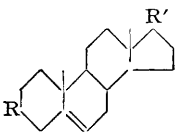
224. *The Constitution of Conessine. Part V.* Synthesis of Some Basic Steroids.*

By R. D. Haworth, J. McKenna, and R. G. Powell.

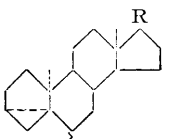
The synthesis is described of a variety of amines related to cholestane and *allo*pregnane. Some of these are identical with conessine degradation products, and the constitution of others has not yet been determined. Significant differences in ease of Hofmann decomposition have been observed with saturated epimeric 3-amines.

The synthesis of some basic derivatives of steroids has been described by Dodgson and Haworth (*J.*, 1952, 67 †), and the present paper records further work in this field, some of which was undertaken in order to provide synthetic samples for comparison with conessine degradation products described in the preceding paper.

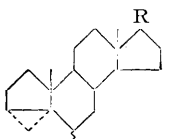
3β-Hydroxypregn-5-ene (I; R = OH, R′ = Et) was prepared by Huang-Minlon's method (*J. Amer. Chem. Soc.*, 1949, **71**, 3301), and the toluene-*p*-sulphonyl ester (I; R = *p*-O·SO_2·C_6H_4Me, R′ = Et) treated with dimethylamine at 100°. The sole product was a base $C_{23}H_{39}N$, m. p. 130°, which yielded a dihydro-derivative $C_{23}H_{41}N$, m. p. 78—79°, on catalytic hydrogenation. The base did not liberate iodine when its solution in glacial acetic acid was boiled for two minutes with a solution of potassium iodate in 2N-sulphuric acid; under the same conditions conessine and authentic 3β-dimethylaminocholest-5-ene



(I)



(II)



(III)

(Dodgson and Haworth, *loc. cit.*) were readily oxidised. Furthermore, the dihydro-derivative was not identical with 3α- or 3β-dimethylamino*allo*pregnane prepared by the unambiguous syntheses described below. It was evident therefore that the reaction of the toluene-*p*-sulphonyl ester with dimethylamine gave not dimethylaminopregn-5-ene (I; R = NMe_2, R′ = Et) but an isomeric base, $C_{23}H_{39}N$, the structure of which is under investigation. It may have a 3 : 5-*cyclo*-structure such as (II or III; R = Et; cf. Julian, Magnani, Meyer, and Cole, *J. Amer. Chem. Soc.*, 1948, **70**, 1834).

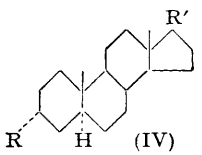
For the preparation of 3α-dimethylamino*allo*pregnane (IV; R = NMe_2, R′ = Et), allopregnan-3β-ol (V; R = OH, R′ = Et) was prepared by Huang-Minlon's method (*loc. cit.*), and the corresponding toluene-*p*-sulphonyl ester (V; R = *p*-O·SO_2·C_6H_4Me, R′ = Et) treated at 100° with dimethylamine. The product is assigned the 3α-configuration, as displacement reactions of 3-toluene-*p*-sulphonates in steroids saturated in rings A and B are known to be accompanied by Walden inversion (Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold, New York, 1947, pp. 642, 643). The isomeric 3β-dimethylamino*allo*pregnane was prepared from *allo*pregnan-3-one (Ruzicka, Meister, and Prelog, *Helv. Chim. Acta*, 1947, **30**, 877) by reduction of the oxime with sodium and amyl alcohol and proved to be identical with the base, m. p. 96°, obtained by degradation of conessine as described in the preceding paper. The oxime reduction was expected to yield predominantly the 3β-isomer (equatorial) as in the case of the similar reduction of the oxime of cholestan-3-one (Dodgson and Haworth, *loc. cit.*). The configuration assigned to these basic *allo*pregnanes is confirmed by the results of the Hofmann degradation described below.

* Part IV, preceding paper.

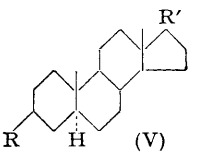
† We draw attention to some errors in this paper:
P. 68, l. 5 (from bottom). *For* "bishydroxyaminoandrostane" *read* "dioximinoandrostane."
P. 69, l. 19. *For* "Hydroxyaminocholestane" *read* "Oximinocholestane."
P. 71, l. 31. *For* "(III)" *read* "(IV)." *For* "Bishydroxyaminoandrostane" *read* "dioximinoandrostane."
l. 38. *For* "(V)" *read* "(IV)."

For the synthesis of 3β-*N*-acetyl-*N*-methylaminopregna-5 : 20-diene (I; R = NMeAc, R′ = $CH{:}CH_2$) required for comparison with the acetylmethylaminopregnadiene, m. p. 182—183°, obtained from conessine, the toluene-*p*-sulphonyl ester of 3β-hydroxypregna-5 : 20-diene (I; R = *p*-$O{\cdot}SO_2{\cdot}C_6H_4Me$, R′ = $CH{:}CH_2$) was prepared as described by Julian, Meyer, and Printy (*J. Amer. Chem. Soc.*, 1948, **70**, 887) and treated with methylamine at 100° in the usual way. Two isomeric bases, $C_{22}H_{35}N$, were obtained. One of these, which gave a negative iodate reaction, yielded an *N*-acetyl derivative, m. p. 113—114°, and was converted on methylation and catalytic hydrogenation into the base, $C_{23}H_{41}N$, m. p. 78—79°, obtained as described above; this isomer must therefore have a structure analogous to that of the base $C_{23}H_{39}N$, m. p. 130°, obtained by reaction of dimethylamine with the toluene-*p*-sulphonyl ester of 3β-hydroxypregn-5-ene. The second isomer, $C_{22}H_{35}N$, gave an acetyl derivative, m. p. 182—183°, identical with the acetylmethylaminopregnadiene obtained by degradation of conessine as described in the preceding paper. This base is designated as 3β-methylaminopregna-5 : 20-diene (I; R = NHMe, R′ = $CH{:}CH_2$) because methylation and catalytic hydrogenation gave 3β-dimethylamino*allo*pregnane (V; R = NMe_2, R′ = Et) and because of the identity of the acetyl derivative with the conessine degradation product. As already shown, the latter contains the original conessine double bond, which on the basis of the physical evidence is situated at position 5 : 6; a 3 : 5-*cyclo*-structure analogous to (II) or (III) may therefore be excluded for the second isomer.

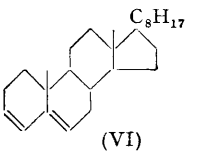
The reaction between cholesteryl toluene-*p*-sulphonate (I; R = *p*-$O{\cdot}SO_2{\cdot}C_6H_4{\cdot}CH_3$, R′ = C_8H_{17}) and liquid ammonia has been described by Julian, Magnani, Meyer, and Cole (*loc. cit.*) who obtained 3β-aminocholest-5-ene * (I; R = NH_2, R′ = C_8H_{17}) and 6ξ-amino-3 : 5-*cyclo*cholestane (II; R = C_8H_{17}). On repetition of this experiment, in addition to the two products named, we have also obtained a third isomeric base, m. p. 90—91°. The constitution of the base is not yet known, but it seems possible that it may be analogous to the bases of unknown constitution obtained in the pregnane series (see above). Related secondary and tertiary bases, $C_{28}H_{49}N$ and $C_{29}H_{51}N$, of unknown structure, were obtained by using methylamine or dimethylamine respectively in place of ammonia in the above experiment; the reaction between dimethylamine and cholesteryl toluene-*p*-sulphonate also yielded 3β-dimethylaminocholest-5-ene (I; R = NMe_2, R′ = C_6H_{17}). All three bases of unknown structure, like the known 6ξ-amino-3 : 5-*cyclo*cholestane, gave a negative iodate reaction when tested as described on p. 1110. The dimethylamino-compound, $C_{29}H_{51}N$, of unknown constitution like the isomeric 3β-dimethylaminocholest-5-ene, gave



(IV)



(V)



(VI)

cholesta-3 : 5-diene (VI) on Hofmann degradation. Catalytic hydrogenation gave a dihydro-derivative, $C_{29}H_{53}N$, which resisted further Hofmann degradation and was not identical with 3β- (Dodgson and Haworth, *loc. cit.*) or 3α-dimethylaminocholestane (IV; R = NMe_2, R′ = C_8H_{17}) obtained by the action of dimethylamine on cholestan-3β-yl toluene-*p*-sulphonate (V; R = *p*-$O{\cdot}SO_2{\cdot}C_6H_4Me$, R′ = C_8H_{17}), a Walden inversion being assumed to occur here as in the case of the preparation of the corresponding *allo*pregnane base.

The Hofmann decomposition of quaternary ammonium hydroxides proceeds by a bimolecular elimination mechanism, and hence in alicyclic compounds the quaternary centre must be *trans* to the hydrogen attached to a β-carbon atom (*inter alia*, Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2093). Owing, however, to the preferred

* Described by Julian *et al.* as "cholesterylamine." The structure assigned here follows readily from the analogous preparation of, and the structural relation to, 3β-dimethylaminocholest-5-ene (Dodgson and Haworth, *loc. cit.*; see also below). The configurations tentatively assigned to 3β-dimethylamino-cholest-5-ene and -cholestane are confirmed by work described in this paper, particularly the preparation of 3α-dimethylaminocholestane, and the evidence from the Hofmann elimination.

conformation of the *trans*-A/B steroid molecule, a 3α-(polar) substituent, either *trans*-hydrogen atom in the β-position (at $C_{(2)}$ or $C_{(4)}$) and the two intervening carbon atoms together form a *coplanar* arrangement, and this is not so in the case of 3β-(equatorial) substituents. Since bimolecular 1 : 2-elimination reactions are particularly favoured by such a coplanar arrangement, 3α-substituents in the cholestane and *allo*pregnane nucleus should undergo bimolecular elimination more readily than the 3β-epimers (cf. Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066; Barton, *Experientia*, 1950, **6**, 316; *J.*, 1951, 1048). We have found this to be the case for Hofmann decomposition of the epimeric 3α- and 3β-trimethylammonium hydroxides of *allo*pregnane and cholestane. A good yield of unsaturated hydrocarbon was obtained in each case with the 3α-compounds, but scarcely any with the 3β-epimers, the original bases being recovered instead in high yield. This work therefore furnishes two excellent examples of the stereochemical specificity of the Hofmann reaction.

Experimental

*Action of Dimethylamine on Pregn-5-en-3β-yl Toluene-*p*-sulphonate.*—3β-Hydroxypregn-5-ene (I; R = OH, R′ = Et) prepared by Huang-Minlon's method (*loc. cit.*) (0·35 g.) was treated at 60° for 30 min. with toluene-*p*-sulphonyl chloride (0·35 g.) and pyridine (1·5 c.c.), and the mixture kept overnight at room temperature. The resultant *pregn-5-en-3β-yl toluene-*p*-sulphonate* separated from ether–light petroleum (b. p. 40—60°) in colourless needles (0·35 g.), $[\alpha]_D$ −52° (in $CHCl_3$, *c* 1·3), m. p. 111—113° (Found: C, 73·7; H, 8·8. $C_{28}H_{40}O_3S$ requires C, 73·7; H, 8·8%). This compound (0·32 g.) was heated overnight with dimethylamine (7 c.c.), at 100° in a small glass-lined autoclave. The excess of dimethylamine was then allowed to evaporate, and the residue treated with ester and dilute sodium hydroxide solution. The ethereal extract was washed with water, a slight excess of 3N-hydrochloric acid added, and the gelatinous precipitated hydrochloride collected. Only a little unchanged ester was recovered from the filtrate. The *base* (0·16 g.) from the hydrochloride separated from acetone in colourless plates, m. p. 130° (Found: N, 4·4. $C_{23}H_{39}N$ requires N, 4·2%). No other compound was obtained from the mother-liquids.

Reduction of the foregoing base. The base (50 mg.) in glacial acetic acid (10 c.c.) was shaken in hydrogen with Adams's platinum oxide catalyst (35 mg.) at 170°/748 mm. Hydrogen uptake (11 c.c. Calc. for one double bond and the catalyst: 11 c.c.) was complete in 30 min. The dihydro-base, isolated in the usual way and recrystallised from acetone, had m. p. 78—79°, undepressed on admixture with the base, $C_{23}H_{41}N$, obtained from 3β-hydroxypregn-5 : 20-diene (see below).

*3α-Dimethylamino*allo*pregnane* (IV; R = NMe_2, R′ = Et).—3β-Hydroxy*allo*pregnane (V; R = OH, R′ = Et), m. p. 134—136°, was prepared essentially by Huang-Minlon's method (*loc. cit.*). The *toluene-*p*-sulphonate* separated from ether–light petroleum (b. p. 40—60°) in prisms, $[\alpha]_D$ −2° (in $CHCl_3$, *c* 1·3), m. p. 110—111° (Found: C, 73·4; H, 9·2. $C_{28}H_{42}O_3S$ requires C, 73·5; H, 9·3%). This compound (0·24 g.) on treatment with dimethylamine at 100° in the manner described above gave rectangular plates (from acetone) of *3α-dimethylamino*allo*pregnane* (0·12 g.), $[\alpha]_D$ +16° (in $CHCl_3$, *c* 1·5), m. p. 108—110° (Found: C, 82·9; H, 12·3; N, 3·9. $C_{23}H_{41}N$ requires C, 83·4; H, 12·4; N, 4·2%).

*3β-Dimethylamino*allo*pregnane* (V; R = NMe_2, R′ = Et).—*allo*Pregnan-3-one was prepared by oxidation of 3β-hydroxy*allo*pregnane (V; R = OH, R′ = Et) (Ruzicka, Meister, and Prelog, *loc. cit.*). The *oxime* formed colourless prisms (from ethanol), $[\alpha]_D$ +19° (in $CHCl_3$, *c* 1·9), m. p. 196—197° (Found: C, 79·0; H, 11·0; N, 4·1. $C_{21}H_{33}ON$ requires C, 79·5; H, 11·0; N, 4·4%). To a refluxing solution of the oxime (0·45 g.) in dry technical amyl alcohol (50 c.c.) was added sodium (3·5 g.) during 2 hours; the crude primary base from the reaction mixture was methylated by 3 hours' heating on the water-bath with formic acid (0·25 c.c. of 90%), water (0·5 c.c.), and formaldehyde (0·35 c.c. of 40%). *3β-Dimethylamino*allo*pregnane* (0·20 g.) separated from acetone in colourless needles, $[\alpha]_D$ +14° (in $CHCl_3$, *c* 1·7), m. p. 96° (Found: C, 83·2; H, 12·3; N, 4·4. $C_{23}H_{41}N$ requires C, 83·3; H, 12·5; N, 4·2%), undepressed on admixture with the base of the same m. p. obtained by degradation of conessine (see Part IV, *loc. cit.*).

Hofmann Decomposition of 3β- *and* 3α-*Dimethylamino*allo*pregnanes.*—3β-Dimethylamino-*allo*pregnane (0·1 g.) was refluxed in acetone with excess of methyl iodide for 2 hours; the solvents were then evaporated and the residue, after being washed with ether, dissolved in aqueous methanol and shaken overnight with excess of silver oxide. The methohydroxide solution was evaporated, finally at 15 mm., and the residue distilled at 200° (bath temp.)/0·005

mm. The distillate was separated into crystalline basic (50 mg.) and neutral fractions (4 mg.). Recrystallisation of the basic fraction from acetone gave colourless needles of 3β-dimethylamino-*allo*pregnane, m. p. 96°. The neutral fraction on recrystallisation from methanol gave colourless plates, m. p. 80°, of *allo*pregn-2- or -3-ene.

A similar experiment with 3α-dimethylamino*allo*pregnane (0·30 g.) returned the base (25 mg.), m. p. 108—110°, after recrystallisation from acetone; the neutral fraction (100 mg.) of the reaction product on crystallisation from methanol gave the *allo*pregnene as colourless plates, $[\alpha]_D$ +67° (in $CHCl_3$, *c* 1·5), m. p. 81—82° (Found: C, 88·0; H, 11·8. $C_{21}H_{34}$ requires C, 88·1; H, 11·9%), undepressed on admixture with the product obtained from 3β-dimethylamino*allo*-pregnane, but depressed to 75—76° on admixture with *allo*pregnane, m. p. 84°.

Reduction of the allo*Pregnene, m. p.* 81—82°.—The hydrocarbon (11 mg.) dissolved in glacial acetic acid (1 c.c.) and ether (1 c.c.) was shaken in hydrogen with Adams's platinum oxide catalyst (11 mg.) at 20°/750 mm. Hydrogen uptake (3·0 c.c. Calc. for one double bond and the catalyst: 3·3 c.c.) was complete in 5 min. The product on crystallisation from methanol gave characteristic colourless prisms of *allo*pregnane, m. p. 83—84°, undepressed on admixture with an authentic specimen.

*Action of Methylamine on Pregna-5:20-dien-3β-yl Toluene-*p*-sulphonate* (I; R = *p*-O·SO_2·C_6H_4Me, R′ = CH:CH_2).—The toluene-*p*-sulphonyl ester (Julian, Meyer, and Printy, *loc. cit.*) (1·42 g.) was treated with methylamine at 100° for 12 hours as above and yielded a mixture of bases (0·717 g.), m. p. 89—100°, after recrystallisation from acetone. The collected product was dissolved in benzene (40 c.c.) and chromatographed on alumina (Spence's Type H, activated for 10 min. at 160—170°; 20 g.), benzene followed by chloroform being used as eluants. Three fractions were obtained: (*a*) a pasty solid (10%); (*b*) a white solid (80%); (*c*) a white solid (10% of total).

Fraction (*a*) on further chromatography yielded uncrystallisable oils and traces of fraction (*b*). Fraction (*b*) on repeated crystallisation from acetone gave a *base* as colourless plates, m. p. 108—109° (Found: C, 83·9; H, 11·5; N, 4·4. $C_{22}H_{35}N$ requires C, 84·4; H, 11·2; N, 4·5%), yielding an N-*acetyl* derivative which separated from light petroleum (b. p. 40—60°) in colourless plates, m. p. 113—114° (Found: C, 80·9; H, 10·3. $C_{24}H_{37}ON$ requires C, 81·1; H, 10·5%).

Fraction (*c*) on recrystallisation from acetone yielded 3β-methylaminopregna-5:20-diene (I; R = NHMe, R′ = CH:CH_2) as colourless needles, m. p. 114—115°, which on acetylation gave 3β-N-*acetyl*-N-*methylaminopregna*-5:20-*diene* (I; R = NMeAc, R′ = CH:CH_2) as needles (from light petroleum, b. p. 40—60°), m. p. 182—183° [Found (on very small quantity): C, 80·4; H, 9·7. $C_{24}H_{37}ON$ requires C, 81·1; H, 10·5%], undepressed on admixture with the acetyl derivative of the same m. p. obtained by degradation of conessine.

The base from fraction (*b*) (35 mg.) was methylated by 3·5 hours' heating at 100° with formic acid (0·2 c.c. of 90%) and formaldehyde (0·1 c.c. of 35%). The tertiary base, purified by vacuum-sublimation (30 mg.), was dissolved in acetic acid (5 c.c.), and the solution shaken in hydrogen with Adams's platinum oxide catalyst (10 mg.) at 17°/760 mm. Hydrogen uptake (7·5 c.c. Calc. for two double bonds and the catalyst: 6·5 c.c.) was complete in 6 hours. The *tetrahydro*-derivative (30 mg.), isolated in the usual way, was purified by sublimation at 180° (bath temp.)/0·1 mm., followed by crystallisation from acetone; colourless plates, m. p. 77—79·5° (Found: C, 83·0; H, 12·2. $C_{23}H_{41}N$ requires C, 83·3; H, 12·4%), were obtained, giving no depression in m. p. on admixture with the base, m. p. 78—79°, obtained as above from pregn-5-en-3β-yl toluene-*p*-sulphonate and dimethylamine, followed by catalytic hydrogenation.

Methylation and reduction in a similar manner of the 3β-methylaminopregna-5:20-diene (15 mg.) from fraction (*c*) gave 3β-dimethylamino*allo*pregnane (12 mg.), m. p. 92—93·5°, undepressed with the base, m. p. 95—96°, obtained by degradation of conessine.

*Action of Ammonia on Cholesteryl Toluene-*p*-sulphonate.*—Cholesteryl toluene-*p*-sulphonate (I; R = *p*-C_6H_4Me·SO_2·O, R′ = C_8H_{17}) (17 g.) and liquid ammonia (200 c.c.) were heated at 100° for 8 hours, excess of ammonia allowed to evaporate, and the resulting basic mixture separated into (*a*) bases with hydrochlorides insoluble in ether (5 g.), and (*b*) bases with hydrochlorides soluble in ether (6 g.) (cf. Julian, Magnani, Cole, and Meyer, *loc. cit.*). Bases (*a*) were chromatographed in light petroleum (b. p. 40—60°) on alumina (Spence Type H, activated at 160° for 10 min.; 150 g.), elution being carried out successively with light petroleum (b. p. 40—60°), ether–light petroleum (b. p. 40—60°), ether, and chloroform. There were thus obtained 3β-aminocholest-5-ene (I; R = NH_2, R′ = C_8H_{17}) (2 g.), which on recrystallisation from ether formed needles, m. p. 90—91° (Julian *et al.*, *loc. cit.*, give m. p. 89—94°, $[\alpha]_D$ −26°), and, in the final eluates, a base (2·5 g.) recrystallising from light petroleum (b. p. 40—60°) in needles, m. p. 190°, which is being examined further.

From bases (*b*) was obtained 6ξ-amino-3 : 5-*cyclo*cholestane (II; R = C_8H_{17}) as colourless rosettes (from hexane), m. p. 77—79° (Julian *et al.*, *loc. cit.*, give m. p. 77—79°).

Action of Methylamine on Cholesteryl Toluene-p-*sulphonate.*—The ester (10 g.) and methylamine (10 c.c.) were heated at 100° for 8 hours, and the crude basic product (3·7 g.; from ether-insoluble hydrochloride) chromatographed essentially in the manner described above, yielding (*a*) a *base* (2·2 g.), m. p. 84—86°, and (*b*) a base (50 mg.), m. p. 109—113°, in addition to oily fractions. Fraction (*a*) on recrystallisation from acetone gave colourless needles, m. p. 85·5—86·5° (Found : C, 84·1; H, 12·3; N, 3·1. $C_{28}H_{49}N$ requires C, 84·1; H, 12·4; N, 3·5%).

Methylation of the base $C_{28}H_{49}N$, *m. p.* 85·5—86·5°. The base (310 mg.) was methylated in the usual manner with formic acid (1·4 c.c. of 90%) and formaldehyde (0·2 c.c. of 40%) for 4 hours at 100°. The product (300 mg.) separated from acetone in colourless plates, m. p. 69—70°, undepressed on admixture with the base $C_{29}H_{51}N$, m. p. 70—71°, obtained as described below by the action of dimethylamine on cholesteryl toluene-*p*-sulphonate.

Action of Dimethylamine on Cholesteryl Toluene-p-*sulphonate.*—The sulphonate (10 g.) and dimethylamine (9 c.c.) were heated at 100° for 8 hours, and the crude bases (5 g. from hydrochlorides insoluble in ether) chromatographed as above, yielding successively (*a*) an oil (0·1 g.), (*b*) a colourless solid, m. p. 66—69° (4 g.), and (*c*) a colourless solid, m. p. 151·5—152° (0·6 g.). Recrystallisation of fraction (*b*) from acetone gave the *base* as colourless plates, m. p. 70—71° (Found : C, 84·2; H, 12·1; N, 3·7. $C_{29}H_{51}N$ requires C, 84·2; H, 12·5; N, 3·4%). Fraction (*c*) was recrystallised from ether and yielded colourless neeeles of 3β-dimethylaminocholest-5-ene (I; R = NMe_2, R′ = C_8H_{17}), $[\alpha]_D$ −32° (in $CHCl_3$, *c* 0·5), m. p. 151·5—152° undepressed on admixture with an authentic speciman. Dodgson and Haworth (*loc. cit.*) give m. p. 151°, $[\alpha]_D$ −31·5° (in $CHCl_3$, *c* 0·5). Catalytic hydrogenation according to Dodgson and Haworth's method gave 3β-dimethylaminocholestane, m. p. 105—106°. Separation of the above two bases may also be effected by fractional crystallisation of the hydrochlorides from methanol. A similar mixture is produced by heating cholesteryl toluene-*p*-sulphonate (11·9 g.), ethanol (15 c.c.), toluene-*p*-sulphonic acid (3 g.), and dimethylamine (13·5 g.) for 24 hours at 120° (we thank Dr. G. H. Whitfield for this experiment) or, significantly, by methylating with formaldehyde and formic acid the basic mixture (from hydrochlorides insoluble in ether), obtained as above by the action of ammonia on cholesteryl toluene-*p*-sulphonate.

Hofmann Degradation of 3β-*Dimethylaminocholest*-5-*ene.*—*Cholest*-5-*ene*-3β-*trimethylammonium iodide* (I; R = NMe_3I, R′ = C_8H_{17}) separated from aqueous alcohol as a colourless microcrystalline powder, $[\alpha]_D$ −20° (in $CHCl_3$ *c* 2·0), m. p. 295—298° (decomp.) (Found : N, 2·3; I, 23·0. $C_{30}H_{54}NI$ requires N, 2·5; I, 22·8%). An aqueous solution of the corresponding methohydroxide was evaporated and heated to 180° (bath-temp.) at 0·1 mm. Recrystallisation of the sublimate from ether–methanol gave colourless needles of cholesta-3 : 5-diene (VI), m. p. 77—78°, undepressed on admixture with an authentic specimen.

Hofmann Degradation of the Base, $C_{29}H_{51}N$, *m. p.* 70—71°.—The base (116 mg.) yielded a *methiodide* (158 mg.), which separated from aqueous alcohol in colourless needles, m. p. 270—272° (decomp.) (Found : C, 65·0; H, 9·9; N, 2·4; I, 22·4. $C_{30}H_{54}NI$ requires C, 64·8; H, 9·8; N, 2·5; I, 22·8%). This salt (55 mg.) was converted into an aqueous solution of the corresponding methohydroxide, which was evaporated and heated at 160° (bath-temp.)/0·1 mm. The white sublimate (32 mg.) of cholesta-3 : 5-diene had m. p. 77—78°, undepressed on admixture with an authentic specimen. No basic material was isolated. A similar result was obtained by heating the quaternary iodide (100 mg.) with water (2·4 c.c.), ethylene glycol (27 c.c.), and potassium hydroxide (4 g.) at the reflux temperature (140°) for 4 hours.

Reduction of the base, $C_{29}H_{51}N$, *m. p.* 70—71°. The base (317 mg.) was shaken in glacial acetic acid (7 c.c.), in hydrogen at 19°/769 mm. in the presence of Adams's platinum oxide catalyst (25 mg.). Hydrogen uptake (24 c.c. Calc. for one double bond and the catalyst : 23·4 c.c.) was complete in 6 hours. The *dihydro-base* (320 mg.), isolated in the usual way, separated from acetone as colourless plates, m. p. 73—74° (Found : C, 83·3; H, 12·6; N, 3·9. $C_{29}H_{53}N$ requires C, 83·8; H, 12·9; N, 3·4%), depressed to 58° on admixture with the original base, m. p. 70—71°. The reduced base was recovered unchanged on attempted Hofmann degradation, no non-basic product being isolated.

Attempted isomerisation of the base $C_{29}H_{51}N$, *m. p.* 70—71°. The base (500 mg.) and dimethylammonium toluene-*p*-sulphonate (500 mg.) were heated with dimethylamine (10 c.c.) for 12 hours at 108°. The recovered base (485 mg.) had m. p. 69—70°, raised to 70—71° on recrystallisation from acetone. No depression in m. p. was observed on admixture with the original base.

3α-*Dimethylaminocholestane* (IV; R = NMe_2, R′ = C_8H_{17}).—Cholestan-3β-yl toluene-*p*-

sulphonate (V; R = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$, R′ = C_8H_{17}) (0·25 g.), prepared by Stoll's method (*loc. cit.*), was heated with dimethylamine (6 c.c.) at 100° for 8 hours. The basic product (100 mg.) was recrystallised from acetone, and the *3α-dimethylaminocholestane* thus obtained as colourless plates, $[\alpha]_D$ +22° (in $CHCl_3$, *c* 2·0), m. p. 90·5—91·5° (Found: C, 84·0; H, 12·8. $C_{29}H_{53}N$ requires C, 83·8; H, 12·9%).

Hofmann Decomposition of 3α- and 3β-Dimethylaminocholestanes.—*3α-Cholestanyltrimethylammonium iodide* (IV; R = NMe_3I, R′ = C_8H_{17}) separated from aqueous alcohol in colourless needles, m. p. 289—290° (decomp.) (Found: C, 64·8; H, 10·1. $C_{30}H_{56}NI$ requires C, 64·6; H, 10·1%). The quaternary iodide (161 mg.) was converted into methohydroxide in the usual way, and the aqueous methanolic solution evaporated and heated at 160—180° (bath-temp.)/0·5 mm. for 30 min. The mixture was extracted with ether, and the residue from the ether separated into a basic (20 mg.) and a non-basic fraction (85 mg.). The former had m. p. 90—91°, undepressed on admixture with 3α-dimethylaminocholestane; the latter began to melt at 58° (Found: C, 87·1; H, 12·4. Calc. for $C_{27}H_{46}$: C, 87·5; H, 12·5%), and had $[\alpha]_D$ +63° (in $CHCl_3$, *c* 2·0); it appeared to be a mixture of cholest-2-ene, m. p. 74·5—75°, $[\alpha]_D$ +69° (in $CHCl_3$, *c* 1·6), and cholest-3-ene, m. p. 72—72·5°, $[\alpha]_D$ +57° (in $CHCl_3$, *c* 1·4) (Barton and Rosenfelder, *J.*, 1951, 1048). Hydrogenation of the mixture (40 mg.) in ether (2 c.c.) and glacial acetic acid (5 c.c.) in the presence of Adams's platinum oxide catalyst (13 mg.) was complete in 8 hours (Hydrogen uptake, 5·3 c.c. Calc. for one double bond and the catalyst: 5·5 c.c.). The crude hydrogenation product (40 mg.) had m. p. 75° and, after recrystallisation from ether–ethanol, colourless plates of cholestane were obtained, $[\alpha]_D$ +26° (in $CHCl_3$, *c* 2·0), m. p. 78—79°. Barton and Cox (*J.*, 1948, 783) give m. p. 80°, $[\alpha]_D$ +25° (in $CHCl_3$, *c* 1·5).

3β-Cholestanyltrimethylammonium iodide (V; R = NMe_3I, R′ = C_8H_{17}) separated from aqueous alcohol as a colourless, microcrystalline powder, m. p. 290° (decomp.), $[\alpha]_D$ +33° (in $CHCl_3$, *c* 1·1) (Found: I, 20·7. $C_{30}H_{56}NI$ requires I, 22·8%). Attempted Hofmann decomposition of this salt (170 mg.) in the manner described above gave a mixture of a neutral oil (5 mg.), which was not examined further, and a base (117 mg.), m. p. 103—104°, raised to 105—106° on recrystallisation from ether. No depression in m. p. was observed on admixture with 3β-dimethylaminocholestane. A similar result was obtained by heating the methiodide (100 mg.) with water (2·4 c.c.), ethylene glycol (27 c.c.), and potassium hydroxide (4 g.) for 4 hours at 140°.

Our thanks are offered to the University for the award of a Henry Ellison Fellowship to R. G. Powell, to Imperial Chemical Industries Limited for a grant which has defrayed some of the expenses of this investigation, and to the British Schering Research Institute and Dr. P. L. Julian for generous gifts of chemicals.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, November 17th*, 1952.]