

### Constituents of *Rhizoma Nupharis*. XXV.<sup>1)</sup> Formation of Dehydro-deoxynupharidine from Nupharidine<sup>2)</sup>

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(Received March 18, 1968)

The sesquiterpene alkaloids isolated from the roots of *Nuphar japonicum* DC. can conveniently be divided into piperidine- and quinolizidine-group, to the latter of which belong nupharidine (I), deoxynupharidine (II), and dehydro-deoxynupharidine (III). I was reduced to II,<sup>4)</sup> which was oxidized to I,<sup>4)</sup> sodium borohydride reduction of III gave II,<sup>5)</sup> and thus the steric structural correlation among these alkaloids had been able to be achieved. In addition, nuphamine (IV), one of the piperidine-type alkaloids, when hydrogenated catalytically, gave II.<sup>6)</sup> On the other hand, it had been already clarified that nicotine<sup>7)</sup> is metabolized

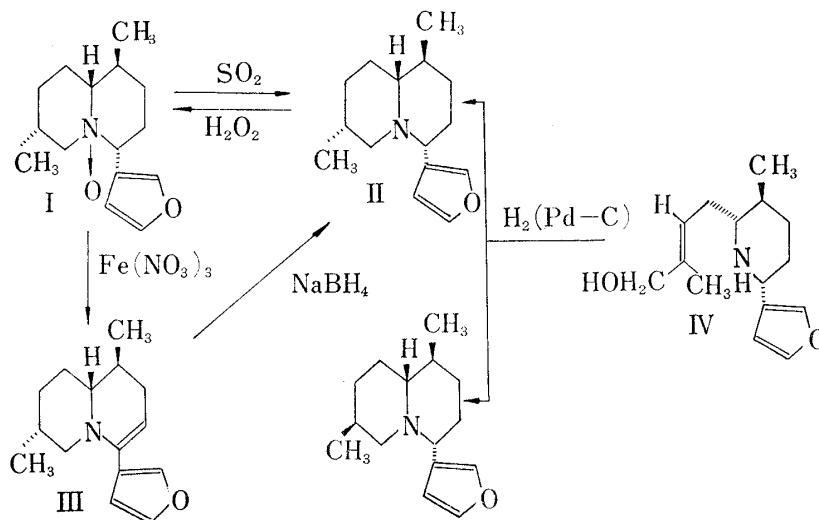


Chart 1

in plants and animals to give nicotine-1'-oxide ("oxynicotine"), 3-methylaminopropyl-3'-pyridyl ketone ("pseudooxynicotine") (which is present in aqueous solution), nornicotine and others.

From these facts, it would be assumed that II is biogenetically derived from IV and further oxidized into I, and that III is consequently derived from either I or II. This paper describes synthetic methods which allow the formation of dehydro-quinolizidine derivatives from 4-phenylquinolizidine (VII) and its N-oxide, and its application in the nuphar alkaloids field.

- 1) Part XXIV: Y. Arata, T. Ohashi, M. Yonemitsu, and S. Yasuda, *Yakugaku Zasshi*, **87**, 1094 (1967).
- 2) Presented in part at the Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, November 1967.
- 3) Location: *Takara-machi 13, Kanazawa*.
- 4) Y. Arata and T. Ugai, *Yakugaku Zasshi*, **66**, 138 (1946).
- 5) Y. Arata, *Chem. Pharm. Bull.* (Tokyo), **13**, 907 (1965).
- 6) Y. Arata and T. Ohashi, *Chem. Pharm. Bull.* (Tokyo), **13**, 1247 (1965).
- 7) J.C. Craig, N.Y. Mary, N.L. Goldman, and L. Wolf, *J. Am. Chem. Soc.*, **86**, 3866 (1964).

Sodium borohydride reduction of  $\Delta^{3,4}$ dehydro-quinolizidine compound (VI) (perchlorate: mp 182.5—183°, IR  $\text{cm}^{-1}$  1635 (iminium)) obtained by the action of phenyl magnesium bromide on 4-oxoquinolizidine (V), followed by chromatography on alumina, led to the formation of *trans*- (VII) (hydrobromide: mp 286—287°) and a trace of *cis*-quinolizidine compound (VIII) (hydrobromide: mp 242.5—243.5°).

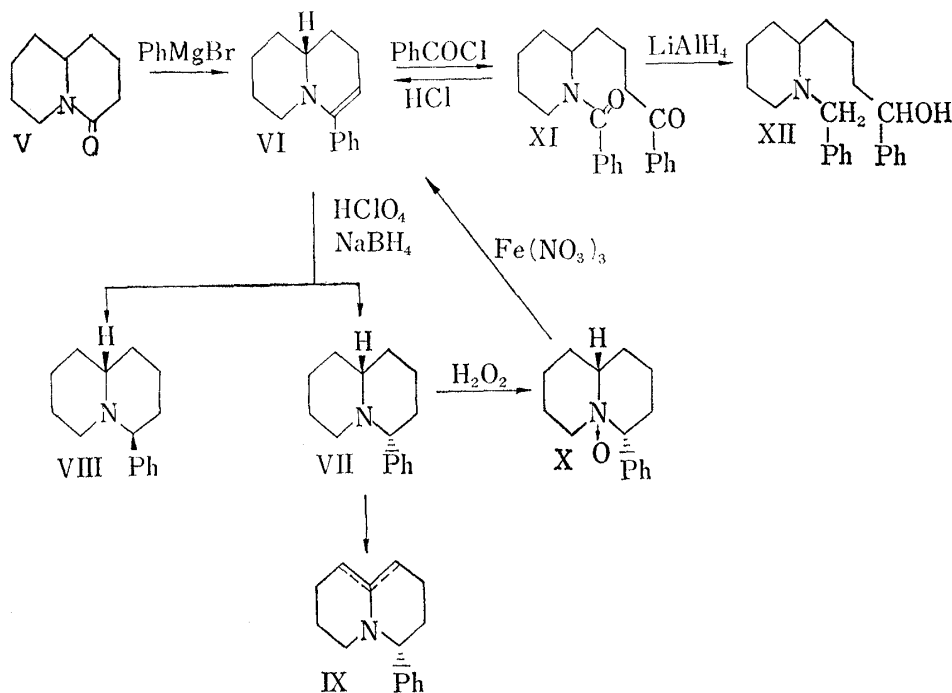


Chart 2

According to the procedure of Bohlmann, *et al.*, mercuric acetate oxidation of VII<sup>8)</sup> was carried out affording  $\Delta^{9,10}$  dehydro- and/or  $\Delta^{1,10}$  dehydroquinolizidine derivative (IX) (perchlorate: mp 117—118°, IR  $\text{cm}^{-1}$  1655 (iminium)), but not VI. The action of N-bromosuccinimide on VII<sup>9)</sup> also yielded IX.

Now, oxidation of VII with hydrogen peroxide afforded an N-oxide (X) (picrate: mp 179—180°), which, on warming in a tartaric acid solution containing ferric nitrate, gave a dehydro-quinolizidine compound,<sup>7)</sup>  $\text{C}_{15}\text{H}_{19}\text{N}$ , which formed perchlorate (mp 182.5—183°, IR  $\text{cm}^{-1}$  1635 (iminium)). The perchlorate was shown to be identical with that of VI by the melting point determination and comparison of their infrared spectra.

The action of benzoyl chloride on VI<sup>10)</sup> gave an N-benzoyl aminoketone (XI) (mp 70.5—71.5°, IR  $\text{cm}^{-1}$  1690 (carbonyl), 1635 (amide)), which, on reduction with lithium aluminum hydride, afforded an N-benzyl aminoalcohol (XII) (mp 84—85°, IR  $\text{cm}^{-1}$  3230 (hydroxyl)). XI was hydrolyzed in dilute hydrochloric acid to give VI (perchlorate: mp 182.5—183°, IR  $\text{cm}^{-1}$  1635 (iminium)).

Hereupon, when treated with the same solution with which X had been treated, I gave an unstable base,  $\text{C}_{15}\text{H}_{21}\text{ON}$ , which formed perchlorate, mp 159—159.5°,  $[\alpha]_D^{25} +134^\circ$  (in chloroform). The infrared spectrum of the perchlorate in chloroform showed bands at 877, 1510, and 3128  $\text{cm}^{-1}$  attributable to the furan ring, and at 1640  $\text{cm}^{-1}$  supposedly owing to an iminium salt conjugated with the furan. The degree of specific rotation and infrared spectrum of the perchlorate were completely coincident with those of perchlorate of dehydro-deoxy-

8) F. Bohlmann and P. Strehlke, *Tetrahedron Letters*, **1965**, 167.

9) S. Dunstan and H.B. Henbest, *J. Chem. Soc.*, **1957**, 4905. L. Horner, E. Winkelmann, K.H. Knapp, and W. Ludwig, *Chem. Ber.*, **92**, 288 (1959).

10) C. Schöpf and W. Merkel, *Ann. Chem.*, **701**, 180 (1967).

nupharidine (III) obtained from the roots of *Nuphar japonicum* DC. and both perchlorates did not show any melting point depression on the admixture.

### Experimental<sup>11)</sup>

**4-Phenyl-octahydroquinolizines (VII and VIII)**—To a solution of perchlorate of VI (1 g) in EtOH (100 ml) was gradually added sodium borohydride (0.5 g) under cooling, and the mixture was kept standing overnight. After the evaporation of the solvent, to the residue was added water, followed by the extraction with ether. From the ether solution which was washed with water and desiccated, colorless liquid (VII and VIII), bp 120—121° (4 mmHg) (bath temperature) was obtained. Yield: 0.5 g. The distillate (0.5 g) was developed over the thin-layer chromatography (Al<sub>2</sub>O<sub>3</sub> containing 15% CaSO<sub>4</sub>, solvent: petroleum ether-ether=95:5) to separate into VII (0.4 g) (*R<sub>f</sub>*=0.9) and a trace of VIII (*R<sub>f</sub>*=0.4).

**4-Phenyl-*trans*-octahydroquinolizine<sup>12)</sup> (VII)**: Colorless liquid, bp 120—125° (4 mmHg) (bath temperature). IR cm<sup>-1</sup> (liq): 2770, 2740 (*trans*-quinolizidine). Hydrobromide: Recrystallized from EtOH to give colorless needles, mp 286.5—287.5°. *Anal.* Calcd. for C<sub>15</sub>H<sub>22</sub>NBr: C, 60.81; H, 7.15; N, 4.72. Found: C, 61.08; H, 7.60; N, 4.53.

**4-Phenyl-*cis*-octahydroquinolizine<sup>12)</sup> (VIII)**: Colorless liquid, bp 120—125° (4 mmHg) (bath temperature). No IR absorption based on *trans*-quinolizidine was observed. Hydrobromide: Recrystallized from a mixture of EtOH and ether to give colorless plates, mp 242.5—243.5°.

**4-Phenyl-1,3,4,6,7,8-hexahydro- and/ or 4-Phenyl-3,4,6,7,8,9-hexahydro-2H-quinolizine<sup>8)</sup> (IX)**—1) By the action of *N*-bromosuccinimide on VII: To a solution of VII (1.2 g) in a mixture of dioxane (10 ml) and water (10 ml) was added *N*-bromosuccinimide (1.6 g). After it was kept for 3 hr under nitrogen atmosphere, the solvent was removed *in vacuo*. The residue was made alkaline with sodium hydroxide solution and extracted with ether. From the ether layer which was washed with water and then desiccated, pale yellow liquid (IX), bp 125—130° (5 mmHg) (bath temperature) was obtained. Yield: 0.5 g. Perchlorate: Recrystallized from EtOH to give colorless prisms, mp 117—118°. IR cm<sup>-1</sup> (Nujol): 1655 (iminium), 760, 1495, 1600 (phenyl). *Anal.* Calcd. for C<sub>15</sub>H<sub>20</sub>O<sub>4</sub>NCl: C, 57.54; H, 6.42; N, 4.46. Found: C, 57.34; H, 6.59; N, 4.29. No melting point depression was observed by the admixture of this perchlorate with that of IX obtained by mercuric acetate oxidation of 4-phenylquinolizidine (VII). The IR absorption spectra of both perchlorates were completely coincident in nujol.

2) By mercuric acetate oxidation of VII: To a solution of mercuric acetate (22 g) in 5% aqueous acetic acid (100 ml) was added VII (2.5 g), and the mixture was heated for 1.5 hr at 60°. After the reaction solution was chilled, mercurous acetate was removed by filtration, and the filtrate was saturated with hydrogen sulfide to remove excess mercuric ion. Centrifugation gave a yellow supernatant, which was made alkaline with sodium hydroxide and extracted with ether. From the ether layer which was washed with water and then desiccated, pale yellow liquid (IX), bp 124—126° (4 mmHg) (bath temperature). Yield: 1.1 g.

Perchlorate: Recrystallized from EtOH to give colorless prisms, mp 117—118°.

**4-Phenyl-1,6,7,8,9,9a-hexahydro-2H-quinolizine (VI)**—1) By the action of phenyl magnesium bromide on V: A solution of 4-oxoquinolizidine (V) (20 g) in dry ether (20 ml) was added dropwise to Grignard reagent prepared from Mg (3.2 g) and bromobenzene (20 ml) in dry ether (50 ml), and the mixture was refluxed for 3 hr. After cooling, the reaction mixture was made alkaline with sodium carbonate solution, and extracted with ether. From the ether solution, pale yellow liquid (VII), bp 125—130° (5 mmHg) (bath temperature) was obtained. Yield: 11 g.

Perchlorate: Recrystallized from EtOH to give colorless needles, mp 182.5—183°. IR cm<sup>-1</sup> (Nujol): 1635 (iminium), 760, 1600 (phenyl). *Anal.* Calcd. for C<sub>15</sub>H<sub>20</sub>O<sub>4</sub>NCl: C, 57.41; H, 6.44; N, 4.46. Found: C, 57.22; H, 6.61; N, 4.46.

2) By hydrolysis of XI: *N*-Benzoyl derivative (XI) (0.1 g) was refluxed for 40 hr in 15% HCl (20 ml). After cooling, the solution was extracted with ether. From the ether solution, benzoic acid (mp 122—123°) was obtained. The aqueous layer was made alkaline with sodium carbonate, and extracted with ether. The ether solution was washed with water, desiccated, and the residue obtained on evaporation of ether afforded pale yellow liquid (VI), bp 170—180° (15 mmHg) (bath temperature). Yield: 0.04 g.

Perchlorate: Recrystallized from EtOH to give colorless needles, mp 182.5—183°. No melting point depression was observed by the admixture of this perchlorate with that of VI mentioned above. The IR spectra of both perchlorates in nujol were completely in accordance.

11) IR spectra were measured with a Spectrophotometer, IRDS-402G of Japan Spectroscopic Co., Ltd.. Melting points were measured with a Yanagimoto Micro Melting Point Apparatus.

12) F. Bohlmann, E. Winterfeldt, P. Stoudt, H. Laurent, G. Boroschewski, and K. Kleine, *Chem. Ber.*, **94**, 3151 (1961).

3) By migration of X: To a solution of ferric nitrate·ninehydrates (2.5 g) and tartaric acid (0.9 g) in water (30 ml) was added phenylquinolizidine N-oxide (X) (0.5 g). After being kept for 1.5 hr at 80°, the reaction solution was made alkaline with sodium hydroxide, and extracted with ether. The ether layer was washed with water, desiccated, and ether was evaporated. The residue afforded pale yellow liquid (VI), bp 125—130° (4 mmHg) (bath temperature). Yield: 0.2 g.

Perchlorate: Recrystallized from EtOH to give colorless needles, mp 182.5—183°. IR  $\text{cm}^{-1}$  (Nujol): 1635 (iminium), 760, 1600 (phenyl). *Anal.* Calcd. for  $\text{C}_{15}\text{H}_{20}\text{O}_4\text{NCl}$ : C, 57.41; H, 6.44; N, 4.46. Found: C, 57.28; H, 6.41; N, 4.63. No melting point depression was observed by the admixture of this perchlorate with that of VI obtained by the action of phenyl magnesium bromide on V. The IR spectra of both perchlorates in nujol were completely in accordance.

**1-Benzoyl-2-(3-benzoyl)-piperidine (XI)**—To a suspension of perchlorate (1.5 g) of VI in a mixture of ether (60 ml) and 10% sodium hydroxide solution (40 ml) was added dropwise benzoyl chloride (4.9 g) under chilling, stirred for 12 hr and then extracted with ether. The ether solution was washed with water, desiccated, and then evaporated. The syrupy residue soon solidified and was recrystallized from petroleum ether to give white plates, mp 70.5—71.5°. Yield: 1.35 g. IR  $\text{cm}^{-1}$  (Nujol): 1690 (carbonyl), 1635 (amide), 745, 1580, 1595, 3060 (phenyl). *Anal.* Calcd. for  $\text{C}_{22}\text{H}_{25}\text{O}_2\text{N}$ : C, 78.77; H, 7.51; N, 4.18. Found: C, 78.52; H, 7.42; N, 4.10.

**4-[2-(1-Benzylpiperidyl)]-1-phenyl-1-butanol (XII)**—To a suspension of lithium aluminum hydride (3.06 g) in dry ether (30 ml) was added N-benzoyl derivative (XI) (0.54 g) under stirring. After being stirred for 5 hr at room temperature, an excess of lithium aluminium hydride was decomposed with water, and the reaction solution was extracted with ether. The ether layer was washed with water, desiccated, and then evaporated. From the residue, a crystalline solid (XII) was obtained. Yield: 0.25 g. Recrystallization from petroleum ether gave white needles, mp 84—85°. IR  $\text{cm}^{-1}$  (Nujol): 3230 (hydroxyl), 740, 755, 1490, 3040 (phenyl). *Anal.* Calcd. for  $\text{C}_{22}\text{H}_{29}\text{ON}$ : C, 81.69; H, 9.04; N, 4.33. Found: C, 81.81; H, 9.17; N, 4.09.

**4-Phenyl-octahydro-2H-quinolizine 5-Oxide (X)**—To a solution of VII (6 g) in acetone (180 ml) was added dropwise 20% hydrogen peroxide (60 ml) under cooling and stirring. After being kept for 10 hr at 55°, the mixture was diluted with water (30 ml), warmed *in vacuo* removing acetone, and then extracted with chloroform several times. The chloroform solution was desiccated and evaporated to dryness *in vacuo* and the crystalline residue was recrystallized from acetone to give colorless plates (X), mp 190°. IR  $\text{cm}^{-1}$  (Nujol): 755, 1495 (phenyl). *Anal.* Calcd. for  $\text{C}_{15}\text{H}_{21}\text{ON}\cdot\text{H}_2\text{O}$ : C, 72.25; H, 9.30; N, 5.62. Found: C, 72.36; H, 9.32; N, 5.54.

Picrate: Recrystallized from EtOAc to give yellow needles, mp 179—180°. *Anal.* Calcd. for  $\text{C}_{21}\text{H}_{24}\text{O}_8\text{N}_4$ : C, 54.78; H, 5.25; N, 12.17. Found: C, 54.98; H, 5.94; N, 12.32.

**Nupharidine<sup>4)</sup> (I)**—To a solution of deoxynupharidine (II) (1 g) obtained from *Nuphar japonicum* DC. in acetone (10 ml) was added dropwise 30% hydrogen peroxide (10 ml) diluted with acetone (20 ml) under cooling and stirring. After being kept for 10 hr at 45°, the reaction solution diluted with water (20 ml), warmed *in vacuo* removing acetone, and then extracted with chloroform several times. A crystalline residue obtained from the chloroform solution was recrystallized from acetone to give colorless scales (I), mp 201—202° (decomp.). Yield: 0.86 g. IR  $\text{cm}^{-1}$  (Nujol): 870, 1505, 3075 (furan). *Anal.* Calcd. for  $\text{C}_{15}\text{H}_{23}\text{O}_2\text{N}$ : C, 72.25; H, 9.30; N, 5.62. Found: C, 72.35; H, 8.90; N, 5.55. The IR spectra of I and nupharidine isolated from *Nuphar japonicum* DC. in nujol were completely in accordance.

Picrate: Recrystallized from EtOH to give yellow needles, mp 169—170°. No melting point depression was observed by the admixture of this picrate with that of nupharidine obtained from *Nuphar japonicum* DC.

**Dehydro-deoxynupharidine (III)**—To a solution of ferric nitrate·ninehydrates (2.5 g) and tartaric acid (0.9 g) in water (30 ml) was added nupharidine (I) (0.5 g). After being kept for 1.5 hr at 80°, the reaction solution was made alkaline with sodium hydroxide, and extracted with ether. From the ether solution which was washed with water and desiccated, pale yellow liquid (III), bp 150—160° (8 mmHg) (bath temperature) was obtained. Yield: 0.2 g.

Perchlorate: Recrystallized from EtOH to give colorless needles, mp 159—159.5°. IR  $\text{cm}^{-1}$  (chloroform): 1640 (iminium), 877, 1510, 3128 (furan).  $[\alpha]_D^{25} +134^\circ$  ( $c=4.4$ ,  $l=1$ , chloroform,  $a=+5.89$ ). *Anal.* Calcd. for  $\text{C}_{15}\text{H}_{22}\text{O}_5\text{NCl}$ : C, 54.30; H, 6.68; N, 4.42. Found: C, 54.24; H, 6.84; N, 4.42. No melting point depression was observed by the admixture of this perchlorate with that of dehydro-deoxynupharidine (III) isolated from *Nuphar japonicum* DC. The IR spectrum and degree of specific rotation of this perchlorate were completely coincident with those of perchlorate of III obtained from *Nuphar japonicum* DC.

**Acknowledgement** The authors are indebted to Mr. Yoshitaka Itatani for the elementary analysis.