Synthesis of [2.2]paracyclophane-*pseudo-ortho*-dicarboxylic acid

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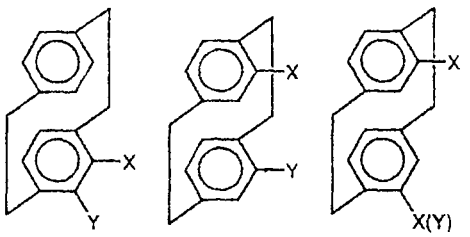
An efficient three-step synthesis of [2.2]paracyclophane-*pseudo-ortho*-dicarboxylic acid by dibromination of [2.2]paracyclophane, thermal isomerization of the resulting *pseudo-para*-dibromide to *pseudo-ortho*-isomer, followed by lithiation/carboxylation was developed. The possibility of preparation of two other novel *pseudo-ortho*-disubstituted carbonyl derivatives, 4-carboxy-12-(1-oxopenthyl)-[2.2]paracyclophane and di(4-carboxy[2.2]paracyclophanyl-12)ketone, was demonstrated when an excess of lithiation reagent (4 or 10 eq.) was used in the final step.

Key words: [2.2]paracyclophane, [2.2]paracyclophane-*pseudo-ortho*-dicarboxylic acid, lithiation, carboxylation.

[2.2]Paracyclophane (**1**) has attracted considerable attention as a perspective model compound for versatile structural and stereochemical studies[1]. To date, starting from resolved [2.2]paracyclophane-4-dicarboxylic acid,[2] a number of optically active mono-[3] and disubstituted [2.2]paracyclophanes[4] have been synthesized. However, the use of optically active derivatives of [2.2]paracyclophane as chiral auxiliaries and ligands in catalytic and stoichiometric asymmetric synthesis has been reported only recently.[5,6] Systems bearing two functional groups located on the same side of the plane formed by four bridge carbon atoms of [2.2]paracyclophane (in *ortho*- (**A**) and *pseudo-gem*-positions (**B**)) provide highly stereoselective reactions.



A **B** **C**

Thus, the *ortho*-disubstituted [2.2]paracyclophanes derived from optically active 4-formyl-5-hydroxy[2.2]paracyclophane have been employed as effective auxiliaries in the asymmetric synthesis of α-amino acids[5]. The stereochemical control in the reactions was achieved due to the ability of functional groups to coordinate with a metal atom. The introduction of a bulky substituent into the *pseudo-gem*-position to a selenide group has a considerable influence upon the stereochemistry of the oxidation of 4-(methylseleno)-15-(*p*-toluenesulfonyl)-[2.2]paracyclophane.[6] However, other disubstituted [2.2]paracyclophanes, namely, *pseudo-ortho*-derivatives (**C**), are also of considerable interest for the asymmetric synthesis, because their two proximal functional groups belonging to different benzene rings form a system where the substituents can either coordinate with a metal atom or affect each other sterically. Moreover, in contrast to structures **A** or **B** the *pseudo-ortho* disubstituted [2.2]paracyclophanes **C** are chiral even with two identical substituents. This feature can greatly facilitate synthetic approaches to the compounds because both functional groups can be incorporated at a time.

Here we report an efficient synthesis of the hitherto unknown [2.2]paracyclophane-*pseudo-ortho*-dicarboxylic acid (**2**).

In the first step bromination of [2.2]paracyclophane **1** was carried out with excess of Br_2 without catalyst, using the synthetic technique developed by us earlier.[7] Formed as the main product *pseudo-para*-dibromo[2.2]paracyclophane (**3**) was isolated from the reaction mixture as a less soluble isomer in 50 % yield.*

Pseudo-para-/pseudo-ortho-thermal rearrangements are known for [2.2]paracyclophane derivatives; however, in the preparative scale they were carried out for bromoacetyl[2.2]paracyclophane in the absence of a solvent and for bromocarbomethoxy[2.2]paracyclophane in triglyme. For derivatives **3** and **4** the principal possibility of the rearrangement of such a kind in triglyme have been shown by NMR ^1H spectroscopy[9]. We have carried

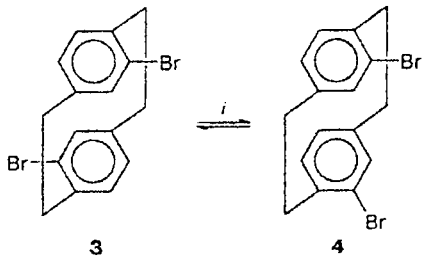
*It should be noted that the synthetic technique described earlier[8] (Fe-catalyzed bromination of **1**) and further resolution of the isomeric dibromides allows one to obtain **3** in a low yield (as much as 26%).

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 11, pp. 2001—2004, November, 1997.

1066-5285/97/4611-1897 $18.00

out the thermal rearrangement of dibromide **3** in benzene at 200 °C. *Pseudo-ortho*-dibromo[2.2]paracyclophane **4** was formed as an equilibrium product with respect to **3** in a 1 : 1 ratio (Scheme 1). Compounds **3** and **4** were separated by crystallization of the reaction mixture from CCl_4 as a result of which isomer **3** precipitated and isomer **4** dissolved in the mother liquor was additionally purified by chromatography on a silica gel. Thus, the efficient preparative technique developed in the present work allows one to obtain *pseudo-ortho*-dibromo[2.2]paracyclophane **4** from the *pseudo-para*-isomer **3** in virtually quantitative yield.

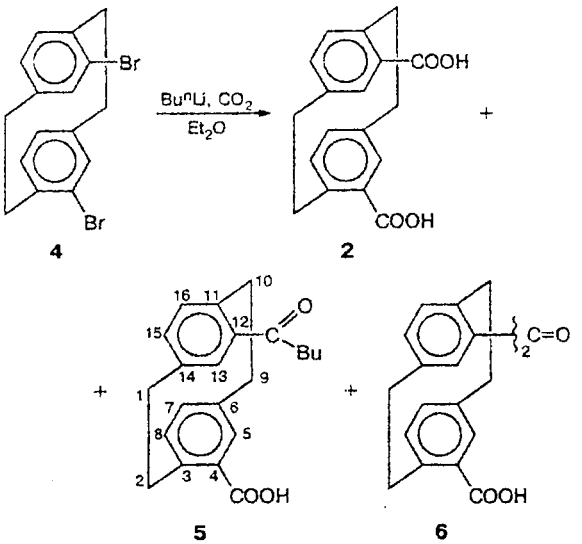
Scheme 1



3 **4**

i. C_6H_6, 200 °C, P, 24 h.

Scheme 2

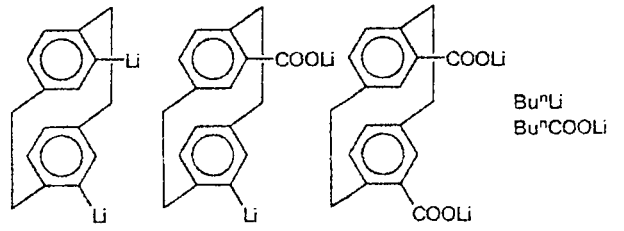


4 **2** **5** **6**

Run	Bu^{n}Li/eq.	Yield (%)		
		2	**5**	**6**
a	10	7.8	38	10
b	4	25	—	11
c	2	82	—	—

To date, a successful exchange of both bromine atoms in *pseudo-para*-(**3**), *pseudo-ortho*-(**4**), and *pseudo-meta*-dibromo[2.2]paracyclophanes with lithium required a tenfold excess of Bu^{n}Li (ether, 20 °C)[10]. The action of two[11] or three[12] equivalents of Bu^{n}Li in the same solvent led to exchange of only one of the two bromine atoms present in *pseudo-para*-dibromo[2.2]paracyclophane (**3**). Varying the Bu^{n}Li/dibromide **4** ratio, we have carried out a series of experiments (Scheme 2) to find the optimal conditions for the final step of the synthesis.

When dibromide **4** was lithiated with 10 eq. of Bu^{n}Li (ether, 20 °C) with subsequent carboxylation of the resultant organolithium intermediate with dry ice (Scheme 2, ***a***), the target dicarboxylic acid **2** was formed in a very low yield (7.8%). The formation of ketoacid **5** and dicyclophanylketone **6** has also been observed. The application of a fourfold excess of Bu^{n}Li in the reaction (Scheme 2, ***b***) leads to a somewhat higher yield of **2**. Nevertheless the formation of by-product **6** was detected in this experiment too. The best result was achieved when a twofold excess of Bu^{n}Li was used for the lithiation of **4**. Acid **2** has formed here (Scheme 2, ***c***) without by-products in a high yield (82 %). Apparently the formation of compounds **5** and **6** can be accounted for by the interaction between organolithium derivatives and lithium carboxylates present in the reaction mixture as well by their reactions with Bu^{n}Li and CO_2*.



The structures of compounds **2**, **5** and **6** were unequivocally established by ^1H and ^{13}C NMR, MS, and the elemental analysis data.

Thus, a simple and efficient synthetic procedure for the preparation of [2.2]paracyclophane-*pseudo-ortho*-dicarboxylic acid has been developed in the present work. This acid (together with *pseudo-ortho*-dibromo[2.2]paracyclophane) can serve as a convenient starting material for the synthesis of a wide range of new chiral *pseudo-ortho*-disubstituted [2.2]paracyclophanes.

Experimental

All reactions were carried out in an argon atmosphere. The monitoring of the reactions was performed on silica gel plates

* For instance, for [2.2]paracyclophane the formation of 4-benzoyl[2.2]paracyclophane under the action of 2 eq. of PhLi on [2.2]paracyclophane-4-carboxylic acid is described.[13]

"Silufol-UV 254"; preparative column chromatography was carried out on silica gel "Kieselgel 60" (Merck). NMR spectra were recorded on a "Bruker AMX-400" instrument (400.13 (^{1}H) and 100.61 (^{13}C) MHz), using the signals of the remaining protons of deuterated solvents as an internal standard. EI-mass-spectra were recorded on an "MS-90" instrument (70 eV).

All solvents were carefully purified according to standard procedures.

Thermal rearrangement 3 ⇌ 4. A mixture of *pseudo-para*-dibromo[2.2]paracyclophane **3** (25 g, 0.0683 mol) and abs. benzene (300 mL) was kept in a stirring autoclave for 24 h at 200 °C, then cooled down to ~20 °C. The precipitate was filtered off and extracted with $CHCl_3$ (2×100 mL) (the insoluble solid residue was defined as starting **3**). The combined chloroform extracts and mother liquor were evaporated, the residue was crystallized from CCl_4, and the precipitate was separated. The filtrate was passed through a silica gel column (eluent CCl_4, d = 2.5, l = 20 cm), the eluate was evaporated, and the residue was crystallized from ethanol. The yield of *pseudo-ortho*-dibromo[2.2]paracyclophane **4** was 12 g (48 %), m.p. 182—183 °C (cf. Ref. 8: m.p. 185—186 °C).

Reaction of *pseudo-ortho*-dibromo[2.2]paracyclophane 4 with Bu^nLi/CO_2. *a*. The ratio 4/Bu^nLi = 1 : 10. A 3 *N* solution of Bu^nLi in *n*-hexane (16 mL, 48 mmol) was added to a solution of cyclophane **4** (1.65 g, 4.51 mmol) in ether (150 mL) at 20 °C. After stirring for 3 h an excess of dry ice was added to the reaction mixture. The resultant mixture was warmed up to ~20 °C, treated with 2 *N* HCl (30 mL), then extracted with ether (3×50 mL). The combined organic phase was dried with $MgSO_4$, evaporated to dryness, and washed with n-pentane. The insoluble residue was washed with $CHCl_3$ (8 mL), and air dried to afford 0.1 g (7.8%) of **[2.2]paracyclophane-*pseudo-ortho*-dicarboxylic acid (2)**, m.p. 295—297 °C (with decomposition). Found (%): C, 73.11; H, 5.39. $C_{18}H_{16}O_4$. Calculated (%): C, 72.96; H, 5.44. NMR ^{1}H (DMSO-d_6, δ, ppm, J/Hz): 2.85—3.40 (m, 6 H, 2 —C<u>H</u>H—C<u>H</u>H—); 4.00—4.20 (m, 2 H, 2 —C<u>H</u>H-C<u>H</u>H—); 6.70 (d, 2 H, H-8, H-16, ^3J = 7.8); 6.87 (d.d, 2 H, H-7, H-15, ^3J = 7.8, ^4J = 1.9); 7.15 (d, 2 H, H-5, H-13, ^4J = 1.9); 12.50 (br.s., 2 H, 2 COO<u>H</u>). NMR ^{13}C {^{1}H} (DMSO-d_6, δ, ppm): 33.7 (C-2, C-10); 35.1 (C-1, C-9); 130.7 (C-4, C-12); 133.2 (C-8, C-16); 135.8, 136.0 (C-5, C-13, C-7, C-15); 139.6 (C-3, C-11); 141.8 (C-6, C-14); 167.6 (<u>C</u>OOH). MS (EI, 70 eV), m/z (I_{rel} (%)): 278 $[M-H_2O]^+$ (31); 148 $[M/2]^+$ (100); 104 (100).

The combined pentane and chloroform solutions were evaporated, and the resultant mixture was separated by column chromatography on a silica gel (eluent benzene—ether, 5 : 1). The combined fractions with R_f = 0.9 afforded 0.11 g (10 %) of **di(4-carboxy[2.2]paracyclophanyl-12)ketone (6)**, m.p. 235—237 °C. NMR ^{1}H ($CDCl_3$, δ, ppm, J/Hz): 2.70—3.30 (m, 10 H, 4 —C<u>H</u>H—C<u>H</u>H—); 3.60 (m, 2 H, 2 —C<u>H</u>H—C<u>H</u>H—); 3.77 (m, 2 H, 2 —C<u>H</u>H—C<u>H</u>H—); 4.04 (m, 2 H, —C<u>H</u>H-C<u>H</u>H—); 6.17 (br.d., 2 H, arom.); 6.46 (d, 2 H, arom., ^3J = 8.0); 6.60 (m, 4 H, arom.); 6.77 (d.d, 2 H, arom., ^3J = 8.0, ^4J = 1.8); 7.52 (d, 2 H, arom., ^4J = 1.8). NMR ^{13}C {^{1}H} ($CDCl_3$, δ, ppm): 34.11, 34.89, 35.19 and 35.77 (C-1, C-2, C-9, C-10); 130.36, 132.97, 133.63, 135.71 (2 C); 135.95, 137.28, 137.59, 139.18, 140.97, 142.07, 142.85 (all C arom.); 171.43 (<u>C</u>OOH); 198.06 (CO). MS (EI, 70 eV), m/z (I_{rel} (%)): 530 $[M]^+$ (28); 486 (2); 278 (4); 235 (61); 233 (46); 205 (50); 191 (57); 178 (28); 165 (26); 148 (30); 131 (75); 104 (100).

The combined fractions of R_f = 0.7 afforded 0.57 g (38 %) of **4-carboxy-12-(1-oxopentyl)[2.2]paracyclophane (5)**: m.p. 146—147 °C (heptane). Found (%): C, 78.60; H, 7.16. $C_{22}H_{24}O_3$. Calculated (%): C, 78.54; H, 7.19. NMR ^{1}H ($CDCl_3$, δ, ppm, J/Hz): 0.97 (t, 3 H, $C_3H_7C\underline{H}_3$); 1.30—1.45 (m, 2 H, $C_2H_4C\underline{H}_2CH_3$); 1.55—1.80 (m, 2 H, $CH_2C\underline{H}_2C_2H_5$); 2.60—2.75 (m, 1 H, CH<u>H</u>Pr); 2.80—3.00 (m, 3 H, —C<u>H</u>H—C<u>H</u>H—); 3.05—3.20 (m, 1 H, CH<u>H</u>Pr); 3.20—3.35 (m, 3 H, —C<u>H</u>H—C<u>H</u>H—); 3.95 (d.d, 1 H, CH<u>H</u>—CH_2); 4.12 (d.d, 1 H, —C<u>H</u>H—CH_2—); 6.57 (d, 1 H, arom., ^3J = 7.8); 6.64 (d, 1 H, arom., ^3J = 7.8); 6.75 (d.d, 1 H, arom., ^3J = 7.8, ^4J = 1.3); 6.79 (d.d, 1 H, arom., ^3J = 7.8, ^4J = 1.3); 7.03 (d, 1 H, arom., ^4J = 1.3); 7.26 (d, 1 H, arom., ^4J = 1.9); 12.60 (br.s, 1 H, COO<u>H</u>). NMR ^{13}C {^{1}H} ($CDCl_3$, δ, ppm): 14.21 (C-22); 22.66 (C-21); 26.79 (C-20); 34.57, 34.64, 36.19 and 36.26 (C-1, C-2, C-9, C-10); 40.02 (C-19); 129.86, 137.71, 140.26, 141.09, 141.49 и 143.21 (C-3, C-4, C-6, C-11, C-12, C-14); 132.12, 134.25, 136.22, 136.29, 136.49 and 137.46 (C-5, C-7, C-8, C-13, C-15, C-16); 172.68 (<u>C</u>OOH); 203.33 (<u>C</u>O). MS (EI, 70 eV), m/z (I_{rel} (%)): 336 $[M]^+$ (22); 307 $[M-Et]^+$ (100); 279 (41); 252 (7); 188 (59); 147 (33); 105 (59).

***b*. The ratio 4/Bu^nLi = 1 : 4.** A 3 *N* solution of Bu^nLi in *n*-hexane (10.9 mL, 32.7 mmol) was added to a solution of cyclophane **4** (3.0 g, 8.2 mmol) in ether (250 mL) at 20 °C. After stirring for 5 h an excess of dry ice was added to the reaction mixture. The resultant mixture was warmed up to ~20 °C and treated with water (150 mL). The water phase was separated off, washed with ether (3×50 mL), and acidified with 2 *N* HCl to pH 1. The precipitate formed was washed to the neutral pH of the washing water and dried *in vacuo* over potassium hydroxide. The obtained solid (1.2 g) was extracted with chloroform (50 mL), and the insoluble residue was dried *in vacuo* to afford 0.6 g (25 %) of diacid **2**. The organic extract was evaporated, and a portion of the resultant residue (0.1 g) was separated by TLC on silica gel (eluent benzene-ether, 5 :1). The calculated overall yield of ketone **6** 11 %.

***c*. The ratio 4/Bu^nLi = 1 : 1.** A 3 *N* solution of Bu^nLi in *n*-hexane (3 mL, 9 mmol) was added to a solution of cyclophane **4** (1.66 g, 4.52 mmol) in ether (250 mL) at 20 °C. After stirring for 5 h an excess of dry ice was added to the reaction mixture. The resultant mixture was warmed up to ~20 °C. The above procedure afforded 1.1 g (82 %) of diacid **2**.

This work was supported by the Russian Foundation for Basic Research (Project No 97-03-32972a), INTAS (grant 94-1393) и EU INCO-COPERNICUS (grant PL 964206).

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Recieved April 30, 1997