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Studies on Pyrazolo[3,4-*d*]pyrimidine Derivatives. V.[1] On the Transformation of 1*H*-Pyrazolo[3,4-*d*]pyrimidines into 1*H*-Pyrazolo[3,4-*b*]pyridines

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The direct reaction of 1,5-dimethyl- (XIm), 5-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]-pyrimidinium iodide (XIp), 1-methyl- (XIIm), and 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidinium hydrogen sulfate (XIIp) with active methylene compound and ketone (NuH) were carried out. NuH used in this study were as follows: malononitrile (NuH-1), ethyl cyanoacetate (NuH-2), ethyl acetoacetate (NuH-3), ethyl benzoylacetate (NuH-4), acetylacetone (NuH-5), acetone (NuH-6), cyclopentanone (NuH-7), cyclohexanone (NuH-8), and acetophenone (NuH-9).

Thus, XI was transformed into the 5,6-disubstituted 1-methyl- (or 1-phenyl)-1*H*-pyrazolo[3,4-*b*]pyridines (IX) by the direct reaction with NuH in butanol. Similar transformation took place in the reaction of XII with NuH yielding IX together with 5-amino-1-methyl (or 1-phenyl)-1*H*-pyrazole (XIV).

These 1*H*-pyrazolo[3,4-*b*]pyridines (IX) were also prepared by the Friedlaender synthesis with 5-amino-1-methyl (or phenyl)-1*H*-pyrazole-4-carboxaldehyde (XV) and NuH in the presence of ethoxide ion.

The three possible reaction mechanisms; path A, B, and C, were proposed. And it might be concluded that the path A stood to reason than the path B or C for the ring transformation of XI and it was not clear which path of A, B or C, was the most suitable for the ring transformation of XII.

Keywords——pyrazolopyrimidine; active methylene compd.; ketone; ring transformation; pyrazolopyridine; ring opening; pyrazole; mechanism; Friedlaender synthesis;

This paper reports one of our researches on the reaction of the condensed pyrimidine ring of 1*H*-pyrazolo[3,4-*d*]pyrimidines with nucleophile.[3] Many of the heterocycles having the condensed pyrimidine ring such as quinazoline (I)[4a], its 3-oxide (II)[4b,c], pyrido[2,3-*d*]pyrimidine 3-oxide (III)[4d,e], pteridine (IV)[4f], 1,2,3-triazolo[4,5-*d*]pyrimidine (V)[4g], have been shown to transform the pyrimidine ring into pyridine ring by the direct reaction with active methylene

1) Part IV: T. Higashino, Y. Iwai, and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **24**, 3120 (1976).

2) Location: *2-2-1 Oshika, Shizuoka-shi.*

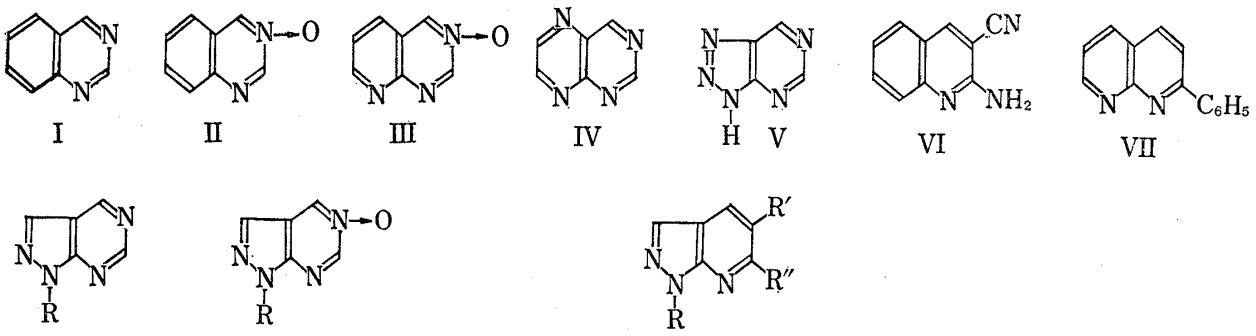
3) *a*) T. Higashino, Y. Iwai, and E. Hayashi, *Yakugaku Zasshi*, **94**, 666 (1974); *b*) *Idem*, *ibid.*, **94**, 1191 (1974); *c*) *Idem*, *ibid.*, **96**, 1532 (1976).

4) *a*) T. Higashino, H. Ito, and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1544 (1972); *b*) T. Higashino, Y. Nagano, and E. Hayashi, *ibid.*, **21**, 1943 (1973); *c*) T. Higashino, K. Suzuki, and E. Hayashi, *ibid.*, **23**, 746 (1975); *d*) T. Higashino and E. Hayashi, *ibid.*, **21**, 2643 (1973); *e*) T. Higashino, K. Suzuki, and E. Hayashi, *ibid.*, **23**, 2939 (1975); *f*) A. Albert and H. Mizuno, *J. Chem. Soc.* Perkin I, **1973**, 1615; *g*) A. Albert and W. Pendergast, *ibid.*, **1973**, 1620.

compound and ketone (NuH). For example, I reacted with malononitrile to give 2-amino-3-quinolinecarbonitrile (VI),[4a] and the reaction of III with acetophenone gave 2-phenyl-1,8,-naphthyridine (VII).[4e] In the previous paper[1] it was also reported that 1-methyl-(VIIIm) and 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (VIIIp) were not transformed into 1-methyl-(IXm) and 1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridines (IXp) by the direct reaction with NuH, but their 5-oxides (Xm and Xp) were transformed into IXm and IXp by the direct reaction with NuH. These results were probably caused by the fact that a greater nucleophilic activity of the ring carbon atom at the 4-position of X, due to the electronic effect of the N-oxide group, than that of VIII, markedly reduced the stability of the condensed pyrimidine ring, resulting in the facile ring fission between the 5- and 6-positions.

As the nucleophilic activity of the ring carbon atom at the 4-position of 1,5-dimethyl-(XIm), 5-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidinium iodide (XIp), 1-methyl- (XIIm) and 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidinium hydrogen sulfate (XIIp) seemed to be approximate to that of X, we carried out the reaction of XI and XII with NuH, and found that XI and XII were transformed into IX.

NuH used in this study were as follows; malononitrile (NuH-1), ethyl cyanoacetate (NuH-2), ethyl acetoacetate (NuH-3), ethyl benzoylacetate (NuH-4), acetylacetone (NuH-5), acetone (NuH-6), cyclopentanone (NuH-7), cyclohexanone (NuH-8) and acetophenone (NuH-9). The molar ratio between XI or XII and NuH was set at 1: 2.



I II III IV H V VI VII

VIII R
VIIIm : CH_3
VIIIp : C_6H_5

X R
Xm : CH_3
Xp : C_6H_5

IX	R	R′	R″
IXm-1	CH_3	CN	NH_2
IXm-3	CH_3	$COOC_2H_5$	CH_3
IXm-4	CH_3	$COOC_2H_5$	C_6H_5
IXm-5	CH_3	$COCH_3$	CH_3
IXm-6	CH_3	H	CH_3
IXm-7	CH_3	$(CH_2)_3$	
IXm-8	CH_3	$(CH_2)_4$	
IXm-9	CH_3	H	C_6H_5

IXp-1	C_6H_5	CN	NH_2
IXp-2	C_6H_5	CN	OH
IXp-3	C_6H_5	$COOC_2H_5$	CH_3
IXp-4	C_6H_5	$COOC_2H_5$	C_6H_5
IXp-5	C_6H_5	$COCH_3$	CH_3
IXp-6	C_6H_5	H	CH_3
IXp-7	C_6H_5	$(CH_2)_3$	
IXp-8	C_6H_5	$(CH_2)_4$	
IXp-9	C_6H_5	H	C_6H_5

XI R
XIm : CH_3
XIp : C_6H_5

XII R
XIIm : CH_3
XIIp : C_6H_5

XIII	R	R′
XIIIm-1	CH_3	CN
XIIIp-1	C_6H_5	CN
XIIIp-2	C_6H_5	$COOC_2H_5$

XIV R
XIVm : CH_3
XIVp : C_6H_5

XV R
XVm : CH_3
XVp : C_6H_5

XVI R
XVIm : CH_3
XVIp : C_6H_5

XVII R
XVIIm : CH_3
XVIIp : C_6H_5

Chart 1

When a mixture of XI and NuH was refluxed for 24 hr in butanol, most of the reactions gave IX with varying the yields, except the reaction of XIp with NuH-2 giving the ring fission product between the 5- and 6-position such as ethyl α-cyano-(5-amino-1-phenyl-1-*H*-pyrazol-4-ylmethylene)acetate (XIIIp-2), as shown in Table I. Moreover, in the case of the reaction of XIp with NuH-6, 6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (IXp-6) was formed together with VIIIp.

When a mixture of VIII and NuH in 20% ethanolic sulfuric acid (in the case of the reaction with NuH-6 to 9, 2 N sulfuric acid was used as a solvent) was refluxed for 24 hr, most of the reactions gave the ring transformation products (IX) with varying the yields, as shown in Table II. In the cases of the reactions of XIIp with NuH-3 and 6, 5-amino-1-phenyl-1*H*-pyrazole (XIVp) was formed together with ethyl 6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]-

Table I. Reaction of XI with NuH

NuH	XI	Product					
		IX	(%)	XIII	(%)	VIII	(%)
NuH-1	XIm	IXm-1	55.2				
NuH-3	XIm	IXm-3	75.0				
NuH-4	XIm	IXm-4	trace				
NuH-5	XIm	IXm-5	39.4				
NuH-6	XIm	IXm-6	trace				
NuH-7	XIm	IXm-7	51.4				
NuH-8	XIm	IXm-8	51.0				
NuH-9	XIm	IXm-9	5.5				
NuH-1	XIp	IXp-1	57.0				
NuH-2	XIp			XIIIp-2	30.0		
NuH-3	XIp	IXp-3	72.0				
NuH-5	XIp	IXp-5	62.5				
NuH-6	XIp	IXp-6	2.4			VIIIp	16.1
NuH-7	XIp	IXp-7	48.2				
NuH-8	XIp	IXp-8	28.8				
NuH-9	XIp	IXp-9	33.4				

Table II. Reaction of XII with NuH

NuH	XII	Product			
		IX	(%)	XIV	(%)
NuH-1[a]	XIIm	IXm-1	23.4		
NuH-2[a]	XIIm	IXm-2	—	XIVm	trace
NuH-3[a]	XIIm	IXm-3	6.6		
NuH-4[a]	XIIm	IXm-4	—	XIVm	trace
NuH-5[a]	XIIm	IXm-5	—	XIVm	trace
NuH-6[b]	XIIm	IXm-6	4.8		
NuH-7[b]	XIIm	IXm-7	43.0		
NuH-8[b]	XIIm	IXm-8	59.7		
NuH-9[b]	XIIm	IXm-9	22.9		
NuH-3[a]	XIIp	IXp-3	15.8	XIVp	25.0
NuH-4[a]	XIIp	IXp-9	quant.		
NuH-5[a]	XIIp	IXp-5	34.1		
NuH-6[b]	XIIp	IXp-6	47.1	XIVp	39.7
NuH-7[b]	XIIp	IXp-7	44.2		
NuH-8[b]	XIIp	IXp-8	67.2		
NuH-9[b]	XIIp	IXp-9	55.2		

a) in 20% ethanolic sulfuric acid
b) in 2 N sulfuric acid

pyridine-5-carboxylate (IXp-3) and 6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (IXp-6). The reaction of XIIm with NuH-2, 4 and 5 did not give the ring transformation products, but formed 5-amino-1-methyl-1*H*-pyrazole (XIVm), although the yield of XIVm was very poor (trace).

The identification of VIIIp, XIVm, XIVp, IXm-1, 3, 5, 8, IXp-1, 3, 5, and 8 was respectively made by the mixed melting point test using the corresponding authentic specimen prepared by each specific route.[1, 3a, 5a,b, 6a,b] The compounds, IXm-4, 6, 7, 9, IXp-2, 4, 6, 7 and 9, were prepared by the Friedlaender synthesis with 5-amino-1-methyl-(XVm) or 5-amino-1-phenyl-1*H*-pyrazole-4-carboxaldehyde (XVp)[1] and NuH in the presence of ethoxide ion as catalyst. (Table III). Nuclear magnetic resonance (NMR) and infrared (IR) spectra of IX were shown in Table IV. The compound XIIIp-2 was also prepared from the reaction of XVp with NuH-2 in piperidine. Similarly, the reaction of XVm and XVp with NuH-1 in piperidine yielded 1-methyl- (XIIIm-1) and 1-phenyl-1*H*-pyrazol-4-ylmethylenemalononitrile

Table III. The Friedlaender Synthesis of XV with NuH in the Presence of Ethoxide Ion

NuH	XV	Product IX	Product (%)	Product mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
NuH-4	XVm	IXm-4	22.8	120—121	$C_{16}H_{15}O_2N_3$	68.31	5.38	14.94	68.03	5.37	14.92
NuH-6	XVm	IXm-6	18.9	55— 56	$C_{14}H_{12}O_7N_6$ [a]	44.68	3.21	22.34	45.23	3.19	22.14
NuH-7	XVm	IXm-7	44.1	88— 89	$C_{10}H_{11}N_3$	69.34	6.40	24.26	69.30	6.37	24.62
NuH-9	XVm	IXm-9	64.2	66— 67	$C_{13}H_{11}N_3$	74.62	5.30	20.08	74.96	5.19	20.23
NuH-2	XVp	IXp-2	68.5	321—322	$C_{13}H_8ON_4$	66.09	3.41	23.72	65.92	3.63	23.22
NuH-4	XVp	IXp-4	41.3	97— 98	$C_{21}H_{17}O_2N_3$	73.45	4.99	12.24	73.23	5.01	12.76
NuH-6	XVp	IXp-6	11.1	28— 29	$C_{19}H_{14}O_7N_6$ [b]	52.06	3.22	19.17	51.78	3.08	19.24
NuH-7	XVp	IXp-7	57.0	103—104	$C_{15}H_{13}N_3$	76.57	5.57	17.86	76.17	5.56	17.77
NuH-9	XVp	IXp-9	68.5	119—120	$C_{18}H_{13}N_3$	79.68	4.83	15.49	79.54	5.06	15.51

a) picrate of IXm-6, mp 165—167°
b) picrate of IXp-6, mp 144—145°

Table IV. NMR and IR Spectra of IX

IX	NMR (τ) in $CDCl_3$ 1-CH_3[s]	1-C_6H_5[m]	3-H[s]	4-H	5-H	Other (J=8 cps)	IR ν_{max}^{KBr} cm^{-1}: >C=O
IXm-4	5.76		1.79	1.32[s]		2.2—2.7[m](-C_6H_5), 5.90[q], 8.97[t](-OCH_2CH_3)	1710
IXm-6	5.93		2.23	2.25[d]	3.13[d]	7.73[s](-CH_3)	
IXm-7	5.94		2.37	2.29[s]		6.7—7.3[m](2×-CH_2-), 7.5—8.1[m](-CH_2-)	
IXm-9	5.87		2.13	—[a]	—[a]	1.8—2.8[m](-C_6H_5)	
IXp-2[b]		1.7—2.8	1.63	1.23[s]		2.8—3.7[bs](>NH or -OH)	1650, 2230 (-C≡N)
IXp-4		1.4—2.9	1.70	1.37[s]		1.4—2.9[a,m](-C_6H_5), 5.80[q], 8.93[t](-OCH_2CH_3)	1720
IXp-6		1.4—2.8	1.92	—[a]	2.95[d]	7.31[s](-CH_3)	
IXp-7		1.4—2.9	2.22	1.96[s]		6.7—7.2[m](2×-CH_2-), 7.4—8.2[m](-CH_2)	
IXp-9		1.3—2.8	1.85	—[a]	—[a]	1.3—2.8[a,m](-C_6H_5)	

a) overlapping with hydrogens of phenyl group
b) in $(CD_3)_2SO$
bs: broad singlet and exchangeable with D_2O; d: doublet; m: multiplet; q: quartet; s: singlet; t: triplet; J_{4-5}=8cps

5) *a*) H. Dorn, G. Hilgetag, and A. Zubek, *Angew. Chem.*, **76**, 920 (1964); *b*) S. Hayashi, *Yakugaku Zasshi*, **85**, 442 (1965).
6) *a*) P. Schmidt and J. Druey, *Helv. Chim. Acta*, **41**, 306 (1958); *b*) A. Takamizawa and S. Hayashi, Japan. Patent 1438 (1964) [*C.A.*, **60**, 12019^h (1964)].

(XIIIp-1). These compounds (XIIIm-1 and XIIIp-1, 2) were converted, in good yield, into 1*H*-pyrazolo[3,4-*b*]pyridines (IXm-1, IXp-1, 2) by ethoxide ion.

There are three possible reaction mechanisms for the ring transformation of XI and XII; path A, B, and C. These mechanisms are assumed to exist from the results obtained from the present and previous studies[1,3a]: i) An addition across the 4—5 bond and a facile ring fission between the 5- and 6-positions took place through the reaction of the pyrazolo[3,4-*d*]-pyrimidine ring system with many of the nucleophiles.[1,3a] ii) When a solution of VIII dissolved in 2N sulfuric acid was refluxed for 24 hr, XIV was obtained in good yield together with XV (trace).

The path A is similar to the path of the transformation of the condensed pyrimidine ring system into the condensed pyridine ring system reported previously,[4a-e] and can be shown as in Chart 2. The first step is the formation of a adduct across the 4—5 bond (**a**) by the attack of NuH at the most reactive 4-position of XI or XII. Then the second molecule of NuH is added to **a** to form a 4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine intermediate (**b**). The subsequent ring fission of **b** between the 5- and 6-positions followed by elimination of amine gives **d** *via* **c**. Finally, IX is formed from **d** through **e**; that is to say, the ring closure of **d** and the loss of carbonium ion (**f**)[4a] give **e**, and the loss of hydroxide ion from **e** leades to IX.

The first step of the path B is the same with that of the path A; that is the formation of **a**. As the second step, water is added to **a** to form an intermediate (**b'**). The ring fission of

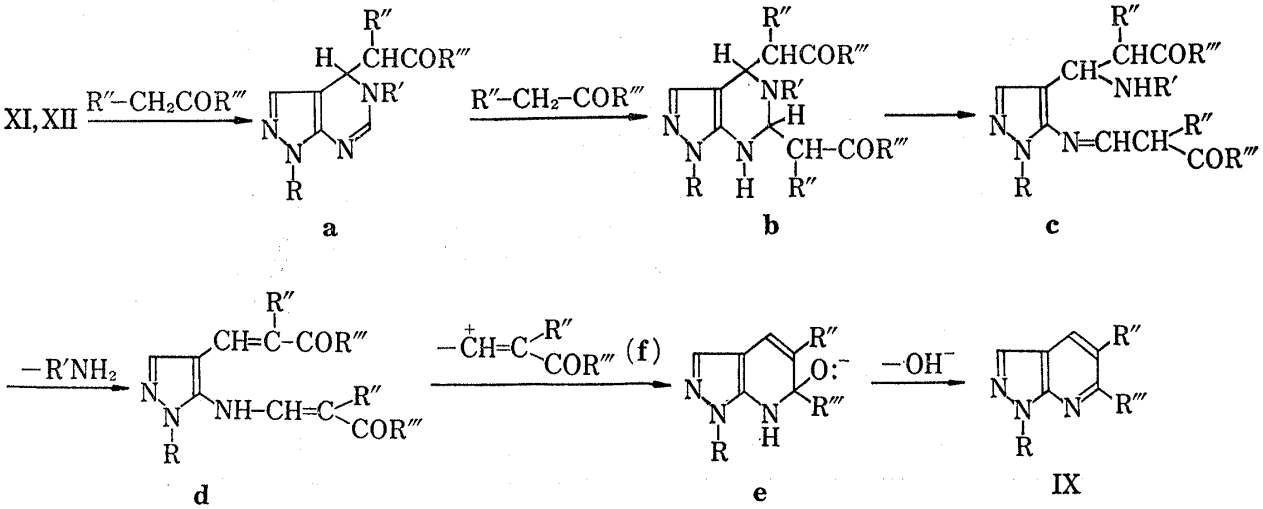


Chart 2

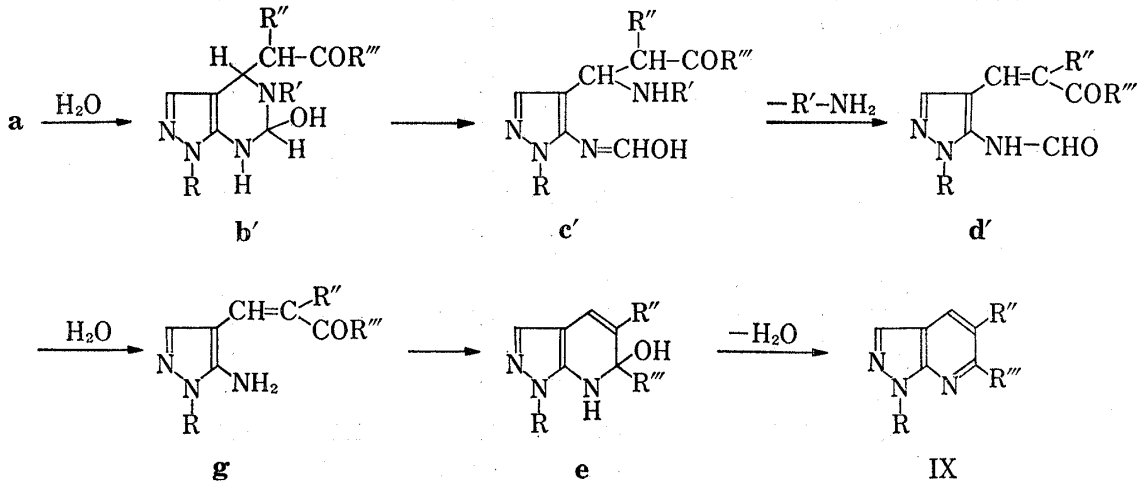


Chart 3

b′ and the elimination of amine give an intermediate **d′** *via* **c′**. The ring closure of **g**, resulting from the hydrolysis of **d′**, gives **e** which leads to IX, as shown in Chart 3.

An intermediate **b″** in the path C is probably formed by the addition of two moles of water in the first and second steps. Then the ring fission of **b″** gives **c″** which eliminates ammonia to form an intermediate **h**. XV, resulting from the hydrolysis of **h**, reacts with NuH in acid solution to give IX, as shown in Chart 4. In fact, XV reacted with NuH in 2 N sulfuric acid under the same condition as applied to the transformation of XII to give IX together with XIV as shown in Table V. The formation of XIV probably originates from

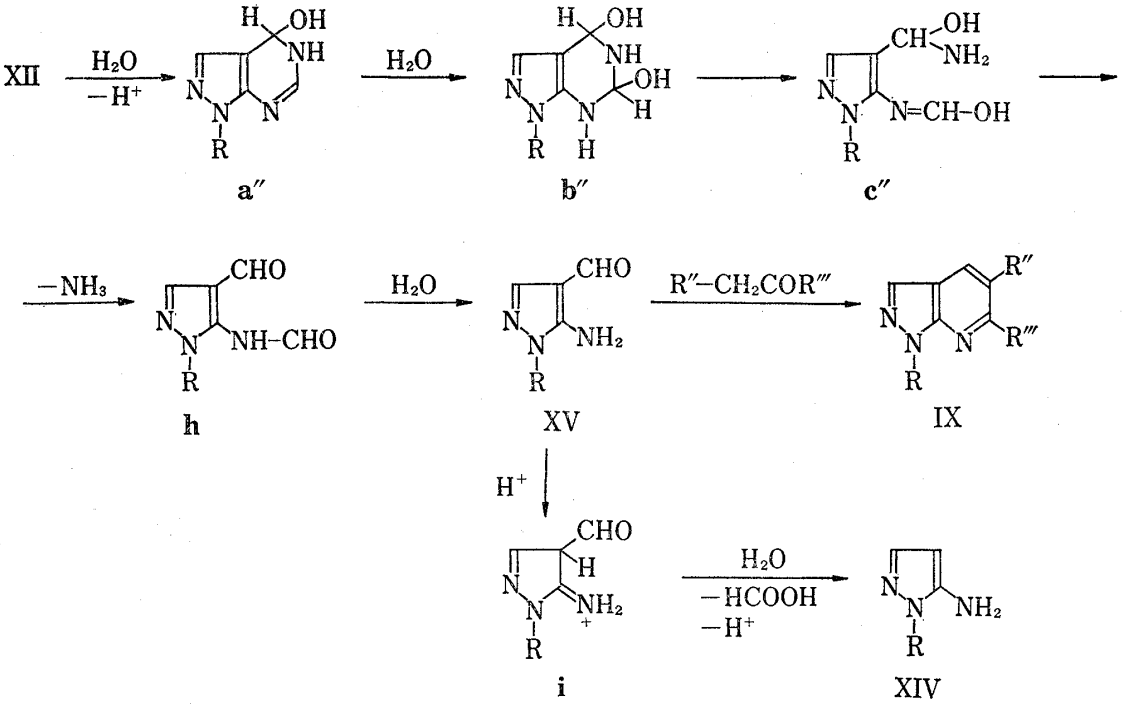


Chart 4

Table V. Reaction of XV with NuH in 2 N Sulfuric Acid

NuH	XV	Product			
		IX	(%)	XIV	(%)
NuH-1[a)]	XVm	IXm-1	3.6	XIVm	5.2
NuH-3[a)]	XVm	IXm-3	6.6	XIVm	7.7
NuH-4[a)]	XVm	IXm-4	8.3	XIVm	10.3
NuH-5[a)]	XVm	IXm-5	6.6	XIVm	8.4
NuH-6	XVm	IXm-6	trace	XIVm	6.3
NuH-7	XVm	IXm-7	18.3	XIVm	30.2
NuH-8	XVm	IXm-8	14.0	XIVm	40.2
NuH-9	XVm	IXm-9	5.0	XIVm	1.5
NuH-1[a)]	XVp	IXp-1	40.7	XIVp	38.6
NuH-3[a)]	XVp	IXp-3	20.5	XIVp	56.7
NuH-4[a)]	XVp	IXp-4	4.5	XIVp	30.1
NuH-5[a)]	XVp	IXp-5	3.2	XIVp	5.6
NuH-6	XVp	IXp-6	15.1	XIVp	80.8
NuH-7	XVp	IXp-7	22.5	XIVp	65.5
NuH-8	XVp	IXp-8	51.8	XIVp	43.1
NuH-9	XVp	IXp-9	7.4	XIVp	80.4

a) in 20% ethanolic sulfuric acid

XV. Thus, the protonation of XV forms an intermediate **i** which leads to XIV through the elimination of formic acid from **i**, as shown in Chart 4.

It may be concluded that the path A stands to reason better than the path B or C for the ring transformation of XI, because there is no water in the reaction medium, and it is not clear as yet which path of A, B or C, is the most suitable for the ring transformation of XII.

Experimental[7]

IR spectra were recorded with a Jasco Grating Infrared Spectrophotometer Model IRA-1. NMR spectra were measured at 60 Mc at 23° on a Hitachi High Resolution NMR Spectrometer Model R-24. Tetramethylsilane was used as an internal standard.

Preparation of XI——To a solution of 13.4 g (0.10 mole) of VIIIm dissolved in 100 ml of MeOH, 28.4 g (0.20 mole) of CH_3I was added, and the mixture was refluxed for 1 hr. After cooling MeOH was removed under the reduced pressure. The residue was recrystallized from MeOH to give XIm, mp 159—160° as yellow prisms, in 59.8% yield (16.5 g). *Anal.* Calcd. for $C_7H_9N_4I$ (1,5-dimethyl-1*H*-pyrazolo[3,4-*d*]pyrimidinium iodide): C, 30.45; H, 3.29; N, 20.29. Found: C, 30.18; H, 3.46; N, 19.98.

Similarly, 19.6 g (0.10 mole) of VIIIp and 28.4 g (0.20 mole) of CH_3I gave XIp, mp 182—183° as brownish yellow plate from MeOH, in 84.4% yield (28.5 g). *Anal.* Calcd. for $C_{12}H_{11}N_4I$ (5-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidinium iodide): C, 42.62; H, 3.28; N, 16.57. Found: C, 42.66; H, 3.44; N, 16.43.

Oxidation of XIp with $K_3Fe(CN)_6$——To a solution of 676 mg (0.002 mole) of XIp in 2 ml of MeOH, a solution of 3.29 g of $K_3Fe(CN)_6$ in 30 ml of H_2O and 2 ml of 33% KOH was added, and the reaction mixture was allowed to stand 1 hr. The separated crystals were collected and recrystallized from MeOH to give XVIp, mp 205—206° as colourless needles, in 42.3% yield (191 mg). This compound (XVIp) was undepressed on admixture with the specimen prepared from the reaction of 1,5-dihydro-1-phenylpyrazolo[3,4-*d*]pyrimidin-4-one (XVIIp) with CH_3I.

Preparation of XVIp——A solution of 10 g of CH_3I in 100 ml of MeOH was added to a solution of 5.0 g of XVIIp in 30 ml of 10% KOH, and the reaction mixture was refluxed for 4 hr. The separated crystals on cooling was collected and washed with H_2O and MeOH. The recrystallization from MeOH gave XVIp, mp 205—206° as colourless needles, in 85.1% yield (4.3 g). *Anal.* Calcd. for $C_{12}H_{10}ON_4$ (1,5-dihydro-5-methyl-1-phenylpyrazolo[3,4-*d*]pyrimidin-4-one): C, 63.70; H, 4.46; N, 24.77. Found: C, 63.56; H, 4.41; N, 24.74. NMR (in $(CD_3)_2SO$): 1.53, 1.68 (2×H, singlet, H-3 or H-6), 6.45 (3H, singlet, N–CH_3), 1.8—2.7 (5H, multiplet, N–C_6H_5). IR ν_{max}^{KBr} cm^{-1}: 1705 (>C=O).

Oxidation of XIm with $K_3Fe(CN)_6$——To a solution of 552 mg (0.002 mole) of XIm in 2 ml of MeOH, a solution of 3.3 g of $K_3Fe(CN)_6$ in 30 ml of H_2O and 2 ml of 33% KOH was added. The reaction mixture was allowed to stand for 4 hr. The addition of 2 ml of MeOH to the reaction mixture separated the crystals. Recrystallization from MeOH gave 1,5-dihydro-1,5-dimethylpyrazolo[3,4-*d*]pyrimidin-4-one (XVIm), mp 193—195° as colourless needles, in 15.3% yield (50 mg). This compound was undepressed on admixture with an authentic specimen[8] prepared from the reaction of 1,5-dihydro-1-methylpyrazolo[3,4-*d*]pyrimidin-4-one (XVIIm) with CH_3I.

Reaction of XI with NuH——A solution of 0.002 mole of XI and 0.004 mole of NuH in 20 ml of BuOH was refluxed for 24 hr. The residue, resulting from the removal of BuOH under the reduced pressure, was extracted with $CHCl_3$, and dried over anhyd. Na_2SO_4. The extract was passed through a column of alumina. From the first elution with benzene, IX was obtained, as colourless needles from petr. ether. The second elution with benzene gave VIIIp[3a] (only in the case of the reaction of XIp with NuH-6), mp 79—81° as white needles from petr. ether.

In the case of the reaction of XI with NuH-1, the residue, resulting from the removal of BuOH, was recrystallized from MeOH to give IX-1.[1]

The yields of IX and VIIIp were listed in Table I.

Reaction of XIp with NuH-2——A solution of 676 mg (0.002 mole) of XIp and 452 mg (0.004 mole) of NuH-2 in 20 ml of BuOH was refluxed for 24 hr. The residue, resulting from the removal of BuOH under the reduced pressure, was extracted with $CHCl_3$, and dried over anhyd. Na_2SO_4. The extract was passed through a column of alumina to remove impurities. Recrystallization from EtOH gave XIIIp-2, mp 183—184° as yellow needles, in 30.0% yield (169 mg). This product was identical to that prepared by the reaction of XVp with NuH-2 in the presence of piperidine as judged by mixture melting point data.

Reaction of XII with NuH——A mixture of 0.002 mole of VIII and 0.004 mole of NuH in 20 ml of 2 N H_2SO_4 (in the case of NuH-1 to 5, 20 ml of 20% ethanolic H_2SO_4 was used as a solvent) was refluxed for 24 hr. After cooling, the reaction mixture was extracted with $CHCl_3$, and the extract was dried over anhyd. Na_2SO_4. (in the case of the reaction with NuH-1 to 5, after removing EtOH under the reduced pressure, H_2O was

7) All melting points were not corrected.
8) C.C. Cheng and R.K. Robins, *J. Org. Chem.*, **21**, 1240 (1956).

added to the residue, and the resulting reaction mixture was extracted with $CHCl_3$). The extract was passed through a column of alumina to remove impurities. Recrystallization from petr. ether gave IX.

The acid solution was neutralized with K_2CO_3 and extracted with $CHCl_3$. After drying over anhyd. Na_2SO_4, removing $CHCl_3$ gave XIV; XIVm,[5] picrate mp 178—180° yellow needles from MeOH, XIVp,[6] picrate mp 155—157° as yellow needles from MeOH.

The yields of IX and XIV were listed in Table II.

Preparation of XIII——i) A solution of 250 mg (0.002 mole) of XVm, 264 mg of NuH-1 and a few drops of piperidine in 20 ml of EtOH was allowed to stand 1 hr. The separated crystals was filtered and recrystallized from EtOH gave XIIIm-1, mp 239—240° as yellow needles, in 84.7% yield (293 mg). *Anal.* Calcd. for $C_8H_7N_5$ (5-amino-1-methyl-1*H*-pyrazol-4-ylmethylenemalononitrile): C, 55.48; H, 4.07; N, 40.44. Found: C, 55.48; H, 4.31; N, 40.43. NMR (in CF_3COOD) τ: 1.05 (1H, singlet, H-3); 2.05 (1H, singlet, $-CH=C\langle^{CN}_{CN}$), 6.09 (3H, singlet, N–CH_3). IR ν_{max}^{KBr} cm^{-1}: 2200, 2220 (–CN), 3370, 3430 ($-NH_2$).

ii) A solution of 374 mg (0.002 mole) of XVp, 264 mg of NuH-1 and a few drops of piperidine in 20 ml of EtOH was allowed to stand 1 hr. The isolation procedure was carried out in the same fashion as for the preparation of XIIIm-1. Recrystallization from ether gave XIIIp-1, mp 218—219° as yellow plates, in 78.3% yield (368 mg). *Anal.* Calcd. for $C_{13}H_9N_5$ (5-amino-1-phenyl-1*H*-pyrazol-4-ylmethylenemalononitrile): C, 66.37; H, 3.86; N, 29.77. Found: C, 66.21; H, 4.05; N, 29.71. NMR (in $(CD_3)_2SO$) τ: 1.80 (1H, singlet, H-3), 1.87 (1H, singlet, $-CH=C\langle^{CN}_{CN}$), 2.0—2.7 (5H, multiplet, N–C_6H_5), 2.72 (2H, broad singlet and exchangeable with D_2O, $-NH_2$). IR ν_{max}^{KBr} cm^{-1}: 2220 (–CN), 3360, 3440 ($-NH_2$).

iii) A solution of 374 mg (0.002 mole) of XVp, 452 mg (0.004 mole) of NuH-2 and a few drops of piperidine in 20 ml of EtOH was refluxed for 1 hr. EtOH was removed under the reduced pressure and the residue was recrystallized from EtOH to give XIIIp-2, mp 183—184° as yellow needles, in 68.6% yield (387 mg). *Anal.* Calcd. for $C_{15}H_{14}O_2N_4$ (ethyl α-cyano-(5-amino-1-phenyl-1*H*-pyrazol-4-ylmethylene)-acetate): C, 63.82; H, 5.00; N, 19.85. Found: C, 63.88; H, 5.08; N, 19.92. NMR (in $(CD_3)_2SO$): 1.75 (1H, singlet, H-3), 1.89 (1H, singlet, $-CH=C\langle^{CN}_{COO-}$), 2.62 (5H, singlet, N–C_6H_5), 2.94 (2H, broad singlet and exchangeable with D_2O, $-NH_2$), 5.91 (2H, quartet, $-\underline{CH_2}-CH_3$), 8.86 (3H, triplet, $-CH_2-\underline{CH_3}$, $J=8$ cps). IR ν_{max}^{KBr} cm^{-1}: 2210 (–CN), 3300, 3440 ($-NH_2$), 1710 (=C=O).

Reaction of XIII with EtO^- Ion——A solution of 0.001 mole of XIII and EtONa solution (46 mg (0.002 mole) of Na dissolved in 20 ml of EtOH) was refluxed for 1 hr. After cooling, the reaction mixture was neutralized with 10% AcOH. EtOH was removed under the reduced pressure to separate crystals. The crystals were filtered and recrystallized from EtOH to give IX.

Thus, XIIIm-1 and EtO^- ion gave IXm-1, mp 252—253°,[1] in 42.2% yield (73 mg). The reaction of XIIIp-1 and 2 with EtO^- ion, respectively, afforded IXp-1, mp 232—233°,[1] in 83.0% yield (195 mg), and IXp-2, mp 321—322°, in 37.4% yield (88 mg).

The Friedlaender Synthesis of XV with NuH in the Presence of EtO^- Ion (Preparation of IX)——A solution of 0.002 mole of XV, 0.004 mole of NuH in EtONa solution (230 mg of Na dissolved in 20 ml of EtOH) was refluxed for 1 hr. The reaction mixture was neutralized with 10% AcOH, and EtOH was removed under the reduced pressure. The residue was recrystallized from a suitable solvent such as EtOH or petr. ether to give IX. The yields, melting points and elemental analyses of IX were listed in Table III. And NMR spectra of IX were in Table IV.

Reaction of XV with NuH in 2 N H_2SO_4——A mixture of 0.002 mole of XV and 0.004 mole of NuH in 20 ml of 2 N H_2SO_4 (in the case of the reaction with NuH-1 to 5, 20 ml of 20% ethanolic H_2SO_4 was used as a solvent) was refluxed for 24 hr. The isolation and purification procedure were carried out in the same fashion as for the reaction of XII with NuH. The yields of IX and XIV were listed in Table V.

Reaction of VIII with 2 N H_2SO_4——A solution of 0.002 mole of VIII and 20 ml of 2 N H_2SO_4 was refluxed for 24 hr. The reaction mixture was neutralized with K_2CO_3 and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and passed through a column of alumina. The first elution with $CHCl_3$ gave XIV, and from the second elution XV was given in very poor yield (trace).

Thus, VIIIm gave XIVm, picrate mp 178—180°[5] from MeOH, in 68.0% yield (132 mg), and XVm, mp 148—149°[1] from MeOH. Also VIIIp gave XIVp, picrate mp 155—157°[6] from MeOH, in 71.3% yield (226 mg), and XVp, mp 120—121°[1] from benzene.

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