41. *Acyl Migration in Steroids.*

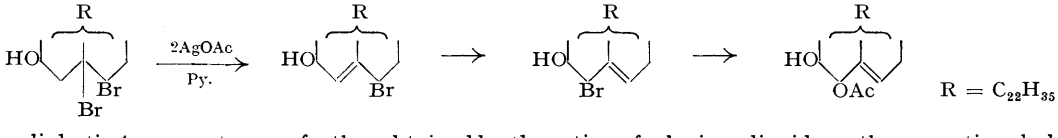
By V. A. Petrow, O. Rosenheim, and W. W. Starling.

A remarkably facile acyl migration, so far without analogy in the steroid series, occurs in the monoesters of *cis*-Δ^5-cholestene-3 : 4-diol. The intermediate formation of orthocarbonic esters, analogous to that occurring in acyl derivatives of glycerol and carbohydrates, is suggested in explanation of the reaction. An alternative mechanism assuming a transannular tautomerisation, due to the presence of a potential tautomeric system in the Δ^5-unsaturated diol, is discussed.

A series of the two possible monoesters of the unsaturated α-glycol, *cis*-Δ^5-cholestene-3 : 4-diol (Rosenheim and Starling, J., **1937**, 377) has been prepared by various methods.

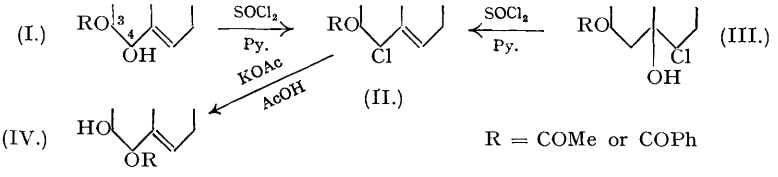
The 3-monoesters (I) are obtained (*a*) by the action of the respective acyl or aryl chlorides, or anhydrides, in molecular proportion on the diol in pyridine solution; (*b*) by the action of selenium dioxide on cholesteryl esters in dioxan solution at 90°.

The 4-monoesters (IV) are smoothly formed from cholesterol by converting it into its dibromide and allowing the latter to react with the silver salts of the respective acids in pyridine solution. The reaction is applicable to other steroids possessing the same configuration as cholesterol in rings I and II. We have thus prepared 4-*acetoxy*-Δ^5-*androsten*-3(β)-*ol*-17-*one* from *trans*-dehydroandrosterone. The method has the advantage of obviating the use of selenium dioxide in the preparation of the *cis*-diols. The reaction proceeds rapidly at room temperature and may be formulated as follows :



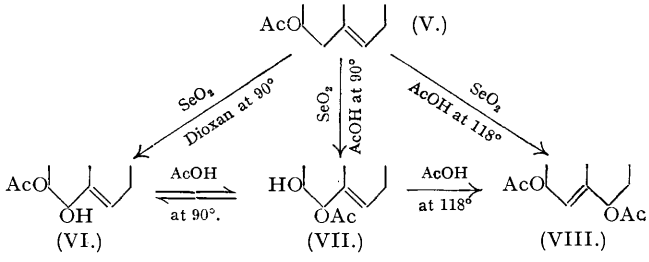
The aliphatic 4-monoesters are further obtained by the action of selenium dioxide on the respective cholesteryl esters in acetic acid solution at 90°. An acyl migration evidently occurs during this reaction (see p. 136).

The position of the esterified hydroxyl group in these esters has been established in the case of the 3-monoesters by the following facts: (1) Oxidation of *cis*-3-acetoxy-Δ^5-cholesten-4-ol (I,R = COMe) yields an unsaturated keto-acetate, $C_{29}H_{46}O_3$, m. p. 124°. This ketone shows the characteristic ultra-violet absorption band of $\alpha\beta$-unsaturated ketones with a maximum at 2400 A. and must, therefore, be formulated as 3-acetoxy-Δ^5-cholesten-4-one. The unesterified hydroxyl group of the monoester is accordingly at C_4.* (2) On chlorination with thionyl chloride the 3-monoesters of the *cis*-diol (I) yield the esters of 4-chloro-Δ^5-cholesten-3-ol (II). The position of the esterified hydroxyl at C_3 in these esters is established by their identity with the esters obtained from the 3-monoesters of 6-chlorocholestane-3 : 5-diol (III) by a Darzens dehydration (cf. Petrow, Rosenheim, and Starling, J., 1938, 677), which is accompanied by an allylic rearrangement. The benzoate of (II), obtained in the same way, has previously been described as 6-chloro-3-benzoyloxy-Δ^4-cholestene (Spring and Swain, J., 1939, 1356).



The constitution of the 4-monoesters (IV) follows by implication and from the fact that the mixed esters obtained from them by acetylation and benzoylation are identical with the mixed esters obtained from the respective 3-monoesters.

An acyl migration from C_3 to C_4 occurs when the 3-monoacetate of the *cis*-diol (VI) is warmed to 90° in acetic acid solution, yielding the 4-monoacetate (VII). The reaction takes place slowly even at 37° and is reversible, the equilibrium apparently being shifted in favour of the less soluble 4-monoester. At temperatures higher than 90° and rapidly at 118° in boiling acetic acid, the two monoesters undergo an allylic rearrangement, the acetyl group migrating to C_6, and yield the esters of Δ^4-cholestene-3 : 6-diol (VIII). The latter diol is the main product when cholesteryl acetate (V) is oxidised with selenium dioxide in boiling acetic acid (Rosenheim and Starling, *loc. cit.*; Butenandt and Hausmann, *Ber.*, 1937, **70**, 1154; Petrow, Rosenheim, and Starling, J., 1938, 677). These intramolecular changes may be formulated as follows:



Still another instance of acyl migration in the 3-monoesters was observed when it was found that substitution of chlorine for hydroxyl at C_4 in 3-acetoxy-Δ^5-cholesten-4-ol (I, R = COMe), m. p. 194°, and of the former by hydroxyl, yielded *4-acetoxy-Δ^5-cholesten-3-ol* (IV, R = COMe), m. p. 165°. In the same way 3-benzoyloxy-Δ^5-cholesten-4-ol, m. p. 210°, is transformed into *4-benzoyloxy-Δ^5-cholesten-3-ol*, m. p. 155°. These substances are identical with the corresponding 4-monoesters obtained from cholesteryl dibromide by the method described in a previous section. The fact that they yield the *cis*-diol, m. p. 176°, on hydrolysis suggests that the expected Walden inversion has not occurred in their formation from (I), unless it has occurred twice.

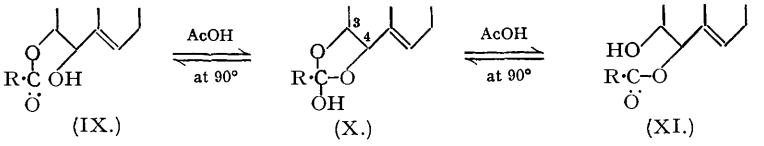
This series of observations affords an explanation for some of the results obtained by Spring and Swain (*loc. cit.*) in the dehalogenation of 6-chloro-3-benzoyloxy-Δ^4-cholestene, which yielded, amongst others, a compound (C), m. p. 154°, a monobenzoate of the *cis*-3 : 4-diol. Compound (C) differed from the monobenzoate of the *cis*-diol previously obtained by Rosenheim and Starling (*loc. cit.*). The former authors recognised that during the formation of one of the monobenzoates a migration of the benzoyl group had occurred, but left the position of the ester group in the two benzoates undecided. The above results show that compound (C) is identical with 4-benzoyloxy-Δ^5-cholesten-3-ol (IV, R = COPh).

This migration of acyl radicals in steroids is analogous to the acyl migration in glycerides, observed by Fischer in the reaction α-iodohydrin $\alpha'\beta$-distearate $\longrightarrow$ glycerol $\alpha\alpha'$-distearate (*Ber.*, 1920, **53**, 1621). The interpretation of the reaction by Fischer assumes the intermediate formation of orthocarbonic esters and applies equally well to acyl migrations in the sugar group (Haworth, Hirst, and Teece, J., 1930, 1405). The mechanism first proposed by Fischer received strong support by the isolation of the postulated cyclic intermediate dioxolone derivative by Hibbert and Greig (*Canadian J. Res.*, 1931, **4**, 254; cf. Meerwein and Sönke, *Ber.*, 1931, **64**, 2375).

An intermediate unstable five-membered cyclic acetal ring (X) being assumed, it is evident that the rupture

* Owing to a clerical error the maximum of the absorption band of the $\alpha\beta$-unsaturated ketone was given at 2800 A. instead of at 2400 A. by Petrow and Starling (J., 1940, 60).

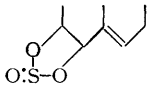
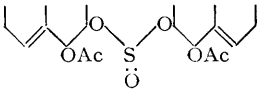
of such a ring system can give rise in steroids to either 3- or 4-monoesters (IX and XI), thus explaining the above described reversibility of acyl migration. The stereochemical configuration of the diol with its hydroxyls at C_3 and C_4 in the *cis*-position may be held to facilitate this interchange :



(IX.) (X.) (XI.)

An alternative mechanism of acyl migration in steroids is suggested by the fact that their ring system contains an unsaturated linkage, in contrast to glycerol and carbohydrates, which forms part of a potential tautomeric system. It has been pointed out (Rosenheim, *Nature*, 1941, **147**, 776) that a transannular anionotropic change in this system affords a possible explanation for the formation of the bridge linkage from C_3 to C_5 in *i*-cholesteryl acetate. Attractive as the assumption of an intermediate labile pentacyclic compound of the *i*-cholesterol type would be in explaining acyl migration in steroids, it lacks at present experimental confirmation.

Incidental observations are recorded on the action of thionyl chloride on the *cis*-diol and its 4-monoacetate, which yield a cyclic *sulphite*, $C_{27}H_{44}O_3S$ (XII), m. p. 146°, and a bis-sulphite, $C_{58}H_{94}O_7S$ (XIII), m. p. 160°, respectively.

(XII.)   (XIII.)

Experimental.

4-Acetoxy-Δ⁵-cholesten-3-ol (IV; R = Ac).—(*a*) Silver acetate (14 g.; 2 mols.), dissolved in pyridine (40 ml.), was added rapidly with shaking to cholesteryl dibromide (20 g.; 1 mol.) suspended in ether (200 ml.) and pyridine (20 ml.). The resulting clear solution rapidly deposited a heavy greenish precipitate. Ether (600 ml.) was added after 10 minutes, the precipitated silver bromide (13·9 g.) removed, the ethereal solution freed from pyridine by washing with dilute sulphuric acid and water and dried, and the ether removed. When the crystalline residue, dissolved in chloroform (10 ml.), was treated with acetic acid (100 ml.), the acetic acid compound (10·5 g.) of the 4-monoacetate crystallised, m. p. 143—144° after softening at 124°. On crystallisation from 85% alcohol (10 vols.) the *4-monoacetate* separated in plates, m. p. 164—165°, $[\alpha]_D^{24°}$ −88·8°; $[\alpha]_{5461}^{24°}$ −107·8° (*c*, 1·312);* α_{5461}/α_D = 1·21 (Found :† C, 78·2; H, 10·5. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%), which gave deep blue colorations with the trichloroacetic acid and the antimony trichloride reagent. In contrast to the 3-monoacetate, the 4-monoacetate and its homologues crystallise from acetic or propionic acid, etc., with 1 mol. of the acid (cf. cholesterol). These addition compounds melt lower than the respective 4-monoesters, lose the acid of crystallisation in a vacuum at 120°, and dissociate on recrystallisation from dilute alcohol. The 4-monoacetate gave 3-benzoyloxy-4-acetoxy-Δ⁵-cholestene, m. p. 166—167°, and 3 : 4-diacetoxy-Δ⁵-cholestene, m. p. 169—170°, on benzoylation and acetylation, identified by mixed m. p. with authentic specimens prepared from the respective 3-monoesters (Rosenheim and Starling, *loc. cit.*).

(*b*) Selenium dioxide (1·6 g.; 0·5 mol.), dissolved in water (0·8 ml.) and acetic acid (30 ml.), was added to cholesteryl acetate (10 g.; 1 mol.) dissolved in benzene (20 ml.). After 3 hours' refluxing on the water-bath, sodium acetate (3 g.) was added, the heating continued for 10 minutes, the solution filtered (norit), and the filtrate concentrated by distillation in a vacuum at 30° until crystallisation commenced. Acetic acid (10 ml.) was added, the crystals redissolved by warming, and the solution set aside for 24 hours. The product (4 g.) in 5 vols. of dioxan was freed from residual selenium (sintered glass filter). On addition of an equal volume of acetic acid the acetic acid compound, m. p. 144°, separated; it afforded 4-acetoxy-Δ⁵-cholesten-3-ol, m. p. 164—165° (alone or in admixture with the specimen described under *a*), on crystallisation from 85% alcohol. On addition of water to the mother-liquor and recrystallisation of the precipitate from spirit the 3-monoacetate, m. p. 193—194°, was obtained (*ca.* 5% yield).

The monoesters, m. p. 165° and 191°, of the *cis*-diol mentioned incidentally by Marker and Rohrmann (*J. Amer. Chem. Soc.*, 1939, **61**, 3022), and erroneously described as polymorphic forms of the 3-monoacetate, are actually the 4-mono- and the 3-mono-acetate respectively, the latter having previously been obtained by Rosenheim and Starling (*Chem. and Ind.*, 1933, **52**, 1056) and fully described by Petrow and Starling (*loc. cit.*). The so-called 3-acetates of 4-hydroxysitosterol and 4-hydroxystigmasterol (Marker and Rohrmann, *J. Amer. Chem. Soc.*, 1938, **60**, 1071, 1073) are similarly the 4-monoacetates of the corresponding *cis*-3 : 4-diols, an acyl migration as above having occurred in their preparation from sitosteryl and stigmasteryl acetates in benzene–acetic acid solution.

(*c*) Cholesteryl acetate (10 g.), dissolved in pure dioxan (20 ml.), was mixed with a solution of selenium dioxide (1·6 g.; 0·5 mol.) in water (0·8 ml.) and acetic acid (30 ml.). After 3 hours at 90° sodium acetate (5 g.) was added, the heating continued for about 10 minutes, the liquid filtered through a hot-water funnel, and after 24 hours the cream-coloured crystalline product (6·2 g.) collected. It was dissolved in dioxan (5 vols.) and filtered from residual selenium, and an equal volume of acetic acid added. Recrystallisation from 15 vols. of acetic acid at 90° yielded the acetic acid compound, m. p. 144°, which was converted into the 4-monoacetate, m. p. 164—165° (alone or in admixture with an authentic specimen), by recrystallisation from 15 vols. of 85% alcohol. The mother-liquors from the first crystallisation gave *ca.* 5% of the 3-monoacetate, m. p. 193—194°.

(*d*) From the 3-monoacetate : (1) The 3-monoacetate (2 g.) in a mixture of dioxan (15 ml.) and acetic acid (15 ml.) was kept at 90° for 1 hour. After 24 hours at room temperature crystals of the acetic acid compound (0·8 g.) were collected and identified as above. Owing to the disturbance of the equilibrium 3- ⇌ 4-monoacetate by the removal of the 4-acetate, the filtrate yielded a further crop of the latter after heating at 90° for 1 hour. (2) The 3-monoacetate (1 g.) in a mixture of benzene (5 ml.) and acetic acid (10 ml.) was refluxed for 1 hour. After removal of the benzene in a vacuum at room temperature, the acetic acid compound (0·4 g.) of the 4-monoacetate separated; it was identified as above.

4-Propionoxy-Δ⁵-cholesten-3-ol (IV; R = COEt).—(*a*) Silver propionate (3·8 g.) in pyridine (10 ml.) was rapidly mixed with cholesteryl dibromide (5 g.) in ether (40 ml.) and pyridine (25 ml.). After 1 hour, ether (200 ml.) was added, and the procedure described above followed. The ether residue (3·8 g.), recrystallised from 85% alcohol or acetone, gave 4-

* All rotations were measured in chloroform solution in a 4 dm. tube.

† Microanalyses by Drs. Weiler and Strauss.

propionoxy-Δ⁵-cholesten-3-ol in fine needles, m. p. 134—135°, $[\alpha]_D^{18°}$ −87·8°; $[\alpha]_{5461}^{18°}$ −104·8° (*c*, 1·076); α_{5461}/α_D = 1·2 (Found: C, 78·2; H, 10·8. $C_{30}H_{50}O_3$ requires C, 78·5; H, 10·9%). The acetic acid compound formed long needles, m. p. 110—112°.

(*b*) Cholesteryl propionate (5 g.) in benzene (10 ml.) was mixed with a solution of selenium dioxide (2 g.) in water (1 ml.) and acetic acid (20 ml.). After 1 hour's refluxing at 90°, sodium acetate (4 g.) was added, and after a further 10 minutes the solution poured into water and extracted with ether. The ethereal layer was washed, dried, concentrated, and diluted with acetic acid; crystals of the acetic acid compound (1·15 g.), m. p. 110—112°, were then obtained, which yielded the 4-monopropionate on recrystallisation from 85% alcohol.

3-*Acetoxy*-4-*propionoxy*-Δ⁵-*cholestene*, needles from 85% alcohol, m. p. 156—157°, $[\alpha]_D^{20°}$ −96·5°; $[\alpha]_{5461}^{20°}$ −114·0° (*c*, 1·19); α_{5461}/α_D = 1·2 (Found: C, 76·6; H, 10·5. $C_{32}H_{52}O_4$ requires C, 76·6; H, 10·4%), was obtained by acetylation of 4-propionoxy-Δ⁵-cholesten-3-ol or by propionylation of 3-acetoxy-Δ⁵-cholesten-4-ol.

4-*Butyroxy*-Δ⁵-*cholesten*-3-*ol* (IV; R = COPr).—Silver butyrate (4·7 g.) in pyridine (15 ml.) was added to cholesteryl dibromide (6·5 g.) in pyridine (25 ml.). The product (4·6 g.), isolated as above, was treated with methanol (20 ml.) and after recrystallisation from acetone gave 4-*butyroxy*-Δ⁵-*cholesten*-3-*ol* in fine needles, m. p. 125—126°, $[\alpha]_D^{21°}$ −75·3°; $[\alpha]_{5461}^{21°}$ −90·2° (*c*, 1·086); α_{5461}/α_D 1·2 (Found: C, 78·9; H, 11·0. $C_{31}H_{32}O_3$ requires C, 78·8; H, 11·1%). The acetic acid compound formed needles, m. p. 99—100°.

3-*Acetoxy*-4-*butyroxy*-Δ⁵-*cholestene*, silky needles from methyl–ethyl alcohols, m. p. 139—140°, $[\alpha]_D^{16°}$ −90·8°; $[\alpha]_{5461}^{16°}$ −107·5° (*c*, 1·116); α_{5461}/α_D = 1·2 (Found: C, 76·9; H, 10·6. $C_{33}H_{54}O_4$ requires C, 76·9; H, 10·4%), was obtained by acetylation of 4-butyroxy-Δ⁵-cholesten-3-ol, or by treatment of the 3-monoacetate with butyric anhydride.

4-*Benzoyloxy*-Δ⁵-*cholesten*-3-*ol* (IV; R = Bz).—Silver benzoate (10 g.) in pyridine (40 ml.) was added rapidly to a suspension of cholesteryl dibromide (10 g.) in pyridine (10 ml.) and ether (100 ml.). The product (7 g.), isolated as before, gave 4-*benzoyloxy*-Δ⁵-*cholesten*-3-*ol*, which formed prisms from acetone, m. p. 154—155°, $[\alpha]_D^{18°}$ −29·5°; $[\alpha]_{5461}^{18°}$ −35·0° (*c*, 1·066); α_{5461}/α_D = 1·2 (Found: C, 80·8; H, 9·8. $C_{34}H_{50}O_3$ requires C, 80·6; H, 9·9%), not depressed in admixture with the compound (C) of Spring and Swain (*loc. cit.*), kindly supplied by Dr. F. S. Spring. On acetylation 4-benzoyloxy-3-acetoxy-Δ⁵-cholestene was obtained, needles from spirit, m. p. 132—134°, $[\alpha]_D^{19°}$ −59·5°; $[\alpha]_{5461}^{19°}$ −70° (*c*, 1·044); α_{5461}/α_D = 1·2, also obtained by benzoylation of the 3-monoacetate (Spring and Swain, *loc. cit.*, give m. p. 130—131° and $[\alpha]_D^{20°}$ −54·8°).

4-*Acetoxy*-Δ⁵-*androsten*-3(β)-*ol*-17-*one*.—Solutions of Δ⁵-androsten-3(β)-ol-17-one (2 g.) and bromine (0·38 ml.) in chloroform (20 ml.) were mixed, and the solvent removed in a vacuum at room temperature. The residue, dissolved in ether (20 ml.) and pyridine (10 ml.), was treated with silver acetate (2·3 g.) in pyridine (10 ml.) and kept for 20 minutes in the dark; ether (250 ml.) was then added. The ethereal residue (2·08 g.), obtained by the usual procedure, was triturated with hexane and ether to remove yellow pigment and gave 4-*acetoxy*-Δ⁵-*androsten*-3(β)-*ol*-17-*one* in prismatic needles from 50% alcohol or dioxan, m. p. 192—193°, $[\alpha]_D^{20°}$ −60·7; $[\alpha]_{5461}^{20°}$ −69·2° (*c*, 0·910); α_{5461}/α_D = 1·14 (Found: C, 72·6; H, 8·3. $C_{19}H_{28}O_3$ requires C, 72·8; H, 8·7%). This gave an intense blue coloration with the trichloroacetic acid reagent.

cis-Δ⁵-*Androstene*-3 : 4-*diol*-17-*one*, shiny plates from 50% aqueous dioxan, m. p. 204—205°, $[\alpha]_D^{20°}$ −28·5° (*c*, 0·228) (Found: C, 74·7; H, 9·0. $C_{19}H_{28}O_3$ requires C, 74·9; H, 9·3%), was obtained on hydrolysis. Biological assays by the capon growth method, kindly carried out by Dr. W. Emmens, showed that the diol was devoid of androgenic activity.

3-*Acetoxy*-Δ⁵-*cholesten*-4-*ol* (I; R = Ac).—(*a*) Cholesteryl acetate (10 g.) in dioxan (30 ml.) was mixed with selenium dioxide (1·6 g.; 0·5 mol.) in water (0·8 ml.) and dioxan (10 ml.). After 3 hours' heating on the water-bath the solution was decanted from black selenium and poured in a thin stream with mechanical stirring into half-saturated brine. The granular deposit was collected without suction, washed with water, and dried in a vacuum. The yellowish powder was boiled out under reflux with 95% methanol (200 ml.), and the residual resinous material treated twice with smaller quantities of the solvent. When the combined extracts were kept at −4°, crude 3-monoacetate (3·0 g.) separated. After grinding with cold light petroleum (15 ml.) and recrystallisation from alcohol, 3-acetoxy-Δ⁵-cholesten-4-ol was obtained, m. p. 192—193°, not depressed in admixture with a specimen prepared by partial acetylation of the *cis*-3 : 4-diol (Petrow and Starling, *loc. cit.*).

(*b*) The 4-monoacetate (1 g.) in dioxan–acetic acid (1 : 1; 30 ml.) was kept at 90° for 1 hour. After 24 hours at room temperature the deposited acetic acid compound of the 4-monoacetate was removed. The filtrate on treatment with water gave the 3-monoacetate (0·4 g.), m. p. 192—193° after recrystallisation from spirit, alone or in admixture with an authentic specimen. 4-Benzoyloxy-3-acetoxy-Δ⁵-cholestene, m. p. 132—134°, obtained on benzoylation, was identical with the acetylation product of 4-benzoyloxy-Δ⁵-cholesten-3-ol (see above).

3-*Benzoyloxy*-Δ⁵-*cholesten*-4-*ol* (I; R = Bz).—Solutions of cholesteryl benzoate (5 g.) in dioxan (10 ml.) and selenium dioxide (0·6 g.; 0·5 mol.) in water (0·3 ml.) and dioxan (5 ml.) were mixed. After 3 hours' heating on a water-bath the solution, decanted from black selenium, was kept, the crude monobenzoate (3·6 g.) then deposited yielding 3-benzoyloxy-Δ⁵-cholesten-4-ol, m. p. 205—206° on recrystallisation from ethyl acetate and benzene, not depressed in admixture with a specimen prepared by partial benzoylation of the *cis*-3 : 4-diol (Rosenheim and Starling, *loc. cit.*). On acetylation 3-benzoyloxy-4-acetoxy-Δ⁵-cholestene, m. p. 166°, was obtained (see above).

Preparation of Δ⁴-*Cholestene*-3 : 6-*diol from* cis-Δ⁵-*Cholestene*-3 : 4-*diol or its Monoacetates*.—A solution of the respective monoacetates or the *cis*-diol (1 g.) in acetic acid was refluxed for 5 minutes, the solvent removed in a vacuum, and the residue acetylated by boiling with acetic anhydride; 3 : 6-diacetoxy-Δ⁴-cholestene thus obtained had m. p. 134—135°, not depressed by an authentic specimen. Hydrolysis furnished Δ⁴-cholestene-3 : 6-diol, m. p. 255—256° alone or in admixture with an authentic specimen (Rosenheim and Starling, *loc. cit.*).

4-*Chloro*-3-*acetoxy*-Δ⁵-*cholestene* (II; R = Ac).—(*a*) Thionyl chloride (1 ml.; 1 mol.) in ether (10 ml.) was added dropwise to a solution of 3-acetoxy-Δ⁵-cholesten-4-ol (5 g.; 1 mol.) in ether (200 ml.) containing pyridine (1 ml.; 1 mol.). After 24 hours at room temperature or gentle refluxing on a water-bath for 3 hours, the ethereal solution was decanted from pyridine hydrochloride (1·4 g.), washed with sodium bicarbonate and water, and dried, and the ether removed, to give 4-*chloro*-3-*acetoxy*-Δ⁵-*cholestene* (5·6 g.), which formed prismatic needles from ether–alcohol (1 : 2), m. p. 108—109°, $[\alpha]_D^{19°}$ −70·4°; $[\alpha]_{5461}^{19°}$ −85·0° (*c*, 1·366); α_{5461}/α_D = 1·12 (Found: C, 75·4; H, 9·9; Cl, 7·7. $C_{29}H_{47}O_2Cl$ requires C, 75·2; H, 10·2; Cl, 7·7%). The compound gave an intense blue coloration with the trichloroacetic acid reagent.

(*b*) To a solution of 6-chloro-3-acetoxycholestan-5-ol (5 g.) (Ruzicka and Bosshard, *Helv. Chim. Acta*, 1937, **20**, 244; Chakravorty and Levin, *J. Amer. Chem. Soc.*, 1942, **64**, 2317) (III; R = Ac) in pyridine (20 ml.) cooled in a freezing mixture, thionyl chloride (0·8 ml.) was added dropwise with shaking. After 5 minutes the mixture was poured into water, and the precipitated solids collected and recrystallised from ether–methyl alcohol (1 : 2) to give 4-chloro-3-acetoxy-Δ⁵-cholestene (3·5 g.), m. p. 108—109° alone or in admixture with a specimen prepared by method (*a*).

Preparation of 4-*Acetoxy*-Δ⁵-*cholesten*-3-*ol and* 3 : 6-*Diacetoxy*-Δ⁴-*cholestene from* 4-*Chloro*-3-*acetoxy*-Δ⁵-*cholestene*.—Solutions of 4-chloro-3-acetoxy-Δ⁵-cholestene (1 g.) in dioxan (5 ml.) and potassium acetate (1 g.) in acetic acid (10 ml.) were mixed and heated for 1 hour on the water-bath. Potassium chloride was removed from the hot solution, which deposited the acetic acid compound (0·5 g.) of the 4-monoacetate, m. p. 142—144°, on cooling; this was identified as above. A solution of 4-chloro-3-acetoxy-Δ⁵-cholestene (1 g.) in acetic acid (10 ml.) containing potassium acetate (1 g.) was refluxed

for 5 minutes, after being kept at 90° for 1 hour; acetylation of the residue obtained on removal of the solvent in a vacuum yielded 3 : 6-diacetoxy-Δ^4-cholestene, m. p. 134—135° alone or in admixture with an authentic specimen.

4-Chloro-3-benzoyloxy-Δ^5-cholestene (II; R = Bz).—Thionyl chloride (0·4 ml.; 1 mol.) in ether (8 ml.) was added dropwise to 3-benzoyloxy-Δ^5-cholesten-4-ol (2·5 g.; 1 mol.) dissolved in ether (100 ml.) and benzene (25 ml.) containing pyridine (0·4 ml.; 1 mol.). The mixture was treated as above. The product in ether (10 ml.) was precipitated with alcohol (10 ml.) to give needles (2·14 g.), m. p. 124—126°, which yielded on recrystallisation from ethyl acetate–alcohol 4-chloro-3-benzoyloxy-Δ^5-cholestene, m. p. 127—128°, $[\alpha]_D^{18°}$ −81·9; $[\alpha]_{5461}^{18°}$ −101·1° (*c*, 1·132); $\alpha_{5461}/\alpha_D = 1·23$ (Found: C, 77·3; H, 9·3; Cl, 6·4. Calc. for $C_{34}H_{49}O_2Cl$: C, 77·7; H, 9·4; Cl, 6·7%), not depressed in admixture with the substance described as 6-chloro-3-benzoyloxy-Δ^4-cholestene, prepared from 6-chloro-3-benzoyloxycholestan-5-ol and kindly supplied by Dr. F. S. Spring.

cis-*Δ^5-Cholestene-3 : 4-diol* endo-*Sulphite* (XII).—Thionyl chloride (1 ml.; 1 mol.) in ether (15 ml.) was slowly added to a solution of the *cis*-diol (5 g.; 1 mol.) in ether (180 ml.) and pyridine (1 ml.; 1 mol.), and the mixture refluxed for 3 hours. The ethereal solution was decanted from pyridine hydrochloride, washed, and concentrated to *ca.* 20 ml. The crystalline precipitate (3·1 g.) obtained by adding an equal volume of alcohol gave the endo-*sulphite*, which formed needles from ether–alcohol (1 : 1) or acetone, m. p. 146—148° (decomp.), $[\alpha]_D^{19°}$ −64·6; $[\alpha]_{5461}^{19°}$ −77·4° (*c*, 1·172); $\alpha_{5461}/\alpha_D = 1·2$ (Found: C, 72·2; H, 9·9; S, 7·1. $C_{27}H_{44}O_3S$ requires C, 72·3; H, 9·9; S, 7·2%). The compound was recovered unchanged after heating with acetic anhydride (absence of hydroxyl groups) and yielded the *cis*-diol on hydrolysis. With the trichloroacetic acid reagent on warming a deep blue coloration was produced (for a similar steroid *endo*-sulphite, see Jacobs and Elderfield, *J. Biol. Chem.*, 1932, **97**, 727; Tschesche, *Z. physiol. Chem.*, 1934, **229**, 224).

Bis-(4 : 4′-acetoxycholesteryl) Sulphite (XIII).—Thionyl chloride (0·4 ml.; 1 mol.) in ether (10 ml.) was added dropwise to a solution of the 4-monoacetate (2·2 g.; 1 mol.) in ether (50 ml.) containing pyridine (0·4 ml.; 1 mol.), and the mixture refluxed for 3 hours. The liquid was decanted from pyridine hydrochloride (0·52 g.), which was washed with ether by decantation. The ethereal solution was washed and dried, the ether removed, and alcohol added. The product (1·6 g.) gave *bis-(4 : 4′-acetoxycholesteryl) sulphite*, which formed shiny prisms from ether–alcohol (1 : 2), m. p. 159—160°, $[\alpha]_D^{18°}$ −106·1°; $[\alpha]_{5461}^{18°}$ −127·0° (*c*, 1·060); $\alpha_{5461}/\alpha_D = 1·2$ (Found: C, 74·7; H, 10·0; S, 3·6. $C_{58}H_{94}O_7S$ requires C, 74·4; H, 10·2; S, 3·4%). The compound gave a deep blue coloration with the trichloroacetic acid reagent on warming, and furnished the *cis*-diol on hydrolysis with alcoholic potash (for bis-cholesteryl sulphite, see Daugenbaugh and Allison, *J. Amer. Chem. Soc.*, 1939, **51**, 3665).

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