H-6 signals at τ *ca.* 7.[11] [The α-epoxides' doublets, *J ca.* 3·5 Hz, are at higher field than those, *J ca* 2 Hz, of the β-epoxides. With cholesterol (III) the isolation procedure led to some decomposition, and percentage α-epoxide figures are not given.] While a few of the reactions could be followed conveniently by polarimetry, the change in rotation was too small for accurate study in other cases, and the kinetic data in the Table were obtained by titrimetric estimation of the peroxy-acid concentration.

The results show how changes in the 3-substituent, the peroxy-acid, and the solvent influence the rate of epoxidation and the isomer proportions. The rate constants of the oxidations with peroxylauric acid in benzene at various temperatures (11—30 °C) were used to evaluate activation energies (correlation coefficients of linear regression analyses >0·995) and entropies of activation. Our original intention was to study the temperature dependence of the isomer proportions and to obtain activation energies for attack at each of the two faces. However, in the limited temperature range examined the variations in isomer proportions were less than the uncertainty of the analytical method. Most of the changes in rates and proportions are relatively small, and since they could be attributed to a variety of effects detailed discussion is unwarranted. The salient results are as follows: (i) the high proportion of the β-epoxide not only from 3α-methoxycholest-5-ene (II) but also from the 3,3-disubstituted compound (IX), (ii) the increase in the proportion of the α-epoxide with peroxylauric acid in benzene over that with the more usual combination of peroxybenzoic acid in chloroform, (iii) the decrease in rate caused by electron-withdrawing groups in the steroid, and the increase resulting from similar groups in the peroxy-acid (as expected [2b]), (iv) the decrease in rate with ethyl acetate as solvent, but (unexpectedly [2b]) the similar rates found with benzene and chloroform.

Comparison of the present *k* figures (peroxybenzoic acid–chloroform at 12 °C) for cholesteryl acetate (IV) and cholest-5-ene (I) with previous values [12] ($39·3 \times 10^{-3}$ and $39·7 \times 10^{-3}$, respectively, at 25 °C) shows reasonable agreement for the acetate but a marked discrepancy with the hydrocarbon. The reactions of peroxylauric acid in benzene at the Δ^5-bond of lumisteryl esters, which form mainly 5β,6β-epoxides, are ten times faster [13] than those of the cholesteryl analogues, in agreement with the general high reactivity of conjugated 5,7-dienes noted earlier.[14] The very marked rate difference between lumisterol itself [13] and cholesterol (a factor of 200) confirms the operation of anchimeric assistance by the 3β-hydroxy-group of lumisterol. The reaction of cholesteryl dinitrobenzoate (VIII) with peroxylauric acid–benzene gives a very high proportion of α-epoxide: this leads conveniently to cholestane-3β,5α-diol [15] and thence, by an established sequence,[16] to epicholesterol.

EXPERIMENTAL

For general directions see *J. Chem. Soc.* (*C*), 1968, 2674.

Preparative Work.—The constants found for the following compounds are in satisfactory agreement with the values recorded in the references (superscripts): (I),[17] m.p. 91—92°, $[\alpha]_D$ −58°; (II),[7] 90·5—91·5, −49; (III) [17] [purified *via* the ester (VII)], 148—149, −42; (IV),[17] 115—116, −47; (V),[17] 159—161, −38; (VI),[18] 191—192, −5; (VII),[1] 194—196, −14; (VIII),[19] 84·5—85·5, −41; (IX),[20] 133—134, −27.

Epicholesterol (*Cholest-5-en-3α-ol*). (a) *From cholest-5-en-3-one.* Raney nickel (type W2; 9 ml of the sludge which had been stored under dry EtOH for 3 months) was washed with dry cyclohexane. Cholest-5-en-3-one [9] (5 g) in cyclohexane (120 ml) was added and the mixture was hydrogenated for 30 min (H_2 uptake 1·2 mol. equiv.). The product was chromatographed on neutral Al_2O_3 [230 g; deactivated with H_2O (5%)]. Material eluted with light petroleum–benzene mixtures was discarded. Elution with C_6H_6 and crystallisation from EtOH gave epicholesterol (1·3 g), m.p. 142—143·5°, $[\alpha]_D$ −42° (*c* 1·8) (lit.,[21,22] m.p. 140—141°, $[\alpha]_D$ −42°).

(b) *From cholest-5-en-3β-yl 3,5-dinitrobenzoate* (VII). The ester (8·5 g) was treated with peroxylauric acid in C_6H_6 as described previously.[1] One crystallisation from EtOAc gave material (6·1 g) shown by n.m.r. to contain the 5α,6α- and 5β,6β-epoxides in a ratio of 96 : 4. Reduction with an excess of $LaAlH_4$ afforded cholestane-3β,5α-diol [15] (3·2 g), m.p. 225—227°, which reacted with $MeSO_2Cl$ in C_5H_5N at 20 °C to give 5α-hydroxycholestan-3β-yl methanesulphonate [16] (2·4 g), m.p. 113—114°. A solution

[8] L. Ruzicka and M. W. Goldberg, *Helv. Chim. Acta*, 1936, **19**, 1407.
[9] L. F. Fieser, *Org. Synth.*, Coll. Vol. IV, 1964, 195.
[10] G. Berti and F. Bottari, *J. Org. Chem.*, 1960, **25**, 1286.
[11] A. D. Cross, *J. Amer. Chem. Soc.*, 1962, **84**, 3206.
[12] R. Cetina, J. L. Mateos, and E. Trabulse, *Bol. Inst. Quím. Univ. nac. auton. Mexico*, 1965, **17**, 56.
[13] K. D. Bingham, G. D. Meakins, and J. Wicha, *J. Chem. Soc.* (*C*), 1969, 510.
[14] G. M. L. Cragg and G. D. Meakins, *J. Chem. Soc.*, 1965, 2054.
[15] L. C. King and M. J. Bigelow, *J. Amer. Chem. Soc.*, 1952, **74**, 6238.
[16] P. A. Plattner, A. Furst, F. Koller, and W. Lang, *Helv. Chim. Acta*, 1948, **31**, 1455.
[17] Elsevier's 'Encyclopædia of Organic Chemistry,' vol. 14 and supplements.
[18] D. Kritchevsky, *J. Amer. Chem. Soc.*, 1943, **65**, 480.
[19] D. M. Rathmann and L. R. Morrow, *J. Amer. Chem. Soc.*, 1950, **72**, 5647.
[20] R. Antonucci, S. Bernstein, R. Littell, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, 1952, **17**, 1341.
[21] E. J. Becker and E. S. Wallis, *J. Org. Chem.*, 1955, **20**, 353.
[22] M. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, *Tetrahedron*, 1959, **6**, 36.

of this compound in $CHCl_3$ was heated under reflux with $PhNEt_2$–AcCl [16] for 5 h, and the product was chromatographed on neutral Al_2O_3 (5% deactivated) to give epicholesteryl acetate (1·1 g), m.p. 84—85°, $[\alpha]_D$ −15° (*c* 0·9) (lit.,[16] m.p. 85°, $[\alpha]_D$ −13°). Hydrolysis with 5% KOH–EtOH afforded epicholesterol (0·95 g), m.p. 141—142°.

3-*Methoxycholest-5-ene* (II). Treatment of epicholesterol with CH_2N_2–HBF_4 in CH_2Cl_2 in usual way [22] gave the 3α-ether [7] (79% yield), m.p. 90·5—91·5°.

Peroxy-acids. These were prepared according to ref. 23. Solutions of the peroxyacids in $CHCl_3$ (or, for BzO_2H, in the solvent required for the epoxidation) were shaken with Na_2CO_3 (0·1 equiv.) to ensure removal of $MeSO_3H$. *p*-Nitroperoxybenzoic and peroxylauric acids were crystallised until their purity (by iodometric titration) exceeded 96%. The BzO_2H solutions contained 87—92% of peroxy-acid.

Percentages of 5α,6α-Epoxides.—The procedure is illustrated for the 3β-acetate (IV). Solutions of the acetate (100 mg) in $CHCl_3$ (5 ml) and of BzO_2H in $CHCl_3$ (0·93 ml of 0·38M-solution) were mixed at 20 °C. After 20 h the solution was poured on neutral Al_2O_3 [10 g; deactivated with H_2O (5%)]. Elution with Et_2O gave material (102 mg) which was examined by i.r. spectroscopy (to demonstrate the absence of OH absorption) and t.l.c. (to establish the presence of major and minor products, and the absence of starting material). A solution of this material in CCl_4 was evaporated, the residue was dissolved in CCl_4 or $CDCl_3$, and the solution was examined by n.m.r. spectroscopy in the region τ 6—9.

The 5α,6α- and 5β,6β-epoxides [17] obtained from the 3β-acetate (2 g) were separated by careful column chromatography, and appropriate amounts were combined to give mixtures of known composition. The percentages of α-epoxide found by n.m.r. analysis are shown in parentheses after the correct values: 37·9 (37·1), 45·5 (46·7), 51·8 (51·7), 64·2 (63·8), 67·9 (67·4), 89·2 (90·3).

Kinetic Work.—This is illustrated by the procedure of the oxidations with peroxylauric acid in C_6H_6. Peroxylauric acid (*ca.* 1·4 g) was dissolved in dry C_6H_6 to give a solution of vol. 20 ml at the required temp. A portion (2 ml) was shaken for 1 min with a mixture of KI (2 g), H_2O (20 ml), Et_2O (20 ml), and AcOH (9 ml), and the liberated iodine was titrated with standard thiosulphate solution. A further portion (5 ml) was added to a solution of the steroid (*ca.* 0·48 g) in C_6H_6 (previously made up to 20 ml at the required temp.). Samples (2 ml) were withdrawn at intervals and the peroxylauric acid concentration was estimated as before. A typical run gave:

Time/min	1·2	4·8	8·0	11·5	15·0	19·0
Titre of thiosulphate/ml	20·43	17·80	16·05	14·65	13·39	12·20

Variation in rate with temperature is illustrated by the results for cholest-5-ene (I)

Temp./°C	11·5	14·7	20·1	24·7	29·8
10^3k/l mol^{-1} s^{-1}	16·7	22·0	30·3	39·4	56·2

Selected runs were repeated with solutions containing amounts of lauric or benzoic acids equal to the initial weights of the peroxy-acids; the *k* values remained within the limits of accuracy given in the Table.

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[23] L. S. Silbert, E. Siegel, and D. Swern, *J. Org. Chem.*, 1962, **27**, 1336.