729. *The Constitution of Conessine. Part IX.* Further Studies with Steroidal Amines related to Conessine.*

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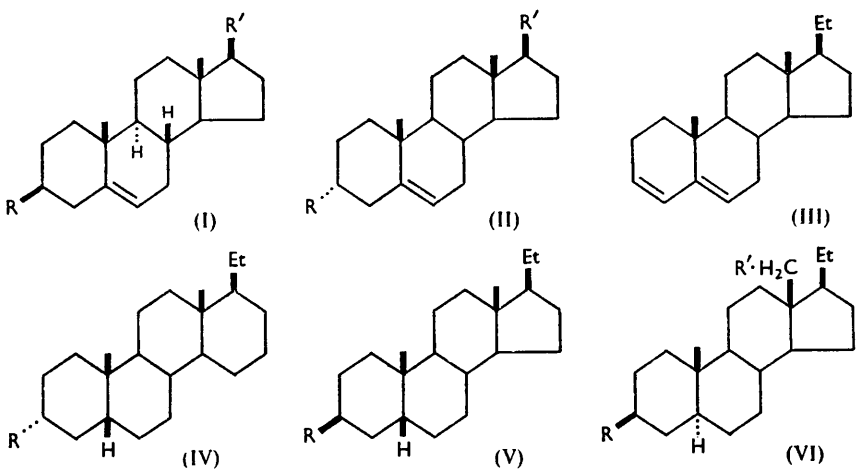
The base, m. p. 130°, previously [1] obtained by treatment of pregn-5-en-3β-yl toluene-*p*-sulphonate with dimethylamine has been identified as 3α-dimethylaminopregn-5-ene by its properties and reactions including Hofmann degradation to pregna-3 : 5-diene, and by identification of its dihydro-derivative as 3α-dimethylaminopregnane; the results † demonstrate that virtually complete inversion of configuration at $C_{(3)}$ occurs during the replacement reaction with the unsaturated toluene-*p*-sulphonate, in opposition to Shoppee's earlier generalisation.[3] The synthesis is reported of 3β-dimethylaminopregn-5-ene, a conessine degradation product, and some Emde reductions of other conessine derivatives and related amines are described.

HAWORTH, MCKENNA, and POWELL [1] found that the reaction of dimethylamine with pregn-5-en-3β-yl toluene-*p*-sulphonate (I; R = *p*-Me·C_6H_4·SO_3, R′ = Et) failed to yield the then expected 3β-dimethylaminopregn-5-ene (I; R = NMe_2, R′ = Et), an amine previously [4] isolated by degradation of conessine; an isomeric amine, m. p. 130°, which furnished a dihydro-derivative, m. p. 78—79°, was instead obtained in the replacement reaction. Parallel reactions [1] with cholest-5-en-3β-yl toluene-*p*-sulphonate (I; *p*-Me·C_6H_4·SO_3, R′ = C_8H_{17}) were subsequently found,[5,6] unexpectedly,‡ to yield



3α-amines (II; R = NH_2, NHMe, NMe_2, R′ = C_8H_{17}), and the data now presented indicate that the base, m. p. 130°, is 3α-dimethylaminopregn-5-ene (II; R = NMe_2, R′ = Et). Thus the infrared absorption spectrum (max. at 797, 826, and 1667 $cm.^{-1}$; the corresponding cholestene base has bands [6] at 796, 827, and 1660 $cm.^{-1}$) and optical rotation (" Δ value " [7] of the unsaturated amine relative to 3α-dimethylaminopregnane is −247°)

* Part VIII, *J.*, 1955, 986.

† This work was essentially complete in March, 1954, when Professor C. W. Shoppee, F.R.S., was informed of our views on the structure of the dimethylaminopregnene. The unsaturated base was subsequently synthesised by Shoppee and his collaborators.[2]

‡ Cf. ref. 3.

[1] Haworth, McKenna, and Powell, *J.*, 1953, 1110.
[2] Pierce, Richards, Shoppee, Stephenson, and Summers, *J.*, 1955, 694.
[3] Shoppee, *J.*, 1946, 1147.
[4] Haworth, McKenna, and Whitfield, *J.*, 1953, 1102.
[5] Šorm, Lábler, and Černý, *Chem. Listy*, 1953, **47**, 418; 1954, **48**, 1058.
[6] Haworth, Lunts, and McKenna, *J.*, 1955, 986.
[7] Barton and Klyne, *Chem. and Ind.*, 1948, 755.

support this structure. Hofmann degradation of the base yielded pregna-3 : 5-diene (III), which we synthesised for comparison by reaction of pregn-5-en-3β-yl toluene-*p*-sulphonate (I; R = *p*-Me·C_6H_4·SO_3, R′ = Et) with boiling dimethylaniline.[8] Finally, the dihydro-derivative, m. p. 78—79°, of the unsaturated amine was identified as 3α-dimethylamino-pregnane (IV; R = NMe_2) by synthesis of this base from pregnan-3-one, obtained in our work by catalytic hydrogenation under alkaline conditions of pregn-4-en-3-one.[9] Reduction of the ketoxime with sodium and pentyl alcohol gave a mixture of 3α(equatorial; main component)- and 3β(axial)-aminopregnanes (IV and V; R = NH_2); methylation of this mixture yielded 3α- and 3β-dimethylaminopregnane (IV and V; R = NMe_2). The latter base was identical with the product, m. p. 124°, obtained by Shoppee and his co-workers [2] by treatment of pregnan-3α-yl toluene-*p*-sulphonate (IV; R = *p*-Me·C_6H_4·SO_3) with dimethylamine, and the yield in our reaction sequence is very low owing to the axial conformation of the corresponding primary amine; Shoppee and his co-workers [2] did not isolate any 3β-amine on reduction of pregnan-3-one oxime with sodium and ethyl alcohol.

3β-Dimethylaminopregn-5-ene (I; R = NMe_2, R′ = Et) has been prepared in the following manner. Ammonolysis of pregn-5-en-3β-yl toluene-*p*-sulphonate yielded a mixture of amines from which, after experience with the related cholesterylamines, the primary 3β-epimer was isolated by precipitation with digitonin. After decomposition of the digitonin complex in the usual manner, methylation of the primary base yielded 3β-dimethylaminopregn-5-ene, identical with the conessine degradation product.[4]

3β-Dimethylamino*allo*pregnane (VI; R = NMe_2, R′ = H), previously obtained by a lengthy degradation sequence [4] from conessine, has now been prepared from the alkaloid by the following simple process. Tetrahydroconessimethine (VI; R = R′ = NMe_2), obtained by partial Hofmann degradation (ring fission only) of conessine or dihydro-conessine followed by catalytic hydrogenation,[4,10] was converted into the dimethiodide. Previous attempts [11] to effect Emde reductions of dimethochlorides related to conessine by treatment with sodium amalgam in aqueous medium failed, but under the modified Emde conditions (sodium–liquid ammonia) described in the Experimental section reduction of tetrahydroconessimethine dimethiodide yielded *allo*pregnane (VI; R = R′ = H) and 3β-dimethylamino*allo*pregnane (VI; R = NMe_2, R′ = H). No hexahydro*apo*conessine (VI; R = H, R′ = NMe_2) was isolated from the reaction mixture, but this base was obtained by sodium–liquid ammonia reduction of a monomethiodide (VI; R = NMe_3I, R′ = NMe_2) prepared by partial methylation of tetrahydroconessi-methine; this result supports the expectation from previous experience that the 3β-dimethylamino-group in the reduced methine should quaternise much more rapidly than the dimethylamino-group originally derived by fission of the conessine heterocyclic ring. The sodium–liquid ammonia method appears in general to be superior to the conventional Emde procedure for the reduction of steroidal quaternary salts: reduction of the methiodides of monoacid bases such as hexahydro*apo*conessine gave better yields of hydrocarbon than those previously recorded.[12]

Experimental

Hofmann Degradation of 3α-Dimethylaminopregn-5-ene.—3α-Dimethylaminopregn-5-ene [1] (21 mg.) was converted into dimethiodide and thence into an aqueous solution of dimetho-hydroxide in the usual way; the solution was concentrated and the residue pyrolysed at 140° (bath)/0·005 mm. Crystallisation of the product from acetone gave pregna-3 : 5-diene (6 mg.), m. p. 84°, undepressed on admixture with a specimen prepared as described below.

Pregna-3 : 5-diene.—Pregna-5-en-3β-yl toluene-*p*-sulphonate (89 mg.) in dry dimethyl-aniline (1 c.c.) was heated under reflux for 20 min., and the neutral *product* (50 mg.) isolated with ether in the usual way and recrystallised from acetone; it then had m. p. 87—88°, $[\alpha]_D$

[8] Cf. ref. 4.
[9] Cf. Wilds, Johnson, and Sutton, *J. Amer. Chem. Soc.*, 1950, **72**, 5524.
[10] Favre, Haworth, McKenna, Powell, and Whitfield, *J.*, 1953, 1115.
[11] Haworth, McKenna, Powell, and Woodward, *J.*, 1951, 1736.
[12] Haworth, McKenna, and Whitfield, *J.*, 1949, 3127.

$-138°$ (*c* 0·52 in $CHCl_3$), $\lambda_{max.}$ 2280, 2350, 2435 Å (ε 19,600, 20,600, 13,500 respectively) (Found : C, 88·8; H, 11·2. $C_{21}H_{32}$ requires C, 88·7; H, 11·3%).

Pregnan-3-one.—Pregn-4-en-3-one (242 mg.) in 0·5% alcoholic potassium hydroxide (10 c.c.) was hydrogenated (uptake at N.T.P., 19·4 c.c. Calc. for one double bond, 18·1 c.c.) in presence of 15% palladised charcoal (100 mg.); the product had m. p. (from acetone) 114° (lit.,[13] 115°). The oxime crystallised from ethanol in colourless rods, m. p. 161—162° (Found : N, 4·5. Calc. for $C_{21}H_{35}ON$: N, 4·4%). Pierce *et al.*[2] give m. p. 165—167°.

3α- and 3β-Dimethylaminopregnane.—Pregnan-3-one (128 mg.) in dry technical pentyl alcohol (20 c.c.) was treated at reflux temperature with sodium (2·5 g.) added portionwise during 1·25 hr., and the basic product was isolated as mixed hydrochlorides (92 mg.), m. p. 320—322°. The basic mixture was methylated with formaldehyde and formic acid, and the tertiary bases were again isolated as a mixture of hydrochlorides (103 mg.) which was fractionally crystallised from acetone, yielding needles (7 mg.), m. p. 290—294° (decomp.), and needles (48 mg.), m. p. 239—241° (decomp.). The amine from the first hydrochloride, on crystallisation from acetone, had m. p. 132° undepressed on admixture with an authentic but lower-melting (m. p. 124°) sample of 3β-dimethylaminopregnane kindly supplied by Professor C. W. Shoppee, F.R.S. The lower-melting hydrochloride yielded a base which crystallised from acetone in plates, m. p. 77—78°, undepressed on admixture with a sample of 3α-dimethylaminopregnane prepared by reduction of 3α-dimethylaminopregn-5-ene [1] (Found : N, 4·4. Calc. for $C_{23}H_{41}N$: N, 4·2%).

Separation of 3β- from 3α-Aminocholest-5-ene with Digitonin.—A mixture of 3α-*iso*propylideneaminocholest-5-ene [6] (10 mg.) and the 3β-epimer (13 mg.) was hydrolysed with hydrochloric acid, and the mixture of primary bases in 95% ethanol (5 c.c.) was treated with digitonin (5 c.c. of 1% solution in 95% ethanol). After 42 hr. the insoluble digitonide (24 mg.) was collected and decomposed with pyridine–ether in the usual manner. Methylation of the basic product from this decomposition yielded 3β-dimethylaminocholest-5-ene, m. p. and mixed m. p. 146—147° (4 mg.).

Synthesis of 3β-Dimethylaminopregn-5-ene.—Pregn-5-en-3β-yl toluene-*p*-sulphonate (355 mg.) was heated with excess of liquid ammonia at 95° for 9·5 hr., and the hydrochlorides of steroidal basic products separated into fractions (96 and 32 mg.) respectively soluble and insoluble in ether. Recrystallisation of the soluble fraction from acetone yielded fine needles, m. p. 264—265°, $[\alpha]_D$ +18° (*c* 0·7 in $CHCl_3$) (Found : Cl, 10·2. $C_{21}H_{36}NCl$ requires Cl, 10·5%), presumably [14] *6β-amino-3 : 5-cyclopregnane hydrochloride.* The ether-insoluble hydrochloride fraction was basified and the product treated with digitonin in the manner described above for the aminocholestenes; the insoluble digitonide (20 mg.) was then decomposed and the resultant amine methylated with formaldehyde and formic acid. Crystallisation of the product from acetone gave 3β-dimethylaminopregn-5-ene, needles, m. p. 115°, not depressed on admixture with a sample, m. p. 117°, prepared [4] from conessine.

Emde Reduction of Tetrahydroconessimethine Dimethiodide.—The *dimethiodide*, needles (from ether–methanol), m. p. 307—308° (decomp.) (Found : N, 4·6; I, 39·4, 37·9. $C_{25}H_{46}N_2,2CH_3I$ requires N, 4·3; I, 38·6%), was prepared by heating the methine with excess of methyl iodide at 100° for 49 hr. This salt (375 mg.) in liquid ammonia (100 c.c.) was treated portionwise with sodium until a permanent blue colour developed. After 8 hr. the ammonia was allowed to evaporate and neutral and basic fractions were isolated. Crystallisation of the neutral fraction from ether–methanol yielded *allo*pregnane (18 mg.) as needles, m. p. and mixed m. p. 80°. The basic product, which yielded a hydrochloride insoluble in water, crystallised from acetone in needles (135 mg.), m. p. 95—96° undepressed on admixture with an authentic specimen of 3β-dimethylamino*allo*pregnane of the same m. p. No hexahydro*apo*conessine could be isolated from the basic fraction from the reduction by either chromatography or selective quaternisation with methyl iodide (hexahydro*apo*conessine quaternises very much more slowly than 3β-dimethylamino*allo*pregnane).

Reduction of Tetrahydroconessimethine Monomethiodide.—Tetrahydroconessimethine (215 mg.) and methyl iodide (1 c.c.) were heated under reflux in methanol (10 c.c.) for 3 hr. *Tetrahydroconessimethine monomethiodide*, precipitated with ether and recrystallised from ether–methanol, was obtained as needles (203 mg.), m. p. 297° (decomp.) (Found : I, 24·0. $C_{25}H_{46}N_2,CH_3I$ requires I, 24·6%). Reduction of this salt as before yielded hexahydro*apo*conessine (7 mg.), m. p. and mixed m. p. 63—64°, and tetrahydroconessimethine (88 mg.), m. p. 80—81° after recrystallisation from acetone.

[13] Marker and Lawson, *J. Amer. Chem. Soc.*, 1938, **60**, 2438.
[14] Cf. Julian, Magnani, Meyer, and Cole, *J. Amer. Chem. Soc.*, 1948, **70**, 1834.

*Reduction of Hexahydro*apo*conessine Methiodide.*—The conversion of hexahydro*apo*conessine (158 mg.) into methiodide by refluxing in methanol (10 c.c.) with methyl iodide (1 c.c.) was only 34% complete in 4 hr., and more prolonged heating (>12 hr.) was required for reasonable yields by this method. Reduction of the methiodide (204 mg.) in the manner described above yielded *allo*pregnane (15 mg.), m. p. 83—84°, and hexahydro*apo*conessine (125 mg.), m. p. 64—65°.

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