NMR ($CDCl_3$) δ: 2.4 (3H, s, $>NCH_3$), 7.0 (1H, d.d, $J=7.5$, 4.5 Hz, arom.), 7.4 (1H, broad d, $J=7.5$ Hz, arom.), 8.3 (1H, broad d, $J=4.5$ Hz, arom.). Mass Spectrum *m/e*: 188 (M^+). *Anal.* Calcd. for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.38; H, 8.63; N, 14.59.

Acknowledgement The authors are grateful to Mr. M. Morikoshi for measurements of NMR and mass spectra, and to Mr. H. Hori for elemental analyses.

[Chem. Pharm. Bull. 24(11)2880—2882(1976)]

UDC 547.339.2.04 : 547.234.04

Reaction of Ethoxymethylenemalononitrile with Hydrazine Hydrate

KATSUHIKO NAGAHARA, KANAME TAKAGI, and TAKEO UEDA

School of Pharmaceutical Sciences, Kitasato University[1]

(Received February 10, 1976)

The reaction of ethoxymethylenemalononitrile (EMMN) with hydrazine hydrate in the presence of ethanol at room temperature gave 3-amino-4-cyanopyrazole (I) and a novel pyrazole derivative, 3-amino-4-cyano-2-hydrazonomethylpyrazole (II). When this reaction was carried out under reflux, II was not obtained. The result of various solvents for the preparation of II was found at present acetonitrile as a solvent most suitable. The reaction of EMMN with hydrazine hydrate in water at room temperature gave I in good yield. On the other hand, the reaction of hydrazine hydrate with excess EMMN afforded 7-amino-3,6-dicyanopyrazolo[1,5-*a*]pyrimidine.

In our recent publication, we have reported that the reaction of ethoxymethylenemalononitrile (EMMN) with hydrazine hydrate in ethanol at room temperature gave 3-amino-4-cyanopyrazole (I) and a novel pyrazole derivative, 3-amino-4-cyano-2-hydrazonomethylpyrazole (II).[2] The 3-amino-4-cyanopyrazole ring system was first described in 1956 by Robins,[3] who obtained only compound I by the reaction of EMMN with hydrazine hydrate in the absence of a solvent. Similarly, refluxing of EMMN with hydrazine hydrate in anhydrous ethanol or ethanol gave only compound I.[4]

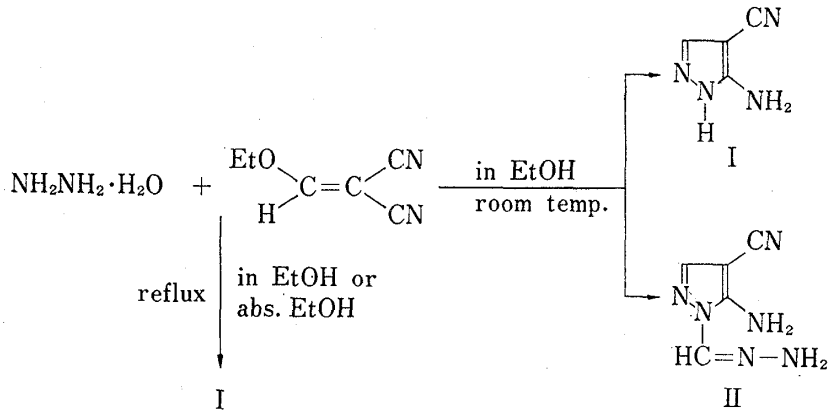

Chart 1

1) Location: *Shirokane 5-9-1, Minato-ku, Tokyo 108, Japan.*
2) K. Takagi, K. Nagahara, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo)., **18**, 2353 (1970).
3) R.K. Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).
4) *a*) G.H. Hitching and E.A. Falco, U.S. Patent 2759949 (1956) [*C.A.*, **51**, 11391 (1957)]; *b*) Wellcome Foundation Ltd., Br. Patent 798662 (1958) [*C.A.*, **53**, 1382 (1959)]; *c*) E.B. Towne, W.H. Moore, and J.B. Dickey, U.S. Patent 3336289 (1967) [*C.A.*, **68**, 14072 (1968)].

In our method,[2] the yield of II was not over 10%.

Therefore, we studied now the formation of the novel pyrazole compound II by using various solvents; water, methanol, ethanol, propanol, isobutanol, acetone, N,N-dimethylformamide, or acetonitrile, in order to increase of the yield of II. Furthermore, we have newly found that the reaction of hydrazine hydrate with excess EMMN gave 7-amino-3,6-dicyanopyrazolo[1,5-*a*]pyrimidine.

We also investigated the relationship between the yield of II and the concentration of alcoholic solution, and found that the formation of II is correlated to the concentration of alcohol. For example, none of compound II was detected in concentration from 0 to 50% ethanol, however, the use of higher concentration of alcohol (60 to 100%) increased the yield of II (Table I). The use of propanol as a solvent gave II in about 2% yield, while the use of isobutanol, acetone, and N,N-dimethylformamide afforded only I. When the reaction was carried out in acetonitrile, II was obtained in somewhat better yield. The yield of II on using methanol was comparable to that by the use of 100% ethanol.

Table I. Reaction of EMMN and 2 Equiv. of Hydrazine Hydrate in EtOH

Compound		Concentration of EtOH (%)										
		0	10	20	30	40	50	60	70	80	90	100
I	yield (%)	90	72	66	65	56	41	45	31	52	54	57
II	yield (%)	0	0	0	0	0	0	6	7	9	13	15

Table II. Reaction of EMMN and 2 Equiv. of Hydrazine Hydrate in Various Solvents

Compound		*n*-Propyl alcohol	iso-Butyl alcohol	Acetone	DMF[a]	MeOH	Acetonitrile		No solvent
I	yield (%)	58	40	74	34	34	51	49[b]	61
II	yield (%)	2	0	0	0	11	38	0[b]	0

a) N,N-dimethylformamide, *b*) reflux

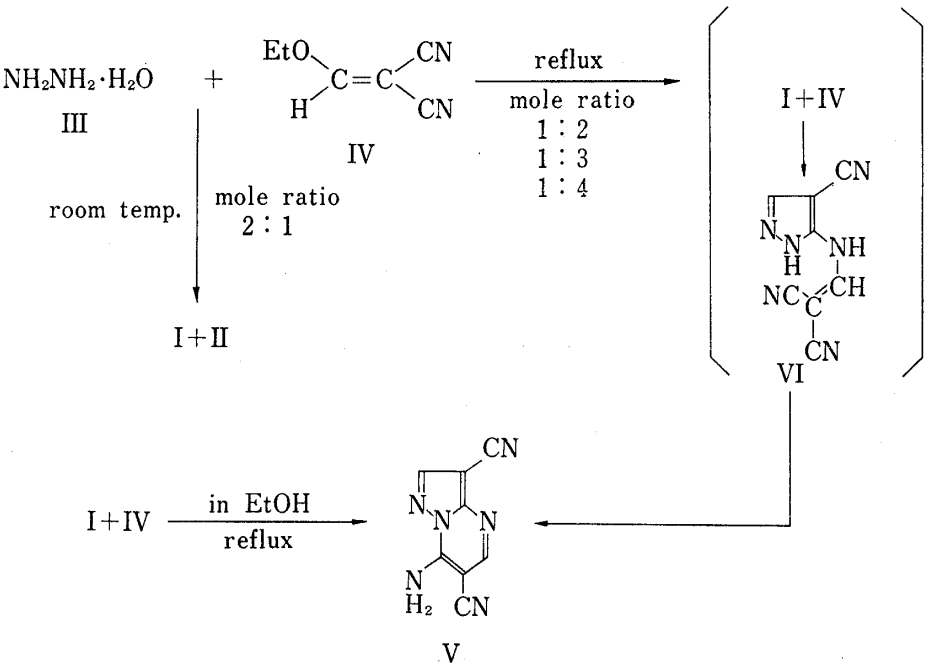

Chart 2

Table III. Reaction of Hydrazine Hydrate and Excess of EMMN

Mole ratio of III to IV	Yield of V (%)	
	EtOH	CH_3CN
1:1[a]	0	0
1:2	26.7	68.0
1:3	46.0	73.3
1:4	46.5	74.7

a) The yield of compound I was 90%.

II was obtained in the highest yield by the use of acetonitrile as a solvent. Therefore, the use of acetonitrile seemed to be most suitable for the formation of II. However, it is noted that when this reaction was heated under reflux, it gave only I (Table II).

The synthesis of I by using water as a solvent at room temperature has not been reported. Regarding to this reaction we found that I was obtained in a higher yield by the reaction of EMMN with hydrazine hydrate in water under the same conditions as described above.

On the other hand, heating of hydrazine hydrate with excess EMMN in ethanol under reflux for 4 hr afforded the pale-yellow product, $C_8H_4N_6$, mp>300°, which was not I or II. The mass spectrometry showed a parent ion (*m/e* 184) and the infrared (IR) spectrum revealed the presence of the bands at 3125, 3275, 3325, and 3425 cm^{-1}. (associated N–H), at 2225 cm^{-1} (C≡N) and at 1670 and 1610 cm^{-1}. (C=N).

From the above evidence, it would appear that the pale-yellow material is 7-amino-3,6-dicyanopyrazolo[1,5-*a*]pyrimidine (V). V was identical with the authentic sample[5] prepared by the reaction of I with EMMN in ethanol under reflux for 3 hr.

The relationship between the yield of V and the mole ratio of III to IV is summarized in Table III. In conclusion, the result of various solvents for the preparation of II or V was found at present acetonitrile as solvent most suitable.

Experimental[6]

Reaction of EMMN and 2 Equiv. of Hydrazine Hydrate——To an ice-cold solution of 4.0 g (0.033 mole) of EMMN in 10 ml of a solvent was added with stirring dropwise into the suspension of 3.2 g (0.066 mole) of hydrazine hydrate. After stirring for 10 min, the reaction mixture was continued to stir for 2 hr at room temperature. Precipitated crystals were filtered by suction, and recrystallized from ethanol-water to give 3-amino-4-cyano-2-hydrazonomethylpyrazole (II), as colorless needles, mp 157°. Mass Spectrum *m/e*: 150 (M^+). *Anal.* Calcd. for $C_5H_6N_6$: C, 40.00; H, 4.03; N, 55.97. Found: C, 40.16; H, 4.05; N, 56.15.

The mother liquid was concentrated *in vacuo* and the precipitated crystals were filtered off. Recrystallization from water gave 3-amino-4-cyanopyrazole (I), mp 172—173°. Mass Spectrum *m/e*: 108 (M^+). *Anal.* Calcd. for $C_4H_4N_4$: C, 44.44; H, 3.37; N, 51.83. Found: C, 44.12; H, 3.65; N, 51.97.

The use of EtOH, MeOH, Propanol and CH_3CN as a solvent afforded compound I and II, under the same conditions as described above. Also, the use of isobutanol, acetone, dimethyl formamide (DMF) and water as a solvent: Precipitated crystals were filtered by suction, and recrystallized from water to give only I.

Reaction of Hydrazine Hydrate and Excess of EMMN——In the Case of Mole Ratio (1: 2): To a solution of 0.2 g (0.004 mole) of hydrazine hydrate in 15 ml EtOH or CH_3CN was added 1 g (0.008 mole) of EMMN and the mixture was refluxed on a water bath for 4 hr. After cooling, the product was removed by filtration and recrystallized from DMF-water to give 7-amino-3,6-dicyanopyrazolo[1,5-*a*]pyrimidine (V), mp>300°. Mass Spectrum *m/e*: 184 (M^+). *Anal.* Calcd. for $C_8H_4N_6$: C, 52.17; H, 2.19; N, 45.64. Found: C, 51.96; H, 2.13; N, 45.43.

5) A Part of this work was reported by K. Nagahara, K. Takagi, A. Takada, and T. Ueda, at the 92 nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, Apl. 1972.

6) All melting point are uncorrected. The IR spectra were recorded on a Japan Spectroscopic Model IRA-1 spectrometer. Mass spectra were obtained on a JMS-OlS spectrometer (Japan Electron Optics Laboratory Co., Ltd.).