[Chem. Pharm. Bull. 18(5)1026—1033(1970)]

UDC 547.834.2.04 : 546.322.67.04

Syntheses of Nitrogen-containing Heterocyclic Compounds. XV.[1] The Reissert Reaction of 1,6-Naphthyridine

Yoshiki Hamada, Isao Takeuchi, and Hideko Matsuoka

Faculty of Pharmacy, Meijo University[2]

(Received October 13, 1969)

(1) By the application of potassium cyanide and the corresponding acyl chloride to 1,6-naphthyridine (II) in methylene chloride–water or in aqueous solvent, Reissert compounds (V—VII) were obtained. Reaction of II with potassium cyanide and benzoyl chloride afforded a Reissert compound (VIII) not possessing a cyano group.

(2) Application of benzenesulfonyl chloride or methylsulfonyl chloride and potassium cyanide to II afforded desulfonylated compound (IV) in either case.

(3) Reaction of II with potassium cyanide and N,N-diphenylcarbamoyl chloride gave IX.

Structure of these Reissert compounds (IV to IX) was examined through nuclear magnetic resonance and ultraviolet spectra, and their antibacterial activity was tested.

One of the authors (Y. Hamada)[3] has already reported on the reaction for the preparation of the Reissert compounds, which are increasingly being used for the syntheses of various heterocyclic compounds.[4] We showed that the Reissert reaction of 3-bromo-, and 4-, 5-, and 8-chloro-quinolines in aqueous medium afforded the Reissert compound of dehalogenated quinoline, 1-benzoyl-1,2-dihydroquinaldonitrile[3a] (I). Later, Popp and others[5] used methylene chloride–water as the solvent, and the Reissert compound of 3-bromo, and 4-chloroquinoline obtained. In addition, they were able to obtain Reissert compounds of heterocyclic compounds, such as various quinolines and isoquinolines, which could not be obtained by the reaction in aqueous solvent.[6]

We first attempts that the Reissert reaction of 5-chloroquinoline by the method of Popp and others[5a] afforded dehalogenated I in a high yield. We are interested in use of methylene chloride–water as solvent.

There has not been any report on the Reissert reaction of naphthyridines and, as the first attempt in this series of compounds, 1,6-naphthyridine (II) was taken up because it has the chemical properties of both quinoline and isoquinoline, and is also interesting as a pharmaceutic.[7] Attempts were made to synthesize the following three types, A, B, and C, accord-

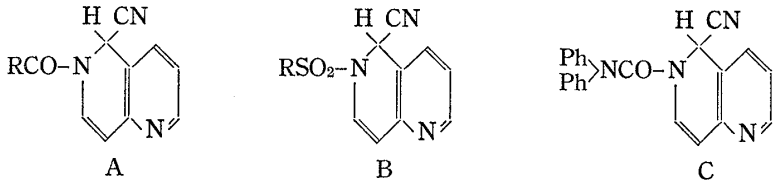


Chart 1

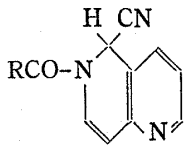
1) Part XIV: T. Takahashi, Y. Hamada, and Y. Ito, *Chem. Pharm. Bull.* (Tokyo), **17**, 2250 (1969).
2) Location: *Yagoto-Urayama, Tempaku-cho, Showa-ku, Nagoya, 468, Japan.*
3) *a*) T. Takahashi, J. Okada, and Y. Hamada, *Yakugaku Zasshi*, **77**, 1243 (1957); *b*) Y. Hamada, *ibid.*, **80**, 1573 (1960).
4) W.E. McEwen and R.L. Cobb, *Chem. Rev.*, **55**, 511 (1955); L.R. Walters, E.G. Podrebac, and W.E. McEwen, *J. Org. Chem.*, **26**, 1161 (1961).
5) *a*) F.D. Popp, W. Blount, and P. Melvin, *J. Org. Chem.*, **26**, 4930 (1961); *b*) F.D. Popp and A. Soto, *J. Chem. Soc.*, **1963**, 1760.
6) A.R. Katritzky and A.J. Boulton, *Advan. Heterocyclic Chem.*, **9**, 1 (1968).
7) T. Takahashi, Y. Hamada, I. Takeuchi, and H. Matuoka, *Yakugaku Zasshi*, **89**, 1260 (1969).

ing to the reagent used. II has two nitrogens, at 1- and 6-positions, but from the chemistry of quinolines,[8] it was assumed that the reaction would occur at the nitrogen in 6-position.

The structure of these compounds was determined by nuclear magnetic resonance (NMR) spectral measurements. Substances synthesized were examined for antibacterial and plant physiological actions. The Reissert reaction of 1,6-naphthyridine 6-oxide[7,9] (III) produced 1,6-naphthyridine-5-carbonitrile (IV).

Comparative examination was made on the synthesis of A-type compounds by using either methylene chloride–water or water as a solvent. Application of potassium cyanide and acetyl, propionyl, or butyryl chloride to II afforded the Reissert compounds (V to VII), results of which are summarized in Table I.

TABLE I



Compd. No.	RCOCl R	Base	Method	Yield (%)	mp (°C)	Appearance	Formula
V	CH_3	II	a	10.4	133—135	colorless prisms	$C_{11}H_9ON_3$
			b	1.3			
VI	C_2H_5	II	a	2.4	99—102	white needles	$C_{12}H_{11}ON_3$
			b	0.6			
VII	C_3H_7	II	a	5.7	113—115	pale yellow prisms	$C_{13}H_{13}ON_3$
			b	4.6			

	Analysis (%) Calcd. C	H	N	Found C	H	N	UV $\lambda_{max}^{95\%EtOH}$ mμ (log ε)	IR ν_{max}^{KBr} cm^{-1} (C≡N)	(CO—N<)	MS (m/e)
V	66.32	4.55	21.10	66.27	4.45	21.32	221.5 (3.96) 305.5 (4.04)	2240	1676	199 (M^+) 155 130
VI	67.59	5.20	19.71	67.51	4.95	19.26	222 (3.96) 307 (4.04)	2250	1674	213 (M^+) 155 130
VII	68.70	5.77	18.49	69.08	5.81	18.69	221 (3.95) 306 (4.01)	2240	1670	227 (M^+) 155 130

a: CH_2Cl_2–water method b: water method

It will be seen from Table I that the yield is poor when R is ethyl, compared to that when R is methyl or propyl. Also, the yield was better when methylene chloride–water was used as a solvent. The NMR spectra of V, VI, and VII showed δ values of 6.73, 6.75, and 6.72 for H–C(5), which are in higher magnetic field than that of H–C(5) (9.28 δ) in II. From this evidence and by comparison of their ultraviolet (UV) spectra with those of known Reissert compounds, the compounds V to VII were determined as the A type. The mass spectra of the compounds V to VII all showed a weak molecular ion peak and its fragments were observed at *m/e* 155 and 130 (base peak).

8) I.W. Elliott, *J. Am. Chem. Soc.*, **77**, 4409 (1955).
9) T. Kato, F. Hamaguchi, and T. Oiwa, *Chem. Pharm. Bull.* (Tokyo), **4**, 178 (1956).

Application of potassium cyanide and benzoyl chloride to II afforded a substance (VIII), mp 180—182°, which did not possess a cyano group, whose molecular formula was calculated from its elemental analytical values and mass spectrum as $C_{15}H_{10}O_2N_2$: IR ν_{max}^{KBr} 1665 cm^{-1} (CO–N=); mass spectrum, *m/e* 252 (M^+), 235 (M^+–OH). Its NMR spectrum also showed the shift of H–C(5) signal to a higher magnetic field than that of II, as in the case of above V to VII and a signal (6.65 δ) for OH to be deuterated. The UV spectrum of VIII was also similar to those of V and 2-benzoyl-1,2-dihydroisoquinoline-1-carbonitrile (XIII), that this compound was determined as 6-benzoyl-5,6-dihydro-1,6-naphthyridin-5-ol. Such formation of a compound (VIII) with a hydroxyl group in the 5-position has never been witnessed in the Reissert reaction of quinolines and isoquinolines to date and the fact is of great interest. In this case, the yield of VIII was slightly better when water was used as a solvent.

The Reissert reaction with potassium cyanide and alkyl (or aryl)sulfonyl chloride on quinoline and 6-methoxyquinoline had produced quinaldonitrile and 6-methoxyquinaldonitrile, respectively, in a low yield without giving the Reissert compounds, either with water or with methylene chloride–water as a solvent. In the case of isoquinoline, and 3-methyl- and 4-bromo-isoquinolines, the reaction in methylene chloride–water had afforded the corresponding Reissert compounds, while 7-methoxyisoquinoline gave the corresponding Reissert compound in aqueous solvent but 7-methoxyisoquinaldonitrile in methylene chloride–water solvent.[10]

Application of potassium cyanide with methylsulfonyl chloride or benzenesulfonyl chloride to II in water or methylene chloride–water solvent afforded a substance of mp 138—140°, whose molecular formula was calculated as $C_9H_5N_3$ from its elemental analytical values and mass spectrum. This substance showed no depression in the melting point on admixture with IV, synthesized earlier, and also their IR and NMR spectra were found to be identical. Consequently, this product was found to be 5-cyano-1,6-naphthyridine. Details of this reaction are shown in Table II.

It was assumed that, as the mechanism for the formation of IV, the B-type compound is unstable and undergoes decomposition to form IV, as illustrated in Chart 1. Also, Table II shows that the yield of IV with introduction of a cyano group is better when R is phenyl than

Table II $\xrightarrow[KCN]{RSO_2Cl}$ IV

Compd. No.	RSO_2Cl R	Base	Method	Yield (%)	mp (°C)	Appearance	Formula
IV	CH_3	II	a	25.2	138—140	colorless needles	$C_9H_5N_3$
			b	46.2			
IV	C_6H_5	II	a	42.0	138—140	colorless needles	
			b	71.4			

	Analysis (%)						UV $\lambda_{max}^{95\%EtOH}$ mμ (log ε)	IR λ_{max}^{KBr} cm^{-1} (C≡N)	MS (*m/e*)
	Calcd.			Found					
	C	H	N	C	H	N			
IV	69.67	3.25	27.09	70.04	2.99	26.87	218 (4.40) 279 (3.24) 314 (3.66) 322.5 (3.66)	2240	155 (M^+)

a: CH_2Cl_2–water method b: water method

10) J.M. Wefer, A. Catala, and F.D. Popp, *J. Org. Chem.*, **30**, 3075 (1965).

when methyl, and that a better result is obtained when using water than when methylene chloride–water is used. The present method[7] seems to be the best for synthesis of IV because, in the hitherto used method, IV was produced by the Reissert reaction of III[7,9] but there is no practical method for the synthesis of III. Since the compound IV has a physiological action against plants, as will be described elsewhere, the present method would be of interest for the introduction of a cyano group into 5-position of 1,6-naphthyridine.

For the Reissert reaction with potassium cyanide and N,N-diphenylcarbamoyl chloride, quinoline remains inert and the compound is recovered, while isoquinoline and phthalazine undergo the reaction in methylene chloride–water system to give the corresponding Reissert compounds.[11] The reaction of II with potassium cyanide and N,N-diphenylcarbamoyl chloride in methylene chloride–water for 22 hr gave the product (IX) in a quantitative yield. Its IR absorption maxima (in KBr) at 2250 (C≡N) and 1660 (CO–N=) cm^{-1}, and the shift of its 5H to a higher magnetic field (6.36 δ), and similarity of its UV spectrum to those of the compounds V to VII, indicated that this compound (IX) is a C type.

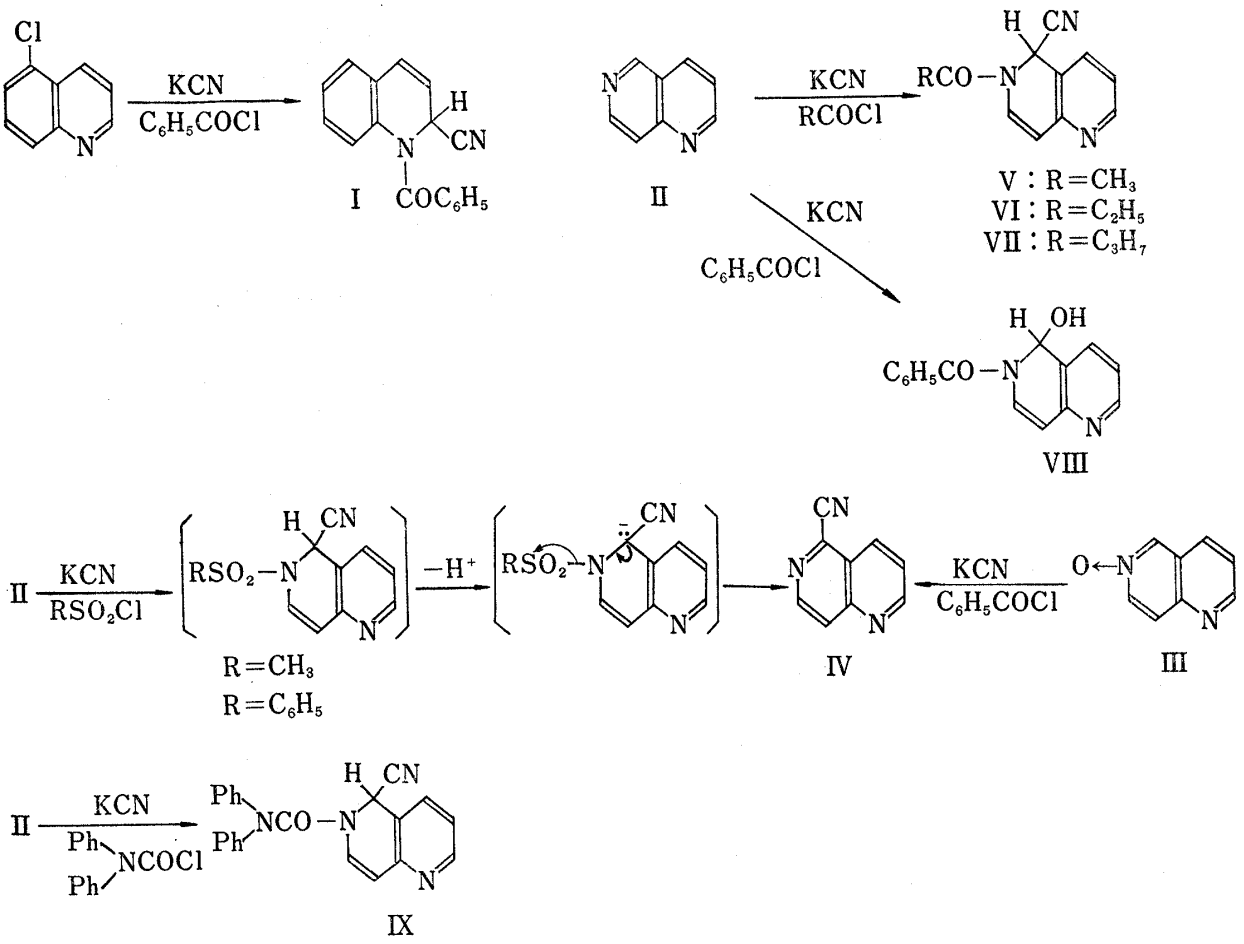


Chart 2

UV Spectra of Reissert Compounds

Acetyl, propionyl, or butyryl chloride was applied to isoquinoline by the method of Popp and others[5b] to synthesize their corresponding Reissert compounds (X, XI, XII), and these compounds were used to make comparative examination of the UV spectra of IV, V, VI, VII, VIII, and IX. Their UV spectra are given in Fig. 1—4.

11) F.D. Popp, J.M. Wefer, and A. Catala, *J. Heterocyclic Chem.*, **2**, 317 (1965).

From the comparison of these spectra, following points may be raised.

(1) From Fig. 1, it is seen that the UV spectra of the Reissert compounds, V and VIII, from II are similar to that of the Reissert compound (XIII)[12] of isoquinoline rather than that of I[13] of quinoline.

(2) From Fig. 2, comparison of the UV spectra of X and V shows that absorption spectrum is shifted to a longer wave-length region in V which has one nitrogen more than X.

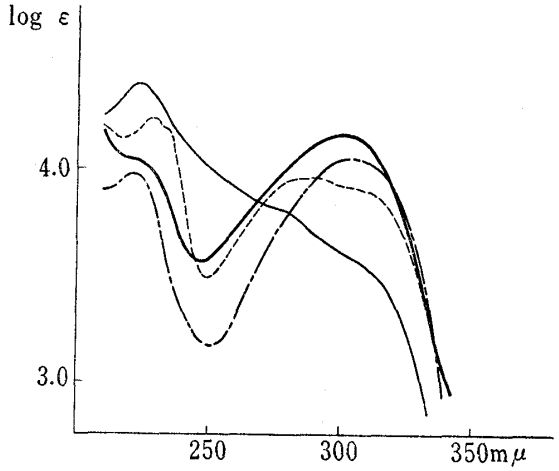


Fig. 1. Ultraviolet Absorption Spectra in 95% EtOH

—— : 6-benzoyl-5,6-dihydro-1, 6-naphthyridin-5-ol (VIII)
—— : 1-benzoyl-1,2-dihydroquinoline-2-carbonitrile (I)
-------- : 2-benzoyl-1, 2-dihydroisoquinoline-1-carbonitrile (XIII)
----- : 6-acetyl-5,6-dihydro-1,6-naphthyridine-5-carbonitrile (V)

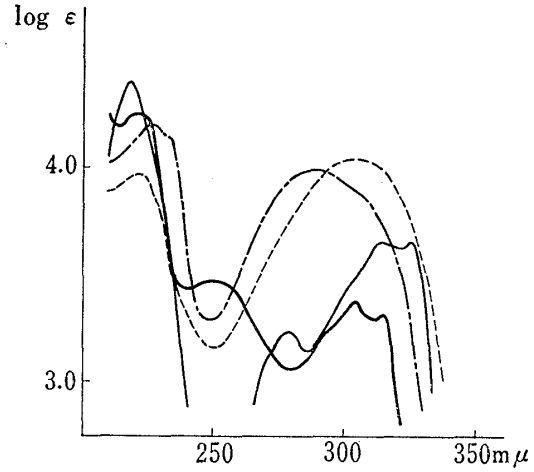


Fig. 2. Ultraviolet Absorption Spectra in 95% EtOH

—— : 1,6-naphthyridine (II)
—— : 1,6-naphthyridine-5-carbonitrile (IV)
-------- : 6-acetyl-5,6-dihydro-1,6-naphthyridine-5-carbonitrile(V)
----- : 2-acetyl-1,2-dihydroisoquinoline-1-carbonitrile (X)

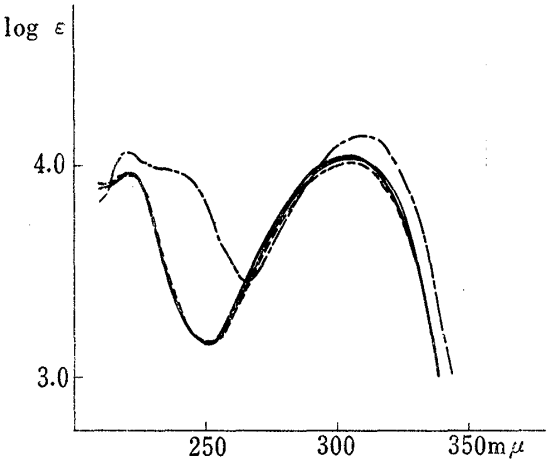


Fig. 3. Ultraviolet Absorption Spectra in 95% EtOH

—— : 6-acetyl-5,6-dihydro-1,6-naphthyridine-5-carbonitrile (V)
—— : 6-propionyl-5,6-dihydro-1,6-naphthyridine-5-carbonitrile (VI)
-------- : 6-*n*-butyryl-5,6-dihydro-1,6-naphthyridine-5-carbonitrile (VII)
----- : 5-cyano-5,6-dihydro-1,6-naphthyridin-6-yl N,N-diphenylcarbamate(IX)

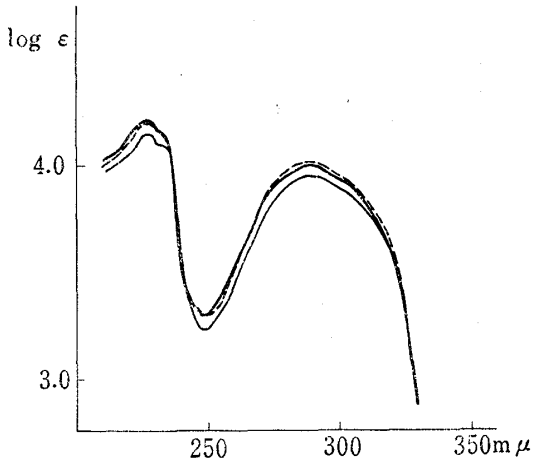


Fig. 4. Ultraviolet Absorption Spectra in 95% EtOH

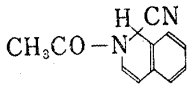
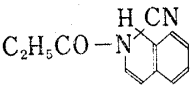
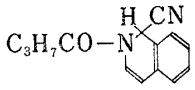
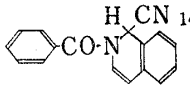
—— : 2-acetyl-1,2-dihydroisoquinoline -1-carbonitrile (X)
—— : 2-propionyl-1,2-dihydroisoquinoline 1-carbonitrile (XI)
-------- : 2-*n*-butyryl-1,2-dihydroisoquinoline-1-carbonitrile (XII)

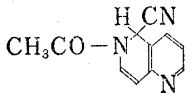
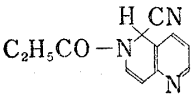
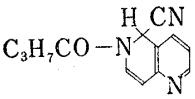
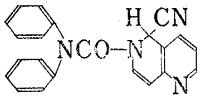
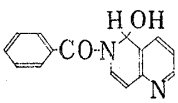
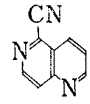
12) I.W. Elliott and Jr. R.B. McGriff, *J. Org. Chem.*, **22**, 514 (1957).
13) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, **74**, 660 (1952).

(3) From Fig. 2, comparison of the UV spectra of IV and V—VII shows that the two absorptions for 1,6-napthyridine ring becomes one in V by the bonding of RCO group with nitrogen, with concurrent shift to a shorter wave-length region and a deepening in optical density.

NMR Spectra of Reissert Compounds

Table III. NMR Spectral Data of Reissert Compounds in $CDCl_3$

Compd.	Chemical shift (δ)						Coupling constants (cps)	
	1H	3H	4H	CH_3-	$-CH_2-$	$-CH_2CO-$	$J_{1.3}$	$J_{3.4}$
	7.69	7.01	d 6.03					
	6.66	6.72	d 6.10	s 2.26				7.8
	6.68	6.76	d 6.09	t 1.22		q 2.51		8.0
	6.66	6.76	d 6.09	t 0.98	m 1.73	t 2.48		8.0
 14)	6.64	6.69	d 6.10				0.8	8.0

	2H	3H	4H	5H	7H	8H	CH_3-	$-CH_2-$	$-CH_2CO-$	$J_{2.3}$	$J_{2.4}$	$J_{3.4}$	$J_{4.8}$	$J_{5.7}$	$J_{7.8}$
 7)	q 9.10	q 7.52	m 8.28	d 9.28	q 8.76	d 7.93				4.2	1.8	8.3		1.0	6.0
	q 8.58	q 7.21	q 7.62	d 6.73	q 7.01	d 6.28	s 2.33			5.0	1.7	7.8		1.0	8.4
	q 8.59	q 7.21	q 7.63	d 6.75	q 7.06	d 6.29	t 1.25		q 2.58	5.0	1.7	7.8		1.0	8.1
	q 8.56	q 7.18	q 7.61	d 6.72	q 7.05	d 6.27	t 1.00	m 1.76	t 2.53	4.8	1.8	7.8		1.0	8.0
	q 8.49			d 6.36	q 6.73	d 5.88				5.0	1.7			1.1	8.0
 a)	q 8.52	q 7.24	q 7.77	d 6.62	q 7.13	d 6.19	-OH s 6.65	$-C_6H_5$ s 7.58		5.0	1.5	7.4		1.0	8.1
	q 9.25	q 7.75	m 8.66		q 8.90	d 8.18				4.4	1.7	8.6	1.3		5.8

a) in d_6-DMSO
s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet

14) R. Bramley and M.D. Johnson, *J. Chem. Soc.*, **1965**, 1372.

It will be seen from Table III that the NMR spectra of the Reissert compounds V to IX of II indicate the shift of H–C(5), H–C(7) and H–C(8) signals to a higher magnetic field than those in II, and that of 5H is especially marked. The signal of 1H in the Reissert compounds X, XI, and XII is also in higher magnetic field than that in isoquinoline. For the reason of this shift, the following may be considered.

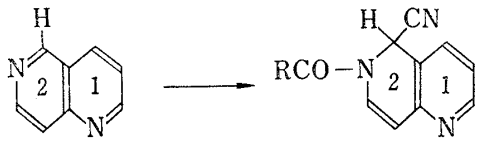


Chart 3

(1) As shown in Chart 3, the ring 2 is fundamentally an aromatic ring. Since H–C(5) (or 1H) is in the plane of the aromatic ring, it had shifted to a lower magnetic field but, in the Reissert compound, the ring 2 is not an aromatic ring and there is no anisotropic effect due to ring current that would produce a shift to the lower magnetic field.

(2) Hybridization at 5 (or 1) position has changed from sp^2 to sp^3 and the carbon has become quaternary. In general, hydrogen bonded to the sp^2 carbon exhibits a signal in a lower magnetic field than that bonded to sp^3 carbon. Further, in the Reissert compounds, hydrogen is not in the plane of the aromatic ring but is outside this plane so that the shift to a lower magnetic field by the effect of ring 1 becomes smaller and has a possibility of coming into the region of a shift to a higher magnetic field.

From these facts, it will be seen that the behavior of H–C(5) of naphthyridine (or H–C(1) of isoquinoline) is due to the above reasons (1) and (2), and that of 7H and 8H of naphthyridine to the reason (1).

From the foregoing NMR and UV spectral data, it has become clear that 1,6-naphthyridine undergoes reaction at the nitrogen atom in the 6-position, as expected, and shows both the properties of quinoline and isoquinoline, as well as the characteristic properties of 1,6-naphthyridine.

Antibacterial activities were tested on several microorganisms using the compounds IV to IX. Results of antibacterial tests showed that none of the compounds were effective below 10,000 dilution but the Reissert compounds IV to VII, IX, and X to XIII were found to inhibit the growth of plants, details of which will be given in a separate paper. The fact that the Reissert compounds show such a physiological activity evokes interest in the study of this kind of compounds in the agricultural chemical field.

Experimental

6-Acyl-5,6-dihydro-1,6-naphthyridine-5-carbonitriles (V—VII)——Method A: A solution of 0.012 mole of KCN dissolved in 2 ml of H_2O was added to a solution of 0.004 mole of 1,6-naphthyridine (II) dissolved in 5 ml of CH_2Cl_2, the mixture was stirred, and 0.008 mole of the corresponding acid chloride was added during 30 min. The mixture was further stirred for 4—6 hr and CH_2Cl_2 layer was separated. The aqueous layer was washed 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 filtered. The solvent was evaporated and the residue was washed with ether.

Method B: To a solution of 0.004 mole of II in 5 ml of H_2O, a solution of 0.012 mole of KCN dissolved in 2 ml of H_2O was added, and the mixture was treated as in method A. The residue was recrystallized from cyclohexane or EtOH. Details are shown in Table I.

Reissert Reaction of 5-Chloroquinoline——To a mixture of 1.0 g of 5-chloroquinoline, 20ml of CH_2Cl_2, 1.2 g of KCN, and 8 ml of H_2O, 1.8 g of BzCl was added during 2 hr. The reaction mixture was treated as in method A and the residue was recrystallized from cyclohexane to colorless neeldes, mp 154—155°, Yield, 1.28g (80.5%). *Anal.* Calcd. for $C_{17}H_{12}ON_2$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.18; H, 4.30; N, 10.41.

This product (I) was found to be identical with 1-benzoyl-1,2-dihydroquinoline-2-carbonitrile by admixture and IR spectral comparison.

1,6-Naphthyridine-5-carbonitrile (IV)——To a solution of 0.6 g of 1,6-naphthyridine 6-oxide and 0.5 g of KCN in 20 ml of H_2O, 0.4 g of BzCl was added during 2 hr and the mixture was stirred for further 4 hr. The precipitate was collected by filtration and recrystallized from petr. ether to colorless needles, mp 143—145°. Yield, 0.45 g (62.5%). *Anal.* Calcd. for $C_9H_5N_3$: C, 69.79; H, 3.25; N, 27.09. Found: C, 70.00; H,

3.24; N, 26.67. UV $\lambda^{95\%\ EtOH}$ mμ (log ε): 218 (4.40), 279 (3.24), 314 (3.66), 325.5 (3.66). IR ν_{max}^{KBr} cm^{-1}: 2240 (C≡N). Mass spectrum *m/e*: 155 (M^+).

Reaction of II with Methylsulfonyl Chloride and Benzenesulfonyl Chloride——(1) To a mixture of 1.0 g of II, 10 ml of CH_2Cl_2, 1.5 g of KCN, and 4 ml of H_2O, 1.76 g of $MeSO_2Cl$ or 2.8 g of $PhSO_2Cl$ was added during 0.5 or 2 hr, and the reaction mixture was treated as in method A.

2) To a mixture of 1.0 g of II, 14 ml of H_2O, and 1.5 g of KCN, 1.76 g of $MeSO_2Cl$ or 2.8 g of $PhSO_2Cl$ was added during 0.5 or 2 hr, and the reaction mixture was treated as in method B. The residual product was recrystallized from cyclohexane and identified with IV by admixture and IR spectral comparison. Details are given in Table II.

6-Benzoyl-5,6-dihydro-1,6-naphthyridine-5-ol (VIII)——1) To a mixture of 1.0 g of II, 10 ml of CH_2Cl_2, 1.6 g of KCN, and 4 ml of H_2O, 2.2 g of BzCl was added during 2 hr, and the reaction mixture was treated as in method A. Recrystallization of the residual product afforded colorless needles, mp 180—182°. Yield, 1.2 g (60.6%).

2) To a mixture of 1.0 g of II, 1.6 g of KCN, and 14 ml of H_2O, 2.2 g of BzCl was added during 2 hr, and the reaction mixture was treated as in method B. Recrystallization of the product from EtOH gave colorless needles, mp 180—182°. Yield, 1.4 g (70.7%). *Anal.* Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.75; H, 4.37; N, 11.18. UV $\lambda^{95\%\ EtOH}$ mμ (log ε): 302 (4.17). IR ν_{max}^{KBr} cm^{-1}: 1665 (CO–N=). Mass Spectrum *m/e*: 252 (M^+), 235 (M^+–OH), 144 (M^+–C_6H_5CO).

5-Cyano-5,6-dihydro-1,6-naphthyridin-6-yl-N,N-diphenylcarbamate (IX)——To a solution of 0.5 g of II, 9.5 ml of CH_2Cl_2, and 0.77 g of KCN in 4 ml of H_2O, 3.6 g of Ph_2NCOCl was added during 2 hr and reacted for 22 hr. The reaction mixture was treated as in method A and the product was recrystallized from EtOH to colorless needles, mp 233—236°. Yield, 1.0 g (74.1%). *Anal.* Calcd. for $C_{22}H_{16}ON_4$: C, 74.98; H, 4.58; N, 15.90. Found: C, 75.36; H, 4.51; N, 15.59. UV $\lambda^{95\%\ EtOH}$ mμ (log ε): 220.5 (4.06), 311 (4.13). IR ν_{max}^{KBr} cm^{-1}: 2250 (C≡N), 1660 (CO–N=).

Acknowledgement The authors are grateful to Mr. N. Sato of the Central Research Laboratory, Yamanouchi Pharmaceutical company, for the antibacterial tests and to the Analysis Center of the Meijo University for elemental analyses.

15) Appasatus for direct insertion of the sample was used.