223. *The Constitution of Conessine. Part IV.* The Position of the Double Bond and Dimethylamino-group.*

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Pregna-3 : 5 : 20-triene has been synthesised and found to be identical with the unsaturated hydrocarbon, $C_{21}H_{30}$, obtained by Emde reduction of *apo*-conessine methochloride. The physical data and the degradation of conessine to 3β-dimethylaminopregn-5-ene indicate the positions of the double bond and dimethylamino-group in the alkaloid.

In Part III * the pregnatriene, $C_{21}H_{30}$, m. p. 74—76°, first isolated by Späth and Hromatka (*Ber.*, 1930, **63**, 126) by Emde degradation of *apo*conessine, was shown to yield a mixture of pregnane and *allo*pregnane on catalytic hydrogenation, and it was suggested that the conjugated double bond system of the unsaturated hydrocarbon was in the 3 : 5-position. This conjugated system is formed during Hofmann decomposition of conessine, and is derived from the original double bond of the alkaloid and that formed by the elimination of the dimethylamino-group (Part II, *J.*, 1949, 3127); the isolated double bond of *apo*-conessine and the derived pregnatriene results from the opening of the heterocyclic ring. Analogy with the other steroidal alkaloids suggested that the methylimino-group of the heterocyclic ring in conessine would probably involve the two-carbon side chain at $C_{(17)}$, so that *apo*conessine should have (*a*) a double bond at the 17 : 20-position, (*b*) a double

* Part III, *J.*, 1951, 1736.

bond at the 20 : 21-position, or (*c*) a dimethylamino-group at $C_{(20)}$ or $C_{(21)}$. Of these possibilities, (*a*) appeared to be excluded by the generalised Hofmann rule (formation of the least substituted ethylene), and (*c*) by the fact that neither *apo*conessine nor its hexahydro-derivative can be degraded to a hydrocarbon by further Hofmann decomposition (Späth and Hromatka, *loc. cit.*; Part II, *loc. cit.*; Favre, Haworth, McKenna, Powell, and Whitfield, *J.*, 1953, 1115). No structural, polar, or stereochemical influences could be envisaged which would completely prevent the elimination of trimethylamine from a $C_{(20)}$- or $C_{(21)}$-trimethylammonium hydroxide, and indeed Julian, Meyer, and Printy (*J. Amer. Chem. Soc.*, 1948, **70**, 887) have recorded two examples of ready Hofmann decomposition of $C_{(20)}$-amines. It seemed possible, therefore, that the isolated double bond in *apo*conessine and the derived pregnatriene, m. p. 74—76°, was at the 20 : 21-position, and the synthesis of pregna-3 : 5 : 20-triene (I) was accordingly undertaken (as already briefly recorded: Haworth and McKenna, *Chem. and Ind.*, 1951, 312).

The preparation of 3β-hydroxypregna-5 : 20-diene and the corresponding toluene-*p*-sulphonate has been described by Julian, Meyer, and Printy (*loc. cit.*), and we are greatly indebted to Dr. Julian for a generous sample of 3β-acetoxy-20-dimethylaminopregn-5-ene from which these two compounds were obtained. Dehydration of the hydroxy-diene by heating it with anhydrous copper sulphate, or treatment of the toluene-*p*-sulphonyl ester with boiling dimethylaniline gave a hydrocarbon $C_{21}H_{30}$, m. p. 74—76°, identical with the pregnatriene obtained from *apo*conessine. This hydrocarbon is formulated as (I) because of the analogous dehydration of cholesterol to cholesta-3 : 5-diene (Mauthner and Suida, *Monatsh.*, 1896, **17**, 29) and of the characteristic ultra-violet absorption ($\lambda_{max.}$, in ethanol, 2350 Å; $\log \varepsilon = 4{\cdot}4$) and high lævorotation.

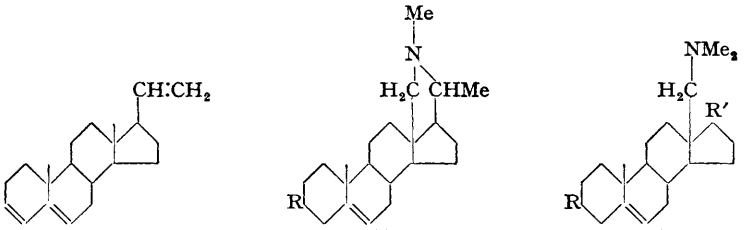
The structure of Späth and Hromatka's pregnatriene being thus demonstrated, two important conclusions (which had been anticipated earlier) followed: first, that the conessine heterocyclic methylimino-group does indeed involve $C_{(20)}$ or $C_{(21)}$ and some other carbon atom in the neighbourhood; and, secondly, that the double bond and the dimethylamino-group of the alkaloid are situated in the neighbourhood of $C_{(5)}$. Preliminary attempts to identify the position of the conessine double bond were made by a study of the base dioxyconessine (more correctly dihydroxydihydroconessine), $C_{24}H_{42}O_2N_2$, produced by oxidation of conessine with potassium iodate (Warnecke, *Arch. Pharm.*, 1888, **226**, 248). A Zerewitinoff determination showed the presence of two active hydrogen atoms, and the simplest formulation for the base would be an α-glycol formed by hydroxylation of the conessine double bond; a solution of dioxyconessine in dilute sulphuric acid was unattacked, however, by periodic acid at room temperature. Oxidation of 3β-dimethylaminocholest-5-ene (Dodgson and Haworth, *J.*, 1952, 67) with potassium iodate gave a similar high-melting base, $C_{29}H_{53}O_2N$, which is regarded as 3β-dimethylamino-5ξ : 6ξ-dihydroxycholestane. Like dioxyconessine, this base contained two active hydrogen atoms.

Dioxyconessine is more soluble in water than conessine, and it was at first thought that it was a ψ-base, similar to berberine or cotarnine (for a recent discussion, see Skinner, *J.*, 1950, 823). Potentiometric titration of an aqueous solution of dioxyconessine dihydrochloride with standard alkali showed, however, that the basic strength is of the same order as that of ammonia; and no sensible differences in the titration curves were observed when the dihydrochlorides of conessine and dioxyconessine were titrated against standard alkali in 20% aqueous acetone or absolute methanol. The titration curve for 3β-dimethylamino-5ξ : 6ξ-dihydroxycholestane in 20% aqueous acetone indicates that this base is weaker than dioxyconessine, probably because it lacks the second basic centre of the alkaloid derivative.

In a more systematic effort to identify the positions of the dimethylamino-group and the double bond, conessine was submitted to a series of degradation reactions, the ultimate aim of which was to eliminate the methylimino-group without disturbing the position of the other two functions. Formula (II; $R = NMe_2$) has been proposed for conessine (Haworth, McKenna, Powell, and Whitfield, *Chem. and Ind.*, 1952, 215) and is now employed for illustrating the degradation reactions; more detailed arguments in favour of

this formula are developed in this paper (for rings A and B) and in Part VI (*J.*, 1953, 1115, for the heterocyclic structure).

Degradation of conessine with cyanogen bromide according to Siddiqui and Siddiqui's method (*J. Indian Chem. Soc.*, 1934, **11**, 787) gave *iso*conessimine (II; R = NHMe); the



(I) (II) (III)

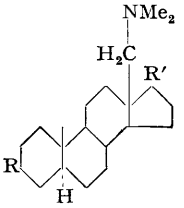
formulation $NHMe{\cdot}C_{21}H_{31}{>}NMe$, proposed without proof by these authors for this base (which also occurs in Nature associated with conessine) is confirmed by our work. Thus the demethylation of conessine to *iso*conessimine, and the methylation of the latter to conessine (*idem ibid.*), indicate that *iso*conessimine must have one of the formulations $NHMe{\cdot}C_{21}H_{31}{>}NMe$ or $NMe_2{\cdot}C_{21}H_{31}{>}NH$; if, however, the latter were correct, the Hofmann degradation of *N*-acetyl*iso*conessimine described below should give a non-basic compound containing only one nitrogen atom.

N-Acetyl*iso*conessine (II; R = NMeAc) was converted into its methiodide, and this salt submitted to Hofmann degradation in the usual manner. The product was a dinitrogenous monoacid base, *N*-acetyl*iso*conessimine methine (III; R = NMeAc, R′ = $CH{:}CH_2$). Pyrolysis of the methohydroxide derived from this base did not result in further Hofmann degradation. *N*-Acetyl*iso*conessimine methine was cyclised to a quaternary methoacetate on being refluxed in acetic acid solution. This behaviour is typical of that of methine bases in the conessine series (Part III, *loc. cit.*; Favre, Haworth, McKenna, Powell, and Whitfield, *J.*, 1953, 1115) and serves to indicate, together with the relations established (see below) with conessimethine and tetrahydroconessimethine, that during the Hofmann reaction of *N*-acetyl*iso*conessimine, the heterocyclic ring has opened in the usual way, leaving a dimethylamino-group in the *apo*conessine position, and a double bond at position 20 : 21. Partial hydrogenation of the acetyl-methine in alcohol gave *N*-acetyl-20 : 21-dihydro*iso*conessimine methine (III; R = NMeAc, R′ = Et), so formulated because it was not cyclised in boiling acetic acid. Hydrogenation of this base in glacial acetic acid gave the fully saturated *N*-acetyltetrahydro*iso*conessimine methine (IV; R = NMeAc, R′ = Et).

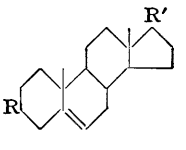
At this point a detour was made from the main degradation scheme in order to relate *N*-acetyl*iso*conessimine methine to other methine bases in the conessine series. Alkaline hydrolysis of the acetyl methine (III; R = NMeAc, R′ = $CH{:}CH_2$) gave *iso*conessimine methine (III; R = NHMe, R′ = $CH{:}CH_2$); on methylation with formaldehyde and formic acid this gave the base conessimethine (III; R = NMe_2, R′ = $CH{:}CH_2$), m. p. 77—78°, which had shortly before been isolated from the reaction mixture obtained by partial Hofmann decomposition of conessine (*idem, ibid.*, p. 1127). Conessimethine gave a little impure *apo*conessine on Hofmann degradation. Hydrolysis of *N*-acetyltetrahydro*iso*conessimine methine with concentrated hydrochloric acid gave tetrahydro*iso*conessimine methine (IV; R = NHMe, R′ = Et), which was methylated with formaldehyde and formic acid to tetrahydroconessimethine (IV; R = NMe_2, R′ = Et). This base may also be obtained by reduction of conessimethine or of the methine base, $C_{25}H_{46}N_2$, m. p. 66—70°. from dihydroconessine (Haworth, McKenna, and Whitfield, *loc. cit.*; Part III, *loc. cit.*; Favre, Haworth, McKenna, Powell, and Whitfield, *J.*, 1953, 1126). It was evident, therefore, that Hofmann decomposition of *N*-acetyl*iso*conessimine had resulted in a fission of the heterocyclic ring in the usual way, thus justifying the placing of a double bond at position 20 : 21 in the derived methine.

In continuation of the main degradation scheme, Emde reduction of *N*-acetyl*iso*conessimine methine methochloride gave an *N*-acetyl-*N*-methylaminopregnadiene (V;

R = NMeAc, R′ = CH:CH$_2$), m. p. 184—185°, yielding an *N*-acetyl-*N*-methylaminopregnene (V; R = NMeAc, R′ = Et) on partial hydrogenation in alcohol. Hydrolysis of this pregnene with alcoholic potash gave a methylaminopregnene (V; R = NHMe, R′ = Et); this base on methylation with formaldehyde and formic acid gave a dimethylaminopregnene (V; R = NMe$_2$, R′ = Et), m. p. 119°, which on hydrogenation gave the saturated tertiary base, m. p. 95—96°. The course of the above series of reactions indicated that the *N*-acetyl-*N*-methylaminopregnadiene, m. p. 184—185°, had an acetylmethylamino-group corresponding in position to the conessine dimethylamino-group, a double bond corresponding in position to the original conessine double bond, and a 20 : 21-double bond. By analogy with the result of partial hydrogenation of *N*-acetyl*iso*conessimine methine (see above) it was argued that the 20 : 21-double bond underwent preferential hydrogenation at the next stage in the reaction scheme, so that the dimethylaminopregnene, m. p. 119°, and the saturated base, m. p. 96°, should correspond respectively to conessine and dihydroconessine.



(IV)



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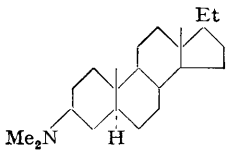


(VI)

At this stage an evaluation was made of the available physical evidence relating to the position of the double bond in conessine and in the corresponding dimethylaminopregnene, m. p. 119°.

(a) *Infra-red absorption.* The infra-red absorption curves of conessine and the dimethylaminopregnene, m. p. 119°, show maxima at 798, 826, 1665 cm.$^{-1}$ and 797, 829, and 1660 cm.$^{-1}$, respectively. The curve for 3β-dimethylaminocholest-5-ene shows maxima at 796, 827, and 1660 cm.$^{-1}$. These results indicate that conessine and the dimethylaminopregnene, m. p. 119°, have the double bond situated at either the 5 : 6- or the 7 : 8-position (Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402); it is not possible to differentiate these two positions by this method, but other trisubstituted positions such as the 4 : 5 and all disubstituted positions are excluded.

(b) *Ultra-violet absorption.* A valuable new spectroscopic method for determining the degree of substitution and sometimes the actual position of an isolated double bond in the steroid nucleus by measurement of the " end absorption " has recently been introduced by Bladon, Henbest, and Wood (*J.*, 1952, 2737). Application of this method showed that the absorption curves (see Fig.) of the dimethylaminopregnene, m. p. 119°, and 3β-dimethylaminocholest-5-ene were practically superimposed in both neutral and acidic ethanol solution, and that either curve in neutral ethanol is very nearly identical with that given by cholest-5-ene. Although the hydrocarbons cholest-4- and -5-ene can hardly be distinguished by this method, it seems likely that the close agreement established between the two unsaturated *bases* is very significant, as one might well expect a different curve with a 3-dimethylamino-$\Delta^{4:5}$-steroid on account of the proximity of the basic centre to the double bond (compare Bladon, Henbest, and Wood's discussion, *loc. cit.*). It is rather surprising, in fact, that the absorption curves for cholest-5-ene and 3β-dimethylaminocholest-5-ene are so similar. The absorption curves for conessine, in neutral and acidic ethanol (see Fig.), are quite different from those given by the monoacid bases, and at first gave rise to errors in interpretation, but it now seems evident that the methylimino-group alters the absorption due to the double bond so much that nothing can be deduced by this method from a study of the alkaloid itself.

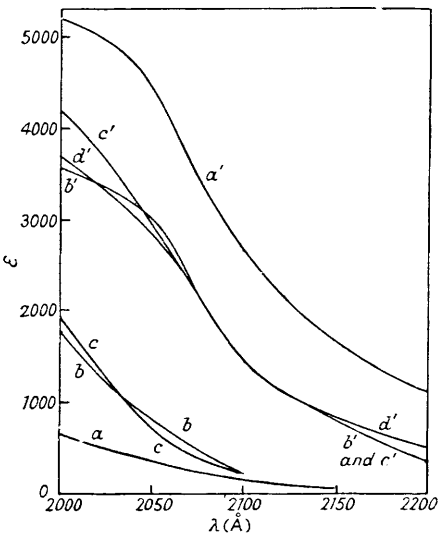
(c) *Optical-rotation studies.* Molecular-rotation data favour a 5 : 6-double bond for conessine and the derived dimethylaminopregnene. A detailed discussion is given in Part VI (*J.*, 1953, 1115).

Taken as a whole, therefore, the physical data and the properties of dioxyconessine suggested that the conessine double bond was at position 5 : 6, and the ultra-violet absorption evidence favoured a 3β-dimethylamino-group. These conclusions were confirmed by complementary synthetical work described in Part V (following paper) by which the acetylmethylaminopregnadiene, m. p. 184—185°, and the saturated tertiary base, m. p. 96°, obtained from conessine have been identified with synthetic specimens of 3β-acetylmethylaminopregna-5 : 20-diene (V; R = NMeAc, R′ = CH:CH_2) and 3β-dimethylamino*allo*pregnane (VI) respectively. The position of attachment of the heterocyclic methylimino-group is considered in Part VI (*J.*, 1953, 1115).

Experimental

Optical rotatory values given in this and the two following papers were determined at room temperature (15—25°).

Pregna-3 : 5 : 20-*triene* (I).—(*a*) A mixture of 3β-hydroxypregna-5 : 20-diene (Julian, Meyer, and Printy, *loc. cit.*) (500 mg.) and anhydrous copper sulphate (10 g.) was distilled at 0·01 mm.



In acidic ethanol	In ethanol	
a	*a′*	Conessine.
b	*b′*	3β-Dimethylaminocholest-5-ene.
c	*c′*	3β-Dimethylaminopregn-5-ene.
	d′	Cholest-5-ene.

(bath temp. 200°), and the distillate (200 mg.) recrystallised several times from methanol, yielding the hydrocarbon as colourless, prismatic needles, $[\alpha]_D$ −210° (in $CHCl_3$, *c* 0·3), m. p. 74—76° (Found: C, 88·8; H, 10·8. Calc. for $C_{21}H_{30}$: C, 89·3; H, 10·7%), undepressed on admixture with the hydrocarbon, $C_{21}H_{30}$, m. p. 74—76°, $[\alpha]_D$ −210° (in $CHCl_3$, *c* 0·3), obtained from conessine.

(*b*) A solution of pregna-5 : 20-dien-3β-yl toluene-*p*-sulphonate (Julian, Meyer, and Printy, *loc. cit.*) (70 mg.) in dry dimethylaniline (1 c.c.) was refluxed for 20 minutes, cooled, treated with excess of dilute hydrochloric acid, and extracted with ether. The extract was washed with hydrochloric acid and water, and evaporated; the partly crystalline residue (35 mg.), which could not be purified by chromatography, was distilled at 0·005 mm. (bath temp. 100°), and the distillate (20 mg.) crystallised several times from methanol, giving colourless prismatic needles, $[\alpha]_D$ −200° (in $CHCl_3$, *c* 0·07), m. p. 74—76°, undepressed on admixture with the hydrocarbon, $C_{21}H_{30}$, obtained from conessine.

3β-*Dimethylamino*-5ξ : 6ξ-*dihydroxycholestane*.—A solution of the 3β-dimethylaminocholest-5-ene (V; R = NMe_2, R′ = C_8H_{17}) (0·6 g.) (Dodgson and Haworth, *loc. cit.*) in glacial acetic acid (10 c.c.) was treated with potassium iodate (0·6 g.) in 2N-sulphuric acid (10 c.c.), and the mixture boiled for 15 minutes, evolution of iodine then having ceased. The solution was cooled, made alkaline with ammonia, and extracted five times with ether. Evaporation of the extracts and crystallisation of the residue from ethanol gave the dihydroxy-*base* as colourless, rectangular needles (0·41 g.), m. p. 208—209° (Found: C, 77·4; H, 12·0; N, 3·2. $C_{29}H_{53}O_2N$ requires C, 77·8; H, 11·9; N, 3·1%). The compound evolved 2·1 mols. of methane on treatment with methylmagnesium iodide in anisole at 18°. The *hydrochloride* separated from ether–acetic acid

in needles, m. p. 304—305° (Found: C, 72·5; H, 11·3; N, 3·0. $C_{29}H_{53}O_2N$,HCl requires C, 72·0; H, 11·2; N, 2·9%), almost insoluble in water and ether, and very sparingly soluble in alcohol and acetone.

Dioxyconessine, m. p. 290°, was prepared by oxidising conessine with potassium iodate and dilute sulphuric acid (Warnecke, *loc. cit.*); it immediately evolved 2·05 mols. of methane on treatment with methylmagnesium iodide in boiling anisole.

Attempted Oxidation of Dioxyconessine with Periodic Acid.—Dioxyconessine (0·107 g.) in 2N-sulphuric acid (5 c.c.) and water (10 c.c.) was treated with approx. M/4-periodic acid prepared from sodium paraperiodate and dilute sulphuric acid (5 c.c.); the mixed solution was kept at room temperature and 1-c.c. aliquots were withdrawn from time to time and titrated with 0·1012N-sodium thiosulphate solution. Immediately after the mixing, the titre was 4·55 c.c., and no change in titre was observed over 60 hours (calculated reduction in titre for one α-glycol group, 0·25 c.c.). Dioxyconessine was recovered unchanged.

Potentiometric Titrations.—The apparatus used was a Marconi pH meter with glass and calomel electrodes which were allowed to reach equilibrium with the solvents for 1½ hours before a titration was carried out; the glass electrode was at other times during the period of the experiments kept in a solution of the solvent in which it was next to operate which had been acidified to N/10 with hydrochloric acid. During the titrations nitrogen was passed over the surface of the solution. Standard N/10- and N/20-sodium hydroxide solutions were made up in the presence of an equivalent normality of barium chloride. N/10-Sodium hydroxide in methanol was obtained by dissolving sodium (0·29 g.) in dry methanol (250 c.c.) and adding distilled water (0·25 c.c.).

iso*Conessimine* (II; R = NHMe).—This compound was obtained from conessine by degradation with cyanogen bromide according to Siddiqui and Siddiqui's method (*loc. cit.*). The base separated from aqueous dioxan in fine, colourless needles, m. p. 95—96°; Siddiqui (*J. Indian Chem. Soc.*, 1934, **11**, 283) gives m. p. 92°. The compound, like conessine, gave no precipitate with digitonin when tested under the usual conditions (Bertho, *Annalen*, 1950, **569**, 1, claims to have obtained an adduct of conessine and digitonin, but we have not been able to confirm this with our samples). The *N*-acetyl derivative separated from light petroleum (b. p. 60—80°) as clumps of needles, m. p. 161° (Found: C, 78·4; H, 10·5; N, 7·9. Calc. for $C_{25}H_{40}ON_2$: C, 78·1; H, 10·4; N, 7·3%) (Siddiqui and Siddiqui, *loc. cit.*, give m. p. 127—128°; this may be a solvated form, as in some of our experiments a product, m. p. 133°, was obtained before drying *in vacuo*).

*Dihydro*iso*conessimine.*—*iso*Conessimine (0·34 g.) in glacial acetic acid (10 c.c.) was hydrogenated in the presence of Adams's platinum oxide catalyst (35 mg.) at 20°/728 mm. Hydrogen uptake (32·3 c.c. Calc. for one double bond and the catalyst: 32·7 c.c.) was complete in 25 minutes. After being shaken in a hydrogen atmosphere overnight, the mixture was filtered, the filtrate evaporated, and the residue treated with ammonia and ether; the *base* from the ethereal extract formed colourless needles (0·19 g.), m. p. 97—98°, from aqueous dioxan (Found: C, 80·2; H, 11·5; N, 7·8. $C_{23}H_{40}N_2$ requires C, 80·2; H, 11·6; N, 8·1%). The N-*acetyl* derivative crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 175—176° (Found: C, 78·0; H, 10·6; N, 6·7. $C_{25}H_{42}ON_2$ requires C, 77·7; H, 10·9; N, 7·3%).

Hofmann Degradation of N-*Acetyl*iso*conessimine.*—N-*Acetyl*iso*conessimine methiodide* separated from aqueous methanol in small, colourless needles, m. p. 290° (decomp.) (Found: C, 58·7; H, 8·5; I, 24·0. $C_{25}H_{40}ON_2,CH_3I$ requires C, 59·3; H, 8·2; I, 24·2%). This salt (6·0 g.) in water (250 c.c.) was shaken overnight with excess of silver oxide, the mixture filtered, the filtrate evaporated to dryness, and the residue heated at 200° (bath temp.)/0·05 mm. in a vacuum-sublimation apparatus. Sublimate and residue were combined and extracted with ether. The N-*acetyl*iso*conessimine methine* (III; R = NMeAc, R′ = CH·CH_2), recovered from the ethereal extract and recrystallised from light petroleum (b. p. 40—60°), formed hard rosettes of colourless needles (3·6 g.), m. p. 121—122° (Found: C, 78·0; H, 10·4; N, 7·3. $C_{26}H_{42}ON_2$ requires C, 78·4; H, 10·6; N, 7·0%).

Cyclisation of N-*Acetyl*iso*conessimine Methine.*—The base (III; R = NMeAc, R′ = CH·CH_2) (0·11 g.) was refluxed in glacial acetic acid (2 c.c.) for 30 minutes. The solvent was evaporated, and the residue treated with ammonia; the clear solution yielded no basic material on extraction with ether, but addition of potassium iodide gave an immediate heavy white precipitate (0·12 g.) which on recrystallisation from aqueous methanol gave colourless plates of the cyclised *methiodide*, m. p. 298—300° (decomp.) (Found: C, 59·1; H, 7·6; N, 5·2; I, 24·7. $C_{25}H_{40}ON_2,CH_3I$ requires C, 59·5; H, 8·2; N, 5·3; I, 24·2%).

N-*Acetyl*-20: 21-*dihydro*iso*conessimine Methine* (III; R = NMeAc, R′ = Et).—An ethanolic

solution of *N*-acetyl*iso*conessimine methine (0·47 g.) was shaken in hydrogen at 190°/758 mm. in the presence of Adams's platinum oxide catalyst (50 mg.). The rate of uptake of hydrogen decreased abruptly after 30 minutes, when 37·4 c.c. had been absorbed (Calc. for one double bond and the catalyst: 39·9 c.c.). The *N-acetyl-20 : 21-dihydroisoconessimine methine* separated from ether–light petroleum (b. p. 40—60°) as clumps of colourless needles (0·35 g.), m. p. 135—136° (Found: C, 78·0; H, 11·0; N, 7·0. $C_{26}H_{44}ON_2$ requires C, 78·0; H, 10·8; N, 7·1%). The base was unaffected by refluxing its solution in glacial acetic acid for 30 minutes. It was unsaturated to cold acid permanganate, and liberated iodine readily on boiling with potassium iodate and dilute sulphuric acid.

N-*Acetyltetrahydroisoconessimine Methine* (IV; R = NMeAc, R′ = Et).—The above dihydrobase (0·262 g.) in glacial acetic acid (10 c.c.) was hydrogenated in the presence of Adams's platinum oxide catalyst (27 mg.) at 16°/740 mm. Hydrogen uptake (23·2 c.c. Calc. for one double bond and the catalyst: 21·8 c.c.) was complete in 15 hours. The *methine* was isolated in the usual way and recrystallised from light petroleum (b. p. 60—80°) as colourless needles (0·211 g.), m. p. 157—158° (Found: C, 78·0; H, 11·3; N, 7·3. $C_{26}H_{46}ON_2$ requires C, 77·6; H, 1·4; N, 7·0%).

iso*Conessimine Methine* (III; R = NHMe, R′ = CH:CH_2).—*N*-Acetyl*iso*conessimine methine (0·278 g.) was hydrolysed with 20% ethanolic potassium hydroxide at 130° for 40 hours. The *product* separated from ethanol in colourless rhombs (0·113 g.), m. p. 113—114° (Found: C, 80·4; H, 11·3; N, 8·2. $C_{24}H_{40}N_2$ requires C, 80·9; H, 11·2; N, 7·9%).

Conessimethine (III; R = NMe_2, R′ = CH:CH_2).—*iso*Conessimine methine (0·54 g.) was methylated by formic acid (98%; 2·5 c.c.), water (5 c.c.), and formaldehyde (40%; 2·5 c.c.) on the water-bath for 2 hours. The well-cooled solution was basified with dilute sodium hydroxide and extracted with ether, and the base recovered from the ether with dilute hydrochloric acid. This procedure was repeated and the crude *conessimethine* (0·46 g.) was recrystallised from acetone, yielding fine colourless needles (0·42 g.), m. p. 77—78° (Found: C, 81·8; H, 11·1; N, 7·9. $C_{25}H_{42}N_2$ requires C, 81·1; H, 11·3; N, 7·6%) undepressed on admixture with a sample prepared by partial Hofmann degradation of conessine (see Part VI, *J.*, 1953, 1127). Only a small proportion of the unsaturated bases was cyclised during the methylation.

Hofmann Degradation of Conessimethine.—Conessimethine dimethiodide separated from aqueous methanol as colourless prismatic needles, m. p. 320° (decomp.) (Found: N, 4·7. $C_{25}H_{42}N_2,2CH_3I$ requires N, 4·5%). Distillation of the corresponding methohydroxide, prepared in the usual way, at 140° (bath temp.)/0·005 mm., yielded a base which after purification *via* the insoluble sulphate and several recrystallisations gave a somewhat impure sample of *apo*conessine, m. p. 65—67° undepressed on admixture with an authentic specimen, m. p. 68—69°.

Tetrahydroisoconessimine Methine (IV; R = NHMe, R′ = Et).—*N*-Acetyltetrahydro*iso*conessimine methine (IV; R = NMeAc, R′ = Et) was not hydrolysed by refluxing for 20 hours with equal volumes of ethanol and concentrated hydrochloric acid. The acetyl derivative (0·21 g.) was heated at 140° for 40 hours with concentrated hydrochloric acid (5 c.c.). The acid solution was diluted, extracted with ether, and basified, and the base taken up in ether; the ethereal extract was washed and evaporated, leaving a brown oil (0·18 g.), which was treated with light petroleum (b. p. 40—60°) (10 c.c.) and the solution filtered. The base (IV; R = NHMe, R′ = Et) recovered from the filtrate was sublimed at 0·05 mm. (bath temp. 230°) and recrystallised from acetone, separating as colourless needles (80 mg.), m. p. 74° (Found: C, 80·0; H, 12·1; N, 7·9. $C_{24}H_{44}N_2$ requires C, 80·0; H, 12·2; N, 7·8%).

Tetrahydroconessimethine (IV; R = NMe_2, R′ = Et).—Methylation of tetrahydro*iso*conessimine methine (42 mg.) with formic acid (98%; 0·5 c.c.), water (1 c.c.), and formaldehyde (40%; 0·5 c.c.) for 3 hours on the water-bath in the usual way gave *tetrahydroconessimethine* (42 mg.), which on recrystallisation from acetone formed colourless needles (30 mg.), m. p. 83—84°. After vacuum sublimation and further recrystallisation the m. p. was 88—89° (Found: C, 79·4; H, 12·2; N, 7·9. $C_{25}H_{46}N_2$ requires C, 80·2; H, 12·3; N, 7·5%), undepressed on admixture with a sample, m. p. 85—86°, prepared by hydrogenation of dihydroconessine methine (Part III, *loc. cit.*).

Attempted Hofmann Degradation of N-*Acetyl*iso*coneSSimine Methine.*—N-*Acetyl*iso*conessimine methine methiodide* separated from methanol in small, colourless needles, m. p. 247° (decomp.) (Found: N, 5·6; I, 23·9. $C_{26}H_{42}ON_2,CH_3I$ requires N, 5·2; I, 23·5%). The methohydroxide solution from this salt (0·5 g.) was evaporated, and the residue heated at 0·05 mm. (bath temp. 200°). The resulting base (0·285 g.) separated from light petroleum (b. p. 40—60°) in colourless needles, m. p. 110—113°, not raised by repeated recrystallisation, or by chromatography on

alumina. No depression in m. p. was observed on admixture with *N*-acetyl*iso*conessimine methine, m. p. 121—122°.

Emde Reduction of N-*Acetyl*iso*conessimine Methine Methochloride*.—The foregoing methiodide (0·7 g.) was converted into methochloride by heating its solution in water (25 c.c.) with excess of silver chloride for 12 hours at 100°. The *methochloride* crystallised from methanol–ether as small, colourless needles (0·45 g.), m. p. 207° (decomp.) (Found: N, 6·3; Cl, 8·0. $C_{26}H_{42}ON_2,CH_3Cl$ requires N, 6·2; Cl, 7·9%). A continuous stream of carbon dioxide was passed through a solution of the methochloride (0·2 g.) in water (100 c.c.) at 100° during the addition (12 hours) of 5% sodium amalgam (200 g.). The mixture was cooled and extracted with ether, and the extract washed with water and then with dilute hydrochloric acid; from the acidic washings *N*-acetyl*iso*conessimine methine (40 mg.) was recovered. The residue (72 mg.) from the ethereal solution was recrystallised from ethanol, yielding colourless leaflets of 3β-*acetylmethylaminopregna-5 : 20-diene* (V; R = NMeAc, R′ = $CH{\cdot}CH_2$), m. p. 184—185° (Found: C, 80·8; H, 10·1; N, 3·9. $C_{24}H_{37}ON$ requires C, 81·1; H, 10·4; N, 3·9%), undepressed on admixture with an authentic specimen (see Part V, *J.*, 1953, 1113).

3-*Acetylmethylaminopregn-5-ene* (V; R = NMeAc, R′ = Et).—A solution of the foregoing compound (0·72 g.) in warm ethanol (50 c.c.) was hydrogenated in the presence of Adams's platinum oxide catalyst (22 mg.). Hydrogen uptake (54 c.c. at 18°/751 mm. Calc. for one double bond and the catalyst: 53·7 c.c.) was complete in 2·5 hours. The *product*, recrystallised from chloroform–light petroleum (b. p. 90—120°), formed colourless needles (0·68 g.), m. p. 206° (Found: C, 80·2; H, 10·6; N, 4·1. $C_{24}H_{39}ON$ requires C, 80·7; H, 10·9; N, 3·9%).

3β-*Methylaminopregn-5-ene* (V; R = NHMe, R′ = Et).—The above acetyl derivative (0·6 g.) was hydrolysed by 20% ethanolic potassium hydroxide (15 c.c.) at 140° for 50 hours. The resultant *base* (0·54 g.) crystallised from ethanol as colourless, silky needles, m. p. 134—135° (Found: C, 83·7; H, 11·5; N, 4·5. $C_{22}H_{37}N$ requires C, 83·8; H, 11·7; N, 4·4%).

3β-*Dimethylaminopregn-5-ene* (V; R = NMe_2, R′ = Et).—Methylation of (V; R = NHMe, R′ = Et) (0·2 g.) with formic acid (2·5 c.c. of 90%), water (5 c.c.), and formaldehyde (2·5 c.c. of 40%) for 3 hours at 100° and recrystallisation of the product from acetone gave the *dimethylamino*-compound as colourless needles, m. p. 119°, $[\alpha]_D$ −37·5° (in $CHCl_3$, *c* 1·5) (Found: C, 83·3; H, 11·9; N, 4·4. $C_{23}H_{39}N$ requires C, 83·9; H, 11·9; N, 4·3%).

3β-*Dimethylamino*allo*pregnane* (VI).—The above unsaturated base (0·1 g.) in glacial acetic acid (10 c.c.) was hydrogenated overnight in the presence of Adams's platinum oxide catalyst (39 mg.) (Hydrogen uptake, 16·4 c.c. at 20°/757 mm. Calc. for one double bond and the catalyst: 16·1 c.c.). The saturated *base* crystallised from acetone as colourless needles (87 mg.), $[\alpha]_D$ +17·5° (in $CHCl_3$, *c* 2·0), m. p. 96—56° (Found: C, 83·3; H, 12·5; N, 4·0. $C_{23}H_{41}N$ requires C, 83·4; H, 12·4; N, 4·2%) undepressed on admixture with an authentic specimen of 3β-dimethylamino*allo*pregnane (*J.*, 1953, 1112).

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