and the product was redissolved in methanol and reduced to dryness. This process was repeated 2 or 3 times until a completely crystalline mass was obtained. The crystals were triturated in 50 ml. of warm petroleum ether (30–60°), filtered, and dried at 60° to give the desired product (see Table I).

Method C.—This method is identical to method A except that the crude reaction mixture was cooled and filtered and the precipitate washed with water and dried. The crude product was finely pulverized and triturated with 100 ml. of petroleum ether, filtered, and dried at 60° to give the desired product.

Method D.—Method D is identical to method C except that no dioxane was employed.

2-Amino-6-[(6-methyl-2-pyridyl)methylthio]purine.—To 10.0 g. of 2-amino-6-purinethiol,[3] dissolved in 150 ml. of concd. ammonium hydroxide, was added with stirring and heating at 40° 11.0 g. of 6-methyl-2-picolyl chloride hydrochloride. The reaction temperature was maintained for one additional hr., then the product was filtered, washed with water, and recrystallized twice from ethanol. The yield was 11.2 g., m.p. 236–237°.

Anal. Calcd. for $C_{12}H_{12}N_6S$: C, 53.1; H, 4.4; N, 30.9. Found: C, 53.6; H, 4.5; N, 30.6.

Pyrimidines. IX. 4- and 5-(Substituted-anilino)pyrimidines[1,2]

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Received March 26, 1962

A number of 4- and 5-(substituted-anilino)pyrimidines have been synthesized as potential riboflavin antagonists. These compounds represent four general types of the uncyclized isoalloxazine ring. A new general synthetic method for the synthesis of 5-anilinopyrimidines has been devised.

Interference of the biosynthesis of important enzymes and cofactors, such as DPN, TPN, FAD (flavin-adenine-dinucleotide) and coenzyme A, has generally been accepted as one of the best methods to block cellular growth.[3] This interference has also been postulated[4]

(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.

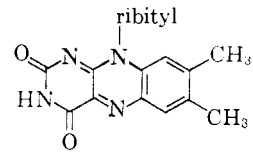
(2) Presented in part before the Div. of Med. Chem., 139th Meeting of the American Chemical Society, St. Louis, Missouri, March, 1961.

(3) F. Bergel, "Chemistry of Enzymes in Cancer," Charles C Thomas, Springfield, Ill., 1961, pp. 47–80.

(4) M. R. Atkinson, J. F. Jackson and R. K. Morton, *Nature*, **192**, 946 (1961), and references listed therein.

as the basis of antitumor activity exhibited by the purine antagonists. Accordingly, the inhibition of tumor growth might be expected from compounds that are riboflavin antagonists since riboflavin is directly concerned with the biosynthesis of the oxidation-reduction enzyme FAD. Compounds exerting anti-riboflavin activity should then act synergistically with the purine and pyrimidine antagonists. A number of compounds related to riboflavin have been shown already to possess certain carcinostatic properties.[5-11]

An examination of the structure of riboflavin (I) indicates that a



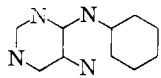
I

pyrimidine might well be its biological precursor. Natural purines such as xanthine, adenine, guanine, and uric acid stimulate the biosynthesis of riboflavin in *Eremothecium ashbyii*.[12] The possibility of a "purine pathway" has been further supported by various tracer studies.[13-18] These studies demonstrated that the biosynthesis of riboflavin from naturally occurring purines must involve a biochemical intermediate or precursor closely related to a 4,5-diaminopyrimidine. The literature also reveals that the naturally occurring pyrimidines do not stimulate the growth of riboflavin.[19] This could be due to the fact that none of the pyrimidines of the natural nucleic acids possess a nitrogenous substituent at the 5-position.

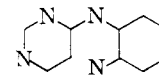
(5) H. P. Morris and W. B. Robertson, *J. Natl. Cancer Inst.*, **3**, 479 (1943).
(6) H. C. Stoerk and G. A. Emerson, *Proc. Soc. Exptl. Biol. Med.*, **70**, 703 (1949).
(7) W. W. Ackermann and V. R. Potter, *ibid.*, **72**, 1 (1949).
(8) (a) F. W. Holly, E. W. Peel, R. Mozingo, J. J. Cahill, F. R. Koniuszy, C. H. Shunk and K. Folkers, *J. Am. Chem. Soc.*, **72**, 5416 (1950); (b) C. H. Shunk and K. Folkers, *ibid.*, **74**, 4047, 4251 (1952).
(9) (a) D. M. Shapiro and R. A. Fugmann, *Proc. Soc. Exptl. Biol. Med.*, **81**, 239 (1952); (b) L. S. Dietrich and D. M. Shapiro, *Cancer Res.*, **13**, 699 (1953); (c) D. M. Shapiro, L. S. Dietrich and M. E. Shils, *ibid.*, **16**, 575 (1956).
(10) G. L. Woodside and D. E. Kelton, *ibid.*, **15**, 390 (1955).
(11) K. Yagi, J. Okuda and Y. Matsuoka, *Nature*, **175**, 555 (1955).
(12) (a) J. A. MacLaren, *J. Bact.*, **63**, 233 (1952); (b) W. S. McNutt, *J. Am. Chem. Soc.*, **83**, 2303 (1961).
(13) G. W. E. Plaut, *Federation Proc.*, **12**, 254 (1953).
(14) W. S. McNutt, *J. Biol. Chem.*, **210**, 511 (1954).
(15) L. Klungsøyr, *Acta. Chem. Scand.*, **8**, 723, 1292 (1954).
(16) A. Albert, *Biochem. J.*, **65**, 124 (1957).
(17) I. Ziegler-Günder, H. Simon and A. Wacker, *Z. Naturforsch.*, **11B**, 82 (1956).
(18) W. S. McNutt, *Federation Proc.*, **19**, 241 (1960).
(19) (a) T. W. Goodwin and S. Pendlington, *Biochem. J.*, **57**, 631 (1954); (b) E. C. Brown, T. W. Goodwin and S. Pendlington, *ibid.*, **57**, 37 (1955).

During our investigation of the synthesis and testing of various pyrimidines as possible antitumor agents, a number of 4- and 5-(substituted-anilino)pyrimidines resembling the uncyclized riboflavin nucleus (isoalloxazine ring) have been prepared. Rose and co-workers[20a] have indicated that the antimalarial activity of certain 2-(substituted-anilino)pyrimidines might be due to an interference with one or more riboflavin-containing enzyme systems. Fall and Petering[20b] have synthesized a series of biologically active isoalloxazine analogs as riboflavin antagonists.

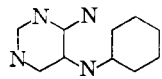
All the pyrimidines synthesized for this study can be divided into four general types



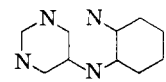
Type 1



Type 2



Type 3



Type 4

Type 1 consists of 4-(substituted-anilino) pyrimidines containing nitrogenous (nitroso or amino) group at the 5-position. The preparation of certain 2-amino-4-(substituted-anilino)-6-pyrimidinols and 2,4-diamino-6-(substituted-anilino) pyrimidines have previously been reported.[21] Several of the 2,4 - diamino - 5 - nitroso - 6-(substituted-anilino)pyrimidines described here were previously prepared (as the synthetic intermediates for 9-aryl-2,6-diaminopurines) but were not characterized.[22] The 2,4,5 - triamino - 6 - (substituted - anilino)-pyrimidines were prepared by the general method of Bendich, *et al.*,[23] for the reduction of the corresponding 5-nitrosopyrimidines.

The nitrosation of 2-amino-6-(substituted-anilino)-4-pyrimidinols has not been described previously. Direct nitrosation of these compounds in acidic media was not successful. It was found that nitrosation finally occurred when 2-amino-6-(substituted-anilino)-4-pyrimidinols were dissolved in 1 *N* sodium hydroxide containing a stoichiometric amount of sodium nitrite, stirred at room temperature, and acidified slowly with dilute hydrochloric acid. The isomeric

(20) (a) See series of papers by F. L. Rose and co-workers, *J. Chem. Soc.*, 343-384 (1946). (b) H. H. Fall and H. G. Petering, *J. Am. Chem. Soc.*, **78**, 377 (1956).

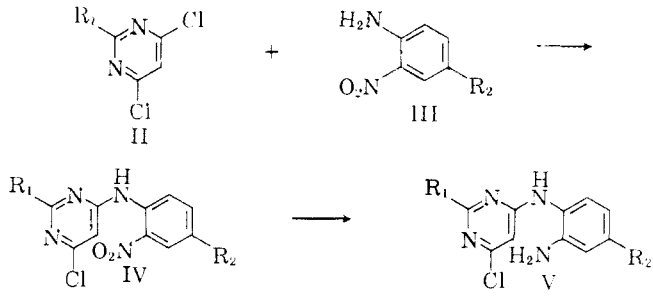
(21) D. E. O'Brien F. Baiocchi, R. K. Robins and C. C. Cheng, *J. Org. Chem.*, **27**, 1104 (1962).

(22) H. C. Koppel, D. E. O'Brien, and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 3046 (1959).

(23) A. Bendich, J. F. Tinker and G. B. Brown, *ibid.*, **70**, 3109 (1948).

4-amino-6-(substituted-anilino)-5-nitroso-2-pyrimidinols were prepared by the reaction of 4-amino-6-chloro-2-pyrimidinol[24] and the appropriate aniline followed by nitrosation of the resulting 6-anilinopyrimidine. Similarly, 4-(substituted-anilino)-5-nitroso-2,6-pyrimidinediol was prepared from 4-chloro-2,6-pyrimidinediol.[25]

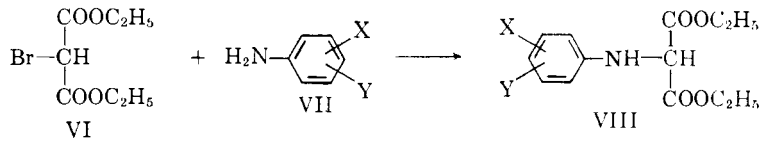
In Type 2, the nitro or amino group is attached to the *ortho* position of the phenyl ring. This type of compound was prepared by the reaction of a 4-chloropyrimidine and an *o*-nitroaniline, followed by reduction of the nitro group. Attempts to hydrolyze the 4-chloro group in compound V were unsuccessful.



Type 3 requires the synthesis of 4-amino-5-(substituted-anilino)-pyrimidines. The only recorded synthesis for 5-(substituted-anilino)-pyrimidines[26] was found to be restricted in application. Existing methods for the preparation of 5-(substituted-amino)pyrimidines[27–29] could not be successfully utilized for the preparation of 5-(substituted-anilino)pyrimidines; a general approach for the synthesis of this type of compound was therefore undertaken.

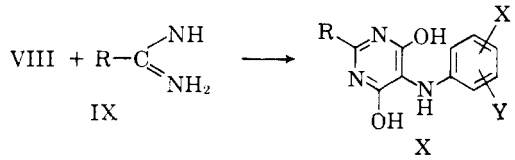
One possibility for synthesizing 5-anilinopyrimidines is to attach the anilino moiety to a three-carbon fragment (such as a malonic ester) prior to the formation of the pyrimidine ring. Thus, diethyl bromomalonate (VI) was treated with anilines (VII),[30] to obtain various diethyl 2-(substituted-anilino)malonates (VIII); anilines and bromomalononitrile[31] or ethyl bromocyanoacetate,[32] however,

(24) H. L. Wheeler and G. S. Jamieson, *Am. Chem. J.*, **32**, 342 (1904).
(25) H. C. Koppel, R. H. Springer, R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, **26**, 792 (1961).
(26) D. M. Besly and A. A. Goldberg, *J. Chem. Soc.*, 4997 (1957).
(27) A. P. Phillips, *J. Am. Chem. Soc.*, **73**, 1061 (1951).
(28) E. Fischer, *Ber.*, **30**, 559 (1897).
(29) H. Rudy and K. E. Kramer, *ibid.*, **72**, 227 (1939).
(30) (a) R. S. Curtiss, *Am. Chem. J.*, **19**, 603 (1897); (b) M. Conrad and H. Reinbach, *Ber.*, **35**, 511 (1902).
(31) J. F. Thorpe and W. J. Young, *J. Chem. Soc.*, **77**, 938 (1900).
(32) N. E. Goldthwaite, *Am. Chem. J.*, **30**, 466 (1903).



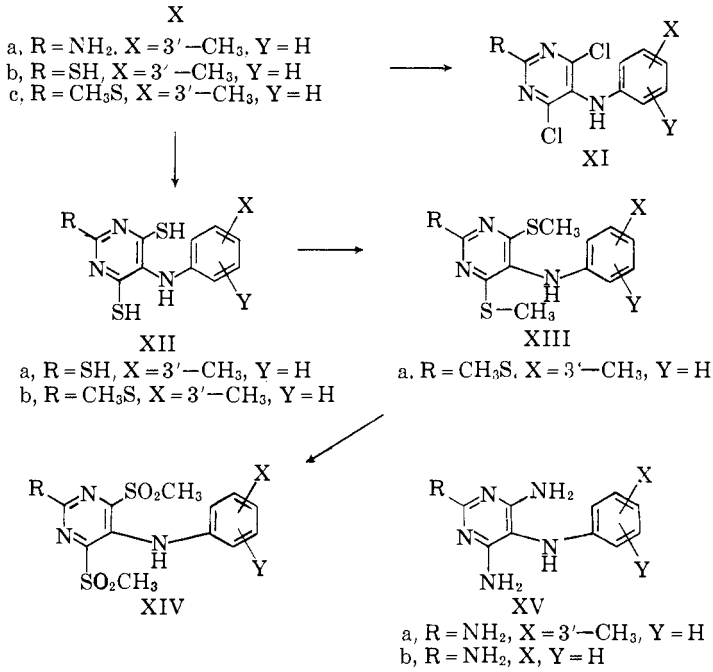
VI VII VIII

failed to react in a similar fashion. Compound VIII was treated with urea, thiourea and guanidine (IX, R = OH, SH, and NH_2, respectively) to yield the corresponding 4,6-dihydroxy-5-(substituted-anilino)pyrimidines (X). A logical approach to convert X to 4-(and/or 6-) amino-5-(substituted-anilino)pyrimidines (XV, Area 3)



IX X

is *via* the corresponding chloropyrimidine (XI), thiopyrimidine (XII), methylthiopyrimidine (XIII), or methylsulfonylpyrimidine (XIV). Attempts to thiate 2-amino-5-(*m*-toluidino)-4,6-pyrimidinediol (Xa) with phosphorus pentasulfide in tetralin, pyridine, α-picoline or 5-



X
a, R = NH_2, X = 3′—CH_3, Y = H
b, R = SH, X = 3′—CH_3, Y = H
c, R = CH_3S, X = 3′—CH_3, Y = H

XI

XII
a, R = SH, X = 3′—CH_3, Y = H
b, R = CH_3S, X = 3′—CH_3, Y = H

XIII
a, R = CH_3S, X = 3′—CH_3, Y = H

XIV

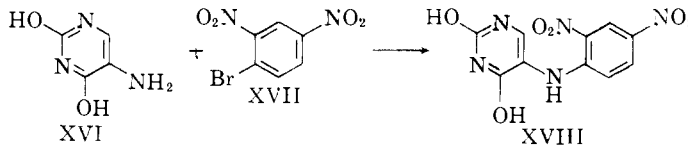
XV
a, R = NH_2, X = 3′—CH_3, Y = H
b, R = NH_2, X, Y = H

ethyl-2-methylpyridine resulted in failure. 5-(*m*-Toluidino)-2-thiobarbituric acid (Xb), when treated with phosphorus pentasulfide in pyridine, gave a poor yield of 5-(*m*-toluidino)-2,4,6-pyrimidinetrithiol (XIIa). Methylation of Xb formed 2-(methylthio)-5-(*m*-toluidino)-4,6-pyrimidinediol (Xc), which was then treated with phosphorus pentasulfide in pyridine to give 2-(methylthio)-5-(*m*-toluidino)-4,6-pyrimidinedithiol (XIIb). Methylation of XIIa and XIIb under alkaline conditions gave 5-(*m*-toluidino)-2,4,6-tris-(methylthio)pyrimidine (XIIIa). Ethanolic ammonia, however, failed to convert XIIIa to the desired amino derivative XV even at high temperature in an autoclave.

The methylsulfonyl groups at the 2, 4, and 6 positions of a pyrimidine ring should be more readily replaced by a nucleophile than the corresponding methylthio groups.[25] The usual method of preparation of a methylsulfonyl derivative[33] from XIIIa gave a product which indicated that three chlorine atoms had entered the phenyl ring (see Experimental).

Much difficulty was encountered in the chlorination of 2-amino-5-(substituted-anilino)-4,6-pyrimidinediols (Xa, R = NH_2) or their formylated derivatives with phosphorus oxychloride. Hence 2-methylthio-5-(substituted-anilino)-4,6-pyrimidinediols (X, R = CH_3S) were chosen for the chlorination studies. As a result, a phosphorus complex of the desired chlorinated products was isolated. Treatment of the complex with base followed by extraction yielded 2-methylthio-4,6-dichloro-5-(substituted-anilino)pyrimidines (XI). Finally, ethanolic ammonia at 185° in an autoclave converted XI to the desired 2,4,6-triamino-5-(substituted-anilino)pyrimidines (XV).

Compounds of type 4 consist of a 5-anilinopyrimidine with a nitrogenous group substituted *ortho* to the anilino nitrogen. For this study 5-(2′-4′-dinitroanilino)-2,6-pyrimidinediol (XVIII) was prepared by treating 5-aminouracil (XVI) with 2,4-dinitrobromobenzene (XVII) in aqueous ethanol, according to the method employed by Besly and Goldberg.[26]



(33) J. M. Sprague and T. B. Johnson, *J. Am. Chem. Soc.*, **57**, 2252 (1935).

Preliminary biological evaluation[34] of these compounds indicated that 2,4-diamino-6-(*p*-bromoanilino)-5-nitrosopyrimidine,[35] 2,4-diamino-6-(3′,4′-dichloroanilino)-5-nitrosopyrimidine and 2,4-diamino-6-(*p*-iodoanilino)-5-nitrosopyrimidine possess confirmed carcinostatic activity against adenocarcinoma 755 in mice. Further antitumor investigation is currently in progress.

Experimental[36]

2,4-Diamino-5-nitroso-6-(substituted-anilino)pyrimidines (Table II). **General Procedure.**—A solution of 2,4-diamino-6-(substituted-anilino)pyrimidine (0.2 mole) in 200 ml. of water and 400 ml. of glacial acetic acid was stirred and cooled to 5°. Sodium nitrite (13.8 g., 0.2 mole) dissolved in 75 ml. of water was added dropwise to the cooled solution, maintaining the internal temperature below 10°. After the addition was complete, the bright red mixture was stirred for 3 hr. The highly colored precipitate was separated by filtration, washed with 3 × 100 ml. of water, 2 × 75 ml. of ethanol and 3 × 150 ml. of ether. The product was dried at 80° and purified by recrystallization from a mixture of dimethylformamide and water.

2,4-Diamino-6-(N-methyl-*p*-toluidino)-5-nitrosopyrimidine was similarly prepared in 68% yield, m.p. 268–269° dec., $\lambda_{max}^{pH\ 1}$ 269 mμ (ε 13,600), $\lambda_{max}^{pH\ 11}$ 241 mμ (ε 12,900), 271 mμ (ε 12,900), 319 mμ (ε 8,800).

Anal. Calcd. for $C_{12}H_{14}N_6O$: C, 55.8; H, 5.5; N, 32.5. Found: C, 55.5; H, 5.3; N, 32.1.

Sulfate Salts of 2,4,5-Triamino-6-(substituted-anilino)pyrimidines (Table II). **General Procedure.** — 2,4-Diamino-5-nitroso-6-(substituted-anilino)pyrimidine (0.1 mole) was suspended in 800 ml. of boiling water with gentle agitation. Sodium hydrosulfite (50 g., 0.24 mole) was added in small portions to the boiling suspension. After the addition was complete the mixture was boiled for 10 min. followed by careful addition of 100 ml. of 18 *N* sulfuric acid. The bleached solution was treated with charcoal and filtered. On cooling, the filtrate deposited pale yellow crystals of the sulfate salts of 2,4,5-triamino-6-(substituted-anilino)-pyrimidine which are purified by recrystallization from 2 *N* sulfuric acid. These products contain water of hydration, and darken when heated above 130°.

2-Amino-5-nitroso-6-(substituted-anilino)-4-pyrimidinols (Table II). **General Procedure.**—A solution of 2-amino-6-(substituted-anilino)-4-pyrimidinol (0.1 mole) in 1 l. of 1 *N* sodium hydroxide was stirred at room temperature. Sodium nitrite (6.9 g., 0.1 mole) dissolved in 50 ml. of water was added all at once to this alkaline solution. The resulting clear solution was slowly acidified to *p*H 4 by the dropwise addition of 6 *N* hydrochloric acid. After the addition was complete, the orange mixture was stirred at room temperature for 3 hr. The highly colored

(34) The biological testing was performed by Battelle Memorial Institute, Microbiological Associates, Inc., and Wisconsin Alumni Research Foundation under the contracts with the Cancer Chemotherapy National Service Center.

(35) When this compound was reduced (by sodium hydrosulfite) and cyclized (by formamide), the resulting compound, 9-(*p*-bromophenyl)-2,6-diaminopurine, possesses no carcinostatic activity in mice. This is in agreement with our postulate that the uncyclized pyrimidines in our series act anti-riboflavinically rather than antifolinically.

(36) All melting points were taken on a Thomas-Hoover melting point apparatus. The ultraviolet absorption spectra were determined on the Beckman DK-2.

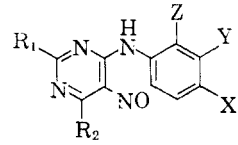
precipitate was filtered, washed with water, ethanol and ether. The product was dried at 80° and purified by recrystallization from a mixture of dimethylformamide and water.

4-Amino-6-(substituted-anilino)-2-pyrimidinols (Table II). **General Procedure.**—A mixture of 4-amino-6-chloro-2-pyrimidinol (14.7 g., 0.1 mole) and substituted aniline (0.11 mole) in 125 ml. of ethylene glycol was heated at 195° for 0.5 hr. The resulting clear solution was carefully added to 1 l. of dilute sodium hydroxide. This mixture was heated to boiling, treated with charcoal, and filtered. The colorless filtrate was acidified with glacial acetic acid to yield a white precipitate. The precipitate was filtered, washed with water, and dried at 80°. Further purification was afforded by recrystallization from aqueous ethanol.

4-Amino-5-nitroso-6-(substituted-anilino)-2-pyrimidinols (Table I). **General Procedure.**—A solution of 4-amino-6-(substituted-anilino)-2-pyrimidinol (0.1 mole) in 75 ml. of water and 225 ml. of glacial acetic acid was stirred and cooled to 5°. Sodium nitrite (6.9 g.), dissolved in 50 ml. of water, was added dropwise to the cooled solution, maintaining the internal temperature below 10°. After the addition was complete, the orange reaction mixture was stirred for 3 hr. at

TABLE I

ANTITUMOR ACTIVITY OF SOME 4-(SUBSTITUTED-ANILINO)-5-NITROSOPYRIMIDINES



					Preliminary Screening Results[a]		
R_1	R_2	X	Y	Z	Sa-180	Le-1210	Ca-755
NH_2	NH_2	H	H	H	−	−	−
NH_2	NH_2	OH	H	H	−	−	−
NH_2	NH_2	OCH_3	H	H	−	−	−
NH_2	NH_2	CH_3	H	H	−	−	−
NH_2	NH_2	F	H	H	±	−	−
NH_2	NH_2	Cl	H	H	±	−	±
NH_2	NH_2	Br	H	H	−	−	+
NH_2	NH_2	I	H	H	±	−	+
NH_2	NH_2	H	Cl	H	−	−	−
NH_2	NH_2	$COOC_2H_5$	H	H	±	−	−
NH_2	NH_2	Br	H	CH_3	−	−	−
NH_2	NH_2	Cl	Cl	H	±	−	+
NH_2	NH_2	Br	Br	H	−	−	±
NH_2	NH_2	CH_3	CH_3	H	−	−	−
NH_2	OH	Br	H	H	−	−	−
OH	NH_2	Cl	Cl	H	−	−	−

[a] −, low or no activity; ±, activity not confirmed, +, activity confirmed. Test done by the Contract Screeners of CCNSC, see ref. 34.

10°. The colored precipitate was filtered, washed with water, ethanol, and ether. The product was dried at 80° and purified by recrystallization from dimethylformamide and water.

6-(p-Toluidino)-2,4-pyrimidinediol (Table I).—A mixture of 4-chloro-2,6-pyrimidinediol (50 g., 0.34 mole) and *p*-toluidine (37.6 g., 0.35 mole) was added to 200 ml. of ethylene glycol. This suspension was then heated in an oil bath. A clear yellow solution was obtained at 145°. When the temperature reached 175° a mild exothermic reaction and partial solidification occurred. The hot reaction mixture was dissolved in 1 l. of dilute sodium hydroxide and heated to boiling. The hot solution was treated with charcoal and filtered. The filtrate was acidified with glacial acetic acid to yield a white precipitate. This precipitate was filtered and dried at 80°. The analytically pure 6-(*p*-toluidino)-2,4-pyrimidinediol was obtained by recrystallization from aqueous ethanol.

5-Nitroso-6-(*p*-toluidino)-2,4-pyrimidinediol (Table I).—6-(*p*-Toluidino)-2,4-pyrimidinediol (30 g., 0.14 mole) and 2 l. of 1.5 *N* sodium hydroxide were added to a 3 l., three-necked, round bottom flask. This flask was equipped with a condenser and a mechanical stirrer. The mixture was heated on a steam bath until a complete solution resulted. Sodium nitrite (9.5 g., 0.14 mole) dissolved in 50 ml. of water was added all at once to the hot solution. The resulting solution was slowly acidified, by the dropwise addition of dilute hydrochloric acid, to *p*H 4. After the acidification was complete, the mixture was heated and stirred for 4 hr. The yellow product was filtered, washed with water, and dried at 80°. Analytically pure product was afforded by recrystallization from dimethylformamide and water.

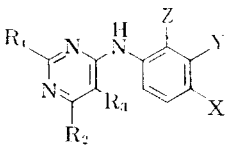
2-Amino-4-chloro-6-(2′-nitro-4-toluidino)pyrimidine (**IV,** $R_1 = NH_2$, $R_2 = CH_3$).—A mixture of 2-amino-4,6-dichloropyrimidine (35 g., 0.21 mole), 4-methyl-2-nitroaniline (33.4 g., 0.22 mole) and acetic acid (12.7 g., 0.21 mole) was heated to 175°. The reaction mixture solidified gradually at this temperature to a yellow mass. After 30 min. the solidified mixture was dissolved in 1 l. of boiling water, treated with charcoal and filtered. The filtrate was adjusted to *p*H 8 by the addition of dilute sodium hydroxide. The resulting orange precipitate was filtered and dried at 80°. The yield of the product was 40 g. (68%), m.p. 216–220° dec. For analysis, the compound was recrystallized from aqueous ethanol to yield orange crystals that melted at 218–220° dec., $\lambda_{max}^{ethanol}$ 247 mμ (ε 23,600); $\lambda_{max}^{ethanol}$ 286 mμ (ε 16,100).

Anal. Calcd. for $C_{11}H_{10}ClN_5O_2$: C, 47.3; H, 3.6; N, 25.1. Found: C, 47.6; H, 3.7; N, 24.8.

2-Amino-4-chloro-6-(2′-amino-4-toluidino)pyrimidine hydrochloride (**V,** $R_1 = NH_2$, $R_2 = CH_3$).—A mixture of 2-amino-4-chloro-6-(2′-nitro-4-toluidino)-pyrimidine (5 g., 0.03 mole), absolute ethanol (600 ml.), and Raney nickel (50 g.) was refluxed with vigorous stirring for 6 hr. The reaction mixture then was filtered and the filtrate evaporated to 100 ml. On cooling a solid product was obtained. This product became highly colored on exposure to air. The solid product was dissolved in ethanolic hydrogen chloride and precipitated by the addition of anhydrous ether. The hydrochloride salt was separated by filtration, triturated with ether, and dried at 80°. The yield of product was 3 g. (37%), m.p. 268–270° dec., $\lambda_{max}^{pH\ 1}$ 285 mμ (ε 14,300); $\lambda_{max}^{pH\ 11}$ 293 mμ (ε 12,600); $\lambda_{max}^{ethanol}$ 295 mμ (ε 11,900).

Anal. Calcd. for $C_{11}H_{12}ClN_5 \cdot HCl$: C, 46.1; H, 4.6; N, 24.5. Found: C, 46.0; H, 5.1; N, 24.6.

TABLE II



									Analyses						Ultraviolet absorption (mμ)			
									Calcd.			Found			pH 1		pH 11	
R_1	R_2	R_3	X	Y	Z	Empirical Formula	Yield (%)	M.p.° dec.	C	H	N	C	H	N	λ_{max}	$\epsilon \times 10^{-3}$	λ_{max}	$\epsilon \times 10^{-3}$
NH_2	NH_2	NO	Br	H	H	$C_{10}H_9BrN_6O$	97	229	38.8	2.9	27.2	38.5	2.9	27.1	250	21.0	251	20.1
															326	13.3	330	19.1
NH_2	NH_2	NO	OCH_3	H	H	$C_{11}H_{12}N_6O_2$	98	245–246	50.7	4.7	32.2	50.6	5.0	31.9	257	18.1	242	13.0
																	320	17.5
NH_2	NH_2	NO	OH	H	H	$C_{10}H_{10}N_6O_2$	92	>360	48.7	4.1	34.3	48.5	4.3	34.1	253	17.0	245	14.8
															322	7.9	322	14.0
NH_2	NH_2	NO	H	CH_3	CH_3	$C_{12}H_{14}N_6O$	90	283–285	55.8	5.5	32.5	55.5	5.6	32.8	263	20.2	240	11.6
															326	9.5	324	19.3
NH_2	NH_2	NO	CH_3	H	CH_3	$C_{12}H_{14}N_6O$	86	273–274	55.8	5.5	32.5	56.0	5.3	32.5	264	13.5	241	9.5
															322	7.5	322	18.1
NH_2	NH_2	NO	CH_3	CH_3	H	$C_{12}H_{14}N_6O$	57	298–299	55.8	5.5	32.5	56.1	5.7	32.6	250	16.7	243	16.7
																	322	17.7
NH_2	NH_2	NO	H	Cl	H	$C_{10}H_9ClN_6O$	72	265–266	45.4	3.4	31.6	45.2	3.4	31.8	290	15.6	243	14.0
																	326	19.8
NH_2	NH_2	NO	H	H	Cl	$C_{10}H_9ClN_6O$	71	271–272	45.4	3.4	31.6	45.4	3.5	31.4	260	8.7	240	8.5
															325	6.1	325	12.5
NH_2	NH_2	NO	Cl	H	H	$C_{10}H_9ClN_6O$	93	263–264	45.4	3.4	31.6	45.1	3.4	31.6	251	13.2	242	12.5
																	323	14.4

NH_2	NH_2	NO	F	H	H	$C_{10}H_9FN_6O$	82	270-271	48.3	3.7	33.8	48.8	4.0	33.7	260	13.6
															324	6.2
NH_2	NH_2	NO	Cl	Cl	H	$C_{10}H_8Cl_2N_6O$	87	289–291	40.0	2.7	28.0	39.8	2.9	27.8	250	12.3
															330	12.3
NH_2	NH_2	NO	CH_3	H	H	$C_{11}H_{12}N_6O$	89	249–250	53.9	5.0	34.3	53.8	5.0	34.6	255	14.4
NH_2	NH_2	NO	H	H	CH_3	$C_{11}H_{12}N_6O$	68	254–256	53.9	5.0	34.3	53.3	5.2	34.8	264	18.8
															323	10.1
NH_2	NH_2	NO	H	CH_3	H	$C_{11}H_{12}N_6O$	75	262–263	53.9	5.0	34.3	53.6	4.9	34.2	260	14.6
															326	12.2
NH_2	NH_2	NO	I	H	H	$C_{10}H_9IN_6O$	92	285–286	33.7	2.5	23.6	33.7	2.6	23.2	234	10.3
															252	10.7
NH_2	NH_2	NO	C_2H_4OH	H	H	$C_{14}H_{14}N_6O_2$	71	281–282	52.4	5.1	30.5	52.7	4.8	30.4	246	18.1
															325	9.9
NH_2	NH_2	NO	CH_3	Cl	H	$C_{11}H_{11}ClN_6O$	69	287–288	47.3	4.0	30.1	47.0	4.0	30.3	260	5.6
NH_2	NH_2	NO	SO_2NH_2	H	H	$C_{10}H_{11}N_7O_3S$	74	308–309	38.8	3.6	31.7	38.9	3.8	31.4	257	17.6
															328	15.5
NH_2	NH_2	NO	H	H	H	$C_{10}H_{10}N_6O$	92	254–255	52.1	4.4	36.6	52.1	4.3	36.9	263	14.0
															327	5.8
NH_2	NH_2	NO	Br	Br	H	$C_{10}H_8Br_2N_6O$	83	302–303	30.6	2.1	21.6	30.6	1.9	21.3	255	5.3
															327	5.1
NH_2	NH_2	NO	Br	H	CH_3	$C_{11}H_{11}BrN_6O$	81	276–277	40.8	3.4	26.0	41.1	3.6	25.9	265	12.2
															322	6.5
NH_2	NH_2	NH_2	CH_3	H	H	$C_{11}H_{14}N_6$	40	207–208	38.1	5.2	24.2[a]	38.3	4.9	23.9	290	17.8
NH_2	NH_2	NH_2	H	CH_3	H	$C_{11}H_{14}N_6$	43	209–210	38.8	5.1	24.9[b]	38.4	5.1	24.9	290	12.8
NH_2	NH_2	NH_2	CH_3	CH_3	H	$C_{12}H_{16}N_6$	37	192–194 (no dec.)	38.1	5.9	22.2[c]	38.3	6.0	22.6	290	21.1

NH_2	NH_2	NO	F	H	H	$C_{10}H_9FN_6O$	82	270-271	48.3	3.7	33.8	48.8	4.0	33.7	237	11.2
															322	18.1
NH_2	NH_2	NO	Cl	Cl	H	$C_{10}H_8Cl_2N_6O$	87	289–291	40.0	2.7	28.0	39.8	2.9	27.8	245	16.2
															326	16.3
NH_2	NH_2	NO	CH_3	H	H	$C_{11}H_{12}N_6O$	89	249–250	53.9	5.0	34.3	53.8	5.0	34.6	239	12.5
															318	17.1
NH_2	NH_2	NO	H	H	CH_3	$C_{11}H_{12}N_6O$	68	254–256	53.9	5.0	34.3	53.3	5.2	34.8	244	15.8
															322	15.8
NH_2	NH_2	NO	H	CH_3	H	$C_{11}H_{12}N_6O$	75	262–263	53.9	5.0	34.3	53.6	4.9	34.2	239	12.4
															322	19.0
NH_2	NH_2	NO	I	H	H	$C_{10}H_9IN_6O$	92	285–286	33.7	2.5	23.6	33.7	2.6	23.2	246	19.6
															323	17.1
NH_2	NH_2	NO	C_2H_4OH	H	H	$C_{14}H_{14}N_6O_2$	71	281–282	52.4	5.1	30.5	52.7	4.8	30.4	243	15.8
															324	19.6
NH_2	NH_2	NO	CH_3	Cl	H	$C_{11}H_{11}ClN_6O$	69	287–288	47.3	4.0	30.1	47.0	4.0	30.3	242	10.1
															325	12.7
NH_2	NH_2	NO	SO_2NH_2	H	H	$C_{10}H_{11}N_7O_3S$	74	308–309	38.8	3.6	31.7	38.9	3.8	31.4	255	19.0
															330	19.8
NH_2	NH_2	NO	H	H	H	$C_{10}H_{10}N_6O$	92	254–255	52.1	4.4	36.6	52.1	4.3	36.9	239	12.8
															322	17.5
NH_2	NH_2	NO	Br	Br	H	$C_{10}H_8Br_2N_6O$	83	302–303	30.6	2.1	21.6	30.6	1.9	21.3	245	6.5
															324	7.4
NH_2	NH_2	NO	Br	H	CH_3	$C_{11}H_{11}BrN_6O$	81	276–277	40.8	3.4	26.0	41.1	3.6	25.9	242	11.4
															322	16.5
NH_2	NH_2	NH_2	CH_3	H	H	$C_{11}H_{14}N_6$	40	207–208	38.1	5.2	24.2[a]	38.3	4.9	23.9	243	11.6
															297	16.6
NH_2	NH_2	NH_2	H	CH_3	H	$C_{11}H_{14}N_6$	43	209–210	38.8	5.1	24.9[b]	38.4	5.1	24.9	236	11.4
															300	12.8
NH_2	NH_2	NH_2	CH_3	CH_3	H	$C_{12}H_{16}N_6$	37	192–194 (no dec.)	38.1	5.9	22.2[c]	38.3	6.0	22.6	245	12.1
															298	20.4

Table II

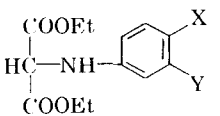
NH_2	NH_2	NH_2	CH_3	H	CH_3	$C_{12}H_{16}N_6$	38	165-166	40.1	5.5	23.0[a]	40.0	5.3	22.5	281	13.7	243	11.9
																	283	10.4
NH_2	NH_2	NH_2	CH_3	Cl	H	$C_{11}H_{13}ClN_6$	41	298-300	34.7	4.5	22.0[a]	34.8	4.5	22.4	293	17.9	246	11.1
																	298	17.1
NH_2	NH_2	NH_2	Br	H	H	$C_{10}H_{11}BrN_6$	37	>300	29.4	3.7	20.4[a]	29.7	3.7	20.3	296	23.8	302	24.2
NH_2	NH_2	NH_2	OCH_3	H	H	$C_{11}H_{14}N_6O$	35	218–219	36.3	4.9	23.1[a]	36.1	4.6	23.1	286	17.2	245	10.5
																	296	15.6
NH_2	NH_2	NH_2	OH	H	H	$C_{10}H_{12}N_6O$	42	210–212	34.4	4.6	24.1[a]	34.1	4.8	24.2	285	20.0	249	11.5
																	295	17.4
NH_2	NH_2	NH_2	C_2H_4OH	H	H	$C_{12}H_{16}N_6O$	33	212–213	38.3	5.3	22.3[a]	38.1	5.1	22.3	292	22.2	246	13.3
																	301	22.2
NH_2	NH_2	NH_2	H	H	H	$C_{10}H_{12}N_6$	35	232–234	38.2	4.5	26.7[d]	38.2	4.6	26.6	289	18.6	245	10.7
																	300	17.6
NH_2	OH	NO	CH_3	H	H	$C_{11}H_{11}N_5O_2$	73	297–298	53.8	4.5	28.6	53.6	4.6	28.2	254	14.1	242	12.0
															325	8.3	320	17.9
NH_2	OH	NO	H	H	CH_3	$C_{11}H_{11}N_5O_2$	75	286–287	53.8	4.5	28.6	53.3	4.5	28.9	266	13.1	247	10.8
															321	8.1	322	21.0
NH_2	OH	NO	CH_3	CH_3	H	$C_{12}H_{13}N_5O_2$	89	295–296	55.6	5.1	27.0	55.7	5.2	27.0	256	13.0	241	10.1
																	318	14.3
NH_2	OH	NO	Cl	Cl	H	$C_{10}H_7Cl_2N_5O_2$	79	302–303	40.0	2.3	23.4	39.8	2.6	23.6	250	16.4	245	14.4
															322	10.5	321	18.5
NH_2	OH	NO	CH_3	Cl	H	$C_{11}H_{10}ClN_5O_2$	90	315–317	47.2	3.6	25.0	47.0	3.7	24.7	326	8.7	244	13.8
																	328	16.4
NH_2	OH	NO	Br	H	H	$C_{10}H_8BrN_5O_2$	68	330–331	38.7	2.6	22.6	38.6	2.5	23.0	250	8.5	244	10.5
																	325	11.4
OH	NH_2	H	CH_3	H	H	$C_{11}H_{12}N_4O$	67	348-349	61.1	5.5	25.9	61.2	5.7	25.8	285	24.0	284	19.8
OH	NH_2	H	CH_3	CH_3	H	$C_{12}H_{14}N_4O$	74	328-329	62.6	6.1	24.3	63.0	6.3	24.1	285	26.0	284	19.8
OH	NH_2	H	OCH_3	H	H	$C_{11}H_{12}N_4O_2$	76	357-359	56.8	5.2	24.1	56.3	5.3	23.9	282	23.4	284	18.1
OH	NH_2	H	Cl	Cl	H	$C_{10}H_8Cl_2N_4O$	70	>360	44.3	3.0	20.7	44.0	3.1	20.8	285	26.8	285	27.0

OH	NH_2	NO	CH_3	H	H	$C_{11}H_{11}N_5O_2$	68	270–271	53.8	4.5	28.6	53.5	4.5	28.8	241	22.8
															325	10.5
OH	NH_2	NO	CH_3	CH_3	H	$C_{12}H_{13}N_5O_2$	97	295–296	55.6	5.1	27.0	55.6	5.2	26.6	241	15.5
															320	5.2
OH	NH_2	NO	OCH_3	H	H	$C_{11}H_{11}N_5O_3$	82	286–287	50.6	4.3	26.8	50.7	4.3	26.6	241	26.3
															320	10.8
OH	NH_2	NO	Cl	Cl	H	$C_{10}H_7Cl_2N_5O_2$	93	302–304	40.0	2.4	23.3	40.2	2.4	23.3	252	14.2
OH	OH	H	CH_3	H	H	$C_{11}H_{11}N_3O_2$	59	326-327	60.8	5.1	19.3	60.8	5.5	19.0	277	26.4
OH	OH	NO	CH_3	H	H	$C_{11}H_{10}N_4O_3$	50	>360	53.7	4.1	22.7	54.0	4.0	22.6	266	7.1

244	14.7															
315	17.2															
241	10.6															
313	16.6															
248	15.1															
314	17.5															
244	11.0															
310	12.3															
284	21.7															
266	23.1															

[a] As sulfate monohydrate. [b] As sulfate hemihydrate. [c] As sulfate dihydrate. [d] As sulfate.

TABLE III



					Analyses						Ultraviolet absorption (mμ)			
					Calcd.			Found			pH 1		pH 11	
X	Y	Empirical formula	Yield, %	M.p., °C.	C	H	N	C	H	N	λ_{max}	$\epsilon \times 10^{-3}$	λ_{max}	$\epsilon \times 10^{-3}$
H	H	$C_{13}H_{17}NO_4$	96	48–49	62.1	6.8	5.6	61.9	6.8	5.3	240	11.8	245	11.9
Cl	H	$C_{14}H_{16}ClNO_4$	95	85–87	54.5	5.6	4.9	54.6	5.6	4.8	244	12.3	247	12.9
H	Cl	$C_{13}H_{16}ClNO_4$	97	70–71	54.5	5.6	4.9	54.6	5.5	4.7	240	11.5	244	11.7
Cl	Cl	$C_{13}H_{15}Cl_2NO_4$	93	84–86	48.7	4.7	4.4	48.7	4.6	4.0	247	12.8	249	14.1
H	CH_3	$C_{14}H_{19}NO_4$	93	46–47	63.4	7.2	5.3	63.0	7.2	5.3	236	10.1	241	10.1
CH_3	H	$C_{14}H_{19}NO_4$	99	45–46	63.4	7.2	5.3	63.3	6.8	5.3	236	9.3	239	10.2
CH_3	CH_3	$C_{15}H_{21}NO_4$	99	56–57	64.5	7.6	5.0	64.3	7.5	4.7	236	7.0	239	9.8
CH_3	Cl	$C_{14}H_{18}ClNO_4$	99	67-69	56.1	6.1	4.7	56.2	6.3	4.6	240	10.8	242	11.4
Br	H	$C_{13}H_{16}BrNO_4$	99	90–91	47.3	4.9	4.2	47.6	4.9	4.1	245	14.9	248	16.8

Ethyl 2-(Substituted-anilino)malonates (VIII, Table III). **General Procedure.**—A mixture of ethyl bromomalonate (47.8 g., 0.2 mole) and a substituted aniline (0.6 mole) was stirred at room temperature. After 30 min. an exothermic reaction occurred and the reaction temperature rose to 85°. The mixture was then heated at 95° for 3 hr., and then allowed to stand overnight at room temperature. The solidified reaction mixture was triturated with 6 × 150 ml. of ether and the crystalline aniline hydrobromide was discarded. The ethereal extract was washed with 3 × 150 ml. of water, 3 × 150 ml. of 1.5 *N* hydrochloric acid, and again with 3 × 150 ml. of water. The extract was treated with charcoal and dried over anhydrous sodium sulfate. Evaporation of the filtered ethereal solution yielded the ethyl 2-(substituted-anilino)malonate. Purification was afforded by recrystallization from hexane.

2-Amino-5-(substituted-anilino)-4,6-pyrimidinediols (X, Table IV). **General Procedure.**—To a solution of guanidine hydrochloride (9.6 g., 0.1 mole) in 250 ml. of absolute ethanol was added a solution of sodium (7.7 g., 0.3 g.-atom) in 500 ml. of absolute ethanol. The resulting mixture was stirred at room temperature for 10 min. and the precipitated sodium chloride separated by filtration. The filtrate was heated to gentle reflux, and with good agitation a solution of ethyl 2-(substituted-anilino)malonate (0.1 mole) in 250 ml. of absolute ethanol was added. The resulting solution was refluxed and stirred for 6 hr. At the end of this time the tan precipitate was filtered and redissolved in 500 ml. of water, treated with charcoal, and filtered. The filtrate was acidified to *p*H 5 by the addition of glacial acetic acid. The precipitated product was collected by filtration, washed with water, and dried at 80°. Purification was afforded by recrystallization from aqueous ethanol.

N-(2-Amino-4,6-dihydroxy-5-pyrimidinyl)-N-formyl-(*m*-toluidine): A solution of 2-amino-5-(*m*-toluidino)-4,6-pyrimidinediol (11.5 g., 0.05 mole) in 125 ml. of 90% formic acid was refluxed for 30 min. The solution was then evaporated to dryness. The solid residue was dissolved in boiling water, treated with charcoal and filtered. On cooling the analytically pure formyl derivative crystallized from the filtrate. This product was collected by filtration and dried at 80°. The yield was 7 g. (54%), m.p. 289–290° dec., $\lambda_{max}^{pH\ I}$ 255 mμ (ε 20,300); $\lambda_{max}^{pH\ II}$ 257 mμ (ε 12,800).

Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.4; H, 4.6; N, 21.5. Found: C, 55.8; H, 4.6; N, 21.4.

5-(Substituted-anilino)barbituric Acids (X, R = OH; Table IV).—To 6.6 g. (0.1 mole) of urea dissolved in 250 ml. of absolute ethanol was added a solution of sodium ethoxide, prepared by dissolving 7.7 g. (0.3 g.-atom) of sodium in 500 ml. of absolute ethanol. The combined solution was heated to reflux and, with stirring, was added a solution of 0.1 mole of ethyl 2-(substituted-anilino)malonate in 250 ml. of absolute ethanol. The resulting solution was refluxed with stirring for 15 hr. The off-white precipitate was collected by filtration. It was redissolved in 500 ml. of boiling water, treated with charcoal and filtered. The filtrate was acidified to *p*H 2 with dil. hydrochloric acid and the precipitated white product was filtered, washed with water and dried at 80°. Recrystallization from a mixture of dimethylformamide and water yielded analytically pure product.

In a similar manner, 2-thio-5-(substituted-anilino)barbituric acids and 5-(substituted-anilino)-4,6-pyrimidinediols were prepared from the corresponding malonic ester with thiourea and formamidine, respectively. These compounds were purified from aqueous ethanol.

2-(Methylthio)-5-(substituted-anilino)barbituric acids (**X,** R = CH_3S; Table IV). **General Procedure.**—A solution of 0.1 mole of 2-thio-5-(substituted-anilino)barbituric acid in 1 l. of 1 *N* sodium hydroxide was cooled to 10°. Iodomethane (14.9 g.) was added to the cooled solution, with good stirring. This solution was stirred for 6 hr. during which time it was allowed to warm gradually to room temperature. At the end of this time the clear solution was treated with charcoal and filtered. The filtrate was acidified with glacial acetic acid to yield the product which was filtered, washed with water, and dried at 80°. Recrystallization from an ethanol–water mixture gave the analytically pure product.

5-(*m*-Toluidino)-2,4,6-pyrimidinetrithiol (**XIIa,** see Table IV).—2-Thio-5-(*m*-toluidino)barbituric acid (24.9 g., 0.1 mole) and 75 g. of phosphorus pentasulfide were intimately mixed and suspended in 1 l. of dry pyridine. This mixture was refluxed for 12 hr. (a complete solution was obtained after 1 hr. of reflux) and evaporated to dryness to yield a dark semisolid residue. To this residue was added 500 ml. of water. After standing at room temperature for 30 min. the mixture was heated on the steam bath for 3 hr. The *p*H of the mixture was brought to 9 by the addition of sodium hydroxide. It was then treated with charcoal and filtered. The red filtrate was acidified to *p*H 2 with dilute hydrochloric acid, chilled overnight, and the product that separated was collected by filtration. Purification was afforded by recrystallization from dimethylformamide and water.

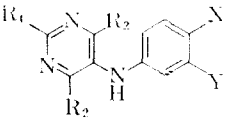
2-(Methylthio)-5-(*m*-toluidino)-4,6-pyrimidinedithiol (**XIIb,** Table IV).—2-(Methylthio)-5-(*m*-toluidino)barbituric acid (26.3 g., 0.1 mole) and 79 g. of phosphorus pentasulfide were intimately mixed and suspended in 1 l. of dry pyridine. This solution was refluxed for a total of 18 hr. and then evaporated to dryness. To the residue was added 59 ml. of water. This mixture was allowed to stand at room temperature for 30 min., heated on the steam bath for 3 hr., and then chilled overnight. The orange crystalline material was filtered, washed with water, and ether. It was then purified by dissolving in 500 ml. of dilute sodium hydroxide, treated with charcoal, and filtered. The filtrate was acidified with glacial acetic acid, the product was collected by filtration and dried at 80°. Recrystallization from dimethylformamide and water afforded an analytically pure sample.

5-(*m*-Toluidino)-2,4,6-tris(methylthio)pyrimidine (**XIIIa,** Table IV). **Method A.**—To a solution of 14.8 g. (0.05 mole) of 2-(methylthio)-5-(*m*-toluidino)-4,6-pyrimidinedithiol in 1 l. of 14% aqueous ammonia cooled at 10° was added, with stirring, 14.2 g. of iodomethane. After a few minutes a precipitate started to appear. This mixture was stirred for 3 hr. and allowed to warm slowly to room temperature. The 5-(*m*-toluidino)-2,4,6-tris(methylthio)pyrimidine was filtered, washed with water and dried at 80°. Purification was afforded by recrystallization from aqueous ethanol.

Method B.—To a solution of 2.8 g. (0.01 mole) of 5-(*m*-toluidino)-2,4,6-pyrimidinetrithiol in 100 ml. of 14% aqueous ammonia cooled at 10° was added, with stirring, 4.3 g. (0.03 mole) of iodomethane. A precipitate appeared almost immediately. This mixture was allowed to warm slowly (3 hr. with stirring) to room temperature. The product was filtered and was treated in the manner described for Method A.

Treatment of 5-(*m*-Toluidino)-2,4,6-tris(methylthio)pyrimidine with Chlorine.—Dry chlorine was bubbled through a cold (5°) suspension of 3.2 g. (0.01 mole) of 5-(*m*-toluidino)-2,4,6-tris(methylthio)pyrimidine in 100 ml. of absolute methanol,

TABLE IV



R_1	R_2	X	Y	Empirical formula	Yield, %	M.p., °C. dec.	Analyses — Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Ultraviolet Absorption (mμ) pH 1 λ_{max}	pH 1 $\epsilon \times 10^{-3}$	pH 11 λ_{max}	pH 11 $\epsilon \times 10^{-3}$
NH_2	OH	H	CH_3	$C_{11}H_{12}N_4O_2$	40	233–235	54.9	5.4	23.3[a]	55.2	5.8	23.1	251	15.1	253	13.3
NH_2	OH	Cl	Cl	$C_{10}H_8Cl_2N_4O_2$	81	220–221	41.8	2.8	19.5	41.5	3.0	19.1	256	18.0	262	17.8
SH	OH	H	H	$C_{10}H_9N_3O_2S$	78	265–266	51.1	4.1	17.8	51.1	4.1	17.8	239	17.5	237	9.4
													290	14.8	289	13.0
SH	OH	Cl	H	$C_{10}H_8ClN_3O_2S$	53	250–251	44.5	3.0	15.6	44.7	3.1	15.8	244	13.8	237	17.0
													288	16.6	280	14.7
SH	OH	H	Cl	$C_{10}H_8ClN_3O_2S$	78	235–236	44.5	3.0	15.6	44.6	3.2	15.7	243	13.2	237	21.1
													286	17.0	286	17.5
SH	OH	CH_3	CH_3	$C_{12}H_{13}N_3O_2S$	53	230 231	54.8	5.0	16.0	54.9	5.0	15.6	238	10.0	233	11.6
													293	13.4	270	11.3
SH	OH	Br	H	$C_{10}H_8BrN_3O_2S$	51	265–267	38.2	2.6	13.4	38.4	2.6	12.9	240	9.4	238	18.9
													292	13.8	284	14 1
OH	OH	CH_3	H	$C_{11}H_{11}N_3O_3$	40	330–332	56.7	4.7	18.0	56.8	4.7	17.7	252	11.4	247	15.6
OH	OH	Cl	Cl	$C_{10}H_7Cl_2N_3O_3$	35	240–243	41.7	2.5	14.6	41.4	2.8	14.5	255	18.9	257	21.3
OH	OH	Cl	H	$C_{10}H_8ClN_3O_3$	40	225- 226	47.3	3.2	16.5	47.1	3.2	16.5	252	20.3	255	22.2
H	OH	H	CH_3	$C_{11}H_{11}N_3O_2$	52	268–269	60.9	5.1	19.3	61.0	5.4	19.6	244	9.9	247	10.6
													280	5.0		
H	OH	CH_3	CH_3	$C_{12}H_{13}N_3O_2$	56	288–289	62.0	5.7	18.2	62.0	5.7	17.8	244	10.4	245	11.3
													280	5.1	290	6.5
H	OH	H	Cl	$C_{10}H_8ClN_3O_2$	42	291- 292	50.5	3.4	17.7	50.7	3.8	17.5	245	10.7	250	11.4
													285	6.0		
—SCH_3	OH	H	H	$C_{11}H_{11}N_3O_2S$	78	268–269	53.0	4.4	16.8	53.1	4.1	16.4	239	12.2	243	12.1
													280	10.2	274	9.2
—SCH_3	OH	Cl	H	$C_{11}H_{10}ClN_3O_2S$	88	269 270	46.5	3.5	11.8	46.7	3.7	15.1	247	14.9	255	13.9

—SCH_3	OH	H	Cl	$C_{11}H_{10}ClN_3O_2S$	92	242–243	46.5	3.5	14.8	46.2	3.4	14.9	245	12.6	254	13.1
													283	10.4		
—SCH_3	OH	Cl	Cl	$C_{11}H_9Cl_2N_3O_2S$	93	250–251	41.5	2.8	13.2	41.2	2.9	13.5	250	15.7	264	15.8
													280	10.8		
—SCH_3	OH	Br	H	$C_{11}H_{10}BrN_3O_2S$	90	250–251	40.0	3.1	12.8	40.3	3.3	12.8	249	17.0	239	15.1
															304	10.1
—SCH_3	OH	H	CH_3	$C_{12}H_{13}N_3O_2S$	91	239–240	54.8	5.0	16.0	54.6	5.0	16.4	240	11.2	240	10.3
													280	9.5	276	9.5
—SCH_3	OH	CH_3	CH_3	$C_{13}H_{15}N_3O_2S$	89	253–255	56.4	5.5	15.1	56.6	5.5	14.9	240	13.9	234	13.5
													280	12.2	273	10.3
SH	SH	H	CH_3	$C_{11}H_{11}N_3S_3$	10	256–257	46.9	3.9	14.9[b]	46.9	3.9	14.5	282	21.7	246	21.7
													368	16.3	298	24.5
															374	12.1
—SCH_3	SH	H	CH_3	$C_{12}H_{13}N_3S_3$	40	260–261 (no dec.)	48.8	4.4	14.2[c]	48.5	4.0	13.9	258	16.2	250	18.2
													282	16.8	297	17.3
													368	11.8	375	8.9
—SCH_3	—SCH_3	H	CH_3	$C_{14}H_{17}N_3S_3$	87	155–156 (no dec.)	52.0	5.3	13.0[d]	51.8	5.4	13.0	250[e]	45.2		
													298	13.3		
—SCH_3	Cl	H	H	$C_{11}H_9Cl_2N_3S$	87	130–131 (no dec.)	46.1	3.2	14.7	46.8	3.8	14.7	238[e]	10.6		
													256	14.9		
													306	9.7		
—SCH_3	Cl	Cl	Cl	$C_{11}H_7Cl_4N_3S$	10	122–123 (no dec.)	37.2	2.0	11.8	37.5	2.2	11.6	257[e]	19.4		
													304	16.3		
NH_2	NH_2	H	CH_3	$C_{11}H_{14}N_6$	8[f]	237–238	57.4	6.1	36.5	56.7	6.2	36.9	241	15.9	245	17.3
													273	16.6	266	13.1
NH_2	NH_2	CH_3	CH_3	$C_{12}H_{16}N_6$	6[f]	215–217	59.0	6.6	34.4	58.6	6.8	34.7	241	14.6	245	16.0
													272	15.3	264	12.0
NH_2	NH_2	H	H	$C_{10}H_{12}N_6$	70[f]	250-252	55.5	5.6	38.9	55.2	6.0	38.7	238	14.0	244	15.6
													273	14.9	269	11.5
NH_2	NH_2	Cl	Cl	$C_{10}H_{10}Cl_2N_6$	7.5[f]	277–279	42.2	3.5	29.5	42.3	3.6	29.0	252	16.5	257	17.1
													270	13.4		

TABLE IV FOOTNOTES

[a] As hemihydrate. [b] Calcd.: S, 34.2. Found: S, 34.5. [c] Calcd.: S, 32.6. Found: S, 32.0. [d] Calcd.: S, 29.7. Found: S, 30.2. [e] In ethanol. [f] Yields calculated from 2-(methylthio)-5-(substituted-anilino)-4,6-pyrimidinediols.

with stirring and cooling. The gas was delivered at such a rate that the internal temperature did not exceed 10°. Complete solution was achieved after 30 min. At the end of 90 min. the chlorine flow was stopped and the solution evaporated to 30 ml. The white crystalline solid which separated was collected by filtration, washed with water and dried at 80° to yield 1.6 g., m.p. 219–220°. Recrystallization from aqueous ethanol yielded 1.4 g. of pure product, m.p. 226–227°; λ_{max}^{EtOH} 294 mμ (ε 14,400).

This product gave the following analytical data: C, 33.0; H, 2.4; N, 8.9; Cl, 28.6; S, 13.3. The empirical formula was thus $C_{13}H_{11}Cl_4N_3O_4S_2$ (calcd.: C, 32.7; H, 2.3; N, 8.8; Cl, 29.3; S, 13.4). The structure of this product, which gave a single spot in three different paper chromatographic systems, is therefore either 5-(2,4,6-trichloro-3-methylanilino)-2-chloro-4,6-bis(methylsulfonyl)pyrimidine or 5-(2,4,6-trichloro-3-methylanilino)-4-chloro-2,6-bis(methylsulfonyl)-pyrimidine. The identity of this product was not further investigated.

2-(Methylthio)-4,6-dichloro-5-(substituted-anilino)pyrimidines (XI, Table IV). **General Procedure.**—A suspension of 40 g. of 2-(methylthio)-5-(substituted-anilino)barbituric acid in 1 l. of phosphorus oxychloride was refluxed with gentle stirring for 18 hr. (a complete solution was obtained after 15 min.). The excess phosphorus oxychloride was then removed *in vacuo* on a steam bath and the residual brown syrup was added slowly to *ca.* 1 kg. of flaked ice with vigorous stirring. The temperature during this addition was maintained below 5°. After the addition was complete the mixture was stirred for 30 min. at the same temperature. Saturated ammonia water was added dropwise to the cold mixture until the *p*H was 8. Anhydrous ammonia was then bubbled through the icy mixture (< 15°) for 3 hr. The resulting alkaline solution was then extracted with 5 × 600 ml. of 2-butanone. The extract was treated with charcoal and dried overnight with anhydrous sodium sulfate.

The dried ketone extract was then evaporated at 40° *in vacuo* to yield the crude 2-(methylthio)-4,6-dichloro-5-(substituted-anilino)pyrimidine, which was dried in a vacuum desiccator over calcium chloride. Purification was afforded by recrystallization from heptane.

2,4,6-Triamino-5-(substituted-anilino)pyrimidines (XV, Table IV). **General Procedure.**—A solution of 10 g. of crude 2-(methylthio)-4,6-dichloro-5-(substituted-anilino)pyrimidine in 200 ml. of 24% ethanolic ammonia was heated in an autoclave at 180° for 24 hr. The resulting brown solution was evaporated to one-third of its original volume and the tan crystalline material separated by filtration. It was redissolved in a minimum amount of boiling 1-butanol, treated with charcoal, and filtered. The filtrate deposited the pure 2,4,6-triamino-5-(substituted anilino)pyrimidine on cooling.

5-(2,4-Dinitroanilino)-2,4-pyrimidinediol (XVIII).—A mixture of 25 g. (0.2 mole) of 5 aminouracil, 60 g. (0.24 mole) of 2,4-dinitrobromobenzene, 1 g. of powdered cupric oxide, and 10 g. of sodium bicarbonate in 400 ml. of ethanol and 200 ml. of water was refluxed with stirring for 9 hr. The red precipitate that initially formed was replaced by small crystalline yellow solid. The reaction mixture was then cooled and the solid filtered and triturated with 3 × 200

ml. of ether, 3 × 200 ml. of acetone, and 3 × 200 ml. of boiling water. The product was then recrystallized from dimethylformamide and water to yield 27 g. (46%) of 5-(2,4-dinitroanilino)-2,4-pyrimidinediol, as golden needles, m.p. 312–313° dec.; $\lambda_{max}^{pH\ 1}$ 246 mμ (ε 15,800); $\lambda_{shoulder}^{pH\ 1}$ 285 mμ (ε 10,000), 340 mμ (ε 5,800); $\lambda_{max}^{pH\ 11}$ 286 mμ (ε 12,400), 346 mμ (ε 10,000).

Anal. Calcd. for $C_{10}H_7N_5O_6 \cdot H_2O$: C, 38.6; H, 2.9; N, 22.5. Found: C, 38.2; H, 3.1; N, 22.4.

The water of hydration can be removed by drying at 130° in a vacuum oven for 24 hr. (*Anal.* Calcd.: C, 41.0; H, 2.4. Found: C, 41.2; H, 2.8.)

Acknowledgment.—The authors wish to express their appreciation to Mr. Wayne H. Nyberg, Mrs. Margaret L. Rounds, Miss Phyllis G. Shaul, Mrs. Beverly Ann Smith, Mrs. Carol R. Tuttle and Mr. Hal P. Van Fossen for their valuable assistance in performing analytical, instrumental and paper chromatographic measurements.

5-Benzyl-2,4-diaminopyrimidines as Antibacterial Agents. I. Synthesis and Antibacterial Activity *in vitro*

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Received May 31, 1962

A series of 5-benzyl-2,4-diaminopyrimidines has been synthesized and tested for antibacterial activity. Maximal activity occurs among those compounds which are unsubstituted in the pyrimidine 6-position, possess unsubstituted amino groups in the 2- and 4-positions and bear one or more alkoxyl groups in the *meta* and *para* positions of the benzene nucleus. These compounds have high activity against Gram positive microorganisms and significant activity against a variety of Gram negative bacteria. Trimethoprim, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine, has been selected for further study on the basis of the magnitude and breadth of its antibacterial activities.

The discovery that many 5-benzyl-2,4-diaminopyrimidines[1] possess a high degree of antibacterial, as well as antimalarial, activity[1–5] has