Proc. Indian natn. Sci. Acad. **55**, A, No. 2, 1989, pp. 229–242.

BORON ANALOGUES OF α-AMINO ACIDS, THEIR PRECURSORS AND RELATED COMPOUNDS

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(*Received 15 January 1988; Accepted 13 October 1988*)

Consideration of the isoelectronic nature of BH_2^- and CH_2 (or BH^- and CH) gives rise to the prediction of a novel class of organoboron compounds—the isoelectronic and isosteric boron analogues of α-amino acids of the general formula $R_3N.BH_2CO_2H$ (R = H, alkyl, aryl or mixtures thereof). The amine-carboxyboranes, as they are often referred to, may be considered as amine adducts of the BH_2CO_2H moiety which is unknown in the free state. A number of such compounds have been synthesized and characterized by various spectroscopic methods, and their acidity constants have been determined. Formation of amide bond between a boron amino acid and an amine may be considered as a preliminary step towards the formation of peptide bond between an amino acid and a boron analogue. Such reactions have been investigated with a representative amine-carboxyborane. Further reactivity has been studied by converting them to their esters.

Precursors to the amine-carboxyboranes, viz., the amine-cyanoboranes, and some related compounds have been synthesized. As phosphorus is an essential constituent of biological systems, we also synthesized a few phosphorus analogues of the amine-organoboron moieties, for their probable biological activity.

Present status of work in this area including some biological studies will be reviewed.

Key Words: Organoboron Compounds; Amine-carboxyboranes; α-Amino Acids; Amine-cyanoboranes; Biological Activity

INTRODUCTION

CONSIDERATION of the isoelectronic nature of BH_2^- and BH^- with CH_2 and CH respectively has led to the prediction and consequent synthesis of a novel class of organoboron compounds, $R_3N.BH_2CO_2H$ (R = H, alkyl or mixture thereof). These are termed boron analogues of dipolar forms of α-amino acids. Since boron has one less charge on its nucleus than carbon, the boron counterparts of the amino acids will be anionic and therefore most likely to exist in their protonated forms in the free state. Some simple boron analogues which may be envisioned are shown in Table I.

BORON ANALOGUES OF α-AMINO ACIDS

Soloway[1] advanced the concept of preparing boron containing antimetabolites or other carcinostatic agents for neutron capture therapy of neoplasm.[2] Consider-

TABLE I

Boron analogues of α-amino acids

	α-Amino Acids (dipolar form)	Boron Analogues
Glycine	$H_3\overset{+}{N}CH_2CO_2^-$	$H_3\overset{+-}{N}BH_2CO_2H$
Alanine	$H_3\overset{+}{N}CH(Me)CO_2^-$	$H_3\overset{+-}{N}BH(Me)CO_2H$
Sarcosine	$Me\overset{+}{N}H_2CH_2CO_2^-$	$Me\overset{+}{N}H_2\overset{-}{B}H_2CO_2H$
Betaine	$Me_3\overset{+}{N}CH_2CO_2^-$	$Me_3\overset{+-}{N}BH_2CO_2H$

ing the enormous biological activity of α-amino acids, it was thought that the corresponding boron analogues were likely to show some biological activity, in particular antitumour activity. Thus, direct inhibition of tumour growth by the boron compound could be coupled with possible selective incorporation of the compound into the neoplasm with concommitant use of neutron capture therapy. This concept has served to stimulate the synthesis of this special class of compounds.

Before 1976,[3] none of this type of compounds was known, although conceptually, they look very simple and the parent amine-boranes were known for some time.[4] There may be two approaches to the synthesis of the amine-carboxyboranes. In organic chemistry, glycine may be synthesized by the reaction of chloroacetic acid with ammonia (eq. 1). An alternative approach is the hydrolysis of an amino nitrile, as shown for glycine (eq. 2). Like glycine, in boron chemistry, we could consider the aminolysis of a halosubstituted boranocarbonate $XBH_2CO_2^{=}$ to give the boron analogue of glycine (eq. 3) or the hydrolysis of $H_3N.BH_2CN$ to give the same (eq. 4). The former method (eq. 3) which involves the aminolysis of halogenated boranocarbonate is not feasible because the synthesis of boranocarbonate and its halogenation would be expected to be quite difficult. Therefore, hydrolysis of the amino nitrile (eq. 4) may be the method of choice. However, this method

Amino acids

$$ClCH_2CO_2H \xrightarrow{NH_3} H_3\overset{+}{N}CH_2CO_2^- \quad \ldots(1)$$

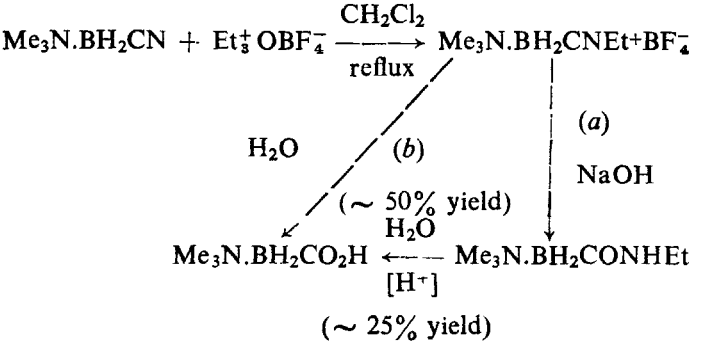
$$H_2NCH_2CN \xrightarrow{H_2O} H_3\overset{+}{N}CH_2CO_2^- \quad \ldots(2)$$

Boron Analogues

$$XBH_2\overset{\|}{C}O_2 \xrightarrow{NH_3} H_3N.BH_2CO_2^- \quad \ldots(3)$$

$$H_3N.BH_2CN \xrightarrow{H_2O} H_3N.BH_2CO_2H \quad \ldots(4)$$

is also not feasible, contrary to that found in organic chemistry, because the cyano compounds are converted to boric acid or borate salts in attempted direct hydrolysis by acid or base.[3] Hydrolysis of the amine-cyanoboranes has been possible by a different route (Scheme 1).[3,5] $Me_3N.BH_2CO_2H$ is the boron analogue



SCHEME 1

of betaine, N,N,N-trimethylglycine and was the first boron analogue to be synthesized.[3] By the above procedure, some amine-carboxyboranes, such as $O(CH_2CH_2)_2NMe.BH_2CO_2H$, $(CH_2NMe_2)_2.2(BH_2CO_2H)$ and $C_5H_5N.BH_2COH$ have been prepared.[6]

It has been observed that any amine having a hydrogen on nitrogen cannot be converted to their carboxyborane adducts even by the above procedure. For example, to date no aniline-carboxyborane or ethylenediamine-carboxyborane has been prepared. The B=H bonds are hydrolysed on attempted conversion of their cyanoborane adducts to the corresponding carboxyborane adducts.[7] It was found that $H_3N.BH_2CN$ can be obtained in ~ 20 per cent yield by amine exchange from $Me_3N.BH_2ON$ and liquid NH_3 under pressure.[8] Subsequently, it was found to be a very suitable method of preparation for a number of carboxyboranes (eq. 5).

$$Me_3N.BH_2CO_2H + R_3N \rightarrow R_3N.BH_2CO_2H + Me_3N \qquad ...(5)$$

The amine exchange reactions have been utilized for the synthesis of $H_3N.BH_2CO_2H$, the boron analogue of glycine[8] and a few others (Table II).[9,10] The amine exchange reactions have been carried out either by refluxing $Me_3N.BH_2CO_2H$ with the corresponding amines (*1–4*)[9] or under pressure in sealed tubes (*5–8*).[10] All the eight amine-carboxyboranes (*1–8*) prepared in our laboratory have been found to be dimers like $Me_3N.BH_2CO_2H$[3] or $H_3N.BH_2CO_2H$.[8] They have been characterized by UV, IR and ^1H, ^{13}C, ^{11}B and ^{14}N NMR spectra. Important characteristics are given in Table II. Some interesting features found in the spectra of isopropylamine-carboxyborane (*5*) and diisopropylamine-carboxyborane (*6*) need special mention. In the ^1H NMR spectra, two separate signals were observed at δ 3.15 and 3.50 as quartets for the CH

TABLE II

Some spectroscopic data of amine-carboxyboranes, $R_{3-n}H_nN.BH_2CO_2H$ (boron analogues of α-amino acids)

Compd	$R_{3-n}H_nN.BH_2CO_2H^{a,b}$ ($R_{3-n}H_nN$=)	mp (°C)	IR data (cm^{-1})			NMR data (δ)[c]			
			ν(NH)	ν(BH)	ν(CO)	^{11}B (J_{B-H},Hz)	^{13}C		^{14}N
1	Et_2NH	82	3200	2400 2360	1638	−15.0(t) (96)	11.19 47.55 204	(CH_3) (CH_2) (CO_2H)	−334
2	*n*-$PrNH_2$	90–92	3260 3240	2402 2362	1640	−17.5(t) (96)	10.81 22.30 48.84	(CH_3) (CH_3CH_2) (CH_2N)	−346
3	*n*-$BuNH_2$	88	3278 3240	2405–2345	1635	−17.6(t) (96)	13.46 19.66 31.01 46.87 201	(CH_3) (CH_3CH_2) (CH_2NCH_2) (NCH_2) (CO_2H)	−350
4	*s*-$BuNH_2$	74–75	3250 3220	2400 2362	1650	−18.6 (br)	9.68 18.26 28.56 54.26 202.2	(CH_3CH_2) (CH_3CH) (CH_3CH_2) (CHN) (CO_2H)	−330
5	*i*-$PrNH_2$	98	3280 3238	2365 2315	1650	−17.2(t) (96)	22.7 23.4 50.8 50.9	(CH_3) (CH)	−331.5
6	*i*-Pr_2NH	102–104	3198	2398 2320	1650	−18.8(t) (96)	18.56 20.10 51.34 51.96	(CH_3) (CH)	−289
7	*n*-Bu_2NH	78	3200	2400 2320	1640	−14.6 (br)	13.46 19.81 27.28 53.35 202.5	(CH_3) (CH_3CH_2) (CH_2CH_2) (CH_2N) (CO_2H)	−348
8	*i*-Bu_2NH	112	3240	2400 2385	1650	−14.2 (br)	19.6 24.2 61.7 203.7	(CH_3) (CH) (CH_2) (CO_2H)	−330

[$H_3N.BH_2CO_2H$,[8] $MeNH_2.BH_2CO_2H$,[21] $Me_2NH.BH_2CO_2H$[21] were prepared by amine exchange.]

[a] All are dimers in $CHCl_3$.

[b] UV absorptions in H_2O are in the range 192–223nm.

[c] ^1H NMR spectra conform to the formulae

proton in *5*, while for *6* only one multiplet was observed for the same. Also, the CH_3 protons in di-isopropyl-carboxyborane (*6*) appeared as a quartet, which was possibly due to two sets of magnetically non-equivalent doublets.

In the ^{13}C NMR spectra, two pairs of signals for CH (δ 50.8 and 50.9) and CH_3 (δ 22.7 and 23.4) were found for isopropylamine-carboxyborane (*5*), while for di-isopropylamine-carboxyborane (*6*), two pairs of signals at δ 51.34 and 51.96 and at δ 18.56 and 20.10 were again obtained for the respective carbon atoms. In the spectra of di-isobutylamine-carboxyborane no such splitting could be observed. The splitting in the ^1H and ^{13}C NMR spectra of isopropylamine- and di-isopropylamine-carboxyboranes may possibly be due to the prochiral centre at CH or to restricted rotation about the B-N bonds, caused by the presence of bulky isopropyl groups on nitrogen, or may arise because of monomer-dimer equilibria in solution. The δ_c absorptions of the BCO_2H unit were found at 201–204ppm (where they could be detected), and are rather broad signals because of relaxation, as this carbon is bonded to boron. The boron substituent would not therefore influence the shielding of the carboxy group to any significant extent.

The ^{11}B NMR spectra do not present any unusual characteristics. $Et_2NH.BH_2CO_2H$ (*1*), *n*-$PrNH_2.BH_2CO_2H$ (*2*), *n*-$BuNH_2.BH_2CO_2H$ (*3*), *i*-$PrNH_2.BH_2CO_2H$ (*5*), *i*-$Pr_2NH.BH_2CO_2H$ (*6*) exhibit 1:2:1 triplets at δ-15.0 to − 18.8 with $J(^{11}B - ^1H)$ 96 HZ, while the rest of the compounds exhibit broad signals at δ − 14.2 to − 18.6, all δ_B values being with reference to $BF_3.OEt_2$. The δ_B values for the amine-carboxyboranes resemble those of the $Me_3N.BH_2CN$ (δ_B − 14.9),[11] N-methylmorpholine-BH_2CN (δ_B − 15.3),[11] morpholine-BH_2CN (δ_B − 20.5)[11] or py-BH_2CN (δ_B − 16.8),[12] and the coupling constants to that of morpholine-BH_2CN.[11] No heteronuclear NMR data for $Me_3N.BH_2CO_2H$ or $H_3N.BH_2CO_2H$ or any other amine-carboxyborane have been reported before. Both δ_B and $J(^{11}B - ^1H)$ values imply that the CO_2H substituent is fairly electronegative.

The ^{14}N NMR spectra of the compounds show fairly broad resonances, no fine structure due to B-N coupling being observed. The δ_N values (− 289 to − 350ppm) correspond fully to tetracoordinate nitrogen. When compared to the corresponding borane adducts, the nitrogen atoms are less shielded by about 20–30 ppm.[11]

The IR spectra of the acids exhibit ν(N–H) and ν(B–H) frequencies in the regions 3280–3198 and 2405–2280cm^{-1} respectively, as one would expect for them. The ν(O–H) of the carboxy group occurs at 3158–2720cm^{-1}, somewhat lower than that for a free carboxy group, indicating dimerization through hydrogen bonding. Further support for this is obtained from the lowering of the $\nu_{(C=O)}$ frequencies which occur at 1650–1635cm^{-1}.[9,10]

The acid dissociation constants of the eight amine-carboxyboranes have been determined by *p*H titration method at ionic strength of 0.5M in KNO_3 solution. The calculations of the acid dissociation constants have been made based on Irving and Rossotti.[13] The results (*p*Ka values) are given in Table III. The

TABLE III

Acidity constants of amine-carboxyboranes $R_{3-n}H_nN.BH_2CO_2H$

Acid	*p*Ka	Acid	*p*Ka
$Et_2NH.BH_2CO_2H$ (*1*)	8.33	*n*-$Bu_2NH.BH_2CO_2H$ (7)	8.76
n-$PrNH_2.BH_2CO_2H$ (*2*)	8.24	*i*-$Bu_2NH.BH_2CO_2H$ (8)	8.54
n-$BuNH_2.BH_2CO_2H$ (*3*)	8.61	$Me_3N.BH_2CO_2H$	8.38[a]
s-$BuNH_2.BH_2CO_2H$ (*4*)	8.31	$Me_2NH.BH_2CO_2H$	8.14[a]
i-$PrNH_2.BH_2CO_2H$ (*5*)	8.26	$MeNH_2.BH_2CO_2H$	8.23[a]
i-$Pr_2NH.BH_2CO_2H$ (*6*)	8.62	$H_3N.BH_2CO_2H$	8.33[a]

[a]Reference 14

acids have an average *p*Ka value of 8.46, which is in good agreement with the *p*Ka values for $H_3N.BH_2CO_2H$ (8.33), $MeNH_2.BH_2CO_2H$ (8.23), $Me_2NH.BH_2CO_2H$ (8.14), $Me_3N.BH_2CO_2H$ (8.38) with an average *p*Ka of 8.33.[14] The acids studied by us and those reported before have been found to be much weaker than the N-methyl substituted glycines.[15]

The amine-carboxyboranes are stable in air and water permitting *p*H titrations in water, and can be recrystallized from water. They are however unstable in mineral acid medium with evolution of gases.

Formation of an amide bond between a boron-amino acid and an amine may be considered as a preliminary step towards the formation of a peptide bond between an amino acid and a boron analogue. The amide trimethylamine-(ethylcarbamoyl)borane, $Me_3N.BH_2CONHEt$ – the precursor in the synthesis of $Me_3N.BH_2CO_2H$, has been reported earlier and prepared according to the followinge equation (eq. 6).[3] The other amides, viz., $H_3N.BH_2CONHEt$. $MeNH_2.BH_2CONHEt$ and $Me_2NH.BH_2CONHEt$ were prepared by amine exchange from $Me_3N.BH_2CONHEt$.[16] Preparation of $Me_3N.BH_2CONHEt$ itself is a difficult procedure involving careful working up and high vacuum

$$Me_3N.BH_2CN \xrightarrow[CH_2Cl_2/\text{reflux}]{Et_3O^+BF_4^-} Me_3N.BH_2CNEt^+BF_4^- \xrightarrow{NaOH} Me_3N.BH_2CONHEt \qquad \ldots(6)$$

distillation.[3] Moreover, only N-ethyl-amides can be formed by this method. Considering the limitations of this preparative method resulting only to N-ethyl amides, and also in respect of time, reagents and yield, we have devised a simple method involving the direct reaction of an acid in the presence of N,N′-dicyclohexylcarbodiimide (DCCD), a peptide condensing agent (eq. 7).[10,17]

$$Me_3N.BH_2CO_2H + HN(R)R' \xrightarrow[CH_2Cl_2/r.t.]{DCCD} Me_3N.BH_2CON(R)R' \qquad \ldots(7)$$

(R = H, alkyl
R' = alkyl, aryl)

So far, we have prepared, by this method, several amides, of which complete characterization data are available for the N-aryl amides.[10] The amides are shown in Table IV. It is thus possible to synthesize both N-aryl and N-alkyl amides. As the reactions are carried out under non-rigorous conditions, Me_3N group is not exchanged. Presumably any other amine-carboxyborane can be converted to the desired amide. These reactions also exemplify the reactivity of the carboxy group.

TABLE IV

Trimethylamine-(organylcarbamoyl) boranes, $Me_3N.BH_2CON(R)\,R'$ (Acid amides)

$Me_3N.BH_2CON(R)R'$		m.p. (°C)	IR data (cm^{-1})			NMR data (δ)[a]	
R	*R*		ν(NH)	ν(BH)	ν(CO)	^{11}B (J_{B-H}, Hz)	^{14}N
H	C_6H_5	158–160	3320	2360	1622	—8.2 (br)	—341
H	4-MeC_6H_4	178–180	3320	2350	1620	—8.4(t) (89)	—350 —288
H	*i*-C_3H_7	*b*	3040	2380	1660	c	c
i-C_3H_7	*i*-C_3H_7	112–114	—	2360	1570	c	c
n-C_4H_9	*n*-C_4H_9	*b*	—	2380	1570	c	c
$Me_3N.BH_2CONHEt$[d]		*b*	3289	2330	1590	—7.4(t) (90)	—
$MeNH_2.BH_2CONHEt$[d]		*b*	3440	2365	1590	—11.55(t) (88)	—
$MeNH_3.BH_2CONHEt$[d]		99–100	3330	2380	1620	—15.37(t) (84)	—
$H_3N.BH_2CONHEt$[d]		125–126	3350	2340	1620	—15.59(t) (80)	—

[a] ^1H NMR spectra conform to the formulae
[b] Liquid at room temperature
[c] Not recorded.
[d] Reference[16]

Another example of reactivity is the conversion of the acids to their methyl esters (Scheme 2). Methyl esters prepared by this method are shown in Table V. Both the routes shown in Scheme 2 are satisfactory.

$$\begin{array}{ccc} Me_3N.BH_2CO_2H & \xrightarrow[DCCD]{+\,CH_3OH} & Me_3N.BH_2CO_2Me \\ \downarrow\ R_{3-n}H_nN & & \downarrow\ R_{3-n}H_nN \\ R_{3-n}H_nN.BH_2CO_2H & \xrightarrow[DCCD]{+\,CH_3OH} & R_{3-n}H_nN.BH_2CO_2Me \end{array}$$

SCHEME 2

TABLE V

Amine-carbomethoxyboranes, $R_{3-n}H_nN.BH_2CO_2Me$ (Methyl esters)

$R_{3-n}H_nN.BH_2CO_2Me$ ($R_{3-n}H_nN$ =)	m.p. (°C)	IR data (cm^{-1})			NMR data (δ)[b] ^{11}B (J_{B-H}, Hz)
		ν(NH)	ν(BH)	ν(CO)	
Et_2NH	a	3180	2395	1660	c
i-Pr_2NH	a	3160	2400 2360	1660	c
n-Bu_2NH	a	3180	2400 2380	1658	c
i-Bu_2NH	a	3160	2400 2380	1660	c
i-$PrNH_2$	76	3240 3160	2390 2300	1660	c
n-$PrNH_2$	a	3235 3145	2380 2300	1652	c
n-$BuNH_2$	a	3240 3158	2395 2290	1660	c
s-$BuNH_2$	a	3220 3130	2400 2300	1658	c
Me_3N[d]	90–92		2385	1660	— 9.09(t) (99)
Me_2NH[d]	52–53		2380	1660	—12.57(t) (95)
$MeNH_2$[d]	56–57		2400	1650	—16.22(t) (98)
NH_3[d]	92–93		2370	1660	—20.47(t) (94)

[a] Liquid at room temperature
[b] ^1H NMR spectra conform at the formulae
[c] Not recorded
[d] Reference[18]

Methyl esters of some amine-carboxyboranes have been obtained by amine exchange from $Me_3N.BH_2CO_2Me$.[18] Other esters have been prepared by direct reaction of $Me_3N.BH_2CO_2H$ with corresponding alcohol (eq. 8) or by its lithiation followed by reection with Me_3SiCl (eq. 9).[18]

$$Me_3N.BH_2CO_2H + ROH \xrightarrow[CH_2Cl_2]{DCCD} Me_3N.BH_2CO_2R \qquad ...(8)$$

(R = Me, Et, CH_2CH_2Cl)

$$Me_3N.BH_2CO_2H + n\text{-BuLi} \longrightarrow Me_3N.BH_2CO_2Li \xrightarrow{Me_3SiCl} Me_3N.BH_2CO_2SiMe_3 \qquad ...(9)$$

Recently, a method involving the reaction of amine-carboxyboranes and carbonochloridates (eq. 10) and claimed to be facile and convenient has been reported.[19] Some compounds prepared by this method are shown in Table VI.

TABLE VI

Few more esters, $Me_3N.BH_2CO_2R$[a]

$Me_3N.BH_2CO_2R$ (R =)	m.p. (°C)	IR data (cm^{-1})		NMR data (δ)[b] ^{11}B (J_{B-H}, Hz)
		ν(BH)	ν(CO)	
C_2H_5	45–47	2380	1660	—9.17(t) (99)
CH_2CH_2Cl	liquid	2400	1660	—9.42 (br)
CH_2CH_2Br	liquid	2400	1660	—9.51 (br)
$CH_2C_6H_5$	45–46	2380	1660	—9.73(t) (99)

[a]Reference 19

[b]^1H NMR spectra conform to the formulae

However, this method also suffers from side reaction producing symmetrical acid anhydrides and carbonates (eq. 10).

$$R^1-C(=O)-OH + ClC(=O)-OR^2 \xrightarrow[Et_3N,\ 0°C]{DMAP^*/CH_2Cl_2} R^1-C(=O)-OR^2 + R^1-C(=O)-O-C(=O)-R^1 + R^2O-C(=O)-OR^2 + CO_2 \quad ...(10)$$

*4-Dimethylaminopyridine as catalyst

($R^1 = Me_3N.BH_2$; $R^2 = CH_3$, C_2H_5, $CH_2C_6H_5$, C_6H_5, CH_2CH_2Cl, CH_2CH_2Br)

One important reason for the synthesis of the amides and esters is for the purpose of testing for biological activity.

PRECURSORS TO THE AMINE-CARBOXYBORANES

It has been seen before that $Me_3N.BH_2CO_2H$, the parent amine-carboxyborane for many syntheses, is prepared from trimethylamine-cyanoborane, $Me_3N.BH_2CN$.[3] Few other amine-carboxyboranes have been prepared from the corresponding amine-cyanoborane through route (*b*) of Scheme 1. Although most of the amine-carboxyboranes have been obtained from $Me_3N.BH_2CO_2H$ through amine

exchange,[8–10] the corresponding amine-cyanoboranes, nevertheless, can be regarded as their precursors. Suitable method of preparation of amine-cyanoboranes was not available for long time. Thus, on passing HCl gas into THF solution of $NaBH_3CN$, the polymeric $[BH_2CN]_x$ is formed in solution. Addition of bases such as trimethylamine gives amine-cyanoborane adducts.[20,21] But a more convenient general synthesis was developed by refluxing a mixture of amine hydrochloride and $NaBH_3CN$ in THF (eq. 11).[22,23]

$$NaBH_3CN + R_{3-n}H_nN.HCl \xrightarrow[\text{reflux}]{\text{THF}} R_{3-n}H_nN.BH_2CN + NaCl + \tfrac{1}{2}H_2 \quad \ldots(11)$$

The compounds prepared in our laboratory are shown in Table VII while those prepared elsewhere are mentioned at the bottom. All the compounds have been characterized by usual spectroscopic methods. We have recorded the ^{11}B NMR of the three pyridine-cyanoboranes. Their δ_B values (— 15.4 to — 20.7, vide Table VII) are in conformity with those of other pyridine-cyanoboranes.[12]

TABLE VII

Amine-cyanoboranes, $R_3N.BH_2CN$

$R_3N.BH_2CN$ (R_3N =)	m.p. (°C)	IR data (cm^{-1})			NMR data (δ)[a] ^{11}B (J_{B-H}, Hz)
		ν(NH)	ν(BH)	ν(CN)	
Et_2NH	*b*	3100	2320	2178	*c*
Et_3N	*b*	—	2330 2255	2175	*c*
n-$PrNH_2$	*b*	3140	2310	2175	*c*
i-$PrNH_2$	*b*	3140	2345	2180	*c*
i-Pr_2NH	107–108	3130	2300	2175	*c*
n-Pr_3N	*b*	—	2322 2260	2180	*c*
n-$BuNH_2$	*b*	3125	2360	2180	*c*
n-Bu_2NH	13.5	3100	2310	2182	*c*
i-Bu_2NH	128–130	3160	2450	2220	*c*
2-NH_2Py	104	3450 3360	2460 2420	2220	—20.7(t) (100)
4-NH_2Py	126	3440 3360	2440 2420	2220	—17.5(t) (100)
4-CNPy	134	—	2440 2320	2220 2190	—15.4 (br)

[Amine-BH_2CN, where amine = Me_3N, Me_2NH, $MeNH_2$, C_5H_5N, $PhNH_2$ and *p*-MeC_6H_4 = NH_2,[22] $O(CH_2CH_2)NMe$, $Me_2NCH_2CH_2CH_2CN$,[6] and diamine-2(BH_2CN) where diamine = $NH_2CH_2CH_2NH_2$, $Me_2NCH_2CH_2NMe_2$[6] have been known.

[a] ^1H NMR spectra conform to the formulae [b]Liquid [c]Not recorded

It has been shown by Martin *et al.*,[12] that on adding I_2 to a solution of $NaBH_3CN$ in THF or monoglyme, $[BH_2CN]_x$ is produced.[12] For those amines which form hydrochlorides only with difficulty or do not form hydrochlorides at all, the $[BH_2CN]_x$ produced *in-situ* may be allowed to react directly with them to produce amine-BH_2CN. This reaction has been utilized in an attempt to prepare 1,10-phenanthroline-2(BH_2CN) or 2, 2′-bipyridyl-2(BH_2CN) (eq. 12).

$$NaBH_3CN \xrightarrow[\text{THF or monoglyme}]{I_2} [BH_2CN]_x \xrightarrow{L-L} L-L.\ 2(BH_2CN) \qquad \ldots(12)$$

$L-L$ = 1,10-phen (m.p. 144 °C),
2,2′-bipy (m.p. 114 °C).

However, the ^{11}B NMR spectra of the products in both reactions exhibit the presence two boron moieties in approximately equal intensity, a triplet at $\delta \sim -27$ (J 91 Hb) and a quartet at $\delta \sim 43$ (J 92 Hb). These spectra are consistent with the presence of $[BH_3CNBH_2CN]^-$ moiety[24] and not BH_2CN moiety, indicating presumably the presence of such species as [1,10-phen H] $[BH_3CNBH_2CN]$ or [2,2′-bipy H] $[BH_3CNBH_2CN]$. Although it is not clear how the bases are protonated, the presence of $[BH_3CNBH_2CN]^-$ can be explained (eq. 13 and 14). However, further work is in progress in this regard.

$$[BH_3CN]^- + \tfrac{1}{2} I_2 \rightarrow [BH_2CN] + I^- + \tfrac{1}{2} H_2 \qquad \ldots(13)$$

$$[BH_3CN]^- + [BH_2CN] \rightarrow [BH_3CNBH_2CN]^- \qquad \ldots(14)$$

Phosphorus Analogues

A number of phosphorus analogues of the amine-cyanoboranes and carboxyboranes have been synthesized and characterized.[25,26] This has been achieved according to the following reaction (eq. 15) :—

$$NaBH_3CN \xrightarrow[\text{monoglyme}]{I_2} [BH_2CN_x] \xrightarrow{R_3P} R_3P.BH_2CN \qquad \ldots(15)$$

This method is specially suitable for those phosphines or phosphites which do not form hydrochlorides. The compounds synthesized are given in Table VIII. We have also been able to prepare two phosphine-carboxyboranes by the same general procedure[3,5] as for trimethylamine-carboxyborane (eq. 16), and are also given in Table VIII.

$$R_3P.BH_2CN \xrightarrow[CH_2Cl_2/\text{reflux}]{Et_3O^+BF_4^-} R_3P.BH_2CNEt^+BF_4^- \xrightarrow{H_2O} R_3P.BH_2CO_2H \qquad \ldots(16)$$

Biological Studies

A series of amine-carboxyboranes and their precursor amine-cyanoboranes, and related organoboron moieties have been reported to afford antineoplastic activity

TABLE VIII

Phosphine- and phosphite-cyanoboranes, $R_3P.BH_2CN$ and phosphine-carboxyboranes, $R_3P.BH_2CO_2H$.

$R_3P.BH_2CN$[a,b] (R_3P =)	IR data (cm^{-1}) ν(BH)	ν(CN)
$(n\text{-}C_4H_9)_3P$	2410 2350	2260
$(n\text{-}C_6H_{13})_3P$	2410 2350	2260
$(C_6H_{11})_3P$	2400 2360	2260
$(n\text{-}C_8H_{17})_3P$	2400 2330	2260
$(C_6H_5)_2(4\text{-}CH_3C_6H_4)P$	2400 2360	2260
$(C_2H_5O)_3P$	2410 2380	2260
$(n\text{-}C_4H_9O)_3P$	2410 2350	2250

Acid	m.p. (°C)	ν(BH)	ν(CO)
$(n\text{-}C_4H_9)_3$ $P.BH_2CO_2H$	78	2380	1635
$(n\text{-}C_8H_{17})_3$ $P.BH_2CO_2H$	38–40	2380	1640

[a] All are liquids at room temperature.

[b] ^1H NMR spectra conform to the formulae. ^{11}B NMR spectra not taken

TABLE IX

Summary of biological screens on rodents

Compd	LD_{50} mg/kg	%Inhibition: Erhlich Ascites Screen 20mg/kg/day	Anti-inflammatory Screen 10mg/kgX2	Antiarthritic Screen 2.5 mg/kg/day	Serum cholesterol Screen after 16 days (approx. value)
$Me_3N.BH_2CN$	70	98	58	96	28
$Me_2NH.BH_2CN$	39	81	51	75	28
$Me_3N.BH_2CONHEt$	320	69	37	36	42
$Me_3N.BH_2CO_2H$	1800	82	21	47	49
$[CH_2NMe_2.BH_2CN]_2$	200	68	5	23	27
$[CH_2NMe_2.BH_2CO_2H]_2$	> 1000	87	42	81	11
$[CH_2NMe_2.BH_2CONHEt]_2$	> 1000	94	35	76	10
$O(CH_2CH_2)_2NMe.BH_2CN$	23	100	9+	84	27
$C_5H_5N.BH_2CN$	25	65	17+	55	34
$C_5H_5N.BH_2CO_2H$	> 200	40	26+	56	29
$H_3N.BH_2CN$	30	45	49	68	15
$Me_3N.BH_2CO_2Et$	> 500	66	13	74	35
$NCCH_2CH_2NMe_2.BH_2CN$	140	89	26	87	24
$H_3N.BH_2CO_2H$	> 200	77	16	—	56
$MeNH_2.BH_2CO_2H$	> 1000	94	46	—	35
$Me_2NH.BH_2CO_2H$	> 200	95	9	—	37
$Me_2NH.B(CHMe_2)_2CN$	> 150	59	—	—	—
$(CH_2NH_2.BH_2CN)_2$	> 150	98	13	0	4

Most promising antineoplastic agents are : $MeNH_2.BH_2CO_2H$, $Me_2NH.BH_2CO_2H$ and $[CH_2NMe_2.BH_2CONHEt]_2$, and possibly $(CH_2NH_2.BH_2CN)_2$

+ ½ dose

against Ehrlich ascites carcinoma, Walker 256 carcinosarcoma, P-388 lymphocytic leukemia.[5,27] They have also been tested for hypolipidemic[23,29] and anti-inflammatory[30] activities, and have been found to possess encouraging results in a few cases. Table IX shows a summary of the biological screens of the novel compounds on rodents. From the acute toxicity studies in CF_1 male mice it would appear that those compounds with the best therapeutic index and which retain good antineoplastic activity are $MeNH_2.BH_2CO_2H$, $Me_2NH.BH_2CO_2H$, $[CH_2NMe_2.BH_2CONHEt]_2$ and possibly $[CH_2NH_2.BH_2CN]_2$.[27]

ACKNOWLEDGEMENT

The author gratefully acknowledges the support of this work by the Department of Science and Technology and the Council of Scientific and Industrial Research, Government of India. He also sincerely thanks Professors H Nöth and J H Morris for heteronuclear NMR data. The work was executed by coworkers of the author Dr P Mukherjee, Sri P K Maiti and Smt S Roy.

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