[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, ARIZONA STATE UNIVERSITY]

Potential Purine Antagonists. XXV. Some Purine Sulfonic Acid Derivatives and a New Preparation of 2,6,8-Trichloropurine[1]

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A new synthesis of 2,6,8-trichloropurine (VIII) has been accomplished from 2,6,8-purinetrithiol (VII) with chlorine gas in the presence of methanol and excess hydrochloric acid. These reaction conditions have been utilized for a new synthesis of 2,8-dichloro-6-hydroxypurine (XI) and 8-chloro-6-hydroxypurine (XIV). The synthesis of 6-chloro-2,8-dihydroxypurine (III) has been similarly accomplished from 2,8-dihydroxy-6-purinethiol (VI). Chlorination of 2,6,8-purinetrithiol (VII) in anhydrous methanol has been shown to yield 6-chloro-8-hydroxypurine-2-sulfonic acid (IV). 8-Hydroxypurine-2,6-disulfonic acid (II) has similarly been prepared from 8-hydroxy-2,6-purinedithiol (I).

Recent studies from this laboratory[2] have shown that methylthiopurines when treated with chlorine give the corresponding methylsulfonyl- or chloropurines depending on the position of the substituent group and the reaction conditions. A recent patent[3] describes the preparation of 6-chloropurine from 6-purinethiol and chlorine in ethanol solution.

For an extension of this reaction to the purinethiols in general, 2,6,8-purinetrithiol (VII) was selected for detailed investigation. This compound has recently been made readily available by treatment of 6-hydroxy-2,8-purinedithiol (X) with phosphorus pentasulfide in pyridine.[2] When 2,6,8-purinetrithiol (VII) was treated with chlorine in absolute methanol at 10–15°, 6-chloro-8-hydroxypurine-2-sulfonic acid (IV)was isolated. Although IV probably was formed from 6,8-dichloropurine-2-sulfonic acid, which hydrolyzed in the acidic media, all attempts to isolate 6,8-dichloropurine-2-sulfonic acid from the reaction failed. The product, 6-chloro-8-hydroxypurine-2-sulfonic acid (IV) is not entirely unexpected as 2,6,8-trismethylthiopurine under similar conditions gives 6-chloro-8-hydroxy-2-methylsulfonylpurine.[2] Early attempts to obtain 2,6,8-trichloropurine (VIII) directly from 2,6,8-purinetrithiol (VII) were unsuccessful. Consideration of the probable mechanism of replacement of the thio group by chlorine led to the postulation that a positive halogen ion attacks the sulfur atom to form a sulfenyl halide. Further chlorination could oxidize the sulfur atom further.

At some stage of oxidation the sulfur atom becomes electron deficient, and the electron density on the purine ring is lowered sufficiently to encourage attack by a nucleophilic chloride ion present in the reaction mixture. It is quite possible that a sulfonyl chloride group is an intermediate in this reaction, as this group is known to be susceptible to nucleophilic displacement by chloride ion in other heterocyclic systems.[4] Nucleophilic attack on the purine ring proceeds most readily at the 6-position and in the presence of acid can readily be accomplished at the 8-position.[5] As the reaction medium is acidic in this instance, it follows that nucleophilic displacement by chloride ion is the most difficult at the 2-position.

An attempt was then made to assist the reaction at position 2 by increasing the chloride ion concentration by the addition of concentrated hydrochloric acid to the reaction mixture. This resulted in the isolation of some 2,6,8-trichloropurine. When a mixture of methanol and concentrated hydrochloric acid, saturated with dry hydrogen chloride, was utilized as the reaction medium, chlorine gas converted 2,6,8-purinetrithiol (VII) to 2,6,8-trichloropurine (VIII) in nearly quantitative yield. It would appear that, besides supplying additional chloride ion, the more concentrated acid also ensures protonation of the nitrogen atoms in the heterocyclic ring which is an additional aid to nucleophilic displacement by chloride ion due to the further lowering of the electron density at positions 2, 6, and 8.

2,6,8-Trichloropurine was utilized by Fischer for his classical synthesis of the natural purines.[6] This compound which Fischer placed "an die Spitze"[7] in importance in the chemistry of the purines is now for the first time readily available. As much as 200 g. of 2,6,8-trichloropurine, isolated as the ammonium salt, has been prepared from 200 grams of 2,6,8-purinetrithiol in a single afternoon in the author's laboratory. Previously, this compound has been obtained only by chlorination of uric acid in a stepwise manner involving sealed tube reactions with phosphorus oxychloride[8–12]

(1) Supported by Contract SA-43-ph-1928 with the Cancer Chemotherapy National Service Center of the National Cancer Institute of the National Institutes of Health.

(2) C. W. Noell and R. K. Robins, *J. Am. Chem. Soc.*, 81, 5997 (1959).

(3) G. H. Hitchings and G. B. Elion, U. S. patent 2,815,346 Dec. 3, 1957, [*Chem. Abstr.*, 52, 6417a (1958)].

(4) R. O. Roblin, Jr., and J. W. Clapp, *J. Am. Chem. Soc.*, 72, 4890 (1950).

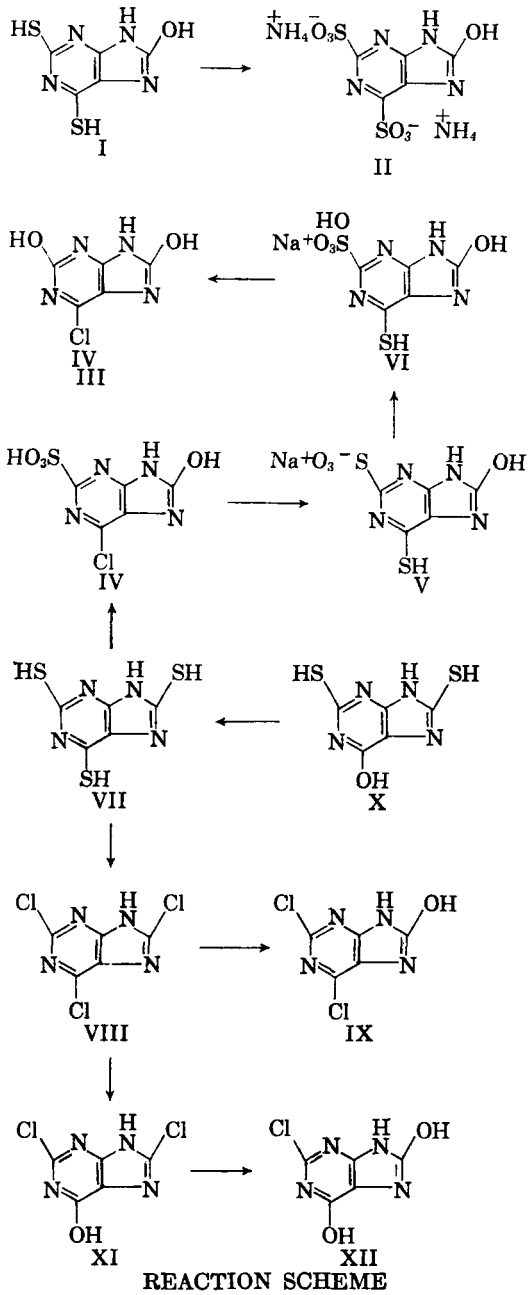
(5) R. K. Robins, *J. Am. Chem. Soc.*, 80, 6671 (1958). See additional references listed therein.

(6) E. Fischer, *Ber.*, 30, 2226 (1897).

(7) E. Fischer, *Ber.*, 32, 435 (1899).

(8) E. Fischer, *Ber.*, 30, 2220 (1897).

(9) J. M. Gulland and L. F. Story, *J. Chem. Soc.*, 260 (1938).

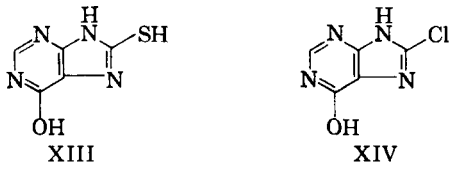


REACTION SCHEME

or by chlorination of uric acid in the presence of *N,N*-dimethylaniline and phosphorus oxychloride.[13]

During the conversion of VII to VIII if the reaction temperature were allowed to rise to 35° with no external cooling the product isolated was 2,6-dichloro-8-hydroxypurine (IX). The identity of this product was established on the basis of its ultraviolet absorption spectra which were identical with those of IX prepared from 2,6,8-trichloropurine by the method of Fischer.[8] It is assumed that IX resulted as a hydrolysis product of 2,6,8-trichloropurine in the acid medium.

A limited study of the extension of the general reaction of the replacement of a mercapto group has shown that the reaction takes place readily even in the presence of an electron-rich hydroxy group. 6-Hydroxy-2,8-purinedithiol (X) in the presence of excess hydrochloric acid, methanol, and chlorine gave an excellent yield of 2,8-dichloro-6-hydroxypurine (XI). In the absence of added hydrochloric acid, no XI was isolated. The structure of the product, 2,8-dichloro-6-hydroxypurine (XI), was established by comparison with XI prepared by the method of Fischer[6] from 2,6,8-trichloropurine and aqueous potassium hydroxide. Similarly, 6-hydroxy-8-purinethiol (XIII) was converted in good yield to 8-chloro-6-hydroxypurine (XIV). The identity of XIV was established by comparison with an authentic sample previously prepared[5] from 6,8-dichloropurine and potassium hydroxide.



The structure of 6-chloro-8-hydroxypurine-2-sulfonic acid (IV) [prepared from 2,6,8-purinetrithiol (VII) and chlorine in anhydrous methanol] was established by conversion to the known 8-hydroxy-6-mercaptopurine-2-sulfonic acid (V)[14] with thiourea in refluxing ethanol. The compound V had previously been converted[14] to 2,8-dihydroxy-6-purinethiol (VI), a recently reported metabolite of 6-purinethiol (6-mercaptopurine), isolated from human urine.[14,15] Thus, the preparation of IV provides a readily available route to the synthesis of 2,8-dihydroxy-6-purinethiol (VI).

The utility of the method of changing a mercapto group to chlorine was strikingly demonstrated by the successful conversion of 2,8-dihydroxy-6-purinethiol (VI) to 6-chloro-2,8-dihydroxypurine (III) by the use of chlorine in the presence of a solution of methanol and concentrated hydrochloric acid saturated with hydrogen chloride. Duggan and Titus[16] record a number of unsuccessful attempts to prepare 6-chloro-2,8-dihydroxypurine (III) by conventional procedures. The synthesis here recorded verifies the structure 6-chloro-2,8-

(10) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 836 (1946).

(11) B. G. Boldyrev and R. G. Makitra, *J. Applied Chem., USSR*, **28**, 399–404 (1955), [*Chem. Abstr.*, **50**, 2611c].

(12) H. Biltz and H. Bulow, *Ann.*, **423**, 159 (1921).

(13) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **73**, 2936 (1951). Although Davoll and Lowy report 16–25% yield of trichloropurine from uric acid utilizing *N,N*-dimethylaniline and phosphorus oxychloride, this reaction proved impractical in our laboratory for the synthesis of quantities of 2,6,8-trichloropurine in excess of 5 to 10 grams.

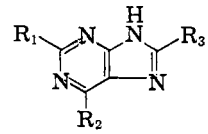
(14) G. B. Elion, S. Mueller, and G. H. Hitchings, *J. Am. Chem. Soc.*, **81**, 3042 (1959).

(15) T. L. Loo, M. E. Michael, A. J. Garceau, and J. C. Reid, *J. Am. Chem. Soc.*, **81**, 3039 (1959).

(16) D. E. Duggan and E. Titus, *J. Biol. Chem.*, **234**, 2100 (1959).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF SOME 2,6,8-TRISUBSTITUTED PURINES



Compound	R_1	R_2	R_3	λ_{max}, mμ, *p*H 1	ϵ_{max}	λ_{max}, mμ, *p*H 11	ϵ_{max}
VIII	Cl	Cl	Cl	246	4,900	225	18,300
				281	12,700	286	12,300
IV	SO_3H	Cl	OH	283	12,500	293	13,500
II	SO_3NH_4	SO_3NH_4	OH	253	6,600	300	18,100
				290	15,300		
XII	Cl	OH	OH	273	11,900	285	10,300
XI	Cl	OH	Cl	255	12,700	269	12,900
III	OH	Cl	OH	316	7,400	243[a]	7,100
						316	11,500
IX	Cl	Cl	OH	248	5,500	300	13,300
				288	12,100		

[a] Inflection.

hydroxypurine (III) which Duggan and Titus[16] assigned to the product of the reaction of xanthine oxidase and 6-chloropurine. The ultraviolet and infrared spectra of 6-chloro-2,8-dihydroxypurine were identical to those recorded[16] for the product obtained by enzymatic oxidation of 6-chloropurine. 6-Chloro-2,8-dihydroxypurine (III) has been found to be a potent inhibitor of the oxidation of uric acid by uricase.[16] Several attempts to prepare 6-chloro-2,8-dihydroxypurine directly from 6-chloro-8-hydroxypurine-2-sulfonic acid (IV) by acid hydrolysis gave only starting material or uric acid.

When 8-hydroxy-2,6-purinedithiol (I) was treated with chlorine gas in anhydrous methanol, the diammonium salt of 8-hydroxypurine-2,6-disulfonic acid (II) was isolated in approximately 40% yield. The ammonium ions presumably arise from oxidative degradation of the purine nucleus.[17,18] The oxidation of uric acid with chlorine water is known to result in degradation of the purine ring. Fischer[19] records that 2,6-dihydroxy-8-purinethiol is readily oxidized by chlorine water. Oxidation of xanthine with chlorine water to alloxan and urea is the basis for the murexide test.[20,21]

The purinesulfonic acid derivatives II and V were surprisingly stable to aqueous base. Refluxing 2*N* sodium hydroxide was without effect.

Attempts to replace the 6-chloro group of 6-chloro-8-hydroxypurine-2-sulfonic acid (IV) with various amines led only to the isolation of the amine salt of the starting sulfonic acid derivative (IV). Several unsuccessful attempts were made to replace the 6-sulfonic acid group of 8-hydroxypurine-2,6-disulfonic acid (II) by various nucleophilic reagents. It would appear that the presence of the 8-hydroxy group in compounds II and IV acts to stabilize the 6-position against attack by the usual nucleophilic reagents. Controlled acid hydrolysis of 2,8-dichloro-6-hydroxypurine (XI) gave the previously unreported 2-chloro-6,8-dihydroxypurine (XII) as expected. The structure of XII was established, as the compound was found to be different from 6-chloro-2,8-dihydroxypurine (III) or the other possible isomer, 8-chloro-2,6-dihydroxypurine.[22]

The ultraviolet absorption spectral data for the purines here described are listed in Table I.

EXPERIMENTAL[23]

Preparation of diammonium salt of 8-hydroxypurine-2,6-disulfonic acid (II). Twenty grams of 8-hydroxy-2,6-purinedithiol(I)[2] was added to 150 ml. of absolute methanol. The solution was cooled to 10° in an ice bath, and a stream of chlorine gas was gently passed into the solution. The flow of chlorine was regulated so that the temperature did not rise above 15°. After 1.5 hr. all the starting material was in solution. The flow of chlorine was continued for 15 min. more to ensure completion of the reaction. The clear, light-green solution was placed in a crystallizing dish and placed in the hood overnight. During this time the solution was evaporated to one half its original volume, and the mushy solution was diluted with 100 ml. of methanol, boiled for 10 min., and filtered hot. The precipitate was washed with methanol and dried. The yield was 10.2 g. For analysis a sample was recrystallized from methanol, containing a small amount of water, and finally dried at 130°.

Anal. Calcd. for $C_5H_{10}N_6S_2O_7.H_2O$: C, 17.2; H, 3.5; N, 24.1. Found: C, 16.7; H, 3.6; N, 24.4.

(17) Brugnatelli, *Ann. Chim. Phys.*, **8**, 201 (1817).

(18) H. Blitz and H. Schauder, *J. Prakt. Chem.* [2], **106**, 114 (1923).

(19) E. Fischer, *Ber.*, **32**, 503 (1899).

(20) E. Fischer, *Ber.*, **30**, 2226 (1897).

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

(22) R. K. Robins and B. E. Christensen, *J. Am. Chem. Soc.*, **74**, 3624 (1952).

(23) All melting points were taken on a Fischer-Johns melting point block and are uncorrected unless otherwise indicated.

This product was boiled with dilute aqueous ammonia, and the solution was acidified with acetic acid. Upon long standing in the refrigerator, crystals appeared. Recrystallization from methanol, containing a little water, gave the same product as above as judged on the basis of identical ultraviolet spectral data. The sample was dried at 130°.

Anal. Calcd. for $C_5H_{10}N_6S_2O_7.H_2O$: N, 24.1. Found: N, 23.8.

8-Hydroxypurine-2,6-disulfonic acid monosodium salt. Three grams of the diammonium salt (II) prepared above was added to 100 ml. of 2*N* sodium hydroxide. The solution was boiled gently for 20 min., and the volume of the solution was reduced to 30 ml. The solution was acidified with an excess of concd. hydrochloric acid and allowed to cool overnight in the refrigerator. The product was filtered and recrystallized from methanol-water and dried at 110°.

Anal. Calcd. for $C_5H_3N_4S_2O_7Na\cdot1^1/_2H_2O$: C, 17.4; H, 1.7. Found: C, 17.4; H, 1.7.

6-Chloro-8-hydroxypurine-2-sulfonic acid (IV). Thirty-two grams of 2,6,8-purinetrithiol (VII),[2] dried at 130°, was added to 300 ml. of absolute methanol (dried over magnesium and redistilled). The solution was cooled to 10° in an ice bath, and chlorine gas was slowly passed into the solution, with stirring, at such a rate that the temperature did not rise above 15°. After 3 hr. all the 2,6,8-purinetrithiol had dissolved, and the clear light-green solution was placed in a crystallizing dish and allowed to evaporate to one third its original volume in the hood. The mushy product was then filtered and washed with cold ethyl acetate. The damp white solid was then added to 300 ml. of boiling acetone and filtered from the hot solution. The product was washed with 300 ml. of cold acetone and then allowed to air-dry. The yield was 30.8 g. of white crystalline solid which was above 95% pure as judged by the ultraviolet absorption spectra. A small sample was recrystallized from a large volume of acetone for analysis.

Anal. Calcd. for $C_5H_3N_4SO_4Cl.2H_2O$: C, 20.9; H, 2.4; N, 19.5. Found: C, 21.0; H, 3.0; N, 19.4.

Sample dried at 130°: *Anal.* Calcd. for $C_5H_3N_4SO_4Cl.H_2O$: C, 22.3; H, 1.9. Found: C, 22.5; H, 2.2.

Sample dried at 160°, neut. equiv. calcd. for $C_5H_3N_4SO_4Cl$: 134.25. Found: neut. equiv. 133.

Methylamine salt of 6-chloro-8-hydroxypurine-2-sulfonic acid. Five grams of the free acid, X, was dissolved in 100 ml. of water, and 20 ml. of 40% aqueous methylamine was added. The solution was heated on the steam bath, and the volume was reduced to 25 ml. The hot solution was adjusted to *p*H 1 with hydrochloric acid and cooled. The crude product was recrystallized from methanol and a small amount of water.

Anal. Calcd. for $C_6H_8N_5SO_4Cl$: C, 25.8; H, 2.8; N, 25.0. Found: C, 25.9; H, 3.0; N, 25.0.

Monosodium salt of 6-chloro-8-hydroxypurine-2-sulfonic acid. To 30 ml. of water and 2.0 g. of sodium hydroxide was added 1.0 g. of 6-chloro-8-hydroxypurine-2-sulfonic acid (IV). The solution was refluxed for 10 min. and then carefully neutralized with hydrochloric acid and allowed to cool. The product was filtered and washed with a small amount of cold water and recrystallized from water to give dense prisms, yield 0.4 g. A sample was dried in the oven at 130° for analysis.

Anal. Calcd. for $C_5H_2N_4ClSO_4Na\cdot H_2O$: C, 20.6; H, 1.4; N, 19.2. Found: C, 20.5; H, 1.5; N, 18.8.

2,6,8-Trichloropurine (VIII)[6] *from 2,6,8-purinetrithiol* (VII). A cooled mixture of 200 ml. of concd. hydrochloric acid and 300 ml. of methanol was saturated with gaseous hydrogen chloride at 0°. To this solution was added 100 g. of 2,6,8-purinetrithiol (VII)[2] previously dried at 130°.

The reaction mixture was cooled in an ice bath and stirred with a magnetic stirrer. Chlorine was then added at such a rate that the inside temperature was maintained between 15–20°. After approximately 6 hr. all the starting material had gone into solution and had been replaced by a thin, white solid. The contents of the flask were then added carefully with stirring to 800 ml. of concd. ammonium hydroxide and approximately 3 kg. of crushed ice. A voluminous mass of the ammonium salt of 2,6,8-trichloropurine gradually crystallized after standing for 10 min. The solution was cooled in the deep freeze for 1 hr. and filtered. The white product was washed with a small amount of ice water and dried at 50° to yield 95.0 g. of the dry ammonium salt. A small amount was recrystallized from water and allowed to air dry.

Anal. Calcd. for $C_5H_4N_5Cl_3\cdot2H_2O$: N, 25.3. Found: N, 25.2.

Sample dried at 85°: *Anal.* Calcd. for $C_4H_4N_5Cl_3$: C, 24.9; H, 1.7. Found: C, 24.9; H, 1.9.

For conversion to 2,6,8-trichloropurine 20 g. of the ammonium salt was added to 150 ml. of boiling water. The clear solution was cooled to 50° and acidified to *p*H 1 with dilute hydrochloric acid. The solution was then further cooled to 0° and filtered. The product was washed free of acid and dried to yield 17.5 g. of white product, m.p. 187–188° dec. The anhydrous compound was obtained by boiling the product in benzene until most of the water left as an azeotrope. The cooled benzene solution yielded plates, m.p. 188–189°. 2,6,8-Trichloropurine also recrystallized readily from methanol to give white needles, m.p. 188–189°. Fischer[6] records 187–189° for the melting point of this compound. The product was then dried at 110° for 2 hr. before analysis.[24]

Anal. Calcd. for $C_5HN_4Cl_3$: C, 26.8; H, 0.45; N, 25.1; Cl, 47.7. Found: C, 26.9; H, 0.52; N, 24.9; Cl, 47.8.

2,8-Dichloro-6-hydroxypurine (XI). To 200 ml. of a solution of methanolic hydrochloric acid (prepared by the addition of 200 ml. of concd. hydrochloric acid to 300 ml. of methanol and saturating this solution with hydrogen chloride gas at 0°) was added 25.0 g. of 6-hydroxy-2,8-purinedithiol(X).[2] The mixture was cooled in an ice-bath while chlorine was bubbled into the solution at a moderate rate. The reaction temperature was 10°. After 2.5 hr. all the starting material had dissolved. The solution was poured onto ice and neutralized with ammonium hydroxide at 0°. The *p*H was then adjusted to 1 with dilute hydrochloric acid and the solution cooled and filtered. The product was washed with distilled water and dried at 110° to give 15.5 g. The ultraviolet absorption spectra of this compound and 2,8-dichloro-6-hydroxypurine (XI), prepared by the method of Fischer[6] from 2,6,8-trichloropurine, were identical. A small sample was recrystallized from ethanol for analysis.

Anal. Calcd. for $C_5H_2N_4Cl_2O$: C, 29.2; H, 1.0; N, 27.3; Cl, 34.1. Found: C, 29.2; H, 1.3; N, 27.1; Cl, 34.0.

8-Hydroxy-6-mercaptopurine-2-sulfonic acid sodium salt (V). Ten grams of 6-chloro-8-hydroxypurine-2-sulfonic acid (IV) was added to 250 ml. of absolute methanol and 7 g. of thiourea. The solution was refluxed for 1.5 hr. and cooled and filtered. The crude product (7.1 g.) was added to 60 ml. of water containing 4.0 g. of sodium hydroxide. The solution was boiled gently with charcoal for 5 min. and filtered. The colorless filtrate was adjusted to *p*H 3 with dilute hydrochloric acid and cooled. The light-yellow product was washed with distilled water and allowed to air dry.

Anal. Calcd. for $C_5H_3N_4S_2O_4Na\cdot3H_2O$: C, 18.5; H, 2.8. Found: C, 18.5; H, 2.9.

Sample dried at 110°: *Anal.* Calcd. for $C_5H_3N_4S_2O_4Na.H_2O$: C, 21.6; H, 1.7; N, 19.5. Found: C, 21.6; H, 2.0; N, 20.0.

This product possessed an ultraviolet absorption spectrum essentially in agreement with that reported for 2-

(24) The author has verified the observation of Baddiley, *et al.* [J. Baddiley, J. G. Buchanan, F. J. Hawker, and J. E. Stephenson, *J. Chem. Soc.*, 4660 (1956)] that 2,6,8-trichloropurine upon long storage slowly evolves hydrogen chloride. This is especially true if the preparation is not anhydrous. If the compound is to be kept for long periods of time, it should be stored as the stable ammonium salt.

hydroxy-6-mercaptopurine-2-sulfonic acid sodium salt prepared by another method.[13]

2,8-Dihydroxy-6-purinethiol (VI).[13,14] Twenty grams of 8-hydroxy-6-mercaptopurine-2-sulfonic acid sodium salt (V) was added to 220 ml. of concd. hydrochloric acid and 1500 ml. of water. The solution was refluxed for 4 hr. during which time the solid dissolved, and gradually the product crystallized from the hot solution. The solution was then filtered hot and the product washed with water. The yield of pure 2,8-dihydroxy-6-purinethiol was 11.2 g. The ultraviolet absorption spectrum of this compound was found to be essentially in agreement with that previously recorded.[13,14] $\lambda_{max}^{pH\ 1}$ 259, 358 mμ, ε 7,400, 30,200; $\lambda_{max}^{pH\ 11}$ 235, 346 mμ, ε 16,700; 21,700.

Anal. Calcd. for $C_5H_4N_4O_2S \cdot H_2O$: N, 27.7. Found: N, 27.8.

6-Chloro-2,8-dihydroxypurine (III). Two grams of 2,8-dihydroxy-6-purinethiol (VI) was added to 50 ml. of methanol-hydrochloric acid solution (see preparation of VII) and the solution cooled to 0° and stirred vigorously with a magnetic stirrer. Chlorine was carefully bubbled into the reaction mixture so that the temperature was kept below 5°. After approximately 5 min. all the solid was in solution, and the reaction was stopped (continued chlorination resulted in further oxidation of the desired product).

The reaction mixture was poured onto ice and the solution adjusted to *p*H 14 with concentrated aqueous ammonia. A precipitate of white needles of the ammonium salt of 6-chloro-2,8-dihydroxypurine gradually appeared in the solution. This product was filtered and dried to yield 1.6 g. The ammonium salt was dissolved in 100 ml. of boiling water and the solution acidified with hydrochloric acid and cooled to yield 1.1 g. of 6-chloro-2,8-dihydroxypurine (III). The product was recrystallized from water for final purification to give white crystals which gradually decomposed above 200° without melting. An attempt to convert the compound into an anhydrous product at 130° resulted in considerable decomposition.

Anal. Calcd. for $C_5H_3N_4ClO_2 \cdot H_2O$: C, 29.3; H, 2.4; N, 27.3. Found: C, 29.4; H, 2.5; N, 27.1.

8-Chloro-6-hydroxypurine (XIV). To 100 ml. of methanol-hydrochloric acid solution (see preparation of VII) was added 14.5 g. of 6-hydroxy-8-purinethiol hydrate (XIII).[4] The solution was cooled to 10° and chlorine passed into the reaction mixture for 40 min. until the reaction mass became too solid to stir. The crude product was added to ice and the solution made basic with concd. aqueous ammonia and finally acidified to *p*H 1 with hydrochloric acid. The solution was cooled and filtered, and the crude product was washed with water. 8-Chloro-6-hydroxypurine (XIV) was purified by reprecipitation from hot, dilute sodium hydroxide by the addition of acetic acid to yield 8.1 g. The ultraviolet absorption spectrum of the product was identical with that previously reported[4] for 8-chloro-6-hydroxypurine (XIV).

2-Chloro-6,8-dihydroxypurine (XII). Two grams of 2,8-dichloro-6-hydroxypurine (XI) was added to 100 ml. of concd. hydrochloric acid, and the mixture was heated for 2 hr. on the steam bath. The cooled solution was filtered and the product washed with distilled water. The crude product was added to 200 ml. of boiling water, and just enough potassium hydroxide was added to effect solution. The solution was treated with charcoal and boiled gently for 5 min. and filtered. The hot filtrate was acidified with hydrochloric acid and allowed to cool. The white crystals which slowly formed were filtered and washed with distilled water and dried at 110° to yield 1.1 g.

Anal. Calcd. for $C_5H_3N_4O_2Cl$: C, 32.1; H, 1.6; N, 30.0. Found: C, 32.0; H, 1.7; N, 29.5.

TEMPE, ARIZ.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

Pyrazolono(3,4-d)pyrimidines. II. 6-Methylpyrazolono(3,4-d)pyrimidines and Some Reactions of Pyrazolono(3,4-d)pyrimidines[1,2]

MARTIN HAUSER,[3] EARL PETERS,[4] AND HOWARD TIECKELMANN

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6-Methylpyrazolono(3,4-d)pyrimidines have been synthesized from 2-methyl-4-chloro-5-carbethoxypyrimidine and hydrazines. Several reactions of 6-methylthiopyrazolono(3,4-d)pyrimidines, including oxidation, hydrolysis, amination, chlorination, and alkoxylation, are described.

In the preceding paper in this series,[5] the preparation of several 4-substituted hydrazinopyrimidines and 6-methylthiopyrazolono(3,4-d)pyrimidines by the reaction of 2-methylthio-4-chloro-5-carbethoxypyrimidine (I) with substituted-hydrazines was described. The present paper discusses the reactions of 2-methyl-4-chloro-5-carbethoxypyrimidine (II)[6] with several of the same hydrazines and some reactions of 6-methylthiopyrazolono(3,4-d)pyrimidines.

When II was treated with *p*-bromophenyl- and *p*-carboxyphenylhydrazine, the corresponding pyrazolono(3,4-d)pyrimidines (XIII and XIV) were obtained directly. These results are identical with those obtained with I.

Treatment of II with methylhydrazine led to isolation of a low-melting solid which on heating in water gave 1,6-dimethylpyrazolono(3,4-d)-

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