

previously used for assay of dihydrofolic reductase.³⁶ This fraction (1 ml/g of wet cells) was diluted 1:20 for assay.

Buffer was 0.05 *M* Tris (pH 7.4). 2'-Deoxycytidine was stored frozen as a 3.1 *mM* solution in buffer in order to avoid mold growth, but was kept at 0° during the day's runs. In a 3-ml quartz cuvette were placed 2.60 ml of buffer, 100 μ l of 3.1 *mM* 2'-deoxycytidine, and 0.30 ml of DMSO. When the system had

balanced at 290 *m* μ , 100 μ l of enzyme was added and the decrease in optical density was recorded with a Gilford spectrophotometer; the rate was about 0.01 OD unit/min. Inhibitors were dissolved in DMSO. The inhibitor concentration for 50% inhibition (I_{50}) was determined by plotting V_0/V_1 against $[I]$ where V_0 = velocity without inhibitor, V_1 = velocity with inhibitor, and $[I]$ = inhibitor concentration;³⁷ $[I] = I_{50}$ when $V_0/V_1 = 2$.

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Irreversible Enzyme Inhibitors. CXXXI.^{1,2} Cytosine Nucleoside Deaminase. II. Hydrophobic Bonding with Disubstituted Uracils and Cytosines

B. R. BAKER AND JAMES L. KELLEY

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

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Twelve 1,6- and 1,5-disubstituted uracils have been compared for their ability to inhibit *E. coli* B cytosine nucleoside deaminase. In addition to a hydrophobic interaction between the enzyme and a 1-phenylpropyl or 1-phenoxypropyl group on uracil, further hydrophobic interaction was seen with a 6-(*n*-amyl), 5-phenyl, or 5-phenylalkyl group. Among the best inhibitors found in this series was 1-phenoxypropyl-5-phenyluracil (**11**) which was complexed to the enzyme about half as well as the substrate, 2'-deoxycytidine, and about eightfold better than the reference inhibitor, thymidine. The amino analog of **11**, 1-phenoxypropyl-6-phenylecytosine (**21**), was only half as good an inhibitor of the enzyme as **11**, in spite of the fact that 2'-deoxycytidine was complexed to the enzyme 16-fold better than thymidine.

In the previous paper of this series,² it was shown that uracils substituted with a hydrocarbon moiety at the 1 position, such as phenylpropyl (**5**) (Table I), gave better binding to cytosine nucleoside deaminase than 1-methyluracil (**2**) due to hydrophobic bonding to the enzyme. Similarly, a benzyl (**4**) or *n*-amyl (**3**) group at the 6 position gave an increment in binding compared to uracil (**1**). Therefore a study has now been made to see if better inhibition of cytosine nucleoside could be achieved with an aralkyl group at the 1 position and a hydrocarbon moiety at either the 5 or 6 position of uracil.

For initial study, the 1-aralkyl group on uracil was held constant at 1-phenylpropyl and the substituents at the 5 and 6 positions were varied. Insertion of a 6-(*n*-propyl) group (**7**)³ on 1-phenylpropyluracil (**5**) gave a twofold increment in binding; when this group was increased to *n*-amyl (**8**),³ the increment was increased to 16-fold. A comparison of 5-(*n*-amyl)uracil (**3**) and its 1-phenylpropyl derivative (**8**) shows that the phenylpropyl group gives a 21-fold increment in binding.

An 11-fold increment in hydrophobic bonding could also be achieved with a 5-phenyl group as shown by comparison of **5** and **9**.³ The 5-ethoxymethyl group of **10**³ was considerably less effective in hydrophobic bonding than the 5-phenyl group of **9**.

The 5-phenyl group was then held constant while the 1-aralkyl group was varied. Replacement of the phenylpropyl group of **9** by phenoxypropyl (**11**) resulted in about the same degree of inhibition; however, replacement by the shorter phenoxyethyl (**13**) or longer

phenoxybutyl (**12**) group gave about a twofold decrease in binding. 1-Methyl-5-phenyluracil (**14**), a baseline compound for hydrophobic bonding, was too insoluble to show inhibition.

The phenoxypropyl group of **11** was then held constant while the 5-phenyl group was varied; the 5-phenethyl (**16**) and 5-phenylpropyl (**17**) groups were about equivalent to the 5-phenyl of **11** in binding to the enzyme, but the 5-benzyl (**15**) group was slightly less effective; the 5-phenylbutyl derivative (**18**) was too insoluble to measure.

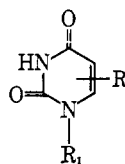
Since there is little difference in the binding of **8**, **9**, **11**, **16**, or **17** to the enzyme, the choice for further work resides primarily in the ease of synthesis for further structural variation. The 6-substituted uracils give alkylation mainly at N-3, rather than N-1; therefore, further studies with 6-substituted uracils related to **8** would suffer from low yields.³ In contrast, most 5-substituted uracils alkylate at the desired N-1 position.³ Of the various side chains at the 5 position, the 5-phenyl is the easiest to synthesize with substituents. Furthermore, the 1-phenoxypropyl group is preferred to 1-phenylpropyl since the substituted phenoxypropyl bromides needed for studying substituent effects on benzene binding are more easily prepared.

These studies indicated that a 5-phenyl substituent gave about as good hydrophobic bonding as higher 5-phenylalkyl groups and suggested that attention be directed to the synthesis of 1-substituted 5-phenylecytosines, particularly since 5-phenylecytosine can be prepared easily in good yield from phenylacetonitrile (see Chemistry section). 1-Phenoxypropyl-5-phenylecytosine (**21**) was only half as effective as 1-phenoxypropyl-5-phenyluracil (**11**) as an inhibitor; this result was surprising in view of the fact that 2'-deoxycytidine (**19**) binds about 16-fold better than thymidine (**20**), and further exploration of this discrepancy is underway.

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

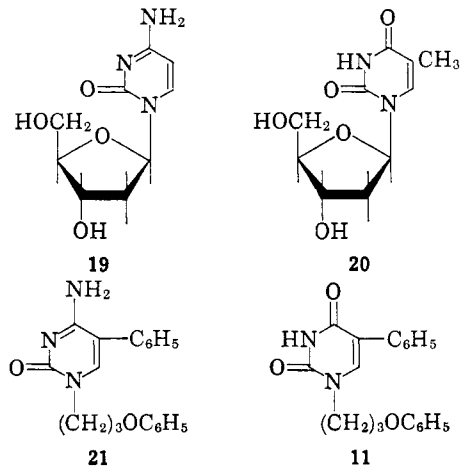
(2) For the previous paper in this series see B. R. Baker and J. L. Kelley, *J. Med. Chem.*, **11**, 682 (1968).

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TABLE I
 INHIBITION^{a,b} OF CYTOSINE NUCLEOSIDE DEAMINASE BY


No.	R ₁	R	Concn, mM	% inhibn	Estd I ₅₀ , mM	I/TdR ^c
1	H	H	1.6	0	>6.4 ^{d,e}	>4
2	CH ₃	H	3.0	0	>12 ^{d,e}	>7.5
3	H	6- <i>n</i> -C ₆ H ₁₁	3.0	50	3.0 ^d	1.9
4	H	6-C ₆ H ₅ CH ₂	1.8	50	1.8 ^d	1.1
5	C ₆ H ₅ (CH ₂) ₃	H	1.0	31	2.3 ^d	1.4
6	C ₆ H ₅ O(CH ₂) ₃	H	1.0 ^f	33	2.0 ^d	1.2
7 ^g	C ₆ H ₅ (CH ₂) ₃	6- <i>n</i> -C ₈ H ₇	0.94	50	0.94	0.59
8 ^g	C ₆ H ₅ (CH ₂) ₃	6- <i>n</i> -C ₅ H ₁₁	0.14	50	0.14	0.088
9 ^g	C ₆ H ₅ (CH ₂) ₃	5-C ₆ H ₅	0.20	50	0.20	0.12
10 ^g	C ₆ H ₅ (CH ₂) ₃	5-CH ₂ OC ₂ H ₅	0.30 ^f	23	1.0	0.62
11	C ₆ H ₅ O(CH ₂) ₃	5-C ₆ H ₅	0.10 ^f	29	0.23	0.14
12	C ₆ H ₅ O(CH ₂) ₄	5-C ₆ H ₅	0.30 ^f	40	0.37	0.23
13	C ₆ H ₅ O(CH ₂) ₂	5-C ₆ H ₅	0.20 ^f	35	0.38	0.24
14	CH ₃	5-C ₆ H ₅	0.10 ^f	0	>0.4 ^e	>0.25
15	C ₆ H ₅ O(CH ₂) ₃	5-C ₆ H ₅ CH ₂	0.10 ^f	23	0.34	0.21
16	C ₆ H ₅ O(CH ₂) ₃	5-C ₆ H ₅ (CH ₂) ₂	0.050 ^f	22	0.18	0.11
17	C ₆ H ₅ O(CH ₂) ₃	5-C ₆ H ₅ (CH ₂) ₃	0.15	50	0.15	0.094
18	C ₆ H ₅ O(CH ₂) ₃	5-C ₆ H ₅ (CH ₂) ₄	0.040 ^f	0	>0.16 ^e	>0.10

^a The technical assistance of Pepper Caseria and Susan Black with these assays is acknowledged. ^b The enzyme from *E. coli* B was assayed with 0.1 μ M 2'-deoxycytidine in pH 7.4 Tris buffer containing 10% DMSO as previously described.² ^c Ratio of concentration of inhibitor to that of thymidine (1.6 mM) required for 50% inhibition. ^d Data from ref 2. ^e Since 20% inhibition is readily detected, the I₅₀ is greater than four times the concentration measured. ^f Maximum solubility or maximum concentration allowing full light transmission. ^g For synthesis see ref 3.



Current studies involve the cytosine derivative (**21**) as a prototype. By judicious choice of substituents on each of the benzene rings it should be possible to increase binding of each benzene ring 10–100-fold, as previously discovered with benzene binding to thymidine phosphorylase,⁴ guanine deaminase,⁵ xanthine oxidase,⁵ dihydrofolate reductase,^{6,7} and chymotrypsin.⁸ Once these studies on optimum binding are completed, then

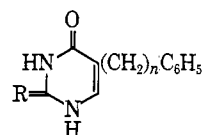
(4) B. R. Baker and W. Rzeszutarski, *J. Med. Chem.*, **11**, 639 (1968), paper CXXXI of this series.

(5) B. R. Baker and W. F. Wood, *ibid.*, **11**, 644 (1968), paper CXXXII of this series.

(6) (a) B. R. Baker and B.-T. Ho, *J. Heterocycl. Chem.*, **2**, 340 (1965); (b) B. R. Baker, B.-T. Ho, and G. J. Lourens, *J. Pharm. Sci.*, **56**, 737 (1967), paper LXXXVI of this series.

(7) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors. The Organic Chemistry of the Enzymic Active-Site," John Wiley and Sons, Inc., New York, N. Y., 1967, Chapter X.

(8) B. R. Baker and J. A. Hurlbut, *J. Med. Chem.*, **10**, 1129 (1967), paper CVII of this series.

 TABLE II
 PHYSICAL PROPERTIES OF


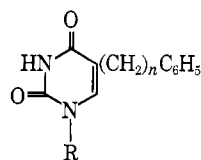
No.	n	R	Method	% yield	Mp, °C	Formula
24a	0	S	A	30	308–311 ^{a,b}	C ₁₀ H ₈ N ₂ OS
24b	1	S	A	22 ^c	209–210 ^{d,e}	C ₁₁ H ₁₀ N ₂ OS
24c	2	S	A	16	197–199 ^f	C ₁₂ H ₁₂ N ₂ OS
24d	3	S	A	24	177–179 ^f	C ₁₃ H ₁₄ N ₂ OS
24e	4	S	A	15	194–196 ^g	C ₁₄ H ₁₆ N ₂ OS
26a	0	O	B	75	>350 ^{h,i}	C ₁₀ H ₈ N ₂ O ₂
26b	1	O	B	92	291–293 ^j	C ₁₁ H ₁₀ N ₂ O ₂
26c	2	O	B	86	307–308 ^k	C ₁₂ H ₁₂ N ₂ O ₂
26d	3	O	B	94	251–253 ^h	C ₁₃ H ₁₄ N ₂ O ₂
26e	4	O	B	90	256–258 ^{g,k}	C ₁₄ H ₁₆ N ₂ O ₂

^a Recrystallized from *i*-PrOH. ^b Lit.^{11a} mp 313–315°. ^c Enol ether step omitted.¹⁰ ^d Recrystallized from EtOH. ^e Lit.¹⁰ mp 210–211°. ^f Recrystallized from BuOH. ^g Recrystallized from PrOH. ^h Recrystallized from MeOEtOH. ⁱ Lit.^{11a} mp >350°. ^j Lit.¹⁰ mp 294–295°. ^k A dimorph, mp 285°, was isolated in an earlier run that gave acceptable C, H, N analyses and had ir, uv, and tlc data identical with the material mp 258°.

active-site-directed irreversible inhibitors will be constructed with the potential for tissue-specific inhibition of cytosine nucleoside deaminase.

Chemistry.—The 1-substituted uracils (**27**, **28**) in Tables I and III were synthesized by alkylation of the uracil (**26**) (Table II) with the appropriate phenoxyalkyl bromide in DMSO with K₂CO₃ or NaH as an acid acceptor.^{3,9} Of the required uracils (**26**), the synthesis

(9) B. R. Baker and G. B. Chheda, *J. Pharm. Sci.*, **54**, 25 (1965).

TABLE III
PHYSICAL PROPERTIES OF

No.	n	R	Methods	Uracil ratio ^a	% yield	Mp, °C	Formula
11, 27d	0	C ₆ H ₅ O(CH ₂) ₃	C ^b	2.6	35	181–183°	C ₁₉ H ₁₈ N ₂ O ₃
12, 27e	0	C ₆ H ₅ O(CH ₂) ₄	D, ^b F	2.6	34 ^c	135–136	C ₂₀ H ₂₀ N ₂ O ₃
13, 27c	0	C ₆ H ₅ O(CH ₂) ₂	D ^b	3	31	157–159	C ₁₈ H ₁₆ N ₂ O ₃
14	0	CH ₃	D, ^d E	1	4	216–218	C ₁₁ H ₁₀ N ₂ O ₂
15, 28b	1	C ₆ H ₅ O(CH ₂) ₃	D, ^e F	3	33	118–120 ^f	C ₂₀ H ₂₂ N ₂ O ₃
16, 28c	2	C ₆ H ₅ O(CH ₂) ₃	D ^d	1	3 ^f	144–145	C ₂₁ H ₂₂ N ₂ O ₃
17, 28d	3	C ₆ H ₅ O(CH ₂) ₃	C, ^d F	2	6 ^f	102–103	C ₂₂ H ₂₄ N ₂ O ₃
18, 28e	4	C ₆ H ₅ O(CH ₂) ₃	D ^d	2	7 ^g	115–116	C ₂₃ H ₂₆ N ₂ O ₃

^a Ratio of uracil to alkyl halide. ^b Product extracted from starting material with EtOH. ^c Recrystallized from EtOH. ^d No preliminary solvent extraction was employed prior to Na salt precipitation. ^e Product extracted from starting material with CHCl₃. ^f Recrystallized from BuOH. ^g Fractionally crystallized successively from *n*-PrOH, EtOAc, and finally BuOH.

for additional data and other compounds prepared by this method.

5-Phenylpropyluracil (26d) (Method B).—A mixture of 0.51 g (2.1 mmoles) of **24d**, 5 ml of HOAc, and 15 ml of 10% aqueous chloroacetic acid was refluxed with stirring for 3 hr during which time solution took place and the product separated. The cooled mixture was filtered and the product was washed (H₂O); yield 0.45 g (94%), mp 250–253°. Recrystallization from MeOEtOH gave white crystals, mp 251–253°. See Table II for additional data and other compounds prepared by this method.

1-Phenoxypropyl-5-phenyluracil (11, 27d) (Method C).—A mixture of 2.00 g (10.6 mmoles) of **26a**, 22 ml of DMSO, and 0.42 g (10.5 mmoles) of NaH (59% dispersion in mineral oil) was stirred for 30 min when solution was complete. Then 0.87 g (4.0 mmoles) of phenoxypropyl bromide was added and the mixture was stirred in a bath at about 90° for 4 hr. The cooled reaction mixture was poured into 40 ml of ice H₂O and acidified with HCl to about pH 2. The solid was collected on a filter and washed with H₂O; tlc with 3:1 C₆H₆–EtOH showed that this was a mixture of **26a** and **27d**. The solid was extracted with several portions of hot EtOH until tlc showed no more **27d** was being extracted. The combined EtOH solutions were spin evaporated *in vacuo*. The residue was heated with 40 ml of hot 5% NaOH, then cooled. The insoluble sodium salt was collected on a filter and washed with 5% NaOH; if tlc showed some **26a** was still present, the sodium salt was recrystallized from 5% NaOH. The wet sodium salt was suspended in H₂O and acidified with HCl. The product was collected on a filter and washed with H₂O; yield 0.59 g (45%), mp 176–181°. Recrystallization from EtOH gave white crystals, mp 181–183°. See Table III for additional data and for additional compounds prepared by this method.

The following modifications were employed, depending on the particular product: (1) in method D, K₂CO₃ was used in place of NaH; (2) in method E, NaCl was added to salt out the Na salt of the product; (3) in method F, the sodium salt was not isolable and the product was isolated by fractional crystallization. No effort was made to recover additional material from the filtrates in any of the methods; therefore yields are minimum values.

5-Phenyl-2-thiocytosine (31).—Condensation of phenylacetoneitrile with ethyl formate in ethanolic NaOMe gave **29**¹³ in 81% yield, mp 156–159°. A solution of 28 g (0.19 mole) of **29** in 80 ml of triethyl orthoformate and 0.5 ml of 96% H₂SO₄ was slowly distilled until the vapor temperature reached 90°. The volatiles were then removed by spin evaporation *in vacuo*. The residual oil was dissolved in CHCl₃, washed with excess 5% NaHCO₃, then dried (MgSO₄) and evaporated *in vacuo*. The residual enol ether (**30**) was refluxed with stirring with a solution of 14 g (0.26 mole) of NaOMe and 10 g (0.19 mole) of thiourea in 200 ml of EtOH for 30 min during which time the product separated. The mixture was diluted with 500 ml of H₂O, then washed (CH₂Cl₂). The aqueous solution was clarified by filtration, then acidified to pH 5. The product was collected on a filter and

washed (H₂O); yield 16 g (40%), mp 275–282°, that was suitable for further transformations. Recrystallization of a sample from 1:3 DMF–MeOEtOH gave white crystals, mp 296–299°; no literature¹⁴ melting point has been recorded.

4-Amino-2-carboxymethylthio-5-phenylpyrimidine (33).—A mixture of 300 mg (1.3 mmoles) of **31**, 5 ml of HOAc, and 10 ml of 10% aqueous chloroacetic acid was refluxed with stirring for 3 hr. The solution was spin evaporated *in vacuo*. The residue was treated with 5 ml of H₂O and the pH was adjusted to 5–6 with 5% NaOH. The product was collected on a filter and washed (H₂O); yield 290 ml (85%), mp 124–135°. Recrystallization from toluene gave white crystals, mp 138–140°, lit.^{14b} mp 135–138°.

5-Phenylcytosine (32). **A.**—A mixture of 250 mg (0.96 mole) of the above **33** and 5 ml of 12 *N* HCl was refluxed for 2 hr, then evaporated *in vacuo*. The residue was dissolved in 5 ml of H₂O and the solution was neutralized with NH₄OH. The product was collected on a filter and washed with H₂O; yield 150 mg (83%) of product, mp >340°, that was uniform on tlc and had λ_{max} pH 1, 290; pH 7, 240, 281 (inf); pH 13, 263, 293 mμ. The synthesis of this compound, mp >310°, by a less convenient alternate route has been described;¹⁹ the conversion of **33** to **32** is described in a patent in lower yield.^{14b}

B.—A mixture of 9.0 g (44.2 mmoles) of **31**, 150 ml of H₂O, 15 g of chloroacetic acid, and 100 ml of 12 *N* HCl was refluxed with stirring for 2 hr. The hot solution was clarified by filtration, then spin evaporated *in vacuo* to about half the volume and neutralized with NH₄OH. The product was collected on a filter and washed (H₂O); yield 6.2 g (75%) of product identical with preparation A.

1-Phenoxypropyl-5-phenylcytosine (21).—To a stirred mixture of 810 mg (4.32 mmoles) of **31**, 25 ml of DMSO, and 152 mg (3.78 mmoles) of NaH (59% dispersion in mineral oil) was stirred for 1 hr when H₂ evolution ceased. The mixture was warmed to 70°, then was treated with 815 mg (3.78 mmoles) of phenoxypropyl bromide. After an additional 2 hr at 70°, the mixture was cooled, diluted with 40 ml of ice H₂O, then adjusted to pH 10–11 with 10% NaOH. After being stirred 15 min, the mixture was filtered and the product was washed (H₂O). The solid was dissolved in 50 ml of hot 6 *N* HCl, then cooled to 0°. The HCl salt was collected, then it was dissolved in 30 ml of hot H₂O. The solution was clarified by filtration and neutralized with NH₄OH. The product was collected on a filter and washed (H₂O); yield 900 mg (74%), mp 134–138°. An additional 45 mg (total 78%), mp 133–139°, was obtained by neutralization of the HCl filtrate. Recrystallization of a sample from EtOAc gave white crystals, mp 98–102°, that was an EtOAc solvate; after being dried at 100° in high vacuum, the solvent-free product, mp 142–

144°, was obtained; λ_{\max} (10% EtOH), 242, 268–293 (plateau); pH 1, 299; pH 13, 277 (plateau) m μ . Anal. (C₁₈H₁₈N₃O₂) C, H, N.

Deamination of 1-Phenoxypropyl-5-phenyleytosine (21) to 27d.—To a gently stirred solution of 200 mg (0.62 mmole) of 21 in 5 ml of HOAc cooled in an ice bath was added dropwise a

solution of 175 mg (2.48 mmoles) of NaNO₂ in 5 ml H₂O. The solution was allowed to stand at ambient temperature for 24 hr during which time the product separated. The solid was collected on a filter and washed with H₂O; yield 113 g (57%) of 27d, mp 178–180°, that was identical with 27d prepared *via* 26a (Table II).

Potential Antitumor Agents. VIII. Bisquaternary Salts

G. J. ATWELL, B. F. CAIN,¹ AND R. N. SEELYE

Cancer Chemotherapy Laboratory, Cornwall Geriatric Hospital, Auckland, New Zealand

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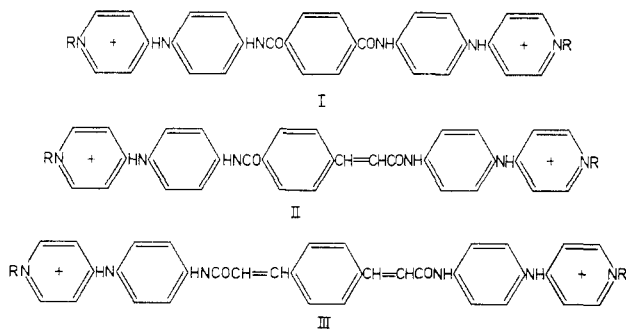
An investigation of types of quaternary ammonium heterocycles acceptable as basic functions in experimental antileukemic bisquaternary salts is described. Some aspects of the dependence for activity on charge separation and on certain steric features are discussed.

Since the initial observation of experimental antileukemic activity in quaternary salts of N,N'-(6-quinolyl)terephthalamide² we have demonstrated that acceptable basic functions in this type of molecule are the quaternary salts of 6-acylaminoquinolines,^{2,3} 3- and 4-(*p*-acylamino)phenylpyridines,^{2,3} and 3-benzamidopyridines.^{3,4} The researches described in this paper detail investigations of further acceptable basic functions as well as the effect of certain steric factors on biological activity.

The alteration of basic functions in many cases changes charge separation in the resultant molecules. If biological activity was critically dependent on such separation, acceptable bases might be overlooked due to the resultant molecules possessing an unacceptable charge separation.

Fortunately in our series of bisquaternary compounds activity has been observed where distances between the quaternary nitrogen atoms are as low as 18 Å (as in the parent N,N'-(6-quinolyl)terephthalamide series) which can be increased by small increments to a maximum of 27 Å in the extended amide series described in our previous paper.⁴

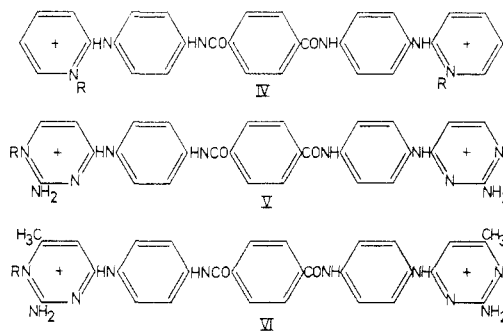
A further example of the permissibility of variable charge separation is provided by the three series I–III which all show convincing experimental antileukemic effectiveness in mice.



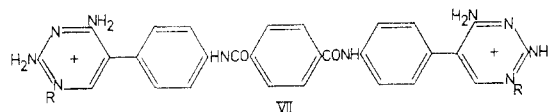
These three series utilize the new basic function 4-anilino-2-pyridine; this function is somewhat more

lipophilic than those previously used; for example, antileukemic effectiveness drops from I (R = CH₃) to higher members. This could have been predicted from the relative R_f values if these were taken as giving a measure of lipophilic–hydrophilic balance.²

In contrast, the corresponding 2-anilino-4-pyridine series IV, covering a similar range of R_f values to the 4-anilino-2-pyridines, contained no active members. Further variants of the 4-anilino heterocycle system have been examined. The 2-amino-4-anilino-6-methylpyrimidine series V gave life extensions in the L1210 system similar to the corresponding pyridines but were less active on a molar basis. The 2-amino-4-anilino-6-methylpyrimidine series (VI) utilizing the pyrimidine function present in the trypanocides antrycide⁵ and prothidium⁶ also contained active members but these were even less active than the pyrimidines V on a molar basis; a dose of several hundred mg/kg being required to demonstrate an effect.



Consideration of the above results coupled with the activity of the 3-phenylpyridine series described earlier² led to the preparation of the 2,4-diamino-5-phenylpyrimidines VII. These compounds proved to be extremely potent experimental antileukemic drugs with the ethyl quaternary salt (VII, R = C₂H₅) in early treatment groups giving a proportion of 100-day survivors.



(1) Author to whom inquiries should be addressed.

(2) Part V: G. J. Atwell and B. F. Cain, *J. Med. Chem.*, **10**, 706 (1967).

(3) Part VI: G. J. Atwell and B. F. Cain, *ibid.*, **11**, 295 (1968).

(4) Part VII: G. J. Atwell, B. F. Cain, and R. N. Seelye, *ibid.*, **11**, 300 (1968).

(5) A. D. Ainley, F. H. S. Curd, W. Hepworth, A. G. Murray, and C. H. Vasey, *J. Chem. Soc.*, 59 (1953).

(6) T. I. Watkins and G. Woolfe, *Nature*, **178**, 368, 727 (1956).