[CONTRIBUTION FROM ARIZONA STATE COLLEGE]

Potential Purine Antagonists. XIII. Synthesis of Some 8-Methylpurines[1]

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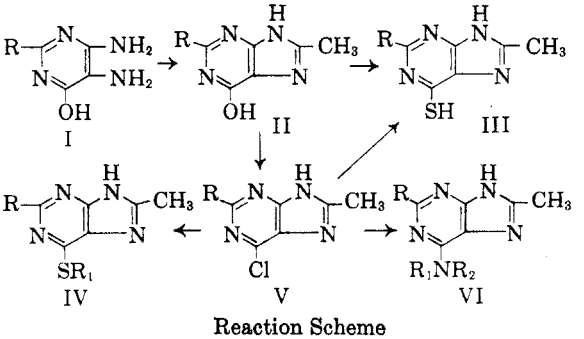
The use of acetic anhydride as a general cyclizing agent for 4,5-diaminopyrimidines has been investigated. A number of new 8-methylpurines have been prepared.

The anti-tumor activity exhibited by certain 6-substituted purines[2-4] prompted the synthesis of several 8-methyl-6-substituted purines as homologs for anti-tumor testing. Several 8-methylpurines have previously been reported[5-8]. From earlier work[5,6] it appeared that cyclization of the requisite 4,5-diaminopyrimidine with acetic anhydride might serve as a good general method of preparation of the desired compounds.

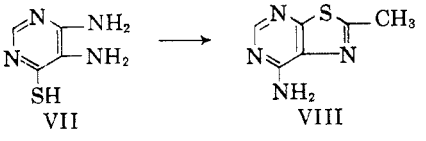
In the present work a general study has been made utilizing acetic anhydride as a cyclizing agent in the preparation of new 8-methylpurines.

The synthesis of 6-hydroxy-8-methylpurine (II, R=H) from 4,5-diamino-6-hydroxypyrimidine (I, R=H)[9] and acetic anhydride was accomplished in an over-all yield of 70%. Similarly, 4,5-diamino-6-hydroxy-2-pyrimidinethiol (I, R=SH)[10] gave 6-hydroxy-8-methyl-2-purinethiol (II, R=SH), and 4,5-diamino-6-hydroxy-2-methylthiopyrimidine (I, $R=CH_3S$)[11] gave 6-hydroxy-8-methyl-2-methylthiopurine (II, $R=CH_3S$). The latter compound, II, $R=CH_3S$, was also prepared by the methylation of 6-hydroxy-8-methyl-2-purinethiol (II, R=SH). When an attempt was made to cyclize 4,5-diamino-6-pyrimidenethiol (VII)[12] with acetic anhydride, the cyclization proceeded through the sulfur atom yielding 2-methyl-7-aminothiazolo-[5,4-*d*]pyrimidine (VIII) as evidenced by the insolubility in base of the product. Further verification was obtained from a comparison of the ultraviolet absorption spectrum of the product with that of an authentic sample of 8-methyl-6-purinethiol (III, R=H) prepared from 8-methyl-6-chloropurine (V, R=H). A similar cyclization

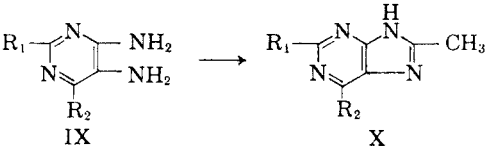


Reaction Scheme

has been reported with 4,5-diamino-6-purinethiol and formic acid.[13] 4,5,6-Triaminopyrimidine (IX, $R_1=H$, $R_2=NH_2$)[14] was cyclized with acetic anhydride to yield 6-amino-8-methylpurine (X, $R_1=H$, $R_2=NH_2$). The treatment of 4,5-diamino-2,6-dihydroxypyrimidine (IX, $R_1=R_2=OH$) in acetic anhydride for 12 hr. yielded 8-methyl-2,6-dihydroxypurine (X, $R_1=R_2=OH$). An attempt was made to cyclize 6-hydroxy-2,4,5-triaminopyrimidine (IX, $R_1=NH_2$, $R_2=OH$) with acetic anhydride. Only starting material was isolated; however, a 1:1 mixture of acetic anhydride and ethylorthoacetate and 6-hydroxy-2,4,5-triaminopyrimidine gave 2-amino-6-hydroxy-8-methylpurine (X, $R_1=NH_2$, $R_2=OH$).



VII VIII



IX X

(1) This work was aided in part by a research grant from Parke, Davis & Company, Detroit, Mich.

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

(3) C. F. Rhodes and G. H. Hitchings, *Ann. N. Y. Acad. Sci.*, **60**, 183 (1954).

(4) R. K. Robins and H. H. Lin, *J. Am. Chem. Soc.*, **79**, 490 (1957).

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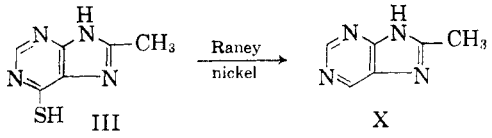
(13) G. B. Elion, W. Lange, and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 2858 (1956).

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

Treatment of II, R=H, with phosphorus oxychloride and *N,N*-diethylaniline gave 6-chloro-8-methylpurine (V, R=H). V, R=H, readily converted to III, R=H, by refluxing with thiourea in absolute ethanol. 8-Methyl-6-purinethiol (III, R=H) and Raney nickel in an aqueous solution provided a new method of synthesis for 8-methylpurine (X, $R_1=R_2=H$). When V, R=H, was treated with various amines in alcoholic solution, the corresponding 8-methyl-6-substituted aminopurine (VI, R=H) was obtained. Treatment of V, R=H, in dilute base with various alkylthiols



III X

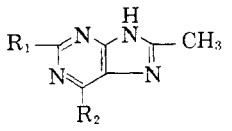
yielded the corresponding 8-methyl-6-alkylthiopurines (IV, R=H). Treatment of II, $R=CH_3S$, with phosphorus oxychloride and *N,N*-diethylaniline yielded 6-chloro-8-methyl-2-methylthiopurine (V, $R=CH_3S$) in 55% yield. 8-Methyl-2-methylthio-6-purinethiol (III, $R=CH_3S$) was prepared from V, $R=CH_3S$. A number of 8-methyl-2-methylthio-6-substituted aminopurines (VI, $R=CH_3S$) were also prepared from 6-chloro-8-methyl-2-methylthiopurine (V, $R=CH_3S$). Treatment of II, R=SH, with phosphorus pentasulfide in pyridine yielded 8-methyl-2,6-purinedithiol (III, R=SH).

An interesting general water-solubilizing effect of the 8-methyl group as compared to the corresponding simple purine[15] derivative was noted. It would appear that the 8-methyl group interferes somewhat with the intermolecular hydrogen bonding forces in the crystal lattice. This effect is not noted in the parent compound, 8-methylpurine, which could be predicted in the absence of the strong hydrogen bonding groups such as OH, NH_2, and SH.

The ultraviolet absorption spectra of some 8-methylpurines are recorded in Table I.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF SOME 8-METHYLPURINES



		*p*H 1		*p*H 11	
R_1	R_2	λ_{max}	ϵ_{max}	λ_{max}	ϵ_{max}
HS	OH	230	10,600	233	11,200
		287	15,800	280	12,000
OH	OH	265	7,800	237	9,700
				281	8,500
H	OH	260	8,000	257	2,100
HS	HS	256	12,500	253	19,800
		296	26,100	346	13,500
		354	10,100		
CH_3S	OH	233	13,700	223	13,700
		277	8,800	265	8,000
H	NH_2	269	13,400	266	14,900
H	Cl	265	10,100	277	7,900
H	SH	226	10,300	234	13,400
		328	17,700	312	18,000
NH_2	OH	249	12,900	275	9,700
		278	8,200		
CH_3S	SH	244	13,000	262	16,000
		265	12,600	324	18,600
		336	19,800		
H	H	264	8,800	275	10,000
CH_3S	Cl	232[a]	20,300[a]		
		260[a]	11,200[a]		
		306[a]	8,300[a]		

[a] Absorption spectra determined in absolute ethanol.

EXPERIMENTAL[16]

6-Hydroxy-8-methylpurine (II, R = H). Fifteen grams of 4,5-diamino-6-hydroxypyrimidine (I, R = H)[8] was refluxed in 250 ml. of acetic anhydride. A clear yellow solution resulted after 20 min. Reflux was continued 1 more hr.; at the end of this time the excess acetic anhydride was distilled under reduced pressure and the sirupy residue boiled in 250 cc. of 1.5*N* sodium hydroxide for 10 min. The solution was treated with charcoal and acidified while hot with glacial acetic acid. Upon cooling, the solution yielded 14 g. of long white needles. For analysis the product was recrystallized from water. The product analyzed for a monohydrate, m.p. >300°. This compound was soluble one part in three parts of water at 100°.

Anal. Calcd. for $C_6H_6N_4O.H_2O$: C, 42.8; H, 4.2; N, 33.3. Found: C, 42.8; H, 4.5; N, 33.2.

6-Chloro-8-methylpurine (V, R = H). To 500 ml. of phosphorus oxychloride, containing 50 ml. of *N,N*-diethylaniline, was added 35 g. of 8-methyl-6-hydroxypurine (II, R = H), and after the initial vigorous reaction, the mixture was refluxed for 5.5 hr. The excess phosphorus oxychloride was then distilled under reduced pressure and the residue poured on cracked ice. The solution was made strongly basic with 10*N* potassium hydroxide and allowed to stand for 20 min., then extracted with ether (2 × 1000 ml.). The solution was then acidified to *p*H 1 with concentrated hydrochloric acid and continuously extracted with ether for 48 hr. The ether was distilled to yield 18 g. of yellow, well defined crystals. The crude product was recrystallized from toluene to yield pale-yellow needles, m.p. 212–213°. This compound was soluble one part in less than one part water at 100°.

Anal. Calcd. for $C_6H_5N_4Cl$: C, 42.7; H, 2.9; N, 33.2. Found: C, 42.9; H, 3.0; N, 33.2.

8-Methyl-6-purinethiol (III, R = H). To 150 ml. of ethanol, containing 10 g. of thiourea, was added 5 g. of V, R = H, and the mixture refluxed for 1 hr. Solution took place immediately, and crystallization occurred after 0.5 hr. The mixture was chilled, filtered, and the product was boiled in 150 ml. of dilute sodium hydroxide. The solution was treated with charcoal and acidified while hot with acetic acid. The cooled solution yielded 3.9 g. of light-yellow needles, m.p. >300°. For analysis the product was recrystallized from water. This compound was soluble one part in 120 parts of water at 100°.

Anal. Calcd. for $C_6H_6N_4S$: C, 43.4; H, 3.6; N, 33.7. Found: C, 43.5; H, 3.4; N, 33.7.

(15) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).

(16) All melting points are uncorrected and were taken on the Fisher-Johns melting point apparatus, unless otherwise stated.

8-Methylpurine (X, $R_1 = R_2 = H$).[5,6] To 100 ml. of water, containing 15 g. of Raney nickel (the nickel catalyst used in all the experiments described herein was Davison Sponge Catalyst obtained from The Denver Fire Clay Co., Denver 17, Colo.) was added 5 g. of III, R = H, and the mixture refluxed for 6 hr. At the end of this time the Raney nickel was filtered and washed with 50 ml. of boiling water. The combined filtrate and washings were evaporated to dryness *in vacuo*. The crude product, which weighed 3.2 g., was recrystallized from benzene-heptane-methanol. A second recrystallization yielded very light-tan crystals. This compound was soluble one part in six parts of water at 100°.

Anal. Calcd. for $C_6H_6N_4$: C, 53.7; H, 4.4; N, 41.7. Found: C, 53.6; H, 4.5; N, 41.3.

8-Methyl-6-methylaminopurine (VI, R = R_1 = H, R_2 = CH_3). To 50 ml. of water, containing 50 ml. of 40% aqueous methylamine solution, was added 5 g. of V, R = H. Solution occurred immediately when the mixture was heated on the steam bath, and after 2 hr. crystallization began. The solution was chilled to yield 3.8 g. of product. Recrystallization from water yielded white crystals, m.p. >300°. This compound was soluble one part in twenty-five parts of water at 100°.

Anal. Calcd. for $C_7H_9N_5$: C, 51.5; H, 5.5. Found: C, 51.4; H, 5.2.

8-Methyl-6-p-chlorobenzylaminopurine (VI, R = R_1 = H, R_2 = p-$ClC_6H_4CH_2NH_2$). To 150 ml. of ethanol, containing 9 g. (0.06 mole) *p*-chlorobenzylamine, was added 5 g. (.03 mole) of V, R = H. This mixture was heated on the steam bath for 2 hr. The hot solution was then treated with charcoal, filtered, and chilled to yield 4.2 g. of white needles. For analysis the product was recrystallized from ethanol, m.p. >300°.

Anal. Calcd. for $C_{13}H_{12}N_5Cl$: C, 58.0; H, 4.3. Found: C, 58.3; H, 4.3.

6-(2,4-Dichlorobenzylamino)-8-methylpurine (VI, R = R_1 = H, R_2 = 2,4-$Cl_2C_6H_3CH_2NH_2$). To 150 ml. of ethanol, containing 10 g. (.06 mole) of 2,4-dichlorobenzylamine, was added 5 g. (.03 mole) of V, R = H. After heating on the steam bath for 3 hr. the solution was treated with charcoal and chilled. The chilled solution yielded 4.0 g. of white needles, m.p. 286–287°. For analysis the product was recrystallized from ethanol, which resulted in no change in the m.p. of the product.

Anal. Calcd. for $C_{13}H_{11}N_5Cl_2$: C, 50.7; H, 3.6. Found: C, 50.7; H, 3.5.

8-Methyl-6-methylthiopurine (IV, R = H, R_1 = CH_3). To 5 g. of III, R = H, dissolved in 100 ml. of water, containing 5 g. of potassium hydroxide, was added 4 g. of methyl iodide, and the mixture was vigorously stirred for 3 hr. The *p*H of the solution was carefully adjusted to 7 with dilute hydrochloric acid and the solution cooled to yield 3.0 g. of product. Recrystallization from a benzene-heptane-methanol mixture gave light-yellow crystals, m.p. 223–224°. This compound was soluble one part in ten parts of water at 100°.

Anal. Calcd. for $C_7H_8N_4S$: C, 46.6; H, 4.4. Found: C, 46.5; H, 4.3.

General method for synthesis of some 6-alkylthio-8-methylpurines. The 6-alkylthio-8-methylpurines listed below were made by the general method illustrated by the following synthesis:

6-Ethylthio-8-methylpurine (IV, R = H, R_1 = C_2H_5). To 75 ml. of water, containing 3 g. of potassium hydroxide and 10 g. of ethanethiol, was added 5 g. of III, R = H. This mixture was reacted on the steam bath for 30 min. The *p*H of the solution was adjusted to 7 with dilute hydrochloric acid, and the crude product that crystallized was filtered and washed with ligroin. Recrystallization from ethylacetate-heptane yielded 3.6 g. of long white needles, m.p. 206–207°.

Anal. Calcd. for $C_8H_{10}N_4S$: C, 49.4; H, 5.2. Found: C, 49.6; H, 5.5.

6-n-Propylthio-8-methylpurine (IV, R = H, R_1 = *n*-C_3H_7). This compound was prepared in a manner similar to that employed for the preparation of 6-ethylthio-8-methylpurine. The compound was recrystallized from benzene-heptane to give a m.p. of 214–215°.

Anal. Calcd. for $C_9H_{12}N_4S$: C, 51.9; H, 5.7. Found: C, 51.6; H, 5.9.

6-Isopropylthio-8-methylpurine (IV, R = H, R_1 = iso-C_3H_7). This compound was prepared in a manner similar to that employed for the preparation of 6-ethylthio-8-methylpurine. The compound was recrystallized from ethylacetate-heptane to give a m.p. of 256–257°.

Anal. Calcd. for $C_9H_{12}N_4S$: C, 51.9; H, 5.7. Found: C, 51.9; H, 6.0.

6-n-Butylthio-8-methylpurine (IV, R = H, R_1 = *n*-C_4H_9). This compound was prepared in a manner similar to that employed for the preparation of 6-ethylthio-8-methylpurine. The compound was recrystallized from a benzene-heptane-methanol mixture to give a m.p. of 179–180°.

6-Hydroxy-8-methyl-2-purinethiol (II, R = SH). Ten grams of 4,5-diamino-6-hydroxy-2-mercaptopyrimidine (I, R = SH)[9] was refluxed in 250 ml. of acetic anhydride for 9 hr. The mixture was then cooled and the solid product filtered and washed with water to remove the excess acetic anhydride. The crude product was then boiled in 250 ml. of 1.5*N* sodium hydroxide for 10 min. and the solution acidified while hot with glacial acetic acid. The crude product was filtered and reprecipitated with glacial acetic acid from a dilute sodium carbonate solution. The yield of product was 11.5 g. For analysis the product was recrystallized from dilute acetic acid and dried at 160° for 24 hr., m.p. >300°. This compound was soluble one part in 190 parts of water at 100°.

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.6; H, 3.3; N, 30.8. Found: C, 39.7; H, 3.6; N, 30.9.

6-Hydroxy-8-methyl-2-methylthiopurine (II, R = CH_3S). *Method 1.* To twenty grams of II, R = SH, dissolved in 500 ml. of .5*N* sodium hydroxide, was added 15 g. of methyl iodide. The mixture was stirred until only one phase was present. The solution was then heated to 80°, treated with charcoal, and acidified while hot with glacial acetic acid. Upon cooling the solution yielded 14 g. of long white needles, m.p. >300°. For analysis the product was recrystallized from water.

Anal. Calcd. for $C_7H_8N_4OS.H_2O$: C, 39.3; H, 4.7; N, 26.1. Found: C, 39.6; H, 4.8; N, 26.0.

Method 2. Twenty-three grams of 4,5-diamino-6-hydroxy-2-methylthiopyrimidine (I, R = CH_3S)[10] was refluxed in 250 ml. of acetic anhydride for 2 hr. The excess acetic anhydride was distilled under reduced pressure, and the sirupy residue was boiled in 250 ml. of 1.5*N* sodium hydroxide until a clear solution had resulted. The solution was treated with charcoal and acidified while hot with glacial acetic acid. Upon cooling the solution yielded 22 g. of long white needles. Comparison of the ultraviolet spectra of the compounds prepared by Methods 1 and 2 showed the compounds to be identical.

8-Methyl-2,6-purinedithiol (III, R = SH). Fifteen grams of 6-hydroxy-8-methyl-2-purinethiol (II, R = SH) was refluxed for 5 hr. in 500 ml. of dry pyridine containing 60 g. of phosphorus pentasulfide. The excess pyridine was distilled under reduced pressure; 300 ml. of water was carefully added and the mixture heated on the steam bath for 3 hr. and finally cooled. The crude product was filtered and reprecipitated twice from dilute sodium carbonate with hydrochloric acid to yield yellow crystals, m.p. >300°.

Anal. Calcd. for $C_6H_6N_4S_2$: C, 37.4; H, 3.0; N, 28.2. Found: C, 37.4; H, 3.0; N, 28.5.

6-Chloro-8-methyl-2-methylthiopurine (V, R = CH_3S). To 500 ml. of phosphorus oxychloride, containing 70 ml. of *N,N*-diethylaniline, was added 35 g. of II, R = CH_3S, and the mixture refluxed for 3.5 hr. The initial reaction was extremely vigorous, and solution took place after 2 hr. At the end of the reflux period the excess phosphorus oxychloride was distilled under reduced pressure and the residue

poured on cracked ice. The ice mixture was made strongly basic with 10*N* potassium hydroxide and allowed to cool for 30 min. The solution was extracted with ether (2 × 1000 ml.). The aqueous solution was kept at 10°, acidified to *p*H 1 with concentrated hydrochloric acid, and allowed to stand for 3 hr. At the end of this time a precipitate had formed, which was filtered and washed with water. The product was allowed to dry and then washed with ligroin. The crude product was recrystallized from toluene-methanol to yield 21 g. of product. A second recrystallization from toluene yielded white needles, m.p. 268–270°.

Anal. Calcd. for $C_7H_7N_4SCl$: C, 39.2; H, 3.2; N, 26.1. Found: C, 39.6; H, 3.3; N, 25.8.

8-Methyl-2-methylthio-6-purinethiol (III, R = CH_3S). To 125 cc. of ethanol, containing 10 g. of thiourea, was added 5 g. of V, R = CH_3S. This mixture was refluxed; solution occurred immediately, and crystallization began soon after. At the end of 1 hr. the mixture was chilled and filtered, and the crude product was dissolved in dilute potassium hydroxide and reprecipitated with glacial acetic acid. For analysis the product was recrystallized from dilute acetic acid, to give crystals melting >300°. Yield of product was 4.1 g.

Anal. Calcd. for $C_7H_8N_4S_2$: C, 39.6; H, 3.8; N, 26.4. Found: C, 39.3; H, 3.7; N, 26.2.

6-p-Chlorobenzylamino-8-methyl-2-methylthiopurine (VI, R = CH_3S, R_1 = H, R_2 = *p*-$ClC_6H_4CH_2$). To 5 g. of III, R = CH_3S, dissolved in 150 ml. of ethanol, was added 10 g. of *p*-chlorobenzylamine. The solution was heated on the steam bath until the volume was reduced to 75 ml., at which time crystals appeared. The solution was chilled to yield 5.4 g. of product. Recrystallization from ethanol yielded white needles, m.p. 265–266°.

Anal. Calcd. for $C_{14}H_{14}N_5ClS$: C, 52.6; H, 4.4. Found: C, 52.6; H, 4.1.

6-(unsymmetrical)-Dimethylhydrazino-8-methyl-2-methylthiopurine [VI, R = CH_3S, R_1 = H, R_2 = NH—$N(CH_3)_2$]. To 5 g. of 6-chloro-8-methyl-2-methylthiopurine (V, R = CH_3S), dissolved in 100 ml. of ethanol, was added 10 g. of unsymmetrical dimethylhydrazine. The solution was heated on the steam bath. Crystallization began after 0.5 hr., and heating was continued until the volume had been reduced by half; then the mixture was chilled to yield 3.9 g. of product. Recrystallization from ethanol yielded long white needles, m.p. 289–291°.

Anal. Calcd. for $C_9H_{14}N_6S$: C, 45.4; H, 5.8. Found: C, 45.5; H, 6.2.

6-Diethylamino-8-methyl-2-methylthiopurine (VI, R = CH_3S, R_1 = R_2 = C_2H_5). To 125 ml. of ethanol, containing 10 g. of diethylamine, was added 5 g. of V, R = CH_3S. The mixture was heated on the steam bath, where solution occurred immediately. Heating was continued until the solution was evaporated to dryness. The solid residue, 4.3 g., was recrystallized from heptane-ethanol to yield 2.8 g. of white crystals, m.p. 216–218°.

Anal. Calcd. for $C_{11}H_{17}N_6S$: C, 52.5; H, 6.7. Found: C, 52.4; H, 6.6.

8-Methyl-6-methylamino-2-methylthiopurine (VI, R = CH_3S, R_1 = H, R_2 = CH_3). To 5 g. of V, R = CH_3S, dissolved in 100 ml. of 40% aqueous methylamine solution, was added 50 ml. of water. The solution was heated on the steam bath until the volume was reduced by half. The cooled solution gave 4.0 g. of product. Recrystallization from ethanol yielded white crystals, m.p. 209°.

Anal. Calcd. for $C_8H_{11}N_{15}S$: C, 45.9; H, 5.2. Found: C, 45.5; H, 5.5.

6-Dimethylamino-8-methyl-2-methylthiopurine (VI, R = CH_3S, R_1 = R_2 = CH_3). This compound was prepared in a manner similar to that for the preparation of 8-methyl-6-methylamino-2-methylthiopurine using aqueous dimethylamine.

Anal. Calcd. for $C_9H_{13}N_5S$: C, 48.4; H, 5.8. Found: C, 48.3; H, 6.0.

6-Amino-8-methylpurine (X, R_1 = H, R_2 = NH_2). Fifteen grams of 4,5,6-triaminopyrimidine (IX, R_1 = H, R_2 = NH_2)[8] was refluxed in 150 ml. of acetic anhydride for 2 hr. Solution occurred after 15 min. At the end of the reflux period the excess acetic anhydride was distilled under reduced pressure. The solid residue was dissolved in 300 ml. of boiling dilute ammonium hydroxide. The cooled solution was filtered and the solid purified, reprecipitated from dilute hydrochloric acid with ammonium hydroxide, and then recrystallized from dilute *N,N'*-dimethylformamide to yield 12 g. of white crystals, m.p. >300°. This compound was soluble one part in twenty-two parts of water at 100°.

Anal. Calcd. for $C_6H_7N_5$: C, 48.3; H, 4.7; N, 47.0. Found: C, 48.1; H, 4.6; N, 47.3.

2-Amino-6-hydroxy-8-methylpurine (X, R_1 = NH_2, R_2 = OH).[7] Twenty-two grams of 2,4,5-triamino-6-hydroxypyrimidine (IX, R_1 = NH_2, R_2 = OH)[8] was refluxed in 500 ml. of a 1:1 mixture of acetic anhydride and ethyl orthoacetate for 5 hr. At the end of the reflux period the solution was filtered and then the excess solvents distilled under reduced pressure. The sirupy residue was boiled for 10 min. in 250 ml. of 2*N* sodium hydroxide. The solution was then acidified with acetic acid, cooled, and filtered. The crude product was recrystallized from water to yield 12 g. of white crystals, m.p. >300°. This compound was soluble one part in 150 parts of water at 100°.

Anal. Calcd. for $C_6H_7N_5O$: C, 43.6; H, 4.2; N, 42.4. Found: C, 43.6; H, 4.6; N, 42.4.

2,6-Dihydroxy-8-methylpurine (X, R_1 = R_2 = OH). Ten grams of 2,6-dihydroxy-4,5-diaminopyrimidine (IX, R_1 = R_2 = OH)[8] was refluxed in 250 ml. of acetic anhydride for 12 hr. The reaction mixture was cooled, and the solid was filtered and washed with water. The crude product was dissolved in 250 ml. of boiling 2*N* sodium hydroxide and the hot filtrate acidified with acetic acid and filtered. The crude product was reprecipitated twice from dilute sodium carbonate solution with hydrochloric acid to yield 10 g. of light-yellow crystals, m.p. >300°. This compound was soluble one part in 280 parts of water at 100°.

Anal. Calcd. for $C_6H_6N_4O_2$: C, 43.4; H, 3.6; N, 33.7. Found: C, 43.5; H, 3.6; N, 33.8.

7-Amino-2-methylthiazolo[5,4-d]pyrimidine (VIII). To 50 ml. of acetic anhydride was added 2.5 g. of 4,5-diamino-6-pyrimidinethiol (VII).[9] This mixture was refluxed for 3 hr., and at the end of this time the excess acetic anhydride was distilled under reduced pressure using a steam bath as a source of heat. The sirupy residue was dissolved in 100 ml. of boiling dilute ammonium hydroxide for 10 min. The solution was chilled to yield 2 g. of product, which was reprecipitated from dilute hydrochloric acid with ammonium hydroxide. For analysis the product was recrystallized from water.

Anal. Calcd. for $C_6H_6N_4S$: C, 43.4; H, 3.6; N, 33.7. Found: C, 43.4; H, 3.7; N, 33.5.

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