ISSN 1070-3632, Russian Journal of General Chemistry, 2008, Vol. 78, No. 3, pp. 424–428. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © E.A. Dikusar, V.I. Potkin, T.D. Zvereva, D.A. Rudakov, A.P. Yuvchenko, M.P. Bey, 2008, published in Zhurnal Obshchei Khimii, 2008, Vol. 78, No. 3, pp. 440–443.

Esters of *o*- and *m*-Carborane-*C*-carboxylic Acids with *o*- and *m*-*C*-Carborane Alcohols

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Received July 6, 2007

Abstract–Acid chlorides of *o*- and *m*-carborane-*C*-carboxylic acids reacted with primary *o*- and *m*-*C*-carborane alcohols in anhydrous benzene to form previously unknown corresponding *o*- and *m*-carborane-containing two- and three-nuclear esters.

DOI: 10.1134/S1070363208030146

The derivatives of carborane polyhedral cluster systems are of interest for the pharmacokinetic studies in the field of the boron neutrone capturing therapy (BNCT) of tumor diseases, and of the radionuclide diagnostics and therapy [1]. We have reported previously on the synthesis of esters derived from *m*-C(7)-*iso*-propylcarborane-C(1)-carboxylic acid [2], *m*-carborane-C(1),C(7)-dicarboxylic acid [3], *o*-carborane-*C*-carboxylic acid [4–6], and the peroxide-containing esters of the carboranecarboxylic and carboranylacetic acids [7]. The boron content in these compounds usually does not exceed 15–30% that is not sufficient for the therapeutic concentration of boron in the target cells. This fact prevents their use in the BNCT [8].

The aim of this work was developing a preparative procedure for the synthesis of previously unknown *o*- and *m*-carborane-containing two- and three-nuclear esters with high boron content (up to 53–62%) suitable for further investigations as antitumor preparations. The esters **I-XIX** were obtained by the reaction of the corresponding *o*- and *m*-carborane-*C*-carboxylic acid chlorides with *o*- and *m*-*C*-carborane alcohols and diols in anhydrous benzene in the presence of pyridine. The reaction of acid chlorides with alcohols lead to the formation of binuclear carborane esters **I–VII, X–XVI**, and the analogous reaction with diols proceeded with the participation of both hydroxy groups to form the three-nuclear carborane systems **VIII, IX, XVII-XIX**. The stoichiometric reagent ratio [acid chloride–-alcohol-pyridine 1:1:1 for the compounds **I-VII, X-XVI**, and acid chloride–diol-pyridine 2:1:2 for the substances **VIII, IX, XVII-XIX**] was proved to be optimum. The yields of *o*- and *m*-carborane-containing two- and three-nuclear esters were 81–86%.

$$RC(O)Cl + R^1OH \xrightarrow{Py} RC(O)OR^1,$$
I–VII, X–XVI

$$RC(O)Cl + HOR^2OH \xrightarrow{Py} RC(O)OR^2O(O)CR,$$
VIII, IX, XVII–XIX

R = *o*-$HCB_{10}H_{10}C$ (**I–X**), *m*-$HCB_{10}H_{10}C$ (**XI–XIX**); R^1 = *o*-$HCB_{10}H_{10}CCH_2$ (**I, X**), *o*-$MeCB_{10}H_{10}CCH_2$ (**II, XI**), *o*-$Me_2CHCB_{10}H_{10}C(CH_2)_2$ (**III, XII**), *o*-CH_2= $CMeCB_{10}H_{10}C\cdot(CH_2)_2$ (**IV, XIII**), *m*-$HCB_{10}H_{10}CCH_2$ (**V**, **XIV**), *m*-$HCB_{10}H_{10}C(CH_2)_2$ (**VI, XV**), *m*-$Me_2CHCB_{10}H_{10}C(CH_2)_2$ (**VII, XVI**); R^2 = *o*-$CH_2CB_{10}H_{10}CCH_2$ (**VIII, XVII**), *m*-$CH_2CB_{10}H_{10}CCH_2$ (**IX, XVIII**), *m*-$(CH_2)_2CB_{10}H_{10}C(CH_2)_2$ (**XIX**).

The composition and structure of the esters obtained **I–XIX** was confirmed by the elemental analyses, the cryoscopic molecular weight evaluation (Table 1), and the IR, UV, and ^{1}H NMR spectral data (Table 2). According to the ^{1}H NMR spectroscopy the purity of the compounds obtained was 98 ±1%. Results of the elemental analysis and the molecular weight evaluation agree with the calculated values. Besides, for the compounds **I** and **V** the ^{11}B NMR spectra were

Table 1. Properties of *o*- and *m* -carborane-containing two- **I–VII, X–XVI** and three-nuclear **VIII, IX, XVII–XIX** esters

Comp. no.	Yield, %	T_m, °C	Found, %			Formula	Calculated, %			*M*	
			C	H	B		C	H	B	found	calculated
I	83	265, ignition	20.64	7.15	62.37	$C_6H_{24}B_{20}O_2$	20.92	7.02	62.77	338.4	344.5
II	86	240, ignition	23.65	7.39	59.94	$C_7H_{26}B_{20}O_2$	23.45	7.31	60.31	347.0	358.5
III	85	97–98	30.14	8.22	53.76	$C_{10}H_{32}B_{20}O_2$	29.98	8.05	53.98	387.7	400.6
IV	84	106–107	30.46	7.74	53.90	$C_{10}H_{30}B_{20}O_2$	30.13	7.59	54.25	385.1	398.6
V	83	222, ignition	20.77	7.16	62.53	$C_6H_{24}B_{20}O_2$	20.92	7.02	62.77	331.9	344.5
VI	84	146–147	23.82	7.45	60.08	$C_7H_{26}B_{20}O_2$	23.45	7.31	60.31	347.2	358.5
VII	86	30–31	30.14	8.19	53.67	$C_{10}H_{32}B_{20}O_2$	29.98	8.05	53.98	387.1	400.6
VIII	82	115–116	22.23	6.72	59.11	$C_{10}H_{36}B_{30}O_4$	22.05	6.66	59.54	529.7	544.7
IX	81	105–106	22.18	6.8	59.23	$C_{10}H_{36}B_{30}O_4$	22.05	6.66	59.54	528.3	544.7
X	86	260, ignition	21.23	7.19	62.50	$C_6H_{24}B_{20}O_2$	20.92	7.02	62.77	330.4	344.5
XI	85	250, ignition	23.58	7.45	60.03	$C_7H_{26}B_{20}O_2$	23.45	7.31	60.31	339.6	358.5
XII	85	113–114	30.30	8.19	53.71	$C_{10}H_{32}B_{20}O_2$	29.98	8.05	53.98	387.0	400.6
XIII	81	102–103	30.45	7.72	53.97	$C_{10}H_{30}B_{20}O_2$	30.13	7.59	54.25	390.8	398.6
XIV	84	228, ignition	21.20	7.18	62.54	$C_6H_{24}B_{20}O_2$	20.92	7.02	62.77	325.9	344.5
XV	86	142–143	23.63	7.48	59.97	$C_7H_{26}B_{20}O_2$	23.45	7.31	60.31	349.3	358.5
XVI	84	83–84	30.25	8.13	53.82	$C_{10}H_{32}B_{20}O_2$	29.98	8.05	53.98	381.7	400.6
XVII	83	53–54	22.28	6.79	59.21	$C_{10}H_{36}B_{30}O_4$	22.05	6.66	59.54	520.8	544.7
XVIII	83	63–64	22.36	6.70	59.38	$C_{10}H_{36}B_{30}O_4$	22.05	6.66	59.54	522.5	544.7
XIX	82	38–39	25.43	7.23	56.34	$C_{12}H_{40}B_{30}O_4$	25.16	7.04	56.63	553.2	572.8

Table 2. ^{1}H NMR, IR, and UV spectral data for the *o*- and *m*-carborane-containing two- **I–VII, X–XVI** and three-nuclear **VIII, IX, XVII–IX** esters

Comp. no.	^{1}H NMR spectrum, δ, ppm.	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (ε)
I[a]	–1.50–6.50 m (20H, 2 $B_{10}H_{10}$), 4.09 br..s (2H, 2$CH_{o\text{-Carbonate}}$), 4.67 s (2H, CH_2)	3065, 720 ($CH_{o\text{-Carbonate}}$); 2963, 2924, 2849 (CH_{Alk}); 2587 (BH); 1760 (C=O); 1275, 1178, 1013 (C–O)	201 (200), 251 (100)
II	–1.50–6.60 m (20H, 2 B_{1010}), 2.06 s (3H, Me), 4.07 br.s (1H, $CH_{o\text{-Carbonate}}$), 4.77 s (2H, CH_2)	3066, 727 ($CH_{o\text{-Carbonate}}$); 265, 2945, 2930, 2870, 2855 (CH_{Alk}); 2585 (BH); 1760 (C=O); 1271, 1175, 1011 (C–O)	08 (250), 255 (150)
III	–1.50–6.90 m (20H, 2 $B_{10}H_{10}$), 1.11 d (6H, Me_2C), 2.00–2.40 m (1H, CH), 2.35 t (2H, CH_2), 4.06 br.s (1H, $CH_{o\text{-Carbonate}}$), 4.15 t (2H, CH_2O)	3066, 728 ($CH_{o\text{-Carbonate}}$); 2988, 2971, 2940, 2929, 2899, 2883, 2852 (CH_{Alk}); 2585 (BH); 1760 (C=O); 1274, 1175, 1012 (C–O)	210 (250), 256 (150)
IV	–1.50–7.00 m (20H, 2 $B_{10}H_{10}$), 1.97 d (3H, Me), 2.43 t (2H, CH_2), 4.07 br. s (1H, $CH_{o\text{-Carbonate}}$), 4.34 t (2H, CH_2O), 5.54 d (1H, $H_\alpha C{=}C$), 5.61 s (1H, $H_\beta C{=}C$)	3075, 729, 716 ($CH_{o\text{-Carbonate}}$ and $=CH_2$), 2985, 2958, 2926, 2865, 2850 (CH_{Alk}); 2606, 2582 (BH); 1744 (C=O); 1631 (C=C); 1284, 1185, 1014 (C–O)	204 (4000)

Table 2. (Contd.)

Comp. no.	^{1}H NMR spectrum, δ, ppm	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (ε)
	–1.30–6.50 m (20H, 2 $B_{10}H_{10}$), 3.04 br.s (1H, $CH_{m\text{-Carbonate}}$), 4.08 br.s (1H,$CH_{o\text{-Carbonate}}$), 4.41 s (2H, CH_2)	3065, 729 ($CH_{o\text{-Carbonate}}$ и $CH_{m\text{-Carbonate}}$); 2965, 2924, 2900, 2842 (CH_{Alk}); 2599 (BH); 1755 (C=O); 1277, 1179, 1013 (C–O)	207 (250), 254 (150)
VI	–1.50–6.60 m (20H, 2 $B_{10}H_{10}$), 2.24 t (2H, CH_2), 3.01 br.s (1H, $CH_{m\text{-Carbonate}}$), 4.04 br.s (1H, $CH_{o\text{-Carbonate}}$), 4.20 t (2H, CH_2O)	3072, 728, 725 ($CH_{o\text{-Carbonate}}$ и $CH_{m\text{-Carbonate}}$); 2960, 2931, 2900, 2867, 2856 (CH_{Alk}); 2600 (BH); 1754 (C=O); 1280, 1180, 1015 (C–O)	208 (250), 254 (150)
VII	–1.50–6.70 m (20H, 2 $B_{10}H_{10}$), 1.09 d (6H, Me_2C), 2.00–2.40 m (1H, CH), 2.36 t (2H, CH_2), 4.02 br.s (1H, $CH_{o\text{-Carbonate}}$), 4.16 t (2H, CH_2O)	3074, 732, 726 ($CH_{o\text{-Carbonate}}$ и $CH_{m\text{-Carbonate}}$); 2973, 2941, 2900, 2878, 2855 (CH_{Alk}); 2599 (BH); 1751 (C=O); 1277, 1185, 1015 (C–O)	207 (250), 254 (150)
VIII	–1.50–7.10 m (30H, 3 $B_{10}H_{10}$), 4.08 br.s (2H, 2 $CH_{o\text{-Carbonate}}$), 4.70 s (4H, 2 CH_2)	3069, 728 ($CH_{o\text{-Carbonate}}$); 2961, 2925, 2848 (CH_{Alk}); 2586 (BH); 1759 (C=O); 1272, 1175, 1012 (C–O)	220 (300)
IX	–1.50–7.00 m (30H, 3 $B_{10}H_{10}$), 4.04 br.s (2H, 2 $CH_{o\text{-Carbonate}}$), 4.60 s (4H, 2 CH_2)	3069, 728 ($CH_{o\text{-Carbonate}}$); 2960, 2926, 2855 (CH_{Alk}); 2590 (BH); 1757 (C=O); 1275, 1175, 1012 (C–O)	222 (300)
X	–1.50–6.50 m (20H, 2 $B_{10}H_{10}$), 3.07 br.s (1H, $CH_{m\text{-Carbonate}}$), 3.75 br.s (1H, $CH_{o\text{-Carbonate}}$), 4.57 c (2H, CH_2)	3065, 3059, 723 ($CH_{o\text{-Carbonate}}$ и $CH_{m\text{-Carbonate}}$); 2967, 2921, 2859 (CH_{Alk}); 2601 (BH); 1754 (C=O); 1248, 1116, 1002 (C–O)	215 (150), 265 (50)
XI	–1.50–6.90 m (20H, 2 $B_{10}H_{10}$), 2.04 c (3H, Me), 3.07 br.s (1H, $CH_{m\text{-Carbonate}}$), 4.67 s (2H, CH_2)	3060, 727 ($CH_{m\text{-Carbonate}}$); 2970, 2960, 2924, 2875, 2850 (CH_{Alk}); 2599 (BH); 1756 (C=O); 1245, 1114, 1003 (C–O)	225 (200), 270 (100)
XII	–1.50–6.90 m (20H, 2 $B_{10}H_{10}$), 1.08 d (6H, Me_2C), 2.00–2.40 m (1H, CH), 2.30 t (2H, CH_2), 3.06 br.s (1H, $CH_{m\text{-Carbonate}}$), 4.15 t (2H, CH_2O)	3060, 728 ($CH_{m\text{-Carbonate}}$); 2988, 2971, 2940, 2929, 2899, 2883, 2852 (CH_{Alk}); 2598 (BH); 1756 (C=O); 1247, 1155, 1002 (C–O)	227 (200), 268 (150)
XIII	–1.50–7.10 m (20H, 2 $B_{10}H_{10}$), 1.96 d (3H, Me), 2.38 t (2H, CH_2), 3.05 br.s (1H, $CH_{m\text{-Carbonate}}$), 4.23 t (2H, CH_2O), 5.53 d (1H, $H_\alpha C{=}C$), 5.60 c (1H, $H_\beta C{=}C$)	3068, 729 ($CH_{m\text{-Carbonate}}$ and $=CH_2$), 2990, 2960, 2926, 2900, 2875, 2852 (CH_{Alk}); 2605, 2577 (BH); 1749 (C=O); 1635 (C=C); 1266, 1118, 1008 (C–O)	204 (4000)
XIV	–1.50–6.85 m (20H, 2 $B_{10}H_{10}$), 3.03 br.s (2H, $CH_{m\text{-Carbonate}}$), 4.30 c (2H, CH_2)	3062, 722 ($CH_{m\text{-Carbonate}}$); 2965, 2930, 2895, 2870, 2845 (CH_{Alk}); 2601 (BH); 1750 (C=O); 1256, 1117, 1070, 1023, 998 (C–O)	220 (150), 265 (50)
XV	–1.50–6.80 m (20H, 2 $B_{10}H_{10}$), 2.32 t (2H, CH_2), 3.03 br.s (2H, $CH_{m\text{-Carbonate}}$), 4.08 t (2H, CH_2O)	3063, 720 ($CH_{m\text{-Carbonate}}$); 2956, 2924, 2865, 2853 (CH_{Alk}); 2603 (BH); 1744 (C=O); 1273, 1070, 1025, 992 (C–O)	219 (150), 265 (50)

Table 2. (Contd.)

Comp. no.	^{1}H NMR spectrum, δ, ppm	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (ε)
XVI	–1.50–6.70 m (20H, 2 $B_{10}H_{10}$), 1.09 d (6H, Me_2C), 2.00–2.40 m (1H, CH), 2.28 t (2H, CH_2), 3.02 br.s (1H, $CH_{m\text{-Carbonate}}$), 4.15 t (2H, CH_2O)	3059, 734, 724 ($CH_{m\text{-Carbonate}}$); 2987, 2971, 2940, 2929, 2899, 2880, 2855 (CH_{Alk}); 2603 (BH); 1733 (C=O); 1273, 1065, 1025, 1004 (C–O)	225 (250), 270 (150)
XVII	–1.45–7.10 m (30H, 3 $B_{10}H_{10}$), 3.03 br.s (2H, $CH_{m\text{-Carbonate}}$), 4.69 s (4H, $2CH_2$)	3059, 728 ($CH_{m\text{-Carbonate}}$); 2958, 2933, 2900, 2878 (CH_{Alk}); 2611, 2571 (BH); 1735 (C=O); 1281, 1066, 1024, 1002 (C-O)	220 (300)
XVIII	–1.40–6.95 m (30H, 3 $B_{10}H_{10}$), 3.04 br.s (2H, $CH_{m\text{-Carbonate}}$), 4.69 s (4H, 2 CH_2)	3059, 727 ($CH_{m\text{-Carbonate}}$); 2959, 2933, 2920, 2897, 2872, 2840 (CH_{Alk}); 2610, 2573 (BH); 1735 (C=O); 1280, 1256, 1062, 1025, 1003 (C–O)	221 (350)
XIX	–1.40–7.00 m (30H, 3 $B_{10}H_{10}$), 2.31 t (4H, 2 CH_2), 3.01 br.s (2H, $CH_{m\text{-Carbonate}}$), 4.15 t (4H, 2 CH_2O)	3060, 728 ($CH_{m\text{-Carbonate}}$); 2962, 2933, 2874, 2840 (CH_{Alk}); 2608 (BH); 1745 (C=O); 1280, 1256, 1062, 1003 (C–O)	220 (300)

[a] ^{11}B NMR spectra, δ_B, ppm (J_{BH}, Hz): compound **I**: –1.2 d (2B, *J* 141), –1.8 d (1B, *J* 113), –3.3 d (1B, *J* 153), –8.2 d (2B, *J* 156), –8.3 d (2B, *J* 151), –11.1 d, –11.5 d (6B, *J* was not evaluated because of the overlapping of signals), –12.4 d, –12.8 d (6B, *J* was not evaluated because of the overlapping of signals); compound **V**: –1.9 d (2B, *J* 149), –4.0 d (1B, *J* 162), –7.8 d (1B, *J* 169), –8.2 d (2B, *J* 148), –9.9 d (2B, *J* 173), –11.3 d (6B, *J* 198), –12.7 d (4B, – 177), –15.3 d (2B, *J* 181).

taken that additionally confirmed the structure of the compounds obtained (Table 2). The structure of the ester **V** containing *o*- and *m*-carborane blocks in one molecule was confirmed by the signal at δ_B –15.3 ppm which is absent in the spectrum of the compound **I** containing only the *o*-carborane framework.

EXPERIMENTAL

The IR spectra were recorded on a Nicolet Protege-460 IR Fourier spectrometer from KBr pellets. The UV spectra were obtained on a Varian Cary-300 UV-Vis spectrophotometer from 1×10^{-4} M methanol solutions. The ^{1}H NMR spectra were taken on a Tesla BS-587A spectrometer (100 MHz) from 5% $CDCl_3$ solutions, internal reference TMS. The ^{11}B NMR spectra were taken on an AVANCE-500 instrument (160.4 MHz) in $CDCl_3$, internal reference $BF_3\cdot Et_2O$. Molercular weight of compounds under study was estimated by cryoscopy in benzene. The column chromatography was carried out on a L5/40 mm silica gel, elution with hexane.

The starting *o*- and *m*-carborane-*C*-carboxylic acids, acid chlorides, and *o*- and *m*-*C*-carborane alcohols were prepared according to [9].

***o*- and *m*-Carborane-containing two- and three--nuclear esters (I–XIX)** *(general procedure).* The corresponding *o*- or *m*-*C*-carborane alcohol, 5 mmol, was dissolved in 50 ml of anhydrous benzene. To the solution obtained 5 mmol of anhydrous pyridine was added, and then 5 mmol of *o*- or *m*-carborane-*C*-carboxylic acid chloride **I–VII, X–XVI** was added at 10ºC under shaking of the reaction mixture. For the synthesis of compounds **VIII, IX, XVII–XIX** 2.5 mmol of *o*- or *m*-*C*-carborane diol, 5 mmol of pyridine, and 5 mmol of acid chloride were taken. The reaction mixture was closed hermetically and left for 2–3 days at 20–23 ºC. The pyridine hydrochloride precipitate was filtered off, the filtrate was thoroughly washed with water and 5% sodium bicarbonate solution, and dried over calcium **c**hloride. The solvent was removed in a vacuum, and the residue was purified by column

chromatography on silica gel, elution with hexane. The product obtained was further purified by the low-temperature crystallization from 96% ethanol.

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