Communications to the Editor

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STEPHADIAMINE, A NEW SKELETAL ALKALOID FROM STEPHANIA JAPONICA: THE FIRST EXAMPLE OF A C-NORHASUBANAN ALKALOID

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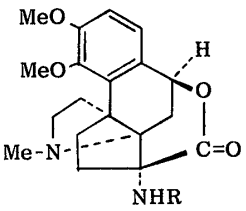
Spectroscopic methods and X-ray diffraction analysis have been used to elucidate the structure of the novel pentacyclic C-norhasubanan alkaloid stephadiamine isolated from *Stephania japonica*.

KEYWORDS —— *Stephania japonica;* stephadiamine; C-norhasubanan alkaloid; N-p-bromobenzoylstephadiamine; X-ray analysis

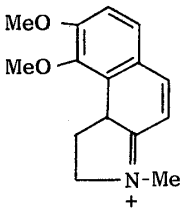
A Chinese medicine, an extract of *Stephania japonica*, has been used in China as an anti-diarrheal, an anti-anetus, an anti-febrile, a tonic, a diuretic, and a remedy for podagra and cholera.[1] The ethanolic extract of the whole plant of *S. japonica* collected in Taiwan was previously reported to yield many alkaloids such as metaphanine.[2,3] This report concerns the constitution of a novel skeletal lactonic alkaloid, stephadiamine (1), isolated from *S. japonica* harvested in Taiwan. The structure of the new base has a hasubanan-like pentacyclic skeleton, which, to our knowledge, has not previously been found in nature.

The new base (1) was isolated with difficulty in 4×10^{-6}% yield from the mother liquor after removal of metaphanine[2,3a] by repeated alumina column as well as preparative thin-layer chromatography. Stephadiamine (1) [mp 180°C; colorless prisms from acetone; $[\alpha]_D^{20}$ +51.8° (c = 0.54, $CHCl_3$); analyzed for $C_{19}H_{24}N_2O_4$ (high resolution mass spectrometry and elemental analysis); IR ($CHCl_3$): 3375 (NH_2) and 1720 cm^{-1} (δ-lactone); ^{1}H-NMR ($CDCl_3$) δ: 2.54 (3H, s, N-CH_3), 3.87 (6H, s, OCH_3 × 2), 5.39 (1H, dd, J = 4.3 and 2.0 Hz, C-10-H), 6.80 (1H, d, J = 8 Hz, C-2-H), and 7.00 (1H, d, J = 8 Hz, C-1-H)] gave, upon treatment with acetic anhydride and pyridine, N-acetylstephadiamine (2) [mp 248°C; $C_{21}H_{26}N_2O_5$; IR ($CHCl_3$): 3440 (NH), 1723 (lactone), and 1680 cm^{-1} (amide)]. The mass spectral feature of hasubanan-type bases exhibits a very characteristic fragmentation pattern and therefore provides a rapid and convenient method for structure elucidation of hasubanan-type alkaloids, especially that of alkaloids obtained in small amounts.[4] The mass spectrum of the new base (1) showed a base ion peak at *m/z* 243 (exact mass, found: 243.1264, $C_{15}H_{17}NO_2$) which is represented by the structure (3). This diagnostic ion must be the same fragment ion as the hasubanan-type alkaloids oxygenated at the C-10 position.[3a,4]

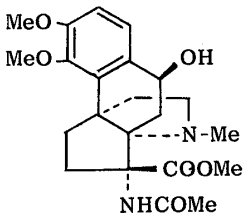
The presence of a lactone group in 1 was substantiated by hydrolysis of the N-acetyl derivative (2) with 2% potassium hydroxide in methanol followed by methylation, after acidification with 5% hydrochloric acid, with diazomethane to yield a hydroxy ester (4) [mp 228°C; $C_{22}H_{30}N_2O_6$; IR ($CHCl_3$): 3280 (NH and OH), 1730 (ester), and 1666 cm^{-1} (amide)] in 93% yield.



(1) R = H
(2) R = COMe
(5) R = $COC_6H_4Br(p)$



(3)



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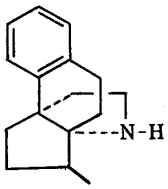

(6)

Chart 1

Too little stephadiamine (1) was obtained to permit further detailed chemical investigation and the structure was solved by X-ray diffraction analysis of stephadiamine (1) (Fig. 1) and N-p-bromobenzoylstephadiamine (5).[5] Crystal data of stephadiamine (1) were as follows: $C_{19}H_{24}N_2O_4$, M = 334.4, monoclinic, space group $p2_1$, a = 14.661(4), b = 9.060(3), c = 7.303(2)Å, β = 118.87(2)°, U = 849.5 Å^3, Z = 2, D_c = 1.346 g cm^{-3}. The structure of 1 was solved by direct method.[6] Hydrogen atoms were located in a difference Fourier synthesis at a late stage in the analysis. Block-diagonal least squares refinement of the positional and thermal (anisotropic C, O, N; isotropic H) parameters converged to R = 0.037 and R_w = 0.041 over 1342 reflections [$F_o \geq 3\sigma(F_o)$] recorded on a RIGAKU AFC-5 diffractometer (graphite monochromated Cu-Kα radiation, ω - 2θ scans, θ_{max} = 60°). The solid-state conformation with the atom numbering scheme is provided in Fig. 1. Although the relative stereochemistry of stephadiamine (1) was clarified by the above X-ray analysis, the absolute configuration of the new base was solved by X-ray analysis of N-p-bromobenzoylstephadiamine (5)[5] derived from the base (1).

As shown in Chart 1 and Fig. 1, the new C-norhasubanan base stephadiamine with a novel skeleton (6) is not regarded as a member of hasubanan in the strictest sence. This new alkaloid is the first example of a lactonic C-norhasubanan base isolated from natural sources. Furthermore, all natural hasubanan bases have one nitrogen atom (N_1-base), whereas the new one is an N_2-base.

Recently, naturally occurring amino acids and their derivatives have received much attention.[7] The present new alkaloid is regarded as a new member of an α-amino acid derivative.

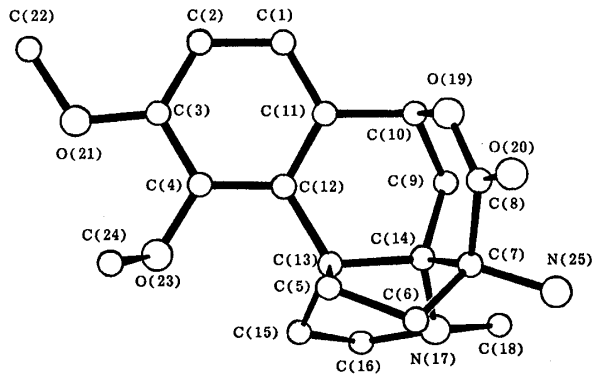

Fig. 1. Structure and Solid-State Conformation of Stephadiamine (1)
(Hydrogen atoms have been omitted for clarity.)

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5) N-p-Bromobenzoylstephadiamine (5) was crystallized from MeOH-Me_2CO (1:1) as colorless prisms (methanol solvate), mp 156°C. Crystal data of the N-p-bromobenzoylstephadiamine methanol solvate were as follows: M = 559.5 ($C_{26}H_{27}N_2O_5Br.CH_3OH$), monoclinic, space group $p2_1$, a = 11.975(2), b = 14.103(4), c = 7.562(2) Å, β = 94.17 (2)°, U = 1274.2 Å^3, Z = 2, D_c = 1.458 g cm^{-3}. The structure of 5 was solved by heavy-atom method. The two enantiomorph structures were examined by the least-squares refinement of the atomic parameters, using the Friedel pairs of 4097 reflections [$F_o \geq 3\sigma(F_o)$] measured on a RIGAKU AFC-5 diffractometer. The final R-value is 0.030 for the absolute structure (5) depicted in Fig. 2, while it is 0.044 for the opposite configuration. Thus, it appears that the correct absolute configuration of the new alkaloid stephadiamine (1) is that in Fig. 1. All crystallographic calculations were performed on a FACOM M-382 at the Data Processing Center of Kyoto University.

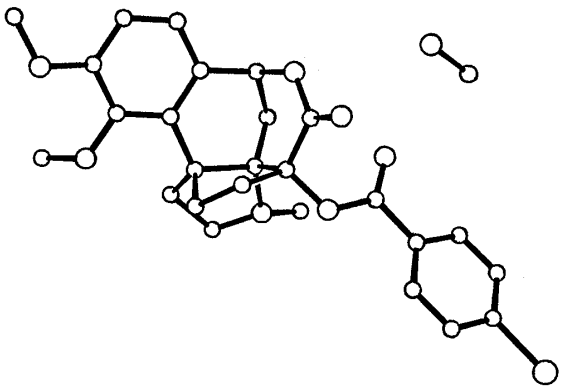

Fig. 2. Structure, Absolute Stereochemistry, and Solid-State Conformation of N-p-Bromobenzoylstephadiamine (5) Methanol Solvate (Hydrogen atoms have been omitted for clarity.)

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