Isolation and Some Reactions of Lanosterol. A Synthesis of Agnosterol

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A convenient and efficient method for the isolation of lanosterol from ' isocholesterol ' is described. Some synthetic potentials of the intermediate dibromides are discussed and are illustrated by an efficient synthesis of agnosterol [lanosta-7,9(11),24-trien-3β-ol].

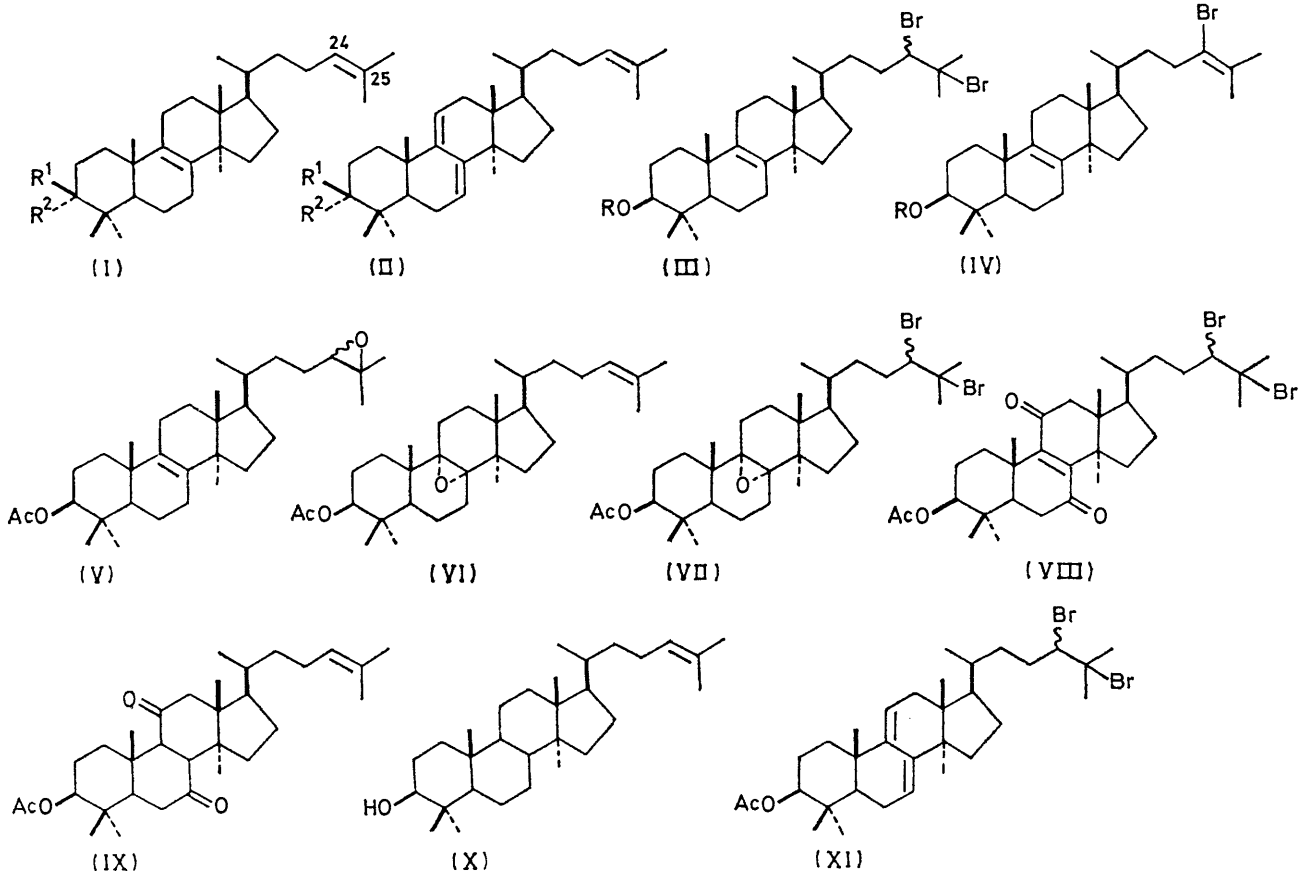
ISOCHOLESTEROL is the name given by Schulze [1] to the non-saponifiable portion of wool fat. The homogeneity of isocholesterol was always in doubt [2] and the presence of four closely related compounds was eventually established.[3] These are 5α-lanosta-8,24-dien-3β-ol (lanosterol) (I; $R^1 = OH$, $R^2 = H$), 5α-lanost-8-en-3β-ol (dihydrolanosterol) (I; $R^1 = OH$, $R^2 = H$, 24,25-dihydro), 5α-lanosta-7,9(11),24-trien-3β-ol (agnosterol) (II; $R^1 = OH$, $R^2 = H$), and 5α-lanosta-7,9(11)-dien-3β-ol (dihydroagnosterol) (II; $R^1 = OH$, $R^2 = H$, 24,25-dihydro). Lanosterol and dihydrolanosterol normally

[1] E. Schulze, *Ber.*, 1872, **5**, 1075; 1873, **6**, 252; *J. prakt. Chem.*, 1873, **7**, 169.

[2] (*a*) J. C. Drummond and L. C. Baker, *J. Soc. Chem. Ind.*, 1929, **48**, 232; (*b*) A. Windaus and R. Tschesche, *Z. physiol. Chem.*, 1930, **190**, 51; (*c*) C. Doree and D. C. Garratt, *J. Soc. Chem. Ind.*, 1933, **52**, 141 and 355.

[3] L. Ruzicka, Ed. Rey, and A. C. Muhr, *Helv. Chim. Acta*, 1944, **27**, 472; J. F. McGhie, Ph.D. Thesis, London, 1947.

comprise at least 90% of the mixture. Of the various ways that have been devised for the fractionation of isocholesterol [2b,3,4] the method [5] involving the intermediate bromination of isocholesteryl acetate remains the most convenient to apply and the most efficient. We now report the details of this method together with some related experiments. Bloch and his co-workers [6] have independently described a similar, but in our hands less satisfactory, method in which it is isocholesterol rather than the corresponding acetate that is brominated.



Acetylation of commercial 'pure lanosterol' with acetic anhydride in pyridine afforded isocholesteryl acetate, which was dissolved in ether and treated with a solution of bromine in glacial acetic acid. The less soluble 24,25-dibromo-5α-lanost-8-en-3β-yl acetate isomer B (IIIB; R = Ac), m.p. 176—177°, $[\alpha]_D$ +6·8°, slowly separated from the reaction mixture in an essentially pure form in approximately 8% yield (if we assume [7] isocholesteryl acetate to contain 50% of 5α-lanosta-8,24-dien-3β-yl acetate). Further processing of the filtrate gave 24,25-dibromo-5α-lanost-8-en-3β-yl acetate isomer A (IIIA; R = Ac), m.p. 166—167°, $[\alpha]_D$ +47°, in approximately 62% yield. Material with the same constants was also obtained by bromination of pure 5α-lanosta-8,24-dien-3β-yl acetate. Barton and Carlisle and their co-workers [8] have recently shown that the two isomeric dibromides are initially formed in essentially equal amounts, and that a subsequent thermodynamic equilibration is responsible for the final five-fold predominance of isomer A. Proof that the two dibromides are simply C-24 stereoisomers (it is now known [8] that isomer A has the 24*S* absolute configuration) was obtained in two ways. First, reaction of either dibromide with ethanolic potassium hydroxide gave the same product, 24-bromo-5α-lanosta-8,24-dien-3β-ol (IV; R = H),[9] and secondly, debromination of (IIIA or B; R = Ac) by means of sodium iodide in acetone or zinc dust in benzene–methanol afforded 5α-lanosta-8,24-dien-3β-yl acetate (I; R^1 = OAc, R^2 = H). The latter reaction completes a route to pure 5α-lanosta-8,24-dien-3β-yl acetate, which, unlike material prepared by some other methods, is completely devoid of impurities containing the 7,9(11)-diene chromophore (u.v. spectroscopy). This increased purity is reflected in the lower rotations of 5α-lanosta-

[4] (*a*) J. F. Cavalla, Ph.D. Thesis, London, 1951; (*b*) M. Maienthal and P. J. Franklin, *J. Org. Chem.*, 1955, **20**, 1627.
[5] D. A. Lewis and J. F. McGhie, *Chem. and Ind.*, 1956, 550.
[6] K. Bloch, F. Gautschi, and J. D. Johnston, *J. Biol. Chem.*, 1957, **224**, 185.
[7] W. Voser, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 497.
[8] D. H. R. Barton, H. MacGrillen, P. D. Magnus, C. H. Carlisle, and P. A. Timmins, *J.C.S. Perkin I*, 1972, 1584. We thank Professor Barton for the communication of this information prior to publication.
[9] R. G. Curtis and H. Silberman, *J. Chem. Soc.*, 1952, 1187.

8,24-dien-3β-ol (I; R^1 = OH, R^2 = H) and its derivatives when prepared by the foregoing route (see Table).

Constants of 5α-lanosta-8,24-dien-3β-ol and derivatives

	This paper		Literature		
	M.p. (°C)	$[\alpha]_D$ (°)	M.p. (°C)	$[\alpha]_D$ (°)	Ref.
5α-Lanosta-8,24-dien-3β-ol (I; R^1 = OH, R^2 = H)	140	+57·7	138—140 139—140	+59·5 +62	4*b* 6
5α-Lanosta-8,24-dien-3β-yl acetate (I; R^1 = OAc, R^2 = H)	129—130	+57·1	127—128 130—131	+64 +64·3	6 †
5α-Lanosta-8,24-dien-3β-yl benzoate (I; R^1 = OCOPh, R^2 = H)	193—194	+66·9	192	+70·5	4*a*
5α-Lanosta-8,24-dien-3-one (I; R^1R^2 = O)	80—81	+74·6	87—89 81—82	+82 +81·7	6 †

† L. Ruzicka, R. Denss, and O. Jeger, *Helv. Chim. Acta*, 1945, **28**, 759.

In addition to their role in the fractionation of isocholesterol, the dibromides (IIIA and B; R = Ac) are valuable as synthetic intermediates. In particular they allow reactions to be carried out specifically at the sterically hindered 8,9-double bond whilst incorporating a functional group that makes subsequent regeneration of the 24,25-double bond a simple matter. For example, whereas the C-24 stereoisomers of the 24,25-monoepoxide (V) are readily available [10] from the controlled epoxidation of 5α-lanosta-8,24-dien-3β-yl acetate (I; R^1 = OAc, R^2 = H), the same is not true of the alternative 8α,9-monoepoxide (VI). However, treatment of the dibromide (IIIA or B; R = Ac) with perbenzoic acid in chloroform gives the 24,25-dibromo-8α,9-epoxide (VIIA or B, respectively), both of which are debrominated by zinc dust in benzene–methanol to afford 8α,9-epoxy-5α-lanost-24-en-3β-yl acetate (VI).

Under basic conditions the 24,25-dibromide grouping undergoes dehydrobromination to give a 24-bromo-24-ene. This should not be regarded as a disadvantage to the use of the former as a protecting group, since the latter function can itself be reconverted into the original 24,25-ene by the use of lithium in ammonia and has the added advantage that it is stable to a wide range of other reagents.[4b,11]

Oxidation of the dibromides (IIIA or B; R = Ac) with chromium trioxide in acetic acid gives the isomeric 24,25-dibromo-7,11-dioxo-5α-lanost-8-en-3β-yl acetates (VIIIA or B, respectively), which when treated with zinc dust in glacial acetic acid suffer debromination and reduction of the 8,9-double bond to give 7,11-dioxo-5α-lanost-24-en-3β-yl acetate (IX). The ready availability of compounds (VIII) and (IX) facilitates the synthesis of many oxygenated lanosterol derivatives in which the 24,25-double bond is still present. Wolff–Kishner reduction of the 7,11-diketone (IX) under forcing conditions [12] afforded the hitherto unprepared 5α-lanost-24-en-3β-ol (X).

Finally, since the isolation of agnosterol from isocholesterol is an exceedingly tedious and low-yielding process,[3] we sought to make this compound readily available by synthesis. This was achieved in excellent overall yield by debromination and dehydration of the 24,25-dibromo-8α,9-epoxides (VIIA or B). The two reactions can be applied in either order so that the intermediates are the 8α,9-epoxy-24-ene (VI) or the 24,25-dibromo-7,9(11)-dienes (XIA or B, respectively). The constants of this synthetic material suggested that it was purer than the material isolated by Ruzicka and his co-workers.[12]

EXPERIMENTAL

M.p.s were determined for samples in open tubes. Optical rotations refer to solutions in chloroform and u.v. spectra to solutions in absolute ethanol. N.m.r. data refer to solutions in deuteriochloroform with tetramethylsilane as internal standard. It is now known that the compounds referred to as isomers A and B are the 24*S*- and the 24*R*-isomer, respectively.[8]

Isocholesteryl Acetate.—Commercial 'pure lanosterol' † (300 g) in pyridine (300 ml) and acetic anhydride (1·2 l) was heated on a steam bath for 3 h, and then left to cool overnight. The solution was poured into ice–water (4 l). The precipitate was recrystallised from ethyl acetate–methanol to afford isocholesteryl acetate (250 g), m.p. 125—130°.

Bromination of Isocholesteryl Acetate.—A solution of isocholesteryl acetate (50 g) in ether (500 ml) was treated over 30 min with a solution of bromine (5·0 ml) in glacial acetic acid (270 ml), the temperature being maintained between 0 and 5° by means of an ice-bath. The mixture was left overnight at room temperature and then filtered to yield *24,25-dibromo-5α-lanost-8-en-3β-yl acetate isomer B* (IIIB; R = Ac) (3·0 g), m.p. 175—176° [m.p. 176—177° (from benzene–methanol)], $[\alpha]_D$ +6·8° (*c* 2·1), no absorption in the range 230—260 nm, τ 9·29 (3H, s, 13β-CH_3), 9·12 (9H, s, 4α-, 4β-, and 14α-CH_3), 8·99 (3H, s, 10β-CH_3), 8·15 (3H, s, 25-CH_3), 7·99 and 7·93 (each 3H, s, 25-CH_3 and acetate), 5·82 (1H, d, *J* 10 Hz), and 5·54 (1H, m, 3α-H) (Found: C, 61·3; H, 8·0; Br, 25·6. $C_{32}H_{52}Br_2O_2$ requires C, 61·1; H, 8·3; Br, 25·4%). A current of dry air was drawn through the filtrate until all the ether had been removed (4—5 h). The resulting crystalline precipitate was collected, washed with methanol, and air-dried to give material (34 g) of m.p. 141—146°. Three recrystallisations from benzene–methanol (1 : 1·8 v/v) yielded *24,25-dibromo-5α-lanost-8-en-3β-yl acetate isomer A* (IIIA; R = Ac) (20 g), m.p. 166—167°, $[\alpha]_D$ +47° (*c* 1·6), no absorption in the range 230—260 nm, τ 9·29 (3H, s, 13β-CH_3), 9·13 (9H, s, 4α-, 4β-, and 14α-CH_3), 9·00 (3H, s, 10β-CH_3), 8·17 (3H, s, 25-CH_3), 8·00 and 7·96 (each 3H, s, 25-CH_3 and acetate), 5·84 (1H, d, *J* 10 Hz), and 5·47 (1H, m, 3α-H) (Found: C, 61·3; H, 8·3; Br, 25·6. $C_{32}H_{52}Br_2O_2$ requires C, 61·1; H, 8·3; Br, 25·4%). This process yields consistent results even on a 500 g scale.

Bromination of 5α-Lanosta-8,24-dien-3β-yl Acetate.—A solution of the diene (5 g) in ether (60 ml) at 0—5° was

† Purchased from Croda Ltd., Cowick Hall, Snaith, Goole, Yorkshire.

[10] R. B. Boar, D. A. Lewis, and J. F. McGhie, *J.C.S. Perkin I*, 1972, 2231.

[11] D. H. R. Barton and D. Kumari, *Annalen*, 1970, **737**, 108.

[12] L. Ruzicka, R. Denss, and O. Jeger, *Helv. Chim. Acta*, 1946, **29**, 204.

treated with bromine (0·5 ml) in glacial acetic acid (28 ml). The slight precipitate that formed towards the end of the addition was dissolved by gentle warming and the solution was then left overnight at room temperature. Filtration gave 24,25-dibromo-5α-lanost-8-en-3β-yl acetate isomer B (800 mg after one recrystallisation from chloroform–methanol), m.p. 176—177°, $[\alpha]_D$ +6·6 (*c* 1·5). Treatment of the filtrate as before afforded isomer A (3·1 g), m.p. 166—167°, $[\alpha]_D$ +48° (*c* 1·2).

Dehydrobromination of the Dibromides (IIIA and B; R = Ac).—The dibromide (IIIB; R = Ac) (700 mg) in benzene (20 ml) was treated with ethanolic N-potassium *hydroxide* (100 ml). The solution was refluxed for 3 h, then evaporated to small bulk and poured into N-hydrochloric acid. The mixture was extracted with ether and the combined extracts were washed thoroughly with water, dried, and evaporated. The residue was recrystallised from chloroform–methanol to yield 24-bromo-5α-lanosta-8,24-dien-3β-ol (IV; R = H) (450 mg, 80%), m.p. 199—200°, $[\alpha]_D$ +49·8° (*c* 0·80) (lit.,[9] m.p. 196—198°, $[\alpha]_D$ +51·4°) (Found: C, 71·1; H, 9·6; Br, 15·9. Calc. for $C_{30}H_{49}BrO$: C, 71·3; H, 9·8; Br, 15·8%). The 3-acetate (IV; R = Ac) had m.p. (from acetone) 186—187°, $[\alpha]_D$ +49·4° (*c* 1·1) (lit.,[4b] m.p. 181—182°) (Found: C, 70·5; H, 9·2; Br, 14·5. Calc. for $C_{32}H_{51}BrO_2$: C, 70·2; H, 9·4; Br, 14·5%). A similar treatment of the dibromide (IIIA; R = Ac) gave identical products (mixed m.p.s).

Debromination of the Dibromides (IIIA and B; R = Ac).—(i) *With sodium iodide.* A solution of the dibromide (IIIA or B; R = Ac) (1·0 g) and sodium iodide (3·4 g) in acetone (100 ml) was refluxed for 8 h. The solution was evaporated to *ca.* 25 ml and poured into sodium thiosulphate solution. The product was extracted into ether and washed thoroughly with water. Crystallisation from benzene–methanol gave 5α-lanosta-8,24-dien-3β-yl acetate (I; R^1 = OAc, R^2 = H) (620 mg, 83%), m.p. 129—130°, $[\alpha]_D$ +56·8° (*c* 1·2) (Found: C, 81·9; H, 11·2. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%).

(ii) *With zinc dust.* AnalaR zinc dust (16 g) was added over 4 h to a refluxing solution of the dibromide (IIIA or B; R = Ac) (8 g) in benzene–methanol (360 ml; 5 : 1 v/v). The mixture was filtered and the residual zinc was washed thoroughly with boiling benzene. The combined filtrates were washed with water and then evaporated. Crystallisation from benzene–methanol afforded 5α-lanosta-8,24-dien-3β-yl acetate (I; R^1 = OAc, R^2 = H) (5·5 g, 92%), m.p. 129—130°, $[\alpha]_D$ +57·1° (*c* 1·1), τ 9·32 (3H, s, 13β-CH_3), 9·16 (9H, s, 4α-, 4β-, and 14α-CH_3), 9·01 (3H, s, 10β-CH_3), 8·39 and 8·31 (each 3H, s, 25-CH_3), 7·98 (3H, s, acetate), 5·5 (1H, m, 3α-H), and 4·95 (1H, t, 24-H).

5α-Lanosta-8,24-dien-3β-ol (I; R^1 = OH, R^2 = H).—The acetate (I; R^1 = OAc, R^2 = H) (1·5 g) was hydrolysed by refluxing with 10% ethanolic potassium hydroxide (50 ml) for 2 h. The resulting alcohol had m.p. 140° (from chloroform–methanol), $[\alpha]_D$ +57·7° (*c* 1·7) (Found: C, 84·1; H, 11·6. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%).

5α-Lanosta-8,24-dien-3β-yl Benzoate (I; R^1 = OBz, R^2 = H).—A solution of the alcohol (I; R^1 = OH, R^2 = H) (2·5 g) and benzoyl chloride (5 ml) in dry pyridine (40 ml) was heated on a steam-bath for 2 h, poured into water, and extracted with ether. The extracts were washed successively with water, 2N-sulphuric acid, 2N-potassium hydroxide, and water. The benzoate had m.p. 193—194° (from chloroform–methanol), $[\alpha]_D$ +66·9° (*c* 1·0).

5α-Lanosta-8,24-dien-3-one (I; R^1R^2 = O).—A solution of the alcohol (I; R^1 = OH, R^2 = H) (300 mg) in acetic acid–benzene (80 ml; 1 : 1 v/v) was stirred vigorously and treated with Kiliani's chromic acid (3 ml) over 15 min. After a further 15 min the mixture was poured into sodium disulphite solution, and extracted with ether. The extracts were washed thoroughly with sodium carbonate solution, then water, and evaporated. The residue was taken up in benzene and filtered through a short alumina column. Crystallisation from acetone–methanol yielded the ketone, m.p. 80—81°, $[\alpha]_D$ +74·6° (*c* 0·90).

Similarly, the alcohol (IV; R = H) afforded *24-bromo-5α-lanosta-8,24-dien-3-one*, m.p. (from chloroform–methanol) 158—159°, $[\alpha]_D$ +63·5° (*c* 0·7) (Found: C, 71·1; H, 9·5; Br, 16·0. $C_{30}H_{47}BrO$ requires C, 71·5; H, 9·4; Br, 15·9%).

Epoxidation of the Dibromides (IIIA and B; R = Ac).—The dibromide (IIIB; R = Ac) (2 g) in chloroform (10 ml) was treated with perbenzoic acid in chloroform (10 ml; 1·1 mol. equiv.) at 0° for 2 days. The solution was washed thoroughly with 2N-sodium hydroxide, then with water, and evaporated. Crystallisation of the residue from chloroform–methanol gave *24,25-dibromo-8α,9-epoxy-5α-lanostan-3β-yl acetate isomer B* (VIIB) (1·8 g, 79%), m.p. 190°, $[\alpha]_D$ −26° (*c* 1·7), no absorption in the range 230—260 nm, τ 9·21 (3H, s, 13β-CH_3), 9·18 (3H, s, 4α-CH_3), 9·16 (3H, s, 4β-CH_3), 9·10 (3H, s, 10β-CH_3), 8·88 (3H, s, 14α-CH_3), 8·19 (3H, s, 25-CH_3), 8·03 and 7·99 (each 3H, s, 25-CH_3 and acetate), 5·85 (1H, d, *J* 10 Hz), and 5·55 (1H, m, 3α-H) (Found: C, 59·5; H, 8·2; Br, 24·7. $C_{32}H_{52}Br_2O_3$ requires C, 59·6; H, 8·1; Br, 24·8%). Similarly, the dibromide (IIIA; R = Ac) afforded 24,25-dibromo-8α,9-epoxy-5α-lanostan-3β-yl acetate isomer A (VIIA), double m.p. 159 and 190°, $[\alpha]_D$ +31° (*c* 1·3).

8α,9-Epoxy-5α-lanost-24-en-3β-yl Acetate (VI).—AnalaR zinc dust (1 g) was added to a solution of 24,25-dibromo-8α,9-epoxy-5α-lanostan-3β-yl acetate isomer A or B (1 g) in benzene–methanol (60 ml; 5 : 1 v/v) and the mixture was heated under reflux for 2 h. More zinc dust (1 g) was then added, and the refluxing was continued for a further 2 h. The solution was filtered and the zinc was washed thoroughly with hot benzene. The combined filtrates were washed with water and then evaporated. Crystallisation of the residue from chloroform–methanol afforded needles of *8α,9-epoxy-5α-lanost-24-en-3β-yl acetate* (500 mg), m.p. 146—147°, $[\alpha]_D$ +30·5° (*c* 0·57), τ 9·22 (3H, s, 13β-Me), 9·18 (3H, s, 4α-Me), 9·15 (3H, s, 4β-Me), 9·12 (3H, s, 10β-Me), 8·85 (3H, s, 14α-Me), 8·37 and 8·28 (each 3H, s, 25-Me), and 4·9 (1H, t, 24-H) (Found: C, 79·3; H, 10·6. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%).

Oxidation of the Dibromides (IIIA and B; R = Ac).—The dibromide (IIIA; R = Ac) (5 g) was dissolved in chloroform (5 ml) and glacial acetic acid (85 ml) was added. The suspension was stirred whilst a solution of chromium trioxide (5 g) in 90% acetic acid (50 ml) was added during 3 min. The temperature rose to 40°. The mixture was left at room temperature for 14 h, then poured into sodium disulphite solution and extracted with ether. The combined extracts were washed with 2N-sodium hydroxide solution, then water, and evaporated. Crystallisation of the residue from chloroform–methanol gave yellow needles of *24,25-dibromo-7,11-dioxo-5α-lanost-8-en-3β-yl acetate isomer A* (VIIIA) (2·8 g, 53%), m.p. 197—199°, $[\alpha]_D$ +99·6° (*c* 0·60), $\lambda_{max.}$ 271 nm (log ε 3·98) (Found: C, 58·2; H, 7·6; Br, 24·6. $C_{32}H_{48}Br_2O_4$ requires C, 58·5; H, 7·4; Br, 24·3%). Similarly, the dibromide (IIIB; R = Ac) afforded 24,25-dibromo-7,11-dioxo-5α-lanost-8-en-3β-yl acetate isomer B (VIIIB), m.p. 192—193°, $[\alpha]_D$ +26·7°.

7,11-*Dioxo*-5α-*lanost*-24-*en*-3β-*yl Acetate* (IX).—AnalaR zinc dust (1 g) was added in portions over 3 h to a refluxing solution of the dibromo-diketone (VIIIA or B; R = Ac) (500 mg) in glacial acetic acid. The mixture was filtered and the zinc was washed thoroughly with hot acetic acid. The combined filtrates were poured into water and extracted with ether. The extracts were washed with sodium carbonate solution, then water, and evaporated. Crystallisation of the residue from dichloromethane–methanol gave 7,11-dioxo-5α-lanost-24-en-3β-yl acetate (360 mg, 95%), m.p. 204—205°, $[\alpha]_D$ +58·2° (*c* 1·3) (lit.,[7] m.p. 203—204°, $[\alpha]_D$ +58°).

3β-*Hydroxy*-5α-*lanost*-24-*ene*-7,11-*dione*.—The acetate (IX) was hydrolysed with methanolic 5% potassium hydroxide to give the 3β-*alcohol*, m.p. 215—216°, $[\alpha]_D$ +57·3° (*c* 0·70) (Found: C, 78·8; H, 10·5. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

5α-*Lanost*-24-*ene*-3,7,11-*trione*.—The foregoing 3β-alcohol was oxidised with Kiliani's chromic acid to give the corresponding 3-*ketone*, m.p. 155—156°, $[\alpha]_D$ +50·5 (*c* 0·38) (Found: C, 79·1; H, 10·1. $C_{30}H_{46}O_3$ requires C, 79·2; H, 10·2%).

Dehydrobromination of the Dibromo-diketones (VIIIA and B).—The dibromo-diketone (VIIIA or B) was treated with ethanolic N-potassium hydroxide as described for the dibromide (IIIA; R = Ac). The resultant 24-*bromo*-3β-*hydroxy*-5α-*lanosta*-8,24-*diene*-7,11-*dione* was crystallised from chloroform–methanol; m.p. 241—242°, $[\alpha]_D$ +79·9° (*c* 0·77), $\lambda_{max.}$ 271 nm (log ε 3·91) (Found: C, 67·6; H, 8·5; Br, 14·8. $C_{30}H_{45}BrO_3$ requires C, 67·5; H, 8·5; Br, 15·0%). The 3β-*acetate* had m.p. 196°, $[\alpha]_D$ +76·2° (*c* 0·67), $\lambda_{max.}$ 270 nm (log ε 3·85) (Found: C, 66·6; H, 8·1; Br, 13·7. $C_{32}H_{47}BrO_4$ requires C, 66·7; H, 8·2; Br, 13·9%).

24-*Bromo*-5α-*lanosta*-8,24-*diene*-3,7,11-*trione*.— Oxidation of the foregoing 3β-alcohol with Kiliani's chromic acid gave the 3-*ketone*, m.p. 206—207°, $[\alpha]_D$ +142·5° (*c* 0·21), $\lambda_{max.}$ 270 nm (log ε 3·82) (Found: C, 68·0; H, 8·2; Br, 15·0. $C_{30}H_{43}BrO_3$ requires C, 67·8; H, 8·15; Br, 15·0%).

Reduction of the three last-mentioned products with zinc dust in glacial acetic acid exactly as described for the dibromo-diketone (VIIIA; R = Ac) gave, respectively, 24-*bromo*-3β-*hydroxy*-5α-*lanost*-24-*ene*-7,11-*dione*, m.p. 246—247°, $[\alpha]_D$ +42·8° (*c* 0·33) (Found: C, 67·3; H, 8·8; Br, 15·4. $C_{30}H_{47}BrO_3$ requires C, 67·3; H, 8·8; Br, 14·9%), 24-*bromo*-7,11-*dioxo*-5α-*lanost*-24-*en*-3β-*yl acetate*, m.p. 226—227°, $[\alpha]_D$ +45·4° (*c* 0·45) (Found: C, 66·3; H, 8·4; Br, 13·9. $C_{32}H_{49}BrO_4$ requires C, 66·5; H, 8·55; Br, 13·8%), and 24-*bromo*-5α-*lanost*-24-*ene*-3,7,11-*trione*, m.p. 206°, $[\alpha]_D$ +36·9° (*c* 0·61) (Found: C, 67·4; H, 8·6; Br, 15·1. $C_{30}H_{45}BrO_3$ requires C, 67·5; H, 8·5; Br, 15·0%).

24,25-*Dibromo*-5α-*lanosta*-7,9(11)-*dien*-3β-*yl Acetate Isomers A and B* (XI).—A solution of the dibromo-epoxide (VIIA) (200 mg) in dry benzene (10 ml) was treated under reflux with boron trifluoride–ether complex (0·3 ml) for 3 min. The solution was diluted with ether, washed with sodium carbonate solution, then water, and evaporated. Crystallisation of the residue from dichloromethane–methanol yielded 24,25-*dibromo*-5α-*lanosta*-7,9(11)-*dien*-3β-*yl acetate isomer A* (XIA) (150 mg, 77%), m.p. 178—179°, $[\alpha]_D$ +66·2° (*c* 1·6), $\lambda_{max.}$ 236, 243, and 252 nm (log ε 4·24, 4·31, and 4·13) (Found: C, 61·6; H, 8·1; Br, 25·4. $C_{32}H_{50}Br_2O_2$ requires C, 61·3; H, 8·0; Br, 25·55%). Similarly, the dibromo-epoxide (VIIB) afforded isomer B (XIB), m.p. 194—195°, $[\alpha]_D$ +37·0° (*c* 1·1), $\lambda_{max.}$ 236, 243, and 252 nm (log ε 4·24, 4·31, and 4·13).

5α-*Lanosta*-7,9(11),24-*trien*-3β-*yl* (*Agnosteryl*) *Acetate* (II; R^1 = OAc, R^2 = H).—*Method* (i). Debromination of the dibromide (XIA or B) with zinc dust as described for the dibromide (IIIA; R = Ac) afforded the required triene, m.p. 186—187°, $[\alpha]_D$ +92·1° (*c* 0·83) (lit.,[12] m.p. 174—175°, $[\alpha]_D$ +87·8°), $\lambda_{max.}$ 236, 243, and 252 nm (log ε 4·19, 4·26, and 4·09) (Found: C, 82·3; H, 10·7. Calc. for $C_{32}H_{50}O_2$: C, 82·3; H, 10·8%).

Method (ii). A solution of the 8α,9-epoxide (VI) (1 g) in ether (30 ml) was shaken with constant boiling 48% hydrobromic acid (2 ml) for 30 min. Water (10 ml) was added and the aqueous layer separated. The organic layer was washed with 2N-sodium carbonate solution, then water, dried, and evaporated. Crystallisation of the residue from chloroform–methanol gave the triene (900 mg, 93%) as lustrous plates, m.p. 186—187°, $[\alpha]_D$ +92·3° (*c* 1·0).

5α-*Lanosta*-7,9(11),24-*trien*-3β-*ol* (II; R^1 = OH, R^2 = H).—The acetate (II; R^1 = OAc, R^2 = H) was hydrolysed by refluxing with ethanolic 10% potassium hydroxide in the presence of sufficient benzene to ensure homogeneity. The resulting alcohol had m.p. 168—169°, $[\alpha]_D$ +69·0 (*c* 1·2) (lit.,[12] m.p. 164—165°, $[\alpha]_D$ +65·9°), $\lambda_{max.}$ 236, 243, and 252 nm (log ε 4·24, 4·29, and 4·13) (Found: C, 84·7; H, 11·2. Calc. for $C_{30}H_{48}O$: C, 84·8; H, 11·4%).

5α-*Lanosta*-7,9(11),24-*trien*-3-*one* (II; R^1R^2 = O).—Oxidation of the alcohol (II; R^1 = OH, R^2 = H) with Kiliani's chromic acid gave the 3-ketone, m.p. 97°, $[\alpha]_D$ +47·1° (*c* 0·42) (lit.,[12] m.p. 93—94°, $[\alpha]_D$ +47·2 and +51·6°), $\lambda_{max.}$ 236, 243, and 252 nm (log ε 4·22, 4·28, and 4·11) (Found: C, 85·3; H, 10·8. Calc. for $C_{30}H_{46}O$: C, 85·2; H, 11·0%).

24-*Bromo*-8α,9-*epoxy*-5α-*lanost*-24-*en*-3β-*ol*.—The dibromo-epoxide (VIIA or B) was treated with ethanolic N-potassium hydroxide as described for the dibromide (IIIA; R = Ac). The resultant 24-*bromo*-8α,9-*epoxy*-5α-*lanost*-24-*en*-3β-*ol* had m.p. 164—165°, $[\alpha]_D$ +1·9° (*c* 1·9), no absorption in the region 230—260 nm (Found: C, 69·0; H, 9·5; Br, 15·5. $C_{30}H_{49}BrO_2$ requires C, 69·1; H, 9·5; Br, 15·3%).

Dehydrobromination of the Dibromides (XIA and B).—The dibromide (XIA or B) was treated with ethanolic N-potassium hydroxide as described for the dibromide (IIIA; R = Ac) except that sufficient benzene was added to ensure homogeneity. The 24-*bromo*-5α-*lanosta*-7,9(11),24-*trien*-3β-*ol* thus obtained had m.p. 206—207°, $[\alpha]_D$ +58·9° (*c* 1·2), $\lambda_{max.}$ 236, 243, and 252 nm (log ε 4·11, 4·20, and 4·07) (Found: C, 71·4; H, 9·4; Br, 15·75. $C_{30}H_{47}BrO$ requires C, 71·5; H, 9·4; Br, 15·9%). Identical material was obtained by the action of boron trifluoride–ether complex on 24-bromo-8α,9-epoxy-5α-lanost-24-en-3β-ol. Acetylation gave 24-*bromo*-5α-*lanosta*-7,9(11),24-*trien*-3β-*yl acetate*, m.p. 222—223°, $[\alpha]_D$ +81·3° (*c* 0·99), $\lambda_{max.}$ 236, 243, and 252 nm (log ε 4·17, 4·24, and 4·10) (Found: C, 70·2; H, 9·0; Br, 14·5. $C_{32}H_{49}BrO_2$ requires C, 70·4; H, 9·05; Br, 14·65%), and oxidation with Kiliani's chromic acid afforded 24-*bromo*-5α-*lanosta*-7,9(11),24-*trien*-3-*one*, m.p. 188—189°, $[\alpha]_D$ +22·5° (*c* 0·68), $\lambda_{max.}$ 236, 243, and 252 nm (log ε 4·15, 4·21, and 4·09) (Found: C, 71·8; H, 8·8; Br, 16·1. $C_{30}H_{45}BrO$, requires C, 71·8; H, 9·0; Br, 15·9%).

5α-*Lanost*-24-*en*-3β-*ol* (X).—Sodium (2 g) was dissolved in redistilled diethylene glycol (200 ml). The solution was heated to 180° and anhydrous hydrazine was distilled in until the former refluxed freely at 180°. The solution was cooled, 7,11-dioxo-5α-lanost-24-en-3β-yl acetate (6·4 g) was added, and the mixture was then refluxed for 17 h. Hydrazine was then distilled out until the reflux temperature had risen to 210°. After a further 24 h at this temperature

the solution was cooled and poured into 50% hydrochloric acid (1 l). The mixture was extracted with ether and ethyl acetate. The combined extracts were washed with water and evaporated. Crystallisation of the residue from chloroform–methanol gave *5α-lanost-24-en-3β-ol* (4·15 g, 75%), m.p. 168—169°, $[\alpha]_D$ +31·2° (*c* 1·0) (Found: C, 84·0; H, 12·0; $C_{30}H_{52}O$ requires C, 84·0; H, 12·2%); the 3-*acetate* had m.p. 160—161°, $[\alpha]_D$ +38·6° (*c* 2·4) (Found: C, 81·6; H, 11·7. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·6%).

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