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SYNTHESES OF 3,3'-BIPYRIDAZINE DERIVATIVES[1]

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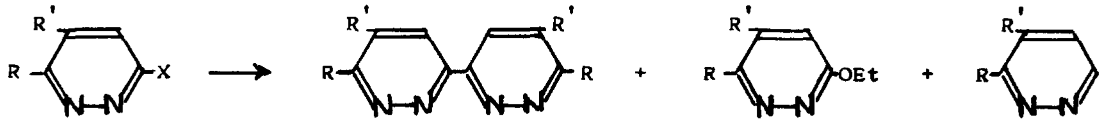
The studies on the syntheses and the properties of ring assemblies of aza-aromatic compounds have been carried out by many workers. But, so far as we are aware, very few dimeric compounds[2] of pyridazine derivatives are known and all these compounds have at least one 3-pyridazone ring as their components.

Our interest in the syntheses of pyridazine derivatives led to find out a general method for the synthesis of 3,3'-bipyridazine derivatives (II), whose synthesis has not been reported as yet.

3-Halogenopyridazine derivatives (I) were reacted with hydrazine hydrate for 5-12 hrs. at room temperature in 5% ethanolic sodium or pottasium hydroxide solution in the presence of Pd-CaCO$_3$[3] under vigorous stirring.[4] After removal of the catalyzer, the solvent was evaporated to dryness under reduced pressure, and the residue was purified either by recrystallization from an appropriate solvent or by column chromatography over alumina.



I　　II　　III　　IV

X : Cl or Br

The products (II_{a-e}) obtained from corresponding monomeric 3-chloropyridazines are shown in Table I.

When 3-bromopyridazines are used, the yields of the dimeric compounds are somewhat lower than those from 3-chloropyridazines.

The dimeric nature of these compounds are confirmed from the acceptable elemental analyses and molecular weight determination by mass spectrometry.

TABLE I

	Substituent		M.P. °C (Solvent for recrystallization)	Yield(%)	UV λ_{max}^{EtOH} mμ (log ε)
	R	R'			
IIa	H	H	227-228 (AcOEt)	40-50	234 (3.60) 261 (3.26)
IIb	CH_3	H	234-235 (AcOEt)	50-60	241 (3.80) 267 (3.51)
IIc	OCH_3	H	237-238 (MeOH)	30-40	239 (3.42) 263 (3.12)
IId	NH_2	H	ca. 320 (MeOH)	20-30	218 (3.77)
IIe	H	CH_3	163-164 (AcOEt)	40-50	239 (3.35) 263 (3.05)

3,3'-Bipyridazine structures (II) are then assigned to these dimeric compounds from the NMR spectra, which are summarized in Table II.

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.

TABLE II

NMR Spectral Data for 3,3'-Bipyridazine Derivatives (II)$^{a)}$

		τ						
Compound	H_4	H_5	H_6	$J^{b)}_{4,5}$	$J_{5,6}$	$J_{4,6}$		τ
IIa	1.16	2.34	0.71	9.2	6.0	1.5		
IIb	1.31	2.50	---	9.2	--	--	$-CH_3$	7.20
IIc	1.40	2.90	---	9.2	--	--	$-OCH_3$	5.81
IId	1.40	---	0.92	--	--	--	$-CH_3$	7.51

a) 60 M/C in $CDCl_3$ with TMS as internal reference.

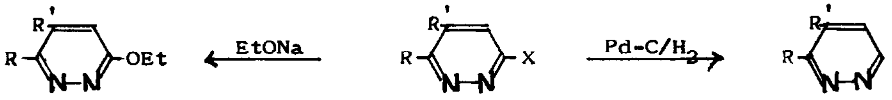
b) Coupling constants are indicated by c.p.s.

Thus, only three sets of signals with equal intensity centered at 1.16, 2.34, and 0.71τ are observed in the spectrum of IIa, while the spectra of IIb and IIc showed only two sets of signals at around 1.3-1.4τ and 2.5-2.9τ and IId showed them at 1.4τ and 0.9τ due to the ring protons. Since pyridazine shows two sets of signals ($H_{3,6}$: 0.79τ and $H_{4,5}$: 2.50τ)$^{5)}$, the signals at around 0.7-0.9τ and 2.3-2.9τ in these spectra are assigned to H_6 and H_5 respectively.

The assignment of the signals at around 1.1-1.4τ region to H_4 is reasonable when the large anisotropic effect of the neighboured aromatic ring is considered.

The assignment of the signals as above are also supported from the magnitudes of the coupling constants among each signal(Table II), since these values are approximately coincident with those of pyridazines and pyridazine N-oxides.$^{5)}$

In this reaction, a small amount of by-products, in which halogen atom of the starting material was replaced by alkoxyl group (III), or hydrogen atom (IV), was also obtained. The structures of these monomeric products were all confirmed by the direct comparison of the samples prepared from the starting material by alternative methods as follows.



III I IV

It should be noted that in case of 4-substituted 3-halogenopyridazines such as 3-chloro-4-methylpyridazine, the dimeric compound (II) were not obtained under these conditions, and thus, the present method may not be applied when such steric hindrance is considered.

Preliminary studies indicate that these 3,3'-bipyridazines form chelate compounds with Fe^{II}, Co^{II}, and Ni^{II}.

A detailed study of these chelate compounds is in progress and will be reported later.

REFERENCES

1) Part XII of the series entitled " Studies on Pyridazines. " by H.Igeta
Part XI : H.Igeta, T.Tsuchiya, M.Nakajima, and H.Yokogawa, *Chem. Pharm. Bull. (Tokyo)*, **17**, 763 (1969).

2) J.Druey, K.Meier, and K.Eichenberger, *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*, 1459 (1963).

3) M.Busch and W.Schmidt, *Ber.*, **62**, 2612 (1929).

4) S.Nakano, *Yakugaku Zasshi*, **79**, 310, 314 (1959).

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