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STRUCTURE OF SERRATINIDINE: CORRELATION WITH SERRATININE

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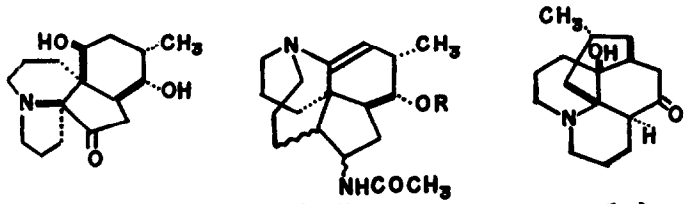
In a recent paper, we have reported the isolation and characterization of three new alkaloids, serratinine, serratanine and serratine, from Lycopodium serratum THUNB. var. Thunbergii MAKINO (Lycopodiaceae)[1], and most recently, the complete structure of serratinine[2] has been shown to be represented by the formula (I). Serratinidine is another minor alkaloid, newly isolated from the same plant. In this communication we wish to present the proof of structure of serratinidine (IIa).

Serratinidine, $C_{18}H_{28}O_2N_2$ *1, m.p. 232-234°*1, $[\alpha]_D^{10°}$ + 224.2° (c, 1.08 in EtOH) showed IR*2 ν_{max} 3310 (NH and OH), 3110 (=CH), 1659 (-CO-NH-) and 1563 cm^{-1} (amide II band), and NMR signals*3 at 4.72 (1H, broad, half-band width 4.0 c.p.s., olefinic proton), centered at 5.67 (1H, broad, $\geq$CH-NH-$COCH_3$), 6.31 (1H, broad, $\geq$CH-OH), 8.01 (3H, s., -CO-CH_3), and 8.89 τ (3H, d., J=7.5 c.p.s., $\geq$CH-CH_3). Acetylation of serratinidine afforded acetylserratinidine (IIb), $C_{20}H_{30}O_3N_2.2H_2O$, m.p. 105-108°; $[\alpha]_D^{16}$+172.0° (c, 1.192 in EtOH), NMR 4.52 (1H, d., J=4.4 c.p.s., olefinic proton), 4.99 (1H, q., J_1=5.0 c.p.s., J_2=8.0 c.p.s., $\geq$CH-OAc),



(I) (IIa) R=H serratinidine (III)

(IIb) R= Ac

centered at 5.50 (1H, broad, $\geq$C<u>H</u>-NH-CO-CH_3), 7.89 (3H,s., -CO-C<u>H</u>$_3$), 8.01 (3H, s., -CO-C<u>H</u>$_3$), and 8.97 τ (3H, d., J=7.5 c.p.s., $\geq$CH-C<u>H</u>$_3$). Decoupling experiments[*3] were performed on this acetate.

Irradiation on around 7.5 τ (the signal due to a proton geminal to a methyl group) resulted in the changes of two doublets attributable to olefinic proton and methyl protons into two singlets. This finding suggested the presence of (C or N)$\geq$C=CH-CH(CH_3)- system in the serratinidine molecule.

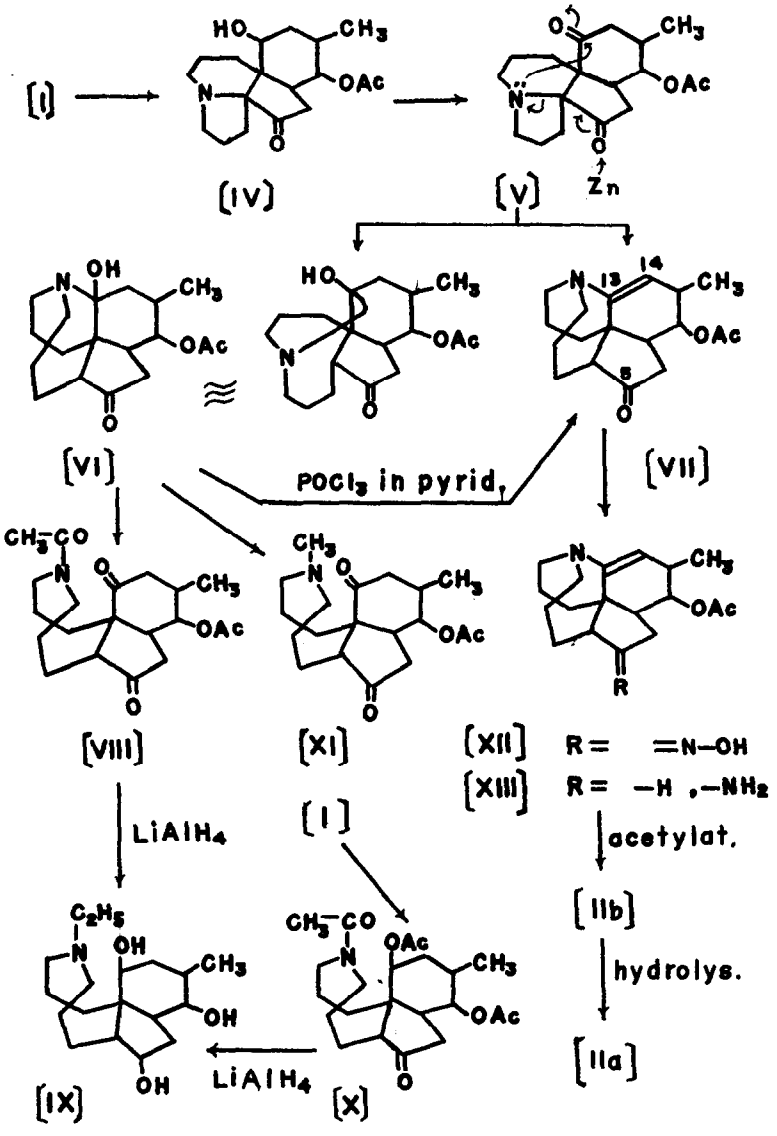
A clue for the structure of serratinidine came from an unexpected source. In connection with the biogenesis of serratinine which has been suggested in the preceding communication[2], attempts were made to transform serratinine into lycodoline (III)[3] or vice versa in view of that the transformation would lend satisfactory support for the biogenetic scheme suggested.

Oxidation of monoacetylserratinine I[2] (IV) with Jones' reagent gave dehydromonoacetylserratinine I (V), $C_{18}H_{25}O_4N$, m.p. 96-97°, IR ν_{max} 1735 (five membered ketone and acetyl),

1701 cm^{-1} (six membered ketone), which was then submitted to Zn-AcOH reduction. Chromatographic separation of the reaction product on neutral alumina (Grade II) gave two crystalline substances, acetylaposerratinine (VI), $C_{18}H_{27}O_4N$, m.p. 172-175°, IR ν_{max} 3450 (OH) and 1725 cm^{-1} (five membered ketone and acetyl), NMR 4.98 (1H, broad, $\geq$C<u>H</u>-OAc), 7.88 (3H, s., -CO-C<u>H</u>$_3$), 9.05 τ (3H, d., J=6.5 c.p.s., $\geq$CH-C<u>H</u>$_3$), and acetylanhydroaposerratinine (VII), $C_{18}H_{25}O_3N$, m.p. 153-155°.

The presence of the masked ketone group in the former compound (VI) was shown by the following reactions. Acetylation of (VI) with Ac_2O in alkaline medium of sodium hydroxide solution gave a neutral compound (VIII), oil, which shows IR ν_{max}^{film} 1735 (five membered ketone and acetyl), 1695 (six membered ketone), and 1635 cm^{-1} (amide carbonyl group). Reduction of this amide with $LiAlH_4$ furnished a crystalline basic compound (IX), $C_{18}H_{33}O_3N$, m.p. 194°, whose IR spectrum showed no carbonyl band. This compound was proved to be identical in all respects with the reduction product of O,O,N-triacetylchanodihydroserratinine (X)[2]. The α-carbinolamine structure of (VI) was supported by the following observations. Reaction of (VI) with methyl iodide, followed by treatment with cold ammonia solution afforded a tertiary amine (XI), $C_{19}H_{29}O_4N$, m.p. 134-137°, IR ν_{max} 1742 (five membered ketone and acetyl) and 1692 cm^{-1} (six membered ketone), NMR 7.71 and 7.76 τ (each 3H, s., $\geq$N-C<u>H</u>$_3$ and -COC<u>H</u>$_3$).

Acetylanhydroaposerratinine (VII) was also obtained by dehydration of (VI) with $POCl_3$ in pyridine. Basicity measurement of (VII) (pKa' 6.4)[4] showed that this compound


[I]
[IV]
[V]
Zn
[VI]
[VII]
POCl₃ in pyrid.
[VIII]
[XI]
[XII] R = =N-OH
[XIII] R = -H , -NH₂
acetylat.
[IIb]
hydrolys.
[IIa]
LiAlH₄
[I]
LiAlH₄
[IX]
[X]

is relatively weak base. Unsaturation at C_{13}-C_{14} would be expected to result in a relatively weak base because of the proximity of a such double bond to the basic nitrogen and its inability to migrate to the nitrogen in acid solution[4] (the bridge-head nitrogen). The compound (VII) showed IR ν_{max} 1740, 1728 (five membered ketone and acetyl) and 1662 cm^{-1} ($\geq C=C\leq$) and NMR signals at 4.39 (1H, d., J=6.0 c.p.s., olefinic proton), 5.55 (1H, q., J_1=6.0 c.p.s., J_2=10.0 c.p.s., $\geq C\underline{H}$-OAc), 8.93 (3H, s., -CO-C$\underline{H}_3$), 9.02 τ (3H, d., J=7.0 c.p.s. $\geq$CH-C$\underline{H}_3$). From these observations the structure of acetylanhydroaposerratinine is unequivocally assigned to the formula (VII).

An analogy between acetylserratinidine (IIb) and acetylanhydroaposerratinine (VII) was found in their NMR spectra, especially in decoupling experiments. In the NMR spectrum of (VII), irradiation on the signal due to a proton geminal to a methyl group (around 7.3 τ) resulted in the changes of two doublets attributable to olefinic proton and methyl protons into respective singlet and of a quartet due to a proton geminal to acetoxyl group to a doublet. From the empirical correlations observed in the NMR spectra, it was anticipated that the ring system of serratinidine (IIa) bears a remarkable resemblance to that of acetylanhydroaposerratinine (VII). In addition, it seems quite likely in viewpoint of biogenesis of lycopodium alkaloids that the position of an acetylamino group in serratinidine would be at the carbon atom 5.

At this stage of studies, an attempt was made to correlate serratinidine directly with anhydroaposerratinine in

order to establish firmly the structure of the former.

The compound (VII) was derived to its oxime (XII), oil, which upon catalytic hydrogenation with Raney Ni gave a colorless oil (XIII) showing clean two spots on thin layer chromatography.*5 This mixture, without separation, was acetylated with Ac_2O in pyridine, and the product was purified by careful chromatography on neutral alumina (Grade II). The earlier fractions gave a crystalline compound, m.p. 103-106°, $[\alpha]_D^{16}$ +162.5 (c, 0.625 in EtOH), which was identified with a sample of natural acetylserratinidine. The free base, m.p. 231-234°, obtained by hydrolysis of the O-acetyl group was also confirmed to be identical with natural serratinidine (IIa) by comparison of IR spectra and mixed melting point determination.

REFERENCES

*1 All melting points were observed on a microscopic hotstage and are uncorrected. All compounds given by formulae gave satisfactory elementary analyses.

*2 Unless otherweise noted, IR spectra were measured on Nujol mulls.

*3 NMR spectra were taken on a Varian Associates Recording Spectrometer (A-60) at 60 Mc. in $CDCl_3$. Chemical shifts are reported in τ values, using tetramethylsilane as an internal reference. Decoupling experiments were carried out by the magnetic field swept method using the same machine.

*4 pKa' values were measured in 1/100 N H_2SO_4-50% EtOH solvent system by titration with 1/10 N NaOH- 50% EtOH solution.

*5 The product seems to be the epimeric mixture due to the configuration of the primary amino group. Details will be presented in full publication.

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