

**Trifluoromethylglyoxal Bis(guanyldiazone) Sulfate. A.**—An aqueous solution of dibromomethyl trifluoromethyl ketone<sup>8</sup> and aminoguanidine sulfate<sup>9</sup> (in the ratio of 1:2) was refluxed for 5–15 hr. On cooling, the separated solid was filtered and recrystallized from water. Yields generally were in the range of 40–70%. The product, which decomposed at *ca.* 240° and had a characteristic ultraviolet absorption maximum of 304 m $\mu$  at pH 1, failed to yield a satisfactory analysis. (Typical analysis: C, 18.1; H, 3.78; N, 31.8.)

**B.**—A mixture of 111 g. of selenium dioxide, 600 ml. of dioxane, 20 ml. of glacial acetic acid, and 20 ml. of water was warmed on a steam bath for 3 hr. and cooled to room temperature. To the stirred suspension was added 112 g. of trifluoroacetone in one portion and the reaction mixture refluxed with stirring for 5 hr. The liquid was separated by filtration and the solid was washed with two 75-ml. portions of water. The combined filtrate and washings were distilled at atmospheric pressure to a volume of about 350 ml. The liquid was decanted from a slight amount of precipitated selenium and the volume was adjusted to about 500 ml. by addition of water. Lead acetate solution (25%) was added in slight excess. The lead selenite was removed by filtration and the filtrate was saturated with hydrogen sulfide to remove all traces of lead. Approximately 20 g. of activated charcoal was added. The mixture was warmed to about 40°, filtered with suction, and the colorless filtrate concentrated to about 300 ml. This concentrate was added dropwise to a 500-ml. stirred solution of 2 moles of aminoguanidine sulfate in water (prepared from 274 g. of aminoguanidine bicarbonate and 98 g. of sulfuric acid). The resulting turbid solution was refluxed for 3 hr. and stirred at room temperature for 48 hr. The yellow solid which separated (38 g.) decomposed at *ca.* 242°. Concentration of the filtrate yielded an additional 45 g. After recrystallization from water, it melted at 244–246° dec.,  $\lambda_{\text{max}}^{\text{UV}}$  304 m $\mu$  ( $\epsilon$  16,600),  $\lambda_{\text{max}}^{\text{IR}}$  349 m $\mu$  ( $\epsilon$  26,900).

*Anal.* Calcd. for C<sub>3</sub>H<sub>9</sub>F<sub>3</sub>N<sub>3</sub>·H<sub>2</sub>SO<sub>4</sub>·H<sub>2</sub>O: C, 17.0; H, 3.67; N, 31.6. Found: C, 17.3; H, 3.69; N, 31.9.

**Trifluoromethylglyoxal Bis(guanyldiazone) (II).**—A suspension of trifluoromethylglyoxal bis(guanyldiazone) sulfate in water was carefully neutralized with dilute sodium hydroxide at room temperature, and the resultant solution was extracted several times with butanol. The butanol extract was evaporated *in vacuo* to yield a yellow solid which, after recrystallization from a mixture of 2-propanol and heptane, gave II, m.p. 210° dec.,  $\lambda_{\text{max}}^{\text{UV}}$  304 m $\mu$  ( $\epsilon$  18,700),  $\lambda_{\text{max}}^{\text{IR}}$  348 m $\mu$  ( $\epsilon$  21,400).

*Anal.* Calcd. for C<sub>3</sub>H<sub>9</sub>F<sub>3</sub>N<sub>3</sub>: C, 25.2; H, 3.78; N, 47.1. Found: C, 25.5; H, 4.20; N, 47.0.

**1,1,1-Trifluoroacetone Guanyldiazone Hemisulfate.**—To a solution of aminoguanidine sulfate, prepared from 40.5 g. (0.30 mole) of aminoguanidine bicarbonate and 15.0 g. (0.153 mole) of sulfuric acid in 200 ml. of water was added at room temperature, 33.6 g. (0.30 mole) of 1,1,1-trifluoroacetone. The reaction mixture was stirred at room temperature for 2 hr., then warmed on a steam bath for 3 hr. Addition of approximately 20 ml. of absolute ethanol to the cooled solution caused immediate precipitation of a white solid which was isolated by filtration. The product (almost quantitative yield) was washed with a small quantity of cold absolute ethanol and dried, m.p. 190–191° (analyzed without further purification),  $\lambda_{\text{max}}^{\text{UV}}$  226 m $\mu$  ( $\epsilon$  15,800),  $\lambda_{\text{max}}^{\text{IR}}$  248 m $\mu$  ( $\epsilon$  15,900).

*Anal.* Calcd. for C<sub>4</sub>H<sub>7</sub>F<sub>3</sub>N<sub>3</sub>·0.5H<sub>2</sub>SO<sub>4</sub>: C, 22.1; H, 3.69; N, 25.8. Found: C, 22.1; H, 4.10; N, 25.9.

**1,2-Bis(guanidinoamino)propane Sulfate. A.**—A suspension of 25.7 g. (0.1 mole) of methylglyoxal bis(guanyldiazone) dichloride monohydrate in 250 ml. of 60% acetic acid containing 0.1 g. of platinum oxide was hydrogenated at 4.22 kg./cm.<sup>2</sup> for 24 hr. during which time the reaction vessel was intermittently warmed to about 50°. The theoretical amount of hydrogen was consumed. The catalyst was removed and the filtrate was evaporated *in vacuo* to give a very hygroscopic solid to which was added 100 ml. of water and 31.1 g. of silver sulfate. The mixture was shaken for 2 hr. and filtered to remove the silver chloride. Ethanol was added to the warmed filtrate until turbid, and the solution was allowed to cool slowly. The product, which failed to absorb in the ultraviolet region, was recrystallized from a mixture of water and methanol to give 10 g. of white solid, m.p. 290° dec.

*Anal.* Calcd. for C<sub>3</sub>H<sub>16</sub>N<sub>8</sub>·H<sub>2</sub>SO<sub>4</sub>: C, 21.0; H, 6.30; N, 39.2. Found: C, 21.2; H, 6.76; N, 39.6.

**B.**—A suspension of 15 g. of methylglyoxal bis(guanyldiazone) sulfate in 200 ml. of 50% acetic acid containing 1 g. of

platinum oxide was hydrogenated at 65° and 4.22 kg./cm.<sup>2</sup>. During 3 hr. the calculated amount of hydrogen was consumed. The warm solution was filtered, and the filtrate was evaporated to dryness *in vacuo*. Recrystallization of the residue from water yielded 11.5 g. (74% yield) of a white solid which decomposed rapidly at 299° with evolution of gas. The infrared absorption spectra of the products prepared by both methods were identical.

*Anal.* Calcd. for C<sub>3</sub>H<sub>16</sub>N<sub>8</sub>·H<sub>2</sub>SO<sub>4</sub>: N, 39.2. Found: N, 39.2.

**Acknowledgment.**—The authors wish to express their appreciation to Dr. James J. Downs for the n.m.r. interpretations; to Mr. Hal P. Van Fossen, Mrs. Margaret L. Rounds, and Mr. John R. Gravatt for their analytical and instrumental measurements; and to Dr. Jack D. Davidson for his continued interest and advice.

## Pyrimidines. IV. 2-, 5-, and 2,5-Substituted Chloropyrimidines

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Received June 1, 1964

In our studies on ring-polychlorinated pyrimidines, it became desirable to prepare a number of analogs with substituents in the 2-, 5-, and 2,5-positions.

The preparation of the 2-substituted 4,6-pyrimidinediols and the corresponding dichloropyrimidines (CH<sub>3</sub>,<sup>2</sup> C<sub>2</sub>H<sub>5</sub>,<sup>3,4</sup> C<sub>3</sub>H<sub>7</sub>,<sup>5</sup> and C<sub>6</sub>H<sub>5</sub><sup>6</sup>) has been reported. Of the corresponding 4,5,6-trichloropyrimidines, only the 2-methyl and 2-chloromethyl analogs are known.<sup>7</sup> In the 5-substituted barbituric acid and 2,4,6-trichloropyrimidine series, the methyl,<sup>8</sup> bromomethyl,<sup>7,9</sup> ethyl,<sup>10</sup> *sec*-butyl,<sup>11</sup> and phenyl<sup>12,13</sup> derivatives are also known. 5-Propyl- and 5-isopropylbarbituric acids had also been reported.<sup>14</sup>

In this study ten additional ring-polychlorinated pyrimidines and the necessary intermediates will be described. Scheme I indicates the synthetic sequence employed.

The appropriate amidine or urea was condensed with the corresponding ethyl malonate in the presence of sodium ethoxide to form a 4,6-pyrimidinediol (I), which was then treated with phosphorus oxychloride, phosphorus oxychloride-dimethylaniline, or phosphorus oxychloride-pentachloride to yield II. Compounds of IIi and IIj were converted to the 5-bromo-

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(2) J. Baddiley, B. Lythgoe, D. McNeil, and A. R. Todd, *J. Chem. Soc.*, 383 (1943).

(3) W. Huber and H. A. Hölcher, *Ber.*, **71B**, 87 (1938).

(4) H. R. Henze and J. L. McPherson, *J. Org. Chem.*, **18**, 653 (1953).

(5) H. R. Henze and S. O. Wintrop, *J. Am. Chem. Soc.*, **79**, 2230 (1957).

(6) J. A. Hendry and R. F. Hower, *J. Chem. Soc.*, 328 (1952).

(7) H. Gershon, K. Dittmer, and R. Braun, *J. Org. Chem.*, **26**, 1874 (1961).

(8) O. Gerngross, *Ber.*, **38**, 3394 (1905).

(9) M. Hasegawa, *Pharm. Bull. (Tokyo)*, **1**, 387 (1953); *Chem. Abstr.*, **49**, 10970 (1955).

(10) A. v. Merkatz, *Ber.*, **52B**, 869 (1919).

(11) A. W. Dox, *J. Am. Chem. Soc.*, **53**, 1559 (1931).

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

(13) J. B. Dickey and J. G. McNally, U. S. Patent 2,578,290 (1951).

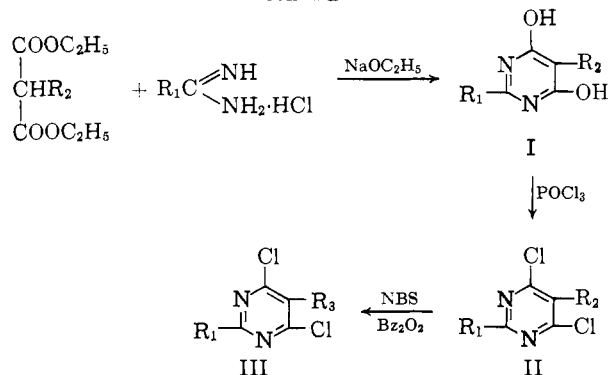
(14) H. E. Volwiler, *J. Am. Chem. Soc.*, **47**, 2236 (1925).

TABLE I  
 2-, 5-, AND 2,5-SUBSTITUTED PYRIMIDINES

Compd.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Yield, %	B.p. (mm.) or m.p., °C. <sup>a</sup>	Formula	Calcd., %		Found, %	
								N	Cl	N	Cl
Ic <sup>b,c</sup>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	HO	H	HO	24.5	296-297 dec.	C <sub>7</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub> <sup>d</sup>	18.17		18.11	
Id <sup>e</sup>	C <sub>2</sub> H <sub>5</sub>	HO	Cl	HO	62.0	318-319 dec.	C <sub>6</sub> H <sub>7</sub> ClN <sub>2</sub> O <sub>2</sub>	16.05	20.31	16.17	20.59
Ie <sup>e</sup>	C <sub>3</sub> H <sub>7</sub>	HO	Cl	HO	38.8	294 dec.	C <sub>7</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>2</sub>	14.86	18.80	14.81	18.40
If <sup>e</sup>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	HO	Cl	HO	69.8	>365	C <sub>7</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>2</sub>	14.86	18.80	14.37	18.96
Ig <sup>e</sup>	C <sub>17</sub> H <sub>35</sub>	HO	Cl	HO	31.2	285 dec.	C <sub>21</sub> H <sub>37</sub> ClN <sub>2</sub> O <sub>2</sub>	7.28	9.21	7.15	9.39
Ih <sup>e</sup>	C <sub>6</sub> H <sub>5</sub>	HO	Cl	HO	58.5	329-330 dec.	C <sub>10</sub> H <sub>7</sub> ClN <sub>2</sub> O <sub>2</sub>	12.58	15.93	13.05	15.69
Ij	HOCH <sub>2</sub>	HO	CH <sub>3</sub>	HO	59.0	289 dec.	C <sub>6</sub> H <sub>8</sub> N <sub>2</sub> O <sub>3</sub> <sup>f</sup>	17.94		17.66	
In <sup>g</sup>	HO	HO	C <sub>17</sub> H <sub>35</sub>	HO	95.0	186-189	C <sub>21</sub> H <sub>38</sub> N <sub>2</sub> O <sub>3</sub> <sup>h</sup>	7.64		7.37	
IIc <sup>i</sup>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	Cl	H	Cl	85.0	47-48 (0.6)	C <sub>7</sub> H <sub>9</sub> Cl <sub>2</sub> N <sub>2</sub>	14.66	37.11	14.35	37.52
IIId <sup>i</sup>	C <sub>2</sub> H <sub>5</sub>	Cl	Cl	Cl	84.9	45 (0.2)	C <sub>6</sub> H <sub>5</sub> Cl <sub>3</sub> N <sub>2</sub>	13.25	50.31	13.68	50.10
IIe <sup>j</sup>	C <sub>3</sub> H <sub>7</sub>	Cl	Cl	Cl	79.5	65 (0.75)	C <sub>7</sub> H <sub>7</sub> Cl <sub>3</sub> N <sub>2</sub>	12.43	47.18	12.74	47.29
IIIf <sup>j</sup>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	Cl	Cl	Cl	96.5	38.5-39.5	C <sub>7</sub> H <sub>7</sub> Cl <sub>3</sub> N <sub>2</sub>	12.43	47.18	12.72	47.42
IIg <sup>j</sup>	C <sub>17</sub> H <sub>35</sub>	Cl	Cl	Cl	85.8	55	C <sub>21</sub> H <sub>35</sub> Cl <sub>3</sub> N <sub>2</sub>	6.64	25.21	6.50	25.02
IIh <sup>j</sup>	C <sub>6</sub> H <sub>5</sub>	Cl	Cl	Cl	69.5	125-126	C <sub>10</sub> H <sub>5</sub> Cl <sub>3</sub> N <sub>2</sub>	10.79	40.98	10.73	40.69
IIj <sup>k</sup>	ClCH <sub>2</sub>	Cl	CH <sub>3</sub>	Cl	66.3	39.5-40.5	C <sub>6</sub> H <sub>5</sub> Cl <sub>3</sub> N <sub>2</sub>	13.25	50.30	13.63	50.06
III <sup>i</sup>	Cl	Cl	C <sub>3</sub> H <sub>7</sub>	Cl	74.2	30-32	C <sub>7</sub> H <sub>7</sub> Cl <sub>3</sub> N <sub>2</sub>	12.43	47.18	12.64	47.00
IIIm <sup>i</sup>	Cl	Cl	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	Cl	77.2	69-71	C <sub>7</sub> H <sub>7</sub> Cl <sub>3</sub> N <sub>2</sub>	12.43	47.18	12.58	46.71
IIIj	ClCH <sub>2</sub>	Cl	BrCH <sub>2</sub>	Cl	10.0	127-129	C <sub>6</sub> H <sub>4</sub> Cl <sub>3</sub> N <sub>2</sub> Br <sup>l</sup>	9.65		9.95	

<sup>a</sup> Analytical sample. <sup>b</sup> Recrystallized from isopropyl alcohol. <sup>c</sup> Compound mentioned but not described, ref. 13. <sup>d</sup> Anal. Calcd.: C, 54.53; H, 6.54. Found: C, 54.80; H, 6.83. <sup>e</sup> Recrystallized from dimethylformamide. <sup>f</sup> Anal. Calcd.: C, 46.15; H, 5.16. Found: C, 46.41; H, 5.18. <sup>g</sup> Recrystallized from methanol. <sup>h</sup> Anal. Calcd.: C, 68.81; H, 10.45. Found: C, 68.82; H, 10.49. <sup>i</sup> POCl<sub>3</sub> used to replace OH with Cl. <sup>j</sup> POCl<sub>3</sub> + dimethylaniline used to replace OH with Cl. <sup>k</sup> POCl<sub>3</sub> + PCl<sub>5</sub> used to replace OH with Cl. <sup>l</sup> Anal. Calcd.: C, 24.82; H, 1.39. Found: C, 25.11; H, 1.82.

SCHEME I



Ia, IIa,	R <sub>1</sub> = C <sub>2</sub> H <sub>5</sub> ; R <sub>2</sub> = H	Ik,	R <sub>1</sub> = HO; R <sub>2</sub> = C <sub>2</sub> H <sub>5</sub>
Ib, IIb,	R <sub>1</sub> = C <sub>3</sub> H <sub>7</sub> ; R <sub>2</sub> = H	Il,	R <sub>1</sub> = HO; R <sub>2</sub> = C <sub>3</sub> H <sub>7</sub>
Ic, IIc,	R <sub>1</sub> = <i>i</i> -C <sub>3</sub> H <sub>7</sub> ; R <sub>2</sub> = H	Im,	R <sub>1</sub> = HO; R <sub>2</sub> = <i>i</i> -C <sub>3</sub> H <sub>7</sub>
Id, IId,	R <sub>1</sub> = C <sub>2</sub> H <sub>5</sub> ; R <sub>2</sub> = Cl	In,	R <sub>1</sub> = HO; R <sub>2</sub> = C <sub>17</sub> H <sub>35</sub>
Ie, IIe,	R <sub>1</sub> = C <sub>3</sub> H <sub>7</sub> ; R <sub>2</sub> = Cl	Io,	R <sub>1</sub> = HO; R <sub>2</sub> = C <sub>6</sub> H <sub>5</sub>
If, IIIf,	R <sub>1</sub> = <i>i</i> -C <sub>3</sub> H <sub>7</sub> ; R <sub>2</sub> = Cl	Iik,	R <sub>1</sub> = Cl; R <sub>2</sub> = C <sub>2</sub> H <sub>5</sub>
Ig, IIg,	R <sub>1</sub> = C <sub>17</sub> H <sub>35</sub> ; R <sub>2</sub> = Cl	III,	R <sub>1</sub> = Cl; R <sub>2</sub> = C <sub>3</sub> H <sub>7</sub>
Ih, IIh,	R <sub>1</sub> = C <sub>6</sub> H <sub>5</sub> ; R <sub>2</sub> = Cl	IIIm,	R <sub>1</sub> = Cl; R <sub>2</sub> = <i>i</i> -C <sub>3</sub> H <sub>7</sub>
Ii, IIi,	R <sub>1</sub> = CH <sub>3</sub> ; R <sub>2</sub> = CH <sub>3</sub>	IIo,	R <sub>1</sub> = Cl; R <sub>2</sub> = C <sub>6</sub> H <sub>5</sub>
Ij,	R <sub>1</sub> = HOCH <sub>2</sub> ; R <sub>2</sub> = CH <sub>3</sub>	IIIi,	R <sub>1</sub> = CH <sub>3</sub> ; R <sub>3</sub> = BrCH <sub>2</sub>
IIj,	R <sub>1</sub> = ClCH <sub>2</sub> ; R <sub>2</sub> = CH <sub>3</sub>	IIIj,	R <sub>1</sub> = ClCH <sub>2</sub> ; R <sub>3</sub> = BrCH <sub>2</sub>

methyl derivatives (IIIi and IIIj) by treatment with N-bromosuccinimide (NBS) in the presence of benzoyl peroxide (Bz<sub>2</sub>O<sub>2</sub>). It had been established previously,<sup>7</sup> that bromination of the methyl group in the 5-position of the pyrimidine ring with NBS in the presence of Bz<sub>2</sub>O<sub>2</sub> was nearly quantitative, whereas, the methyl group in the 2-position was not at all brominated.

The amidines were prepared by modifications of the methods of Pinner,<sup>15</sup> and in the case of benzamidine hydrochloride, since a hydrated product was reported, a method was devised to prepare the anhydrous com-

TABLE II

ULTRAVIOLET DATA FOR RING-POLYCHLORINATED PYRIMIDINES

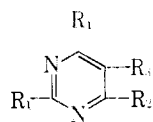
Pyrimidine	Method of prepn. (lit. ref.)	Spectral data λ <sub>max</sub> <sup>CH<sub>3</sub>OH</sup>	log ε
4,6-Dichloro-2-ethyl-	3	257	3.68
4,6-Dichloro-2-propyl-	5	257	3.68
4,6-Dichloro-2-isopropyl-		254	3.66
2-Ethyl-4,5,6-trichloro-		270	3.73
2-Propyl-4,5,6-trichloro-		268	3.74
2-Isopropyl-4,5,6-trichloro-		268	3.73
2-Heptadecyl-4,5,6-trichloro-		270	3.68
2-Phenyl-4,5,6-trichloro-		275	4.52
5-Ethyl-2,4,6-trichloro-	10	268	3.77
5-Propyl-2,4,6-trichloro-		268	3.77
5-Isopropyl-2,4,6-trichloro-		268	3.75
5-Phenyl-2,4,6-trichloro-	12	265	3.99
4,6-Dichloro-2,5-dimethyl-	3	263	3.78
2-Chloromethyl-4,6-dichloro-5-methyl-		261	3.71
5-Bromomethyl-4,6-dichloro-2-methyl-	9	259	3.67
5-Bromomethyl-2-chloro-methyl-4,6-dichloro-		261	3.72

ound which afforded improved yields of 5-chloro-2-phenyl-4,6-pyrimidinediol.

Table I summarizes the pertinent data on the 2-, 5-, and 2,5-substituted pyrimidines, and Table II contains a summary of the ultraviolet spectral data obtained on the ring-polychlorinated pyrimidines.

All of the pyrimidines were screened by the Cancer Chemotherapy National Service Center against at least three mouse tumors, Sarcoma-180, Carcinoma-755 and/or Ehrlich Ascites and/or Friend Virus Leukemia, and Leukemia-1210. These data are contained in Table III. Many of these compounds were screened

TABLE III

SUMMARY OF ANTICANCER SCREENING DATA AGAINST SARCOMA-180, CARCINOMA-755 AND/OR EHRLICH ASCITES AND/OR FRIEND VIRUS LEUKEMIA, AND LEUKEMIA-1210<sup>a</sup>

Compd.				Compd. no. or source	S-180		Ca-755 and/or E.A. and/or F.V.L.		L-1210	
R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>		N.T.L. <sup>a</sup> mg./kg.	T/C <sup>b</sup> %	N.T.L. mg./kg.	T/C %	N.T.L. mg./kg.	T/C %
H	HO	H	HO	Commercial	500	130	400	C <sup>i</sup> 100	225	90
HO	HO	H	HO	Commercial	500	156	350	C 77	500	107
HO	HO	Cl	HO	<i>b</i>	125	82	100	C 85	100	85
							100	E 123		
HO	HO	CH <sub>3</sub>	HO	Ref. 8	500	83	450	C 100	450	90
							450	E 126		
HO	HO	C <sub>2</sub> H <sub>5</sub>	HO	Ik	500	62	350	F 81	350	94
							350	C 119		
HO	HO	C <sub>3</sub> H <sub>7</sub>	HO	Il	500	73	450	C 75	450	104
HO	HO	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	HO	Im	500	116	350	F 187	350	91
							350	C 108		
HO	HO	C <sub>6</sub> H <sub>5</sub>	HO	Commercial	500	101	400	F 189	400	96
							400	C 89		
HO	HO	CH <sub>3</sub>	H	Commercial	350	100	315	C 67	315	69
CH <sub>3</sub>	HO	H	HO	Commercial			75	C 100	85	82
HOCH <sub>2</sub>	HO	H	HO	Ref. 7	500	100	450	C 113	450	69
							400	E 136		
CH <sub>3</sub>	HO	CH <sub>3</sub>	HO	<i>c</i>	30	92	30	E 89	25	95
HOCH <sub>2</sub>	HO	CH <sub>3</sub>	HO	Ij	500	63	500	E 98	400	95
HO	HO	CH <sub>3</sub>	CH <sub>3</sub>	Commercial	250	107	50	C 108	100	102
H	HO	Cl	HO	<i>d</i>	500	71	350	C 68	35	95
CH <sub>3</sub>	HO	Cl	HO	Ref. 7	500	96	450	C 56	450	84
							500	E 100		
HOCH <sub>2</sub>	HO	Cl	HO	Ref. 7	375	81	300	C 69	300	85
C <sub>2</sub> H <sub>5</sub>	HO	Cl	HO	Id	500	113	400	F 141	400	88
C <sub>3</sub> H <sub>7</sub>	HO	Cl	HO	Ie	500	151	400	F 120	400	88
<i>i</i> -C <sub>3</sub> H <sub>7</sub>	HO	Cl	HO	If	500	72	350	F 181	175	95
C <sub>17</sub> H <sub>35</sub>	HO	Cl	HO	Ig	500	103	400	F 151	400	133
C <sub>6</sub> H <sub>5</sub>	HO	Cl	HO	Ih	500	82	87	F 85	175	98
CH <sub>3</sub>	Cl	CH <sub>3</sub>	HO	<i>e</i>	125	68	125	E 122	88	77
H	Cl	H	Cl	Commercial	238	43	238	E 100	190	90
					238	95				
CH <sub>3</sub>	Cl	H	Cl	Ref. 2	500	96	450	C 84	450	91
CH <sub>3</sub>	Cl	CH <sub>3</sub>	Cl	Ref. 3	500	54	250	E 90	100	93
ClCH <sub>2</sub>	Cl	CH <sub>3</sub>	Cl	IIj	30	50	30	E 105	30	103
					30	63				
CH <sub>3</sub>	Cl	BrCH <sub>2</sub>	Cl	Ref. 9	3	157	2	C 50	3	96
							2	C 109		
ClCH <sub>2</sub>	Cl	BrCH <sub>2</sub>	Cl	IIIj	16	111	31	C 49	125	96
							31	C 85		
Cl	Cl	H	Cl	Commercial	15	77	12	C 112	15	98
Cl	Cl	CH <sub>3</sub>	Cl	Ref. 8	25	127	22.5	C 69	32.5	115
							22.5	E 141		
Cl	Cl	BrCH <sub>2</sub>	Cl	Ref. 7	6	67	5.4	E 87	5.4	89
Cl	Cl	C <sub>2</sub> H <sub>5</sub>	Cl	Ref. 10	125	58	50	F 151	100	94
Cl	Cl	C <sub>3</sub> H <sub>7</sub>	Cl	III	62	59	25	F 159	50	92
Cl	Cl	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	Cl	IIIm	125	109	44	F 106	87	98
Cl	Cl	C <sub>6</sub> H <sub>5</sub>	Cl	Ref. 12	30	80	24	F 132	24	91
H	Cl	Cl	Cl	<i>d</i>	25	69	20	F 151	20	111
CH <sub>3</sub>	Cl	Cl	Cl	Ref. 7	31	76	28	E 120	28	96
ClCH <sub>2</sub>	Cl	Cl	Cl	Ref. 7	3.75	72	3.5	C 31	17	96
							1.7	C 93		
							3.75	E 86		
C <sub>2</sub> H <sub>5</sub>	Cl	Cl	Cl	IIId	100	83	80	F 88	80	111
C <sub>3</sub> H <sub>7</sub>	Cl	Cl	Cl	IIe	46	87	40	F 79	40	104
<i>i</i> -C <sub>3</sub> H <sub>7</sub>	Cl	Cl	Cl	IIIf	25	101	20	F 104	20	103

TABLE III (Continued)

Compd.				Compd. no. or source	S-180		Ca-775 and/or E.A. and/or F.V.L.		L-1210	
R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>		NTL, <sup>a</sup> mg./kg.	T/C, <sup>h</sup> %	NTL, mg./kg.	T/C, %	NTL, mg./kg.	T/C, %
C <sub>6</sub> H <sub>5</sub>	Cl	Cl	Cl	IIh	125	41	100	F 70	100	102
					125	97				
Cl	Cl	CH <sub>3</sub>	H	Commercial	375	52	263	C 135	262	97
					375	69				
Cl	Cl	CH <sub>3</sub>	CH <sub>3</sub>	f	125	98	28	C 68	113	101

<sup>a</sup> We are indebted to Dr. Howard W. Bond, Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda 14, Md., for making these data available to us. The details of the screening procedures can be found in "CCNSC Specifications for Screening Chemical Agents and Natural Products against Animal Tumors," *Cancer Chemotherapy Rept.*, 1, 42 (1959). <sup>b</sup> Prepared by treating barbituric acid with sulfuryl chloride in 5% acetic anhydride in acetic acid with FeCl<sub>3</sub> as the catalyst; cf. ref. 7. <sup>c</sup> H. R. Henze, W. J. Clegg, and C. W. Smart, *J. Org. Chem.*, 17, 1320 (1952). <sup>d</sup> J. Chesterfield, J. F. W. McOmie, and E. R. Sayer, *J. Chem. Soc.*, 3478 (1955). <sup>e</sup> F. R. Basford, F. H. S. Curd, E. Hoggarth, and F. L. Rose, *ibid.*, 1354 (1947). <sup>f</sup> J. Schlenker, *Ber.*, 34, 2812 (1901). <sup>g</sup> NTL = maximum nontoxic level. <sup>h</sup> T/C = treated tumor/control tumor. <sup>i</sup> C = Carcinoma-755; E = Ehrlich Ascites; F = Friend Virus Leukemia.

in tissue culture. It was found that a series of 5-substituted 2,4,6-trichloropyrimidines showed confirmed activity in the KB cell culture test system.<sup>16</sup> These results are summarized in Table IV. It should also be pointed out that none of these compounds demonstrated *in vivo* activity in the usual tumor systems<sup>17a</sup>; however, 5-propyl-2,4,6-trichloropyrimidine has shown a sufficient degree of cytotoxicity to warrant further evaluation in other *in vivo* systems.<sup>17b</sup> Additional members of the series are in preparation. The antifungal properties of these ring chlorinated pyrimidines were reported by Gershon and Parmegiani.<sup>18</sup>

TABLE IV  
SCREENING DATA OF 5-SUBSTITUTED 2,4,6-TRICHLORO-  
PYRIMIDINES IN THE KB CELL CULTURE SYSTEM<sup>a</sup>

Substituent in 5-position	Compd.	Slope	ED <sub>50</sub> , γ/ml.	Status code <sup>b</sup>
H-	Commercial	-0.79	3.0	20C
CH <sub>3</sub> -	Ref. 8	-0.80	0.25	20C
BrCH <sub>2</sub> -	Ref. 7		1.0	20C
C <sub>2</sub> H <sub>5</sub> -	IIk	-0.97	1.4	20C
<i>i</i> -C <sub>3</sub> H <sub>7</sub> -	IIIm	-1.6	3.4	20C
C <sub>3</sub> H <sub>7</sub> -	III	-0.68	0.37	20C
C <sub>6</sub> H <sub>5</sub> -	IIo	-1.1	0.66	20C
Cl	Commercial	-0.43	14	2

<sup>a</sup> We are indebted to Dr. Howard W. Bond, Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda 14, Md., for making these data available to us. The details of the screening procedures can be found in ref. 15a. <sup>b</sup> 20C, confirmed activity; 2, inactive in first test, ref. 15a.

#### Experimental<sup>19</sup>

**Benzamide Hydrochloride.**<sup>15</sup>—To a mixture of 251.3 g. (2.44 moles) of dry benzonitrile and 143 ml. (2.5 moles) of absolute ethyl alcohol was added 95.0 g. (2.6 moles) of anhydrous HCl. The mixture was allowed to stand under refrigeration overnight. Anhydrous ethyl ether was added to the crystalline mass which

had been reduced to small particles. The crystals were removed by filtration and washed with additional ether. The product was dried under vacuum over H<sub>2</sub>SO<sub>4</sub> and was sufficiently pure for the next step. The ethyl benzimidate hydrochloride was slurried in 150 ml. of absolute ethyl alcohol, and 500 ml. of 10% ethanolic ammonia was added with agitation. The mixture was stirred 3 hr., warmed to 60–70°, and filtered to remove ammonium chloride. The filtrate was evaporated to a thick sirup in a flash evaporator. Two volumes of a 10% mixture of methanol in ether was added and the product was shaken until crystallization occurred. After cooling in the refrigerator overnight, the product was removed by filtration, washed with ether, and dried under vacuum over H<sub>2</sub>SO<sub>4</sub>. The over-all yield of product was 144 g. (37.6%), m.p. 165–168°, sufficiently pure for analysis.

*Anal.* Calcd. for C<sub>7</sub>H<sub>8</sub>ClN<sub>2</sub>: Cl, 22.64. Found: Cl, 22.70.

**4,6-Dihydroxy-5-methyl-2-pyrimidinemethanol (Ij).**—To 1000 ml. of absolute ethyl alcohol, in which 69.0 g. (3 g.-atoms) of sodium had been dissolved, was added 215 g. (1.0 mole) of benzoylglycolamide<sup>20</sup> and 174 g. (1.0 mole) of ethyl methylmalonate. The mixture was shaken for 1 hr. and allowed to stand overnight. Sufficient water was added to form a clear solution, which was then treated with decolorizing carbon and acidified to pH 1–2 with HCl. After cooling overnight in the refrigerator, the product was removed by filtration, washed free of chloride with water, then rinsed successively with alcohol and ether. The yield of compound was 92.0 g. (59%), m.p. 282° dec.

An analytical sample was prepared, m.p. 289° dec., by crystallization from a mixture of 10% dimethylformamide in isopropyl alcohol.

**2-Chloromethyl-4,6-dichloro-5-methylpyrimidine (IIj).**—A mixture of 70.0 g. (0.45 mole) of Ij and 700 ml. of phosphorus oxychloride was heated under reflux overnight. After cooling to room temperature, 240 g. (1.35 moles) of phosphorus pentachloride was added to the mixture and refluxing was continued overnight again. The excess POCl<sub>3</sub> was removed under vacuum, and the residue was poured onto flaked ice and allowed to stand 0.5 hr. The product was extracted with ethyl ether, decolorized with charcoal, dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent was removed by evaporation. The product was crystallized from ethanol in 66.3% yield (63.0 g.), m.p. 38–41°. An analytical sample, m.p. 39.5–40.5°, was prepared by recrystallization from isopropyl alcohol.

**5-Bromomethyl-2-chloromethyl-4,6-dichloropyrimidine (IIIj).**—A mixture of 18.0 g. (0.085 mole) of IIj, 15.2 g. (0.085 mole) of N-bromosuccinimide, and 1.7 g. (10 mole %) of benzoyl peroxide in 180 ml. of dry carbon tetrachloride was heated under reflux with agitation for 16 hr. After cooling to room temperature, succinimide was removed by filtration (8.0 g., 94.2%), the filtrate was treated with decolorizing carbon, and the solvent was removed under vacuum. The residue was dissolved in 100 ml. of isopropyl alcohol, decolorized with charcoal, diluted with 100 ml. of dry ethyl ether, and seeded. The mixture was cooled to -12° overnight, and 2.5 g. of product was obtained, m.p. 121–125°. For analysis, a sample was prepared by recrystallization from isopropyl alcohol, m.p. 127–129°.

(16) J. Leiter, M. M. Macdonald, and S. A. Schepartz, *Cancer Research*, 24, 665 (1964).

(17) (a) J. Leiter and S. A. Schepartz, Cancer Chemotherapy National Service Center, personal communication; (b) M. M. Macdonald, Cancer Chemotherapy National Service Center, personal communication.

(18) H. Gershon and R. Parmegiani, *Appl. Microbiol.*, 11, 78 (1963); (b) H. Gershon and R. Parmegiani, *Trans. N. Y. Acad. Sci.*, [2]25, 638 (1963).

(19) This work was completed several years ago, and melting points were then taken in a Hershberg melting point apparatus and are uncorrected. Ultraviolet data were obtained with a Beckman DU. The synthetic procedures are general, and the malonic acid esters were commercially available except ethyl heptadecylmalonate which was prepared by the method of D. C. Grimshaw, J. B. Guy, and J. C. Smith [*J. Chem. Soc.*, 68 (1940)].

(20) W. Klarer and E. Urech, *Helv. Chim. Acta*, 27, 1762 (1944).