Rhazya Alkaloids: the Secamines, a New Group of Indole Alkaloids

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A new group of indole alkaloids, the secamines, has been isolated from *Rhazya stricta* Decaisne and *R. orientalis A. DC. R. stricta* leaf bases were fractionated, mainly by countercurrent distribution, and crude secamine concentrates further fractionated by reverse-phase buffer partition chromatography, which gave five fairly symmetrical eluent bands: two of these corresponded to tetrahydrosecamines (T.H.Sec.) $C_{42}H_{56}N_4O_4$ (0·016% of dry wt. of leaves), two were dihydrosecamines (D.H.Sec.) $C_{42}H_{54}N_4O_4$ (0·015%), and the fifth was secamine $C_{42}H_{52}N_4O_4$ (0·004%). None of these materials has yet crystallised, nor has any of the salts tried. Each of these fractions is quite homogeneous with respect to mass spectra and behaviour on t.l.c., the complexity of the n.m.r. spectra in the aliphatic CH regions however suggests mixtures of stereoisomers or conformers, or both.

Although the structural work has been carried out on these stereochemically probably nonhomogeneous bases, it allows the assignment of two possible structures in which the stereochemistry is not defined; secamine itself is defined by either (I) or (II); in T.H.Sec. both C-15–C-20 and C-15′–C-20′ double bonds are saturated and in D.H.Sec. only one.[1]

The following constitutes the main evidence for the above structures.

T.H.Sec. is hydrolysed (aq. NaOH) and decarboxylated (N-HCl/100°/20 hr.) to an oxygen-free base, didemethoxycarbonyl-T.H.Sec., $C_{38}H_{52}N_4$, (III)(R and D=H) in *ca.* 20% yield: this ease of decarboxylation suggests the presence of two 2-indolylacetic acid units.[2]

Similar didemethoxycarbonylation in D_2O–DCl leads to deuteriated base of which the major component is $C_{38}H_{39}D_{13}N_4$, which represents the highest level of deuteriation: in this product five aliphatic CH (in addition to the eight aromatic CH) have exchanged.[3] Deuteriation studies on simple models and analysis of mass spectra lead to the conclusion that the five aliphatic CD are on the central ring (C-16, 17, 16′, and 17′). Mass spectra unfortunately cannot place these deuteriums, but the following chemical argument shows the proposed structures to be consistent with the introduction of the 5D: direct displacement of CO_2H accounts for the D on C-16′ and one of the 2D on C-16; the other D on C-16 is accounted for by the normal exchange undergone by 2-indolylalkyl CH (the 2-methyl in 2,3-dimethylindole is completely deuteriated under mild acidic conditions[4]); the remaining two exchanges are believed to occur at C-17′ by the following reversible ring-opening sequence, the equilibrium (V) ⇌ (VI) being the point at which exchange occurs. The 5D should thus be distributed as shown in (III) (R = D).

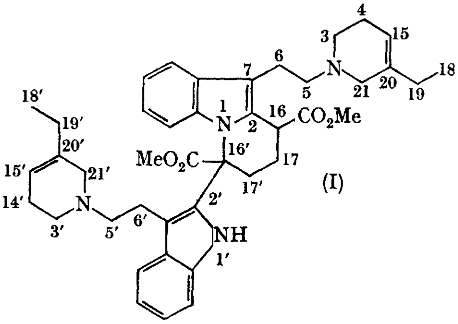
The alternative structure for T.H.Sec. (T.H.II) could also lead to (III) (R and D=H) by way of (IV) (R and D=H) and a rearrangement to (V) (R and D=H), which is electronically equivalent to a pinacol-pinacolone transformation.

The demethoxcarbonylation of T.H.Sec. also leads to the formation of (VII), identified with synthetic material by mass spectra and t.l.c., in 10—15% yield: this fission is accounted for in terms of either protonation of C-2′ in (III) (R and D=H) leading to a reverse Mannich reaction (*cf.* skatole dimer → skatole[5]) or hydration of (V) (R and D=H) at C-16′ followed by a reverse aldol reaction.

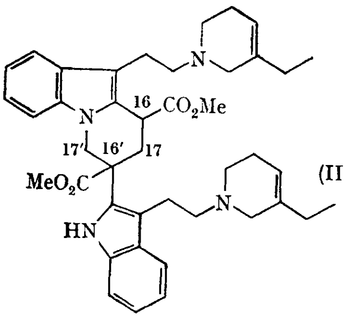
Reductive decarbomethoxylation (aq. $SnCl_2$/5N HCl/100°/3 days) of T.H.Sec. leads to a base $C_{38}H_{54}N_4$ (15—20% yield) (VIII) (R = $C_9H_{18}N$). The structure has been proved by ozonolysis[6] and hydrolysis to be (IX) and a 2 : 1 mixture of adipic and glutaric acids, and by synthesis of mixed racemic and *meso*- (VIII) (R = $C_9H_{18}N$) from (VIII) (R = H)[8] and racemic 3-ethylpiperidine by the oxalyl chloride method.[8,9] Degradation and synthetic products show identical n.m.r. and mass spectra, and R_f values in three different solvent systems and on two different adsorbents: ozonolysis and hydrolysis of synthetic (VIII) (R = $C_9H_{18}N$) also leads to a 2 : 1 mixture of adipic and glutaric acids.

The position of the C-15–C-20 and C-15′–C-20′ double bonds in secamine was demonstrated by Hofmann degradation of the dimethiodide to 3-ethyl-1,2,5,6-tetrahydro-*N*-methylpyridine, identical with authentic synthetic material:[10] that no migration of the double bond from C-14–C-15 has occurred in the Hofmann reaction is indicated by the n.m.r. spectrum of secamine, which shows the presence of two olefinic hydrogens only. Similar degradation of T.H.Sec. yields 3-ethyl-*N*-methylpiperidine:[10] D.H.Sec. yields a mixture of 3-ethyl-*N*-methylpiperidine and 3-ethyl-1,2,5,6-tetrahydro-*N*-methylpyridine.

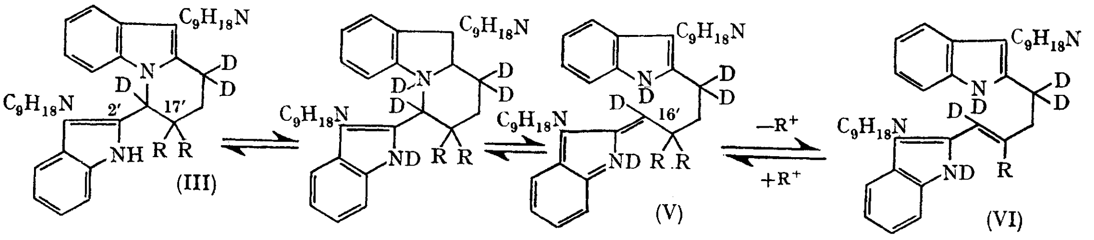
The action of MeO^-–MeOD at 100° on T.H.Sec.

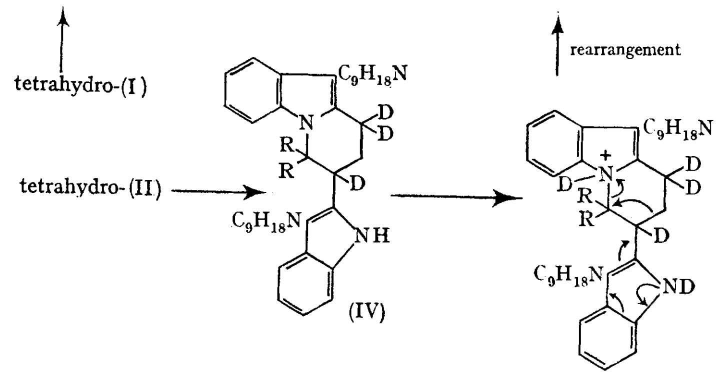


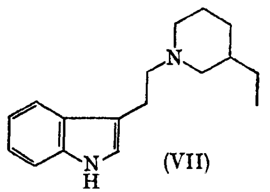
(I)



(II)

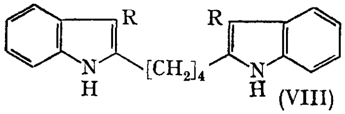




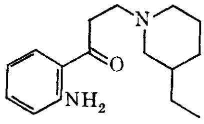


(VII)

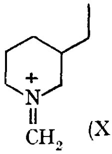
T. H. Sec $\longrightarrow$ [(V) (R=D=H)] $\xrightarrow[\text{Cf. Ref. 7.}]{2H}$



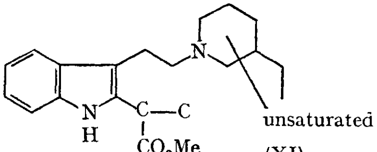
(VIII)



(IX)



(X)



(XI)

introduces only one D, indicating the presence of only one CH adjacent to CO_2Me. This receives support from the mass spectra of the diol (produced by lithium aluminium hydride reduction of

T.H.Sec.) and of the corresponding diacetate which show loss of only one H_2O and one $MeCO_2H$ respectively.

The presence of one indolic NH group was demonstrated by an increase of only one mass unit in the mass spectrum (run in a spectrometer which had been previously saturated with D_2O) of T.H.Sec. which had been dissolved in excess of MeOD.[11]

The base peak in the mass spectrum of T.H.Sec. is at *m/e* **126** ($C_8H_{16}N$) and corresponds to fragment ion (X): this ion is extraordinarily intense, being about 50 times more intense than any other peak in the spectrum. Its mass ratio of 126 is unique in the indole alkaloid field, 125 having hitherto been the highest for a C_8 piperidine fragment:[12] the appearance of this 126 peak in *Rhazya* fractions showed the presence of a new and important group of bases and allowed easy monitoring of fractions.

The secamines are of considerable biogenetic interest, for they are the first indole alkaloids to contain the unit (XI), which may well represent a key stage in the interconversion of strychnos, aspidosperma, and iboga-type bases.[13]

U.v., i.r., n.m.r., unit mass spectra, and high resolution mass measurements on parent peaks and main fragments determined on the alkaloids and the degradation products were all in accordance with the proposed structures. Satisfactory elemental analyses were obtained for synthetic compounds.

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