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Reactions of α-Cyano-β-methoxy-β-alkylacrylic Esters with Hydrazine and Hydroxylamine

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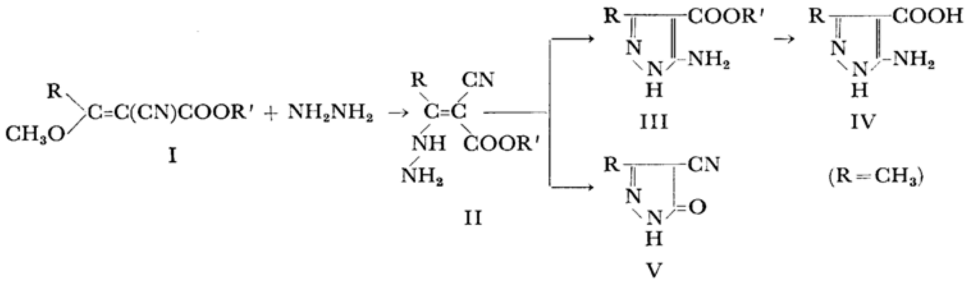
α-Cyano-β-methoxy-β-alkyl (Me, Et, *n*-Pr, *n*-Bu, *n*-Am, and *i*-Bu)-acrylic esters (I) react with hydrazine to give β-hydrazino intermediates. The hydrazino group of these intermediates is cyclized preferentially between its terminal NH_2 and the cyano group in a neutral or acidic medium to give 5-aminopyrazole derivatives, and preferentially between the terminal NH_2 and the ester group in the presence of a base to give 5-pyrazolone derivatives. When the β-alkyl of I is isopropyl, *t*-butyl, *etc.*, I affords only the 5-pyrazolone derivatives in the reaction with hydrazine. The reactions of I with hydroxylamine gave 5-aminoisoxazole derivatives, but in the case of the β-*t*-butyl derivative of I they gave 5-aminoisoxazole accompanied by the 5-isoxazolone derivative.

It has recently been found that the alkoxyl group of α-cyano-β-methoxycrotonic esters is easily displaced with such simple amines as ammonia, alkylamine, and benzylamine to give α-cyano-β-aminocrotonic esters, which exist in the enamine form, with an intramolecular hydrogen-bond between the amino and the ester carbonyl group.[1]

The reaction has now been extended to use with hydrazine and hydroxylamine as the amine in view of the formation of two possible cyclized compounds, as is illustrated in Charts 1 and 2.

Both geometric isomers of methyl α-cyano-β-methoxycrotonate (Ia) reacted rapidly with one mole of hydrazine hydrate in water at room temperature to form the same methyl α-cyano-β-hydrazinocrotonate (IIa) in a 90% yield. Similarly, from Ib—g the corresponding intermediates (IIb—g) were obtained.

The cyclization of II took place preferentially



I, II, III	R	R′
a	Me	Me
b	Me	Et
c	Et	Me
d	*n*-Pr	Me
e	*n*-Bu	Me
f	*n*-Am	Me
g	*i*-Bu	Me

V	R
a	Me
b	Et
c	*n*-Pr
d	*n*-Bu
e	*n*-Am
f	*i*-Bu
g	*i*-Pr
h	*t*-Bu
i	Ph

Chart 1

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[1] T. Hayashi, I. Hori, H. Baba and H. Midorikawa, This Bulletin, **40**, 2160 (1967).

between the hydrazino and the cyano group to afford only the corresponding 3-alkyl-4-alkoxycarbonyl-5-aminopyrazole (III) in a neutral or acidic medium. That is, II cyclized to III slowly when left standing at room temperature for prolonged periods, when heated over the melting point, when refluxed in ethanol-water (4:1), or immediately after being dissolved in 15% hydrochloric acid. However, in the presence of a base such as hydrazine, ammonia or potassium carbonate, II cyclized preferentially between the hydrazino and the ester group to give only the corresponding 3-alkyl-4-cyano-5-pyrazolone (Va—f), while II was recovered in abundance.

V was also isolated along with a large amount of II when I was reacted with an excess of hydrazine. That this reaction perhaps proceeds through II can be seen by the experimental results shown in Table 1. Namely, the variations in the amounts of IIb and Va with the variety of the reaction time in Reactions (1) and (2) were approximately equal. Furthermore, this result indicetes that the cyclization of II to V is significantly slower than the formation of II from I.

TABLE 1. THE RESULTS OF THE REACTIONS OF Ib OR IIb WITH HYDRAZINE BY VARING THE REACTION TIME

$$\left.\begin{array}{ll}(1) & \text{Ib} + 2\,\text{NH}_2\text{NH}_2 \\ (2) & \text{IIb} + \text{NH}_2\text{NH}_2\end{array}\right] \rightarrow \text{IIb} + \text{Va}$$

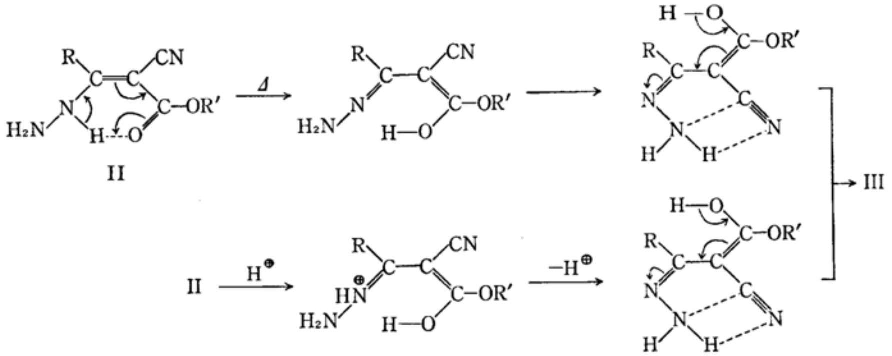
Reaction time hr	Yield in (1), %		Yield in (2), %	
	IIb	Va	IIb	Va
0.25	87	2	90	trace
1	79	9.7	78	8.3
2	72	13.9	73	12.5
5	50	26.4	56	26.4

The infrared spectra of II exhibited an intense cyano band due to conjugation with an unsaturated bond in the 2198—2210 cm^{-1} region similar to that of β-aminoacrylonitriles.2) The NMR spectra of II and ethyl α-cyano-β-(2,2-dimethylhydrazino)-crotonate (VI) prepared from Ib and 1,1-dimethylhydrazine indicated broad signals in the highly deshielded region (10.63—10.79 ppm). These signals were assigned to the NH proton hydrogen-bonded with the ester carbonyl group, much as with the simple β-amino derivatives described in a previous report.1) Therefore, these spectral observations reveal that II has a hydrazino-ethylene structure rather than a tautomeric hydrazone structure; moreover, there is a *cis*-relation between the hydrazino and the ester group. Consequently, the following courses (Schema 1—3) for the cyclizations of II to III and V are possible.

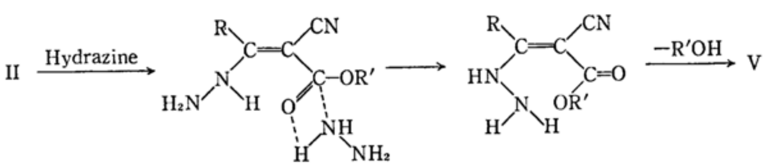
On the other hand, I with a bulky β-alkyl group such as isopropyl or *t*-butyl, or with a β-aryl group instead of β-alkyl, on a similar reaction with one mole of hydrazine hydrate, gave merely the corresponding 3-alkyl(aryl)-4-cyano-5-pyrazolone (Vg—i) as the cyclized product, plus a fairly large amount of the unchanged material (I); no open-chain intermediate was isolated. In order to obtain a high yield of V, an excessive use of hydrazine was necessary because hydrazine was consumed to form its salt of the acidic V. For example, one hour's treatment of I (R=*i*-Pr, R'=Me) with one mole of hydrazine gave 41.4% of the pyrazolone (Vg), whereas a similar treatment with two moles of hydrazine gave almost a two-fold yield. In these reactions, the formation of Vg—i was distinctly faster than that of Va from Ib or IIb, as is shown in Table

Scheme 1

Scheme 2



Scheme 3



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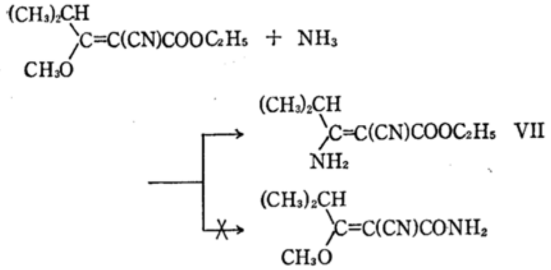
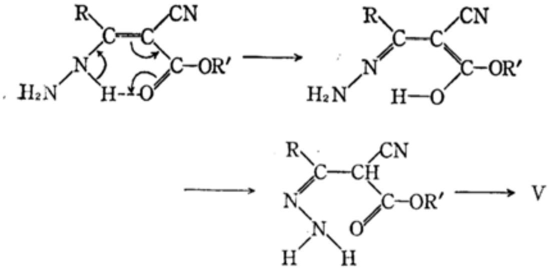
2) F. Scotti and E. J. Frazza, *J. Org. Chem.*, **29**, 1800 (1964).

1, although this primary nucleophilic attack by hydrazine on the β-carbon atom was expected to be probably more restricted by the steric hindrance than that in the case of I (R=*n*-alkyl and *i*-Bu).

It is evident that no hydrazine attaches to the ester group of I to form the acid hydrazide, for the reaction of I (R=*i*-Pr, R′=Et) with ammonia gave only the normal enamine (VII) instead of the acid amide expected.



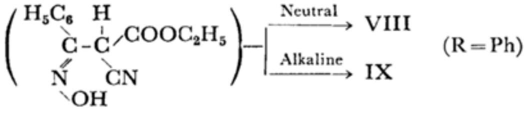
For the intermediate (II) in the formation of Vg—i, a strong steric compression is expected between the bulky β-alkyl (or aryl) and the hydrazino group on the β-carbon atom. Presumably the bulky alkyl groups push against the ester guoup to strengthen the hydrogen-bonding between the hydrazino and the ester group and follow the cyclization between them, as is illustrated below:



(R=*i*-Pr, *t*-Bu, Ph)

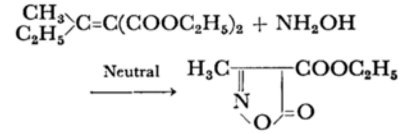
On the other hand, under conditions similar to those in the reaction with hydrazine, the starting materials (I, except for R=*t*-Bu) and hydroxylamine reacted readily to give only the 3-alkyl(aryl)-4-alkoxycarbonyl-5-aminoisoxazoles (VIII) in better yields. I (R=*t*-Bu) afforded approximately equivalent amounts of 5-aminoisoxazole (VIIIi) and 3-*t*-butyl-4-cyano-5-isoxazolone (IX) in poor total yields. However, in all cases, no open-chain intermediate was isolated.

Dornow and Teckenburg[3] have reported that I (R=Ph, R′=Et) reacted with hydroxylamine to form the 5-aminoisoxazole (VIIIj) in a neutral medium and the 5-isoxazolone (IX, R=Ph) in an alkaline medium, presumably by means of the cyclization of the intermediate α-cyano-β-oximino ester (X).



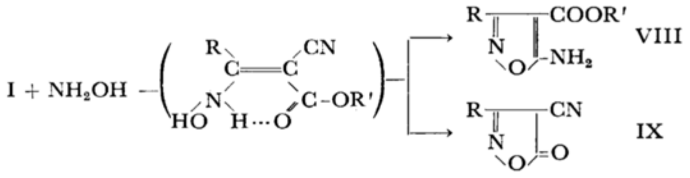
X

However, the similar reaction of diethyl 1-ethoxyethylidenemalonate with hydroxylamine in a neutral medium easily gave the cyclized product, 3-methyl-4-ethoxycarbonyl-5-isoxazolone (XI), no intermediate being isolated. Therefore, if the reaction



XI

reported proceeds *via* the β-oximino ester (X), the VIII yielded in the neutral medium will be contaminated by the IX cyclized on the ester group. Furthermore, ethyl α-cyano-β-methoxyaminocrotonate (XII), which can not be cyclized, was prepared from the reaction of Ib with *O*-methylhydroxylamine. The broad NH signal in the highly deshielded region (11.64 ppm) observed



VIII	R	R′
a	Me	Me
b	Me	Et
c	Et	Me
d	*n*-Pr	Me
e	*n*-Bu	Me

VIII	R	R′
f	*n*-Am	Me
g	*i*-Bu	Me
h	*i*-Pr	Me
i	*t*-Bu	Me
j	Ph	Et

Chart 2

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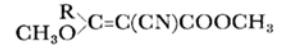
[3] A. Dornow and H. Teckenburg, *Chem. Ber.*, **93**, 1103 (1960).

TABLE 2. METHYL ACYLCYANOACETATE R-CO-CH(CN)COOCH$_3$

R	Bp, °C 10 mmHg	Yield %	Formula	Calcd, %			Found, %		
				C	H	N	C	H	N
n-Pr	111—113[a)]	30.1	$C_8H_{11}O_3N$	56.79	6.55	8.28	56.75	6.58	8.82
n-Bu	123—124	24.5	$C_9H_{13}O_3N$	59.00	7.15	7.65	58.98	6.58	7.72
n-Am	128—130	27.4	$C_{10}H_{15}O_3N$	60.89	7.67	7.10	60.51	7.88	7.22
i-Bu	118—120	26.3	$C_9H_{13}O_3N$	59.00	7.15	7.65	58.78	6.95	7.73

a) Lit, mp 135.3°C/25 mmHg, J. Guinchant, *Compt. Rend.*, **121**, 72 (1895).

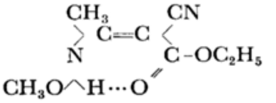
TABLE 3. METHYL α-CYANO-β-METHOXY-β-ALKYLACRYLATE



$$\overset{R}{\underset{CH_3O}{>}}C{=}C(CN)COOCH_3$$

R	Bp, °C 10 mmHg	Yield %	Formula	Calcd, %			Found, %		
				C	H	N	C	H	N
Id *n*-Pr	151—152	51.8	$C_9H_{13}O_3N$	59.00	7.15	7.65	58.69	7.47	7.52
Ie *n*-Bu	171—172	66.0	$C_{10}H_{15}O_3N$	60.89	7.67	7.10	60.88	7.55	6.97
If *n*-Am	160—162	32.7	$C_{11}H_{17}O_3N$	62.54	8.11	6.63	62.40	7.96	6.31
Ig *i*-Bu	151—152	29.5	$C_{10}H_{15}O_3N$	60.89	7.67	7.10	60.82	7.32	7.17

in its NMR spectrum showed that it has the structure of the enamine with hydrogen-bonding:



XII

From these observations, it seems likely that the formations of VIII and IX proceed *via* the β-hydroxyamino analog (II') of II and follow the mode of the cyclization represented in Schema 1 and 3 respectively.

Experimental[4)]

Materials. Methyl α-cyano-β-methoxy-β-alkylacrylates (Id—g, Table 3) were synthesized, by the use of a method described in a previous paper[5)], from the corresponding acylcyanoacetic esters (Table 2), which had themselves been prepared from a modification of the Hori and Midorikawa method[6)] using acid chloride instead of acid anhydride.

The Reaction of Ia—g with Hydrazine (The Formation of II). To a solution of 80% hydrazine hydrate (5 mmol) in water (4 m*l*), there was added I (5 mmol) all at once; the mixture was then stirred at room temperature for 15—30 min. The resulting precipitate was collected by filtration, washed with a small quantity of ice water, and recrystallized from methanol (IIa and IIb), ethanol (IIe and IIg), or benzene (IIc, IId, and IIf).

In the reaction of both Ia and Ic, two geometric isomers[5)] were used as the starting material, but both the isomers gave the same product (IIa and IIc, respectively) in approximately equal yields. Therefore, only a stable isomer or an equilibrium mixture was used as the starting material (I) in all the reactions to be described below.

Methyl α-cyano-β-hydrazinocrotonate (IIa): colorless needles, mp 133—134°C, yield 90% from either of the geometric isomers. IR (νcm^{-1}): 2198 (νC≡N), 1667 (νC=O). NMR: 10.68 (NH).

Found: C, 46.75; H, 5.57; N, 26.84%. Calcd for $C_6H_9O_2N_3$: C, 46.44; H, 5.58; N, 27.08%.

Ethyl α-cyano-β-hydrazinocrotonate (IIb): colorless plates, mp 116—117°C, yield 90.5%. IR (cm^{-1}): 2201 (νC≡N), 1664 (νC=O). NMR: 10.73 (NH).

Found: C, 50.09; H, 6.44; N, 24.54%. Calcd for $C_7H_{11}O_2N_3$: C, 49.69; H, 6.55; N, 24.84%.

Methyl α-cyano-β-hydrazino-β-ethylacrylate (IIc): colorless needles, mp 100—101°C, yields 86% from a stable isomer, and 85% from a labile isomer. IR (cm^{-1}): 2208 (νC≡N), 1664 (νC=O). NMR: 10.63(NH).

Found: C, 49.49; H, 6.68; N, 24.49%. Calcd for $C_7H_{11}O_2N_3$: C, 49.69; H, 6.55; N, 24.84%.

Methyl α-cyano-β-hydrazino-β-*n*-propylacrylate (IId)-colorless needles, mp 114.5—115.5°C, yield 83%. IR (cm^{-1}): 2198 (νC≡N), 1667 (νC=O). NMR: 10.70(NH).

Found: C, 52.74; H, 7.15; N, 22.85%. Calcd for $C_8H_{13}O_2N_3$: C, 52.44; H, 7.15; N, 22.94%.

Methyl α-cyano-β-hydrazino-β-*n*-butylacrylate (IIe): colorless prisms, mp 109—110°C, yield 90%. IR (cm^{-1}): 2208(νC≡N), 1664 (νC=O). NMR: 10.68 (NH).

Found: C, 54.97; H, 7.43; N, 21.49%. Calcd for $C_9H_{15}O_2N_3$: C, 54.80; H, 7.67; N, 21.31%.

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4) All melting points and boiling points were uncorrected. The infrared absorption spectra were measured with a Shimadzu Model IR-27A infrared spectrophotometer in Nujol solid state. The NMR spectra were recorded with a JNM-C-60 high-resolution NMR spectrometer operating at 60 Mc. The chemical shift values for imino group of IIa—g, VI and XII were reported in ppm downfield from tetramethylsilane as an internal standard, in deuteriochloroform (carbon tetrachloride for VI) as solvent.

5) T. Hayashi, I. Hori, H. Baba and H. Midorikawa, *J. Org. Chem.*, **30**, 695 (1965).

6) I. Hori and H. Midorikawa, *Sci. Papers Inst. Phys. Chem. Res. (Tokyo)*, **56**, 216 (1962).

Methyl α-cyano-β-hydrazino-β-*n*-amylacrylate (IIf): colorless plates, mp 117—118°C, yield 85.3%. IR (cm^{-1}): 2208 (νC≡N), 1664 (νC=O). NMR: 10.74 (NH).

Found: C, 57.15; H, 7.19; N, 19.85%. Calcd for $C_{10}H_{17}O_2N_3$: C, 56.85; H, 8.11; N, 19.89%.

Methyl α-cyano-β-hydrazino-β-isobutylacrylate (IIg): colorless needles, mp 97—98°C, yield 86.8%. IR (cm^{-1}): 2210 (νC≡N), 1667 (νC=O). NMR: 10.79 (NH).

Found: C, 55.13; H, 7.59; N, 21.63%. Calcd for $C_9H_{15}O_2N_3$: C, 54.80; H, 7.67; N, 21.31%.

The Formation of 3-Alkyl-4-alkoxycarbonyl-5-aminopyrazoles (III) from II. (i) The foregoing β-hydrazino compound (IIa, IIb, or IIc) was heated to 130—140°C for 3 hr. After cooling, the resinous product was triturated in ether to give a precipitate. Recrystallization from benzene afforded IIIa and IIIb in yields of over 80%.

(ii) A mixture of II (6 mmol) and ethanol (4 m*l*) containing water (1 m*l*) was refluxed for 4—8 hr on a steam bath. The resulting clear solution was evaporated under reduced pressure. The resinous residue was cooled in an ice-box for 2—3 days; the crystallization was induced by scratching the inside wall of the vessel with a glass rod. It was purified by recrystallization from benzene to obtain III in yields of 75—90%.

(iii) To a suspended mixture of 2 mmol of the β-hydrazino compound (IIa, IIb, or IIc) in water (4 m*l*) there was added 15% hydrochloric acid (2 m*l*); the mixture was then warmed on a steam bath until it became a clear solution. After cooling to room temperature, the mixture was neutralized with an aqueous potassium carbonate solution. The crystalline substance thus formed was recrystallized from benzene, affording III in yields over 75.5%.

The same product (IIIa, IIIb, or IIIc) was obtained from all three reactions. For the formation of IIId—g only the method (ii) was used; IIId was obtained as a hydrate. Also, IIIg afforded a benzene-addition product (determined by a study of the IR and the NMR spectra). The benzene-free product of IIIg was obtained by triturating it with ether instead of by recrystallization from benzene. IIIb and IIIc easily took the water of crystallization when they were allowed to stand in moist air or were recrystallized from water. These crystal waters (IIIb, IIIc, and the forgoing IIId) were driven off by heating the substances under reduced pressure or by leaving them standing in a desiccator ($CaCl_2$).

3-Methyl-4-methoxycarbonyl-5-aminopyrazole (IIIa): colorless microcrystals, mp 145—146.5°C.

Found: C, 46.83; H, 5.43; N, 27.36%. Calcd for $C_6H_9O_2N_3$: C, 46.44; H, 5.85; N, 27.08%.

3-Methyl-4-ethoxycarbonyl-5-aminopyrazole (IIIb): colorless prisms, mp 109—110°C (lit[7] 113°C).

Found: C, 49.83; H, 6.48; N, 25.07%. Calcd for $C_7H_{11}O_2N_3$: C, 49.69; H, 6.55; N, 24.84%.

Hydrate: colorless needles (from water), mp 66—67°C (lit[7] 69°C).

Found: C, 44.77; H, 7.01; N, 22.63%. Calcd for $C_7H_{11}O_2N_3\cdot H_2O$: C, 44.91; H, 7.00; N, 22.45%.

3-Ethyl-4-methoxycarbonyl-5-aminopyrazole (IIIc): colorless needles, mp 102—103°C.

Found: C, 49.94; H, 6.37; N, 24.34%. Calcd for $C_7H_{11}O_2N_3$: C, 49.69; H, 6.55; N, 24.84%.

Hydrate: colorless needles (from water), mp 81—82°C.

Found: C, 47.24; H, 6.64; N, 23.38%. Calcd for $C_7H_{11}O_2N_3\cdot\frac{1}{2}H_2O$: C, 47.18; H, 6.79; N, 23.58%.

3-*n*-Propyl-4-methoxycarbonyl-5-aminopyrazole(IIId): colorless prisms, mp 80—81°C

Found: C, 52.70; H, 6.80; N, 23.61%. Calcd for $C_8H_{13}O_2N_3$: C, 52.44; H, 7.15; N, 22.94%.

Hydrate: colorless needles (from water) or colorless prisms (from benzene), mp 70—71°C.

Found: C, 50.22; H, 7.12; N, 22. 20%. Calcd for $C_8H_{13}O_2N_3\cdot\frac{1}{2}H_2O$: C, 49.99; H, 7.34; N, 21.86%.

3-*n*-Butyl-4-methoxycarbonyl-5-aminopyrazole(IIIe): colorless capillaries, mp 72—73°C.

Found: C, 54.88; H, 7.59; N, 21. 71%. Calcd for $C_9H_{15}O_2N_3$: C, 54.80; H, 7.67; N, 21.31%.

3-*n*-Amyl-4-methoxycarbonyl-5-amipopyrazole(IIIf): colorless capillaries, mp 73—74°C.

Found: C, 56.58; H, 7.84; N, 19.88%. Calcd for $C_{10}H_{17}O_2N_3$: C, 56.85; H, 8.11; N, 19.89%.

3-Isobutyl-4-methoxycarbonyl-5-aminopyrazole(IIIg): colorless microcrystals, mp 104—106°C.

Found: C, 55.27; H, 7.57; N, 21.25%. Calcd for $C_9H_{15}O_2N_3$: C, 54.80; H, 7.67; N, 21.31%.

Benzene-addition compound: colorless microcrystals, mp 109—110°C. IR (cm^{-1}): 684 (benzene, -CH, out of plane). NMR: 7.36 (benzene).

Found: C, 59.17; H, 7.32; N, 19.07%. Calcd for $C_9H_{15}O_2N_3\cdot\frac{1}{3}C_6H_6$: C, 59.17; H, 7.68; N, 18.82%.

The formation of III was proved by the absence of the cyano group in the infrared spectra and by the reaction to be described below.

The Hydrolysis of IIIa or IIIb. A mixture of IIIa or IIIb (3 mmol) and 4N sodium hydroxide (6 m*l*) was gently refluxed for 2 hr. After this mixture had been cooled, the resulting clear solution was adjusted to pH 5 with hydrochloric acid under cooling in ice water. The crystals which separated were collected and washed with water and ethanol.

3-Methyl-5-aminopyrazole-4-carboxylic acid (IV): colorless needles, mp 124—125°C, yields 87—95%.

Found: C, 42.76; H, 4.90; N, 29.71%. Calcd for $C_5H_7O_2N_3$: C, 42.55; H, 5.00; N, 29.78%.

Both IIIa and IIIb gave the same product.

The Decarboxylation of IV. A mixture of 2.5 g of the foregoing carboxylic acid (IV) in water (20 m*l*) was boiled for 2 hr, and then the solvent was evaporated under reduced pressure. In order to remove a trace of water, benzene (3 m*l*) was added to it and again evaporated. The distillation of the residue gave 1.5 g (87.5%) of a fraction distilling at 146.5—147°C/4 mmHg; it became a crystalline mass on cooling.

3-Methyl-5-aminopyrazole: hygroscopic colorless needles, mp 47—48°C (lit 47°C,[8] 94°C[9]).

Found: C,48.61; H, 7.15; N, 40.71%. Calcd for $C_4H_7N_3$: C, 49.46; H, 7.27; N, 43.27%.

Picrate: yellow needles, mp 206—207°C (lit 213—214°C,[7] 205—209°C[9]).

Found: C, 36.79; H, 2.81; N, 25.79%. Calcd for $C_{10}H_{10}O_7N_6$: C, 36.81; H, 3.09; N, 25.76%.

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[7] H. Beyer and G. Wolter, *Chem. Ber.*, **89**, 1658 (1956).

[8] P. Kurtz, H. Gold and H. Disselnkötter, *Ann.*, **624**, I (1959).

[9] M. J. S. Dewar and F. E. King, *J. Chem. Soc.*, **1945**, 114.

The Formation of 3-Alkyl-4-cyano-5-pyrazolones (V). A. By the Base Treatment of II. (i) A suspension of powdered IIa—g (6 mmol) and 80% hydrazine hydrate (6 mmol) in water (8 m*l*) was stirred at room temperature for 1 hr. The reaction mixture was filtered to give a large amount of unchanged material (the melting point was not depressed on admixture with II). After the filtrate had been acidified with hydrochloric acid, the resulting precipitate was collected by filtration, washed with a small amount of ice water, and recrystallized from water to give Va—f.

Both IIa and IIb gave the same product (Va); the yields were 6.3% and 8.3% respectively. Vb was obtained in a yield of 12.8%. The results of this reaction (for IIb) obtained by varying the reaction period are shown in Table 1 (Reaction 2). In the case of IId—g, the reaction period was extended to 5 hr, giving the corresponding yields of 50% (Vc), 6.06% (Vd), 20% (Ve), and 78.2% (Vf).

(ii) To a solution of 28% ammonia water (3 m*l*) and water (3 m*l*), 3.3 mmol of powdered IIa or IIb were added; the mixture was then stirred at room temperature for 4 hr. Filtration gave the unchanged material. The filtrate was worked up as before to afford Va in a yield of 76%.

(iii) A mixture of IIa or IIb (0.2 g) and a 10% aqueous potassium carbonate solution (4 m*l*) was stirred at room temperature for 1 hr. After the resulting clear solution had been acidified with hydrochloric acid, the separated crystals were purified as before to obtain 43.6—50% of Va.

In the reaction of IIa and IIb, the same product (as shown by the melting point and the infrared spectrum) was obtained from all three reactions (A(i)—(iii)).

3-Methyl-4-cyano-5-pyrazolone (Va): colorless prisms, mp 275—277°C (dec). IR (cm^{-1}): 2242 (νC≡N).

Found: C, 48.68; H, 4.30; N, 34.08%. Calcd for $C_5H_5ON_3$: C, 48.78; H, 4.09; N, 34.14%.

3-Ethyl-4-cyano-5-pyrazolone (Vb): colorless prisms, mp 232—234°C. IR (cm^{-1}): 2242 (νC≡N).

Found: C, 52.63; H, 4.93; N, 30.70%. Calcd for $C_6H_7ON_3$: C, 52.54; H, 5.15; N, 30.64%.

3-*n*-Propyl-4-cyano-5-pyrazolone (Vc): colorless plates, mp 215—216°C. IR (cm^{-1}): 2232 (νC≡N).

Found: C, 55.87; H, 6.30; N, 28.05%. Calcd for $C_7H_9ON_3$: C, 55.61; H, 6.00; N, 27.80%.

3-*n*-Butyl-4-cyano-5-pyrazolone (Vd): colorless plates, mp 174—175°C. IR (cm^{-1}): 2237 (νC≡N).

Found: C, 58.28; H, 6.54; N, 25.64%. Calcd for $C_8H_{11}ON_3$: C, 58.16; H, 6.71; N, 25.44%.

3-*n*-Amyl-4-cyano-5-pyrazolone (Ve): colorless plates, mp 168—169°C. IR (cm^{-1}): 2237 (νC≡N).

Found: C, 60.45; H, 7.40; N, 23.23%. Calcd for $C_9H_{13}ON_3$: C, 60.31; H, 7.31; N, 23.45%.

3-Isobutyl-4-cyano-5-pyrazolone (Vf): colorless plates, mp 220—221°C. IR (cm^{-1}): 2232 (νC≡N).

Found: C, 58.09; H, 6.31; N, 25.92%. Calcd for $C_8H_{11}ON_3$: C, 58.16; H, 6.71; N, 25.44%.

B. By the Reaction of Ia and Ib with an Excess of Hydrazine. Into a solution of 80% hydrazine hydrate (12 mmol) in water (8 m*l*), I (6 mmol) was stirred at room temperature, and then the mixture was stirred for an additional hour. Filtration gave a large amount of II (mp and mixed mp 131°C (IIa) or 115°C (IIb)). The treatment of the filtrate as A(i) gave Va in yields of 6.3—9.7%; mp 275—276°C. The product was identified with the Va obtained by Procedure A by a mixed-melting-point determination and by a study of the infrared spectra. The results of this reaction (for Ib) are shown in Table 1 (Reaction 1).

C. By the Reaction of I (R=*i*-Pr, *t*-Bu and Ph, R′=Me) with Hydrazine. I (3.3 mmol) was stirred into a solution of 80% hydrazine hydrate (3.3 mmol) and water (4 m*l*) at room temperature, and then the mixture was stirred for 1 hr. After the same work-up as in A(i), the separated V was recrystallized from water, benzene-methanol (Vg), or methanol-water (Vh and Vi). The use of more hydrazine resulted in an increase in the yield. Thus, the use of two equivalent moles of hydrazine nearly doubled the yield. In the case of I (R=Ph), a large amount of the starting material was recovered.

3-Isopropyl-4-cyano-5-pyrazolone (Vg): colorless microcrystals, mp 222—223°C, yield 41.4% and 80% (with two equivalent moles of hydrazine). IR (cm^{-1}): 2227 (νC≡N).

Found: C, 55.80; H, 5.72; N, 27.90%. Calcd for $C_7H_9ON_3$: C, 55.61; H, 6.00; N, 27.80%.

3-*t*-Butyl-4-cyano-5-pyrazolone (Vh): colorless prisms, mp 254—255°C, yields 30% and 73% (with two equivalent moles of hydrazine). IR (cm^{-1}): 2232 (νC≡N).

Found: C, 57.94; H, 6.44; N, 25.91%. Calcd for $C_8H_{11}ON_3$: C, 58.16; H, 6.71; N, 25.44%.

3-Phenyl-4-cyano-5-pyrazolone (Vi): colorless microcrystals, mp 254—255°C, yields 3.5% and 7.5% (with two equivalent moles of hydrazine). IR (cm^{-1}): 2237 (νC≡N).

Found: C, 64.79; H, 3.63; N, 22.60%. Calcd for $C_{10}H_7ON_3$: C, 64.86; H, 3.81; N, 22.69%.

All the compounds of V obtained by all the procedures (A, B, and C) gave a positive color reaction with ferric chloride, and their infrared spectra all indicated the presence of the cyano group and the disappearance of the ester-carbonyl group.

The Preparation of Ethyl *α*-Cyano-(2,2-dimethylhydrazino)crotonate (VI). A mixture of 1,1-dimethylhydrazine (0.36 g) in water (8 m*l*) and 1 g of powdered Ib was stirred at room temperature for 1 hr. The resulting precipitate was collected by filtration, washed thoroughly with water, and recrystallized from acetone-water to give 0.75 g (63.5%) of VI. Colorless needles, mp 83—85°C. IR (cm^{-1}): 2203(νC≡N), 1668 (νC=O). NMR: 10.26 (NH).

Found: C, 54.75; H, 7.63; N, 21.38%. Calcd for $C_9H_{15}O_2N_3$: C, 54.80; H, 7.67; N, 21.31%.

The Reaction of I (R=*i*-Pr, R′=Et) with Ammonia. A mixture of 28% ammonia water (1 m*l*) in water (2 m*l*) and I (3.3 mmol) was stirred at room temperature for 1 hr. The resulting precipitate was collected by filtration, washed with water, and recrystallized from benzene to give 0.4 g (74.2%) of ethyl *α*-cyano-*β*-amino-*β*-isopropylacrylate (VII). Colorless columns, mp 119—120°C. IR(cm^{-1}): 2203(νC≡N), 1686(νC=O).

Found: C, 59.65; H, 7.47; N, 15.37%. Calcd for $C_9H_{14}O_2N_2$: C, 59.32; H, 7.74; N, 15.37%.

The Reaction of Ia—g and I (R=*i*-Pr and Ph) with Hydroxylamine. A solution of hydroxylamine hydrochloride (5 mmol) in water (3 m*l*) was neutralized with a solution of potassium carbonate (2.5 mmol) in water (3 m*l*). Into this I (5 mmol) was stirred at room temperature. (In the reactions of Id—g, methanol was added to the mixture until it became a clear solution.) After it had been stirred for 1 hr, the precipitate which separated was recrystallized from ethanol (VIIIa, b, c, f, and VIIIj), ethanol - water (VIIIe,d, and VIIIg), or benzene (VIIIh). All the infrared spectra showed the disappearance of the cyano group.

3 - Methyl - 4 - methoxycarbonyl - 5 - aminoisoxazole (VIIIa): colorless prisms, mp 140—141°C, yield 78%.

Found: C, 46.20; H, 4.93; N, 17.81%. Calcd for $C_6H_8ON_2$: C, 46.15; H, 5.16; N, 17.94%.

3-Methyl-4-ethoxycarbonyl-5-aminoisoxazole (VIIIb): colorless needles, mp 133—134°C (lit[10]) 133—134°C), yield 88.2%.

Found: C, 49.80; H, 5.91; N, 16.59%. Calcd for $C_7H_{10}O_3N_2$: C, 49.40; H, 5.92; N, 16.46%.

3-Ethyl-4-methoxycarbonyl-5-aminoisoxazole (VIIIc): colorless prisms, mp 151—152°C, yield 97%.

Found: C, 49.40; H, 5.71; N, 16.70%. Calcd for $C_7H_{10}O_3N_2$: C, 49.40; H, 5.92; N, 16.46%.

3 - *n* - Propyl - 4 - methoxycarbonyl -5- aminoisoxazole (VIIId): colorless prisms, mp 116—117°C, yield 56.5%.

Found: C, 52.06; H, 6.40; N, 15.36%. Calcd for $C_8H_{12}O_3N_2$: C, 52.16; H, 6.57; N, 15.21%.

3 - *n* - Butyl - 4 - methoxycarbonyl - 5 - aminoisoxazole (VIIIe): colorless needles, mp 97—98°C, yield 75.8%.

Found: C, 54.48; H, 6.86; N, 14.24%. Calcd for $C_9H_{14}O_3N_2$: C, 54.53; H, 7.12; N, 14.13%.

3 - *n* - Amyl - 4 - methoxycarbonyl - 5 - aminoisoxazole (VIIIf): colorless needles, mp 129—130°C, yield 84.5%.

Found: C, 56.75; H, 7.25; N, 13.20%. Calcd for $C_{10}H_{16}O_3N_2$: C, 56.59; H, 7.60; N, 13.20%.

3 - Isobutyl - 4 - methoxycarbonyl - 5 - aminoisoxazole (VIIIg): colorless prisms, mp 99—100°C, yield 50%.

Found: C, 54.54; H, 6.99; N, 14.08%. Calcd for $C_9H_{14}O_3N_2$: C, 54.53; H, 7.12; N, 14.13%.

3 - Isopropyl - 4 - methoxycarbonyl - 5 - aminoisoxazole (VIIIh): colorless prisms, mp 121—122°C, yield 54.5%.

Found: C, 52.50; H, 6.61; N, 14.92%. Calcd for $C_8H_{12}O_3N_2$: C, 52.16; H, 6.57; N, 15.21%.

3-Phenyl-4-ethoxycarbonyl-5-aminoisoxazole (VIIIj): colorless needles, mp 123°C (lit[3]) 123°C), yield 85%.

Found: C, 62.23; H, 5.14; N, 12.11%. Calcd for $C_{12}H_{12}O_3N_2$: C, 62.06; H, 5.21; N, 12.06%.

In the case of the reaction of I (R = *t*-Bu) with hydroxylamine, an excess of hydroxylamine (10 mmol) was used, and to the mixture ethanol was added until it became a clear solution. The mixture was then stirred for 30 hr at room temperature and subsequently concentrated to about 2 m*l*. Upon the cooling of the mixture in an ice-chest, the product was obtained. Recrystallization from ethanol - water gave VIIIi, whose infrared spectrum indicated the absence of the cyano group.

3 - *t* - Butyl - 4 - methoxycarbonyl - 5 - aminoisoxazole (VIIIi): colorless needles, mp 112—113°C, yield 16.7%.

Found: C, 54.59; H, 7.22; N, 14.50%. Calcd for $C_9H_{14}O_3N_2$: C, 54.53; H, 7.12; N, 14.13%.

Furthermore, the filtrate was acidified with hydrochloric acid to give a precipitate whose recrystallization from ethanol yielded IX. Its ferric chloride test was positive.

3 - *t* - Butyl - 4 - cyano -5- isoxazolone (IX): colorless prisms, mp 217—218°C, yield 12.7%. IR (cm^{-1}): 2237(νC≡N).

Found: C, 57.82; H, 5.89; N, 17.11%. Calcd for $C_8H_{10}O_2N_2$: C, 57.82; H, 6.07; N, 16.86%.

The Reaction of Diethyl 1-Ethoxyethylidenemalonate with Hydroxylamine. To a neutralized solution of hydroxylamine hydrochloride (0.18 g) with potassium carbonate, diethyl 1-ethoxyethylidenemalonate (0.6 g) was added at room temperature, and then the mixture was stirred for 1 hr. After the reaction mixture had been acidified with hydrochloric acid, the crystallization of the resulting product from methanol afforded 0.31 g (69.5%) of 3-methyl-4-ethoxycarbonyl-5-isoxazolone (XI), whose ferric chloride test was positive. Colorless needles, mp 167—168°C (lit 170—171°C,[11]) 166°C[12])).

Found: C, 49.37; H, 5.20; N, 8.09%. Calcd for $C_7H_9O_4N$: C, 49.12; H, 5.30; N, 8.18%.

The Preparation of Ethyl α-Cyano-β-methoxyaminocrotonate (XII). *O*-Methylhydroxylamine hydrochloride (0.85 g) was neutralized with a solution of potassium carbonate (0.7 g) in water (10 m*l*). To the solution there was added Ib (1.6 g), and then the mixture was stirred at room temperature for 3 hr. After the usual work-up, the recrystallization of the resulting precipitate from methanol - water gave 1.6 g (87%) of XII. Colorless needles, mp 60—62°C. IR (cm^{-1}): 2198 (νC≡N), 1667 (νC=O). NMR: 11.64 (NH).

Found: C, 52.27; H, 6.72; N, 14.98%. Calcd for $C_{18}H_{12}O_3N_2$: C, 52.16; H, 6.57; N, 15.21%.

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