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Syntheses of Nitrogen-containing Compounds. XVII.[1] Improvement of One-Step Synthesis of Naphthyridine Derivatives and Their Methylation with Dimethyl Sulfoxide in the Presence of Base

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1,8-Naphthyridines (III to VI) were synthesized in a high yield by the reaction of 2-aminopyridines with glycerol, in the presence of sodium *m*-nitrobenzenesulfonate, in sulfuric acid. Methylation of naphthyridines with dimethyl sulfoxide in the presence of sodium hydride or potassium *tert*-butoxide afforded their monomethyl or dimethyl compounds. This methylation with methylsulfinyl carbanion was examined from the Hückel molecular orbital method and its result agreed well with experimental results.

During the preparation of N-oxide compounds of 1,5- and 1,6-naphthyridine, we found that the products obtained were different[3] and became interested in the difference in chemical properties due to the difference in the position of ring-nitrogen. In order to see the difference in the reactivity of naphthyridines according to the position of their ring-nitrogen, methods for syntheses of 1,5-, 1,6-, and 1,8-naphthyridines to be used as the starting materials were examined and some new observations were made on a new method of synthesis. At the same time methylation of naphthyridines with dimethyl sulfoxide was carried out to compare the difference in their reactivity, and to examine their reactivity to methylation with $CH_3SOCH_2^-$ by the Hückel molecular orbital (HMO) method.

The past methods for the synthesis of naphthyridines[4] required several steps but Paudler and Kress[5] recently succeeded in one-step synthesis by the use of a sulfo-mix[6] and a marked advance was made in this synthesis, especially for that of 1,6-naphthyridine (I).

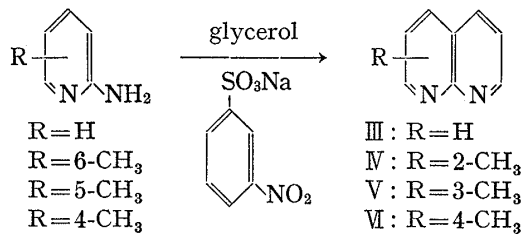


Chart 1

1) Part XVI: Y. Hamada, Y. Ito, and M. Hirota, *Chem. Pharm. Bull.* (Tokyo), **18**, 2094 (1970)
2) Location: *a*) *Yagoto-Urayama, Tempaku-cho, Showa-ku, Nagoya*, 468, *Japan*; *b*) *Ooka Minami-ku, Yokohama*, 233, *Japan*.
3) T. Takahashi, Y. Hamada, I. Takeuchi, and H. Matsuoka, *Yakugaku Zasshi*, **89**, 1260 (1969).
4) *a*) C. Koller, *Ber.*, **60**, 1918 (1927); *b*) A. Albert, *J. Chem. Soc.*, **1960**, 1790.
5) *a*) T.J. Kress and W.W. Paudler, *Chem. Commun.*, **1**, 3 (1967); *b*) *Idem*, *J. Org. Chem.*, **32**, 832 (1967); *c*) *Idem*, *J. Heterocyclic Chem.*, **4**, 284 (1967).
6) W.P. Utermohlen, Jr., *J. Org. Chem.*, **8**, 544 (1943).

In the present series of work, synthesis of I followed the method for 1,5-naphthyridine (II)[4b] from 4-aminopyridine, glycerol, and sodium *m*-nitrobenzenesulfonate, and examinations were made on the concentration of sulfuric acid to be used but I was not obtained in sufficiently high yield recorded in the literature.[5a] 1,8-Naphthyridine (III) was obtained in higher yield than that recorded in the literature[5b] by the use of sodium *m*-nitrobenzenesulfonate. Therefore, sodium *m*-nitrobenzenesulfonate was used in the reaction with 2-amino-4-methyl-, 2-amino-5-methyl-, and 2-amino-6-methylpyridines, and as a result, 2-methyl-, 3-methyl-, and 4-methyl-1,8-naphthyridines (IV—VI) were obtained, respectively, in higher yields than that recorded in the literature.[5b,c] These reaction routes are shown in Chart 1 and detailed conditions of the experiments in Table I.

Table I

Compound No.	Raw material	Reagent	Oxidazing agent	Temp (°C)	Time (hr)	Yield (%)
III	2-aminopyridine	glycerol	NO_2-C_6H_4-SO_3Na	135	4	45 (30)[5b]
IV	2-amino-6-metylpyridine	glycerol	NO_2-C_6H_4-SO_3Na	135	4	28 (10)[5b]
V	2-amino-5-metylpyridine	glycerol	NO_2-C_6H_4-SO_3Na	135	4	52 (17)[5c]
VI	2-amino-4-metylpyridine	glycerol	NO_2-C_6H_4-SO_3Na	135	4	35 (17)[5b]

Methylation[7] with dimethyl sulfoxide in the presence of a base has been effected in quinoline and isoquinoline by reacting at 70°, affording 4-methylquinoline and 1-methyl isoquinoline in a quantitative yield, but was not effected in benzene, pyridine, naphthalene, or thianaphthene, and the reaction at 70° did not succeed with phenazine. The same methylation of anthracene gave 9-methyl- or 9,10-dimethylanthracene, and that of phenanthridine and acridine respectively gave 6-methylphenanthridine and 9-methylacridine. Based on these past reports, 1,5-, 1,6-, and 1,8-naphthyridines were reacted with dimethyl sulfoxide in the presence of sodium hydride. Monomethylation occurred in the case of 1,6-naphthyridine to give VII, while dimethylation occurred with other compounds to from VIII and IX. VII and IX were respectively identified with 4-methyl-1,6-naphthyridine and 4,5-dimethyl-1,8-naphthyridine, synthesized by the route reported in literature,[5c,8] by mixed melting point determination and by infrared (IR) and nuclear magnetic resonance (NMR) spectral comparison. VIII was proved to be 4,8-dimethyl-1,5-naphthyridine from its elemental analyses, and IR, NMR, and mass spectra. Methylation of 1,5-and 1,8-naphthyridines with dimethyl

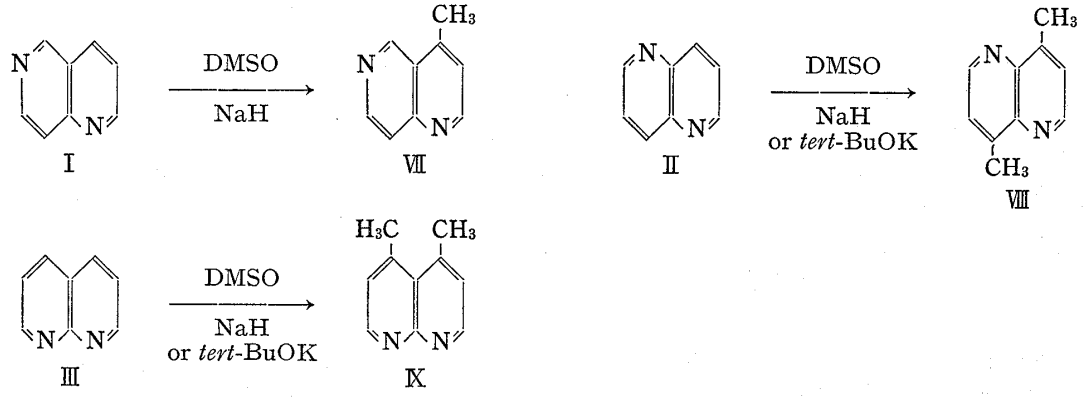


Chart 2

7) *a*) H. Nozaki, Y. Yamamoto, and R. Noyori, *Tetrahedron Letters*, **1966**, 1123; *b*) G.A. Russell and S.A. Weiner, *J. Org. Chem.*, **31**, 248 (1966).
8) W.W. Paudler and T.J. Kress, *J. Org. Chem.*, **31**, 3055 (1966).

sulfoxide in the presence of potassium *tert*-butoxide, a condition under which monomethyl and dimethyl derivatives were obtained from anthracene, failed to afford the monomethyl compounds and only dimethyl derivatives were obtained. These experiments were carried out under various conditions, and results of reaction are shown in Chart 2 and detailed conditions of the experiments in Table II.

Table II. Methylation Products of Naphthyridines

Compound No.	Raw material	Method	Solvent DMSO(%)	Solvent THF(%)	Temp. (°C)	Time (hr)	Base (ratio of B^-/naphthyridines)	Yield (%)
VII	I	a	100		70	4	NaH (5.5/1)	4
VII	I	b	80	20	25	8	NaH (4/1)	1
VIII	II	a	100		70	4	NaH (5.5/1)	19
VIII	II	b	80	20	25	8	NaH (4/1)	17
VIII	II	c	100		70	2.5	*tert*-BuOK (4.5/1)	4
VIII	II	d	80	20	25	2.0	*tert*-BuOK (1.2/1)	4
IX	III	a	100		70	4	NaH (5.5/1)	6
IX	III	b	80	20	25	8	NaH (4/1)	4
IX	III	c	100		70	2.5	*tert*-BuOK (4.5/1)	0.2
IX	III	d	80	20	25	2.0	*tert*-BuOK (1.2/1)	trase

Compound No.	Apearance	mp (°C)	Picrate mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VII	colorless needles	60— 63	180—183							
VIII	colorless needles	112—113		$C_{10}H_{10}N_2$	75.92	6.37	17.71	76.36	6.24	17.63
IX	colorless needles	150—152	248—250							

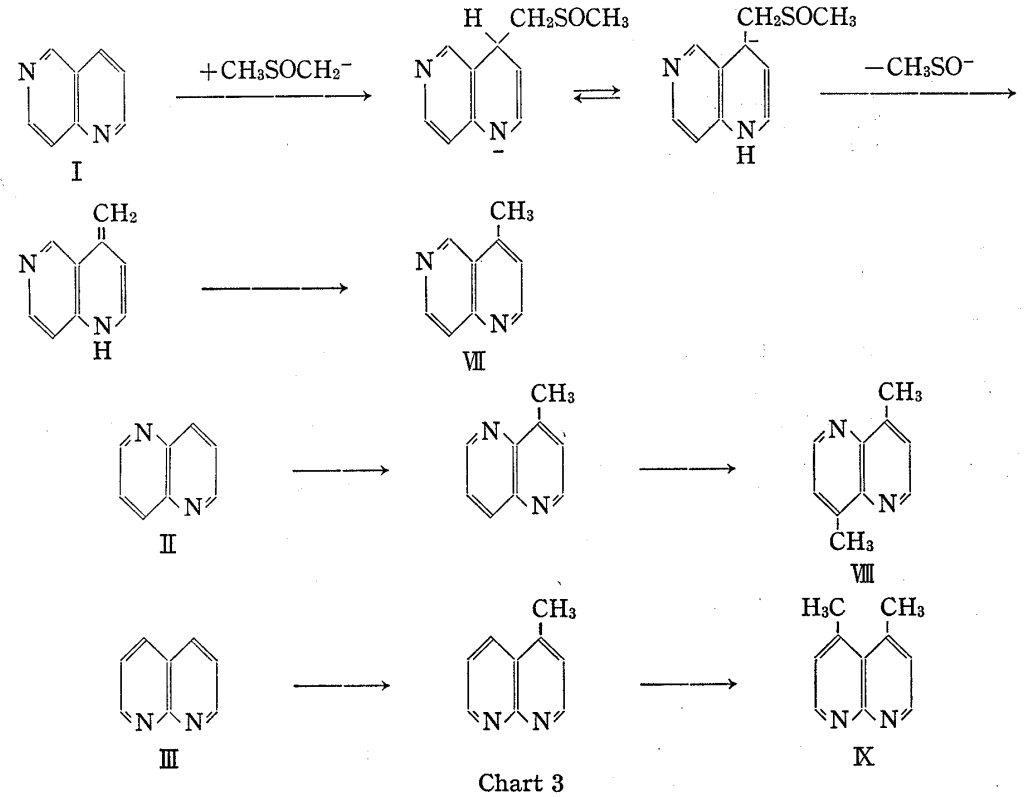
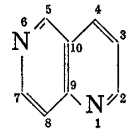
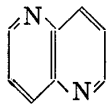


Chart 3

It will be seen from Table II that, under the conditions for methylation of II, the use of potassium *tert*-butoxide in place of sodium hydride results in decreased yield of the methylated product, while in method (b), the yield becomes the same as that in method (a) if a mixed solvent of dimethyl sulfoxide and tetrahydrofuran is used in the presence of sodium hydride. The same tendency is also seen in the case of III, but the behavior is different in the case of I where the yield of methylated product from method (b) is small. The reaction mechanism of this methylation was assumed to be as shown in the Chart 3.

In the case of anthracene, methylation with dimethyl sulfoxide gives both 9-methyl and 9,10-dimethyl derivatives in spite of the fact that the value of qr (π-electron density of r-th atom) in HMO method is the same in 9- and 10-positions.[7b] Therefore, examination of HMO method was made for the reaction of naphthyridines with $CH_3SOCH_2^-$ using the following parameters: $\alpha=\alpha+1.1\beta$ for the nitrogen and $\alpha=\alpha+0.4\beta$ for the carbon adjacent to nitrogen and $\alpha=\alpha+0.1\beta$ for carbon next but one to nitrogen. Result of this calculation agreed well with experimental result, as indicated in Table III.

Table III[a]

Compound	Reactivity indices	Position of reaction (r)									
		1	2	3	4	5	6	7	8	9	10
	qr[b]	1.339	0.894	0.967	0.794	0.888	1.283	0.964	0.946	0.953	0.972
	fr(−)[c]		0.404	0.015	0.448	0.463		0.031	0.246		
	Sr(−)[d]		2.945	1.105	3.064	3.262		1.585	2.062		
	qr	1.309	0.902	0.933	0.850	1.309	0.902	0.933	0.850	1.006	1.006
	fr(−)		0.280	0.068	0.345		0.280	0.068	0.345		
	Sr(−)		3.199	1.521	3.468		3.199	1.521	3.468		
	qr	1.325	0.901	0.962	0.798	0.798	0.962	0.901	1.325	1.057	0.971
	fr(−)		0.363	0.014	0.404	0.404	0.014	0.363			
	Sr(−)		2.734	1.099	2.841	2.841	1.099	2.734			

parameters: $\alpha_N=\alpha+1.1\beta$, $\alpha_{C_\alpha}=\alpha+0.4\beta$, $\alpha_{C_\beta}=\alpha+0.1\beta$

a) corrected and submitted on april 16, 1971
b) qr: π-electron density
c) fr(−): frontier electron density for nucleophilic substitution
d) Sr(−): superdelocalizability for nucleophilic substitution

It will be seen from this table that the reaction occurs in the position with minimum qr. In other words, the reaction should occur in 4 position in 1,6-naphthyridine, 4 and 8 positions in 1,5-naphthyridine, and 4 and 5 positions in 1,8-naphthyridine, and these agree entirely with experimental results. A complete agreement with experimental results was also observed in other reaction indices such as fr(−) (frontier electron density of r-th atom) and Sr(−) (superdelocalizability of r-th atom) except 1,6-naphthyridine.

These experiments reveal that naphthyridine derivatives can be synthesized in a satisfactory yield by the application of sulfo-mix or sodium *m*-nitrobenzenesulfonate in the Skraup reaction, and that methylation of naphthyridines with dimethyl sulfoxide in the presence of a base shows different reactivity in 1,5- and 1,8-naphthyridines from that of anthracene or from that of 1,6-naphthyridine. These experimental results agreed well with the data calculated by the HMO method.

Experimental

1,8-Naphthyridine (III)——A mixture of 82 g of H_2SO_4 and 35 g of sodium *m*-nitrobenzenesulfonate was chilled to 0—5°, 25 ml of anhyd. glycerol was added, followed by 7.5 g (0.08 mole) of 2-aminopyridine and 45 ml of H_2O, and the mixture was stirred at 135° for 4 hr. The reaction mixture was basified with

NaOH and extracted with $CHCl_3$. The extract was dried over $MgSO_4$, the solvent was evaporated, and the residue was recrystallized from cyclohexane to crystals of mp 95—97°. Picrate: Colorless plates, mp 207—208°, yield 4.7 g. This product was found to agree in IR and NMR spectra with III, synthesized by the route reported in literature,[5b] and its picrate by mixed mp.

2-Methyl-1,8-naphthyridine (IV)——The same route of synthesis as for III was carried out using 4.3 g (0.04 mole) of 2-amino-6-methylpyridine, and 1.6 g of colorless fluffy crystals, mp 95—97°, was obtained. This was also identified with IV, synthesized by the route reported in lieterature,[5b] by mixed mp, and by comparison of IR and NMR spectra.

3-Methyl-1,8-naphthyridine (V)——The same route of synthesis as for III was carried out using 4.3 g (0.04 mole) of 2-amino-5-methylpyridine and 3.0 g of colorless prisms, mp 117—118°, was obtained. This was identified with V, synthesized by the reported method,[5c] by mixed mp, and by comparison of IR and NMR spectra.

4-Methyl-1,8-naphthyridine (VI)——The same route of synthesis as for III was carried out using 4.3 g (0.04 mole) of 2-amino-4-methylpyridine, and 2.0 g of colorless oil (picrate, mp 202—204°) was obtained. This picrate was identified with the picrate of VI, synthesized by the reported method,[5b] through mixed mp and comparison of IR and NMR spectra.

1,6-Naphthyridine (I)——The same synthesis as for III was carried out using 7.5 g (0.08 mole) of 4-aminopyridine, and 1.5 g of colorless prisms, mp 29—31°, was obtained. Picrate, mp 219—220°. This substance and its picrate were identified with I, synthesized by the reported procedure,[5a] and its picrate by mixed mp and by comparison of their IR and NMR spectra.

Methylation With Methylsulfinyl Carbanion ($CH_3SOCH_2^-$)——Method (a): A solution of 1.32 g (0.055 mole) of NaH dissolved in 50 ml of Me_2SO at 70° in N_2 stream, added with 1.3 g (0.01 mole) of one of naphthyridines was stirred at 70° for 4 hr. To this reaction mixture, 50 ml of H_2O was added and the diluted mixture was poured into 750 ml of H_2O. The aqueous solution was extracted with $CHCl_3$, the extract was dried over $MgSO_4$, and the solvent was evaporated. The residue was dissolved in ether, passed through an Al_2O_3 column, and each effluent fraction was recrystallized from ether.

Method (b): To a solution of 0.75 g (0.031 mole) of NaH dissolved in 10.7 ml of Me_2SO maintained in N_2 stream, a mixture of 12.1 ml of Me_2SO containing 1 g (0.0077 mole) of one of naphthyridines and 5.7 ml of tetrahydrofuran was added at 25° during 5 min, and the mixture was stirred vigorously at the same temperature for 8 hr. The reaction mixture was poured into 300 ml of H_2O and subsequently treated as in method (a).

Method (c): To a solution of 3.9 g (0.035 mole) of *tert*-BuOK dissolved in 75 ml of Me_2SO at 70° in N_2 stream, a warm solution of 1 g (0.0077 mole) of one of naphthyridines dissolved in 75 ml of Me_2SO was added, and the mixture was stirred at 70° for 2.5 hr. The reaction mixture was poured into 1 l of H_2O and subsequently treated as in method (a).

Method (d): To a solution of 1 g (0.009 mole) of *tert*-BuOK dissolved in 75 ml of Me_2SO at 70° in N_2 stream, a warm solution of 1 g (0.0077 mole) of one of naphthyridines dissolved in 75 ml of Me_2SO was added and the mixture was stirred at 70° for 2 hr. The reaction mixture was diluted with 50 ml of H_2O and then poured into 1.5 l of H_2O. This was subsequently treated as in method (a).

4-Methyl-1,6-naphthyridine (VII)——Methylation of I was carried out under the conditions of methods (a) and (b), and VII was obtained as shown in Table II. This was identified with VII, synthesized by the route reported in literature,[8] by mixed mp, and by comparison of IR and NMR spectra.

4,8-Dimethyl-1,5-naphthyridine (VIII)——Methylation of II was carried out under the conditions of methods (a), (b), (c), and (d), and VIII was obtained as shown in Table II. IR ν_{max}^{KBr} cm^{-1}: 2920, 1440 (CH_3), 1580 (C=N). NMR (in $CDCl_3$) δ: 8.81 (2H, doublet, J=4.2 cps, C_2-H, C_6-H), 7.43 (2H, doublet, J=4.2 cps, C_3-H, C_7-H), 2.83 (3H, singlet, CH_3). Mass Spectrum *m/e*: 158 (M^+), 143 (M^+-CH_3), 130 (M^+-28). Therefore, VIII was proved to be 4,8-dimethyl-1,8-naphthyridine.

4,5-Dimethyl-1,8-naphthyridine (IX)——Methylation of III was carried out under the conditions of method (a), (b), (c), and (d), and IX was obtained as shown in Table II. This was identified with IX, synthesized by the route reported in literature,[5c] by mixed mp, and by comparison of IR and NMR spectra.

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