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Azole Series. II.[1] Reactions of 2-Acylamino-2-cyanoacetamides leading to 5-Acylaminooxazole-4-carboxamides and to Oxazolo[5,4-*d*]pyrimidines

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Reaction for preparation of a new series of 5-acylaminooxazole-4-carboxamides has been found.

5-Acetamidooxazole-4-carboxamides were obtained by heating 2-acylamino-2-cyanoacetamides with acetic anhydride in the presence of perchloric acid. Analogous 5-formamido derivatives were also obtained by heating the same substrates with a mixture of formic acid and acetic anhydride in the presence of hydrochloric acid.

Trials for synthesis of oxazolo[5,4-*d*]pyrimidine-7-ol from the 5-acylaminooxazole-4-carboxamide obtained were also successful in some cases by means of heating with potassium bicarbonate solution.

After the previous work on the syntheses of thiazolo[5,4-*d*]pyrimidines through the route from thiazole moieties, we were tempted to synthesize analogous oxazolo[5,4-*d*]pyrimidines. A goal appeared set to find a synthetic method of 5-aminooxazole-4-carboxamide and their

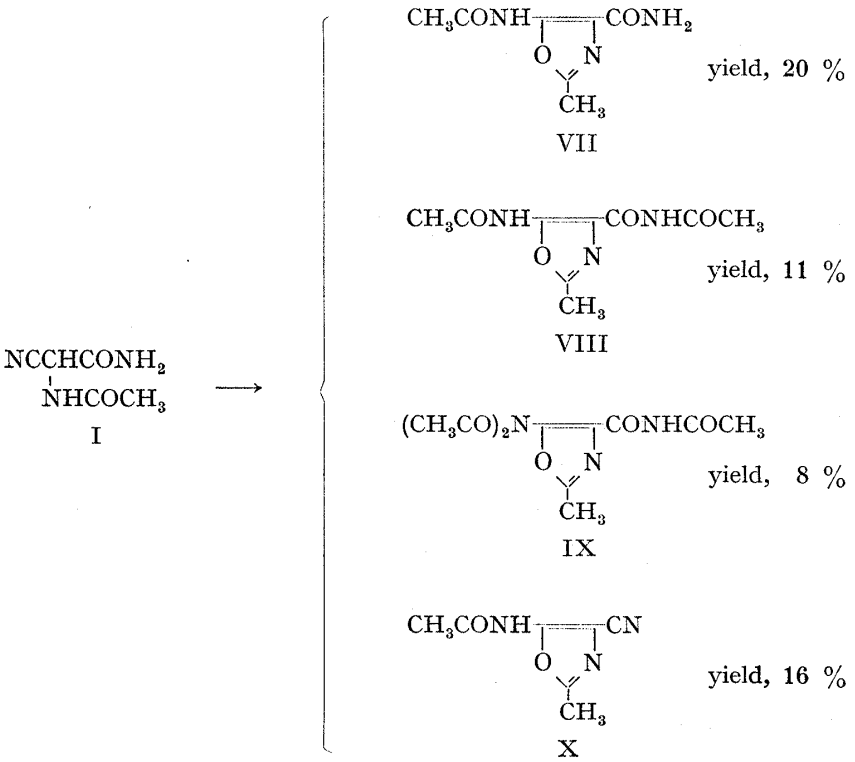


Chart 1. Reaction[a] of 2-Acetamido-2-cyanoacetamide with Acetic Anhydride

a) substrate: 0.035 mole, acetic anhydride: 30 ml, refluxing for 1.5 hr

1) Part I: M. Sekiya and Y. Osaki, *Chem. Pharm. Bull.* (Tokyo), **13**, 1319 (1965).
2) Location: *160, Oshika, Shizuoka.*

derivatives, referred to as intermediates for the syntheses, while no work on syntheses of these compounds has been reported. On referring to the well-known reaction of the azlactone formation from amino acid by action of acetic anhydride, we began with an experiment of refluxing acetic anhydride solution of 2-acetamido-2-cyanoacetamide(I), in the expectaion of 5-acetamidooxazole-4-carboxamide(VII) formation. A previous approach to this has been reported,[3] in which ethyl 2-benzamido-2-cyanoacetate, on refluxing with acetic anhydride, give two products, which are possibly assigned as ethyl 2-phenyl-5-acetamidooxazole-4-carboxylate and ethyl 2-phenyl-5-diacetamidooxazole-4-carboxylate. By carrying out the reaction of 2-acetamido-2-cyanoacetamide with acetic anhydride, we obtained four oxazole compounds as reaction products, inclusive of the desired 5-acetamidooxazole-4-carboxamide (VII) and its acetyl derivatives, as shown in Chart 1. The four products showed resemblance of their ultraviolet (UV) absorbances (*ca.* 220 mμ and *ca.* 260 mμ) suggestive of the oxazole skeleton. The identities of these products were made by noting exact correspondences of their nuclear magnetic resonance (NMR) and infrared (IR) spectra (see Table III).

For preparation of the desired compound the above result seemed insufficient in yield and isolation, then it was needed to rise the yield with modification. For oxazole ring closure of

Table I. Reactions[a] of 2-Acylamino-2-cyanoacetamides with Acetic Anhydride in the Presence of Perchloric Acid

Substrate	Product (Yield, %)	
$NCCHCONH_2$ $NHCOCH_3$ I	CH_3CONH, $CONH_2$, CH_3 (6) VII	CH_3CONH, $CONHCOCH_3$, CH_3 (82) VIII
$NCCHCONH_2$ $NHCHO$ II	CH_3CONH, $CONHCOCH_3$ (87) XI	
$NCCHCONHCH_3$ $NHCOCH_3$ III	CH_3CONH, $CONHCH_3$, CH_3 (41) XIII	$(CH_3CO)_2N$, $CONHCH_3$, CH_3 (38) XIV
$NCCHCONHCH_3$ $NHCHO$ IV	CH_3CONH, $CONHCH_3$ (67) XV	CH_3CONH, $CON(CH_3)COCH_3$ (6) XVI
$NCCHCON(CH_3)_2$ $NHCOCH_3$ V	CH_3CONH, $CON(CH_3)_2$, CH_3 (84) XVII	
$NCCHCON(CH_3)_2$ $NHCHO$ VI	CH_3CONH, $CON(CH_3)_2$ (71) XVIII	

a) substrate: 0.03 mole, acetic anhydride: 24 ml, 70% perchloric acid: 0.3 ml, heating at 60—65° for 1.5 hr

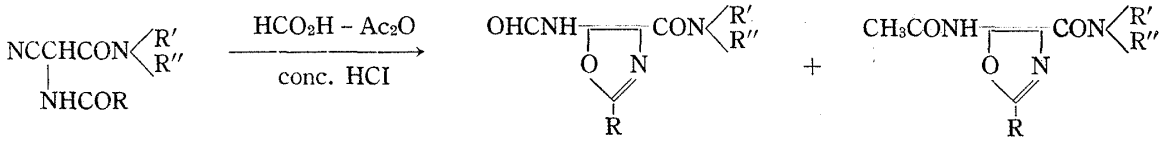
3) W.R. Boon, H.C. Carrington, W.G.M. Jones, G.R. Ramage and W.S. Waring, "The Chemistry of Penicillin," Princeton University Press, 1948, p. 726.

α-acylaminonitrile acid catalyst seemed efficient, on referrring to the work reported by Lichtenberger,*et al.*[4] Then we conducted the above acetic anhydride reaction in the presence of perchloric acid and found increase of the yield of 5-acetamidooxazole-4-N-acetylcarboxamide (VIII) in a great deal (Table I).

With this result a variety of 2-acylamino-2-cyanoacetamides were processed by the same reaction procedure under uniform condition, heating at 60—65° for 1.5 hr. Yields of 5-acetamidooxazole-4-carboxamides together with by-products are listed in Table I. As can be seen from the Table I, 2-formamido-2-cyanoacetamides gave 2-unsubstituted oxazoles.

A further need arose to prepare 5-formamidooxazole-4-carboxamides for the syntheses of 5-unsubstituted oxazolo[5,4-*d*]pyrimidines. Syntheses of the oxazoles were also successfully performed by the additional use of formic acid together with acetic anhydride and hydrochloric acid as acid catalyst. That is, the reactions were carried out by heating a mixture of 2-acylamino-2-cyanoacetamide, acetic anhydride and 99% formic acid in 1:5:5.4 molar proportion together with small amount of hydrochloric acid for 1.5 hr at 65—70°. The results of the experiments with a variety of substrates are summarized in Table II.

Table II. Reactions[a] of 2-Acylamino-2-cyanoacetamides with Formic Acid –Acetic Anhydride Mixture in the Presence of Hydrochloric Acid



Substrate compd. No.	R	R′	R″	Yield: 5-Formamido product compd. No.	%	5-Acetamido product compd. No.	%
I	CH_3	H	H	XIX	84	VII	12
II	H	H	H	XX	63	XII	34
III	CH_3	CH_3	H	XXI	71	XIII	12
IV	H	CH_3	H	XXII	26	XV	55
V	CH_3	CH_3	CH_3	XXIII	81	XVII	11
VI	H	CH_3	CH_3	XXIV	72	XVIII	20

a) substrate: 0.03 mole, 99% formic acid: 7.5 ml, acetic anhydride: 12 ml, 35% hydrochloric acid: 0.15 ml, heating at 65—70° for 1.5 hr

As can be seen, sufficient yields of 5-formamidooxazole-4-carboxamides were obtained in spite of spontaneous formations of 5-acetamido compounds. For increasing the yields of 5-formamido compounds, the results would be suggestive of carrying out the reaction with increasing amount of formic acid.

None of the 5-acylaminooxazole-4-carboxamides obtained in the above work have been previously known. Identities of these compounds were made by their compositions and spectral data shown in Table III. UV absorbances shows at *ca.* 225 mμ and *ca.* 266 mμ suggestive of this type of oxazole skeleton and their NMR and IR spectra are in agreement with the assigned structures.

When we speculate on a mechanism of the reactions, it is very possible that the reaction proceeds *via* protonation of nitrile group by perchloric acid or hydrochloric acid giving iminium ion followed by oxazole ring closure, as shown in Chart 2.

Attaining availability of 5-acylaminooxazole-4-carboxamides from the above work, we then examined to synthesize oxazolo[5,4-*d*]pyrimidine directly from those. After trials

4) J. Lichtenberger and J.P. Fleury, *Bull. Soc. Chim. France*, **1956**, 1184.

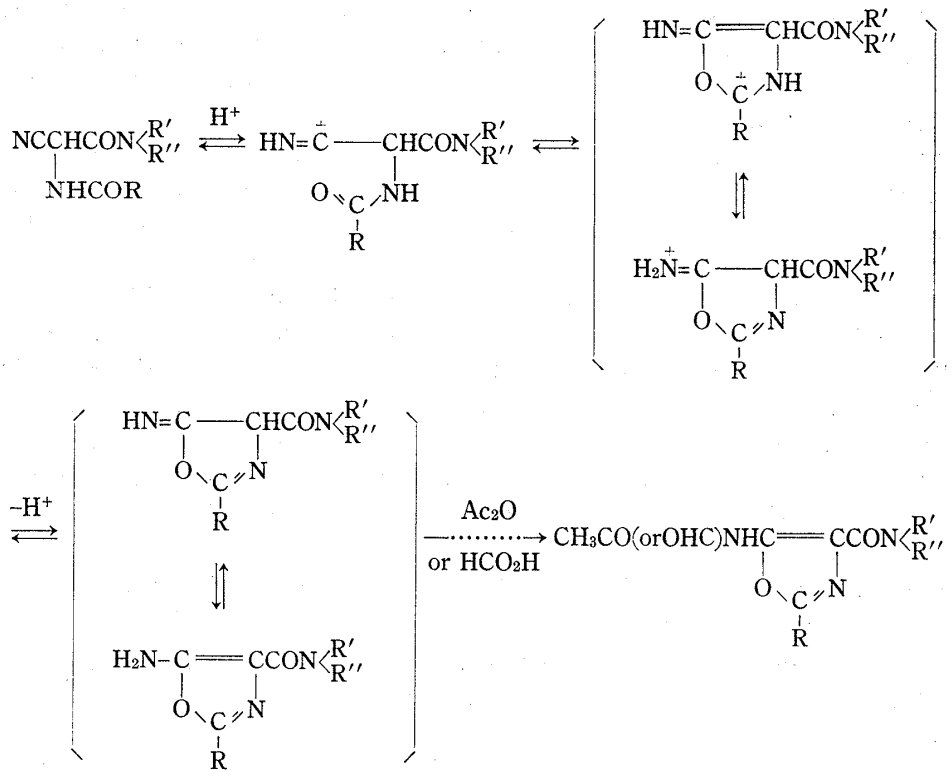


Chart 2. Possible Reaction Path of the Formation of 5-Acylaminooxazole-4-carboxamide

of experiments with several bases, aqueous potassium bicarbonate only was shown to have little efficiency for the pyrimidine ring closure, but not so effective. Under conditions of heating 0.5N potassium bicarbonate solution of 5-formamidooxazole-4-carboxamide (XX) on a boiling water-bath for 5 hr oxazolo[5,4-*d*]pyrimidine-7-ol (XXV) was obtained in 5.4% yield. Under the same conditions, 2-methyl-5-formamidooxazole-4-carboxamide (XIX) gave 2-methyloxazolo[5,4-*d*]pyrimidine-7-ol (XXVI) in 8.8% yield.

Experimental

Reaction of 2-Acetamido-2-cyanoacetamide with Acetic Anhydride——To 30 ml of acetic anhydride 5.0 g (0.035) mole of 2-acetamido-2-cyanoacetamide was added. The mixture was refluxed for 1.5 hr on an oil-bath. The reaction mixture was concentrated under reduced pressure. The resulting brown resinous residue was submitted to column chromatography on silica gel using $CHCl_3$ as an eluent to give 2-methyl-5-acetamidooxazole-4-carboxamide derivatives, VII, VIII, and IX, and 2-methyl-5-acetamidooxazole-4-carbonitrile (X). Analytical and spectral data are summarized in Table III.

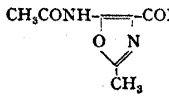
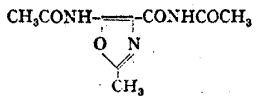
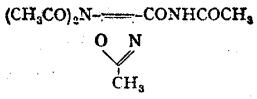
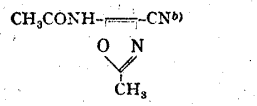
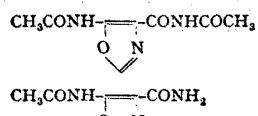
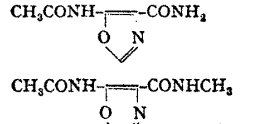
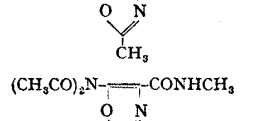
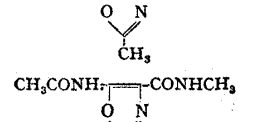
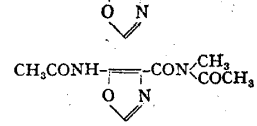
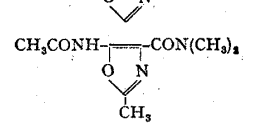
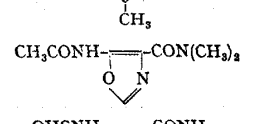
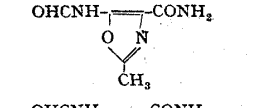
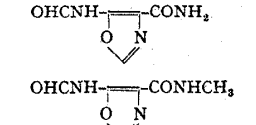
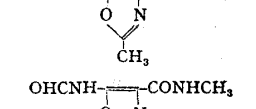
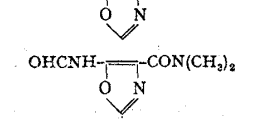
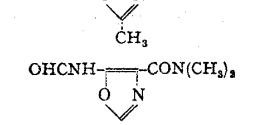
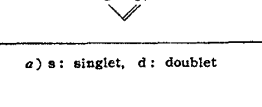
Reaction of 2-Acylamino-2-cyanoacetamides with Acetic Anhydride in the Presence of Perchloric Acid General Procedure——Six 2-acylamino-2-cyanoacetamides (I—VI) shown in Table I were used as substrates for this reaction. Twenty four ml of acetic anhydride and 0.3 ml of 70% perchloric acid were mixed. To the mixture, preferrably preheated for a while, 0.03 mole each of 2-acylamino-2-cyanoacetamides was added and heated at 60—65° for 1 hr. To the reaction mixture 0.4 g of ammonium acetate was dissolved and chilled in a refrigerator overnight. The separated ammonium perchlorate was filtered off and the filtrate was concentrated under reduced pressure. After standing the resulting residue in a refrigerator overnight, most of the 5-acetamidooxazole-4-carboxamide product (VIII, XIV, XV, XVII, and XVIII shown in Table I) was deposited as crystals, which was collected by filtration, washde, dried, and weighed. Recrystallization was needed for obtaining analytical pure product.

The above filtrate combined with washings was concentrated under reduced pressure. The residue was submitted to column chromatography on silica gel using $CHCl_3$ as an eluent to give additional amount of the above product and, in some cases, minor by-product (VII, XIII and XVI).

Yields of the products are shown in Table I and their analytical and spectral data are listed in Table III.

Reactions of 2-Acylamino-2-cyanoacetamides with Formic Acid-Acetic Anhydride Mixture in the Presence of Hydrochloric Acid General Procedure——Six 2-acylamino-2-cyanoacetamides (I—VI) shown in Table II

TABLE III. Data of 5-Acylaminooxazole-4-carboxamides and Related Compounds

Compound	Compd. No.	Appearance (Recryst. solvt.)	mp (°C)	Formula	Analysis (%) Calcd. / Found C	H	N	UV λ_{max}^{EtOH} mμ (log ε)	NMR[a] τ (in $CDCl_3$)
	VII	leaflets (EtOH)	175—177	$C_7H_9O_3N_3$	45.90 46.01	4.95 5.07	22.94 23.14	216 (3.98) 260 (3.91)	7.74 (3H, s, $NCOCH_3$) 7.53 (3H, s, CCH_3)
	VIII	needles (AcOEt)	86—87	$C_9H_{11}O_4N_3$	48.00 47.89	4.92 4.98	18.66 18.62	218 (4.17) 280 (3.95)	7.70 (3H, s, $NCOCH_3$) 7.54 (3H, s, CCH_3) 7.48 (3H, s, $CONCOCH_3$)
	IX	prisms (AcOEt)	100—102	$C_{11}H_{13}O_5N_3$	49.48 49.54	4.90 5.01	15.73 15.66	213 (4.16) 240 (3.96)	7.66 (6H, s, $N(COCH_3)_2$) 7.51 (6H, s, CCH_3 and $CONCOCH_3$)
	X	plates (EtOH)	136—137	$C_7H_7O_2N_3$	50.91 50.88	4.29 4.29	25.45 25.41	256 (3.92)	7.74 (3H, s, $NCOCH_3$) 7.55 (3H, s, CCH_3)
	XI	needles (EtOH)	156—157	$C_8H_9O_4N_3$	45.50 45.63	4.30 4.55	19.90 19.80	218 (4.10) 274 (3.96)	7.68 (3H, s, $NCOCH_3$) 2.40 (1H, s, CH)
	XII	prisms (EtOH)	166—167	$C_6H_7O_3N_3$	42.60 42.51	4.17 4.40	24.85 24.53	213 (3.95) 258 (3.91)	7.71 (3H, s, $NCOCH_3$) 2.42 (1H, s, CH)
	XIII	needles (EtOH)	122—123	$C_8H_{11}O_3N_3$	48.72 48.98	5.62 5.77	21.31 21.56	221 (4.05) 258 (3.92)	7.76 (3H, s, $NCOCH_3$) 7.55 (3H, s, CCH_3) 7.07 (3H, d, J=5 cps, $NHCH_3$)
	XIV	prisms ($CHCl_3$)	159—160	$C_{10}H_{13}O_4N_3$	50.20 50.23	5.48 5.63	17.57 17.77	210 (3.81)	7.64 (6H, s, $N(COCH_3)_2$) 7.52 (3H, s, CCH_3) 7.07 (3H, d, J=5 cps, $NHCH_3$)
	XV	needles (EtOH)	159—160	$C_7H_9O_3N_3$	45.90 45.61	4.95 5.03	22.94 22.88	224 (4.03) 255 (3.98)	7.73 (3H, s, $NCOCH_3$) 7.02 (3H, d, J=5 cps, $NHCH_3$) 2.45 (1H, s, CH)
	XVI	needles (EtOH)	115—116	$C_9H_{11}O_4N_3$	48.00 47.89	4.92 4.95	18.66 18.63	227 (4.11) 268 (3.77)	7.68 (3H, s, $NCOCH_3$) 7.57 (3H, s, $CONCOCH_3$) 6.55 (3H, s, NCH_3) 2.39 (1H, s, CH)
	XVII	prisms (EtOH)	134—135	$C_9H_{13}O_3N_3$	51.17 51.03	6.20 6.22	19.90 19.58	224 (4.00) 254 (3.85)	7.77 (3H, s, $NCOCH_3$) 7.51 (3H, s, CCH_3) 6.90 and 6.48 (3H, s, $N(CH_3)_2$)
	XVIII	prisms (EtOH)	166—167	$C_8H_{11}O_3N_3$	48.74 48.57	5.62 5.94	21.31 21.11	227 (3.99) 252 (3.90)	7.77 (3H, s, $NCOCH_3$) 6.94 and 6.45 (3H, s, $N(CH_3)_2$) 2.47 (1H, s, CH)
	XIX	needles (EtOH)	206 (decomp.)	$C_6H_7O_3N_3$	42.60 42.65	4.17 4.23	24.85 24.97	217 (4.03) 268 (4.07)	c)
	XX	needles (EtOH–H_2O)	210—211	$C_5H_5O_3N_3$	38.71 38.63	3.25 3.49	27.09 26.70	220 (3.90) 263 (4.03)	c)
	XXI	leaflets (EtOH)	173—174	$C_7H_9O_3N_3$	45.90 46.06	4.95 4.95	22.94 23.01	226 (3.98) 266 (4.08)	7.53 (3H, s, CCH_3) 7.04 (3H, d, J=6 cps, $NHCH_3$) 2.68 (1H, s, NCHO)
	XXII	prisms (EtOH)	186—187 (decomp.)	$C_6H_7O_3N_3$	42.60 42.76	4.17 4.23	24.85 24.98	230 (3.98) 262 (4.08)	c)
	XXIII	needles (AcOEt–Ligroin)	101—102	$C_8H_{11}O_3N_3$	48.72 48.65	5.62 5.52	21.31 21.57	229 (4.01) 273 (3.99)	7.53 (3H, s, CCH_3) 6.91 and 6.46 (3H, s, $N(CH_3)_2$) 2.66 (1H, s, NCHO)
	XXIV	needles (EtOH)	155—156	$C_7H_9O_3N_3$	45.90 45.85	4.95 4.97	22.94 22.75	232 (4.00) 267 (4.05)	6.92 and 6.44 (3H, s, $N(CH_3)_2$) 2.68 (1H, s, NCHO) 2.43 (1H, s, CH)

a) s: singlet, d: doublet b) IR ν_{max}^{KBr} cm^{-1}: 2240 (CN-) c) There was no sufficient solvent for measurement NMR spectrum

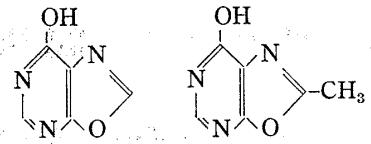
were used as substrates for this reaction. To a preheated mixture of 7.5 ml of 99% formic acid, 12 ml of acetic anhydride and 0.15 ml of conc. hydrochloric acid was added 0.03 mole each of 2-acylamino-2-cyanoacetamides. The mixture was allowed to react on heating at 65—70° for 1.5 hr on a water-bath. In the cases of the substrate I and II almost insoluble XIX and XX were respectively crystallized in the reaction solution of standing in a refrigerator overnight and collected by filtration. Concentration of the filtrate under reduced pressure gave 5-acetaminooxazole-4-carboxamides VII and XII, which were recrystallized from ethanol.

The reaction solutions obtained from the substrate III, IV and VI were concentrated under reduced pressure, and resulting residue were subjected to fractional crystallization from ethanol to give 5-formamidooxazole-4-carboxamides, XXI, XXII and XXIV, and 5-acetamido analogs, XIII, XV and XVIII, the formers were less soluble than the latters. Because of easier solubility of the products XXIII and XVII, the separation was carried out by column chromatography on silica gel using $CHCl_3$ as an eluent.

Yields of the products are shown in Table II and their analytical and spectral data are listed in Table III.

Cyclization of 5-Formamidooxazole-4-carboxamides General Procedure——To 100 ml of 0.5N $KHCO_3$ aqueous solution 0.003 mole each of 5-formamidooxazole-4-carboxamides, XIX and XX was added. The mixture was heated for 5 hr on a boiling water-bath. The reaction mixture showed chracteristic peaks of oxazolo[5,4-*d*]pyrimidine-7-ol in the UV region and was applied to a Amberite IRC-50 column using H_2O as an eluent. Individual fractions of about 20 ml each were collected and the UV spectrum of each fraction was checked. The eluates showing characteristic peak of oxazolo[5,4-*d*]pyrimidine-7-ol were pooled and concentrated under reduced pressure. The oxazolo[5,4-*d*]pyrimidine-7-ols, XXV (5.4%) and XXVI (8.8%) were obtained by recrystallization of the resulting crystalline residues respectively from methanol and water. Analytical and spectral data are summarized in Table IV.

Table IV. Data of Oxazolo [5,4-*d*]pyrimidine-7-ols



XXV XXVI

Compd. No.	Appearance (Recryst. solvt.)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XXV	needles (MeOH)	>300	$C_5H_3O_2N_3$	43.80	2.22	30.65	43.70	2.33	30.55
XXVI	needles (H_2O)	281—282 (281—282)[c]	$C_6H_5O_2N_3$	47.68	3.34	27.81	47.99	3.60	27.90

Compd. No.	UV[a] λ_{max}^{EtOH} mμ (log ε)	IR ν_{max}^{KBr} cm^{-1}	NMR[b] τ (in CF_3COOH)
XXV	234 (3.98)s, 238 (4.02)	2870 (>NH, –OH)	1.37 (1H, s, =CH– (oxazole))
	244 (3.93)s, 269 (3.69)	1699 (C=O)	1.23 (1H,s, =CH– (pyrimidine))
XXVI	234 (4.06)s, 239 (4.13)	2860 (>NH, –OH)	7.03 (3H, s, $>CCH_3$)
	245 (4.05)s, 272 (3.79)	1710 (C=O)	1.28 (1H, s, =CH– (pyrimidine))

a) s: shoulder *b*) s: singlet *c*) M. Ishidate and H. Yuki, *Chem. Pharm. Bull.* (Tokyo), **8**, 137 (1960)

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