and melted at 80–82° after recrystallization, $[\alpha]^{24}D$ +177.0 ± 2.0° (methanol).

3-{*m*-[Bis(2-chloroethyl)amino]phenyl}-N-phthalyl-L-alanine methyl ester (L-V) was prepared with thionyl chloride, as for D-V, in 57% yield, m.p. 70–72°, m.p. after recrystallization 77–79° and $[\alpha]^{23}D$ −177.0 ± 2.0° (methanol), R_f 0.06.

3-{*m*-[Bis(2-chloroethyl)amino]phenyl}-L-alanine (L-VI).—The hydrolysis described[4] for DL-VI was carried out at 90–95° for 4 hr. After filtration from red-stained phthalic acid, the solution was diluted with several vols. of water. The chloroform extracts were washed only twice with water and then not dried before concentration, because in these steps the product tended to separate as a gel. Finally, trituration with refluxing 95% ethanol for no more than several min. was preferred for crystallizing the product, which was washed with acetone while on the filter. The yield was 55%, m.p. 181–183°, $[\alpha]^{29}D$ +26.5 ± 0.5° (1 *M* hydrochloric acid), $[\alpha]^{25}D$ −21.7 ± 1.0° (methanol), R_f 0.34 on Whatman No. 1 paper in water-saturated 1-butanol (ninhydrin-positive).

Anal. Calcd. for $C_{13}H_{18}Cl_2N_2O_2$: C, 51.2; H, 5.92; Cl, 23.2; N, 9.18. Found: C, 51.2; H, 5.84; Cl, 23.1; N, 9.10.

Purity of other samples, of $[\alpha]D$ sometimes as low as +20° in 1 *M* hydrochloric acid, could be improved to $[\alpha]D$ +26° by a second treatment with refluxing 95% ethanol. Small samples for rotation could be recrystallized with low[8] recovery from hot 95% ethanol (0.3 g. in 40 ml.) containing charcoal, by concentrating the solution to one-half the volume and chilling at 0° for 24 hr.

3-{*m*-[Bis(2-chloroethyl)amino]phenyl}-D-alanine (D-VI) was similarly prepared after 4.5 hr. heating in 65–75% yields, m.p. 180–182°, $[\alpha]^{27}D$ −26.5 ± 0.5° (1 *M* hydrochloric acid), R_f 0.34 as for L-VI.

Acknowledgment.—The authors are indebted to Dr. Peter Lim for infrared interpretations, to his staff for paper chromatography and optical rotation measurements, and to Mr. O. P. Crews and staff for preparation of intermediates.

Pyrimidines. III. Some 6-Substituted Di- and Trichloropyrimidines

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In a previous paper,[2] it was reported that the three monomethyltrichloropyrimidines were prepared and submitted to Cancer Chemotherapy National Service Center, National Institutes of Health, for anticancer screening. It appeared that 6-methyl-2,4,5-trichloropyrimidine was active[3] against Ehrlich ascites tumor in the hands of one screener, but that this activity was not reproducible in other laboratories. Consequently, it was decided to prepare several 6-substituted trichloropyrimidines to determine whether related compounds would show any measure of activity against this tumor.

The 6-substituted pyrimidines were prepared by condensing the appropriate β-ketoester with thiourea in the presence of sodium ethoxide to 6-substituted-2-thiouracils, according to the general procedure of Anderson, *et al.*[4] The conversion of the thiouracils to uracils was accomplished by hydrolysis with chloroacetic and hydrochloric acids. The uracils were chlorinated in the 5-position with sulfuryl chloride by the method of Barrett, Goodman, and Dittmer.[5] The dichloro- and trichloropyrimidines were prepared from the uracils and 5-chlorouracils, respectively, by means of phosphorus oxychloride. This synthetic sequence is summarized in Scheme I.

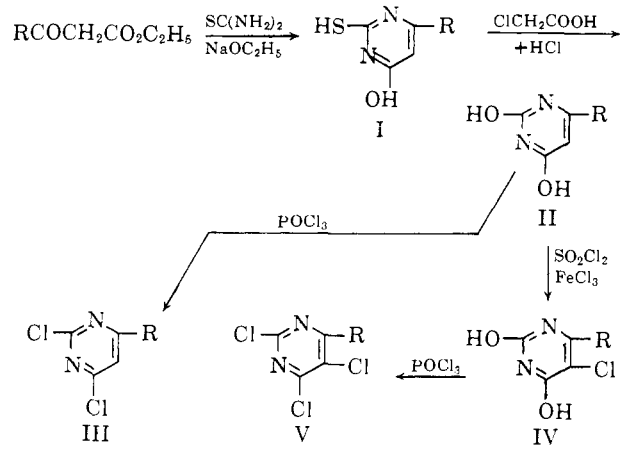
Of the 28 compounds prepared in this study, the ethyl, propyl, isopropyl and phenyl substituted thiouracils and uracils had been reported previously.[4,6,7]

Table I summarizes the pertinent data on the 6-substituted pyrimidines, and Table II contains a summary of the ultraviolet spectral data obtained on the di- and trichloropyrimidines.

These compounds have been submitted for anticancer screening, and the results on the three tumor system (Sarcoma-180, Carcinoma-755, and Leukemia-1210) are listed in Table III. None of the compounds showed reproducible activity. The Ehrlich ascites tumor is no longer included in the screening system.[3]

SCHEME I

R for a = H, b = C_2H_5, c = C_3H_7, d = *i*-C_3H_7, e = *n*-$C_{17}H_{37}$, f = C_6H_5



Experimental[8]

The methods of synthesis of the analogous compounds are similar, and the particular derivatives described in detail are for illustrative purposes.

6-*n*-Heptadecyl-2-thiouracil (Ie).—To a solution of sodium ethoxide, prepared from 6.6 g. (0.287 g.-atom) of sodium dissolved in 300 ml. of ethanol, was added 15.1 g. (0.198 mole) of thiourea and 50.0 g. (0.142 mole) of ethyl stearoylacetate. The mixture was heated on the steam bath for 6 hr. with agitation and allowed to stand overnight. The alcohol was removed in a flash evaporator and the residue was dissolved in water, decolorized with charcoal, and acidified with hydrochloric acid. The product was removed by filtration, washed with water and dried at 70° overnight. The yield was 48.5 g. (93%), m.p. 120–135°. An analytical sample was prepared by recrystallizing several times from methanol, m.p. 147.5–149°.

Anal. Calcd. for $C_{21}H_{38}N_2OS$: N, 7.64; S, 8.73. Found: N, 7.66; S, 8.96.

(1) To whom requests for reprints should be sent at Boyce Thompson Institute for Plant Research, Inc., Yonkers 3, N. Y.

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

(3) Communication from Dr. Howard Bond, CCNSC, NIH, Bethesda 14, Md.

(4) G. W. Anderson, I. F. Halverstadt, W. H. Miller, and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, **67**, 2197 (1945).

(5) H. W. Barrett, I. Goodman, and K. Dittmer, *J. Am. Chem. Soc.*, **70**, 1753 (1948).

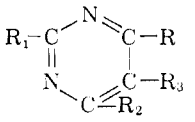
(6) J. H. Burckhalter and H. C. Scarborough, *J. Am. Pharm. Assoc.*, **44**, 545 (1955).

(7) R. M. Evans, P. G. Jones, P. J. Palmer, and F. F. Stephens, *J. Chem. Soc.*, 4106 (1956).

(8) All melting points were taken in a Hershberg melting point apparatus; the β-ketoesters are commercially available.

TABLE I

6-SUBSTITUTED PYRIMIDINES



Compound	R	R_1	R_2	R_3	Yield, %	Analytical sample, m.p. or b.p. °C.	Mm.	Empirical Formula	Calcd., % N	Calcd., % Cl	Found, % N	Found, % Cl
IIIc	n-C_3H_7	Cl	Cl	H	87	91.5	5	$C_7H_8Cl_2N_2$	14.66	37.11	14.71	36.67
IIId	i-C_3H_7	Cl	Cl	H	71	82.5	5	$C_7H_8Cl_2N_2$	14.66	37.11	14.20	37.01
IIIe	n-$C_{17}H_{35}$	Cl	Cl	H	90	[a]	[a]	$C_{21}H_{36}Cl_2N_2$	7.24	18.30	7.48	18.30
IVa[b]	H	OH	OH	Cl	80	315–318 dec.[c]		$C_4H_3ClN_2O_2$		24.19		24.00
IVb	C_2H_5	OH	OH	Cl	86	260.5–261.5 dec.		$C_6H_7ClN_2O_2$	16.05	20.31	15.80	20.34
IVc	n-C_3H_7	OH	OH	Cl	83	242–244 dec.		$C_7H_9ClN_2O_2$	14.86	18.80	14.81	19.14
IVd	i-C_3H_7	OH	OH	Cl	70	259.5–260 dec.		$C_7H_9ClN_2O_2$	14.86	18.80	15.32	19.15
IVe	n-$C_{17}H_{35}$	OH	OH	Cl	89	210–211.5 dec.		$C_{21}H_{37}ClN_2O_2$	7.28	9.21	7.48	9.04
IVf	C_6H_5	OH	OH	Cl	91	270–272 dec.[d]		$C_{10}H_7ClN_2O_2$	12.58	15.92	12.63	16.23
Vb	C_2H_5	Cl	Cl	Cl	73	87.8	5	$C_6H_5Cl_3N_2$	13.25	50.31	13.65	50.18
Vc	n-C_3H_7	Cl	Cl	Cl	80	98.2	5	$C_7H_7Cl_3N_2$	12.43	47.18	12.51	47.28
Vd	i-C_3H_7	Cl	Cl	Cl	50	89.5	5	$C_7H_7Cl_3N_2$	12.43	47.18	12.11	46.86
Ve	n-$C_{17}H_{35}$	Cl	Cl	Cl	92	[a]	[a]	$Cl_{21}H_{37}Cl_3N_2$	6.64	25.21	6.33	26.19
Vf	C_6H_5	Cl	Cl	Cl	93	87–88		$C_{10}H_5Cl_3N_2$	10.79	40.99	10.75	40.62

[a] Did not distil below 190° (0.3 mm.). [b] IVa to IVf, all compounds were crystallized from methyl alcohol. [c] Lit.[9] m.p. 314–318° dec. [d] Lit.[10] m.p. 260–261°.

TABLE II

ULTRAVIOLET DATA FOR 6-SUBSTITUTED 2,4-DI- AND 2,4,5-TRICHLOROPYRIMIDINES

Substituent in 6-position	Spectral data in methanol: 2,4-Dichloropyrimidines $\lambda_{max.}$ mμ	log ε	2,4,5-Trichloropyrimidines $\lambda_{max.}$ mμ	log ε
H	259	3.58	225	3.95
			275	3.51
CH_3	258	3.64	227	3.94
			271	3.62
C_2H_5	258	3.65	227	3.95
			271.5	3.68
n-C_3H_7	259	3.69	226	3.95
			272.5	3.69
i-C_3H_7	258	3.68	226	3.93
			272	3.69
n-$C_{17}H_{35}$	259	3.68	227	3.97
			272.5	3.72
C_6H_5	262	4.05	259	3.84
	287.5	4.26	293	4.01

6-n-Heptadecyluracil (IIe).—The hydrolysis of the thiouracil to the uracil was carried out by the procedure of Kaiser and Burger.[11] A mixture of Ie (105 g., 0.3 mole) and 56.7 g. (0.06 mole) of chloroacetic acid in 600 ml. of water was heated for 4 hr. under reflux with agitation. An emulsion formed which on cooling to room temperature yielded a crystalline product. Concentrated hydrochloric acid (150 ml.) was added and refluxing with agitation was continued for an additional 8 hr. A white solid was produced which was removed by filtration, washed free of acid with water and then acetone, and dried at 70° overnight. The yield of IIe was 84 g. (80%), m.p. 164–167°. An analytical sample was crystallized from methanol, m.p. 171.5–172°.

Anal. Calcd. for $C_{21}H_{38}N_2O_2$: C, 71.95; H, 10.93; N, 7.99. Found: C, 72.27; H, 10.34; N, 7.89.

5-Chloro-6-n-heptadecyluracil (IVe).—Fifty four grams (0.154 mole) of IIe was dissolved in 500 ml. of 5% acetic anhydride in

(9) J. Chesterfield, J. F. W. McOmie, and E. R. Sayer, *J. Chem. Soc.*, 4378 (1955).

(10) T. B. Johnson, *J. Am. Chem. Soc.*, **66**, 148 (1944).

(11) CCNSC Specifications for Screening Chemical Agents and Natural Products Against Animal Tumours, compiled by Drug Evaluation Branch, *Cancer Chemother. Rep.*, 1, 12 (1959).

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TABLE III

SUMMARY OF ANTICANCER SCREENING DATA AGAINST THREE TUMORS: SARCOMA-180, CARCINOMA-755 AND/OR EHRLICH ASCITES AND LEUKEMIA-1210[a,11]

Part A, Uracils

Compound	Number or source	NSC no.	S-180 NTL,[b] mg./kg.	S-180 T/C,[c] %	Ca-755 or E.A. NTL, mg./kg.	Ca-755 or E.A. T/C, %	L-1210 NTL, mg./kg.	L-1210 T/C, %
6-Ethyl-2-thio-	Ib	58555	250	117	125	C[d] 85	250	101
6-Isopropyl-2-thio-	Id	58556	250	92	250	C 148	250	93
6-Heptadecyl-2-thio-	Ie	58557	250	93	125	C 115	250	92
6-Phenyl-2-thio-	If	42600	500	65	225	C 71	450	86
2-Thioorotic acid	Comm.	39961	500	84	450	C 61	450	95
Uracil	avail.	3970	500	112	250	C 97	500	110
6-Ethyl-	IIb	58558	250	104	250	C 114	250	101
6-Propyl-	IIc	58559	250	123	250	C 70	250	95
6-Isopropyl-	IId	58560	250	98	250	C 127	250	92
6-Heptadecyl-	IIe	58561	250	100	250	C 79	125	86
6-Phenyl-	IIf	49019	500	71	400	C 72	400	95
5-Chloro-	IVa	28172	500	73	500	E 33	450	93
						E 94		

(continued)

TABLE III (*continued*)

Compound	Number or source	NSC no.	S-180 NTL,[b] mg./kg.	S-180 T/C,[c] %	Ca-775 or E.A. NTL, mg./kg.	Ca-775 or E.A. T/C, %	L-1210 NTL, mg./kg.	L-1210 T/C, %
5-Chloro-6-methyl	Ref. 1	26542	500	89	225	E 75	450	78
5-Bromo-6-methyl	Ref. 1	53064	300	79	300	C 102	300	84
5-Chloro-6-ethyl-	IVb	58562	250	86	62	C 79	125	104
5-Chloro-6-propyl-	IVc	58563	250	101	125	C 77	250	92
5-Chloro-6-isopropyl-	IVd	58564	125	86	125	C 78	250	87
5-Chloro-6-heptadecyl-	IVe	58565	250	73	250	C 121	250	95
5-Chloro-6-phenyl-	IVf	58567	250	107	250	C 96	250	91
Methyl 5-chloroorotate	*e*	64341	500	81	450	C 97	450	104
Part B, Polychloropyrimidines								
2,4-Dichloro-	Comm. avail.	37531	125	87	125	E 112	100	104
					100	E 147		
2,4-Dichloro-6-methyl-		13199	500	71	400	C 100	500	108
2,4-Dichloro-6-ethyl-	IIIb	58568	63	101	125	C 105	63	96
2,4-Dichloro-6-propyl-	IIIc	58569	63	75	250	C 108	250	102
2,4-Dichloro-6-isopropyl-	IIId	58570	250	116	62	C 95	62	97
2,4-Dichloro-6-heptadecyl-	IIIe	58571	250	93	250	C 87	250	104
2,4-Dichloro-6-phenyl-	IIIf	49018	125	104	25	C 107	100	97
2,4,5-Trichloro-	Va	40593	31	86	7	C 124	25	98
2,4,5,6-Tetrachloro-	*e*	35123	125	49	3.75	C 37	1.9	104
			30	85	24	E 78		
6-Methyl-2,4,5-trichloro-	Ref. 1	26541	500	72	450	C 54	450	111
						E *f*		
6-Bromomethyl-2,4,5-trichloro	Ref. 1	30721	10	47	7	E 131	7	100
			10	70		C 85		
6-Ethyl-2,4,5-trichloro-	Vb	58573	16	95	31	C 91	62	105
6-Propyl-2,4,5-trichloro-	Vc	58574	63	60	31	C 78	62	102
6-Isopropyl-2,4,5-trichloro-	Vd	58575	21	68	31	C 117	62	100
6-Heptadecyl-2,4,5-trichloro-	Ve	58576	250	126	250	C 120	250	104
6-Phenyl-2,4,5-trichloro-	Vf	53184	63	128	15	C 71	250	88
4-Carbomethoxy-2,5,6-trichloro-	Ref. 12		8	48				
		64342	2	106	2	C 129	2	97

[a] We are indebted to Dr. Howard Bond, Cancer Chemotherapy, National Service Center, NIH, Bethesda 14, Md., for making these data available to us. The details of the screening procedures can be found in ref. 12. [b] NTL = maximum non-toxic level. [c] T/C = treated tumor/control tumor. [d] C = Carcinoma-755; E = Ehrlich ascites. [e] H. Gershon, *J. Org. Chem.*, **27**, 3507 (1962). [f] Test results on Ehrlich ascites from 3 laboratories:

Lab	1										2				3
NTL	450	450	450	450	450	450	750	600	450	225	750	600	450	225	225
T/C	42	16	20	32	5	34	2	27	0	49	87	78	103	83	116

(12) CCNSC Specifications for Screening Chemical Agents and Natural Products Against Animal Tumours, compiled by Drug Evaluations Branch, *Cancer Chemother. Rep.*, **1**, 12 (1959).

acetic acid. About 50–100 mg. of ferric chloride was added, and the solution was brought to near boiling. Sulfuryl chloride (23.0 g., 0.17 mole) was added dropwise with agitation. Upon completion of addition of the sulfuryl chloride, the solution was heated under reflux till no more hydrogen chloride was evolved. The mixture was allowed to cool to room temperature with agitation and 53 g. of product was obtained after filtration and washing with water and acetone. The yield was 89%, m.p. 204–210°. An analytical sample was crystallized from methanol, m.p. 210–211.5°.

2,4-Dichloro-6-*n*-heptadecylpyrimidine (IIIe).—A mixture of 35.0 g. (0.1 mole) of IIe in 350 ml. of phosphorus oxychloride was heated under reflux with agitation till hydrogen chloride evolution nearly ceased. The excess phosphorus oxychloride was removed in a flash evaporator and the residue was poured into an ice-water slurry. The dichloropyrimidine was extracted with ether, which was dried, decolorized with charcoal, filtered and evaporated under vacuum. The oily residue did not distil below 190° (0.3 mm.) and could not be purified further.

6-*n*-Heptadecyl-2,4,5-trichloropyrimidine (Ve).—A mixture of 29.0 g. (0.075 mole) of IVe in 290 ml. of phosphorus oxychloride was treated as above. A yield of 29.2 g. (92%) of Ve was obtained which could not be distilled below 190° (0.3 mm.) or crystallized.

Antiamebic Agents. VI.[1] Analogs of Bialamicol and Related Quinolinols

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Bialamicol is a useful antiamebic agent.[4,5] A recent publication[6] in which the diethylamino of bialamicol

(1) Previous paper: J. H. Burckhalter and R. I. Leib, *J. Org. Chem.*, **26**, 4078 (1961).

(2) College of Pharmacy, The University of Michigan, Ann Arbor, Mich.

(3) Parke, Davis and Co. Fellow.

(4) J. H. Burckhalter, F. H. Tendick, E. M. Jones, W. F. Holcomb and A. L. Rawlins, *J. Am. Chem. Soc.*, **68**, 1894 (1946). Trade name of bialamicol: Camoform®.

(5) P. E. Thompson, J. W. Reinertson, D. A. McCarthy, A. Bayles and A. R. Cook, *Antibiotics & Chemotherapy*, **8**, 433 (1955); R. V. Taylor, *Am. J. Gastroenterol.*, **26**, 713 (1956).

(6) E. F. Elslager and F. H. Tendick, *J. Med. Pharm. Chem.*, **5**, 646 (1962).