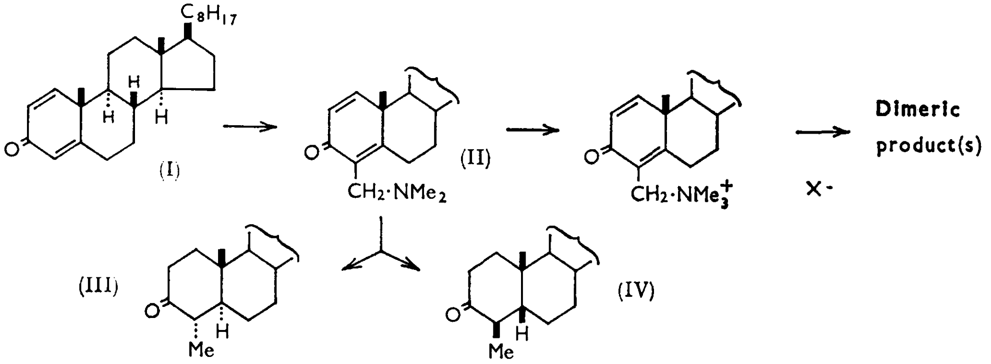
585. *The Mannich Reaction with Cholesta*-1,4-*dien*-3-*one.*

By G. I. Gregory and A. G. Long.

4-Dimethylaminomethylcholesta-1,4-dien-3-one has been prepared from cholesta-1,4-dien-3-one, formaldehyde, and dimethylamine hydrochloride. From the hydrogenation of this Mannich base 4α-methyl-5α-cholestan-3-one and 4β-methyl-5β-cholestan-3-one were isolated. Of the several by-products formed during the Mannich reaction one has been identified as the formal of 2-hydroxymethyl-4-methyl-19-norcholesta-1,3,5(10)-trien-1-ol. An attempt to apply the Hofmann degradation to the methiodide of 4-dimethylaminomethylcholesta-1,4-dien-3-one gave rise to a non-basic dimer or mixture of dimers of undetermined structure.

In our search for new methods of introducing methyl groups into the steroid nucleus we made several unsuccessful attempts to introduce substituents at position 6 in cholesta-1,4-dien-3-one (I) by base-catalysed reaction with methyl iodide and by Knoevenagel condensation with benzaldehyde. Finally we considered the Mannich reaction on 1,4-dien-3-ones as a means of introducing a dimethylaminomethyl group at the 6-position, which we hoped to be suitably activated (*e.g.*,[1] introduction of a bromine atom at position 6 in 1,4-dien-3-ones). We do not know [2] of any examples of substitution of an αβ-unsaturated ketone in the γ-position during the Mannich reaction.

Cholesta-1,4-dien-3-one (I), when treated with dimethylamine hydrochloride and formaldehyde under the usual conditions for the Mannich reaction,[2] gave a low yield of basic products. In view of the success of acetic acid as solvent in the aminomethylation of, *e.g.*, ferrocene,[3] indole,[4] and acetone,[5] we refluxed cholesta-1,4-dien-3-one (I) with dimethylamine hydrochloride and formaldehyde in glacial acetic acid and isolated an oily basic fraction and a neutral fraction. The oily base gave an oxalate, platinichloride and methiodide, and analyses indicated that it was monoacidic and contained a $CH_2{\cdot}NMe_2$ group in the cholesta-1,4-dien-3-one framework. The ultraviolet absorption maximum was at 242 mμ (near those for unsubstituted 1,4-dien-3-ones and 4-methyl- [6] and 6α-methyl-1,4-dien-3-ones; [7] known 2-methyl-1,4-dien-3-ones [8] show $\lambda_{max.}$ 245—248 mμ). Peaks at



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[1] Romo, Djerassi, and Rosenkranz, *J. Org. Chem.*, 1950, **15**, 896.

[2] Reichert, " Die Mannich-Reaktion," Springer Verlag, Berlin, 1959; Schröter, " Methoden der Organischen Chemie," Houben-Weyl (Band 11, Teil 1), Georg Thieme Verlag, Stuttgart, 1957, pp. 731 *et seq.*: Blicke, " Organic Reactions," Vol. I, 1942, pp. 303 *et seq.*

[3] Lindsay and Hauser, *J. Org. Chem.*, 1957, **22**, 355.

[4] Snyder and Eliel, *J. Amer. Chem. Soc.*, 1948, **70**, 1703.

[5] Blicke and McCarty, *J. Org. Chem.*, 1959, **24**, 1376.

[6] Sondheimer and Mazur, *J. Amer. Chem. Soc.*, 1957, **79**, 2906.

[7] Spero, Thompson, Magerlein, Hanze, Murray, Sebek, and Hogg, *J. Amer. Chem. Soc.*, 1956, **78**, 6213; Spero, Thompson, Lincoln, Schneider, and Hogg, *ibid.*, 1957, **79**, 1515; Fried, Arth, and Sarett, *ibid.*, 1959, **81**, 1235.

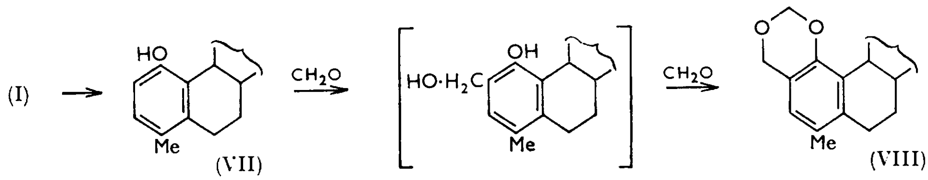
[8] Iriarte and Ringold, *Tetrahedron*, 1958, **3**, 28; Bernstein. Heller, Littell, Stolar, Lenhard, Allen, and Ringler, *J. Amer. Chem. Soc.*, 1959, **81**, 1696.

1660, 1628, 856, and 820 cm.$^{-1}$ in the infrared spectra suggested that the substituent was at position 4, for a similar absorption pattern is reported[6] for 1,2-dehydro-4-methyltestosterone. Introduction of the $CH_2{\cdot}NMe_2$ group into the ketone (I) had increased the molecular rotation by +128°. In general, 6α-methyl-[7] and 2-methyl-1,4-dien-3-ones[8] have a lower molecular rotation than their unsubstituted analogues;[7] on the other hand introduction of a 4-methyl group into 4-en-3-ones or 1,4-dien-3-ones[6] enhances the molecular rotation. The physical properties of our base thus favoured its formulation as 4-dimethylaminomethylcholesta-1,4-dien-3-one (II) although the analogies, derived as they are from the properties of methyl-steroids, were too tenuous to constitute structural proof.

Conclusive evidence for structure (II) came from a study of the reduction of the compound. Hydrogenation (3 mol.) of the purified base over palladium or Raney nickel in ethyl acetate or benzene provided a nitrogen-free, neutral product showing a single unconjugated ketone absorption in the infrared region. The product was separated into 4α-methyl-5α-[9,10] (III) and 4β-methyl-5β-cholestan-3-one[10] (IV). A careful search failed to detect the presence of 4β-methyl-5α-cholestan-3-one, which had been isolated[10] together with its isomers (III) and (IV) from the product of hydrogenation of 4-methylcholest-4-en-3-one.

Hydrogenation of the base (II) in acetic acid over platinum resulted in the uptake of 3 mol. of hydrogen, giving a basic oil. The infrared spectrum showed the absence of ketone absorption and the presence of a strongly hydrogen-bonded hydroxyl group. We have not characterised this product further but suggest that it is a mixture of isomeric 4-dimethylaminomethylcholestan-3-ols.

Boiling an aqueous solution of the methohydroxide (VI) of the Mannich base (II) gave a nitrogen-free, neutral glass. Attempts to purify this failed to yield fractions with properties significantly different from those of the crude material. The ultraviolet ($\lambda_{max.}$ 237, 271 infl. mμ) and infrared ($\nu_{max.}$ 1656, 1624, 830, and 800 cm.$^{-1}$) spectra were not readily fitted to known conjugated-ketone absorptions. Ozonolysis of this product gave formaldehyde, suggesting the presence of a methylene group. The Rast method gave a molecular weight of 810, indicating that the product is dimeric. There are many precedents for such a dimerisation among simpler α-methylene-ketones.[2,11]



Reaction of the dienone (I) with paraformaldehyde and dimethylamine hydrochloride in acetic acid provided, besides the base (II), a neutral oil. Chromatography furnished a new crystalline compound, whose high specific rotation and characteristic ultraviolet spectrum suggested that it contained an aromatic ring.[1,12,13] The infrared spectrum proved the absence of hydroxy- and keto-groups, but provided strong evidence for the presence of a ketal ($\nu_{max.}$ 1240, 1102, 1050, and 1018 cm.$^{-1}$). The absorption due to the aromatic ring suggested[14] the presence of one unsubstituted C–H bond ($\nu_{max.}$ 856 cm.$^{-1}$).

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[9] Meakins and Rodig, *J.*, 1956, 4679; Beton, Halsall, Jones, and Phillips, *J.*, 1957, 753; Djerassi, Mills, and Villotti, *J. Amer. Chem. Soc.*, 1958, **80**, 1005.

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

[11] *E.g.*, Pummerer and Cherbuliez, *Ber.*, 1919, **52**, 1392; Romann, Frey, Stadler, and Echenmoser, *Helv. Chim. Acta*, 1957, **40** 1900.

[12] Inhoffen and Huang-Minlon, *Naturwiss.*, 1938, **26**, 756; Inhoffen and Zühlsdorff, *Ber.*, 1941, **74**, 604; Wilds and Djerassi, *J. Amer. Chem. Soc.*, 1946, **68**, 1712; Woodward, Inhoffen, Larson, and Menzel, *Chem. Ber.*, 1953, **86**, 594.

[13] Dreiding, Pummer, and Tomasewski, *J. Amer. Chem. Soc.*, 1953, **75**, 3159.

[14] Bellamy, "The Infra-Red Spectra of Complex Molecules," Methuen, London, 2nd edn., 1958, p. 79.

A colour test[15] for a 1,3-dioxen was positive whereas the phenol (VII) and several other steroids did not give the test (see Experimental section). These properties are consistent with a compound of structure (VIII) that may arise by aromatisation of cholesta-1,4-dien-3-one (I) to 4-methyl-19-norcholesta-1,3,5(10)-trien-1-ol (VII), subsequent hydroxymethylation at the *ortho*-position (2), and formation of the dioxen with a second molecule of formaldehyde. In order to discount structures arising from a similar sequence of reactions with alternative rearrangement products[1,6,13,16] we subjected the triene (VII) to the conditions used to prepare the Mannich base (II). Chromatography of the product yielded a single formal having properties identical with those of the by-product (VIII).

An attempted acid-catalysed dienone–phenol rearrangement of 4-dimethylaminomethylcholesta-1,4-dien-3-one (II) failed under conditions that had furnished a high yield of the phenol (VII) from cholesta-1,4-dien-3-one (I). This may be attributed to the proximity of the positively charged ammonium ion to the ketone group; protonation of the latter, which necessarily precedes aromatisation,[1,12,13,17] is thus hindered.

EXPERIMENTAL

Unless other conditions are specified, solutions in chloroform (18—22°, 0·5—1·5%), ethanol, and carbon disulphide, respectively, were used for measurements of optical rotation, and of ultraviolet and infrared spectra; m. p.s were measured on a Kofler block and are uncorrected; products were dried in solvents with anhydrous magnesium sulphate; alumina (Hopkin and Williams MFC grade, Brockmann Activity Grade I) was used for chromatography.

Reaction of Cholesta-1,4-dien-3-one (I) with Formaldehyde and Dimethylamine Hydrochloride.—The dienone[12] (I) (10·0 g.), 36% aqueous formaldehyde (10·9 ml., 5 equiv.), and dimethylamine hydrochloride (10·65 g., 5 equiv.) were heated in refluxing acetic acid (200 ml.) for 18 hr. The initially colourless solution had become light orange-brown. As much as possible of the solvent was evaporated at 100° *in vacuo*; then toluene (2 × 200 ml.) was evaporated likewise. Addition of water and continuous ether-extraction led to a brown neutral oil (A) (2·4 g.) (see below).

The aqueous phase from the extraction was adjusted to pH 9—10 with sodium carbonate, then re-extracted continuously with ether, giving a basic fraction B as a light brown oil (5·5 g.). When the aqueous phase from this separation was made strongly alkaline with 40% sodium hydroxide solution a bright yellow precipitate,[18] insoluble in ether, was formed; it gave a colourless solution in acetic acid. We did not study this product further.

Formal of 2-Hydroxymethyl-4-methyl-19-norcholesta-1,3,5(10)-trien-1-ol (VIII).—Fraction A (above) (2·4 g.) was chromatographed from alumina (100 g.); elution with hexane and hexane–benzene (95 : 5) yielded a crude product (0·45 g.), which crystallised successively from methanol and hexane, to give the *formal* (VIII) as needles, m. p. 132—134°, $[\alpha]_D$ +194°, $\lambda_{max.}$ 209 (ε 33,200), 228sh (ε 8800), 279 (ε 1870), and 287 mμ (ε 2090) (Found: C, 82·0; H, 10·15. $C_{29}H_{44}O_2$ requires C, 82·0; H, 10·4%).

Another method of making the formal is described below.

4-Dimethylaminomethylcholesta-1,4-dien-3-one (II).—Fraction B (above) (5·5 g.) in ethanol (20 ml.) was treated with anhydrous oxalic acid (1·13 g., reckoned as 1 equiv.) in ethanol (5 ml.). A white solid (4·45 g.), m. p. 200—202°, crystallised; several recrystallisations from ethanol or, better, propan-1-ol gave the pure *oxalate*, m. p. 210·5—212°, $[\alpha]_D$ +69°, $\lambda_{max.}$ 247 mμ (ε 15,200), $\nu_{max.}$ (Nujol) 1700, 1660, and 1600 cm.$^{-1}$ (Found: C, 72·3; H, 9·7; N, 3·0. $C_{32}H_{51}NO_5$ requires C, 72·5; H, 9·7; N, 2·65%), of base (II). This salt (0·50 g.) with ether and sodium carbonate afforded the oily base (II) (0·41 g.), $[\alpha]_D$ +57°, $\lambda_{max.}$ 241—242 mμ (ε 14,500), $\nu_{max.}$ 1660, 1628, 856, and 820 cm.$^{-1}$, in which form it was used in this work. It gave a *chloroplatinate*, m. p. 186—188° (from ethanol) (Found: C, 54·8; H, 8·2; N, 2·4; Pt, 15·0. $C_{60}H_{100}Cl_6N_2O_2Pt$ requires C, 55·9; H, 7·8; N, 2·2; Pt, 15·1%).

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[15] Labat, *Bull. Soc. chim. France*, 1909, **5**, 745.

[16] Clemo, Haworth, and Walton, *J.*, 1930, 1110.

[17] Woodward and Singh, *J. Amer. Chem. Soc.*, 1950, **72**, 494.

[18] Burke, Barton, Gardner, and Lewis, *J. Amer. Chem. Soc.*, 1958, **80**, 3438.

The base (II) was also obtained, in 8% yield, when the Mannich reaction was conducted for 65 hr. in refluxing isopentyl alcohol.

4α-*Methyl*-5α- (III) *and* 4β-*Methyl*-5β-*cholestan*-3-*one* (IV).—4-Dimethylaminomethylcholesta-1,4-dien-3-one (II) (0·83 g.), dissolved in benzene (30 ml.), was reduced with hydrogen over 2% palladium–charcoal (100 mg.). The reduction curve showed an inflection after absorption of *ca.* 1·3 mol. The reduction ended after the uptake of 3 mol. of hydrogen and gave a neutral wax (0·63 g., 84%), $[\alpha]_D$ +30°, which was chromatographed; elution with hexane–benzene (9 : 1) gave material that crystallised from methanol to give pure 4β-methyl-5β-cholestan-3-one (IV) (0·14 g., 19%), m. p. 55—57°, $[\alpha]_D$ +35°, $\nu_{max.}$ 1710 cm.$^{-1}$ (Found: C, 83·7; H, 11·7. Calc. for $C_{28}H_{48}O$: C, 83·9; H, 12·0%). Mixed m. p. and comparison of the infrared spectrum with an authentic specimen [10] kindly provided by Professor F. Sondheimer confirmed their identity. Later fractions from this column were combined, crystallised from methanol, and recrystallised from aqueous acetic acid, to give 4α-methyl-5α-cholestan-3-one (III) (0·176 g., 23%) as needles, m. p. 118·5—119·5°, $[\alpha]_D$ +27°, $\nu_{max.}$ 1712 cm.$^{-1}$ (Found: C, 83·9; H, 12·1%). Mixed m. p. and comparison of the infrared spectrum with an authentic specimen [9] kindly provided by Professor E. R. H. Jones confirmed their identity. The remainder of the neutral material was present in the intermediate fractions from the chromatographic separation. Previous workers [9,10] have shown that 4β-methyl-5α-cholestan-3-one, m. p. 125—127°, $[\alpha]_D$ +36°, is less easily eluted than the 4α-methyl isomer; consequently we carefully scanned the tail fractions from the column but found no evidence for the presence of a third isomer. The fourth isomer, 4α-methyl-5β-cholestan-3-one, has not been described. Optical rotatory dispersion curves of the isomers (III) and (IV) were in good agreement with published results.[19]

Hydrogenation of 4-*Dimethylaminomethylcholesta*-1,4-*dien*-3-*one* (II).—Reduction with Adams catalyst in glacial acetic acid at room temperature led to the uptake of 3 mol. of hydrogen in 45 min. The product was a basic, uncrystallisable foam, whose infrared spectrum showed the presence of a strongly bonded hydroxyl group ($\nu_{max.}$ 3230 cm.$^{-1}$). This product was not studied further.

Trimethyl-(3-*oxocholesta*-1,4-*dien*-4-*yl*)*methylammonium Iodide* (V).—The tertiary base (II) (0·32 g.) in dry ether (30 ml.) containing a few drops of absolute ethanol was treated with methyl iodide (1 ml.). The solution became cloudy and was refluxed for 1·5 hr. The *methiodide* (V) separated as a white precipitate (0·37 g.), m. p. 197—200°, $[\alpha]_D$ +46°, $\lambda_{max.}$ (in EtOH) 247·5 (ε 18,700), (in H_2O) 251 (ε 14,550) and 227 mμ (ε 18,750) (due to the iodide ion), $\nu_{max.}$ (in $CHBr_3$) 1660, 1626, and 1593 cm.$^{-1}$ (Found: C, 63·5; H, 9·0; N, 2·3; I, 21·6. $C_{31}H_{52}INO$ requires C, 64·0; H, 9·0; N, 2·4; I, 21·8%).

Attempts at the Hofmann Degradation of the Methiodide (V).—The methiodide (V) (0·45 g.) in water (30 ml.) was shaken overnight with freshly precipitated silver oxide (0·5 g.). Ether extracted a glass (21 mg.), softening at 80—85°, $[\alpha]_D$ +58°; the aqueous layer was boiled in a stream of nitrogen until the evolution of basic gases ceased. Ether then extracted a glass (135 mg.), softening 110—115°, $[\alpha]_D$ +63°, $\lambda_{max.}$ 237 mμ ($E_{1\,\text{cm.}}^{1\%}$ 222), infl. 269 mμ ($E_{1\,\text{cm.}}^{1\%}$ 101), $\nu_{max.}$ 1656, 1624, 830, and 800 cm.$^{-1}$. The infrared absorption at 830 and 800 cm.$^{-1}$ suggests the presence of triply substituted double bonds (cf. ref. 14). This substance resisted our attempts at purifying it.

In another experiment the methiodide (V) (1·0 g.) in water (300 ml.) was passed through a column of an Amberlite IR-4B ion-exchange resin (basic form) (20 g.). The eluates, which contained no halide ion, were refluxed for 2 hr., after which evolution of volatile bases was imperceptible. The *product* separated as a glassy precipitate (0·35 g.) of indefinite softening point, $[\alpha]_D$ +57°, $\lambda_{max.}$ 237 mμ ($E_{1\,\text{cm.}}^{1\%}$ 229), infl. 271 mμ ($E_{1\,\text{cm.}}^{1\%}$ 99), $\lambda_{min.}$ 218 mμ ($E_{1\,\text{cm.}}^{1\%}$ 160) [Found: *M* (Rast), 810. $C_{56}H_{84}O_2$ requires *M*, 789]. Sublimation at 10^{-4} mm. failed to effect a purification.

The product of the Hofmann degradation (117 mg.) in methylene dichloride (15 ml.) was subjected at −10° to a stream of ozone for 1·5 hr. at the rate of 0·5 mmole/min. Formaldehyde was identified as its dimedone derivative (13 mg.), m. p. and mixed m. p. 189°, in the volatile components of the reaction.

The Formal (VIII) *from* 4-*Methyl*-19-*norcholesta*-1,3,5(10)-*trien*-1-*ol* (VII).—A mixture of the phenol [12] (VII) (1·0 g.), dimethylamine hydrochloride (16 g.), and paraformaldehyde (12 g.) in acetic acid (200 ml.) was refluxed for 18 hr. The solvent was removed *in vacuo*, and the resulting oil shaken with ether and water. The ether phase was treated with aqueous sodium

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[19] Djerassi, Halpern, Halpern, and Riniker, *J. Amer. Chem. Soc.*, 1958, **80**. 4001.

hydrogen carbonate; on evaporation it then yielded an oil (0·93 g.) that was chromatographed on alumina (30 g.; Grade O from Peter Spence and Sons Ltd., Widnes, Lancs.). Hexane eluted a fraction (0·36 g.) that yielded the formal (VIII) as white needles (from ethanol), m. p. 131—133°, $[\alpha]_D$ +193°, identified by mixed m. p. and absorption spectroscopy with the product obtained as described above from cholestadienone (I).

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GLAXO LABORATORIES LTD.,
GREENFORD, MIDDLESEX.

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