## 306. *Compounds Related to the Steroid Hormones. Part VIII.*[1] *The Mannich Reaction with 3- and 20-Oxo-steroids.*

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Mannich reactions have been used to introduce dimethylaminomethyl groups into ring A of 4,5α-dihydrocortisone acetate (I; R = H) and prednisone acetate (V; R = R′ = H); cortisone acetate (III) gave a base that decomposed readily into the 2-methylene-ketone (IV), from which 2-methylprednisone acetate (V; R = Me, R′ = H) was obtained by treatment with palladized charcoal. Such substitutions can be achieved without prior suppression of the carbonyl functions at the 11-position and in the side chain. Reaction with the $\Delta^{16}$-11,20-dione (VII; R = H) yielded the 21-dimethylaminomethyl compound (VII; R = $CH_2 \cdot NMe_2$).

The utility of the Mannich reaction for alkylating steroids has been demonstrated on saturated 3-oxo-5α-,[2] 17-oxo-,[3] and 20-oxo-steroids,[4] the substituents entering the 2-, 16-, and 21-position, respectively; in special conditions, attack occurred at the 4-position of cholesta-1,4-dien-3-one, giving a base from which 4-methyl-3-oxo-steroids were derived.[5] We have now extended the application of these special conditions to alkylations in the nucleus of steriods with the (unprotected) 21-acetoxy-17-hydroxy-20-oxo-system and in the side-chain of the $\Delta^{16}$-20-ketone (VII; R = H).

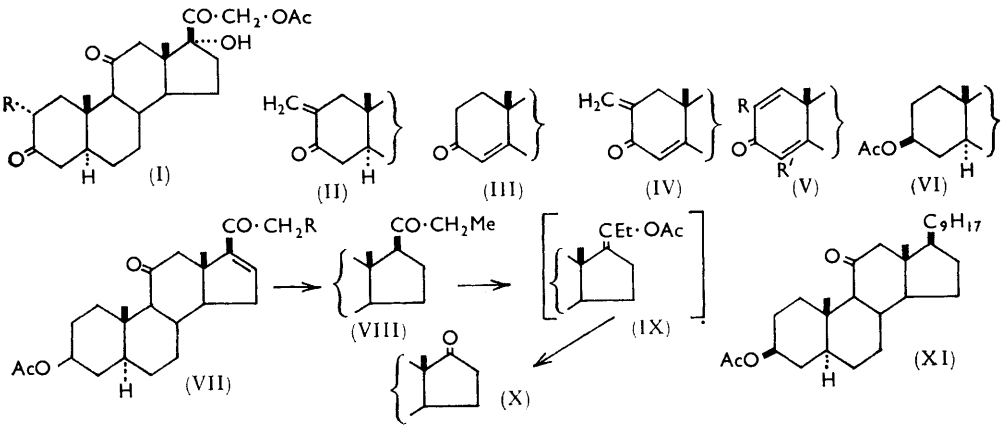
Tests with 3β-acetoxy-5α-ergost-22-en-11-one (XI) and the 3,21-diacetate (VI) showed that attack on such 11- and 20-ketones was very slow; on the other hand, 4,5α-dihydrocortisone acetate (I; R = H) underwent a quicker change, which was demonstrated by paper chromatography and electrophoresis of the products, so as to distinguish new neutral and basic compounds with the reducing properties of the intact side-chain. Conditions were chosen to avoid the formation of polyamines, even if some of the starting material remained; some separation of the amines could be secured by extraction of the monobases from aqueous solutions at pH 8·5, the others being extracted at pH >10.

The reaction with 4,5α-dihydrocortisone acetate (I; R = H) in acetic acid at 80° gave the 2α-dimethylaminomethyl derivative (I; R = $CH_2 \cdot NMe_2$) in 33% yield, the optical

[1] Part VII, *J.*, 1961, 4573.
[2] Djerassi *et al.*, *J. Amer. Chem. Soc.*, 1958, **80**, 4001; 1960, **82**, 5494; de Stevens and Halamandaris, *J. Org. Chem.*, 1961, **26**, 1614.
[3] Julian, Meyer, and Printy, *J. Amer. Chem. Soc.*, 1948, **70**, 3872; Neumann, Mancera, Rosenkranz, and Sondheimer, *ibid.*, 1955, **77**, 5676; ref. 4.
[4] Glidden Co. Inc., U.S.P. 2,562,194.
[5] Gregory and Long, *J.*, 1961, 3059.

rotation (at various wavelengths) and analogy with other work [2] indicating this structure. The neutral by-product consisted mainly of an αβ-unsaturated ketone, probably the 2-methylene derivative (II). Although we have some evidence of the formation of a bis-steroid, competition from such side reactions seems to be less severe when acetic acid, rather than ethanol,[2] is used as solvent for such Mannich reactions.

The Mannich reaction with cortisone acetate (III) in acetic acid gave a basic fraction, $\lambda_{max.}$ 239 mμ, that lost volatile base in subsequent manipulations; the ultraviolet absorption precludes the possibility of substitution at the 4-position, which might have been




expected from the action of formaldehyde and thiols on $\Delta^4$-3-ketones.[6] The neutral compound obtained by adventitious decomposition of the base or, better, by treatment with Florisil had properties consistent with its being 2-methylenecortisone acetate (IV): in particular, its ultraviolet ($\lambda_{max.}$ 258 mμ) and infrared absorption spectra [7] confirmed this supposition, and treatment with palladized charcoal converted it into a dienone, $\lambda_{max.}$ 243 mμ, that we regard as 2-methylprednisone acetate (V; R = Me, R′ = H). These results rule out the possibility of substitution at the 6-position. [Methods for making both the 2-methylene-$\Delta^4$-3-ketone [7] (IV) and 2-methyl-1,4-dienone [8] (V; R = Me, R′ = H) have been mentioned in the literature, but without details.]

The Mannich reaction with prednisone acetate (V; R = R′ = H) was slower than with cortisone acetate and 4,5α-dihydrocortisone acetate, and occurred hardly at all with ethanol as solvent. The neutral fraction from the reaction consisted almost entirely of the starting material, with traces of benzenoid compounds; polyacidic bases were also formed in small amounts. The fraction containing monoacidic bases yielded two compounds: one was analogous in its spectroscopic and polarimetric properties and in its nuclear magnetic resonance to the product [5] from cholesta-1,4-dien-3-one, and we therefore consider it to be the 4-dimethylaminomethyl derivative (V; R = H, R′ = $CH_2 \cdot NMe_2$); the other might be a 2- or a 6-derivative, with a greater likelihood of the former (V; R = $CH_2 \cdot NMe_2$, R′ = H) on the strength of the infrared absorption spectra, which indicated substitution on the 1,4-dienone chromophore. Owing in part to the difficulties in separating this mixture of dimethylaminomethyl compounds, the yields amounted to only about 15% and 5% of the 2- and 4-substituted derivatives (based on the amount of prednisone acetate consumed).

With acetic acid as solvent, we achieved satisfactory conversion of the $\Delta^{16}$-20-ketone

[6] Kirk and Petrow, *Proc. Chem. Soc.*, 1961, 114; cf. Meier, *Chimia*, 1959, **13**, 65; ref. 17.
[7] Beal, Lincoln, and Hogg, Amer. Chem. Soc., Abs. of Papers, 132nd Meeting, Sept., 1957, p. 12-O; Upjohn Co. Inc., B.P. 810,858; U.S.P. 2,847,430.
[8] See ref. 7; Upjohn Co. Inc., B.P. 794,485; Merck Co. Inc., B.P. 838,228.

(VII; R = H) into a Mannich base. Analogy, in particular with the behaviour of 1-acetylcyclopentene,[9] suggested that the product would be the 21-dimethylaminomethyl derivative (VII; R = $CH_2$·$NMe_2$), and this view was upheld by hydrogenation of the base to a ketone (VIII) that did not give iodoform with sodium hypoiodite; moreover, oxidation by ozone of the mixture of enol acetates from this ketone gave the 11,17-dioxo-steroid (X), which proved that alkylation of the nucleus (for instance, at the 15-position) had not occurred.

The resistance of the diacetate (VI) to the Mannich reagents demonstrated the deactivating influence of the 21-acetate group, so we tested with the unsaturated 21-acetoxy-20-ketone (VII; R = Ac) the possibilities of attack at the 15-position alone. Bases were formed very slowly and the attempt was abandoned as unpromising.

## Experimental

Unless other conditions are specified, solutions in chloroform (18—25°, 0·5—1·5%), and n ethanol and bromoform, severally, were used for measurements of optical rotation and of ultraviolet and infrared spectra. M. p.s were measured on a Kofler block. Products were identified by mixed m. p. and infrared spectroscopy with specimens made in other ways.

An atmosphere of nitrogen was maintained over mixtures undergoing Mannich reactions. The products were then isolated as follows. The reaction mixture was evaporated *in vacuo* to dryness, toluene being evaporated off finally to help remove the less volatile components. The residue was shaken with chloroform and water; the chloroform extracted neutral material, which was recovered by evaporation after the solution had been washed with water. The aqueous phase was washed with chloroform, brought to pH 8—9 with sodium hydrogen carbonate or ammonia, and the steroidal bases were then extracted with chloroform or ethyl acetate, from which the product was isolated as described for the neutral fraction. This extract consisted mainly of monoacidic amines; when the aqueous phase was subsequently brought with sodium carbonate to pH 10, polyacidic bases were extracted but were not studied further. The different types of amines could be recognised by paper chromatography and electrophoresis.

Solutions in chloroform, ether, and ethyl acetate were dried before evaporation with magnesium sulphate. Florisil was a product manufactured by the Floridin Co., Tallahassee, Florida, U.S.A.

*Paper Chromatography.*—Basic steroids were separated on Whatman No. 2 papers at 30° with 3-methylbutan-1-ol–acetic acid–water (4 : 1 : 5), chromatograms being run downwards with the upper phase (after equilibration overnight with the lower). $R_F$ values pertain to this system. Neutral steroids were separated by solvent L, as described before; [10] the results are given as $R_F$(L) values. Spots were detected by the TSTZ spray-reagent [10] (which revealed reducing α-ketols and their derivatives) by dark spots on a white background when the papers were examined in ultraviolet light (which revealed αβ-unsaturated ketones), and by brown spots on a nearly white background when the papers were exposed to iodine vapour.[11]

*Paper Electrophoresis.*—Whatman No. 2, 4, or 54 papers (30 × 20 cm.) were used, with 3% acetic acid in water as the electrolyte, at 16 v per cm. Mono-, di-, and tri-acidic bases moved, in 1½ hr., *ca.* 3, 6, and 9 cm., respectively, towards the cathode.

*Attempted Mannich Reaction with 3β,21-Diacetoxy-17-hydroxy-5α-pregnan-20-one* (VI).—A mixture of the diacetate [12] (VI) (2·24 g.), dimethylamine hydrochloride (2·04 g.), 36% formaldehyde solution (2 ml.), and acetic acid (38 ml.) was refluxed. Parts (10 ml.) of the mixture were withdrawn at intervals; these were separated into neutral and basic fractions, which were studied by paper chromatography and infrared spectroscopy. The neutral fraction showed some change after 7 hr.; the diacetate (VI) was then accompanied by more polar substances. The basic fraction, $R_F$ 0·80, did not exceed 30% of the product, even after 12 hours' refluxing. The diacetate (VI), m. p. 218—222° (pure material,[12] m. p. 221—224°), was recovered in 80% yield after 1 hour's refluxing; a crude specimen, m. p. 203—212°, was recovered in 99% yield after 4 hours' refluxing; specimens removed after 7 hr. failed to give crystalline neutral fractions. These and the basic products were not further studied. The $\Delta^{16}$-steroid (VII; R = OAc) (whose preparation is to be described later) was also very slowly affected in these conditions.

[9] Jacquier, Mousseron, and Boyer, *Bull. Soc. chim. France*, 1956, 1653.
[10] Brooks, Evans, Green, Hunt, Long, Mooney, and Wyman, *J.*, 1958, 4614.
[11] Brante, *Nature*, 1949, **163**, 651; Marini-Bettòlo-Marconi and Guarino, *Experientia*, 1950, **6**, 309.
[12] Reichstein and Shoppee, *Vitamins and Hormones*, 1943, **1**, 345.

*Attempted Mannich Reaction with* 3β-*Acetoxy*-5α-*ergost*-22-*en*-11-*one* (XI).—A mixture of the ergostenone [13] (XI) (2·26 g.), dimethylamine hydrochloride (2·04 g.), 36% formaldehyde solution (2 ml.), and acetic acid (30 ml.) was refluxed for 11 hr. The starting material was recovered almost in its entirety; the basic fraction amounted to <2% of the input.

*Mannich Reaction with* 4,5α-*Dihydrocortisone Acetate* (I; R = H).—A solution of the steroid (I; R = H) [14] (4·0 g.) in acetic acid (125 ml.) was heated for 1·5 hr. at 80° with dimethylamine hydrochloride (4·0 g.) and 36% formaldehyde solution (4 ml.). Neutral (0·77 g.) and basic fractions (2·94 g.) were isolated in the usual way; the former consisted mainly of the starting material. The basic fraction was leached with benzene (at *ca.* 30°), and the residue (1·99 g.) crystallized at 0° from a solution at 30° in aqueous *NN*-dimethylacetamide, which gave 2α-*dimethylamino*-4,5α-*dihydrocortisone acetate* (I; R = $CH_2$·$NMe_2$) (1·53 g., 33%), m. p. 203—216° (decomp.). Part (0·8 g.) of this product was recrystallized likewise, giving needles (0·44 g.) of the pure base, m. p. 209—212° (decomp.), $[\alpha]_D$ +76°, $R_F$ 0·57, $[\alpha]_{312}$ +1200° (max.), $[\alpha]_{292}$ ±0° {4,5α-dihydrocortisone acetate (I; R = H), $[\alpha]_{313}$ +1600° (max.), $[\alpha]_{291}$ ±0°}, $\nu_{max.}$ 1745 and 1230 (21-OAc), 1735 (20-C=O), and 1702 cm.$^{-1}$ (C=O) (Found: C, 67·7; H, 8·7; N, 3·3. $C_{26}H_{39}NO_6$ requires C, 67·7; H, 8·5; N, 3·0%). The *oxalate* (from methanol) had m. p. 126—129°, $\nu_{max.}$ (in Nujol) 3450—2500 (bonded OH), 1740 and 1245 (21-OAc), 1720 (20-C=O), 1702 (C=O and $CO_2H$) and 1640 cm.$^{-1}$ ($CO_2^-$) (Found: C, 59·85; H, 7·55; N, 2·3. $C_{28}H_{41}NO_{10}$,$CH_3$·OH requires C, 59·7; H, 7·8; N, 2·4%).

The conditions described above for the Mannich reaction were best for the production of monobasic material; longer heating converted most of this fraction into di- and tri-basic compounds that were not studied.

Crystallization of the crude base (I; R = $CH_2$·$NMe_2$) from aqueous *NN*-dimethylacetamide at 80° gave a neutral substance, $R_F$(L) 0·77, m. p. 206—214° (decomp.), $\lambda_{max.}$ 229 mμ ($E^{1\%}_{1\,cm.}$ 74), $\nu_{max.}$ 1745 and 1232 (21-OAc), 1722 (20-C=O), 1702—1690 (3- and 11-C=O), and 935 cm.$^{-1}$ (exocyclic =$CH_2$), probably a 2-methylene-3-ketone. Deamination also occurred when solutions of the base were stirred for 16 hr. with Florisil; the neutral substance so obtained, m. p. 228—235°, from aqueous acetone, $R_F$(L) 0·70, had no max. between 220 and 300 mμ ($E^{1\%}_{1\,cm.}$ 21 at 230 mμ), and was probably a dimer.[2]

*Mannich Reaction with Cortisone Acetate* (III).—A solution of the steroid (III) (8·0 g.) and dimethylamine hydrochloride (8·0 g.) in acetic acid (200 ml.) and 36% formaldehyde solution (8 ml.) was heated at 80° for 140 min. Neutral (0·49 g.), $\lambda_{max.}$ 239 mμ ($E^{1\%}_{1\,cm.}$ 243), and basic fractions (6·83 g.), $\lambda_{max.}$ 239 mμ ($E^{1\%}_{1\,cm.}$ 218), were separated in the usual way; the neutral fraction contained at least four substances, the main component probably being the starting material (III). The basic fraction in benzene (100 ml.) was stirred for 17 hr. with Florisil (70 g.), and the mixture was then filtered through a column of fresh Florisil (30 g.), which was washed with benzene–ethyl acetate (9 : 1) until the eluates no longer reacted with TSTZ. This fraction (2·12 g.) contained mainly neutral material. The column was next washed with methanol–ethyl acetate (1 : 3), which eluted basic products (2·85 g.) similar to the material originally treated with Florisil. This fraction was not studied further. The first fraction (2·12 g.) in benzene (75 ml.) was stirred with Florisil (30 g.) for 16 hr., and the products were chromatographed as described above, the course of the separation being surveyed by paper chromatography and electrophoresis. Benzene–ethyl acetate (9 : 1) eluted neutral material (1·16 g.) that crystallized from methanol as prisms (0·60 g.), m. p. 202—205°; two further crystallizations gave pure 2-*methylenecortisone acetate* (IV), m. p. 213—217°, $[\alpha]_D$ +260°, $[\alpha]_{383}$ +1000° (max.), $[\alpha]_{353}$ +390° (min.), $R_F$(L) 0·72, $\lambda_{max.}$ 257·5 mμ (ε 13,700), $\nu_{max.}$ 3600 (OH), 1745 and 1230 (21-OAc), 1725 (20-C=O), 1706 (11-C=O), 1664, 1618, and 888 (αβ-unsaturated ketone), and 940 cm.$^{-1}$ (exocyclic =$CH_2$) [Found: C, 69·4; H, 7·3%; *M*, 398 (Rast). $C_{24}H_{30}O_6$ requires C, 69·55; H, 7·3%; *M*, 414]. Isolation of this compound has been mentioned,[7] but without details.

The Mannich reaction proceeded quickly in refluxing acetic acid, giving polyacidic bases, $\lambda_{max.}$ 242—248 mμ. The monoacidic bases were deaminated when heated in water.

Application of the Mannich reaction to the $\Delta^1$-5α-isomer [15] of cortisone acetate (III) gave mono- and poly-acidic bases. The monobasic fraction, $\lambda_{max.}$ 227 mμ ($E^{1\%}_{1\,cm.}$ 194), contained at least five components and was not studied further.

[13] Elks, Evans, Robinson, Thomas, and Wyman, *J.*, 1953, 2933.
[14] Evans, Hamlet, Hunt, Jones, Long, Oughton, Stephenson, Walker, and Wilson, *J.*, 1956, 4356.
[15] Green and Long, *J.*, 1961, 2532.

*2-Methylprednisone Acetate* (V; R = Me, R′ = H).—A solution of 2-methylenecortisone acetate (IV) (0·15 g.) in redistilled mesitylene (5 ml.) was refluxed for 1·5 hr. with 5% palladium–charcoal (0·1 g.) in an atmosphere of nitrogen.[7] The catalyst was filtered off and washed with ethyl acetate; evaporation of the filtrate and washings left a residue (0·13 g.), two crystallizations of which from aqueous acetone gave *2-methylprednisone acetate*, m. p. 194—197°, $[\alpha]_D$ +206°, $[\alpha]_{373}$ +980° (max.), $[\alpha]_{343}$ +640° (min.), $\lambda_{max.}$ 243 mμ (ε 15,900), $\nu_{max.}$ 1745 and 1232 (21-OAc), 1728 and 1710 (C=O), and 1668 and 1628 cm.$^{-1}$ (αβ-unsaturated ketone) (Found: C, 69·1; H, 7·5. $C_{24}H_{30}O_6$ requires C, 69·55; H, 7·3%). Claims to have made this compound by other methods are not accompanied by a description of its properties.[8]

*Mannich Reaction with Prednisone Acetate* (V; R = R′ = H).—A solution of prednisone acetate (V; R = R′ = H) (16·0 g.) and dimethylamine hydrochloride (16·0 g.) in acetic acid (240 ml.) and 36% formaldehyde solution (16 ml.) was heated under reflux for 50 min. The neutral part of this product crystallized from anhydrous methanol, to give prednisone acetate (V; R = R′ = H) (7·5 g., 47% recovery) in three crops.

Chromatography of the basic fraction (6·77 g.) on Florisil, with benzene progressively enriched with ethyl acetate as eluant, gave products that were examined polarimetrically and by paper chromatography. Mixtures richer than 35% in ethyl acetate yielded material (3·64 g.) that gave crystals (1·37 g.), m. p. 201—207°, from benzene (the mother-liquors from this separation were kept; see below). Subsequent crystallizations from aqueous *NN*-dimethylformamide and aqueous acetone gave pure *2-dimethylaminomethylprednisone acetate* (V; R = $CH_2$·$NMe_2$, R′ = H), m. p. 215—216·5°, $[\alpha]_D$ +147° (in dioxan), $[\alpha]_{319}$ +1400° (max.), $R_F$ 0·58, $\lambda_{max.}$ 241 mμ (ε 14,600), $\nu_{max.}$ (in Nujol) 3450 (OH), 1725 and 1280 (21-OAc), 1712 (C=O), and 1675, 1638, 896 cm.$^{-1}$ (αβ-unsaturated ketone), with no band at 1600 cm.$^{-1}$ (see below) (Found: C, 68·05; H, 7·75; N, 3·3. $C_{26}H_{35}NO_6$ requires C, 68·25; H, 7·7; N, 3·1%). It gave an *oxalate* (from methanol, then from ethyl acetate–methanol), m. p. 203—205° (decomp.), $\lambda_{max.}$ 238·5 mμ (ε 12,200), $\nu_{max.}$ (in Nujol) 3160 (OH), 1745 and 1240 ($CO_2H$), 1710 and 1245 (21-OAc), and 1658, 1630, and 886 cm.$^{-1}$ (αβ-unsaturated ketone) (Found: C, 61·35; H, 7·1; N, 2·8. $C_{28}H_{37}NO_{10}$ requires C, 61·4; H, 6·8; N, 2·6%), and a *platinichloride* as a yellow precipitate from dilute hydrochloric acid (Found: N, 2·4; Pt, 15·3. $C_{52}H_{72}Cl_6N_2O_{12}Pt$ requires N, 2·1; Pt, 14·7%).

The aforementioned benzene mother-liquors were diluted with cyclohexane, giving crystals (1·20 g.) of m. p. 174—192°; recrystallization from aqueous dimethylformamide furnished pure *4-dimethylaminomethylprednisone acetate* (V; R = H, R′ = $CH_2$·$NMe_2$) (0·44 g.), m. p. 188—191° (decomp.), $[\alpha]_D$ +193° (in $CHCl_3$), +178° (in dioxan), $[\alpha]_{321}$ +1400° (max.), $R_F$ 0·51, $\lambda_{max.}$ 238·5 mμ (ε 13,300), $\nu_{max.}$ 1746 and 1234 (21-OAc), 1726 (20-C=O), 1708 (C=O), and 1660, 1624, 1604, 856, and 828 cm.$^{-1}$ (αβ-unsaturated ketone) (Found: C, 68·3; H, 7·9; N, 3·2%). [These crystals gave depressed m. p.s on admixture with those of the isomeric base (V; R = $CH_2$·$NMe_2$, R′ = H).] The *oxalate*, from ethyl acetate, had m. p. 206—208°, $\lambda_{max.}$ 239 mμ (ε 13,100), $\nu_{max.}$ (in Nujol) 3480 (OH), 1745 and 1230 (21-OAc), 1736 (20-C=O), 1703 (C=O), 1662 and 1604 (αβ-unsaturated ketone), and 1626 cm.$^{-1}$ ($CO_2^-$) (Found: C, 61·1; H, 6·8; N, 2·5%).

Electrophoresis and paper chromatography indicated the presence of polyacidic bases in the crude product from the Mannich reaction. Only the monoacidic bases were extracted at pH 9; the other components were not investigated. We showed likewise that prednisone acetate (V; R = R′ = H) was hardly changed during an attempted Mannich reaction carried out for 4 hr. in refluxing ethanol.

Substitution at the 2- and the 4-position in prednisone acetate (V; R = R′ = H) to give the above-mentioned bases is accompanied in the 2-dimethylaminomethyl compound (V; R = $CH_2$·$NMe_2$, R′ = H) by $\Delta M_D$ −62° and Δλ +3 mμ, and in its isomer (V; R = H, R′ = $CH_2$·$NMe_2$) by $\Delta M_D$ +75° and Δλ −0·5 mμ. Substitution of a methyl group at the 2-position of 1,4-dien-3-ones [16] results in $\Delta M_D$ −20° to −40° and Δλ +3 to 6 mμ, and at the 4-position the changes [17] are $\Delta M_D$ +70° to +130°, and Δλ ±0°. Introduction of the 4-dimethylaminomethyl group into cholesta-1,4-dien-3-one is accompanied [5] by $\Delta M_D$ +138° and Δλ −2·5 mμ. Our isomers are distinguished further by their infrared spectra, $\nu_{max.}$ at *ca.* 890 cm.$^{-1}$ indicating the unsubstituted 4,5-double bond in the base (V; R = $CH_2$·$NMe_2$, R′ = H), and at 1604 and

[16] Cf. Iriarte and Ringold, *Tetrahedron*, 1958, **3**, 58; Bernstein, Heller, Littell, Stolar, Lenhard, Allen, and Ringler, *J. Amer. Chem. Soc.*, 1959, **81**, 1696.

[17] Cf. Sondheimer and Mazur, *J. Amer. Chem. Soc.*, 1957, **79**, 2906; ref. 5.

828 cm.$^{-1}$ indicating the unsubstituted 1,2-double bond in the isomer (V; R = H, R′ = $CH_2$·$NMe_2$). 4-Dimethylaminomethylcholesta-1,4-dien-3-one and the base (V; R = H, R′ = $CH_2$·$NMe_2$) gave (as solutions in chloroform) similar nuclear magnetic resonance curves in the olefinic region; we thank Dr. N. Sheppard of Cambridge University for providing and interpreting these results.

*Mannich Reaction with* 3β-*Acetoxy*-5α-*pregn*-16-*ene*-11,20-*dione* (VII; R = H).—A solution of the dione (VII; R = H) [17] (8·0 g.) and dimethylamine hydrochloride (8·0 g.) in acetic acid (160 ml.) and 36% formaldehyde solution (8·0 ml.) was heated at 95° for 3 hr. The solvents were then evaporated. A solution of the residual gum in ethyl acetate was extracted with 0·1N-hydrochloric acid, and the combined aqueous layers were made slightly alkaline with sodium hydrogen carbonate. The steroidal base was extracted into ethyl acetate, evaporation of which left a gum (6·1 g.) that contained only one compound behaving as a base on an electrophoretogram. Crystallization and recrystallization of this material from aqueous *NN*-dimethylacetamide at 0° gave needles (4·6 g., 50%) of 3β-*acetoxy*-21-*dimethylaminomethyl*-5α-*pregn*-16-*ene*-11,20-*dione* (VII; R = $CH_2$·$NMe_2$), m. p. 119—122°, $[\alpha]_D$ +50°, $\lambda_{max.}$ 236 mμ (ε 9300), $\nu_{max.}$ (in $CS_2$) 1735 and 1240 (OAc), 1710 (C=O), and 1670 cm.$^{-1}$ (αβ-unsaturated ketone) (Found: C, 72·5; H, 9·2; N, 3·3. $C_{26}H_{39}NO_4$ requires C, 72·7; H, 9·15; N, 3·3%), whose *oxalate* formed needles (from methanol–ethyl acetate), m. p. 190—192°, $\lambda_{max.}$ 237·5 mμ (ε 9660) (Found: C, 64·5; H, 8·0; N, 2·8. $C_{28}H_{41}NO_8$ requires C, 64·2; H, 7·95; N, 2·7%).

3β-*Acetoxy*-21-*methyl*-5α-*pregnane*-11,20-*dione* (VIII).—A solution of the Mannich base (VII; R = $CH_2$·$NMe_2$) (5·37 g.) in ethyl acetate (60 ml.) was shaken with prereduced 5% palladium–charcoal (2·4 g.) under hydrogen at ~1 atm. In 24 hr. at room temperature, ~2 mol. were absorbed. The catalyst was filtered off and washed with ethyl acetate, and filtrate and washings were washed with 0·1N-hydrochloric acid. The combined ethyl acetate phases yielded a solid (2·34 g.); the aqueous phases, after having been made alkaline with sodium hydrogen carbonate and subsequent extraction with ethyl acetate, yielded a crude base (2·54 g.) that was not worked on further. On crystallization from aqueous *NN*-dimethylacetamide the neutral solid gave the *dione* (VIII) as needles (1·47 g.), double m. p. 130°, 136—137°, $[\alpha]_D$ +88°, $\nu_{max.}$ (in $CS_2$) 1735 and 1244 (OAc), and 1712 cm.$^{-1}$ (C=O) (Found: C, 74·1; H, 9·5. $C_{24}H_{36}O_4$ requires C, 74·2; H, 9·3%).

3β-*Acetoxy*-5α-*androstane*-11,17-*dione* (X).—A solution of the dione (VIII) (0·50 g.) in carbon tetrachloride (2·5 ml.) was treated [18] at room temperature with part (1·7 ml.) of a solution of 60% perchloric acid (0·4 ml.; *d* 1·54) in acetic anhydride (20 ml.). After 5 hr. (this time was considered, from a polarimetric study, the best) the cherry-red solution was diluted with carbon tetrachloride, then shaken with aqueous sodium acetate. The organic layer was washed with aqueous sodium hydrogen carbonate, then with water, and evaporated. The product, a gum (0·57 g.), appeared (by infrared spectroscopy) to be a pure enol acetate (although it may have contained geometrical isomers) and was used for the next stage. Accordingly, its solution in methanol (200 ml.) and ethyl acetate (200 ml.) was treated at 40° with ozonized oxygen containing ~5 mol. of ozone. The solution was left for 5 min. after the gas stream had been cut off; 5% palladium–barium sulphate (2·5 g.) was added, and the mixture shaken at atmospheric pressure with hydrogen. After absorption (126 ml.) had ceased, the catalyst was filtered off and washed with ethyl acetate. The filtrate and washings yielded, after evaporation, an oil (0·50 g.) that was dissolved in 1 : 1 ether–light petroleum (b. p. 40—60°) and chromatographed on Florisil (20 g.). Elution gave the crude 11,17-dione (X) (0·156 g.), which recrystallized from hexane as needles, m. p. 162—163·5° (sweating at >154°), $[\alpha]_D$ +100°, $\nu_{max.}$ (in $CS_2$) 1742 and 1244 (OAc), 1740 (17-C=O), and 1716 cm.$^{-1}$ (C=O), that were identified with material prepared by oxidizing 3β-acetoxy-17α-hydroxy-5α-pregnane-11,20-dione [19] with chromic oxide in acetic acid (cf. ref. 20).

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