533. *The Chemistry of the Triterpenes and Related Compounds. Part XXXIX.* Some Derivatives of 4,4-Dimethylcholestan-3-one.*

By G. R. Chaudhry, T. G. Halsall, and E. R. H. Jones.

Several 2-substituted derivatives of 4,4-dimethylcholestan-3-one have been prepared so that their properties can be compared with those of certain bitter principles which have been assigned comparable structures for ring A. The $\Delta[M]_D$ value for the conversion of 2α-hydroxy-4,4-dimethylcholestan-3-one (X) into 2-hydroxy-4,4-dimethylcholest-1-en-3-one (XI) is markedly different from the corresponding values for the conversions of cucurbitacins B (II) into E (I) and D (IV) into I (III).

Structure (IV) has been proposed [1] for cucurbitacin D (elatericin A) and structures (I), (II), and (III) then follow for the related cucurbitacins E (α-elaterin), B, and I (elatericin B). Noller, Melera, Gut, Shoolery, and Johnson [2] have criticised structure (II), pointing out that the nuclear magnetic resonance spectrum of the diosphenols prepared from dihydro- and deacetoxydihydro-cucurbitacin B indicate that $C_{(10)}$ carries a hydrogen atom and hence is not quaternary as in structure (II).

* Part XXXVIII, *J.*, 1961, 646.

[1] Lavie and Shvo, *Chem. and Ind.*, 1960, 403; Lavie, Shvo, and Gottlieb, *Tetrahedron Letters*, 1960, No. 22, 23.

[2] Noller, Melera, Gut, Shoolery, and Johnson, *Tetrahedron Letters*, 1960, No. 15, 15.

Recently we have prepared model compounds starting from 4,4-dimethylcholestan-3-one to obtain optical-rotation data for comparison with those available for the cucurbitacins described above. Our primary aim was to prepare the α-hydroxy-ketone (X) and the diosphenol (XI).

Cholest-4-en-3-one was methylated according to the method of Woodward, Patchet, Barton, Ives, and Kelly [3] to give 4,4-dimethylcholest-5-en-3-one. This was converted into the saturated ketone (V) by hydrogenation and oxidation of the resulting 4,4-dimethyl-5α-cholestan-3β-ol. Besides the 4,4-dimethyl-5α-cholestan-3β-ol the corresponding 3α-alcohol was isolated, as were also 4,4-dimethyl-5β-cholestan-3α- and -3β-ol. The last two alcohols were distinguished on the basis of their ease of elution from alumina, the more easily eluted being assumed to have an axial (3β) hydroxyl group. Oxidation of the two 4,4-dimethyl-5β-cholestan-3-ols gave 4,4-dimethyl-5β-cholestan-3-one.

The ketone (V) was treated with bromine (1·1 mol.) in acetic acid containing a little hydrobromic acid, and two crystalline monobromo-ketones, m. p.s 110—112° and 71°, were isolated. These must be epimeric at position 2. The one with m. p. 110—112° had an ultraviolet maximum at a wavelength 50 Å less than that of the parent ketone. The infrared frequency of its carbonyl group was 23 cm.$^{-1}$ greater. The corresponding figures for the bromo-ketone, m. p. 71°, were −30 Å and +20 cm.$^{-1}$. These results indicate [4,5] that in both bromo-ketones the bromine is equatorially disposed. Barton, Lewis, and McGhie,[6] and Cummins and Page,[7] have obtained similar spectroscopic results with the two epimeric 2-bromo-derivatives of lanostan-3-one and lanost-8-en-3-one. As in these cases [6] our results can be explained by assuming that we have a 2α-bromo-ketone (VI) with ring A in the chair conformation and a 2β-bromo-ketone (VII) with ring A as a boat. The $\Delta[M]_D$ for the introduction of the 2β-bromine atom in lanostan-3-one is +544° and for the 2α-bromine +69°.[6] The $\Delta[M]_D$ value for the 2-bromo-ketone, m. p. 110—112°, was +227° and for the other, m. p. 72°, was −48°, indicating that the former is the 2β-bromo-derivative (VII) and the latter the 2α-bromo-derivative (VI). These configurational assignments are supported by optical rotatory dispersion data (cf. Table) and are consistent with an analysis of these data according to the " octant rule." [8]

Compound	Amplitude *	Δ (Subst. ketone − parent ketone)
4,4-Dimethylcholestan-3-one	−11°	
2α-Bromo-4,4-dimethylcholestan-3-one	+20	+31°
2β-Bromo-4,4-dimethylcholestan-3-one	+75	+86
Lanostan-3-one	−13	
2α-Bromolanostan-3-one	+23	+36
4,4-Dimethylcholest-5-en-3-one	+62	
2α-Bromo-4,4-dimethylcholest-5-en-3-one	+60	−2
2,2-Dibromo-4,4-dimethylcholest-5-en-3-one	−118	−180
2α-Acetoxy-4,4-dimethylcholestan-3-one	+38	+49
2β-Acetoxy-4,4-dimethylcholestan-3-one	+124	+135

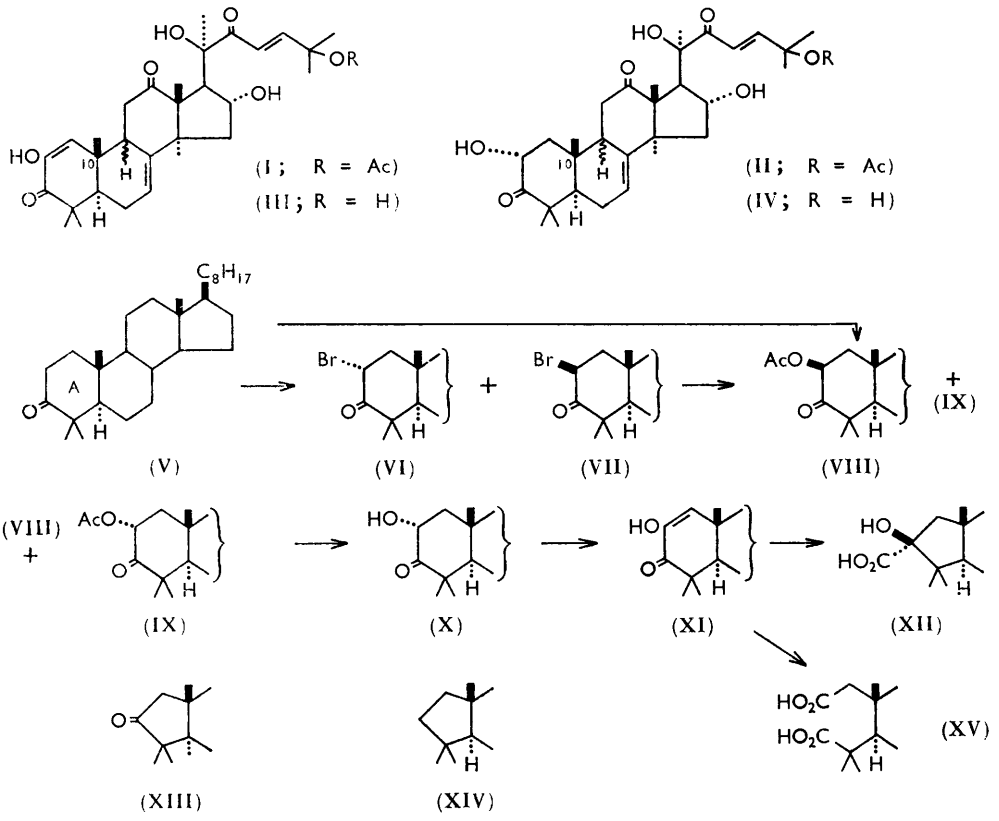
* Amplitude is the difference between the molecular rotations × 10^{-2} at the peak and trough of the Cotton curve.

Hanna, Sandris, and Ourisson [9] have also brominated 4,4-dimethylcholestan-3-one (V) but obtained only the 2,2-dibromo-derivative. The ketone has also been brominated by Sigg and Tamm [10] who obtained an amorphous monobromo-ketone, $[\alpha]_D$ +12°, which they claim is 2α-bromo-4,4-dimethylcholestan-3-one, and the 2,2-dibromo-ketone; their

[3] Woodward, Patchet, Barton, Ives, and Kelly, *J.*, 1957, 1131.
[4] Jones, Ramsey, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.
[5] Cookson, *J.*, 1954, 282.
[6] Barton, Lewis, and McGhie, *J.*, 1957, 2907.
[7] Cummins and Page, *J.*, 1957, 3847.
[8] Moffitt, Muscovitz, Woodward, Djerassi, and Klyne, unpublished work; cf. Klyne, *J. Roy. Inst. Chem.*, 1960, **84**, 50.
[9] Hanna, Sandris, and Ourisson, *Bull. Soc. chim. France*, 1959, 1454.
[10] Sigg and Tamm, *Helv. Chim. Acta*, 1960, **43**, 1402.

constants, however, indicate that their monobromo-ketone is a mixture of *ca.* 40% of the 2β-bromo- and *ca.* 60% of the 2α-bromo-ketone.

4,4-Dimethylcholest-5-en-3-one was also brominated: the 2,2-dibromo-derivative [11] and a monobromo-derivative identical with that said [11] to be 2α-bromo-4,4-dimethylcholest-5-en-3-one were obtained. No evidence for the 2α-configuration was given. The ultraviolet maxima in both cases were at wavelengths 250 Å greater than for the parent ketone, whereas the infrared carbonyl stretching frequency was unchanged in the case of



the monobromo-ketone and only shifted by +4 cm.$^{-1}$ for the dibromo-ketone. The bromine atom in the monobromo-ketone is therefore axially disposed.[4,5] The only structure which permits the bromine atom to have an axial conformation and yet not interact with the 4- and 10-methyl groups is that with the bromine atom in the 2α-configuration and with ring A in a boat form with $C_{(1)}$ and $C_{(4)}$ at the bow and stern.

The amplitude of the Cotton effect for the monobromo-ketone is almost identical with that of the parent ketone, but uncertainty about the effect of the 5,6-double bond and the consequential flexible conformations of ring A do not allow a prediction of the configuration of the bromine atom to be made with certainty on the basis of the " octant rule." [8]

Acetoxylation of 4,4-dimethylcholestan-3-one with lead tetra-acetate in acetic acid [12] gave a mixture from which the two epimeric 2-acetates, m. p.s 115° and 147°, were isolated.

[11] Adams, Patel, Petrow, Stuart-Webb, and Sturgeon, *J.*, 1956, 4490.

[12] Cf. Ehrhart, Rushig, and Amuller, *Ber.*, 1939, **72**, 2035; Reichstein and Montigel, *Helv. Chim. Acta*, 1939, **22**, 1212; Seebeck and Reichstein, *Helv. Chim. Acta*, 1944, **27**, 948; Sondheimer, Kaufmann, Romo, Martinez, and Rosenkranz, *J. Amer. Chem. Soc.*, 1953, **75**, 4712; Rosenkranz, Mancera, and Sondheimer, *J. Amer. Chem. Soc.*, 1955, **77**, 145; Clarke, Dobriner, Morradian, and Martini, *J. Amer. Chem. Soc.*, 1955, **77**, 661; Axelrod and Rao, *Chem. and Ind.*, 1959, 1454.

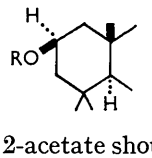
Both were also obtained by acetolysis of 2β-bromo-4,4-dimethylcholestan-3-one. The $\Delta\lambda_{max.}$ and $\Delta\nu_{max.}$ (C=O) for both compounds compared with the parent ketone were ±0 Å and +24 cm.$^{-1}$, again indicative of the equatorial conformation of the acetoxy-group in both cases. The correlation between wavelength shifts and the conformation of the acetoxy-group is, however, not always valid.[13] The acetate, m. p. 147°, shows the greater positive amplitude in its Cotton effect (cf. Table). As 2β-bromo- and 2β-methoxy-4,4-dimethylcholestan-3-one [10] show bigger positive amplitudes than the corresponding 2α-derivatives, the acetate of m. p. 147° must be 2β-acetoxycholestan-3-one (VIII) with ring A in a flexible conformation, and the acetate of m. p. 115° is the corresponding 2α-acetate (IX).

Careful hydrolysis of the 2α-acetate (IX) with alcoholic potassium hydroxide gave the 2α-hydroxy-ketone (X) as the major product, along with some of the diosphenol (XI). Hydrolysis of the 2β-acetate (VIII) also gave the 2α-hydroxy-ketone (X). This was oxidised to the diosphenol (XI) by bismuth trioxide in acetic acid (Rigby's method [14]) as well as by copper acetate in methanol.[15] This diosphenol has recently been prepared by Sigg and Tamm [10] starting from 2β-methoxy-4,4-dimethylcholestan-3-one. Its nuclear magnetic resonance spectrum was determined in chloroform. It showed a band at $\tau = 3{\cdot}6$ indicative of a β-hydrogen atom on the diosphenol group and the absence of a γ-hydrogen atom in agreement with the findings of Noller *et al.*[2]

The diosphenol (XI) underwent the benzilic acid rearrangement, which is also characteristic of ring A of cucurbitacin E (I), to give the hydroxy-acid (XII).[16] Consideration of the stereochemistry of the rearrangement indicates that attack by hydroxyl ion at either position 2 or position 3 of the diketone form of (XI) will lead to a β-orientation for the hydroxyl group of the hydroxy-acid. Fission of the hydroxy-acid (XII) with lead tetra-acetate gave the A-nor-ketone (XIII) recently described by Hanna, Sandris, and Ourisson [9] and also prepared in reasonable yield by pyrolysis, after treatment with acetic anhydride, of the *seco*-diacid (XV) obtained by oxidation of the diosphenol (XI) with alkaline hydrogen peroxide. Wolff–Kishner reduction of the A-nor-ketone gave 3,3-dimethyl-A-norcholestane (XIV). The $\Delta[M]_D$ for the reduction (−402°) is as expected.[17]

The $\Delta[M]_D$ value for the conversion of the 2α-hydroxy-ketone (X) into the diosphenol (XI) is +110° whereas the values for the conversion of cucurbitacin B (II) [18] into E (I) [19] and of cucurbitacin D (IV) [20] into I (III) [20] are −847° and −509° respectively. This very significant difference between the 4,4-dimethylcholestane derivatives and the cucurbitacins could well be due to the 7,8-double bond if structures (I—IV) are correct. It does, however, also suggest that there may be some profound difference between rings A of cucurbitacins E and I and ring A of 2-hydroxy-4,4-dimethylcholest-1-en-3-one, as is suggested in the recent paper of Noller and his co-workers.[2]

Lavie and Gottlieb [21] recently described the 2β-epimers of dihydrocucurbitacins B and D and the acetate of the second of the epimers. If structures (I—IV) are correct these 2β-epimers should have partial structure (XVI; R = H or Ac). By analogy with 2β-acetoxy-4,4-dimethylcholestan-3-one (VIII) and the related 2β-substituted 4,4-dimethylcholestan-3-ones discussed above the hydroxy- and acetoxy-groups in the 2β-epimers of dihydrocucurbitacins B and D and of dihydrocucurbitacin D 2-acetate should be equatorially disposed. The evidence of Lavie and Gottlieb [21] indicates that their conformation is axial. This conclusion again suggests the absence of a



(XVI)

[13] Elks, Phillips, Walker, and Wyman, *J.*, 1956, 4330.
[14] Rigby, *J.*, 1951, 793.
[15] Wendler, Taub, and Graber, *Tetrahedron*, 1959, **7**, 173.
[16] Lavie, *Chem. and Ind.*, 1956, 466.
[17] Klyne, *J.*, 1952, 2916.
[18] Chaudhry and Halsall, *Chem. and Ind.*, 1959, 1119.
[19] Chaudhry, D.Phil. Thesis, Oxford, 1960.
[20] Lavie and Willner, *J. Amer. Chem. Soc.*, 1958, **80**, 710.
[21] Lavie and Gottlieb, *Chem. and Ind.*, 1960, 929.

10-methyl group. Clearly an attempt to extend unsaturation to position 10 in elaterin would be of interest.

Experimental

Rotations refer to solutions in $CHCl_3$ at room temperature unless otherwise stated. M. p.s were determined on a Kofler block and are corrected. The alumina used for chromatography was alumina of activity I—II; " 5% deactivated " refers to deactivation of this alumina with 5% of 10% aqueous acetic acid. Light petroleum refers to the fraction with b. p. 40—60°. Unless otherwise stated, ultraviolet spectra were determined on ethanol solutions and infrared spectra on carbon disulphide solutions.

4,4-Dimethylcholestan-3-one (V).—Cholest-4-en-3-one was converted into 4,4-dimethylcholest-5-en-3-one essentially by the method of Woodward *et al.*[3] 4,4-Dimethylcholest-5-en-3-one (30 g.) in acetic acid (700 c.c.) was shaken with hydrogen at 80—90°/1 atm. in the presence of Adams catalyst (2 g.). Absorption of hydrogen was very slow even after the addition of more catalyst (3 g.). After 16 hr. absorption of hydrogen ceased (uptake 4·5 l.; calc., 4·25 l.). After removal of the catalyst the solution was concentrated and cooled, to give needles (15 g.), m. p. 155—156°. Extraction of the mother-liquors with benzene gave further product (13 g.). The infrared spectrum of this extract indicated that acetylation had occurred during the hydrogenation. The total hydrogenation product (28 g.) was hydrolysed with 3% methanolic potassium hydroxide (500 c.c.) under reflux for 2 hr. The product crystallised from ether–methanol to give 4,4-dimethylcholestan-3β-ol (15 g.). Concentration of the mother-liquors afforded a viscous mass (13 g.) whence chromatography gave a fraction (950 mg.), m. p. 147—150°, and a second fraction (6·5 g.). The latter fraction was separated by treatment with digitonin into 4,4-dimethylcholestan-3β-ol (5 g.) and two fractions, m. p. 44—55°, $[\alpha]_D$ +22°, and m. p. 80—95°. The two crops (20 g.) of 4,4-dimethylcholestan-3β-ol were crystallised from methylene dichloride–methanol, to give needles (18 g.), m. p. 157—158°, $[\alpha]_D$ +11° (*c*, 1·0). Mazur and Sondheimer [22] report m. p. 157—158°, $[\alpha]_D$ +11°.

The fraction, m. p. 147—150°, was adsorbed on alumina (5% deactivated). Elution with benzene gave a fraction which crystallised from ether–methanol to give *4,4-dimethylcholestan-3α-ol* as needles, m. p. 145—147°, $[\alpha]_D$ +50° (*c* 1·0), $\nu_{max.}$ 3571, 1060, and 990 cm.$^{-1}$ (Found: C, 83·3; H, 12·3. $C_{29}H_{52}O$ requires C, 83·6; H, 12·6%). Oxidation of the alcohol in acetone with 8N-chromic acid [23] gave 4,4-dimethylcholestan-3-one (see below), m. p. and mixed m. p. 103—104°, $[\alpha]_D$ +3°.

The fraction, m. p. 44—55°, $[\alpha]_D$ +22°, was adsorbed on alumina (5% deactivated). Elution with benzene gave a fraction which crystallised from ether–methanol to give *4,4-dimethyl-5β-cholestan-3β-ol* as needles, m. p. 70—72°, $[\alpha]_D$ +33° (*c* 1·0), $\nu_{max.}$ 3571, 1039, 975, and 925 cm.$^{-1}$ (Found: C, 83·55; H, 12·2. $C_{29}H_{52}O$ requires C, 83·6; H, 12·6%). Oxidation of the alcohol in acetone with 8N-chromic acid [23] gave a product which on chromatography on alumina gave *4,4-dimethyl-5β-cholestan-3-one* as plates (from ether–methanol), m. p. 62—65°, $[\alpha]_D$ +15° (*c* 1·0), $\nu_{max.}$ 1706, 1127, and 1114 cm.$^{-1}$, $\lambda_{max.}$ 2870 Å (ε 30) (Found: C, 83·85; H, 12·1. $C_{29}H_{50}O$ requires C, 84·0; H, 12·15%). R.D. in MeOH (*c* 0·1), [*M*]: (3100 Å), −1480°; (2750 Å) +1240°.

The fraction, m. p. 80—95°, was adsorbed on alumina (5% deactivated). Elution with benzene gave material which crystallised from ether–methanol to give *4,4-dimethyl-5β-cholestan-3α-ol* as plates, m. p. 98—100°, $[\alpha]_D$ +23° (*c* 1·0), $\nu_{max.}$ 3559, 1039, 975, and 925 cm.$^{-1}$ (Found: C, 83·2; H, 12·45. $C_{29}H_{52}O$ requires C, 83·6; H, 12·6%). The alcohol was oxidised as described above to 4,4-dimethyl-5β-cholestan-3-one, m. p. and mixed m. p. 62—65°, $[\alpha]_D$ +14° (*c* 1·0).

4,4-Dimethylcholest-5-en-3-one (5 g.) was also hydrogenated at 50—60°/1 atm. in acetic acid (100 c.c.) containing 2 drops of 60% perchloric acid and Adams catalyst (1 g.). Hydrogenation was complete after 3 hr. After removal of the catalyst and concentration of the solution crystals (3·7 g.) were formed at 20°. Recrystallisation of these from methylene dichloride–methanol gave 4,4-dimethylcholestan-3β-ol as needles (3·3 g.), m. p. 157—158°, $[\alpha]_D$ +11° (*c* 1·07).

4,4-Dimethylcholestan-3β-ol (18 g.) was oxidised in acetone (1500 c.c.) with 8N-chromic

[22] Mazur and Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 5220.
[23] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2555.

acid.[23] 4,4-Dimethylcholestan-3-one was obtained as needles (16 g.) (from methylene dichloride–methanol), m. p. 103—104°, $[\alpha]_D$ +2°. R.D. in MeOH (*c* 0·1), [*M*]: (3200 Å), −800°; (2850 Å), +300°.

Bromination of 4,4-*Dimethylcholestan*-3-*one*.—Bromine (470 mg., 1·1 mol.) in acetic acid (2 c.c.) containing 2 drops of hydrobromic acid was added in ½ hr. to a stirred solution of 4,4-dimethylcholestan-3-one (1·13 g.) in acetic acid (20 c.c.) at 20°. The stirring was continued for ½ hr. and then the solution was kept at 20° for 48 hr.; a product (300 mg.) crystallised as needles. These were isolated. The mother-liquor was diluted with water and extracted with ether. The extract (400 mg.) was dissolved in ether (5 c.c.), and the solution was diluted with ethanol (25 c.c.) and kept at 0° for several days. Further crystals (300 mg.) separated. The total crystalline product (600 mg.) was repeatedly crystallised from ether–ethanol, to give crude 2β-bromo-4,4-dimethylcholestan-3-one, m. p. 106—108°. The crude 2β-bromo-product (500 mg.) was chromatographed on silica gel (160 g.). Elution with light petroleum–benzene afforded 2β-*bromo*-4,4-*dimethylcholestan*-3-*one* (VII) (450 mg.) which crystallised from ether–ethanol as needles, m. p. 110—112°, $[\alpha]_D$ +47° (*c* 1·0), $\lambda_{max.}$ 2850 Å (ε 45), $\nu_{max.}$ 1727, 952, 757, and 714 cm.$^{-1}$ (Found: C, 70·5; H, 10·0; Br, 16·2. $C_{29}H_{49}BrO$ requires C, 70·5; H, 10·0; Br, 16·2%), R.D. in MeOH (*c* 0·1), [*M*]: (3085 Å), +4700°; (2610 Å) −2800°.

The mother-liquors left after removal of the crude 2β-bromo-4,4-dimethylcholestan-3-one for chromatography afforded the 2α-bromo-derivative which was crystallised twice from ethanol to give 2α-*bromo*-4,4-*dimethylcholestan*-3-*one* (VI) as needles, m. p. 70—71° $[\alpha]_D$ −8° (*c*, 1·0), $\lambda_{max.}$ 2870 Å (ε 30), $\nu_{max.}$ 1724, 952, and 757 cm.$^{-1}$ (Found: C, 70·5; H, 10·0; Br, 16·2%). R.D. in MeOH (*c* 0·1), [*M*]: (3375 Å) −120°; (2960 Å) +2150°.

Reduction of 2β-*Bromo*-4,4-*dimethylcholestan*-3-*one*.—This ketone (150 mg.), zinc dust (500 mg.), and acetic acid (10 c.c.) were heated at 100° for 2 hr. After filtration and dilution with water, ether-extraction afforded 4,4-dimethylcholestan-3-one (75 mg.), m. p. and mixed m. p. 103°.

Bromination of 4,4-*Dimethylcholest*-5-*en*-3-*one*.—4,4-Dimethylcholest-5-en-3-one (6·9 g.) in chloroform (60 c.c.) and acetic acid (60 c.c.) was treated at 20° during 1 hr., with stirring, with bromine (3·5 g., 1·3 mol.) in acetic acid (5 c.c.) containing 2 drops of 50% hydrobromic acid in acetic acid. The solvent was removed at 20°. The resulting crystalline product was washed with methanol (3 × 5 c.c.), affording prisms (4·5 g.). After three crystallisations from chloroform–methanol, the fraction, m. p. 135—138°, was recrystallised thrice from ethanol, to give 2α-bromo-4,4-dimethylcholest-5-en-3-one as plates (2 g.), m. p. 138—139°, $[\alpha]_D$ −28° (*c* 1·0), $\lambda_{max.}$ 3150 Å (ε 140), $\nu_{max.}$ 1724, 1105, 1026, and 769 cm.$^{-1}$ (Found: C, 70·7; H, 9·5; Br, 16·0. Calc. for $C_{29}H_{47}BrO$: C, 70·9; H, 9·6; Br, 16·3%). R.D. in MeOH (*c* 0·1), [*M*]: (3360 Å) +1300°, (2800 Å) −4750°. Adams *et al.*[11] give m. p. 136—137°, $[\alpha]_D$ −25°.

The intermediate fractions (2 g.), m. p. 80—95°, obtained during the fractional crystallisation were chromatographed on silica gel (200 g.). Light petroleum–benzene (9 : 1; 500 c.c.) eluted a fraction (700 mg.) which crystallised from chloroform–methanol to give 2,2-dibromo-4,4-dimethylcholest-5-en-3-one as rods, m. p. 94—95°, $[\alpha]_D$ −34°, $\lambda_{max.}$ 3150 Å (ε 120), $\nu_{max.}$ 1724, 1042, 1031, 952, 877, 787, and 702 cm.$^{-1}$ (Found: C, 60·8; H, 8·1; Br, 28·2. Calc. for $C_{29}H_{46}Br_2O$: C, 61·0; H, 8·1; Br, 28·1%). R.D. in MeOH (*c* 1·0), [*M*]: (3475 Å), −4050° (2975 Å), +7750°. Adams *et al.*[11] give m. p. 94—96°.

Acetolysis of 2β-*Bromo*-4,4-*dimethylcholestan*-3-*one*.—The bromo-ketone (500 mg.) in acetic acid (10 c.c.) and freshly fused potassium acetate (2·0 g.) were heated under reflux under nitrogen for 4 hr. After dilution with water, ether-extraction afforded an oil (400 mg.) which was triturated with methanol. The resulting solution was boiled with charcoal and then concentrated and kept at 0°. The crude crystalline product (200 mg.) was resolved by several crystallisations from ether–methanol into two crystalline components: (a) 2α-*acetoxy*-4,4-*dimethylcholestan*-3-*one* (IX) (50 mg.), m. p. 115°, $[\alpha]_D$ +38° (*c* 1·0), $\lambda_{max.}$ 2900 Å (ε 38), $\nu_{max.}$ 1748, 1727, 1230, 1084, 1047, and 1031 cm.$^{-1}$ (Found: C, 78·7; H, 11·0; Ac, 9·0. $C_{31}H_{52}O_3$ requires C, 78·75; H, 11·1; Ac, 9·1%) {R.D. in MeOH (*c*, 0·104). [*M*]: (3120 Å), +2140°, (2720 Å) −1640°}, and (b) 2β-*acetoxy*-4,4-*dimethylcholestan*-3-*one* (VIII) (45 mg.), m. p. 145°, $[\alpha]_D$ +59° (*c* 1·0), $\lambda_{max.}$ 2900 Å (ε 40), $\nu_{max.}$ 1748, 1727, 1227, 1084, and 1047 cm.$^{-1}$ (Found: C, 78·75; H, 11·1; Ac, 9·0%) {R.D. in MeOH (*c* 0·106), [*M*]: (3070 Å), +7050°; (2700 Å) −5400°}.

Acetoxylation of 4,4-*Dimethylcholestan*-3-*one*.—4,4-Dimethylcholestan-3-one (10 g.), lead tetra-acetate (15 g.), and acetic acid (100 c.c.) were heated for 4 hr. at 100°. Most of the solvent was removed under reduced pressure and the resulting viscous mass was macerated with water

(300 c.c.). A sticky pale-yellow solid separated and the aqueous layer was decanted. The solid was again macerated with water (2 × 100 c.c.), and the combined aqueous washings were partially neutralised with sodium hydrogen carbonate solution and extracted with benzene. The solid was dissolved in the benzene extract which was then worked up in the usual manner, to give a residue (12 g.) which was adsorbed from light petroleum on alumina (5% deactivated) (1 kg.). The following fractions were eluted with the solvents indicated: (i) light petroleum (3 l.), 100 mg.; (ii) light petroleum–benzene (2 l.; 19 : 1) 70 mg.; (iii) light petroleum–benzene (4 l.; 9 : 1), 760 mg.; (iv) and (v) light petroleum–benzene (4 : 1), (1 l.), 130 mg., (5 l.), 805 mg.; (vi) and (vii) light petroleum–benzene (7 : 3), (1 l.), 340 mg.; (500 c.c.), 530 mg.; (viii)—(xix) light petroleum–benzene (7 : 3) (12 × 600 c.c.), 5·91 g. Fractions (i)—(vii) did not crystallise. Each of the twelve fractions (viii)—(xix) was fractionally crystallised from ether–methanol, to give crops of the two acetoxy-isomers (m. p.s 113—115° and 145—146°). The earlier fractions were richer in the lower-melting isomer, the later fractions in the higher-melting.

The fractions (2·5 g.) with m. p.s 113—115° were combined and crystallised from ether–methanol, to give 2α-acetoxy-4,4-dimethylcholestan-3-one as needles, m. p. and mixed m. p. 115°, $[\alpha]_D$ +38° (*c* 1·0). The fractions (3·0 g.) melting at 143—145° were combined and crystallised from ether–methanol, to give 2β-acetoxy-4,4-dimethylcholestan-3-one as needles, m. p. and mixed m. p. 146—147°, $[\alpha]_D$ +61°. In other experiments the proportion of the two isomers varied, but the 2β-acetoxy-isomer was always predominant.

Hydrolysis of 2α-Acetoxy-4,4-dimethylcholestan-3-one (IX).—The acetate (700 mg.) in ethanol (15 c.c.) was treated with M-potassium hydroxide (5 c.c.) under nitrogen. The mixture was shaken at 20° and after 10 min. the product began to be precipitated. After a further 5 min. the solution was acidified with alcoholic M-acetic acid (5 c.c.). The solvent was removed under reduced pressure and the residue was extracted with ether to give a product which contained both saturated and αβ-unsaturated ketones ($\nu_{max.}$ 3460, 1718, 1675, and 1650 cm.$^{-1}$). The mixture (520 mg.) was chromatographed on silica gel (150 g.). Light petroleum–benzene (1 : 1) eluted a product (30 mg.), m. p. 161—162° raised by crystallisation from ether–methanol to 166—167°. Its infrared spectrum ($\nu_{max.}$ 3425, 1672, and 1650 cm.$^{-1}$) indicated that it was a diosphenol. Elution with light petroleum–benzene (3 : 7; 500 c.c.) gave a product (400 mg.) which was crystallised from ether–methanol to give 2α-*hydroxy*-4,4-*dimethylcholestan*-3-*one* (X) as needles, m. p. 133—134°, $[\alpha]_D$ +24° (*c* 1·0), $\lambda_{max.}$ 2820—2830 Å (ε 41), $\nu_{max.}$ 3460, 1718, 1136, 1092, and 1056 cm.$^{-1}$ (Found: C, 80·45; H, 11·8. $C_{29}H_{50}O_2$ requires C, 80·85; H, 11·7%).

Hydrolysis of 2β-*Acetoxy*-4,4-*dimethylcholestan*-3-*one* (VIII).—The acetate (1·23 g.) was hydrolysed as described above, to give also 2α-hydroxy-4,4-dimethylcholestan-3-one (800 mg.), m. p. and mixed m. p. 133—134°, $[\alpha]_D$ +24° (*c* 1·0).

Oxidation of 2α-*Hydroxy*-4,4-*dimethylcholestan*-3-*one* (X).—The hydroxy-ketone (800 mg.) in acetic acid (15 c.c.) was heated under reflux with bismuth oxide (400 mg.) at 100° for ½ hr. More bismuth oxide (400 mg.) was added and the heating was continued for a further ½ hr. After filtration of inorganic material, the yellow filtrate was diluted with ether. A precipitate (1·8 g.) consisting of the diosphenol and bismuth acetate was obtained. It was washed with water, and the washings and the filtrate from the precipitate were extracted with benzene. The washed precipitate was dissolved in the benzene extract which was then purified in the usual manner and evaporated. The residue (600 mg.) was chromatographed on silica gel (200 g.). Light petroleum–benzene (7 : 3; 1·5 l.) eluted a product (500 mg.) which crystallised from ether–methanol to give 2-hydroxy-4,4-dimethylcholest-1-en-3-one (XI) as plates, m. p. 168°, $[\alpha]_D$ +50° (*c* 1·0), $\lambda_{max.}$ 2680—2700 Å (ε 10,650), $\lambda_{max.}$ (alcoholic alkali) 3100—3120 Å (ε 10,000), $\nu_{max.}$ 3425, 1672, 1647, 1225, and 1053 cm.$^{-1}$ (Found: C, 81·0; H, 11·2. Calc. for $C_{29}H_{48}O_2$: C, 81·25; H, 11·3%). Sigg and Tamm [10] give m. p. 165—167°, $[\alpha]_D$ +47° ± 3°. R.D. in MeOH (*c* 0·1), [*M*]: (3580 Å) −1700°; (3340 Å) ±0°; (3024 Å) +6000°.

Rearrangement of 2-*Hydroxy*-4,4-*dimethylcholest*-1-*en*-3-*one* (XI).—The diosphenol (500 mg.) in ethanol (15 c.c.) was heated under reflux with 10% alcoholic sodium hydroxide (10 c.c.) for 5 hr. Most of the ethanol was removed under reduced pressure. After dilution with water and acidification with hydrochloric acid ether-extraction afforded a solution which was extracted with 1% sodium hydrogen carbonate solution. This was acidified with hydrochloric acid and extracted with ether and ethyl acetate. The extracts afforded a residue (400 mg.) which was further purified by dissolution in 2% sodium hydrogen carbonate solution followed by filtration, acidification, and extraction. The resulting product (300 mg.) was triturated with methylene chloride and then acetone. The residue (254 mg.) crystallised from ether–methanol to give

2β-hydroxy-3,3-dimethyl-A-norcholestane-2α-carboxylic acid (XII) as leaflets, m. p. 247—250°, $[\alpha]_D$ +21° (*c* 1·0 in pyridine), $\nu_{max.}$ 3484, 1704, 1180, 1089, 1073, 1055, and 727 cm.$^{-1}$ (Found: C, 77·65; H, 11·1. Calc. for $C_{29}H_{50}O_3$: C, 77·95; H, 11·3%). Hanna, Sandris, and Ourisson [9] give m. p. 263—265° (evacuated capillary), $[\alpha]_D$ +25° (in dioxan).

Preparation of 2β-*Hydroxy*-3,3-*dimethyl*-A-*norcholestane*-2α-*carboxylic Acid* (XII) *from* 2α- *and* 2β-*Acetoxy*-4,4-*dimethylcholestan*-3-*one*.—The 2α-acetate (1·0 g.) in 25% alcoholic potassium hydroxide (20 c.c.) was kept at 20° for 1 hr. and then heated under reflux for 5 hr. The resulting hydroxy-acid (500 mg.), m. p. 245—250°, $[\alpha]_D$ +25° (*c* 1·0 in pyridine), was then isolated in a manner similar to that described above. The acid was similarly obtained from the 2β-acetate.

3,3-*Dimethyl*-A-*norcholestan*-2-*one* (XIII).—Lead tetra-acetate (750 mg.) and 2β-hydroxy-3,3-dimethyl-A-norcholestane-2α-carboxylic acid (500 mg.) in acetic acid (20 c.c.) were heated at 100° for 4 hr. and then kept overnight at 20°. Water (25 c.c.) was added and a solid separated. It was filtered off and the filtrate extracted with benzene. The solid was dissolved in the extract which was washed with water, sodium hydrogen carbonate solution, and water, and dried. Evaporation gave a crystalline residue (350 mg.) which crystallised from ether–methanol as needles, m. p. 130—134°. These were purified by chromatography on alumina (50 g.; 5% deactivated) and then crystallised from ether–methanol to give 3,3-dimethyl-A-norcholestan-2-one as needles (250 mg.), m. p. 134°, $[\alpha]_D$ +115°, $\lambda_{max.}$ 2980 Å (ε 38), $\nu_{max.}$ 1742 cm.$^{-1}$ (Found: C, 83·75; H, 12·0. Calc. for $C_{28}H_{48}O$: C, 83·95; H, 12·1%). R.D. in MeOH (*c* 0·1), [*M*]: (3170 Å) +11,400°; (2790 Å) −10,500°. Hanna, Sandris, and Ourisson [9] give m. p. 131°, $[\alpha]_D$ +110°.

Oxidation of 2-*Hydroxy*-4,4-*dimethylcholest*-1-*en*-3-*one with Alkaline Hydrogen Peroxide*.—Hydrogen peroxide (100-vol.; 6 c.c.) and 10% potassium hydroxide (12 c.c.) were added in 3 equal portions at intervals of 15 min. to a solution of the diosphenol (700 mg.) in ethanol (25 c.c.) which was heated under reflux. After the mixture had been kept at 20° for 2 hr. it was diluted with water and extracted with ether. The aqueous portion was acidified and extracted with ether to give a crystalline residue (540 mg.) which was triturated with methylene dichloride. The insoluble acid crystallised from ether–methanol to give 4,4-*dimethyl*-2,3-*secocholestane*-2,3-*dioic acid* (XV) as leaflets, m. p. 205—207°, $\nu_{max.}$ 1724 and 1701 (sh) cm.$^{-1}$, (Found: C, 75·5; H, 10·85%; equiv., 231. $C_{29}H_{50}O_4$ requires C, 75·3; H, 10·9%; equiv., 231·5).

Pyrolysis of 4,4-*Dimethyl*-2,3-seco*cholestane*-2,3-*dioic Acid*.—The acid (350 mg.) was heated under reflux for 1 hr. in acetic anhydride. The anhydride was then distilled off and the temperature raised to 250°. When evolution of gas had ceased the residue was distilled at 280—300°/0·02 mm. The distillate (250 mg.) crystallised on cooling. It was heated under reflux under nitrogen for 30 min. with 5% alcoholic sodium hydroxide (5 c.c.). After evaporation of the ethanol, dilution with water and ether-extraction afforded a crystalline product (200 mg.). It was purified by chromatography on alumina (5% deactivated; 50 g.) and crystallised from ether–methanol to give 3,3-dimethyl-A-norcholestan-2-one as needles, m. p. and mixed m. p. 134°.

Wolff–Kishner Reduction of 3,3-*Dimethyl*-A-*norcholestan*-2-*one*.—The ketone (250 mg.) was heated under reflux under nitrogen with diethylene glycol (40 c.c.) and 100% hydrazine hydrate (2·5 c.c.) for 2 hr. The excess of hydrazine and water were removed by distillation, potassium hydroxide (600 mg.) was added, and the mixture was heated at 210—220° for 6 hr. After dilution with water, ether-extraction afforded a liquid (200 mg.) which was adsorbed from light petroleum on alumina (15 g.). Elution with light petroleum (200 c.c.) gave 3,3-*dimethyl*-A-*norcholestane* (XIV) which crystallised from acetone as needles, m. p. 99—100°, $[\alpha]_D$ +15°, no carbonyl band in the infrared spectrum (Found: C, 86·6; H, 13·0. $C_{28}H_{50}$ requires C, 87·0; H, 13·0%). R.D. in MeOH (*c* 0·1), [*M*]: (5000 Å) +75°, (4000 Å) +287°, (3000 Å) +600°; plain positive curve.

The authors thank Professor D. H. R. Barton for samples of lanostan-3-one and 2α-bromo lanostan-3-one, Professor W. Klyne and Miss Jane Jackson for determinations of optical rotatory dispersion data, and Dr. R. E. Richards and Dr. E. O. Bishop for the nuclear magnetic resonance determinations. One of them (G. R. C.) held a Colombo Plan Fellowship.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, December 22nd*, 1960.]