[Chem. Pharm. Bull. 24(8)1813—1821(1976)]

UDC 547.834.2.04 : 547.426.1.04

Syntheses of Nitrogen-containing Heterocyclic Compounds. XXIII.[1] Reaction of Naphthyridine Derivatives, with Special Reference to that of 1,7-Naphthyridine[2]

Isao Takeuchi and Yoshiki Hamada

Faculty of Pharmacy, Meijo University[3]

(Received November 12, 1975)

1,7-Naphthyridine (II) was prepared by the reduction of 8-chloro-1,7-naphthyridine over palladium–carbon. 1,5-Naphthyridine 1-oxide (III) and 1,5-naphthyridine (IV) were synthesized by the reaction of 3-aminopyridine 1-oxide with glycerol in the presence of Sulfo-mix, ferrous sulfate, and boric acid. Phenylation of 1,X-naphthyridine (X= 5,6,7, and 8) with phenyllithium afforded monophenylated compounds, phenyllithium having reacted in the 2-position. Methylation of II with methylsulfinyl carbanion afforded 4,8-dimethyl-1,7-naphthyridine (XI), and the Reissert reaction of II with benzoyl chloride and potassium cyanide afforded the normal Reissert compound (XII). Insecticidal activity of V, VIII—X, and XIII—XVIII was also examined.

We have previously developed a modified method for the synthesis of naphthyridines,[4] and reported their chemical reactivity.[4a,c,5] In the present series of work, synthesis of 1,7-naphthyridine, which has not been studied in detail, was examined and its reactivity, such as phenylation, methylation, and the Reissert reaction, was compared with that of 1,6-naphthyridine. Examinations were also made on the physiological activity of naphthyridines synthesized to date. The present paper concerns informations on these.

1,7-Naphthyridine was first prepared by Ikekawa[6] and then by Albert,[7] and required six steps starting with 3-aminopyridine 1-oxide and ethoxymethylenemalonate. The Skraup reaction of 3-aminopyridine[8] and its N-oxide[9] results in deoxygenation to form 1,5-naphthyridine. The method for the synthesis of 1,7-naphthyridine used by Rapoport and Bacho,[8] obtained in four steps from 3-aminopyridin-2(1*H*)-one (I) seemed to be the best. We have utilized this method but, as shown in Chart 1, I was prepared by the reduction of 3-nitropyridin-2(1*H*)-one with Raney nickel in 80% hydrazine hydrate,[10] in 1.4-fold yield of the past experi-

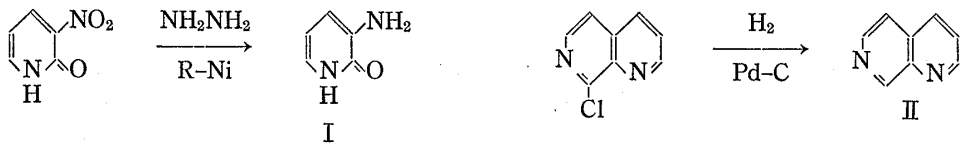


Chart 1

1) Part XXII: Y. Hamada, M. Sato, and I. Takeuchi, *Yakugaku Zasshi*, **95**, 1492 (1975).
2) A part of this work was reported at the Third International Congress of Heterocyclic Chemistry, Sendai, August, 1971.
3) Location: *Yagoto-Urayama, Tempaku-cho, Tempaku-ku, Nagoya, 468, Japan.*
4) *a*) Y. Hamada and I. Takeuchi, *Chem. Pharm. Bull.* (Tokyo), **19**, 1751 (1971); *b*) Y. Hamada and I. Takeuchi, *ibid.*, **19**, 1857 (1971); *c*) Y. Hamada, I. Takeuchi, and M. Hirota, *ibid.*, **22**, 485 (1974); *d*) Y. Hamada, I. Takeuchi, and M. Sato, *Yakugaku Zasshi*, **94**, 1328 (1974).
5) *a*) T. Takahashi, Y. Hamada, I. Takeuchi, and H. Uchiyama, *Yakugaku Zasshi*, **89**, 1260 (1969); *b*) Y. Hamada, I. Takeuchi, and H. Matsuoka, *Chem. Pharm. Bull.* (Tokyo), **18**, 1026 (1970).
6) N. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **6**, 401 (1958).
7) A. Albert, *J. Chem. Soc.*, **1960**, 1790.
8) H. Rapoport and A.D. Bacho, *J. Org. Chem.*, **28**, 1753 (1963).
9) J.G. Murray and C.R. Hauser, *J. Org. Chem.*, **19**, 2008 (1954).
10) Binz and Maier-Bode, *Angew. Chem.*, **49**, 486 (1936).

ments. I was then derived to 8-chloro-1,7-naphthyridine and catalytically reduced over 10% palladium-carbon to 1,7-naphthyridine (II) in 30% yield. The method used by Rapoport and Bacho[8] require two steps here and the yield was 23%. The present method was shortened by one step than the previous method.

The skraup reaction of 3-aminopyridine 1-oxide has been considered to effect cyclization at 4-position because of the electron-donating nature of the N-oxide group and the formation of 1,5-naphthyridine was thought to be the result of cyclization after deoxygenation.[9] Therefore, a modified Skraup reaction of 3-aminopyridine 1-oxide was carried out at 120°, where the temperature effect of the N-oxide group would appear and deoxygenation would not take place, and a compound (III) of mp 150—151° was obtained with a small amount of 1,5-naphthyridine (IV) of mp 60—62°. The mass spectrum of III exhibited *m/e* 146 (M^+) and 130 (M^+-O) and its elemental analytical values indicated the formula of $C_8H_8ON_2$. Since its infrared (IR) spectrum suggested that the compound is an N-oxide, III was deoxygenated with phosphoryl chloride. The nuclear magnetic resonance (NMR) and ultraviolet (UV) spectra of the product indicated it to be 1,5-naphthyridine and the fact was confirmed by admixture with 1,5-naphthyridine and comparison of their IR spectra. This result is shown in Chart 2 and Table I.

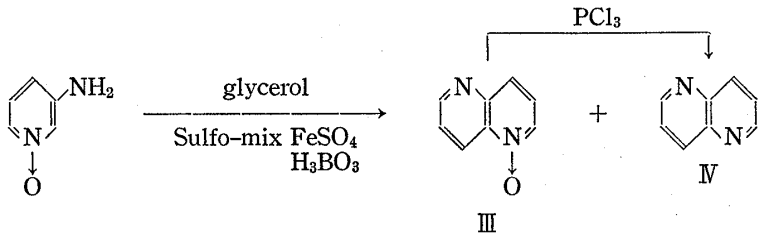


Chart 2

TABLE I

Raw material	Reagent	Method	Temp. (°C)	Time (hr)	Yield of products (%) III	IV
3-Aminopyridine 1-oxide	glycerol	a [a]	110	5	15.7	2.0
3-Aminopyridine 1-oxide	glycerol	a	120	5	16.2	5.8
3-Aminopyridine 1-oxide	glycerol	a	130	5	19.2	9.6
3-Aminopyridine 1-oxide	glycerol	a	140	5	17.1	14.4
3-Aminopyridine 1-oxide	glycerol	a	150	5	2.1	28.8
3-Aminopyridine 1-oxide	glycerol	b [b]	135	4	8.5	12.0

a) using of Sulfo-mix, $FeSO_4$, and H_3BO_3
b) using of sodium *m*-nitrobenzenesulfonate, $FeSO_4$, and H_3BO_3

As shown in Table I, amount of deoxygenated 1,5-naphthyridine increases as the reaction temperature becomes higher. Consequently, contrary to past belief, deoxygenation must occur after cyclization. Cyclization of 3-aminopyridine 1-oxide with acrolein diacetal in Dowtherm A, instead of glycerol, afforded only a small amount of deoxygenated 1,5-naphthyridine. This fact indicates that the effect of the N-oxide group hardly appears and that cyclization at 4-position by the use of ethoxymethylenemalonate is due to the specificity of the reagent.

According to the report on the phenylation of heterocyclic compounds with phenyllithium,[11] pyridine,[12] quinoline,[13] isoquinoline,[13] and phenanthridine[14] are all phenylated at the position *ortho* to the ring-nitrogen, but there has been no report on the phenylation of naphthyridines with phenyllithium. It seemed of interest, therefore, to examine position *ortho* to which of the nitrogen atoms would be phenylated in 1,6- and 1,7-naphthyridines, and to examine the difference in reactivity according to the difference of nucleophiles in amination[15] and in methylation with methylsulfinyl carbanion,[4] and also from the interest in the fact that phenyl-1,8-naphthyridine derivatives have antibacterial activity,[16] phenylation of 1,X-naphthyridine (X=5, 6, 7, 8) with phenyllithium was attempted.

Phenyllithium was reacted with 1,6-naphthyridine under the same condition as for the phenylation of quinoline and isoquinoline, and a compound (V) of mp 94—96° was obtained. V was confirmed to be a monophenylated compound from its mass spectrum of *m/e* 206 (M^+) and from its elemental analysis corresponding to the formula $C_{14}H_{10}N_2$. Position of the phenyl group was considered to be 2, giving 2-phenyl-1,6-naphtyridine, from the disappearance of the proton signal of 2-position and appearance of a singlet at 10.25 δ as a proton signal of 5-position, compared to that of 1,6-naphthyridine.

Conditions for the phenylation of 1,6-naphthyridine was then examined, and details of this experiment are summarized in Chart 3 and Table II.

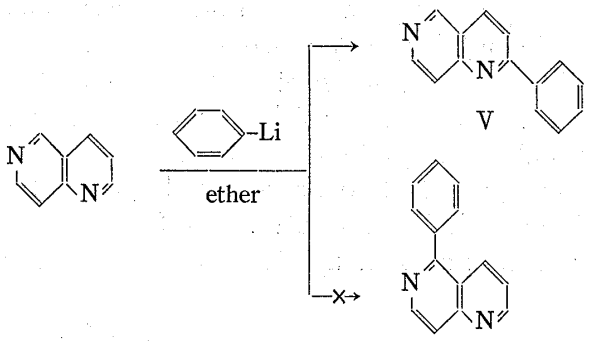


Chart 3

TABLE II

1,6-Naphthyridine (g)	Ether (ml)	Temp. (°C)	Time (hr)	Yield (%) V
1	4.5 + toluene 3	110	8	6.3[a]
1	12	0	2	25.3
1	12	15—20	2	28.9[b]
1	12	25—30	2	22.2
1	12	35—40	2	18.0
1	12	15—20	1	6.4
1	12	15—20	4	25.3
1	20	15—20	2	33.2
1	32	15—20	2	6.4

a) condition of pyridine phenylation[12]
b) condition of quinoline and isoquinoline phenylation[13]

As shown in Table II, the best result was obtained at the reaction temperature of 15—20° and reaction period of 2 hr, using 20 ml of ether. In order to confirm that the position of phenylation occurred at 2- and not at 5-position, the following experiment was carried out. V was N-methylated with methyl iodide in acetone and the methiodide (VI) so obtained was

11) R.G. Jones and H. Gilman, *Org. Reactions*, **6**, 339 (1951).
12) K. Ziegler and H. Zeiser, *Chem. Ber.*, **63**, 1849 (1930).
13) K. Ziegler and H. Zeiser, *Ann.*, **485**, 185 (1931).
14) H. Gilman and R.D. Nelson, *J. Am. Chem. Soc.*, **70**, 3316 (1948).
15) W.W. Paudler and T.J. Kress, *J. Org. Chem.*, **33**, 1384 (1968).
16) E.M. Hawes and D.G. Wibberley, *J. Chem. Soc. C*, **1966**, 315.

oxidized with potassium ferricyanide and sodium hydroxide to VII. Disappearance of the proton signal of 5-position at 10.25 δ from the NMR spectrum of VII, compared to that of V, proved that the phenyl group was at 2-position and not at 5-position. This result is shown in Chart 4.

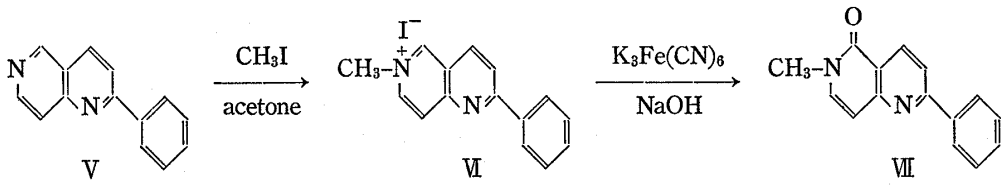


Chart 4

Phenylation of 1,7-naphthyridine was then carried out under the conditions giving a good yield of phenylated 1,6-naphthyridine. A monophenylated compound (VIII), $C_{14}H_{10}N_2$, giving *m/e* 206 (M^+), was obtained. Comparison of its NMR spectrum with that of II indicated disappearance of a proton signal due to 2-position and appearance of a singlet signal at 9.53 δ for a proton at 8-position, and the product was presumed to be 2-phenyl-1,7-naphthyridine. Similar phenylation of 1,5- and 1,8-naphthyridines gave monophenylated products which were presumed to be 2-phenyl-1,5-naphthyridine (IX) and 2-phenyl-1,8-naphthyridine (X) from their NMR spectra. VIII and X have already been synthesized in the past and their structure as 2-phenylated compounds was confirmed from the melting points reported in the

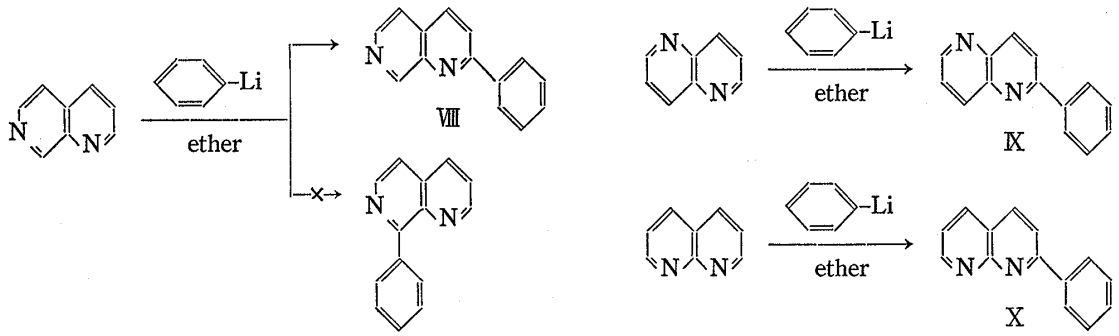


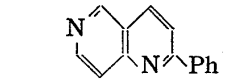
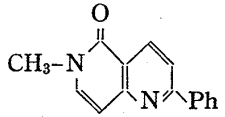
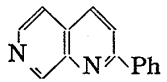
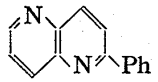
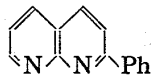
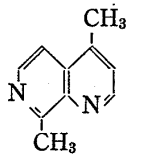
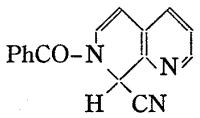
Chart 5

TABLE III

Compound No.	Raw material	Solvent	Reagent	Temp (°C)	Time (hr)	Yield (%)	mp (°C)
V	1,6-naphthyridine	ether	C_6H_5Li	15—20	2	33.2	97— 98
VIII	1,7-naphthyridine	ether	C_6H_5Li	15—20	2	22.0	113—115
IX	1,5-naphthyridine	ether	C_6H_5Li	15—20	2	23.7	82— 84
X	1,8-naphthyridine	ether	C_6H_5Li	15—20	2	34.8	109—111

Compound No.	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	Mass spectrum (*m/e*)
V	colorless plates	$C_{14}H_{10}N_2$	81.53	4.89	13.58	81.31	4.55	13.57	206(M^+)
VIII	colorless plates	$C_{14}H_{10}N_2$	81.53	4.89	13.58	81.64	4.76	13.55	206(M^+)
IX	colorless powder	$C_{14}H_{10}N_2$	81.53	4.89	13.58	81.49	4.68	13.56	206(M^+)
X	colorless powder	$C_{14}H_{10}N_2$	81.53	4.89	13.58	81.35	4.69	13.34	206(M^+)

TABLE IV. NMR Spectral Data

Compound No.		Solvent	Chemical shift (δ)									Coupling constants (CPS)					
			2-H	3-H	4-H	5-H	6-H	7-H	8-H	C_6H_5	N-CH_3	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$
V		CF_3COOH	—	8.87	9.60	9.75	—	9.26	9.09	8.31 7.97				9.0			7.0
VII		$CDCl_3$	—	7.82	8.70	—	—	7.32	7.28	8.12 7.48	3.62			8.5			7.7
VIII		$CDCl_3$	—	7.94	8.13	7.47	8.54	—	9.53	8.04 7.47					5.6		
IX		CF_3COOH	—	8.69	9.60	—	9.60	8.75	9.60	8.21 7.91				8.0		8.0	8.0
X		CF_3COOH	—	8.58	9.15	9.15	8.21	9.33	—	8.25 7.02				9.0	9.0	5.0	
XI		$CDCl_3$	8.85	7.40	—	7.62	8.48	—	—	4-CH_3 8-CH_3 2.65 3.08		4.5			6.0		
XII		$CDCl_3$	8.53	7.54	—	6.17	6.82	—		7.62		3.4	1.6	5.4	5.6		

a) NMR spectra were taken with a Varian A-60 spectrometer.
Ph=phenyl

literature.[17] Details of these experiments are given in Chart 5 and Table III. NMR spectral data of the compounds obtained are given in Table IV.

Synthesis of X had required 3 steps from 2-aminonicotinaldehyde and the total yield was 48% in the past[17] but the present method of using phenyllithium requires only one step, although the yield was slightly low 35%. As will be stated later, IX and X showed a biological activity, though weak, and the synthesis of these compounds may offer an interesting tool in the future.

The Reissert reaction[5b] and methylation[4a] of naphthyridines with methylsulfinyl carbanion[4a] have been reported but these reactions have not been made on 1,7-naphthyridine. Therefore, methylation of 1,7-naphthyridine with dimethyl sulfoxide was carried out in the same way as for 1,6-naphthyridine, and a dimethylated compound (XI), $C_{10}H_{10}N_2$, *m/e* 158 (M^+), was obtained. This product was considered to be 4,8-dimethyl-1,7-naphthyridine from its NMR spectrum indicating disappearance of 8-H and 4-H in the lower magnetic field and appearance of doublet signals for 2-, 3-H and 5-, 6-H, compared with the spectrum of II.

Application of benzoyl chloride and potassium cyanate to 1,7-naphthyridine in water afforded a Reissert compound (XII), $C_{16}H_{11}ON_3$, *m/e* 261 (M^+), whose NMR spectrum indicated disapearance of the sp^2 proton signal of 8-position in the lowest magnetic field and appearance of the non-aromatic sp^3 proton signal in the higher magnetic field at 6.82 δ. These facts suggested that this is a product formed by reaction with the nitrogen at 7-position. The UV spectrum of XII showed absorptions similar to those of the Reissert compound of the isoquinoline type. Details of this experiment are given in Chart 6 and Fig. 1.

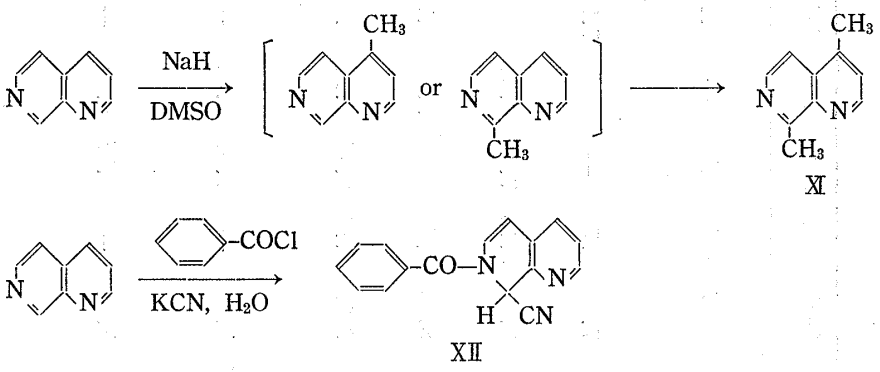


Chart 6

Comparison of the reactivity of 1,6- and 1,7-naphthyridines indicates that while methylation of 1,6-naphthyridine gives a monomethyl compound, that of 1,7-naphthyridine gave a dimethyl compound, and that the Reissert reaction of 1,6-naphthyridine in water failed to give the usual Reissert compound and a hydroxyl compound was formed in stead of cyano compound, whereas the usual Reissert compound was formed from 1,7-naphthyridine. In the phenylation reaction, the quinoline-type nitrogen showed a reactivity but the isoquinoline-type nitrogen was reactive in the Reissert reaction. These facts indicate that the two nitrogen atoms in naphthyridines show selective reactivity according to the reagent present.

Screening for insecticidal activity of naphthyridine derivatives was carried out since 2-phenyl-1,8-naphthyridine[16] (X) was found to have an antibacterial activity and we had found that the dimethyl derivatives of 1,8-naphthyridine were effective as a herbicide.[4d] In the primary screening, phenylated compounds, IX and X, showed a weak effect against housefly. 1,6-Naphthyridine-5-carboxamide[18] (XIII), obtained by hydrolysis of 5-cyano-1,6-naph-

17) *a*) H.E. Baumgarten and A.L. Krieger, *J. Am. Chem. Soc.*, **77**, 2438 (1955); *b*) E.M. Hawes and D.G. Wibberley, *J. Chem. Soc.*, C, **1967**, 1564.
18) Y. Hamada, H. Matsuoka, and H. Fukatsu, *Yakugaku Zasshi*, **91**, 565 (1971).

thyridine[5b] with 10% sodium hydroxide in ethanol, was found to have insecticidal activity against *Nepotettix cincticeps* Uhler comparable to that of commercial products, though its yield was no greatly different from that reported in past literature. These details are given in Table V and VI.

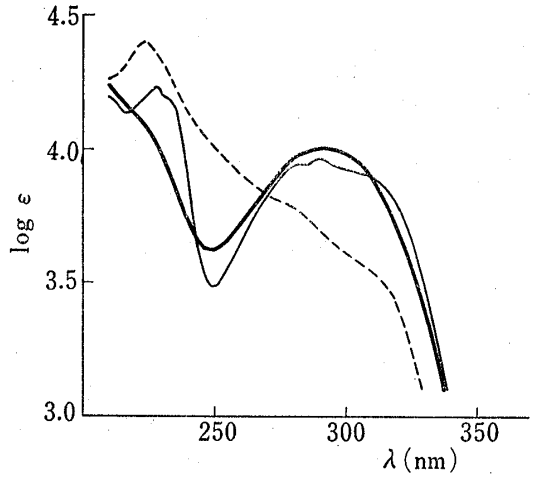


Fig. 1. Ultraviolet Absorption Spectra in EtOH

——: 7-benzoyl-7,8-dihydro-1,7-naphthyridine-8-carbonitrile (XII)
——: 2-benzoyl-1,2-dihydroisoquinoline-1-carbonitrile
--------: 1-benzoyl-1,2-dihydroquinoline-2-carbonitrile

Table V. Chemical Structure of Test Compound

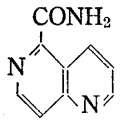
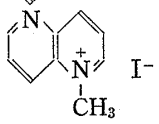
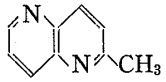
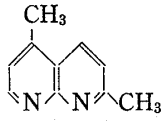
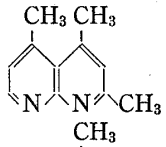
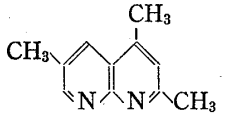
Compound No.	Chemical structure
XIII	
XIV	
XV	
XVI	
XVII	
XVIII	

Table VI. Insecticidal Activity of V, VIII—X, and XIII—XVIII (Concentration of 0.01%)

Compound No.		*Nephotettix cincticeps* Uhler		*Musca domestica* Linné	*Tetranychus vrticae* Koch		*Mysus* (*Nectarosiphon*) *persicae* Sulzer	
		24 hr[a]	48 hr[b]	24 hr	24 hr	48 hr	24 hr	48 hr
	test method	leaf-dipping		dry film	spray		root-dipping	
V		0	0	0	0	0	0	0
VIII		0	0	0	0	0	0	0
IX		0	0	10	0	0	0	0
X		0	10	10	0	0	0	0
VII		0	20	0	0	0	0	0
XIII		60	100	30	0	0	0	0
XIV		0	20	0	0	0	0	0
XV		0	0	70	0	0	0	0
XVI		0	0	0	0	0	0	0
XVII		0	0	0	0	0	0	0
XVIII		0	10	0	0	0	0	0
Sevin		90	100					
Elthane				100				
kelthane					80	100		
Dimethoate							100	100

a) the insecticidal rate of after 24 hr
b) the insecticidal rate of after 48 hr

Experimental

3-Aminopyridin-2(1*H*)-one (I)——To a solution of 4 g of 3-nitropyridin-2(1*H*)-one and 160 ml of EtOH, 24 ml of 80% $NH_2NH_2 \cdot H_2O$, 4 g of Raney–Ni was added, and the mixture was refluxed for 1 hr. After Ni was filtered off, the filtrate was evaporated and the residue was recrystallized from cyclohexane to give 2.83 g (90%) of I as pale yellow needles, mp 121—123°. I was identified with 3-aminopyridin-2(1*H*)-one, synthesized by the method of literature,[10] by mixed mp and by the comparison of IR spectra.

1,7-Naphthyridine (II)——To a solution of 0.17 g of 8-chloro-1,7-naphthyridine and 20 ml of dry methanol, 0.7 g of fused AcOK, 50 ml of 10% Pd-C was added, and the mixture was stirred with H_2 had been absorbed. After filtration, the solvent was evaporated, and residue was dissolved in 15 ml of saturated aqueous Na_2CO_3. This solution was extracted with CH_2Cl_2, and the extract was dried over $MgSO_4$, the solvent was evaporated and the residue was chromatographed over alumina, and eluted with CH_2Cl_2. The effluent fraction was purified by sublimation at 60°/0.1 mm, to give 0.04 g (30%) of II as colorless needles, mp 58—60°. *Anal.* Calcd. for $C_8H_6N_2$: C, 73.83; H, 4.65; N, 21.53. Found: C, 73.40; H, 4.67; N, 21.20. Mass Spectrum *m/e*: 130 (M^+). II was identified with 1,7-naphthyridine, synthesized by the method of literature,[8] by mixed mp and by the comparison of IR and UV spectra.

Skraup Reaction of 3-Aminopyridine 1-Oxide——A mixture of Sulfo-mix[19] (prepared from 19 g of $H_2SO_4 \cdot SO_3$ (20%), and 4.4 g of nitrobenzene), 0.56 g of $FeSO_4 \cdot 7H_2O$, and 0.96 g of H_3BO_3 was chilled to 0—5°, 5 ml of anhyd. glycerol was added, followed by 1.76 g of 3-aminopyridine 1-oxide and 5 ml of warmed water (50°), and the mixture was stirred at 130°, 5 hr. The reaction mixture was neutralized with Na_2CO_3 and extraction with $CHCl_3$. The extract was dried over $MgSO_4$, the solvent was evaporated, and the residue was chromatographed over silica gel, and eluted with benzene. First effluent fraction was recrystallized from cyclohexane to give 0.45 g (19.2%) of III as colorless plates, mp 150—151°. *Anal.* Calcd. for $C_8H_8ON_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.64; H, 4.11; N, 19.06. IR ν_{max}^{KBr} cm^{-1}: 1258 (N→O). Mass Spectrum *m/e*: 146 (M^+), 130 (M^+-O). III was confirmed in 1,5-naphthyridine 1-oxide, because III was deoxygenated with PCl_3 and to give 1,5-naphthyridine as shown in the later. Second effluent fraction was recrystallized from benzene to give 0.20 g (9.6%) of IV as colorless needles, mp 60—62°. IV was identified with 1,5-naphthyridine, synthesized by the method of literature,[8] by mixed mp and by the comparison of IR and UV spectra.

Deoxygenation of III with PCl_3——A solution of 0.2 g of III in 5 ml of $CHCl_3$ was ice cooled, 0.5 g of PCl_3 in 1 ml of $CHCl_3$ was added and the mixture was heated on the water bath, after 1 hr, $CHCl_3$ was evaporated, and ice water was added. The aqueous solution was made alkaline with NaOH, and extracted with CH_2Cl_2 and the extract was dried over $MgSO_4$, the solvent was evaporated, and the residue was recrystallized from cyclohexane to give 0.1 g (60%) of IV′ as colorless needles, mp 60—62°. IV′ was identified with 1,5-naphthyridine, synthesized by the method of literature,[8] by mixed mp and by the comparison of IR and UV spectra.

Cyclization of 3-Aminopyridine 1-Oxide with Acrolein Diacetal——A solution of 1.1 g of 3-aminopyridine 1-oxide and 1.54 g of acroleine diacetal in 180 ml of Dowtherm A[20] was heated at 250° for 30 min. The reaction mixture was extracted with 10% HCl and the aqueous solution was neutralized with 20% NaOH, and extracted with CH_2Cl_2, the extract was dried over $MgSO_4$, and the solvent was evaporated. The residue was recrystallized from cyclohexane to give trace of IV′ as colorless needles, mp 60—62°. IV′ was identified with 1,5-naphthyridine, synthesized by the literature,[8] by mixed mp and by the comparison of IR and UV spectra.

Phenylation of 1,X-Naphthyridine (X=5, 6, 7, 8) with Phenyllithium——To a solution of phenyllithium prepared from 0.12 g of small pieces of lithium, 1.3 g of bromobenzene and 20 ml of ether, was added with cooling by an ice-bath, 1 g of 1,X-naphthyridine (X=5, 6, 7, 8). The ice-bath was removed, the mixture was stirred at 15—20° for 30 min, in nitrogen. After stirring for 2 hr, the reaction mixture was hydrolyzed by adding 5 ml of water. The ether layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined ether and $CHCl_3$ solution was washed with water, dried over $MgSO_4$, and the solvent was evaporated. The residue was chromatographed over alumina, and eluted with $CHCl_3$. The effluent fraction was recrystallized from cyclohexane to give each monophenylated compounds of IX, VIII, V, and X. Their structure of the each monophenylated products were presumed to be 2-phenylated compounds from their NMR spectra. VIII and X was confirmed from the melting points reported in the literature.[17] These experimental details are summarized in Table III and IV.

2-Phenyl-1,6-naphthyridine 6-Methiodide (VI)——A solution of 0.2 g of V in acetone (5 ml) containing 0.14 ml of MeI was heated under reflux overnight. The resulting precipitate was collected and recrystallized from acetone to 0.3 g (86%) of VI as yellow needles, mp 238—240°. *Anal.* Calcd. for $C_{15}H_{13}N_2I$: C, 51.78; H, 3.76; N, 8.05. Found: C, 51.64; H, 3.53; N, 7.64.

2-Phenyl-6-methyl-1,6-naphthyridin-5-one (VII)——To a stirring solution of 0.3 g of VI in 70 ml of water, cooled in an ice-methanol bath, a solution of 0.17 g of NaOH in 0.4 ml of water was added dropwise during 5 min, and 0.7 g of $K_3Fe(CN)_6$ in 15 ml of water during 30 min, both additions starting at the same time.

19) W.P. Utermohlen, Jr., *J. Org. Chem.*, **8**, 544 (1943).
20) A mixture of diphenyl (26.5%) and diphenyl ether (73.5%) of the Dow Chemical Company.

After 1.5 hr, the ice bath was removed and stirring was continued for additional 5 hr at room temperature. The reaction mixture was extracted with $CHCl_3$. The extract was dried over $MgSO_4$, the solvent was evaporated, and the residue was recrystallized from acetone to give 0.16 g (80%) of VII as colorless needles, mp 154—155°. *Anal.* Calcd. for $C_{15}H_{12}ON_2$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.76; H, 5.18; N, 11.80. Mass Spectrum *m/e*: 236 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1630 (C=O).

Methylation with Methylsulfinyl Carbanion of II——A solution of 0.53 g (0.022 mole) of NaH dissolved in 20 ml of Me_2SO at 70° in N_2 stream, added with 0.52 g (0.004 mole) of II was stirred at 70° for 4 hr. To this reaction mixture, 20 ml of H_2O was added and the diluted mixture was poured into 300 ml of H_2O. The aqueous solution was neutralized with H_2SO_4, and extracted with $CHCl_3$, and the extract was washed with H_2O, the extract was dried over $MgSO_4$, and the solvent was evaporated. The residue was chromatographed over silica gel, and eluted with benzene. The effluent fraction was recrystallized from petroleum ether (bp 30—70°) to give 60 mg (18%) of XI as colorless needles, mp 95—96°. *Anal.* Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.51; H, 6.22; N, 17.86. IR ν_{max}^{KBr} cm^{-1}: 2920 (CH_3). Mass Spectrum *m/e*: 158 (M^+). NMR spectral data was summarized in Table IV. Therefore, XI was confirmed in 4,8-dimethyl-1,7-naphthyridine.

The Reissert Reaction of II——To a mixture of 0.1 g of II, 0.16 g of KCN, and 1.4 ml of H_2O, 0.22 g of BzCl was added during 30 min. The reaction mixture was further stirred for 4 hr. The aqueous layer was extracted with two 10 ml portions of CH_2Cl_2 and the combined organic layer was washed consecutively with two 5 ml portions of H_2O, 5% HCl, H_2O, 5% NaOH, and finally with H_2O, dried over $MgSO_4$, and the solvent was evaporated and the residue was chromatographed over silica gel, and eluted with benzene. The effluent fraction was recrystallized from Cyclohexane to give 25 mg (18%) of XII as colorless needles, mp 190—192°. *Anal.* Calcd. for $C_{16}H_{11}ON_3$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.27; H, 4.03; N, 15.82. UV λ_{max}^{EtOH} nm (log ε): 293 (4.05). IR ν_{max}^{KBr} cm^{-1}: 1665 (CO–N=). Mass Spectrum *m/e*: 261 (M^+). NMR spectral data was summarized in Table IV. Therefore, XII was confirmed in 7-benzoyl-7,8-dihydro-1,7-naphthyridine-8-carbonitrile.

Insecticidal Activity Tests——A definite number of adult insects were placed in a thermostatic chamber of 25° in which 2 ml of an aqueous emulsion of 0.01% of the test compound had been dispersed, and the percentage of dead insects was examined after 24 and 48 hr.

Acknowledgement We are grateful to Mr. Toshio Ito and Mr. Norihisa Kanda whose carried out a part of this experiment, and to the staff of the Analysis Center of this University for elemental analyses and to the staff of Biochemical Research Laboratory, Nissan Chemical Co., for biological testing.