[Chem. Pharm. Bull. 18(6)1228—1232(1970)]

UDC 547.852.2.04 : 547.852.3.07

Studies on Pyridazines. XIV.[1] Syntheses of 3,3′-Bipyridazines[2]

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(Received January 14, 1970)

3-Halogenopyridazines (I) were alloued to react with hydrazine hydrate in the presence of Pd–$CaCO_3$ and alkali to afford the symmetrical 3,3′-bipyridazines (IIa—IIg). When an equimolar mixture of two kinds of 3-chloropyridazines of different substituents was subjected to this condensation reaction, the unsymmetrical 3,3′-bipyridazines (VIIa—VIId) were formed. Various 3-chloropyridazine N-oxides (X) were subjected to the condensation reaction and the expected 3,3′-bipyridazine di-N-oxides (XI) were obtained in low yields.

Many studies have been reported on the syntheses and the properties of the ring assemblies of aza-aromatic compounds such as bipyridines and biquinolines. Of them, the compounds having ferroin group (–N=C–C=N–) in their molecules are known to form the chelate compounds with metals.[4]

As for bipyridazines, several compounds, in which the pyridazine rings are bonded together by C–N or C–C linkage, are known, but all these compounds have at least one pyridazone ring as their components.[5] Recently, Lafferty[6] reported that 3,3′-bipyridazine was obtained by refluxing pyridazine (Ia) with Pd–charcoal in 10% yield. But the application of Lafferty's method to the substituted pyridazines was unsuccessful.

In the meanwhile, our interest in the syntheses of pyridazine derivatives led to find out a general method for the syntheses of 3,3′-bipyridazine derivatives (IIa—IIg, VIIa—VIId), a part of which was outlined in a preliminary communication.[7] The present paper describes full details of this work.

Symmetrical 3,3′-Bipyridazines

Various 3-halogenopyridazines (Ia—Ig) were allowed to react with hydrazine hydrate in 5% methanolic potassium or sodium hydroxide in the presence of Pd–$CaCO_3$ under vigorous stirring at room temperature, to afford the corresponding symmetrical 3,3′-bipyridazine (IIa—IIg) in moderate yields (20—50%), respectively. In this reaction, the monomeric compounds, in which halogen atom of the starting material was replaced by alkoxyl groups (IIIa—IIIg) or hydrogen atoms (IVa—IVg), were formed[8] as by-products in every case.

1) Part XIII: H. Igeta, T. Tsuchiya, and T. Nakai, *Tetrahedron Letters*, **1969**, 2667.
2) This work was presented at the 2nd Symposium of Chemistry on Heterocyclic Compounds, Nagasaki, Novermber 1969.
3) Location: *Hatanodai, Shinagawa-ku, Tokyo.*
4) F. Blau, *Monatsh.*, **19**, 647 (1898); F. Case, *J. Heterocyclic Chem.*, **5**, 223 (1968).
5) J. Druey, K. Meier, and K. Eischenberger, *Helv. Chim. Acta*, **37**, 121 (1954); H. Feuer and H. Rubinstein, *J. Org. Chem.*, **24**, 811 (1959); P. Coad and R.A. Coad, *ibid*, **28**, 1919 (1963); T. Kauffmann and A. Risberg, *Tetrahedron Letters*, **1963**, 1459.
6) J.J. Lafferty and F.H. Case, *J. Org. Chem.*, **32**, 1591 (1967).
7) H. Igeta, T. Tsuchiya, M. Nakajima, and H. Yokogawa, *Tetrahedron Letters*, **1969**, 2359.
8) R.H. Mizzoni and P.E. Spoerri, *J. Am. Chem. Soc.*, **73**, 1873 (1951); T. Itai and H. Igeta, *Yakugaku Zasshi*, **74**, 1195 (1954); O. Poppenberg, *Chem. Ber.*, **34**, 3257 (1901); N. Clauson-Kass and F. Linborg, *Acta. Chem. Scand.*, **1**, 619 (1947); K. Kumagai, *Nippon Kagaku Zasshi*, **81**, 489 (1960); W.G. Overend, L.M. Turton, and L.F. Wiggins, *J. Chem. Soc.*, **1950**, 3500; E.A. Steck, R.P. Brundage, and L.T. Fletcher, *J. Am. Chem. Soc.*, **76**, 3225 (1954).

The yields of the dimeric compounds (II) depended on the nature of solvent used and also of the halogen atom. Use of EtOH instead of MeOH, and use of the chloro compound in place of the bromo compound, led to the better yields.

In the case of 4-substituted-3-halogenopyridazines such as 4-methyl-3-chloropyridazine, the expected dimeric compound was not obtained under these conditions, which means the present method may not be available when such steric hindrance is considered.

Dimeric nature of these compounds are confirmed from the acceptable elemental analyses, molecular weight determination by mass spectrometry, and also nuclear magnetic resonance (NMR) spectral data.

As seen from the Table, symmetric arrangements of these dimeric compounds to the newly formed C–C bond are obvious from the simple pattern of each NMR spectrum.

Thus, only three sets of signals with equal intensity centered at 8.84, 7.66, and 9.29 δ are observed in the spectrum of IIa, while the spectra of IIb and IIc showed only two sets of

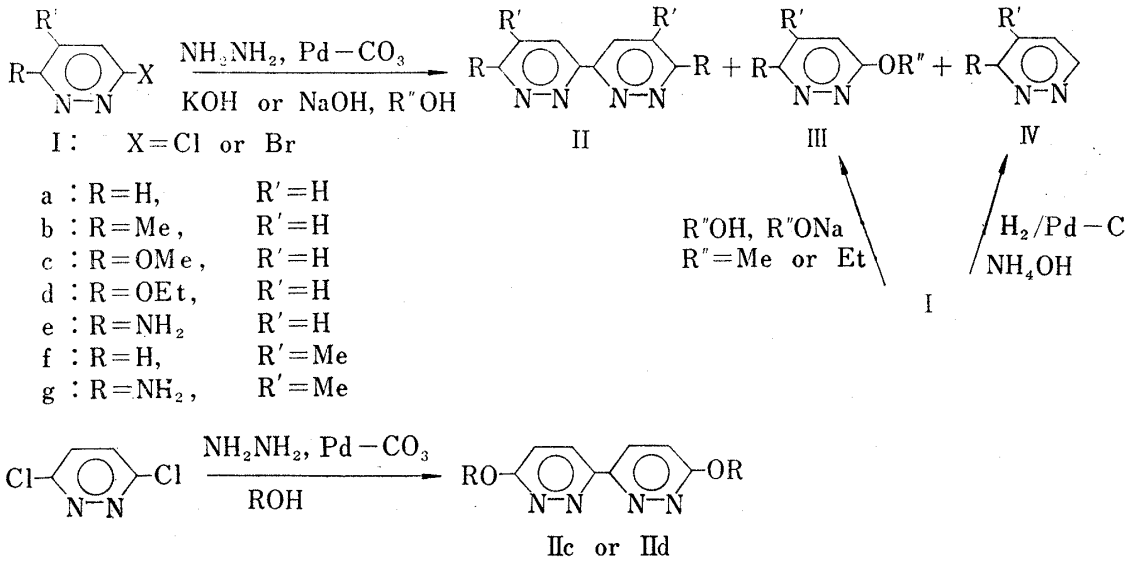


Chart 1

TABLE I. Spectral Data for Compounds (II)

	NMR[a] δ			NMR[a] cps					UV λ_{max}^{EtOH} mμ (log ε)
	$H_{4,4'}$	$H_{5,5'}$	$H_{6,6'}$	$J_{4,5}$	$J_{5,6}$	$J_{4,6}$			
IIa	8.84	7.66	9.29	9.2	6.0	1.5			234 (3.60) 261 (3.26)
IIb	8.69	7.50	—	9.2	—	—	$-CH_3$:	2.80	241 (3.80) 267 (3.51)
IIc	8.60	7.10	—	9.2	—	—	$-OCH_3$:	4.19	239 (3.42) 263 (3.12)
IId	8.50	6.99	—	9.2	—	—	$-O\underline{CH_2}\underline{CH_3}$[a]:	4.58	252 (3.08)
							[a] [b] [b]:	1.49	278 (3.75)
IIf	8.60	—	9.08	—	—	1.2	$-CH_3$:	4.49	239 (3.35) 263 (3.05)
IIg[b]	7.92	—	—	—	—	—	$-CH_3$:	2.05	282 (3.26)
							$-NH_2$:	6.18	

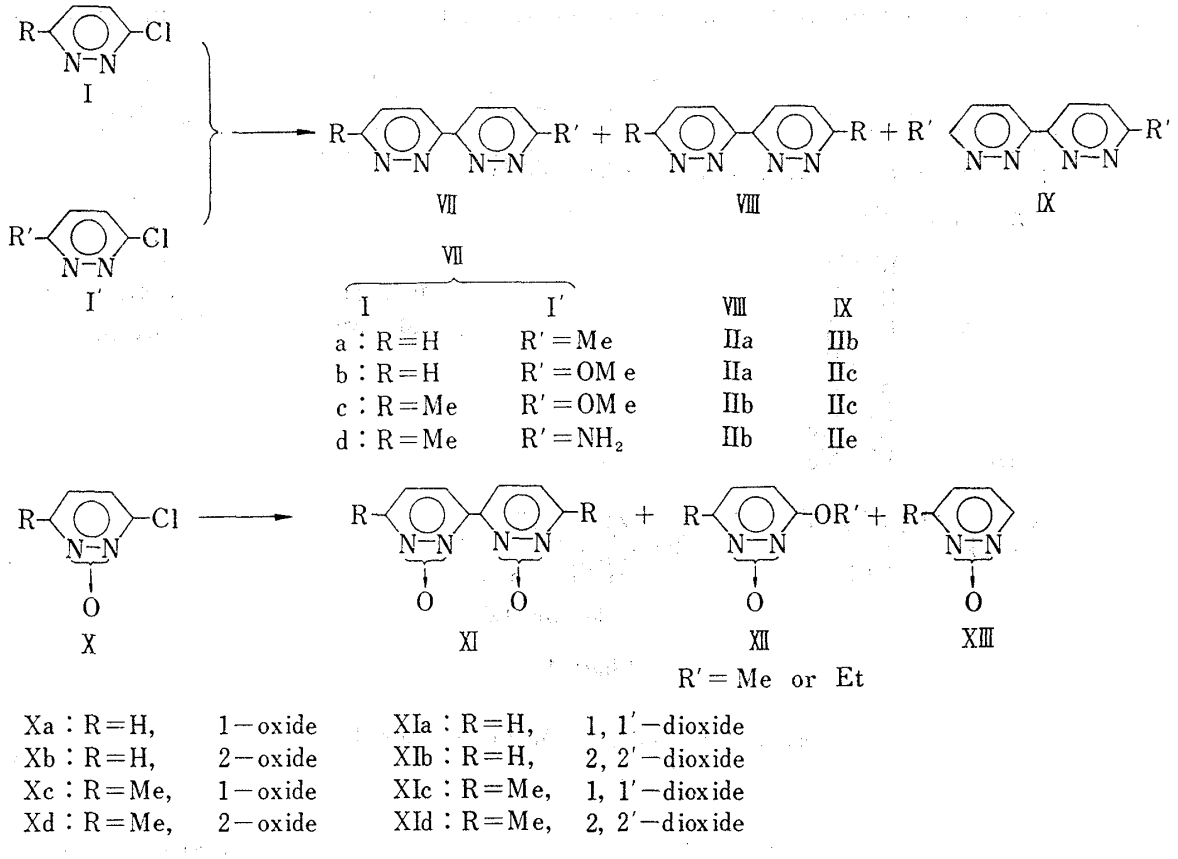
a) 60 Mc in $CDCl_3$ with TMS as internal reference
b) DMSO-d_6

signals at around 8.7—8.6 and 7.5—7.1 δ and that of IIe showed them at 8.6 and 9.1 δ due to the ring protons. Since pyridazine shows two sets of signals ($H_{3,6}$: 9.21 and $H_{4,5}$: 7.50 δ[9]), the signals at arround 9.3—9.1 and 7.7—7.1 δ in these spectra are assigned to H_6 and H_5 respectively.

The assignment of the signals as above are also supported from the magnitudes of the coupling constants among each signal (Table I), since these values are approximately coincident with those of pyridazines and their N-oxides.[9]

Unsymmetrical 3,3'-Bipyridazines

When an equimolar mixture of two kinds of 3-chloropyridazines with different substituents was subjected to this condensation reaction, the unsymmetrical 3,3'-bipyridazines (VII) were formed, accompanied by two kinds of the symmetrical dimers (VIII and IX). In all cases,



Xa : R=H, 1-oxide
Xb : R=H, 2-oxide
Xc : R=Me, 1-oxide
Xd : R=Me, 2-oxide

XIa : R=H, 1, 1'-dioxide
XIb : R=H, 2, 2'-dioxide
XIc : R=Me, 1, 1'-dioxide
XId : R=Me, 2, 2'-dioxide

Chart 2

Table II. NMR Spectral Data for Compounds (VII)[a]

VII			H_4	H_5	H_6	$H_{4'}$	$H_{5'}$	$H_{6'}$		
a	R=H,	R'=Me	8.82	7.64	9.24	8.69	7.49	—	$-CH_3$	2.79
b	R=H,	R'=OMe	8.84	7.64	9.25	8.61	7.08	—	$-OCH_3$	4.18
c	R=Me,	R'=OMe	8.66	7.31	—	8.55	7.09	—	$-CH_3$	2.78
									$-OCH_3$	4.19

a) 60 Mc in $CDCl_3$ with TMS as internal reference
Values of chemical shift are indicated by ppm.

9) K. Tori, M. Ogata, and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 235 (1963); K. Tori and M. Ogata, *ibid.*, **12**, 272 (1964).

the symmetrical dimer (VIII, IX) were main products and the unsymmetrical dimers (VII) were usually obtained in relatively low yields (3—5%), and the total yields were 30—40%.

While NMR spectra of the symmetrical dimers show the simple patterns due to the symmetrical structures, those of the unsymmetrical dimers exhibit the overlapped patterns of the corresponding two kinds of the symmetrical dimers, which support the correctness of the structures of the dimers (Table II).

3,3′-Bipyridazine Di-N-oxides

Various 3-chloropyridazine N-oxides (X) were subjected to this condensation reaction and the expected 3,3′-bipyridazine di-N-oxides (XI) were obtained in low yields (2—3%). In all cases, the monomeric alkoxypyridazine N-oxides (XII)[10] were obtained as main products, along with the compounds (XIII),[10] in which the halogen atom of the starting material was replaced by hydrogen atom.

3,3′-Bipyridazine Chelates

Most of these 3,3′-bipyridazines thus obtained form the chelate compounds with Fe^{II}, producing red colour. The analytical chemical study on these chelate compounds is to be reported separately in a following paper.

Experimental

General Procedure for the Syntheses of 3,3′-Bipyridazines——To a mixture of 5 g of 3-halogenopyridazine and 5 g of Pd–$CaCO_3$, 100 ml of 5% methanolic or ethanolic KOH or NaOH solution was added, and then 4 ml of 80% hydrazine hydrate solution was added dropwise under vigorous stirring at room temperature. Stirring was continued for further 6 hr, and the catalyst was removed by filtration. The filtrate was evaporated to dryness *in vacuo*, and the residue was subjected to separation and purification.

Symmetrical 3,3′-Bipyridazines, IIa, IIb, IIc, IId and IIf——According to the general procedure as mentioned above, the reaction was carried out. The residue was extracted with CH_2Cl_2 and the CH_2Cl_2 layer

Table III

	Yield (%)	mp (°C) (decomp.)	Recryst. solv.	Formula	Analyses (%) Calcd. C	H	N	Found C	H	N
Compounds (II)										
IIa	40—50	227—228	AcOEt	$C_8H_6N_4$	60.75	3.82	35.43	61.07	4.16	35.21
IIb	50—60	234—235	AcOEt	$C_{10}H_{10}N_4$	64.50	5.41	30.09	64.53	5.41	29.84
IIc	30—40	237—238	MeOH	$C_{10}H_{10}O_2N_4$	55.04	4.62	25.68	55.43	4.79	25.52
IId	25—30	206—207	AcOEt	$C_{12}H_{14}O_2N_4$	58.52	5.73	22.75	58.48	5.80	22.51
IIe	20—30	*ca.* 320	MeOH	$C_8H_8N_6$	51.05	4.28	44.66	51.09	4.42	44.36
IIf	40—50	163—164	AcOEt	$C_{10}H_{10}N_4$	64.50	5.41	30.09	64.72	5.37	30.05
IIg	20—30	>300	MeOH	$C_{10}H_{12}N_6$	55.54	5.59	38.87	55.66	5.51	38.67
Compounds (VII)										
VIIa	4—5	228—230	benzene	$C_9H_8N_4$	62.77	4.68	32.54	62.70	4.83	32.44
VIIb	3—4	134—135	AcOEt	$C_9H_8ON_4$	57.44	4.29	29.77	57.41	4.35	29.88
VIIc	3—4	174—175	AcOEt	$C_{10}H_{10}ON_4$	59.39	4.98	27.71	59.69	5.12	27.52
VIId	*ca.* 2	247—248	MeOH	$C_9H_9N_5$	57.74	4.85	37.41	57.68	4.55	37.38
Compounds (XI)										
XIa	3—4	328	MeOH	$C_8H_6O_2N_4$	50.53	3.18	29.47	50.14	3.15	29.20
XIb	1—2	318—320	MeOH	$C_8H_6O_2N_4$	50.53	3.18	29.47	50.79	3.13	29.08
XIc	2—3	293—294	MeOH–AcOEt	$C_{10}H_{10}O_2N_4$	55.04	4.62	25.68	55.44	4.66	25.46
XId	1—2	252—254	MeOH–AcOEt	$C_{10}H_{10}O_2N_4$	55.04	4.62	25.68	55.23	4.61	25.70

10) H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **7**, 938 (1959); M. Yanai, T. Kuraishi, and T. Kinoshita, *Yakugaku Zasshi*, **81**, 708 (1961); T. Nakagome, *Yakugaku Zasshi*, **81**, 1048 (1961); K. Kumagai, *Nippon Kagaku Zasshi*, **81**, 1148 (1960); M. Ogata and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 29, 35 (1963).

was washed with water and dried on Na_2SO_4. After removal of the solvent, the residue was dissolved in benzene and was passed through a column of alumina. After elution of the monomeric compounds (III and IV) with benzene, the column was again eluted with benzene or benzene–CH_2Cl_2 (1;:1) and the eluate was evaporated to afford the dimer.

IIe and IIg——The residue of the reaction was washed with water and a small amount of MeOH, and then recrystallized from MeOH. In these cases, the monomers (III and IV) were obtained from the washings and the mother liquor of the recrystallization (Table III).

Unsymmetrical 3,3′-Bipyridazines (VII)——The residue obtained according to the method described for IIa, was dissolved in benzene and passed through a column of alumina. The elution orders were IIb, VIIa, IIa in the case of a series, IIc, VIIb, IIa in b, IIb, VIIc, IIc in c, and IIb, VIId in d series, respectively. Since IIe was not soluble in CH_2Cl_2, the crude residue was washed with water and then recrystallized from MeOH (Table III).

3,3′-Bipyridazine Di-N-oxides (XI)——The residue obtained according to the general procedure, was washed with water and then extrated with CH_2Cl_2. The materials insoluble in CH_2Cl_2 were recrystallized from EtOH to give XI. From the CH_2Cl_2 extract, XII and XIII were obtained separately by column chromatography on alumina (Table III).

Acknowledgement The authors wish to express their deep appreciation to Mrs. Y. Ishiguro and Miss T. Kihara for elemental microanalyses, to Miss F. Suzuki for measurements of NMR spectra.