*Resolution of dl-Deoxynupharidine; The Total Synthesis of Nupharidine**

By Munio KOTAKE, Ichiro KAWASAKI, Shigeru MATSUTANI, Shiro KUSUMOTO and Takeo KANEKO

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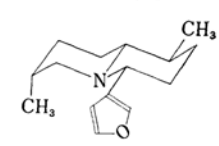
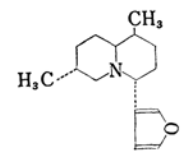
Recently we have suggested that the absolute configuration of deoxynupharidine should be represented as formula I[1]. In the course of the synthetic route of deoxynupharidine, it seems that the 7-axial methyl group has mainly been produced by catalytic reduction of the pyridine nucleus of ethyl 4-[5-methylpyridyl-(2)]-valerate and the 4-equatorial furyl group has been produced by catalytic reduction of 1, 7-dimethyl-4-[furyl-(3)]-dehydroquinolizidine-3. From the results that 3-methylquinolizidine obtained from 2, 5-lutidine through catalytic reduction of pyridine nucleus afforded mainly 3(a)-methyl form[2] and 4-methylquinolizidine obtained by Murakoshi's method[3] afforded only one diastereomer of 4-methylquinolizidine the synthetic mixture of deoxynupharidine[4] may be contained isomer Ia and Ib predominantly. A chromatography of the diastereoisomeric mixtures of synthetic sample on alumina[5] resulted in the separation of the following fractions. The first fraction eluted by petroleum ether gave an isomer, which was crystallized as hydrochloride. This isomer could not be lead to *N*-oxide and to iodomethylate by the same condition as used with success in case of a natural product. From the suggestion, that the 1(a)-methyl group of this isomer will hinder sterically the above reactions and from the evidence of NMR spectra, this isomer should be presented as 1-epimer (Ib). The fraction eluted by petroleum ether-ether, which has the infrared and NMR spectrum similar to that of natural deoxynupharidine, was oxidized with hydrogen peroxide to *N*-oxide and recrystallized as its hydrochloride (infrared spectrum in Nujol was found to be identical with that of nupharidine hydrochloride), and then reduced smoothly with palladium charcoal to give *dl*-deoxynupharidine. The treatment of *dl*-form with *l*-tartaric acid afforded *l*-deoxynupharidine *l*-tartrate as less soluble salt and the regenerated *l*-base from the tartrate oxidized to *d*-nupharidine, which was identical with a natural product in all aspects. The *d*-base also has been isolated with the aid of *d*-tartaric acid.

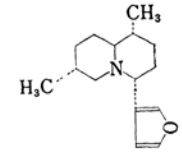
Chart I



I



Ia



Ib

* Short communication, This Bulletin, 35, 698 (1962).

1) M. Kotake et al., ibid., 35, 697 (1962).

2) T. Kaneko et al., *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), 83, 949 (1962).

3) I. Murakoshi, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*) 78, 594 (1958).

4) M. Kotake, I. Kawasaki, T. Okamoto, S. Kusumoto and T. Kaneko, *Ann.*, 636, 158 (1960).

5) In the course of this resolution, we found the contribution of F. Bohlmann, E. Winterfeld, P. Studt, H. Laurent, G. Boroschewoki and K-M. Kleine, *Chem. Ber.*, 94. 3151 (1961).

6) Y. Arata and T. Asai, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), 79, 1442 (1959).

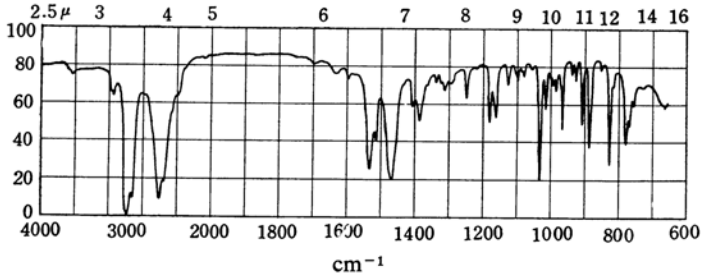


Fig. 1. *dl*-Nupharidine hydrochloride (Nujol).

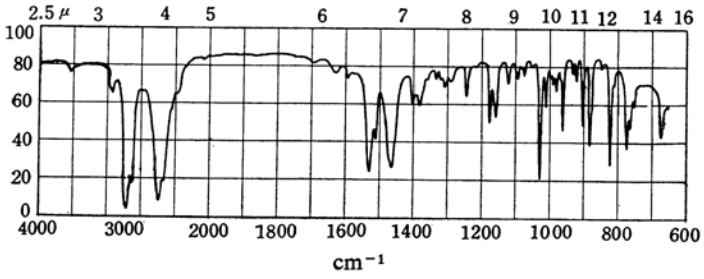


Fig. 2. Nupharidine hydrochloride (natural) (Nujol).

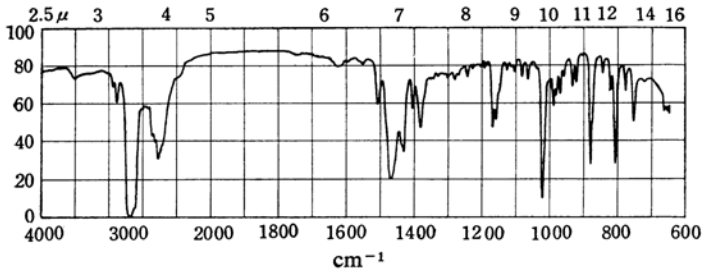


Fig. 3. 1(epi)-Deoxynupharidine hydrochloride (Nujol).

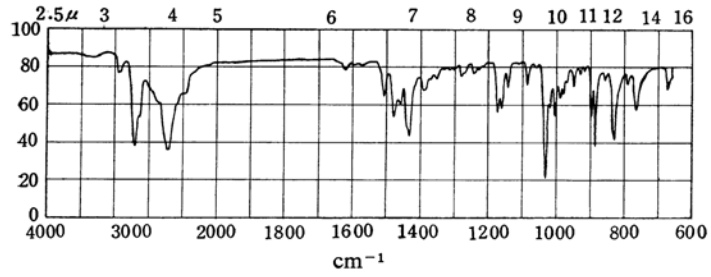


Fig. 4. *dl*-Deoxynupharidine hydrochloride (Nujol).

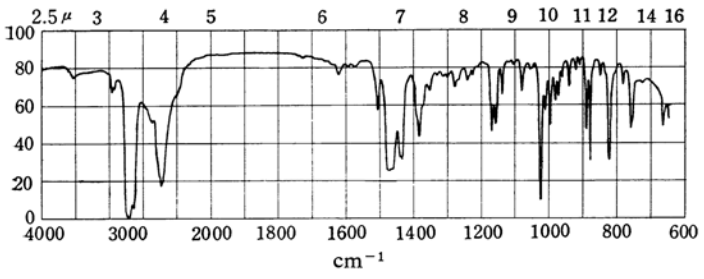


Fig. 5. Deoxynupharidine hydrochloride (natural) (Nujol).

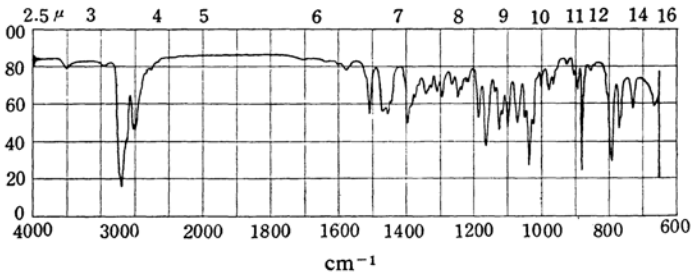


Fig. 6. *l*-Deoxynupharidine (synthetic) (liquid).

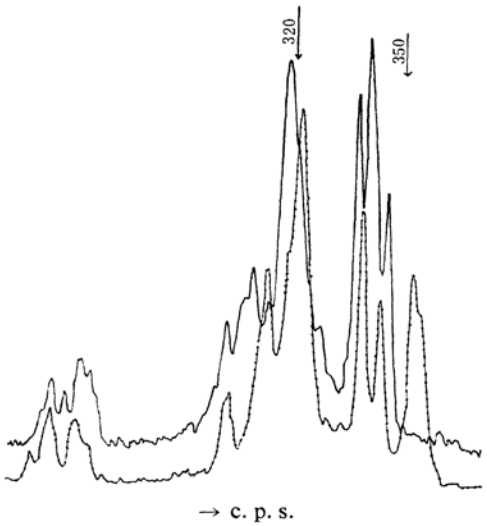


Fig. 7. The NMR spectra were measured in benzene solution at 56.4 Mc. using a Varian spectrometer and c. p. s. values calculated from benzene.
—— 1(epi)-Deoxynupharidine
------ *dl*-Deoxynupharidine

Experimental

To purify the reaction product, diethyl 2-[5-methylpyridyl-(2)]-allylmalonate was reduced partially with Pd-C in ethanol to diethyl 2-[5-methyl-(2)]-propylmalonate (picrate from ether, m. p. 84～85.5C, Found: C, 50.54; H, 5.01; N, 10.76. Calcd. for $C_{22}H_{26}O_{11}N_4$: C, 50.57; H, 5.02; N, 10.72%)[6] and then hydrolyzed to 4-[5-methylpyridyl-(2)]-valeric acid (m. p. 77～77.5°C, Found: C, 68.45; H, 7.88; N, 7.06. Calcd. for $C_{11}H_{15}O_2N$: C, 68.35; H, 7.82; N, 7.25%, the hydrochloride, m. p. 145～146°C, Found: C, 57.42; H, 7.06; N, 5.88. Calcd. for $C_{11}H_{15}O_2N$-HCl: C, 57.51; H, 7.02; N, 6.09%). Ethyl 4-[5-methyl-pyridyl-(2)]-valerate (b. p. 102～104°C/2 mmHg) was reduced with platinum oxide in acetic acid and then acylated with furoyl chloride immediately to give furoyl derivatives.

Natural Deoxynupharidine.—$[\alpha]_D$ −109.86° (*c* 1.16, in ethanol), the hydrochloride, m. p. 261～263°C, $[\alpha]_D$ −21.4° (*c* 0.98, in 1 N HCl).

Natural Nupharidine.—$[\alpha]_D$ +17.2° (*c* 1.10, in ethanol).

***l*-Deoxynupharidine-*l*-tartrate.** —*l*-Deoxynupharidine (0.76 g.) and *l*-tartaric acid (0.5 g.) were mixed in acetone (8 ml.) and deposited the tartrate (1.3 g.), which recrystallized from acetone-ethanol and ethyl methyl ketone, m. p. 151～152°C, $[\alpha]_D$ −14.65° (*c* 1.11, in ethanol).

Found: C, 59.26; H, 7.73; N, 3.59. Calcd. for $C_{19}H_{29}O_7N$: C, 59.51; H, 7.62; N, 3.65%.

***d*-Nupharidine-*d*-camphorsulfonate.** —*d*-Nupharidine (0.3 g.) and *d*-camphorsulfonic acid (0.3 g.) were mixed in chloroform (10 ml.) and the deposited salt (0.5 g.) recrystallized from ether-ethanol in needles, m. p. 182～183°C (decomp.), $[\alpha]_D$ +39.0° (*c* 0.9, in ethanol).

Found: C, 61.86; H, 8.25; N, 2.85. Calcd. for $C_{25}H_{40}O_6NS$: C, 62.21; H, 8.35; N, 2.90%.

Chromatography of Synthetic Deoxynupharidine. —The synthetic deoxynupharidine (42.15 g., b. p. 93～98°C/2 mmHg was chromatographed on alumina and resulted in the separation of following fractions (the fraction was checked by the infrared NMR spectroscopy);

Chromatography No. 1—1

Synthetic sample (13.3 g.) was dissolved in petroleum ether (50 ml.) and chromatographed on alumina (80 g.).

Fraction	Eluent	Volume ml.	Weight g.
1—1	Pet. ether	200	3.4
2—1	Pet. ether	200	1.7
3—1	Pet. ether	200	0.25
4—1	Pet. ether : Ether	100	0.8
5—1	Ether	100	0.65
6—1	Ether	310	0.2
7—1	Ethanol	120	4.4

Chromatography No. 1—2

Synthetic sample (15.5 g.) was dissolved in peteroleum ether (100 ml.) and chromatographed on alumina (100 g.).

Fraction	Eluent	Volume ml.	Weight g.
1—2	Pet. ether	200	2.3
2—2	Pet. ether	100	4.5
3—2	Pet. ether : Ether	100	0.8
3—2	Ether	100	1.9
5—2	Ether	200	0.3
6—2	Ether	400	0.2
7—2	Ethanol	150	4.5

Chromatography No. 1—3

Synthetic sample (13.35 g.) was dissolved in petroleum ether (100 ml.) and chromatographed on alumina (100 g.).

Fraction	Eluent	Volume ml.	Weight g.
1—3	Pet. ether	200	3.4
2—3	Pet. ether	100	4.5
4—3	Pet. ether	100	0.3
4—3	Pet. ether : Ether	100	0.5
5—3	Ether	100	2.9
6—3	Ether	200	0.3
7—3	Ethanol	150	1.9

Chromatography No. 2

Fractions except 7 of chromatography No. 1—1, 2, 3 were dissolved in peteroleum ether (50 ml.) and chromatographed on alumina (125 g.).

Fraction	Eluent	Volume ml.	Weight g.
8	Pet. ether	200	21.7
9	Pet. ether	100	2.1
10	Pet. ether : Ether	100	0.6
11	Pet. ether : Ether	100	2.8
12	Ether	225	1.5
13	Ether	200	0.5
14	Ethanol	100	0.3

Chromatography No. 3

The fractions 8 and 9 (23.8 g.) were dissolved in petroleum ether (100 ml.) and chromatographed on alumina (130 g.).

Fraction	Eluent	Volume ml.	Weight g.
15	Pet. ether	200	14.4
16	Pet. ether	100	5.2
17	Pet. ether : Ether (7 : 3)	100	0.8
18	Pet. ether : Ether (7 : 3)	100	3.7
19	Ether	100	0.3
20	Ether	300	0.05
21	Ether	120	Trace

Chromatography No. 4

The fractions 15 and 16 (19.6 g.) were dissolved in petroleum ether (80 ml.) and chromatographed on alumina (115 g.).

Fraction	Eluent	Volume ml.	Weight g.
22	Pet. ether	100	11.1
23	Pet. ether	100	4.7
24	Pet. ether : Ether (7 : 3)	100	0.7
25	Pet. ether : Ether (7 : 3)	100	2.5
26	Ether	100	0.05
27	Ether	300	0.05
28	Ethanol	125	Trace

Chromatography No. 5

The fractions 22 and 23 (15.8 g.) were dissolved in petroleum ether (60 ml.) and chromatograph on alumina (125 g.).

Fraction	Eluent	Volume ml.	Weight g.
29	Pet. ether	200	10.6
30	Pet. ether	100	2.2
31	Pet. ether : Ether (7 : 3)	100	2.2
32	Pet. ether : Ether (7 : 3)	100	1.6
33	Ether	100	Trace
34	Ether	300	Trace
35	Ethanol	120	Trace

Infrared spectra of the fractions 11, 18, 25 and 32 were similar to that of natural deoxynupharidine.

***dl*-Nupharidine Hydrochloride.**—A part (2.2 g.) of the above fractions 11, 18, 25 and 32 was dissolved in acetone and added 15% of hydrogen peroxide (2.3 g.) The reaction mixture was heated on a steam bath at 50°C for 3 hr. and then evaporated in vacuo. The residue was dissolved in ethanol (4.5 g.) and added concentrated hydrochloric acid (0.7 ml.) and ether (38 ml.) and then kept in a refrigerator to give a precipitate (m. p. 193 ~196°C), which was recrystallized from ethanol-ether in needles, m. p. 222~223°C (decomp.).

Found : C, 62.85 ; H, 8.29 ; N, 4.98. Calcd. for $C_{15}H_{23}O_2N \cdot HCl$: C, 63.03 ; H, 8.46 ; N, 4.90%.

***dl*-Deoxynupharidine Hydrochloride.**—*dl*-Nupharidine hydrochloride (1 g.) was dissolved in ethanol (30 ml.), added 10% palladium charcoal (0.4 g.) and hydrogenated at ordinary pressure and temperature. Eighty-seven milliliters of hydrogen (theoretical amount, 79 ml.) were absorbed in 2 hr. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue recrystallized from ether and ethanol gave *dl*-deoxynupharidine hydrochloride (0.85 g.), m. p. 218~220°C, yield 93%. Analytical sample obtained by further recrystallization melted at 224~225°C.

Found : C, 66.69 ; H, 8.84. Calcd. for $C_{15}H_{23}ON \cdot HCl$: C, 66.77 ; H, 8.97%.

Resolution of *dl*-Deoxynupharidine.—The *dl*-base (1.5 g.) which was obtained by several runs as above mentioned and *l*-tartaric acid (0.6 g.) were dissolved in acetone (9 ml.) and ether (ca. 0.5 ml.) and left overnight in the refrigerator. The precipitated crude tartrate (0.5 g., m. p. 141~144°C) was recrystallized several times from ethyl methyl ketone. The final product (0.2 g.) melted at 151.5 ~152°C (mixed melting point with authentic *l*-deoxynupharidine *l*-tartrate, 152~154°C) and showed $[\alpha]_D$ −11.54° (*c* 1.00, in ethanol).

Found : C, 59.30 ; H, 7.64 ; N, 3.58%.

The base recovered from the above tartrate showed $[\alpha]_D$ −68.82° (*c* 1.01, in ethanol), the hydrochloride, $[\alpha]_D$ −17.03° (*c* 1.02, in 1 N HCl), m. p. 258~261°C.

Found : C, 66.82 ; H, 8.96 ; N, 5.03%.

***d*-Nupharidine.**—The synthetic *l*-deoxynupharidine (64 mg.) was dissolved in acetone (2 ml.) and added 15% hydrogen peroxide (0.6 ml.). The mixture was kept at 50°C for 2 hr. and the solvent was evaporated under reduced pressure. The residue was dissolved in chloroform and washed with water. The residue (68 mg.) obtained from the

chloroform solution by evaporation was recrystallized from acetone in plates (8 mg.), 222°C (decomp.), $[\alpha]_D$ +13.00° (*c* 0.38, in ethanol). Found: C, 71.81; H, 9.57%. The hydrochloride, m. p. 245~246°C (decomp.).

Found: C, 63.25; H, 8.48%.

***d*-Deoxynupharidine-*d*-tartrate.** — The mother-liquor from the first crop of *l*-deoxynupharidine *l*-tartrate was evaporated, the residue dissolved in water, basified, and extrated with ether, giving the crude *d*-base (1.0 g.). This was combined with *d*-tartaric acid (0.64 g.) in ethyl methyl ketone (10 ml.) and the *d*-tartrate (0.9 g. m. p. 138~140°C) repeatedly crystallized from ethyl methyl ketone, the last fraction (0.35 g.) having m. p. 152~154°C, $[\alpha]_D$ +13.5° (*c* 1.66, in ethanol).

Found: C, 59.48; H, 7.62; N, 3.76%.

***d*-Deoxynupharidine.** — *d*-Deoxynupharidine recovered from the above showed $[\alpha]_D$ +108.58° (*c* 0.99, in ethanol), the hydrochloride, m. p. 259~261°C. Found: C, 66.50; H, 8.85; N, 5.18%.

1-(epi)-Deoxynupharidine.—Fraction 29 (10.6 g.) was dissoved in ethanol (50 ml.) and concentrated hydrochloric acid (5 ml.) and then added ether (50 ml.). The precipitated hydrochloride (7.7 g. m. p. 220~222°C) was recrystallized from acetone-methanol in prisms, m. p. 224~225°C.

Found: C, 66.65; H, 8.87; N, 5.36%.

The free base (400 mg.) was dissolved in acetone (6 ml.) and added 15% hydrogen peroxide (1 ml.). After the mixture was kept at 50°C for 2 hr., the solvent was removed in vacuo and the residue dissolved in chloroform. The chloroform solution was washed with water and then evaporated. The residual oil (400 mg.) was identical with starting material in infrared spectra.

The free base (350 mg.) was mixed with methyl iodide (5 ml.) and then left overnight. To the reaction mixture ether was added and the ethereal solution washed with bisulfite solution. By removing of solvent, starting material was recovered (350 mg.).

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Deartment of Chemistry
Faculty of Science
Osaka University
Nakanoshima, Osaka