boiling water. The mixture was boiled and stirred for 1 hr. Ice was added until the total volume was 25 l. and the mixture kept at 0° for 2 hr. The crude solid was collected, washed with water, and reprecipitated from hot dilute potassium hydroxide and then from hot dilute ammonia (charcoal) with concd. hydrochloric acid (*p*H 1–2) to give 278 g. (49%) of light yellow 6,8-purinedithiol identified by its characteristic ultraviolet absorption spectrum.[27]

TEMPE, ARIZ.

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, ARIZONA STATE UNIVERSITY]

Potential Purine Antagonists. XXIX. The Synthesis of 1-Methylpurine and Related Derivatives[1]

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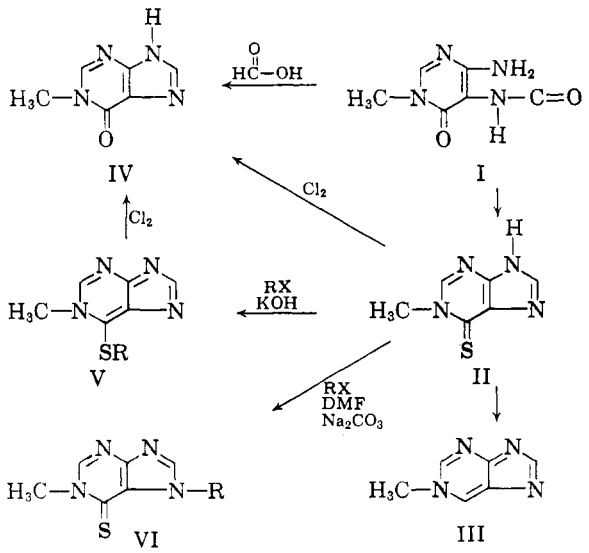
The synthesis of 1-methyl-6-purinethione (II) has been accomplished in a single step from 4-amino-5-formylamino-1-methyl-6-pyrimidone (I). Treatment of II with Raney nickel provided 1-methylpurine (III). A study of the alkylation of 1-methyl-6-purinethione has revealed that alkylation takes place at position 7 or on the sulfur atom depending on reaction conditions.

Antitumor testing of 9-methyl-6-purinethiol[2] and 7-methyl-6-purinethiol[3,4] has revealed that the 9-methyl derivative is active against adenocarcinoma 755 while the 7-isomer is inert. In an effort to extend the study of methyl derivatives of 6-purinethiol, the synthesis of 1-methyl-6-purinethione was explored in our laboratory.

Although Elion[5] discussed the preparation of II in 1954, no experimental directions were given or have since been published. This preparation was readily accomplished in our laboratory by the treatment of 4-amino-5-formylamino-1-methyl-6-pyrimidone (I) with phosphorus pentasulfide in pyridine. The structure of II was verified by conversion to 1-methylhypoxanthine (IV) with chlorine in ethanol. 1-Methylhypoxanthine (IV) was prepared independently by ring closure of I with formic acid. Since the synthesis of 7-methylhypoxanthine,[4] 9-methylhypoxanthine,[2] and 3-methylhypoxanthine[6] have all been previously described, there can be no doubt as to the structure of II. Furthermore since the structure of the intermediate, 4-amino-1-methyl-2-methylthio-5-nitroso-6-pyrimidone,[7] has now been established by the unambiguous synthesis of 4,5-diamino-1-methyl-6-pyrimidone,[8] the structure of I is certain.



REACTION SCHEME I

It is of interest that 1-methylhypoxanthine (IV) has recently been reported as occurring in human urine.[9,10]

Although Bergmann and co-workers[6] have reported the failure to synthesize 3-methylpurine by Raney nickel dethiation of 3-methyl-6-purinethione, similar treatment of 1-methyl-6-purinethione (II) with Raney nickel in boiling water gave 1-methylpurine (III) in reasonable yield.

Alkylation of 1-methyl-6-purinethione (II) with excess *o*-chlorobenzyl chloride in the presence of aqueous potassium hydroxide gave a product (V. R = $CH_2C_6H_4Cl$-*o*) which could be changed to 1-methylhypoxanthine by oxidation with chlorine. Thus, in this instance alkylation had occurred on the sulfur atom. When *o*-chlorobenzyl chloride

(1) Supported by Research Grant No. T-181 from the American Cancer Society.

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

(3) E. Fischer, *Ber.*, **31**, 431 (1898).

(4) R. N. Prasad and R. K. Robins, *J. Am. Chem. Soc.*, **79**, 6401 (1957).

(5) G. B. Elion in *The Chemistry and Biology of Purines*, G. E. W. Wolstenholme and C. M. O'Connor, eds., Little, Brown and Company, Boston, 1957, p. 43.

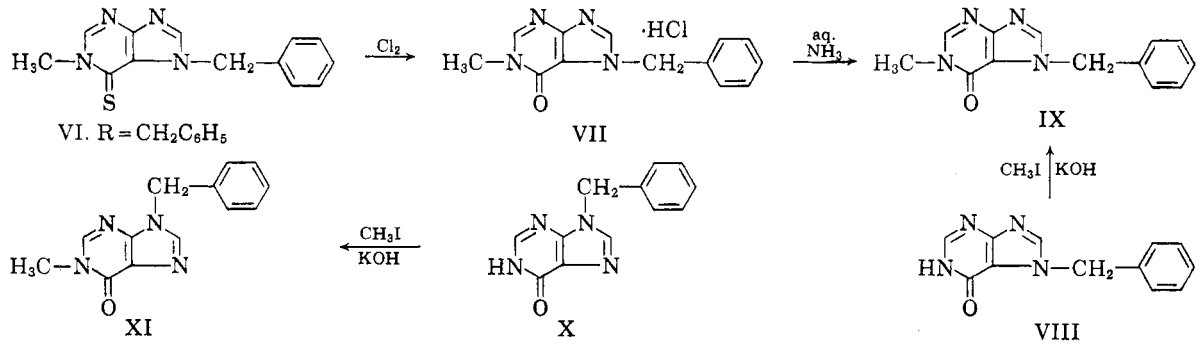
(6) F. Bergmann, G. Levin, A. Kalmus, and H. Kwietny-Govrin, *J. Org. Chem.*, **26**, 1504 (1961).

(7) C. O. Johns and B. M. Hendrix, *J. Biol. Chem.*, **20**, 153 (1915).

(8) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1298 (1961).

(9) B. Weissman, P. A. Bromberg, and A. B. Gutman, *J. Biol. Chem.*, **224**, 407 (1957).

(10) B. Weissman, P. A. Bromberg, and A. B. Gutman, *J. Biol. Chem.*, **224**, 423 (1957).



VI. R = $CH_2C_6H_5$ VII IX XI X VIII

REACTION SCHEME II

was used to alkylate II in the presence of dimethylformamide and sodium carbonate, a different product (VI. R = $CH_2C_6H_4Cl$-*o*) was isolated. Similarly, two different reaction products were obtained (V. R = $CH_2C_6H_5$ and VI. R = $CH_2C_6H_5$) when benzyl chloride was employed under similar reaction conditions. Since V had been established as alkylated on the sulfur atom, compound VI was probably alkylated either at position 7 or 9. The alkylation was established as 7 in the case of benzyl chloride as follows. Chlorine changed VI (R = $CH_2C_5H_5$) to 7-benzyl-1-methyl-6-purinone hydrochloride (VII) which was converted to the free base IX by the use of aqueous ammonia.

The synthesis of 7-benzylhypoxanthine (VIII) has recently been reported by Montgomery and Temple.[11] Methylation of VIII with methyl iodide gave IX which proved to be identical to the product obtained from 1-methyl-6-purinethione. The methylation of 9-benzylhypoxanthine (X)[11] gave 9-benzyl-1-methylhypoxanthine (XI) which proved to be different from the 7-benzyl-1-methyl derivative (IX).

It would appear that in the presence of strong aqueous base an anion is formed on the sulfur which encourages alkylation. The alkylation on the sulfur atom of 3-methyl-6-purinethione has been reported[6] under similar conditions. It is interesting to note that prolonged treatment with base degraded the purine ring. 6-Benzylthio-1-methylpurine decomposed gradually on exposure to sunlight and proved unstable to boiling dilute base. The 7-alkyl-1-methyl-6-purinethiones prepared by alkylation in dimethylformamide are listed in Table II. The 6-alkylthio-1-methylpurines prepared by alkylation in aqueous potassium hydroxide are listed in Table III.

The 7-alkyl-1-methyl-6-purinethiones (VI) exhibited a maximum in the ultraviolet at 324 mμ, which is followed by a hypsochromic shift of approximately 12 mμ by alkylation of the sulfur (V). It is interesting that there is no large bathochromic shift due to the 1-methyl substituent such as is found in the case of the 3-methylpurines.

(11) J. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **83**, 630 (1961).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF SOME 1-METHYLPURINES

Compound	*p*H 1 λ_{max}, mμ	ε	*p*H 11 λ_{max}, mμ	ε
1-Methylhypoxanthine	249	10,000	260	9,750
1-Methyl-6-purinethione	229	10,600	238	12,000
	321	18,800	322	25,600
1-Methylpurine	268	6,600	275	6,050
7-Benzyl-1-methyl-6-purinone	255	9,800	258	9,100
9-Benzyl-1-methyl-6-purinone	252	11,300	252	11,300
7-Benzyl-1-methyl-6-purinethione	324	17,400	238	10,200
			324	18,700
7-(*o*-Chlorobenzyl)-1-methyl-6-purinethione	323	18,300	238	10,500
			325	19,200
7-*n*-Butyl-1-methyl-6-purinethione	323	18,000	238	9,500
			324	19,500
6-(*o*-Chlorobenzylthio)-1-methylpurine	312	13,700		
6-Benzylthio-1-methylpurine	312	15,900		

The ultraviolet absorption spectral data of the 1-methylpurines studied are recorded in Table I.

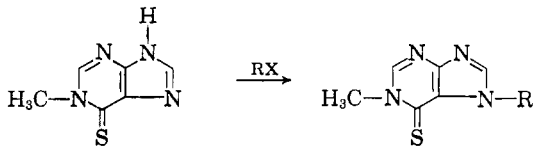
NOTE ADDED IN PROOF: Since this work was completed the synthesis of 1-ethylpurine has been reported from 7,8-dihydrothiazolo [2,3-*i*]-purine and Raney nickel, R. W. Balsiger, A. L. Fikes, T. P. Johnston and J. A. Montgomery, *J. Org. Chem.*, **26**, 3446 (1961). The synthesis of 1-methylhypoxanthine has recently been reported by N. Yamaoka and K. Aso, *J. Agric. Chem. Soc. Japan*, **35**, 280 (1961).

EXPERIMENTAL[12]

4-Amino-5-formylamino-1-methyl-2-methylthio-6-pyrimidone. 4-Amino-1-methyl-2-methylthio-5-nitroso-6-oxopyrimidine[7] (100 g.) was suspended in 1000 ml. of formamide and 250 ml. of formic acid (90%) at 60°. Sodium hydrosulfite was added until the reaction mixture turned a pale yellow color. The reaction mixture was then boiled for 15 min., diluted with 2100 ml. of water, then boiled for an

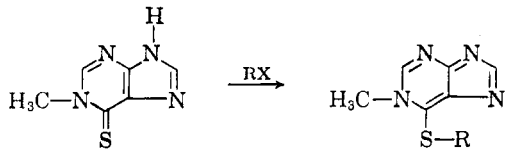
(12) All melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected unless otherwise stated.

TABLE II



R	M.P.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield, %	Recrystn. Solvent	Method of Prepn.
$CH_2C_6H_5$	171	61.0	60.99	4.7	4.72	21.9	22.3	39	Ethyl acetate	1
$CH_2C_6H_4Cl$-*o*	166–167	53.6	54.0	3.78	3.59	19.3	19.4	52	Acetone–pet. ether (60–110°)	1
n-C_4H_9	124–125	54.1	54.07	6.3	6.16	25.2	25.35	30	Ethyl acetate–*n*-heptane	1

TABLE III



R	M.P.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield, %	Recrystn. Solvent	Method of Prepn.
$CH_2C_6H_4Cl$-*o*	152	53.6	53.6	3.78	3.88	19.3	19.15	65	Ethyl acetate–*n*-heptane	2
$CH_2C_6H_4$	144–145	61.0	60.8	4.70	4.86	21.9	21.70	45	Ethyl acetate–*n*-heptane	2

additional 15 min., treated with charcoal, and filtered. The filtrate was cooled and the product filtered and washed with cold water to yield 65 g. Recrystallization was accomplished from water to give a product of m.p. 260°.

Anal. Calcd. for $C_7H_{10}N_4O_2S$: C, 39.25; H, 4.68; N, 26.2. Found: C, 39.5; H, 4.61; N, 26.5.

4-Amino-5-formylamino-1-methyl-6-pyrimidone (I). Fifty grams of 4-amino-5-formylamino-1-methyl-2-methylthio-6-pyrimidone was suspended in 1700 ml. of water containing 400 g. of activated Davison sponge nickel catalyst.[13] This mixture was then refluxed for 6 hr. and the catalyst filtered. The filtrate was evaporated to dryness *in vacuo* to yield 34 g. of crude product, m.p. 258–261°. A small sample recrystallized from aqueous ethanol gave a melting point of 266–267°.

Anal. Calcd. for $C_6H_8N_4O_2$: C, 42.8; H, 4.76; N, 33.4. Found: C, 42.6; H, 4.89; N, 33.6.

1-Methyl-6-purinone (*1-methylhypoxanthine*) (IV). *Method 1.* Ten grams of I was added to 300 ml. of formic acid (90%) and the solution refluxed for 6 hr. The formic acid was then removed *in vacuo*, and the residue was recrystallized from water to yield 8.2 g. of 1-methyl-6-purinone, m.p. > 300°.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.0; N, 37.3. Found: C, 47.68; H, 3.97; N, 37.2.

Method 2. Two grams of 1-methyl-6-purinethione (II) was suspended in 25 ml. of absolute ethanol cooled in an ice-salt bath. Chlorine gas was passed through the solution while keeping the temperature below 25° until there was no further rise in temperature upon further addition of chlorine. The precipitate which appeared was filtered and recrystallized from methanol–benzene to yield 1.4 g. of the hydrochloride salt of 1-methyl-6-purinone, m.p. >300°.

Anal. Calcd. for $C_6H_6N_4O.HCl$: C, 38.7; H, 3.76; N, 30.1. Found: C, 38.46; H, 3.61; N, 29.9.

The above salt (0.3 g.) was dissolved in 5 ml. of cold water and 2.5 ml. of concd. aqueous ammonia. The solution was then allowed to stand at room temperature. The precipitate which formed was filtered to yield 0.2 g. of product. Recrystallization was effected from methanol and benzene, m.p. >300°.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.0; N, 37.3. Found: C, 47.7; H, 4.01; N, 37.2.

1-Methyl-6-purinethione (II). A mixture of 50 g. of 4-amino-5-formylamino-1-methyl-6-pyrimidone (I) and 150 g. of phosphorus pentasulfide was suspended in 2000 ml. of pyridine and the solution refluxed and stirred for 24 hr. The excess pyridine was distilled under reduced pressure using a water bath as the source of heat. Water (1500 ml.) was added to the residue and the reaction mixture heated on a water bath for 2 hr. The reaction mixture was then allowed to stand overnight in the refrigerator. The resulting precipitate was filtered and dissolved in 1500 ml. of dilute aqueous ammonia, boiled with charcoal, and filtered. The filtrate was then adjusted to *p*H 6 with acetic acid. The solution was cooled and the product filtered and reprecipitated again to yield 30 g. of 1-methyl-6-purinethione, m.p. >300°. Recrystallization from water provided a pure sample for analysis.

Anal. Calcd. for $C_6H_6N_4S$: C, 43.4; H, 3.62; N, 33.95. Found: C, 43.5; H, 3.76; N, 33.8.

1-Methylpurine (III). Four grams of 1-methyl-6-purinethione (II) was dissolved in 500 ml. of hot water and 48 g. of activated Davison sponge nickel catalyst[13] added. This mixture was refluxed for 20 min. and the catalyst filtered. The filtrate was evaporated to dryness *in vacuo* to yield a dark residue. This residue was extracted with 800 ml. of cold acetone. The volume of acetone was reduced to 100

(13) Purchased from Davison Chemical Co., Baltimore 3, Md.

ml., and petroleum ether (b.p. 60–110°) was added to the boiling solution until crystals began to appear. The solution was then cooled and filtered to yield 1.8 g. of light yellow compound, which was approximately 90% pure (judged by comparison of ultraviolet absorption data with an analytically pure sample obtained later). This compound was then extracted with 500 ml. of boiling ethyl acetate. The volume of ethyl acetate was reduced on a water bath until crystals began to deposit on the sides of the beaker. The solution was then cooled and filtered. A small sample was recrystallized from acetone–petroleum ether (60–110°) for analysis, m.p. 234–235°.

Anal. Calcd. for $C_6H_6N_4$: C, 53.7; H, 4.48; N, 41.8. Found: C, 53.9; H, 4.73; N, 41.8.

9-Benzyl-1-methyl-6-purinone (XI). One gram of 9-benzylhypoxanthine[11] was added to 25 ml. of methanol. Methyl iodide (4 ml.) and 1 g. of solid potassium hydroxide were added and the solution refluxed for 2 hr. The excess solvents were removed on the steam bath *in vacuo*. The residue was dissolved in 20 ml. of hot water and the solution filtered and allowed to cool to yield 0.6 g. The product was recrystallized from benzene–heptane for analysis, m.p. 207–208°.

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 65.0; H, 5.0; N, 23.3. Found: C, 65.1; H, 5.13; N, 23.3.

7-Benzyl-1-methyl-6-purinone (IX). *Method 1.* VII (0.2 g.) was dissolved in 5 ml. of water and 2.5 ml. of concd. aqueous ammonia. The solution was then allowed to stand at room temperature and the precipitate filtered after 1 hr. to yield 0.15 g. The product was recrystallized from benzene–heptane for analysis, m.p. 159–160°.

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 65.0; H, 5.0; N, 23.3. Found: C, 64.8; H, 5.14; N, 23.3.

Method 2. One gram of 7-benzylhypoxanthine[11] was added to 25 ml. of methanol. Methyl iodide (4 ml.) and 1 g. of solid potassium hydroxide were added and the solution refluxed for 2 hr. The excess solvents were removed on the steam bath and the residue extracted with 150 ml. of boiling benzene. The volume of benzene was reduced to 30 ml. and *n*-heptane added until a precipitate separated from the solution. The product was recrystallized from benzene–*n*-heptane, m.p. 156–158°. A mixed melting point with the product prepared by Method 1 showed no depression. The compounds exhibited identical ultraviolet absorption spectra and had the same R_f in several different solvents.

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 65.0; H, 5.0; N, 23.3. Found: C, 65.2; H, 5.4; N, 23.2.

Oxidation of 7-benzyl-1-methyl-6-purinethione (VI. R = $CH_2C_6H_5$) *to give 7-benzyl-1-methyl-6-purinone hydrochloride* (VII). One gram of VI (R = $CH_2C_6H_5$) was suspended in 25 ml. of absolute ethanol. Chlorine gas was passed through the solution for 1.5 hr. maintaining the temperature below 15°. The precipitate was filtered and triturated with a small amount of benzene to yield 0.8 g. of crude product. Recrystallization was effected from a methanol and benzene mixture for analysis.

Anal. Calcd. for $C_{13}H_{12}N_4O\cdot HCl$: C, 56.5; H, 4.75; N, 20.4. Found: C, 56.3; H, 4.85; N, 20.8.

Oxidation of 6-o-chlorobenzylthio-1-methylpurine (V. R = $CH_2C_6H_4$-*o*-Cl) *to yield 1-methylhypoxanthine hydrochloride.* V. (R = $CH_2C_6H_4$-*o*-Cl) (0.5 g.) was suspended in 15 ml. of absolute ethanol, and chlorine gas was passed through the solution keeping the temperature below 25° until there was no further rise in temperature upon addition of chlorine gas. The precipitate was filtered and washed with benzene to yield 0.25 g. of product. Recrystallization was from methanol–benzene, m.p. >300°.

Anal. Calcd. for $C_6H_6N_4O\cdot HCl$: C, 38.7; H, 3.76; N, 30.1. Found: C, 38.8; H, 4.0; N, 30.3.

The product was identified by its ultraviolet absorption spectra and conversion to the free base, 1-methylhypoxanthine.

Alkylation of 1-methyl-6-purinethione (II). *Method I.* One gram of II was suspended in 30 ml. of dimethylformamide and 1 molar equivalent of sodium carbonate added. One molar equivalent of the alkyl halide was then added and the mixture stirred at room temperature for 3 hr. The temperature was raised to 40–45° and stirred for another hour. The solution was cooled and poured into 300 ml. of water. The precipitate was filtered and recrystallized as indicated in Table II.

Method 2. II (2.5 g.) was added to 25 ml. of water containing 1.5 g. of potassium hydroxide. Then twice the equimolar quantity of the appropriate alkylating agent and 10 ml. of *p*-dioxane were added gradually over a 2-hr. period at 40–45° with continuous stirring. The stirring was continued for 1 hr. after the addition of the alkyl halide. The solution was cooled, and the precipitate which formed was filtered and triturated with petroleum ether (60–110°). Recrystallization was accomplished from the solvents indicated in Table III.

TEMPE, ARIZ.