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Studies on Pyrazolo[3,4-*d*]pyrimidine Derivatives. IV.[1] On 1-Methyl- and 1-Phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5-Oxide

TAKEO HIGASHINO, YOSHIHISA IWAI, and EISAKU HAYASHI

Shizuoka College of Pharmacy[2]

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Various reactions usually carried out on heterocyclic N-oxides were examined on 1-methyl- (IIm-0) and 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5-oxide (IIp-0) prepared from the condensation-cyclization of 1-methyl- (IIIm-1) or 1-phenyl-5-amino-4-hydroxyiminomethyl-1*H*-pyrazole (IIIp-1) and ethyl orthoformate.

The reaction of IIp-0 with alkaline solution gave the ring fission product between the 5- and 6-position such as 5-formamido- (IIIp-5) and 5-amino-4-hydroxyiminomethyl-1-phenyl-1*H*-pyrazole (IIIp-1). Application of the Reissert reaction to II-0 resulted in the formation of the ring fission products such as O-benzoyl derivative of IIIp-1 (IIIp-6) and 5-amino-1-methyl-1*H*-pyrazole-4-carbonitrile (IIIm-3). Acetic anhydride and IIm-0 gave 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol-(Im-4). But the reaction with IIp-0 gave both 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-ol (Ip-4) and 5-acetamido-1-phenyl-1*H*-pyrazole-4-carbonitrile (IIIp-8). Ip-4 was also obtained from the reaction of IIp-0 with tosyl chloride. The thermal decomposition of II-0 afforded 4,4′-bis[1-methyl-1*H*-pyrazolo-[3,4-*d*]pyrimidine] (IXm) and 4,4′-bis[1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrinidime] (IXp) together with 1-methyl- (Im-0) and 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (Ip-0). The Grignard reaction of II-0 gave 1-Methyl- (IIm-7—9) and 1-phenyl-4-alkyl-1*H*-pyrazolo-[3,4-*d*]pyrimidine 5-oxide (IIp-5—9). Im-0 and II-0 were transformed into 1-methyl- (XIXm) and 1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridines (XIXp) by the reaction with some active methylene compounds or ketone such as malononitrile (A-1), ethyl cyanoacetate (A-2), ethyl acetoacetate (A-3), acetylacetone (A-4) and cyclohexanone (A-5). Thus, in the presence of ethoxide ion Im-0 reacted with A-1 to give 6-amino-1-methyl-1*H*-pyrazolo-[3,4-*d*]pyridine-5-carbonitrile (XIXm-1). The direct reaction of IIm-0 with A-1 and A-2 gave 4,5-dihydro-5-hydroxy-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-malononitrile (XXm) and ethyl α-cyano-4,5-dihydro-5-hydroxy-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-acetate (XXm-2). But the direct reaction with A-3, 4 and 5 afforded the corresponding XIXm (XIXm-3, 4, and 5), respectively. The reaction of IIp-0 with A-1, 3, and 4 formed the corresponding XIXp (XIXp-1, 3, and 4) together with IXp (in the case of A-3 and 4), Ip-0 (in the case of A-4) and the ring fission product such as ethyl 2-(4-cyano-1-phenyl-1*H*-pyrazol-5-ylaminomethylene)-3-oxobutyrate (XXIp-3) and ethyl 2-(4-hydroxy-iminomethyl-1-phenyl-1*H*-pyrazol-5-ylaminomethylene)-3-oxobutyrate (XXIp-3′) (in the case of (A-3).

In a series of studies on the chemical properties of the pyrimidine portion in 1-substituted 1*H*-pyrazolo[3,4-*d*]pyrimidine ring, the present authors reported the reaction of nucleophilic reagent on 1-methyl- (Im-0), 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (Ip-0)[3a] and their 4-chloro-derivatives (Im-1, Ip-1),[1,3b] and gained some interesting observations regarding the properties of the pyrimidine portion. In this study the chemical properties of 1-methyl- (IIm-0) and 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5-oxide (IIp-0) were examined.

The 5-oxides (II-0) used in this paper were obtained by condensation-cyclization of 1-methyl- (IIIm-1) or 1-phenyl-5-amino-4-hydroxyiminomethyl-1*H*-pyrazole (IIIp-1) and ethyl ortho-formate. In general, the deoxygenation of heterocyclic N-oxide is effected by

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[1] Part III: T. Higashino, Y. Iwai, and E. Hayashi, *Yakugaku Zasshi*, **96**, 1352 (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).

application of phosphorus trichloride[4] or by catalytic reduction with Raney nickel.[5] Both of the reactions were found to arise and I-0 was obtained from II-0.

The usual N-oxidation of Im-0 or its 4-methoxy derivative (Im-2) with hydrogen peroxide in acetic acid or monoperphthalic acid did not afford their N-oxides (IIm-0,2), and resulted in the recovery to Im-0 or Im-2. But the N-oxidation of 1-methyl-(Im-3) or 1-phenyl-4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidine (Ip-3) with hydrogen peroxide in acetic acid gave their 5-oxides (IIm-3, IIp-3) which were identified by their synthesis from condensation-cyclization of 1-methyl- (IIIm-4) or 1-phenyl-5-amino-1*H*-pyrazole-4-carboxamidoxime (IIIp-4) with ethyl orthoformate. And IIm-3 and IIp-3 showed the depression by the mixed melting point test with 1-methyl- (Im-10) or 1-phenyl-4-hydroxylamino-1*H*-pyrazolo[3,4-*d*]pyrimidine (Ip-10) prepared from another route.[6]

Various reactions usually carried out on heterocyclic N-oxides were then examined on II-0.

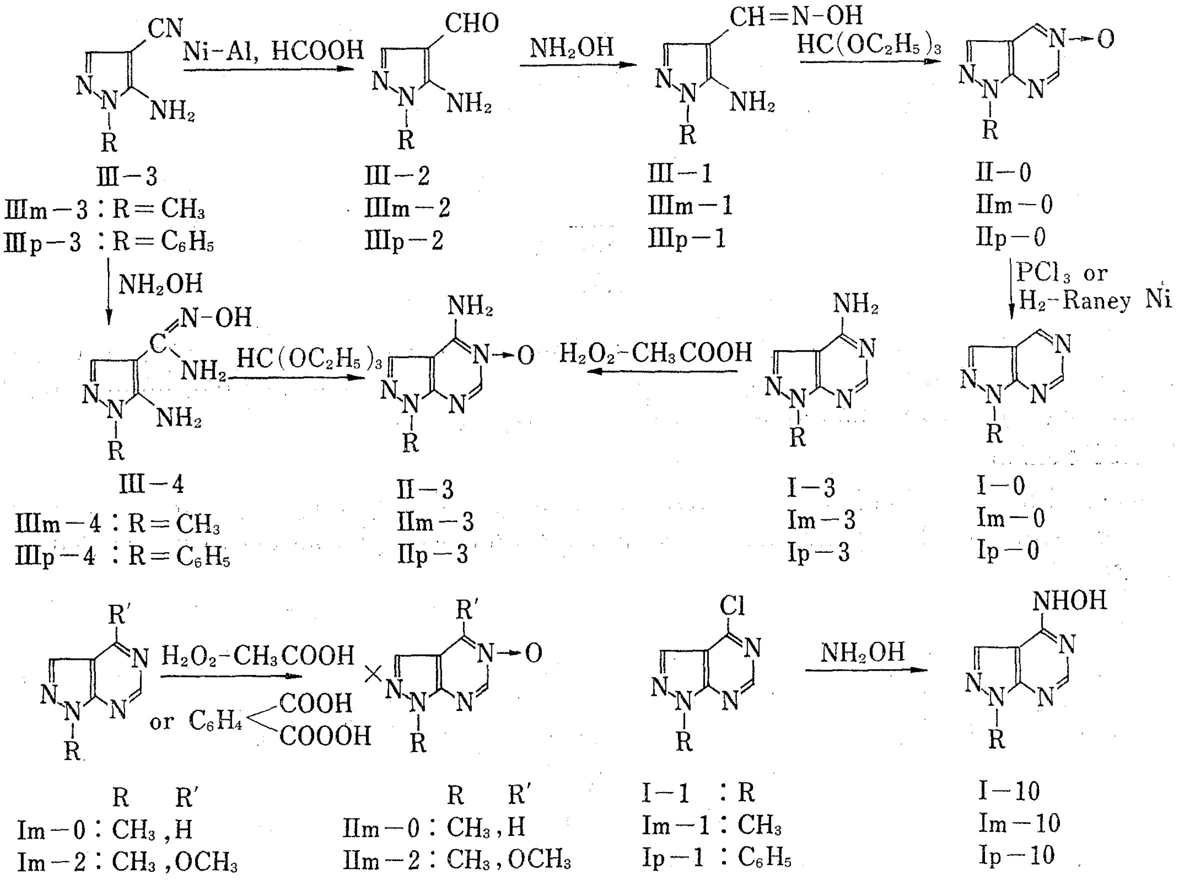

Chart 1

Behavior in Alkaline Solution

When a solution of IIp-0 dissolved in 1N sodium hydroxide was allowed to stand for 20 min at room temperature, the ring fission between the 5- and 6-positions occurred to form 5-formamido-4-hydroxyiminomethyl-1-phenyl-1*H*-pyrazole (IIIp-5). In the case of the reaction for 24 hr, the product was hydrolyzed to result in deformylation and formation of IIIp-1. And this even occurred in passing through a column of alumina with a result that II-0 easily underwent the ring fission to form III-5.

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4) M. Hamana, *Yakugaku Zasshi*, 75, 123 (1955).
5) E. Hayashi, H. Yamanaka, and K. Shimizu, *Chem. Pharm. Bull.* (Tokyo), 7, 141 (1959).
6) J. Druey and P. Schmidt, U.S. Patent, 2965643 (1960) [*Chem. Abstr.* 57, 11211*f* (1962)].

Hydroxide ion used as nucleophilic reagent may attack the 4-position of II-0 to form a type of an intermediate such as 1-substituted 4,5-dihydro-4,5-dihydroxy-1*H*-pyrazolo[3,4-*d*]-pyrimidine (**a**). The excess of hydroxide ion probably attack the 6-position of **a** to form an intermediate (**b**). The successive ring fission between the 5- and 6-positions of **b** results in the formation of III-5 and in the elimination of hydroxide ion. And the resulting hydrolysis of III-5 probably forms III-1, as shown in Chart 2.

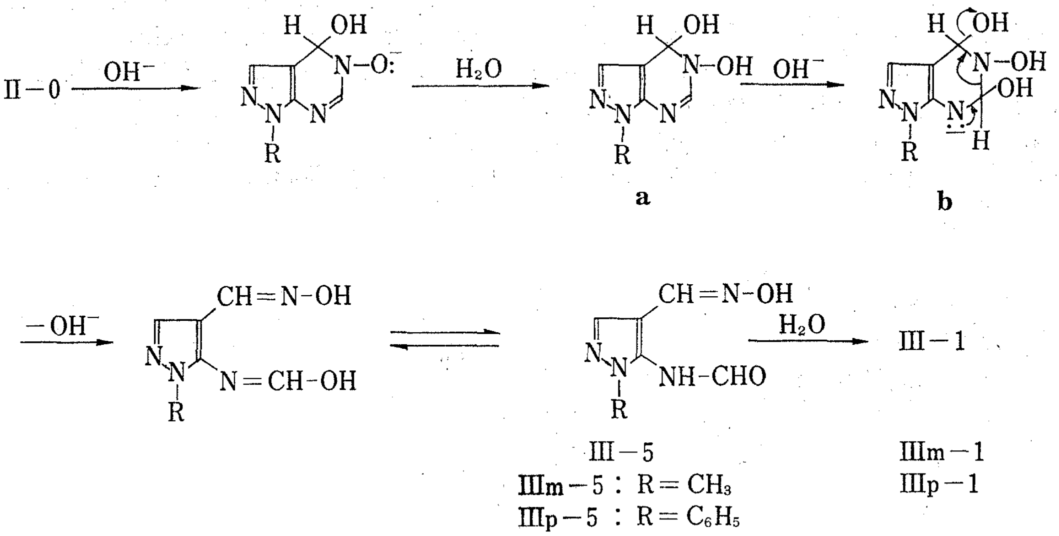

Chart 2

It is also known that the application of hydroxide ion to quinazoline 3-oxide (IV) or pyrido[2,3-*d*]pyrimidine 3-oxide (V) results in the formation of 2′-(hydroxyiminomethyl)-formanilide (VI) or 2-formamidonicotinoaldehyde oxime (VII).[7]

Reissert Reaction

The Reissert reaction is representative reaction by which cyano group is introduced into the 2- or 4-positions by application of cyanide ion and benzoyl chloride to heterocyclic N-oxides.[8]

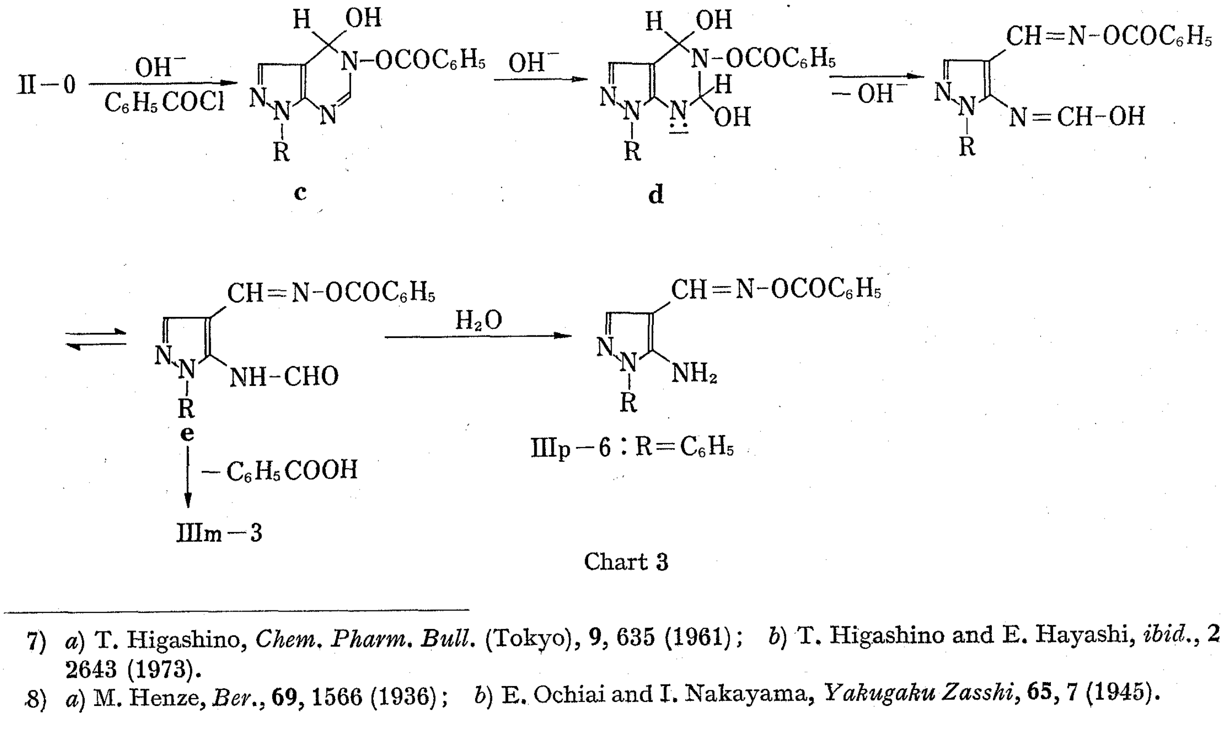

Chart 3

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7) *a*) T. Higashino, *Chem. Pharm. Bull.* (Tokyo), **9**, 635 (1961); *b*) T. Higashino and E. Hayashi, *ibid.*, **21**, 2643 (1973).

8) *a*) M. Henze, *Ber.*, **69**, 1566 (1936); *b*) E. Ochiai and I. Nakayama, *Yakugaku Zasshi*, **65**, 7 (1945).

Application of this reaction to II-0 resulted in the formation of ring fission products such as 5-amino-4-(benzoyloxyiminomethyl)-1-phenyl-1*H*-pyrazole (IIIp-6) and 5-amino-1-methyl-1*H*-pyrazole-4-carbonitrile (IIIm-3). The same ring fission product (IIIp-6) from IIp-0 was obtained by the reaction with hydroxide ion even used instead of cyanide ion. Identity of IIIp-6 was established by its synthesis from IIIp-1 and benzoyl chloride in the presence of hydroxide ion. A similar ring fission on IV by the Reissert reaction has been reported by Higashino.[7a)]

Reaction with Acetic Anhydride

The reaction of heterocyclic N-oxides with acetic anhydride is a representative one by which acetoxyl group is introduced into the 2- or 4-positions to N-oxide group (this acetoxyl group is easily hydrolyzed to hydroxy group).[9)]

The application of this reaction to IIm-0 resulted both in the introduction of the expected hydroxy group in the 4-position and in the deoxygenation of N-oxide proup. On the other

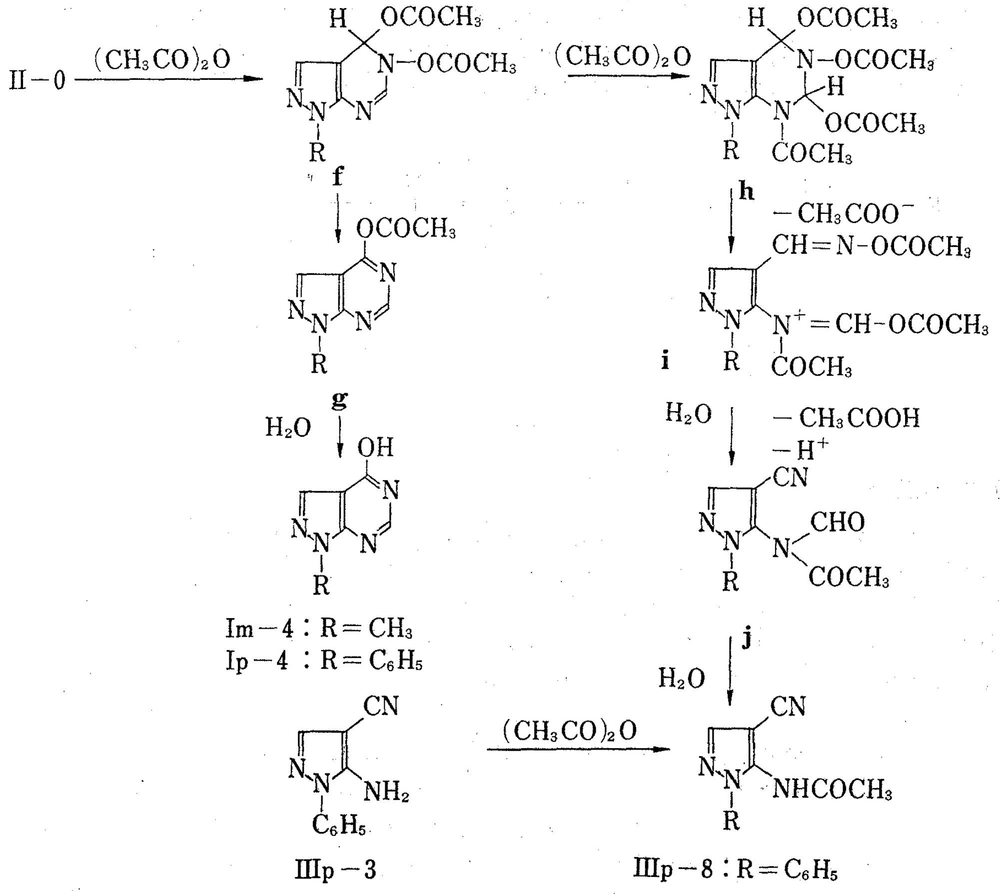


Chart 4

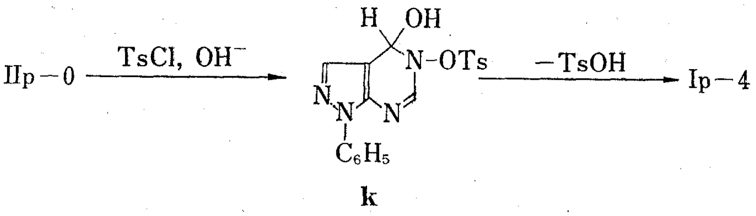


Chart 5

[9)] M. Katada, *Yakugaku Zasshi*, **67**, 51 (1947).

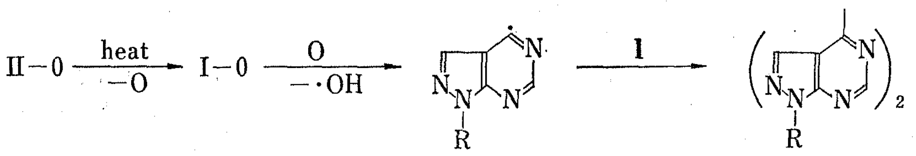
hand the reaction on IIp-0 gave both the expected reaction product, 1-phenyl-1*H*-pyrazolo-[3,4-*d*]pyrimidin-4-ol (Ip-4),[10] and the ring fission product, 5-acetamido-1-phenyl-1*H*-pyrazole-4-carbonitrile (IIIp-8). The identity of IIIp-8 was established by its synthesis from the acetylation of IIIp-3. A similar ring fission has been observed in the reaction of IV with acetic anhydride giving *o*-isocyanobenzonitrile (VIII).[7a]

Reaction with *p*-Toluenesulfonyl (Tosyl) Chloride

The introduction of hydroxy group into the 2- or 4-positions to N-oxide group by use of tosyl chloride and alkali is well known on heterocyclic N-oxides.[11] This reaction on IIp-0 failed to cause the ring fission and gave Ip-4, as shown in Chart 5.

Thermal Decomposition

When II-0 was heated at the temperature near its melting point, an explosive reaction took place and 4,4′-bis[1-substituted 1*H*-pyrazolo[3,4-*d*]pyrimidine] (IX)[12] as a major product was obtained together with I-0 as a minor product. The thermal deoxygenation of N-oxide group of II-0 seems to produce I-0 and the oxygen atom this liberated removes the hydrogen at the 4-position of I-0 by radical course to form pyrazolo[3,4-*d*]pyrimidinyl radical (**1**). The radical **1**, in turn, couples with each other to form IX, as shown in Chart 6.



1 IX

R = CH_3, IXm

C_6H_5 IXp

Chart 6

Grignard Reaction

It has been reported by Kato, *et al.*,[13a,b] that the Grignard reaction of quinoline 1-oxide (X-0) gave 2-alkylquinoline 1-oxide (X-1) as a major product together with 2-alkylquinoline (XI-1) and quinoline (XI-0) as minor products and when this reaction was carried out at low temperature, 2-alkyl-1,2-dihydro-1-hydroxyquinoline (XII) was formed. A similar result has been reported by Hayashi, *et al.*[13c] on 2-phenylquinoxaline 4-oxide (XIII-0) yielding 2-alkyl-3-phenylquinoxaline 1-oxide (XIII-1), 2-alkyl-3-phenylquinoxaline (XIV).

With the expectation that the introduction of alkyl group into the 4-position might take place when II-0 was treated with Grignard reagent, the investigation was carried out and the introduction of the expected alkyl group into the 4-position took place. Thus II-0 formed 4-alkyl derivatives of II-0 (II-5—II-9) with the following Grignard reagents: methylmagnesium iodide, ethyl-, isopropyl-, phenyl-megnesium bromide and benzylmagnesium chloride, although the yields of II-5—II-9 were small in some cases as shown in Chart 7. But each of the reaction of IIm-0 with methylmagnesium chloride or ethyl magnesium bromide did not give 4-methyl- (IIm-5), or 4-ethyl-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5-oxide (IIm-6), and resulted in the recovery of the starting N-oxide (IIm-0). The structures of II-5 to II-9 were indicated by elemental analyses (Table I) and confirmed by nuclear magnetic resonance (NMR) spectra (Table II) and by the conversion of IIm-7, 8, IIp-8 and 9 into the

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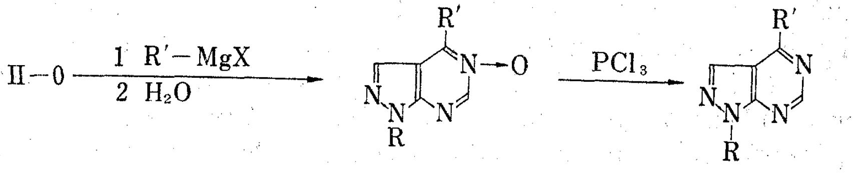
[10] C.C. Cheng and R.K. Robins, *J. Org. Chem.*, **21**, 1240 (1956).

[11] E. Ochiai and T. Yokokawa, *Yakugaku Zasshi*, **75**, 213 (1955).

[12] T. Higashino, M. Goi, and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **24**, 238 (1976).

[13] *a*) T. Kato and H. Yamanaka, *J. Org. Chem.*, **30**, 910 (1965); *b*) T. Kato, H. Yamanaka, and M. Hikichi, *Yakugaku Zasshi*, **85**, 331 (1965); *c*) E. Hayashi and C. Iijima, *ibid.*, **86**, 571 (1966).



-R		-R'	II	%	I	%
$-CH_3$	IIm–0	$-iso-C_3H_7$	IIm–7	10.3	Im–7	trace
$-CH_3$	IIm–0	$-C_6H_5$	IIm–8	trace	Im–8	trace
$-CH_3$	IIm–0	$-CH_2C_6H_5$	IIm–9	8.2	Im–9	—
$-C_6H_5$	IIp–0	$-CH_3$	IIp–5	3.2	Ip–5	—
$-C_6H_5$	IIp–0	$-C_2H_5$	IIp–6	3.7	Ip–6	—
$-C_6H_5$	IIp–0	$-iso-C_3H_7$	IIp–7	12.5	Ip–7	—
$-C_6H_5$	IIp–0	$-C_6H_5$	IIp–8	8.7	Ip–8	6.0
$-C_6H_5$	IIp–0	$-CH_2C_6H_5$	IIp–9	16.7	Ip–9	8.4

Chart 7

TABLE I. 4-Alkyl Derivatives of II-0 (II-5—9)

Compd.	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIm-7a)	179—180	$C_9H_{12}ON_4$	56.23	6.29	29.15	56.71	6.33	28.79
IIm-8b)	219—220	$C_{12}H_{10}ON_4$	63.70	4.46	24.77	63.40	4.24	24.34
IIm-9c)	185d)	$C_{19}H_{15}O_8N_7$	48.62	3.22	20.89	48.43	3.43	20.62
IIp-5b)	213—215	$C_{12}H_{10}ON_4$	63.70	4.46	24.77	63.48	4.39	24.25
IIp-6b)	165—167	$C_{13}H_{12}ON_4$	64.98	5.03	23.32	65.08	5.13	23.20
IIp-7b)	153—155	$C_{14}H_{14}ON_4$	66.12	5.55	22.04	66.76	5.65	21.80
IIp-8b)	255—260	$C_{17}H_{12}ON_4$	70.82	4.20	19.44	70.85	4.27	19.80
IIp-9b)	169—173	$C_{18}H_{14}ON_4$	71.51	4.67	18.53	71.44	4.67	18.57

a) slightly yellow plates b) slightly yellow needles c) yellow oil d) mp of picrate

TABLE II. NMR Spectra of II-0 and II-5—9

Compd.	4–R	NMR (τ) in $CDCl_3$ $1-CH_3^{s}$	$1-C_6H_5^{m}$	$3-H^{s}$	$6-H^{s}$	4-R
IIm-0	-H	5.98		1.87	1.08	0.90^{s} (1×H)
IIm-7	$-CH<^{CH_3}_{CH_3}$	6.06		1.90	1.21	6.00^{sep} (1×H), 8.46^{d} (6×H)
IIm-8	$-C_6H_5$	5.95		1.50	1.11	$1.8—2.8^{m}$ (5×H)
IIm-9	$-CH_2C_6H_5$	6.06		—a)	1.21	5.54^{s} (2×H), $2.6—3.3^{m}$ (5×H)
IIp-0	-H		1.9—2.9	1.82	1.11	1.11^{s} (1×H)
IIp-5	$-CH_3$		1.9—2.9	1.19	1.19	7.20^{s} (3×H)
IIp-6	$-C_2H_5$		1.9—2.9	1.89	1.20	6.75^{q} (2×H), 8.50^{t} (3×H)
IIp-7	$-CH<^{CH_3}_{CH_3}$		1.8—2.8	1.76	1.17	5.88^{sep} (1×H), 8.47^{d} (6×H)
IIp-8	$-C_6H_5$		1.7—2.8	1.83	1.10	$1.7—2.8^{m}$ (5×H)a
IIp-9	$-CH_2C_6H_5$		1.9—3.0	—a)	1.19	5.48^{s} (2×H), $1.9—3.0^{m}$ (5×H)a

a) overlapping with phenyl protons
d: doublet; m:multiplet; s: singlet; sep: septet; q: quartet; t: triplet

corresponding alkyl derivatives of I-0 (Im-7, 8, Ip-8,9) by deoxygenation of N-oxide group with phosphorus trichloride.

Hayashi, *et al.* have shown that the addition of *p*-benzoquinone prior to hydrolysis after heating and refluxing XIII-0 and phenylmagnesium bromide resulted in overwhelming formation of 2,3-diphenylquinoxaline 1-oxide (XIII-1′) over 2,3-diphenylquinoxaline (XIV′).[13c] The application of this oxidation to the reaction mixture of IIp-0 and Grignard reagents caused IIp-5 to 9 to increase in a little amount but not markedly (Table III). In the case of the reaction with benzylmagnesium chloride, 4-benzoyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5-oxide (IIp-10) was formed in stead of 4-benzyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5-oxide (IIp-9). The structure of IIp-10 was indicated by elemental analyses and confirmed by NMR and infrared (IR) spectra. The compound IIp-10 showed the signals due to the hydrogens of the 3- and 6-positions at 1.02 and 1.90τ, respectively, and gave the peak of carbonyl group at 1675 cm^{-1}. The formation process of II-5 to 9 can be illustrated as shown in Chart 8, similar to that proposed by Kato, *et al.*,[13a,b] But it is not clear as yet what substances act as hydride ion acceptor in oxidation step.

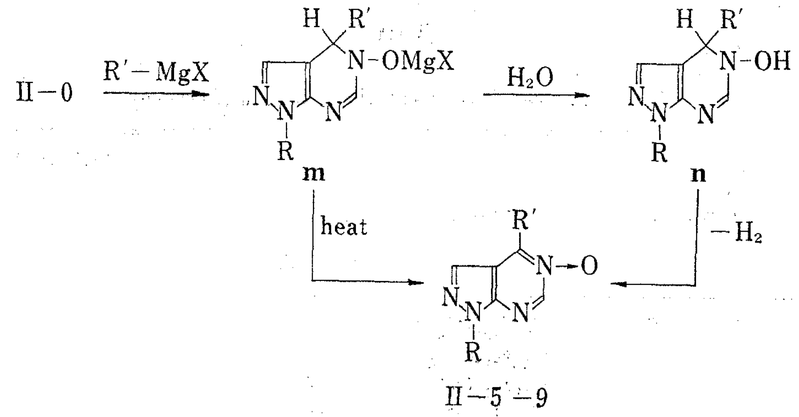


Chart 8

TABLE III. Grignard Reaction of IIp-0 being added with *p*-Benzoquinone

	R′-MgX --R′	Product			
		IIp	Yield(%)	Ip-0	Yield(%)
IIp-0	$-C_2H_5$	IIp-6	5.1		1.6
IIp-0	$-CH\langle^{CH_3}_{CH_3}$	IIp-7	17.3		2.5
IIp-0	$-C_6H_5$	IIp-8	19.7		1.8
IIp-0	$-CH_2C_6H_5$	IIp-9	2.6		1.2

Reaction with Active Methylene Compounds and Ketone

Many of the heterocycles having pyrimidine ring such as quinazoline (XV),[14a] IV,[14b,c] V,[7b,14d] pteridine (XVI)[14e] and 1,2,3-triazolo[4,5-*d*]pyrimidine (XVII)[14f] have been shown to transform pyrimidine ring into pyridine ring by direct reaction with active methylene compounds or ketone. For example, XV reacted with malononitrile to give 2-amino-3-quinolinecarbonitrile (XI-2),[14a] and V and acetophenone gave 2-phenyl-1,8-naphthyridine (XVIII).[14d] As a similar transformation on pyrazolo[3,4-*d*]pyrimidine ring system was expected to take place, we carried out the reaction of I-0 and II-0 with active methylene compounds and ketone, and found that I-0 and II-0 were transformed into pyrazolo[3,4-*b*]pyridine derivatives (XIX) in some cases, although the yield of XIX was small.

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14) *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*) *Idem*, *ibid.*, **23**, 2939 (1975); *e*) A. Albert and H. Mizuno, *J. Chem. Soc.*; *Perkin* I. **1973**, 1615; *f*) A. Albert and W. Pendergast, *ibid.*, *Perkin* I, **1973**, 1620.

Thus the direct reaction of I-0 with active methylene compounds or ketone resulted in the recovery of the starting heterocycle (I-0), but in the presence of ethoxide ion Im-0 reacted with malononitrile to give 6-amino-1-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (XIXm-1).

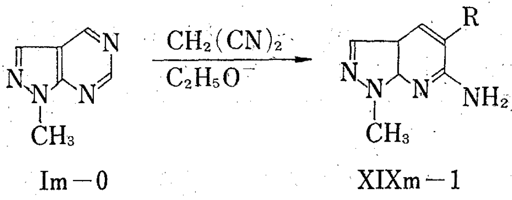
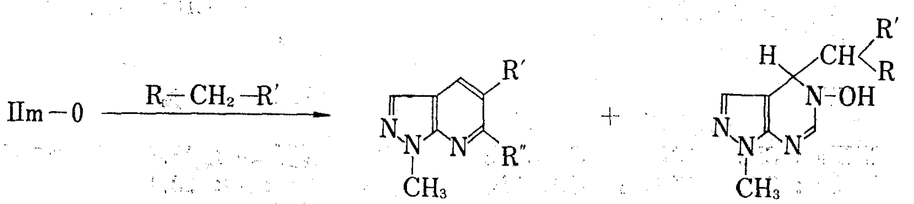


Chart 9

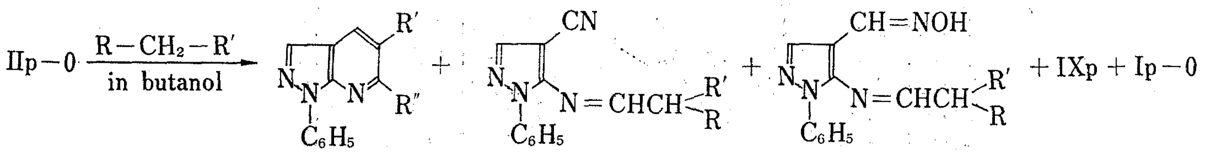
Direct reaction of IIm-0 with active methylene compounds or ketone resulted in the formation of the 4,5-adducts of IIm-0 (XXm) and XIXm. Thus IIm-0 reacted with malononitrile and ethyl cyanoacetate to give 4,5-dihydro-5-hydroxy-1-methyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine-4-malononitrile (XXm-1) and ethyl α-cyano-4,5-dihydro-5-hydroxy-1-methyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine-4-acetate (XXm-2) in good yield. While the reaction with ethyl acetoacetate, acetylacetone and cyclohexanone in butanol gave the corresponding 1-methyl-1*H*-pyrazolo-[3,4-*b*]pyridines (XIXm-3,4,5), respectively. The reaction of IIp-0 with active methylene compounds or ketone in butanol gave 1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridines (XIXp), the ring fission products (XXI-p), IXp and Ip-0. Thus malononitrile reacted with IIp-0 to give 6-amino-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (XIXp-1). Also IIp-0 and ethyl acetoacetate gave ethyl 6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (XIXp-3) together with IXp, ethyl 2-(4-cyano-1-phenyl-1*H*-pyrazol-5-ylaminomethylene)-3-oxobutyrate (XXIp-3) and ethyl 2-(4-hydroxyiminomethyl-1-phenyl-1*H*-pyrazol-5-ylaminomethylene)-3-oxobutyrate (XXIp-3′). In the case of acetylacetone, 5-acetyl-6-methyl-1-



R	R′	XIXm R″		%	XXm	%
CN	CN$^{a)}$				XXm-1	87.0
CN	$COOC_2H_5$$^{a)}$				XXm-2	95.4
$COCH_3$	$COOC_2H_5$$^{b)}$	CH_3	XIXm-3	21.0		—
$COCH_3$	$COCH_3$$^{b)}$	CH_3	XIXm-4	33.0		—
$-CO-(CH_2)_4-$$^{b)}$		$(CH_2)_4-$	XIXm-5	6.6		—

Chart 10

a) in methanol *b*) in butanol

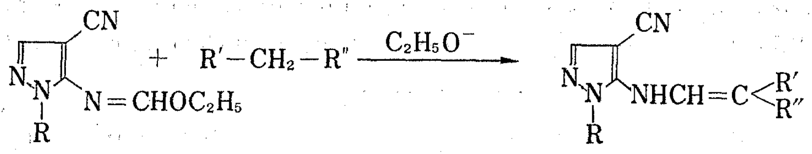


R	R′	XIXp R″		%	XXIp-3 %	XXIp-3′ %	%	%
CN	CN	NH_2	XIXp-1	22.1	—	—	—	—
$COCH_3$	$COOC_2H_5$	CH_3	XIXp-3	3.6	2.9	3.0	42.7	—
$COCH_3$	$COCH_3$	CH_3	XIXp-4	4.2	—	—	7.2	17.4
$CO(CH_2)_4-$				—	—	—	—	43.8
H	COC_6H_5			—	—	—	7.6	12.3

Chart 11

phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (XIXp-4) was formed together with IXp and Ip-0. These compounds (IXp and Ip-0) also obtained from the reaction of IIp-0 with cyclohexanone or acetophenone.

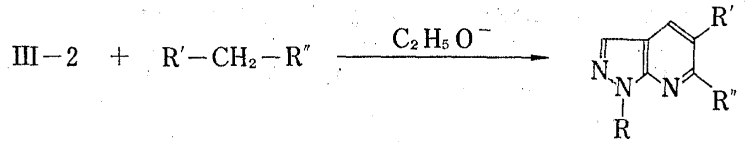
The assignments of XXm-1 and 2 were made on the following bases. Elemental analyses showed that IIm-0 had been combined with malononitrile in a ratio of 1: 1. There were four singlet at 1.40, 1.84, 2.19 and 5.97τ due to hydrogens of the 3-, 6-, 4-positions and 1-methyl group. Signals due to the hydrogens of the α-position and hydroxy group of the 5-position were not recognized because of the deutrium exchange by CF_3COOD used as solvent, in NMR spectrum of XXm-1. Its IR spectrum showed the absorption peaks at 2220 cm^{-1} and 3310 cm^{-1} due to cyano and hydroxy groups. The structure of XXm-2 was indicated by elemental analyses and IR spectrum and was confirmed by NMR spectrum, according to the same assignment used in XXm-1. The compounds XXI were prepared by the condensation with 1-methyl- (XXIIm) or 1-phenyl-5-ethoxymethyleneimino-1*H*-pyrazole-4-carbonitrile (XXIIp) and active methylene compounds in the presence of ethoxide ion (Chart 12). The structure of XIXp-3′ was indicated by elemental analyses and IR spectrum showing the peak of hydroxy group at 3200—2800 cm^{-1} (broad) and that of carbonyl group at 1710 and 1655 cm^{-1}. The compounds XIX were also prepared by the Friedlaender synthesis with III-2 and active methylene compounds or ketone in the presence of ethoxide ion as catalyst (Chart 13).



XXII XXI

XXII	R	R′	R″	XXI	%
XXIIm:	CH_3	CN	$COOC_2H_5$	XXIm-2:	13.8
XXIIm:	CH_3	$COCH_3$	$COOC_2H_5$	XXIm-3:	20.1
XXIIm:	CH_3	$COOC_2H_5$	$COOC_2H_5$	XXIm-4:	29.8
XXIIp:	C_6H_5	$COCH_3$	$COOC_2H_5$	XXIp-5:	27.3

Chart 12



XIX

	R	R′	R″		R‴	%
IIIm-2:	CH_3	CN	CN	XIXm-1:	NH_2	3.6
IIIm-2:	CH_3	$COOC_2H_5$	$COCH_3$	XIXm-3:	CH_3	35.2
IIIm-2:	CH_3	$COCH_3$	$COCH_3$	XIXm-4:	CH_3	trace
IIIm-2:	CH_3	$-CO-(CH_2)_4-$		XIXm-5:	$(CH_2)_4-$	83.0
IIIp-2:	C_6H_5	CN	CN	XIXp-1:	NH_2	78.2
IIIp-2:	C_6H_5	$COOC_2H_5$	$COCH_3$	XIXp-3:	CH_3	95.2
IIIp-2:	C_6H_5	$COCH_3$	$COCH_3$	XIXp-4:	CH_3	83.2
IIIp-2:	C_6H_5	$-CO-(CH_2)_4-$		XIXp-5:	$(CH_2)_4-$	93.5

Chart 13

It is clear that XXIp-3 and 3′ are the ring fission product between the 5- and 6-positions of IIp-0, XXm-1 and 2 are the adduct across the 4—5 bond of IIm-0, and IXp and Ip-0 which were formed by thermalysis are not the products concerned with active methylene compounds or ketone. From the facts that the 4,5-adduct (XXm, II-5—9) and the ring fission products

(III-1,3,5, IIIp-6,8 and XXIp-3) were formed by the reaction of II-0 with several nucleophilic reagents in this paper, the transformation mechanism may be analogous to that of quinazoline ring system into quinolines proposed by Higashino *et al.*[14a,b,c] Thus, the pyrazolo[3,4-*b*]-pyridines (XIX) are probably formed *via* the addition of two moles of active methylene

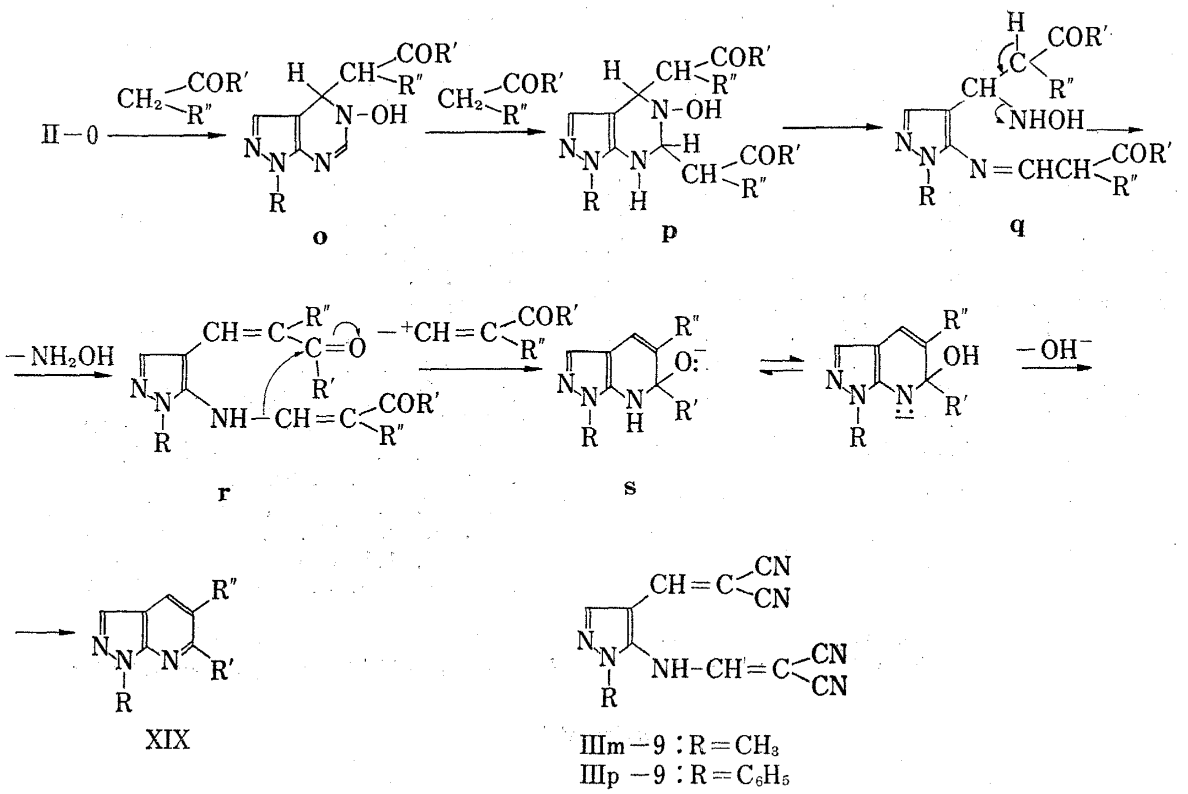


Chart 14

Table IV. Elemental Analyses and IR Spectra of XIX and XXI

Compd.[a]	mp (°C)	Formula	Analysis (%)						IR ν_{max}^{KBr} cm^{-1}:		
			Calcd.			Found					
			C	H	N	C	H	N	-CN	>C=O	-NH$_2$
XIXm-1	252—253	$C_8H_7N_5$	55.48	4.07	40.44	55.20	4.31	40.43	2220		3360 3430
XIXm-3	88—90	$C_{11}H_{13}O_2N_3$	60.26	5.98	19.15	60.26	6.00	19.03		1730	
XIXm-4	80—82	$C_{10}H_{11}ON_3$	63.47	5.86	22.21	63.68	5.91	21.99		1680	
XIXm-5	85—86	$C_{11}H_{13}N_3$	70.56	7.00	22.44	70.83	7.01	22.56			
XIXp-1	232—233	$C_{13}H_9N_5$	66.37	3.86	29.77	66.51	3.94	29.81	2220		3340 3380
XIXp-3	85—86	$C_{16}H_{15}O_2N_3$	68.31	5.38	14.94	68.10	5.46	14.97		1720	
XIXp-4	135—136	$C_{15}H_{13}ON_3$	71.69	5.21	16.72	71.81	5.43	17.03		1680	
XIXp-5	103—104	$C_{16}H_{15}N_3$	77.08	6.06	16.86	76.84	5.95	16.76			
XXIm-2	219—220	$C_{11}H_{11}O_2N_5$	53.87	4.52	28.56	53.64	4.66	28.75	2205 2220	1640 1730	
XXIm-3	111—112	$C_{12}H_{14}O_3N_4$	54.95	5.38	21.37	54.84	5.37	21.39	2230	1645 1720	
XXIm-4	125—126	$C_{13}H_{16}O_4N_4$	53.42	5.52	19.17	53.45	5.47	19.23	2225	1655 1730	
XXIp-3	137—138	$C_{17}H_{16}O_3N_4$	62.95	4.97	17.28	63.11	5.12	17.15	2240	1650 1730	

a) colourless needles

compounds or ketone across the 4—5 and 6—7 bonds and ring fission between the 5- and 6-positions, and subsequent cyclization involving loss of N-5 and C-6 atoms, as shown in Chart 14. But the likely intermediate such as [[1-methyl- (IIIm-9) or 1-phenyl-5-[(2,2-dicyanovinyl)-amino]-1*H*-pyrazol-4-yl]methylene]malononitrile (IIIp-9) was not isolated.

TABLE V. NMR Spectra of XIX and XXI

Compd.	NMR (τ) in $CDCl_3$				
	$1\text{-}CH_3^{s}$	$1\text{-}C_6H_5^{m}$	$3\text{-}H^{s}$	$4\text{-}H^{s}$	Other
XIXm-1[a]	5.83		1.73	1.41	
XIXm-3	5.90		2.09	1.44	$7.10^{s}(-CH_3)$, 5.63^{q}, $8.59^{t}(-OC_2H_5)$
XIXm-4	5.98		2.18	1.77	$7.24^{s}(-CH_3)$, $7.44^{s}(-COCH_3)$
XIXm-5	6.00		2.50	2.32	$6.7—7.4^{m}$, $7.8—8.5^{m}(-(CH_2)_4-)$
XIXp-1[b]		1.6—3.2	1.84	1.52	$1.6—3.2^{bs,c}(-NH_2)$
XIXp-3		1.4—2.8	1.77	1.25	$7.02^{s}(-CH_3)$, 5.55^{q}, $8.57^{t}(-OC_2H_5)$
XIXp-4		1.3—2.8	1.76	1.48	$7.08^{s}(-CH_3)$, $7.33^{s}(-COCH_3)$
XIXp-5		1.4—2.8	2.17	1.93	$6.6—7.4^{m}$, $7.7—8.4^{m}(-(CH_2)_4-)$
XXIm-2[a]	6.09		2.14		$1.74^{s}(-N-CH=)$, 5.67^{q}, $8.67^{t}(-OC_2H_5)$
XXIm-3	6.20		2.40		$-3.35^{bd,c}$, $1.39^{d}(-NHCH=$, $J=11.4$ cps), $7.44^{s}(-COCH_3)$, 5.79^{q}, $8.66^{t}(-OC_2H_5)$
XXIm-4	6.21		2.42		$-1.30^{bd,c}$, $1.46^{d}(-NHCH=$, $J=12.0$ cps), 5.71^{q}, 5.80^{q}, 8.61^{t}, $8.69^{t}(2\times-OC_2H_5)$
XXIp-3		2.3—2.9	2.12		$-2.90^{bd,c}$, $1.19^{d}(-NHCH=$, $J=12.0$ cps), $7.47^{s}(-COCH_3)$, 5.73^{q}, $8.67^{t}(-OC_2H_5)$

a) in CF_3COOD *b*) in $SO(CD_3)_2$
bd: broad doublet; bs: broad singlet; c: exchangeable with D_2O; d: doublet; m: multiplet; q: quartet; s: singlet; t: triplet

Experimental[15]

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

1-Methyl (IIIm-2) and 1-Phenyl-5-amino-1*H*-pyrazole-4-carboxaldehyde (IIIp-2)——A mixture of 12.20 g of 5-amino-1-methyl-1*H*-pyrazole-4-carbonitrile (IIIm-3),[10] 120 ml of 75% formic acid and 12.0 g of Raney nickel alloy was refluxed for 1 hr. The warm reaction mixture was filtered off, and formic acid was removed from the filtrate under the reduced pressure to give resinous substances which were dissolved in 25% NH_4OH. The NH_4OH solution was extracted with ether and the ether solution was dried over anhyd. Na_2SO_4. Evaporation of ether gave crude IIIm-2. Recrystallization of crude IIIm-2 from MeOH gave yellow prisms, mp 148—149°, in 26.9% yield (3.36 g). *Anal.* Calcd. for $C_5H_7ON_3$ (5-amino-1-methyl-1*H*-pyrazole-4-carboxaldehyde): C, 47.99; H, 5.64; N, 33.58. Found: C, 48.34; H, 5.58; N, 33.98. IR ν_{max}^{KBr} cm^{-1}: 1650 ($>C=O$), 3320, 3420 ($-NH_2$). NMR (in $CDCl_3$) τ: 0.40 (1H, singlet, $-CH=O$), 2.42 (1H, singlet, H-3), 6.40 (3H, singlet, $N-CH_3$), 4.7 (2H, broad singlet, $-NH_2$).

The treatment of a mixture of 18.40 g of 5-amino-1-phenyl-1*H*-pyrazole-4-carbonitrile (IIIp-3),[10] 120 ml of 75% formic acid and 12.0 g of Raney nickel alloy by the same manner described above gave IIIp-2, mp 120—121° as yellow plates from benzene, in 72.2% yield (13.5 g). *Anal.* Calcd. for $C_{10}H_9ON_3$ (5-amino-1-phenyl-1*H*-pyrazole-4-carboxaldehyde): C, 64.16; H, 4.85; N, 22.45. Found: C, 64.09; H, 4.81; N, 22.37. IR ν_{max}^{KBr} cm^{-1}: 1660 ($>C=O$), 3320, 3440 ($-NH_2$). NMR (in $CDCl_3$) τ: 0.49 (1H, singlet, $-CH=O$), 2.38 (1H, singlet, H-3), 2.5—2.9 (5H, multiplet, $-C_6H_5$), 4.17 (2H, broad singlet, $-NH_2$).

IIIm-1 and IIIp-1——A solution of 13.90 g of $NH_2OH \cdot HCl$ in 50 ml of MeOH and 3.50 g of Na dissolved in 50 ml of MeOH was added to a solution of 12.50 g of IIIm-2 in 100 ml of MeOH, and the reaction mixture was allowed to stand for 24 hr at room temperature. MeOH was removed under the reduced pressure and H_2O was added to the residue. Recrystallization of separated crystals from H_2O gave IIIm-1, mp 165—166° as colorless prisms, in 74.3% yield (10.40 g). *Anal.* Calcd for $C_5H_8ON_4$ (5-amino-4-hydroxyiminomethyl-1-methyl-1*H*-pyrazole): C, 42.85; H, 5.75; N, 39.98. Found: C, 42.93; H, 5.60; N, 40.17. NMR (in $CDCl_3$) τ: 0.0 (1H, broad singlet, $=N-OH$), 2.06 (1H, singlet, $-CH=N-O$), 2.80 (1H, singlet, H-3), 4.22 (2H, broad singlet, $-NH_2$), 6.45 (3H, singlet, $-CH_3$).

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15) All melting points are not corrected.

The treatment of a mixture of 18.70 g of IIIp-2 in 50 ml of MeOH, 13.9 g of $NH_2OH\cdot HCl$ in 50 ml of MeOH and 3.50 g of Na dissolved in 50 ml of MeOH by the same manner described above gave IIIp-1, mp 190—191° as slightly yellow prisms from MeOH, in 63.9% yield (12.90 g). *Anal.* Calcd. for $C_{10}H_{10}ON_4$ (5-amino-4-hydroxyiminomethyl-1-phenyl-1*H*-pyrazole): C, 59.39; H, 4.98; N, 27.71. Found: C, 59.63; H, 5.01; N, 27.70. NMR (in $CDCl_3$) τ: -2.0 (1H, broad singlet, =N–OH), 1.97 (1H, singlet, –CH=N–O), 2.3—2.8 (6H, multiplet, $-C_6H_5$ and H-3), 4.90 (2H, broad singlet, $-NH_2$).

Preparation of IIm-0 and IIp-0——A mixture of 14.00 g of IIIm-1 and 148 g of ethyl orthoformate was refluxed for 1 hr. After cooling the separated crystals were collected by suction. Recrystallization of the crystals from MeOH gave IIm-0, mp 187—189° as yellow needles, in 39.3% yield (5.89 g). *Anal,* Calcd. for $C_6H_6ON_4$ (1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5-oxide): C, 48.00; H, 4.03; N, 37.32. Found: C, 48.47; H, 4.07; N, 37.34. NMR spectrum of IIm-0 is shown in Table II.

The treatment of a mixture of 20.20 g of IIIp-1 and 148 g of ethyl orthoformate by the same manner described above gave IIp-0, mp 195—196° as yellow needles from EtOH, in 38.3% yield (8.11 g). *Anal.* Calcd. for $C_{11}H_8ON_4$ (1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5-oxide): C, 62.25; H, 3.80; N, 26.40. Found: C, 61.83; H, 3.77; N, 26.78. NMR spectrum of IIp-0 is shown in Table II.

Deoxygenation of II-0——i) To a solution of 751 mg of IIm-0 dissolved in 20 ml of $CHCl_3$, 1370 mg of PCl_3 was gradually added with shaking under cooling and the reaction mixture was refluxed for 1 hr. The reaction mixture was poured into a large amount of H_2O–ice mixture, neutralized with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4. Evaporation of $CHCl_3$ gave 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (Im-0), mp 124—125° as colorless needles from petr. ether, in 43.9% yield (294 mg). The compound (IIm-0) was identified by the mixed melting point test with the authentic specimen prepared from another route.[10]

The treatment of a mixture of 1006 mg of IIp-0 and 1370 mg of PCl_3 in 20 ml of $CHCl_3$ by the same manner used in IIm-0 gave Ip-O, mp 79—80°, as colorless needles from petr. ether, in 40.8% yield (379 mg). The compound (Ip-0) was identified by the mixed melting point test with the authentic specimen prepared from another route.[3a]

ii) Raney Ni prepared from 1000 mg of Ni-Al alloy was added to 751 mg (0.005 mole) of IIm-0 in 15 ml of MeOH and the mixture was shaken in H_2 stream. The reaction was stopped when 0.005 mole of H_2 (110 ml) had been absorbed. The catalyst was filtered off, and the filtrate was evaporated to afford Im-0 in 71.7% yield (481 mg).

The reduction of 1006 mg of IIp-0 over Raney Ni catalyst by the same manner described above afforded Ip-0 in 81.2% yield (755 mg).

Preparation of IIm-3 and IIp-3——i) A solution of 14.90 g of Im-3 and 30 ml of 30% H_2O_2 in 100 ml of AcOH was allowed to stand overnight at room temperature. AcOH was removed under the reduced pressure and the separated crystals were recrystallized from H_2O to give IIm-3, mp 155—156° as colorless needles, in 52.5% yield (9.60 g). *Anal.* Calcd. for $C_6H_7ON_5\cdot H_2O$ (4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5-oxide hydrate): C, 39.34; H, 4.95; N, 38.24. Found: C, 39.45; H, 5.07; N, 38.69.

The N-oxidation of 2.12 g of Ip-3 with 30 ml of 30% H_2O_2 in AcOH by the same manner described above afforded IIp-3, mp above 250° as colourless needles from H_2O, in 50.2% yield (1.14 g). *Anal.* Calcd. for $C_{11}H_9ON_5$ (4-amino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5-oxide): C, 58.14; H, 3.99; N, 30.82. Found: C, 58.30; H, 4.29; N, 31.11.

ii) A mixture of 3.10 g of IIIm-4 and 29.60 g of ethyl orthoformate was refluxed for 1 hr. After cooling the separated crystals were collected by suction and recrystallized from H_2O to give IIm-3 in 44.1% yield (1.61 g).

The treatment of a mixture of 4.35 g of IIIp-4 and 29.60 g of ethyl orthoformate by the same manner described above gave IIp-3 in 25.3% yield (1.15 g).

Preparation of IIIm-4 and IIIp-4——To a solution of 8.33 g of $NH_2OH\cdot HCl$ in 150 ml of EtOH and 2.53 g of Na dissolved in 50 ml of EtOH, 12.20 g of IIIm-3 was added, and the reaction mixture was refluxed for 2 hr. EtOH was removed under the reduced pressure and the separated crystals were collected by suction, washed with H_2O and recrystallized from EtOH to give IIIm-4, mp 174—175° as yellow prisms, in 34.9% yield (5.40 g). *Anal.* Calcd. for $C_5H_9ON_5$ (5-amino-1-methyl-1*H*-pyrazole-4-carboxamidoxime): C, 38.70; H, 5.85; N, 45.14. Found: C, 38.39; H, 5.75; N, 44.62.

The treatment of 9.20 g of IIIp-3 with $NH_2OH\cdot HCl$ by the same manner described above gave IIIp-4, mp 180—181° as colorless prisms from $CHCl_3$, in 59.6% yield (6.46 g). *Anal.* Calcd. for $C_{10}H_{11}ON_5$ (5-amino-1-phenyl-1*H*-pyrazole-4-carboxamidoxime): C, 55.29; H, 5.10; N, 32.24 .Found: C, 55.20; H, 5.42; N, 32.38.

Preparation of Im-10——To a solution of 2.09 g of $NH_2OH\cdot HCl$ in 30 ml of EtOH and 0.46 g of Na in 10 ml of EtOH, 1.68 g of 4-chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (Im-1)[10] was added and stirred for 1 hr at room temperature. The separated crystals were collected by suction and recrystallized from MeOH to give Im-10, mp 215—216° as white needles, in 77.5% yield (1.27 g). *Anal.* Calcd. for $C_6H_7ON_5$ (4-hydroxylamino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine): C, 43.63; H, 4.27; N, 42.41. Found: C, 43.82; H, 4.49; N, 42.08.

N-Oxidation of Im-0 and Im-2——i) A solution of 0.01 mole (1.34 g) of Im-0 and 6.0 ml of 30% H_2O_2 in 50 ml of AcOH was allowed to stand overnight at room temperature. The reaction mixture was poured into

30 ml of H_2O, and AcOH was removed under the reduced pressure. The separated oily substance was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4 and evaporation of $CHCl_3$ recovered the starting Im-0 in 90.1% yield (1.20 g).

N-oxidation of 0.01 mole (1.64 g) of Im-2 by the same manner described above recovered Im-2 in 87.6% yield (1.43 g).

ii) To a solution of 0.02 mole (2.68 g) of Im-0 in 50 ml of ether, 8 ml of monoperphthalic acid–ether solution (1 ml contains 0.05 g of active oxygen) was added and the reaction mixture was allowed to stand overnight at room temperature in a dark place. After removing ether the reaction mixture was decomposed with 10% K_2CO_3. The alkaline mixture was extracted with $CHCl_3$ and dried over anhyd. Na_2SO_4. Evaporation of $CHCl_3$ gave the starting Im-0 in 75.8% yield (3.03 g).

The treatment of 0.02 mole (3.28 g) of Im-2 by the same manner described above recovered the starting Im-2 in 78.4% yield (2.57 g).

Reaction of II-0 with 1N Sodium Hydroxide Solution——i) A solution of 150 mg of IIm-0 and 2 ml of 1N NaOH was allowed to stand at room temperature for 24 hr. The reaction mixture was neutralized with 10% AcOH under cooling to separate the crystals which were collected by suction. Recrystallization from MeOH gave IIIm-1, mp 165—166° as colorless prisms, in 21.4% yield (29.9 mg).

The treatment of 212 mg of IIp-0 with 1N NaOH by the same manner described above gave IIIp-1, mp 190—191° as colorless prisms from MeOH, in 54.4% yield (110 mg).

ii) A solution of 106 mg of IIp-0 and 1 ml of 1N NaOH was allowed to stand at room temperature for 20 min. The reaction mixture was neutralized with 10% AcOH to separate the crystals which were collected by suction. Recrystallization from benzene–MeOH mixture gave IIIp-5, mp 156—157° as white needles, in 73.9% yield (85.0 mg). *Anal.* Calcd. for $C_{11}H_{10}O_2N_4$ (5-formamido-4-hydroxyiminomethyl-1*H*-pyrazole): C, 57.38; H, 4.38; N, 24.34. Found: C, 57.34; H, 4.54; N, 24.50. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3540 (>NH), 3200 (–OH), 1675 (>C=O).

Reaction of II-0 with H_2O absorbed in Alumina Column——A solution of 150 mg of IIm-0 in 5 ml of $CHCl_3$ was passed through a column of alumina. The elution with MeOH gave IIIm-5, mp 167—168° as colorless needles from MeOH, in 72.6% yield (122 mg). *Anal.* Calcd. for $C_6H_8O_2N_4$ (5-formamido-4-hydroxyiminomethyl-1-methyl-1*H*-pyrazole): C, 42.85; H, 4.80; N, 33.32. Found: C, 42.66; H, 5.01; N, 33.61. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2900—3300 (–OH and >NH, broad band), 1720 (>C=O).

The treatment of 50 mg of IIp-0 by the same manner described above gave IIIp-5, mp 156—157° as colorless needles from benzene–MeOH mixture, in 66.0% yield (36 mg).

Hydrolysis of III-5——A solution of 90 mg of IIIm-5 dissolved in 1 ml of 2N NaOH was heated at 90—93° for 20 min. The reaction mixture was neutralized with 10% AcOH. The separated crystals were recrystallized from H_2O to give IIIm-1 in 58.6% yield (75 mg).

The same hydrolysis of 83 mg of IIIp-5 gave IIIp-1 in 68.1% yield (49 mg).

Reissert Reaction of II-0——A mixture of 751 mg of IIm-0, 844 mg of benzoyl chloride and 488 mg of KCN dissolved in 2 ml of H_2O was shaken for 4 hr. After allowing to stand overnight, the oily substances were extracted with $CHCl_3$ and the $CHCl_3$ solution was washed with 2N NaOH. After drying over anhyd. Na_2SO_4, the extract was passed through a column of alumina to remove impurities. Recrystallization from MeOH afforded IIIm-3,[10] mp 222—230° as yellow needles, in 10.8% yield (66 mg).

The treatment of a mixture of 370 mg of IIp-0, 340 mg of benzoly chloride and 160 mg of KCN in 2 ml of H_2O by the same manner described above gave IIIp-6, mp 181—182° as colorless needles from benzene, in 21.5% yield (115 mg). *Anal.* Calcd. for $C_{17}H_{14}O_2N_4$ (5-amino-4-benzoyloxyiminomethyl-1-phenyl-1*H*-pyrazole): C, 66.65; H, 4.61; N, 18.29. Found: C, 66.42; H, 4.79; N, 18.41. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3420, 3300 (–NH_2), 1730 (>C=O).

Preparation of IIIp-6——A mixture of 101 mg of IIIp-1, 20 ml of 2N NaOH and 72 mg of benzoyl chloride was vigorously shaken for 2 hr. The reaction mixture was extracted with $CHCl_3$ and dried over anhyd. Na_2SO_4. Evaporation of $CHCl_3$ gave IIIp-6 in 17.7% yield (26 mg).

Reaction of IIp-0 with Benzoyl Chloride in the Presence of Hydroxide Ion——A mixture of 370 mg of IIp-0, 340 mg of benzoyl chloride and 5 ml of 1N NaOH was vigorously shaken for 4 hr. After allowing to stand overnight, the reaction mixture 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 benzene gave IIIp-6 in 16.5% yield (88 mg).

Reaction of IIm-0 with Ac_2O——A mixture of 751 mg of IIm-0 and 2 ml of Ac_2O was refluxed for 20 min. The reaction mixture was poured into 20 ml of H_2O and neutralized with K_2CO_3 to separate the crystals. Recrystallization from MeOH gave Im-4, mp above 260°,[10] in 20.8% yield (156 mg).

Reaction of IIp-0 with Ac_2O——A mixture of 424 mg of IIp-0 and 1.3 ml of Ac_2O was heated at 90—93° for 1.5 hr. After allowing to stand overnight at room temperature, the separated crystals were filtered off and recrystallized from MeOH to give Ip-4,[10] mp 297—299° as colorless needles, in 8.7% yield (37 mg). After removing Ac_2O from the filtrate under the reduced pressure, the residue was neutralized with 50% K_2CO_3 and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and passed through a column of alumina to remove impurities. Recrystallization from benzene–MeOH mixture gave IIIp-8, mp 157—158° as colorless needles, in 19.0% yield (86 mg). *Anal.* Calcd. for $C_{12}H_{10}ON_4$ (5-acetamido-1-phenyl-1*H*-pyrazole-4-carbonitrile): C, 63.70; H, 4.46; N, 24.77. Found: C, 63.66; H, 4.21; N, 24.85. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3200 (>NH), 2240 (–CN), 1690 (>C=O).

Preparation of IIIp-8——A mixture of 100 mg of IIIp-3 and 1 ml of Ac_2O was heated at 90—93° for 1 hr. The reaction mixture was poured into 10 ml of H_2O. The separated crystals were recrystallized from benzene–MeOH mixture to give IIIp-8 in 28.1% yield (34 mg).

Reaction of IIp-0 with Tosyl Chloride——A solution of 1060 mg of IIp-0 and 950 mg of tosyl chloride in $CHCl_3$ was refluxed for 1 hr. The reaction mixture was neutralized with 2N K_2CO_3 and shaken vigorously for 10 min. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4 and evaporation of $CHCl_3$ gave Ip-4[10]) in 32.3% yield (342 mg).

Thermal Decomposition of II-0——When 150 mg of IIm-0 was heated at 170° for 5 min, Im-0[10]) (trace) sublimed. The residue was recrystallized from MeOH to give IXm,[12]) mp 288—289° as yellow needles, in 35.3% yield (47 mg). The compound (IXm) was identified by the mixed melting point test with the authentic specimen prepared from another route.[12])

When 300 mg of IIp-0 was heated at 200°, the explosive reaction took place and Ip-0 (trace) sublimed. The residue was recrystallized from MeOH to give IXp,[12]) mp above 300° as yellow needles, in 30.5% yield (84 mg). IR spectrum of IXp coresponded to that of the authentic specimen prepared from another route.[12])

Grignard Reaction of II-0——i) Grignard reagent was prepared by the usual method from 365 mg of Mg and 0.010 mole of alkyl halide in 30 ml of ether. This solution was added in small portions with shaking to a solution of 0.005 mole of II-0 in 25 ml of dioxane and refluxed for 1 hr. The reaction mixture was poured into a solution of 20 g of NH_4Cl, 4 ml of 25% NH_4OH and 70 ml of H_2O, and stirred for 30 min. The reaction mixture was extracted with $CHCl_3$ and dried over anhyd. Na_2SO_4. The residue obtained by evaporation of $CHCl_3$ was recrystallized from benzene or MeOH. The yields of II-5-9 were listed in Chart 7, and melting points, elemental analyses and NMR spectra were in Table I and II, respectively.

ii) Grignard reagent was prepared by the usual method from 182 mg of Mg and 0.005 mole of alkyl halide in 10 ml of ether. This solution was added in a small portions with shaking to a solution of 530 mg (0.0025 mole) of IIp-0 in 20 ml of dioxane. The reaction mixture was refluxed for 1 hr. And then a solution of 270 mg (0.0025 mole) of *p*-benzoquinone in 10 ml of ether was added and refluxed for 1 hr. The reaction mixture was poured into a solution of 20 g of NH_4Cl, 4 ml of 25% NH_4OH and 70 ml of H_2O, stirred for 30 min, and extracted with $CHCl_3$. After drying over anhyd. Na_2SO_4, $CHCl_3$ was removed by distillation and the resulting crystals were passed through a column of silicic acid. The elution with benzene gave Ip-0.[3a]) The elution with $CHCl_3$ gave IIp-6-8. The yields of II-6-8 were listed in Table III.

In the case of the reaction with benzylmagnesium chloride, IIp-10, mp 183—188° as orange needles from MeOH, was obtained from the elution with $CHCl_3$ (Table III). *Anal.* Calcd. for $C_{18}H_{12}O_2N_4$ (4-benzoyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5-oxide): C, 68.35; H, 3.82; N, 17.71. Found: C, 68.50; H, 3.91; N, 17.46. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1675 (>C=O). NMR (in $CDCl_3$) τ: 1.02 (1H, singlet, H-6), 1.90 (1H, singlet, H-3), 1.7—2.8 (10H, multiplet, $2\times$–C_6H_5).

Deoxygenation of IIm-7, 8, IIp-8 and 9——To a solution of 0.001 mole of the 5-oxide (IIm-7, 8, IIp-8, 9) dissolved in 4 ml of $CHCl_3$, 0.002 mole of PCl_3 in 1 ml of $CHCl_3$ was gradually added with shaking under cooling. The treatment of the reaction mixture by the same manner described in deoxygenation of II-0 with PCl_3 gave the corresponding 1-methyl- (Im-7,8) or 1-phenyl-4-alkyl-1*H*-pyrazolo[3,4-*d*] pyrimidines (Ip-8,9).[3a]) The yields of these compounds are listed in Chart 7.

Reaction of Im-0 with Malononitrile in the Presence of Ethoxide Ion——A mixture of 268 mg (0.002 mole) of Im-0, 264 mg (0.004 mole) of malononitrile and sodium ethoxide solution (460 mg of Na dissolved in 20 ml of EtOH) was refluxed for 1 hr. The reaction mixture was neutralized with 10% AcOH. Evaporation of EtOH gave XIXm-1, mp 252—253° as colorless needles from MeOH, in 63.2% yield (219 mg).

Reaction of IIm-0 with Malononitrile and Ethyl Cyanoacetate——A mixture of 750 mg (0.005 ml) of IIm-0 and 660 mg (0.01 mole) of malononitrile in 7.5 ml of MeOH was allowed to stand overnight. The separated crystals were collected and recrystallized from MeOH to give XXm-1, mp 138—139° (decomp.) as yellow prisms, in 87.0% yield (940 mg). *Anal.* Calcd. for $C_9H_8ON_6$ (4,5-dihydro-5-hydroxy-1-methyl-1*H*-pyrazolo-[3,4-*d*]pyrimidine-4-malononitrile): C, 50.00; H, 3.73; N, 38.88. Found: C, 49.64; H, 3.99; N, 39.03. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2220 (–CN), 3310 (–OH). NMR (in CF_3COOD) τ: 1.40 (1H, singlet, H-3), 1.84 (1H, singlet, H-6), 2.19 (1H, singlet, H-4), 5.97 (3H, singlet, N-CH_3).

The same reaction used 750 mg (0.005 mole) of IIm-0 and 1110 mg (0.010 mole) of ethyl cyanoacetate gave XXm-2, mp 149—150° as yellow needles from EtOH, in 95.4% yield (1255 mg). *Anal.* Calcd. for $C_{11}H_{13}O_3N_5$ (ethyl α-cyano-4,5-dihydro-5-hydroxy-1-methyl-1*H*-pyrazolo[3,4-*d*] pyrimidine-4-acetate): C, 50.18; H, 4.98; N, 26.61. Found: C, 50.20; H, 5.05; N, 26.74. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3310 (–OH), 2220 (–CN), 1700 (>C=O), NMR (in CF_3COOD) τ: 1.32 (1H, singlet, H-3), 2.74 (1H, singlet, H-6), 2.78 (1H, singlet, H-4), 5.55 (2H, quartet, –$\underline{CH_2}$–CH_3), 5.95 (3H, singlet, N–CH_3), 8.57 (3H, triplet, –CH_2–$\underline{CH_3}$).

Reaction of IIm-0 with Active Methylene Compounds or Ketone——A solution of 300 mg (0.002 mole) of IIm-0 and 0.004 mole of active methylene compounds or ketone in 20 ml of BuOH was refluxed for 24 hr. BuOH was removed under the reduced pressure and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was passed through a column of alumina to remove impurities. Recrystallization from petr. ether gave the

5,6-disubstituted 1-methyl-1*H*-pyrazolo[3,4-*d*]pyridines (XIXm-3, 4, 5), as colorless needles. The yields of XIXm-3, 4, and 5 are listed in Chart 10, and the melting points are shown in Table IV.

Reaction of IIp-0 with Active Methylene Compounds or Ketone——i) A solution of 424 mg (0.002 mole) of IIp-0 and 0.004 mole of active methylene compounds or ketone in 20 ml of BuOH was refluxed for 24 hr. The reaction mixture was allowed to stand overnight to separate IXp.[12] BuOH was removed from the filtrate under the reduced pressure and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was extracted with 2N NaOH. The NaOH layer was neutralized with AcOH and extracted with $CHCl_3$. The extract was passed through a column of alumina. The elution with benzene gave XXIp-3, mp 137—138° as colorless needles from MeOH. The elution with MeOH gave XXIp-3′, mp 172—173° as slightly yellow needles from MeOH. *Anal.* Calcd. for $C_{17}H_{18}O_4N_4$ (ethyl 2-(4-hydroxyiminomethyl-1-phenyl-1*H*-pyrazol-5-ylamino-methylene)-3-oxobutyrate): C, 59.64; H, 5.30; N, 16.37. Found: C, 59.70; H, 5.40; N, 16.15. IR ν_{max}^{KBr} cm^{-1}: 3200—2800 (–OH), 1710, 1655 (>C=O).

The $CHCl_3$ solution (insoluble in 2N NaOH) was dried over anhyd. Na_2SO_4, and passed through a column of alumina. From the elution with petr. ether the 5,6-disubstituted 1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridines (XIXp-1, 3, 4), as colorless needles from petr. ether. The elution with benzene gave Ip-0.[3a)]

The yields of the reaction products are listed in Chart 11, and the melting points and IR spectra of XIXp and XXIp-3 are shown in Table IV.

Preparation of XXII——A solution of 24.4 g (0.20 mole) of IIIm-3, 29.6 g of ethyl orthoformate and 100 ml of Ac_2O was refluxed for 3 hr. Ac_2O was removed under the reduced pressure and the residue was poured into a large amount of H_2O. The separated crystals were 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 XXIIm, mp 214—215° as yellow amorphous crystals, in 66.1% yield (23.7 g). *Anal.* Calcd. for $C_8H_{10}ON_4$ (5-ethoxymethyleneimino-1-methyl-1*H*-pyrazole-4-carbonitrile): C, 53.92; H, 5.66; N, 31.45. Found: C, 54.03; H, 5.62; N, 31.27. IR ν_{max}^{KBr} cm^{-1}: 2230 (–CN).

The same procedure using 18.4 g (0.10 mole) of IIIp-3 gave XXIIp, mp 138—139° as colourless amorphous crystals from EtOH, in 74.2% yield (17.8 g). *Anal.* Calcd. for $C_{13}H_{12}ON_4$ (5-ethoxymethyleneimino-1-phenyl-1*H*-pyrazole-4-carbonitrile): C, 64.98; H, 5.03; N, 23.32. Found: C, 64.88; H, 5.08; N, 23.71.

Preparation of XXI——A solution of 0.010 mole of XXII, 0.010 mole of active methylene compounds in sodium ethoxide solution prepared from 460 mg (0.020 mole) of Na and 30 ml of EtOH, was refluxed for 1 hr. The reaction mixture was neutralized with 5% AcOH and EtOH was removed under the reduced pressure. The residue was recrystallized from benzene gave XXI as colorless needles. The yield of XXI is listed in Chart 12, and the melting points and the elemental analyses, and NMR spectra are shown in Table IV and V.

Preparation of XIX——A solution of 0.002 mole of III-2, 0.004 mole of active methylene compounds or ketone in sodium ethoxide solution prepared from 230 mg (0.001 mole) of Na and 20 ml of EtOH was refluxed for 1 hr. The reaction mixture was neutralized with 5% AcOH and EtOH was removed under the reduced pressure. The residue was dissolved in benzene and dried over anhyd. Na_2SO_4. The benzene solution was passed through a column of alumina to remove impurities. Recrystallization from petr. ether gave XIX as colorless needles.

In the case of the reaction of malononitrile, the residue was recrystallized from MeOH gave XIX-1.

The yield of XIX was listed in Chart 13, and the melting points and the elemental analyses, and NMR spectra of XIX are summerized in Table IV and V.

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