[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

5-Arylthiopyrimidines. II. 2- and 4-Alkylamino and 4-Amino Derivatives[1]

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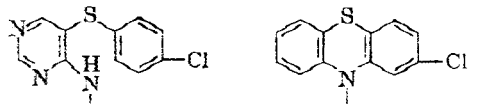
5-Bromoisocytosine and 5-bromouracil react readily with arylmercaptans in ethylene glycol at 150° to produce 5-arylthiopyrimidines in 40–50% yields. The 5-unsubstituted pyrimidines and the disulfide of the mercaptan are by-products of this reaction. 2-Amino-, 2-dialkylamino-, and 2-mercapto-4-hydroxy-5-arylthiopyrimidines can also be prepared by the condensation of guanidines or thiourea with α-alkoxymethylenearylthioacetic esters. Chlorination and amination of the hydroxypyrimidines yields the corresponding alkylamino derivatives. 4-Amino-5-arylthiopyrimidines can be obtained by condensation of arylthioacetonitriles with formamide, or alternatively, from 2-mercapto-4-hydroxy-5-arylthiopyrimidines, by removal of the 2-mercapto group with Raney nickel, followed by chlorination and amination. The ultraviolet absorption spectra of the arylthio derivatives are described.

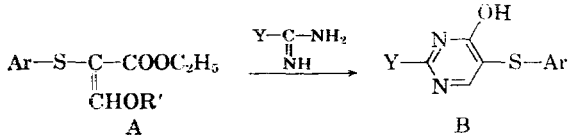
The preparation of a series of 2,4-diamino-5-arylthiopyrimidines was reported by Falco, Roth, and Hitchings.[2] Since some of those derivatives were found to have activity as central nervous system depressants, it was considered of interest to prepare a related series of alkylated aminopyrimidines of increased solubility and basicity. It was observed also that this type of structure bears a formal resemblance to open chain analogs of pharmacologically active phenothiazines. Thus, 4-(3-dimethylaminopropylamino)-5-(4-chlorophenylthio) pyrimidine (XVII) can be compared to chlorpromazine as follows:



XVII

Chlorpromazine

The most readily accessible compounds of this type appeared to be 2-amino-4-(substituted amino) derivatives, which should be obtained by the chlorination and amination of 2-amino-4-hydroxy-5-arylthiopyrimidines. Falco *et al.*[2] prepared 2,4-diamino-5-arylthiopyrimidines by the reaction of guanidine with α-arylthio-β-methoxyacrylonitriles, and it was to be expected that the corresponding esters would yield the 4-hydroxy analogs. This was found to be the case.



A

B

Y = NH_2, NR_2, SH

R, R' = alkyl

The alkoxymethylene esters (A) were prepared from the formylated esters by the method of Chase, Thurston, and Walker,[3] with slight modifications. The reaction of guanidine, alkylguanidines, or thiourea with A proceeded to give 2-amino-, 2-alkylamino-, or 2-mercaptopyrimidines (B) in high yield. Attempts to react thiourea with the formyl precursor of A led to very low yields of pyrimidine.

It seemed possible that a simpler and more general route to compounds of type B (where Y = NH_2 or OH) might be through the reaction of the corresponding 5-bromopyrimidines with arylmercaptans. 5-Halogenopyrimidines are characterized in general by very low reactivity of the halogen atom.[4] However, Barker and Luthy[5] reported that 5-bromobarbituric acid and 5-bromo-6-amino-uracil react readily with thiourea to produce the 5,5'-disulfide and the sulfide, respectively, of the pyrimidines. Although 5-bromouracil fails to react, 5-bromo-6-aminouracil yields the corresponding disulfide upon treatment with sodium disulfide in alcohol. On the other hand, 5-bromouracil and also 5-bromoisocytosine have been found to react with various aliphatic amines.[6–8] Caldwell and Sayin[9] found that 2-amino-5-iodopyrimidine could be made to react with thiophenol in the form of its copper salt at 190–200° in quinoline.

It was found here that thiophenol salts react readily with both 5-bromouracil and 5-bromoisocytosine at 150° in ethylene glycol to form 5-arylthiopyrimidines in 40–50% yields. This reaction did not proceed by displacement only, however, but also partially by electron transfer, so that a 5-

(1) Paper presented in part before the Medicinal Division at the 137th Meeting of the American Chemical Society, Cleveland, April 1960.

(2) E. A. Falco, B. Roth, and G. H. Hitchings, *J. Org. Chem.*, **26**, 1143(1961).

(3) B. H. Chase, J. P. Thurston, and J. Walker, *J. Chem. Soc.*, 3439 (1951).

(4) G. W. Kenner and A. Todd, *Heterocyclic Compounds*, Vol. **6**, R. C. Elderfield, ed., J. Wiley and Sons, Inc., New York, 1957, p. 301.

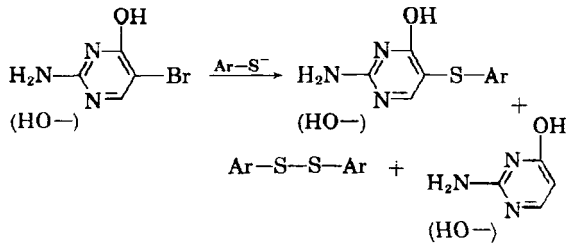
(5) G. R. Barker and N. G. Luthy, *J. Chem. Soc.*, 4206 (1954); *Chem. & Ind. (London)*, 983 (1955).

(6) H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, **32**, 355 (1904).

(7) T. B. Johnson and I. Matsuo, *J. Am. Chem. Soc.*, **41**, 788 (1919).

(8) A. P. Phillips, *J. Am. Chem. Soc.*, **73**, 1061 (1951); **75**, 4092 (1953).

(9) W. T. Caldwell and A. N. Sayin, *J. Am. Chem. Soc.*, **74**, 4314 (1952).



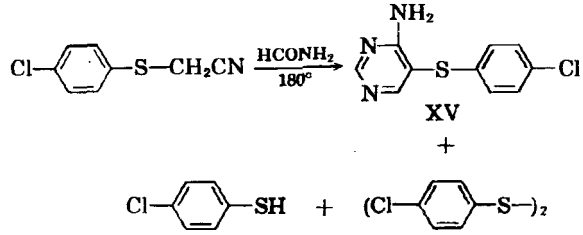
unsubstituted pyrimidine and a diaryl disulfide were by-products. These products were easily separable, however, and this proved to be the method of choice for the preparation of most of the products described here. Phenols, such as *p*-cresol, did not react with 5-bromouracil or 5-bromoisocytosine under similar conditions.

The reactivity of 2,4-diamino-5-bromopyrimidine toward thiophenols was also investigated. For this purpose, 2,4-diaminopyrimidine was prepared by the reaction of β-ethoxyacrylonitrile with guanidine. However, the 5-bromo derivative was recovered unchanged when treated with 4-chlorothiophenol.

The chlorination of the 2- and 4-hydroxy-5-arylthiopyrimidines with phosphoryl chloride proceeded smoothly, but the products usually were obtained as phosphorus complexes. These, however, reacted easily with amines to produce the desired 2- and 4-alkylamino analogs.

The preparation of 2-unsubstituted 4-amino-5-arylthiopyrimidines was accomplished by dethiolation of 2-mercapto-4-hydroxy-5-arylthiopyrimidines with Raney nickel, followed by chlorination and amination in the 4-position. The 5-sulfide group is stable under these conditions. It was found possible to prepare 2-mercapto-4-(4-methyl-1-piperazinyl)-5(4-chlorophenylthio)pyrimidine from the 2-mercapto-4-hydroxy derivative *via* chlorination with phosphoryl chloride, albeit in low yield. Usually, it is necessary to protect the mercapto group in carrying out this latter type of reaction.

Another possible and simpler route to 4-amino-5-arylthiopyrimidines was suggested by the Davies and Piggott synthesis[10] of 4-amino-5-phenylpyrimidine from phenylacetonitrile plus formamide and ammonia gas. They had deduced that their product was the above-named pyrimidine; its structure was verified by an independent synthesis by Russell and Hitchings.[11] It was found in the current study that 4-chlorophenylthioacetonitrile[2] reacts with formamide at 180° to produce a mixture of products, which includes the desired 4-amino-5-(4-chlorophenylthio)pyrimidine (XV) identical in properties with the product obtained from the 2-mercaptopyrimidine. The yields, however, were only about 10%. The major product of the reaction was 4,4′-dichlorodiphenyl disulfide, which was obtained in greater than 70% yield. A little of the corresponding 4-chlorothiophenol was also obtained. Additional water soluble products were not identified.



The 4-amino group of XV is stable to boiling 6*N* hydrochloric acid, and is not replaced by boiling with dialkylaminoalkylamines.

The ultraviolet absorption spectrum of 2-amino-4-hydroxy-5-phenylthiopyrimidine is characterized by maxima at 245 mμ at *pH* 1 and 11, by a second maximum at 283 mμ in alkali, and a weak maximum at 305 mμ in acid. The spectrum of the corresponding 2,4-diamino derivative[2] differs in having much more intense absorption in the 245 mμ region. The second maximum is at 289 mμ in the neutral molecule, but virtually disappears in the cationic species. These spectra differ from those of the corresponding 5-phenoxy- and 5-benzylpyrimidines[12,13] with respect to the 245 mμ peak, which is not present in the latter compounds. These absorb in the 230 mμ region instead. The bathochromic shift to 245 mμ can be ascribed to the presence of the 5-arylthio grouping. Substitution in the benzene ring produces small shifts in this peak. This absorption maximum is close to that produced by the parent arylmercaptan and its disulfide. The peak in the 290 mμ region can be ascribed to resonance of the aminopyrimidine moiety.

When secondary amino groups are introduced into the 4-position of the pyrimidine ring, virtually no change in spectrum occurs, and the 2,4-bis-secondary amino derivatives have absorptions which are more intense but qualitatively similar. On the other hand, a tertiary amino group in the 4-position causes reduction of the 290 mμ peak to a small shoulder, whereas tertiary amino groups in both the 2- and 4-positions result in greatly increased extinction values at 245 mμ, with virtual elimination of the 290 mμ maximum. In the 2-unsubstituted 4-tertiary amino compounds, the 290 mμ maximum is lost entirely.

The 4-(substituted amino)-5-arylthiopyrimidines were found not to possess any significant activity on the central nervous system of the type shown by chlorpromazine. However, various members of the series did show marked hypotensive activity in cats or dogs which had been anesthetized with pento-

(10) W. H. Davies and H. A. Piggott, *J. Chem. Soc.*, 347 (1945); British Patent **573,576** (1945).

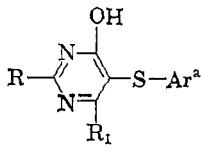
(11) P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3763 (1951).

(12) E. A. Falco, P. B. Russell, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3753 (1951).

(13) E. A. Falco, S. DuBreuil, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3758 (1951).

TABLE I

4-HYDROXY-5-ARYLTHIOPYRIMIDINES



Cpd. No.	R	Ar	Formula	M.P.	M.W.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	H	C_6H_4Cl (4)	$C_{10}H_7ClN_2OS$	172	238.7	50.31	2.95	11.73	50.12	2.97	11.90
II	OH	C_6H_4Cl (4)	$C_{10}H_7ClN_2O_2S$	324–326	254.7	47.15	2.77	11.00	46.71	2.23	11.12
III	SH	C_6H_4Cl (4)	$C_{10}H_7ClN_2OS_2$	264	270.8	44.36	2.61	10.35	44.47	2.46	10.17
IV	NH_2	C_6H_5	$C_{10}H_9N_3OS$	258–259	219.3	54.77	4.14	19.17	54.09	4.00	19.25
V	NH_2	C_6H_4Cl (4)	$C_{10}H_8ClN_3OS$	320	253.7	47.33	3.16	16.56	47.36	3.23	16.44
VI[a]	NH_2	C_6H_4Cl (4)	$C_{11}H_{10}ClN_3OS$	285	267.7	49.34	3.76	15.69	49.39	3.63	15.57
VII	NH_2	$C_6H_4CH_3$ (2)	$C_{11}H_{11}N_3OS$	262–266	233.3	56.63	4.75	18.01	56.44	4.86	17.56
VIII	NH_2	$C_6H_4CH_3$ (3)	$C_{11}H_{11}N_3OS$	265–269	233.3	—	—	18.01	—	—	17.90
IX	NH_2	$C_6H_4CH_3$ (4)	$C_{11}H_{11}N_3OS$	233–245	233.3	—	—	18.01	—	—	17.91
X	NH_2	$C_6H_2Cl_3$ (x)[b]	$C_{10}H_6Cl_3N_3OS$	331–334	322.6	37.23	1.88	13.03	37.43	2.38	13.04
XI	$(CH_3)_2N$	C_6H_4Cl (4)	$C_{12}H_{12}ClN_3OS$	215	281.8	51.14	4.29	14.91	51.13	4.17	14.69

[a] R_1 = H in all cases except compound VI, where R_1 = CH_3. [b] Trichlorothiophenol supplied by Evans Chemetics, Inc.

barbital or chloralose. This activity was most pronounced in derivatives containing a primary amino group in the 2-position of the pyrimidine ring and an alkylaminoalkylamino substituent in the 4-position. Such compounds gave a fall in the arterial pressure which lasted for more than two hours. This was accompanied in general by a decrease in heart rate. Compound XXX (Table III, 2-amino-4-(4-methyl-1-piperazinyl)-5-(4-chlorophenylthio)pyrimidine hydrochloride, B.W. 57-301) was selected for extended pharmacological evaluation.

In the dog anesthetized with pentobarbital, the hypotension and bradycardia caused by this drug have been shown to be accompanied by peripheral vasodilatation and a decreased cardiac contractile force.[14,15] Neither premedication with atropine nor bilateral vagotomy prevents the fall in arterial pressure and cardiac slowing. The substance has been shown by conventional pharmacological methods not to possess ganglionic blocking or adrenergic blocking properties; it is also not a cholinomimetic.[15]

EXPERIMENTAL

2-Amino-4-hydroxy-(or 2,4-dihydroxy)-5-arylthiopyrimidines. General method via 5-bromopyrimidine condensations. The appropriate thiophenol was condensed with 5-bromoisocytosine or 5-bromouracil by heating to 140–160° in ethylene glycol for 1 to 3 hr. in the presence of potassium carbonate. A nitrogen atmosphere was employed to minimize disulfide formation. Upon cooling at the end of the reaction period, the disulfide of the mercaptan precipitated as a by-product of the reaction, and was separated by filtration. By adding several volumes of water to the filtrate and neutralizing with acid, the product precipitated and left the by-products isocytosine or uracil in solution. Any residual thiophenol was removed by extracting the product with alcohol or ether. After reprecipitation from alkali, the pyrimidine was sufficiently pure for subsequent reactions. This method is exemplified below by the preparation of 2-amino-4-hydroxy-5-(4-chlorophenylthio)pyrimidine. The 5-arylthiopyrimidines prepared by this method are listed in Table I. (Compounds I, III, and XI in this Table were prepared by other methods described below.)

2-Amino-4-hydroxy-5-(4-chlorophenylthio)pyrimidine (V). (*a*) *From 5-bromoisocytosine.* A mixture of 100 g. (0.525 mole) of 5-bromoisocytosine,[16] 76 g. (0.525 mole) 4-chlorothiophenol, 73 g. (0.53 mole) anhydrous potassium carbonate, and 1 l. of ethylene glycol, contained in a 2-l. flask equipped with stirrer, condenser, and gas inlet tube, was heated to 150–155° for 3 hr. in an atmosphere of nitrogen. Evolution of carbon dioxide occurred as the reaction temperature reached approximately 100°, and complete solution was obtained when the temperature reached 150–155°. When the temperature dropped slightly below this point, a second liquid phase began to separate. This solidified on cooling, and was separated by filtration. The precipitate, which weighed approximately 36 g., was recrystallized from ethanol or hexane, and then melted at 70°. It was insoluble in dilute sodium hydroxide and had an ultraviolet absorption maximum at 246 mμ ($E_m \times 10^{-3}$ = 23.7) in ethanol. The analysis indicated that it was 4,4′-dichlorodiphenyl disulfide[17] (XLV).

Anal. Calcd. for $C_{12}H_8Cl_2S_2$: C, 50.18; H, 2.81. Found: C, 50.25; H, 2.59. The ultraviolet absorption spectrum of *p*-chlorothiophenol is very similar to that of XLV. (λ max. (cyclohexane) = 245 mμ ($E_m \times 10^{-3}$ = 10.9; λ max (pH_{11}) = 272 mμ ($E_m \times 10^{-3}$ = 11.5).

The filtrate from the reaction mixture was poured into approximately 5 volumes of water, followed by neutralization with hydrochloric acid, which yielded a white precipitate. This was filtered off and reprecipitated from alkali. It was then extracted with warm ethanol and ether to remove any unreacted thiophenol, followed by a final reprecipitation from alkali. The product (V) then weighed 53 g. (40%).

(14) C. H. Ellis, *Am. J. Physiol.*, 199, 167 (1960).

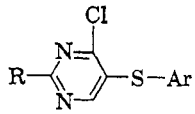
(15) K. I. Colville, M. M. Jacobson, and C. H. Ellis, *Federation Proc.*, 19, 120 (1960).

(16) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, 29, 504 (1903).

(17) R. Otto, *Ann.*, 143, 111 (1867).

TABLE II

4-CHLORO-5-ARYLTHIOPYRIMIDINES



Cpd. No.	R	Ar	Formula	M.P.	M.W.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XII	NH_2	C_6H_5	$C_{10}H_8ClN_3S$	189–192	237.7	50.52	3.39	17.68	50.19	3.18	17.76
XIII	NH_2	C_6H_4Cl (4)	$C_{10}H_7Cl_2N_3S$	208	272.2	44.13	2.59	15.44	44.24	2.48	15.72
XIV	Cl	C_6H_4Cl (4)	$C_{10}H_5Cl_2N_2S$	100–102	291.5	41.19	1.73	9.61	41.47	1.78	9.84

(*b*) *From ethyl α-(4-chlorophenylthio)acetate.* Ethyl α-(4-chlorophenylthio)acetate[18] was prepared by the reaction of equimolar quantities of 4-chlorothiophenol, sodium ethylate, and ethyl chloroacetate in ethanol (10 volumes per weight of thiophenol). After refluxing for an hour, the mixture was filtered from salt, followed by removal of the solvent, and distillation of the product under vacuum. The product boiled at 126–130°/1 mm., and had n_D^{25} 1.5550 (82%).

Anal. Calcd. for $C_{10}H_{11}ClO_2S$: C, 52.05; H, 4.81. Found: C, 51.60; H, 5.30.

This ester was formylated by reaction in ethanol with 2 moles of ethyl formate in the presence of 2 moles of sodium ethylate (molarity = 1.7). After 4 hr. refluxing the product was obtained as the sodium salt, insoluble in the reaction medium. This was separated, dissolved in water, extracted with ether, and then neutralized with acid, which precipitated the product. The *α-formyl derivative* (XLVI) melted at 41° after recrystallization from hexane.

Anal. Calcd. for $C_{11}H_{11}ClO_3S$: C, 51.06; H, 4.28. Found: C, 50.96; H, 4.46.

The ethyl α-formyl-α-(4-chlorophenylthio)acetate (XLVI) (4.2 g., 0.016 mole) was treated with an excess of diazomethane in ether to convert it to ethyl α-methoxymethylene-α-(4-chlorophenylthio)acetate. The product was obtained as a sirup which was converted directly to the pyrimidine by reaction with one equivalent of guanidine (obtained from 1.53 g. of guanidine hydrochloride plus 0.37 g. of sodium in 40 ml. of absolute ethanol). This mixture was refluxed for 6 hr., followed by removal of the solvent. The residue was extracted with alkali, and the soluble portion was neutralized with acid. The white precipitate which formed was isolated, and washed with acetone and ether. The product (V), 1.3 g., had physical properties which were identical with those of the product obtained by procedure (a).

2-Amino-4-hydroxy-5-phenylthiopyrimidine (IV). A mixture of 38 g. (0.2 mole) of 5-bromoisocytosine, 25 g. (0.22 mole) thiophenol, 27.6 g. (0.22 mole) potassium carbonate, and 350 ml. ethylene glycol was heated at 150° under nitrogen for 2 hr. On cooling, a precipitate formed, which was filtered off and recrystallized from ethanol. White needles were obtained (6.2 g.), which melted at 58–60°, and were insoluble in alkali. The analysis indicated that the substance was diphenyl disulfide[19] (XLVII).

Anal. Calcd. for $C_{12}H_{10}S_2$: C, 66.01; H, 4.62. Found: C, 65.65; H, 4.92.

The ultraviolet absorption spectrum showed a maximum at 239 mμ ($E \times 10^{-3} = 16.4$) in ethanol.

The filtrate from the reaction mixture was treated as in V above, followed by a final recrystallization of the product (IV) from a dimethylformamide-ethanol mixture. The pyrimidine weighed 11.8 g. (27%).

2-Amino-4-hydroxy-5-(4-chlorophenylthio)-6-methylpyrimidine (VI). A mixture of 32.1 g. (0.157 mole) of 2-amino-4-hydroxy-5-bromo-6-methylpyrimidine,[20] 21.2 g. (0.147 mole) 4-chlorothiophenol, 21.7 g. (0.157 mole) potassium carbonate and 300 ml. ethylene glycol was heated at 155° under nitrogen for 5 hr., after which it stood at room temperature overnight. The product was isolated and purified as described for V above. There was obtained 19.3 g. (48.5%) of VI.

2-Amino-4-alkylamino-(or 2,4-bis(alkylamino)-5-arylthiopyrimidines. General method. The aminohydroxy or dihydroxypyrimidines obtained in the previous step were heated in an excess of phosphoryl chloride until the pyrimidine was all in solution. The excess of phosphoryl chloride was removed under reduced pressure, and the residual sirup was poured on ice, and neutralized with sodium carbonate. The product usually was obtained as a phosphorus complex of the chlorinated pyrimidine which slowly decomposed in alkali. The pure chloro derivative could be isolated from this, if desired, by extraction of the product with hot benzene or sometimes hexane. However, it was found more convenient to use the crude phosphorus complex directly in subsequent reactions with amines. Purified chloro compounds are listed in Table II.

For reactions with high boiling amines, the chlorinated pyrimidine was boiled with an excess of the amine for several hours. The excess amine could be recovered, if desired, by distillation. The product was obtained on adding water or aqueous alkali to the residue. Usually it was obtained as a gum which gradually solidified after washing with fresh portions of water. Where the gummy products did not crystallize, they were converted to the hydrochloride in alcohol, and recrystallized from this medium, or from alcohol-ether. The free bases were recrystallized from alcohol, alcohol-water mixtures, or from ethyl acetate.

Reactions in which the volatile amines (methyl- or dimethylamine) were employed were carried out with a several-fold excess of the amine in alcoholic medium in an autoclave at 120–130° for 16 hr. These reactions are exemplified below. The substituted aminopyrimidines are listed in Table III.

2-Amino-4-chloro-5-(4-chlorophenylthio)pyrimidine (XIII). A mixture of 2.5 g. of 2-amino-4-hydroxy-5-(4-chlorophenylthio)pyrimidine and 20 ml. of phosphoryl chloride was heated to reflux temperature until all of the pyrimidine had dissolved (2 hr.). The excess phosphoryl chloride was distilled, and the residue poured on ice and neutralized with sodium carbonate. A cream colored solid separated. Upon standing, the mixture slowly became acidic, and the character of the precipitate seemed to change. It was allowed to stand for 2 hr. in the cold, and repeatedly neutralized before filtration. The crude product weighed 2.6 g. and gradually melted and decomposed between 200–260°. The substance was extracted with hot benzene. The soluble portion yielded a white precipitate (XIII) on cooling; this melted at 208° dec.

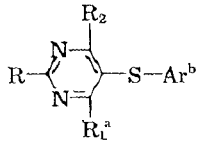
2,4-Dichloro-5-(4-chlorophenylthio)pyrimidine (XIV). A mixture of 7.4 g. of 2,4-dihydroxy-5-(4-chlorophenylthio)-

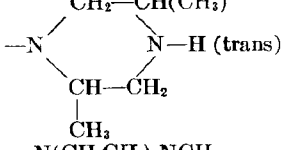
(18) This compound was mentioned by H. E. Thompson, C. P. Swanson, and A. G. Norman, *Botan. Gaz.*, **107**, 476 (1946); however, no preparation or properties are recorded.

(19) C. Vogt, *Ann.*, 119, 149 (1861).

(20) J. Jaeger, *Ann.*, **262**, 366 (1891).

TABLE III. 4-*N*-SUBSTITUTED 5-ARYLTHIOPYRIMIDINES



Cpd. No.	R	R_2	Formula	M.P.	M.W.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XV	H	NH_2	$C_{10}H_8ClN_3S$	126–127	237.7	50.52	3.39	17.68	50.25	3.59	17.60
XVI	H	$-NH(CH_2)_2N(CH_3)_2$	$C_{14}H_{17}ClN_4S\cdot 2HCl\cdot {}^1/_2H_2O$	178–181	390.8	43.02	5.15	14.33	43.32	5.07	14.42
XVII	H	$-NH(CH_2)_3N(CH_3)_2$	$C_{15}H_{19}ClN_4S\cdot 2HCl$	239–246	396.8	45.40	5.33	14.12	45.06	5.60	13.95
XVIII	H	$-N(CH_2CH_2)_2NCH_3$	$C_{15}H_{17}ClN_4S$	109	320.8	56.14	5.34	17.46	56.07	5.31	17.22
XIX	NH_2	$-NHCH_3$	$C_{11}H_{11}ClN_4S$	144–145	266.8	49.53	4.16	21.01	49.26	3.97	20.87
XX	NH_2	$-NH(CH_2)_3OCH_3$	$C_{14}H_{17}ClN_4OS$	102.5–103.5	324.8	51.76	5.28	17.25	51.68	5.40	17.00
XXI	NH_2	$-NH(CH_2)_2N(CH_3)_2$	$C_{14}H_{18}ClN_5S$	101–103	323.8	51.93	5.59	21.63	51.58	5.30	21.30
XXII	NH_2	$-NH(CH_2)_2N(C_2H_5)_2$	$C_{16}H_{22}ClN_5S\cdot H_2SO_4$	—	450.0	42.70	5.38	15.56	42.22	5.88	15.06
XXIII	NH_2	$-NH(CH_2)_3N(CH_3)_2$	$C_{15}H_{20}ClN_5S$	119–120	337.9	53.32	5.97	20.73	52.87	5.59	20.84
XXIV	NH_2	$-NH(CH_2)_3NHC_3H_7(i)$	$C_{16}H_{22}ClN_5S$	112–113	351.9	54.61	6.30	19.90	54.92	5.99	19.77
XXV	NH_2	$-N(CH_3)_2$	$C_{12}H_{13}ClN_4S\cdot HCl$	221–224	317.2	45.43	4.45	17.66	44.86	4.29	17.49
XXVI	NH_2	$-N-(CH_2)_5-$	$C_{15}H_{17}ClN_4S\cdot HCl$	202	357.3	50.42	5.08	15.68	50.61	5.49	15.12
XXVII	NH_2	$-N=(CH_2CH_2)_2O$	$C_{14}H_{16}ClN_4OS$	140–141	322.8	52.08	4.68	17.35	51.96	4.38	17.09
XXVIII	NH_2	$-N(CH_2CH_2)_2N-COOC_2H_5$	$C_{17}H_{20}ClN_5OS$	165	393.7	51.86	5.08	17.78	51.78	4.87	17.61
XXIX	NH_2	$-N(CH_2CH_2)_2NH$	$C_{14}H_{16}ClN_5S\cdot H_2O$	160	339.8	49.47	5.33	20.60	49.10	5.18	20.88
XXX	NH_2	$-N(CH_2CH_2)_2NCH_3$	$C_{15}H_{18}ClN_5S\cdot 2HCl\cdot H_2O$	238	426.8	42.41	5.20	16.41	42.47	5.13	16.26
XXXI	NH_2	$-N(CH_2CH_2)_2NC_2H_4OH$	$C_{16}H_{20}ClN_5OS$	177	365.9	52.51	5.50	—	52.63	5.33	—
XXXII	NH_2		$C_{16}H_{18}ClN_5S\cdot 2HCl\cdot H_2O$	215	438.8	43.79	5.05	15.96	43.88	5.04	15.71
XXXIII[a]	NH_2	$-N(CH_2CH_2)_2NCH_3$	$C_{16}H_{20}ClN_5S$	152	349.9	54.92	5.76	—	55.26	5.67	—
XXXIV	NH_2	$-N(C_2H_5)CH_2CH_2N(CH_3)_2$	$C_{15}H_{22}ClN_5S\cdot 2HCl$	201–202	424.8	45.23	5.69	16.48	44.80	5.65	16.31
XXXV	$-NHCH_3$	$-NHCH_3$	$C_{12}H_{13}ClN_4S\cdot HCl$	229–233	317.2	45.43	4.45	17.66	45.10	4.18	17.84
XXXVI	$-N(CH_3)_2$	$-N(CH_3)_2$	$C_{14}H_{17}ClN_4S\cdot HCl$	170–171	345.3	48.70	5.26	16.23	49.07	5.58	15.83
XXXVII	$-N(CH_3)_2$	$-N(CH_2CH_2)_2NCH_3$	$C_{17}H_{22}ClN_5S$	117–119	363.9	56.10	6.09	19.24	55.96	6.23	18.88
XXXVIII	$-N(CH_2CH_2)_2NCH_3$	$-N(CH_2CH_2)_2NCH_3$	$C_{20}H_{27}ClN_6S$	110–111	419.0	57.32	6.49	20.05	57.51	6.80	19.74
XXXIX[c]	NH_2	$-N(CH_2CH_2)_2NCH_3$	$C_{15}H_{19}N_5S$	133–134	301.4	59.77	6.35	23.24	59.98	6.20	23.05
XL[d]	NH_2	$-N(CH_2CH_2)_2NCH_3$	$C_{16}H_{21}N_5S$	145	315.4	60.91	6.71	—	61.00	6.30	—
XLI[e]	NH_2	$-N(CH_2CH_2)_2NCH_3$	$C_{16}H_{21}N_5S$	135–136	315.4	60.91	6.71	—	61.19	6.36	—
XLII[f]	NH_2	$-N(CH_2CH_2)_2NCH_3$	$C_{15}H_{21}N_5S$	115–116	315.4	60.91	6.71	22.20	60.71	6.50	22.53
XLIII[g]	NH_2	$-N(CH_2CH_2)_2NCH_3$	$C_{15}H_{16}Cl_3N_5S$	181–183	404.8	44.51	3.98	17.30	44.80	3.89	16.90
XLIV	SH	$-N(CH_2CH_2)_2NCH_3$	$C_{15}H_{17}ClN_4S_2$	204–206	352.9	51.05	4.86	—	51.06	4.63	—

[a] R_1 = H in all cases except compound XXXIII, where R_1 = CH_3. [b] Ar = C_6H_4Cl (4), except in XXXIX–XLIII. [c] Ar = C_6H_5. [d] Ar = $C_6H_4CH_3$ (4). [e] Ar = $C_6H_4CH_3$ (3). [f] Ar = $C_6H_4CH_3$ (2). [g] Ar = $C_6H_2Cl_3$ (x).

TABLE IV

ULTRAVIOLET ABSORPTION SPECTRA OF 4-HYDROXY-5-ARYLTHIOPYRIMIDINES[a]

Cpd. No.	pH = 1				pH = 11			
	Maximum		Minimum		Maximum		Minimum	
	λ, mμ	E × 10^{-3}	λ, mμ	E × 10^{-3}	λ, mμ	E × 10^{-3}	λ, mμ	E × 10^{-3}
I	254	9.7	237	7.0	255	13.2	240	10.0
	305	6.3	291	6.1	sh. 280	7.4	—	—
II	250	16.8	—	—	251	15.9	270	8.6
	sh. 300	3.8	—	—	292	11.8	—	—
III	252	13.4	235	8.9	256	16.9	296	8.5
	280	15.8	262	12.1	sh. 315	11.0	—	—
	sh. 290	15.0	—	—	331	12.9	—	—
	sh. 310	13.4	—	—	—	—	—	—
IV	245	12.6	289	3.2	245	14.4	267	7.8
	305	3.7	—	—	283	9.5	—	—
V	251	18.4	296	4.2	253	16.8	272	10.6
	305	4.3	—	—	285	11.7	—	—
VI	251	19.8	—	—	258	19.0	—	—
	sh. 305	3.7	—	—	sh. 280	13.4	—	—
VII	241	12.7	294	3.7	244	14.9	266	7.6
	305	4.1	—	—	283	9.7	—	—
VIII	247	12.1	292	3.0	247	13.6	267	7.5
	305	3.4	—	—	283	9.0	—	—
IX	247	15.1	231	12.0	248	16.1	267	8.8
	305	4.0	295	3.9	284	10.2	—	—
X	255	16.2	240	13.7	sh. 245	13.9	264	10.9
	sh. 290	6.4	—	—	sh. 272	12.1	—	—
	—	—	—	—	288	13.8	—	—
XI	250	19.4	—	—	257	24.3	278	10.9
	sh. 305	5.6	—	—	295	12.7	—	—

[a] Abbreviations: sh. = shoulder. Midpoints are given in all cases.

pyrimidine and 60 ml. of phosphoryl chloride was refluxed for 8 hr., at which time practically all of the pyrimidine had dissolved. The solution was filtered and the crude product isolated by the procedure of XIII above; weight 7.1 g. This was extracted with boiling hexane. On cooling, the product (XIV) crystallized as large off-white needles which weighed 5.3 g.

2-Amino-4-(2-dimethylaminoethylamino)-5-(4-chlorophenylthio)pyrimidine (XXI). Ten grams of crude 2-amino-4-chloro-5-(4-chlorophenylthio)pyrimidine, phosphorus complex, was mixed with 25 ml. of *N,N*-dimethylethylenediamine. An exothermic reaction took place immediately, which raised the temperature to 70°. The mixture was then heated to reflux temperature for 4 hr. On cooling, a crystalline precipitate was present in the reaction mixture. The entire mixture was poured into several volumes of water, which dissolved the crystalline material and caused a gummy precipitate to separate. This crystallized after standing for an hour; dry weight, 7.9 g. The substance (XXI) was recrystallized twice from dilute ethanol, yielding white crystals.

2-Amino-4-(1-piperazinyl)-5-(4-chlorophenylthio)pyrimidine (XXIX). Five grams of 2-amino-4-(4-carbethoxy-1-piperazinyl)-5-(4-chlorophenylthio)pyrimidine (XXVIII) was mixed with 500 ml. of absolute ethanol plus 73.5 ml. of 17*N* sodium hydroxide and heated on the steam bath overnight. Most of the ethanol was distilled, and water was then added to the residue. The resultant solid product was isolated and recrystallized from dilute ethanol; weight 4.0 g.

2,4-Bis(methylamino)-5-(4-chlorophenylthio)pyrimidine (XXXV). A mixture of 6.3 g. of 2,4-dichloro-5-(4-chlorophenylthio)pyrimidine (XIV) and 63 ml. of ethanol saturated with methylamine was heated at 125° for 16 hr. in an autoclave. The solvent was removed, and the residue extracted with water, in which it was essentially insoluble. It was then recrystallized once from dilute ethanol, followed by conversion to the hydrochloride, using ethanolic hydrochloric acid plus ether.

TABLE V

ULTRAVIOLET ABSORPTION SPECTRA OF 4-CHLORO-5-ARYLTHIOPYRIMIDINES

Cpd. No.	Solvent	λ_{max}, mμ	E × 10^{-3}
XIII	$(CH_2Cl)_2$	253[a]	25.8
		sh. 290	10.2
XIV	$(CH_2Cl)_2$	259	14.0
		sh. 310	3.6

[a] Determined at 5 mg./l.

2-Mercapto-4-hydroxy-5-(4-chlorophenylthio)pyrimidine (III). A mixture of 46 g. (0.18 mole) of ethyl α-formyl-α-(4-chlorophenylthio)acetate, 0.2 g. of *p*-toluenesulfonic acid, 450 ml. of toluene, and 32 g. of isoamyl alcohol (0.36 mole) was heated to boiling for 16 hr. in a round-bottomed flask equipped with a 1-foot Vigreux column, at the top of which was attached a Dean-Stark trap for collecting water, and a reflux condenser.[3] After the separation of water had ceased, the mixture was partially cooled, and added to a solution of 20 g. (0.37 mole) of sodium methylate and 14 g. (0.184 mole) of thiourea in 450 ml. of absolute ethanol. The resultant mixture was heated with stirring for 6 hr., and allowed to stand overnight. A small precipitate was then present, which was filtered off, dissolved in water, and precipitated by the addition of hydrochloric acid (ppt. A). The filtrate from the reaction was concentrated to remove the solvents, and the residue was dissolved in water. This mixture was extracted twice with benzene and twice with ether, followed by neutralization of the aqueous solution with hydrochloric acid. The product precipitated as a tan solid which had the same spectrum as ppt. A. The two were combined and extracted with warm ethanol and ether, which served to remove a brown impurity. The product (III) weighed 41 g. (84%).

4-Hydroxy-5-(4-chlorophenylthio)pyrimidine (I). Eighteen

TABLE VI

ULTRAVIOLET ABSORPTION SPECTRA OF 4-AMINO- AND SUBSTITUTED AMINO-5-ARYLTHIOPYRIMIDINES[a]

	pH = 1				pH = 11			
	Maximum		Minimum		Maximum		Minimum	
Cpd. No.	λ, mμ	E × 10^{-3}	λ, mμ	E × 10^{-3}	λ, mμ	E × 10^{-3}	λ, mμ	E × 10^{-3}
	A. 2-Unsubstituted-4-NH_2, NHR, and NR_2-5-(4-chlorophenylthio)pyrimidines							
XV	245	18.8	—	—	245	16.7	273	6.4
	ssh 280	6.4	—	—	282	6.7	—	—
XVI	247	20.9	—	—	246	23.4	280	6.3
	bo 270	10.9	—	—	290	6.5	—	—
XVII	247	20.4	—	—	247	21.6	280	5.5
	bo 270	10.7	—	—	293	6.0	—	—
XVIII	251	16.9	—	—	256	18.3	—	—
	B. 2-NH_2-4-NHR-5-(4-chlorophenylthio)pyrimidines							
XIX	244	22.9	232	19.1	252	19.5	275	8.4
	ssh 280	6.5	—	—	289	9.8	—	—
XX	245	22.5	232	19.6	252	18.9	275	8.2
	ssh 280	7.1	—	—	289	9.7	—	—
XXI	245	26.9	233	23.6	252	24.8	277	11.5
	ssh 290	6.1	—	—	290	12.6	—	—
XXII	244	24.4	232	21.4	252	19.6	277	8.8
	ssh 280	6.9	—	—	292	9.9	—	—
XXIII	245	24.0	232	20.6	252	19.9	277	9.0
	ssh 280	7.6	—	—	290	10.3	—	—
XX1V	245	25.6	232	21.2	251	19.8	277	8.5
	ssh 280	7.8	—	—	292	10.0	—	—
	C. 2-NH_2-4-NRR_1-5-(4-chlorophenylthio)pyrimidines							
XXV	249	23.6	236	20.2	226	19.7	223	19.3
	ssh 280	10.2	—	—	257	18.1	239	15.1
					sh 290	8.5		
XXVI	220[b]	28.6	241	22.5	258[c]	21.4	246	20.6
	248	23.9	—	—	sh 290	11.2	—	—
	ssh 280	11.8	—	—	—	—	—	—
XXVII	250	22.9	236	19.0	252	21.2	240	20.0
	ssh 285	10.8	—	—	sh 290	11.3	—	—
XXVIII	250	24.8	237	21.2	231[c]	30.6	243	22.2
	ssh 280	13.2	—	—	255	23.2	—	—
	—	—	—	—	sh 290	10.8	—	—
XXIX	250	24.2	238	20.2	254	20.2	241	18.6
	ssh 285	10.0	—	—	sh 300	8.9	—	—
XXX	250	25.6	238	21.1	252	20.5	240	18.8
	ssh 280	11.8	—	—	sh 290	10.4	—	—
XXXI	250	21.9	238	17.9	252	17.3	241	15.7
	ssh 280	10.4	—	—	sh 290	8.9	—	—
XXXII	250	24.6	238	20.2	255	19.6	243	18.6
	ssh 285	10.1	—	—	ssh 300	8.1	—	—
XXXIII	250	29.6	238	23.8	255	24.2	245	22.3
	ssh 285	12.2	—	—	sh 290	14.5	—	—
XXXIV	249	22.8	237	19.2	255	18.2	240	15.3
	ssh 280	9.1	—	—	sh 290	7.7	—	—
	D. 2,4-Bis-NHR-5-(4-chlorophenylthio)pyrimidines							
XXXV	244.5	29.0	239	27.8	253	24.1	234	17.4
	—	—	—	—	295	10.0	278	8.5
	E. 2-NR_2-4-NR_2'-5-(4-chlorophenylthio)pyrimidines							
XXXVI	243.5[b]	34.6	—	—	242[c]	32.0	—	—
	ssh 305	6.5	—	—	sh 260	26.2	—	—
	—	—	—	—	sh 300	8.3	—	—
XXXVII	248	37.4	—	—	243	32.1	—	—
	—	—	—	—	ssh 260	26.8	—	—
	—	—	—	—	sh 310	7.3	—	—
XXXVIII	245	33.4	—	—	243	31.6	—	—
	sh 310	8.7	—	—	sh 310	8.7	—	—
	F. 2-Amino-4-(4-methyl-1-piperazinyl)-5-arylthiopyrimidines[d]							
XXXIX	221	29.8	—	—	sh 240	18.1	—	—
	sh 240	21.0	—	—	sh 300	8.0	—	—
	ssh 280	10.0	—	—	—	—	—	—

TABLE VI (*Continued*)

	*p*H = 1				*p*H = 11			
	Maximum		Minimum		Maximum		Minimum	
Cpd. No.	λ, mμ	E × 10^{-3}	λ, mμ	E × 10^{-3}	3, mμ	E × 10^{-3}	3, mμ	E × 10^{-3}
XL	247	24.6	238	23.2	245	20.7	241	20.5
	ssh 280	11.8	—	—	sh 290	10.0	—	—
XLI	243	26.2	239	26.1	sh 245	21.4	—	—
	ssh 280	12.9	—	—	sh 290	10.7	—	—
XLII	ssh 240	26.3	—	—	sh 300	10.6	—	—
	ssh 270	15.7	—	—	—	—	—	—
XLIII	252	24.2	245	23.2	252	21.0	247	20.6
	ssh 290	9.3	—	—	295	13.1	—	—

[a] Abbreviations: sh = shoulder; ssh = slight shoulder; bo = bend out. [b] Hydrochloride in ethanol. [c] Base in ethanol. [d] For the 4-chlorophenyl derivative, see compound XXX above.

grams of 2-mercapto-4-hydroxy-5-(4-chlorophenylthio)pyrimidine was slurried in 180 ml. of water, and a solution of 11 g. of sodium carbonate monohydrate in 110 ml. of water was added. The mixture was heated until the pyrimidine had dissolved, and clarified to remove traces of impurities. The solution was then heated under reflux with rapid stirring, and activated Raney nickel added in small portions from time to time. The course of the reaction was determined by following the ultraviolet spectral changes. The reduction was found to be complete after 13 hr. heating time. The mixture was then filtered, and the Raney nickel residue was extracted with dilute alkali to remove adsorbed product. The combined filtrates were neutralized with hydrochloric acid, which yielded a white product (I) weighing 10.5 g. This was purified by reprecipitation from alkali and recrystallization from 75% ethanol.

4-Amino-5-(4-chlorophenylthio)pyrimidine (XV). (a) *From 4-hydroxy-5-(4-chlorophenylthio)pyrimidine.* Two grams of 4-hydroxy-5-(4-chlorophenylthio)pyrimidine was mixed with 10 ml. of phosphoryl chloride and heated under reflux until the pyrimidine had all dissolved (1 hr.). The resultant 4-chloropyrimidine was isolated in the crude state by distilling off most of the excess phosphoryl chloride, pouring the residue on ice, and neutralizing the product with sodium carbonate. An orange precipitate was formed. This was air dried overnight and mixed with 20 ml. of absolute ethanol which had been saturated with ammonia at 0°. The mixture was heated in an autoclave at 130° for 1.5 hr. Upon cooling, a cream-colored precipitate was present (0.5 g.). The remainder of the product was isolated after concentration of the yellow mother liquor. The substance was extracted with dilute hydrochloric acid, and the solution was neutralized to *p*H 10 to precipitate the product. This was then recrystallized from a mixture of hexane and absolute ethanol, yielding white crystals melting at 126–127° (XV).

(b) *From 4-chlorophenylthioacetonitrile.* A mixture of 25 g. (0.136 mole) of 4-chlorophenylthioacetonitrile[3] and 28.4 g. (0.63 mole) of formamide, contained in a round-bottom flask equipped with an air condenser, was heated to 180–190° in a Wood's metal bath for 24 hr. Upon cooling, the mass solidified to a black crystalline solid. This had a strong thiophenol-like odor. The product was extracted with warm water, which yielded a water-insoluble residue weighing 22.5 g. This material was extracted several times with hot dilute hydrochloric acid. The acid extracts yielded a tan crystalline precipitate upon neutralization with alkali; weight, 7.3 g. Upon recrystallization of this substance from hexane-ethanol mixtures, with the aid of Darco, there was obtained a light crystalline product (XV) melting at 124–126°, weight 3.2 g. (10%). This had an ultraviolet absorption spectrum identical with that of the product obtained by procedure (a) above, and a mixed melting point showed no depression. Found: C, 51.03; H, 3.31; N, 17.70.

The acid-insoluble product of the reaction (15 g.) was recrystallized from ethanol. This yielded cream colored plates melting at 70°. The substance was identical in properties with the 4,4′-dichlorodiphenyl disulfide (XLV) obtained as a by-product in V (a) above. A sublimate in the condenser was found to be partially alkali-soluble. This fraction on neutralization melted at 47–48°. The spectrum was identical with that of 4-chlorothiophenol. The remainder of the sublimate was XLV.

4-(3-Dimethylaminopropylamino)-5-(4-chlorophenylthio)-pyrimidine dihydrochloride (XVII). A 4.2-g. sample of 4-hydroxy-5-(4-chlorophenylthio)pyrimidine (I) was chlorinated as described under XIII above. The product was then refluxed with 20 ml. of 3-dimethylaminopropylamine for 3 hr. The excess amine was removed by distillation, and the residue extracted with water. A semisolid product remained, which did not crystallize on standing. This was dissolved in an ether-ethanol mixture and converted to the hydrochloride by the addition of ethanolic hydrochloric acid. The product slowly crystallized. It was purified by recrystallization twice from ethanol.

Other 4-alkylaminoalkylamino-5-(4-chlorophenylthio)-pyrimidines were prepared by the same technique, and are characterized in Table III.

2-Mercapto-4-(4-methyl-1-piperazinyl)-5-(4-chlorophenylthio)pyrimidine (XLIV). Five grams of 2-mercapto-4-hydroxy-5-(4-chlorophenylthio)pyrimidine (III) was refluxed with 50 ml. of phosphoryl chloride for 1.5 hr., at which time a clear solution was present. After removal of excess phosphoryl chloride, drowning on ice, and neutralization, there was present a yellow gum, which reacted slowly with excess alkali. This substance was mixed with 30 ml. of *N*-methylpiperazine, which resulted in an immediate vigorous reaction. The mixture was allowed to stand overnight, and then heated to refluxing for 3 hr. It was filtered from a slight precipitate and poured into water, followed by neutralization of the resultant solution with acid. A gummy precipitate formed, which slowly crystallized during a 3-day period. The product was extracted with a small amount of ethanol, which served to remove gummy material, leaving a white powdery solid, which was then recrystallized from 250 ml. of ethanol. A matte of fine white needles was obtained, 0.72 g. Ultraviolet absorption maxima (E × 10^{-3}) were as follows: (a) 0.1*N* hydrochloric acid, λ max. = 280 mμ (shoulder) (10.6); 358 mμ (7.1); λ min. = 330 mμ (6.4); (b) *p*H 11 buffer, λ max. = 260 mμ (27.2), 330 mμ (shoulder) (7.2).

2-Dimethylamino-4-hydroxy-5-(4-chlorophenylthio)pyrimidine (XI). A 10.6-g. (0.04 mole) quantity of ethyl α-formyl-α-(4-chlorophenylthio)acetate was treated with isoamyl alcohol by the technique described above for preparation of the 2-mercaptopyrimidine analog (III), to yield the crude isoamyloxymethylene derivative. This was then mixed with an ethanolic solution of *N,N*-dimethylguanidine prepared from 5.5 g. (0.04 eq.) dimethylguanidine sulfate plus 1.38 g. (0.06 mole) sodium in 125 ml. absolute ethanol. This mixture was heated under reflux for 5 hr., filtered, and concentrated. The residue was dissolved in acid, extracted with ether to remove by-products, neutralized, and the resultant

precipitate recrystallized from dilute ethanol. This yielded 5.5 g. (49%) of XI, obtained as white crystals.

2,4-Diaminopyrimidine (XLVIII).[21] To a solution of sodium ethylate prepared from 12.7 g. (0.55 mole) sodium in 400 ml. absolute ethanol was added 47.7 g. (0.5 mole) guanidine hydrochloride. After stirring for 10 min., 48.6 g. (0.5 mole) of β-ethoxyacrylonitrile was added. The mixture was heated under reflux for 7 hr., allowed to stand overnight, and filtered from salt. Most of the ethanol was distilled, and the residue was refrigerated overnight. A yellow solid was then filtered off; weight, 31.3 g. (57% crude). This crude 2,4-diaminopyrimidine contained a yellow impurity which was removed by recrystallization from absolute ethanol-ether or -ethyl acetate mixtures. The recrystallized product (XLVIII) was white and melted at 145–146.5°. Ultraviolet absorption maxima (E × 10^{-3}) were as follows: (a) 0.1*N* hydrochloric acid, λ max. = 267 mμ (5.6); λ min. = 253 mμ (4.8). (b) *p*H 11.0 buffer, λ max. = 282 mμ (7.1); λ min. = 253 mμ (1.7).

Ultraviolet absorption spectra. The ultraviolet absorption spectra of the compounds listed in Tables I–III are shown in Tables IV–VI. Measurements were made on the Beckman model DU spectrophotometer at a concentration of 10 mg. per liter, in 0.1*N* hydrochloric acid and in Sørensen glycine–sodium hydroxide buffer at *p*H 11.0, except where otherwise stated.

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Synthesis of the *s*-Triazine System. III.[1] Trimerization of Imidates

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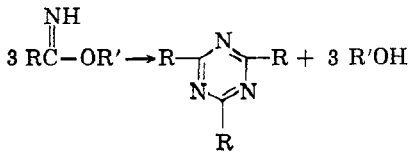
Alkyl imidates, RC(=NH)OR′, derived from a wide variety of nitriles are converted to symmetrically trisubstituted *s*-triazines by acid catalysts. The reaction provides a useful route to many rare or previously unknown members of this class.

In this paper we report the results of an investigation of the trimerization of imidates to form 2,4,6-trisubstituted *s*-triazines and the development of this reaction into a useful synthetic method of broad scope.



R

I. C_6H_5
II. CH_3
III. CH_2Cl

The formation of 2,4,6-triphenyl-*s*-triazine (I) by spontaneous decomposition of alkyl benzimidates has been reported by several authors.[2] In most cases the yields obtained were acknowledged to be negligible or the reaction was exceedingly slow.[3] Wheeler and Johnson[4] became interested in this spontaneous trimerization reaction, and in 1900 they carefully purified and stored samples of methyl *p*-toluimidate and of methyl, ethyl, and isobutyl benzimidates. These were examined in 1922 by Johnson and Bass[5] who found that in the interim the methyl benzimidate and *p*-toluimidate had been completely converted to 2,4,6-triaryl-*s*-triazines and methanol. The other imidates were also partly converted to 2,4,6-triphenyl-*s*-triazine but both starting material and benzonitrile were present. Our own observation is that the spontaneous formation of 2,4,6-triphenyl-*s*-triazine from either crude or purified alkyl benzimidates is less than 1% complete in the first year of storage.

The original preparation of *s*-triazine itself by Nef involved trimerization of ethyl formimidate although this was not appreciated,[6] but until the present work was undertaken no case had been

(1) Paper II, F. C. Schaefer and G. A. Peters, *J. Am. Chem. Soc.*, **81**, 1470 (1959).

(2)(a) A. Pinner, *Die Imidoäther und ihre Derivate*, Robert Oppenheim, (Gustav Schmidt), Berlin, Germany, 1892, p. 58; (b) G. Glock, *Ber.*, **21**, 2650 (1888); (c) W. Wislicenus and M. Goldschmidt, *Ber.*, **33**, 1467 (1900); (d) H. L. Wheeler, P. T. Walden, and H. F. Metcalf, *Am. Chem. J.*, **20**, 68 (1898).

(3) A. Pinner, *Ber.*, **22**, 1610 (1889), recommended the gradual spontaneous decomposition of crude ethyl benzimidate as the best available method for the preparation of 2,4,6-triphenyl-*s*-triazine, but he did not indicate the yield to be expected or the time required. A. H. Cook and D. G. Jones, *J. Chem. Soc.*, 278 (1941), were subsequently unable to obtain any *s*-triazine compound by decomposition of ethyl *m*- and *p*-nitrobenzimidates in the manner suggested by Pinner.

(4) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **23**, 135 (1900).

(5) T. B. Johnson and L. W. Bass, *J. Am. Chem. Soc.*, **44**, 1341 (1922).

(6) J. U. Nef, *Ann.*, **287**, 337 (1895). The product was erroneously believed to be a dimer of hydrogen cyanide until 1954 when its true nature was discovered by Ch. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.*, **76**, 632, 5646 (1954).