Cell Culture Studies. L5178Y cells were grown in suspension culture in Fischer's medium supplemented with 10% horse serum and 0.1% Pluronic F68; the inhibition of cell growth was measured as described previously.[14]

Thymidylate Synthetase Assay. The ability of **4a-c** to inhibit thymidylate synthetase activity from *Lactobacillus casei* was assayed according to the method of Wahba and Friedkin.[15]

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Optically Active Derivatives of Imidazolines. α-Adrenergic Blocking Properties

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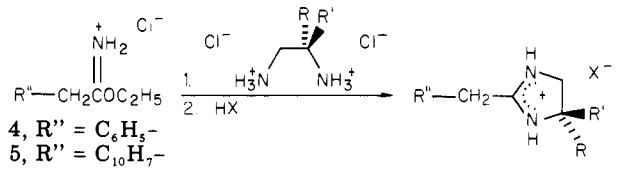
The synthesis and α-adrenergic blocking activity of a series of optically active 2,4-disubstituted imidazolines are presented. The substituted analogues of naphazoline, tolazoline, and clonidine possess moderate α-adrenergic blocking activity with $-\log K_B$ values in the range from 4.77 to 6.57. The differences between the α-adrenergic blocking activity of the stereoisomers of the 2,4-disubstituted imidazolines were small or insignificant in the rabbit aortic tissue preparations.

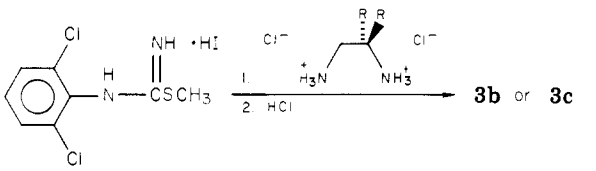
In addition to the well-known phenethanolamines, an important group of drugs capable of interacting with α-adrenergic receptors consists of imidazoline derivatives. It is known that appropriately substituted imidazolines can act either as an agonist or antagonist on α-adrenergic receptors.[1-9] The imidazoline derivatives, unlike their phenethanolamine counterparts, apparently do not possess β-adrenergic agonist activity, although Sanders and coworkers[2] did report that tetrahydrozoline and tolazoline possess histamine H_2-agonist activity. Yellin and coworkers[10] extended these studies and found significant differences between the optical isomers of tetrahydrozoline on both histamine H_2 receptors and α-adrenergic receptors. Few studies have appeared on the actions of optically active imidazoline derivatives in adrenergic systems,[6,10,11] and this is striking in comparison to the extensive number of stereochemical studies carried out with phenethanolamines.[1]

Scheme I



1 or 2

Scheme II



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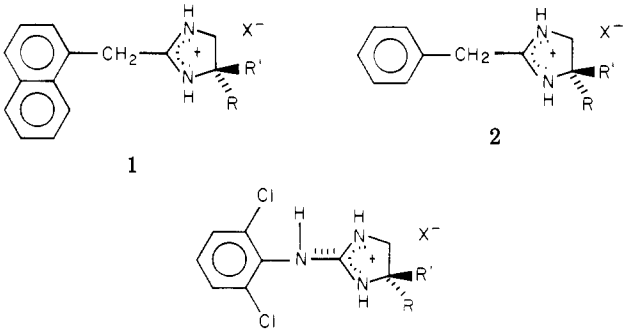
Initially, it was noted that substitution of a methyl group at the 4 position of the imidazoline ring of naphazoline (1)



1 2

3

a, R = R' = H; b, R = H, R' = CH_3; c, R = CH_3, R' = H; d, R = H, R' = $C_6H_5CH_2$; e, R = $C_6H_5CH_2$, R' = H

converted the adrenergic agonist molecule into an antagonist with little differences being noted between the isomeric compounds, e.g., **1b** and **1c**.[6] In an extension of

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Table I. Physical Properties of Optically Active Imidazolines

compd	X^-	final crystn solvent	mp, °C	$[\alpha]^{28}$, deg Na_{589}	$[\alpha]^{28}$, deg Hg_{578}	concn, % (solvent)
2b	picrate	95% EtOH	112-114	+29.0	+30.4	1.12 (MeOH)
2c	picrate	95% EtOH	112-114	-30.1	-31.43	0.91 (MeOH)
3b	Cl^-	MeOH-Et_2O	260-262 (dec)	+17.92	+19.01	1.01 (MeOH)
3c	Cl^-	MeOH-Et_2O	260-262 (dec)	-18.87	-19.65	1.15 (MeOH)
1d	Cl^-	MeOH-Et_2O	189-191.5	+79.84	+83.87	1.24 (MeOH)
1e	Cl^-	MeOH-Et_2O	189-191.5	-79.32	-83.16	0.95 (MeOH)
2d	oxalate	MeOH-Et_2O	174-176 (dec)	+72.4	+77.1	0.44 (MeOH)
2e	oxalate	MeOH-Et_2O	176-178 (dec)	-72.8	-77.2	0.46 (MeOH)

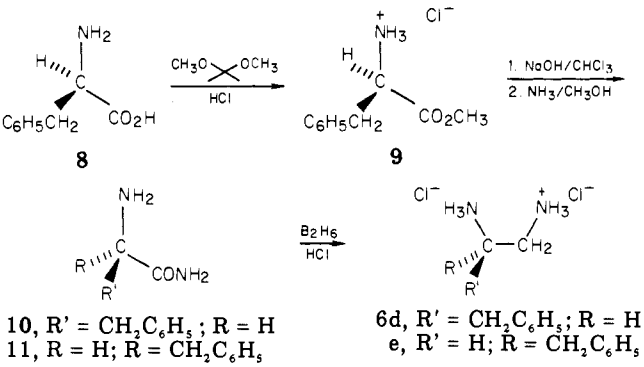
this work we proposed to examine the effects of a small substituent added to the imidazoline ring of tolazoline (**2**) and clonidine (**3**) to see if such substitution would provide results similar to those seen with naphazoline (**1**). It was also of interest to investigate the addition of a larger substituent on the imidazoline ring system at the 4 position to see if a greater difference in adrenergic activity might exist between the optical isomers of such derivatives. We report here the synthesis of the optically active 4-methyl analogues of tolazoline, **2b** and **2c**, and clonidine, **3b** and **3c**, along with the 4-benzyl analogues of naphazoline, **1d** and **1e**, and tolazoline, **2d** and **2e**, and the α-adrenergic activity of these derivatives on rabbit aortic strips.

Chemistry. The synthesis of the 4-methyltolazoline analogues, **2b** and **2c**, was carried out by treatment of ethyl phenyliminoacetate hydrochloride (**4**)[12] with the *R* and *S* isomers of 1,2-diaminopropane (**6b** and **6c**) in the presence of triethylamine, followed by picrate salt formation (see Scheme I). Attempts at forming a solid hydrochloride salt of **2b** and **2c** failed, but the picrate salt could be readily obtained as a crystalline solid. The synthesis of the clonidine analogues, **3b** and **3c**, involved heating in a sealed tube, at 140 °C, *S*-methyl-(2,6-dichlorophenyl)isothiouronium iodide (**7**)[13] with the optically active diamines **6b** and **6c** in the presence of triethylamine and propanol (Scheme II). Rather than conventional resolution, the synthesis of the optically active isomers of 3-phenyl-1,2-diaminopropane was carried out in a fashion similar to that reported for the optical isomers of 1,2-diaminopropane[6] (Scheme III).

(*R*)-Phenylalanine (**8**) was converted to the methyl ester **9** by treatment with 2,2-dimethoxypropane and concentrated hydrochloric acid at room temperature using the procedure of Rachele.[14] The free base of **9** was then treated with methanol, saturated with ammonia, in a manner analogous to the method of Yang and Riring[15] to yield optically active phenylalanine amide **10**. Diborane reduction[6] of **10** or commercially available **11**,[16] followed by the addition of MeOH and dry HCl, gave the desired 3-phenyl-1,2-diaminopropane dihydrochlorides **6d** and **6e**, respectively. This method of preparing optically active substituted 1,2-diaminopropanes from amino acids of known absolute configuration has proven to be very useful and appears to have a wide application.

The synthesis of the optically active analogues **1d** and **1e** of naphazoline (**1**) was carried out by allowing the optically active 3-phenyl-1,2-diaminopropane dihydrochlorides (**6d** and **6e**) to react with ethyl 1-naphthyliminoacetate hydrochloride[6] (**5**) via a modification of the procedure of King and Acheson.[17] The resulting imidazolines were isolated as the crystalline HCl salts **1d** and **1e**. The 4-benzyltolazoline analogues **2d** and **2e** were prepared in an analogous manner, utilizing ethyl phenyliminoacetate hydrochloride (**4**) as the starting imidate. Attempts at isolating **2d** and **2e** as solid hydrochloride salts failed, but crystalline oxalate salts were isolated.

Scheme III



10, R' = $CH_2C_6H_5$; R = H
11, R = H; R = $CH_2C_6H_5$

6d, R' = $CH_2C_6H_5$; R = H
e, R' = H; R = $CH_2C_6H_5$

Table II. α-Adrenergic Blocking Activity on Rabbit Aortic Tissue Preparation

compd	X^-	$-\log K_B$[a]
1b[b]	Cl^-	5.60
1c[b]	Cl^-	5.76
2b	picrate	4.77
2c	picrate	4.85
3b	Cl^-	5.08
3c	Cl^-	5.27
1d	Cl^-	6.34
1e	Cl^-	6.57
2d[c]		4.98
2e[c]		5.00

[a] Calculated at a single concentration of antagonist according to the formula described by Furchgott.[18,19] In each experiment, the number of observations varied from 3 to 5, and the standard error of the mean of each value was less than ±0.30. [b] Reported previously, ref 6. [c] Pharmacological activity was determined on the free base rather than the oxalate salt.

Biological Results. In our earlier work[6] we had noted that the *R* and *S* isomers of 4-methylnaphazoline, **1b** and **1c**, were competitive inhibitors of the α-adrenergic receptor with $-\log K_B$ values of 5.60 and 5.76. Extending this study, we examined the addition of a methyl group to tolazoline (**2a**) and clonidine (**3a**) to give analogues **2b**, **2c**, **3b**, and **3c**, respectively. These compounds did not possess α-agonist activity in rabbit aorta. These analogues, however, did possess moderate α-adrenergic blocking properties with the $-\log K_B$ values shown in Table II. As can be seen in Table II, the differences in α-adrenergic blocking activity between isomers were very small or nondetectable, which is in agreement with our earlier studies with the isomeric

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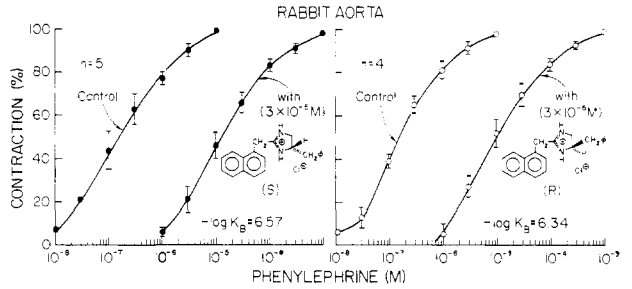

Figure 1. The dose–response curves of the α-agonist phenylephrine in the absence (control) and in the presence of the *S* or *R* isomer of 2-(1-naphthylmethyl)-4-benzylimidazoline hydrochloride. The $-\log K_B$ value for the competitive antagonism of each isomer is calculated according to the procedure of Furchgott.[19] This illustrates the typical type of dose–response curve observed with the optical isomers of the 2,4-disubstituted imidazolines.

4-methylnaphazoline derivatives **1b** and **1c**.[6]

The substitution of a benzyl group for the methyl group at the 4 position on the imidazoline ring provided compounds which again possessed moderate α-adrenergic blocking activity with an apparent lack of stereoselectivity; e.g., **1d** and **1e** provided a $-\log K_B$ of 6.34 and 6.57, respectively (see Figure 1). In all cases, the replacement of a methyl group with a benzyl group gave a larger $-\log K_B$ value; e.g., **1b** and **1d** had values of 5.60 and 6.34, respectively. Whereas we have previously reported[2] that both naphazoline and tolazoline are partial agonists on rabbit aorta, the present study indicates that the addition of a small (methyl) or large (benzyl) substituent at the 4 position of the imidazoline ring gives compounds with moderate α-blocking activity. We have found no apparent stereoselectivity with such substitutions on the imidazoline molecule.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. IR spectral data were obtained using a Perkin-Elmer 257 or Beckman 4230 infrared spectrophotometer, and NMR spectral data were obtained using a Varian A-60A (60 MHz) or Bruker HX-90E NMR spectrometer (90 MHz) in the pulse mode. Mass spectra were obtained with a Dupont Model 21-491 double-focusing mass spectrometer. The optical rotations were obtained by using a Perkin-Elmer 240 polarimeter. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Analytical results for elements indicated were within ±0.4% of the theoretical values.

(*R*)-(+)-1,2-Diaminopropane Dihydrochloride (6b) and (*S*)-(−)-1,2-Diaminopropane Dihydrochloride (6c). These compounds were prepared according to our reported procedure.[6]

(*R*)-(+)-1,2-Diamino-3-phenylpropane Dihydrochloride (6d). A solution of (*R*)-phenylalanine (5 g, 30.27 mmol) and 31 mL of concentrated HCl (36%) in 300 mL of 2,2-dimethoxypropane was stirred at room temperature for 18 h. The resulting mixture was evaporated to about 50 mL, which was added sufficient Et_2O until a turbid solution formed. The crystalline product was collected and recrystallized from MeOH–Et_2O to give **9** (6.1 g, 94%): mp 159–161 °C (lit.[15] 159–161 °C); $[\alpha]^{24}_D$ −16.5° (MeOH). To the free base of the amino ester (5 g, 27.9 mmol) was added at 0 °C a solution of 25 mL of MeOH saturated with NH_3. The mixture was allowed to stand at room temperature for 3 days, and the excess solvent and ammonia were evaporated to give 3.86 g of (*R*)-(−)-phenylalanine amide (**10d**), as a white solid recrystallized from benzene: mp 91–93 °C; $[\alpha]^{24}_D$ −13.41° (MeOH).

To a suspension of 3.4 g (20.7 mmol) of the amide **10d** in 50 mL of dry THF at 10 °C was added dropwise 100 mL of 1 M diborane in THF. The clear solution was allowed to stir at room temperature for 1 h after the addition was completed and then refluxed for 5 h. The solution was then cooled in an ice bath and 35 mL of absolute MeOH was added. This solution was allowed to stir overnight and then dry HCl gas was passed into the solution with stirring until the solution reached pH 2. The solution was evaporated in vacuo and taken up and recrystallized from 95% EtOH–ether to give 2.9 g of **6d** as a white crystalline material (63% yield): mp 200–201 °C; $[\alpha]^{24}_D$ +32°; NMR (D_2O) δ 3.08–3.45 (m, 4 H, benzylic and $-CHCH_2-$), 3.74–4.17 (m, 1 H, methine), 7.4 (s, 5 H, aromatic). Anal. Calcd for $C_9H_{16}N_2Cl_2 \cdot H_2O$: C, 44.80; H, 7.53; N, 11.62. Found: C, 44.90; H, 7.40; N, 11.57.

(*S*)-(−)-1,2-Diamino-3-phenylpropane Dihydrochloride (6e). Reduction of commercially available **11** was carried out with the diborane method used in the previous procedure for **10**. The final reaction mixture after treatment with dry HCl was evaporated to give a crude product, which was dissolved in MeOH. The MeOH solution was refluxed for 10 min and then evaporated to give a solid, which was recrystallized from 95% EtOH–ether to afford the optically active diamine **6e** (72%): mp 200–201 °C; $[\alpha]^{24}_D$ −31.43°; NMR (CD_3OD) δ 3.08–3.43 (m, 4 H, benzylic and $-CHCH_2-$), 3.65–4.17 (m, 1 H, $-CHCH_2-$), 7.37 (s, 5 H, aromatic). Anal. Calcd for $C_9H_{16}N_2Cl_2 \cdot 0.75H_2O$: C, 45.92; H, 7.43; N, 11.91. Found: C, 45.79; H, 7.64; N, 11.71.

General Procedure for the Preparation of Imidate Ester Hydrochlorides. A mixture of nitrile (0.1 mol) and absolute EtOH (0.12 mol) was cooled in an ice bath and treated with dry HCl (0.115 mol). The mixture was then kept at 4 °C for 4 days. The resultant viscous liquid was treated with an equal volume of Et_2O. The hydrochloride salt which precipitated was filtered off and washed with Et_2O.

Ethyl phenyliminoacetate hydrochloride (4): yield 98%; mp 105–106 °C (lit.[12] softens at 60 °C).

Ethyl 1-naphthyliminoacetate hydrochloride (5) was found to be a highly viscous oil and was used without further purification as described previously.[6]

General Procedure for Optically Active 2-(Arylmethyl)-4-substituted-2-imidazolines. The optically active imidazolines were prepared via a modification of the procedure of King and Acheson.[17] To an ice-cooled solution of optically active 1,2-diamine dihydrochloride (10.2 mmol) and Et_3N (2.28 g, 22.5 mmol) in 8 mL of MeOH was added a cold solution of imino ester hydrochloride (10.57 mmol) in 5 mL of MeOH. The reaction mixture was refluxed for 1 h and evaporated to give an oil. This crude product was treated with 25 mL of 1 N NaOH and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried (Na_2SO_4), and evaporated to afford an oil product for the imidazoline optical isomers in each case. Each isomer was then converted to a stable solid salt form.

(*R*)-(+)-4-Methyl-2-(1-naphthylmethyl)imidazoline hydrochloride (1b) and (*S*)-(−)-4-methyl-2-(1-naphthylmethyl)imidazoline hydrochloride (1c) were previously reported.[6]

(*R*)-(+)-2-Benzyl-4-methylimidazoline picrate (2b): yield 70%; mp 112–114 °C. Anal. ($C_{17}H_{17}N_5O_7$) C, H, N.

(*S*)-(−)-2-Benzyl-4-methylimidazoline picrate (2c): yield 76%; mp 112–114 °C. Anal. ($C_{17}H_{17}N_5O_7$) C, H, N.

(*R*)-(+)-2-(1-Naphthylmethyl)-4-benzylimidazoline hydrochloride (1d): yield 58%; mp 189–191 °C. Anal. ($C_{21}H_{21}N_2Cl_2$) C, H, N.

(*S*)-(−)-2-(1-Naphthylmethyl)-4-benzylimidazoline hydrochloride (1e): yield 66%; mp 189–191.5 °C. Anal. ($C_{21}H_{21}N_2Cl_2$) C, H, N.

(*R*)-(+)-2,4-Dibenzylimidazoline oxalate (2d): yield 77%; mp 174–176 °C. Anal. ($C_{19}H_{20}N_2O_4$) C, H, N.

(*S*)-(−)-2,4-Dibenzylimidazoline oxalate (2e): yield 72%; mp 176–178 °C. Anal. ($C_{19}H_{20}N_2O_4$) C, H, N.

(*R*)-(+)-2-[(2,6-Dichlorophenyl)imino]-4-methylimidazolidine Hydrochloride (3b). A solution of **7**[13] (1.48 g, 4.08 mmol), **6b** (800 mg, 5.04 mmol), and Et_3N (1.15 g, 11.36 mmol) in 8 mL of *n*-PrOH was heated in a sealed tube at 140 °C for 12 h. The resulting yellow solution was evaporated and then taken into 15 mL of 1 N NaOH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried ($MgSO_4$), and evaporated to yield a yellow oil (887 mg, 89%), which was converted to the hydrochloride salt **3b**. The hydrochloride salt of **3b** was washed with $CHCl_3$ and recrystallized from MeOH–Et_2O to yield a white solid: mp 260–262 °C (dec). Anal. ($C_{10}H_{12}N_3Cl_3$) C, H, N.

(*S*)-(−)-2-[(2,6-Dichlorophenyl)imino]-4-methylimidazolidine Hydrochloride (3c). The hydrochloride salt **3c** was prepared in a manner similar to the procedure used in pre-

paring 3b: yield 89%; mp 260–262 °C (dec). Anal. ($C_{10}H_{12}N_3Cl_3$) C, H, N.

Pharmacological Testing. Rabbits were killed by injecting air into the marginal ear veins, and thoraic aorta were isolated in a petri dish containing physiological salt solution. Aorta strips 4 cm × 2.5 mm wide were prepared as described by Furchgott and Bhadrakom.[18] The tissues were mounted in a 10-mL jacketed tissue bath containing oxygenated (95% O_2 and 5% CO_2) physiological salt solution at 37 °C. The resting tension of 4 g was maintained and the drug-induced changes in the tension were recorded via a transducer on a polygraph. After an hour of tissue equilibrium, the strip was exposed to 10^{-6} M phenylephrine, and the tissue was thoroughly washed. Subsequently, the cumulative dose–response of (−)-phenylephrine was obtained in the presence and in the absence of antagonist, which was incubated for 60 min. Either single or multiple concentrations of antagonists were used to calculate the dissociation constant as described by Furchgott.[19] When phentolamine was used as a blocker, the dissociation constant was 1.5×10^{-8} M.

Acknowledgment. This investigation was supported by the U.S. Public Health Service (Grant NS 14774).

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Synthesis and Antineoplastic Activity of a Novel Series of Phosphoramide Mustard Analogues of Pyrimidine Deoxyribonucleosides[1]

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A novel series of cyclophosphamide derivatives of pyrimidine deoxyribonucleosides (**6**–**9**) has been synthesized from the corresponding amino nucleosides. Our preliminary findings have shown that three of these cyclophosphamide nucleoside analogues, **6**, **7**, and **9**, have potent inhibitory effects on the replication of L1210 cells in vitro (ED_{50} = 1.2–1.5 × 10^{-5} M). Since cyclophosphamide (cytoxan) has no cytotoxicity under these conditions, our findings indicate that these novel phosphamide derivatives have unusual biological properties which may include a unique mode of activation.

The synthesis of phosphoramide mustards as latent alkylating agents that might be selectively "activated" in tumors by enzymatic (hydrolytic) release of nornitrogen mustard represents one of the earliest design strategies in cancer chemotherapy.[3] Hundreds of candidate compounds belonging to this structural class have been screened[4-9] and cyclophosphamide,[4] 2-[bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxazaphosphorine 2-oxide, has uniquely emerged as the one which exhibits clinical effectiveness against a relatively wide spectrum of human cancers.[10] Cyclophosphamide requires activation by hepatic microsomal mixed function oxidases, and in animals its rate of activation was shown to be increased by barbiturate induction of these enzymes and decreased by inhibition of these enzymes.[11]

Although many phosphoramide mustard derivatives have been synthesized and screened, the previous synthesis of 3′,5′-[[bis(2-chloroethyl)amino]phosphoryl] mustard nucleoside analogues has not been reported. Our concept to combine a nucleoside moiety and a phosphoramide mustard functionality into *one molecule* has evolved a new series of phosphoramide mustard nucleoside analogues, which may, by virtue of affecting specific metabolic pathways, have unique and desirable pharmacologic properties with good clinical potential as antineoplastic agents.

The addition of a nucleoside moiety to the phosphoramide mustard molecule provides a versatile handle for pharmacologic manipulation. For example, attaching an acyl group (acetyl or longer chain acyl) to the pyrimidine (cytosine) or purine (adenine, guanine) base will increase the lipophilicity of the compound. Such modification may increase transport across membranes and thereby favorably affect the pharmacologic and biological properties.

A possible way to modulate the distribution of biologically active compounds is by using selective moieties, such as nucleosides, sugars, amino acids, etc., which are actively transported in the body by a specific transport mechanism. Ascites tumor cells, for instance, are reported to have a high capacity for uptake of amino acids, sugars, and nucleosides. Therefore, joining the phosphoramide mustard group with nucleosides may lead to compounds which would fit the "latency" and "carrier" principles with hopefully preferential distribution into tumor cells. *ara*-C, for example, is a nucleoside of great clinical utility in therapy of certain neoplasms. Recently, we have syn-

(1) Presented in part at 176th American Chemical Society National Meeting. See T.-S. Lin, P. H. Fisher, and W. H. Prusoff in "Abstracts of Papers", 176th National Meeting of the American Chemical Society, Miami Beach, FL, Sept 11–17, 1978, American Chemical Society, Washington D.C., Abstr CARB 26.

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