109. *Steroids. Part IV.* Solvolysis of* epi*Cholesteryl Toluene*-p-*sulphonate and other Steroid Toluene*-p-*sulphonates.*

By D. D. Evans and C. W. Shoppee.

Acetolysis of *epi*cholesteryl toluene-*p*-sulphonate leads exclusively to cholesta-3 : 5-diene, but methanolysis furnishes in addition to this hydrocarbon two isomeric methoxy-compounds for which structures are suggested. The reactions of the epimeric coprostanyl toluene-*p*-sulphonates have been examined; on solvolysis the *epi*coprostanyl derivative undergoes substitution whereas the epimeride undergoes elimination.

Solvolysis of 3β-substituted Δ^5-steroids may lead either to replacement of the 3β-substituent with complete retention of configuration (Shoppee, *J.*, 1946, 1147) or to 6β-substituted 3 : 5-*cyclo*steroids with inversion of configuration at $C_{(3)}$ (Shoppee and Summers, *J.*, 1952, 3361). In 1948 an examination of the solvolysis of 3α-substituted Δ^5-steroids was commenced with *epi*cholesteryl toluene-*p*-sulphonate, methanesulphonate and, it was hoped, the chloride. We recently learnt that a similar investigation has been carried out with the toluene-*p*-sulphonate independently by Professor Hans Schmid of the University of Zurich. This account of our results is presented by agreement with Professor Schmid, who is publishing his results simultaneously in Switzerland.

Notwithstanding the presence of an adjacent unsaturated linking which confers trigonal symmetry on $C_{(5)}$ and $C_{(6)}$, ring A in Δ^5-steroids forms a slightly distorted chair somewhat inclined to the general plane of the ring system; paradoxically the inclusion of a 5 : 6-double bond deforms rather than flattens the ring system. The 3β-hydroxyl group of the sterols therefore possesses the equatorial conformation. The geometry of the system is thus favourable to interaction between $C_{(5)}$ and the α-face of $C_{(3)}$ (cf. Roberts, Bennett, and Armstrong, *J. Amer. Chem. Soc.*, 1950, **72**, 3329), and unfavourable to ionic 1 : 2-elimination reactions involving the 3β-substituent and requiring a *trans*-arrangement of the groups eliminated, whilst homogeneous unimolecular † thermal 1 : 2-elimination reactions involving the 3β-substituent and requiring a *cis*-disposition of the groups eliminated [3β-X(equatorial)/4α- or 2α-H(polar)] (cf. Bartow, *J.*, 1949, 2174) should proceed with some difficulty. It is consistent that reactions leading from cholesterol to cholesta-3 : 5-diene generally require elevated temperatures, *e.g.*, dehydration with copper sulphate at 200°, pyrolysis of the methyl xanthate at 200—205°, and decomposition of potassium cholesteryl sulphate in decyl alcohol–sodium decyloxide at 160—180°. It is possible however that in the last-named case an ionic mechanism supervenes in view of the strength of sulphuric acid.

The 3α-hydroxyl group in *epi*cholesterol (I*a*) possesses the polar conformation. The geometry of the system is now favourable to ionic 1 : 2-elimination reactions [3α-OH(polar)/4β- or 2β-H(polar)], but unfavourable to thermal elimination reactions and to interaction between $C_{(5)}$ and the β-face of $C_{(3)}$. We have found that simple chromatography of *epi*cholesteryl toluene-*p*-sulphonate in pentane on neutral aluminium oxide furnishes cholesta-3 : 5-diene in 94% yield, so that 1 : 2-elimination occurs with extreme ease. Nevertheless an examination of the methanolysis and acetolysis of *epi*cholesteryl toluene-*p*-sulphonate (I*b*), methanesulphonate (I*c*), and chloride (I*d*) was undertaken in the hope that, despite the ease of ionic elimination [mechanism *E*2] or of possible internal depolarisation of the cation (II) [mechanism *E*1] to yield cholesta-3 : 5-diene, rearrangement of the cation (II) might occur with formation of 6-substituted derivatives of 3 : 5-*cyclo*coprostane (III). It was realised that alternatively the cation (II) might undergo Wagner change leading to 2- or 4-substituted cholest-5-enes (IV), or, after triad change, to 6-substituted cholest-4-enes (V).

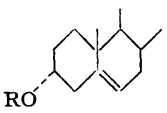
The *epi*cholesterol derivatives (I*b* and *c*) were prepared in good yield by use of the appropriate acid chloride in pyridine ‡ at 0—15°; both compounds give red colours on

* Part III, *J.*, 1952, 2528.

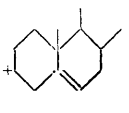
† In the sense in which this term is used in regard to gas-phase reactions.

‡ All attempts directly to convert *epi*cholesterol into *epi*cholesteryl chloride failed, giving cholesta-3 : 5-diene as the sole crystalline product; the chloride was obtained subsequently by an indirect method (Shoppee and Summers, *J.*, 1952, 1790).

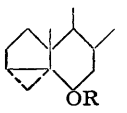
melting (also in nitrogen or in a vacuum), which are probably due to halochromic salts formed as the result of decomposition to cholesta-3 : 5-diene and the appropriate sulphonic acid. Although (I*b*) is converted into cholesta-3 : 5-diene by neutralised aluminium oxide at 20°, it gives the Rosenheim test only after an appreciable induction period. Acetolysis of (I*b*, *c*, or *d*) with potassium acetate–acetic acid or with silver acetate–acetic acid gives 92—99% of cholesta-3 : 5-diene. Clearly 1 : 2-ionic elimination proceeds, as expected, with great ease.



(I*a*; R = H) (I*b*; R = *p*-$C_6H_4Me{\cdot}SO_3$) (I*c*; R = $Me{\cdot}SO_2$) (I*d*; Cl for RO)



(II)



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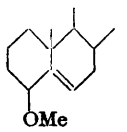
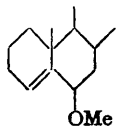


(IV)



(V)

Methanolysis of the toluene-*p*-sulphonate (I*b*) gave cholesta-3 : 5-diene (76%) and a methyl ether, m. p. 96°, $[\alpha]_D$ +82°, provisionally regarded as 6β-methoxycholest-4-ene (V) (7% yield). Methanolysis in the presence of potassium acetate afforded cholesta-3 : 5-diene (56, 57%), the methyl ether (V) (11, 13%), and an isomeric methyl ether, m. p. 66°, $[\alpha]_D$ −73°, provisionally regarded as 4β-methoxycholest-5-ene (IV) (19, 23%). Both methyl ethers give a positive Rosenheim test and a *pale* yellow colour (as also does pure 3 : 5-*cyclo*cholestane) with tetranitromethane–chloroform.

At first the two isomeric ethers were regarded as epimeric 6-methoxy-3 : 5-*cyclo*coprostanes (III); by treatment with hydrochloric acid–acetic acid at 20° both furnished cholesta-3 : 5-diene. Their infra-red spectra, determined by Dr. S. F. D. Orr of the Chester Beatty Research Institute, by examination of the solids in Nujol on a Perkin-Elmer instrument showed, in addition to the C–O–Me stretching vibration at 1094—1097 cm.$^{-1}$ (cf. Josien, Fuson, and Cary, *J. Amer. Chem. Soc.*, 1951, **73**, 4445), bands in the 850—910-cm.$^{-1}$ region and a rather weak band at 1019 ± 5 cm.$^{-1}$ where a *cyclo*propane ring structure might be expected to absorb (cf. Barton, *J.*, 1951, 1444). The spectra of *epi*cholesteryl methyl ether and 3β-methoxycoprostane show intense bands at 1097 and 1094 cm.$^{-1}$ respectively, and weak bands at 1026 and 1022 cm.$^{-1}$ respectively, but are noticeably free from bands in the 850—910-cm.$^{-1}$ region. On the other hand, the spectra of the epimeric ethers show a band at 812—815 cm.$^{-1}$, which also appears, slightly displaced, at 822 cm.$^{-1}$, in the spectrum of *epi*cholesteryl methyl ether but not in that of 3β-methoxycoprostane; this may be identified with the δ(CH) vibration in –CH=C< (Günthard and Ruzicka, *Helv. Chim. Acta*, 1948, **31**, 642) and suggests the presence of an ethylenic linkage.*

Examination of the ultra-violet spectra of the epimeric ethers disclosed some selective absorption in the 205—215-mμ region, where 3 : 5-*cyclo*cholestane does not absorb and saturated steroids are practically transparent. The values of the molecular extinction coefficients for various cholestenes and the two isomeric ethers are as follows (cf. Bladon, Henbest, and Wood, *Chem. and Ind.*, 1951, 866) :

λ (mμ)	Cholest-2-ene	Cholest-3-ene	Cholest-4-ene	Cholest-5-ene	Ether (IV ?), m. p. 66°	Ether (V ?), m. p. 96°
205	400	1700	3900	3700	2220	2870
210	200	650	3000	2700	850	960
215	—	200	1500	1400	390	300
220	—	—	850	700	280	160

Measured in ethanol on a Unicam instrument with corrected scale.

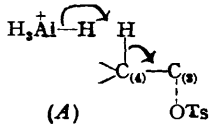
These figures show the presence of an ethylenic linkage in both ethers but do not differentiate clearly between the types CHR=CHR (Δ^2, Δ^3) and $CHR{=}CR_2$ (Δ^4, Δ^5). The less intense absorption observed in the two ethers, compared with chloest-4-ene and cholest-5-ene, may be due to the presence of a methoxy-group on the carbon atom adjacent, and *cis* rather than *trans*, to a double bond (cf. IV, V), since, although cholest-4-ene-3α- and 3β-

* The infra-red spectra of the epimeric ethers, kindly furnished by Professor Schmid for comparison, extend to the 1600 cm.$^{-1}$ region, and both show the weak but unmistakable C=C band at 1665 cm.$^{-1}$ (Jones, Humphries, Packard, and Dobriner, *J. Amer. Chem. Soc.*, 1950, **72**, 86).

ol and cholest-5-ene-3β : 7α- and -3β : 7β-diol show higher maximal absorption than cholest-4-ene and cholesterol respectively, introduction of a 5α-hydroxyl group into cholest-6-en-3β-ol causes diminished absorption (Bladon, Henbest, and Wood, *J.*, 1952, 2737). The presence of one double bond in the two ethers has been confirmed by titration with permonophthalic acid; Professor Schmid has actually isolated the two crystalline epoxides. A single attempt catalytically to hydrogenate the ether, m. p. 66° (IV), with platinum oxide–acetic acid furnished only cholestane; the catalytic hydrogenation of the epimeric ethers will be further examined in the hope of confirming the structures proposed.

The two ethers are different from cholesteryl methyl ether, m. p. 84°, $[\alpha]_D$ −46°, *epi*-cholesteryl methyl ether, m. p. 89°, $[\alpha]_D$ −46°, 3 : 5-*cyclo*cholestanyl methyl ether, m. p. 79°, $[\alpha]_D$ +55°, and cholest-4-en-3β-yl methyl ether, double m. p. 65° and 81°, $[\alpha]_D$ +23°. The provisional formulæ (IV) and (V) are consistent with the molecular rotations of the isomeric ethers found and calculated (from the constants given by Barton and Klyne, *Chem. and Ind.*, 1948, 755). For the ether, m. p. 66° (IV), $[M]_D$ found −292°; calculated for 4α-methoxycholest-5-ene,* −282°, for 4β-methoxycholest-5-ene, −229°; for the ether, m. p. 96° (V), $[M]_D$ found +328°; calculated for 6β-methoxycholest-4-ene, +346°, for 6α-methoxycholest-4-ene, +249°. The provisional formulæ (IV, V) are also consistent with the conversion of the ethers into cholesta-3 : 5-diene by the action of hydrochloric acid; attack by a proton at a lone pair of the methoxyl-oxygen atom would lead to elimination of methanol and production of cations, which by internal depolarisation would furnish respectively cholesta-3 : 5-diene and cholesta-4 : 6-diene, the latter being known to be converted by hydrochloric acid into the former (Eck and Hollingsworth, *J. Amer. Chem. Soc.*, 1941, **63**, 107).

In an attempt to obtain evidence of isomerisation of the cation (II) to cations corresponding to (III) or (V), reduction of *epi*cholesteryl toluene-*p*-sulphonate (I*b*) with lithium aluminium hydride was examined (cf. Karrer and Schmid, *Helv. Chim. Acta*, 1949, **32**, 1371); repeated chromatography of the reduction product led to the isolation only of cholest-5-ene (30%) and cholesta-3 : 5-diene (~40%). The ready formation of the diene appears to be a consequence of the geometry of (I*b*), the facility of the elimination reaction involving four coplanar centres in the transition state (*A*), cutting down the reduction reaction involving simple S_N2 replacement of OTs^- by H^- (cf. Cram, *J. Amer. Chem. Soc.*, 1952, **74**, 2149, 2152).



(*A*)

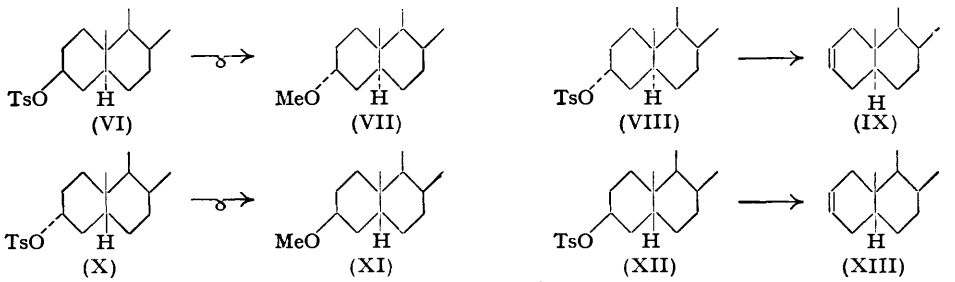
It thus appears that reactions which convert cholesteryl toluene-*p*-sulphonate into derivatives of 3 : 5-*cyclo*cholestane do not permit the conversion of *epi*cholesteryl toluene-*p*-sulphonate into derivatives of 3 : 5-*cyclo*coprostane.

Solvolysis of saturated toluene-*p*-sulphonates occurs with inversion of configuration (Kenyon and Phillips, *J.*, 1923, 44), although in the presence of suitably placed aromatic π-electrons participation can lead to retention of configuration (Winstein, Brown, Schreiber, and Schlesinger, *J. Amer. Chem. Soc.*, 1952, **74**, 1140). The solvolysis of stanyl toluene-*p*-sulphonates was first examined by Stoll (*Z. physiol. Chem.*, 1931, **202**, 232; 1932, **207**, 147; 1937, **246**, 1), and more recently by Plattner (with Fürst and Lang, *Helv. Chim. Acta*, 1943, **26**, 2266; 1944, **27**, 1872), Prelog and Szpilfogel (*ibid.*, 1944, **27**, 390), and Elks and Shoppee (*J.*, 1953, 241). Stoll found that methanolysis of the cholestanyl derivative [VI; 3β-OTs (equatorial)] was largely complete in two hours at 65°, giving a non-crystalline product containing one methoxyl group which we regard as 3α-methoxycholestane (VII) formed with inversion by substitution; when *epi*cholestanyl toluene-*p*-sulphonate [VIII; 3α-OTs (polar)] was refluxed with methanol at 65° 1 : 2-elimination was complete in two hours, yielding cholest-2-ene (IX), m. p. 69°, $[\alpha]_D$ + 64°.

We have examined the reactions of the epimeric coprostanyl toluene-*p*-sulphonates because the stereoelectronic relations here become inverted. *epi*Coprostanyl toluene-*p*-sulphonate [X; 3α-OTs (equatorial)] is unaffected by chromatography on neutralised aluminium oxide; methanolysis is incomplete (82%) after 5 hours at 65° and gives a

* Professor Schmid has informed us recently that he has prepared 4α-methoxycholest-5-ene, m. p. 85—86°, and that it is different from the ether, m. p. 66° (IV), so that this structure must be excluded leaving only the 4β-methoxy-epimeride in the field.

crystalline compound, which we regard as 3β-methoxycoprostane (XI) formed by substitution with inversion, accompanied by only a small amount (18%) of unsaturated hydrocarbon. The coprostanyl derivative [XII ; 3β-OTs (polar)] decomposes readily above 35° and is completely converted by chromatography on neutralised aluminium oxide by a 1 : 2-elimination reaction into coprost-2-ene (XIII), m. p. 47°, $[\alpha]_D$ +23° (some coprost-3-ene may be present in this material).



(Ts = p-$C_6H_4Me{\cdot}SO_2$)

The contrasting principal modes of reaction of the A/B-*trans*-epimerides (VI; S_N2; VIII, *E*1 or *E*2) and the A/B-*cis*-epimerides (X, S_N2; XII *E*1 or *E*2) illustrate the influence of molecular geometry and the resulting steric compression on the course of reaction.

Experimental

For general details see *J.*, 1953, 243, except that neutralised aluminium oxide * was used for chromatography.

*Cholest-5-en-3α-yl Toluene-*p*-sulphonate.*—To *epi*cholesterol (m. p. 140°; 350 mg., dried at 60°/0·01 mm.) in dry pyridine (10 c.c.), purified † toluene-*p*-sulphonyl chloride (900 mg.) was added gradually at 0°. After 3 days at 20°, ice was added and the mixture set aside for 1·5 hr.; the product was extracted with ether, and the extract washed with cold 2N-hydrochloric acid, water, 2N-sodium hydrogen carbonate, and to neutrality with water, dried, and evaporated. The solid residue (484 mg.) was crystallised several times from acetone to give *cholest-5-en-3α-yl toluene-*p*-sulphonate* (86%), m. p. 96° (with development of a deep red colour; also observed in N_2 or in a vacuum), $[\alpha]_D^{20}$ +6·5° ± 2° (*c*, 1·064 in $CHCl_3$) (Found, after drying at 40—50°/0·005 mm. for 1 hr.: C, 75·4; H, 9·7. $C_{34}H_{52}O_3S$ requires C, 75·5; H, 9·7%).

Cholest-5-en-3α-yl Methanesulphonate.—*epi*Cholesterol (117 mg., dried at 60°/0·01 mm.) in dry pyridine (3 c.c.) was treated dropwise at −10° with methanesulphonyl chloride (0·1 c.c., 4 mols.; prepared according to Johnson and Sprague, *J. Amer. Chem. Soc.*, 1936, **58**, 1348). The mixture was kept at 20° for 3 days, decomposed with ice, and worked up in the usual way. The colourless solid product (140 mg.) after crystallisation from acetone furnished *cholest-5-en-3α-yl methanesulphonate*, m. p. 110—112° (with production of a red colour), $[\alpha]_D^{20}$ −26° ± 1° (*c*, 0·96 in $CHCl_3$) (Found, after drying at 65°/0·005 mm. for 2 hr.: C, 72·6; H, 10·7. $C_{28}H_{48}O_3S$ requires C, 72·35; H, 10·4%).

Action of Aluminium Oxide.—The above toluene-*p*-sulphonate (50 mg., dried at 20°/0·01 mm. for ½ hr.) was chromatographed on aluminium oxide (1·6 g.) prepared in pentane. Repeated elution with pentane (4 × 5 c.c.) gave fractions (31 mg.), m. p. 74—75°, consisting essentially of cholesta-3 : 5-diene (calc., 33·5 mg.); recrystallisation from acetone–methanol furnished material, m. p. 79° undepressed by admixture with a genuine specimen, and giving an immediate positive Rosenheim test.

Acetolysis.—(a) *With silver acetate.* Cholest-5-en-3α-yl toluene-*p*-sulphonate (100 mg.) and silver acetate (100 mg.) were dried at 50—60°/0·01 mm. for ½ hr., and then refluxed with acetic acid (10 c.c.) under anhydrous conditions for ½ hr., whereafter the bulk of the acetic acid was removed under reduced pressure. The product, isolated in the usual way, formed a pale yellow oil which solidified when dried at 20°/0·01 mm. Crystallisation from ether–ethanol gave colourless needles (26 mg.) of cholesta-3 : 5-diene, m. p. 78°; from the mother-liquor two further crops, m. p. 75—77° (22 mg.) and 73—77° (9 mg.) were obtained. These fractions depressed the m. p.

* Prepared by treatment with 5% nitric acid on a steam-bath for 1 hr., filtration, washing till free from NO_3^-, boiling with methanol, filtration, and reactivation at 250°/10 mm. for 1 hr.

† The ethereal solution was washed with 2N-sodium carbonate, and with water, and evaporated; the product was crystallised several times from benzene, dried in a vacuum, and sealed in small ampoules.

(84°) of *epi*cholesteryl acetate but not that of cholesta-3 : 5-diene, and gave immediate positive Rosenheim tests. The product was unaltered by hot 5% methanolic potassium hydroxide during 2·5 hr., subsequent recrystallisation from ether–ethanol giving fractions, m. p. 78° (9·5 mg.), 76—78° (5 mg.), and 76° (4 mg.), all of which gave immediate positive Rosenheim tests. The residues from these crystallisations were combined with the mother-liquors from the crystallisations of the original acetolysis product and the material (19 mg.) treated with hot 5% methanolic potassium hydroxide; chromatography of the product failed to furnish *epi*cholesterol.

Cholest-5-en-3α-yl methanesulphonate (80 mg.) and silver acetate (75 mg.) were dried and refluxed with acetic acid (5 c.c.) for ½ hr. The product (65 mg.) was crystallised from ether–ethanol to give cholesta-3 : 5-diene (48 mg.), m. p. 76—78°. After removal of a further small crop of crystals (5 mg.), m. p. 70—75°, the residue (11 mg.) obtained by evaporation was chromatographed; elution with pentane gave slightly impure cholesta-3 : 5-diene (6 mg.) as the only crystalline material which could be isolated.

(b) *With potassium acetate.* Cholest-5-en-3α-yl toluene-*p*-sulphonate (100 mg.) and freshly fused potassium acetate (200 mg.) were dried at 40—50°/0·005 mm. for ½ hr. and refluxed with acetic acid (5 c.c.) for 3 hr. The reaction product (71 mg.), crystallised from ether–acetone, gave cholesta-3 : 5-diene (45 mg.), m. p. and mixed m. p. 78°; a second crop (9 mg.) had m. p. 75°. In a repetition, the product was chromatographed on aluminium oxide (2 g.) prepared in pentane. A single elution with pentane gave cholesta-3 : 5-diene (67 mg.), m. p. 76°, giving an immediate positive Rosenheim reaction; hydrolysis with hot 5% methanolic potassium hydroxide and chromatography of the product gave cholesta-3 : 5-diene (61 mg.), m. p. 75°, but no *epi*cholesterol.

Methanolysis.—(a) *In presence of potassium acetate.* Cholest-5-en-3α-yl toluene-*p*-sulphonate (600 mg.) and freshly fused potassium acetate (1·6 g.) were dried together at 20°/0·005 mm. for ½ hr. and refluxed with dry methanol (90 c.c.) under anhydrous conditions for 3 hr. After cooling and addition of water most of the methanol was removed under reduced pressure and the product isolated in the usual way. The crystalline product (436 mg.) was chromatographed on a long column of aluminium oxide (26 g.) prepared in pentane. Elution with pentane (5 × 40 c.c.) gave fractions: A1, m. p. 75° (226 mg.); A2, m. p. 74—91° (43 mg.); A3, m. p. 46—52° (86 mg.); A4, m. p. 61—63° (23 mg.); A5, m. p. 45—53° (2 mg.). Further elution with pentane produced no material, but use of benzene–pentane (1 : 1) and of ether–benzene (1 : 1) gave oils (27 and 5 mg.), which failed to crystallise and were not investigated. Fraction A1 consisted of nearly pure cholesta-3 : 5-diene (mixed m. p.). Fractions A3 and A4 were united and rechromatographed similarly, to give by elution with pentane (7 × 10 c.c.) fractions: B1, oil (7 mg.), discarded; B2, m. p. 58—89° (18 mg.); B3, m. p. 56—60° (32 mg.); B4, m. p. 60·5—63·5° (16 mg.); B5, m. p. 60—63° (7 mg.); B6, m. p. 60—62° (4 mg.); B7, oil (2 mg.). Fractions B3, 4, 5, and 6 were united and recrystallised from ether–methanol, to give 4β-*methoxycholest-5-ene* (IV) (35 mg.), m. p. 66°, $[\alpha]_D^{20}$ −73° ± 2° (*c*, 1·10 in $CHCl_3$) (Found, after drying at 20°/0·005 mm. for 4·5 hr.: C, 83·65; H, 11·85; OMe, 8·1. $C_{27}H_{45}$·OMe requires C, 83·9; H, 12·05; OMe 7·8%), unchanged by sublimation in a high vacuum, giving a pale yellow colour with tetranitromethane in chloroform and a positive Rosenheim test. The yield of the pure compound was 23%, and in a second experiment 19%.

Fractions A2 and B2 were united and rechromatographed, to give by elution with pentane (7 × 6 c.c.) fractions: C1, oil (2 mg.), discarded; C2, m. p. 75—90° (26 mg.); C3, m. p. 89—94° (15 mg.); C4, m. p. 83—89° (7 mg.); C5, 6, and 7, oils (4, 2, and 1·5 mg.), discarded. Fraction C2 was rechromatographed, to give by elution with pentane (4 × 2·5 c.c.) fractions: D1 oil (1·5 mg.), discarded; D2, m. p. 85—93° (15 mg.); D3, m. p. 92—96° (8 mg.); D4, m. p. 88—94° (2·5 mg.). Fraction D2 was again chromatographed to give by elution with pentane (8 × 1·5 c.c.) fractions: E1 no material; E2 and 3, oils (each 1 mg.), discarded; E4, m. p. 89—93° (5 mg.); E5, m. p. 91—94° (3 mg.); E6, m. p. 90—94° (1·5 mg.); E7 and 8 cryst. (1 and 0·3 mg.). Fractions C3, C4, D3, D4, E4—8 were united and recrystallised from methanol, to give 6β-*methoxycholest-4-ene* (V) (17 mg.), needles, m. p. 96°, $[\alpha]_D^{20}$ +82° ± 4° (*c*, 0·523 in $CHCl_3$) (Found, after drying at 55—60°/0·005 mm. for 4·5 hr.: C, 84·2; H, 12·25; OMe, 7·7%), giving a pale yellow colour with tetranitromethane–chloroform and a positive Rosenheim test. The yield of the pure compound was 11% and of cholesta-3 : 5-diene was 57%; in a second experiment 13% and 56% respectively.

(b) *In absence of potassium acetate.* Cholest-5-en-3α-yl toluene-*p*-sulphonate (200 mg., dried at 20°/0·005 mm. for 3 hr.) was refluxed with dry methanol (30 c.c.) with exclusion of moisture for 2·5 hr. Working up as in (a) gave a product (145 mg.). Chromatography on a long column of aluminium oxide (8 g.), prepared in pentane, and elution with pentane (6 × 15

c.c.) gave fractions: F1, m. p. 72—76° (96 mg.); F2, m. p. 55—76° (20 mg.); F3, m. p. 49—57° (7 mg.); F4, m. p. 71—78° (3 mg.); F5, m. p. 68—77° (3 mg.); F6, m. p. 66—77° (1 mg.) Further elution with benzene–pentane and with benzene gave only insignificant traces of oil. Fraction F1 consisted essentially of cholesta-3 : 5-diene, m. p. and mixed m. p. 76°, after recrystallisation from ether–acetone. Fractions F2—6 were united and rechromatographed similarly, to give by elution with pentane fractions: G1, m. p. 59—70° (4 mg.); G2, m. p. 51—69° (26 mg.); G3, oil (3 mg.). Fraction G2 was again chromatographed similarly, to give by elution with pentane fractions: H1, no material; H2, m. p. 85° (6 mg.); H3, oil (13 mg.) which crystallised; H4 and 5, oils (4 and 1 mg.); fraction H2, recrystallised from methanol, gave 6β-methoxycholest-4-ene (V), needles, m. p. 91°, which depressed the m. p. (88—89°) of 3α-methoxycholest-5-ene but not that of the material described under (a). Further chromatography of H3 gave, by elution with pentane, fractions: J1 and 2, no material; J3, m. p. 85—89° (3 mg.); J4, m. p. 84—88° (4 mg.), consisting of 6β-methoxycholest-4-ene (V). The yield of this was 8%; that of cholesta-3 : 5-diene ~75%.

Action of Hydrochloric Acid on the Ethers (IV) *and* (V).—(*a*) 4β-Methoxycholest-5-ene (IV) (12 mg.) was treated in acetic acid (2·5 c.c.) with concentrated hydrochloric acid (0·15 c.c.) at 20° for 19 hr. Crystals were deposi ed and were filtered off (m. p. 70—73°; 8 mg.); recrystallisation from acetone gave cholesta-3 : 5-diene, m. p. and mixed m. p. 77°. Chromatographic examination of the material recovered from the original filtrate furnished no crystals. (*b*) 6β-Methoxycholest-4-ene (V) (10 mg.) similarly gave cholesta-3 : 5-diene.

*Reduction of Cholest-5-en-3α-yl Toluene-*p*-sulphonate with Lithium Aluminium Hydride.*—The compound (600 mg.) was dried at 20°/0·005 mm. for 2·5 hr., dissolved in dry benzene (50 c.c.) and one half of the benzene removed by distillation; the resulting solution was treated with lithium aluminium hydride (500 mg.) in refluxing ether for 22 hr. Excess of reagent was decomposed by dropwise addition of ethyl acetate at 0°, and the product isolated in the usual way as an oil (520 mg.) which crystallised after removal of solvents in a high vacuum (m. p. 46—58°). This material was chromatographed on a long column of aluminium oxide (32 g.) prepared in pentane. Elution with pentane (6 × 50 c.c.) gave fractions: K1, m. p. 59—68° (286 mg.); K2, m. p. 70—74° (40 mg.); K3, oil (3 mg.); K4, 5, 6, no material. Elution with benzene–pentane (1 : 1) gave only traces of oil, but use of benzene gave a yellow oil (23 mg.) from which no crystalline material could be isolated. Fraction K2 consisted essentially of cholesta-3 : 5-diene, m. p. 74·5—76°, after crystallisation from ether–methanol, and had m. p. 75—76° on admixture with a genuine specimen. Fraction K1 was rechromatographed (Al_2O_3; 18 g.) and gave by elution with pentane (5 × 30 c.c.) fractions: L1, m. p. 80—87° (55 mg.); L2, m. p. 60—64° (198 mg.); L3, m. p. 68—74° (20 mg.); L4, m. p. 66—73° (4 mg.); L5, oil (2 mg.), discarded. Fraction L1, recrystallised from acetone–methanol, gave cholest-5-ene, m. p. and mixed m. p. 87—89°, $[\alpha]_D^{20}$ −55°; fractions L3 and L4 consisted essentially of cholesta-3 : 5-diene, m. p. 75—76°, after recrystallisation from ether–methanol. Fraction L2 was rechromatographed (Al_2O_3; 12 g.) and gave by elution with pentane (4 × 15 c.c.) fractions: M1, m. p. 80—86° (40 mg.); M2, m. p. 60—66° (147 mg.); M3, m. p. 66—72° (7 mg.); and M4, oil (1 mg.), discarded. Fraction M1, recrystallised from ether–methanol, gave cholest-5-ene, m. p. 87·5—89·5°. Fractions M2 and M3 were united and again chromatographed (Al_2O_3; 9 g.) and gave by elution with pentane (3 × 10 c.c.) fractions: N1, m. p. 81—85·5° (26 mg.); N2, m. p. 64—69° (109 mg.); N3, m. p. 65—70° (5 mg.). Recrystallisation of N1 from acetone–methanol gave cholest-5-ene, m. p. 86—87°. Fractions N2 and N3 were united and again chromatographed (Al_2O_3; 6 g.), to give by elution with pentane (4 × 5 c.c.); O1, trace; O2, m. p. 69° (75 mg.); O3, m. p. 70° (21 mg.); O4, solid (5 mg.), discarded. Fractions O2 and O3, recrystallised from ether–methanol, gave nearly pure cholesta-3 : 5-diene, m. p. 74° and 74—76°, giving no m. p. depressions on admixture with a genuine specimen and positive Rosenheim tests. The yields of cholest-5-ene and cholesta-3 : 5-diene were thus 30 and ~40% respectively; these two substances were the only crystalline compounds isolated in a second experiment in which the steroid was added to the lithium aluminium hydride.

3α-Methoxycholest-5-ene.—Finely divided potassium (65 mg.) and *epi*cholesterol (130 mg.) were shaken in dry benzene (2·5 c.c.) in nitrogen at 25° for 3·5 hr. Methyl iodide (1 c.c.) in benzene (2·5 c.c.) was added and the mixture refluxed for 3·5 hr. The product was a yellow oil (132 mg.) which was chromatographed on aluminium oxide (4 mg.) prepared in pentane. Elution with pentane (5 × 13 c.c.) gave fractions of m. p. 81—86°, 83—88°, 84—88°, 84—87°, 84·5—88°, and 81—86·5° (total, 42 mg.), which were united and crystallised from acetone, to give 3α-methoxycholest-5-ene as plates, double m. p. 80—82° and 88—89°; Wallis and Ford (*J. Amer. Chem. Soc.*, 1937, **59**, 1415) give m. p. 88—89°. Subsequent elution with

benzene and ether–benzene (1 : 19) gave *epi*cholesterol (20 mg.), m. p. 140°, after crystallisation from methanol.

3β-*Methoxycholest*-4-*ene*.—Finely divided potassium (100 mg.) and 3β-hydroxycholest-4-ene (180 mg. prepared according to Plattner *et al.*, *Helv. Chim. Acta*, 1949, **32**, 265) were shaken in dry benzene in nitrogen at 50—60° for 2 hr., whereafter methyl iodide (2·5 c.c.) was added and the mixture refluxed for 3 hr. The product, isolated in the usual way, was chromatographed on aluminium oxide (5 g.) prepared in pentane. Elution with pentane (9 × 20 c.c.) furnished crystalline material in fractions 3—9, m. p. ~60°. These were united (56 mg.) and recrystallised from acetone–methanol, giving 3β-*methoxycholest*-4-*ene*, m. p. 68—70°, $[\alpha]_D^{20}$ −37° ± 2° (*c*, 0·49 in $CHCl_3$) (Found, after drying at 20°/0·01 mm. for 16 hr.: C, 83·85; H, 12·15. $C_{28}H_{48}O$ requires C, 83·9; H, 12·05%).

Coprostan-3α-*yl Toluene*-p-*sulphonate* (prepared by R. J. Bridgwater).—Coprostan-3α-ol (m. p. 116—117°; 600 mg.) in dry pyridine (5 c.c.) and pure toluene-*p*-sulphonyl chloride (430 mg.) were allowed to react at 20° for 60 hr., and furnished an oil (800 mg.) which crystallised on scratching. Recrystallisation from acetone gave the 3α-*toluene*-p-*sulphonate* (520 mg.), m. p. 116—118°, $[\alpha]_D^{18}$ +38° ± 1° (*c*, 1·852 in $CHCl_3$) (Found, after drying at 100°/0·01 mm. for 3 hr.: C, 75·0; H, 10·0. $C_{34}H_{54}O_3S$ requires C, 75·2; H, 10·0%), which depressed the m. p. of coprostan-3α-ol to 95—98°. The compound (50 mg.) was eluted unchanged (m. p. 115—118°; 45 mg.) from aluminium oxide (1·5 g.) by benzene–pentane (1 : 4 and 1 : 2).

Methanolysis. The compound (100 mg.; dried at 50°/0·02 mm. for 1 hr.) was refluxed with dry methanol for 55 hr. Some methanol was removed and a little ether added, whereupon a white solid was deposited and filtered off (m. p. 75—106°; 22 mg.). The product from the filtrate was a yellow oil which was chromatographed on aluminium oxide (2 g.) prepared in pentane. Elution with pentane (4 × 6 c.c.) gave fractions which crystallised when kept and scratched: 1, m. p. 60—61° (9 mg.); 2, m. p. 60—62° (22 mg.); 3, m. p. 60—62° (7 mg.); 4, m. p. 57—60° (2 mg.); but further elution with benzene–pentane (1 : 9, 1 : 4, 1 : 1) and with benzene gave only small amounts of oil. Fractions 1—4 by crystallisation from acetone–methanol yielded 3β-*methoxycoprostane*, double m. p. 64—65° and 79—81°, $[\alpha]_D^{12}$ +23° ± 2° (*c* = 1·038 in $CHCl_3$) (Found, after drying at 39—40°/0·01 mm. for 9 hr.: C, 83·65; H, 12·3; OMe 7·85. $C_{27}H_{47}$·OMe requires C, 83·5; H, 12·5; OMe, 7·7%), giving no colour with tetranitromethane in chloroform. The white solid precipitate gave, by chromatography and elution with pentane, 3β-methoxycoprostane), m. p. 55° and 74° (2 mg.), whilst use of benzene–pentane (1 : 1) furnished coprostan-3α-yl toluene-*p*-sulphonate, m. p. 116—118° (16 mg.). Similar results were obtained in a second experiment. Babcock and Fieser (*J. Amer. Chem. Soc.*, 1952, **74**, 5472) have just described the preparation, by reductive methylation of coprostan-3-one, of a compound, m. p. 62—63°, $[\alpha]_D^{23}$ +27·5°, regarded as 3β-methoxycoprostane.

Coprostan-3β-*yl Toluene*-p-*sulphonate* (prepared by R. J. Bridgwater).—Coprostan-3β-ol (m. p. 100—101°; 600 mg.) gave, as in the preceding esterification, the 3β-*toluene*-p-*sulphonate*, very soluble in acetone but crystallising from acetic acid as plates (346 mg.), m. p. 106—108°, $[\alpha]_D^{18}$ +0·5° ± 1° (*c*, 1·313 in $CHCl_3$) (Found, after drying at 20°/0·01 mm. for 5 hr.: C, 75·1; H, 10·0%), giving no colour with tetranitromethane in chloroform but decomposing readily above 35°. Chromatography on neutralised aluminium oxide, prepared in pentane, and elution with pentane afforded an unsaturated oil, which by crystallisation from ether–methanol furnished *coprost*-2-*ene*, needles, m. p. 46—47°, $[\alpha]_D^{22}$ +23° ± 1° (*c*, 1·59 in $CHCl_3$) (Found, after drying at 35—40°/0·01 mm. for 4 hr.: C, 87·2; H, 12·9. $C_{27}H_{46}$ requires C, 87·5; H, 12·5%). It is not possible to guarantee absence of coprost-3-ene from this material.

epi*Cholesteryl Chloride*.—A considerable series of experiments, with variation of the proportions of the reactants, the order of addition, duration, and temperature, were carried out in which *epi*cholesterol was treated with the following reagents PCl_5–$CaCO_3$–$CHCl_3$, PCl_5–pyridine, PCl_5–$POCl_3$, $SOCl_2$, $SOCl_2$–Et_2O, $SOCl_2$–pyridine, $SOCl_2$–$NPhEt_2$, but failed to give *epi*cholesteryl chloride. Chromatographic examination of the products gave by elution with pentane variable quantities of oil, giving positive Beilstein and Rosenheim tests, which proved extremely difficult to crystallise. Cholesta-3 : 5-diene was sometimes isolated but in poor yield; in the experiments with thionyl chloride a solid, insoluble in ether but crystallisable from benzene (m. p. 238°), was encountered which may have been *epi*cholesteryl sulphite.

Acetolysis. *epi*Cholesteryl chloride (m. p. 107°; 91 mg.; prepared according to Shoppee and Summers, *J.*, 1952, 1790), acetic acid (5 c.c.) and anhydrous potassium acetate (200 mg.) were refluxed for 6 hr.; after dilution with water the product was extracted with pentane, to give in the usual way a colourless oil (86 mg.) which rapidly crystallised. After 1 hour's drying at 60°/0·01 mm., the product (85 mg.) was chromatographed on aluminium oxide (10 g.), and

eluted with pentane (4 × 10 c.c.), to give crystals (83 mg.) which gave the Rosenheim test. Nucleation of a solution in ether–methanol with authentic cholesta-3 : 5-diene caused immediate crystallisation of cholesta-3 : 5-diene (99%) as needles, m. p. 76—78°.

We thank Dr. G. W. Wood for a specimen of pure cholest-3-ene, Dr. S. F. D. Orr of the Chester Beatty Research Institute for measuring the infra-red absorption spectra, and Professor A. Haddow for the permission to use his infra-red spectrometer; we also acknowledge the support of a Grant from The Royal Society (to C. W. S.) and an Award from the Department of Scientific and Industrial Research (to D. D. E.).

UNIVERSITY COLLEGE, SWANSEA, UNIVERSITY OF WALES. [*Received, September 9th,* 1952.]