allowed to stir at room temperature overnight. A slow rise in temperature to 35–40° usually occurred during the first 2 hr., and a very fine precipitate of sodium chloride could be observed. The mixture was filtered with the aid of Hyflo and solvent was removed from the filtrate *in vacuo*. The viscous residue was treated with 100–200 ml. toluene and filtered again, to recover unchanged I. The toluene solution was washed with 10% sodium carbonate solution until the washings gave no precipitate when acidified. Finally solvent was allowed to evaporate in an air stream, whereupon the product usually crystallized.

Method B. Equimolar quantities of the sodium salt of I and *O,O*-dialkyl phosphorochloridothioate were used. Otherwise the procedure was the same as in Method A.

Method C. Equimolar amounts of potassium hydroxide and I were dissolved in a minimum volume of water. Then a 10% excess of *O,O*-dialkyl phosphorochloridothioate was added and the emulsion was stirred vigorously for 3 to 4 hr. The mixture was treated with an equal volume of toluene and filtered to remove unreacted I. The two-phase filtrate was separated and the aqueous portion was extracted with additional toluene. Evaporation of the organic solution yielded crystalline product. Acidification of the aqueous portion gave additional I.

The compounds (II) prepared are shown in Table I. In most cases it was possible to recover sufficient I from the reaction mixtures to bring the material balance of starting I to 90–95%.

O,O-Diethyl O-(6-chloro-3-pyridazinyl) phosphorothioate (XLI). XLI was obtained in 45% yield from XL by Method C. After recrystallization from heptane-ether, a m.p. 46.5–47.5° was observed.

Anal. Calcd. for $C_8H_{12}ClN_2O_3PS$: P, 10.96 Found: P, 10.56.

XLI changed to a green gum on standing overnight in air, and even samples stored under nitrogen in the dark turned green after several months. The decomposed mixture no longer dissolved completely in ether.

O,O-Diethyl O-[1,6-dihydro-1-(hydroxymethyl)-6-oxo-3-pyridazinyl] phosphorothioate (XVI). IV (31.7 g., 0.12 mole) was added to 37% methanol-free formaldehyde solution (39.0 g., 0.48 mole) to give a thick white paste. Two immiscible liquid layers appeared above 49°, and the mixture was heated at 70–72° for 2 hr. The mixture was cooled and the lower organic layer was separated. The aqueous portion was extracted with ether and the latter combined with the main organic fraction. This was then washed repeatedly with saturated sodium chloride solution and dried. Removal of the solvent *in vacuo* yielded crystalline product, which after extensive drying *in vacuo* over calcium chloride, showed a formaldehyde content of 10.7% (theory 10.2%).

STAMFORD, CONN.

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

The Use of *N,N*-Dimethylformamide in the Carbon Disulfide Ring Closure of 4,5-Diaminopyrimidines[2]

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Received January 24, 1961

An improved procedure for the preparation of purine-8-thiols by the reaction of 4,5-diaminopyrimidines with carbon disulfide in *N,N*-dimethylformamide is described. Application of this procedure to 4,5-diaminopyrimidines containing a group in the 6-position susceptible to nucleophilic attack resulted in intramolecular displacement of this group by the intermediate dithiocarbamate anions to give thiazolo[5,4-*d*]pyrimidine-2-thiols.

The general utility of this ring closure for the preparation of other heterocyclic systems is also demonstrated.

It became necessary to prepare some purine-8-thiols (III) as intermediates in the synthesis of hemisulfur mustard derivatives of purines[3] which might prove to be of interest as anticancer agents.

Purine-8-thiols are most commonly prepared form 4,5-diaminopyrimidines by reaction with carbon disulfide in pyridine[4,5] or fusion with thiourea.[6–9] In an effort to improve the preparation of purine-8-thiol (IIIa)[6,7] itself, the reaction of 4,5-diaminopyrimidine (Ia) and carbon disulfide in *N,N*-dimethylformamide was investigated and, indeed, an almost quantitative yield of the purine was obtained in this manner. This marked improvement in yield over that reported in the literature[7] encouraged us to attempt to extend the application of this procedure. A good yield of 9-ethyl-9*H*-purine-8-thiol (IIIb) was obtained from 5-amino-4-ethylaminopyrimidine (Ib),[10] but when the procedure was applied to 4,5-diamino-6-chloropyrimidine (Ic),[11] the expected product—6-chloropurine-8-thiol—was not obtained. Instead, a compound containing no chlorine was isolated in good yield. The same compound resulted when 4,5-diamino-6-

(1) Affiliated with the Sloan-Kettering Institute.

(2) This investigation was supported by the C. F. Kettering Foundation and the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, contract no. SA 43-ph-1740.

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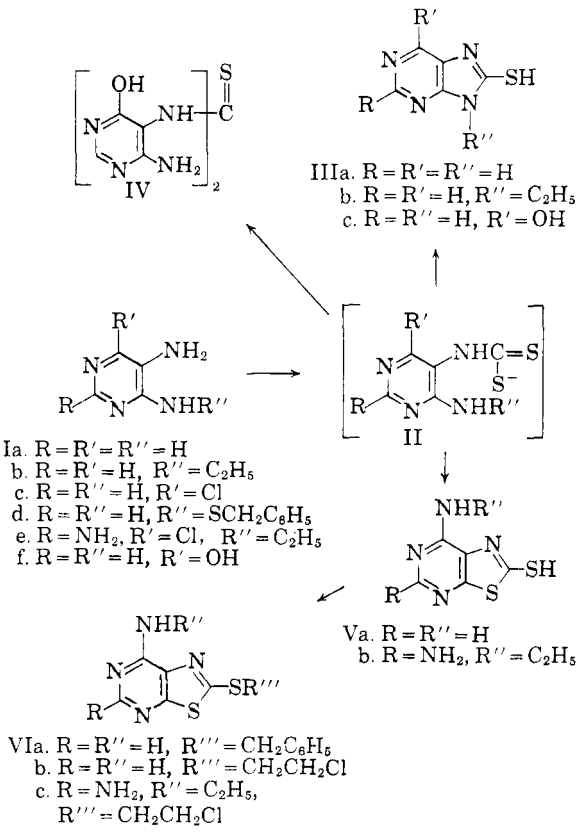
TABLE I

Compound No.	Reaction Conditions: Ratio Reactants[a]	Vol. DMF[b]	Time, hr.	Temp.	Yield, %	Recrystn. Solvent[c]	M.P.[d]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
IIIa[e]	1:7.3	8	72	R.t.[f]	95	AB	317[g]	39.48	39.65	2.65	2.78	36.84	36.64		
b	1:1	13.6	18	R.t.	73	AB	264	46.66	46.39	4.48	4.58	17.76	17.47		
c[h]	1:9	10	18	R.t.	20[i]	B	>350[g]	35.72	35.56	2.40	2.56	33.33	33.09		
Va	1:9.6	7.5	24	60–70	55[j]	C	270[g]	32.62	32.58	2.19	2.26			34.76	34.91
			24	60	48[k]	AB	270[g]								
b	1:13	10	2	R.t.	80	B	—[l]	37.01	37.00	3.99	4.15			28.17	27.46
VIa			2	50	60	BC	137	52.55	52.43	3.68	3.55	20.43	20.55		
b			2	45	67	D[m]	155	34.02	34.16	2.85	2.82	14.35[n]	14.28[n]		
c			2	40	75	BC	75	35.20[o]	35.64	4.92[o]	4.61	11.20[n,o]	11.18[n]	20.21[o]	19.94

[a] Wt. pyrimidine: wt. carbon disulfide. [b] Ml./g. pyrimidine. [c] A = *N,N*-Dimethylformamide, B = water, C = methanol, D = ether. [d] Except where indicated melting points were determined on a Kofler Heizbank. [e] See ref. 7. [f] Room temperature. [g] Capillary in an aluminum block, not corrected. [h] See reference 9. [i] The major product of this reaction was 1,3-bis(4-amino-6-hydroxypyrimidin-5-yl)thiourea. See text. [j] From 4,5-diamino-6-chloropyrimidine. [k] From 4,5-diamino-6-(benzylthio)pyrimidine. [l] Decomposes without melting. [m] Trituration. [n] % Chlorine. [o] Calcd for $C_9H_{12}ClN_5S^{-1}/_2H_2O$.



(benzylthio)pyrimidine (Id)[12] was allowed to react with carbon disulfide in *N,N*-dimethylformamide. Elemental analyses and spectral data establish the identity of this compound to be 7-aminothiazolo[5,4-*d*]pyrimidine-2-thiol (Va). Although the ultraviolet spectrum is not definitive, the presence of bands in the infrared spectrum due to a primary amino group at 3400, 3290, and 1645 cm.$^{-1}$, and heterocyclic bands in the double bond region of the spectrum at 1590, 1530 (sh.), and 1495 cm.$^{-1}$ are good confirmatory evidence. The thiazolo[5,4-*d*]-pyrimidine apparently results from the intramolecular displacement of a relatively labile group, such as the 6-chloro group of the pyrimidine, by the intermediate dithiocarbamate anion II in preference to the more usual ring closure on the 4-amino group of the pyrimidine.[4,5]

Application of the reaction to 2,5-diamino-4-chloro-6-ethylaminopyrimidine[13] (Ie) gave 5-amino-7-ethylaminothiazolo[5,4-*d*]pyrimidine-2-thiol (Vb), again by displacement of the chlorine atom. These reactions constitute the first reported preparation of a thiazolo[5,4-*d*]pyrimidine-2-thiol and represent a rather unusual ring closure.

Attempted Raney nickel desulfurization of 7-aminothiazolo[5,4-*d*]pyridine-2-thiol (Va) to the known 7-aminothiazolo[5,4-*d*]pyrimidine[12] re-

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sulted in removal of the sulfur from the ring also, giving 4,5-diaminopyrimidine as the only product.

The reaction of 4,5-diaminopyrimidin-6-ol (If) with carbon disulfide in *N,N*-dimethylformamide gave only a 20% yield of 8-mercaptohypoxanthine (IIIc).[9] The major product of this reaction is a compound that we have tentatively identified as 1,3-bis(4-amino-6-hydroxypyrimidin-5-yl)thiourea (IV) formed by the reaction of the dithiocarbamate anion II with a second molecule of the pyrimidine. This compound is very intractable, being insoluble in all the organic solvents tried, and would dissolve only in aqueous base from which it precipitated on acidification. This treatment, however, failed to give a sample that analyzed consistently correctly for the proposed thiourea structure. Still, the carbon, hydrogen, nitrogen, and sulfur values were fairly close to the calculated values, and the ultraviolet and infrared spectral data also support this structure. The ultraviolet spectrum is very similar to that of 4-amino-5-formamidopyrimidin-6-ol and the infrared spectrum shows bands due to NH at 3300 and 3120 cm.$^{-1}$ and pyrimidine carbonyl absorption at 1640 cm.$^{-1}$ Also, the general appearance of the infrared spectrum is very similar to that of 4,5-diaminopyrimidin-6-ol.

The general applicability of the carbon disulfide-*N,N*-dimethylformamide ring closure to other heterocyclic ring systems was demonstrated by the preparation of 5(6)-nitrobenzimidazole-2-thiol in 88% yield (lit.[14] yield, 47%) from 4-nitro-*o*-phenylenediamine and of imidazo[4,5-*d*]pyridine-2-thiol in 78% yield (lit.[15] yield 58%) from 2,3-diaminopyridine.

Alkylation[16] of the thiazolo[5,4-*d*]pyrimidine-2-thiols with 1-bromo-2-chloroethane gave the corresponding 2-chloroethylthio derivatives. These compounds failed to exhibit any interesting biological activity, possibly because of the chemically inert nature of the chlorine atom of the 2-chloroethylthio group, in contrast to the chemical behavior of similar compounds which do show biologic activity.[3]

EXPERIMENTAL

General procedure for the carbon disulfide ring closure. A mixture of the 4,5-diaminopyrimidine and an excess of carbon disulfide in *N,N*-dimethylformamide was stirred until the reaction was complete (see Table I for time and temperature). The solution was then cooled (if necessary) and poured into cold water from which the excess carbon disulfide was evaporated. The product that separated was recrystallized either from the *N,N*-dimethylformamide-water mixture or from the specified solvent (see Table I) and dried *in vacuo* over phosphorus pentoxide. The yields, melting points, and analyses are reported in Table I. The ultraviolet absorption spectra of these compounds are recorded in Table II.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA[a]

Compound No.	pH 1 λ_{max}, mμ	pH 1 $\epsilon \times 10^{-3}$	pH 7 λ_{max}, mμ	pH 7 $\epsilon \times 10^{-3}$	pH 13 λ_{max}, mμ	pH 13 $\epsilon \times 10^{-3}$
IIIa[b]	237	15.1	228	12.6	230	15.8
	326	18.6	312	23.1	315	20.7
b	241	13.4	234	12.5	236	13.8
	329	18.8	313	25.3	313	20.8
c	233.5	9.3	234	12.9	232	21.5
	289	24.1	291	19.1	289	21.8
Va	240	13.4	225	16.7	226	15.9
	322	22.0	241	16.3	242	15.6
			304	17.1	303	16.6
b	241	16.4				
	329	24.4	313	20.3	313	21.8
VIa	293	15.3	240[c]	14.4	240[c]	15.0
			289	12.0	289	12.2
			305	12.0	305	12.1
b	224	17.2	240	14.2	240	14.3
	291	15.0	286	11.3	286	11.5
			303	10.2	303	10.3
c	234	18.1	232	13.8		
	296	17.6	306	15.4	305	15.6

[a] These spectra were determined in aqueous solution with a Beckman DK-2 spectrophotometer (optical densities at the maxima with a Beckman DU), or with a Cary Model 14 spectrophotometer. [b] In agreement with literature values. See ref. 7. [c] Shoulder.

General procedure for the alkylation of the thiazolo[5,4-d]-pyrimidine-2-thiols. A mixture of the thiazolo[5,4-*d*]pyrimidine, organic halide, and potassium carbonate (mole ratio—1:1:1) in *N,N*-dimethylformamide (10 ml./g. thiazolo[5,4-*d*]pyrimidine) was stirred at 40–50° for 2 hr. The reaction mixture was cooled and poured into three times its volume of cold water. The aqueous mixture was neutralized and the precipitate that formed was collected and recrystallized from the specified solvent. The recrystallization solvent, yields, melting points and analyses are given in Table I. The ultraviolet absorption spectra of these compounds are recorded in Table II.

Acknowledgment. The authors are indebted to Dr. W. J. Barrett and the members of the Analytical Section of Southern Research Institute who performed the spectral and most of the microanalytical determinations reported. Some of the analyses reported were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

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