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A Novel Synthesis of Pyrimidines. II.[1] Cyclization of Alkyl N-Cyano Cyanoacetimidates with Hydrogen Halides

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The synthesis of alkyl N-cyano cyanoacetimidates (II) and the action of hydrogen halides on II have been examined. The reaction of alkyl cyanoacetimidates (I) with cyanamide in the presence of a dispersing agent gave II in good yields. The cyclization of II with hydrogen chloride gave a mixture of 4-alkoxy-6-amino-2-chloropyrimidines (IV) and 4-alkoxy-2-amino-6-chloropyrimidines (V), but the addition of a Lewis acid led the cyclization in one specific direction exclusively giving IV. Hydrogen bromide and iodide effected cyclization reversely to give 2-amino-6-bromo-4-hydroxy(alkoxy)pyrimidines (IX, X) and 2-amino-4-hydroxy-6-iodopyrimidine (XII) as main products, respectively.

In previous papers,[1] we reported that the cyclization of N-cyanoaceto derivatives of cyanamide mainly with hydrogen halides gave directly halogeno- or alkoxy-pyrimidines. The successful cyclization of the N-cyanoaceto derivatives to the pyrimidine ring suggested that analogous alkyl N-cyano cyanoacetimidates (II) might be led to the corresponding pyrimidines. Although the cyclization of II to the pyrimidine ring was presented in a preliminary communication,[3] we wish to give here more details on the synthesis and cyclization of II.

Alkyl N-Cyano Cyanoacetimidates (II)

The chief difficulty in extending the scope of the cyclization to pyrimidines laid in the unavailability of the starting materials II. Some applications of the known methods for preparing N-cyanoimidates[4a,b] to the preparation of II failed as follows. a) The reaction of methyl cyanoacetimidate hydrochloride (Ia)[5] with cyanamide in methanol[4a] afforded methyl orthocyanoacetate and in phosphate buffer[4b] gave methyl cyanoacetate, respectively. b) Heating methyl orthocyanoacetate with cyanamide in acetic anhydride[4a] produced only resinous products. However, when Ia was mixed with cyanamide[6] without a solvent at room temperature, methyl N-cyano cyanoacetimidate (IIa) was found to form in 50% yield together with cyanoacetamide (III). In order to improve the yield of IIa, reaction conditions were examined. Consequently, by using both an inert solvent and some dispersing agents, the reaction was found to proceed smoothly to give IIa in good yield. In this reaction, the solvent and dispersing agent appeared to play an important role. Satisfactory solvents were benzene, chloroform and ethylene dichloride, but not ether, acetone or acetic acid. As a dispersing agent, molecular sieves, calcium carbonate, and aluminum oxide were used in the form of fine powders for practical purposes (Table I).

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[1] Part I: T. Hirayama, M. Kamada, H. Tsurumi, and M. Mimura, *Chem. Pharm. Bull.* (Tokyo), **24**, 26 (1976). "submitted."

[2] Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*

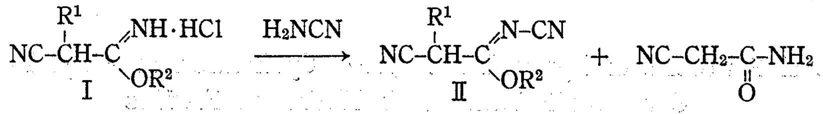
[3] T. Hirayama, M. Kamada, M. Mimura, and H. Tsurumi, *Heterocycles*, **2**, 461 (1974).

[4] *a*) K.R. Huffman and F.C. Schaefer, *J. Org. Chem.*, **28**, 1816 (1963); *b*) W. Lwowski, *Synthesis*, **1971**, 263.

[5] S.M. McElvain and J.P. Schroeder, *J. Am. Chem. Soc.*, **71**, 40 (1949).

[6] Crystalline cyanamide was easily obtained by evaporation of the commercially available 50% aqueous solution.

Table I. Effects of Dispersing Agent



Ia: $R^1=H, R^2=CH_3$ IIa: $R^1=H, R^2=CH_3$ III

Dispersing agent	IIa yield (%)[a]	III yield (%)[b]
—	61	17.3
MS-4A[c]	86—91	1.9—2.3
MS-13X[c]	85	6.5
$CaCO_3$	79	—[d]
Al_2O_3	82	4.2

reaction solvent: benzene

a) crude yield, purity 90—95%. NMR determination conditions: solvent CCl_4; signal, IIa CH_3O- 4.08 ppm, *p*-nitrotoluene (internal standard) CH_3- 2.47 ppm.

b) Gas chromatographic determination conditions: 5% PEG/Anakrom ABS 60—70 mesh; 200 × 0.3 cm; 170° N_2 40 ml/min; Retention time, III 7.0, N-benzoylcyclohexylamine (internal standard) 12.8.

c) MS: molecular sieves

d) not determined

In this manner, a series of II could be prepared from the corresponding I and cyanamide in good yields. The imidates I were easily prepared from malononitriles[7] according to the method of McElvain.[5] The procedure for preparing II consisted simply of stirring the suspension of I, cyanamide and a dispersing agent in the solvent at room temperature, filtering the ammonium chloride produced and the dispersing agent after several hours, and isolating II by evaporation of the filtrate. It is important to maintain strictly anhydrous conditions throughout this reaction. Generally, II thus obtained were directly used for the next cyclization without further purification. The N-cyanoimidates II thus prepared are summarized in Table II.

Table II. Alkyl N-Cyano Cyanoacetimidates (II)

Reactant	R^1	R^2	Product/ Yield (%)	mp (°C)	Recrystn. solvent	IR: ν_{max}^{KBr} cm^{-1} CH-CN	N-CN	C=N	Formula	*Anal.* or Mass (M^+) Calcd. (Found) C	H	N
Ia	H	CH_3	IIa/91	45—46	benzene-ether	2260	2210 2180	1630	$C_5H_5ON_3$	48.78 (48.61)	4.09 (4.12)	34.13 (33.98)
Ib	CH_3	CH_3	IIb/74	68—68.5	$CHCl_3$	2260	2220	1630	$C_6H_7ON_3$	52.54 (52.57)	5.15 (5.14)	30.64 (30.62)
Ic	C_6H_5	CH_3	IIc/81	oil	—	2250	2210	1620	$C_{11}H_9ON_3$	M^+ 199		
Id	H	C_2H_5	IId/87	64—65	$CHCl_3$	2230	2190	1620	$C_6H_7ON_3$	52.54 (52.47)	5.15 (5.12)	30.64 (30.38)
Ie	H	C_3H_7	IIe/92	oil	—	2250	2190	1625	$C_7H_9ON_3$	M^+ 151		
If	H	iso-C_3H_7	IIf/98	65.5—66.5	$CHCl_3$	2250	2190	1615	$C_7H_9ON_3$	55.62 (55.41)	6.00 (5.91)	27.80 (27.66)
Ig	H	C_4H_9	IIg/95	oil	—	2240	2190	1620	$C_8H_{11}ON_3$	M^+ 165		

solvent: benzene, dispersing agent: molecular sieves (MS)-4A

The structural assignments of II rest on elemental analyses, spectral data (infrared (IR), nuclear magnetic resonance (NMR), and mass spectra) and the following cyclization to the pyrimidine ring.

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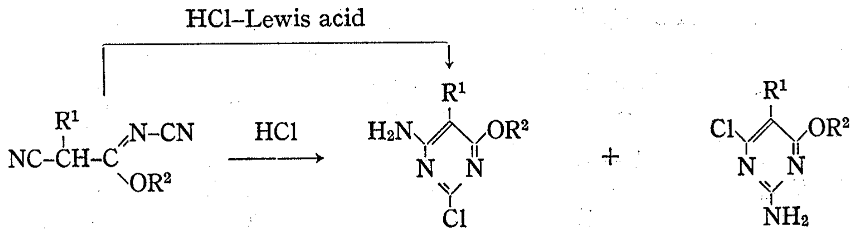
[7] Malononitrile was commercially available. Methyl and phenylmalononitriles were respectively prepared from methyl and phenylcyanoacetamides according to the method of "Org. Syn.", Col. Vol. III, p. 535.



IIa : $R^1=H, R^2=CH_3$
IIb : $R^1=CH_3, R^2=CH_3$
IIc : $R^1=C_6H_5, R^2=CH_3$
IId : $R^1=H, R^2=C_2H_5$
IIe : $R^1=H, R^2=C_3H_7$
IIf : $R^1=H, R^2=\text{iso-}C_3H_7$
IIg : $R^1=H, R^2=C_4H_9$

IVa : $R^1=H, R^2=CH_3$
IVb : $R^1=CH_3, R^2=CH_3$
IVc : $R^1=C_6H_5, R^2=CH_3$
IVd : $R^1=H, R^2=C_2H_5$
IVe : $R^1=H, R^2=C_3H_7$
IVf : $R^1=H, R^2=\text{iso-}C_3H_7$
IVg : $R^1=H, R^2=C_4H_9$

Va : $R^1=H, R^2=CH_3$
Vb : $R^1=CH_3, R^2=CH_3$
Vc : $R^1=C_6H_5, R^2=CH_3$

Chart 1

Cyclization of Alkyl N-Cyano Cyanoacetimidates (II) with Hydrogen Chloride

In this cyclization, reaction conditions such as catalysts and solvents considerably influenced the product formed. When IIa was treated with hydrogen chloride in an inert solvent at room temperature, reaction occurred and the salts of a mixture of two isomers, 6-amino-2-chloro-4-methoxypyrimidine (IVa) and 2-amino-6-chloro-4-methoxypyrimidine (Va), were separated from the solution, which were neutralized with aqueous sodium bicarbonate to afford the free bases IVa and Va in the ratio of 70: 30 in 90% yield. The direction of cyclization of IIa was found to be affected largely by a Lewis acid such as BF_3·etherate, ferric chloride, and aluminum chloride. The addition of BF_3·etherate led the cyclization in one specific direction to give only IVa. Although the cyclization could be accomplished in any inert solvents, acetic acid showed higher selective direction to IVa even in the absence of a Lewis acid. Similar results were obtained in the cyclization of IIb and IIc. In this manner, IIa—g could be cyclized with hydrogen chloride exclusively to IVa—g in good yields regardless of the bulkyness of R^1 and the length of alkyl chain R^2. These data are described in Table III. The pyrimidines thus obtained are listed in Table IV.

The pyrimidines IVa[8] IVd[8] Va[9] among those obtained in this manner were already known and their physical properties agreed well with those published for these compounds. The structures of 4-alkoxy-6-amino-2-chloropyrimidines (IVa, IVb, IVe, IVg) were identified by treatment with the corresponding sodium alkoxide giving the known 6-amino-2,4-dimethoxypyrimidine (VIa),[10] 6-amino-2,4-dimethoxy-5-methylpyrimidine (VIb),[11] 6-amino-2,4-dipropoxypyrimidine (VIe),[12] and 6-amino-2,4-dibutoxypyrimidine (VIg),[12] respectively. The structural assignments of IVc and IVf were primarily made on the basis of elemental analyses, ultraviolet (UV) spectra comparing with those of IVa, IVb, IVe, IVg, and assigned by analogy with the direction of cyclization of II in the presence of BF_3·etherate. The structure of Vb was confirmed by treatment with sodium methoxide to give the known 2-amino-4,6-dimethoxy-5-methylpyrimidine (VIIb)[9] and that of Vc was assigned by elemental analysis, UV spectra comparing with those of Va, Vb and also by treatment with sodium methoxide to give 2-amino-4,6-dimethoxy-5-phenylpyrimidine (VIIc),[11] whose NMR spectrum (DMSO-d_6) exhibited a single peak at 3.77 ppm due to the 4,6-dimethoxyl groups, whereas the 2,4-dimethoxyl groups of VIa, VIb showed two peaks due to each methoxyl group.

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[8] Y. Nitta, K. Okui, and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **13**, 557 (1965).

[9] F.L. Rose and G.A.P. Tuey, *J. Chem. Soc.*, **1946**, 81.

[10] *a)* K. Yanai, *Yakugaku Zasshi*, **62**, 315 (1942); *b)* Sankyo Co., Ltd. Japan Patent 10697 (1962) [*C.A.*, **59**, 5177^b (1963)].

[11] See experimental section.

[12] Y. Nitta and K. Okui, Japan Patent 10336 (1962) [*C.A.*, **59**, 5177^d (1963)].

TABLE III. Cyclization of IIa—g with Hydrogen Chloride

Reactant	R^1	R^2	Reaction solvent[a]	Lewis acid (mol. eq.)	Product	Yield (%)	Ratio[b] IV	V
IIa	H	CH_3	B—E	—	IVa+Va	90	70	30
IIa	H	CH_3	A	—	IVa+Va	88	90	10
IIa	H	CH_3	B—E	BF_3 (1.0)	IVa	93	100	—
IIa	H	CH_3	A	$FeCl_3$ (1.0)	IVa+Va	85	93	7
IIa	H	CH_3	A	$AlCl_3$ (1.0)	IVa	75	100	—
IIb	CH_3	CH_3	B—E	—	IVb+Vb	25	30	70
IIb	CH_3	CH_3	B—E	BF_3 (0.1)	IVb+Vb	76	98	2
IIc	C_6H_5	CH_3	B—E	—	IVc+Vc	63	40	60
IIc	C_6H_5	CH_3	B—E	BF_3 (1.0)	IVc	95	100	—
IId	H	C_2H_5	B—E	BF_3 (1.0)	IVd	95	100	—
IIe	H	C_3H_7	B—E	BF_3 (1.0)	IVe	81	100	—
IIf	H	iso-C_3H_7	B—E	BF_3 (1.0)	IVf	97	100	—
IIg	H	C_4H_9	B—E	BF_3 (1.0)	IVg	93	100	—

[a] B: benzene, E: ether, A: acetic acid

[b] determination by NMR (DMSO-d_6)

TABLE IV. 6-Amino-4-alkoxy-2-chloropyrimidines (IV) and 2-Amino-4-alkoxy-6-chloropyrimidines (V)

Compound	R^1	R^2	mp (°C)	Recrystn. solvent	UV λ_{max}^{MeOH} nm (log ε)	Formula	*Anal.* Calcd. (Found) C	H	N	Cl
IVa[8]	H	CH_3	184—185	MeOH	210(4.34) 239(3.86)	$C_5H_6ON_3Cl$	37.63 (37.47)	3.79 (3.74)	26.33 (26.41)	22.22 (22.66)
IVb	CH_3	CH_3	168—169	MeOH	208(4.37) 245(3.80) 261(3.79)	$C_6H_8ON_3Cl$	41.51 (41.67)	4.65 (4.60)	24.20 (24.44)	20.42 (20.59)
IVc	C_6H_5	CH_3	174—175	MeOH	210(4.48) 258(3.93)	$C_{11}H_{10}ON_3Cl$	56.06 (56.36)	4.28 (4.27)	17.81 (17.62)	15.04 (15.33)
IVd[8]	H	C_2H_5	132—133	MeOH	209(4.48) 239(3.86)	$C_6H_8ON_3Cl$	41.51 (41.69)	4.65 (4.67)	24.20 (24.34)	20.42 (20.63)
IVe	H	C_3H_7	104—105	MeOH-H_2O	210(4.44) 238(3.86)	$C_7H_{10}ON_3Cl$	44.81 (44.72)	5.37 (5.37)	22.40 (22.14)	18.90 (18.94)
IVf	H	iso-C_3H_7	119—120	MeOH-H_2O	210(4.46) 240(3.83)	$C_7H_{10}ON_3Cl$	44.81 (44.77)	5.37 (5.37)	22.40 (22.51)	18.90 (19.21)
IVg	H	C_4H_9	91.5—92.5	MeOH-H_2O	210(4.57) 238(3.91)	$C_8H_{12}ON_3Cl$	47.65 (47.73)	6.00 (5.92)	20.84 (20.68)	17.58 (17.36)
Va[9]	H	CH_3	168—169	MeOH	233(4.11) 278(3.74)	$C_5H_6ON_3Cl$	37.63	3.79	26.33	22.22
Vb	CH_3	CH_3	187—189	MeOH	233(4.16) 284(3.76)	$C_6H_8ON_3Cl$	41.51 (41.55)	4.65 (4.59)	24.20 (23.77)	20.42 (20.66)
Vc	C_6H_5	CH_3	211—213	MeOH	245(4.22) 284(3.87)	$C_{11}H_{10}ON_3Cl$	56.06 (56.04)	4.28 (4.31)	17.81 (17.71)	15.04 (14.92)

The reaction of IIa with an equimolar amount of hydrogen chloride in methanol at 0—5° gave methyl cyanoacetate and O-methylisourea hydrochloride (VIII).[13] Under these conditions IIa effected no cyclization, in contrast to those of cyanoacetylcyanamides previously reported[1] (Chart 2).

Cyclization of Alkyl N-Cyano Cyanoacetimidates (II) with Hydrogen Bromide and Iodide

The action of hydrogen bromide and iodide on II was somewhat different from that of hydrogen chloride (Chart 3). When IIa was allowed to react with hydrogen bromide in

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[13] W. S. Johnson(ed.), "Organlc Syntheses," Vol. 34, John Wiley & Sons. Inc., New York, 1954, p. 67.

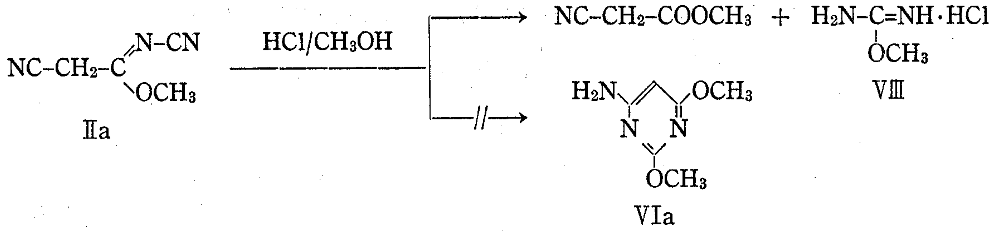

Chart 2

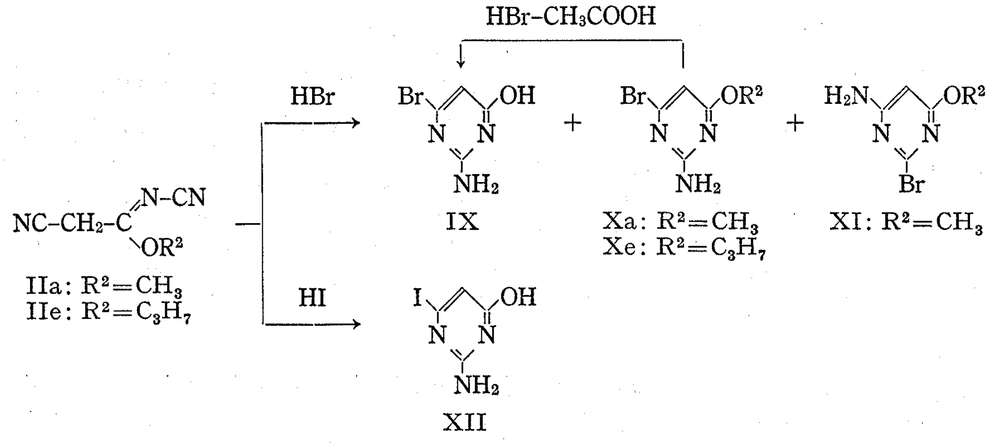

Chart 3

ethylene dichloride-ether in the presence of BF_3·etherate at room temperature for 6 hr, a mixture of three pyrimidines, 2-amino-6-bromo-4-hydroxypyrimidine (IX), 2-amino-6-bromo-4-methoxypyrimidine (Xa) and 6-amino-2-bromo-4-methoxypyrimidine (XI), was formed. In contrast with hydrogen chloride, no selective cyclization to XI occurred even in the presence of BF_3·etherate. However, the reaction of IIa with hydrogen bromide in acetic acid for 6 hr resulted in the formation of IX and Xa as main products along with a small amount of XI. On prolonged stirring in the same medium for 40 hr, IX was obtained in 93% yield together with a small amount of XI. Where R^2 was propyl (IIe), a similar result to those of methyl group (IIa) was obtained. These data are listed in Table V. The formation of IX was confirmed by the reaction of Xa or 2-amino-6-bromo-4-propoxypyrimidine (Xe) with an excess of hydrogen bromide in acetic acid to give IX. These results indicate that IX was formed by subsequent dealkylation of Xa or Xe, which was initially formed in these reactions. The hydrogen iodide treatment of IIa in acetic acid gave rise to 2-amino-4-hydroxy-6-iodopyrimidine (XII)[14] in 65.9% yield and none of the other pyrimidines could be detected in the reaction mixture. The pyrimidines thus prepared are summarized in Table VI.

TABLE V. Cyclization of IIa, e with Hydrogen Bromide and Iodide

Reactant	R^1	R^2	Reaction solvent[a]	HX	BF_3·etherate (mol. eq.)	Product	Yield (%)	Ratio[b] IX or XII	X	XI
IIa	H	CH_3	ED—E	HBr	0.5	IX+Xa+XI	49	15	65	20
IIa	H	CH_3	A	HBr	—	IX+Xa+XI	97	75	20	5
IIe	H	C_3H_7	A	HBr	—	IX+Xe	71.2	65	35	—
IIa	H	CH_3	A	HI	—	XII	65.9	100	—	—

a) ED: ethylene dichloride, E: ether, A: acetic acid
b) determination by NMR (DMSO-d_6)
reaction time: 6 hr

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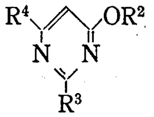
[14] E. Bütter, *Chem. Ber.*, 36, 2227 (1903).

Table VI. Bromo- and Iodo-pyrimidines (IX—XII)



Compound	R^2	R^3	R^4	mp (°C)	Recrystn. solvent	UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ε)	Formula	*Anal.* Calcd. (Found) C	H	N	X
IX	H	NH_2	Br	233—234 (decomp.)	MeOH	225(3.92) 289(4.00)	$C_4H_4ON_3Br$	25.28 (25.63)	2.12 (2.20)	22.12 (22.54)	42.06 (42.05)
Xa	CH_3	NH_2	Br	161—163	MeOH	233(4.07) 279(3.75)	$C_5H_6ON_3Br$	29.43 (29.48)	2.96 (3.05)	20.60 (20.76)	39.17 (39.08)
Xe	C_3H_7	NH_2	Br	81.5—82.5	MeOH-H_2O	232(4.10) 280(3.79)	$C_7H_{10}ON_3Br$	36.23 (36.37)	4.34 (4.37)	18.11 (18.23)	34.43 (34.66)
XI	CH_3	Br	NH_2	186—188 (decomp.)	MeOH	210(4.38) 240(3.86)	$C_5H_6ON_3Br$	29.43 (29.25)	2.96 (2.98)	20.60 (20.47)	39.17 (39.06)
XII[14]	H	NH_2	I	243—244 (decomp.)	MeOH-H_2O	227(4.17) 294(3.94)	$C_4H_4ON_3I$	20.27 (20.35)	1.70 (1.75)	17.73 (17.93)	53.55 (53.43)

Consequently, in the cases of hydrogen bromide and iodide, the direction of cyclization was reversed to that of hydrogen chloride. The pyrimidine XII[14] among those obtained in this manner was the known compound. The structures of IX and XII were confirmed by hydrogenation over Pd/C giving the known 2-amino-4-hydroxypyrimidine (XIII).[15] The structures of Xa, Xe and XI were identified by treatment with the corresponding sodium alkoxide to give the known 2-amino-4,6-dimethoxypyrimidine (VIIa),[9] 2-amino-4,6-dipropoxypyrimidine (VIIe),[9] and 6-amino-2,4-dimethoxypyrimidine (VIa),[10] respectively.

This method represents a one-step synthesis of a type of 4-alkoxy-6-amino-2-chloropyrimidine (IV) and 2-amino-6-bromo (or iodo)-4-hydroxypyrimidine (IX, XII) and provides an economical means for the preparation of these useful pyrimidines from inexpensive and readily available starting materials.

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. Gas chromatographic determination was carried out using a Shimazu 5APFF.

Alkyl N-Cyano Cyanoacetimidates (II)——General Procedure: In a 100 ml test tube shaped flask, a suspension of cyanamide[6] (0.84 g, 0.02 moles), alkyl cyanoacetimidate hydrochlorides[4] (I, 0.02 moles) and a finely powdered dispersing agent (molecular sieves-4A, $CaCO_3$, Al_2O_3. 1—3 g) in a pertinent solvent (benzene, ethylene dichloride, *etc.* 30 ml) was vigorously stirred for 6 hr at 20—25°, then the reaction mixture was filtered and washed with the same solvent used. The combined filtrate and washings were evaporated to dryness under reduced pressure below 40° giving II as a pale yellow oil. On standing in a refrigerator, IIa, b, d, f crystallized. These compounds were recrystallized from the solvents described in Table II. The others (IIc, e, g) did not give satisfactory elemental analyses, but their spectral data (IR, NMR, mass spectra) were well consistent with those of their structures. The yields, physical properties and IR spectra are also described in Table II.

Determination of III: The insoluble materials filtered from the reaction mixture of IIa with cyanamide were extracted repeatedly with hot EtOH, and the solution was evaporated to dryness *in vacuo*. The residue was taken for the gas chromatographic determination of III (Table I).

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15) W.T. Caldwell and H.B. Kime, *J. Am. Chem. Soc.*, **62**, 2365 (1940).
16) O. Gerngross, *Chem. Ber.*, **38**, 3394 (1905).
17) W. Bergmann and T.B. Johnson, *J. Am. Chem. Soc.*, **55**, 1733 (1933).

Cyclization of IIa—c with HCl in the Absence of a Lewis Acid——To a solution of IIa (1.23 g, 0.01 mole) in ether–benzene (2: 1, 6 ml) added dropwise 16.7% HCl-ether (13 g, HCl 0.06 moles) at 20—25° with stirring. After 6 hr, the reaction mixture was evaporated *in vacuo*. The residue was added to H_2O (20 ml) and the suspension was neutralized with $NaHCO_3$. The precipitates were collected by filtration, washed with H_2O and dried to give colorless crystals (1.44 g). These crystals were a mixture of IVa and Va in the ratio of 70: 30, which was estimated by NMR measurement (DMSO-d_6). The mixture (200 mg) was separated by preparative thin-layer chromatography (TLC) (benzene: isopropyl ether: EtOH 3: 3: 1) on Kieselgel GF 254 into IVa (*Rf* 0.40) and Va (*Rf* 0.52). IIb and IIc were treated in a similar manner described above and the ratio of their corresponding two isomers was estimated, and then the mixtures were separated into IVb: Vb, and IVc: Vc, respectively. The data of these experiments are described in Table III and the elemental analyses, melting points and UV spectra are listed in Table IV.

Cyclization of IIa—g with HCl in the Presence of BF_3·Etherate——General Procedure: To a mixture of IIa—g (0.01 mole), BF_3·etherate (0.001—0.01 mole) in a solvent (10 ml, *e.g.* ether-benzene 2: 1, ethylene dichloride, AcOH) was added dropwise an HCl-ether solution (HCl 0.04—0.06 moles) during 10 min or introduced directly the same molar amount of dry HCl gas at 20—25° with stirring. The mixture was stirred for another 6 hr at the same temperature. The precipitates separated were collected by filtration, washed with ether and added to H_2O (20 ml). The suspension was neutralized with $NaHCO_3$ to give colorless crystals, which were collected by filtration, washed with H_2O and dried to give IVa—g. Recrystallization was carried out by the solvents shown in Table IV. The data of their yields, elemental analyses, melting points and UV spectra are also listed in Table IV.

Reaction of IVa, b, e, g with MeONa to 2,4-Dialkoxy-6-aminopyrimidines (VI)——i) A mixture of IVa (160 mg) and Na (46 mg) in MeOH (3 ml) was refluxed for 6 hr and then evaporated to dryness. The residue was added to H_2O (1 ml) to give VIa (143 mg, mp 150—151° from MeOH), which was identical with an authentic sample[10] by mixed melting point and IR spectrum. ii) A mixture of IVb (174 mg) and Na (46 mg) in MeOH (3 ml) was similarly treated to give colorless crystals (139 mg, mp 125—127° from MeOH), which were identical with VIb prepared as shown below (mixed melting point and IR spectrum). iii) A mixture of IVe (188 mg) and Na (46 mg) in PrOH (3 ml) was refluxed for 3 hr and then evaporated. The residue was added to H_2O and the oil separated was extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated to give an oil (194 mg). The oil was mixed with picric acid (0.4 g) in EtOH (4 ml) to afford yellow needles (323 mg, mp 178—179° from EtOH), which were identical with the picrate of VIe prepared from VIe[12] with picric acid in a usual manner (mixed melting point and IR spectrum). *Anal.* Calcd. for $C_{16}H_{20}O_9N_6$: C, 43.64; H, 4.58; N, 19.08. Found: C, 43.98; H, 4.65; N, 19.26. iv) A mixture of IVg (202 mg) and Na (46 mg) in BuOH (10 ml) was similarly treated as in the experimental (iii) to give an oil (231 mg). The oil was similarly mixed with picric acid-EtOH giving yellow needles (281 mg, mp 149—150° from EtOH), which were identical with the picrate of VIg prepared from VIg[12] with picric acid in a usual manner (mixed melting point and IR spectrum). *Anal.* Calcd. for $C_{18}H_{24}O_9N_6$: C, 46.15; H, 5.16; N, 17.94. Found: C, 45.86; H, 4.93; N, 17.95.

6-Amino-2,4-dimethoxy-5-methylpyrimidine (VIb)——A mixture of 6-amino-2,4-dichloro-5-methylpyrimidine[16] (0.30 g), which was prepared by heating 6-amino-2,4-dihydroxy-5-methylpyrimidine[17] with $POCl_3$-dimethylaniline at 130° for 6 hr, and Na (0.236 g) in MeOH (6 ml) was refluxed for 15 hr and then evaporated. The residue was added to H_2O and the precipitates were collected by filtration to give VIb (0.255 g, 82%, mp 125.5—126.5° from MeOH). *Anal.* Calcd. for $C_7H_{11}O_2N_3$: C, 49.70; H, 6.55; N, 24.84. Found: C, 49.68; H, 6.55; N, 24.70.

Reaction of Vb, c with MeONa——i) A solution of Vb (100 mg) and Na (63 mg) in MeOH (4 ml) in a sealed tube was heated at 120° for 5 hr. The reaction mixture was treated in a usual manner to give VIIb (74 mg, 85%, mp 117.5—119° from MeOH), which was identical with an authentic sample[9] by mixed melting point and IR spectrum. ii) A solution of Vc (125 mg) and Na (86 mg) in MeOH (4 ml) was similarly treated and worked up as before to give VIIc as colorless crystals (92 mg, 74%, mp 138—140° from MeOH). *Anal.* Calcd. for $C_{12}H_{13}O_2N_3$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.15; H, 5.71; N, 17.97. NMR (5% in DMSO-d_6) ppm; 3.77 (6H, s, $-OC\underline{H}_3\times 2$), 7.27 (5H, s, $-C_6\underline{H}_5$), 6.5 (2H, broad, $-N\underline{H}_2$).

IIa with HCl in MeOH——To a solution of IIa (246 mg, 2 mmoles) in cold MeOH (2 ml) was added 27.4% HCl-ether (270 mg, HCl 2 mmoles) at 0—5° with stirring. After stirring for 2 hr at the same temperature, the reaction mixture was evaporated *in vacuo* at 15—20°. The residue crystallized on standing. The crystals were collected by filtration and washed with ether to give VIII as colorless needles (180 mg, 81.5%), which was identical with an authentic sample[13] by IR spectrum. The combined filtrate and washings were evaporated to give an oil (230 mg), which was purified by preparative thin-layer chromatography (benzene: isopropyl ether:EtOH 3: 3: 1, *Rf* 0.55) and identified with the authentic methyl cyanoacetate by IR spectrum.

Cyclization of IIa with HBr——i) To a stirred solution of IIa (1.23 g, 0.01 mole) and BF_3·etherate (0.71 g, 0.005 moles) in ethylene dichloride (20 ml) was added dropwise 30% HBr-ether (10.8 g, HBr 0.04 moles) during 10 min at 20—25°. After stirring at the same temperature for 6 hr, the precipitates were collected by filtration, washed with ether and dried to give the powders (2.46 g). The powders (2.00 g) were added to H_2O (8 ml) and the mixture was neutralized with $NaHCO_3$ to give colorless crystalline powders (990 mg), which were a mixture of IX, Xa and XI in a ratio of 15: 65: 20 by NMR measurement (DMSO-d_6, calculation from the areas obtained by integration of each 5-H proton). The mixture (640 mg) in 10% aqueous NH_4OH (15 ml) was stirred for 1 hr at room temperature, and then insoluble materials (520 mg) were collected by filtration. The filtrate was evaporated to 1 ml to deposit crystals, which were collected by filtration, washed with H_2O, dried to give colorless crystals (IX, 94.4 mg). The analytical data and UV spectrum are listed in Table VI. The crystals were identified by hydrogenation (Pd/C) to XIII as shown below. The insoluble materials (450 mg) were recrystallized from MeOH (3 ml) to give colorless prisms (Xa, 200 mg). The analytical data and UV spectrum are listed in Table VI. The structure of Xa was confirmed by treatment with MeONa to give VIIa as shown below. The mother liquors were evaporated to give crystalline residue (250 mg), which was a mixture of Xa and XI in a ratio of 3: 2 on the basis of NMR measurement. The residue (90 mg) was separated TLC by ($CHCl_3$, Xa *Rf* 0.46, XI *Rf* 0.30) and then lower *Rf* zone was extracted with hot MeOH to give prisms (XI, 37 mg). The analytical data and UV spectrum are listed in Table VI. This compound was identified by treatment with MeONa to give VIa as shown below. ii) To a stirred solution of IIa (1.23 g, 0.01 mole) in AcOH (10 ml) was added dropwise 23% HBr-AcOH (14.1 g, HBr 0.04 moles) at 20—25°. After stirring for 40 hr at room temperature, the precipitates were collected by filtration, washed with ether and neutralized with $NaHCO_3$ to afford crystalline powders (1.90 g), which were recrystallized from MeOH to give pure IX (1.76 g, 93%), identical with IX obtained above.

Cyclization of IIe with HBr-AcOH——To a stirred solution of IIe (1.95 g, 12.8 mmoles) in AcOH (10 ml) was added dropwise 26.7% HBr–AcOH (19.4 g, HBr 64 mmoles) at 20—25° during 10 min. After stirring for 6 hr, the precipitates were similarly filtered, washed and neutralized to give crystalline powders (1.97 g), which were a mixture of IX and Xe in a ratio of 60: 40 (NMR measurement). The crystalline powders (1.50 g) were stirred in 10% aqueous NH_4OH (40 ml) at room temperature for 1 hr and the insoluble materials (Xe, 0.590 g) were filtered. The filtrate was evaporated to 2 ml *in vacuo* to give crystals (IX, 0.840 g). The analytical data, melting points and UV spectra of IX and Xe are listed in Table VI. The compound Xe was identified by treatment with PrONa to give VIIe as described below by mixed melting point and IR spectrum. The compound IX was identical with that obtained by aforementioned experimental on the basis of IR and NMR spectra.

Xa or Xe with HBr–AcOH——i) A mixture of Xa (340 mg) in 30% HBr–AcOH (5 ml) was stirred at 20—25° overnight. The precipitates were collected by filtration, then dissolved in 10% aqueous NH_4OH (10 ml). The solution was evaporated to 1 ml to give crystals (IX, 260 mg, 82.1%), which were identical with IX by IR and NMR spectra. ii) A mixture of Xe (250 mg) was similarly treated with 30% HBr–AcOH (3 ml) to afford crystals (189 mg, 92.3%), which were identical also with IX in the same manner.

Cyclization of IIa with HI–AcOH——To a stirred solution of IIa (0.739 g, 6 mmoles) in AcOH (5 ml) was added dropwise 15.3% HI-AcOH (30.15 g, HI 4.61 g, 36 mmoles) during 10 min at 20—25°. After stirring for 6 hr at the same temperature, the precipitates were treated as in the cases with HCl and HBr to afford pale yellow powders (1.42 g), which were neutralized with $NaHCO_3$ to give XII (0.937 g, 65.9%). The analytical data, melting point and UV spectrum are listed in Table VI. The compound XII was identified by hydrogenation (Pd/C) to give XIII[15] as described below.

Reaction of Xa with MeONa——A mixture of Xa (37 mg) and Na (8.3 mg) in MeOH (1 ml) was refluxed for 3 hr and then evaporated *in vacuo*. The residue was dissolved in H_2O (1 ml) and the solution was neutralized with dil. HCl to give VIIa (15.8 mg, mp 95—97°), which was identical with an authentic sample[9] (mixed melting point and IR spectrum).

Reaction of XI with MeONa——A mixture of XI (17.2 mg) and Na (8.3 mg) in MeOH (1 ml) was refluxed for 3 hr and treated in a usual manner to give VIa (7.5 mg, mp 150—151°), which was identical with an authentic sample[10] (mixed melting point and IR spectrum).

Reaction of Xe with PrONa——A mixture of Xe (116 mg) and Na (46 mg) in PrOH (5 ml) was refluxed for 1 hr and then evaporated *in vacuo*. The residue was treated in a usual manner to give VIIe (110 mg, mp 75.5—76.5° from petroleum ether, picrate mp 194—195° from EtOH), which was identical with an authentic sample[9] (mixed melting point and IR spectrum).

Hydrogenation (Pd/C) of IX and XII——i) IX (190 mg) was reduced with H_2 in MeOH (40 ml) over 5% Pd/C (200 mg) at atmospheric pressure and room temperature for 30 min. The mixture was filtered and washed with hot MeOH (50 ml). The combined filtrate and washings were evaporated. The residue was dissolved in dil. aqueous NH_4OH and then the solution was concentrated to *ca.* 1 ml giving XIII (73 mg, mp 274—275° (decomp.) from MeOH), which was identical with an authentic sample[15] (IR and NMR spectra). ii) A mixture of XII (200 mg), conc. NH_4OH (1.5 ml) and MeOH (40 ml) was similarly reduced with H_2 over 5% Pd/C (200 mg) to give XIII (42 mg, mp 274—275° (decomp.)), which was identical with an authentic sample as shown above.

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