Letters to the Editor

Unexpected racemization in the series of 4,5-disubstituted [2.2]paracyclophanes

R. P. Zhuravsky, V. I. Rozenberg, E. V. Sergeeva, and E. V. Vorontsov*

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation. Fax: +7 (495) 135 5085. E-mail: ineos-ghkl@yandex.ru

During the development of approaches to regioselective synthesis of novel types of planar chiral ligands from [2.2]paracyclophane,[1] we studied the possibility of obtaining 5-hydroxy-4-methoxy[2.2]paracyclophane (**1**), a chiral analog of guaiacol. For this purpose, we carried out *ortho*-lithiation of racemic 4-carbamoyloxy[2.2]paracyclophane (**2**) (Bu^sLi/THF, −78 °C)[2] followed by treatment of the reaction mixture with $B(OMe)_3$ and oxidation of the intermediate boronic derivative with a H_2O_2—NaOH system. 4-Carbamoyloxy-5-hydroxy[2.2]paracyclophane (**3**) (70%) obtained for the first time was converted into the respective *O*-methyl derivative **4** (NaH/DMF, then MeI). Selective elimination of the carbamoyl group from compound **4** ($LiAlH_4$/ether) gave the target racemic *ortho*-methoxyphenol **1** in 76% yield (Scheme 1).

It is known[3] that the paracyclophane framework is very stable and racemization is possible only upon cleavage of the ethano bridges at $T > 200$ °C. Because of this, scalemic planar chiral compounds of this series can be obtained by transformations of the starting optically active paracyclophane derivatives under typical conditions of fine organic synthesis.[1]

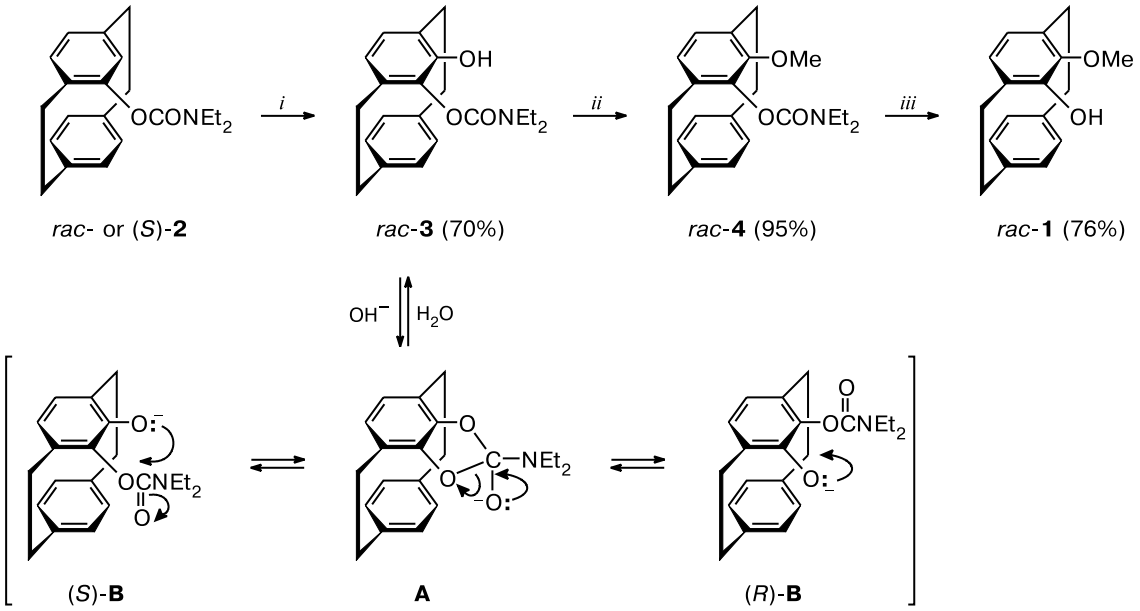
We tried to synthesize optically active compound **1** from nonracemic paracyclophane **2**, which is accessible from the enantiomers of 4-hydroxy[2.2]paracyclophane.[4] Unexpectedly, the aforementioned sequence of transformations of compound (*S*)-**2** gave products **3**, **4**, and **1** with nearly zero optical rotation values and HPLC analysis of compound **1** on a chiral phase revealed its racemic nature. Cleavage of the ethano bridges in paracyclophane is impossible under the reaction conditions used, which was experimentally confirmed by the retained optical rotation value of partially recovered compound (*S*)-**2**. The observed racemization of *o*-hydroxy derivative **3** (during its formation from (*S*)-**2**) can be explained by the O ⇄ O migration of the carbamoyl group under basic conditions since intermediate paracyclophanes (*R*)-**B** and (*S*)-**B** formed in this case are enantiomers interconvertible through cyclic intermediate **A** (or, less probably, in an intermolecular way). The evidence for this explanation is such processes as anionic O→C rearrangements in aryl carbamates[5,2] and O→O migrations of acyl groups in aliphatic and aromatic polyols.[6]

Thus, we proposed the approach to the regioselective synthesis of racemic chiral monomethyl ether **1** in total 53% yield. The next task is to resolve it into enantiomers. We discovered a novel type of racemization for paracyclophane derivatives, which is associated with O ⇄ O migration of the carbamoyl group in a basic medium.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2614—2615, November, 2005.

1066-5285/05/5411-2702

Scheme 1



Reagents and conditions: *i.* 1) Bu^{s}Li/THF, −78 °C, 2 h; 2) $B(OMe)_3$, −78 to 25 °C, 12 h; 3) $H_2O_2/NaOH/H_2O$, 2 h. *ii.* 1) NaH/DMF, 25 °C, 2 h; 2) MeI. *iii.* $LiAlH_4/Et_2O$, Δ, 6 h.

4-Carbamoyloxy-5-hydroxy[2.2]paracyclophane (3), m.p. 124—124.5 °C. Found (%): C, 74.39; H, 7.49; N, 4.20. $C_{21}H_{25}NO_3$. Calculated (%): C, 74.31; H, 7.42; N, 4.13. ^{1}H NMR (400.13 MHz, $CDCl_3$), δ: 1.23, 1.45 (both t, 3 H each, $CH_2C\underline{H}_3$, ^3J = 7.2 Hz); 2.55—2.74 (m, 2 H, $CH_2C\underline{H}_2$); 2.86—2.97 (m, 1 H, $CH_2C\underline{H}_2$); 2.98—3.16 (m, 4 H, $CH_2C\underline{H}_2$); 3.30—3.51 (m, 3 H, $CH_2C\underline{H}_2$ and $C\underline{H}_2CH_3$); 3.54—3.72 (m, 2 H, $C\underline{H}_2CH_3$); 6.22 (s, 1 H, OH); 6.23 (d, 1 H, C(6)H or C(7)H, ^3J = 7.8 Hz); 6.39 (d, 1 H, C(7)H or C(8)H, ^3J = 7.8 Hz); 6.49, 6.53, 6.70, 6.89 (all dd, 1 H each, H arom., ^3J = 7.8 Hz, ^4J = 1.8 Hz). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 339 $[M]^+$ (82); 235 $[M - CH_2C_6H_4CH_2]^+$ (18); 205 $[M - CH_2C_6H_4CH_2 - CH_2 - OH]^+$ (31); 135 $[M - CH_2C_6H_4CH_2 - CONEt_2]^+$ (16); 104 $[CH_2C_6H_4CH_2]^+$ (64); 100 $[CONEt_2]^+$ (100).

5-Hydroxy-4-methoxy[2.2]paracyclophane (1), m.p. 141—142 °C. Found (%): C, 80.41; H, 7.17. $C_{17}H_{18}O_2$. Calculated (%): C, 80.28; H, 7.13. ^{1}H NMR (400.13 MHz, $CDCl_3$), δ: 2.49—2.60, 2.60—2.69 (both m, 1 H each, $CH_2C\underline{H}_2$); 2.91—3.10 (m, 4 H, $CH_2C\underline{H}_2$); 3.13—3.23, 3.26—3.36 (both m, 1 H each, $C\underline{H}_2CH_2$); 3.70 (s, 3 H, OCH_3); 5.45 (s, 1 H, OH); 6.18 (d, 1 H, C(6)H or C(7)H, ^3J = 7.8 Hz); 6.28 (d, 1 H, C(7)H or C(8)H, ^3J = 7.8 Hz); 6.44, 6.50, 6.68, 6.85 (all dd, 1 H each, H arom., ^3J = 7.8 Hz, ^4J = 1.8 Hz). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 254 $[M]^+$ (86); 150 $[M - CH_2C_6H_4CH_2]^+$ (100); 135 $[M - CH_2C_6H_4CH_2 - OH]^+$ (39); 121 $[M - CH_2C_6H_4CH_2 - OH - CH_2]^+$ (30); 104 $[CH_2C_6H_4CH_2]^+$ (53).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 03-03-32957).

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Received August 19, 2005

Yu. T. Struchkov Prize

The Yu. T. Struchkov Prize is awarded annually (starting from 1997) for the best research in crystal chemistry or application of the X-ray diffraction method for solving chemical problems.*

Scientists aged below 36 by the date of application, living in CIS or Baltic countries are eligible. The work should be submitted in the name of one author, and only one work may be submitted by an applicant to the Competition of a given year. At least one paper on the topic of the research being nominated should have been published or accepted for publication by a journal with the practice of reviewing publications. The winner is chosen by the special Jury formed by the management of the X-Ray Diffraction Research Center from among leading Russian specialists in crystal chemistry and X-ray diffraction. The Jury´s decision should be announced by the 1st of November of the current year.

Eighteen young scientists from Moscow, St. Petersburg, Kazan, Apatity, Novosibirsk, Voronezh, Vladimir, Tashkent, and Kharkov took part in the competition in 2005.

Yu. T. Struchkov Prize of 2005 was awarded to *S. V. Krivovichev* (St. Petersburg State University) for the study "Crystal Chemistry of Uranium Inorganic Compounds with Hexavalent Cations (S, Cr, Se, Mo, W). "

The incentive prizes for the competitors highly appreciated by the Jury were presented to D. V. Al´bov, P. S. Berdonosov, N. V. Zubkova, S. Ya. Istomin (M. V. Lomonosov Moscow State University), and M. Zh. Krzhizhanovskaya (St. Petersburg State University).

In addition, four special incentive prizes were awarded to the following participants: E. V. Mironova (Kazan), O. N. Kazheva (Chernogolovka), T. A. Borisova (Moscow), and K. Yu. Dorogov (Moscow).

Awarding the incentive prizes does not rule out nomination to the subsequent competitions.

Those who wish to participate in the Competition of 2006 should forward the following documents to the X-Ray Diffraction Research Center by June 1, 2006:

— an application form of a participant (the first and last names; the title of the study nominated to the competition; the date and the year of birth; the academic degree; the post and the place of employment (full name); postal address of the institution; telephone number of the office, fax, and e-mail address);

— an abstract of the work (not exceeding 3 pages, 38 lines each, 65 characters in each line) indicating the personal contribution of the competitor to the study;

— the list of publications and studies prepared for publication relevant to the topic of the nominated work; enclosing reprints or Xerox copies of all (or some) papers is optional.

The documents should be addressed to the *X-Ray Diffraction Research Center, A. N. Nesmeyanov Institute of Organoelement Compounds, 28 ul. Vavilova, 119991 Moscow, Russian Federation*.

In addition, the information should be presented to the Jury as DOC or RTF files. The files can be sent by e-mail to *premiya@xrlab.ineos.ac.ru*.

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* Starting from 2000, the bonus fund of the Competition for the Prize is formed from the funds of the International Crystallographic Society "Struchkov Prize Society", which unites former Yu. T. Struchkov´ students and colleagues.