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

(2-Chloroethylthio)purines and the Corresponding Dihydrothiazolopurines[2]

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The preparation of 6-(2-chloroethylthio)purine (II) and 2-(2-chloroethylthio)purine (XI) and their conversion to the corresponding dihydrothiazolopurines (III and XII or XIII) are described. 8-(2-Chloroethylthio)purine could not be isolated as such but only a mixture of the two isomeric dihydrothiazolopurines (XVII and XVIII) derived from it. The proof of structure of the dihydrothiazolopurines is presented.

Although sulfur mustard [bis(2-chloroethyl) sulfide] has not been used extensively in the treatment of human neoplastic disease, its effectiveness in the treatment of certain lymphomas and adenocarcinomas has been established.[3] Further a so-called "one-armed" derivative of sulfur mustard, hemisulfur mustard [2-(2-chloroethylthio)ethanol], has been shown clinically to possess unequivocal anticancer activity.[4,5] Both of these drugs owe their anticancer activity to the chemical reactivity of cyclic sulfonium ions which they readily form. These cyclic sulfonium ions, although very reactive, retain a high degree of discrimination among nucleophiles.

One approach to the synthesis of a more effective anticancer agent in the purine series might be the preparation of a purine capable of forming a cyclic sulfonium ion which, if located in the proper position, might cause the purine to combine irreversibly with an enzyme important to purine metabolism, resulting in a more effective block to nucleic acid synthesis, and, therefore, in a more effective inhibition of rapidly dividing cancer cells.

Previous work from this laboratory showed that 6-(2-chloroethylthio)purine (II) could be obtained from purine-6(1*H*)-thione (I) by alkylation in *N*,*N*-dimethylformamide with 1-bromo-2-chloroethane using potassium carbonate as the acid acceptor.[6] The yields were poor and attempted scale-ups were only partially successful; it was extremely difficult to free the reaction product from unchanged starting material, as 6-(2-chloroethylthio)-purine (II), on attempted recrystallization, is easily converted into a water-soluble compound which is identical with the hydrochloride of a by-product of the alkylation step. This by-product was actually the major product of these initial reactions, although it was not isolated and identified. By adding I in small portions to 1-bromo-2-chloroethane in *N*,*N*-dimethylformamide, using triethylamine instead of potassium carbonate, and modifying the isolation procedure, we can now consistently prepare II on a relatively large scale and in about 42% yield.

The water-soluble compound alluded to above was isolated by extraction of the crude product with acetonitrile and purified by recrystallization from ethyl alcohol. This compound is the only product if the above reaction is carried out at 50–60° rather than at room temperature. It is also the only product from the reaction of I with 1,2-dibromoethane even at room temperature, although it is necessary to heat this reaction to 50–60° also to force it to completion. Elemental analyses and a molecular weight determination showed this compound to have the empirical formula $C_7H_6N_4S$, and paper chromatography in four solvent systems showed it to be a single substance. On being heated in ethyl alcohol at 60°, 6-(2-chloroethylthio)purine (II) is converted essentially quantitatively to the hydrochloride of this substance, and the hydrochloride can be converted without difficulty to the free base and the free base back to the hydrochloride. This compound must be the result of nucleophilic displacement of the chlorine atom of the 2-chloroethylthio group of II by either N_1 or N_7 of the purine ring and, therefore, must be either 7,8-dihydrothiazolo-[2,3-*i*-]purine (III) or 5,6-dihydro[1,4]thiazino-[4,3,2-*gh*]purine (IV). Even under the optimal conditions for the preparation of 6-(2-chloroethylthio)purine described above we were unable to completely suppress its conversion to the tricyclic compound (III or IV). To decide between these two structures, III (or IV) was subjected to acid and to base hydrolysis. In contrast to the behavior or 6-(alkylthio)purines, the tricyclic compound was unaffected by dilute acid but yielded to dilute base treatment, giving a compound whose ultraviolet spectrum resembled that of a 1-substituted hypoxanthine, and whose elemental analyses were in agreement with the values calculated for the disulfide VI. Raney nickel dethiolation of the disulfide was incomplete, but recycling the product three times gave a good sample of a compound whose identity was established as 1-ethylhypoxanthine (IX) by comparison with material prepared

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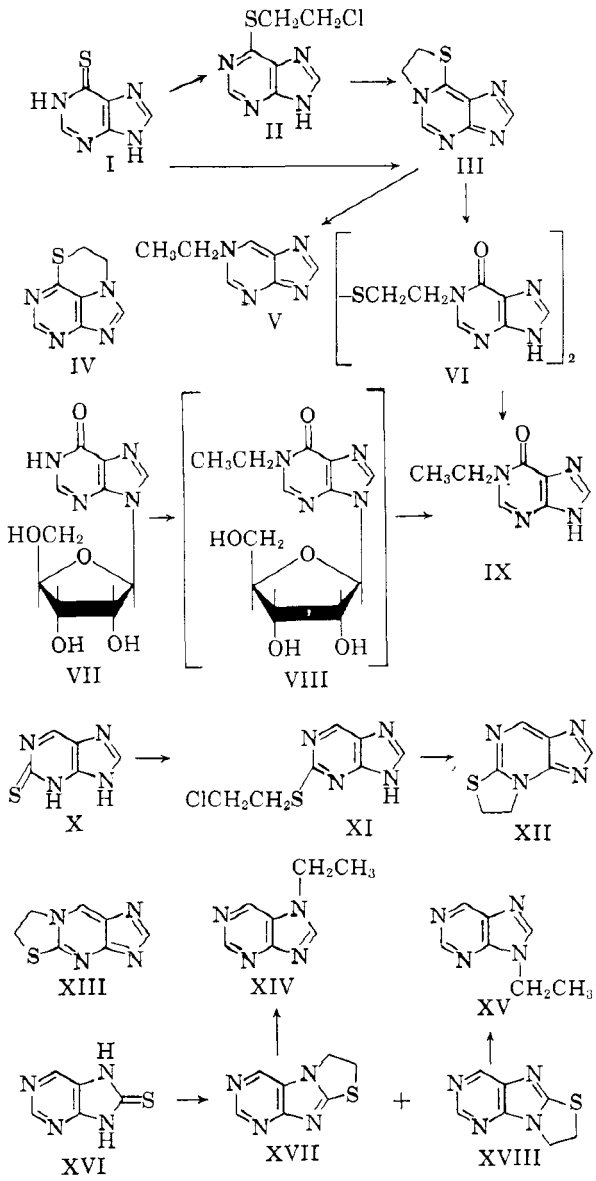
(3) L. K. Alpert, *Ann. N. Y. Acad. Sci.*, **68**, 1223 (1958).

(4) A. M. Seligman, A. M. Rutenburg, L. Persky, and O. M. Friedman, *Cancer*, **5**, 354 (1952).

(5) A. M. Rutenburg and A. M. Seligman, *New Engl. J. Med.*, **255**, 361 (1956).

(6) T. P. Johnston, L. B. Holum, and J. A. Montgomery, *J. Am. Chem. Soc.*, **80**, 6265 (1958).



in an unambiguous manner from inosine (VII) by the method of Shaw.[7] Thus the hydrolysis product was identified as 1,1′-(dithiodiethylene)dihypoxanthine (VI) and the tricyclic compound must be 7,8-dihydrothiazolo[2,3-*i*]purine (III), resulting from cyclization at N_1 of the purine ring.

Raney nickel dethiolation of III itself was also difficult, but enough material was obtained to separate it from unchanged starting material by paper chromatography and to identify it as 1-ethyl-1H-purine (V), a light-sensitive, somewhat unstable compound. Although 7-methyl-7*H*-purine[8,9] and a number of 9-alkyl-9*H*-purines[8-10] are well known, this compound (V) represents the first alkyl derivative of purine itself in which the alkyl group is attached to one of the pyrimidine ring nitrogens. This compound is of particular interest because the double bonds of the rings are forced into an unnatural, *p*-quinoid type of arrangement and resonance of the Kekulé type is not possible.

1-Ethyl-1*H*-purine (V) has a pK_a of 5.08 as compared to a pK_a of 2.67 for 7-ethyl-7*H*-purine and 9-ethyl-9*H*-purine. The base strength of the latter two compounds is about the same as that of purine (pK_a 2.39[11]), whereas V is considerably more basic. This increased basicity and its significantly different ultraviolet and infrared spectra (see below) are probably reflections of the unusual bond structure of V.

As an examination of Stuart-Briegleb models[12] of the three isomeric (2-chloroethylthio)purines showed that 2-(2-chloroethylthio)purine (XI) would probably have the least tendency to undergo ring closure to a tricyclic structure, we undertook its synthesis next.

2-(2-Chloroethylthio)purine can be obtained in high yield from purine-2-(1- or 3*H*)-thione (X)[11,13] by Johnston's procedure.[6] As predicted by the Stuart-Briegleb models, no trouble due to tricycle formation was encountered. However, heating the reaction mixture to 50–60° gave, as in the case of 6-(2-chloroethylthio)purine, a water-soluble product having the tricyclic structure XII or XIII, resulting from ring closure at N_1 or N_3 of the purine ring. Again chromatography indicated the presence of only one isomer. Dethiolation of this dihydrothiazolopurine would give either 1-ethyl-1H-purine (from XIII) or 3-ethyl-3*H*-purine (from XII). Attempts to dethiolate this compound were not completely successful because of the instability of the product. However, differences in behavior of this material and the 1-ethyl-1*H*-purine (V) prepared from III as described above, indicate that it is not V and, therefore, must be 3-ethyl-3*H*-purine, which in turn indicates that the tricyclic compound is probably 7,8-dihydrothiazolo[2,3-*b*]purine (XII).

In contrast to the behavior of purine-6(1*H*)-thione (I) and purine-2-(1 or 3*H*)-thione (X), purine-8(7*H*)-thione did not afford 8-(2-chloroethylthio)purine even when the reaction with 1-bromo-2-chloroethane was carried out at room temperature. The material isolated, by acetonitrile extraction of the crude product, was water-soluble and analyzed for the empirical formula $C_7H_6N_4S$. This material was shown by paper chromatography to be a mixture of the two possible isomers resulting from ring closure at N_7 and N_9 of the purine ring. These isomers were separated by cyclohexane ex-

(7) E. Shaw, *J. Am. Chem. Soc.*, **80**, 3899 (1958).
(8) E. Fischer, *Ber.*, **31**, 2550 (1898).
(9) A. Bendich, P. J. Russell, and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).
(10) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **79**, 5238 (1957); *J. Am. Chem. Soc.*, **80**, 409 (1958).
(11) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).
(12) Arthur S. LaPine and Co., 6001 S. Knox Ave., Chicago 29, Ill.
(13) R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Am. Chem. Soc.*, **75**, 263 (1953).

traction. Raney nickel dethiolation of the cyclohexane-soluble material gave 9-ethyl-9*H*-purine[10] and thus this tricyclic compound must be 7,8-dihydrothiazolo[3,2-*e*]purine (XVIII). Dethiolation of the cyclohexane-insoluble material gave an *N*-ethylpurine whose spectra are very similar to those of 7-methyl-7*H*-purine and which must then be 7-ethyl-7*H*-purine, derived from 6,7-dihydrothiazolo[2,3-*f*]purine (XVII). This ring system, at the the thiazolopurine level of unsaturation, has been reported as resulting from the reaction of chloroacetone with purine-8(7*H*)-thiones.[14-16] These authors report the formation of only one isomer and offer no proof that, in fact, ring closure does occur at N_7 of the purine ring.

2-(Benzylthio)purine, 8-(benzylthio)-9-ethyl-9*H*-purine, and 8-(2-chloroethylthio)-9-ethyl-9*H*-purine were prepared for spectral comparisons.

Infrared spectra. The infrared spectra (see Experimental) of 6-(2-chloroethylthio)purine (II) and 2-(2-chloroethylthio)purine (XI) are similar to those of other, corresponding (alkylthio)purines. However, the infrared spectra of the corresponding dihydrothiazolopurines III and XII (or XIII) are quite different. As would be expected, the spectra of these compounds show no absorption in the 2800–2400 cm.$^{-1}$ region (due to acidic NH), but of greater interest is the difference in the absorption in the 1600–1500 cm.$^{-1}$ (double bond) region. In this region the thiazolopurines (III and XII or XIII), both of which have the fixed double bond, quinoid type of structure, show only two intense rather widely separated bands, whereas the spectra of most (alkylthio)purines capable of normal Kekulé resonance show three or four closely grouped bands of medium to weak intensity in this region. In this respect the infrared spectrum of 1-ethyl-1*H*-purine, which also has the fixed double bond structure, resembles those of III and XII (or XIII) and is quite different from those of 7-ethyl-7*H*-purine, 9-ethyl-9*H*-purine, and the corresponding thiazolopurines XVII and XVIII, all of which have the normal purine bond structure.

Ultraviolet spectra. As was the case with their infrared spectra, the ultraviolet spectra of II and XI agree well with those of other (alkylthio)purines but the maxima of the spectra of the thiazolopurines derived from them (III and XII or XIII) show a distinct bathochromic shift of 5–16 mμ, again probably due to their unusual double bond structure, since the maximum of 1-ethyl-1*H*-purine also shows a bathochromic shift of 5–11 mμ from those of 7-ethyl-7*H*-purine and 9-ethyl-9*H*-purine whose spectra more closely resemble that of purine (except, of course, at *p*H 13 where the spectrum is that of the purine anion). The pK_a values for these latter two compounds (XIV and XV) were determined by the spectrophotometric method of Fox[17] and the values found (2.62 for the 9-isomer and 2.70 for the 7-isomer) are in good agreement with the electrometrically determined values (2.67 for both isomers).

Chromatography. Table I lists the R_f values of these compounds in four solvent systems. It was not possible to obtain R_f values for 6-(2-chloroethylthio)purine because this compound undergoes cyclization during the chromatographic period. The difference in rate of travel of the dihydrothiazolopurines and the corresponding (alkylthio)purines [III and 6-(ethylthio)purine; XVII and XVIII and 8-(methylthio)purine] is easily discernible, particularly in solvent systems A and D, and is due to the absence of an ionizable hydrogen in the case of the dihydrothiazolopurines.

TABLE I

Compound	R_f Values, Solvent System[a] A	B	C	D
I	0.42	0.56	0.45	0.40
6-(Ethylthio)purine	0.82	0.88	0.73	0.47
III	0.28	0.50	0.45	0.62
V	0.45	0.58	0.63	0.80
VI	0.32	0.49	0.36	0.61
IX	0.63	0.74	0.65	0.74
X	0.11	0.30	0.37	0.44
XII (or XIII)	0.37	0.54	0.50	0.64
XIV	0.61	0.83	0.74	0.71
XV	0.75	0.89	0.79	0.80
XVI	0.52	0.66	0.50	0.42
8-(Methylthio)purine	0.66	0.76	0.65	0.44
XVII	0.47	0.71	0.62	0.60
XVIII	0.58	0.76	0.68	0.57

[a] The paper chromatograms were run by the descending technique on Whatman No. 1 paper in the following solvent systems: A, water-saturated butyl alcohol [J. G. Buchanan, C. A. Dekker, and A. G. Long, *J. Chem. Soc.*, 3162 (1950)]; B, butyl alcohol–acetic acid–water (5:2:3) [D. M. Brown, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956)]; C, isopropyl alcohol–ammonium hydroxide–water (70:5:25) [R. Markham and J. D. Smith, *Nature*, **168**, 406 (1951)]; D, 0.1*M* phosphate buffer, *p*H 6.7 [J. A. Johnson and H. J. Thomas, *J. Am. Chem. Soc.*, **78**, 3863 (1956)].

EXPERIMENTAL

The melting points below 260° were determined on a Kofler Heizbank and are corrected. Those above 260° were determined in a capillary in an aluminum block and are uncorrected. The ultraviolet spectra were determined in aqueous solution with a Beckman DK-2 (optical densities at the maxima with a Beckman DU) or a Cary Model 14. The infrared spectra were determined in pressed potassium bromide disks with a Perkin-Elmer Model 21 spectrophotometer.

6-(2-Chloroethylthio)purine (II).[6] Purine-6(1*H*)-thione monohydrate (2.0 g., 8.5 mmoles) was added in small portions over a 1-hr. period to a stirred mixture of 1-bromo-2-chloroethane (2.0 ml., 23.6 mmoles) and triethylamine (1.7 ml.,

(14) A. R. Todd and F. Bergel, *J. Chem. Soc.*, 1559 (1936).
(15) E. Ochiai, *Ber.*, **69**, 1650 (1936).
(16) M. Gordon, *J. Am. Chem. Soc.*, **73**, 984 (1951).
(17) J. J. Fox and D. Shugar, *Bull. soc. chim. Belg.*, **61**, 44 (1952); D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).

12.2 mmoles) in *N,N*-dimethylformamide (15 ml.). The mixture was kept at 31–32° during the addition and for an additional hr. The whole slurry which formed was poured into 100 ml. of 10% potassium bicarbonate solution and the resulting clear solution was extracted with three 100-ml. portions of ether. The ether extracts were combined, dried over magnesium sulfate, and concentrated until crystallization began. The ether solution was then cooled in a Dry Ice–acetone bath and the white crystals that deposited were removed by filtration and dried *in vacuo* over phosphorus pentoxide; yield, 0.62 g., m.p. 154–155° (resolidified and melted at 270°).[18] An additional 0.24 g. of material was obtained on concentration of the mother liquor; total yield, 0.86 g. Acidification of the aqueous solution described above gave 0.36 g. of unchanged purine-6(1*H*)thione, so that the conversion to 6-(2-chloroethylthio)purine was 42%. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—321, 290 (8.9, 14.7); *p*H 7—216, 289 (11.7, 16.2); *p*H 13—unstable; methyl alcohol—215, 279.5, 286 (11.7, 16.7, 16.5). $\bar{\nu}_{max}$ in cm.$^{-1}$: 3050 (ring CH); 2950 (aliphatic CH); 2800–2400 (acidic H); 1635, 1600, 1582, 1515 (C=N, C=C); 1480, 1450, 1420 (CH); 950, 900, 860 (ring CH).

In a larger run 3.92 g. of 6-(2-chloroethylthio)purine was obtained from 9 g. of purine-6(1*H*)-thione and 1.6 g. of unchanged starting material was recovered so that the conversion again was 42%.

7,8-Dihydrothiazolo[2,3-i]purine (III). *A*. To a stirred mixture of purine-6(1*H*)-thione monohydrate (50.0 g., 0.293 mole) and anhydrous potassium carbonate (45.0 g., 0.322 mole) in *N,N*-dimethylformamide (500 ml.) was added dropwise 1,2-dibromoethane (27.7 ml., 0.322 mole), and this mixture was then heated at 60–65° for 3hr. The resulting thick slurry was cooled in an ice bath and the solid collected by filtration, air-dried, and extracted overnight in a Soxhlet extractor with acetonitrile (1 l.). The acetonitrile extract was cooled and the crystalline poduct removed by filtration and dried *in vacuo* at 60° for 4 hr. over phosphorus pentoxide; yield, 32.5 g. (62%); m.p., 270–271°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—228, 302 (14.0, 15.2); *p*H 7—218, 297 (16.9, 12.8); *p*H 13—297 (11.9). $\bar{\nu}$ in cm.$^{-1}$: 3020, 2990 (ring CH), 2950 (aliphatic CH); 1610, 1505, (C=N, C=C); 1480 sh., 1450, 1420 (CH); 980, 920, 880 (ring CH).

Anal. Calcd. for $C_7H_6N_4S$: C, 47.18; H, 3.40; S, 17.98. Found: C, 47.46; H, 3.84; S, 18.06.

B. A solution of 6-(2-chloroethylthio)purine (0.186 g.) in ethyl alcohol (3 ml.) was heated at 60° for 1 hr. The precipitate that formed was dissolved by the addition of hot alcohol (17 ml.), and the solution filtered and allowed to stand in the refrigerator. The crystalline product, 7,8-dihydrothiazolo[2,3-*i*]purine hydrochloride, was collected by filtration and dried *in vacuo* over phosphorus pentoxide; yield, 0.11 g. (58%). λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—229, 301 (14.2, 15.3); *p*H 7—298 (13.1); *p*H 13—298 (11.8); ethyl alcohol—228, 300 (16.0, 13.5).

Anal. Calcd. for $C_7H_6N_4S \cdot HCl$: C, 39.16; H, 3.29; Cl, 16.52; N, 26.10. Found: C, 38.80; H, 3.64; Cl, 16.01; N, 25.95.

1-Ethyl-1H-purine (V). A mixture of 7,8-dihydrothiazolo-[2,3-*i*]purine (500 mg., 2.8 mmoles) and Raney nickel[19] (2.5 g.) in ethyl alcohol (30 ml.) was refluxed for 5 hr. and then filtered. The Raney nickel was extracted with four 10-ml. portions of boiling ethyl alcohol and the extracts added to the filtrate. The white residue from evaporation of the combined extracts and filtrate was triturated with 25 ml. of cold ethyl alcohol, and evaporation of this alcohol solution gave 210 mg. of white crystalline solid which was chromatographed on 9 in. sheets of Whatman No. 3 filter paper using water-saturated butyl alcohol as the developer. The faster traveling material (R_f 0.44) was eluted from the paper with four 50-ml. portions of ethyl alcohol. Evaporation of the resulting solution gave a white crystalline solid, which was dried at 60° for 4 hr. *in vacuo* over phosphorus pentoxide; yield, 86 mg. (21%); m.p., 198°. pK_a by titration at 27° in 0.15*M* sodium chloride—5.08. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—268 (6.6); *p*H 7—218.5, 274 (10.6, 6.2); *p*H 13—274 (6.3). $\bar{\nu}$ in cm.$^{-1}$: 3100, 3075, 3020, 2990, 2975, 2942, (CH); 1642, 1538, 1518 (C=N, C=C); 1460, 1440 sh. (CH), 970 (ring CH).

Anal. Calcd. for $C_7H_8N_4$: C, 56.72; H, 5.44; N, 37.81. Found: C, 56.53; H, 5.23; N, 37.52.

This compound is light and air-sensitive; it rapidly turns dark on exposure.

1,1′-(Dithiodiethylene)dihypoxanthine (VI). A solution of 7,8-dihydrothiazolo[2,3-*i*]purine (20.0 g., 0.112 mole) in 0.1*N* aqueous sodium hydroxide (1.1 l.) was refluxed for 3 hr., acidified to *p*H 5 with concentrated hydrochloric acid, and concentrated to one-half volume *in vacuo*. The yellow solid that crystallized on cooling the solution was collected by filtration; crude yield, 6.94 g. (30%) of 95% pure (by ultraviolet spectrum) product. This material was recrystallized from aqueous methyl alcohol; yield, 2.96 g. (13.5%); m.p. >260°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—249 (10.0); *p*H 7—252 (18.2); *p*H 13—261 (19.6). The disulfide structure VI was assigned because a nitroprusside test for thiol was positive only after the product had been subjected to reduction with zinc in hydrochloric acid.

Anal. Calcd. for $C_{14}H_{14}N_8O_2S_2$: C, 43.07; H, 3.62; N, 28.70; S, 16.42. Found: C, 42.76; H, 4.03; N, 28.32; S, 16.58.

1-Ethylhypoxanthine (IX) *A*. A solution of 1,1′-(dithiodiethylene)dihypoxanthine (500 mg., 1.28 mmoles) in propyl alcohol (20 ml.) was refluxed for 48 hr. with Raney nickel[19] (2.5 g.). The Raney nickel was removed by filtration and washed four times with portions of boiling propyl alcohol. Evaporation of the combined filtrate and washings gave a white crystalline solid shown by paper chromatography to be a mixture of starting material and product. The dethiolation procedure was repeated three times until no starting material could be detected. Recrystallization of the product from ethyl alcohol gave a low yield product; m.p., 275–276°. A mixed melting point with a sample prepared as described in *B* below was undepressed.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.20; H, 4.91; N, 34.13. Found: C, 51.47; H, 5.01; N, 34.15.

In a second similar run a 23% yield of 1-ethylhypoxanthine was obtained.

B. A mixture of inosine (1.0 g., 3.76 mmoles), ethyl iodide (0.33 ml., 4.13 mmoles), and potassium carbonate (579 mg., 4.13 mmoles) in *N,N*-dimethylformamide (10 ml.) was stirred at 80–100° for 6 hr. The cooled reaction mixture was poured into 50 ml. of ice water and the resulting solution evaporated to dryness *in vacuo*. The residue was dissolved in 5*N* ethanolic hydrogen chloride and the solution refluxed for 2 hr. The brown, solid residue from evaporation of the ethyl alcohol solution was purified by partition chromatography on a Celite column developed with water-saturated butyl alcohol. The tan solid from the column was recrystallized from ethyl alcohol; yield, 240 mg. (40%); m.p., 276°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—248.5 (9.5); *p*H 7—250.5 (9.1); *p*H 13–260 (9.8).

Anal. Calcd. for $C_7H_8N_4O$: C, 51.20; H, 4.91; N, 34.13. Found: C, 51.11; H, 5.02; N, 33.79.

The samples prepared by methods A and B were identical in all respects.

2-(2-Chloroethylthio)purine (XI). A mixture of purine-2(1 or 3*H*)-thione monohydrate (500 mg., 2.94 mmoles), 1-bromo-2-chloroethane (0.30 ml., 3.55 mmoles), and anhydrous potassium carbonate (408 mg., 2.94 mmoles) in *N,N*-dimethylformamide (4 ml.) was stirred at room temperature for 2 hr. and then poured into 20 ml. of cold water. The light yellow solid that precipitated was collected by filtration and dried *in vacuo* at room temperature over phos-

(18) This melting point behavior indicates that dry fusion of 6-(2-chloroethylthio)purine converts it to 7,8-dihydrothiazolo[2,3-*i*]purine. The lower melting point is not observed if a capillary melting point determination is made.

(19) Raney Catalyst Co., 1322 Hamilton National Bank Building, Chattanooga 2, Tenn.

phorus pentoxide; yield, 520 mg. (83%); m.p., 152°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—228, 245, 305 (12.6, 13.7, 4.2); *p*H 7—220, 250, 298 (16.1, 12.7, 5.5); *p*H 13—242.5, 296 (17.6, 4.9). $\bar{\nu}$ in cm.$^{-1}$: 3055, 2990, 2950 (CH); 2800–2300 (acidic H); 1638, 1610, 1580, 1560 (C=N, C=C); 1460, 1440 sh., 1420 (CH), 925, 870 (ring CH).

Anal. Calcd. for $C_7H_7ClN_4S$: C, 39.16; H, 3.29; Cl, 16.52; S, 14.94. Found: C, 38.91; H, 3.54; Cl, 15.11; S, 14.70.

7,8-Dihydrothiazolo[2,3-b]purine (XII) *or 6,7-dihydrothiazolo[3,2-a]purine* (XIII). A mixture of purine-2(1 or 3*H*)-thione monohydrate (500 mg., 2.94 mmoles), 1-bromo-2-chloroethane (0.25 ml., 2.94 mmoles), and anhydrous potassium carbonate (408 mg., 2.94 mmoles) in *N,N*-dimethylformamide (4 ml.) was stirred for 2 hr. at 50°, then cooled and poured into 25 ml. of ice water. The resulting solution was acidified to *p*H 5, filtered, and evaporated to dryness *in vacuo*. The resulting residue was extracted with acetonitrile and the extract evaporated to dryness *in vacuo*. The residue of yellow needles was dried *in vacuo* at room temperature for 4 hr. over phosphorus pentoxide; yield, 202 mg. (54%); m.p., 254°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—246, 270, 321 (20.9, 8.7, 2.8); *p*H 7—251.5, 281, 296 (sh.), 330 (sh.), (22.8, 5.0, 3.6, 1.6); *p*H 13—251.5, 281, 297 (sh.), 314 (sh.) (21.5, 5.1, 3.8, 2.6); methanol—250, 284, 295 (sh.), 321 (sh.) 22.6, 5.2, 4.2, 2.0). $\bar{\nu}$ in cm.$^{-1}$: 3050, 3010, 2990, 2950 (CH); 1620, 1520 (C=N, C=C); 1485, 1460, 1440 (CH); 950, 880 (ring CH).

Anal. Calcd. for $C_7H_6N_4S \cdot {}^1/_4\ H_2O$: C, 45.80; H, 3.59; N, 30.66; S, 17.55. Found: C, 45.57; H, 3.54; N, 30.61; S, 17.22.

Drying at elevated temperatures *in vacuo* resulted in decomposition.

6,7-Dihydrothiazolo[2,3-f]purine (XVII) *and 7,8-dihydrothiazolo[3,2-e]purine* (XVIII). A mixture of purine-8(7*H*)-thione (12.0 g., 70.3 mmoles), 1,2-dibromoethane (6.05 ml., 70.3 mmoles), and potassium carbonate (9.70 g., 70.3 mmoles) in *N,N*-dimethylformamide (100 ml.) was stirred and heated at 60–70° for 3 hr. with the addition of 0.6 ml. of 1,2-dibromoethane at the end of 1 hr. The reaction mixture was stirred for 12 hr. at room temperature and then cooled in an ice bath. The solid that formed was collected by filtration and separated from inorganic material by partition chromatography on a Celite column using water-saturated butyl alcohol as the developer. The residue from evaporation of the butyl alcohol was extracted in a Soxhlet extractor for 12 hr. with cyclohexane. The cyclohexane extract was evaporated to dryness and the residue recrystallized from methyl alcohol. The residue in the Soxhlet thimble was also recrystallized from methyl alcohol. Paper chromatography showed that complete separation of the two isomers (XVII and XVIII) obtained from the reaction had been effected. The cyclohexane-soluble material, identified below as 7,8-dihydrothiazolo[3,2-e]purine (XVIII), was obtained in 18.5% yield (2.28 g.); m.p., 204°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—228, 299 (12.2, 15.1); *p*H 7—216, 289 (12.8, 17.6); *p*H 13—289 (17.7). ν in cm.$^{-1}$: 3040, 2980, 2890 (CH); 1600, 1575, 1560 sh., 1545 sh. (C=N, C=C); 1490, 1460, 1420 (CH); 940, 925, 870 (ring CH).

Anal. Calcd. for $C_7H_5N_4S$: C, 47.18; H, 3.40; N, 31.44; S, 17.98. Found: C, 47.01; H, 3.49; N, 31.49; S, 17.86.

The other isomer, identified below as 6,7-dihydrothiazolo-[2,3-f]purine (XVII), was obtained in 37% yield (4.62 g.); m.p., 212°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—231, 307 (13.0, 16.3); *p*H 7—220, 293 (18.2, 17.2); *p*H 13—220, 293 (18.4, 17.3). $\bar{\nu}$ in cm.$^{-1}$: 3070, 3040, 2920 (CH); 1605, 1585 sh., 1555, 1520 sh. (C=N, C=C); 1480, 1450, 1425 (CH); 920, 880 (ring CH).

Anal. Calcd. for $C_7H_6N_4S$: C, 47.18; H, 3.40; N, 31.44; S, 17.98. Found: C, 47.22; H, 3.51; N, 31.46; S, 17.74.

9-Ethyl-9H-purine (XV). A mixture of 7,8-dihydrothiazolo-[3,2-e]purine (500 mg., 2.81 mmoles) and Raney nickel[19] (2.5 g.) in ethyl alcohol (30 ml.) was refluxed for 4 hr., filtered, and evaporated to dryness *in vacuo*. The white residue was extracted with three 10-ml. portions of 60–90° petroleum ether, which were combined and concentrated to 20 ml. On cooling, the solution deposited white needles, which were removed by filtration and dried *in vacuo* at room temperature for 4 hr. over phosphorus pentoxide; yield, 100 mg. (24%); m.p. 56°. A mixed melting point with authentic 9-ethyl-9*H*-purine[10] was undepressed. pK_a by titration at 27° in 0.15*M* sodium chloride 2.67. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—263 (5.4); *p*H 7—264 (7.3); *p*H 13—263(7.2). $\bar{\nu}$ in cm.$^{-1}$ 3110, 3080, 3040, 2990, 2940, 2890 (CH); 1600, 1580 1505 (C=N, C=C); 1480 sh., 1450, 1410, (CH); 960, 935, 920, 905 (ring CH).

Anal. Calcd. for $C_7H_8N_4$: C, 56.72; H, 5.44; N, 37.81. Found: C, 56.76; H, 5.36; N, 37.36.

7-Ethyl-7H-purine (XIV). In the manner described above for the preparation of 9-ethyl-9*H*-purine, 6,7-dihydrothiazolo[2,3-f]purine was dethiolated to give 75 mg. (18%) of 7-ethyl-7*H*-purine (recrystallized from cyclohexane); m.p., 107°. pK_a by titration at 27° in 0.15*M* sodium chloride-2.67. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—258 (4.6); *p*H 7—267 (5.6); *p*H 13-266 (5.6). $\bar{\nu}$ in cm.$^{-1}$: 3100, 3080, 3050, 2970, 2940 (CH); 1605, 1580 sh., 1560, 1540 sh., 1482, 1455 sh., 1445 (CH); 960, 920, 900 (ring CH).

Anal. Calcd. for $C_7H_8N_4$: C, 56.72; H, 5.44; N, 37.81. Found: C, 56.54; H, 5.14; N, 37.47.

6,7-Dihydrothiazolo[2,3-f]purine (260 mg., 52%) was recovered so that the conversion to 7-ethyl-7*H*-purine was 38%.

2-(Benzylthio)purine. A mixture of purine-2(1 or 3*H*)-thione monohydrate (500 mg., 294 mmoles), α-chlorotoluene (0.35 ml., 3.06 mmoles), and potassium carbonate (408 mg., 2.94 mmoles) in *N,N*-dimethylformamide (4 ml.) was stirred at 40° for 16 hr. The mixture was then poured into 25 ml. of ice water, and the white precipitate that formed was collected by filtration and recrystallized from aqueous ethyl alcohol. This material was dried at room temperature *in vacuo* over phosphorus pentoxide; yield, 412 mg. (58%); m.p., 202°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—224, 253, 310 (15.9, 12.7, 5.0); *p*H 7—230, 250 (sh.), 303 (19.6, 11.1, 6.3); *p*H 13—239, 300 (18.6, 6.5).

Anal. Calcd. for $C_{12}H_{10}N_4S$: C, 59.50; H, 4.16; S, 13.21. Found: C, 49.47; H, 4.21; S, 13.16.

8-(Benzylthio)purine. A mixture of purine-8(7*H*)-thione (500 mg., 3.28 mmoles), α-chlorotoluene (0.41 ml., 3.6 mmoles), and potassium carbonate (454 mg., 3.28 mmoles) in *N,N*-dimethylformamide (5 ml.) was stirred at 80° for 3 hr. The cooled mixture was poured into 20 ml. of ice water and the resulting solution acidified. Ethyl alcohol was added to dissolve the solid that had precipitated. The solution was concentrated and allowed to cool. The solid that crystallized was collected by filtration, washed with cold water, and dried at 100° *in vacuo* over phosphorus pentoxide; yield, 390 mg. (49%); m.p., 204°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—306 (20.5); *p*H 7—295 (19.1); *p*H 13—298 (19.7).

Anal. Calcd. for $C_{12}H_{10}N_4S$: C, 59.50; H, 4.16; S, 13.21. Found: C, 59.73; H, 4.12; S, 13.13.

8-(Benzylthio)-9-ethyl-9H-purine. A mixture of 9-ethyl-9*H*-purine-8(7*H*)-thione (500 mg., 2.78 mmoles), α-chlorotoluene (0.32 ml., 3.1 mmoles), potassium carbonate (384 mg. 2.98 mmoles) in *N,N*-dimethylformamide (5 ml.) was stirred at 45–55° for 2 hr. The cooled reaction mixture was poured into 20 ml. of ice water and the bright yellow oil that formed was separated by decantation and allowed to crystallize in the refrigerator. The low-melting solid was purified by partition chromatography on a Celite column using water-saturated butyl alcohol as the developer; yield, 600 mg. (80%); m.p. *ca.* 32°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—238, 303 (14.7, 14.1); *p*H 7—293 (16.8); *p*H 13—292 (17.0).

Anal. Calcd. for $C_{14}H_{14}N_4S$: C, 62.20; H, 5.23; N, 20.73; S, 11.86. Found: C, 62.09; H, 5.53; N, 20.64; S, 11.93.

8-(2-Chloroethylthio)-9-ethyl-9H-purine. A mixture of 9-ethyl-9*H*-purine-8(7H)-thione (500 mg., 2.71 mmoles), 1-bromo-2-chloroethane (0.24 ml., 2.83 mmoles), and potassium carbonate (384 mg., 2.78 mmoles) in *N,N*-dimethylformamide (5 ml.) was heated at 60–65° for 1 hr., cooled,

and poured into 15 ml. of ice water. The white solid that precipitated was removed by filtration and dried at 60° *in vacuo* over phosphorus pentoxide; yield, 430 mg. (64%); m.p., 83.5°. λ_{max} in mμ ($\epsilon \times 10^{-3}$): *p*H 1—238, 298 (15.9, 14.3); *p*H 7—288 (17.9); *p*H 13—288 (17.9).

Anal. Calcd. for $C_9H_{11}ClN_4S$: C, 44.50; H, 4.51; Cl, 14.59. Found: C, 44.46; H, 4.50; Cl, 14.52.

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BIRMINGHAM, ALA.

[CONTRIBUTION FROM ROHM & HAAS CO., REDSTONE ARSENAL RESEARCH DIVISION]

Preparation and Some Reactions of Thiobis-*N*-(trifluoromethyl)amines[1]

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The fluorination of aryl and alkyl isothiocyanates with iodine pentafluoride in pyridine solution has been found to produce thiobis-*N*-substituted *N*-(trifluoromethyl)amines. The preparation and some of the reactions of these novel compounds are discussed. A unique rearrangement of a thiobisamine to a diphenyl sulfide is reported.

Although iodine pentafluoride is a mild fluorinating agent,[2] very few fluorinations of organic compounds have been explored with this reagent.[3] During the course of an investigation of the reactions of iodine pentafluoride and organic compounds it was found that aryl and alkyl isothiocyanates were converted cleanly to thiobis-*N*-(trifluoromethyl)amines[4] (I) by iodine pentafluoride in pyridine solution.

$$R{-}N{=}C{=}S + IF_5 \longrightarrow \underset{\textbf{I}}{R{-}\overset{CF_3}{\overset{|}{N}}{-}S{-}\overset{CF_3}{\overset{|}{N}}{-}R}$$

Formulation of these products as thiobis amines is based on the analytical data given in Table I, the NMR spectra, and the other experiments discussed below.

Preparation. Fluorination of aromatic isothiocyanates[5] occurred much more readily than did fluorination of their alkyl counterparts, although this is not obvious from the yields reported in Table I. In all the aromatic cases, fluorination was complete after a few minutes at 75–90° and a product free of isothiocyanate was isolated in almost quantitative yield. However, recrystallization of these products from ethanol or hexane was necessary to obtain the melting points reported in Table I. Since the infrared spectrum of the crude product essentially was identical with that of the purified thiobis amine, the material removed by recrystallization may have been the dithiobis-*N*-(trifluoromethyl)amine.[6]

Iodination of the ring of the aromatic isothiocyanates was observed only with phenyl isothiocyanate. Some of the *N*-(*p*-iodophenyl)thiobisamine was isolated in most experiments. If any unsymmetrical thioamine formed it was not isolated.

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(2) M. C. Sneed, J. L. Maynard, and R. C. Brasted, *Comprehensive Inorganic Chemistry, Vol. III, The Halogens*, Van Nostrand, New York, 1954, pp. 210–213, General Chemical Division, Allied Chemical and Dye Corporation, Technical Bulletin TA-8532-2, *Chlorine Trifluoride and Other Halogen Fluorides*.

(3) Fluorinations utilizing iodine pentafluoride that have been reported to lead to a trifluoromethyl group include the conversion of ICN to $CF_3{-}N{=}N{-}CF_3$ [O. Ruff and W. Willenberg, *Ber.*, **73**, 724 (1940)] and the formation of trifluoromethyl disulfide from carbon disulfide [R. N. Haszeldine and J. M. Kidd, *J. Chem. Soc.*, 3219 (1953)].

(4) In a preliminary report of this work [T. E. Stevens, Tetrahedron Letters, **17**, 16 (1959)] these compounds were called bis-*N*-(trifluoromethyl)amino sulfides. The name bisamino sulfide is used in E. E. Reid, *Organic Chemistry of Bivalent Sulfur*, Chemical Publishing Co., New York, Vol. II, to denote the symmetrical alkyl sulfides containing amine functions. A section on p. 296 of this volume discusses thioamines.

(5) In an earlier communication[4] it was reported that the fluorination of *p*-nitrophenyl, *p*-acetylphenyl and *p*-dimethylaminophenyl isothiocyanates did not yield thiobisamines. Since then the conversion of the first two compounds to the desired product has been accomplished. The initial failure with the *p*-nitrophenyl isothiocyanate can be attributed to an impure sample; the lack of success with the *p*-acetyl member was due to too stringent reaction conditions (see Experimental). However, several attempts to fluorinate *p*-dimethylaminophenyl isothiocyanate led only to intractable tars.

(6) It generally was observed that attempts to concentrate the mother liquors from the recrystallization of the thiobisamines led to oily products, the infrared spectra of which were indistinguishable from those of the purified products or of the crude products. An oily residue from the *p*-chlorophenyl isothiocyanate reaction contained 10.6% sulfur. The related thiobisamine contains 7.6% sulfur, the dithiobisamine, 14.1% sulfur.