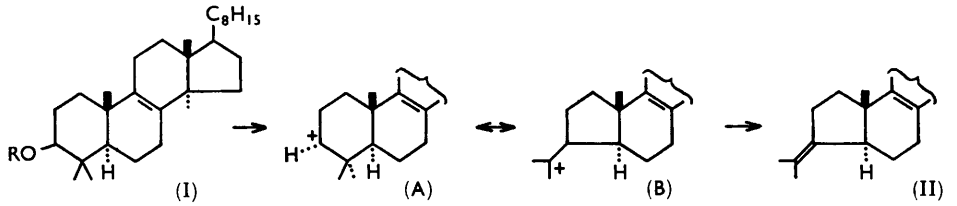
645. *Some Reactions of 4,4,14α-Trimethyl-5α-cholesta-8,24-dien-3α-yl and -3β-yl Toluene-p-sulphonates.*

By G. Bancroft, Y. M. Y. Haddad, and G. H. R. Summers.

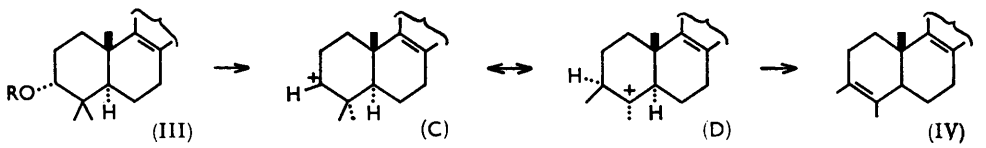
Acetolysis of 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-yl toluene-*p*-sulphonate yields 3,4,14α-trimethyl-5α-cholesta-3,8,24-triene and 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-yl acetate. A kinetic study of the acetolyses of both these esters shows that their rearrangements involve a unimolecular mechanism.

The behaviour of both toluenesulphonates to basic aluminium oxide and lithium aluminium hydride is described.

In a previous paper [1] we described the acetolyses of the toluene-*p*-sulphonates of 4,4-dimethylcholest-5-en-3β-ol and 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3β-ol (lanosterol) (I; R = *p*-$C_6H_4Me{\cdot}SO_2$). That and subsequent work [2] showed these reactions to involve Wagner rearrangement with cleavage of the 4,5-bond and contraction of ring A to produce principally isopropylidene-A-nor-derivatives * (II). The rearrangement products arise



because 3-substituted 4,4-dimethyl-steroids and terpenes contain an α-substituted neopentyl system which is especially prone to rearrangement.[3] The only other products of acetolysis were the 3β-acetates (I; R = Ac) formed with retention of configuration. The overall reaction pattern was explained by assuming an ionic mechanism proceeding through cations (A, B) either as separate classical entities, or through a non-classical bridged carbonium ion in which the charge is distributed over $C_{(3)}$ and $C_{(4)}$.



By analogy, solvolytic reactions of toluene-*p*-sulphonyl derivatives of 3α-hydroxy-4,4-dimethyl-steroids (III; R = *p*-$C_6H_4Me{\cdot}SO_2$) would also be expected to lead to rearrangement, this time without ring contraction, but with formation of 3,4-dimethyl-steroids (IV) by migration of the 4β-methyl group. This reaction similarly would probably occur through classical cations (C, D) or a non-classical ion.

A decision between the two possibilities in both the 3α- and the 3β-series would depend on whether the rates of solvolysis were normal or accelerated (anchimeric assistance or synartesis). We now show from a kinetic study of the acetolyses of 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3β-yl and -3α-yl toluene-*p*-sulphonate that these 1,2-shifts proceed initially by the classical route. We also describe some further reactions of these compounds which involve rearrangement.

Oxidation of commercial 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3β-ol (I; R = H)

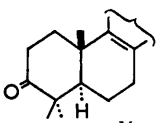
* These are sometimes accompanied by endocyclic isomers.[2]

[1] Haddad and Summers, *J.*, 1959, 769.

[2] Moriarty and Wallis, *J. Org. Chem.*, 1959, **24**, 1274, 1987; Beillmann and Ourisson, *Bull. Soc. chim. France*, 1960, 348.

[3] Ingold, *J.*, 1953, 2845.

with chromium trioxide in acetone or in pyridine gave 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3-one (V), which had been previously prepared [4] in an impure form by oxidation of lanosterol with chromium trioxide in acetic acid followed by dehydrogenation with copper bronze. Oppenauer oxidation of the alcohol (I; R = H) failed to give any of the ketone (V). Lithium aluminium hydride or sodium borohydride reduced 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3-one (V) to 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-ol (III; R = H) (5% and 7%) and the 3β-alcohol (I; R = H) (86% and 92%): the latter alcohol was used in all subsequent reactions. This result agrees with Cavalla's observation [5] that reduction of 4,4,14α-trimethyl-5α-cholest-8-en-3-one gave an almost quantitative yield of the 3β-alcohol, though Huffman [6] obtained a 69% yield of the 3α-alcohol. Huffman's assignment of orientation is, however, based on incorrect conclusions drawn from conformational arguments and dehydration experiments. Reduction of the ketone (V) with aluminium isopropoxide gave 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-ol (35%). The alcohol (III; R = H) was characterised by hydrogenation of its acetate to the known 4,4,14α-trimethyl-5α-cholest-8-en-3α-yl acetate.[7,8] Similar reduction of 4,4-dimethyl-5α-cholestan-3-one [9] gave 4,4-dimethyl-5α-cholestan-3α-ol (42%). Oppenauer oxidation of 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-ol (III; R = H) gave the ketone (V) (33%). This disparity in the oxidation behaviour of the 3α- and the 3β-alcohol agrees with the hydrolysis behaviour of analogous acetates [10] and is in accord with their steric environment.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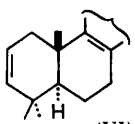
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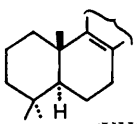
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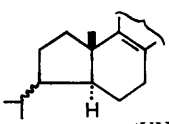
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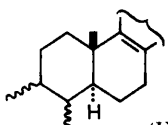

(IX)

Because of the tedious chromatographic separation of the epimeric 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3-ols (I and III; R = H) alternative methods for the preparation of the 3α-alcohol (III; R = H) were examined. It has recently been shown [11] that epimerisation of equatorial steroidal toluene-*p*-sulphonates on aluminium oxide sometimes provides a useful method for obtaining the less accessible axial alcohols. Adsorption of 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3β-yl toluene-*p*-sulphonate (I; R = *p*-$C_6H_4Me{\cdot}SO_2$) on a basic alumina column for three days gave a hydrocarbon mixture, difficultly separable into 4,4,14α-trimethyl-5α-cholesta-2,8,24-triene (VI) and 3-isopropylidene-14α-methyl-A-nor-5α-cholesta-8,24-diene (II). A similar result was obtained on treating the toluenesulphonate (I; R = *p*-$C_6H_4Me{\cdot}SO_2$) with dimethylformamide.[12] A similar result was also obtained with 4,4,14α-trimethyl-5α-cholest-8-en-3β-yl toluene-*p*-sulphonate,[8] and these observations contrast with the behaviour of the esters of the α- and β-amyrins and lupeol.[11] Decomposition of 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-yl toluene-*p*-sulphonate (III; R = *p*-$C_6H_4Me{\cdot}SO_2$) on basic alumina also gave a hydrocarbon mixture of (VI) and the rearranged hydrocarbon, 3,4,14α-trimethyl-5α-cholesta-3,8,24-triene (IV). In neither case was an inverted alcohol obtained (cf. cholesteryl toluene-*p*-sulphonate [11]). The structure of the unsaturated hydrocarbon (VI) was proved by its preparation from 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3β-ol (I; R = H) by pyrolysis of its benzoate and by its hydrogenation to 4,4,14α-trimethyl-5α-cholest-8-ene

[4] Ruzicka, Denss, and Jeger, *Helv. Chim. Acta*, 1945, **28**, 759.
[5] Cavalla, Ph.D. Thesis, London, 1951.
[6] Huffman, *J. Org. Chem.*, 1959, **24**, 447.
[7] Marker and Wittle, *J. Amer. Chem. Soc.*, 1937, **59**, 2289; Allsop, Cole, White, and Willis, *J.*, 1956, 4868.
[8] McGhie, Palmer, Rosenberger, Birchenough, and Cavalla, *Chem. and Ind.*, 1959, 1221.
[9] Beton, Halsall, Jones, and Phillips, *J.*, 1957, 753.
[10] Ruzicka and Gubser, *Helv. Chim. Acta*, 1945, **28**, 1054, 1372.
[11] Chang and Blickenstaff, *Chem. and Ind.*, 1958, 590; Douglas, Ellington, Meakins, and Swindells, *J.*, 1959, 1720.
[12] Chang and Blickenstaff, *J. Amer. Chem. Soc.*, 1958, **80**, 2906.

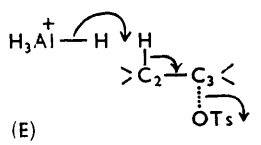
(VII). Attempted preparation from 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3-one (V) by the Bamford–Stevens reaction [13] surprisingly gave a quantitative yield of the 3-isopropylidene-14α-methyl-A-nor-5α-cholesta-8,24-diene (II). The occurrence of Wagner rearrangement has also been encountered in the alkaline decomposition of the toluene-*p*-sulphonylhydrazones of camphor [13] and hecogenin.[14]

Acetolysis of 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3β-yl toluene-*p*-sulphonate (I; R = *p*-$C_6H_4Me{\cdot}SO_2$) with potassium acetate in acetic acid at 95° for 3 hr. has already been shown [1] to yield, after hydrolysis, 3-isopropylidene-14α-methyl-A-nor-5α-cholesta-8,24-diene (II) and the parent alcohol (I; R = H). Similar treatment of 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-yl toluene-*p*-sulphonate (III; R = *p*-$C_6H_4Me{\cdot}SO_2$) gave, after hydrolysis, 3,4,14α-trimethyl-5α-cholesta-3,8,24-triene (IV) (52%) and the parent alcohol (III; R = H) (15%). Again there was no evidence of inversion without rearrangement, and this reaction represents another example contrasting with the accepted behaviour of nucleophilic reaction at position 3 in saturated steroids.[15] Similarly 4,4,14α-trimethyl-5α-cholest-8-en-3α-yl toluene-*p*-sulphonate and 4,4-dimethyl-5α-cholestan-3α-yl toluene-*p*-sulphonate gave, respectively, 3,4,14α-trimethyl-5α-cholesta-3,8-diene and 3,4-dimethyl-5α-cholest-3-ene.

The structures of the rearranged trimethyl hydrocarbons are assigned by analogy, since the product from the cholestane series proved to be identical with the 3,4-dimethylcholest-3-ene synthesised by Beton, Halsall, Jones, and Phillips.[9] The hydrocarbon (IV) was also obtained, mixed with 4,4,14α-trimethyl-5α-cholesta-2,8,24-triene (VI), by dehydration of 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-ol (III; R = H) in hexane with phosphorus pentachloride.

Catalytic hydrogenation of 3-isopropylidene-14α-methyl-A-nor-5α-cholest-8-ene has previously been reported [6] as giving a 14α-methyl-A-norcholestane compound in which the normally inert 8,9-double bond [16,17] has been reduced. Repetition of this reduction with this compound and with 3-isopropylidene-14α-methyl-A-nor-5α-cholesta-8,24-diene (II) showed this finding to be incorrect since these hydrocarbons absorbed one and two mol. of hydrogen, respectively, to give 3ξ-isopropyl-14α-methyl-A-nor-5α-cholest-8-ene (VIII) in which presumably the isopropyl group is β-orientated. 3,4,14α-Trimethyl-5α-cholesta-3,8,24-triene (IV) and -3,8-diene, on catalytic hydrogenation, absorbed two and one mol. of hydrogen, respectively, to give 3ξ,4ξ,14α-trimethyl-5α-cholest-8-ene (IX).

Reduction of 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3β-yl toluene-*p*-sulphonate (I; R = *p*-$C_6H_4Me{\cdot}SO_2$) with lithium aluminium hydride for 30 hr. gave principally the isopropylidene derivative (II), with some parent alcohol (I; R = H). It seems that the mechanism of reduction involved is akin to that of solvolytic reactions of the ester (I; R = *p*-$C_6H_4Me{\cdot}SO_2$) (cf. reduction of toluene-*p*-sulphonic esters of 3β-hydroxy-Δ⁵-steroids [18]). Reduction of the toluene-*p*-sulphonates of the alcohol (III; R = H) and of 4,4,14α-trimethyl-5α-cholest-8-en-3α-ol for 40 hr. surprisingly gave only 4,4,14α-trimethyl-5α-cholesta-2,8,24-triene (VI) and -2,8-diene and some of the parent alcohols but no isolable rearrangement products. The ready formation of the 2,3-double bond appears to be a consequence of the geometry of compound (III), the facility of the elimination involving four coplanar centres in the transition state (E) (cf. Cram [19] and Evans *et al.*[20]).



(E)

[13] Bamford and Stevens, *J.*, 1952, 4735.
[14] Elks, Phillipps, Taylor, and Wyman, *J.*, 1954, 1739; Hirschmann, Snoddy, Hiskey, and Wendler, *J. Amer. Chem. Soc.*, 1954, **76**, 4013.
[15] Shoppee, *J.*, 1946, 1138; Bridgewater and Shoppee, *J.*, 1953, 1709.
[16] Simonsen and Ross, " The Terpenes," Cambridge Univ. Press, 1957, Vol. IV, p. 39.
[17] Lowenthal, *Tetrahedron*, 1959, **6**, 269.
[18] Schmid and Karrer, *Helv. Chim. Acta*, 1949, **32**, 1371; Schmid and Kägi, *ibid.*, 1952, **35**, 214; Karrer and Asmis, *ibid.*, p. 1926; Strating and Backer, *Rec. Trav. chim.*, 1950, **69**, 638.
[19] Cram, *J. Amer. Chem. Soc.*, 1952, **74**, 2149, 2152.
[20] Evans and Shoppee, *J.*, 1953, 540.

To obtain further detail about the proposed mechanisms of rearrangement we next examined kinetically acetolysis of the toluene-*p*-sulphonates (I, III; R = *p*-$C_6H_4Me{\cdot}SO_2$). Results of typical runs are given in Tables 1 and 2. Table 3 summarises the results obtained in the kinetic studies. These measurements indicate both acetolyses to be unimolecular and thus to involve a rate-determining heterolysis. The rate of solvolysis

TABLE 1. *Acetolysis of* 0·0174M-4,4,14α-*trimethyl*-5α-*cholesta*-8,24-*dien*-3β-*yl toluene*-p-*sulphonate in anhydrous acetic acid at* 76·75° ± 0·05°.

Time (min.)	15	28	43	58	73
10^3k (min.$^{-1}$)	6·15	6·17	6·28	6·19	6·26

Initial specific rate constant = 6·21 × 10^{-3} min.$^{-1}$.

TABLE 2. *Acetolysis of* 0·0201M-4,4,14α-*trimethyl*-5α-*cholesta*-8,24-*dien*-3α-*yl toluene*-p-*sulphonate in anhydrous acetic acid at* 76·95° ± 0·05°.

Time (min.)	15	30	45	65	80
10^3k (min.$^{-1}$)	17·26	15·85	14·87	13·57	12·87

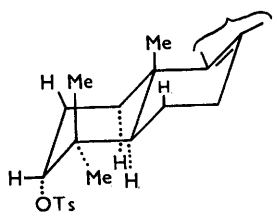
Initial specific rate constant = 17·1 × 10^{-3} min.$^{-1}$.

TABLE 3. *Rates of acetolysis of* 0·01—0·2M-*solutions of* 4,4,14α-*trimethyl*-5α-*cholesta*-8,24-*dien*-3β-*yl and* -3α-*yl toluene*-p-*sulphanate.*

3β-Ester			3α-Ester		
Temp.	* Added acetate (M)	10^3k (min.$^{-1}$) (average)	Temp.	* Added acetate (M)	10^3k (min.$^{-1}$) (average)
76·8	—	6·30	76·9	—	16·9
76·8	0·02	6·30	77·0	0·02	15·7
77·3	0·01	4·95	77·3	0·01	15·4
86·6	—	17·8	67·6	—	5·20
86·5	0·02	16·0	68·3	0·02	5·40
60·1	—	0·92	59·7	—	2·04
60·3	0·02	1·03	59·8	0·02	2·27
			55·5	0·02	1·26

* Diphenylguanidinium acetate.

of the axial 3α-ester is ~3 times greater than that of the equatorial 3β-ester. This difference is similar to that met in the acetolyses of the 5α-cholestanyl toluene-*p*-sulphonates.[21] Thus 5α-cholestan-3α-yl toluene-*p*-sulphonate is solvolysed ~6 times faster than its 3β-isomer at 75°. Attempts have been made to correlate solvolysis rate differences in rigid cyclohexane systems with conformational effects,[21,22,23] and application of these ideas to our problem supports them. The greater reactivity of 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-yl toluene-*p*-sulphonate (III; R = *p*-$C_6H_4Me{\cdot}SO_2$) can be related, first, to two axial (1,3-H) non-bonded interactions on the α-side of ring A, and, secondly, to four axial (1,3-Me–H) and one axial (1,3-Me–Me) interactions on the β-side of the molecule. Any relief of strain on the α-face, by a minor movement of the toluene-*p*-sulphonate group away from the axial 1- and 5-hydrogen atoms would be opposed by a stiffening of ring A by the interactions on the β-face. Reactions of both the toluene-*p*-sulphonates are probably influenced by conformational long range effects, although not identically so. From the work of Barton *et al.*[24] it would be expected that the 8,9-double bond may bring about major effects at position 3, but as yet no quantitative information is available.



The above steric and structural factors very probably account for the relatively

[21] Moritani, Nishida, and Murakami, *J. Amer. Chem. Soc.*, 1959, **81**, 3420.
[22] Nishida, *J. Amer. Chem. Soc.*, 1960, **82**, 4290.
[23] Winstein and Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562.
[24] Barton, McCapra, May, and Thudium, *J.*, 1960, 1297.

slightly faster acetolysis of the toluene-*p*-sulphonate esters (I, III; R = *p*-$C_6H_4Me{\cdot}SO_2$) than of cyclohexyl toluene-*p*-sulphonate ($k = 2{\cdot}56 \times 10^{-3}$ min.$^{-1}$ at 79°) and the 5α-cholestan-3-yl toluene-*p*-sulphonates (3α, $k = 10{\cdot}2 \times 10^{-3}$ min.$^{-1}$; 3β, $k = 1{\cdot}7 \times 10^{-3}$ min.$^{-1}$; at 75·3°). The occurrence of these rearrangements by a " normal rate " process and not by one involving synartesis [3] seemingly excludes the formation of bridged carbonium-ion intermediates. Even so we think that there are legitimate objections to abandoning this mechanistic pathway altogether. It is difficult to account for the absence of inverted 3-acetates, 3,4,14α-trimethylcholesta-8,24-dien-4-yl acetates, and 3,4,14α-trimethylcholesta-4,8,24-triene. Moriarty and Wallis [2] have suggested that in the hydrolysis of 4,4-dimethylcholest-5-en-3β-yl toluene-*p*-sulphonate in aqueous acetone containing potassium acetate the formation of 4,4-dimethylcholesterol may be due to oxygen–sulphur bond fission rather than alkyl–oxygen bond fission. We think that this mechanism is not applicable to the above acetolyses since the products of retention of configuration are acetates. These difficulties can be resolved if it is assumed that the initial classical ions (A and C) rearrange to non-classical bridged ions of greater thermodynamic stability, at a rate which is fast compared with that of the initial heterolysis. The absence of any tertiary acetates * derived from ions (B and D) or bridged ions is probably due, first, to the weak nucleophilic power of the acetate ion and, secondly, to preferential stabilisation of weakly solvated ions by loss of a proton rather than by co-ordination with an acetate ion.

These preliminary kinetic results show some unusual features. In acetolysis of 4,4,14α-trimethylcholesta-8,24-dien-3β-yl toluene-*p*-sulphonate (I; R = *p*-$C_6H_4Me{\cdot}SO_2$) (Table 1) good first-order constants were obtained, showing little downward drift with time, whereas for acetolysis of 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-yl toluene-*p*-sulphonate (III; R = $C_6H_4Me{\cdot}SO_2$) (Table 2) the first-order constants show a marked downward drift. The solvolyses of both compounds were slower after addition of diphenylguanidinium acetate. Also the entropy of activation for the first reaction was negative ($\Delta S = -3{\cdot}1$ cal. mole^{-1} deg.$^{-1}$), whilst in the second reaction it was positive ($\Delta S = +4{\cdot}6$ cal. mole^{-1} deg.$^{-1}$). Inferences to be drawn from these observations will be deferred for a more thorough investigation of salt effects in these reactions and until the kinetics of acetolysis of related systems (*e.g.*, 5α-cholest-8-en-3α-yl and -3β-yl toluene-*p*-sulphonates) have been studied.

Experimental

The aluminium oxide used, unless stated otherwise, was Spence type H. $[\alpha]_D$ are for chloroform solutions.

4,4,14α-*Trimethyl*-5α-*cholesta*-8,24-*dien*-3-*one*.—(*a*) 4,4,14α-Trimethyl-5α-cholesta-8,24-dien-3β-ol (lanosterol) (20 g.) in acetone (350 ml.) was stirred at room temperature and treated with a solution of chromium trioxide in sulphuric acid. The addition was stopped when the solution became light orange. After 0·5 hr. the solution was diluted with water and filtered, and the solid obtained was extracted with ether and worked up in the usual way, to give an oil (16 g.) which solidified. Repeated crystallisation from methanol–ether gave 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3-one, m. p. 107—109°, $[\alpha]_D$ +71° (*c* 1·0). Ruzicka, Denss, and Jeger [4] give m. p. 82—82·5°, $[\alpha]_D$ +81·7°.

(*b*) Lanosterol (14·2 g.) in pyridine (284 ml.) was treated with powdered chromium trioxide (14·2 g.) and left for 16 hr. Isolation of the product in the usual way gave an oil which was chromatographed on aluminium oxide (400 g.). Elution with benzene–pentane (1 : 9) (9 × 150 ml.) gave an oil (6·1 g.) which by crystallisation from ether–methanol gave the above ketone, m. p. 111—114°, $[\alpha]_D$ +72° (*c* 0·9). Elution with ether gave lanosterol.

Attempted Oppenauer oxidation of lanosterol gave only starting material.

Reduction of 4,4,14α-*Trimethyl*-5α-*cholesta*-8,24-*dien*-3-*one*.—(*a*) A solution of 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3-one (2 g.) in ether (200 ml.) was heated with lithium aluminium hydride (700 mg.) for 1·5 hr. The product was chromatographed on aluminium oxide (60 g.).

* 3β-(1-Hydroxy-1-methylethyl)-A-nor-derivatives have been isolated from solvolyses in buffered media and deaminations of 3β-amino-4,4-dimethyl-5α-steroids in aqueous acetic acid. 3β-(1-Hydroxy-1-methylethyl)-A-norcholest-5-ene [2] was in our original paper wrongly considered to be 4,4-dimethyl-3α,5-cyclocholestan-6β-ol.

Elution with benzene (3 × 100 ml.) gave a solid (109 mg.) which after crystallisation from acetone–methanol gave 4,4,14α-*trimethyl*-5α-*cholesta*-8,24-*dien*-3α-*ol*, m. p. 132—134°, $[\alpha]_D$ +43° (*c* 0·7) (Found: C, 84·6; H, 12·0. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). Further elution with benzene (15 × 100 ml.), ether–benzene (1 : 9) (5 × 100 ml.), and ether–benzene (1 : 1) (6 × 100 ml.) gave lanosterol (1·73 g.), m. p. 138—141°.

The lanosterol obtained by this method was used in subsequent chemical and kinetic experiments.

(*b*) The ketone (2 g.) in ethanol (150 ml.) was reduced with sodium borohydride (700 mg.) at room temperature. Chromatography of the product gave 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-ol (101 mg.), lanosterol (1·3 g.), and unchanged starting material (585 mg.).

(*c*) The ketone (30 g.) in propan-2-ol (400 ml.) was treated with aluminium isopropoxide (40 g.). Reduction was complete in 3 hr. The product was chromatographed on aluminium oxide (500 g.). Elution with benzene (8 × 1 l.) gave 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-ol, m. p. 130—131° (10·48 g.). Further elution with benzene gave a mixture (1·45 g.) and then lanosterol (15 g.).

4,4-*Dimethyl*-5α-*cholestan*-3α-*ol and* -3β-*ol*.—4,4-Dimethyl-5α-cholestan-3-one (2 g.) was added to a solution of aluminium isopropoxide (2·5 g.) in propan-2-ol (25 ml.). The mixture was distilled slowly until the distillate was free from acetone, the volume being maintained by addition of propan-2-ol when necessary. The product was chromatographed on aluminium oxide (60 g.). Elution with ether–benzene (1 : 4) (6 × 200 ml.) gave a solid (840 mg.) which by crystallisation from acetone yielded 4,4-dimethyl-5α-cholestan-3α-ol, m. p. 150—151°, $[\alpha]_D$ +5·5° (*c* 1·0) (Found: C, 83·6; H, 12·0. $C_{29}H_{52}O$ requires C, 83·6; H, 12·5%). Elution with ether and chloroform gave 4,4-dimethyl-5α-cholestan-3β-ol (1·1 g.), m. p. 155°, $[\alpha]_D$ +12° (*c* 1·0) (lit.,[25] m. p. 157—158°, $[\alpha]_D$ +11°).

4,14,14α-*Trimethyl*-5α-*cholest*-8-*en*-3α-*yl Acetate*.—Acetylation of 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-ol with pyridine–acetic anhydride gave the *acetate* (needles from acetone), m. p. 158—161°, $[\alpha]_D$ +5·5° (*c* 1·3) (Found: C, 81·8; H, 11·4. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). Hydrogenation of this compound (500 mg.) in acetic acid (50 ml.) in the presence of platinum oxide (110 mg.) gave a solid which on crystallisation from acetone gave 4,4,14α-trimethyl-5α-cholest-8-en-3α-yl acetate, m. p. 169—171°, $[\alpha]_D$ +3·7° (*c* 1·3). Marker and Wittle [7] give m. p. 167·5°.

Treatment of this acetate with lithium aluminium hydride in boiling ether gave 4,4,14α-trimethyl-5α-cholest-8-en-3α-ol, m. p. 136—138° $[\alpha]_D$ +50° (*c* 0·8). Marker and Wittle [7] give m. p. 139°.

4,4,14α-*Trimethyl*-5α-*cholesta*-8,24-*dien*-3α-*yl Toluene*-p-*sulphonate*.—4,4,14α-Trimethyl-5α-cholesta-8,24-dien-3α-ol (5·8 g.) in pyridine (50 ml.) was treated at 0° with toluene-*p*-sulphonyl chloride (5·8 g.) and left at 25° for 40 hr. The solid product, crystallised from ether, had m. p. 143—146°. Recrystallisation from benzene–pentane (1 : 9) gave 4,4,14α-*trimethyl*-5α-*cholesta*-8,24-*dien*-3α-*yl toluene*-p-*sulphonate*, m. p. 144° (decomp.), $[\alpha]_D$ +19° (*c* 1·0) (Found: C, 76·3; H, 9·4. $C_{37}H_{56}O_3S$ requires C, 76·5; H, 9·7%). Another preparation gave a sample of m. p. 126—127° (decomp.), $[\alpha]_D$ +13·7° (*c* 0·9), when crystallised from ethyl acetate.

4,4,14α-*Trimethyl*-5α-*cholest*-8-*en*-3α-*yl Toluene*-p-*sulphonate*.—4,4,14α-Trimethyl-5α-cholest-8-en-3α-ol (2 g.) in pyridine (20 ml.) was treated with toluene-*p*-sulphonyl chloride (2 g.) and left for 3 days. The product, on crystallisation from acetone, gave 4,4,14α-*trimethyl*-5α-*cholest*-8-*en*-3α-*yl toluene*-p-*sulphonate*, m. p. 138—139° (decomp.), $[\alpha]_D$ −4° (*c* 1·1) (Found: C, 76·5; H, 9·7. $C_{37}H_{58}O_3S$ requires C, 76·2; H, 10·0%).

4,4-*Dimethyl*-5α-*cholestan*-3α-*yl Toluene*-p-*sulphonate*.—4,4-Dimethyl-5α-cholestan-3α-ol (1 g.) in pyridine (10 ml.) was treated with toluene-*p*-sulphonyl chloride (1 g.) and left for 4 days. Crystallisation of the product from acetone–methanol gave 4,4-*dimethyl*-5α-*cholestan*-3α-*yl toluene*-p-*sulphonate*, m. p. 156—158° (decomp.), $[\alpha]_D$ −8° (*c* 0·9) (Found: C, 75·8; H, 9·85. $C_{36}H_{58}O_3S$ requires C, 75·1; H, 10·4%).

Acetolysis of 4,4,14α-*Trimethyl*-5α-*cholesta*-8,24-*dien*-3α-*yl Toluene*-p-*sulphonate*.—4,4,14α-Trimethyl-5α-cholesta-8,24-dien-3α-yl toluene-*p*-sulphonate (1 g.) in acetic acid (50 ml.) containing anhydrous potassium acetate (8·5 g.) was heated at 95° for 3 hr. The product, an oil, was hydrolysed by refluxing it with 5% methanolic potassium hydroxide (50 ml.) for 1 hr. The resulting oil was chromatographed on aluminium oxide (40 g.). Elution with pentane (4 × 100 ml.) gave an oily fraction A (558 mg.). Elution with benzene–pentane gave an oil

[25] Mazur and Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 5220.

(33 mg.). Elution with ether–benzene (1 : 9) (6 × 100 ml.) gave 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-ol, m. p. 132—134° (110 mg.); ether and chloroform gave an oil (20 mg.). Fraction A was repeatedly recrystallised from acetone, and successive crops of crystals were obtained with m. p. 100—102°, 106—108° ($[\alpha]_D$ +79°), 109—111° ($[\alpha]_D$ +65·5°). A final recrystallisation gave 3,4,14α-*trimethyl-5α-cholesta*-3,8,24-*triene*, m. p. 110—112°, $[\alpha]_D$ +63·7° (*c* 0·95) (Found: C, 88·0; H, 11·8. $C_{30}H_{48}$ requires C, 88·2; H, 11·8%). The residue from the above crystallisations, on further crystallisation from acetone, gave fractions of m. p. 88—100°, $[\alpha]_D$ +92·5°, and m. p. 75—100°, $[\alpha]_D$ +105·5°. This second hydrocarbon could not be further purified and appears to be a mixture of the above compound with 4,4,14α-trimethyl-5α-cholesta-2,8,24-triene.

Acetolysis of 4,4,14α-*Trimethyl-5α-cholest-8-en-3α-yl Toluene*-p-*sulphonate*.—4,4,14α-Trimethyl-5α-cholest-8-en-3α-yl toluene-*p*-sulphonate (1·1 g.) in acetic acid (100 ml.) containing anhydrous potassium acetate (8 g.) was heated at 95° for 3 hr. The product, after hydrolysis, gave an oil which was chromatographed on aluminium oxide (30 g.). Elution with pentane gave an oil which by crystallisation from ether–ethanol gave 3,4,14α-*trimethyl-5α-cholesta*-3,8-*diene* (580 mg.), m. p. 90—94°, $[\alpha]_D$ +61·7° (*c* 0·8) (Found: C, 87·2; H, 11·9. $C_{30}H_{50}$ requires C, 87·75; H, 12·25%). Elution with chloroform gave 4,4,14α-trimethyl-5α-cholest-8-en-3α-ol (140 mg.), m. p. 135—138°, $[\alpha]_D$ +45° (*c* 1·2).

Acetolysis of 4,4-*Dimethyl-5α-cholestan-3α-yl Toluene*-p-*sulphonate*.—The toluene-*p*-sulphonate (500 mg.) in acetic acid (100 ml.) containing anhydrous potassium acetate was heated at 95° for 3 hr. Working up in the usual way gave an oil which was chromatographed on aluminium oxide (20 g.). Elution with pentane gave an oil which by crystallisation from acetone gave 3,4-dimethyl-5α-cholest-3-ene, m. p. 107—108°, $[\alpha]_D$ +6° (*c* 1·1). Beton *et al.*[9] give m. p. 106·5—108°, $[\alpha]_D$ +5°. Elution with chloroform gave 4,4-dimethyl-5α-cholestan-3α-ol (65 mg.), m. p. 150°.

Dehydration of 4,4,14α-*Trimethyl-5α-cholesta*-8,24-*dien-3α-ol*.—4,4,14α-Trimethyl-5α-cholesta-8,24-dien-3α-ol (1 g.) in light petroleum (b. p. 60—80°; 100 ml.) was shaken with phosphorus pentachloride (1 g.) for 0·5 hr., then added to aluminium oxide in pentane and eluted with pentane. This gave an oil (744 mg.). Repeated crystallisation from acetone gave crops of crystals melting in the range 55—65° to 110—112°. Final recrystallisation of the last fraction from ether gave 3,4,14α-trimethyl-5α-cholesta-3,8,24-triene, $[\alpha]_D$ +55·6° (*c* 0·94), m. p. 114—116° undepressed on admixture with the specimen obtained from the acetolysis. A fraction of m. p. 64—68°, clearing at 90°, had $[\alpha]_D$ +97·5°, indicating that this reaction again gave a mixture of 3,4,14α-trimethyl-5α-cholesta-3,8,24-triene and 4,4,14α-trimethyl-5α-cholesta-2,8,24-triene.

4,4,14α-*Trimethyl-5α-cholesta*-2,8,24-*triene*.—Pyrolysis of lanosteryl benzoate at 320° under reduced pressure gave an oil which was filtered through a column of aluminium oxide. Crystallisation from ethyl acetate–acetone gave rods, m. p. 69—71°, $[\alpha]_D$ +129°, and recrystallisation from acetone gave 4,4,14α-*trimethyl-5α-cholesta*-2,8,24-*triene*, m. p. 76—78°, $[\alpha]_D$ +126° (*c* 0·9) (Found: C, 87·9; H, 11·4. $C_{30}H_{48}$ requires C, 88·2; H, 11·8%).

3-*Isopropylidene*-14α-*methyl*-A-*nor*-5α-*cholesta*-8,24-*diene*.—4,4,14α-Trimethyl-5α-cholesta-8,24-dien-3-one (2 g.) was treated with toluene-*p*-sulphonhydrazide (2 g.) in refluxing ethanol for 1 hr. The product, a gel, was extracted with methylene dichloride–ether, and worked up in the usual way; it gave a jelly. The crude dried material had m. p. 238—240° (decomp.). This material in refluxing ethylene glycol (350 ml.) was treated during 1 hr. with sodium (12 g.). After a further 3 hours' refluxing, the solution was cooled, treated with ethanol to destroy the excess of sodium, and worked up in the usual way. The oily product was filtered in pentane through a column of aluminium oxide in pentane. Repeated crystallisation of the still oily product from the eluate gave 3-isopropylidene-A-nor-5α-cholesta-8,24-diene, m. p. and mixed m. p. 136—140°, $[\alpha]_D$ +77·7° (*c* 1·2).

Reduction of the Toluene-p-*sulphonates by Lithium Aluminium Hydride*.—(1) 4,4,14α-*Trimethyl-5α-cholesta*-8,24-*dien-3β-yl toluene*-p-*sulphonate*. The toluene-*p*-sulphonate (2 g.) in ether (500 ml.) was heated under reflux with lithium aluminium hydride (2 g.) for 24 hr. The product, an oil, was chromatographed on aluminium oxide (100 g.). Elution with pentane (3 × 50 ml.) gave an oil (1·29 g.) which crystallised from ethyl acetate, to give 3-isopropylidene-14α-methyl-A-nor-5α-cholesta-8,24-diene, m. p. 138—140°, $[\alpha]_D$ +84° (*c* 1·2). The oily residues gave a fraction of m. p. 45—65°, which indicated the presence of another hydrocarbon. Elution with ether and chloroform gave lanosterol (165 mg.).

(2) 4,4,14α-*Trimethyl-5α-cholesta*-8,24-*dien-3α-yl toluene*-p-*sulphonate*. The toluene-*p*-sulphonate (1·83 g.) in ether (500 ml.) was heated under reflux with lithium aluminium hydride

(2·1 g.) for 39 hr. The product, an oil (1·33 g.), was chromatographed on aluminium oxide (70 g.). Elution with pentane gave an oil (876 mg.) which on crystallisation from acetone gave 4,4,14α-trimethyl-5α-cholesta-2,8,24-triene, $[\alpha]_D$ +118° (*c* 1·0), m. p. 78—79° undepressed on admixture with the specimen obtained from the pyrolysis of lanosteryl benzoate. The infrared curves of these two products were identical. Elution with ether gave 4,4,14α-trimethyl-5α-cholesta-8,24-dien-3α-ol (384 mg.).

(3) 4,4,14α-*Trimethyl*-5α-*cholest*-8-*en*-3α-*yl toluene*-p-*sulphonate.* The toluene-*p*-sulphonate (540 mg.) in ether (100 ml.) was heated under reflux with lithium aluminium hydride (540 mg.) for 40 hr. The oily product was chromatographed on aluminium oxide (20 g.). Elution with pentane gave an oil (234 mg.) which on repeated crystallisation from chloroform in methanol gave 4,4,14α-trimethyl-5α-cholesta-2,8-diene, m. p. 80—81°, $[\alpha]_D$ +124·5° (*c* 0·9). Elution with ether gave 4,4,14α-trimethyl-5α-cholest-8-en-3α-ol (117 mg.), m. p. 140°.

Reaction of the Toluene-p-*sulphonates on Alkaline Aluminium Oxide.*—(1) 4,4,14α-*Trimethyl*-5α-*cholesta*-8,24-*dien*-3β-*yl toluene*-p-*sulphonate.* The toluene-*p*-sulphonate (1·1 g.) in benzene was adsorbed on a column of basic aluminium oxide (Woelm; 100 g.). More benzene (10 ml.) was run on to the column which was then stoppered for 3 days. Elution with benzene gave an oil (696 mg.) which, on repeated crystallisation from ether–ethanol, gave the less soluble 3-isopropylidene-14α-methyl-A-nor-5α-cholesta-8,24-diene, m. p. 136—139°. Crystallisation of the residues from ethanol finally gave needles, m. p. 72—76°, $[\alpha]_D$ +112°, of impure 4,4,14α-trimethyl-5α-cholesta-2,8,24-triene. Treatment of this toluene-*p*-sulphonate with dimethylformamide at 78° for 72 hr. gave an oil from which after many recrystallisations the above pair of hydrocarbons was isolated in small quantity.

(2) 4,4,14α-*Trimethyl*-5α-*cholesta*-8,24-*dien*-3α-*yl toluene*-p-*sulphonate.* The toluene sulphonate (1·1 g.) was treated as in the previous experiment for 8 days. Elution with benzene gave an oil (556 mg.), whilst chloroform gave the 3α-alcohol (257 mg.), m. p. 131—132°. The oil was fractionally crystallised from ethyl acetate–methanol, to give 3,4,14α-trimethyl-5α-cholesta-3,8,24-triene, m. p. 106—110°, $[\alpha]_D$ +62°, and impure 4,4,14α-trimethyl-5α-cholesta-3,8,24-triene, m. p. 69—74°, $[\alpha]_D$ +105°.

4,4,14α-*Trimethyl*-5α-*cholest*-8-*ene.*—4,4,14α-Trimethyl-5α-cholesta-2,8,24-triene (325 mg.) [obtained from the lithium aluminium hydride reduction (above) of the 3α-toluene-*p*-sulphonate] in acetic acid–ethyl acetate (1 : 1) (60 ml.) was hydrogenated in the presence of platinum oxide (113 mg.). The oily product was filtered in pentane through aluminium oxide; it then crystallised from acetone, giving 4,4,14α-trimethyl-5α-cholest-8-ene, m. p. 76—78°, $[\alpha]_D$ +63·5° (*c* 1·0), undepressed in m. p. on admixture with an authentic sample of m. p. 74·5—75·5°, $[\alpha]_D$ +65·4° (*c* 1·2).

3ξ-*Isopropyl*-14α-*methyl*-A-*nor*-5α-*cholest*-8-*ene.*—(*a*) 3-Isopropylidene-14α-methyl-A-nor-5α-cholesta-8,24-diene (315 mg.) in acetic acid–ethyl acetate (1 : 1) (60 ml.) was hydrogenated in the presence of platinum oxide (129 mg.). Two mol. of hydrogen were absorbed by the compound. The oily product, after filtration of a pentane solution through a column of aluminium oxide, crystallised from ether–ethanol, to give 3ξ-*isopropyl*-14α-*methyl*-5α-*cholest*-8-*ene*, m. p. 63—65°, $[\alpha]_D$ +49·6° (*c* 1·05) (Found: C, 87·0; H, 12·5. $C_{30}H_{52}$ requires C, 87·3; H, 12·7%). (*b*) 3-Isopropylidene-14α-methyl-A-nor-5α-cholest-8-ene (143 mg.) in ethyl acetate–acetic acid (1 : 1) (60 ml.) was hydrogenated in the presence of platinum oxide (50 mg.). One mol. of hydrogen was absorbed by the compound. Crystallisation of the product from ether–ethanol gave 3-isopropyl-14α-methyl-A-nor-5α-cholest-8-ene, m. p. 60—64°, $[\alpha]_D$ +48·5° (*c* 0·93).

3ξ,4ξ,14α-*Trimethyl*-5α-*cholest*-8-*ene.*—(*a*) 3,4,14α-Trimethyl-5α-cholesta-3,8,24-triene (288 mg.) in ethyl acetate–acetic acid (1 : 1) (60 ml.) was hydrogenated in the presence of platinum oxide (101 mg.). Two mol. of hydrogen were absorbed by the compound. Filtration of a pentane solution of the product through aluminium oxide in pentane, followed by crystallisation, gave 3ξ,4ξ,14α-*trimethyl*-5α-*cholest*-8-*ene*, m. p. 98—101°, $[\alpha]_D$ +78° (*c* 1·0) (Found: C, 87·3; H, 12·4. $C_{30}H_{52}$ requires C, 87·3; H, 12·7%).

(*b*) 3,4,14α-Trimethyl-5α-cholesta-3,8-diene (61 mg.) in ethyl acetate–acetic acid (1 : 1) (50 ml.) was hydrogenated in the presence of platinum oxide (63 mg.). One mol. of hydrogen was absorbed. Crystallisation of the product several times from acetone gave 3β,4β,14α-trimethyl-5α-cholest-8-ene, m. p. 99—103°, $[\alpha]_D$ +70° (*c* 1·1).

Kinetic Measurements.—Preliminary runs established that the reactions proceeded at convenient rates in the temperature range 60—90°. "AnalaR" glacial acetic acid was employed as solvent, and solutions were made up by weight in stoppered flasks. Constant

temperature was maintained by using a vapour-thermostat in which chloroform, ethanol, hexane, or trichloroethylene were employed as boiling liquid. Temperature fluctuations during a day did not exceed 0·05°. The liberated toluene-*p*-sulphonic acid was determined by withdrawing 5 ml. portions at intervals and adding a known excess of diphenylguanidinium acetate in acetic acid as base. The excess of base was titrated against a standard solution (0·05 or 0·01M) of perchloric acid in acetic acid. A 0·1% solution of quinaldine red in ethanol [26] proved to be a sensitive indicator, and the equivalence point was confirmed potentiometrically. The strength of the perchloric acid solution was checked before each run in order to avoid the effect of fluctuations in room temperature. Reactions were followed up to about 50% completion, this limit being determined by darkening of solutions in the case of lanosteryl toluene-*p*-sulphonate which reduced the sensitivity of the titrimetric end-point.

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[26] Highuchi, Feldman, and Rehm, *Analyt. Chem.*, 1956, **28**, 1120.