Synthesis of Quinuclidine–Benzyl(ethylcarbamoyl)borane: The First Boron Analogue of a Phenylalanine Derivative

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The title compound, the first non-glycine, boron analogue of an α-amino acid derivative, was prepared by base hydrolysis of the *N*-ethylnitrilium salt of quinuclidine–benzylcyanoborane which is formed by treatment of the readily available quinuclidine–benzylborane with I_2 and then sodium cyanide; the analogue has been fully characterized spectroscopically and by *X*-ray diffraction.

In 1976, Spielvogel reported the synthesis and characterization of $Me_3N{\cdot}BH_2$–CONHEt and $Me_3N{\cdot}BH_2$–CO_2H (**1**),[1] which are analogues of betaine (Me_3N^+–CH_2–CO_2^-), the *N*-methylated derivative of glycine (**2**), (H_3N^+–CH_2–CO_2^-). Over sixty related compounds have since been prepared,[2] which have attracted considerable interest owing to their biological activity. They display anti-neoplastic, anti-hypercholestremic, anti-hyperlipidemic, and anti-inflammatory properties in tests on laboratory animals.[2] All except $Me_2N(H){\cdot}B(Pr^i_2)CN$, prepared in very low yield,[2] have been derived from amine–dihydrocyanoboranes, possessing a central $-BH_2-$ moiety in place of the central methylene group of glycine (**2**).

We now report the preparation and characterization of Q·BH(Bzl)–CONHEt (**3**); the carboxyborane, Q·BH(Bzl)–CO_2H (**4**) has been detected spectroscopically. These compounds represent the first boron analogues of an α-amino acid derivative not related to glycine. The use of quinuclidine, a tied-back equivalent of triethylamine, was suggested by the work of Geanangel *et al.*[3] and was chosen to promote the formation of more easily purified solid derivatives.

The key precursors of the boron analogues are amine–cyanoboranes (*e.g.* $Me_3N{\cdot}BH_2CN$). In order to prepare non-glycine analogues, we attempted to synthesize mono-*B*-alkylated amine–cyanoboranes, hydrolysis of which was expected to give rise to derivatives of other amino acids depending on the choice of the alkyl group. We discovered that Q·BH(Bzl)CN (**5**) could indeed be converted to (**3**) and (**4**).

Cyanoborane (**5**) was obtained from Li(TMED)BH_3Bzl (**6**)[4] in three steps (Scheme 1). Successive treatment of (**6**) with ethereal HCl and quinuclidine in Et_2O[5] gave (**7**) (m.p.

$Me_3N{\cdot}BH_2{-}CO_2H$ (1) $H_3N^+{-}CH_2{-}CO_2^-$ (2)

Q·BH(Bzl)–CONHEt (3) Q·BH(Bzl)–CO_2H (4)

Li(TMED)BzlBH$_3$ (6) —a,b→ Q·BH$_2$Bzl (7) —c→ Q·BH(Bzl)I (8)

Q·BH(Bzl)CN (5) ←—d— Q·BH(Bzl)I (8)

Scheme 1. Synthesis of (**5**). *Reagents and conditions:* a, HCl·OEt$_2$; b, Q, Et$_2$O, reflux; c, I$_2$, C$_6$H$_6$, reflux, 15 min; d, NaCN, THF, room temp., 48 h.

TMED = tetramethylethylenediamine; Bzl = benzyl; Q (quinuclidine) = HC(CH$_2$CH$_2$)$_3$N.

133—135 °C)† which was converted to iodoborane (**8**) by reaction with I$_2$.[6] The crude iodoborane† was used immediately after isolation without purification.

A reported method[7] for the exchange of iodide in $Me_3N{\cdot}BH_2I$ by various anionic nucleophiles prompted us to treat (**8**) with NaCN in tetrahydrofuran (THF) at room temperature. Evaporation, CHCl$_3$ extraction of the residue, and recrystallization (CHCl$_3$/hexane) gave cyanoborane (**5**) (m.p. 128—130 °C)† in 20% yield [based on (**7**)].

Treatment of (**5**) with an excess of triethyloxonium tetrafluoroborate[8] according to the method of Dallacker *et al.*[2] afforded the nitrilium salt [Q·BH(Bzl)–CNEt]$^+$BF$_4^-$ (**9**), m.p. 152—154 °C (decomp.), in *ca.* 95% yield. To our knowledge, (**9**) is the first fully characterized nitrilium salt of its kind to be reported.† The solid (**9**) is not affected by moist air for short periods of time. It has been stored for up two weeks under dinitrogen without noticeable decomposition.

The nitrilium salt was treated with NaOH (1 equiv.) in acetonitrile/water (1 : 1, v : v) and gently heated overnight. Chloroform extraction yielded an oil whose i.r. spectrum included two carbonyl stretching bands (1660 and 1590 cm^{-1}) attributed to amide (**3**) and acid (**4**), respectively, and an amide II band (1470 cm^{-1}). These absorptions are consistent with those reported for the glycine analogues.[1,2] The proton decoupled ^{11}B n.m.r. spectrum of the oil indicated two compounds (δ −3.0, −4.3) and a small amount of benzylboronic acid. The oil was cooled with solid carbon dioxide and the resulting solid was recrystallized (CHCl$_3$/hexane) to give pure (**3**) [m.p. 76.5—78 °C, *ca.* 50% yield from (**5**)].†

Low temperature crystallization of amide (**3**) from CHCl$_3$/hexane produced crystals suitable for *X*-ray diffraction analysis, and the structure is shown in Figure 1.‡

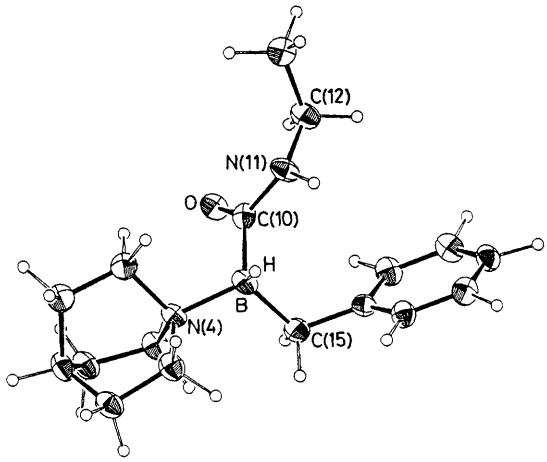

Figure 1. Crystal structure of (**3**)·2CHCl$_3$ (ORTEP, 50% probability ellipsoids). Selected bond lengths (Å) and angles (°); B–N(4) 1.637(9), B–H 1.09(5), B–C(10) 1.604(9), B–C(15) 1.622(9), C(10)–O 1.261(7), C(10)–N(11) 1.349(8), N(4)–B–C(15) 111.0(5), N(4)–B–C(10) 111.4(5), N(4)–B–H 103.6(27), B–C(10)–N(11) 116.0(5), B–C(10)–O 126.1(5), O–C(10)–N(11) 117.6(5), C(10)–N(11)–C(12) 125.0(5).

Structural data are not available for other amine–amidoboranes; this structure showed no unusual features. As expected, the boron–amine bond is longer than that in carboxy-borane (**1**) [1.589(8) Å][1] owing to non-bonded interactions between the amine and the boron-bound alkyl group. Similar sterically induced bond lengthening has recently been reported for $Me_2N(H){\cdot}BMe_3$ [1.656(4) Å],[9] which has the longest B–N bond known for an amine–borane. The C=O distance in (**3**) is similar to the phenyalanine carbonyl bond length in the natural polypeptide glycyl-phenyalanyl-glycine [1.23(2) Å].[10] Figure 1 shows a single enantiomer of the amide (**3**), but the centrosymmetric unit cell contains an (*R*) and an (*S*) molecule; no attempt has yet been made to resolve these isomers.

Work is continuing on the complete characterization of acid (**4**). Protracted reaction of the pure amide under the reaction conditions noted above does not produce the acid. This finding is consistent with the known inefficiency of base-

† (**7**): δ_B (115.8 MHz, THF, ref. Et$_2$O·BF$_3$) −3.21 (t, J_{BH} 81 Hz); ν_{max} (KBr) 2320s, 2280s, 2205m cm^{-1}.

(**8**): δ_B (CH$_2$Cl$_2$) −1.19 (d, *J* 128 Hz, 66 mole %); ν_{max} (KBr) 2780vs, 2740s, 2700s, 2650vs, 2590s cm^{-1}.

(**5**): δ_B (CD$_2$Cl$_2$) −8.61 (d, *J* 98 Hz); ν_{max} (KBr) 2390vs, 2180m cm^{-1}.

(**9**): δ_B (CD$_3$CN) −0.76 (s), −7.4 (d, *J* 100 Hz); δ_H (361.1 MHz, CD$_3$CN) 7.16 (m, ArH), 3.80 (br. m, C≡N–C*H*$_2$–), 3.13 (2nd order t, B·N–C*H*$_2$–), 2.06 [septet, *J* 3.3 Hz, (–CH$_2$)$_3$C*H*], 1.83 [m, (–C*H*$_2$)CH and B–C*H*$_2$], 1.24 (t, *J* 7.2 Hz, –CN–CH$_2$C*H*$_3$); μ_{max} (KBr pellet) 3400vbr. m, 3070m, 3040w, 3015m, 2950vs, 2875s, 2420s, 2310s, 1600m, 1485s, 1460s, 1280s, 1230vs, 1140—1000br. vs, 755s, 520m, 500m cm^{-1}; satisfactory elemental analyses.

(**3**): δ_B (CDCl$_3$) −2.92 (br. d, *J* 65 Hz); δ_H (CD$_3$COCD$_3$) 7.02 (m, *J* 7.02 Hz, 4H, ArH), 6.90 (t, *J* 6.84 Hz, 1H, ArH), 5.53 (br., –N*H*–, 1H), 3.42 [m, 3H, diastereotopic B·N(C*H*$_2$–)$_3$], 2.96 [complex m, 5H, diastereotopic B·N(C*H*$_2$–)$_3$ and –NH–C*H*$_2$–], 1.94 [m, *J* 3.25 Hz, 1H, (–CH$_2$)$_3$C*H*], 1.92 and 1.99 (each br. d, *J* 2.81, 3.22 Hz respectively, 2H, diastereotopic B–C*H*$_2$–), B*H* detected by integration (1H) but obscured by peaks from 1.9–1.6, 1.75 [dt, *J* 3.11, 7.93 Hz, 6H, (–C*H*$_2$)$_3$CH], 0.79 (t, *J* 7.26 Hz, 3H, NH–CH$_2$C*H*$_3$]; δ_C (75.4 MHz, CDCl$_3$) 195 (vbr.), 146.5, 128.5, 127.4, 122.8, 49.9, 31.7, 27.0 (br.), 24.6, 20.4, 15.0; ν_{max} (KBr pellet) 3460m, 3430m, 3065w, 3045m, 3015m, 2960s, 2920s, 2870s, 2820m, 2340sh, 2320m, 1590vs, 1470vs, 1455s, 1445s, 1215s, 1205s, 1085s, 1035s, 840s, 840m, 810m, 690m, 490m, cm^{-1}; *m/z* (relative intensity, electron impact, 35 eV): 286 (*M*$^+$, 1), 214(18), 167(6), 147(22), 132(4), 111(94), 96(38), 91(25), 82(100), 69(21); *m/z* 286.2224. $C_{17}H_{27}{}^{11}BN_2O$ requires 286.2220; satisfactory elemental analyses except for C (found 70.3, calc. 71.3%).

‡ *Crystal data* for (**3**): $C_{17}H_{27}BNO_2{\cdot}2CHCl_3$, *M* = 524.98, triclinic, space group $P\bar{1}$, *a* = 10.701(13), *b* = 13.329(18), *c* = 10.041(11) Å, α = 95.28(7), β = 116.85(6), γ = 98.64(7)°. *U* = 1242.32 Å^3, *Z* = 2, D_c = 1.403 g cm^{-3}, μ(Mo-K_α) = 0.71069 Å. Data were collected at −155 °C on a locally designed diffractometer. The structure was solved by a combination of direct methods (MULTANTS) and Fourier techniques. All hydrogen atoms were refined isotropically and non-hydrogen atoms anisotropically. *R* = 0.0648 for 3322 reflections measured to $2\theta_{max}$ = 45°. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

catalysed hydrolysis of normal organic amides.[11] However, as with normal amides, acid catalysis of the amido-borane is more effective. Room temperature reaction of amide (**3**) in water buffered at pH 3.0 gives *ca.* 25% conversion to the acid in 7 days. Longer times result in competing BH hydrolysis.

Professor I. H. Hall, University of North Carolina, Chapel Hill, is testing the biological properties of (**3**); preliminary results show that it has anti-hyperlipidemic and anti-tumour activity.

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