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

Potential Purine Antagonists. XXVIII. The Preparation of Various Bromopurines[1]

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The synthesis of various bromopurines has been accomplished from the corresponding purinethiols and bromine in the presence of aqueous hydrobromic acid and methanol. This reaction appears quite general and proceeds readily in the presence of amino or hydroxy groups. A number of bromopurine derivatives have been prepared which were previously inaccessible by other synthetic methods.

Recent studies from this laboratory[2] have resulted in a very convenient method of synthesis of certain chloropurines from the corresponding readily available mercaptopurines by the use of chlorine gas and methanolic hydrochloric acid. The present study was initiated to see if this type of reaction could be extended to the preparation of various bromopurines by the use of bromine and methanolic hydrobromic acid and the requisite mercaptopurines. Prior to this study the only recorded instance of a reaction of this type was that of Biltz and Sauer[3] who report that 2,6-dihydroxy-9-methylpurine-8-thiol in bromine water gave 8-bromo-2,6-dihydroxy-9-methylpurine.

Introduction of bromine into position 8 of both methylated[4–6] and certain unmethylated[4,7–9] purines has been readily accomplished by direct bromination, but the preparation of purines substituted with bromine at positions 2 and 6 has, up to this time, been achieved only by treatment of the corresponding hydroxypurines with phosphoryl bromide.[10]

The present study has revealed that in general the various bromopurines are readily available from the corresponding mercaptopurines by utilizing bromine as an oxidizing agent in the presence of excess methanolic hydrobromic acid. This procedure has successfully provided all of the following

(1) This research has been supported by grant NSF-G13291 from the National Science Foundation.

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

(3) H. Biltz and J. Sauer, *Ber.*, **64**, 752 (1931).

(4) E. Fischer, *Ann.*, **215**, 253 (1882).

(5) E. Yoshitomi, *Chem. Zentr.*, **II**, 1593 (1924).

(6) A. Lespagnol and A. Gaumeton, *Bull. soc. chim. France*, 253 (1961).

(7) E. Fischer and L. Reese, *Ann.*, **221**, 336 (1883).

(8) M. Kruger, *Z. physiol. Chem.*, **16**, 5 (1892).

(9) S. Chu, J. E. Harris, and H. G. Mautner, *J. Org. Chem.*, **25**, 1759 (1960).

(10) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 3508 (1956); **73**, 5235 (1951).

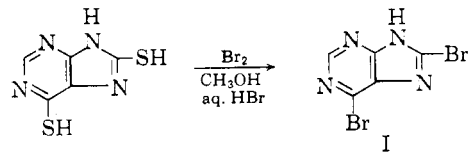
TABLE I

8-PURINETHIOLS

Starting Material, Pyrimidine	S.M. G.	Pyridine, Ml.	CS_2, Ml.	KOH, G.	H_2O, Ml.	Reflux Time, Hr.	Distn. Time, Hr.	Vol. H_2O Purification, L.	Product, Purine	Yield G.	Yield %
4,5-Diamino	150	900	500	0	0	1.5	1.5[+] 1.5[b]	2.8[a]	8-Thiol	200	96
4,5-Diamino-6-hydroxy, sulfate[c]	350	1750	600	250	250	1	2	8	6-Hydroxy-8-thiol·H_2O	240	65
4,5,6-Triamino, sulfate[c]	25	125	50	21	50	2.25	1	0.2	6-Amino-8-thiol	16	93
4,5-Diamino-2-thiol[d]	350	2800	900	70	70	2	4	4.5[e]	2,8-Dithiol	385	85
4,5-Diamino-6-thiol[f]	70	700	350	35	150	2.5	2	2.5[g]	6,8-Dithiol	78	86

[a] The slurry (600 ml.) was cooled, the solid filtered, washed with water, dissolved in 2.8 l. of water by addition of potassium hydroxide solution, and the product precipitated with hydrochloric acid (*p*H 2). [b] The mixture was cooled, an additional 300 ml. of carbon disulfide added, and then distilled for the second period. [c] Purchased from Aldrich Chemical Co., Milwaukee, Wis. [d] D. J. Brown, *J. Appl. Chem.*, **2**, 239 (1952). [e] The crude product was reprecipitated from solution in 5.5 l. of dilute ammonia (charcoal) with hydrochloric acid (*p*H 1). [f] See reference cited in footnote 15. [g] The original product is 7-aminothiazolo[5,4-*d*]pyrimidine-2-thiol (*Anal.* Calcd. for $C_5H_4N_4S_2$: C, 32.6; H, 2.2; N, 30.4; S, 34.8. Found: C, 32.4; H, 2.1; N, 30.5; S, 34.5). This was boiled 45 min. in 3 l. of 1 *N* sodium hydroxide and the solution acidified to *p*H 1.5 with hydrochloric acid to give 6,8-purinedithiol. If the original reaction mixture is cooled and the crystalline potassium salt of the thiazolo[5,4-*d*]pyrimidine collected and treated separately from the additional material obtained upon acidification of the diluted (with water) filtrate from this salt, the 6,8-purinedithiol obtained from the potassium salt is especially pure.

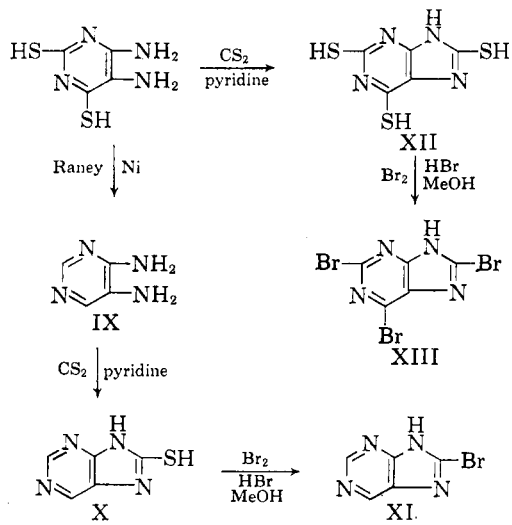
previously unknown bromopurines: 2-bromopurine, 8-bromopurine (XI), 6,8-dibromopurine (I), 2,6,8-tribromopurine (XIII), and 2,8-dibromopurine, although in the last case the product was not readily purified. The preparation of 6-bromopurine (II) and 2,6-dibromopurine (III) has also been successfully accomplished from 6-purinethiol and 2,6-purinedithiol, respectively, and compares favorably with the previously reported syntheses[10] utilizing phosphoryl bromide.



I

The versatility of this method of introducing a bromo group into a purine is demonstrated by its application to the synthesis of 2-amino-6-bromopurine, 8-bromo-2,6-diaminopurine, 8-bromoadenine, 8-bromo-6-hydroxypurine, 2-bromo-6-hydroxypurine, 2 - bromo - 6,8 - dihydroxypurine, and 8-bromoxanthine.

The 8-purinethiol[11] required for the synthesis of 8-bromopurine (XI) lead to a new and most convenient synthesis of the important intermediate 4,5-diaminopyrimidine[12,13] (IX) from the Raney nickel treatment of 4,5-diaminopyrimidine-2,6-dithiol.[14,15] Ring closure of 4,5-diaminopyrimidine (IX) to 8-purinethiol (X) was best accom-

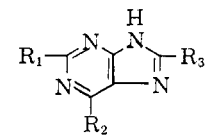


plished by carbon disulfide in the presence of pyridine.

In the synthesis of 8-purinethiols the use of carbon disulfide as a cyclizing agent has the advantage that the isolation and purification of the product is much simpler than with thiourea.[11,16-18] Carbon disulfide has been used alone,[19] with pyridine,[20-23] with triethylamine,[23] with pyridine plus a small amount of solid sodium hydroxide,[24] and with *N,N*-dimethylformamide.[25] The chief limitation of the carbon disulfide method is that in some cases the insolubility of the requisite 4,5-diaminopyrimidine prevents the reaction from going to completion.[26] We have overcome this difficulty by the addition of aqueous potassium hydroxide solution to the usual carbon disulfide–pyridine reaction mixture. This modification results in an improved and general method by which 8-purine-

TABLE II

ULTRAVIOLET ABSORPTION OF SOME BROMOPURINES



			*p*H 1		*p*H 11	
			λ_{max},		λ_{max},	
R_1	R_2	R_3	mμ	ε	mμ	ε
Br	H	H	274	8,300	279	8,500
H	Br	H	266	10,300	275	9,000
H	H	Br	272	13,100	276	15,000
Br	Br	H	250	4,000	283	8,200
			279	8,400		
H	Br	Br	250[a]	5,800	282	14,600
			274	15,400		
Br	Br	Br	254	4,600	289	13,500
			285	13,600		
NH_2	Br	H	318	7,400	274	3,700
					310	6,600
H	NH_2	Br	266	17,000	272	15,500
Br	OH	H	252	11,400	265	11,200
Br	H	OH	242	6,500	297	12,400
			287	11,400		
H	OH	Br	255	13,100	264	13,700
OH	OH	Br	274	13,200	287	11,300
Br	OH	OH	261	12,200	276	14,200
			286[a]	6,900		
NH_2	NH_2	Br	243	11,400	288	11,000
			289	11,900		

[a] Inflection.

(11) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).
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(13) D. J. Brown, *J. Soc. Chem. Ind.*, **69**, 353 (1950).
(14) G. Leven, A. Kalmus, and F. Bergmann, *J. Org. Chem.*, **25**, 1752 (1960).
(15) A. G. Beaman and R. K. Robins, *J. Am. Chem. Soc.* **83**, 4038 (1961).
(16) O. Isay, *Ber.*, **39**, 250 (1906)
(17) M. I. Shidate and H. Yuki, *Pharm. Bull.* (*Tokyo*), **5**, 240 (1957).
(18) D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 682 (1957).
(19) Boehringer and Sohne, German Patent **142,468**; [*Chem. Zentr.*, **II**, 80 (1903)].
(20) A. H. Cook and E. Smith, *J. Chem. Soc.*, 3001 (1949).
(21) B. R. Baker, J. P. Joseph, and R. E. Schaub, *J. Org. Chem.*, **19**, 631 (1954).
(22) B. R. Baker, J. P. Joseph, and J. H. Williams, *J. Org. Chem.*, **19**, 1793 (1954).
(23) B. R. Baker and R. E. Schaub, U. S. Patent **2,705,715** (1955); [*Chem. Abstr.*, **50**, 5041c (1956)].

thiol,[11] 2,8-purinedithiol,[24] 6,8-purinedithiol,[27,28] 2,6,8-purinetrithiol,[24,29] 6-amino-8-purinethiol,[27] and 6-hydroxy-8-purinethiol[27] have been readily synthesized. It should be noted that in the case of the soluble 4,5-diaminopyrimidine a 96% yield of 8-purinethiol can be obtained without the use of any aqueous potassium hydroxide. In the case of 2,8-purinedithiol a better yield is obtained with aqueous potassium hydroxide than with solid sodium hydroxide. The case of 6,8-purinedithiol is most interesting in that from 4,5-diamino-6-pyrimidinethiol,[30,31] which has only recently become readily available,[15] we isolated the same 7-aminothiazolo[5,4-*d*]pyrimidine (identified by its ultraviolet absorption spectrum) which has recently been prepared[25] in lower yield from 6-chloro-4,5-diaminopyrimidine and carbon disulfide in *N*,*N*-dimethylformamide. When this compound was boiled with aqueous 1 *N* sodium hydroxide solution, it was quantitatively isomerized to 6,8-purinedithiol.

The experimental details for the synthesis of several 8-purinethiols are given in Table I.

The mechanism of the general replacement of the mercapto group by bromine is visualized as occurring through an oxidized sulfur intermediate (presumably the sulfonyl bromide) which is displaced by bromide ion in acid solution. The inherent acidity of the reaction mixture gives rise to several isolation problems since most of the bromopurines are susceptible to acid hydrolysis, especially at elevated temperature. In the case of the preparation of 2,8-dibromopurine from 2,8-purinedithiol the product consisted of a compound with λ_{max} 282 mμ at *p*H 1 and λ_{max} 286 mμ at *p*H 11. When this crude compound was deliberately boiled with dilute acid or simply recrystallized from methanol in an attempted purification, it was transformed into 2(8)-bromo-8(2)-hydroxypurine, which substance sometimes accompanied the initial compound as isolated. The spectral shifts observed in going from the initial compound to 2(8)-bromo-8(2)-hydroxypurine are completely analogous to those which accompany the transformation of 2,6,8-trichloropurine to 2,6-dichloro-8-hydroxypurine,[2] and the transformation of 2,8-dichloropurine to 2-chloro-8-hydroxypurine.[32] Thus, it is concluded that the original product is the desired 2,8-dibromopurine and that the hydrolysis product is 2-bromo-8-hydroxypurine.

The preparation of 8-bromopurine is noteworthy since this is the first reported instance of an 8-halogenated purine unsubstituted in the remaining positions of the purine ring.

The ultraviolet absorption spectra of the various bromopurines prepared are given in Table II. In general, the spectra resemble rather closely those

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(25) R. W. Balsiger, A. L. Fikes, T. P. Johnson, and J. A. Montgomery, *J. Org. Chem.*, **26**, 3386 (1961).
(26) Unpublished observations of the authors.
(27) R. K. Robins, *J. Am. Chem. Soc.*, **80**, 6671 (1958).
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(29) E. Fischer, *Ber.*, **31**, 431 (1898).
(30) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 3832 (1954).
(31) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **76**, 4027 (1954).
(31a) This type of rearrangement has previously been noted by Brown and Mason, *J. Chem. Soc.*, 682 (1957).
(32) Observations of the authors to be published.

TABLE III

SYNTHESIS OF BROMOPURINES

Starting Material, Purine	S.M., G.	CH_3OH, Ml.	48% HBr, Ml.	Br_2, Ml.	Addn. of Br_2 Time, hr.	Addn. of Br_2 Temp.	Addnl. Stirring Time, hr.	Addnl. Stirring Temp.	Isol. Method
6-Thiol[a]	35	105	210	45	2	15–20	1.5	10	A[b]
8-Thiol	5	25	12	6.5	1.5	5–10	1	7	A
6,8-Dithiol	10	60	50	28	1.67	5–7	1	5	A
2-Amino-6-thiol[d]	25	100	125	32.5	1.5	10	1.5	10	[e]
6-Hydroxy-2-thiol[g]	5	25	50	10	1.5	5–6	4	5	B[b]
6,8-Dihydroxy-2-thiol[h]	5	25	25	6.5	0.5	8–10	1.17	8	B
2,6-Dihydroxy-8-thiol[i]	20	100	80	26	2	8–10	3	10	B
6-Amino-8-thiol	5	25	30	6.5	0.67	7–8	1	7–8	[j]
2,6,8-Trithiol	20	60	120	60	5.5	20–24	15+25	0+20–25	A
2,6-Dithiol[a]	40	120	240	90	5.5	20–24	15	0	A[l]
2,6-Diamino-8-thiol[m]	10	50	50	13	0.5	10	1.25	10	B
2,8-Dithiol	5	25	20	14	2.25	0–5	1	5–10	A

[a] See reference cited in footnote 15. [b] See Experimental section. [c] From dilute ammonia with dilute hydrochloric acid. [d] G. D. Davis, Jr., C. W. Noell, R. K. Robins, H. C. Koppel, and A. G. Beaman, *J. Am. Chem. Soc.*, **82**, 2633 (1960). [e] The reaction mixture was poured on ice, the *p*H adjusted to 8 with aqueous ammonia, the solid collected, washed with water and acetone, and reprecipitated from solution in dilute potassium hydroxide with dilute hydrochloric acid. [f] From dilute sodium hydroxide with dilute hydrochloric acid. [g] A. G. Beaman, *J. Am. Chem. Soc.*, **76**, 5633 (1954). [h] C. W. Noell and

of the corresponding chloropurines with a small bathochromic shift of from 2 to 7 mμ.

The experimental details for the synthesis of several bromopurines are given in Table III.

EXPERIMENTAL

2-Bromopurine. (Illustrates Isolation Method A.) 2-Purinethiol[33] (10.0 g.) was added to a solution of 60 ml. of aqueous hydrobromic acid (48%) and 30 ml. of methanol previously cooled to 6°. The solution was stirred while 12.0 ml. of bromine was added dropwise over a period of 45 min., during which time the reaction temperature was maintained at 6–9°. The reaction mixture was stirred for an additional 45 min. at 5–10° and was then poured over ice with stirring. The stirred solution was carefully adjusted to *p*H 10 with concentrated aqueous potassium hydroxide while the temperature was maintained below 0°. Acidification of the solution to *p*H 2–3 with aqueous hydrobromic acid, with cooling, precipitated a solid which was filtered and discarded. The filtrate was extracted with 4 × 500 ml. of ethyl acetate. Evaporation of the ethyl acetate gave 6.7 g. (51%) of light yellow solid which was recrystallized from absolute ethanol, m.p. 243° dec.

Anal. Calcd. for $C_5H_3N_4Br$: C, 30.2; H, 1.52; N, 28.2; Br, 40.2. Found: C, 30.4; H, 1.72; N, 28.3; Br, 40.3.

8 - Bromo - 6 - hydroxypurine (VI). (Illustrates Isolation Method B). To a solution of methanol (50 ml.) and aqueous hydrobromic acid (50 ml.) was added 10 g. of 8-mercapto-6-hydroxypurine. The suspension was then cooled to 8°, and the addition of bromine (14 ml.) was started. After 1.25 hr. the bromine addition was complete, and the suspension was stirred for an additional 1.75 hr. at 10°. The suspension was then filtered and the moist solid immediately washed with acetone. This dry solid was slurried with cold water and filtered and washed with water and acetone to yield 6.8 g. of 8-bromo-6-hydroxypurine. This was dissolved in very dilute sodium hydroxide solution and reprecipitated with dilute hydrochloric acid. A small amount was recrystallized from water and dried *in vacuo* for analysis.

Anal. Calcd. for $C_5H_3N_4BrO$: C, 27.9; H, 1.41; N, 26.0; Br, 37.2. Found: C, 28.3; H, 1.65; N, 26.1; Br, 36.8.

4,5-Diaminopyrimidine (IX). Six liters of distilled water, 600 ml. of concd. aqueous ammonia, 300 g. of 4,5-diamino-2,6-dimercaptopyrimidine,[16] and 600 g. of freshly prepared Raney nickel[13] were boiled in an open stainless steel pail, with stirring, for 1.5 hr., a little concd. aqueous ammonia being added every 15 min. The nickel was filtered hot and washed with boiling distilled water, containing ammonia. The filtrate plus 400 ml. of concd. aqueous ammonia were boiled and stirred for 1.5 hr. with a fresh 600-g. portion of Raney nickel. This nickel was filtered and washed with boiling distilled water, and the filtrate was evaporated to 2 l. under vacuum. Any insoluble, noncrystalline solid which formed on standing overnight was removed and discarded, and the filtrate was evaporated to dryness under vacuum to give 150–160 g. (79–84%) of light yellow needles. The crude material was recrystallized from absolute ethanol (Nuchar) to give 135–140 g., m.p. 205° (Brown[34] gives 200–201°), of pure 4,5-diaminopyrimidine identified by its ultraviolet absorption spectrum.[35]

2,6,8-Purinetrithiol (XII). A mixture of 3200 ml. of pyridine, 800 ml. of carbon disulfide, 100 ml. of 50% aqueous potassium hydroxide, and 400 g. of 4,5-diaminopyrimidine-2,6-dithiol[15] was refluxed with stirring for 2 hr. The reflux condenser was replaced with a distillation assembly, and with continued stirring the mixture was distilled at atmospheric pressure until the head temperature reached 115° (3.5 hr.). The hot contents of the flask were poured at once into 11 l. of boiling water, and the hot solution was immediately acidified to *p*H 1 by the addition of concd. hydrochloric acid with stirring. The deep yellow solid was filtered after 15 min., washed, and dried to give 450–475 g. (91–96%) of 2,6,8-purinetrithiol identified by its characteristic ultraviolet absorption spectrum.[24]

6,8-Purinedithiol. Pyridine (5 l.) was heated to 85°, and with stirring 1600 g. of phosphorus pentasulfide was added carefully, followed by 575 g. of 6-hydroxy-8-purinethiol. The mixture was refluxed for 3 hr., the excess pyridine removed under vacuum, and the hot sirup poured into 14 l. of

(33) R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Am. Chem. Soc*, **75**, 263 (1953).
(34) D. J. Brown, *J. Appl. Chem.*, **2**, 239 (1952).
(35) S. F. Mason, *J. Chem. Soc.*, 2071 (1954).

TABLE III (*Continued*)

Product Purine	Prod. G.	Recrystn. Solvent	M.P.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Bromine, % Calcd.	Bromine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
6-Bromo	30	H_2O	194 d.	30.2	30.6	1.5	1.8	40.2	40.2	28.2	28.6
8-Bromo	2	Repptd.[e]		30.2	30.6	1.5	1.8	40.2	40.1	28.2	28.2
6,8-Dibromo	7	Ethanol	223 d.	21.7	22.0	0.7	1.0	57.7	57.6	20.2	20.5
2-Amino-6-bromo	20	Repptd.[f]		28.0	28.4	1.9	2.0	37.4	37.4	32.8	32.7
2-Bromo-6-hydroxy	5	H_2O		27.9	28.0	1.4	1.7	37.2	37.6	26.0	25.9
2-Bromo-6,8-dihydroxy	3	Repptd.[f]		26.0	26.3	1.3	1.6	34.6	34.2	24.2	24.2
8-Bromo-2,6-dihydroxy	18	Repptd.[f]		26.0	26.2	1.3	1.4	34.6	34.8	24.2	24.5
8-Bromo-6-amino	4	Repptd.[k]		28.0	28.3	1.9	2.8	37.4	37.8	32.8	33.0
2,6,8-Tribromo	10	Benzene	223 d.	16.9	17.5	0.3	0.8	67.4	67.2	15.8	15.9
2,6-Dibromo	22	Ethanol	207 d.	21.7	21.8	0.7	1.8	57.5	57.6	20.2	20.3
8-Bromo-2,6-diamino	6	Repptd.[k]		26.2	26.4	2.2	2.4	34.9	35.2	36.7	36.8
2,8-Dibromo → 2-Bromo-8-hydroxy	3	Methanol		27.9	28.3	1.4	1.7	37.2	37.5	26.0	25.8

R. K. Robins, *J. Org. Chem.*, **24**, 320 (1959). [f] T. L. Loo, M. E. Michael, A. J. Garceau, and J. C. Reid, *J. Am. Chem. Soc.*, **81**, 3039 (1959). [j] The reaction mixture was poured on ice, and the resulting white solid filtered, washed with water, and reprecipitated from dilute aqueous ammonia with acetic acid. [k] From dilute ammonia with acetic acid. [l] Just before the extraction with ethyl acetate a large amount of crystalline solid may form. This is not the desired product. [m] M. Gordon, *J. Am. Chem. Soc.*, **73**, 984 (1951).

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]

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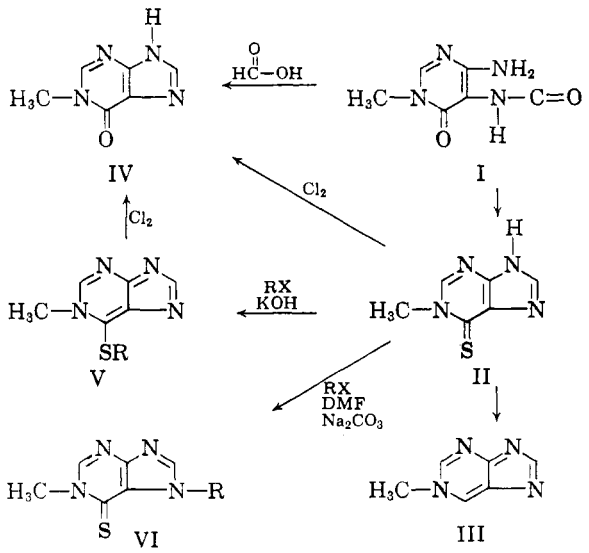
The synthesis of 1-methyl-6-purinethione (II) has been accomplished in a single step from 4-amino-5-formylamino-1-methyl-6-pyrimidone (I). Treatment of II with Raney nickel provided 1-methylpurine (III). A study of the alkylation of 1-methyl-6-purinethione has revealed that alkylation takes place at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

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