Preparation and Characterization of Some Isoelectronic Boron-Nitrogen Analogs of Substituted Uracil [1]

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Boron-Nitrogen Compounds, Azaborauracils, 1,3,5-Triaza-2-boracyclohexa-4,6-diones, Spiroboron Compound, NMR Spectra

Several 1,3,5-triaza-2-boracyclohexa-4,6-diones, which are isoelectronic analogs of substituted uracil, have been prepared by condensation reactions of boranes with biurets. They include species containing a NH or BH unit as potentially reactive sites. The latter are extremely sensitive to hydrolysis but are readily handled as the 2-methylaminoethanol derivative containing four-coordinate boron.

Introduction

The sparse literature on isoelectronic boron-nitrogen analogs of substituted uracils of type 1 (= 1,3,5-triaza-2-boracyclohexa-4,6-diones) has been summarized in previous work, in which detailed syntheses of a few representative species as well as some of their properties were described [2].

The preparation of compounds of type 1 with R² to R² = CH₃ and R = organyl was readily accomplished by a transamination reaction between N,N',N"-trimethylbiuret and the appropriate bis(dimethylamino)organylborane, RB[N(CH₃)₂]₂. However, all attempts to prepare compounds of type 1 in which R constitutes a good leaving group failed.

While the present work was in progress, the preparation of 1a: R = CH₃, R¹ = R² = R³ = C₅H₅; 1b: R = R¹ = CH₃, R² = R³ = H; 1c: R = C₆H₅, R¹ = CH₃, R² = R³ = H via the reaction of ureas with (organyl)haloboranes was reported [3]. In addition, the previously described [2] compound 1d: R = R¹ = R² = R³ = CH₃ was also obtained but could not be isolated in pure state; and mass spectral data gave evidence for the existence of 1e: R = CI, R¹ = R² = R³ = CH₃.

Uracil is a constituent of many nucleic acids. Physiological studies of the latter material containing isoelectronic boron-nitrogen analogs of uracil would require species of type 1 with good leaving groups to be used as starting materials in syntheses. The NH groups of 1b and 1c would seem to offer potentially reactive sites. In the search for compounds of type 1 containing a reactive boron site, and in order to evaluate the general utility of the transamination reaction as described above, some additional studies on the interaction of boranes with biurets have been performed and are reported herewith.

Results and Discussion

Initial experiments of the present work were directed to determine the general utility of the cited transamination reaction. As examples, N,N'-dimethylbiuret, N-ethyl-N',N"-dimethylbiuret or N-phenyl-N',N"-dimethylbiuret were reacted with a bis(dimethylamino)organylborane. In this manner, the species 1f: R = C₅H₅, R¹ = R² = CH₃, R³ = H; 1g: R = C₆H₅, R¹ = R² = CH₃, R³ = C₅H₅; 1h: R = R¹ = R² = CH₃; 1i: R = R¹ = R² = C₅H₅, R³ = CH₃; 1j: R = CH₃, R¹ = R² = CH₃ were obtained in good yields. These data suggest that the principal reaction,

RB[N(CH₃)₂]₂ + R¹HN-CO-NR²-CO-NHR³ → 1 + 2 (CH₃)₂NH

is general and limited only by the availability of the appropriate starting materials. Compound 1f represents another example of a species containing a potentially reactive nitrogen site, i.e., a NH group.

As noted previously, no compounds of type 1 could be obtained from the condensation of either B[N(CH₃)₂]₃ or BH₃ (employed as its trimethylamine
adduct) with N,N',N''-trimethylbiuret [2]. Renewed attempts to obtain the species 1 with R = N(CH<sub>3</sub>) for example, by using relatively low boiling solvents such as ether or chloroform for the reaction between tris(dimethylamino)borane and N,N',N''-trimethylbiuret, gave results essentially in agreement with the previous work, i.e., ready release of all three dimethylamino groups from the boron. In another set of experiments, bis(dimethylamino)borane was reacted with the cited biuret. On refluxing the two reagents in chloroform, a material was obtained the mass spectrum of which was essentially that expected for 1j: R = H, R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = CH<sub>3</sub>. However, various peaks were observed in the mass spectrum for ions of higher mass than that calculated for the parent ion of 1j, and NMR as well as elemental analysis data confirmed the material to be impure and all purification attempts failed. (The latter were severely hampered by the extreme hydrolytic sensitivity of the material.) Surprisingly, (–CO–NCH<sub>3</sub>–)<sub>3</sub> was consistently observed as one of the impurities; additional ones were identified as the betaine 2 [2] and the diboryl oxide 3 (R = CH<sub>3</sub>).

Similarly, reaction of THF-BH<sub>3</sub> with N,N',N''-trimethylbiuret yielded 1j as a THF adduct. Mass spectral and NMR data showed the product again to be contaminated by the same species as indicated above. On the other hand, when (CH<sub>3</sub>)<sub>2</sub>S–BH<sub>3</sub> was reacted with the cited biuret in refluxing CH<sub>2</sub>Cl<sub>2</sub> it was possible to obtain 1j of sufficient purity to characterize the compound by relevant NMR data. In similar fashion, reaction of (CH<sub>3</sub>)<sub>2</sub>S–BH<sub>3</sub> with N-phenyl-N',N''-dimethylbiuret yielded 1k: R = H, R<sup>1</sup> = R<sup>2</sup> = CH<sub>3</sub>, R<sup>3</sup> = C<sub>6</sub>H<sub>5</sub> of sufficient purity to obtain characteristic NMR data for the compound.

In order to circumvent the difficulties in handling the cited B–H derivatives, 1j was converted to the spiro chelate 4.

Although this latter compound is hygroscopic, it is not readily affected by water; an aqueous solution of 4 was stored for several days without showing any signs of noticeable decomposition. Moreover, when 4 was prepared without actual isolation of its monocyclic precursor 1j, the former was obtained in excellent yield. This observation suggests that even if 2 and/or 3 are formed as byproducts in the synthesis of 1j, these are also readily converted to 4 thus rendering the overall preparation highly effective.

Finally, the reaction of BBr<sub>3</sub> with N,N',N''-trimethylbiuret resulted in a product consisting, as based on mass spectral data, primarily of 1l: R = Br, R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = CH<sub>3</sub>. Again, no pure material could be isolated although 4 was readily obtained from the crude product by reaction with 2-methylaminoethanol. However, since this method of preparing 4 is neither more convenient nor more efficient than the route described above, this aspect was not further pursued.

The present study illustrates that isoelectronic boron-nitrogen analogs of substituted uracils of type 1 are readily prepared. If linking of the boron atom of such uracil analogs to a complex substituent is desired, it seems sufficient to prepare the BH species and, without isolation, interact it with the respective component.

**Experimental Section**

Reactions and transfers were carried out in an anhydrous atmosphere. N,N'-Dimethylbiuret, N,N',N''-trimethylbiuret and N-ethyl-N',N''-dimethylbiuret were prepared by reaction of 3,5-dimethyl-1,3,5-oxodiazocyclohexa-2,4,6-trione (obtained by a modified [4] reaction of CO<sub>2</sub> with CH<sub>3</sub>NCO [5]) with anhydrous ammonia, methylamine or ethylamine, respectively [5]. N-Phenyl-N',N''-dimethylbiuret was prepared from phenyl isocyanate and N,N'-dimethylurea [6]. Bis(dimethylamino)borane [7], bis(dimethylamino)methylborane
[8] and bis(dimethylamino)phenylborane [9] were prepared by the indicated literature procedures. Elemental analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, NY. Melting points (uncorr.) were determined in sealed capillaries on a Mel-Temp block.

Infrared spectra were recorded on a Perkin-Elmer Model 621 spectrometer under standard operating conditions, mass spectral data were obtained on a Hitachi-Perkin-Elmer RMU-7 instrument. NMR spectra were recorded on a Varian XL-200 spectrometer. Chemical shift data are given in ppm with positive values indicating downfield from the reference (internal TMS for 1H and 13C, external (C2H5)2OBF5 for 11B). Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = unresolved multiplet. An asterisk denotes a broad signal. Coupling constants J are given in Hz.

N,N'-Dimethylbiuret

NMR data (solution in CDCl3): δ1H = 7.56* (1H, s), 6.12* (2H, s), 3.26 (3H, s), 2.82 (3H, d, J = 4 to 5); δ13C (proton-decoupled) = 155.7, 156.6, 30.3, 29.1. — The mass spectrum of the material showed the parent ion cluster with the base peak m/z = 185, 173, 159, 130, 116 and 89.

N-Ethyl-N',N"-dimethylbiuret

NMR data (solution in CDCl3): δ1H = 7.16* (2H, s), 3.23 (2H, ill-resolved q), 3.20 (3H, s), 2.83 (3H, d, J = 4 to 5), 1.53 (3H, t, J = 6 to 7); δ13C (proton-decoupled) = 157.1, 156.3, 35.5, 29.8, 27.2, 14.9.

N,Phenyl-N',N"-dimethylbiuret

The compound was prepared according to the general directions [6] by refluxing equimolar amounts of N,N'-dimethylurea and phenyl isocyanate for 4 h in toluene solution. On cooling to room temperature, the desired compound precipitated in 69% yield, m.p. 84 to 86 °C.

NMR data (solution in CDCl3): δ1H = 10.91* (1H, s), 7.45 (2H, d, J = 7–8), 7.32 (2H, t, J = 7–8), 7.08 (1H, t, J = 7–8), 6.13* (1H, s), 3.22 (3H, s), 2.83 (3H, d, J = 4.5); δ13C (proton-decoupled) = 157.7, 153.4, 138.1, 128.9, 123.9, 120.6, 29.9, 27.5.

1,5-Dimethyl-2-phenyl-1,3,5-triaza-2-boracyclohexa-4,6-dione (1i)

A mixture of 5.64 g (43 mmole) of N,N'-dimethylbiuret, 7.92 g (45 mmole) of bis(dimethylamino)phenylborane, and 50 ml benzene was refluxed with stirring for 18 h. Insolubles were collected and dried (m.p. 170 to 178 °C). Sublimation under vacuum yielded 7.2 g (73%) of the desired colorless product, m.p. 175 to 178 °C.

Analysis for C16H16BN3O2 (217.04)

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NMR data (in CDCl3): δ1H = 7.53* (6H, s, phenyl protons and NH proton), 3.31 (3H, s), 3.17 (3H, s); δ13C (proton-decoupled) = 155.5, 153.8, 132.4, 130.4, 128.1, 32.4, 29.1. — The mass spectrum of the material showed a parent ion cluster with the base peak at m/z = 216 and major fragments with m/z = 185, 216, 159, 130, 116 and 89.

1,5-Dimethyl-2-phenyl-1,3,5-triaza-2-boracyclohexa-4,6-dione (1g)

A mixture of 8.76 g (55 mmole) of N-ethyl-N',N"-dimethylbiuret, 10.00 g (57 mmole) of bis(dimethylamino)phenylborane, and 50 ml benzene was refluxed for 18 h. Solids were collected and dried (m.p. 76 to 82 °C). A second crop of material remained after evaporation of the filtrate (m.p. 66 to 78 °C). Sublimation of the combined product under vacuum yielded 10.3 g (76%) of the desired compound as colorless crystals, m.p. 84 to 85 °C; m.p. 87 to 88 °C after recrystallization from heptane.

Analysis for C16H16BN3O2 (245.09)

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NMR data (in CDCl3): δ1H = 7.47 (5H, s), 3.40 (3H, s), 3.34 (2H, ill-resolved q), 2.90 (3H, s), 1.05 (3H, t, J = 4–5); δ13B = 33.8 (H12 = 425 Hz); δ13C (proton-decoupled) = 154.8, 154.2, 130.4, 129.0, 128.3, 40.5, 32.8, 29.6, 15.3. — The mass spectrum of the material showed the parent ion cluster with the base peak m/z = 245 and major fragments with m/z = 230, 216, 173, 130, 117, 115 and 89.

1,5-Dimethyl-2-phenyl-1,3,5-triaza-2-boracyclohexa-4,6-dione (1h)

A mixture of 6.2 g (30 mmole) of N-phenyl-N',N"-dimethylbiuret, 6.1 g (35 mmole) of bis(dimethylamino)phenylborane, and 80 ml benzene was refluxed for 14 h. The precipitate was collected to give 5.0 g of crude product, melting near 175 °C; another 3.7 g, m.p. 167 to 170 °C, was obtained on evaporation of the filtrate to give a combined yield of 99%. A pure product, m.p. 176 to 178 °C, was obtained by precipitation with diethyl ether from chloroform solution.

Analysis for C16H16BN3O2 (293.13)

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NMR data (in CDCl$_3$): $\delta^1$H = 7.53 to 6.95 (10H, unresolved m), 3.44 (3H, s), 3.06 (3H, s); $\delta^{11}$B = 33.8 (h$_{1/2}$ = 475 Hz). – The mass spectrum of the compound exhibited a parent ion cluster near m/z = 293 and major fragments with m/z = 236, 207, 180, 179 (base peak), 178, 93, 88, 78 and 51.

1.2.5-Trimethyl-3-phenyl-1,3,5-triaza-2-boracyclohexa-4,6-dione (1i)

A mixture of 6.2 g (30 mmole) of N-phenyl-N’N”-dimethylbiuret, 3.8 g (33 mmole) of bis(dimethylamino)methylborane, and 100 ml benzene was refluxed for 10 h. After evaporation of volatile material under vacuum there remained 6.9 g (99.8%) of crude product, m.p. 112 to 119 °C. The material can be purified by precipitation with hexane from benzene solution, m.p. 122 to 125 °C.

Analysis for C$_{11}$H$_{14}$BN$_3$O$_3$ (231.06)

Found C 56.62 H 6.09 B 4.78 N 18.12.
Calcd C 57.18 H 6.11 B 4.68 N 18.12.

NMR data (in CDCl$_3$): $\delta^1$H = 7.44 to 7.08 (5H, unresolved m), 3.37 (3H, s), 3.17 (3H, s), 0.37 (3H, s); $\delta^{11}$B = 35.8 (h$_{1/2}$ = 460 Hz); $\delta^{13}$C (proton-decoupled) = 154.8, 154.2, 141.3, 129.3, 128.1, 127.7, 31.8, 29.8 (the boron-bonded carbon was not observed). – The mass spectrum of the material exhibited a parent ion cluster with the base peak m/z = 231 and major fragments with m/z = 230, 174, 173, 117, 116, 111 and 110.

1,3,5-Trimethyl-1,3,5-triaza-2-boracyclohexa-4,6-dione (1j)

and its 2-Methyleniminoborane Derivative (4a)

A 2M solution of dimethyl sulfide-borane in toluene (16 ml = 32 mmole) was added to a solution of 4.4 g (30 mmole) of N,N’,N”-trimethylbiuret in 80 ml of methane chloride. Vigorous hydrogen evolution began immediately. Subsequently, the mixture was gently refluxed for 8 h.

For the isolation of (impure) 1j, 50 ml of the solvent were removed under vacuum to yield 0.6 g of precipitate which was discarded. Upon evaporation to dryness, 3.8 g of crude product, melting near 240 °C, remained. Some impurities could be sublimed off to leave ca. 3.5 g of material, m.p. 245 to 248 °C; featureless v(BH) near 2500 cm$^{-1}$. Based on $^1$H NMR and mass spectral data as well as elemental analysis, the material was not completely pure but characteristic NMR signals of 1j could be deduced as follows (solution in CDCl$_3$): $\delta^1$H = 3.35 (3H, s), 3.01 (2H, t, $\beta$ = 4-5), 2.85 (3H, s), 2.57 (2H, t, $\beta$ = 4-5), 2.36 (3H, unresolved d), 2.24 (6H, s); $\delta^{11}$B = +2.4 (h$_{1/2}$ = 20 Hz).

1,5-Dimethyl-3-phenyl-1,3,5-triaza-2-boracyclohexa-4,6-dione (1k)

A 2M solution of dimethyl sulfide-borane in toluene (16 ml = 32 mmole) was added to a solution of 6.2 g (30 mmole) of N-phenyl-N’N”-dimethylbiuret in 150 ml of methane chloride. The mixture was refluxed for 18 h and solvent was evaporated to give 6.5 g of crude product 1k, m.p. 105 to 112 °C. NMR data (solution in CD$_2$OD): $\delta^1$H = 3.41 (2H, t, $J$ = 4-5), 2.85 (3H, s), 2.57 (2H, t, $J$ = 4-5), 2.36 (3H, unresolved d), 2.24 (6H, s); $\delta^{11}$B = $+2.4$ (h$_{1/2}$ = 20 Hz). Additional peaks that were observed in the NMR spectra are readily assigned to impurities as discussed above. All attempts to obtain a pure material were unsuccessful.