647. *Steroids and Walden Inversion. Part VII.* The Stereochemistry and the Mechanism of the* i-*Steroid Rearrangement.*

By C. W. Shoppee and G. H. R. Summers.

The *i*-steroid rearrangement is shown to involve inversion of configuration at $C_{(3)}$ and to yield 6β-substituted derivatives of 3 : 5-*cyclo*steroids. A 6α-substituted 3 : 5-*cyclo*steroid has been prepared indirectly. The rearrangement exhibits some analogies with Wagner substitution and a mechanism for the change is suggested and discussed.

The *i*-steroid rearrangement is a general reaction whereby derivatives of 3β-hydroxy-Δ^5-steroids afford 6-substituted 3 : 5-*cyclo*steroids. Thus methanolysis of cholesteryl toluene-*p*-sulphonate or chloride gives cholesteryl methyl ether, m. p. 84°, $[\alpha]_D$ −46°, but in the presence of potassium acetate furnishes *i*-cholestanyl methyl ether (6-methoxy-3 : 5-*cyclo*cholestane), m. p. 79°, $[\alpha]_D$ +55° (Stoll, *Z. physiol. Chem.*, 1932, **207**, 147; Wagner-Jauregg and Werner, *ibid.*, 1932, **213**, 119). These observations were, some four years later, the subject of intensive investigation by Heilbron and his collaborators in this country and by Wallis and his co-workers in America; both schools at one time or another regarded the "abnormal" methyl ether as *epi*cholesteryl methyl ether (Heilbron, Beynon, and Spring, *J.*, 1936, 907; 1937, 406; Wallis, Fernholz, and Gephart, *J. Amer. Chem. Soc.*, 1937, **59**, 137). This interim conclusion, which had been criticised by Ruzicka, Goldberg, and Bosshard (*Helv. Chim. Acta*, 1937, **20**, 541), was shown to be incorrect by the preparation of genuine *epi*cholesteryl methyl ether, m. p. 88—89°,† $[\alpha]_D$ −46° (Wallis and Ford, *J. Amer. Chem. Soc.*, 1937, **59**, 1415). Lack of olefinic unsaturation in the "abnormal" ether, the related acetate, and the parent alcohol was explained by Wallis in terms of the 3 : 5-*cyclo*steroid formulation, which he suggested by analogy with the transformation of sabinene hydrate into terpinen-4-ol. The formula requires the presence of a secondary hydroxyl group at $C_{(6)}$, which was proved by oxidation of the alcohol to a ketone *i*-cholestanone (Ford, Chakravorty, and Wallis, *J. Amer. Chem. Soc.*, 1938, **60**, 413) recognised by Heilbron as 3 : 5-*cyclo*cholestan-6-one and hydrogenated to give cholestan-6-one (Heilbron, Hodges, and Spring, *J.*, 1938, 759). Similarly 3 : 5-*cyclo*androstane-6 : 17-dione was converted into 3′ : 3′ : 9-trimethyl*cyclo*pentanophenanthrene to prove the presence of an oxygen atom at $C_{(6)}$ (Butenandt and Suranyi, *Ber.*, 1942, **75**, 597).

Further chemical and physical evidence for the presence of a 3-membered ring in 3 : 5-*cyclo*steroids has recently been given by the conversion of 3 : 5-cholestane with hydrogen chloride–acetic acid into A-norcholest-3(5)-ene (Schmid and Kägi, *Helv. Chim. Acta*, 1950, **33**, 1582), the partial synthesis of which we have recently achieved (Shoppee and Summers, *J.*, 1952, 2528). Indirect evidence is provided by simple aliphatic analogues of the *i*-steroid change; thus 4-methylpent-3-enyl chloride is hydrolysed by water to dimethyl*cyclo*propylcarbinol which is reconverted by hydrochloric acid into 4-methylpent-3-enyl chloride (Bruylants and Dewael, *Bull. Sci. Acad. Roy., Belg.*, 1928, [v], **14**, 140; Favorskaya and Fridman, *J. Gen. Chem. U.S.S.R.*, 1945, **15**, 421); *cyclo*propylcarbinol with phosphorus tribromide gives a bromide converted by the action of magnesium followed by carbon dioxide into allylacetic acid (L. I. Smith and McKenzie, *J. Org. Chem.*, 1950,

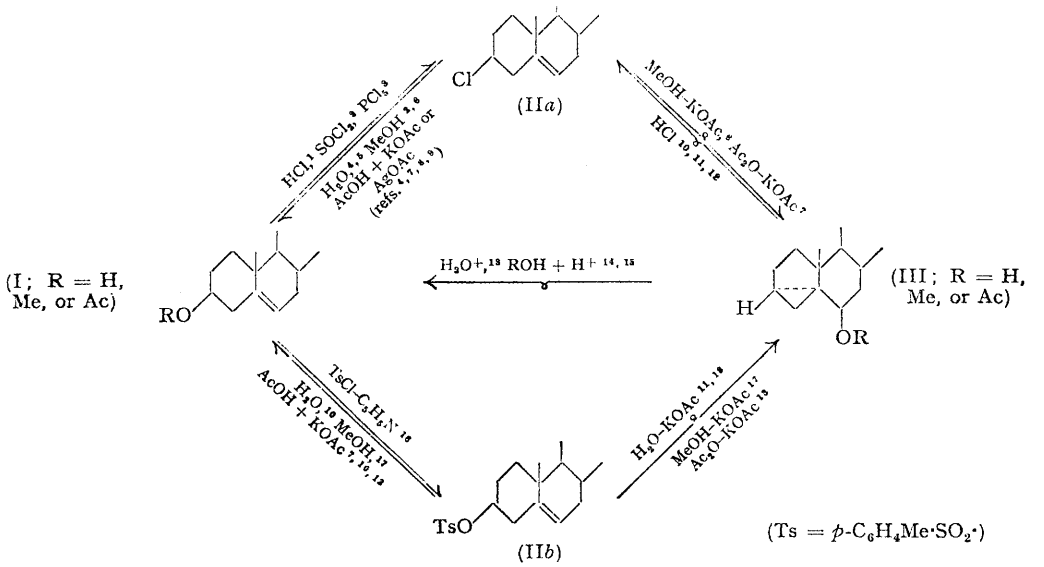
* Part VI, *J.*, 1950, 687.

† We have observed a double m. p. 82—84° with resolidification and remelting at 88—89°.

15, 74); and chlorination of methyl*cyclo*propane gives a mixture containing approximately equal quantities of *cyclo*propylmethyl chloride and but-3-enyl chloride (Roberts and Mazur, *J. Amer. Chem. Soc.*, 1951, **73**, 2509).

The infra-red absorption spectra of 3 : 5-*cyclo*cholestane (Barton, *J.*, 1951, 1444) and of various 6-methoxy-3 : 5-*cyclo*steroids (Josien, Fuson, and Cary, *J. Amer. Chem. Soc.*, 1951, **73**, 4445) show bands in the region 1010—1020 and at 890 cm.$^{-1}$, which have been tentatively identified with deformation of the *cyclo*propane ring and with the band at 1000—1020 cm.$^{-1}$ reported for alkyl-substituted *cyclo*propane derivatives by Derfer, Pickett, and Boord (*ibid.*, 1949, **71**, 1482).

The principal experimental facts concerning the *i*-steroid rearrangement relate to the cholestane series, and may be summarised as follows :

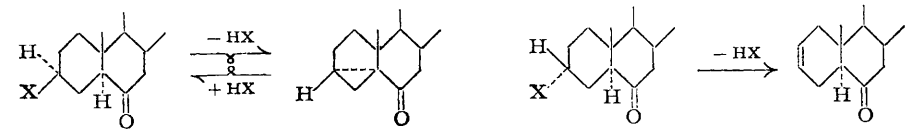


[1] Shoppee and Summers, *J.*, 1952, 1786. [2] Diels, Abderhalden, and Blumberg, *Ber.*, 1904, **37**, 3092; 1911, **44**, 2847. [3] Mauthner, *Monatsh.*, 1894, **15**, 87. [4] *Idem*, *ibid.*, p. 362. [5] Marker, *J. Amer. Chem. Soc.*, 1935, **57**, 1755. [6] Wagner-Jauregg and Werner, *Z. physiol. Chem.*, 1932, **213**, 119. [7] Shoppee and Summers, this paper. [8] Bergmann, *J. Amer. Chem. Soc.*, 1938, **60**, 1996. [9] Shoppee, *J.*, 1946, 1147. [10] Heilbron, Beynon, and Spring, *J.*, 1936, 907. [11] *Idem*, *J.*, 1937, 1459. [12] Wallis and Ford, *J. Amer. Chem. Soc.*, 1937, **59**, 1415. [13] Wallis, Fernholz, and Gephart, *ibid.*, p. 137. [14] McKennis, *ibid.*, 1947, **69**, 2565; 1948, **70**, 675. [15] Winstein and Schlesinger, *ibid.*, 1948, **70**, 3528. [16] Freudenberg and Hess, *Annalen*, 1926, **448**, 121. [17] Stoll, *Z. physiol. Chem.*, 1932, **207**, 147. [18] Hafez, Halsey, and Wallis, *Science*, 1949, **110**, 474.

The reaction (I ⟶ II) proceeds with complete retention of configuration at $C_{(3)}$. A complete proof of the β-configuration at $C_{(3)}$ of cholesterol (I; R = H) has been given (Shoppee, *J.*, 1948, 1032). The structure of cholesteryl chloride (II*a*), suggested by that of cholesteryl iodide (Carlisle and Crowfoot, *Proc. Roy. Soc.*, 1945, *A*, **184**, 64), is established by the proof that its 5 : 6-dihydro-derivative is 3β-chlorocholestane (Shoppee, *J.*, 1946, 1138, 1147); the structure of the toluene-*p*-sulphonate (II*b*) follows from that of cholesterol.

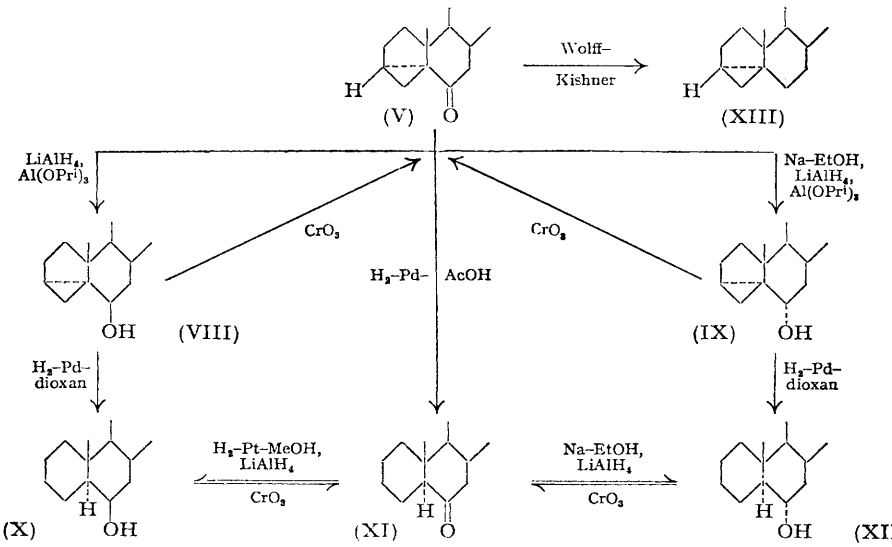
Contrariwise, the reaction (II ⟶ III) involves inversion of configuration at $C_{(3)}$, and 3 : 5-*cyclo*cholestane compounds contain a distorted *cis*-hexahydroindane structure. The configuration of the 3β-halogeno-ketones (IV; X = Cl, Br, or I) and 3β-toluene-*p*-sulphonyloxy-ketone (IV; X = *p*-C_6H_4·SO_2) is established (Shoppee, *J.*, 1948, 1032); these ketones, by ionic *trans*-elimination [*E*1 or *E*2], are converted quantitatively into *i*-cholestanone (3 : 5-*cyclo*cholestan-6-one) (V), which is obtained by oxidation of *i*-cholestan-6-ol (III) (formerly termed *i*-cholesterol), and can quantitatively be reconverted by the hydrogen halides into the 3β-halogeno-ketones (IV; X = Cl, Br, or I) (Heilbron, Hodges, and Spring, *J.*, 1938, 759; Wallis and Ford, *loc. cit.*; Ford, Chakravorty,

and Wallis, *loc. cit.*; Shoppee and Summers, *J.*, 1952, 1786). In a similar way, hydration of *i*-cholestanone (V) with dilute sulphuric acid in acetic acid gives 3β-hydroxycholestan-6-one (IV; X = OH) (Wallis, Fernholz, and Gephart, *loc. cit.*). It may be noted that the 3α-epimeric ketones (VI; X = Cl, Br, or *p*-$C_6H_4Me{\cdot}SO_2$) undergo 1 : 2-elimination with difficulty, to give poor yields of cholest-2-en-6-one (VII) (Ford, Chakravorty, and Wallis, *loc. cit.*; Blunschy, Hardegger, and Simon, *Helv. Chim. Acta*, 1946, **29**, 199; Riegel and Dodson, *J. Org. Chem.*, 1948, **13**, 424).



(IV; X = Cl, Br, I, or *p*-$C_6H_4Me{\cdot}SO_2$·) (V) (VI; X = Cl, Br, or *p*-$C_6H_4Me{\cdot}SO_2$·) (VII)

The 6-substituent in the derivatives (III) of 3 : 5-*cyclo*cholestane produced by the *i*-steroid rearrangement possesses the β-configuration. This result, which is probably general for 3 : 5-*cyclo*steroids, has been proved as follows. Hydrogenation of *i*-cholestanone (V) with palladium–acetic acid gives cholestan-6-one (XI) (Windaus, and Dalmer, *Ber.*, 1919, **52**, 162; Windaus and von Staden, *ibid.*, 1921, **54**, 1059; Ford, Chakravorty, and Wallis, *loc. cit.*; Heilbron, Hodges, and Spring, *J.*, 1938, 759), but when reduction is brought about by treatment with lithium aluminium hydride, little *i*-cholestanol (VIII) and much *epi-i*-cholestanol, m. p. 85—86°, $[\alpha]_D$ +83° (IX), are obtained. The latter substance has recently also been described (m. p. 86°, $[\alpha]_D$ +81°) by Wagner and Wallis (*J. Amer. Chem. Soc.*, 1950, **72**, 1047), and forms the only crystalline product isolated when reduction is effected with sodium–ethanol. It is difficult to obtain crystalline, but is oxidised by chromium trioxide to *i*-cholestanone (V), and smoothly converted by the appropriate halogen acid–acetic acid at 20°, into cholesteryl chloride, bromide, and iodide; its acetate, m. p. 60°, $[\alpha]_D$ +82°, appears to have been isolated but not identified by Heilbron, Hodges, and Spring (*J.*, 1938, 759) after acetylation of the product obtained by reduction of *i*-cholestanone with aluminium *iso*propoxide–*iso*propanol.

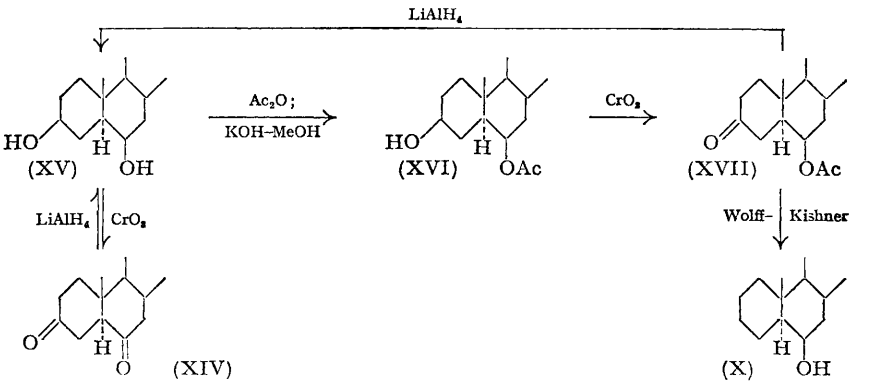


Low-pressure Wolff–Kishner reduction of *i*-cholestanone (V) gives *i*-cholestane (XIII), m. p. 78°, $[\alpha]_D$ +80°; this hydrocarbon, which gives a pale but distinct yellow colour with tetranitromethane, was described (m. p. 78—79°, $[\alpha]_D$ +80°), after our preparation of it, by Karrer and Schmid (*Helv. Chim. Acta*, 1949, **32**, 1371) and by Schmid and Kägi (*loc. cit.*).

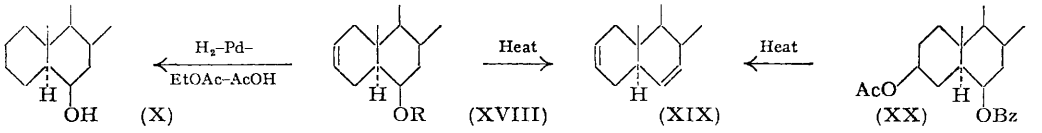
Hydrogenation of *i*-cholestanol (VIII) with palladium–dioxan in the presence of a *trace*

of acetic acid * affords, despite much hydrogenolysis leading to cholestane and an unidentified hydrocarbon, m. p. 61—65°, which is being investigated, cholestan-6β-ol (X), m. p. 82°, $[\alpha]_D$ +8°. Similar hydrogenation of *epi-i*-cholestanol (IX) gives cholestane and cholestan-6α-ol (XII), m. p. 129°, $[\alpha]_D$ +35°.

The substance (X) (acetate, m. p. 75°) is also obtained by hydrogenation of cholestan-6-one (XI) with platinum–methanol, and is identical with the compound obtained by reduction with zinc of 3β-iodocholestan-6β-ol, in which the β-configuration of the hydroxyl group is indicated by its ready ionic 5 : 6-*trans*-dehydration to cholesteryl iodide (Shoppee and Summers, *J.*, 1952, 1786). It has also been obtained from cholestane-3 : 6-dione (XIV); this by reduction with lithium aluminium hydride gives cholestane-3β : 6β-diol (XV), which by acetylation and partial hydrolysis furnishes the 6-monoacetate (XVI), oxidised by chromium trioxide to 6β-acetoxycholestan-3-one (XVII), which regenerates



the diol (XV) by lithium aluminium hydride reduction, and affords cholestan-6β-ol (X) by low-pressure Wolff–Kishner reduction. Finally, cholestan-6β-ol (X) is obtained by hydrogenation of cholest-2-en-6β-ol (XVIII; R = H); this substance, whose preparation is described in the following communication, by pyrolysis as the benzoate (XVIII; R = Bz) gives cholesta-2 : 6-diene (XIX), recently obtained by Barton and Rosenfelder (*J.*, 1950, 2459) by pyrolysis of cholestane-3β : 6β-diol 3-acetate 6-benzoate (XX). Since thermal elimination reactions require *cis*-geometry (Barton, *J.*, 1949, 2174), and steroid 6β-benzoates are known to yield cholest-6-enes by pyrolysis (Barton and Rosenfelder, *Nature*, 1949, **164**, 316; Wintersteiner and Moore, *ibid.*, p. 316), these observations again indicate the β-configuration of the hydroxyl group in (X).



The substance (XII) (acetate, m. p. 95°) is cholestan-6α-ol and identical with the compound obtained from cholestan-6-one (XI) by reduction with sodium–ethanol (Tschesche, *Ber.*, 1932, **65**, 1842), and incorrectly described as cholestan-6β-ol in Elsevier's "Encyclopaedia" (Vol. XIV, p. 66). The greater thermodynamic stability of the equatorial conformation of the 6α-hydroxyl group in the cholestane series is consistent with this method of preparation, and is indicated by the partial conversion by extended treatment with sodium–amyl alcohol at 200° of cholestane-3β : 6β-diol (XV) into cholestane-3β : 6α-diol (see following paper).

* Hydrogenation of *i*-cholestanyl acetate with platinum–acetic acid furnishes cholestanyl acetate (Wallis, Fernholz, and Gephart, *loc. cit.*), probably as a consequence of rearrangement induced by the high concentration of acetic acid (see p. **3366**) to cholesteryl acetate and reduction of this. Hydrogenation of *i*-cholestanyl methyl ether with platinum–acetic acid to a compound, $C_{28}H_{50}O$, m. p. 78°, which depressed the m. p. (82·5—83°) of cholestanyl methyl ether and was stable to hydrochloric acid at 100°, has been reported (Wagner–Jauregg and Werner, *loc. cit.*); the production of 6β-methoxycholestane under these conditions would not be expected and the matter is being investigated.

Reduction of cholestan-6-one (XI) with lithium aluminium hydride furnishes a mixture of cholestan-6β-ol (X) (95%) and cholestan-6α-ol (XII) (5%) which may be separated chromatographically.

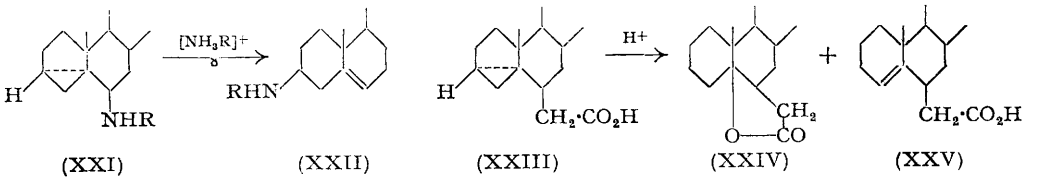
Finally, the configurations assigned chemically to the epimeric cholestan-6-ols are confirmed physically by the agreement shown by the molecular rotations observed by us and those calculated by the method of molecular rotation differences (Barton and Klyne, *Chem. and Ind.*, 1948, 755) :

Cholestan-6α-ol (XII)	$[M]_D$ (obs.) + 136°	$[M]_D$ (calc.) + 147°
Cholestan-6β-ol (X)	,, + 31	,, + 39

These results show that *i*-cholestanol is 3 : 5-*cyclo*cholestan-6β-ol, and suggest that other *i*-steroids formed from 3β-hydroxy-Δ^5-steroids are 6β-substituted compounds.

From the first reaction scheme (p. 3362) it will be seen that in media which become increasingly acidic as solvolysis proceeds derivatives of cholesterol are produced, but that in buffered media 3 : 5-*cyclo*cholestane derivatives are formed in high yield.* There is one exception to this generalisation; acetolysis in the presence of acetate ion furnishes *only* cholesteryl acetate. This fact is clearly related to the observations that 6β-methoxy-3 : 5-*cyclo*cholestane and 6β-methoxy-3 : 5-*cyclo*stigmast-22-ene, when heated with potassium or zinc acetate in acetic acid, undergo quantitative conversion into cholesteryl and stigmasteryl acetate respectively (Heilbron *et al.*, *J.*, 1936, 907; Fernholz and Ruigh, *J. Amer. Chem. Soc.*, 1940, **62**, 3346).

3 : 5-*cyclo*Steroids are sensitive to acids. 6β-Methoxy-3 : 5-*cyclo*cholestane is hydrolysed (and rearranged to cholesterol) under conditions in which cholesteryl methyl ether (II) is completely stable (Wagner-Jauregg and Werner, *loc. cit.*; Heilbron *et al.*, *locc. cit.*); it has been shown to react with alcohols (McKennis, *loc. cit.*; Winstein and Schlesinger, *loc. cit.*), with alkanethiols (Ralls, Dodson, and Riegel, *J. Amer. Chem. Soc.*, 1949, **71**, 3320), with pyridine, and with thiourea (King, Dodson, and Sablusky, *ibid.*, 1948, **70**, 1176) in the presence of small quantities of toluene-*p*-sulphonic acid, to give cholesteryl alkyl ethers, cholesteryl ethyl sulphide, cholesteryl pyridinium and thiuronium salts respectively. These acid-catalysed reactions probably involve addition of a proton, or in pyridine of the pyridinium cation $[PyH]^+$, which functions as an acid like $[NH_4]^+$ in liquid ammonia, to a lone pair of the oxygen atom of the methoxyl group. Similarly, 6β-amino-3 : 5-*cyclo*steroids (XXI; R = Ph or CH_2Ph) in aniline or benzylamine in the presence, but not in the absence, of the appropriate cation $[NH_3R]^+$ undergo rearrangement to substituted cholesterylamines (XXII) after attack at the lone pair of electrons on the nitrogen atom (Julian, Magnani, Meyer, and Cole, *ibid.*, p. 1834).



(XXI) (XXII) (XXIII) (XXIV) (XXV)

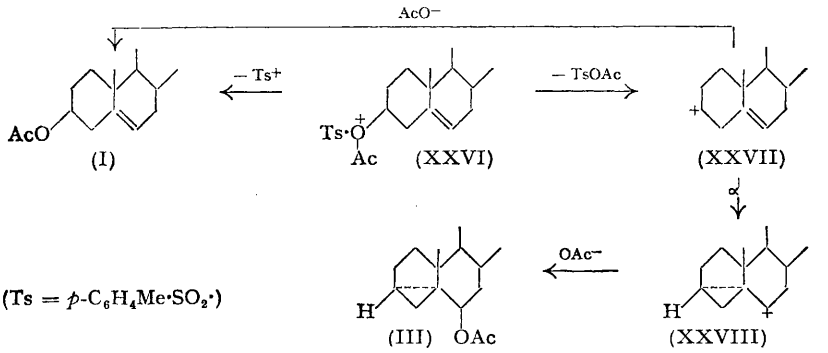
If the $C_{(6)}$-substituent in a 3 : 5-*cyclo*steroid possesses no lone pair of electrons, rearrangement to a cholest-5-ene derivative does not take place; 3 : 5-*cyclo*cholestanyl-6β-acetic acid (XXIII) by treatment with dilute sulphuric acid–acetic acid yields a lactone, formulated as the 6β→5β-lactone † (XXIV), accompanied by a dehydration product formulated as the cholest-4-ene-6β-acetic acid † (XXV) (Kaiser and Svarz, *ibid.*, 1945, **67**, 1309; 1947, **69**, 847; 1949, **71**, 517).

* Compare the discussion of the reaction of cholesteryl chloride with alcohols in presence of etched magnesium given by Wagner-Jauregg and Werner (*loc. cit.*); the reversion of 3 : 5-*cyclo*cholestan-6β-ol to 3β : 5α : 6β-tribromocholestane with bromine in ether (Heilbron *et al.*, *loc. cit.*) is curious and noteworthy as occurring in an apparently neutral medium.

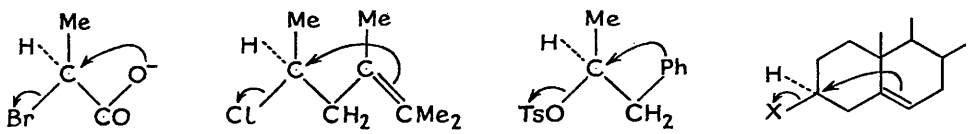
† Alternatively, these compounds may be formulated as a 6β→3β-lactone and a cholest-2-ene-6β-acetic acid, or, by fission of the $C_{(4)}$–$C_{(5)}$-bond (cf. Schmid and Kägi, *loc. cit.*), as 3-methyl-5β-hydroxy-A-norcholestane-6β-acetic acid 6β→5β-lactone and 3-methyl-A-norcholest-3(5)-ene-6β-acetic acid.

The apparently anomalous action of acetic acid or its conjugate acid $[AcOH_2]^+$ seems to depend on concentration; by contrast with the solvolysis of (II) conducted in acetic acid with or without added acetate ion, a solvolysis in an alcohol proceeding in the presence of acetate ion can give rise to only one molecular proportion of acetic acid. Experiments are being made to determine the rate of rearrangement of 3 : 5-*cyclo*steroids as a function of the acetic acid concentration.

Solvolysis of cholesteryl toluene-*p*-sulphonate with acetic anhydride–potassium acetate gives both cholesteryl acetate (I) and 3 : 5-*cyclo*cholestan-6β-yl acetate (III), together with an unsaturated hydrocarbon, probably cholesta-3 : 5-diene. We find that cholesteryl chloride behaves similarly. The results suggest that a carbonium ion (XXVII) is produced, which can undergo either elimination [*E*1] to give cholesta-3 : 5-diene, or rearrangement to a second carbonium ion (XXVIII) which furnishes the acetate (III). Acetic anhydride undergoes ionisation: $Ac_2O \rightleftharpoons Ac^+ + OAc^-$ (Mackenzie and Winter, *Trans. Faraday Soc.*, 1948, **44**, 161), and in the presence of potassium acetate an active entity will also be the ion $[Ac_2OK]^+ = Ac^+ + KOAc$ (Burton and Praill, *J.*, 1950, 1203), so that as suggested privately by Professor Burton in the case of the toluene-*p*-sulphonate, reaction with the acetylium ion can give (XXVI) which by acyl–oxygen fission furnishes only cholesteryl acetate (I), but by alkyl–oxygen fission affords the carbonium ion (XXVII), which may or may not rearrange to (XXVIII) before attack by an acetate ion. A similar scheme for cholesteryl chloride would involve a chloronium ion as an intermediate.



The acetolysis of cholesteryl toluene-*p*-sulphonate with or without acetate ion is kinetically of the first order (Winstein and Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838); we have confirmed this and have identified the product as cholesteryl acetate; we have found a similar kinetic result for the acetolysis of cholesteryl bromide in the presence of acetate ion, which affords cholesteryl acetate as the sole isolatable product (Davies, Meecham, and Shoppee, unpublished work). These acetolyses thus appear to fit into a series of solvolyses proceeding by a unimolecular mechanism and involving control of the stereochemical course of substitution by neighbouring unshared electrons (Cowdrey, Hughes, and Ingold, *J.*, 1937, 1208; Davies, Hughes, and Ingold, unpublished work; Winstein, *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 1140; Shoppee, *loc. cit.*). Wallis, Hafez, and Halsey



Reaction :
Methanolysis Hydrolysis Formolysis Acetolysis

(In all cases the reaction is of first order and has S_N1 mechanism, and there is retention of configuration at the seat of substitution.)

(*loc. cit.*) also found a first-order rate constant for the hydrolysis of cholesteryl toluene-*p*-sulphonate in aqueous acetone in the presence of acetate ion and showed that the rate of

hydrolysis increased with increasing ease of separation of the 3β-substituent as the anion : p-$C_6H_4Me{\cdot}SO_3^- < Ph{\cdot}SO_3^- < p$-$NO_2{\cdot}C_6H_4{\cdot}SO_3^-$; this sequence is consistent with a reaction of S_N1 type, but the product is known to be largely 3 : 5-*cyclo*cholestan-6β-ol (Beynon, Heilbron, and Spring, *J.*, 1937, 1459). Clearly the main sequel here to formation of a carbonium ion is rearrangement followed by addition of an anion so that the situation has some analogies with the Wagner change (cf. Dostrovsky, Hughes, and Ingold, *J.*, 1946, 192).

There are three mechanistic possibilities for the conversion of cholest-5-ene compounds into 3 : 5-*cyclo*steroids. Mechanism 1 involves participation of the π-electrons of the double bond *subsequently* to the rate-determining ionisation of the 3β-substituent; it postulates the existence of the cholest-5-enyl cation and the 3 : 5-*cyclo*cholestanyl cation as individual stereochemical entities separated by an energy hill of height sufficient to preclude interaction. Mechanism 2 involves participation *simultaneously* with the rate-determining ionisation, which is thereby facilitated, leading to the formation of a mesomeric ion. The canonical forms of a mesomeric ion are believed not to exist as separate chemical entities and must be distinguished from the isomeric cations of mechanism 1; the picture here is that of the hypothetical canonical structures * separated by an energy valley and interacting to produce a more stable structure. This mechanism has been considered without regard to stereochemical implications by Shoppee (*Ann. Reports*, 1947, **44**, 173), Winstein and Adams, Winstein and Schlesinger, and Hafez, Halsey, and Wallis (*locc. cit.*). In both these mechanisms, the reaction will be of first order with respect to the steroid molecule and zero order with respect to the reactant anion, and so will exhibit overall first-order kinetics. Mechanism 3 involves participation of the π-electrons in a *synchronous* bond-forming bond-breaking process leading *via* a linear transition state to inversion at $C_{(3)}$ and introduction of a new anion at $C_{(6)}$. It has been envisaged as operating under appropriate conditions by Winstein and Schlesinger (*loc. cit.*), when it will exhibit second-order kinetics, but it does not seem to offer an explanation of the stereospecificity of the 3 : 5-*cyclo*steroid rearrangement at $C_{(6)}$.

It is difficult to distinguish between mechanisms 1 and 2. Formation of cholesta-3 : 5-diene suggests the real existence of the cholest-5-enyl cation as in mechanism 1, although formation of 3 : 5-*cyclo*cholest-6-ene [the *i*-cholestadiene of Riegel, Hager, and Zenitz (*J. Amer. Chem. Soc.*, 1946, **68**, 2562)] from the 3 : 5-*cyclo*cholestanyl cation, if this exists as a separate entity, has not been observed; on the other hand, the increased reactivity of cholest-5-enyl compounds compared with their cholestanyl analogues supports mechanism 2. It is however possible, by using either mechanism 1 or mechanism 2, to give an explanation of the phenomena of the 3 : 5-*cyclo*steroid rearrangement in terms of the thermodynamic and kinetic control of equilibria.

It is difficult to assess the thermodynamic stabilities of the isomeric Δ^5-steroid and 3 : 5-*cyclo*steroid molecules, and the relative stabilities of their carbonium ions and the reactivities of these to nucleophilic reagents. The thermodynamic stability of the cholest-5-ene molecule has been estimated to exceed that of 3 : 5-*cyclo*cholestane by some 7 kcal. (Roberts *et al.*, *ibid.*, 1950, **72**, 3116); and we hope shortly to report a determination of the heats of combustion of 3β-methoxycholest-5-ene and 6β-methoxy-3 : 5-*cyclo*cholestane. There is no evidence as to the relative stability of the Δ^5-cation and the 3 : 5-*cyclo*-cation but it seems probable that they are not greatly different; the Δ^5-cation possesses as a major factor of stability conjugation of the π-electrons with the cationic centre at $C_{(3)}$, whilst if the 3 : 5-bond is regarded as a partial and modified linkage of sp^2 type (Walsh, *Trans. Faraday Soc.*, 1949, **45**, 179; cf. however, Coulson and Moffitt, *J. Chem. Phys.*, 1947, **15**, 151) there will be similar if somewhat less effective conjugation in the 3 : 5-*cyclo*-cation. The contribution of hyperconjugation to these stabilities will be small. If we assume that the transition state for the ionic recombination, Δ^5-cation $\longrightarrow$ Δ^5-molecule, lies energetically

* The canonical structures appear to differ in regard to the position of the hydrogen nucleus at $C_{(3)}$ and so to break the rules relating to resonance hybrids; this difficulty is probably more apparent than real. Just as in benzene a compression energy of 33 kcal. is required to deform the structure of a Kékulé individual to a canonical structure capable of resonance with an energy of 40 kcal., so here a compression energy is required to deform the structure so that the hydrogen nucleus occupies a mean position and the distance between $C_{(3)}$ and $C_{(5)}$ is reduced from about 2·5 to 1·5 Å (cf. Coulson and Altmann, *Trans. Faraday Soc.*, 1952, **48**, 293).

higher than that for the ionic recombination : 3 : 5-*cyclo*-cation ⟶ 3 : 5-*cyclo*-molecule, it becomes possible to explain the occurrence of the 3 : 5-*cyclo*steroid rearrangement in terms of a symbolic energy diagram (Fig. *A*) (cf. Catchpole, Hughes, and Ingold, *J.*, 1948, 11).

In Fig. *A* the reaction path enters from the left; in a medium, which is neutral or maintained near neutrality by buffering with acetate ion, a Δ^5-steroid molecule ionises to give the Δ^5-ion, which may either reassociate slowly with an external anion, or rearrange with some loss of free energy to give the 3 : 5-*cyclo*-cation, which rapidly combines with an external anion to give the 3 : 5-*cyclo*-steroid molecule. Despite the lesser thermodynamic stability of the 3 : 5-*cyclo*-steroid, it may thus be formed as the main or even as the sole reaction product as a result of kinetic control of the equilibria. If these conditions obtain for a sufficiently long time, thermodynamic control of the equilibria must eventually furnish Δ^5-steroid molecules if the disparity between (*a*) the energies of the two cations and (*b*) the speeds of their anionic recombination is not too great; a sufficient period in a polar solvent of large dielectric constant might in favourable circumstances be expected to permit the conversion of 3 : 5-*cyclo*steroid into Δ^5-steroid, but we were unable to convert 6β-methoxy-3 : 5-*cyclo*cholestane into 3β-methoxycholest-5-ene by heating it in methyl cyanide (dielectric constant, 37·5) at 82° for long periods. Under acid conditions any

FIG. *A*.

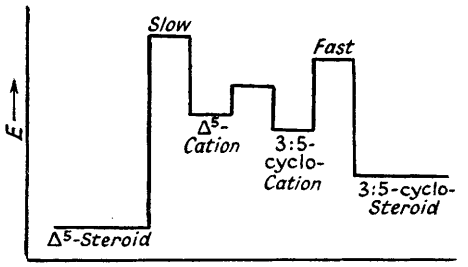
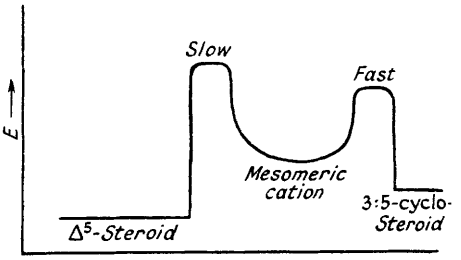


FIG. *B*.



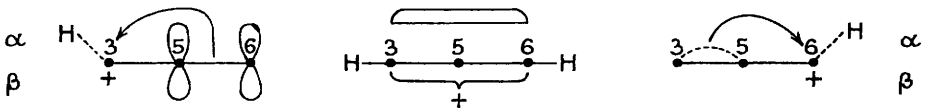
3 : 5-*cyclo*steroid molecule, formed by traversing the reaction path completely from left to right, will continually be attacked by protons or their conjugates and so re-ionised to give the 3 : 5-*cyclo*-cation and rearranged to the Δ^5-cation, eventually to yield the Δ^5-steroid molecule. The instability of the 3 : 5-*cyclo*steroid molecule to acids thus enables the thermodynamic control of equilibria to become effective; in a limited time and in the presence of a very small concentration (0·001M) of toluene-*p*-sulphonic acid, 6β-methoxy-3 : 5-*cyclo*cholestane in ethanol at 78° gives 68% of 6β-ethoxy-3 : 5-*cyclo*cholestane and 32% of 3β-ethoxycholest-5-ene together with some unaltered material (Winstein and Schlesinger, *loc. cit.*). This result clearly indicates the initial conversion of the 6β-methoxy-3 : 5-*cyclo*cholestane into the analogous ethoxy-compound; this may be represented in Fig. *A* by considering the reaction path entering from the right, traversing the lower heterolytic transition state, and returning by the same route.

Fig. *A*, which was drawn early in 1951 and formed part of the manuscript of a contribution to the Steroid Symposium held by the American Chemical Society in September, 1951, bears a close resemblance to a broken-line diagram given subsequently by Brown, Hughes, Ingold, and Smith (*Nature*, 1951, **168**, 65, Fig. 2) to illustrate certain aspects of the Wagner change. Just as Fig. *A* illustrates mechanism 1 for the 3 : 5-*cyclo*steroid rearrangement, so Fig. *B*, which is analogous to the full line diagram (Fig. 2) of Hughes, Ingold, *et al.*, can be drawn to illustrate mechanism 2 (involving a mesomeric cation) for the 3 : 5-*cyclo*steroid rearrangement. Both mechanisms are consistent with the facts cited previously in this paper and with the observations that 6β-acetoxy-3 : 5-*cyclo*cholestane can readily be obtained from the parent alcohol, although the 3 : 5-dinitrobenzoate is always accompanied by some cholesteryl 3 : 5-dinitrobenzoate (Wallis, Fernholz, and Gephart, *loc. cit.*), whilst 6β-chloro-3 : 5-*cyclo*cholestane seems incapable of preparation [tendency to separate as anion : $OAc^- < (NO_2)_2{\cdot}C_6H_4{\cdot}CO_2^- \ll Cl^-$], and that lithium

aluminium hydride reduction of cholesteryl toluene-*p*-sulphonate gives both cholest-5-ene and 3 : 5-*cyclo*cholestane (Karrer and Schmid, *loc. cit.*). Fortunately, either mechanism gives a reasonable explanation of the stereochemistry of the 3 : 5-*cyclo*steroid rearrangement.

Figures *C*, *D*, and *E* represent diagrammatic views, vertically down the $C_{(5)}$–$C_{(10)}$ bond axis in the general plane of the ring system and without regard to geometric detail,* of the Δ^5-cation, the 3 : 5-*cyclo*-cation, and the mesomeric cation. Knowledge of the retention of configuration in substitution reactions at $C_{(3)}$ in Δ^5-steroids (Shoppee, *J.*, 1946, 1147) shows that the charge cloud resulting from the π-electrons of the double bond has maximum density at the α-face of $C_{(3)}$ (Fig. *C*); this must clearly also be the case for the α-face of $C_{(6)}$ (Fig. *D*), and for the α-faces of $C_{(3)}$, $C_{(5)}$, and $C_{(6)}$ in the mesomeric cation (Fig. *E*). When the 3 : 5-*cyclo*-cation represented by (*D*) combines with an anion, or when the distributed charge of the mesomeric cation represented by (*E*) becomes concentrated at $C_{(6)}$ co-ordination of an anion will furnish the 6β-configuration. A somewhat similar argument

FIG. *C*. FIG. *E*. FIG. *D*.



has been used by Dodson and Riegel (*J. Org. Chem.*, 1948, **13**, 424). The suggestion of Winstein and Adams (*loc. cit.*) that substitutions at $C_{(3)}$ take place by way of 3 : 5-*cyclo*-steroids, so that the observed complete retention of configuration at $C_{(3)}$ is the result of two successive inversions, Δ^5-steroid $\xrightarrow{-s}$ 3 : 5-*cyclo*-steroid $\xrightarrow{-s}$ Δ^5-steroid, cannot be excluded; it appears, however, to be difficult to apply this proposal to the replacement of hydroxyl by chlorine in the conversion of cholesterol into cholesteryl chloride by hydrogen chloride (Shoppee and Summers, *J.*, 1952, 1786).

The conversion of *both* 3 : 5-*cyclo*cholestan-6β- and -6α-ol into cholesterol in acidic media, reported by Wagner and Wallis (*loc. cit.*) and confirmed by us, is consistent with the foregoing stereochemical picture. It does not seem to furnish a means of distinguishing between mechanism 1 and mechanism 2; in the mesomeric cation (*E*) both $C_{(3)}$ and $C_{(6)}$ will possess trigonal sp^2-configurations, so that both the 6-epimerides will afford the same structure, whilst if the Δ^5-cation (*C*) and the 3 : 5-*cyclo*-cation (*D*) are separate structures with maintained tetrahedral sp^3-configurations only the 3 : 5-*cyclo*-cation represented by (*D*) will exist. For if an epimeric 3 : 5-*cyclo*-cation with a β-orientated hydrogen atom at $C_{(6)}$ were to arise from 3 : 5-*cyclo*cholestan-6α-ol, the influence of the electron cloud derived from the 3 : 5-bond might be expected to lead at once to inversion at $C_{(6)}$ with production of the 3 : 5-*cyclo*-cation represented by (*D*).

EXPERIMENTAL

M. p.s were determined thermo-electrically on a Kofler block; limit of error ±2°. Solvents for chromatographic operations were rigorously purified and dried and, unless stated otherwise, aluminium oxide (Spence type H, activity ~II) was used. For drying of ethereal extracts, brief treatment with anhydrous sodium sulphate was used. [α] refers to chloroform solutions.

Cholestan-6-one (XI).—This ketone was obtained as described by Windaus (*Ber.*, 1919, **52**, 162) and by Shoppee and Summers (*J.*, 1952, 1786); we examined a modification of the route used by Riegel and Dodson (*J. Org. Chem.*, 1948, **13**, 424) involving nitration of cholesteryl acetate (Mauthner and Suida, *Monatsh.*, 1903, **24**, 648; cf. Heilbron *et al.*, *J.*, 1938, 104, and Fieser and Rigaudy, *J. Amer. Chem. Soc.*, 1951, **73**, 4660); this at first gave variable results, but the following procedure appears satisfactory. Finely powdered cholesteryl acetate (m. p. 115°; 20 g.) was added to nitric acid (300 c.c.; *d* 1·42) rapidly stirred at 20°; powdered potassium nitrite (2 g.) was then added and a remarkable change occurred. Nitrogen oxides were evolved and simultaneously the cholesteryl acetate was transformed into a flocculent material which later became crystalline; the reaction appeared to be almost instantaneous. Stirring was continued for 1 hour, the nitric acid removed by filtration, and the reaction product digested

* In Δ^5-steroids ring A is a chair form, whilst in 3 : 5-*cyclo*steroids ring B also has the chair conformation.

with a large volume of water, filtered, washed very thoroughly with water, and dried on porous porcelain and finally in a vacuum desiccator (yield, 21 g.). The crude dry product by crystallisation from ethanol gave 3β-acetoxy-6-nitrocholest-5-ene in prismatic needles, m. p. 103° (18·3 g., 80%). The ketone (XI) was also obtained (*a*) from 3β-chloro-6-nitrocholest-5-ene by prolonged reduction with zinc–acetic acid (cf. Windaus and von Staden, *Ber.*, 1921, **54**, 1059) and chromatographic separation from 3β-chlorocholestan-6-one, and (*b*) from 3β-bromo-6-nitrocholest-5-ene.

Cholesteryl bromide (m. p. 98°; 4 g.) was stirred at 20° with concentrated nitric acid (*d* 1·42; 30 c.c.) and fuming nitric acid (*d* 1·54; 50 c.c.), and powdered sodium nitrite (3 g.) was added gradually during 10 minutes; stirring was continued for 0·75 hour at 20°. The solid yellow product was filtered off on sintered glass, washed with much water and with ethanol, dried on porous porcelain, and crystallised from acetic acid, to give 3β-bromo-6-nitrocholest-5-ene as needles, m. p. 153° (cf. Vanghelovici and Angelescu, *Bull. Soc. chim. România*, 1935, **17**, 251). The nitro-compound (1·5 g.) was heated under reflux with zinc dust (2 g.) in acetic acid for 2 hours. The solution was poured into water and extracted with benzene. After being washed to neutrality and dried in the usual way, the extract by evaporation gave an oil, which after filtration of a pentane solution through a column of aluminium oxide, crystallised from methanol, in plates, m. p. 96—98°, undepressed by admixture with authentic cholestan-6-one.

Cholestan-6β-ol (X).—(*a*) Cholestan-6-one (XI) (102 mg.) dissolved in methanol (or ethanol) (10 c.c.) was hydrogenated at 30° in the presence of platinum oxide (60 mg.); absorption of 1 mol. of hydrogen required 8 hours. The catalyst was removed and the filtrate evaporated completely in a vacuum. The residue was chromatographed on alumina (4 g.) prepared in pentane, eluates of 5 c.c. each being examined. The material from fractions 1—4 (eluant, pentane; 27 mg.; an oil which, crystallised from ether–methanol, had m. p. 79—80°) was cholestane and did not depress the m. p. of an authentic specimen. From fractions 11—16 (eluant, 1 : 1-benzene–pentane; total 53 mg. of oil) was obtained *cholestan-6β-ol*, m. p. 80—82°, $[\alpha]_D$ +8°±2° (*c*, 0·602) [Found, after drying at 60—65°/0·01 mm. for 3 hours: C, 83·0; H, 12·4. $C_{27}H_{48}O$ requires C, 83·4; H, 12·4%).

(*b*) To a solution of lithium aluminium hydride (1·7 g.) in boiling ether (200 c.c.) was added dropwise a solution of cholestan-6-one (3·5 g.) in ether (200 c.c.) at a rate sufficient to keep the ether gently refluxing. After 20 minutes the reaction was stopped, the reaction mixture cooled in ice, and ice-cold 2N-sulphuric acid added carefully to destroy excess of the reducing agent. The ethereal solution was washed with 2N-sulphuric acid, and with water to neutrality (litmus), dried, and evaporated. The resultant colourless oil (3·5 g.) was chromatographed on aluminium oxide (110 g.) prepared in pentane, eluates of 300 c.c. each being collected. Fractions 1—4 (eluant, pentane) furnished unchanged cholestan-6-one (60 mg. of m. p. 92—96°), m. p. 96—98° after recrystallisation from acetone. Fractions 11—23 (eluant, 1 : 9 ⟶ 1 : 1 benzene–pentane) were united (total, 3·25 g.; m. p. 71—75°) and recrystallised from methanol, to give cholestan-6β-ol in prisms, m. p. 79—81°, giving no depression with the material obtained by method (*a*). The material from fractions 26—29 (eluant, 1 : 9 ether–benzene) consisted of cholestan-6α-ol (230 mg.), m. p. 127° after recrystallisation from methanol; it gave no depression with authentic cholestan-6α-ol (see below).

Cholestan-6β-ol (100 mg.), dissolved in acetic acid (2 c.c.) and oxidised with chromium trioxide (2 c.c. of a 2% solution in acetic acid) for 15 hours at 20°, gave by the usual procedure cholestan-6-one as plates (from methanol), m. p. 96—97°. The *acetate*, prepared by use of acetic anhydride–pyridine at 100° for 3 hours and isolated in the usual way, crystallised from methanol in needles, m. p. 75°, $[\alpha]_D$ −7·5°±1° (*c*, 2·497) (Found, after drying at 20°/0·05 mm. for 20 hours: C, 81·0; H, 11·9. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7%). Benzoylation with benzoyl chloride–pyridine at 20° for 24 hours, followed by working up in the usual way, gave the *benzoate* as prismatic needles (from acetone), m. p. 79—80° (Found, after drying at 20°/0·05 mm. for 8 hours: C, 82·7; H, 10·4. $C_{34}H_{52}O_2$ requires C, 82·9; H, 10·6%).

Cholestan-6α-ol (XII).—This was prepared by the reduction of cholestan-6-one with sodium–ethanol according to the directions of Tschesche (*Ber.*, 1932, **65**, 1842) and had m. p. 129—130° after crystallisation from methanol. The acetate prepared by acetic anhydride–pyridine at 20° had m. p. 96°. Benzoylation as above gave the *benzoate* as prismatic needles (from acetone–methanol), m. p. 103—105°, $[\alpha]_D$ +62·5°±3° (*c*, 1·045) (Found, after drying at 20°/0·05 mm. for 8 hours: C, 82·5; H, 10·3%). The toluene-*p*-sulphonate, prepared by use of toluene-*p*-sulphonyl chloride–pyridine for 15 hours at 25°, crystallised from acetone–pentane in very thin needles m. p. 109—110°, $[\alpha]_D$ +68°±2° (*c*, 2·484) (cf. Karrer *et al.*, *Helv. Chim. Acta*, 1951, **34**, 1022, who give m. p. 108·5—110°, $[\alpha]_D$ +64° in chloroform).

3 : 5-cyclo*Cholestan*-6-*one* (VIII).—This was prepared (cf. Dodson and Riegel, *J. Org. Chem.*, 1948, **13**, 424) by heating 3β-chlorocholestan-6-one with refluxing 5% ethanolic potassium hydroxide for 0·5 hour, purified by filtration of a pentane solution through alumina and by recrystallisation from methanol, the compound having m. p. 96°. Hydrogenation with palladium oxide–acetic acid at 25° gave crude cholestan-6-one, m. p. 88—92°, raised by chromatography and subsequent recrystallisation from acetone to 96—97·5°.

3 : 5-cyclo*Cholestan*-6β-*ol* (VIII) *and* 3 : 5-cyclo*Cholestan*-6α-*ol* (IX).—(*a*) 3 : 5-*cyclo*Cholestan-6-one (V) (1·24 g.) in ether (150 c.c.) was added during 1 hour to a solution of lithium aluminium hydride (2·32 g.) in boiling ether (300 c.c.); refluxing was continued for 1·5 hours. The ethereal solution was treated with ice-water at 0° and cold 2N-sulphuric acid, washed with sodium hydrogen carbonate and with water, dried, and evaporated. The resultant oil (1·2 g.) was chromatographed on alumina (35 g.), 120 c.c. eluates being collected (see Table).

Fraction	Eluant	Eluates
1—6	Pentane	Cryst. (13 mg.), m. p. 92—96°, 3 : 5-*cyclo*cholestan-6-one
7—9	Benzene–pentane (1 : 19)	Oil (3 mg.)
10—12	Benzene–pentane (1 : 9)	Crystd. spontaneously (25 mg.), m. p. 81—84°, 3 : 5-*cyclo*cholestan-6α-ol
13—18	Benzene–pentane (1 : 4)	Oil (200 mg.)
19—23	Benzene–pentane (1 : 1)	Oil (220 mg.)
24—28	Benzene	Oil (525 mg.)
29—31	Ether–benzene (1 : 19)	Oil (125 mg.), crystd. from methanol at −10°, m. p. 70—74°, 3 : 5-*cyclo*cholestan-6β-ol

A further quantity of 3 : 5-cyclo*cholestan*-6α-*ol* (IX) was obtained as follows. Fractions 13—23 were distilled in a molecular flask at 120—134°/0·01 mm. but the distillate failed to crystallise and was rechromatographed on a long column of alumina (65 g.) and eluted continuously with benzene–pentane (1 : 9). The material so obtained was distilled in a molecular flask at 120—130°/0·01 mm.; the distillate (400 mg.) crystallised at once when cooled and moistened with pentane, and had m. p. 85—86°, $[\alpha]_D$ +83°±3° (*c*, 0·714) (Found, after drying at 20°/0·01 mm. for 3 hours: C, 84·1; H, 12·2. $C_{27}H_{46}O$ requires C, 83·9; H, 12·0%); the m. p. was depressed to 59° by admixture with 3 : 5-*cyclo*cholestan-6β-ol (VIII), m. p. 74°. Similar treatment of fractions 24—28 failed to yield crystalline material. Fractions 29—31 yielded 3 : 5-*cyclo*cholestan-6β-ol (VIII), m. p. 71—74°, undepressed by admixture with a genuine specimen.

(*b*) 3 : 5-*cyclo*Cholestan-6-one (V) (365 mg.) in ethanol (30 c.c.) was heated on a steam-bath with sodium (2·6 g.). After dissolution of the sodium, the reaction mixture was poured into water, ethanol partly removed in a vacuum, and the product isolated as an oil (320 mg.) which was chromatographed on alumina (9 g.) prepared in pentane. Only the fractions obtained by elution with benzene–pentane (1 : 9) could be caused to crystallise; by cooling of a solution in acetone at −10° plates, m. p. 78—86°, were obtained which recrystallised readily from acetone after inoculation, to yield 3 : 5-*cyclo*cholestan-6α-ol (140 mg.), m. p. 85—86°, giving no depression by admixture with the specimen prepared by method (*a*). Acetylation of the new alcohol with acetic anhydride–pyridine at 20° for 15 hours, followed by the usual working up, gave an oily acetate; alkaline hydrolysis regenerated the parent alcohol.

3 : 5-cyclo*Cholestan*-6-*one* (V) *from* 3 : 5-cyclo*Cholestan*-6α-*ol* (IX).—3 : 5-*cyclo*Cholestan-6α-ol (10 mg.) in acetic acid (0·5 c.c.) was treated with 2% solution of chromium trioxide in acetic acid (0·5 c.c.) at 20° for 15 hours; the product, isolated in the usual manner as an oil, was purified by passage of its solution in pentane through aluminium oxide (300 mg.), to give 3 : 5-*cyclo*cholestan-6-one, m. p. 92—95°, which did not depress the m. p. of an authentic sample.

Cholesteryl Chloride, Bromide, and Iodide from 3 : 5-cyclo*Cholestan*-6α-*ol* (IX).—Treatment of 3 : 5-*cyclo*cholestan-6α-ol with hydrogen chloride, hydrogen bromide, or hydrogen iodide in acetic acid at 20° for 3 hours (cf. Beynon, Heilbron, and Spring, *J.*, 1936, 907) gave cholesteryl chloride, bromide, and iodide respectively in quantitative yield.

Cholestan-6β-*ol* (X) *from* 3 : 5-cyclo*Cholestan*-6β-*ol* (VIII).—3 : 5-*cyclo*Cholestan-6β-ol (220 mg.), dissolved in dioxan (15 c.c.) containing a trace of acetic acid (0·75 c.c.), was shaken with palladium oxide (150 mg.; not freshly prepared) in an atmosphere of hydrogen at 30°. After an induction period of about 2 hours, hydrogen was absorbed and absorption was allowed to proceed until 1 mol. had been taken up. After separation of the catalyst and removal of the solvent under reduced pressure, an oily product was obtained which tended to crystallise when scratched but did not appear to be homogeneous. It was dissolved in pentane and

chromatographed on alumina (7·5 g.) prepared in pentane. Elution with pentane (20 c.c.) gave an oil (30 mg.) which solidified and was recrystallised from ether–methanol, to yield cholestane in plates, m. p. 79°, undepressed by admixture with cholestane. Further elution with pentane (3 × 20 c.c.) gave material which solidified only after many months and was found to crystallise readily from aqueous dioxan in plates (134 mg.), m. p. 61—65°; the identity of this hydrocarbon is being investigated. Further elution with benzene–pentane gave small quantities of oil which did not crystallise; these were united (28 mg.) and acetylated with acetic anhydride–pyridine at 20°. The material obtained by working up in the usual way was filtered in pentane through alumina; the resultant oil solidified on inoculation with 6β-acetoxycholestane, and the product was then sublimed in a molecular flask at 80—95°/0·01 mm., whereafter it readily crystallised from methanol in needles, m. p. 74°, which did not depress the m. p. of an authentic specimen of 6β-acetoxycholestane.

Cholestan-6α-ol (XII) *from* 3 : 5-cyclo*Cholestan-6α-ol* (IX).—3 : 5-*cyclo*Cholestane-6α-ol (158 mg.) was hydrogenated in presence of palladium oxide (92 mg.) in dioxan (10 c.c.) containing acetic acid (0·5 c.c.). After absorption of 1 mol. of hydrogen, the reduction was stopped, the catalyst removed, and the filtrate evaporated in a vacuum. The product was chromatographed in pentane on aluminium oxide (5 g.), 10 c.c. eluates being collected. Elution with pentane furnished cholestane and subsequently considerable quantities of oil which could not be induced to crystallise. Elution with benzene gave only traces of material, but ether yielded a solid (41 mg.), m. p. 115—123° which after repeated crystallisation from methanol furnished cholestan-6α-ol, m. p. 126—129°, undepressed by admixture with a genuine specimen.

Cholestane-3β : 6β-diol 6-Monoacetate (XVI).—Cholestane-3β : 6β-diol diacetate (2·5 g.) was heated under reflux with a solution of potassium hydroxide (6·25 g.) in methanol (1500 c.c.). The cold solution was then acidified with concentrated hydrochloric acid and the excess of acid neutralised with ammonia. After removal of methanol under reduced pressure, the residual oil was dried by azeotropic distillation with benzene and chromatographed on alumina (100 g.) prepared in pentane. Elution with benzene–pentane (1 : 4) (5 × 200 c.c.) gave an oil (1·13 g.) which by crystallisation from methanol gave cholestane-3β : 6β-diol 6-monoacetate in needles, m. p. 70°, with resolidification and remelting at 128° (cf. Plattner and Lang, *Helv. Chim. Acta*, 1944, **27**, 1872). Elution with benzene–pentane (1 : 1) (3 × 200 c.c.) gave a further quantity (0·68 g.) of the same monoacetate, whilst elution with chloroform gave cholestane-3β : 6β-diol (0·37 g.), m. p. 185—190°.

6β-*Acetoxycholestan-3-one* (XVII).—Cholestane-3β : 6β-diol 6-monoacetate (5·5 g.) in acetic acid (75 c.c.) was treated with 2% chromium trioxide–acetic acid (40 c.c.) and set aside for 15 hours at 25°. Excess of chromium trioxide was destroyed by addition of methanol, and the solvent removed under reduced pressure. The residual oil (5·03 g.) was extracted with ether and purified in the usual way; it crystallised from methanol in needles, m. p. 85—97°. The product was purified by chromatography on alumina (150 g.) prepared in pentane. Elution with benzene–pentane (1 : 1) and with benzene gave 6β-acetoxycholestan-3-one, which crystallised from methanol in needles, m. p. 100—101·5°.

6β-*Hydroxycholestan-3-one*.—6β-Acetoxycholestan-3-one (0·53 g.) was refluxed for 0·5 hour with 5% methanolic potassium hydroxide solution (50 c.c.). After addition of a little water and passage of excess of carbon dioxide, methanol was removed in a vacuum, water was added, and the product filtered off, to yield a solid (0·49 g.) which crystallised from acetone–methanol, to give 6β-hydroxycholestan-3-one as prisms, m. p. 181—184°, $[\alpha]_D$ +9°±2° (*c*, 0·542) (Marker and Krueger, *J. Amer. Chem. Soc.*, 1940, **62**, 79, give m. p. 190°).

Cholestan-6β-ol (X).—6β-Hydroxycholestan-3-one (158 mg.), hydrazine hydrate (0·2 c.c.), and a solution of potassium hydroxide (0·2 g.) in triethylene glycol (2·5 c.c.) was heated for 0·5 hour at 140—160° and then at 200° for 2 hours. The product was poured into water, the liquid acidified, the solution extracted with ether, and the ethereal extract purified in the usual way, to give an oil (85 mg.) which after 3 crystallisations from methanol gave prismatic needles, m. p. 79°, undepressed by admixture with authentic cholestan-6β-ol.

Cholestane-3β : 6β-diol (XV).—6β-Hydroxycholestan-3-one (51 mg.) in ether (5 c.c.) was added to lithium aluminium hydride (70 mg.) in ether (10 c.c.) and the reaction mixture left at 20° for 0·5 hour. Excess of lithium aluminium hydride was destroyed with 2N-sulphuric acid and the ethereal solution washed to neutrality with water, dried, and evaporated, to yield a solid (50 mg.), which after repeated crystallisation from acetone–methanol gave needles, m. p. 190—194°, undepressed by admixture with authentic cholestane-3β : 6β-diol.

Cholesta-2 : 6-diene (XIX).—Benzoylation of cholest-2-en-6β-ol (XVIII) (113 mg.) with benzoyl chloride (2 c.c.) in pyridine (4 c.c.) at 20° gave an oil which did not crystallise, even after

filtration of a solution in pentane through alumina. The oil, after being dried at 60°/0·05 mm. for 1 hour, was heated at 320°/10 mm. The residue was then distilled at 0·1 mm., the distillate extracted with pentane, and benzoic acid removed with 2N-sodium carbonate solution. The oil obtained by evaporation was chromatographed on alumina (3 g.) prepared in pentane. Elution with pentane (3 × 5 c.c.) gave an oil (22 mg.), which crystallised from ether–methanol and from methanol, to give cholesta-2 : 6-diene as long needles, m. p. 69—71°, $[\alpha]_D$ −1°±2° (*c*, 1·201) (Barton and Rosenfelder, *J.*, 1949, 2459, give m. p. 70—72°, $[\alpha]_D$ ±0°). Further elution with pentane and benzene–pentane gave small amounts of oil which failed to crystallise.

3 : 5-cyclo*Cholestane*.—3 : 5-*cyclo*Cholestan-6-one (0·58 g.) was heated under reflux for 0·5 hour with diethylene glycol (4·3 c.c.), hydrazine hydrate (0·43 c.c.), and sodium (0·6 g.) at 150° for 0·5 hour. The temperature was then allowed to rise to 195—200°, and refluxing continued for a further 2·5 hours. The cooled reaction mixture was diluted with water and extracted with pentane. The extract, after being washed with 2N-hydrochloric acid and with water, dried, and evaporated, gave an oil (0·59 g.) which was dried in a high vacuum and crystallised from acetone in needles, m. p. 74—75°. Filtration of a pentane solution through alumina gave 3 : 5-*cyclo*cholestane, m. p. 77—78°, $[\alpha]_D$ 80°±1° (*c*, 1·501) (Found, after drying at 60°/0·05 mm. for 6 hours : C, 87·3; H, 12·55. $C_{27}H_{46}$ requires C, 87·5; H, 12·5%).

Acetolysis of Cholesteryl Toluene-p-*sulphonate*.—Cholesteryl toluene-*p*-sulphonate (101 mg.) was heated under reflux with acetic acid (10 c.c.) for 36 hours under anhydrous conditions. Acetic acid was removed under reduced pressure, and the oily residue taken up in ether and washed successively with 2N-sodium carbonate and with water, dried, and evaporated. The resultant oil slowly crystallised and was chromatographed on alumina (4 g.) prepared in pentane; the column was eluted repeatedly with benzene–pentane (1 : 9; 10-c.c. fractions). Fractions 1—3 furnished a small amount of oil (13 mg.) which did not solidify on inoculation with *i*-cholesteryl acetate; this product consisted essentially of cholesteryl acetate since alkaline hydrolysis yielded slightly impure cholesterol, m. p. 143° after some softening. Eluates 6—15 furnished an oil (60 mg.) which solidified and by recrystallisation from ether–methanol gave plates, m. p. 103—112°, giving a positive test with tetranitromethane in chloroform; recrystallisation raised the m. p. to 111—114°, undepressed by admixture with authentic cholesteryl acetate.

Acetolysis of Cholesteryl Chloride.—(a) *With acetic anhydride and potassium acetate*. Cholesteryl chloride (5·13 g.) was heated with acetic anhydride (300 c.c.) (in which it is not very soluble) and anhydrous potassium acetate (7·5 g.) under reflux for 30 hours, whereupon the solution became deep brown. Acetic anhydride was removed under reduced pressure and the resulting oil purified in the usual manner. The product failed to crystallise and was hydrolysed with 5% ethanolic potassium hydroxide (250 c.c.) to give material which readily solidified. This was chromatographed on alumina (200 g.) prepared in pentane, and the chromatogram developed, eluates of 250 c.c. each being collected. Elution with pentane (fractions 3—7) gave a considerable amount of oil which solidified but proved difficult to recrystallise; this product gave a negative Beilstein test and was unsaturated, giving a yellow colour with tetranitromethane in chloroform, and appeared to contain cholesta-3 : 5-diene. Further elution with pentane yielded no significant amount of material, but use of benzene–pentane (1 : 4 and 1 : 1; 6 fractions) gave an oil (110 mg.) which crystallised partly on inoculation with 3 : 5-*cyclo*cholestanol; by treatment with hydriodic acid–acetic acid at 20° and subsequent chromatographic purification, with pentane as eluant, this material yielded cholesteryl iodide, m. p. 107°, and so must have consisted originally of 3 : 5-*cyclo*cholestanyl acetate, converted by hydrolysis into 3 : 5-*cyclo*cholestanol. Finally, the column was exhaustively eluted with ether, to yield a solid (3·43 g.), which crystallised from acetone in plates, m. p. 142—148° undepressed by admixture with cholesterol.

(b) *With acetic acid*. Cholesteryl chloride (200 mg.) was heated with acetic acid (20 c.c.) in a sealed tube at 95° for 72 hours; the reaction mixture was poured into water and the product isolated by repeated extraction with benzene. After hydrolysis with hot 5% ethanolic potassium hydroxide (25 c.c.) for 0·5 hour, the solvent was largely removed in a vacuum, and the product extracted with ether–benzene, to yield, after the usual purification, an oil (205 mg.) which crystallised. This material by chromatography on alumina (10 g.) and elution with pentane gave cholesteryl chloride, m. p. 93° (158 mg., 77·5%), and with ether gave cholesterol (43 mg.; calc. for 22·5% conversion, 43 mg.).

(c) *With acetic acid and silver acetate*. Cholesteryl chloride (500 mg.) and silver acetate (500 mg.) were dried separately at 50—60°/0·01 mm. for 30 minutes, and thereafter heated under reflux with acetic acid (30 c.c.) for 2·5 hours. The reaction mixture was concentrated in a vacuum to about one-quarter volume, diluted with water, and extracted with ether. The

product (528 mg.) was chromatographed on alumina (16 g.) prepared in pentane, with 40-c.c. eluates. Elution with pentane (fractions 1—3) gave 7 mg. of oil; further elution with pentane and pentane–benzene (fractions 4—17) gave cholesteryl acetate (473 mg.) which, recrystallised from acetone, had m. p. 112—114° (314 mg.). The material from the mother-liquors (147 mg.) and the oil (1·5 mg.) eluted from the column with benzene were combined and hydrolysed with methanolic potassium hydroxide, to give material (140 mg.), m. p. 144—148°, consisting of nearly pure cholesterol.

Action of Acetic Acid on 6β-*Methoxy*-3 : 5-cyclo*cholestane*.—6β-Methoxy-3 : 5-*cyclo*cholestane (m. p. 79°; 2·76 g.) was heated with acetic acid (50 c.c.) under reflux for 10 hours; on cooling, a crop of needles separated. Acetic acid was removed under reduced pressure and the residue taken up in ether, washed with 2N-sodium carbonate and with water, dried, and evaporated, to give an oil which solidified when dried at reduced pressure (wt., 2·9 g.). The product was chromatographed on alumina (100 g.) prepared in pentane and eluted with pentane, to furnish material, m. p. 89—101°, which from its behaviour on crystallisation was heterogeneous. The column was therefore washed with much ether and the eluates combined and evaporated. The residue was hydrolysed by boiling 3·3% methanolic potassium hydroxide for 1·5 hours; the product was worked up in the usual way to give a solid which was chromatographed on alumina (150 g.) prepared in pentane. Elution with pentane (10 × 200 c.c.) yielded an oil (156 mg.) which crystallised from acetone, to give a hydrocarbon as plates, m. p. 64—65°; this gave a yellow colour with tetranitromethane in chloroform and is being investigated. Elution with benzene–pentane, with benzene, and with ether failed to give any significant amount of material, but use of chloroform–ether gave cholesterol (2·50 g.) which separated from acetone in needles, m. p. 146—148° undepressed by admixture with a genuine specimen.

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