1140. *The Methylation of* 3-*Oxo*-B-*norcholestanes*

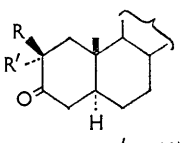
By Y. M. Y. Haddad, W. T. Pike, G. H. R. Summers, and W. Klyne

The syntheses of the various 2- and 4-methylated saturated 3-oxo- and 3-hydroxy-steroids of the B-nor-5α- and -5β-cholestane series are described.

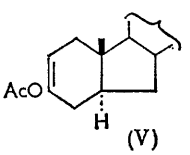
The optical rotatory dispersion measurements of the methylated ketones are recorded and compared with theoretical expectations.

Several cases have been reported where the introduction of a double bond into ring B influences the direction of enolisation of the 3-oxo-group.[1-4] These unexpected results may be due to the extra strain in ring B caused by the olefinic linkage. Such strain in the B-ring can also be brought about by reducing it to a 5-membered ring. It was of interest to study the methylation of B-nor-3-ketones and in this Paper we describe the preparation of the various 2- and 4-methylated saturated 3-oxo- and 3-hydroxy-steroids of the B-nor-5α- and -5β-cholestane series.

The direct methylation of B-nor-5α-cholestan-3-one (I) with methyl iodide and 1·9 molar equivalents of potassium t-butoxide in boiling t-butyl alcohol after 20 min. yielded mainly 2α-methyl-B-nor-5α-cholestan-3-one (II). The structural assignment rests on the independent method by which the same substance was subsequently prepared, on its stability towards both acids and bases, and on the behaviour of ketone (I) to bromination. The reaction also produced smaller amounts of 2,2-dimethyl-B-nor-5α-cholestan-3-one (III), which proved to be the major product when the alkylation was carried out for a longer time with a large excess of potassium t-butoxide and methyl iodide. The structure (III) follows from the analogous dimethylation of other 3-oxo-5α-steroids.[5,6] The monomethylation at C-2 of B-nor-5α-cholestan-3-one (I) could alternatively be brought about by the base-catalysed condensation of (I) with ethyl formate to give 2-hydroxymethylene-B-nor-5α-cholestan -3-one (IV), which on catalytic hydrogenolysis yielded the same 2α-methyl-B-nor-5α-cholestan-3-one (II) as had been obtained directly.



(I: R = R′ = H)
(II: R = H, R′ = Me)
(III: R = R′ = Me)
(IV: R = HO·CH:)
(VI: R = H, R′ = Br)



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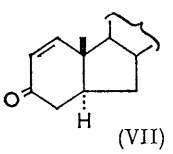

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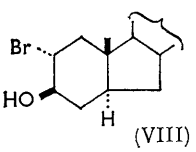

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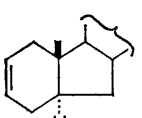
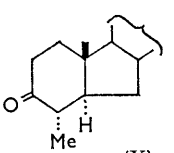
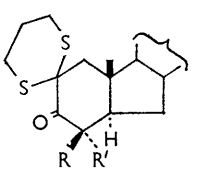


(IX)



(X)



(XI: R = R′ = H)
(XII: R = H, R′ = Me)

That methylation of B-nor-5α-cholestan-3-one has taken place at C-2 follows from the fact that bromination of its enol acetate (V) by one molar equivalent of bromine, in the presence of potassium acetate,[7] led to 2α-bromo-B-nor-5α-cholestan-3-one (VI). This

[1] W. W. Wells and D. H. Neiderhiser, *J. Amer. Chem. Soc.*, 1957, **79**, 6569; *Arch. Biochem. Biophys.*, 1959, **81**, 300.
[2] Y. Mazur and F. Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 6296.
[3] J. Pudles and K. Bloch, *J. Biol. Chem.*, 1960, **235**, 3417.
[4] R. ÓDorchaí, P. J. Flanagan, and J. B. Thomson, *J.*, 1964, 1142.
[5] H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, 1956, **21**, 1333.
[6] Y. Mazur and F. Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 5220.
[7] C. Djerassi, N. Finch, R. C. Cookson, and C. W. Bird, *J. Amer. Chem. Soc.*, 1960, **82**, 5488.

assignment of structure for the bromo-ketone is based on the following evidence. Dehydrobromination *via* the semicarbazone [8,9] afforded a product shown by its light absorption to be a Δ^1-3-ketone (VII). Reduction of the bromo-ketone (VI) by sodium borohydride afforded a bromohydrin showing an equatorial bromine infrared band at 724 cm.$^{-1}$. Treatment of the bromohydrin with activated zinc dust in acetic acid gave B-nor-5α-cholest-2-ene [10] (IX). These facts establish the configuration of the bromohydrin as (VIII) and hence of the parent ketone as (VI). The equatorial orientation of the bromine atom in the bromo-ketone (VI) was confirmed by the study of its infrared absorption spectrum [11] (band at 1730 cm.$^{-1}$) and by the optical rotatory dispersion measurements. Thus, 2α-bromo-B-nor-5α-cholestan-3-one (VI) shows a strong positive Cotton effect ($10^{-2}a = +99$) which is similar to the unsubstituted ketone ($10^{-2}a = +73$). This is in complete agreement with the axial halogeno-ketone rule [12] which predicts an insignificant contribution to the Cotton effect by an equatorially disposed halogen atom at C-2.

For the synthesis of 4α-methyl-B-nor-5α-cholestan-3-one (X), the procedure developed by Woodward and his co-workers [13] was used. Treatment of the hydroxymethylene ketone (IV) with trimethylene-ditoluene-*p*-thiosulphonate [14] in the presence of potassium acetate gave the dithioketal (XI). Direct methylation of this compound with methyl iodide and potassium t-butoxide in boiling t-butylalcohol, followed by chromatography, led to the isolation of 4α-methyl-3-oxo-B-nor-5α-cholestane-2-spiro-2′-1′,3′-dithian (XII). Cleavage of this ketone with Raney nickel gave 4α-methyl-B-nor-5α-cholestan-3-one (X).

Treatment of B-nor-5β-cholestan-3-one (XIII) with methyl iodide and potassium t-butoxide in t-butyl alcohol resulted in methylation at C-4. Chromatographic purification gave 45% of 4β-methyl-B-nor-5β-cholestan-3-one (XIV). That monomethylation of ketone (XIII) has occurred at C-4 follows from the fact that its enol acetate (XV), when brominated with 1 molar equivalent of bromine in acetic acid, afforded 4β-bromo-B-nor-5β-cholestan-3-one (XVI). This assignment of structure for the bromo-ketone follows from its dehydrobromination with *s*-collidine to give B-norcholest-4-en-3-one (XVII). The equatorial orientation of the bromine atom in the bromo-ketone (XVI) was confirmed by its infrared absorption spectrum, and also by its optical rotatory dispersion curve which shows a powerful negative Cotton effect rather similar to the unsubstituted ketone.

In order to establish that the ketone (XIV) obtained from the methylation of B-nor-5β-cholestan-3-one was the monomethyl product, a method was devised for the synthesis of 4,4-dimethyl-B-nor-5β-cholestan-3-one.

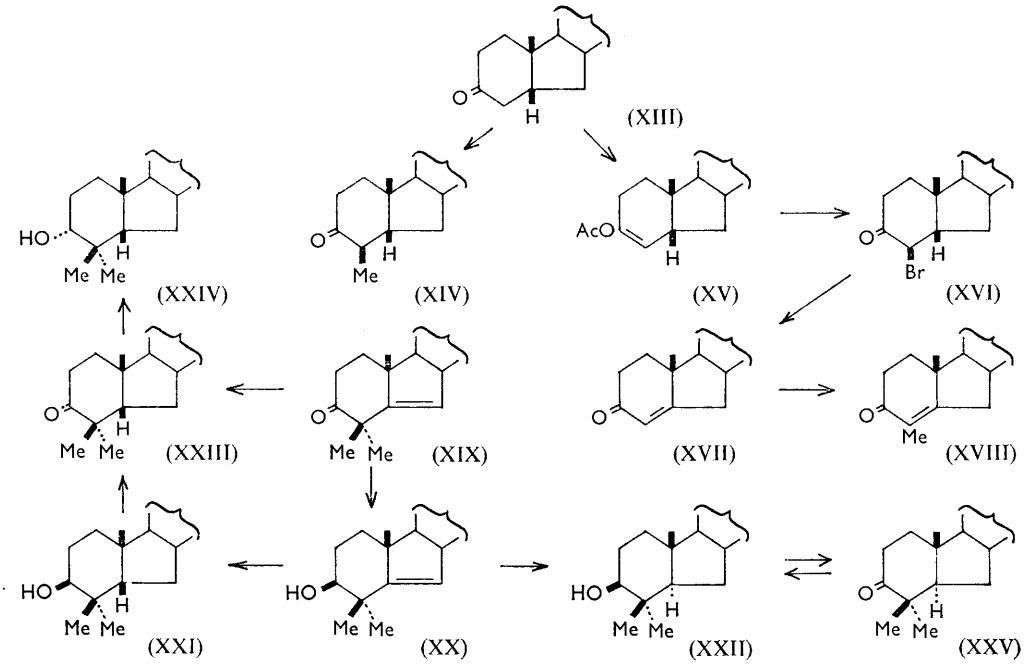
Direct methylation of B-norcholest-4-en-3-one (XVII) with methyl iodide and 1·5 molar equivalents of potassium t-butoxide in boiling t-butyl alcohol under the conditions described by Atwater,[15] yielded mainly 4-methyl-B-norcholest-4-en-3-one (XVIII) as an oil. The structure of (XVIII) was confirmed by the infrared spectrum, which indicated the presence of an α,β-unsaturated ketone, and especially the ultraviolet absorption spectrum. The latter showed a bathochromic shift of +8 mμ, which is in good agreement with the value (+11 mμ) to be expected for the introduction of an alkyl substituent at the α-position in α,β-unsaturated ketones.[16,17] The methylation of B-norcholest-4-en-3-one (XVII) when carried out for a longer period with a large excess of methyl iodide and potassium t-butoxide yielded mainly 4,4-dimethyl-B-norcholest-5-en-3-one (XIX), the constitution of which is defined by the absence of an α,β-unsaturated ketone band in the infrared and ultraviolet spectra.

[8] V. R. Mattox and E. C. Kendall, *J. Amer. Chem. Soc.*, 1948, **70**, 882.
[9] C. Djerassi, *J. Amer. Chem. Soc.*, 1949, **71**, 1003.
[10] G. H. R. Summers, *J.*, 1959, 2908.
[11] D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, 1956, **10**, 64.
[12] C. Djerassi and W. Klyne, *J. Amer. Chem. Soc.*, 1957, **79**, 1506.
[13] R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J.*, 1957, 1131.
[14] Private communication from Professor Sir E. R. H. Jones.
[15] N. W. Atwater, *J. Amer. Chem. Soc.*, 1960, **82**, 2847.
[16] L. K. Evans and A. E. Gillam, *J.*, 1941, 815.
[17] R. B. Woodward, *J. Amer. Chem. Soc.*, 1942, **64**, 76.

Reduction of 4,4-dimethyl-B-norcholest-5-en-3-one (XIX) by lithium aluminium hydride afforded 4,4-dimethyl-B-norcholest-5-en-3β-ol (XX). Catalytic hydrogenation of 4,4-dimethyl-B-norcholest-5-en-3β-ol in acetic acid over platinum oxide gave a separable mixture of two alcohols, which from their relative ease of elution from alumina [18] were considered to be 4,4-dimethyl-B-nor-5β-cholestan-3β-ol (OH-axial) (XXI) and 4,4-dimethyl-B-nor-5α-cholestan-3β-ol (XXII), respectively. The alcohol (XXI) on oxidation with chromium trioxide in acetic acid gave 4,4-dimethyl-B-nor-5β-cholestan-3-one (XXIII). This was also obtained by catalytic hydrogenation of 4,4-dimethyl-B-norcholest-5-en-3-one (XIX) in ethanol over palladium–charcoal. Reduction of ketone (XXIII) by lithium aluminium hydride proceeded normally and yielded mainly 4,4-dimethyl-B-nor-5β-cholestan-3α-ol (XXIV).

Oxidation of 4,4-dimethyl-B-nor-5α-cholestan-3β-ol (XXII) with chromium trioxide in acetic acid afforded 4,4-dimethyl-B-nor-5α-cholestan-3-one (XXV). This ketone on reduction by lithium aluminium hydride gave back the alcohol (XXII).

The rotatory dispersion curves of B-nor-5α-cholestan-3-one (I) and B-nor-5β-cholestan-3-one (XIII) have been measured by Djerassi *et al.*[19] and by Klyne;[12] they show no abnormal features when considered in the light of the octant rule.[20]



Whereas the curve for 2α-methyl-B-nor-5α-cholestan-3-one shows no abnormal features when considered in the light of the octant rule, the curve for the 2,2-dimethyl ketone (III) is certainly anomalous. The octant rule would predict a more positive Cotton effect for the ketone (III) than for (I), and this is observed in the " normal " series where ring B is 6-membered, since 2,2-dimethyldihydrotestosterone [21] shows a stronger positive effect than the parent unmethylated ketone ($\Delta a = +34$). This difference between the two dimethylated ketones must be due to a somewhat distorted A-ring in compound (III) which in turn must be due to minor differences in angle strain at C-5 and C-10.

[18] K. Savard, *J. Biol. Chem.*, 1953, **202**, 457.
[19] C. Djerassi, D. Marshall, and T. Nakano, *J. Amer. Chem. Soc.*, 1958, **80**, 4853.
[20] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013.
[21] C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 4001.

The curves for 4α-methyl-B-nor-5α-cholestan-3-one (X) and 4,4-dimethyl-B-nor-5α-cholestan-3-one (XXV) are in complete agreement with theoretical expectation. It is pertinent to note that, whereas introduction of a *gem*-dimethyl group at C-4 in the "normal" steroid 5α-series alters the sign of the Cotton effect, the introduction of such a group at C-4 in the B-nor-5α-series does not cause inversion of the Cotton effect. This is analogous to the case where ring A is five-membered.[22]

The amplitude for 4β-methyl-B-nor-5β-cholestan-3-one (XIV), which is somewhat similar to the unmethylated ketone (XIII), agrees well with the octant rule. The curve for 4,4-dimethyl-B-nor-5β-cholestan-3-one (XXIII) shows a positive Cotton effect. The introduction of a *gem*-dimethyl group at C-4 thus caused an inversion of the Cotton effect.

It has been observed previously that molecular-rotation changes following acetylation (Δ_1) of a 3β-hydroxy-group are generally negative in the case of saturated steroids and positive with triterpenes.[6,23] This reversal of the direction of the shift in molecular rotation following acetylation has been attributed by Klyne and Stokes [23] to the presence of the *gem*-dimethyl group at C-4 in the triterpenes. These authors have pointed out that the

Molecular-rotation data of substituted 2- and 4-methyl-3-hydroxy-steroids and their acetates

Compound	$[M]_D^{OH}$	$[M]_D^{OAc}$	Δ_1	$\Delta_1{}^a$
2,2-Dimethyl-B-nor-5α-cholestan-3β-ol	−20	−115	−95	−42
4,4-Dimethyl-B-nor-5α-cholestan-3β-ol	+149	+226	+77	+70
4,4-Dimethyl-B-nor-5β-cholestan-3β-ol	−12	+34	+46	
4,4-Dimethyl-B-nor-5β-cholestan-3α-ol	+7	−61	−68	−115 *

$\Delta_1{}^a$ Refers to the corresponding Δ_1 values for the "normal" steroid series with a six-membered B-ring.

* Refers to the corresponding shift for 4β-methyl-5β-cholestan-3α-ol.

observed direction of the shift in the triterpenes (positive when a 3β-ol is acetylated, negative when a 3α-ol is acetylated) is as expected from the known absolute configurations. The direction of the shift in molecular rotation (Δ_1) observed on acetylating the various methylated 3-hydroxy-B-nor-steroids is in agreement with the assigned structures for these alcohols.

Experimental

$[\alpha]_D$ are for $CHCl_3$ solutions. Chromatograms were carried out with Spence alumina type "H."

B-*Nor*-5α-*cholestan*-3β-*ol*.—The alcohol was prepared by the method of Summers.[10]

B-*Nor*-5α-*cholestan*-3-*one* (I).—A solution of B-nor-5α-cholestan-3β-ol (3·0 g.) in acetone (300 ml.) was titrated with a solution of chromic acid in sulphuric acid (8N w.r.t. active oxygen) until the supernatant liquid became yellow. After being shaken for 2 min. the mixture was poured into iced water (1 l.) and the insoluble material collected, dried, and recrystallised from methanol to give B-nor-5α-cholestan-3-one (2·7 g.) as plates, m. p. 95—97°, $[\alpha]_D$ +26° (*c* 1·0) (lit.,[10,24–26] m. p. 98—99°, $[\alpha]_D$ +25·5°; m. p. 90—93°, $[\alpha]_D$ +44°; m. p. 96—97°, $[\alpha]_D$ +36°; m. p. 96—97°, $[\alpha]_D$ +28°).

Methylation of B-*Nor*-5α-*cholestan*-3-*one*.—(*a*) *To give mainly* 2α-*methyl*-B-*nor*-5α-*cholestan*-3-*one* (II). A boiling solution of B-nor-5α-cholestan-3-one (1·26 g.) in benzene (25 ml.) was treated successively with potassium t-butoxide [prepared from potassium (246 mg.) and t-butyl alcohol (22 ml.)] and methyl iodide (1·3 ml.) in benzene (7 ml.). After 20 min. under reflux the mixture was poured on to ice, extracted with ether, and worked up in the usual way to give an oil which was adsorbed from pentane on alumina (60 g.). Elution with pentane–benzene (97 : 3) yielded 2,2-*dimethyl*-B-*nor*-5α-*cholestan*-3-*one* (57 mg.) which, on crystallisation from ether–methanol, gave rods, m. p. 118—119°, $[\alpha]_D$ +36° (*c* 1·2) (Found: C, 83·9; H, 12·1. $C_{28}H_{48}O$ requires C,

[22] C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, New York, 1960, ch. 6, p. 90.
[23] W. Klyne and W. M. Stokes, *J.*, 1954, 1979.
[24] T. Goto, *J. Amer. Chem. Soc.*, 1960, **82**, 2005.
[25] W. G. Dauben, G. A. Boswell, W. Templeton, J. W. McFarland, and G. H. Berezin, *J. Amer. Chem. Soc.*, 1963, **85**, 1672.
[26] J. Joska, J. Fajkoš, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1960, **25**, 2341.

83·9; H, 12·1%). Further elution with pentane–benzene (97 : 3) gave an oil (340 mg.) which, on crystallisation from ether–methanol, gave 2α-*methyl*-B-*nor*-5α-*cholestan*-3-*one* as flat rods, m. p. 108—109°, $[\alpha]_D$ +39° (*c* 0·9) (Found: C, 83·5; H, 12·3. $C_{27}H_{46}O$ requires C, 83·9; H, 12·0%). Elution with pentane–benzene (97 : 3) gave an oil (378 mg.) which, on crystallisation from methanol, gave crystals melting in the range 84—100°, evidently a mixture of 2α-methyl-B-nor-5α-cholestan-3-one and unchanged starting material. Finally, pentane–benzene (19 : 1) eluted B-nor-5α-cholestan-3-one (326 mg.) having m. p. and mixed m. p. 96—97°, $[\alpha]_D$ +26° (*c* 0·8) (from methanol).

(*b*) *To give mainly* 2,2-*dimethyl*-B-*nor*-5α-*cholestan*-3-*one* (III). A boiling solution of B-nor-5α-cholestan-3-one (700 mg.) in benzene (18 ml.) and t-butyl alcohol (9 ml.) was treated successively with potassium t-butoxide [prepared from potassium (700 mg.) and t-butyl alcohol (18 ml.)] and methyl iodide (5·3 ml.) in benzene (18 ml.). After 1 hr. under reflux, the product was isolated as previously and was chromatographed on alumina (60 g.). Elution with pentane and crystallisation from methanol furnished 2,2-dimethyl-B-nor-5α-cholestan-3-one (583 mg.) as rods, m. p. 118—119°, $[\alpha]_D$ +36°. Identity with the sample prepared by method (*a*) was established by non-depression in m. p. on admixture and by infrared comparison. Further elution with pentane gave 2α-methyl-B-nor-5α-cholestan-3-one (25 mg.) which on crystallisation from methanol gave needles, m. p. 108—109°, undepressed by the previously described sample.

Methylation of B-*Nor*-5α-*cholestan*-3-*one* via *the Hydroxymethylene Derivative* (IV).—B-Nor-5α-cholestan-3-one (9·0 g.) in ether (200 ml.) was treated with sodium methoxide [prepared from sodium (7·5 g.) in methanol (120 ml.)] and ethyl formate (120 ml.) for 6 days at room temperature with occasional shaking. The mixture was then treated with a buffered phosphate solution (pH = 8·1; 200 ml.). Ether extraction afforded 2-*hydroxymethylene*-B-*nor*-5α-*cholestan*-3-*one* (8·5 g.) as an oil which crystallised. Recrystallisation from methanol gave the analytical sample, m. p. 94—96°, $[\alpha]_D$ +52·3° (*c* 0·87); $\lambda_{max.}$ 284 mμ (ε 7600) (Found: C, 80·6; H, 10·8. $C_{27}H_{44}O_2$ requires C, 80·9; H, 11·1%).

2-Hydroxymethylene-B-nor-5α-cholestan-3-one (300 mg.), in thiophen-free benzene (10 ml.) and ethanol (12 ml.), was shaken with 10% palladium–charcoal (550 mg.) in an atmosphere of hydrogen for 2 days. The catalyst was removed by filtration, and removal of the solvent under reduced pressure gave an oil which was chromatographed on alumina (20 g.). Pentane–benzene (4 : 1) eluted 2α-methyl-B-nor-5α-cholestan-3-one (200 mg.) which crystallied from methanol as rods, m. p. 106—108°, $[\alpha]_D$ +40·1°. Identity with the above-described sample was established by mixed m. p. and infrared comparison.

2,2-*Dimethyl*-B-*nor*-5α-*cholestan*-3β-*ol*.—A solution of lithium aluminium hydride (90 mg.) in ether (15 ml.) was added to a solution of 2,2-dimethyl-B-nor-5α-cholestan-3-one (105 mg.) in ether (20 ml.) and the mixture heated under reflux for 1 hr. The solution was cooled, treated with ethyl acetate to destroy the excess of reagent, and the product isolated with ether. Recrystallisation from ether–methanol furnished 2,2-*dimethyl*-B-*nor*-5α-*cholestan*-3β-*ol* (90 mg.) as needles, m. p. 126—127°, $[\alpha]_D$ −5° (*c* 1·0) (Found: C, 83·6; H, 12·0. $C_{28}H_{50}O$ requires C, 83·5; H, 12·5%).

Treatment with pyridine–acetic anhydride overnight at 20° gave the *acetate*, which, on crystallisation from methanol, showed m. p. 116—117°, $[\alpha]_D$ −26° (*c* 1·1) (Found: C, 81·1; H, 11·6. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

B-*Nor*-5α-*cholest*-2-*en*-3-*yl Acetate* (V).—B-Nor-5α-cholestan-3-one (750 mg.) in isopropenyl acetate (25 ml.) was treated with 2 drops of concentrated sulphuric acid and kept at 100° for 3 hr. The product, isolated with ether in the usual way, was passed in pentane solution through deactivated alumina (40 g.). Crystallisation of the eluates from ether–methanol gave B-*nor*-5α-*cholest*-2-*en*-3-*yl acetate* (700 mg.) as plates, m. p. 69—71°, $[\alpha]_D$ +57° (*c* 1·1) (Found: C, 81·2; H, 11·0. $C_{28}H_{46}O$ requires C, 81·1; H, 11·2%).

2α-*Bromo*-B-*nor*-5α-*cholestan*-3-*one* (VI).—The solvent used in this experiment was prepared by mixing glacial acetic acid (160 ml.), carbon tetrachloride (40 ml.), and anhydrous sodium acetate (2·0 g.). The enol acetate (1·1 g.) was dissolved in this solvent (78 ml.) and a solution of bromine in the same solvent (9·4 ml.; 1·5% v/v) was added dropwise with stirring over 30 min. After an additional 20 min. stirring, the mixture was diluted with water and the product extracted with light petroleum (b. p. 40—60°) and worked up in the usual way. Crystallisation from ether–methanol afforded 2α-*bromo*-B-*nor*-5α-*cholestan*-3-*one* (850 mg.) as prisms, m. p. 150—152°, $[\alpha]_D$ +34° (*c* 1·06); $\nu_{max.}$ (CCl_4) 1730 cm.$^{-1}$ (Found: C, 69·25; H, 9·55; Br, 17·3. $C_{26}H_{43}BrO$ requires C, 69·2; H, 9·6; Br, 17·7%).

B-*Nor*-5α-*cholest*-1-*en*-3-*one* (VII).—A solution of 2α-bromo-B-nor-5α-cholestan-3-one (150 mg.) in glacial acetic acid (3 ml.) was heated with finely powdered semicarbazide hydrochloride (40 mg.) for 10 min. Dilution with water, and extraction with ether. gave an oil which gave a negative Beilstein test. The crude semicarbazone was cleaved readily on treatment with dioxan containing sulphuric acid (10 ml.; 40% v/v). Dilution with water, and extraction with ether gave an oil (120 mg.) which was adsorbed from pentane on alumina (6 g.). Elution with pentane gave an oil (101 mg.) which, on crystallisation from ether–methanol, afforded B-*nor*-5α-*cholest*-1-*en*-3-*one* as plates, m. p. 106—108°, $[\alpha]_D$ +58° (*c* 1·14); $\lambda_{max.}$ 231 mμ (ε 8500); $\nu_{max.}$ (CCl_4) 1671 cm.$^{-1}$ (Found: C, 84·2; H, 11·8. $C_{26}H_{42}O$ requires C, 84·25; H, 11·4%).

Reduction of 2α-*Bromo*-B-*nor*-5α-*cholestan*-3-*one with Sodium Borohydride*.—Sodium borohydride (100 mg.) was added in portions to a solution of 2α-bromo-B-nor-5α-cholestan-3-one (580 mg.) in ethanol–ether (2 : 1, 45 ml.). After 16 hr. at 20°, water was added, and the product extracted with ether to give an oil. This was chromatographed on deactivated alumina (50 g.). Pentane (50 ml.) eluted an oil (257 mg.) giving crystals, m. p. 100—108° (from methanol), which gave a positive Beilstein test. This was probably a mixture of the two epimeric alcohols. Further elution with pentane gave 2α-*bromo*-B-*nor*-5α-*cholestan*-3β-*ol* (269 mg.) which, on crystallisation from methanol, had m. p. 106—108°, $[\alpha]_D$ −11·5° (*c* 0·92); $\nu_{max.}$ 3620, 1038 cm.$^{-1}$ (equatorial OH), 712 cm.$^{-1}$ (equatorial bromine) (Found: C, 68·7; H, 9·7; Br, 17·4. $C_{26}H_{45}BrO$ requires C, 68·85; H, 10·0; Br, 17·6%). Finally, elution with pentane gave B-nor-5α-cholestan-3β-ol (43 mg.), m. p. and mixed m. p. 131—132°, $[\alpha]_D$ −10° (*c* 0·96).

B-*Nor*-5α-*cholest*-2-*ene* (IX).—A mixture of 2α-bromo-B-nor-5α-cholestan-3β-ol and the 3α-epimer (230 mg.) was mixed with acetic acid (15 ml.) and activated zinc [27] dust (500 mg.). The mixture was refluxed for 30 min., the solution filtered while hot, and the zinc washed with hot acetic acid. The filtrate was evaporated to dryness under reduced pressure, and the oily product purified by chromatography on alumina (10 g.). Elution with pentane afforded B-nor-5α-cholest-2-ene (158 mg.) which, on crystallisation from acetone, furnished plates, m. p. and mixed m. p. 83—84°, $[\alpha]_D$ +62° (*c* 0·93) (lit.,[10] m. p. 82—84°, $[\alpha]_D$ +61·2°). Elution with ether gave B-nor-5α-cholestan-3β-ol (28 mg.) which, on crystallisation from methanol, had m. p. and mixed m. p. 131—133°, $[\alpha]_D$ −9° (*c* 1·13).

3-*Oxo*-B-*nor*-5α-*cholestane*-2-*spiro*-2′-1′,3′-*dithian* (XI).—2-Hydroxymethylene-B-nor-5α-cholestan-3-one (5·8 g.) and trimethylene ditoluene-*p*-thiosulphonate [14] (7·4 g.) in warm absolute ethanol (100 ml.) was treated with dry potassium acetate (16·7 g.) in absolute ethanol (220 ml.), and the mixture kept under an atmosphere of carbon dioxide for 7 hr. under reflux. Removal of the solvent under reduced pressure gave a yellow solid which was partitioned between benzene and water. The benzene layer was washed with water and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a yellow oil which was adsorbed on alumina (250 g.) from pentane. Elution with pentane–benzene (4 : 1) gave 3-*oxo*-B-*nor*-5α-*cholestane*-2-*spiro*-2′-1′,3′-*dithian* (2·8 g.) as a foam. Crystallisation from acetone gave the analytical sample, m. p. 106—109°, $[\alpha]_D$ −9·4° (*c* 0·68); $\nu_{max.}$ (KBr) 1698 cm.$^{-1}$ (Found: C, 73·4; H, 10·4. $C_{29}H_{48}OS_2$ requires C, 73·1; H, 10·2%).

Methylation of 3-*Oxo*-B-*nor*-5α-*cholestane*-2-*spiro*-2′-1′,3′-*dithian*.—To a boiling solution of the spiro-compound (1·04 g.) in benzene (40 ml.) and t-butyl alcohol (17 ml.) was added firstly a solution of potassium (1·1 g.) in t-butyl alcohol (25 ml.) and benzene (20 ml.), and then a solution of methyl iodide (10 ml.) in benzene (30 ml.). The mixture was heated under reflux for 1 hr., cooled, and ice added. Ether extraction gave an oil which was chromatographed on neutral Woelm alumina (60 g.). Pentane–benzene (3 : 2) eluted 4α-*methyl*-3-*oxo*-B-*nor*-5α-*cholestane*-2-*spiro*-2′-1′,3′-*dithian* (150 mg.), which crystallised from ether–methanol as plates, m. p. 115—117°, $[\alpha]_D$ −16·8° (*c* 0·74); $\nu_{max.}$ (KBr) 1695 cm.$^{-1}$ (Found: C, 73·2; H, 10·2. $C_{30}H_{50}OS_2$ requires C, 73·4; H, 10·3%). Elution with benzene–ether (17 : 3) gave 650 mg. of starting material, m. p. and mixed m. p. 106—109°, $[\alpha]_D$ −10°.

4α-*Methyl*-B-*nor*-5α-*cholestan*-3-*one* (X).—The foregoing methylspiran (100 mg.) in ethanol (40 ml.) was refluxed with Raney nickel (3·3 g.; wet weight) for 7 hr. Filtration through charcoal, followed by removal of the solvent under reduced pressure, gave an oil (50 mg.). Oxidation of the product in acetic acid (3 ml.) with a 2% chromium trioxide–acetic acid solution (1 ml.) gave 4α-*methyl*-B-*nor*-5α-*cholestan*-3-*one* (40 mg.) which crystallised from methanol as rods, m. p. 105—107°, $[\alpha]_D$ +26° (*c* 0·6) (Found: C, 84·1; H, 12·1. $C_{27}H_{46}O$ requires C, 83·9; H, 12·0%).

Methylation of B-*Nor*-5β-*cholestan*-3-*one*.—A boiling solution of B-nor-5β-cholestan-3-one [10]

[27] L. F. Fieser and W. S. Johnson, *J. Amer. Chem. Soc.*, 1940, **62**, 575.

(800 mg.) in benzene (20 ml.) and t-butyl alcohol (10 ml.) was treated successively with potassium t-butoxide [prepared from potassium (800 mg.) and t-butyl alcohol (20 ml.)] and methyl iodide (6 ml.) in benzene (20 ml.). After 1·5 hr. under reflux, the product was isolated as previously described to give an oil which was adsorbed from pentane on alumina (100 g.). Elution with pentane gave an oil (368 mg.) which after several crystallisations from ethanol furnished 4β-*methyl*-B-*nor*-5β-*cholestan*-3-*one* as blades, m. p. 89—90°, $[\alpha]_D$ −28° (*c* 0·74) $\nu_{max.}$ 1715 cm.$^{-1}$ (Found: C, 84·3; H, 11·85. $C_{27}H_{46}O$ requires C, 83·9; H, 12·0%). Further elution with pentane gave an oil (360 mg.) which did not crystallise $[\alpha]_D$ −3° (*c* 0·91). This is probably a mixture of 4β-methyl-B-nor-5β-cholestan-3-one and starting material. Further elution with pentane gave unchanged B-nor-5β-cholestan-3-one which crystallised from methanol, m. p. and mixed m. p. 67—69°, $[\alpha]_D$ +18° (*c* 1·08).

4β-*Methyl*-B-*nor*-5β-*cholestan*-3α-*ol*.—A solution of lithium aluminium hydride (100 mg.) in ether (20 ml.) was added to a solution of 4β-methyl-B-nor-5β-cholestan-3-one (108 mg.) in ether (10 ml.). The mixture was refluxed for 1 hr. and the excess of reagent decomposed by the careful addition of ice and dilute hydrochloric acid. Working up in the usual way gave an oil which, on crystallisation from methanol, gave 4β-*methyl*-B-*nor*-5β-*cholestan*-3α-*ol* (88 mg.) as plates, m. p. 117—118°, $[\alpha]_D$ +3·3° (*c* 0·85) (Found: C, 83·5; H, 12·2. $C_{27}H_{48}O$ requires C, 83·4; H, 12·45%).

B-*Nor*-5β-*cholest*-3-*en*-3-*yl Acetate* (XV).—B-Nor-5β-cholestan-3-one (800 mg.) in isopropenyl acetate (30 ml.) was treated with two drops of concentrated sulphuric acid and kept at 100° for 3 hr. The solution was cooled, water added, and the product isolated with ether. The product in pentane was adsorbed on deactivated alumina (40 g.). Elution with pentane gave an oil (870 mg.) which did not crystallise from various solvents and solvent mixtures.

4β-*Bromo*-B-*nor*-5β-*cholestan*-3-*one* (XVI).—The solvent used in this experiment was prepared by mixing glacial acetic acid (160 ml.), carbon tetrachloride (40 ml.), and anhydrous sodium acetate (2·0 g.). The enol acetate (550 mg.) was dissolved in the above solvent (39 ml.) and a solution of bromine in the same solvent (4·7 ml.; 1·5% v/v) was added dropwise with stirring over 15 min. After an additional 20 min. of stirring, the mixture was diluted with water and the product extracted with light petroleum (b. p. 40—60°) and worked up in the usual way. Crystallisation from ether–methanol afforded 4β-*bromo*-B-*nor*-5β-*cholestan*-3-*one* (350 mg.) as plates, m. p. 104—106°, $[\alpha]_D$ −39° (*c* 0·93); $\nu_{max.}$ 1736 cm.$^{-1}$ (Found: C, 69·3; H, 9·4; Br, 17·9. $C_{26}H_{43}BrO$ requires C, 69·2; H, 9·6; Br, 17·7%).

B-*Norcholest*-4-*en*-3-*one*.—4β-Bromo-B-nor-5β-cholestan-3-one (246 mg.) was refluxed with *s*-collidine (2 ml.) in a current of dry nitrogen for 1 hr. The usual working up gave an oil (180 mg.) which was purified by chromatography on alumina (8 g.). Elution with pentane gave an oil (200 mg.) which, on crystallisation from methanol, afforded B-norcholest-4-en-3-one, m. p. and mixed m. p. 64—65°, $[\alpha]_D$ +4° (*c* 1·12); $\nu_{max.}$ (CCl_4) 1669 cm.$^{-1}$; $\lambda_{max.}$ 240 mμ (ε 14,800).

Methylation of B-*Norcholest*-4-*en*-3-*one*.—(*a*) *To give mainly* 4-*methyl*-B-*norcholest*-4-*en*-3-*one* (XVIII). A boiling solution of B-norcholest-4-en-3-one (1·35 g.) in t-butyl alcohol (21 ml.) was added to a boiling solution prepared from potassium (219 mg.) in the same solvent (12 ml.). A solution of methyl iodide (0·23 ml.) in t-butyl alcohol (60 ml.) was added dropwise over 2·5 hr. to the refluxing solution. After a further 30 min. of refluxing, the solution was cooled, ice added, and the product isolated with ether in the usual way to give an oil (1·33 g.) which was adsorbed from pentane on alumina (60 g.). Elution with pentane gave an oil (260 mg.), which did not crystallise from various solvents, $[\alpha]_D$ −1°, −3° (*c* 0·92, 0·74); $\nu_{max.}$ (CCl_4) 1664 cm.$^{-1}$, 1712 cm.$^{-1}$; $\lambda_{max.}$ 247, 296 mμ (ε 20,420, 64). This is evidently a mixture of 4,4-dimethyl-B-norcholest-5-en-3-one and 4-methyl-B-norcholest-4-en-3-one. Further elution with pentane gave 4-*methyl*-B-*norcholest*-4-*en*-3-*one* (670 mg.) as an oil which did not crystallise, $[\alpha]_D$ −1° (*c* 1·21); $\nu_{max.}$ (CCl_4) 1664 cm.$^{-1}$. Finally, elution with pentane–benzene (9 : 1) gave B-norcholest-4-en-3-one (390 mg.), m. p. and mixed m. p. 64—65°, $[\alpha]_D$ +3° (*c* 0·92) (from methanol).

(*b*) *To give mainly* 4,4-*dimethyl*-B-*norcholest*-5-*en*-3-*one* (XIX). A boiling solution of B-norcholest-4-en-3-one (1·89 g.) in benzene (50 ml.) and t-butyl alcohol (25 ml.) was treated successively with potassium t-butoxide [prepared from potassium (1·89 g.) and t-butyl alcohol (50 ml.)] and methyl iodide (15 ml.) in benzene (50 ml.). After 1 hr. under reflux, the product was isolated as previously and was chromatographed on alumina (100 g.). Elution with pentane gave an oil (850 mg.) which, on crystallisation from methanol, furnished 4,4-*dimethyl*-B-*norcholest*-5-*en*-3-*one* as plates, m. p. 80—81°, $[\alpha]_D$ −6° (*c* 1·11); $\nu_{max.}$ (CCl_4) 1715 cm.$^{-1}$ (Found:

C, 84·3; H, 11·7. $C_{28}H_{46}O$ requires C, 84·35; H, 11·6%). Further elution with pentane gave 4-methyl-B-norcholest-4-en-3-one (800 mg.) as an oil which did not crystallise from various solvents, $[\alpha]_D$ −4° (*c* 1·12); $\nu_{max.}$ 1664 cm.$^{-1}$; $\lambda_{max.}$ 247 mμ (ε 19,500).

4-Methyl-B-norcholest-4-en-3β-ol.—A solution of lithium aluminium hydride (100 mg.) in ether (10 ml.) was added to a solution of 4-methyl-B-norcholest-4-en-3-one (100 mg.) in ether (10 ml.). The mixture was left at 20° for 2 hr. and the excess reagent decomposed by the addition of water. Working up in the usual way gave an oil which crystallised. Recrystallisation from methanol gave *4-methyl-B-norcholest-4-en-3β-ol* (70 mg.) as needles, m. p. 124—125°, $[\alpha]_D$ −4° (*c* 0·85) (Found: C, 83·6; H, 12·1. $C_{27}H_{46}O$ requires C, 83·9; H, 12·0%).

4,4-Dimethyl-B-norcholest-5-en-3β-ol (XX).—4,4-Dimethyl-B-norcholest-5-en-3-one (800 mg.) in ether (40 ml.) was reduced with 560 mg. of lithium aluminium hydride in 60 ml. of ether as previously. Crystallisation of the product from methanol afforded *4,4-dimethyl-B-norcholest-5-en-3β-ol* as needles, double m. p. 93—94° and 115—116°, $[\alpha]_D$ −61° (*c* 0·83); $\nu_{max.}$ 3632, 1030 cm.$^{-1}$ (equatorial OH) (Found: C, 83·6; H, 12·3. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%).

Catalytic Hydrogenation of 4,4-Dimethyl-B-norcholest-5-en-3β-ol.—4,4-Dimethyl-B-norcholest-5-en-3β-ol (630 mg.) in glacial acetic acid (30 ml.) was hydrogenated in the presence of Adams catalyst (68 mg.) until there was no further uptake. The catalyst was removed and the solvent evaporated under reduced pressure to give an oil which was adsorbed from pentane on aluminium oxide (30 g.). Elution with pentane–benzene (4 : 1) gave an oil (417 mg.) which, on crystallisation from ether–methanol, gave *4,4-dimethyl-B-nor-5β-cholestan-3β-ol* as plates, double m. p. 58—60° and 79—80°, $[\alpha]_D$ +37° (*c* 1·18) (Found: C, 83·5; H, 12·6. $C_{28}H_{50}O$ requires C, 83·5; H, 12·5%).

The derived *acetate* (prepared by pyridine–acetic anhydride overnight at room temperature) formed needles from acetone–methanol, m. p. 69—71°, $[\alpha]_D$ +51° (*c* 0·89) (Found: C, 80·7; H, 11·8. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

Further elution with pentane–benzene (4 : 1) gave a solid (99 mg.) which, on crystallisation from ether–methanol, gave *4,4-dimethyl-B-nor-5α-cholestan-3β-ol* as needles, m. p. 153—155°, $[\alpha]_D$ −2°, −4° (*c* 1·07, 0·55) (Found: C, 83·6; H, 12·6. $C_{28}H_{50}O$ requires C, 83·5; H, 12·5%).

Treatment with acetic anhydride–pyridine overnight at room temperature, afforded the *acetate*, which, on crystallisation from acetone–methanol, had m. p. 84—86°, $[\alpha]_D$ +7·7° (*c* 1·06) (Found: C, 81·25; H, 11·6. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

4,4-Dimethyl-B-nor-5β-cholestan-3-one.—(*a*) A solution of 4,4-dimethyl-B-nor-5β-cholestan-3β-ol (80 mg.) in glacial acetic acid (5 ml.) was treated with a 2% solution of chromium trioxide in acetic acid (1 ml.). The solution was left at 20° for 16 hr. and the excess of chromic acid was destroyed by the addition of methanol. Dilution with water, extraction with ether, and working up in the usual way gave an oil which was purified by chromatography on alumina (4 g.). Elution with pentane furnished *4,4-dimethyl-B-nor-5β-cholestan-3-one* (76 mg.) which, on crystallisation from acetone–methanol, had m. p. 53—55°, $[\alpha]_D$ +72° (*c* 1·04); $\nu_{max.}$ (CCl_4) 1712 cm.$^{-1}$ (Found: C, 84·2; H, 12·2. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%).

(*b*) 4,4-Dimethyl-B-norcholest-5-en-3-one (220 mg.) in ethanol (30 ml.) was hydrogenated in the presence of 10% palladium–charcoal (100 mg.). Uptake of hydrogen was complete in 1 hr. The catalyst was removed and the solvent evaporated under reduced pressure to give an oil which was adsorbed from pentane on alumina (10 g.). Elution with pentane gave an oil which, on two crystallisations from methanol, afforded 4,4-dimethyl-B-nor-5β-cholestan-3-one (130 mg.) as prisms, m. p. 53—55°, $[\alpha]_D$ +72° (*c* 1·10).

4,4-Dimethyl-B-nor-5α-cholestan-3-one (XXV).—A solution of 4,4-dimethyl-B-nor-5α-cholestan-3β-ol (24 mg.) in glacial acetic acid (3·5 ml.) was treated with a solution of chromium trioxide (10 mg.) in water (0·05 ml.) and left at 20° for 16 hr. The excess of chromic acid was destroyed by the addition of methanol. Dilution with water, extraction with ether, and working up in the usual way gave an oil which was purified by chromatography on alumina (2 g.). Pentane eluted *4,4-dimethyl-B-nor-5α-cholestan-3-one* (22 mg.) which, on crystallisation from methanol, had m. p. 66—69°, $[\alpha]_D$ +29° (*c* 0·99); $\nu_{max.}$ (CCl_4) 1706 cm.$^{-1}$ (Found: C, 84·1; H, 12·0. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%).

Reduction of 4,4-Dimethyl-B-nor-5α-cholestan-3-one by Lithium Aluminium Hydride.—A solution of lithium aluminium hydride (50 mg.) in ether (10 ml.) was added to a solution of 4,4-dimethyl-B-nor-5α-cholestan-3-one (34 mg.) in ether (5 ml.). The mixture was refluxed for 1 hr. and the excess reagent decomposed by the addition of ice and dilute hydrochloric acid. Working up in the usual way gave a solid (33 mg.) which, on recrystallisation from methanol,

afforded 4,4-dimethyl-B-nor-5α-cholestan-3β-ol as fine needles, m. p. and mixed m. p. 153—154°, $[\alpha]_D$ −2° (*c* 1·06); $\nu_{max.}$ 3630, 1030 cm.$^{-1}$ (equatorial OH).

4,4-Dimethyl-B-nor-5β-cholestan-3α-ol.—4,4-Dimethyl-B-nor-5β-cholestan-3-one (60 mg.) in ether (5 ml.) was reduced with 60 mg. of lithium aluminium hydride in 10 ml. of ether as previously. Crystallisation of the product from acetone–methanol afforded *4,4-dimethyl-B-nor-5β-cholestan-3α-ol* as needles, m. p. 126—127°, $[\alpha]_D$ +1·7° (*c* 0·99) (Found: C, 84·0; H, 12·0. $C_{28}H_{50}O$ requires C, 83·5; H, 12·5%).

The derived *acetate* (prepared using pyridine–acetic anhydride overnight at room temperature) formed plates from acetone–methanol, m. p. 75—77°, $[\alpha]_D$ −14° (*c* 0·83) (Found: C, 80·7; H, 11·8. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

Optical Rotatory Dispersion Data.—General experimental details for the rotatory dispersion were as described by Jones and Klyne.[28] All curves were measured for methanol solutions (*c* 0·01) at 18—20°. All values are as molecular rotations.

Optical rotatory dispersion data

Compound	Peak (mμ)	Trough (mμ)	$10^{-2}a$	Compound	Peak (mμ)	Trough (mμ)	$10^{-2}a$
(II)	+3700 (308)	−4500 (270)	+82	(X)	+3450 (307·5)	−4500 (270)	+79·5
(III)	+1500 (325)	0 (283)	+15	(XXIII)	+1800 (320)	0 (290)	+18
(VI)	+5200 (312)	−6300 (270)	+115	(XXV)	+1600 (312)	−2700 (275)	+43
Compound	Trough (mμ)	Peak (mμ)	$10^{-2}a$	Compound	Trough (mμ)	Peak (mμ)	$10^{-2}a$
(XIV)	−3900 (314)	+6600 (278)	−105	(XVI)	−6800 (312)	+8300 (275)	−151

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[28] P. M. Jones and W. Klyne, *J.*, 1960, 871.