tion of 10 g. (0.043 mole) of XVIII in 100 ml. of absolute alcohol cooled to 15° at such a rate that the temperature remained at about 15°. After standing for 1 hr. at 15°, the precipitate was filtered, washed thoroughly with water, and recrystallized from benzene-ligroin (b.p. 30–60°).

2-Methylthio-4-(1-methyl-2-propylidenehydrazino)-5-carbethoxypyrimidine. A solution of 0.50 g. (0.0021 mole) of 2-methylthio-4-(1-methylhydrazino)-5-carbethoxypyrimidine and 0.50 g. (0.0086 mole) of propionaldehyde in 25 ml. of absolute alcohol was allowed to stand overnight at room temperature. The solution was then evaporated to dryness in a stream of dry air and the residue recrystallized from ligroin (b.p. 30–60°) to give 0.37 g. (62%) of white solid; m.p. 66–67°.

Anal. Calcd. for $C_{12}H_{18}N_4O_2S$: C, 51.04; H, 6.43; N, 19.85. Found: C, 50.99; H, 6.42; N, 19.38.

2-Methylthio-4-(2-arylhydrazino)-5-carbethoxypyrimidines (III–IV). *General method.* A solution of 10 g. (0.043 mole) of XVIII in 150 ml. of absolute alcohol was added to a solution of 0.088 mole of the arylhydrazine in the minimum amount of absolute alcohol. The resulting solution was heated at 50° for 30 min., then allowed to stand 4 hr. at room temperature. It was next diluted with twice its volume of water and refrigerated overnight at 1°. The precipitate was filtered, triturated with 300 ml. of 5% hydrochloric acid, washed thoroughly with water, and recrystallized from alcohol-water.

2-Methylthio-4-(2-acetyl-2-phenylhydrazino)-5-carbethoxypyrimidine (V). To a solution of 2.3 g. (0.015 mole) of 1-acetyl-1-phenylhydrazine[16] in 55 ml. of absolute alcohol was added a solution of 1.8 g. (0.0075 mole) of XVIII in 25 ml. of absolute alcohol. The resulting solution was allowed to stand 4 hr., diluted with an equal volume of water, and refrigerated overnight at 1°. The precipitate of 2-phenyl-6-methylthiopyrazolono(3,4-d)pyrimidine (X) was removed and 150 ml. of water was added to the solution. After several hours of refrigeration, the solution was filtered and the precipitate recrystallized from water.

Cyclization of hydrazinopyrimidine (I–IV) *to pyrazolono (3,4 d)pyrimidines* (VI, VII, XVI, and XVII). *General method.* A solution of 1 g. of the hydrazinopyrimidine in 10 ml. of 10% potassium hydroxide was boiled for 15 min., cooled, and acidified with 25% acetic acid. The precipitate was washed with water and recrystallized from *n*-butyl alcohol.

1-Isopropyl-6-methylthiopyrazolono(3,4-d)pyrimidine (VIII). A solution of 3.3 g. (0.020 mole) of isopropylhydrazine oxalate, 35 ml. of water, and 2.8 g. of potassium hydroxide was diluted with 350 ml. of alcohol and the precipitate of potassium oxalate removed by filtration. To the filtrate was added a solution of 2.3 g. (0.010 mole) of XVIII in 50 ml. of alcohol and the solution warmed at 60° for 30 min. After cooling, the solution was diluted with 500 ml. of water and placed in the refrigerator at 1°. The precipitate was filtered and recrystallized from *n*-butyl alcohol.

1,2-Dimethyl-6-methylthiopyrazolono(3,4-d)pyrimidine (IX). A solution of 5.3 g. (0.088 mole) of 1,2-dimethylhydrazine in 25 ml. of absolute alcohol was added slowly, with stirring, to 10 g. (0.043 mole) of XVIII dissolved in 125 ml. of absolute alcohol. The temperature was maintained at 25° by cooling. When the reaction subsided, the solution was allowed to stand for 4 hr. and diluted with three volumes of water. After overnight refrigeration at 1°, the precipitate was filtered, washed thoroughly with water, and recrystallized from benzene-ligroin (b.p. 30–60).

2-Phenyl-6-methylthiopyrazolono(3,4-d)pyrimidine (X). *From* XVIII. A solution of 9.5 g. (0.088 mole) of phenylhydrazine in 25 ml. of absolute alcohol was added slowly, with stirring, to 10 g. (0.043 mole) of XVIII dissolved in 200 ml. of absolute alcohol. After standing 2 hr., the solution was poured into three times its volume of 5% hydrochloric acid and stirred for 1 hr. The precipitate was filtered, washed with water, and recrystallized from alcohol.

From V. A solution of 0.5 g. (0.0015 mole) of V in 30 ml. of 2% hydrochloric acid was refluxed for 30 min., cooled, and made just basic to litmus with 10% sodium hydroxide. After 1 hr. in the refrigerator at 1°, the precipitate was filtered, washed with water, and recrystallized from alcohol to give 0.21 g. (56%) of white solid; m.p. 276–278°. Mixed melting points, infrared and ultraviolet spectra showed this material to be identical with that from the preceding preparation.

2-Aryl-6-methylthiopyrazolono(3,4-d)pyrimidines (XI–XV). *General method.* A solution of 2.3 g. (0.01 mole) of XVIII in 25 ml. of absolute alcohol was added to a solution of 0.02 mole of the arylhydrazine in the minimum amount of absolute alcohol. The resulting solution was warmed at 50–60° for 30 min. and allowed to stand for 4 hr., diluted with three times its volume of water and refrigerated overnight at 1°. The precipitate was filtered, washed with water, and recrystallized from *n*-butyl alcohol.

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[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY,[1] SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XXV. Preparation of 6-Alkoxy-2-aminopurines[2]

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Some 6-alkoxy-2-aminopurines have been prepared from 2-amino-6-chloropurine.

As a part of our general program to investigate purines in search of more effective anticancer agents, a number of 6-alkoxy-2-aminopurines (I) (Table I) have been prepared. Although they are closely related to guanine(2-amino-6-purinol) (II), they cannot be prepared from this substance directly. Traube and Dudley[3] found that treatment of guanine in aqueous-alcoholic sodium hydroxide solution with iodomethane gave 7-methyl- and 1,7-dimethylguanine.

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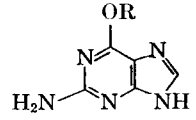
(2) This work was supported by funds from the National Institutes of Health, Contract No. SA-43-ph-1740, and from the C. F. Kettering Foundation. For paper XXIV of this series see J. A. Montgomery and C. T. Temple Jr., *J. Am. Chem. Soc.*, in press.

(3) W. Traube and H. W. Dudley, *Ber.*, **46**, 3844 (1913).

TABLE I

6-ALKOXY-2-AMINOPURINES



Compound[a]	R	Solvent for Recrystallization	Yield, %	M.P.[b]	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Ultraviolet Spectra[c]: pH 1 mμ	pH 1 (ε × 10⁻³)	pH 7 mμ	pH 7 (ε × 10⁻³)	pH 13 mμ	pH 13 (ε × 10⁻³)	CH₃OH mμ	CH₃OH (ε × 10⁻³)
Ia	CH_3—	H_2O	85	>260	43.63	43.18	4.27	4.44	42.41	42.56	286	(11.2)	240	(7.86)	246[f]	(4.49)	242	(8.73)
													280	(7.88)	284	(7.86)	282	(8.06)
Ib	C_2H_5—	H_2O	69.5	293[d,e]	46.92	46.68	5.06	5.15	39.09	38.56	286	(11.7)	240	(8.20)	246[f]	(4.07)	241	(8.83)
													280.5	(8.27)	284	(8.19)	282	(8.40)
Ic	C_3H_7—	H_2O	52	208	49.73	49.31	5.74	5.80	36.25	36.22	286	(11.5)	241	(7.96)	246[f]	(4.35)	241	(8.90)
													281	(8.40)	283	(8.31)	282	(8.66)
Id	iso-C_3H_7—	H_2O	58.5	177	49.73	49.80	5.74	5.83	36.25	35.64	286	(12.2)	240	(8.06)	246.5[f]	(3.78)	241	(8.78)
													281	(8.50)	285	(8.05)	282	(8.78)
Ie	n-C_4H_9—	H_2O/C_2H_5OH	40	175	52.16	51.90	6.32	6.24	33.80	34.38	286	(11.7)	240	7.73	246[b]	(3.79)	241	(8.86)
													281	(8.37)	285	(8.18)	282	(8.66)

[a] Compound II, R = OH; III, R = Cl; IV, R = SH. [b] Except where indicated, melting points were determined on a Kofler Heizbank. [c] Determined with a Beckman model DK-2 spectrophotometer, but the optical densities at the maxima were measured with a Beckman DU. [d] Capillary in aluminum block, not corrected. [e] Decomposition. [f] Shoulder.

The work of Huber[4] on 6-alkoxypurines suggested that 6-alkoxy-2-aminopurines (I) could be obtained readily from 2-amino-6-chloropurine (III).

The classical chlorination procedure using phosphoryl chloride has only recently been successfully applied to guanine to give III[5]; we obtained III by treating thioguanine (2-amino-6-purinethiol) (IV) in methanolic suspension with chlorine, a slight modification of a process described in a British patent.[6] This procedure permitted us to isolate the hydrochloride of III in 50–60% yield from the reaction mixture. The free base could be obtained by treating an aqueous suspension of the hydrochloride with sodium hydroxide solution.

2-Amino-6-chloropurine (III) is more resistant to hydrolysis than is 6-chloropurine[7]: The conversion to guanine (II) is complete after six hours in boiling 0.1*N* hydrochloric acid, whereas after boiling in 0.1*N* sodium hydroxide solution, more than 75% of III (by ultraviolet absorption) remained unchanged; the corresponding figures for the hydrolysis of 6-chloropurine to 6-purinol(hypoxanthine) are one hour in boiling 0.1*N* hydrochloric acid and four hours in boiling 0.1*N* sodium hydroxide.[7]

However, boiling the hydrochloride of III in methanol in the presence of a catalytic amount of water leads to the formation of 2-amino-6-methoxypurine (Ia) (identified by ultraviolet absorption spectrum).

For the preparation of 6-alkoxy-2-aminopurines (I) we treated the hydrochloride of III with a solution of a ten-fold excess of sodium alkoxide in the corresponding alcohol. After the solutions had been refluxed for eighteen hours, the compounds listed in Table I were isolated in yields ranging from 40% (Ie) to 85% (Ia) (yields of purified product). The 6-alkoxy-2-aminopurines are crystalline, white materials, soluble in alcohols and hot water; the lower members do not melt without decomposition.

(4) G. Huber, *Chem. Ber.*, **90**, 698 (1957).

(5) M. H. von Saltza, Ph. D. thesis, University of Wisconsin 1958.

(6) Wellcome Foundation, Ltd., British Patent, **767,216**, Jan. 30, 1957. Note Added in Proof: R. K. Robins has recently published a similar procedure for the preparation of 2-amino-6-chloropurine from 2-amino-6-methylthiopurine [*J. Am. Chem. Soc.*, **82**, 2633 (1960)].

(7) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).

EXPERIMENTAL

2-Amino-6-chloropurine (III) *hydrochloride.* A suspension of thioguanine (500 mg. 3.3 mmoles) in methanol (25 ml.) was cooled to 2° in an ice bath. Dry chlorine gas was bubbled through the mixture at such a rate that the temperature did not rise above 15°. As soon as the temperature began to drop, the stream of chlorine was replaced by a stream of dry nitrogen. When the clear solution was almost colorless, it was filtered and evaporated until crystallization set in. The crystals were collected, washed with ether, and dried *in vacuo* over phosphorus pentoxide; yield, 415 mg. (61%). *Spectral data:* λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 239 (6.32), 318 (6.80); *p*H 7, 242 (6.06), 308 (6.80); *p*H 13, 309 (5.82); CH_3OH, 243 (6.68), 314 (6.37).

Anal. Calcd. for $C_5H_4ClN_5 \cdot HCl$: C, 29.15; H, 2.44; Cl, 34.42; N, 33.99. Found: C, 29.22; H, 2.76; Cl, 34.26; N, 33.74.

2-Amino-6-chloropurine (III). 2-Amino-6-chloropurine hydrochloride (1.1 g., 5.3 mmoles) was suspended in 10 ml. of water; aqueous sodium hydroxide solution was added dropwise until the reaction mixture was slightly basic. The clear solution was filtered and neutralized with hydrochloric acid. The precipitate was recrystallized from aqueous ethanol, yielding 880 mg. (97%) of the free base (III). *Spectral data:* λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 238 (6.83), 316 (7.25); *p*H 7, 241 (6.23), 308 (6.96); *p*H 13, 273 (3.25), 309 (6.30); CH_3OH,2 43 (7.10), 309 (7.16).

Anal. Calcd. for $C_5H_4ClN_5$: C, 35.41; H, 2.38; N, 41.30; Cl, 20.91. Found: C, 35.48; H, 2.58; N, 41.56; Cl, 20.51.

6-Alkoxy-2-aminopurines. 2-Amino-6-chloropurine hydrochloride (500 mg., 2.4 mmoles) was added to a solution of metallic sodium (550 mg., 24 mmoles) in the appropriate alcohol (20 ml.) and the mixture kept at reflux temperature for 18 hr. The reaction mixture was cooled to room temperature, the calculated amount of glacial acetic acid (1.2 ml. 20 mmoles) was added, and the volatile material were removed *in vacuo*. The residue was recrystallized from the solvent specified in Table I. The physical constants of the compounds and their analyses are summarized in Table I.

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