Trifluoromethylglyoxal Bis(guanylhydrazone) Sulfate. A.—An aqueous solution of dibromomethyl trifluoromethyl ketone[8] and aminoguanidine sulfate[5] (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 mμ 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., λ_{max}^{pH1} 304 mμ (ε 16,600), λ_{max}^{pH11} 349 mμ (ε 26,900).

Anal. Calcd. for $C_5H_9F_3N_8 \cdot H_2SO_4 \cdot H_2O$: C, 17.0; H, 3.67; N, 31.6. Found: C, 17.3; H, 3.69; N, 31.9.

Trifluoromethylglyoxal Bis(guanylhydrazone) (II).—A suspension of trifluoromethylglyoxal bis(guanylhydrazone) 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., λ_{max}^{pH1} 304 mμ (ε 18,700), λ_{max}^{pH11} 348 mμ (ε 21,400).

Anal. Calcd. for $C_5H_9F_3N_8$: C, 25.2; H, 3.78; N, 47.1. Found: C, 25.5; H, 4.20; N, 47.0.

1,1,1-Trifluoroacetone Guanylhydrazone 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), λ_{max}^{pH1} 226 mμ (ε 15,800), λ_{max}^{pH11} 248 mμ (ε 15,900).

Anal. Calcd. for $C_4H_7F_3N_4 \cdot 0.5H_2SO_4$: 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(guanylhydrazone) dihydrochloride monohydrate in 250 ml. of 60% acetic acid containing 0.1 g. of platinum oxide was hydrogenated at 4.22 kg./cm.^{2} 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 $C_5H_{16}N_8 \cdot H_2SO_4$: 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(guanylhydrazone) sulfate in 200 ml. of 50% acetic acid containing 1 g. of platinum oxide was hydrogenated at 65° and 4.22 kg./cm.^{2}. 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 $C_5H_{16}N_8 \cdot H_2SO_4$: 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

HERMAN GERSHON,[1] RICHARD BRAUN, ALFRED SCALA, AND RAYMOND RODIN

Pfister Chemical Works, Inc., Ridgefield, New Jersey

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_3,[2] C_2H_5,[3,4] C_3H_7,[5] and C_6H_5[6]) has been reported. Of the corresponding 4,5,6-trichloropyrimidines, only the 2-methyl and 2-chloromethyl analogs are known.[7] In the 5-substituted barbituric acid and 2,4,6-trichloropyrimidine series, the methyl,[8] bromomethyl,[7,9] ethyl,[10] *sec*-butyl,[11] and phenyl[12,13] derivatives are also known. 5-Propyl- and 5-isopropylbarbituric acids had also been reported.[14]

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-

(1) To whom requests for reprints should be made: Boyce Thompson Institute for Plant Research, Yonkers, N. Y.

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

(3) W. Huber and H. A. Hölscher, *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. Winthrop, *J. Am. Chem. Soc.*, **79**, 2230 (1957).

(6) J. A. Hendry and R. F. Homer, *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).

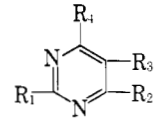
(12) B. H. Chase, J. P. Thurston, and J. Walker, *J. Chem. Soc.*, 3439 (1951).

(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

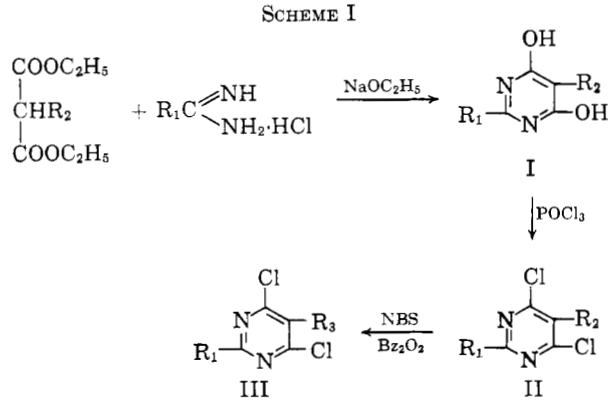
2-, 5-, AND 2,5-SUBSTITUTED PYRIMIDINES



Compd.	R_1	R_2	R_3	R_4	Yield, %	B.p. (mm.) or m.p., °C.[a]	Formula	Calcd., % N	Calcd., % Cl	Found, % N	Found, % Cl
Ic[b,c]	i-C_3H_7	HO	H	HO	24.5	296–297 dec.	$C_7H_{10}N_2O_2$[d]	18.17		18.11	
Id[e]	C_2H_5	HO	Cl	HO	62.0	318–319 dec.	$C_6H_7ClN_2O_2$	16.05	20.31	16.17	20.59
Ie[e]	C_3H_7	HO	Cl	HO	38.8	294 dec.	$C_7H_9ClN_2O_2$	14.86	18.80	14.81	18.40
If[e]	i-C_3H_7	HO	Cl	HO	69.8	>365	$C_7H_9ClN_2O_2$	14.86	18.80	14.37	18.96
Ig[e]	$C_{17}H_{35}$	HO	Cl	HO	31.2	285 dec.	$C_{21}H_{37}ClN_2O_2$	7.28	9.21	7.15	9.39
Ih[e]	C_6H_5	HO	Cl	HO	58.5	329–330 dec.	$C_{10}H_7ClN_2O_2$	12.58	15.93	13.05	15.69
Ij	$HOCH_2$	HO	CH_3	HO	59.0	289 dec.	$C_6H_8N_2O_3$[f]	17.94		17.66	
In[g]	HO	HO	$C_{17}H_{35}$	HO	95.0	186–189	$C_{21}H_{38}N_2O_3$[h]	7.64		7.37	
IIc[i]	i-C_3H_7	Cl	H	Cl	85.0	47–48 (0.6)	$C_7H_8Cl_2N_2$	14.66	37.11	14.35	37.52
IId[j]	C_2H_5	Cl	Cl	Cl	84.9	45 (0.2)	$C_6H_5Cl_3N_2$	13.25	50.31	13.68	50.10
IIe[j]	C_3H_7	Cl	Cl	Cl	79.5	65 (0.75)	$C_7H_7Cl_3N_2$	12.43	47.18	12.74	47.29
IIf[j]	i-C_3H_7	Cl	Cl	Cl	96.5	38.5–39.5	$C_7H_7Cl_3N_2$	12.43	47.18	12.72	47.42
IIg[j]	$C_{17}H_{35}$	Cl	Cl	Cl	85.8	55	$C_{21}H_{35}Cl_3N_2$	6.64	25.21	6.50	25.02
IIh[j]	C_6H_5	Cl	Cl	Cl	69.5	125–126	$C_{10}H_5Cl_3N_2$	10.79	40.98	10.73	40.69
IIj[k]	$ClCH_2$	Cl	CH_3	Cl	66.3	39.5–40.5	$C_6H_5Cl_3N_2$	13.25	50.30	13.63	50.06
III[j]	Cl	Cl	C_3H_7	Cl	74.2	30–32	$C_7H_7Cl_3N_2$	12.43	47.18	12.64	47.00
IIm[j]	Cl	Cl	i-C_3H_7	Cl	77.2	69–71	$C_7H_7Cl_3N_2$	12.43	47.18	12.58	46.71
IIIj	$ClCH_2$	Cl	$BrCH_2$	Cl	10.0	127–129	$C_6H_4Cl_3N_2Br$[l]	9.65		9.95	

[a] Analytical sample. [b] Recrystallized from isopropyl alcohol. [c] Compound mentioned but not described, ref. 13. [d] *Anal.* Calcd.: C, 54.53; H, 6.54. Found: C, 54.80; H, 6.83. [e] Recrystallized from dimethylformamide. [f] *Anal.* Calcd.: C, 46.15; H, 5.16. Found: C, 46.41; H, 5.18. [g] Recrystallized from methanol. [h] *Anal.* Calcd.: C, 68.81; H, 10.45. Found: C, 68.82; H, 10.49. [i] $POCl_3$ used to replace OH with Cl. [j] $POCl_3$ + dimethylaniline used to replace OH with Cl. [k] $POCl_3$ + PCl_5 used to replace OH with Cl. [l] *Anal.* Calcd.: C, 24.82; H, 1.39. Found: C, 25.11; H, 1.82.

SCHEME I



Ia, IIa, $R_1 = C_2H_5$; $R_2 = H$ — Ik, $R_1 = HO$; $R_2 = C_2H_5$
Ib, IIb, $R_1 = C_3H_7$; $R_2 = H$ — Il, $R_1 = HO$; $R_2 = C_3H_7$
Ic, IIc, $R_1 = i$-C_3H_7; $R_2 = H$ — Im, $R_1 = HO$; $R_2 = i$-C_3H_7
Id, IId, $R_1 = C_2H_5$; $R_2 = Cl$ — In, $R_1 = HO$; $R_2 = C_{17}H_{35}$
Ie, IIe, $R_1 = C_3H_7$; $R_2 = Cl$ — Io, $R_1 = HO$; $R_2 = C_6H_5$
If, IIf, $R_1 = i$-C_3H_7; $R_2 = Cl$ — IIk, $R_1 = Cl$; $R_2 = C_2H_5$
Ig, IIg, $R_1 = C_{17}H_{35}$; $R_2 = Cl$ — IIl, $R_1 = Cl$; $R_2 = C_3H_7$
Ih, IIh, $R_1 = C_6H_5$; $R_2 = Cl$ — IIm, $R_1 = Cl$; $R_2 = i$-C_3H_7
Ii, IIi, $R_1 = CH_3$; $R_2 = CH_3$ — IIo, $R_1 = Cl$; $R_2 = C_6H_5$
Ij, $R_1 = HOCH_2$; $R_2 = CH_3$ — IIIi, $R_1 = CH_3$; $R_3 = BrCH_2$
IIj, $R_1 = ClCH_2$; $R_2 = CH_3$ — IIIj, $R_1 = ClCH_2$; $R_3 = BrCH_2$

methyl derivatives (IIIi and IIIj) by treatment with N-bromosuccinimide (NBS) in the presence of benzoyl peroxide (Bz_2O_2). It had been established previously,[7] that bromination of the methyl group in the 5-position of the pyrimidine ring with NBS in the presence of Bz_2O_2 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,[15] and in the case of benzamidine hydrochloride, since a hydrated product was reported, a method was devised to prepare the anhydrous compound which afforded improved yields of 5-chloro-2-phenyl-4,6-pyrimidinediol.

(15) A. Pinner, *Ber.*, **16**, 1643 (1883); **17**, 171 (1884).

TABLE II

ULTRAVIOLET DATA FOR RING-POLYCHLORINATED PYRIMIDINES

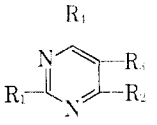
 Pyrimidine	Method of prepn. (lit. ref.)	Spectral data $\lambda_{max}^{CH_3OH}$	Spectral data log ϵ
4,6-Dichloro-2-ethyl-	3	257	3.68
4,6-Dichloro-2-propyl-	5	257	3.68
4,6-Dichloro-2-isopropyl-		254	3.66
2-Ethyl-4,5,6-trichloro-		270	3.73
2-Propyl-4,5,6-trichloro-		268	3.74
2-Isopropyl-4,5,6-trichloro-		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-chloromethyl-4,6-dichloro-		261	3.72

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[a]



Compd.				Compd. no. or source	S-180		Ca-755 and/or E.A. and/or F.V.L.			L-1210	
R_1	R_2	R_3	R_4		NTL,[a] mg./kg.	T/C,[b] %	NTL, mg./kg.		T/C, %	NTL, mg./kg.	T/C, %
H	HO	H	HO	Commercial	500	130	400	C[c]	100	225	90
HO	HO	H	HO	Commercial	500	156	350	C	77	500	107
HO	HO	Cl	HO	*b*	125	82	100	C	85	100	85
							100	E	123		
HO	HO	CH_3	HO	Ref. 8	500	83	450	C	100	450	90
							450	E	126		
HO	HO	C_2H_5	HO	Ik	500	62	350	F	81	350	94
							350	C	119		
HO	HO	C_3H_7	HO	Il	500	73	450	C	75	450	104
HO	HO	*i*-C_3H_7	HO	Im	500	116	350	F	187	350	91
							350	C	108		
HO	HO	C_6H_6	HO	Commercial	500	101	400	F	189	400	96
							400	C	89		
HO	HO	CH_3	H	Commercial	350	100	315	C	67	315	69
CH_3	HO	H	HO	Commercial			75	C	100	85	82
$HOCH_2$	HO	H	HO	Ref. 7	500	100	450	C	113	450	69
							400	E	136		
CH_3	HO	CH_3	HO	*c*	30	92	30	E	89	25	95
$HOCH_2$	HO	CH_3	HO	Ij	500	63	500	E	98	400	95
HO	HO	CH_3	CH_3	Commercial	250	107	50	C	108	100	102
H	HO	Cl	HO	*d*	500	71	350	C	68	35	95
CH_3	HO	Cl	HO	Ref. 7	500	96	450	C	56	450	84
							500	E	100		
$HOCH_2$	HO	Cl	HO	Ref. 7	375	81	300	C	69	300	85
C_2H_5	HO	Cl	HO	Id	500	113	400	F	141	400	88
C_3H_7	HO	Cl	HO	Ie	500	151	400	F	129	400	88
i-C_3H_7	HO	Cl	HO	If	500	72	350	F	181	175	95
$C_{17}H_{35}$	HO	Cl	HO	Ig	500	103	400	F	131	400	133
C_6H_5	HO	Cl	HO	Ih	500	82	87	F	85	175	98
CH_3	Cl	CH_3	HO	*e*	125	68	125	E	122	88	77
H	Cl	H	Cl	Commercial	238	43	238	E	100	190	90
					238	95					
CH_3	Cl	H	Cl	Ref. 2	500	96	450	C	84	450	91
CH_3	Cl	CH_3	Cl	Ref. 3	500	54	250	E	90	100	93
$ClCH_2$	Cl	CH_3	Cl	IIj	30	50	30	E	105	30	103
					30	63					
CH_3	Cl	$BrCH_2$	Cl	Ref. 9	3	157	2	C	50	3	96
							2	C	109		
$ClCH_2$	Cl	$BrCH_2$	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_3	Cl	Ref. 8	25	127	22.5	C	69	32.5	115
							22.5	E	141		
Cl	Cl	$BrCH_2$	Cl	Ref. 7	6	67	5.4	E	87	5.4	89
Cl	Cl	C_2H_5	Cl	Ref. 10	125	58	50	F	151	100	94
Cl	Cl	C_3H_7	Cl	IIl	62	59	25	F	159	50	92
Cl	Cl	*i*-C_3H_7	Cl	IIm	125	109	44	F	106	87	98
Cl	Cl	C_6H_5	Cl	Ref. 12	30	80	24	F	132	24	91
H	Cl	Cl	Cl	*d*	25	69	20	F	151	20	111
CH_3	Cl	Cl	Cl	Ref. 7	31	76	28	E	120	28	96
$ClCH_2$	Cl	Cl	Cl	Ref. 7	3.75	72	3.5	C	31	17	96
							1.7	C	93		
							3.75	E	86		
C_2H_5	Cl	Cl	Cl	IId	100	83	80	F	88	80	111
C_3H_7	Cl	Cl	Cl	IIe	46	87	40	F	79	40	104
i-C_3H_7	Cl	Cl	Cl	IIf	25	101	20	F	104	20	103

TABLE III (*Continued*)

Compd.				Compd. no. or source	S-180 NTL,[g] mg./kg.	S-180 T/C,[h] %	Ca-775 and/or E.A. and/or F.V.L. NTL, mg./kg.	Ca-775 and/or E.A. and/or F.V.L. T/C, %	L-1210 NTL, mg./kg.	L-1210 T/C, %
R_1	R_2	R_3	R_4							
C_6H_5	Cl	Cl	Cl	IIh	125	41	100	F 70	100	102
					125	97				
Cl	Cl	CH_3	H	Commercial	375	52	263	C 135	262	97
					375	69				
Cl	Cl	CH_3	CH_3	*f*	125	98	28	C 68	113	101

[a] 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). [b] Prepared by treating barbituric acid with sulfuryl chloride in 5% acetic anhydride in acetic acid with $FeCl_3$ as the catalyst; *cf.* ref. 7. [c] H. R. Henze, W. J. Clegg, and C. W. Smart, *J. Org. Chem.*, **17**, 1320 (1952). [d] J. Chesterfield, J. F. W. McOmie, and E. R. Sayer, *J. Chem. Soc.*, 3478 (1955). [e] F. R. Basford, F. H. S. Curd, E. Hoggarth, and F. L. Rose, *ibid.*, 1354 (1947). [f] J. Schlenker, *Ber.*, **34**, 2812 (1901). [g] NTL = maximum nontoxic level. [h] T/C = treated tumor/control tumor. [i] C = Carcinoma-755; E = Ehrlich Ascites; F = Friend Virus Lukemia.

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.[16] 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[17a]; however, 5-propyl-2,4,6-trichloropyrimidine has shown a sufficient degree of cytotoxicity to warrant further evaluation in other *in vivo* systems.[17b] Additional members of the series are in preparation. The antifungal properties of these ring chlorinated pyrimidines were reported by Gershon and Parmegiani.[18]

TABLE IV

SCREENING DATA OF 5-SUBSTITUTED 2,4,6-TRICHLOROPYRIMIDINES IN THE KB CELL CULTURE SYSTEM[a]

Substituent in 5-position	Compd.	Slope	ED_{50}, γ/ml.	Status code[b]
H–	Commercial	−0.79	3.0	20C
CH_3–	Ref. 8	−0.80	0.25	20C
$BrCH_2$–	Ref. 7		1.0	20C
C_2H_5–	IIk	−0.97	1.4	20C
i-C_3H_7–	IIm	−1.6	3.4	20C
C_3H_7–	III	−0.68	0.37	20C
C_6H_5–	IIo	−1.1	0.66	20C
Cl	Commercial	−0.43	14	2

[a] 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. [b] 20C, confirmed activity; 2, inactive in first test, ref. 15a.

Experimental[19]

Benzamidine Hydrochloride.[15]—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_2SO_4 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_2SO_4. The over-all yield of product was 144 g. (37.6%), m.p. 165–168°, sufficiently pure for analysis.

Anal. Calcd. for $C_7H_9ClN_2$: 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 benzoylglycolamidine[20] 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 $POCl_3$ 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_2SO_4), 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).