Structure of Serratandine

In previous publications, we have described the isolation and characterization of four known alkaloids and seven new alkaloids from _Lycopodium serratum Thunb._ var. _serratum f. serratum_ Thunb. var. _Thunbergii Mako_ (hosobatohogeshiba) and the structures of three among these new alkaloids, serratamine (I), serratine (II) and serratidine (III), which are the unique skeletal lycopodium alkaloids, have been established.

This communication deals with structure establishment of serratandine (IV), one of seven new bases, mp 210—211°, C₁₈H₂₃O₄N₂ [α]D₂⁻⁻⁻⁻⁵₂.0° (c=1.01 in EtOH), IRνmax cm⁻¹: 3510, 3470, 3150 (OH), 1720 (C=O), 1415 (–CH₂-CO–).

Acetylation of serratandine (IV) with Ac₂O–pyridine at room temperature for two days afforded diacetyl serratandine (V), mp 203—205°, C₂₀H₂₆O₅N, IR νmax cm⁻¹: 3510 (OH), 1725, 1705 (C=O). NMR: 8.82 (3H, s, >C–CH₃), 8.06 (3H, s, –OCOCH₃), 7.93 (3H, s, –OCOCH₃), 7.48 (1H, s, –OH), 5.18 (1H, t, J=3 cps, >CH–OAc), 4.92 (1H, br. s, >CH–OAc).

The mass spectrum of diacetyl serratandine (V) showed the four significant peaks at M–28, M–57, m/e 194, m/e 152 which are diagnostically important for serratamine type alkaloid carrying an acetoxyl group at C₁₃. This result suggests that serratandine (IV) possesses the serratamine skeleton containing a hydroxyl group at C₁₃.

Hydrolysis of diacetyl serratandine (V) with aq. 10% HCl unexpectedly afforded a ketonic compound (VI), mp 201—204°, C₁₈H₂₅O₄N, IR νmax cm⁻¹: 3100 (OH), 1735, 1700 (C=O), which was identified with 8-dehydro serratamine (VI) derived from 8-dehydro–13–acetyl-serratamine (VII), by comparison of IR spectra and mixed melting point determination. Acetylation of 8-dehydro serratamine (VI) with Ac₂O–pyridine regenerated 8-dehydro–13–acetyl-serratamine (VII), showing that no skeletal change during hydrolysis with aq. 10% HCl solution had occurred. These results permit to deduce a plane structure for serratandine as (IV), and the remaining problem to be established on the structure of serratandine is concerned with the stereochemistry of the hydroxyl group at C₈ and C₁₅ respectively.

Osmolation of 8-anhydro–13–acetyl serratamine (VIII) provided cis–dioxol–A (IX), mp 222—223°, C₁₈H₂₅O₅N, IR νmax cm⁻¹: 3450 (OH), 1735, 1720 (OAc and C=O), NMR: 8.65 (3H, s, >C–CH₃), 8.08 (3H, s, –OCOCH₃), 6.30 (1H, d, J=4 cps, >CH–OH), 5.20 (1H, t, J=3 cps, >CH–OAc). Hydrolysis of cis–dioxol–A (IX) with alkali afforded cis–triole–A (X), mp 231—232°, C₁₈H₂₅O₄N, IR νmax cm⁻¹: 3450 (OH), 1735 (C=O) which was not identical with serratandine. Attempt to obtain diastereoisomeric cis–dioxol by Woodward’s–cis–hydroxylation of (VIII) failed to recover the starting material.

1) All melting points were observed on a microscopic hotstage and are uncorrected.
2) All compounds given by molecular formula gave satisfactory elementary analyses. IR spectra were measured on Nujol mulls and unless otherwise noted, NMR spectra were taken in CDCl₃ on a Varian A–60 at 60 Mc. Chemical shifts are reported in τ values, using tetramethylsilane as an internal reference.
Oxidation of cis-diol-A (IX) with Jones' reagent gave a diketone (XI), mp 230–232°, C_{15}H_{20}O_{2}N, IR ν_{max} cm^{-1}: 3430 (OH), 1720 (C=O), which upon NaBH₄ reduction, followed by hydrolysis afforded trans-triol-A (XII), mp 273–274°, C_{15}H_{19}O_{4}N, IR ν_{max} cm^{-1}: 3460, 3320, 3220 (OH) and 1720 (C=O). It is certain that trans-triol (XII) is epimeric in configuration at C₈ with cis-triol (X), since the mass spectrum of this trans-triol (XII) showed three characteristic fragment ion peaks, M−28, m/e 152 and m/e 150⁹ appeared in all serratinine derivatives which leave the original ketone group at C₃ intact, eliminating the possibility of reduction of the C₅ carbonyl group by this NaBH₄ treatment.

Then, oxidation by H₂O₂−HCOOH, followed by hydrolysis, which has been well known to give trans-diol derivative,⁹ was applied to 8-anhydro-13-acetylserotonin (VIII) and the product, trans-triol-B (IV), mp 209–212°, [α]_D^{25} −44.0° (c = 1.0 in EtOH) was not identical both with (X) and (XII) but proved to be identical with an authentic sample of natural serratine in all respects.

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10) The foregoing experiments have shown that sodium borohydride was inactive to the carbonyl group at C₈ in serratinine and its derivatives carrying the β-hydroxy group at C₁₃.⁶
This observation indicated that the configurational relationship between two hydroxyl groups at C₈ and C₁₅ in serrataneidine is trans. However, it is still obscure which hydroxyl group is situated in the β configuration. This ambiguity was solved by the following experiment.

Treatment of serrataneidine (IV) with phosgene in pyridine afforded serrataneidine carbonate (XIII), mp 277–278°, C₁₁H₂₂O₄N, IR νmax cm⁻¹: 3050 (OH), 1747 (C=O). IR spectral data showed that the carbonyl group in this carbonate ester is situated on the six-membered ring or larger. The formula (XIII) and (XIV) for serrataneidine carbonate are still possible but the latter was excluded by the following NMR observations. The NMR spectrum of the carbonate in DMSO revealed three signals at 6.28 (1H, br. d., J = 4 cps, ˃CH–OH), 5.55 (1H, br. d., J = 4.3 cps, ˃CH–OCO–), 4.26 (1H, d., J = 4 cps, –OH) and the last signal disappeared by treatment with D₂O, suggesting that the free hydroxyl group in the carbonate is the secondary one. The double resonance technique supported also the correctness of this assignment. These observations show clearly the cis relationship between the C₁₅ and C₁₅ hydroxy group.

Since the absolute configuration of serratinine (I) which was correlated with serrataneidine through the compound (VI) with the original hydroxyl group at C₁₃ intact, has been firmly established, the absolute stereostructure of serrataneidine should be represented by the formula (IV) and cis–dil–A which seems to arise from (VIII) by attack of OsO₄ from the less hindered a side, is depicted by the formula (IX).

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Received November 20, 1967

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Synthesis of Ecdysone

Insect moulting hormone ecdysone (I) was isolated in pure state in 1954 by Butenandt and Karlson¹) and its chemical structure was elucidated as 2β,3β,14a,22β, 25–penta-hydroxy–5β–cholest–7–en–6–one (I) by X-ray analysis in 1965.²) Only one year after establishment of structure, two groups³,⁴) succeeded in the synthesis of ecdysone. In our program to synthesize ecdysone, its chemical structure was divided into three partial structures, namely, A–ring (II), B,C–ring (III) and side chain (IV) structure, and novel and improved methods of preparation of these partial structures were developed, two of these methods being already reported. We now succeeded in synthesis of ecdysone by using above–mentioned methods.