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A Novel Synthesis of Pyrimidines. I.[1] Cyclization of N-Cyano-cyanoaceto Derivatives

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The action of anhydrous hydrogen chloride and bromide on sodium cyanoacetylcyanamides (II) and N-cyano-cyanoacetamidines (IV) was shown to undergo cyclization to give exclusively corresponding 2-halogenopyrimidines (VI, XV), whereas the hydrogen iodide treatment of II caused no cyclization and that of IV gave an unexpected 6-amino-4-iodopyrimidine (XVI). The reaction of II with alcoholic hydrogen chloride afforded 2,6-dialkoxy-4-hydroxypyrimidines (VIII) *via* N-cyanoacetyl-O-alkylisoureas (VII). The intermediates (VII) were independently cyclized in water with heating to give 2-alkoxy-6-amino-4-hydroxypyrimidines (IX).

In our previous papers,[1] α,ω-dinitriles having the general structure, NC–CH(R)–C(Y)=N–CN, were found to undergo cyclization mainly with hydrogen halides to form pyrimidine ring. This paper describes more details on these cyclization reactions to the pyrimidine ring.[1a,b] The cyclization of various α,ω-dinitriles with hydrogen halides to heterocyclic compounds[3] was already reported, however, relatively little study has been made on the cyclization of dinitriles to the pyrimidine ring except those to 5-cyanopyrimidines.[3l,m]

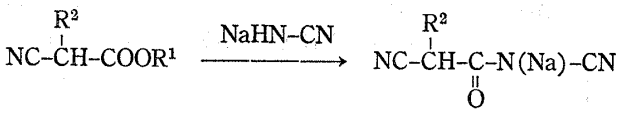
The first starting materials, sodium cyanoacetylcyanamides (II), were prepared according to the method of Dewar, *et al.*[4] by the reaction of alkyl cyanoacetates (I) with sodium cyanamide, and cyanoacetylcyanamide (II'a) was obtained by the treatment of its sodium salt (IIa) with cation exchange resin. The second starting materials, N-cyano-cyanoacetamidines (IV), were prepared according to the method of Schaefer, *et al.*[5] by the reaction of methyl cyanoacetimidate hydrochlorides (III),[6] which were easily obtained from malononitriles, with cyanamide in the presence of sodium methoxide. The structures of these compounds (II, IV) were confirmed on the basis of elemental analyses, infrared (IR) and nuclear magnetic resonance (NMR) spectra. They are summarized in Table I and II.

Cyclization of Cyanoacetylcyanamides

The cyclization of sodium cyanoacetylcyanamides (II) has been found to give three types of pyrimidines (VI, VIII, IX) according to the reaction conditions as shown in Chart 1.

1) *a*) T. Hirayama, M. Kamada, H. Tsurumi, and M. Mimura, *Heterocycles*, **2**, 451 (1974); *b*) T. Hirayama, M. Kamada, and M. Mimura, *ibid.*, **2**, 457 (1974); *c*) T. Hirayama, M. Kamada, M. Mimura, and H. Tsurumi, *ibid.*, **2**, 461 (1974).
2) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
3) *a*) J.J. Roemer and D.W. Kaiser, U.S.Patent 2658893 (1953) [*C.A.*, **48**, 12813^f (1954)]; *b*) F. Johnson, J.P. Panella, A.A. Carlson, and D.H. Hunneman, *J. Org. Chem.*, **27**, 2473 (1962); *c*) F. Johnson and W.A. Nasutavicus, *ibid.*, **27**, 3953 (1962); *d*) *Idem, ibid.*, **28**, 1877 (1963); *e*) *Idem, ibid.*, **29**, 153 (1964); *f*) *Idem, J. Heterocyclic Chem.*, **2**, 26 (1965); *g*) R. Tan and A. Taurins, *Tetrahedron Letters*, **1965**, 2737; *h*) L.G. Duquette and F. Johnson, *Tetrahedron*, **23**, 4517 (1967); *i*) *Idem, ibid.*, **23**, 4539 (1967); *j*) W.A. Nasutavicus and F. Johnson, *J. Org. Chem.*, **32**, 2367 (1968); *k*) W.A. Nasutavicus, R.W. Tobey, and F. Johnson, *ibid.*, **32**, 3325 (1968); *l*) E. Allenstein and R. Fuchs, *Chem. Ber.*, **101**, 1244 (1968); *m*) H. Kristinsson, *J.C.S. Chem. Comm.*, **1974**, 350; *n*) R.J. Rousseau, J.A.J. May, and R.K. Robins, *J. Heterocyclic Chem.*, **11**, 233 (1974); *o*) A. Taurins and R.T. Li, *Can. J. Chem.*, **52**, 843 (1974).
4) J.H. Dewar and G. Shaw, *J. Chem. Soc.*, **1965**, 1642.
5) K.R. Huffman and F.C. Schaefer, *J. Org. Chem.*, **28**, 1812 (1963).
6) S.M. McElvain and J.P. Schroeder, *J. Am. Chem. Soc.*, **71**, 40 (1949).

Table I. Sodium Cyanoacetylcyanamides (II)

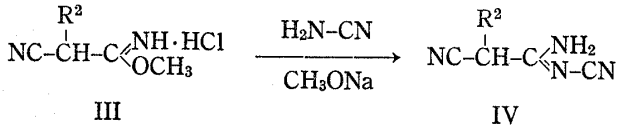


I II

Reactant	R^1	R^2	Product	mp (°C)	Yield (%)	Recrystn. solvent	Formula	*Anal.* Calcd. (Found) C	H	N	Na
Ia	CH_3	H	IIa[a]	197—198 (decomp.)	97	MeOH–EtOH	$C_4H_2ON_3Na$	36.66 (36.42)	1.54 (1.65)	32.06 (31.79)	17.54 (17.26)
Ib	CH_3	CH_3	IIb	161—162	98	MeOH–EtOH	$C_5H_4ON_3Na$	41.39 (41.16)	2.78 (2.78)	28.96 (28.74)	15.84 (15.82)
Ic	CH_3	C_2H_5	IIc	87—91[b]	90	MeOH–EtOH	$C_6H_6ON_3Na\cdot 1/2H_2O$	42.86 (43.17)	4.20 (4.38)	24.99 (24.50)	13.68 (—)
Id	C_2H_5	C_6H_5	IId	*ca.* 50[c]	22	MeOH–ether	$C_{10}H_6ON_3Na\cdot H_2O$	53.34 (54.24)	3.58 (3.72)	18.66 (19.68)	10.21 (9.44)

a) lit.[4]: 3/4 hydrate. The melting point was not reported.
b) 1/2 hydrate
c) about monohydrate

Table II. N-Cyano-cyanoacetamidines (IV)



III IV

Reactant	R^2	Product	mp (°C)	Yield (%)	Recrystn. solvent	Formula	*Anal.* Calcd. (Found) C	H	N
IIIa	H	IVa	126	76	EtOH	$C_4H_4N_4$	44.44 (44.37)	3.73 (3.70)	51.83 (51.72)
IIIb	CH_3	IVb	141—142	48	EtOH	$C_5H_6N_4$	49.17 (49.05)	4.95 (4.89)	45.87 (45.89)
IIIc	C_2H_5	IVc	97—99	47	EtOH	$C_6H_8N_4$	52.93 (53.16)	5.92 (5.65)	41.15 (41.04)
IIId	C_6H_5	IVd	163.5—164.5	11	EtOH	$C_{10}H_8N_4$	65.21 (65.25)	4.38 (4.41)	30.42 (30.30)

When the reaction of IIa with hydrogen chloride or bromide was carried out in acetic acid at room temperature, the product isolated depended upon the reaction time and the molar equivalent of the hydrogen halides. The reaction of IIa with a large excess of hydrogen chloride or bromide (4—6 mol. eq.) for a short period (15—30 min) gave imidyl halides (Va, b). On prolonged stirring in the same medium, the cyclization of Va and Vb occurred gradually to form 6-amino-2-halogeno-4-hydroxypyrimidines (VIa, d). On the other hand, IIa treated with two molar or less equivalent of hydrogen chloride or bromide gave the imidyl halides (Va, b), but no pyrimidines. The reaction of IIa with hydrogen iodide proceeded in the similar manner as with hydrogen chloride and bromide to give imidyl iodide (Vc). In contrast to Va and Vb, the imidyl iodide (Vc) did not undergo further cyclization under the similar reaction conditions. The imidyl bromide (Vb) being the easiest to prepare, most of the structural studies were carried out with this material. Analytically pure imidyl bromide (Vb) was

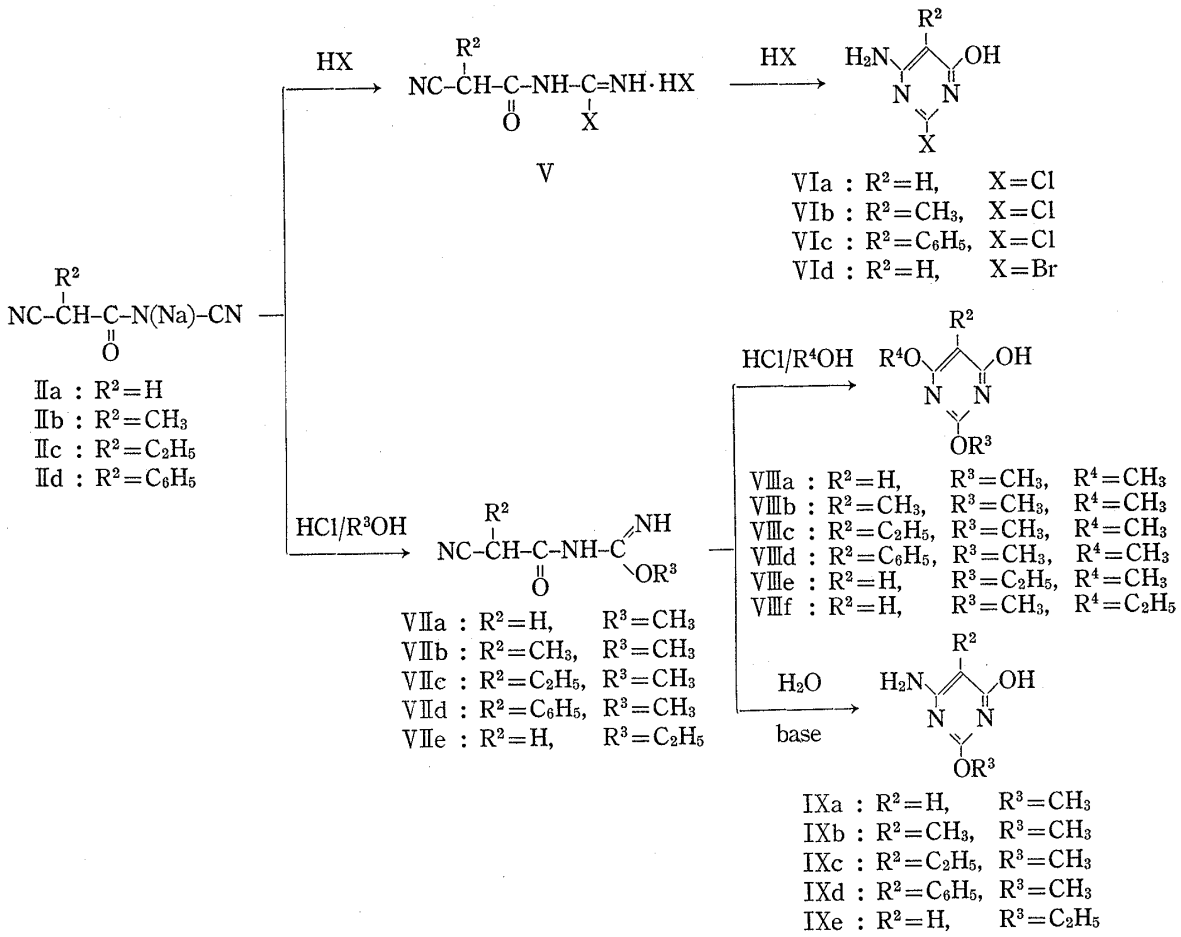


Chart 1

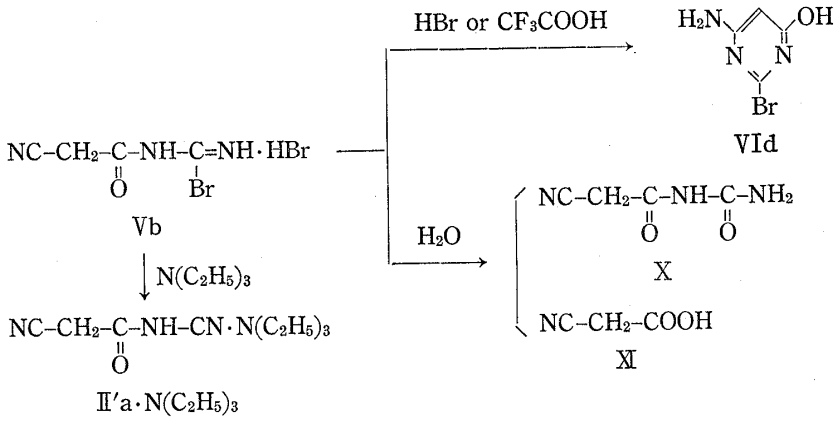


Chart 2

obtained by the reaction of cyanoacetylcyanamide (II'a) with two molar equivalents of hydrogen bromide in acetic acid as colorless powders, mp 174—176° (decomp.), whose structure was presumed on the basis of the following spectral data together with elemental analysis, $C_4H_4ON_3Br \cdot HBr$. The IR spectrum of Vb showed absorptions at 2250 cm^{-1} ($-CH_2-\underline{C}N$) and 1750 cm^{-1}, which was characteristic of a group of Va—c. The mass spectrum gave no parent ion peak, but a fragment ion peak at *m/e* 68 presumably due to $NC-CH_2-CO^{+}$ ion. The NMR spectrum (DMSO-d_6) exhibited each singlet at 4.05 ppm and 8.0 ppm due to a methylene and amino or imino groups, respectively. These spectral data suggested that Vb is an open chain structure and not a cyclic one. Further, the structure of Vb was confirmed by the following reactions (Chart 2). The treatment of Vb with triethyl-

amine in benzene gave II'a in the form of triethylamine salt as a hygroscopic oil. The hydrolysis of Vb in acidic medium gave cyanoacetylurea (X) together with cyanoacetic acid (XI). In addition, when Vb was treated with an excess of hydrogen bromide in acetic acid or with trifluoroacetic acid, the pyrimidine (VId) was obtained. Although imidyl chloride (Va) and iodide (Vc) could not be obtained in pure stage, the IR spectra in the 1500—1800 cm^{-1} region and the mass spectra of these three halides were similar, indicating that they all had the same basic structure. These results lead to conclusion that the cyclization of cyanoacetylcyanamides with hydrogen chloride or bromide proceeded *via* corresponding imidyl halides (Va, b) as an intermediate. The pyrimidines thus prepared are listed in Table III.

Table III. 6-Amino-2-halogeno-4-hydroxypyrimidines (VI)

Compd. No.	R^2	X	Reactn. solvent	Yield (%)	mp[a] (°C)	UV λ_{max}^{MeOH} nm (log ε)	Formula	*Anal.* Calcd. (Found) C	H	N	X
VIa	H	Cl	AcOH	56	>300	214(4.39) 257(3.73)	$C_4H_4ON_3Cl$	33.01 (33.14)	2.77 (2.74)	28.87 (28.86)	24.36 (24.19)
VIb	CH_3	Cl	acetone	97	220	213(4.31) 267(3.85)	$C_5H_6ON_3Cl$	37.63 (37.63)	3.79 (3.83)	26.33 (26.73)	22.22 (22.08)
VIc	C_6H_5	Cl	acetone	72	260—261 (decomp.)	218(4.33) 265(3.85)	$C_{10}H_8ON_3Cl$	54.19 (54.11)	3.64 (3.74)	18.96 (19.20)	16.00 (15.81)
VId	H	Br	AcOH	72	>280	216(4.36) 259(3.73)	$C_4H_4ON_3Br$	25.28 (25.21)	2.12 (2.26)	22.12 (22.42)	42.06 (41.89)

a) Recrystn. solvent: MeOH

The structures of VIa, d were confirmed by treatment with sodium methoxide to give 6-amino-4-hydroxy-2-methoxypyrimidine (IXa)[7] and VIb, c were identified by catalytic hydrogenation (Pd/C) to give 5-substituted 6-amino-4-hydroxypyrimidines (XIIa: C_5–CH_3, XIIb: C_5–C_6H_5), which were prepared by desulfulization (Raney Nickel) of corresponding 5-substituted 6-amino-4-hydroxy-2-mercaptopyrimidines (XIIIa: C_5–CH_3,[8] XIIIb: C_5–C_6H_5).

When sodium cyanoacetylcyanamides (II) were allowed to react with an excess of alcoholic hydrogen chloride at room temperature, 2,6-dialkoxy-4-hydroxypyrimidines (VIII) were

Table IV. N-Cyanoacetyl-O-alkylisoureas (VII)

Compd. No.	R^2	R^3	mp (°C)	Yield (%)	Recrystn. solvent	Formula	*Anal.* Calcd. (Found) C	H	N
VIIa	H	CH_3	118—119	75	H_2O	$C_5H_7O_2N_3$	42.55 (42.04)	5.00 (4.98)	29.78 (35.08)
VIIb[a]	CH_3	CH_3	184—185	92	HCl–MeOH	$C_6H_9O_2N_3 \cdot HCl$	37.61 (37.87)	5.26 (5.39)	21.93 (22.24)
VIIc	C_2H_5	CH_3	oil[b]	69	—	$C_7H_{11}O_2N_3$	49.69	6.55	24.84
VIId	C_6H_5	CH_3	68—69	82	H_2O–MeOH	$C_{11}H_{11}O_2N_3$	60.82 (60.89)	5.10 (5.34)	19.35 (19.79)
VIIe	H	C_2H_5	94—95	82	H_2O	$C_6H_9O_2N_3$	46.45 (46.66)	5.83 (5.73)	27.08 (27.92)

a) HCl salt
b) characterized by IR and NMR spectra

7) a) M. Engelmann, *Chem. Ber.*, **42**, 177 (1909); b) W. Pfleiderer, *Chem. Ber.*, **90**, 2272 (1957).
8) H.J. Bielig and A. Loester, Ger. Patent 859168 (1952) [*C.A.*, **50**, 9452^h (1956)].

formed *via* N-cyanoacetyl-O-alkylisoureas (VII) as intermediates, which could be obtained by the reaction of II with an excess of alcoholic hydrogen chloride at 0—5° followed by neutralization with aqueous sodium bicarbonate solution (Chart 1). However, the yields of VIII were not satisfactory due to the side reaction which provided the formation of dialkyl malonates. The structures of VII rest on elemental analyses, IR absorption at 2240 cm^{-1} (>CH–CN), and cyclization to IX as shown in Chart 1. N-Cyanoacetyl-O-alkylisoureas (VIIa—e) are listed in Table IV.

Dialkoxypyrimidines (VIIIe, f) which have different alkoxy groups at the 2- and 6-positions of the pyrimidine ring, could be obtained also by the reaction of VIIe and VIIa with hydrogen chloride in the different alcohols from those used in the preparation of VIIe and VIIa, respectively. The pyrimidines (VIII) thus obtained are summarized in Table V.

Table V. 2,6-Dialkoxy-4-hydroxypyrimidines (VIII)

Compd. No.	R^2	R^3	R^4	Yield (%)	mp (°C)	Recrystn. solvent	UV λ_{max}^{MeOH} nm (log ε)	Formula	*Anal.* Calcd. (Found) C	H	N
VIIIa	H	CH_3	CH_3	26	195	H_2O	223(3.60) 261(3.92)	$C_6H_8O_3N_2$	46.15 (45.85)	5.16 (5.10)	17.94 (18.00)
VIIIb	CH_3	CH_3	CH_3	47	224—226	H_2O–MeOH	230(3.57) 270(3.89)	$C_7H_{10}O_3N_2$	49.41 (49.80)	5.92 (5.89)	16.46 (16.53)
VIIIc	C_2H_5	CH_3	CH_3	12	221	H_2O–MeOH	230(3.69) 270(4.00)	$C_8H_{12}O_3N_2$	52.17 (52.00)	6.57 (6.54)	15.21 (15.51)
VIIId	C_6H_5	CH_3	CH_3	60	239—240	H_2O–MeOH	280(4.06)	$C_{12}H_{12}O_3N_2$	62.06 (61.87)	5.21 (5.21)	12.06 (12.48)
VIIIe	H	C_2H_5	CH_3	27	150—152	MeOH	224(3.61) 262(3.91)	$C_7H_{10}O_3N_2$	49.41 (49.34)	5.92 (5.88)	16.46 (16.55)
VIIIf	H	CH_3	C_2H_5	32	184—185	MeOH	223(3.60) 260(3.92)	$C_7H_{10}O_3N_2$	49.41 (49.34)	5.92 (5.82)	16.46 (16.59)

The structure of VIIIa was established by its independent synthesis from methyl ethoxycarbonylthionacetate (XIV), bp 64—65° (3 mmHg), with O-methylisourea (Chart 3). Compound XIV was prepared by the analogous procedure given by Barnikow, *et al.*[9] The other pyrimidines (VIIIb—f) were assigned by analytical and spectral data (ultraviolet (UV), IR and NMR spectra) comparing with those of VIIIa.

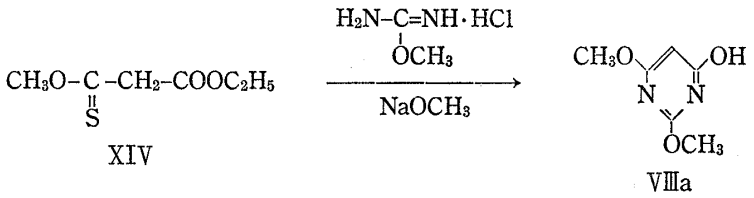


Chart 3

Heating VII in water in the presence of a weak base such as sodium bicarbonate and sodium carbonate afforded 2-alkoxy-6-amino-4-hydroxypyrimidines (IX), which are listed in Table VI.

The structures of IXa, IXb and IXe were confirmed by direct comparison with the authentic samples,[7,10,11] and other pyrimidines (IXc, d) were confirmed by elemental analyses and comparison of spectral data (UV, IR and NMR) with those of IXa, b, e.

9) G. Barnikow and G. Strickman, *Chem. Ber.*, **100**, 1428 (1967).
10) W. Pfleiderer and G. Strauss, *Ann. Chem.*, **612**, 173 (1958).
11) Bayer & Co., Ger. Patent 155732 (1909) [*Beil.*, **25**, 63 (1939)].

Table VI. 2-Alkoxy-6-amino-4-hydroxypyrimidines (IX)

Compd. No.	R^2	R^3	Yield (%)	mp (°C)	Recrystn. solvent	UV λ_{max}^{MeOH} nm (log ε)	Formula	*Anal.* Calcd. (Found) C	H	N
IXa[a]	H	CH_3	76	221 (decomp.)	H_2O	211(4.35) 262(4.23)	$C_5H_7O_2N_3$	42.55	5.00	29.78
IXb[b]	CH_3	CH_3	91	243	H_2O	211(4.12) 269(4.11)	$C_6H_9O_2N_3$	46.45 (46.32)	5.85 (5.75)	27.08 (27.16)
IXc	C_2H_5	CH_3	49	226	MeOH	211(4.20) 270(4.16)	$C_7H_{11}O_2N_3$	49.61 (48.99)	6.55 (6.44)	24.84 (24.58)
IXd	C_6H_5	CH_3	74	241 (decomp.)	MeOH	210(4.38) 267(4.11)	$C_{11}H_{11}O_2N_3$	60.82 (60.70)	5.10 (5.11)	19.35 (19.38)
IXe[c]	H	C_2H_5	75	245—246 (decomp.)	H_2O	210(4.29) 263(4.11)	$C_6H_9O_2N_3$	46.45 (46.25)	5.85 (5.77)	27.08 (27.18)

a) lit.,[7a] mp 214—216°; lit.,[7b] mp 227—229°
b) lit.,[10] mp 237—238°
c) lit.,[11] mp 247°

Cyclization of N-Cyano-cyanoacetamidines (IV) with Hydrogen Halides

N-Cyano-cyanoacetamidines (IV) were similarly cyclized with hydrogen chloride or bromide in acetic acid to give exclusively 4,6-diamino-2-halogenopyrimidines (XV) after neutralization of the corresponding halide salts of XV in good yields (Chart 4).

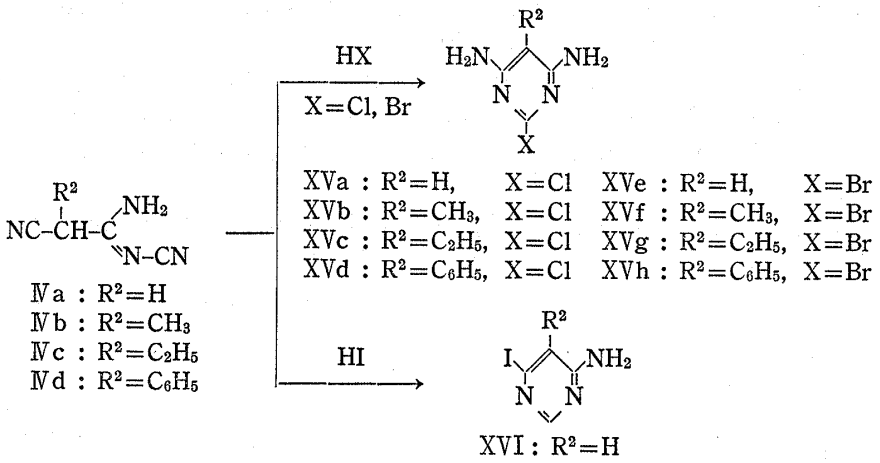


Chart 4

This cyclization might proceed analogously *via* an imidyl halide intermediate, but all attempts to detect the intermediate were not successful. The pyrimidines (XV) thus obtained are listed in Table VII.

In marked contrast to the hydrogen chloride and bromide, the treatment of IVa with hydrogen iodide in acetic acid gave 6-amino-4-iodopyrimidine (XVI)[12] in 43.5% yield unexpectedly. This cyclization might occur *via* 6-amino-2,4-diiodopyrimidine involving reductive deiodination at the 2-position with the excess hydrogen iodide. This estimation was supported by the analogous cyclization[3c] and the following reactions: the treatment of XVe with an excess of hydrogen iodide in acetic acid gave 4,6-diaminopyrimidine (XVIII)[13] and in the

12) E. Bütter, *Chem. Ber.*, **36**, 2227 (1903).
13) R.M. Evans, P.G. Jones, P.J. Palmar, and F.F. Stephens, *J. Chem. Soc.*, **1956**, 4106.

Table VII. 4,6-Diamino-2-halogenopyrimidines (XV)

Compd. No.	R^2	X	Yield (%)	mp (°C)	Recrystn. solvent	UV λ_{max}^{MeOH} nm (log ε)	Formula	*Anal.* Calcd. (Found) C	H	N	X
XVa	H	Cl	51	273—274 (decomp.)	H_2O	223(4.36) 262(3.73)	$C_4H_5N_2Cl$	33.23 (33.07)	3.49 (3.47)	38.76 (38.42)	24.52 (24.76)
XVb	CH_3	Cl	56	244—245	H_2O	218(4.43) 268(3.91)	$C_5H_7N_2Cl$	30.79 (30.71)	4.13 (4.09)	28.72 (28.37)	36.35 (36.47)
XVc	C_2H_5	Cl	77	238.5—239.5	AcOEt–acetone	219(4.49) 268(3.92)	$C_6H_9N_2Cl$	41.75 (41.81)	5.26 (5.38)	32.46 (32.31)	20.54 (20.65)
XVd	C_6H_5	Cl	47	249—251	MeOH	211(4.42) 289(3.93)	$C_{10}H_9N_2Cl$	54.43 (54.37)	4.11 (4.20)	25.39 (25.66)	16.07 (16.25)
XVe	H	Br	77	255 (decomp.)	MeOH	224(4.36) 263(3.76)	$C_4H_5N_2Br$	25.42 (25.54)	2.67 (2.67)	29.64 (29.86)	42.28 (41.99)
XVf	CH_3	Br	86	208—210	MeOH	208(4.24) 288(3.89)	$C_5H_7N_2Br$	29.58 (29.59)	3.47 (3.37)	27.59 (27.78)	39.35 (39.30)
XVg	C_2H_5	Br	95	241—244	MeOH	219(4.50) 268(3.93)	$C_6H_9N_2Br$	33.20 (33.21)	4.18 (4.14)	25.81 (26.06)	36.81 (36.86)
XVh	C_6H_5	Br	91	250—252	MeOH	211(4.45) 290(3.93)	$C_{10}H_9N_2Br$	45.30 (45.20)	3.42 (3.42)	21.13 (21.34)	30.14 (30.02)

similar manner, 6-amino-2,4-dichloropyrimidine (XIX)[14] gave 6-amino-4-chloropyrimidine (XVII).[15]

In addition, the reaction of IVa with methanolic hydrogen chloride was found to give dimethyl malonate with decomposition and to give neither the desired intermediate corresponding to VIIa nor a pyrimidine derivative.

The structures of XVa and XVe were confirmed by catalytic hydrogenation (Pd/C) to give 4,6-diaminopyrimidine (XVIII).[13] The structures of other pyrimidines (XVb—d and XVf—h) rest on elemental analyses and comparison of their spectral data (UV, IR and NMR) with those of XVa and XVe.

Although numerous methods for the synthesis of pyrimidine rings were summarized by Brown,[16] the methods described in this paper for the direct preparation of halogeno- and alkoxy-pyrimidines provide many advantages over conventional method.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Hitachi EPI-G2 and a Hitachi 285. NMR spectra were taken at 60 MHz with tetramethylsilane as an internal standard using a Hitachi Perkin Elmer R-20B and a Varian anaspect EM 360. Mass spectra were measured on a Jeol-01SG-2 mass spectrometer. UV spectra were taken on a Hitachi spectrophotometer 124.

Sodium Cyanoacetylcyanamides (II)——General Procedure: A solution of cyanamide (1.68 g, 0.04 mole) and alkyl cyanoacetates (I: 0.04 mole) in a methanolic solution of NaOMe[prepared with 0.92 g (0.04 mole) of Na and 40 ml MeOH] was allowed to stand at room temperature for 3—5 hr. The solvent was removed by evaporation and the residue was treated with EtOH to give II. Recrystallization was carried out by the solvents described in Table I.

Cyanoacetylcyanamide (II'a)——A solution of IIa (13.1 g, 0.1 mole) in H_2O (130 ml) was passed over the column packed with the cation exchange resin, Diaion SK-1B (H-form, 100 ml), with cooling and then cold H_2O (200 ml) was passed over the column. The effluent and washing were combined and concentrated *in vacuo* below 25° until most of crystals were precipitated. After chilling, the crystals were collected by filtration and washed with a small amount of cold H_2O, and dried under reduced pressure over $CaCl_2$ to give II'a;

14) H. Bretschneider, W. Klötzer, and G. Spiteller, *Monatsh. Chem.*, **92**, 128 (1961).
15) D.J. Brown and J.S. Harper, *J. Chem. Soc.*, **1961**, 1298.
16) D.J. Brown, "The Pyrimidines," John Wiley and Sons Inc., New York and London, 1962, pp. 31—110.

8.31 g, yield 76.2%, mp 84.5—85.5° (prisms from H_2O). *Anal.* Calcd. for $C_4H_3ON_3$: C, 44.04; H, 2.77; N, 38.52. Found: C, 43.85; H, 2.77; N, 38.55.

N-Cyano-cyanoacetamidines (IV)——General Procedure: To a cold solution of methyl cyanoacetimidate hydrochlorides (III)[6] (0.021 mole) and cyanamide (883 mg, 0.021 mole) in MeOH (20 ml) was added a methanolic solution of NaOMe [prepared with 483 mg (0.021 mole) of Na and 10 ml MeOH]. The mixture was stirred at room temperature for 3 hr. Sodium chloride separated was removed by filtration and washed with MeOH. The filtrate and washings were evaporated *in vacuo* to yield an oily residue. Crystallization of the residue from EtOH yielded IV, which are shown in Table II.

6-Amino-2-halogeno-4-hydroxypyrimidines (VI)——General Procedure: i) To a solution of IIa (1.31 g, 0.01 mole) in AcOH (10 ml) was added dropwise a solution of 5—6 molar equivalents of hydrogen halides in AcOH (HCl 8%, HBr 23% solution) at 20—25° during 5 min with stirring. After 6 hr, the precipitates separated were collected by filtration and washed subsequently with AcOH and ether, and then suspended in H_2O. Neutralization of the suspension with $NaHCO_3$ yielded VIa, d. Recrystallization from MeOH gave pure VIa, d, which are shown in Table III. ii) To a suspension of IIb, d (5.0 mmole) in acetone (30 ml) was gradually introduced 1.8 g (50 mmoles) of dry HCl gas at 0—5°, and then the mixture was allowed to stand overnight at room temperature. After evaporation of the solvent *in vacuo*, H_2O was added to the residue. The aqueous solution was extracted with benzene to remove side products, if neccessary. The aqueous layer was neutralized with aq. $NaHCO_3$ solution to give colorless crystals, which were collected by filtration and washed with H_2O to give VIb, c, which are shown in Table III.

Reaction of II'a with HBr to Vb——To a solution of II'a (546 mg, 5.0 mmoles) in AcOH (10 ml) was added dropwise 26% HBr–AcOH (3.5 g, HBr: 11 mmoles) during 5 min at 20—25°. After stirring for an additional 30 min, the precipitates separated were collected by filtration and washed successively with AcOH and ether, and quickly dried under reduced pressure over $CaCl_2$ to give Vb as colorless crystalline powders in analytically pure stage. Yield, 1.21 g, 89.6%, mp 174—176° (with decomposition sintering at 155°). *Anal.* Calcd. for $C_4H_4ON_3Br \cdot HBr$: C, 17.73; H, 1.86; N, 15.51; Br, 58.99. Found: C, 17.94; H, 1.95; N, 15.53; Br, 59.27. IR (KBr) cm^{-1}: 2250, 1750, 1610, 1505. NMR (DMSO-d_6) ppm: 4.05 (s, $-C\underline{H}_2-$), 8.0 (broad, s, amino or imino H). Mass Spectrum: *m/e* 82, 80, 68, 43, 40.

Va and Vc were similarly prepared from IIa with HCl and HI in AcOH in impure form, respectively. Va: mp 121—125° (decomp.). IR (KBr) cm^{-1}: 2250, 1745, 1620, 1520. Mass Spectrum: *m/e* 68, 43, 40, 38, 36. Vc: mp 118—122° (decomp.). IR (KBr) cm^{-1}: 2250, 1745, 1585, 1500. Mass Spectrum: *m/e* 128, 68, 43, 40.

Reaction of Vb with Triethylamine——To a suspension of Vb (271 mg, 1.0 mmole) in benzene (5 ml) was added dropwise a solution of triethylamine (309 mg, 3 mmoles) in benzene (3 ml) with stirring at room temperature for 6 hr. The insoluble materials were removed by filtration, and the filtrate was evaporated *in vacuo* below 40° to give a pale yellow oil, 0.13 g, (61.9%), which was identical with that obtained by the reaction of II'a (110 mg, 1.0 mmole) with triethylamine (103 mg, 1.0 mmole) in benzene in a quantitative yield (IR, NMR spectra). *Anal.* Calcd. for $C_{10}H_{18}ON_4 \cdot 1/2H_2O$: N, 25.55. Found: 25.82.

Hydrolysis of Vb——A solution of Vb (1.35 g, 5 mmoles) in H_2O (4 ml) was allowed to stand at room temperature for 1 hr, then the mixture was evaporated at 50—60° *in vacuo*. The residue was crystallized by treatment with H_2O. The crystals were collected by filtration to give cyanoacetylurea (X), 0.12 g, mp 203—205°, which was identical with an authentic sample[17] (mixed melting point, IR spectrum). The filtrate was extracted with ether, and the ether solution was evaporated to dryness to give an solid, 0.158 g, which was identical with the authentic cyanoacetic acid (XI)[18] on the basis of IR spectrum.

Reaction of Vb with HBr——To a suspension of Vb (255 mg, 0.94 mmole) in AcOH (3 ml) was added dropwise 26% HBr–AcOH (1.54 g, HBr 5 mmoles) with stirring at room temperature and the mixture was stirred for 5 hr at the same temperature. The precipitates were collected by filtration, washed with AcOH and ether, added to H_2O, and neutralized with $NaHCO_3$ to give crystalline powders, 60 mg, which were identical with VId obtained above (IR, NMR spectra).

Reaction of Vb with Trifluoroacetic Acid——A suspension of Vb (158 mg, 0.58 mmole) in CF_3COOH (1 ml) was stirred for 24 hr at room temperature. The precipitates were worked up in the same manner as described above to give colorless powders, 59 mg, which were purified by preparative thin-layer chromatography (TLC) to give VId, 30 mg, yield 27.0%, which was identical with VId obtained above (Table III) on the basis of IR and NMR spectra.

Reaction of VIa, d with NaOMe——i) VIa (100 mg) was added to a solution of NaOMe [prepared with 37 mg of Na and 2 ml MeOH]. The solution was heated in a sealed tube at 120° for 5 hr. The mixture was treated in a usual manner to give IXa (75 mg, yield 77%), which was identical with an authentic sample[7] (mixed melting point, IR spectrum). ii) A solution of VId (190 mg) and Na (50.6 mg) in MeOH (6 ml) was treated in the same manner to give IXa (72 mg, yield 52%), which was identical with an authentic sample[7] (mixed melting point, IR spectrum).

17) M. Conrad and A. Schulze, *Chem. Ber.*, **42**, 735 (1909).
18) Commercially available (Tokyo Kasei Kogyo Co., Ltd., Tokyo).

Hydrogenation (Pd/C) of VIb, c——VIb (300 mg) was reduced with H_2 in 90% MeOH (40 ml) over 5% Pd/C (280 mg) at atmospheric pressure and room temperature. The mixture was filtered and the filtrates were evaporated. The residue was crystallized from EtOH to give XIIa (185 mg, yield 79%, mp 240—242°). *Anal.* Calcd. for $C_5H_7ON_3$: C, 47.99; H, 5.64; N, 33.58. Found: C, 47.85; H, 5.39; N, 33.57. VIc (200 mg) was reduced similarly to give XIIb (148 mg, yield 87%, mp 286—288° (decomp.) from MeOH). *Anal.* Calcd. for $C_{10}H_9ON_3$: 64.11; H, 4.85; N, 22.45. Found: C, 63.73; H, 4.81; N, 22.12.

6-Amino-4-hydroxy-2-mercapto-5-phenylpyrimidine (XIIIb)——A mixture of ethyl α-phenylcyanoacetate (Id: 2.84 g, 15 mmoles), thiourea (1.14 g, 15 mmoles) and an ethanolic solution of NaOEt [prepared with 1.035 g (45 mmoles) of Na and 30 ml EtOH] was refluxed for 9 hr, and the mixture was evaporated. The residue was added to H_2O (30 ml), and the mixture was adjusted to pH 4 with 10% AcOH to separate crystals together with the recovered Id, which was removed by extraction with benzene. The crystals were collected by filtration to give XIIIb (223 mg, yield 6.8%, mp>300° from MeOH). *Anal.* Calcd. for $C_{10}H_9ON_3S$: C, 54.78; H, 4.14; N, 19.17; S, 14.62. Found: C, 54.51; H, 4.15; N, 19.00; S, 14.88.

Desulfulization (Raney Nickel) of XIIIa, b to XIIa, b——A suspension of XIIIa[8] (1.00 g), Raney Nickel catalyst (W-4) freshly prepared from Raney Nickel alloy (20 g) in EtOH (60 ml) refluxed for 3.5 hr. The mixture was filtered on hot and washed with hot MeOH. The combined filtrate and washings were evaporated. The residue (0.31 g) was crystallized from EtOH to give XIIa, identical with that obtained by the hydrogenation (Pd/C) of VIb as shown above (mixed melting point, IR spectrum). In the same manner, XIIIb (100 mg) was reduced to give XIIb (32.3 mg, mp 286—288° (decomp.), yield 37.8%), identical with that obtained by the hydrogenation (Pd/C) of VIc as shown above (mixed melting point, IR spectrum).

N-Cyanoacetyl-O-alkylisoureas (VII)——General Procedure: To a solution of IIa—d (10 mmoles) in alcohols (10 ml) was added dropwise 35% HCl–alcohol solution (HCl, 5—10 molar equivalents) at 0—5° with stirring during 10 min. The mixture was stirred for additional 1—2 hr at the same temperature and then neutralized with $NaHCO_3$ to pH 6 with cooling. The aqueous solution was evaporated to remove the alcohol *in vacuo* below 25° and the aqueous residue was extracted with ethyl acetate of ether. The organic layer was evaporated *in vacuo* at room temperature to give crude VII (crystals or oil), which were purified by recrystallization or as hydrochloride salt as shown in Table IV.

2,6-Dialkoxy-4-hydroxypyrimidines (VIII)——General Procedure: i) $R^3=R^4$: To a solution of IIa—d (10 mmoles) in MeOH (10 ml) was added dropwise 35% HCl–MeOH (HCl, 10 molar equivalents) at 0—5° with stirring, and then the mixture was allowed to stand overnight at room temperature, and was evaporated *in vacuo*. The residue was dissolved in H_2O, and the aqueous solution was extracted with benzene to remove side products, if neccessary, and evaporated to a small volume to separate crystals. The crystals were collected by filtration and washed with H_2O to give VIIIa—d. Recrystallization was carried out by the solvents shown in Table V. ii) $R^3\neq R^4$: To a solution of VIIa, e (10 mmoles) in alcohols (VIIa in EtOH, VIIe in MeOH) was added dropwise 35% HCl–alcohol (HCl, 10 molar equivalents). The mixture was allowed to stand overnight at room temperature (on using EtOH as solvent, the reaction was carried out at 40—60° for 6 hr). The mixture was treated in the same manner as procedure i) to give VIIIf, e (Table V).

VIIIa from XIV with O-Methylisourea——To a mixture of O-methylisourea hydrochloride (1.11 g, 0.01 mole) and a solution of NaOMe [prepared with 0.46 g of Na and 15 ml MeOH] was added methyl ethoxycarbonylthionacetate (XIV: 1.62 g, 0.01 mole). The mixture was refluxed for 2.5 hr, and then evaporated. The residue was added to H_2O, and the aqueous solution was neutralized with 10% AcOH. The precipitates separated were collected by filtration and dried to give colorless crystals, 1.10 g, mp 191° (from MeOH), which was identical with VIIIa obtained above (mixed melting point, IR spectrum).

2-Alkoxy-6-amino-4-hydroxypyrimidines (IX)——General Procedure: To a solution of VIIa—e (2.0 mmoles) and Na_2CO_3 (0.21 g) in H_2O (5 ml) was heated at 90—95° for 1 hr. After cooling, the mixture was neutralized to pH 6 with 10% AcOH. The precipitates separated were collected by filtration and dried to give IXa—e (Table VI).

4,6-Diamino-2-halogenopyrimidines (XV)——General Procedure: To a suspension of IVa—d (0.01 mole) in AcOH (25 ml) was slowly introduced dry HCl gas (0.04—0.06 mole) with stirring during 4 hr or was added dropwise 26% HBr–AcOH (HBr, 0.04 molar equivalents) at 20—25° with additional stirring for 2—4 hr. Then the precipitates separated was collected by filtration , washed with AcOH and ether to give the halide salts of XV, which were suspended in a small amount of H_2O and neutralized with $NaHCO_3$. The precipitates were collected by filtration and dried to give XV. The filtrate (AcOH) and washings (ether) were evaporated and the residue was dissolved in H_2O followed by neutralization with $NaHCO_3$ to give a second crop of XV. XV were purified by recrystallization from the solvents shown in Table VII. When no halide salt of XV was separated, the reaction mixture was evaporated and the residue was dissolved in H_2O followed by neutralization with $NaHCO_3$ to give XV.

Reaction of IVa with HI——To a suspension of IVa (0.162 g, 1.5 mmoles) in AcOH (2 ml) was added 15.3% HI–AcOH[3b] (5.1 g, 6.1 mmoles) at room temperature and the mixture was stirred for 1.5 hr. The precipitates separated were collected by filtration, washed with ether, and added to H_2O (2 ml) and neutralized with $NaHCO_3$ to give XVI, 0.144 g, yield 43.5%, mp 207—210° (from H_2O–MeOH), which was identical with an authentic sample[12] (mixed melting point, IR spectrum).

Reaction of XVe with HI to XVIII——To a mixture of XVe (94.5 mg, 0.5 mmoles) and AcOH (0.5 ml) was added 15.3% HI–AcOH (2.13 g, HI 2.5 mmoles) at room temperature. The mixture was stirred for 1 hr at room temperature, and the precipitates were collected by filtration, washed with ether, and added to H_2O (2 ml) followed by neutralization with $NaHCO_3$ to recover XVe (60.7 mg, 64.2%), which was collected by filtration. The filtrate was evaporated and the residue was dissolved in 95% EtOH (2 ml). The solution was mixed with picric acid (100 mg) in 95% EtOH (5 ml) to give the picrate of XVIII as yellow needles (56.4 mg, 33.2%, mp 299—300°), which was identical with an authentic sample prepared from XVIII[13] with picric acid in a usual manner (mixed melting point, IR spectrum). *Anal.* Calcd. for $C_{10}H_9O_7N_7$: C, 35.41; H, 2.67; N, 28.90. Found: C, 35.39; H, 2.67; N, 28.95.

Reaction of XIX with HI to XVII——To a suspension of XIX[14] (0.82 g, 5 mmoles) in AcOH (10 ml) was added 15.3% HI–AcOH (21.3 g, HI 25 mmoles) with stirring at room temperature. The mixture was stirred for 3 hr at the same temperature, and then evaporated *in vacuo*. The residue was mixed with H_2O (50 ml), and iodine separated was filtered off. The filtrate was treated with $CHCl_3$, and the aqueous layer was evaporated to dryness. The residue was added to H_2O (30 ml) and insoluble materials were filtered off. The filtrate was decolorized with $Na_2S_2O_4$ and concentrated to *ca.* 5 ml to give XVII (163 mg, 25.1%, mp 206—207°), which was identical with an authentic sample[15] (mixed melting point, IR spectrum).

Reaction of IVa with HCl-MeOH——To a solution of IVa (1.08 g, 0.01 mole) in MeOH (5 ml) was added 41.7% HCl–MeOH (8.8 g, HCl 0.1 mole) with stirring at 0—5°, and the mixture was stirred at the same temperature for 4 hr and then allowed to stand overnight at room temperature. The mixture was evaporated *in vacuo*. The residue, in which no pyrimidine derivative was detected by TLC, was extracted with benzene and the benzene solution was evaporated to give an oil, 0.50 g, which was identical with the authentic dimethyl malonate[18] (IR, NMR spectra and TLC).

Hydrogenation (Pd/C) of XVa, e to XVIII——XVa (150 mg) was reduced with H_2 in MeOH (15 ml) over 5% Pd/C (200 mg) at atmospheric pressure and room temperature for 4 hr. The mixture was filtered and the filtrate was evaporated. The residue was treated with 5% $NaHCO_3$ to give XVIII (78 mg, 68.5%), which was identical with an authentic sample[13] (mixed melting point, IR spectrum). Similarly a solution of XVe (100 mg) and 5% Pd/C (100 mg) in MeOH (10 ml) was reduced with H_2 to give XVIII (47.9 mg, 58.3%) after preparative TLC ($CHCl_3$: MeOH, 1: 1), which was identical with an authentic sample[13] as shown above.

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