Transport Studies. The procedures and transport conditions to assay for the uptake of labeled trimethionine in the presence of polyoxin compounds have been previously described.[34] When assayed for the uptake of uridine, the cells were incubated in 2% dextrose at 37 °C for 10 min and added to an equal volume (0.5 mL) of reaction mixture containing 30 mM Bis-Tris buffer (pH 6.5) and 0.2 mM [^{14}C]uridine (10 mCi/mmol) with or without polyoxin analogues at a 10-fold concentration of uridine.

At intervals of 0, 1, 3, 5, and 7 min, aliquots of the reaction mixtures were withdrawn and applied to prewet filters (pore size 0.45 μm) and washed twice with 2 mL of cold distilled water. The filters were placed in Bray's scintillation cocktail and were counted. The uptake results were expressed as nanomoles of trimethionine (1.0 mCi/mmol) and picomoles of uridine (10 mCi/mmol) taken up per milligram of dry weight cells.

Determination of MIC, MEC, Growth Inhibition, and Viability. The methods and procedures employed for the determinations of the MIC, MEC, growth inhibition, and viability of *C. albicans* H317 in the presence of the polyoxin analogues has been previously described.[5] For the microtiter assay, the MIC was recorded as the lowest concentration of drug that inhibited clearly visible growth; the MEC was defined as the lowest concentration of drug that results in (5%) morphologically abnormal cells at 48 h; growth inhibition was calculated by comparison of the number of cells at 48 h in the control well (no treatment) with the number of cells in drug-treated wells; the percentage of viability was calculated by comparing the number of viable colonies with the number of potential viable cells by direct counting.

(34) Logan, D. A.; Becker, J. M.; Naider, F. *J. Gen. Microbiol.* **1979**, *114*, 179.

Acknowledgment. This work was supported by grants from the National Institute of Allergy and Infectious Disease (AI-14387 and AI-42651), the American Cancer Society (CH290), and the PSC-BHE Awards Program of CUNY.

Registry No. 1, 22976-86-9; **2**, 24695-48-5; **3**, 38930-96-0; 4, 100995-65-1; **5**, 100995-66-2; **6**, 100995-67-3; **7**, 100995-68-4; 8, 101009-62-5; **9**, 100995-69-5; **10**, 100995-70-8; BOC-MeNle-ONp, 100995-71-9; Z-(allyl)Leu-ONp, 100995-72-0; Z-L-(aminooxy)-3-phenylpropionic, 100995-73-1; acid *p*-nitrophenyl ester chitin synthetase, 9030-18-6.

Synthesis and Antiviral Properties of 5-(2-Substituted vinyl)-6-aza-2′-deoxyuridines†

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The following 5-(2-substituted vinyl)-6-aza-2′-deoxyuridines were synthesized: (*E*)-5-(2-bromovinyl) (**2**) (6-aza-BVDU), 5-(2-bromo-2-fluorovinyl) (a mixture of *E* and *Z* isomers) (**3**), (*E*)-5-(2-chlorovinyl) (4), (*E*)-5-[2-(methylthio)vinyl] (**5**), 5-(2,2-dibromovinyl) (**6**), and 5-(3-furyl) (**7**). The synthesis of **2–6** utilized Wittig-type reactions on 5-formyl-1-(2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-6-azauracil (**16**). 6-Aza-BVDU (and its α-anomer) was also synthesized from (*E*)-5-(2-bromovinyl)-6-azauracil (**12**) by using standard deoxyribosidation methodology. Compound **7** was prepared from 5-(3-furyl)-6-azauracil (**33**) via a ribosidation/deoxygenation sequence. An attempt to prepare the corresponding 5-(2,2-difluorovinyl) analogue afforded instead a mixture of the 5-[(2,2-difluoro-2-methoxy)ethyl] and 5-(2,2,2-trifluoroethyl) derivatives **29** and **30**. Compounds **2–7**, **29**, and **30** were tested for in vitro activity against herpes simplex virus types 1 and 2 (HSV-1, HSV-2). 6-Aza-BVDU (**2**) exhibited ID_{50}s of 8 μg/mL vs. HSV-1 and 190 μg/mL vs. HSV-2. BVDU (1) had ID_{50}s of 0.015 and 1.6 μg/mL against HSV-1 and HSV-2, respectively. Compound 4 showed a similar profile of activity, but the other analogues were either weakly active or inactive.

5-(2-Halovinyl)-2′-deoxyuridines are among the most active and selective inhibitors of herpes simplex virus type 1 (HSV-1) and varicella zoster virus (VZV) in cell culture.[1,2] Within this series of compounds (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU; 1) has emerged as the most potent analogue, and its efficacy against HSV-1 and VZV infections has been demonstrated in animal models and in phase I clinical trials.[2,3] However, limitations to the use of BVDU include its poor activity vs. HSV-2 and its rapid degradation by pyrimidine nucleoside phosphorylases.[4] A number of research groups have therefore conducted extensive analogue programs[1] with a view to improving the antiviral profile of BVDU. However, much of this work has been devoted to modification of the vinylic C-5 substituent and the carbohydrate moiety, and little attention has been given to changes in the heterocyclic nucleus.

During the 1960s several 5-substituted 6-aza-2′-deoxyuridines were synthesized as potential antiviral and antitumor agents. However, the nature of the 5-substitution was limited to halogen,[5] methyl[6], hydroxymethyl,[7] and trifluoromethyl.[5,8] Although these earlier studies did not

† Presented in part at the 6th International Round Table Nucleosides, Nucleotides and Their Biological Applications, La Grand Motte, France, 1984.

(1) For an excellent review on the synthesis and antiviral properties of 5-vinylpyrimidine nucleoside analogues, see: De Clercq, E.; Walker, R. T. *Pharmacol. Ther.* **1984**, *26*, 1.

(2) De Clercq, E.; Descamps, J.; Maudgal, P. C.; Missotten, L.; Leyten, R., Verhelst, G.; Jones, A. S.; Walker, R. T.; Busson, R.; Vanderhaeghe, H., De Somer, P. "Developments in Antiviral Therapy"; Collier, L. H., Oxford, J., Eds.; Academic Press: London, 1980; p 21. De Clercq, E. "Problems of Antiviral Therapy"; Stuart-Harris, C. H., Oxford, J., Eds.; Academic Press: London, 1983; p 295.

(3) Maudgal, P. C.; Missotten, L.; De Clercq, E.; Descamps, J.; De Meuter, E. *Albrecht von Graefes Arch. Klin. Ophthalmol.* **1981**, *216*, 261. Maudgal, P. C.; Dralands, L.; Lamberts, L.; De Clercq, E.; Descamps, J.; Missotten, L. *Bull. Soc. Belge Ophtalmol.* **1981**, *193*, 49. Maudgal, P. C.; De Clercq, E.; Missotten, L. *Antiviral Res.* **1984**, *4*, 281. De Clercq, E.; De Greef, H.; Wildiers, J.; De Jonge, G.; Drochmans, A.; Descamps, J.; De Somer, P. *Br. Med. J.* **1980**, *281*, 1178. Wildiers, J.; De Clercq, E. *Eur. J. Cancer Clin. Oncol.* **1984**, *20*, 471. Benoit, Y.; Laureys, G.; Delbeke, M.-J.; De Clercq, E. *Eur. J. Pediatr.* **1985**, *143*, 198.

(4) Desgranges, C.; Razaka, G.; Rabaud, M.; Bricaud, H.; Balzarini, J.; De Clercq, E. *Biochem. Pharmacol.* **1983**, *32*, 3583.

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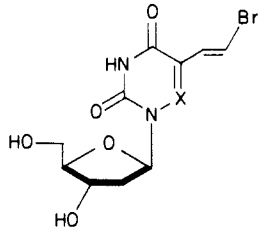
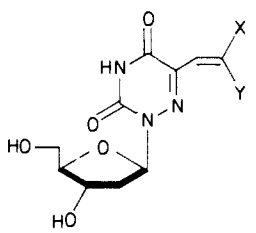
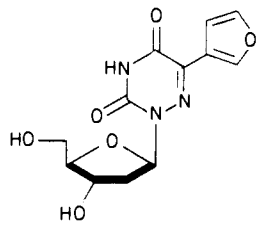
provide compounds of notable activity, the striking antiviral activity of BVDU encouraged us to evaluate 5-(2-substituted vinyl)-6-aza-2′-deoxyuridines as potential antiviral agents. Specifically, we herein describe the synthesis and antiherpes activity of (*E*)-5-(2-bromovinyl)-6-aza-2′-deoxyuridine (6-aza-BVDU; **2**) and some closely related derivatives (**3**–**7**).



1, X = CH (BVDU)
2, X = N (6-aza-BVDU)



3, X = Br; Y = F
4, X = Cl; Y = H
5, X = SMe; Y = H
6, X = Y = Br

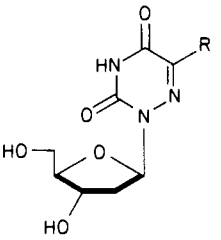


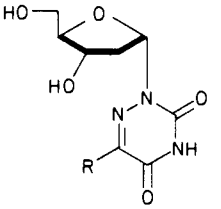
7

Chemistry

Our first synthesis of 6-aza-BVDU (**2**) required (*E*)-5-(2-bromovinyl)-6-azauracil (**12**). 5-(Hydroxymethyl)-6-azauracil (**8**), conveniently obtained by hydrolysis of the corresponding chloromethyl derivative **9**,[9] was oxidized to the carboxaldehyde **10** in high yield with use of benzeneseleninic anhydride.[10] The remaining steps in the preparation of **12** paralleled those employed by Jones et al. for the synthesis of (*E*)-5-(2-bromovinyl)uracil.[11] Thus, condensation of **10** with malonic acid in the presence of piperidine afforded 5-(2-carboxyvinyl)-6-azauracil (**11**), which upon treatment with *N*-bromosuccinimide in aqueous potassium acetate at 60 °C gave **12** in 30% overall yield from **10**. The *E* configuration of **12** was confirmed by the 14-Hz coupling constant for the vinylic protons. The bis(trimethylsilyl) derivative of **12** was condensed with 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride,[12] in the presence of stannic chloride catalyst, to give an anomeric mixture of the blocked 2′-deoxyribonucleosides **13**. Deprotection of **13** with sodium methoxide in methanol followed by chromatographic separation of the anomers provided 6-aza-BVDU (**2**) in 32% yield and its α-anomer **14** in 40% yield. The anomeric configuration of these compounds was initially assigned by using an empirical correlation based on the chemical shift differences of the H-3′ and H-4′ protons of azathymidine and some alkoxy- and (alkylthio)-6-aza-deoxyuridines.[13] Thus, for the β-anomers Δδ(H-3′/H-4′) is ca. 0.6 ppm whereas for the α-anomers Δδ is much smaller (ca. 0.2 ppm) (see Table I). These configuration assignments to **2** and **14** were later confirmed by an unequivocal synthesis of **2** (vide infra).

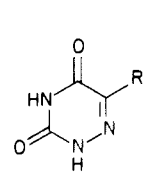
Table I. Assignment of Anomeric Configuration of 6-Aza-2′-deoxyuridines



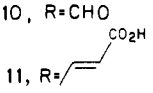


R	Δδ(H-3′/H-4′)	
Me[a]	0.58	0.20
CH_2OMe[b]	0.55	0.18
CH_2SMe[b]	0.56	0.22
	0.63	0.15
	0.68	0.13

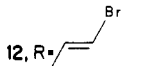
[a] Reference 6b. [b] Reference 13.



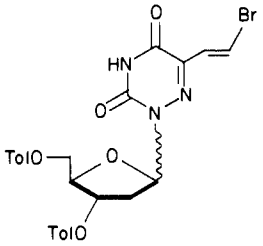
8, R = CH_2OH
9, R = CH_2Cl
10, R = CHO



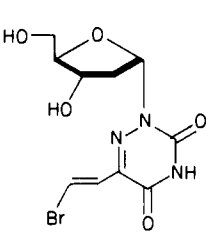
11, R =



12, R =



13

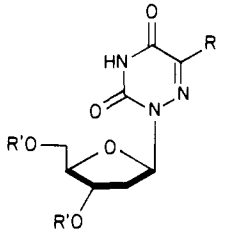


14

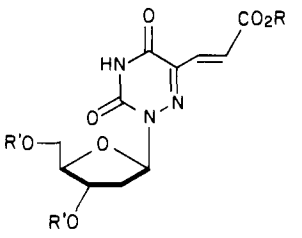
The somewhat tedious separation of **2** and **14** directed us to adopt an alternative approach. This utilized the known di-*O*-toluoyl-protected 5-(hydroxymethyl)-6-aza-2′-deoxyuridine (**15**),[7,14] readily obtainable as its pure β-anomer in consistent yields (ca. 30%). Oxidation of **15** with diphenyl diselenide–*tert*-butyl hydroperoxide[15] in benzene at reflux afforded in 80% yield the carboxaldehyde **16**, a versatile intermediate for our synthesis of 5-(2-substituted vinyl)-6-aza-2′-deoxyuridines. 5-Formyl-6-aza-2′-deoxyuridine (**17**) was obtained after deblocking with sodium methoxide in methanol–benzene.

(5) Shen, T. Y.; Ruyle, W. V.; Bugianesi, R. L. *J. Heterocycl. Chem.* **1965**, *2*, 495.
(6) (a) Pliml, J.; Prystas, M.; Sorm, F. *Collect. Czech. Chem. Commun.* **1963**, *28*, 2588. (b) Shiau, G. T.; Prusoff, W. H. *Carbohydr. Res.* **1978**, *62*, 175.
(7) Bobek, M.; Farkas, J.; Sorm, F. *Collect. Czech. Chem. Commun.* **1967**, *32*, 3581.
(8) (a) Mertes, M. P.; Saheb, S. E.; Miller, D. *J. Heterocycl. Chem.* **1965**, *2*, 493. (b) Dipple, A.; Heidelberger, C. *J. Med. Chem.* **1966**, *9*, 715.
(9) Alekseeva, I. V.; Shalamai, A. S.; Chernetskii, V. P. *Ukr. Khim. Zh.* **1976**, *42*, 398.
(10) Barton, D. H. R.; Brewster, A. G.; Hui, R. A. H. F.; Lester, D. J.; Ley, S. V.; Back, T. G. *J. Chem. Soc., Chem. Commun.* **1978**, 952.
(11) Barr, P. J.; Jones, A. S.; Verhelst, G.; Walker, R. T. *J. Chem. Soc., Perkin Trans 1* **1981**, 1665.
(12) Bhat, C. C. In "Synthetic Procedures in Nucleic Acid Chemistry"; Zorbach, W. W., Tipson, R. S., Eds.; Wiley: New York, 1968; Vol. 1, p 521.
(13) Mitchell, W. L.; Scopes, D. I. C., unpublished results.
(14) The anomeric configuration and site of ribosidation of **15** was confirmed by sodium methoxide–methanol deprotection to the corresponding nucleoside and the close correlation of its ^1H NMR and UV spectral data with that of azathymidine.[6b]
(15) Kuwajina, I.; Shimizu, M.; Urabe, H. *J. Org. Chem.* **1982**, *47*, 837.

Treatment of **16** with (carbomethoxymethylene)triphenylphosphorane in acetonitrile at reflux effected smooth conversion to the α,β-unsaturated ester **18** in 85% yield. Base hydrolysis of the ester function with concomitant deblocking of the sugar residue afforded the carboxylic acid **19** in 82% yield. Alternatively, treatment of **18** with sodium methoxide in methanol gave the nucleoside **20**. Brominative decarboxylation of **19**, using *N*-bromosuccinimide under the usual conditions, gave anomerically pure 6-aza-BVDU (**2**), identical with the material described above and assigned as the β-anomer.

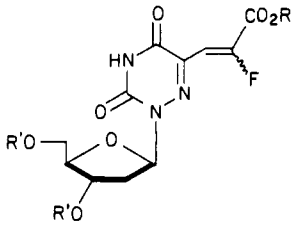


15, R = CH_2OH; R′ = Tol
16, R = CHO; R′ = Tol
17, R = CHO; R′ = H

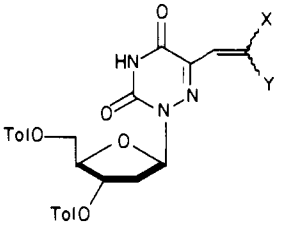


18, R = Me; R′ = Tol
19, R = R′ = H
20, R = Me; R′ = H

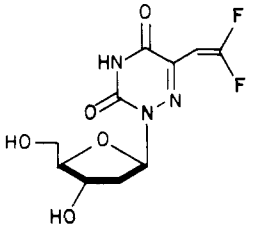
The corresponding 2-fluoro-substituted system **3** was obtained via a similar strategy. Wadsworth–Emmons reaction of **16** with the anion derived from diethyl (carbethoxyfluoromethyl)phosphonate[16] afforded the fluoroacrylates **21** as a mixture of *E* and *Z* isomers, hydrolysis of which gave the acids **22**. Treatment of **22** with *N*-bromosuccinimide in aqueous potassium acetate at 100 °C provided a 20% yield of **3**, as a 3:1 mixture of *E* and *Z* isomers. Wittig reaction of **16** with (chloromethylene)-triphenylphosphorane gave an 81% yield of a 1:1 mixture of *E*–*Z* isomers **23**, which were deprotected and separated to provide (*E*)-5-(2-chlorovinyl)-6-aza-2′-deoxyuridine (**4**). Similar schemes employing [(methylthio)methylene]- and (dibromomethylene)triphenylphosphoranes[17] and proceeding via **24** and **25** gave the nucleoside analogues **5** and **6**, respectively.



21, R = Et; R′ = Tol
22, R = R′ = H



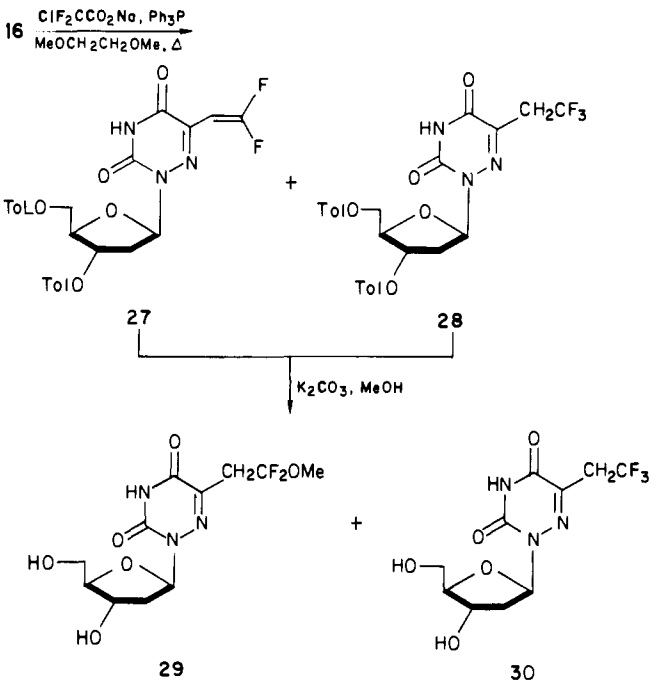
23, X = Cl; Y = H
24, X = SMe; Y = H
25, X = Y = Br



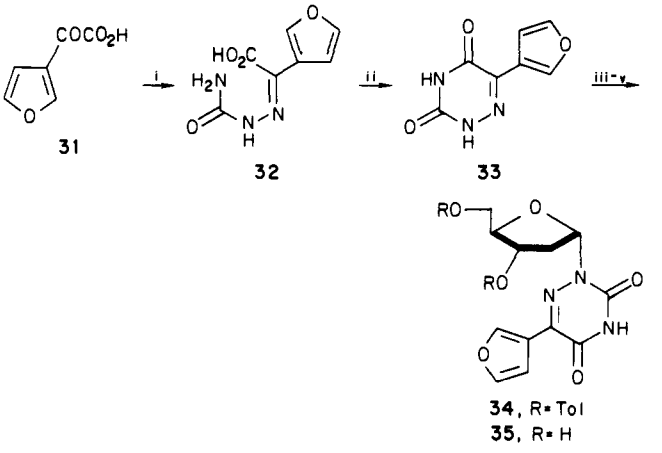
26

We also investigated the synthesis of the 2,2-difluorovinyl analogue **26**. In situ generation of (difluoromethylene)triphenylphosphorane, via thermal decomposition of sodium chlorodifluoroacetate in the presence of triphenylphosphine,[18] and reaction with the carboxaldehyde **16** led to a 1:1 mixture of two products: the desired adduct **27** and the 2,2,2-trifluoroethyl derivative **28**, the latter presumably arising from addition of hydrogen fluoride to **27** (Scheme I). Deprotection of this mixture of **27** and **28** using potassium carbonate in methanol afforded **29** and the 2,2,2-trifluoroethyl analogue **30**, the facile addition of methanol to the difluorovinyl moiety precluding isolation of **26**.

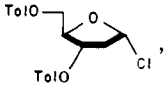
Scheme I



Scheme II[a]



[a] (i) $H_2NNHCONH_2 \cdot HCl$, EtOH–H_2O, (ii) NaOEt, EtOH, $MeCH(OH)CH_2OH$, Δ, (iii) $(Me_3Si)_2NH$, Me_3SiCl, MeCN, Δ, (iv),

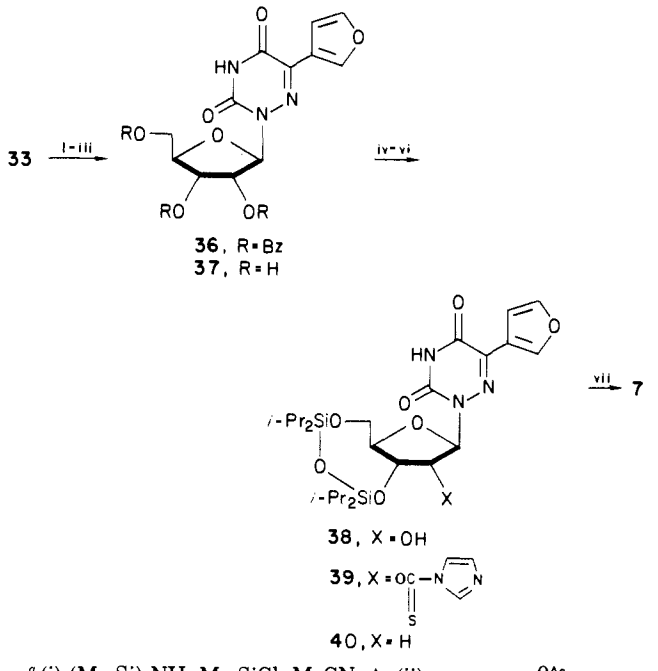


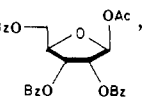
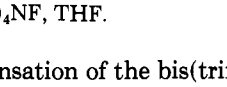
, $ClCH_2CH_2Cl$, (v) NaOMe, MeOH.

The synthesis of 5-(3-furyl)-6-aza-2′-deoxyuridine (**7**) required the novel azauracil **33**, which was prepared from the keto acid **31**[19] via standard methodology[20] (Scheme II). However, despite numerous variations of reaction condi-

(16) U.S. Patent (to Squibb) 3 281 440, 1966.
(17) Compare Sharma, R. A.; Bobek, M. *J. Org. Chem.* **1978**, *43*, 367. Perman, J.; Sharma, R. A.; Bobek, M. *Tetrahedron Lett.* **1976**, 2427.
(18) Fuqua, S. A.; Duncan, W. G.; Silverstein, R. M. *Org. Synth.* **1967**, *47*, 49.
(19) Brit. Patent (to Glaxo) 1 447 114, 1976.
(20) Compare Hayes, K. *J. Med. Chem.* **1964**, *7*, 819.

Scheme III[a]



[a] (i) $(Me_3Si)_2NH$, Me_3SiCl, MeCN, Δ, (ii)  , $SnCl_4$, $ClCH_2CH_2Cl$, (iii) NaOMe, MeOH, (iv) $(i\text{-}Pr)_2Si(Cl)O(Cl)Si(i\text{-}Pr)_2$, (v)  DMF, (vi) $(n\text{-}Bu)_3SnH$, AIBN, toluene, Δ, (vii) $(n\text{-}Bu)_4NF$, THF.

tions, condensation of the bis(trimethylsilyl) derivative of **33** with 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride gave either the undesired α-anomer **34** or an inseparable mixture of α- and β-anomers. To circumvent this problem, the β-ribonucleoside **36** was prepared and the deoxygenation sequence of Robins et al.[21] was utilized to obtain **7** (Scheme III). Although appearing somewhat lengthy, this sequence provided pure β-anomer **7** in 25% overall yield from 5-(3-furyl)-6-azauracil (**33**) without the need for isomer separation. The α-nucleoside **35** was obtained by deprotection of **34** using sodium methoxide in methanol. The ^1H NMR spectral data for furans **7** and **35** are in line with the empirical correlation given in Table I.[28]

Antiviral Activity

The 6-aza-2′-deoxyuridines **2–7**, **17**, **19**, **20**, **29**, and **30** were evaluated for antiviral activity in vitro against HSV-1 and HSV-2 (Table II). 6-Aza-BVDU (**2**) was the most potent compound in this series and showed modest activity vs. HSV-1 but was about 500-fold less active than BVDU. 6-Aza-BVDU (**2**) exhibited only weak activity against HSV-2, thus paralleling the differential effect found with BVDU. Apart from the 2-chlorovinyl analogue **4**, none of the other nucleosides showed significant, selective activity against HSV-1 and HSV-2. The inactivity of **5** and **6** vs. HSV-1 parallels the considerably lower activity of (*E*)-5-[2-(methylthio)vinyl]-2′-deoxyuridine and 5-(2,2-dibromovinyl)-2′-deoxyuridine relative to BVDU.[1] The furyl analogue **7** was cytotoxic, and this probably accounts for the observed antiviral activity of this compound. The α-anomers **14** and **35** were inactive against both virus types.

Table II. Antiherpes Activity of 6-Aza-2′-deoxyuridines

compd	5-substituent	ID_{50},[a] μg/mL HSV-1	HSV-2	cytotoxicity
2		8	190	355
3		>250	>250	>500
4		20	215	>500
5		>250	>250	420
6		100	100	>500
7		42	39	45
17	CHO	>500	NT[c]	180
19		>250	NT	>500
20		>500	NT	>500
29	CH_2CF_2OMe	82	>250	>500
30	CH_2CF_3	>250	>250	>500
BVDU		0.015	1.6	50

[a] ID_{50} = concentration required for 50% reduction of plaque formation or 50% reduction of [*methyl*-^3H]thymidine incorporation. [b] 3:1 mixture of *E* and *Z* isomers. [c] Not tested.

6-Aza-BVDU was an effective substrate for HSV-1 thymidine kinase and was phosphorylated at 116% the rate of thymidine (100%); the corresponding rate for BVDU was 218%. The presence of N-6 precludes 6-aza-BVDU-5′-monophosphate from acting as a thymidylate synthetase substrate.[22]

Introduction of the 6-aza group into the uracil ring of potent 5-(2-substituted vinyl)-2′-deoxyuridines clearly causes a substantial loss of antiherpetic activity and presumably reflects fundamental differences in the physicochemical properties of 6-azauracil and uracil nucleosides and nucleotides.

Experimental Section

^1H NMR spectra were measured [$SiMe_4$ or sodium 3-(trimethylsilyl)propane-1-sulfonate internal standards] on a Varian EM 390 (90 MHz) or a Bruker WM 250 (250 MHz) spectrometer (by Dr. J. H. Hunt and his staff). IR spectra were recorded on Perkin-Elmer 357 or 377 spectrophotometers, and UV spectra were measured on a Perkin-Elmer 402 spectrophotometer (by Dr. J. H. Hunt and his staff). Mass spectral data were obtained (by Dr. R. Tanner and his staff) with either a Kratos MS 30 instrument interfaced to a DS 55 data system or a VG Analytical Ltd. VG 7070E instrument interfaced to a Multispec 11 data system. Microanalyses were performed by Dr. T. J. Cholerton and his staff. Column chromatography was performed on Merck Kieselgel 60

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(28) At 250 MHz the H-1′ signal of the β-anomers (**4**, **5**, **7**, **17**, **20**, **29**, and **30**) is resolved into a doublet of doublets (J = 7, 5 Hz). A similar splitting is reported for H-1′ of 6-azathymidine,[6b] thus demonstrating that many 5-substituted 6-aza-2′-deoxyuridines deviate from the "triplet-quartet peak-width" rule.

(Art. 7734; Art. 9385 for flash chromatography[23] unless otherwise stated). Solvents were dried and *N*-bromosuccinimide purified according to standard procedures.[24]

5-(Hydroxymethyl)-6-azauracil (8). 5-(Chloromethyl)-6-azauracil (**9**; 10.0 g, 62 mmol) was stirred in water (250 mL) at reflux for 7 h. The resultant solution was concentrated to ca. 40 mL and allowed to crystallize. The crystals were collected by filtration and dried to give 5-(hydroxymethyl)-6-azauracil (6.2 g, 70%); mp 175–178 °C (lit.[7] mp 176.5–178 °C); UV (EtOH) λ_{max} 263 nm (ϵ 5900); ^{1}H NMR (Me_2SO-d_6) δ 4.28 (2 H, s, CH_2OH).

5-Formyl-6-azauracil (10). Compound 8 (2.00 g, 14.0 mmol), finely powdered, and benzeneseleninic anhydride (4.90 g, 14.0 mmol) in THF (50 mL) were heated at reflux under nitrogen for 1 h. The reaction mixture was absorbed onto silica gel and applied to a column of flash silica gel. Elution with ethyl acetate afforded 5-formyl-6-azauracil (1.65 g, 84%) as a white foam; UV (EtOH) λ_{max} 266 nm (ϵ 5100); IR (Nujol) ν_{max} 1690 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 9.77 (1 H, s, CHO); MS found $[M + H]^+$, 142.025, $C_4H_4N_3O_3$ requires 142.023.

(*E*)-5-(2-Carboxyvinyl)-6-azauracil (11). Compound **10** (3.80 g, 27.0 mmol), malonic acid (2.80 g, 27.0 mmol), and piperidine (0.68 mL) in pyridine (14 mL) were heated at 100 °C for 2 h. The reaction mixture was cooled and filtered. The collected solid was dissolved in the minimum amount of 2 N sodium hydroxide, and the resultant solution was extracted with ether (3 × 50 ml). The aqueous phase was acidified with 2 N hydrochloric acid, and the resultant precipitate was filtered off, washed with water, and dried in vacuo at 65 °C to give (*E*)-5-(2-carboxyvinyl)-6-azauracil (2.31 g, 47%); mp 264–270 °C; UV (EtOH) λ_{max} 225 nm (ϵ 11 600), 299 (13 700); IR (Nujol) ν_{max} 1730, 1700, 1650 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 6.90 (1 H, d, J = 17 Hz), 7.30 (1 H, d, J = 17 Hz). Anal. ($C_6H_5N_3O_4$) C, H, N.

(*E*)-5-(2-Bromovinyl)-6-azauracil (12). (*E*)-5-(2-Carboxyvinyl)-6-azauracil (**11**; 2.14 g, 11.7 mmol) and potassium acetate (2.29 g, 23.4 mmol) in water (175 mL) were heated at 60 °C until a clear solution was obtained. *N*-Bromosuccinimide (2.08 g, 11.07 mmol) was added in small portions over 10 min, and the mixture was stirred at 60 °C for a further 1 h. The reaction mixture was cooled, and the precipitate was collected by filtration to give (*E*)-5-(2-bromovinyl)-6-azauracil (1.60 g, 63%) as an off-white solid; mp 246–248 °C dec; UV (EtOH) λ_{max} 230 nm (ϵ 12 200), 296 (11 700); IR (Nujol) ν_{max} 1710, 1670 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 6.98 (1 H, d, J = 14 Hz, CH=C*H*Br), 7.7 (1 H, d, J = 14 Hz, C*H*=CHBr). Anal. ($C_5H_5BrN_3O_2$) C, H, N.

(*E*)-5-(2-Bromovinyl)-1-(2'-deoxy-3',5'-di-*O*-*p*-toluoyl-α- and -β-D-*erythro*-pentofuranosyl)-6-azauracils (13). Compound **12** (2.44 g, 11.2 mmol), hexamethyldisilazane (HMDS; 12 mL), and chlorotrimethylsilane (0.1 mL) in acetonitrile (36 mL) were heated at reflux for 1 h when complete solution was obtained. The reaction mixture was evaporated to dryness, and the residue was coevaporated twice with dry xylene (20 mL). The resultant residue at 0 °C, under nitrogen, was treated with a solution of 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride (4.35 g, 11.2 mmol) in 1,2-dichloroethane (60 mL). This was followed by the addition of stannic chloride (3.20 g, 12.3 mmol) in 1,2-dichloroethane (5 mL). The reaction mixture was stirred at room temperature for 2.5 h and then poured into a mixture of dichloromethane (250 mL)–saturated aqueous sodium bicarbonate (250 mL). This mixture was shaken vigorously and then filtered through hyflo-sand (1:1). The aqueous phase was separated and further extracted with dichloromethane (2 × 250 mL). The combined organic extracts were dried (Na_2SO_4), the solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel. Elution with ethyl acetate–cyclohexane (1:2) afforded an anomeric mixture of the title compounds (2.20 g, 34%) as a colorless foam. This mixture was used directly in the next stage without separation.

(*E*)-5-(2-Bromovinyl)-6-aza-2'-deoxyuridine (6-Aza-BVDU) (2) and Its α-Anomer 14 (Method A). The toluoyl esters **13** (2.15 g, 3.77 mmol) were treated with 0.1 M sodium methoxide in methanol (113 mL, 11.3 mmol) at room temperature for 2 h. Ion-exchange resin (Bio-Rad, AG 50W-X8 [H^+]) was added to adjust the solution to pH 4. The resin was filtered off, the filtrate was evaporated, and the resultant residue was purified by column chromatography on silica gel (Art. 7729). Elution with dichloromethane–methanol (4:1) afforded first the α-anomer **14** (0.37 g, 29%); mp 194–196 °C; UV (EtOH) λ_{max} 228 nm (ϵ 13 500), 300 (12 300); UV (EtOH + NaOH) λ_{max} 292 nm; ^{1}H NMR (Me_2SO-d_6) δ 2.20–2.46 (1 H, m, H-2'), 2.47–2.70 (1 H, m, H-2'), 3.28–3.70 (2 H, m, H-5'), 3.93 (1 H, m, H-4'), 4.08 (1 H, m, H-3'), 6.27 (1 H, t, H-1'), 7.06 (1 H, d, J = 14 Hz, CH=C*H*Br), 7.72 (1 H, d, J = 14 Hz, C*H*=CHBr). Anal. ($C_{10}H_{12}BrN_3O_5$) C, H, N. This was followed by (*E*)-5-(2-bromovinyl)-6-aza-2'-deoxyuridine (0.42 g, 33%) as a colorless foam; UV (EtOH) λ_{max} 230 nm (ϵ 12 400), 300 (11 600); UV (EtOH + NaOH) λ_{max} 291 nm; ^{1}H NMR (Me_2SO-d_6) δ 2.00–2.20 (1 H, m, H-2'), 2.39–2.55 (1 H, m, H-2'), 3.20–3.60 (2 H, m, H-5'), 3.72 (1 H, m, H-4'), 4.35 (1 H, m, H-3'), 6.38 (1 H, dd, H-1'), 7.00 (1 H, d, J = 14 Hz, CH=C*H*Br), 7.69 (1 H, d, J = 14 Hz, C*H*=CHBr). Anal. ($C_{10}H_{12}BrN_3O_5$) C, H, N.

(*E*)-5-(2-Bromovinyl)-6-aza-2'-deoxyuridine (2) (Method B). The acid **19** (1.50 g, 5.0 mmol) and potassium acetate (0.98 g, 10.0 mmol) in water (75 mL) were heated at 60 °C until a clear solution was obtained. *N*-Bromosuccinimide (0.89 g, 5.0 mmol) was added portionwise over 15 min, and the mixture was stirred at 60 °C for a further 1 h. The reaction mixture was evaporated to dryness and the residue purified by column chromatography on silica gel. Elution with dichloromethane–methanol (8:1) gave (*E*)-5-(2-bromovinyl)-6-aza-2'-deoxyuridine (0.79 g, 47%) as a colorless foam, identical with material prepared by method A.

5-Formyl-1-(2'-deoxy-3',5'-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-6-azauracil (16). The hydroxymethyl derivative **15**[7] (500 mg, 1.06 mmol) and diphenyl diselenide (50 mg, 0.16 mmol) were dissolved in benzene (1 mL). To this mixture was added *tert*-butyl hydroperoxide solution (0.17 mL, 70% aqueous solution, 1.27 mmol), and the resulting mixture was heated under reflux for 4.5 h. The reaction mixture was diluted with dichloromethane (20 mL) [negative in Merckoquant peroxide test] and washed with water (20 mL). The organic phase was dried ($MgSO_4$) and then evaporated under reduced pressure to give a pale yellow solid. This material was purified by flash chromatography on silica gel, eluting with chloroform-2-propanol (30:1), to afford 5-formyl-1-(2'-deoxy-3',5'-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-6-azauracil (329 mg, 65%) as a colorless solid; mp 185–187 °C; ^{1}H NMR ($CDCl_3$) δ 6.71 (1 H, t, 1'-H), 9.60 (1 H, s, CHO). Anal. ($C_{25}H_{23}N_3O_8$) C, H, N.

5-Formyl-6-aza-2'-deoxyuridine (17). Compound **16** (0.20 g, 0.41 mmol) was dissolved in a mixture of dry methanol (4 mL) and benzene (4 mL), and 0.5 M sodium methoxide in methanol (3 mL) was added. The solution was allowed to stand at room temperature for 18 h and then evaporated to dryness (at ≤25 °C). The residue was dissolved in water (20 mL) and extracted with ether (3 × 25 mL). The aqueous was adjusted to pH 6 by addition of Dowex 50W-X8 [H^+] and filtered, and the water was removed in vacuo at 20 °C to afford 5-formyl-6-aza-2'-deoxyuridine (98 mg, 94%) as an amorphous white foam; IR (KBr) ν_{max} 1695 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.08–2.22 (1 H, m, H-2'), 2.36–2.52 (1 H, m, H-2'), 3.40 (1 H, dd, H-5'), 3.52 (1 H, dd, H-5'), 3.76 (1 H, m, H-4'), 4.38 (1 H, m, H-3'), 6.48 (1 H, dd, H-1'), 9.25 (1 H, s, CHO); MS found, $[M + NH_4]^+$, 275.099, $C_9H_{15}N_4O_6$ requires 275.099.

(*E*)-5-(2-Carbomethoxyvinyl)-1-(2'-deoxy-3',5'-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-6-azauracil (18). Compound **16** (1.60 g, 3.24 mmol) and (carbomethoxymethylene)triphenylphosphorane (1.14 g, 3.41 mmol) in dry acetonitrile (50 mL) were heated at reflux for 5 h. The reaction mixture was evaporated to dryness and the residue purified by flash chromatography on silica gel. Elution with cyclohexane–ethyl acetate (7:3) provided the title compound (1.52 g, 85%); mp 193–196 °C; ^{1}H NMR ($CDCl_3$) δ 6.70 (1 H, t, J = 6.5 Hz, H-1'), 7.23 (1 H, d, J = 16 Hz), 7.43 (1 H, d, J = 16 Hz). Anal. ($C_{28}H_{27}N_3O_9$) C, H, N.

(*E*)-5-(2-Carboxyvinyl)-6-aza-2'-deoxyuridine (19). Compound **18** (1.50 g, 2.73 mmol) and potassium hydroxide (0.51 g, 9.0 mmol) in 30% aqueous methanol (35 mL) were heated at reflux for 1 h. The solution was cooled, the majority of the methanol removed under reduced pressure, and the residue diluted further with water (15 mL). Dowex 50W-X8[H^+] was added to adjust the solution to pH 2, and the mixture was filtered. The filtrate was washed with ether (2 × 25 ml) and evaporated to dryness. The resultant oily residue was triturated with diethyl ether to give (*E*)-5-(2-carboxyvinyl)-6-aza-2'-deoxyuridine (0.67 g, 82%); mp 200 °C dec, as a cream crystalline powder; UV (EtOH) λ_{max}

227 nm (ε 12 400), 304 (11 000); IR (Nujol) ν_{max} 1710–1675 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.40 (1 H, dd, H-1′), 6.94 (1 H, d, J = 16 Hz, vinylic H), 7.30 (1 H, d, J = 16 Hz, vinylic H). Anal. ($C_{11}H_{13}N_3O_7 \cdot H_2O$) C, H, N.

(*E*)-5-(2-Carbomethoxyvinyl)-6-aza-2′-deoxyuridine (20). Compound 18 (110 mg, 0.2 mmol) was treated with 0.25 M sodium methoxide in methanol (4 mL, 1.0 mmol) at room temperature for 3 h. The solution was then adjusted to pH 6 by addition of Dowex 50W-X8 [H^+]. The resin was filtered off, the filtrate was evaporated, and the resultant residue was purified by column chromatography on silica gel. Elution with dichloromethane–methanol (10:1) gave (*E*)-5-(2-carbomethoxyvinyl)-6-aza-2′-deoxyuridine (47 mg, 75%); mp 97–99 °C; UV (EtOH) λ_{max} 221 nm (ε 14 500), 303 (13 300); IR (Nujol) ν_{max} 1735–1680 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.16 (1 H, m, H-2′), 2.48 (1 H, m, H-2′), 3.3–3.6 (2 H, m, H-5′), 3.77 (1 H, m, H-4′), 3.80 (3 H, s, OCH_3), 4.40 (1 H, m, H-3′), 6.43 (1 H, dd, J = 7, 4.5 Hz, H-1′), 7.00 (1 H, d, J = 16 Hz, vinylic H), 7.38 (1 H, d, J = 16 Hz, vinylic H). Anal. ($C_{12}H_{15}N_3O_7 \cdot 0.5H_2O$) C, H, N.

(*E*)- and (*Z*)-5-(2-Carbethoxy-2-fluorovinyl)-1-(2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-6-azauracil (21). A solution of diethyl (carbethoxyfluoromethyl)phosphonate (1.93 g, 7.97 mmol) in dry THF was added dropwise to a stirred suspension of sodium hydride (384 mg of a 50% dispersion in oil, 8.0 mmol) in dry THF (10 mL) cooled to 0 °C, under nitrogen. The mixture was stirred at 0 °C for 1.5 h and then a solution of **16** (1.97 g, 4.00 mmol) in THF (20 mL) was added dropwise over a 10-min period. The reaction mixture was allowed to warm to room temperature and after 18 h the THF was evaporated and the residue partitioned between brine and ethyl acetate (100 mL). The aqueous phase was further extracted with ethyl acetate (50 mL), the combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated to afford crude product. This material was purified by flash chromatography on silica gel, eluting with ethyl acetate–hexane (2:3), to give the title compounds (1.80 g, 78%) as a colorless foam; ^1H NMR (Me_2SO-d_6) δ 6.16 (1 H, d, J = 15 Hz, cis C*H*=CFCO$_2$Et), 7.14 (1 H, d, J = 20 Hz, trans C*H*=CFCO$_2$Et). Anal. ($C_{29}H_{28}FN_3O_9$) C, H, N.

(*E*)- and (*Z*)-5-(2-Carboxy-2-fluorovinyl)-6-aza-2′-deoxyuridines (22). A mixture of **21** (291 mg, 0.50 mmol) and potassium hydroxide (93 mg, 1.65 mmol) in methanol (5 mL) and water (5 mL) was heated at reflux for 1 h. The reaction mixture was diluted with water (10 ml) and allowed to cool. The methanol was removed in vacuo at 35 °C and the aqueous solution adjusted to pH 2 by addition of Dowex 50W-X8 [H^+]. The precipitated *p*-toluic acid was removed by extraction with ether (2 × 20 ml). The aqueous phase was filtered and evaporated to dryness and triturated with ether to afford (*E*)- and (*Z*)-5-(2-carboxy-2-fluorovinyl)-6-aza-2′-deoxyuridines (137 mg, 86%) as an amorphous white solid, which was used directly in the next stage; ^1H NMR (Me_2SO-d_6) δ 6.48 (1 H, d, J_{HF}(cis) = 18 Hz, C*H*=CFCO$_2$H), 6.94 (1 H, d, J_{HF}(trans) = 35 Hz, C*H*=CFCO$_2$H).

(*E*)- and (*Z*)-5-(2-Bromo-2-fluorovinyl)-6-aza-2′-deoxyuridine (3). A solution of the acids **22** (505 mg, 1.50 mmol) and potassium acetate (295 mg, 3.0 mmol) in water (25 mL) was heated to 95 °C and *N*-bromosuccinimide (795 mg, 4.5 mmol) was added portionwise over 10 min. The reaction mixture was heated at 100 °C for a further 30 min before working up as described for the preparation of **2** (method B). This afforded 5-(2-bromo-2-fluorovinyl)-6-aza-2′-deoxyuridine (104 mg, 20%) as a (3:1) mixture of *E* and *Z* isomers; mp 78–82 °C; ^1H NMR (Me_2SO-d_6) δ 6.40 (1 H, overlapping multiplets, H-1′), 6.36 (1 H, d, J_{HF} = 32 Hz, (trans)CH=CFBr), 6.92 (1 H, d, J_{HF} = 14 Hz, (cis)CH=CFBr); MS, found [M − H]$^-$ 349.9792, $C_{10}H_{10}F^{79}BrN_3O_5$ requires 349.9788.

(*E*)-5-(2-Chlorovinyl)-1-(2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-6-azauracil (23). (Chloromethyl)triphenylphosphonium chloride (1.55 g, 4.46 mmol) was suspended in dry THF (80 mL) at −70 °C. *n*-Butyllithium (1.5 M, 3 mL, 4.5 mmol) was added, with stirring, and after 20 min a solution of **16** in dry THF (20 mL) was introduced. The reaction mixture was maintained at −70 °C for a further 10min and then allowed to warm to room temperature. The reaction mixture was filtered, and the filtrate was evaporated to give a foam, which was purified by column chromatography on silica gel. Elution with cyclohexane–ethyl acetate (3:1) afforded the *E isomer* **23** (238 mg, 20%); mp 208–211 °C; ^1H NMR ($CDCl_3$) δ 6.49 (1 H, d, J = 14 Hz, CH=C*H*Cl), 7.68 (1 H, d, J = 14 Hz, C*H*=CHCl). Anal. ($C_{26}H_{24}ClN_3O_7$) C, H, N. Further elution gave a mixture of *E* and *Z* isomers (710 mg, 61%).

(*E*)-5-(2-Chlorovinyl)-6-aza-2′-deoxyuridine (4). The diesters **23** (192 mg, 0.37 mmol) were treated with potassium carbonate (101 mg, 0.73 mmol) in methanol (100 mL) at room temperature for 16 h. The reaction was worked up as described for **20** to provide (*E*)-5-(2-chlorovinyl)-6-aza-2′-deoxyuridine (54 mg, 51%) as a cream foam; UV (EtOH) λ_{max} 224 nm (ε 13 000), 296 (10 200); ^1H NMR (Me_2SO-d_6) δ 2.16 (1 H, m, H-2′), 2.50 (1 H, m, H-2′), 3.34–3.64 (2 H, m, H-5′), 3.79 (1 H, m, H-4′), 4.40 (1 H, m, H-3′), 6.44 (1 H, dd, H-1′), 6.80 (1 H, d, J = 14 Hz, C*H*=CHCl), 7.60 (1 H, d, J = 14 Hz, CH=C*H*Cl); MS, found M^+· 289.0459, $C_{10}H_{12}ClN_3O_5$ requires m/z 289.0466.

(*E*)-5-[2-(Methylthio)vinyl]-1-(2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-6-azauracil (24). [(Methylthio)methyl]triphenylphosphonium chloride (2.96 g, 8.24 mmol) was suspended in dry ether (16 mL) under nitrogen. Phenyllithium (2.09 M solution in benzene–ether, 3.94 mL, 8.24 mmol) was added, and the mixture was heated at reflux, with stirring, for 2 h to give a golden yellow precipitate containing [(methylthio)methylene]triphenylphosphorane. Compound **16** (2.03 g, 4.12 mmol) in dry THF (5 mL) was added at room temperature and stirring was continued for 2 h. The reaction mixture was diluted with ethyl acetate (15 mL) and acidified to pH 2 with Dowex 50W-X8 [H^+]. The resin was removed by filtration, and the filtrate was evaporated to dryness and the residue purified by flash chromatography on silica gel. Elution with ethyl acetate–hexane (1:2) afforded a mixture of *E* and *Z* isomers (1.74 g, 78%). Fractional crystallization from ethyl acetate–hexane gave pure *E* isomer as colorless needles; mp 178–183 °C; ^1H NMR (Me_2SO-d_6) δ 6.18 (1 H, d, CH=C*H*SMe), 7.78 (1 H, d, C*H*=CHSMe). Anal. ($C_{27}H_{27}N_3O_7S$) C, H, N.

(*E*)-5-[2-(Methylthio)vinyl]-6-aza-2′-deoxyuridine (5). Compound **24** was deprotected, as described for **13**, to give the title compound **5** (11%) as pale yellow needles; mp 193–194 °C; ^1H NMR (Me_2SO-d_6) δ 2.08 (1 H, m, H-2′), 2.40 (3 H, s, SMe), ca. 2.45 (1 H, m, H-2′), 3.71 (1 H, m, H-4′), 4.35 (1 H, m, H-3′), 6.20 (1 H, d, J = 15 Hz, CH=C*H*SMe), 6.38 (1 H, dd, H-1′), 7.69 (1 H, d, J = 15 Hz, C*H*=CHSMe). Anal. ($C_{11}H_{15}N_3O_5S$) C, H, N.

5-(2,2-Dibromovinyl)-1-(2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-6-azauracil (25). Carbon tetrabromide (8.09 g, 24.3 mmol) and freshly activated zinc (1.59 g, 24.3 mmol) were stirred in dry dichloromethane (100 mL) under nitrogen. Triphenylphosphine (6.39 g, 24.3 mmol) was added and stirring was continued for 5 h. This was followed by the addition of a solution of **16** in dichloromethane (150 mL). After 20 h the reaction mixture was filtered and the filtrate was evaporated to a gum, which was purified by flash chromatography on silica gel. Elution with cyclohexane–ethyl acetate (7:3) gave **25** (1.04 g, 55%) as a colorless foam; ^1H NMR ($CDCl_3$) δ 6.70 (1 H, dd, H-1′), 7.62 (1 H, s, CH=CBr_2); MS, found [M − H]$^-$ 645.9819, $C_{26}H_{22}N_3O_7{}^{79}Br_2$ requires m/z 645.9825.

5-(2,2-Dibromovinyl)-6-aza-2′-deoxyuridine (6). Compound **25** (0.42 g, 0.65 mmol) was dissolved in saturated methanolic ammonia (70 mL) and allowed to stand at room temperature for 2.5 days. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel. Elution with dichloromethane–ethanol (9:1) gave 5-(2,2-dibromovinyl)-6-aza-2′-deoxyuridine (0.12 g, 46%) as a white solid; mp 179–183 °C; ^1H NMR (Me_2SO-d_6) δ 2.06 (1 H, m, H-2′), ca. 2.60 (1 H, m, H-2′), 3.72 (1 H, m, H-4′), 4.35 (1 H, m, H-3′), 6.40 (1 H, t, H-1′), 7.60 (1 H, s, CH=CBr_2); MS, found [M + NH_4)$^+$ 432.9347, $C_{10}H_{11}{}^{81}Br_2N_3O_5 \cdot NH_4$ requires m/z 432.9376.

1-(2′-Deoxy-3′,5′-di-*O*-*p*-toluoyl-β-D-erythro-pentofuranosyl)-5-(2,2-difluoroethenyl)-6-azauracil (27) and 1-(2′-Deoxy-3′,5′-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-5-(2,2,2-trifluoroethyl)-6-azauracil (28). A mixture of **16** (1.23 g, 2.50 mmol), triphenylphosphine (1.44 g, 5.50 mmol), and sodium chlorodifluoroacetate (1.14 g, 7.50 mmol) in dry 1,2-dimethoxyethane (50 mL) was stirred, under nitrogen, and heated at reflux for 40 h. The cooled reaction mixture was evaporated under reduced pressure and the residue purified by flash chromatography on silica gel. Elution with hexane–ethyl acetate (2:1) afforded an inseparable mixture (0.32 g) of **27**, ^1H

NMR ($CDCl_3$) δ 5.65 (1 H, dd, J = 24, 2 Hz, CH=CF_2), and 28, ^{1}H NMR ($CDCl_3$) δ 3.20 (1 H, dq, J = 15, 10 Hz, $CHCF_3$), 3.52 (1 H, dq, J = 15, 10 Hz, $CHCF_3$).

5-(2,2-Difluoro-2-methoxyethyl)-6-aza-2'-deoxyuridine (29) and 5-(2,2,2-Trifluoroethyl)-6-aza-2'-deoxyuridine (30). The above mixture of **27** and **28** (0.25 g) and finely ground anhydrous potassium carbonate (130 mg) in methanol (150 mL) was stirred at room temperature for 48 h. The solution was adjusted to pH 5 by the addition of Dowex 50W-X8 [H^+] resin and filtered, and the filtrate was evaporated to dryness. The resultant residue was purified by column chromatography on silica gel, eluting with dichloromethane–methanol (8:1), to provide 5-(2,2-difluoro-2-methoxyethyl)-6-aza-2'-deoxyuridine (36 mg) as colorless needles [mp 155–157.5 °C; ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 2.25 (1 H, m, H-2'), 2.56 (1 H, m, H-2'), 3.32 (2 H, m, CH_2CF_2OMe), 3.55 (3 H, s, OMe), 3.68 (2 H, *A*BX, H-5'), 3.98 (1 H, m, H-4'), 4.51 (1 H, m, H-3'), 6.57 (1 H, dd, H-1'); MS, found $[M + NH_4]^+$ 341.1278, $C_{11}H_{15}F_2N_3O_6 \cdot NH_4$ requires m/z 341.1273] and then 5-(2,2,2-trifluoroethyl)-6-aza-2-deoxyuridine (33 mg) as a colorless foam [^{1}H NMR (Me_2SO-d_6) δ 2.10 (1 H, m, H-2'), 2.40 (1 H, m, H-2'), 3.3–3.6 (2 H, m, H-5'), 3.62 (2 H, q, J_{HF} = 11 Hz, CH_2CF_3), 3.72 (1 H, m, H-4'), 4.28 (1 H, m, H-3'), 6.38 (1 H, dd, H-1'); MS, found $[M + NH_4]^+$ 329.1065, $C_{10}H_{12}F_3N_3O_5 \cdot NH_4$ requires m/z 329.1073].

3-Furylglyoxylic Acid Semicarbazone (32). To a solution of 3-furylglyoxylic acid[19] (**31**; 6.10 g, 43.6 mmol) in ethanol (6 mL) was added a solution of semicarbazide hydrochloride (5.31 g, 47.6 mmol) in water (50 mL). The reaction mixture deposited a gum, which crystallized on trituration. After a further 1 h at −5 °C, the crystalline material was separated, washed with water, cold ethanol, and ether. The crude semicarbazone derivative thus obtained was dissolved in a mixture of 0.880 ammonia solution (11 mL) and water (165 mL), heated to 90 °C on a steam bath, and treated with charcoal (3 g). After cooling, the charcoal was filtered off and the aqueous filtrate acidified to pH 1.3 with concentrated hydrochloric acid. The mixture was cooled to 5 °C and the deposited crystals collected by filtration to give 3-furylglyoxylic acid semicarbazone (3.19 g, 37%); mp 204 °C dec (from H_2O–2-propanol); UV (EtOH) λ_{max} 268 nm (ε 9600); ^{1}H NMR (Me_2SO-d_6) δ 6.82 (2 H, br, NH_2), 7.11 (1 H, m, furan H-4), 7.58 (1 H, m, furan H-5), 8.00 (1 H, d, furan H-2), 11.36 (1 H, br, CO_2H). Anal. ($C_7H_7N_3O_4$) C, H, N.

5-(3-Furyl)-6-azauracil (33). 3-Furylglyoxylic acid semicarbazone (**32**; 0.35 g, 1.78 mmol) was dissolved in propane-1,2-diol (12 mL). Sodium ethoxide (1.7 M) in ethanol (5 mL) was added, and the reaction mixture was heated at reflux for 24 h. The solvents were removed under reduced pressure, and the residue was dissolved in water (10 mL). The resultant solution was adjusted to pH 5 by addition of concentrated hydrochloric acid. The precipitate was collected by filtration and purified by column chromatography on silica gel. Elution with ethyl acetate–methanol (9:1) gave 5-(3-furyl)-6-azauracil (0.18 g, 57%) as fawn crystals; mp 281–283 °C; UV (EtOH) λ_{max} 304 nm, (ε 7700); ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 6.73 (1 H, d, furan H-4), 7.45 (1 H, t, furan H-5), 8.30 (1 H, s, furan H-2); ^{13}C NMR (Me_2SO-d_6) δ 107.7 (d, furan C-4), 118.9 (s, furan C-3), 136.7 (s, azauracil C-5), 143.7 (d, furan C-2, furan C-5), 148.9 (s, azauracil C-2), 156.3 (s, azauracil C-4). Anal. ($C_7H_5N_3O_3 \cdot 0.1H_2O$) C, H, N.

5-(3-Furyl)-1-(2'-deoxy-3',5'-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl)-6-azauracil (34). A mixture of **33** (0.82 g, 4.58 mmol), hexamethyldisilazane (10 mL), and trimethylsilyl chloride (0.5 mL) in dry acetonitrile (30 mL) was heated at reflux for 1.5 h. The reaction mixture was then evaporated to dryness and the residue dissolved in 1,2-dichloroethane (50 mL). The resultant solution was treated with 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride[12] (1.81 g, 4.66 mmol) and stirred at room temperature under nitrogen for 2.5 h. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel. Elution with cyclohexane–ethyl acetate (4:1 → 1:1) gave 5-(3-furyl)-1-(2'-deoxy-3',5'-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl)-6-azauracil (0.81 g, 33%) as a colorless gum; ^{1}H NMR ($CDCl_3$) δ 2.70 (1 H, dt, H-2'), 3.10 (1 H, m, H-2'), 6.70 (1 H, dd, H-1'), 6.75 (1 H, d, furan H-4), 8.42 (1 H, br s, furan H-2). Anal. ($C_{28}H_{25}N_3O_8 \cdot H_2O$) C, H, N.

5-(3-Furyl)-6-aza-α-2'-deoxyuridine (35). Compound **34** was deprotected, as described for **13**, to give the title compound **35** (41%) as colorless needles; mp 197–198 °C; UV (EtOH) λ_{max} 309 nm (ε 7600); IR (Nujol) ν_{max} 1710, 1680 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.38 (1 H, m, H-2'), 2.62 (1 H, m, H-2'), 3.4–3.7 (2 H, m, H-5'), 4.02 (1 H, m, H-4'), 4.15 (1 H, m, H-3'), 6.46 (1 H, t, H-1'), 7.02 (1 H, d, furan H-4), 7.82 (1 H, t, furan H-5), 8.47 (1 H, d, furan H-2). Anal. ($C_{12}H_{13}N_3O_6$) C, H, N.

5-(3-Furyl)-1-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl)-6-azauracil (36). A mixture of **33** (1.15 g, 6.41 mmol), hexamethyldisilazane (25 ml), and trimethylsilyl chloride (0.5 mL) in dry acetonitrile (100 mL) was heated at reflux under nitrogen for 2 h. The reaction mixture was evaporated to dryness and treated with a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (3.25 g, 6.45 mmol) in dry 1,2-dichloroethane (100 mL). Stannic chloride (0.75 mL, 1.70 g, 6.51 mmol) was introduced and the resulting solution stirred at room temperature under nitrogen for 2 h. The reaction mixture was diluted with dichloromethane (150 mL) and poured into saturated aqueous $NaHCO_3$ solution (100 mL). The resulting emulsion was filtered through hyflo-sand to remove tin residues, and the organic layer of the filtrate was separated, dried (Na_2SO_4), and evaporated to give an off-white solid. Recrystallization from ethyl acetate–light petroleum (40–60 °C) afforded the title compound **36** (3.53 g, 88%); mp 209–210 °C; ^{1}H NMR ($CDCl_3$) δ 4.57 (1 H, dd, H-5'), 4.80 (1 H, dd, H-5'), 4.82 (1 H, m, H-4'), 6.15 (2 H, m, H-2', H-3'), 6.60 (1 H, s, H-1'), 7.03 (1 H, d, furan H-4), 7.15–7.65 (10 H, multiplets, Ar H, furan H-5), 7.95 (6 H, m, Ar H), 8.48 (1 H, s, furan H-2). Anal. ($C_{33}H_{25}N_3O_{10} \cdot 0.2H_2O$) C, H, N.

5-(3-Furyl)-6-azauridine (37). Compound **36** (3.65 g, 5.90 mmol) was dissolved in 0.7 M sodium methoxide in methanol (110 mL) and the solution allowed to stand at room temperature for 18 h. After neutralization by addition of Dowex 50W-X8 [H^+], the solution was filtered and the filtrate evaporated in vacuo. The residue was triturated with diethyl ether to remove methyl benzoate and then recrystallized from water to afford 5-(3-furyl)-6-azauridine (1.69 g, 93%) as colorless needles; mp 224–226 °C; UV (EtOH) λ_{max} 308 nm (ε 8300); IR (Nujol) ν_{max} 1700 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.48 (1 H, dd, H-5'), 3.66 (1 H, dd, H-5'), 3.88 (1 H, m, H-4'), 4.25 (1 H, t, H-3'), 4.35 (1 H, dd, H-2'), 6.04 (1 H, d, J = 2 Hz, H-1'), 6.88 (1 H, d, furan H-4), 7.84 (1 H, t, furan H-5), 8.46 (1 H, d, furan H-2). Anal. ($C_{12}H_{13}N_3O_7 \cdot H_2O$) C, H, N.

5-(3-Furyl)-1-[(3',5'-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]-6-azauracil (38). A mixture of **37** (1.31 g, 4.22 mmol) and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (1.63 g, 5.17 mmol) in dry pyridine (40 mL) was allowed to stand at room temperature for 18 h. The solvent was removed and the residue partitioned between water (50 mL) and ethyl acetate (50 mL). The ethyl acetate layer was dried (Na_2SO_4) and evaporated under reduced pressure to give a foam. This material was purified by column chromatography on silica gel, eluting with cyclohexane–ethyl acetate (2:1), to afford the title compound (1.27 g, 54%) as a colorless foam; UV (EtOH) λ_{max} 308 nm (ε 7600); IR ($CHBr_3$) ν_{max} 1730, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.25 (1 H, s, H-1'), 4.55 (1 H, d, J = 6 Hz, H-2'). Anal. ($C_{24}H_{39}N_3O_8Si_2$) C, H, N.

5-(3-Furyl)-1-[2'-*O*-[(imidazol-1-yl)thiocarbonyl]-3',5'-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]-6-azauracil (39). To a solution of **38** (1.09 g, 1.96 mmol) in dry DMF (15 mL) was added 1,1'-thiocarbonyldiimidazole (542 mg, 3.05 mmol). The yellow solution was allowed to stand overnight at room temperature and then treated with a further portion of 1,1'-thiocarbonyldiimidazole (512 mg, 2.88 mmol). After a further 3 h at room temperature, the solvent was evaporated and the residue purified by flash chromatography on silica gel. Elution with cyclohexane–ethyl acetate (2:1) gave the title compound (1.26 g, 97%) as a pale yellow foam; ^{1}H NMR ($CDCl_3$) δ 6.29 (1 H, d, J = 6 Hz, H-2'), 6.45 (1 H, s, H-1'); mass spectrum (FAB), m/z 664 $(M + H)^+$.

5-(3-Furyl)-1-(2'-deoxy-3',5'-tetraisopropyldisiloxane-1,3-diyl-β-D-*erythro*-pentofuranosyl)-6-azauracil (40). Compound **39** (1.15 g, 1.73 mmol) was dissolved in dry toluene (11 mL) and heated to reflux under nitrogen. A solution of tri-*n*-butylstannane (2.02 g, 6.94 mmol) and AIBN (0.19 g, 1.16 mmol) in toluene (14 mL) was added to the refluxing mixture over a period of 1 h. After a further period of 1 h at reflux, the cooled solution was evaporated to dryness and the residue purified by flash chromatography on silica gel. Elution with cyclohexane–ethyl acetate (2:1) afforded the title compound (0.62 g, 65%) as a

colorless foam. Anal. ($C_{24}H_{39}N_3O_7Si_2$) C, H, N.

5-(3-Furyl)-6-aza-2′-deoxyuridine (7). To a solution of **40** (0.54 g, 1.01 mmol) in THF (25 mL) was added a 1 N solution of tetra-*n*-butylammonium fluoride in THF (2.5 mL, 2.5 mmol) and the mixture stirred at room temperature for 3 h. The reaction mixture was concentrated to 5-mL volume and applied to a column of flash silica gel. Elution with dichloromethane–ethanol (5:1) gave 5-(3-furyl)-6-aza-2′-deoxyuridine (265 mg, 89%); mp 225–227 °C; UV (H_2O, pH 7) λ_{max} 308 nm (ϵ 7400), (H_2O, pH 13) 298 nm (ϵ 7100); ^1H NMR (Me_2SO-d_6) δ 2.15 (1 H, m, H-2′), 2.55 (1 H, m, H-2′), 3.5 (2 H, ABX, H-5′), 3.77 (1 H, m, H-4′), 4.45 (1 H, m, H-3′), 6.45 (1 H, dd, H-1′), 6.85 (1 H, d, furan H-4), 7.83 (1 H, t, furan H-5), 8.45 (1 H, d, furan H-2). Anal. ($C_{12}H_{13}N_3O_6$) C, H, N.

Antiviral Activity. Antiherpes activity was measured in a plaque reduction assay.[25] Confluent monolayers of Vero cells, in 24-mm diameter dishes, were infected with 30–40 plaque-forming units of either HSV-1 (strain HFEM) or HSV-2 (strain 196). The infected monolayers were incubated at 37 °C for 1 h and then overlayed with maintenance medium containing 0.75% carboxymethylcellulose and various concentrations of the test compound. The monolayers were incubated for a further 2 days at 37 °C, after which the cells were fixed and stained, the plaques counted, and the concentration of compound resulting in 50% inhibition of plaque formation was calculated.

Cytotoxicity Test. Cytotoxicity was measured by determining the incorporation of [*methyl*-^{3}H]thymidine into DNA of Vero cells. Subconfluent monolayers of Vero cells in 16-mm diameter dishes were overlayed with maintenance medium containing 1 μCi/mL [*methyl*-^{3}H]thymidine and various concentrations of the test nucleoside. After 18 h of incubation at 37 °C, DNA synthesis was determined by measuring the amount of [*methyl*-^{3}H]thymidine incorporated into acid-precipitable material.

Nucleoside Phosphorylation Studies. Thymidine kinases were isolated and purified from HSV1-infected Vero cells as previously described.[26] The relative phosphorylation rates of the nucleosides (50 μM) by these kinases were determined by an adenosine 5′-triphosphate transfer assay.[27]

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Registry No. **2**, 97776-64-2; (*E*)-**3**, 100348-16-1; (*Z*)-**3**, 100348-17-2; **4**, 100348-18-3; **5**, 100348-19-4; **6**, 97776-76-6; **7**, 100244-31-3; **8**, 4449-45-0; **9**, 24753-63-7; **10**, 97776-60-8; **11**, 100244-18-6; **12**, 97776-61-9; α-**13**, 97776-62-0; β-**13**, 97776-63-1; **14**, 97776-65-3; **15**, 20258-32-6; **16**, 97776-66-4; **17**, 100244-19-7; **18**, 97776-67-5; **19**, 97776-68-6; **20**, 100244-20-0; (*E*)-**21**, 97776-69-7; (*Z*)-**21**, 97776-70-0; (*E*)-**22**, 97776-71-1; (*Z*)-**22**, 97776-72-2; (*E*)-**23**, 97776-77-7; (*Z*)-**23**, 97776-78-8; (*E*)-**24**, 100244-21-1; (*Z*)-**24**, 100244-22-2; **25**, 100244-23-3; **27**, 100244-24-4; **28**, 100244-25-5; **29**, 100244-26-6; **30**, 100244-27-7; **31**, 54280-70-5; **32**, 100244-28-8; **33**, 100244-29-9; **34**, 100297-29-8; **35**, 100244-30-2; **36**, 100297-30-1; **37**, 100297-31-2; **38**, 100297-32-3; **39**, 100297-33-4; **40**, 100297-34-5; 2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentafuranosyl chloride, 52304-86-6; 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, 6974-32-9; 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride, 4330-21-6.

Thromboxane Synthetase Inhibitors and Antihypertensive Agents. 2. *N*-[(1*H*-Imidazol-1-yl)alkyl]-1*H*-isoindole-1,3(2*H*)-diones and *N*-[(1*H*-1,2,4-Triazol-1-yl)alkyl]-1*H*-isoindole-1,3(2*H*)-diones as Unique Antihypertensive Agents

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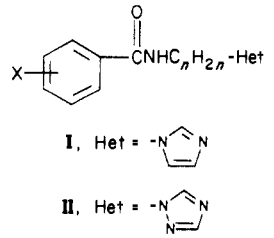
A series of *N*-[(1*H*-heteroaryl)alkyl]-1*H*-isoindole-1,3(2*H*)-diones were prepared as part of a continuing investigation into the biological properties of compounds that were both thromboxane synthetase inhibitors and potential antihypertensive agents. The most active thromboxane synthetase inhibition was found for the title imidazole derivatives wherein a hexyl or octyl chain separated the heterocyclic ends of the molecule (**5**, **6**) or with substitution on the isoindole portion of the molecule (**18**, **19**, **21**, **22**, **25**, **26**). Compounds with shorter alkyl chain separations had good antihypertensive effects (**1**–**5**, **8**–**10**, **19**–**22**, **27**–**30**). Butyl derivative **3** was chosen for further evaluation as a potential antihypertensive agent with thromboxane synthetase inhibitory properties.

In a previous paper[2] we described a series of *N*-[(1*H*-imidazol-1-yl)alkyl]arylamides (I) and *N*-[(1*H*-1,2,4-triazol-1-yl)alkyl]arylamides (II) that were potent thromboxane (TX) synthetase inhibitors and also had interesting antihypertensive activity. A number of other laboratories have had active research programs investigating selective TX synthetase inhibitors as potential therapeutic agents,[3-5] and a number of such compounds are presently under clinical evaluation.



In addition to the possible treatment of ischemia, arrhythmias, fibrillation, and sudden death, we were interested in developing a class of TX synthetase inhibitors with antihypertensive activity as agents that might be useful in the treatment of certain forms of hypertension. Selective inhibition of the production of thromboxane A_2 (TXA_2) not only removes a source of potent vasoconstriction but also might lead to the enhancement of prostacyclin (a potent vasodilator) production through a

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