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# 93. Shojiro Uyeo, Hiroshi Irie, and Hiroshi Harada : The Structure of Stenine, a New Alkaloid Occurring in *Stemona Tuberosa*.

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A new alkaloid, stenine, has been isolated from the roots of *Stemona tuberosa* and its structure established as represented by formula II.

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From a basic fraction of the extracts of the roots of *Stemona tuberosa* (Stemonaceae), four crystalline alkaloids, tuberostemonine,[1] oxotuberostemonine,[2] isotuberostemonine,[3] and hypotuberostemonine[3] have been isolated, and characterized so far. Of these, the major alkaloid, tuberostemonine (I) is the only one whose structure has been firmly established.[4a~4d] In this paper we are reporting the isolation, characterization and elucidation of the structure of a hitherto unknown alkaloid stenine (II).

The presence of this new base was indicated by thin-layer chromatography of the total alkaloidal mixture, and its isolation was effected by chromatography over Florisil and silica gel (washed with ammonia) columns. Later it was found that among the alkaloids of this plant stenine was the only one readily soluble in hexane. We now isolate stenine conveniently in a better yield by extracting the total crude alkaloids with hexane.

Stenine has m.p. 65~67°, $[\alpha]_D$ −30.2° (MeOH) and the formula $C_{17}H_{27}O_2N$, calculated from the elemental analyses of the base and its methiodide, is supported by the parent peak ($M^+$ 277) observed in the mass spectrum.

The infrared spectrum of stenine exhibited a $\gamma$-lactone carbonyl band at 1775 $cm^{-1}$ but no absorption for a hydroxyl or an N-H group. In agreement with this finding no decrease in the number of protons was observed under deuterium-exchange conditions. Stenine showed an end absorption in the ultraviolet spectrum, but neither infrared absorptions characteristic for the presence of double bonds nor nuclear magnetic resonance (NMR) signals for vinylic protons were observed. It is highly probable that this alkaloid contains no double bond.

The NMR spectrum of stenine showed a broad triplet (1*H*) which had the chemical shift expected for a proton on the carbon bearing the secondary, lactonized hydroxyl group. The signal suggested that there were at least two hydrogens on the carbons adjacent to the carbon bearing the oxygen function. While tuberostemonine has three C-methyl groups, stenine showed only two C-methyl signals in the NMR spectrum, one of which was a doublet centered at 8.73$\tau$ (3H, J=6.5 c.p.s.) and assigned to the secondary methyl group located at the $\alpha$-position of the lactone carbonyl. The other signal appeared as a triplet centered at 9.09$\tau$ (3H, J=6.8 c.p.s.), which indicated the presence of an ethyl or longer side chain in the molecule. Further evidence pertinent to the structure of stenine (II) was provided by the mass spectrum. The base peak at

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1) K. Suzuki : Yakugaku Zasshi, **54**, 573 (1934); H. Schild : Ber., **69**, 74 (1936).
2) H. Kondo, M. Satomi, T. Kotera : Ann. Rep. ITSUU Lab., **5**, 46 (1954).
3) *Idem* : *Ibid.*, **7**, 24 (1956).
4) *a*) S. Uyeo, T. Shingu, Y. Tsuda : Yakugaku Zasshi, **84**, 663 (1964). *b*) M. Götz, T. Bögri, A. H. Gray: Tetrahedron Letters, **20**, 707 (1961). *c*) O. E. Edwards, G. Feniak : Can. J. Chem., **40**, 2416 (1962). *d*) T. Kaneko : Ann. Rep. ITSUU Lab., **14**, 49 (1965).
5) S. Uyeo, H. Irie, H. Harada : Unpublished work.

m/e 276 ($M-C_5H_7O_2$) in the spectrum of tuberostemonine has been assigned to the structure (Ⅵ).[5] The presence of the same peak (M–1) also as the base peak in the spectrum of stenine suggested that stenine might have the same structural features as that of tuberostemonine fragmentation product (Ⅵ). It seemed likely, therefore, that stenine could be represented by formula (Ⅱ).

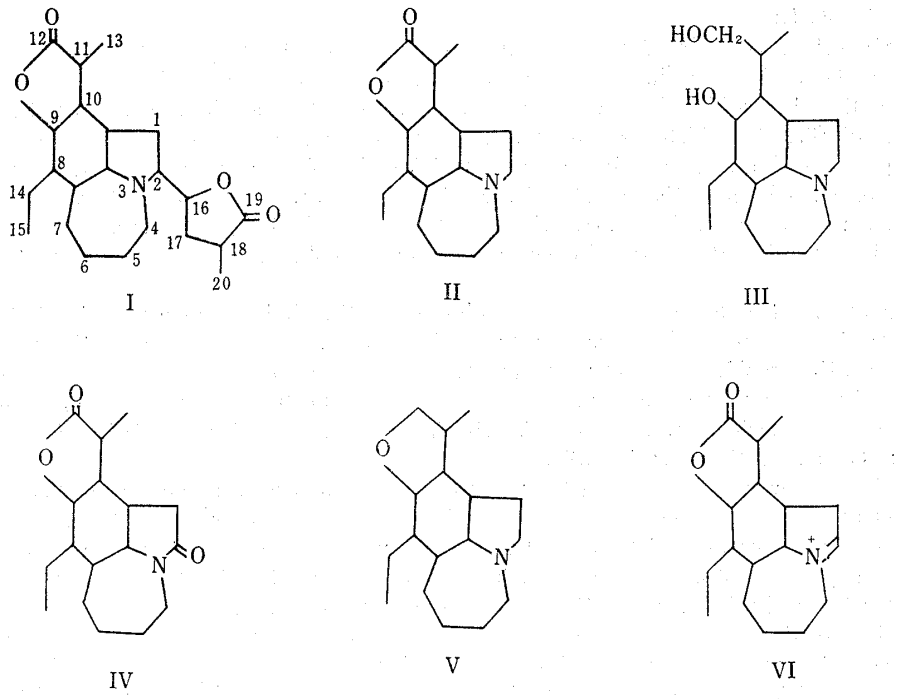


Chart 1.

This was proven by correlating stenine with certain derivatives of tuberostemonine of firmly established structure. Treatment of stenine with lithium aluminum hydride in tetrahydrofuran gave a diol, $C_{17}H_{31}O_2N$, m.p. 92~94°, which was shown to be identical in all respects with the product (Ⅲ) obtained by lithium aluminum hydride reduction of the lactam (Ⅳ) which in turn was obtained by permanganate oxidation of tuberostemonine (I).[4c,d]

The ease of formation of the tetrahydrofuran (Ⅴ) from the diol (Ⅲ) is noteworthy. The ethiodide of Ⅴ can be obtained be simply refluxing Ⅲ in ethanolic ethyl iodide. The ethiodide could also be prepared from Ⅴ which in turn was formed when Ⅲ was treated with 10% sulfuric acid on a steam bath. The ethiodide of Ⅲ was obtained when the diol (Ⅲ) reacted with ethyl iodide at room temperature.

The stereochemistry of tuberostemonine and stenine is under investigation, and will be reported in a forthcoming paper.

## Experimental

**Isolation of Stenine**——A methanolic extract of the roots (33 g.) of *Stemona tuberosa* deposited on concentration and standing crystals of tuberostemonine which were removed by filtration. The mother liquor was taken up in AcOEt (200 ml.) and extracted with dil. HCl. The aqueous phase was basified with $K_2CO_3$, and extracted with hexane and then with AcOEt. The hexane extract was washed with $H_2O$, dried over $K_2CO_3$ and evaporated to dryness to give an oil (5.5 g.) which was again dissolved in hexane, filtered clear and concentrated to dryness under reduced pressure to give stenine (4.5 g.) as prisms, m.p. 65~67° (4.3 g.) (from hexane). *Anal.* Calcd. for $C_{17}H_{27}O_2N$: C, 73.60; H, 9.81; N, 5.05. Found: C, 73.76; H, 9.94; N, 4.87. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1775 (CO). NMR ($CDCl_3$) $\tau$: 5.53 (1H, triplet, J=8 c.p.s.); 8.73 (3H, doublet, J=6.5 c.p.s., $-\dot{C}H-C\underline{H}_3$); 9.09 (3H, triplet, J=6.8 c.p.s., $-CH_2-C\underline{H}_3$). Mass spectrum $M^+=277$.

**Reduction of Stenine with Lithium Aluminum Hydride**——Stenine (0.5 g.) was heated under reflux with lithium aluminum hydride (0.2 g.) in tetrahydrofuran (20 ml.) for 3 hr. After decomposition of the excess lithium aluminum hydride by adding a few drops of $H_2O$, the mixture was filtered and concentrated to dryness under reduced pressure to yield an oil which was taken up in ether. The ethereal solution was extracted with a saturated sodium dihydrogen phosphate, and the aqueous layer was basified with $K_2CO_3$ and extracted with ether. Removal of the ether gave the diol (Ⅲ) (0.45 g.). which crystallized from hexane–ether as prisms, m.p. 92~94°. *Anal.* Calcd. for $C_{17}H_{31}O_2N$: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.30; H, 11.32; N, 4.99. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3230. NMR ($CDCl_3$) $\tau$: 8.94 (3H, doublet, J=7.5 c.p.s., -CH-C$\underline{H}_3$); 9.04 (3H, triplet, J=5.5 c.p.s., -$CH_2$-C$\underline{H}_3$).

**Acid Treatment of the Diol (III)**——A solution of the diol (0.3 g.) in 10% $H_2SO_4$ (10 ml.) was heated on a water bath for 3 hr. After cooling, the aqueous solution was washed with ether, basified with $K_2CO_3$, and extracted with ether which in turn was washed with $H_2O$ and dried over $K_2CO_3$. Removal of the solvent gave an oil (0.23 g.) which was chromatographed in benzene over alumina (activity Ⅲ). First elution with benzene gave an oil (0.2 g.) which was converted into its picrate in the usual manner. Recrystallization of the picrate from EtOH gave the picrate of the ether (V), m.p. 141~143°. *Anal.* Calcd. for $C_{17}H_{29}ON \cdot C_6H_3O_7N_3$: C, 56.09; H, 6.55; N, 11.38. Found: C, 56.19; H, 6.82; N, 11.10. Regeneration of the ether (V) was effected by passing the picrate in benzene through a column of alumina and the ether (V) was isolated as an oil.

**The Ethiodide of the Ether (V)**——a) A solution of the diol (Ⅲ) (50 mg.) and ethyl iodide (0.2 ml.) in EtOH (3 ml.) was heated under reflux on a water bath for 3 hr. After removal of the solvent under reduced pressure, the resulting residue was taken up in water. The aqueous solution was washed with AcOEt and concentrated to dryness under reduced pressure to give the ethiodide of the ether (V) (25 mg.) which crystallized from acetone as needles, m.p. 227~228°. *Anal.* Calcd. for $C_{17}H_{29}ON \cdot C_2H_5I$: C, 54.41; H, 8.17; N, 3.34. Found: C, 54.24; H, 8.34; N, 3.23.

b) A solution of the ether (V) (20 mg.) regenerated from its picrate as described above and ethyl iodide (0.2 ml.) in EtOH (3 ml.) was allowed to stand overnight. After working up in the same way as mentioned above, the product was crystallized from EtOH to give the ethiodide of the ether (V). The infrared spectrum of this salt was superimposable upon the ethiodide prepared from the diol (Ⅲ) as described in (a).

**Treatment of the Diol (III) with Ethyl Iodide at Room Temperature**——A solution of the diol (Ⅲ) (30 mg.) and ethyl iodide (3 ml.) in EtOH (0.5 ml.) was allowed to stand at room temperature overnight. The crystals were collected and recrystallized from EtOH–ether to give the ethiodide of the diol (Ⅲ), (15 mg.) as needles, m.p. 100~110°. The m.p. was raised to 204~205° on drying *in vacuo* over $P_2O_5$ at 80° for 4 hr. *Anal.* Calcd. for $C_{17}H_{31}O_2N \cdot C_2H_5I$: C, 52.17; H, 8.30; N, 3.20. Found: C, 52.09; H, 8.54; N, 3.08.

**Reduction of the Lactam (IV) with Lithium Aluminum Hydride**——The lactam (Ⅳ)[4d] (40 mg.) was heated under reflux with lithium aluminum hydride (30 mg.) in tetrahydrofuran (10 ml.) for 3 hr. The excess reagent was destroyed by adding a few drops of water and the mixture was filtered. The filtrate was concentrated to dryness to give an oil (30 mg.) which was taken up in ether. The ethereal solution was extracted with aqueous sodium dihydrogen phosphate. The aqueous extract was basified with $K_2CO_3$ and extracted with ether which was washed with $H_2O$, dried, and evaporated to yield the diol (Ⅲ) (22 mg.). Crystallization from hexane–ether gave prisms, m.p. and mixed m.p. 92~94°. The infrared and NMR spectra of this diol were superimposable upon those of the diol prepared by lithium aluminum hydride reduction of stenine.