Triterpenoids. Part XVII. The Transformation of Lanostadienol (Lanosterol) into 14-Methylcholestan-3β-ol.†*

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[Reprint Order No. 4800.]

Lanostanol has been transformed, by stepwise contraction and expansion of ring A, into 14-methylcholest-4-en-3-one and thence into 14-methylcholestan-3β-ol. An alternative route for the modification of the triterpenoid ring A has been explored. Molecular-rotation data are briefly discussed.

This paper is concerned with continued studies on the conversion of the triterpenoid lanostadienol (I) into 14-methylated steroids (cf. Barton and Thomas, *Chem. and Ind.*, 1953, 172; *J.*, 1953, 1842; Voser, Heusser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1953, **36**, 299).

Treatment of lanostanol (II) (Voser, Montavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893; McGhie, Pradhan, and Cavalla, *J.*, 1952, 3176) with phosphorus pentachloride afforded the olefin (III), which on ozonolysis at −60° furnished the derived ketone, 14-methyl-A-norcoprostan-3-one (IV). This showed an infra-red maximum at 1738 cm.$^{-1}$ (five-ring ketone) in agreement with the assigned constitution. Ring expansion of this compound was achieved by the elegant procedure of Voser, White, Heusser, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1952, **35**, 830). Reaction with excess of methylmagnesium iodide gave the tertiary alcohol (V). This was not crystalline, so it was at once dehydrated with fuller's earth to furnish a mixture of olefins containing (VI). Treatment of the olefin mixture with osmium tetroxide followed by cleavage of the derived osmate with lithium aluminium hydride gave the crystalline glycol (VII). We would emphasise the use of lithium aluminium hydride in this connection, as it provides a more convenient method of processing osmates than those currently in use: it has been employed by us on a number of occasions. Fission of the glycol (VII) with lead tetra-acetate followed by base-catalysed cyclisation afforded the desired 14-methylcholest-4-en-3-one (VIII), characterised as the 2 : 4-dinitrophenylhydrazone.

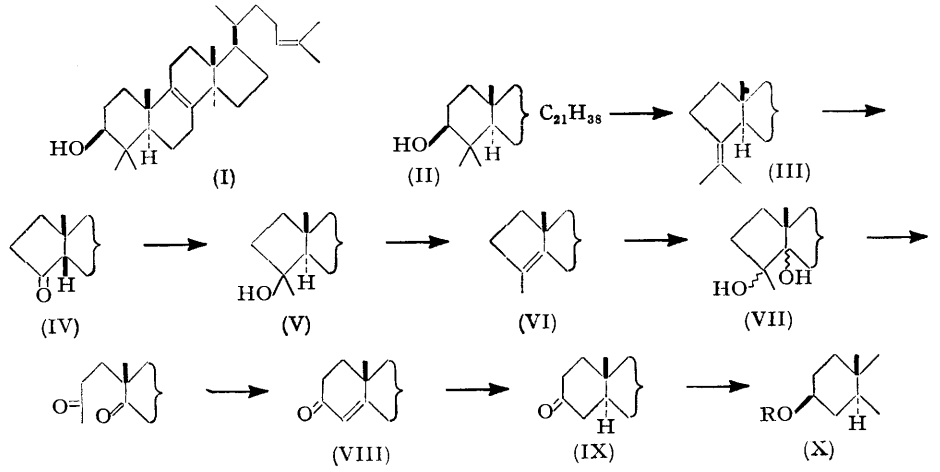
Preliminary experiments showed that reduction of cholest-4-en-3-one by lithium and liquid ammonia (Wilds and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5360) gave a good yield of cholestanone and that similar reduction of stigmasta-4 : 22-dien-3-one and of ergosta-4 : 22-dien-3-one likewise afforded satisfactory routes to stigmast-22-en-3-one (Barton and Brooks, *J. Amer. Chem. Soc.*, 1950, **72**, 1633) and ergost-22-en-3-one (Barton, Cox, and Holness, *J.*, 1949, 1771) respectively. By this method (VIII) was smoothly reduced to

* Part XVI, preceding paper.

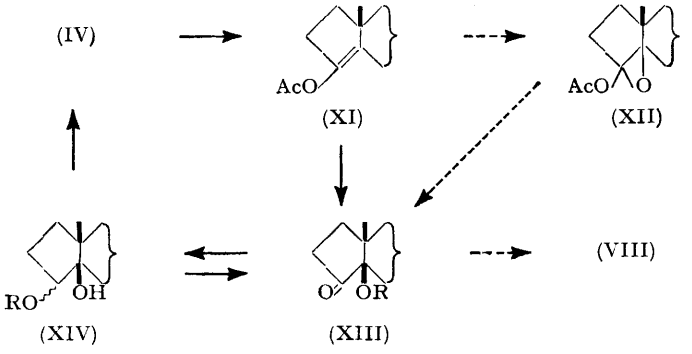
† The results in part have been summarised in a preliminary communication (*Chem. and Ind.*, 1953, 1180).

14-methylcholestan-3-one (IX), whence by lithium aluminium hydride reduction the desired 14-methylcholestan-3β-ol (X; R = H), characterised as the acetate, was obtained. The configuration assigned is based on molecular-rotation considerations (see below) and upon sound analogy (Shoppee and Summers, *J.*, 1950, 687).

We have taken the occasion to explore an alternative route for the conversion of the triterpenoid ring A into the Δ^4-3-one system characteristic of many physiologically



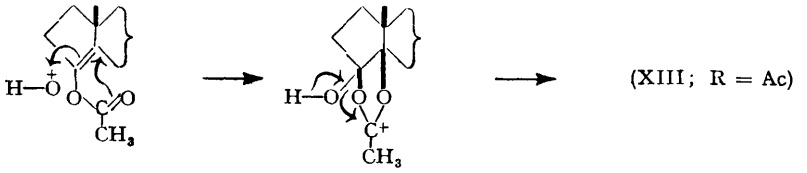
important steroids. Treatment of 14-methyl-A-norcoprostan-3-one (IV) with acetic anhydride and perchloric acid in carbon tetrachloride (Barton, Evans, Hamlet, Jones, and Walker, *J.*, 1954, 747) gave the derived enol acetate (XI), showing characteristic bands in the infra-red at 1760 and 1204 cm.$^{-1}$. It was then intended to follow the route indicated by the broken arrows, which is based in part on the elegant process of Kritchevsky, Garmaise, and Gallagher, *J. Amer. Chem. Soc.*, 1952, **74**, 483) for the elaboration of the



adrenocortical side chain. However treatment of (XI) with perphthalic acid afforded, with uptake of one mol. of oxidant, not the expected epoxide (XII), but a compound shown to have the rearranged structure (XIII; R = Ac) on the basis of the following evidence.* The ultra-violet absorption spectrum showed a distinct ketonic band at 303 mμ (ε 80), not altered on repeated fractionation. The infra-red spectrum revealed a broad, unsymmetrical, band at 1760 cm.$^{-1}$ indicative, by its intensity, of an acetate and of a *cyclo*pentanone, one or both bands being somewhat displaced. The presence of the acetate residue was confirmed by a band at 1232 cm.$^{-1}$. Attempted alkaline hydrolysis gave only amorphous products, but reduction with lithium aluminium hydride furnished the glycol (XIV; R = H), converted into the monoacetate (XIV; R = Ac) by pyridine–

* Dr. T. F. Gallagher of the Sloan-Kettering Institute for Cancer Research (New York) has very kindly informed us that he has observed an analogous rearrangement in the steroid series.

acetic anhydride. Oxidation of (XIV; R = H) with chromic acid afforded the keto-alcohol (XIII; R = H), which was recognised as a *cyclo*pentanone (infra-red maximum at 1740 cm.$^{-1}$) and as a tertiary alcohol (infra-red maxima at 3620 and 3500 cm.$^{-1}$; resistance to chromic acid oxidation). Acetylation of this keto-alcohol with acetic anhydride–perchloric acid gave (XIII; R = Ac), identical with the compound obtained directly from (XI); similar treatment of (XIV; R = H) furnished, not unexpectedly, the parent *cyclo*pentanone (IV). Attempts to convert (XIII; R = H or Ac) into (VII) and



thence into (VIII) by using either methylmagnesium iodide or methyl-lithium have not, so far, proved efficacious. The assignment of the β-configuration to the $C_{(5)}$-hydroxyl group in (XIII and XIV; R = H) is based on molecular-rotation considerations (Klyne, *J.*, 1952, 2916). The interesting rearrangement disclosed by our experiments presumably proceeds according to the annexed scheme.

The availability of 14-methylated steroids suggests that a comparison of molecular rotations might prove instructive. The data summarised in the Table show that, as would be expected from our previous work (Barton and Cox, *J.*, 1948, 783), significant vicinal effects can only be detected in the case of the 14-methylcholest-4-en-3-one (VIII).

	$[M]_D$						
Alcohol	Alcohol	Acetate	Derived 3-one	Derived Δ^4-3-one	Δ_1	Δ_2	Δ_3
Cholestan-3β-ol [a]	+ 89°	+ 60°	+162°	+357°	−29°	+73°	+268°
14-Methylcholestan-3β-ol [b]	+157	+120	+244	+460	−37	+87	+303

[a] Barton and Cox, *J.*, 1948, 783. [b] Experimental section.

14-Methylcholestenone has also been prepared independently of our work by Dr. O. Jeger and his collaborators in the laboratories of the Eidgenossische Technische Hochschule, Zürich. We express our cordial appreciation to Dr. Jeger for this information.

Experimental

For general experimental see Part VII (*J.*, 1952, 2339). Rotations were determined in $CHCl_3$ solution. All ultra-violet absorption spectra were taken in ethanol solution, with a Unicam S.P. 500 Spectrophotometer. Infra-red spectra were kindly determined by Messrs. Glaxo Laboratories Ltd., using carbon disulphide as solvent.

14-*Methyl*-3-iso*propylidene*-A-*norcholestane* (III).—Lanostanol (1·1 g.) in light petroleum (b. p. 60—80°) (100 ml.) was stirred at 0° with phosphorus pentachloride (700 mg.) for 30 min. Filtration of the product in light petroleum (b. p. 40—60°) through alumina gave 14-*methyl*-3-iso*propylidene* A-*norcholestane* (III) (800 mg.). Recrystallised from chloroform–methanol, this had m. p. 110—112°, $[\alpha]_D$ +33° (*c*, 2·2) (Found: C, 87·05; H, 12·5. $C_{30}H_{52}$ requires C, 87·3; H, 12·7%).

14-*Methyl*-A-*norcoprostan*-3-*one* (IV).—The above-mentioned olefin (200 mg.) in methylene dichloride (20 ml.) at −60° was ozonised until the solution no longer gave a colour with tetranitromethane, then was diluted with acetic acid (5 ml.) and stirred with zinc dust at 0°. The product was filtered in benzene solution through alumina, to give 14-*methyl*-A-*norcoprostan*-3-*one* (IV) (170 mg.). Recrystallised from methanol this had m. p. 124—125°, $[\alpha]_D$ +142° (*c*, 1·7) (Found: C, 83·8; H, 12·05. $C_{27}H_{46}O$ requires C, 83·85; H, 12·0%).

3 : 14-*Dimethyl*-A-*norcholestane*-3 : 5-*diol* (VII).—14-Methyl-A-norcoprostan-3-one (1·0 g.) was treated with methylmagnesium iodide and the product dehydrated with activated fuller's earth according to the directions of Voser *et al.* (*loc. cit.*). The resulting olefinic material (370 mg.) was treated with osmium tetroxide (250 mg.) in dry ether (50 ml.) for 24 hr. at room temperature. Excess of lithium aluminium hydride in ethereal solution was added and the mixture refluxed on the steam-bath for 2 hr., to give 3 : 14-*dimethyl*-A-*norcholestane*-3 : 5-*diol*

(VII), m. p. 155—157° (from methanol), $[\alpha]_D$ +35° (*c*, 1·6) (Found: C, 80·15; H, 11·75. $C_{28}H_{50}O_2$ requires C, 80·3; H, 12·05%).

14-*Methylcholest*-4-*en*-3-*one* (VIII).—3 : 14-Dimethyl-A-norcholestane-3 : 5-diol (100 mg.) in acetic acid (5 ml.) containing lead tetra-acetate (140 mg.) was left at room temperature. The uptake of 1 mol. of the oxidant was complete within 30 min. The product was treated with sodium methoxide in methanol (25 ml.; 3%) for 2 hr. at room temperature, the cyclisation of the intermediate diketone being followed spectroscopically. Chromatography over alumina and elution with 9 : 1 benzene–ether afforded 14-*methylcholest*-4-*en*-3-*one* (30 mg.). Recrystallised from methanol this had m. p. 113—114°, $[\alpha]_D$ +116° (*c*, 1·0), $\lambda_{max.}$ 241 mμ (ε 14,500) (Found: C, 83·95; H, 11·5. $C_{28}H_{46}O$ requires C, 84·35; H, 11·6%). The derived 2 : 4-*dinitrophenylhydrazone*, prepared in the usual way and recrystallised from chloroform–methanol, had m. p. 240—241°, $\lambda_{max.}$ 392 mμ (in $CHCl_3$; ε 21,000) (Found: N, 9·7. $C_{34}H_{52}O_4N_4$ requires N, 9·65%).

14-*Methylcholestan*-3β-*ol* (X; R = H).—14-Methylcholest-4-en-3-one (see above) (100 mg.) in dry ether (20 ml.) was added to a solution of lithium (50 mg.) in liquid ammonia (50 ml.) and the solution stirred for 20 min. Filtration of the product through alumina and elution with 1 : 1 light petroleum (b. p. 40—60°)–benzene gave 14-*methylcholestan*-3-*one* (IX) (70 mg.). Recrystallised from chloroform–methanol, this had m. p. 161—162°, $[\alpha]_D$ +61° (*c*, 1·33) (Found: C, 83·6; H, 12·25. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%).

Reduction of this ketone (250 mg.) in dry ether (20 ml.) with lithium aluminium hydride (250 mg.) in the same solvent (40 ml.) under reflux for 2 hr. gave 14-*methylcholestan*-3β-*ol* (X; R = H), m. p. 144—145° (from methanol), $[\alpha]_D$ +39° (*c*, 1·29) (Found: C, 83·3; H, 12·6. $C_{28}H_{50}O$ requires C, 83·5; H, 12·5%). Treatment with pyridine–acetic anhydride on the steam bath for 1 hr. gave the corresponding *acetate* (X; R = Ac), m. p. 98—99° (from aqueous ethanol), $[\alpha]_D$ +27° (*c*, 1·23) (Found: C, 81·2; H, 12·0. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

14-*Methyl*-A-*norcholest*-3(5)-*en*-3-*yl Acetate* (XI).—14-Methyl-A-norcoprostan-3-one (see above) (500 mg.) in carbon tetrachloride (20 ml.), treated with acetic anhydride (1 ml.) containing perchloric acid (4 drops; 70%) for 15 min. at room temperature, gave 14-*methyl*-A-*norcholest*-3(5)-*en*-3-*yl acetate* (XI), m. p. 111—112° (from methanol), $[\alpha]_D$ +86° (*c*, 1·9) (Found: C, 80·85; H, 11·35. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%). This enol acetate (500 mg.) in chloroform (10 ml.) was treated with ethereal perphthalic acid (10 ml.; excess) for 2 hr. at room temperature (uptake of 1 mol. of oxidant), to give 14-*methyl*-3-*oxo*-A-*norcoprostan*-5β-*yl acetate* (XIII; R = Ac). Recrystallised from methanol this had m. p. 139—140°, $[\alpha]_D$ +156° (*c*, 2·4), $\lambda_{max.}$ 303 mμ (ε 80) (Found: C, 78·4; H, 10·9. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%). For larger-scale preparation of this compound, the total enol acetylation product was treated with perphthalic acid, to give the ketone acetate in about 60% overall yield.

14-*Methyl*-A-*norcoprostane*-3 : 5β-*diol* (XIV; R = H) *and its Derivatives*.—14-Methyl-3-oxo-A-norcoprostan-5β-yl acetate (see above) (100 mg.) in dry ether (10 ml.) was added to a solution of lithium aluminium hydride (100 mg.) in dry ether (40 ml.) and the mixture refluxed for 3 hr., to give 14-*methyl*-A-*norcoprostane*-3 : 5β-*diol* (XIV; R = H). Recrystallised as long needles from chloroform–light petroleum (b. p. 40—60°), this had m. p. 188—195°, $[\alpha]_D$ +30° (*c*, 1·15) (Found: C, 80·3; H, 12·1. $C_{27}H_{48}O_2$ requires C, 80·15; H, 11·95%). Treatment with pyridine–acetic anhydride on the steam-bath for 1 hr. and chromatography over alumina with elution by ether containing 1% of methanol gave the 3-*monoacetate* (XIV; R = Ac). Recrystallised from aqueous methanol this had m. p. 121—122°, $[\alpha]_D$ +27° (*c*, 1·5) (Found: C, 78·3; H, 11·55. $C_{29}H_{50}O_3$ requires C, 78·0; H, 11·3%).

14-Methyl-A-norcoprostane-3 : 5β-diol (100 mg.) in acetic anhydride (3 ml.) was treated at room temperature with perchloric acid (1 drop; 70%) for 10 min. Filtration in benzene solution through alumina and crystallisation from methanol furnished 14-methyl-A-norcoprostan-3-one (see above), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +142° (*c*, 1·6)}.

The diol (100 mg.) in " AnalaR " acetic acid (10 ml.) was treated with chromium trioxide (20 mg.) in the same solvent (10 ml.), and the solution left at room temperature for 15 min. Crystallisation of the product from aqueous acetic acid afforded 14-*methyl*-3-*oxo*-A-*norcoprostan*-5β-*ol* (XIII; R = H), m. p. 185—187°, $[\alpha]_D$ +135° (*c*, 0·88) (Found: C, 80·35; H, 11·3. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%). This hydroxy-ketone (25 mg.) with acetic anhydride (1 ml.) containing perchloric acid (1 drop; 70%) for 5 min. at room temperature gave 14-methyl-3-oxo-A-norcoprostan-5β-yl acetate (see above), identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +151° (*c*, 1·0)}.

Reduction of Some αβ-*Unsaturated Ketones with Lithium and Liquid Ammonia*.—Cholest-4-en-3-one (250 mg.) in ether (50 ml.) was added rapidly to an excess of lithium metal in liquid

ammonia (50 ml.), and the mixture stirred for 5 min. Ethereal *tert.*-butanol was added to destroy the excess of lithium. Chromatography of the product over alumina, elution with benzene, and crystallisation from methanol gave cholestanone (155 mg.), identified by m. p., mixed m. p., and rotation $\{[\alpha]_D +42°$ (*c*, 1·6)$\}$.

Similarly stigmasta-4 : 22-dien-3-one (250 mg.) gave stigmast-22-en-3-one (130 mg.), identified by m. p., mixed m. p., and rotation $\{[\alpha]_D +21°$ (*c*, 2·1)$\}$, and ergosta-4 : 22-dien-3-one afforded ergost-22-en-3-one, similarly identified $\{[\alpha]_D +5°$ (*c*, 0·9)$\}$.

We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University and Imperial Chemical Industries Limited for financial assistance. Two of us (D. A. J. I. and B. R. T.) are indebted to the International Wool Secretariat for (respectively) Predoctorate and Postdoctorate Research Fellowships.

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