Intramolecular Catalysis. Part II.[1] Electrophilic Anchimeric Assistance by a Hydroxy-group in the Opening of Steroidal Epoxides by Azide Anions

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5α,6α-Epoxycholestane and its 3-substituted derivatives and 4α,5α-epoxycholestane and its 7-substituted derivatives have been prepared and their structures established. The stereochemistry of epoxidation of 7-substituted cholest-4-enes and 3-substituted cholest-5-enes with *m*-chloroperbenzoic acid is discussed in detail. The reactions of the 4α,5α- and 5α,6α-epoxides with sodium azide in refluxing acetone–water (2 : 1) gave the corresponding *trans*-diaxial hydroxy-azides. The presence of a 7α-hydroxy-group in a 4α,5α-epoxycholestane, and of a 3α-hydroxy-group in a 5α,6α-epoxycholestane, strongly accelerated the opening of the epoxide ring by the nucleophile. Evidence is given for an intramolecular electrophilically assisted reaction, and various factors which may affect the mechanisms of these reactions are discussed.

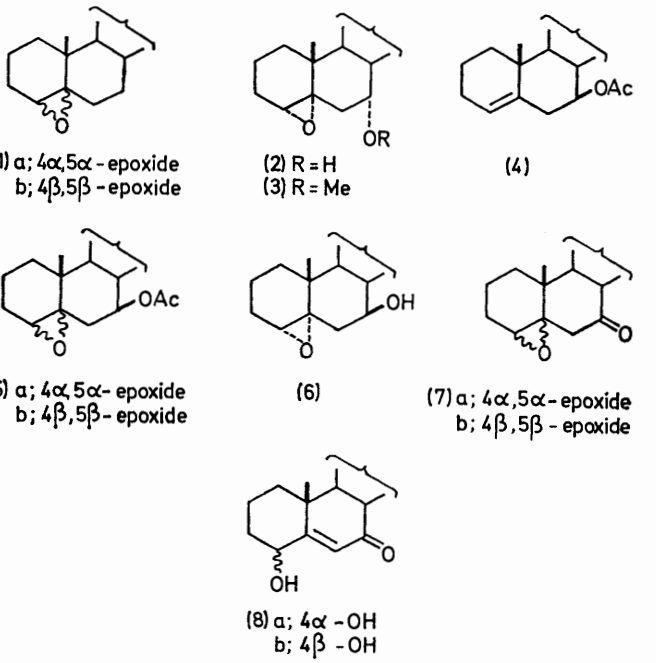
ORGANIC reactions involving neighbouring group participation have received growing attention in recent years.[2-8] In many reactions possessing 'cationic' transition states, a hydroxy-group is known to participate as an internal nucleophile, usually by delocalization of the positive charge developing in the transition state.[2,3,8-10] However, in reactions possessing 'anionic' transition states only a few examples have been reported in which a hydroxy-group participates as an internal electrophile.[4-6,11-13] We have recently observed neighbouring hydroxy-group participation in the reductive elimination of chlorine from 5α,6β-dichlorocholestanes with sodium borohydride.[1] In these systems evidence has been found for the existence of an intramolecular electrophilically assisted reaction.[1,14]

Barton *et al.*[15] have reported an unusual neighbouring hydroxy-group participation in the base-catalysed isomerization of steroidal βγ-methylene ketones to the corresponding γ-methyl-αβ-unsaturated ketones. The hydroxy-group accelerates this process by protonation of the incipient negative charge developing on a carbon atom of the cyclopropane ring during the opening of

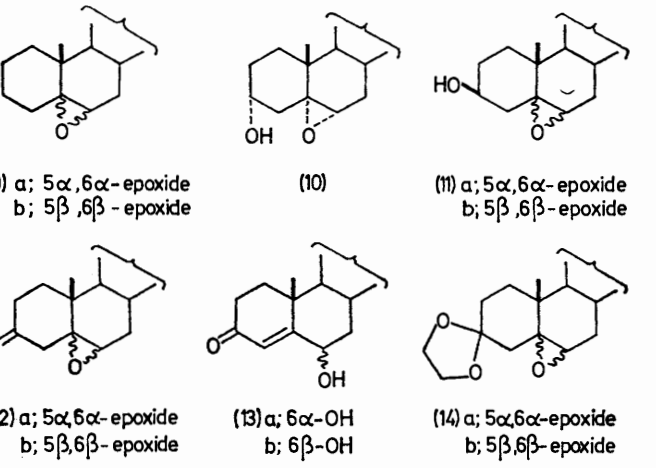
[1] Part I, Y. Houminer, *J.C.S. Perkin I*, 1975, 277.
[2] B. Capon, *Quart. Rev.*, 1964, **18**, 45.
[3] L. Goodman, *Adv. Carbohydrate Chem.*, 1967, **22**, 109.
[4] T. C. Bruice and S. Benkovic, 'Bio-organic Mechanisms,' Benjamin, New York, 1966, vol. 1, p. 119.
[5] W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969, p. 8.
[6] M. L. Bender, 'Mechanisms of Homogeneous Catalysis from Protons to Proteins,' Wiley–Interscience, New York, 1971, p. 281.
[7] G. C. Wolf, E. Emerson, L. Foster, and R. T. Glickenstaff, *J. Org. Chem.*, 1973, **38**, 1276, and papers cited therein.
[8] M. Miljkovic, T. Satoh, M. Konopka, E. A. Davidson, and D. Miljkovic, *J. Org. Chem.*, 1973, **38**, 716, and papers cited therein.
[9] B. Capon, S. T. McDowell, and M. V. Raftery, *Chem. Comm.*, 1971, 389, and papers cited therein.
[10] P. Salomaa, A. Konkaanpera, and K. Pihlaza, in 'The Chemistry of the Hydroxyl Group,' ed. S. Patai, Interscience, New York, 1971, p. 453.
[11] S. M. Kupchan, P. Slade, R. J. Young, and G. W. A. Milne, *Tetrahedron*, 1962, **18**, 499.
[12] H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1957, 1965.
[13] R. P. Bell and M. I. Page, *J.C.S. Perkin II*, 1973, 1681.
[14] Y. Houminer, *J. Org. Chem.*, 1975, **40**, 1361.
[15] D. H. R. Barton, C. F. Garbers, D. Giacopello, R. G. Harvey, J. Lessard, and D. R. Taylor, *J. Chem. Soc.* (C), 1969, 1050.

the latter.[15] A similar base-catalysed rearrangement of steroidal βγ-epoxy-ketones to the corresponding γ-hydroxy-αβ-unsaturated ketones failed to show hydroxy-group anchimeric assistance.[16] Since here the rate-determining step is the enolization of the ketone and not the opening of the epoxide ring, any delocalization of the negative charge developing on the ring oxygen atom by the neighbouring hydroxy-group, which could lead to acceleration, was masked and was not detected. We were therefore interested in determining whether neighbouring hydroxy-group participation exists in the opening of epoxides with nucleophiles, since these bimolecular processes involve cleavage of the epoxide ring in their rate-determining step.[17] Angyal *et al.* have observed an anomalous direction of opening of the epoxide ring by benzoate anion in certain cyclitol epoxides.[18] It has been suggested that the opening of the epoxide ring is directed by a neighbouring hydroxy-group which provides solvation of the transition state in one preferred route.[18] Abnormal reduction by lithium aluminium hydride of 3α,4α-epoxy-5α-hydroxycholestane was observed by Glotter *et al.*[19] and a mechanism involving neighbouring hydroxy-group participation was proposed.[19] We have previously reported[20] neighbouring hydroxy-group participation in the reaction of 4α,5α-epoxycholestan-7α-ol with sodium azide. The present investigation was aimed at extending this study to other steroidal epoxides having similar stereochemistry, and, particularly, at clarifying some aspects of the mechanisms of these reactions. Most of the epoxides required were prepared by epoxidation of the corresponding olefins with *m*-chloroperbenzoic acid in methylene chloride. The stereochemistry of epoxidation of 3-substituted cholest-5-enes, with a variety of peroxy-acid–solvent combinations, has been studied extensively.[21,22] However, no study has been reported on the *m*-chloroperbenzoic acid–methylene chloride system, nor on the stereochemistry of epoxidation of 7-substituted cholest-4-enes. Our study was also intended to obtain information on these subjects.

Epoxidation Studies.—4,5-Epoxycholestanes (1a)[23] and (1b)[24] were prepared from cholest-4-ene. 4α,5α-Epoxycholestan-7α-ol (2) was obtained either by epoxidation of cholest-4-en-7α-ol or by reduction of the epoxy-ketone (7a) with sodium borohydride. Its formation by these two routes established its structure. Treatment of the epoxide (2) with sodium hydride and methyl iodide afforded 4α,5α-epoxy-7α-methoxycholestane (3). Cholest-4-en-7α-ol was resistant to methylation under conditions where the epoxide (2) was smoothly methylated. The reason for this behaviour is not yet understood. Acetylation of cholest-4-en-7β-ol gave the acetate (4), which on epoxidation



gave a mixture (5a and b). The smooth transformation of the epoxide (5a) into the hydroxy-enone (8a), *via* (6)



and (7a) (see Experimental section), provided chemical proof for the 4α,5α-configuration in both (5a) and (6).[16,25] Similarly, the epoxide (5b) was transformed into the hydroxy-enone (8b), and thus its 4β,5β-configuration

[15] D. H. R. Barton and Y. Houminer, *J.C.S. Perkin I*, 1972, 919.
[16] A. Rosowsky in ' Heterocyclic Compounds,' ed. A. Weissberger, Interscience, New York, Part I, 1964, p. 270.
[17] S. J. Angyal and T. S. Stewart, *Austral. J. Chem.*, 1967, **20**, 2117.
[18] E. Glotter, S. Greenfield, and D. Lavie, *Tetrahedron Letters*, 1967, 5261.
[19] D. H. R. Barton and Y. Houminer, *J.C.S. Chem. Comm.*, 1973, 839.
[20] M. Mousseron-Canet and J.-C. Guilleux, *Bull. Soc. chim. France*, 1966, 3853.
[21] K. D. Bingham, T. M. Blaiklock, R. C. B. Coleman, and G. D. Meakins, *J. Chem. Soc.*, (*C*) 1970, 2330, and references cited therein.
[22] R. E. Ireland, T. I. Wrigley, and W. G. Young, *J. Amer. Chem. Soc.*, 1958, **80**, 4604.
[23] B. N. Blackett, J. M. Coxon, M. P. Hartshorn, and K. E. Richards, *Tetrahedron Letters*, 1969, 1737.
[24] C. Djerassi, E. Batres, M. Velasco, and G. Rosenkranz, *J. Amer. Chem. Soc.*, 1952, **74**, 1712; J. P. Ruelas, J. Iriarte, F. Kincl, and C. Djerassi, *J. Org. Chem.*, 1958, **23**, 1744; F. Sondheimer and S. Burstein, *Proc. Chem. Soc.*, 1959, 228; F. Sondheimer, S. Burstein, and R. Mechoulam, *J. Amer. Chem. Soc.*, 1960, **82**, 3209.

was established.[16] 5α,6α-Epoxycholestane (9a), 5β,6β-epoxycholestane (9b), and their derivatives (10)—(12) and (14), were prepared from the corresponding olefins. The epoxides (10) and (11a) were also obtained by reduction of the ketone (12a) with sodium borohydride.

Table 1 summarizes the results obtained for the

TABLE 1

Stereochemistry of epoxidation of cholest-4-ene, cholest-5-ene, and their derivatives, with *m*-chloroperbenzoic acid

Steroid	Yield of epoxides (%)	Proportions of epoxides in the mixture [a] α-Epoxide (%)	β-Epoxide (%)
Cholest-4-ene	84	61	39
Cholest-4-en-7β-ol	86	57	43
Cholest-4-en-7α-ol [b]	65	>95	0
7β-Acetoxycholest-4-ene	87	56	44
Cholest-4-en-7-one [c]	61	57	43
Cholest-5-ene	91	79	21
Cholest-5-en-3β-ol	>90	81	19
Cholest-5-en-3α-ol	91	>95	0
Cholest-5-en-3-one	>81	72	28

[a] Values accurate to ±3%. [b] Epoxidation carried out with monoperphthalic acid. [c] Figures taken from ref. 16.

epoxidation of 7-substituted cholest-4-enes and 3-substituted cholest-5-enes. The epoxide mixture was usually separated by t.l.c. and the yields of both α- and β-epoxides were determined by weighing. In some cases, a different method was used (see Experimental section). In the 5,6-epoxide series, the relative amounts of the two isomers could also be determined from the n.m.r. spectra of the crude epoxidation mixtures:[22] the doublet (*J ca.* 4.0 Hz) corresponding to the 6β-proton in the 5α,6α-epoxide appears at a higher field than that (*J ca.* 2.0 Hz) corresponding to the 6α-proton in the 5β,6β-epoxide, and each signal could be accurately integrated. However, this method for analysing mixtures of 4α,5α- and 4β,5β-epoxides could not be used since in each of these pairs the signals corresponding to the 4β- and the 4α-protons either overlapped or were too close to each other. In addition, these signals appeared in both cases as multiplets with $W_{\frac{1}{2}}$ *ca.* 6.0 Hz.

Table 1 demonstrates the well known [21,22] effect of a neighbouring hydroxy-group on the stereochemistry of double bond epoxidation; thus, like cholest-5-en-3α-ol,[21] cholest-4-en-7α-ol produces exclusively the α-epoxide.

The relative amounts of α- and β-epoxides obtained in the epoxidation of the 3-substituted cholest-5-enes with *m*-chloroperbenzoic acid (Table 1) are similar to those obtained with various other peroxy-acids.[22] Our results do not support the claim [26] that *m*-chloroperbenzoic acid is of superior stereoselectivity to other peroxy-acids. *m*-Chloroperbenzoic acid and *p*-nitroperbenzoic acid are much more reactive epoxidation agents than perbenzoic acid itself.[16,22] However, we doubt whether there is much connection between the reactivity of a peroxy-acid and its stereoselectivity, and there is evidence [21,22] that other factors, mainly the polarity of the solvent and the bulkiness of the peroxy-acid molecule, dominate the stereochemistry of these reactions.

The proportions of the α-epoxides in the epoxidation of the 7-substituted cholest-4-enes are smaller than those obtained from the corresponding 3-substituted cholest-5-enes (Table 1). Apparently, the stereochemistry of epoxidation of either the 4,5- or the 5,6-double bond in cholestane is mainly determined by the angular 10-methyl group which makes the β-face of the molecule sterically more hindered, so that the α-epoxide is preferred in both systems. On this basis, we would also expect similar proportions of the α-epoxides in the two systems, since the symmetry [27] of rings A and B in the cholestane skeleton indicates that the 4,5- and 5,6-double bonds occupy formally equivalent positions with respect to the 10-methyl group. However, our results (Table 1) show remarkable differences between the two systems. We believe that this is due to the presence of the 13-methyl group. Dreiding models reveal that this is closer to the 5,6-double bond of cholest-5-ene than to the 4,5-double bond in cholest-4-ene. Consequently, the 4,5-double bond is sterically less hindered at its β-face than the 5,6-double bond, resulting in a smaller proportion of the β-epoxide in the latter case. Differences may also result from disparity of the conformations of rings A and B. The more flexible ring A in cholest-4-ene may twist more easily towards the α-face of the molecule than ring B in cholest-5-ene. This again may increase the proportion of the α-epoxides from the 3-substituted cholest-5-enes as compared with the isomeric 7-substituted cholest-4-enes.

Nucleophilic Opening of Epoxides.—Treatment of each of the 4α,5α- and 5α,6α-epoxides with *ca.* 100-fold excess of sodium azide in refluxing acetone–water (2 : 1 v/v) afforded the corresponding azides: (15) from (1a), (16) from (2), (18) from (6), (19) from (9a), (20) from (10), (21) from (11a), and (22) from (14a). In general the reactions were clean and no side products were detected by t.l.c. In each case, the reaction could have been brought to completion by applying sufficiently long refluxing times, indicating that the reverse reaction, *i.e.* the conversion of hydroxy-azides into epoxides,[28] is negligible under our conditions.

The n.m.r. spectrum of the azide (15) indicated its structure. The hydrogen atom geminal to the azido-group gives rise to a multiplet of $W_{\frac{1}{2}}$ 6.8 Hz. This value is characteristic of an equatorial proton,[29] thus establishing that the 4-azido-group is axial and in the β-configuration. The azides (16) and (18) were insufficiently soluble in conventional n.m.r. solvents for structural evidence to be obtained. The structure of

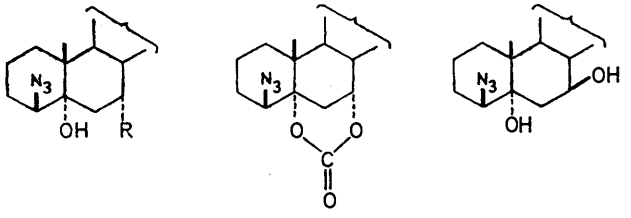
[26] L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 136.

[27] N. S. Bhacca and D. H. Williams, ' Applications of N.m.r. Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, p. 29.

[28] B. A. Marples, B. M. O'Callaghan, and J. L. Scottow, *J.C.S. Perkin I*, 1974, 1026.

[29] L. M. Jackman and S. Sternhell, ' Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, London, 1969, p. 288.

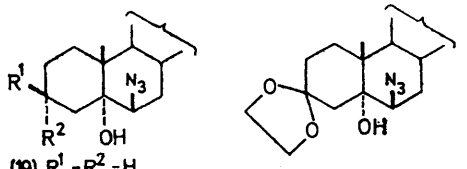
(16) was demonstrated chemically as follows. Treatment with phosgene in chloroform–pyridine afforded the corresponding cyclic carbonate (17). This established the 5α,7α-configuration in (16), and showed that the 4-azido-group is axial. The production of both (15) and (16) indicates that the ring opening of the 4α,5α-epoxides with sodium azide produces the *trans*-diaxial hydroxy-azides. In the n.m.r. spectra of the azides (19)—(22) the signals of the protons geminal to the



(15) R = H
(16) R = OH

(17)

(18)



(19) $R^1 = R^2 = H$
(20) $R^1 = H, R^2 = OH$
(21) $R^1 = OH, R^2 = H$

(22)

azido-groups appeared at about δ 3.5, with $W_{\frac{1}{2}}$ *ca.* 5 Hz. This establishes the 6-azido-groups in all of these azides as axial and in the β-configuration. Therefore, in the opening of the epoxide rings of the 5α,6α-epoxides, the 5-hydroxy-6-azido-systems also assume a diaxial relationship. These stereochemical results are similar to those obtained [30,31] in the acid-catalysed opening of epoxides with azide ions. They also fit the general pattern of opening of steroidal epoxides with nucleophiles which give *trans*-diaxially substituted products in almost every case.[32]

Table 2 summarizes the yields of azides obtained from the corresponding epoxides after various refluxing times. Comparison of the yields (which are proportional to the rates) indicates significant rate enhancement for the reaction of (2) with sodium azide in comparison with (1a), (3), and (6) in the 4α,5α-epoxide series (*cf.* runs 1, 3, 5, and 7 or 2, 4, 6, and 8 in Table 2). Similarly, the epoxide (10) reacts faster than (9a), (11a), and (14a) in the 5α,6α-epoxide series (*cf.* runs 9, 11, 13, and 15 or 10, 12, 14, and 16).

The greater reactivity of (2) among the 4α,5α-epoxides, and of (10) among the 5α,6α-epoxides, results from intramolecular electrophilic neighbouring group assistance, since only in these epoxides are the neighbouring 7α- and 3α-hydroxy-groups, respectively, in positions which enable electrophilic participation by the hydroxy-protons with consequent negative charge delocalization in the transition states [see (23) and (24), respectively].

[30] K. Ponsold, *Chem. Ber.*, 1962, **95**, 1727.
[31] W. J. Wechter, *J. Org. Chem.*, 1966, **31**, 2136.

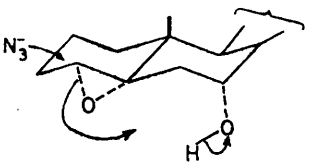
TABLE 2

Reactions of 4α,5α- and 5α,6α-epoxycholestanes and their derivatives with sodium azide [a] in refluxing acetone–water (2 : 1)

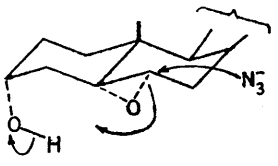
Steroid [b]		Run no.	Reflux time (h)	Yield of azide [c] (%)	Unchanged epoxide [c] (%)
4α,5α-Epoxides	(1a)	1	5	Trace	97
		2	450	51	44
	(2)	3	5	48	49
		4	50	93	0
	(3)	5	5	0	98
		6	500	Trace (?) [d]	94
	(6)	7	5	6	91
		8	90	46	48
5α,6α-Epoxides	(9a)	9	8	2	96
		10	185	45	48
	(10)	11	8	52	39
		12	46	94	0
	(11a)	13	8	6	86
		14	80	50	41
	(14a)	15	8	Trace	93
		16	195	31	64

[a] $[NaN_3] = 0.308$ mol l^{-1}. [b] [Steroid] $= 3.73 \times 10^{-3}$ mol l^{-1}. [c] Accurate to ±3%. [d] No azide isolated but the crude mixture showed very weak absorption at *ca.* 2 100 cm^{-1}.

The i.r. spectrum of the epoxide (10) in CCl_4 shows O–H stretching absorption at 3 570 cm^{-1}. The corresponding absorption in the spectrum of (11a) appears at



(23)



(24)

3 630 cm^{-1}. This has been taken as evidence for the existence of intramolecular hydrogen bonding between the 3-hydroxy-group and the oxygen atom of the 5α,6α-epoxide ring in (10).[21] Similarly, the i.r. spectrum of (2) in CCl_4 shows O–H stretching absorption at 3 580 cm^{-1}, whereas (6) shows absorption at 3 645 cm^{-1}, again suggesting intramolecular hydrogen bonding in (2). Such ground-state internal hydrogen bonds may increase the reactivity of both (2) and (10), since they produce a positive charge on the epoxide ring, thus enabling easier attack by the nucleophile. Indeed, the opening of an epoxide ring by nucleophiles proceeds much faster under acid catalysis.[32] However, Dreiding models of structures (2) and (10) show that the approach of the hydroxylic hydrogen atom towards the free orbitals of the epoxide ring oxygen is limited, and does not enable the formation of a strong hydrogen bond. In fact we believe that the differences in the i.r. spectra of the pairs (2) and (6) and (10) and (11a), which might have been taken as evidence for intramolecular hydrogen bonding,[21] result mainly from differences in the characteristic O–H stretching absorptions of axial and equatorial OH groups; *e.g.* cholesterol shows $\nu_{max.}$ (CCl_4) 3 640

[32] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 112.

cm^{-1} whereas epicholesterol shows $\nu_{max.}$ 3 610 cm^{-1}; similarly, cholest-4-en-7β-ol shows $\nu_{max.}$ 3 655 cm^{-1} and the 7α-epimer 3 610 cm^{-1}. We conclude that the greater reactivities of the epoxides (2) and (10) are mainly due to the delocalization of negative charge in the transition states [see (23) and (24)].

Other noteworthy observations are the low reactivities of the methoxy-derivative (3) compared with (1a), (2), and (6), and the acetal (14a) compared with (9a), (10), and (11a). The occurrence of intramolecular electrophilic catalysis with (2) and (10) is by itself an indication of the importance of solvation of the corresponding transition states, particularly with respect to the negative charge developing on the leaving group (the ring oxygen). In compounds (1a), (3), (6), (9a), (11a), and (14a), in which intramolecular solvation is impossible, the transition states can be stabilized only by intermolecular solvation, *e.g.* by water molecules. In compound (3) there is considerable steric hindrance by the 7α-methoxy-group to the approach of solvent molecules. Similar factors operate in the case of the acetal (14a). This rationalisation is supported by the work of Angyal and Stewart, who observed neighbouring hydroxy-group participation in the reactions of certain cyclitol epoxides with sodium benzoate in dimethylformamide.[18] This solvent solvates anions very poorly, and the appearance of internal electrophilic catalysis demonstrates the requirement for solvation of the transition state of these reactions.[18] In the acid-catalysed reaction in dimethylformamide, no such catalysis was observed.[18]

Isomeric epoxides show only slight differences in reactivity: thus, (1a), (2), and (6) resemble (9a), (10), and (11a) respectively (Table 2). This is to be expected from the similarity in symmetry of the 4α,5α- and 5α,6α-epoxides. The pair (14a) and (3) is an exception, the latter being much less reactive. There are also significant differences in reactivities of epoxides belonging to the same class, *e.g.* (1a) and (6), or (9a) and (11a). We are aware of no simple explanation for these phenomena, but it is reasonable to assume that owing to slight conformational differences the corresponding transition states may be stabilized differently by solvation.

EXPERIMENTAL

M.p.s were determined with a Fisher-Johns apparatus. I.r. spectra were recorded with a Perkin-Elmer 254 spectrophotometer. N.m.r. spectra were taken for solutions in deuteriochloroform with a Varian T60 spectrometer, with tetramethylsilane as internal standard. Optical rotations were determined for solutions in chloroform with a Perkin-Elmer 141 polarimeter. Mass spectra were recorded on a MAT 311 spectrometer. T.l.c. was carried out on silica gel G. Plates were eluted with light petroleum (b.p. 60—80°) containing 10—20% acetone. Work-up of epoxidation reactions was carried out according to the literature.[26] Unless otherwise stated, other work-up procedures have been previously described.[16]

[33] D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1951, 1048.

4α,5α-Epoxycholestane (1a).—Cholest-4-ene [33] (m.p. 78—81°, $[\alpha]_D$ +75°) (500 mg) in methylene chloride (50 ml) was treated at room temperature with a slight excess of *m*-chloroperbenzoic acid for 2 h. Work-up as usual and repeated t.l.c. gave pure 4α,5α-epoxycholestane (1a) (280 mg, 51%), m.p. 101—102° (needles from acetone–water), $[\alpha]_D$ +71° (*c* 4.16) (lit.,[23] m.p. 101—103°, $[\alpha]_D$ +77°), δ 1.07 (s, 19-H_3) and 2.93 (m, $W_{\frac{1}{2}}$ 6.0 Hz, H-4). Also separated was 4β,5β-epoxycholestane (1b) (200 mg, 33%), m.p. 62—64°, $[\alpha]_D$ +8° (*c* 1.40) (lit.,[24] m.p. 64—65°, $[\alpha]_D$ +6°), δ 1.02 (s, 19-H_3) and 2.98 (m, $W_{\frac{1}{2}}$ 6.0 Hz, H-4), M^+ 386.

4α,5α-Epoxycholestan-7α-ol (2).—(a) *By reduction of 4α,5α-epoxycholestan-7-one.* The steroid [16] (75 mg) in methanol (40 ml) at 0 °C was treated with a slight excess of sodium borohydride for 1 h. Work-up as usual and t.l.c. gave the 7α-*ol* (2) (63 mg, 84%) as needles (from methanol–ether), m.p. 107—109°, $[\alpha]_D$ +38° (*c* 0.47), $\nu_{max.}$ (CCl_4) 3 580 cm^{-1}, δ 1.05 (s, 19-H_3), 2.88 (m, $W_{\frac{1}{2}}$ 6.4 Hz, H-4), and 3.85 (m, $W_{\frac{1}{2}}$ 7.6 Hz, H-7) (Found: C, 80.45; H, 11.4. $C_{27}H_{46}O_2$ requires C, 80.55; H, 11.5%).

(b) *By epoxidation of cholest-4-en-7α-ol.* The steroid [34] (120 mg) in ether (40 ml) was treated with an excess of monoperphthalic acid and the solution was left at room temperature for 2 h. Work-up and t.l.c. gave pure 4α,5α-epoxide (2) (81 mg, 65%; the rest of the material was the starting olefin), m.p. 107—109° (from methanol–ether), identical with the sample obtained by method (a) (mixed m.p., i.r. spectrum, and t.l.c.).

4α,5α-Epoxy-7α-methoxycholestane (3).— 4α,5α-Epoxycholestan-7α-ol (100 mg) in dry benzene (50 ml) was treated with methyl iodide (5 ml) and sodium hydride (200 mg), and the solution was refluxed for 16 h. The mixture was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. T.l.c. gave pure 4α,5α-*epoxy*-7α-*methoxycholestane* (3) (83 mg, 80%). Recrystallization from ethanol–water gave needles, m.p. 64—65°, $[\alpha]_D$ +48° (*c* 0.28), $\nu_{max.}$ ($CHCl_3$) 1 095 cm^{-1}, δ 1.06 (s, 19-H_3), 2.73 (m, $W_{\frac{1}{2}}$ 6.0 Hz, H-4), 3.27 (s, OCH_3), and 3.33 (m, $W_{\frac{1}{2}}$ 7.6 Hz, H-7) (Found: C, 80.85; H, 11.9. $C_{28}H_{48}O_2$ requires C, 80.7; H, 11.6%). Cholest-4-en-7α-ol did not react under the same conditions.

Cholest-4-en-7β-yl Acetate (4).—A solution of cholest-4-en-7β-ol (1.0 g) in dry pyridine (50 ml) and acetic anhydride (10 ml) was left at room temperature for 16 h. Work-up as usual and recrystallization from methanol gave the acetate (950 mg, 87%) as plates, m.p. 94—96°, $[\alpha]_D$ +70° (*c* 0.48) (lit.,[35] m.p. 97—99°, $[\alpha]_D$ +72°), $\nu_{max.}$ (Nujol) 1 730 cm^{-1}, δ 1.00 (s, 19-H_3), 1.84 (s, OAc), 4.20 (m, $W_{\frac{1}{2}}$ *ca.* 20 Hz, H-7), and 5.23 (H-4).

Epoxidation of the Acetate (4).—The steroid (1.0 g) in chloroform (100 ml) at 0 °C was treated with a slight excess of *m*-chloroperbenzoic acid and left at 0 °C for 1 h. Work-up as usual and repeated t.l.c. gave 4α,5α-*epoxycholestan*-7β-*yl acetate* (5a) (510 mg, 49%) as plates, m.p. 104—106° (from acetone–water), $[\alpha]_D$ +85° (*c* 1.08), $\nu_{max.}$ (Nujol) 1 730, 1 243, and 1 026 cm^{-1}, δ 1.11 (s, 19-H_3), 2.03 (s, OAc), 2.98 (m, $W_{\frac{1}{2}}$ 6.0 Hz, H-4), and 4.73 (m, $W_{\frac{1}{2}}$ 22.0 Hz, H-7) (Found: C, 78.45; H, 11.05. $C_{29}H_{48}O_3$ requires C, 78.35; H, 10.9%).

Also separated was the 4β,5β-epoxide (5b) (390 mg, 38%). The compound failed to crystallize from a variety of solvents although t.l.c. and n.m.r. evidence indicated

[34] G. J. Kent and E. S. Wallis, *J. Org. Chem.*, 1959, **24**, 1235.
[35] J. Fajkos, J. Joska, and F. Sorm, *Coll. Czech. Chem. Comm.*, 1968, **33**, 3324 (*Chem. Abs.*, 1968, **69**, 106,960).

high purity. It showed $[\alpha]_D$ +18.5 (*c* 2.05), $\nu_{max.}$ (CCl_4) 1 730 cm^{-1}, δ 1.03 (s, 19-H_3), 2.01 (s, OAc), 3.02 (m, $W_{\frac{1}{2}}$ 6.5 Hz, H-4), and 4.57 (m, $W_{\frac{1}{2}}$ 24.0 Hz, H-7), M^+ 444. The structure was proven by transformation into (8b) (see below).

4α,5α-Epoxycholestan-7β-ol (6).—A solution of the acetate (5a) (100 mg) in methanol (80 ml) and water (20 ml) containing potassium carbonate (800 mg) was refluxed for 5 h. Water was added and the product extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. T.l.c. afforded pure 7β-*ol* (6) (78 mg, 87%), as needles from acetone–water, m.p. 60—62°, $[\alpha]_D$ +91° (*c* 1.50), $\nu_{max.}$ (CCl_4) 3 645 cm^{-1}, δ 1.08 (s, 19-H_3), 2.94 (m, $W_{\frac{1}{2}}$ 6.0 Hz, H-4), and 3.68 (m, $W_{\frac{1}{2}}$ 26.0 Hz, H-7) (Found: C, 80.3; H, 11.4. $C_{27}H_{46}O_2$ requires C, 80.55; H, 11.5%).

Oxidation of 4α,5α-Epoxycholestan-7α-ol.—The steroid (6) (50 mg) in pyridine (5 ml) was treated with chromium trioxide (150 mg) and the solution was left at room temperature for 6 h. It was then poured into water and the product extracted with ether. The extract was washed with dilute hydrochloric acid and water, dried ($MgSO_4$) and evaporated under reduced pressure. T.l.c. gave 4α,5α-epoxycholestan-7-one (7a) (44 mg, 87%) as needles, m.p. 119—122° (from ethanol–water), $[\alpha]_D$ +15° (*c* 1.12) (lit.,[16] m.p. 119—122°, $[\alpha]_D$ +16°), identical with authentic [16] (7a) (mixed m.p., t.l.c., and i.r. spectrum). Compound (7a) was smoothly isomerized into 4α-hydroxycholest-5-en-7-one (8a) according to the method previously described.[16]

Transformation of the Acetoxy-epoxide (5b) *into the Hydroxy-enone* (8b).—Hydrolysis of (5b) (100 mg), followed by oxidation, was carried out as in the case of (5a) and (6) respectively (see above). The crude reaction mixture, after work-up, was treated with triethylamine in methanol as previously described.[16] T.l.c. gave pure 4β-hydroxycholest-5-en-7-one (8b) (61 mg, 83%) as needles, m.p. 150—152° (from acetone–water) (lit.,[16] m.p. 150—152°), identical with an authentic sample (mixed m.p., u.v., i.r., and n.m.r. spectra, and t.l.c.).

Epoxidation of Cholest-4-en-7β-ol.—The steroid (500 mg) in methylene chloride (100 ml) was treated with a slight excess of *m*-chloroperbenzoic acid and the solution was left at room temperature for 4 h. Work-up as usual (see above) and t.l.c. afforded an oil (450 mg, 86%) which was a mixture of the corresponding 4α,5α- and 4β,5β-epoxides. The two hydroxy-epoxides could not be separated by t.l.c. under various conditions. The relative amounts were determined by the following procedure. The mixture (200 mg) in pyridine (50 ml) at 0 °C was treated with chromium trioxide (500 mg). After 5 h the solution was poured into water and the products were extracted with ether. The extract was washed with water, dilute hydrochloric acid, and water again, dried (Na_2SO_4), and evaporated under reduced pressure. The crude mixture was dissolved in methanol (30 ml) and treated with triethylamine (5 ml). The solution was refluxed for 3 h, and then the solvent was removed under reduced pressure. T.l.c. afforded pure 4α-hydroxycholest-5-en-7-one (8a) (102 mg, 50%) and pure 4β-hydroxycholest-5-en-7-one (8b) (76 mg, 38%), both of which were identical with authentic samples [16] (mixed m.p. and u.v., i.r., and n.m.r. spectra). Since t.l.c. indicated that (8a) and (8b) are the two major products in the overall reaction, their ratio was taken as a measure of the ratio of the two original hydroxy-epoxides.

Epoxidation of Cholest-5-ene.—The steroid (1.0 g) {m.p. 91—92°, $[\alpha]_D$ −53° (*c* 1.05); lit.,[36] m.p. 92—94°, $[\alpha]_D$ −55°} in methylene chloride (30 ml) was treated at room temperature with *m*-chloroperbenzoic acid (0.8 g) for 30 min. Work-up as usual and repeated t.l.c. gave 5α,6α-epoxycholestane (9a) (700 mg, 67%), m.p. 73—74° (from acetone–water), $[\alpha]_D$ −50° (*c* 0.80) (lit.,[37] m.p. 74—75°, $[\alpha]_D$ −56°), δ 1.02 (s, 19-H_3) and 2.88 (d, *J* 4.0 Hz, H-6). Also separated was 5β,6β-epoxycholestane (9b) (190 mg, 18%), m.p. 52—55° (from acetone–water), $[\alpha]_D$ −7.5° (*c* 0.58) (lit.,[37] m.p. 55—57°, $[\alpha]_D$ −9°), δ 0.98 (s, 19-H_3) and 3.00 (d, *J* 2.0 Hz, H-6). The relative amounts of (9a) and (9b) in the crude epoxidation mixture could also be determined from its n.m.r. spectrum.[22] We obtained 79 and 21% of (9a) and (9b), respectively.

5α,6α-Epoxycholestan-3α-ol (10).—Cholest-5-en-3α-ol [14] (100 mg) in methylene chloride (25 ml) was treated with a slight excess of *m*-chloroperbenzoic acid, and the solution was left at room temperature for 15 min. Work-up as usual and t.l.c. afforded pure 5α,6α-epoxide (10) (95 mg, 91%) as needles, m.p. 124—125° (from methanol–water), $[\alpha]_D$ −48° (*c* 2.10) {lit.,[21] m.p. 124°, $[\alpha]_D$ −51.5° (dioxan)}, $\nu_{max.}$ (CCl_4) 3 570 cm^{-1}, δ 1.02 (s, 19-H_3), 2.87 (d, *J* 4.0 Hz, H-6), and 4.09 (m, $W_{\frac{1}{2}}$ 7.0 Hz, H-3). The corresponding 5β,6β-epoxide was not detected in the crude epoxidation mixture by either t.l.c. or n.m.r.

Epoxidation of Cholesterol.—The steroid (10 g) was epoxidized with *m*-chloroperbenzoic acid according to the procedure of Fieser *et al.*[26] Two recrystallizations from acetone–water afforded pure 5α,6α-epoxide (11a), m.p. 141—142°, $[\alpha]_D$ −47° (*c* 1.50) (lit.,[26] m.p. 141—143°, $[\alpha]_D$ −46°), $\nu_{max.}$ (CCl_4) 3 630 cm^{-1}, δ 1.03 (s, 19-H_3), 2.90 (d, *J* 3.8 Hz, H-6), and 3.85 (m, $W_{\frac{1}{2}}$ 26.0 Hz, H-3). The n.m.r. spectrum of the crude epoxidation mixture also showed weak signals at δ 0.98 (s, 19-H_3), 3.07 (d, *J* 2.4 Hz, H-6α), and 3.65 (m, $W_{\frac{1}{2}}$ *ca.* 25 Hz, H-3α) corresponding to 5β,6β-epoxycholestan-3β-ol (11b). Indeed, in repeated t.l.c. separations of a portion of the crude epoxidation mixture (200 mg), we were able to isolate a small amount of (11b) (29 mg), m.p. 130—132° (from methanol), $[\alpha]_D$ +9° (*c* 0.80) (lit.,[38] m.p. 131°, $[\alpha]_D$ +10°), identical with authentic material (mixed m.p. and i.r. and n.m.r. spectra). The relative amounts of (11a) and (11b) in the crude epoxidation mixture were determined from its n.m.r. spectrum,[22] and we obtained 81 and 19% of (11a) and (11b), respectively.

Epoxidation of Cholest-5-en-3-one.—The steroid (10.0 g) {m.p. 126—128°, $[\alpha]_D$ −3° (*c* 1.55); lit.,[39] m.p. 126—129°, $[\alpha]_D$ −2.5°}, in methylene chloride (200 ml), was treated at 0 °C with *m*-chloroperbenzoic acid (8.0 g), and the solution was left at 0 °C for 30 min. Work-up as usual, and two recrystallizations from ethanol–water, gave pure 5α,6α-epoxycholestan-3-one (12a) (5.1 g, 49%) as needles, m.p. 123—125°, $[\alpha]_D$ −40° (*c* 3.20) (lit.,[40] m.p. 122—123°, $[\alpha]_D$ −39°), $\nu_{max.}$ (CCl_4) 1 715 cm^{-1}, δ 1.23 (s, 19-H_3) and 2.97 (d, *J* 4.4 Hz, H-6). Attempted t.l.c. separation of either (12a) or (12b) failed, since both epoxides rearranged on silica gel to the corresponding hydroxy-enones (see below). Some rearrangement occurred also during work-up. The

[36] R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Amer. Chem. Soc.*, 1957, **79**, 4122.
[37] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 1957, 4596.
[38] L. F. Fieser and M. Fieser, ' Steroids,' Reinhold, New York, 1959, p. 198.
[39] L. F. Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 5421.
[40] B. Ellis and V. Petrow, *J. Chem. Soc.*, 1956, 4417.

relative amounts of (12a) and (12b) were determined by the following procedure. A solution of the crude epoxidation mixture (0.6 g) in methanol (80 ml) and triethylamine (5 ml) was refluxed for 2 h. The solvent was removed under reduced pressure. T.l.c. gave pure 6α-hydroxycholest-4-en-3-one (13a) (350 mg, 58%), m.p. 153—155° (needles from acetone), $[\alpha]_D$ +79° (*c* 1.65), $\lambda_{max.}$ (EtOH) 240 nm (ε 16 900) {lit.,[41] m.p. 155—156°, $[\alpha]_D$ +81°, $\lambda_{max.}$ (EtOH) 240 nm}, $\nu_{max.}$ (CCl_4) 3 600 and 1 670 cm^{-1}, δ 1.17 (s, 19-H_3), 4.28 (m, $W_{\frac{1}{2}}$ *ca.* 20 Hz, H-6), and 6.18 (d, *J* 1.8 Hz, H-4). Also separated was pure 6β-hydroxycholest-4-en-3-one (13b) (136 mg, 23%), m.p. 188—190° (needles from acetone), $[\alpha]_D$ +27° (*c* 0.80), $\lambda_{max.}$ (EtOH) 236 nm (ε 13 500) {lit.,[41] m.p. 193—194°, $[\alpha]_D$ +27°, $\lambda_{max.}$ (EtOH) 236 nm}, $\nu_{max.}$ (CCl_4) 3 600 and 1 670 cm^{-1}, δ 1.30 (s, 19-H_3), 4.21 (m, $W_{\frac{1}{2}}$ 6.8 Hz, H-6), and 5.78 (s, H-4).

Reduction of 5α,6α-*Epoxycholestane*-3-*one*.—The steroid (500 mg) in ethanol (100 ml), at 0 °C, was treated with a slight excess of sodium borohydride (*ca.* 1.1 equiv.) for 2 h. Work-up as usual and t.l.c. gave 5α,6α-epoxycholestan-3α-ol (10) (134 mg, 26%) as needles, m.p. 124—125° (from methanol), identical with authentic material (mixed m.p., i.r. spectrum, $[\alpha]_D$, and t.l.c.). Also formed was 5α,6α-epoxycholestan-3β-ol (11a) (164 mg, 32%) as needles, m.p. 141—142° (from acetone–water), identical with authentic material (mixed m.p., i.r. spectrum, $[\alpha]_D$, and t.l.c.).

5α,6α-*Epoxy*-3,3-*ethylenedioxycholestane* (14a).—A solution of 3,3-ethylenedioxycholest-5-ene (1.0 g) (m.p. 133—134°, $[\alpha]_D$ −30°; lit.,[42] m.p. 134—135°, $[\alpha]_D$ −31°) in methylene chloride (50 ml) was treated at room temperature with a slight excess of *m*-chloroperbenzoic acid for 1 h. Work-up as usual and t.l.c. afforded pure 5α,6α-epoxy-3,3-ethylenedioxycholestane (14a) (410 mg, 39%) as blades, m.p. 144—146° (from methanol), $[\alpha]_D$ −45° (*c* 1.35) (lit.,[43] m.p. 118—120°, $[\alpha]_D$ −33°), δ 1.03 (s, 19-H_3), 2.83 (d, *J* 3.8 Hz, H-6), and 3.95 (m, O·CH_2·CH_2·O). The rest of the material was mainly 5β,6β-epoxy-3,3-ethylenedioxycholestane (14b), m.p. 128—131° (from methanol), $[\alpha]_D$ +11° (*c* 1.80) (lit.,[43] m.p. 126—127°, $[\alpha]_D$ +9°), δ 1.00 (s, 19-H_3), 3.03 (d, *J* 2.1 Hz, H-6), and 3.90 (s, O·CH_2·CH_2·O).

Reactions of the 4α,5α- *and* 5α,6α-*Epoxides with Sodium Azide*.—The procedure is illustrated for 4α,5α-epoxycholestan-7α-ol (2). A solution of the steroid (2) (150 mg, 3.73×10^{-4} mol), in AnalaR acetone (B.D.H.)–distilled water (2 : 1 v/v) (100 ml), containing sodium azide (B.D.H.) (2.00 g, 3.08×10^{-2} mol), was refluxed for 57 h; needles started to separate after 1 h. Water was added and the product was extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. T.l.c. gave pure 4β-*azidocholestane*-5α,7α-*diol* (16) (155 mg, 93%) as large needles, m.p. 216—218° (from acetone), $[\alpha]_D$ +48° (*c* 0.14), $\nu_{max.}$ ($CHCl_3$) 3 480, 3 350sh,br, and 2 140 cm^{-1}; material insufficiently soluble to give a reliable n.m.r. spectrum; *m/e* 417 (100%, *M* − N_2), 402 (30), 399 (35), and 384 (56) (Found: C, 72.8; H, 10.45; N, 9.3. $C_{27}H_{47}N_3O_2$ requires C, 72.75; H, 10.65; N, 9.45%).

The reactions of the other epoxides were carried out under the same conditions, and were followed by t.l.c. In general, reactions were clean; no side-products were detected. The results are summarized in Table 2; characteristic constants for the other azides are given below.

4β-*Azidocholestane*-5α,7α-*diyl Carbonate* (16).—The diol (16) (120 mg) in chloroform (60 ml) and pyridine (30 ml) was treated with an excess of phosgene, at room temperature, for 2 h. The solution was poured into ice-cold aqueous sodium hydrogen carbonate, and the product was extracted with chloroform. The extract was washed with dilute hydrochloric acid and water, then dried (Na_2SO_4), and evaporated under vacuum. Several t.l.c. separations afforded the pure *cyclic carbonate* (17) (55 mg, 42%), needles (from acetone–water), m.p. 204—210° (starts to decompose at *ca.* 180°), $[\alpha]_D$ −25° (*c* 0.09), $\nu_{max.}$ (CCl_4) 1 750 and 2 140 cm^{-1}, δ 1.15 (s, 19-H_3), 3.63 (m, $W_{\frac{1}{2}}$ 6.2 Hz, H-4), and 4.48 (m, $W_{\frac{1}{2}}$ 8 Hz, H-7) (Found: C, 74.1; H, 9.9; N, 9.0. $C_{28}H_{45}N_3O_2$ requires C, 73.8; H, 9.95; N, 9.2%).

4β-*Azidocholestan*-5α-*ol* (15) *from* (1a).—The pure azide (15) showed m.p. 127—128° (plates from acetone–water), $[\alpha]_D$ +74° (*c* 1.05) (lit.,[30] m.p. 122°, $[\alpha]_D$ +70°), $\nu_{max.}$ (CCl_4) 3 605 and 2 085 cm^{-1}, δ 1.12 (s, 19-H_3) and 3.42 (m, $W_{\frac{1}{2}}$ 6.8 Hz, H-4), *m/e* 401 (100%, *M* − N_2), 386 (62), 383 (88), 367 (88), and 332 (38) (Found: C, 75.6; H, 10.95; N, 9.95. Calc. for $C_{27}H_{47}N_3O$: C, 75.45; H, 11.05; N, 9.8%).

4β-*Azidocholestane*-5α,7β-*diol* (18) *from* (6).—The pure *azide* (18) showed m.p. 239—241° (needles from acetone–water), $[\alpha]_D$ +85° (*c* 0.12), $\nu_{max.}$ (Nujol) 3 460, 3 300br, and 2 080 cm^{-1}; material insufficiently soluble to give a reliable n.m.r. spectrum; *m/e* 417 (88%, *M* − N_2), 402 (84), 399 (39), and 384 (100) (Found: C, 73.0; H, 10.75; N, 9.4. $C_{27}H_{47}N_3O_2$ requires C, 72.75; H, 10.65; N, 9.45%).

6β-*Azidocholestan*-5α-*ol* (19) *from* (9a).—The pure *azide* (19) showed m.p. 106—108° (needles from acetone–water), $[\alpha]_D$ −55° (*c* 0.45), $\nu_{max.}$ (CCl_4) 3 645 and 2 095 cm^{-1}, δ 1.10 (s, 19-H_3) and 3.32 (m, $W_{\frac{1}{2}}$ 5.6 Hz, H-6), *m/e* 401 (23%, *M* − N_2), 386 (100), 383 (14), 372 (27), and 358 (18) (Found: C, 75.5; H, 10.8; N, 9.4. $C_{27}H_{47}N_3O$ requires C, 75.45; H, 11.05; N, 9.8%).

6β-*Azidocholestane*-3α,5α-*diol* (20) *from* (10).—The pure *azide* (20) crystallized from acetone–water as needles, m.p. 183—184°, $[\alpha]_D$ −57° (*c* 1.02), $\nu_{max.}$ (CCl_4) 3 470 and 2 090 cm^{-1}, δ 1.03 (s, 19-H_3), 3.42 (m, $W_{\frac{1}{2}}$ 5.0 Hz, H-6), and 4.27 (m, $W_{\frac{1}{2}}$ 7.2 Hz, H-3), *m/e* 417 (30%, *M* − N_2), 402 (100), and 384 (41) (Found: C, 72.7; H, 10.65; N, 9.8. $C_{27}H_{47}N_3O_2$ requires C, 72.75; H, 10.65; N, 9.45%).

6β-*Azidocholestane*-3β,5α-*diol* (21) *from* (11a).—The pure *azide* (21) crystallized from acetone as long needles, m.p. 135—138°, $[\alpha]_D$ −37.5° (*c* 1.00), $\nu_{max.}$ (CCl_4) 3 610, 3 420vbr, and 2 105 cm^{-1}, δ 1.12 (s, 19-H_3), 3.38 (m, $W_{\frac{1}{2}}$ 5.1 Hz, H-6), and 4.03 (m, $W_{\frac{1}{2}}$ 22 Hz, H-3), *m/e* 417 (23%, *M* − N_2), 402 (100), and 384 (64) (Found: C, 73.0; H, 10.65; N, 9.15. $C_{27}H_{47}N_3O_2$ requires C, 72.75; H, 10.65; N, 9.45%).

6β-*Azido*-3,3-*ethylenedioxycholestan*-5α-*ol* (22) *from* (14a).—The pure azide (22) showed m.p. 90—93° (lit.,[31] m.p. 89—91°), $[\alpha]_D$ −56° (*c* 0.55), $\nu_{max.}$ (CCl_4) 3 650, 3 490br and 2 100 cm^{-1}, δ 1.04 (s, 19-H_3), 3.42 (m, $W_{\frac{1}{2}}$ 5.0 Hz, H-6), and 3.99 (m, O·CH_2·CH_2·O), *m/e* 459 (4%, *M* − N_2), 444 (22), 426 (5), and 99 (100).

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[41] L. F. Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 4377.

[42] R. Antonucci, S. Bernstein, R. Littell, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, 1952, **17**, 1341.

[43] G. Cooley, B. Ellis, D. N. Kirk, and V. Petrow, *J. Chem. Soc.*, 1957, 4112.