nickel (about 30 g.).[17] Warm water (100 ml.) was added and the mixture was distilled with steam. About 200 ml. of distillate was collected. This distillate was diluted to 500 ml. with water and potassium chloride (30 g.) was added. The product was extracted with petroleum ether (b.p. 30–60°) and dried ($MgSO_4$). The solvent was distilled until a 1- to 2-ml. residue remained in the distillation flask.

A sample of this residue was analyzed in a Perkin-Elmer vapor phase chromatograph using a diisodecyl phthalate column set at 148°, and a carrier gas (helium) flow rate of 8.5. The spectrum showed the presence of 5 components (other than solvent peaks). Four of the components were present in 1% or less concentration (not identified) and the major component was shown to be *n*-butylbenzene by the addition of authentic *n*-butylbenzene to a second sample. The calculated yield of *n*-butylbenzene was 0.42 g. (72.5%).

Degradation of the Mixture of 2-Dichloromethyl-2H-1-benzothiopyran (II) and 4-Dichloromethyl-4H-1-benzothiopyran (III).—A mixture of II and III (1.09 g., 0.00472 mole) was treated with Raney nickel by a procedure identical with that described above. Chromatographic analysis of the product showed 8 components, 6 of which were present in 1% or less concentration and not identified. The two major components were identified as *n*-butylbenzene and *sec*-butylbenzene (by the addition of knowns to separate samples). The calculated yields of *n*-butyl and *sec*-butylbenzene were 0.234 g. (37%) and 0.256 g. (40.5%), respectively thus indicating an approximately equal distribution of dichloromethyl derivatives in the starting mixture.

The nuclear magnetic resonance spectrum of the mixture of II and III indicated that the ratio (II/III) was approximately 4/6.

Reaction of 4H-1-Benzothiopyran (IX) with Dichlorocarbene. (A) Ethyl Trichloroacetate–Sodium Methoxide Method.—The procedure used was identical with that described for 2H-1-benzothiopyran. Ethyl trichloroacetate (38.78 g., 0.202 mole) was added to a mixture of 4H-1-benzothiopyran (15.48 g., 0.105 mole) in petroleum ether (b.p. 30–60°) and sodium methoxide (11 g., 0.204 mole). The product was processed as previously described and 1,1-dichlorocyclopropa[b][1]benzothiopyran (IV) (20.52 g., 84.9%) was obtained by distillation, b.p. 100–105° (0.06–0.08 mm.), $n^{52}D$ 1.6211. A sample, redistilled for analysis, was collected at 101° (0.2 mm.), $n^{52}D$ 1.6213; infrared spectrum (neat): 3075m, 3025m, 2980m, 2940w, 2860w, 1958w, 1918w, 1822w, 1800w, 1749w, 1627w, 1598m, 1582m, shoulder 1488s, 1479s, 1460s, 1445s, 1359w, 1338w, 1293w, 1278m, 1260s, 1227s, 1206m, 1167w, 1135m, 1096m, 1076s, 1070m, 1045s, shoulder 1008s, 984w, 956m, 938m, 921s, 874m, 857s, broad 810s, broad 755s, 721w, 687m.

The nuclear magnetic resonance spectrum of this product showed the following peaks: 2.94 τ, a singlet, weight 4.00, assigned to the aromatic hydrogens; 6.79 and 7.09 τ, doublets, weight 2.39, assigned to the C-7 hydrogens[18]; 7.42 τ, a doublet, weight 0.77 assigned to the C-9 hydrogen; 7.88 τ, a complex multiplet, weight 1.62, assigned to the C-8 hydrogen.

The ultraviolet spectrum showed $\lambda_{max}^{95\% EtOH}$ 241 mμ (shoulder) (log ε 3.691), 255 mμ (log ε 3.813).

Anal. Calcd. for $C_{10}H_8Cl_2S$: C, 51.96; H, 3.49. Found: C, 51.76; H, 3.91.

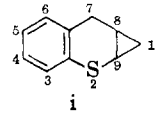
(B) Sodium Trichloroacetate Method.—The procedure used was identical with that described for 2H-1-benzothiopyran. A mixture of 4H-1-benzothiopyran (15.33 g., 0.104 mole), sodium trichloroacetate (38.6 g., 0.208 mole) and 1,2-dimethoxyethane (100 ml.) was refluxed for 22 hours. The product was distilled and 1,1-dichlorocyclopropa[b][1]benzothiopyran (5.76 g., 24.1%) was obtained, b.p. 102–118° (0.3 mm.), $n^{25}D$ 1.6225. A pure sample, b.p. 94–96° (0.07 mm.), $n^{25}D$ 1.6234, was obtained by redistillation of the crude material.

The spectra (infrared, n.m.r., ultraviolet) of this material were identical with those of the material prepared by the ethyl trichloroacetate–sodium methoxide procedure.

Attempted Ring Expansion of 1,1-Dichlorocyclopropa[b][1]benzothiopyran (IV) with Quinoline.—A solution of 1,1-dichlorocyclopropa[b][1]benzothiopyran (4.33 g., 0.0187 mole) and quinoline (4.86 g.) was heated to reflux in an atmosphere of nitrogen. Soon after refluxing had started, the odor of hydrogen sulfide was apparent. After 15 minutes of refluxing, the reaction was cooled and ether and water were added. The layers were separated and the ether layer was extracted with water and 10% hydrochloric acid solution. The ether was dried ($MgSO_4$) and evaporated. The dark red solid which remained was chromatographed on alumina using petroleum ether (b.p. 30–60°) as eluent. Crude 2-chloronaphthalene (m.p. 56–58°, 1.11 g., 36.4%) was obtained. After recrystallization from ethanol–water, the product (0.82 g., 26.9%) melted at 57–58°. A mixture m.p. with authentic material was undepressed.

(17) R. Mozingo, *et al.*, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

(18) The numbering system (Patterson, "Ring Index," 2nd Edition, p. 275) refers to i.



i

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ARIZONA STATE UNIVERSITY, TEMPE, ARIZ.]

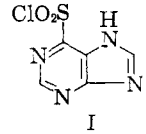
Potential Purine Antagonists. XXVII. Synthesis and Reactions of Some Purinesulfonyl Fluorides[1]

BY ALDEN G. BEAMAN AND ROLAND K. ROBINS

RECEIVED APRIL 6, 1961

The introduction of the fluorosulfonyl group has been accomplished for the first time in a nitrogen heterocyclic system. The appropriate heterocyclic thiol upon oxidation with chlorine in the presence of potassium fluoride and hydrofluoric acid affords the desired compound. Thus, the synthesis of purine-6-sulfonyl fluoride (III) has been accomplished from 6-purinethiol (6-mercaptopurine). This reaction is also successful in the presence of other groups on the heterocyclic ring. The reactivity of the fluorosulfonyl group at various positions in the purine ring has been studied. A number of interesting and previously inaccessible purinesulfonamide derivatives have been prepared from the corresponding purinesulfonyl fluorides.

Very few organic sulfonyl fluorides have been reported,[2] and the fluorosulfonyl group has not previously been introduced into heterocyclic compounds. In the oxidation of a mercaptopurine[3] with chlorine gas a probable reactive intermediate may be the sulfonyl chloride, such as I. Thus, Roblin and Clapp[4] isolated several chlorosulfonylpyri-



I

(1) Supported by Research Contract No. SA-43-ph-1928 with the Cancer Chemotherapy National Service Center of the National Cancer Institute, National Institutes of Health, Public Health Service.

(2) See Friedrich Muth in Houben-Weyl, "Methoden der Organischen Chemie," edited by Eugen Müller, Vol. 9, p. 561, Georg Thieme Verlag, Stuttgart, 4th edition, 1955 (Literature covered until 1955).

(3) R. K. Robins, *J. Org. Chem.*, **26**, 447 (1961).

(4) R. O. Roblin, Jr., and J. W. Clapp, *J. Am. Chem. Soc.*, **72**, 4890 (1950).

midines by this general method. No stable chlorosulfonylpurines have as yet been isolated. In this instance the highly reactive chlorosulfonyl group is replaced by chloride ion under the reaction conditions or hydrolyzed to the sulfonic acid.[3] Stable sulfonyl chlorides may be converted to the corresponding sulfonyl fluorides by the action of potassium fluoride or, preferably, potassium bifluoride.[2] It has been found that in general sulfonyl fluorides are considerably more stable than sulfonyl chlorides.[2] Applying the above considerations it has been possible to devise a new and novel reaction whereby mercaptopurines can be converted directly into purinesulfonyl fluorides. Thus, when a suspension of a simple or substituted purinethiol in methanol, aqueous hydrofluoric acid and potassium fluoride is treated with chlorine gas at 0°, the corresponding purinesulfonyl fluoride is obtained in excellent yield (reaction Schemes I and II). The hydrofluoric acid–potassium fluoride mixture is not only an excellent reagent for the conversion of the chlorosulfonyl group to the fluorosulfonyl, but it also provides a buffered reaction medium in which it keeps the acidity low and prevents acid-catalyzed nucleophilic replacement of the entire chlorosulfonyl group. This proposed function of the fluoride is supported by obtaining from purine-2,6-dithiol (X) either 6-chloropurine-2-sulfonyl fluoride (XI) (displacement at the more reactive[5] 6-position) or purine-2,6-disulfonyl fluoride (XV) by using a greater amount of potassium fluoride (reaction Scheme I). In a hydrochloric acid medium 2,6-dichloropurine is formed.[6]

When 6-purinethiol (II) was suspended in a mixture of methanol, aqueous hydrofluoric acid and potassium fluoride and treated with chlorine gas near 0°, purine-6-sulfonyl fluoride (III) was formed in about 90% yield (reaction Scheme I). Similarly, 2-purinethiol (VI)[7] gave purine-2-sulfonyl fluoride (VII) in 95% yield.

Recently Ham, *et al.*,[8] made assignments of the symmetric and antisymmetric SO_2 stretching frequencies and the S–F stretching frequency in methanesulfonyl fluoride and benzenesulfonyl fluoride. The infrared spectrum of purine-6-sulfonyl fluoride possesses very strong bands in the regions assigned by Ham to the SO_2 and S–F frequencies (Table I). In the spectrum of purine-6-sulfonyl fluoride the band at 813 cm.$^{-1}$ is very strong and characteristic of the fluorosulfonyl group.

TABLE I

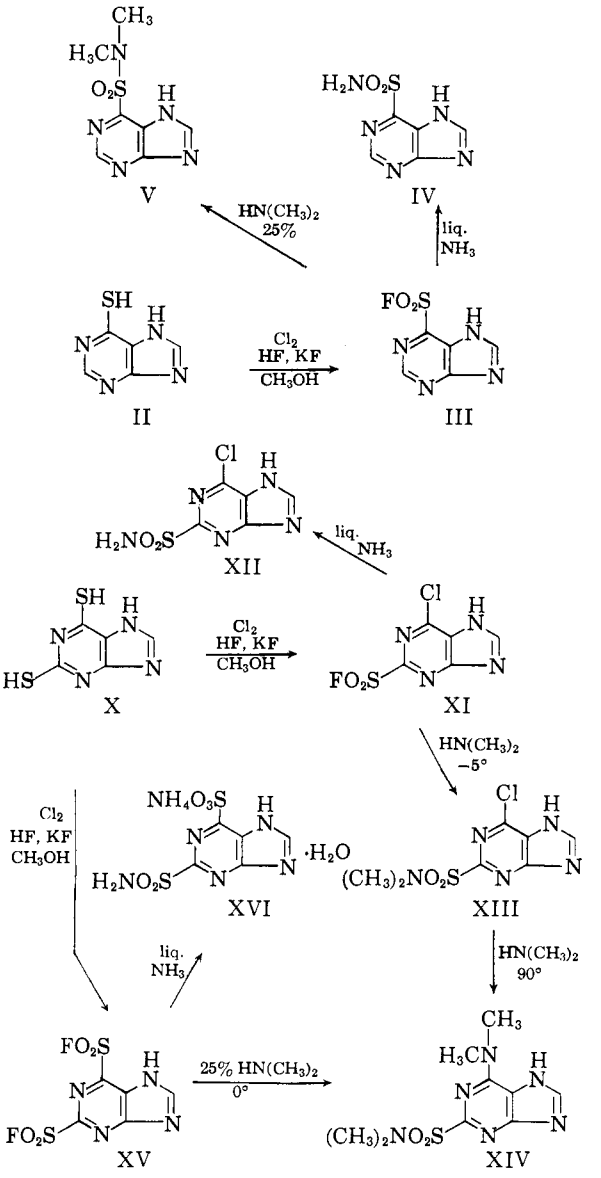
INFRARED FREQUENCIES AND VIBRATIONAL ASSIGNMENTS FOR SOME SULFONYL FLUORIDES

Compound	Sym. SO_2 stretch, cm.$^{-1}$	Antisym. SO_2 stretch, cm.$^{-1}$	S–F stretch, cm.$^{-1}$
CH_3SO_2F[a]	1214v.s.	1426s.; 1402v.s.[b]	815s.
$C_6H_5SO_2F$[a]	1213v.s.	1412v.s.	779v.s.
Purine-6-SO_2F	1250v.s.	1450v.s.	813v.s.

[a] Data from ref. 8. [b] Two bands from Fermi resonance between C–H antisym. deformation and SO_2 antisym. stretch, av. 1414 cm.$^{-1}$.

(5) E. Fischer, *Ber.*, **30**, 2227 (1897).
(6) Observations of the authors, to be published.
(7) R. K. Robins, K. J. Dille, C. H. Willits and B. E. Christensen, *J. Am. Chem. Soc.*, **75**, 263 (1953).
(8) N. S. Ham, A. N. Hambly and R. H. **Laby**, ***Australian***, *J. Chem.*, **13**, 443 (1960).

The fluorosulfonyl group is rather reactive and especially useful for the preparation of purinesulfonamides, a type of compound hitherto unreported. Thus, treatment of purine-6-sulfonyl



REACTION SCHEME I

fluoride (III) with liquid ammonia gave purine-6-sulfonamide (IV) in 85 to 90% yield. Treatment of purine-6-sulfonyl fluoride with cold 25% aqueous dimethylamine gave purine-6-(N,N-dimethyl)-sulfonamide (V). Purine-6-(N-methyl)-sulfonamide (XXVIII) and purine-6-(N-ethyl)-sulfonamide (XXIX) were obtained similarly from III and cold aqueous methylamine and ethylamine, respectively. Purine-2-sulfonyl fluoride (VII) gave the corresponding sulfonamide VIII with either liquid ammonia or with cold concentrated aqueous ammonia. With cold 25% aqueous dimethylamine, VII gave purine-2-(N,N-dimethyl)-sulfonamide (IX).

6-Chloropurine-2-sulfonyl fluoride (XI) with liquid ammonia gave 6-chloropurine-2-sulfonamide

(XII) (reaction Scheme I). When 6-chloropurine-2-sulfonyl fluoride was treated with 25% aqueous dimethylamine below 0°, and the solution was heated to 90°, 6-dimethylaminopurine-2-(N,N-dimethyl)-sulfonamide (XIV) was obtained. When XI was treated with aqueous dimethylamine below 0°, the chief product was 6-chloropurine-2-(N,N-dimethyl)-sulfonamide (XIII). Purine-2,6-disulfonyl fluoride (XV), when treated with 25% aqueous dimethylamine below 0°, gave only 6-dimethylaminopurine - 2 - (N,N - dimethyl) - sulfonamide (XIV) which was identical with that obtained from 6-chloropurine-2-sulfonyl fluoride (XI) and dimethylamine at 90°. This indicates that the oxidized sulfur group is more readily replaced than the 6-chloro atom. Treatment of purine-2,6-disulfonyl fluoride (XV) with liquid ammonia gave a compound, $C_5H_{10}N_6O_6S_2$, which was considerably more water soluble than the other sulfonamidopurines investigated and was assigned structure XVI.

The fluorosulfonyl group is interesting from a chemical point of view because it may react in two different ways. Under mild conditions the sulfur–fluorine bond is ruptured as in the formation of the purinesulfonamides and the purinesulfonic acids (or their salts). Under more vigorous conditions the carbon–sulfur bond is cleaved, and the entire oxidized sulfur group is replaced. Thus, although purine-6-sulfonyl fluoride (III) and liquid ammonia gave purine-6-sulfonamide (IV), upon heating with concentrated aqueous ammonia at 100° in a sealed tube for three hours III gave adenine. It is interesting to note in this connection that 6-chloropurine is unchanged under these conditions.[9] Upon storage, certain samples of fluorosulfonylpurines lost sulfur dioxide, especially when crude. The possible utilization of this property of fluorosulfonylpurines for the synthesis of fluoropurines is currently under investigation.

Ultraviolet absorption data for several purinesulfonyl fluorides and purinesulfonamides are given in Tables II and III, respectively.

TABLE II

ULTRAVIOLET ABSORPTION OF CERTAIN PURINESULFONYL FLUORIDES

	Methanol		pH 1		pH 11[a]	
Fluoride	λ_{max}, mμ	ε	λ_{max}, mμ	ε	λ_{max}, mμ	ε
Purine-6-sulfonyl	283	8000	283	8600	281	8,600
Purine-2-sulfonyl	268	7700	267	8400	275	7,500
Purine-2,6-disulfonyl	285	6700	278[b]	9600	283	7,800
6-Chloropurine-2-sulfonyl	270	8800	270	9300	277	7,800
6-Hydroxypurine-2-sulfonyl	..	..	263[b]	8800	252	10,100

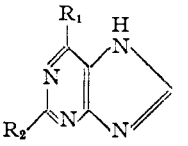
[a] All pH 11 data are for the corresponding sulfonic acids. [b] In these cases the samples were first dissolved in cold 1 *N* NaOH; thus, the data are for the corresponding sulfonic acids.

A comparison of the stability of purine-6-sulfonyl fluoride and purine-2-sulfonyl fluoride toward acid and base was made utilizing a recording ultraviolet spectrophotometer (see Table IV). A similar comparison of the stabilities of purine-6-sulfonamide and purine-2-sulfonamide also was made (see Table V).

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

TABLE III

ULTRAVIOLET ABSORPTION OF SOME PURINESULFONAMIDES



R_1	R_2	pH 1 λ_{max} mμ	pH 1 ε	pH 11 λ_{max}, mμ	pH 11 ε
SO_2NH_2	H	276	9,700	283	9,400
$SO_2N(CH_3)_2$	H	280	9,400	285	7,200
SO_2NHCH_3	H	279	9,700	284	8,700
$SO_2NHC_2H_5$	H	280	10,100	285	8,400
H	SO_2NH_2	267	9,400	278	7,900
H	$SO_2N(CH_3)_2$	269	10,500	277	8,100
Cl	SO_2NH_2	269	9,600	280	8,300
Cl	$SO_2N(CH_3)_2$	272	11,300	279	8,900
NH_2	SO_2NH_2	265	12,700	271	11,800
$N(CH_3)_2$	$SO_2N(CH_3)_2$	280	14,100	280	13,200
OH	SO_2NH_2	253	9,000	263	9,700
OH	$SO_2N(CH_3)_2$	250	10,400	263	8,500
SH	SO_2NH_2	326	18,400	244	17,500
				313	17,400
SO_2ONH_4	SO_2NH_2	278	9,500	288	7,800

6-Chloropurine-2-sulfonyl fluoride (XI) was found to be a very versatile intermediate from which a large variety of substituted sulfonamidopurines could be prepared. Its reactivity also permitted a conclusive proof of its structure which was initially believed to be XI rather than the isomeric 2-chloropurine-6-sulfonyl fluoride because the 6-position in purines is more reactive toward nucleophilic displacement than the 2-position,[5] and therefore it was considered more likely that chloride ion replaced an oxidized sulfur radical at position 6 rather than at position 2. When 6-chloropurine-2-sulfonamide (XII) was boiled at 60–93° with aqueous ammonia solution, into which was bubbled ammonia gas, 6-aminopurine-2-sulfonamide (XIX) gradually crystallized from the hot solution. The latter compound (XIX) also was synthesized by an unambiguous route (reaction Scheme II). 6-Amino-2-purinethiol (XVII)[10,11] upon oxidation with chlorine at 0° in the presence of methanol, aqueous hydrofluoric acid, and potassium fluoride gave 6-aminopurine-2-sulfonyl fluoride (XVIII). With liquid ammonia, crude XVIII gave 6-aminopurine-2-sulfonamide (XIX) which had the same ultraviolet and infrared curves and the same R_f value in four solvent systems as XIX prepared from 6-chloropurine-2-sulfonamide, thus establishing that the chlorine atom in 6-chloropurine-2-sulfonyl fluoride is at position 6.

6-Hydroxy-2-purinethiol (XX)[12] similarly gave 6-hydroxypurine-2-sulfonyl fluoride (XXI), which was treated with liquid ammonia to yield 6-hydroxypurine-2-sulfonamide (XXII). Aqueous dimethylamine and XXI gave 6-hydroxypurine-2-(N,N-dimethyl)-sulfonamide (XXIII). 6-Chloro-

(10) A. Bendich, J. F. Tinker and G. B. Brown, *ibid.*, **70**, 3109 (1948).

(11) W. Traube, *Ann.*, **331**, 64 (1904).

(12) A. G. Beaman, *J. Am. Chem. Soc.*, **76**, 5633 (1954).

TABLE IV

RELATIVE STABILITY OF PURINE-6-SO_2F (III) AND PURINE-2-SO_2F (VII)

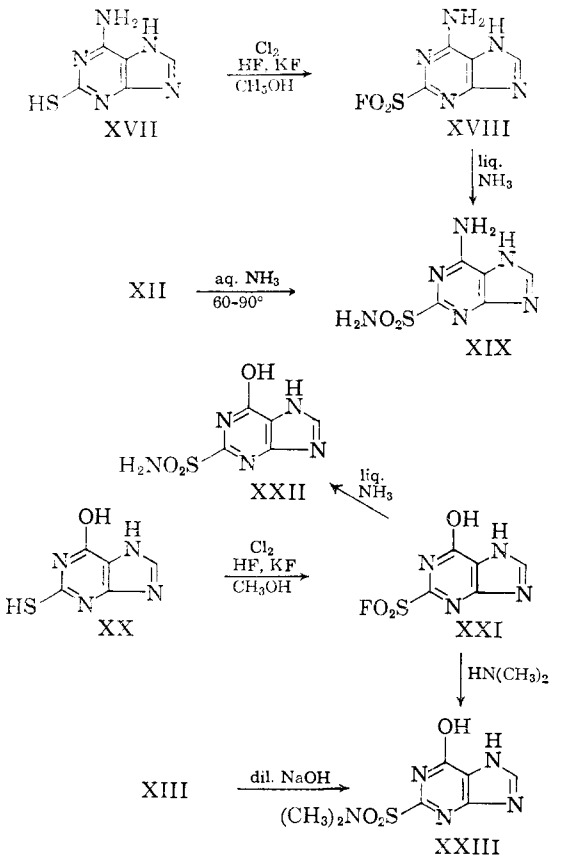
Treatment	Product from III	Product from VII
Dissolve 1 *N* HCl r.t.	Unchanged	Unchanged
Dissolve 0.01 *N* NaOH r.t.	Na^+ salt of purine-6-sulfonic acid	Na^+ salt of purine-2-sulfonic acid
Dissolve concd. aq. NH_3 r.t.	Purine-6-sulfonamide + purine-6-sulfonic acid NH_4^+ salt	Purine-2-sulfonamide
Heat 100° in dist. H_2O 10 min., concn., 10 mg./l.	Purine-6-sulfonic acid	Unchanged
Heat 100° in dist. H_2O 15 min., concn. 10 g./l.	Hypoxanthine	.....
Heat 100° in 0.01 *N* HCl 20 min., concn. 10 mg./l.	Hypoxanthine	Purine-2-sulfonic acid
Heat 100° in 1 *N* HCl 25 min., concn. 1 g./l.	Hypoxanthine	Purine-2-sulfonic acid + a small amt. 2-hydroxypurine
Heat 100° in 1 *N* NaOH 10 min., concn. 1 g./l.	Na^+ salt of purine-6-sulfonic acid + about 10% hypoxanthine	Na^+ salt of purine-2-sulfonic acid

TABLE V

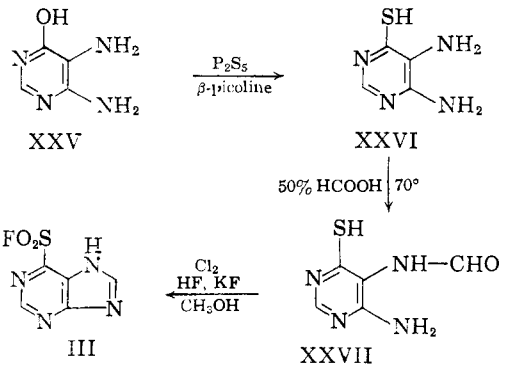
RELATIVE STABILITY OF PURINE-6-SO_2NH_2 (IV) AND PURINE-2-SO_2NH_2 (VIII)

Treatment	Product from IV	Product from VIII
Heat 100° in dist. H_2O 50 min., concn. 20 g./l.	NH_4^+ salt of purine-6-sulfonic acid	Unchanged
Heat 100° in 1 *N* HCl 20 min.	Hypoxanthine	Unchanged
Heat 100° in 1 *N* NaOH 20 min.	Partial conversion to Na^+ salt of purine-6-sulfonic acid	Unchanged
Boil in concd. aq. NH_3 15 min.	Partial conversion to NH_4^+ salt of purine-6-sulfonic acid	Unchanged

purine-2-(N,N-dimethyl)-sulfonamide (XIII) upon boiling with dilute sodium hydroxide solution gave a poor yield of 6-hydroxypurine-2-(N,N-dimethyl)-sulfonamide, identical (as judged by ultraviolet and infrared absorption spectra and R_f value in three solvent systems) with that obtained from 6-hydroxypurine-2-sulfonyl fluoride. When 6-chloropurine-2-sulfonamide (XII) was boiled briefly with an aqueous solution of 2 moles of sodium hydrosulfide, a 48% yield of 6-purinethiol-2-sulfonamide (XXIV) was obtained along with 21% of purine-2,6-dithiol (X), showing that under certain conditions the 2-sulfonamido group also is replaced quite readily.



REACTION SCHEME II



REACTION SCHEME III

An efficient alternate synthesis of purine-6-sulfonyl fluoride (III) (and consequently also of the sulfonamides derived therefrom) which does not involve the use of 6-purinethiol was discovered (reaction Scheme III). Thus, when 4-amino-5-formylamino-6-pyrimidinethiol (XXVII)[13] was suspended in a solution of methanol, aqueous hydrofluoric acid and potassium fluoride and treated with chlorine gas at about 0°, III was obtained directly. Since 4,5-diamino-6-pyrimidinethiol (XXVI) (the immediate precursor of XXVII) previously has been prepared by a tedious route,[14] a new synthesis of this compound was developed in order to make the new synthetic route to III of preparative value. It was found that the readily available 4,5-diamino-6-hydroxypyrimidine (XXV)[15] could be thiated directly to XXVI with phosphorus pentasulfide,

(13) G. B. Elion, W. H. Lange and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 2858 (1956).

(14) A. Albert, D. J. Brown and H. C. S. Wood, *J. Chem. Soc.*, 3832 (1954); G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **76**, 4027 (1954).

(15) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

TABLE VI

SYNTHESIS OF PURINESULFONYL FLUORIDES

Purine sulfonyl fluoride	Starting material	Wt. s.m., g.	Crude yield, %	Recrystn. solvent	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Fluorine, % Calcd.	Fluorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
III	XXVII	7.0	65	Methanol		29.7	29.6	1.5	1.6	9.4	9.7	27.7	27.7	15.9	15.5
VII	VI	40.0	96	Methanol	178–179	29.7	29.7	1.5	1.6	9.4	9.6	27.7	27.4	15.9	15.5
XV	X	30.1	59	None	182 d.	21.1	21.5	0.7	1.0	13.4	13.2	19.7	20.3	22.6	22.4
XXI	XX	200.0	94	None						8.7	9.0			14.7	14.7
XVIII	XVII	5.0	78	The crude material was used at once as an intermediate without purification											

provided that a higher boiling pyridine derivative, such as β-picoline, were used as a reaction solvent instead of pyridine.

The essential data for the synthesis of some purinesulfonyl fluorides and purinesulfonamides (not given in detail in the Experimental section) are presented in Tables VI and VII, respectively.

Other reactions of the purinesulfonyl fluorides are currently under investigation. In preliminary antitumor testing against Adenocarcinoma 755 in the mouse, purine-6-sulfonamide (IV) and the purine-6-N-alkylsulfonamides V, XXVIII and XXIX exhibit complete tumor inhibition at dosages of approximately 75 mg./kg. per day. Purine-6-sulfonyl fluoride (III) and 6-chloropurine-2-sulfonyl fluoride (IX) have shown significant tumor inhibition at one dosage level, although these latter compounds are somewhat toxic. The complete testing results of these and related derivatives will be reported elsewhere at a later date.

Experimental[16]

6-Purinethiol (6-Mercaptopurine) (II).—The large quantities of 6-purinethiol required for these studies led to an improved synthesis from hypoxanthine using pyridine as a reaction solvent. The previously reported synthesis of 6-purinethiol[17] from hypoxanthine by thiation in tetralin gives a mixture of product and unreacted starting material and is not practical for large-scale synthesis.

Pyridine (8 l.) was heated to 65–70°, and, with stirring, 2600 g. of phosphorus pentasulfide was added in portions. Then 1500 g. of synthetic hypoxanthine was added in portions. The mixture was refluxed and stirred for 3 hr. The excess pyridine was distilled under vacuum. The hot sirup was poured slowly with stirring into 15 l. of boiling water. The resulting solution was stirred and boiled for 1 hr.; then ice was added until a small amount remained unmelted. After 2 hr. at 0° the solid was filtered and washed with water. The moist crude solid was reprecipitated twice from solution in hot dilute NH_3 (charcoal) with acetic acid to give 1200 g. (64% yield) of pale-yellow crystalline 6-purinethiol monohydrate of excellent purity based on the characteristic ultraviolet absorption spectrum of this compound.[17]

Purine-6-sulfonyl Fluoride (III).—To a polyethylene beaker, cooled in an ice–salt-bath, were added 500 ml. of methanol, 750 ml. of 49% HF and 750 g. of $KF \cdot 2H_2O$. The solution was cooled to 15°, and 125 g. of 6-purinethiol was added. The mixture was cooled to 0°, and with stirring a fast stream of chlorine gas was bubbled into the reaction mixture. The rate of chlorine introduction was adjusted so that a reaction temp. of −2 to +3° was maintained. At no time should the reaction temp. exceed 5°. The time required for the reaction was 3 to 6 hr. The end of the reaction was indicated by a drop in the reaction temp. while the rate of chlorine introduction and the efficiency of cooling were held constant. This was checked by removing the chlorine inlet tube for 5 min. and placing a drop of the reaction mixture on *p*H "Hydrion" paper. If the reaction was complete, excess chlorine present bleached the paper in a few seconds. The reaction mixture was poured slowly with stirring onto 4 kg. of crushed ice. The mixture was stirred for 5 min. (excess ice must always be present), and the pale-yellow solid was collected, washed very thoroughly with ice-cold water, pressed dry, and air-dried without external heat. The thorough washing was essential in order to remove all traces of acid. The crude yield was 129–138 g. (87–93%). This material was sufficiently pure for use in the synthesis of sulfonamides. Crude purine-6-sulfonyl fluoride may be recrystallized from boiling absolute ethanol (charcoal) to give snow-white crystals with a recovery of about 65%. Although crude samples of purine-6-sulfonyl fluoride lost SO_2 on standing, a pure sample gave correct analyses after 1 yr.

Anal. Calcd. for $C_5H_3FN_4O_2S$: C, 29.7; H, 1.5; F, 9.4; N, 27.7; S, 15.9. Found: C, 30.2; H, 1.9; F, 9.3; N, 27.7; S, 15.9.

Purine-2-sulfonyl fluoride (VII), purine-2,6-disulfonyl fluoride (XV), 6-aminopurine-2-sulfonyl fluoride (XVIII), and 6-hydroxypurine-2-sulfonyl fluoride (XXI) were prepared by the general method employed for the synthesis of purine-6-sulfonyl fluoride. Details are given in Table VI.

2,6-Purinedithiol (X).—The method of Beaman[12] for the synthesis of 2,6-purinedithiol proved impractical for large-scale runs. The present method is a large-scale adaptation of the procedure of Dille and Christensen[18] which recently has become of significant importance by the ready availability of 4,5-diamino-2,6-pyrimidinedithiol.[19]

Pyridine (7.5 l.) was heated to 75–80°, and 3400 g. of phosphorus pentasulfide was added in portions. Then 1700 g. of 4,5-diamino-6-hydroxy-2-pyrimidinethiol[12] was added slowly in small portions. The reaction mixture was refluxed with stirring for 1 hr., and then the reflux condenser was replaced with a distillation assembly. The mixture was distilled at atmospheric pressure with stirring for 1 hr. The hot reaction mixture was poured cautiously with stirring into 36 l. of boiling water. The mixture was stirred for 10 min. After 24 hr. the fine, tan crystals of 4,5-diamino-2,6-pyrimidinedithiol were collected and washed with water and acetone. The yield was 1500–1575 g. (80–84%). The ultraviolet absorption data for the crude 4,5-diamino-2,6-pyrimidinedithiol were: at *p*H 1, λ_{max} 287, 329 mμ, ϵ_{max} 29,000, 20,900; at *p*H 11, λ_{max} 246, 285 (plateau), 346 mμ, ϵ_{max} 23,100, 9,700, 12,900.

Formamide (5.6 l.) was heated to 110°, and, with stirring, 1865 g. of 4,5-diamino-2,6-pyrimidinedithiol was added. The mixture was heated to 175° and stirred at 175–180° for 30 min. After brief cooling, the flask was nearly filled with water, the *p*H of the slurry adjusted to 5 with acetic acid, and the mixture kept at 0° for 2 hr. The crude solid was collected, washed with water, and reprecipitated from solution in hot, dilute NH_3 (charcoal) with acetic acid. The yield of light-yellow 2,6-purinedithiol was 1430 g. (73%). The compound was quite pure as judged by its characteristic ultraviolet absorption spectrum.[12]

6-Chloropurine-2-sulfonyl Fluoride (XI).—To a polyethylene beaker, cooled in a Dry Ice–acetone-bath at −35°, were added 620 ml. of methanol, 1240 ml. of 49% HF and 500 g. of $KF \cdot 2H_2O$. The solution was cooled to 8°, and 214 g. of 2,6-purinedithiol was added. The suspension was cooled to 0°, and with stirring a fast stream of chlorine gas was bubbled into the reaction mixture. As soon as the reaction temp. reached 5°, the bath temp. was lowered to −55°, and the rate of chlorine addition was increased

(16) All melting points were taken on a Fisher–Johns melting point apparatus unless otherwise indicated.

(17) G. B. Elion, E. Burgi and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952).

(18) K. L. Dille and B. E. Christensen, *ibid.*, **76**, 5087 (1954).

(19) G. Leven, A. Kalmus and F. Bergmann, *J. Org. Chem.*, **25**, 1752 (1960).

TABLE VII

SYNTHESIS OF PURINESULFONAMIDES

Purinesulfonamide	Starting material	Wt. s.m., g.	Amine	Vol. amine, ml.	Crude yield, %	Recrysn. solvent	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
VIII	VII	10.0	Liquid NH_3	100	92	Water	>320	30.2	30.3	2.5	2.5			35.2	35.1	16.1	15.9
IX	VII	10.0	25% aq. $HN(CH_3)_2$	80	94	Water	271	37.0	37.2	4.0	4.1			30.8	30.9	14.1	13.8
XII	XI	125.8	Liquid NH_3	800	93	Ethanol		25.7	26.0	1.7	2.1	15.2	15.1	30.0	30.1	13.7	13.4
XIII	XI	80.0	8% aq. $HN(CH_3)_2$	720	89	Water	270	32.1	32.4	3.1	3.4	13.6	13.6	26.8	26.7	12.2	12.2
XIV	XV	10.0	25% aq. $HN(CH_3)_2$	200	22	Methanol	305 d.	40.0	40.1	5.2	5.2			31.1	31.0	11.9	12.0
XXVIII	III	6.0	40% aq. H_2NCH_3	60	94[a]	Water	225 d.	33.8	33.8	3.3	3.4			32.8	32.4		
XXIX	III	7.0	35% aq. $H_2NC_2H_5$	70	84	Water	227 d.	37.0	37.2	4.0	4.1			30.8	30.8		
XIX	XVIII	5.1	Liquid NH_3	60	90[b]	Dil. NaOH ppt. w./HOAc		28.0	28.0	2.8	2.7			39.2	39.0	15.0	14.6
XXII	XXI	60.0	Liquid NH_3	400	98	Water		27.9	27.9	2.4	2.5			32.5	32.2	14.9	14.5
XXIII	XXI	60.1	25% aq. $HN(CH_3)_2$	420	96	Water		34.6	34.4	3.7	3.7			28.8	28.9		

[a] Following acidification with glacial acetic acid, 75 ml. of water added to precipitate the product. [b] The product is insoluble in dilute aqueous ammonia.

so that a reaction temp. of 5–8° was maintained. After about 2 hr. the reaction was complete as indicated by a drop in the reaction temp. and by complete solution of the solid. The chlorine inlet tube was removed for 5 min. and a drop of the reaction mixture placed on *p*H "Hydrion" paper. A rapid bleach of the paper indicated excess chlorine and confirmed that the reaction had been completed. The solution was then poured slowly, with stirring, over 6–7 kg. of crushed ice, whereupon a white solid formed. Excess ice must always be present. The mixture was allowed to stand for 15 min., and the solid was filtered, washed very thoroughly with ice-water, pressed dry, and air-dried without external heat. The crude yield was 224–232 g. (81–84%). The crude material from 2 runs (456 g.) was dissolved in 1000 ml. of acetone (25°), filtered, and the acetone allowed to evaporate to give 396 g. (72%) of 6-chloropurine-2-sulfonyl fluoride which was sufficiently pure for use in the synthesis of sulfonamides. A sample was recrystallized twice from methanol to give chunky, pale-yellow crystals, m.p. 205–207°.

Anal. Calcd. for $C_5H_2ClFN_4O_2S$: C, 25.4; H, 0.9; Cl, 15.0; F, 8.0; N, 23.7; S, 13.5. Found: C, 25.6; H, 0.4; Cl, 14.8; F, 8.1; N, 23.4; S, 13.2.

Purine-6-sulfonamide (IV).—To 125 ml. of liquid ammonia was added, with stirring, 20.0 g. of crude purine-6-sulfonyl fluoride in small portions over a period of 5–10 min. The ammonia was allowed to evaporate, with stirring, over a period of 30–45 min. To the resulting moist solid was added 200 g. of crushed ice and then 100 ml. of water, and the mixture was stirred until the solid dissolved. With ice still present the *p*H was adjusted to 5 (temperature always below 0°) by the dropwise addition, with stirring, of acetic acid. The purine-6-sulfonamide precipitated as a white solid. The mixture was cooled for 20 min. and the solid filtered, washed thoroughly with water, pressed dry, and air-dried without external heat. The yield was 16.7–17.7 g. (85–90%). Purine-6-sulfonamide may be recrystallized from boiling water (3 g. per 100 ml.) provided the solid is added to boiling water, the solution boiled very briefly with charcoal, filtered rapidly, and the filtrate immediately cooled in ice. If the solution was boiled too long, the filtrate turned yellow and no crystals formed, the sulfonamide having been hydrolyzed to the ammonium salt of the sulfonic acid. Purine-6-sulfonamide melted with decomposition at 258° if placed on a block preheated to 250°.

Anal. Calcd. For $C_5H_5N_5O_2S$: C, 30.2; H, 2.5; N, 35.2; S, 16.1. Found: C, 30.2; H, 2.5; N, 35.4; S, 15.8.

Purine-6-(N,N-dimethyl)-sulfonamide (V).—To 125 ml. of 25% aqueous dimethylamine, cooled to −12°, was added, with stirring, 15.0 g. of crude purine-6-sulfonyl fluoride in small portions over a period of 5–10 min. (reaction temp. −15 to −10°). The mixture was allowed to stir in the same temp. range for 30 min. more. The *p*H was adjusted to 5 at −15 to −10° by the dropwise addition, with stirring, of acetic acid, giving a white solid. After cooling 15 min. this solid was collected, washed with water, and air-dried. The yield was 15.7 g. (93%). Purine-6-(N,N-dimethyl)-sulfonamide was recrystallized from boiling water to give colorless needles, m.p. 179–181°.

Anal. Calcd. for $C_7H_9N_5O_2S$: C, 37.0; H, 4.0; N, 30.8; S, 14.1. Found: C, 37.2; H, 4.0; N, 31.0; S, 14.5.

Purine-2-sulfonamide (VIII), 6-chloropurine-2-sulfonamide (XII), 6-aminopurine-2-sulfonamide (XIX) and 6-hydroxypurine-2-sulfonamide (XXII) were prepared by the general method employed for the synthesis of purine-6-sulfonamide. Details are given in Table VII.

Purine-2-(N,N-dimethyl)-sulfonamide (IX), 6-chloropurine-2-(N,N-dimethyl)-sulfonamide (XIII), 6-dimethylaminopurine-2-(N,N-dimethyl)-sulfonamide (XIV), purine-6-(N-methyl)-sulfonamide (XXVIII), purine-6-(N-ethyl)-sulfonamide (XXIX) and 6-hydroxypurine-2-(N,N-dimethyl)-sulfonamide (XXIII) were prepared by the general method employed for the synthesis of purine-6-(N,N-dimethyl)-sulfonamide. Details are given in Table VII.

6-Dimethylaminopurine-2-(N,N-dimethyl)-sulfonamide (XIV).—Forty milliliters of 25% dimethylamine was cooled to −4°, and, with stirring, 5.0 g. of finely-powdered 6-chloropurine-2-sulfonyl fluoride was added in small portions

over a period of 15 min. After stirring a further 15 min. at 0°, the flask was transferred to a boiling water-bath and heated for 8 min. (reaction temp. 85–93°) during which time a thick, white solid formed. The mixture was cooled to 15° and the solid filtered, washed with water, and dried. The yield was 4.1 g. (72%). 6-Dimethylaminopurine-2-(N,N-dimethyl)-sulfonamide was recrystallized from boiling water to give colorless needles, m.p. 305°dec., "Mel-Temp" metal block.

Anal. Calcd. for $C_9H_{14}N_6O_2S$: C, 40.0; H, 5.2; N, 31.1; S, 11.9. Found: C, 40.2; H, 5.1; N, 31.1; S, 11.8.

Purine-2-sulfonamide-6-sulfonic Acid, Ammonium Salt, Monohydrate (XVI).—To 100 ml. of liquid ammonia was added 13.4 g. of freshly prepared purine-2,6-disulfonyl fluoride in small portions, with stirring, over a period of 15 min. The ammonia was allowed to evaporate, with stirring, over 1 hr. and the moist solid dissolved in 60 ml. of cold water; the solution was acidified to *p*H 5 in the cold by the dropwise addition, with stirring, of acetic acid. The solution was refrigerated several days to give 9.0 g. of solid. A sample was recrystallized from boiling water to give large, chunky crystals. These were powdered and dried 3 hr. at 100° under vacuum over P_2O_5.

Anal. Calcd. for $C_5H_8N_6O_5S \cdot H_2O$: C, 19.1; H, 3.2; N, 26.7; S, 20.4. Found: C, 19.7; H, 3.2; N, 26.9; S, 20.4.

6-Aminopurine-2-sulfonamide (XIX).—A solution of 22.6 g. of 6-chloropurine-2-sulfonamide, in 220 ml. of concd. (28%) aq. NH_3, was boiled for 8 hr. in an open flask with ammonia gas bubbling through the solution. Every 30 min. an additional 100 ml. of concd. aq. NH_3 solution was added to maintain the volume. The reaction temp. was 60–93°. Gradually a yellow-tan solid crystallized from the boiling solution. After cooling 1 hr. the solid was filtered, washed with water, and dried. The crude yield was 16.9 g. (81%). A sample was reprecipitated from hot, dilute NaOH solution with dilute acetic acid to give nearly colorless crystals.

Anal. Calcd. for $C_5H_6N_6O_2S$: C, 28.0; H, 2.8; N, 39.2; S, 15.0. Found: C, 27.7; H, 2.6; N, 39.0; S, 14.9.

6-Hydroxypurine-2-(N,N-dimethyl)-sulfonamide (XXIII).—6-Chloropurine-2-(N,N-dimethyl)-sulfonamide (5.0 g.) was dissolved in a solution of 1.6 g. of NaOH in 20 ml. of water. The solution was refluxed for 2 hr., cooled to 50°, and acidified to *p*H 6 with acetic acid. The solid which formed in the warm solution was filtered (judged to be 6-dimethylaminopurine-2-(N,N-dimethyl)-sulfonamide by ultraviolet absorption) and discarded, and the filtrate allowed to evaporate to about 5 ml. The solid which formed was dissolved in 50 ml. of water, the solution treated with charcoal, filtered, and the filtrate acidified to *p*H 2 with HCl and refrigerated. The yellow solid which formed (1.0 g.) was recrystallized from boiling water.

Anal. Calcd. for $C_7H_9N_5O_3S$: N, 28.8; S, 13.2. Found: N, 28.9; S, 13.5.

6-Purinethiol-2-sulfonamide, Monohydrate (XXIV).—6-Chloropurine-2-sulfonamide (43.7 g.) was dissolved in a solution of 30.0 g. of 70% NaSH in 440 ml. of water. The solution was refluxed for 25 min. and cooled in an ice-bath (Norite). The charcoal was filtered and the yellow filtrate acidified to *p*H 4.5–5 by the slow addition, with stirring, of acetic acid. After 5 min. the yellow solid which formed was filtered. It was identified as 2,6-purinedithiol by its ultraviolet absorption and weighed 7.2 g. (21%). The filtrate was adjusted to *p*H 4 by the addition of acetic acid and allowed to evaporate to 300 ml. The light-yellow solid which formed was collected, washed with water, and dried. The yield of 6-purinethiol-2-sulfonamide monohydrate was 22.5 g. (48%). A sample was reprecipitated from solution in cold, dilute NH_3 with dilute HCl (*p*H 2) to give a light-yellow solid. After drying 3.5 hr. at 100° under vacuum over P_2O_5 the crystals retained 1 mole of water.

Anal. Calcd. for $C_5H_5N_5O_2S_2 \cdot H_2O$: C, 24.1; H, 2.8; N, 28.1; S, 25.7. Found: C, 24.5; H, 2.8; N, 28.2; S, 25.7.

4,5-Diamino-6-pyrimidinethiol (XXVI).—Two liters of β-picoline was heated to 120°. With stirring 400 g. of P_2S_5 was added slowly, followed by 100 g. of 4,5-diamino-6-hydroxypyrimidine.[15] The mixture was stirred and refluxed for 40 min. Water (10 ml.) was added dropwise and the mixture stirred and refluxed for 5.5 hr. The excess β-picoline was removed under vacuum, and the brown paste which remained was washed from the flask with 5.5 l. of boiling water. The slurry was stirred and boiled for 45 min. The insoluble yellow solid was filtered and weighed 84 g. The filtrate was refrigerated a week to give 70 g. of tan solid. The 154 g. of crude material was recrystallized from boiling 12% sulfuric acid, and the resulting sulfate salt dissolved in dilute NaOH solution and reprecipitated with acetic acid to give 77 g. (68%) of 4,5-diamino-6-pyrimidinethiol. (If pyridine, b.p. 115°, was used as the solvent, only a small yield of 4,5-diamino-6-pyrimidinethiol was obtained, most of the 4,5-diamino-6-hydroxypyrimidine not having reacted after 6-hr. reflux. When 5-ethyl-2-methylpyridine, b.p. 178°, was used, there was considerable tar formation after 2-hr. reflux, and the crude 4,5-diamino-6-pyrimidinethiol crystallized very slowly in 41% yield.) The crude material was recrystallized from boiling water, using charcoal, to give colorless needles of 4,5-diamino-6-pyrimidinethiol, identified by its ultraviolet absorption spectrum.[14]

4-Amino-5-formylamino-6-pyrimidinethiol (XXVII) was prepared by the method of Elion,[13] except that a reaction temp. of 70° for 15 min. was used.