Notes

Synthesis of [2.2]Metacyclophanes[1]

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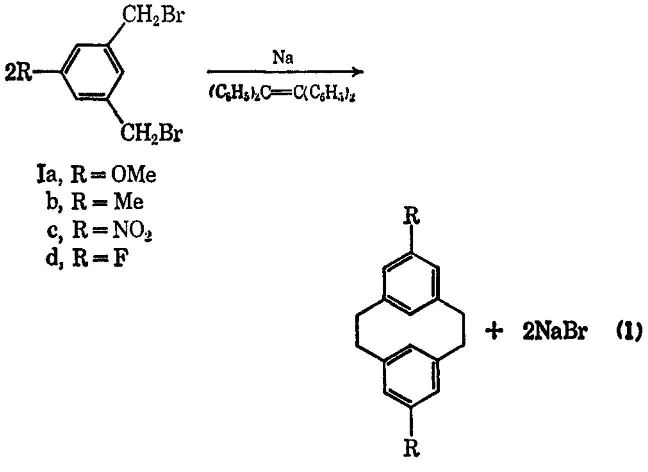
The successful synthesis of 15,16-dihydropyrene derivatives evolved out of an approach involving intermediate [2.2]metacyclophanes.[3,4] In the preliminary work directed toward this approach extensive studies were made on the synthesis of [2.2]metacyclophanes utilizing model compounds. In the present communication we report on a portion of these preliminary studies because of its relevance to later work currently being published.[5]

Of the various methods that have been reported for the synthesis of [2.2]metacyclophanes,[6] the only generally useful one has been the Wurtz reaction. For our purposes it was of interest to examine the electronic and steric effects of substituent groups on the Wurtz reaction and, because of the over-all plan involving phenolic–oxidation radical coupling,[3] it was of particular interest to prepare 5,13-dimethoxy derivatives.[7] In this study the Wurtz reaction, as modified by Müller and Röscheisen,[8] was utilized to convert *m*-xylyl dibromides, as illustrated by Ia–Id, into the corresponding [2.2]metacyclophanes (IIa–IIe) (eq 1).



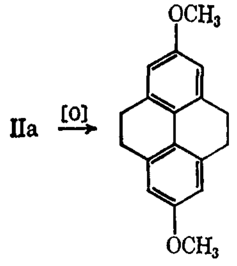
(1)

Ia, R = OMe
b, R = Me
c, R = NO_2
d, R = F

IIa, R = OMe
b, R = Me
c, R = NO_2
d, R = F
e, R = NH_2

The synthesis of the requisite *m*-xylyl dibromides (Ia–Id) was straightforward, is described in the Experimental Section, and requires no special comment. The conditions of the Wurtz reaction are relatively severe and the choice of substituents was made to determine what functional groups, if any, would survive these reaction conditions, permitting the isolation of useful quantities of substituted [2.2]metacyclophanes. In fact, the Wurtz dimerization of 3,5-bis(bromomethyl)anisole (Ia) proceeded smoothly to give the requisite 5,13-dimethoxy[2.2]metacyclophane (IIa) in 27% yield. Likewise, the dimerization of 3,5-bis(bromomethyl)toluene proceeded satisfactorily, but in lower yield, to give IIb. However, the dimerization of 3,5-bis(bromomethyl)nitrobenzene occurred in very poor yield with the production of many side products. Reduction of the crude 5,13-dinitro[2.2]metacyclophane (IIc) did allow the isolation of crystalline 5,13-diamino[2.2]metacyclophane (IIe). Finally, the dimerization of the fluoro analog (IId) was studied. In this case, again, the yield of dimeric product was very low and spectral evidence indicated it to be a mixture of the parent hydrocarbon, [2.2]metacyclophane, and its fluorinated analog (IId). Clearly, the conditions of the Wurtz reaction effect partial elimination of aromatic fluoride.

With the ready availability of 5,13-dimethoxy[2.2]metacyclophane (IIa), it was of interest to study its oxidation under conditions effecting radical coupling *via* phenolic oxidation. Chromic acid oxidation of 5,13-dimethoxy[2.2]metacyclophane led to its conversion in excellent yield into the corresponding 2,7-dimethoxy-4,5,9,10-tetrahydropyrene (III).[9] The extreme ease with which the metacyclophane structure of IIa is converted into the corresponding pyrene derivative (III) (eq 2) is reminiscent of the studies of Allinger on the nitration of [2.2]metacyclophane.[10,11]



III

(2)

Experimental Section[12]

3,5-Bis(hydroxymethyl)anisole.—In the thimble of a Soxhlett was placed 60 g of 3,5-bis(carbomethoxy)anisole[13] and extraction

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[1] Abstracted from the Ph.D. Thesis of R. W. Griffin, Jr., University of Rochester, 1960.

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[3] V. Boekelheide and J. B. Phillips, *J. Amer. Chem. Soc.*, **89**, 1695 (1967).

[4] V. Boekelheide and T. Miyasaka, *ibid.*, **89**, 1709 (1967).

[5] V. Boekelheide, C. Ramey, E. Sturm, T. Miyasaka, and B. A. Hess, Jr., *J. Org. Chem.*, **34**, 1956 (1969).

[6] See B. H. Smith, "Bridged Aromatic Compounds," Academic Press, New York, N. Y., 1964, for a comprehensive review.

[7] The numbering used for the [2.2]metacyclophanes is that recommended by Smith, ref 6, p 8.

[8] E. Müller and G. Röscheisen, *Ber.*, **90**, 543 (1957).

[9] We are indebted to Dr. E. Sturm for the details of this experiment.

[10] N. L. Allinger, M. A. Da Rooge, and R. B. Hermann, *J. Amer. Chem. Soc.*, **83**, 1974 (1961).

[11] N. L. Allinger, B. J. Gordon, S.-E. Hu, and R. A. Ford, *J. Org. Chem.* **32**, 2272 (1967).

[12] Analyses were performed by Micro-Tech Laboratories and by Miss Annette Smith; nmr spectra were taken by Professor David Wilson using a Varian HR-60 MHz, infrared spectra were obtained with a Perkin-Elmer Model 21 spectrometer, and ultraviolet spectra were recorded using a Cary 11 spectrometer.

[13] L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer, and A. F. St. Andre, *Helv. Chim. Acta*, **37**, 59 (1954).

was carried out into a suspension of 41.5 g of lithium aluminum hydride in 1.5 l. of ether. After extraction was complete, the excess lithium aluminum hydride was destroyed by addition of methanol followed by aqueous sulfuric acid. The ether layer was separated, dried, and concentrated to give 42 g (93%) of white crystals, mp 66–67°. A sample recrystallized from acetone gave white needles, mp 68.5–69.0°.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 63.88; H, 7.37.

3,5-Bis(bromomethyl)anisole (Ia).—A mixture of 40 g of 3,5-bis(hydroxymethyl)anisole and 44 g of phosphorus tribromide in 500 ml of benzene was boiled under reflux for 4 hr and allowed to stand at room temperature overnight. Then the benzene solution was decanted from the inorganic residue, washed with water, and concentrated to give 50 g (70%) of white crystals, mp 70–74°. A sample recrystallized from ether melted at 76.0–76.5°.

Anal. Calcd for $C_9H_{10}OBr_2$: C, 36.76; H, 3.43. Found: C, 36.67; H, 3.47.

5,13-Dimethoxy[2.2]metacyclophane (IIa).—A solution of 22.5 g of 3,5-bis(bromomethyl)anisole (Ia) in 1 l. of dry tetrahydrofuran was added dropwise through a Hershberg funnel over a period of 65 hr to a rapidly stirred suspension of 20 g of sodium granules in 1 l. of tetrahydrofuran containing 2 g of tetraphenylethylene and held at room temperature. At the end of the addition the unreacted sodium was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was taken up in methylene chloride, passed over a short column of Florisil to remove polymeric material, and concentrated. This residue, in turn, was taken up in benzene and chromatographed over neutral alumina (Woelm, activity I). The first substance to be eluted was tetraphenylethane followed by 2.97 g (27%) of white crystals, mp 169–170°. A sample recrystallized from a benzene–methanol mixture gave white cubes: mp 170.5–171.0°; nmr ($CDCl_3$) multiplet at τ 3.45 (4 H), singlet at 5.99 (2 H), singlet at 6.25 (6 H), and two doublets at 7.11 and 8.01 (8 H); λ_{max}^{KBr} 7.87 μ; λ_{max}^{EtOH} 210 mμ (log ε 4.63) and 292 (3.39).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.82; H, 7.60.

5,13-Dimethyl[2.2]metacyclophane (IIb).—The preparation of 3,5-bis(bromomethyl)toluene was carried out in 20% yield by treating mesitylene with N-bromosuccinimide in carbon tetrachloride and the physical properties of the product were in agreement with those reported.[14] Its dimerization to 5,13-dimethyl-[2.2]metacyclophane (IIb) was carried out as described for the dimerization of Ia above. From 6.85 g of 3,5-bis(bromomethyl)-toluene there was isolated, after recrystallization from a benzene–methanol mixture, 226 mg (8%) of white rhombic crystals, mp 153.0–153.5°.[15]

5,13-Diamino[2.2]metacyclophane (Ie).—The dimerization of 5.5 g of 3,5-bis(bromomethyl)nitrobenzene[16] was carried out in a manner similar to that described previously for the preparation of IIa. After removal of the sodium granules and concentration, there remained a brown semisolid residue. This was partially soluble in benzene; chromatography of the benzene solution yielded a mixture of tetraphenylethane and tetraphenylethylene. The benzene-insoluble portion, presumably containing some IIc, was placed in dilute hydrochloric acid, tin shot was added, and the mixture was boiled under reflux for 16 hr. The aqueous solution was decanted, made basic, and extracted with ether. Concentration of the ether extract gave a solid which, after recrystallization from an ether–methanol mixture, yielded 40 mg of light tan crystals: mp 230–240° dec; λ_{max}^{Nujol} 2.95–3.25 (broad absorption with discernible maxima), 11.66, and 13.58 μ.

Anal. Calcd for $C_{16}H_{18}N_2$: C, 81.32; H, 6.83. Found: C, 80.96; H, 6.88.

Dimethyl 5-Fluoroisophthalate.—To a solution of 84 ml of 12 *N* hydrochloric acid containing 33.3 g of dimethyl 5-aminoisophthalate[17] held at 0° was added a cold solution of 11.2 g of sodium nitrite in 50 ml of water. After the diazotized solution had been filtered through a sintered-glass disk, a cold solution of 22 g of sodium fluoroborate in 80 ml of water was added. The light orange precipitate, which separated, was collected and washed successively with cold 5% aqueous sodium fluoroborate, methanol, and ether. It was then dried in a desiccator to give 40.6 g (83%) of crystalline diazonium fluoroborate, mp 139–140° dec. This was placed in a large distilling flask and gently heated with a free flame until a highly exothermic reaction was initiated. After the evolution of boron trifluoride and nitrogen was complete, distillation of the residue was continued until the oil distilling over became highly colored. The distillate solidified and was sublimed to give 14.6 g (52%) of white crystals: mp 55.0–55.5°; λ_{max}^{KBr} 5.79, 11.15, 11.45, and 13.86 μ.

Anal. Calcd for $C_{10}H_9O_4F$: C, 56.60; H, 4.28. Found: C, 56.55; H, 4.26.

3,5-Bis(hydroxymethyl)fluorobenzene.—A solution of 13.6 g of dimethyl 5-fluoroisophthalate in 50 ml of tetrahydrofuran was added dropwise with stirring at room temperature to a solution of 5.3 g of lithium aluminum hydride in 100 ml of tetrahydrofuran. After the solution had been boiled under reflux for 1 hr, it was cooled and decomposed by addition of a saturated aqueous solution of sodium sulfate. The solids, which precipitated, were removed by filtration and the filtrate was concentrated. Recrystallization of the solid residue from ether gave 4.98 g (50%) of white crystals, mp 85–86°.

Anal. Calcd for $C_8H_9O_2F$: C, 61.53; H, 5.81. Found: C, 61.67; H, 6.06.

3,5-Bis(bromomethyl)fluorobenzene (Id).—A mixture of 4.75 g of 3,5-bis(hydroxymethyl)fluorobenzene and 5.65 g of phosphorus tribromide in 40 ml of benzene was boiled under reflux for 30 min. The benzene solution was then separated by decantation, washed with water, and concentrated. The solid residue was recrystallized from hexane to give 4.71 g (55%) of white crystals, mp 56–57°.

Anal. Calcd for $C_8H_7Br_2F$: C, 34.07; H, 2.50. Found: C, 34.17; H, 2.78.

Dimerization of 3,5-Bis(bromomethyl)fluorobenzene (Id).—The Wurtz dimerization of 5.3 g of 3.5-bis(bromomethyl)fluorobenzene (Id) was carried out as described previously for the preparation of IIa. From the elution of the alumina column with benzene there was isolated 126 mg of a sticky white solid. Although this was obviously a mixture, attempts at separation of the mixture were unsuccessful. Elementary analysis and spectral data of this solid suggest that it was a mixture of approximately equal parts of [2.2]metacyclophane and 5,13-difluoro-[2.2]metacyclophane.

Oxidation of 5 13-Dimethoxy[2.2]metacyclophane (IIa) to 2,7-Dimethoxy-4,5,9,10-tetrahydropyrene (III).—Chromic acid reagent was made by adding a solution of 2.67 g of chromium trioxide in 5 ml of water to 2.13 g of concentrated sulfuric acid and diluting the whole to a volume of 10 ml with water; 0.50 ml of this chromic acid reagent was added dropwise with stirring to a suspension of 100 mg of 5,13-dimethoxy[2.2]metacyclophane in 25 ml of acetone. A precipitate formed and the solution became red. After 1 hr, the mixture was poured into ice–water and extracted with methylene chloride. The methylene chloride extract was washed with water, dried, and concentrated. The residue was taken up in chloroform and chromatographed over neutral alumina (Woelm, activity III). From the first eluate fractions there was isolated a fluorescent solid which, after recrystallization from ethanol, gave 55 mg of white plates: mp 181.0–181.5°; nmr ($CDCl_3$) singlet at τ 3.40 (4 H), singlet at 6.20 (6 H), and singlet at 7.18 (8 H).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.86; H, 7.05.

Registry No.—Ia, 19254-79-6; Ib, 19294-04-3; Id, 19254-80-9; Ie, 19254-81-0; IIa, 19254-82-1; III, 19254-83-2; 3,5-bis(hydroxymethyl)anisole, 19254-84-3; dimethyl 5-fluoroisophthalate, 17449-48-8; 3,5-bis(hydroxymethyl)fluorobenzene, 19254-86-5.

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[14] J. von Braun and O. Engel, *Ber.*, **58**, 283 (1919).

[15] The nmr data for 5,13-dimethyl[2.2]metacyclophane were first recorded using a Varian HR-60 [D. J. Wilson, V. Boekelheide, and R. W. Griffin, Jr., *J. Amer. Chem. Soc.*, **82**, 6302 (1960)]. Subsequently, N. L. Allinger, B. J. Gorden, S.-E. Hu, and R. A. Ford [*J. Org. Chem.*, **32**, 2272 (1967)] have described an independent preparation of 5,13-dimethyl[2.2]metacyclophane and their nmr data showed discrepancies with that which we had recorded earlier. We have recently reexamined the nmr spectra of a number of compounds in the [2.2]metacyclophane series using a Varian A-60 and find that these spectra are very concentration dependent. This we feel is probably responsible for the discrepancies noted by Allinger and his collaborators.

[16] F. G. Mann and F. H. C. Stewart, *J. Chem. Soc.*, 2819 (1954).

[17] E. I. du Pont de Nemours and Co., British Patent 695,164 (1955); *Chem. Abstr.*, **49**, 755 (1955).