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Studies on Pyrimidine Derivatives and Related Compounds. LVII.[1] Cyclization Mechanisms of Ethyl 2-(5-Pyrazolyl)aminoalkylidenecyanoacetates

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It was found that the orientation of cyclization reaction of ethyl 2-(5-pyrazolyl)aminomethylenecyanoacetates (Va—c) and ethyl 1-cyano-2-(5-pyrazolyl)aminocrotonates (Xa—c) largely depends on the catalyst used: for example, the cyclization of Va by the acid catalyst results in only 7-amino derivative; on the other hand, the mixture of 7-amino derivative and 7-hydroxy derivative is obtained in the presence of the base catalyst. In order to clarify the mechanism of this reaction, we studied spectrophotometrically the behaviors of these compounds in basic solution, taking ethyl 2-(1,4-dimethylpyrazol-5-yl)aminomethylenecyanoacetate (XV), and ethyl 1-cyano-2-(1,4-dimethylpyrazol-5-yl)aminocrotonate (XVI) as model compounds. Consequently, it was found that the proton dissociation of the C_2-amino group is greatly disturbed by the methyl substitution on that carbon atom. This finding is used for explaining the fact that the base catalyzed cyclization of X is insensitive to the amount of catalyst used while that of V shows some dependency on the concentration of alkali.

Detailed investigation on the cyclization mechanism of 2-aminoalkylidenecyanoacetates has not yet been carried out. Recently, Midorikawa, *et al.*[2] reported that the condensation of methyl *cis*-1-cyano-2-methoxyacrylate and methyl *trans*-1-cyano-2-methoxycinnamate with hydrazine to pyrazole derivatives was mainly controlled by their geometric factors.

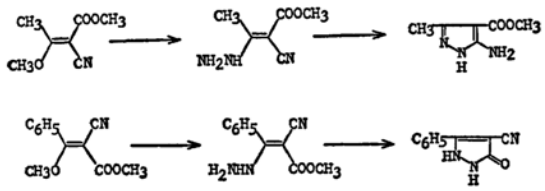

Chart 1

Previously,[3,4] it was suggested that the synthesis of 7-amino- or 7-hydroxypyrazolo[1,5-*a*]pyrimidine derivatives by the cyclization of ethyl 2-(5-pyrazolyl)-aminoalkylidenecyanoacetates was characteristically effected by acid or base catalysts, and, particularly in the latter case, was also effected by the amount of the catalyst used. This paper deals with the details of these reaction mechanisms.

Jones prepared ethyl ethoxymethylenecyanoacetate[5] (III) by the reaction of ethyl cyanoacetate (I), acetic anhydride, and ethyl orthoformate (II) and measured its NMR spectrum. He found a sharp singlet signal at τ 1.95 corresponding to the C_2 proton. We have prepared ethyl 2-(5-pyrazolyl)-aminomethylenecyanoacetates (Va—c) by the condensation of III with 5-aminopyrazoles (IVa—c) and have measured their NMR spectra with the results shown in Fig. 1. According to this figure, the NMR spectra of Va and Vc show the doublet signals of =CH-N< at τ 1.92 (J=13.8 cps) and at τ 1.86 (J=13.0 cps), respectively, each doublet being due to the coupling with adjacent NH proton. This indicates that Va and Vc consist of single ester, respectively. On the contrary, Vb shows the two doublet proton signals of =CH-N< at τ 1.72 (J=13.8 cps) and τ 2.00 (J=14.4 cps). From the intensities of these two doublet signals, the ratio of isomers is known to be approximately 1 : 1. Each doublet is converted into singlet by an addition of deuterium oxide. Jackman[6-8] and other several

1) Part LVI. A. Takamizawa, K. Hirai and S. Matsumoto, *Tetrahedron Letters*, **1968**, 4027.
2) H. Midorikawa, H. Baba and I. Hori, Presented at the 17th Annual Meeting of Chem. Soc. Japan, Tokyo, April, 1964.
3) A. Takamizawa, S. Hayashi, Y. Hamashima and R. Kido, *Yakugaku Zasshi* (*J. Pharmac. Soc. Japan*), **83**, 745 (1963).
4) S. Hayashi, *ibid.*, **85**, 442 (1965).
5) R. G. Jones, *J. Am. Chem. Soc.*, **74**, 4889 (1952).
6) L. M. Jackman and R. H. Wiley, *Proc. Chem. Soc.*, **1958**, 196.
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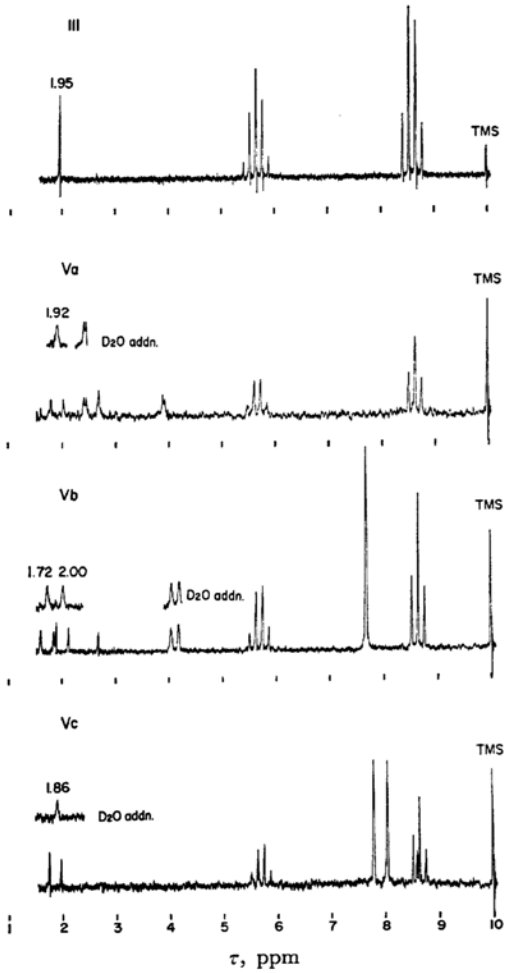

Fig. 1. The NMR spectra of III and Va—c at 60 Mc.

authors[9-12] demonstrated that, provided both isomers of a pair are available, NMR spectroscopy can be used to establish the geometric configurations of some α,β-unsaturated esters. This method is based on the fact that the protons of a *cis*-β-methyl group are more deshielded than those of a *trans*-β-methyl group. More recently, Hayashi, Hori, Baba and Midorikawa[13] and also McGreer *et al.*[14,15] reported that a *cis*-β-methyl group against the ester group of methyl 1-methoxyethylidenecyanoacetate is more deshielded than that of *trans*-isomer, but the authors have no definite confidence for deciding the geometric configurations of Va—c from the data or NMR.

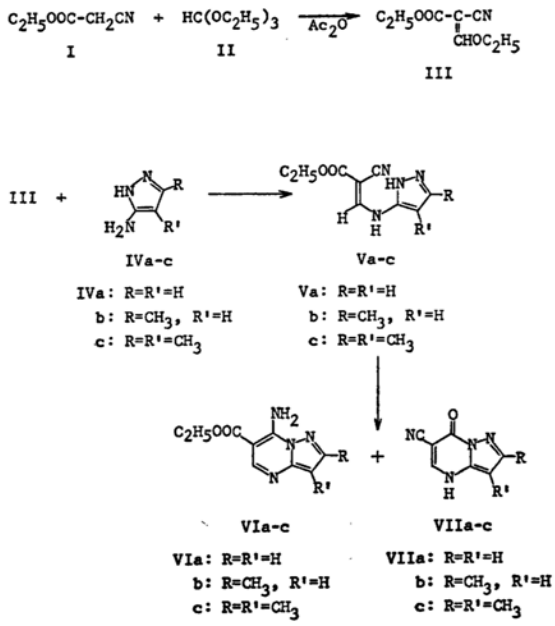

Chart 2

Now let us turn to the cyclization reaction of Va—c. The results obtained under various conditions are fairly systematic as is shown in Table 1a-d. The cyclization reaction of Va—c in the presence of acid catalysts gives only 7-amino derivatives (VIa—c). On the other hand, the reaction is rather complicated under base catalysts, and the mixture of VIa—c and 7-hydroxy derivatives (VIIa—c) can be obtained with

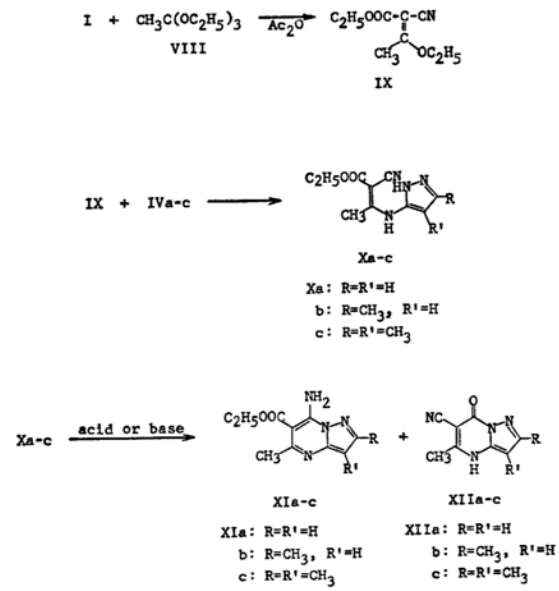

Chart 3

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10) R. O. Morris, C. A. Vernon and R. F. M. White, *ibid.*, **1958**, 304.
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12) S. Fujiwara, H. Shimizu, Y. Arata and S. Akabori, This Bulletin, **33**, 428 (1960).
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Table 1a. Ratios of VIa and VIIa prepared under various reaction conditions

Run	Va, mol	$NaOC_2H_5$,[a] mol	Time, hr	Temp., °C	Total yield, %	VIa/VIIa
1	0.002	0.001	91	Room	96.2	41.5/58.5
2	0.002	0.002	91	Room	86.1	29.9/70.1
3	0.002	0.004	43	Room	91.7	67.2/32.8
4	0.002	0.006	43	Room	86.7	77.7/22.3
5	0.002	0.001	2	Reflux	92.2	47.4/52.6
6	0.002	0.002	2	Reflux	91.7	30.8/69.2
7	0.002	0.004	2	Reflux	88.9	76.5/23.5
8	0.002	0.006	2	Reflux	83.6	88.8/11.2

Table 1b. Ratios of VIb and VIIb prepared under various reaction conditions

Run	Vb, mol	$NaOC_2H_5$,[a] mol	Time, hr	Temp., °C	Total yield, %	VIb/VIIb
1	0.002	0.001	148	Room	98.5	53.2/46.8
2	0.002	0.002	148	Room	94.2	54.6/45.4
3	0.002	0.004	148	Room	97.7	71.1/28.9
4	0.002	0.006	148	Room	96.3	81.0/19.0
5	0.002	0.001	2	Reflux	87.5	52.0/48.0
6	0.002	0.002	2	Reflux	94.3	43.6/56.4
7	0.002	0.004	2	Reflux	90.5	77.3/22.7
8	0.002	0.006	2	Reflux	92.6	81.9/18.1

Table 1c. Ratios of VIc and VIIc prepared under various reaction conditions

Run	Vc, mol	$NaOC_2H_5$,[a] mol	Time, hr	Temp., °C	Total yield, %	VIc/VIIc
1	0.002	0.001	144	Room	96.6	51.7/48.3
2	0.002	0.002	68	Room	90.3	62.4/37.6
3	0.002	0.004	43	Room	97.3	74.2/25.8
4	0.002	0.001	2	Reflux	95.5	60.4/39.6
5	0.002	0.002	2	Reflux	88.3	62.8/37.2
6	0.002	0.004	2	Reflux	95.3	79.4/20.6
7	0.002	0.006	2	Reflux	95.1	85.6/14.4
8	0.002	0.006	2	Reflux	92.3	89.8/10.2

Table 1d. Ratios of VI and VII prepared under various reaction conditions

Run	Starting material mol	Catalyst[a] mol	Time hr	Temp. °C	Total yield %	VI/VII
1	Va, 0.002	conc. HCl 0.004	2	Reflux	95.0	100/ —
2	Vb, 0.002	conc. HCl 0.004	2	Reflux	98.8	100/ —
3	Vc, 0.002	conc. HCl 0.004	2	Reflux	94.5	100/ —
4	Va, 0.002	CH_3COOH[b]	3	100	97.2	100/ —
5	Vb, 0.002	CH_3COOH[b]	3	100	97.7	100/ —
6	Vc, 0.002	CH_3COOH[b]	3	100	95.5	100/ —
7	Va, 0.002	Na_2CO_3[c]	0.02	100	84.5	—/100
8	Vb, 0.002	Na_2CO_3[c]	1	100	62.5	7.8/92.2
9	Vc, 0.002	Na_2CO_3[c]	1	100	80.0	34.3/65.7
10	Va, 0.002	NaOH[d]	0.03	100	81.6	—/100
11	Vb, 0.002	NaOH[d]	1	100	76.1	—/100
12	Vc, 0.002	NaOH[d]	1	100	78.5	—/100

a) 40 m*l* of C_2H_5OH was used as a solvent.
b) 3 m*l* of CH_3COOH was used as a solvent.
c) 10 m*l* of 10% aqueous Na_2CO_3 solution was used.
d) 10 m*l* of 5% aqueous NaOH solution was used.

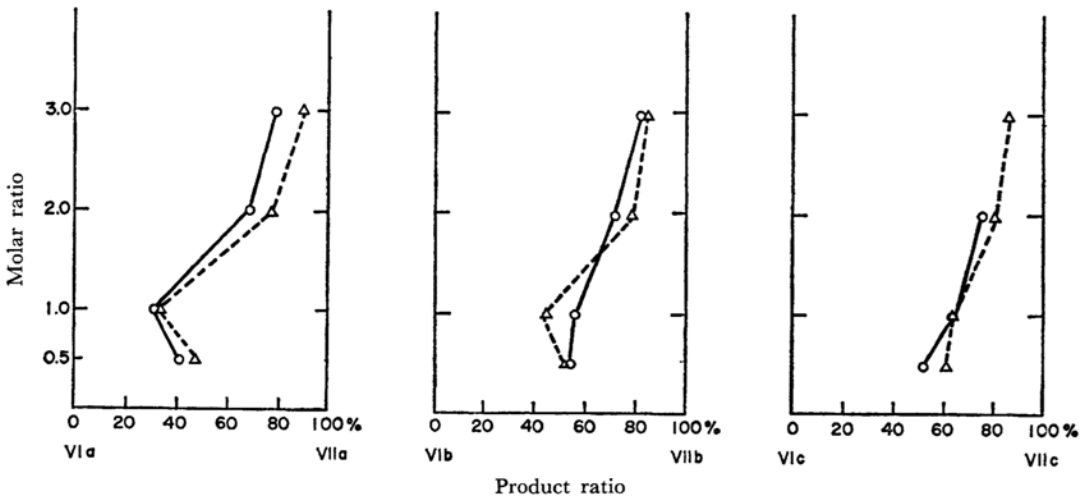

Fig. 2. Plot of the ratios of the products (VI and VII) at room temperature (——) and at refluxing temperature (----).

TABLE 2. RATIOS OF XI AND XII PREPARED UNDER VARIOUS REACTION CONDITIONS

Run	Starting material mol	Catalyst, mol	Solvent[a]	Time hr	Temp. °C	Total yield %	XI/XII
1	Xa, 0.002	conc. HCl, 0.004	C_2H_5OH	2	Reflux	86.5	54.6/45.4
2	Xb, 0.002	conc. HCl, 0.004	C_2H_5OH	2	Reflux	90.2	55.6/44.4
3	Xc, 0.002	conc. HCl, 0.004	C_2H_5OH	2	Reflux	95.0	38.3/61.7
4	Xa, 0.002	$NaOC_2H_5$,[b] 0.006	DMF	2	100	90.1	0/100
5	Xb, 0.002	$NaOC_2H_5$,[b] 0.006	DMF	2	100	98.3	0/100
6	Xc, 0.002	$NaOC_2H_5$,[b] 0.006	DMF	2	100	96.5	0/100
7	Xa, 0.002	$NaOC_2H_5$, 0.002	C_2H_5OH	2	Reflux	90.6	0/100
8	Xa, 0.002	$NaOC_2H_5$, 0.004	C_2H_5OH	2	Reflux	94.0	0/100
9	Xa, 0.002	$NaOC_2H_5$, 0.006	C_2H_5OH	24	Room	94.2	0/100
10	Xb, 0.002	$NaOC_2H_5$, 0.004	C_2H_5OH	2	Reflux	87.8	0/100
11	Xc, 0.002	$NaOC_2H_5$, 0.004	C_2H_5OH	2	Reflux	93.2	0/100
12	Xa, 0.002	CH_3COOH,	CH_3COOH[c]	3	100	94.4	58.9/41.1
13	Xa, 0.002	NaOH	H_2O[d]	24	Room	75.8	0/100

a) 40 m*l* of each solvent was used.
b) 1% $NaOC_2H_5$ in C_2H_5OH was used.
c) 3 m*l* of CH_3COOH was used as a solvent.
d) 10 m*l* of 5% NaOH solution was used as a solvent.

the general tendency that the proportion of VIa—c increases with the increasing amount of catalysts. Correlations of the ratios of the products with the amounts of catalysts are summarized in Fig. 2. The correlation curves for Va and Vb show the minimum ratios of VI to VII when an equimolar amount of catalyst is used.

Ethyl 1-cyano-2-ethoxycrotonate (IX) obtained by the reaction of I with ethyl orthoacetate (VIII) in acetic anhydride consists of the geometric isomers in the ratio of approximately 96 : 4. IX was used without further purification to prepare ethyl 1-cyano-2-(5-pyrazolyl)aminocrotonates (Xa—c), which were all decided by the NMR measurement to consist of a single component, respectively. The treatment of Xa—c with acid or alkali gives cyclization products in good yield. The results are given in Table 2. As is clearly seen in this table, only 7-hydroxy derivatives (XIIa—c) can be obtained under basic conditions regardless of the amount of the catalysts. On the other hand, the cyclization reaction of Xa—c under acidic conditions gives 7-amino- (XIa—c) and 7-hydroxy derivatives (XIIa—c) in the ratio of approximately 1 : 1.

From the above-mentioned results, it is clear that the orientation of cyclization reaction of Va—c is effected by the kind of catalyst used, namely, by acid or base catalyst used. Moreover, in the case of the base catalyzed cyclization, the reaction is sensitive to the amount of the catalyst. The similar situation concerning the dependence on the kind of catalyst was found for the reaction of Xa—c. In this

case, however, we could not observe the dependence upon an amount of base. In order to clarify the reason for the difference in the reaction between Va—c and Xa—c, their behaviors in alkaline medium have been studied by measuring ultraviolet absorption spectra of ethyl 2-(1,4-dimethylpyrazol-5-yl)-aminomethylenecyanoacetate (XV), and ethyl 1-cyano-2-(1,4-dimethylpyrazol-5-yl)aminocrotonate (XVI) which are similar in their structures to V and X, respectively, but cannot be expected to take pyrazolopyrimidine condensation because of the methylation on the N atom. In XV, as is shown in Fig. 3, the ultraviolet absorption maximum at 286 mμ shifts to 318 mμ by an addition of the base even in alcoholic medium, indicating the occurrence of deprotonation at the C_2-amino group.[16] The

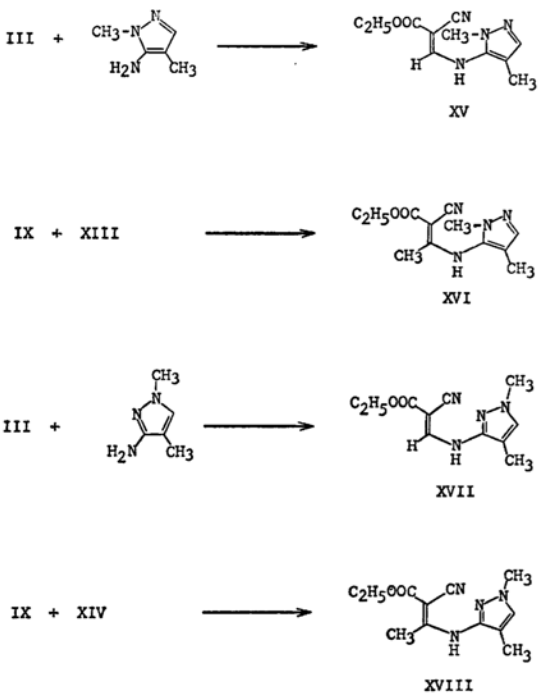

Chart 4

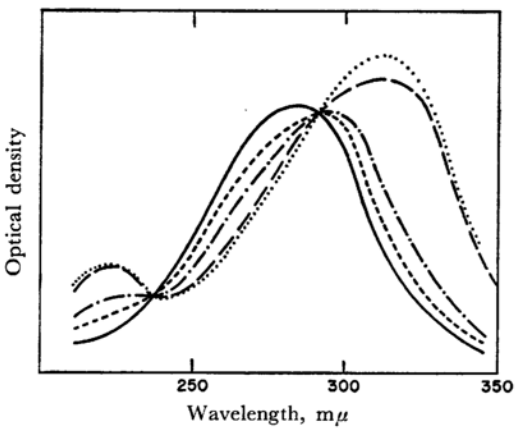

Fig. 3. Ultraviolet absorption curves of XV under various conditions.
——: Neutral in C_2H_5OH (λ_{max} 286 mμ)
----: In the presence of 0.5 eq. mole of $NaOC_2H_5$
·—·: In the presence of 1.0 eq. mole of $NaOC_2H_5$
—— : In the presence of 3.0 eq. mole of $NaOC_2H_5$
·····: In the presence of excess of $NaOC_2H_5$

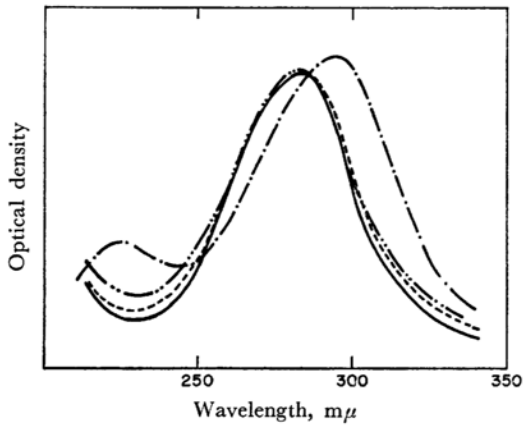

Fig. 4. Ultraviolet absorption curves of XVI under various conditions.
——: Neutral in C_2H_5OH (λ_{max} 285 mμ)
----: In the presence of $NaOC_2H_5$ (λ_{max} 285 mμ)
·—·: In the presence of NaOH dil. C_2H_5OH (λ_{max} 227.5, 296 mμ)
··—··: In the presence of conc. HCl in C_2H_5OH (λ_{max} 285 mμ)

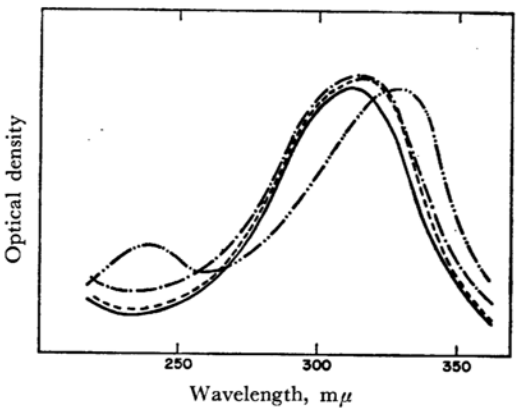

Fig. 5. Ultraviolet absorption curves of Vb under various conditions.
——: Neutral in C_2H_5OH (λ_{max} 314 mμ)
----: In the presence of excess of $NaOC_2H_5$ (λ_{max} 318 mμ)
·—·: In the presence of NaOH in dil. C_2H_5OH (λ_{max} 318 mμ)
··—··: In the presence of excess of NaOH in H_2O (λ_{max} 239, 327 mμ)

16) Deprotonation may conceivably occur in the other groups. For example, the C_2-H of XV may dissociate proton in basic media. This possibility, however, is very likely excluded, because the C_2-H dissociation product is less stabilized by the resonance than the C_2-N-H dissociation product.

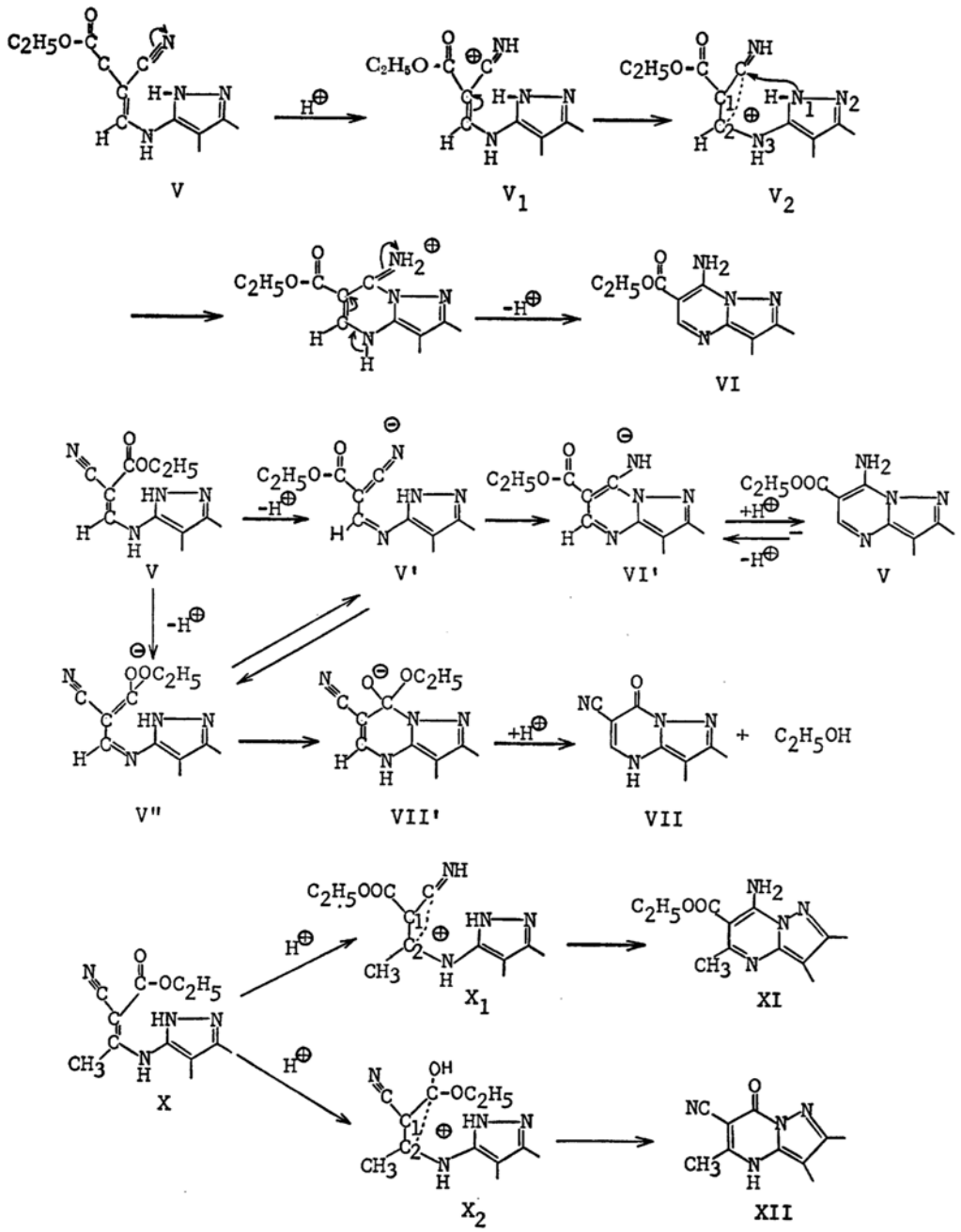

Chart 5

pK_a value of XV can be evaluated to be 8.45 by the aid of the usual equation.[17] In the presence of more than 5 equivalents of the base, the absorption curve becomes constant because of the complete dissociation. In XVI the dissociation hardly occurs in alcoholic medium, but by the addition to water, the dissociation may be thought to occur in view of the appearance of a new absorption maximum at 227.5 mμ (Fig. 4). This means that the methyl substitution at the C_2 position makes the dissociation more difficult.[18]

17) $pK_a = pH - \log((A-b)/(b-B))$ (A, B and b are the molecular extinction coefficients of the acidic form, the basic form and the equilibrium mixture of them, respectively, under the conditions that the total concentration of XV is constant).

18) The ultraviolet absorption spectra of ethyl 2-(1,4-dimethylpyrazol-3-yl)aminomethylenecyanoacetate (XVII) and ethyl 1-cyano-2-(1,4-dimethylpyrazol-3-yl)aminocrotonate (XVIII) were measured in solutions with various pH values. The results show that XVIII is dissociated with more difficulty than XVII is.

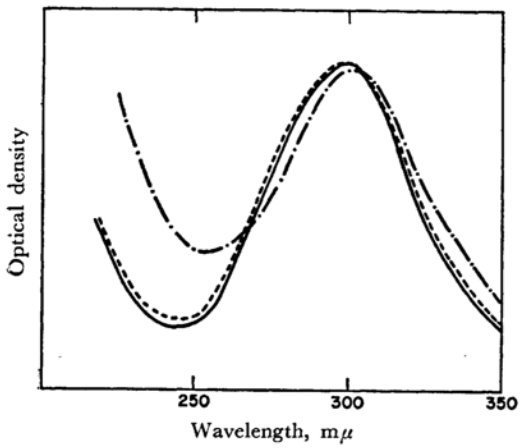

Fig. 6. Ultraviolet absorption curves of Xa under various conditions.
——: Neutral in C_2H_5OH (λ_{max} 298 mμ)
----: In the presence of $NaOC_2H_5$ (λ_{max} 298 mμ)
·—·: In the presence of excess of NaOH in H_2O (λ_{max} 303 mμ)

The same tendency was also observed in Va—c and Xa—c. For example, at room temperature dissociation of Vb in basic alcohol, which could hardly be expected to cause the cyclization reaction, was not detected, but the dissociation proceeded by the addition of water and the maximum at 318 mμ shifted to 327 mμ accompanied with an appearance of a new maximum at 239 mμ. On the contrary, as is shown in Fig. 6, dissociation was scarcely detected in Xa by the addition of excess of base in alcohol or even in water. From the above-mentioned experimental results of ultraviolet absorption spectra, it may be obvious that the dissociation of 2-(5-pyrazolyl)aminoalkylidenecyanoacetates in alkaline medium becomes difficult by the substitution of methyl group at the C_2 position. This seems to correspond to the fact that the cyclization of Va—c is more sensitive to the amount of alkali as catalyst than Xa—c.

As a whole, possible cyclization mechanisms of this series may be considered as follows: As is shown in Chart 5, protonation will occur in acidic medium at the cyano group[19] in V to give a carbonium ion intermediate such as V_2. In this intermediate cation, rotation may be possible around the C_1-C_2 bond, and the nucleophilic attack of pyrazole N_1 to the cyano group may preferentially give VI. With base catalyst, deprotonation from the N_3 amino group may easily give V′ or V″. The orientation of the reaction will be influenced by the stability of V′ and V″,[20] and the equilibrium (V′ ⇌V″) will be inclined towards V′ with the increasing amount of the base.

In X protonation occurs at the cyano or carbonyl group and the carbonium ions such as X_1 and X_2 are produced. In these ions rotation around the C_1-C_2 bond may be somewhat hindered sterically by the methyl group resulting in a mixture of 7-amino- (XI) and 7-oxo (XII) compounds. In the consideration of the base catalyzed cyclization of X, we must give attention to the spectrophotometric observation that deprotonation at the N_3 amino group is prohibited by the steric effect of the adjacent methyl group in addition to its hyperconjugation effect. From this it may be inferred that only 7-oxo compound (XII) is produced mainly because of its original geometric factor. In this series of reactions, the details of orientation mechanism may be thought to be controlled by various factors such as solvent effect, reaction temperature and so on. Further work on the reaction mechanisms for this series is in progress.

Experimental[21]

Cyclization Reactions of Va—c under Various Conditions. A. Vc (0.4685 g) was dissolved in 40 m*l* of ethanol by warming. After being cooled, the solution was mixed with 2 m*l* of ethanol containing 0.046 g of sodium, and stirred at room temperature for 68 hr. Evaporation of the mixture gave solids. To the residue was added water and the precipitated solids were filtered, washed and dried to give 0.268 g (56.3%) of VIc. The filtrate was made acidic by acid and the precipitated solids were filtered and dried. Recrystallization from methanol gave colorless needles, which were proved to be identical with an authentic sample. Yield, 34%.

B. Vb (0.44 g) was dissolved in 40 m*l* of ethanol by warming. After cooled, the solution was mixed with 1 m*l* of ethanol containing 0.023 g of sodium, and heated to reflux for 2 hr, and concentrated. To the residue was added water and the precipitated solids were collected and dried to give 0.2 g (45.5%) of VIb. From the mother liquid was obtained 0.146 g (42.0%) of VIIb neutralized by acetic acid.

C. To 10 m*l* of 5% sodium hydroxide in water was suspended 0.4124 g of Va, and the mixture was heated at 100°C for 20 min to become clear solution. After cooled, the solution was neutralized by acetic acid to give 0.261 g (81.6%) of VIIa as colorless prisms.

D. To 10 m*l* of 10% sodium carbonate in water was added 0.4685 g of Vc, and the mixture was heated on a steam bath for 1 hr resulting to obtain clear solution. After being cooled, the precipitated solids were collected and washed to give 0.103 g (27.4%) of VIc. The filtrate

19) The intermediate produced by protonation on the carbonyl oxygen atom can be considered. This intermediate, however, is disregarded for the cyclization of V, because the actual reaction does not occur through it.

20) In Chart 5, V′ and V″ are, respectively, represented by one of various resonance structures. In these intermediates, the negative charge may be considered to be delocalized all-around the molecule.

21) All NMR spectra were obtained on the Varian A-60 spectrometer in deuterio chloroform using tetramethylsilane (TMS) as an internal reference. The ultraviolet absorption spectra were recorded by Hitachi ELS-3 recording spectrophotometer.

was neutralized with acetic acid to precipitate a colorless solid, which was proved to be VIIc by the comparisons of infrared spectra. Yield, 0.246 g (52.6%).

E. To the suspension of 0.4124 g of Va in 40 m*l* of ethanol was added 0.42 g of conc. hydrochloric acid, and the mixture was heated to reflux on a steam bath for 2 hr. Evaporation of the solution resulted colorless residue, which was dissolved in water and neutralized with sodium carbonate to precipitate VIa as colorless needles, yield, 0.391 g (95%).

Cyclization Reactions of Xa—c under Various Conditions. A. To a solution of 0.4405 g of Xa in 40 m*l* of ethanol was added 0.42 g of conc. hydrochloric acid, and the mixture was heated to reflux for 2 hr and evaporated. The residues were dissolved in water and neutralized with sodium carbonate to obtain colorless solids, which were extracted with cold sodium hydroxide solution and filtered. The solid was proved to be identical with XIa by the comparisons of their infrared spectra. Yield, 0.137 g (39.4%). Sodium hydroxide solution was neutralized with acetic acid to obtain XIIa as colorless needles, yield, 0.208 g (47.2%).

B. To a solution of 0.4405 g of XIa in 40 m*l* of ethanol was added 0.092 g of sodium in ethanol (9 m*l*), and the mixture was heated to reflux on a steam bath for 2 hr. Evaporation of the solution gave colorless solid, which was dissolved in water and neutralized with acetic acid to give XIIa as colorless sticks, yield. 0.327 g (94%).

Ethyl 2-(1,4-Dimethylpyrazol-5-yl)aminomethylenecyanoacetate (XV). A solution of 1.7 g of III and 1.12 g of XIII in 30 m*l* of ethanol was heated to reflux for 3 hr, and concentrated. The residue was recrystallized from ethanol - ether to give XV as colorless sticks, mp 112—113°C, yield, 2.12 g (90.6%).

Found: C, 56.50; H, 6.35; N, 23.98%. Calcd for $C_{11}H_{14}O_2N_4$: C, 56.40; H, 6.02; N, 23.92%.

Ethyl 1-Cyano-2-(1,4-dimethylpyrazol-5-yl)aminocrotonate (XVI). A solution of 0.366 g of IX and 0.222 g of XIII in 3 m*l* of ethanol was heated to reflux for 10 hr, and concentrated to afford colorless residue, which was recrystallized from acetone - ether to give XVI as colorless rhombi, mp 142—144°C. Yield, 0.42 g (84.6%).

Found: C, 58.28; H, 6.32; N, 22.63%. Calcd for $C_{12}H_{16}O_2N_4$: C, 58.05; H, 6.50; N, 22.57%.

Ethyl 2-(1,4-Dimethylpyrazol-3-yl)aminomethylenecyanoacetate (XVII). A mixture of 0.85 g of III and 0.56 g of XIV in 20 m*l* of ethanol was heated on a steam bath for 5 hr, and concentrated to give colorless solid, which was recrystallized from ethanol to give XVII as colorless needles, mp 122—123°C. Yield, 1.02 g (87.2%).

Found: C, 56.50; H, 6.35; N, 23.98%. Calcd for $C_{11}H_{14}O_2N_4$: C, 56.40; H, 6.02; 23.92%.

Ethyl 1-Cyano-2-(1,4-dimethylpyrazol-3-yl)aminocrotonate (XVIII). A solution of 1.5 g of XIV and 2.6 g of IX in 10 m*l* of ethanol was stirred at room temperature for 30 min to give colorless solid, which was filtered and recrystallized from ether to obtain XVIII as colorless silky needles, mp 143°C. Yield, 2.3 g (71.7%).

Found: C, 58.36; H, 6.72; N, 22.83%. Calcd for $C_{12}H_{16}O_2N_4$: C, 58.05; H, 6.50; N, 22.57%.