[Chem. Pharm. Bull. 24(2) 238—252 (1976)]

UDC 547.85.04 : 547.571.04 : 546.267.04

Studies on the Reaction of π-Deficient Heterocycles with Aromatic Aldehyde in the Presence of Cyanide Ion

Takeo Higashino, Masami Goi, and Eisaku Hayashi

Shizuoka College of Pharmacy[1]

(Received May 29, 1975)

Dimerization of π-deficient heterocyles by the catalytic action of cyanide ion in DMSO was carried out. Thus, reaction of quinoxaline (V), 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (VI), 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (VII), and pyrido[2,3-*b*]pyrazine (VIII) with cyanide ion gave 2,2′-biquinoxaline (IX), 4.4′-bis[1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine] (X), 4,4′-bis[1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine] (XI), and 2,2′-bipyrido[2,3-*b*]pyrazine (XII), respectively, although the yields of these dimers were very poor. The formation of dimer is assumed to be oxidation following a benzoin condensation-like reaction by the catalysis of cyanide ion.

Also we carried out the reaction of π-deficient heterocycles with aromatic aldehyde (XVI) in the presence of cyanide ion in DMSO, and found that the expected cross benzoin condensation-like reaction has developed. Thus, 4-isoquinolinecarbonitrile (II) reacted with XVI to give α-aryl-4-cyano-1-isoquinolinemethanol (XIX) and aryl 4-cyano-1-isoquinolyl ketone (XX) together with 1,1′-biisoquinoline-4,4′-dicarbonitrile (IV). Similarly, V and XVI gave α-aryl-2-quinoxalinemethanol (XXI) and aryl 2-quinoxalinyl ketone (XXII), VI and XVI afforded α-aryl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-methanol (XXX) and aryl 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl ketone (XXXI), VII and XVI produced α-aryl-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-methanol (XXXIV) and aryl 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl ketone (XXXV), and VIII and XVI formed aryl 2-pyrido[2,3-*b*]pyrazinyl ketone (XXXIV). It seems that XIX, XXI, XXX, and XXXIV are a formal product of a cross benzoin condensation-like reaction, and XX, XXII, XXXI, XXXV, and XXXVI are oxidation product of a formal product of the reaction. And limitation of this reaction was also discussed.

Dimerization of π-Deficient Heterocycles

It has been reported that quinazoline (I) gave 4,4′-biquinazoline (III) by the action of cyanide ion,[2,3a,c] and similarly 4-isoquinolinecarbonitrile (II) was dimerized by the action of cyanide ion to give 1,1′-biisoquinoline-4,4′-dicarbonitrile (IV).[3b] Now this dimerization was applied to other π-deficient heterocycles such as quinoxaline (V),[4] 1-phenyl-1*H*-pyrazolo-[3,4-*d*]pyrimidine (VI),[5] 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (VII),[6] and pyrido[2,3-*b*]-pyrazine (VIII).[7]

Thus, when a mixture of V and potassium cyanide in dimethyl sulfoxide (DMSO) was reacted under the condition shown in Table I, 2,2′-biquinoxaline (IX)[8] was formed. Similarly VI, VII, and VIII yielded 4,4′-bis[1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine] (X), 4,4′-bis[1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine] (XI), and 2,2′-bipyrido[2,3-*b*]pyrazine (XII), respective-

1) Location: *2-2-1, Oshika, Shizuoka-shi.*
2) W.L.F. Armarego and R.E. Willette, *J. Chem. Soc.*, **1965**, 1258.
3) *a*) T. Higashino, M. Goi, and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 2493 (1974); *b*) E. Hayashi, H. Makino, and T. Higashino, *Yakugaku Zasshi*, **94**, 1041 (1974); *c*) T. Higashino, M. Goi, and E. Hayashi, *ibid.*, "accepted."
4) R.G. Jones and K.C. Mclaughlin, "Organic Syntheses," Coll. Vol. IV, ed by N. Rabjohn, John Wiley and Sons, Inc., New York, 1963, p. 824.
5) T. Higashino, Y. Iwai, and E. Hayashi, *Yakugaku Zasshi*, **94**, 666 (1974).
6) C.C. Cheng and R.K. Robins, *J. Org. Chem.*, **21**, 1240 (1956).
7) C.L. Leese and H.N. Rydon, *J. Chem. Soc.*, **1955**, 303.
8) C. Iijima, *Yakugaku Zasshi*, **87**, 942 (1967).

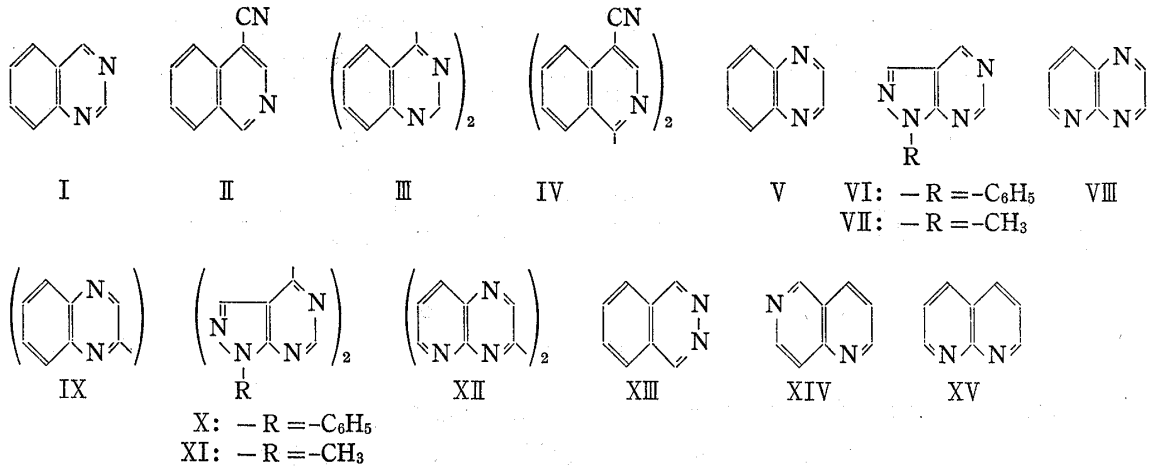


Chart 1

TABLE I. Reaction of π-Deficient Heterocycles with Potassium Cyanide in DMSO

Heterocycles	Dimer	Melting point (°C)	Yield (%)	Reaction temperature (°C)	Reaction time (hr)	Recovery (%)
V	IX	276	0.6	120—130	15	42
VI	X	above 300	0.6	120—130	15	30
VII	XI	288—290	0.4	120—130	15	46
VIII	XII	315—316	35.7	70— 80	4	—

ly, although the yield of dimer was very poor. But each of phthalazine (XIII),[9] 1,6-naphthyridine (XIV),[10] and 1,8-naphthyridine (XV)[10] did not give its dimer, and resulted in the recovery of the starting heterocycles together with the formation of some resinous substances.

The compound IX was identified by admixture with an authentic specimen[8] prepared by another route. The structures of X, XI, and XII were assigned on the bases of elemental analyses and nuclear magnetic resonance (NMR) spectra, shown in Table II.

TABLE II. Elemental Analyses and NMR Spectra of X, XI, and XII

Dimer	Formula	Analysis (%) Calcd. (Found) C	H	N	NMR (τ) in CF_3COOD 3-H	5-H	6-H	7-H	$-CH_3$	$-C_6H_5$
X	$C_{22}H_{14}N_8$	67.68 (67.33)	3.61 (3.97)	28.70 (28.33)	1.8—3.34	—	0.83^s	—	—	1.0—3.34^m
XI	$C_{12}H_{10}N_8$	54.13 (53.77)	3.79 (3.61)	42.09 (42.19)	1.00^s	—	0.50^s	—	5.60^s	—
XII	$C_{14}H_8N_6$	64.61 (64.54)	3.10 (3.01)	32.29 (32.59)	−0.40^s	1.43^q	2.29^q	0.75^q	—	—

s: singlet; q: quartet (J_{5-6}=9.0 cps, J_{5-7}=2.0 cps, J_{6-7}=5.0 cps); m: multiplet

The possible dimerization mechanism is similar to those of I,[3a] and II[3b] previously reported, and that is oxidation following a benzoin condensation-like reaction by the catalytic action of cyanide ion. For example, the dimerization mechanism of VIII may be written as Chart 2.

9) S. Gabriel and F. Müller, *Ber.*, **25**, 1831 (1895).
10) Y. Hamada and I. Takeuchi, *Chem. Pharm. Bull.* (Tokyo), **19**, 1857 (1971).

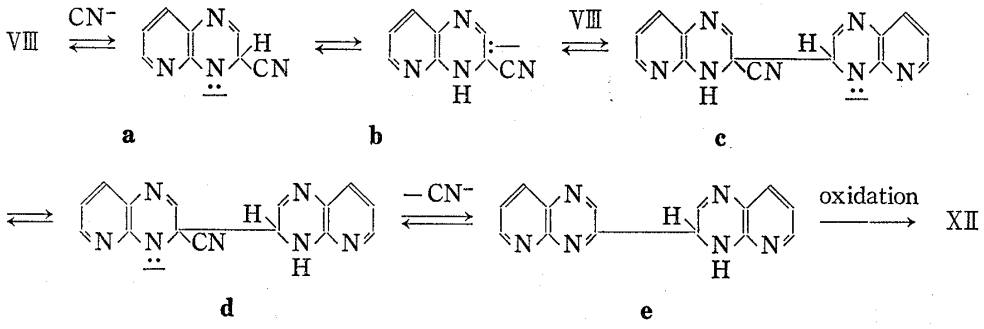


Chart 2

The Reaction of π-Deficient Heterocycles with Aromatic Aldehyde

We have reported that I reacted with aromatic aldehyde (XVI) in the presence of cyanide ion in methanol or DMSO to give α-aryl-4-quinazolinemethanol (XVII) and aryl 4-quinazolinyl ketone (XVIII) together with III, in which XVII was a formal cross benzoin condensation-like reaction product, and XVIII might be an oxidation product of XVII, as shown in Chart 3.[3a,c]

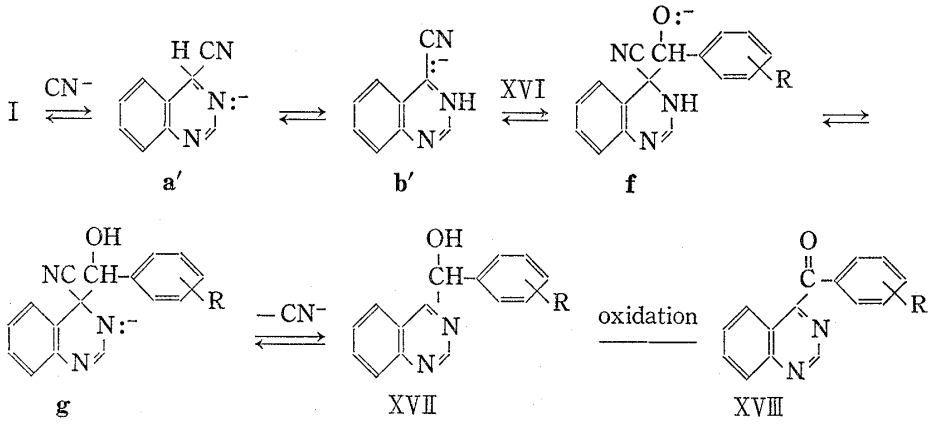


Chart 3

With expectation that a similar reaction would take place, we carried out the reaction of other π-deficient heterocycles with XVI in the presence of cyanide ion in DMSO, and found that the expected cross benzoin condensation-like reaction has developed.

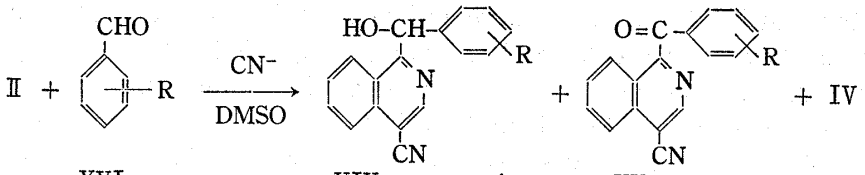
Aromatic aldehyde (XVI) used in this study was as follows; benzaldehyde (XVI-1), *o*-(XVI-2), *m*-(XVI-3), *p*-anisaldehyde (XVI-4), *o*-(XVI-5), *m*-(XVI-6), *p*-chlorobenzaldehyde (XVI-7), *o*-(XVI-8), *m*-(XVI-9), *p*-tolualdehyde (XVI-10), *p*-acetamidobenzaldehyde (XVI-11), furfural (XVI-12), and isonicotinaldehyde (XVI-13).

4-Isoquinolinecarbonitrile (II)

When a mixture of II, XVI and potassium cyanide in DMSO was stirred overnight at room temperature, α-aryl-4-cyano-1-isoquinolinemethanol (XIX) (except the cases of XVI-6 and XVI-12) and aryl 4-cyano-1-isoquinolyl ketone (XX) (in the cases of XVI-4, XVI-10, and XVI-12) were obtained together with its dimer (IV).

Most of the reactions with XVI gave only XIX, but not XX, and the results were probably caused by the fact that separation of XIX from the reaction medium by its small solubility to DMSO made oxidation into XX difficult.

The structures of XIX and XX were indicated by elemental analyses and confirmed by NMR and infrared (IR) spectra. The compounds XIX showed peaks of cyano and hydroxy groups in IR spectra, and signals due to hydrogen atoms of the 3-, α-positions and hydroxy group in NMR spectra. The compounds XX also showed peaks of cyano and carbonyl groups in IR spectra, and a signal due to the hydrogen of the 3-position in NMR spectra.



XVI	XIX	%	XX	%	%
XVI-1	XIX-1	28.4	—		6.9
XVI-2	XIX-2	52.4	—		1.8
XVI-3	XIX-3	10.4	—		8.4
XVI-4	XIX-4	40.1	XX-4	1.7	5.8
XVI-5	XIX-5	20.2	—		9.1
XVI-6	—		—		10.3
XVI-7	XIX-7	3.0	—		21.7
XVI-8	XIX-8	15.1	—		7.8
XVI-9	XIX-9	10.1	—		9.7
XVI-10	XIX-10	53.2	XX-10	1.0	—
XVI-11	XIX-11	24.4	—		5.5
XVI-12	—		XX-12	14.9	9.0
XVI-13	XIX-13	9.1	—		—

Chart 4

TABLE III. α-Aryl-4-cyano-1-isoquinolinemethanol (XIX) and Aryl 4-Cyano-1-isoquinolyl Ketone (XX)

Compd.	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XIX-1[a]	182—184	$C_{17}H_{12}ON_2$	78.44	4.65	10.76	78.36	5.03	10.55
XIX-2[a]	154—155	$C_{18}H_{14}O_2N_2$	74.47	4.86	9.65	74.16	5.08	9.61
XIX-3[b]	145—146	$C_{18}H_{14}O_2N_2$	74.47	4.86	9.65	74.45	5.12	9.85
XIX-4[c]	160—161	$C_{18}H_{14}O_2N_2$	74.47	4.86	9.65	73.98	5.14	9.43
XIX-5[d]	169—170	$C_{17}H_{11}ON_2Cl$	69.28	3.76	9.50	69.24	4.04	9.51
XIX-7[e]	189—190	$C_{17}H_{11}ON_2Cl$	69.28	3.76	9.50	68.78	4.13	9.43
XIX-8[f]	157—159	$C_{18}H_{14}ON_2$	78.81	5.14	10.21	78.58	5.35	10.18
XIX-9[c]	127—129	$C_{18}H_{14}ON_2$	78.81	5.14	10.21	78.83	5.37	10.33
XIX-10[g]	173—175	$C_{18}H_{14}ON_2$	78.81	5.14	10.21	78.56	5.39	10.11
XIX-11[a]	244—245	$C_{19}H_{15}O_2N_3$	71.91	4.76	13.24	71.34	5.01	13.08
XIX-13[a]	199	$C_{16}H_{11}ON_3$	73.55	4.24	16.08	73.61	4.52	15.65
XX-4[c]	187—189	$C_{18}H_{12}O_2N_2$	74.99	4.20	9.72	74.58	4.53	9.54
XX-10[a]	155—158	$C_{18}H_{12}ON_2$	79.39	4.44	10.29	79.21	4.96	9.84
XX-12[h]	194—196	$C_{15}H_8O_2N_2$	72.57	3.25	11.29	72.50	3.67	10.97

a) colourless particles; *b*) yellow prisms; *c*) colourless needles; *d*) yellow needles; *e*) brownish yellow particles; *f*) colourless scales; *g*) colourless plates; *h*) yellow particles

Quinoxaline (V)

Quinoxaline (V) reacted with XVI-1, XVI-2, XVI-6, and XVI-8 to yield the corresponding α-aryl-2-quinoxalinemethanol (XXI), with XVI-3, XVI-4, XVI-7, XVI-10, XVI-11, and XVI-12 to give the corresponding aryl 2-quinoxalinyl ketone (XXII), and with XVI-9, and XVI-13 to form both the corresponding XXI and XXII, although the yields of XXI and XXII were very poor as shown in Chart 5. Moreover, in the case of XVI-1,α-phenyl-2-hydroxy-3-quinoxalinemethanol (XXIII) (0.7%), 2-quinoxalinecarboxamide (XXIV)[11] (0.7%), benzoin (XXV)[12] (0.9%), and O-benzoylbenzoin (XXVI)[13] (24%) were formed in addition to α-phenyl-2-quinoxalinemethanol (XXI-1).

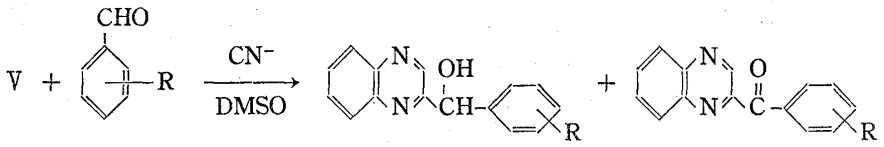
11) E. Hayashi and C. Iijima, *Yakugaku Zasshi*, **84**, 163 (1964).
12) R. Adams and C.S. Marvel, "Organic Syntheses," Coll. Vol. I, ed by H. Gilman, John wiley and Sons, Inc., New York, 1941, p. 94.
13) E.P. Kohler and J.L.E. Erickson, *J. Am. Chem. Soc.*, **53**, 2301 (1931).

The structures of XXI and XXII were assigned on the bases of elemental analyses, IR, and NMR spectra, shown in Table V and VI. The compounds XXI showed a peak of hydroxy group in IR spectra, and signals due to hydrogens of the 3- and α-positions in NMR spectra respectively. Moreover, α-(*m*-chlorophenyl)-(XXI-6), and α-(*m*-methylphenyl)-2-quinoxaline-methanol (XXI-9) obtained as oily substance were easily oxidized into *m*-chlorophenyl 2-quinoxalinyl ketone (XXII-6), and *m*-methylphenyl 2-quinoxalinyl ketone (XXII-9), respectively, by allowing XXI-6 and XXI-9 to stand overnight in methanolic potassium carbonate solution. The compounds (XXII) also showed a peak of carbonyl group in IR spectra, and a signal due to a hydrogen of the 3-position in NMR spectra. The structure of XXIII was established as follows. The values of elemental analysis of XXIII corresponded to $C_{15}H_{12}O_2N_2$, and its-IR spectrum confirmed the presence of peaks of alcoholic hydroxy group and lactam-lactim tautomerism. Its NMR spectrum showed signals due to hydrogens of aromatic ring

Table IV. NMR and IR Spectra of XIX and XX

Compd.	NMR (τ) in $CDCl_3$					IR ν_{max}^{KBr} cm^{-1}			
	3-H^s	>CH-O-^{s}	-OH^{bs}	Aromatic H^m	Other H	-OH	-CN	>C=O	>NH
XIX-1	1.25	3.69	5.12	1.7—2.7(9×H)		3400	2240	—	—
XIX-2	1.23	3.18	5.65	1.7—3.4(8×H)	6.12^s(OCH_3)	3360	2240	—	—
XIX-3	1.25	3.70	5.27	1.7—3.5(8×H)	6.35^s(OCH_3)	3440	2240	—	—
XIX-4	1.22	3.69	5.20	1.8—3.3(8×H)	6.35^s(OCH_3)	3200	2240	—	—
XIX-5	1.18	3.18	5.55	1.7—3.4(8×H)		3400	2240	—	—
XIX-7	1.16	3.65	5.70	1.7—2.9(8×H)		3400	2240	—	—
XIX-8	1.30	3.55	5.80	1.7—3.3(8×H)	7.45^s(CH_3)	3240	2240	—	—
XIX-9	1.22	3.71	5.48	1.8—3.0(8×H)	7.80^s(CH_3)	3400	2240	—	—
XIX-10	1.21	3.68	4.98	1.8—3.0(8×H)	7.80^s(CH_3)	3400	2240	—	—
XIX-11[a]	1.08	3.60	3.60	1.3—3.2(8×H)	8.00^s ($COCH_3$), 0.28^{bs}(>NH)	3600 ≀ 2800	2240	1670	3600 ≀ 2800
XIX-13	1.20	3.20	5.70	1.4—3.0(8×H)		3200	2240	—	—
XX-4	1.19	—	—	1.7—3.2(8×H)	6.18^s(OCH_3)	—	2240	1670	—
XX-10	1.20	—	—	1.5—3.0(8×H)	7.38^s(CH_3)	—	2240	1670	—
XX-12	1.17	—	—	1.4—3.5(7×H)		—	2240	1645	—

a) in $(CD_3)_2SO$; s: single t; bs: broad singlet and exchangeable with D_2O:, m: multiplet



XVI	XXI	%	XXII	%
XVI-1	XXI-1	0.2	—	
XVI-2	XXI-2	13.6	—	
XVI-3	—		XXII-3	0.9
XVI-4	—		XXII-4	15.3
XVI-5	—		—	
XVI-6	XXI-6[a]	5.8	—	
XVI-7	—		XXII-7	0.5
XVI-8	XXI-8	3.3	—	
XVI-9	XXI-9[a]	2.6	XXII-9	0.3
XVI-10	—		XXII-10	2.3
XVI-11	—		XXII-11	1.6
XVI-12	—		XXII-12	8.0
XVI-13	XXI-13	0.7	XXII-13	3.7

Chart 5

a) yellow oil

(9×H), the α-position, alcoholic hydroxy group, and lactam-lactim tautomerism. The identification of XXIV, XXV, and XXVI was, respectively, made by the melting point test mixed with the corresponding authentic specimen prepared by each specific route.[11–13]

It is clear that XVI-1 is not concerned with the formation of XXIV, and V is not with that of XXVI. The compound (XXIV) may be produced by hydrolysis of 2-quinoxalinecar-

Table V. α-Aryl-2-quinoxalinemethanol (XXI), Aryl 2-Quinoxalinyl Ketone (XXII) and α-Phenyl-2-hydroxy-3-quinoxalinemethanol (XXIII)

Compd.	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XXI-1[a]	138—140	$C_{15}H_{12}ON_2$	76.25	5.12	11.86	76.01	4.91	12.03
XXI-2[b]	137—138	$C_{16}H_{14}O_2N_2$	72.16	5.30	10.52	71.75	5.44	10.70
XXI-8[c]	132—133	$C_{16}H_{14}ON_2$	76.78	5.64	11.19	76.59	5.79	11.22
XXI-13[a]	129—130	$C_{14}H_{11}ON_3$	70.87	4.67	17.71	70.48	4.90	17.73
XXII-3[d]	96	$C_{16}H_{12}O_2N_2$	72.71	4.58	10.60	72.70	4.74	10.45
XXII-4[e]	112—113	$C_{16}H_{12}O_2N_2$	72.71	4.58	10.60	72.57	4.82	10.50
XXII-6[d]	89— 90	$C_{15}H_9ON_2Cl$	67.05	3.38	10.42	67.04	3.71	10.43
XXII-7[d]	114	$C_{15}H_9ON_2Cl$	67.05	3.38	10.42	66.63	3.75	10.36
XXII-9[b]	82— 83	$C_{16}H_{12}ON_2$	77.40	4.87	11.28	77.31	5.17	11.30
XXII-10[d]	100—102	$C_{16}H_{12}ON_2$	77.40	4.87	11.28	77.21	5.15	11.55
XXII-11[b]	187—188	$C_{17}H_{13}O_2N_3$	70.09	4.50	14.43	69.89	4.69	14.41
XXII-12[d]	127—128	$C_{13}H_8O_2N_2$	69.64	3.60	12.50	69.76	4.09	12.32
XXII-13[b]	140—142	$C_{15}H_9ON_3$	71.48	3.86	17.86	71.65	4.24	18.01
XXIII[d]	194—195	$C_{15}H_{12}O_2N_2$	71.41	4.80	11.11	71.30	5.01	11.15

a) yellow particles; b) yellow needles; c) red particles; d) colourless needles; e) yellow powders

Table VI. NMR and IR Spectra of XXI, XXII and XXIII

Compd.	NMR (τ) in $CDCl_3$ 3-H[s]	>CH-O-[s]	-OH[bs]	Aromatic H[m]	Other H	IR ν_{max}^{KBr} cm^{-1} -OH	>C=O	>NH
XXI-1						3230	—	—
XXI-2	1.31	3.70	5.26	1.9—3.5(8×H)	6.25[s] (OCH_3)	3180	—	—
XXI-6	1.36	4.12	5.40	1.8—3.0(8×H)				
XXI-8	1.49	3.89	5.52	1.9—3.1(8×H)	7.68[s] (CH_3)	3140	—	—
XXI-9	1.78	4.03	4.83	1.7—3.3(8×H)	7.72[s] (CH_3)			
XXI-13	1.29	4.04	4.95	1.5—2.6(8×H)		3100 ≀ 2600	—	—
XXII-3	0.65	—	—	1.7—3.1(8×H)	6.14[s] (OCH_3)	—	1680	—
XXII-4	0.67	—	—	1.6—3.2(8×H)	6.19[s] (OCH_3)	—	1660	—
XXII-6	0.64	—	—	1.7—2.9(8×H)		—	1660	—
XXII-7	0.64	—	—	1.7—2.7(8×H)		—	1670	—
XXII-9	0.69	—	—	1.8—2.8(8×H)	7.61[s] (CH_3)	—	1660	—
XXII-10	0.63	—	—	1.7—2.8(8×H)	7.55[s] (CH_3)	—	1670	—
XXII-11[a]	0.74	—	—	1.7—2.7(8×H)	7.88[s] ($COCH_3$), −0.26[bs] (>NH)	—	1680, 1650	3300
XXII-12	0.56	—	—	1.9—3.5(7×H)		—	1655	—
XXII-13	0.58	—	—	1.2—2.5(8×H)		—	1690	—
XXIII	—	3.96	6.00	2.1—3.0(9×H)	−2.26[bs] (>NH)	3360	1660	3100 ≀ 2600 (>NH or-OH)

a) in $(CD_3)_2SO$; s: singlet; bs: broad singlet and exchangeable with D_2O; m: multiplet

bonitrile (XXVII), formed through the nucleophilic attack of cyanide ion on V and the resulting elimination of hydride ion as shown in Chart 6. The nucleophilic attack of O-anion of XXV (**h**), formed by the benzoin condensation, on carbonyl carbon atom of unchanged XVI-1 and the succeeding elimination of hydride ion may give XXVI.

There may be two possible reaction processes of the formation of XXIII as shown in Chart 6; one involves N-anion of α-phenyl-2-cyano-1,2-dihydro-3-quinoxalinemethanol (**j**) as an intermediate, and another is concerned with XXVII. But, from the following experimental result it seems that the former is more reasonable than the latter. The nitrile (XXVII) and XVI-1 reacted under the same condition as the reaction of V with XVI-1 to give XXIV (2.7%) and XXVI (45.8%) with recovery of XXVII (62.0%), but not XXIII or α-phenyl-2-cyano-3-quinoxalinemethanol (XXVIII). The nucleophilic addition of cyanide ion across the 3,4-position of XXI-1, formed by a cross benzoin condensation-like reaction, gives N-anion (**j**). The aromatization of **j** and succeeding hydrolysis afford XXIII *via* XXVIII.

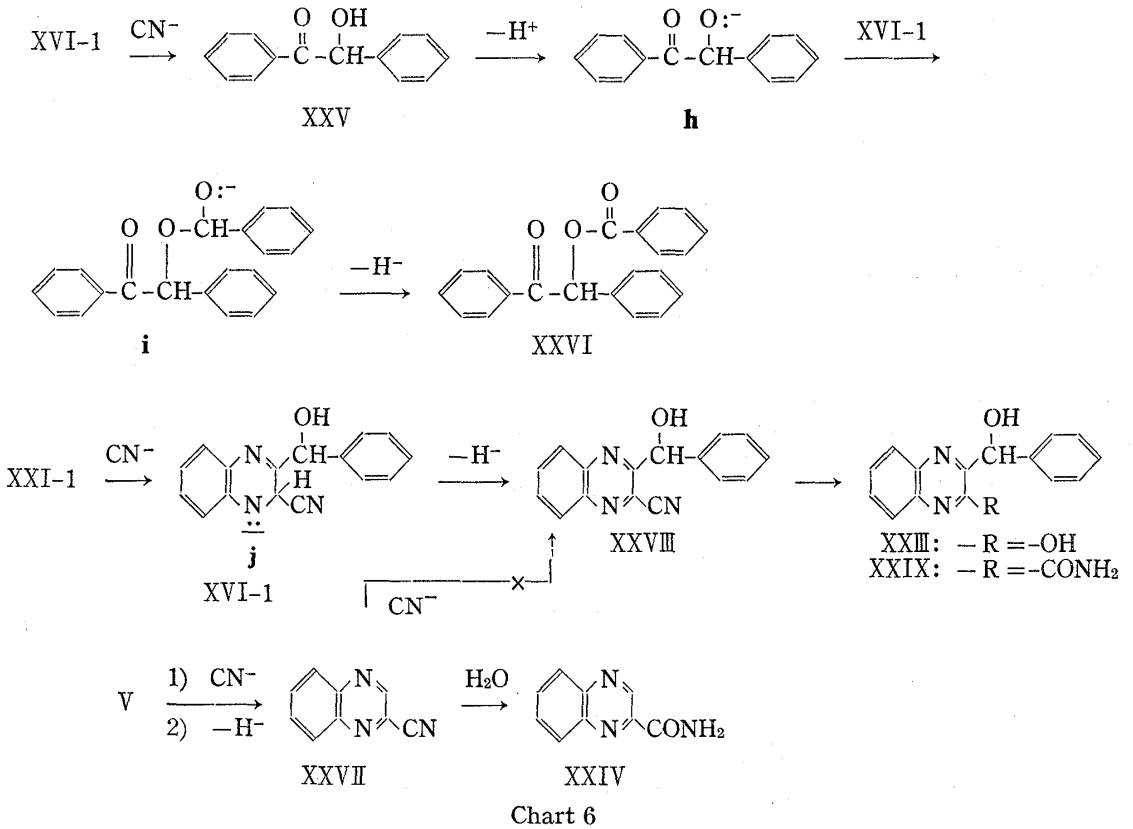
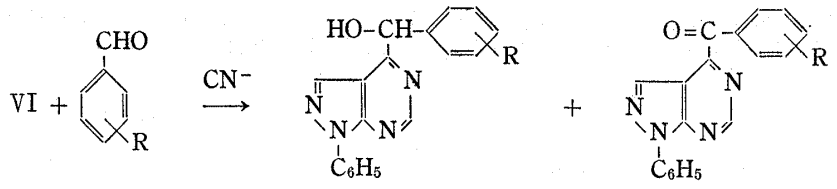


Chart 6

1-Phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (VI)

The reaction of VI with XVI-1, XVI-2, XVI-3, XVI-6, XVI-7, XVI-8, and XVI-10 in the presence of cyanide ion in DMSO gave the corresponding α-aryl-1-phenyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine-4-methanol (XXX) and aryl 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl ketone (XXXI). The reaction with XVI-5, XVI-9, and XVI-11 afforded the corresponding XXX, but not XXXI. On the other hand the reaction with XVI-4, and XVI-12 produced only the corresponding XXXI, but not XXX. The yields of XXX and XXXI were listed in Chart 7. In the case of XVI-1, 4-hydroxy-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (XXXII)[6] (0.7%) and XXVI (11.7%) were formed together with XXX-1 and XXXI-1.

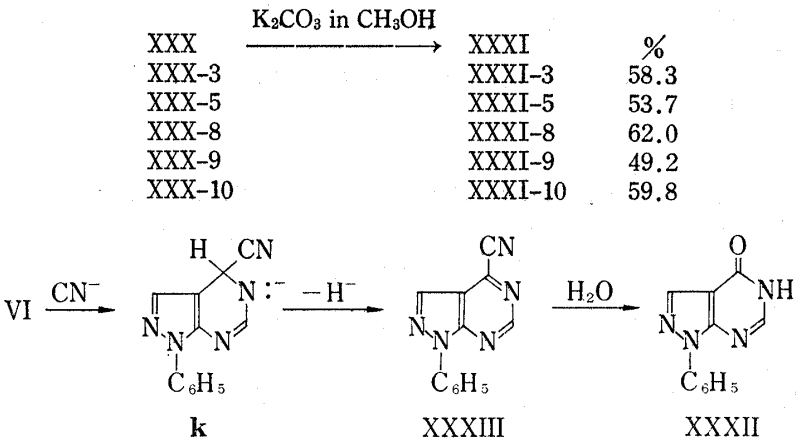
The structures of XXX were indicated by elemental analyses and IR spectra, and confirmed by NMR spectra, shown in Table VII and VIII. The compounds (XXX) showed a peak of hydroxyl group in IR spectra, and signals due to hydrogens of the 3-, 6-, α-positions and hydroxy group in NMR spectra. Moreover, the oxidation of XXX-3, XXX-5, XXX-8,



XVI	XXX	%	XXXI	%
XVI-1	XXX-1	36.0	XXXI-1	0.6
XVI-2	XXX-2	21.4	XXXI-2	10.6
XVI-3	XXX-3[a)]	23.6	XXXI-3	4.8
XVI-4	—		XXXI-4	7.4
XVI-5	XXX-5[a)]	61.6	—	
XVI-6	XXX-6	25.6	XXXI-6	4.0
XVI-7	XXX-7	23.9	XXXI-7	20.7
XVI-8	XXX-8[a)]	62.0	XXXI-8	1.4
XVI-9	XXX-9[a)]	53.4	—	
XVI-10	XXX-10[a)]	34.1	XXXI-10	0.2
XVI-11	XXX-11	15.0	—	
XVI-12	—		XXXI-12	21.8
XVI-13	—		—	

Chart 7

a) oil



XXX	XXXI	%
XXX-3	XXXI-3	58.3
XXX-5	XXXI-5	53.7
XXX-8	XXXI-8	62.0
XXX-9	XXXI-9	49.2
XXX-10	XXXI-10	59.8

Chart 8

XXX-9, and XXX-10, isolated as oily substance, with methanolic potassium carbonate solution gave the corresponding XXXI.

Assignment of XXXI were established on the bases of elemental analyses, IR and NMR spectra, shown in Table VII and VIII. There was a peak of carbonyl group in IR spectra, and signals due to hydrogens of the 3- and 6-positions in NMR spectra. The identity of XXXII was made by the melting point test mixed with an authentic specimen[6)] prepared by another route.

The formation of XXXII is analogous to that of 4(3*H*)-quinazolinone (XXXVIII) in the reaction of I with XVI previously reported,[3a)] and may be originated from N-anion (**k**) which leads to 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile (XXXIII) with the loss of hydride ion. The succeeding hydrolysis of XXXIII gives XXXII, as shown in Chart 8. This shows that cyanide ion attacks the 4-position of VI in the first step of the reaction process.

1-Methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (VII)

1-Methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (VII) and XVI in the presence of cyanide ion in DMSO gave the corresponding α-aryl-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-methanol (XXXIV) or aryl 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl ketone (XXXV). The yields of XXXIV and XXXV were listed in Chart 9. Thus, XVI, which afforded XXXIV, is XVI-2,

TABLE VII. α-Aryl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-methanol (XXX) and Aryl 1-Phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl Ketone (XXXI)

Compd.	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XXX-1[a]	107—110	$C_{18}H_{14}ON_4$	71.51	4.67	18.53	70.74	5.11	18.18
XXX-2[b]	145—146	$C_{19}H_{16}O_2N_4$	68.66	4.58	16.86	68.46	5.05	16.87
XXX-6[a]	126—127	$C_{18}H_{13}ON_4Cl$	64.20	3.89	16.64	64.11	4.13	16.50
XXX-7[a]	138—143	$C_{18}H_{13}ON_4Cl$	64.20	3.89	16.64	63.86	4.09	16.59
XXX-11[c]	192—195	$C_{20}H_{17}O_2N_5$	66.84	4.77	19.49	66.37	4.93	19.15
XXXI-1[d]	109—110	$C_{18}H_{12}ON_4$	71.99	4.03	18.66	71.75	4.31	18.55
XXXI-2[d]	124—125	$C_{19}H_{14}O_2N_4$	69.08	4.27	16.96	69.40	4.67	16.74
XXXI-3[e]	111—112	$C_{19}H_{14}O_2N_4$	69.08	4.27	16.96	68.72	4.53	16.95
XXXI-4[f]	150—151	$C_{19}H_{14}O_2N_4$	69.08	4.27	16.96	69.02	4.63	16.64
XXXI-5[d]	147—148	$C_{18}H_{11}ON_4Cl$	64.58	3.31	16.74	64.20	3.59	16.64
XXXI-6[c]	125	$C_{18}H_{11}ON_4Cl$	64.58	3.31	16.74	64.53	3.64	16.57
XXXI-7[c]	177—179	$C_{18}H_{11}ON_4Cl$	64.58	3.31	16.74	64.18	3.67	16.70
XXXI-8[a]	126—127	$C_{19}H_{14}ON_4$	72.60	4.49	17.83	72.48	4.33	17.95
XXXI-9[d]	129—130	$C_{19}H_{14}ON_4$	72.60	4.49	17.83	72.36	4.76	17.84
XXXI-10[c]	120—121	$C_{19}H_{14}ON_4$	72.60	4.49	17.83	72.21	4.77	17.70
XXXI-12[d]	165—166	$C_{16}H_{10}O_2N_4$	66.20	3.47	19.30	65.95	3.81	19.25

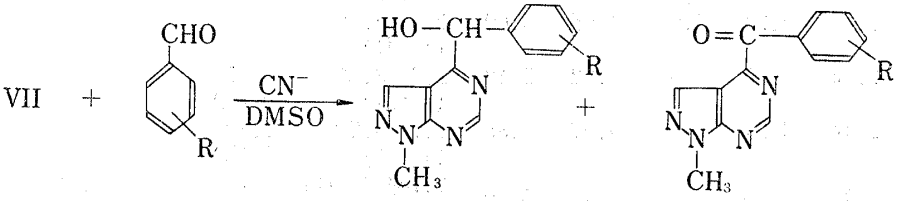
a) yellow particles; *b*) yellow prisms; *c*) yellow powders; *d*) yellow needles; *e*) colourless needles; *f*) pale yellow needles

TABLE VIII. NMR and IR Spectra of XXX and XXXI

Compd.	NMR (τ) in $CDCl_3$ 3-H[s]	6-H[s]	>CH-O-[s]	-OH[bs]	Aromatic H[m]	Other H	IR ν_{max}^{KBr} cm^{-1}
XXX-1	1.99	1.11	3.99	6.32	1.8—3.0(10×H)		3100 ≀ (–OH) 2800
XXX-2	1.97	1.08	3.58	5.72	1.7—3.3(9×H)	6.22[s](OCH$_3$)	3170(–OH)
XXX-3	1.99	1.18	4.10	5.90	1.8—3.5(9×H)	6.32[s](OCH$_3$)	
XXX-5	2.11	1.12	3.56	4.94	1.8—3.1(9×H)		
XXX-6	1.96	1.16	4.03	5.70	1.8—3.0(9×H)		3100(–OH)
XXX-7	1.98	1.08	4.03	5.60	1.7—3.0(9×H)		3100(–OH)
XXX-8	2.33	1.10	3.87	5.53	1.7—3.3(9×H)	7.66[s](CH$_3$)	
XXX-9	2.00	1.23	4.14	5.45	1.8—3.3(9×H)	7.18[s](CH$_3$)	
XXX-10	2.00	1.18	4.08	5.42	1.8—3.1(9×H)	7.72[s](CH$_3$)	
XXX-11[a]	1.30	1.11	4.02[d]	3.42[d]	1.7—3.0(9×H)	7.98[s](COCH$_3$) 0.21[bs](>NH)	3600(–OH ≀ or 2800>NH) 1690(=C=O)
XXXI-1							1670(=C=O)
XXXI-2	1.52	0.98	—	—	1.7—3.3(9×H)	6.48[s](OCH$_3$)	1700(=C=O)
XXXI-3	1.52	0.91	—	—	1.7—3.1(9×H)	6.22[s](OCH$_3$)	1680(=C=O)
XXXI-4	1.46	0.83	—	—	1.6—3.3(9×H)	6.14[s](OCH$_3$)	1660(=C=O)
XXXI-5	1.33	0.93	—	—	1.7—3.0(9×H)		1695(=C=O)
XXXI-6	1.43	0.84	—	—	1.7—3.0(9×H)		1680(=C=O)
XXXI-7	1.41	0.86	—	—	1.7—3.0(9×H)		1670(=C=O)
XXXI-8	1.45	0.91	—	—	1.7—3.0(9×H)	7.53[s](CH$_3$)	1685(=C=O)
XXXI-9	1.49	0.89	—	—	1.7—3.0(9×H)	7.61[s](CH$_3$)	1670(=C=O)
XXXI-10	1.49	0.89	—	—	1.7—3.0(9×H)	7.60[s](CH$_3$)	1680(=C=O)
XXXI-12	1.29	0.90	—	—	1.7—2.9(8×H)		1650(=C=O)

a) in $(CD_3)_2SO$; s: singlet; d: doublet (J=9.0 cps); bs: broad singlet and exchangeable with D_2O; m: multiplet

XVI-5, XVI-6, XVI-8, XVI-9, and XVI-10. On the other hand XVI, which gave XXXV, is XVI-1, XVI-3, XVI-4, XVI-7, and XVI-12. The fact that the small solubility of XXXIV to the reaction medium makes oxidation difficult may cause the formation of XXXIV only. In the cases of XVI-11 and XVI-13 the expected cross condensation products were not isolated, and only dark brown resinous substance was given with the recovery of the starting material. Moreover, XVI-1 gave XXV (6.2%) and XXVI (6.6%) as by-products together with phenyl 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl ketone (XXXV-1).



XVI	XXXIV	%	XXXV	%
XVI-1	—		XXXV-1	17.4
XVI-2	XXXIV-2	18.4	—	
XVI-3	—		XXXV-3	3.8
XVI-4	—		XXXV-4	6.1
XVI-5	XXXIV-5	70.4	—	
XVI-6	XXXIV-6	65.2	—	
XVI-7	—		XXXV-7	43.3
XVI-8	XXXIV-8	26.2	—	
XVI-9	XXXIV-9	18.4	—	
XVI-10	XXXIV-10[a]	68.4	—	
XVI-11	—		—	
XVI-12	—		XXXV-12	16.9
XVI-13	—		—	

Chart 9

a) oil

The structure of XXXIV and XXXV were respectively indicated by elemental analyses and IR spectra, and were confirmed by NMR spectra, according to the same assignment used in XXX and XXXI. And the structure of XXXIV-10, obtained as oily substance, was established by its oxidation with methanolic potassium carbonate solution into *p*-methylphenyl 1-methyl-1*H*-pyrazolo[3,4-*d*]pyridin-4-yl ketone (XXXV-10) (46%).

Table IX. α-Aryl-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-methanol (XXXIV) and Aryl 1-Methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl Ketone (XXXV)

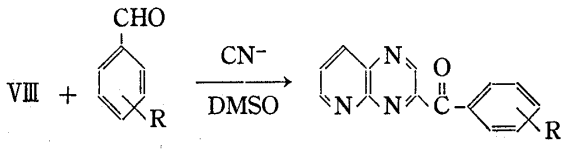
Compd.	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XXXIV-2[a]	142—144	$C_{14}H_{14}O_2N_4$	62.21	5.22	20.73	62.28	5.31	20.63
XXXIV-5[b]	159—161	$C_{13}H_{11}ON_4Cl$	56.84	4.04	20.40	56.70	4.22	20.24
XXXIV-6[a]	137—139	$C_{13}H_{11}ON_4Cl$	56.84	4.04	20.40	56.84	4.26	20.13
XXXIV-8[a]	147—149	$C_{14}H_{14}ON_4$	66.12	5.55	22.04	66.18	5.61	22.02
XXXIV-9[c]	112—113	$C_{14}H_{14}ON_4$	66.12	5.55	22.04	66.42	5.70	22.16
XXXV-1[d]	96— 97	$C_{13}H_{10}ON_4$	65.53	4.23	23.52	65.25	4.49	23.73
XXXV-3[e]	81— 82	$C_{14}H_{12}O_2N_4$	62.68	4.51	20.89	62.82	4.75	21.06
XXXV-4[e]	123—124	$C_{14}H_{12}O_2N_4$	62.68	4.51	20.89	62.53	4.46	20.95
XXXV-7[e]	135—136	$C_{13}H_9ON_4Cl$	57.26	3.33	20.55	57.38	3.60	20.66
XXXV-10[e]	84— 85	$C_{14}H_{12}ON_4$	66.65	4.79	22.21	66.39	4.95	22.01
XXXV-12[e]	156—157	$C_{11}H_8O_2N_4$	57.89	3.53	24.55	57.64	3.90	24.53

a) pale yellow particles; *b*) pale yellow prisms; *c*) colourless particles; *d*) yellow scales; *e*) pale yellow needles

Table X. NMR and IR Spectra of XXXIV and XXXV

Compd.	NMR (τ) in $CDCl_3$							Coupling constant J (cps)	IR ν_{max}^{KBr} cm^{-1}	
	3-H[s]	6-H[s]	1-CH_3	>CH-O-[s]	-OH[bs]	Aromatic H	Other H		-OH	=C=O
XXXIV-2	2.29	1.29	6.10	3.71	5.60	2.7—3.4[m] (4×H)	6.38[s] (OCH_3)		3240	—
XXXIV-5	2.30	1.18	4.93	3.56	4.66	2.5—3.0[m] (4×H)			3230	
XXXIV-6	2.09	1.24	5.00	4.05	4.60	2.5—3.0[m] (4×H)			3250	—
XXXIV-8	2.54	1.25	6.02	3.92	5.12	2.6—3.2[m] (4×H)	77.7[s] (CH_3)		3220	—
XXXIV-9	2.14	1.21	6.00	4.07	4.85	2.7—3.2[m] (4×H)	7.70[s] (CH_3)		3210	—
XXXIV-10	2.19	1.29	6.07	4.13	5.40	2.78[d](2×H) 3.03[d](2×H)	7.80[s] (CH_3)	9.0		
XXXV-1	1.63	0.91	5.82	—	—	1.7—2.7[m] (5×H)			—	1680
XXXV-3	1.65	0.95	5.84	—	—	2.1—3.1[m] (4×H)	5.15[s] (OCH_3)		—	1670
XXXV-4	1.70	0.98	4.90	—	—	1.84[d](2×H) 3.10[d](2×H)	5.15[s] (OCH_3)	8.9	—	1650
XXXV-7	1.62	0.93	5.85	—	—	1.88[d](2×H) 2.61[d](2×H)		9.0	—	1660
XXXV-10	1.69	0.99	5.90	—	—	1.99[d](2×H) 2.82[d](2×H)	7.62[s] (CH_3)	8.8	—	1675
XXXV-12	1.43	0.94	5.83	—	—	1.80[d](1×H) 2.24[d](1×H) 3.39[q](1×H)		4.0, 2.0	—	1650

s: singlet; bs: broad singlet and exchangeable with D_2O; d: doublet; q: quartet; m: multiplet



XVI	XXXVI	%
XVI-1	XXXVI-1	10.6
XVI-2	XXXVI-2	38.5
XVI-3	XXXVI-3	18.8
XVI-4	XXXVI-4	24.4
XVI-5	XXXVI-5	17.5
XVI-6	XXXVI-6	18.3
XVI-7	XXXVI-7	5.0
XVI-8	XXXVI-8	19.0
XVI-9	XXXVI-9	18.3
XVI-10	XXXVI-10	34.9
XVI-11	XXXVI-11	5.7
XVI-12	XXXVI-12	9.0
XVI-13	XXXVI-13	2.4

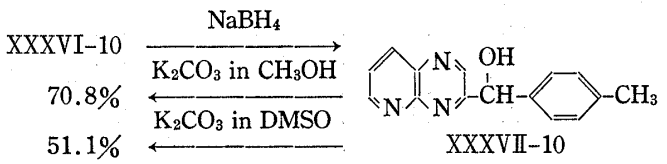


Chart 10

Pyrido[2,3-*b*]pyrazine (VIII)

Pyrido[2,3-*b*]pyrazine (VIII) reacted with XVI in the presence of cyanide ion in DMSO to result in only the formation of aryl 2-pyrido[2,3-*b*]-pyrazinyl ketone (XXXVI). The yield of XXXVI was listed in Chart 10. This fact may be caused by the easy oxidation of α-aryl-2-pyrido[2,3-*b*]pyrazine-methanol (XXXVII), formed as an intermediate, into XXXVI. In fact, the treatment of α-(*p*-methylphenyl)-2-pyrido[2,3-*b*]pyrazinemethanol (XXXVII-10), prepared by the reduction of *p*-methylphenyl 2-pyrido[2,3-*b*]pyrazinyl ketone (XXXVI-10) with sodium borohydride in methanol, with potassium carbonate in methanol or in DMSO regenerated XXXVI-10 in a moderate yield. In the case of XVI-1, XXVI was also obtained together with phenyl 2-pyrido[2,3-*b*]pyrazinyl ketone (XXXVI-1).

The structures of XXXVI and XXXVII-10 were established on the bases of elemental analyses, IR and NMR spectra, shown in Table XI and XII.

Table XI. Aryl 2-Pyrido[2,3-*b*]pyrazinyl Ketone (XXXVI)

Compd.	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XXXVI-1[a]	147—149	$C_{14}H_9ON_3$	71.48	3.86	17.86	71.27	4.29	17.64
XXXVI-2[a]	143—144	$C_{15}H_{11}O_2N_3$	67.91	4.18	15.84	67.80	4.49	15.72
XXXVI-3[b]	117—120	$C_{15}H_{11}O_2N_3$	67.91	4.18	15.84	67.82	4.49	15.77
XXXVI-4[c]	182—184	$C_{15}H_{11}O_2N_3$	67.91	4.18	15.84	67.56	4.51	15.43
XXXVI-5[b]	157—158	$C_{14}H_8ON_3Cl$	62.35	2.99	15.58	62.21	3.41	15.33
XXXVI-6[d]	156—158	$C_{14}H_8ON_3Cl$	62.35	2.99	15.58	61.91	3.37	15.22
XXXVI-7[a]	163—165	$C_{14}H_8ON_3Cl$	62.35	2.99	15.58	62.20	3.37	15.67
XXXVI-8[a]	143—144	$C_{15}H_{11}ON_3$	72.27	4.45	16.86	72.37	4.75	16.81
XXXVI-9[a]	120	$C_{15}H_{11}ON_3$	72.27	4.45	16.86	72.14	4.75	16.68
XXXVI-10[d]	134—135	$C_{15}H_{11}ON_3$	72.27	4.45	16.86	72.02	4.75	16.66
XXXVI-11[b]	248—250	$C_{16}H_{12}O_2N_4$	65.75	4.14	19.17	65.63	4.04	19.23
XXXVI-12[e]	151—153	$C_{12}H_7O_2N_3$	64.00	3.13	18.66	63.64	3.47	18.48
XXXVI-13[d]	201—203	$C_{13}H_8ON_4$	66.09	3.41	23.72	65.89	3.77	23.40

a) yellow scales; *b*) brown particles; *c*) orange needles; *d*) yellow particles; *e*) yellow needles

Table XII. NMR and IR Spectra of XXXVI and XXXVII-10

Compd.	NMR (τ) in $CDCl_3$ 3-H[s]	5-H[q]	6-H[q]	7-H[q]	Aromatic H	Other H	Coupling constant (cps) $J_{5,6}$	$J_{5,7}$	$J_{6,7}$	$J_{o,m}$	IR ν_{max}^{KBr} cm^{-1} =C=O
XXXVI-1	0.55	1.52	2.23	0.83	1.6—1.9[m](2×H), 2.3—2.7[m](3×H)		9.0	1.9	4.9		1670
XXXVI-2	0.68	1.56		0.95	1.1—3.3[m](5×H)	6.50[s](OCH_3)	9.0	2.0	4.9		1680
XXXVI-3	0.57	1.58		0.83	2.1—3.6[m](5×H)	6.20[s](OCH_3)	8.9	1.9	5.0		1670
XXXVI-4	0.53	1.54	2.27	0.82	1.72[d](2×H), 3.08[d](2×H)	6.18[s](OCH_3)	9.0	1.9	5.0	9.0	1660
XXXVI-5	0.47	1.56	2.28	0.91	2.4—3.0[m](4×H)		8.9	1.9	5.1		1700
XXXVI-6	0.52	1.52	2.24	0.81	1.7—2.0[m](2×H), 2.4—2.7[m](2×H)		8·9	2.0	5.0		1680
XXXVI-7	0.52	1.50	2.22	0.78	1.74[d](2×H), 2.56[d](2×H)		8.9	2.0	5.0	8.8	1675
XXXVI-8	0.48	1.56		0.87	2.1—3.0[m](5×H)	7.51[s](CH_3)	8.8	1.9	5.0		1670
XXXVI-9	0.53	1.51	2.23	0.81	1.8—2.1[m](2×H), 2.5—3.0[m](2×H)	7.59[s](CH_3)	9.0	2.0	4.9		1680
XXXVI-10	0.55	1.55	2.27	0.81	1.86[d](2×H), 2.26[d](2×H)	7.60[s](CH_3)	8.9	1.9	5.0	8.8	1670
XXXVI-11[a]	0.68	1.49	2.15	0.86	1.96[d](2×H), 2.36[d](2×H)	7.90[s]($COCH_3$), −0.25[bs](>NH)	8.9	2.0	4.9	8.7	1675, 3400—3000 (>NH)
XXXVI-12	0.42	1.55	2.25	0.84	1.74[d](1×H), 2.29[d](1×H), 3.43[d](1×H)		9.0	2.0	5.1	3.8 ($J_{1',2'}$), 1.9 ($J_{2',3'}$),	1660
XXXVI-13	0.42	1.46	2.17	0.77	1.0—1.3[m](2×H), 1.8—2.0[m](2×H)		9.0	2.0	5.0		1680
XXXVII-10	1.18	1.78	2.23	1.11	2.67[d](2×H), 3.06[d](2×H)	7.80[s](CH_3), 4.83[bs](-OH), 3.92[s](>CH-O-)	8.9	1.8	4.8	9.0	

a) in $(CD_3)_2SO$; s: singlet; bs: broad singlet and exchangeable with D_2O; d: doublet; q: quartet; m: multiplet

Mechanism and Limitation

The formation of alcohol (XIX, XXI, XXX and XXXIV) and ketone (XX, XXII, XXXI, XXXV and XXXVI), and the easy oxidation of alcohol into ketone by treatment with methanolic potassium carbonate solution, suggest that the reaction mechanism may be analogous to that of I with XVI in the presence of cyanide ion as shown in Chart 3,[3a,c] in which alcohol is a formal product of the cross benzoin condensation-like reaction, and ketone may be an oxidation product of alcohol.

The following two limitations may be given by the results obtained from the present and previous studies[3a-c]: i) The π-deficient heterocycles, which are dimerized by the catalytic action of cyanide ion, undergo the cross benzoin condensation-like reaction, but this was not so with not dimerized. In fact, XIII, XIV, or XV gave neither the corresponding dimer nor the corresponding alcohol or ketone. ii) When the strongly electron-donating N,N-dimethylamino and hydroxy groups or the strongly electron attracting nitro group were substituted *para*, *ortho* and *meta* to the aldehyde group in XVI-1, the reaction failed. In other words, XVI, which undergoes the benzoin condensation, reacts with π-deficient heterocycles to give the product of a cross benzoin condensation-like reaction such as alcohol or ketone, but the same reaction does not result from *m*-hydroxybenzaldehyde (XVI-14) and *o*-nitrobenzaldehyde (XVI-15).

Experimental[14]

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.

Dimerization of π-Deficient Heterocycles (V, VI, VII, and VIII)——A mixture of 500 mg of π-deficient heterocycles and 500 mg of KCN in 2 ml of DMSO was heated under the condition shown in Table I. The reaction mixture was poured into an excess of ice–H_2O mixture, neutralyzed with 1 N HCl, and extracted with $CHCl_3$. After drying over anhyd. Na_2SO_4, removing $CHCl_3$ gave sticky substance. Addition of MeOH to sticky substance separated crude dimer (IX, X, XI, and XII) which was recrystalized from MeOH.

The residue obtained from evaporation of MeOH from the filtrate was passed through a column of alumina. The elution with benzene gave the starting heterocycles.

The yield of the dimer and recovery of starting heterocycles were listed in Table I, and elemental analyses and NMR spectra were in Table II.

Each of the reaction of 500 mg of XIII, XIV, or XV with 500 mg of KCN in 2 ml of DMSO at 120—130° for 15 hr did not give the its dimer, and resulted in recovery of the starting heterocycle (XIII, 120 mg (24%), XIV, 260 mg (52%), XV, 210 mg (42%)) together with the formation of some resinous substances.

Reaction of II with XVI——A mixture of 0.0065 mole of II (1000 mg), 0.0094 mole of XVI and 1000 mg of KCN in 5 ml of DMSO was allowed to stand overnight with stirring. The reaction mixture was poured into an excess of ice–H_2O mixture, neutralized with 1N HCl, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4, and $CHCl_3$ was evaporated to dryness. Addition of MeOH to the residue, so obtained, separated crystal which was collected by suction and recrystallized from MeOH to give IV, mp above 310°, as yellow powder. The residue obtained by evaporation of MeOH from the filtrate was recrystallized from MeOH. From the first crystals, XIX was obtained, and XX was from the second crystals.

The yields of IV, XIX, and XX were listed in Chart 4, melting points and elemental analyses, and IR and NMR spectra of XIX and XX were in Table III, and IV, respectively.

Reaction of V with XVI——A mixture of 0.0076 mole (1000 mg) of V, 0.0094 mole of XVI and 1000 mg of KCN in 5 ml of DMSO was allowed to stand overnight with stirring (in the cases of XVI-2, XVI-3, XVI-4, XVI-8, XVI-9, and XVI-10, reaction temperature was 70—80° (oil bath)). The reaction mixture was poured into an excess of ice–H_2O mixture, neutralized with 1 N HCl, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4, and $CHCl_3$ was evaporated to dryness. The residue, thus obtained, was passed through a column of alumina. The elution with benzene gave XXII which was recrystallized from MeOH, and the elution with $CHCl_3$ afforded XXI.

In the case of XVI-1, the first elution with benzene gave XXVI, mp 123—124°, as colorless crystals from MeOH, and the second elution afforded XXV, mp 133°, as colorless needles from MeOH. And the first elution with $CHCl_3$ gave α-phenyl-2-quinoxalinemethanol (XXI-1), and the second elution afforded XXIV, mp 200°,

14) All melting points were not corrected.

as colorless crystals from MeOH. Moreover the elution with MeOH gave XXIII, mp 194—195°, as colorless needles from MeOH.

The yields of XXI and XXII were listed in Chart 5, and melting points and elemental analyses, and IR and NMR spectra of XXI, XXII, and XXIII were in Table V, and VI, respectively.

Reaction of XXVII with XVI-1——A mixture of 500 mg of XXVII, 500 mg of XVI-1 and 500 mg of KCN in 3 ml of DMSO was allowed to stand overnight with stirring. The reaction mixture was treated by the same manner used in the reaction of V with XVI.

The first elution with benzene gave XXVI, and XXVII was recovered in 62.0% yield (310 mg) from the second elution. The elution with $CHCl_3$ gave XXIV.

Oxidation of XXI——A solution of 200 mg of K_2CO_3 dissolved in 5 ml of H_2O was added to a solution of 120 mg of α-(*m*-chlorophenyl)-2-quinoxalinemethanol (XXI-6) dissolved in 20 ml of MeOH, and the reaction mixture was allowed to stand overnight. MeOH was removed under reduced pressure to separate *m*-chlorophenyl 2-quinoxalinyl ketone (XXII-6), mp 89—90°, as colorless needles from MeOH, in 64.7% yield (77 mg).

The same oxidation of 500 mg of α-(*m*-methylphenyl)-2-quinoxalinemethanol (XXI-9) gave *m*-methylphenyl 2-quinoxalinyl ketone (XXII-9), mp 82—83°, as yellow needles from MeOH, in 50.0% yield (25 mg).

Reaction of VI with XVI——A mixture of 0.0026 mole (500 mg) of VI, 0.0038 mole of XVI and 500 mg of KCN in 3 ml of DMSO was allowed to stand overnight with stirring (in the cases of XVI-2, XVI-3, XVI-4, XVI-8, XVI-9, and XVI-10, reaction temperature was 70—80°)). The reaction mixture was poured into an excess of ice-H_2O mixture, neutralized with 1N HCl, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4, and $CHCl_3$ was evaporated to dryness. The residue, thus obtained, was passed through a column of alumina. The elution with benzene gave XXXI which was recrystallized from MeOH, and the elution with $CHCl_3$ afforded XXX which was recrystallized from MeOH.

In the case of XVI-1, the first elution with benzene gave XXVI, and the second elution afforded XXXI-1. The elution with $CHCl_3$ gave XXX-1, and the elution with MeOH afforded XXXII, mp 299°, as colorless needles from MeOH.

The yields of XXX and XXXI were listed in Chart 7, and melting points and elemental analyses, and IR and NMR spectra of XXX and XXXI were in Table VII, and VIII, respectively.

Oxidation of XXX——A solution of 200 mg of K_2CO_3 dissolved in 5 ml of H_2O was added to a solution of 500 mg of XXX dissolved in 20 ml of MeOH, and the reaction solution was allowed to stand overnight. Evaporation of MeOH gave XXXI which was collected by suction and recrystallized from MeOH.

The yield of XXXI was listed in Chart 8.

Reaction of VII with XVI——A mixture of 0.0037 mole (500 mg) of VII, 0.0047 mole of XVI and 500 mg of KCN in 3 ml of DMSO was allowed to stand overnight with stirring (in the cases of XVI-2, XVI-3, XVI-4, XVI-8, XVI-9, and XVI-10, reaction temperature was 70—80° (oil bath)). The reaction mixture, thus obtained, was treated by the same manner used in the reaction of VI with XVI. The elution with benzene gave XXXV which was purified by recrystallization from MeOH, and the elution with $CHCl_3$ afforded XXIV which was purified by recrystallization from MeOH.

In the case of XVI-1, the first, second, and third elution with benzene gave XXVI, XXV, and XXXV-1, respectively.

The yields of XXXIV and XXXV were listed in Chart 9, and melting points and elemental analyses, and IR and NMR spectra were in Table IX, and X, respectively.

Oxidation of XXXIV-10——A solution of 200 mg of K_2CO_3 dissolved in 5 ml of H_2O was added to a solution of 1300 mg of XXXIV-10 dissolved in 20 ml of MeOH was allowed to stand overnight. Evaporation of MeOH separated XXXV-10 in 46.2% yield (596 mg) which was collected by suction and purified by recrystallization from MeOH.

Reaction of VIII with XVI——A mixture of 0.0034 mole (500 mg) of VIII, 0.0047 mole of XVI and 500 mg of KCN in 3 ml of DMSO was allowed to stand overnight with stirring. The reaction mixture was treated by the same manner used in the reaction of VI with XVI. The elution with benzene gave XXXVI which was purified by recrystallization from MeOH.

In the case of XVI-1, the first, and second elution with benzene gave XXVI in 32.1% yield (160 mg), and XXXVI-1, respectively.

The yield of XXXVI was listed in Chart 10. Melting points and elemental analyses, and IR and NMR spectra of XXXVI were in Table XI, and XII, respectively.

Preparation of XXXVII-10——To a solution of 200 mg of XXXVI-10 dissolved in 15 ml of MeOH, 30 mg of $NaBH_4$ was added, and the reaction mixture was stirred for 30 min, and neutralized with CH_3COOH. MeOH was removed under reduced pressure, and H_2O was added to the residue which was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4. The residue obtained from evaporation of $CHCl_3$, was passed through a column of alumina. The elution with benzene gave XXXVII-10 in 56.2% yield (112 mg) which was oily substance. NMR spectrum of XXXVII-10 was listed in Table XII.

Oxidation of XXXVII-10——i) A solution of 200 mg of K_2CO_3 dissolved in 5 ml of H_2O was added to a solution of 100 mg of XXXVII-10 dissolved in 20 ml of MeOH, and the reaction mixture was allowed to stand for 5 hr. Evaporation of MeOH under reduced pressure separated XXXVI-10 which was purified by recrystallization from MeOH. The yield of XXXVI-10 was listed in Chart 10.

ii) A mixture of 50 mg of XXXVII-10 and 50 mg of K_2CO_3 in 1 ml of DMSO was allowed to stand overnight with stirring. The reaction mixture was poured into an excess of ice–H_2O mixture, neutralized with 1N HCl, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4, and $CHCl_3$ was removed under reduced pressure to give XXXVI-10 which was purified by recrystallization from MeOH. The yield of XXXVI-10 was listed in Chart 10.

Oxidation of XIX-4——A solution of 200 mg of K_2CO_3 dissolved in 5 ml of H_2O was added to a solution of 200 mg of XIX-4 dissolved in 20 ml of MeOH. The reaction mixture was allowed to stand for 2 days. The solid obtained from evaporation of MeOH under reduced pressure was collected by suction, and recrystallized from MeOH. From the first crystals XIX-4 was recovered in 45.0% yield (90 mg), and XX-4 was obtained in 28.1% yield from the second crystals.

Acknowledgement The authors are indebted to Miss H. Kawamura for the measurement of microanalytical data in this college.

A part of the expenses for this work was defrayed by Grant-in-Aid of Scientific Research from the Ministry of Education, Science and Culture and of Cancer Research From the Ministry of Welfare in 1973 and 1974, for which is deeply indebted.