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Reaction of N-Aminopyridinium Derivatives. XIII.[1] Syntheses of Pyrazolodiazines by Cyclization of N-Aminodiazinium Salts

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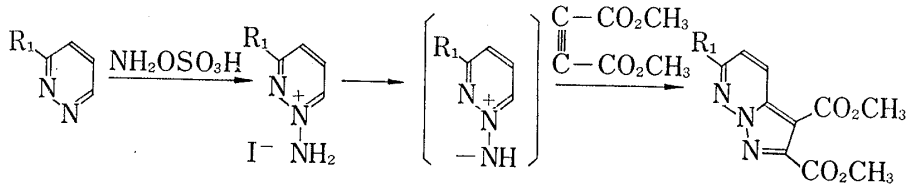
N-Aminopyridazinium (IV) and N-aminopyrazinium (VI, VIII) derivatives were synthesized by N-amination of pyridazine (III) or pyrazine (V, VII) derivatives with hydroxylamine-O-sulfonic acid. By the reaction of pyrimidine derivatives (IX, XI) with hydroxylamine-O-sulfonic acid, N-aminopyrimidinium derivatives were not obtained, but pyrimidine N-oxide derivatives (X, XII) or 1-amino-4-methyl-6-oxo-1,6-dihydropyrimidine (XIV, XVI, XVII) were obtained. Therefore, N-aminopyrimidinium derivatives (XXI, XXII, XXIV, and XXVI) were synthesized by N-amination of IX and XI with O-mesitylenesulfonylhydroxylamine. Pyrazolo-diazines (XXVII—XXX, XXXV—XXXVIII) were synthesized by cycloaddition reaction of these N-aminodiazinium derivatives with acetic anhydride and sodium acetate or methyl acetylenecarboxylate. Pyrazolo[1,5-*c*]pyrimidine derivatives (XXXVII—XXXVIII), which are different in orientation, were obtained by 1,3-dipolar cycloaddition reaction of XXI and XXIV with methyl acetylenecarboxylate.

Recent reports[3,4] stated that pyrazolo[1,5-*a*]pyridine derivatives, obtained from N-iminopyridine or its salts, had some interesting chemical reactivities and pharmacological activities. On the other hand, N-amination of diazines, such as pyridazine, pyrazine, and pyrimidine that had one more nitrogen in the pyridine ring, was recently attempted with only pyridazine. With respect to the syntheses of pyrazolo-diazine ring, such as pyrazolo-[1,5-*b*]pyridazine, pyrazolo[1,5-*a*]pyrazine, pyrazolo[1,5-*a*]pyrimidine, and pyrazolo[1,5-*c*]-pyrimidine using N-aminodiazinium salts, only pyrazolo[1,5-*b*]pyridazine (II) has been to date.[5] The pyrazolo-diazines synthesized without using N-aminodiazinium salts were pyrazolo[1,5-*a*]pyrimidine[6] and pyrazolo[1,5-*c*]pyrimidine.[7]



R1=H, CH3O I II

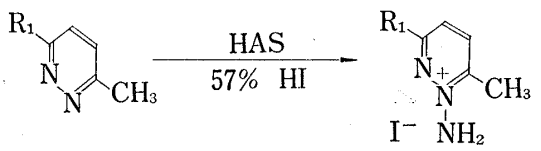
Chart 1

1) A. Ohsawa, M. Hirobe, and T. Okamoto, *Yakugaku Zasshi*, **92**, 73 (1972).
2) Location: *Hongo 7-3-1, Bunkyo-ku, Tokyo, 113, Japan*; *a*) Present address: *Kyorin Chemical Laboratory, Ukima 1-3, Kita-ku, Tokyo, 115, Japan.*
3) S. Suzue, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* (Tokyo), **21**, 2146 (1973).
4) M. Hirobe, Y. Minamoto, and T. Okamoto, Abstracts. of papers, 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, July, 1970, II-47.
5) Y. Kobayashi, T. Kutsuma, and K. Morinaga, *Chem. Pharm. Bull.* (Tokyo), **19**, 2106 (1971).
6) E. Meyer, *J. Prakt. Chem.*, **52**, 81 (1895); *idem, ibid.*, **92**, 185 (1951); Y. Makisumi, *Chem. Pharm. Bull.* (Tokyo), **10**, 612 (1962); A. Takamizawa and Y. Hamashima, *ibid.*, **13**, 142, 1207 (1965); M.A. Khan, *J. Heterocyclic Chem.*, **7**, 247 (1970); I. Hori, *Bull. Chem. Soc. Japan*, **43**, 894 (1970); H. Reimlinger, *Chem. Ber.*, **103**, 3252 (1970).
7) E. Kraz, *Chem. Ber.*, **105**, 388 (1972).

For this reason, we attempted N-amination of diazines with potassium hydroxylamine O-sulfonate[8] and syntheses of novel pyrazolo-diazines through N-aminodiazinium salts of diazine.[9]

1. N-Amination of Diazines

i) Reaction of Pyridazine Derivatives with H_2NOSO_3K——Kobayashi, *et al.*[5] recently reported that 1-amino-3-methoxypyridazinium salt was synthesized by the reaction of 3-methoxypyridazine with H_2NOSO_3K. We employed 3-methylpyridazine (IIIa) and 3-methyl-6-methoxypyridazine (IIIc) as starting materials in consideration of directing substituents, and it was found that these reactions gave only 2-amino-3-methylpyridazinium salts (IVa) and 2-amino-3-methyl-6-methoxypyridazinium salts (IVc) as shown in Chart 2.



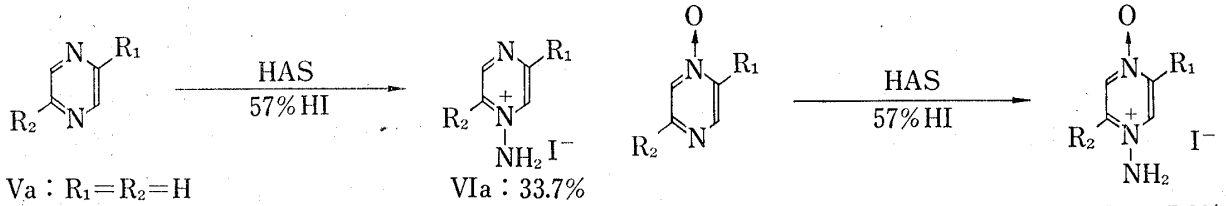
IIIa : R_1=H IVa : 22.2%
IIIb : R_1=CH_3 IVb : 55.6%
IIIc : R_1=CH_3O IVc : 49.7%

Chart 2

In nuclear magnetic resonance (NMR) spectrum of IVa, methyl protons at 3-position were recognized as a singlet. From this result, it was presumed that the reaction product of IIIa was not a mixture of 1-amino and 2-amino compounds, and the cyclization reaction of IVa with acetic anhydride-anhydrous sodium acetate gave pyrazolo[1,5-*b*]pyridazine as will be described later, confirming the structure of IVa. In the N-amination of IIIa and IIIc, it was presumed that IVa was obtained because of inductive (+I) effect of the 3-methyl group, and IVc was obtained because of steric hindrance or —I effect of 6-methoxyl group.

ii) Reaction of Pyrazine Derivatives with H_2NOSO_3K——N-Amination of pyrazines (V) was carried out in the same way as above and N-amino compounds (VI) were obtained, as shown in Chart 3. NMR spectrum of VIb exhibited a singlet at 0.76 due to C-2 proton, each doublet at 1.16 and 0.98 τ due to C-5 and C-6 protons and a singlet at 0.97 τ due to proton of N-amino group. The reaction of VIb with acetic anhydride-anhydrous sodium acetate did not afford a cyclization product, but the cycloaddition reaction of VIb with acetylene derivative gave pyrazolo[1,5-*a*]pyrazine. From these results, the structure of VIb was confirmed to be not 1-amino-2-methylpyrazinium salt but 1-amino-3-methylpyrazinium salt (VIb). In this connection, pK_a of pyrazine ring is lower than that of pyridazine ring. Consequently, it was presumed that VIb, in which the steric hindrance of methyl group appeared stronger with bulk effect of H_2NOSO_3K than +I effect of methyl group, was obtained. When a number of methyl groups were substituted in the pyrazine ring, the yield increased with increase in the electron density of the whole ring system.

N-Amination of pyrazine N-oxide derivatives (VII) was then attemped, and 1-amino-4-oxidopyrazinium salt (VIIIa) and 1-amino-2,5-dimethyl-4-oxidopyrazinium salt (VIIIb) were



Va : R_1=R_2=H
Vb : R_1=CH_3, R_2=H
Vc : R_1=R_2=CH_3

VIa : 33.7%
VIb : 21.7%
VIc : 55.2%

VIIa : R_1=R_2=H
VIIb : R_1=R_2=CH_3

VIIIa : 5.6%
VIIIb : 18.6%

Chart 3

8) An aqueous solution of H_2NOSO_3K (HAS) was prepared by neutralization of H_2NOSO_3H with an equal mole of KOH.

9) Abstracts of papers, 92th Annual Meeting of Pharmaceutecal Society of Japan, Osaka, April, 1972, II-80; Abstracts of papers, 93th Annual Meeting Pharmaeeutical Society of Japan, 1973, II-87.

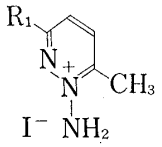
obtained in the yield shown in Chart 3. Compounds (VIIIa, b) are new diylides having an N-oxide group and an N-amino group as precursor of N-imine group. From comparison of NMR spectrum, it was observed that N-amino group of VIIIa, b shifted to a higher magnetic field because of back donation effect of N-oxide against N-amino group of IVa, b (Table I). The compounds obtained by these reactions are summarized in Table II and III.

Table I. NMR Spectra of Diazine Ylides

Compd. No.	Chemical shift (τ)									Coupling constant (Hz)
	$-NH_2$	2-H	3-H	4-H	5-H	6-H	CH_3	CH_3O	Phenyl proton	
IVa	0.81	—	—	1.85	1.45	0.82	7.2	—	—	$J_{4,5}=8$, $J_{5,6}=5$
IVb	1.00	—	—	1.94	1.6	—	7.21 7.32	—	—	$J_{4,5}=8$
IVc	1.1	—	—	2.23	1.64	—	7.25	5.93	—	$J_{4,5}=8.5$
VIa	0.44	0.78	1.19	—	1.19	0.78	0.78	—	—	$J_{2,3}=2.5$, $J_{3,5}=1.5$
VIb	0.97	0.76	—	—	1.16	0.98	7.35	—	—	$J_{5,6}=4$
VIc	1.18	0.92	—	—	1.34	—	7.37 7.32	—	—	
VIIIa	1.34	1.17	1.17	—	1.17	1.17	—	—	—	
VIIIb	1.94	1.04	—	—	1.14	—	7.64 7.42			
XXI	1.53	0.45	—	—	0.88	1.41	—	—	1.75 2.42	$J_{2,6}=2$
XXII	2.28	0.64	—	—	2.08	—	7.37 7.44	—	—	
XXIV	1.47	0.4	—	—	0.82	1.35	—	—	1.82 2.27	$J_{2,6}=2$, $J_{2',3'}=9$ $J_{5',6'}=9$

a) Me_2SO-d_6

Table II. N-Aminopyridazinium Iodides

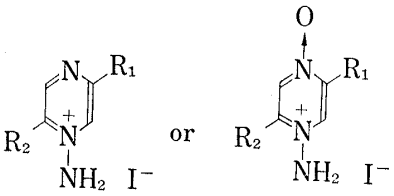


Compd. No.	R_1	Formula	mp (°C)	Appearance	Recrystn. solvent	Analysis (%) Calcd. (Found) C	H	N
IVa	H	$C_5H_8N_3I$	129—130 (decomp.)	pale yellow needles	EtOH	25.33 (25.50)	3.40 (3.22)	17.72 (16.86)
		$C_{11}H_{10}O_7N_6$ (picrate)	164—166	yellow needles	H_2O	39.06 (39.07)	2.98 (3.08)	24.85 (24.96)
IVb	CH_3	$C_6H_{10}N_3I$	134—136 (decomp.)	pale yellow needles	iso-PrOH	28.70 (28.76)	4.01 (4.01)	16.73 (16.46)
IVc	OCH_3	$C_6H_{10}ON_3I$	124—125 (decomp.)	yellow needles	iso-PrOH	26.98 (27.13)	3.77 (3.78)	15.73 (15.71)

iii) Reaction of Pyrimidine Derivatives with H_2NOSO_3K——By the reaction of pyrimidine derivatives with H_2NOSO_3K, N-aminopyrimidinium salts were not obtained in the same way as above. Therefore, the reaction of 4-phenylpyrimidine (IX) with H_2NOSO_3K was attempted for studying in further detail.

This reaction was carried out at 70—72° for 4 hr. When cooled, the reaction mixture was made alkaline with K_2CO_3, extracted with CH_2Cl_2, and the residue was separated by column

Table III. N-Aminopyrazinium or 1-Amino-4-oxidopyrazinium Iodides



Compd. No.	R_1	R_2	N→O	Formula	mp (°C)	Appearance	Recrystn. solvent	Analysis (%) Calcd. (Found) C	H	N
VIa	H	H	—	$C_4H_6N_3I$	178—180 (decomp.)	yellow needles	EtOH	21.54 (21.79)	2.70 (2.73)	18.84 (18.35)
	(picrate)			$C_{10}H_8O_7N_6$	234—236	yellow needles	H_2O	37.04 (36.89)	2.49 (2.77)	25.92 (26.21)
VIb	CH_3	H	—	$C_5H_8N_3I$	132—134 (decomp.)	yellow needles	EtOH	25·33 (25.33)	3.40 (3.44)	17.72 (17.74)
VIc	CH_3	CH_3	—	$C_6H_{10}N_3I$	145—146 (decomp.)	pale yellow needles	EtOH	28.70 (28.70)	4.01 (4.07)	16.73 (16.43)
VIIIa	H	H	N→O	$C_4H_6ON_3I$	144—145 (decomp.)	yellow needles	EtOH	20.09 (20.40)	2.52 (2.55)	17.58 (17.38)
VIIIb	CH_3	CH_3	N→O	$C_6H_{10}ON_3I$	172—174 (decomp.)	yellow needles	EtOH	26.98 (26.62)	3.77 (3.73)	15.73 (15.69)

chromatography over Al_2O_3. The crystalline product (X) obtained from this reaction had a molecular formula of $C_{10}H_8ON_2$, which showed N-oxide absorption bond at 1248 cm^{-1} in its infrared (IR) spectrum. The NMR spectrum of X exhibited a singlet at 0.92 τ due to C-2 proton, each doublet at 1.5 and 2.3 τ due to C-5 and C-6 protons, and signals at 1.96 and 2.5 τ due to the phenyl protons. The structure of X was presumed to be 4-phenylpyrimidine 1-oxide. On treatment with Raney nickel, X reverted to IX almost quantitatively and X agreed as 4-phenylpyrimidine 1-oxide by IR comparison with an authentic sample.[10] When 3 moles of H_2NOSO_3K was used, the yield of X was the highest. In order to examine the limit of application of this abnormal reaction, the reaction of XI with H_2NOSO_3K was attempted, and the expected N-oxide derivatives (XII) were obtained. Their IR spectra agreed with that of the authentic sample.[11] These results are summarized in Chart 4.

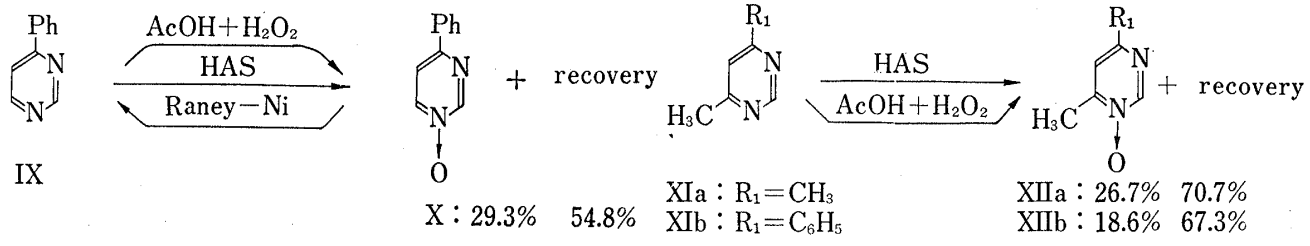


Chart 4

The reactivity of H_2NOSO_3K with compounds having hydroxyl and methoxyl groups in the pyrimidine ring system was examined. Klötzer[12] reported that N-3-aminouracil was obtained by the reaction of uracil with H_2NOSO_3K. Broom and Robins[13] reported that

10) T. Kato, H. Yamanaka, and T. Shibata, *Yakugaku Zasshi*, **87**, 1096 (1967).
11) *a*) R.H. Hunt, J.F.W. MeOmie, and E.R. Sayer, *J. Chem. Soc.*, **1959**, 525; *b*) K. Adachi, *Chem. Pharm. Bull.* (Tokyo), **7**, 479 (1959).
12) W. Klötzer, *Monatsh. Chem.*, **97**, 117 (1966).
13) A.D. Broom and R.K. Robins, *J. Org. Chem.*, **34**, 1025 (1969).

N-aminopurine nucleosides were synthesized by the reaction of various purine nucleosides with H_2NOSO_3K. However, the reaction of pyrimidine derivatives having a methoxyl group with H_2NOSO_3K has not been reported to the present. Therefore, the reaction of 4-hydroxy-6-methyl (XIII) and 4,6-dimethoxy (XV) derivatives with H_2NOSO_3K was attempted and gave 1-amino-1,6-dihydro-4-methyl-6-oxo derivative (XIV), 1-amino-4-methoxy-6-oxopyrimidine (XVI) having N-amino group and 4-methoxy-1-methyl-6-oxo derivative (XVII), in which the methyl in the methoxy group had rearranged to nitrogen, as shown in Chart 5. In the case of H_2NOSO_3K, the expected N-aminopyrimidinium salts were not obtained from pyrimidine derivatives such as pyrimidine, 2-methylpyrimidine, and 4-methylpyrimidine.

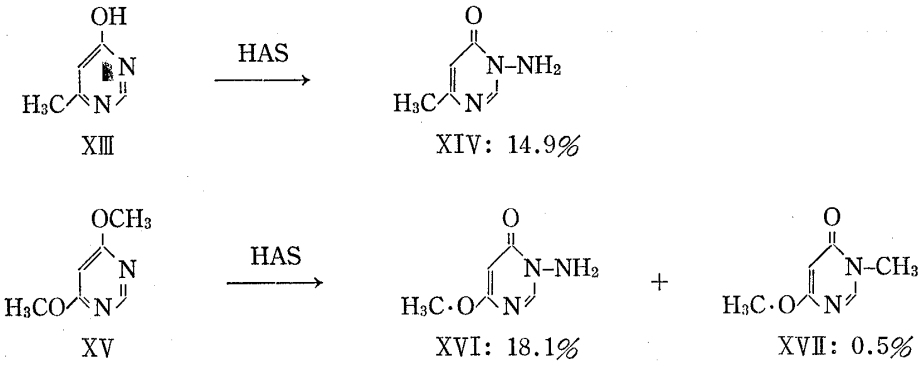


Chart 5

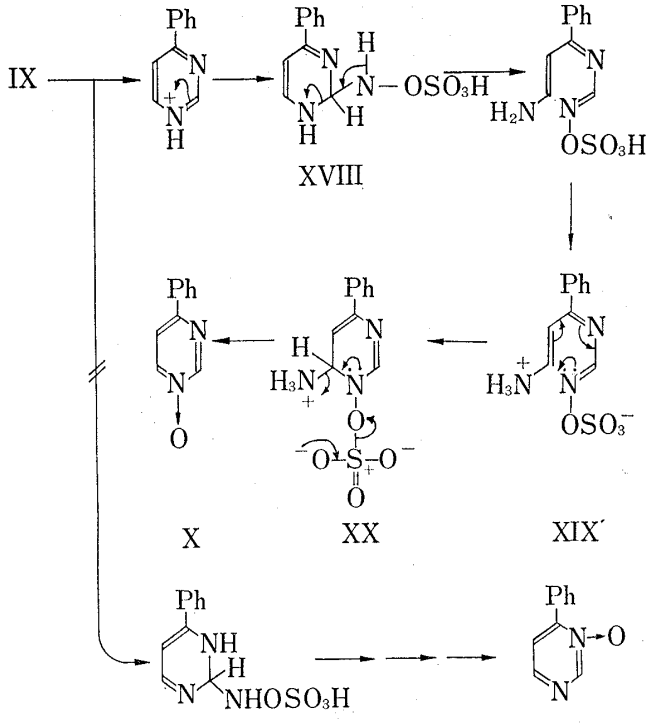


Chart 6 Ph=pheryl

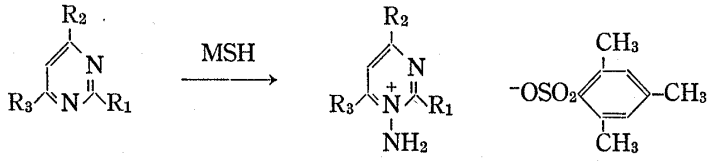
The reaction mechanism producing X can be proposed as shown in Chart 6. First protonation in nitrogen at 1-position of 4-phenylpyrimidine (IX) occurred and, by the addition reaction of H_2NOSO_3K as a nucleophilic reagent, XVIII may be formed as an intermediate such as 1,2-dihydro compound. Successive ring fission between 1- and 2-position such as XIX and elimination of sulfur trioxide and ammonia may give X. In this reaction, 4-phenylpyrimidine 3-oxide was not obtained.

It was concluded that the expected electrophilic N-amination did not occur because H_2NOSO_3K has not only electrophilic but also nucleophilic nature.

iv) Reaction of Pyrimidine Derivatives with MSH——Since N-aminopyrimidinium salt was not obtained by the reaction of pyrimidine derivatives with H_2NOSO_3K, amination with O-mesitylenesulfonylhydroxylamine (MSH),[14] whose scope of wide application became known recently, was attempted.

N-Aminopyrimidine salts (XXI, XXII, XXIV and XXVI) were obtained by the reaction of pyrimidine derivatives (X, XIa, XXIII, and XXV) with MSH as shown in Chart 7.

14) Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Letters*, **1972**, 4133.

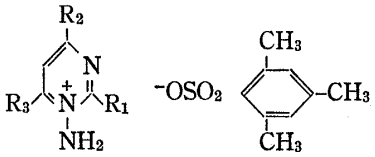


IX
XIa
XXIII
XXV

XXI: R_1=H, R_2=C_6H_5, R_3=H; 49.9%
XXII: R_1=H, R_2=R_3=CH_3; 66%
XXIV: R_1=H, R_2=*p*-BrC_6H_4, R_3=H; 50%
XXVI: R_1=CH_3, R_2=R_3=H; 43.1%

Chart 7

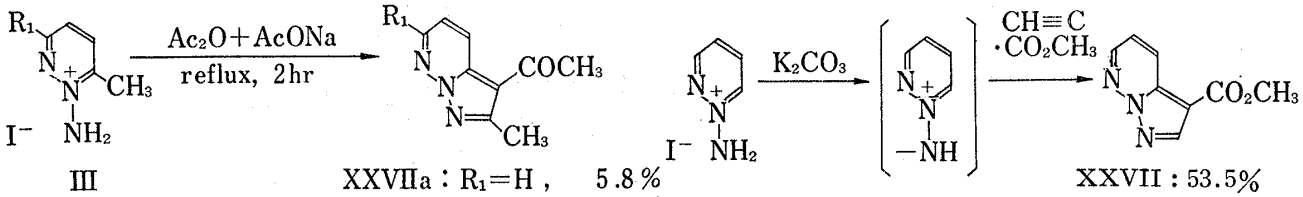
TABLE IV. N-Aminopyrimidinium Mesitylenesulfonates



Compd. No.	R_1	R_2	R_3	Formula	mp (°C)	Appearance	Recrystn. solvent	Analysis (%) Calcd. (Found) C	H	N
XXI	H	C_6H_5	H	$C_{19}H_{21}O_3N_2S$	85	pale yellow prisms	iso-PrOH	61.44 (61.28)	5.70 (6.03)	11.32 (11.10)
XXII	H	CH_3	CH_3	$C_{15}H_{21}O_3N_3S$	141—143	pale yellow prisms	iso-PrOH	55.72 (55.86)	6.55 (6.27)	13.00 (12.84)
XXIV	H	*p*-BrC_6H_4	H	$C_{19}H_{20}O_3N_3SBr$	158—160	pale yellow plates	iso-PrOH	50.67 (50.81)	4.47 (4.58)	9.33 (9.24)
XXVI	CH_3	H	H	$C_{14}H_{19}O_3N_3S$	212—214	pale yellow plates	iso-PrOH	54.36 (54.28)	6.19 (6.11)	13.59 (13.33)

2. Syntheses of Pyrazolo-diazines by Cyclization Reaction of N-Aminodiazinium Salts

i) Syntheses of Pyrazolo[1,5-*b*]pyridazines——Cyclization methods using N-aminopyridinium salts are already known; the excellent methods of acetic anhydride-sodium acetate[4] (method A) and 1,3-dipolar cycloaddition[15] reaction using an acetylene derivative (method B). The desired pyrazolo[1,5-*b*]pyridazines (XXVII and XXVIII) were obtained by the cyclization of N-aminopyridazinium salts using these methods (Chart 8). The yield of XXVII



III

XXVIIa : R_1=H, 5.8%
XXVIIb : R_1=CH_3, 13.8%
XXVIIc : R_1=CH_3O, 6.1%

I[5]

XXVII : 53.5%

Chart 8

was generally worse compared with the case of pyridine and much tarry matter was produced. From this fact, it was presumed that intermediates in the reaction of N-aminopyrazinium salts were more unstable than those of N-aminopyridinium salts for heat. On the other hand,

15) R. Huisgen, *Proc. Chem. Soc.*, **1961**, 357; *idem*, *Tetrahedron Letters*, **1962**, 387; *idem*, *Angew. Chem.*, **75**, 604, 742 (1963).

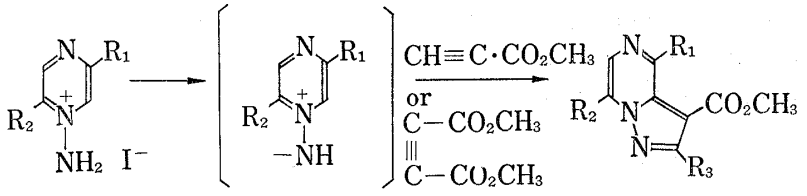
in the method B with cyclization at room temperature, XXVIII was obtained in a moderate yield. These compounds were identified on the basis of elemental analysis and the spectral data, and these are summarized in Table V.

Table V. NMR[a] and IR Spectra of Pyrazolo-diazines

Compd. No.	Chemical shift (τ)									Coupling constant (Hz)	IR(cm^{-1}) KBr C=O
	2-H	4-H	5-H	6-H	7-H	3-$COCH_3$ or 3-CO_2CH_3	CH_3	CH_3O	Phenyl proton		
XXVIIa	—	1.64	2.77	1.37	—	7.40	7.40	—	—	$J_{4,5}=9$, $J_{5,6}=4$	1650
XXVIIb	—	1.56	2.9	—	—	7.44	7.28 7.39	—	—	$J_{4,5}=9$	1633
XXVIIc	—	1.62	3.15	—	—	7.47	7.32	5.95	—	$J_{4,5}=9$	1648
XXVIII	1.43	1.56	2.78	1.56	—	6.06	—	—			1697
XXIXa	1.55	0.42	—	1.55	1.93	6.03	—	—	—	$J_{6,7}=5$	1710[b]
XXIXb	—	0.52	—	1.04	1.76	6.02 6.08	—	—	—	$J_{6,7}=5$	1745 1713
XXIXc	1.6	—	—	2.09	1.73	6.06	6.9	—	—	$J_{6,7}=5$	1696[b]
XXIXd	1.55	—	—	2.21	—	6.1	6.93 7.3	—	—		1724[b]
XXX	1.62	—	—	2.36	—	6.12	7.00 7.36	—	—		1723[b]
XXXV	—	—	0.77	2.15	0.18	7.01	7.12	—	—	$J_{6,7}=7$ $J_{5,6}=7$	1645
XXXVI	—	2.2	—	—	0.94	7.34	7.46 7.48	—	—		1645
XXXVII	1.57	1.65	—	—	0.68	6.05	—	—	1.18 2.52	$J_{4,7}=1.5$	1700
XXXVIII	1.54	1.64	—	—	0.68	6.05	—	—	2.00 2.37	$J_{4,7}=1.5$	1690

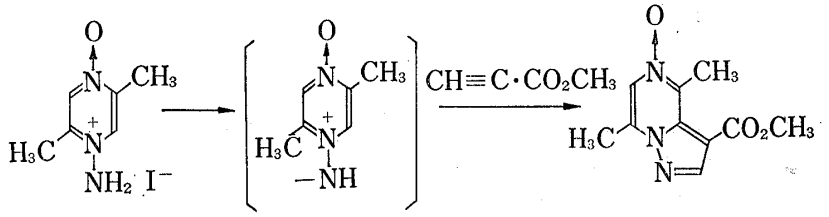
a) ia $CDCl_3$ b) IR (cm^{-1}), $CHCl_3$, C=O

ii) Syntheses of Pyrazolo[1,5-*a*]pyrazines——3-Methoxycarbonyl-4-methylpyrazolo-[1,5-*a*]pyrazine (XXIXc) was obtained by the reaction of VIb by the method B (Chart 9).



VI

XXIXa : $R_1=R_2=R_3=H$, 10.5%
XXIXb : $R_1=R_2=H$, $R_3=CO_2CH_3$, 2.3%
XXIXc : $R_1=CH_3$, $R_2=R_3=H$, 9.0%
XXIXd : $R_1=R_2=CH_3$, $R_3=H$, 10.9%



VIII

XXX : 41.2%

Chart 9

The structure of XXIXc was supported by its NMR spectrum showing a singlet at 1.6 τ due to C-2 proton, and each doublet at 1.73 and 2.07 τ due to C-6 and C-7 protons of pyrazine ring. It is already known[16] that 1,3-dipolar cycloaddition of VIb has occurred at the hindered 2-position.

When VIc was carried out with acetic anhydride-sodium acetate by the method A, contrary to expectation, 2,6-dimethyl-3-acetoxypyrazolo[1,5-*a*]pyrazine (XXXI) and diacetamide (XXXII) were obtained. Compound (XXXI) $C_{10}H_{11}O_2N_3$, came as pale yellow needles mp 137—138°. This structure was presumed on the basis of the following data together with elemental analysis. IR spectrum of XXXI showed absorptions at 1749 and 1218 cm^{-1} due to a carbonyl bond and its NMR spectrum exhibited each singlet at 2.01 and 1.24 τ due to C-4 and C-7 protons of pyrazine ring and each singlet at 7.5, 7.6, and 7.62 τ due to protons of three methyl groups. Further, the structure of XXXI was confirmed by the following reaction. Hydrolysis of XXXI with conc. HCl gave a 3-hydroxy derivative (XXXIII) and XXXIV was obtained by the reaction of XXXIII with BzCl as shown in Chart 10.

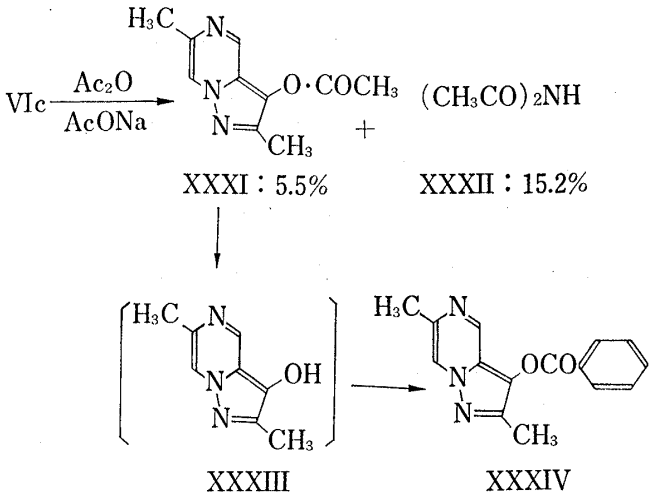


Chart 10

Compound (XXXII) was identified of the authentic sample by IR their spectra. From the fact, the intermediate in the reaction of VIc with acetic anhydride-sodium acetate may be considered to be more unstable for heat. A part of VIc was decomposed to 2,5-dimethylpyrazine, XXXII, and iodine, which gave XXXI through the ring contraction mechanism to a five-membered ring system from a six-membered ring system,[3] as shown in Chart 11. The analytical data of the compounds obtained are summarized in Tables VI and VII.

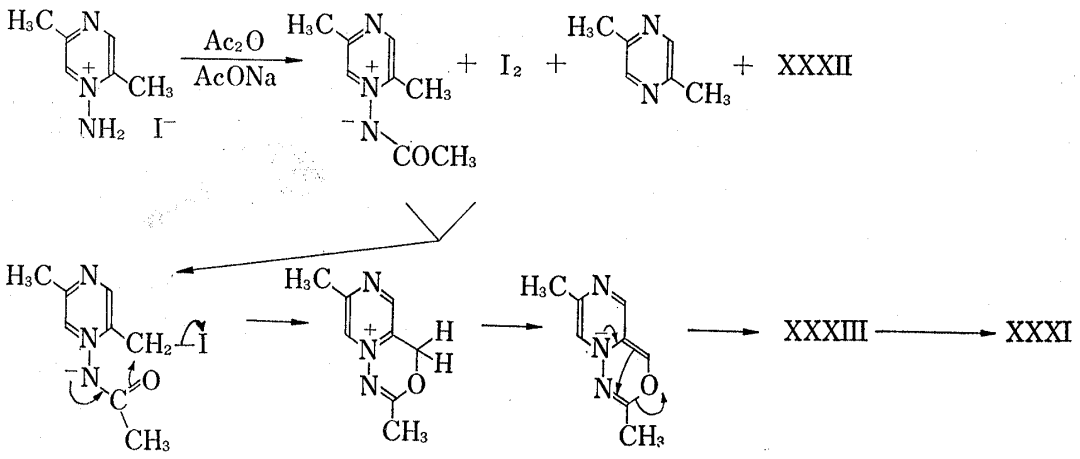
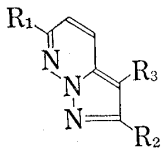


Chart 11

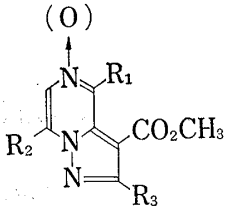
16) T. Okamoto, M. Hirobe, and E. Yabe, *Chem. Pharm. Bull.* (Tokyo), **14**, 523 (1966); Y. Tamura, N. Tsujimoto, and M. Ikeda, *Chem. Commun.*, **1971**, 310; Y. Tamura, N. Tsujimoto, Y. Sumida, and M. Ikeda, *Tetrahedron*, **28**, 21 (1972); T. Sasaki, K. Kanematsu, Y. Yukimoto, and S. Ochiai, *J. Org. Chem.*, **36**, 813 (1971).

Table VI. Pyrazolo[1,5-*b*]pyridazines



Compd. No.	R_1	R_2	R_3	Formula	mp (°C)	Appearance	Recrystn. solvent	Analysis (%) Calcd. (Found) C	H	N
XXVIIa	H	CH_3	$COCH_3$	$C_9H_9ON_3$	130—131	colorless needles	hexane	61.70 (61.76)	5.18 (5.12)	23.99 (24.02)
XXVIIb	CH_3	CH_3	$COCH_3$	$C_{10}H_{11}ON_3$	131—133	colorless needles	hexane	63.47 (63.68)	5.86 (5.86)	22.21 (22.34)
XXVIIc	OCH_3	CH_3	$COCH_3$	$C_{10}H_{11}O_2N_3$	131—132	colorless needles	hexane	58.53 (58.68)	5.40 (5.47)	20.48 (20.72)
XXVIII	H	H	CO_2CH_3	$C_8H_7O_2N_3$	125—126	colorless needles	H_2O	54.23 (54.48)	3.98 (4.03)	23.72 (23.99)

Table VII. Pyrazolo[1,5-*a*]pyrazines



Compd. No.	R_1	R_2	R_3	N→O	Formula	mp (°C)	Appearance	Recrystn. solvent	Analysis (%) Calcd. (Found) C	H	N
XXIXa	H	H	H	—	$C_8H_7O_2N_3$	137—138	colorless needles	iso-PrOH	54.23 (54.20)	3.98 (4.06)	23.72 (23.99)
XXIXb	H	H	CO_2CH_3	—	$C_{10}H_9O_4N_3$	139—140	pale yellow needles	EtOH	54.06 (51.09)	3.86 (3.99)	17.87 (17.82)
XXIXc	CH_3	H	H	—	$C_9H_9O_2N_3$	137—139	colorless needles	iso-PrOH	56.54 (56.75)	4.75 (5.00)	21.98 (21.81)
XXIXd	CH_3	CH_3	H	—	$C_{10}H_{11}O_2N_3$	130—131	pale yellow needles	hexane	58.53 (58.60)	5.40 (5.53)	20.48 (20.22)
XXX	CH_3	CH_3	H	N→O	$C_{10}H_{11}O_3N_3$	238—240	pale yellow needles	C_6H_6	54.29 (54.35)	5.01 (5.04)	19.00 (18.70)

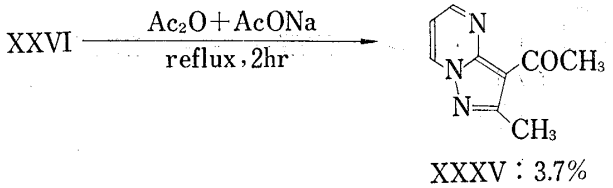


Chart 12

iii) Syntheses of Pyrazolo[1,5-*a*]pyrimidines——When XXVI was carried out with acetic anhydride-anhydrous sodium acetate by the method A, 3-acetyl-2-methylpyrazolo[1,5-*a*]pyrimidine (XXXV) was obtained in a poor yield. The structure of XXXV was proved on the basis of analytical data, and NMR and mass spectra, together with IR spectrum, which showed an absorption at 1645 cm^{-1} due to a carbonyl group.

iv) Syntheses of Pyrazolo[1,5-*c*]pyrimidines——3-Acetyl-2-methylpyrazolo[1,5-*c*]-pyrimidine (XXXVI) was obtained from XXII by the method A. The structure of XXXVI

was proved on the basis of analytical data, and NMR and mass spectra, together with IR spectrum, which showed an absorption at 1645 cm^{-1} due to a carbonyl group. The reaction of XXI and XXIV with methyl acetylenecarboxylate by the method B gave 3-methoxycarbonyl-5-phenylpyrazolo[1,5-*c*]pyrimidine (XXXVII) and 3-methoxycarbonyl-5-(*p*-bromophenyl)pyrazolo[1,5-*c*]pyrimidine (XXXVIII), respectively, as shown in Chart 13. In this reaction, a primarily expected compound was XXXVII′ because the electron density of C-2 position may be considered lower than C-6 position, and it was thought that 1,3-dipolar cycloaddition occurred in this position. However, the structures of XXXVII and XXXIII were presumed to be 3-methoxycarbonyl-5-phenylpyrazolo[1,5-*c*]pyrimidine and 3-methoxycarbonyl-5-(*p*-bromophenyl)pyrazolo[1,5-*c*]-pyrimidine by the following data. IR spectrum of XXXVII and XXXVIII showed absorptions at 1700 and 1690 cm^{-1} respectively due to a carbonyl group, NMR spectrum of XXXVII exhibited a singlet at 1.57 τ due to C-2 proton, each doublet at 0.68 and 1.65 τ due to C-4 and C-7 ring protons with *p*-coupling (J= 1.5 Hz), at multiplet at 1.8 and 2.52 τ due to the proton of phenyl group, and a singlet at 6.05 τ due to the proton of a methyl group.

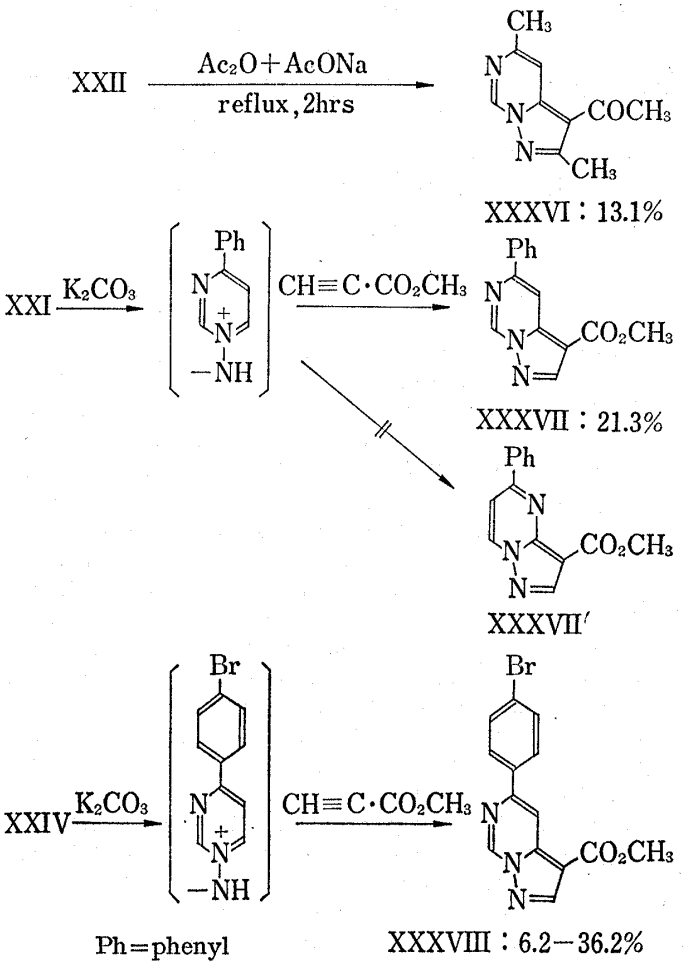
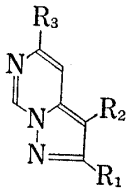


Chart 13

TABLE VIII. Pyrazolo[1,5-*c*]pyrimidines



Compd. No.	R_1	R_2	R_3	Formula	mp (°C)	Appearance	Recrystn. solvent	Analysis (%) Calcd. (Found) C	H	N
XXXVI	CH_3	$COCH_3$	CH_3	$C_{10}H_{11}ON_3$	137—138.5	pale yellow needles	hexane	63.47 (63.67)	5.86 (5.93)	22.21 (22.35)
XXXVII	H	CO_2CH_3	C_6H_5	$C_{14}H_{11}O_2N_3$	176—177	yellow needles	EtOH	66.39 (66.14)	4.38 (4.39)	16.59 (16.82)
XXXVIII	H	CO_2CH_3	*p*-BrC_6H_4	$C_{14}H_{10}O_2N_3Br$	201—202	yellow needles	iso-PrOH	50.62 (50.83)	3.03 (3.26)	12.65 (12.41)

NMR spectrum of XXXVIII exhibited a singlet at 1.54 τ due to C-2 proton, doublets at 0.68 and 1.64 τ due to C-4 and C-7 ring protons with p-coupling (J=1.5 Hz), each doublet (J=9 Hz) at 2.00 and 2.37 τ due to four protons of phenyl group, and a singlet at 6.05 τ due to proton of methyl group. When XXIV was reacted with methyl acetylenemonocarboxylate at 50° for 6 hr for the object of examining the influence of reaction temperature, the yield of XXXVIII increased. The mechanism for the formation of XXXVII and XXXVIII is not yet clear.

Experimental

All melting points were taken on a micro-hot stage and are not corrected. The spectra were recorded on the following instruments: IR, Nihon-Bunko DS-403G; mass, Hitachi RM60; UV, Hitachi EPS-2U; NMR, Japan Electron Optics (JEOL) JNM-PS 100 using tetramethylsilane as an internal standard. Abbreviations: s=singlet, d=doublet, m=multiplet, and br=broad.

General Preparation of N-Aminopyridazinium Iodide (IVa, *cf.* Tables II and III)——To a solution of 3-methylpyridazine (IIIa, 15 g) in H_2O (63.4 ml), an aqueous H_2NOSO_3K (prepared by neutralizing a solution of H_2NOSO_3H (18.05 g) in H_2O (80 ml) with a solution of KOH (8.95 g) in H_2O (47.8 ml) at 0°) was added dropwise at 60° over a period of 10 min. The reaction mixture was heated at 70—72° on a water bath for 4 hr. When cooled, the solution was made alkaline (pH 8—9) with 50% K_2CO_3, the separated K_2SO_4 was filtered off, and the filtrate was extracted with CH_2Cl_2. The aqueous solution was acidified (pH 3) with 57% HI and concentrated under a reduced pressure at below 50°. The residue was extracted with hot EtOH (50 ml) and the insoluble matter was filtered off. Same operation was repeated three times. The filtrate was concentrated under a reduced pressure. The resulting residue was dried under a reduced pressure and recrystallized from abs. EtOH to give 6.89 g of 2-amino-3-methylpyridazinium iodide (IVa) as pale yellow needles. Further 1.5 g of the same crystals was obtained from the recrystallization mother liquor. Total yield, 22.2%.

Reaction of 4-Phenylpyrimidine (IX) with H_2NOSO_3K——To a solution of IX (2 g) in MeOH (9 ml) and H_2O (4 ml), an aqueous solution of H_2NOSO_3K (prepared by neutralizing a solution of H_2NOSO_3H (4.34 g) in H_2O (10 ml) with a solution of KOH (2.16 g) in H_2O (5 ml) at 0°) was added dropwise at 60° over a period of 10 min. The reaction mixture was heated at 70—72° on a water bath for 4 hr. When cooled, the solution was made alkaline (pH 8—9) with K_2CO_3 and extracted several times with CH_2Cl_2. The CH_2Cl_2 layer was dried over anhyd. Na_2SO_4, evaporated, and the residue was chromatographed over Al_2O_3. From the first fraction eluted with CH_2Cl_2, 1.099 g (54.8%) of the starting material (IX) was obtained. From the second fraction eluted with CH_2Cl_2, 0.646 g (29.3%) of 4-phenylpyrimidine 1-oxide (X) was obtained as colorless needles (from benzene), mp 137—138°. *Anal.* Calcd. for $C_{10}H_8ON_2$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.75; H, 4.81; N, 16.38. Mass Spectrum *m/e*: 172 (M^+). X was identified with the authentic sample[10] by IR spectral comparison and mixed melting point determination.

Catalytic Reduction of 4-Phenylpyrimidine 1-Oxide (X)——4-Phenylpyrimidine (IX, 71.2%) was obtained from X according to the method of Kato, *et al.*,[10] and was identified with the authentic sample by IR spectral comparison.

4,6-Dimethylpyrimidine 1-Oxide (XIIa)——A mixture of XIa (3.24 g) and an aqueous solution of H_2NOSO_3H (6.78 g) and KOH (3.36 g) was worked up as described for X. The resulting residue was dissolved in CH_2Cl_2 and chromatographed over Al_2O_3. From the first fraction eluted with CH_2Cl_2, 2.294 g (70.7%) of the starting material (XIa) was obtained, and from the second fraction eluted with CH_2Cl_2–MeOH (19: 1), 0.993 g (26.7%) of XIIa was obtained as colorless needles (from benzene), mp 114.5—116°. *Anal.* Calcd. for $C_6H_8ON_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.10; H, 6.44; N, 22.68. Mass Spectrum *m/e*: 124 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1240 (N→O). NMR (in $CDCl_3$) τ: 1.06 (1H, s, C2–H), 2.83 (1H, s, C5–H), 7.52 (6H, s, $CH_3\times2$). XIIa was identified with the authentic sample by IR spectral comparison and mixed melting point determination.[11]

6-Methyl-4-phenylpyrimidine 1-Oxide (XIIb)——A mixture of XIb (2 g) and an aqueous solution of H_2NOSO_3H (2.66 g) and KOH (1.32 g) was worked up as described for X, and the residue was chromatographed over Al_2O_3. From the first fraction eluted with CH_2Cl_2, 1.345 g (67.3%) of the starting material XIb was recovered, and from the fraction eluted with CH_2Cl_2–MeOH (19: 1), 0.417 g (18.4%) of XIIb was obtained as pale yellow needles (from benzene–petr. ether), mp 139—141°. *Anal.* Calcd. for $C_{11}H_{10}ON_2$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.10; H, 5.41; N, 14.94. Mass Spectrum *m/e*: 186 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1248 (N→O). NMR (in Me_2SO-d_6) τ: 0.99 (1H, s, C2–H), 1.87 (1H, s, C5–H), 7.54 (3H, s, CH_3), 1.97 (2H, m, phenyl proton C2–H, C6–H), 2.55 (3H, m, phenyl proton C′3–H, C′4–H, C′5–H). XIIb was identified with the authentic sample by IR spectral comparison and mixed melting point determination.[11]

Reaction of 4-Hydroxyl-6-methylpyrimidine (XIII) with H_2NOSO_3K——To a solution of XIII (2.2 g) in H_2O (8 ml), an aqueous solution of H_2NOSO_3H (1.56 g) and KOH (1.12 g) was added dropwise at 60°. After working up as described for X, the residue was purified by chromatography over Al_2O_3 and elution

with CH_2Cl_2 gave 0.372 g (14.9%) of 1-amino-4-methyl-6-oxo-1,6-dihydropyrimidine (XIV) as colorless needles (from benzene), mp 115—117°. *Anal.* Calcd. for $C_5H_7ON_3$: C, 47.99; H, 5.64; N, 33.58. Found: C, 48.03; H, 5.58; N, 33.46. Mass Spectrum *m/e*: 125 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3335 (NH_2), 1685 (C=O). UV λ_{max}^{EtOH} nm(ε): 277.2 (3160). NMR (in $CDCl_3$) τ: 1.72 (1H, s, C2–H), 3.72 (1H, s, C5–H), 5.00 (2H, s, NH_2), 7.72 (3H, s, CH_3).

Reaction of 4,6-Dimethoxypyrimidine (XV) with H_2NOSO_3K——To solution of XV (1.96 g) in H_2O (6 ml) and MeOH (4 ml), an aqueous solution of H_2NOSO_3H (1.56 g) and KOH (0.77 g) was added dropwise at 60°. After working up as described for X, the residue was purified by chromatography over Al_2O_3 and eluted with CH_2Cl_2. From the first fraction, 1.079 g (54.9%) of the starting material XV was recovered and from the second fraction, 9 mg (0.44%) of 1-methyl-4-methoxy-6-oxo-1,6-dihydropyrimidine (XVII) was obtained as pale yellow plates (from benzene–hexane), mp 144.5—145.5°. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.50; H, 5.80; N, 19.79. Mass Spectrum *m/e*: 140 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1665 (C=O). UV λ_{max}^{EtOH} nm(ε): 271 (2740), 232 (1840). NMR (in $CDCl_3$) τ: 1.98 (1H, s, C2–H), 4.25 (1H, s, C5–H), 6.08 (3H, s, OCH_3), 6.46 (3H, s, CH_3).

From the third fraction, 0.356 g (18.1%) of 1-amino-4-methoxy-6-oxo-1,6-dihydropyrimidine (XVI) was obtained as pale yellow needles (from benzene), mp 140—141°. *Anal.* Calcd. for $C_5H_7O_2N_3$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.75; H, 5.09; N, 29.48. Mass Spectrum *m/e*: 141 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1673 (C=O). UV λ_{max}^{EtOH} nm(ε): 274 (2600). NMR (in $CDCl_3$) τ: 1.8 (1H, s, C2–H), 4.35 (1H, s, C5–H), 4.64 (2H, s, NH_2), 6.14 (3H, s, OCH_3).

General Preparation for N-Substituted Aminopyrimidinium Mesitylenesulfonate (XXIV, *cf.* Table IV)——To an ice cooled solution of 4-(*p*-bromophenyl)pyrimidine (XXIII, 17.5 g) in CH_2Cl_2 (100 ml), a solution of MSH (16 g) in CH_2Cl_2 (70 ml) was added dropwise and the reaction mixture was allowed to stand at room temperature for 1 hr. After addition of ether, the precipitated crystals were collected and recrystallized from iso-PrOH to 16.7 g (50%) of 1-amino-4-(*p*-bromophenyl)pyrimidinium mesitylene sulfonate (XXIV).

General Preparation of Substituted Pyrazolo[1,5-*b*]pyridazine (XXVIIa, *cf.* Table VI)——A solution of IVa (4.785 g) in Ac_2O (100 ml) was warmed for 0.5—1 hr at 70—80° with stirring. To the reaction mixture, anhyd. NaOAc (9.6 g) was added and the mixture was heated at 130—135° on an oil bath for 2 hr. When cooled, the reaction mixture was evaporated under a reduced pressure, the residue was basified with saturated Na_2CO_3 solution under ice cooling, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was purified by chromatography over Al_2O_3 with hexane–CH_2Cl_2 (1: 1) to give 205 mg (5.8%) of 3-acetylpyrazolo[1,5-*b*]pyridazine (XXVIIIa).

General Preparation of Substituted Pyrazolo[1,5-*a*]pyrazine (XXIX, *cf.* Table VII)——To a mixture of 1-aminopyrazinium iodide (Va, 8.92 g) in dimethylformamide (80 ml) and K_2CO_3 (2.76 g), methyl acetylenecarboxylate (6.72 g) was added dropwise with cooling and stirring. The mixture was stirred for 24 hr and allowed to stand for 1—2 days at room temperature. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by chromatography over Al_2O_3 with CH_2Cl_2 to give 0.744 g (10.5%) of 3-methoxycarbonylpyrazolo[1,5-*a*]pyrazine (XXIXa).

3-Acetoxy-2,6-dimethylpyrazolo[1,5-*a*]pyrazine (XXXI)——A solution of 1-amino-2,5-dimethylpyrazinium iodide (VIc, 3.56 g) in Ac_2O (45 ml) was warmed with stirring for 1 hr on a water bath. To the reaction mixture, anhyd. NaOAc (4.3 g) was added and the mixture was heated at 130—135° on an oil bath for 2.5 hr. The reaction mixture was treated in the same procedure as that described for XXVIIa. The residue was chromatographed over Al_2O_3 with hexane–CH_2Cl_2 (1: 1). From the first fraction, 0.17 g (5.5%) of XXXI was obtained as pale yellow needles (from hexane), mp 137—138°. *Anal.* Calcd. for $C_{10}H_{11}O_2N_3$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.60; H, 5.40; N, 20.40. Mass Spectrum *m/e*: 205 (M^+). IR λ_{max}^{KBr} cm^{-1}: 1749, 1218 (–OCOCH$_3$). NMR (in $CDCl_3$) τ: 1.24 (1H, s, C7–H), 2.01 (1H, s, C4–H), 7.5 (3H, s, –OCOCH$_3$), 7.6 (3H, s, 2-CH$_3$), 7.62 (3H, s, 6-CH$_3$). From the second fraction, 0.218 g (15.5%) of diacetylamine (XXXII) was obtained as pale yellow needles (from hexane), mp 73°. *Anal.* Calcd. for $C_4H_7O_2N$: C, 47.52; H, 6.98; N, 13.86. Found: C, 46.86; H, 6.70; N, 13.51. Mass Spectrum *m/e*: 101 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1738, 1695 (amide). NMR (in $CDCl_3$) τ: 0.36 (1H, br, NH), 7.68 (6H, s, $CH_3\times2$).

3-Benzoyloxy-2,6-dimethylpyrazolo[1,5-*a*]pyrazine (XXXIV)——A mixture of XXXI (0.1411 g) in conc. HCl (4 ml) was warmed on a water bath (70—80°) for 4 hr. The reaction mixture was evaporated to dryness, the residue was basified with 28% NH_4OH, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over anhyd. Na_2SO_4 and evaporated to give 2,6-dimethyl-3-hydroxypyrazolo[1,5-*a*]pyrazine (XXXIII), mp 204—205°, Mass Spectrum *m/e*: 163 (M^+). Then to a solution of 0.1 g of crude XXXII and K_2CO_3 (0.5 g) in H_2O (5 ml), BzCl (0.1 g) in CH_2Cl_2 (5 ml) was added dropwise. The reaction mixture was stirred for 5 hr and extracted with CH_2Cl_2. The dried extract was concentrated and chromatographed over Al_2O_3 with CH_2Cl_2 to give 72 mg of XXXIV as colorless needles (from hexane), mp 148—149°. *Anal.* Calcd. for $C_{15}H_{13}O_2N_3$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.42; H, 4.82; N, 15.45. Mass Spectrum *m/e*: 267 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1744, 1252 (ester).

3-Acetyl-2-methylpyrazolo[1,5-*a*]pyrimidine (XXXV)——A solution of XXVI (10.141 g) in Ac_2O (150 ml) was warmed for 30 min at 80° with stirring. To the reaction mixture, anhyd. NaOAc (15 g) was added. The reaction mixture was treated in the same procedure as that described for XXVIIa. The residue was purified by chromatography over Al_2O_3 with hexane–CH_2Cl_2 (1: 1) to give 0.215 g (3.7%) of XXXV as fine

pale yellow needles (from hexane), mp 174—175°. *Anal.* Calcd. for $C_9H_9ON_3$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.69; H, 5.19; N, 24.18. Mass Spectrum *m/e*: 175 (M^+).

General Preparation of Substituted Pyrazolo[1,5-*c*]pyrimidine (XXXVIII, *cf.* Table VIII)——1) To a mixture of XXIV (10 g) in dimethylformamide (100 ml) and K_2CO_3 (1.54 g), methyl acetylenecarboxylate (4.36 g) was added dropwise with cooling and stirring. The reaction mixture was treated in the same procedure as that described for XXVIIa. The residue was purified by chromatography over Al_2O_3 with hexane–CH_2Cl_2 (1:1) to give 0.458 g (6.23%) of 5-(*p*-bromophenyl)-3-methoxycarbonylpyrazolo[1,5-*c*]pyrimidine (XXXVIII).

2) To a solution of XXIV (2 g) in dimethylformamide (25 ml), K_2CO_3 (0.77 g) and methyl acetylenecarboxylate (0.87 g) were added. The reaction mixture was warmed at 50° for 6 hr and allowed to stand overnight. The reaction mixture was treated in the same procedure as that described in 1) to give 0.355 g (25.1%) of XXXVIII.

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