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

Potential Purine Antagonists VII. Synthesis of 6-Alkylpyrazolo-[3,4-*d*]pyrimidines[1,2a]

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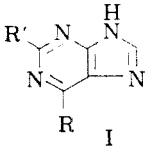
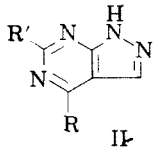
A synthesis of 6-alkyl-4-hydroxypyrazolo[3,4-*d*]pyrmidines (VI) has been devised from the corresponding 5-acylamino-4-cyanopyrazoles (IV) which were in turn prepared from 5-amino-4-cyanopyrazoles (III). Evidence is presented to show that the 5-acylaminopyrazole-4-carboxamide is an intermediate in this cyclization. Chlorination of the various 6-alkyl-4-hydroxypyrazolo[3,4-*d*]pyrimidines yielded the corresponding 6-alkyl-4-chloropyrazolo[3,4-*d*]pyrimidines (XI). Nucleophilic displacement of the chlorine atom in XI resulted in the preparation of a large number of 6-alkylpyrazolo[3,4-*d*]pyrimidines substituted in position 4.

The discovery[3,4] of 6-amino-2-methylpurine (I, R = NH_2, R′ = CH_3) and 6-hydroxy-2-methylpurine (I, R = OH, R′ = CH_3) as degradation products of pseudovitamin B_{12} prompted the investigation of the preparation of the corresponding analogs in the pyrazolo[3,4-*d*]pyrimidine series (II, R = NH_2, R′ = CH_3, and R = OH, R′ = CH_3).



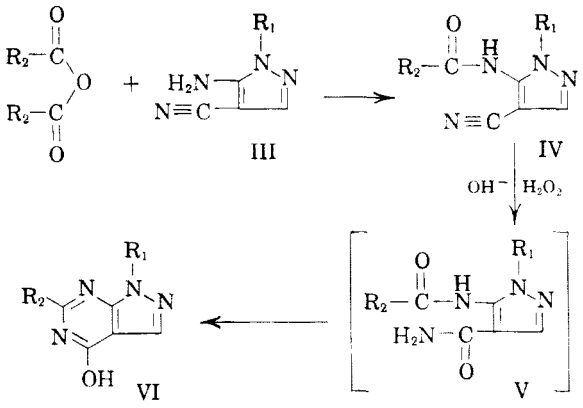
I



II

The general synthesis of the pyrazolo[3,4-*d*]pyrimidine system previously developed in this laboratory[5,6] proceeds *via* the appropriate 5-amino-4-cyanopyrazole (III). The ready accessibility of the corresponding 5-acylaminopyrazole led to a study of the use of this compound in an effort to find a general synthesis of 6-alkyl-4-substituted pyrazolo-[3,4-*d*]pyrimidines.

Bogert and Hand reported that the preparation of 2-methyl-4-hydroxyquinazoline could be accomplished by the action of warm alkaline peroxide solution upon acylanthranilic nitriles.[7] Following this lead it was found that when the 5-amino-4-cyanopyrazoles[5,6] (III) were acylated by either acetic or propionic anhydride to give the corresponding 5-acylamino-4-cyanopyrazoles (IV), these derivatives (IV) when treated with hydrogen peroxide in alkaline solution at 70–80° gave the desired 6-alkyl-4-hydroxypyrazole[3,4-*d*]pyrimidines (VI) in excellent yield.



III IV V VI

In succeeding reactions it proved unnecessary to isolate and purify the 5-acylamino-4-cyanopyrazole (IV). The crude syrupy residue (IV) remaining after distillation of the excess anhydride gave VI directly when treated with hydrogen peroxide in alkaline solution.

The over-all yield of the desired 6-alkyl-4-hydroxypyrazolo[3,4-*d*]pyrimidines (VI) obtained in this manner was even improved.

In the case of acetylation of 5-amino-4-cyano-1-β-hydroxyethylpyrazole(III, R_1 = CH_2CH_2OH), the acetylated product obtained was 1-β-acetoxyethyl-5-acetylamino-4-cyanopyrazole (IV, R_1 = $CH_2CH_2OCOCH_3$). It is interesting to note that when his product was cyclized in the base-peroxide medium, the original R_1 group was regenerated and 4-hydroxy-1-β-hydroxyethyl-6-methylpyrazolo[3,4-*d*]pyrimidine was the product obtained.

The probable intermediate, 5-acylaminopyrazole-4-carboxamide (V), could not be isolated during the process of cyclization. An attempt to prepare 5-acetylamino-1-phenylpyrazole-4-carboxamide (V, R_1 = C_6H_5, R = CH_3) from 5-acetylamino-4-cyano-1-phenylpyrazole (IV, R_1 = C_6H_5, R_2 = CH_3) and concentrated sulfuric acid at 15–20° was unsuccessful. The product isolated was identified as 5-amino-1-phenylpyrazole-4-carboxamide (VII). VII has previously been reported, prepared by the action of concentrated sulfuric acid on 5-amino-4-cyano-1-phenylpyrazole.[6]

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

(2) (a) Presented in part before the Division of Medicinal Chemistry, 128th Meeting of the American Chemical Society, Minneapolis, Minn., September 1955. (b) Present address: Dept. of Chemistry, Arizona State College, Tempe, Arizona.

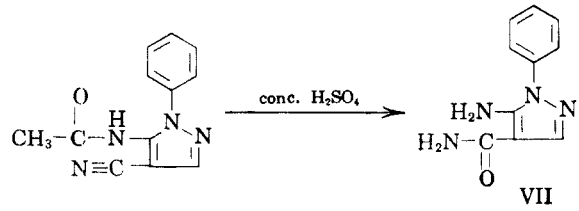
(3) Dion, Calkins and Pfiffner, *J. Am. Chem. Soc.*, **76**, 948 (1954).

(4) Brown and Smith, *Biochem. J.*, **56**, 34 (1954).

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

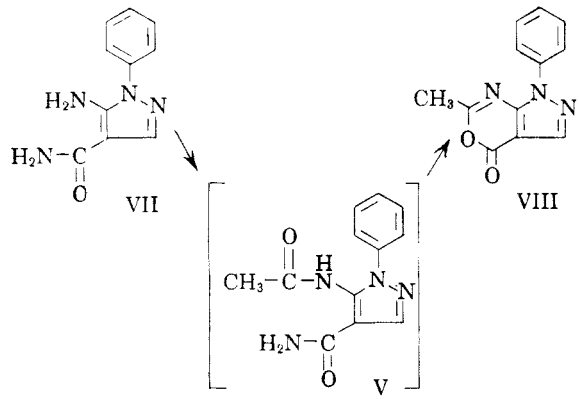
(6) Cheng and Robins, *J. Org. Chem.*, **21**, 1240 (1956).

(7) Bogert and Hand, *J. Am. Chem. Soc.*, **24**, 1048 (1902).

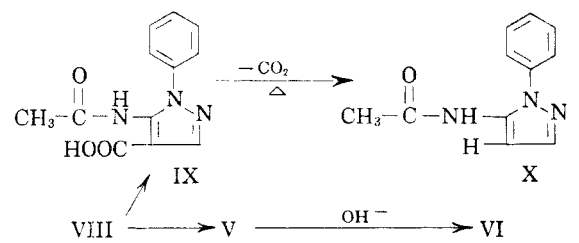


VII

Another attempt to prepare the suspected intermediate 5-acetylamino-1-phenylpyrazole-4-carboxamide from the acetylation of 5-amino-1-phenylpyrazole-4-carboxamide (VII) resulted in the formation of 6-methyl-4-keto-1-phenylpyrazolo[3,4-*d*]-5,7-oxazine (VIII). The formation of VIII is not entirely unexpected since benzoxazines can be prepared by heating anthranilic acid, substituted anthranilic acids and *N*-acetyl or *N*-benzoyl derivatives with acetic anhydride.[8]



The desired intermediate, 5-acetylamino-1-phenylpyrazole-4-carboxamide (V), was finally prepared from VIII and alcoholic ammonia on the steam bath. Treatment of V with 10% potassium hydroxide cyclized the acetylated amide almost immediately to 4-hydroxy-6-methyl-1-phenylpyrazolo[3,4-*d*]pyrimidine (VI, $R_1 = C_6H_5$, $R_2 = CH_3$).



The oxazone ring in 6-methyl-4-keto-1-phenylpyrazolo[3,4-*d*]5,7-oxazine is not very stable and is ruptured easily in basic solution to form 5-acetylamino-1-phenylpyrazole-4-carboxylic acid (IX) which loses carbon dioxide readily on heating. It is interesting to note that the 5-acetylamino group was retained in warm alkaline solution but hydrolyzed quite readily in the cold acidic medium.

Justoni and Fusco[9] prepared "1′,3′-diphenyl-6-hydroxy-2-methyl(pyrazolo-5′,4′:4,5-pyrimidine)" which is the only 6-alkylpyrazolo[3,4-*d*]pyrimidine reported prior to this work, from the dehydration of 5-acetylamino-1,3-diphenylpyrazole-4-carboxamide by heating with a direct flame. In this regard it is noteworthy that in the case of 5-acetylamino-1-phenylpyrazole-4-carboxamide a definite melting point could not be obtained on the Fisher-Johns melting point apparatus since thermal cyclization took place in a similar manner to give 1-phenyl-6-methyl-4-hydroxypyrazolo[3,4-*d*]pyrimidine.

The preparation of the pyrazolo[3,4-*d*]pyrimidine ring system by the fusion of formamide with the corresponding 5-amino-4-cyanopyrazoles of 5-aminopyrazole-4-carboxamide has been employed quite extensively.[5,6] Several attempts under various conditions to utilize acetamide or *p*-nitrobenzamide in place of formamide in the fusion reaction to give the corresponding 6-methyl or 6-*p*-nitrophenylpyrazolo[3,4-*d*]pyrimidine were unsuccessful. In both cases the unreacted pyrazoles were recovered.

A methyl group substituted on the pyrazolo[3,4-*d*]pyrimidine ring at the position "3"[6] was also prepared in the 6-alkyl series by acylation of the corresponding 3-methyl-5-amino-4-cyanopyrazole followed by base-peroxide cyclization.

Chlorination of the 4-hydroxy-6-alkyl-1-alkyl-(aryl)pyrazolo[3,4-*d*]pyrimidines was carried out under conditions similar to those employed for compounds having no alkyl substituent at the 6-position.[6] However, for the chlorination of 4-hydroxy-6-methylpyrazolo[3,4-*d*]pyrimidine (where the substituent at the 1- position is hydrogen) a considerable amount of *N*,*N*-dimethylaniline was required in addition to phosphorus oxychloride to effect successful chlorination. A similar situation has been found with 4-hydroxypyrazolo[3,4-*d*]pyrimidine[5] as compared to the case of the 1-alkyl (aryl)-4-hydroxypyrazolo[3,4-*d*]pyrimidines.[6]

The compound, 4-amino-6-methylpyrazolo[3,4-*d*]pyrimidine, an analog of 6-amino-2-methylpurine, was prepared by heating XI with alcoholic ammonia in a bomb. Various substituted amino derivatives were prepared by the reaction of XI with various primary and secondary amines, heated in aqueous or alcoholic solution on the steam bath, as shown in the reaction scheme. These compounds are listed in Table III.

The 4-mercapto-6-alkylpyrazolo[3,4-*d*]pyrimidines (XII) were prepared by two methods—either by the thiation of the corresponding 4-hydroxy compound (VI) with phosphorus pentasulfide in tetralin or by the reaction of the 4-chloro compound (XI) with thiourea in alcoholic solution. Samples

(8) (a) Bredy and Hof, *Ber.*, **33**, 29 (1900); (b) Bogert and Seil, *J. Am. Chem. Soc.*, **29**, 517 (1907); (c) Lothrop and Goodwin, *J. Am. Chem. Soc.*, **65**, 363 (1943); (d) Zentmyer and Wagner, *J. Org, Chem.*, **14**, 967 (1949); (e) Tomisek and Christensen, *J. Am. Chem. Soc.*, **70**, 2423 (1948).

(9) Justoni and Fusco, *Gazz. chim. ital.*, **68**, 66 (1938).

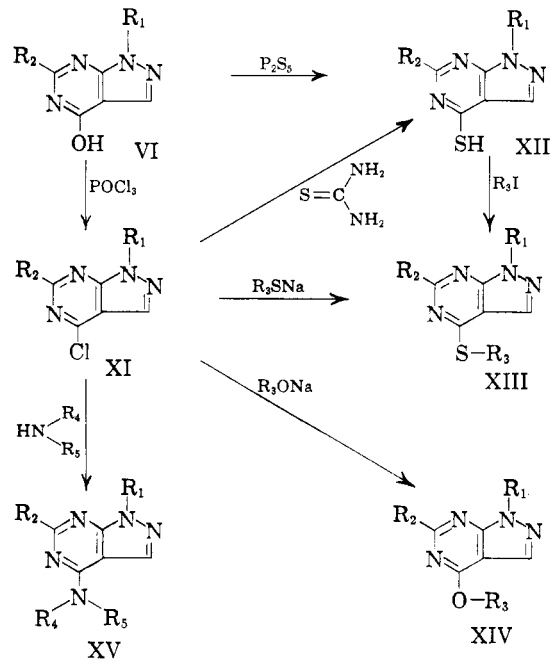
of products which were prepared by both methods were identical.

4-Alkoxy-6-alkyl derivatives (XIV) (Table II) were prepared from XI and sodium alkoxide at comparatively low temperatures. The sulfur analogs, 4-alkylmercapto-6-alkyl derivatives (XIII), were prepared by either the reaction of XI and potassium alkyl mercaptide or by the alkylation of XII in basic media with methyl iodide.

The presence of an alkyl group at the 6 position caused a definite hypsochromic shift in the absorption spectra in the ultraviolet region of the order of 2 to 10 mμ.

In the 6-alkyl-4-substituted pyrazolo[3,4-*d*]pyrimidines, ortho substitution of the aromatic ring at position 1 appears to cause interference to the conjugation of the pyrazole and the benzene ring. This was indicated by the ultraviolet absorption measurements as illustrated by strong absorption in ethanol for 4-chloro-6-methyl-1-phenylpyrazolo-[3,4-*d*]pyrimidine (λ_{max} 238 mμ, ϵ = 28,200), 4-chloro-6-ethyl-1-phenylpyrazolo[3,4-*d*]pyrimidine (λ_{max} 239 mμ, ϵ = 30,000), 4-chloro-6-methyl-1-*p*-tolylpyrazolo[3,4-*d*]pyrimidine (λ_{max} 249 mμ, ϵ = 35,200), 4-chloro-6-methyl-1-*p*-chlorophenylpyrazolo[3,4-*d*] pyrimidine (λ_{max} 249 mμ, ϵ = 60,000) and 4-chloro-6-methyl-1-*p*-bromopyrazolo[3,4-*d*]-pyrimidine (λ_{max} 251 mμ, ϵ = 40,400); whereas the corresponding 4-chloro-6-methyl-1-(*o*-chlorophenyl)pyrazolo[3,4-*d*]pyrimidine exhibited a weak absorption peak at 264 mμ (ϵ = 7500). The latter compound showed rather closely the ultraviolet absorption characteristic of the 1-alkyl series. Thus the absorption spectra for 4-chloro-6-methylpyrazolo[3,4-*d*]pyrimidine (λ_{max} 265 mμ, ϵ = 5050) and 4-chloro-1,6-dimethylpyrazolo[3,4-*d*]pyrimidine (λ_{max} 266 mμ, ϵ = 5470) are typical. The absorption spectra of 4-chloro-6-methyl-1-(*o*-chlorophenyl)pyrazolo[3,4-*d*]pyrimidine is probably due to the hypsochromic shift of the interfered conjugated absorption caused by the ortho substitution, thus revealing the original absorption due to the nucleus, which exhibits a rather low optical intensity.

The screening of these compounds against tumors in mice thus far has not revealed any significant antitumor agents in this series. A full report of this testing has appeared.[10] Some interesting observations of these compounds in inhibiting the growth of *Neurospora crassa* has been observed.[11] The compound 4-dimethylamino-6-methyl-1-(*p*-tolyl)pyrazolo[3,4-*d*]pyrimidine at a low dosage showed relatively pronounced inhibition, however at larger dosages growth was supported by the same compound. Further microbiological testing is in progress.



EXPERIMENTAL

All melting points are uncorrected and, unless otherwise stated, were taken on a Fisher-Johns melting point apparatus.

Preparation of 1-alkyl(aryl)-5-acetylamino-4-cyanopyrazoles. See Table I. *Example (1) 5-Acetylamino-4-cyanopyrazole*[5] (IV, R_1 = H, R_2 = CH_3). A mixture of 250 ml. of acetic anhydride and 80 g. of 5-amino-4-cyanopyrazole[5] (III, R_1 = H) was refluxed for 10 hr. Excess acetic anhydride was distilled off under reduced pressure. The syrupy substance was poured into 30 ml. of benzene. The mixture was stirred for several minutes, and the product crystallized slowly. The solid was filtered and recrystallized from water to give 89 g. (76%) of white crystals, m.p. 214–218°. A second recrystallization from water gave a m.p. of 221–222°.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.02; N, 37.3. Found: C, 47.9; H, 4.36; N, 37.4.

Example (2) 5-Acetylamino-4-cyano-1-methylpyrazole (IV, R_1, R_2 = CH_3). The procedure was similar to that for the acetylation of 5-amino-4-cyanopyrazole. The crude product (yield 90%) was recrystallized from water to give a white powder, m.p. 210–211°.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.1; H, 4.91. Found: C, 51.1; H, 4.91.

Example (3) 5-Acetylamino-4-cyano-1-phenylpyrazole (IV, R_1 = C_6H_5, R_2 = CH_3). One hundred fifty g. of 5-amino-4-cyano-1-phenylpyrazole[6] (III, R_1 = C_6H_5) was treated with 200 ml. of acetic anhydride and refluxed for 19 hr. Excess solvent was taken off under reduced pressure. To the syrupy residue was added a small amount of benzene and skellysolve (b.p. 60°). The product crystallized gradually. It was filtered and washed with a little benzene and was recrystallized from water to give 171 g. (92%) of a white crystalline compound which melted at 171–172°.

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 63.6; H, 4.45. Found: C, 63.2; H, 4.44.

Preparation of 5-amino-1-phenylpyrazole-4-carboxamide (VII) *by the action of concentrated sulfuric acid on 5-acetylamino-4-cyano-1-phenylpyrazole.* To 120 ml. of concentrated sulfuric acid cooled in icebath was gradually added, with continuous stirring, 30 g. of finely powdered 5-acetylamino-4-cyano-1-phenylpyrazole. The inside temperature was maintained at 15–20°. After the reaction was complete, the clear solution was allowed to stir for 30 min. It was then

(10) Skipper, Robins, Thomson, Cheng, Brockman, and Schabel, *Cancer Research*, **17**, 579 (1957).

(11) Fuerst, Somers, and Hsu, *J. Bacteriol.*, **72**, 387 (1956).

TABLE I

5-ACYLAMINO-4-CYANOPYRAZOLES

R_1	R_2	R_3	M.P., °C.	Yield, %	U.V. Absorption $pH = 1$, λ_{max}	ϵ	U.V. Absorption $pH = 11$, λ_{max}	ϵ	Recrystallization Solvents	Analyses Calcd. C	H	N	Found C	H	N
H	H	CH_3	221°–222°	76			234	7,050	Water	48.0	4.02	37.3	47.9	4.36	37.4
CH_3	H	CH_3	210–211	72	228	8,800	231	5,900	Water	41.2	4.91		51.2	4.91	
C_6H_5	H	CH_3	155–156	92	248	15,400	245	16,300	Water	63.6	4.45	24.8	63.2	4.44	24.1
o-ClC_6H_4	H	CH_3	175–175.5	82					ethanol, water	55.3	3.48	21.5	54.5	3.45	21.5
p-ClC_6H_4	H	CH_3	173–175	96	238	20,800	246	21,300	ethanol, water			21.5			21.3
p-BrC_6H_4	H	CH_3	175–175	98	238	22,300	237	26,500	ethanol, water	47.3	2.97		47.0	3.57	
p-$NO_2C_6H_4$	H	CH_3	198–200	95	286	12,400	290	11,100	ethanol, water	53.2	3.34		52.8	3.34	
p-$CH_3C_6H_4$	H	CH_3	128	96	238	13,900	239	17,800	ethanol, water			23.3			23.4
$CH_3—C(=O)—O—CH_2—CH_2$	H	CH_3	155–157	81	226	7,300			ethanol	50.9	5.12	23.7	51.1	5.04	24.0

poured with vigorous stirring, onto 1 kg. of crushed ice. The solution was then neutralized with concentrated ammonium hydroxide. A white precipitate which formed instantly was filtered and washed with water, dried, and recrystallized from benzene and methanol to give 20 g. (78%) of a white solid, m.p. 171–172°. Recrystallization from ethanol and water raised the melting point of the product to 172–175°.

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

A mixture of this compound and the compound prepared from the hydrolysis of 5-amino-4-cyano-1-phenylpyrazole[6] showed no depression in melting point.

6-Methyl-4-keto-1-phenylpyrazolo[3,4-d]-5,7-oxazine (VIII). A mixture of 20 g. of 5-amino-1-phenylpyrazole-4-carboxamide and 200 ml. of acetic anhydride was refluxed for 15 hr. Excess anhydride was distilled under reduced pressure. The residue solidified on cooling. It was recrystallized from a mixture of benzene and heptane to give 15 g. (67%) of a yellow solid, m.p. 184.5–185.5° (sublimed at 145°).

Anal. Calcd. for $C_{12}H_9N_3O_2$: C, 63.6; H, 4.00; N, 18.5. Found: C, 63.3; H, 4.11; N, 18.6.

5-Acetylamino-1-phenylpyrazole-4-carboxylic acid (IX). Two and one-half g. of 6-methyl-4-keto-1-phenylpyrazolo-[3,4-*d*]-5,7-oxazine were mixed with 200 ml. of water containing 2 g. of potassium h ide. The mixture was kept at room temperature for 2 d then heated on a steam bath for 10 hr. and finally acidified with glacial acetic acid. A white precipitate gradually formed. The compound was filtered and reprecipitated from base with acetic acid to give 2 g. (74%) of white needles, m.p. 201–202° (with evolution of gas).

Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.9; H, 4.52; N, 17.2. Found: C, 58.7; H, 4.37; N, 17.1.

Preparation of 5-acetylamino-1-phenylpyrazole-4-carboxamide (V). Two g. of 6-methyl-4-keto-1-phenylpyrazolo[3,4-*d*]-5,7-oxazine were added to 100 ml. of alcoholic ammonia. The mixture was allowed to stand at room temperature for 30 min. with occasionally shaking. It was then heated briefly on a steam bath until a solid product precipitated from the alcoholic solution. The product was filtered, and, the product dried at 100° for 5 hr. The m.p. was 301–302°. Owing to the relative instability of this compound, it was analyzed without further purification.

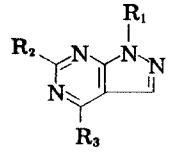
Anal. Calcd. for $C_{12}H_{12}N_4O_2$: C, 59.1; H, 4.94; N, 22.0. Found: C, 59.6; H, 5.06; N, 23.0.

The melting point of this compound was the same as that for 4-hydroxy-6-methyl-1-phenylpyrazolo[3,4-*d*]pyrimidine. A mixed melting point indicated no depression. However, the ultraviolet absorption spectra for the carboxamide (in neutral solution, λ_{max} 230 mμ) and that for the cyclized pyrazolo[3,4-*d*]pyrimidine (in neutral solution, λ_{max} 233 mμ, 269 mμ) were different. So were the analyses of these two compounds. This indicated that the carboxamide cyclized at elevated temperature during the melting point determination. The thermal cyclization was further confirmed by the determination of ultraviolet absorption spectra of the acetylated carboxamide after heating at 350° for 30 min. The spectra were found to be identical to that of 4-hydroxy-6-methyl-1-phenylpyrazolo[3,4-*d*]pyrimidine.

Preparation of 1-alkyl(aryl)-4-hydroxy-6-methylpyrazolo-(3,4-d) pyrimidines (VI). See Table II. *4-Hydroxy-6-methylpyrazolo[3,4-d]pyrimidine* (VI, R_1 = H, R_2 = CH_3). A mixture of 1.5 g. of 5-acetylamino-4-cyanopyrazole, 7 ml. of 10% potassium hydroxide, and 15 ml. of 3% hydrogen peroxide was warmed on a water bath for 30 min. The temperature of the bath was kept at 70–75°. The mixture was then acidified with glacial acetic acid. A white precipitate was formed gradually from the clear solution. It was filtered and reprecipitated from dilute potassium hydroxide and acetic acid to give 1.1 g. (74%) of white powder, m.p. 336–338° (dec.). The melting point was determined on a copper block.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.00; N, 37.3. Found: C, 48.3; H, 3.98; N, 37.4.

TABLE II. 6-ALKYL 1,4-DISUBSTITUTED PYRAZOLO[3,4-*d*]PYRIMIDINES



R_1	R_2	R_3	M.P., °C.	Yield, %	U.V. Absorption *p*H 1, λ_{max}	*p*H 1, ϵ	*p*H 11, λ_{max}	*p*H 11, ϵ	Recrystallization Solvents	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	CH_3	OH	336–338	73.5	252	8,550	259	8,850	Acetic acid	48.0	4.30	37.3	48.3	3.98	37.4
H	CH_3	Cl	140 (dec.)	70.0	256	5,700	265	4,700	Benzene	42.7	2.97	33.3	42.5	2.91	33.6
H	CH_3	SH	>300	80.0	232	8,150			Repptd.			33.8			34.1
					323	20,400	315	18,000							
H	C_2H_5	OH	>300	82.0	253	10,200	259	10,300	Ethanol, water	51.4	4.87	34.1	51.1	4.78	33.8
CH_3	CH_3	OH	277–278	72.5	253	10,300	268	10,800	Ethanol, water	51.4	4.87	34.1	51.7	4.88	34.2
CH_3	CH_3	Cl	74	70.2	267	8,650	268	9,150	Heptane	46.1	3.84	30.7	45.9	4.01	30.6
CH_3	CH_3	SH	264–265	98.0	236	7,100	232	12,100	Repptd.			31.1			31.0
					322	21,200	318	16,600							
CH_3	CH_3	OCH_3	107.5–108.5	67.5	252	5,500	252	7,500	Methanol	53.9	5.66	31.4	54.0	5.91	31.4
CH_3	CH_3	SCH_3	74–75	90.2	251	6,800	261	8,150	Methanol, water			28.8			28.7
CH_2CH_2OH	CH_3	OH	265–266	54.8	253	9,100	253	10,100	Water	49.5	5.18	28.9	49.7	5.18	29.0
C_6H_5	CH_3	Cl	85–86	83.5					Heptane	58.9	3.72	23.0	59.0	3.54	23.4
C_6H_5	CH_3	SH	268.5	83.3	226	19,360	238	26,000	Repptd.	59.5	4.16	23.1	59.4	4.16	23.4
					259	12,800	319	20,300							
					320	21,000									
C_6H_5	CH_3	OCH_3	121.5–122						Methanol	65.0	5.04	23.3	64.5	5.00	23.6
C_6H_5	CH_3	OC_2H_5	95–95.5						Ethanol	66.2	5.51	22.0	66.2	5.64	22.5
C_6H_5	CH_3	SCH_3	135–137						Methanol, water			21.9			21.7
C_6H_5	CH_3	SC_2H_5	86–88						Ethanol, water			20.7			20.9
C_6H_5	C_2H_5	OH	295	88.5	229	28,300	275	14,400	Ethanol, water			23.3			23.5
C_6H_5	C_2H_5	SH	248–249	91.6	231	12,300	239	26,400	Repptd.	69.9	4.72	21.9	60.4	5.05	21.7
					275	13,600	319	18,200							
					320	15,600									
p-$CH_3C_6H_4$	CH_3	OH	298–300	93.6	230	35,700	275	15,400	Ethanol, water			23.4			23.5
p-$CH_3C_6H_4$	CH_3	Cl	89–91	78.1					Heptane			21.6			21.6
p-$CH_3C_6H_4$	CH_3	OCH_3	121–122	81.2					Methanol			22.0			21.7
p-$CH_3C_6H_4$	CH_3	OC_2H_5	93–94	53.0					Ethanol			20.9			20.8
o-ClC_6H_4	CH_3	Cl	121	77.8					Hexane			20.1			20.1
p-BrC_6H_4	CH_3	OH	>315	86.6	239	37,200	240	32,000	Ethanol, water			18.4			18.3
							277	18,300							
p-BrC_6H_4	CH_3	Cl	130.5–131	88.7					Hexane			17.3			17.3
p-ClC_6H_4	CH	OH	>310	94.5	240	36,400	240	41,700	Ethanol, water	55.4	3.46	21.5	55.1	3.37	21.2
							278	17,400							
p-ClC_6H_4	CH_3	Cl	129	82.6					Heptane	51.7	2.89	20.1	52.2	2.99	19.9
p-ClC_6H_4	CH_3	SH	>305	75.2					Repptd.			25.3			25.2
p-$NO_2C_6H_4$	CH_3	OH	>310	90.0	248	14,350	256	16,000	Repptd.	53.1	3.34	25.8	53.7	2.76	25.3
					306	14,900	321	13,800					52.4	3.26	
p-$NO_2C_6H_4$	CH_3	Cl	184	82.0					Toluene			24.2			24.2

4-Hydroxy-1,6-dimethylpyrazolo[3,4-d]pyrimidine (VI, R_1, R_2 = CH_3). One hundred twenty-one g. of 5-acetylamino-1-methyl-4-cyanopyrazole were added to a mixture of 1500 ml. of 3% hydrogen peroxide and 400 ml. of 10% potassium hydroxide. The mixture was warmed at 70° for 10 hr. It was then filtered and acidified to yield light yellow crystalline precipitate. The crude product was recrystallized from ethanol to give 103 g. (73%) of needles, m.p. 277–278° (sublimed at 180°).

Anal. Calcd. for $C_7H_8N_4O$: C, 51.2; H, 4.90; N, 34.2. Found: C, 51.2; H, 4.88; N, 34.2.

4-Hydroxy-6-methyl-1-phenylpyrazolo(3,4-d)pyrimidine (VI, R_1 = C_6H_5, R_2 = CH_3). *Method (1)*: 5-Acetylamino-4-cyano-1-phenylpyrazole (14.5 g.) was dissolved in a solution of 5 g. of potassium hydroxide and 200 ml. of 3% hydrogen peroxide. The mixture was warmed at 70–75° for 5 hr. It was then acidified with glacial acetic acid to give a white precipitate. The product was recrystallized from ethanol to give 14 g. (97%) of white needles which melted at 298–300°. Another recrystallization raised the melting point to 301–302°.

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 64.0; H, 4.42; N, 24.8. Found: C, 63.7; H, 4.33; N, 24.6.

Method (2): One g. of 5-acetylamino-1-phenylpyrazole-4-carboxamide was added to 100 ml. of 10% potassium hydroxide solution. The mixture was heated on a water bath (70°) for 20 min. and then acidified with glacial acetic acid. The white precipitate which formed immediately was filtered and washed with water. Recrystallization from ethanol gave 0.8 g. of white needles which melted at 301°. The mixed melting point of this product and that prepared by Method (1) showed no depression. The ultraviolet absorption spectra of this compound and the compound made from Method (1) were identical.

Preparation of 1-alkyl(aryl)-4-chloro-6-methylpyrazolo[3,4-d]pyrimidines (XI). See Table II. *4-Chloro-6-methylpyrazolo[3,4-d]pyrimidine* (XI, R_1 = H, R_2 = CH_3). Fifty g. of finely powdered 4-hydroxy-6-methylpyrazolo[3,4-*d*]pyrimidine were added to a mixture of 140 ml. of *N*,*N*-dimethylaniline (mono-free) and 1 l. of phosphorus oxychloride. The mixture was refluxed for 2 hr. until all the solid went into solution. Excess phosphorus oxychloride was distilled under reduced pressure, and the syrupy residue was poured onto crushed ice with vigorous stirring. The aqueous suspension was extracted with ether (6 l. required). The ethereal extract was washed well with water until absolutely free from acid. The ether extract was dried over magnesium sulfate for 12 hr. and finally distilled slowly from a water bath. The last trace of ether was removed with a stream of air. This procedure was necessary to avoid the decomposition of the chloro- compound by overheating. The crude compound was recrystallized from dry benzene to give 35 g. (62%) of the product which decomposed without melting at 135–140°.

Anal. Calcd. for $C_6H_5N_4Cl$: C, 42.7; H, 2.70; N, 33.3. Found: C, 42.5; H, 2.91; N, 33.6.

4-Chloro-1,6-dimethylpyrazolo[3,4-d]pyrimidine (XI, R_1, R_2 = CH_3). Twenty-five g. of 4-hydroxy-1,6-dimethylpyrazolo[3,4-*d*]pyrimidine and 400 ml. of phosphorus oxychloride were refluxed for 2 hr. Excess solvent was distilled from the clear solution. The syrup, which contained a small amount of phosphorus oxychloride so that it could be poured out easily, was poured slowly onto 1 kg. of crushed ice with vigorous stirring. The cold aqueous suspension was allowed to stand for 15 min. and then extracted with chloroform. The extract was dried over anhydrous sodium sulfate overnight. Chloroform was distilled at room temperature and a brownish yellow liquid resulted which solidified on cooling. The product was recrystallized from *n*-heptane to give 24 g. (87%) of white needles, m.p. 74°.

Anal. Calcd. for $C_7H_7N_4Cl$: C, 46.1; H, 3.84; N, 30.7. Found: C, 45.9; H, 4.01; N, 30.6.

4-Chloro-6-methyl-1-(p-nitrophenyl)pyrazolo[3,4-d]pyrimidine (XI, R_1 = *p*-$NO_2C_6H_4$, R_2 = CH_3). To 250 ml. of phosphorus oxychloride were added 20 g. of powdered 4-hydroxy-6-methyl-1-(*p*-nitrophenyl)pyrazolo[3,4-*d*]pyrimidine. The mixture was refluxed for 3 hr. Excess phosphorus oxychloride was then distilled at reduced pressure, and the syrupy residue was added cautiously, a little at a time, onto finely crushed ice with vigorous stirring. The resulting solid product was filtered and washed well with ice water followed by ether. It was recrystallized from toluene to give 17.5 g. (82%) of light yellow powder, m.p. 184°.

Anal. Calcd. for $C_{12}H_8N_5O_2Cl$: N, 24.2. Found: N, 24.2.

Preparation of 1-alkyl(aryl)-6-alkyl-4-mercaptopyrazolo[3,4-d]pyrimidines (XII). See Table II. *4-Mercapto-6-methyl-1-1-phenylpyrazolo(3,4-d)pyrimidine* (XII, R_1 = C_6H_5, R_2 = CH_3). *Method (1)*. A mixture of finely powdered, intimately mixed 4-hydroxy-6-methyl-1-phenylpyrazolo[3,4-*d*]pyrimidine (11 g.) and phosphorus pentasulfide (50 g.) was added portionwise to 400 ml. of tetralin, preheated to 165°. During the addition, which required 45 min., the temperature was allowed to rise to 185°. The reaction mixture was then heated to 190–195° for 6 hr., with continuous stirring. The solution was then cooled overnight and filtered. The product was washed with Skellysolve "B," and finally dissolved in dilute potassium hydroxide solution. Precipitation of the product with acetic acid gave 5.5 g. (46.6%), m.p. 266–268°.

For analytical purposes part of the product was recrystallized from ethanol to give a light yellow solid, m.p. 268.5°.

Anal. Calcd. for $C_{12}H_{10}N_4S$: C, 59.5; H, 4.16; N, 23.1. Found: C, 59.4; H, 4.16; N, 23.4.

Method (2). A mixture of 14 g. of 4-chloro-6-methyl-1-phenylpyrazolo [3,4-*d*]pyrimidine and 14 g. of C.P. thiourea in 120 ml. of absolute ethanol was refluxed for 4 hr. A light yellow solid separated on cooling. The product was filtered and washed well with cold ethanol and water. The product was further purified by precipitation from a hot basic solution with acetic acid to give 11.5 g. (83.3%) of a white solid, m.p. 268.5°. A mixed melting point of the product and the one prepared by method (1) indicated no depression. Their ultraviolet absorption spectra were identical.

All the other 4-mercapto derivatives were prepared by essentially the same procedure as Method (2).

Preparation of 1-alkyl(aryl)-6-alkyl-4-alkylmercaptopyrazolo[3,4-d]pyrimidines (XIII). See Table II. *1,6-Dimethyl-4-methylmercaptopyrazolo(3,4-d)pyrimidine* (XIII, R_1, R_2, R_3 = CH_3). A mixture of 13 g. of 1,6-dimethyl-4-mercaptopyrazolo[3,4-*d*]pyrimidine, 40 ml. of 4*N* potassium hydroxide, 18 g. of methyl iodide, and 30 ml. of methanol was shaken vigorously in a separatory funnel for 30 min. The contents were allowed to stand overnight at 40°. The white solidwas filtered and recrystallized from dilute methanol. The yield was 12.5 g. (90.2%), m.p. 74–75°.

Anal. Calcd. for $C_8H_{10}N_4S$: N, 28.8. Found: N, 28.7.

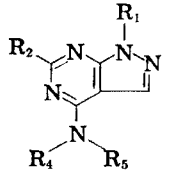
4-Ethylmercapto-6-methyl-1-phenylpyrazolo[3,4-d]pyrimidine (XIII, R_1 = C_6H_5, R_2 = CH_3, R_3 = C_2H_5). Nine g. of 4-mercapto-6-methyl-1-phenylpyrazolo[3,4-*d*]pyrimidine was added to 200 ml. of water containing 15 g. of potassium hydroxide and 21 g. of ethyl iodide. To this mixture was added 100 ml. of ethanol to make the solution homogeneous. The mixture was refluxed for 5 hr. It was then reduced in volume until an oily product appeared which solidified slowly on standing. The product was filtered, washed well with water, and recrystallized from dilute ethanol. The yield of slightly yellow needles was 3 g. (30%), m.p. 86–88°.

Anal. Calcd. for $C_{14}H_{14}N_4S$: N, 20.7. Found: N, 20.9.

Preparation of 4-alkoxy-1-alkyl(aryl)-6-methylpyrazolo[3,4-d]pyrimidines (XIV). See Table II. *4-Ethoxy-6-methyl-1-p-tolylpyrazolo[3,4-d]pyrimidine* (XIV, R_1 = *p*-CH_3-C_6H_4, R_2 = CH_3, R_3 = C_2H_5). To a solution of 100 ml. absolute ethanol and 5.5 g. of 4-chloro-6-methyl-1-(*p*-tolyl)pyrazolo-[3,4-*d*]pyrimidine was added, slowly, with shaking, a solution prepared by dissolving 2 g. of sodium in 70 ml. of ethanol. The mixture was allowed to stand at room temperature for 2 hr., with occasional shaking. It was then heated on a steam bath for 40 min. and sodium chloride

TABLE III

6-ALKYL-4-*N*-SUBSTITUTED PYRAZOLO[3,4-*d*]PYRIMIDINES



R_1	R_2	R_4	R_5	M.P., °C.	Method of Prepn.	U.V. Absorption: Yield, %	*p*H 1, λ_{max}	*p*H 1, ϵ	*p*H 11, λ_{max}	*p*H 11, ϵ	Recrystallization Solvents	Analyses: Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	CH_3	H	H	>300	A	73.0	259	8,650	265	8,800	Ethanol, water	48.3	4.60	47.0	48.4	4.95	46.7
H	CH_3	H	CH_3	>300	B	60.0	265	7,650	275	9,950	Ethanol, water			42.9			42.7
H	CH_3	H	C_2H_5	273–274	B	56.0	269	10,100	275	12,600	Ethanol			39.5			39.7
H	CH_3	H	CH_2—CH_2—CH_3	220–222	B	49.1	270	10,700	276	12,700	Ethanol			34.2			34.5
H	CH_3	H	CH_2—C_6H_5	241	B	87.2					Ethanol			29.3			29.1
H	CH_3	H	Furfuryl	243–244	C	59.0			275	12,900	Ethanol	57.7	4.83	30.6	57.5	4.75	30.4
CH_3	CH_3	H	H	251–252	A	90.0	260	9,450	262	9,300	Ethanol, water			42.9			42.8
CH_3	CH_3	H	CH_3	136–138	B	77.2	265	11,700	279	13,500	Water			39.5			39.5
CH_3	CH_3	H	C_2H_5	131.5–132	C	66.9	266	21,000	279	22,000	Toluene, heptane	56.5	6.85	36.6	57.0	7.10	
CH_3	CH_3	H	CH_2—C_6H_5	180–182	B	83.0					Ethanol			27.7			27.4
CH_3	CH_3	H	Furfuryl	140–141.5	C	54.6					Ethanol			28.8			28.6
CH_3	CH_3	H	*o*-Cl—C_6H_4	223.5–224	B	60.0					Ethanol	57.1	4.33	25.6	57.2	4.37	25.9
CH_3	CH_3	H	*p*-Cl—C_6H_4	231.5	B	67.0					Ethanol, water			25.6			25.5
CH_3	CH_3	H	*o*-CH_3—C_6H_4	224–225.5	B	60.0	270	15,400	282	16,000	Ethanol			27.7			27.6
CH_3	CH_3	H	*p*-CH_3—C_6H_4	225–227	B	74.7					Ethanol	66.5	5.98	27.7	66.7	5.97	27.3
CH_3	CH_3	H	2,6-Diethylphenyl	218–218.5	B	48.5	215 269	24,800 13,000	279	13,000	Ethanol	69.2	7.17	23.7	68.8	7.00	23.9
CH_3	CH_3	H	NH_2	259–260	B	87.3	223 265	22,000 13,200	278	11,100	Ethanol	47.1	5.65		47.5	5.83	
C_6H_5	CH_3	H	H	287–289	A	82.5	238	25,200	236 278	18,700 9,000	Ethanol, water	64.0	4.92	31.1	64.0	4.73	30.9
C_6H_5	CH_3	H	CH_3	162–163	B	80.2	242	36,000	238 236	26,000 16,200	Ethanol, water	65.3	5.48	29.3	65.7	5.47	29.7
C_6H_5	CH_3	CH_3	CH_3	117–117.5	C	82.5	247	30,600	236 288	24,300 18,200	Ethanol	66.5	5.94	27.7	66.4	5.82	27.2
C_6H_5	CH_3	H	C_2H_5	87	B	87.2	232	29,400	235	23,000	Ethanol			27.7			27.9
C_6H_5	CH_3	C_2H_5	C_2H_5	66–68	C	83.0					Ethanol			25.0			24.8
C_6H_5	CH_3	H	$CH(CH_3)_2$	143–144	B	86.0	243	30,800	238 286	23,400 16,700	Ethanol, water	67.4	6.37	26.2	66.8	6.34	26.4
C_6H_5	CH_3	H	$C(CH_3)_3$	175–177	C	61.0					Ethanol, water	68.4	6.81	25.0	67.7	6.68	25.2
C_6H_5	CH_3	H	CH_2—CH_2—$N(C_2H_5)_2$	159–160	C	49.1	243	22,300	238 286	21,000 13,900	Heptane			25.9			25.5
C_6H_5	CH_3	CH_2—C_6H_5		187–188	B	92.0	245	29,000	237 282	16,800 11,300	Ethanol	72.4	5.44	22.2	71.7	5 10	22.4

TABLE III (*Continued*)

R_1	R_2	R_4	R_5	M.P., °C.	Method of Prepn.	Yield, %	U.V. Absorption pH 1, λ_{max}	pH 1, ϵ	pH 11, λ_{max}	pH 11, ϵ	Recrystallization Solvents	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_6H_5	CH_3	H	Furfuryl	153–154.5	C	56.2	243	39,400	238	28,800	Toluene,	67.0	4.96	23.0	67.3	4.87	23.1
									284	17,200	heptane						
C_6H_5	CH_3	H	C_6H_5	262–263	B	50.5	246	9,600	247	26,500	2-Ethoxy-			23.3			23.4
							300	7,200			ethanol						
C_6H_5	CH_3	H	*m*-Br—C_6H_4	215–127	B	68.0					Ethanol	57.0	3.71	18.4	56.7	3.93	18.3
C_6H_5	CH_3	H	*o*-Cl—C_6H_4	175–176	B	51.3					Ethanol			20.9			21.1
C_6H_5	CH_3	H	*m*-Cl—C_6H_4	192–193	B	90.0	247	28,800	238	17,400	Ethanol	64.6	4.21	20.9	64.2	4.60	20.9
									305	16,400							
C_6H_5	CH_3	H	*p*-Cl—C_6H_4	226–226.5	B	82.0	248	25,800	252	73,500	Ethanol, water	64.6	4.21	20.9	64.0	4.33	20.7
C_6H_5	CH_3	H	2,6-Diethylphenyl	189–190	B	71.2					Ethanol			19.6			19.8
C_6H_5	CH_3	H	NH_2	243–244	B	80.1	242	25,200	239	19,200	Pyridine	60.0	5.00	35.0	60.2	5.12	35.4
									283	11,300							
C_6H_5	CH_3	H	NH—C_6H_5	240–241	B	47.5					Pyridine	67.3	5.10	26.6	67.7	5.05	26.5
C_6H_5	C_2H_5	CH_3	CH_3	90.5–91	B	55.5					Ethanol	67.5	6.41	26.2	67.7	6.62	26.3
C_6H_5	C_2H_5	H	$C(CH_3)_3$	148–148.5	C	73.3	238	15,900	240	2,950	Ethenol,	69.2	7.17	23.7	69.4	7.07	23.7
									286	3,250	sublimed						
C_6H_5	C_2H_5	H	CH_2—C_6H_5	129–129.5	C	48.5	245	24,300	239	9,530	Benzene,			21.3			21.3
									287	6,250	ethanol						
C_6H_5	C_2H_5	H	*o*-Cl—C_6H_5	168–168.5	B	71.5					2-Ethoxy-	65.5	4.62	20.0	66.0	4.71	19.9
											ethanol						
C_6H_5	C_2H_5	H	*m*-Cl—C_6H_5	187–189	B	74.0					Ethanol			20.0			19.9
C_6H_5	C_2H_5	H	*p*-Cl—C_6H_5	208.5–209.5	B	87.8					2-Ethoxy-			20.0			19.8
											ethanol						
C_6H_5	C_2H_5	H	*o*-CH_3—C_6H_5	175–176	B	75.5	247	29,800	242	19,600	Ethanol			21.3			21.0
									291	16,300							
C_6H_5	C_2H_5	H	*m*-CH_3—C_6H_5	169.5	B	58.0					Ethanol			21.3			21.3
C_6H_5	C_2H_5	H	*p*-CH_3—C_6H_5	199–200	B	78.6					Ethanol			21.3			21.1
C_6H_5	C_2H_5	H	2,5-Dichlorophenyl	181–183	B	42.1					Ethanol			18.2			18.4
C_6H_5	C_2H_5	H	2,6-Diethylphenyl	191–191.5	B	38.0	244	28,200	252	25,600	Ethanol			18.7			18.9
									304	18,500							
C_6H_5	C_2H_5	H	NH_2	198–199	B	87.5					Ethanol	61.5	5.55	33.1	61.4	5.29	33.2
p-CH_3—C_6H_4	CH_3	H	H	296.5–298	A	75.7	233	7,650			Ethanol			29.3			29.4
p-CH_3—C_6H_4	CH_3	H	CH_3	181–182.5	B	86.0	244	29,600	239	22,500	Methanol,			27.6			27.7
									283	14,200	water						
p-CH_3—C_6H_4	CH_3	CH_3	CH_3	149–151	B	82.2	248	24,800	239	22,200	Ethanol			26.2			26.2
									289	16,300							
p-CH_3-C_6H_4	CH_3	H	C_2H_5	144–146	B	80.0					Ethanol, water			26.2			26.0
p-CH_3—C_6H_4	CH_3	H	CH_2—CH_2—$N(C_2H_5)_2$	165	C	62.8	244	25,700	239	23,300	Toluene,			24.8			24.8
									283	14,900	heptane						
p-CH_3—C_6H_4	CH_3	H	*o*-Cl—C_6H_4	219–221	B	76.5					Pyridine	65.4	4.62	20.0	65.2	4.44	20.2
p-CH_3—C_6H_4	CH_3	H	*m*-Br—C_6H_4	218–220	B	63.5	253	30,000	241	23,200	Ethanol			17.8			18.0
									315	19,300							
o-Cl—C_6H_4	CH_3	H	H	294.5–295.5	A	71.8					Ethanol			27.0			27.1
o-Cl—C_6H_4	CH_3	CH_3	CH_3	152–153	C	77.7					Ethanol			24.4			24.4

TABLE III (*Continued*)

R_1	R_2	R_4	R_5	M.P., °C.	Method of Prepn.	Yield, %	U.V. Absorption *p*H 1, λ_{max}	ϵ	*p*H 11, λ_{max}	ϵ	Recrystallization Solvents	Analyses Calcd. C	H	N	Found C	H	N
o-Cl—C_6H_4	CH_3	H	*o*-Cl—C_6H_4	196–198	B	63.0					Ethanol			18.9			19.0
p-Br—C_6H_4	CH_3	C_2H_5	C_2H_5	123–124	B	51.6					2-Ethoxyethanol, water			19.4			19.5
p-Cl—C_6H_4	CH_3	H	H	>300	A	36.0					Ethanol			27.0			27.3
p-Cl—C_6H_4	CH_3	H	CH_3	218–219	B	57.2					Ethanol, water			25.6			25.3
p-ClC_6H_4	CH_3	H	CH_2—CH_2—CH_2—O—$CH(CH_3)_2$	109–110	B	51.1					Methanol, water	60.2	6.14	19.5	60.3	6.08	19.3
p-ClC_6H_4	CH_3	CH_2—CH_2—CH_2—CH_2—CH_2		127.5–128.5	B	61.3					Ethanol, water	62.5	5.55		62.0	5.28	
p-ClC_6H_4	CH_3	H	CH_2—C_6H_5	214	B	93.3					2-Ethoxyethanol	65.4	4.61	20.0	65.5	4.50	20.1
p-ClC_6H_4	CH_3	H	CH_2—CH_2—C_6H_5	175–176	B	60.1			246 294	46,000 24,600	Ethanol	66.0	4.98	19.3	65.7	5.12	19.7
p-ClC_6H_4	CH_3	H	*o*-Cl—C_6H_4	221–222	B	62.0					Pyridine	58.5	3.54		58.2	3.58	
p-ClC_6H_4	CH_3	H	*m*-ClC_6H_4	222–223	B	85.5					2-Ethoxyethanol			18.9			18.6
p-ClC_6H_4	CH_3	H	*p*-ClC_6H_4	239–239.5	B	88.0					Pyridine	58.5	3.54	18.9	59.0	3.84	18.7
p-ClC_6H_4	CH_3	H	*m*-BrC_6H_4	230–232	B	74.2					Pyridine	52.2	3.17	16.9	51.8	3.44	16.6
p-ClC_6H_4	CH_3	H	2,5-Dichlorophenyl	200	B	71.5					2-Ethoxyethanol			17.4			17.3
p-$NO_2C_6H_4$	CH_3	H	CH_3	248–249	B	69.0	269 319	15,600 13,300	267	19,600	Ethanol			24.2			24.1
p-$NO_2C_6H_4$	CH_3	CH_3	CH_3	196	B	51.2	273	11,600	271	12,200	Ethanol, water			28.2			28.0
p-$NO_2C_6H_4$	CH_3	H	$CH(CH_3)_2$	190–192	B	81.1	232 281	21,200 21,800	271 316	17,800 14,400	Ethanol			26.9			26.7
p-$NO_2C_6H_4$	CH_3	H	CH_2—CH_2—CH_2—CH_3	147	B	66.6	239 270 327	10,800 12,100 9,450	269	21,200	Ethanol	58.8	5.53	25.8	59.0	5.68	25.6
p-$NO_2C_6H_4$	CH_3		[CH_2—CH_2—CH_2—CH_2—CH_2]	189–191	B	96.0	237 279	15,200 25,400	240 292 344	13,900 12,500 13,400	Pyridine	60.5	5.35	24.8	61.0	5.50	23.4
p-$NO_2C_6H_4$	CH_3	H	CH_2—CH_2—$N(C_2H_5)_2$	145	B	91.7	269 315	17,000 14,000	272	22,500	Ethanol, water			26.5			26.1
p-$NO_2C_6H_4$	CH_3	H	*o*-ClC_6H_4	227–228	B	43.2	276	21,300	238 285	18,200 13,300	Ethanol			22.1			22.2
p-$NO_2C_6H_4$	CH_3	H	*p*-ClC_6H_4	278	B	87.0					Acetic acid			22.1			22.4

filtered from the hot reaction mixture. To the filtrate was added 50 ml. of water, and the clear solution was cooled overnight. White, fluffy long needles were formed the second day, which were filtered and recrystallized from dilute ethanol to give 3.1 g. (53%) of the desired product, m.p. 93–94°.

Anal. Calcd. for $C_{15}H_{16}N_4O$: N, 20.0. Found: N, 20.8.

The other 4-alkoxy compounds were prepared by essentially the same method.

Preparation of 6-alkyl-4-N-substituted aminopyrazolo[3,4-d]pyrimidines (XV). See Table III. *General Method* (*A*). This method is illustrated by the following example. *4-Amino-6-methylpyrazolo[3,4-d]pyrimidine* (XV, R_1, R_4, R_5 = H, R_2 = CH_3). A mixture of 10 g. of 4-chloro-6-methylpyrazolo[3,4-*d*]pyrimidine (XI, R_1 = H, R_2 = CH_3) and 120 ml. of alcoholic ammonia was heated in a bomb at 160° for 8 hr. The reaction product was evaporated on a steam bath to dryness. The residue was boiled with dilute hydrochloric acid. The solution was treated with charcoal and filtered. The product was reprecipitated by the addition of ammonium hydroxide. The product was then filtered and recrystallized from dilute ethanol to give 6.5 g. (73%) of light yellow needles, m.p. > 300°.

Anal. Calcd. for $C_6H_7N_5$: C, 48.3; H, 4.60; N, 47.0. Found: C, 48.4; H, 4.95; N, 46.7.

General Method (*B*). This method is illustrated by the following specific examples. *4-n-Butylamino-6-methylpyrazolo[3,4-d]pyrimidines* (XV, R_1, R_4 = H, R_2 = CH_3, R_5 = CH_2—CH_2—CH_2—CH_3). Five g. of 4-chloro-6-methylpyrazolo(3,4-*d*)pyrimidine was added to a mixture of 7 g. of *n*-butylamine and 120 ml. of absolute ethanol. The mixture was refluxed on a steam bath for 7 hr., light yellow needles formed in the hot solution. The product was filtered and recrystallized from ethanol to give 3 g. (49.1%) of white needles, m.p. 220–222°.

Anal. Calcd. for $C_{10}H_{15}N_5$: N, 34.2. Found: N, 34.5.

4-(p-Chloroanilino)-6-methyl-1-phenylpyrazolo[3,4-d]pyrimidine (XV, R_1 = C_6H_5, R = CH_3, R_4 = H, R_5 = *p*-Cl-C_6H_4). Five g. of 4-chloro-6-methyl-1-phenylpyrazolo[3,4-*d*]-pyrimidine was added to a mixture of 8 g. of *p*-chloroaniline and 75 ml. of absolute ethanol. The mixture was refluxed on a water bath for 40 min., and a yellow solid separated from the hot solution. The mixture, after cooling in an ice bath for 3 hr. was filtered. The crude product, 6.2 g., m.p. 220–223°, was recrystallized from dilute ethanol to give 5.6 g. (82%) of white needles, m.p. 226–226.5°.

Anal. Calcd. for $C_{18}H_{13}N_5Cl$: C, 64.4; H, 4.21; N, 20.9. Found: C, 64.0; H, 4.33; N, 20.7.

1-(p-Chlorophenyl)-6-methyl-4-(p-phenylethylamino)pyrazolo[3,4-d]pyrimidine (XV, R_1 = *p*-Cl-C_6H_4, R_2 = CH_3, R_4 = H, R_5 = CH_2—CH_2—C_6H_5). Nine g. of 4-chloro-1-(*p*-chlorophenyl)-6-methylpyrazolo[3,4-*d*]pyrimidine was added to 160 ml. of absolute ethanol containing 10 g. of β-phenylethylamine. The mixture was boiled gently on a steam bath to near dryness. To the residue was added 20 ml. of methanol. The solid produce was filtered and recrystallized from ethanol to give 11 g. (94%) of white needles, m.p. 175–176°.

Anal. Calcd. for $C_{20}H_{18}N_5Cl$: C, 66.0; H, 4.98; N, 19.3. Found: C, 65.7; H, 5.12; N, 19.7.

General Method (*C*) is illustrated by the following examples. *4-Furfurylamino-1,6-dimethylpyrazolo[3,4-d]pyrimidine* (XV, R_1, R_2 = CH_3, R_4 = H, R_5 = CH_2—C_4H_3O). A mixture of 5.5 g. of 4-chloro-1,6-dimethylpyrazolo[3,4-*d*]pyrimidine, 5.5 g. of furfurylamine, and 200 ml. of absolute ethanol was heated on a steam bath for 8 hr. The mixture was then evaporated, and the syrupy residue was stirred with 30 ml. of 10% potassium hydroxide solution so as to neutralize the hydrochloride salt. The alkaline solution was decanted, and the syrup was boiled with 100 ml. of benzene for 2 hr. The hot benzene solution was filtered and evaporated to dryness. The light yellow solid remaining was recrystallized twice from ethanol to give 4 g. (54.6%) of white needles, m.p. 140–141.5°.

Anal. Calcd. for $C_{12}H_{13}N_4O$: N, 28.8. Found: N, 28.6.

4-Benzylamino-6-ethyl-1-phenylpyrazolo[3,4-d]pyrimidine (XV, R_1 = C_6H_5, R_2 = C_2H_5, R_4 = H, R_5 = CH_2—C_6H_5). To a solution of 13 g. of 4-chloro-6-ethyl-1-phenylpyrazolo-[3,4-*d*]pyrimidine in 150 ml. of absolute ethanol was added slowly, with stirring, a solution of 13 g. of benzylamine in 50 ml. of absolute ethanol. The mixture was refluxed for 12 hr. Excess ethanol was evaporated, and the syrupy product was treated with benzene and several drops of methanol. The compound solidified slowly after refrigeration. The product was recrystallized from a mixture of ethanol and benzene to give 8 g. (48.5%) of white crystals, m.p. 129–129.5°.

Anal. Calcd. for $C_{20}H_{19}N_5$: N, 21.3. Found: N, 21.4.

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