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STRUCTURES OF TWO CEVANINE ALKALOIDS, SHINONOMENINE AND VERAFLORIZINE, AND A CEVANIDANE ALKALOID, PROCEVINE, ISOLATED FROM ILLUMINATED VERATRUM

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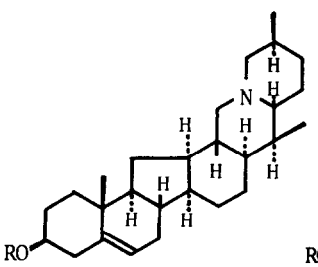
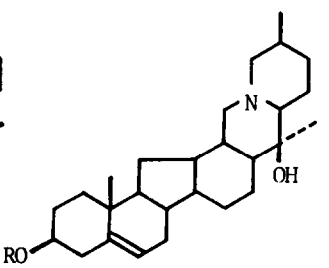
In our previous work on the biosynthesis of Veratrum alkaloids, it was found that solanidine (V) that accumulated in the etiolated Veratrum was converted to jervine and veratramine under illuminated cultivation with white light.[1] This evidence suggests the participation of light on the reaction of C-nor-D-homo rearrangement in the biosynthesis of Veratrum alkaloids and further possibility of the detection of intermediates in the process of C-nor-D-homo rearrangement from solanidine by a definite condition of illumination. In our detailed experiments on steroidal alkaloids which accumulate particularly in illuminated plants but not found in etiolated plants, two new cevanine alkaloids, shinonomenine (Ia) and veraflorizine (IIa) were isolated from the tertiary base fraction of rhizome of *Veratrum grandiflorum* (Max.) Loesen that was cultivated under illuminated condition, red fluorescent light, maximum energy at 660 nm, for 4 days, and a new cevanidane alkaloid, procevine (IIIa) was isolated from the aerial part of the Veratrum plant that was cultivated under sunlight lamp, maximum 30,000 lux, for 2 days, and procevine (IIIa) was accompanied with isorubijervine (IV) from this plant.

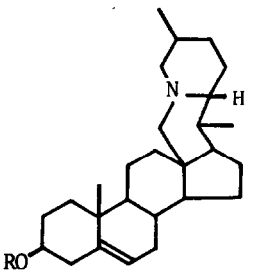
Shinonomenine (Ia), named after the Japanese name for the Veratrum plant shinonomesô, $C_{27}H_{43}ON$, mp 95-96°, $[\alpha]_D$ -90.7° (*c* 0.33, $CHCl_3$), MS: *m/e* 397 (M^+) and 112 (base peak), PMR: δ 1.04 (3H, s, 19-Me), 0.84 and 1.12 (3H each, d, *J* = 6 Hz, 21 and 27-Me), δ 3.52 (1H, m, 3α-H, this signal shifted downfield to δ 4.60 on acetylation), δ 5.42 (vinyl proton at C-6),



Ia:R=H Shinonomenine
Ib:R=Ac



IIa:R=H Veraflorizine
IIb:R=Ac

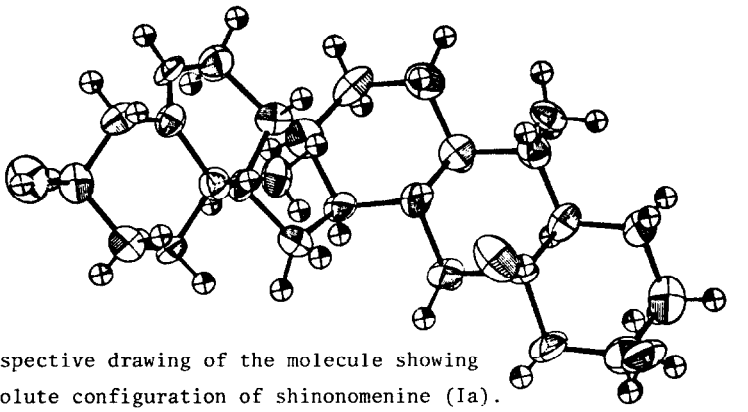


IIIa:R=H Procevine
IIIb:R=Ac

IR: $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH) and 2750 (*trans*-quinolizidine moiety), afforded on acetylation in pyridine a monoacetate (Ib), mp 206-208°, IR: $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (OAc), PMR: δ 2.06 (3H, s, OAc). These spectral data indicated that Ia is a C-nor-D-homo-steroidal alkaloid having the cevanine skeleton, and shinonomenine is represented by formula Ia except for the disposition of the methyl group at C-20 and the ring juncture D/E.

The final structural proof of Ia was elucidated by the X-ray crystal structure analysis of the hydriodide, mp 305° (decomp.). Crystals of shinonomenine hydriodide are monoclinic, space group $P2_1$, a = 13.722(2), b = 8.229(1), c = 11.765(2) Å, β = 100.27(3)°, z =2.

Three-dimensional intensity data were collected on a Hilger and Watts automatic four-circle Y 290 diffractometer controlled by a PDP 8 computer. Integrated intensities were measured for Θ<27.5° by the Θ-2Θ scan technique with Mo-Kα radiation, and 2526 of these above background were used for the structure determination. The structure was solved by the SEARCHER programme for automatic heavy-atom analysis, written for the CDC 3600 computer (later modified for the CDC 6600 computer), and refined by full-matrix anisotropic least-squares calculations to R 0.065. Hydrogen atoms were located from a difference-Fourier synthesis. Most observed bond distances and angles are comparable to those found in other alkaloids. Mean estimated standard deviations are ca. 0.01 Å 0.7°. The absolute configuration was determined using the anomalous despersion effect of the iodine atom. The structure of the molecule is shown below.



Perspective drawing of the molecule showing absolute configuration of shinonomenine (Ia).

As can be seen from this figure, all six-membered rings in this compound are in the chair conformation, with the ring fusions as follows: B/C *trans*, C/D *cis*, D/E *trans*, and E/F *trans*. The configuration at other chiral centers would be settled at C-3 hydroxyl *equatorial*, C-10 methyl *axial*, C-25 methyl *axial*, lone pair on nitrogen *axial*, and all these groups are in the β-orientation. From these evidences, shinonomenine (Ia) was identified as (25S)-20-epi-cev-5-enin-3β-ol (20β-methyl). Shinonomenine (Ia) is the first isolated cevanine alkaloid having 20β-methyl configuration to be identified from natural sources.

Veraflorizine (IIa), $C_{27}H_{43}O_2N$, mp 175-176°, $[\alpha]_D$ -91° (*c* 1, $CHCl_3$), MS: *m/e* 413 (M^+), 112 (base peak), PMR: δ 1.03 (6H, s, 19 and 21-Me), δ 1.10 (3H, d, *J* = 6 Hz, 27-Me), δ 3.52 (1H, 3α-H, this signal shifted downfield to δ 4.60 on acetylation), δ 5.34 (1H, vinyl proton

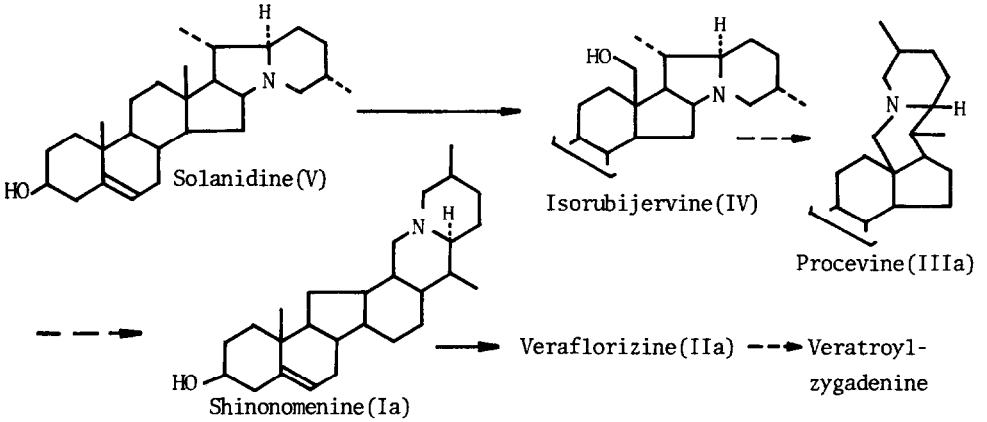
at C-6), IR: $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 2750 (*trans*-quinolizidine moiety), afforded on acetylation in pyridine a monoacetate (IIb), mp 201-204°, $[\alpha]_D$ -88° (*c* 1, $CHCl_3$), IR: $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (*ter*-OH) and 1730 (OAc), PMR: δ 2.03 (3H, s, OAc). From these spectral data of IIa and IIb, veraflorizine (IIa) was assumed to be as (25S)-cev-5-enin-3β,20β-diol.

In order to confirm the absolute configuration of veraflorizine (IIa), it was synthesized from verticinone. Verticinone monoacetate was reduced with $NaBH_4$ in EtOH, and afforded 6-epi-verticine-3-acetate (VI), predominantly. VI was dehydrolyzed by phosphoryl chloride in pyridine at room temperatrue, and resulting dehydrolyzed product (VII) was purified by silica gel 60 PF_{254} (tlc) (yield, 78%). Physical constants of the deacetylated alkaloid (VIII) from VII agreed well with that of veraflorizine (IIa), and mp of VIII was not depressed by admixture with IIa. From this synthetic evidence, the structure of veraflorizine (IIa) was finally confirmed as (25S)-cev-5-enin-3β,20β-diol, and it possesses B/C *trans*, C/D *cis*, D/E *trans*, and E/F *trans* ring fusion.

Procevine (IIIa), $C_{27}H_{43}NO$, mp 235-237°, $[\alpha]_D$ -12.2° (*c* 0.33, $CHCl_3$), MS: *m/e* 397 (M^+) and 112 (base peak), IR: $\nu_{max}^{CHCl_3}$ cm^{-1}, 3575, 1025 (OH), 2730 (*trans*-quinolizidine moiety), PMR: δ 1.01 (3H, s, 19-Me), δ 0.81 (6H, d, *J* = 6 Hz, 21 and 27-Me), δ 3.57 (1H, m, 3α-H, this signal shifted downfield to δ 4.56 on acetylation), δ 5.36 (1H, vinyl proton at C-6) afforded on acetylation in pyridine a monoacetate (IIIb), mp 166-168°, IR: $\nu_{max}^{CHCl_3}$ cm^{-1}, 1705, 1240 (OAc), MS: *m/e* 439 (M^+), PMR: δ 2.03 (3H, s, OAc). In the light of these spectral data, IIIa seems to possess a *trans*-quinolizidine moiety at the rings E and F. While the structure of IIIa can be assigned to that of shinonomenine (Ia), its spectral data, Rf value, and coloration by $SbCl_3$ on silica gel tlc of IIIa differed from those of shinonomenine (Ia).

Pelletier and Jacobs[2] determined the structure of isorubijervine (IV) through the conversion of IV to solanidine (V) and in this reaction, they also isolated a new compound, pseudosolanidine (IX), as a by-product. The structure of IX is quite similar to cevanine alkaloids in the rings E and F, and Pelletier and Jacobs[3] concluded that these two products, V and IX, were formed from tosyl ester of the primary hydroxyl group at C-18 by the displacement of the tosyl group by lone pair electrons on the nitrogen, forming a C-18-N bond, and then the cleavage of C-18-N bond of the salt-like derivative (X) for V, and of the C-16-N bond for IX by Na-EtOH reduction. Subsequently, Weisenborn[4] settled the structure of IX. Sheehan *et al.*[5] synthesized IX by a different approach and reconfirmed the structure of IX and the mechanism of formation of IX from IV which was proposed by Pelletier and also they proposed the name "cevanidane" for this new skeleton. Since the mp and $[\alpha]_D$ of both IIIa and IX (by Pelletier) are closely similar, we have carried out the synthesis of IX from isorubijervine (IV), following the method of Pelletier and obtained two products in 7:3 ratio. After separation of the two alkaloids on tlc, the main product, IX, showed the same physical properties as IIIa, and the mp of IX was not depressed by admixture with IIIa. Procevine (IIIa) was thus identified as (25S)-cevanid-5-en-3β-ol. The minor product in the above reaction was identified with solanidine (V), from spectral data and the mixed mp. Then, the steric structure of procevine (IIIa) was completely determined, and procevine (IIIa) is the first compound to be isolated as cevanidane alkaloid from natural sources.

Shinonomenine (Ia), veraflorizine (IIa) and procevine (IIIa) can be isolated from shortly illuminated Veratrum plant (within 1 week cultivation), but not from the etiolated, naturally dormant, and excessively illuminated more than 2 weeks plants. It appears that these alkaloids accumulate in a definite period after illumination and are quickly metabolized to ordinary cevanine alkaloids. After due consideration of these phenomena in Veratrum plant and the structural relationships among these alkaloids, it seems that solanidine (V) is first oxygenated at C-18 methyl group to isorubijervine (IV) in the aerial part of Veratrum under illuminated condition and the attachment of a leaving group at C-18 initiates the formation of C-18-N bond through the same mechanism as the chemical rearrangement of isorubijervine (IV) to procevine (IIIa) after cleavage of C-16-N bond. The rearrangement of rings C and D in procevine (IIIa), after oxygenation of C-12, would directly produce shinonomenine (Ia) with correct steric configuration, except the configuration of C-22 hydrogen. Also, it seems that shinonomenine (Ia) converts to veraflorizine (IIIa)after reversion of C-21 methyl group with reverse orientation (20α-Me) during oxygenation at C-20, and shinonomenine (Ia), veraflorizine (IIa) and procevine (IIIa) are intermediates of the primary stage in the biogenesis of ordinary cevanine alkaloids.



Biogenesis of cevanine alkaloids

In this hypothetical pathway, the configuration at C-22(α-H) in shinonomenine (Ia) is difficult to explain from the result of conversion of the F-ring in solanidanine skeleton through the introduction of C-18-N bond, because the configuration of solanidanine alkaloid at C-22 is α-oriented, and the mechanism of the conversion of this hydrogen from solanidine to shinonomenine, by way of procevine (22β-H), still remains uncertain in our present studies.

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