Synthetic Steroids. Part IV.[1] The Reaction of 3β-Hydroxy-5α-cholest-1-ene and 3β-Hydroxycholest-4-ene with Toluene-*p*-sulphonyl Chloride in Pyridine

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The reaction of 3β-hydroxy-5α-cholest-1-ene with toluene-*p*-sulphonyl chloride in pyridine does not yield the expected Δ^1-3β-toluene-*p*-sulphonyl ester but results directly in the production of *N*-(5α-cholest-1-en-3α-yl)-pyridinium tosylate (44%) and 1α,5-cyclo-5α-cholest-2-ene (22%). Similar rearrangements of the allylic alcohols androst-1-en-3β-ol and 17β-methoxyandrost-1-en-3β-ol are also reported.

An attempted preparation of cholest-4-ene 3β-toluene-*p*-sulphonyl ester yielded directly a mixture of cholesta-3,5-diene (24%), 3α,5-cyclo-5α-cholest-6-ene (3%), *N*-(cholest-4-en-3α-yl)pyridinium tosylate (28%), the balance of the reaction product being cholest-4-en-3β-ol.

The Δ^1-3β-alcohol and the Δ^4-3β-alcohol systems have both been shown to be unstable towards analysis by gas chromatography, each compound decomposing into a mixture of a cyclo-steroid and a diene.

The visible absorption spectra of the complexes formed between various cyclo-steroids and tetranitromethane are reported.

A GENERAL feature of 3β-hydroxy-Δ^5-steroids is that their solvolysis in buffered media yields 3,5-cyclosteroids as the kinetically controlled products of the reaction.[2] This reaction is known as the *i*-steroid transformation and has been interpreted in terms of a transitional intermediate, formulated as a nonclassical homoallylic bridged ion,[3] formed from participation of the 5,6-π-electrons. It was, therefore, of interest to examine the solvolysis products of a system which does not formally possess the configurational requirements for such π-electron participation. Systems suitable for this purpose, *i.e.*, possessing a β-alcohol along with a neighbouring double bond, are the αβ-unsaturated alcohols 3β-hydroxy-5α-cholest-1-ene and 3β-hydroxycholest-4-ene.

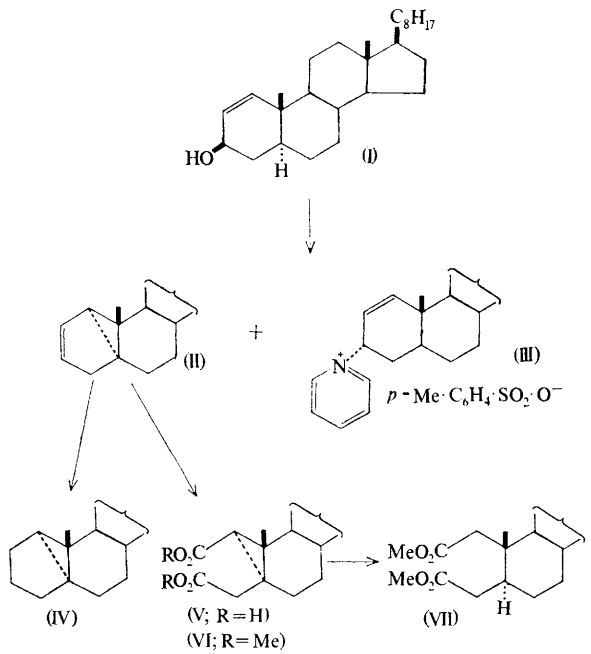
[1] Part III, R. W. Kelly and P. J. Sykes, preceding Paper.

[2] N. L. Wendler in 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1964, p. 1075.

[3] S. Winstein and E. M. Kosover, *J. Amer. Chem. Soc.*, **1959**, **81**, 4399.

Accordingly, 3β-hydroxy-5α-cholest-1-ene (I) was treated with an equimolar quantity of toluene-*p*-sulphonyl chloride in pyridine at 0° for 24 hr. Ice was then added and the steroids were isolated with ether; an infrared spectrum of the reaction product indicated that the expected Δ^1-3β-toluene-*p*-sulphonyl ester had not been obtained. Addition of hexane to the reaction product precipitated a white amorphous solid (27%), m. p. 220—222°, whose nuclear magnetic resonance (n.m.r.) spectrum showed peaks at τ 0·7—3·0 (nine aromatic protons), 4·4 (two olefinic protons), 7·68 (one aromatic methyl group), and 9·09, 9·18, and 9·31 (skeletal methyl groups), consistent with this compound being *N*-(5α-cholest-1-en-3α-yl)pyridinium tosylate (III). The compound (III) gave a satisfactory elemental analysis and could be converted into *N*-(5α-cholest-1-en-3α-yl)pyridinium iodide by treatment with sodium iodide in ethanol. It is designated as a 3α-compound since during quaternisation an asymmetric centre is generally inverted in configuration.[4]

The petrol-soluble fraction from the tosylation reaction was fractionated by alumina chromatography. Elution with petrol gave a hydrocarbon (22%) of molecular weight 368 (mass spectrum) which was homogeneous to gas-chromatographic analysis, and was subsequently



shown to be 1α,5-cyclo-5α-cholest-2-ene (II). Elution with petrol–benzene gave starting material (I) (33%) whilst elution with chloroform–methanol gave a further 17% of the salt (III).

The cyclo-steroid (II) could also be obtained as the sole reaction product in a yield of 51% by the dehydration of the alcohol (I) with phosphorus oxychloride in pyridine at reflux temperature.

Quantitative microhydrogenation [5] of the hydrocarbon (II) using a 10% palladium on charcoal catalyst showed that the compound rapidly took up two moles of hydrogen. The product isolated from the reduction was 5α-cholestane, thereby indicating that no skeletal rearrangements had occurred during the initial tosylation reaction. The ease of conjugate addition of hydrogen stereospecifically to a cyclopropyl olefin has previously been reported.[6] Compound (II) took up one mole of hydrogen over 4 hr. when it was subjected to catalytic hydrogenation using the soluble catalyst tris(triphenylphosphine)rhodium chloride.[7] The reduction product was shown to be 1α,5-cyclo-5α-cholestane (IV) from the position and intensity of the absorption of its tetranitromethane complex (see below) and from its n.m.r. spectrum which had peaks at τ 9·38 (C-18 methyl), 9·27, 9·19, 9·09 (side chain methyls), and 8·78 (C-19 methyl). Using these same hydrogenation conditions 3α,5-cyclo-5α-cholest-6-ene was selectively reduced to 3α,5-cyclo-5α-cholestane.

Oxidation of the cyclo-steroid (II) with potassium permanganate and sodium periodate [8] at pH 8 yielded 1α,5-cyclo-2,3-seco-5α-cholestane-2,3-dioic acid (V), the infrared spectrum of which showed absorptions at 1710 and 2400—3500 cm.$^{-1}$. The diacid (V) was methylated with diazomethane to give 1α,5-cyclo-2,3-seco-5α-cholestane-2,3-dioic dimethyl ester (VI), the infrared spectrum of which showed a peak at 1740 cm.$^{-1}$ and its n.m.r spectrum had peaks at τ 9·35 (C-18 methyl), 9·20, 9·09 (side-chain methyls), 8·74 (C-19 methyl), and 6·33 (two methyl ester groups).

The cyclopropyl diester (VI), however, proved difficult to hydrogenate, which is in agreement with the fact that compounds containing cyclopropylcarboxylic acids show a diminished reactivity of the three-membered ring.[9] Reduction of the compound (VI) was therefore accomplished by shaking it with Adams platinum oxide catalyst at room temperature for 22 hr. with hydrogen at 90 atmospheres pressure. Gas-chromatographic analysis of the reduction product showed it to contain three components whose retention times relative 5α-cholestane were 1·56 (20%), 2·05 (20%), and 2·72 (60%), of which the peak at retention time 2·05 represented unreduced cyclopropyl diester (VI). Column chromatography on alumina (grade I) allowed the isolation of a crystalline diester (VII), whose gas-chromatographic retention time relative 5α-cholestane was 2·72. This diester (VII) was shown to be 2,3-seco-5α-cholestane-2,3-dioic dimethyl ester by comparison of its m. p. and optical rotation with those of an authentic sample. The third component from the reduction of the compound (VI)

[4] E. N. Shaw in 'Heterocyclic Compounds, Pyridine and Derivatives,' ed. E. Klingsberg, Interscience, New York, 1961, p. 5.
[5] N. Clauson-Kaus and F. Limborg, *Acta Chem. Scand.*, 1947, **1**, 884.
[6] E. F. Ullman, *J. Amer. Chem. Soc.*, 1959, **81**, 5386.
[7] C. Djerassi and J. Gutzwiller, *J. Amer. Chem. Soc.*, 1966, **88**, 4537.
[8] J. T. Edward, D. Holder, W. H. Lunn, and I. Puskas, *Canad. J. Chem.*, 1961, **39**, 599.
[9] E. E. Royals, 'Advanced Organic Chemistry,' Constable, London, 1955.

was probably 5,5-bis(methoxycarbonylmethyl)-des-A-cholestane, resulting from reductive fission of the 1,10-bond.

It therefore follows from the results of the reduction and oxidation of the hydrocarbon (II) that this compound is 1α,5-cyclo-5α-cholest-2-ene, a structure which is also supported by the spectral evidence given below.

The infrared spectrum of the cyclopropyl olefin (II) showed only weak absorptions at 1030 (cyclopropyl ring deformation [10]) and 3025, 730 cm.$^{-1}$ (*cis*-olefinic hydrogens). The principal absorption in the ultraviolet spectrum of compound (II) was at 212 mμ (ε 7500), which is in precise agreement with the calculated value for this absorption maximum using the rules developed by Pete [11] for conjugated cyclopropyl olefins. The dihedral angle between the planes of the two chromophores in compound (II) has been taken as 109° (measured from Dreiding models). Other less intense maxima present in the ultraviolet spectrum of this compound occur at 237, 246, and 263 mμ. The cyclopropyl olefin (II) gives a strongly coloured complex with tetranitromethane and we report below a relationship, based upon that of Heilbronner,[12] allowing the presence of either a conjugated or isolated cyclopropane ring to be detected. Finally, the n.m.r. spectrum of the hydrocarbon (II) shows peaks at τ 9·35 (C-18 methyl), 9·25, 9·19, 9·10 (side-chain methyls), 8·75 (C-19 methyl), and 4·36, shoulder at 4·40 (two olefinic protons). From an initial consideration of the structure of this molecule, a multiplet might have been expected for the 2,3-olefinic protons, due to coupling with the C-1 and two C-4 protons. However, the coupling constant between the C-1 cyclopropyl proton and the unsaturated protons will be only approximately 1 c./sec.[13] and, as has been shown for the spectrum of the two olefinic protons in 5α-cholest-2-ene [14] (τ 4·36, shoulder 4·40), a simple spectrum may result from various small coupling constants largely nullifying each other.[15] The assignment of the peak at τ 8·75 to the C-19 methyl group was made initially by analogy with the position of the C-19 methyl signal in the spectrum of lumicholestenone [16] (τ 8·83) and similar steroids obtained from the photolysis of testosterone acetate [17] (τ 8·82) and 10α-testosterone [18] (τ 8·85). A conclusive C-19 methyl assignment was made by carrying out the initial rearrangement reaction on two steroids which do not contain the C-17 side-chain, thereby eliminating the three superimposed doublets [19] (τ 9·05—9·25) due to the side-chain methyls from the n.m.r. spectra of the products.

5α-Androst-1-en-3-one was reduced with lithium aluminium hydride to give 5α-androst-1-en-3β-ol which was treated with toluene-*p*-sulphonyl chloride in pyridine in the manner already described for the analogous cholestenol. The reaction product was chromatographed on alumina, and elution with petrol gave a hydrocarbon fraction which was shown by gas-chromatographic analysis to contain two components. The two compounds had retention times relative to 5α-androstane of 0·89 (60%) and 1·14 (40%). It was not possible to separate these two hydrocarbons by alumina chromatography, but 3 mg. of each component was isolated by preparative gas chromatography. Each component was hydrogenated to 5α-androstane. The more polar material showed an ultraviolet maximum at 262 mμ (ε 5100) and proved to be identical to 5α-androsta-1,3-diene, synthesised independently by the hydrolysis of 5α-androst-1-en-3β-ol benzoate, according to the method of Tamm and Albrecht.[20] The less polar material had an ultraviolet maximum at 212 mμ (ε 7100) and its n.m.r. spectrum, obtained by using a computer to average transients, showed peaks at τ 9·30 (C-18 methyl) and 8·74 (C-19 methyl). (This spectrum was not sufficiently intense to permit observation of the olefinic protons.)

Lastly, 17β-methoxy-5α-androst-1-en-3β-ol was prepared and submitted to the same rearrangement reaction. 17β-Hydroxy-5α-androstan-3-one was converted by treatment with methyl iodide and silver oxide [21] into 17β-methoxy-5α-androstan-3-one; bromination [22] gave the 2α-bromo-steroid which was not isolated but was converted directly into 17β-methoxy-5α-androst-1-en-3-one by dehydrobromination with lithium carbonate and dimethylformamide.[23] This αβ-unsaturated ketone showed n.m.r. peaks at τ 9·20 (C-18 methyl), 8·98 (C-19 methyl), 6·65 (17β-methoxy), 4·14 (doublet *J* 10 c./sec.) (C-2 proton), and 2·83 (doublet, *J* 10 c./sec.) (C-1 proton). Lithium aluminium hydride reduction of this ketone led to 17β-methoxy-5α-androst-1-en-3β-ol which was treated with toluene-*p*-sulphonyl chloride in pyridine at 0°. Isolation of the steroids present after the reaction gave a glass which was chromatographed on alumina. Elution with petrol gave a hydrocarbon fraction which was shown by gas-chromatographic analysis to contain two components. Careful re-chromatography on alumina, eluting again with petrol, allowed these two fractions to be separated to give 17β-methoxy-1α,5-cyclo-5α-androst-2-ene (80%) which had an ultraviolet absorption maximum at 212 mμ and an n.m.r. spectrum with peaks at τ 9·25 (C-18

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[23] G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 1961, 2532.

methyl), 8·75 (C-19 methyl), 6·70 (methoxy), and 4·36, shoulder at 4·39 (C-2 and C-3 olefinic protons). This cyclo-steroid was readily reduced by two moles of hydrogen to give 17β-methoxy-5α-androstane. The second component of the hydrocarbon fraction was shown to be 17β-methoxy-5α-androsta-1,3-diene (20%) from its ultraviolet absorption maximum at 264 mμ and its n.m.r. peaks at τ 9·26 (C-18 methyl), 9·22 (C-19 methyl), 6·70 (methoxy), 4·27 multiplet (four olefinic protons).

From the n.m.r. spectra of the two reaction products obtained from the rearrangements with androstane derivatives, the cyclopropyl C-19 methyl signal can be assigned unequivocally to the region of the spectrum τ 8·74—8·75. The signal at τ 8·75 in the spectrum of the compound (II) is therefore assigned to the C-19 methyl group.

In view of the non-formation of a toluene-*p*-sulphonyl ester from the steroid (I), it was not surprising that the toluene-*p*-sulphonyl ester of cholest-4-en-3β-ol did not form either. Chromatography on alumina of the tosylation reaction product gave three fractions, a hydrocarbon (27%, eluted with petrol), unchanged cholest-4-en-3β-ol (44%, eluted with petrol–benzene), and *N*-(cholest-4-en-3α-yl)pyridinium tosylate (28%, eluted with chloroform–methanol). The hydrocarbon fraction was crystallised from acetone and was shown to be cholesta-3,5-diene by comparison with an authentic sample. Examination of the mother-liquors from this crystallisation by gas chromatography showed, however, that the residual material contained a second component, which was isolated by preparative gas chromatography and was shown to be 3α,5-cyclo-5α-cholest-6-ene by comparison with an authentic sample. This cyclo-steroid represents 3% of the original rearrangement products.

The mechanism involved in these rearrangements brought about by the tosylation of the Δ^1-3β-hydroxy- and Δ^4-3β-hydroxy-steroids will be discussed in a later Paper, as will some further reactions of the 1α,5-cyclo-Δ^2-steroid system.

Tetranitromethane Complexes.—Both 9,19-cyclolanostan-3β-ol,[24] and 3α,5-cyclo-5α-cholestane [24,25] have previously been reported to give a pale yellow colour with tetranitromethane, due to the presence of a cyclopropyl group. We have confirmed these observations and shown that a steroid containing an isolated cyclopropyl group gives a tetranitromethane complex with a λ_0 within the range reported [12] for the complex formed with a disubstituted double bond (440—478 mμ) (see Table). (Using the nomenclature of Heilbronner,[12] λ_0 is the wavelength of absorption of the complex extrapolated to a standard extinction coefficient.) We have also found that a cyclopropyl group conjugated to a double bond gives a complex with a λ_0 approximately within the range quoted by Heilbronner for a tetrasubstituted double bond complex (550—580 mμ). Since it is possible to differentiate between an olefin and a cyclopropyl group by their ultraviolet absorption maxima, the tetranitromethane complexes may be used as evidence for the presence of a cyclopropyl group. The method is helpful if n.m.r. spectroscopy is not applicable, *i.e.*, when the cyclopropyl group is heavily substituted or the cyclopropyl proton signals are masked by other absorptions.

Absorptions of tetranitromethane complexes

Steroid	λ_0 at standard extinction coefficient (mμ)
5α-Cholest-1-ene	450
5α-Cholest-2-ene	466
3-Methylenecholestane	452
1α,5-Cyclo-5α-cholestane	448
3α,5-Cyclo-5α-cholestane	440
2,3-Dimethyl-5α-cholest-2-ene	572
1α,5-Cyclo-5α-cholest-2-ene	564
17β-Methoxy-1α,5-cyclo-5α-androst-2-ene	566
3α,5-Cyclo-5α-cholest-6-ene	588

Gas Chromatography of αβ-Unsaturated Steroid Alcohols.—It has been shown that whereas the steroid Δ^5-3β-alcohols are stable to gas chromatography, their toluene-*p*-sulphonyl esters decompose quantitatively during chromatography.[26] Thus cholesteryl tosylate gives 3α,5-cyclo-5α-cholest-6-ene, cholesta-3,5-diene, and a third component, probably cholesta-2,4-diene. This is a decomposition reaction similar in nature to the *i*-steroid rearrangement. Gas chromatography of the Δ^4-3β-alcohols, however, has shown that this system is itself thermally unstable [27,28] and that androst-4-en-3β-ol gives two compounds, one identified as a 3,5-diene and the other presumed to be a 2,4-diene.[27]

We have found that gas chromatography of cholest-4-en-3β-ol leads to its quantitative decomposition and gives two peaks of retention times relative to 5α-cholestane of 0·79 and 1·11. Both compounds were isolated by preparative gas chromatography and were identified from their ultraviolet spectra, and comparison with authentic samples, as 3α,5-cyclo-5α-cholest-6-ene and cholesta-3,5-diene, respectively. In this instance there was no formation of the homoannular 2,4-diene. Likewise, gas chromatography of 5α-cholest-1-ene-3β-ol produces two compounds by the elimination of the alcohol group. These compounds have retention times relative to 5α-cholestane of 0·83 and 1·25 and have been identified as 1α,5-cyclo-5α-cholest-2-ene (II) and cholesta-1,3-diene, respectively, by comparison with authentic samples.

The elimination of the alcohol group is not caused solely by the high temperature of 260° at the injector block, but is a surface reaction. Heating cholest-4-en-3β-ol to 260° sublimes the allylic alcohol unchanged, but if the sublimation is carried out from brick dust

[24] D. H. R. Barton, *J. Chem. Soc.*, 1951, 1444.
[25] C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 1952, 3361.
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then the same mixture of compounds is produced as is obtained by gas chromatography. The decomposition is temperature dependent and is also dependent on the amount of liquid phase on the column;[27] as the percentage of stationary phase on the support is decreased, the decomposition increases.

EXPERIMENTAL

For general experimental details see Part I.[28]

Gas-chromatographic separations were carried out using a Perkin-Elmer model 801 instrument. The glass injection area was heated to 260° and the flame ionisation detector to 230° whilst using a column temperature of 220°. An inlet pressure of 30 lb./in.^{2} achieved a flow rate of 25 ml./min. of nitrogen through glass columns 1·5 mm. internal diameter and 2 m. long. The columns were packed with 2½% E 301 on A.W.D.M.C.S. Chromosorb G. Steel columns $\frac{3}{16}$ in. diameter and 6 ft. long were used for some of the preparative chromatography, the steroids were collected by condensation within a glass tube outside the column oven, after passing through an effluent gas splitter.

Reaction of 5α-*Cholest*-1-*en*-3β-*ol with Toluene*-p-*sulphonyl Chloride in Pyridine*.—5α-Cholest-1-en-3β-ol[29] (I) (2·0 g.) was dissolved in pyridine (30 ml.) and cooled to 0°. To this was added a solution of toluene-*p*-sulphonyl chloride (2 g.) in pyridine (30 ml.) also at 0°. The mixture was allowed to warm to room temperature and was left for 39 hr. Ice was then added and the steroids were extracted with dichloromethane. The solution was washed with aqueous sodium carbonate, water, dilute hydrochloric acid, and water again until the washings were neutral. The solution was dried ($MgSO_4$) and evaporated to give a pale brown gum (2·9 g.). Addition of hexane gave a white amorphous solid which was filtered off and recrystallised from benzene to give white plates of N-(5α-*cholest*-1-*en*-3α-*yl*)*pyridinium tosylate* (III) (0·62 g.), m. p. 220—222°, $[\alpha]_D$ +35° (*c* 0·1) (Found: C, 75·1; H, 9·1; N, 2·4; S, 5·0. $C_{39}H_{57}O_3NS$ requires C, 75·5; H, 9·2; N, 2·3; S, 5·1%).

The hexane-soluble fraction was chromatographed on alumina; elution with petrol afforded a clear glass (0·45 g.) which was crystallised with difficulty from acetone. Elution with petrol–benzene (98 : 2) gave 5α-cholest-1-en-3β-ol (0·62 g.), m. p. 129—131°, whilst further elution with chloroform–methanol (95 : 5) gave the compound (III) (0·23 g.), m. p. 220—222° (from benzene), undepressed on admixture with the material isolated before chromatography. The fraction which was eluted with petrol was rechromatographed on neutral alumina (activity I) from which it was again eluted with petrol, to give 1α,5-*cyclo*-5α-*cholest*-2-*ene* (II) (needles from acetone, 0·424 g.), m. p. 71—72°, $[\alpha]_D$ +40° (*c* 0·07) (Found: C, 88·0; H, 11·8. $C_{27}H_{44}$ requires C, 88·0; H, 12·0%). The compound has an ultraviolet spectrum with maxima at 212 mμ (ε 7500), 237 (ε 3500), 246 (ε 2900), and 263 (ε 2200).

This experiment was repeated several times and was found to be reproducible.

Reaction of N-(5α-*Cholest*-1-*en*-3α-*yl*)*pyridinium Tosylate with Sodium Iodide*.—The compound (III) (0·5 g.) was dissolved in hot ethanol (1 ml.) and this solution was added to sodium iodide (0·5 g.) in hot ethanol (5 ml.). On cooling, a pale yellow precipitate formed which was filtered off. Recrystallisation from ethanol gave N-(5α-*cholest*-1-*en*-3α-*yl*)*pyridinium iodide* (0·43 g.), m. p. 283—285°, $[\alpha]_D$ +57° (*c* 0·11) (Found: C, 66·5; H, 8·7; N, 2·3; I, 21·9. $C_{32}H_{50}IN$ requires C, 66·7; H, 8·8; N, 2·4; I, 22·0%).

Reaction of 5α-*Cholest*-1-*en*-3β-*ol* (I) *with Phosphorus Oxychloride*.—Phosphorus oxychloride (1 ml.) was added to a solution of 5α-cholest-1-en-3β-ol (0·5 g.) in pyridine (10 ml.) and the solution was heated under reflux for 30 min. during which time it turned pale brown. Ether and water were added and the mixture was washed with dilute hydrochloric acid and then water until the washings were neutral. The ether extract was dried ($MgSO_4$) and was evaporated to give an oil which was chromatographed on neutral alumina (activity I). Elution with petrol afforded a clear glass (0·27 g.) which was crystallised from acetone to give 1α,5-cyclo-5α-cholest-2-ene (0·254 g., 51%), m. p. 70—72°, identical to the sample prepared previously.

Hydrogenation of 1α,5-*Cyclo*-5α-*cholest*-2-*ene* (II).—Microhydrogenation of the hydrocarbon (II) was carried out using the apparatus designed by Clauson-Kaus and Limborg.[5] The hydrocarbon (0·01324 g.) was reduced using ethanol as solvent and 10% palladium on charcoal as catalyst, the hydrogen uptake was 1·571 ml. and hence the compound (II) contains 1·93 double-bond equivalents. A repeat determination indicated that 1·96 double-bond equivalents were present in the compound.

The products from both hydrogenations, after removal of the catalyst, were combined and the product was crystallised from acetone to give 5α-cholestane (0·027 g.), m. p. 80—82° (lit.,[30] m. p. 80°).

1α,5-*Cyclo*-5α-*cholestane* (IV).— 1α,5-Cyclo-5α-cholest-2-ene (II) (50 mg.) was dissolved in benzene (5 ml.) and tris-(triphenylphosphine)rhodium chloride[31] (30 mg.) was added. The mixture was hydrogenated at room temperature and atmospheric pressure for 4 hr. The catalyst quickly dissolved as the solution became saturated with hydrogen. The solution was chromatographed on alumina and elution with benzene gave a clear glass, which was crystallised from acetone to give 1α,5-*cyclo*-5α-*cholestane* (40 mg., 80%), m. p. 73·5—75°, $[\alpha]_D$ +21° (*c* 0·08) (Found: C, 87·3; H, 12·4. $C_{27}H_{46}$ requires C, 87·5; H, 12·5%).

Reduction of 3α,5-*Cyclo*-5α-*cholest*-6-*ene*.—3α,5-Cyclo-5α-cholest-6-ene[32] (50 mg.) was dissolved in benzene (5 ml.) and tris(triphenylphosphine)rhodium chloride (30 mg.) was added. The mixture was hydrogenated at room temperature and atmospheric pressure for 4 hr. The solution was chromatographed on alumina and elution with benzene gave a clear glass, which was crystallised from acetone to give 3α,5-cyclo-5α-cholestane (45 mg.), m. p. 77·5—79° (lit.,[33] m. p. 79°), $[\alpha]_D$ +79° (*c* 0·086) (lit.,[33] $[\alpha]_D$ +80°).

Periodate–Permanganate Oxidation of 1α,5-*Cyclo*-5α-*cholest*-2-*ene* (II).—1α,5-Cyclo-5α-cholest-2-ene (II) (200 mg.) was dissolved in t-butyl alcohol (15 m.) and to this was added potassium carbonate (200 mg.) in water (1·6 ml.), solid sodium periodate (3·2 g.), and potassium permanganate (15 mg.). The mixture was stirred vigorously and it developed a brick red colour. After 3 hr. more potassium permanganate (80 mg.) was added and the stirring was continued for 18 hr. The solution was then acidified with dilute hydrochloric acid and sodium bisulphite was added

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until the solution became almost colourless. The steroid was extracted with ether and the ether solution was washed with acid and then water until it was neutral, it was then dried ($MgSO_4$) and evaporated to dryness. Crystallisation of the residue from petrol gave 1α,5-*cyclo*-2,3-*seco*-5α-*cholestane*-2,3-*dioic acid* (60 mg.), m. p. 172—177°, $[\alpha]_D$ +8° (*c* 0·1), $\nu_{max.}$ 1710 and 2400—3500 cm.$^{-1}$ (Found: C, 74·9; H, 10·6. $C_{27}H_{44}O_4$ requires C, 74·9; H, 10·3%).

The diacid (V) (60 mg.) was methylated with redistilled diazomethane–ether solution prepared from *N*-nitrosomethylurea (100 mg.). After a reaction time of 3 hr. at room temperature, the solvent and excess of reagent were removed by distillation at reduced pressure. Crystallisation from acetone–petrol gave 1α,5-cyclo-2,3-seco-5α-cholestane-2,3-dioic dimethyl ester (VI) (40 mg.), m. p. 73—75°, $[\alpha]_D$ +46° (*c* 0·11), $\nu_{max.}$ 1740 cm.$^{-1}$.

The diester (VI) (100 mg.) was dissolved in ethanol (20 ml.) and Adams catalyst (0·5 g.) was added. The solution was hydrogenated at 90 atmospheres pressure for 22 hr. at room temperature and then was filtered free of catalyst and the solvent removed under reduced pressure. The product was filtered through alumina in petrol–benzene to give material which was shown by gas-chromatographic analysis to contain three components with retention times, relative to 5α-cholestane, of 1·56 (20%), 2·05 (20%), and 2·72 (60%). The final component has the same relative retention time as 2,3-seco-5α-cholestane-2,3-dioic dimethyl ester. Rechromatography of the total reduction product on alumina (activity I), afforded a crystalline diester, which was recrystallised from acetone–petrol to give 2,3-seco-5α-cholestane-2,3-dioic dimethyl ester (30 mg.), m. p. and mixed m. p. 59—60° (lit.,[34] m. p. 60°), $[\alpha]_D$ +22° (*c* 0·13) (lit.,[34] $[\alpha]_D$ +23°).

5α-*Androst*-1-*en*-3β-*ol*.—5α-Androst-1-en-3-one [35] (0·35 g.) in dry ether (10 ml.) was added to a solution of lithium aluminium hydride (0·3 g.) in dry ether (30 ml.) and the solution was heated under reflux for 1 hr. After decomposition of the excess of reagent with ethyl acetate, dilute hydrochloric acid was added. The solution of steroid in ether was washed with water and dried ($MgSO_4$) and evaporated to dryness to give a white solid which was crystallised from acetone to give 5α-*androst*-1-*en*-3β-*ol* (2·6 g.), m. p. 102·5—104·5°, $[\alpha]_D$ +36° (*c* 0·17). $\nu_{max.}$ 3500, 1070, 1030, and 755 cm.$^{-1}$, ^{1}H n.m.r. peaks at τ 9·29 (C-18 methyl group), 9·09 (C-19 methyl group), 4·60, 4·42, 4·14, and 3·98 (two olefinic protons) (Found: C, 83·6; H, 11·3. $C_{19}H_{30}O$ requires C, 83·2; H, 11·0%).

Reaction of 5α-*Androst*-1-*en*-3β-*ol with Toluene*-p-*sulphonyl Chloride and Pyridine*.—5α-Androst-1-en-3β-ol (0·3 g.) was dissolved in pyridine and cooled to 0°. This was added to a solution of toluene-*p*-sulphonyl chloride (0·3 g.) in pyridine (5 ml.) and the combined solutions were allowed to stand at room temperature for 16 hr. The solution was then poured into water and the steroids were extracted into dichloromethane, and this solution was washed with aqueous sodium carbonate, water, dilute hydrochloric acid, and water again until it was neutral. After drying ($MgSO_4$), the solvent was evaporated to give a pale brown gum which was dissolved in petrol and chromatographed on alumina. Elution with petrol gave a clear glass (0·1 g.) which would not crystallise. Analytical gas chromatography showed this material to be a mixture of two components with retention times relative to 5α-androstane of 0·89 (60%) and 1·14 (40%). It was not possible to separate these two compounds by alumina chromatography.

Part of this hydrocarbon mixture (10 mg.) was dissolved in acetic acid and was hydrogenated over a 10% palladium on charcoal catalyst for 3 hr. The catalyst was then filtered off, water was added, and the steroid was extracted into ether. The solution was washed with water, dried ($MgSO_4$), and evaporated to dryness. Examination of the product by gas chromatography showed that it only contained one component, which had an identical retention time to that of 5α-androstane.

Preparative gas chromatography of the remaining hydrocarbon mixture enabled 3 mg. of each of the two hydrocarbons to be obtained pure. The less-polar material was identified as 1α,5-cyclo-5α-androst-2-ene from its ultraviolet maximum at 212 mμ (ε 7100) and its ^{1}H n.m.r. peak at τ 9·30 (C-18 methyl) and 8·74 (C-19 methyl). The more-polar component had an ultraviolet maximum at 262 mμ (ε 5100) and two peaks in its ^{1}H n.m.r. spectrum at τ 9·38 (C-18 methyl) and 9·03 (C-19 methyl), identified as 5α-androsta-1,3-diene by comparison with an authentic sample.

Elution with methanol–chloroform (5 : 95) of the alumina chromatogram of the reaction product from the tosylation experiment gave a brown gum (0·25 g.) which gave crystals from benzene, but these melted over a wide range. The material appeared from its n.m.r. spectrum to be a pyridinium tosylate, but was not further investigated.

5α-*Androsta*-1,3-*diene*.—A sample of 5α-androsta-1,3-diene was prepared from 5α-androst-1-en-3β-ol benzoate by reaction with alumina according to the method of Tamm and Albrecht.[20] The sample of 5α-androsta-1,3-diene could not be crystallised but was shown to be homogeneous by gas-chromatographic analysis. It had a maximum in its ultraviolet spectrum at 262 mμ (ε 5100) and its ^{1}H n.m.r. spectrum had peaks at τ 9·38 (C-18 methyl), 9·03 (C-19 methyl) and 4·31 multiplet (4 olefinic protons).

17β-*Methoxy*-5α-*androstan*-3-*one*.—17β-Hydroxy-5α-androstan-3-one [36] (6·6 g.), silver oxide (12 g.), and methyl iodide (50 ml.) were stirred vigorously and the mixture heated under reflux for 18 hr. After cooling, the solution was filtered and evaporated to dryness. Crystallisation of the residue from petrol gave 17β-*methoxy*-5α-*androstan*-3-*one* (6·4 g.), m. p. 125—126°, $[\alpha]_D$ +14° (*c* 0·14), $\nu_{max.}$ 1720 and 1130 cm.$^{-1}$, ^{1}H n.m.r. τ 9·25 (C-18 methyl group), 8·99 (C-19 methyl group), and 6·66 (methyl ether group) (Found: C, 78·6; H, 10·6. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%).

17β-*Methoxy*-5α-*androst*-1-*en*-3-*one*.—17β-Methoxy-5α-androstan-3-one (4·2 g.) was dissolved in dimethylformamide (100 ml.) and treated over 15 min. with a solution of bromine (1·1 g.) and hydrobromic acid (0·4 ml.) in dimethylformamide (25 ml.), and the solution was stirred for 3 hr. Lithium carbonate (5 g.) was then added and the solution was heated under reflux for 1 hr. After cooling, solid material was filtered off, water was added, and the steroid was extracted into ether. The ethereal solution was washed with dilute hydrochloric acid and with water, then it was dried ($MgSO_4$) and evaporated to dryness. An infrared spectrum indicated that the product was a mixture of

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saturated and unsaturated ketones, which were separated by chromatography on alumina. Elution with petrol–benzene (1 : 1) gave starting material (2·2 g.) and several fractions which contained both ketones. Further elution with the same solvent gave 17β-*methoxy*-5α-*androst*-1-*en*-3-*one* (1·38 g.), m. p. 117—118° (from acetone), $[\alpha]_D$ +21° (*c* 0·17), $\nu_{max.}$ 1680, 1120, and 785 cm.$^{-1}$ (Found: C, 79·2; H, 10·1. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%).

17β-*Methoxy*-5α-*androst*-1-*en*-3β-*ol*.— 17β-Methoxy-5α-androst-1-en-3-one (0·9 g.) dissolved in dry ether (10 ml.) was added to lithium aluminium hydride (0·8 g.) in dry ether (30 ml.) and the solution was heated under reflux for 1 hr. The excess of reagent was decomposed with ethyl acetate, dilute hydrochloric acid was added, and the ether layer separated. This was washed with water, dried ($MgSO_4$), and evaporated to dryness. Crystallisation of the residue from methanol gave 17β-*methoxy*-5α-*androst*-1-*en*-3β-*ol* (0·84 g.), m. p. 164·5—166°, $[\alpha]_D$ +9° (*c* 0·16), $\nu_{max.}$ 3600, 3400, 1105, 1025, and 750 cm.$^{-1}$; ^{1}H n.m.r. τ 9·25 (C-18 methyl), 9·10 (C-19 methyl), 6·70 (methyl ether), 4·64, 4·45, 4·18, and 4·01 (two olefinic protons) (Found: C, 78·9; H, 10·6. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%).

Reaction of 17β-*Methoxy*-5α-*androst*-1-*en*-3β-*ol with Toluene*-p-*sulphonyl Choride in Pyridine*.—17β-Methoxy-5α-androst-1-en-3β-ol (0·4 g.), in pyridine, was added to a solution of toluene-*p*-sulphonyl chloride (0·4 g.) in pyridine at 0°. After standing for 18 hr. at room temperature, the mixture was poured into ice and water and the steroids were extracted with dichloromethane. This solution was washed with aqueous sodium carbonate, water, dilute hydrochloric acid, and water again until it was neutral. The solution was dried ($MgSO_4$) and evaporated to dryness to give a brown solid which was chromatographed on alumina. Elution with petrol gave a clear glass (0·32 g.) $\nu_{max.}$ 1120 cm.$^{-1}$, which by gas chromatography was shown to contain two components. Further elution of the alumina column gave very small amounts of polar material, which was not identified.

Re-chromatography of the glass on alumina (activity I) was carried out, and elution with petrol gave two hydrocarbons. The first (0·25 g.) could not be crystallised, but gave a yellow complex with tetranitromethane, from which it could be deduced that it was the alkenylcyclopropane, 17β-methoxy-1α,5-cyclo-5α-androst-2-ene. This was supported by an ultraviolet maximum at 212 mμ (ε 7000) and ^{1}H n.m.r. peaks at τ 9·25 (C-18 methyl), 8·75 (C-19 methyl), 6·70 (methoxy), and 4·36, shoulder 4·39 (2 olefinic protons). The second hydrocarbon to be eluted was 17β-methoxy-5α-androsta-1,3-diene, $\lambda_{max.}$ 264 mμ and was also noncrystalline. It showed ^{1}H n.m.r. peaks at τ 9·26 (C-18 methyl), 9·22 (C-19 methyl), and 4·27, multiplet (4 olefinic protons).

Catalytic Reduction of 17β-*Methoxy*-1α,5-*cyclo*-5α-*androst*-2-*ene*.—17β-Methoxy-1α,5-cyclo-5α-androst-2-ene (40 mg.) was dissolved in ethanol and hydrogenated over 10% palladium on charcoal catalyst. After 4 hr. the catalyst was filtered off and the solvent was evaporated. The ^{1}H n.m.r. spectrum of the resulting 17β-methoxy-5α-androstane was identical to that from an authentic sample.

17β-*Methoxy*-5α-*androstane*.—17β-Methoxy-5α-androstan-3-one (0·5 g.) in Digol (100 ml.) was treated with potassium hydroxide (1 g.) and hydrazine hydrate (4 ml.) and the mixture was heated under reflux for 30 min. at 100°. The temperature was raised to 220° and heating was continued for 2 hr. The solution was cooled, water was added, and the steroid was extracted into ether. The ethereal solution was washed with dilute hydrochloric acid, water, and then dried ($MgSO_4$). Evaporation of the solvent gave a clear glass, which was crystallised from acetone to give 17β-*methoxy*-5α-*androstane* (0·43 g.), m. p. 83·5—85°, $[\alpha]_D$ +20° (*c* 0·17), $\nu_{max.}$ 985 and 1110 cm.$^{-1}$; ^{1}H n.m.r. peaks at τ 9·26 (C-18 methyl), 9·20 (C-19 methyl), and 6·67 (methoxy) (Found: C, 82·5; H, 11·6. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%).

Reaction of Cholest-4-*en*-3β-*ol with Toluene*-p-*sulphonyl Chloride and Pyridine*.—Cholest-4-en-3β-ol [37] (3 g.) in pyridine (10 ml.) was added to a solution of toluene-*p*-sulphonyl chloride (3 g.) in pyridine (10 ml.) at 0°. After standing at room temperature for 24 hr., the solution was poured into water and the steroids extracted with dichloromethane. The solution was washed with aqueous sodium carbonate, water, dilute hydrochloric acid, and finally water until the washings were neutral. The solution was dried ($MgSO_4$) and evaporated to give a gum which was dissolved in light petroleum (60 ml.) and chromatographed on alumina. Elution with petrol gave a glass, which was crystallised from acetone to give cholesta-3,5-diene (0·63 g.), m. p. and mixed m. p. 79—80° (lit.,[38] m. p. 80°), $[\alpha]_D$ +122° (*c* 0·18) (lit.,[38] $[\alpha]_D$ +123°). This material was homogeneous to gas chromatography, with a retention time relative to 5α-cholestane of 1·11; examination of the mother-liquors from the crystallisation, however, showed that two components were present, the 3,5-diene and a component with retention time 0·79 (12% of the hydrocarbon mixture), which was shown to be 3α,5-cyclo-5α-cholest-6-ene. A pure sample of this minor product was obtained by preparative gas chromatography, and its infrared spectrum, obtained using a beam condenser, was identical to the spectrum of an authentic sample.

Elution with petrol–benzene afforded unchanged cholest-4-en-3β-ol and no further material was eluted until a solid was eluted with chloroform–methanol (95 : 5). This was crystallised from benzene to give N-(*cholest*-4-*en*-3α-*yl*)-*pyridinium tosylate* (0·6 g.), m. p. 170—172°, $[\alpha]_D$ +32° (*c* 0·1) (Found: C, 75·3; H, 9·25; N, 2·5; S, 5·0. $C_{39}H_{57}O_3NS$ requires C, 75·6; H, 9·3; N, 2·3; S, 5·2%).

Tetranitromethane Complexes.—The olefinic or cyclopropyl steroid under examination (one thirtieth of the molecular weight in milligrams) was weighed accurately into a 1 cm. ultraviolet spectrometer cell, with a ground-glass stopper. A standard solution (0·95M) of tetranitromethane (3·00 ml.) was added to the cell, and as soon as the compound had dissolved, the visible spectrum was recorded at room temperature. From the optical density, the log $E^*(\lambda)$ was calculated.[12] The yellow solutions decolourise on standing, the more intense quite quickly, and the less intense over about 24 hr.

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