(yield 37%) of the ald-chlorimine as long colorless needles, m.p. 54° dec.

Anal. Calcd. for $C_6H_5ClN_2$: C, 51.3; H, 3.6. Found: C, 51.4; H, 3.8.

The following ald-chlorimines were similarly prepared:

3-Pyridinalchlorimine (II). Colorless needles (7.1 g., yield 51%) from methanol, m.p. 51–52° dec.

Anal. Calcd. for $C_6H_5ClN_2$: C, 51.3; H, 3.6; Cl, 25.2. Found: C, 51.4; H, 3.6; Cl, 25.0.

4-Pyridinalchlorimine (III). Colorless needles (10.0 g., yield 71%) from methanol. The sample melted at 104°, resolidified and finally decomposed at 175°.

Anal. Calcd. for $C_6H_5ClN_2$: C, 51.3; H, 3.6; Cl, 25.2. Found: C, 51.1; H, 3.6; Cl, 25.1.

Isonicotinonitrile (IV). To 2.8 g. (0.02 mole) of 4-pyridinalchlorimine in 20 ml. of absolute methanol was added triethylamine (5 ml.); the clear solution turned light yellow. Heat was generated and the solution was kept below reflux temperature by means of an ice bath. At the end of 1 hr. about 200 ml. of absolute ether was added. Triethylamine hydrochloride was filtered and the filtrate was evaporated to dryness in a rotating type evaporator. The residue 1.9 g. (92% yield) was recrystallized from benzene giving 1.7 g. of crystalline solid, m.p. 78–79° (m.p. reported[7] 78.5–80°).

4-Pyridinalchlorimine hydrochloride (V). A solution of 1.4 g. (0.01 mole) of freshly prepared 4-pyridinalchlorimine in 50 ml. of dry ether was maintained at room temperature while a stream of dry hydrogen chloride was added for 5 min. with stirring. The mixture was filtered and the precipitate washed twice, each time with 20 ml. of dry ether, to give the hydrochloride 1.1 g. (yield 62%) as colorless fine powder, m.p. 114° dec.

Anal. Calcd. for $C_6H_6Cl_2N_2$: Cl, 40.0; neut. equiv., 178. Found: Cl, 39.5; neut. equiv., 177.

pK_a *Value.* The pK_a value was determined to be 4.3 at room temperature (25–27°), from potentiometric data, assuming pK_a to be pH of half neutralization. Approximately 100 mg. of sample dissolved in 5 ml. of water was titrated with 0.1*N* sodium hydroxide.

4-Pyridinalchlorimine dimethyl sulfate (VI). To 5.6 g. (0.04 mole) of 4-pyridinalchlorimine in 80 ml. of acetone cooled to 0° by means of an ice-water bath was added 4.8 g. (0.038 mole) dimethyl sulfate. The clear colorless solution was allowed to warm to room temperature. At the end of 15 min. long needles were noticed growing in feather like structures at the bottom of the flask. After a total of 4 hr. standing, the mixture was filtered and gave 8.4 g. (yield 79%) of the quaternary salt as long colorless needles, m.p. 58–60° dec.

Anal. Calcd. for $C_8H_{11}Cl_1H_2O_4S$: C, 36.0; H, 4.1; Cl, 13.3. Found: C, 35.9; H, 4.7; Cl, 13.2.

Determination of ultraviolet absorption spectra. The absorption spectra were obtained using a Perkin-Elmer Model 13-U spectrophotometer unless otherwise indicated. The compounds were dissolved in anhydrous methanol and diluted to the desired concentration with additional solvent. The measurements were first performed using the I/I_0 scale, then repeated with the I_0/I scale. This gave both absorption and emission readings as a function of instrument drum readings. The readings were then converted to wave length from an available calibration curve, corrected for the air blank, and plotted to give continuous curves encompassing both absorption and emission character (see Fig. 1). To simplify assigning maxima and minima, emission readings were considered negative and the curve treated as an absorption entity.

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

The Synthesis of Some 2,4,5-Trisubstituted Pyrimidines[1]

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Condensation of acetamidine and *S*-alkylthioureas with diethyl ethoxymethylenemalonate and diethyl formylsuccinate by known methods gave 2-methyl- and 2-alkylthio-5-substituted 4-pyrimidones. The 4-pyrimidones were converted to the corresponding 4-alkylthio- and 4-(substituted-amino)pyrimidines, through the intermediate 4-chloropyrimidines. Several pyrimidines were converted to 2-hydrazinopyrimidines, 5-pyrimidinecarboxylic acid hydrazides, or 5-hydroxymethylpyrimidines.

The biological activity of 2-methylthio-4-amino-5-hydroxymethylpyrimidine (methioprim),[4,5] first prepared by Ulbricht and Price[6] has prompted us to synthesize a variety of 2,4,5-trisubstituted pyrimidines.[7,8,9] Many of these compounds have been assayed for activity in experimental rodent

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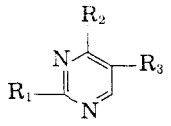
tumors[7,10,11] and in microbiological systems.[12] Two of the compounds, 2-methylthio-4-*o*-chloroanilino- and 2-methylthio-4-*o*-bromoanilino-5-carbethoxypyrimidine, substantially inhibited the growth of five experimental mouse tumors.[7] These results encouraged the synthesis of further variations.

Many of the new compounds described in this paper have been assayed for microbiological activity[12] and in experimental rodent tumors[10,11] and the results of the assays were, in general, negative.



	R_1	R_2	R_3
I	CH_3S	Cl	$COOC_2H_5$
II	CH_3S	NHR	$COOC_2H_5$
IIa	CH_3S	NH_2	$COOC_2H_5$
IIb	CH_3S	$NHCH_2CH_2SO_3H$	COOH
III	CH_3S	SR	$COOC_2H_5$
IV	CH_3	Cl	$COOC_2H_5$
V	CH_3	NHR	$COOC_2H_5$
VI	$C_6H_5CH_2S$	Cl	$COOC_2H_5$
VII	$C_6H_5CH_2S$	NHR	$COOC_2H_5$
VIII	Cl	Cl	$COOC_2H_5$
IX	Cl	NHR	$COOC_2H_5$
IXa	Cl	*o*-ClC_6H_4NH	$COOC_2H_5$
X	C_6H_5NH	C_6H_5NH	$COOC_2H_5$
XI	CH_3	NHR	CH_2OH
XII	CH_3S	NHR	CH_2OH
XIII	CH_3S	OH	$CH_2COOC_2H_5$
XIV	CH_3S	Cl	$CH_2COOC_2H_5$
XV	CH_3S	C_6H_5NH	$CH_2COOC_2H_5$
XVI	CH_3S	Cl	$CH_2(CO)NH_2$
XVII	CH_3S	OH	$CH_2(CO)NHNH_2$
XVIII	CH_3SO_2	NH_2	$COOC_2H_5$
XIX	NH_2	NH_2	$COOC_2H_5$
XX	NH_2NH	*o*-ClC_6H_4NH	$COOC_2H_5$
XXI	NH_2NH	OH	$COOC_2H_5$
XXII	NH_2NH	NH_2	$(CO)NHNH_2$

Generally, these compounds were synthesized by condensing acetamidine or the appropriately substituted thiourea with an α-ethoxymethylene or α-formyl ester by known methods to give the 2-methyl- or 2-alkylthio-5-substituted 4-pyrimidone. This was followed by transformations at the 2-, 4-, and 5-ring positions. 2-Methylthio-4-chloro-5-carbethoxypyrimidine (I) was prepared by the method previously described.[7] The 4-(substituted-amino)pyrimidines (II, IIa, IIb, V, VII, IX, XV) and 4-alkylthiopyrimidines (III) were prepared from the appropriate 4-chloropyrimidine by treatment with amines and mercaptans. 2-Methyl-4-chloro-5-carbethoxypyrimidine (IV) was prepared by the method of Todd and Bergel[13] with some modifications. Several of the 4-(substituted-amino)-5-carbethoxypyrimidines (II, V) prepared from I and IV were reduced with lithium aluminum hydride to the corresponding hydroxymethylpyrimidines (XI, XII).

Two 4-arylaminopyrimidines (VII) were prepared from VI, a compound previously prepared by Ballard and Johnson.[14] They condensed 2-benzyl-2-thiopseudourea and diethyl ethoxymethylenemalonate with sodium in absolute ethanol. On acidification, they obtained the 4-hydroxypyrimidine which was treated with phosphorus oxychloride to give VI. We obtained VI in better over-all yield by the more convenient condensation of the ester and the urea with sodium hydroxide in aqueous medium, followed by treatment of the sodium salt of the 4-hydroxypyrimidine directly with phosphorus oxychloride.

Several 2-chloro-4-(substituted-anilino)-5-carbethoxypyrimidines (IX) were prepared from the 2,4-dichloropyrimidine, (VIII)[15] and one equivalent of the appropriate aniline. One of these, 2-chloro-4-*o*-chloroanilino-5-carbethoxypyrimidine, (IXa) was converted with methanethiol to the known 2-methylthio-4-*o*-chloroanilino-5-carbethoxypyrimidine.[7] When VIII was treated with two equivalents of aniline, 2,4-dianilino-5-carbethoxypyrimidine (X) resulted.

Diethyl formylsuccinate, from diethyl succinate and ethyl formate,[16] was condensed with 2-methyl-2-thiopseudourea to yield XIII. When XIII was treated with phosphorus oxychloride, it gave the 4-chloropyrimidine (XIV). When XIV was treated with ammonia, reaction took place with the carbethoxy group and not at the 4-position (XVI). This is in contrast to the behavior of the 4-chloro-5-carbethoxypyrimidines (I, IV, VI), where, under mild conditions, ammonia, amines, and hydrazine react at the 4-position. However, when XIV was treated with aniline under more vigorous conditions, substitution took place exclusively at the 4-position to give XV.

2-Methylsulfonyl-4-amino-5-carbethoxypyrimidine (XVIII) was readily converted to XIX by treatment with concentrated ammonium hydroxide at room temperature. Compound XIX was first prepared by Sprague and Johnson[17] from the corresponding 2-ethylsulfonylpyrimidine and alcoholic ammonia in a sealed tube. Compound XVIII was prepared from 2-methylthio-4-amino-5-carbethoxypyrimidine, (IIa) which, in turn, was prepared by the treatment of I in ethanol with concen-

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TABLE I

2-METHYLTHIO-4-R-5-CARBETHOXYPYRIMIDINES

R	Method of Isolation	Yield, %	M.P.°, Crude Material	M.P.°, Recryst. Material	Empirical Formula	% Nitrogen		% Carbon		% Hydrogen	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3NH	[a]	93	91–93	93–94	$C_9H_{12}N_3O_2S$	18.49	18.73	47.56	47.75	5.76	5.85
$CH_2{=}CH{-}CH_2NH$	D	95	[b]	44–45	$C_{11}H_{15}N_3O_2S$	16.59	16.22				
t-C_4H_9NH[c]	B	90	[b]	63–64	$C_{12}H_{19}N_3O_2S$	15.60	15.25				
Morpholino	B	90	82–83	83–84	$C_{12}H_{17}N_3O_3S$	14.83	14.52				
Piperidino	B	93	[b]	64–65	$C_{13}H_{19}N_3O_2S$	14.93	14.75				
Furfurylamino[d]	C	[b]	[b]	56–57	$C_{13}H_{15}N_3O_3S$	14.32	14.75				
$C_6H_5CH_2NH$	B	[b]	[b]	68–69	$C_{15}H_{17}N_3O_2S$	13.85	13.90	59.38	58.83	5.65	5.68
o-$ClC_6H_4CH_2NH$	A	86	[b]	86–87	$C_{15}H_{16}ClN_3O_2S$	12.44	12.31				
2,4-$Cl_2C_6H_3CH_2NH$	A	85	90–94	98–100	$C_{15}H_{15}Cl_2N_3O_2S$	11.29	11.11				
$HOCH_2CH_2NH$	B[e]	92	[b]	158–160	$C_{10}H_{15}N_3O_3S$	16.33	16.06	46.67	46.29	5.88	5.59
$(COOC_2H_5)_2CHNH$[f]	B	90	60–62	64–66	$C_{15}H_{21}N_3O_6S$	11.31	11.82	48.50	48.51	5.70	5.45
N-$CH_3C_6H_5N$	B	83	71–72	74–75	$C_{15}H_{17}N_3O_2S$	13.85	14.17				
N-$C_2H_5C_6H_5N$	B	79	91–94	96–97	$C_{16}H_{19}N_3O_2S$	13.24	13.10				
o-$NH_2C_6H_4NH$	[g]	80	[b]	123–124	$C_{14}H_{16}N_4O_2S$	18.41	18.25	55.24	54.92	5.30	4.99
$C_6H_5CH_2CH_2NH$	D	88	[b]	45–49[h]	$C_{16}H_{19}N_3O_2S{\cdot}H_2O$	12.53	12.88	57.29	57.97	6.31	6.60
o-$CF_3C_6H_4NH$	A	90	[b]	103–104	$C_{15}H_{14}F_3N_3O_2S$	11.76	11.75	50.41	50.05	3.95	3.90
m-$CF_3C_6H_4NH$	A	90	[b]	97–98	$C_{15}H_{14}F_3N_3O_2S$	11.76	11.73	50.41	50.52	3.95	3.34
$(CH_3)_2NNCH_3$	B	95	[b]	92–93	$C_{11}H_{18}N_4O_2S$	20.72	20.71				

[a] Prepared by treatment of I in ethanol with aqueous methylamine. The precipitated product was filtered from the reaction mixture after a few hours. Compound IIa may also be prepared in this fashion from I and concentrated ammonium hydroxide. [b] Not determined. [c] t-Butylamine was kindly donated by the Monsanto Chemical Company. [d] The amine was distilled before use. [e] The ratio of amine to chloropyrimidine was 4.2:1. [f] The diethyl aminomalonate was kindly donated by Dr. William Garner. [g] Product collected directly from reaction mixture by filtration. [h] Monohydrate.

TABLE II

2-METHYLTHIO-4-R-5-CARBETHOXYPYRIMIDINES

R	M.P.°-B.P.	Empirical Formula	% Nitrogen		% Carbon		% Hydrogen		% Sulfur	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3S	86–88	$C_9H_{12}N_2O_2S_2$	11.47	11.43	44.24	44.42	4.95	5.05		
C_2H_5S	168/0.8 mm.	$C_{10}H_{14}N_2O_2S_2$	10.85	11.03	46.49	46.42	5.46	5.43	24.82	24.76
n-C_3H_7S	187/2.5 mm.	$C_{11}H_{16}N_2O_2S_2$	10.29	10.59	48.50	48.65	5.92	6.01	23.54	23.51
i-C_3H_7S	161/0.8 mm.	$C_{11}H_{16}N_2O_2S_2$	10.29	10.84	48.50	48.38	5.92	5.70	23.54	23.96
n-C_4H_9S	177/1.0 mm.	$C_{12}H_{18}N_2O_2S_2$	9.78	9.97	50.32	50.37	6.33	6.27	22.39	22.49
t-C_4H_9S	153/0.4 mm.	$C_{12}H_{18}N_2O_2S_2$	9.78	10.11	50.32	50.35	6.33	6.18		

trated ammonium hydroxide. Ulbricht and Price[6] prepared IIa by methylation of 2-mercapto-4-amino-5-carbethoxypyrimidine with methyl sulfate. The corresponding 4-methylaminopyrimidine, (II, R = CH_3) was prepared by treatment of I in ethanol with aqueous methylamine.

Treatment with hydrazine of the appropriate 2-methylthio-4-substituted 5-carbethoxypyrimidine led to XX, XXI, and XXII, respectively.

EXPERIMENTAL[18]

2-Methylthio-4-(substituted-amino)-5-carbethoxypyrimidines, (II), *Table I*. These compounds were prepared by treatment of 10 g. of I with 1 or 2 equivalents of the appropriate amine as was previously described.[7] The products were isolated by one of the following methods:

A. The reaction mixture was poured into 250 ml. of 5% hydrochloric acid and diluted to 1 l. with water. The precipitated product was collected and washed with water.

B. The reaction mixture was poured into 800–900 ml. of cold water. The resulting mixture, containing an oil or a precipitate, was placed in a refrigerator for several hours. The solid was then collected and washed with water.

C. The reaction mixture was poured into 800–900 ml. of water, and extracted with ether. The combined ether extracts were washed with water and dried. The residual solid was collected after evaporation of the ether.

D. Solvent ethanol was removed at room temperature by evaporation. Water or ice was then added to the residual oil or solid. Method B was then followed.

2-Methylthio-4-β-sulfoethylamino-5-pyrimidinecarboxylic acid dihydrate (IIb). A mixture of 10 g. (41 mmoles) of I, dissolved in approximately 50 ml. of acetone and 10 g. (68 mmoles) of the sodium salt of taurine was shaken at room temperature for 12 hr. After the solvent was removed by evaporation, the residue, in 75 ml. of water, was acidified with 10% hydrochloric acid. After standing in the cold for a short time, the precipitate was collected by filtration; yield, 5.2 g. (43%); m.p. 299–300°. The sample for analysis, m.p. 299–300°, was obtained by recrystallization from water.

Anal. Calcd. for $C_8H_{15}N_3O_7S_2$: C, 29.17; H, 4.59; N, 12.75; water, 10.9. Found: C, 29.23; H, 4.70; N, 12.95; water, 10.7; (determined by heating to constant weight at 180°).

2-Methylthio-4-alkylthio-5-carbethoxypyrimidines (III), *Table II*. The appropriate alkanethiol (60 mmoles) was added to a solution of 12 g. of sodium carbonate dissolved in 120 ml. of water. This mixture was then added to a solution of 13.9 g. (60 mmoles) of I in 210 ml. of ethanol. After 2 min., the reaction mixture was heated to boiling. After removal of most of the ethanol by evaporation at room temperature, the reaction mixture was diluted to 600 ml. with water. The inorganic salts dissolved and an oil separated. An exception was the 4-methylthiopyrimidine which precipitated at this point. It was collected by filtration, washed with a little water, and recrystallized from ethanol-water. In the other cases, the reaction mixture was extracted with ether. After drying and removal of ether, the yields of crude material were above 90%. The oils were purified by distillation.

The 4-*t*-butylthiopyrimidine could not be separated from the starting material, I, by this method. Instead, the crude oil, before the ether extraction, was washed with water to remove inorganic salts. It was then dissolved in 200 ml. of ethanol and 8 ml. of 40% aqueous methylamine was added. Thus, the contaminant I was converted to the acid-soluble 2-methylthio-4-methylamino-5-carbethoxypyrimidine. After 30 min., 100 ml. of 5% hydrochloric acid was added to the reaction mixture and the volume was brought up to 1 l. with water. The oil that separated at this point was dissolved in ether, washed with dilute hydrochloric acid, and then with water. The isolation of the product then proceeded as above.

2-Methyl-4-chloro-5-carbethoxypyrimidine, (IV). This was prepared by treatment of 2-methyl-4-hydroxy-5-carbethoxypyrimidine[19] with phosphorus oxychloride according to Todd and Bergel[13] with this modification: The 4-hydroxypyrimidine and phosphorus oxychloride were not refluxed but only heated slowly until solution had taken place (about 80° bath temperature). Phosphorus oxychloride was then removed under reduced pressure at 70° or less. The residual resinous mass was dissolved in chloroform. This solution, in turn, was treated with aqueous potassium carbonate until the aqueous layer remained basic. After drying and removal of the chloroform, the residue was distilled at 1 mm. or less, b.p. about 100°. (Andersag and Westphal[20] reported 110° at 4 mm.) Yield, 65%.

2-Methyl-4-(substituted-amino)-5-carbethoxypyrimidines, (V), *Table III*. To IV (1 to 7 g., 5 to 35 mmoles) dissolved in acetone (10 ml. of each gram of chloro compound) was added twice the calculated amount of the amines (dissolved in acetone in the case of solid amines). Unless the solution began to show evidence of reaction (heat evolution or formation of a precipitate) within a few minutes, a few drops of hydrochloric acid were added. After standing at ambient temperature for 2 to 10 hr., the reaction mixture, sometimes containing a precipitate, was poured into water (10 vol.). The resulting milky mixture was refrigerated for a few hours. The precipitated product was collected and washed until the wash water was no longer acid to litmus. The crude product was recrystallized from ethanol or ethanol-water, and decolorized with charcoal where necessary. The yields ranged from 60–90%.

2-Benzylthio-4-chloro-5-carbethoxypyrimidine, (VI). This was prepared by the procedure of Peters, *et al.*,[7] for the preparation of I. The overall yield was 63%, b.p. 206°

(18) All melting and boiling points are uncorrected. Microanalyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn, and several other commercial laboratories.

(19) A generous sample of this material was kindly donated by Dr. K. Pfister of Merck, Sharp and Dohme, Inc.

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TABLE III

2-METHYL-4-R-5-CARBETHOXYPYRIMIDINES

R	M.P.°, Crude	M.P.°, Recryst.	Empirical Formula	% Nitrogen Calcd.	% Nitrogen Found	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found
C_6H_5NH	83–86	85–86	$C_{14}H_{15}N_3O_2$	16.33	16.38	65.35	65.35	5.88	5.80
o-ClC_6H_4NH	97–99	98–99	$C_{14}H_{14}ClN_3O_2$	14.40	14.71	57.63	58.15	4.84	4.87
o-BrC_6H_4NH	108–109	110–111	$C_{14}H_{14}BrN_3O_2$	12.50	12.85	50.01	50.40	4.20	4.24
o-FC_6H_4NH	87–89	92–93	$C_{14}H_{14}FN_3O_2$	15.26	15.32				
o-IC_6H_4NH	95–97	97–98	$C_{14}H_{14}IN_3O_2$	10.97	11.31				
o-$CH_3C_6H_4NH$	95–97	92–93[a] 97–98	$C_{15}H_{17}N_3O_2$	15.49	15.49				
2,6-$(CH_3)_2C_6H_3NH$	93–94	96–97	$C_{16}H_{19}N_3O_2S$	14.73	14.52				
$C_6H_5CH_2NH$	69–71	70–71	$C_{15}H_{17}N_3O_2$	15.49	14.96				
Furfurylamino	56–58	58–60	$C_{13}H_{15}N_3O_3$	16.08	16.38				

[a] Apparent change of crystal habit.

at 1 mm. (lit.:[14] 32% on a comparable basis, b.p. 248° at 11 mm.).

2-Benzylthio-4-anilino and 2-benzylthio-4-o-chloroanilino-5-carbethoxypyrimidine, (VII). These were prepared by treatment of aniline and *o*-chloroaniline, respectively, with distilled VI. A mixture of ethanol and acetone was used as solvent. The remainder of the procedure followed that used for the 2-methylthio-4-(substituted-anilino)pyrimidines, (Method B). Yields were over 90%. The compounds were recrystallized from ethanol-water.

2-Benzylthio-4-anilino-5-carbethoxypyrimidine melted at 76–77°.

Anal. Calcd. for $C_{20}H_{19}N_3O_2S$: C, 65.73; H, 5.24; N, 11.50. Found: C, 65.66; H, 5.46; N, 11.22.

2-Benzylthio-4-o-chloroanilino-5-carbethoxypyrimidine melted at 91–92°.

Anal. Calcd. for $C_{20}H_{18}ClN_3O_2S$: C, 60.07; H, 4.54; N, 10.51. Found: C, 60.48; H, 4.88; N, 10.11.

2-Chloro-4-(substituted-anilino)-5-carbethoxypyrimidines, (IX). To 2.21 g. (10.0 mmoles) of VIII, prepared by the method of Dornow and Petsch,[15] dissolved in 25 ml. of ethanol and cooled to 0°, an equimolar quantity of the proper aniline, dissolved in 25 ml. of ethanol was added over a period of 30 min. The reaction mixture was allowed to warm to room temperature, and then was poured into a large excess of water. The precipitated product was collected by filtration, washed with water, and dried. Yields ranged from 60–80%. The analytical samples were recrystallized from ethanol or ethanol-water.

2-Chloro-4-o-chloroanilino-5-carbethoxypyrimidine, (IXa) melted at 142–143°.

Anal. Calcd. for $C_{13}H_{11}Cl_2N_3O_2$: C, 50.02; H, 3.55; N, 13.46. Found: C, 49.91; H, 3.84; N, 13.59.

2-Chloro-4-o-bromoanilino-5-carbethoxypyrimidine melted at 154–155°.

Anal. Calcd. for $C_{13}H_{11}BrClN_3O_2$: C, 43.78; H, 3.11; N, 11.78. Found: C, 44.18; H, 2.86; N, 12.22.

2-Chloro-4-o-iodoanilino-5-carbethoxypyrimidine melted at 158–159°.

Anal. Calcd. for $C_{13}H_{11}ClIN_3O_2$: C, 38.68; H, 2.75; N, 10.41. Found: C, 38.48; H, 2.69; N, 10.30.

In attempts to prepare the 4-anilino- and the 4-*o*-fluoroanilinopyrimidines, the above method yielded products contaminated with substantial quantities of the 2,4-diarylaminopyrimidines. Recrystallization from several solvents gave no pure monoanilinopyrimidines.

2,4-Dianilino-5-carbethoxypyrimidine, (X) was obtained by treating VIII with 2 equivalents of aniline at room temperature and isolating the product as described above; yield, 86%; recrystallized from ethanol-water, m.p. 187–188°.

Anal. Calcd. for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43. Found: C, 68.00; H, 5.28.

2-Methylthio-4-o-chloroanilino-5-carbethoxypyrimidine was prepared from IXa and methanethiol as described above for the conversion of I to 2,4-dimethylthio-5-carbethoxypyrimidine. Melting point and mixed melting point showed that the product was identical with 2-methylthio-4-*o*-chloroanilino-5-carbethoxypyrimidine.

2-Methyl- and 2-methylthio-4-(substituted-amino)-5-hydroxymethylpyrimidines, (XI and XII), *Table IV*. The lithium aluminum hydride reductions were performed in the usual manner in ether or tetrahydrofuran. The crude 5-hydroxymethylpyrimidines were occasionally contaminated by sizable amounts of starting material and considerable product was lost during numerous recrystallizations. Yields of the pure products ranged from 30–55%.

2-Methylthio-4-hydroxy-5-pyrimidineacetic acid, ethyl ester, (XIII) was prepared by the method used by Johnson and Speh[16] for the 2-ethylthio analog, m.p. 188–189°.

Anal. Calcd. for $C_9H_{12}N_2O_3S$: C, 47.35; H, 5.30; N, 12.27. Found: C, 47.47; H, 5.77; N, 12.50.

2-Methylthio-4-chloro-5-pyrimidineacetic acid, ethyl ester, (XIV). A mixture of 20 g. (88 mmoles) of dry XII and 60 ml. of phosphorus oxychloride was allowed to stand at room temperature until all of the pyrimidine had dissolved (about 1.5 hr.). After all the phosphorus oxychloride had been removed under reduced pressure, the chloropyrimidine could be distilled directly at 148–149° at 1 mm. A more satisfactory procedure consisted of adding water to the viscous residue and chilling the resulting mixture. The precipitated chloropyrimidine was then collected, dried, and distilled; yield of distilled material, 17.1 g. (79%). The analytical sample was obtained by recrystallization from ethanol-water, m.p. 38–39°.

Anal. Calcd. for $C_9H_{11}ClN_2O_2S$: C, 43.81; H, 4.38; N, 11.36. Found: C, 43.93; H, 4.47; N, 11.29.

Ethyl 2-methylthio-4-anilino-5-pyrimidineacetate, (XV). A mixture of 0.5 g. (2 mmoles) of XIV, 0.2 g. (2 mmoles) of aniline, and 3 drops of 2% hydrochloric acid in 15 ml. of acetone, was refluxed for 1 hr. Evaporation of the solvent under reduced pressure and trituration of the residue with water gave a near-white solid. Recrystallization from ethanol gave 0.4 g. (66%) of glistening, white plates, m.p. 100–101°.

Anal. Calcd. for $C_{15}H_{17}N_3O_2S$: C, 59.38; H, 5.65; N, 13.85. Found: C, 59.52; H, 5.51; N, 13.94.

2-Methylthio-4-chloro-5-pyrimidineacetamide, (XVI). A suspension of XIV, 2.0 g. (8.1 mmoles), in 25 ml. of concd. ammonium hydroxide was shaken continuously for 12 hr. The solvent was removed by evaporation under reduced pressure. The residue, after trituration with water, was recrystallized from ethanol; yield, 1.5 g. (79%), m.p. 167–169°. A second recrystallization gave the sample for analysis, m.p. 168–170°.

Anal. Calcd. for $C_7H_8ClN_3OS$: C, 38.62; H, 3.70; N, 19.30. Found: C, 39.05; H, 4.08; N, 18.84.

2-Methylthio-4-hydroxy-5-pyrimidineacetic acid hydrazide, (XVII). A mixture of 10 g. (44 mmoles) of XII and 2.2 g.

TABLE IV

2-R_1-4-R_2-5-HYDROXYMETHYLPYRIMIDINES

R_1	R_2	M.P.°	Recryst. Solvent	Empirical Formula	% Nitrogen		% Carbon		% Hydrogen	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3	C_6H_5NH	132–133	C_2H_5OH—H_2O	$C_{12}H_{13}N_3O$	19.52	19.75	66.96	66.98	6.09	6.36
CH_3	*o*-ClC_6H_4NH	143–144	C_2H_5OAc	$C_{12}H_{12}ClN_3O$	16.83	16.65	57.71	58.03	4.85	4.84
CH_3S	*p*-ClC_6H_4NH	200–201	C_2H_5OH—H_2O	$C_{12}H_{12}ClN_3OS$	14.91	14.60	51.15	51.37	4.29	4.48
CH_3S	*p*-BrC_6H_4NH	202–204	C_2H_5OH—H_2O	$C_{12}H_{12}BrN_3OS$	12.88	12.80	44.18	44.21	3.71	4.01
CH_3S	*o*-ClC_6H_4NH	138–140	C_2H_5OAc	$C_{12}H_{12}ClN_3OS$	14.91	14.95	51.15	51.47	4.29	4.23
CH_3S	*o*-BrC_6H_4NH	143–145	C_2H_5OAc	$C_{12}H_{12}BrN_3OS$	12.88	12.89	44.18	44.42	3.71	3.57
CH_3S	Furfurylamino	149–150	C_2H_5OH—H_2O	$C_{11}H_{13}N_3O_2S$	16.72	16.30	52.57	52.32	5.21	5.11

(68 mmoles) of hydrazine in 350 ml. of absolute ethanol was refluxed for 2 hr. The solution was allowed to stand overnight and the near-white precipitate was collected by filtration. Cooling the filtrate to 0° gave a second crop of crystals. Recrystallization from approximately 85% ethanol yielded 6.0 g. (64%) of white crystals, m.p. 208–210° dec. A second recrystallization gave the sample for analysis, m.p. 209–210° dec.

Anal. Calcd. for $C_7H_{10}N_4O_2S$: N, 26.15. Found: N, 26.39.

2-Methylsulfonyl-4-amino-5-carbethoxypyrimidine (XVIII). Five grams of IIa dissolved in 250 ml. of 5% hydrochloric acid was cooled to 0–2°. Chlorine was passed in rapidly for 20 min. The mixture was treated with sodium bisulfite solution, filtered, and the precipitate was washed successively with water, sodium bisulfite, water, 95% ethanol, and absolute ethanol. The yield of crude product was 5.7 g. The analytical sample was recrystallized from absolute ethanol, m.p. 163–164°.

Anal. Calcd. for $C_8H_{11}N_3O_4S$: C, 39.17; H, 4.52; N, 17.13; S, 13.07. Found: C, 39.16; H, 4.59; N, 17.28; S, 13.00.

2,4-Diamino-5-carbethoxypyrimidine, (XIX). Crude damp XVIII prepared from 5 g. of IIa was immediately triturated under 150 ml. of concd. ammonium hydroxide, until the yellow color which initially formed, had disappeared. The mixture was allowed to stand 1 hr. The precipitate was filtered and washed with water and cold ethanol to give 3.5 g. (83%) of XIX. The analytical sample was recrystallized from alcohol; m.p. 206°, (lit.,[15] m.p. 207°).

Anal. Calcd. for $C_7H_{10}N_4O_2$: N, 30.75. Found: N, 30.81, 31.07.

2-Hydrazino-4-o-chloroanilino-5-carbethoxypyrimidine, (XX). A suspension of 10 g. (31 mmoles) of 2-methylthio-4-*o*-chloroanilino-5-carbethoxypyrimidine[7] in 30 ml. of ethanol and 10 ml. of hydrazine was heated on a steam bath for 15 min. The starting material went into solution and the product precipitated. After cooling, the precipitate was collected by filtration and recrystallized from ethanol; yield, 7.1 g. (74%), m.p. 180–182°. (There was some ethanol-insoluble material, presumed to be the acid hydrazide.)

Anal. Calcd. for $C_{13}H_{14}ClN_5O_2$: C, 50.73; H, 4.58; N, 22.76. Found: C, 50.23; H, 4.29; N, 22.90.

2-Hydrazino-4-hydroxy-5-carbethoxypyrimidine, (XXI). A solution of 10 g. (47 mmoles) of 2-methylthio-4-hydroxy-5-carbethoxypyrimidine[21] in 500 ml. of hot absolute ethanol and 3 ml. of hydrazine was refluxed for 3 hr. and allowed to stand overnight at room temperature. The solvent was removed by evaporation under reduced pressure and the residue was recrystallized from ethanol-water; yield, 6.1 g. (66%), m.p. 237° (gradual dec.).

Anal. Calcd. for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.93; H, 5.18; N, 28.57.

2-Hydrazino-4-amino-5-pyrimidinecarboxylic acid hydrazide, (XXII). A suspension of 12 g. (56 mmoles) of IIa in 30 ml. of water and 15 ml. of hydrazine was heated on a steam bath for 1 hr. After cooling, the precipitate was collected and extracted with hot benzene. The residue was recrystallized from ethanol-water; yield, 8.7 g. (85%), tan crystals, m.p. 247–248°.

Anal. Calcd. for $C_5H_9N_7O$: C, 32.78; H, 4.95; N, 53.53. Found: C, 32.58; H, 5.23; N, 54.78.

Less of the desired product and more of the benzene-soluble material, probably 2-hydrazino-4-amino-5-carbethoxypyrimidine, was formed when the period of heating was shortened.

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