## 225. *The Constitution of Conessine. Part VI.* The Heterocyclic Ring.*

By H. Favre, R. D. Haworth, J. McKenna, R. G. Powell, and G. H. Whitfield.

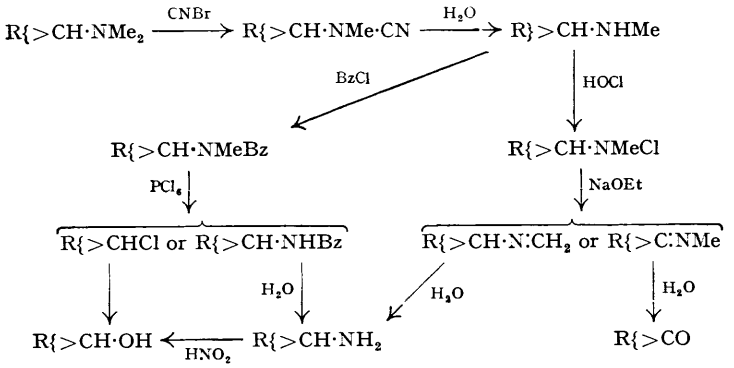
Attempts to replace the dimethylamino-group of hexahydro*apo*conessine by oxygen functions are described. *apo*Conessine and other methine bases related to conessine are cyclised by heating them in neutral or alkaline solution, and the nature of this reaction is discussed. Evidence is presented relating to the mechanism of *hetero*conessine formation, and to the structure of the conessine heterocyclic ring. Preliminary experiments on tetramethylholarrhimine are described, and molecular-rotation differences in the conessine field are briefly discussed.

The work described in the two foregoing papers has led to the establishment of the positions in the conessine molecule of the dimethylamino-group and double bond. The

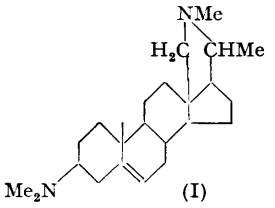
* Part V, preceding paper.

present paper describes a variety of experiments which bear on the structural position around the heterocylic ring, and includes observations on the chemistry of *hetero*conessine (Haworth, McKenna, and Whitfield, *J.*, 1949, 3127) and holarrhimine (Siddiqui *et al.*, *J. Indian Chem. Soc.*, 1932, **9**, 553, and later papers; Bertho, *Ber.*, 1947, **80**, 316). A discussion on molecular-rotation data in the conessine field is appended.

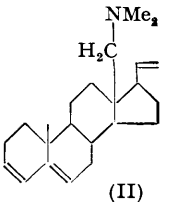
It follows from earlier work that the methylimino-group of the heterocyclic ring in the conessine molecule is attached to either $C_{(20)}$ or $C_{(21)}$ and some other carbon atom in the neighbourhood to which is also attached the dimethylamino-group in *apo*conessine. A series of degradation studies was accordingly planned with hexahydro*apo*conessine, the ultimate aim of which was to replace the dimethylamino-group by an oxygen function (ketonic or alcoholic), the position of which might then be recognised. The reactions evisaged are indicated in the annexed scheme, in which the tertiary amino-group is assumed to be attached to a methylene or methine carbon atom ($R = C_{20}H_{34}$). Formula (I) for conessine, proposed in an earlier note (Haworth, McKenna, Powell, and Whitfield, *Chem. and Ind.*, 1952, 215) and utilised in Part IV (*J.*, 1953, 1102), will be employed also in this paper, where arguments in favour of the heterocyclic arrangement shown are developed. On this basis *apo*conessine will have structure (II), and hexahydro*apo*conessine structure (III; $R = NMe_2$).




After some experience with *cyclo*hexyldimethylamine, which was degraded to methyl-*cyclo*hexylamine and *cyclo*hexanone, by the cyanogen bromide–hypochlorous acid procedure (cf. von Braun, *Ber.*, 1900, **33**, 1438, 2730; Hellerman and Sanders, *J. Amer. Chem. Soc.*, 1927, **49**, 1742; Julian, Magnani, Meyer, and Cole, *ibid.*, 1948, **70**, 1834), a similar series of reactions was attempted with hexahydro*apo*conessine. The base did not combine readily with cyanogen bromide, but in boiling benzene solution (Winterfield, *Ber.*, 1931, **64**, 137, 150) *N*-cyano-*N*-demethylhexahydro*apo*conessine (III; R = NMe·CN) was formed, which on hydrolysis with aqueous-alcoholic hydrochloric acid gave *N*-demethylhexahydro*apo*conessine (III; R = NHMe) characterised by its *N*-acetyl, *N*-benzoyl, and *N*-nitroso-derivatives. Methylation with formaldehyde and formic acid gave back hexahydro*apo*conessine.



(I)



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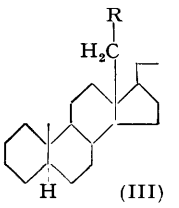


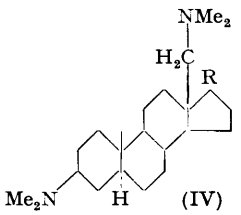
(III)

Treatment of *N*-demethylhexahydro*apo*conessine with ethereal hypochlorous acid gave *N*-chloro-*N*-demethylhexahydro*apo*conessine (III; R = NClMe) from which, how-

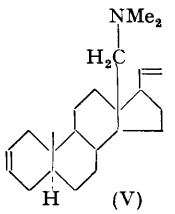
ever, no primary base or ketone could be obtained on treatment with alcoholic sodium ethoxide followed by acid hydrolysis. The primary amino*allo*pregnane (III; R = $NH_2$), however, was obtained by treatment of the benzoyl derivative of the secondary amine (III; R = NMeBz) with phosphorus pentachloride (cf. von Braun, *Ber.*, 1904, **37**, 2812, 2915, 3210, 4581) followed by hydrolysis of the product with hydrochloric acid. The primary base gave an *N*-acetyl derivative; a Zerewitinoff determination showed the presence of two active hydrogen atoms, but the base did not react with benzaldehyde. Methylation with formaldehyde and formic acid gave back hexahydro*apo*conessine. Treatment of the primary amine with nitrous acid followed by oxidation of the reaction mixture with chromic acid gave no recognisable product, and these experiments were accordingly abandoned.

The preparation of *hetero*conessine in small yield by treatment of conessine dimethiodide with potassium hydroxide in ethylene glycol solution has been described in Part II (Haworth, McKenna, and Whitfield, *loc. cit.*), but a considerable increase in yield may be obtained by using the modified conditions described on p. 1126. Since this isomer of conessine on reduction gives the base dihydro*hetero*conessine, which may also be obtained from dihydroconessine by decomposition of the dimethohydroxide in alkaline glycol (Part II, *loc. cit.*), it was evident that the isomerisation change does not involve the double bond. A close relationship between conessine and *hetero*conessine was indicated by the oxidation of *hetero*conessine to dioxy*hetero*conessine, analogous to dioxyconessine, by the infra-red absorption curve of the base which shows maxima at 799, 831, and 1660 $cm.^{-1}$ as required for a 5 : 6-double bond (cf. the conessine infra-red curve discussed in Part IV), and by the optical-rotation data presented below. Hofmann decomposition of *hetero*conessine gave *apo*conessine, indicating that the point or points of dissimilarity between the two bases are removed by elimination of the dimethylamino-group and/or fission of the heterocyclic ring. Hofmann decomposition of dihydro*hetero*conessine dimethohydroxide gave the methine base,* $C_{25}H_{44}N_2$, previously obtained from dihydroconessine (Haworth, McKenna, and Whitfield, *loc. cit.*; Haworth, McKenna, Powell, and Woodward, *loc. cit.*); this base may now be designated as 5 : 6-dihydroconessimethine (IV; R = $CH{:}CH_2$). It follows that the dissimilarity between conessine and *hetero*conessine (or between the dihydro-derivatives) involves the arrangement around the heterocyclic ring only, and disappears on ring fission.

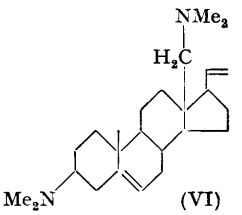
This conclusion was confirmed by partial Hofmann degradation of conessine and of *hetero*conessine. Decomposition of conessine dimethohydroxide in alkaline glycol solution, at a temperature higher than that found to give a favourable yield of *hetero*conessine, gave a diacid base, $C_{25}H_{42}N_2$, m. p. 79°, in addition to the monomethiodide, $C_{22}H_{33}N,CH_3I$, previously described (Haworth, McKenna, and Whitfield, *loc. cit.*). This base was formulated as conessimethine (VI) because it was cyclised in boiling glacial acetic acid, and the structure was confirmed by preparation of conessimethine by a different route (Haworth, McKenna, and Whitfield, *J.*, 1953, 1102). *hetero*Conessine dimethiodide on similar treatment also yielded conessimethine, in agreement with the conclusion already reached on the relation between *hetero*conessine and conessine.



(IV)



(V)

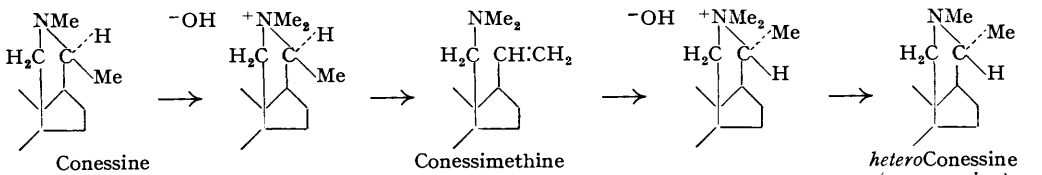


(VI)

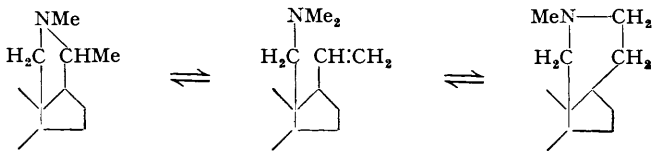
Our first tentative hypothesis on the mechanism of formation of *hetero*conessine was that an inversion of configuration had taken place at an asymmetric centre to which the

* A small quantity of a monoacid base, either 5 : 6-dihydro*apo*conessine or an isomer (V), was also attained.

ring-nitrogen atom was attached, *e.g.*, $C_{(20)}$ in (I). Such an epimeric change might conceivably have taken place by labilisation of a hydrogen atom at the asymmetric centre by the attached quaternary nitrogen (in the metho-salt), but we appreciated the theoretical objections to this possibility, and indeed recently Doering and Meislich (*J. Amer. Chem. Soc.*, 1952, **74**, 2099) have adduced strong evidence against it. An alternative mechanism was however perceived. The isomerisation reaction involves the heterocyclic ring, and a structure epimeric with that of conessine at $C_{(20)}$ [on the basis of (I)] could be produced from conessine dimethiodide if the ring first opened to give conessimethine (VI) (normal Hofmann decomposition) and subsequently *closed* again by the addition of the elements of water (*i.e.*, a reversal of the Hofmann reaction); loss of methyl alcohol from the quaternary salt would then give the isomeric base :

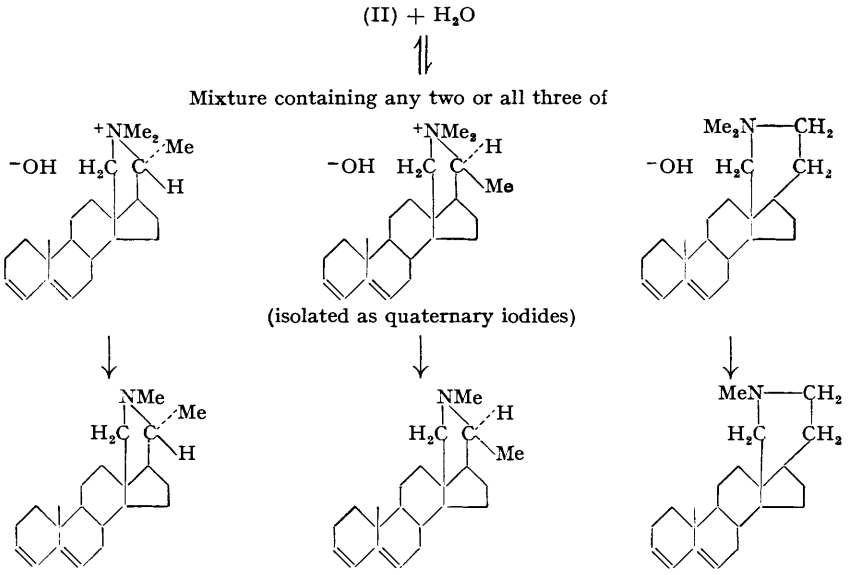



Again, the possibility being granted of such a reaction sequence, conessine and *hetero*-conessine might also be formulated as structural isomers, the methylimino-group engaging $C_{(20)}$ in one of the bases and $C_{(21)}$ in the other. No strictly comparable cyclisation reaction of an unsaturated tertiary amine to quaternary salt by heating in *alkaline* solution is on record, although cyclisation in acid solution is well known both with methine bases in the conessine series and in numerous other cases (for reference, see Haworth, McKenna, Powell, and Woodward, *loc. cit.*), and Pyman (*J.*, 1913, **103**, 817) prepared tetrahydroberberine methohydroxide by heating anhydromethylcanadine (which contains an unsaturated ten-membered ring) in aqueous alcohol. It was found, however, that *apo*conessine was cyclised when heated in aqueous glycol to about 150°, with or without the addition of potassium hydroxide; a quaternary salt (isolated as iodide) was produced along with an oily base. A similar result was obtained by heating *apo*conessine in aqueous ethanol solution at 150°. Evidence of non-homogeneity of the methiodides thus formed was obtained on fractional crystallisation, but in all cases the main fractions * obtained after several crystallisations appeared to be identical with one another and with the mono-



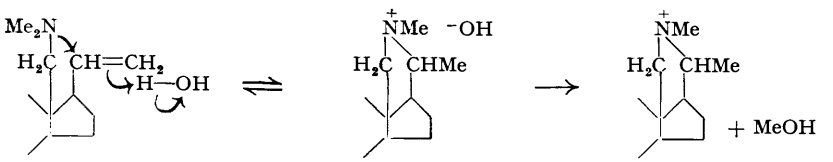

methiodides * obtained by cyclisation of *apo*conessine in glacial acetic acid or by treatment of conessine dimethiodide in alkaline glycol (Haworth, McKenna, Powell, and Woodward, *loc. cit.*). One may thus infer that ring closure of *apo*conessine, at least in alkaline solution, takes place in more than one way. The oily monoacid bases (evidently also mixtures) accompanying the methiodides were not methines, as they did not react as such with acetic acid, and they were clearly formed by loss of methyl alcohol from the corresponding quaternary hydroxides which are the first products of the cyclisation reaction. The reactions, which are analogous to those suggested above for *hetero*conessine formation (except that the ring closure takes place in more than one way), may be represented as follows :

* There is no evidence that these are homogeneous apart from the constancy of m. p. on repeated recrystallisation. It will be evident from the work described in this paper that the argument in favour of a five-membered heterocyclic ring in conessine based on methiodide identities described in Part III (*loc. cit.*) now becomes invalid.




When 5 : 6-dihydroconessimethine (IV; R = $CH{:}CH_2$) was heated with alkaline glycol, or in 90% aqueous alcohol, cyclisation and loss of methyl alcohol took place in the same way, and the basic product of each reaction was dihydro*hetero*conessine, which was readily obtained in a pure state. Likewise treatment of conessimethine (VI) with potassium hydroxide in glycol readily gave *hetero*conessine. No conessine or dihydroconessine was formed. The formation of *hetero*conessine and dihydro*hetero*conessine in this way is in conformity with either of the two mechanisms suggested above (p. 1118) for the isomerisation of conessine and its dihydro-derivative by treatment of the dimethiodides with alkaline glycol; it is evident that the corresponding methine is first formed by ordinary Hofmann fission, and that this reaction is followed by recyclisation and loss of methyl alcohol. The isolation of only *one* basic product (the *hetero*-base) from the direct cyclisation of conessimethine or dihydroconessimethine is in contrast to the results just described for *apo*conessine, but does not necessarily imply that the cyclisation of the diacidic methines takes place in only one direction; * the *hetero*-quaternary hydroxide may undergo loss of methyl alcohol faster than any isomers produced.

A possible analogy to this cyclisation reaction is the case of unsaturated tertiary vinylamines, which are stronger bases than the corresponding saturated amines, although the reverse would normally be expected. Adams and Mahan (*J. Amer. Chem. Soc.*, 1942, **64**, 2588) have suggested that this result is explained by the formation in solution of an equilibrium proportion of quaternary hydroxide. In our case a similar reaction would result in cyclisation as follows :




Significant use may be made of the relationship established between conessine and *hetero*conessine in an analysis of the structural position around the heterocyclic ring in these two bases. The conessine methylimino-group is attached to $C_{(20)}$ or $C_{(21)}$;

* There is evidence (see p. 1127) that the *acetic acid* cyclisation of 5 : 6-dihydroconessimethine gives a mixture of quaternary salts. Low yields of quaternary salts (isolated as iodides) are also obtained after the cyclisation of the diacidic methines in alkaline solution, but these have not been examined further.

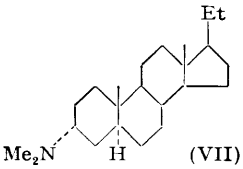
construction of models indicates that on steric grounds the other carbon atom involved is probably $C_{(18)}$, $C_{(12)}$, or (less likely) $C_{(15)}$, if the methylimino-group is also attached to $C_{(20)}$; or $C_{(18)}$, $C_{(12)}$, $C_{(16)}$, or (less likely) $C_{(15)}$, if it is also attached to $C_{(21)}$. If the methylimino-group involves $C_{(12)}$, $C_{(15)}$, or $C_{(16)}$, the steric orientation must be β. Of the various possibilities, the attachment of the ring nitrogen at $C_{(16)}$ may be excluded, since on the above evidence conessine and *hetero*conessine must either be (*a*) epimeric at $C_{(20)}$ or (*b*) structurally isomeric, with the methylimino-group attached at $C_{(20)}$ in one base and at $C_{(21)}$ in the other. Of the remaining possibilities ($C_{(12)}$, $C_{(15)}$, and $C_{(18)}$), $C_{(15)}$ appears unlikely on biogenetic grounds, and in addition the conessine and *hetero*conessine heterocyclic rings would be rather more strained than would be expected from the ready ring closure of the related methine bases. $C_{(18)}$ appears a more likely position of attachment than either $C_{(12)}$ or $C_{(15)}$ because of the failure of *apo*conessine and its hexahydro-derivative to yield any hydrocarbon on attempted Hofmann decomposition (Spath and Hromatka, *Ber.*, 1930, **63**, 126; Haworth, McKenna, and Whitfield, Part II, *loc. cit.*). The negative result has been confirmed again for each of these two bases; hexahydro*apo*conessine was recovered from the reaction in almost quantitative yield but the product obtained by pyrolysis of *apo*conessine methohydroxide was not *apo*conessine, but a base, m. p. 93—94°, which did not appear to be a methine as it was unaffected by refluxing in acetic acid. It is possible that in the latter case ring closure has taken place by a sequence of reactions similar to that described above for the formation of the *hetero*-bases, and the matter is being further investigated. The simplest interpretation of the failure of *apo*conessine and (more particularly) its hexahydro-derivative to yield any hydrocarbon on attempted Hofmann decomposition would be that neither base has a *trans*-hydrogen atom attached to the carbon atom in the β-position to the quaternary ammonium centre; thus, of the three remaining probable positions listed above for the attachment of the basic centre in *apo*-conessine, $C_{(12)}$ and $C_{(15)}$ would be eliminated, leaving $C_{(18)}$.*

Additional evidence in favour of $C_{(18)}$ as a position of attachment for the basic centre, and for (I) and (III; R = $NMe_2$) for conessine and hexahydro*apo*conessine respectively may be derived from the Kuhn–Roth *C*-methyl results given below:

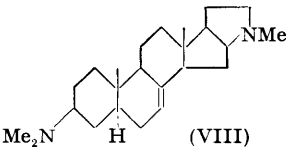
| Compound | *C*-Me, % | No. of *C*-methyl groups in molecule |
|---|---|---|
| Conessine * | 5·30 | 1·27 |
| *hetero*Conessine | 6·84 | 1·63 |
| Hexahydro*apo*conessine | 5·80 | 1·29 |
| 3α-Dimethylamino*allo*pregnane | 9·80 | 2·17 |

* Bertho (*Annalen*, 1950, **569**, 1) reports 1·29 *C*-methyl groups in conessine.

The best interpretation of these results is that the first three compounds each contains two *C*-methyl groups; the contrasting result obtained for 3α-dimethylamino*allo*pregnane (VII, an isomer of hexahydro*apo*conessine which contains three *C*-methyl groups) is significant. On the basis of these results conessine and *hetero*conessine are not structural isomers, but are epimeric with one another at $C_{(20)}$. A model of formula (I) indicates that the heterocyclic ring is virtually strain-free, in keeping with the ready cyclisation reactions described above.



(VII)



(VIII)

The preferred position of attachment of the conessine heterocyclic ring ($C_{(18)}$) is not, in general, a position of substitution in steroids. Recently, however, it has been suggested (Jacobs and Sato, *J. Biol. Chem.*, 1951, **191**, 65; Pelletier and Jacobs, *J. Amer. Chem. Soc.*,

* The retardation of the Hofmann reaction in the case of hexahydro*apo*conessine may of course be of stereochemical origin (see Part V). It is noteworthy, however, that a steroidal 12-trimethylammonium salt has been degraded to the 11 : 12-ethylene by McPhillamy and Scholz (*J. Org. Chem.*, 1949, **14**, 643), although the steric orientation of the quaternary centre has not been proved.

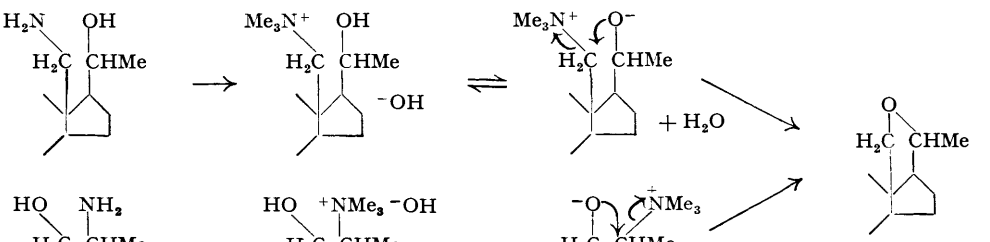
1952, **74**, 4218) that the veratrine alkaloid *iso*rubijervine is a $C_{(18)}$-hydroxylated solanidine, although the evidence is not conclusive.

In recent communications Bertho (*loc. cit.*; *Annalen*, 1951, **573**, 210) has proposed the structure (VIII) for conessine; no substantial evidence, however, is adduced in favour of this formula (compare the criticisms given in Part III), which can therefore be abandoned in view of the work described in the present series of papers.

Some preliminary experiments have been carried out with the base *N*-tetramethylholarrhimine, which was readily isolated through its insolubility in light petroleum from the alkaloidal extract of Kurchi bark after methylation. Holarrhimine contains two primary amino-groups, a hydroxyl group, and a double bond, previously characterised by the preparation of a dibromide and by iodate oxidation of *N*-tetramethylholarrhimine to a dioxy-derivative similar in properties to dioxyconessine. There has been no demonstration of the presence of a steroidal nucleus, nor has any relation been established with the heterocyclic Kurchi alkaloids, but it has been suggested (Siddiqui, *Proc. Indian Acad. Sci.*, 1936, **3**, *A*, 249) that the hydroxyl group and one amino-group of holarrhimine may correspond structurally to the bivalent imino- or methylimino-group in the other bases, a hypothesis which is attractive on biogenetic grounds provided that holarrhimine has the usual pregnane nucleus.

We have confirmed the presence of a double bond in *N*-tetramethylholarrhimine by catalytic reduction to the dihydro-derivative. Attempted dehydration of dihydro-*N*-tetramethylholarrhimine by heating it with boric oxide (cf. Prelog and Szpilfogel, *Helv. Chim. Acta*, 1944, **27**, 390) resulted in elimination of the elements of dimethylamine instead of water; the unsaturated product, $C_{23}H_{39}ON$, was reduced catalytically to a dihydro-derivative, but we have not yet been able to decide whether the unsaturation is due to the presence of a hindered carbonyl group or of an ethylenic linkage.

Hofmann decomposition of *N*-tetramethylholarrhimine resulted in elimination of both basic centres and gave a product $C_{21}H_{30}O$. The ultra-violet absorption curve of this substance strongly suggests the presence of a conjugated steroidal 3 : 5-diene system as in *apo*conessine, indicating that *N*-tetramethylholarrhimine and conessine may have the same carbon framework, and correspond in detail around rings A and B. Catalytic hydrogenation gave a mixture of tetrahydro-derivatives (of which one was obtained pure), as would be expected on reduction of a 3 : 5-diene system. The tetrahydro-mixture gave negative tests for hydroxyl, keto-, or olefinic groups, and the last two were also excluded on ultra-violet absorption evidence (no selective absorption : ε at 2000 Å was 100). The oxygen atom in the compound $C_{21}H_{30}O$ and its tetrahydro-derivatives is therefore present as a cyclic ether. Analogous formation of cyclic ethers during Hofmann decomposition of hydroxylated amines has been observed in morphine chemistry (cf. Cahn, *J.*, 1926, 2562). The ready formation of the oxygen bridge parallels the ready cyclisation of methine bases in the conessine series; on the basis of Siddiqui's proposals (cf. above), and structure (I) being used for conessine, the reactions may be represented as follows :




A list of specific and molecular rotations measured in this laboratory for the more significant conessine derivatives and related synthetic compounds is given below. Values

| Substance | $[\alpha]_D$ | $[M]_D$ | *c* | Solvent |
|---|---|---|---|---|
| Conessine | −1° | −4° | 5·6 | $CHCl_3$ |
| Conessine dimethiodide | +6 | +38 | 2·0 | MeOH |
| Dihydroconessine | +46 | +165 | 3·0 | $CHCl_3$ |
| Dihydroconessine dihydriodide | +36 | +221 | 0·9 | MeOH |
| Dihydroconessine dimethiodide | +26 | +167 | 2·8 | ,, |
| Chlorodihydroconessine | +25 | +98 | 8·9 | $CHCl_3$ |
| Formaldehyde addition base, $C_{25}H_{42}ON_2$, m. p. 171—173° | +65 | +251 | 5·4 | ,, |
| *apo*Conessine | −120 | −390 | 2·7 | ,, |
| *apo*Conessine methiodide | −54 | −253 | 2·3 | ,, |
| Hexahydro*apo*conessine | +48 | +159 | 2·8 | ,, |
| Hexahydro*apo*conessine methiodide | +25 | +118 | 2·4 | ,, |
| Methiodide, $C_{22}H_{33}N,CH_3I$, from cyclisation of apoconessine in acetic acid | −38 | −171 | 1·3 | ,, |
| Tetrahydro-derivative of methiodide, $C_{22}H_{33}N,CH_3I$ | +29 | +133 | 1·8 | ,, |
| Conessimethine | −25 | −93 | 1·4 | ,, |
| 5 : 6-Dihydroconessimethine | +27 | +101 | 2·9 | ,, |
| Tetrahydroconessimethine | +34 | +127 | 3·1 | ,, |
| *neo*Conessine | +76 | +270 | 4·7 | ,, |
| *neo*Conessine dihydriodide | +1 | +6 | 0·6 | MeOH |
| *neo*Conessine dimethiodide | +15 | +96 | 1·7 | ,, |
| *neo*Conessimethine | +85 | +315 | 1·9 | $CHCl_3$ |
| Dihydro*neo*conessimethine | +90 | +335 | 3·3 | ,, |
| *hetero*Conessine | −25 | −89 | 1·1 | ,, |
| *hetero*Conessine dimethiodide | +13 | +83 | 1·0 | MeOH |
| Dihydro*hetero*conessine | +15 | +54 | 1·8 | $CHCl_3$ |
| Dihydro*hetero*conessine dimethiodide | +31 | +200 | 2·0 | MeOH |
| Tetramethylholarrhimine | −32 | −124 | 2·1 | $CHCl_3$ |
| Benzoyltetramethylholarrhimine | −16 | −79 | 2·5 | ,, |
| Dihydrotetramethylholarrhimine | +11 | +43 | 2·5 | ,, |
| Cyclic ether, $C_{21}H_{30}O$ | −139 | −414 | 1·5 | ,, |
| Tetrahydro-cyclic ether | +4 | +12 | 1·6 | ,, |
| Pregna-3 : 5 : 20-triene | −210 | −592 | 0·3 | ,, |
| 3β-Dimethylaminocholest-5-ene | −32 | −132 | 0·5 | ,, |
| 3β-Dimethylaminocholest-5-ene methiodide | −20 | −111 | 2·1 | ,, |
| 3β-Dimethylaminocholestane | +23 | +95 | 1·1 | ,, |
| 3β-Dimethylaminocholestane methiodide | +33 | +184 | 1·1 | ,, |
| 3α-Dimethylaminocholestane | +22 | +91 | 2·1 | ,, |
| 3β-Dimethylaminopregn-5-ene (*ex* conessine) | −38 | −125 | 1·5 | ,, |
| 3β-Dimethylamino*allo*pregnane (*ex* conessine) | +18 | +60 | 2·0 | ,, |
| 3α-Dimethylamino*allo*pregnane | +16 | +52 | 1·5 | ,, |

for most of these compounds have not been reported previously. The average probable error in specific rotation is about ±3°, corresponding to an error of about ±25° in molecular-rotation differences.

## Discussion

(a) *The "Conessine Double Bond."*—The Δ values (Barton and Klyne, *loc. cit.*) calculated from the above data for the double bond in conessine, the derived 3β-dimethylaminopregn-5-ene, *hetero*conessine, tetramethylholarrhimine, and for the "conessine double bond" in conessimethine are −169°, −185°, −143°, −167°, and −194°, respectively. These values are sufficiently close to indicate that the double bond occupies the same nuclear position in all five compounds. The Δ values quoted are all lower (arithmetically) than would be expected for a double bond in the 5 : 6-position, but the agreement is closer than for any other position for which the necessary data are recorded. The Δ values for the 5 : 6-double bond in cholesterol, 3β-dimethylaminocholest-5-ene, and 3β-hydroxypregn-5-ene (Barton and Holness, *J. Amer. Chem. Soc.*, 1950, **72**, 3274) are −243°, −227°, and −229°, respectively; introduction of a dimethylamino-group at $C_{(3)}$ *or* replacement of the *iso*octyl side chain at $C_{(17)}$ by ethyl thus reduces the Δ value, and the operation of *both* factors in conessine and its derivatives may explain the low results quoted.

(b) *The* neo*Conessine Double Bond.*—The Δ value for the *neo*conessine double bond (related to dihydroconessine) is +105°, which would agree with the values for a double bond in the 7 : 8- (A/B *cis*) or 8 : 9- (A/B *trans*) positions, which are +119° and +96°, respectively. The formation of *neo*conessine from conessine, however, may involve a

deep-seated change, such as the rearrangement of the carbon skeleton,* and as the structure of the base is under active investigation, we prefer to postpone further discussion.

(c) *Other Groups.*—All compounds containing or postulated as containing the conjugated 3 : 5-diene system have high negative rotations of the order expected, but most of them are unsuitable for quantitative comparisons (cf. Barton and Klyne, *loc. cit.*). 3α- and 3β-Dimethylamino-groups have very low Δ values resembling those for the corresponding hydroxy-groups. The Δ value for the chlorine atom in chlorodihydroconessine is −67°, in good agreement with the value −71° for the halogen atom in 5-chlorocholestane (Mauthner, *Monatsh.*, 1906, **27**, 305; 1907, **28**, 1113).

## Experimental

*Degradation of* cyclo*Hexyldimethylamine.*—A solution of the amine (Skita and Rolfes, *Ber.*, 1920, **53**, 1250) (28 g.) in dry ether (50 c.c.) was added dropwise during 2 hours to a stirred solution of cyanogen bromide (*Org. Synth.*, Vol. II, p. 30) (11·7 g.) in dry ether (50 c.c.) at 0°. The resultant *N*-cyano-compound was not purified but was directly hydrolysed by refluxing it with concentrated sulphuric acid (10 c.c.) diluted with water (30 c.c.) for 5 hours, yielding *N-cyclo*hexylmethylamine (7·5 g.), b. p. 148—150°, giving a benzoyl derivative, m. p. 84° (Skita and Rolfes, *loc. cit.*, report b. p. 148° and benzoyl derivative, m. p. 76°). A solution of this secondary amine (1·8 g.) in dry ether (25 c.c.) was treated at −10° with ethereal hypochlorous acid solution (0·02 g./c.c.; 80 c.c.) prepared by Goldschmidt's method (*Ber.*, 1913, **46**, 2728). After 10 minutes the ethereal solution was washed successively with dilute hydrochloric acid, dilute sodium hydroxide solution, and water, dried ($Na_2SO_4$), and, after the addition of more ether to give a volume of 150 c.c., mixed with a solution of sodium ethoxide (from 1 g. of sodium) in ethanol (50 c.c.). After 48 hours the solution was free from active halogen, and was washed with water and concentrated to 40 c.c. (Widmer fractionating column). The residual alcoholic solution was treated with saturated alcoholic hydrogen chloride (25 c.c.), and refluxed on the water-bath for 15 minutes. The resultant neutral oil was identified as *cyclo*hexanone by the preparation of its 2 : 4-dinitrophenylhydrazone, m. p. 160°, undepressed on admixture with an authentic specimen.

*Hexahydro*apo*conessine* (III; R = $NMe_2$).—This base was prepared by hydrogenation of a solution of *apo*conessine in glacial acetic acid solution as described in Part II (*loc. cit.*). The yield of pure compound was not increased appreciably by substituting ethanol for acetic acid as solvent.

N-*Cyano*-N-*demethylhexahydro*apo*conessine* (III; R = NMe·CN).—A solution of hexahydro-*apo*conessine (7·4 g.) in anhydrous benzene (100 c.c.) was treated with cyanogen bromide (6 g.) and refluxed for 2 hours with exclusion of moisture. A further 6 g. of cyanogen bromide was added, and the refluxing continued for another 2 hours. Solvent and excess of cyanogen bromide were removed under reduced pressure, and the residue was extracted (Soxhlet) for 11 hours with light petroleum (b. p. 40—60°). The extracted solid was dissolved in benzene, and the solution washed with dilute hydrochloric acid and water, and evaporated. The residue was triturated with boiling light petroleum (b. p. 40—60°) to remove colour, and then crystallised from ethanol; the N-*cyano*-compound (III; R = NMe·CN) was thus obtained as colourless, rectangular needles (4·5 g.), m. p. 150—151° (Found: C, 80·5; H, 11·1; N, 8·4. $C_{23}H_{38}N_2$ requires C, 80·7; H, 11·1; N, 8·2%). The residue left in the Soxhlet thimble (2 g.) yielded, on treatment with silver oxide, hexahydro*apo*conessine (0·65 g.) and more of the *N*-cyano-derivative (0·37 g.), m. p. 146—147°.

N-*Demethylhexahydro*apo*conessine* (III; R = NHMe).—A solution of the *N*-cyano-derivative (III; R = NMe·CN) (4 g.) in ethanol (160 c.c.) and concentrated hydrochloric acid (120 c.c.) was refluxed for 36 hours with intermittent removal of precipitated hydrochloride. The solution was then evaporated to dryness *in vacuo*, and the residue and combined precipitates were extracted with five 100-c.c. portions of boiling ether. Evaporation of the ether left a neutral residue (0·2 g.). The hydrochloride (4 g.) was decomposed with ammonia, and the *base*, isolated with ether, was recrystallised from ethanol, giving colourless needles (2·7 g.), m. p. 80—81° (Found: C, 83·6; H, 12·1; N, 4·1. $C_{22}H_{39}N$ requires C, 83·3; H, 12·3; N, 4·4%). The N-*acetyl* derivative (III; R = NMeAc) separated from light petroleum (b. p. 90—120°)

* Thus 3-methyl-A-norcholest-3(5)-ene (Schmidt and Kägi, *Helv. Chim. Acta*, 1950, **33**, 1582; Shoppee and Summers, *J.*, 1952, 2528) has $[M]_D$ 109° more positive than cholestane. The difficulty of hydrogenating *neo*conessine and the infra-red spectrum of the base suggest the presence of a tetra-substituted ethylene linkage.

in colourless needles, m. p. 123° (Found : C, 80·3; H, 11·6; N, 3·9. $C_{24}H_{41}ON$ requires C, 80·2; H, 11·4; N, 3·9%). The N-*nitroso*-derivative (III; R = NMe·NO) separated from ethanol in colourless needles, m. p. 131° (Found : C, 76·5; H, 10·7; N, 8·4. $C_{22}H_{38}ON_2$ requires C, 76·3; H, 11·0; N, 8·1%). The N-*benzoyl* derivative (III; R = NMeBz), prepared in pyridine, formed needles (from ethanol), m. p. 161° (Found : C, 82·4; H, 9·9; N, 3·1. $C_{29}H_{43}ON$ requires C, 82·7; H, 10·2; N, 3·3%). This benzoyl derivative (36 mg.) was unaffected by refluxing its solution in ethanol (2 c.c.) and hydrochloric acid (2 c.c.) for 20 hours. Treatment with concentrated hydrochloric acid at 140° for 18 hours in a sealed tube gave, however, a good yield of the secondary base, m. p. 81°.

*Methylation of* N-*Demethylhexahydro*apo*conessine*.—The secondary amine (III; R = NHMe) (30 mg.) was heated with water (1 c.c.), 90% formic acid (0·5 c.c.), and 33% formaldehyde (0·5 c.c.) on the steam-bath for 4 hours; the mixture was then treated with concentrated hydrochloric acid (1 c.c.), evaporated to 0·5 c.c. under reduced pressure, diluted with water, washed with ether, and made alkaline, and the base extracted with ether. The ethereal extract was washed and evaporated, and the residue (29 mg.) recrystallised from ethanol, giving colourless needles, m. p. 67°, undepressed on admixture with hexahydro*apo*conessine of the same m. p.

N-*Chloro*-N-*demethylhexahydro*apo*conessine* (III; R = NClMe).—A solution of *N*-demethylhexahydro*apo*conessine (III; R = NHMe) (0·39 g.) in dry ether (50 c.c.) was treated with ethereal hypochlorous acid (0·11 g./c.c.; 25 c.c.) and kept for 2 hours in the dark at −5°. The ethereal solution was then washed successively with dilute hydrochloric acid, dilute sodium hydroxide solution, and water, and evaporated to dryness, and the residue dried ($P_2O_5$) *in vacuo* and recrystallised from dry ethanol yielding colourless, prismatic needles (0·33 g.), m. p. 99—100° (Found : C, 75·1; H, 10·7; N, 3·6; Cl, 10·2. $C_{22}H_{38}NCl$ requires C, 75·1; H, 10·8; N, 4·0; Cl, 10·1%). An ethereal solution of this *chloramine* liberated iodine when shaken with acidified aqueous potassium iodide.

The chloramine (0·33 g.) in dry ethanol (10 c.c.) was treated with a solution of sodium ethoxide [from sodium (0·5 g.) and dry ethanol (20 c.c.)], and the mixture refluxed for 30 minutes with exclusion of moisture, and then evaporated to dryness. The residue was treated with ether and water; the aqueous solution on titration with silver nitrate solution (0·0197N) required 42·6 c.c. (Calc. for 1 mol. of NaCl : 47·6 c.c.). The residue (0·307 g.) from the ethereal extract was separated into a basic oil (0·275 g.) giving a neutral amorphous nitroso-derivative (Found : N, 6·0%), and a neutral oil (16 mg.), which was refluxed with ethanol (1 c.c.) and concentrated hydrochloric acid (0·5 c.c.) for 30 minutes, yielding a non-crystalline product (12 mg.) which did not react with 2 : 4-dinitrophenylhydrazine.

Treatment of the chloramine (0·75 g.) with dry pyridine (100 c.c.) at the b. p. for 5 hours gave a base (0·56 g.), essentially *N*-demethylhexahydro*apo*conessine, m. p. 79—80°, after chromatography on alumina, and a neutral oil (92 mg.) which after hydrolysis with concentrated hydrochloric acid for 5 hours at the b. p. yielded a non-crystalline product which did not exhibit ketonic reactivity.

*Reaction of* N-*Benzoyl*-N-*demethylhexahydro*apo*conessine with Phosphorus Pentachloride*.—The benzoyl derivative (III; R = NMeBz) (1·15 g.) and phosphorus pentachloride (0·67 g.) were heated together at 180° for 8 hours, and the product, isolated with ether, was heated with concentrated hydrochloric acid (10 c.c.) at 140° for 20 hours. The mixture was diluted with water and extracted with ether; the ethereal extract yielded a neutral residue (0·36 g.), and from the acidic solution was obtained a base (0·44 g.). The basic fraction was chromatographed in light petroleum (b. p. 40—60°) on alumina (10 g.), the column being developed successively with benzene–light petroleum (b. p. 40—60°), benzene, ether–benzene, ether, and acetone. There were thus obtained some *N*-demethylhexahydro*apo*conessine and the crude *amino*allo*pregnane* (III; R = $NH_2$) (0·21 g.) which after crystallisation from acetone gave colourless needles (0·17 g.), m. p. 98°, raised on further crystallisation to 99—100° (Found : C, 83·9; H, 11·8; N, 4·1. $C_{21}H_{37}N$ requires C, 83·2; H, 12·2; N, 4·6%), depressed to 65° on admixture with *N*-demethylhexahydro*apo*conessine (III; R = $NH_2$), m. p. 80—81°. The amine (III; R = $NH_2$) evolved 1·8 mols. of methane on treatment with excess of methylmagnesium iodide for 1 hour at 100°. The *acetyl* derivative separated from acetone–light petroleum (b. p. 60—80°) in colourless needles, m. p. 171° (Found : C, 80·0; H, 11·2; N, 4·0. $C_{23}H_{39}ON$ requires C, 80·0; H, 11·3; N, 4·1%).

The neutral oil, after further heating with concentrated hydrochloric acid, and chromatography, gave a non-crystalline product (Found : N, 1·1; Cl, 2·9%).

*Methylation of* (III; R = $NH_2$).—The primary base (III; R = $NH_2$) (12 mg.) was methylated by heating it on the water-bath for 3 hours with formic acid (0·5 c.c. of 90%), water

(1 c.c.), and formaldehyde (0·5 c.c. of 33%). Concentrated hydrochloric acid (1 c.c.) was then added, and the solution concentrated to 0·5 c.c., diluted with water, washed with ether, basified with ammonia, and extracted again with ether. The product (11 mg.) separated from ethanol in fine needles, m. p. 67°, undepressed on admixture with hexahydro*apo*conessine.

*Action of Nitrous Acid on* (III; R = $NH_2$).—The amine (III; R = $NH_2$) (45 mg.) in ether (5 c.c.) was treated at −5° with 2N-hydrochloric acid (5 c.c.) and sodium nitrite (0·2 g.) in water (2 c.c.). After an hour's shaking all the precipitated hydrochloride had disappeared. The ethereal solution was separated, washed with dilute sodium hydroxide solution and water, and evaporated, leaving a colourless oil (43 mg.), not entirely free from nitrogen, from which no crystalline product could be obtained by chromatography. Oxidation of the oil (69 mg.) with chromium trioxide (35 mg.) in acetic acid–light petroleum (b. p. 40—60°) at 0° for 16 hours, and treatment of the non-acidic reaction product (68 mg.) with Girard-T reagent, gave a ketonic (28 mg.) and a non-ketonic fraction (40 mg.). The former after chromatography on alumina gave a colourless nitrogen-free solid (12 mg.) which crystallised from light petroleum (b. p. 60—80°) in plates, m. p. 251—254°. No crystalline product could be obtained from the non-ketonic fraction.

*Cyclisation of* apo*Conessine*.—(a) *In aqueous glycol in the presence of potassium hydroxide.* A mixture of *apo*conessine (0·5 g.), ethylene glycol (60 c.c.), potassium hydroxide (12 g.), potassium iodide (2 g.), and water (8 c.c.) was concentrated slightly until the temperature of the boiling liquid was 150°, heated under reflux for 6 hours, cooled, diluted with water, and extracted successively with ether and chloroform. The extracts yielded respectively a non-crystalline basic fraction (0·2 g.) and a methiodide (0·15 g.). The basic fraction was refluxed in glacial acetic acid (5 c.c.) for 1 hour, concentrated, diluted with water, basified, and extracted with ether. The extract yielded an oily base (0·14 g.) unaffected by further treatment with acetic acid; addition of potassium iodide to the aqueous alkaline solution gave a precipitate of cyclised methiodide (0·06 g.).

The methiodide (0·15 g.) from the above chloroform extract was recrystallised twice from water, yielding colourless, rectangular plates with characteristic edge irregularities, $[\alpha]_D$ −25° (in MeOH, *c* 1·2), m. p. 318° (decomp.) (Found: C, 60·9; H, 7·8; N, 3·2; I, 28·1. Calc. for $C_{22}H_{33}N{\cdot}CH_3I$: C, 60·9; H, 7·9; N, 3·1; I, 28·0%). Samples of much lower m. p. (290°), $[\alpha]_D$ −34° (in MeOH, *c* 0·8), were obtained from the mother-liquors. The monomethiodide, $C_{22}H_{33}N,CH_3I$, obtained from conessine dimethiodide by treatment with potassium hydroxide in aqueous glycol (Part II, *loc. cit.*) and the monomethiodide obtained by cyclisation of *apo*conessine in acetic acid (Part III, *loc. cit.*) were found on repeated recrystallisation from water to form colourless plates with similar edge irregularities and had m. p. 316°, $[\alpha]_D$ −24° (in MeOH, *c* 1·0), and m. p. 308°, $[\alpha]_D$ −24° (in MeOH, *c* 1·0), respectively, the m. p.s being determined under standard conditions. No depression in m. p. was observed on admixture of any pair of these monomethiodides.

(b) *In aqueous ethylene glycol.* A solution of *apo*conessine (0·5 g.) in warm glycol (50 c.c.) was heated under reflux, and water added dropwise until the temperature of the boiling liquid was 150°. The solution was then refluxed for 2 hours, cooled, diluted with water, and basified with potassium hydroxide, and potassium iodide (2 g.) added. Extraction successively with ether and chloroform gave respectively an oily base (0·1 g.) which was not examined further, and a monomethiodide (0·4 g.). After one crystallisation from water the methiodide had m. p. 298—302°, and after a second crystallisation characteristic, irregular, rectangular plates, m. p. 318°, were obtained, unchanged on further purification, $[\alpha]_D$ −28° (in MeOH, *c* 0·9) (Found: C, 61·5; H, 8·1; N, 3·3. Calc. for $C_{22}H_{33}N,CH_3I$: C, 60·9; H, 7·9; N, 3·1%). The mother-liquors yielded a fraction, m. p. 280—290°, which was converted into methohydroxide in the usual way, and the product heated to 200° (bath-temp.)/0·1 mm. The oily distillate solidified when scratched, and after one crystallisation from methanol, colourless needles of *apo*conessine were obtained, m. p. 69°, undepressed on admixture with an authentic specimen.

(c) *In aqueous ethanol.* A solution of *apo*conessine (0·3 g.) in 90% aqueous ethanol (10 c.c.) was heated in an autoclave at 150° for 4 hours. After cooling, the solution was basified with aqueous potassium hydroxide, potassium iodide (1·5 g.) added, and the mixture concentrated to a low bulk. The residue was extracted successively with ether and chloroform; the extracts yielded respectively an oily base (0·24 g.) and a monomethiodide (0·07 g.). The monomethiodide separated from water in characteristic irregular rectangular prisms, $[\alpha]_D$ −26° (in MeOH, *c* 0·8), m. p. 315° (Found: C, 60·7; H, 7·7; N, 3·2. Calc. for $C_{22}H_{33}N,CH_3I$: C, 60·9; H, 7·9; N, 3·1%). The oily base was subjected to Hofmann decomposition in the usual way, and yielded *apo*conessine, m. p. 67—68°.

*Attempted Hofmann Decomposition of* apo*Conessine*.—*apo*Conessine methiodide (350 mg.) was converted in the usual way into the methohydroxide, which was decomposed at 160—200°/10 mm. The base was taken up in light petroleum (b. p. 40—60°), and hydrochloric acid (5N) added until no further precipitation occurred. The light petroleum extract yielded a colourless oil (0·75 mg.), and the bases (150 mg.) recovered from the hydrochloride were dissolved in light petroleum (b. p. 40—45°) and chromatographed on alumina (Spence's Type H, 4·5 g.). Elution with light petroleum (b. p. 40—45°) gave fractions: (*a*) colourless oil (50 mg.); (*b*) crystalline solid (40 mg.), m. p. *ca.* 80°; (*c*) yellow oil (45 mg.). Crystallisation of fraction (*b*) from methyl alcohol gave a *compound* as colourless needles (14 mg.), m. p. 93—94° (Found: C, 84·1; H, 11·0; N, 5·0. $C_{22}H_{33}N$ requires C, 84·8; H, 10·7; N, 4·5%), which were not cyclised by boiling acetic acid in the usual way.

*Attempted Hofmann Decomposition of Hexahydro*apo*conessine*.—Hexahydro*apo*conessine (Part II, *loc. cit.*) (1·1 g.) was converted *via* the methiodide in the usual way into an aqueous solution of the methohydroxide, the solution was evaporated, and the residue heated to 160° (bath temp.)/0·1 mm. for 30 minutes, a portion distilling. Residue and distillate were extracted with light petroleum (b. p. 40—60°), and the extracted product gave hexahydro*apo*conessine (746 mg., 98%) as colourless needles, m. p. 66—67° (without recrystallisation), undepressed on admixture with an authentic specimen (m. p. 67—68°), and a non-basic fraction (7 mg.) from which no crystalline product could be isolated.

*Preparation of* hetero*Conessine from Conessine Dimethiodide* (cf. Part II, *loc. cit.*).—A mixture of conessine dimethiodide (4 g.), ethylene glycol (300 c.c.), potassium hydroxide (60 g.), and water (50 c.c.) was concentrated until the temperature of the boiling liquid was 160°, and refluxed for 6 hours. Water (1 l.) was then added, and the bases (2 g.) were isolated with ether and refluxed in glacial acetic acid (50 c.c.) for 1 hour to remove *apo*conessine (Part II, *loc. cit.*) and conessimethine (see below). The acetic acid was removed *in vacuo*, and the residue treated with ether and aqueous ammonia. The basic residue from the ether was separated by treatment with dilute sulphuric acid into a fraction A (1·6 g.) (with sulphates soluble in cold dilute sulphuric acid) and a fraction B (0·27 g.) (with sulphates insoluble in cold dilute sulphuric acid). Fraction A on repeated recrystallisation from acetone gave *hetero*conessine (0·35 g.), m. p. 130·5—131°; a small quantity of conessine, m. p. 124°, was obtained from the mother-liquors. Fraction B, which was partly crystalline after several weeks, could not be purified by recrystallisation or chromatography.

apo*Conessine from* hetero*Conessine*.—hetero*Conessine dimethiodide* separated from water in colourless, prismatic needles, $[\alpha]_D$ +13° (in MeOH, *c* 1·0), m. p. 312° (decomp.) (Found: N, 4·1; I, 39·7. $C_{24}H_{40}N_2,2CH_3I$ requires N, 4·4; I, 39·7%). This salt (200 mg.) was converted in the usual way into an aqueous solution of the corresponding methohydroxide, which was evaporated *in vacuo*, and the residue heated to 240° (bath-temp.)/0·05 mm. The distillate (60 mg.) on crystallisation from methanol gave colourless needles of *apo*conessine, m. p. 69—70°, undepressed on admixture with an authentic specimen.

apo*Conessine from Fraction B* (*above*).—The collected oily bases (0·82 g.) from several experiments were converted into the methiodide (1·2 g.) in the usual way, and the corresponding methohydroxide was heated at 200° (bath-temp.)/0·08 mm. *apo*Conessine, m. p. 68—69°, was obtained from the distillate.

*Preparation of* hetero*Conessine from its Dimethiodide*.—The dimethiodide (500 mg.) was treated with potassium hydroxide in boiling aqueous glycol as described above for conessine dimethiodide. *hetero*Conessine, m. p. 131—132° (50 mg.), was obtained along with further fractions (35 mg.) melting a few degrees lower. An oily base (15 mg.) corresponding to Fraction B (above) was also obtained but was not examined further.

*Dioxy*hetero*conessine*.—A solution of *hetero*conessine (201 mg.) in sulphuric acid (2N; 3·3 c.c.) was boiled with potassium iodate (197 mg.) for a few minutes until most of the iodine had been volatilised. The pale yellow solution was basified with ammonia, and the precipitated base (220 mg.) collected and crystallised from methanol–acetone, giving *dioxy*hetero*conessine* as colourless prisms, m. p. 260° (Found: C, 74·1; H, 10·5. $C_{24}H_{42}O_2N_2$ requires C, 73·8; H, 10·8%). A fraction of m. p. 250° (Found: C, 65·7; H, 10·3%) was obtained from the mother-liquors.

*Preparation of* 5 : 6-*Dihydroconessimethine* (*Dihydroconessine Methine*) (IV; R = $CH{\cdot}CH_2$) *and Tetrahydroconessimethine* (IV; R = Et).—(a) *From dihydroconessine dimethiodide*. The dimethiodide, m. p. 302—304° (decomp.), $[\alpha]_D$ +26° (in MeOH, *c* 2·0) (2 g.), was submitted to Hofmann decomposition essentially as described in Part II (*loc. cit.*), but the crude basic distillate (0·72 g.) was treated with 2N-sulphuric acid (10 c.c.) instead of concentrated hydro-

chloric acid, and thus separated into fractions A and B (with sulphates respectively soluble and insoluble in cold dilute sulphuric acid). The Hofmann decomposition was repeated twice with dihydroconessine dimethiodide (2 g. and 2·8 g.), and the combined fractions A (1·6 g.) were recrystallised from aqueous acetone to give 5 : 6-dihydroconessimethine, m. p. 64—66° (0·9 g.), together with a second crop (0·3 g.), m. p. 62—65°.

The combined fractions B were crystallised from acetone, yielding a monoacid *base* $C_{23}H_{37}N$,* which may be formulated as 5 : 6-dihydro*apo*conessine or an isomer (V) (95 mg.), $[\alpha]_D$ +64° (in $CHCl_3$, *c* 1·2), m. p. 76° (Found : C, 83·7; H, 11·1; N, 4·7. $C_{23}H_{37}N$ requires C, 84·4; H, 11·4; N, 4·3%). When this base (28·7 mg.) was hydrogenated in alcoholic solution at 20° and 732 mm. in the presence of Adams's platinum oxide catalyst (2 mg.; pre-hydrogenated) 4·6 c.c. of hydrogen were taken up in 55 minutes (calc. for two double bonds : 4·4 c.c.). The hydrogenation mixture was worked up in the usual way, and colourless needles of hexahydro*apo*conessine, m. p. 66—66·5°, were obtained, undepressed on admixture with an authentic specimen. By interrupting the hydrogenation after one mol. of hydrogen had been taken up, a base, m. p. 59—60°, was obtained, which was unaffected by boiling glacial acetic acid, indicating that the 20 : 21-double bond had undergone preferential hydrogenation.

Catalytic reduction of 5 : 6-dihydroconessimethine by the method described in Part III (*loc. cit.*) gave tetrahydroconessimethine (the " dihydromethine " of Part III), m. p. 87—89°.

(b) *From dihydro*hetero*conessine dimethiodide.* Dihydro*hetero*conessine, m. p. 104—105°, was converted in the usual way into the *dimethiodide*, which separated from methanol in colourless prisms, $[\alpha]_D$ +31° (in MeOH, *c* 2·0), m. p. 320—322° (decomp.) (Found : C, 48·6; H, 7·5. $C_{24}H_{42}N_2,2CH_3I$ requires C, 49·2; H, 7·5%). The mixed m. p. with dihydroconessine dimethiodide (m. p. 302—304°, decomp.) was 312—314°. Dihydro*hetero*conessine dimethiodide (0·77 g.) was subjected to Hofmann decomposition in the manner described above and yielded 5 : 6-dihydroconessimethine (210 mg.), m. p. 61—64° (Found : N, 7·7. Calc. for $C_{25}H_{44}N_2$ : N, 7·5%), undepressed on admixture with the base prepared from dihydroconessine dimethiodide. A very small quantity of base with an insoluble sulphate (corresponding to Fraction B above) was also obtained. Catalytic hydrogenation of the dihydroconessimethine gave tetrahydroconessimethine, m. p. 88° (Found : C, 79·9; H, 12·2. Calc. for $C_{25}H_{46}N_2$ : C, 80·2; H, 12·4%) undepressed on admixture with the base, m. p. 87—89°, prepared as described above.

*Preparation of Conessimethine* (VI).—(a) *From conessine dimethiodide* (cf. Part II, *loc. cit.*). A mixture of conessine dimethiodide (4 g.), ethylene glycol (60 c.c.), and potassium hydroxide (12 g.) was boiled for 5 minutes (internal temp. 180°), cooled, diluted with water, and extracted with chloroform, and the residue (2·5 g.) from the chloroform separated into a basic oil (1 g.) soluble in ether and the monomethiodide (1·5 g.), insoluble in ether, already described in Part II (*loc. cit.*). The basic oil was freed from *apo*conessine *via* the insoluble sulphate, and the residual base (0·81 g.), previously obtained as an oil, crystallised slowly during 6 months. The base (0·81 g.) was chromatographed in benzene on alumina (Spence's Type H; 20 g.); elution with benzene followed by ether gave a fraction (*a*) (385 mg.), m. p. 74°, fraction (*b*) (100 mg.), m. p. 90—100°, and other oily or semi-crystalline fractions. Crystallisation of (*a*) from acetone gave colourless needles of conessimethine, $[\alpha]_D$ −25° (in $CHCl_3$, *c* 1·4), m. p. 78—79° (Found : C, 81·0; H, 11·0; N, 7·5. Calc. for $C_{25}H_{42}N_2$ : C, 81·1; H, 11·3; N, 7·6%) undepressed on admixture with the product, m. p. 77—78°, obtained from *iso*conessimine (Part IV, *loc. cit.*). A small yield of *hetero*conessine, m. p. 132°, was obtained by repeated crystallisation of fraction (*b*) from acetone.

(b) *From* hetero*conessine dimethiodide.* Decomposition of this dimethiodide as described above gave very similar yields of conessimethine, m. p. 77—78°, and a small quantity of *hetero*conessine.

*Cyclisation of* 5 : 6-*Dihydroconessimethine* (IV; R = $CH{\cdot}CH_2$).—(a) *In glacial acetic acid.* This reaction was carried out as described in Part III (*loc. cit.*) for " the unsaturated methine, $C_{25}H_{44}N_2$." After treatment of the cyclised product with potassium iodide and methylation of the cyclised monomethiodide with methyl iodide, the resulting dimethiodide † separated from

* In the formation of this monoacid base from dihydroconessine, the dimethylamino-group undergoes Hofmann elimination, and the low yield may be contrasted with the high yield of *apo*conessine obtained by Hofmann decomposition of conessine dimethohydroxide, where the 5 : 6-double bond activates the elimination reaction. The yield of monoacid base from dihydroconessine is of the order expected from a 3β-(equatorial) dimethylamino*allo*pregnane (cf. Parts IV and V).

† Although in Part III (*loc. cit.*) this dimethiodide was stated to be identical with dihydroconessine dimethiodide, it now seems more probable that the product is a mixture of dihydroconessine and dihydro*hetero*conessine dimethiodides.

water in colourless needles, $[\alpha]_D$ +26° (in MeOH, *c* 2·0), m. p. 310—312° (Found: C, 48·4; H, 7·5. Calc. for $C_{24}H_{42}N_2,2CH_3I$: C, 48·6; H, 7·5%). The mixed m. p. with dihydroconessine dimethiodide (m. p. 302—304°) was 310°; with dihydro*hetero*conessine dimethiodide (m. p. 320—321°) the mixed m. p. was 314°.

(b) *In aqueous glycol in the presence of potassium hydroxide.* A mixture of 5 : 6-dihydroconessimethine (0·5 g.), ethylene glycol (60 c.c.), potassium hydroxide (12 g.), potassium iodide (2 g.), and water (8 c.c.) was concentrated until the temperature of the boiling liquid was 150°, refluxed for 6 hours, cooled, diluted with water, and extracted successively with ether and chloroform. The basic oil from the ethereal extract was refluxed with glacial acetic acid (5 c.c.), and the base (380 mg.), which was not cyclised by this treatment, was recovered in the usual way and crystallised several times from acetone, giving dihydro*hetero*conessine as colourless needles, m. p. 102—103° (Found: C, 79·9; H, 11·8. Calc. for $C_{24}H_{42}N_2$: C, 80·4; H, 11·8%) undepressed on admixture with an authentic specimen. The chloroform extract (above) yielded a methiodide (30 mg.), which was not examined further.

(c) *In 90% aqueous alcohol.* A solution of 5 : 6-dihydroconessimethine (300 mg.) in 90% aqueous alcohol (10 c.c.) was heated in an autoclave at 150° for 6 hours, and cooled, and an aqueous solution containing potassium iodide (2 g.) added. The solvents were removed under reduced pressure, and the residue was extracted successively with ether and chloroform, yielding respectively a basic mixture (240 mg.) and a methiodide (100 mg.); the latter was not examined further. The basic mixture was refluxed with acetic acid (5 c.c.) for 1 hour, and the recovered bases (170 mg.) were chromatographed in light petroleum (b. p. 40—60°) on alumina (Spence's Type H; 4·5 g.); light petroleum (b. p. 40—60°), benzene, and ether were employed successively for elution. Several oily fractions were obtained, followed by a crystalline fraction (72 mg.) which on recrystallisation from acetone gave colourless needles of dihydro*hetero*conessine, m. p. 103—104°, undepressed on admixture with an authentic specimen.

*Cyclisation of Conessimethine* (VI) *in Aqueous Ethylene Glycol in the Presence of Potassium Hydroxide.*—A mixture of conessimethine (190 mg.), glycol (24 c.c.), potassium hydroxide (5 g.), potassium iodide (1 g.), and water (3 c.c.) was treated as in (b) above, yielding a basic oil (170 mg.) and a monomethiodide (3 mg.), which was not examined further. The basic oil was dissolved in acetic acid (3 c.c.), and the solution refluxed for 1 hour. The recovered base (120 mg.) on crystallisation from acetone gave prismatic needles of *hetero*conessine, m. p. 131—132°, undepressed on admixture with an authentic specimen.

*Isolation of Conessine and Tetramethylholarrhimine.*—The following modification of the extraction procedure described in Part I (*loc. cit.*) has proved very successful. A mixture of crushed seeds or bark of *Holarrhena antidysenterica* and half the weight of quicklime was extracted with ethanol (Soxhlet) for 3 days. The solvent was removed *in vacuo*, and the warm fatty residue exhaustively extracted by shaking it with 3N-hydrochloric acid. The acid extract was washed once with ether, then basified with ammonia, and the bases were extracted by shaking the whole five times with ether. The extracts were evaporated, and the basic residue was methylated with formaldehyde and formic acid as described in Part I (*loc. cit.*). The methylated basic mixture was distilled at 0·01 mm. (bath-temp., 250°), and the distillate triturated with light petroleum (b. p. 40—60°) in the proportion 100 g. of bases per l. of solvent. After 24 hours at 5°, the insoluble crude tetramethylholarrhimine was filtered off (yield variable: up to 0·03%). Evaporation of the filtrate gave crude conessine, which had m. p. 122—123° after recrystallisation from acetone. The yield of conessine was 0·4% from bark, and 0·7% from seeds.

*Purification of crude tetramethylholarrhimine.* The crude base as obtained above was benzoylated by the Schotten–Baumann procedure, and the crude product recrystallised several times from ethanol, yielding colourless needles of benzoyltetramethylholarrhimine, $[\alpha]_D$ −16° (in $CHCl_3$, *c* 2·5), m. p. 174—175°. Siddiqui (*loc. cit.*) gives m. p. 176°. Hydrolysis of the benzoyl derivative with aqueous-methanolic potassium hydroxide and crystallisation of the product from ethanol gave tetramethylholarrhimine as colourless needles, $[\alpha]_D$ −32° (in $CHCl_3$, *c* 2·1), m. p. 227—228° (Found: C, 77·6; H, 10·9; N, 7·1. Calc. for $C_{25}H_{44}ON_2$: C, 77·3; H, 10·4; N, 7·2%). Siddiqui (*loc. cit.*) gives $[\alpha]_D$ −45·5° (in EtOH, *c* 1), m. p. 233—235°.

*Hofmann Degradation of Tetramethylholarrhimine.*—Tetramethylholarrhimine (102 mg.) was converted in the usual way *via* the methiodide into an aqueous solution of the methohydroxide; the solution was evaporated, and the residue heated to 170° (bath-temp.)/0·1 mm. for 30 minutes. The white sublimate (74 mg.) was dissolved in ether, dry hydrogen chloride passed through the solution, and a precipitate (1 mg.) collected. The product (73 mg.), m. p. 94°, recovered from the filtrate was crystallised from aqueous acetone, and the cyclic *ether* thus

obtained as colourless plates, $[\alpha]_D$ −139° (in $CHCl_3$, *c* 1·5), m. p. 95—96° (Found: C, 84·1; H, 9·6; N, nil. $C_{21}H_{30}O$ requires C, 84·5; H, 10·1%). Light absorption in ethanol: $\lambda_{max.}$, 2270, 2350, 2430 Å (log ε, 4·3, 4·35, 4·1). The compound contained no active hydrogen.

*Reduction of the Cyclic Ether*, $C_{21}H_{30}O$.—A solution of this ether (158 mg.) in glacial acetic acid (7 c.c.) was shaken in a hydrogen atmosphere at 17·5°/750 mm. in the presence of Adams's platinum oxide catalyst (23 mg.). Hydrogen uptake (30·5 c.c. Calc. for two double bonds and the catalyst: 30·4 c.c.) was complete in 2 hours. The resulting product (160 mg.; probably a mixture of stereoisomers) separated from ethanol in colourless needles, m. p. 79—99°, and did not react with benzoyl chloride, toluene-*p*-sulphonyl chloride, 2 : 4-dinitrophenylhydrazine, or Girard-T reagent under the usual experimental conditions. The product contained no active hydrogen, and gave a negative result in the Tortelli–Jaffe test, and no colour with tetranitromethane in chloroform. No selective absorption was noted in the region 2000—3000 Å. The hydrogenated product, m. p. 79—99° (160 mg.), was repeatedly chromatographed in benzene (10 c.c.) on active charcoal in the manner described in Part III (*loc. cit.*) for a mixture of pregnane and *allo*pregnane, except that benzene was used as eluant. The "tail" fractions (30 mg.), m. p. 98—99·5°, on crystallisation from aqueous ethanol gave colourless needles of the *tetrahydro-ether*, $[\alpha]_D$ +4° (in $CHCl_3$, *c* 1·6), m. p. 98—99·5° (Found: C, 82·9; H, 11·3. $C_{21}H_{34}O$ requires C, 83·4; H, 11·3%). A considerable depression in m. p. was observed on admixture with the original product, $C_{21}H_{30}O$, m. p. 95—96°. From the "head" fractions (40 mg.), m. p. 56—68°, no homogeneous compound was isolated.

*Dihydrotetramethylholarrhimine*.—A solution of tetramethylholarrhimine (208 mg.) in glacial acetic acid (6 c.c.) was shaken in hydrogen at 17°/760 mm. in the presence of Adams's platinum oxide catalyst (17 mg.). Hydrogen uptake (16·6 c.c. Calc. for one double bond and the catalyst: 16·7 c.c.) was complete in 12 hours. The product was refluxed with aqueous-methanolic potassium hydroxide for 2 hours, and the *dihydrotetramethylholarrhimine* crystallised from aqueous ethanol as colourless needles, $[\alpha]_D$ +11° (in $CHCl_3$, *c* 2·5), m. p. 209—210° (Found: C, 76·4; H, 11·6; N, 7·5. $C_{25}H_{46}ON_2$ requires C, 76·9; H, 11·9; N, 7·2%).

*Attempted Dehydration of Dihydrotetramethylholarrhimine*.—The base (52 mg.), intimately mixed with boric oxide (178 mg.), was heated at 280° for 2 minutes at atmospheric pressure, and then at the same temperature for 15 minutes at 16 mm. (cf. Prelog and Szpilfogel, *loc. cit.*). The product, isolated with light petroleum (b. p. 40—60°), was sublimed at 180° (bath-temp.)/0·1 mm. The colourless basic sublimate (32 mg.) was converted into its hydrochloride, which was crystallised from water; the recovered *base* was obtained on crystallisation from acetone as colourless needles, m. p. 127—128° (Found: C, 79·9; H, 11·7; N, 3·8. $C_{23}H_{39}ON$ requires C, 79·9; H, 11·4; N, 4·1%). The base was unsaturated to cold permanganate, and failed to yield a 2 : 4-dinitrophenylhydrazone. Conessine, *apo*conessine, hexahydro*apo*-conessine, and 20-dimethylamino-3β-hydroxypregn-5-ene (Julian, Meyer, and Printy, *J. Amer. Chem. Soc.*, 1948, **70**, 887) were recovered unchanged after similar treatment with boric oxide.

The base (24 mg.) was shaken in glacial acetic acid (2 c.c.) in hydrogen at 19°/750 mm. in the presence of Adams's platinum oxide catalyst (5 mg.). Hydrogen uptake (2·7 c.c. Calc. for one double bond and the catalyst: 2·7 c.c.) was complete in 4 hours. Sublimation of the product at 180° (bath-temp.)/0·2 mm. and crystallisation from acetone gave the dihydro-base as colourless plates, m. p. 107—108°, saturated to cold permanganate.

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