Of interest is the report[10] that substitution of the β-hydrogen on (III) by a methyl group[7] abolishes blocking activity even though the carbonium ion is remarkably stable in solution.[7] However this result is in agreement with the postulate that close approach of a positive ion to the receptor anionic site is hindered when the ion is bulky. It may be recalled that the triggering of an excitatory response has been attributed to ion-pair formation between the small cationic head (primary ammonium group) of norepinephrine[2,3] and an anionic active site and that the effect of substituents on the cationic head would be to prevent ion-pair formation, thus precluding the initiation of an excitatory response. It can be seen, therefore, that very similar trends would actually operate both in the carbonium ion and the ammonium ion series, the effect of substitution being presumably to hinder close approach to the anionic site. These considerations fully support the hypothesis that carbonium ions and ammonium ions may be bound by the same anionic site.

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Pyrimidines. VIII. Pyrimidine Derivatives of Thioguanine[1]

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The antitumor activity of 2-amino-6-purinethiol (thioguanine, I; R_1, R_2 = H) has been well established.[2] The high toxicity of this compound has prompted many investigators to modify the structure of thioguanine in order to obtain less toxic derivatives with greater specificity at enzyme sites. As a part of our general investigating program on pyrimidines, some pyrimidine derivatives of thioguanine have been synthesized Elion, *et al.*, prepared some imidazole deriva-

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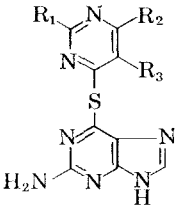
(2) *Cf. Cancer Chemotherapy Reports*, **11**, 202 (1961).

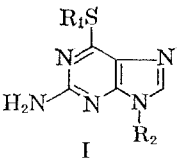
TABLE I

SUBSTITUTED (2-AMINO-6-PURINYLTHIO)PYRIMIDINES



					Analyses, %							Preliminary screening results[b]		
				Yield,	Calcd.			Found			NSC	Sa-	Le-	Ca-
R_1	R_2	R_3	M.p., °C.	%	C	H	N	C	H	N	Nos.[a]	180	1210	755
Cl	H	CH_3	230 dec	24	40.9	2.7	33.3	40.9	3.0	33.3	51563	−	−	+
CH_3S	Cl	H	266 dec	60	36.9	2.5	30.1	37.2	2.6	29.9	51564	±	−	±
CH_3S	H	Br	220 dec	30	32.5	2.2	26.5	32.9	2.4	26.3	51562	±	±	+
CH_3S	CH_3	Br	225 dec	21	34.3	2.6	25.4	34.2	2.7	25.1	52382	+	−	+
CH_3S	Cl	Br	240 dec	19	29.8	1.7	24.3	29.7	1.6	24.3	52383	−	−	+
C_2H_5S	H	Br	220 dec	26	34.4	2.3	25.5	34.6	2.6	25.3	52384	−	−	+
C_2H_5S	Cl	H	240 dec	30	38.8	3.3	28.8	38.5	3.5	28.6	52385	+	−	+

[a] Number assigned by the Cancer Chemotherapy National Service Center. [b] +, activity confirmed; ±, activity not yet confirmed; −, no or low activity. Testing done by the Contract Screeners of CCNSC.



I

tives of thioguanine in an anhydrous solvent.[3] Our synthesis was carried out in aqueous solvent by treating thioguanine with an appropriate chloropyrimidine under alkaline conditions. Aqueous ammonia, which caused less side reactions, was found to be more suitable than sodium or potassium hydroxide for this type of reaction.

The selection of appropriate chloropyrimidines to react with thioguanine presented a rather interesting problem. Not very many chloropyrimidines are suitable for this reaction. This is illustrated by examples: 4,6-dichloro-5-nitropyrimidine,[4] 2,4-dichloro-5-nitropyrimidine,[5] 2,4-dichloro-5-ethoxycarbonylpyrimidine,[6] and 2,4,6-trichloropyrimidine,[7] of which the chloro groups are easily replaceable by nucleophilic agents, would react preferentially with ammonia rather than the dissolved thioguanine under our reaction conditions. On the other hand, with 5-amino-4,6-dichloropyrimidine,[8] 2-chloropyrimidine,[9] 4-chloro-2-methylthiopyrimidine,[10] 5-amino-2,4-dichloropyrimidine,[8] and 2-amino-4,6-dichloropyrimidine,[11] the chloro groups were so unreactive that only starting materials were isolated from the reaction mixture.

Preliminary biological evaluations of many of these compounds have passed the confirmation tests for Sarcoma-180 and Carcinoma-755 tumor systems.[12] The compounds and their activities are listed in Table I.

Experimental

General Methods for the Preparation of Pyrimidine Derivatives of Thioguanine.—To 200 ml. of warm concentrated aqueous ammonia was added 0.1 mole of 6-thioguanine. The resulting solution was heated to 70° while 0.1 mole of the appropriate chloropyrimidine dissolved in 100 ml. of *p*-dioxane was added, with stirring. The reaction mixture then was stirred at 70° for 90 min.; during this time a precipitate had formed. The product was filtered while hot and washed well with aqueous ammonia to dissolve unreacted thioguanine, and then with acetone to dissolve unreacted chloropyrimidine. Recrystallization of the product from a mixture of water and dimethylformamide gave the product with analytical and chromatographic purity.

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