chromatography (SiO_2, cyclohexane/benzene). The isomer ratio was determined by the comparison of methyl signals in the 200-MHz ^1H NMR spectrum of the mixture. Both isomers were separated by HPLC (Cosmosil C-18, methanol, 30 °C), in which generally the anti isomer **6** was eluted more slowly than the syn isomer **5**. These products throughout the work were recrystallized from methanol.

Cyclophanes derived from St-C3-VN were prepared in the same manner as above, but they were isolated by HPLC, using Develosil-PYE instead of Cosmosil C-18, because the latter gave rather poor separation.

The analytical data of naphthalenophanes are summarized in Table VII and their ^1H NMR spectroscopic data are available.[18]

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Registry No. **1a**, 94645-41-7; **1b**, 91922-63-3; **1c**, 94730-81-1; **1d**, 94645-45-1; **2a**, 94730-09-3; **2b**, 92008-74-7; **2c**, 94645-43-9; **2d**, 94730-12-8; **3a**, 94645-42-8; **3b**, 91922-64-4; **3c**, 94645-44-0; **3d**, 94645-46-2; **4a**, 94730-10-6; **4b**, 92008-75-8; **4c**, 94730-11-7; **4d**, 94730-13-9; **5a**, 94645-47-3; **5b**, 91922-62-2; **5c**, 94645-48-4; **5d**, 94645-49-5; **6a**, 94730-14-0; **6b**, 92008-73-6; **6c**, 94730-15-1; **6d**, 94730-16-2; **7**, 94645-50-8; **8**, 94730-17-3; St-C3-VN, 91922-65-5; VN-C3-VN, 79541-70-1; 1-(α-naphthyl)-3-phenylpropane, 29908-29-0; 1-[1-(4-acetylnaphthyl)]-3-(*p*-acetylphenyl)propane, 94645-39-3; 1-[1-(4-(1-hydroxyethyl)naphthyl]-3-[*p*-(1-hydroxyethyl)phenyl]propane, 94645-40-6; 2-phenylpropene, 98-83-9; indene, 95-13-6; 1,1-diphenylethylene, 530-48-3; styrene, 100-42-5.

Supplementary Material Available: Tables of parameters for ^1H NMR simulation and of ^1H NMR spectroscopic data of naphthalenophanes (5 pages). Ordering information is given on any current masthead page.

Synthesis of 5-(Dihydroxyboryl)-2′-deoxyuridine and Related Boron-Containing Pyrimidines[1a]

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Organoboron derivatives of pyrimidines and of 2′-deoxyribonucleosides have been synthesized as potential antiviral and anticancer agents. The first 5-boron-substituted pyrimidine nucleoside, 5-(dihydroxyboryl)-2′-deoxyuridine, has been prepared via a metal–halogen exchange at −50 °C in tetrahydrofuran on 5-bromo-3′,5′-bis(*O*-trimethylsilyl)-2′-deoxyuridine using *n*-butyllithium followed by boronation at −65 °C with tri-*n*-butyl borate in the presence of HMPT. After hydrolysis, the product was purified by column chromatography and repeated fractional crystallization and the purity determined by HPLC. This hydrolytically stable compound showed no activity against Sarcoma 180 (S-180) but inhibited herpes simplex virus type 1 at a nontoxic concentration. The compound sensitized hamster V-79 cells to neutrons and could be of potential use in boron neutron capture therapy. 5-(Dihydroxyboryl)uracil and 6-(dihydroxyboryl)uracil were prepared also by a similar route from the corresponding 5- or 6-bromo-2,4-bis(benzyloxy)pyrimidine. However, the mixture was maintained at −85 °C during the whole reaction sequence and the product was obtained by hydrolysis followed by catalytic hydrogenation. The physical characteristics of these analogues, as well as those of their iminodiethanol esters, are described.

There is an increased interest in the preparation of boron compounds for their potential medicinal and biochemical applications. Numerous organoboron compounds have been investigated in the past with respect to their possible use in cancer therapy based on the ability of the ^{10}B isotope to absorb thermal neutrons thereby producing a cell-destroying nuclear reaction.[2] In addition, the utility of boron as a tool for providing insight into structure and reaction mechanisms rests on its close relationship to carbon. The fact that boron has a vacant p orbital is the origin of the strong electron acceptor properties of tricoordinate boron compounds and the ease with which tetracoordinated boron structures are formed. This unusual property has led to the synthesis of a host of boron-containing compounds as effective transition-state analogues for enzymes-catalyzing acyl-transfer reactions.[3,4] Many other organoborons have been reported to be of potential pharmaceutical importance as diuretics, anticoagulants, or tranquilizers.[2,5] Recently, synthetic models containing boron have been prepared for betaine,[6] glycine[7,8] and phenylalanine,[9-12] and acetylcholine.[13] Models for copper-blue proteins,[14] oxygen transporting proteins such

(1) (a) A preliminary communication was published: *Tetrahedron Lett.* **1978**, 4981. This research was supported by U.S. Public Health Service Research Grant CA-05262 from the National Cancer Institute. R.F.S. is supported by a Merit Award from the Veterans Administration and by Grant AI-18600 from the National Institutes of Health. We acknowledge the support of the Southern New England High Field NMR Facility made possible by a grant from the Biotechnology Resources Program of the NIH (1-P07-PR 798). The boron NMR spectra were obtained through NSF regional NMR Center at the University of South Carolina (CHE 82-07445). (b) Emory University/VA. (c) Yale University.

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0022-3263/85/1950-0841$01.50/0

Table I. ^{13}C NMR Spectral Data[a]

	1	2	3	4	5	6	9
C-2	150.90	150.77[b]	152.24[b]	136.26[b]	135.97[b]	136.57[b]	135.97[b]
C-4	170.20[b]	166.24[b]	167.14[b]	159.53	167.63	163.57	171.17[b]
C-5	99.92[b]	101.91	102.08[b]	77.08[b]	81.14[b]	c	105.38
C-6	149.92[b]	143.60[b]	150.06	127.71	128.14	128.56	152.29[b]
C-1′			86.87				
C-2′			40.55				
C-3′			71.70				
C-4′			88.26				
C-5′			62.49				
$C_6H_5CH_2$				69.70	69.48	68.68	69.88
				69.13	69.04	68.35	68.93
C_6H_5				128.45[d]	128.65[d]	128.41[d]	128.35[d]
OCH_a						62.96	
NCH_b						51.49	

[a] Chemical shifts are in parts per million from Me_4Si at 308 °C. [b] Weak and/or broad. [c] Not observed. [d] Multiplet.

as hemerythrin, and enzymes involved in nucleoside biosynthesis such as ribonucleoside diphosphate reductase[15] have also been prepared. The discovery of two boron-containing naturally occurring antibiotics, boromycin[16] and aplasmomycin,[17] has raised intriguing questions about the biochemical importance of boron in nature, which still remains to be understood.

The potential of purine and pyrimidine nucleoside analogues has been well recognized for the chemotherapy of viruses and cancers. These compounds have been extensively reviewed.[18] Soloway,[19] and more recently Matteson et al.[20] and Maitra,[21] have discussed the difficulties involved in making boron analogues of purines and pyrimidines. Various boron heterocycles which resemble the bases of DNA have been tested for anticancer activity but have been found to be either hydrolytically and biologically unstable or too toxic. Others were inactive probably due to deboronation, high polarity, or more likely the fact that these bases are poorly utilized for the biosynthesis of DNA. Thus, Liao et al.[22] found 5-(dihydroxyboryl)uracil (1) to have no inhibiting effect on cancer cells (private communication); a finding we have confirmed in Sarcoma 180 cells at concentrations up to 200 μM. Although halogenated pyrimidine bases (ClUra, BrUra, IUra) are readily incorporated into DNA of various microorganisms, they are poorly utilized in mammalian systems in contrast to the corresponding 2′-deoxyribonucleosides.[23] The concept for incorporation of a boron atom into a nucleoside had been discussed previously;[24] hence, it became appropriate that the corresponding 2′-deoxynucleoside 3 (Scheme IV) be synthesized and evaluated. The 5-dihydroxyboryl function should be well tolerated in DNA since pyrimidine nucleosides with large 5-substituents have been shown to be incorporated into DNA.[18]

At physiological pH, 6-(dihydroxyboryl)uracil (2) (Scheme II) is approximately isosteric as well as isoelectronic with orotic acid, a natural metabolite in the de novo pathway for the synthesis of pyrimidine components of nucleic acids.[25] Orotidine 5′-phosphate pyrophosphorylase, orotidine 5′-phosphate decarboxylase and an enzyme complex of these two activities which exists in some cells[26] are all involved in the conversion of orotate into UMP. The boron analogue 2 could act as an inhibitor of either one or all of these enzymes. To test this hypothesis, the analogue 2 was synthesized because, if hydrolytically stable, it may mimic orotic acid more effectively than other 6-substituted uracils which had been previously prepared for that purpose.[27,28]

Results and Discussion

The general method for preparing boronic acids employing the reaction of the appropriate organometallic compounds with esters of boric acid was adopted for our synthesis. The formation of 5- or 6-lithio-2,4-substituted pyrimidines toward electrophiles was first described by Langley.[29] These organometallic compounds have been proven to be versatile intermediates for the preparation of bipyrimidines,[30-32] 2′-deoxypseudouridine[33,34] and related *C*-glycosyl nucleosides,[35-38] 5-alkyl;[39] 5-arylhydroxymethyl; and acylpyrimidines,[40] and carboxylic acid[41] and mercapto derivatives[42] of pyrimidines, as well as a convenient method for introducing a C-14 label[43-45] into biologically important

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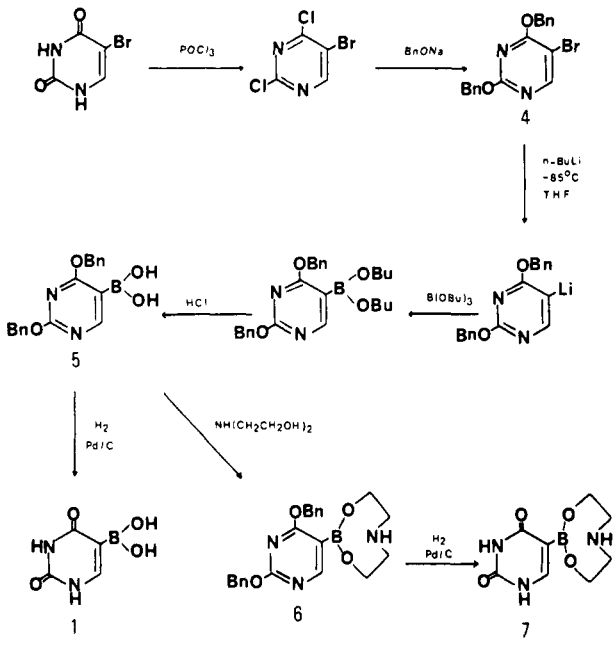
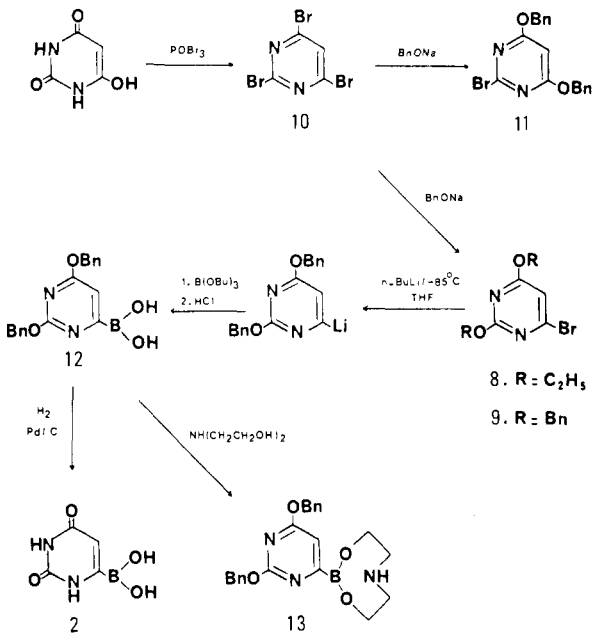
Scheme I



Scheme II



pyrimidines. More recently, 5-(trimethylsilyl)pyrimidines and 5-(fluoroalkenyl)pyrimidine nucleosides have been synthesized by this method.[46,47]

5-(Dihydroxyboryl)uracil (1) was originally prepared by Liao et al.[22] via a halogen–metal exchange reaction on 5-bromo-2,4-bis(benzyloxy)pyrimidine (4) followed by boronation. However, the product was not isolated and it was converted directly to compound 1 by hydrogenation. Initially, we followed their procedure and, although the halogen–metal interchange readily took place at −80 °C with *n*-butyllithium (*n*-BuLi) according to Langley's method,[29] we were unable to form the boron-containing pyrimidine even when a large excess of tri-*n*-butyl borate was added at temperatures ranging from −65 to −80 °C (Scheme I); 2,4-bis(benzyloxy)pyrimidine was the major reaction product. However, the desired product was obtained in excellent yield provided a temperature of −85 to −95 °C and an argon atmosphere was maintained during the whole reaction sequence. Precooling of the reagents to the bath temperature as well as the time between the formation of the lithio–pyrimidine complex and addition of tri-*n*-butyl borate were critical. Maximum yield was achieved when 4–5 min had elapsed between the additions. On hydrolysis and workup 5-(dihydroxyboryl)-2,4-bis(benzyloxy)pyrimidine (5) (Scheme I) was obtained as an oil which solidified to low melting point crystals when left at room temperature. The product was further characterized by the formation of the hydrolytically stable iminodiethanol derivative 6. The ^{1}H NMR of this compound exhibited a clear ABCD pattern for the methylene groups of the cyclic ester and suggest that the iminodiethanol structure was symmetrical about B and N (for ^{13}C NMR, see Table I). Catalytic hydrogenation of 6 furnished the deblocked compound 7 which was shown to slowly decompose in H_2O to 5-(dihydroxyboryl)uracil (1) and diethanolamine. The formation of the hydrolysis products could be observed in the ^{1}H NMR on addition of D_2O to compound 6 in Me_2SO. 5-(Dihydroxyboryl)uracil (1) was obtained by hydrogenation of 5 and was fully characterized.

Langley[29] had prepared 6-bromo-2,4-diethoxypyrimidine (8) (Scheme II) from 2,4,6-tribromopyrimidine (10) as a precursor for labeled orotic acid. Applying this method to the preparation of 6-(dihydroxyboryl)uracil (2) could result in deboronation since the conditions used for deblocking the diethoxy acid are too severe (6 N HCl, heat for 2 h). The *tert*-butoxy-protecting group had previously been used by other workers,[33] since it is stable to strong base and, due to its steric volume, it reduces self-condensation reactions. However, this protecting group is readily hydrolyzed in acid and the reaction product, being extremely water soluble, would be separated with difficulty from salts and byproducts. To surmount these difficulties and in view of the fact that the benzyl groups proved to be a good solubilizing and protecting group for the formation of 5-(dihydroxyboryl)uracil, 6-bromo-2,4-bis(benzyloxy)pyrimidine (9) was synthesized by the reaction of sodium benzyl oxide on 2,4,6-tribromopyrimidine (10) (Scheme II). At 10 °C the reaction gave a high-boiling-point oil which was shown by its ^{1}H NMR spectrum to be a mixture of 2-bromo-4,6-bis(benzyloxy)pyrimidine (11) and the desired product 9 in a ratio of 1:3. However, at lower temperature (0 to 5 °C) compound 9 was obtained as the only product. Lithiation followed by boronation and hydrolysis as described for compound 4 (Scheme I) furnished an oil which was shown by TLC to contain mostly 6-(dihydroxyboryl)-2,4-bis(benzyloxy)pyrimidine (12). The structure was further confirmed by forming the cyclic iminodiethanol ester 13. Catalytic hydrogenation of 12 afforded analytically pure 6-(dihydroxyboryl)uracil (2) as white crystalline prisms.

The stability of compounds 1 and 2 in acids, bases, and organic solvents was investigated. Compound 1 was stable in H_2O, acid, or base (pH 2 and 12, respectively), EtOH, and Me_2SO over a period of at least 6 weeks as determined by ^{1}H NMR and/or UV spectroscopy. The 6-boronic acid 2 was also stable in H_2O, acid, or EtOH over the same period. However, in base a hypsochromic shift was noted in the UV spectrum, λ_{max} decreasing (but not the absorbance) from 264 to 260 nm over a period of 8 days. This

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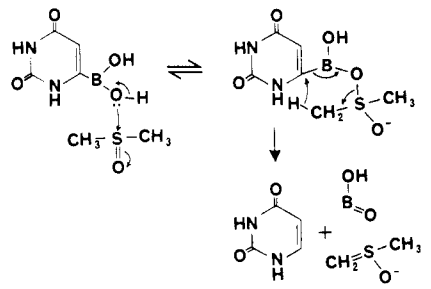
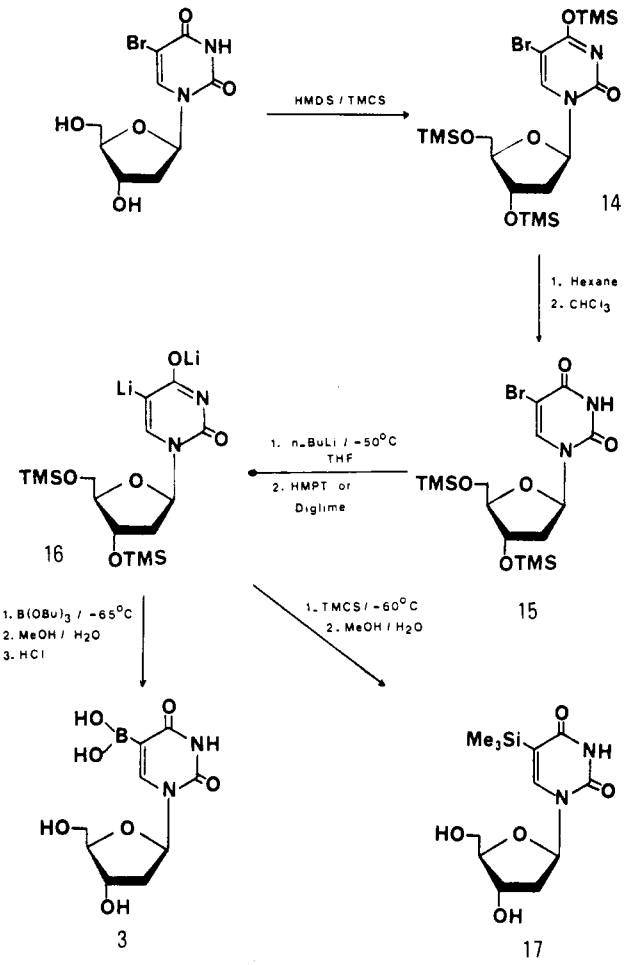
Scheme III



suggests that uracil (λ_{max} in base = 284 nm) is not formed but that possibly barbituric acid is formed (λ_{max} in base = 260 nm). This phenomenon had previously been observed in the case of 6-uracilsulfonic acid (and other 6-substituted pyrimidines), where displacement of the sulfonic acid group by a hydroxy function at pH 12, yielded barbituric acid.[48,49] More interestingly, in Me_2SO-d_6 which contained traces of water, compound **2** gave a ^1H NMR spectrum similar to uracil, indicating that deboronation had taken place. Although Me_2SO is a well-known oxidant,[50] the surprising formation of uracil instead of barbituric acid can be explained by the following hypothesis: initial attack of the O of the 6-dihydroxyboryl function onto the sulfur atom of Me_2SO (Scheme III); a hydride ion is then transferred from one of the methyl groups on Me_2SO to the partially electropositive C-6. Subsequently, uracil and boric acid are formed and Me_2SO is regenerated. This scheme probably takes place by a concerted process via a six-membered cyclic transition state. Presumably, displacement of the dihydroxyboryl function from the 5-isomer, compound **1**, does not take place because of the partial negative charge present at C-5 which stabilizes the dihydroxyboryl function.

5-(Dihydroxyboryl)-2′-deoxyuridine (DBDU). As mentioned above, the lithium–halogen interchange on 5-bromo-2′-deoxyuridine has been used for the preparation of $^{14}CH_3$-labeled thymidine,[43] and 5-carboxy-2′-deoxyuridine.[41] The low yields obtained were ascribed to the heterogeneity of the reaction mixture due to the insolubility of the tetralithium intermediate in tetrahydrofuran (THF). Pichat and co-worker[45] have studied the exchange reaction in detail on trimethylsilyl (Me_3Si) protected nucleosides. They concluded that for optimum yield, the lithiation should be conducted in THF at −40 °C and the alkylation at −60 °C in the presence of 8% hexamethylphosphoric triamide (HMPT). Initially, they were unable to obtain the 5-alkylated product by the use of tris-*O*-trimethylsilyl derivative **14** (Scheme IV), 2′-deoxyuridine being the main reaction product. However, the use of Me_3Si substituents only in the carbohydrate moiety, such as compound **15**, yielded the desired product. Furthermore, the authors reported that lithiation of 5-bromo-2′,3′,5′-tris-(*O*-trimethylsilyl)uridine followed by hydrolysis gave uridine as well as 5-(trimethylsilyl)uridine (19.5% yield). The surprising formation of the latter was explained as due to the addition of trimethylchlorosilane (TMCS) to the 5,6-double bond of uridine formed during the protection of the nucleoside, followed by elimination of HCl by the action of *n*-BuLi. However, more recently, Arai et al.[51,52] demonstrated that an intramolecular rearrangement of the Me_3Si group can occur from O-4 to the C-5 carbanionic center on treatment of 5-bromo-2,4-bis-(*O*-trimethylsilyl)uracil with *n*-BuLi. This phenomenon could account for the preponderance of uridine in the metal–halogen exchange of **14** and also suggests that 5-bromo-2′,3′,5′-tris(*O*-trimethylsilyl)uridine used above may have been contaminated with the 2′,3′,4,5′-tetrakis-*O*-trimethylsilyl derivative which could on lithiation rearrange to give 5-(trimethylsilyl)uridine.

Scheme IV



This indicates that although the Me_3Si group is a good acid-labile protecting group which is able to confer at low temperature high solubility to lithionucleosides in THF, care should be taken so as only to block the glycosyl hydroxyls of the 5-halopyrimidine nucleosides. We thought we could overcome this problem by using 3′,5′-di-*O*-benzyl, -trityl or -tetrahydropyranyl derivatives for the preparation of 5-(dihydroxyboryl)-2′-deoxyuridine. However, these protected compounds proved unsuccessful since the boronation did not take place under a variety of reaction conditions. Hence, we reverted to the Me_3Si protection group and prepared 5-bromo-3′,5′-bis(*O*-trimethylsilyl)-2′-deoxyuridine (**15**) according to the method of Pichat et al.[45] This compound was obtained as an oil on silyating 5-bromo-2′-deoxyuridine with an excess of a mixture of 1,1,1,3,3,3-hexamethyldisilizane (HMDS) and trimethylchlorosilane (TMCS), followed by selective hydrolysis of the 4-*O*-trimethylsilyl group by successively evaporating a solution of the product in benzene and hexane. However, we found that when the resulting oil was reevaporated in

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$CHCl_3$, compound **15** was obtained for the first time as a stable white solid, making this derivative easier to handle. Lithiation of this compound in dry THF with precooled *n*-BuLi at −45 to −50 °C for 8 min under rigorously anhydrous conditions, followed by rapid cooling to −75 °C and addition of 8% HMPT or diglyme and then excess tri-*n*-butyl borate, gave a clear solution which was kept for 3 h at −65 °C (Scheme IV). After workup (see the Experimental Section), pure 5-(dihydroxyboryl)-2′-deoxyuridine (**3**) was obtained in a 12% yield (based on **15**). The time between the addition of *n*-BuLi and tri-*n*-butyl borate as well as the temperature for the boronation was varied in an attempt to increase the yield without success. The formation of 6-(dihydroxyboryl)-2′-deoxyuridine was not observed even though Pichat and co-workers[45] had reported the formation of 6-methyl-2′-deoxyuridine together with thymidine during the reaction of the lithium complex of **15** with methyl iodide.

5-(Trimethylsilyl)uridine had been prepared by Pichat et al.[45] and more recently by Zagulyaeva and co-workers.[47] Having the protected bromonucleoside **15** in hand prompted us to prepare 5-(trimethylsilyl)-2′-deoxyuridine (**17**) under analogous conditions to those described for the preparation of the 5-dihydroxyboryl derivative **3**. The product, however, was separated from HMPT and salts by partitioning several times the aqueous phase with EtOAc. Evaporation of the organic phase and chromatographic separation gave the product as an amorphous white solid in a 26% yield. Since our initial report[1a] on the preparation of **17**, Coe et al.[46] have also obtained this compound as a byproduct of a similar halogen–lithium exchange reaction.

With use of a high-pressure liquid chromatographic separation method, compounds **3** and **17** were found to contain no detectable amount of 5-bromo-2′-deoxyuridine. The presence of minute traces of this compound could significantly affect the biological evaluation.

^{13}C NMR. The preparation of these new boron-substituted pyrimidines and nucleosides has allowed us to study their interesting physical properties by proton-decoupled ^{13}C NMR. Although ^{13}C NMR of carboranes have been extensively studied,[53] there are few reports on other organoboron compounds.[54-57] To date, much of the interest has focused on vinyl type of compounds in an attempt to elucidate the effect of various substituents, including boron, on the delocalization of the π-electron density of the vinyl group.[54,55] Of particular significance was the finding that the 5,6-double bond of pyrimidines can be considered as trisubstituted ethylenes and that the vinyl group of vinylboranes behave as mesomeric donors toward boron in tricoordinate boron compounds. Natural boron is composed of two isotopes which are NMR active, ^{10}B and ^{11}B in the ratio of about 20% and 80%, respectively. The number spin of ^{10}B is 3 and that of ^{11}B is $^3/_2$, leading to complex spectra.[58] Unless the boron quadrupole moment is removed, the spectra are further complicated, resulting in lines of substantial width. Boron ^{13}C coupling sometimes has not been observed due to this partial decoupling phenomenon by the boron quadrupolar relaxation effect. A number of boron compounds which we have synthesized also exhibited this unusual phenomenon (see Table I), thus, unambiguously confirming the presence of a dihydroxyboryl function at the assigned position. In general, the mesomeric interactions between the boron substituent and the π-electron system of the C5–C6 bond were felt more effectively at the carbon atom more remote from the substituent than the actual point of substitution. For example, the C-6 resonance for compound **3** appeared about 10 ppm downfield from that of 2′-deoxyuridine;[59] this suggests that π-conjugation occurs in this compound.

Biological Evaluation. Most of the compounds reported here were screened for activity against murine S-180 and HSV-1 (yield reduction assay) in vitro according to the methods described by Lin and Prusoff[60] and Schinazi et al.[61]

Compounds **1** and **2** were found to be inactive in both test systems at a concentration of 200 μM. The nucleoside **3** was also inactive against S-180 at 200 μM. However, it inhibited the replication of HSV-1 by 91% to 97% at 800 μM. The inhibition of viral replication was prevented by thymidine but not by other natural 2′-deoxy or ribonucleosides. Compound **3** was not cytotoxic to the host Vero cells even at a concentration of 1600 μM. DBDU was shown to sensitize hamster V-79 cells to neutrons. The biological activity of these compounds have recently been described in more detail.[59] Compound **3** was recently synthesized starting with 94.5% ^{10}B-enriched tri-*n*-butyl borate. Preliminary results[62] indicate that utilization of this compound amplified its neutron sensitizing ability and biological response by a factor greater than 2. Compound **2** was a poor inhibitor of orotate phosphoryboryl transferase with an apparent K_i value of 22.1 ± 7.1 mM.[64]

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Ultraviolet absorption spectra were obtained on a Beckman Model 25 spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 21 infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Brucker 270 HX spectrometer. Unless otherwise stated, all NMR data reported below are ^{1}H NMR. Chemical shifts are reported downfield from internal Me_4Si. Double resonance studies support the assignment of the positions. ^{11}B NMR chemical shifts are relative to external standard $BF_3{\cdot}Et_2O$. The solvent used for the ^{11}B and ^{13}C NMR spectra (see Table I) was the same as that reported below for ^{1}H NMR. Mass spectra were obtained on an AEI MS 9 high-resolution instrument at an ionization potential of 70 eV. TLC was performed on EM silica gel sheets with fluorescent indicator. All glassware were dried at 150 °C and cooled under dry argon immediately before use. HMPT and diglyme were distilled from calcium hydride and stored under nitrogen. Tetrahydrofuran was distilled from the sodium ketyl of benzophenone. The elemental analyses were carried out by Barons Consulting Co., Analytical Services, Orange, CN.

5-Bromo-2,4-bis(benzyloxy)pyrimidine (4). A stirred solution of benzyl alcohol (6.7 mL, 64.8 mmol) in anhydrous toluene (70 mL) was treated with 50% w/w NaH in oil (2.9 g, 60.4 mmol) under a static N_2 atmosphere. The mixture was warmed to 50 °C to facilitate the formation of the Na salt. After all the NaH had reacted, the suspension was cooled and 5-bromo-2,4-dichloropyrimidine[63] (4.56 g, 20 mmol) was added dropwise so that

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the temperature did not exceed 25 °C. After stirring overnight, the precipitate of NaCl was filtered and thoroughly washed with toluene. The filtrate was then evaporated under reduced pressure to give an oil which solidified on cooling. The solid was redissolved in EtOH and left to crystallize to afford fine white needles: 6.8 g, yield 91.6%; mp 89–91 °C (lit.[39] mp 86–88 °C); NMR ($CDCl_3$) δ 5.40 and 5.49 (2 s, 4, CH_2), 7.38 (m, 10, C_6H_5), 8.37 (s, 1, 6-H); TLC (benzene) R_f 0.37.

5-(Dihydroxyboryl)-2,4-bis(benzyloxy)pyrimidine (5). The following procedure is representative of the laboratory manipulation of moisture-sensitive reactions. A dry 100-mL flask, equipped with a septum inlet, low-temperature thermometer, and magnetic stirrer was flushed with argon and maintained under a positive pressure of gas. By means of a hypodermic syringe, a solution of 5-bromo-2,4-bis(benzyloxy)pyrimidine (**4**) (1.6 g, 4.3 mmol) in freshly distilled THF (35 mL) was introduced into the flask and the mixture was cooled to −95 °C (liquid N_2/EtOH). A *precooled* solution of *n*-BuLi (3.2 mL of a 1.6 M solution in hexane, 5.1 mmol) was added at such a rate that the internal temperature did not exceed −85 °C. The yellow solution was stirred for 4 min and an excess of dry tri-*n*-butyl borate (1.5 mL, 5.56 mmol) precooled in dry ice was added at −85 °C. The solution was kept at that temperature for a further 20 min and then allowed to warm up to room temperature over 2 h. The clear solution was evaporated to almost dryness under reduced pressure and then H_2O (30 mL) was added. The solution was acidified to pH 2.5 with 1 M HCl and then extracted with ethyl ether (4 × 30 mL), and the combined ether extracts were dried over $MgSO_4$. After filtration, the solvent was removed in vacuo to furnish an oil (1.5 g) which was left at room temperature for 1 week. The colorless crystals which had formed were filtered and washed with petroleum ether (bp 35–60 °C) and then with $CHCl_3$ to give white prisms: 381 mg, yield 26.5%; mp 99–102 °C, NMR ($CDCl_3$) δ 5.46 (s, 4, CH_2), 5.63 (bs, 2 OH), 7.39 (m, 10, C_6H_5), 8.74 (s, 1, 6-H); MS, *m/e* 292 (M^+ − HBO_2), 201 (292 − benzyl); TLC ($CHCl_3$–EtOH, 19:1), R_f = 0.62. Anal. Calcd for $C_{18}H_{17}BN_4O_4 \cdot 0.25\ H_2O$: C, 63.46; H, 5.18; N, 8.23. Found: C, 63.67; H, 5.22; N, 7.89.

Iminodiethanol Derivatives 6 and 7. The mother liquor obtained from the above experiment containing impure boronic acid **5** was evaporated to dryness, and the resulting oil (1 g) was dissolved in ethyl ether (10 mL). To this was added dropwise a solution of diethanolamine (1 g) in ethyl ether (25 mL). A white precipitate immediately formed which was allowed to settle and then filtered and washed with ethyl ether (15 mL). The white solid obtained was dissolved in the minimum amount of EtOH, and then petroleum ether (bp 35–60 °C) was added until a slight turbidity resulted. The solution was left for 3 h, and the white prisms of the iminodiethanol derivative **6** which had formed were filtered; 0.7 g, yield 58%; mp 167–170 °C; NMR ($CDCl_3$) δ 2.58 (m, 2, $2CH_aNH$), 3.10 (m, 2, CH_bNH), 3.77 (m, 2, $2CH_cOB$), 3.94 (m, 2, $2CH_dOB$), 5.21 (bs, 1, NH), 5.27 and 5.38 (2 s, 4, $2C_6H_5CH_2$), 7.39 (m, 10, $2C_6H_5CH_2$), 8.41 (s, 1, 6-H); precision MS, *m/e* 405.1863 (M^+, calcd for $C_{22}H_{24}BN_3O_4$ 405.1860). Anal. Calcd for $C_{22}H_{24}BN_3O_4$: C, 65.20; H, 5.97; B, 2.67; N, 10.37. Found: C, 65.19; H, 6.34; B, 2.98; N, 10.28. The product obtained above (160 mg, 3.9 mmol) was dissolved in EtOH (10 mL) and the solution was hydrogenated at room temperature for 45 min at 30 psi (162 KN/m^2) in the presence of 10% Pd/C (50 mg). The suspension was warmed and then filtered through Celite. Evaporation of the filtrate furnished a solid which was recrystallized from EtOH to give the diethanolamine ester **7**: 49 mg, yield 55%; mp 230 °C dec; NMR [$(CD_3)_2SO$] δ 2.74 (m, 2, $2CH_aNH$), 3.19 (m, 2, $2CH_bNH$), 3.61 (m, 2, $2CH_cOB$), 3.71 (m, 2, $2CH_dOB$), 6.77 (bs, 1, CH_2NH), 6.96 (s, 1, 6-H), 10.33 and 10.51 (2 bs, 2, NH) [on deuteration, three new peaks appeared at δ 2.57 (t, J = 5.7 Hz, CH_2ND), 3.38 (t, J = 5.7 Hz, CH_2OD), 7.73 (s, 6-H) corresponding to diethanolamine and **1**]; MS, *m/e* 224/225 (M^+), 182.

5-(Dihydroxyboryl)uracil (1). Compound **5** was hydrogenated at room temperature for 2 h at 30 psi (162 KN/m^2) as described previously.[22] The product was recrystallized from EtOH, yielding white prisms which began to decompose at 330 °C (lit.[22] mp 330 °C dec); yield 65%; NMR [$(CD_3)_2SO$] δ 7.73 (s, 1, 6-H), 8.11 (bs, 2, OH), 11.41 (bs, 2, NH); MS, *m/e* 112 (M^+ − HBO_2); UV (0.01 N HCl) λ_{max} 266 nm (ϵ 9220), λ_{min} 235 nm (ϵ 2270); UV (0.01 N NaOH) λ_{max} 282 nm (ϵ 10 900), λ_{min} 248 nm (ϵ 7270). Anal. Calcd for $C_4H_5BN_2O_4$: C, 30.81; H, 3.23; N, 17.97. Found: C, 30.43; H, 3.31; N, 17.72.

2,4,6-Tribromopyrimidine (10). This compound was prepared by the action or phosphorus oxybromide on barbituric acid in *N,N*-dimethylaniline and toluene according to the method of Langley:[29] yield 68%; mp 109–111 °C (lit.[29] mp 113–115 °C); NMR ($CDCl_3$) δ 7.70 (s, 5-H). *Great care is necessary in handling this compound since it can cause severe contact dermatitis.*

6-Bromo-2,4-bis(benzyloxy)pyrimidine (9). This compound was prepared according to the method of Bryant and Leonard,[30] except that benzyl alcohol was used instead of ethyl alcohol: yield 82%; NMR ($CDCl_3$) δ 5.34 and 5.37 (2 s, 4, CH_2), 6.58 (1, s, 5-H), 7.26–7.43 (m, 10, C_6H_5). When the reaction was carried out at 10 °C a mixture of compound **9** and 2-bromo-4,6-bis(benzyloxy)pyrimidine [δ 6.8 (5-H)] was obtained in the ratio 3:1 (determined from NMR integral). Compound **9** was obtained pure by passing the mixture through a silica column, eluting with 1:1 $CHCl_3$–petroleum ether (bp 30–60 °C).

6-(Dihydroxyboryl)-2,4-bis(benzyloxy)pyrimidine (12). Treatment of 6-bromo-2,4-bis(benzyloxy)pyrimidine (**9**) (1.7 g, 4.6 mmol) as described for the preparation of compound **4** gave on extraction with $CHCl_3$ and evaporation an oil which was left at room temperature for 4 days. The crystals which had formed were filtered and washed with cold EtOH: 876 mg, yield 57%; mp 108–109 °C; NMR ($CDCl_3$) δ 5.06 (s, 1, 5-H), 5.31 and 5.38 (2, s, C_6H_5CH), 7.36 [m, 12, $C_6H_5CH_2$ and $B(OH)_2$].

Iminodiethanol Derivative of 13. The oil (200 mg), obtained from evaporation of part of the mother liquor in the above experiment, was dissolved in dry THF (20 mL) and diethanolamine (200 mg) in THF (5 mL) was added. The mixture was left stirring overnight and then the solvent allowed to slowly evaporate at room temperature to afford **13** as white needles which were filtered and washed with cold EtOH: 67 mg, yield 28%; mp 174–176 °C; NMR ($CDCl_3$) δ 2.80 (m, 2, 2 CH_aNH), 3.33 (m, 2, $2CH_bNH$), 3.87 (m, 2, 2 CH_2OB), 4.07 (m, 2, 2 CH_2OC), 5.36 and 5.37 (2, s, 4, C_6H_5CH), 6.00 (bs, 1 NH), 6.76 (s, 1, 5-H), 7.32 (m, 10, $C_6H_5CH_2$); MS, *m/e* 405 (M^+), 362. Anal. Calcd for $C_8H_{12}BN_3O_4 \cdot H_2O$: C, 62.42; H, 6.19; N, 9.93. Found: C, 62.70; H, 6.32; N, 10.47.

6-(Dihydroxyboryl)uracil (2). Part of the oil (0.8 g, 2.3 mmol) obtained from evaporation of the mother liquor in the preparation of **12** was converted directly to the title compound by catalytic hydrogenation as described for **1**: 126 mg, yield 34%; mp 303 °C dec; NMR (D_2O) δ 5.52 (5-H); UV (0.01 N HCl) λ_{max} 266 nm (ϵ 8730), λ_{min} 236 nm (ϵ 3270); UV (0.01 N NaOH) λ_{max} 264 nm (ϵ 6700), λ_{min} 240 nm (ϵ 3350). Anal. Calcd for $C_4H_5BN_2O_4$: C, 30.81; H, 3.23; B, 6.93; N, 17.97. Found: C, 31.04; H, 3.41; B, 6.74; N, 18.15.

5-Bromo-3′,5′-bis(*O*-trimethylsilyl)-2′-deoxyuridine (15). The title compound was prepared according to a method analogous to Pichat et al.[45] 5-Bromo-2′-deoxyuridine (3.08 g, 10 mmol) was dissolved in dry pyridine (50 mL). To this magnetically stirred solution was added dropwise a mixture of 1,1,1,3,3,3-hexamethyldisilizane (20 mL) and trimethylchlorosilane (10 mL) under anhydrous conditions. A white precipitate of $(NH_4)_2SO_4$ instantaneously formed. The mixture was stirred for 15 h and then quickly filtered. The filtrate was evaporated under high vacuum and the residual pyridine removed by redissolving and reevaporating the oil 4 times from dry benzene (20 mL). The oily residue was then coevaporated twice with hexanes (15 mL), redissolved in hexanes (15 mL), and filtered through a Millipore filter (0.45 μm). The filtrate was then reevaporated and the residue redissolved in $CHCl_3$ (20 mL). Removal of the $CHCl_3$ furnished an oil which slowly crystallized at room temperature, affording a stable white solid: 3.83 g, yield 85%; mp 71–73 °C; NMR ($CDCl_3$) δ 0.15 and 0.22 [2 s, 18, $Si(CH_3)_3$], 2.28 (m, 2, 2′-H), 3.82 (m, 2, 5′-CH_2), 4.04 (m, 1, 4′-H), 4.42 (m, 1, 3′-H), 6.34 (t, J = 6 Hz, 1, 1′-H), 8.30 (s, 1, 6-H), 9.40 (bs, 1, NH).

5-(Dihydroxyboryl)-2′-deoxyuridine (3). A solution of the protected nucleoside **15** (3 g, 6.65 mmol), in freshly distilled THF (45 mL), was cooled to −45 to −50 °C. Precooled *n*-BuLi (9.14 mL of a 1.6 M solution in hexane, 14.63 mmol) was added dropwise to the stirring solution under an argon atmosphere. The solution developed a red-orange color on addition of the first drops of *n*-BuLi. The mixture was left to react for 8 min and then rapidly

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cooled (liquid N_2/EtOH) to -75 °C. Dry hexamethylphosphoric triamide (HMPT, 5 mL) was then introduced into the stirred solution followed by excess precooled tri-*n*-butyl borate (4.5 mL, 16.68 mmol). The cooling bath was replaced with a solid CO_2/acetone bath and the mixture was left for 3 h at -60 to -65 °C. The HMPT which had solidified slowly melted at that temperature. The yellow solution was then allowed to warm up slowly to room temperature and then MeOH/H_2O (1:1, 20 mL) was added. Partial evaporation of the organic phase was followed by addition of H_2O (20 mL), and the pH of the solution was adjusted to 3 with AG 50 WX 2 (H^+) resin. The resin was filtered and washed with H_2O and the filtrate was extracted 3 times with $CHCl_3$ (50 mL) to remove HMPT. TLC ($CHCl_3$-EtOH, 2:1) of the aqueous layer revealed two major components [R_f 0.13 (product); 0.34 (2'-deoxyuridine, dUrd)]. 5-Bromo-2'-deoxyuridine could not be detected by TLC. Partial evaporation (10 mL) of the aqueous layer under reduced pressure furnished on cooling a white solid which was shown to be inorganic salts. Evaporation of the aqueous layer to dryness gave a residue which was loaded onto a silica column (300 g). Elution with $CHCl_3$-EtOH (2:1) initially afforded fractions which contained dUrd followed by fractions rich in product but still containing dUrd. The latter were pooled and evaporated to dryness, and the residue was dissolved in MeOH (8 mL). The light-brown solution was then fractionally crystallized in that solvent at room temperature. Initially, crops of almost pure dUrd (mp 163-165 °C) were recovered from the solution (545 mg). Two crops of compound **3** (326 mg, 18%) were then obtained. HPLC revealed that these had about a 5% impurity of dUrd and that these two samples did not contain any detectable traces of 5-bromo-2'-deoxyuridine. Recrystallization twice from MeOH afforded chromatographically pure compound **3** as white prisms: 208 mg, yield 12%; mp 226-227 °C dec; NMR [$(CD_3)_2SO$] δ 2.12 (m, 2, 2'-H), 3.54 (m, 2, 5'-CH_2), 3.80 (m, 1, 4'-H), 4.22 (bs, 1, 3'-H), 4.95 (t, J = 5.3 Hz, 1, 5'-OH), 5.28 (d, J = 3.5 Hz, 1, 3'-OH), 6.14 (t, J = 6.6 Hz, 1, 1'-H), 8.12 [s, 2, $B(OH)_2$], 8.13 (s, 1, 6-H), 11.67 (s, 1, NH); ^{11}B NMR δ -41.84 (bs); UV (0.01 N HCl) λ_{max} 268 nm (ϵ 12 500), λ_{min} 236 (ϵ 2310); UV (0.01 N NaOH) λ_{max} 265 nm (ϵ 10 200), λ_{min} 236 (ϵ 4350); IR ν (KBr, cm^{-1}) 3450 m, 3350 s, 3150 w, 3100 w, 3020 w, 2945 w, 2820 w, 1740 s, 1675 vs, 1620 w, 1475 s, 1415 m, 1375 m, 1310 m, 1280 s, 1230 vw, 1205 m, 1193 sh, 1150 w, 1123 m, 1100 s, 1092 sh, 1075 m, 1060 w, 1040 sh, 1030 s, 980 w, 950 sh, 940 m, 918 vs, 882 w, 848 w, 802 s, 787 m. Anal. Calcd for $C_9H_{13}BN_2O_7$: C, 39.75; H, 4.78; B, 3.98; N, 10.30. Found: C, 40.04; H, 5.03; B, 4.01; N, 10.64. Omitting HMPT or diglyme from the reaction reduced the yield to 7%. However, replacement of HMPT by diglyme (5 mL) did not significantly increase the yield of product.

5-(Trimethylsilyl)-2'-deoxyuridine (17). Substituting trimethylchlorosilane (3 mL, 23.6 mmol) for tri-*n*-butyl borate in the above experiment afforded on addition of MeOH/H_2O (1:1) an acidic solution. Partial evaporation of the solvents was followed by addition of H_2O and then the pH of the solution was adjusted to 5.5 with 1 M NaOH. Extraction of the aqueous layer twice with EtOAc and evaporation of the organic phase under reduced pressure furnished an oil which was loaded onto a silica column. Elution with $CHCl_3$-EtOH (9:1) and evaporation under high vacuum of the early fractions containing the desired product, afforded an amorphous white solid: 517 mg, yield 26%, mp 62-64 °C; NMR [$(CD_3)_2SO$] δ 0.16 [s, 9, $Si(CH_3)_3$] 2.11 (m, 2, 2'-H), 3.34 (m, 2, 5'-CH), 3.80 (bs, 1, 4'-H), 4.25 (m, 1, 3'-H), 5.02 (m, 1, 5'-OH), 5.25 (d, J = 3.5 Hz, 1, 3'-OH), 6.22 (m, 1, 1'-H), 7.73 (s, 1, 6-H), 11.18 (s, 1, NH); MS, m/e 300 (M^+), 184 (base), 169 (base - Me); TLC ($CHCl_3$-EtOH, 4:1) R_f 0.48; UV (0.01 N HCl) λ_{max} 266 nm (ϵ 9430), λ_{min} 236 (ϵ 2900); UV (0.01 N NaOH) λ_{max} 266 (ϵ 8460), λ_{min} 237 (ϵ 3210). Anal. Calcd for $C_{12}H_{20}N_2O_5Si \cdot 0.25\ H_2O$: C, 47.27; H, 6.78; N, 9.19. Found: C, 47.08; H, 6.56; N, 8.94. This compound can also be successfully prepared by using diglyme instead of HMPT.

High-Pressure Liquid Chromatography. The high-pressure liquid chromatograph used to determine the purity of the nucleosides was an Altex Model 110. The conditions used were as follows: Zorbax C-8 Column (Dupont), 25 cm × 4.6 mm id; ambient temperature; isocratic; mobile phase: 0.1 M sodium phosphate, pH 5.5; flow rate 0.5 mL/min; UV detection at 280 and 254 nm. The retention time (min) for the compounds analyzed measured at 280 nm were as follows: 2'-deoxyuridine, 9.2; 5-bromo-2'-deoxyuridine, 24.0; 5-(dihydroxyboryl)-2'-deoxyuridine, 16.6; 5-(trimethylsilyl)-2'-deoxyuridine, 9.1. The reproducibility was found to be within ±2%. Limit of detection, measured by relative ϵ_{280} for 5-bromo-2'-deoxyuridine was about 0.005%.

Registry No. **1**, 70523-22-7; **2**, 70523-23-8; **3**, 70577-63-8; **4**, 41244-53-5; **5**, 70523-24-9; **6**, 70523-25-0; **7**, 70523-26-1; **9**, 70523-27-2; **10**, 36847-11-7; **11**, 94706-32-8; **12**, 70523-28-3; **13**, 94706-33-9; **15**, 34279-86-2; **17**, 70523-31-8; 5-bromo-2,4-dichloropyrimidine, 36082-50-5; tributyl borate, 688-74-4; diethanolamine, 111-42-2; barbituric acid, 67-52-7; 5-bromo-2'-deoxyuridine, 59-14-3.

Nucleophilic Additions to *N*-Propargylpyridinium and *N*-Allenylpyridinium Salts and to 1,3-Propenediylbis(pyridinium) Salts

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Benzyl mercaptan adds to *N*-propargylpyridiniums to give *N*-[β-(benzylthio)allyl]pyridiniums, probably via an initial rearrangement to *N*-allenylpyridinium intermediates. Thiophenol reacts similarly, except that the 1-propargyl-4-(dimethylamino)pyridinium gives the *N*-[*cis*-γ-(phenylthio)allyl]pyridinium analogue. 2-Propene-1,3-diylbis(pyridinium) salts with 1 or 2 mol of thiol react by addition–elimination to form *N*-[1-(phenylthio)propen-2-yl]-, *N*-[3-(phenylthio)propen-2-yl]-, or *N*-[1,3-bis(phenylthio)propan-2-yl]pyridinium salts. *N*-(Oxiranylmethyl)pyridinium salts are prepared and converted into (2-hydroxypropane-1,3-diyl)bis(pyridinium) salts and corresponding propene-1,3-diylbis(pyridiniums). Semiquantitative studies of the base-catalyzed hydrogen–deuterium exchange of some of these compounds are reported, and the relative stability of the six possible isomeric 1-[(phenylthio)propenyl]pyridinium cations is discussed.

Pyridinium salts with unsaturated N substituents have recently received attention.[1-3] We reported on *N*-vinyl-,[1] *N*-propargyl-,[2] and *N*-propadienylpyridinium salts.[2] *N*-Vinylpyridinium cations act as Michael-type acceptors.[3]

We now describe the addition of sulfur nucleophiles to multiple bonds activated by an adjacent pyridinium moiety. A major aim of our work was to prepare as many of the possible isomers of the 1-[(phenylthio)propenyl]-pyridinium cation as possible and to study their relative stability. Additionally we were interested in the structural influences of the pyridinio substituent toward nucleophilic

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