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Studies on the Reactions of Heterocyclic Compounds. V.[1] Syntheses of Diazinium Ylides and Their Conversion to Azaindolizines[2]

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Four types of azaindolizines, pyrrolo[1,2-*b*]pyridazines (XVIa,b), pyrrolo[1,2-*a*]-pyrimidine (XVII), pyrrolo[1,2-*a*]pyrazines (XIXa,b) and pyrazolo[1,5-*b*]pyridazines (XXIa,b) were synthesized by the 1,3-dipolar cycloaddition of diazinium dicyanomethylides (IVa,b V and VIa,b) and pyridazine N-imines (VII and VIII) with dimethyl acetylenedicarboxylate. Imidazo[1,2-*b*]pyridazine (XXII) was synthesized by the intramolecular cyclization of VII and VIII with sodium methoxide. Further, an improved method for VII and VIII by N-amination of pyridazines with hydroxylamine O-sulfonic acid was devised. The nuclear magnetic resonance, ultraviolet and infrared spectra of the ylides and azaindolizines mentioned above were also discussed.

In the previous paper[1] we described the syntheses of pyridinium and isoquinolinium methylides and some observations made during the process. In this paper we report the syntheses of ylides of diazines such as pyrazine, pyrimidine, and pyridazine and the synthesis of azaindolizines by dipolar cycloaddition of the ylides obtained above with dimethyl acetylenedicarboxylate. We also describe the cycloaddition of pyridazine N-imines, where azaindolizines are produced in the same way, and the intramolecular cyclization of pyridazinium dicyanomethylide by sodium methoxide.

The usual method for synthesizing dicyanomethylide is through the reaction of heterocyclic aromatic amines with tetracyanoethylene oxide,[4] which proceeds through the nucleophilic attack of the nitrogen atom of the amine on the carbon atom of dicyanomethylene group of tetracyanoethylene oxide (TCNEO). Therefore, this reaction must partly depend on the electron density of the nitrogen atom in the heterocycles. On the other hand, as regards the reaction of TCNEO with the amines having two nitrogen atoms, it seemed interesting to know whether only one dicyanomethylide group or two would be introduced. To make these points clear we tried to examine the reaction of diazines-pyridazine (Ia), pyrimidine (IIa), and pyrazine (IIIa)-considering the relative positions of each two nitrogen atoms and their basicities. About the reaction of IIIa, Linn, *et al.*[4] reported only one dicyanomethylide group was introduced in a poor yield. But they did not give any detailed speculation. As a result, the yield of VIa was found to be as poor as was reported in the case of IIIa, which must be due to the difference in basicity.[5] Our examination of pyridazine and pyrimidine proved that the ylide (IVa) is obtained in a considerable yield from pyridazine (Ia), whose basicity is considered to be the strongest among the diazines,[6] and that the expected ylide cannot be obtained from

1) Part IV: Y. Kobayashi, T. Kutsuma, K. Morinaga, M. Fujita, and Y. Hanzawa, *Chem. Pharm. Bull.* (Tokyo), **18**, 2489 (1970).
2) Presented at the Meeting of the Society of Synthetic Organic Chemistry, Japan, Tokyo, November 1969.
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4) W.J. Linn, O.W. Webster, and R.E. Benson, *J. Am. Chem. Soc.*, **87**, 3651 (1965).
5) H.C. Brown, D.H. McDaniel, and O. Häfliger. "Determination of Organic Structures by Physical Methods," ed. E.A. Braude and F.C. Nached, Academic Press Inc., New York, 1955, p. 599.
6) T.L. Jacobs. "Heterocyclic Compounds," Vol. 6, ed. R.C. Elderfield, John Wiley & Sons, Inc., New York, 1957, p. 110.

pyrimidine (IIa), except for a trace of yellow needles whose structure is not determined, and no products with two dicyanomethylide were obtained in all these cases. This shows that the ylide group first introduced lowers the electron density of the other nitrogen atom.

Therefore, in order to ascertain the effect of increasing the electron density on each nitrogen atom, the reaction of diazines with a methoxyl group, that is, 3-methoxypyridazine (Ib), 4-methoxypyrimidine (IIb), and 2-methoxypyrazine (IIIb) was studied. Ib, like Ia, produced IVb and IIb produced the expected ylide (V), although in a poor yield, both facts supporting the above speculation; with IIIb, the yield did not increase notably and a small amount of ylide (VIb) was obtained. The structures of IVb, V, and VIb were determined by nuclear magnetic resonance (NMR). Considering the facts that the substituent in α-position prevents amines from formation of the ylide[1,7] and that pyridinium dicyanomethylide possesses an almost plane structure,[8] it is assumed that the steric factor predominated over the electronic effect, resulting in the formation of the ylide with the nitrogen atom which does not have a methoxyl group in α-position. Accordingly, the yiled was improved in IIb by the M-effect of the methoxyl group in the position para to the nitrogen atom; in the case of IIIb, the poor yiled of VIb, as in VIa, could easily be attributed to the fact that the nitrogen atom is meta to the methoxyl group, which prevented the atom from receiving the contribution of the M-effect. The above result shows that this reaction depends on the basicity of the nitrogen atom as well as the steric factor.[7]

Next, the synthesis of diazine N-imines, especially those of Ia and Ib considering the ready formation of the above-mentioned ylides, was attempted in order to utilize them for producing azaindolizines. Because the usual method[9] was inapplicable with pyridazine due to the instability of N-imine, a method which will be described in detail in the Experimental was devised, according to which N-aminopyridazinium halides (VIIa, VIIb, VIIIa, and VIIIb) were synthesized and separated as their acetyl derivatives (XIa and XIIa) and benzoyl derivatives (XIb and XIIb). While N-benzoyl-ylides formed stable crystals, N-acetyl-ylides were rather unstable hygroscopic crystals, which decomposed by being heated or kept at room temperature for a long time.

1-Aminopyridazinium chloride (VIIa), unlike 1-aminopyridinium salt,[10] was readily reduced to pyridazine by catalytic hydrogenation in the presence of palladium on charcoal. When the aqueous solution of VIIa and VIIb was allowed to stand with a base such as potassium carbonate, it decomposed into ammonia and a dark brown tar. This fact shows that pyridazine N-imine (IX) is fairly unstable compared with pyridine N-imine. Thus, from the stability of the N-imines (IX and X) and the behavior of VIIa in catalytic hydrogenation, an interesting fact was found that the N-N bond in N-amino derivatives of pyridazine is weaker than that in pyridine N-amino compounds. NMR spectra of the diazinium ylides obtained as above are shown in Table I and ultraviolet (UV) and infrared (IR) spectra in Table II. For the sake of comparison, the data of free bases are included in Table I.

It is noteworthy that, in NMR, the order of chemical shift of ring proton in IVa and XIa agreed with that in pyridazine 1-oxide,[11] and that in VIa agreed with that in pyrazine 1-oxide,[11a] thereby proving that in ylides there was an electronic effect similar to that in N-oxide. In other words, the hydrogen atoms in α- and γ-positions show up-field shifts due to N-oxidation and this phenomenon can be observed in IVa, IVb, VIa, and VIb. As for V, because back donation of electrons from the ylide group is inhibited by the M-effect of *p*-

7) T. Kutsuma, K. Sato, T. Chida, and Y. Tsukuno, *Yakugaku Zasshi*, **90**, 251 (1970).
8) C. Bragg, R. Desiderato, and R.L. Sass, *J. Am. Chem. Soc.*, **86**, 3157 (1964); C. Bragg and R.L. Sass, *Acta Cryst.*, **18**, 591 (1965).
9) R. Gösl and A. Meuwsen, *Chem. Ber.*, **92**, 2521 (1959); *idem*, Org. Syntheses, **43**, 1 (1963).
10) T. Okamoto and M. Hirobe, *Yuki Gosei Kagaku Kyokaishi*, **26**, 746 (1968).
11) *a*) K. Tori, M. Ogata, and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 235 (1963); *b*) Y. Kawazoe and S. Natsume, *Yakugaku Zasshi*, **83**, 523 (1963).

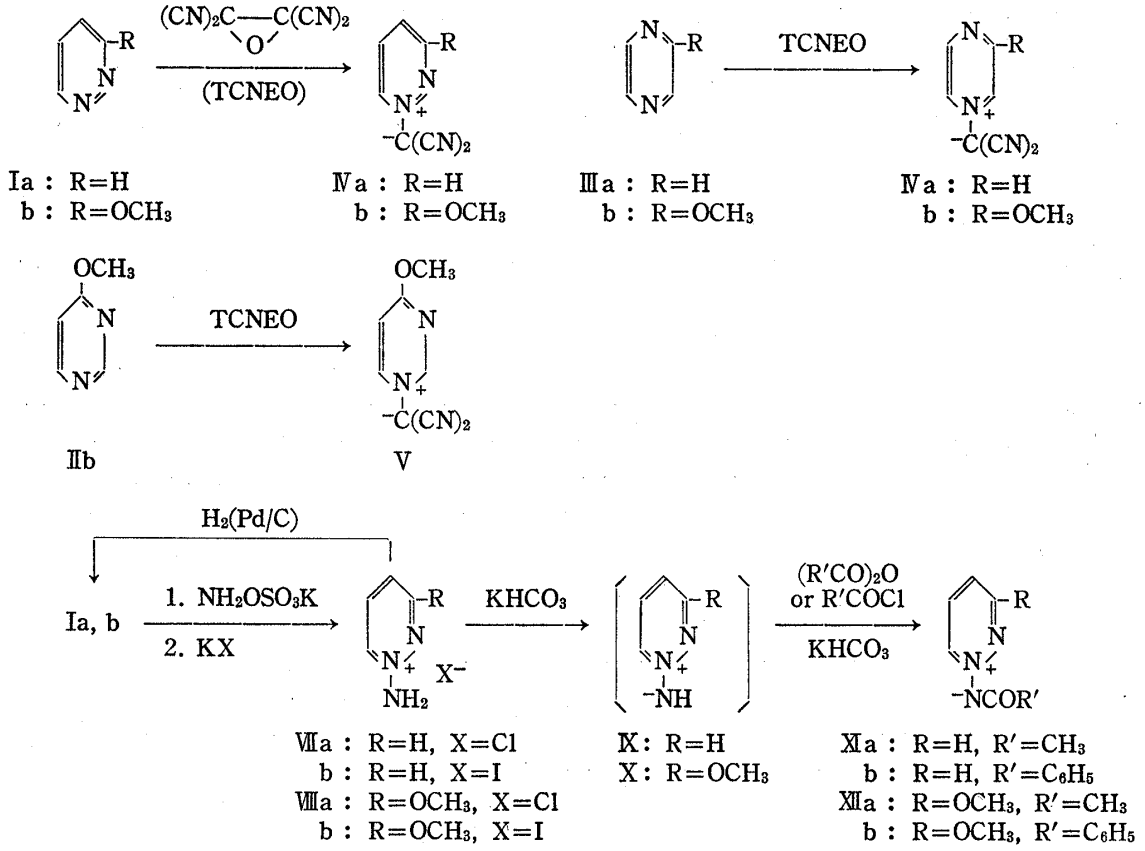
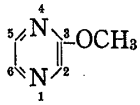


Chart 1

TABLE I. NMR Spectra of Diazines and Their Ylides[a)]

Compound	Chemical shift (δ) 2-H	3-H	4-H	5-H	6-H	CH_3O	CH_3CON	Coupling constant J (Hz)
Ia	—	9.27	7.72	7.72	9.27	—	—	$J_{3,4}=J_{4,5}=3.7$
Ib	—	—	7.25	7.66	8.96	4.06	—	$J_{4,5}=8.3$, $J_{5,6}=5.0$, $J_{4,6}=1.5$
IIb	8.75	—	—	6.88	8.47	3.93	—	$J_{5,6}=5.5$, $J_{2,6}=\sim 0$
IIIa	8.67	8.69	—	8.67	8.67	—	—	$J_{2,3}=0$
IIIb[b)]	8.21	—	—	8.31	8.21	3.90	—	$J_{5,6}=\sim 0$
IVa	—	8.95[c)]	7.47	8.02	8.77	—	—	$J_{3,4}=5.0$, $J_{3,5}=2.0$, $J_{4,5}=7.5$ $J_{5,6}=6.7$, $J_{3,6}=1.3$, $J_{4,6}=1.0$
IVb	—	—	7.09	7.93	8.55	3.97	—	$J_{4,5}=8.5$, $J_{5,6}=5.7$
V	9.10	—	—	7.37	8.64	4.07	—	$J_{2,6}=2.5$, $J_{5,6}=7.2$, $J_{2,5}\fallingdotseq 1.0$
VIa	8.39[d)]	8.70[d)]	—	8.70[d)]	8.39[d)]	—	—	$J_{2,3}=J_{5,6}=1.8$
VIb	7.87	—	—	8.35	8.07	3.94	—	$J_{2,6}=2.0$, $J_{5,6}=4.0$, $J_{2,5}\fallingdotseq 1.0$
XIa	—	9.16[c)]	7.97	8.33	9.54	—	1.87	$J_{3,4}=5.2$, $J_{3,5}=2.5$, $J_{4,6}=1.0$ $J_{3,6}=1.5$, $J_{4,5}=8.0$, $J_{5,6}=6.2$
XIIa	—	—	7.53	8.13	9.40	3.95	1.85	$J_{4,5}=8.5$, $J_{5,6}=5.8$, $J_{4,6}=1.2$

a) All the spectra were measured at 100 MHz by JNM-4H-100 spectrometer (Japan Electron Optics Lab., Co., Ltd.) in *ca.* 5% (w/v) solution of DMSO-d_6 using tetramethylsilane as an internal standard.

b) Tentative numbering is used for IIIb,  , to compare it with ylide VIb.

c) Broad signal due to the quadruple relaxation and spin coupling effects of ^{14}N nucleus.

d) The spectrum is composed of two quartets (A_2X_2 type) centered at 8.39 δ and 8.70δ.

Table II. UV and IR Spectra of Ylides

Compound	Solvent	UV λ_{max} nm ($\varepsilon \times 10^{-3}$)				IR (cm^{-1}) $\nu^{KBr}_{C\equiv N}$	$\nu^{KBr}_{C=O}$
IVa	CH_3CN	428(19.70)	357(5.86)	287[a](2.36)	271(3.55)	2205 2180	—
	95% EtOH	427(20.20)	366[a](5.56)				
	0.1N HCl–EtOH	428(23.50)	366[a](6.10)				
	dioxane	438(22.10)	378[a](8.20)				
IVb	CH_3CN	428(25.40)	332(2.32)	263(1.01)		2205 2180	—
	95% EtOH	427(25.60)	332(2.42)	260[a](1.28)			
	dioxane	444(29.00)	340(3.18)	261(1.35)			
V	CH_3CN	393(12.30)				2195 2150	—
	dioxane	408(13.10)					
VIa	CH_3CN	410(26.90)	254(7.20)			2210 2190	—
	dioxane	**422(24.00)**	**254(5.70)**				
VIb	CH_3CN	406(16.50)	340(4.15)	278(5.35)		2210 2185	—
	dioxane	417(28.00)	344(4.05)	282(6.30)			
XIa	95% EtOH	345(5.65)	305[a](3.84)			—	1560
	0.1N HCl–EtOH	276(5.30)					
	dioxane	365(9.10)	315(4.05)	249(3.50)			
XIIa	95% EtOH	345(5.50)	305[a](4.22)			—	1581
	0.1N HCl–EtOH	290(5.00)	263[a](4.22)				
	dioxane	365(10.40)	293(2.32)	242(5.00)		—	1551
XIb	95% EtOH	358(7.10)	314[a](4.02)	240[a](9.50)	218(10.30)	—	
	0.1N HCl–EtOH	358(1.18)	277(4.60)	230(8.50)			
	dioxane	378(11.20)	320[a](3.62)	248(6.10)			
XIIb	95% EtOH	364(9.00)	314[a](5.74)	268(8.70)		—	1550
	0.1N HCl–EtOH	377(1.10)	358[a](1.00)	270(13.40)	262[a](11.70)		
	dioxane	382(16.60)	284(4.27)	260[a](5.80)	238[a](7.80)		

a) Numerals indicate inflexions.

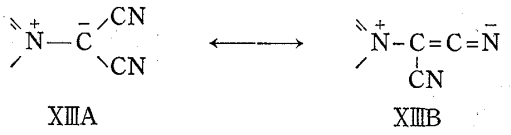
methoxyl group, only the electron-withdrawing effect by quaternarization operates, whereby the chemical shifts of all the ring protons are to the down field. In the NMR of pyrimidine, it has been reported that $J_{2,6}$ can be increased by deriving it to the N-oxide[12]; as for V and VIb, the fact that they are increased to 2.5 and 2.0 Hz, respectively, shows the position of each N-ylide to be as expected.

The longest wave-length bands of pyridinium ylides in UV spectra have been assigned to the intramolecular charge-transfer transition based on their solvent shifts.[13,14] The visible absorption bands of diazinium ylides are, as shown in Table II, also sensitive to the change of the solvent, which were assigned to the same transition. Introduction of another nitrogen atom into the ring of ylides, especially into the positions *ortho* and *para* to its positively charged nitrogen atom, decreased its transition energy and caused a bathochromic shift of its absorption bands. On the other hand, on introducing electron donating groups, its absorption bands are expected to show a hypsochromic shift, perhaps because of the increased transition energy. The visible absorption bands of IVa and VIa, whose second nitrogen atoms were introduced into *o*- and *p*-positions, respectively, shifted to the longer wave-length

12) M. Ogata, H. Watanabe, K. Tori, and H. Kano, *Tetrahedron Letters*, **1964**, 19.
13) E.M. Kosower, *J. Am. Chem. Soc.*, **80**, 3253 (1958).
14) *a*) E.M. Kosower and B.G. Ramsey, *J. Am. Chem. Soc.*, **81**, 856 (1959); *b*) G.V. Boyd, *Tetrahedron Letters*, **1966**, 3369; *c*) C.A. Henrick, E. Ritchie, and W.C. Taylor, *Aust. J. Chem.*, **20**, 2467 (1967).

side than that of pyridinium dicyanomethylide ($\lambda_{max}^{95\%EtOH}$ 392 nm)[7] by 35 nm and 18 nm, respectively.

The absorption band of V, however, appeared in almost the same position as that of pyridinium ylide; this fact apparently shows that the hypsochromic effect of *p*-methoxyl group and the bathochromic one of *m*-nitrogen atom cancel each other. In the case of pyridinium ylides, weak hypsochromic effect of 4-methyl group (4 nm) has also been recognized.[7]



XIIIA XIIIB

Fig. 1

In the IR spectrum, the stretching bands of two nitrile groups of V, characteristic of the anionic nature (XIIIB),[4,15] showed absorptions in almost the same positions as those of pyridinium dicyanomethylides,[7] 2195 and 2150 cm^{-1}; they appear in the lower frequency region than those of diazinium ylides (IVa, IVb, VIa, and VIb) appear (2210—2205 and 2190—2180 cm^{-1}). The above fact, along with the result of NMR and UV spectra, shows that *p*-methoxyl group repels the electron in the ring toward dicyanomethylene group and possesses the effect of increasing the contribution of XIIIB with ionic structure among the resonance hybrids of the ylide. The results concerning these spectra agree with the fact that the yields of ylides were improved only in the case of IIb.

Dicyanomethylides are shown in the UV spectrum to be stable even in 0.1N hydrochloric acid. It was also found that N-acetylimines (XIa and XIIa) were completely and N-benzoylimines (XIb and XIIb) were over 80% changed into quaternary salt structure[16] under the same conditions. The IR spectrum of acylimine ylides shows strong absorption bands due to ylide carbonyl[14c,17] in the low-frequency region of 1550—1580 cm^{-1}.

Next, we describe the conversion of the ylides obtained as above to azaindolizines. For this purpose two methods are possible; the known method of 1,3-dipolar addition[4,18] of pyridinium ylides and cyclization of pyridinium dicyanomethylide by sodium alkoxides, which we have reported.[7] Their application to the above-mentioned ylides enabled us to develop a new synthetic method for the ring system with one more nitrogen atom than usual. First, 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate to dicyanomethylides was studied. From each of the ylides (IVa, IVb, V, VIa, and VIb), their corresponding cyclized products (XVIa, XVIb,[19] XVII, XIXa, and XIXb) were obtained. Each of these, like the case of pyridinium ylides,[4] was produced by the elimination of HCN right after 1,3-dipolar cycloaddition.[20]

Secondly, 1,3-dipolar cycloaddition of pyridazine N-imine, which was too unstable to be separated, was attempted. The reaction of 1-aminopyridazinium salts (VII and VIII) with dimethyl acetylenedicarboxylate in the presence of a base gave XXIa and XXIb. When the reaction of dicyanomethylide with sodium methoxide mentioned above was applied to IVa, the reaction proceeded smoothly to afford 2-methoxyimidazo[1,2-*b*]pyridazine-3-carbonitrile (XXII).

15) W.J. Middleton, E.L. Blue, J.G. McNelly, and M. Zanger, *J. Org. Chem.*, **30**, 2384 (1965).
16) T. Okamoto, M. Hirobe, C. Mizushima, and A. Osawa, *Yakugaku Zasshi*, **83**, 308 (1963).
17) H. Nozaki, D. Tunemoto, S. Matubara, and K. Kondo, *Tetrahedron*, **23**, 545 (1967).
18) *a*) C.A. Henrick, E. Ritchie, and W.C. Taylor, *Aust. J. Chem.*, **20**, 2455 (1967); *b*) V. Boeckelheide and N.A. Fedoruk, *J. Am. Chem. Soc.*, **90**, 3830 (1968).
19) Sasaki, *et al.* independently reported the production of XVIa and XVIb from the reaction of IVa and IVb with dimethyl acetylenedicarboxylate. T. Sasaki, K. Kanematsu, Y. Yukimoto, and S. Ochiai, *J. Org Chem.*, **36**, 813 (1971).
20) The production of the primary 1:1 adduct by the reaction of isoquinolinium ylides with dimethyl acetylenedicarboxylate will be described in our following paper.

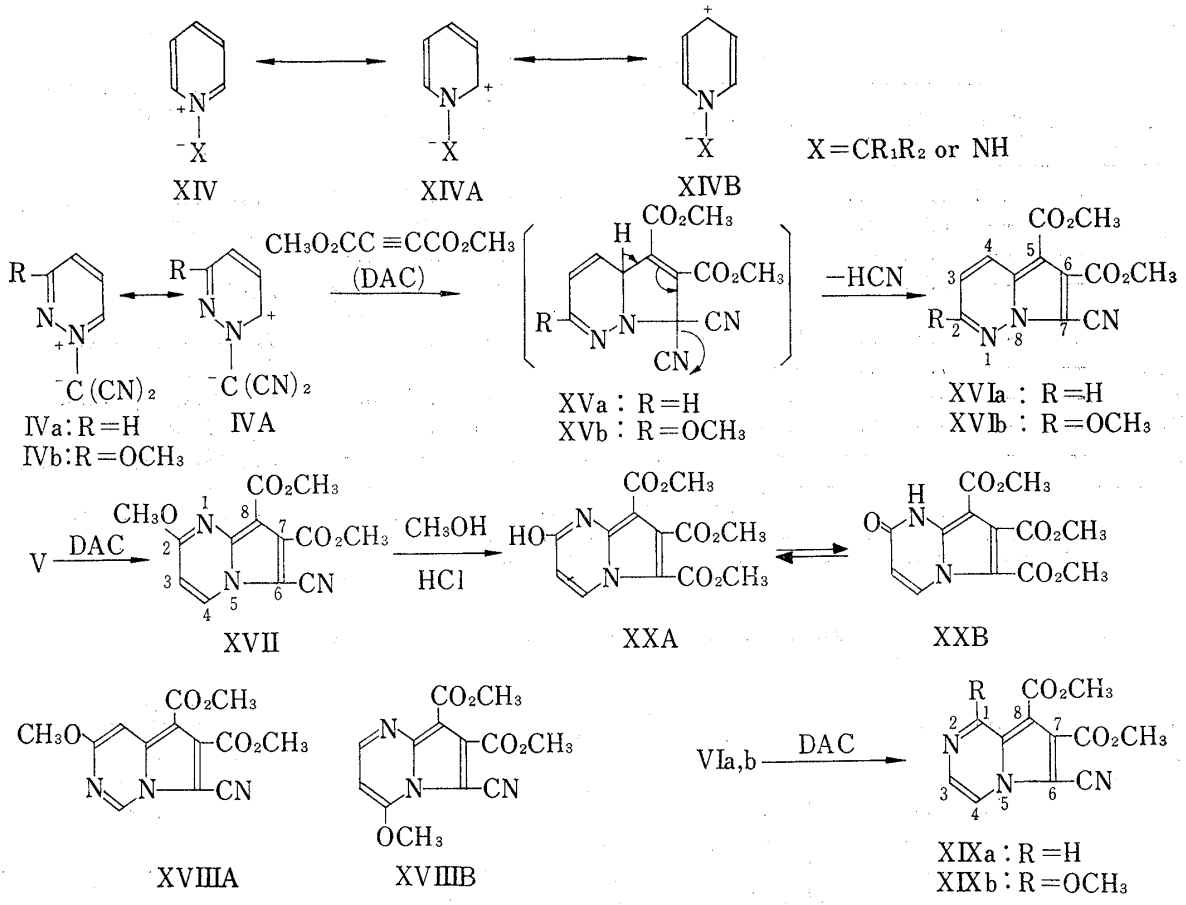


Chart 2

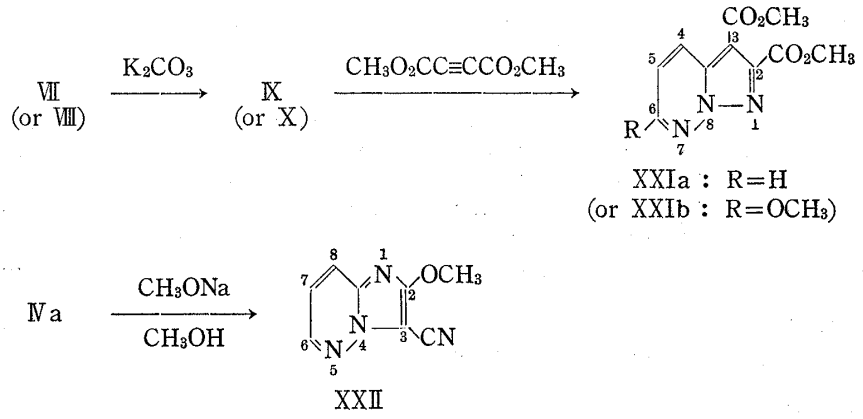


Chart 3

The process of the above reaction is shown in Charts 2 and 3; the NMR spectra are shown in Table III, and the spectra of IR and UV, in Table IV. These spectral data support our assumption of the structure of each product; that is, the NMR of XVI, XXIa, and XXII can be easily interpreted from their J values. $J_{2,3}$ of XVIa, $J_{5,6}$ of XXIa, $J_{6,7}$ of XXII are smaller than $J_{3,4}$ of XVIa, $J_{4,5}$ of XXIa, and $J_{7,8}$ of XXII, respectively, thereby agreeing with the result reported on indolizines.[21] The fact that $J_{3,4}$ of XVII is 7.5 Hz shows that it is not the cyclized XVIIIA and, inversely, the fact that its esterification (XX) caused 4-H

21) R.W. Acheson and D.A. Robinson, *J. Chem. Soc.* (C), **1968**, 1633.

Table III. NMR Spectra[a] of Azaindolizines[b]

Compound No.	Chemical shift (δ) 1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	CH_3 (ether)	CH_3 (ester)		Coupling constant (Hz)
XVIa	—	8.53	7.18	8.56	—	—	—	—	—	4.02	3.93	$J_{2,3}=4.8$, $J_{2,4}=2.2$, $J_{3,4}=9.5$
XVIb	—	—	6.80	8.33	—	—	—	—	4.07	3.98	3.90	$J_{3,4}=10.0$
XVII	—	—	6.62	8.28	—	—	—	—	4.08	3.98	3.92	$J_{3,4}=7.5$
XX	—	—	6.26	9.07	—	—	—	—	—	3.94	3.85 3.85	$J_{3,4}=8.5$
XIXa	9.62	—	8.23	8.16	—	—	—	—	—	4.03	3.98	$J_{1,4}=2.0$, $J_{3,4}=4.8$
XIXb	—	—	7.82	7.53	—	—	—	—	4.05	3.95	3.93	$J_{3,4}=4.7$
XXIa	—	—	—	8.56	7.32	8.53	—	—	—	4.01	3.92	$J_{4,5}=9.3$, $J_{4,6}=2.0$, $J_{5,6}=4.8$
XXIb	—	—	—	8.34	6.96	—	—	—	4.06	3.98	3.91	$J_{4,5}=10.0$
XXII	—	—	—	—	—	8.52	7.31	7.90	4.16	—	—	$J_{6,7}=4.7$, $J_{6,8}=2.0$, $J_{7,8}=9.5$

a) All the spectra were measured at 100 MHz by JNM-4H-100 spectrometer (Japan Electron Optics Lab. Co., Ltd.) in *ca.* 5% (w/v) solution of $CDCl_3$ with TMS as an internal standard.
b) Numbering of various azaindolizines is shown in Charts 2 and 3.

Table IV. UV and IR Spectra of Azaindolizines

Compound	Solvent	UV λ_{max}nm ($\varepsilon\times10^{-3}$)			IR (cm^{-1}) $\nu^{KBr}_{OH\text{ or }NH}$	$\nu^{KBr}_{C\equiv N}$	$\nu^{KBr}_{C=O}$
XVIa	CH_3CN	347(3.80)	302(5.04)	292(5.10)		2240	1753
		260[a](18.60)	247(31.50)	217(19.80)			1731
XVIb	CH_3CN	331(5.65)	290[a](5.17)	264(19.80)		2242	1738
		247(29.00)	241(28.80)	223(19.90)			1712
XVII	CH_3CN	330[a](3.64)	298(7.74)	269[a](12.80)		2233	1730
		247(35.80)	241[a](34.70)				1725
	$CHCl_3$	330[a](3.60)	300.5(7.90)	270(13.10)			
XX	$CHCl_3$	314(5.80)	273(20.40)		3180[b]	—	1742[c]
							1720
							1690
							1675
XIXa	CH_3CN	320(8.05)	244(38.60)	216(18.80)	—	2235	1732
XIXb	CH_3CN	340(3.93)	327(6.05)	319(6.50)		2238	1745
		244(57.00)	231(57.40)				1734
XXIa	CH_3CN	311(4.87)	285(4.15)	276(4.12)		—	1752
		240[a](16.00)	226(32.80)			—	1728
XXIb	CH_3CN	295(6.45)	232(35.00)			—	1750
							1724
XXII	CH_3CN	341(5.90)	277(5.36)	270(5.40)		2228	
		248(17.10)	232(19.90)				

a) Numerals indicate inflexions. b) broad c) associated carbonyl frequency

to shift into the lower magnetic field proved that the cyclized product is XVII and not XVIIIB, which might have been produced when dicyanomethylene group of the starting material V was attached to the other nitrogen atom. The structure of V, therefore, was made more certain. The low-field shift[21,22] of 4-H by peri–ester group mentioned above is generally observed in these ring systems including XVIa, XVIb, XXIa, and XXIb. As regards discrimination of chemical shift of hydrogen atoms in 3- and 4-positions of XIXa, the hydrogen atom coupling with 1-H more strongly is thought to be 4-H from the fact of $J_P>J_m$ in this

22) R.M. Acheson and M.W. Foxton, *J. Chem. Soc.* (*C*), **1966**, 2218; R.L. Letsinger and R. Lasco, *J. Org. Chem.*, **21**, 764 (1956).

series of compound.[23] As for XX, because the band of ν_{NH} appears broad and $\nu_{C=O}$ is at 1675 cm^{-1} in its IR spectrum, it was assumed to take the keto form (XXB); the shift in its NMR is the same as shown when methoxyl group of pyrimidine[24] was hydrolyzed to pyrimidone. The longest wave-length bands in the UV spectra of XVIa, XXIa, and XXII show greater bathochromic shift than those with one less nitrogen atom, namely, dimethyl-3-cyanoindolizine-1,3-dicarboxylate[4] (317 nm), ethyl pyrazolo[1,5-*a*]pyridine-3-carboxylate[25] (303 nm), and 2-methoxyimidazo[1,2-*a*]pyridine-3-carbonitrile[7] (315 nm).

Experimental[26]

Reaction of Diazines with Tetracyanoethylene Oxide——Method A[4]: To a solution of pyridazines (Ia and Ib, 20 mmole) in tetrahydrofuran (8 ml), a solution of tetracyanoethylene oxide (20 mmole) in tetrahydrofuran (10 ml) was added dropwise with stirring and cooling in an ice-bath over 20 min. The mixture was stirred for additional 3 hr at ice-bath temperature, and the precipitated ylide was collected and purified by recrystallization from 50% aqueous EtOH.

Method B[27]: To a boiling solution of tetracyanoethylene oxide (20 mmole) in ether (200 ml), a solution of bases (II and IIIb, 20 mmole) in ether (20 ml) was added dropwise and refluxed with stirring for 5 hr. The reaction mixture was cooled in an ice-bath and allowed to stand overnight at this temperature. The precipitated fine crystals were collected by filtration and purified by Al_2O_3 column chromatography with CH_2Cl_2 as eluant.

Pyridazinium Dicyanomethylide (IVa)——Prepared by method A described above from pyridazine (Ia). Orange yellow needles, mp 204—205°. Yield, 2.01 g (70%). *Anal.* Calcd. for $C_7H_4N_4$: C, 58.33; H, 2.80; N, 38.87. Found: C, 58.57; H, 2.98; N, 39.02.

3-Methoxypyridazinium Dicyanomethylide (IVb)——Prepared by method A from 3-methoxypyridazine[28] (Ib). Yellow needles, mp 209—210°. Yield, 2.90 g (83.4%). *Anal.* Calcd. for $C_8H_6ON_4$: C, 55.17; H, 3.47; N, 32.17. Found: C, 54.73; H, 3.61; N, 32.23.

4-Methoxypyrimidinium Dicyanomethylide (V)——Prepared by method B from 4-methoxypyrimidine[29] (IIb). Yellow needles (from CH_3CN), mp 192—193°. Yield, 0.95 g (27.2%). *Anal.* Calcd. for $C_8H_6ON_4$: C, 55.17; H, 3.47; N, 32.17. Found: C, 55.17; H, 3.77; N, 32.57.

3-Methoxypyrazinium Dicyanomethylide (VIb)——Prepared by method B from 3-methoxypyrazine[30] (IIIb). Yellow needles (from MeOH), mp 205—206°. Yield, 0.82 g (23.2%). *Anal.* Calcd. for $C_8H_6ON_4$: C, 55.17; H, 3.47; N, 32.17. Found: C, 55.31; H, 3.66; N, 32.05.

General Procedure for N-Amination of Pyridazines——To a solution of pyridazines (20 mmole) in H_2O (10 ml), a solution of potassium hydroxylamine O-sulfonate, prepared by the addition of a solution of $KHCO_3$ (2.00 g, 20 mmole) in ice-water (15 ml) to a solution of hydroxylamine O-sulfonic acid[9] (2.26 g, 20 mmole) in ice-water (5 ml), was added, and the reaction mixture was heated at 70° for 4.5 hr. After KCl or KI (20 mmole) was added to and dissolved in the mixture, H_2O was evaporated *in vacuo*. To the residual solid, abs. EtOH or *iso*-PrOH (50 ml) was added, and after the insoluble K_2SO_4 was filtered off, the filtrate was concentrated to give a solid, which was recrystallized from abs. EtOH to afford 1-aminopyridazinium salts.

1-Aminopyridazinium Chloride (VIIa)——Hygroscopic colorless needles, mp 153—154°. Yield, 1.85 g (70.7%). *Anal.* Calcd. for $C_4H_6N_3Cl$; C, 36.51; H, 4.60; N, 31.94. Found: C, 36.28; H, 4.57; N, 31.75.

Picrate: Yellow needles (from EtOH), mp 169—179°. *Anal.* Calcd. for $C_{10}H_8O_7N_6$: C, 37.04; H, 2.49; N, 25.92. Found: C, 37.30; H, 2.60; N, 25.66.

1-Aminopyridazinium Iodide (VIIb)——Faintly yellow prisms, mp 176—177°. Yield, 2.88 g (64.5%). *Anal.* Calcd. for $C_4H_6N_3I$: C, 21.54; H, 2.71; N, 18.80. Found: C, 21.86; H, 2.76; N, 18.94.

1-Amino-3-methoxypyridazinium Chloride (VIIIa)——Slightly hygroscopic colorless cubes, mp 150°. Yield, 1.51 g (47.1%). *Anal.* Calcd. for $C_5H_8ON_3Cl$: C, 37.16; H, 4.99; N, 26.01. Found: C, 37.10; H, 5.11; N, 26.01.

Picrate: Yellow plates (from *iso*-PrOH), mp 139—139.5°. *Anal.* Calcd. for $C_{11}H_8O_8N_6$: C, 37.51; H, 2.29; N, 23.86. Found: C, 37.46; H, 2.80; N, 23.77.

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25) V. Boechelheide and N.A. Fedoruk, *J. Org. Chem.*, **33**, 2062 (1968).
26) All the melting points are uncorrected.
27) A. Reiche and P. Dietrich, *Chem. Ber.*, **96**, 3044 (1963).
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29) H. Yamanaka, *Chem. Pharm. Bull.* (Tokyo), **7**, 297 (1959).
30) A. Albert and J.N. Phillips, *J. Chem. Soc.*, **1950**, 1294.

1-Amino-3-methoxypyridazinium Iodide (VIIIb)——Yellow needles, mp 93—94°. Yield, 3.14 g (62%). *Anal.* Calcd. for $C_5H_8ON_3I$: C, 23.73; H, 3.19; N, 16.61. Found: C, 23.70; H, 3.31; N, 16.58.

Pyridazine 1-Acetylimine (XIa)——To a solution of VIIa (1.32 g, 10 mmole) in cold H_2O (10 ml), $KHCO_3$ (4.5 g, 45 mmole) and Ac_2O (2 ml, *ca.* 20 mmole) were slowly added with stirring. After the stirring was continued for 10 min, the mixture was extracted 5 times with $CHCl_3$ (10 ml). The extract was dried over Na_2SO_4 and chromatographed over Al_2O_3 with $CHCl_3$. The eluted solution was concentrated *in vacuo* below 40° to afford a faintly yellow solid, which was recrystallized from EtOH–benzene (1:10) to hygroscopic pale yellow needles, mp 125—127° (decomp.). Yield, 0.99 g (72.1%). *Anal.* Calcd. for $C_6H_7ON_3$: C, 52.54; H, 5.15; N, 30.64. Found: C, 52.50; H, 5.21; N, 30.57.

Picrate: Yellow needles (from EtOH), mp 128—129°. *Anal.* Calcd. for $C_{12}H_{10}O_8N_6$: C, 39.35; H, 2.75; N, 22.95. Found: C, 39.30; H, 2.93; N, 22.70.

Pyridazine 1-Benzoylimine (XIb)——To a solution of VIIb (2.23 g, 10 mmole) in H_2O (10 ml), a solution of $KHCO_3$ (3.5 g, 35 mmole) in H_2O and a solution of BzCl (2.10 g, 15 mmole) in $CHCl_3$ (10 ml) were added with cooling in ice and stirring. The mixture was stirred for additional 30 min at ice-bath temperature and the aqueous and $CHCl_3$ layers were separated. The aqueous layer was extracted with three 10 ml portions of $CHCl_3$. All $CHCl_3$ layers were combined and added with MeOH (2 ml). After the mixture was dried over K_2CO_3, it was concentrated to dryness. The residual brown solid was treated with active charcoal and recrystallized from *iso*-PrOH (25 ml) to pale yellow flakes, mp 156—157°. Yield, 1.74 g (87.5%). *Anal.* Calcd. for $C_{11}H_9ON_3$: C, 66.32; H, 4.55; N, 21.10. Found: C, 66.56; H, 4.65; N, 21.06.

Picrate: Yellow needles (from iso-PrOH), mp 135—136°. *Anal.* Calcd. for $C_{17}H_{11}O_8N_6$: C, 47.67; H, 2.58; N, 19.62. Found: C, 47.97; H, 2.75; N, 19.86.

3-Methoxypyridazine 1-Acetylimine (XIIa)——To a solution of VIIIb (5.06 g, 20 mmole) in H_2O (10 ml), a solution of K_2CO_3 (5.52 g, 40 mmole) in H_2O (10 ml) was added, followed by the addition of a solution of Ac_2O (3.06 g, 30 mmole) in $CHCl_3$ (20 ml) under ice-cooling and stirring. Stirring was continued for 30 min. After the reaction was completed, KCl (4.5 g) was added to the mixture and the $CHCl_3$ layer was separated; the aqueous layer was extracted with $CHCl_3$ 5 times. After the $CHCl_3$ layer was dried over K_2CO_3, the solution was concentrated under 40° and chromatographed over Al_2O_3 (30 g) with $CHCl_3$. The orange-yellow solid obtained was recrystallized from EtOAc to hygroscopic pale yellow plates, mp 136—137°. Yield, 2.65 g (79.4%). *Anal.* Calcd. for $C_7H_9O_2N_3$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.52; H, 5.63; N, 25.00.

Picrate: Yellow flakes (from EtOH), mp 145—146°. *Anal.* Calcd. for $C_{13}H_{12}O_9N_6$: C, 39.40; H, 3.05; N, 21.21. Found: C, 39.37; H, 3.19; N, 21.26.

3-Methoxypyridazine 1-Benzoylimine(XIIb)——**VIIIa** (4.0 g, 25 mmole) was treated as in the case of of XIb, and yellow-brown prisms (from EtOH) mp 169—169.5°, were obtained. Yield, 5.25 g (91.4%). *Anal.* Calcd. for $C_{12}H_{11}O_2N_3$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.98; H, 4.90; N, 18.60.

Picrate: Yellow needles (from EtOH), mp 176—177° *Anal.* Calcd. for $C_{22}H_{19}O_7N_7$: C, 53.56; H, 3.87; N, 19.88. Found: C, 53.50; H, 3.98; N, 19.67.

Reduction of VIIa——VIIa (1.32 g) in 50% EtOH (50 ml) was hydrogenated over 5% Pd-C (1 g). After rapid absorption of H_2 (250 ml), Pd-C was filtered off and conc. HCl (2 ml) was added to the filtrate; the solution was concentrated to dryness. The residual solid was treated with *iso*-PrOH (20 ml) and, after the insoluble NH_4Cl was filtered off, an EtOH–solution of picric acid was added to the filtrate to give yellow crystals, which were recrystallized from EtOH to give yellow needles, mp 169—170°, which showed no depression on admixture with pyridazine picrate.

Reaction of Diazinium Dicyanomethylides with Dimethyl Acetylenedicarboxylate——To a suspension of the ylide (IVa, IVb, V, VIa,[7] or VIb, 10 mmole) in acetonitrile (10 ml), a solution of dimethyl acetylenedicarboxylate (1.42 g, 10 mmole) in acetonitrile (5 ml) was added dropwise with stirring at room temperature. After the addition was completed, the mixture was stirred for 1 hr at room temperature, except in the case of VIa, which was kept at about 60°, and concentrated under reduced pressure. The residue was chromatographed over Al_2O_3 with benzene–CH_2Cl_2 (1:5) as eluant and the eluted solid was purified by recrystallization.

Dimethyl 7-Cyanopyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylate (XVIa)——Colorless needles (from MeOH), mp 137—138°. Yield, 0.84 g (32.6%). *Anal.* Calcd. for $C_{12}H_9O_4N_3$: C, 55.60; H, 3.50; N, 16.21. Found: C, 55.53; H, 3.56; N, 16.41.

Dimethyl 7-Cyano-3-methoxypyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylate (XVIb)——Colorless needles (from MeOH), mp 152.5—153°. Yield. 2.25 g (82%). *Anal.* Calcd. for $C_{13}H_{11}O_5N_3$: C, 53.98; H, 3.80; N, 14.53. Found: C, 53.95; H, 4.00; N, 14.63.

Dimethyl 6-Cyano-2-methoxypyrrolo[1,2-*a*]pyrimidine-7,8-dicarboxylate (XVII)——Colorless needles (from MeOH), mp 220—221°. Yield, 1.21 g (42%). *Anal.* Calcd. for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.80; N, 14.53. Found: C, 53.74; H, 3.92; N, 14.49.

Dimethyl 6-Cyanopyrrolo[1,2-*a*]pyrazine-7,8-dicarboxylate (XIXa)——Colorless needles (from benzene), mp 162—163°. Yield, 1.62 g (62.5%). *Anal.* Calcd. for $C_{12}H_9O_4N_3$: C, 55.60; H, 3.50; N, 16.21. Found: C, 55.54; H, 3.71; N, 16.36.

Dimethyl 6-Cyano-1-methoxypyrrolo[1,2-*a*]pyrazine-7,8-dicarboxylate (XIXb)——Colorless needles (from MeOH), mp 178—179°. Yield, 1.26 g (43.5%). *Anal.* Calcd. for $C_{13}H_{11}O_5N_3$: C, 53.98; H, 3.83; N, 14.53. Found: C, 53.99; H, 3.92; N, 14.63.

Trimethyl 1-Hydroxypyrrolo[1,2-*a*]pyrazine-6,7,8-tricarboxylate (XX)——A suspension of XVII (0.05 g) in abs. MeOH (5 ml) was saturated with dry HCl in an ice–salt bath. The mixture was kept overnight at ice–salt bath temperature, and concentrated under reduced pressure. The residue was neutralized with aq K_2CO_3 and extracted with CH_2Cl_2. After being dried over Na_2SO_4, the extract was concentrated and washed with MeOH to give colorless crystals of the starting material (0.031 g), mp 178—179°. The MeOH washings were concentrated and the residue was recrystallized from EtOH to give XX (0.005 g), sa colorless meedles mp 198—200°. *Anal.* Calcd. for $C_{13}H_{12}O_7N_2$: C, 50.65; H, 3.92; N, 9.09. Found: C, 50.48; H, 3.95; N, 9.00.

Dimethyl Pyrazolo[1,5-b]pyridazine-2,3-dicarboxylate (XXIa)——A solution of the chloride (VIIa, 0.66 g, 5 mmole) and anhyd. K_2CO_3 (0.69 g, 5 mmole) in freshly distilled dimethylformamide (10 ml) was stirred at room temperature for 5 min. Then, dimethyl acetylenedicarboxylate (1.42 g, 10 mmole) was added dropwise with continued stirring to this solution. The mixture was stirred for additional 5 hr, diluted with H_2O (100 ml), and extracted with five 30-ml portions of ether. The extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residual reddish–brown solid obtained was chromatographed over silica gel with CH_2Cl_2 as eluant to give faintly yellow crystals, which on recrystallization from EtOH, afforded colorless needles (0.64 g, 54.4%), mp 124—125°. *Anal.* Calcd. for $C_{10}H_9O_4N_3$: C, 51.06; H, 3.86; N, 17.87. Found: C, 51.59; H, 4.06; N, 18.15.

Dimethyl 6-Methoxypyrazolo[1,5-*b*]pyridazine-2,3-dicarboxylate (XXIb)——The iodide (VIIIb, 1.27 g, 5 mmole) was treated as in the case of XXIa to give XXIb (0.5 g, 37.7%) as colorless needles (from EtOH), mp 153°. *Anal.* Calcd. for $C_{11}H_{11}O_5N_3$: C, 49.81; H, 4.18; N, 15.83. Found: C, 49.62; H, 4.26; N, 15.79.

2-Methoxyimidazo[1,2-*b*]pyridazine-3-carbonitrile (XXII)——To a solution of Na (0.46 g, 20 mg atom) in abs. MeOH (80 ml), IVa (1.44 g, 10 mmole) was added and the mixture was stirred for 5 hr at room temperature. After the brown reaction mixture was cooled in ice bath, it was neutralized by cautious addition of AcOH (1.3 ml) and concentrated *in vacuo* to dryness. To the residue, H_2O (2 ml) was added and the insoluble substance was extracted with $CHCl_3$. After being dried over K_2CO_3, the $CHCl_3$ layer was concentrated and chromatographed over Al_2O_3 (30 g) to give colorless crystals, which, on recrystallization from MeOH, gave colorless needles, mp 170—171°. Yield, 0.69 g. *Anal.* Calcd. for $C_8H_6ON_4$: C, 55.17; H, 3.47; N, 32.17. Found: C, 55.13; H, 3.51; N, 32.20.

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