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Structure of Serratanidine

In previous publications,[3,4] we have described the isolation and characterization of four known alkaloids and seven new alkaloids from *Lycopodium serratum* THUNB. var. *serratum* f. *serratum*=*L. serratum* THUNB. var. *Thunbergii* MAKINO (hosobatohogeshiba) and the structures of three among these new alkaloids, serratinine (I),[5] serratine (II)[6] and serratinidine (III),[7] which are the unique skeletal lycopodium alkaloids, have been established.

This communication deals with structure establishment of serratanidine (IV),[4] one of seven new bases, mp 210—211°.[1] $C_{16}H_{23}O_4N$,[2] $[\alpha]_D^{12.5}$ $-52.0°$ ($c=1.01$ in EtOH), IR[2] ν_{max} cm^{-1}: 3510, 3470, 3150 (OH), 1720 (C=O), 1415 (–CH_2–CO–).

Acetylation of serratanidine (IV) with Ac_2O–pyridine at room temperature for two days afforded diacetylserratanidine (V), mp 203—205°, $C_{20}H_{29}O_6N$, IR ν_{max} cm^{-1}: 3510 (OH), 1725, 1705 (C=O). NMR[2]: 8.82 (3H, s., $\geqslant$C–C$\underline{H}_3$), 8.06 (3H, s., –OCOC$\underline{H}_3$), 7.93 (3H, s., –OCOC$\underline{H}_3$), 7.48 (1H, s., –O$\underline{H}$), 5.18 (1H, t., $J=3$ cps, $\rangle$C$\underline{H}$–OAc), 4.92 (1H, br. s., $\rangle$C$\underline{H}$–OAc).

The mass spectrum of diacetylserratanidine (V) showed the four significant peaks at M–28, M–87, *m/e* 194, *m/e* 152 which are diagnostically important for serratinine type alkaloid carrying an acetoxyl group at C_{13}.[8] This result suggests that serratanidine (IV) possesses the serratinine skeleton containing a hydroxyl group at C_{13}.

Hydrolysis of diacetylserratanidine (V) with aq. 10% HCl unexpectedly afforded a ketonic compound (VI), mp 201—204°, $C_{16}H_{23}O_3N$, IR ν_{max} cm^{-1}: 3100 (OH), 1735, 1700 (C=O), which was identified with 8-dehydroserratinine (VI) derived from 8-dehydro-13-acetylserratinine (VII), by comparison of IR spectra and mixed melting point determination. Acetylation of 8-dehydroserratinine (VI) with Ac_2O–pyridine regenerated 8-dehydro-13-acetylserratinine (VII), showing that no skeletal change during hydrolysis with aq. 10% HCl solution had occurred. These results permit to deduce a plane structure for serratanidine as (IV), and the remaining problem to be estalished on the structure of serratanidine is concerned with the stereochemistry of the hydroxyl group at C_8 and C_{15}, respectively.

Osmolation of 8-anhydro-13-acetylserratinine (VIII) provided *cis*-diol-A (IX), mp 222—223°, $C_{18}H_{25}O_5N$, IR ν_{max} cm^{-1}: 3450 (OH), 1735, 1720 (OAc and C=O), NMR: 8.65 (3H, s., $\geqslant$C–C$\underline{H}_3$), 8.08 (3H, s., –OCOC$\underline{H}_3$), 6.30 (1H, d., $J=4$ cps, $\rangle$C$\underline{H}$–OH), 5.20 (1H, t., $J=3$ cps, $\rangle$C$\underline{H}$–OAc). Hydrolysis of *cis*-diol-A (IX) with alkali afforded *cis*-triol-A (X), mp 231—232°, $C_{16}H_{25}O_4N$, IR ν_{max} cm^{-1}: 3450 (OH), 1735 (C=O) which was not identical with serratanidine. Attempt to obtain diastereoisomeric *cis*-diol by Woodward's-*cis*-hydroxylation[9] of (VIII) failed to recover the starting material.

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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 $CDCl_3$ on a Varian A-60 at 60 Mc. Chemical shifts are reported in τ values, using tetramethylsilane as an internal reference.
3) Y. Inubushi, Y. Tsuda, H. Ishii, T. Sano, M. Hosokawa, and T. Harayama, *Yakugaku Zasshi*, **84**, 1108 (1964).
4) Y. Inubushi, H. Ishii, B. Yasui, T. Harayama, M. Hosokawa, R. Nishino, and Y. Nakahara, *Yakugaku Zasshi*, **87**, 1394 (1967).
5) Y. Inubushi, H. Ishii, B. Yasui, M. Hashimoto, and T. Harayama, *Tetrahedron Letters*, No. **14**, 1537 (1966); *idem, ibid.*, No. **14**, 1551 (1966); *Chem. Pharm. Bull.* (Tokyo), **16**, 82 (1968).
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8) Y. Inubushi, H. Ishii, T. Ibuka, and T. Harayama, *Tetraherdon*, in press.
9) "Advance in Organic Chemistry" ed. Raphael, Taylor and Wynberg, Interscience Publ. Inc., New York, Vol. 1, 1960, p. 117.

Oxidation of *cis*-diol-A (IX) with Jones' reagent gave a diketone (XI), mp 230—232°, $C_{18}H_{25}O_5N$, IR ν_{max} cm^{-1}: 3430 (OH), 1720 (C=O), which upon $NaBH_4$ reduction, followed by hydrolysis afforded *trans*-triol-A (XII),[10] mp 273—274°, $C_{16}H_{25}O_4N$, 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 C_8 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* 150[8] appeared in all serratinine derivatives which leave the original ketone group at C_5 intact, eliminating the possibility of reduction of the C_5 carbonyl group by this $NaBH_4$ treatment.

Then, oxidation by H_2O_2–HCOOH, followed by hydrolysis, which has been well known to give *trans*-diol derivative,[9] was applied to 8-anhydro-13-acetylserratinine (VIII) and the product, *trans*-triol-B (IV), mp 209—212°, $[\alpha]_D^{27}$ −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 serratanidine in all respects.

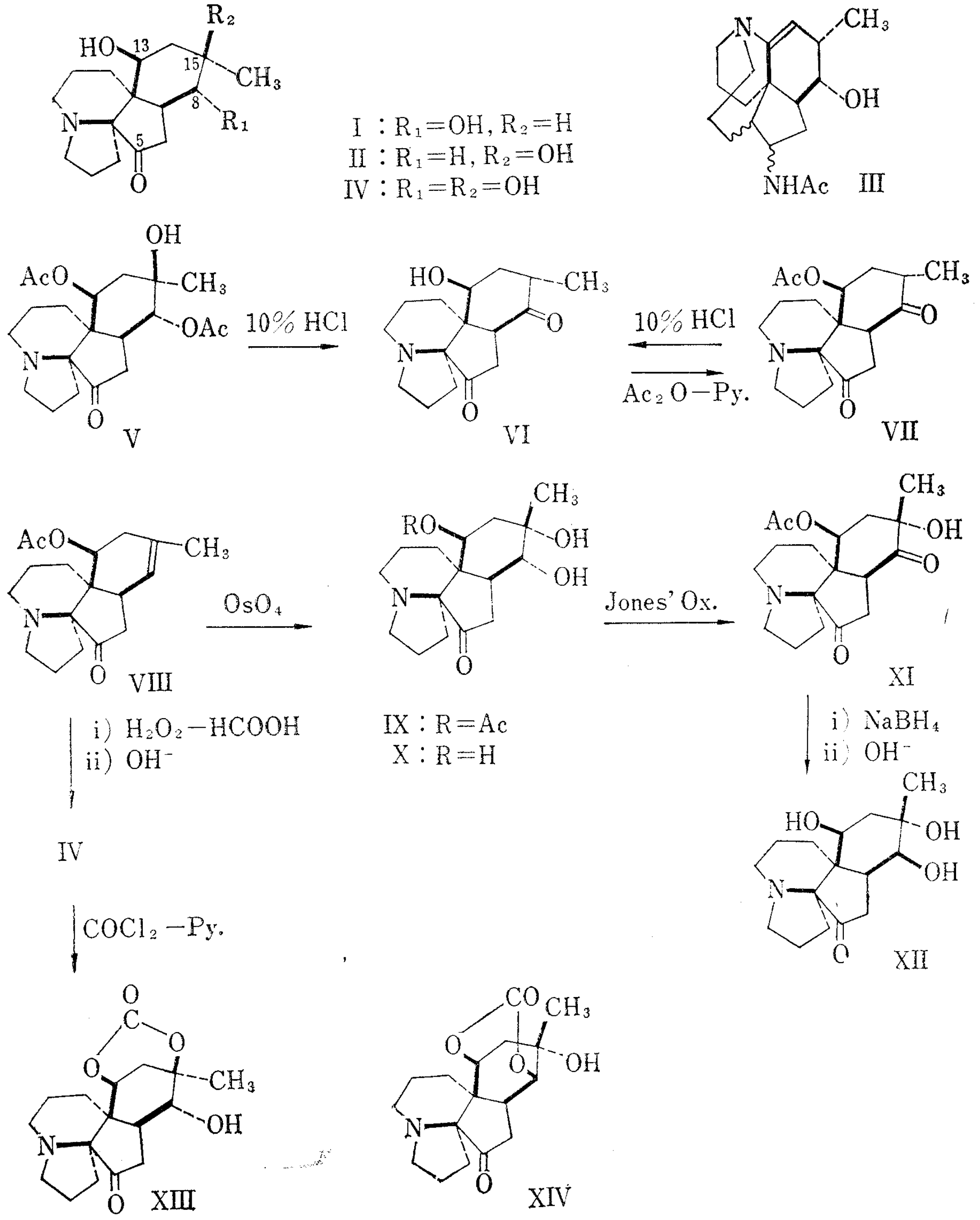

Chart 1

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[10] The foregoing experiments have shown that sodium borohydride was inactive to the carbonyl group at C_5 in serratinine and its derivatives carrying the β-hydroxyl group at C_{13}.[5]

This observation indicated that the configurational relationship between two hydroxyl groups at C_8 and C_{15} in serratanidine 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 serratanidine (IV) with phosgene in pyridine afforded serratanidine carbonate (XIII), mp 277—278°, $C_{17}H_{23}O_5N$, IR ν_{max} 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 formulae (XIII) and (XIV) for serratanidine 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, $\rangle C\underline{H}\text{-OH}$), 5.55 (1H, br. d., $J=4.3$ cps, $\rangle C\underline{H}\text{-OCO-}$), 4.26 (1H, d., $J=4$ cps, $\text{-O}\underline{H}$) and the last signal disappeared by treatment with D_2O, 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 C_{13} and C_{15} hydroxyl group.

Since the absolute configuration of serratinine (I) which was correlated with serratanidine through the compound (VI) with the original hydroxyl group at C_{13} intact, has been firmly established, the absolute stereostructure of serratanidine should be represented by the formula (IV) and *cis*-diol-A which seems to arise from (VIII) by attack of OsO_4 from the less hindered α side, is depicted by the formula (IX).

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Synthesis of Ecdysone

Insect moulting hormone ecdysone (I) was isolated in pure state in 1954 by Butenandt and Karlson[1] and its chemical structure was elucidated as $2\beta,3\beta,14\alpha,22\beta_F$, 25-pentahydroxy-$5\beta$-cholest-7-en-6-one (I) by X-ray analysis in 1965.[2] Only one year after establishment of structure, two groups[3,4] succeeded in the synthesis of ecdysone. In our program to synthesize ecdysone, its chemical structure was divided in three partial structures, namely, A-ring (II), B,C-ring (III) and side chian (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.

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