6.2 g. of redistilled ethylene glycol and 0.2 g. of *p*-toluenesulfonic acid. The mixture was azeotroped for 3 hr. and washed with 40% sodium hydroxide solution. The toluene solution was azeotroped for 1 hr. over 2 g. of potassium hydroxide, filtered and added to a suspension of 4.5 g. of freshly prepared sodamide in 100 ml. of dry toluene. The mixture was refluxed and stirred under nitrogen for 20 min. To the mixture was added a solution of 4-methyl-4-(3-chloropropyl) piperazine (20 g.) in 50 ml. of dry toluene. The mixture was refluxed and stirred under nitrogen for 4 hr. On cooling, 150 ml. of water was added. The toluene layer was extracted with dilute hydrochloric acid. The acid extracts were made alkaline and extracted with benzene. The benzene was evaporated and the residual oil was distilled; b.p. 255°–260°/75 mm.; 23 g. (60%). The free base was dissolved in 100 ml. of ethyl acetate and added to a solution of ethyl acetate containing 2 equimolar amounts of maleic acid. The precipitated dimaleate salt was recrystallized from methanol; m.p. 179–180°.

2-(1-Hydroxyisopropyl)-10-dimethylaminopropylphenothiazine (XIV). To a solution of methyllithium prepared from 2 g. of lithium and 18.2 g. of methyl iodide in ether was added a solution of 41.7 g. of 2-acetyl-10-dimethylaminopropylphenothiazine[8] in 100 ml. of ether. The mixture was stirred and refluxed for 2.5 hr. and then poured into water. The organic layer was washed with water, dried and evaporated to give 43.5 g. of brown viscous oil. By trituration of 24 g. of this material with an ether-petroleum ether mixture 14.4 g. of yellow solid, m.p. 97.5–100.5°, was obtained. Further purification of the product by distillation, b.p. 203–210° (50 microns), followed by recrystallization from hexane gave pure carbinol (XIV), m.p. 107.5–109°.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, THE WELLCOME RESEARCH LABORATORIES]

5-Arylthiopyrimidines. I. 2,4-Diamino Derivatives

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Arylmercaptoacetonitriles are readily acylated with lower aliphatic esters. Their crude enol ethers, obtained by reaction with diazomethane, condense with guanidine to produce 2,4-diamino-5-arylmercaptopyrimidines. In contrast with the closely related 5-phenoxy- and 5-benzylpyrimidines, these compounds are practically devoid of activity *vs.* protozoan and bacterial infections. However, several members of the series are central nervous system depressants.

Derivatives of 2,4-diaminopyrimidine bearing weighty substituents in the 5-position are, in general, antimetabolites with considerable potency as antifolic acids.[2,3] Several subseries, the 5-phenyl-, 5-benzyl-, and 5-phenoxypyrimidines, were found to possess antimicrobial activity, which is most strikingly exemplified by the antimalarial activity of pyrimethamine, 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine.[4–6] It was of considerable interest, therefore, to prepare the isologous 5-phenylmercaptopyrimidines for comparison.

Very few 5-pyrimidyl aryl or alkyl sulfides have been reported in the literature. P. F. Hu[9] reported the synthesis of 2-amino-4-hydroxy-5-(4′-nitrophenylmercapto)-6-methylpyrimidine and the corresponding 4,6-dimethyl derivative. These were obtained by condensations of guanidine with ethyl α-(4′-nitrophenylmercapto)acetoacetate and 3-(4′-nitrophenylmercapto)-2,4-pentanedione, respectively. Johnson and Guest[10] prepared some 5-benzylmercaptopyrimidines by condensing *S*-ethylisothiourea with ethyl α-formylbenzylmercaptoacetate. Subsequent conversions yielded 5-benzylmercaptouracil and -cytosine. No 2,4-diamino derivatives were described, however.

It was found here that 2,4-diamino-5-arylmercaptopyrimidines could be obtained by the condensation of guanidines with α-arylmercapto-β-methoxyacrylonitriles. This procedure is similar to that reported by Russell and Hitchings[7] for the corresponding 5-phenyl derivatives. The intermediate arylmercaptoacetonitriles were most conveniently prepared by the reaction of arylmercaptans with chloroacetonitrile[11]; however, some of the nitriles employed here were obtained by dehydration of the corresponding amides. The nitriles were readily acylated by treatment of the esters in ethanol with two moles of sodium methylate. The resultant α-acylphenylmercaptoacetonitriles (I) failed to condense with guanidine to form pyrimidines, as was found earlier with the phenyl derivatives.[7] However, their crude enol ether derivatives (presumably of structure II),

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(2) G. B. Elion, H. VanderWerff, and E. A. Falco, *J. Biol. Chem.*, **174**, 765 (1948).

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(4) E. A. Falco, L. G. Goodwin, G. H. Hitchings, I. M. Rollo, and P. B. Russell, *Brit. J. Pharm.*, **6**, 185 (1951).

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(9) P. F. Hu, *Sci. Repts. Natl. Tsing Hua Univ. Ser.* **A5**, 260 (1948); *Chem. Abstr.*, **43**, 6634 (1949).

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TABLE I

ARYLMERCAPTOACETAMIDES $ArSCH_2CONH_2$

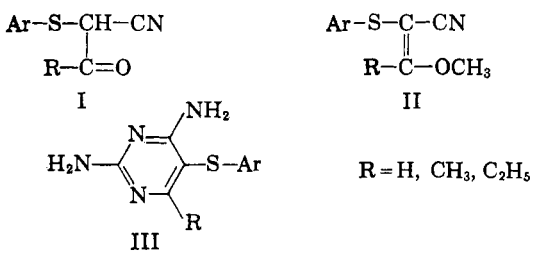
Compound No.	Ar	M.P.	Formula	Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found
I	C_6H_5	108–109	C_8H_9NOS	57.5	57.9	5.4	5.3
II	$C_6H_4Cl(2)$	117–118	C_8H_8ClNOS	47.6	47.9	4.0	4.4
III	$C_6H_4Cl(4)$	130–131	C_8H_8ClNOS	47.6	47.6	4.0	4.0
IV	$C_6H_4OCH_3(4)$	111–112	$C_9H_{11}NO_2S$	54.8	54.7	5.6	5.5

TABLE II

ARYLMERCAPTOACETONITRILES $ArSCH_2CN$

Compound No.	Ar	B.P./3 mm.	Formula	Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found
VI	$C_6H_4Cl(2)$	160–166	C_8H_6ClNS	52.3	52.3	3.3	3.6
VII	$C_6H_4OCH_3(4)$	168–173	C_9H_9NOS	60.3	60.6	5.0	4.9

prepared by reaction with diazomethane readily yielded the desired pyrimidines (III).



The isomeric 2,4-diamino-6-arylmercaptopyrimidines could be prepared readily by the reaction of 2,4-diamino-6-chloropyrimidine with a thiophenol in ethylene glycol in the presence of potassium carbonate. One such example, described in the experimental section, was prepared for pharmacological comparisons.

The ultraviolet absorption spectrum of 2,4-diamino-5-phenylmercaptopyrimidine (XII) is characterized by maxima at 245 and 289 mμ in alkaline or neutral medium, and in acid by a high maximum in the very low wave-length region at 211 mμ, which very nearly obscures a second peak at 235 mμ, creating a shoulder. A slight suggestion of a third peak is given by an inflection at 270 mμ. The acid shoulder is of higher intensity than the alkaline peak at 245 mμ (Table V).

The effect of substituents either in the 6-position of the pyrimidine ring or in the benzene nucleus produced minor changes in spectrum, which in general are similar to those observed in the 5-phenoxypyrimidine series.[5]

The introduction of a *p*-chlorophenylmercapto group into the 6-position of the 2,4-diaminopyrimidine nucleus produced a quite different spectrum, as was to be expected. The neutral molecule had a single maximum at 288 mμ, which underwent a hyperchromic and slight bathochromic shift in acid.

The 5-phenylmercaptopyrimidines were tested against *Plasmodium gallinaceum* infections in chicks and *vs. P. berghei* in mice, and found to be surprisingly devoid of activity. They were also found to have very low activity as antagonists of pteroylglutamic acid in the *L. casei* screen, and to have little or no antibacterial action against a variety of bacteria. However, it was observed that several derivatives in this series produced hypnotic and hypothermic effects in mice and other animals. The corresponding 6-*p*-chlorophenylmercapto analog had no such activity. The results of pharmacological testing of these compounds will be reported elsewhere.

EXPERIMENTAL[12]

Arylmercaptoacetamides. These compounds were prepared from the corresponding ethyl arylmercaptoacetates by treatment with saturated ethanolic ammonia solutions containing trace amounts of sodium methoxide.[13] These compounds are listed in Table I; all crystallized from ethanol in colorless plates.

Arylmercaptoacetonitriles. (a) *From thiophenols plus chloracetonitrile.* This procedure, which is essentially that of Dijkstra and Backer[11] is exemplified by the preparation described below.

4-Chlorophenylmercaptoacetonitrile (V). To a solution of 38 g. (0.7 mole) sodium methylate in 1 l. of absolute ethanol was added 100 g. (0.69 mole) of 4-chlorothiophenol, followed by the slow addition of 53 g. (0.7 mole) of chloroacetonitrile. The mixture was then heated under reflux for 1 hr. It was filtered hot to remove sodium chloride, and the filtrate then was refrigerated overnight. The shiny white plates which precipitated were filtered off and air dried; weight, 103 g. (81%); m.p. 88–90°.

Anal. Calcd. for C_8H_6ClNS: C, 52.3; H, 3.3. Found: C, 52.3; H, 3.6.

(b) *From arylmercaptoacetamides.* The arylmercaptoacetamides were treated with a slight excess of thionyl chloride in boiling benzene. Excess thionyl chloride was removed by partial distillation of the reaction mixture. The residual solution was washed with dilute sodium carbonate solution, dried over sodium carbonate, and distilled to remove benzene, followed by vacuum distillation of the product. The compounds of Table II were prepared by this procedure.

(12) Melting points are uncorrected.

(13) P. B. Russell, *J. Am. Chem. Soc.*, **72**, 1853 (1950).

TABLE III

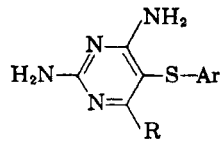
ULTRAVIOLET ABSORPTION SPECTRA OF INTERMEDIATE NITRILES

Compound No.	Solvent	Maximum		Minimum	
		λ mμ	Em × 10^{-3}	λ mμ	Em × 10^{-3}
V	Ethanol	258	5.7	244	4.6
	Cyclohexane	227, 259	12.6, 4.4	247	3.3
VIII	Ethanol	250	14.3	—[a]	—
IX	Ethanol	255	20.8	222	9.3
	*p*H 11 buffer	257	21.5	—[a]	—
	0.1*N* HCl	248	18.0		
	Cyclohexane	243	16.9		

[a] Spectrum not determined below 230 mμ.

TABLE IV

2,4-DIAMINO-5-ARYLMERCAPTOPYRIMIDINES



Compound No.	Ar	R	M.P.	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
XII	C_6H_5	H	217–220	$C_{10}H_{10}N_4S$	55.0	54.9	4.6	4.6	25.7	25.3
XIII	C_6H_5	CH_3	173	$C_{11}H_{12}N_4S$	56.9	57.1	5.2	4.9	24.1	24.1
X	$C_6H_4Cl(4)$	H	231–233	$C_{10}H_9ClN_4S$	47.5	47.4	3.6	3.5	22.2	22.3
XI	$C_6H_4Cl(4)$	CH_3	223–224	$C_{11}H_{11}ClN_4S$	49.6	49.6	4.2	4.3	21.0	21.1
XIV	$C_6H_4Cl(4)$	C_2H_5	188–190	$C_{12}H_{13}ClN_4S$	51.3	51.2	4.7	4.4	20.0	20.5
XV	$C_6H_4Cl(2)$	CH_3	206–208	$C_{11}H_{11}ClN_4S$	49.6	49.1	4.2	4.3	21.0	21.5
XVI	$C_6H_4OCH_3(4)$	H	196–197	$C_{11}H_{12}N_4OS$	53.2	53.4	4.8	4.7	22.6	22.6
XVII	$C_6H_4CH_3(4)$	CH_3	221–222	$C_{12}H_{14}N_4S$	58.5	58.9	5.7	5.4	22.8	23.1

TABLE V

ULTRAVIOLET ABSORPTION SPECTRA OF 2,4-DIAMINO-5-ARYLMERCAPTOPYRIMIDINES

Compound No.	*p*H 1				*p*H 11			
	Maximum		Minimum		Maximum		Minimum	
	λ mμ	Em × 10^{-3}	λ mμ	Em × 10^{-3}	λ mλ	Em × 10^{-3}	λ mμ	Em × 10^{-3}
XII	211	41.9	—		245	18.3	271	7.3
	235[a]	21.4			289	9.2		
	270[a]	6.3						
XIII	237	23.6	—		246	20.0	270	8.5
	270[a]	7.8			285	9.1		
X	245	21.6	—		251[b]	20.6	277	8.2
					290	9.6		
XI	244	23.4	—		252	22.5	275	10.0
	275[a]	8.0			284	10.4		
XIV	246	23.9	—		250	20.7	277	7.6
	275[a]	8.3			284	7.9		
XV	238	23.6	—		247	20.3	270	8.0
	270[a]	8.0			285	9.8		
XVI	243	22.4	232	20.8	248	20.4	275	7.7
	275[a]	7.1			290	9.1		
XVII	241	23.9	—		247	21.4	270	8.7
	270[a]	8.4			286	9.9		

[a] Inflection. [b] In 95% ethanol.

α-Acylarylmercaptoacetonitriles. These compounds were prepared by the condensation of the above nitriles with the appropriate ester in the presence of 2 moles of sodium ethylate.[14] In some instances the compounds were utilized in the crude form. The preparation of two of these compounds is given below.

α-Formyl-4-chlorophenylmercaptoacetonitrile (VIII). To a solution of 11.14 g. (0.484 g.-atom) of sodium in 450 ml. of absolute ethanol was added 44.4 g. (0.242 mole) of 4-chlorophenylmercaptoacetonitrile and 37 g. (0.5 mole) of ethyl formate. The mixture was heated under reflux for 3.5 hr., followed by distillation of the solvent from the reaction mixture. The residue was slurried in water and filtered from a small amount of insoluble material, followed by one extraction with ether. The resultant aqueous solution yielded an oil on acidification. This was extracted with ether, and dried over Drierite, followed by removal of the ether. The residual oil solidified on chilling. The substance was recrys-

(14) W. Wislicenus, *Ann.*, **291**, 202 (1896).

tallized from a benzene-hexane mixture, giving 29 g. (57%) of white product melting at 97–98°.

Anal. Calcd. for C_9H_6ClNOS: C, 51.06; H, 2.85; N, 6.61. Found: C, 51.18; H, 3.27; N, 6.23.

α-Acetyl-4-chlorophenylmercaptoacetonitrile (IX). From the reaction of 7.5 g. (0.041 mole) of 4-chlorophenylmercaptoacetonitrile with 9 g. (0.1 mole) of ethyl acetate in 100 ml. of absolute ethanol containing 4.5 g. (0.083 mole) of sodium methylate there was obtained by the above procedure 3.9 g. of crude product, which crystallized on acidification of the aqueous extract of the reaction mixture. After two recrystallizations from benzene-hexane, with the aid of decolorizing charcoal (Darco G 60), rosettes of white needles were obtained, melting at 113°.

Anal. Calcd. for $C_{10}H_8ClNOS$: C, 53.21; H, 3.57. Found: C, 53.43; H, 3.40.

2,4-Diamino-5-arylmercaptopyrimidines. The preparation of these compounds followed the method of Russell and Hitchings[7] for 2,4-diamino-5-arylpyrimidines. The α-acylarylmercaptoacetonitriles (crude in most cases) were treated with an excess of diazomethane in ether and the resulting β-methoxyacrylonitriles were condensed with guanidine. This procedure is exemplified below. The pyrimidines prepared by this procedure are listed in Table IV.

2,4-Diamino-5-(4'-chlorophenylmercapto)pyrimidine (X). To 12 g. (0.057 mole) of α-formyl-4-chlorophenylmercaptoacetonitrile in 150 ml. of ether was added an ethereal solution of diazomethane prepared from 12.4 g. (0.12 mole) of nitrosomethylurea. The mixture was allowed to stand in an open wide-mouthed Erlenmeyer flask for 2 days, after which time a sirupy residue remained. This was dissolved in 75 ml. of absolute ethanol and added to a solution of guanidine in ethanol, prepared by dissolving 1.31 g. (0.057 g. atom) sodium in 75 ml. of absolute ethanol, followed by the addition of 5.42 g. (0.057 mole) of guanidine hydrochloride. This mixture was heated to reflux temperature for 5 hr., cooled, and filtered. The precipitate was washed well with water and dried; weight, 8.3 g. (58% crude yield); m.p. 228–231°. Recrystallization from an 85:15 ethanol-toluene mixture with the aid of decolorizing charcoal (Darco G 60) yielded 5.9 g. of off-white product melting at 231–233°.

2,4-Diamino-5-(4'-chlorophenylmercapto)-6-methylpyrimidine (XI). α-Acetyl-4-chlorophenylmercaptoacetonitrile (17 g., 0.075 mole) was treated with diazomethane [from nitrosomethylurea (15 g., 0.15 mole)] as in the previous experiment. The product, after removal of the ether and excess diazomethane, was treated with guanidine [from the hydrochloride (8.0 g., 0.084 mole)] and sodium (1.8 g., 0.078 g.-atom) in 200 ml. of ethanol. After 5 hr. on the steam bath, the product was isolated as in the previous example. It was purified by reprecipitation with sodium hydroxide from solution in acetic acid, followed by recrystallization from 85% ethanol. Colorless needles were obtained (5.0 g., 25%); m.p. 223–224°.

2,4-Diamino-6(4'-chlorophenylmercapto)pyrimidine. A mixture of 5 g. (0.035 mole) of 2,4-diamino-6-chloropyrimidine,[15] 5 g. (0.035 mole) of 4-chlorothiophenol, 4.8 g. (0.035 mole) of anhydrous potassium carbonate, and 50 ml. of ethylene glycol was heated to refluxing for 10 min., and then placed on the steam bath overnight. The mixture was then poured into several volumes of water, made strongly basic with sodium hydroxide, chilled, and filtered. The white precipitate, 6.0 g., was recrystallized three times from ethanol, yielding long white needles (4.1 g.) melting at 219°.

Anal. Calcd. for $C_{10}H_9ClN_4S$: C, 47.52; H, 3.59; N, 22.17. Found: C, 47.75; H, 3.25; N, 22.57.

Ultraviolet absorption peaks were as follows: (a) in 0.1*N* hydrochloric acid: λ_{max}, 292 mμ (Em × 10^{-3} 12.6); λ_{min} 264 mμ (Em × 10^{-3} 7.7). (b) in *p*H 11.0 buffer: λ_{max} 288 mμ (Em × 10^{-3} 9.5); λ_{min} 262 mμ (Em × 10^{-3} 6.1).

Absorption spectra. Ultraviolet absorption spectra were obtained on a Beckman DU spectrophotometer, with 1 cm. quartz cuvettes. The absorptions were measured at a concentration of 10 mg. per liter in 0.1*N* hydrochloric acid and Sørensen glycine–sodium hydroxide buffer at *p*H 11.0, or in 95% ethanol or other solvents as noted.

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TUCKAHOE, N. Y.

(15) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, *J. Am. Chem. Soc.*, 72, 1914 (1950).

[CONTRIBUTION FROM THE INDUSTRIAL AND BIOCHEMICALS DEPARTMENT
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The Reaction of Disodium Ethylenebisdithiocarbamate with Trichloromethanesulfenyl Chloride[1]

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The reaction between disodium ethylenebisdithiocarbamate (I) and trichloromethanesulfenyl chloride (II) in aqueous medium gives a complex mixture of solids. The main components of this mixture are a polymer (III), bis(trichloromethyl)-ethylenebistrithiopercarbamate (IV), bis(trichloromethyl)-*N*-(trichloromethylthio)ethylenebistrithiopercarbamate (V), and bis(trichloromethyl)-*N,N'*-bis(trichloromethylthio)ethylenebistrithiopercarbamate (VI). The mechanism of formation of these compounds is discussed. A method for the specific synthesis of the most chemically stable component (IV) is described. This method, which involves inactivation of the —NH— groups of I toward II, consists in reaction of an emulsion containing free ethylenebisdithiocarbamic acid (IX), water, and an inert immiscible solvent with II in the presence of a large excess of hydrogen ions.

The reaction between disodium ethylenebisdithiocarbamate (I) and trichloromethanesulfenyl chloride[2] (II) was considered to be of interest because I contains four sites capable of reacting with II (two —NH—groups and two mercaptide groups), and II contains four chlorine atoms all of which