Synthesis of 5,10,15,20-tetra[3-(*o*- and *m*-carboranyl)butyl]porphyrins containing the C—B σ-bond

L. I. Zakharkin,[a] V. A. Ol'shevskaya,[a] R. P. Evstigneeva,[b] V. N. Luzgina,[b] L. E. Vinogradova,[a] and P. V. Petrovskii[a]*

[a]A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 117813 Moscow, Russian Federation. Fax: +7 (095) 135 5085

[b]M. V. Lomonosov Moscow State Academy of Fine Chemical Technology, 86 prosp. Vernadskogo, 117571 Moscow, Russian Federation. Fax: +7 (095) 430 7983

5,10,15,20-Tetra[3-(*o*- and *m*-carboranyl)butyl]porphyrins containing carborane groups bonded to alkyl substituents of the porphyrin cycle by the C—B σ-bond were obtained by condensation of 4-(*o*- and *m*-carboran-9-yl)pentanals with pyrrole.

Key words: pyrrole, 4-(*o*- and *m*-carboran-9-yl)pentanals, condensation, porphyrins.

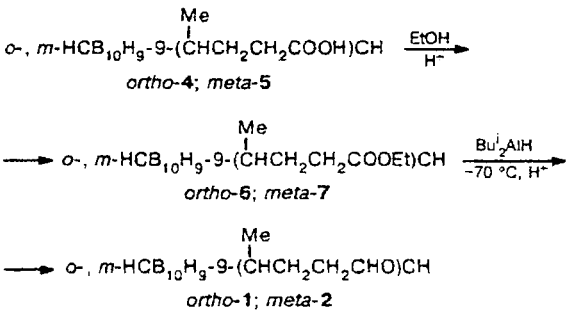
Two of the carborane-containing porphyrins[1] known to date, *meso*-tetracarboranylporphyrins $H_2[P(CH_2C_2B_{10}H_{10}R)_n$ (where *P* is the porphyrin macrocycle, and R = H and Me), were obtained from *o*-carboranylacetaldehyde and (2-methyl-*o*-carboran-1-yl)acetaldehyde by monopyrrole condensation in yields of 1% and 10—15%, respectively.[2] One of the interesting properties of carboranylporphyrins is that the carborane cage can be modified, which can result in considerable changes in the physical properties of the porphyrin macrocycle. In addition, the ability of porphyrins to be concentrated in tumor tissues makes it possible to use carboranylporphyrins as drugs for antitumor boron neutron capture therapy.

In this work, 5,10,15,20-tetra[3-(*o*- and *m*-carboranyl)butyl]porphyrins in which the carborane groups are bonded to the substituent in the porphyrin cycle by the C—B σ-bond were obtained by condensation of 4-(*o*- and *m*-carboran-9-yl)pentanals (**1**) and (**2**) with pyrrole. Condensation of (*m*-carboran-9-yl)acetaldehyde (**3**), which differs in reactivity from aldehydes **1** and **2**, was also studied.

Aldehydes **1** and **2** were obtained from the known[3] 4-(*o*- and *m*-carboran-9-yl)pentanoic acids (**4**) and (**5**) (Scheme 1).

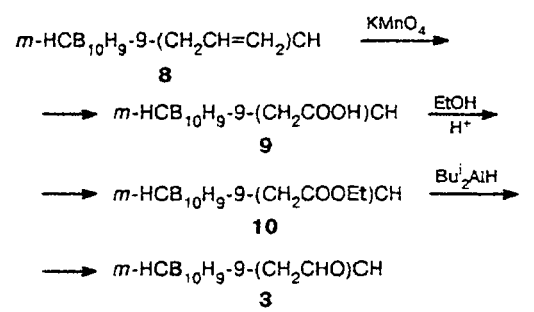
It should be noted that the esterification of acid **5** proceeds faster than that of acid **4**, which is likely associated with different spatial orientations of the alkyl chains of the acids.[4] Aldehydes **1** and **2** were obtained in high yield by reduction of ethyl esters **6** and **7** with Bu^i_2AlH in toluene at −70°C following the known procedure.[5]

Scheme 1



9-Allyl-*m*-carborane (**8**) was oxidized with $KMnO_4$ under conditions of phase transfer catalysis with the formation of acid **9**, which was transformed into ester **10** and reduced to aldehyde **3** (Scheme 2).

Scheme 2



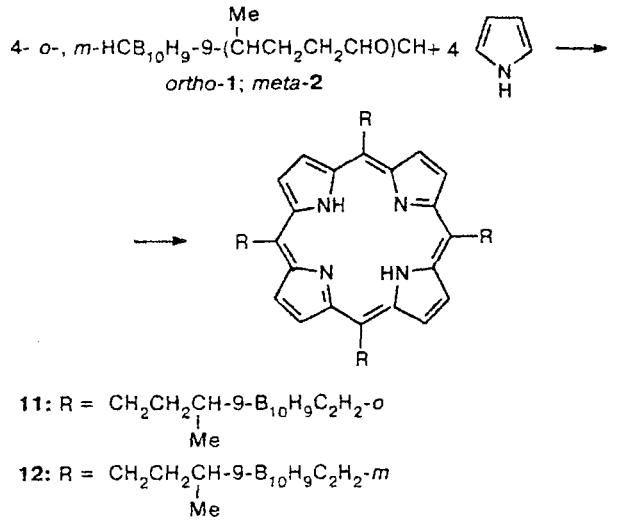
Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 347—349, February, 1998.

1066-5285/98/4702-0340 $20.00

This procedure for the oxidation of the allyl group also works well in the case of oxidation of 9-allyl-*o*-carborane.

Condensation of aldehydes **1** and **2** with pyrrole in *o*-xylene in the presence of chloroacetic acid[6] results in 5,10,15,20-tetra[3-(*o*- and *m*-carboran-9-yl)butyl]-porphyrins (**11**) and (**12**), respectively, in yields 38—41% (Scheme 3).

Scheme 3



11: R = $CH_2CH_2\underset{\underset{Me}{|}}{C}H$-9-$B_{10}H_9C_2H_2$-*o*

12: R = $CH_2CH_2\underset{\underset{Me}{|}}{C}H$-9-$B_{10}H_9C_2H_2$-*m*

The condensation of aldehyde **3** with pyrrole under the same conditions did not result in the formation of porphyrin; it was found that the resin-like reaction products contain no porphyrin system. The different course of the reaction in the case of aldehyde **3** can be explained by the reduced reactivity of the aldehyde group. This manifests itself in the rate of formation of 2,4-dinitrophenylhydrazones. Aldehydes **1** and **2** readily form 2,4-dinitrophenylhydrazones, whereas the formation of hydrazone of aldehyde **3** takes 48 h. In addition, the bulky carboranyl group in α-position to the aldehyde group produces steric hindrances to the formation of the porphyrin macrocycle.

In this connection it should be noted that the reaction of (*o*-carboran-1-yl)acetaldehyde (an analog of aldehyde **3**) with pyrrole also proceeded with difficulty[2] and the yield of the corresponding carboranylporphyrin was less than 1%.

Experimental

UV spectra were recorded on a Specord M 20 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AMX-400 spectrometer (400.18 MHz) in acetone-d_6 with hexamethyldisiloxane as the internal standard. The purity of compounds was monitored by TLC on Silufol plates.

(*m*-Carboran-9-yl)acetic acid (9). $KMnO_4$ (12 g, 75.9 mmol) was added portionwise with stirring at 0 °C to a mixture of 9-allyl-*m*-carborane (5 g, 27 mmol), CH_2Cl_2 (96 mL), water (96 mL), 50% H_2SO_4 (15 mL), MeCOOH (2 mL), and $PhCH_2Et_3NBr$ (1.2 g), and the mixture was kept for 40 min at 0 °C. Then the temperature was raised to 20 °C. A saturated solution of $NaHSO_3$ was added to the reaction mixture at 10—15 °C until decoloration. After the usual workup, acid **9** (4 g, 74%) was obtained, m.p. 108—110 °C (from heptane). Found (%): C, 23.85; H, 6.73; B, 53.65. $C_4H_{14}B_{10}O_2$. Calculated (%): C, 23.76; H, 6.93; B, 53.46. IR, ν/cm^{-1}: 1710 (CO); 2600 (BH); 2880—3300 (OH); 3070 (carborane CH).

(*o*-Carboran-9-yl)acetic acid was obtained analogously from 9-allyl-*o*-carborane (5 g, 27.0 mmol) and $KMnO_4$ (12 g, 75.9 mmol), yield 3 g (56%), m.p. 161—162 °C (from a C_6H_6—heptane mixture). Found (%): C, 23.43; H, 6.81; B, 53.18. $C_4H_{14}B_{10}O_2$. Calculated (%): C, 23.76; H, 6.93; B, 53.46.

Ethyl 4-(*o*-carboran-9-yl)pentanoate (6). A mixture of acid **4** (9 g, 37 mmol), EtOH (20 mL), and H_2SO_4 (1.5 mL) was refluxed for 24 h until disappearance of acid **4**, poured into water, and extracted with benzene. The benzene solution was washed with a saturated solution of $NaHCO_3$, water, and dried with Na_2SO_4. Removal of benzene and distillation *in vacuo* gave ester **6** (9.3 g, 93%), b.p. 190—192 °C (1 Torr). Found: B, 40.12%. $C_9H_{24}B_{10}O_2$. Calculated: B, 39.85%. ^{1}H NMR, δ: 4.37 (br.s, 2 H, carborane CH); 4.03 (q, 2 H, $O\underline{CH_2}CH_3$); 2.34 and 2.18 (both m, 2×1 H, diastereotopic protons $\underline{CH_2}COOC_2H_5$); 1.76 and 1.21 (both m, 2×1 H, diastereotopic protons $\underline{CH_2}CHCH_3$); 1.17 (t, 3 H, $OCH_2\underline{CH_3}$); 0.83 (br.s, 4 H, 9-BCHCH$_3$).

Ethyl 4-(*m*-carboran-9-yl)pentanoate (7) was obtained analogously by refluxing a mixture of acid **5** (8 g, 33.0 mmol) in EtOH (20 mL) for 10 h, yield 8.3 g (92%), b.p. 164 °C (1 Torr). Found: B, 39.40%. $C_9H_{24}B_{10}O_2$. Calculated: B, 39.85%. ^{1}H NMR, δ: 4.31 (br.s, 2 H, carborane CH); 4.05 (q, 2 H, $O\underline{CH_2}CH_3$); 2.32 and 2.16 (both m, 2×1 H, diastereotopic protons $\underline{CH_2}COOC_2H_5$); 1.74 and 1.22 (both m, 2×1 H, diastereotopic protons $\underline{CH_2}CH(CH_3)$; 0.86 (br.s, 4 H, 9-BCHCH$_3$).

Ethyl (*m*-carboran-9-yl)acetate (10) was obtained analogously from acid **9** (4.5 g, 22.0 mmol) in EtOH (15 mL), yield 4.9 g (98%), m.p. 56 °C (from hexane). Found (%): C, 31.54; H, 7.87. B, 47.13. $C_6H_{18}B_{10}O_2$. Calculated (%): C, 31.30; H, 7.83; B, 46.95.

4-(*o*-Carboran-9-yl)pentanal (1). A solution of Bu^i_2AlH (4.1 g, 29.0 mmol) in anhydrous toluene (5 mL) was added to a solution of ester **6** (7.6 g, 28.0 mmol) in anhydrous toluene (15 mL) at −70 °C, and the mixture was stirred for 1.5 h at −70 °C. The reaction mass was added to a saturated solution of NH_4Cl (25 mL) with stirring at 0 °C, and then the mixture was acidified with a 10% HCl. The toluene layer was separated, and the aqueous layer was extracted with benzene. The organic extracts were washed with water to neutral reaction and dried with Na_2SO_4. Removal of the solvent *in vacuo* gave aldehyde **1** (5.3 g, 85%). IR, ν/cm^{-1}: 1720 (CO); 2599 (BH); 2721 (CH aldehyde); 3070 (carborane CH). 2,4-Dinitrophenylhydrazone of aldehyde **1**: m.p. 168—169 °C (from ethanol). Found (%): B, 26.33; N, 13.60. $C_{13}H_{24}B_{10}N_4O_4$. Calculated (%): B, 26.47; N, 13.72.

4-(*m*-Carboran-9-yl)pentanal (2) was obtained analogously from ester **7** (7.6 g, 28.0 mmol) and Bu^i_2AlH (4.1 g, 29.0 mmol) in anhydrous toluene (15 mL), yield 5.4 g (86%). IR, ν/cm^{-1}: 1720 (CO); 2596 (BH); 2720 (CH aldehyde); 3064 (carborane CH). 2,4-Dinitrophenylhydrazone of aldehyde **2**: m.p. 147 °C (from ethanol). Found (%): B, 26.83; N, 13.61. $C_{13}H_{24}B_{10}N_4O_4$. Calculated (%): B, 26.47; N, 13.72.

(*m*-Carboran-9-yl)acetaldehyde (3) was obtained analogously from ester **10** (6.44 g, 28.0 mmol) and Bu^i_2AlH (4.1 g, 29.0 mmol) in anhydrous toluene (15 mL), yield 4.2 g (80%). IR, ν/cm^{-1}: 1714 (CO); 2599 (BH); 2722 (CH aldehyde); 3062 (carborane CH). 2,4-Dinitrophenylhydrazone of aldehyde **3**: m.p. 110 °C (from toluene). Found: N, 15.28%. $C_{10}H_{18}B_{10}N_4O_4$. Calculated: N, 15.30%.

5,10,15,20-Tetra[3-(*o*-carboran-9-yl)butyl]porphyrin (11). Chloroacetic acid (0.17 g) and *o*-xylene (20 mL) were placed into a flask equipped with a Dean—Stark trap, a reflux condenser, and a dropping funnel, and the mixture was heated to boiling. A mixture of aldehyde **1** (0.2 g, 0.88 mmol) and pyrrole (0.059 g, 0.88 mmol) in *o*-xylene (3 mL) was added to the boiling solution in an argon atmosphere, and the solution was refluxed for 2 h. After cooling to 20 °C, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.01 g) was added to the reaction mixture, and air was passed for 8 h. Then *o*-xylene was removed *in vacuo*, and the residue was chromatographed on a column with silica gel L (40—100 μ) with a $CHCl_3$—MeOH (9 : 1) mixture as the eluent to give porphyrin **11** (0.092 g, 38%). Found (%): B, 38.91; N, 5.24. $C_{44}H_{86}B_{40}N_4$. Calculated (%): B, 39.20; N, 5.08. ^{1}H NMR, δ: 9.68 (s, 8 H, β-pyrrole); 4.31 (br.s, 8 H, carborane CH); 2.35 and 2.03 (both m, 2×4 H, diastereotopic protons *meso*-C—CH_2—); 1.91 and 1.58 (both m, 2×4 H, diastereotopic protons —$\underline{CH_2}CHCH_3$); 0.91 (m, 16 H, —$CH(CH_3)$—); −2.85 (2 H, NH). UV, λ_{max}/cm^{-1} ($\varepsilon \cdot 10^{-3}$): 419 (71); 522 (3); 557 (2.6); 663 (2).

5,10,15,20-Tetra[3-(*o*-carboran-9-yl)butyl]porphyrin (12) was obtained analogously from aldehyde **2** (0.2 g, 0.88 mmol) and pyrrole (0.059 g, 0.88 mmol) in *o*-xylene (25 mL), yield 0.1 g (41%). Found (%): B, 39.47; N, 5.29. $C_{44}H_{86}B_{40}N_4$. Calculated (%): B, 39.20; N, 5.08. ^{1}H NMR, δ: 9.71 (s, 8 H, β-pyrrole); 4.37 (br.s, 8 H, carborane CH); 2.38 and 2.10 (both m, 2×4 H, diastereotopic protons *meso*-C—CH_2; 1.87 and 1.43 (both m, 2×4 H, diastereotopic protons $\underline{CH_2}CH(CH_3)$; 0.85 (m, 16 H, $CH(CH_3)$); −2.89 (2 H, NH). UV, λ_{max}/cm^{-1} ($\varepsilon \cdot 10^{-3}$): 421 (73); 525 (3.2); 558 (3.0); 661 (2.6).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 97-03-33158a).

References

1. C. Morin, *Tetrahedron*, 1994, **50**, 12553.
2. R. C. Haushalter, W. M. Butler, and R. W. Rudolph, *J. Am. Chem. Soc.*, 1981, **103**, 2620.
3. L. I. Zakharkin, V. A. Ol'shevskaya, and E. V. Anikina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 869 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 795 (Engl. Transl.)].
4. V. M. Orlov, V. N. Pustobaev, T. Yu. Poroshina, V. A. Ol'shevskaya, L. I. Zakharkin, and G. L. Gal'chenko, *Dokl. Akad. Nauk SSSR*, 1989, **309**, 892 [*Dokl. Chem.*, 1989 (Engl. Transl.)].
5. L. I. Zakharkin and I. M. Khorlina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1962, 538 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1962, **11** (Engl. Transl.)].
6. E. I. Fillipovich, R. P. Evstigneeva, V. N. Luzgina, T. G. Egorova, N. R. Kurdyumova, and I. E. Mikerin, *Zh. Obshch. Khim.*, 1990, **60**, 2511 [*J. Gen. Chem. USSR*, 1990, **60** (Engl. Transl.)].

Received July 2, 1997