ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 3, pp. 482–485. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © D.A. Rudakov, P.V. Kurman, E.A. Dikusar, T.D. Zvereva, V.I. Potkin, 2014, published in Zhurnal Obshchei Khimii, 2014, Vol. 84, No. 3, pp. 424–427.

Synthesis of Iodinated *meta*-Carboranecarboxylic Acids

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Received May 23, 2013

Abstract—A new method for introduction of one and two iodine atoms into the *meta*-carborane fragments containing carboxy groups at the core carbon atoms C^1/C^2 was developed. Reaction proceeded in acetic acid at heating in the presence of concentrated nitric and sulfuric acids.

DOI: 10.1134/S1070363214030128

Halogenated carboranes are of interest for the preparation of boron-containing compounds used in boron neutron capture therapy (BNCT) of cancer and radiodiagnosis [1–8], in the cross-coupling reactions as co-reactants [9, 10], as well as in processes for recycling of wastes of nuclear energy production by UNEX-technology [11–14]. The presence of carboxy groups in the carborane scaffold allows obtaining water-soluble salts [15, 16] and the presence of iodine atoms makes it possible to introduce ^{123}I and ^{125}I radioactive isotopes into the molecule structure for detecting the distribution of these compounds in the organism, which is extremely important for BNCT. Thus, the synthesis of iodinated carboranecarboxylic acids is an actual task.

Halogenated carbon-substituted *meta*-carboranes are known [17]. Most of these compounds are *C*-methyl derivatives of X_n-1-R^1-7-R^2-1,7-$C_2B_{10}H_{10-n}$ type (R^1 = Me, R^2 = H; R^1 = R^2 = Me; X = F, Cl, Br, I; n = 1–4). In a recently published monograph on carborane compounds [17] halogenated *meta*-carboranecarboxylic acids were not described.

In previous studies we have performed an introduction of iodine atoms into the *ortho*-carborane scaffold under oxidative substitution conditions [18]. First oxidative iodination and bromination has been used for halogenation of the corresponding *ortho*- and *meta*-carboranes [19] and of the *C*-phenyl substituted *ortho*-carboranes [20]. We presumed that this approach will be suitable for iodination of *meta*-carborane mono- and dicarboxylic acids of 1-COOH-7-R-1,7-$C_2B_{10}H_{10}$ type, where R = H (**I**), COOH (**II**). The method of oxidative iodination consists in the action of a mixture of concentrated sulfuric and nitric acids on a mixture of carborane and elemental iodine in acetic acid at 100°C.

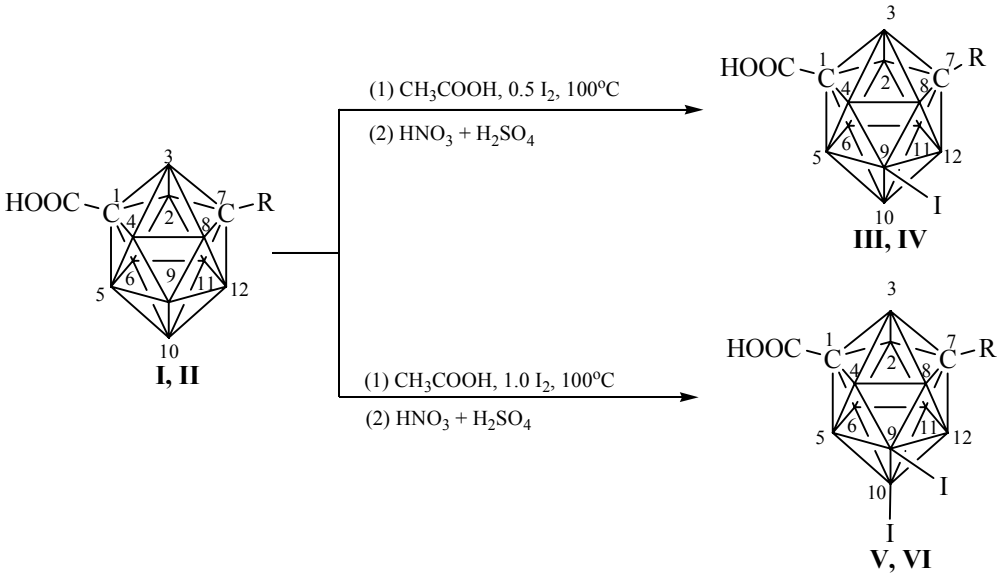
Varying the iodine amount, we obtained both the monoiodinated carboranecarboxylic acids 9-I-1-COOH-7-R-1,7-$C_2B_{10}H_8$ [R = H (**III**), COOH (**IV**)] and their diiodinated analogs 9,10-I_2-1-COOH-7-R-1,7-$C_2B_{10}H_8$ [R = H (**V**), COOH (**VI**)]. Corresponding monoiodinated acids **III** and **IV** were obtained in yields of 56–59% when using 0.5 equiv. of I_2. An increase in the iodine amount up to 1 equiv. resulted in diiodinated monocarboxylic **V** (67%) and dicarboxylic acids **VI** (20%). It should be noted that this approach is suitable for introduction of the iodine radioisotopes into the molecules (Scheme 1).

The structure of the compounds obtained **III**–**VI** was confirmed by IR, ^1H, ^{11}B, $^{11}B-\{^1H\}$, $^{11}B-^{11}B$ COSY spectroscopy and gas chromatography-mass spectrometry. The main characteristic bands in the IR spectra of **III**–**VI** are listed in Table 1.

The IR spectra of iodinated acids **III**–**VI** contained absorption bands at 1717–1731 and 806–820 cm^{-1} belonging to the carboxy and B–I moieties, respectively.

In the ^1H NMR spectra of **III**–**VI** the signal of COOH group is shifted upfield at going from mono- to diiodinated derivatives. Furthermore, in the case of monocarboxylic acids **III** and **IV** the signal of CH_{carb} group is shifted downfield (see Table 2). It can be assumed that increasing the amount of the iodine

Scheme 1.



R = H (**I, III, V**), COOH (**II, IV, VI**).

atoms in the molecule of carboranecarboxylic acid leads to a decrease in the acidity of carboxy groups and to increase in the acidity of CH_{carb} fragment. As expected, the acidity of dicarboxylic acids was higher than that of monocarboxylic.

Unlike the ^{11}B NMR spectra of dicarboxylic acids **V** and **VI**, the spectra of **III** and **IV** contained clearly resolved signals. Thus, in the ^{11}B NMR spectrum of 9-I-1-COOH-1,7-$C_2B_{10}H$ (**III**) there were ten signals, one of which was a broad singlet at 23.4 ppm corresponding to the B^9–I fragment, and other signals were doublets. The ^{11}B NMR of 9,10-I_2-1-COOH-1,7-$C_2B_{10}H_9$ (**IV**) contained the signals with a ratio of integral intensities of 1 : 1 : 2 : 2 : 2 : 2. The singlet with double integral intensity at –20.7 ppm belongs to the B^9–I and B^{10}–I groups, the remaining signals were doublets. A doublet at –2.7 ppm can be assigned to the B^{12} atom *para*-positioned relative to the C^1COOH fragment. The presence of a carboxy group in the carborane scaffold also causes a downfield shift of the signals of $B^{2,3}$ and $B^{4,6}$ atoms compared with the diiodo-substituted *meta*-carborane 9,10-I_2-1,7-$C_2B_{10}H_{10}$ containing no COOH fragment.

The ^{11}B NMR spectra of *meta*-carboranes **V** and **VI** contained singlet signals at –23.8 (B^9–I, **V**) and –20.9 ppm (B^9–I and B^{10}–I, **VI**).

In the mass spectra of iodinated *meta*-carborane-carboxylic acids there were peaks of the molecular ions with *m*/*z* 270 $[9\text{-I-1,7-}C_2B_{10}H_{11}]^+$ and *m*/*z* 396 $[9,10\text{-}I_2\text{-1,7-}C_2B_{10}H_{10}]^+$ formed via decarboxylation.

In sodium bicarbonate aqueous solution the iodinated carboranecarboxylic acids dissolved completely due to formation of sodium salts. It is essential

Table 1. Characteristic absorption bands (ν, cm^{-1}) in the IR spectra of **III–VI**

III	V	IV	VI	Assignment
2853–3061	2854–3091	2853–3105	2853–3096	ν(CH_{carb})
2612	2520–2649	2586–2653	2519–2643	ν(BH)
1717	1717	1731	1723	ν(COOH)
1414	1416	1390–1414	1407	δ(OH)
1280	1270	1225–1280	1270	ν(C–O)
809	810–824	806	810–820	δ(B–I)
702–738	721–741	686–730	706–726	δ(B–B)

Table 2. ^1H NMR spectral parameters of CH_{carb} and COOH fragments of carboranecarboxylic acids **III–VI**

Comp. no.	δ, ppm	
III	9.24 s (1H, COOH)	3.92 s (1H, CH_{carb})
IV	7.34 s (1H, COOH)	4.18 s (1H, CH_{carb})
V	10.28 s (1H, COOH), 10.18 s (1H, COOH)	–
VI	9.63 s (2H, COOH)	–

for creation of water-soluble carboranes and their further study as agents in boron neutron capture therapy of cancer and radiodiagnosis.

EXPERIMENTAL

IR spectra were recorded on a Fourier spectrophotometer Protege-460 from KBr pellets. ^{1}H NMR and ^{11}B spectra were registered on a Bruker AVANCE-500 spectrometer, internal reference TMS (^{1}H) or $Et_2O{\cdot}BF_3$ (^{11}B). Deuterated acetone was used as a solvent. GC-MS spectra were registered on an Agilent 6890N/5975Inert instrument equipped with a capillary column HP-5MS (30 m × 0.25 mm × 0.25 μm). Carrier gas helium (0.8 mL min^{-1}), the evaporator temperature 250°C, the ionization energy 70 eV, methylene chloride was used as the solvent.

Column chromatography was performed on silica gel Kieselgel (70–230 μ) eluting with a mixture hexane–methylene chloride (1 : 1).

Synthesis of 9-I-1-COOH-1,7-$C_2B_{10}H_{10}$ (III). A solution of 0.3 g (1.59 mmol) of *meta*-carborane-carboxylic acid **I** and 0.2 g (0.79 mmol) of iodine in 45 mL of acetic acid was heated to 100°C. Then a mixture of 15 mL of conc. nitric acid and 15 mL of conc. sulfuric acid was added dropwise within 25–30 min under vigorous stirring. Upon completion of the reaction, the resulting solution was poured onto ice and diluted with water to 300 mL. The reaction product was extracted with 100 mL of methylene chloride. The extract was washed with aqueous Na_2SO_3 and evaporated to dryness. The resulting oil was dried in a vacuum over $CaCl_2$ to yield 0.43 g of a mixture of 1-COOH-1,7-$C_2B_{10}H_{11}$ (5%), 9-I-1-COOH-1,7-$C_2B_{10}H_{10}$ (79%), 9,10-I_2-1-COOH-1,7-$C_2B_{10}H_9$ (11%). The products ratio was determined by GC-MS. The main reaction product **III** was isolated by column chromatography on silica gel. Yield 59 %. IR spectrum, ν, cm^{-1}: 3061 w, 2923 m, 2853 w, 2614 s, 1717 v.s, 1648 m, 1454 w, 1415 v.s, 1280 v.s, 1143 w, 1120 m, 1054 w, 1009 w, 985 w, 931 m, 903 m, 824 w, 809 s, 782 w, 738 m, 721 s, 702 m, 673 w, 629 m, 436 m. ^{1}H NMR spectrum, δ, ppm: 9.24 s (1H, COOH), 3.92 s (1H, CH_{carb}), 3.8–2.1 m (9H, BH). ^{11}B NMR spectrum, δ_B, ppm: –3.7 d (1B, B^5, *J* 168 Hz), –5.7 d (1B, B^{12}, *J* 162 Hz), –8.4 d (1B, B^{10}, *J* 166 Hz), –9.7 d (1B, B^4, *J* 202 Hz), –10.7 d (1B, B^6, *J* 126 Hz), –11.4 d (1B, B^8, *J* 173 Hz), –12.6 d (1B, B^{11}, *J* 181 Hz), –14.8 d (1B, B^3, *J* 186 Hz), –16.9 d (1B, B^2, *J* 189 Hz), –23.4 (1B, B^9).

9-Iodo-1,7-dicarboxy-1,7-dicarba-*closo*-dodecyl-caborane (IV) was prepared analogously from *meta*-carboranedicarboxylic acid **II**. Yield 56%. IR spectrum, ν, cm^{-1}: 3161 w, 2923 m, 2853 w, 2653 w, 2620 m, 2586 w, 1731 v.s, 1686 s, 1414 s, 1390 s, 1280 s, 1225 v.s, 1125 w, 1031 w, 991 w, 934 w, 898 m, 881 w, 847 w, 806 s, 730 m, 709 s, 686 s, 624 m, 429 s. ^{1}H NMR spectrum, δ, ppm: 10.28 s (1H, COOH), 10.18 s (1H, COOH), 5.0–2.0 m (9H, BH). ^{11}B NMR spectrum, δ_B, ppm: –4.5 (1B), –8.8 d (2B, *J* 160 Hz), –10.7 d (3B, *J* 135 Hz), –13.9 (2B), –15.6 (1B), –23.8 (1B, B^9).

Synthesis of 9,10-I_2-1-COOH-1,7-$C_2B_{10}H_9$ (V). A solution of 0.3 g (1.59 mmol) of *meta*-carborane-carboxylic acid **I** in 45 mL of acetic acid containing 0.4 g (1.59 mmol) of iodine was heated to 100°C. Then a mixture of 15 mL conc. nitric acid and 15 mL of conc. sulfuric acid was added dropwise within 25–30 min under vigorous stirring. Upon completion of the reaction, the resulting solution was poured onto ice and diluted with water to 300 mL. The reaction product was extracted with 100 mL of methylene chloride. The extract was washed with aqueous Na_2SO_3. The organic solution was evaporated, and the precipitate formed was filtered off, washed with water, and dried in a vacuum over $CaCl_2$ to yield 0.55 g of a mixture of 9,10-I_2-1-COOH-1,7-$C_2B_{10}H_9$ (86%) and 9-I-1-COOH-1,7-$C_2B_{10}H_{10}$ (11%). The products ratio was determined by GC-MS. The target product **V** was isolated by column chromatography on silica gel. Yield 67%. IR spectrum, ν, cm^{-1}: 3094 w, 3033 s, 2967 w, 2921 w, 2854 w, 2647 w, 2617 s, 2519 w, 1717 v.s, 1415 v.s, 1269 v.s, 1120 m, 1049 m, 985 m, 930 сл, 918 m, 906 m, 880 m, 836 m, 824 v.s, 811 v.s, 779 w, 741 m, 721 s, 706 w, 689 w, 674 w, 634 m, 613 w, 591 w, 485 w, 433 s. ^{1}H NMR spectrum, δ, ppm: 7.34 s (1H, COOH), 4.18 s (1H, CH_{carb}), 4.0–2.1 m (8H, BH). ^{11}B NMR spectrum, δ_B, ppm: –2.7 d (1B, B^{12}, *J* 174 Hz), –4.6 d (1B, B^5, *J* 173 Hz), –9.8 d (2B, B^{4,6}, *J* 179 Hz), –11.5 d (2B, B^{8,11}, *J* 175 Hz), –16.8 d (2B, B^{2,3}, *J* 190 Hz), –20.7 (2B, B^{9,10}).

9,10-Diiodo-1,7-dicarboxy-1,7-dicarba-*closo*-do-decaborane (VI) was prepared analogously from acid **II**. Yield 20%. IR spectrum, ν, cm^{-1}: 3373 w, 3094 w, 2956 w, 2923 m, 2853 m, 2643 m, 2620 m, 2518 w, 1724 v.s, 1407 s, 1268 s, 1137 w, 1021 w, 967 w, 920 m, 890 m, 869 m, 820 w, 810 m, 761 w, 727 m, 720 m, 706 m, 690 m, 624 m, 576 w, 524 w, 488 w, 436 s. ^{1}H NMR spectrum, δ, ppm: 9.63 s (2H, COOH), 5.0–0.0 m (8H, BH). ^{11}B NMR spectrum, δ_B, ppm: –3.6 d (2B,

$B^{5,12}$), –10.3 d (4B, $B^{4,6,8,11}$), –15.6 d (2B, $B^{2,3}$), –20.9 (2B, $B^{9,10}$).

ACKNOWLEDGMENTS

This work was financially supported by the Belarusian Republican Foundation for Fundamental Research (grant no. X12M -004).

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