Some Unusual Reactions of 6-Chloropurines with Thioureas. 6-Alkylthiopurines and 2,2-Diamino-2H-thiazolo[3,4,5-*gh*]purines from 2-(Purin-6-yl)-2-thiopseudoureas[1]

CARROLL TEMPLE, JR., AND JOHN A. MONTGOMERY

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

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Reaction of 6-chloropurine (**1**) with thiourea gave, in addition to purine-6(1H)-thione (**6**), 2,2-diamino-2H-thiazolo[3,4,5-*gh*]purine (**14**). 1-Ethyl-2-thiourea and **1** provided the corresponding ethyl derivative **15** of **14**. From the reaction of 6-chloro-2-ethylpurine (**2**) and thiourea in propanol, 2-ethylpurine-6(1H)-thione (**8**), 2,2-diamino-7-ethyl-2H-thiazolo[3,4,5-*gh*]purine (**13**), and 2-ethyl-6-(propylthio)purine (**11**) were obtained, the formation of **11** resulting from solvent participation. 6-Chloro-2,9-diethylpurine (**3**) and thiourea in propanol gave 2,9-diethyl-2-(propylthio)purine (**9**) as a major component. Treatment of **1**, 2,6-dichloropurine (**26**), and 2-amino-6-chloropurine (**27**) with 2-imidazolidinethione gave the corresponding 6-(2-imidazolinylthio)purine hydrochlorides **28**, **29**, and **30**, respectively. The free base of **28** and **29** but not of **30** appeared to form derivatives of **14** by intramolecular addition. Basic hydrolysis conuerted **28** to **6**, **29** to 2-chlorohypoxanthine (**36**), and **30** to thioguanine (**34**) containing a trace of guanine (**37**).

The 2-(purin-6-yl)-2-thiopseudoureas resulting from the treatment of 6-chloropurine (**1**) and some of its derivatives with various thioureas have been found to react by four different routes. See Scheme I. The most common route provides a thione as previously described in the preparation of purine-6(1H)-thione (**6**) from **1**.[2] In another route the 2-(purin-6-yl)-2-thiopseudourea is hydrolyzed in sodium hydroxide solution to give a hypoxanthine.[3] The other two routes, heretofore unreported, involve addition to the C=N of the 2-thiopseudourea group. In one case the alcohol used as solvent appears to add to give an ether intermediate (**5**), which then undergoes rearrangement to give a 6-(alkylthio)purine. In the second case the 7-nitrogen of the purine ring adds to give a 2,2-diamino-2H-thiazolo[3,4,5-*gh*]purine (**13**), a new ring system.[4]

6-Chloro-2-ethylpurine (**2**) and 6-chloro-2,9-diethylpurine (**3**) were prepared from the common intermediate, 5-amino-4,6-dichloro-2-ethylpyrimidine, by standard procedures (see Experimental Section).[5] Interaction of **3** with thiourea in refluxing propanol gave a 38% yield of 2,9-diethylpurine 6(1H)-thione (**7**) and a 18% yield of 2,9-diethyl-6-(propylthio)purine (**9**). The latter was identified by elemental analyses and comparison of its spectra and refractive index with those of a sample of the compound prepared by the alkylation of 2,9-diethylpurine-6(1H)-thione (**7**).[3] This compound is apparently formed by the reaction of the solvent, propanol, with the intermediate 2-thiopseudourea salt similar to **4**. The initial attack is probably the addition of propanol across the carbon to nitrogen double bond of the salt followed by an O → S migration of the propyl group with concomitant elimination of urea. It is necessary to propose a mechanism of this type because the more conventional alternatives have been eliminated: (1) addition of 1-chloropropane to the reaction mixture did not increase the yield of 6-(propylthio)purine; (2) 2,9-diethylpurine-6(1H)-thione failed to react with 1-chloropropane in refluxing propanol; (3) 6-chloro-2,9-diethylpurine did not react with 1-propanethiol in propanol; (4) 6-chloro-2,9-diethylpurine did not react with 2-methyl-2-thiopseudourea hydrochloride;[6] (5) prolonged reflux of the reaction mixture increased the crude yield of the 6-(propylthio)-purine from 22 to 33%; and (6) urea, which is a by-product of the proposed reaction, was identified as a component of the reaction mixture by means of paper chromatography. In order to determine whether this reaction is general, ethanol rather than propanol was used as the solvent, and 2,9-diethyl-6-(ethylthio)-purine (**10**) was apparently formed. This compound was not isolated analytically pure but was identified by its ultraviolet spectrum which was practically identical with that of the 6-(propylthio)purine and quite different from that of the purine-6(1H)-thione. A search of literature has failed to reveal any report of a reaction of this kind with thiourea, an organic halide, and an alcohol.

The reaction of thiourea with 6-chloro-2-ethylpurine gave three products: 2-ethylpurine-6(1H)-thione (**8**, 38.5%), 2-ethyl-6-(propylthio)purine (**11**, 2.5%), and 2,2-diamino-7-ethyl-2H-thiazolo[3,4,5-*gh*]purine (**13**, 17.5%). The structure of **11** is based on its elemental analysis and comparison of its ultraviolet spectrum with that of 6-(propylthio)purine.[3] Compound **13** was identified by elemental analyses and by comparison of its infrared, ultraviolet, and proton magnetic resonance spectra with those of the parent compound discussed below.

From the action of thiourea on 6-chloropurine (**1**), purine-6(1H)-thione (**6**)[2] was obtained along with a by-product identified as 2,2-diamino-2H-thiazolo[3,4,5-*gh*]purine (**14**). The latter material has a pK_a of 6.77 (50% ethanol), a neutralization equivalent of 199 (calculated 194), and little or no solubility in 1 *N* so-

(1) This investigation was supported by funds from the C. F. Kettering Foundation and the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH-43-64-51.

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

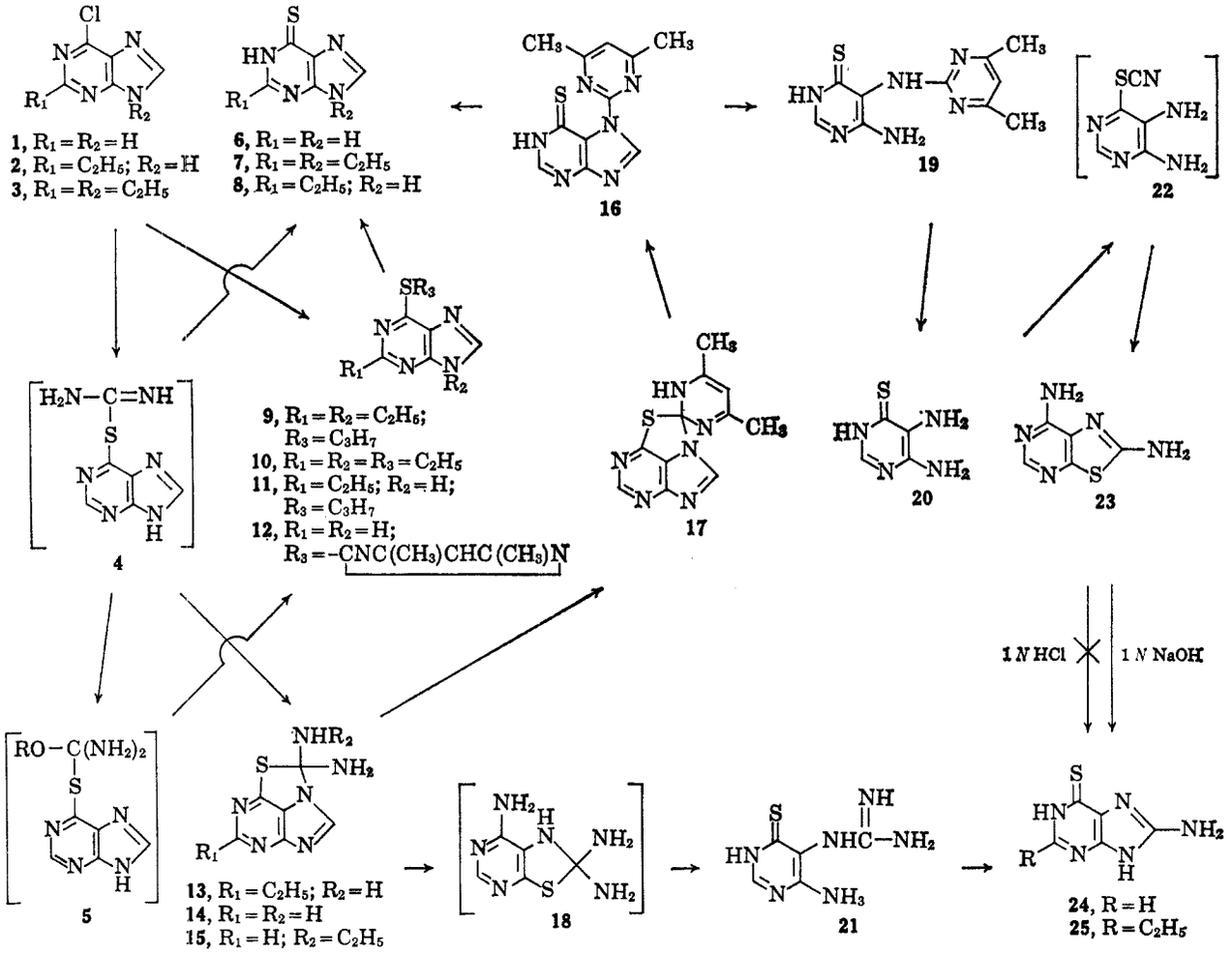
(3) T. P. Johnston, L. B. Holum, and J. A. Montgomery [*ibid.*, **80**, 6265 (1958)] reported that 6-(2-hydroxyethylthio)purine underwent hydrolysis t give hypoxanthine.

(4) A. Giner-Sorolla, L. Medrek, and A. Bendich (Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 7 N) reported that (purin-6-yl)methyl thiocyanate underwent this type of ring closure.

(5) (a) H. R. Henze and J. L. McPherson, *J. Org. Chem.*, **18**, 653 (1953); (b) W. R. Boon, W. G. M. Jones, and G. R. Ramage, *J. Chem. Soc.*, 96 (1951); (c) R. K. Robins, K. J. Dille, and B. E. Christensen, *J. Org. Chem.*, **19**, 930 (1954); (d) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **79**, 5238 (1957); **80**, 409 (1958).

(6) This experiment was performed since T. B. Johnson and J. M. Sprague [*ibid.*, **58**, 1348 (1936)] reported that propanol and thiourea react in the presence of anhydrous hydrogen chloride to give 2-propyl-2-thiopseudourea hydrochloride.

SCHEME I



dium hydroxide at room temperature. Compound **14** can be prepared in 8.8–13.5% yield from **1** and thiourea in ethanol, in ethanol containing either pyridine or hydrochloric acid, or even by fusion of the reactants above 100°. No reaction was observed between **1** and thiourea in ethanolic triethylamine, presumably because of an interaction between triethylamine and thiourea. In addition, only slight reaction was detected when the solvent was either acetone at 50° or water at reflux. Furthermore, the by-product is not limited to the reaction of thiourea itself with 6-chloropurine (**1**) since the interaction of 1-ethyl-2-thiourea with **1** resulted in the formation of 2-amino-2-ethylamino-2H-thiazolo[3,4,5-*gh*]purine (**15**) in 5% yield. Finally, it was shown that **14** did not result from the reaction of **6** with cyanamide either in propanol containing a catalytic amount of hydrochloric acid or in aqueous sodium hydroxide at room temperature.

Although the structure assigned to **14** is quite unusual, its properties (see below) justify this choice. The insolubility of the by-product in aqueous base, and the fact that a similar product is not obtained in the reaction of thiourea with a 9-substituted 6-chloropurine, *e.g.*, **3**, strongly suggests the involvement of the imidazole NH.

Treatment of **14** either with hot hydrochloric acid or with hot aqueous sodium hydroxide provided a product that was identified as the known 8-aminopurine-6(1H)-thione (**24**).[7] Similarly, the action of hydrochloric acid on **13** gave 8-amino-2-ethylpurine-6(1H)-thione (**25**). In both the acid and base hydrolyses of **14**, a second compound was obtained that was assigned the structure **21**, based on its elemental analyses and its conversion to **24** with hot hydrochloric acid. In the formation of **21** both the thiazole and the imidazole rings are opened. Cleavage of the imidazole ring probably occurs first since the 7-substituted purine-6(1H)-thione resulting from the initial cleavage of the thiazole ring should undergo further hydrolysis to purine-6(1H)-thione (**6**).

A pure sample of **24** was not obtained by the conventional methods,[7] and another route to this compound was devised. Treatment of the sodium salt of 5,6-diaminopyrimidine-4(1H)-thione (**20**) with cyanogen bromide in tetrahydrofuran gave 2,7-diaminothiazolo[5,4-*d*]pyrimidine (**23**), presumably *via* the thiocyanate **22**. Other derivatives of this ring system are rearranged to purine-6(1H)-thiones with aqueous base,[8] and the rearrangement of **23** to **24** was also successful; however, **23** was found to be stable in hot 1 *N* hydrochloric acid. Compound **24** was also obtained without the isolation of **23** by treatment of a hot solution of **20** in sodium hydroxide with cyanogen

(7) R. K. Robins, *J. Am. Chem. Soc.*, **80**, 6671 (1958).

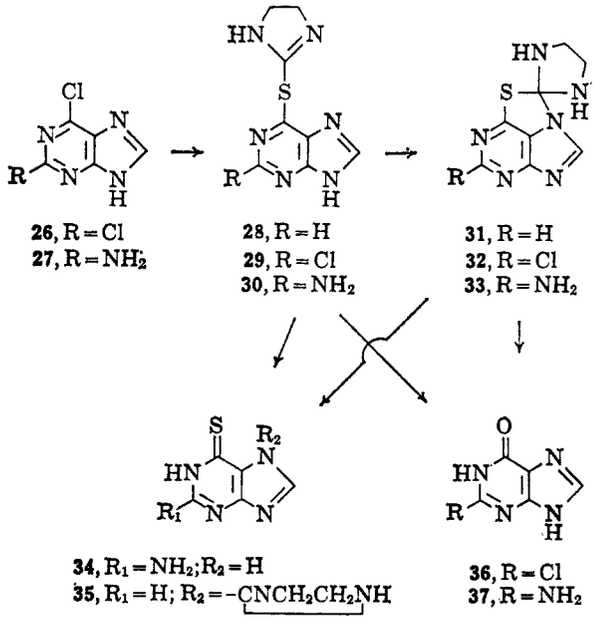
(8) (a) D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 682 (1957); (b) A. G. Beaman, J. F. Gerster, and R. K. Robins, *J. Org. Chem.*, **27**, 986 (1962).

bromide. As expected, **24** was stable either in hot 1 *N* sodium hydroxide or in hot 6 *N* hydrochloric acid.

The condensation of **14** with acetylacetone was effected in the presence of piperidine to give spiro-[1,2-dihydro-4,6-dimethylpyrimidine-2,2′-2′H-thiazolo-[3′,4′,5′-*gh*]purine] (**17**). The structure of this compound is based on spectral data, its elemental analyses, and a molecular weight determination. A second compound, isomeric with **17** was isolated from the condensation reaction and identified as 7-(4,6-dimethylpyrimidin-2-yl)purine-6(1H)-thione (**16**). The latter was shown to result from the action of piperidine on **17**. The alternative ring opening at the C–N bond of the thiazolo ring of **17** was eliminated from consideration by the preparation of 6-(4,6-dimethylpyrimidin-2-ylthio)purine (**12**). The latter was obtained practically pure from the reaction of **1** with 4,6-dimethylpyrimidine-2(1H)-thione. Whereas treatment of **12** with hot 1 *N* hydrochloric acid gave a mixture of hypoxanthine and **6**, the action of 1 *N* hydrochloric acid on **16** appeared to give the dihydrochloride of 6-amino-5-(4,6-dimethylpyrimidin-2-yl)aminopyrimidine-4-(1H)-thione (**19**). In addition, treatment of **16** with hot 4 *N* potassium hydroxide gave a mixture containing 5,6-diaminopyrimidine-4(1H)-thione (**20**) and purine-6(1H)-thione (**6**), both identified by thin layer chromatography.

The preparation of some stable 2-(2-substituted purin-6-yl)-2-thiopseudoureas allowed us to examine the effect of different groups in the 2-position of the purine ring on the reactions of the 2-thiopseudourea group (Scheme II). Reaction of 2-imidazolidinethione

SCHEME II



with the 6-chloropurines **1** and **26** in propanol, and **27** in butanol provided high yields of the corresponding 6-(2-imidazolinylthio)purine hydrochlorides, **28**, **29**, and **30**. On treatment of the salts with excess aqueous sodium hydroxide, **28** gave **6**, **29** gave **36**, and **30** gave **34** containing a trace of **37**. Careful neutralization of aqueous solutions of the hydrochlorides of **28**, **29**, and **30** deposited the free bases. Comparison of the ultraviolet spectra of the hydrochlorides of **28** and **29** with those of the corresponding free bases indicated that the 7-nitrogen of the purine ring had added to the thiopseudourea group to give **31** and **32** (see Table I). In contrast, the ultraviolet spectra of the hydrochloride of **30** and its free base were practically identical, implying that the tricyclic structure **33** was not formed. When **31** was recrystallized from tetrahydrofuran, only **6** deposited. Apparently, in this solvent only heat is required to open the C–S bond of the thiazolo ring to give **35**, which is then hydrolyzed to **6** by the water in the solvent. In the conversion of the hydrochloride of **29** to **36** with sodium hydroxide, the intermediate may be the anion of either **29** or **32**. Whatever the structure of the intermediate, the attack of hydroxide on the purine ring carbon displacing sulfur can be attributed to the electron-withdrawing effect of the 2-chloro group.

The ultraviolet and infrared spectra for some of the compounds are presented in Table I. Proton magnetic resonance spectra assignments for **13**–**15** are given in the Experimental Section.

Experimental Section

Melting points below 260° were determined on a Kofler Heizbank; those above 260° were determined in a capillary tube in an aluminum block and are uncorrected. The ultraviolet spectra were determined either with a Cary Model 14 or with a Beckman Model DK-2 spectrophotometer. When the latter was used, the optical densities at the maxima were determined with a Beckman DU. The infrared spectra were run in pressed potassium bromide pellets with a Perkin-Elmer Model 21 or 221-G spectrophotometer. The pmr spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane as internal reference.

4,6-Dihydroxy-2-ethyl-5-nitropyrimidine.—4,6-Dihydroxy-2-ethylpyrimidine[5a] (61 g) was nitrated by the method of Boon, Ramage, and Jones:[5b] yield, 57.8 g (72%); decomposes above 260°.

Anal. Calcd for $C_6H_7N_3O_4$: C, 38.92; H, 3.81; N, 22.70. Found: C, 38.93; H, 3.92; N, 23.00.

4,6-Dichloro-2-ethyl-5-nitropyrimidine.—4,6-Dihydroxy-2-ethyl-5-nitropyrimidine (52.5 g) was chlorinated by the method of Boon, Ramage, and Jones.[5b] The product was distilled at 78° (0.1–0.2 mm) to give a yellow liquid: yield, 56.5 g (90%).

Anal. Calcd for $C_6H_5Cl_2N_3O_2$: C, 32.40; H, 2.25; N, 18.90. Found: C, 32.76; H, 2.48; N, 19.00.

5-Amino-4,6-dichloro-2-ethylpyrimidine.—A solution of 4,6-dichloro-2-ethyl-5-nitropyrimidine (15.5 g) in ethanol (200 ml) was hydrogenated at room temperature using Raney nickel.[5c] The product was distilled under reduced pressure to give a low-melting solid: yield, 10.8 g (80.5%); bp 86° (0.3 mm).

Anal. Calcd for $C_6H_7Cl_2N_3$: C, 37.50; H, 3.64; N, 21.85. Found: C, 38.04; H, 3.93; N, 21.28.

4,5-Diamino-6-chloro-2-ethylpyrimidine.—A solution of 5-amino-4,6-dichloro-2-ethylpyrimidine (10.7 g) in 10% (w/v) ethanolic ammonia (50 ml) was heated in a Parr bomb for 5.5 hr at 130°.[5d] The solid obtained was collected by filtration and dried *in vacuo* over phosphorus pentoxide: yield, 8.43 g (88%); mp 261–262° (fast from 200°). Recrystallization of a small sample from a methanol–water mixture gave a light yellow solid, mp 262° (rapid heating from 200°).

Anal. Calcd for $C_6H_9ClN_4$: C, 41.70; H, 5.21; N, 32.45. Found: C, 41.50; H, 5.32; N, 32.42.

5-Amino-6-chloro-2-ethyl-4-ethylaminopyrimidine.—A solution of 5-amino-4,6-dichloro-2-ethylpyrimidine (5.0 g) in 10% (w/v) ethanolic ethylamine (50 ml) was heated in a Parr bomb at 125° for 5.5 hr.[5d] The product was a gray solid: yield, 4.8 g (92%); mp 92–94°. A small sample of this material was dissolved in hot petroleum ether (bp 85–105°) (25 ml) and treated with Norit, and the solution was allowed to cool. The solid that deposited was collected by filtration and dried *in vacuo* over phosphorus pentoxide: mp 94–95°.

Anal. Calcd for $C_8H_{13}ClN_4$: C, 47.89; H, 6.48; N, 27.93. Found: C, 48.07; H, 6.27; N, 27.73.

TABLE I

ULTRAVIOLET AND INFRARED ABSORPTION SPECTRA

Compd	0.1 *N* HCl	pH 7	0.1 *N* NaOH	Infrared bands in the 1700–1500-cm^{-1} region			
2	268 (9.0)	270 (8.8)	276 (8.7)	1620	1570	1490	
3	270 (9.4)	271 (9.3)	271 (9.3)	1600	1555	1510	
7	227 (10.0)	229 (10.2)	235 (16.4)	1585	1550	1500	
	326 (19.0)	325 (23.6)	310 (21.7)				
8	227 (9.4)	227 (9.9)	231 (14.8)	1615	1580	1530	
	329 (17.2)	326 (19.0)	309 (16.6)				
9	227 (12.3)	224 (13.6)	290 (15.8)	1570	1510		
	306 (14.4)	290 (15.8)					
11	228 (10.1)	225 (11.8)[a]	225 (16.2)	1600	1575	1530	
	271 (5.2)	291 (15.5)	296 (13.9)				
	311 (18.0)						
12	298 (>11.0)	295 (>10.8)	301 (>11.4)	1580	1560	1520	
13	266 (13.9)[b]	284 (12.9)[b]	237 (12.9)	1640	1610	1550	1510
			298 (26.1)				
14	218 (29.3)	217 (21.8)	237 (11.8)	1645	1600	1560	
	264 (15.1)	282 (13.2)	297 (27.5)				
		292 (15.2)					
15	267 (16.9)	302 (19.7)	238 (11.2)	1665	1590	1560	1515
			302 (29.2)	1500			
16	227 (15.6)	233 (18.2)	232 (22.3)	1640	1610	1590	1555
	321 (21.5)	315 (18.2)	310 (20.5)	1515			
17	215 (19.3)	239 (11.2)	220 (13.7)	1610	1590	1565	1535
	221 (19.3)	290 (25.8)	318 (17.2)[b]	1505			
	267 (13.9)						
	307 (23.3)						
	348 (4.34)						
19	235 (17.7)	242 (15.6)	244 (18.4)				
	287 (9.2)	272 (10.5)	333 (12.1)				
	300 (9.35)	292 (8.9)[a]					
	385 (16.4)	372 (14.2)					
21	227 (16.8)	226 (15.3)		1690	1620	1600	1580
	297 (5.18)	339 (11.1)		1540			
	364 (17.0)	368 (13.3)					
23	225 (18.3)	220 (22.8)	220 (21.5)	1665	1635	1580	1540
	280 (13.4)	274 (13.8)	274 (12.9)	1520			
	310 (6.58)[a]						
24	238 (13.8)	248 (18.7)	241 (18.2)	1680	1620	1600	1550
	332 (18.5)	333 (23.8)	314 (19.8)	1520			
28[c]	280 (14.4)	282 (11.8)	291 (11.0)	1600	1575	1540	
29[c]	291 (12.2)	294 (9.7)	299 (10.7)	1635	1595	1560	1540
30[c]	237 (14.2)[a]	324 (8.22)	322 (8.05)	1625	1570	1540	1510
	328 (8.20)						
30[d]	237 (13.7)[a]	324 (9.45)[e]	321 (9.93)	1630	1560	1530	
	329 (8.70)						
31	281[e]	283 (9.8)	302 (12.2)	1640	1590[b]	1560	
	323[e]	312 (7.8)					
32	213 (15.1)	220 (15.1)	227 (14.1)	1625	1595[b]	1555	
	292 (8.30)	312 (9.2)	309 (10.9)				
	327 (5.34)						

[a] Shoulder. [b] Broad. [c] Hydrochloride. [d] Free base. [e] Unstable.

6-Chloro-2-ethylpurine (**2**).—A solution of 6-chloro-4,5-diamino-2-ethylpyrimidine (7.50 g) in diethoxymethyl acetate (50 ml) was heated at 90–95° for 1 hr and evaporated to dryness, and the residue was dissolved in hot methyl isobutyl ketone (125 ml). After cooling the solution, the solid that precipitated was collected by filtration and dried *in vacuo* over phosphorus pentoxide: yield, 1.26 g. Recrystallization of this solid from hot 1:2 dioxane–petroleum ether (200 ml) gave 0.75 g of pure 6-chloro-2-ethylpurine. This material decomposes near 235° when taken fast from 200°.

Anal. Calcd for $C_7H_7ClN_4$: C, 46.03; H, 3.84; N, 30.68. Found: C, 46.38; H, 4.15; N, 30.39.

The methyl isobutyl ketone filtrate was evaporated to dryness, the residue was dissolved in warm 2 *N* sodium hydroxide (35 ml), and a small amount of insoluble material was removed by filtration. After standing at room temperature for several hours, the solution deposited the sodium salt of 6-chloro-2-ethylpurine. The salt was collected by filtration and dissolved in water (100 ml), and the solution was neutralized to pH 5 with acetic acid. The pure 6-chloro-2-ethylpurine which precipitated was collected by filtration, washed with cold water, and dried *in vacuo* over phosphorus pentoxide at 100°: yield, 4.48 g. The total yield of pure 6-chloro-2-ethylpurine was 5.23 g (66%).

6-Chloro-2,9-diethylpurine (**3**).—A solution of 5-amino-6-chloro-2-ethyl-4-ethylaminopyrimidine (3.72 g) in diethoxymethyl acetate (40 ml) was heated at 100° for 1.5 hr and evaporated to a small volume *in vacuo*, and the residue was distilled under reduced pressure to give a low-melting solid: yield, 2.50 g (64%); bp 140° (0.5 mm).

Anal. Calcd for $C_9H_{11}ClN_4$: C, 51.30; H, 5.22; N, 26.60. Found: C, 51.38; H, 5.32; N, 26.44.

2,9-Diethylpurine-6(1H)-thione (**7**) **and 2,9-Diethyl-6-(propylthio)purine** (**9**).—A solution of **3** (4.94 g) in propanol (50 ml) containing thiourea (2.00 g) was refluxed for 4 hr and evaporated to dryness *in vacuo*, and the residue was warmed for 5 min in 2 *N* sodium hydroxide (25 ml). After cooling the mixture, the insoluble liquid was extracted with ether (three 10-ml portions), and the combined dried extracts were evaporated to dryness

in vacuo: yield, 1.26 g (22%). Distillation of the residue under high vacuum gave a light yellow liquid: yield, 1.03 g (18%); bp *ca.* 140° (0.1 mm). This material was identified as **9** by comparison of its ultraviolet and infrared spectra, and its index of refraction ($n^{25}D$ 1.5673) with those of a sample synthesized by an unambiguous method (see below).

Anal. Calcd for $C_{12}H_{18}N_4S$: C, 57.58; H, 7.25; N, 22.39; S, 12.78. Found: C, 57.91; H, 7.55; N, 21.92; S, 12.68.

Neutralization of the basic solution from the ether extraction with acetic acid deposited 2.16 g of **7**, mp 200–206°. This solid was purified by recrystallization from a mixture of benzene–methyl isobutyl ketone: yield, 1.85 g (38%); mp 211–213°.

Anal. Calcd for $C_9H_{12}N_4S$: C, 51.91; H, 5.81; N, 26.91. Found: C, 52.08; H, 6.01; N, 27.12.

2-Ethylpurine-6(1H)-thione (8).[9]—A solution of **2** (2.00 g) in methanol (50 ml) was added to a saturated solution (75 ml) of hydrogen sulfide in methanolic sodium methoxide (1.80 g), and the solution was refluxed for 2 hr. During the reflux period, anhydrous hydrogen sulfide was passed into the solution. After cooling the solution, a small amount of insoluble material was removed by filtration, and the filtrate was neutralized with acetic acid. The mixture was evaporated to dryness *in vacuo*, the residue was triturated with warm 2 *N* sodium hydroxide (12 ml), and a small amount of insoluble material was removed by filtration. The filtrate was neutralized with acetic acid, and the solid that deposited was collected by filtration, washed with water (15 ml), and dried *in vacuo* over phosphorus pentoxide at 100°: yield, 1.61 g (82%). A small sample of this material was purified by recrystallization from methyl ethyl ketone: mp >260°.

Anal. Calcd for $C_7H_8N_4S$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.91; H, 4.60; N, 30.89.

2-Ethylpurine-6(1H)-thione (8), 2-Ethyl-6-(propylthio)purine (11), and 2,2-Diamino-7-ethyl-2H-thiazolo[3,4,5-*gh*]purine (13).—A solution of **2** (4.41 g) in propanol (100 ml) containing thiourea (2.00 g) was refluxed for 4 hr. After cooling the solution, the small amount of solid that deposited was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residue was triturated with 2 *N* sodium hydroxide (25 ml), and the mixture was warmed for 10 min. After cooling the mixture, **13** was collected by filtration, washed with water (15 ml), and dried *in vacuo* over phosphorus pentoxide: yield, 930 mg (17.5%); mp 248–250° when taken from 220°; pmr spectrum (10% DMSO-d_6 w/v), τ = 8.71 (CH_3), 7.17 (CH_2), 2.33 (NH), and 0.92 (H_4) ppm.

Anal. Calcd for $C_8H_{10}N_6S$: C, 43.24; H, 4.54; N, 37.83; S, 14.40. Found: C, 43.00; H, 4.38; N, 37.92; S, 14.30.

The basic filtrate was neutralized with acetic acid, and the solid that precipitated was collected by filtration, washed with water (25 ml), and dried *in vacuo* over phosphorus pentoxide. This solid was extracted with hot chloroform (three 25-ml portions), and the combined extracts were evaporated to dryness *in vacuo:* yield, 130 mg (2.5%). Recrystallization of this sample from ether gave a pure sample of **11**, mp 202–203°.

Anal. Calcd for $C_{10}H_{14}N_4S$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.54; H, 6.31; N, 24.75.

The residue from the chloroform extraction was practically pure **8**: yield, 1.67 g (38.5%).

2,9-Diethyl-6-(propylthio)purine (9).—Anhydrous potassium carbonate (140 mg) was added to a solution of **7** (185 mg) in dimethylformamide (3 ml) containing 1-bromopropane (120 mg). The mixture was warmed with stirring in a water bath (50°) for 30 min and diluted with water (20 ml), and the resulting cloudy solution was extracted with ether (three 10-ml portions). Evaporation of the combined dried extracts to dryness *in vacuo* and distillation of the residue under reduced pressure gave a light yellow liquid: yield, 120 mg. The ultraviolet and infrared spectra and the index of refraction of this material were practically identical with those of the compound described above.

6-(4,6-Dimethylpyrimidin-2-ylthio)purine (12).—A solution of 6-chloropurine (1.0 g), 4,6-dimethylpyrimidine-2(1H)-thione hydrochloride (1.2 g), and sodium acetate (1.6 g) in water was refluxed for 4 hr and evaporated to dryness *in vacuo*. The residue was extracted with hot ethanol (30 ml), the extract was diluted with ether (75 ml), and the residue was removed by filtration. The filtrate was evaporated to dryness *in vacuo*, and the residue was recrystallized twice from tetrahydrofuran–petroleum ether to give an impure sample of **12**. Thin layer chromatography indicated that this sample contained trace amounts of **6** and 4,6-dimethylpyrimidine-2(1H)-thione: yield, 600 mg.

Anal. Calcd for $C_{11}H_{10}N_6S$: C, 51.13; H, 3.88; N, 32.55. Found: C, 50.69; H, 4.54; N, 31.62.

When **12** was refluxed in 1 *N* hydrochloric acid, it was converted to a mixture of hypoxanthine and purine-6(1H)-thione, identified by thin layer chromatography.

2,2-Diamino-2H-thiazolo[3,4,5-*gh*]purine (14).—A solution of 6-chloropurine (1.00 g) and thiourea (1.00 g) in 40 ml of absolute ethanol was refluxed for 1 hr and then evaporated to dryness. The yellow residue was treated with an excess of 2 *N* sodium hydroxide (10 ml). The material partially dissolved to give a cream precipitate and a yellow solution. The precipitate was removed by filtration, washed with several portions of water, and dried *in vacuo* over phosphorus pentoxide: yield, 0.15 g (11.7%); mp 239° dec; pmr spectrum (5% DMSO-d_6), τ = 2.42 (NH_2), 1.51 (H_7), and 0.84 (H_4) ppm.

Anal. Calcd for $C_6H_6N_6S$: C, 37.11; H, 3.11; N, 43.29; S, 16.48. Found: C, 36.86; H, 3.46; N, 43.00; S, 16.80.

Acidification of the sodium hydroxide solution from above with acetic acid gave the hydrate of **6**: yield, 0.74 g (67%); mp 314–315°.[2]

2-Amino-2-ethylamino-2H-thiazolo[3,4,5-*gh*]purine (15).—A solution of 6-chloropurine (1.0 g) and 1-ethyl-2-thiourea (700 mg) in propanol (20 ml) was refluxed for 2 hr. The solid that deposited was collected by filtration and washed with 2 *N* sodium hydroxide (10 ml), then with water (5 ml), and finally with acetone (20 ml). Neutralization of the basic washing with glacial acetic acid gave 400 mg (36%) of the hydrate of **6**. Evaporation of the acetone wash to dryness yielded 70 mg (5%) of **15**: mp 201–202° dec; pmr spectrum (10% DMSO-d_6), τ = 8.81 (CH_3), 6.63 (CH_2), 2.00 (NH), 1.53 (H_7), and 0.84 (H_4) ppm.

Anal. Calcd for $C_8H_{10}N_6S$: C, 43.24; H, 4.54; N, 37.83; S, 14.40. Found: C, 43.01; H, 4.53; N, 37.50; S, 14.20.

7-(4,6-Dimethylpyrimidin-2-yl)purine-6(1H)-thione (16) and Spiro[1,2-dihydro-4,6-dimethylpyrimidine-2,2′-2′H-thiazolo[3′,4′,5′-*gh*]purine] (17).—A suspension of **14** (210 mg) in acetylacetone (5 ml) containing 3 drops of piperidine was heated with stirring at 115° for 20 hr. The mixture was allowed to cool to room temperature, and the solid was removed by filtration and recrystallized from ethanol. The hygroscopic precipitate of **16** was collected by filtration and dried *in vacuo* over phosphorus pentoxide at 78°: yield, 90 mg; mp >264°.

Anal. Calcd for $C_{11}H_{10}N_6S$: C, 51.13; H, 3.88; N, 32.55. Found: C, 51.10; H, 4.30; N, 32.20.

A solution of **16** in 4 *N* potassium hydroxide was refluxed for 3 hr to give a mixture containing **6** and **20**, identified by thin layer chromatography.

The solid (100 mg) that deposited from the acetylacetone filtrate was collected by filtration and recrystallized from acetonitrile to give **17**, mp 212–213° with sublimation.

Anal. Calcd for $C_{11}H_{10}N_6S$: C, 51.13; H, 3.88; N, 32.55; S, 12.40; mol wt, 258. Found: C, 51.06; H, 3.68; N, 32.45; S, 12.2; mol wt, 237.

The ultraviolet spectrum indicated that **17** was converted to **16** either in 0.1 *N* sodium hydroxide at room temperature or in tetrahydrofuran containing piperidine at reflux.

6-Amino-5-(4,6-dimethylpyrimidin-2-yl)aminopyrimidine-4(1H)-thione Dihydrochloride (19).—A suspension of **19** (20 mg) in 1 *N* hydrochloric acid (2 ml) was stirred at room temperature for 48 hr and then evaporated to dryness *in vacuo*. The hygroscopic solid was washed with ether and dried *in vacuo* over phosphorus pentoxide.

Anal. Calcd for $C_{10}H_{14}Cl_2N_6S$: C, 37.35; H, 4.37; N, 26.15. Found: C, 37.00; H, 4.78; N, 25.55.

6-Amino-5-guanidinopyrimidine-4(1H)-thione (21) and 8-Aminopurine-6(1H)-thione (24). A.—A solution of **14** (500 mg) in 1 *N* hydrochloric acid (10 ml) was refluxed for 1 hr. The resulting mixture was evaporated to dryness *in vacuo*, and the residue was washed with hot water (40 ml) and dissolved in hot 1 *N* ammonium hydroxide. This solution was neutralized with glacial acetic acid to deposit **24**, which was collected by filtration and dried *in vacuo* over phosphorus pentoxide at 78°: yield, 120 mg; mp >264°. The ultraviolet and infrared spectra of this material were practically identical with those of the compound prepared below.

(9) H. J. Schaeffer and H. J. Thomas, *J. Am. Chem. Soc.*, **80**, 4896 (1958).

Anal. Calcd for $C_5H_5N_5S$: C, 35.93; H, 3.02; N, 41.91; S, 19.15. Found: C, 35.81; H, 3.27; N, 41.37; S, 18.75.

The hot water wash from above was evaporated to dryness *in vacuo*, the residue was dissolved in a hot 3:1 ethanol–water mixture (20 ml), and the resulting solution was concentrated to deposit the hydrochloride of **21**: yield, 115 mg; mp >264°.

Anal. Calcd for $C_5H_6ClN_5S$: C, 27.20; H, 4.08; N, 38.10; S, 14.50. Found: C, 27.33; H, 4.20; N, 38.45; S, 14.34.

This material was converted to **24** in hot 1 *N* hydrochloric acid.

B.—A suspension of **14** (500 mg) in 1 *N* sodium hydroxide (15 ml) was refluxed for 2 hr. The solid dissolved in about 20 min, and the resulting solution evolved ammonia. This solution was neutralized with glacial acetic acid, and the solid (370 mg) that deposited was collected by filtration. This residue was washed with hot water (25 ml) to give 90 mg of **24**. The hot filtrate was treated with charcoal and cooled to deposit 65 mg of **21**, mp >264°. For analysis the sample was dried *in vacuo* over phosphorus pentoxide at 100° for 6 hr.

Anal. Calcd for $C_5H_3N_6S$: C, 32.61; H, 4.38; S, 17.38. Found: C, 32.35; H, 4.21; S, 17.52.

2,7-Diaminothiazolo[5,4-*d*]pyrimidine (23).—A solution of **20** (840 mg) in 1 *N* sodium hydroxide (6 ml) was evaporated to dryness *in vacuo*, the residue was suspended in tetrahydrofuran (25 ml), and cyanogen bromide (750 mg) was added with stirring. After 3 days the mixture was evaporated to dryness *in vacuo*, and the residue was washed with water to give 610 mg of **23**. Recrystallization of this solid from water gave the analytical sample, which did not melt below 264°.

Anal. Calcd for $C_5H_5N_5S$: C, 35.93; H, 3.02; N, 41.91; S, 19.15. Found: C, 36.07; H, 2.99; N, 41.85; S, 18.9.

In hot 1 *N* sodium hydroxide but not in hot 1 *N* hydrochloric acid, **23** was converted to 8-amino-6-mercaptopurine (**24**).

8-Aminopurine-6(1H)-thione (24).—Cyanogen bromide (300 mg) was added to a solution of **20** (400 mg) in 1 *N* sodium hydroxide (10 ml), and the whole was refluxed for 2 hr. The solution was treated with charcoal and neutralized with glacial acetic acid, and the solid that deposited was collected by filtration and dried *in vacuo* over phosphorus pentoxide at 78°: yield, 147 mg (31%); mp >264°.

Anal. Calcd for $C_5H_5N_5S$: C, 35.93; H, 3.02; N, 41.91. Found: C, 35.95; H, 3.13; N, 41.63.

When a solution of **24** in 6 *N* hydrochloric acid was refluxed for 18 hr, no rearrangement occurred. On cooling the solution, the hydrochloride of **24** deposited.

Anal. Calcd for $C_5H_6ClN_5S$: N, 34.40. Found: N, 34.47.

8-Amino-2-ethylpurine-6(1H)-thione (25).—A solution of **13** (100 mg) in 1 *N* hydrochloric acid (12 ml) was refluxed for 1 hr and adjusted to pH 6 with 10 *N* sodium hydroxide. The precipitate was collected by filtration and recrystallized from water: yield, 30 mg.

Anal. Calcd for $C_7H_9N_5S$: C, 43.10; H, 4.62; N, 35.90; S, 16.40. Found: C, 42.90; H, 4.98; N, 36.00; S, 15.85.

6-(2-Imidazolinylthio)purine Hydrochloride (28).—A solution of **1** (1.0 g) in propanol (20 ml) containing 2-imidazolidinethione (1.0 g) was refluxed for 2 hr. The resulting mixture was cooled to room temperature, and the solid was collected by filtration and dried *in vacuo* over phosphorus pentoxide: yield, 1.42 g (85.5%). This sample decomposed above 200° with partial melting.

Anal. Calcd for $C_8H_9ClN_6S$: C, 37.40; H, 3.51; Cl, 13.09; N, 32.75; S, 12.45. Found: C, 37.40; H, 3.69; Cl, 138.5; N, 32.74; S, 12.70.

The hydrate of **6** was obtained in 88% yield when the hydrochloride of **28** was treated with hot 2 *N* sodium hydroxide.

2-Chloro-6-(2-imidazolinylthio)purine Hydrochloride (29).—A solution of **26** (1.0 g) in propanol (10 ml) containing 2-imidazolidinethione (550 mg) was refluxed for 45 min. The solid was collected by filtration, washed with propanol (5 ml), and dried *in vacuo* over phosphorus pentoxide: yield, 1.09 g (71%).

Anal. Calcd for $C_8H_8Cl_2N_6S$: C, 33.00; H, 2.75; Cl, 24.40; N, 28.85; S, 11.00. Found: C, 33.20; H, 3.00; Cl, 24.08; N, 28.93; S, 11.13.

When the hydrochloride of **34** was refluxed in 2 *N* sodium hydroxide, 2-chlorohypoxanthine (**26**) was obtained in 94% yield.

2-Amino-6-(2-imidazolinylthio)purine Hydrochloride (30).—A suspension of **27** (2.0 g) in butanol (50 ml) containing 2-imidazolidinethione (1.3 g) was refluxed for 1 hr; the solid was collected by filtration, washed with methanol (25 ml) and then ether (100 ml), and dried *in vacuo* over phosphorus pentoxide: yield, 2.6 g (81%); decomposed about 250°.

Anal. Calcd for $C_8H_{10}ClN_7S$: C, 35.35; H, 3.69; Cl, 13.08; N, 36.10; S, 11.79. Found: C, 35.24; H, 3.92; Cl, 12.87; N, 35.94; S, 11.68.

A suspension of the hydrochloride (205 mg) in water (5 ml) dissolved on neutralization with 1 *N* sodium hydroxide. Within 10 min the free base deposited, which was collected by filtration and dried *in vacuo* over phosphorus pentoxide: yield, 150 mg (84%). This material softened but did not melt below 250°.

Anal. Calcd for $C_8H_9N_7S$: C, 40.80; H, 3.83; N, 41.70; S, 13.61. Found: C, 40.58; H, 4.08; N, 41.54; S, 13.35.

In hot 1 *N* sodium hydroxide, the hydrochloride of **30** was converted to thioguanine (**24**) containing a small amount of guanine (**37**).

Spiro[imidazolidine-2,2′-2′H-thiazolo[3′,4′,5′-*gh*]purine] (31).—A solution of the hydrochloride of **33** in water (20 ml) was neutralized with 1 *N* sodium hydroxide; the solid that dep sited was collected by filtration, washed with water, and dried *in vacuo* over phosphorus pentoxide.

Anal. Calcd for $C_8H_8N_6S$: C, 43.60; H, 3.64; N, 38.20; S, 14.55. Found: C, 42.86; H, 4.03; N, 37.55; S, 14.90.

Purification of this material was attempted by recrystallization from tetrahydrofuran, but only **6** deposited (72%).

Spiro[imidazolidine-2,2′-2′H-7′-chlorothiazolo[3′,4′,5′-*gh*]-purine] (32).—A solution of the hydrochloride of **29** (910 mg) in water (35 ml) was neutralized with 1 *N* sodium hydroxide (3.2 ml). The solid that deposited was collected by filtration, washed with ether, and dried *in vacuo* over phosphorus pentoxide at 56°: yield, 430 mg (54%); softened at 160° but melted >264°.

Anal. Calcd for $C_8H_7ClN_6S$: C, 37.70; H, 2.75; Cl, 13.92; S, 12.55. Found: C, 37.91; H, 3.21; Cl, 13.6; S, 12.36.

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