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Boron Analogues of Valine, Leucine, Isoleucine, and Phenylalanine: Syntheses of Amine-Alkyl(*N*-ethylcarbamoyl)boranes

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A series of recently prepared amine-alkylcyanoboranes (alkyl = *i*-Bu, *sec*-Bu, and benzyl; amine = pyridine and quinuclidine) have been treated with Et_3OBF_4 and then aqueous sodium hydroxide to form selected amine-alkyl(*N*-ethylcarbamoyl)boranes, which are some of the first reported analogues of the α-amino acids, leucine, isoleucine, and phenylalanine, respectively. Two intermediate nitrilium salts (*sec*-Bu and benzyl) have been fully characterized, demonstrating the unusual chemical stability of these boronium species. In addition, the full characterization of two amine-alkylcyanoboranes and one amine-alkyl(*N*-ethylcarbamoyl)borane (R = *i*-Pr; valine analogues) are reported.

Introduction

In 1976, Spielvogel reported the synthesis and characterization of $Me_3N{\cdot}BH_2C(O)NHEt$ and $Me_3N{\cdot}BH_2C(O)OH$,[1] which are analogues of betaine ($Me_3N^+CH_2CO_2^-$), the N-methylated derivative of glycine, ($H_3N^+CH_2CO_2^-$). Over 60 related compounds have since been prepared,[2] which have attracted considerable interest owing to their biological activity. They display significant antineoplastic, antiinflammatory, antiarthritic, analgesic, and hypolipidemic activity in tests on laboratory animals.[2] All, except $Me_2NH{\cdot}B(i\text{-}Pr)_2CN$,[2m] $Me_3N{\cdot}BH(Me)CN$, and $Me_3N{\cdot}BH(Me)C(O)NHEt$,[3] have been derived from amine-cyanoboranes, possessing a central $-BH_2-$ moiety in place of the central methylene group of glycine. In order to prepare carbonyl-containing analogues of other amino acids in high yields, a reliable method for preparing mono-B-alkylated amine-cyanoboranes was developed.[4] The following account presents the results of the subsequent conversion of some of these amine-alkylcyanoboranes into *N*-ethylcarbamoyl-substituted amine-alkylboranes, which are analogues of leucine, phenylalanine, and isoleucine (see Table I). In addition, the first examples of valine analogues containing the isopropyl group attached to the boron center are reported herein.

Experimental Section

Techniques. Unless otherwise noted, all reactions were performed under an atmosphere of N_2 by using methods described by Brown[5] and Shriver.[6] Nitrogen gas was dried by passage through a glass column containing 4-Å molecular sieves. All glassware was dried overnight in an oven at approximately 100 °C or flame dried immediately before use and allowed to cool under dynamic vacuum (0.01-0.2 mmHg). Where noted, reaction solvents were dried by distillation under N_2 from sodium and benzophenone (saturated and aromatic hydrocarbons, and ethers) or P_2O_5 (CH_2Cl_2).[7] Diethyl ether was used as purchased from Mallinckrodt and stored under dry N_2. Acetonitrile was used as purchased and stored over molecular sieves. Chromatographic separations were conducted with HPLC grade solvents. Silica gel (Fisher 100-200 mesh or Aldrich 130-270 mesh) was used for standard gravity chromatography. Flash chromatography was performed according to the method of Still[8] using 230-400 mesh silica gel (Aldrich 60 Å or Merck grade 60).

Table I. Amine-Alkylcyanoboranes and Their Derivatives[a]

py·*sec*-BuBHX (**1**)	quin·*i*BuBHX (**5**)
quin·*sec*-BuBHX (**2**)	py·*i*PrBHX (**6**)
quin·BzlBHX (**3**)	quin·*i*PrBHX (**7**)
py·*i*BuBHX (**4**)	

X = (**a**) -C≡N, (**b**) -C≡NEt$^+$BF$_4^-$, (**c**) -C(=O)NHEt

[a] Abbreviations: py = pyridine; *sec*-Bu = *sec*-butyl; quin = quinuclidine; Bzl = benzyl; *i*-Bu = isobutyl; *i*-Pr = isopropyl.

Reagents. Isopropyllithium was made by using 25% by weight lithium (1% Na, Aldrich) suspension in mineral oil and 2-chloropropane, according to the method of Gilman and Moore.[9] Standardization was by use of 1,3-diphenyl-2-propanone tosylhydrazone in THF.[10] Dimethyl sulfide-borane (Aldrich, 10.0-10.2 M) was used as purchased. Mercury dicyanide was dried under dynamic vacuum, typically for 1 h prior to use. THF·HCl was generated by bubbling dry HCl through a filter stick into ice-cooled dry THF; the bottled HCl was dried by passing it through a dry ice/acetone trap. Quinuclidine (Aldrich) was sublimed under a static vacuum (0.2-20 mmHg) at 40-50 °C. Py·HCl (py = pyridine) was made by addition of concentrated HCl to a Et_2O solution of pyridine near 0 °C. The wet product was obtained by evaporation of the ether and then washed with ethyl acetate. After recrystallization ($CHCl_3$/ethyl acetate), the salt was dried in a vacuum desiccator using $CaSO_4$. Prior to use, the py·HCl was placed under a dynamic vacuum and heated for several hours to drive off any residual water and was handled in a glovebag or under a brisk dry nitrogen purge. Triethyloxonium tetrafluoroborate was synthesized according to the Meerwein protocol.[11] Its potency was maintained by storage of the salt under Et_2O and by doing several washings with fresh Et_2O just prior to use of the salt.

Analysis and Characterization. NMR Analysis. Proton NMR spectra were recorded in deuterated solvents on Bruker AM-500 (500.1 MHz) or Nicolet NT-360 (361.1 MHz) spectrometers locked to the solvent deuterium signal. Chemical shifts were established relative to the residual protons in the solvent and are reported in δ, parts per million (ppm) downfield from TMS: acetone-d_6, 2.08; acetonitrile-d_3, 1.93; chloroform-*d*, 7.25; dichloromethane-d_2, 5.32. Coupling constants (*J*) refer to H-H coupling, unless otherwise noted. Due to qudrupolar effects ($I_{[^{11}B]} = {}^3/_2$; $I_{[^{10}B]} = 3$) and molecular asymmetry B-*H* resonances were, if not indicated, obscured by other resonances or were of low intensity and very broad.

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Boron-11 NMR spectra were recorded at 115.8 MHz on the Nicolet 360 spectrometer in the solvents indicated; the spectrometer was not usually locked to the deuterium signal as signal drift was a couple of orders of magnitude lower than the broadening of the ^{11}B signals. Chemical shifts are reported relative to $Et_2O{\cdot}BF_3$ as an external standard, with positive shift values being downfield. Coupling constants indicate ^1H–^{11}B interactions, unless otherwise noted.

Carbon-13 NMR spectra were obtained in deuterated solvents by using the Bruker (125.76 MHz), Nicolet (90.8 MHz), or Varian XL-300 (75.4 MHz) spectrometers. Chemical shifts are reported in ppm downfield of tetramethylsilane, as established by comparison to the solvent chemical shifts: acetone-d_6, 206.0, 29.8; acetonitrile-d_3, 118.2, 1.3; chloroform-d, 77.0; dichloromethane-d_2, 53.8.

Other Techniques. Infrared spectra were recorded in cm^{-1} on a Perkin-Elmer 283 spectrophotometer as neat oils or KBr pellets and were referenced to polystyrene (1601.4 and 1583.1 cm^{-1}). Intensities are reported in accordance with the literature.[12] Melting points were obtained by using a Meltemp device in sealed, evacuated capillaries and are uncorrected. Mass spectra were determined on a Kratos MS-80 using the technique indicated. Elemental analyses were performed by Galbraith Microanalytical Labs, Knoxville, TN, or Desert Analytics, Tuscon, AZ.

Experimental Procedures. Lithium Isopropyltrihydroborate. Isopropyllithium (361 mL × 0.52 M, 188 mmol) was reacted according to the modified[4] Nöth[13] protocol with 1 equiv of dimethyl sulfide–borane (18.8 mL × 10.0 M, 188 mmol) over 2 h, cooled by a frozen acetonitrile slush (−50 °C), and allowed to warm to room temperature overnight. While the reaction solution was clear at low temperatures, a copious white precipitate appeared by morning. Boron-11 analysis revealed approximately by integration 73% Li-*i*-$PrBH_3$, 17% $LiBH_4$, and about 10% other products: ^{11}B NMR (THF) δ −24.29 (q, J = 75.41 Hz).

Lithium Isopropylcyanodihydroborate. Crude lithium isopropyltrihydroborate (≈73% RBH_3^-, estimated 137 mmol) was dissolved in 110 mL of THF and reacted with a deficiency of $Hg(CN)_2$ (13.0 g, 51 mmol) at room temperature, added as a powder. The reaction was complete in 20 min, as evidenced by clearing of the supernatant and the appearance of elemental mercury. The ^{11}B NMR spectrum of the clear supernatant was obtained. The peak areas of the cyano product [^{11}B NMR (THF) δ −28.17 (br t, J = 74.5 Hz)] relative to the remaining isopropyltrihydroborate was determined by integration. This was used to determine the quantity of $Hg(CN)_2$ needed to complete the reaction and to react with half of the tetrahydroborate side product that was present. The salt (14 g, 55 mmol) was dissolved in 100 mL of THF and added via cannula to the reaction mixture. The resulting solution again cleared after about 20 min and was decanted from over the mercury droplet to a three-necked round-bottomed flask, and the product was used in reactions without being isolated. Subsequent ^{11}B NMR spectra of cyanoborane products from this solution indicated that all of the isopropyltrihydroborate had been cyanated.

Pyridine–Isopropylcyanoborane (6a). Dry pyridine hydrochloride (5.41 g, 46.8 mmol) was transferred in a glovebag to a three-necked round-bottomed flask and weighed by difference. To the dry salt, about 100 mL of dry THF was added via syringe. Lithium isopropylcyanodihydroborate (45.1 mmol) dissolved in (41 mL) THF was decanted to the addition funnel via cannula. Addition was done dropwise, accompanied by some heating and a significant amount of foaming, and was finished in approximately 1 h. The reaction mixture was then placed under reflux for 10 h, during which time it developed a pale yellowish green hue. The reaction mixture was then worked up by evaporating the THF, adding the residues to water, and extracting five times with dichloromethane to afford a crude yellow oil (5.03 g). This was purified by taking three 1–2-g batches of the crude material and purifying each of them separately by flash chromatography (silica gel 150 g, R_f = 0.58, THF) to obtain a colorless oil which solidified at about 10 °C (3.82 g, 23.9 mmol, 52.9%): ^{11}B NMR (THF) δ −6.2 (d, J = 97.9 Hz); ^1H NMR ($CDCl_3$, 361.1 MHz) δ 8.49 (d, J = 5.25 Hz, 2-py, 2 H), 8.09 (t, J = 7.73 Hz, 4-py, 1 H), 7.65 (t, J = 7.07 Hz, 3-py, 2 H), 2.61 (v br, B-*H*, 1 H), 0.71 and 0.60 (br s, d, J = 0, 3.07 Hz, diastereotopic $-CH[CH_3]_2$, 6 H), 0.53 (second-order sepet, J = 3.50 Hz, $BHCH[CH_3]_2$, 1 H); ^{13}C NMR (acetone-d_6) δ 145.92 (2-py), 141.32 (4-py), 125.99 (3-py), 134.4 (br, $-C{\equiv}N$), 20.38 and 20.05 (diastereotopic $-CH[CH_3]_2$), 19.6 (br, $BCH[CH_3]_2$); IR (NaCl) ν_{max} 3110 m, 3090 w, 3065 w, 2940 s (alkyl C—H stretch), 2900 ms, 2870 ms, 2385 ms (B—H stretch), 2172 wm sh (BC≡N stretch), 1622 s (ring distortion), 1493 ms, 1462 s, 1380 m, 1360 m sh, 1260 ms, 1246 ms, 1217 m sh, 1160 m, 1130 s, 1094 s, 1056 s, 1024 ms, 994 m, 954 w, 917 w, 902 w, 817 w, 771 s, 740 mw, 694 ms, 611 m cm^{-1}; HRMS (EI) 160.1177 (M^+; calcd for $C_9H_{13}{}^{11}BN_2$, 160.1171).

Quinuclidine–Isopropylcyanoborane (7a). A THF solution of lithium isopropylcyanodihydroborate (88.35 mL, 97.7 mmol) was transferred via cannula to a three-necked flask, equipped with a reflux condenser and a pressure-equalized addition funnel. A slight excess of 1.05 equiv of THF·HCl (42.4 mL × 2.412 M, 102.5 mmol) was added dropwise over a 1-h period. Noticeable warming of the reaction mixture occurred, and hydrogen evolution was evident. After addition was completed, the reaction mixture was stirred for 1 h more at room temperature. Then ca. 1.1 equiv of quinuclidine (11.9 g, 107 mmol) was dissolved in 50 mL of dry THF and added dropwise at room temperature to the reaction mixture. About half-way through the addition a copious white precipitate appeared and thickened throughout the rest of the addition. The reaction mixture was stirred a further 2 h at room temperature, and a ^{11}B NMR spectrum indicated the reaction was complete at that time. Removal of the THF by rotary evaporation afforded an oily white viscous oil that solidified to oily crystals (ca. 20 g) upon addition to water; extractive work up was not necessary. From these crude crystals, 8.09 g (42.1 mmol, 43.1%) of analytically pure sandlike crystals (R_f = 0.70, THF; 0.61, EtOAc) were directly recrystallized from acetone/water and then hexane/dichloromethane; another ca. 5 g (70% pure, approximately 18 mmol) of oily residues was recovered as well (ca. 60% total yield): mp 132–134 °C; ^{11}B NMR (THF) δ −5.65 (d, J = 97.6 Hz); ^1H NMR ($CDCl_3$, 361.1 MHz) δ 3.09 (second-order quartet, $N[CH_2]_3-$, 6 H), 2.04 (septet, J = 3.20 Hz, $-[CH_2]_3CH$, 1 H), 1.77 (td, J = 7.76, 3.07 Hz, $-[CH_2]_3CH$, 6 H), 0.96 and 0.86 (d, d, J = 6.74, 6.86 Hz, diastereotopic $-CH[CH_3]_2$, 6 H), 0.77 (br septet, J = 7.0 Hz, $BCH[CH_3]_2$, 1 H); ^{13}C NMR ($CDCl_3$) δ 133.6 (br, $-C{\equiv}N$), 51.05 ($N[CH_2]_3-$), 24.28 ($-[C-H_2]_3CH$), 23.92 and 21.99 (diastereotopic $-CH[CH_3]_2$), 19.89 ($HC[C-H_2]_3-$), 13.8 (br, $BCH[CH_3]_2$); IR (KBr) ν_{max} 2980 w, 2945 s (alkyl C—H stretch), 2925 s, 2865 ms, 2850 ms, 2358 s (B—H stretch), 2175 w–m (BC≡N stretch), 1458 s, 1356 m, 1317 ms, 1203 ms, 1160 ms, 1108 s, 1043 ms, 994 m, 850 ms, 833 m, 608 w–m cm^{-1}. Anal. Found (calcd for $C_{11}H_{21}N_2B$): C, 68.99 (68.77), H, 10.98 (11.02).

General Procedure for Synthesizing the Amine–Alkyl(ethylnitrilio)borane Tetrafluoroborate from the Amine–Alkylcyanoborane. The amine–alkylcyanoborane was dried under dynamic vacuum for about an hour prior to use. Triethyloxonium tetrafluoroborate was conditioned for the reaction by washing the stored salt at least three times with dry Et_2O, followed by quantitative decantation of each rinse via cannula before the next rinse. Finally, the salt was dried under dynamic vacuum until the container was no longer cold to the touch. Then the Et_3OBF_4 was placed under N_2. The amine–alkylcyanoborane was placed in a flask stoppered with a rubber septum and purged with dry N_2. The amount of Et_3OBF_4 necessary for about 1.2–3 equiv was calculated and weighed out into a separate nitrogen-purged round-bottomed flask. To the cyanoborane container approximately half of the necessary dry CH_2Cl_2 required to produce about a 1 M solution of amine–alkylcyanoborane was added. After the cyanoborane dissolved in the CH_2Cl_2, it was transferred via cannula to the Et_3OBF_4 container. The salt, being soluble in CH_2Cl_2, immediately dissolved. Two to three more rinses of the cyanoborane container were made with the remaining half of the CH_2Cl_2, with transfer via cannula each time to the main reaction mixture. While the reaction occurred, a nitrogen inlet was left open to the nitrogen manifold to allow for possible hydrogen evolution, and a magnetic stirrer was sometimes used. Complete reaction usually was accomplished at room temperature in about 8 h for pyridine adducts and 1–4 days for quinuclidine adducts. Neither time period nor yields were observed to change significantly with solution concentration, though approximately 1–4 M solutions of the cyanoborane were typically used for convenience. Occasionally, gentle heating of the reaction flask with warm water was used to promote dissolution of the reactants; otherwise, room-temperature conditions or cooler were sufficient for the reaction to occur.

In some reactions Et_2O was used as the solvent. As Et_3OBF_4 was not appreciably soluble in Et_2O, the total volume of the solvent was not as crucial as above, except that it be enough to dissolve the cyanoborane. Meerwein's reagent was prepared as above and dry salt weighed out either under a brisk N_2 purge or in a glovebag. Again 1.5–2 equiv was used of Et_3OBF_4. The cyanoborane solution was decanted via cannula to the dry Et_3OBF_4. This was then stirred from 6 h to 3 days, during which time the crystalline salt would be replaced by an oil layer. The ethereal layer was decanted off, and the oil layer was saved.

Extractive Workup. The reaction mixture was typically added with some prior evaporation to distilled water. The reaction vessel was then rinsed with both CH_2Cl_2 and water until clean, and the washings were added to the main portion. Then the nitrilium salt was extracted from the water with CH_2Cl_2 or $CHCl_3$. If, after the extract was dried over Na_2CO_3 and the liquid was evaporated, silicon grease was suspected by the appearance of a greasy whitish spotty semisolid in place of a dry solid

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or a transparent oil, the MeCN was added. As stopcock grease was not appreciably soluble in MeCN and the nitrilium salt was, the liquid layer could be removed from the grease precipitate by a pipet and then evaporated to yield purified nitrilium salt.

Pyridine–*sec*-Butyl(ethylnitrilio)borane Tetrafluoroborate (1b). Pyridine–*sec*-butylcyanoborane, prepared as previously described[4] (0.74 g, 4.2 mmol), and Et_3OBF_4 (1.39 g, 7.3 mmol) were combined as described above, except that ether was used as the solvent and the nonhomogeneous mixture was left to stand until all oxonium salt had "dissolved" in the cyanoborane oil (6 h). Infrared analysis of the resulting oil showed a complete conversion of starting material to nitrilium salt. After evaporation and water wash, an oil remained that was used without further purification: ^{11}B NMR (THF) δ −1.3 (s, BF_4^-), −7.3 (br d); IR (NaCl plate) ν_{max} 3130 m, 3080 m, 2960 s (alkyl C—H stretch), 2880 m, 2420 br m (B—H stretch), 2310 m–s (BC≡NEt$^+$ stretch), 1630 m–s (ring distortion), 1470 vs, 1150–1010 br vs, 865 m, 790 s, 700 m–s cm^{-1}.

Quinuclidine–*sec*-Butyl(ethylnitrilio)borane Tetrafluoroborate (2b). Quinuclidine–*sec*-butylcyanoborane, synthesized and purified as previously described,[4] (4.02 g, 19.5 mmol) and Et_3OBF_4 (5.2 g, 27.4 mmol) were combined by the general procedure. An oil was isolated and was used directly in most cases. However, an analytically pure sample was obtained by heating a portion of it (100 mg) in distilled water at 65 °C until it dissolved. When the sample was cooled, colorless crystals formed. They were suction filtered off, washed with a small amount of water, and dried over $CaSO_4$ under vacuum (72.8 mg): mp 84.0–85.5 °C; ^{11}B NMR (H_2O) δ −1.57 (s), −6.44 (br); ^{1}H NMR ($CDCl_3$, 361.1 MHz) δ 4.2–4.0 (m, CNCH_2–), 3.13 (second-order t, J = 7.46 Hz, N[CH_2]$_3$–), 2.02 (septet, J = 2.51 Hz, –[CH$_2$]$_3$CH), 1.85 (second-order quintet, J = 4.9 Hz, –[CH_2]$_3$CH), 1.50 (t, J = 7.21 Hz, CNCH$_2$CH_3), 1.26, 1.13, and 1.03 (multiplets, J = 7.08, 7.12, and 7.15 respectively, three of four diastereotopic BCHCH_2–), 0.92–0.80 (m, remaining BCHCH_2– and *sec*-Bu methyl groups), 0.69 (br m, J = 6.5 Hz, BCH–); ^{13}C NMR ($CDCl_3$, 90.8 MHz) δ 121.8 (br, –C≡NEt), 52.31 (N[CH$_2$]$_3$–), 40.91 (CNCH$_2$–), 30.48 and 28.82 (BCHCH$_2$–), 23.98 (–[CH$_2$]$_3$CH), 20.5 (br, BCH–), 19.90 and 19.09 (BCH[CH$_3$]CH$_2$CH$_3$), 19.49 (–[CH$_2$]$_3$CH), 13.47 and 13.39 (CNCH$_2$CH$_3$), 13.17 and 12.73 (BCH[CH$_3$]CH$_2$CH$_3$). Anal. Found (calcd for $C_{14}H_{28}B_2F_4N_2$): C, 51.70 (52.22); H, 8.76 (8.75).

Quinuclidine–Benzyl(ethylnitrilio)borane Tetrafluoroborate (3b). Quinuclidine–benzylcyanoborane (1.28 g, 5.33 mmol) and Et_3OBF_4 (1.26 g, 6.6 mmol) were combined by the general procedure. After the mixture stood overnight, 1.86 g (5.22 mmol, 98%) of a colorless, crystalline solid was isolated: mp 152–154 (dec) °C; ^{11}B NMR (CD_3CN) δ −0.76 (s), −7.4 (d, J = 100 Hz); ^{1}H NMR (CD_3CN, 361.1 MHz) δ 7.16 (m, PHH), 3.80 (br m, CNCH_2–), 3.13 (second-order t, N-[CH_2]$_3$–), 2.06 (septet, J = 3.3 Hz, –[CH$_2$]$_3$CH), 1.83 (br m, –[CH_2]$_3$CH and BCH_2Ph), 1.24 (t, J = 7.2 Hz, CNCH$_2$CH_3); IR (KBr pellet) ν_{max} 3400 v br m, 3070 m, 3040 w, 3015 m, 2950 vs (alkyl C—H stretch), 2875 s, 2420 s (B—H stretch), 2310 s (BC≡NEt$^+$ stretch), 1600 m (ring distortion), 1485 s, 1460 s, 1280 s, 1230 vs, 1140–1000 br vs, 755 s, 710 s, 520 m, 500 m cm^{-1}. Anal. Found (calcd for $C_{17}H_{26}B_2F_4N_2$): C, 56.45 (57.35); H, 7.46 (7.36); N, 8.04 (7.87).

Pyridine–Isobutyl(ethylnitrilio)borane Tetrafluoroborate (4b). Freshly purified pyridine–isobutylcyanoborane was dried under dynamic vacuum for 5 h prior to use. Cyanoborane (1.34 g, 7.72 mmol) was dissolved in dry CH_2Cl_2 and transferred via cannula, followed by two more rinses, to another flask to which 1.75 g (9.20 mmol) of Et_3OBF_4 had been previously added. A substantial darkening of the reaction mixture was observed within minutes of reagent combination, with decomposition being apparent by ^{11}B NMR and IR after workup. An odor indicative of loss of ethyl isonitrile from the nitrilium salt was also quite apparent. Infrared monitoring of the reaction revealed completion in the overnight reaction (ca. 10 h), with replacement of the nitrile peak (2182 cm^{-1}) with the much stronger nitrilium BC≡NEt absorbance (2302 cm^{-1}). The reaction was worked up according to the above procedure to yield a brownish black oil (1.87 g, 6.46 mmol, 83.7%), which could be prevented from decomposing further by storage under nitrogen in a freezer (−15 °C): ^{11}B NMR (THF) δ −1.02 (s, BF_4^-), −9.7 (br d); IR (neat, NaCl) ν_{max} 3108 w, 3058 w, 2944 s (alkyl C—H stretch), 2865 s, 2803 w–m, 2425 ms (B—H stretch), 2302 s sh (BC≡NEt$^+$ stretch), 1486 m, 1457 s, 1380 m, 1360 m, 1340 m, 1280 m, 1257 m–s, 1216 ms, 1060 vs, 900 m, 775 ms, 760 ms, 690 ms cm^{-1}.

Quinuclidine–Isobutyl(ethylnitrilio)borane Tetrafluoroborate (5b). Freshly synthesized and recrystallized quinuclidine–isobutylcyanoborane (2.08 g, 10.07 mmol) was dried under dynamic vacuum for 2 h and then placed under dry N_2. In a second flask, 2.30 g of Et_3OBF_4 (12.1 mmol) was weighed out under nitrogen. The reactants were combined as described for the CH_2Cl_2 protocol and stirred for 22 h. The salt was then worked up as above to obtain a slightly yellow crystalline solid (3.27 g, 10.2 mmol; theoretical 3.24 g): ^{11}B NMR (CH_2Cl_2) δ −9.31 (d, J = 93 Hz), −1.44 (s, BF_4^-); IR (KBr) ν_{max} 2966 s (alkyl C—H stretch), 2896 s, 2830 w–m, 2420 ms (B—H stretch), 2320 ms sh (BC≡NEt$^+$ stretch), 1471 s, 1388 m, 1370 m, 1351 m, 1330 m, 1220 m, 1070 vs, 844 ms, 818 m, 542 s, 531 s cm^{-1}.

Pyridine–Isopropyl(ethylnitrilio)borane Tetrafluoroborate (6b). Pyridine–isopropylcyanoborane (0.800 g, 5.00 mmol) was dried under vacuum for about 2 h, then dissolved in a total of 6 mL of CH_2Cl_2 and reacted with Et_3OBF_4 (1.15 g, 6.05 mmol) for 14 h by the above protocol, and shown to be completely reacted by IR analysis. This afforded a pale yellow viscous oil: ^{11}B NMR (THF) δ −6.6 (br d), −0.95 (s, BF_4^-); IR (neat, NaCl) ν_{max} 2960 s (alkyl C—H stretch), 2870 s, 2420 ms (B—H stretch), 2310 ms sh (BC≡NEt$^+$ stretch), 1630 ms (ring distortion), 1470 s, 1220 m, 1080 vs br, 780 m, 690 m cm^{-1}.

General Procedure for Producing Amine–Alkyl(*N*-ethylcarbamoyl)borane from Amine–Alkyl(ethylnitrilio)borane Tetrafluoroborate. General Method. In a typical reaction, the nitrilium salts (neat oil or 1 M solutions in MeCN) were stirred in 1.2–2 equiv of aqueous NaOH (1.0 N solution, Fisher Scientific, or stock) from 5 min to up to 2 days, depending on the reactivities of the various nitrilium salts, in an open-air Vigreux condenser fitted flask at room temperature. A stir bar was included to mix the sometimes partially immiscible layers and keep the hydrolysis going. After the reaction was finished (monitored by TLC), the reaction mixture was diluted two to five times the original volume with water and then extracted three to six times with $CHCl_3$ or CH_2Cl_2. These were dried over anhydrous $MgSO_4$ or Na_2CO_3 and evaporated to sometimes afford solids; if silicon grease contamination was suspected the amide was purified as described above for the nitrilium salts. The clean oils would then spontaneously crystallize, but occasionally flash chromatography was needed for very impure amides or oil products in order to purify them to analytical quality materials.

Pyridine–*sec*-Butyl(*N*-ethylcarbamoyl)borane (1c). The nitrilium oil (9.35 mmol) was treated with 1 equiv of aqueous NaOH by the general procedure at room temperature for 5 min. A yellowish oil was isolated (1.34 g, 65% from cyanoborane). The solid was purified by flash chromatography (silica gel, 75 g, 32 × 210 mm) using hexane/acetone (1:1 and 2:3) and acetone eluents. The fraction R_f 0.32 (TLC, 1:1 ethyl acetate/acetone) gave a sticky solid that was triturated with pentane and dried under a stream of N_2 to give 1.01 g (4.59 mmol, 32%) of a colorless crystalline solid: mp 74.5–75.5 °C; ^{11}B NMR (CD_2Cl_2) δ −1.39 (d, J = 85 Hz); ^{1}H NMR (CD_2Cl_2, 500.1 MHz) δ 8.88 (dd, J = 1.48, 2.67 Hz, 2-py), 8.87 (dt, J = 1.2, 7.69 Hz, 4-py), 7.56 (t, J = 7.08 Hz, 3-py), 5.82 (br, –C(=O)NH–), 3.27 and 3.13 (m, m, J = 6.60, 6.67 Hz, diastereotopic NHCH_2CH$_3$), 1.53 (t, J = 7.26 Hz, NHCH$_2$CH_3), 1.37, 1.27, 1.16, and 0.96 (second-order multiplets, BCHCH_2–), 0.90 to 0.73 (complex m, *sec*-Bu –CH_3), 0.53 (br m, BCH–); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 196.2 (br, BC(=O)NH–), 147.03, 139.75, and 124.72 (py *C*), 32.18 (NHCH$_2$CH$_3$), 28.6 (br, BHCH–), 27.76 and 27.54 (diastereomeric BHCHCH_2–), 16.96 and 16.72 (diastereomeric BHCHCH_3), 15.27 (NHCH$_2$CH_3), 13.14 and 12.79 (diastereomeric BHCHCH$_2$CH_3); IR (KBr pellet) ν_{max} 3320 vs (N—H stretch), 3110 m, 3040 m, 2940 s (alkyl C—H stretch), 2840 s, 2330 m (B—H stretch), 1615 s (ring distortion), 1575 s (amide I), 1480 vs (amide II), 1455 vs, 1135 s, 1120 s, 1080 s, 765 s, 680 m, 650 m cm^{-1}; HRMS (+CI, NH$_3$) 237.2014 (M$^+$ + NH$_3$; calcd for $C_{12}H_{24}BN_3O$, 237.2012). Anal. Found (calcd for $C_{12}H_{21}BN_2O$): C, 65.32 (65.48); H, 9.50 (9.61); N, 12.66 (12.73).

Quinuclidine–*sec*-Butyl(*N*-ethylcarbamoyl)borane (2c). The nitrilium oil (9.96 mmol) was treated with 1 equiv of aqueous NaOH by the general procedure for 1 h. A crude oil (2.64 g, theoretical 2.51 g) was isolated. The oil was dissolved in hot pentane, and the filtered solution was placed in a freezer (−15 °C) for 48 h. A colorless crystalline solid (594.5 mg, 23.7%) was isolated by suction filtration and dried under vacuum: ^{11}B NMR ($CDCl_3$, {^{1}H}) δ −1.25 (br), −1.00 (br); ^{1}H NMR ($CDCl_3$, 500.1 MHz) δ 5.55 and 5.50 (br, diastereomeric –C(=O)NH–), 3.38 (second-order d of quintets, J = 2.65, 6.93 Hz) and 2.96 (second-order d of sextets, J = 2.76, 7.74 Hz, diastereotopic N[CH_2]$_3$–), 3.28 and 3.11 (complex m, diastereotopic –NHCH_2CH$_3$), 1.93 (septet, J = 3.23 Hz, –[CH$_2$]$_3$CH), 1.68 (dt, J = 3.18, 7.99 Hz, –[CH_2]$_3$CH), 1.48 (m), 1.31 (septet, J = 6.76 Hz), and 1.10 (m, J = 7.00 Hz, diastereotopic BCHCH_2–; the remaining multiplet is partly obscured at ca. 0.77 ppm), 1.03 (t, J = 7.24 Hz, NHCH$_2$CH_3), 0.82 and 0.78 (distorted t, distorted t, J = 6.8, 6.9 Hz, diastereomeric BCHCH$_2$CH_3), 0.81 and 0.72 (superimposed d, d, J = 6.8, 6.5 Hz, diastereomeric BCHCH_3), 0.39 (br m, J = 7.4 Hz, BCH–); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 196 (v br), 49.68 and 49.65 (diastereomeric N[CH$_2$]$_3$–), 31.82 and 27.79 (diastereomeric BCHCH$_2$–), 31.54 and 31.52 (diastereomeric NHCH$_2$CH$_3$), 24.58 (–[CH$_2$]$_3$CH), 23 (v br, BCH), 20.81 and 18.55 (diastereomeric BCHCH$_3$), 20.52 and 20.47 (diastereomeric –[CH$_2$]$_3$CH), 15.52 and 15.48 (diastereomeric NHCH$_2$CH$_3$), 13.84 and 13.62 (BCHCH$_2$CH$_3$); IR (KBr pellet) ν_{max} 3420 m (N—H stretch), 3320 m br, 2920 vs (alkyl C—H stretch), 2850 s, 2300 m (B—H stretch), 1580 s (amide I), 1460

br vs (amide II and B—N stretch), 1120 s-vs, 1025 s, 970 m, 830 s, 805 m, 740 s cm^{-1}. Anal. Found (calcd for $C_{14}H_{29}BN_2O$): C, 66.10 (66.67); H, 11.82 (11.59) N, 10.81 (11.11).

Quinuclidine–Benzyl(*N*-ethylcarbamoyl)borane (3c). The nitrilium salt (1.0 g, 2.8 mmol) was treated with NaOH(aq) (3 mmol) at 45 °C for 18 h, as described above. A solid was isolated and was recrystallized from toluene/hexane at dry ice temperature. The cold crystals melted as they reached room temperature, while being dried under vacuum and resolidifed to give 0.407 g (1.42 mmol, 50%) of a white powdery solid: mp 76.5–78.0 °C; ^{11}B NMR (CH_2Cl_2) δ −3.00 (br d, J = 64.4 Hz); ^{1}H NMR ($CDCl_3$, 362.2 MHz) δ 7.11 (t, J = 7.47 Hz, *m*-Ph), 7.05 (d, J = 7.17 Hz, *o*-Ph), 6.95 (t, J = 7.16 Hz, *p*-Ph), 5.12 (br unresolved t, J = ca. 4 Hz, –C(=O)N*H*–), 3.43 (second-order m, N[CH_2]$_3$–), 3.15–2.89 (m, NHCH_2CH$_3$), 1.97 (m, J = 3.14 Hz, –[CH$_2$]$_3$C*H*), 1.84 (br distorted AB quartet, J = 3.90, 7.79 Hz, BCH_2Ph), 1.72 (dt, J = 2.90, 7.92 Hz, –[CH_2]$_3$CH), 0.79 (t, J = 7.29 Hz, NHCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 195 (v br, B*C*(=O)NH–), 146.5, 128.5, 127.4, and 122.8 (Ph *C*), 49.9 (N[*C*H$_2$]$_3$–), 31.7 (NH*C*H$_2$CH$_3$), 27.0 (br, B*C*H$_2$Ph), 24.6 (–[*C*H$_2$]$_3$CH), 20.4 (–[CH$_2$]$_3$*C*H), 15.0 (NHCH$_2$*C*H$_3$); IR (KBr) ν_{max} 3460 m, 3430 m (N—H stretch), 3065 w, 3045 m, 3015 m, 2960 s (alkyl C—H stretch), 2920 s, 2870 s, 2820 m, 2340 m sh (B—H stretch), 2320 m, 1590 vs (amide I), 1470 vs (amide II), 1455 s, 1445 s, 1215 s, 1205 s, 1085 s, 1035 s, 840 m, 810 m, 690 m, 490 m cm^{-1}; MS (35 eV) *m/e* (relative intensity) 286 (M^+, 1), 214 (18), 167 (6), 147 (22), 132 (4), 111 (94), 96 (38), 91 (25), 82 (100), 69 (21); HRMS (EI, 35 eV) 286.2224 (M^+; calcd for $C_{17}H_{27}{}^{11}BN_2O$, 286.2220). Anal. Found (calcd for $C_{17}H_{27}BN_2O$): C, 70.27 (71.34); H, 9.56 (9.51); N, 9.33 (9.79).

Pyridine–Isobutyl(*N*-etbylcarbamoyl)borane (4c). Freshly synthesized pyridine–isobutyl(ethylnitrilio)borane tetrafluoroborate (1.00 g, 3.46 mmol) was dissolved in 4.0 mL of MeCN, followed by addition of 4.0 mL of 1.0 N NaOH. This was reacted for 24 h with vigorous stirring. A marked fading of the formerly dark brown oil to a medium orange was noted. An oil (0.606 g) was isolated by an extractive workup. Flash chromatography (silica gel 100 g; R_f = 0.20, THF; 0.05, EtOAc) yielded 0.103 g of slightly impure amide that solidified in a freezer (−15 °C) and 0.313 g of spectroscopically pure oily crystalline material (total 0.416 g, 1.89 mmol, 54.7%): mp 33–34 °C; ^{11}B NMR ($CDCl_3$) δ −3.85 (br d, J = 71.5 Hz); ^{1}H NMR ($CDCl_3$, 361.1 MHz) δ 8.75 (d, J = 6.13 Hz, 2-py, 2 H), 7.96 (t, J = 7.67 Hz, 4-py, 1 H), 7.53 (t, J = 6.64 Hz, 3-py, 2 H), 5.72 (br, C(=O)N*H*–, 1 H), 3.24 (second-order diastereotopic multiplet, J = 7.2 Hz, NHCH_2CH$_3$, 2 H), 2.7 (v br virtual d, J = ca. 120 Hz, B*H*, 1 H), 1.20 (complex multiplet, J = 6.5 Hz, –CH$_2$C*H*[CH$_3$]$_2$, 1 H), 1.08 (t, J = 7.24 Hz, NCH$_2$CH_3), 0.85 and 0.78 (d, d, J = 6.50, 6.49 Hz, diastereotopic –CH[CH_3]$_2$, 6 H), 0.59 (second-order multiplet, BHCH_2CH–); ^{13}C NMR acetone-d_6) δ 195.5 (br, B*C*(=O)NH–), 147.87 (2-py), 141.34 (4-py), 126.01 (3-py), 35.4 (br, B*C*H$_2$CH–), 27.66 (–CH$_2$*C*H[CH$_3$]$_2$), 26.38 and 25.17 (diastereotopic, –CH[*C*H$_3$]$_2$), 32.53 (N*C*H$_2$CH$_3$), 15.81 (NCH$_2$*C*H$_3$); IR (neat, NaCl) ν_{max} 3436 w–m sh (N—H stretch), 3118 w, 3102 w, 3085 w, 3052 w, 2940 s (alkyl C—H stretch), 2860 s, 2795 m, 2340 s (B—H stretch), 1618 m sh (ring distortion), 1587 s (amide I), 1483 s (amide II), 1459 s, 1430 s, 1357 m sh, 1229 m, 1210 ms, 1123 s, 1092 m, 858 m sh, 767 m sh, 688 ms; HRMS (CI$^+$, NH$_3$) 220.1861 (M^+ + H; calcd for $C_{12}H_{22}N_2O^{10}B$, 220.1861).

Quinuclidine–Isobutyl(*N*-ethylcarbamoyl)borane (5c). A sample of quinuclidine–isobutyl(ethylnitrilio)borane tetrafluoroborate (0.996 g, 3.09 mmol) was dissolved in 4.5 mL of MeCN and 4.5 mL of 1.0 N NaOH solution in water. This was stirred for 2 days at room temperature and was worked up as delineated in the above general method. A colorless oil was isolated that rapidly solidified at room temperature (0.777 g, 3.08 mmol, apparent yield 99.6%). This was analyzed by ^{11}B NMR and shown to be 99% amide and 1% parent cyanoborane by integration. The amide was recrystallized either from THF/hexane or CH_2Cl_2/hexane at −15 °C to afford analytically pure (R_f = 0.53, THF; 0.13, EtOAc) colorless crystals: mp 76.5–77.5 °C; ^{11}B NMR (THF) δ −3.89 (br d, J = 84 Hz); ^{1}H NMR ($CDCl_3$, 361.1 MHz) δ 5.72 (br s, C(=O)N*H*–), 3.30 and 2.88 (complex second-order pattern, diastereotopic N[CH_2]$_3$–), 3.27 and 3.14 (second-order multiplets, diastereotopic –NHCH_2CH$_3$), 1.92 (septet, J = 3.22 Hz, *H*C[CH$_2$]$_3$–), 1.34 (septet of triplets, J = 6.58, 2.47 Hz, –CH$_2$C*H*[CH$_3$]$_2$), 1.03 (t, J = 7.24 Hz, NHCH$_2$CH_3), 0.82 (d, J = 6.52 Hz, –CH[CH_3]$_2$), 0.45 and 0.10 (second-order septets, diastereotopic BHCH_2CH–); ^{13}C NMR δ 197.2 (br, B*C*(=O)NH–), 49.49 (N[*C*H$_2$]$_3$–), 31.59 (–NH*C*H$_2$CH$_3$), 28.05 (br, B*C*H$_2$CH–), 26.82 (–CH$_2$*C*H[CH$_3$]$_2$), 24.40 and 24.37 (respectively HC[*C*H$_2$]$_3$– and –CH$_2$CH[*C*H$_3$]$_2$, calculated from the gated proton-decoupled spectrum), 20.26 (HC[CH$_2$]$_3$–), 15.21 (NHCH$_2$*C*H$_3$); IR (KBr) ν_{max} 3320 s sh (N—H stretch), 2990 w, 2975 ms, 2945 s (alkyl C—H stretch), 2935 s, 2890 ms, 2870 s, 2800 w, 2325 m sh (B—H stretch), 1580 s (amide I), 1505 s (amide II), 1472 s, 1275 m, 1142 s, 1118 s, 1033 ms, 828 ms, 813 m, 718 wm, 562 wm, 323 w cm^{-1}. Anal. Found (calcd for $C_{19}H_{29}BN_2O$): C, 65.91 (66.67); H, 11.63 (11.59); N, 11.14 (11.11).

Pyridine–Isopropyl(*N*-ethylcarbamoyl)borane (6c). Freshly made pyridine–isopropyl(ethylnitrilio)borane tetrafluoroborate (0.552, 2.00 mmol) was dissolved in 2.5 mL of MeCN; 2.5 mL of 1.0 N NaOH in water was added, and the mixture was stirred for 14 h. Then the reaction mixture was added to excess water and extracted with CH_2Cl_2. Upon evaporation of the dried solvents, a loose, dry yellow crystalline mass was isolated (0.396 g, 1.92 mmol, 96.0%). The amide was recrystallized as analytically pure (R_f = 0.34, THF; 0.07, EtOAc) white crystals from CH_2Cl_2/hexane at −15 °C: mp 94.5–95.5 (dec) °C; ^{11}B NMR (CH_2Cl_2) δ −0.79 (d, J = 89.6 Hz); ^{1}H NMR ($CDCl_3$) δ 8.86 (d, J = 5.50 Hz, 2-py, 2 H), 7.96 (t, J = 7.64 Hz, 4-py, 1 H), 7.54 (t, J = 6.53 Hz, 3-py, 2 H), 5.79 (br s, C(=O)N*H*–, 1 H), 3.34 and 3.19 (second-order multiplets, J = 6.8, 6.4 Hz, diastereotopic NHCH_2CH$_3$), 2.4 (v br virtual doublet, J = 120 Hz, B*H*, 1 H), 1.09 (t, J = 7.24 Hz, NCH$_2$CH_3, 3 H), 0.83 and 0.55 (s, br d, J = 0, 4.9 Hz, diastereotopic BCH[CH_3]$_2$, 6 H), 0.80 (br multiplet [partially obscured by *i*Pr methyl resonance], BHC*H*-[CH$_3$]$_2$, 1 H); ^{13}C NMR (acetone-d_6) δ 194.9 (br, B*C*(=O)NH–), 147.76 (2-py), 141.33 (4-py), 125.87 (3-py), 32.43 (N*C*H$_2$CH$_3$), 22.23 (br, B*C*H[CH$_3$]$_2$), 21.75 and 21.04 (diastereotopic BCH[*C*H$_3$]$_2$), 15.89 (NCH$_2$*C*H$_3$); IR (KBr) ν_{max} 3310 s (N—H stretch), 3113 w, 3072 w, 3057 wm, 2999 vw, 2974 ms, 2925 s (alkyl C—H stretch), 2910 s, 2888 ms, 2849 s, 2519 w, 2359 ms (B—H stretch), 2347 ms, 1928 w, 1845 w, 1617 s sh (ring distortion), 1583 s (amide I), 1480 s (amide II), 1458 s, 1373 w, 1352 w, 1286 wm, 1258 m, 1211 m sh, 1161 ms sh, 1130 s, 1092 s, 1073 wm, 1052 wm sh, 1023 m, 964 w sh, 911 m sh, 899 s sh, 782 ms, 714 w, 697 m sh, 649 ms sh, 584 wm sh, 486 s sh, 322 vw cm^{-1}; HRMS (CI$^+$, NH$_3$) 207.1654 (M^+ + H; calcd for $C_{11}H_{20}N_2O^{11}B$, 207.1639). Anal. Found (calcd for $C_{11}H_{19}BN_2O$): C, 64.22 (64.11); H, 9.22 (9.29).

Results and Discussion

Preparation of Amine–Alkyl(ethylnitrilio)boranes. In our previous report concerning the synthesis and crystal structure of quinuclidine–benzyl(*N*-ethylcarbamoyl)borane (**3c**) (see Table I for numbering), the full characterization of the first amine–alkyl(ethylnitrilio)borane was discussed briefly.[14] Quinuclidine–benzyl(ethylnitrilio)borane tetrafluoroborate (**3b**) was more recently shown to be stable to air and to neutral water at room temperature for an extended period. Other nitrilium salts also proved to display similar stability at room temperature in contrast to materials isolated containing the $-BH_2-$ moiety.[2]

The amine–alkylnitrilium salts were first prepared by heating the amine–alkylcyanoboranes to reflux in CH_2Cl_2 with an excess of Et_3OBF_4.[1,2] Conversion was complete as determined by ^{11}B NMR and IR spectroscopies, but the harsh conditions produced varying degrees of decomposition. In contrast, Dallacker and co-workers, in preparing ^{10}B-enriched isotopomers of $Me_3N{\cdot}BH_2COOH$, formed $[Me_3N{\cdot}BH_2CNEt]BF_4$ in 91% yield by slow crystallization at room temperature over a period of 2 days. The nitrilium salt was obtained as an impure product that was not fully characterized.[2k]

Reaction times with Et_3OBF_4 tended to be shorter for the B-alkylated cyanoboranes than for the $-BH_2-$ containing cyanoboranes, regardless of concentration, probably due to electron donation to the boron center by the alkyl group. The borane center, in turn, would donate some electron density to the cyano moiety, rendering it more susceptible to electrophilic attack. Because of this, reactions were typically complete in less than 24 h; longer periods of time resulted in significantly reduced yields. This, along with some ^{11}B NMR spectroscopic evidence, indicated that some attack also occurred at the boron center, making it imperative that the salts be separated from the excess oxonium salt as soon as evidence of complete reaction could be seen by infrared analysis of reaction oils.

In one case, as the reaction proceeded, crystals of **3b** started to form in 2 h. After 1 day, the crystals were washed with a small amount of water and dried under vacuum. In the other cases, clear solutions remained at the end of 24 h even though infrared analysis of the solutions indicated complete conversion of the cyanoboranes to the nitrilium salts.

All three isolated pyridine–nitrilium salts were oils regardless of spectroscopic purity. In contrast, the quinuclidine adducts were

(14) Mills, W. J.; Todd, L. J.; Huffman, J. C. *J. Chem. Soc., Chem. Commun.* **1989**, 900.

solids. Only in the case of **4b** was there any evidence of decomposition of the purified salt at room temperature to some presently unknown type of boron intermediate and free ethyl isocyanide, as evidenced by both rapid darkening of the concentrated product at room temperature and a very strong isonitrile odor; synthesis of this nitrilium salt proceeded nearly to completion in about 12 h at 0 °C, with little discoloration or isonitrile odor. All other nitrilium salts whether oils or solids were typically colorless or pale yellow. Extended storage of the solid quinuclidine salts in screw-capped vials at room temperature revealed no evidence of either reaction or decomposition for up to several months. Upon passage of about a year, some decomposition could be detected by ^{11}B NMR for **5b** stored at room temperature. Other samples of the same salts stored in a freezer for a year showed no evidence of decomposition by ^{11}B NMR. Those salts isolated as pure solids exhibit sharp melting ranges with no sign of decomposition.

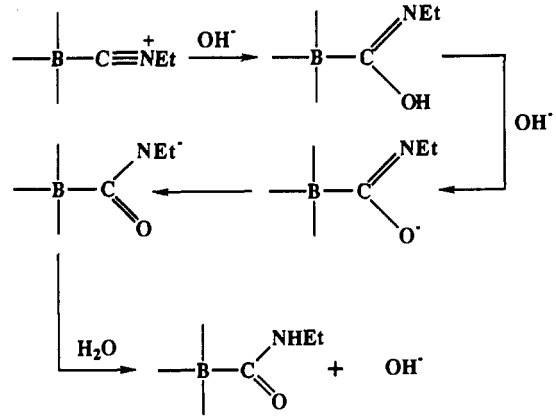
The hydrolytic stability of the isolated nitrilium salts, even **4b**, was quite marked. Due to strong electron donation by the amine–alkylborane moiety, the nitrilium group proved to be relatively inert to neutral water. This stability is in sharp contrast to carbon-bound nitrilium salts, which hydrolyze to amides very readily when exposed to water. Exposure to neutral water at room temperature resulted mostly in complete decomposition of the pyridine adducts to the alkylboronic acid over approximately 2 days, but extractive workup, if done within 30 min of exposure to water, resulted in isolation of apparently pure salts (by infrared and ^{11}B NMR analyses). Exposure of the sparingly soluble quinuclidine salts (**2b** and **5b**) to water over a period of a month at room temperature resulted in the formation of a mixture of carbamoylborane and an approximately equal amount of boronic acid.

Spectroscopic Considerations. NMR. Boron-11 spectra are very similar to the parent cyanoboranes, except that the borane resonance is broader and a BF_4^- resonance is visible at −0.6 to −1.8 ppm, as a sharp singlet. Proton NMR spectra of **2b** and **3b** revealed the presence of the C≡NEt group, in addition to the previously assigned quinuclidine and alkyl group resonances. The methylene is diastereotopic and its signal is somewhat second order in appearance near 4 ppm. The corresponding methyl group is a first-order triplet in both cases around 1.2–1.5 ppm. The carbon-13 NMR spectrum of **2b** revealed that the nitrilium carbon was at 121.8 ppm and that it was broad, similar to other isolated nitrilioboranes.[2] The attached methylene was at 40.9 ppm, and the diastereomerically split methyl resonance was observed at 13.5 and 13.4 ppm. When compared to the carbamoylboranes, it is clear that the ethyl group's electronic environment is much more electron poor, as expected, considering the positively charged nitrilium moiety.

Infrared. The nitrilium salts were clearly and unambiguously identified by their infrared spectra. The C≡N stretching frequency increases by 115–130 cm^{-1} when the cyano group is alkylated. The bis(nitrilium salt), $[TMED{\cdot}2BH_2CNEt][BF_4]_2$, was isolated and fully characterized by Györi.[15] This nitrilium salt had a C≡N– absorbance at 2311 cm^{-1}, which placed it in the middle of the range of our derivatives (2300–2320 cm^{-1}). In addition, Mittakanti and Morse[16] isolated $[py{\cdot}BH_2CNEt]^+BF_4^-$, which had an absorbance at 2314 cm^{-1}. This increase in stretching frequency is well-known for coordination complexes or organic nitriles with Lewis acids and for organic nitrilium salts.[17] For comparison, $[RCNEt]BF_4$ (R = Me, Ph) show increases of +155 and +130 cm^{-1}, respectively. Simple Lewis acid adducts typically display smaller changes, for example $RCN{\cdot}BF_3$ (R = Me, Ph; $\Delta\nu$ +111 cm^{-1}).[17] The absolute frequency of the nitriloboranes is comparable to the BCl_3 complexes of para-substituted benzonitriles (2313–2302 cm^{-1}).[18]

Also comparable to the observed nitrilium infrared bands were isonitriles and their complexes with Lewis acids. The infrared absorbances of the C≡N– moiety of methyl and isopropyl isocyanides are at 2142[19] and 2140 cm^{-1},[20] respectively. Regular borane adducts of isonitriles undergo hydroboration reactions, so they are not available for reference, but trialkylborane adducts are known and show the expected increase in wavenumber ($MeNC{\cdot}BMe_3$ and i-$PrNC{\cdot}BPh_3$, 2247 and 2265 cm^{-1}, respectively).[20,21]

Amine–Alkyl(*N*-ethylcarbamoyl)boranes. In general, the nitrilium salts are only sparingly soluble and relatively unreactive in distilled water. Consistent with the findings of others,[2] the nitrilium boranes were converted to (*N*-ethylcarbamoyl)boranes by aqueous base, probably involving the reaction sequence shown in the following equation.



Reaction of the nitrilium salts with NaOH in water to form the amides proceeds readily and is typically complete in 1–2 h. For pyridine–*sec*-butyl(ethylnitrilio)borane tetrafluoroborate (**1b**), 5 min was sufficient time to complete the conversion. Reaction times as long as 24 h have been used and in some cases lead to increased yield, but the results were not consistent. In the case of $[quin{\cdot}BH(Bzl)CNEt]BF_4$ (**3b**), gentle heating to 45 °C was used to shorten the hydrolysis time of this rather sterically hindered nitrilium salt to 2 h. Normally, such heating is not necessary and, for a less robust adduct, leads to decomposition.

The compounds are air and water stable to varying degrees, and are colorless solids when pure. The pyridine adducts tend to discolor over a period of several weeks when stored in screw-capped vials under air. Concurrent with the observed discoloration, ^{11}B NMR analysis revealed the gradual appearance of alkylboronic acids over time at room temperature, especially in the case of **4c**, whose ^{11}B NMR spectrum showed as much as 20% decomposition in a week's time in air-exposed samples stored at room temperature. The elemental analysis of **4c** was low in carbon, but a good chemical ionization high-resolution mass spectrum of this derivative was obtained. All pyridine adducts proved to be indefinitely stable when stored in sealed vials in a freezer (−15 °C), remaining spectroscopically pure for over a year for both **4c** and **1c**. In the case of **6c**, discoloration at room temperature has not yet been observed. A good elemental analysis was obtained from a sample that had been stored at room temperature in air for a month. The quinuclidine adducts are indefinitely stable at room temperature exposed to air. Samples of many of the amide derivatives when dissolved in water/ethanol (1:1) or water/MeCN (1:1) at pH 7 survived for over 1 month at room temperature without significant decomposition, as indicated by ^{11}B NMR spectra. This solution stability was observed for the pyridine adducts **1c** and **6c** as well. Hydrolytic stability at pH 7 is critical for biological testing.

Strongly acidic conditions, traditionally the best conditions for amide hydrolysis, destroyed the carbamoylborane by preferential attack at the boron center.

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Spectroscopic Considerations. Infrared. Infrared analysis of the isolated carbamoylboranes proved interesting. Like organic secondary amides, amide I and amide II bands were visible at 1575–1595 and 1470–1500 cm^{-1}, respectively. However, these bands were located 30–40 cm^{-1} lower in energy than their organic counterparts (1640 and 1515 cm^{-1}, respectively, for typical secondary amides).[22] This is similar to the amide I bands of non-B-alkylated carbamoylboranes.[2] Fairly strong electron donation from the amine–borane moiety to the carbamoyl group is implicated by this data. The amides described so far are all solids, with melting points from 33 to 96 °C. Pyridine derivatives, which usually were liquid products as the cyanoboranes and the nitrilium salts, in contrast to the solid quinuclidine products, tended to have solid amide derivatives with melting points similar to the quinuclidine amides. Amide **2c** is also a solid a room temperature, but a precise melting point has not yet been determined.

NMR. Due to the presence of a stable asymmetric boron center in these amine–(alkylcarbamoyl)boranes, their NMR spectra have additional complications. There are multiple diastereotopic groups near the boron for each derivative. At least some of the centers display diastereotopic resonances for each carbamoylborane studied. These include methylene protons of both the alkyl side chain (isobutyl, *sec*-butyl, and benzyl), the *N*-ethyl group of all amides **1–6c**, and methyl group protons in the cases of isobutyl and isopropyl. The latter methyl groups also display resolved diastereotopic ^{13}C NMR signals. In addition, the *sec*-butyl group possesses an asymmetric center at the methyne carbon, so that two chiral centers exist side by side, resulting in two distinct pairs of diastereomers. These produce different ^{11}B NMR signals, which in the case of **2c** can be resolved in the broad-band proton-decoupled spectrum. Proton and ^{13}C NMR spectra also distinguish these diastereomers. For the quinuclidine adducts **2c**, **3c**, and **5c**, the $N[CH_2]_3$– methylene protons showed diastereotopic second-order signals, with large separations between the resonances for each proton. The most pronounced differences in chemical shift are due to those nuclei, proton and carbon, that are at least two bonds away from the asymmetric centers. Generally, the alkyl side-chain resonance chemical shifts are similar to normal organic compounds except for the protons bound to the carbon immediately adjacent to the boron. These are shifted about 1 ppm upfield from their purely organic counterparts.

Another characteristic of the spectra of the carbamoylboranes is the presence of broadened signals for atoms adjacent to the quadrupolar boron nucleus. Occasionally, if the boron-bound hydrogen is observed, it is detected as a low bulge at ca. 2.5 ppm, with normally no coupling to boron being observed, though in the case of **4c** a crude coupling constant of about 120 Hz could be determined. By ^{13}C NMR analysis, the carbon atoms directly bound to the boron are also relaxation broadened, especially the carbon of the carbonyl group. Therefore very concentrated samples (50–100 mg in 1 mL of $DCCl_3$) and, often, signal enhancement are needed to clearly detect and define them. The carbamoyl group's unique carbon B*C*(=O)NH– has a resonance at 195–197 ppm that is somewhat deshielded relative to the normal range of 160–175 ppm observed for purely organic amides.[22] The signals, due to their proximity to the ^{14}N and ^{11}B nuclei, are lower intensity and broader than those of the carbons bound only to boron.

In a few cases, three bond coupling of the protons bound to the adjacent carbon and boron nuclei is detected despite the broad signal (**1c** and **2c**). These constants are on the order of 7.3–7.4 Hz. In contrast, the methylene protons of the isobutyl derivatives are not broadened appreciably by the boron center, but instead show coupling to the boron-bound proton, with coupling constants of about 2–2.5 Hz.

Amide N*H* resonances are easily assigned in all derivatives due to their broadness and apparent singlet appearance at about 5.1–5.8 ppm. There is some evidence, based both on the signal shape of the N*H* signal, which occasionally resembles an unresolved triplet, and the complexity of the NCH_2– signals, that HNCH coupling is occurring and has a coupling constant of about 4 Hz. The diastereotopic amide methylene proton resonances have separate signals for each proton, are found in the range of 2.9–3.4 ppm, and have significant second-order multiplicity in all derivatives, possibly due to the above-mentioned coupling to N*H* as well as geminal coupling and coupling to the methyl group protons.

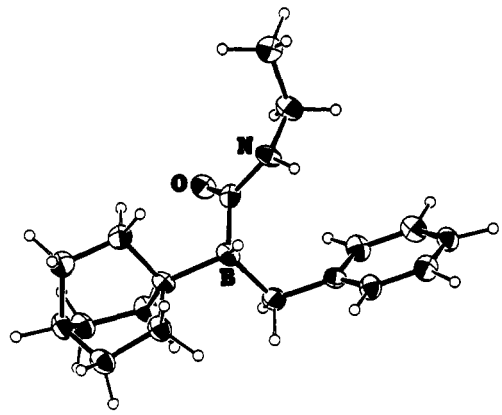

Figure 1. Crystal structure of quinuclidine–benzyl(*N*-ethylcarbamoyl)-borane.

In the case of *sec*-butyl-substituted carbamoylboranes (**1c** and **2c**), the presence of two chiral centers in the molecule, along with a diastereotopic methylene, and two very similar methyl groups makes unambiguous assignment of particular resonances to discrete protons difficult. However, the ^{13}C NMR signals, when compared with the literature,[22] can be assigned relatively easily. To assist in making proper proton resonance assignments, a two-dimensional $^1H/^{13}C$ correlation experiment for compound **2c** was conducted.[23] The result was complete assignment of all resonances for that derivative; results are given in the Experimental Section.

In the ^{11}B NMR spectra, rather significant changes from the parent amine–alkylcyanoboranes were apparent. The ^{11}B signals were broader and less resolved than the parent cyanoboranes, hence the apparent smaller coupling constants. This is attributed to slower tumbling of the bulkier molecules. Furthermore, the boron nucleus is deshielded, probably due to the strong electron withdrawal effects of the carbamoyl group. This results in an average 5 ppm downfield shift from the parent cyanoborane.

Structural Considerations. A single-crystal X-ray structure of **3c** was completed and was the subject of a previous publication.[14] The boron–amine bond is longer in **3c** [1.637 (9) Å] relative to that in $Me_3N{\cdot}BH_2COOH$ [1.589 (8) Å].[1] This is due to nonbonded interactions between the amine and the boron-bound alkyl group of **3c**. Similar sterically induced bond lengthening has recently been reported for $Me_2NH{\cdot}B(CH_3)_3$ [1.656 (4) Å].[24] The C=O distance of **3c** is a bit longer [1.261 (7) Å] than that of the phenylalanine carbonyl bond length in the tripeptide glycyl-phenylalanyl-glycine [1.23 (2) Å].[25] The structure of one of the enantiomers is shown in Figure 1.

Amine–Alkylcyanoboranes and An (*N*-Ethylcarbamoyl)borane Derivative Containing the Isopropyl Group. These analogues were developed in order to complete the series of the five hydrophobic side chain amino acids. As expected, the stability of the amine–boranes was comparable to the others previously synthesized.

Synthesis of the isopropyltrihydroborate proceeded well according to the Nöth[13] protocol, with only a moderate production of disproportionation products observed by ^{11}B NMR, when the modifications previously discussed[4] were employed in the synthesis from isopropyllithium and $Me_2S{\cdot}BH_3$. A white powdery solid was isolated, which was immediately dissolved in THF for the cya-

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nation step. A great amount of heat was given off, causing the THF to reflux during the time the solid isopropyltrihydroborate was dissolving, so slow addition of THF was necessary.

Cyanation went more quickly and at lower temperatures than for isobutyltrihydroborate, probably due to a stronger inductive effect of the secondary carbon of the isopropyl group. The method of at first using a deficiency reaction followed by adding the remainder of required $Hg(CN)_2$ to complete the reaction worked well. Advantage was taken of the apparent order of reactivity of hydroborates with $Hg(CN)_2$: $RBH_3^- > BH_4^- > RBH_2CN^- > BH_3CN^-$, allowing for complete conversion to the desired isopropylcyanodihydroborate, without either the dicyanation product or uncyanated i-$PrBH_3^-$ being present. A ^{11}B NMR spectrum taken of the amine-isopropylcyanoborane products (**6a** and **7a**) revealed that neither over- nor undercyanation had occurred on the isopropyltrihydroborate center and that the tetrahydroborate byproduct had been approximately half-cyanated to give BH_3CN^-.

The pyridine adduct **6a** was a liquid that solidified at approximately 10 °C. Since a small amount of isopropylboronic acid was present in **6a** (as indicated in the ^{11}B NMR spectrum), no elemental analysis was obtained. The carbamoylborane product formed from **6a** proved to have a good elemental analysis, showing that pyridine-isopropylcyanoborane had indeed been synthesized as an intermediate.

The other adduct was the quinuclidine-containing product **7a**. This proved to be a crystalline solid, and it was the first quinuclidine adduct that was directly isolated without the use of column chromatography. After recrystallization to a sandlike colorless crystalline solid that melted at 132-134 °C, a good elemental analysis indicated successful purification of this derivative. Work on the purification of **7c** continues.

Biological Activity. Samples of several of these new compounds have been submitted to Professor Iris Hall (School of Pharmacy, University of North Carolina, Chapel Hill, NC) for biological testing. Preliminary results indicate that these amine-alkylborane derivatives have similar hypolipidemic activity in general to that reported previously for the glycine boron analogues.[2c,26] Some of the new compounds were found to have antiinflammatory activity that was more effective than indomethacin. Of most significance was the antineoplastic activity of selected compounds in vitro with respect to certain murine and human cell lines. In certain cases the cytotoxicity (ED_{50} μg/mL) values were better than those of 5-fluorouracil. A full report of this pharmacological activity will be published in the near future.

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Registry No. **1a**, 124287-27-0; **1b**, 131236-93-6; **1c**, 131250-02-7; **2a**, 124287-29-2; **2b**, 131250-01-6; **2c**, 131237-00-8; **3a**, 124287-33-8; **3b**, 125844-06-6; **3c**, 125844-02-2; **4a**, 124287-30-5; **4b**, 131236-95-8; **4c**, 131237-01-9; **5a**, 124287-31-6; **5b**, 131236-97-0; **5c**, 131237-02-0; **6a**, 131236-90-3; **6b**, 131236-99-2; **6c**, 131237-03-1; **7a**, 131236-91-4; *i*-PrLi, 1888-75-1; $Me_2S{\cdot}BH_3$, 13292-87-0; Et_3OBF_4, 368-39-8; lithium isopropyltrihydroborate, 84280-38-6; lithium isopropylcyanodihydroborate, 131236-89-0; pyridine hydrochloride, 628-13-7; quinuclidine, 100-76-5.

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Conformational Effects of Ring Fusion and Heteroatom Substitution in Six-Membered Rings of Spirocyclic Oxyphosphoranes[1,2a]

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Spirocyclic oxyphosphoranes containing six-membered rings **1-5** were synthesized by oxidative addition of cyclic phosphites with phenanthrenequinone. Substituent variations in **1-5** allowed the examination of the conformational stability of the six-membered ring system. This ring in **4** was trans annelated with cyclopentane, established by X-ray analysis. The latter feature has relevance to c-AMP. A cis-fused phosphorinane derivative containing a furanose ligand **7** was also prepared. X-ray structures revealed trigonal-bipyramidal frameworks with the phosphorinane ring occupying apical-equatorial positions. The saturated six-membered ring was uniformly in a boat conformation. Despite considerable electronegativity and ring substituent effects, no diequatorial ring placement was evident. Variable-temperature ^1H NMR data indicated retention of solid-state structures in solution. Rapid pseudorotation is indicated for the various phosphoranes with the thio derivative **2** appearing more fluxional. Analogies with models for cyclic AMP action are discussed. Phosphorane **1** crystallizes in the orthorhombic space group $P2_12_12_1$ with a = 7.769 (2) Å, b = 10.191 (2) Å, c = 29.594 (5) Å, and Z = 4. The thiophosphorane **2** crystallizes in the orthorhombic space group $P2_12_12_1$ with a = 7.696 (1) Å, b = 10.441 (2) Å, c = 30.130 (6) Å, and Z = 4. The diaminophosphorane **3** crystallizes in the triclinic space group $P\bar{1}$ with a = 10.078 (3) Å, b = 10.133 (3) Å, c = 12.253 (3) Å, α = 101.60 (2)°, β = 92.81 (2)°, γ = 105.00 (2)°, and Z = 2. The fused-ring phosphorane **4** crystallizes in the monoclinic space group $P2_1/c$ with a = 15.147 (3) Å, b = 9.092 (2) Å, c = 18.089 (4) Å, β = 108.92°, and Z = 4. The final conventional unweighted residuals are 0.037 (**1**), 0.036 (**2**), 0.040 (**3**), and 0.040 (**4**).

Introduction

In recent studies on monocyclic and spirocyclic oxyphosphorane compounds,[2-5] we have found that the structures assumed trigonal-bipyramidal forms with the rings, which varied from five- to eight-membered, spanning apical-equatorial positions. For saturated six-membered rings, the preferred conformation is that of a boat with the axial atom at the prow of the boat and the opposing carbon atom at the stern. The latter observation agrees with model considerations presented earlier by Trippett,[6] from which he concluded that the boat conformation is the only one that allows the lone pair on the equatorial atom to be in the favored equatorial plane.

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