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Reaction of Ethoxymethylenemalononitrile with 2-Aminopyridines

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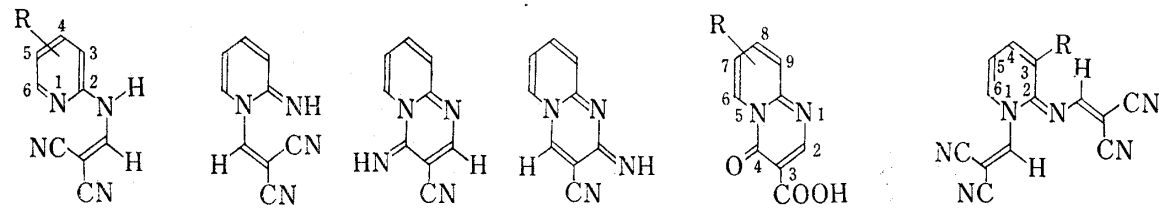
A nucleophilic reaction of 2-aminopyridines (or 2-aminoheterocycles) with ethoxymethylenemalononitrile was investigated and structures of the reaction products were assigned as shown in Table II. Similar reactions using 2-aminopyridine hydrochloride were found to give 1,2-dihydro-1-(2,2-dicyanovinyl)-2-iminopyridine (IV), and 1,2-dihydro-1-(2,2-dicyanovinyl)-2-(2,2-dicyanovinylimino)pyridine (VIa).

A nucleophilic reaction of 2-aminopyridine with imidates may be considered to take place at two possible positions, the one at the amino group nitrogen and the other at ring nitrogen in 2-aminopyridine. This problem was elucidated to a certain extent in a previous report[2] by the reaction of 2-aminopyridine with ethyl chloroacetimidate hydrochloride.

In continuation of this work, we investigated the reactions of 2-aminopyridine and its analogs with ethoxymethylenemalononitrile (I).

Reaction of 2-Aminopyridine with I

It was found that the condensation between I and 2-aminopyridine in carbon tetrachloride or ethanol solution gave yellow needles (IIa), mp 175° (decomp.), which has the molecular formula of $C_9H_6N_4$ from the data of elementary analysis and mass spectroscopy.



(A) (B) (C) (D)

IIa : R=H
IIb : R=3-CH$_3$
IIc : R=4-CH$_3$
IId : R=5-CH$_3$
IIe : R=6-CH$_3$

or IV

or V

IIIa : R=H
IIIb : R=9-CH$_3$
IIIc : R=8-CH$_3$

VIa : R=H
VIb : R=CH$_3$

Chart 1

1) Location: *Shirokane, Minato-ku, Tokyo, 108, Japan.*
2) Y. Okamoto, A. Takada, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **20**, 725 (1972).

The nuclear magnetic resonance (NMR) spectrum of this product IIa showed 3-, 4-, 5- and 6-proton signals at 7.57, 7.92, 7.25 and 9.40 ppm, and an olefinic proton at 8.12 ppm and NH proton at 6.25 ppm. The absorption band at 2260 cm^{-1} in its infrared (IR) spectrum seemed to be due to $-C\equiv N$ group. Taking these data into consideration, the authors postulated the four possible structures, (A) and (B), and their cylcic forms (C) and (D), as shown in Chart 1.

Yoneda and others[3] found that the condensation of ethyl ethoxymethylenecyanoacetate with 2-aminopyridine afforded a mixture of geometric isomers of ethyl N-(2-pyridyl)aminomethylenecyanoacetate, which was converted to 4*H*-pyrido[1,2-*a*]pyrimidin-4-one-3-carboxylic acid (IIIa) by treatment with 15% hydrochloric acid. When IIa was treated with 15% hydrochloric acid according to the procedure of Yoneda and others, IIIa was obtained. This fact suggests that the position in 2-aminopyridine attacked by the nucleophilic agent should be at the nitrogen atom of the amino group.

In order to confirm the structure of IIa as A or C, the reaction of I with 2-amino-6-methylpyridine in place of 2-aminopyridine was carried out. This reaction product should be N-(6-methyl-2-pyridyl)aminomethylenemalononitrile (IIe), related to the structure A, since it has been known that pyrido[1,2-*a*]pyrimidine type compounds are not obtained from such reactions because of the steric hindrance of the 6-methyl group.[3,4] The ultraviolet (UV) spectrum of IIe was similar to that of IIa (Table I) indicating that IIa should possess the structure A, N-(2-pyridyl)aminomethylenemalononitrile.

Table I. UV Spectra of IIa and IIe

Compound	UV $\lambda_{max}^{H_2O}$ nm (log ε)		
IIa	324(3.746)	271(3.486)	262(3.565)
IIe	324(4.086)	273(3.885)	267(3.818)

Syntheses of Compounds (B) and (C)

To collect circumstantial evidences of the compounds of type A, attempts were made to synthesize the compounds of type B and C. When a mixture of 2-aminopyridine hydrochloride and I was refluxed in ethanol for 20 hr, colorless crystals (IV) were obtained after evaporation of the solvent. This substance was proved to have the structure B, 1,2-dihydro-1-(2,2-dicyanovinyl)-2-iminopyridine, from its elementary analysis and IR, UV, NMR and mass spectral data.

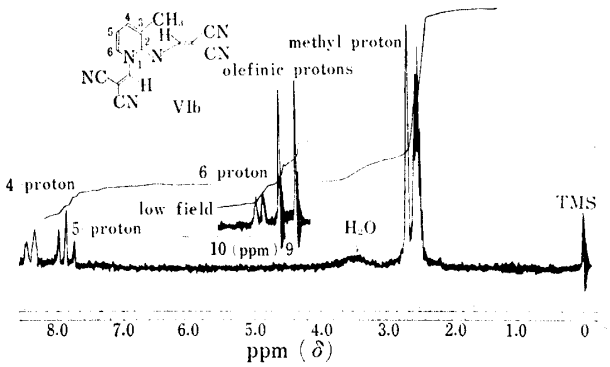


Fig. 1. NMR Spectrum of 1,2-Dihydro-1-(2,2-dicyanovinyl)-2-(2,2-dicyanovinylimino)-3-methylpyridine (60 MHz, 10% solution in Me_2SO-d_6)

Fusion of 2-aminopyridine hydrochloride with I at 120° for 45 min, followed by filtration of the fused mixture, gave colorless crystals (V), and this substance was identified as 4-imino-4*H*-pyrido[1,2-*a*]pyrimidine-3-nitrile (C) from spectral analysis and hydrolysis to IIIa. Dilution of the filtrate from the above fused mixture using ethanol gave colorless crystals, the structure of which was determined as 1,2-dihydro-1-(2,2-dicyanovinyl)-2-(2,2-dicyanovinylimino)pyridine (VIa). It was

3) S. Nishigaki, M. Ichiba, K. Shinomura, and F. Yoneda, *J. Heterocyclic Chem.*, **8**, 759 (1971).
4) Y. Okamoto, A. Takada, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **19**, 764 (1971).

noteworthy that the fusion of 3-methyl-2-aminopyridine hydrochloride with I gave merely 1,2-dihydro-1-(2,2-dicyanovinyl)-2-(2,2-dicyanovinylimino)-3-methylpyridine (VIb) under the same conditions. The NMR spectrum of VIb is shown in Fig. 1. The signals at 8.83 and 9.08 ppm revealed two non-equivalent olefinic protons, 4-, 5- and 6-protons at 8.43, 7.87 and 9.40 ppm, respectively, and methyl protons at 2.70 ppm.

Similar reaction of 6-methyl-2-aminopyridine with I gave exclusively N-(6-methyl-2-pyridyl)aminomethylenemalononitrile IIe. This result may be ascribed to the steric hindrance of 6-methyl group.

Reaction of 2-Aminoheterocycles with I

To examine the scope and limitation of the above reaction, attempts were made to react 2-aminoheterocycles, such as 2-amino-3-, -4- or -5-methylpyridines, 2-aminopyrimidine, 2-aminothiazole, 2-aminopyrazine, 2-aminoquinoline and 2-aminobenzothiazole with I. In these reactions, all of the reaction products were shown to have the type A structure. The products are listed in Table II. Among them, N-(3-methyl-2-pyridyl)aminomethylenemalononitrile (IIb) and N-(5-methyl-2-pyridyl)aminomethylenemalononitrile (IId) were converted to IIIb and IIId by treatment with acidic solution. Compound (IX) was converted with hydrochloric acid into X, which was also obtained by hydrolysis of XI, XII or XIII prepared by alternative routes as shown in Chart 2. From these reactions, it was inferred that the product IX might have the structure of type A.

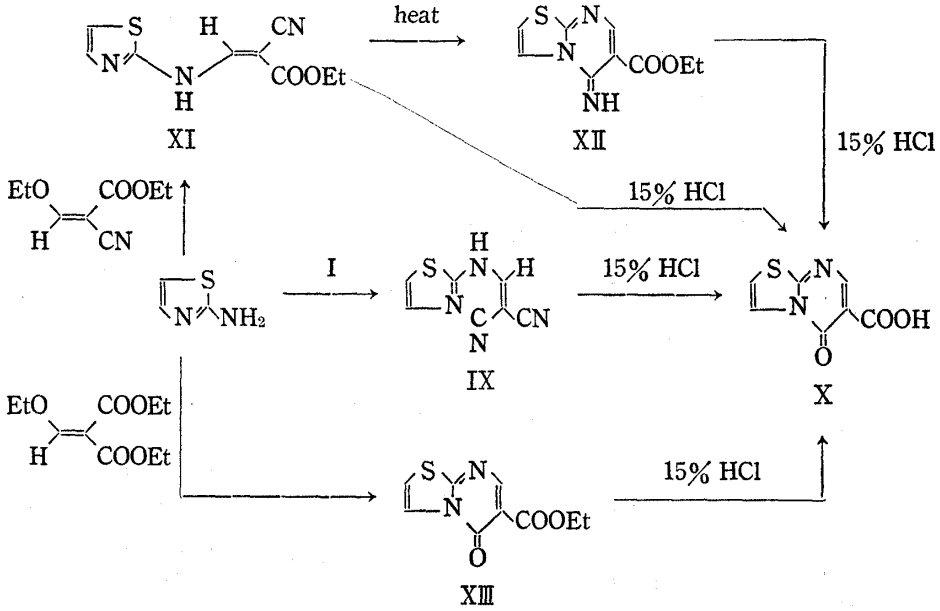


Chart 2

Experimental[5]

General Procedure for Syntheses of Aminomethylenemalononitrile Derivatives (Table II)——A solution of 0.02 mole (2.0 g) of 2-aminopyridine in 50 ml of EtOH was added to 0.02 mole (2.5 g) of I. After the solution had been allowed to stand overnight, resulted precipitates were collected, and recrystallized from EtOH to give yellow needles.

General Procedure for Syntheses of 4*H*-Heterocyclo[1,2-*a*]pyrimidin-4-one-3-carboxylic Acid (Table III)——A solution of 0.5 g of N-(2-pyridyl)aminomethylenemalononitrile in 50 ml of a mixture of H_2O (or EtOH) and conc. HCl (1 : 1) was refluxed for 20 min. After cooling, the reaction mixture was neutralized

5) NMR spectra and mass spectra were obtained with Varian T 60 spectrometer and JMS-01S spectrometer (Japan Electron Optics Laboratory Co., Ltd.), respectively.

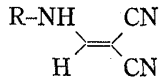
with aqueous ammonia and precipitates were collected by filtration. Recrystallization from methanol gave colorless plates.

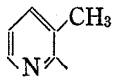
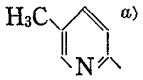
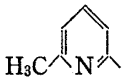
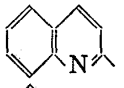
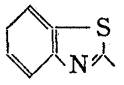
1,2-Dihydro-1-(2,2-dicyanovinyl)-2-iminopyridine (IV)——A solution of 8.3 g of 2-aminopyridine hydrochloride in 150 ml of EtOH was added to 7.5 g of I, and the mixture was refluxed for 20 hr. After the evaporation of the solvent, residues were washed with ice-cooled water. Recrystallization from EtOH gave colorless needles, mp 151°. Yield, 6.1 g (58%). Mass Spectrum *m/e*: 170 (M^+, very weak), 94 (M^+-76, very strong). NMR (10% solution in DMSO-d_6): 6.97 (2H, multiplets, β-protons in the ring), 7.22 (1H, singlet, olefinic proton), 7.95 (1H, a doublet, $J=6$ Hz, α-proton), 8.00 (1H, two doublets, $J_{4,3}=8$ Hz, $J_{4,5}=6$ Hz, γ-proton), 8.00 (1H, broad singlet, imino proton). *Anal.* Calcd. for $C_9H_6N_4$: C, 63.52; H, 3.55; N, 32.93. Found: C, 63.61; H, 3.49; N, 32.87. UV $\lambda_{max}^{H_2O}$ nm (log ε): 345 (4.30), 230 (3.82).

4-Imino-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile (V) and 1,2-Dihydro-1-(2-,2-dicyanovinyl)-2-(2,2-dicyanovinylimino)pyridine (VIa)——Hydrochloride salts of 2-aminopyridine (1.4 g) were fused with I (1.1 g) at 110° for 1 hr. The fused mixture was immediately filtered by suction to obtain brown crystals. The crystals were washed with hot EtOH to give 0.5 g (28%) of a crude compound (V) which has a molecular weight of 170. This compound (V) was hydrolyzed to 4*H*-pyrido[1,2-*a*]pyrimidin-4-one-3-carbocylic acid with 15% HCl solution (yield, 70%).

To the filtrate described above, EtOH was added, and after cooling, precipitated crystals were collected by filtration. Recrystallization from EtOH gave 0.15 g (6%) of orange needles of (VIa), mp 228°. Mass Spectrum *m/e*: 246 (M^+). NMR (10% solution in DMSO-d_6): 8.05 (2H, multiplets, β-proton), 8.47 (1H,

Table II. Aminomethylenemalononitrile Derivatives



No.	R	Yield (%)	Appearance (Recryst. Solvt.)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR (cm^{-1}) (KBr $\nu_{C\equiv N}$)
IIa		72	needles (EtOH)	175 (decomp.)	$C_9H_6N_4$	63.52 (63.30)	3.55 (3.55)	32.93 (32.80)	2260
IIb		80	needles (EtOH)	162	$C_{10}H_8N_4$	65.20 (65.23)	4.38 (4.37)	30.42 (30.15)	2227
IIc		73	needles (EtOH)	203—203.5	$C_{10}H_8N_4$	65.20 (65.20)	4.38 (4.36)	30.42 (30.51)	2230
IId	 a)	46	needles (EtOH)	184—185	$C_{10}H_8N_4$	65.20 (65.15)	4.38 (4.40)	30.42 (30.35)	2225
IIe		88	prisms (EtOH)	182	$C_{10}H_8N_4$	65.20 (65.13)	4.38 (4.39)	30.42 (30.40)	2228
VII		93	powders (MeOH)	200 (decomp.)	$C_8H_5N_5$	56.14 (56.41)	2.94 (2.84)	40.92 (40.86)	2250
VIII		66	plates (EtOH)	208 (decomp.)	$C_8H_5N_5$	56.14 (56.40)	2.94 (2.85)	40.92 (40.83)	2230
IX		87	needles (EtOH)	168—169	$C_7H_4N_4S$	47.72 (47.65)	2.29 (2.22)	31.80 (31.12)	2243
XIV		28	needles (EtOH)	227	$C_{13}H_8N_4$	70.89 (70.60)	3.66 (3.87)	25.44 (25.18)	2227
XV		83	needles (EtOH)	183—184	$C_{11}H_6N_4S$	58.39 (58.34)	2.67 (2.66)	24.76 (24.61)	2239

a) This compound was hydrolyzed to 2-amino-5-methylpyridine hydrochloride under acidic conditions (15% HCl solution).

two doublets, $J_{4,3}=8$ Hz, $J_{4,5}=6$ Hz, γ-proton), 8.80 (1H, singlet, an olefinic proton), 9.03 (1H, singlet, an olefinic proton), 9.47 (1H, a doublet, $J=6$ Hz, α-proton). *Anal.* Calcd. for $C_{13}H_6N_6$: C, 63.41; H, 2.46; N, 34.13. Found: C, 63.11; H, 2.45; N, 34.10.

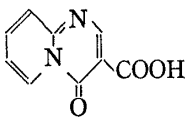
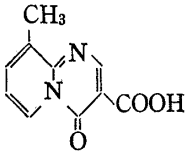
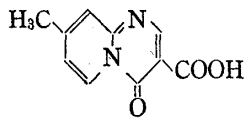
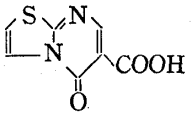
1,2-Dihydro-1-(2,2-dicyanovinyl)-2-(2,2-dicyanovinylimino)-3-methylpyridine (VIb)——A mixture of 1.3 g of 2-amino-3-methylpyridine hydrochloride and 1.1 g of I was fused at 110° for 30 min. EtOH was added and precipitated crystals were filtered. Recrystallization from EtOH gave 1 g (41%) of red needles mp 214° (decomp.). Mass Spectrum *m/e*: 260 (M^+). NMR (10% solution in DMSO-d_6): 2.70 (3H, singlet, 3-CH_3), 7.87 (1H, two doublets, $J_{5,4}=8$ Hz, $J_{5,6}=6$ Hz, 5-proton), 8,43 (1H, a doublet, $J=6$ Hz, 4-proton), 8.83 (1H, singlet, an olefinic proton), 9.08 (1H, singlet, an olefinic proton), 9.40 (1H, a doublet, $J=6$ Hz, 6-proton). *Anal.* Calcd. for $C_{14}H_8N_6$: C, 64.61; H, 3.10; N, 32.29. Found: C, 64.70; H, 3.11; N, 32.10.

A Mixture of Geometrical Isomers of Ethyl N-(2-Thiazolyl)aminomethylenecyanoacetate (XI)——A solution of 2 g of 2-aminothiazole in 35 ml of EtOH was added to 3.4 g of ethyl ethoxymethylenecyanoacetate, and the mixture was allowed to stand for 48 hr. Recrystallization of precipitates from EtOH gave a mixture of needles and prisms, mp 122—123°. Yield, 2.8 g (63%). Mass Spectrum *m/e*: 223 (M^+). NMR (10% solution in DMSO-d_6)[6]: 1.30 and 1.31 (two triplets, $J=6$ Hz, $-CH_3$), 4.25 and 4.26 (two quartets, $J=6$ Hz, $-CH_2-$), 7.30 and 7.48 (two doublets, $J=4$ Hz, ring protons), 8.40 (a doublet, $J=1$ Hz, an olefinic proton), 8.40 and 12.13 (two broad peaks, -NH-), 8.73 (singlet, an olefinic proton). *Anal.* Calcd. for $C_9H_9O_2N_3S$: C, 48.42; H, 4.06; N, 18.82. Found: C, 48.38; H, 4.12; N, 18.76.

Ethyl 4-Imino-4*H*-thiazolo[1,2-*a*]pyrimidine-3-carboxylate (XII)——A solution of 1 g of ethyl N-(2-thiazolyl)aminomethylenecyanoacetate in 10 ml of EtOH was refluxed for 5 hr. After the cooling of the solution, precipitates were collected by filtration and recrystallized from MeOH to give yellow needles, mp 140—141°. Yield, 0.55 g (55%). *Anal.* Calcd. for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82. Found: C, 48.51; H, 4.21; N 18.66.

Ethyl 4*H*-Thiazolo[1,2-*a*]pyrimidin-4-one-3-carboxylate (X)——A solution of 1 g of 2-aminothiazole in 15 ml of EtOH was added to 2.2 g of diethyl ethoxymethylenemalonate and the mixture was refluxed for 5 hr. After removal of the solvent, residual substances were recrystallized from EtOH to give crystals, mp 183—184°. Yield, 0.67 g (30%). *Anal.* Calcd. for $C_9H_8O_3N_2S$: C, 48.21; H, 3.60; N, 12.49. Found: C, 48.03; H, 3.50; N, 12.36.

Table III. 4*H*-Heterocyclo[1,2-*a*]pyrimidin-4-one-3-carboxylic Acid

No.	Compound	Yield (%)	Appearance (Recryst. Solvt.)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
IIIa		35	plates (EtOH+H_2O)	260 (decomp.)[a]	$C_9H_6O_3N_2$	56.85 (56.81)	3.18 (3.20)	14.73 (14.81)
IIIb		48	needles (EtOH+H_2O)	217—219	$C_{10}H_8O_3N_2$	58.82 (58.90)	3.95 (3.96)	13.72 (13.80)
IIIc		51	needles (EtOH+H_2O)	223 (decomp.)[b]	$C_{10}H_8O_3N_2$	58.82 (58.89)	3.95 (3.60)	13.72 (13.93)
X		56	powder (reprecipitation)[c]	270—271	$C_7H_4O_3N_2S$	42.86 (42.90)	2.06 (2.30)	14.28 (14.37)

a) *lit.* 3) mp 278°, *b*) lig. 3) mp 223°, *c*) with 10% Na_2CO_3 and 10% HCl

6) The signals of the ring protons in the mixture are overlapping.