Studies on Nicotinoids as an Insecticide

Part IV¹⁾. Relation of Structure to Toxicity of Pyridylmethyamines*

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3-Pyridylmethyamines, such as 3-pyridylmethyl-N-diethylamine, N-(3-pyridylmethyl)-piperidine and 3-pyridylmethyl-N-dimethylamine provided with the essential moiety of nicotinoids molecule, show comparable toxicity to nicotine against house flies.

3-Pyridylmethyamine without substituent on amino-nitrogen, N-(3-pyridylmethyl)-morpholine having low basic nitrogen, 4-pyridylmethyl-N-diethylamine not provided with proper N-N distance and some nicotine-methiodides having quaternary nitrogen show low or no toxicity.

These data support our proposition¹⁾ that the essential moiety of nicotinoids molecule responsible for high toxicity is 3-pyridylmethyamine grouping.

Studies on the relation of nicotinoids structure to toxicity against insects in a previous paper¹⁾ revealed that the essential moiety of nicotinoids structure responsible for high

toxicity is , in which N in side chain should have high basicity ($\text{pK}_{\text{a}1}' > 7.4$). It can be said that all nicotinoids of high toxicity have the essential moiety in structure, whereas all nicotinoids not provided with the essential moiety are of low or no toxicity.

An important point suggested from the above information is that nicotine structure may be reduced to less complex and more accessible structure, maintaining its toxicity. Some simple compounds were, therefore, prepared to test this idea.

The factors taken into consideration on designing toxic molecules before their syn-

theses were as follows.

(1) The presence of pyridine ring. Compounds, having some features of nicotine but having no pyridine ring, are of low or no toxicity¹⁾.

(2) Highly basic nitrogen should be present at the distance of about 4 Å from pyridyl nitrogen¹⁾. This nitrogen is protonated in insect body and will anchor the molecule to the anionic site of nervous receptor.

(3) This nitrogen should not be quaternary one, as ionic compounds may penetrate difficultly through the outer cuticle and the ion barrier²⁾ around synaptic region. Indeed, low toxicity of nicotine-methiodides both by injection and by spraying has been reported³⁾. We also confirmed this fact using the authentic nicotine monomethiodide (VIII), isomethiodide (IX) and dimethiodide (X). 3-

1) Part I, I. Yamamoto et al., This Journal, **26**, 709 (1962).

* Comm. on Oct. 27, 1962 at the meeting of the Agricultural Chemical Society of Japan.

2) R.D.O'Brien, "Toxic Phosphorus Esters", Academic Press Inc., 1960, p. 330.

3) N. Turner, N. Woodruff, D. Saunders and A. Eisner, *Connecticut Agr. Exp. Sta. Bull.*, **521**, (1948), cited by Metcalf, p. 7.

TABLE I. CHEMICAL STRUCTURES AND NAMES OF COMPOUNDS USED IN THIS EXPERIMENT

3-Pyridylmethyl-N-diethylamine (I)		Nicotine monomethiodide (VIII)	
3-Pyridylmethyl-N-dimethylamine (II)		Nicotine isomethiodide (IX)	
N-(3-Pyridylmethyl)-piperidine (III)		Nicotine dimethiodide (X)	
N-(3-Pyridylmethyl)-morpholine (IV)		3-Pyridylmethyl-N-diethylamine dimethiodide (XI)	
3-Pyridylmethylamine (V)		Metanicotine (XII)	
4-Pyridylmethyl-N-diethylamine (VI)		Dihydrometanicotine (XIII)	
Nicotine (VII)			

Pyridylmethyl-N-diethylamine dimethiodide (XI) shows also no toxicity by injection (Table III).

(4) The proper substitution on the above nitrogen. No substitution may perhaps be unprofitable, as acetylcholine analogs without substituent on nitrogen have much less activity than acetylcholine in mammals⁴. Later, 3-pyridylmethylamine (V) was shown to be less toxic than nicotine (Table III).

(5) No α -substituent on pyridine ring. 6-Methylnornicotine⁵ and the other α -methylated analogs of biologically active compounds show much decreased activities.

(6) No substituent on the bridge carbon between pyridine ring and amino nitrogen.

C. H. Richardson and H. H. Shepard⁶) had shown that 1-(3-pyridyl)-ethyl or -butylamines were of low toxicity.

(7) Ease in synthesis.

Some pyridylmethyl-N-disubstituted amines, which are provided with such requirements, were prepared by (a) reducing N-disubsti-

4) H.R. Ing, *Science*, **109**, 264 (1949).

5) I. Yamamoto and H. Kamimura, *This Journal*, **27**, 445 (1963).

6) C.H. Richardson and H.H. Shepard, *J. Agr. Research*, **40**, 1007 (1930).

TABLE II. TOXICITY AND BASICITY OF PYRIDYLMETHYLAMINES

Compounds	Basicity pK _{a1}	% of ionized form at pH 7	Relative toxicity (house fly)
VII	7.9	88.8	1.0
I	8.4	96.2	2.0
II	8.0	90.9	1.1
III	8.4	96.2	0.9
IV	6.0	9.1	<0.1

tuted nicotinamides with lithium aluminum hydride or (b) amination of 3-chloromethylpyridine.

As seen in Table III, 3-pyridylmethyl-N-diethylamine (I), 3-pyridylmethyl-N-dimethylamine (II) and N-(3-pyridylmethyl)-piperidine (III) show comparable toxicity to that of nicotine (VII) against house flies, *Musca domestica vicina* Macquardt.

The statement¹⁾ that nicotinoids of high toxicity have highly basic nitrogen (but not quaternarized), whereas those having low basic nitrogen are of low or no toxicity, is also applicable to the case of pyridylmethylamines. As seen in Table II, the pyridylmethylamines of high toxicity have highly basic nitrogen, over 90% of all molecules being protonated at pH 7 (25°C), whereas N-(3-pyridylmethyl)-morpholine (IV) having low basic nitrogen is protonated only by 9% at pH 7 (25°C) and shows only slight toxicity.

4-Pyridylmethyl-N-diethylamine (VI), meta-nicotine(XII) and dihydrometanicotine(XIII), which are not provided with proper N-N distance (factor 2), show also low toxicity (Table III).

From the structure-insecticidal action relationship in nicotinoids and in pyridylmethylamines, 3-pyridylmethylamine grouping

(N in side chain should be

highly basic) may be regarded as a new toxophore.

EXPERIMENTAL

Chemical Section.

Preparation of N-diethylnicotinamide from nicotinic acid and diethylamine with phosphorus pentoxide in one step was described by Saha⁷⁾. We employed this method for preparing the following three pyridinecarboxamides with good yield (over 80% yield).

N-Pyridylcarbonylpiperidine. Piperidine (25 g) was added carefully to nicotinic acid (25 g) in dried xylene (80 ml). The mixture was cooled in ice and phosphorus pentoxide (43.2 g) was added in small portions with shaking. The mixture was heated for one hr. to 120°C followed by four hr. at 140~150°C. After cooling, the reaction mixture was dissolved in water (60 ml) and made alkaline with 25% sodium hydroxide solution, then extracted with benzene. The residual oil from benzene evaporation was distilled to give 32.5 g (yield, 84.2%). B.p. 175~176°C/8 mm (310°C⁸⁾). n_D^{27} 1.5420. Picrate, m.p. 131~132°C from acetone.

N-Pyridylcarbonylmorpholine. B.p. 193~194°C/8 mm (192°C/6 mm⁹⁾). n_D^{20} 1.5525. Picrate, m.p. 174~175°C from acetone (174~175°C⁹⁾).

N-Diethylisonicotinamide. B.p. 155~157°C/10 mm (119~120°C/1 mm¹⁰⁾). n_D^{18} 1.5157 (n_D^{20} 1.525¹⁰⁾). Picrate, m.p. 175~176°C.

N-Dimethylnicotinamide. Prepared by the method of Samejima¹¹⁾ from phenyl nicotinate and aqueous dimethylamine. B.p. 132~134°C/6 mm (103~104°C/1 mm¹¹⁾). M.p. 38~45°C. Picrate, m.p. 148~150°C.

Reduction of N-diethylnicotinamide to 3-pyridylmethyl-N-diethylamine (I) with lithium aluminum hydride was first reported by Uffer and Schlittler¹²⁾, later it was improved by Mićović and Mihailović¹³⁾. We employed essentially the same procedure as that of Mićović and Mihailović for the preparation of other pyridylmethylamines. The infrared spectra of the pyridylmethylamines obtained showed the disappearance of the carbonyl bands in the amides, maintaining the bands characteristic to pyridine ring. Yields, however, were not satisfactory.

7) S.K. Saha, *J. Indian Chem. Soc., Ind. and News Ed.* **19**, 165 (1956).

8) Ges. f. chem. Ind. Basel, *D.R.P.*, 351085; 441707.

9) Fabr. Prod. Chimie Org. Laire, *Fr. addn.*, 824,042 (1938).

10) G. Carrara, *U.S. patent*, 2,858,317, Oct. 28, 1958.

11) M. Samejima, *J. Pharm. Soc. Japan*, **80**, 1706 (1960).

12) A. Uffer and E. Schlittler, *Helv. Chem. Acta*, **31**, 1397 (1948).

13) V.M. Mićović and M.Lj. Mihailović, *J. Org. Chem.*, **18**, 1190 (1953).

N-(3-Pyridylmethyl)-piperidine (III). The powdered lithium aluminum hydride (3.0 g) was suspended in dried ether (300 ml). To the stirring and gently boiling suspension, the solution of N-pyridylcarbonylpiperidine (30 g) in dried ether (200 ml) was added from the dropping-funnel within twenty-five min. Stirring and heating were continued for another one hr. The mixture was then cooled in an ice-bath and the reaction product and excess of hydride were decomposed by dropwise addition of water (10 ml) followed by 10% sodium hydroxide (14 ml). After vigorous stirring for another twenty min., the mixture was filtered with suction, and the granular precipitate was washed thoroughly with ether. After drying over anhydrous sodium sulfate, the combined ethereal solutions were evaporated and the residual oil was distilled to give 18.7 g (yield, 68%). B.p. 123~123.5°C/8 mm. n_D^{20} 1.5205. UV: $\lambda_{\text{max}}^{\text{MeOH}}$ 261 m μ . pK_{a1}' 8.4, pK_{a2}' 3.2 (25°C). Picrate, m.p. 172~173°C from acetone. *Anal.* Found: C, 44.19; H, 3.95; N, 17.64. Calcd. for $C_{11}H_{16}N_2 \cdot 2C_6H_5O_7N_3$: C, 43.54; H, 3.49; N, 17.65%. Other fractions: b.p. 27~30°C/10~14 mm, 2.9 g, identified as piperidine; b.p. 112~128°C/3 mm, 1.3 g, identified as 3-pyridylcarbinol.

N-(3-Pyridylmethyl)-morpholine (IV). Prepared by the same procedure as described above. Yield 65%. B.p. 139~142°C/11 mm. n_D^{21} 1.5236. UV: $\lambda_{\text{max}}^{\text{MeOH}}$ 261 m μ . pK_{a1}' 6.0, pK_{a2}' 3.4 (25°C). Picrate, m.p. 217°C from acetone. *Anal.* Found: C, 42.29; H, 3.88; N, 17.24. Calcd. for $C_{10}H_{14}ON_2 \cdot 2C_6H_5O_7N_3$: C, 41.52; H, 3.16; N, 17.6%.

3-Pyridylmethyl-N-dimethylamine (II). Prepared by the same procedure as described above. Yield 66%. B.p. 72~75°C/3 mm. n_D^{20} 1.4952. UV: $\lambda_{\text{max}}^{\text{MeOH}}$ 261 m μ . pK_{a1}' 8.0, pK_{a2}' 3.3 (25°C). Picrate, m.p. 189~190°C from acetone. *Anal.* Found: C, 40.32; H, 3.27; N, 18.69. Calcd. for $C_8H_{12}N_2 \cdot 2C_6H_5O_7N_3$: C, 40.43; H, 3.05; N, 18.85%.

4-Pyridylmethyl-N-diethylamine (VI). Prepared by the same procedure as described above. Yield 50%. B.p. 101~103°C/5 mm. n_D^{17} 1.4943. UV: $\lambda_{\text{max}}^{\text{MeOH}}$ 256 m μ . pK_{a1}' 8.0, pK_{a2}' 3.6 (25°C). Picrate, m.p. 175~177°C from acetone. *Anal.* Found: C, 42.77; H, 3.81; N, 18.16. Calcd. for $C_{10}H_{16}N_2 \cdot 2C_6H_5O_7N_3$: C, 42.45; H, 3.56; N, 18.01%.

4-Pyridylcarbinol (16%) was also obtained: b.p. 123~133°C/5 mm, m.p. 38~51°C (58~60°C¹⁴⁾).

3-Pyridylmethyl-N-diethylamine (I). Prepared by the same procedure as described above. Alternatively, I was prepared by amination of 3-chloromethylpyridine. 3-Chloromethylpyridine-hydrochloride (3 g) (prepared by the method of Mosher and Tessieri¹⁴⁾ from pyridylcarbinol with thionyl chloride, the latter being prepared from ethyl nicotinate by reduction with lithium aluminum hydride¹⁴⁾) was suspended in benzene (10 ml). To the suspension, diethylamine (5 g) in benzene (10 ml) was added with shaking within a few minutes and the mixture was refluxed for two hr. The reaction mixture was filtered with suction and the precipitate was washed with benzene. The combined benzene solution was evaporated and the residual oil was distilled to give 1.9 g (63%). B.p. 96~97°C/3 mm (108~109°C/14 mm¹⁸⁾). n_D^{19} 1.5059. UV: $\lambda_{\text{max}}^{\text{MeOH}}$ 261 m μ . pK_{a1}' 8.4, pK_{a2}' 2.8 (25°C). Picrate, m.p. 183~184°C from acetone. *Anal.* Found: C, 42.25; H, 3.93; N, 18.30. Calcd. for $C_{10}H_{16}N_2 \cdot 2C_6H_5O_7N_3$: C, 42.45; H, 3.56; N, 18.01%.

3-Pyridylmethylamine (V). 3-Pyridylcyanide in methanol was hydrogenated to V by the method of Kolloff¹⁵⁾, Huber¹⁶⁾ and Adkins¹⁷⁾ using Raney nickel under hydrogen (90~70 kg/cm²). B.p. 94~95°C/7 mm (98~99°C/12 mm¹⁸⁾). n_D^{20} 1.5283 (n_D^{25} 1.5485¹⁷⁾). UV: $\lambda_{\text{max}}^{\text{MeOH}}$ 262 m μ . pK_{a1}' 8.2, pK_{a2}' 3.2 (25°C). Picrate, m.p. 211°C (decomp.) (210~211°C¹⁷⁾). Phthalimide, m.p. 153°C.

Nicotine monomethiodide (VIII) and nicotine isomethiodide (IX) were prepared by the method of Barlow¹⁸⁾ and nicotine dimethiodide (X) by that of Späth¹⁹⁾.

Nicotine Monomethiodide (VIII). Sintered from 93°C, melted at 115°C. *Anal.* Found: I, 41.2. Calcd. for $C_{11}H_{17}N_2I$: I, 41.7%. Monohydrate, sintered from 72°C, melted at 89°C (sintered at 73°C and melted at 89°C¹⁸⁾). UV: $\lambda_{\text{max}}^{H_2O}$ 226 and 260 m μ (225 and 260 m μ ¹⁸⁾). IR (Nujol): 1589 and 1574 cm⁻¹ (pyridine ring vibration).

Nicotine Isomethiodide (IX). M.p. 162°C from ethanol, acetone and ether mixture (161°C¹⁸⁾). *Anal.* Found: I, 42.2. Calcd. for $C_{11}H_{17}N_2I$: I, 41.7%. UV: $\lambda_{\text{max}}^{H_2O}$ 224 and 263.5 m μ (224 and 264 m μ ¹⁸⁾). IR (Nujol): 1638 cm⁻¹ (C=N⁺ in pyridine ring).

15) H.G. Kolloff and J.H. Hunter, *ibid.*, **63**, 490 (1941).

16) W. Huber, *ibid.*, **66**, 876 (1944).

17) H. Adkins, I.A. Wolff, A. Pavlic and E. Hutchinson, *ibid.*, **66**, 1293 (1944).

18) R.B. Barlow and N.A. Dobson, *J. Pharm. Pharmacol.*, **7**, 27 (1955).

14) H.S. Mosher and J.E. Tessieri, *J. Am. Chem. Soc.*, **73**, 4925 (1951).

Nicotine Dimethiodide (X). M.p. 219~220°C from methanol (220°C¹⁹). *Anal.* Found: I, 57.3. Calcd. for C₁₂H₂₀N₂I₂: I, 56.9%. UV: $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 226 and 262 m μ . IR (Nujol): 1638 cm⁻¹ (C=N⁺ in pyridine ring).

3-Pyridylmethyl-N-diethylamine Dimethiodide (XI). Prepared from the amine and excess methyl iodide in methanol. Amorphous solid. *Anal.* Found: I, 57.1. Calcd. for C₁₂H₂₂N₂I₂: I, 56.6%. UV: $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 226 and 261.5 m μ . IR (Nujol): 1638 cm⁻¹ (C=N⁺ in pyridine ring).

Metanicotine (XII). Prepared by the method of

TABLE III. TOXICITY OF NICOTINE METHIODIDES, PYRIDYLMETHYLAMINES AND THE RELATED COMPOUNDS

Compounds	<i>M. domestica</i> (house fly) LC ₅₀ % (film method)
VII	0.87
I	0.43
II	0.79
III	0.93
IV	>8.7
	Mortality % at 2% toxicant (film method)
VII	100
V	10
VI	33
	Mortality % at 40 μ g/ female fly after 24 hr. (injection method)
VII	100
VIII	0
IX	0
X	0
XI	0
	Mortality % at 1% toxicant (film method)
VII	100
XII	24
XIII	18

19) E. Späth und G. Bobenberger, *Ber.*, **77**, 362 (1944).

Löffler and Kober²⁰. B.p. 121~122°C/3 mm, 270~273°C (272~274°C²⁰). Picrate, m.p. 171°C (171°C²¹).

Dihydrometanicotine (XIII). Metanicotine was hydrogenated by the method of Löffler and Kober²⁰. B.p. 133~135°C/10 mm (131~132°C/8 mm²⁰). Picrate, m.p. 162~163°C (161~162°C²⁰).

Biological Section.

The insecticidal actions of the pyridylmethyamines by a film method and of the methiodides by an injection method to house flies were summarized in Table III.

The film method is essentially the same as described in a previous paper²¹. The injection was carried out by injecting 1 μ l of 4% aqueous solution of toxicant into the mesonopum of a house fly.

The toxicity of 3-pyridylmethyl-N-diethylamine (PDEN) (I) to mouse, which was tested by Professor Ueda, was summarized in Table IV, comparing with other toxicants.

TABLE IV. TOXICITY OF 3-PYRIDYLMETHYL-N-DIETHYLAMINE (PDEN) (I) AND OTHER TOXICANTS TO MOUSE

Compounds	Oral	LC ₅₀ mg/kg cutaneous
TEPP	3	8
DDVP	71	206
PDEN (I)	445	1050
Allethrin	445	1200
Malathion	570	2330

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20) K. Löffler und S. Kober, *ibid.*, **42**, 3431 (1909).

21) A. Pinner, *ibid.*, **27**, 1058, 2863 (1894).