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

Synthesis of Potential Anticancer Agents. III. Hydrazino Analogs of Biologically Active Purines[2]

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Several hydrazinopurines have been prepared from the appropriate chloropurines. One compound, 2-amino-6-hydrazinopurine, could not be prepared from 2-chloro-6-hydrazinopurine, but was obtained from 2-amino-6-methylmercaptopurine.

There are several purines of biological importance which contain primary amino groups. Among them are adenine, guanine and 2,6-diaminopurine. Adenine and guanine occur naturally in cell nuclei, whereas 2,6-diaminopurine is, curiously enough, incorporated into nucleic acid guanine better than guanine itself[3] and has shown some anticancer activity.[4]

In view of the striking activity produced when the amino group of certain amino acids is replaced by a hydrazino group,[5] it is reasonable to assume that some interesting anticancer agents might result if the amino groups of the above-mentioned compounds are replaced by hydrazino groups (II, III, VI, X and XIV).

Of these compounds, 6-hydrazinopurine (II) has been reported previously,[6] but the method of preparation is inconvenient since it involves heating a sealed tube for 16 hours. In addition to these compounds, 2-hydrazinopurine (V) seemed worthy of synthesis for biological testing.

Two methods of introducing a hydrazino group into the desired positions of the purine ring appeared feasible: the replacement of a methylmercapto group and the replacement of a chlorine atom.

This replacement might be done either before or after ring closure of the appropriate 4,5-diaminopyrimidines to purines, since a new ring closure[7] has made the necessary chloropurines readily available.

The introduction of the hydrazino group prior to ring closure is undesirable for two reasons: the hydrazino group in the 6 position presents the possibility of closure involving the hydrazino group rather than the 4-amino group giving rise to 9-aminopurines, since 6-alkylamino-4,5-diaminopyrimidines give 9-alkylpurines[8]; the intermediate purines such as 2-chloro-6-hydrazinopurine would be more interesting for screening than the intermediate 4,5-diaminopyrimidines such as 2-chloro-4,5-diamino-6-hydrazinopyrimidine.[9]

Although the mercapto group in the 6-position of the purine ring cannot be replaced by amines or hydrazine, the 6-methylmercapto group can be replaced under rather strenuous conditions.[6] Since the chlorine atom is generally more susceptible to nucleophilic attack than the methylmercapto group,[10] it seemed probable that the replacement of the chlorine atom constituted a more desirable method of preparation of 6-hydrazinopurine. Therefore, the preparation of 6-hydrazinopurine *via* 6-chloropurine was attempted; it was found that replacement of the chlorine atom in anhydrous hydrazine took place smoothly at room temperature giving a 92% yield of pure 6-hydrazinopurine, showing that indeed the chlorine atom is more reactive.

It is well known that the substituents in the 2-position of purine are less reactive than substituents in the 6-position. Because of this the chlorine atom in this position, rather than the methylmercapto group, is an even more logical choice for replacement by the hydrazino group. Indeed Todd, *et al.*,[11] found that it was not possible to prepare 2,6-diaminopurine from 2-methylthioadenine under any conditions tried. Hydrazine, while more reactive than ammonia, is still not apt to replace the 2-thio or 2-methylthio group readily, unless an activating group is present in the 6-position.[12] Therefore, 2-chloropurine was chosen as the precursor to 2-hydrazinopurine, and the replacement with hydrazine carried out; although, as predicted, more strenuous conditions than those employed with 6-chloropurine were necessary.

The difference in reactivity of the chloro group in the 2- and 6-position of purine shows up distinctly in the reactions of 2,6-dichloropurine (VIII). This difference is much more pronounced than in the case of the chlorine atoms of 2,4-dichloropyrimidine[14]; it follows closely the comparison of 2-chloropurine and 6-chloropurine. When allowed to react with anhydrous hydrazine, the chlorine atoms of 2,6-dichloropurine are replaced stepwise.

(1) Affiliated with Sloan-Kettering Institute. This work was supported by funds from the C. F. Kettering Foundation. Part II, J. A. Johnson and H. S. Thomas, THIS JOURNAL, **78**, 3863 (1956).

(2) Presented at the Southwide Chemical Conference at Memphis, Tennessee, in December, 1956.

(3) L. L. Bennett, Jr., H. E. Skipper, C. C. Stock and C. P. Rhoads, *Cancer Research*, **15**, 485 (1955).

(4) J. H. Burchenal, A. Bendich, G. B. Brown, G. B. Elion and G. H. Hitchings, *Cancer*, **2**, 119 (1949).

(5) R. W. Brockman, Southern Research Institute, private communication.

(6) G. B. Elion, E. Burgi and G. H. Hitchings, THIS JOURNAL, **74**, 411 (1952).

(7) J. A. Montgomery, *ibid.*, **78**, 1928 (1956).

(8) J. W. Daly and B. E. Christensen, *J. Org. Chem.*, **21**, 177 (1956).

(9) This conclusion is based on the results obtained in screening numerous purines and pyrimidines at Southern Research Institute and Sloan-Kettering Institute for Cancer Research.

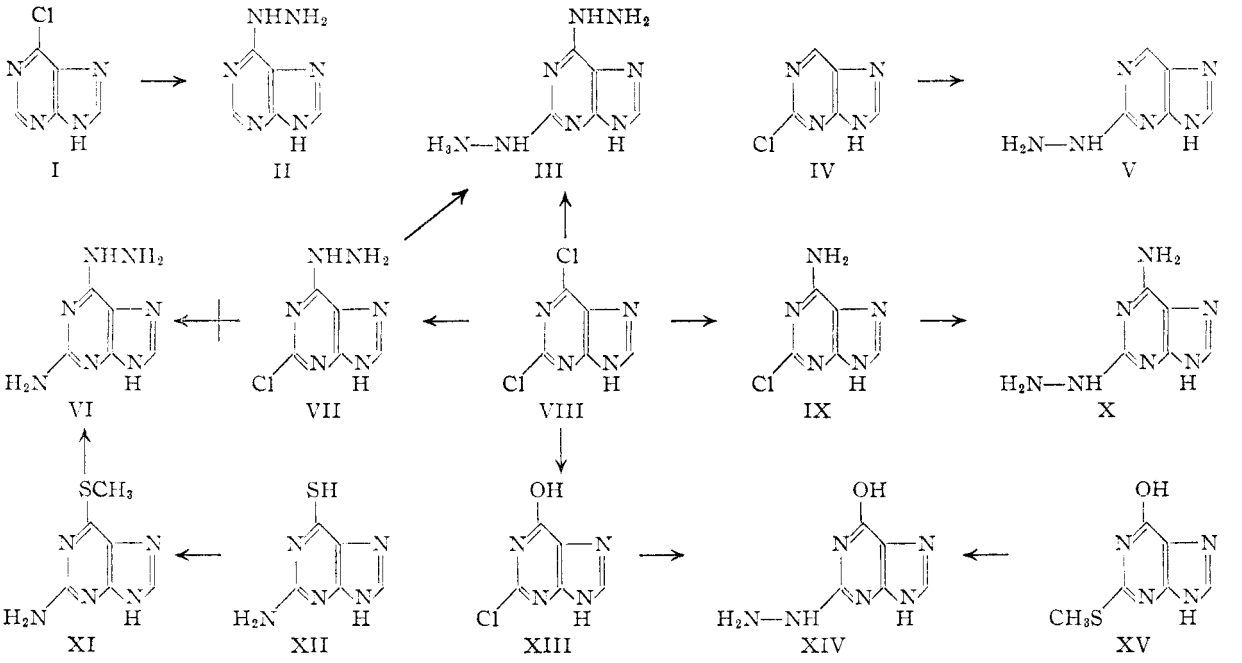
(10) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 294 (1951).

(11) K. J. M. Andrews, N. Anand, A. R. Todd and A. Topham, *J. Chem. Soc.*, 2490 (1949).

(12) Since this work was begun Elion, Lange and Hitchings[13] have reported that, in contrast to the behavior of 2-methylmercapto-6-aminopurine, the methylmercapto group of 2-methylmercapto-6-hydroxypurine can be replaced by amines. We have found that this is also true for hydrazine, although a better yield of 2-hydrazino-6-hydroxypyrine was obtained from 2-chloro-6-hydroxypurine under milder conditions.

(13) G. B. Elion, W. H. Lange and G. H. Hitchings, THIS JOURNAL **78**, 218 (1956).

(14) G. E. Hilbert and T. B. Johnson, *ibid.*, **52**, 1154 (1930).



2-Chloro-6-hydrazinopurine (VII)[15] is obtained at room temperature and it is necessary to heat the solution of 2,6-dichloropurine in anhydrous hydrazine to 80° for 12 hours to obtain 2,6-dihydrazinopurine (III).

Attempts to prepare 2-amino-6-hydrazinopurine (VI) by the reaction of 2-chloro-6-hydrazinopurine (VII) with ammonia failed; only starting material was recovered. These findings agree with those of Adams and Whitmore[16] concerning the reactivity of the 2-chloro group of 6-N-substituted-amino-2-chloro-7-methylpurines. This compound (VI) was successfully prepared from 6-thioguanine (XII) *via* 2-amino-6-methylmercaptopurine (XI). The methylation of thioguanine with dimethyl sulfate worked well, but replacement of the 6-methylmercapto group was slow and the yield was low compared to the replacement of the 6-chloro group.

The synthesis of 6-amino-2-hydrazinopurine (X) was accomplished more readily. 2-Chloroadenine (IX) was prepared by the amination of 2,6-dichloropurine[17]; replacement of the 2-chloro group was accomplished by use of the same reaction conditions employed for the preparation of 2-hydrazinopurine and 2,6-dihydrazinopurine.

The preparation of the hydrazino analog of guanine (XIV) involved the selective hydrolysis of the 6-chlorine of 2,6-dichloropurine followed by reaction of the 2-chloro group with anhydrous hydrazine, as described for the other 2-hydrazinopurines.

The hydrolysis of 2,6-dichloropurine in 0.1 *N* acid or base is much slower than that of 6-chloropurine,[18] but proceeds readily in 1 *N* acid or base. Acid hydrolysis yields xanthine, while basic hydrolysis gives 2-chloro-6-hydroxypurine (XIII). Since XIII, when treated with hydrazine, yields the same compound (XIV) as does 6-hydroxy-2-methylmercaptopurine, this constitutes a chemical proof of structure of XIII. The ultraviolet and infrared spectra of this compound are quite similar to those of hypoxanthine and different from those of 2-hydroxypurine.

Absorption Spectra.—The effect of the hydrazino group on the ultraviolet spectrum of purine is about the same as that of the amino group. The only two comparisons available of the effect of the hydrazino group and the methylamino group (6-methylaminopurine: 6-hydrazinopurine and 6-hydroxy-2-methylaminopurine: 2-hydrazino-6-hydroxypurine) show that these two groups are also similar, as might be expected.

The hydrazino or amino group in the 6-position of the purine nucleus has only a slight effect on the position of the peak, but both groups do exert a pronounced hyperchromic effect.

In the 2-position they produce a large bathochromic effect and a slight hypsochromic effect, although in most cases the bathochromic effect of the 2-hydrazino group is less than that of the 2-amino group. Table I shows these comparisons plainly.

The extreme insolubility of the hydrazino purines in water or the common organic solvents makes the accurate determinations of molar absorbancies difficult; their instability in basic solution precludes entirely the accurate determination of their spectra at the higher *p*H.

As in the case of the ultraviolet absorption spectra, the hydrazino group and the amino group have a very similar effect on the infrared spectrum of purine. The spectra of these hydrazino and amino purines typically exhibit strong broad absorption between 3400–2900 cm.$^{-1}$ due primarily to NH vibrations and to a small extent to CH vibrations.

(15) The assignment of the structure of VII as 2-chloro-6-hydrazinopurine instead of 6-chloro-2-hydrazinopurine was made indirectly on the basis of the compound's ultraviolet and infrared spectra (see Table I and Experimental section), and on the chemical behavior of 2,6-dichloropurine in other instances, *i.e.*, the formation of 2-chloroadenine and 2-chloro-6-hydroxypurine (see Experimental).

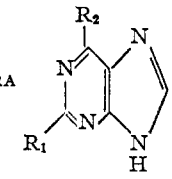
(16) R. R. Adams and F. C. Whitmore, *ibid.*, **67**, 1271 (1945).

(17) G. B. Brown, private communication.

(18) A. Bendich, P. J. Russell, Jr., and J. J. Fox, THIS JOURNAL, **76**, 6073 (1954).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA



		pH 1		pH 7	
R_1	R_2	λ_{max}, mμ	$a_M \times 10^{-3}$	λ_{max}, mμ	$a_M \times 10^{-3}$
H	H	260	6.2	263	7.95
H	HN_2	263	12.6[a]	260	13.5[b]
H	CH_3NH	267[c]	15.1[b]	266	16.2[b]
H	NH_2NH	267	13.7[d]	262	9.4
Cl	NH_2	266	12	266	12
Cl	NH_2NH	267	10.5	271	10.4
NH_2	H	314	4.1	304	6.1[b]
NH_2NH	H	297	5.0	309	4.7
NH_2	NH_2	241[e]	10.0[f]	247[g]	7.0[f]
		282	9.9	280	8.8
NH_2	NH_2NH	238[h]	8.3	240[h]	7.5
		284.5	7.6	283	7.1
NH_2NH	NH_2	267.5	10.2	263	9.85
NH_2NH	NH_2NH	275.5	7.85	272.5	6.45
NH_2	OH	247[i]	10.5[f]	246[i]	10.8[f]
				275	8.6
CH_3NH	OH	250	12.3[k]	..	..
		280	6.9	..	..
NH_2NH	OH	248	10.6	248	10.0
				271[h]	6.5

[a] R. K. Robins, K. J. Dille, C. H. Willits and B. E. Christensen, THIS JOURNAL 75, 263 (1953). [b] S. F. Mason, *J. Chem. Soc.*, 2071 (1954). [c] *p*H 2.02. [d] See footnote 6. [e] *p*H 1.97. [f] L. F. Cavalieri, A. Bendich, J. F. Tinker and G. B. Brown, THIS JOURNAL, 70, 3878 (1948). [g] *p*H 6.49. [h] Point of inflection. [i] *p*H 1.93. [j] *p*H 5.99. [k] G. B. Elion, W. H. Lange and G. H. Hitchings, THIS JOURNAL, 78, 217 (1956).

The characteristic purine absorption between 2900–2400 cm.$^{-1}$ (due to acidic NH) is present in all cases. The most useful region of the spectrum is between 1700–1500 cm.$^{-1}$. In this region absorption due to NH deformation and C=C and C=N vibrations occurs, and differentiation between 2-substituted, 6-substituted, and 2,6-disubstituted (amino or hydrazino) purines is possibly due to the different modes in which the amino (or hydrazino) group interacts with the ring vibrations when in the 2- and in the 6-position. In the 6-position either group causes splitting of the strong absorption band and two distinct peaks occur, one at 1670–1640 cm.$^{-1}$ and the other at 1605–1590 cm.$^{-1}$. In the 2-position either group interacts to give one broad band about 1650 cm.$^{-1}$. The spectra of the 2,6-disubstituted compounds resemble more closely those of the 2-substituted purines, but the peak of the one broad band in this case is found at 1600–1590 cm.$^{-1}$. All these compounds show a weak to medium absorption peak about 1460–1430 cm.$^{-1}$ and one or two weak to medium peaks 960–900 cm.$^{-1}$, the absorption in both regions being due to CH. They also show a medium to strong band at 1340–1300 cm.$^{-1}$ from C–N deformation. The principal absorption maximum of each compound is listed in the Experimental section under the preparation of the compound.

Acknowledgment.—The authors are indebted to Mr. J. P. Holmquist for the microanalytical results reported, to Mr. J. W. Murphy and Mr. J. B. McBrayer for the ultraviolet and infrared spectral determinations, and in particular to Dr. B. R. Baker for his helpful suggestions and encouragement in this work. Some of the Dumas nitrogen determinations were carried out by the Galbraith Microanalytical Laboratories, Knoxville, Tennessee.

Experimental

Spectral Data.—The ultraviolet spectra were first determined with a Beckman Model DK-2 spectrophotometer, but 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 spectrophotometer.

6-Hydrazinopurine (II).—6-Chloropurine[7,18] (5 g., 32.2 m*M*) was added in small portions with stirring to 25 ml. of anhydrous hydrazine over a period of 15–20 minutes. The solution became warm and turned purple so that it was necessary to moderate the reaction with an ice-bath. After standing for half an hour the solution deposited a large amount of fine crystals of 6-hydrazinopurine. The solid was removed by filtration and washed thoroughly with cold *n*-propyl alcohol. The yield of crude material was 4.76 g., m.p. 206–208° dec. (uncor.). Recrystallization of this material from 250 ml. of water gave 4.25 g. of white crystals, m.p. 246–247.5° dec. (cor.) (lit. 244–245°).[6] On standing the reaction mixture deposited more 6-hydrazinopurine. Purification gave 0.22 g. of additional material making the total yield 4.47 g. (92%); γ_{max} 3328 cm.$^{-1}$ (secondary NH), 3230 and 3175 cm.$^{-1}$ (NH_2), 2960 cm.$^{-1}$ (CH), 2800–2400 cm.$^{-1}$ (acidic NH), 1640 cm.$^{-1}$ (NH), 1605 cm.$^{-1}$ (C=C, C=N), 1455 cm.$^{-1}$ (CH), 1322 cm.$^{-1}$ (C–N), 942 cm.$^{-1}$ (CH).

2-Hydrazinopurine (V).—A solution of 2-chloropurine[7] (500 mg.) in 10 ml. of hydrazine was heated for 12 hours at 80°. The excess hydrazine was removed *in vacuo*. The cream-colored residue was triturated with water, removed by filtration, and dried *in vacuo* over P_2O_5 at 80°; yield 280 mg. (57.7%), m.p. >300°; γ_{max} 3265 cm.$^{-1}$ (secondary NH), 3160 cm.$^{-1}$ (NH_2), 2930 cm.$^{-1}$ (CH), 2800–2500 cm.$^{-1}$ (acidic NH), 1655, 1626 (sh) cm.$^{-1}$ (NH), 1585 and 1538 cm.$^{-1}$ (C=C, C=N), 1432 cm.$^{-1}$ (CH), 1328 cm.$^{-1}$ (C–N), 930 cm.$^{-1}$ (CH).

The ultraviolet and infrared absorption spectra of a sample recrystallized from water for analysis were essentially the same as those of the unrecrystallized material.

Anal. Calcd. for $C_5H_6N_6$: C, 40.0; H, 4.00; N, 56.0. Found: C, 40.1; H, 4.05; N, 56.4.

2,6-Dihydrazinopurine (III) (A).—A solution of 2-chloro-6-hydrazinopurine (500 mg.) in 10 ml. of anhydrous hydrazine upon heating at 80° for four hours deposited a white solid which was removed by filtration, washed with water, and dried *in vacuo* over P_2O_5; yield 175 mg., m.p. > 300°; γ_{max} 3215 cm.$^{-1}$ (secondary NH), 3140 and 3000 cm.$^{-1}$ (NH), 2920 cm.$^{-1}$ (CH), 2800–2400 cm.$^{-1}$ (acidic NH), 1650 (sh) and 1625 (sh) cm.$^{-1}$ (NH), 1600 cm.$^{-1}$ (NH and C=C, C=N), 1550 cm.$^{-1}$ (C=C, C=N), 1435 cm.$^{-1}$ (CH), 1325 cm.$^{-1}$ (C–N), 923 cm.$^{-1}$ (C–H).

Anal. Calcd. for $C_5H_8N_8$: C, 33.3; H, 4.45; N, 62.2. Found: C, 33.1; H, 4.42; N, 62.1.

The hydrazine filtrate from above was taken to dryness *in vacuo* and the residue triturated with water, filtered and dried. The yield was 25 mg., λ_{max}^{pH1} 276 mμ ($a_M \times 10^{-3}$ 7), λ_{max}^{pH7} 275 mμ ($a_M \times 10^{-3}$ 6.08). The total yield of 2,6-dihydrazinopurine was 200 mg. (41%).

(B).—2,6-Dichloropurine[7] (1 g.) was added slowly to 11 ml. of anhydrous hydrazine with intermittent cooling. After standing overnight at room temperature, the solution was heated at 80° for 12 hours. The precipitate which formed during the reaction was removed by filtration, washed with cold water, and dried *in vacuo* over P_2O_5; yield 760 mg. Another 20 mg. of product was obtained by concentration of the hydrazine filtrate from above making the total yield 780 mg. (82%). The ultraviolet and infrared spectra of this material were identical with that of the material prepared by A.

6-Amino-2-hydrazinopurine (X).—A solution of 2-chloroadenine[17] (440 mg.) in 15 ml. of anhydrous hydrazine was heated at 80° for 12 hours. The excess hydrazine was removed under reduced pressure and the resultant gray solid triturated with warm water, removed by filtration, and dried *in vacuo* over P_2O_5; yield 200 mg. (47%), m.p. >300°; γ_{max} 3300 cm.$^{-1}$ (secondary NH), 3100 cm.$^{-1}$ (NH_2), 2980 cm.$^{-1}$ (CH), 2800–2500 cm.$^{-1}$ (acidic NH), 1655 cm.$^{-1}$ (NH), 1600 and 1545 cm.$^{-1}$ (C=C, C=N), 1450 cm.$^{-1}$ (CH), 1331 cm.$^{-1}$ (C–N), 934 cm.$^{-1}$ (CH).

A small sample was recrystallized from water for analysis.

Anal. Calcd. for $C_5H_7N_7$: C, 36.40; H, 4.25; N, 59.5. Found: C, 36.2; H, 4.55; N, 60.34.

2-Chloro-6-hydrazinopurine (VII).—2,6-Dichloropurine (2.5 g.) was added to 15 ml. of anhydrous hydrazine with stirring and intermittent cooling. After standing overnight at room temperature the mixture was evaporated under reduced pressure and the solid residue boiled with 25 ml. of distilled water. The suspension was then cooled and the solid removed by filtration and dried *in vacuo* over P_2O_5; yield 1.98 g. (81%), m.p. >300°; γ_{max} 3340 cm.$^{-1}$ (secondary NH), 3250, 3100 cm.$^{-1}$ (NH), 2800–2400 cm.$^{-1}$ (acidic NH), 1665 and 1655 (sh) cm.$^{-1}$ (NH), 1605 cm.$^{-1}$ (C=C, C=N), 1450 cm.$^{-1}$ (CH), 1305 cm.$^{-1}$ (CN), 925 cm.$^{-1}$ (CH).

The ultraviolet and infrared spectra of a small sample recrystallized from water for analysis were practically unchanged.

Anal. Calcd. for $C_5H_5ClN_6$: C, 32.50; H, 2.75; Cl, 19.25. Found: C, 32.6; H, 2.87; Cl, 19.4.

2-Chloro-6-hydroxypurine (XIII).—A solution of 2,6-dichloropurine (500 mg.) in 25 ml. of 1 *N* sodium hydroxide was refluxed for one hour, cooled, neutralized with acetic acid, and allowed to stand in a refrigerator overnight. The light yellow crystals were removed by filtration, washed with ice water, and dried *in vacuo* over P_2O_5; yield of almost pure material, 300 mg. (66%), m.p. >300°.

A small sample was recrystallized from water for analysis; λ_{max}^{pH1} 250 mμ ($a_M \times 10^{-3}$ 11.2), λ_{max}^{pH7} 259 mμ ($a_M \times 10^{-3}$ 10.1), λ_{max}^{pH13} 265 mμ ($a_M \times 10^{-3}$ 11.6); γ_{max} 3020 cm.$^{-1}$ (NH), 2900 cm.$^{-1}$ (CH), 2800–2300 cm.$^{-1}$ (acidic H), 1680 cm.$^{-1}$ (C=O), 1562, 1530 (sh) cm.$^{-1}$ (C=C, C=N), 950 cm.$^{-1}$ (CH).

Anal. Calcd. for $C_6H_3ClN_4O$: C, 35.20; H, 1.76; N, 32.82. Found: C, 35.4; H, 1.93; N, 32.65.

2-Hydrazino-6-hydroxypurine (XIV) (A).—A solution of 6-hydroxy-2-methylmercaptopurine[18] (720 mg.) in 10 ml. of anhydrous hydrazine was refluxed for 20 hours, cooled, and the excess hydrazine removed at reduced pressure. The gray residue was triturated with water, removed by filtration, and dried *in vacuo* over P_2O_5; yield of almost pure material, 200 mg. (30%). A small sample of this material was recrystallized from water for analysis, m.p. >300°; γ_{max} 3305 cm.$^{-1}$ (secondary NH), 3160 cm.$^{-1}$ (NH), 3000 cm.$^{-1}$ (CH), 2800–2300 cm.$^{-1}$ (acidic NH), 1665 cm.$^{-1}$ (NH and C=O), 1600, 1590 (sh), 1537 (sh) cm.$^{-1}$ (C=C, C=N), 1455 cm.$^{-1}$ (CH), 1308 cm.$^{-1}$ (CN), 942 cm.$^{-1}$ (CH).

Anal. Calcd. for $C_5H_6N_6O$: C, 36.2; H, 3.62. Found: C, 36.4; H, 4.17.

(B).—A solution of 2-chloro-6-hydroxypurine (3.5 g.) in 25 ml. of anhydrous hydrazine was heated at 80° for 14 hours, cooled, and the product isolated as described in Method A above; yield of almost pure material, 3.1 g. (91%); the ultraviolet and infrared spectra were identical with that of the material obtained by Method A above.

A 100-mg. sample was recrystallized from 200 ml. of water and dried over P_2O_5 *in vacuo* at 110°; yield 65 mg.

Anal. Calcd. for $C_5H_6N_6O$: C, 36.2; H, 3.62; N, 50.60. Found: C, 36.25; H, 4.13; N, 50.05.

2-Amino-6-methylmercaptopurine (XI).—Thioguanine[19] (5 g., 30 m*M*) was dissolved with heating in 253 ml. of 0.115 *N* sodium hydroxide (30 m*M*). This solution was cooled to 30–40° and dimethyl sulfate (3.79 g., 2.8 ml., 30 m*M*) added dropwise with stirring. After stirring the mixture for another hour, the material which had precipitated was removed by filtration and dried. The yield of almost pure material was 3.5 g., m.p. 239–239.5°; λ_{max}^{pH1} 241, 272, 318 mμ ($a_M \times 10^{-3}$ 6.72, 9.6, 12.4), λ_{max}^{pH7} 242, 310 mμ ($a_M \times 10^{-3}$ 12.1, 10.6), λ_{max}^{pH13} 227, 314 mμ ($a_M \times 10^{-3}$ 19.9, 10.3). An additional gram of material, m.p. 239–240°, was obtained by concentration of the mother liquor.

A small sample of the material was recrystallized from water and dried *in vacuo* at 80–100° for about 6 hours, m.p. 239.5–240°; λ_{max}^{pH1} 241, 273, 317 mμ ($a_M \times 10^{-3}$ 7.0, 10, 13), λ_{max}^{pH7} 242, 309 mμ ($a_M \times 10^{-3}$ 12.7, 11.0), λ_{max}^{pH13} 228, 313 mμ ($a_M \times 10^{-3}$ 20.2, 10.6); γ_{max} 3350–3050 cm.$^{-1}$ (NH), 2960 cm.$^{-1}$ (CH_3), 2800–2400 cm.$^{-1}$ (acidic NH), 1635 (sh) cm.$^{-1}$ (NH), 1600 and 1556 cm.$^{-1}$ (C=C, C=N), 1450 cm.$^{-1}$ (CH), 1308 cm.$^{-1}$ (C–N), 911 cm.$^{-1}$ (CH).

Anal. Calcd. for $C_6H_7N_5S$: C, 39.8; H, 3.86. Found: C, 39.8; H, 3.91.

2-Amino-6-hydrazinopurine (X).—A solution of 2-amino-6-methylmercaptopurine (505 mg.) in 10 ml. of anhydrous hydrazine was refluxed for 12 hours. Most of the excess hydrazine was removed under reduced pressure and 10 ml. of *n*-propanol added to the residue. The resultant gray solid was removed by filtration, triturated with boiling water, again collected by filtration and dried *in vacuo* over P_2O_5 at 100° for 3 hours; yield of almost pure material, 310 mg. (67%). A small amount of this material was recrystallized from water for analysis and dried *in vacuo* over P_2O_5 for 3 hours at 100°, m.p. >300°; γ_{max} 3345 cm.$^{-1}$ (secondary NH), 3250 and 3140 cm.$^{-1}$ (NH), 2930 cm.$^{-1}$ (CH), 2800–2500 cm.$^{-1}$ (acidic NH), 1645 (sh) and 1625 (sh) cm.$^{-1}$ (NH and C=C, C=N), 1590 cm.$^{-1}$ (C=C, C=N), 1436 cm.$^{-1}$ (CH), 1332 cm.$^{-1}$ (C–N), 930 cm.$^{-1}$ (CH).

Anal. Calcd. for $C_5H_7N_7$: C, 36.38; H, 4.23; N, 59.5. Found: C, 36.05; H, 4.29; N, 59.2.

(19) Francis Earle Laboratories.

BIRMINGHAM 5, ALABAMA

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

Synthesis of Potential Anticancer Agents. IV. 4-Nitro- and 4-Amino-5-imidazole Sulfones

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A number of 4-nitro- and 4-amino-5-imidazole sulfones have been prepared as potential antagonists of 4-amino-5-imidazolecarboxamide. Attempts to prepare 4-amino-5-imidazolesulfonamide by several methods were unsuccessful. A convenient preparation of 4-acetamidoimidazole is described.

The synthesis of compounds designed to interfere with purine metabolism has been the subject of considerable recent literature.[2] Most of the com-

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(2) G. B. Brown, in "Antimetabolites and Cancer," edited by C. P. Rhoads, American Association for the Advancement of Science, Washington, D. C., 1955, p. 285.