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The Formation of Pyrazolo[1,5-*a*]pyrimidine Derivatives[1)]

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The combination reactions of 3-alkyl-2-cyano-3-methoxyacrylic esters (I) and their 3-hydrazino derivatives (II) in the presence of pyridine in alcohol at room temperature mostly gave chain intermediates, whose cyclizations led to the formation of only 2,7-dialkyl-5-hydroxypyrazolo-[1,5-*a*]pyrimidine derivatives. On the other hand, the reaction of Ia (3-Me) with the 5-aminopyrazole derivative (IIIa) obtained by the cyclization of IIa (3-Me) gave 7-hydroxy- and 7-aminopyrazolopyrimidine derivatives in alcohol under reflux *via* an intermediate. The reactions of 2-cyano-3-ethoxycrotononitrile with IIa or IIIa both afforded 7-aminopyrazolopyrimidine derivatives directly.

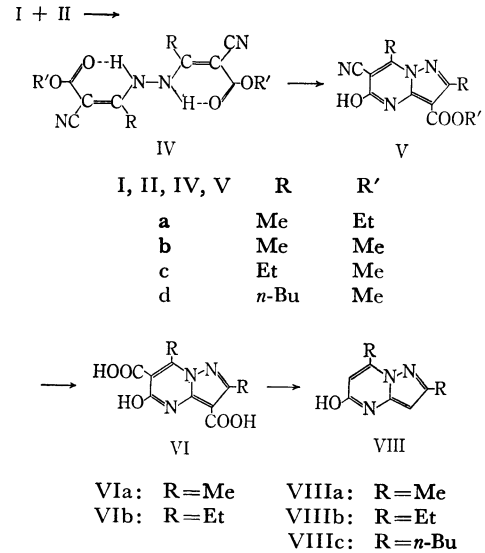
Many pyrazolo[1,5-*a*]pyrimidines, such as the 7-hydroxy and 7-amino derivatives, have, in recent years, been synthesized by the condensation of 1-ethoxyalkylidene-1,3-dicarbonyl compounds with 5-aminopyrazoles.[2-4)] The present investigation will describe mainly the formation of several 5-hydroxypyrazolo[1,5-*a*]pyrimidine derivatives by means of the condensation of 3-alkyl-2-cyano-3-methoxyacrylic esters (I) with their 3-hydrazino derivatives (II),[5)] obtained previously by the action of hydrazine on I.

The reaction of I with the corresponding 3-hydrazino compounds (II) in the presence of pyridine in ethanol at room temperature afforded first the chain intermediates, bis(2-alkoxycarbonyl-1-alkyl-2-cyanovinyl)hydrazines (IV). The symmetrical structure of IV was confirmed by a study of the NMR spectra, shown in Table 1. The intermediates (IV), upon heating in ethanol or even upon treatment in the presence of an acid or base catalyst, readily cyclized to form only 6-cyano-2,7-dialkyl-5-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylic esters (V), with the loss of one molar equivalent of alcohol; they were unchanged upon heating in acetic acid. The saponification of V(a—c) with aqueous sodium hydroxide gave the corresponding 3,6-dicarboxylic acids (VI), which were then decarboxylated by being heated above the melting point to give 2,7-dialkyl-5-hydroxypyrazolo[1,5-*a*]pyrimidines (VIII). The Vd compound on similar alkaline treatment, was converted into 6-carbamoyl-3-carboxylic acid (VII), which gave VIIIc upon further hydrolysis with diluted sulfuric acid.

Table 1. NMR spectra of bis(2-alkoxycarbonyl-1-alkyl-2-cyanovinyl)hydrazines (IV)*

Compound	R	COOR′	NH
IVa	2.31(3)	1.34(3), 4.26(2)	11.09(1)
IVb	2.31(3)	3.82(3)	11.06(1)
IVc	1.29(3), 2.14(2)	3.81(3)	11.12(1)
IVd	0.96(3), 1.20—1.30(4), 2.10(2)	3.82(3)	11.12(1)

* The chemical shifts of protons are expressed as δ value and deuteriochloroform was used as solvent. Relative peak intensities in parentheses.



1) Presented in part at the 22nd Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1969.

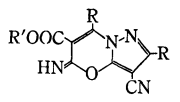
2) Y. Makisumi, *Chem. Pharm. Bull.* (Tokyo), **10**, 620 (1962).

3) A. Takamizawa and S. Hayashi, *Yakugaku Zasshi*, **83**, 313 (1963); A. Takamizawa, Y. Hamashima, S. Hayashi and R. Kido, *ibid.*, **83**, 745 (1963).

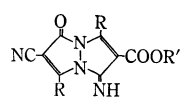
4) S. Hayashi, *ibid.*, **85**, 442 (1965).

5) H. Baba, I. Hori, T. Hayashi and H. Midorikawa, This Bulletin, **42**, 1653 (1969).

The other structures (V′ and V″) considered on the basis of the differential ring closure of IV on dealcoholation can be excluded on the basis of the following chemical evidence.

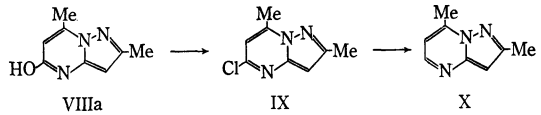


V′

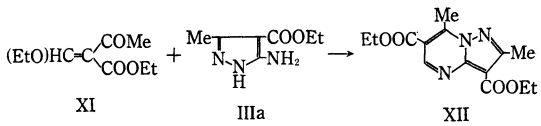


V″

The VIIIa compound was chlorinated, by the action of phosphoryl chloride, to a chloro derivative (IX), which was then catalytically reduced to 2,7-dimethylpyrazolo[1,5-*a*]pyrimidine (X). On the other hand, X could be derived from the condensate (XII) obtained by the reaction of ethyl 2-acetyl-3-ethoxyacrylate (XI) with ethyl 3-methyl-5-aminopyrazole-4-carboxylate (IIIa).



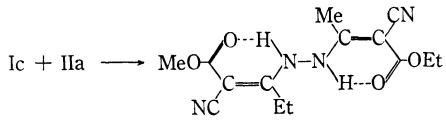
VIIIa IX X



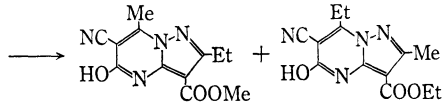
XI IIIa XII

In order to compare this process with the formation of 2,7-dialkyl-5-hydroxypyrazolo[1,5-*a*]pyrimidines described above, the condensation of ethyl 2-cyano-3-methoxycrotonate (Ia) with IIIa, the cyclized compound of IIa, was carried out in ethanol under reflux. The resulting intermediate (XIII) cyclized upon heating in ethanol containing an acid catalyst to give two products, hydroxy- (XIV) and aminopyrazolo[1,5-*a*]pyrimidine derivatives (XV). The hydrolysis and the subsequent decarboxylation of the latter product with diluted sulfuric acid led to the known 7-amino-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (XVI), prepared by a different procedure.[6] The former gave the 7-hydroxy derivative (XVII) by similar treatment. The compound XVII could also be prepared by acid hydrolysis and by the subsequent decarboxylation of the condensate (XVIII) isolated by means of the reaction of ethyl acetoacetate with IIIa. Isomeric hydroxy derivatives (VIIIa and XVII) were distinguishable from each other by means of IR and NMR spectral comparisons. From these results, it is clear that VIII and its original compound (V) are 2,7-dialkyl-5-hydroxypyrazolo-[1,5-*a*]pyrimidine derivatives.

The reaction of Ic (3-Et) with IIa gave the chain intermediate, 1-(2-cyano-2-ethoxycarbonyl-1-methylvinyl)-2-(2-cyano-1-ethyl-2-methoxycarbonylvinyl)hydrazine (XIX). In its cyclization, two kinds of dealcoholation are possible because XIX has an unsymmetrical structure. In fact, when XIX was heated in ethanol or above the melting point, two condensates, XX and XXI, were obtained as a mixture in approximately a 5 : 3 ratio and were isolated by fractional recrystallization. These two structures, XX and XXI, were confirmed to be methyl 6-cyano-2-ethyl-5-hydroxy-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate and ethyl 6-cyano-7-ethyl-5-hydroxy-2-methylpyrazolo[1,5-*a*]-pyrimidine-3-carboxylate respectively by means of the molecular formula and by NMR spectral observations.

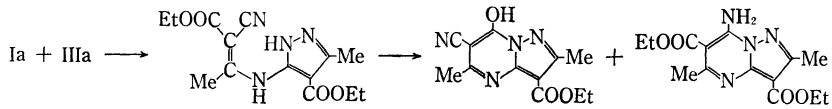


XIX

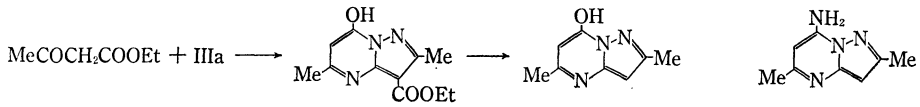


XX XXI

The reaction of Ie (3-Ph) with IIa directly formed two isomeric cyclized products, XXII and

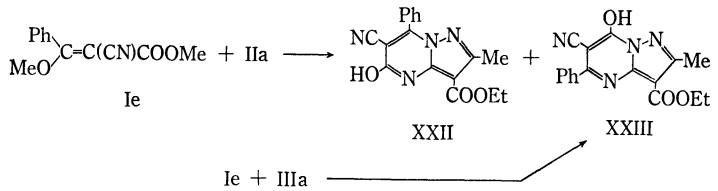


XIII XIV XV



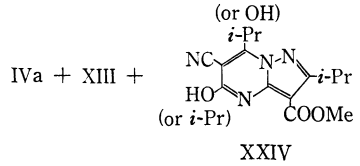
XVIII XVII XVI

6) A. Takamizawa and Y. Hamashima, Japan. 18755 (1965); *Chem. Abstr.*, **64**, 12696g (1966).

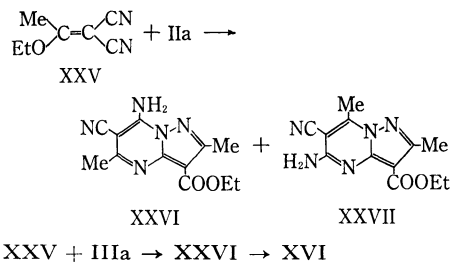


XXIII, but no intermediate could be isolated. The latter product was identical with the condensate prepared from the reaction of Ie with IIIa. Therefore, XXIII is ethyl 6-cyano-7-hydroxy-2-methyl-5-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate, and perhaps XXII is ethyl 6-cyano-5-hydroxy-2-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate.

The reaction of If (3-*i*-Pr) and IIa afforded predominantly IVa and XIII, which were identical with those obtained by the reactions involving the Ia and IIIa related to IIa, as has been described previously, and also a small quantity of methyl 6-cyano-5(or 7)-hydroxy-2,7(or 2,5)-diisopropylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (XXIV). Though the main products (IVa and XIII) were considered to be formed by the self-condensation of the reactant IIa only, the blank experiment without If did not give any product. These results suggest a certain interaction between the two reactants in this reaction, but the reaction mechanism is not clear.



On a similar condensation of 2-cyano-3-ethoxycrotononitrile (XXV) with IIa, the formation of 5-aminopyrazolo[1,5-*a*]pyrimidine derivative can be expected. However, this reaction at room temperature or even below (near 0°C) gave mostly ethyl 2,5-dimethyl-6-cyano-7-aminopyrazolo[1,5-*a*]-pyrimidine-3-carboxylate (XXVI), along with a very small amount of its isomeric substance, mp 301°C (XXVII). The structure of XXVI was proved by the following experiments. The XXVI compound was identical with the product obtained by the reaction of XXV with IIIa in ethanol under reflux, and the treatment of XXVI with diluted sulfuric acid led to the 7-amino-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (XVI). The minor product (XXVII) seems likely to be the expected 5-amino derivative.



The hydroxyl and amino groups at the 5- and 7-positions of pyrazolo[1,5-*a*]pyrimidine are capable of tautomerism to keto and imino forms respectively. Makisumi[2] has observed, in the IR spectra, that the hydroxyl groups at both positions show the keto form, while the amino group at the 7-position shows the amino form in a neutral medium. The IR data of the pyrazolo[1,5-*a*]pyrimidine derivatives obtained in the present work are presented in Table 2. From these data, it can be said that all the 5-hydroxy compounds exist in the keto form, whereas the 7-hydroxy and 7-amino derivatives exist as tautomeric mixtures in the solid state.

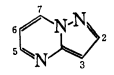
Experimental[7]

Reactions of 3-Alkyl-2-cyano-3-methoxyacrylic Esters (I) with the Corresponding 3-Hydrazino Compounds (II). To a solution of I (3 mmol) and II (3 mmol) 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 precipitate which formed was separated by filtration, washed with ethanol, and recrystallized to give bis(2-alkoxycarbonyl-1-alkyl-2-cyanovinyl)hydrazines (IV) as colorless crystals. The results are given in Table 3.

Cyclization of IV; 6-Cyano-2,7-dialkyl-5-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylic Esters (V). *a*) A mixture of IV in ethanol was refluxed; the IV soon dissolved, and then crystals began to precipitate. After refluxing for 4 hr and cooling, the crystals formed were collected by filtration, washed with methanol,

7) All the melting points are uncorrected. The IR spectra were measured with a Shimadzu 27A spectrophotometer in Nujol mulls. The NMR spectra were obtained with a Nihon-denshi JNM-C-60 high-resolution NMR spectrometer (60 MHz), using tetramethylsilane as the internal reference; the chemical shifts of the protons are presented in terms of δ values; s: singlet, bs: broad singlet, d: doublet, t: triplet, q: quartet, sep: septet, m: multiplet.

Table 2. Characteristic IR data of hydroxy- and aminopyrazolo-[1,5-*a*]pyrimidine derivatives (ν cm^{-1} in Nujol)



	5-Hydroxy compound				NH	C≡N	C(=O)OR	C=O	
	C_2	C_7	C_3	C_6					
Va	Me	Me	COOEt	CN	3135	2232	1701	1689	1631
Vb	Me	Me	COOMe	CN	3125	2232	1724	1669	1629
Vc	Et	Et	COOMe	CN	3165	2237	1736	1669	1631
Vd	*n*-Bu	*n*-Bu	COOMe	CN	3145	2242	1730	1667	1616
XX	Et	Me	COOMe	CN	3135	2227	1724	1667	1616
XXI	Me	Et	COOEt	CN	3145	2227	1727	1669	1621
XXII	Me	Ph	COOEt	CN	3155	2227	1724	1667	1621
VIIIa	Me	Me	H	H				1701	1587
VIIIb	Et	Et	H	H				1672	1590
VIIIc	*n*-Bu	*n*-Bu	H	H				1669	1587

	7-Hydroxy compound				OH and NH	C≡N	C(=O)OR	C=O	
	C_2	C_5	C_3	C_6					
XIV	Me	Me	COOEt	CN	3145 3058	2227	1695	1678	1618
XVII	Me	Me	H	H	3155 3067			1667	1623
XVIII	Me	Me	COOEt	H	3521 3236		1724	1704	1639
XXIII	Me	Ph	COOEt	CN	3289	2232	1706	1689	1626

	7-Amino compound				NH_2 and NH	C≡N	C(=O)OR		
	C_2	C_5	C_3	C_6					
XV	Me	Me	COOEt	COOEt	3367 3257		1695 1669		1616
XXVI	Me	Me	COOEt	CN	3367 3185 3135	2222	1692		1618
XVI	Me	Me	H	H	3390 3226 3115				1639

Table 3. Reactions of I with the corresponding 3-hydrazino compounds (II)

Product	Mp °C (dec)	Yield %	Recryst. solvent	Formula	Calcd, %			Found, %		
					C	H	N	C	H	N
IVa	183	60	chloroform-ethanol	$C_{14}H_{18}O_4N_4$	54.89	5.92	18.29	54.79	5.72	18.45
IVb	207	54	acetone	$C_{12}H_{14}O_4N_4$	51.79	5.07	20.14	51.77	5.26	20.32
IVc	171—172	56	chloroform-ethanol	$C_{14}H_{18}O_4N_4$	54.89	5.92	18.29	54.65	5.74	18.17
IVd	127—130	37	ethanol	$C_{18}H_{26}O_4N_4$	59.65	7.23	15.46	59.71	7.04	15.55

Table 4. Products obtained by cyclization of IV according to the method *a*)

Product	Mp, °C	Formula	Calcd, %			Found, %		
			C	H	N	C	H	N
Va	227—228	$C_{12}H_{12}O_3N_4$	55.38	4.65	21.53	55.15	4.55	21.66
Vb	261—262	$C_{11}H_{10}O_3N_4$	53.66	4.09	22.76	53.90	4.30	22.54
Vc	229—231	$C_{13}H_{14}O_3N_4$	56.93	5.15	20.43	56.67	4.85	20.44
Vd	195—196	$C_{17}H_{22}O_3N_4$	61.80	6.71	16.96	61.58	6.62	16.80

and recrystallized from chloroform-methanol to afford V as colorless needles. The yields were 80—90%. The products (V) obtained are listed in Table 4.

b) To a mixture of 0.61 g of IVa in 40 m*l* of ethanol, 0.41 g of concentrated hydrochloric acid was added, and then the mixture was refluxed for 2 hr. The resulting crystals were separated by filtration to give 0.38 g of colorless needles, mp 228°C, which did not

show any depression when the needles were mixed with the Va obtained above. The mother layer was concentrated to dryness under reduced pressure, and to the residue 15% hydrochloric acid was added. The solid precipitated was filtered and washed with water to give 0.11 g of a colorless solid, which was found to be a mixture of the starting substance (IVa) and Va by a comparison of their IR spectra. The filtrate did not give any precipitate after the solution had been made alkaline with sodium carbonate.

c) The treatment of 0.61 g of IVa with 3 m*l* of acetic acid at 100°C for 3 hr resulted in the recovery of 0.50 g (90%) of the starting substance.

Hydrolysis of V. *a*) A mixture of 0.26 g of Va in 2.5 m*l* of 20% aqueous sodium hydroxide was heated under reflux for 4.5 hr, thus producing a clear solution. After cooling, the solution was diluted with water and acidified with 15% hydrochloric acid. The precipitate formed was separated by filtration, washed with water, and recrystallized from acetone-water to afford colorless needles of 2,7-dimethyl-5-hydroxypyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylic acid (VIa), mp 243—244°C (dec); yield, 0.17 g (67%).

Found: C, 47.78; H, 3.45; N, 16.85%. Calcd for $C_{10}H_9O_5N_3$: C, 47.81; H, 3.61; N, 16.73%.

b) From 0.24 g of Vb, 0.18 g of VIa was obtained by the same procedure. Found: N, 16.78%.

c) A suspension of 0.50 g of Vc in 5 m*l* of 20% aqueous sodium hydroxide was refluxed for 5 hr. Water was then added to the reaction mixture, and it was acidified with 15% hydrochloric acid. The precipitate thus formed was collected by centrifugation and recrystallized from acetone to give 0.31 g of colorless needles of 2,7-diethyl-5-hydroxypyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylic acid (VIb), mp 207°C (dec).

Found: C, 51.32; H, 4.90; N, 15.04%. Calcd for $C_{12}H_{13}O_5N_3$: C, 51.61; H, 4.69; N, 15.05%.

d) Compound Vd (0.25 g) was treated as above (*a*) with 3 m*l* of 20% aqueous sodium hydroxide to form 0.20 g of colorless crystals of 2,7-di-*n*-butyl-6-carbamoyl-5-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (VII), mp 210°C (dec).

Found: C, 57.21; H, 6.34; N, 16.56%. Calcd for $C_{16}H_{22}O_4N_4$: C, 57.47; H, 6.63; N, 16.76%.

2,7-Dialkyl-5-hydroxypyrazolo[1,5-*a*]pyrimidine (VIII). *a*) Compound VIa (2.25 g) was heated on an oil bath at 250°C until the evolution of carbon dioxide ceased. The crude substance thus formed was treated with charcoal in methanol. After the methanol had been concentrated, the residue afforded 1.25 g of colorless needles of pure VIIIa, mp 244—245°C, by the recrystallization from acetone. NMR in CF_3COOH: 2.72 (s, C_2–Me), 2.85 (s, C_7–Me), 6.63 (overlap, C_3– and C_6–H).

Found: C, 58.72; H, 5.52; N, 25.56%. Calcd for $C_8H_9ON_3$: C, 58.88; H, 5.56; N, 25.75%.

b) At 210—215°C, 0.30 g of VIb was heated. After the evolution of carbon dioxide had ceased, this mixture was treated as above. The residue thus obtained was recrystallized from acetone to yield 0.18 g of light yellow needles of VIIIb, mp 125—125.5°C. NMR in CF_3COOH: 1.47 (t) and 3.02(q) (C_2–Et), 1.51 (t) and 3.14(q) (C_7–Et), 6.63 (overlap, C_3– and C_6–H).

Found: C, 62.62; H, 6.59; N, 21.74%. Calcd for $C_{10}H_{13}ON_3$: C, 62.80; H, 6.85; N, 21.98%.

c) A mixture of 0.20 g of VII and 3 m*l* of 50% sulfuric acid was heated under reflux for 2 hr to make it a clear solution. After cooling, water was added to the mixture, and the resulting crystals were filtered, washed with water, and dried in a desiccator. Colorless needles of VIIIc were thus obtained; mp 82—83°C; yield, 0.14 g. NMR in CF_3COOH: 1.04(t), 1.08(t), 1.35—2.05(m), 3.03(t) and 3.15(t) (C_2– and C_7-*n*-Bu), 6.60 (overlap, C_3– and C_6–H).

Found: C, 67.79; H, 8.77; N, 17.00%. Calcd for $C_{14}H_{21}ON_3$: C, 67.98; H, 8.56; N, 16.99%.

5-Chloro-2,7-dimethylpyrazolo[1,5-*a*]pyrimidine (IX). A solution of VIIIa (0.55 g) in 7 m*l* of phosphorus oxychloride was refluxed for 4 hr. After the excess phosphorus oxychloride had then been removed under reduced pressure, the residual syrup was decomposed with crushed ice. The precipitate thus obtained was collected by filtration, washed with water, and recrystallized from ethanol to form 0.50 g of fine, light yellow needles of IX, mp 100—101°C. NMR in $CHCl_3$: 2.45 (s, C_2–Me), 2.66 (s, C_7–Me), 6.30 (s, C_3–H), 6.50 (s, C_6–H).

Found: C, 52.87; H, 4.51; N, 23.13%. Calcd for $C_8H_8N_3Cl$: C, 52.90; H, 4.43; N, 23.16%.

Reduction of IX; 2,7-Dimethylpyrazolo[1,5-*a*]-pyrimidine (X). A suspension of 0.18 g of IX and 0.08 g of sodium acetate in 10 m*l* of ethanol was reduced over 0.08 g of 5% palladised charcoal, and then one equivalent mole of hydrogen was taken up. After the catalyst had been removed by filtration, the solution was concentrated to dryness under reduced pressure, and the residue was dissolved in water and extracted with chloroform. The chloroform extracts were dried over sodium sulfate, and the chloroform was removed to give a colorless oil which solidified after cooling. The recrystallization of this solid from light petroleum-benzene gave 0.12 g of hygroscopic, colorless needles of X, mp 35—36°C. NMR in $CDCl_3$: 2.53 (s, C_2–Me), 2.73 (s, C_7–Me), 6.33 (s, C_3–H), 6.46 (d, J=4.2 Hz, C_6–H), 8.17 (d, J=4.2 Hz, C_5–H).

Found: C, 64.95; H, 6.17; N, 28.13%. Calcd for $C_8H_9N_3$: C, 65.28; H, 6.16; N, 28.55%.

Reaction of Ethyl 2-Acetyl-3-ethoxyacrylate (XI) with IIIa. A mixture of 1.86 g of XI and 1.69 g of IIIa in 15 m*l* of acetic acid was heated on a steam bath for 2.5 hr. After the reaction mixture had been diluted with water, the white precipitate formed was separated by filtration and recrystallized from ethanol-water (3 : 1) to give 2.20 g of colorless needles of diethyl 2,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate (XII), mp 95—97°C. IR: 1727, 1698, 1610 cm^{-1}.

Found: C, 57.73; H, 5.54; N, 14.59%. Calcd for $C_{14}H_{17}O_4N_3$: C, 57.72; H, 5.88; N, 14.43%.

Hydrolysis of XII. A mixture of 1.00 g of XII and 5 m*l* of 50% sulfuric acid was refluxed for 5 hr. After cooling, the mixture was basified with 20% aqueous sodium hydroxide, and then the violet-brown oil thus formed was extracted with chloroform. The chloroform layer was dried over sodium sulfate and chromatographed on alumina. The benzene eluate was recrystallized from light petroleum-benzene to give 0.58 g of hygroscopic, colorless needles, mp 35—36°C, which did not show any depression when the needles were mixed with X; the IR spectrum of the product was identical with that of X.

Reaction of Ethyl 2-Cyano-3-methoxycrotonate (Ia) with IIIa. A solution of 1.10 g of Ia and 1.10 g

of IIIa in 20 ml of ethanol was heated under reflux for 5 hr and then concentrated to about 5 ml under reduced pressure. After cooling, the colorless crystals thus obtained were recrystallized twice from ethanol to give 0.80 g of colorless needles of ethyl 2-cyano-3-(4-ethoxycarbonyl-3-methyl-5-pyrazolylamino) crotonate (XIII), mp 175°C. IR: 3215, 3115, 2217, 1704, 1678 cm^{-1}.

Found: C, 54.61; H, 5.77; N, 18.39%. Calcd for $C_{14}H_{18}O_4N_4$: C, 54.89; H, 5.92; N, 18.29%.

Cyclization of XIII; XIV and XV. To a solution of 0.30 g of XIII in 60 ml of ethanol, 4 ml of concentrated hydrochloric acid was added drop by drop, and then the mixture was refluxed for 3 hr. The solution was concentrated under reduced pressure and diluted with 40 ml of water, and then the white precipitate thus formed was separated by filtration. The recrystallization of the precipitate from ethanol gave 0.15 g of colorless needles of ethyl 6-cyano-2,5-dimethyl-7-hydroxypyrazolo-[1,5-*a*]pyrimidine-3-carboxylate (XIV), mp 262—263°C. NMR in CF_3COOH: 2.80 (s, C_2–Me), 2.97 (s, C_5–Me), 1.55(t) and 4.59(q) (COOEt).

Found: C, 55.36; H, 4.36; N, 21.45%. Calcd for $C_{12}H_{12}O_3N_4$: C, 55.38; H, 4.65; N, 21.53%.

The mother layer of the reaction was made basic with aqueous sodium carbonate. The precipitate thus formed was washed with water, dried in a desiccator, and then recrystallized from ethanol-acetic acid to give 0.09 g of colorless needles of diethyl 7-amino-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine-3,6-dicarboxylate (XV), mp 175°C. NMR in CF_3COOH: 2.76 (s, C_2–Me), 3.21 (s, C_5–Me), 1.55(t), 4.60(q) and 4.65(q)(2COOEt), 8.80(bs) and 10.25(bs) (NH_2).

Found: C, 54.94; H, 5.71; N, 18.48%. Calcd for $C_{14}H_{18}O_4N_4$: C, 54.89; H, 5.92; N, 18.29%.

Hydrolysis of XIV; 2,5-Dimethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine (XVII). A mixture of 0.50 g of XIV and 10 ml of 50% sulfuric acid was heated under reflux for 3 hr; then, after cooling, the pH of the reaction mixture was adjusted with ammonium hydroxide to about 5. The precipitate thus formed was separated by filtration, washed with water, and recrystallized from ethanol to give 0.32 g of colorless needles of XVII, mp 250—251°C. NMR in CF_3COOH: 2.65 (s, C_2–Me), 2.74 (s, C_5–Me), 6.34 (s, C_3–H), 6.61 (s, C_6–H).

Found: C, 58.97; H, 5.49; N, 25.52%. Calcd for $C_8H_9ON_3$: C, 58.88; H, 5.56; N, 25.75%.

Reaction of Ethyl Acetoacetate with IIIa. A mixture of 0.60 g of ethyl acetoacetate and 0.80 g of IIIa in 1.5 ml of acetic acid was refluxed for 2.5 hr. After the mixture had then been diluted with water, the precipitate thus obtained was collected by filtration, washed with water, and dried in a desiccator. The recrystallization of the precipitate from ethanol and benzene afforded 0.75 g of colorless needles of ethyl 2,5-dimethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylate (XVIII), mp 150—151°C. NMR in CF_3COOH: 2.75 (s, C_2–Me), 2.95 (s, C_5–Me), 6.43 (s, C_6–H), 1.55(t) and 4.63(q) (COOEt).

Found: C, 55.91; H, 5.47; N, 17.91%. Calcd for $C_{11}H_{13}O_3N_3$: C, 56.16; H, 5.57; N, 17.86%.

Hydrolysis of XVIII. A mixture of 0.50 g of XVIII and 10 ml of 50% sulfuric acid was heated under reflux for 2.5 hr. After cooling, the mixture was treated with ammonium hydroxide to adjust its pH to about 5. The precipitate thus formed was washed with water and then recrystallized from ethanol to give 0.38 g of colorless needles, mp 250—251°C, which did not show any depression when the needles were mixed with the XVII obtained above; the IR and NMR spectra of the product were identical with those of XVII.

Hydrolysis of XV; 7-Amino-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (XVI). A mixture of 0.50 g of XV and 10 ml of 50% sulfuric acid was refluxed for 3.5 hr; then, after cooling, the mixture was diluted with 10 ml of water and basified with ammonium hydroxide to give a white precipitate. The recrystallization of the precipitate from ethyl acetate afforded 0.33 g of colorless needles, mp 198—200°C, which did not show any depression on admixture with an authentic sample of 7-amino-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (XVI).[6] NMR in CF_3COOH: 2.64 (s, C_2–Me), 2.69 (s, C_5–Me), 6.47 (overlap, C_3– and C_6–H), 8.30 (bs, NH_2).

Reaction of Methyl 2-Cyano-3-ethyl-3-methoxyacrylate (Ic) with IIa. Into a solution of 1.32 g of Ic and 1.32 g of IIa dissolved in ethanol at room temperature, a few drops of pyridine were added. After the solution had then been allowed to stand overnight at room temperature, the white precipitate thus formed was collected by filtration and washed with ethanol. The recrystallization of this from chloroform-ethanol (1 : 2) gave 1.36 g of colorless needles of 1-(2-cyano-2-ethoxycarbonyl-1-methylvinyl)-2-(2-cyano-1-ethyl-2-methoxycarbonylvinyl)hydrazine (XIX), mp 165°C (dec). IR: 3165, 2217, 1689, 1672, 1587 cm^{-1}. NMR in $CDCl_3$: 2.33 (s, vinyl Me), 1.28(t) and 2.64(q) (vinyl Et), 3.82 (s, COOMe), 1.34(t) and 4.25(q) (COOEt), 10.95 (s, NH), 11.07 (s, NH).

Found: C, 54.60; H, 5.87; N, 18.39%. Calcd for $C_{14}H_{18}O_4N_4$: C, 54.89; H, 5.92; N, 18.29%.

Cyclization of XIX; XX and XXI. A mixture of 0.55 g of XIX in 40 ml of ethanol was heated under reflux; soon the XIX completely dissolved, and then a white precipitate was separated out. The whole mixture was refluxed for 3 hr. After cooling, the precipitate formed was collected by filtration. The treatment of this with fresh boiling ethanol gave 0.16 g of insoluble methyl 6-cyano-2-ethyl-5-hydroxy-7-methylpyrazolo-[1,5-*a*]pyrimidine-3-carboxylate (XX) in hot ethanol as colorless prisms, mp 258—260°C. NMR in CF_3COOH: 1.40(t) and 3.16(q) (C_2–Et), 3.09 (s, C_7–Me), 4.15 (s, COOMe).

Found: C, 55.21; H, 4.68; N, 21.54%. Calcd for $C_{12}H_{12}O_3N_4$: C, 55.38; H, 4.65; N, 21.53%.

The mother layer of the boiling-ethanol treatment was concentrated to give colorless crystals, the recrystallization of which from dioxane afforded 0.21 g of colorless needles of ethyl 6-cyano-7-ethyl-5-hydroxy-2-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (XXI), mp 209—210°C. NMR in CF_3COOH: 2.73 (s, C_2–Me), 1.52(t) and 3.45(q) (C_7–Et), 1.56(t) and 4.62(q) (COOEt).

Found: C, 56.70; H, 5.01; N, 20.17%. Calcd for $C_{13}H_{14}O_3N_4$: C, 56.93; H, 5.15; N, 20.43%.

Reaction of Methyl 2-Cyano-3-methoxycinnamate (Ie) with IIa. Compound Ie (1.08 g) and 0.84 g of IIa were dissolved in 35 ml of ethanol by slightly warming the solution, and to this a few drops of pyridine were added; then the mixture was allowed to stand at room temperature for 4 days. The resulting white precipitate was separated by filtration, washed with ethanol, and recrystallized from ethanol to give 0.38 g of

colorless needles of ethyl 6-cyano-5-hydroxy-2-methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (XXII), mp 227—228°C. NMR in CF_3COOH: 2.67 (s, C_2–Me), 7.47 (m, C_7–Ph), 1.53(t) and 4.66(q) (COOEt).

Found: C, 63.27; H, 4.11; N, 17.77%. Calcd for $C_{17}H_{14}O_3N_4$: C, 63.35; H, 4.38; N, 17.38%.

The mother layer of the reaction was concentrated to a small volume under reduced pressure. After the residue had been stored in an ice-box, the precipitate was separated out and washed with ethanol. The recrystallization of this from ethanol gave 0.60 g of the hydrate of ethyl 6-cyano-7-hydroxy-2-methyl-5-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (XXIII) as colorless plates, mp 144—146°C.

Found: C, 61.16; H, 4.29; N, 16.95%. Calcd for $C_{17}H_{14}O_3N_4 \cdot 1/2H_2O$: C, 61.62; H, 4.56; N, 16.91%.

The water of crystallization could be driven off by heating at 110°C in reduced pressure; XXIII was thus obtained as colorless crystals, mp 190—191°C. NMR in CF_3COOH: 2.90 (s, C_2–Me), 7.80 (m, C_5–Ph), 1.63(t) and 4.67(q)(COOEt).

Found: C, 63.46; H, 4.37; N, 17.58%. Calcd for $C_{17}H_{14}O_3N_4$: C, 63.35; H, 4.38; N, 17.38%.

Reaction of Ie with IIIa. A mixture of 0.54 g of Ie and 0.42 g of IIIa in 5 m*l* of ethanol was heated under reflux for 2 hr. The ethanol was removed under reduced pressure, and the residue was washed with ethanol and recrystallized twice from dioxane-water to give 0.58 g of colorless needles, mp 144—145°C. The heating of the needles at 110°C under reduced pressure afforded colorless crystals, mp 190—191°C, which did not show any depression when the crystals were mixed with the XXIII obtained above; the IR and NMR spectra of the product were identical with those of XXIII.

Reaction of Methyl 2-Cyano-3-isopropyl-3-methoxyacrylate (If) with IIa. To a solution of 2.75 g of If and 2.54 g of IIa in 40 m*l* of ethanol, a few drops of pyridine were added, and then the solution was allowed to stand at room temperature overnight. The precipitate thus formed was collected by filtration, and washed with ethanol; the recrystallization of this from chloroform-ethanol gave 1.25 g of colorless needles, mp 183°C (dec), which were proved to be identical with the IVa obtained from the reaction of Ia and IIa by a mixed-melting-point measurement and by an IR spectral comparison. The second crop was 0.05 g. The mother layer of the reaction was evaporated under reduced pressure, and the residue was dissolved in water and acidified with 15% hydrochloric acid. The precipitate thus formed was collected and recrystallized from ethanol to give 0.32 g of colorless crystals, mp 175°C. This was found to be identical with XIII obtained from the reaction of Ia with IIIa by a mixed-melting-point measurement and by an IR spectral comparison.

The filtrate of the acidic solution contained an oily substance which solidified after having been stored in an ice-box. The solid thus separated was washed with water, dried in a desiccator, and recrystallized from ethanol to give 0.43 g of colorless needles of methyl 6-cyano-5 (or 7)-hydroxy-2,7-(or 2,5)-diisopropylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (XXIV), mp 164—165°C. IR: 3279, 2212, 1724, 1695, 1610 cm^{-1}. NMR in $CDCl_3$: 1.41(t), 1.43(t) and 3.49(sep) (2 *i*-Pr), 3.45 (s, COOMe).

Found: C, 59.74; H, 5.69; N, 18.85%. Calcd for $C_{15}H_{18}O_3N_4$: C, 59.59; H, 6.00; N, 18.53%.

Blank Experiment without If in the Above Reaction. To a solution of 0.63 g of IIa in 10 m*l* of ethanol, a few drops of pyridine were added; the solution did not give any precipitate after having been allowed to stand at room temperature for 10 days. The evaporation of the solution resulted in the recovery of the starting substance.

Reaction of 2-Cyano-3-ethoxycrotononitrile (XXV) with IIa. *a*) To a solution of XXV (0.68 g) and 0.84 g of IIa dissolved in 25 m*l* of methanol at room temperature, a few drops of pyridine were added, and then the mixture was allowed to stand at the same temperature for 3 days. The precipitate thus formed was collected by filtration and recrystallized from acetone to afford 0.09 g of light brown plates of, probably, ethyl 5-amino-6-cyano-2,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (XXVII), mp 301°C (dec). IR: 3448, 3247, 3145, 2227, 1698, 1642, 1610 cm^{-1}. NMR in CF_3COOH: 2.73 (s, C_2–Me), 3.18 (s, C_7–Me), 1.55(t) and 4.60(q) (COOEt), 8.25 (bs, NH_2).

Found: C, 55.33; H, 4.89; N, 26.71%. Calcd for $C_{12}H_{13}O_2N_5$: C, 55.59; H, 5.05; N, 27.02%.

The mother layer of the reaction was evaporated under reduced pressure, and the residue thus obtained was recrystallized twice from ethanol-water to give 1.03 g of fine, colorless needles of ethyl 7-amino-6-cyano-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (XXVI), mp 281—282°C. NMR in CF_3COOH: 2.80 (s, C_2–Me), 3.15 (s, C_5–Me), 1.58(t) and 4.66(q) (COOEt), 9.05 (bs, NH_2).

Found: C, 55.70; H, 5.03; N, 26.94%. Calcd for $C_{12}H_{13}O_2N_5$: C, 55.59; H, 5.05; N, 27.02%.

b) When the above reaction was carried out near 0°C, the same results as in *a*) were obtained.

Reaction of XXV with IIIa. A mixture of 0.68 g of XXV and 0.84 g of IIIa in 20 m*l* of ethanol was heated under reflux for 7 hr. After cooling, the precipitate thus obtained was collected by filtration, washed with ethanol, and recrystallized twice from ethanol-water to form 1.17 g of colorless needles, mp 282—283°C, which were proved to be identical with the foregoing XXVI by a mixed-melting-point determination and by IR and NMR spectral comparisons.

Found: C, 55.64; H, 5.01; N, 27.08%.

Hydrolysis of XXVI. Compound XXVI (0.50 g) was dissolved in 10 m*l* of 50% sulfuric acid, and then the mixture was refluxed for 4 hr. After cooling, the reaction mixture was diluted with water and basified with ammonium hydroxide. The precipitate thus formed was collected, washed with water, and dried in a desiccator. The recrystallization of this from ethyl acetate gave 0.35 g of colorless needles, mp 199—201°C, which did not show any depression on admixture with the XVI obtained from the hydrolysis of XV.