[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW MEXICO HIGHLANDS UNIVERSITY]

Potential Purine Antagonists. VI. Synthesis of 1-Alkyl- and 1-Aryl-4-substituted Pyrazolo[3,4-*d*]pyrimidines[1,2]

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Various monosubstituted hydrazines have been reacted with ethoxymethylenemalononitrile to yield the corresponding 1-substituted-5-amino-4-cyanopyrazoles (IV). Treatment of IV with concentrated sulfuric acid gave the corresponding 1-substituted-5-aminopyrazole-4-carboxamides (XVI). The structure of 5-amino-1-phenylpyrazole-4-carboxamide was established by an unambiguous synthesis.

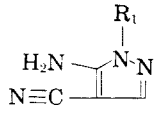
The preparation of 1-alkyl- and 1-aryl-4-aminopyrazolo[3,4-*d*]pyrimidines has been accomplished by treating the corresponding 1-alkyl(or aryl)-5-amino-4-cyanopyrazole (IV) with boiling formamide. Heating 1-alkyl(or aryl)-5-amino-4-pyrazolecarboxamide (XVI) with formamide in a similar manner gave the corresponding 1-alkyl(or aryl)-4-hydroxypyrazolo-[3,4-*d*]pyrimidine (XVII). Phosphorus oxychloride and XVII yielded the 1-alkyl- or 1-aryl-4-chloropyrazolo[3,4-*d*]pyrimidine (XVIII) which then was utilized for the synthesis of various additional 4-substituted pyrazolo[3,4-*d*]pyrimidines by nucleophilic displacement of the chlorine atom.

In accord with a program for the synthesis of various purine antagonists, a number of compounds containing the pyrazolo[3,4-*d*]pyrimidine nucleus have recently been prepared in this laboratory.[3] The inhibition of the growth of Adenocarcinoma 755 and Leukemia 5178 in mice by 4-aminopyrazolo[3,4-*d*]pyrimidine and 1-methyl-4-aminopyrazolo[3,4-*d*]pyrimidine[4] as well as the inhibition of cellular growth by 4-aminopyrazolo[3,4-*d*]pyrimidine in certain tissue culture studies[5] has prompted further investigation of derivatives containing this ring system. In particular, it seemed desirable to synthesize various substituted 4-aminopyrazolo[3,4-*d*]pyrimidines.

Since in the early synthetic studies of this series 1-methyl-4-aminopyrazolo[3,4-*d*]pyrimidine was prepared and found to possess anti-tumor activity,[4] a complete investigation of the preparation of 1-alkyl- and 1-aryl-4-substituted pyrazolo[3,4-*d*]pyrimidines was undertaken.

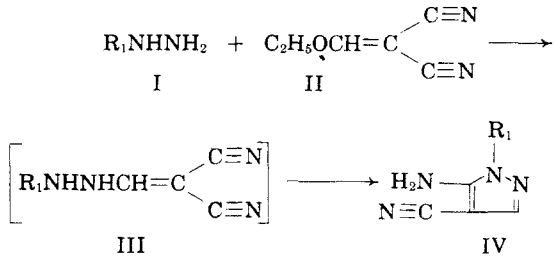
It was discovered that when a mono-substituted hydrazine (I), either aliphatic or aromatic, was reacted with ethoxymethylenemalononitrile (II) in boiling alcoholic solution, the corresponding 1-alkyl- or 1-aryl-5-amino-4-cyanopyrazole (IV) was formed in good yield. The various 1-substituted-5-amino-4-cyanopyrazoles synthesized in this manner are listed in Table I.

TABLE I



1-ALKYL(ARYL)-5-AMINO-4-CYANOPYRAZOLES

R_1	M.P., °C.	Yield (%) of Purified Product	U. V. Absorption $\lambda_{max.}$ (mμ) pH = 1	pH = 11	Recrystallization Solvents	Analyses Calc'd C	H	N	Found C	H	N
CH_3	222–223	86.4	238		Water	49.2	4.92	45.9	49.2	4.62	46.0
CH_2CH_2OH	158–160	83.5	225	235	Ethanol			26.8			26.8
C_6H_5	140	80.0	224		Water	65.1	4.40	30.4	65.2	4.35	30.8
p-Cl-C_6H_4	167–167.5	77.5	230	235	Ethanol			25.7			25.7
p-Br-C_6H_4	168–170	40.0	233	235	Ethanol			21.3			21.4
o-Cl-C_6H_4	124	61.0		234	Ethanol			25.7			25.7
p-NO_2-C_6H_4	224–225	81.0	285	238 285	Ethanol			30.6			30.1
p-CH_3-C_6H_4	158–159	84.0	226		Ethanol and water			28.3			28.2



I II III IV

(1) This investigation was supported by research grant C-2105(C) from the National Cancer Institute of the National Institutes of Health, Public Health Service.

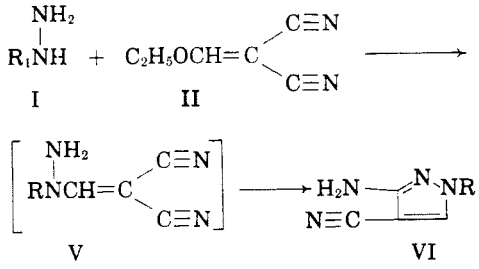
(2) Presented in part before the Division of Organic Chemistry, 129th Meeting of the American Chemical Society, Dallas, Texas, April, 1956.

(3) Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).

(4) Skipper, Robins, and Thompson, *Proc. Soc. Exptl. Biol. Med.*, **89**, 594 (1955).

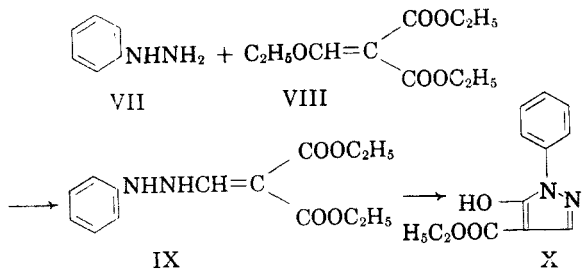
(5) Hsu, Robins, and Cheng, *Science*, **123**, 848 (1956).

The question of the condensation of a mono-substituted hydrazine (I) and ethoxymethylenemalononitrile (II) to form the alternative structure, 1-alkyl(aryl)-3-amino-4-cyanopyrazole (VI), although rather unlikely, cannot entirely be eliminated since the reaction could conceivably proceed as follows:



Several investigations were carried out in order to support the assigned structure of 1-alkyl(aryl)-5-amino-4-cyanopyrazole (IV).

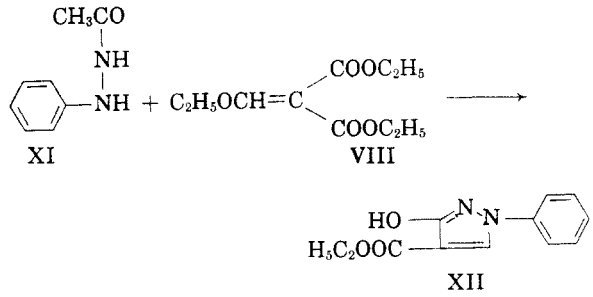
Claisen and Haase[6] prepared 5-hydroxy-1-phenylpyrazole-4-ethylcarboxylate (X) by the reaction of phenylhydrazine (VII) and ethoxymethylenemalonic ester (VIII) in diethyl ether:



The intermediate IX was isolated, m.p. 112°, and cyclization of the pyrazole ring required heating IX to 170–175°. The structure of 5-hydroxy-1-phenylpyrazole-4-ethylcarboxylate was definitely established by Claisen and Haase by hydrolysis of X followed by decarboxylation to give the known 5-hydroxy-1-phenylpyrazole.

The other isomer, 3-hydroxy-1-phenylpyrazole-4-ethylcarboxylate (XII), was prepared by Michaelis and Remy[7] by the reaction of ethoxymethylenemalonic ester (VIII) with β-acetylphenylhydrazine (XI) in phosphorus oxychloride.

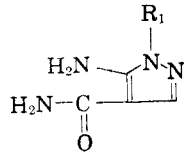
The syntheses of X and XII were repeated in this laboratory. The ultraviolet absorption spectra



of X and XII were found to differ considerably. At *p*H 1, X had $\lambda_{max.}$ 219 mμ and XII had $\lambda_{max.}$ 275 mμ. At *p*H 11, X had $\lambda_{max.}$ 237 mμ and XII had $\lambda_{max.}$ 306 mμ. 5-Amino-4-cyano-1-phenylpyrazole (IV, R_1 = C_6H_5) was converted by concentrated sulfuric acid to 5-amino-1-phenylpyrazole-4-carboxamide (XVI, R_1 = C_6H_5). This latter compound was found to possess $\lambda_{max.}$ of 225 mμ at *p*H 1 and $\lambda_{max.}$ of 240 mμ at *p*H 11. This information suggests that the structure assigned to 5-amino-1-phenylpyrazole-4-carboxamide is correct since the ultraviolet absorption spectra resemble that of X rather closely.

The structure of 5-amino-1-phenylpyrazole-4-carboxamide (XV) was definitely established in the following manner. 5-Hydroxy-1-phenylpyrazole-4-ethylcarboxylate (X) was treated with phosphorus oxychloride and phosphorus pentachloride to give 5-chloro-1-phenylpyrazole-4-ethylcarboxylate, which was treated with alcoholic ammonia in a bomb at 170° to give 5-amino-1-phenylpyrazole-4-carboxamide (XV). This compound was shown to be identical to XVI (R_1 = C_6H_5), synthesized from 5-amino-4-cyano-1-phenylpyrazole (IV, R_1 = C_6H_5).

TABLE II



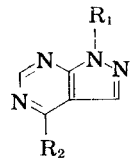
1-ALKYL(ARYL)-5-AMINO-4-PYRAZOLECARBOXAMIDES

R_1	M.P., °C.	Yield (%) of Purified Product	U. V. Absorption $\lambda_{max.}$ (mμ) *p*H = 1	*p*H = 11	Recrystallization Solvents	Analyses Calc'd C	H	N	Found C	H	N
CH_3	237–239	95	223 250	251	Water	42.9	5.72	40.0	43.3	5.60	40.0
CH_2CH_2OH	273–275	98	262	259	Ethanol			20.9			21.0
C_6H_5	172–173	84	225	240	Ethanol and water	59.4	4.95	27.7	59.5	4.87	28.1
p-Cl-C_6H_4	204–205	86	230	239	Ethanol and water			23.6			23.3
p-CH_3-C_6H_4	173–175	80	223 259	236	Water			25.9			25.8

(6) Claisen and Haase, *Ber.*, **28**, 36 (1895).

(7) Michaelis and Remy, *Ber.*, **40**, 1020 (1907).

TABLE III



1-ALKYL(ARYL)-4-SUBSTITUTEDPYRAZOLO[3,4-*d*]PYRIMIDINES

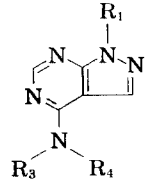
R_1	R_2	M.P., °C.	Yield,[a] %	U. V. Absorption $\lambda_{max.}$ (mμ) *p*H = 1	*p*H = 11	Alcohol	Recrystallization Solvents	Analyses Calc'd C	H	N	Found C	H	N
CH_3	OH	>300	98	252	258 270	252	Water	48.0	4.30	37.3	48.1	4.39	37.5
CH_3	Cl	98–99	92			260	Heptane	42.7	2.97	33.3	42.7	2.91	33.3
CH_3	NH_2	266–268	68	259	262 275		Water	48.3	4.60	47.0	48.7	4.60	47.3
CH_3	SH	>300	81	320	320		Repptd.	43.4	3.61	33.8	43.4	4.00	34.0
CH_3	SCH_3	135	81	255 297	290	283	Methanol	46.4	4.44	31.1	46.6	4.82	31.0
CH_3	S-  -Cl	156–157	70	252	258 269	285	Benzene			20.2			20.0
CH_3	OCH_3	105–106	51	252	252	247	Methanol			34.2			34.2
CH_3	OC_2H_5	93	59	253	251		Ethanol			31.4			31.1
CH_3	OC_6H_5	142.5	20	254	273	252	Ethanol			24.8			24.7
CH_3	O-  -Cl	141	52	257	251		Methanol			21.5			21.4
CH_3	O-  -Br	167	61	255	250		Methanol			18.4			18.6
CH_3	H	125–126	25	261	262		Benzene	53.7	4.50	41.8	53.9	4.55	41.9
CH_2CH_2OH	OH	251–253	66	255	270		2-Ethoxyethanol			31.1			30.8
CH_2CH_2OH	NH_2	223–224	43	258	262 276		Methanol	47.0	5.03	39.1	47.3	4.93	39.1
C_6H_5	OH	299	66	230	231 279		Water	62.2	3.78	26.4	62.3	3.78	26.9
C_6H_5	Cl	128	94			240	Heptane	57.3	3.04	24.3	57.1	3.04	24.6
C_6H_5	NH_2	210	70	240	235 282		Ethanol and water	62.5	4.26	33.2	62.4	3.90	33.4
C_6H_5	SH	280–281	85		232 321		Repptd.	57.8	3.54	24.6	57.6	3.64	24.6
C_6H_5	OCH_3	118.5	35	230	232 275		Methanol			24.7			24.4
C_6H_5	OC_2H_5	92–94	44	230	235 280		Ethanol	65.0	5.03	23.3	65.2	5.28	23.1
p-Cl-C_6H_4	OH	>300	90	235	238 280		Acetic acid	53.7	2.45	22.8	53.7	2.90	22.9
p-Cl-C_6H_4	Cl	138–139	98			248	Heptane	49.8	2.28	21.2	50.1	2.29	21.6
p-Cl-C_6H_4	NH_2	284	46	240	238 282		Pyridine	53.9	3.27	28.5	53.7	3.10	28.4

TABLE III *Continued*

R_1	R_3	M.P., °C.	Yield,[a] %	U. V. Absorption $\lambda_{max.}$ (mμ) *p*H = 1	*p*H = 11	Alcohol	Recrystallization Solvents	Analyses Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
p-Cl-C_6H_4	SH	>300	87		239 322		Repptd.	50.2	3.74	21.3	50.2	3.97	21.5
p-Br-C_6H_4	NH_2	>300	90	244	240 283		Ethanol			24.1			23.9
o-Cl-C_6H_4	NH_2	254	81	255	270		Pyridine and water	53.9	3.27	28.5	53.4	3.23	28.2
p-NO_2-C_6H_4	OH	>300	66	248 315	256 321		Acetic acid			27.3			27.5
p-NO_2-C_6H_4	Cl	204–205	85			225 263 310	Heptane	48.0	2.20	25.4	47.6	2.32	25.4
p-NO_2-C_6H_4	NH_2	>300	72	224 265 300	259 295	224 263 322	Pyridine			32.8			32.4
p-CH_3-C_6H_4	NH_2	>300	90	242	240 280		Ethanol and water			31.1			31.2

[a] Yields are based on products purified by recrystallization.

TABLE IV



1-Alkyl(Aryl)-4-substituted-aminopyrazolo[3,4-*d*]pyrimidines

R_1	R_3	R_4	M.P., °C.	Method of Prepn.	Yield,[a] %	U. V. Absorption $\lambda_{max.}$ (mμ) *p*H = 1	*p*H = 11	Alcohol	Recrystallization Solvents	Analyses Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
CH_3	H	CH_3	200–201	A	79	222 264	230 282		Methanol	51.5	5.55	42.9	51.2	5.80	42.5
CH_3	H	C_2H_5	133–135	B	64	224 265	234 284		Methanol			39.5			39.2
CH_3	H	*n*-C_3H_7	117	B	91	224 265	234 284		Methanol			36.6			36.3
CH_3	H	*n*-C_4H_9	87–88	B	74	224 265	234 284		Benzene and heptane			34.2			34.1
CH_3	H	$CH(CH_3)_2$	106–108	B	70	224 265	234 284		Methanol			36.6			36.6
CH_3	H	CH_2—CH_2—OH	208.5	B	75	225 265	283		Ethanol			36.2			36.0

TABLE IV *Continued*

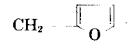
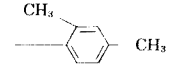
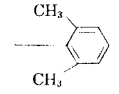
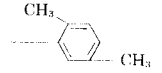
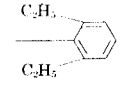
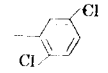
R_1	R_3	R_4	M.P., °C.	Method of Prepn.	Yield,[a] %	U. V. Absorption $\lambda_{max.}$ (mμ) pH = 1	pH = 11	Alcohol	Recrystallization Solvents	Analyses Calc'd C	H	N	Found C	H	N
CH_3	CH_3	CH_3	132	B	95	224 267	284		Ethanol			39.5			39.5
CH_3	H	C_6H_5	173	A	91	271	284		Methanol			31.1			31.2
CH_3	H	o-Cl-C_6H_4	169–170	A	95	270	284		Ethanol			27.0			27.3
CH_3	H	o-CH_3-C_6H_4	164–166	A	61			285	Ethanol	65.2	5.49	29.3	65.2	5.46	29.2
CH_3	H	m-Cl-C_6H_4	213	B	74	273	297		Ethanol			27.0			27.2
CH_3	H	m-CH_3-C_6H_4	179–180	B	42	272	295		Ethanol			29.3			29.3
CH_3	H	p-Br-C_6H_4	250–251	A	58			308	2-Ethoxyethanol			22.8			22.6
CH_3	H	p-Cl-C_6H_4·HCl	234–235	A	88			307	2-Ethoxyethanol			23.6			23.5
CH_3	H	p-CH_3-C_6H_4	186–188	B	50			305	2-Ethoxyethanol			29.3			29.4
CH_3	H	p-NO_2-C_6H_4	293	A	64	263 307	270 350		2-Ethoxyethanol			31.1			30.8
CH_3	H	CH_2—C_6H_5	158–159.5	A	91	224 266	283	283	Ethanol			29.3			29.1
CH_3	H		150	B	90	223 266	283	283	Benzene			30.6			30.7
CH_3	H		192	B	91	220 269	284		Methanol and benzene			27.6			27.6
CH_3	H		188–189	B	70	220 267	288		Methanol and benzene			27.6			27.5
CH_3	H		170 (subl.)	B	99	220 269	284		Methanol and benzene			27.6			27.8
CH_3	H		156	B	77	220 267	289	284	Ethanol			25.0			25.2
CH_3	H		150	B	51			289	Methanol			23.8			23.8
CH_3	H	NH_2	246.5–247.0	A	99	222 264	270 252		50% Ethanol			51.1			50.8
CH_3	H		90–91	B	18	254	268		Ethanol			31.9			31.3

TABLE IV *Continued*

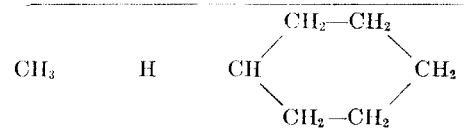
R_1	R_3	R_4	M.P., °C.	Method of Prepn.	Yield,[a] %	U. V. Absorption $\lambda_{max.}$ ($m\mu$) pH = 1	pH = 11	Alcohol	Recrystallization Solvents	Analyses Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
CH_3	H		95–96	B	55	254	270		Methanol			30.3			30.3
CH_3	H	$CH_2—CH_2—NH—CH_2—CH_2—OH$	87	B	64	273	284		Benzene			35.5			35.4
CH_3	H	$CH_2—CH_2—CH_2—O—CH(CH_3)_2$	163–165	B	41	224 266	283		Methanol, benzene, and heptane			28.1			28.3
CH_3	H	$C(CH_3)_2—CH_2—C(CH_3)_3$	132–133.5	B	64	225 270	288	289	Methanol	64.5	8.83	26.8	64.0	9.08	26.7
CH_3	H	$CH_2—CH_2—CH_2—O—CH_3$	227–229	B	50	223 266	283		2-Ethoxyethanol			31.7			31.4
CH_3	H	$NH—CH_2—CH_2—OH$	133–134	A	84	225 270	287		Methanol			40.3			40.1
CH_3	C_2H_5	C_6H_5	175–177	B	80	220 273	240 289		Methanol and benzene			27.7			27.4
CH_3	n-C_3H_7	C_6H_5	127–129	B	70	220 273	240 289		Methanol and benzene			26.5			26.4
CH_3	n-C_4H_9	C_6H_5	98–99	B	65	220 273	240 289		Methanol and water			24.9			24.8
C_6H_5	H	CH_3	203	A	76	242	238 288		Ethanol	64.0	4.92	31.5	64.3	5.26	31.2
C_6H_5	H	C_2H_5	201–203	A	81	243	237 288		Ethanol	65.2	5.48	29.2	65.0	5.64	29.8 28.8
C_6H_5	H	$CH(CH_3)_2$	129–130	B	82	243	238 288		Ethanol			27.7			27.4
C_6H_5	H	n-C_4H_9	118–120	B	76			240 293	95% Ethanol	67.4	6.42	26.2	67.0	6.38	26.2
C_6H_5	H	NH_2	184–186	A	63	241	236 282		2-Ethoxyethanol			37.1			36.8
C_6H_5	H	$NH—CH_3$	153–155	A	79			242 294	Ethanol	60.0	5.03	35.0	60.2	5.01	34.3
C_6H_5	CH_3	CH_3	137–148	B	62	246	238 294		95% Ethanol	65.3	5.48	29.4	65.8	5.41	29.6
C_6H_5	CH_3	C_6H_5	115–116	A	65			240 297	Ethanol	71.7	5.02	23.3	71.2	4.73	23.3
C_6H_5	C_2H_5	C_6H_5	80.5	B	33			241 300	95% Ethanol	72.6	5.44	22.2	72.6	5.46	22.1
C_6H_5	C_2H_5	C_2H_5	79.0–79.5	B	35	246	238 294		95% Ethanol			26.2			26.3

TABLE IV *Continued*

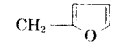
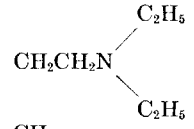
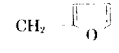
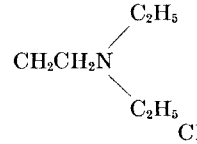
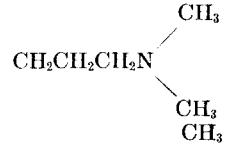
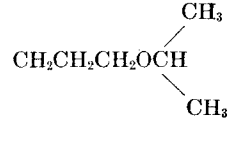
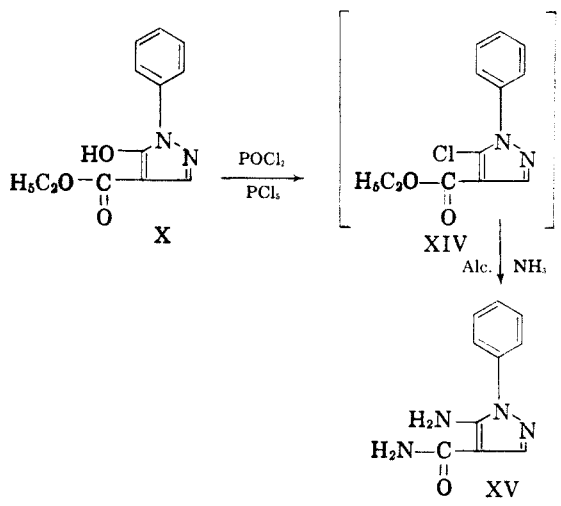
R_1	R_3	R_4	M.P., °C.	Method of Prepn.	Yield,[a] %	U. V. Absorption $\lambda_{max.}$ ($m\mu$) pH = 1	pH = 11	Alcohol	Recrystallization Solvents	Analyses Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
C_6H_5	H	C_6H_5	208–210	A	92	246	307		Ethanol	71.2	4.56	24.4	71.4	4.39	24.1
C_6H_5	H	*o*-Cl-C_6H_4	157–158	A	65	242	295		2-Ethoxyethanol	63.6	3.77	21.8	63.6	3.72	21.9
C_6H_5	H	*o*-CH_3-C_6H_4	175.5–177.5	A	84			242 295	Ethanol	71.7	5.03	23.2	72.1	5.03	23.0
C_6H_5	H	*m*-Br-C_6H_4	210–210.5	A	93			233 248 309	2-Ethoxyethanol			19.1			19.2
C_6H_5	H	*m*-Cl-C_6H_4	192–194	B	87			249 309	2-Ethoxyethanol			21.8			21.4
C_6H_5	H	*p*-Cl-C_6H_4	218–219	A	75			250 306	Ethanol	63.6	3.77	21.8	63.9	3.70	21.9
C_6H_5	H	*p*-CH_3-C_6H_4	240–241	A	98			246 309	95% Ethanol	71.7	5.03	23.3	71.0	5.03	23.5
C_6H_5	H	CH_2—C_6H_5	199–201	A	77	240	293		Ethanol	72.0	5.02	23.3	72.1	5.13	22.8
C_6H_5	H		169–170	A	98			240 292	Ethanol			24.1			24.3
C_6H_5	H		79–80	B	20	241	242 289		Heptane	65.7	7.12	27.1	65.0	7.10	27.6
p-Cl-C_6H_4	H	CH_3	270–272	A	90			245 294	Ethanol	55.5	3.88	27.0	55.2	3.72	26.5
p-Cl-C_6H_4	CH_3	CH_3	205.5	A	84			246 300	Ethanol	57.2	4.43	25.6	57.4	4.25	25.3
p-Cl-C_6H_4	H	CH_2—C_6H_5	227	A	92			241 296	Ethanol	64.6	4.21	20.9	65.0	4.15	20.6
p-Cl-C_6H_4	H		187.5	A	98			244 294	Ethanol			21.5			21.2
p-Cl-C_6H_4	H		105–106	B	65	246	242 289		Water and ethanol			24.4			24.4
p-Cl-C_6H_4	H		147–149	B	60	247	242 289		Benzene			25.4			25.0
p-Cl-C_6H_4	H		137	B	55	250	242 289		Benzene			20.3			20.5

TABLE IV *Continued*

R_1	R_3	R_4	M.P., °C.	Method of Prepn.	U. V. Absorption $\lambda_{max.}$ (mμ) Yield,[a] %	pH = 1	pH = 11	Alcohol	Recrystallization Solvents	Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
p-Cl-C_6H_4	H	$CH_2CH_2CH_2N(C_2H_5)_2$	131	B	56	247	242 289		Methanol and benzene			23.4			23.6
p-Cl-C_6H_4	H	$CH_2CH_2CH_2N$(morpholine)	182–184	A	89	247	242 289		Methanol and 2-ethoxyethanol			22.5			22.8
p-Cl-C_6H_4	H	$CH_2CH_2CH_2OCH_3$	162.5–163	A	99	250	242 289		Benzene and methanol			22.0			21.8
p-Cl-C_6H_4	H	*o*-Cl-C_6H_4	181–182	A	97	254	289		Benzene			19.6			19.6
p-Cl-C_6H_4	H	*o*-CH_3-C_6H_4	167	B	59	256	289	247 298	Benzene and methanol			20.9			21.1
p-Cl-C_6H_4	H	*p*-Cl-C_6H_4	235	A	87			255 312	Benzene and methanol			19.6			19.4
p-Cl-C_6H_4	H	$CH_2CH_2NHCH_2CH_2OH$	154–155	B	50	247	242 289		Benzene and methanol			25.2			25.2

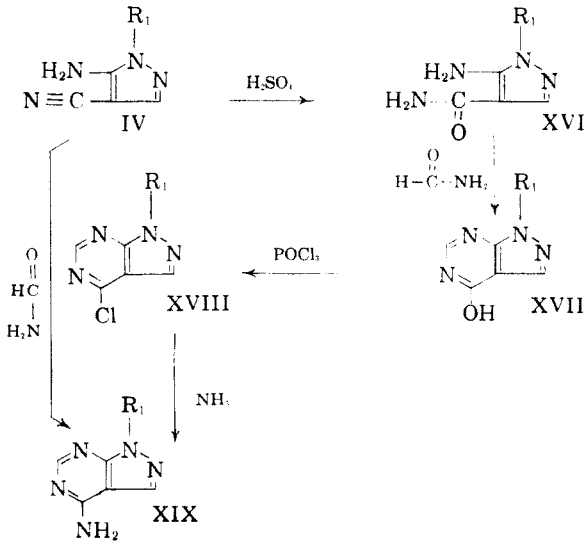
[a] Yields are based on products purified by recrystallization.



This established the structure of 5-amino-4-cyano-1-phenylpyrazole. Since the ultraviolet absorption spectra for 5-amino-1-methylpyrazole-4-carboxamide and 5-amino-1-phenylpyrazole-4-carboxamide are quite similar, it would follow that the structure assigned to 5-amino-4-cyano-1-methylpyrazole (IV, $R_1 = CH_3$) was also correct.

It was found that treatment of the 1-alkyl(aryl)-5-amino-4-pyrazoles (IV) with cold concentrated sulfuric acid gave the corresponding 1-alkyl(aryl)-5-amino-4-pyrazole carboxamide (XVI); (See Table II.) This reaction proceeds in a manner similar to the preparation of 3-aminopyrazole-4-carboxamide from 3-amino-4-cyanopyrazole.[3] 1-Alkyl(Aryl)-5-amino-4-pyrazole carboxamide then was converted to the corresponding 1-alkyl(aryl)-4-hydroxypyrazolo[3,4-*d*]pyrimidine (XVII), (Table III), with boiling formamide.

The 1-alkyl- or 1-aryl-4-chloropyrazolo[3,4-*d*]pyrimidines (XVIII) listed in Table III were obtained by refluxing the corresponding 4-hydroxy derivatives (XVII) with phosphorus oxychloride. Chlorination proceeded smoothly, and it was found that the addition of dimethylaniline to the reaction mix-



ture was unnecessary. This observation is interesting since the chlorination of 4-hydroxypyrazolo[3,4-*d*]pyrimidine requires both dimethylaniline and phosphorus oxychloride.[3]

The preparation of the various 1-alkyl(aryl)-4-aminopyrazolo[3,4-*d*]pyrimidines (XIX) listed in Table IV was accomplished by two routes. The treatment of 1-alkyl(aryl)-5-amino-4-cyanopyrazole (IV) with boiling formamide offered the most direct method of synthesis. It is to be noted that the treatment of an *o*-substituted aminonitrile with formamide to close the pyrimidine ring was first applied successfully to the synthesis of 4-aminopyrazolo[3,4-*d*]pyrimidine.[3] This method has since been utilized effectively in the synthesis of 4-aminopyrimido[4,5-*b*]quinoline.[8] To check on the structures formed by this ring closure, several 4-aminoderivatives were also prepared from the corresponding 4 - chloropyrazolo[3,4 - *d*]pyrimidines (XVIII).

Numerous N-substituted amino derivatives (XXVI) were prepared by the reaction of XVIII with various primary and secondary amines in alcoholic or benzene solution refluxed on the steam bath.

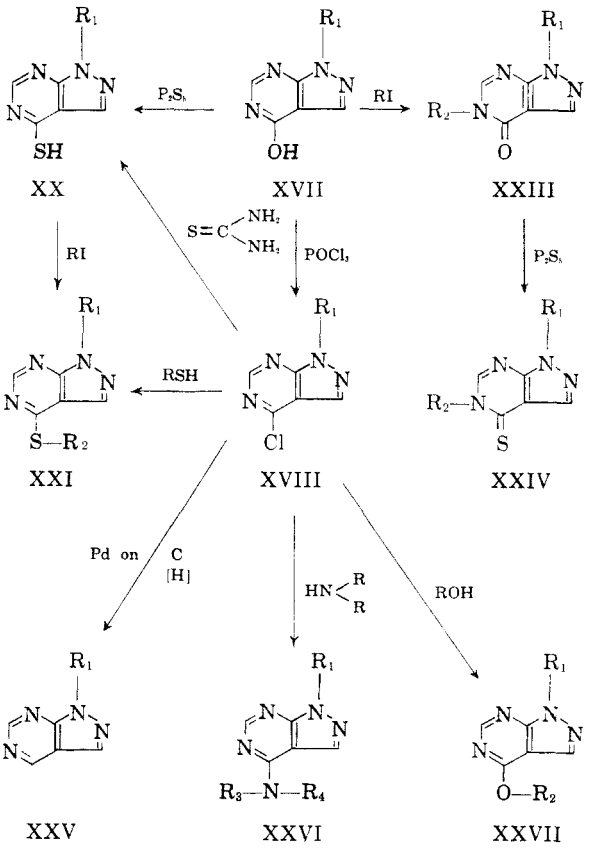
The 1-alkyl(aryl)-4-mercaptopyrazolo[3,4-*d*]pyrimidines (XX) were synthesized from either the corresponding 4-hydroxy derivative (XVII) with phosphorus pentasulfide in tetralin or pyridine, or by treatment of the corresponding 4-chloro compounds (XVIII) with thiourea in boiling ethanol.[9]

Alkylation of XX with alkyl iodides resulted in the 4-alkylmercapto derivatives (XXI).

Several of the 4-alkylmercapto derivatives were also obtained from the 1-alkyl(aryl)-4-chloropyrazolo[3,4-*d*]pyrimidine (XVIII) and the appropriate alkyl mercaptan in basic media.

4-(*p*-Chlorophenylmercapto)-1-methylpyrazolo[3,4-*d*]pyrimidine (XXI, R_2 = *p*-ClC_6H_4) was made by the reaction of *p*-chlorothiophenol and 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine. However, it was found that this reaction proceeded only in anhydrous benzene. The ultraviolet absorption spectra of this compound in ethanol is similar to that of the corresponding 4-methylmercapto derivative; however, in aqueous solution (*p*H 1 and *p*H 11) the spectra is identical to that of 4-hydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine, indicating the rapid hydrolysis of the *p*-chlorophenylmercapto group in aqueous solution.

Various 4-alkoxy derivatives (XXVII) were obtained from the appropriate 1-alkyl(aryl)-4-chloropyrazolo[3,4-*d*]pyrimidine (XVIII) and the corresponding sodium alkoxide. Methylation of 1-methyl - 4 - hydroxypyrazolo[3,4 - *d*]pyrimidine (XVII, R_1 = CH_3) resulted in the preparation of

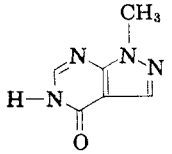


REACTION SCHEME

1,5-dimethylpyrazolo[3,4-*d*]pyrimidone-4 (XXIII, R_1, R_2 = CH_3). Treatment of this compound with phosphorus pentasulfide in tetralin gave a compound which is apparently 1,5-dimethylpyrazolo[3,4-*d*]pyrimidine-4-thione (XXIV, R_1, R_2 = CH_3). A similar thiation has previously been reported by Elion and Hitchings.[10]

1-Methylpyrazolo[3,4-*d*]pyrimidine (XXV, R_1 = CH_3) was prepared by catalytic dehalogenation of 1 - methyl - 4 - chloropyrazolo[3,4 - *d*]pyrimidine (XVIII, R_1 = CH_3) using a palladium on charcoal catalyst. This procedure has been used successfully for the preparation of purine.[9]

Inspection of the ultraviolet absorption spectra of XVII, (R_1 = CH_3), XXIII, (R_1, R_2 = CH_3), and XXVII, (R_1, R_2 = CH_3) in methanol (see Figure 1) reveals that in neutral solution the structure of XVII, (R_1 = CH_3), is probably best represented as 1-methyl - 5 - H - pyrazolo[3,4 - *d*]pyrimidone - 4 (XXII). Similarly, the ultraviolet absorption



XXII

(8) Taylor and Kalenda, *J. Am. Chem. Soc.*, **78**, 5108 (1956).

(9) Bendich, Russell, and Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).

(10) Elion and Hitchings, *J. Am. Chem. Soc.*, **69**, 2138 (1947).

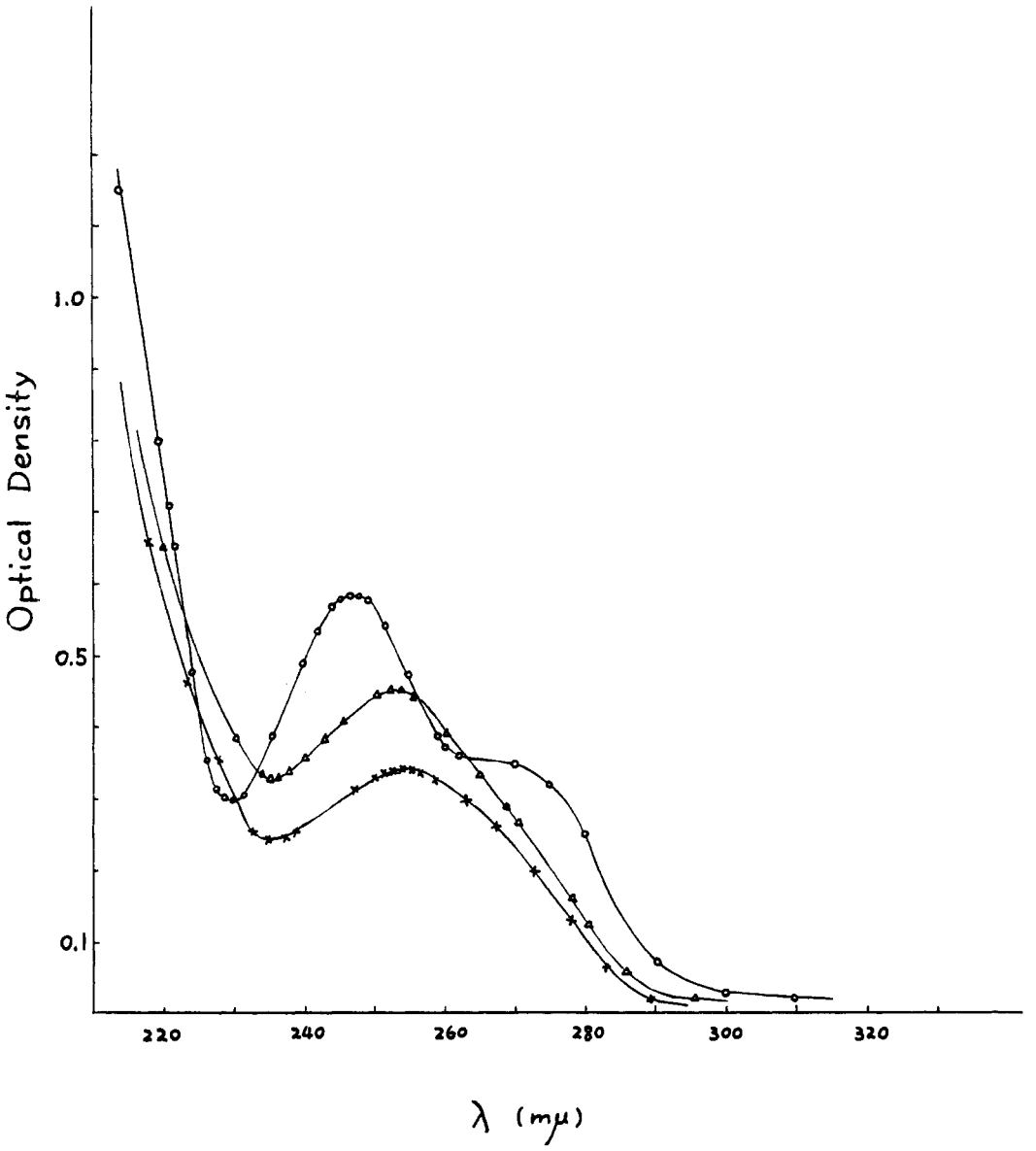
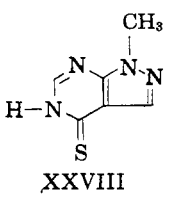


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA OF CERTAIN 1-METHYLPYRAZOLO[3,4-*d*]PYRIMIDINES, concentration 10 mg./liter, run in methanol.

—○—○—○— 1-Methyl-4-methoxypyrazolo[3,4-*d*] pyrimidine (XXVII, R_1, R_2 = CH_3); —△—△—△— 1-Methyl-4-hydroxypyrazolo[3,4-*d*] pyrimidine (XVII, R_1 = CH_3); —×—×—×— 1,5-Dimethylpyrazolo[3,4-*d*]pyrimidone-4 (XXIII R_1, R_2 = CH_3).

curves of XX, (R_1 = CH_3), XXIV, (R_1, R_2 = CH_3), and XXI, (R_1, R_2 = CH_3) (see Figure 2) indicate that XX, (R_1 = CH_3) in neutral solution is predominantly 1-methyl-5-H-pyrazolo[3,4-*d*]pyrimidine-4-thione (XXVIII).



XXVIII

The synthesis of 1-methyl-4-methylmercaptopyrazolo[3,4-*d*]pyrimidine (XXI, R_1, = CH_3) was accomplished by still another route. 4-Mercaptopyrazolo[3,4-*d*]pyrimidine[3] treated with an excess of methyl iodide in the presence of base gave a good yield of XXI, (R_1, R_2 = CH_3). Similarly, methylation of 4-hydroxypyrazolo[3,4-*d*]pyrimidine[3] with methyl iodide yielded 1,5-dimethylpyrazolo[3,4-*d*]pyrimidone-4 (XXIII, R_1, R_2 = CH_3). 4-Dimethylaminopyrazolo[3,4-*d*]pyrimidine[3] and methyl iodide gave 1-methyl-4-dimethylaminopyrazolo[3,4-*d*]pyrimidine (XXVI, R_1, R_3, R_4 = CH_3). In these methylation studies in each instance none of the theoretically possible "2-methyl" isomers were obtained. The structure of the 1-methyl derivative in each case had been previously determined by independent synthesis.

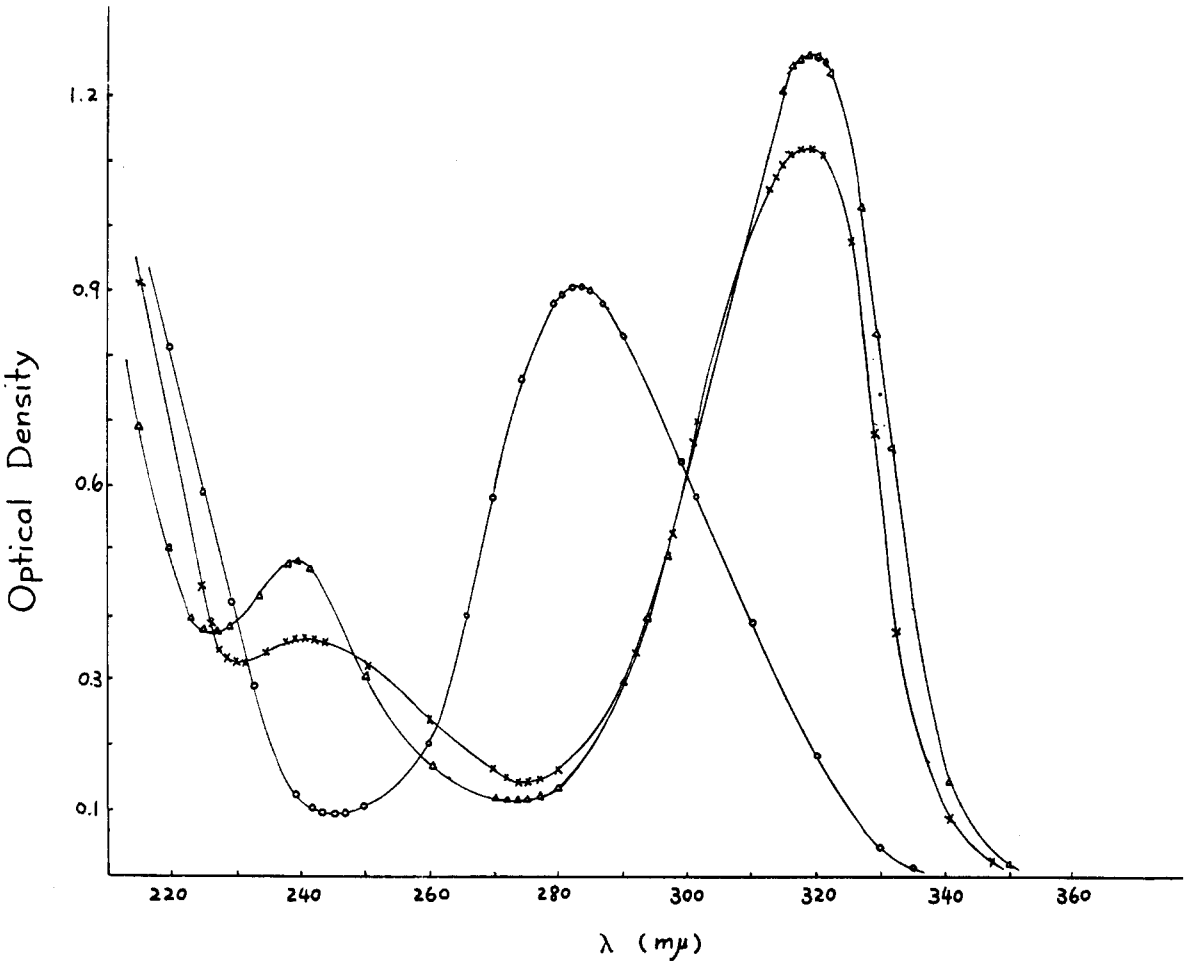
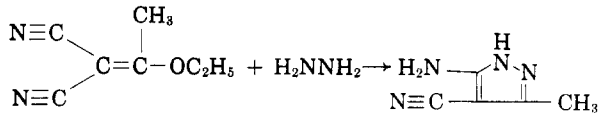


FIG. 2. ULTRAVIOLET ABSORPTION SPECTRA OF CERTAIN 1-METHYLPYRAZOLO[3,4-*d*]PYRIMIDINES, concentration 10 mg./liter, run in methanol.

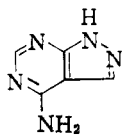
—○—○—○— 1-Methyl-4-methylmercaptopyrazolo [3,4-*d*]pyrimidine (XXI, R_1, R_2 = CH_3); —△—△—△— 1-Methyl-4-mercaptopyrazolo[3,4-*d*]pyrimidine (XX, R_1 = CH_3); —×—×—×— 1,5-Dimethylpyrazolo[3,4-*d*]pyrimidine-4-thione (XXIV, R_1, R_2 = CH_3).

The general method of synthesis of pyrazolo[3,4-*d*]pyrimidines from a pyrazole intermediate[3] has now been further extended to include the synthesis of various 3-methylpyrazolo[3,4-*d*]pyrimidines. The synthesis of methylethoxymethylenemalononitrile (XXIX) was accomplished from triethyl orthoacetate, malononitrile, and acetic anhydride. XXIX and hydrazine gave 3-amino-4-cyano-5-methylpyrazole (XXX) in a manner similar to the

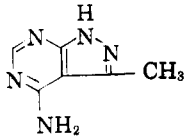


XXIX XXX

synthesis of 3-amino-4-cyanopyrazole.[3] Treatment of XXX with boiling formamide yielded 3-methyl-4-aminopyrazolo[3,4-*d*]pyrimidine (XXXI). This compound is of interest due to its structural relationship to 4-aminopyrazolo[3,4-*d*]pyrimidine[3] which has been shown to possess antitumor activity.[4,5]



4-Aminopyrazolo[3,4-*d*]pyrimidine

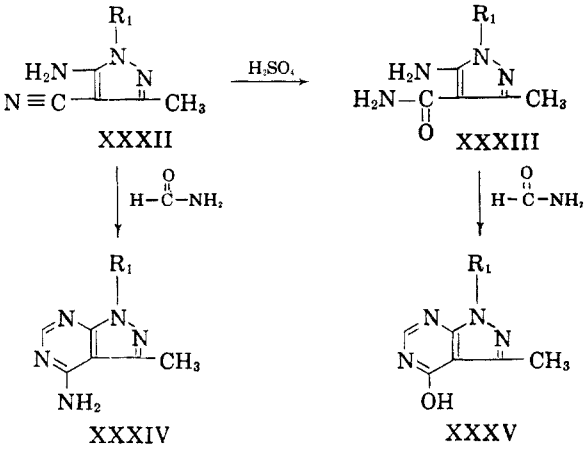


XXXI

Methylethoxymethylenemalononitrile (XXIX) was also reacted with several substituted hydrazines to give the corresponding 1-alkyl(aryl)-3-methyl-5-amino-4-cyanopyrazoles (XXXII). Hydrolysis of XXXII with concentrated sulfuric acid gave 1-alkyl(aryl)-3-methyl-5-aminopyrazole-4-carboxamide (XXXIII). Compounds XXXIV and XXXV were synthesized in the usual manner by heating XXXII and XXXIII respectively with formamide.

With regard to the biological interest in this group of compounds, the anti-tumor activity of 1-methyl-4-aminopyrazolo[3,4-*d*]pyrimidine (XIX, R_1 = CH_3) has already appeared in a preliminary report.[4]

1-Methyl-4-methylaminopyrazolo[3,4-*d*]pyrimi-



dine (XXVI, R_1, R_4 = CH_3, R_3 = H) has recently[11] been found to exhibit a similar activity against Adenocarcinoma 755 and Leukemia 5178. Further biological testing is now in progress. A complete report will appear elsewhere.

Acknowledgment. The authors wish to express their thanks to Merien Lamon Robins and Kwei-Chao Chao for their valuable technical assistance.

EXPERIMENTAL[12]

Preparation of 5-amino-4-cyano-1-methylpyrazole (IV, R_1 = CH_3). To 700 ml. of absolute ethanol and 70 g. of 98% methylhydrazine was carefully added, a little at a time, 121 g. of ethoxymethylenemalononitrile.[13] The addition was carried out at such a rate that the solution was kept boiling smoothly. A white precipitate gradually appeared. The reaction mixture was heated on the steam-bath for 30 minutes to insure the completion of the reaction and then was placed in a refrigerator overnight. The product was filtered and washed with a small amount of cold absolute ethanol. The yield was 109 g. (86.4%), m.p. 221–222°. Recrystallization from water raised the m.p. to 222–223°.

Anal. Calc'd for $C_5H_6N_4$: C, 49.2; H, 4.9; N, 45.9. Found: C, 49.2; H, 4.6; N, 46.0.

Preparation of 5-amino-4-cyano-1-phenylpyrazole (IV, R_1 = C_6H_5). To 88 g. of phenylhydrazine (I, R_1 = C_6H_5) in 360 ml. of absolute ethanol was added slowly, with shaking, 100 g. of ethoxymethylenemalononitrile. After about half of the addition was completed, the solution was carefully heated to boiling. The remaining ethoxymethylenemalononitrile was added at such a rate as to maintain gentle boiling of the solution. After all the ethoxymethylene malononitrile had been added, the solution was gently boiled for an additional 30 minutes and finally was set aside overnight in the refrigerator. The product was filtered and washed with a little ether to give 120 g. of crude material, m.p. 138–139°. The compound was further purified by recrystallization from water to give white crystals, m.p. 140°.

Anal. Calc'd for $C_{10}H_8N_4$: C, 65.1; H, 4.4; N, 30.4. Found: C, 65.2; H, 4.4; N, 30.8.

Preparation of 5-amino-1-(p-chlorophenyl)-4-cyanopyrazole (IV, R_1 = *p*-Cl-C_6H_4). Ethoxymethylenemalononitrile (90 g.) was added slowly to 500 ml. of hot ethanol containing 105 g. of *p*-chlorophenylhydrazine (I, R_1 = *p*-Cl-C_6H_4). The slow addition caused a smooth boiling of the solution, and a yellow, needle-like substance gradually precipitated from the hot solution. The reaction mixture was boiled gently for 15 minutes after the final addition of ethoxymethylenemalononitrile. The solution then was cooled and the product was filtered and washed with a small amount of ether. The yield was 125 g. (77.5%), m.p. 159–163°. Light-yellow crystals, m.p. 167–167.5°, were obtained after recrystallization from ethanol.

Anal. Calc'd for $C_{10}H_7ClN_4$: N, 25.7. Found: N, 25.7.

Preparation of 5-amino-4-cyano-1-β-hydroxyethylpyrazole (IV, R_1 = CH_2CH_2OH). To 42 g. of 70% β-hydroxyethylhydrazine in 100 ml. of ethanol was added carefully 50 g. of ethoxymethylenemalononitrile. The mixture was then boiled gently on a steam-bath for 30 minutes. A white precipitate gradually appeared from the hot solution. The reaction mixture was cooled and filtered and the solid washed with ether. White crystals, m.p. 158–160°, were obtained after recrystallization of the crude product from ethanol. The yield of purified material was 54 g. (83.5%).

Anal. Calc'd for $C_6H_8N_4O$: N, 26.8. Found: N, 26.8.

The other 1-aryl-5-amino-4-cyanopyrazoles listed in Table I were prepared by essentially the same procedure.

Preparation of 5-amino-1-methylpyrazole-4-carboxamide (XVI, R_1 = CH_3). To 100 ml. of concentrated sulfuric acid cooled in an ice-bath was gradually added, with stirring, 40 g. of powdered 5-amino-4-cyano-1-methylpyrazole (IV, R_1 = CH_3). The inside temperature was kept between 15–20°. The addition was accomplished over a period of 2 hours, and the solution then was stirred at room temperature for an additional 30 minutes and then was poured, with stirring, onto 500 g. of crushed ice. The solution was adjusted to *p*H 8 with concentrated ammonium hydroxide. Enough ice was added during the neutralization in order to maintain a temperature below 50°. The final volume was approximately 1200 ml. The solution was cooled overnight and finally filtered to yield 30 g. of colorless crystals, m.p. 232–235°. An additional portion of the product, 13 g., was obtained by evaporating the volume of the filtrate to 400 ml. Recrystallization of the crude product from water raised the melting point to 237–239°.

Anal. Calc'd for $C_5H_8N_4O$: C, 42.9; H, 5.72; N, 40.0. Found: C, 43.3; H, 5.60; N, 40.0.

Preparation of 5-amino-1-phenylpyrazole-4-carboxamide (XVI, R_1 = C_6H_5). To 400 ml. of concentrated sulfuric acid cooled in an ice-bath was added, with stirring, 88 g. of 5-amino-4-cyano-1-phenylpyrazole. During the addition, which required three hours, the inside temperature was maintained between 10–15°. The mixture was stirred at room temperature until solution was complete. The dark sulfuric acid solution then was poured onto crushed ice, and the solution was neutralized with concentrated ammonium hydroxide. The reaction mixture, which was allowed to reach 65–70° during neutralization, was cooled to room temperature and filtered to yield 90 g. of yellow crystalline product, m.p. 169–170°. Recrystallization of the crude compound from water raised the m.p. to 172–173°.

Anal. Calc'd for $C_{10}H_{10}N_4O$: C, 59.4; H, 4.95; N, 27.7. Found: C, 59.5; H, 4.87; N, 28.1.

The other 1-substituted 5-aminopyrazole-4-carboxamides were prepared by essentially the same procedure.

Preparation of 1-alkyl(aryl)-4-hydroxypyrazolo[3,4-d]pyrimidines (XVII). See Table III. *4-Hydroxy-1-methylpyrazolo-[3,4-d]pyrimidine* (XVII, R_1 = CH_3). A solution of 40 g. of 5-amino-1-methylpyrazole-4-carboxamide (XVI, R_1 = CH_3) and 100 ml. of C.P. formamide was boiled gently on a hot plate for 2 hours. An equal volume of water was added to the cooled mixture which then was set aside in a refrigerator overnight and finally was filtered. The crude product was purified by solution in hot, dilute potassium hydroxide followed by reprecipitation from the hot solution with glacial acetic acid. Final purification was accomplished by recrystallization from water to give 36 g. of white crystals, m.p. > 300°.

(11) Skipper, Robins, Thomson, Brockman, Schabel, and Cheng, *Proceedings of the American Association for Cancer Research*, 2, 147 (1956).

(12) All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus.

(13) Huber, *J. Am. Chem. Soc.*, 65, 2224 (1943).

Anal. Calc'd for $C_6H_6N_4O$: C, 48.0; H, 4.30; N, 37.3. Found: C, 48.1; H, 4.39; N, 37.5.

4-Hydroxy-1-phenylpyrazolo[3,4-d]pyrimidine (XVII, $R_1 = C_6H_5$). 5-Amino-1-phenylpyrazole-4-carboxamide (15 g.) was heated with 50 ml. of C.P. formamide at 190–200° for 30 minutes. The cooled solution was diluted with 50 ml. of water and allowed to stand in a refrigerator overnight. The product then was filtered and washed with water, and recrystallized from water to yield 11.0 g. of small needles, m.p. 299°.

Anal. Calc'd for $C_{11}H_8N_4O$: C, 62.2; H, 3.78; N, 26.4. Found: C, 62.3; H, 3.78; N, 26.9.

Preparation of 1-alkyl(aryl)-4-chloropyrazolo[3,4-d]pyrimidines (XVIII). See Table III. *4-Chloro-1-methylpyrazolo[3,4-d]pyrimidine* (XVIII, $R_1 = CH_3$). 4-Hydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine (XVII, $R_1 = CH_3$) (100 g.) was suspended in 600 ml. of phosphorus oxychloride. The mixture was refluxed for two hours after solution had occurred (a total of 4 hours). The excess phosphorus oxychloride was distilled from the clear, yellow solution under reduced pressure, and the residual syrup was poured very slowly, with vigorous stirring, onto 1 kg. of finely crushed ice. The mixture was allowed to stand for 30 minutes, and the white suspension was extracted with ether (approximately 6 × 600 ml.). The ethereal extract was washed well with ice-water. After drying the extract over magnesium sulfate for 12 hours, the ether was distilled to yield 95 g. of long, white needles, m.p. 97–98°. Recrystallization from heptane raised the m.p. to 98–99°.

Anal. Calc'd for $C_6H_5ClN_4$: C, 42.7; H, 2.97; N, 33.3. Found: C, 42.7; H, 2.91; N, 33.3.

4-Chloro-1-phenylpyrazolo[3,4-d]pyrimidine (XVIII, $R_1 = C_6H_5$). A mixture of 300 ml. of phosphorus oxychloride and 44 g. of 4-hydroxy-1-phenylpyrazolo[3,4-*d*]pyrimidine (XVII, $R_1 = C_6H_5$) was refluxed for three hours. Excess phosphorus oxychloride was distilled under reduced pressure, and the residual syrup was poured, with stirring, onto crushed ice. The aqueous suspension was extracted with chloroform. After drying overnight over sodium sulfate the chloroform was distilled to yield a slightly yellow-colored product, m.p. 121–124°. This crude product was recrystallized from heptane to give 45 g. of white needles, m.p. 128°.

Anal. Calc'd for $C_{11}H_7ClN_4$: C, 57.3; H, 3.04; N, 24.3. Found: C, 57.1; H, 3.04; N, 24.6.

4-Chloro-1-(p-nitrophenyl)pyrazolo[3,4-d]pyrimidine (XVIII, $R_1 = p\text{-}NO_2\text{-}C_6H_4$). To 260 ml. of phosphorus oxychloride was added 16 g. of finely powdered 4-hydroxy-1-(*p*-nitrophenyl)pyrazolo[3,4-*d*]pyrimidine (XVII, $R_1 = p\text{-}NO_2\text{-}C_6H_4$). The mixture was refluxed vigorously for six hours until solution was finally effected. The excess phosphorus oxychloride was distilled off under reduced pressure, and the syrupy residue was pured very slowly, with stirring, onto 500 g. of crushed ice. The crude product was only sparingly soluble in ether or chloroform. It was filtered with suction and washed well with ice-water until free from acid. The crude compound was dried in air and recrystallized from *n*-heptane to yield 14.0 g. of yellow needles, m.p. 204–205°.

Anal. Calc'd for $C_{11}H_6ClN_5O_2$: C, 48.0; H, 2.20; N, 25.4. Found: C, 47.6; H, 2.32; N, 25.4.

Preparation of 1-alkyl(aryl)-4-aminopyrazolo[3,4-d]pyrimidines (XIX). See Table III. *4-Amino-1-methylpyrazolo[3,4-d]pyrimidine* (XIX, $R_1 = CH_3$). *Method (1).* To 100 ml. of C.P. formamide was added 35 g. of 5-amino-4-cyano-1-methylpyrazole (IV, $R_1 = CH_3$). The solution was boiled for 1 hour and allowed to cool. To the reaction mixture was added 100 ml. of water and the solution was placed in the refrigerator overnight. After filtration, the crude product was suspended in 300 ml. of boiling water and 20 ml. of concentrated hydrochloric acid was added. The solution was boiled 3 minutes with charcoal and filtered. The hot filtrate was made basic with a solution of sodium hydroxide and allowed to cool. The product crystallized in colorless crystals and was filtered and washed with ice-water. A final recrystallization from water gave 21.0 g. (49%) of an analytically pure product, m.p. 266–268°.

Anal. Calc'd for $C_6H_7N_5$: C, 48.3; H, 4.6; N, 47.0. Found: C, 48.7; H, 4.6; N, 47.3.

Method (2). To 5 g. of 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (XVIII, $R_1 = CH_3$) was added 70 ml. of absolute ethanol previously saturated with dry ammonia gas at 0°. The mixture was heated at 160° in a glass-lined bomb for 6 hours. The solution then was evaporated to dryness on a steam-bath and the solid was crystallized from 95% ethanol containing a small amount of potassium hydroxide. The yield was 3 g. (68%), m.p. 266°. A mixture m.p. of this product and that obtained by *Method (1)* showed no depression. Both preparations gave identical ultraviolet spectra at *p*H 11 and *p*H 1.

4-Amino-1-phenylpyrazolo[3,4-d]pyrimidine (XIX, $R_1 = C_6H_5$). *Method (1).* A mixture of 5 g. of 4-chloro-1-phenylpyrazolo[3,4-*d*]pyrimidine (XVIII, $R_1 = C_6H_5$) and 150 ml. of absolute ethanol saturated with dry ammonia gas at 0° was heated at 160° in a bomb for 10 hours. The solution was evaporated to dryness and the residue was recrystallized from dilute ethanol to which a small amount of potassium hydroxide had been added. The yield was 3.2 g. (70%) of white needles, m.p. 210°.

Method (2). 5-Amino-4-cyano-1-phenylpyrazole (IV, $R_1 = C_6H_5$) (20 g.) was added to 75 ml. of C.P. formamide. The solution was boiled gently for 1 hour. To the warm mixture was carefully added 200 ml. of water and the solution was cooled overnight. The yield of crude product was 22.0 g., m.p. 208–210°. Recrystallization from an ethanol-water mixture raised the m.p. to 210°.

Anal. Calc'd for $C_{11}H_9N_5$: C, 62.5; H, 4.2; N, 33.2. Found: C, 62.4; H, 3.9; N, 33.4.

This product was identical to that prepared by *Method (1)* as judged on the basis of mixture melting points and identical ultraviolet absorption spectra at *p*H 1 and *p*H 11. Other 4-amino-1-substituted phenylpyrazolo[3,4-*d*]pyrimidines (XIX) were prepared in a manner similar to *Method (2)* for the preparation of 4-amino-1-phenylpyrazolo[3,4-*d*]-pyrimidine.

4-Amino-1-(β-hydroxyethyl)pyrazolo[3,4-d]pyrimidine (XIX, $R_1 = CH_2CH_2OH$). To 150 ml. of C.P. formamide was added 70 g. of 5-amino-4-cyano-1-(β-hydroxyethyl)-pyrazole (IV, $R_1 = CH_2CH_2OH$). The solution was boiled for 1 hour and 30 minutes and the warm solution was diluted with 100 ml. of water. Upon cooling the solution overnight, no crystals appeared; therefore, the excess formamide and water were removed under reduced pressure using a steam-bath as a source of heat. To the residue was added 200 ml. of water and 30 ml. of concentrated hydrochloric acid. The solution was boiled for 15 minutes, treated with charcoal, and filtered. The filtrate was made basic with potassium hydroxide and the warm solution was chilled overnight. The yield of crude product was 54.0 g. Recrystallization from water yielded 34.0 g. (42.5%), m.p. 217–219°. A second recrystallization from water raised the m.p. to 223–224°.

Anal. Calc'd for $C_7H_9N_5O$: C, 47.0; H, 5.0; N, 39.1. Found: C, 47.3; H, 4.9; N, 39.1.

Preparation of 1-alkyl(aryl)-4-mercaptopyrazolo[3,4-d]-pyrimidines (XX). See Table III. 4-Mercapto-1-methylpyrazolo[3,4-*d*]pyrimidine (XX, $R_1 = CH_3$). *Method (1).* 4-Chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (XVIII, $R_1 = CH_3$) (5 g.) and 2.5 g. of C.P. thiourea were added to 100 ml. of absolute ethanol. The mixture was refluxed for 1 hour, during which time a white crystalline product deposited in the hot solution. The product was filtered and washed with cold 95% ethanol. The yield was 4 g. (81%), m.p. > 300°.

Anal. Calc'd for $C_6H_6N_4S$: C, 43.4; H, 3.6; N, 33.8. Found: C, 43.4; H, 4.0; N, 34.0.

Method (2). Tetralin (400 ml.) was heated to 165°, and an intimate mixture of 10 g. of finely powdered 4-hydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine (XVII, $R_1 = CH_3$) and

50 g. of phosphorus pentasulfide was slowly added to the mixture, with stirring, over a period of 45 minutes. During that time the temperature of the mixture was allowed to climb to 185°. The reaction mixture then was heated at 190–195° for six hours with continuous stirring. The solution then was cooled overnight and filtered, and the solid was washed with petroleum ether and dried. The crude material then was added slowly to 1000 ml. of boiling water. Just enough potassium hydroxide was added to effect complete solution. The solution was treated with charcoal and filtered and the filtrate was acidified while hot with acetic acid. The solid was filtered immediately and washed with water to yield 8.0 g. (72.2%) of crude product. Reprecipitation of this material yielded a product which showed ultraviolet absorption curves identical with the product obtained by *Method (1)*.

Preparation of 1-(p-chlorophenyl)-4-mercaptopyrazolo[3,4-d]pyrimidine (XX, R_1 = p-Cl-C_6H_4). 4-Chloro-1-(p-chlorophenyl)pyrazolo[3,4-d]pyrimidine (XVIII, R_1 = p-Cl-C_6H_4) (5 g.) and 5.0 g. of thiourea was added to 180 ml. of absolute ethanol. The solution was refluxed for 6 hours. The solid was filtered and purified by dissolving in hot, dilute potassium hydroxide followed by precipitation with acetic acid. The yield of white needles was 4.3 g., m.p. >300°.

Anal. Calc'd for $C_{11}H_7ClN_4S$: C, 50.2; H, 3.7; N, 21.3. Found: C, 50.2; H, 4.0; N, 21.5.

Other 1-aryl-4-mercaptopyrazolo[3,4-d]pyrimidines listed in Table III were prepared in a similar manner from XVIII.

Preparation of 1-methyl-4-methylmercaptopyrazolo[3,4-d]-pyrimidine (XXI, R_1, R_2 = CH_3). *Method (1)*. To 8 g. of 4-mercapto-1-methylpyrazolo[3,4-d]pyrimidine (XX, R_1 = CH_3), dissolved in a solution of 5 g. of potassium hydroxide and 100 ml. of water, was slowly added, with stirring, 12 g. of methyl iodide. The mixture was transferred to a separatory-funnel and 15 ml. of methanol was added. The solution was shaken vigorously for 30 minutes. At the end of this period a white crystalline substance appeared, which was filtered and recrystallized from water. The yield was 7 g. (80.7%) of a white crystalline product which melted at 135°.

Anal. Calc'd for $C_7H_8N_4S$: N, 31.1. Found: N, 31.0.

Method (2). A mixture of 2.5 g. of 4-mercaptopyrazolo-[3,4-d]pyrimidine,[3] 2.5 g. of potassium hydroxide, 30 ml. of water, 15 g. of methyl iodide, and 50 ml. of methanol was refluxed on a steam-bath for 6 hours. The product crystallized from the hot solution as yellow needles. It was recrystallized from water to yield 1.5 g., m.p. 135°. The compound, when mixed with that made from *Method (1)*, showed no depression in melting point.

Method (3). To a mixture of 10 g. of methyl mercaptan, 5 g. of potassium hydroxide, and 20 g. of methanol was added, a little at a time, 5 g. of finely powdered 4-chloro-1-methylpyrazolo[3,4-d]pyrimidine (XVIII, R_1 = CH_3). The reaction proceeded instantly, and a white precipitate appeared in the alkaline solution. The mixture was heated gently on a steam-cone for 30 minutes and the solution was cooled and filtered. The product recrystallized from water to give white needles, m.p. 135°. This product was identical to that prepared by *Methods (1)* and *(2)* as judged by mixture melting point data and identical ultraviolet absorption spectra.

Preparation of 4-(p-chlorophenylmercapto)-1-methylpyrazolo[3,4-d]pyrimidine (XXI, R_1 = CH_3, R_2 = p-Cl-C_6H_4). p-Chlorothiophenol (6.5 g.) and 7.5 g. of 4-chloro-1-methylpyrazolo[3,4-d]pyrimidine (XVIII, R_1 = CH_3) were added to 200 ml. of anhydrous benzene and the solution was refluxed for 4 hours. The mixture solidified on cooling to give a product, m.p. 153–156°. Recrystallization from benzene raised the m.p. to 156–157°, yield 7.2 g.

Anal. Calc'd for $C_{12}H_9ClN_4S$: N, 20.2. Found: N, 20.0.

Preparation of 4-alkoxy-1-alkyl(aryl)pyrazolo[3,4-d]pyrimidine (XXVII). See Table III. *4-Methoxy-1-methylpyrazolo[3,4-d]pyrimidine* (XXVII, R_1 = CH_3, R_2 = CH_3). One gram of sodium was dissolved in 50 ml. of methanol. To this solution was added, very carefully, 50 ml. of a methanolic solution of 5 g. of 4-chloro-1-methylpyrazolo[3,4-d]-pyrimidine. The mixture was cooled in an ice-bath for 10 minutes, then allowed to warm up to room temperature, and finally was heated gently on a steam-bath for 30 minutes. The solution was filtered, and white, silky needles crystallized from the filtrate. The crude product was recrystallized from methanol to yield 2.5 g. (51.2%), m.p. 105–106°.

Anal. Calc'd for $C_7H_8N_4O$: N, 34.2. Found: N, 34.2.

4-Ethoxy-1-phenylpyrazolo[3,4-d]pyrimidine (XXVII, R_1 = C_6H_5, R_2 = C_2H_5). 4-Chloro-1-phenylpyrazolo[3,4-d]-pyrimidine (5 g.) (XVIII) was dissolved in 150 ml. of warm absolute ethanol. To this solution, cooled to 10°, was added 150 ml. of absolute ethanol in which 2 g. of sodium had been dissolved. The mixture was allowed to warm to room temperature and then was heated gently on a steam-bath for two hours. The sodium chloride was filtered from the hot solution, and the filtrate on cooling yielded the crude product. Recrystallization from ethanol gave 3.2 g. of long, white needles, m.p. 92–94°.

Anal. Calc'd for $C_{13}H_{12}N_4O$: C, 65.0; H, 5.03; N, 23.3. Found: C, 65.2; H, 5.28; N, 23.1.

4-(p-Bromophenoxy)-1-methylpyrazolo[3,4-d]pyrimidine (XXVII, R_1 = CH_3, R_2 = p-Br-C_6H_4). To a mixture of 5 g. of p-bromophenol was added 5 g. potassium hydroxide and 150 ml. of water. To this solution was added, a little at a time, 5 g. of finely powdered 4-chloro-1-methylpyrazolo-[3,4-d]pyrimidine (XVIII, R_1 = CH_3). The mixture then was heated on a steam-bath for 30 minutes. A white solid precipitated from the hot solution. The product was filtered and recrystallized from methanol to yield 5.5 g. of white needles, m.p. 167°.

Anal. Calc'd for $C_{12}H_9BrN_4O$: N, 18.4. Found: N, 18.6.

Preparation of 1-alkyl(aryl)-4-substituted amino-pyrazolo-[3,4-d]pyrimidines (XXVI). See Table IV. The compounds listed in Table IV were prepared by either *General Method (A)* or *General Method (B)*.

General Method (A) is illustrated by the following specific examples:

1-Methyl-4-methylaminopyrazolo[3,4-d]pyrimidine (XXVI, R_1 = CH_3, R_3 = H, R_4 = CH_3). To a mixture of 70 ml. of 40% methylamine in 50 ml. of 95% ethanol was added 11 g. of 4-chloro-1-methylpyrazolo[3,4-d]pyrimidine (XVIII, R_1 = CH_3). The solution was refluxed on a steam-bath for 8 hours. The white solid which formed in the hot solution was filtered after the solution had cooled. Recrystallization from methanol yielded 8.5 g., m.p. 200–201°.

Anal. Calc'd for $C_7H_9N_5$: C, 51.5; H, 5.6; N, 42.9. Found: C, 51.2; H, 5.8; N, 42.5.

4-(o-Methylanilino)-1-methylpyrazolo[3,4-d]pyrimidine (XXVI, R_1 = CH_3, R_3 = H, R_4 = o-CH_3-C_6H_4). A mixture of 5 g. of 4-chloro-1-methylpyrazolo[3,4-d]pyrimidine and 4.5 g. of o-toluidine in 200 ml. of absolute ethanol was refluxed on a steam-bath for 5 hours. A white solid crystallized after the solution was cooled overnight. After recrystallization from ethanol the product melted at 164–166°, yield 4.3 g.

Anal. Calc'd for $C_{13}H_{13}N_5$: C, 65.2; H, 5.5; N, 29.3. Found: C, 65.2; H, 5.5; N, 29.2.

4-Hydrazino-1-methylpyrazolo[3,4-d]pyrimidine (XXVI, R_1 = CH_3, R_3 = H, R_4 = NH_2). To a mixture of 300 ml. of 95% ethanol and 90 g. of 85% hydrazine hydrate was added 30 g. of finely powdered 4-chloro-1-methylpyrazolo[3,4-d]-pyrimidine. A white precipitate formed instantly. The mixture was warmed on a steam-bath for ten minutes and filtered. The product was recrystallized from 50% ethanol to yield 29 g. of white needles, m.p. 246.5–247°.

Anal. Calc'd for $C_6H_8N_6$: N, 51.1. Found: N, 50.8.

4-Methylhydrazino-1-phenylpyrazolo[3,4-d]pyrimidine (XXVI, R_1 = C_6H_5, R_3 = H, R_4 = $NHCH_3$). A solution of 5 g. of 4-chloro-1-phenylpyrazolo[3,4-d]pyrimidine, 6 g. of methylhydrazine, and 200 ml. of methanol was heated on the steam-bath until the volume of the solution had been reduced to 50 ml. The solution, upon cooling, yielded white

crystals. Recrystallization of the crude product from ethanol gave 4.1 g., m.p. 153–155°.

Anal. Calc'd for $C_{12}H_{12}N_6$: C, 60.0; H, 5.03; N, 35.0. Found: C, 60.2; H, 5.01; N, 34.3.

4-(o-Chloroanilino)-1-phenylpyrazolo[3,4-d]pyrimidine (XXVI, R_1 = CH_3, R_3 = H, R_4 = *o*-Cl-C_6H_4). 4-Chloro-1-phenylpyrazolo[3,4-*d*]pyrimidine (5 g.) and 11 g. of *o*-chloroaniline were added to 200 ml. of absolute ethanol. The solution was boiled gently on a steam-bath for 4 hours. A solid product separated from the hot solution. Recrystallization from 2-ethoxyethanol gave 4.5 g. of white needles, m.p. 157–158°.

Anal. Calc'd for $C_{17}H_{12}ClN_5$: C, 63.6; H, 3.77; N, 21.8. Found: C, 63.6; H, 3.72; N, 21.9.

4-Benzylamino-1-methylpyrazolo[3,4-d]pyrimidine (XXVI, R_1 = CH_3, R_3 = H, R_4 = CH_2-C_6H_5). Benzylamine (10 g.) and 8 g. of 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine were added to 200 ml. of absolute ethanol, and the solution was heated for 8 hours on the steam-bath. The solid, which separated on cooling, was recrystallized from ethanol to give 11 g. of white leaflets, m.p. 158–159.5°.

Anal. Calc'd for $C_{13}H_{13}N_5$: N, 29.3. Found: N, 29.1.

1-(p-Chlorophenyl)-4-(3'-morpholino-n-propylamino)pyrazolo[3,4-d]pyrimidine (XXVI, R_1 = *p*-Cl-C_6H_4, R_3 = H, R_4 = *n*-C_3H_6-N(-CH_2—CH_2-O-CH_2—CH_2-)). To 160 ml. of methanol was added 8 g. of 4-chloro-1-(*p*-chlorophenyl)pyrazolo[3,4-*d*]pyrimidine (XVIII, R_1 = *p*-Cl-C_6H_4) and 8 g. of 3-morpholino-*n*-propylamine. After boiling on a steam-bath for 40 minutes, a solid appeared which was filtered and recrystallized from 2-ethoxyethanol to yield 10.0 g., m.p. 182–184°.

Anal. Calc'd for $C_{18}H_{21}ClN_6O$: N, 22.5. Found: N, 22.8.

4-(N-Methylanilino)-1-phenylpyrazolo[3,4-d]pyrimidine (XXVI, R_1 = C_6H_5, R_3 = CH_3, R_4 = C_6H_5). A solution of 2.5 g. of 4-chloro-1-phenylpyrazolo[3,4-*d*]pyrimidine (XVIII, R_1 = C_6H_5) and 2 g. of N-methylaniline dissolved in 200 ml. of absolute ethanol was heated on a steam-bath for 10 hours. On cooling, colorless needles crystallized slowly from the purple solution. The product was recrystallized from ethanol to yield 2.2 g. (64.5%), m.p. 115–116°.

Anal. Calc'd for $C_{18}H_{15}N_5$: C, 71.7; H, 5.0; N, 23.3. Found: C, 71.2; H, 4.7; N, 23.3.

4-(β-Hydroxyethylhydrazino)-1-methylpyrazolo[3,4-d]-pyrimidine (XXVI, R_1 = CH_3, R_3 = H, R_4 = $NHCH_2CH_2$-OH). To 100 ml. of methanol was added 9 g. of 70% β-hydroxyethylhydrazine and 8.5 g. of 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine. The mixture was refluxed on a steam-bath for 6 hours. The solid which formed on cooling was recrystallized from methanol to yield 12 g. of white needles, m.p. 133–134°.

Anal. Calc'd for $C_8H_{12}N_6O$: N, 40.3. Found: N, 40.1.

In this particular preparation methanol was found to be much superior to ethanol as a reaction solvent. When the reaction was carried out in ethanol, no product could be isolated.

General Method (*B*) for the preparation of 1-alkyl(aryl)-4-substituted aminopyrazolo[3,4-*d*]pyrimidines is illustrated by the following specific examples:

1-Methyl-4-(1',1',3',3'-tetramethyl-n-butylamino)pyrazolo-[3,4-d]pyrimidine (XXVI, R_1 = CH_3, R_3 = H, R_4 = C_8H_{17}). To 7 g. of 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (XVIII, R_1 = CH_3) dissolved in 100 ml. of methanol was added, with stirring, 12 g. of 1,1,3,3-tetramethyl-*n*-butylamine. The mixture was heated on the steam-bath for 8 hours and finally was allowed to evaporate to a syrupy liquid. To the crude product was added 40 ml. of absolute ethanol. The mixture was boiled, treated with charcoal, and heated with a small amount of diatomaceous earth. To the filtrate was added 20 ml. of water and the product crystallized after standing two weeks in the refrigerator. The yield of white needles, m.p. 132–133.5°, was 9 g.

Anal. Calc'd for $C_{14}H_{23}N_5$: C, 64.5; H, 8.9; N, 26.8. Found: C, 64.0; H, 9.1; N, 26.7.

4-Furfurylamino-1-methylpyrazolo[3,4-d]pyrimidine (XXVI, R_1 = CH_3, R_3 = H, R_4 = C_5H_5O). A mixture of 5 g. of 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (XVIII, R_1 = CH_3) and 4 g. of furfurylamine dissolved in 60 ml. of absolute ethanol was heated on the steam-bath for 8 hours. The solvent then was allowed to evaporate to leave a glassy, gummy substance which would not crystallize after long standing. This substance was treated with dilute potassium hydroxide and the solution was extracted with chloroform. A light-yellow residue, which was obtained after the distillation of the excess chloroform, was recrystallized from benzene to yield 6.1 g. of white needles, m.p. 150°.

Anal. Calc'd for $C_{11}H_{11}N_5O$: N, 30.6. Found: N, 30.7.

4-Cyclohexylamino-1-methylpyrazolo[3,4-d]pyrimidine (XXVI, R_1 = CH_3, R_3 = H, R_4 = C_6H_{11}). A mixture of 10 g. of 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine, 6 g. of cyclohexylamine, and 120 g. of methanol was refluxed on a steam-bath for 4 hours and finally was evaporated to dryness. The product was crystallized by treating the residue with a mixture of ether and methanol. Recrystallization from methanol gave 4.0 g. of white needles, m.p. 95–96°.

Anal. Calc'd for $C_{12}H_{17}N_5$: N, 30.3. Found: N, 30.3.

4-n-Butylamino-1-methylpyrazolo[3,4-d]pyrimidine (XXVI, R_1 = CH_3, R_3 = H, R_4 = *n*-C_4H_9). To 40 g. of *n*-butylamine in 120 ml. of methanol was added 13 g. of 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine. The solution was refluxed on a steam-bath for 8 hours and then was evaporated to dryness. The residue was extracted with boiling benzene, and a small amount of heptane was added to the hot filtrate which crystallized on cooling the solution to give 12 g. of white needles, m.p. 87–88°.

Anal. Calc'd for $C_{10}H_{15}N_5$: N, 34.2. Found: N, 34.1.

1-(p-Chlorophenyl)-4-(2'-N,N-diethylaminoethylamino)-pyrazolo[3,4-d]pyrimidine [XXVI, R_1 = *p*-Cl-C_6H_4, R_3 = H, R_4 = $CH_2CH_2N(C_2H_5)_2$]. 4-Chloro-1-(*p*-chlorophenyl)-pyrazolo[3,4-*d*]pyrimidine (5 g.) was added to a solution of 300 ml. of absolute ethanol and 5 g. of 2-N,N-diethylaminoethylamine (β-diethylaminoethylamine). The solution was refluxed on a steam-bath for 12 hours and then was evaporated to dryness. The residue was treated with cold benzene to which had been added a small amount of methanol, and the product slowly solidified in a refrigerator. The solid was recrystallized from water and a small amount of methanol to yield 4.5 g. of white needles, m.p. 105–106°.

Anal. Calc'd for $C_{17}H_{21}ClN_6$: N, 24.4. Found: N, 24.4.

4-(2'-N-β-Hydroxyethylaminoethylamino)-1-(p-chlorophenyl)pyrazolo[3,4-d]pyrimidine [XXVI, R_1 = *p*-Cl-C_6H_4, R_3 = H, R_4 = $(CH_2)_2$-$NH(CH_2)_2OH$]. A solution of 8 g. of 4-chloro-1-(*p*-chlorophenyl)pyrazolo[3,4-*d*]pyrimidine, 8 g. of 2-N-β-hydroxyethylaminoethylamine (N-aminoethylethanolamine), and 150 ml. of methanol was refluxed on a steam-bath for three hours and finally was evaporated to dryness on the steam-bath. The residual product was recrystallized three times from a mixture of benzene and methanol. There finally was obtained 4 g. of pure product which melted at 154–155°.

Anal. Calc'd for $C_{15}H_{17}ClN_6O$: N, 25.2. Found: N, 25.2.

Preparation of 1-methylpyrazolo[3,4-d]pyrimidine (XXV, R_1 = CH_3) 4-Chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (XVIII, R_1 = CH_3) (5 g.) was added to a solution of 150 ml. of methanol and 4 ml. of concentrated ammonium hydroxide. To this solution was added 1.5 g. of 5% palladium-on-charcoal. The mixture was shaken on a hydrogenator at 20 lb. per sq. in. pressure until the uptake of hydrogen ceased (six hours was required). The solution then was filtered and the black residue was extracted with 100 ml. of methanol. The combined methanolic solution was evaporated to dryness on a steam-bath. The product was recrystallized from benzene and then was sublimed twice at 130° under reduced pressure to give 1 g. of white needles, m.p. 125–126°.

Anal. Calc'd for $C_6H_6N_4$: C, 53.7; H, 4.50; N, 41.8. Found: C, 53.9; H, 4.55; N, 41.9.

Preparation of 1,5-dimethylpyrazolo[3,4-d]pyrimidine-4-thione (XXIV, R_1, R_2 = CH_3). A mixture of 8.6 g. of phosphorus pentasulfide, 4 g. of 1,5-dimethylpyrazolo[3,4-*d*]pyrimidone-4 (XXIII, R_1, R_2 = CH_3), 45 ml. of *o*-xylene, and 45 ml. of toluene was refluxed for 3.5 hours. The mixture, after cooling overnight, was filtered. The solid was recrystallized from 120 ml. of hot water to give light-yellow needles, m.p. 242–243° (sublimed at 210°), yield 2.0 g.

Anal. Calc'd for $C_7H_8N_4S$: C, 46.4; H, 4.44; N, 31.1. Found: C, 46.1; H, 4.56; N, 31.0.

Preparation of 5-amino-1-phenylpyrazole-4-carboxamide (XV) *from 5-hydroxy-1-phenylpyrazole-4-ethylcarboxylate* (X). A mixture of 20 g. of 5-hydroxy-1-phenylpyrazole-4-ethylcarboxylate, 5 g. of phosphorus pentachloride, and 500 ml. of phosphorus oxychloride was refluxed vigorously for 10 hours. All the excess phosphorus oxychloride was distilled off under reduced pressure. The residue, without purification, was transferred to a container with 150 ml. of saturated alcoholic ammonia. The mixture was heated at 180° in a bomb for 6 hours. The solution was evaporated to dryness, and the residue then was recrystallized from 95% ethanol. A small amount of product was obtained which melted at 165–168°. It was recrystallized twice more from water to raise the melting point to 171–172°. The yield of white crystals was 0.5 g. A mixture of this compound and that obtained by the hydrolysis of 5-amino-4-cyano-1-phenylpyrazole (IV, R_1 = C_6H_5) did not lower the melting point.

Anal. Calc'd for $C_{10}H_{10}N_4O$: N, 27.7. Found: N, 27.9.

Preparation of methylethoxymethylenemalononitrile (XXIX). Malononitrile (81 g.), 200 g. of triethyl orthoacetate, and 276 g. of acetic anhydride were mixed in a 2 l. three-necked, round-bottom flask. The mixture was refluxed for 3 hours. During the period the color of the solution changed from light yellow to dark brown. The solvents then were removed by distillation at reduced pressure. The residue, which solidified on cooling, was filtered and washed with a little cold ethanol to give white crystals, m.p. 88.5–89.5°. The yield was 40 g. (83.7%). Recrystallization from ethanol did not change the melting point.

Anal. Calc'd for $C_7H_8N_2O$: C, 61.7; H, 5.9; N, 20.6. Found: C, 62.0; H, 5.6; N, 20.8.

Preparation of 5-amino-4-cyano-3-methylpyrazole (XXX). To 35 g. of 85% hydrazine hydrate in 20 ml. of ethanol was added 50 g. of methylethoxymethylenemalonitrile (XXIX), a little at a time, with outside cooling. The mixture then was heated on the steam-bath for 2 hours. The solution was diluted with 100 ml. of water and allowed to cool. The crude product, m.p. 160–163°, was filtered and recrystallized from ethanol and water to give white needles, m.p. 163°, yield 43 g. (96%).

Anal. Calc'd for $C_5H_6N_4$: C, 49.1; H, 5.0; N, 45.9. Found: C, 49.3; H, 4.8; N, 45.9.

Preparation of 5-amino-4-cyano-1,3-dimethylpyrazole (XXXII, R_1 = CH_3). To 60 g. of 98% methylhydrazine in 300 ml. of ethanol was added 96 g. of methylethoxymethylenemalononitrile (XXIX). The isolation and purification procedure was carried out in the same fashion as for the preparation of 5-amino-4-cyano-1-methylpyrazole. White needles were obtained, m.p. 194°, yield 75 g. (87%).

Anal. Calc'd for $C_6H_8N_4$: C, 53.0; H, 5.9; N, 41.1. Found: C, 53.5; H, 6.3; N, 41.1.

Preparation of 5-amino-4-cyano-3-methyl-1-phenylpyrazole (XXXII, R_1 = C_6H_5). Methylethoxymethylenemalononitrile (50 g.) was slowly added to 45 g. of phenylhydrazine dissolved in 150 ml. of absolute ethanol. The reaction proceeded in a similar manner as for the preparation of 5-amino-4-cyano-1-phenylpyrazole (IV, R_1 = C_6H_5). The crude product, yield 58 g. (80%), melted at 131–132°. Recrystallization from water gave long needles, m.p. 132–133°.

Anal. Calc'd for $C_{11}H_{10}N_4$: C, 66.3; H, 5.1; N, 28.2. Found: C, 65.7; H, 5.2; N, 28.3.

Preparation of 5-amino-1,3-dimethylpyrazole-4-carboxamide (XXXIII, R_1 = CH_3). 5-Amino-4-cyano-1,3-dimethylpyrazole (XXXII, R_1 = CH_3) (50 g.) was added portionwise to 150 ml. of concentrated sulfuric acid. The isolation and purification process was similar to that employed for 5-amino-1-methylpyrazole-4-carboxamide. Thus 42 g. (74%) of white needles were obtained, m.p. 203.5–204.5°.

Anal. Calc'd for $C_6H_{10}N_4O$: C, 47.0; H, 6.5; N, 36.3. Found: C, 47.3; H, 6.5; N, 36.2.

Preparation of 1,3-dimethyl-4-hydroxypyrazolo[3,4-d]pyrimidine (XXXV, R_1 = CH_3). A mixture of 35 g. of 5-amino-1,3-dimethylpyrazole-4-carboxamide (XXXIII, R_1 = CH_3) and 120 ml. of formamide was boiled on a hot plate for 4 hours. An equal volume of water was added to the mixture and the white solid was filtered after standing overnight. The product was recrystallized from ethanol to give m.p. 276.5°. The yield was 27 g. (72.5%).

Anal. Calc'd for $C_7H_8N_4O$: C, 51.3; H, 4.9; N, 34.1. Found: C, 51.5; H, 4.7; N, 34.0.

Preparation of 4-amino-3-methylpyrazolo[3,4-d]pyrimidine (XXXI). A mixture of 50 g. of 5-amino-4-cyano-3-methylpyrazole (XXX) and 100 ml. of formamide was boiled on a hot plate for 45 minutes. The isolation and purification procedure was followed as recorded for the preparation of 4-aminopyrazolo[3,4-*d*]pyrimidine[3] from 3-amino-4-cyanopyrazole and 26 g. (43%) of the purified product was obtained, m.p. > 300°.

Anal. Calc'd for $C_6H_7N_5$: C, 48.4; H, 4.7; N, 46.9. Found: C, 48.6; H, 4.8; N, 46.8.

Preparation of 4-amino-1,3-dimethylpyrazolo[3,4-d]pyrimidine (XXXIV, R_1 = CH_3). A mixture of 50 g. of 5-amino-4-cyano-1,3-dimethylpyrazole (XXXII, R_1 = CH_3) and 100 ml. of formamide was boiled on a hot plate for 45 minutes. The isolation and purification procedure was identical to that employed in the preparation of 1-(β-hydroxyethyl)-4-aminopyrazolo[3,4-*d*]pyrimidine (XIX, R_1 = CH_2CH_2OH). The yield of product was 32.0 g. (53.4%), m.p. 203–204°. This compound was recrystallized from water as the monohydrate which lost water of hydration when heated at 140°.

Anal. Calc'd for $C_7H_9N_5 \cdot H_2O$: C, 46.6; H, 6.1. Found: C, 46.5; H, 5.9.

After heating at 140° it had: *Anal.* Calc'd for $C_7H_9N_5$: N, 43.0. Found: N, 43.4.

Preparation of 1,5-dimethylpyrazolo[3,4-d]pyrimidone-4 (XXIII, R_1, R_2 = CH_3). *Method (1).* To 30 ml. of water was added 3 g. of potassium hydroxide, 5 g. of 1-methyl-4-hydroxypyrazolo[3,4-*d*]pyrimidine (XVII, R_1 = CH_3), 10 g. of methyl iodide, and 100 ml. of methanol. The solution was shaken for 30 minutes with occasional cooling. Then it was allowed to stand at room temperature for 1 hour followed by refluxing on a steam-cone for 4 hours. The solid, which separated from the alkaline solution on cooling, was recrystallized from methanol to yield white needles, 4.1 g. (77%), m.p. 193–195° (sublimed at 130°).

Anal. Calc'd for $C_7H_8N_4O$: N, 34.1. Found: N, 33.9.

Method (2). To a solution of 25 g. of 4-hydroxypyrazolo-[3,4-*d*]pyrimidine,[3] 30 ml. of water, and 2.5 g. of potassium hydroxide was slowly added 10 g. of methyl iodide in 50 ml. of methanol. The solution was refluxed gently for 5 hours on a water-bath and then was evaporated to dryness. The crude compound was recrystallized from water to give m.p. 190–193°. Another recrystallization from water raised the melting point to 193–195°. The final yield was 0.3 g. This product was identical to that prepared by *Method (1)* as judged by mixture melting point data and identical ultraviolet absorption spectra.

Preparation of 4-dimethylamino-1-methylpyrazolo[3,4-d]-pyrimidine (XXVI, R_1, R_3, R_4 = CH_3). *Method (1)* 4-Chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (XVII, R_1 = CH_3) (12 g.) and 150 g. of 25% aqueous dimethylamine were mixed in 50 ml. of ethanol. The solution was refluxed on a steam-bath for two hours and then was evaporated to dry-

ness. The white solid was recrystallized from ethanol to yield 10 g. (95%) of white crystals. Sublimation gave long, white needles, m.p. 132°.

Anal. Calc'd for $C_8H_{11}N_5$: N, 39.5. Found: N, 39.5.

Method (2). One gram of 4-dimethylaminopyrazolo[3,4-*d*]-pyrimidine[3] was dissolved in a solution of 75 ml. of methanol, 20 g. of methyl iodide, 2 g. of potassium hydroxide, and 10 ml. of water. The solution was gently refluxed on a water-bath for 8 hours and then was evaporated to dryness. The white solid was recrystallized from absolute ethanol to yield white crystals, 0.4 g., m.p. 130–131°. This compound was identical to that made by *Method (1)* as judged by mixture melting point determination and comparison of ultraviolet absorption spectra.

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