Irreversible Enzyme Inhibitors. CLXII.[1,2] Hydrophobic Bonding to Cytosine Nucleoside Deaminase with 1-Substituted 5-Arylcytosines[3]

B. R. BAKER AND JAMES L. KELLEY

Department of Chemistry, University of California at Santa Barbara, Santa Barbara, California 93106

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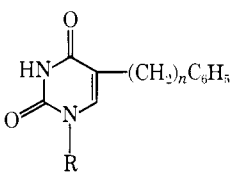
1-Phenoxypropyl-5-phenylcytosine (**2**) was previously reported[3b] to be an inhibitor of cytosine nucleoside deaminase that was complexed one-fourth as well as the substrate, 2'-deoxycytidine. In order to enhance the activity of **2**, 41 variants were synthesized for evaluation: (a) the 1-phenoxypropyl moiety was as good or better than five other **1** substituents studied; (b) when the 5-phenyl group was substituted with ten different groups, optimum binding occurred with the 3,4-Cl_2 substituents; (c) 15 different substituents on the phenoxy moiety gave little change in binding, but showed good bulk tolerance for the large benzamido substituent; (d) five combinations of the substituents on the 2,4 positions of the pyrimidine moiety gave optimum binding with the 2-oxo-4-thione combination. Among the best inhibitors derived from 5-(3,4-dichlorophenyl)cytosine were the 1-(*p*-chlorophenoxypropyl) (**26**) and 1-(*m*-benzamidophenoxypropyl) (**37**) derivatives which were complexed threefold better to the enzyme than the substrate.

In the previous paper[3b] on the cytosine nucleoside deaminase from *Escherichia coli* B, we reported that 1,5-disubstituted uracils (**1**) could inhibit the enzymatic



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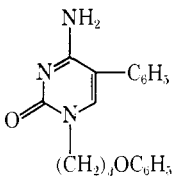


2

a, R = $(CH_2)_3OC_6H_5$

conversion of 2'-deoxycytidine to 2'-deoxyuridine. Optimum inhibition was achieved when **1** had a 1-phenoxypropyl substituent (**1a**) and $n = 0$, 2, or 3. We also observed that the cytosine derivative (**2**) was half as effective as **1a** ($n = 0$).[3b] Therefore, a study has now been made on inhibition of cytosine nucleoside deaminase by 1,5-disubstituted cytosines; the results are the subject of this paper.

Enzyme Results.—The effect of single Cl, Me, and NO_2 substituents on the phenoxy moiety of **2** was first studied (Table I). Only a two- to threefold increase in binding was observed with **3–9** compared to the parent **2** (or **16** in the case of **6**); the best inhibition was seen with a *m*- (**4**) or *p*-Cl atom (**5**).

The effect of substitution on the 5-phenyl group was then studied (**10–18**). With a single Cl, MeO, Me, NH_2, NHAc, or NO_2 substituent, binding could be enhanced two- to threefold. No obvious correlations of binding with electronic or hydrophobic effects were seen. However, the bulk tolerance for the *p*-acetamido group of **17** indicated that this would be a good area for further modification to candidate irreversible inhibitors, as described in the paper that follows.[4]

The effects of the *m*-Cl (**11**) and *p*-Cl (**12**) substituents were found to be additive with 3,4-Cl_2 (**13**); the latter was complexed sevenfold better than the parent **2**. Therefore the 3,4-dichlorophenyl substituent on the 5 position was held constant while a more extensive study of the binding of 1 substituents on this cytosine derivative was performed (Table II).

Phenethyl (**19**) and phenylpropyl (**20**) substituents on the 1 position of the cytosine were less effective than phenoxypropyl (**13**), but phenylhexyl (**21**) was equally effective (Table II). Phenoxyethyl (**22**) and phenoxybutyl (**23**) substituents were as effective as phenoxypropyl (**13**).

Since no substituent was more effective than phenoxypropyl, the effects of additional groups on the phenoxypropyl moiety were studied (**24–37**). Binding was enhanced only twofold at best with a *p*-Cl (**26**) or *m*-benzamido substituent (**37**) while other substituents gave no appreciable enhancement or as much as a twofold loss in binding (see **24**). Again there was no obvious correlation of hydrophobic or electronic effects of the phenoxy substituents on binding. However, the bulk tolerance for the large benzamido group on the *ortho* (**36**) or *meta* (**37**) positions is notable. Surprisingly further substitution on the benzamido moiety of **37** by *p*-SMe (**38**) led to a greater than threefold loss in binding, indicating that there might not be bulk tolerance for additional groups on the benzamido moiety; however, it also indicated that the benzamido group was in contact with the enzyme surface, a requirement needed for active-site-directed irreversible inhibitors.

That the phenoxy group probably resided on a polar area of the enzyme was indicated by the unchanged binding when the phenoxy moiety of **32** was replaced by a phenylthio moiety (**39**). Thus, the combination of some bulk tolerance on the phenoxy moiety and the probability that the phenoxy moiety resided on a polar area of the enzyme made the prospects good for the emergence of active-site directed irreversible inhibitors[5] by appropriate substitution on the phenoxy moiety; such studies are described in the paper that follows.[4]

Some miscellaneous studies are tabulated in Table III. Replacement of the 2-oxo group of **2** with thione (**40**) gave a threefold increment in binding indicating that the 2-oxo group of **2** was not complexed to the enzyme as an electron donor.[6] In contrast, replacement of the

(1) This work was generously supported by Grant CA-08695 from the National Cancer Institute, U. S. Public Health Service.

(2) For the previous paper in this series see B. R. Baker and J. A. Hurlbut, *J. Med. Chem.*, **12**, 902 (1969).

(3) For the previous papers on this enzyme see (a) B. R. Baker and J. L. Kelley, *ibid.*, **11**, 682 (1968); (b) *ibid.*, **11**, 686 (1968).

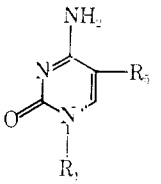
(4) B. R. Baker and J. L. Kelley, *ibid.*, **12**, 1046 (1969), paper CLXIII of this series.

(5) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors," John Wiley and Sons, Inc., New York, N. Y., 1967.

(6) (a) See ref 5, pp 75, 89, 105; (b) B. R. Baker, T. J. Schwan, and D. V. Santi, *J. Med. Chem.*, **9**, 66 (1966); (c) B. R. Baker and M. Kawazu, *ibid.*, **10**, 313 (1967), paper LXXIX of this series; (d) B. R. Baker and D. V. Santi, *ibid.*, **10**, 62 (1967), paper LXXIV of this series.

Table I

Inhibition[a,b] of Cytosine Nucleoside Deaminase by

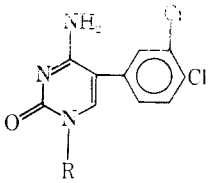


No.	R_1	R_5	Concn, m*M*	% inhibn	Estd I_{50}, m*M*	pH 18[f]
2	$(CH_2)_3OC_6H_5$	C_6H_5	0.44	50	0.44	4.4
3	$(CH_2)_3OC_6H_4Cl$-*o*	C_6H_5	0.40	50	0.40	4.0
4	$(CH_2)_3OC_6H_4Cl$-*m*	C_6H_5	0.15	50	0.15	1.5
5	$(CH_2)_3OC_6H_4Cl$-*p*	C_6H_5	0.16	50	0.16	1.6
6	$(CH_2)_3OC_6H_4CH_3$-*m*	$C_6H_4NH_2$-*p*	0.20	50	0.20	2.0
7	$(CH_2)_3OC_6H_4NO_2$-*o*	C_6H_5	0.28	50	0.28	2.8
8	$(CH_2)_3OC_6H_4NO_2$-*m*	C_6H_5	0.28	50	0.28	2.8
9	$(CH_2)_3OC_6H_4NO_2$-*p*	C_6H_5	0.20[c]	91	0.30	3.0
10	$(CH_2)_3OC_6H_5$	C_6H_4Cl-*o*	0.30[d]	96	0.35	3.5
11	$(CH_2)_3OC_6H_5$	C_6H_4Cl-*m*	0.19	50	0.19	1.9
12	$(CH_2)_3OC_6H_5$	C_6H_4Cl-*p*	0.16	50	0.16	1.6
13	$(CH_2)_3OC_6H_5$	$C_6H_3Cl_2$-3,4	0.0661	50	0.0661	0.661
14	$(CH_2)_3OC_6H_5$	$C_6H_4OCH_3$-*p*	0.12	50	0.12	1.2
15	$(CH_2)_3OC_6H_5$	$C_6H_4CH_3$-*p*	0.19	50	0.19	1.9
16	$(CH_2)_3OC_6H_5$	$C_6H_4NH_2$-*p*	0.16	50	0.16	1.6
17	$(CH_2)_3OC_6H_5$	C_6H_4NHAc-*p*	0.16	50	0.16	1.6
18	$(CH_2)_3OC_6H_5$	$C_6H_4NO_2$-*p*	0.16	50	0.16	1.6

[a] The technical assistance of Julie Leseman, Susan Black, and Maureen Baker with these assays is acknowledged. [b] The enzyme from *E. coli* B was assayed with 0.1 m*M* 2′-deoxycytidine in pH 7.4 Tris buffer containing 10% DMSO as previously described.[5b] [c] Ratio of I_{50} to the substrate concentration (0.1 m*M*). [d] Maximum solubility or maximum concentration allowing full light transmission.

Table II

Inhibition[a,b] of Cytosine Nucleoside Deaminase by



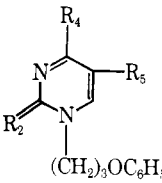
No.	R	Concn, m*M*	% inhibn	Estd I_{50}, m*M*	pH 18[f]
13	$(CH_2)_3OC_6H_5$	0.0661	50	0.0661	0.661
19	$(CH_2)_2C_6H_5$	0.20[c]	35	0.37	3.7
20	$(CH_2)_3C_6H_5$	0.10[e]	28	0.24	2.3
21	$(CH_2)_6C_6H_5$	0.050[e]	44	0.0662	0.662
22	$(CH_2)_2OC_6H_5$	0.0158	50	0.0158	0.158
23	$(CH_2)_4OC_6H_5$	0.0156	50	0.0156	0.156
24	$(CH_2)_3OC_6H_4Cl$-*o*	0.11	50	0.11	1.1
25	$(CH_2)_3OC_6H_4Cl$-*m*	0.0142	50	0.0142	0.142
26	$(CH_2)_3OC_6H_4Cl$-*p*	0.0333	50	0.0333	0.333
27	$(CH_2)_3OC_6H_3Cl_2$-2,3	0.0125[e]	0	>0.10[e]	>1
28	$(CH_2)_3OC_6H_3Cl_2$-3,4	0.0138[d]	46	0.0144	0.144
29	$(CH_2)_3OC_6H_3Cl_2$-3,5	0.0120[e]	14	>0.080[e]	>0.8
30	$(CH_2)_3OC_6H_4NO_2$-*o*	0.0167	50	0.0167	0.167
31	$(CH_2)_3OC_6H_4NO_2$-*m*	0.11	50	0.11	1.1
32	$(CH_2)_3OC_6H_4NO_2$-*p*	0.0175	50	0.0175	0.175
33	$(CH_2)_3OC_6H_4OCH_3$-*p*	0.0180	50	0.0180	0.180
34	$(CH_2)_3OC_6H_3$-3-Cl-4-NO_2	0.0162	50	0.0162	0.162
35	$(CH_2)_3OC_6H_2$-2-NO_2-4,5-Cl_2	0.0173	50	0.0173	0.173
36	$(CH_2)_3OC_6H_4NHCOC_6H_5$-*o*	0.0152	50	0.0152	0.152
37	$(CH_2)_3OC_6H_4NHCOC_6H_5$-*m*	0.0131	50	0.0131	0.131
38	$(CH_2)_3OC_6H_4$-*m*-$NHCOC_6H_4SMe$-*p*	0.0125	0	>0.10	>1.0
39	$(CH_2)_3SC_6H_4NO_2$-*p*	0.0150	50	0.0174	0.174

[a–d] See corresponding footnotes in Table I. [e] Since 20% inhibition is readily detectable, the I_{50} is greater than four times the concentration measured.

4-oxo group of **43** by thione **42**) gave threefold enhanced binding, indicating that the 3-NH was complexed to the enzyme, but the 4-oxo group was not.[6] That the group on the 4 position was not complexed to the enzyme was further substantiated by comparison of the basic 4-amino group of **2** with the acidic 4-NHOH group of **41**, the latter being about a twofold better inhibitor.

TABLE III

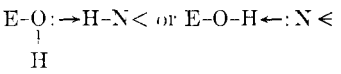
INHIBITION[a,b] OF CYTOSINE NUCLEOSIDE DEAMINASE BY



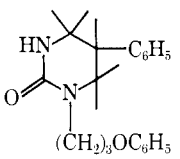
No.	R_2	R_4	R_5	Concn, mM	% inhibn	Estd I_{50}, mM	[I]/[S][c]
2	O	NH_2	C_6H_5	0.44	50	0.44[e]	4.4
13	O	NH_2	$C_6H_3Cl_2$-3,4	0.061	50	0.061	0.61
40	S	NH_2	C_6H_5	0.15	50	0.15	1.5
41	O	NHOH	C_6H_5	0.18	50	0.18	1.8
42	O	SH	C_6H_5	0.071	50	0.071	0.71
43	O	OH	C_6H_5	0.10[d]	29	0.23[e]	2.3
44	O	OH	$C_6H_3Cl_2$-3,4	0.05[d]	30	0.12	1.2

[a–d] See corresponding footnotes in Table I. [e] Data from ref 3.

The suggestion that the 3-NH group of **42** and **43** is complexed to the enzyme would at first glance seem incongruent with the binding of the 4-amino analog (**2**) which has no 3-NH. A similar binding pattern has been previously seen with 4-substituted pyrimidines as inhibitors of thymidylate synthetase.[7] The rationalization previously used for the latter enzyme[7b] is also appropriate in this case; the same enzymic OH group could bind to either a 3-NH or 3-N as respectively

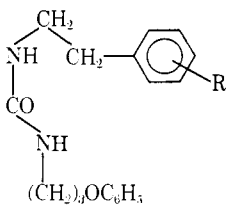


A good way to verify that the group at the 4 position was not complexed with the enzyme would be to replace the 4-group by H; unfortunately desulfurization of **42** (Table III) led to the tetrahydro derivative (**45**). Surprisingly, **45** was as good an inhibitor as the uracil (**43**)

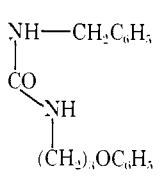


45 (I_{50} = 0.25 mM)

or cytosine (**2**) analogs. Therefore open-chain analogs (**46–48**) of **45** were synthesized for evaluation. The open-chain analog (**46**) of **45** was as good an inhibitor as **45** or **43**. That there were definite spacial requirements for the phenethyl moiety of **46** was indicated by the poor inhibition by **48**.



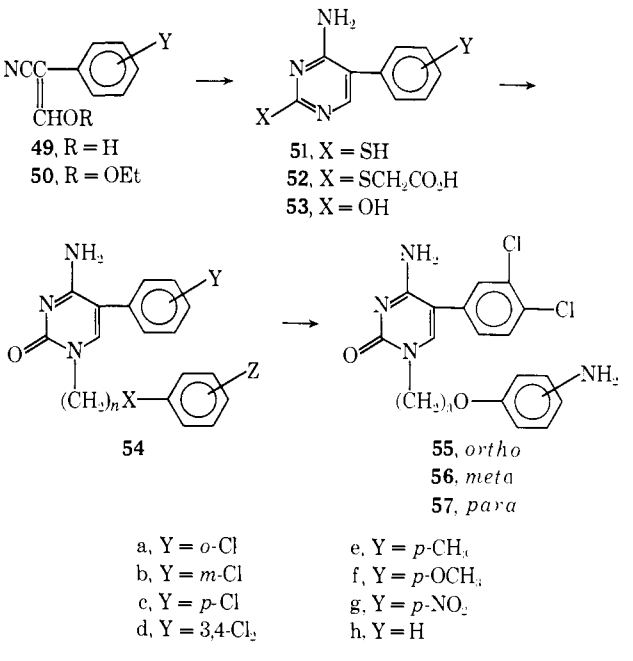
46, R = H (I_{50} = 0.24 mM)
47, R = 3,4-Cl_2 (I_{50} > 0.3 mM)



48 (I_{50} > 1.2mM)

Chemistry.—All of the inhibitors in Tables I and II can be generalized by **54**. Of the required 5-arylcytosines (**53a-h**), the synthesis of 5-phenyl (**53h**) has been described in the preceding paper.[3b] The 5-arylcytosines (**53a-f**) were synthesized by this same general method from the required α-formylphenylacetonitriles (**49**) (see Scheme I); most of these (**49**) have been previously reported[8] and were synthesized by a modified procedure.[3b] Conversion of **49** to enol ethers (**50**) with triethylorthoformate,[9] followed by treatment with thiourea,[3b] gave the 2-thiocytosines (**51**) in 22–61% over-all yields. Acid hydrolysis of **51** with HCl–ClAcOH[3b] afforded the desired 5-arylcytosines (**53**) in high yields. Only in the case of **52d** was the intermediate carboxymethyl thioether isolated[3b] and characterized. Nitration of **53h** afforded 5-(*p*-nitrophenyl)cytosine (**53g**) in 88% yield.[10]

SCHEME I



49, R = H
50, R = OEt

51, X = SH
52, X = SCH_2CO_2H
53, X = OH

54

55, *ortho*
56, *meta*
57, *para*

a, Y = *o*-Cl
b, Y = *m*-Cl
c, Y = *p*-Cl
d, Y = 3,4-Cl_2
e, Y = *p*-CH_3
f, Y = *p*-OCH_3
g, Y = *p*-NO_2
h, Y = H

The requisite substituted phenoxypropyl bromides for synthesis of **54** were prepared by alkylation of the sodium salt of the appropriate phenol with excess 1,3-dibromopropane in DMF or DMSO and were used as their crude oils. In the preparation of 3-bromopropyl *p*-nitrophenyl sulfide (**66**), even though inverse addi-

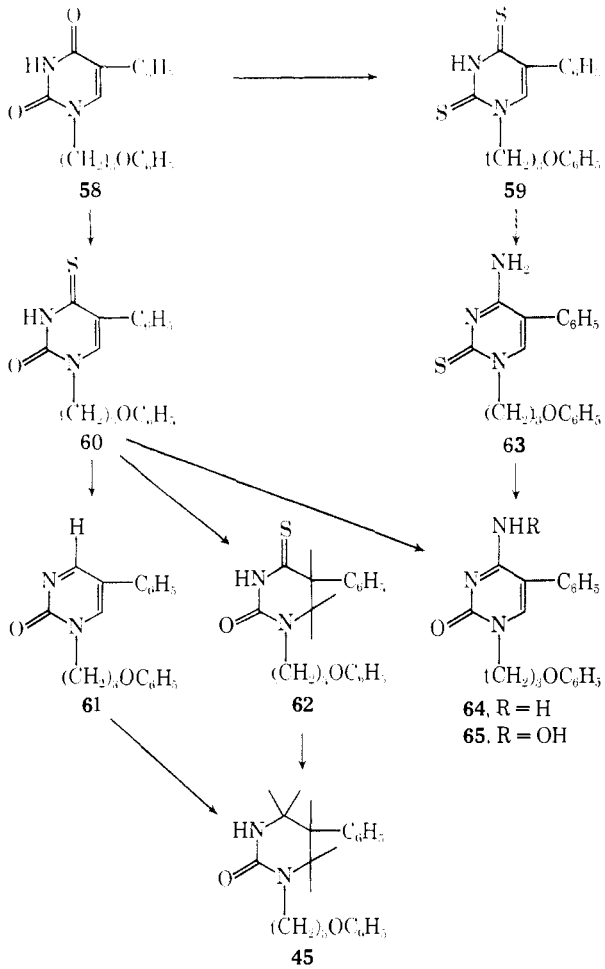
(7) (a) B. R. Baker, B. T. Ho, and T. Neilson, *J. Heterocycl. Chem.*, **1**, 79 (1964); (b) ref 5, p 274.

(8) P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3763 (1951).

(9) P. B. Russell and N. Whittaker, *ibid.*, **74**, 1310 (1952).

(10) Z. Budesinsky, V. Bydzovsky, and Z. Perina, Czechoslovakian Patent 106,227 (1963); *Chem. Abstr.*, **60**, 8042 (1964).

Scheme II



tion was used,[11] a mixture of products was obtained. Purification of the mixture by column chromatography gave the crystalline sulfide **66** in 21% yield.

The previously reported[3h] procedure for alkylation of 5-phenylcytosine (**53h**) was modified for some of the 1-substituted 5-arylcytosines (**54**) in Table V.

Catalytic reduction of **30**–**32** (Table II) in the presence of a large excess of Raney Ni gave the aromatic amines (**55**–**57**) in high yield; attempted reduction with PtO_2 or Pd–C catalysts gave incomplete reduction and mixtures of products. Reduction of **18** (Table I) in the presence of Pd–C was rapid and afforded the amine **16** in 93% yield.

The acylation of **55** and **56** with benzoyl chloride in DMF in the presence of Et_3N afforded the benzamides (**36**, **37**) (Table II) while treatment of **16** with an excess of Ac_2O followed by aqueous work-up gave *p*-acetamidophenyl (**17**) (Table I) in 72% yield. The coupling of **56** with *p*-methylthiobenzoic acid utilizing a water-soluble carbodiimide[12] gave readily isolatable **38** (Table II) although in very poor yield.

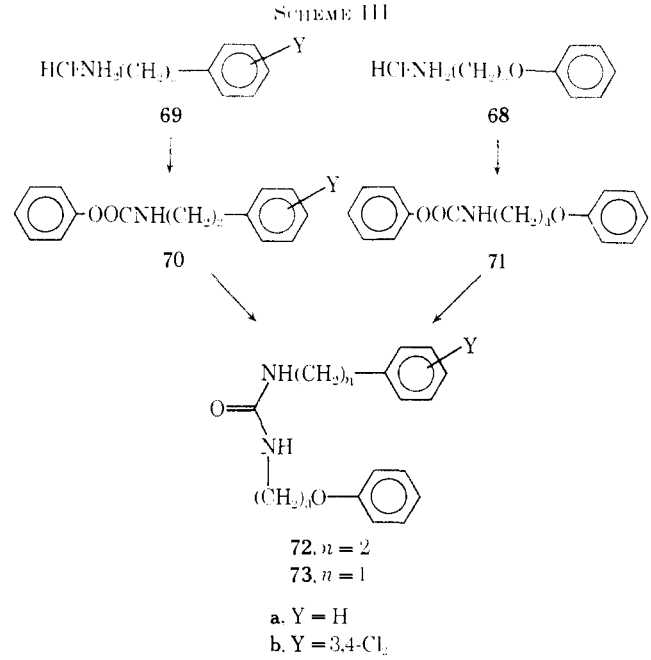
Thiation of uracils with P_2S_5 has been shown to lead to 4-thio- or 2,4-dithiouracils depending upon the reaction conditions.[13] Thus, when **58** (**43**)[3b] was treated with P_2S in tetralin,[13a,b] the dithiouracil (**59**) was the

(11) Addition of excess 1,3-dibromopropane to a DMSO solution of the thiophenol in the usual manner gave predominantly bisalkylated propane.

(12) J. C. Sheehan and J. J. Hlavka, *J. Org. Chem.*, **21**, 439 (1956).

(13) (a) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **69**, 2138 (1947); (b) P. B. Russell, G. B. Elion, E. A. Falco, and G. H. Hitchings, *ibid.*, **71**, 2279 (1949); (c) J. J. Fox, D. V. Prang, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *ibid.*, **81**, 178 (1959).

Scheme III



only product isolated (see Scheme II). Treatment of **59** with ethanolic NH_3 at 80–90° gave the 2-thiocytosine (**63** = **40**) in 45% yield. That the expected[1a,b] displacement of the 4-thione had occurred was shown by hydrolysis of **63** (**40**) to the known **64** (**2**).[3b] Prolonged reflux of **58** (**43**)[3b,c] with P_2S_5 in C_5H_5N[13c] gave the 4-thiouracil (**60** = **42**) in 74% yield; treatment with NH_3 or with NH_2OH gave the respective cytosines (**64** = **2**, **65** = **41**). Attempted displacement of the 4-thione of **60** (**42**) with a few aliphatic amines failed to give the desired products. Desulfuration of **60** (**42**) with excess Raney Ni resulted in reduction of the pyrimidine ring as well as displacement of the sulfur to give the tetrahydropyrimidine (**45**) in 76% yield; whether the reaction proceeded *via* **61** or **62** was not determined.

The synthesis of the ureas (**72** and **73**) (**46** and **48**) was accomplished by reaction of the appropriate carbamate (**70**, **71**), available by the method of Crosby and Niemann,[14] with the appropriate aralkylamine (**68**, **69**) (see Scheme III). The phenoxypropyl amine (**68**) was available by a modification of the literature[15] procedure, whereas **69b**[16] was obtained from catalytic reduction of 3,4-dichlorophenylacetonitrile.[16c]

Experimental Section[17]

5-(3,4-Dichlorophenyl)cytosine (53d) (Method B). A mixture of 8.84 g (32.5 mmoles) of **51d**, 13 g of chloroacetic acid, 50 ml of AcOH, and 100 ml of H_2O was refluxed with stirring for 22 hr. The reaction was filtered while hot through Celite to remove some insoluble tar. The cooled solution was then spin evaporated *in vacuo*. The residue was treated with 200 ml of 12

(14) D. G. Crosby and C. Niemann, *ibid.*, **76**, 4458 (1954).

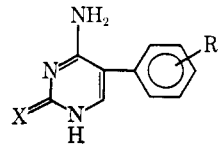
(15) J. Lohmann, *Chem. Ber.*, **24**, 2631 (1891); his procedure was modified by using DMF in the first step (77% yield) and N_2H_4 in the second step (82% yield).

(16) (a) S. Chiavarelli and M. A. Iorio, *Gazz. Chim. Ital.*, **86**, 1054 (1956); *Chem. Abstr.*, **52**, 3832 (1958); (b) W. N. Cannon, C. E. Powell, and R. G. Jones, *J. Org. Chem.*, **22**, 1323 (1957); (c) F. Benington, R. D. Morin, and L. C. Clark, Jr., *ibid.*, **25**, 2066 (1960).

(17) Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. Each analytical sample had ir and nmr spectra compatible with their assigned structures and each moved as a single spot on tlc on Brinkman silica gel GF with the indicated solvent system (A: C_6H_6–EtOH, 3:1; B: EtOAc–petroleum ether (bp 60–110°), 1:2; C: $CHCl_3$–EtOH, 1:1; D: C_6H_6–dioxane–AcOH, 90:25:4). The analytical samples gave combustion values for C, H, and N within 0.4% of theory.

TABLE IV

PHYSICAL PROPERTIES OF



No.	X	R	Method[a]	Reaction time, hr	Yield, %	Mp, °C dec[b]	Formula[c]
51a	S	*o*-Cl	A	8	22[d,e]	278–281 (270)	$C_{10}H_8ClN_3S$
51b	S	*m*-Cl	A	8	37[d,e]	274–276 (270)	$C_{20}H_8ClN_3S$
51c	S	*p*-Cl	A	8	38[d,e]	292–293 (285)	$C_{10}H_8ClN_3S$
51d	S	3,4-Cl_2	A[f]	18	61[d,g]	305–306[h] (290)	
51e	S	*p*-CH_3	A	22	31[d,i]	296–306 (200)	$C_{11}H_{11}N_3S$
51f	S	*p*-OCH_3	A	20	35[d,g]	285–288 (280)	$C_{11}H_{11}N_3OS$
53a	O	*o*-Cl	B	6, 2	95[j]	320–323 (315)	$C_{10}H_8ClN_3O$
53b	O	*m*-Cl	B	3, 2	75[g]	332–333 (329)	$C_{10}H_8ClN_3O$
53c	O	*p*-Cl	B	8, 2	91[g]	>360[k]	
53d	O	3,4-Cl_2	B[l]	22, 22	87[g]	340–343 (300)	$C_{10}H_7Cl_2N_3O$
53e	O	*p*-CH_3	C	8	60[m]	>350	$C_{11}H_{11}N_3O$
53f	O	*p*-OCH_3	B	12, 12	57[g]	332–338 (325)	$C_{11}H_{11}N_3O_2$

[a] A: see preparation of **51h**, except H_2SO_4 was omitted from the $(EtO)_3CH$ step;[3b] B: see Experimental Section; C: see preparation of **53h** (method B).[3b] [b] On block preheated to temperature indicated in parenthesis; no definite melting points could be obtained in the usual manner. [c] Analyzed for C, H, N where formula given. [d] Over-all yield from **49**. [e] Recrystallized from MeOEtOH. [f] Intermediate **49d**, mp 167–170°, from petroleum ether (bp 60–110°) in 83% yield. *Anal.* ($C_9H_5Cl_2NO$) C, H, N. Intermediate **50d**, mp 104–106° from petroleum ether. *Anal.* ($C_{11}H_9Cl_2NO$) C, H, N. [g] Recrystallized from DMF. [h] Burroughs Wellcome and Co. (U. S. A.) Inc., British Patent 671,972 (1952); *Chem. Abstr.*, **47**, 5457 (1953), reports mp 298–302°. [i] Recrystallized from DMF–EtOH. [j] Recrystallized from EtOH–MeOEtOH. [k] Mp 380° dec reported for this compound prepared by an alternate route by D. P. Hansell, *Chem. Ind.* (London), 884 (1959). [l] Intermediate **52d** isolated in 70% yield by omission of second step; mp 162–165° dec (161°). *Anal.* ($C_{12}H_9Cl_2N_3O_2S$) C, H, N. If the block was not preheated, it changed to a different compound, mp 263–265°, as shown by uv change. [m] Recrystallized from DMF–MeOEtOH.

N HCl, then refluxed for 20 hr. The cooled mixture was evaporated to dryness *in vacuo*, the residue was diluted with 100 ml of H_2O and the pH was adjusted to 5–6 with 50% NaOH. The precipitate was collected and washed with H_2O; yield, 7.24 g (87%) of a white powder, mp 332–339°. (This material could be further purified with minimal loss by digestion with MeOEtOH.) Recrystallization of a portion from DMF gave the analytical sample. See Table IV for additional data and other compounds prepared by this method.

3-Bromopropyl *p*-Nitrophenyl Sulfide (66).—To a stirred solution of 1.08 g (20 mmoles) of NaOMe in 75 ml of absolute EtOH was added 3.10 g (20 mmoles) of technical 4-nitrothiophenol. After 0.5 hr the solvent was evaporated *in vacuo* and the residual salt was dissolved in 50 ml of DMSO. This solution was then added in portions to a vigorously stirred solution of 6.8 ml of 1,3-dibromopropane in 25 ml of DMSO. After 1 hr the neutral solution was diluted with 100 ml of $CHCl_3$ and 100 ml of H_2O. The layers were separated, and the aqueous portion was extracted with three 50-ml portions of $CHCl_3$. The combined organic extracts were washed with three 50-ml portions of 0.5 *N* NaOH, two 50-ml portions of saturated aqueous NaCl, then dried ($MgSO_4$). The solvent was spin evaporated *in vacuo* and then at ~1 mm to remove 1,3-dibromopropane. The residual oil was applied to a column of silica gel (400 g of 28–200 mesh, Grade 12, Grace Davidson Chemicals). The column was eluted with PhH until the effluent was free of the highest R_f materials as detected on tlc (B). The eluate was concentrated to an oil which appeared as two close spots on tlc in a ratio of approximately 5:1. The material of lower R_f (major spot) formed crystals when a small portion of the oil was dissolved in Me_2CO and allowed to evaporate slowly. Subsequently, the oil was recrystallized from *i*-PrOH with seeding to give 1.18 g (21%) of yellow flakes, mp 49–53°. Additional recrystallization of a portion gave the analytical sample, mp 53.5–55°; the nmr spectrum was consistent with the assigned structure. *Anal.* ($C_9H_{10}BrNO_2S$) C, H, N.

4,5-Dichloro-2-nitrophenyl 3-Bromopropyl Ether (67) (Method E).—To a stirred mixture of 0.878 g (4.2 mmoles) of 4,5-dichloro-2-nitrophenol[18] in 20 ml of DMF was added 0.168 g (4.2 mmoles) of NaH (59.8% dispersion in mineral oil). After 0.5 hr at ambient temperature a solution of 2 ml of 1,3-dibromopropane in 10 ml of DMF was added. The solution was then stirred at ambient temperature for 4–8 hr within which the pH tested 5–6 when spotted on wet Hydrion E paper. The DMF solution was poured into an equal volume of $CHCl_3$ and was washed successively with four 25-ml portions of 0.5 *N* NaOH, 25 ml of H_2O, 25 ml of saturated aqueous NaCl, then dried ($MgSO_4$). The solvent was spin evaporated *in vacuo*, finally at 1 mm, leaving an oil (0.770 g, 56%) which moved as one spot on tlc (B) and was used as such in subsequent steps.

In **method F**, the anion of the phenol was formed with NaOMe as with **66** and the alkylation was carried out in DMSO; a short period of warming on a steam bath was also employed. In **method G**, the anion of the phenol was formed with NaOMe as with **66**.

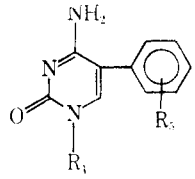
5-(3,4-Dichlorophenyl)-1-(*p*-nitrophenylthiopropyl)cytosine (39) (Method H).—A mixture of 1.28 g (5.0 mmoles) of **53d**, 1.80 g (6.5 mmoles) of **66**, 0.75 g (5.0 mmoles) of NaI, 1.40 g (10.0 mmoles) of K_2CO_3, and 20 ml of DMSO was stirred at ambient temperature for 39 hr. The reaction mixture was poured over 150 ml of iced water and 10 ml of 12% aqueous NaOH was added. The dispersion was stirred at ambient temperature for 0.5 hr. The product was collected on a filter and washed with H_2O. Two recrystallizations from EtOH–MeOEtOH gave 1.41 g (62%) of yellow needles, mp 84–90° which were uniform on tlc (A). An additional recrystallization of a portion gave needles, mp 89–92°. When this sample was dried under high vacuum at 105° solvent of crystallization was removed to afford the analytical sample, mp 178–181°. See Table V for additional data and other compounds prepared by this method.

1-(*o*-Benzamidophenoxypropyl)-5-(3,4-dichlorophenyl)cytosine (36) (Method I).—To a stirred solution of 0.341 g (0.84 mmole) of **55**, 88 mg (0.87 mmole) of Et_3N, and 2 ml of DMF, protected from moisture and cooled on an ice bath, was added 0.118 g (0.84 mmole) of benzoyl chloride in 1 ml of DMF. The resultant mixture was left overnight at ambient temperature and then poured over 25 g of crushed ice, acidified to pH ~3 with 1 *N* HCl, then stirred for 1 hr. The product was collected, washed with H_2O, and recrystallized from EtOAc–EtOH, then EtOH–MeOEtOH; yield 100 mg (26%) of a light brown solid, mp (sinters 140) 228–232°, which gave a negative Bratton–Marshall

(18) This phenol was prepared as described by R. M. Acheson and N. F. Taylor, *J. Chem. Soc.*, 4727 (1956), from 4,5-dichloro-1,2-dinitrobenzene; the latter was available by the method of R. J. W. LeFevre and E. E. Turner, *ibid.*, 1113 (1927).

Table V

Physical Properties of



No.	R6	R5	Method[a]	Yield,[b] %	Mp, °C	Formula[c]
3	$(CH_2)_3OC_6H_4Cl$-*o*	H	F, D	51[d]	149–151	$C_{19}H_{18}ClN_3O_2$
4	$(CH_2)_3OC_6H_4Cl$-*m*	H	G, D	27[e]	141–144	$C_{19}H_{18}ClN_3O_2$
5	$(CH_2)_3OC_6H_4Cl$-*p*	H	F, D	32[d]	184–186	$C_{19}H_{18}ClN_3O_2$
6	$(CH_2)_3OC_6H_4CH_3$-*p*	*p*-NH_2	E, D	10[e]	200–202	$C_{20}H_{22}N_4O_2$
7	$(CH_2)_3OC_6H_4NO_2$-*o*	H	F, D[f]	22[e]	149–151	$C_{19}H_{18}N_4O_4$
8	$(CH_2)_3OC_6H_4NO_2$-*m*	H	E, D	20[e]	167–169	$C_{19}H_{18}N_4O_4$
9	$(CH_2)_3OC_6H_4NO_2$-*p*	H	E, D	68[d]	183–185	$C_{19}H_{18}N_4O_4$
10	$(CH_2)_3OC_6H_5$	*o*-Cl	D[g]	2[e]	227–231	$C_{19}H_{18}ClN_3O_2 \cdot HCl$
11	$(CH_2)_3OC_6H_5$	*m*-Cl	D	21[h]	134–137	$C_{19}H_{18}ClN_3O_2$
12	$(CH_2)_3OC_6H_5$	*p*-Cl	D	27[d]	182–183	$C_{19}H_{18}ClN_3O_2$
13	$(CH_2)_3OC_6H_5$	3,4-Cl_2	D[i]	41[j]	157–158	$C_{19}H_{17}Cl_2N_3O_2$
14	$(CH_2)_3OC_6H_5$	*p*-OCH_3	D	28[d]	157–158	$C_{20}H_{21}N_3O_3$
15	$(CH_2)_3OC_6H_5$	*p*-CH_3	D	53[d]	138–141	$C_{20}H_{21}N_3O_2$
16	$(CH_2)_3OC_6H_5$	*p*-NH_2	Exptl Section	93	243–245[k]	$C_{19}H_{21}N_4O_2$
17	$(CH_2)_3OC_6H_5$	*p*-NHAc	Exptl Section	72	214–215[m]	$C_{21}H_{22}N_4O_3$
18	$(CH_2)_3OC_6H_5$	*p*-NO_2	H	53[n]	189–190[o]	$C_{19}H_{18}N_4O_4$
19	$(CH_2)_2C_6H_5$	3,4-Cl_2	D	28[e]	183–185	$C_{18}H_{15}Cl_2N_3O_2$
20	$(CH_2)_4C_6H_5$	3,4-Cl_2	D	29[d]	165–167	$C_{20}H_{17}Cl_2N_3O_2$
21	$(CH_2)_6C_6H_5$	3,4-Cl_2	D	42[d]	164–166	$C_{22}H_{23}Cl_2N_3O_2$
22	$(CH_2)_2OC_6H_5$	3,4-Cl_2	D[i]	35[e]	177–179	$C_{18}H_{15}Cl_2N_3O_2$
23	$(CH_2)_4OC_6H_5$	3,4-Cl_2	D[i]	34[d]	123–125	$C_{20}H_{19}Cl_2N_3O_2$
24	$(CH_2)_3OC_6H_4Cl$-*o*	3,4-Cl_2	F, D	58[e]	193–195	$C_{19}H_{16}Cl_2N_3O_2$
25	$(CH_2)_3OC_6H_4Cl$-*m*	3,4-Cl_2	G, D	12[e]	153–156	$C_{19}H_{16}Cl_2N_3O_2$
26	$(CH_2)_3OC_6H_4Cl$-*p*	3,4-Cl_2	F, D	15[e]	191–193	$C_{19}H_{16}Cl_2N_3O_2$
27	$(CH_2)_3OC_6H_3Cl_2$-2,3	3,4-Cl_2	E, D	62[d]	212–214	$C_{19}H_{14}Cl_4N_3O_2$
28	$(CH_2)_3OC_6H_3Cl_2$-3,4	3,4-Cl_2	E, D[p]	3[d]	122–127	$C_{19}H_{15}Cl_4N_3O_2$
29	$(CH_2)_3OC_6H_3Cl_2$-3,5	3,4-Cl_2	E, D	33[q]	143–146	$C_{19}H_{15}Cl_4N_3O_2 \cdot 0.5H_2O$
30	$(CH_2)_3OC_6H_4NO_2$-*o*	3,4-Cl_2	E, D	41[e]	199–201	$C_{19}H_{16}Cl_2N_4O_4$
31	$(CH_2)_3OC_6H_4NO_2$-*m*	3,4-Cl_2	E, D[e]	71[d]	124–127	$C_{19}H_{16}Cl_2N_4O_4$
32	$(CH_2)_3OC_6H_4NO_2$-*p*	3,4-Cl_2	G, D[e]	55[e]	193–197	$C_{19}H_{16}Cl_2N_4O_4$
33	$(CH_2)_3OC_6H_4OCH_3$-*p*	3,4-Cl_2	E, D[e]	26[e]	212–216	$C_{20}H_{19}Cl_2N_4O_3$
34	$(CH_2)_3OC_6H_3$-Cl-4-NO_2	3,4-Cl_2	E,[r] D	13[e]	188–190	$C_{19}H_{15}Cl_3N_4O_4$
35	$(CH_2)_3OC_6H_2$-2-NO_2-4,5-Cl_2	3,4-Cl_2	E, D	30[e]	237–239	$C_{19}H_{14}Cl_4H_4O_4$
36	$(CH_2)_3OC_6H_4NHCOC_6H_5$-*o*	3,4-Cl_2	I	26[d]	228–232[s]	$C_{26}H_{22}Cl_2N_4O_2$
37	$(CH_2)_3OC_6H_4NHCOC_6H_5$-*m*	3,4-Cl_2	I	58	277–280[t]	$C_{26}H_{22}Cl_2N_4O_2$
38	$(CH_2)_3OC_6H_4$-*m*-$NHCOC_6H_4SMe$-*p*	3,4-Cl_2	Exptl section	16[d]	247–249	$C_{27}H_{24}Cl_2N_4O_2S$
39	$(CH_2)_3SC_6H_4NO_2$-*p*	3,4-Cl_2	H	62	178–181[u,v]	$C_{19}H_{18}Cl_2N_4O_2S$
55	$(CH_2)_3OC_6N_4NH_2$-*o*	3,4-Cl_2	J	88	93–100[u,w]	$C_{18}H_{16}Cl_2N_4O_2$
56	$(CH_2)_3OC_6H_4NH_2$-*m*	3,4-Cl_2	J	80	211–212[x]	$C_{19}H_{18}Cl_2N_4O_2$
57	$(CH_2)_3OC_6H_4NH_2$-*p*	3,4-Cl_2	J	79	208–210[y]	$C_{19}H_{18}Cl_2N_4O_2$

[a] D: see preparation of 1-phenoxypropyl-5-phenylcytosine, except isolation of the HCl salt was omitted;[20] see Exptl Section for other procedures. [b] Yield of analytically pure material and is minimum, except for **16, 17, 39, 55–57** where the yield is for not quite analytically pure material. [c] Analyzed for C, H, N. [d] Recrystallized from EtOAc. [e] Recrystallized from EtOH. [f] Crude, gummy product dissolved in hot dilute HCl; the solution was filtered through Celite, then basified with NH_4OH. [g] Crude product extracted with $CHCl_3$, then back-extracted into 6 *N* HCl and evaporated *in vacuo*. [h] Recrystallized from MeOH. [i] Crystallized from Me_2CO–petroleum ether (bp 60–110°). [j] Recrystallized from THF–petroleum ether (bp 60–110°). [k] Recrystallized from EtOAc–petroleum ether (bp 60–110°). [l] Recrystallized from MeOEtOH. [m] Recrystallized from 5-PrOH. [n] After drying at 105° under high vacuum to remove solvent of crystallization; solvated crystals had mp 89–92°. [o] Reaction run at room temperature for 20 hr. [p] Recrystallized from MeOEtOH–H_2O. [q] Recrystallized from Me_2CO–H_2O. [r] Recrystallized from EtOAc–EtOH. [s] Recrystallized from EtOH–MeOEtOH. [t] Recrystallized from DMF–H_2O. [u] 3-Cl-4-NO_2-phenol prepared according to H. E. Ungnade and I. Ortega, *J. Org. Chem.*, **17**, 1475 (1952). [v] Initially melts 176–178°, then slowly resolidifies and remelts.

test.[19] See Table V for additional data and other compounds prepared by this method.

1-(*p*-Aminophenoxypropyl)-5-(3,4-dichlorophenyl)cytosine (57) (Method J). To a solution of 2.71 g (6.24 mmoles) of **32** in 200 ml of MeOEtOH was added 15 g of wet Raney Ni. The mixture was shaken with H_2 at 2–3 atm for 1 hr when reduction was complete. The filtered solution was spin evaporated *in vacuo* to give a clear oil which was dissolved in 50 ml of EtOH and then treated with 25 ml of EtOAc. The solvent was evaporated to a small volume *in vacuo*, then the product was collected and washed with cold EtOH; yield 1.99 g (79%), mp 202–209°, which was uniform on tlc (A). Recrystallization of a portion from DMF–H_2O gave the analytical sample as light beige needles. See Table V for additional data and other compounds prepared by this method.

5-(*p*-Aminophenyl)-1-phenoxypropylcytosine (16). A mixture of 4.73 g (12.9 mmoles) of **18**, 200 ml of AcOH, and 250 mg of 10% Pd–C was shaken with H_2 at 2–3 atm for 2.5 hr when reduction was complete. The filtered solution was spin evaporated *in vacuo* to near dryness and the residue was diluted with 50 ml

(19) (a) B. R. Baker, D. V. Santi, J. K. Coward, H. S. Shapiro, and J. H. Jordaan, *J. Heterocycl. Chem.*, **3**, 125 (1966); (b) A. C. Bratton and E. K. Marshall, Jr., *J. Biol. Chem.*, **128**, 537 (1939).

of H_2O. Neutralization with dilute NH_4OH afforded the product which was collected and washed with H_2O; yield 4.03 g (93%), mp (sinters 235) 239–242°. Recrystallization of a sample from EtOH gave yellow needles, mp 240–243°, which were not quite analytically pure but were sufficiently pure for further transformations.[4]

For further purification, a sample was dissolved in 1 *N* HCl and evaporated *in vacuo*. The hydrochloride was recrystallized from EtOH–H_2O to give off-white crystals, mp 234–235° which gave combustion values for 1.5HCl. The hydrochloride was dissolved in H_2O and the solution was basified with NH_4OH. Recrystallization from MeOEtOH gave beige needles, mp 243–245°. See Table V for additional data.

5-(*p*-Acetamidophenyl)-1-phenoxypropylcytosine (17).—A mixture of 0.195 g (0.58 mmole) of **16** and 14 ml of Ac_2O was stirred at ambient temperature for 1 hr during which time solution occurred. The solution was diluted with 30 ml of H_2O and after 0.5 hr the pH was adjusted to 8 with dilute NH_4OH. The mixture was stirred until flocculation occurred, then the product was collected and washed with H_2O; yield, 0.158 g (72%), mp 195–206°. Recrystallization from *i*-PrOH (charcoal) gave off-white flakes, mp (sinters 208) 214–215°, which gave a negative Bratton–Marshall test.[19] See Table V for additional data.

5-(3,4-Dichlorophenyl)-1-[*m*-(*p*-methylthiobenzamido)phenoxypropyl]cytosine (38).—To a stirred solution of 0.360 g (0.89 mmole) of **56** in 2 ml of DMF was added 0.149 g (0.89 mmole) of *p*-methylthiobenzoic acid and 0.381 g (0.90 mmole) of 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate.[12] The reaction was stirred overnight at ambient temperature and then poured over a mixture of 30 g of crushed ice and 5 ml of 1 *N* HCl. The precipitate was collected, dissolved in 5 ml of DMF and then reprecipitated with 2 ml of 12% NaOH and 20 g of crushed ice. The product was collected, washed with H_2O, then recrystallized from MeOEtOH–H_2O to give 28 mg (5.7%) of light brown cubes, mp 247–249°. See Table V for additional data.

2,4-Dithio-1-phenoxypropyl-5-phenyluracil (59).—A mixture of 3.85 g (12.0 mmoles) of **58**, 10 g of P_2S_5, and 40 ml of tetralin was refluxed with stirring for 2 hr. The mixture was cooled, and the yellow precipitate was decanted with the aid of EtOH from the hard gum which formed on the bottom of the container. The product was collected and recrystallized several times from EtOH (carbon) to give 1.21 g (27%) of yellow crystals, mp 163–165°. *Anal.* ($C_{18}H_{18}N_2OS_2$) C, H; N: calcd, 7.89; found, 7.46.

1-Phenoxypropyl-5-phenyl-4-thiouracil (60 = 42).—A solution of 0.842 g (2.61 mmoles) of **58**, 3.0 g of P_2S_5, and 100 ml of pyridine was refluxed with stirring for 50 hr when the reaction was complete. The warm solution was poured into 450 ml of H_2O and then stirred for several hours when flocculation had occurred. The yellow product was collected, washed with H_2O, then recrystallized from *i*-PrOH (charcoal); yield 0.651 g (74%), mp 156–158°. An additional recrystallization gave the analytical sample as yellow needles of unchanged melting point. *Anal.* ($C_{19}H_{18}N_2O_2S$) C, H, N.

That **60** was indeed the 4-thio derivative was shown by treatment of a small sample with ethanolic NH_3 in a metal bomb at 90–100° for 12 hr. The product had uv and tlc properties identical with **64**.

1-Phenoxypropyl-5-phenyl-2-thiocytosine (63 = 40).—A solution of 0.588 g (1.7 mmoles) of **59** in 20 ml of MeOEtOH and 70 ml of EtOH which had been saturated with NH_3 at 0° was heated in a metal bomb at 80–90° for 24 hr. The cooled contents were treated with charcoal and filtered through Celite. The filtrate was spin evaporated *in vacuo* to give a brown oil which solidified upon standing. The product was recrystallized several times from Me_2CO–H_2O and finally from Me_2CO to give 0.251 g (45%) of light brown needles, mp 223–224°. *Anal.* ($C_{19}H_{19}N_3OS$) C, H, N.

A mixture of 20 mg (0.06 mmole) of **63**, a small crystal of NaI, 4 ml of 10% aqueous chloroacetic acid, and 1 ml of 6 *N* HCl was refluxed with stirring for 3.5 days when conversion was complete. The solution was cooled, basified to pH 8–9 with dilute NH_4OH, and the precipitate was collected. This material was identical with **64** by ir, uv, and comparative tlc in solvents A and B.

2-Hydroxy-4-hydroxyamino-1-phenoxypropyl-5-phenylpyrimidine (65 = 41).—To a solution of 0.10 g (0.30 mmole) of **60** in 10 ml of MeOH was added 5.76 mmoles of NH_2OH in 20 ml of MeOH; the NH_2OH was prepared by the dropwise addition of 0.310 g (5.76 mmoles) of NaOMe in 10 ml of MeOH to 0.400 g (5.76 mmoles) of $NH_2OH \cdot HCl$ in 10 ml of MeOH, followed by filtration to remove the insoluble NaCl. The solution was refluxed with stirring for 20 hr, then spin evaporated *in vacuo*. The residue was dissolved in Me_2CO, treated with charcoal, then filtered through Celite. Spin evaporation left a white solid which was recrystallized from *n*-BuOH; yield, 8.1 mg (8%) of analytically pure material, mp 155–157°. Concentration of the mother liquors gave an additional 19 mg (27% total yield), mp 146–150°. Both crops were uniform on tlc (A) and gave a positive $FeCl_3$ test. *Anal.* ($C_{19}H_{19}N_3O_3$) C, H, N.

2-Hydroxy-1-phenoxypropyl-5-phenyl-1,4,5,6-tetrahydropyrimidine (45).—A mixture of 0.548 g (1.62 mmoles) of **60**, 25 ml of MeOEtOH, ~3 g of wet Raney Ni, and 10 ml of EtOH was refluxed with stirring for 4.5 hr. The hot mixture was filtered through Celite and the filter pad was washed with MeOEtOH. The combined filtrate and washings were spin evaporated *in vacuo*. The resultant solid was recrystallized from EtOH–H_2O; yield 0.381 g (76%), mp 121–123°. An additional recrystallization gave white needles, mp 124–125°; the nmr spectrum was consistent with the assigned structure. *Anal.* ($C_{19}H_{22}N_2O_2$) C, H, N.

5-(3,4-Dichlorophenyl)-1-phenoxypropyluracil (44) was prepared as described for the dechloro derivative[3b] by treatment with HNO_2 for 18 hr at ambient temperature, then 1 hr at 100° to complete the reaction; yield, 0.382 g (75%), mp 164–167°. Recrystallization from EtOAc–petroleum ether (bp 60–110°) and then from EtOAc gave the analytical sample, mp 168–170°. *Anal.* ($C_{19}H_{16}Cl_2N_2O_3$) C, H, N.

β-(3,4-Dichlorophenyl)ethylamine Hydrochloride (69b).—A mixture of 5.00 g (26.9 mmoles) of 3,4-dichlorobenzyl cyanide,[16c] 200 mg of PtO_2, and 100 ml of AcOH was shaken with H_2 at 2–3 atm for 4 hr when reduction was complete. The filtered solution was spin evaporated *in vacuo* to leave a light yellow oil which was dissolved in 50 ml of dry THF. The solution was saturated with gaseous HCl at 0° and then left overnight at 0°. The product was collected and washed with THF; yield 3.67 g (60%) of white flakes: mp 165–168°; lit mp 172°,[16a] 169–170°,[16b] and 178–179°,[16c] prepared by LAH reduction in lower yield.

O-Phenyl N-Phenoxypropylcarbamate (71).—To a stirred solution of 0.783 g (5.0 mmoles) of phenyl chloroformate in 10 ml of dry dioxane which had been cooled on an ice bath was added the mixture from 0.954 g (5.1 mmoles) of **68**,[15] 1.092 g (10.8 mmoles) of Et_3N, and 10 ml of dioxane. After 30 min the resulting mixture was poured over 50 g of crushed ice, acidified to pH 1 with 1 *N* HCl, then stirred for 1 hr. The flocculent product was collected, then washed with H_2O; yield 0.955 g (70%), mp (sinters 55°) 67–72°. A single crystallization from petroleum ether (bp 60–110°) gave 0.928 (67%) of white flakes, mp 82–84°. The analytical sample had mp 83.5–85°. *Anal.* ($C_{16}H_{17}NO_3$) C, H, N.

O-Phenyl N-phenethylcarbamate (70a) was prepared in the same manner as **71**; yield 2.09 g (87%), mp 89.5–92°. Recrystallization of a sample from petroleum ether (bp 60–110°) gave the analytical sample as white flakes, mp 91.5–93°. *Anal.* ($C_{15}H_{15}NO_2$) C, H, N.

O-Phenyl N-(3,4-dichlorophenethyl)carbamate (70b) was prepared as described for **71**; yield 1.36 g (87%), mp 71–73°. Recrystallization of a portion from petroleum ether (bp 60–110°) gave the analytical sample, mp 71–73°. *Anal.* ($C_{15}H_{13}Cl_2NO_2$) C, H, N.

N-Phenethyl-N′-phenoxypropylurea (72a).—A mixture of 0.240 g (1.00 mmole) of **70a**, 0.190 g (1.01 mmoles) of **68**,[15] 0.220 g (2.18 mmoles) of Et_3N, and 10 ml of DMF was stirred overnight at ambient temperature. The resultant mixture was poured over 80 g of crushed ice, acidified to pH 1 with dilute HCl, then stirred for 30 min. The product was collected and washed with H_2O; yield 0.245 g (82%), mp (sinters 80°) 95–109°. Recrystallization from EtOAc–petroleum ether (bp 60–110°) gave 0.150 g (50%) of white flakes, mp 125–127°. *Anal.* ($C_{18}H_{22}N_2O_3$) C, H, N.

N-(3,4-Dichlorophenethyl)-N′-phenoxypropylurea (72b).—This procedure was the same as that for **72a** excepting that K_2CO_3 was used as the base and the reaction time was 44 hr; yield 0.351 g (95%), mp 93–96°. Two recrystallizations from petroleum ether (bp 60–110°)–EtOAc gave 0.190 g (52%) of white flakes, mp 100–101°. *Anal.* ($C_{18}H_{20}Cl_2N_2O_2$) C, H, N.

N-Benzyl-N′-phenoxypropylurea (73a) was prepared from **71** and benzylamine as described for **72b** excepting that the reaction time was 17 hr; yield 0.173 g (61%), mp 121–128°. Recrystallization from EtOAc gave white granules, mp (sinters 121°) 125–128°. *Anal.* ($C_{17}H_{20}N_2O_2$) C, H, N.