The Presecamines, a New Group of Dimeric Indole Alkaloids from *Rhazya* Species, and Their Thermally Derived Monomers, Secodine and 15,20-Dihydrosecodine

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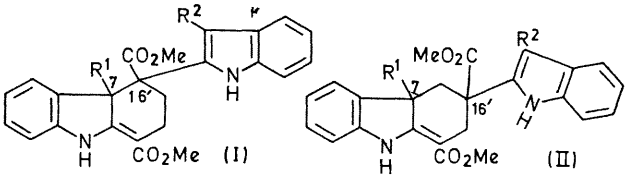
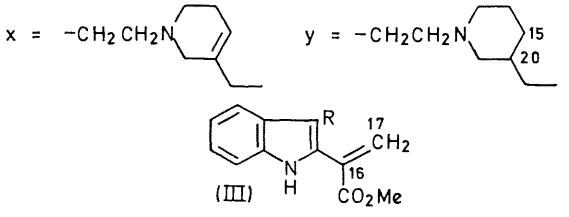
Summary The new alkaloids, the presecamines (I) or (II), rearrange by acid catalysis to the corresponding secamines and are Diels–Alder type dimers of secodines (III) containing an α-acrylic ester function, these thermally derived monomers dimerise back to the corresponding presecamine

THREE new dimeric alkaloids, presecamine, $C_{42}H_{52}N_4O_4$, tetrahydropresecamine, $C_{42}H_{56}N_4O_4$, and dihydropresecamine, $C_{42}H_{54}N_4O_4$ (the latter may be a mixture of two isomers) have been isolated from *Rhazya stricta* leaves in very low yield and tetrahydropresecamine from *R. orientalis* roots in high yield (8% of total alkaloids) by a combination of counter current distribution, column and thin-layer chromatography. Structures (Ia) or (IIa) for presecamine (P S), (Ib) or (IIb) for tetrahydropresecamine (T H P S), and (Ic) or (IIc) for dihydropresecamine (D H P S),[1] all excluding stereochemistry, have been assigned on the following evidence (in order to simplify discussion, we are assuming that C-20 and C-20′ in the tetrahydro-dimeric bases have the same absolute configuration).

The three amorphous alkaloids have almost identical u.v. spectra which correspond to a summation of indole and β-anilinoacrylic ester absorption [for T H P S λ_{max} (EtOH) 227, 288 (infl.) 295, and 329 nm (log ε 4.30, 4.07, 4.14 and 4.17)] they have similar i.r. spectra [for T H P S ν_{max} ($CHCl_3$) 3420, 3360 (NH), 1730 (sat. ester C=O), 1680, and 1610 cm^{-1} (β-anilinoacrylic ester)], the mass spectra do not show a molecular ion and the first observable ion is at $M/2$ even at 120° and 15 ev, with a fragmentation pattern compatible with secodine[2] structures (IIIa) and (IIIb), [for P S m/e 338 (10.5), 307 (0.7), 280 (0.6), 228 (0.7), 214 (1.2), 168 (2.7), 167 (2.0), 154 (3.5), and 124 (100), peaks below m/e 120 are not included and only those peaks of intensity greater than 2% are included below m/e 200]. The n.m.r. spectra, though complex, are fully consistent with the suggested structures (for P S two overlapping one proton signals at τ 4.54 and 4.64 corresponding to one olefinic proton in each of the two piperideine rings, two overlapping triplets at τ 8.95 and 9.06 corresponding to the ethyl CH_3 groups, and two methoxycarbonyl singlets at τ 6.23 and 6.42).



(a) $R^1 = R^2 = x$ (b) $R^1 = R^2 = y$ (c) $R^1 = x$ $R^2 = y$ or $R^1 = y$ $R^2 = x$

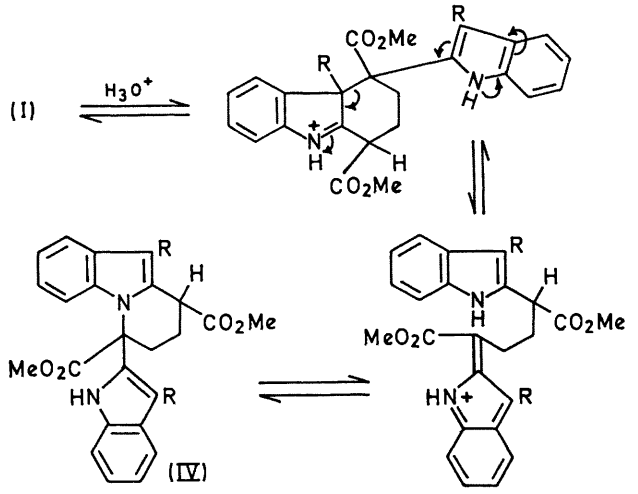


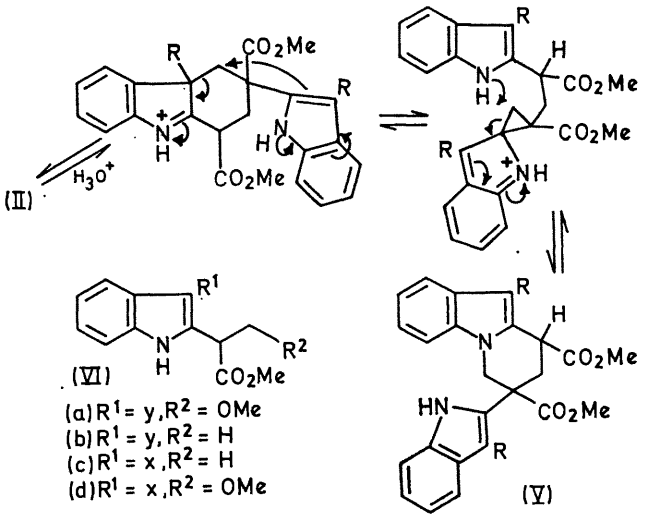
(a) R = x (b) R = y

Both P S and T H P S rearrange quantitatively at room temperature in 2N-aqueous HCl in 15 min to one of the secamines (IV or V)[3] and one of the tetrahydrosecamines[3,4] (stereoisomer with methoxycarbonyl singlets at τ 6.24 and 6.27), respectively this important observation is one of the

main pieces of evidence for the structures suggested and would tend to favour structure type (I).

Type (II) structures are, however, not excluded on mechanistic grounds, for they could (if less plausibly) lead to to the other possible secamine structures (V).





The mass spectra suggested an easy retro-Diels–Alder reaction, and this was indeed realised at 175°/0·2 mm. in a short-path distillation apparatus. The sublimed amorphous product from T.H.P.S. was pure 15,20-dihydrosecodine (IIIb): λ_{max} (MeOH) 278 (infl.), 303 nm, λ_{max} (EtOH) 278 (infl.), 312 nm (ϵ *ca.* 6500) which compares with λ_{max} 303 nm for simple 2-alkenylindoles in which there is free rotation about the indole–alkene link;[5] mass spectrum identical with that of T.H.P.S.; 100 MHz n.m.r. spectrum (CD_3OD), τ 2·40—3·15 (m, 4H), 3·54 (d, J 1·2 Hz, 1H), 4·01 (d, J 1·2 Hz, 1H), 6·17 (s, 3H), 6·85—7·18, 7·2—7·5, 7·8—8·7 (complex, total 13H), 8·76 (q, J 6 Hz, 2H), 9·04 (t, J 6 Hz, 3H), in accord with structure (IIIb). The base is optically active, $[\alpha]_D^{20}$ −2·5 ± 0·5° (MeOH).

15,20-Dihydrosecodine (IIIb) reacted only slowly with MeOH at room temperature: after 10 days the main product was 17-methoxy-16,17,15,20-tetrahydrosecodine (VIa), (structure established by u.v. and mass spectrum). Catalytic reduction of (IIIb) yielded a single product identified as 16,17,15,20-tetrahydrosecodine (VIb) by mass spectral and t.l.c. comparison with synthetic material.[6]

In the absence of solvent at 0° over 2 days, (IIIb) dimerised to a 4 : 1 mixture of T.H.P.S. and its diastereoisomer, separable by t.l.c.[5b] Both products rearranged in 2N-aqueous HCl to the same tetrahydrosecamine (methoxycarbonyl singlets at τ 6·24 and 6·27).

Short-path distillation of P.S. similarly yielded the parent compound, secodine [λ_{max} (Et_2O) 312 nm], which was catalytically reduced to a mixture of 16,17-dihydrosecodine (VIc) and 16,17,15,20-tetrahydrosecodine (VIb).[2,6] Similarly, with MeOH at room temperature, the main product was 17-methoxy 16,17-dihydrosecodine (VId). On standing in the absence of solvent the diastereoisomers of P.S. were formed and characterised by u.v., t.l.c., and mass spectral properties, and rearrangement to secamine.

The "synthetic" T.H.P.S. has an $[\alpha]_D^{20}$ −10 ± 1° (95% EtOH), which is quite surprising in view of the much lower rotation of "natural" T.H.P.S. $[\alpha]_D^{20}$ −1·9 ± 0·5° (95% EtOH). In view of the high specific rotations (300—750°) of all the optically pure alkaloids containing the β-anilinoacrylic ester chromophore,[7] the low specific rotations of the presecamines suggest that these alkaloids are largely racemic at C-7, C-16′. If this is the case, then the presecamines could well arise mainly by non-enzymic dimerisation of secodine units either in the cell or during extraction. The question of whether the presecamines and secamines are artefacts is being studied. It is noteworthy that the high yield of T.H.P.S. from *Rhazya orientalis* roots was obtained by a work-up procedure which avoided the use of acid stronger than pH 4·2, whereas the *Rhazya stricta* alkaloids were exposed to a strongly acidic solution in which most of any presecamine content could have rearranged to secamine.

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[1] The numbering follows that of J. Le Men and W. I. Taylor, *Experientia*, 1965, **21**, 508.
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[7] M. Hesse, "Indolalkaloide in Tabellen" Vol. II, Springer-Verlag, Berlin, 1968.