[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, NEW MEXICO HIGHLANDS UNIVERSITY AND DEPARTMENT OF CHEMISTRY, ARIZONA STATE UNIVERSITY]

# Potential Purine Antagonists. XVII. Synthesis of Some 2-Methyl- and 2-Methylthio-6,8-Disubstituted Purines[1]

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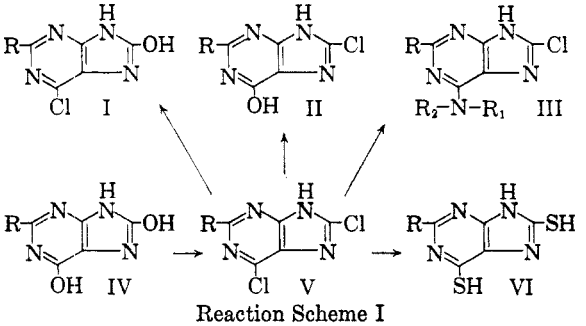
Urea fusion of 4,5-diamino-6-hydroxy-2-methylpyrimidine and 4,5-diamino-6-hydroxy-2-pyrimidinethiol gave 6,8-dihydroxy-2-methylpurine (IV, R = $CH_3$) and 6,8-dihydroxy-2-purinethiol (IV, R = SH), respectively. Methylation of IV (R = SH) gave 6,8-dihydroxy-2-methylthiopurine (IV, R = $SCH_3$). From IV (R = $CH_3$, $SCH_3$) were prepared 6,8-dichloro-2-methyl- and 6,8-dichloro-2-methylthiopurine (V, R = $CH_3$, $SCH_3$). Similarly, 6-hydroxy-2-methylthiopurine (VII) and 8-hydroxy-2-methylthiopurine (XIV) were converted to the corresponding 6-chloro- and 8-chloropurines, respectively. These chloropurines were further converted into additional new purine derivatives.

Renewed interest in 2-methyl- and 2-methylthiopurines has been stimulated by the discovery of 6-amino-2-methylpurine[3] and 6-amino-2-methylthiopurine[4] in natural materials. The present investigation deals with the preparation of a number of derivatives of the purine nucleus containing a 2-methyl or 2-methylthio group.

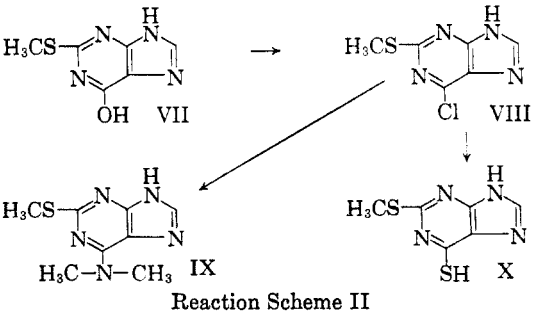
Urea fusion of 4,5-diamino-6-hydroxy-2-methylpyrimidine sulfate[5] gave 6,8-dihydroxy-2-methylpurine (IV, R = $CH_3$) in good yield. 6,8-Dihydroxy-2-purinethiol (IV, R = SH) was similarly prepared from 4,5-diamino-6-hydroxy-2-pyrimidinethiol[6] and urea. 6,8-Dihydroxy-2-methylthiopurine (IV, R = $SCH_3$) was prepared by methylation of IV, R = SH, with methyl iodide in the presence of aqueous base.




Reaction Scheme I

Chlorination of IV (R = $CH_3$, $SCH_3$) with phosphorus oxychloride and *N,N*-diethylaniline readily gave the corresponding 6,8-dichloropurine (V) in good yield. 2-Methyl- and 2-methylthio-6,8-purinedithiol (VI) were prepared from V (R = $CH_3$, $SCH_3$) and refluxing absolute ethanol containing thiourea.

Treatment of V with hot aqueous hydrochloric acid resulted in the preparation of the corresponding 6-chloro-8-hydroxypurine (I) while reaction of V with dilute sodium hydroxide gave the isomeric 8-chloro-6-hydroxy-2-methyl- or 8-chloro-6-hydroxy-2-methylthiopurine (II, R = $CH_3$, $SCH_3$). The structures assigned I and II were made on the basis of similar reactions noted with 6,8-dichloropurine[7] and on the similarity of ultraviolet absorption spectra of II, R = $SCH_3$, to 6-hydroxy-2-methylthiopurine (VII) and I, R = $SCH_3$, to 8-hydroxy-2-methylthiopurine (XIV). This similarity in spectra is to be expected since Mason[8] has shown there is little shift in the wave length maximum due to the presence of a chlorine atom in the purine molecule. Reaction of V with various primary and secondary amines heated on the steam bath readily gave III. This is to be expected since the "6" chlorine atom of 6,8-dichloropurine[7] has previously been shown to be most reactive in the usual nucleophilic replacement reactions. The structure of III, R = $C_3H$, $R_1 = R_2 = C_2H_5$, was further confirmed since the ultraviolet absorption spectra strongly resembled that of the known 6-dimethylamino-2-methylpurine.[9] Similarly, the spectra of III, R = $SCH_3$, $R_1 = R_2 = CH_3$, were




Reaction Scheme II

(1) This investigation was supported in part by research grant C-2845 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

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(3) D. N. Brown and E. L. Smith, *Biochem. J.*, **56**, 34 (1954); H. W. Dion, D. G. Calkins, and J. J. Pfiffner, *J. Am. Chem. Soc.*, **76**, 948 (1954).

(4) F. Wilhelm and K. Bernhauer, *Chem. Ber.*, **90**, 1966 (1957).

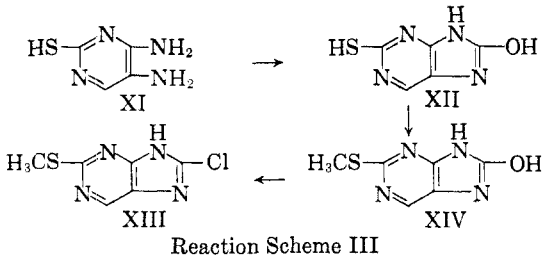
(5) R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Am. Chem. Soc.*, **75**, 265 (1953).

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

(7) R. K. Robins, *Potential Purine Antagonists XV . . . .*, *J. Am. Chem. Soc.*, **80**, 6671 (1958).

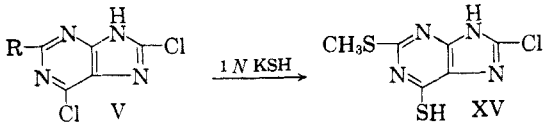
(8) S. F. Mason *J. Chem. Soc.*, 2071 (1954).

(9) R. K. Robins, J. W. Jones, and H. H. Lin, *J. Org. Chem.*, **21**, 696 (1956).



Reaction Scheme III

found similar to the spectra of 6-dimethylamino-2-methylthiopurine (IX). The preparation of IX was accomplished with dimethylamine and 6-chloro-2-methylthiopurine (VIII) which was in turn prepared from 6-hydroxy-2-methylthiopurine (VII)[10] by treatment of VII with phosphorus oxychloride and *N,N*-diethylaniline. 2-Methylthio-6-purinethiol (X) was prepared from 6-chloro-2-methylthiopurine (VIII) and thiourea in refluxing ethanol. The preparation of 8-hydroxy-2-methylthiopurine (XIV) was accomplished by methylation of 8-hydroxy-2-purinethiol (XII) with methyl iodide. The compound, 8-hydroxy-2-purinethiol (XII), was obtained from the thiourea fusion of 4,5-diamino-2-pyrimidinethiol (XI).[11] 8-Chloro-2-methylthiopurine (XIII) was prepared from 8-hydroxy-2-methylthiopurine (XIV) by the use of *N,N*-diethylaniline and phosphorus oxychloride. 6,8-Dichloro-2-methylthiopurine (V, R = $SCH_3$) was treated with boiling *N* potassium hydrosulfide to give a monopurinethiol, judged to be 8-chloro-2-methylthio-6-purinethiol (XV) since the ultraviolet absorption spectra of 2-methylthio-6-purinethiol (X) and that of XV at *p*H 1 and 11 were almost identical. 8-Chloro-2-methyl-6-purinethiol was similarly prepared from V, R = $CH_3$. The ultraviolet



absorption spectra of the 2-methyl- and 2-methylthiopurines prepared are listed in Table I.

## EXPERIMENTAL[12]

*Preparation of 6,8-dihydroxy-2-methylpurine* (IV, R = $CH_3$). 4,5-Diamino-6-hydroxy-2-methylpyrimidine sulfate[5] (100 g.) and 300 g. of urea were ground and mixed thoroughly. This mixture was heated at 160–180° for approximately 30 min. until it became semisolid. The cooled solid was dissolved in hot dilute potassium hydroxide solution. Norit was added, and the solution was filtered. The hot filtrate was acidified with glacial acetic acid, and the precipitate that formed was filtered immediately, washed with water, and dried at 110° to yield 105 g. of product. A small amount was recrystallized from a large volume of water for analysis.

*Anal.* Calcd. for $C_6H_6N_4O_2$: C, 43.3; H, 3.6. Found: C, 42.9; H, 4.0.

*6,8-Dichloro-2-methylpurine* (V, R = $CH_3$). Finely powdered 6,8-dihydroxy-2-methylpurine (IV, R = $CH_3$) (80 g.)

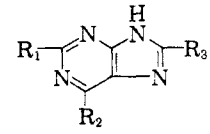
(10) G. B. Elion, W. H. Lange, and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 217 (1956).

(11) D. J. Brown, *J. Appl. Chem. (London)*, **2**, 239 (1952).

(12) All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus, unless otherwise indicated.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF SOME 2-METHYL- AND 2-METHYLTHIOPURINES



| $R_1$ | $R_2$ | $R_3$ | $\lambda_{max}$ *p*H 1 (Mμ) | *e* | $\lambda_{max}$ *p*H 11 (Mμ) | *e* |
|---|---|---|---|---|---|---|
| $CH_3$ | OH | OH | 255 | 6,140 | 273 | 6,300 |
| $CH_3$ | Cl | Cl | 235 | 6,770 | 283 | 11,100 |
| | | | 275 | 14,000 | | |
| $CH_3$ | SH | SH | 270 | 13,400 | 270 | 23,900 |
| | | | 360 | 23,000 | 335 | 43,600 |
| $CH_3$ | Cl | OH | 255 | 14,400 | 273 | 14,400 |
| $CH_3$ | OH | Cl | 255 | 15,200 | 265 | 14,400 |
| $CH_3$ | $N(C_2H_5)_2$ | Cl | 240 | 7,180 | 283 | 14,300 |
| | | | 275 | 14,300 | | |
| $CH_3$ | $N(CH_2)_2CH_3$ / $N(CH_2)_2CH_3$ | Cl | 275 | 11,800 | 279 | 11,200 |
| $CH_3$ | SH | Cl | 230 | 10,000 | 236 | 14,000 |
| | | | 332 | 20,800 | 319 | 18,000 |
| $SCH_3$ | OH | OH | 265 | 10,700 | 224 | 17,000 |
| | | | 298 | 7,500 | 283 | 11,200 |
| $SCH_3$ | Cl | Cl | 230 | 22,100 | 242 | 25,400 |
| | | | 260 | 12,200 | | |
| | | | 310 | 9,160 | 307.5 | 9,850 |
| $SCH_3$ | Cl | OH | 264 | 13,800 | 240 | 16,200 |
| | | | 309 | 8,600 | 308 | 11,900 |
| $SCH_3$ | OH | Cl | 265 | 17,200 | 227 | 21,400 |
| | | | | | 277 | 15,400 |
| $SCH_3$ | SH | Cl | 230 | 17,900 | 243 | 16,800 |
| | | | 265 | 10,600 | 263 | 17,000 |
| | | | 340 | 19,600 | 325 | 17,900 |
| $SCH_3$ | SH | SH | 275 | 23,600 | 227 | 23,600 |
| | | | 310 | 12,600 | 268 | 28,500 |
| | | | 370 | 31,000 | 345 | 32,400 |
| $SCH_3$ | $N(CH_3)_2$ | Cl | 257 | 20,400 | 240 | 25,600 |
| | | | 296 | 19,600 | 292 | 17,300 |
| $SCH_3$ | $N(o\text{-}ClC_6H_4)$ | Cl | 258 | 17,900 | 255 | 22,500 |
| | | | 318 | 15,300 | 330 | 24,100 |
| $SCH_3$ | H | OH | 245 | 19,500 | 238 | 16,400 |
| | | | 270 | 12,200 | | |
| | | | 308 | 5,100 | 305 | 10,200 |
| $SCH_3$ | H | Cl | 240 | 20,000 | 242 | 26,000 |
| | | | 308 | 6,800 | 305 | 11,000 |
| $SCH_3$ | Cl | H | 230 | 16,800 | 243 | 20,200 |
| | | | 259 | 11,000 | | |
| | | | 307 | 5,100 | 305 | 6,600 |
| $SCH_3$ | $N(CH_3)_2$ | H | 255 | 26,900 | 240 | 31,600 |
| | | | 293 | 21,800 | 292 | 19,600 |
| $SCH_3$ | SH | H | 242 | 11,100 | 238 | 12,700 |
| | | | 268 | 10,300 | 263 | 13,800 |
| | | | 338 | 16,600 | 318 | 15,600 |
| $SCH_3$ | OH | H | 265 | 16,000 | 270 | 11,200 |
| SH | OH | OH | 265 | 11,000 | 225 | 28,500 |
| | | | 297 | 7,700 | 283 | 11,800 |
| SH | H | OH | 251 | 19,100 | 250 | 24,200 |
| | | | 285 | 25,200 | 260 | 25,200 |
| | | | | | 320 | 25,200 |

was covered with 1500 ml. of phosphorus oxychloride and 250 ml. of *N,N*-diethylaniline. This mixture was then refluxed 6 hr.; the excess phosphorus oxychloride was removed under reduced pressure, and the residue was poured on chopped ice. The mixture was then allowed to stand 10 min., and the cold solution was extracted with 6 × 1000 ml. portions of ether. The combined ether extract was washed with 3 × 400 ml. portions of ice water and then dried over anhydrous sodium sulfate. Upon removal of the ether by distillation, 59 g. of 6,8-dichloro-2-methylpurine was obtained, m.p. 196–199°. Recrystallization from toluene yielded white crystals, m.p. 205–206°.

*Anal.* Calcd. for $C_6H_4N_4Cl_2$: C, 35.4; H, 2.0; N, 27.6. Found: C, 35.7; H, 1.9; N, 27.5.

*6-Chloro-8-hydroxy-2-methylpurine* (I, R = $CH_3$). 6,8-Dichloro-2-methylpurine (V, R = $CH_3$) (4 g.) was placed in 75 ml. of 3*N* hydrochloric acid solution, and the mixture was refluxed for 12 hr. The solution was then cooled and filtered, and the precipitate was washed with water and dried at 110° to yield 1.5 g. of product. A small portion was recrystallized from water for analysis, m.p. >300°.

*Anal.* Calcd. for $C_6H_5N_4ClO$: C, 38.9; H, 2.7. Found: C, 38.6; H, 3.0.

*8-Chloro-6-hydroxy-2-methylpurine* (II, R = $CH_3$). 6,8-Dichloro-2-methylpurine (V, R = $CH_3$) (10 g.) was covered with 100 ml. of 2*N* sodium hydroxide, and the solution was refluxed for 2 hr. The hot basic solution was then treated with Norit and filtered, and the warm filtrate was acidified with glacial acetic acid. The mixture was allowed to stand 3 days; then it was filtered. The precipitate was washed with water and dried at 110° to yield 3.1 g. of product. A small portion was recrystallized from water for analysis, m.p. >300°.

*Anal.* Calcd. for $C_6H_5N_4ClO$: C, 38.9; H, 2.7; N, 30.2. Found: C, 38.5; H, 2.9; N, 30.1.

*8-Chloro-2-methyl-6-purinethiol.* 6,8-Dichloro-2-methylpurine (V, R = $CH_3$) (3 g.) was added to 50 ml. of a *N* potassium sulfide solution, and the mixture was refluxed for 4 hr. The hot solution was treated with Norit and filtered, and the filtrate was acidified with glacial acetic acid. The mixture was cooled, and the orange needles were filtered and washed with water. The yield was 1.9 g. A small sample was further purified by reprecipitation.

*Anal.* Calcd. for $C_6H_5N_4ClS$: C, 35.9; H, 2.4. Found: C, 35.9; H, 2.9.

*2-Methyl-6,8-purinedithiol* (VI, R = $CH_3$). 6,8-Dichloro-2-methylpurine (V, R = $CH_3$) (8 g.) was covered with 200 ml. of absolute ethanol, and 7 g. of thiourea was added. This mixture was refluxed for 4 hr. and then allowed to cool to room temperature. The precipitate was filtered, washed with alcohol, and dried at 110°. The product obtained (7.9 g.) was purified by reprecipitation with glacial acetic acid from a boiling basic solution.

*Anal.* Calcd. for $C_6H_6N_4S_2$: C, 36.4; H, 3.0; N, 28.2. Found: C, 36.4; H, 3.5; N, 28.4.

*Preparation of some 8-chloro-2-methyl-6-substituted aminopurines* (III). *8-Chloro-6-diethylamino-2-methylpurine hydrochloride* (III, R = $CH_3$, $R_1$, $R_2$ = $C_2H_5$). 6,8-Dichloro-2-methylpurine (V, R = $CH_3$) (2 g.) was covered with 60 ml. of absolute ethanol, and 1.9 g. of diethylamine was added. The mixture was evaporated to dryness on the steam bath. Benzene (60 ml.) was added, and heating was continued until the volume had decreased to approximately 20 ml. The solution was then cooled, and the precipitate was filtered and dried at 110° for 2 hr. to yield 3.0 g. Recrystallization from benzenemethanol gave a pure product, m.p. 163–165°.

*Anal.* Calcd. for $C_{10}H_{14}N_5Cl \cdot HCl$: C, 43.5; H, 5.4; N, 25.3. Found: C, 43.6; H, 5.3; N, 25.0.

*8-Chloro-6-di-n-propylamino-2-methylpurine hydrochloride* (III, R = $CH_3$, $R_1$, $R_2$ = $C_3H_7$). 6,8-Dichloro-2-methylpurine (V, R = $CH_3$) (2 g.) was covered with 60 ml. of absolute ethanol, and 1.2 g. of di-*n*-propylamine was added. The isolation and purification of this compound is identical to that of the 6-diethylamino derivative (IX). Yield of product was 2.3 g., m.p. 163–165°.

*Anal.* Calcd. for $C_{12}H_{18}N_5Cl \cdot HCl$: C, 47.3; H, 5.9. Found: 47.1; H, 6.3.

*6,8-Dihydroxy-2-purinethiol* (IV, R = SH). 4,5-Diamino-6-hydroxy-2-pyrimidinethiol[6] (190 g.) was thoroughly mixed with 380 g. of urea, and the mixture was heated at 160–180°. Heating was continued approximately 30 min. until the liquid melt became quite viscous and difficult to stir. Then 3000 ml. of hot water and sufficient potassium hydroxide were added to dissolve all the solid material. Norit was added to the hot solution, which was then filtered. The filtrate was acidified with concentrated hydrochloric acid. The precipitate that formed was filtered from the hot solution, and the product was washed with water, then acetone, to yield 225 g. This product was shown by ultraviolet absorption spectra to be above 95% pure. An analytically pure sample was obtained by reprecipitation of the crude product from a boiling basic solution with hydrochloric acid.

*Anal.* Calcd. for $C_5H_4N_4O_2S$: C, 32.6; H, 2.2; N, 30.4. Found: C, 32.5; H, 2.1; N, 30.4.

*6,8-Dihydroxy-2-methylthiopurine* (IV, R = $SCH_3$). To 3000 ml. of hot water were added 200 g. of 6,8-dihydroxy-2-purinethiol and sufficient potassium hydroxide to dissolve all solid material. The solution was then cooled to 25° and stirred mechanically while 152 g. of methyl iodide was added. Vigorous stirring was continued for 45 min., after which time, the solution was heated to 50°, treated with charcoal, and filtered. The filtrate was acidified with glacial acetic acid, and the precipitate that formed was filtered immediately. Two more reprecipitations gave 205 g. of pure product, m.p. > 300°.

*Anal.* Calcd. for $C_6H_6N_4O_2S \cdot H_2O$: C, 33.1; H, 4.1; N, 26.0. Found: C, 33.2; H, 3.9; N, 26.2.

*6,8-Dichloro-2-methylthiopurine* (V, R = $SCH_3$). 6,8-Dihydroxy-2-methylthiopurine (IV, R = $SCH_3$) (150 g.), finely powdered, was added to 1500 ml. of phosphorus oxychloride. *N,N*-Diethylaniline (300 ml.) was then added, and the mixture was refluxed for 5 hr. The excess phosphorus oxychloride was removed under reduced pressure with a steam bath as the source of heat. The residue was poured on ice, with manual stirring, and the solution was allowed to stand 10 min. This cold aqueous solution was extracted with 6 × 1000 ml. portions of ether. The combined ether extract was washed with 3 × 400 ml. portions of ice water, and the ethereal solution was dried overnight over anhydrous sodium sulfate. Upon removal of the ether by distillation, 109 g. of product, m.p. 224–227°, was obtained. Recrystallization from a toluene-benzene mixture yielded a product, m.p. 230°.

*Anal.* Calcd. for $C_6H_4N_4Cl_2S$: C, 30.6; H, 1.7; N, 23.8. Found: C, 30.9; H, 2.2; N, 23.9.

*8-Chloro-6-hydroxy-2-methylthiopurine* (II, R = $SCH_3$). 6,8-Dichloro-2-methylthiopurine (V, R = $SCH_3$) (10 g.) was dissolved in 100 ml. of 2*N* sodium hydroxide, and the solution was refluxed for 2 hr. The solution was then filtered, and the filtrate was cooled to room temperature. After acidification with glacial acetic acid, the mixture was allowed to stand for 1 hr., and the precipitate was filtered, washed with water, and dried at 110° to yield 8.5 g. of product. Recrystallization from water gave an analytically pure sample, m.p. > 300°.

*Anal.* Calcd. for $C_6H_5N_4ClOS$: C, 33.2; H, 2.3; N, 25.8. Found: C, 33.1; H, 2.3; N, 25.5.

*6-Chloro-8-hydroxy-2-methylthiopurine* (I, R = $SCH_3$). 6,8-Dichloro-2-methylthiopurine (V, R = $SCH_3$) (10 g.) was covered with 100 ml. of 2*N* hydrochloric acid solution, and the mixture was refluxed for 4 hr. The mixture was allowed to cool to room temperature, and the colorless precipitate was filtered and washed with water to yield 7.5 g. of product. A small portion was recrystallized from water for analysis, m.p. > 300°.

*Anal.* Calcd. for $C_6H_5N_4ClOS$: C, 33.2; H, 2.3. Found: C, 33.1; H, 2.2.

*8-Chloro-2-methylthio-6-purinethiol* (XV). 6,8-Dichloro-2-methylthiopurine (V, R = $SCH_3$) (3 g.) was covered with 40 ml. of *N* potassium sulfide solution, and the mixture was refluxed for 4 hr. The hot solution was then treated with charcoal and filtered, and the warm filtrate was acidified with glacial acetic acid. The mixture was filtered after standing for 30 min., and the product was washed with water and dried at 110° to yield 2.7 g. of yellow needles. Purification for analysis was afforded by reprecipitation with glacial acetic acid from a hot dilute sodium hydroxide solution.

*Anal.* Calcd. for $C_6H_5N_4S_2Cl$: C, 30.9; H, 3.0. Found: C, 30.8; H, 2.9.

*2-Methylthio-6,8-purinedithiol* (VI, R = $SCH_3$). 6,8-Dichloro-2-methylthiopurine (V, R = $SCH_3$) (10 g.) was covered with 350 ml. of absolute ethanol, and 7.5 g. of thiourea was added. This mixture was then refluxed for 4 hr. and allowed to stand at room temperature for 2 hr. The yellow precipitate was filtered, washed with ethanol, and dried at 110° to yield 6.5 g. of product. A small portion of product was recrystallized from *N,N*-dimethylformamide and water.

*Anal.* Calcd. for $C_6H_6N_4S_3$: C, 31.3; H, 2.6; N, 24.3. Found: C, 31.6; H, 2.9; N, 24.7.

*Preparation of some 8-chloro-2-methylthio-6-substituted aminopurines* (III, R = $SCH_3$). *8-Chloro-6-dimethylamino-2-methylthiopurine* (III, R = $SCH_3$, $R_1$, $R_2$ = $CH_3$). 6,8-Dichloro-2-methylthiopurine (V, R = $SCH_3$) (3 g.) was covered with 15 ml. of water, and then 15 ml. of dimethylamine solution (25% in water) was added. This mixture was heated on the steam bath for 3 hr. and allowed to cool in a refrigerator. The precipitate was filtered, washed with water, and dried to yield 3 g. of product. For purification the amine was recrystallized from *N,N*-dimethylformamide and ethanol. The melting point of the product was 291°.

*Anal.* Calcd. for $C_8H_{10}N_5ClS$: C, 39.4; H, 4.1; N, 28.8. Found: C, 39.8; H, 4.3; N, 29.0.

*8-Chloro-6-o-chloroanilino-2-methylthiopurine* (III, R = $SCH_3$, $R_1$ = H, $R_2$ = *o*-$ClC_6H_4$). 6,8-Dichloro-2-methylthiopurine (V, R = $SCH_3$) (3 g.) was covered with 50 ml. of absolute ethanol, and 1.7 g. of *o*-chloroaniline was added. The mixture was placed on the steam bath for 3 hr., then cooled. The precipitate that had formed was filtered and washed with a small portion of ethanol to yield 3.2 g. of product. Recrystallization from ethanol gave a pure sample, m.p. 282°.

*Anal.* Calcd. for $C_{12}H_9N_5Cl_2S$: C, 44.2; H, 2.8. Found: C, 44.6; H, 3.3.

*8-Hydroxy-2-purinethiol* (XII). 4,5-Diamino-2-pyrimidinethiol (XI)[7] (21 g.) was finely ground and thoroughly mixed with 42 g. of urea, and the mixture was heated at 160–180° on a hot plate. After the mixture had become a melt, heating was continued until it became too viscous to stir manually. The solid mass was then dissolved in hot dilute sodium hydroxide, and the solution was treated with Norit and filtered. The hot filtrate was acidified with glacial acetic acid. The precipitate that formed was filtered immediately and washed with water. After drying overnight at 130°, 18 g. of product was obtained. Two more reprecipitations gave a pure sample, m.p. > 300°.

*Anal.* Calcd. for $C_5H_4N_4OS$: C, 35.8; H, 2.4. Found: C, 35.4; H, 2.3.

*8-Hydroxy-2-methylthiopurine* (XIV). 8-Hydroxy-2-purinethiol (XII) (50 g.) was added to 600 ml. of water, and the mixture was stirred mechanically. An adequate amount of sodium hydroxide was added to dissolve all solid material; then 41.3 g. of methyl iodide was added. The mixture was vigorously stirred for 30 min., and then the temperature was finally raised to 70°. The hot solution was treated with charcoal and filtered, and the hot filtrate was acidified with glacial acetic acid. The precipitate that formed was filtered immediately, washed with water, and dried at 110° to yield 42 g. of product. The product was recrystallized from water for analysis.

*Anal.* Calcd. for $C_6H_6N_4OS$: C, 39.5; H, 3.3; N, 30.8. Found: C, 39.1; H, 3.4; N, 30.2.

*8-Chloro-2-methylthiopurine* (XIII). 8-Hydroxy-2-methylthiopurine (XIV) (20 g.) was covered with 300 ml. of phosphorus oxychloride, and 30 ml. of *N,N*-diethylaniline was added. This mixture was refluxed for 5 hr., and the excess phosphorus oxychloride was removed under reduced pressure with a steam bath as the source of heat. The residue was poured on ice, with stirring, and the solution was allowed to stand 10 min. The cold aqueous mixture was extracted with 6 × 500 ml. portions of ether. The combined ether extract was then washed with 3 × 200 ml. portions of water and placed over anhydrous sodium sulfate to dry. After the ether was removed by distillation, 9.9 g. of chloro compound was obtained. Recrystallization from a toluene-methanol mixture yielded a product, m.p. 208°.

*Anal.* Calcd. for $C_6H_5N_4ClS$: C, 36.1; H, 2.5; N, 28.1. Found: C, 36.1; N, 2.8; N, 28.0.

*6-Chloro-2-methylthiopurine* (VIII). 6-Hydroxy-2-methylthiopurine (VII)[10] (20 g.) was covered with 300 ml. of phosphorus oxychloride, and 30 ml. of *N,N*-diethylaniline was added. The mixture was refluxed for 1.5 hr. The excess phosphorus oxychloride was then removed by vacuum distillation with a steam bath as the source of heat. The residue was poured over chopped ice, with stirring, and allowed to stand 10 min. The aqueous mixture was extracted with 6 × 8000 ml. portions of ether. The combined ether extract was washed with 4 × 400 ml. portions of water, and the ether was removed by distillation. The wet chloro compound was first dried under vacuum and then at 80° for 2 hr. to yield 12 g. of yellow needles. Recrystallization from ethanol gave a product, m.p. 274° (dec.).

*Anal.* Calcd. for $C_6H_5N_5ClS$: C, 36.0; H, 2.5; N, 28.1. Found: C, 36.0; H, 3.0; N, 27.9.

*2-Methylthio-6-purinethiol* (X). 6-Chloro-2-methylthiopurine (VIII) (1 g.) was covered with 50 ml. of absolute ethanol, and 1 g. of thiourea was added. This mixture was refluxed for 5 hr. and then allowed to cool to room temperature. The yellow precipitate was filtered, washed with ethanol, and dried at 110° to yield 0.7 g. of product. A pure sample was obtained by reprecipitation with glacial acetic acid from a dilute sodium hydroxide solution.

*Anal.* Calcd. for $C_6H_6N_4S_2$: C, 36.4; H, 3.0; N, 28.3. Found: C, 36.6; H, 3.2; N, 28.9.

*6-Dimethylamino-2-methylthiopurine hydrochloride* (IX). 6-Chloro-2-methylthiopurine (VIII) (1 g.) was covered with 30 ml. of water, and 10 ml. of dimethylamine solution (25% in water) was added. This mixture was heated on the steam bath until the final volume was approximately 15 ml. The mixture was then allowed to cool, and the precipitate was filtered and dried at 110° for 2 hr. to yield 1.1 g. of product, m.p. 297–299°. Recrystallization from methanol did not change the melting point.

*Anal.* Calcd. for $C_8H_{11}N_5S$·HCl: C, 45.9; H, 5.3. Found: 45.5; H, 5.4.

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