The Reaction of Nitriles under High Pressure. III. The Cyclotrimerization of Aliphatic Nitriles in the Presence of Alcohols and the Rearrangement of the Resulting Trialkyl-1,3,5-triazines to 4-Aminopyrimidines[1]

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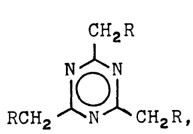
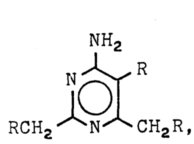
The examination of the simultaneous formation of symmetrically tri-substituted 1,3,5-triazines, 4-amino-2,5,6-substituted pyrimidines and *N*-pyrimidylamidines in mixtures of lower alcohol and nitrile with more than two hydrogen atoms on the α-position under pressures of a few thousand atm afforded the following information: (1) the triazine is formed by the cyclo-trimerization of the iminoether which is derived from the nitrile and the alcohol; (2) the pyrimidine is formed by the rearrangement of the previously-formed triazine. This rearrangement is caused by an attack of the nucleophilic iminoether on a carbon atom of the triazine ring; and (3) the amidine is assumed to be formed, together with the pyrimidine, by the same attacking mechanism.

In 1952 Cairns, Larchar, and McKusic[2] found that the cyclo-trimerization of acetonitrile to 2,4,6-trimethyl-1,3,5-triazine accompanied the formation of 4-amino-2,6-dimethylpyrimidine and *N*-(2,6-dimethylpyrimidin-4-yl)-acetamidine when acetonitrile was kept under a few thousand atm in the presence of methanol or aqueous ammonia or piperidine at elevated temperatures, and that the triazine was slowly converted to the pyrimidine at 8500 kg/cm² and 150 °C in the presence of methanol. They reported that it was not evident to what extent the triazine may have been an intermediate to the pyrimidine in the trimerization of acetonitrile. This investigation was undertaken in an attempt to determine the mechanism of the conversion of nitriles with more than two hydrogen atoms on their α-carbons into the corresponding 2,4,6-tri-substituted 1,3,5-triazines (I) and the mechanism of the rearrangement of I to the isomeric 4-amino-2,5,6-tri-substituted pyrimidines (II) and to *N*-(2,5,6-substituted pyrimidin-4-yl)-amidine (III), which have the same moieties as the nitriles. Another aim was the elucidation of the above-mentioned unsolved problem proposed by Cairns *et al.*[2]



Iabc



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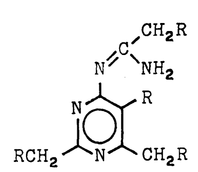

IIIabc

a: R=H, b: R=CH_3, c: R=C_2H_5

Results and Discussion

In order to get an overall view of this reaction, acetonitrile was chosen as the nitrile with more than two α-hydrogen atoms and was kept in lower alcohols or other popular solvents at 6600 kg/cm² and 120 °C for 10 hr. The results listed in Table 1 indicate that alcohol is the only promoter of the formation of Ia and that the promotive effect decreases with the increase in the molecular weight of alcohol.[3] The fact that the formation of IIa and IIIa was always accompanied by that of Ia was remarkable in connection with the mechanism of the formation of II and III, (which will be discussed below).

TABLE 1. INFLUENCE OF SOLVENTS ON THE FORMATION OF Ia, IIa, AND IIIa FROM ACETONITRILE

Solvent[b]	Reaction conditions			Yields (%)[a]		
	kg/cm²	°C	hr	Ia	IIa	IIIa
CH_3OH	7950	120	10	29.0	5.0	4.0
C_2H_5OH	7950	120	10	5.6	0.1	0.2
H_2O	6650	100	10			
$(C_2H_5)_2O$	6650	100	10			
$(CH_3)_2SO$	6650	100	10			

a) Theoretical yield based on nitrogen atom.
b) The weight of each solvent was the same as that of acetonitrile.

To examine the influence of the moieties of the nitriles, mixtures of ethanol and the same-weight acetonitrile or propionitrile or *n*-butyronitrile were kept under the same reaction conditions. The results are collected in Table 2. The yield of I decreased with the increase in the length of the alkyl chain in the moieties. Similar relations are found between the yield of II or III and the chain length. The fact that three

TABLE 2. INFLUENCE OF THE MOIETIES OF NITRILES ON THE COMPOSITION OF REACTION PRODUCTS[a]

R-CH_2CN	Yields (%)				
R	RCH_2CN	$RCH_2C(=NH)OC_2H_5$	I	II	III
H	83.1	1.8_7	11.2	1.5_8	1.5_5
CH_3	90.1	2.1_7	6.6_6	(0.4)[b]	(0.4)[b]
C_2H_5	96.7	1.4_8	1.2_5		

a) Reaction conditions: R-CH_2CN:C_2H_5OH=1:1 (by weight), 8000 kg/cm², 120 °C, and 30 hr.
b) These are assumed to be IIb and IIIb respectively.

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[1] Part II of this series, M. Yasumoto, K. Yanagiya, and M. Kurabayashi, This Bulletin, **46**, 2798 (1973).

[2] T. L. Cairns, A. W. Larchar, and B. C. McKusic, *J. Amer. Chem. Soc.*, **74**, 5633 (1952).

[3] This fact was similar to Cairns's data for benzonitrile[2].

TABLE 3. INFLUENCE OF IMINOETHER ON THE REACTION PRODUCTS[a)]

CH_3CN (g)	$CH_3C(=NH)OC_2H_5$ (g)	(molar ratio)	C_2H_5OH (g)	Yields (%)		
				Ia	IIa	IIIa
1.93	—	(1: 0)	2.17	16.2	7.1	5.2
1.40	1.50	(2: 1)	1.60	23.7	5.6	4.8
0.67	2.91	(1: 2)	0.68	28.4	7.5	5.5
—	5.03	(0: 1)	—	45.9	6.3	5.8

a) Reaction conditions: 7950 kg/cm², 120 °C, and 24 hr.

kinds of ethyl iminoethers were formed from the respective nitriles gives rise to the assumption that I is formed *via* an iminoether, which is known to be quickly produced from a nitrile and an alcohol under high pressures.[4)] To confirm this assumption, acetonitrile, ethyl acetiminoether, and a mixture of the two were kept in the presence of ethanol under the same pressure. As is shown in Table 3, the greater concentration of the iminoether in the initial mixture resulted the greater yield of Ia. This finding supports the above assumption, which is expressed by Eq. (1):

$$RCH_2CN + R'OH \longrightarrow$$
$$RCH_2C(=NH)OR' \longrightarrow 1/3\,I + R'OH \qquad (1)$$

A similar mechanism has been kinetically proven with an aromatic nitrile by the present authors.[4)]

In Fig. 1, the yields of the products in the acetonitrile–methanol mixture are plotted against the reaction time. In contrast to the gradual increases in the yields of IIa and IIIa with the lapse of the reaction time, the yield of Ia increased to a maximum when the reaction time passed about 50 hr and then decreased gradually with the gradual decrease in the acetonitrile. This fact indicates the conversion of the previously-produced Ia into IIa and IIIa. With the view of determining the mechanism of this conversion, several kinds of amines were added one by one to mixtures consisting of Ia and methanol in the same weight. These mixtures were kept under the same high-pressure conditions. The results are listed in Table 4. The formation of IIa and IIIa was seen only when an amine with less than one active hydrogen atom, such as ammonia, primary amine and secondary amine, was added.[5)] The yield of IIa increased with the increase in the number of the active hydrogen atoms of the additives. Considerable amounts of amines were recovered when ammonia or diethylamine was added, but when *n*-butylamine was added considerable

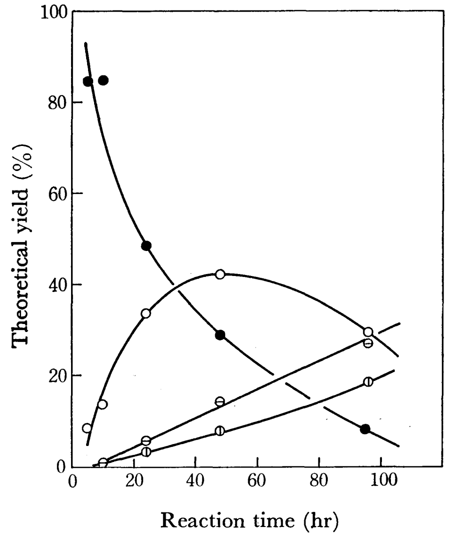


Fig. 1. Time dependence of the composition of the reaction products (theoretical yield based on nitrogen atom) at the starting ratio CH_3CN: CH_3OH=1: 1 (by weight) at 6600 kg/cm² and 100 °C.
●: CH_3CN, ○: Ia, ⊖: IIa, ⦶: IIIa

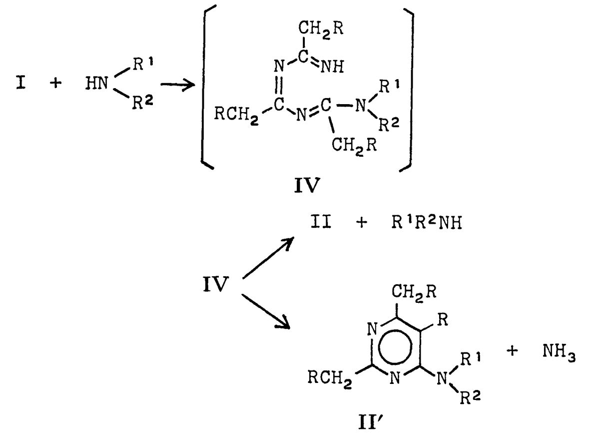
TABLE 4. EFFECT OF AMINES ON THE REARRANGEMENT OF I TO II AND III[a)]

Amines	Yields (%)[c)]						
	CH_3CN[e)]	Ia	IIa	II′a[f)]	IIIa	Amine	Acetamidine[g)]
—[b)]		98.6		—		—	—
NH_3		41.2	38.9	—	5.6	(46.8)[d)]	[h)]
n-$C_4H_9NH_2$		27.3	11.3	42.1 (83.8)[d)]	14.8	[i)]	0.9 (5.2)[d)]
$(C_2H_5)_2NH$		94.9	0.7_5		1.0_7	(69.0)[d)]	3.6 (21.4)[d)]
$(C_2H_5)_3N$		98.8		—		—	—

a) Reaction conditions: Ia: Amine: CH_3OH=1: 0.5 (mole); 1 (weight), 8000kg/cm², 100 °C, and 30 hr.
b) In the case without amine, the mixture of same weight of Ia and ethanol was kept at 8000 kg/cm² and 120 °C for 24 hr.
c) Theoretical yield based on nitrogen in the initial Ia.
d) Figures putted in the parenteses are the theoretical yield based on the amines added.
e) Acetonitrile was never detected in the all runs listed in the table.
f) II′a means IIa with the moiety of added amine on its amino-nitrogen.
g) The yields of amidines were determined by use of glc. The details of the identification of them will be mentioned in a later report.
h) Acetamidine was expected to be produced, but its determination was prevented by the coexistence of inseparable Ia.
i) Ammonia yielded in 53% based on the added *n*-butylamine.

[4)] M. Kurabayashi, K. Yanagiya, and M. Yasumoto, This Bulletin, **44**, 3413 (1971).

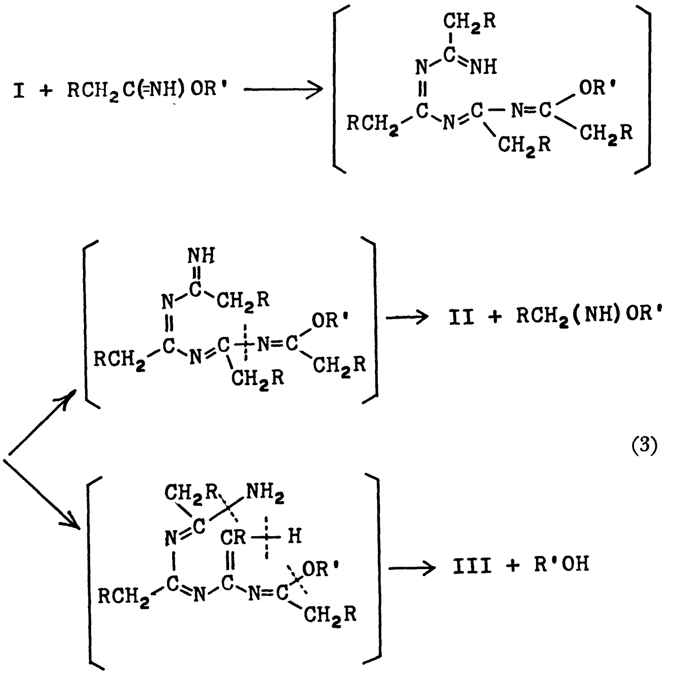
[5)] The promotive effect of ammonia on the rearrangement of Ib to IIb has already been reported.[2)] amounts of 2,6-dimethyl-4-*n*-butylaminopyrimidine (II'a) and ammonia were isolated without any recovery of *n*-butylamine. The following rearrangement mechanism is proposed for the conversion of I into II and II' on the basis of these experimental results:



(2)

A triazine ring is attacked on its carbon atom by a neucleophilic nitrogen atom of amine. An open-chain intermediate (IV) is formed by the cleavage of the ring involving the shift of a hydrogen atom of the attacking amine. A ring closing takes place accompanied by a twist of the C–N bond and an elimination of the amine or ammonia. These eliminations both give II and II'.

It may be inferred that, when a reaction is initiated in a nitrile–alcohol mixture, the intermediate iminoether behaves as an amine with an active hydrogen atom and causes I to shift to II and III in the manner shown by Eq. (3):



(3)

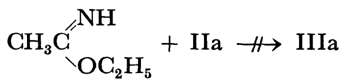
This inference is supported by the experimental results listed in Table 5, in which larger yields of IIa and IIIa are seen both in the ethanolic solution of acetonitrile and Ia and in the ethanolic solution of ethyl acetiminoether and Ia than in the ethanolic solution of acetonitrile alone, while no yield of IIa is seen in the ethanolic solution of Ia alone.

It is assumed that the small amounts of acetamidines, which were isolated in the Ia–methanol–amine mixtures (see Table 4), are formed by the partial decomposition of the IVa intermediate to an amidine and acetonitrile:

$$\text{IV} \longrightarrow \text{RCH}_2\text{C(=NH)NR}^1\text{R}^2 + 2\,\text{RCH}_2\text{CN} \qquad (4)$$

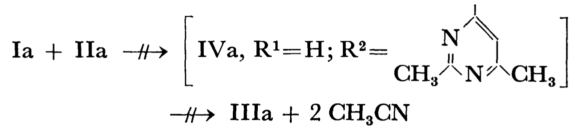
It is also assumed that methyl acetiminoether is formed from the acetonitrile thus liberated to satisfy the equilibrium of Eq. (1) and that it attacks Ia to form IIa and IIIa by means of Eq. (3). These assumptions are substantiated by the experimental results that small amounts of IIIa are formed in Ia–methanol–amine mixtures (see Table 4).

It is not speculated that III is formed by an attack of an amino-nitrogen of II on an iminoether under high pressure because of the experimental finding that IIa and ethyl acetiminoether were recovered unreacted from an ethanolic solution of them after a long reflux.



$$\text{CH}_3\text{C}\begin{matrix}\nearrow\text{NH}\\ \searrow\text{OC}_2\text{H}_5\end{matrix} + \text{IIa} \not\longrightarrow \text{IIIa} \qquad (5)$$

On the other hand, we ignored the possibility that, if I is attacked by an amino-nitrogen of II, the resulting IV will give III by means of Eq. (4); we did this in view of the experimental finding that IIIa was not detected in a methanolic or pyrimidine solution of an equimolar mixture of Ia and IIa after 30 hr's standing at 8000 kg/cm² and 120 °C.



(6)

As is shown in Figs. 2 and 3, the elevation of both the reaction pressure and the temperature caused the yields

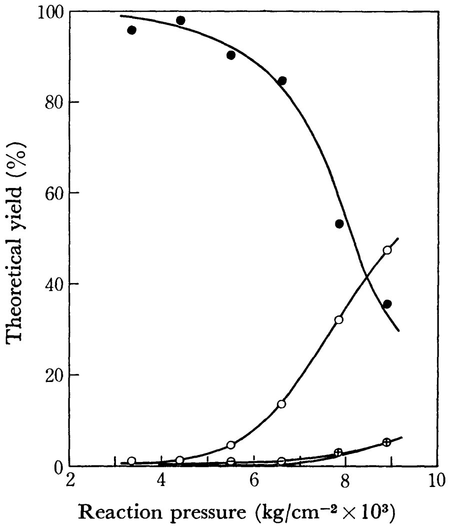


Fig. 2. Pressure dependence of the composition of the reaction products at the same starting ratio CH_3CN/CH_3OH as shown in Fig. 1 at 100 °C for 10 hr.

●: CH_3CN, ○: Ia, ⊖: IIa, ⦶: IIIa.

TABLE 5. EFFECT OF NITRILE OR IMINOETHER ON THE REARRANGEMENT OF Ia TO IIa AND IIIa IN THE PRESENCE OF ETHANOL[a]

CH_3CN (g)	$CH_3C(=NH)OC_2H_5$ (g)	Ia (g)	C_2H_5OH (g)	Yields (%)[b]			
				CH_3CN	Ia	IIa	IIIa
1.47	—	—	1.64	85.7	6.5_9	0.4_4	0.2_9
0.74	—	0.73 (3: 1)[c]	1.65	37.1	41.5	3.8_0	7.1_2
—	1.54	0.73 (3: 1)	0.82	24.7	51.5	5.6_4	7.4_2
—	—	1.46	1.64		96.5		

a) Reaction conditions: 8000 kg/cm², 120 °C, and 8 hr.
b) Theoretical yield based on nitrogen in the initial mixtures.
c) Molar ratio of CH_3CN or $CH_3C(=NH)OC_2H_5$ to Ia.

TABLE 6. IDENTIFICATION OF TRIAZINES PRODUCED IN THE RUNS LISTED IN TABLE 2

Triazines	Preparative glc			Elementary analysis Found (%)			mol wt		IR spectra for triazine ring
	Column conditions	Retention time (min)	Yields (g)	C	H	N	(MS)[a]	(Calcd)	(cm⁻¹)
Ia	DNP, 100°C—, 2 °C/min	13.2	0.42	58.21	7.48	32.42	123	(123.15)	1560, 1540, 1435
Ib	Carbowax-1500, 67 °C—, 4 °C/min	17.4	0.14	65.32	9.16	26.27	165	(165.24)	1540, 1460, 1420
Ic	Polyphenylether(6-ring), 150 °C	15.9	0.21	69.73	10.30	20.24	207	(207.31)	1550, 1535, 1420

a) From a parent peak of mass spectroscopy.

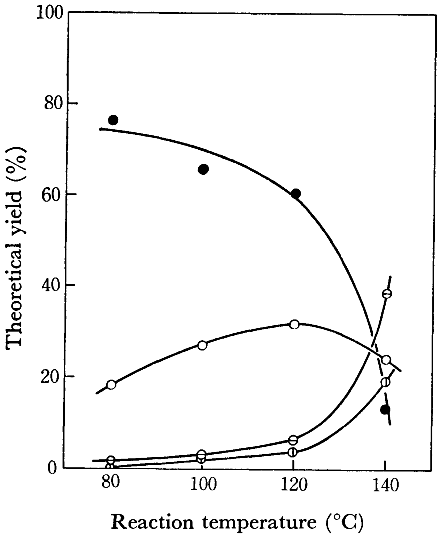


Fig. 3. Temperature dependence of the composition of the reaction products at the same starting ratio CH_3CN/CH_3OH as shown in Fig. 1 at 8900 kg/cm² for 5 hr.
●: CH_3CN, ○: Ia, ⊖: IIa, ⦶: IIIa.

of Ia, IIa, and IIIa to increase and also caused the yield ratio of IIa to Ia and that of IIIa to Ia to increase. One of the most reasonable interpretations of this experimental fact may be that these elevations promote not only the production of Ia but also the conversion of Ia into IIa and IIIa.[6]

It is certain that, in a mixture of nitrile and alcohol under high pressures, II and III are produced by the reaction of I with iminoether, although it can not be decided whether this route is the only possible one for the formation of II and III.

Experimental

Reaction Apparatus and Procedure. A mixture of the starting materials was placed in a collapsible lead capsule, was held in a pressure vessel, and was kept under the desired reaction conditions of pressure, temperature, and time by means of a previously-described high-pressure apparatus and procedure.[4]

Material Supply. The nitriles, alcohols, amines, glacial acetic acid, and solvents were all EP-grade reagents and were dried and distilled. A commercial-grade ammonia was evaporated, dried on sodium hydroxide, and absorbed in methanol.

Ethyl Iminoethers: An iminoether was prepared from a nitrile and ethanol as a hydrochloride by Pinner's method and was liberated by neutralization. $CH_3C(=NH)OC_2H_5$: bp 87—90.5 °C(91[7]); C, 55.54(55.15 Calcd); H, 10.46(10.41); N, 15.31%(16.08). $C_2H_5C(=NH)OC_2H_5$: 58—59 °C/110 mmHg(110—111[7]); 59.62(59.37); 11.10(10.96); 13.61% (13.85). n-$C_3H_7C(=NH)OC_2H_5$: 54—55 °C/70 mmHg, 63.03 (62.57); 11.17(11.38); 11.97%(12.16). Methyl acetiminoether was obtained as a mixture containing large amounts of methanol and acetonitrile because of its instability at distillation.

Trialkyl-1,3,5-triazines: These triazines were prepared by the procedure of Schaefer and Peters,[7] in which an iminoether was cyclotrimerized by the addition of a small amount of acetic acid. Trimethyl-1,3,5-triazine (Ia): yield, 50.7%; bp 155 °C(155[7]); mp 58.1 °C(59—60[2]); C, 58.38(58.52); H, 7.64(7.37); N, 34.44%(34.12). Triethyl-1,3,5-triazine (Ib): 74%; 123—125 °C/90 mmHg(128—130/90[7]); 23 °C(25[7]); 65.63(65.42); 9.18(9.15); 25.19(25.43). Tri-*n*-proply-1,3,5-triazine (Ic): 36%; 120 °C/13 mmHg(71—72/1[8]); 69.83 (69.52); 10.01(10.21); 20.16%(20.27).

4-Amino-2,6-dimethylpyrimidine (IIa): The procedure of

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[6] It will be reported shortly by the present authors that the ring-opening of trialkyl-1,3,5-triazines, similar to that shown by Eq. (3) under high pressures is promoted by the elevation of the pressure or the temperature.

[7] F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2778 (1961).

[8] A. Ya. Yakubovich, E. L. Zaitseva, G. I. Broz, and V. P. Bazov, *Chem. Abstr.*, **58**, 526 (1963).

Ronzio and Cook as modified by Cairns *et al.*[2] was employed. Acetonitrile was kept in an autoclave with a small amount of sodium methoxide at 150 °C for 12 hr; this yielded the pyrimidine in a 53.8% yield (mp 184.4 °C(182—183[2])); N, 33.63%(34.12)).

4-Chloro-2,6-dimethylpyrimidine: The aminopyrimidine (6.16 g) (0.05 mol) was dissolved in concentrated hydrochloric acid (10 ml) (0.11 mol); the solution was placed in a test tube and then cooled. A concentrated sodium nitrate solution (0.1 mol) was then gently poured into the bottom of the tube. The reaction mixture was neutralized after it had stood overnight and was extracted with ether. The extract was distilled to yield the chloropyrimidine (2.88 g, 46.8%) (bp 82 °C/15 mmHg(182[9])); mp 7.3 °C(7[9])); C, 50.42(50.54); H, 5.09(4.95); N, 18.42(19.65); Cl, 24.11%(24.86).

*2,6-Dimethyl-4-*n*-butylaminopyrimidine (II'a, R^1: H, R^2: n-C_4H_9)*: A mixture of 4-chloro-2,6-dimethylaminopyrimidine (1.62 g) (0.011 mol) and *n*-butylamine (1.66 g) (0.022 mol) was heated on a water bath. The amount of pyrimidine aimed at in the reaction mixture was determined to be 1.59 g (77.6%) by means of gas-liquid phase chromatography (glc) glc-a (Reoplex-400, 3×750 mm, 50—200 °C, 4 °C/min, He 25 ml/min). When the mixture was fractionated by preparative glc (Carbowax-20 M, 9×750 mm,[10] 220 °C, He 125 ml/min) it gave essentially one fraction (0.5 g) with the retention time of 6—9 min. Found: C, 64.60; H, 9.53; N, 23.10%; infrared (IR), 2960, 2932, 2872, 2862, 1468, 1460, 1384, and 734 cm^{-1} for the *n*-butyl group, 1600, 1505, 1440, and 1360 cm^{-1} for the pyrimidine ring. Calcd for $C_{10}H_{17}N_3$: C, 67.00; H, 9.56; N, 23.44%.

Identification of Reaction Products. *Iminoethers*: Each experiment listed in Table 2 gave one peak of iminoether upon glc-b (Carbowax-1500, 3×1000 mm, 47 °C, He 25 ml/min). These peaks agreed with the corresponding peaks of the authentic samples described above (ethyl acetiminoether: 5.5 min; ethyl propio-: 7.8 min; ethyl *n*-butyro; 16.7 min). Ethyl propioiminoether (0.01 g) was isolated by glc (Carbowax-1500, 67 °C—, 4 °C/min). The IR spectrum of this fraction (3350, 3000, 1655, 1465, 1380, 1345, 1280, 1090, and 835 cm^{-1}) agreed with that of the authentic sample described above.

Trialkyl-1,3,5-triazines: The reactions listed in Table 2 each gave one fraction of triazine in a preparative glc (see Table 6). The retention times of glc-a and the IR spectra of these fractions agreed individually with those of the authentic samples described above.

IIa and IIIa: The mixture of acetonitrile (4.08 g) and methanol (4.08 g) was kept at 145 °C and 8900 kg/cm^2 for 30 hr. The reaction product was then removed from a volatile matter *in vacuo* and co-distilled with kerosene (25 ml) to yield a yellow solid (1.46 g). This solid was extracted with petroleum ether. The residue amounted to 0.79 g. The 0.79 g portion was recrystallized from toluene to yield a white powder (0.62 g) (mp 182—184 °C; C, 58.61 (58.52); H, 7.54 (7.37); N, 33.73% (34.12); $\lambda_{\max}^{\text{MeOH}}$ 235 mμ (234, EtOH[2]); log ε, 4.11 (4.02, EtOH[2]); IR, 1594, 1541, 1478, and 1410 cm^{-1} for the pyrimidine ring). These data and the retention time of glc-a agreed with those of the above-described authentic sample of 4-amino-2,6-dimethylpyrimidine. The extract (0.37 g) was recrystallized from petroleum ether to give yellow needles (0.28 g) (mp 148.5 °C (147—148[2]); C, 58.21 (58.52); H, 8.29 (7.37); N, 33.76% (34.12); $\lambda_{\max}^{\text{MeOH}}$ 340 mμ (340, EtOH[2]); log ε, 4.51 (4.49, EtOH[2]); IR, 1530 and 1420 cm^{-1} for the pyrimidine ring). This crystal is identical to *N*-(2,6-dimethylpyrimidin-4-yl)-acetamidine.

IIb and IIIb: The reaction products from propionitrile and ethanol listed in Table 2 gave two peaks of glc-a. The former peak, at the retention time of 31 min, is assumed to be that of 4-amino-2,6-diethyl-5-methylpyrimidine. The latter peak, at 35 min, is assumed to be that of *N*-(2,6-diethyl-5-methylpyrimidin-4-yl)-propioamidine.

II'a (R^1: H, R^2: n-C_4H_9): The reaction products from Ia and *n*-butylamine listed in Table 4 were removed from the volatile matter and fractionated by glc (Carbowax-20 M, 312 °C); this gave a fraction (0.2 g) at the retention time of 9 min (C, 66.81; H, 9.49; N, 23.69%; mol wt (from a parent peak of mass spectroscopy), 179 (Calcd 179.25)). These data, the results of glc-a, and the IR spectrum agreed with those of the authentic 2,6-dimethyl-4-*n*-butylaminopyrimidine described above.

Analysis of Reaction Products. The yields of the reaction products were determined mainly by the use of glc-a, but also sometimes by the use of glc (Reoplex-400, 4×2000 mm, 110 °C, He 90 ml/min).

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9) J. Schmidt, *Ber.*, **35**, 1575 (1902).

10) The column size and the flow rate of helium for the preparative glcs were always the same in these experiments.