225. L-*o*-Carboranylalanine, a Boron Analogue of Phenylalanine

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Summary. The synthesis of a new, boron-containing analogue of phenylalanine is described. Carboranylalanine (Car) carries a 1,2-carborane cage in place of the benzene ring of phenylalanine. It is obtained by the reaction of derivatives of propargylglycine with decaborane. Possibilities of practical application derive from the facile neutron activation of boron nuclei with mass number 10.

o-Carborane ($1,2\text{-}C_2B_{10}H_{12}$) and its *C*-derivatives [2] display icosahedral geometry. The dimensions of the cage are only slightly larger than the space occupied by a benzene ring rotating about its C(1)–C(4) axis, and the two carbon atoms participate in the delocalized bonding. It thus appears that *o*-carboranylalanine (**1**; Car) would be sufficiently similar to phenylalanine in order to be an interesting analogue for probing the role of this amino acid in certain biologically active peptides. The likeness becomes apparent from the Figure.

The possible role of **1** as a probe becomes even more intriguing if one considers the interaction of boron with thermal neutrons, having $v \simeq 2{,}220$ m/s at 0.025 eV [3]:

$$^{10}_{5}B + ^{1}_{0}n \text{ (thermal)} \rightarrow \alpha + ^{7}_{3}Li \qquad \text{(a)}$$

$$^{10}_{5}B + ^{1}_{0}n \text{ (thermal)} \rightarrow ^{11}_{5}B \rightarrow \alpha + ^{7}_{3}Li \text{ (excited)} \rightarrow \gamma + ^{7}_{3}Li \qquad \text{(b)}$$

Reaction (a) constitutes ~7%, reaction (b) ~93% of the total number of disintegrations. The total energy is $Q = 2.794$ MeV. It is distributed as follows: $\alpha = 1.78$ MeV (a), 1.47 MeV (b), Li = 1.01 MeV (a), 0.84 MeV (b), and $\gamma = 0.48$ MeV. The ranges of the nuclei in biological materials are in the order of 5 μm [3].

Natural boron is composed of 18.45% ^{10}B and 81.55% ^{11}B; the former has a large capture cross section for thermal neutrons of 3,900 barns ($= 10^{-28}$ m^2). Very pure [^{10}B]-decaborane, the starting material for [^{10}B]-*o*-carboranylalanine, has been prepared in this laboratory (*E. Escher*). From the above data it would appear that *o*-carboranylalanine with – on the average – two or more ^{10}B nuclei would be an excellent molecule for producing ionizing radiation in biological materials.

Boron, introduced into certain parts of the animal or plant body, has been used for auto-radiographic purposes [3], and for the treatment of neoplastic diseases (cancer) [4]. *o*-Carboranylalanine, as a component of peptides such as peptide hormones, might offer an especially attractive means of transporting *via* the blood

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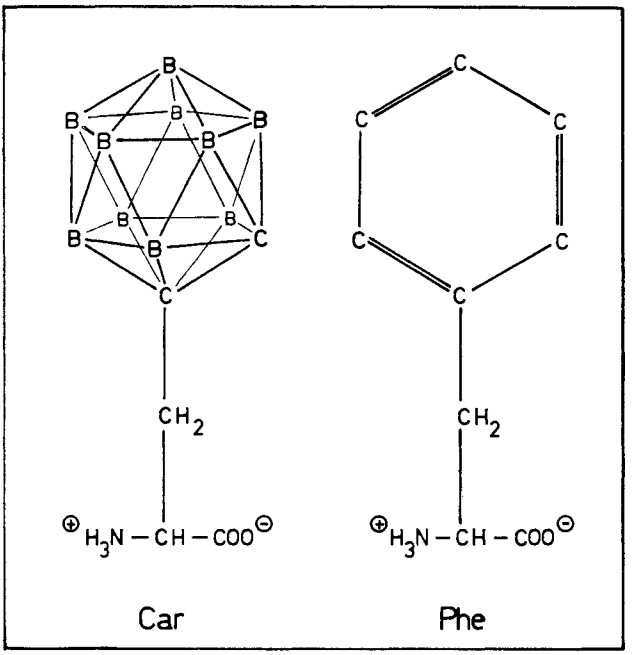
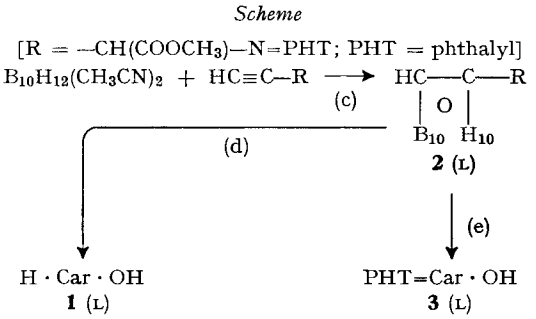


Fig. *Comparison of* o-*carboranylalanine* (*Car*) *and phenylalanine* (*Phe*) *structures.* The cage and ring atoms (B, C) carry one hydrogen atom each (not depicted)

stream rather high concentrations of boron to specifically defined areas (target cells and target organs).

Starting materials for the synthesis of **1** (*Scheme*) were the bis(acetonitrile)-decaborane complex [5], and L-phthalyl-propargylglycine methyl ester [6]:

Scheme



Condensation (c) was carried out according to the general procedure of *Heying* [7], and immediately and stereospecifically gave pure, crystalline **2** in a moderate yield (50–60%). Concentrated boiling HCl solution removed both protecting groups (reaction (d)); the free amino acid **1** was readily obtained, although in a small yield (22%). More diluted HCl-solution in acetic acid, according to the general procedure of *Sheehan et al.* [8], selectively hydrolysed the methoxycarbonyl group to give the *N*-phthalyl-L-amino-acid **3** (reaction (e)).

Whenever, instead of the phthalyl derivative, a derivative of propargylglycine containing an amide proton was used in step (c), the yields of Car derivatives became extremely poor, and it proved impossible to isolate a pure product (examples are condensations with Ac · Pra · OEt, Ac · Pra · OH, and BOC · Pra · OTSE [6]). Similar behaviour has been observed with acetylenic compounds bearing hydroxyl and carboxyl groups [2].

Other compounds described here include L-*N*-(*o*-carboxybenzoyl)-*o*-carboranylalanine, D,L-*N*-phthalyl-*o*-carboranylalanine *t*-butyl ester, and D,L-*N*-phthalyl-*o*-carboranylalanine *N*-hydroxysuccinimide ester.

Peptides containing L-*o*-carboranylalanine have been prepared, and shall be the subject of future communications.

Experimental Part

General comments, thin-layer chromatographic systems, and abbreviations: see [6]. Microanalyses of boron-containing compounds were carried out by *Alfred Bernhardt*, Mikroanalytisches Laboratorium (Prof. Dr. *H. Malissa* and *G. Reuter*), D–5251 Elbach über Engelskirchen (combustion with V_2O_5 for CH determinations).

L-N-*Phthalyl*-o-*carboranylalanine methyl ester* (**2**). 5 g (41 mmol) of decaborane were boiled for 4 h in 50 ml of acetonitrile. On cooling the bis(acetonitrile) complex of decaborane crystallized; it was gathered and washed with a small amount of acetonitrile and much diisopropyl ether: 7.16 g (86.5%), m.p. 165° (dec.), Rf 0.5 (E). A mixture of 1.02 g (5 mmol) of this complex, 690 mg (2.68 mmol) of L-*N*-phthalyl-propargylglycine methyl ester [6], and 50 ml of benzene was boiled for 3 h. The solvent was evaporated, the residue subjected to the usual extraction procedure (diisopropyl ether and water), and a coloration removed with charcoal before drying with $MgSO_4$. The product was crystallized from ethanol/water: 563 mg (56.5%), m.p. 145°, Rf 0.73 (E), 0.83 (A); $[\alpha]_D^{20} = -35.5°$ ($c = 1$, EtOH). – IR.: 2550 (B–H), 1735 (C=O, ester), 1770 and 1705 (C=O, phthalyl).

$C_{14}H_{21}B_{10}NO_4$	Calc.	C 45.00	H 5.67	B 28.45	N 3.75%
(373.64)	Found	,, 45.14	,, 5.61	,, 28.38	,, 3.79%

L-o-*Carboranylalanine* (**1**). 450 mg (1.21 mmol) of **2** were dissolved in glacial acetic acid; concentrated aqueous HCl-solution was added to just beginning turbidity, and the mixture boiled for 72 h. The solvent was evaporated and the residue treated with Amberlyst-15. The resin was washed with water, and the product eluted with 2N ammonia. After evaporation of the ammonia, the product was recrystallized from hot water: 60 mg (22%), m.p. 215–220° (dec.), Rf 0.63 (A), 0.77 (B), 0.08 (F), ninhydrin and *Reindel-Hoppe* positive; $[\alpha]_D^{20} = -21.0°$ ($c = 1$, water). – MS. (*m/e*): 231 (M^+), 186 ($M^+ -$ COOH).

$C_5H_{17}B_{10}NO_2$	Calc.	C 26.17	H 7.47	B 46.32	N 6.10%
(229.51)	Found	,, 26.02	,, 7.30	,, 46.13	,, 6.23%

L-N-*phthalyl*-o-*carboranylalanine* (**3**). 375 mg (1 mmol) of **2** were dissolved in 4 ml of glacial acetic acid/concentrated hydrochloric acid 2:1 (*v/v*) and boiled for 2 h. After evaporation of the solvent, the residue was dissolved in 15 ml of water containing 0.5 g of $KHCO_3$, filtered, and the filtrate evaporated to a volume of 4 ml. The product **3** was precipitated with concentrated HCl-solution and recrystallized from ethanol/water: 237 mg (65%), m.p. 175–180° (dec.), $[\alpha]_D^{20} = -43.2°$ ($c = 1$, EtOH), Rf 0.69 (A). – IR.: 2550 (B–H), 1705 and 1770 (C=O, phthalyl), no absorption at 1735 (C=O, methyl ester).

$C_{13}H_{19}B_{10}NO_4$ (359.53) Calc. C 43.43 H 5.31% Found C 43.40 H 5.35%

D,L-N-*Phthalyl*-o-*carboranylalanine N-hydroxy succinimide ester*. A sample of D,L-*N*-phthalyl-*o*-carboranylalanine (obtained from D,L-*N*-phthalyl-propargylglycine methyl ester [6]) was converted to the *N*-hydroxysuccinimide ester by the usual procedure [1]: fine needles from 2-propanol, m.p. 230° (dec.). – IR.: 2550 (B–H), 1820, 1770, 1740, 1720 (C=O, phthalyl and succinimide).

D,L-N-*Phthalyl-o-carboranylalanine t-butyl ester.* D,L-*N*-Phthalyl-propargylglycine *t*-butyl ester [6] was condensed with bis (acetonitril)-decaborane as described for **2**. The product crystallized from ethanol/H_2O: m.p. 179–180° (rhombohedral crystals), Rf 0.8 (E). – IR.: 2550 (B—H), 1770 and 1705 (C=O, phthalyl), 1730 (C=O, ester).

$C_{17}H_{27}B_{10}NO_4$	Calc.	C 49.12	H 6.55	B 25.57	N 3.37%
(415.72)	Found	,, 49.08	,, 6.39	,, 25.37	,, 3.50%

L-N-(o-*Carboxybenzoyl*)-o-*carboranylalanine.* 68 mg (0.18 mmol) of **2** were dissolved in 3 ml of EtOH, treated with 3.6 ml of 0.1 N KOH and kept for 18 h at 20°. The product was extracted by the usual procedure (ethyl acetate). Recrystallization from chloroform: 65 mg (95%), $[\alpha]_D^{30} = -32.1°$ ($c = 1$, EtOH), Rf 0.65 (A), 0.1 (F), ninhydrin negative, *Reindel-Hoppe* positive.

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226. Hormone-Receptor Interactions. Synthesis and Conformational Study of *cyclo*-L-Cystathionine[1])

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Summary. The purpose of this work was to see whether the replacement of a sulfur atom in a cystine disulfide bridge by a methylene group is an only superficial 'isosteric' substitution, *i.e.* with regard to size, hydrophobia, bond angles, *etc.*, or whether it would also encompass such parameters as preferred conformations in solution (*M*- or *P*-helicity of the bridge). The methods involved the synthesis of a model compound, *cyclo*-L-cystathionine (*cyclo*-L-carbacystine), and its investigation by ^{1}H- and ^{13}C-NMR. It is concluded that the conformations of the $CH_2(\beta)$—$CH_2(\gamma)$—S—$CH_2(\beta')$ bridge, and of the diketopiperazine ring are closely similar to the analogous elements in *cyclo*-L-cystine (DMSO as solvent). This knowledge might help to explain the fact that carba analogs of heterodetic-cyclic polypeptide hormones are often biologically very active.

1. Introduction. – It has been established that neither of the two conspicuous heteroatom groupings of amino-acid and peptide hormones – namely the intrachenar

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