Absolute Configuration of Nupharamine*

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Nupharamine is a minor alkaloid isolated from the root of *Nuphar japonicum* DC. Although structure I was assigned to nupharamine by Arata and Ohashi,[1,2] the configurations of the three asymmetric carbons involved in this alkaloid have not yet been ascertained.

A number of natural products containing a piperidine ring have been isolated, and their chemical structures, together with their stereochemistry, have been elucidated. Leonard and Ryder[3] synthesized 2-butyl-3-methyl piperidine, which had been obtained from lupinane by cyanogenbromide degradation,[4] and found that the infrared spectra of its trans and of its cis isomer differ from one other. This finding led us to guess that the conformation of nupharamine could be determined through its spectral behavior. Recent studies of methyl quinolizidine have indicated that an axial and an equatorial group showed peaks at different positions in the NMR spectra.[5,6] This finding played a important role in the determination of the configuration of deoxynupharidine, the main alkaloid of this plant.[6] As will be described in the following scheme, we wish here to elucidate the conformation of nupharamine by the chemical correlation of it with deoxynupharidine and its diastereoisomer.

Anhydronupharamine was obtained from nupharamine by heating it with hydrochloric acid and then neutralizing it with sodium hydrogen carbonate according to Ohashi's procedure. As this product seemed to be a mixture of two isomers which have double bonds at different positions, it was separated into IIIA and IIIB isomers by chromatography on an alumina column. While the infrared spectrum of the IIIB isomer showed bands at $1360\ \mathrm{cm}^{-1}$ and $1380\ \mathrm{cm}^{-1}$, both assigned to the *gem*-dimethyl group, that of the other isomer, IIIA, showed no such bands, but, rather, two distinctive bands at $875\ \mathrm{cm}^{-1}$ and $880\ \mathrm{cm}^{-1}$. On the other hand, only the latter band was recognized in the infrared spectrum of anhydrotetrahydronupharamine (VIIIA), which had been derived from tetrahydronupharamine by a similar procedure and no longer contained a furan ring. Therefore, this band ($880\ \mathrm{cm}^{-1}$) should be assigned to a double bond of the $CH_2=C<$ type, while the former band ($875\ \mathrm{cm}^{-1}$) should be assigned to the furan ring.

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* Short Communication, This Bulletin, **36**, 623 (1963).

1) Y. Arata and T. Ohashi, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **77**, 792 (1957).

2) T. Ohashi, ibid., **79**, 729, 734 (1959).

3) N. J. Leonard and B. L. Ryder, *J. Org. Chem.*, **18**, 598 (1953).

4) K. Winterfeld and F. W. Holschneider, *Ber.*, **64**, 137 (1931).

5) T. M. Moynehan, K. Schofield, R. A. Y. Jones and A. R. Katritzky, *J. Chem. Soc.*, **1962**, 2637.

6) M. Kotake, I. Kawasaki, T. Okamoto, S. Matsutani, S. Kusumoto and T. Kaneko, This Bulletin, **35**, 1335 (1962).

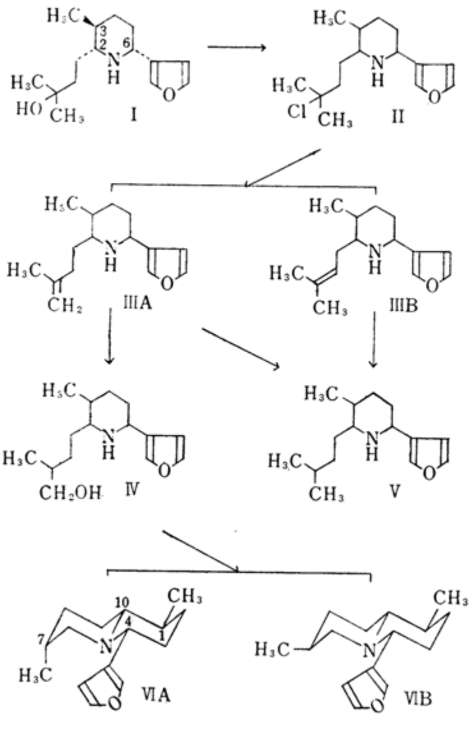

Fig. 1

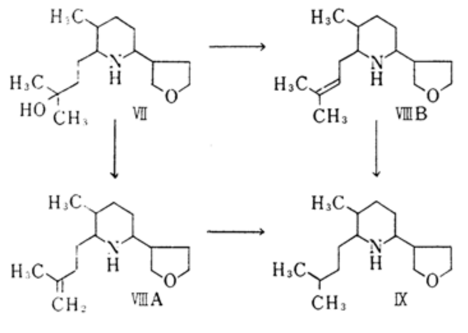

Fig. 2

When the isomer VIIIA or VIIIB was hydrogenated, the same compound, tetrahydrodeoxynupharamine (IX), was obtained in both cases. Similarly, the isomers IIIA and IIIB gave the same hydrogenation product, deoxynupharamine.

These facts indicate that IIIA contains a terminal double bond and that IIIB, an internal double bond in their molecules. With diborane in tetrahydrofuran, IIIA was converted to an organoborane compound, which was then oxidized to isonupharamine (IV) by alkaline hydrogen peroxide. IV was chlorinated with thionyl chloride and then cyclized with methanolic potassium hydroxide to afford a quinolizidine derivative. It was a mixture of diastereoisomers at C-7. The separation of both isomers was carried out by chromatography on an alumina column. From the observation of the infrared spectrum and of the levo rotatory power, one isomer, VIA, was found to be identical with natural deoxynupharidine. The other isomer, VIB, gave an infrared spectrum identical with that of 1(e), 7(e)-dimethyl-4(e)-[furyl-(3)]-quinolizidine⁷⁾ and a showed 1-equatorial methyl doublet at 0.86 p.p.m. and a 7-equatorial one at 0.68 p.p.m. in the NMR spectrum. The NMR spectra of isomer of deoxynupharidine are shown in the following table:**

Deoxynupharidine		Axial p.p.m.	Equatorial p.p.m.
1-epi	1-Me	1.19	
	7-Me	1.09	
Natural	1-Me		0.89
	7-Me	1.10	
7-epi	1-Me		0.86
	7-Me		0.68

The difference between the chemical shifts of the axial and equatorial methyl groups may be due to the long-range shielding effect of a magnetically-anisotropic carbon-carbon single bond or to the diamagnetic anisotropy which arises from furan ring currents. The C-methyl proton resonance signal for the equatorial methyl group (0.89∼0.68 p. p. m.) was found to be at a higher field than the signal for the axial methyl group (1.19∼1.09 p. p. m.). This observation indicates that the compound VIB must carry both methyl groups on equatorial conformation.

From the results obtained, it was concluded that the configurations of the asymmetric carbons, C_2, C_3, and C_6, of nupharamine are identical with those of the C_{10}, C_1 and C_4 of *l*-deoxynupharidine respectively and that, therefore, their absolute configurations may be deduced to be C_2(R), C_3(S) and C_6(R).

Experimental

Chloronupharamine (II).—a) A solution of 2 g. of nupharamine in 20 ml. of 10% hydrochloric acid was heated on a steam bath for 40 min. and then evaporated in vacuo. The residue was dissolved in small amounts of acetone and kept in a refrigerator. The deposited hydrochloride was recrystallized from acetone or ethanol-ether (1 : 5) ; 0.3 g. ; m. p. 194°C (decomp.).

b) To a solution of 1 g. of nupharamine in 15 ml. of anhydrous ether, 0.7 g. of ice-cooled thionyl

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7) F. Bohlmann, E. Winterfeld, P. Studt, H. Lautrent, G. Boroshewoki and K-M. Kleine, *Chem. Ber.*, **94**, 3151 (1961).

** These values were determined at 60 Mc. with a Varian A-60 spectrometer in a benzene solution (using TMS as the internal standard).

chloride were added and then kept at 50°C for 15 min. The solvent was evaporated. The residue was dissolved in 5 ml. of ethanol-ether (1 : 5) and kept in a refrigerator. The obtained hydrochloride (0.7 g.) melted at 196°C (decomp.).

Found : C, 58.59 ; H, 8.17. Calcd. for $C_{15}H_{25}O_2NCl_2$: C, 58.82 ; H, 8.27%.

Anhydronupharamine, IIIA and IIIB.—A solution of 1 g. of chloronupharamine-hydrochloride in water was carefully made basic with sodium carbonate and extracted with ether. The ether solution was dried and the ether was removed by distillation. The product was obtained as an oil (b. p. 113~120°C/3 mmHg, 0.75 g ; 91.4%) which was negative in a Beilstein test. The oil (1.55 g.) obtained was dissolved in petroleum ether and chromatographed on an alumina (55 g.) column.

Fraction	Elute	Volume ml.	Weight g.
1	Petr. ether	280	0
2	Petr. ether : ether (5%)	155	0.33
3	Petr. ether : ether (5%)	150	0.28
4	Petr. ether : ether (5%)	250	0.28
5	Petr. ether : ether (1 : 1)	200	0.29
6	Ether	250	0.31
7	Ethanol	100	0.43

The infrared spectrum of fraction 2 showed bands at 1505 and 875 cm^{-1} (the furan nucleus) and at 1380 and 1360 cm^{-1} (*gem*-dimethyl), and that of fraction 5 at 1505 and 875 cm^{-1} (the furan nucleus) 880 cm^{-1} ($CH_2=C<$) and 1380 cm^{-1}.

Deoxynupharamine (V).—A solution of 0.95 g. of anhydronupharamine (IIIA) in 20 ml. of alcohol was hydrogenated over 10% of palladium-on-charcoal at room temperature and in an ordinary atmosphere. After 98 ml. of hydrogen (one equivalent 90 ml.) had been absorbed over a 14 hr. period, the reduction product was taken up in the usual manner and crystallized as hydrochloride ; m. p. 232~233°C.

Found : C, 66.14 ; H, 9.60. Calcd. for $C_{15}H_{25}ON$-HCl : C, 66.27 ; H, 9.64%.

The hydrogenation of IIIB gave hydrochloride (m. p. 232~233°C) ; these crystals were shown to be identical with those obtained from IIIA (mixed m. p. 232~233°C). The infrared spectra of both hydrochloride were also identical.

Anhydrotetrahydronupharamine, VIIIA and VIIIB.—Tetrahydronupharamine VII (1.7 g. ; its perchloride, m. p. 212°C (decomp.)) was dissolved in 40 ml. of ether ; then a solution of 0.8 g. of thionyl chloride in 20 ml. of ether was slowly added while being ice-cooled. The mixture was warmed at 40~50°C for 3 hr. and then evaporated. The residue was made basic with an aqueous sodium bicarbonate solution and extracted with ether. The ether solution was dried, and the solvent was removed by evaporation. The residual oil (1.3 g.) was chromatographed on an alumina column (80 g.).

The infrared spectrum of fraction 5 showed a band at 880 cm^{-1}, indicating the presence of a $CH_2=C<$ group.

Fraction	Elute	Volume ml.	Weight g.
1	Petr. ether : ether (5%)	200	0
2	Petr. ether : ether (10%)	200	0.14
3	Petr. ether : ether (20%)	250	0.48
4	Ether	100	0.26
5	Ether	400	0.30
6	Ethanol	200	0.04

Tetrahydrodeoxynupharamine (IX).—The anhydrotetrahydronupharamines, VIIIA and VIIIB, gave identical tetrahydrodeoxynupharamine (IX) when reduced over a platinum catalyst. Its hydrochloride was recrystallized from acetone to give colorless needles (m. p. 195°C).

Isonupharamine (IV).—To a mixture of 1.66 g. of anhydronupharamine (IIIA) and 0.61 g. of sodium borohydride in 80 ml. of tetrahydrofuran, a solution of 3.07 g. of boron trifluoride etherate in 10 ml. of tetrahydrofuran was added slowly under an nitrogen atmosphere. After being kept at room temperature for 4 hr., the reaction mixture was decomposed with 2 ml. of water, and then 2 ml. of 6 N sodium hydroxide and 2 ml. of 30% hydrogen peroxide were stirred in. After the mixture had been kept at 45~50°C for 30 min., the solvent layer was separated from a precipitate, which was extracted several times with boiling ether. The solvent layer and the combined ether extracts were mixed up, and the solvent was evaporated. The residue was dissolved in ether, washed with water and dried. On distillation, 1.0 g. of IV (b. p. 145~152°C (bath temp.)/0.001 mmHg.) was obtained. The perchlorate was recrystallized from ethyl acetate to give colorless needles (m. p. 164~166°C).

Found : C, 51.35 ; H, 7.47 ; Cl, 10.07. Calcd. for $C_{15}H_{23}ON$-$HClO_4$: C, 51.20 ; H, 7.44 ; Cl, 10.07%.

Deoxynupharidine, VIA and VIB.—To a solution of 1 g. of isonupharamine (IV) in 10 ml. of ether, 0.5 g. of thionyl chloride in 5 ml. of ether was added slowly. After being kept at 40~50°C for 30 min., the reaction mixture was mixed with 10 ml. of water and 40 ml. of methanol ; it was then made basic potassium hydroxide. The mixture was refluxed for 2 hr. The precipitated inorganic salt was filtered off. The filtrate was made acidic with hydrochloric acid and evaporated in vacuo. Then the residue was neutralized and extracted with ether. The ether extract was dried and evaporated to give an oil (0.6 g.), which was dissolved in petroleum ether ; an insoluble substance (0.07 g.) was then filtered off. The chromatography of this petroleum ether solution on an alumina column (80 g.) resulted in the separation of the following fractions :

Fraction	Elute	Volume ml.	Weight g.
1	Petr. ether	100	0.02
2	Petr. ether	100	0.02
3	Petr. ether	100	0.01
4	Petr. ether : ether	100	0.39
5	Ether	100	0.07

Fraction 4 was rechromatographed on an alumina column (65 g.).

Fraction	Elute	Volume ml.	Weight g.
4-1	Petr. ether : ether (5%)	120	0
4-2	Petr. ether : ether (10%)	65	0.05
4-3	Petr. ether : ether (15%)	105	0.12
4-4	Petr. ether : ether (20%)	105	0.07
4-5	Petr. ether : ether (30%)	65	0.05
4-6	Ether	130	0.10

The infrared spectrum of fraction 4-2 was identical with that of natural deoxynupharidine. The optical rotation of this fraction showed $[\alpha]_D$ −76.8° (*c* 5.6 in ethanol). The corresponding fraction of another run showed $[\alpha]_D$ −97.11° (*c* 1.7 in ethanol), and the hydrochloride melted at 256∼258°C (cf. natural deoxynupharidine: $[\alpha]_D$ −109.86°).

Found: C, 66.98; H, 8.91; N, 5.00. Calcd. for $C_{15}H_{23}ON\text{-}HCl$: C, 66.77; H, 8.97; N, 5.19%.

The infrared spectrum of fraction 4-3 was identical with that of *dl*-7(epi)-deoxynupharidine: $[\alpha]_D$ −110° (*c* 1.06 in ethanol); the hydrochloride, m. p. 246∼248°C.

Found: C, 66.50; H, 8.86; N, 5.22.

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