Boron-Containing Nucleosides. 1. Synthesis of the Novel Heterocycle 2-Benzyl-1,4-dihydro-1-hydroxythieno[3,2-*c*][1,5,2]diazaborin-3(2*H*)-one: A Thieno-fused 4-Borauracil

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The synthesis of the novel boron-containing nucleobase 2-benzyl-1,4-dihydro-1-hydroxythieno[3,2-*c*]-[1,5,2]diazaborin-3(2*H*)-one (**8**), a thieno-fused 4-borauracil, is described. Compound **8** was prepared in three steps starting from 2-thiophenecarbonyl chloride (**4**). A multinuclear and multisolvent nmr study of **8** indicates that the boron atom maintains a trigonal geometry in the solvents used.

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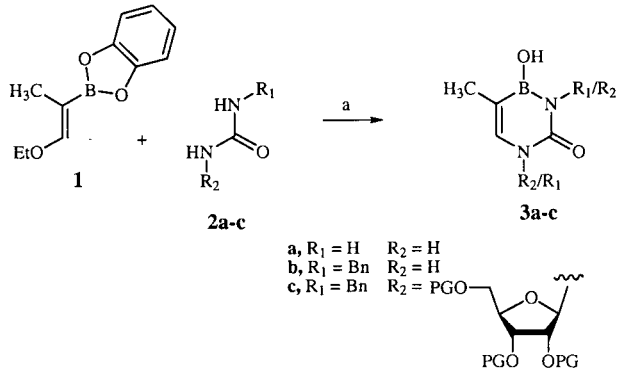
While it has long been appreciated that the unique chemistry of boron makes it a valuable component of synthetic reagents, more recent developments have demonstrated the potential applications of biologically active compounds containing boron [1]. The continuing need for new and effective therapeutic agents prompted us to design and synthesize nucleoside analogues where the carbon atom of a pyrimidine or purine carbonyl is replaced by boron. We were intrigued by the possibility that these endocyclic boron-containing nucleosides (BCNs) might maintain the pattern of Watson-Crick hydrogen bond donors and acceptors found in the parent nucleosides, and thus serve as probes of DNA structure and as potential inhibitors of DNA replication.

The boron-for-carbon replacement has been used to prepare analogues of amino acids [2] and peptides [3]; boron-containing amino acids with pendant boron groups [1b,4], as well as endocyclic boron-containing nucleosides with the boron found as a nucleobase [5,6], sugar [1b], or phosphate [7] substituent are also known. More relevant to this work, at least from a structural standpoint, are the known nucleobase analogues with an endocyclic boron [1e,8-20]. However, the goal of incorporating such endocyclic boron nucleobases into a nucleoside, to our knowledge, remains unrealized [21].

Our first attempt of the synthesis of a borauracil analogue is shown in Scheme 1. This route was based on the large body of work by Shaw [22] and others [23] on the preparation of uridine nucleosides and analogues *via* cyclization of 3-alkoxy-*N*-alkoxycarbonylacrylamides and amines. The expected difficulty in accessing the analogous boron compounds effectively precluded a direct adaptation of this route, and a seemingly more straightforward procedure using *Z*-(1-ethoxy-1-propen-2-yl)-1,3,2-benzodioxaborole (**1**) [24] and various ureas **2a-c** [25] as shown in Scheme 1 was conceived. Unfortunately, trials using a variety of solvents (ethanol, methanol, acetonitrile, ethyl acetate, *N*,*N*-dimethylformamide, acetone, ether, tetrahydrofuran, and dimethyl sulfoxide) with an acid catalyst (sulfuric, acetic, phosphoric acids), base catalyst (anhydrous ammonia, ammonium hydroxide, sodium ethoxide), or no catalyst in no cases produced the desired 4-borauracils **3a-c**.

Scheme 1



a) see text

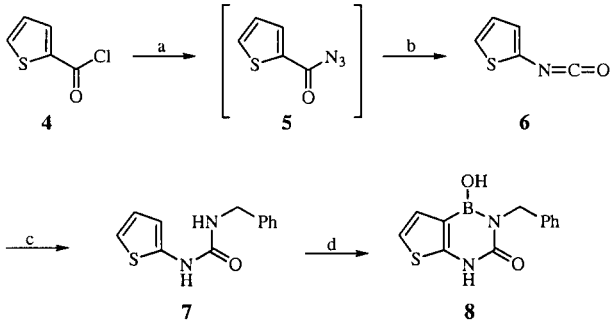
Gronowitz has prepared the related 1,2,3-diazaborine [13,14] and 1,2-azaborine [15-17] heterocycles *via* Raney nickel desulfurization of the corresponding thieno-fused diaza- and azaborines [19]. The advantage of the thieno-fused route is that it permits construction of the boron heterocycle using a stable starting template - the aromatic thiophene ring - rather than vinyl ureas or alkenyl boronates. However, there are no reports describing the synthesis of thieno-fused 1,5,2-diazaborin-3(2*H*)-ones (thieno-fused 4-borauracils) using this, or any other, method. The few reported cases of the 1,5,2-diazaborin-3(2*H*)-one ring system have all been benzo-fused (benzo-fused 4-borauracils); in these cases the 1,5,2-diazaborin-3(2*H*)-one ring system was prepared by reaction of (2-aminophenyl)boronic acids with isocyanates [1e,10-12,20,26,27]. Direct extension of this methodology to thieno-fused 4-borauracils would require (2-amino-3-thiophene)boronic acid, but this route is likely to suffer from the known instability of 2-aminothiophenes lacking strong electron withdrawing groups [17,28].

An alternative but less common procedure is to prepare an acyclic precursor to the desired boron heterocycle; treatment with the appropriate boron reagent then introduces the

boron atom and allows cyclization [15-19]. For the synthesis of a thieno-fused 4-borauracil the required acyclic precursor would be a 2-thienylurea, and this strategy became the basis for the route ultimately used. Access to this urea *via* 2-aminothiophene was still problematic [17,28], but recognition that the urea could be prepared from the known 2-thienylisocyanate [29] presented the solution.

Our successful synthesis of the title compound, 2-benzyl-1,4-dihydro-1-hydroxythieno[3,2-*c*][1,5,2]diazaborin-3(2*H*)-one (**8**) is shown in Scheme 2. Conversion of 2-thiophenecarbonyl chloride (**4**) to the corresponding azide **5** was accomplished with sodium azide in aqueous acetone [30,31]. Our initial attempts to convert **4** to 2-thienylisocyanate (**6**) using the method of Toselli and Zanirato [29] were unsuccessful. Next, azide **5** was converted to 2-thienylisocyanate (**6**, 37%) *via* Curtius rearrangement [32] by heating a carbon tetrachloride solution of **5** at 100° for 13 hours. Analysis of the ^{1}H nmr spectrum of the crude **6** after evaporation of the solvent showed that the 2-thienylisocyanate produced was generally of sufficient purity to use directly, though additional purification could be effected by distillation at reduced pressure. Next, addition of benzyl amine to a carbon tetrachloride solution of isocyanate **6** produced *N*-benzyl-*N'*-2-thienylurea (**7**) in 94% yield. Finally, urea **7** was converted to 2-benzyl-1,4-dihydro-1-hydroxythieno-[3,2-*c*][1,5,2]diazaborin-3(2*H*)-one (**8**) by heating a solution of the urea in 1,2-dichloroethane in the presence of boron trichloride with aluminum chloride as the catalyst. The title compound **8** was purified by preparative hplc (C_{18} column, 65:35 water:acetonitrile) and characterized by ^{1}H, ^{13}C, and ^{11}B nmr spectroscopy as well as elemental analysis and high-resolution fast atom bombardment mass spectrometry.

Scheme 2

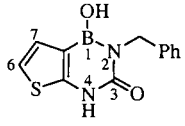


a) NaN_3/acetone/H_2O; b) CCl_4/100°/13 hours; c) $PhCH_2NH_2$/CCl_4; d) BCl_3/$ClCH_2CH_2Cl$/catalytic $AlCl_3$.

The ^{1}H- and ^{11}B nmr data for compound **8** in a variety of solvents are summarized in Table 1. The nmr data is in accord with the proposed structure, as indicated by the presence of a single broad, exchangeable signal (the proton on N4), a single sharper, exchangeable signal (the proton on O1), two doublets (J = 5.4 Hz) for the thiophene protons (H6 and H7), and a singlet for the benzyl methylene group. Further evidence for the structure of **8** was obtained from the ^{13}C nmr spectra. As had been noted previously [8,9,15], the strong quadrupolar line broadening of boron generally precludes observation of the carbon signal for the carbon directly attached to the boron. As expected, compound **8** thus gave rise to only nine carbon signals; in contrast, urea **7** clearly showed the expected ten carbon signals. Finally, the ^{11}B nmr chemical shifts (approximately 33 ppm using the boron trifluoride•etherate scale) are indicative of a trigonal boron atom. Boron-11 nmr spectroscopy is a sensitive probe of boron hybridization [33] and has been used to study the relative tendency of boron heterocycles to undergo a change from trigonal to tetrahedral hybridization due to addition of solvent [8-10,20]. We see no evidence for tetrahedral boron in the ^{11}B nmr spectra (no signal approximately 20-30 ppm

Table 1

^{1}H- and ^{11}B NMR Data for 2-Benzyl-1,4-dihydro-1-hydroxythieno[3,2-*c*][1,5,2]diazaborin-3(2*H*)-one (**8**)



	NH	OH	H6	H7	Ph	CH_2	B1 [d]
acetone-d_6 [a]	10.31 (brs)	8.42 (s)	7.22 (d, 5.4 Hz)	6.85 (d, 5.4 Hz)	7.41 (app dm, 7.6 Hz) 7.26 (app tm, 7.6 Hz) 7.17 (app tm, 7.5 Hz)	4.87 (s)	33.5
deuteriochloroform [b]	8.79 (brs)	4.79 (s)	6.99 (d, 5.4 Hz)	6.77 (d, 5.4 Hz)	7.44 (app d, 6.9 Hz) 7.34-7.22 (m)	4.91 (s)	
acetonitrile-d_3 [b]	9.46 (brs)	7.01 (s)	7.15 (d, 5.4 Hz)	6.81 (d, 5.4 Hz)	7.32 - 7.19 (m)	4.80 (s)	33.7
methanol-d_4 [c]	exch.	exch.	7.36 (d, 5.5 Hz)	6.92 (d, 5.4 Hz)	7.35 - 7.14 (m)	4.81 (s)	32.3

[a] At 600 MHz. [b] At 300 MHZ. [c] At 400 MHz. [d] All ^{11}B nmr spectra were recorded at 128 MHz.

upfield from the observed signal) in any of the solvents used, including methanol-d_4. This is in contrast to the previously reported *benzo-fused* 1,5,2-diazaborin-3(2*H*)-one ring systems which in methanol-d_4 showed partial [10,20] or complete [20] conversion to the tetrahedral adduct. Though less sensitive as indicators of a change from trigonal to tetrahedral hybridization, the ^{1}H- and ^{13}C nmr spectra also show no evidence for tetrahedral boron. At the present time we have no explanation for the apparent resistance of **8** towards tetrahedral adduct formation.

In summary, we have prepared for the first time a thieno-fused 4-borauracil **8**. Further studies on the properties of this compound and our attempts to prepare the corresponding nucleosides will be reported in due course.

EXPERIMENTAL

General Synthetic Procedures.

Nuclear magnetic resonance spectra were obtained on Gemini 300 or Unity Inova 400 or 600 MHz spectrometers from Varian. The ^{1}H- and ^{13}C nmr spectra were referenced to either internal tetramethylsilane or to the central line of the residual solvent multiplet. The ^{11}B nmr spectra are reported on the boron trifluoride•etherate scale (δ = 0 ppm); the spectra were referenced by setting the signal of an external trimethyl borate standard to 18.3 ppm. Infrared spectra were obtained in carbon tetrachloride solution on a System 2000 FT-IR instrument from Perkin-Elmer. Ultraviolet spectra were obtained on a Hewlett-Packard 8453 Diode Array Spectrophotometer. Gas chromatography-mass spectrometry (electron ionization) was performed on a Hewlett-Packard G1800A GCD system. Low resolution fast atom bombardment mass spectra were obtained on a model ZAB-2SE VG Analytical Limited spectrometer. The high resolution fast atom bombardment mass spectra was performed by the Washington University Resource for Biomedical and Bio-organic Mass Spectrometry, St. Louis, MO. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. The hplc system used was a Waters 600E pump/controller outfitted with a 996 photodiode array detector. Analytical hplc runs used a 4.6 x 250 mm (5 micron) MicrosorbMV™ C_{18} reversed-phase column (1 ml/minute) from Rainin; preparative runs used a Dynamax™ 21.4 x 250 mm (8 micron) column (12 ml/minute) also from Rainin. Melting points were determined on a Thomas Hoover apparatus and are uncorrected. Removal of the solvent *in vacuo* was accomplished using a rotary evaporator at 30° and 20 mm Hg (water aspirator). A cylinder of Drierite™ (W.A. Hammond) was placed in the vacuum line between the aspirator and the rotary evaporator to protect the contents from moisture. Drying *in vacuo* refers to removal of residual solvent using an oil pump (<0.1 mm Hg) at room temperature. Thin-layer chromatography was accomplished using Machery-Nagel Polygram Sil G/UV™ plates with detection using either ultraviolet light (254 nm) or *p*-dimethylaminobenzaldehyde stain [34]. Chemicals were purchased from Aldrich and solvents from Fisher Scientific unless stated otherwise. The carbon tetrachloride was dried by distillation from phosphorus pentoxide; all other chemicals and solvents were used as received. All reactions were performed under a dry nitrogen atmosphere.

2-Thienylisocyanate (**6**).

A solution of 2-thiophenecarbonyl chloride (**4**) (4.0 ml, 38 mmoles) in acetone (20 ml) was cooled to 0° followed by dropwise addition of a solution of sodium azide (2.87 g, 44.1 mmoles) in water (24 ml). The cooled solution was stirred for 3.5 hours until analysis by gc-ms indicated complete conversion of **4** to 2-thiophenecarbonyl azide (**5**). Carbon tetrachloride (20 ml) and saturated sodium bicarbonate (10 ml) were added and the organic layer was dried (sodium sulfate), filtered, and evaporated. Curtius rearrangement was performed by dissolving the above crude azide **5** in carbon tetrachloride (25 ml) and heating in a heavy-walled glass pressure vessel sealed with a threaded teflon plug at 100° for 13 hours. **Caution: This step should be conducted behind a blast shield.** After cooling to room temperature, the solvent was removed *in vacuo* with protection from moisture and the residue distilled to give 1.72 g (37%) of **6** [29], bp 71-74° (1.2 mm Hg); ^{1}H nmr (deuteriochloroform, 300 MHz): δ 6.92 (dd, J = 5.7, 1.5 Hz, 1H, H-5), 6.81 (dd, J = 5.8, 3.7 Hz, 1H, H-4), 6.68 (dd, J = 3.7, 1.5 Hz, 1H, H-3); ^{13}C nmr (deuteriochloroform, 75 MHz): δ 133.5, 125.8, 120.6, 120.4; ir (carbon tetrachloride solution): ν 2277 (C=N=O).

N-Benzyl-*N'*-(2-thienyl)urea (**7**).

Benzyl amine (550 µl, 5.1 mmoles) was added dropwise to a stirred solution of 2-thienylisocyanate (**6**, 625 mg, 5.0 mmoles) in 40 ml of carbon tetrachloride. A white solid formed immediately. The reaction was stirred for 15 minutes and then filtered. After washing with additional carbon tetrachloride the white solid was dried *in vacuo* to give 1.10 g (94%) of the desired product, mp 166-167°; R_f (95:5:1 dichloromethane:ethyl acetate: ethanol) 0.26; uv (acetonitrile): λ max 264 nm (ε 12,900); uv (methanol): λ max 264 nm (ε 16,400); ^{1}H nmr (deuteriochloroform, 300 MHz): δ 7.35-7.23 (m, 5H, phenyl), 7.01 (dd, J = 5.6, 1.3 Hz, 1H, thienyl H-5), 6.85 (dd, J = 5.6, 3.7 Hz, 1H, thienyl H-4), 6.69 (ddd, J = 3.6, 1.4, 0.8 Hz, 1H, thienyl H-3), 6.49 (brs, 1H, NH), 5.19 (app brt, 1H, N*H*-CH_2), 4.43 (d, J = 5.9 Hz, 2H, CH_2); (acetone-d_6, 300 MHz): δ 8.88 (brs, 1H, NH), 7.35-7.23 (m, 5H, phenyl), 6.76-6.72 (m, 2H, thienyl H-5 and H4), 6.45 (dd, J = 3.2, 1.9 Hz, 1H, thienyl H-3), 6.35 (brs, 1H, N*H*-CH_2), 4.42 (d, J = 6.0 Hz, 2H, CH_2); (dimethyl sulfoxide-d_6, 300 MHz): δ 9.52 (brs, 1H, NH), 7.34-7.22 (m, 5H, phenyl), 6.75-6.67 (m, 3H, thienyl H-5, H-4, and N*H*-CH_2), 6.41 (dd, J = 3.2, 1.9 Hz, 1H, thienyl H-3), 4.28 (d, J = 6.0 Hz, 2H, CH_2); ^{13}C nmr (acetone-d_6, 75 MHz): δ 155.5, 143.3, 141.4, 129.3, 128.3, 127.8, 124.8, 116.4, 109.8, 44.3; (dimethyl sulfoxide-d_6, 75 MHz): δ 154.5, 142.2, 140.4, 128.4, 127.2, 126.9, 124.1, 115.2, 108.2, 42.9; ms: (low resolution fast atom bombardment; 3-nitrobenzyl alcohol matrix): m/z 233 (MH^+).

Anal. Calcd. for $C_{12}H_{12}N_2OS$: C, 62.05; H, 5.21; N, 12.06. Found: C, 61.92; H, 5.08; N, 12.10.

2-Benzyl-1,4-dihydro-1-hydroxythieno[3,2-*c*][1,5,2]diazaborin-3(2*H*)-one (**8**).

To a stirred solution of boron trichloride (1.20 mmoles, from 1.20 ml of a 1.0 *M* solution in xylene) in 1,2-dichloroethane (Aldrich, 10 ml) was added *via* cannula over 25 minutes a solution of *N*-benzyl-*N'*-(2-thienyl)urea (**7**) (220 mg, 0.95 mmoles) in 1,2-dichloroethane (50 ml). Aluminum trichloride (10.0 mg, 0.08 mmoles) was then added and the reaction refluxed under nitrogen. Reaction aliquots (100 µl) were removed, quenched with a mixture of water (500 µl), sodium phosphate buffer (5 µl of 200 m*M*, *p*H 7.5 buffer), and methanol (1 ml) and analyzed by hplc (C_{18} column,

4.6 x 250 mm, 1 ml/minute, 100:0 water:acetonitrile to 65:35 water:acetonitrile over 35 minutes). After 14 days the reaction was quenched with a mixture of water (20 ml) and sodium phosphate buffer (6 ml of 200 m*M*, *p*H 7.5 buffer). The organic layer was separated, dried (sodium sulfate), filtered, and evaporated. The crude product was purified by preparative hplc (C_{18} column, 21.4 x 250 mm, 12 ml/minute, 65:35 water:acetonitrile). Evaporation of solvent and drying under vacuum afforded 30 mg (13%) of the desired product, mp 109-112°; uv (acetonitrile): λ max 214 nm (ε 34,500), λ max 268 nm (ε 6,500); uv (methanol): λ max 253 nm (ε 17,300), λ max 265 nm (ε 19,700); ^{1}H nmr (acetone-d_6, 600 MHz): δ 10.31 (brs, 1H, NH), 8.42 (s, 1H, OH), 7.40 (app dm, J = 7.6 Hz, 2H, phenyl H2, H2'), 7.26 (app tm, J = 7.6 Hz, 2H, phenyl H3, H3'), 7.22 (d, J = 5.4 Hz, 1H, H-6), 7.17 (app tm, J = 7.5 Hz, 1H, phenyl H4), 6.85 (d, J = 5.4 Hz, 1H, H-7), 4.87 (s, 2H, CH_2); (deuteriochloroform, 300 MHz): δ 8.79 (brs, 1H, NH), 7.44 (app d, J = 6.9 Hz, 2H, phenyl H2, H2'), 7.34-7.22 (m, 3H, phenyl H3, H3', H4), 6.99 (d, J = 5.4 Hz, 1H, H-6), 6.77 (d, J = 5.4 Hz, 1H, H-7), 4.91 (s, 2H, CH_2), 4.79 (s, 1H, OH); (acetonitrile-d_3, 300 MHz): δ 9.46 (brs, 1H, NH), 7.32-7.19 (m, 5H, phenyl), 7.15 (d, J = 5.5 Hz, 1H, H-6), 7.01 (s, 1H, OH), 6.81 (d, J = 5.4 Hz, 1H, H-7), 4.80 (s, 2H, CH_2); (methanol-d_4, 400 MHz): δ 7.36 (d, J = 5.4 Hz, 1H, H-6), 7.35-7.14 (m, 5H, phenyl), 6.92 (d, J = 5.4 Hz, 1H, H-7), 4.81 (s, 2H, CH_2); ^{13}C nmr (acetone-d_6, 75 MHz): δ 156.4, 156.1, 141.5, 129.0, 128.9, 128.2, 127.5, 115.5, 44.8; (acetonitrile-d_3, 75 MHz): δ 156.5, 156.2, 141.3, 129.4, 128.4, 128.3, 127.8, 116.2, 45.0; ^{11}B nmr (acetone-d_6, 128 MHz): δ 33.5 ($\nu_{1/2}$ = 238 Hz); (acetonitrile-d_3, 128 MHz): δ 33.7 ($\nu_{1/2}$ = 275 Hz); (methanol-d_4, 128 MHz): δ 32.3; ms: (low resolution fast atom bombardment; 3-nitrobenzyl alcohol matrix): m/z 259 (MH^+), 394 (MH^+ + matrix - H_2O); (low resolution fast atom bombardment; glycerol matrix): m/z 259 (MH^+), 333 (MH^+ + matrix - H_2O); (high resolution fast atom bombardment): m/z 259.0714 (MH^+); $C_{12}H_{11}BN_2O_2S$ requires 259.07136.

Anal. Calcd. for $C_{12}H_{11}BN_2O_2S$: C, 55.84; H, 4.30; N, 10.85. Found: C, 56.12; H, 4.63; N, 10.66.

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* To whom correspondence should be addressed.

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