TABLE I

5-ALKYL-2-IMINOHEXAHYDRO-s-TRIAZINE-1-CARBONITRILES

Alkyl	Yield, %	M.P., °C.	Analysis					
			Calculated			Found		
			% C	% H	% N	% C	% H	% N
Methyl	92	196–197	43.15	6.52	50.33	43.20	6.58	50.30
Butyl	80	149–150	53.01	8.34	38.64	52.89	8.45	38.80
Isobutyl	88	177–178	53.01	8.34	38.64	52.96	8.35	38.71
Allyl	86	172–173	50.89	6.71	42.40	51.00	6.69	42.30
Cyclohexyl	84	172–173	57.94	8.28	33.79	57.91	8.29	33.69
n-Decyl	94	160–161	63.36	10.25	26.39	63.27	10.29	26.35
n-Dodecyl	92	157–158	65.48	10.65	23.87	65.54	10.59	23.82
n-Octadecyl	92	132.3	69.97	11.48	18.55	69.94	11.42	18.51

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Studies in Purine Chemistry. VII. An Improved Synthesis of Hypoxanthine[1,2]

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The desulfurization of a mercapto or alkylmercapto substituent is often a critical step in heterocyclic synthesis, particularly in pyrimidine and purine chemistry. The most commonly employed desulfurization method is to reflux the compound with an excess of Raney nickel under what are commonly termed "Mozingo conditions,"[3] and this procedure[4] has been employed in syntheses of both hypoxanthine[5] and adenine[6–8] derivatives. Other methods for replacement of the mercapto group by hydrogen include oxidation with nitric acid[9] or with hydrogen peroxide in acidic solution.[9–11]

An attractive alternative has more recently been described which involves oxidation of the mercapto group in alkaline solution with hydrogen peroxide to a sulfinic acid, followed by decomposition with strong acid, and has been applied to the synthesis of 4,5,6-triaminopyrimidine from 2-mercapto-4,5,6-triaminopyrimidine[12,13] and of 4,6-diaminopyrimidine from 2-mercapto-4,6-diaminopyrimidine.[13] By application of this method to the preparation of 4-hydroxy 5,6-diaminopyrimidine from 2-mercapto-4-hydroxy-5,6-diaminopyrimidine, and by means of certain other modifications, we have been able to effect significant improvements in the conventional synthesis of hypoxanthine from thiourea and ethyl cyanoacetate. Details are given in the Experimental.

Evans *et al.*[13] pointed out that the decomposition of 4,6-diaminopyrimidine-2-sulfinic acid to 4,6-diaminopyrimidine required much stronger acid than the analogous decomposition of 4,5,6-triaminopyrimidine-2-sulfinic acid to 4,5,6-triaminopyrimidine and that weaker acid led predominately to the 2-hydroxy derivative. This was attributed to the weaker basicity of the former pyrimidine, coupled with the requirement that diprotonation precede heterolytic cleavage of the C—S bond. We have found that oxidation of 2-mercapto-4-hydroxy-6-aminopyrimidine, a still weaker base, leads directly to 2,4-dihydroxy-6-aminopyrimidine; the 2-sulfinic acid could not even be isolated.

(1) This investigation was supported in part by a grant (C-2551) to Princeton University from the National Cancer Institute of the National Institutes of Health, Public Health Service.

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EXPERIMENTAL

2-Mercapto-4-hydroxy-6-aminopyrimidine.[14] To a solution of sodium ethoxide (prepared by dissolving 9 g. of sodium in 200 ml. of ethanol) was added 22.6 g. of ethyl cyanoacetate. A white precipitate formed immediately. After 15 min., 15.2 g. of thiourea was added with shaking, and the mixture was allowed to stand at room temperature for 1 hr. with occasional shaking. It was then heated under reflux for 2 hr., cooled and filtered. The collected solid was dissolved in boiling dilute potassium hydroxide and reprecipitated by the addition of glacial acetic acid to give 28.4 g. (99%) of white crystals.

2-Mercapto-4-hydroxy-5-nitroso-6-aminopyrimidine.[14] To a solution of 20 g. of 2-mercapto-4-hydroxy-6-aminopyrimidine in 500 ml. of water containing 5.5 g. of sodium hydroxide and 10 g. of sodium nitrite and maintained at room temperature was added dropwise 15 g. of glacial acetic acid. The reaction mixture was stirred overnight and then filtered to give a brownish-red solid in 90% yield. The crude product was extracted with boiling acetone and then with boiling ethanol (thus removing a small amount of colorless impurity) and was then suitable for further reaction.

2-Mercapto-4-hydroxy-5,6-diaminopyrimidine. The procedure used was essentially the same as previously described by Albert *et al.*,[15] except that the temperature of the reduction mixture was maintained below 30° rather than below 50°, and the sodium hydrosulfite was added very slowly rather than all at once. Furthermore, the reduction mixture was stirred for 20 hr. at room temperature following addition of all of the hydrosulfite and was then decolorized with charcoal. The diaminopyrimidine was obtained in 96.5% yield.

4-Hydroxy-5,6-diaminopyrimidine-2-sulfinic acid. To a solution of 1 g. of 2-mercapto-4-hydroxy-5,6-diaminopyrimidine in 90 ml. of water containing 0.6 g. of sodium hydroxide and precooled to −3° was added dropwise 1.8 ml. of 30% hydrogen peroxide in 17 ml. of water. During the addition the temperature was carefully maintained below 0°. The reaction mixture was allowed to stir for 1.5 hr. following addition of the peroxide and was then acidified with glacial acetic acid. Filtration yielded 0.8 g. of a colorless solid, m.p. 188–190°.

4-Hydroxy-5,6-diaminopyrimidine hydrochloride. A mixture of 1.5 g. of 4-hydroxy-5,6-diaminopyrimidine-2-sulfinic acid and 30 ml. of ethanolic hydrogen chloride was stirred at room temperature for 20 hr. in a flask protected from atmospheric moisture by a calcium chloride tube. The reaction mixture was evaporated to dryness, the residue dissolved in water, filtered and the filtrate again evaporated to dryness to give 1.3 g. of a colorless solid, m.p. 249–251°d., identical in all respects with an authentic sample of 4-hydroxy-5,6-diaminopyrimidine hydrochloride prepared by Raney nickel desulfurization of 2-mercapto-4-hydroxy-5,6-diaminopyrimidine.[16]

Decomposition of 4-hydroxy-5,6-diaminopyrimidine-2-sulfinic acid with concentrated hydrochloric acid yielded 2,4-dihydroxy-5,6-diaminopyrimidine hydrochloride rather than the desired product.

Hypoxanthine. A mixture of 2 g. of 4-hydroxy-5,6-diaminopyrimidine hydrochloride and 30 ml. of an equimolar mixture of ethyl orthoformate and acetic anhydride was heated under reflux for 4 hr. and then evaporated to dryness. Recrystallization of the residual solid from aqueous ethanol gave 1.6 g. (95.5%) of pure hypoxanthine, identical in all respects with an authentic sample.

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Potential Anticancer Agents.[1] XXVIII. Synthesis of 5-(Chloromethyl)uracil

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Both 5-fluorouracil[2] and 5-[bis(2-chloroethyl)-amino]uracil[3] have been shown to inhibit the growth of various tumors. Matthews[4] reported that all of the 5-halogenated uracils were incorporated into phage DNA, giving mutants. Hitchings *et al.*,[5] have shown 5-bromouracil to be a competitive thymine antagonist.

Efforts to find new anticancer agents could, therefore, be logically directed toward the preparation of various thymine derivatives such as 5-(fluoromethyl) uracil, 5-[bis(2-chloroethyl)aminomethyl]uracil, and other uracil derivatives containing potential alkylating groups attached to a 5-methyl grouping. The key intermediate to the synthesis of these agents would be 5-(chloromethyl)-uracil (IV). This compound has now been synthesized in 57% yield by the choromethylation of uracil (I).

Early attempts in this laboratory to prepare IV by the chlorination of thymine using *N*-chlorosuccinimide and benzoyl peroxide, as reported by West and Barrett,[6] failed to yield IV. Instead, a compound melting at 224.5–225.5° was obtained. West reported a similar melting point of 222–224° and an empirical formula of $C_5H_5ClN_2O_4$. The failure of this compound to react with alcoholic silver nitrate solution upon heating, its stability toward water (being recrystallized without change from hot water), its lack of absorption in the ultraviolet, and its liberation of iodine from an acetic acid solution of potassium iodide, are convincing

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper in this series, *cf.* E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Am. Chem. Soc.*, in press.

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