with structure 3. Anal. ($C_9H_5F_{10}N_3O_2$) C, H, F, N.

Eluted second was 1-(nonafluorocyclohex-1-enyl)-3-nitrosoimidazolidin-2-one (4, 0.06 g): mp 96–97 °C; IR ν_{max} 1780 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) τ 6.05 (s); ^{19}F NMR, 3 collapsed AB signals (integral ratio 2:2:4) centered at 111.0, 119.3, and 133.5 ppm, and a signal at 120.1 ppm (integral ratio 1) consistent with structure 4. Anal. ($C_9H_4F_9N_3O_2$) C, H, F, N.

In a subsequent decomposition of FCCNU (1 g), when the reaction mixture was worked up almost immediately, 50% of the material (0.7 g) recovered was unreacted FCCNU and the remainder was a mixture of 3 and 4.

1-(3,3,3-Trifluoropropyl)-3-cyclohexyl-1-nitrosourea (5). Cyclohexyl isocyanate (0.63 g, 5 mmol) was added dropwise to a stirred solution of 3,3,3-trifluoropropylamine[23] (0.57 g, 5 mmol) in dry ether (8 mL) at 0 °C. The mixture was then warmed to room temperature and stirred overnight. Removal of the solvent in vacuo and recrystallization of the residue from acetone–water afforded 1-(3,3,3-trifluoropropyl)-3-cyclohexylurea (0.77 g): mp 125–126 °C; IR ν_{max} 3330 (NH), 1625 (C=O), 1575 cm^{-1} (CNH); ^{19}F NMR [$(CD_3)CO$] showed a triplet centered at 64.8 ppm (J = 11.3 Hz); ^{1}H NMR data was consistent with the assigned structure. Anal. ($C_{10}H_{17}F_3N_2O$) C, H, N.

Dry sodium nitrite (0.62 g, 8.98 mmol) was added in small portions to a stirred solution of the foregoing compound (0.71 g, 2.98 mmol) in formic acid (98–100%, 20 mL) at 5 °C. The mixture was stirred at 5 °C for 45 min and then H_2O (20 mL) was added. The yellow precipitate was collected, washed with ice–water, dried, and eluted from a column (30 × 1 cm) of Kieselgel with CH_2Cl_2 to afford 5 (0.63 g): mp 47–48 °C; IR ν_{max} 3390 (NH), 1710 cm^{-1} (C=O). ^{19}F NMR ($CDCl_3$) showed a triplet centered at 66.63 ppm; ^{1}H NMR data was consistent with the assigned structure. Anal. ($C_{10}H_{16}F_3N_3O_2$) C, H, F, N.

Assay of Antitumor Activities. Using the previously described protocol,[24] CCNU and FCCNU (2) were tested against the TLX-5 lymphoma in mice. The results are given in Table I.

The ic implanted leukemia L1210 tests were performed by the Cancer Screening Division of the Southern Research Institute (Birmingham, Ala.) under the direction of Dr. F. M. Schabel. The results are given in Table II.

Toxicity Assay. The mixture 3 + 4 described above was administered ip as a single injection in 10% ethanol/oil to female CBA/LAC mice (two animals in each group). Animals given 40 or 80 mg/kg died within 24 h of injection. A dose of 20 mg/kg elicited no toxic symptoms (death or weight loss) compared with untreated animals, within 10 days after injection.

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Synthesis and Biological Activity of 5-Fluoro-2′-deoxyuridine 5′-Phosphorodiamidates[1]

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Three 5′-phosphorodiamidate derivatives of 5-fluoro-2′-deoxyuridine (FdUrd), 5-fluoro-2′-deoxyuridine 5′-phosphorodiamidate (**4a**), 5′-phosphorodiimidazolidate (**4b**), and 5′-phosphorodimorpholidate (**4c**), were synthesized by aminolysis of 5-fluoro-2′-deoxyuridine 5′-phosphorodichloridate with the respective amine. In culture, these 5′-phosphorodiamidates inhibited the growth of murine leukemia (L5178Y) cells. 5-Fluoro-2′-deoxyuridine 5′-phosphorodiamidate (**4a**) was the most active derivative and, on a molar basis, produced a cytostatic effect comparable to that of FdUrd and 5-fluoro-2′-deoxyuridine 5′-monophosphate (FdUrd-5′-P). Compounds **4b** and **4c** were less active than **4a**, with relative rates of activity **4a** > **4b** > **4c** that corresponded to their rates of hydrolysis to FdUrd-5′-P. None of the 5′-phosphorodiamidates inhibited thymidylate synthetase of concentrations up to 1 mM.

5-Fluorouracil (FUra) and 5-fluoro-2′-deoxyuridine (FdUrd) have been widely used to treat patients with disseminated cancers.[2] The fluoropyrimidines are converted to the active metabolite 5-fluoro-2′-deoxyuridine 5′-monophosphate (FdUrd-5′-P) through several different pathways.[2] FdUrd-5′-P inhibits thymidylate synthetase and thus the biosynthesis of DNA; this activity had been regarded for a long time as the principal mechanism by which these drugs exert their therapeutic cytotoxicity.[3]

(1) A preliminary account of portions of this work was presented by P. V. Danenberg and P. W. Woodman at the 61st Annual Meeting of the Federation of American Societies for Experimental Biology, Chicago, IL, Apr 1977. See P. V. Danenberg and P. W. Woodman, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **36**, 64 (1977).

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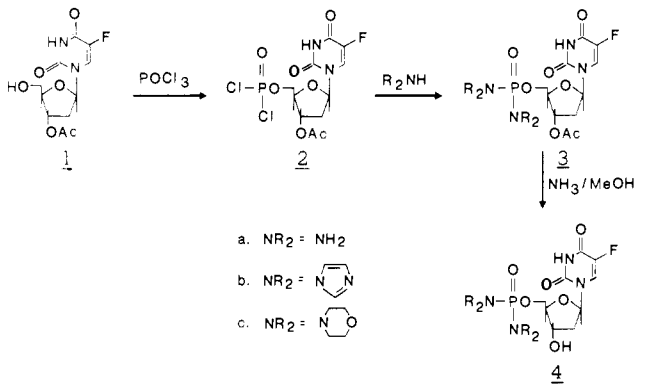
Scheme I



More recent evidence indicates that extensive incorporation of FUra into RNA, which produces some abnormally functioning RNA species, also contributes to the anticancer activity of the drug.[4] Regardless of which mechanism prevails, it is clear that metabolic conversion of FUra to nucleotides by cellular enzymes is necessary to produce a chemotherapeutic effect. There is, for example, an excellent correlation between intracellular levels of phosphoribosyltransferases and the anticancer activity of FUra,[5] whereas low levels of uridine kinase activity have been found in neoplasms resistant to FUra.[6] Several forms of resistance have been characterized for FdUrd; these include a lack of thymidine kinase activity[7] and an alteration in the active site of thymidylate synthetase.[8] Direct administration of the active metabolite, FdUrd-5'-P, would not be effective at overcoming these problems, however, because most nucleotides do not penetrate cell membranes appreciably, but instead are dephosphorylated to the nucleoside at the cell surface.[9] Thus, in order to circumvent most of the common mechanisms of cellular resistance, a derivative of FdUrd-5'-P would ideally have to (a) penetrate the cell membrane intact, (b) not require enzymatic activation and thus inhibit thymidylate synthetase directly, or, alternatively, (c) penetrate the cell membrane and generate FdUrd-5'-P in situ. In attempts to develop a class of drugs with the latter property (c), we have investigated FdUrd-5'-phosphorodiamidates.

Nucleoside phosphorodiamidates are relatively unknown phosphate derivatives.[10] By contrast, phosphoramidates have been widely used in the synthesis of oligophosphates,[11] and their kinetics of hydrolysis have been thoroughly studied.[12] In water, phosphorodiamidates behave in a manner similar to that of the phosphoramidates; that is, they are relatively labile and are hydrolyzed to the parent phosphates at rates that are influenced by both the nature of the amino group and the pH of the medium.[10] Moreover, phosphorodiamidates are neutral compounds that should be able to cross the cell membrane either by diffusion or by the facilitated transport mechanism used by nucleosides. The synthetic method described here for 5'-phosphorodiamidates will allow a wide variety of amino substituents to be placed on the phosphate group. Thus, 5'-phosphorodiamidates of FdUrd with varying degrees of hydrolytic stability and hydrophobic character can be readily synthesized.

Table I. Inhibition of L5178Y Cell Growth in Vitro and Rate of Hydrolysis to FdUrd-5'-P

nucleotide	% inhibn at 10^{-5} M[a]	$t_{1/2}$ for hydrolysis to FdUrd-5'-P at 100 °C, h[b]
FdUrd-5'P	67	
FdUrd-5'-P$(NH_2)_2$ (4a)	45	3.9
FdUrd-5'-P$(Im)_2$ (4b)	16	12
FdUrd-5'-P$(Morph)_2$ (4c)	11	100

[a] Replicate flasks inoculated with 10^5 cells were treated with the nucleotide, and the inhibition of cell growth was determined after 72 h.[14] Values are the means of two experiments (error 8%). [b] The compounds were incubated in 0.1 M phosphate buffer (pH 7.0) at 100 °C. The rate of generation of FdUrd-5'-P was followed by TLC on cellulose plates (*i*-PrOH–NH_4OH–H_2O, 7:1:2). The spots corresponding to FdUrd-5'-P and the phosphorodiamidates were scraped off, the compounds were eluted from the cellulose with water, and the concentration was determined by UV absorbance at 269 nm. The rates of hydrolysis were obtained from first-order plots of disappearance of the phosphorodiamidate and appearance of FdUrd-5'-P.

Chemistry. Nucleoside phosphorodiamidates have been synthesized by treating the phosphorodichloridate derivative with the desired amine;[10] with modifications, this method was applied to FdUrd, as shown in Scheme I. FdUrd was converted to the 3'-OAc derivative and then treated with excess $POCl_3$ in triethyl phosphate. After removal of unreacted $POCl_3$, the intermediate 3'-acetoxy-5-fluoro-2'-deoxyuridine 5'-phosphorodichloridate (**2**) was not isolated but was treated immediately with a fivefold excess of the amine in an organic solvent to give the 3'-acetoxy-5-fluoro-2'-deoxyuridine 5'-phosphorodiamidates. If, however, **2** was treated with a limiting amount of the amine (2 equiv), phosphoramidates predominated (M. E. Phelps and P. V. Danenberg, unpublished results). The 3'-*O*-acetyl group could be quantitatively removed with methanolic ammonia to give the unblocked 5-fluoro-2'-deoxyuridine 5'-phosphorodiamidates (**4**). To obtain derivatives having substituents with a range of basicity, bulk, and hydrophobic character, we used ammonia, imidazole, and morpholine as the amino components to give, respectively, the phosphorodiamidate [FdUrd-5'-P$(NH_2)_2$, **4a**], phosphorodiimidazolidate [FdUrd-5'-P$(Im)_2$, **4b**], and phosphorodimorpholidate [FdUrd-5'-P$(Morph)_2$, **4c**].

None of the three 5-fluoro-2'-deoxyuridine 5'-phosphorodiamidates (**4a–c**) underwent a decomposition of more than 5% upon heating with 1 N NaOH at 65 °C for 2 h. This behavior is in marked contrast to reports for

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Table II. Comparative Inhibition of L5178Y Cell Growth in Vitro

compound	concn, nM, required for 50% inhibn (IC_{50})[a]
FdUrd	0.76
FdUrd-5′-P	1.4
FdUrd-5′-P(NH_2)$_2$ (4a)	2.0

[a] See footnote *a*, Table I.

other nucleoside phosphorodiamidates. For example, guanosine 5′-phosphorodiamidate was quantitatively converted to the nucleoside by mild treatment with base,[10b] whereas thymidine 5′-phosphorodiimidazolidate gave the corresponding phosphorimidazolidate.[10a] A prolonged exposure (3 days at 25 °C) to a saturated solution of ammonia in methanol was necessary to achieve about 50% ammonolysis of the phosphoester bond of **4a** to give FdUrd. These differences in reactivity among 5′-phosphorodiamidates derived from various nucleosides may be due to different conformational relationships of the sugar and base portions that result in a lower reactivity at the 5′ position for some nucleosides. In each instance, acid hydrolysis of **4a–c** produced FdUrd-5′-P, although the rate of hydrolysis of the phosphorodiamidate (**4a**) was much more rapid ($t_{1/2}$ = 15 min at 25 °C in 1 N formic acid) than that of either **4b** ($t_{1/2}$ = 60 min at 65 °C) or **4c** ($t_{1/2}$ = 240 min at 65 °C), and the same order was also observed at pH 7 (Table I). Thus, the relative rates of hydrolysis of these phosphorodiamidates to FdUrd-5′-P (i.e., **4a > 4b > 4c**) do not correlate with the basicity of the amine component but rather appear to correlate better with the steric bulk of the substituent.

Biological Activity. In culture, the 5′-phosphorodiamidates (**4a**, **4b**, or **4c**) inhibited the growth of L5178Y cells to varying degrees (Table I). The order of cytostatic activity for these compounds (i.e., **4a > 4b > 4c**) corresponded with their rates of hydrolysis to FdUrd-5′-P.

None of the 5′-phosphorodiamidates inhibited the thymidylate synthetase activity of *Lactobacillus casei*, even when tested at concentrations of up to 1 mM.

These observations suggest that the phosphorodiamidates themselves have no biological activity, but rather that the factor determining their activity against cells is degradation to some hydrolytic product (presumably FdUrd-5′-P). Whether the cytostatic activity of these compounds (**4a–c**) results from the inhibition of thymidylate synthetase has not yet been established but is currently under investigation.

FdUrd-5′-P(NH_2)$_2$ (**4a**), the most active compound, was compared to FdUrd and FdUrd-5′-P for cytostatic activity (Table II). On the basis of IC_{50} values, **4a** inhibited the growth of L5178Y cells to about the same degree as FdUrd and FdUrd-5′-P.

Continuing experiments to assess the anticancer activity of FdUrd-5′-P(NH_2)$_2$ (**4a**) in tumor-bearing mice indicate that the maximal activity of **4a** is comparable to that of FdUrd. However, the dose–response profiles of **4a** are characterized by a much broader range of optimal activity than that of FdUrd (P. W. Woodman and P. V. Danenberg, unpublished results).

Experimental Section

FdUrd was a gift of Parke-Davis Co., Detroit, MI; all other chemicals, apart from triethyl phosphate and $POCl_3$, were reagent grade and were obtained from the Aldrich Chemical Co., Milwaukee, WI. Melting points were determined with a Thomas-Hoover capillary melting-point apparatus and are uncorrected. UV spectra were recorded with a Gilford 250 spectrophotometer and NMR spectra with a Varian EM-390 spectrometer at 90 MHz. All spectra agreed with the structures assigned, and each analytical sample was homogeneous by TLC. Elemental analyses were within ±0.4% of the theoretical values.

5-Fluoro-2′-deoxyuridine 5′-Phosphorodiamidate (4a). To an ice-cold solution of 3′-OAc-FdUrd[13] (**1**; 1.38 g, 5.0 mmol) in 10 mL of triethyl phosphate was added, dropwise with stirring, 5.0 mL (19.5 mmol) of $POCl_3$. The reaction was incubated for 18 h at 4 °C, followed by 4 h at room temperature under anhydrous conditions. Hexane (50 mL) was then added to the reaction mixture, and the resulting liquid material that separated out was washed with 20-mL portions of hexane until a gummy residue coated the flask and there was no further odor of $POCl_3$. The residue was dissolved in 5 mL of anhydrous dioxane. After the solution was cooled on ice, an additional 50 mL of anhydrous dioxane saturated with gaseous NH_3 was added, and a white precipitate formed. This mixture was stirred at room temperature for 2 h, and the precipitate was removed by filtration and then dissolved in a minimal volume of MeOH. The solution was placed on a silica gel column and eluted with a mixture of $CHCl_3$–MeOH, 4:1. Fractions containing UV-absorbing material were combined to give 1.13 g (61%) of 3′-OAc-FdUrd-5′-P(NH_2)$_2$ (**3a**). The material was recrystallized from MeOH–ether, mp 200–208 °C (dec). The product was homogeneous by TLC on silica gel (R_f 0.6, $CHCl_3$–MeOH, 4:1): UV (MeOH) λ_{max} 269 nm (ϵ 9200). Anal. ($C_{11}H_{16}FN_3O_7P$) C, H, N. Phosphorus–base ratio: calcd, 1:1; found, 1.05:1.

Compound **3a** was dissolved in MeOH–NH_3 and allowed to stand for 12 h. The solvent was evaporated to dryness, and the residue was taken up in MeOH and placed on a column of silica gel. Elution with $CHCl_3$–MeOH, 3:1, gave FdUrd-5′-P(NH_2)$_2$ (**4a**) in an 85% yield. The material precipitated from EtOH with ether to give a white solid product that was homogeneous by TLC on silica gel (R_f 0.2, $CHCl_3$–MeOH, 3:1). The NMR spectrum showed disappearance of the singlet at δ 2.2, corresponding to the acetyl group of **3a**. Anal. ($C_9H_{14}FN_4O_7P$) C, H, N. Phosphorus–base ratio: calcd, 1:1; found, 1.08:1.

5-Fluoro-2′-deoxyuridine 5′-Phosphorodiimidazolidate (4b). A procedure identical with that for **3a** was followed, except that the intermediate phosphoryl chloride **2** (5.0 mmol) was dissolved in 20 mL of $CHCl_3$, to which a solution of imidazole (1.7 g, 25 mmol) in $CHCl_3$ was added. The solution was stirred at 25 °C for 18 h and then placed on a silica gel column. Elution of the column with $CHCl_3$–MeOH, 19:1, gave 702 mg (30%) of 3′-OAc-FdUrd-5′-P(Im)$_2$ (**3b**) as a colorless oil. The product was homogeneous by TLC on silica gel (R_f 0.6, $CHCl_2$–MeOH, 19:1): UV (MeOH) λ_{max} 269 nm (ϵ 9100). Anal. ($C_{17}H_{18}FN_6O_7P$) C, H, N. Phosphorus–base ratio: calcd, 1:1; found, 0.95:1.

Treatment of **3b** with MeOH–NH_3 for 12 h gave a quantitative conversion to FdUrd-5′-P(Im)$_2$ (**4b**). The residue was placed on a column of silica gel and the product, a viscous colorless syrup, was eluted with $CHCl_3$–MeOH, 9:1, in 90% yield. TLC on silica gel disclosed a single spot (R_f 0.4, $CHCl_3$–MeOH, 9:1): UV (MeOH) λ_{max} 269 nm (ϵ 9200). Anal. ($C_{15}H_{16}FN_6O_6P$) C, H, N. Phosphorus–base ratio: calcd, 1:1; found, 0.96:1.

5-Fluoro-2′-deoxyuridine 5′-Phosphorodimorpholidate (4c). The phosphoryl chloride **2** was dissolved in $CHCl_3$ and a solution of morpholine (2.13 g, 25 mmol) in $CHCl_3$ was added. After standing at 25 °C for 4 h, the solution was reduced in volume and then placed on a silica gel column. Elution of the column with $CHCl_3$–MeOH, 19:1, gave 1.21 g (52%) of 3′-OAc-FdUrd-5′-P(Morph)$_2$ (**3c**). The product was crystallized from MeOH–ether, mp 222–223 °C. The white crystalline product was homogeneous by TLC on silica gel (R_f 0.7, $CHCl_3$–MeOH, 9:1): UV (MeOH) λ_{max} 269 nm (ϵ 9100). Anal. ($C_{19}H_{28}FN_4O_9P$) C, H, N. Phosphorus–base ratio: calcd, 1:1; found, 1.0:1.

Treatment of **3c** with NH_3–MeOH and purification as described for **4b** gave a 90% yield of FdUrd-5′-P(Morph)$_2$ (**4c**). Precipitation from methanol with ether gave a white solid that was homogeneous by TLC (R_f 0.3, $CHCl_3$–MeOH, 9:1): UV (MeOH) λ_{max} 269 nm (ϵ 9200). Anal. ($C_{17}H_{26}FN_4O_8P\cdot H_2O$) C, H, N. Phosphorus–base ratio: calcd, 1:1; found, 0.98:1.

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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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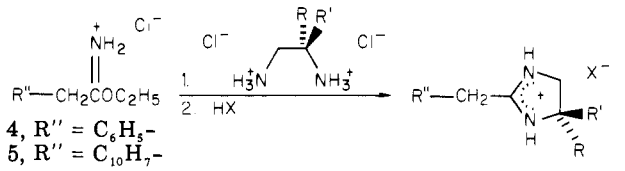
The synthesis and α-adrenergic blocking activity of a series of optically active 2,4-disubstituted imidazolines are presented. The substituted analogues of naphazoline, tolazoline, and clonidine possess moderate α-adrenergic blocking activity with $-\log K_B$ values in the range from 4.77 to 6.57. The 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.

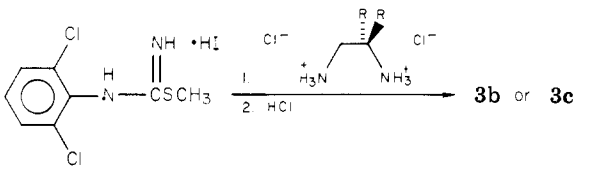
In addition to the well-known phenethanolamines, an important group of drugs capable of interacting with α-adrenergic receptors consists of imidazoline derivatives. It is known that appropriately substituted imidazolines can act either as an agonist or antagonist on α-adrenergic receptors.[1-9] The imidazoline 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



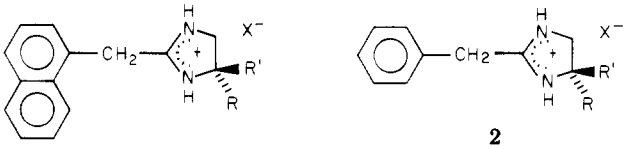
1 or 2

Scheme II

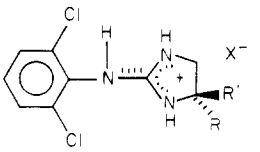


7

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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