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STEREOCHEMISTRY AND BIOGENESIS OF SERRATININE

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In the prededing paper[1] we proposed the structure (I) for serratinine which was isolated from Lycopodium serratum THUNB, var. Thunbergii MAKINO. In this communication the authors wish to present the stereostructure (IX) including the absolute configuration of serratinine and also refer to the hypothetical biogenesis of this alkaloid.

On von Braun degradation diacetylserratinine* (I_e)*1 gave a neutral substance, cyanobromide (II), m.p. 200-202°*2, $C_{21}H_{29}O_5N_2Br$*3; νmax 2188 (N-CN), 1739 and 1729 cm^{-1} (>C=O) in good yield. Treatment of (II) with alkali furnished a ketal (III), m.p. 239-240°, $C_{17}H_{24}O_3N_2$, νmax 3509 (OH) and 2188 cm^{-1} (N-CN), no carbonyl band. Participation of the C_{13} hydroxyl group in this ketal formation was demonstrated by the formation of an

*1 Physical constants and preparation of the compound marked with an asterisk in this paper appeared in the preceding communication.

*2 All melting points were observed on a Kofler type microscope hotstage and are uncorrected.

*3 All compounds given by formulaegave correct elementary analyses.

anhydroketal (IV), m.p. 175-178°, $C_{17}H_{22}O_2N_2$, on treatment of the ketal (III) with $POCl_3$ in pyridine. In the NMR spectrum*4 of (IV), the two signals at 4.37 (1H, m., olefinic proton) and 8.29 τ (3H, s., vinyl methyl) showed that the free hydroxyl in (III) must be located on the carbon atom (C_8) adjacent to the secondary methyl group. Another support came from the following finding. Thus, oxidation of (III) with CrO_3-pyridine gave dehydroketal (V), m.p. 284-285°, $C_{17}H_{22}O_3N_2$, ν_{max} 1692 cm^{-1} (>C=O), NMR 5.8-6.2 (3H, m.,>C<u>H</u>-O-C(-)-O-C<u>H</u>$_2$-). On the other hand, successive treatments of monoacetylserratinine II* (I_b) with Jones' reagent and von Braun degradation gave dehydrocyanobromide (VI), m.p. 169-172°; $C_{19}H_{25}O_4N_2Br$, ν_{max} 2193 (N-CN), 1745, 1733, 1698 cm^{-1} (>C=O) which on treatment with alkali afforded dehydroketal (V).

Although no evidence has been presented that von Braun degradation might cause the cleavage of ring D, a consideration of the steric limitation for ketal formation led to the conclusion that the structure of the ketal should be represented by the formula (III).

Because of this ready ketal formation, the A/B ring junction must be cis, the participating hydroxyl group at C_{13} being axially situated with respect to the ring A as shown in the formula (VII).

Oxidation of monoacetylserratinine II* (I_b) with Jones'

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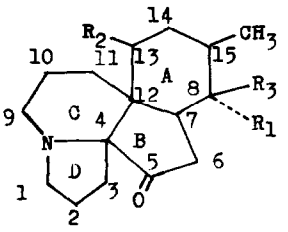
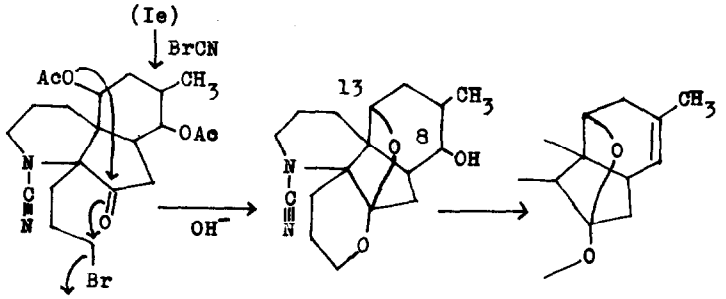
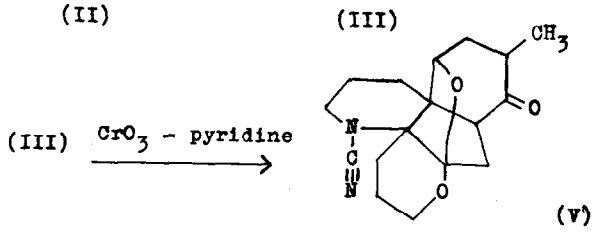
*4 All NMR spectra were taken on a Varian A-60 machine in $CDCl_3$ with $SiMe_4$ as an internal standard by Dr. T. Shingu, Kyoto University, to whom we express our thanks.



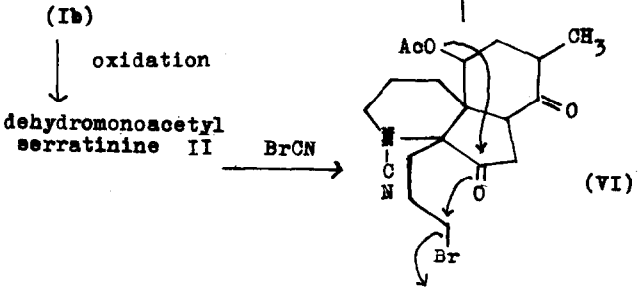
(I) $R_1 = R_2 = OH$, $R_3 = H$
(Ia) $R_1 = OAc$, $R_2 = OH$, $R_3 = H$
(Ib) $R_1 = OH$, $R_2 = OAc$, $R_3 = H$
(Ic) $R_1 = H$, $R_2 = OH$, $R_3 = OH$
(Id) $R_1 = H$, $R_2 = OH$, $R_3 = OAc$
(Ie) $R_1 = R_2 = OAc$, $R_3 = H$



(II) (III) (IV)



(V)



(VI)

reagent afforded the sole oxidation product*5, dehydromonoacetylserratinine II* (Ib : C_8, >C=O); C_{13}, -OAc) in good yield, which upon $NaBH_4$ reduction, followed by hydrolysis gave a mixture showing two spots on thin layer chromatography. On chromatographic purification of this epimeric mixture on alumina with $CHCl_3$, the first eluted component was found to be identical with serratinine in all respects. Subsequent elution with AcOEt gave another crystalline compound, 8-episerratinine (VIII=Ic), m.p. 234-237° , $C_{16}H_{25}O_3N$, ν_{max} 3520, 3340 (OH) and 1737 cm^{-1} (>C=O). The ratio of serratinine and 8-episerratinine was about 1:2.5. These two products must be epimeric at C_8 only, since they were oxidized with Jones' reagent to give the same product, a triketone*. The difference in the chromatographic behavior of two epimeric alcohols, permits to assume that the conformation of C_8 hydroxyl group in serratinine would be axial, that of C_8 hydroxyl group in 8-episerratinine being equatorial with respect to ring A.

This deduction was also confirmed by the spectral means. Acetylation of (VIII=Ic) gave monoacetyl 8-episerratinine (Id)*6, m.p. 220.5-221°, $C_{18}H_{27}O_4N$, ν_{max} 3270 (OH), 1747 and

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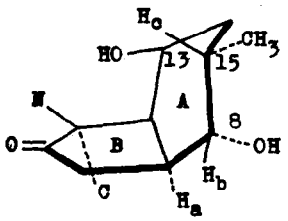
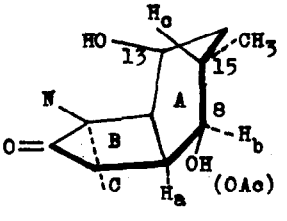
*5 The reaction product showed virtually one spot on thin layer chromatography.

6 That an introduced acetyl group in monoacetyl 8-episerratinine must be at C_8 was based on the fact that dehydromonoacetyl 8-episerratinine, m.p. 169-170° $C_{18}H_{25}O_4N$ (C_{13}, >C=O; R_1=OAc in Id) derived from monoacetyl 8-episerratinine (Id) by oxidation with Jones' reagent, was not identical with both dehydromonoacetylserratinine I (C_{13}, >C=O; R_1=OAc in Ia) and dehydromonoacetylserratinine II* (C_8, >C=O; R_2=OAc in Ib).



(VII)



(VIII)

1732 cm^{-1} (>C=O), NMR 5.17 (1H, clean q., J_1= 5.5 c.p.s., J_2 = 11 c.p.s., >C<u>H</u>-OAc), 6.48 (1H, m.,>C<u>H</u>-OH), 7.96 (3H, s., OAc). The signal attributable to a proton geminal to an acetoxyl group in monoacetylserratinine I* (Ia) appeared at 4.94 τ as a rather sharp multiplet (half-width, 5 c.p.s.) as constrasted to that in monoacetyl 8-episerratinine (Id) suggesting the assignbd conformation to the proton concerned.

On the IR spectra of acetates, it has been well known that the band due to the C-O streching vibration at 1200-1250 cm^{-1} is simple for the equatorial epimers but consists of two or three peaks for the axial substituents[2]. Comparable results have been also obtained by Burnell et al.[3] in acetates of lycopodium alkaloids. The IR spectra of two epimeric acetates from serratinine showed that the assigned conformations are quite reasonable.

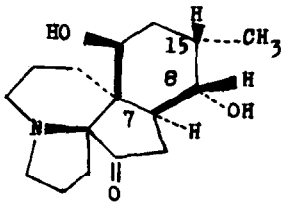
The assignment of equatorial conformation to the secondary methyl group in serratinine came from the NMR spectroscopic findings. In comparison of the chemical shift of methyl group in diacetyl benzylidene serratinine* with that

of this group in derivatives of serratinine, a high field shift (ca. 0.3-0.4 p.p.m.) in the former, which would be ascribed to the anisotropic effect of a benzene ring, was observed. A Dreiding model of diacetyl benzilidene serratinine showed that only the equatorial methyl has the hydrogens favorably situated for long range shielding effect of the benzene ring.

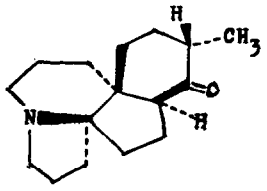
The assigned conformation of methyl group in serratinine was also supported by another finding. The calculated values for J_1 and J_2 corresponding to the dihedral angles, $\theta = 45°$ and $\theta = 170°$ are 4 c.p.s. and 11 c.p.s., respectively[4] and the observed coupling constants in the NMR spectrum of (Id) were $J_1 = 5.5$ c.p.s. and $J_2 = 11$ c.p.s.. The coupling constant $J_1 = 5.5$ c.p.s. for θ = ca. 45° should be allocated to $J^{H_a-H_b}$ in the formula (VIII), since the A/B cis junction has been established. This indicated, in turn, that the coupling constant $J_2 = 11$ c.p.s. must be assigned to $J^{H_b-H_c}$ for $\theta = 170°$. Since the axial conformation of C_8-H_b in (VIII) has been established, it can be deduced that the conformation of $C_{15}-CH_3$ should be equatorial. This deduction would be applicable to the conformational assignment of the methyl group in serratinine, because it would be hardly considered that the equatorial methyl group in (VIII) has resulted from epimerization of that group in serratinine.

The cis relationship of C_4-N and $C_{12}-C_{13}$ bond with respect to ring B was shown by pKa' measurements*7 on two

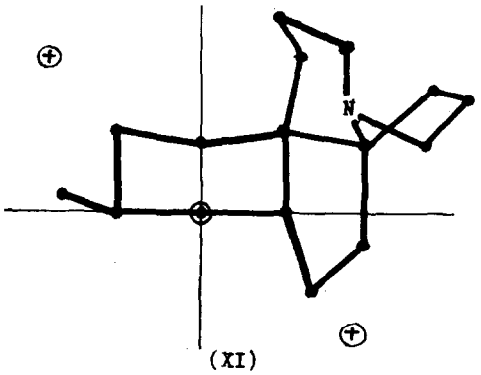
*7 pKa' values were measured in 1/10 N-H_2SO_4 (1 ml)- EtOH (5 ml) - H_2O (4 ml) solvent system by titration with 1/10 N- NaOH solution.



(IX)

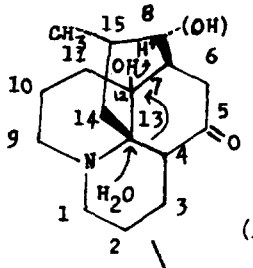


(X)



(XI)

two eight-carbon polyacetate straight chains



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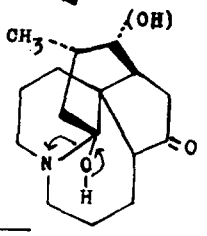

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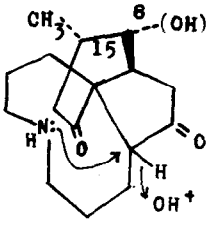
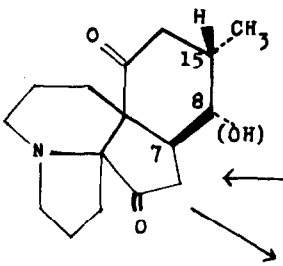


(XIV)



(XV)

(IX)

pairs of the following compounds: serratinine (pKa'7.0) and diacetylserratinine (pKa'5.3), Δ pKa' 1.7; deoxoserratinine (pKa' 10.9) and diacetyldeoxoserratinine (pKa' 9.8), Δ pKa' 1.1. These differences of pKa' values suggested the formation of intramolecular hydrogen bonding between the C_{13} hydroxyl group and protonated nitrogen atom.

Thus, it can be concluded that the stereostructure of serratinine is represented by the formula (IX) or its mirror image.

Application of the benzoate rule[5] to monoacetylserratinine II*, $[\alpha]_D^{23}$ -25.6° (EtOH) and 8-O-benzoyl-monoacetylserratinine II , m.p. 134-135° , $C_{25}H_{31}O_5N$, ν_{max} 1742, 1700 (>C=O) and 1600 cm^{-1}(aromatic), $[\alpha]_D^{23}$ + 14.63° (EtOH); $[M]_D$ (benzoate) + 62.3° - $[M]_D$ (ol) -82.4° = 144.7°, led to the conclusion that the absolute configuration at C_8 asymmetric center is S-form.

Consequently, the absolute stereostructure of serratinine is represented by the formula (IX).

This assignment of the absolute configuration was consistent with the strong positive Cotton effect (RD in MeOH, $[\phi]_{273}$ -1023° (trough), $[\phi]_{308}$ +3735° (peak); a= +47.58) of the ketone*8(X), m.p. 81-85°, $C_{16}H_{25}ON$ whose Octant projection shown by (XI) should give a positive Cotton curve.

It has been suggested by Conroy[6] that the skeleton inherent in lycopodium alkaloids, such as lycopodine and lycodoline (XII; no OH at C_8), might owe to the condensation of two eight-carbon polyacetate straight chains.

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*8 Details of preparation of this ketone will be reported in the full paper.

If lycodoline or a close derivative is the precursor of serratinine in the plant, serratinine could be visualized to arise by the supposed transformation from lycodoline type alkaloid as shown in Chart, although the sequence is somewhat uncertain. This assumption appears reasonable since lycodoline was isolated from the plant together with serratinine, and the proposed absolute configuration of serratinine coincides with that of an alkaloid which might be expected to arise from the lycodoline type alkaloids by the supposed transformation. The hydroxyl group at C_8 in serratinine does not seem to be unaccountable, since the oxygen functions in lycopodium alkaloids are commonly found at C_5, C_8 and C_{12}, especially, lycofawcine[7] possessing three oxygen functions at C_5, C_8 and C_{12}. Of course, while the scheme on this biogenetical transformation is plausible enough , it will require the experimental support.

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