166. *The Methylation of 5α-Cholest-6-en-3-one: Further Examples of the Boat Conformation of Ring-A in the Steroids.*

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Methylation of 5α-cholest-6-en-3-one gives 2,2-dimethyl-5α-cholest-6-en-3-one, 2β-methyl-5α-cholest-6-en-3-one, and 2α-methyl-5α-cholest-6-en-3-one. Chemical evidence and optical rotatory dispersions indicate that in the first two products ring A is in a boat conformation.

The discovery of 4-monomethyl sterols in natural plant [1] and animal [2,3] sources aroused interest, first, as to their significance in the biogenetic conversions of terpenes into sterols [4] and, secondly, as to their chemical synthesis from cholesterol. It has been shown that 5α-cholest-7-en-3-one with methyl iodide and potassium t-butoxide yields 4α-methyl-5α-cholest-7-en-3-one (lophenone),[2,5] rather than the 2α-methyl isomer which would have been expected by analogy with the methylation of 5α-cholestan-3-one under similar conditions.[6] This is undoubtedly a reflection of the fact the Δ^7-double bond causes the 3-keto-group to enolise towards $C_{(4)}$ rather than $C_{(2)}$, and it may be due to the extra strain in ring B caused by the olefinic linkage. It was of interest to study the methylation of

[1] Cox, King, and King, *Proc. Chem. Soc.*, 1957, 290; Djerassi, Krakower, Lemin, Liu, Mills, and Villotti, *J. Amer. Chem. Soc.*, 1958, **80**, 6284; Mazur, Weizmann, and Sondheimer, *Bull. Res. Council Israel*, 1958, **7**, *A*, 82; Amorós-Marin, Torres, and Asenjo, *J. Org. Chem.*, 1959, **24**, 411; Mazur, Weizmann, and Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 6293.

[2] Wells and Neiderhiser, *J. Amer. Chem. Soc.*, 1957, **79**, 6569; *Arch. Biochem. Biophys.*, 1959, **81**, 300.

[3] Kandutsch and Russell, *J. Amer. Chem. Soc.*, 1959, **81**, 4114.

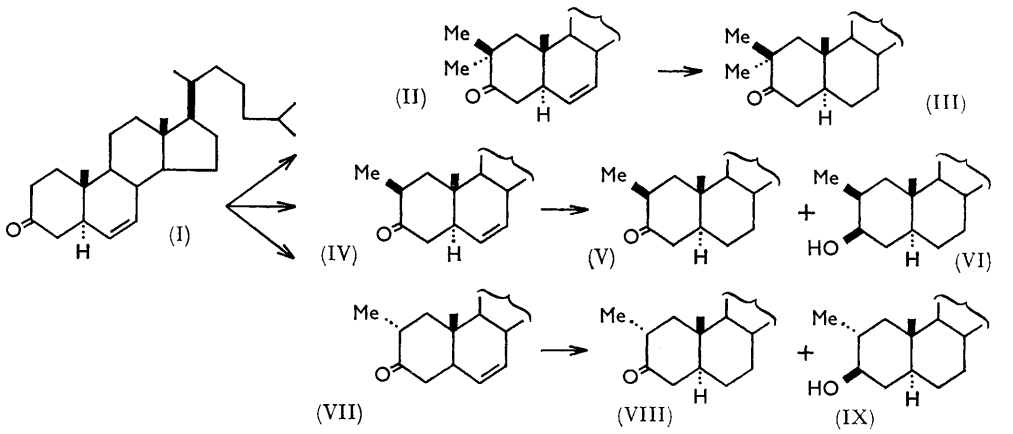
[4] Gautschi and Bloch, *J. Amer. Chem. Soc.*, 1957, **79**, 684.

[5] Mazur and Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 6296.

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

other cholestan-3-one derivatives unsaturated in ring B or C and in this paper we describe the results obtained with 5α-cholest-6-en-3-one (I) (independently by F. S. and Y. K. in Israel and by G. H. R. S. and Y. M. Y. H. at Swansea).

The ketone [7] (I) was obtained most conveniently by the oxidation of 5α-cholest-6-en-3β-ol [8] with chromium trioxide in pyridine.[9] Direct methylation of the ketone with methyl iodide and potassium t-butoxide in t-butyl alcohol under the conditions used previously [5] with the Δ^7-isomer, followed by chromatography, led to three new substances. The least polar was shown to be 2,2-dimethyl-5α-cholest-6-en-3-one (II), since hydrogenation in ethanol over palladium–charcoal yielded a compound with an infrared spectrum



($\lambda_{max.}$ 1703 cm.$^{-1}$ in CS_2) indicating it to be a dimethylated ketone; [6] this proved to be identical with 2,2-dimethyl-5α-cholestan-3-one [6,10] (III). A more polar substance proved to be 2β-methyl-5α-cholest-6-en-3-one (IV). Hydrogenation as before led to a monomethylated ketone ($\lambda_{max.}$ 1710 cm.$^{-1}$ in CS_2) which must be 2β-methyl-5α-cholestan-3-one (V) since its physical properties correspond to those of a known compound [6] and on acid treatment it was isomerised to 2α-methyl-5α-cholestan-3-one (VI), identical with an authentic sample [6,10] and also with the product of hydrogenation of the third ketone, 2α-methyl-5α-cholest-6-en-3-one (VII) isolated from the methylation.

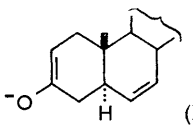
The catalytic hydrogenation of ketones (IV and VII) in acetic acid in the presence of palladium oxide also furnished respectively 2β- (VIII) and 2α-methyl-5α-cholestan-3β-ol (IX), their structures being confirmed by oxidation to their parent ketones (V and VI) by chromium trioxide in acetic acid. The 2β-methyl-5α-cholestan-3β-ol (VIII) was also obtained from 2β-methyl-5α-cholest-6-en-3-one by reduction with lithium aluminium hydride, followed by hydrogenation of the intermediate 2β-methyl-5α-cholest-6-en-3β-ol in ethanol in the presence of palladium–charcoal.

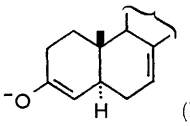
It had been expected that enolisation of the carbonyl group in ketone (I) would occur towards $C_{(2)}$, since the geometric relation between the double bonds in the resulting enol (X) is the same as in the above mentioned preferentially formed Δ^3-enol (XI) of 5α-cholest-7-en-3-one. The rate of condensation of ketone (I) with benzaldehyde,[11] which is much greater than that of the saturated 5α-cholestan-3-one, also indicates that the Δ^2-enol (X) is formed readily. The observed methylation of ketone (I) at position 2 is, therefore, in keeping with expectation.

On the other hand, the fact that one of the methylated products has the 2β-methyl

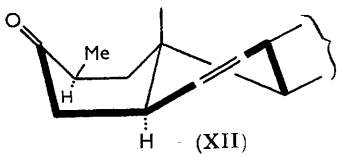
[7] Barton and Rosenfelder, *J.*, 1949, 2459.
[8] Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1950, **72**, 1923; James, Rees, and Shoppee, *J.*, 1955, 1370; Mazur, Nussim, and Sondheimer, *Proc. Chem. Soc.*, 1959, 314.
[9] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[10] Mousseron, Winternitz, and de Paulet, *Compt. rend.*, 1957, **245**, 1859.
[11] Barton, McCapra, May, and Thudium, *J.*, 1960, 1297.

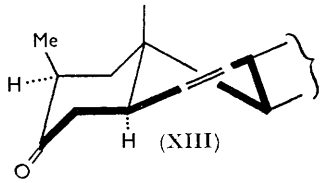
configuration was surprising. Although it has been shown that monomethylation of steroidal ketones may initially give the axial isomer,[12] the 2-methyl group in 2β-methyl-5α-cholest-6-en-3-one (IV) would be expected to epimerise under the strongly basic conditions if it were axially orientated since enolisation towards position 2 should occur


(X)


(XI)

fairly readily. Moreover, the ketone (IV) was unaffected on treatment with sulphuric acid in ethanol, conditions under which in the saturated series the axial 2β-methyl ketone (V) is readily epimerized to the equatorial 2α-isomer (VI).[6] Also 2α-methyl-5α-cholest-6-en-3-one (VII) was partially epimerised to ketone (IV) by this treatment. It, therefore, appears that the ketone (IV) possesses the stable configuration at position 2, *i.e.*, that the 2-methyl group is equatorial. It appears that this substance assumes a boat conformation in ring A (XII) rather than the usual chair conformation (XIII) and this is confirmed by the rotatory dispersion data discussed below.


(XII)


(XIII)

The rotatory dispersion curves of the saturated 3-oxo-5α-steroids with 2α- and 2β-methyl groups have been discussed by Djerassi *et al.*;[13] they show no abnormal features when considered in the light of the octant rule.[14]

The curve for the unsubstituted 5α-cholest-6-en-3-one shows an insignificant Cotton effect, superimposed on a strongly negative plain curve; this strong negative "background" has been found by Djerassi for the non-ketonic 5α-cholest-6-ene,[15] and also by us for 5α-cholest-6-en-3β-ol. The 2α-methyl-5α-cholest-6-en-3-one shows a rather similar curve; on the basis of the octant rule, it would be expected that the introduction of an equatorial methyl group would make a negligible change.

The 2β-methyl-5α-cholest-6-en-3-one, however, shows an unexpected *negative* Cotton effect (amplitude,[16] $10a^{-2} = -41$).

The octant rule would predict a more positive Cotton effect curve for a compound (XIII) than for the ketone (I). The negative curve seems compatible only with a boat (or modified boat) conformation of ring A (XII).

Since the corresponding saturated 2β-methyl-3-ketone gives a normal positive Cotton effect, we suggest that the preference for a boat in compound (XII) is due to some subtle stability change due to the 6,7-double bond.

The 2,2-dimethyl-5α-cholest-6-en-3-one (II) gives a somewhat stronger negative curve than the 2β-methyl derivative; this is consistent with a boat conformation for (II) [as (XII) with an additional 2α-methyl group, which would here be axial and make a negative contribution to the Cotton effect]. 2α-Bromo-2β-methyl-5α-cholestan-3-one also gives a negative Cotton effect, consistent with a boat conformation of ring A.[17]

[12] Beton, Halsall, Jones, and Phillips, *J.*, 1957, 753.
[13] Djerassi, Halpern, Halpern, and Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 4001.
[14] Moffit, Woodward, Moscowitz, Djerassi, and Klyne, unpublished work; cf. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, New York, 1960, Chapter 13; Klyne in "Advances in Organic Chemistry" (ed., Raphael), Interscience, New York, Vol. I, 1960.
[15] Djerassi, Closson, and Lippman, *J. Amer. Chem. Soc.*, 1956, **78**, 3163.
[16] For nomenclature see Djerassi and Klyne, *Proc. Chem. Soc.*, 1957, 55.
[17] Djerassi, Finch, and Mauli, *J. Amer. Chem. Soc.*, 1959, **81**, 4997.

The indeterminate curves of the unsubstituted 6,7-unsaturated 3-ketone (and its 2α-methyl derivative) suggest that these compounds may have an intermediate conformation (possibly the skew type discussed by Dreiding [18]), or they might be the result of a conformational equilibrium between chair and boat forms.

Experimental

$[\alpha]_D$ are for $CHCl_3$ solutions. Chromatograms were carried out with Merck " acid-washed " alumina by F. S. and Y. K. and with Spence alumina type " H " by Y. M. Y. H. and G. H. R. S.

Where duplication of experiments has occurred, those performed by F. S. and Y. K. are given in sections (*a*).

5α-*Cholest*-6-*en*-3β-*ol*.—The alcohol was prepared by the methods of Mazur, Nussim, and Sondheimer [8] and of Corey and Gregoriou.[19]

5α-*Cholest*-6-*en*-3-*one*.—A solution of 5α-cholest-6-en-3β-ol (4 g.) in dry pyridine (75 ml.) was added gradually to chromium trioxide (3·7 g.) in pyridine (75 ml.), and the mixture was left at room temperature for 18 hr. The product was isolated with ether and was chromatographed on aluminium oxide (150 g.). Elution with pentane–benzene (3 : 1) gave 5α-cholest-6-en-3-one (1·94 g.) which on crystallisation from methanol had m. p. 121—122°, $[\alpha]_D$ −75° (Found: C, 84·1; H, 11·5. Calc. for $C_{27}H_{44}O$: C, 84·3; H, 11·5%) (lit.,[7] m. p. 116—117°, $[\alpha]_D$ −76°, −80°). Starting material (1·08 g.) was recovered from later fractions eluted with benzene–ether (9 : 1).

Methylation of 5α-*Cholest*-6-*en*-3-*one*.—(*a*) A solution of potassium (76 mg.) in t-butyl alcohol (7 ml.) was added to a boiling solution of 5α-cholest-6-en-3-one (400 mg.) in benzene (8 ml.) under nitrogen. Methyl iodide (0·4 ml.) in benzene (2 ml.) was then added and boiling under reflux was continued for a further 20 min. The mixture was cooled and poured on ice, and the product obtained by isolation with ether was chromatographed on alumina (16 g.). Elution with pentane yielded 2,2-*dimethyl*-5α-*cholest*-6-*en*-3-*one* (148 mg.), which on crystallisation from methanol gave needles, m. p. 113—114°, $[\alpha]_D$ −67° (Found: C, 84·6; H, 11·4. $C_{29}H_{48}O$ requires C, 84·4; H, 11·7%).

Further elution with pentane yielded 2β-*methyl*-5α-*cholest*-6-*en*-3-*one* (45 mg.), which on crystallisation from methanol gave m. p. 108—110° (depressed on admixture with the 2,2-dimethyl compound), $[\alpha]_D$ −69° (Found: C, 84·1; H, 11·55. $C_{28}H_{46}O$ requires C, 84·35; H, 11·6%).

(*b*) A boiling solution of 5α-cholest-6-en-3-one (1·82 g.) in benzene (36·5 ml.) was treated successively with potassium t-butoxide [prepared from potassium (380 mg.) and t-butyl alcohol (31 ml.)] and methyl iodide (1·8 ml.) in benzene (9 ml.). After being refluxed for 20 min. the mixture was poured on ice, extracted with ether, and worked up in the usual way to give a brown oil which crystallised. The product was chromatographed on aluminium oxide (110 g.). Elution with pentane–benzene (19 : 1) (6 × 100 ml.) gave an oil (79 mg.) which was not investigated further. Elution with pentane–benzene (9 : 1) (10 × 100 ml.) gave a solid (937 mg.) which on crystallisation from acetone–methanol gave 2β-methyl-5α-cholest-6-en-3-one as rods, m. p. 106—108°, $[\alpha]_D$ −68°, −69°, 60° (*c* 1·1, 0·9, 1·0) (Found: C, 84·3; H, 11·8%). Further elution with pentane–benzene (9 : 1) (9 × 100 ml.) gave a solid (243 mg.) which on crystallisation from acetone–methanol gave 2α-*methyl*-5α-*cholest*-6-*en*-3-*one* as needles, m. p. 94—96°, $[\alpha]_D$ −65° (*c* 0·9) (Found: C, 83·9; H, 11·8. $C_{28}H_{46}O$ requires C, 84·35; H, 11·6%). Elution with pentane–benzene (8 : 2) (4 × 100 ml.) gave a solid (112 mg.) which on crystallisation from acetone gave crystals, m. p. 90—108°. Finally pentane–benzene (8 : 2) (10 × 100 ml.) eluted unchanged 5α-cholest-6-en-3-one (205 mg.), m. p. 118—119°, $[\alpha]_D$ −77°.

2,2-*Dimethyl*-5α-*cholestan*-3-*one*.—2,2-Dimethyl-5α-cholest-6-en-3-one (25 mg.) in ethanol (10 ml.) was shaken in hydrogen at room temperature over 10% palladium–charcoal (25 mg.). After 5 min. uptake of gas had stopped. The catalyst was removed, the solvent evaporated, and the residue crystallised from methanol. The resulting 2,2-dimethyl-5α-cholestan-3-one, m. p. 98—100°, $[\alpha]_D$ +79°, was identified with an authentic sample,[6,10] m. p. 99—100°, $[\alpha]_D$ +77°, through infrared comparison and non-depression of the m. p. on admixture (the m. p. 111—113° previously given for this substance [6] was an error).

[18] Dreiding, *Bull. Soc. chim. France*, 1960, in the press; cf. Reeves, *Adv. Carbohydr. Chem.*, 1958, **15**, 27; Hasebrook and Oosterhoff, *Discuss. Faraday Soc.*, 1951, **10**, 87; Howlett, *J.*, 1957, 4353.

[19] Corey and Gregoriou, *J. Amer. Chem. Soc.*, 1959, **81**, 3127.

2β-*Methyl-5α-cholestan-3-one.*—(*a*) The hydrogenation of 2β-methyl-5α-cholest-6-en-3-one (20 mg.) in ethanol over palladium–charcoal was carried out as above. Crystallisation of the product from methanol gave 2β-methyl-5α-cholestan-3-one, m. p. 99—101°, $[\alpha]_D$ +84° (lit.,[6] m. p. 96—97°, $[\alpha]_D$ +86°).*

(*b*) 2β-Methyl-5α-cholest-6-en-3-one (140 mg.) in glacial acetic acid (30 ml.) was hydrogenated at room temperature in the presence of palladium oxide (56 mg.). The oily product was chromatographed on aluminium oxide (8 g.). Elution with pentane–benzene (9 : 1) gave a solid (21 mg.) which on crystallisation from methanol gave 2β-methyl-5α-cholestan-3-one, m. p. 95—97°. Elution with ether (3 × 20 ml.) gave a solid (113 mg.) which on crystallisation from methanol gave 2β-*methyl-5α-cholestan-3β-ol* as needles, m. p. 142—145°, $[\alpha]_D$ +26° (*c* 0·9) (Found: C, 83·3; H, 12·65. $C_{28}H_{50}O$ requires C, 83·5; H, 12·5%).

The alcohol (43 mg.) was oxidised in acetic acid (4 ml.) with a 2% solution of chromium trioxide in acetic acid (1 ml.). The product, a solid, crystallised from acetone–methanol to give 2β-methyl-5α-cholestan-3-one, m. p. 102—103°, $[\alpha]_D$ +78°, +82° (*c* 1·0, 0·7).

2β-*Methyl-5α-cholest-6-en-3β-ol.*—2β-Methyl-5α-cholest-6-en-3-one (145 mg.) in ether (50 ml.) was refluxed for 2 hr. with lithium aluminium hydride (150 mg.). The oily product was chromatographed on aluminium oxide (10 g.). Elution with benzene–ether (9 : 1) (4 × 20 ml.) gave a solid (121 mg.) which on crystallisation from acetone gave 2β-*methyl-5α-cholest-6-en-3β-ol*, m. p. 142—146°, $[\alpha]_D$ −97°, −95° (*c* 0·7, 1·0) (Found: C, 83·6; H, 11·9. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%). Further elution with benzene–ether (9 : 1) (3 × 20 ml.) gave fractions (total 29 mg.) which melted in the range 118—134°.

2β-*Methyl-5α-cholestan-3β-ol.*—2β-Methyl-5α-cholest-6-en-3β-ol (40 mg.) in ethyl acetate (15 ml.) was hydrogenated in the presence of palladium–charcoal (40 mg., 5%). The solid product, on crystallisation from ethyl acetate–methanol, gave 2β-methyl-5α-cholestan-3β-ol, m. p. 145—147°, $[\alpha]_D$ +23° (*c* 0·7), identical (infrared spectrum, mixed m. p.) with the specimen obtained above.

2α-*Methyl-5α-cholestan-3-one.*—(*a*) 2β-Methyl-5α-cholestan-3-one (12 mg.) in ethanol (2 ml.) containing a drop of 20% sulphuric acid was boiled under reflux for 2 hr. Isolation with ether and crystallisation from ether–methanol furnished 2α-methyl-5α-cholestan-3-one, m. p. 116—118°, $[\alpha]_D$ +35°. The m. p. was undepressed on admixture with an authentic sample,[6] and the infrared spectra were identical.

(*b*) 2α-Methyl-5α-cholest-6-en-3-one (120 mg.) in glacial acetic acid (20 ml.) was hydrogenated in the presence of palladium oxide (50 mg.) at room temperature. The product was chromatographed on aluminium oxide (8 g.). Elution with pentane–benzene (8 : 2) (5 × 25 ml.) gave a solid (110 mg.) which on crystallisation from acetone–methanol gave 2α-methyl-5α-cholestan-3-one as prisms, m. p. 119—120°, $[\alpha]_D$ +36° (*c*, 1·0). Elution with ether gave a solid (10 mg.) which on crystallisation from acetone–methanol gave 2α-methyl-5α-cholestan-3β-ol, m. p. 136°, $[\alpha]_D$ +10° (*c* 1·0) (lit.,[6] m. p. 139—140°, $[\alpha]_D$ +8°).

Epimerisation of 2α-*Methyl-5α-cholest-6-en-3-one.*—2α-Methyl-5α-cholest-6-en-3-one (18 mg.) in ethanol (4·5 ml.) containing 20% sulphuric acid (0·1 ml.) was heated under reflux for 4 hr. The product, on crystallisation from acetone–methanol, had m. p. 90—106° and after recrystallisation, m. p. 92—107°, $[\alpha]_D$ −70° (*c*, 1·0). The infrared spectrum of the product indicated it was a mixture of 2α- and 2β-methyl-5α-cholest-6-en-3-one.

2β-Methyl-5α-cholest-6-en-3-one on treatment with sulphuric acid in ethanol under the same conditions was recovered completely unchanged.

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

2α-Methyl-5α-cholestan-3-one. Peak +2620 (305 mμ), trough, −3040 (275). Amplitude $10^{-2}a$, +57 (lit.,[13] $10^{-2}a$, +62).

2β-Methyl-5α-cholestan-3-one. Peak, +4080 (310 mμ), trough, −3840 (270). Amplitude +79 (lit.,[13] +73).

5α-Cholest-6-en-3-one. (No marked peak and trough) −380 (500 mμ); −2040 (308), −1650 (300), −3760 (260).

* *Added, January* 1, 1960.—Dr. A. Nickon, Johns Hopkins University, Baltimore, has recently prepared a specimen of 2β-methyl-5α-cholestan-3-one, m. p. 98—99° $[\alpha]_D$ + 122°, undepressed on admixture with our sample. We are very grateful to Dr. A. Nickon for this unpublished information.

[20] Jones and Klyne, *J.*, 1960, 871.

2α-Methyl-5α-cholest-6-en-3-one. (Resembles preceding compound) −410 (500 mμ), −1200 (328), −890 (320), −2840 (275).

2β-Methyl-5α-cholest-6-en-3-one. Trough, −2900 (312 mμ), peak, +1160 (275). Amplitude, −41.

2,2-Dimethyl-5α-cholest-6-en-3-one. Trough, 4430 (312 mμ), peak +970 (275). Amplitude −54.

5α-Cholest-6-en-3β-ol. Negative plain curve; −615 (500 mμ), −1580 (350), −2720 (300).

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