The Reaction of Ethyl Ethoxymethylenecyanoacetate with Its Hydrazino Derivatives[1]

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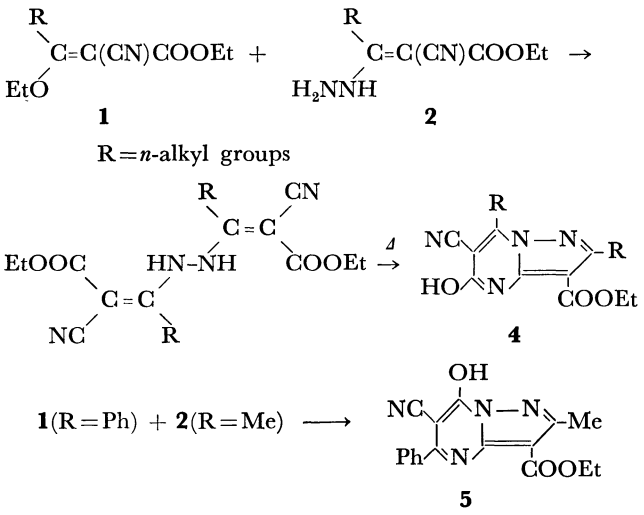
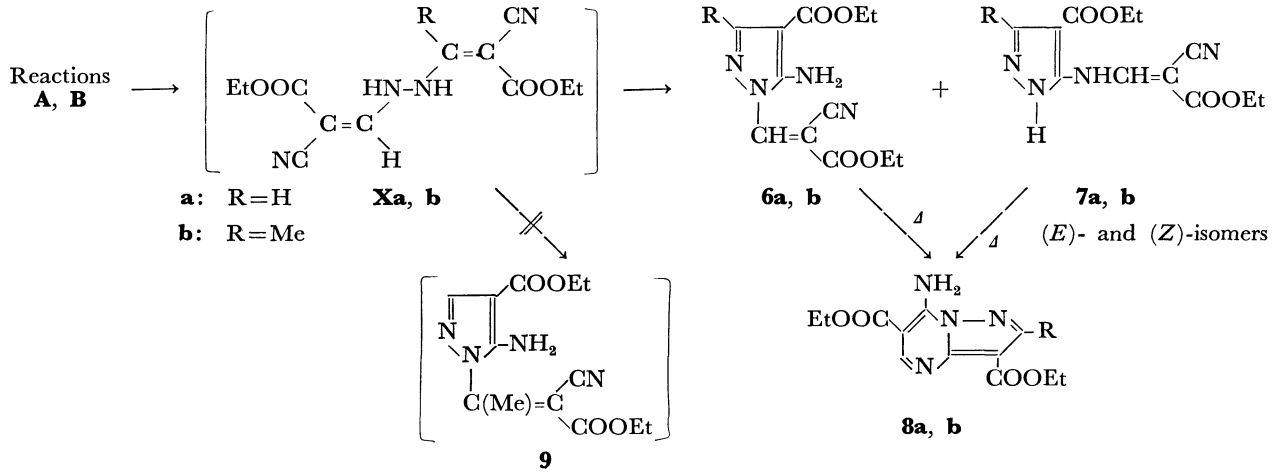
The reaction of ethyl ethoxymethylenecyanoacetate with its hydrazino derivative in the presence of pyridine in ethanol at room temperature gave ethyl (4-ethoxycarbonyl-5-aminopyrazol-1-yl)methylenecyanoacetate(**6**) and two geometric isomers of ethyl (4-ethoxycarbonylpyrazol-5-ylamino)methylenecyanoacetate(**7**). Compound **6** itself, under the same conditions, rearranged to compound **7**. Both compounds, **6** and **7**, upon heating cyclized exclusively to the same product, diethyl 7-aminopyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate(**8**). From the results of other combination reactions on methylenecyanoacetic ester homologs, a plausible reaction mechanism involving a rearrangement is discussed.

A previous work[3] has been shown that the reaction of (1-alkoxyalkylidene)cyanoacetic esters (**1**: R=*n*-alkyl groups) with their hydrazino derivatives (**2**) in the presence of pyridine in ethanol at room temperature gave bis(substituted vinyl)hydrazines, whose cyclization led to the formation of only 5-hydroxypyrazolo[1,5-*a*]pyrimidines(**4**), while methyl (α-methoxybenzylidene)-cyanoacetate(**1**: R=Ph) or (1-ethoxyethylidene)malononitrile reacted with the hydrazino reactant(**2**: R=Me) to afford 7-hydroxy(or amino)pyrazolopyrimidine (**5**) as a major product directly, along with the 5-hydroxy (or amino) one. It has also been found that similar condensations on methylenecyanoacetic ester homologs(**1** and/or **2** being R=H) all lead to the 7-amino product as the only final product. The formation of the 7-amino (or hydroxy) product in these reactions suggests that a certain rearrangement must occur if **2** itself does not initially cyclize to 5-aminopyrazole(**3**) during the reaction.



The reaction of ethyl ethoxymethylenecyanoacetate (**1**: R=H) with its hydrazino derivative (**2**: R=H)[4,5] under the same conditions as have been described in the earlier paper, Reaction **A**, afforded at first ethyl (4-ethoxycarbonyl-5-aminopyrazol-1-yl)methylenecyanoacetate(**6a**) instead of the expected intermediate(**Xa**), followed by two geometric isomers of ethyl (4-ethoxycarbonylpyrazol-5-ylamino)methylenecyanoacetate, (*E*)- and (*Z*)-**7a**. The elemental analyses of all these compounds indicated that they all had the same composition ($C_{12}H_{14}O_4N_4$). Their structures were chiefly verified by the following spectral studies. As can be seen from Table 1, the NMR spectrum of **6a** shows two sharp singlet signals(both 1H), corresponding to the vinyl proton and C–H proton on the pyrazole ring, and a broad singlet signal(2H) of the NH_2 protons. The IR spectrum of **6a** shows the pre-



Scheme 1.

Table 1. Characteristic NMR and IR data of compounds **6** and **7**

Compd	Solv.	NMR (δ-Values from TMS)			NH (Ring)	IR (cm^{-1}, Nujol)		
		R (Ring)	=CH	NH (Exo)		ν NH_2		ν NH
6a	$CDCl_3$	8.29(H)	8.19	5.23(NH_2)		2478	3372	
	CD_3SOCD_3	8.57(H)	8.69	6.35(NH_2)				
6b	$CDCl_3$	2.64(Me)	8.16	5.31(NH_2)		3475	3350	
	CD_3SOCD_3	2.65(Me)	8.18	6.26(NH_2)				
(*E*)-**7a**	CD_3SOCD_3	8.27(H)	8.48 d (J=15 Hz)	9.40 d	13.39		3310(sh)	3250
(*Z*)-**7a**	CD_3SOCD_3	8.26(H)	8.28 d (J=14 Hz)	11.42 d	13.39		3312(sh)	3250
(*E*)-**7b**	$CDCl_3$	2.53(Me)	8.83 d (J=14 Hz)	9.30 d	10.80 br		3309(sh)	3251
	CD_3SOCD_3	2.37(Me)	8.48 d (J=14 Hz)	9.25 d	13.10			
(*Z*)-**7b**	$CDCl_3$	2.53(Me)	8.30 d (J=13 Hz)	11.58 d	10.60 br		3310(sh)	3252
	CD_3SOCD_3	2.38(Me)	8.28 d (J=13 Hz)	11.38 d	13.15			

sence of a typical primary amino group. On the other hand, the NMR spectra of the two isomers of **7a** show the doublet signal due to the vinyl proton coupled with the adjacent NH proton. The downfield NH signal attributed to an intramolecular hydrogen-bonding between the amino and the ester groups was assigned to that of the (*Z*)-form.[5]

Also, a similar reaction of the ethoxy reactant(**1**: R=H) with ethyl (1-hydrazinoethylidene)cyanoacetate(**2**: R=Me), Reaction **B**, gave the corresponding compounds, ethyl (3-methyl-4-ethoxycarbonyl-5-aminopyrazol-1-yl)methylenecyanoacetate (**6b**)[6] and two isomers of ethyl (3-methyl-4-ethoxycarbonylpyrazol-5-ylamino)methylenecyanoacetate, (*E*)- and (*Z*)-**7b**.

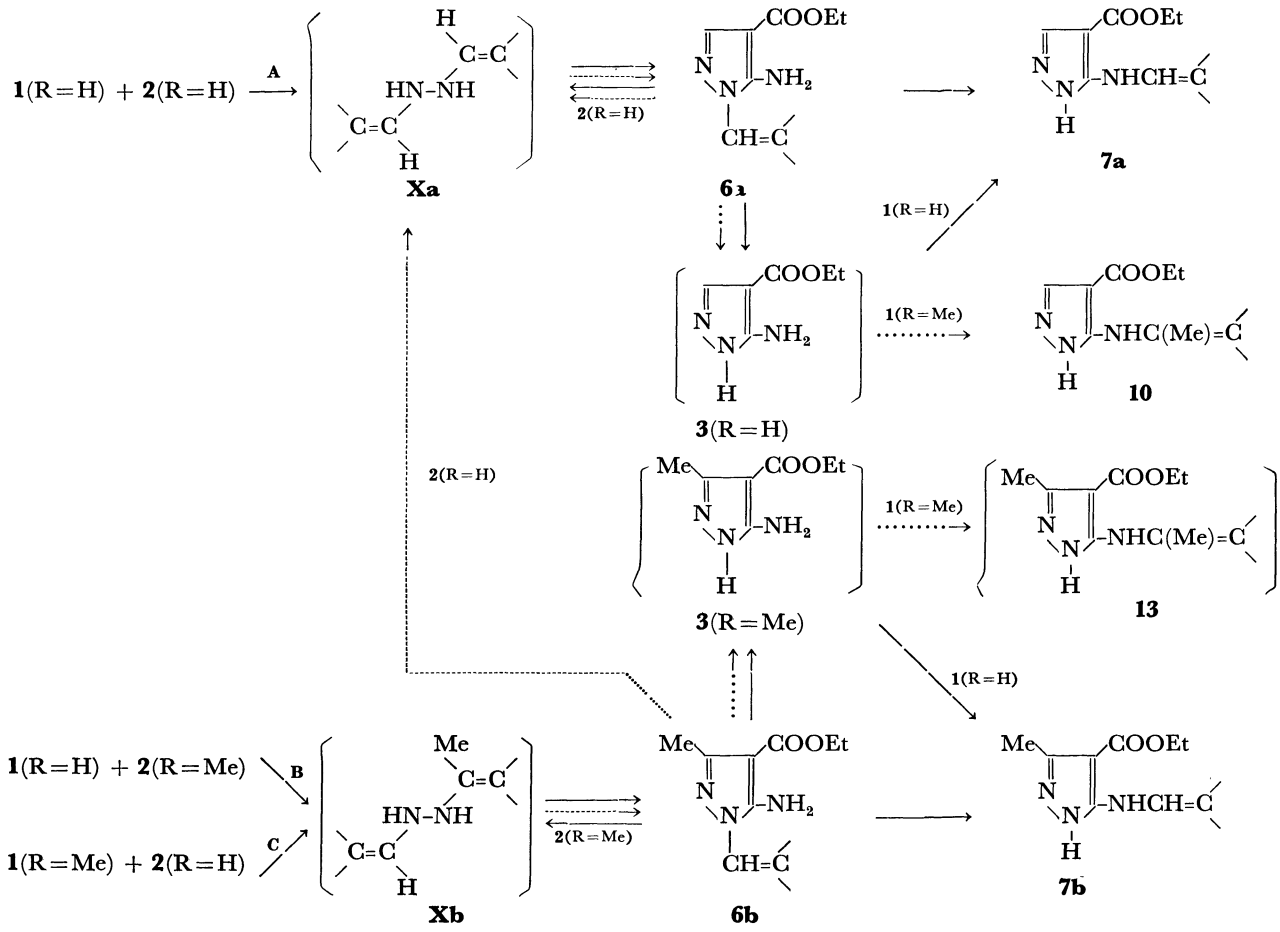
The two isomers of **7** were also prepared by the condensation of the ethoxy reactant(**1**: R=H) with ethyl 5-aminopyrazole-4-carboxylates(**3**), derived from the hydrazino reactants(**2**: R=H and Me), under the same conditions, and upon heating above 210 °C or by refluxing in acetic acid or in ethanolic hydrochloric acid they were cyclized to form the corresponding diethyl 7-aminopyrazolopyrimidine-3,6-dicarboxylates(**8**) exclusively.[7] Also, a similar treatment of **6** resultsed in the same product(**8**) instead of the 5-amino one. This fact implies that **6** must rearrange to **7** prior to its cyclization. In fact, when only **6** was placed under the same conditions as in the original reaction, a rearrangement occurred and a mixture of the geometric isomers of **7** resulted.

In view of the above facts, it seems reasonable to assume that both reactions, **A** and **B**, proceed through an initial intermediate(**X**) which cyclizes partially to **6** without the occurrence of an initial cyclization of the reactant(**2**) to **3**. In Reaction **B** the absence of ethyl [1-(4-ethoxycarbonyl-5-aminopyrazol-1-yl)ethylidene]cyanoacetate(**9**) suggests that the partial cyclization of an initial intermediate(**Xb**) takes place preferentially at the side of the methylvinyl group to give **6b**.

On the other hand, when ethyl (1-ethoxyethylidene)-cyanoacetate(**1**: R=Me) reacts with the hydrazino reactant(**2**: R=H), Reaction **C**, the same result as in Reaction **B** should be obtained because the same initial intermediate(**Xb**) is involved. In practice, however, this reaction afforded, besides **7b**, two unexpected compounds, **6a** and **7a**, which were identical with those obtained previously from Reaction **A**, and a minor compound, ethyl [1-(4-ethoxycarbonylpyrazol-5-ylamino)ethylidene]cyanoacetate(**10**). Compound **10** was also obtained by the condensation of **1**(R=Me) and **3**(R=H) under similar conditions, and when refluxed in ethanolic hydrochloric acid it cyclized to the 7-hydroxy and 7-aminopyrazolopyrimidines(**11** and **12**). These results may be elucidated by the following assumptions.

In connection with the present work, it was found that some 1-acyl-5-aminopyrazoles, on fusing or upon refluxing in acetic acid, rearrange to the corresponding 5-acylaminopyrazoles.[8] Considering that the acyl group of 1-acylpyrazoles is labile and is readily transacylated by aminolysis with strong amines,[9] the rearrangement of 1-(substituted vinyl)-5-aminopyrazoles(**6**) as well as 1-acyl-5-aminopyrazoles, would seem to be based on an intermolecular aminolysis rather than a Dimroth-type intramolecular rearrangement mechanism. In the reaction system, the aminolysis of **6** may occur not only with another molecule of the same type, but also with the hydrazino reactant molecule (**2**). The fact that the isolated **6a** and **6b**, when treated with aniline under the same conditions as in the original reaction, both underwent aminolysis to give the same product, ethyl anilinomethylenecyanoacetate,[5] lends some support to the above speculation.

The present competitive reactions are shown in Scheme 2 below. In Reactions **A** and **B**, the aminolysis of **6** with the hydrazino reactant(**2**) reproduces itself *via* the intermediate (**X**) and simultaneously gives 5-aminopyrazoles(**3**), which then condense with the ethoxy reactant(**1**) to form the same compound (**7**) as that obtained by the aminolysis of **6** with another molecule of the same type. On the other hand, Reaction **C** is complicated by the presence of the different hydrazino reactants(**2**) from Reaction **B**. Thus, **6b** undergoes aminolysis with **2**(R=H) to give **6a** *via*



Scheme 2.

Xa with 5-aminopyrazole(**3**: R=Me), and the additional aminolysis of **6a** with **2**(R=H) leads to **3** (R=H), with the reproduction of **6a**. The condensation of the two resulting 5-aminopyrazoles(**3**: R=H and Me) with the ethoxy reactant(**1**: R=Me) ought to yield compounds **10** and **13** respectively, but an attempt to isolate **13** was unsuccessful. It can, therefore, be presumed that the formation of both **7a** and **7b** in Reaction **C** is based on the intermolecular aminolysis.

Experimental

All the melting points are uncorrected. The melting points of compounds **6** and **7** were determined with rapid heating because they varied with slow heating due to the ease of isomerization or cyclization. The NMR spectra were taken on a Varian HA-100 spectrometer, using TMS as the internal reference. The chemical shifts are expressed in terms of δ values(s: singlet, d: doublet, t: triplet, q: quartet). The IR spectra were recorded on a Hitachi 215 grating spectrophotometer.

*Reaction of Ethyl Ethoxymethylenecyanoacetate(**1**: R=H) with Its Hydrazino Derivative(**2**: R=H); Reaction **A**.* To a solution of 1.69 g (0.01 mol) of **1**(R=H) and 1.55 g(0.01 mol) of **2**(R=H) dissolved in ethanol at room temperature, a few drops of pyridine were added, and then the mixture was allowed to stand overnight at the same temperature. The crystals thus formed were collected and washed with ethanol to give 0.93 g(33.4%) of light yellow needles of ethyl (4-ethoxycarbonyl-5-aminopyrazol-1-yl)methylenecyanoacetate(**6a**), which were later recrystallized from acetone; mp 173—176 °C.

Found: C, 51.98; H, 5.10; N, 20.46%. Calcd for $C_{12}H_{14}O_4N_4$: C, 51.80; H, 5.04; N, 20.14%.

The mother liquor was allowed to stand until the following day at room temperature. The usual work-up of the resulting precipitate, followed by recrystallization from ethanol afforded 1.35 g(47.5%) of colorless needles of ethyl (*E*)-(4-ethoxycarbonylpyrazol-5-ylamino)methylenecyanoacetate (**7a**); mp 181.5—183 °C.

Found: C, 52.10; H, 4.98; N, 21.02%. Calcd: the same value as **6a** above.

Further, after the above filtrate had been allowed to stand for 3 days, the deposit was separated and washed with ethanol. The recrystallization of this from ethanol gave 0.24 g (8.6%) of colorless needles of ethyl (*Z*)-(4-ethoxycarbonylpyrazol-5-ylamino)methylenecyanoacetate(**7a**); mp 178—182 °C.

Found: C, 51.92; H, 4.85; N, 20.06%. Calcd: the same value as **6a** above.

The same esters, (*E*)- and (*Z*)-**7a**, were also prepared *via* a reaction between equimolecular amounts of **1**(R=H) and ethyl 5-aminopyrazole-4-carboxylate(**3**: R=Me) under the conditions described above; yields, 47.0 and 6.1% respectively.

*Reaction of the Ethoxy Reactant(**1**: R=H) with Ethyl (1-Hydrazinoethylidene)cyanoacetate(**2**: R=Me); Reaction **B**.* This reaction was carried out in the same manner as with Reaction **A**. Thus, from 1.69 g(0.01 mol) of **1**(R=H) and 1.69 g(0.01 mol) of **2**(R=Me), there was obtained the following three compounds.

Ethyl (3-methyl-4-ethoxycarbonyl-5-aminopyrazol-1-yl)-

methylenecyanoacetate(**6b**): light yellow needles; mp 184—185.5 °C from ethanol; yield, 0.35 g(12.0%).

Found: C, 53.50; H, 5.44; N, 18.92%. Calcd for $C_{13}H_{16}O_4N_4$: C, 53.40; H, 5.48; N, 19.17%.

When the reaction was conducted at a lower temperature (at about 5 °C), this ester(**6b**) was obtained as a mixture containing mostly another geometric isomer which melted at 164—165 °C. The characteristic NMR data of the other isomer are shown below; NMR($CDCl_3$): 2.41(s, Me-ring), 8.18(s, =CH), 6.05 (s, NH_2); (CD_3SOCD_3): 2.27(s, Me), 8.66(s, =CH), 7.68 (s, NH_2).

Ethyl (*E*)-(3-methyl-4-ethoxycarbonylpyrazol-5-ylamino)-methylenecyanoacetate(**7b**): colorless needles; mp 150—152 °C from ethanol; yield, 1.64 g(55.7%).

Found: C, 53.49; H, 5.37; N, 18.96%. Calcd: the same value as **6b** above.

Ethyl (*Z*)-(3-methyl-4-ethoxycarbonylpyrazol-5-ylamino)-methylenecyanoacetate(**7b**): colorless needles; mp 152—188.5 °C from ethanol; yield, 0.90 g (30.8%).

Found: C, 53.60; H, 5.48; N, 19.08%. Calcd: the same value as **6b** above.

The same esters, (*E*)- and (*Z*)-**7b**, were also obtained by the reaction of an equimolecular mixture of **1**(R=H) and ethyl 3-methyl-5-aminopyrazole-4-carboxylate(**3**: R=Me) under the conditions described above; yield, 24.0 and 31.0% respectively.

Cyclization of **6** *and* **7**. Each compound was treated under the following conditions to yield the corresponding cyclization products(**8**).

i) After the heating of each compound above 210 °C for 2 hr, the reaction mass was recrystallized from ethanol. The yields of **8** were over 80%.

ii) Each compound was refluxed in acetic acid for 3—5 hr, and then the reaction mixture was concentrated to an appropriate volume by means of a rotary evaporator. The resulting crystals were collected and washed with water. The recrystallization of the crystals from ethanol gave **8** in yields of 62—84%.

iii) A mixture of each compound(2 mmol) in ethanol (50 ml) containing a few drops of concentrated hydrochloric acid was refluxed for 4 hr. After the reaction mixture had been evaporated to dryness by means of a flash evaporator, the residue was diluted with water, and then the solution was made alkaline with sodium carbonate. The precipitate thus formed was purified by recrystallization from ethanol. The yields of **8** were 69—93%.

Diethyl 7-aminopyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate (**8a**): colorless plates; mp 243—244 °C; IR(Nujol, cm^{-1}): 3344, 3236, 3125, 1727, 1692; NMR($CDCl_3$): 8.48(s, C_2–H), 8.99(s, C_5–H), 1.42(t), 4.43(q) and 4.44(q) (2COOEt).

Found: C, 51.66; H, 5.05; N, 20.02%. Calcd for $C_{12}H_{14}O_4N_4$: C, 51.80; H, 5.04; N, 20.14%.

Diethyl 2-methyl-7-aminopyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate(**8b**): colorless needles; mp 192—194 °C; IR (Nujol, cm^{-1}): 3344, 3247, 3215, 1730, 1698; NMR($CDCl_3$): 2.64(s, C_2–H), 8.90(s, C_5–H), 1.40(t), 4.39(q) and 4.42(q) (2COOEt).

Found: C, 53.36; H, 5.47; N, 19.10%. Calcd for $C_{13}H_{16}O_4N_4$: C, 53.40; H, 5.48; N, 19.17%.

Rearrangement of **6** *to* **7**. To a solution of **6a**(1 mmol) dissolved in ethanol containing acetone at room temperature, a few drops of pyridine were added, and then the mixture was allowed to stand at the same temperature for 5 days. After the mixture had then been evaporated to dryness at 40 °C by means of a rotary evaporator, the recrystallization of the residue from ethanol gave **7a** as a mixture of the geometric isomers in a yield of 80.5%; it was identified by comparison with samples prepared as has been described in Reaction **A**.

When **6b** was treated in the same manner, (Z)-**7b**, identical with the sample described in Reaction **B**, was obtained in a yield of 67.2%.

*Reaction of Ethyl (1-Ethoxyethylidene)cyanoacetate(***1**: *R=Me) with the Hydrazino Reactant(***2**: *R=H)*; Reaction* **C**. A mixture of 1.83 g(0.01 mol) of **1**(R=Me) and 1.55 g(0.01 mol) of **2**(R=H) was dissolved in ethanol(70 ml) at room temperature, and to this a few drops of pyridine were added. After it had then been allowed to stand at room temperature for 2 days, the reaction mixture was concentrated to one-half of its volume at 40 °C by means of a rotary evaporator. The resulting precipitate was recrystallized from ethanol to give 0.32 g (11.5%) of colorless needles; mp 172—174 °C; the results of the elemental analysis and the IR spectrum of the product were identical with those of **6a**.

The mother liquor was further concentrated and allowed to stand overnight in a refrigerator. The recrystallization of the precipitate formed from ethanol gave colorless needles of 0.42 g(14.4%); mp 178—180 °C; the results of the elemental analysis and the IR spectrum of the product were identical with those of (*Z*)-**7a**.

Furthermore, the above filtrate was evaporated almost to dryness, and then allowed to stand until the following day. There was thus obtained 0.47 g (16.1%) of colorless needles which, on recrystallization from ethanol, melted at 169—180 °C and were identical with (*Z*)-**7b** previously prepared.

Finally, after it had stood in a refrigerator, the resulting viscous filtrate gave 0.05 g(1.6%) of colorless needles of ethyl [1-(4-ethoxycarbonylpyrazol-5-ylamino)ethylidene]cyanoacetate(**10**); mp 201—203 °C from ethanol; IR(Nujol, cm^{-1}): 3300(sh), 3216, 2117, 1672, 1595; NMR(CD_3SOCD_3): 2.68(s, Me), 8.41(s, H-ring), 12.40(s, NH-*exo*), 13.55(s, NH-ring), 1.27(t), 1.30(t), 4.25(q) and 4.31(q) (2COOEt).

Found: C, 53.60; H, 5.42; N, 19.01%. Calcd for $C_{13}H_{16}O_4N_4$: C, 53.40; H, 5.48; N, 19.17%.

Compound **10** was also prepared by the reaction of equimolecular amounts of **1**(R=Me) and the aminopyrazole(**3**: R=H) under the conditions described above; yield, 14.0%. Upon admixture with a sample obtained as has been described above, the melting point was not depressed.

Cyclization of **10**. A solution of **10**(3 mmol) in ethanol containing a few drops of concentrated hydrochloric acid was refluxed for 7 hr, and then the reaction mixture was concentrated to a small volume by means of a rotary evaporator. The precipitate thus formed was collected and recrystallized from ethanol to give 0.4 g(55.2%) of colorless needles of ethyl 5-methyl-6-cyano-7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylate(**11**); mp 244—246 °C; IR(Nujol, cm^{-1}): 3190, 3078, 2233, 1705, 1700, 1675, 1625; NMR(CD_3SOCD_3): 2.63(s, C_5–Me), 8.21(s, C_2–H), 1.32(t) and 4.28(q)(COOEt).

Found: C, 53.82; H, 4.21; N, 22.74%. Calcd for $C_{11}H_{10}O_3N_4$: C, 53.66; H, 4.07; N, 22.76%.

The mother liquor was further allowed to stand overnight in a regrigerator, and the precipitate thus formed was restallized from ethanol to yield 0.05 g(5.7%) of colorless needles of diethyl 5-methyl-7-aminopyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate(**12**); mp 134—136 °C; IR(Nujol, cm^{-1}): 3350, 3245, 1693, 1663, 1620, 1597; NMR(CD_3SOCD_3): 2.67(s, C_5–Me), 8.52(s, C_2–H), 8.64(s, NH), 1.31(t), 1.35(t), 4.28(q) and 4.30(q)(2COOEt).

Found: C, 53.42; H, 5.40; N, 19.12%. Calcd for $C_{13}H_{16}O_4N_4$: C, 53.40; H, 5.48; N, 19.17%.

Aminolysis of **6** *with Aniline*. A mixture of **6a**(1 mmol)

and aniline(1 mmol) was dissolved in ethanol (15 ml) containing one drop of pyridine at room temperature, and then the mixture was allowed to stand overnight at the same temperature. After the solution had been concentrated to a small volume by means of a flash evaporator and cooled in a refrigerator for 2 hr, the collection of the resulting crystals, followed by the recrystallization from ethanol, afforded 0.15 g(69.5%) of long colorless needles of ethyl anilinomethylenecyanoacetate consisting of a mixture of the geometric isomers; mp 108—113 °C.

Found: C, 66.99; H, 5.62; N, 13.08%. Calcd for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96%.

Also, a similar treatment of **6b** with aniline gave the same product as that prepared above in a yield of 73.0%. This compound was identical with the product prepared from the ethoxy reactant (**1**: R=H) and aniline.[5]

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References

1) The Formation of Pyrazolo[1,5-*a*]pyrimidine Derivatives. II. Part I: Ref. 3.

2) To whom correspondence should be addressed.

3) I. Hori, K. Saito, and H. Midorikawa, This Bulletin, **43**, 849 (1970).

4) This ester was prepared from the ethoxy reactant(**1**: R=H) and hydrazine hydrate as the geometric isomers(mp 93—94 °C and 99—100 °C); *cf.* P. Schmidt and J. Druey, *Helv. Chim. Acta*, **39**, 986 (1956), mp 89—90 °C. The present reaction using both isomers led to the same result.

5) H. Baba, I. Hori, T. Hayashi, M. Igarashi, and H. Midorikawa, unpublished data; the structure of these *N*-substituted aminomethylenecyanoacetates will be discussed in more detail in a later communication.

6) When this reaction was carried out under a lower temperature, this ester was obtained as a mixture of the geometric isomers; see experimental section.

7) The formation of the 7-amino and 7-hydroxypyrazolo-[1,5-*a*]pyrimidines by the reaction between the ethoxy reactant(**1**) and 5-aminopyrazoles has been reported; Y. Makisumi *Chem. Parm. Bull.*(Tokyo), **10**, 620(1962); Ref. 3.

8) K. Saito, I. Hori and H. Midorikawa, unpublished result; the detailed result will be reported at a later data.

9) A. N. Kost and I. I. Grandberg, "Advances in Heterocyclic Chemistry," Vol. 6, ed. by A. R. Katritzky and A. J. Boulton, Academic Press, New York, N. Y. (1966), p. 420.