THE ABSOLUTE CONFIGURATION OF STEPHANINE AND CREBANINE[1)]

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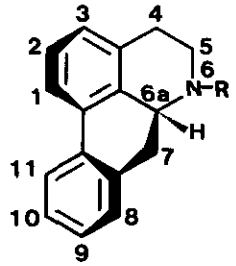
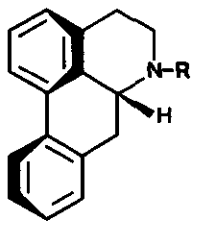
Abstract —— The crystal structure of natural stephanine (1) has been determined by X-ray diffraction. The C-6a position was confirmed to be of the R-configuration. O-Methyl derivatives of the products by cleavage reaction with sodium in liquid ammonia of stephanine (1) and crebanine (2) were both identified as 2,8-dimethoxyaporphine (3). This showed that crebanine (2) was of the R-configuration which has also been reported based on CD data.[4)] This work yielded the exact configuration at C-6a for all known aporphine-type alkaloids.

For many kinds of aporphine-type alkaloids, the C-6a position based on the bridged biphenyl is of either the R- or the S-configuration.[2)]



S-configuration



R-configuration

The absolute configuration at C-6a in almost all naturally occurring aporphine-type alkaloids has been determined by chemical correlation or X-ray crystallographic analysis.[2] The ORD curves and the CD curves of this type alkaloids have been discussed elsewhere.[2,3] As for the absolute configuration of stephanine (1) and crebanine (2) as 1,2,8-trisubstituted or 1,2,8,9-tetra-substituted aporphine-type alkaloids, only one report has appeared describing the R-configuration for the negative Cotton effect at 237 nm in the CD curve of crebanine (2).[4] Now we wish to report the determination of the configuration of stephanine (1) by X-ray diffraction.

The crystals of stephanine (1), mp 154∿156°C, were well-formed transparent plates, belong to the monoclinic space group $P2_1$ with the cell dimensions of $\underline{a}$ = 9.886(1), $\underline{b}$ = 7.419(1), $\underline{c}$ = 11.295(2) Å, β = 112.43(1)° and $\underline{U}$ = 765.8(2) Å^3. The density was determined to be 1.342(1) g·cm^{-3} by flotation methods in a carbon tetrachloride-benzene mixture; the calculated value was 1.342 g·cm^{-3} with two formula units per cell. Intensity data were measured with a Rigaku four-circle diffractometer with graphite monochromated Cu Kα radiation(λ = 1.5405 Å) using the ω-2θ scan technique at a rate of 4° min^{-1}. Four standard reflections measured at 100-reflection intervals to check for variation in the crystal remained essentially constant throughout the run. Out of 1452 possible independent reflection ($2\theta \leq 130°$), 1382 were considered to be non-zero, using a 3σ criterion based on counting statistics. The data were corrected for Lorentz and polarization effects but not for absorption because of the small size of the crystal used (ca. 0.40×0.40×0.50 mm).

The structure was solved by a combination of direct methods, Patterson vector

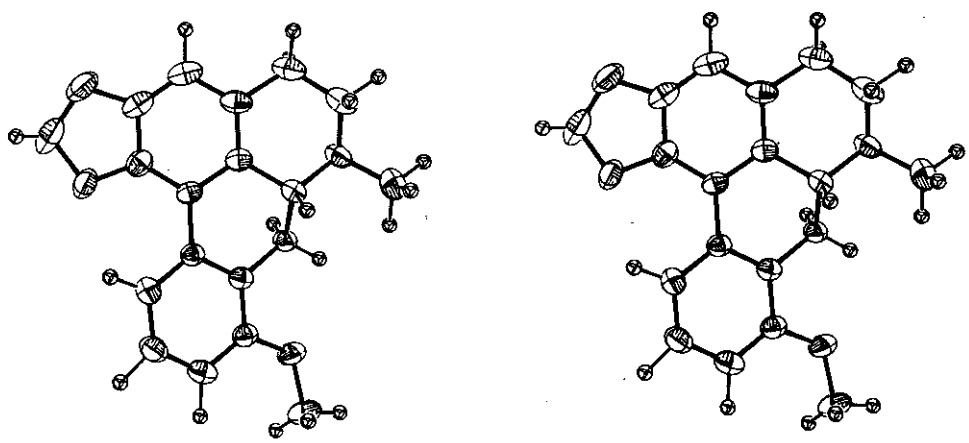


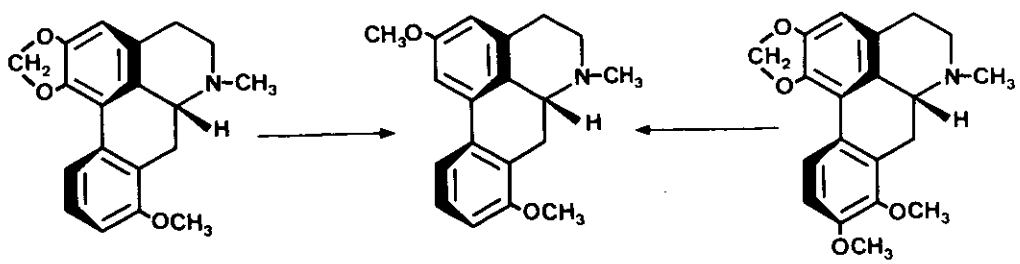
Figure. A stereoview of the molecular structure of stephanine (1)

search and Fourier techniques, and refined by least squares methods to a final discrepancy index of 0.059. All hydrogen atoms were located from electron-density difference maps and their parameters were refined using individual isotropic thermal parameters.

The molecular structure and conformation are displayed in the Figure. Our results led to the conclusion that stephanine (1) has the R-configuration.

Studies have been done on the reduction with sodium in liquid ammonia of several aporphine-type alkaloids, and the cleavage reaction of the methylenedioxy group and the elimination of methoxyl group at C-1 or C-11 in the molecule are known.[2] We examined whether the same result would be obtained even with reduction of stephanine (1) and crebanine (2) having a methylenedioxy group and a methoxyl group at C-8 in the molecule, respectively.

The cleavage reaction of stephanine (1) by sodium in liquid ammonia using anhyd. ether as a solvent affords one kind of reaction product from the phenolic base fraction, and O-methyl derivatives of this phenolic base from the diazomethane ethereal solution forms colorless needles, mp 125~126°C, $[\alpha]_D$-160.4°(in $CHCl_3$); the elemental analysis and mass spectrum (MS) established the formula as $C_{19}H_{21}NO_2$. The proton magnetic resonance data (^1H NMR) revealed two methoxyl groups (δ 3.85, 3.88), and this compound is presumed to be 1,8- or 2,8-dimethoxyaporphine, which is the O-methyl derivative of the phenolic base by cleavage of the methylenedioxy group. But the chemical shifts of the two methoxyl groups do not appear at higher fields like C-1 or C-11, being hindered by aporphine biphenylic structure, and the structure of this compound was determined to be 2,8-dimethoxyaporphine (3). Similarly, cleavage of crebanine (2) gave the same compound (3), excluding optical rotatory dispersion that identified it with the O-methyl derivative from stephanine (1).



(1) (3) (2)

Accordingly, crebanine was determined to have the R-configuration like stephanine (1). This showed that the determination of configuration based on the

CD curve[3] of crebanine (2) is valid. The ORD and CD curves of stephanine (1) and crebanine (2), given in the Table, agree with the relationship of the configuration to other substituted aporphine-type alkaloids.

Table ORD and CD data of stephanine (1) and crebanine (2)

Stephanine (1)	Crebanine (2)
$[\alpha]_D$:($CHCl_3$)	
-92.5°	-61.0°
ORD max:λ nm($[\phi]\times10^{-3}$)(MeOH)	
238(-87.2)	245(-146.5)
215(+78.6)	225(+173.0)
	205(-44.1)
CD max:λ nm($[\theta]\times10^{-3}$)(MeOH)	
270(+41.7)	280(+40.6)
233(-184.1)	236(-220.7)
215(+64.2)	217(+97.1)

These findings have exactly established the configuration at C-6a of almost all naturally occurring aporphines.

EXPERIMENTAL

All melting points are not corrected. ^1H NMR spectra were recorded on a 60 MHz spectrometer with TMS as an internal standard. MS were recorded on a direct inlet system at 70 eV using a Hitachi RMU-6E spectrometer. Specific rotation, ORD and CD were determined using JASCO DIP-4 digital and J-20 spectrometer, respectively.

Cleavage reaction of stephanine (1) by sodium in liquid ammonia To 150 ml of liquid NH_3 containing 100 mg of Na was added dropwise a solution of stephanine (1) (100 mg) in anhyd. Et_2O (15 ml) at -60±5°C for 1 hr, and stirring was continued for 1.5 hr more. The NH_3 was allowed to evaporate overnight. The residue was dissolved in 5% NaOH aqueous solution. This alkaline solution was washed with Et_2O, then changed to an ammoniacal alkaline solution by adding crystalline NH_4Cl and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried over anhyd. $MgSO_4$ and evaporated to dryness. The residual crude base, which showed approximately one spot on TLC, was used without purification in the following reaction.

O-Methylation of cleaved phenolic base [production of 2,8-dimethoxyaporphine (3)] The above phenolic base (70 mg) was dissolved in a small volume of MeOH, and excess diazomethane in Et_2O was added and the mixture was kept at room temp. for 1 day. The excess reagent and the solvent were removed by distillation, and the residual base was taken into aqueous 10% HCl, and washed with Et_2O. The acidic layer was made alkaline with aqueous 10% NaOH and extracted with Et_2O. The ethereal solution was washed with H_2O and dried over anhyd. $MgSO_4$, and then the solvent allowed to evaporate. The residue was purified by column chromatography on silica gel (from CH_2Cl_2 and eluted with the same solvent). Recrystallization from MeOH gave colorless needles, mp 125∿126°C, $[\alpha]_D$-160.4°(c = 0.374, $CHCl_3$). UV λ_{max}^{EtOH} nm(log ε): 223(4.61), 268(4.16), 275(4.16), 297(3.88), 316(sh, 3.49). ^{1}H NMR(in $CDCl_3$) δ: 2.59(3H, s, NCH_3), 3.84, 3.88(3H×2, s, OCH_3×2), 6.63(1H, d, J = 2.5Hz, C_3-H), 6.85(1H, d.d, J = 1.5, 8.0Hz, C_9-H), 7.12(1H, d, J = 2.5Hz, C_1-H), 7.33(1H, t, J = 8.0Hz, C_{10}-H), 7.34(1H, d.d, J = 1.5, 8.0Hz, C_{11}-H). MS m/z(%): 295(M^+, 67.9), 294(M^+-1, 100), 293(20.0), 280(M^+-CH_3, 4.2), 278(10.9), 264(8.3), 252(M^+-CH_2=NCH_3, 14.1). *Anal.* Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.00; H, 7.30; N, 4.59.

Cleavage reaction of crebanine (2) by sodium in liquid ammonia and O-methylation of the cleaved phenolic base The cleavage reaction of crebanine (2)(200 mg) and the methylation of the cleaved phenolic base by the same method described above for stephanine (1), afforded the pure non-phenolic base. Recrystallization from MeOH gave colorless needles, mp 125∿126°C, $[\alpha]_D$-158.8°(c = 0.372, $CHCl_3$), which were identified by direct comparison with the authentic sample (3) with respect to UV (EtOH), IR($CHCl_3$), ^{1}H NMR($CDCl_3$), MS, TLC, specific rotation and mixed melting point. *Anal.* Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 76.90; H, 7.30; N,4.49.

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