The amount of 4-picoline (0.7 mole) was increased relative to the amount of aluminum chloride (0.84 mole) and bromine (0.35 mole). No brominated product at all was obtained.

Ferric chloride (0.42 mole) together with aluminum chloride (0.42 mole) was used as a catalyst in place of aluminum chloride alone. No brominated product at all could be found.

A small scale run similar to the best preparation of 3-bromo-4-picoline was made. The crude product was worked up carefully to avoid losses and was analyzed by gas chromatography (75 ml./min., furnace temperature 114°, Gowmac temperature 179°, 2 ft. of 4.5 mm. copper tubing packed with Columnpak impregnated with 20% Dow Corning High Vacuum Silicon Grease). Retention volume for 4-picoline was 195 ml., and for 3-bromo-4-picoline was 765 ml. The per cent of each was obtained by measuring the respective areas with a planimeter. The area ratio, obtained from a calibration curve, was related fortuitously to the per cent 3-bromo-4-picoline in 4-picoline within the 30–70% range by the equation; area ratio = 0.0975 per cent 3-bromo-4-picoline. The yield of 3-bromo-4-picoline was estimated to be 50%. The estimate is highly dependent on complete recovery of both starting material and product and is most likely to be a maximum yield.

Attempts to run bromination at 140° yielded considerable resinous material and no brominated picoline.

5-Bromo-2-picoline. 2-Picoline (b.p. 143°, n_D^{25} 1.5030, hygroscopic, 0.7 mole) and aluminum chloride (1.7 mole) were mixed in the usual manner, and bromine (0.7 mole) added to the mixture at 100° over a period of 5 hr. After the usual work-up, the crude product (48 g., 40% based on a monobromopicoline) was separated by slow fractionation in a Helipak-filled column at water-aspirator pressure. An impure liquid fraction was obtained (b.p. 79–83°, 20 g., n_D^{25} 1.5493–1.5561).

Anal. Calcd. for C_6H_6BrN: Br, 46.20. Found: Br, 46.25.

The next fraction solidified (8 g., 6.5%) which on recrystallization from hexane gave 5 g. of colorless crystals, m.p. 36.5–37°, reported[14] m.p. for 5-bromo-2-picoline 32°. The compound was oxidized to 5-bromo-2-picolinic acid, m.p. 176.5–178.5° after recrystallization from water, reported[14] m.p. 175°. Attempts to oxidize the impure liquid fraction gave only small amounts of the same acid. However, seeding the liquid bromopicoline with 5-bromo-2-picoline did not induce crystallization. The liquid fraction undoubtedly was a mixture of 5-bromo- and 3-bromo-2-picoline, as the other isomers were shown to be absent by the aniline test. The liquid fraction showed no displacement of bromine with aniline under conditions where 2-bromopyridine reacted rapidly.

Attempted bromination of 4-picoline using boron trifluoride as a catalyst. Boron trifluoride was passed through 4-picoline (33 g., 0.4 mole) for 1 hr. Considerable heat was evolved and a solid separated which melted approximately at 80–85°. Bromine (64 g., 0.4 mole) was added dropwise to the molten complex while a slow stream of boron trifluoride was passed over the surface. No reaction was evident at the end of 32 hr., but all the bromine had been swept out by the boron trifluoride. After the usual decomposition and work-up, 4-picoline (29 g., 88%, n_D^{25} 1.5026) was recovered with no indication of an accompanying brominated product.

Acknowledgment. The authors are indebted to the National Science Foundation for a grant in support of this work.

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(14) R. Graf, *J. prakt. Chem.*, **133**, 19 (1932).

[CONTRIBUTION FROM MIDWEST RESEARCH INSTITUTE]

Pyrimidines. I. Synthesis of Pyrimidinethiols[1,2]

HENRY C. KOPPEL, ROBERT HENRE SPRINGER, ROLAND K. ROBINS, AND C. C. CHENG

Received May 27, 1960

With the publication of this work all twenty-two possible isomers of pyrimidinethiols, aminopyrimidinethiols, and hydroxypyrimidinethiols substituted at positions 2, 4, and 6 of the pyrimidine ring have now been reported. Methods of synthesis for all the new compounds as well as improved methods for the preparation of some previously reported compounds in this series have been recorded.

Derivatives of pyrimidinethiols have also been prepared for preliminary screening as possible antitumor agents.

The inhibition of various animal tumors by certain pyrimidine derivatives[3] has focused attention on this group of compounds. It therefore seemed worth while to begin a systematic study of certain simple pyrimidines in order to gain additional information regarding the type of pyrimidine structure necessary for antitumor activity.

Purines and pyrimidines appear to be of similar importance in the formation of nucleic acids, and

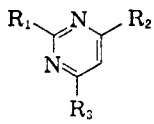
(1) This investigation was supported by research contract SA-43-ph-3025 from the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) Presented in part before the Division of Medicinal Chemistry, 137th Meeting of the American Chemical Society, Cleveland, Ohio, April 1960.

(3) See, for example: (a) L. F. Larionov, *Brit. J. Cancer*, 10, 26 (1956); (b) D. M. Shapiro and R. A. Fugman, *J. Nat. Cancer Inst.*, 18, 201 (1957); (c) C. Heidelberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duchinsky, R. J. Schnitzer, E. Pleven, and J. Scheiner, *Nature*, 179, 663 (1957); (d) A. R. Curreri, F. J. Ansfield, F. A. McIver, H. A. Waisman, and C. Heidelberger, *Cancer Research*, 18, 478 (1958); (e) W. H. Prusoff, *Cancer Research*, 18, 603 (1958); (f) M. A. Rich, J. L. Bolaffi, J. E. Knoll, L. Cheong, and M. L. Eidinoff, *Cancer Research*, 18, 730 (1958); (g) J. F. Holland, R. Guthrie, P. Sheehe, and H. Tickelmann, *Cancer Research*, 18, 776 (1958); (h) G. B. Elion, S. Bieker, H. Nathan, and G. H. Hitchings, *Cancer Research*, 18, 802 (1958); (i) J. J. Jaffe and J. R. Cooper, *Cancer Research*, 18, 1089 (1958); (j) D. A. Lyttle and H. G. Petering, *J. Am. Chem. Soc.*, 80, 6459 (1958); (k) D. A. Lyttle and H. G. Petering, *J. Nat. Cancer Inst.*, 23, 153 (1959).

since certain purinethiols[4-6] and alkylthiopurines[7-10] have exhibited significant antitumor activity, the preparation of a number of simple pyrimidinethiols for preliminary investigation was undertaken. Because the naturally occurring pyrimidines, uracil, thymine, and cytosine, possess the hydrogen bonding groups, hydroxy or amino, the preparation of pyrimidinethiols containing these substituents was accordingly studied.

Theoretically, the arrangements of hydrogen, hydroxy, amino, and thio substituents at positions 2, 4, and 6 of the pyrimidine ring form twenty-two possible structural isomers:



I-XXII

*two mono*substituted pyrimidinethiols;

I. R_1 = SH; R_2, R_3 = H
II. R_1, R_3 = H; R_2 = SH

*six di*substituted pyrimidine*mono*thiols;

III. R_1 = SH; R_2 = OH; R_3 = H
IV. R_1 = OH; R_2 = SH; R_3 = H
V. R_1 = H; R_2 = SH; R_3 = OH
VI. R_1 = SH; R_2 = NH_2; R_3 = H
VII. R_1 = NH_2; R_2 = SH; R_3 = H
VIII. R_1 = H; R_2 = SH; R_3 = NH_2

*two di*substituted pyrimidine*di*thiols;

IX. R_1, R_2 = SH; R_3 = H
X. R_1 = H; R_2, R_3 = SH

*seven tri*substituted pyrimidine*mono*thiols;

XI. R_1 = SH; R_2, R_3 = OH
XII. R_1 = SH; R_2 = OH; R_3 = NH_2
XIII. R_1 = SH; R_2, R_3 = NH_2
XIV. R_1, R_2 = OH; R_3 = SH
XV. R_1 = OH; R_2 = SH; R_3 = NH_2
XVI. R_1 = NH_2; R_2 = SH; R_3 = OH
XVII. R_1, R_2 = NH_2; R_3 = SH

*four tri*substituted pyrimidine*di*thiols;

XVIII. R_1 = OH; R_2, R_3 = SH
XIX. R_1 = NH_2; R_2, R_3 = SH
XX. R_1, R_2 = SH; R_3 = OH
XXI. R_1, R_2 = SH; R_3 = NH_2

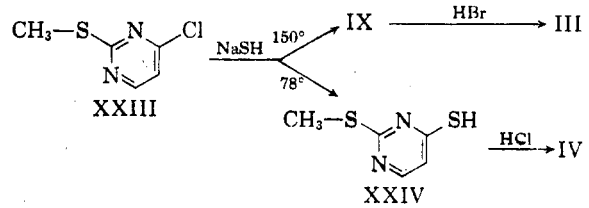
and *one* pyrimidine*tri*thiol.

XXII. R_1, R_2, R_3 = SH

A literature survey has indicated that 2-pyrimidinethiol (I), 4-pyrimidinethiol (II) and 2,4-dithiouracil (IX) were prepared by Boarland and McOmie,[11a] 2-thiouracil (III) and 4-thiouracil (IV) were synthesized by Wheeler and Liddle,[11b] 6-hydroxy-4-pyrimidinethiol (V) and 2-amino-6-hydroxy-4-pyrimidinethiol (XVI) have recently been reported by Isbecque and co-workers,[11c] 4-amino-2-pyrimidinethiol (VI) was made by Hitchings and co-workers[11d] and 2,6-diamino-4-pyrimidinethiol (XVII) has also been reported by Daves and co-workers.[9] Michael[11e] synthesized 2-thiobarbituric acid (XI) in 1887. 6-Amino-2-thiouracil (XII) was prepared by Traube[11f] and 4,6-diamino-2-pyrimidinethiol (XIII) by Traube[11f] and by Bendich and co-workers.[11g] The preparation of 2,4,6-trithiobarbituric acid (XXII) has been reported by Büttner[11h] and by Pavolini and Gambarin.[11i]

The remainder of these compounds have been synthesized for the first time in our laboratories. A number of new and improved procedures for the preparation of some of the known pyrimidines have been recorded here since these compounds were resynthesized for the purpose of biological testing or for use as intermediates for the preparation of other derivatives.

The two isomeric thiouracils (III and IV) were prepared from the same intermediate, 4-chloro-2-(methylthio)pyrimidine (XXIII),[12] by merely changing the reaction conditions. Thus, when compound XXIII was reacted with sodium hydrosulfide at 150°, 2,4-dithiouracil (IX)[11a] was formed. Concentrated hydrobromic acid converted IX into 2-thiouracil (III). When the sodium hydrosulfide reaction was carried out at 78°, 2-(methylthio)-4-pyrimidinethiol (XXIV) was obtained, which yielded 4-thiouracil (IV) upon hydrolysis with dilute hydrochloric acid. The formation of IX from XXIII is the first recorded instance in pyrimidine chemistry of the replacement of a 2-



XXIII XXIV

(4) G. H. Hitchings, C. P. Rhoads (Conference Co-chairman), 6-Mercaptopurine Conference, *Ann. N. Y. Acad. Sci.*, **60**, 186–508 (1954).

(5) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **77**, 1676 (1955).

(6) H. C. Koppel and R. K. Robins, *J. Am. Chem. Soc.*, **80**, 2751 (1958).

(7) H. C. Koppel, D. E. O'Brien, and R. K. Robins, *J. Org. Chem.*, **24**, 259 (1959).

(8) T. P. Johnston, L. B. Holum, and J. A. Montgomery, *J. Am. Chem. Soc.*, **80**, 6265 (1958).

(9) G. D. Daves, C. W. Noell, R. K. Robins, H. C. Koppel, and A. G. Beaman, *J. Am. Chem. Soc.*, **82**, 2633 (1960).

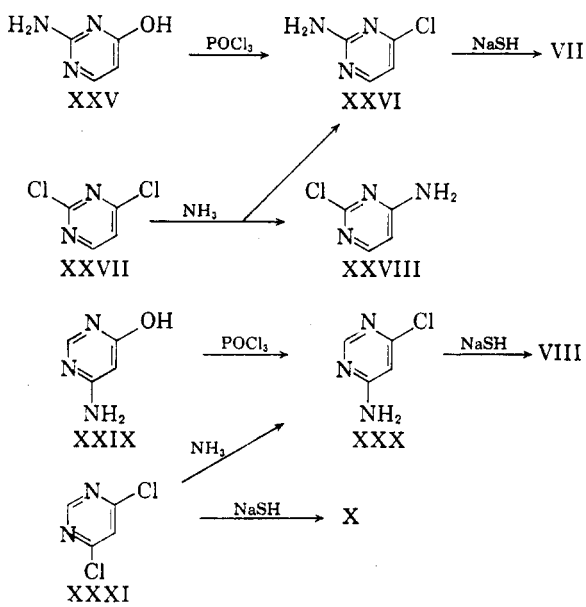
(10) For a study of structural activity relationship of certain purinethiols and alkylthiopurines against experimental neoplasms, see H. E. Skipper, J. A. Montgomery, J. R. Thomson, and F. M. Schabel, Jr., *Cancer Research*, **19**, 425 (1959).

(11) (a) M. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 1218 (1951); (b) H. L. Wheeler and L. M. Liddle, *Am. Chem. J.*, **40**, 547 (1908); (c) D. Isbecque, R. Promel, R. C. Quimaux, and R. H. Martin, *Helv. Chim. Acta.*, **42**, 1319 (1959); (d) G. H. Hitchings, G. B. Elion, E. A. Falco, and P. B. Russell, *J. Biol. Chem.*, **177**, 357 (1949); (e) H. Michael, *J. prakt. Chem.*, [2], **35**, 456 (1887); (f) W. Traube, *Ann.*, **331**, 64, 71 (1904); (g) A. Bendich, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, **70**, 3109 (1948); (h) H. Büttner, *Ber.*, **36**, 2234 (1903); (i) F. Pavolini and F. Gambarin, *Anal. Chim. Acta.*, **3**, 180 (1949).

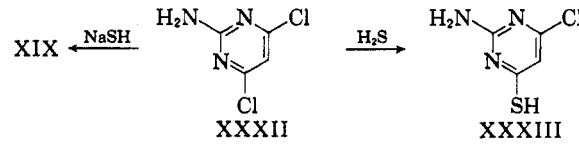
(12) T. Matsukawa and B. Ohta, *J. Pharm. Soc. Japan*, **69**, 489 (1949).

methylthio group directly by the nucleophilic sulfide ion. The conversion of IX to III with concentrated hydrobromic acid is the first recorded direct hydrolysis of a 4-thio group in the pyrimidine system under atmospheric conditions. The stability of the 2-thio group under these conditions is certainly of note.

The chlorine atom in both 2-amino-4-chloropyrimidine (XXVI)[13] and 4-amino-6-chloropyrimidine (XXX)[14] was readily replaced with sodium hydrosulfide at elevated temperatures to give 2-amino-4-pyrimidinethiol (VII) and 6-amino-4-pyrimidinethiol (VIII), respectively. The intermediate XXVI was obtained by the chlorination of the corresponding hydroxypyrimidine (XXV)[13] rather than from 2,4-dichloropyrimidine (XXVII)[15] and ammonia, since the reactivities of the chlorine atom at positions 2 and 4 in XXVII are essentially equal.[15,16] On the other hand, the isomeric 6-amino-4-pyrimidinol (XXX) could be obtained by either chlorination of 4-amino-6-hydroxypyrimidine (XXIX)[17] or amination of 4,6-dichloropyrimidine (XXXI).[18] Compound XXXI reacted exothermically with sodium hydrosulfide in ethanol with the formation of 4,6-pyrimidinedithiol (X).

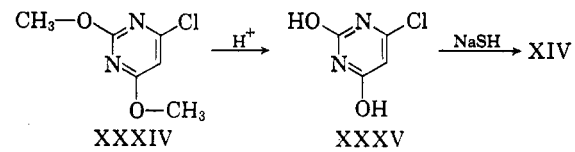


6-Amino-2,4-dithiouracil (XXI) was prepared by direct thiation of 6-amino-2-thiouracil (XII)[11f] with phosphorus pentasulfide.



The isomeric 2-amino-4,6-pyrimidinedithiol (XIX) was prepared from 2-amino-4,6-dichloropyrimidine (XXXII)[11h] by the action of sodium hydrosulfide in ethylene glycol. Heating XXXII with ethanolic sodium hydroxide saturated with hydrogen sulfide gave the monothio compound, 2-amino-6-chloro-4-pyrimidinethiol (XXXIII).

4-Chloro-2,6-dimethoxypyrimidine (XXXIV),[19] when treated with concentrated hydrochloric acid, gave 4-chloro-2,6-pyrimidinediol (XXXV). The chlorine atom in XXXV was very inactive



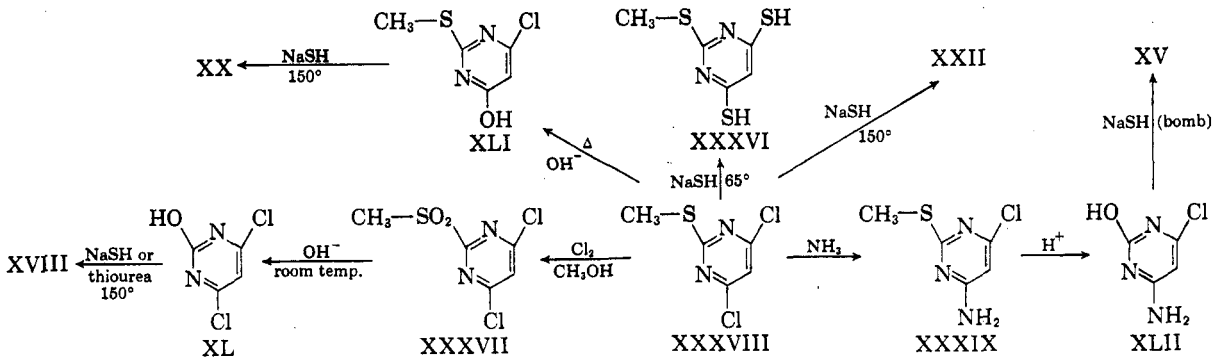
toward nucleophilic agents and attempts to replace it under atmospheric conditions with a thio group by either sodium hydrosulfide or thiourea were unsuccessful. The conversion was finally accomplished with sodium hydrosulfide in a bomb to give the desired 4-thiobarbituric acid (XIV).

When the very important intermediate, 4,6-dichloro-2-methylthiopyrimidine (XXXVIII)[20] was treated with sodium hydrosulfide at 150° in ethylene glycol, 2,4,6-trithiobarbituric acid (XXII) was obtained, which was found to be identical with the trithiol prepared from 2,4,6-trichloropyrimidine.[11b,c] Less vigorous conditions, such as refluxing in methanolic sodium hydrosulfide, resulted in replacement of the two chlorine groups but not the methylthio group, giving 2-(methylthio)-4,6-pyrimidinedithiol (XXXVI).

Although compound XXXVIII contains two chloro groups and one methylthio group, it showed remarkable stability toward acids, in spite of the fact that all three groups are located on the "active" (in the sense of nucleophilic substitution) positions on the pyrimidine ring. When XXXVIII was refluxed with 1*N* hydrochloric acid for several hours, only starting material was isolated. Basic hydrolysis of XXXVIII resulted in replacement of one chlorine to yield 6-chloro-2-(methylthio)-4-pyrimidinol (XLI), which in turn gave 2,4-dithiobarbituric acid (XX) when treated with sodium hydrosulfide at 150°.

The corresponding isomer, 4,6-dithiobarbituric acid (XVIII), was prepared by the following sequence of reactions. Gaseous chlorine, when passed through a methanolic solution of XXXVIII,

(13) W. Gabriel and B. Coleman, *Ber.*, **36**, 3383 (1903).
(14) C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **80**, 2185 (1958).
(15) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 1152 (1930).
(16) G. H. Hitchings, G. B. Elion, E. A. Falco, and P. B. Russell, *J. Biol. Chem.*, **177**, 357 (1949).
(17) D. J. Brown, *J. Soc. Chem. Ind.*, **69**, 353 (1950).
(18) G. W. Kenner, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 574 (1943).
(19) S. B. Greenbaum and W. L. Holmes, *J. Am. Chem. Soc.*, **76**, 2899 (1954).
(20) H. L. Wheeler and G. S. Jamieson, *Am. Chem. J.*, **32**, 342 (1904).



oxidized the latter to 4,6-dichloro-2-(methylsulfonyl)pyrimidine (XXXVII). Compound XXXVII was easily hydrolyzed in base at room temperature to yield 4,6-dichloro-2-pyrimidinol (XL). The sodium salt of XL, when refluxed with thiourea in ethanol or heated with sodium hydrosulfide in ethylene glycol, was converted to XVIII.

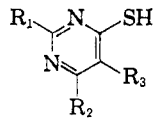
The third positional isomer of XII and XVI, 6-amino-4-thiouracil (XV), was also prepared from the versatile intermediate XXXVIII. Amination of XXXVIII resulted in replacement of one chloro group to give XXXIX,[20] which was converted to XLII by acid hydrolysis.[20] Compound XLII was then treated with sodium hydrosulfide in a bomb to yield the desired XV.[21]

The synthesis of all the possible isomers of pyrimidinethiols, aminopyrimidinethiols, and hydroxypryimidinethiols substituted at positions 2, 4, and 6 of the pyrimidine ring is therefore complete.

A study of the ultraviolet absorption spectra of this series of pyrimidinethiols has revealed some interesting facts. In general, the approximate positions of the maximum absorption of the major peak of pyrimidinethiols in *p*H 1 can be summarized as follows: 280 mμ for 2-pyrimidinethiols, 300–320 mμ for 4-pyrimidinethiols, 320–340 mμ for 2,4-pyrimidinedithiols, and 360–370 mμ for 4,6-pyrimidinedithiols.

In the case of 4-pyrimidinethiols, the presence of an additional thio- group at position 6 greatly increases the extinction coefficient of the major absorption peak. An additional thio group at position 2 decreases the extinction coefficient of the major peak, but increases the extinction coefficient of the minor peak, which usually absorbs at a lower wave length. The presence of a hydroxy or amino group at position 6 of 2,4-pyrimidinedithiol shifts the absorption maxima of the parent compound to a lower wave length, while, on the other hand, the presence of those groups at position 2 of 4,6-pyrimidinedithiols gives little or no effect on the position of the absorption maxima. The absorption maxima of pyrimidinethiols at *p*H 11 are always at slightly lower wave lengths than the corresponding maxima at *p*H 1. There is no distinctive way to differentiate a hydroxypyrimidinethiol from its analogous aminopyrimidinethiol. Their ultraviolet absorption spectra are, in general, quite similar. The ultraviolet absorption spectra data are recorded in Table I. The data for a number of known thiopyrimidines have been included for comparison, since this information has not been previously published.

For the comparison of structure and biological activities in pyrimidinethiols, a number of new related 4-pyrimidinethiols with groups at position 5, such as carboxyl-, phenyl-, halogeno-, and methyl-, have also been synthesized. Included are certain 5-bromo- and 5-chloro-4,6-pyrimidinedithiols (XLIII, R_1 = H, R_2 = SH, R_3 = Br, Cl)



XLIII

which were prepared from 5-bromo-4,6-dichloropyrimidine[22] and 4,5,6-trichloropyrimidine,[22] respectively, by the action of sodium hydrosulfide in ethanol. The conversion of 2-amino-4,6-dichloro-5-phenylpyrimidine to 2-amino-5-phenyl-4,6-pyrimidinedithiol (XLIII R_1 = NH_2, R_2 = SH, R_3 = C_6H_5) by sodium hydrosulfide required more drastic conditions. 2,4-Dithio-5-pyrimidinecarboxylic acid (XLIII R_1 = SH, R_2 = H, R_3 = COOH) was prepared from thiourea and 2,4-dichloro-5-pyrimidinecarboxylic acid.[23] 2-Amino-6-methyl-4-pyrimidinethiol (XLIII R_1 = NH_2, R_2 = CH_3, R_3 = H) was prepared by the action of sodium hydrosulfide on 2-amino-4-chloro-6-methylpyrimidine[24] in ethylene glycol. The reactivity of the 4-chloro group was greatly increased by the presence of a 5-bromo group; thus, 2-amino-5-bromo-4-chloro-6-methyl-

(21) Following the presentation of this work at the 137th American Chemical Society Meeting, it was called to our attention that this compound has been independently prepared by Dr. Edward J. Modest and co-workers (unpublished work), Children's Cancer Research Foundation, Inc., Boston, Mass.

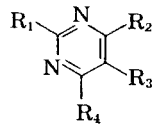
(22) J. Chesterfield, J. F. W. McOmie, and E. R. Sayer, *J. Chem. Soc.*, 3478 (1955).

(23) V. H. Smith and B. E. Christensen, *J. Org. Chem.*, **20**, 829 (1955).

(24) W. Gabriel and B. Coleman, *Ber.*, **32**, 2921 (1899).

TABLE I

PYRIMIDINETHIOLS



Cpd. No.	R_1	R_2	R_3	R_4	Method of Synthesis	M.P.	Yield, %	U.V. Absorption pH 1 λ_{max}	pH 1 ϵ	pH 11 λ_{max}	pH 11 ϵ	Recrystallization Solvents[a]	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	SH	H	H	H	Ref. 11a	229–230 dec.	70	283	17,200	235	3,750	c			25.0			25.0
										269	13,150							
II	H	SH	H	H	[b]	190–192	69	293	10,700	293	13,300	b			25.0			24.6
								310	10,700									
IV	OH	SH	H	H	Ref. 11b [b]	298–300	88	242	3,500	334	17,900	a + b	37.5	3.1	21.9	37.8	3.4	22.0
								326	19,200									
III	SH	OH	H	H	Ref. 11b [b]	310–312 dec.	73	273	13,800	233	11,000	b			21.9			21.9
										259	10,200							
										310	6,950							
VII	NH_2	SH	H	H	A	231–233	68	256	4,800	262	6,100	a + b	37.8	3.9	33.1	37.8	3.9	33.1
								325	14,700	311	13,300							
V	H	SH	H	OH	Ref. 11c	247 dec.	79	243	9,000	239	17,600	b			21.9			21.8
								304	17,400	288	13,300							
VIII	H	SH	H	NH_2	A	306	61	237	6,600	244	7,000	a + b			33.1			33.1
								303	28,700	289	16,300							
IX	SH	SH	H	H	Ref. 11a	300 dec.	70	280	22,300	272	19,300	b			19.4			19.6
								345	10,000	321	6,000							
										360	8,900							
X	H	SH	H	SH	B	250–252	70	280	14,400	268	24,600	b	33.3	2.7	19.4	33.7	2.7	19.4
								370	57,600	316	20,000							
XI	SH	OH	H	OH	Ref. 11e	>360	84	234	8,500	235	13,800	a + b			19.4			19.6
								282	21,600	280	11,200							
XIV	OH	SH	H	OH	E	245 dec.	54	306	19,600	302	25,200	b	33.3	2.8	19.4	33.3	2.8	19.4
XV	OH	SH	H	NH_2	E	355 dec.	43	242	7,600	303	27,500	a + b	33.6	3.5	29.4	33.7	3.5	29.6
								317	40,500									
XVI	NH_2	SH	H	OH	Ref. 11c	>360	82	237	12,200	296	19,000	a + b			29.4			29.4
								309	26,200									
XVII	NH_2	SH	H	NH_2	Ref. 9	>360	50	243	10,800	299	19,000	f			39.4			39.7
								323	33,000									
XII	SH	OH	H	NH_2	Ref. 11f	>360	91	245	8,200	241	17,700	f			29.4			29.3
								276	20,100	289	13,300							
XIII	SH	NH_2	H	NH_2	Ref. 11f	>360	93	286	22,700	267	11,500	f			39.4			39.2
XX	SH	SH	H	OH	A	262–264	79	274	20,300	238	15,000	a + b	30.2	2.6	17.5	30.2	3.0	17.6
								308	13,600	304	12,500							
XXI	SH	SH	H	NH_2	[b]	>360	60	281	29,400	247	16,900	a + b	30.3	3.1	26.4	30.3	3.2	26.5
								326	26,600	306	28,200							

TABLE I (*Continued*)

Cpd. No.	R_1	R_2	R_3	R_4	Method of Synthesis	M.P.	Yield, %	U.V. Absorption *p*H 1 λ_{max}	*p*H 1 ε	*p*H 11 λ_{max}	*p*H 11 ε	Recrystallization Solvents[a]	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XVIII	OH	SH	H	SH	A	266–267	46	244	5,600	244	7,800	a + b	30.2	2.6	17.5	30.1	2.6	17.5
								277	7,500	278	8,400							
								360	40,400	340	26,100							
XIX	NH_2	SH	H	SH	A	267 dec.	76	247	10,700	253	10,500	b	30.3	3.1	26.4	30.6	2.9	26.3
								278	11,500	325	25,600							
								370	62,700									
XXII	SH	SH	H	SH	B	>360	70	282	31,000	258	16,700	d			15.9			15.7
								371	71,000	295	22,600							
										355	22,400							
XXXIII	NH_2	SH	H	Cl	[b]	>360	63	263	6,300	267	7,200	b + e	29.6	2.4	25.9	29.6	2.5	25.7
								341	17,700	314	14,700							
XLIII	NH_2	SH	H	CH_3	A	321 dec.	84	254	5,200	262	6,500	f	42.5	4.9	29.8	42.7	4.6	29.7
								328	19,600	308	16,100							
XLIII	NH_2	SH	Br	CH_3	A	207 dec.	98	265	5,900	320	11,700	a + b	27.3	2.7	19.1	27.6	2.9	19.3
								341	14,400									
XLIII	SH	SH	H	CH_3	Ref. 24	>360	70	283	23,300	276	18,900	a + b			17.4			17.4
								342	12,200	354	10,900							
XLIII	SH	SH	COOH	H	D	261–263	63	297	38,300	287	19,200	a + b	31.9	2.1	14.9	32.1	2.2	15.2
								350	6,600	370	9,200							
XLIII	H	SH	Cl	SH	B	215–217	70	282	12,700	268	22,000	d	26.8	1.7	15.6	26.8	1.7	15.8
								376	31,700	323	18,900							
XLIII	H	SH	Br	SH	B	213 dec.	92	283	12,800	270	23,000	d	21.5	1.4	12.6	21.5	1.6	12.7
								378	37,000	324	18,900							
XLIII	NH_2	SH	C_3H_5	SH	A	266–268	60	252	29,400	255	24,400	a + b	51.1	3.8	17.8	50.8	3.8	17.5
								285	7,400	333	26,600							
								374	46,500									
XXIV	CH_3S	SH	H	H	C	203	96	244	17,700	252	24,300	a + b	37.9	3.9	17.7	38.0	4.1	18.0
								270	16,300	310	11,400							
								338	11,800									
XLIII	CH_3S	SH	H	CH_3	[c]	239	78	242	11,400	252	15,300	a + b			16.3			16.2
								274	8,400	309	12,700							
								331	14,600									
XXXVI	CH_3S	SH	H	SH	[b]	>360	80	257	18,000	247	16,500	b + c	31.5	3.1	14.7	31.5	2.8	14.7
								280	22,700	312	10,900							
								350	9,900									

[a] Recrystallization solvents: (a) dimethylformamide, (b) water, (c) ethanol, (d) reprecipitation from hot, dilute alkaline solution by dilute hydrochloric acid, (e) acetic acid, and (f) reprecipitation from hot, dilute alkaline solution by glacial acetic acid. [b] Method of synthesis discussed individually in experimental section. [c] M. Polonovski and H. Schmidt, *Bull. soc. chim. France* [55], **17**, 616 (1950).

pyrimidine[25] was converted smoothly to 2-amino-5-bromo-6-methyl-4-pyrimidinethiol (XLIII R_1 = NH_2, R_2 = CH_3, R_3 = Br) in aqueous sodium hydrosulfide at a much lower temperature.

A representative selection of (alkylthio)pyrimidines and (aralkylthio)pyrimidines have also been prepared from the corresponding thiopyrimidines by alkylation and aralkylation (see Table II.)

EXPERIMENTAL[26]

General methods for the preparation of pyrimidinethiols (see Table I). *Method A* is illustrated by the following specific examples: *Example (1): 2,4-Dithiouracil* (IX). To 200 ml. of ethylene glycol was added 200 g. of sodium hydrosulfide followed by 125 g. of 4-chloro-2-(methylthio)pyrimidine (XXIII).[12] The mixture was heated slowly to 100°, at which time a great amount of frothing and bubbling took place. When this had somewhat subsided, the reaction mixture was carefully heated to 150° and maintained at that temperature for 30 min. The dark solution was poured into 1500 ml. of water, and the resulting straw-colored solution was boiled, treated with charcoal, and filtered. The hot filtrate was acidified with acetic acid. The crude yellow product, which precipitated from the acidified solution, was redissolved in hot dilute aqueous ammonia and reprecipitated by acetic acid to give 85 g. of light yellow crystals of IX. The ultraviolet and infrared absorption spectra of this product were identical with those reported for 2,4-dithiouracil prepared by the method of Boarland and McOmie.[11a]

Example (2): 2,4-Dithiobarbituric acid (XX). A mixture of 13 g. of 6-chloro-2-(methylthio)-4-pyrimidinol and 42 g. of sodium hydrosulfide was added to 120 ml. of ethylene glycol. The mixture was heated to 150° and kept at that temperature for 30 min. The reaction mixture was cooled and poured into 500 ml. of water. The resulting solution was boiled and decolorized with charcoal. The solution was acidified with glacial acetic acid to *p*H 5, and a small amount of sulfur was removed by filtration. The filtrate was then acidified to *p*H 1 with dilute hydrochloric acid. The crude product was collected and reprecipitated from dilute aqueous ammonia solution with hydrochloric acid to give light yellow crystals. Recrystallization of this product from a mixture of dimethylformamide and water gave 9.0 g. of light yellow needles, m.p. 262–264°, of XX.

Method B: Sixty grams of the appropriate chloropyrimidine was suspended in 500 ml. of absolute ethanol. To this mixture was added 150 g. of sodium hydrosulfide and the resulting mixture was refluxed for 3 hr. During this time, a clear solution first formed which soon was followed by precipitation. The reaction mixture was chilled and the precipitate was filtered and washed with ethanol. For purification, the solid product was dissolved in 1 l. of boiling water, treated with charcoal, and filtered. The filtrate was acidified and the resultant solid collected and recrystallized from the appropriate solvent.

Method C: This procedure is the same as Method B, except that a precipitate was not formed after the reaction. The light yellow alcoholic solution was diluted with 1 l. of boiling water, boiled with charcoal, and filtered. The filtrate was then acidified as described in the preceding procedure to precipitate the product.

Method D: Forty grams of the appropriate chloropyrimidine was added to 500 ml. of absolute ethanol containing 40 g. of thiourea. The mixture was refluxed for 2 hr. The contents dissolved in the beginning but soon a precipitate was formed. The mixture was chilled and the crude product was filtered and washed with ligroin. It was then purified by reprecipitation, followed by recrystallization.

Method E: To 400 ml. of water in a 1 l. stainless steel bomb was added 35 g. of the appropriate chloropyrimidine and 70 g. of powdered sodium hydrosulfide. The mixture was heated at 150° and under 120 lb./sq. in. for 4 hr. The resulting straw-colored solution was boiled, treated with charcoal, and filtered. The filtrate was acidified with glacial acetic acid (for the preparation of 6-amino-4-thiouracil, XII) or dilute hydrochloric acid (for the preparation of 4-thiobarbituric acid, XIV). The product was further purified by recrystallization from the solvents listed in Table I.

4-Pyrimidinethiol (II).[27] A mixture of 52 g. of 4-pyrimidinol[17] and 125 g. of *purified* phosphorus pentasulfide (see below) was refluxed in 1 l. of pyridine with vigorous mechanical stirring for 1 hr. The hot, dark brown solution was carefully poured into 1 l. of water. The resulting aqueous solution was heated on the steam bath for 3 hr. and a small amount of insoluble substance was separated by filtration. The filtrate was then evaporated under reduced pressure to about 200 ml. After being cooled in the refrigerator, the solution yielded a brown crystalline solid which was filtered, washed with ice water, and recrystallized (treated with charcoal) from 500 ml. of boiling water. Forty-two grams of yellow needles were obtained. Two more recrystallizations from water gave pale yellow, long needles with silky luster, m.p. 190–192°.

Purified phosphorus pentasulfide may be prepared by extraction of commercial grade phosphorus pentasulfide in a Soxhlet apparatus using carbon disulfide as the extraction solvent. Pure P_2S_5 crystallized as yellow crystals in the extraction flask.

6-Amino-2,4-dithiouracil (XXI). A finely powdered mixture of 50 g. of 6-amino-2-thiouracil[11f] predried at 100° and 150 g. of phosphorus pentasulfide was added to 1.5 l. of dry pyridine. The mixture was refluxed for 2 hr.; during that time a dark red solution was formed. The excess of pyridine was removed by distillation under reduced pressure. To the residue was added, with caution, 750 ml. of water. The mixture was refluxed on a steam bath till the evolution of hydrogen sulfide had ceased (2 hr.). The solution was chilled and a small amount of insoluble material was filtered. The filtrate was acidified to *p*H 2 and its volume was reduced to one third under reduced pressure. A yellow precipitate which appeared during this process was filtered after the reaction mixture had been cooled. The solid was washed with cold water and redissolved in dilute aqueous ammonia. The solution was boiled, decolorized with charcoal, and filtered. Addition of dilute hydrochloric acid to the filtrate gave light yellow crystals. The product was further purified by recrystallization from a mixture of dimethylformamide and water to give 35 g. of light yellow needles.

2-Thiouracil (III). A mixture of 40 g. of 2,4-dithiouracil and 1 l. of 40% hydrobromic acid was refluxed for 1 hr. The solid material dissolved slowly, and an orange solution was formed. The solution was chilled overnight and 13 g. of light yellow needles were obtained. An additional 15 g. of the same material was isolated after the volume of the filtrate was reduced by one half by distillation under reduced pressure. It was concluded from a comparison of ultraviolet and infrared absorption spectra and paper chromatography that the product was identical with an authentic sample of 2-thiouracil prepared by the method according to Wheeler and Liddle.[11b]

4-Thiouracil (IV). Ten grams of 2-(methylthio)-4-pyrimidinethiol (XXIV) was added to 250 ml. of 2*N* hydro-

(25) C. C. Price, N. J. Leonard, and R. H. Reitsema, *J. Am. Chem. Soc.*, 68, 766 (1946).

(26) All melting points were taken on a Thomas-Hoover melting point apparatus. The infrared spectra were taken with a Perkin-Elmer infracord and the ultraviolet absorption spectra were determined with a Beckman DK-2.

(27) The authors wish to thank Professor J. F. W. McOmie of Bristol University, England, who kindly furnished this direct thiation procedure which had been devised in his laboratory.

TABLE II. ALKYLTHIO- AND ARALKYLTHIOPYRIMIDINES

R_1	R_2	R_3	R_4	Method of Synthesis	M.P.	U.V. Absorption pH 1 λ_{max}	pH 1 ϵ	pH 11 λ_{max}	pH 11 ϵ	Ethanol λ_{max}	Ethanol ϵ	Recrystallization Solvents[a]	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	OH	H	CH_3S	B	230	237 277	14,200 8,100	266	5,200			b			19.7			19.7
H	OH	H	$C_6H_5CH_2S$	B	238–239					236 282	18,500 6,900	a + b	60.5	4.6	12.8	60.6	4.6	12.5
H	OH	H	$(2,4)Cl_2C_6H_3CH_2S$	B	191–193					233 282	23,800 6,600	a + b	46.0	2.7	9.8	46.1	2.7	9.7
H	NH_2	H	CH_3S	A	168–170					237 275	29,600 11,500	a + b	42.5	5.0	29.8	42.5	5.0	30.1
H	NH_2	H	C_2H_5S	A	147–149					237 275	23,200 5,300	a + b	46.4	5.8	27.3	46.4	5.7	27.3
H	NH_2	H	$C_6H_5CH_2S$	A	140					235 275	28,200 5,800	a + b	60.8	5.1	19.3	60.8	5.1	19.2
H	NH_2	H	$(2,4)Cl_2C_6H_3CH_2S$	A	184–186					235 275	33,400 6,900	a + b	46.2	3.2	14.7	46.5	3.4	14.7
H	NH_2	H	p-$NO_2C_6H_4CH_2S$	A	165–167					235 272	26,200 14,400	a + b	50.4	3.8	21.4	50.2	3.7	21.3
H	CH_3S	H	CH_3S	A	52–54					252 294	25,400 12,600	c	42.0	4.6	16.3	42.4	4.4	16.6
H	CH_3S	NH_2	CH_3S	A	79					230 310	16,700 12,900	a + b	38.5	4.8	22.4	38.4	4.8	22.5
H	CH_3S	Cl	CH_3S	A	118–120					250 300	27,800 15,100	a + b	34.8	3.4	13.6	35.2	3.4	13.5
H	C_2H_5S	Cl	C_2H_5S	A	58–59					251 301	29,400 23,600	a + b	40.8	4.7	11.9	41.1	4.8	12.0
H	$C_6H_5CH_2S$	Cl	$C_6H_5CH_2S$	A	86–88					253 302	29,100 20,000	a + b	60.4	4.2	7.6	60.2	4.1	7.6
H	$(2,4)Cl_2C_6H_3CH_2S$	Cl	$(2,4)Cl_2C_6H_3CH_2S$	A	155					252 302	36,800 23,800	a + b	43.4	2.2	5.6	43.5	2.2	5.6
H	CH_3S	Br	CH_3S	A	155					251 300	26,600 14,800	a + b	28.6	2.8	11.1	28.5	3.0	11.3
H	n-C_3H_7S	Br	n-C_3H_7S	A	44–46					253 302	26,800 16,400	a + b	39.9	4.8	9.1	39.9	5.0	8.9
H	$C_6H_5CH_2S$	Br	$C_6H_5CH_2S$	A	95–97					254 303	31,700 20,900	a + b	53.9	3.7	7.0	54.2	3.9	6.9
H	$(2,4)Cl_2C_6H_3CH_2S$	Br	$(2,4)Cl_2C_6H_3CH_2S$	A	149					253 302	32,200 24,600	a + b	39.9	2.0	5.2	39.9	1.9	4.9
H	p-$NO_2C_6H_4CH_2S$	Br	p-$NO_2C_6H_4CH_2S$	A	168–170					253 302	33,000 28,600	a + b	43.9	2.6	11.3	44.0	2.7	.115

TABLE II (*Continued*)

R_1	R_2	R_3	R_4	Method of Synthesis	M.P.	U. V. Absorption pH 1 λ_{max}	pH 1 ϵ	pH 11 λ_{max}	pH 11 ϵ	Ethanol λ_{max}	Ethanol ϵ	Recrystallization Solvents[a]	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
OH	NH_2	H	CH_3S	B	294 dec.	295	13,300	285	11,900			b	38.3	4.4	26.8	38.3	4.4	36.5
OH	OH	H	$C_6H_5CH_2S$	B	242					280	11,300	a + b	49.2	3.4	10.4	49.1	3.5	10.4
OH	o-$ClC_6H_4CH_2S$	H	H	A	174–176					297	10,800	a + b	52.1	3.6	11.1	52.4	4.0	11.1
OH	(2,4)$Cl_2C_6H_3CH_2S$	H	H	A	193–194					297	10,900	a + b	46.1	2.7	9.8	46.5	2.7	9.9
NH_2	H	H	CH_3S	A	150–153					232	16,200	a + b	41.5	5.0	29.8	42.6	4.9	29.8
										300	9,000							
NH_2	H	H	C_2H_5	A	155					232	14,000	a + b	46.4	5.8	27.1	46.6	5.7	27.3
										301	9,000							
NH_2	H	H	$C_6H_5CH_2S$	A	178–180					301	10,400	a + b	60.8	5.1	19.3	61.0	5.1	19.6
NH_2	H	H	(2,4)$Cl_2C_6H_3CH_2S$	A	155–157					301	9,700	a + b	46.5	3.1	14.6	46.2	3.1	14.6
NH_2	CH_3	H	CH_3S	A	152	233	10,900	232	12,100			a + b	46.1	5.8	27.1	46.3	6.0	26.8
						300	13,900	298	10,300									
NH_2	CH_3	H	C_2H_5S	A	122–124	232	11,900	232	13,200			a + b	49.7	6.5	24.8	50.0	6.5	24.4
						302	14,800	298	10,600									
NH_2	CH_3	H	n-C_4H_9S	A	70–72	304	14,800	300	10,200			a + b	54.7	7.6	21.3	54.4	7.5	21.3
NH_2	CH_3	H	$C_6H_5CH_2S$	A	118–120	304	15,600	232	13,400			a + b	62.5	5.6	18.2	62.2	5.2	18.2
								300	11,000									
NH_2	CH_3	H	o-$ClC_6H_4CH_2S$	A	143–145					300	11,200	a + b	54.1	4.5	15.8	53.7	4.3	15.8
NH_2	CH_3	H	(2,4)$Cl_2C_6H_3CH_2S$	A	157–160	302	16,200	300	5,500			a + b	48.0	3.6	14.0	47.7	3.5	14.0
NH_2	CH_3	H	p-$NO_2C_6H_4CH_2S$	A	157–159	302	21,200	297	16,600			a + b	52.3	4.3	20.2	52.1	4.3	20.2
NH_2	OH	H	CH_3S	B	274–276	230	12,100	227	17,800			a + b	38.3	4.4	26.8	38.6	4.3	26.8
						280	14,500	278	9,200									
NH_2	OH	H	C_2H_5S	B	248	230	12,400	227	16,500			a + b	42.1	5.5	24.5	42.2	5.2	24.6
						282	14,500	279	9,000									
NH_2	OH	H	n-C_3H_7S	B	228–232	230	11,100	227	18,000			a + b	45.4	5.9	22.7	45.2	5.8	22.6
						282	12,800	280	10,200									
NH_2	OH	H	n-C_4H_9S	B	240–242	230	12,200	228	17,400			a + b	48.4	6.5	21.1	48.7	6.5	21.4
						282	14,800	280	9,400									
NH_2	OH	H	n-$C_6H_{11}S$	B	185	230	12,400	227	18,100			a + b	53.2	6.7	18.6	52.8	6.7	18.4
						282	14,800	280	11,200									
NH_2	Cl	H	CH_3S	A	106–108					237	15,800	a + b	34.2	3.4	23.9	34.6	3.5	23.9
										301	9,500							
NH_2	Cl	H	C_2H_5S	A	109–110					237	15,400	a + b	37.9	4.4	22.1	38.2	4.7	22.1
										302	10,200							
NH_2	Cl	H	n-C_3H_7S	A	105–106					237	13,300	a + b	41.2	4.9	20.6	41.5	4.9	20.4
										301	9,200							
NH_2	Cl	H	(2,4)$Cl_2C_6H_3CH_2S$	A	153–155					302	12,000	a + b	42.1	2.4	13.1	42.2	2.6	12.8
NH_2	CH_3	Br	CH_3S	A	140–142	224	17,900	238	17,300			a + b	30.8	3.4	17.9	30.9	3.7	17.6
						277	10,300	310	8,200									
						315	10,000											
NH_2	CH_3	Br	n-C_3H_7S	A	95–97					238	19,200	a + b	36.1	4.5	15.8	36.1	4.3	15.7
										310	8,600							
NH_2	CH_3	Br	$C_6H_5CH_2S$	A	135–137	280	9,800	238	15,800			a + b	46.4	3.9	13.5	46.5	4.0	13.3
						318	10,300	310	8,700									

TABLE II (*Continued*)

R_1	R_2	R_3	R_4	Method of Synthesis	M.P.	U.V. Absorption pH 1 λ_{max}	pH 1 ϵ	pH 11 λ_{max}	pH 11 ϵ	Ethanol λ_{max}	Ethanol ϵ	Recrystallization Solvents[a]	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
NH_2	CH_3	Br	o-$ClC_6H_4CH_2S$	A	138–140					238	19,300	a + b	41.8	3.2	12.2	42.1	3.2	12.2
										311	8,600							
NH_2	CH_3	Br	p-$NO_2C_6H_4CH_2S$	A	226–228					238	21,300	a + b	40.1	3.1	15.7	40.3	3.2	15.9
										308	11,400							
NH_2	CH_3S	H	CH_3S	A	116–118	278	10,600	241	16,000			a + b	38.7	4.8	22.4	38.4	5.0	22.4
						326	22,800	308	14,000									
NH_2	C_2H_5S	H	C_2H_5S	A	54					240	16,800	a + b	44.8	6.0	19.6	44.6	5.9	19.6
										307	12,200							
NH_2	n-C_3H_7S	H	n-C_3H_7S	A	85–87					240	16,300	a + b	49.4	7.0	17.5	49.3	6.8	17.6
										308	11,500							
NH_2	$C_6H_5CH_2S$	H	$C_6H_5CH_2S$	A	134–136					240	23,700	a + b	63.7	5.0	12.4	63.7	5.0	12.1
										310	17,300							
NH_2	(2,4)$Cl_2C_6H_3CH_2S$	H	(2,4)$Cl_2C_6H_3CH_2S$	A	159–161					238(s)	25,000	a + b	45.3	2.7	8.8	45.4	2.8	8.9
										310	18,600							
NH_2	CH_2S	C_6H_5	CH_3S	A	128–129					243	24,300	c	54.7	4.9	16.0	54.6	4.8	16.1
										311	13,900							
NH_2	$C_6H_5CH_2S$	C_6H_5	$C_6H_5CH_2S$	A	207–209					243	24,900	c	69.4	5.0	10.1	69.6	5.1	9.7
										314	16,600							
NH_2	o-$ClC_6H_4CH_2S$	C_6H_5	o-$ClC_6H_4CH_2S$	A	174–175					243	37,700	e	59.5	3.9	8.6	59.8	4.0	8.4
										315	24,200							
NH_2	(2,4)$Cl_2C_6H_3CH_2S$	C_6H_5	(2,4)$Cl_2C_6H_3CH_2S$	A	164–167					244(s)	25,000	f	53.1	3.1	7.6	53.1	3.1	7.6
										315	17,100							
CH_3S	CH_3	H	CH_3S	A	43–45					252	23,000	c	45.2	5.3	15.0	45.4	5.3	14.9
										297	7,100							
CH_3S	CH_3	H	(2,4)$Cl_2C_6H_3CH_2S$	A	100–102					253	22,800	a + b	47.3	3.3	8.5	47.5	3.7	8.2
										300	8,300							
CH_3S	CH_3S	H	OH	B	197	253	20,300	280	6,200			b	38.2	4.2	14.9	38.5	4.2	14.9
						293	9,600											
CH_3S	CH_3S	H	NH_2	A	121–123					244	24,800	a + b	38.7	4.8	22.4	38.4	4.8	22.6
										290	6,900							
CH_3S	CH_3S	H	CH_2S	A	114–116					252	37,900	a + b	38.5	4.6	12.8	38.8	4.7	13.0
										309	11,100							
CH_2S	CH_2S	COOH	H	B	201–203					268	24,600	a + b	38.9	3.7	12.9	39.2	3.6	12.9
$C_6H_5CH_2S$	CH_3	H	$C_6H_5CH_2S$	A	37–39					255	22,800	c	67.6	5.3	8.2	67.8	5.1	8.2
										300	7,900							
o-$ClC_6H_4CH_2S$	o-$ClC_6H_4CH_2S$	H	o-$ClC_6H_4CH_2S$	A	117–118					255	40,700	b + d	54.5	3.4	5.1	54.7	3.4	4.8
										312	16,500							
(2,4)$Cl_2C_6H_3CH_2S$	H	H	(2,4)$Cl_2C_6H_3CH_2S$	A	94–96					255	27,200	c	46.7	2.6	6.1	46.8	2.6	6.2
										300	9,200							
(2,4)$Cl_2C_6H_3CH_2S$	CH_3	H	(2,4)$Cl_2C_6H_3CH_2S$	A	107–109					255	24,800	c	47.9	2.9	5.8	48.2	3.1	5.7
										298	8,600							
(2,4)$Cl_2C_6H_3CH_2S$	(2,4)$Cl_2C_6H_3CH_2S$	H	NH_2	A	125–127					290	4,100	c	52.9	3.6	10.3	52.7	4.0	10.3
(2,4Cl_2)$C_6H_3CH_2S$	(2,4)$Cl_2C_6H_3CH_2S$	H	(2,4)$Cl_2C_6H_3CH_2S$	A	120–124					255	39,900	a + b	46.0	2.4	4.3	46.3	2.7	4.3
										312	17,000							

[a] Recrystallization solvents: (a) dimethylformamide, (b) water, (c) heptane, (d) ethanol, (e) ethyl acetate, and (f) toluene.

chloric acid. The suspension was refluxed for 4 hr., during which time the starting material slowly dissolved and was gradually replaced by somewhat lighter colored needles. Upon chilling, a mass of fine crystals deposited. The product was filtered and washed with a large amount of water. The yield of 4-thiouracil was 7 g., m.p. 298–300°.

2-Amino-6-chloro-4-pyrimidinethiol (XXXIII). Forty grams of sodium hydroxide and 800 ml. of ethanol were added to 200 ml. of water. The solution was cooled and saturated with hydrogen sulfide. To the saturated solution was added 83 g. of 2-amino-4,6-dichloropyrimidine (XXXII)[11b] and the mixture was stirred and refluxed while a stream of hydrogen sulfide was passed through it. The clear solution which resulted after 2 hr. was boiled, treated with charcoal and filtered. The filtrate was acidified with acetic acid to give 42 g. of light yellow crystals, m.p. >360°. For analysis, the compound was reprecipitated by acetic acid from a cold, dilute ammonium hydroxide solution to give light yellow crystals.

Anal. Calcd. for $C_4H_4ClN_3S$: C, 29.6; H, 2.4; N, 25.9. Found: C, 29.6; H, 2.5; N, 25.7.

6-Chlorouracil (XXXV). Fifty grams of 4-chloro-2,6-dimethoxypyrimidine (XXXIV)[19] was added to 50 ml. of boiling concentrated hydrochloric acid, and the mixture was stirred for 15 min. The solid slowly melted in the beginning and gradually dissolved in the acid. A white precipitate appeared at the end of 15 min. The mixture was then cooled and diluted with 300 ml. of ice water. The resultant precipitate was filtered, washed with water, and acetone. It was purified by recrystallization from water to yield 25 g. (60%) of XXXV as white crystals which decomposed at 302°.

Anal. Calcd. for $C_4H_3ClN_2O_2$: C, 32.6; H, 2.4; N, 19.1. Found: C, 32.6; H, 2.2; N, 19.1.

The ultraviolet absorption spectra of this product of *p*H 1 gave λ_{max} at 260 mμ (ε 9800); at *p*H 11 gave λ_{max} at 280 mμ (ε 12,500).

2-(Methylthio)-4,6-pyrimidinediol. This compound was previously synthesized by Wheeler and Jamieson[20] using methyl iodide as the methylation agent and the yield was rather low. An improved method is described as follows:

Sixty grams of 2-thiobarbituric acid (XI)[11e] was dissolved in 1 l. of 2*N* sodium hydroxide. To this solution was added, dropwise with stirring, 50 g. of dimethyl sulfate. The stirring was continued for 3 hr. and then the solution was heated briefly to boiling, treated with charcoal, and acidified with hydrochloric acid to *p*H 1. The crude product was filtered and recrystallized from water to give 50 g. of white crystals of 2-(methylthio)-4,6-pyrimidinediol, m.p. >360°.

Anal. Calcd. for $C_5H_6N_2O_2S$: C, 37.9; H, 3.8; N, 17.7. Found: C, 38.3; H, 3.8; N, 17.7.

The ultraviolet absorption spectra of this product at *p*H 1 gave λ_{max} at 242 mμ (ε 7300) and 275 mμ (ε 9300); at *p*H 11 gave λ_{max} at 259 mμ (ε 8300).

4,6-Dichloro-2-(methylthio)pyrimidine (XXXVIII). To 500 ml. of phosphorus oxychloride was added 80 g. of 2-(methylthio)-4,6-pyrimidinediol. The mixture was refluxed for 2 hr. (complete solution occurred after 15 min.). The solution slowly turned dark red. After 2 hr., the excess of phosphorus oxychloride was removed by distillation under reduced pressure and the residue was poured, with stirring, over crushed ice. The icy residue was stirred for 20 min. at 0°. During this period, a light tan precipitate appeared. The precipitate was filtered and washed in ice water until the *p*H of the washings was no longer below 5. The crude material was dried in a vacuum desiccator overnight. It was recrystallized from methanol and water to yield 64 g. of white needles of XXXVIII, m.p. 43°.

Anal. Calcd. for $C_5H_4Cl_2N_2S$: C, 30.8; H, 2.1; N, 14.3. Found: C, 31.2; H, 2.1; N, 14.6.

2-(Methylthio)-4,6-pyrimidinedithiol (XXXVI). See Table I. To 500 ml. of methanol was added 75 g. of sodium hydrosulfide. The mixture was heated to 50° and 50 g. of 4,6-dichloro-2-(methylthio)pyrimidine was added portionwise, with constant stirring. The reaction was rather vigorous. After the addition was complete, the dark yellow solution was stirred for an additional 30 min. It was then diluted with 1 l. of water, boiled, charcoaled, filtered, and acidified. The crude product was reprecipitated by acetic acid from dilute aqueous ammonia solution followed by recrystallization from a mixture of dimethylformamide and water to give 40 g. of pale yellow crystals, m.p. >360°.

6-Chloro-2-(methylthio)-4-pyrimidinol (XLI). To 500 ml. of 2*N* sodium hydroxide was added 50 g. of 4,6-dichloro-2-(methylthio)pyrimidine. The mixture was refluxed with stirring for 4 hr. The resulting straw-colored solution was decolorized with charcoal, filtered, and acidified with acetic acid to yield a light yellow precipitate. The crude product was purified by reprecipitation followed by recrystallization from a mixture of dimethylformamide and water to yield XLI as white crystals, m.p. 208°. The yield was 40 g.

Anal. Calcd. for $C_5H_5ClN_2OS$: C, 33.9; H, 2.8; N, 15.8. Found: C, 34.0; H, 2.9; N, 15.9.

4,6-Dichloro-2-(methylsulfonyl)pyrimidine (XXXVII). To 150 ml. of absolute methanol cooled in an ice bath was added 30 g. of finely powdered 4,6-dichloro-2-(methylthio)pyrimidine. The mixture was stirred while a stream of dry chlorine gas was passed through it. After a few minutes, all the solid had dissolved to give a light yellow solution. At the end of 30 min., a white precipitate had formed and the passage of chlorine gas was continued for another 15 min. The solid, when filtered and washed with ligroin, weighed 8 g. The filtrate was evaporated at room temperature by a gentle air stream to give an additional 12 g. Recrystallization of the white solid from a mixture of ethyl acetate and heptane gave 17 g. of XXXVII as white crystals, m.p. 119°. This product gave a positive test for sulfur.

Anal. Calcd. for $C_5H_4Cl_2N_2O_2S$: C, 26.4; H, 1.7; N, 12.3. Found: C, 26.5; H, 1.8; N, 12.2.

4,6-Dichloro-2-pyrimidinol (XL). Fifteen grams of 4,6-dichloro-2-(methylsulfonyl)pyrimidine was added to 200 ml. of 1*N* sodium hydroxide. The mixture was warmed slightly until solution was effected. It was then filtered from a small amount of insoluble material. The filtrate was then chilled to precipitate the sodium salt, which was filtered and washed with cold water and ethanol to give 11.6 g. of white solid. This product gave a negative test for sulfur.

Anal. Calcd. for $C_4HCl_2N_2ONa \cdot H_2O$ (sodium salt): C, 23.3; H, 1.4; N, 13.6. Found: C, 23.6; H, 1.4; N, 13.6.

The salt was suspended in 150 cc. of water. It was neutralized very carefully with hydrochloric acid. At that time all the solid dissolved. The solution was evaporated to dryness under reduced pressure and the residue was taken up in boiling isopropyl alcohol. To the solution was added *n*-heptane. Light yellow crystals were formed. Recrystallization of the product from the same solvent pair gave 5 g. of white crystals, m.p. 262°.

Anal. Calcd. for $C_4H_2Cl_2N_2O$: N, 17.0. Found: N, 17.1.

General methods for the preparation of (alkylthio)pyrimidines (see Table II). *Method A:* To 250 ml. of 1*N* sodium hydroxide was added 0.08 mole of the thiopyrimidine to be alkylated. The suspension was stirred at room temperature until solution was complete. Then a stoichiometric amount of the appropriate alkyl halide was added and the mixture was stirred for 3 hr. (The temperature of the reaction was governed by the boiling point and relative reactivity of the alkyl halide.) The precipitate which formed during the reaction was filtered, washed with water, and then recrystallized.

Method B: This procedure is identical with Method A except that at the end of the reaction period a clear solution rather than a precipitate was obtained. This solution was heated, decolorized with charcoal, and filtered. The filtrate was acidified with glacial acetic acid. Upon cooling, crystals appeared gradually. The crystalline product was filtered, washed with cold water and recrystallized from the appropriate solvent.

The yields of all the alkylated thiopyrimidines were usually

very high. The crude products were obtained in quantitative yields and the yields of recrystallized products were usually 80–95%.

Acknowledgments. The authors wish to express their appreciation to Mr. Wayne H. Nyberg, Mrs. Beverly Ann Smith, and Mrs. Carol R. Tuttle for their valuable assistance in performing analytical, instrumental, and paper chromatographic measurements.

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[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Cinnolines. VIII. The Reaction of 3-Aminocinnolines and 3-Aminoisoquinoline with Nitrous Acid[1,2]

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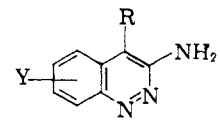
Received July 5, 1960

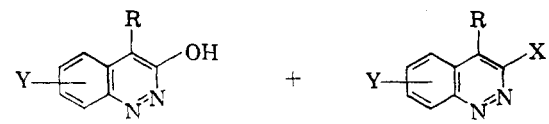
The reactions of 3-aminocinnoline and 3-aminoisoquinoline with nitrous acid in dilute mineral acid solution yielded 3-cinnolinol and 3-isoquinolinol. In concentrated hydrochloric or hydrobromic acids, 3-chloro- or 3-bromocinnoline were formed along with the 3-cinnolinol. Other 3-aminocinnolines behaved in an analogous fashion. Ionization constants for the amino and hydroxy compounds prepared are reported as are the infrared spectra of eight 3-cinnolinols and a number of related compounds.

Alford and Schofield[3c] have reported that, although 3-aminoquinoline is readily diazotized and thd diazonium salt forms a deep red azo compound with α-naphthol,[4] 3-aminocinnoline (Ia) in a similar test gave only a reddish-brown solution, and they concluded tentatively that Ia does not readily form a diazonium salt, if it does so at all. This communication reports the results of a study of the reactions of Ia and other 3-aminocinnolines as well as 3-aminoisoquinoline (IV) with nitrous acid in the presence of various mineral acids. After the preparative work in this study had been completed, a paper by Boyer and Wolford[5] appeared describing their experiments on the reaction of IV with nitrous acid, the results of which differed from ours in several minor respects. We have repeated both their and our own work and offer here a rationalization of the differences.

When solutions of Ia in dilute sulfuric or hydrochloric acids were treated with aqueous sodium nitrite in the cold, nitrogen was immediately evolved and 3-cinnolinol (3-hydroxycinnoline, IIa) was formed. When Ia was treated with nitrous acid in concentrated hydrochloric acid or in 48% hydrobromic acid solution, IIa was again formed but in lower yield accompanied by 3-chloro- (IIIa) or 3-bromocinnoline (IIIc), respectively. As indicated in Table I several other 3-aminocinnolines (Ib–d) showed similar behavior. In the case of 3-amino-4-methylcinnoline (Ib), none of the products analogous to those obtained by Ockenden and Schofield[6] from the reaction of nitrous acid and 3-aminolepidine were formed.



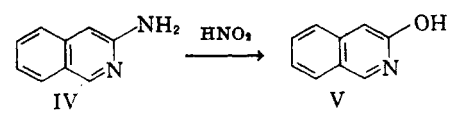
Ia. R = H, Y = H
Ib. R = CH_3, Y = H
Ic. R = H, Y = 6-Cl
Id. R = H, Y = 7-Cl



IIa. R = H, Y = H
IIb. R = CH_3, Y = H
IIc. R = H, Y = 6-Cl
IId. R = H, Y = 7-Cl

IIIa. R = H, X = Cl, Y = H
IIIb. R = CH_3, X = Cl, Y = H
IIIc. R = H, X = Br, Y = H
IIId. R = CH_3, X = Br, Y = H

In the reaction of IV with nitrous acid Boyer and Wolford[5] reported only an 18% yield of 3-isoquinolinol (3-hydroxyisoquinoline, V). This low yield we attribute to their use of three equivalents of sodium nitrite in the reaction, for in the present work, using one equivalent of the nitrite, yields of 53–65% were readily obtained. We observed (as did Boyer and Wolford[5]) that V reacted further with nitrous acid to give a substance of unknown



IV V

(1) Paper VII. *J. Am. Chem. Soc.*, 82, 4634 (1960).

(2) This work was initiated with the support of grant G-1090 of the National Science Foundation and completed with the support of grant CY-3090 of the U. S. Public Health Service.

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