ish brown precipitate which was collected was washed with water and amounted to 3.4 g. (quantitative yield), m.p. 141° dec. Recrystallization from ethanol gave yellowish-brown granules, m.p. 141° dec. The infrared spectrum shows absorption peaks at 1635(w) cm.$^{-1}$, 1580(m), 1550(s), 1510(m), 1420(m), 1325(s), 1250(m), 1165(m), 1140(m), 1100(m), 935(w), 918(w), 895(w), 830(m), 795(w), 770(s), 723(m), 700(m).

Anal. Calcd. for $C_{18}H_7N_3O_2$: C, 59.69; H, 3.50. Found: C, 59.62; H, 3.31.

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

7-Substituted 7*H*-Purines[1]

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A general method for the preparation of 7-substituted 7*H*-purines has been developed. The key steps in this synthesis are the alkylation of *N*-(4-amino-5-pyrimidinyl)formamides in *N,N*-dimethylformamide followed by ring closure in this medium.

Although the syntheses of a number of 7-substituted 7*H*-purines have appeared in the literature, none of the methods employed is generally applicable to the preparation of this type of compound. For example, a variety of 2,6-disubstituted 7-methyl-7*H*-purines have been prepared from 2,6-dichloro-7-methyl-7*H*-purine[2-4] which in turn is obtained by the phosphorus oxychloride chlorination of theobromine.[5] Thus these compounds come from a natural product and are limited to 7-*methyl*-7*H*-purines. Another method of preparation of 7-methylpurines[6,7] depends on the cyclization of *N,N'*-dimethyloxamide to 1-methyl-5-chloroimidazole.[8] In addition to being lengthy, this method is also confined to 7-*methyl*-7*H*-purines. Other 7-substituted 7*H*-purines have been prepared by the *N*-alkylation of purines.[9] In the case of theophylline, and closely related compounds,[10] a variety of 7-substituted derivatives have been prepared in good yield, but in most cases the directive influence of the pyrimidine substituents give rise to a mixture of 7- and 9-isomers, with the 9-isomer predominating.[7,11] In these cases, although the 9-isomer can usually be obtained pure, the 7-isomer usually cannot be[11] and, therefore, this approach, with one or two exceptions,[9,11] is not applicable as a practical method of preparation of 7-substituted 7*H*-purines.

We have now developed a synthesis of this type of compound that seems to have wide potential application. This method depends upon the alkylation of *N*-(4-amino-5-pyrimidinyl)formamides (V–VIII) with an alkyl halide and potassium carbonate in *N,N*-dimethylformamide, a solvent which has proven its utility in many other alkylations.[11,12] This reaction was first applied to *N*-[4-amino-6-(benzylthio)-5-pyrimidinyl]formamide (V)[13] and α-chlorotoluene and was carried out at room temperature giving a good yield of *N*-[4-amino-6-(benzylthio)-5-pyrimidinyl]-*N*-benzylformamide (IX). Cyclization of this compound to 7-benzyl-6-(benzylthio)-7*H*-purine (XVII)[12] was accomplished by heating it in formamide. Although the reaction solution discolored badly, a good yield of the purine was isolated.

In order to extend this reaction to chloropyrimidines, it was necessary to prepare the requisite 5-pyrimidinylformamides (VII and VIII). Since it is known that the chlorine atoms of these pyrimidines

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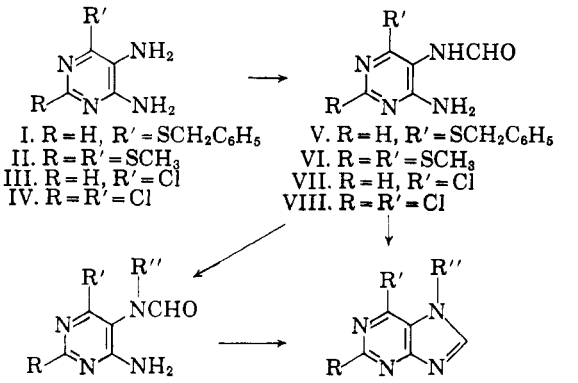
TABLE I

Compound No.	Reactants	Reaction Time, Hr.	Reaction Temp. °C.	Crude Yield, %	Recrystn. Solvent	M.P.	R_f[a]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
V	0.23[b]	2	80–95	89	—	227[c]	0.80						
VI	0.25[b]	2	80–95	92	Ethanol	260	0.71	36.23	36.24	4.40	4.34	24.35	24.49
VII	0.35[b]	504	r.t.	100	Ethanol	254	0.63	34.89	34.84	2.94	2.85	32.56	32.43
VIII	0.08[b]	24	r.t.	60	Ethanol	224	0.74	29.14	29.43	1.96	1.94	27.18	27.05
IX	0.5[d]	72	r.t.	85	—	197	0.89	65.13	65.27	5.19	5.37	16.00	15.95
X	5.0[d]	18	r.t.	64	Ethanol	180	0.84	58.33	58.40	5.61	5.49	19.45	19.47
XI	5.0[d]	18	r.t.	89	Ethanol	149	0.86	52.50	52.36	5.05	5.08	17.50	17.62
XII	1.7[d]	18	r.t.	63	Ethanol	209	0.86	48.66	48.75	3.41	3.45	18.91	18.90
XIII	2.0[e]	18	r.t.	62	Ethanol	221	0.80	35.90	35.79	3.45	3.41	23.93	23.93
XIV	2.0[d]	192	r.t.	61	Ethanol	191	0.81	54.96	54.77	4.24	4.29	21.37	21.41
XV	2.0[e]	168	r.t.	33	Ethanol	161	0.82	47.37	47.41	5.76	6.04	24.56	24.57
XVI	0.1[b]	96	101	76	Water	340[f]	0.40	42.42	42.78	5.10	5.14	28.28	28.16
XVII	0.16[f]	0.5	210	51	—	121[g]	0.94						
XVIII	21.0[h]	1.5	155	47	Ethanol	99	0.85	62.21	61.91	5.24	5.10	20.74	20.86
XIX	0.3[h]	2	155	74	Ethanol	121	0.89	55.63	55.78	4.68	4.66	18.54	18.87
XX	5.0[h]	48	r.t.	45	Ethanol	148	0.89	51.81	51.32	2.91	3.09	20.05	20.00
XXI	0.2[b]	96	101	75	Water	183	0.74	56.23	55.98	6.29	6.33	29.15	29.09
XXII[i]	0.08[b]	24	101	56	—	270	0.74						
XXIII	0.27[k]	4	115	58	80% Ethanol	220	0.78	51.91	51.83	5.83	5.86	26.93	26.79

[a] Solvent system—Isopropyl alcohol, water, concd. ammonium hydroxide (70/25/5). [b] Mmoles pyrimidine/ml., 98% formic acid. [c] Lit. m.p. 202–203°; see ref. 13. [d] Mmole pyrimidine, potassium carbonate. [e] Mmole pyrimidine, sodium hydride. [f] Mmole pyrimidine, formamide. [g] Lit. m.p. 120°; see ref. 12. [h] Mmole pyrimidine, potassium carbonate, *N*,*N*-dimethylformamide. [i] See ref. 11. [j] In a capillary in an aluminum block, melts with decomposition. [k] Mmoles purine/mmole phosphorus pentasulfide, in pyridine.



I. R = H, R' = $SCH_2C_6H_5$
II. R = R' = SCH_3
III. R = H, R' = Cl
IV. R = R' = Cl
V. R = H, R' = $SCH_2C_6H_5$
VI. R = R' = SCH_3
VII. R = H, R' = Cl
VIII. R = R' = Cl

IX. R = H, R' = $SCH_2C_6H_5$, R'' = $CH_2C_6H_5$
X. R = H, R' = $SCH_2C_6H_5$, R'' = CH_2CH_3
XI. R = R' = SCH_3, R'' = $CH_2C_6H_5$
XII. R = R' = Cl, R'' = $CH_2C_6H_5$
XIII. R = R' = Cl, R'' = CH_2CH_3
XIV. R = H, R' = Cl, R'' = $CH_2C_6H_5$
XV. R = H, R' = Cl, R'' = $(CH_2)_3CH_3$
XVI. R = R' = OH, R'' = CH_2CH_3
XVII. R = H, R' = $SCH_2C_6H_5$, R'' = $CH_2C_6H_5$
XVIII. R = H, R' = $SCH_2C_6H_5$, R'' = CH_2CH_3
XIX. R = R' = SCH_3, R'' = $CH_2C_6H_5$
XX. R = R' = Cl, R'' = $CH_2C_6H_5$
XXI. R = H, R' = OH, R'' = $(CH_2)_3CH_3$
XXII. R = H, R' = OH, R'' = $CH_2C_6H_5$
XXIII. R = H, R' = SH, R'' = $(CH_2)_3CH_3$

are easily hydrolyzed,[14] the formylation reaction was carried out in 98% formic acid at room temperature. In this manner *N*-(4-amino-6-chloro-5-pyrimidinyl)formamide (VII) and *N*-(4-amino-2,6-dichloro-5-pyrimidinyl)formamide (VIII) were obtained.

Alkylation of the latter compound with α-chlorotoluene was accomplished as described above but the reaction was allowed to proceed for three days at room temperature. At the end of this period the ultraviolet spectrum of the reaction solution indicated that alkylation of the formamide followed by cyclization to the purine had taken place, and both *N* - (4 - amino - 2,6 - dichloro - 5 - pyrimidinyl)-*N*-benzylformamide (XII) and 2,6-dichloro-7-benzyl-7*H*-purine (XX) were isolated from the mixture. This reaction, then, appears to constitute not only a facile alkylation of the formamide, but also an extraordinarily easy purine cyclization. By merely selecting the proper reaction time either the 5-pyrimidinylformamide (XII) or the purine (XX) can be isolated in good yield.

N - [4 - Amino - 6 - (benzylthio) - 5 - pyrimidinyl] *N* - ethylformamide (X) and *N*-[4-amino-2,6-bis-(methylthio) - 5 - pyrimidinyl] - *N* - benzylformamide (XI) were both prepared and cyclized in formamide, in low yield, to 6-(benzylthio)-7-ethyl-7*H*-purine (XVIII) and 7-benzyl-2,6-bis(methylthio)-7*H*-purine (XIX), respectively. After the discovery that cyclization would take place in the alkylation reaction mixture, these two purines were prepared in this manner in 74 and 47% yields, respectively, from the *N*-(4-amino-5-pyrimidinyl)-formamides. In these two cases heating for two hours at 155° was necessary to effect cyclization. *N*-(4-Amino-2,6-dichloro-5-pyrimidinyl)-*N*-ethylformamide (XIII), *N*-(4-amino-6-chloro-5-pyrimi-

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TABLE II

ULTRAVIOLET ABSORPTION SPECTRA

Compound No.	*p*H 1		*p*H 7		*p*H 13	
	λ_{max} mμ	ε × 10^{-3}	λ_{max}, mμ	ε × 10^{-3}	λ_{max}, mμ	ε × 10^{-3}
V	245[a]	14.8[a]	226	23.1	230	19.4
	300[a]	13.4[a]	281	8.4	295	11.2
VI	259	19.7	223	21.3	240	18.8
	312.5	1.9	247	23.4	305	9.9
			293	8.5		
VII	237	8.2	237	9.6	257	7.0
	278	4.5	278	4.0	284	7.0
VIII	239	8.9	239	8.9	262.5	7.8
	282	5.2	282.5	5.2	289	7.9
IX	246	13.1	225	sh[b]	225	sh
	304	10.9	240	sh	240	sh
			284	7.3	285	7.5
X	245	15.0	228	23.1	282	8.2
	300.5	12.4	282	8.2		
XI	259	17.6	250	22.2	250	22.2
	280	sh	294	7.86	294	8.0
	312	9.35				
XII	240.5	8.95	241	9.0	215	20.0
	283.5	4.70	283.5	4.7	242	6.54
			—		266	6.95
XIII	239	9.6	239	9.6	241	6.55
	282	4.9	282	4.9	269	5.5
					276	sh
XIV	237	9.0	237	9.7	238	7.7
	279	3.9	280	3.8	275	4.4
XV	237	9.15	237	9.8	236	9.5
	277	4.10	279	3.8	276	4.1
XVI	263	18.1	263	18.1	264.5	15.3
XVII	304[c]	13.1[c]	298[c]	13.9[c]	298[c]	13.9[c]
XVIII	295	sh	295	15.7	294	15.7
	302	15.2	300	sh	300	sh
	315	sh				
XIX	263	18.3	242	18.6	242	18.7
	285	sh	259	17.5	259	17.5
	321	9.6	318	8.8	318	8.85
XX	216	28.7	216	29.0	242	sh
	278	7.05	278	7.05	263	sh
	290	sh	290	sh	267[c]	7.8
					277	sh
					293	sh
XXI	250	9.8	256	9.2	262	10.0
XXII	253	9.3	257	8.7	263	9.4
XXIII	220	8.2			228	11.0
	329	17.3	328	17.9	316	17.6

[a] Lit.: 248 (15.1), 300 (13.3), see ref. 13. [b] Shoulder. [c] Lit.: *p*H 1—305 (13.1); *p*H 7—301 (13.7); *p*H 13—297–301 (13.7), see ref. 12.

dinyl)*N*-benzylformamide (XIV), and *N*-(4-amino-6 - chloro - 5 - pyrimidinyl) - *N* - butylformamide (XV), prepared as described above, were treated with refluxing 98% formic acid. Ring closure with concomitant hydrolysis of the chlorine atom of XIV and XV gave 7-butylhypoxanthine (XXI) and 7-benzylhypoxanthine (XXII).[11] The formic acid treatment hydrolyzed both chlorine atoms of XIII but failed to effect ring closure so that *N*-(4-amino-2,6 - dihydroxy - 5 - pyrimidinyl) - *N* - ethylformamide (XVI) was obtained as the principal product, with only a small amount of 7-ethylxanthine being formed. Thiation of 7-butylhypoxanthine with phosphorus pentasulfide in pyridine[15] gave 7-butyl-7*H*-purine-6(1*H*)-thione (XXIII). Yields, reaction times and temperatures, recrystallization solvents, and elemental analyses are reported in Table I.

Since both chlorine atoms and alkylthio groups of purines are readily displaced by nucleophilic reagents, the reactions described above now make it possible to prepare a wide variety of 2,7- and 6,7-disubstituted, and 2,6,7-trisubstituted 7*H*-purines. The alkylation-cyclization reaction is now being extended to a number of substituted alkyl halides.

Spectral data. The ultraviolet spectral data obtained on these compounds are summarized in Table II. The instability indicated for 7-benzyl-2,6-dichloro-7*H*-purine (XX) in 0.1*N* sodium hydroxide is a result of hydrolysis of the 6-chlorine

(15) A. G. Beaman, *J. Am. Chem. Soc.*, **76**, 5633 (1954).

atom, so the spectrum obtained is actually that of the corresponding hypoxanthine.

Biological data. Some of the 7-substituted-7*H*-purines which we have screened have shown cell cytotoxicity (H. Ep-2) and activity against Adenocarcinoma 755. A comparison of the activity of the corresponding 7- and 9-substituted purines can now be made.

EXPERIMENTAL

Melting points were determined on a Kofler Heizbank and are corrected. The ultraviolet spectra were determined in aqueous solution with a Cary Model 14 spectrophotometer or a Beckman DK-2 (optical densities at the maxima with a Beckman DU).

Preparation of N-(4-amino-5-pyrimidinyl)formamides. A dry sample of the 4,5-diaminopyrimidine was dissolved in an excess of 98% formic acid and the formylation reaction allowed to proceed under the appropriate conditions. The reaction mixture was then evaporated to dryness *in vacuo* with additions of ethanol, before it was transferred to a sintered glass funnel and triturated with several small portions of ethanol. The insoluble solid was dried by ether trituration, then *in vacuo*, to give the crude product, which was recrystallized, if necessary, from ethanol. Details of the individual reactions are given in Table I.

Alkylation of N-(4-amino-5-pyrimidinyl)formamides. The 5-pyrimidinylformamide was dissolved in *N,N*-dimethylformamide with an equivalent (mole/mole) of anhydrous potassium carbonate (or 1.5 equivalents of sodium hydride) and the reaction mixture stirred vigorously. Two equivalents of *o*-chlorotoluene (or iodoalkane) were added to the reaction mixture and the resulting mixture stirred vigorously at room temperature.

After the reaction was complete, the mixture was evaporated to dryness and the residue triturated with water. The insoluble solid was collected by filtration, washed with ethanol and ether, and dried *in vacuo*. The crude product was recrystallized from ethanol if necessary. Details of individual reactions are given in Table I.

Cyclization of N-(4-amino-5-pyrimidinyl)-N-substituted formamides. A. In N,N-dimethylformamide. The *N*-(4-amino-5-pyrimidinyl)-*N*-substituted formamide, with or without previous isolation, was allowed to react in *N,N*-dimethylformamide containing 1 equivalent of anhydrous potassium carbonate. The mixture was stirred vigorously under anhydrous conditions until cyclization was complete, and then poured into ice water from which the crude product that precipitated was collected by filtration, washed with water and dried with ethyl alcohol and ether to give the 7-substituted purine. If necessary, the crude product was recrystallized from ethyl alcohol. Details of each reaction are given in Table I.

B. In 98% formic acid. A solution of dry *N*-(4-amino-5-pyrimidinyl)-*N*-alkylformamide in a large excess of 98% formic acid was refluxed until hydrolysis of the chlorine atoms and cyclization were complete, as indicated by the ultraviolet spectrum of reaction aliquots. The reaction mixture was then evaporated to dryness *in vacuo* several times with additions of ethyl alcohol to give the crude hypoxanthine which was recrystallized from water. Details of the individual reactions are given in Table I.

7-Benzyl-6-(benzylthio)-7H-purine (XVII). A solution of *N*-[4-amino-6-(benzylthio)-5-pyrimidinyl]-*N*-benzylformamide (50 mg., 0.16 mmole) in formamide (5 ml.) was refluxed for 30 min. After being cooled to room temperature, the reaction mixture was diluted with two volumes of cold water and the insoluble grey solid that precipitated was collected by filtration and air dried. The solid was triturated in boiling cyclohexane, the mixture filtered to remove insoluble material, and the filtrate allowed to stand in the cold until crystallization was complete. The white solid was collected by filtration and dried *in vacuo*; yield, 24 mg. (51%) of purified product.

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BIRMINGHAM 5, ALA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ROOSEVELT UNIVERSITY]

Synthesis and Properties of 5-(Substituted) Mercaptotetrazoles[1]

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Improved procedures for the synthesis of aryl thiocyanates have been developed. A series of alkyl and aryl thiocyanates has been converted to 5-(substituted) mercaptotetrazoles by reaction with azide ion in dimethylformamide in the presence of ammonium chloride. The 5-(substituted) mercaptotetrazoles undergo decomposition, at or near their melting points, to hydrazoic acid and the corresponding thiocyanate. The ultraviolet spectra indicates that the tetrazolyl sulfide group is electron donating. The 5-(substituted) mercaptotetrazoles are acids with pK_a values in the range 3.08–4.53 and their acidities are influenced by the electron-donating or -withdrawing nature of the R substituent on the sulfur atom.

A recent study by Finnegan[4] has shown that when aliphatic and aromatic nitriles are treated with azide ion in the presence of a suitable catalyst, using dimethylformamide (DMF) as a solvent, 5-(substituted) tetrazoles (I) are obtained in excellent yields. They also reported that when benzyl thiocyanate was used instead of the nitrile, the primary reaction was that of displacement although a substantial amount of 5-benzylmercaptotetrazole (I.

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