Acetolytic Cleavage of the Epimeric 2- and 6-Methoxy-5α-cholestanes involving a 1,2-Hydride Shift to C-2

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Acetolytic cleavage of 2β-methoxy-5α-cholestane with boron trifluoride in acetic anhydride followed by hydrolysis gave 5α-cholestan-3α-ol as the major non-olefinic product, along with some of the epimeric 2-ols. 2α-Methoxy-5α-cholestane gave 5α-cholestan-2α-ol as the major non-olefinic product, with some 2β-ol and the rearrangement product, 5α-cholestan-3α-ol. Deuterium exchange studies showed that hydride shifts of both 3α- and 3β-hydrogen atoms were involved in the formation of 5α-cholestan-3α-ol from both ethers.

Similar cleavage of 6α-methoxy-5α-cholestane gave only 5α-cholestan-6α-ol, probably formed by nucleophilic attack at the methoxy carbon atom. 6β-Methoxy-5α-cholestane gave only cholest-5-ene.

BORON TRIFLUORIDE–ETHER complex in acetic anhydride has been used extensively for cleavage of steroid ethers.[1-8] Narayanan and Iyer[3] showed that the cleavage of 3α- and 3β-methoxy-5α-cholestane gave different ratios of 3β- and 3α-acetoxy-5α-cholestane and 5α-cholest-2-ene (Table 1). To account for the greater amount of retention in the products, they proposed[4,5] that cleavage took place both at the steroid carbon atom, leading to racemisation, and at the methyl carbon atom, leading to acetates with retention of configuration.

TABLE 1

Acetolysis of 5α-cholestane derivatives

	Products			
		Acetates		
Substrate	Olefinic	Retention	Inversion	Rearranged
3α-OMe [a] (*ax*)	*ca.* 68	*ca.* 20	*ca.* 12	
3β-OMe [a] (*eq*)	*ca.* 30	*ca.* 40	*ca.* 30	
2β,19-Epoxide [b] (*ax*)	*ca.* 35		*ca.* 45	*ca.* 20
2β,19-Epoxy-3-one [c] (*ax*)			100	
6β,19-Epoxide [d] (*ax*)		100		
6β-OMe [e] (*ax*)	99			
6α-OMe [e] (*eq*)	Trace	90		
2β-OMe [e] (*ax*)	82	2	4·5	11·5
2α-OMe [e] (*eq*)	41	39·5	10	9·5

[a] Ref. 5. [b] Ref. 6. [c] Ref. 8. [d] Ref. 7. [e] This work.

Recently, the boron trifluoride-catalysed acetolysis of 2β,19-epoxy-5α-cholestane[6] and of 2β,19-epoxy-5α-cholestan-3-one[8] has been reported to give no products of retention, whereas 6β,19-epoxy-5α-cholestane gave only the product of retention (Table 1). These results indicate that, in these cyclic ethers at least, the products arise from nucleophilic attack by acetic anhydride on the least hindered carbon atom. We report here an investigation into the mechanisms involved in the cleavage of the epimeric 2- and 6-methoxy-5α-cholestanes.

The epimeric 2-methoxy-5α-cholestanes and 6α-methoxy-5α-cholestane were prepared from the corresponding alcohols by treatment with an excess of diazomethane.[6,9] 5α-Cholestan-6β-ol was unchanged under these conditions but was smoothly converted into 6β-methoxy-5α-cholestane by refluxing in benzene with potassium followed by addition of an excess of methyl iodide.[5]

Cleavage of 2β-methoxy-5α-cholestane (1a) with boron trifluoride in acetic anhydride afforded mainly 5α-cholest-2-ene, with the rearrangement product 3α-acetoxy-5α-cholestane (IIa) as the major non-olefinic product, together with small amounts of the epimeric 2-acetates (Ib) and (IIIb). Since the acetates were not separated by preparative t.l.c. or g.l.c., the crude mixture was hydrolysed and the proportions of alcohols were estimated quantitatively by g.l.c. as cholest-2-ene (82%), 5α-cholestan-3α-ol (IIb) (11·5%), 5α-cholestan-2α-ol (IIIc) (4·5%), and 5α-cholestan-2β-ol (Ic) (2·0%) (Table

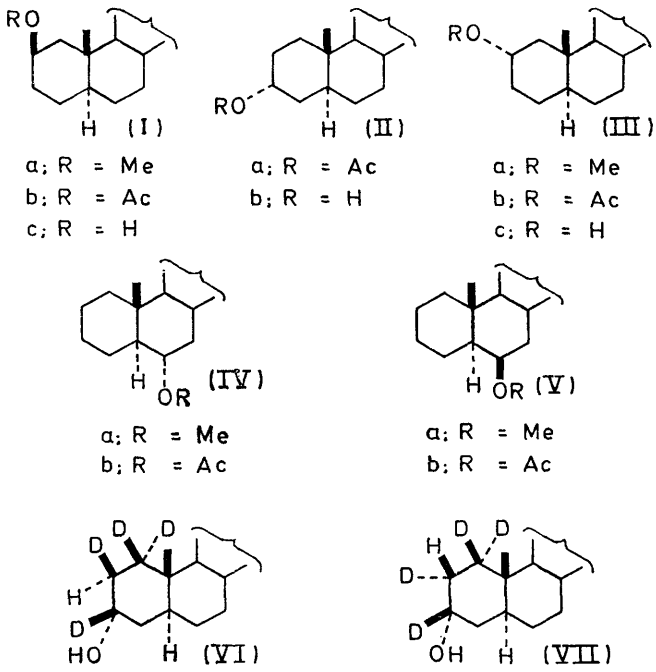
[1] B. Kamber, G. Cainelli, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, 1960, **43**, 347.
[2] R. D. Youssefyeh and Y. Mazur, *Tetrahedron Letters*, 1962, 1287.
[3] C. R. Naryanan and K. N. Iyer, *Tetrahedron Letters*, 1964, 759.
[4] C. R. Naryanan and K. N. Iyer, *Tetrahedron Letters*, 1965, 1369.
[5] C. R. Naryanan and K. N. Iyer, *J. Org. Chem.*, 1965, **30**, 1734.
[6] C. W. Shoppee, J. C. Coll, and R. E. Lack, *J. Chem. Soc.* (*C*), 1970, 1893.
[7] A. Bowers, L. C. Ibanez, M. E. Cabezas, and A. J. Ringold, *Chem. and Ind.*, 1960, 1299.
[8] R. E. Lack and A. B. Ridley, *J. Chem. Soc.* (*C*), 1970, 1437.
[9] C. W. Shoppee, M. E. Howden, and R. E. Lack, *J. Chem. Soc.*, 1960, 4874.

1). Similar proportions were obtained when the crude reaction product was treated with lithium aluminium hydride. The mixture of alcohols was separated by preparative t.l.c. and the products identified by comparison with authentic samples.

Similar cleavage of 2α-methoxy-5α-cholestane (IIIa) afforded different proportions of the same four products, which were also hydrolysed and analysed by g.l.c. to show cholest-2-ene (41%), 5α-cholestan-2α-ol (IIIc) (39·5%), 5α-cholestan-2β-ol (Ic) (10%), and 5α-cholestan-3α-ol (IIb) (9·5%) (Table 1).

Treatment of 6α-methoxy-5α-cholestane (IVa) with boron trifluoride in acetic anhydride afforded mainly 6α-acetoxy-5α-cholestane (IVb), with a trace of cholest-5-ene, but no 6β-acetoxy-5α-cholestane (Vb). Similar treatment of 6β-methoxy-5α-cholestane (Va) afforded 99% of cholest-5-ene (Table 1).

The absence of any 6β-acetate from the acetolysis of the ether (IVa) and the formation of only traces of olefin precludes the occurrence of S_N1 or S_N2 attack at C-6.



S_N2 Attack would be unlikely since the presence of the C-10 methyl group and the fixed chair conformation of ring B would result in hindrance to the formation of a linear transition state at C-6, and it has been shown [9] that the 6α-ol (IVc) with phosphorus pentachloride gives the chloride exclusively with retention of configuration. Nucleophilic attack by acetic anhydride on the methoxy carbon atom would be relatively unhindered and would account for the exclusive formation of the 6α-acetate (IVb). No product with retention of configuration was observed on acetolysis of the 6β-methyl ether (Va), indicating too much steric hindrance for nucleophilic attack on the methoxy carbon atom. S_N2 Attack at C-6 would be unlikely; [9] apparently a more favoured pathway involves concerted diaxial elimination to give cholest-5-ene as the only product.

A study of the methyl ethers (Ia) and (IIa) labelled with deuterium in the 1- and 3-positions, and the observation that acetic acid does not add to cholest-2-ene

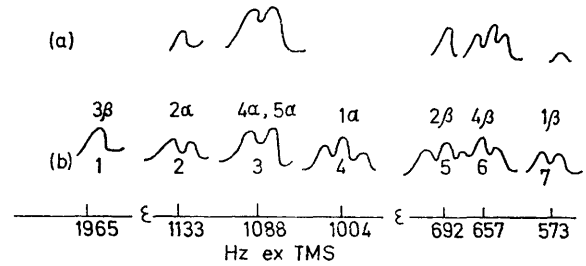


FIGURE 1 Chemical shifts (δ in p.p.m. from Me_4Si) of protons in 5α-cholestan-3α-ol in the presence of 0·625 mol. equiv. of $Eu(dpm)_3$; (a) 5α-cholestan-3α-ol prepared by acetolysis of 1,1,3,3-tetradeuterio-5α-cholestane, (b) 5α-cholestan-3α-ol

under the reaction conditions, indicated that 3α-acetoxy-5α-cholestane is formed *via* a hydride shift.

5α-Cholestan-2-one was deuteriated [10] to yield the 1,1,3,3-tetradeuterio-compound, which was reduced with lithium aluminium hydride to give the corresponding tetradeuterio-2-ols, which were then converted into the corresponding methyl ethers [6] by treatment with diazomethane. A comparison of the spectrum of the europium-complexed 1,1,3,3-tetradeuterio-5α-cholestan-2β-ol with that of the non-deuteriated 2β-ol (Ic) indicated that both the 3-protons and the 1α-proton were fully exchanged, whereas the more hindered 1β-proton was about 75% exchanged.

The n.m.r. spectrum of 5α-cholestan-3α-ol complexed with tris(dipivaloylmethanato)europium(III) [$Eu(dpm)_3$] showed resonances of eight protons shifted downfield sufficiently to separate them from the steroid methylene envelope (Figure 1). Peaks were assigned on the basis of widths at half height [11] and the results of double-irradiation experiments. The singlet peak (1) at lowest field (δ 19·65 p.p.m.) was assigned to the 3β-H as this was expected to be most affected by the europium-complexed 3α-hydroxy-group. On the basis of width, peaks 2 and 7 were assigned to equatorial protons whereas 4, 5, and 6 were assigned to axial protons. The signal (3) at δ 10·88 p.p.m. corresponded to two protons. Irradiation at the frequency of peak 5 caused changes in peaks 2, 4, and 7; these four peaks were therefore assigned to the four protons at C-1 and C-2. The downfield axial proton signal at δ 10·04 p.p.m. was assigned to the 1α-H, since this bears a 1,3-diaxial relationship to the complexed 3α-hydroxy-group. The signal (5) for the other axial proton is thus assigned to the 2β-H. The peak 7 (δ 5·73) was assigned to the equatorial

[10] C. W. Shoppee, F. P. Johnson, R. E. Lack, J. S. Shannon, and S. Sternhell, *Tetrahedron*, 1966, Suppl. 8, Part II, 421.

[11] A. Hassner and C. Heathcock, *J. Org. Chem.*, 1964, **29**, 1352.

1β-H, which lies *trans* to the 3α-hydroxy-group and would be expected to be less affected than the equatorial 2α-H (peak 2). The remaining two peaks (3 and 6; δ 10·88 and 6·57 p.p.m.) must then comprise the signals for 4α-H, 4β-H, and 5α-H. Irradiation at the frequency of peak 3 (δ 10·88) only affected peak 6. The equatorial 4α-H must give rise to part of peak 3, which also includes the signal for the axial 5α-H. The latter bears a 1,3-diaxial relationship to the europium-complexed 3α-hydroxy-group and would be expected to resonate further downfield than the axial 4β-H (peak 6; δ 6·57 p.p.m.).

Sanders and Williams [12] have shown a good linear relationship between the proton shifts for a given proton

TABLE 2

Induced shifts for protons in 5α-cholestan-3α-ol in the presence of $Eu(dpm)_3$

	Induced shifts (p.p.m. from Me_4Si)				
$Eu(dpm)_3$ (mol. equiv.)	2β-H	4β-H	1β-H	2α-H	5α- and 4α-H
0·575	6·57	6·23	5·42	10·74	10·28
0·714	7·72	7·38	6·34	12·86	12·32
0·820	8·39	8·00	6·85	14·09	13·22

and the concentration of $Eu(dpm)_3$; this was found to hold in the present study (Figure 2 and Table 2).

The n.m.r. spectrum of the sample of 5α-cholestan-3α-ol obtained from the acetolysis of the 1,1,3,3-tetradeuterio-2β-methyl ether [as (Ia)] was obtained in the presence of the same concentration of $Eu(dpm)_3$ as before (Figure 1). Signals were observed for the 4α-, 5α-, and 4β-protons and, in addition, sharp signals, of intensity less than one proton, at the expected chemical shifts for the 2α- and 2β-protons in the ratio of 1 : 2. The absence of geminal coupling for these protons and the fact that the sum of their integrals corresponded to

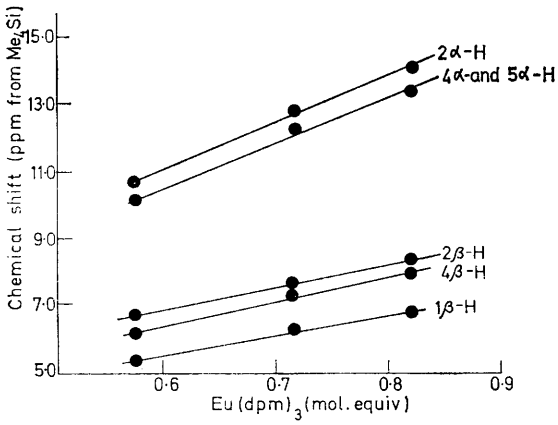


FIGURE 2 Induced shifts for protons in 5α-cholestan-3α-ol in the presence of $Eu(dpm)_3$

one proton indicated the presence of 1,1,2β,3β-tetradeuterio-5α-cholestan-3α-ol (VI) and the 2α-deuterio-epimer (VII) in the ratio of *ca.* 1 : 2. A similar spectrum of the 5α-cholestan-3α-ol obtained from the cleavage of the 1,1,3,3-tetradeuteriated 2α-methyl ether [as (IIIa)] also showed a mixture of the two species (VI) and (VII), present in *ca.* equal amounts.

The presence of the deuteriated species (VI) and (VII) is evidence that a hydride shift is occurring. It appears probable that the cleavage of the 2β-methyl ether (Ia) involves initial ionisation of the boron trifluoride-complexed 2β-methoxy-group to form an ion pair. Hydride migration is occurring from the 3α- and 3β-positions, with the 3α-hydride shift predominating, since this hydrogen is axial and *trans* to the leaving group. With the cleavage of the 2α-methoxy-compound (IIIa), the probable formation of the ion pair is presumably followed by hydride migration from either the 3α- or the 3β-position. Neither of the resultant species predominates, possibly because neither migration is as favourable as the *trans*-axial 3α-hydrogen migration from the 2β-methoxy-compound (Ia). In both cases the resulting C-3 carbonium ion must be attacked preferentially by the bulky acetic anhydride molecule, from the least hindered α-side since no trace of 3β-acetoxy-5α-cholestane was observed.

Whereas the cleavage of the 2β,19- and 6β,19-epoxides appears to involve S_N2 attack at the least hindered carbon atom, the course of the cleavage of the epimeric 2- and 6-methyl ethers is influenced by the steric effect of the 10β-methyl group; clearly a 1,2-hydride shift is involved in the formation of the rearrangement product from the epimeric 2-methyl ethers.

EXPERIMENTAL

M.p.s were determined with a Köfler hot-stage apparatus. I.r. absorption spectra (solutions in carbon tetrachloride) were measured with a Perkin-Elmer 221 spectrophotometer. N.m.r. spectra were measured with a Varian A60 or HA100 instrument, with deuteriochloroform as solvent and tetramethylsilane as internal reference. Mass spectra were measured with an MS9 double-focusing spectrometer. Column chromatography was performed on alumina deactivated by washing with 2N-acetic acid or on silica (Davison, 100—200 mesh). T.l.c. was carried out on silica plates in benzene; plates were developed by spraying with conc. sulphuric acid and heating. Preparative t.l.c. was carried out on silica plates in ether–hexane (1 : 4); the plates were sprayed with berberine hydrochloride and examined under u.v. light. G.l.c. was performed in a Hewlett–Packard 402 instrument on a column (1·75 m × 3 mm diam.) packed with 1% silicone rubber (nitrile) XE60 or acid-washed silanised GasChrom Q (100—120 mesh) or on a column (1·5 m × 3 mm diam.) packed with 3% OV17 (25% phenyl and 75% methyl silicone gum) on acid-washed silanised GasChrom Q (100—120 mesh). The injection port and detector were at a temperature *ca.* 60° higher than that of the column, and helium was used as the carrier gas at a flow rate of 80 ml min^{-1} (inlet pressure 60 lb in^{-2}); hydrogen flow rate was 60 ml min^{-1} and air flow rate was 600 ml min^{-1}.

Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

2β-Methoxy-5α-cholestane (Ia).—5α-Cholestan-2β-ol [13] (Ic)

[12] J. K. A. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, 1971, **93**, 641.

[13] A. Furst and P. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, 1944, **27**, 524; E. J. Corey, *J. Amer. Chem. Soc.*, 1955, **75**, 4832.

(300 mg) in dry ether (20 ml) was treated with an excess of diazomethane at 0°. Boron trifluoride–ether complex (0·5 ml) was added dropwise and the mixture was left for 5 h at 0°. Glacial acetic acid was added to destroy the excess of diazomethane and the product was extracted with ether and chromatographed on alumina (10 g) in hexane to give 2β-*methoxy*-5α-*cholestane* (Ia) (230 mg), m.p. 67—69° (from acetone), $[\alpha]_D$ +30° (Found: C, 83·6; H, 12·5. $C_{28}H_{50}O$ requires C, 83·6; H, 12·4%), δ 0·65 (18-H_3), 0·96 (19-H_3), 3·28 (2β-O·CH_3), and 3·50 p.p.m. ($W_{\frac{1}{2}}$ 9 Hz, 2α-H).

2α-*Methoxy*-5α-*cholestane* (IIIc).—5α-Cholestan-2α-ol [13] (IIIc) was similarly treated to give 2α-*methoxy*-5α-*cholestane* (IIIc), m.p. 47—50° (from acetone), $[\alpha]_D$ +17° (Found: C, 83·7; H, 12·5%), δ 0·64, (18-H_3), 0·88 (19-H_3), and 3·30 p.p.m. (2β-H).

6α-*Methoxy*-5α-*cholestane* (IVa).—5α-Cholestan-6α-ol [14] was similarly treated to give 6α-*methoxy*-5α-*cholestane* (IVa), m.p. 51—54° (from acetone), $[\alpha]_D$ +67° (Found: C, 83·3; H, 12·7%), δ 0·65 (18-H_3), 0·88 (19-H_3), 3·30 (6α-OMe), and 6·7 p.p.m. ($W_{\frac{1}{2}}$ 23 Hz, 6β-H).

6β-*Methoxy*-5α-*cholestane* (Va).—5α-Cholestan-6β-ol (100 mg) in dry benzene (10 ml) was treated with potassium metal (100 mg) under reflux for 2 h. Methyl iodide (4 ml) was added and the mixture was refluxed for 3 h. After cooling, methanol was added and most of the solvent was removed under reduced pressure. The residue was extracted with ether and the crude product (90 mg) was purified on a column of alumina (10 g) in hexane. Elution with hexane gave 6β-*methoxy*-5α-*cholestane* (Va) (64 mg), m.p. 44—46° (from acetone), $[\alpha]_D$ +2° (Found: C, 83·6; H, 12·4%), δ 0·69 (18-H_3), 0·94 (19-H_3), 3·25 (6β-OMe), and 3·23 p.p.m. (6α-H).

General Procedure for the Cleavage of Methyl Ethers.—The methyl ether (300 mg) in dry ether (5 ml) and acetic anhydride (16 ml) was treated with boron trifluoride–ether complex (3 ml) at 0° overnight. The mixture was poured into ice–water and extracted with ether.

(i) 2β-*Methoxy*-5α-*cholestane*. The crude reaction product was refluxed in methanolic potassium hydroxide (1%; 100 ml) for 2 h and separated by preparative t.l.c. in ether–hexane (1 : 50) to give cholest-2-ene containing a trace of cholest-1-ene (180 mg), m.p. 75° (from methanol) (lit.,[15] 75—76°) $\nu_{max.}$ (CS_2) 660s, 770s, 695w, and 715w cm^{-1} [lit.,[16] 660 and 770 (5α-cholest-2-ene); 695 and 715 cm^{-1} (5α-cholest-1-ene)]. Also isolated was 5α-cholestan-3α-ol (25 mg), m.p. and mixed m.p. 187—189° (lit.,[17] 186—187°), δ 0·66 (18-H_3), 0·78 (19-H_3), and 4·03 p.p.m. ($W_{\frac{1}{2}}$ 3·5 Hz, 3α-H). The total product was analysed by g.l.c. 5α-Cholestan-2α-ol and 5α-cholestan-2β-ol were separated completely on XE60 at 225° although on this column their acetates had identical retention times which were indistinguishable from that of the 2α-ol. On the OV17 column at 250°, the epimeric 2-acetates could be separated from the epimeric 2-alcohols (Table 3). The response of the machine to the 2-ols and 2-acetates was calibrated relative to 5α-cholest-2-ene. For both XE60 and OV17 columns the ratio of the response per mol of alcohol to the response per mol of olefin was 0·82 and that of the acetate to olefin was 0·92.

The cleavage products from the 2β-methyl ether (Ia) were estimated by obtaining the ratio of olefin to total acetates on an XE60 column. The product was then hydrolysed and the material obtained was analysed on an XE60 column at 225°. The results, an average of at least three injections, are shown in Table 1.

TABLE 3

G.l.c. data for epimeric 2-ols and 2-acetates

Compound	Column	Temp. (°C)	Retention time (min.)
2α-ol (IIIc)	XE60	225	14·65
	OV17	250	11·70
	OV17	220	37·00
2β-ol (Ic)	XE60	225	12·85
	OV17	250	11·70
	OV17	220	37·00
2α-Acetate (IIIb)	OV17	250	15·72
2β-Acetate (Ib)	OV17	250	15·72
Cholest-2-ene	XE60	225	7·20
	OV17	250	5·20

(ii) 2α-*Methoxy*-5α-*cholestane*. The crude product was hydrolysed as in (i) to give 5α-cholestan-3α-ol (2 mg), m.p. and mixed m.p. 186—188°. Also isolated were cholest-2-ene, 5α-cholestan-2α-ol, m.p. and mixed m.p. 181°,[13] and 5α-cholestan-2β-ol, m.p. and mixed m.p. 154—155°.[13] The cleavage products before and after hydrolysis were analysed on an XE60 column (see Table 1).

(iii) 6α-*Methoxy*-5α-*cholestane*. This gave 6α-acetoxy-5α-cholestane (IVb), m.p. and mixed m.p. 94—96° (lit.,[18] 94°). T.l.c. of the crude product indicated only a trace of olefin.

(iv) 6β-*Methoxy*-5α-*cholestane*. This gave cholest-5-ene. G.l.c. indicated 99·0% purity.

1,1,3,3-*Tetradeuterio*-5α-*cholestan*-2-*ols*.— 5α-Cholestan-2-one [19] (1·5 g) in dioxan (150 ml) and deuterium oxide (30 ml) was heated under reflux with sodium metal (1·5 g) for 2 h to give 1,1,3,3-tetradeuterio-5α-cholestan-2-one (1·5 g). This ketone was refluxed with excess of lithium aluminium hydride for 3 h and the product was worked up to afford crude material (1·43 g) which was separated by preparative t.l.c. to give 1,1,3,3-tetradeuterio-5α-cholestan-2β-ol (407 mg). Comparison of the n.m.r. spectrum run in the presence of 0·65 mol. equiv. of $Eu(dmp)_3$ with a sample of undeuteriated 5α-cholestan-2β-ol in the presence of the same concentration of $Eu(dpm)_3$ showed that the signals at δ 9·74, 9·58, and 9·06 (3α-, 3β-, and 1α-protons) were no longer present, but a signal corresponding to 0·25 of a proton remained at δ 8·92 p.p.m. (1β-H).

2-*Methoxy*-1,1,3,3-*tetradeuterio*-5α-*cholestanes*.— Methylation was carried out with diazomethane as already described for 5α-cholestan-2α-ol. The 2α-ol (474 mg) afforded 2α-methoxy-1,1,3,3-tetradeuterio-5α-cholestane [as (IIIa)] (243 mg) and the 2β-ol (Ic) (407 mg) afforded the 2β-methoxy-compound [as (Ia)] (320 mg).

Acetolysis of Tetradeuterio-ethers.—The 1,1,3,3-tetradeuteriated methyl ethers were cleaved as described for the undeuteriated ethers. After hydrolysis, 5α-cholestan-3α-ol was separated by preparative t.l.c.; the n.m.r. spectrum in the presence of $Eu(dpm)_3$ (0·625 mol. equiv.) is depicted in Figure 1.

[2/716 *Received*, 27*th March*, 1972]

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[19] L. Ruzicka, P. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, 1944, **27**, 524.