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Metacyclophane and Related Compounds. 22. Bromination of 8,16-Dimethyl-5-nitro[2.2]metacyclophane with Bromine and N-Bromosuccinimide¹

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When 8,16-dimethyl-5-nitro[2.2]metacyclophane (**7**) was treated with bromine under day light in the absence or in the presence of Fe powder, a mixture of 16-bromomethyl-8-methyl-5-nitro[2.2]MCP (**8a**) and 8,16-bis(bromoethyl)-5-nitro[2.2]MCP (**8b**) or a mixture of 5-bromo-8,16-dimethyl-13-nitro[2.2]MCP (**10**) and 5-bromo-8-bromomethyl-16-methyl-13-nitro[2.2]MCP (**11**) were obtained, respectively. However, under shielding from light, the former reaction gave no product and the latter reaction afforded **10** in 91% yield. Bromination of **7** with 1.2 equivalents of NBS afforded **8a**, and bromination with 2.5 equivalents of NBS afforded **8b**.

It has been previously reported that²⁾ bromination of 8,16-dimethyl[2.2]metacyclophane (**1a**, MCP) with bromine in the presence or in the absence of Fe powder as a catalyst afforded different types of products **2** or **3a-3b** and that similar reactions of 5,13-di-tert-butyl-8,16-dimethyl[2.2]MCP (**1b**) gave also different types of products **4** or **5** depending upon the conditions used. It was also reported that bromination of both **1a** and **1b** with NBS afforded the corresponding bis(bromomethyl)[2.2]MCPs **6a** and **6b**, respectively.

We initiated the present work in order to obtain information about the effect of substituents at the 5 position of 8,16-dimethyl[2.2]MCPs on bromination with bromine and NBS.

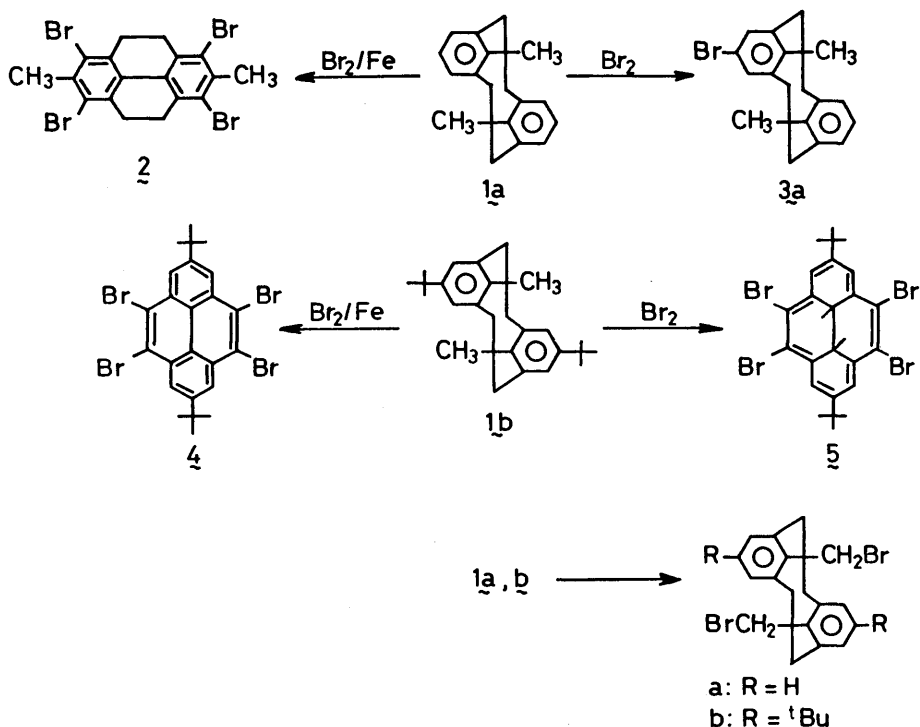
Results and Discussion

When 8,16-dimethyl-5-nitro[2.2]MCP (**7**)³⁾ was treated with bromine in carbon tetrachloride, a mixture of unexpected 8-bromomethyl-16-methyl-5-nitro[2.2]MCP (**8a**) and 8,16-bis(bromomethyl)-5-nitro[2.2]MCP (**8b**) was obtained. The molar ratio of **8a** and **8b** in the mixture was 1:1, which was determined by ¹H-NMR spectral data. However, **8a** and **8b** were not isolated in pure from the mixture. It was also found that treatment of **7** with 1.2 equivalent of NBS afford a mixture of **8a** and recovered **7**, however, **8a** was also not isolated from the mixture. Treatment of the mixture with silver nitrate in acetone-water solution afforded a mixture of recovered **7** and 16-hydroxymethyl-8-methyl-5-nitro[2.2]MCP (**9**) which could be easily separated from the mixture by chromatography. Treatment of **7** with 2.5 equivalents of NBS afforded **8b** in 70% yield.

Bromination of **7** in the presence of Fe powder afforded the expected 5-bromo-8,16-dimethyl-13-nitro[2.2]MCP (**10**) and the unexpected 5-bromo-8-bromomethyl-16-methyl-13-nitro[2.2]MCP (**11**) in 7.3% and 31% yields.

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Scheme 1

The above results suggest that radical bromination might occur in the described reactions with bromine as well as the reactions with NBS and that **7** having an attracting group might be less active than **1a** for the electrophilic attack of bromine.

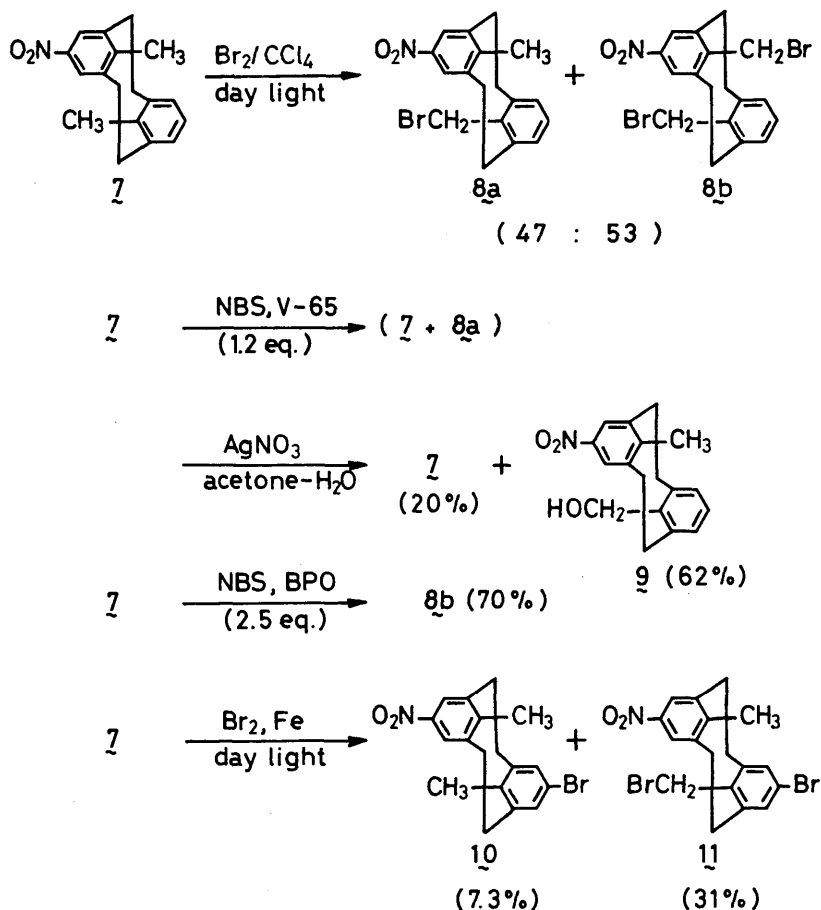
On the base of the above considerations, the reaction conditions were checked and it was found that the bromination of **7** with bromine was carried out in a draft chamber with a fluorescent lamp. The light from the lamp might generate bromo radicals from bromine to give the unexpected products. Indeed, bromination of **7** with bromine under shielding from the light gave no product and **7** was recovered in almost quantitative yield. The bromination of **7** in the presence of Fe powder under the same conditions afforded only **10** in 91% yield. Under shielding from the light, only the electrophilic bromination of **7** should occur in this reaction.

It was previously found that³⁾ auto oxidation of **7** in basic medium afforded 8-hydroxymethyl-16-methyl-5-nitro [2.2] MCP (**12**) which is an isomer of **9**. This result supported strongly the proposed structures of **8a** and **9**.

The structures of the products obtained in the present work were determined by their spectral data and elemental analyses.

Experimental Section

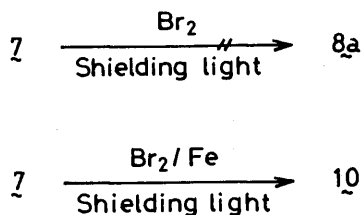
Bromination of 5-Nitro-8,16-dimethyl[2.2]metacyclophane (7). With Bromine in Carbon Tetrachloride Solution. To a solution of 100 mg (0.356 mmol) of **7** in 60 ml of carbon tetrachloride was gradually added at room temperature a solution of 0.1 ml of



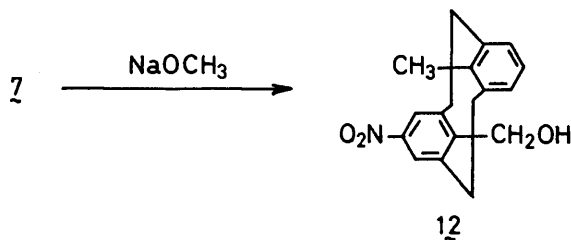
Scheme 2

bromine in 10 ml of the same solvent. After the reaction mixture was stirred at room temperature for 2 h, it was evaporated in vacuo to leave a residue which was washed with a small amount of hexane to give 150 mg of a mixture of **8a** and **8b**. Their molar ratio was determined by $^1\text{H NMR}$ as 1:1. Neither **8a** nor **8b** from the reaction mixture could be isolated by usual method such as column chromatography and recrystallization. These compounds **8a** and **8b** were obtained in pure form by the reactions described below. When this reaction was carried out under shielding from light, no product was observed.

With Bromine in the Presence of Fe Powder in Carbon Tetrachloride. To a mixture of 1,000 mg (3.56 mmol) of **7**, and 500 mg of Fe powder in 50 ml of carbon tetrachloride was gradually added a solution of 0.5 ml of bromine in 100 ml of the same solvent over a period of 3 h. The reaction mixture was then washed with sodium thiosulfate solution and water, dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel using toluene as an eluant to give a mixture of **10** and **11**. From the mixture, **10** and **11** were isolated in 7.4% and 31% yield by recrystallization from



Scheme 3



Scheme 4

toluene.

5-Bromo-8,16-dimethyl-13-nitro[2.2]metacyclophane (**10**): pale yellow needles (toluene), mp 295°C (dec.); ¹H NMR (CDCl₃) δ 0.54 (3H, s), 0.8 (3H, s), 2.56–3.26 (8H, m), 7.24 (2H, s), 7.97 (2H, s); IR (KBr) 3100, 2960, 1560, 1510, 1375, 1340, 1325, 1185, 1160, 1090, 910, 855, 830, 795 cm⁻¹; MS, m/e 359, 361 (M⁺). Anal. Calcd for C₁₈H₁₈BrNO₂: C, 60.01; H, 5.04; N, 3.89. Found: C, 60.01; H, 5.10; N, 4.26.

5-Bromo-8-bromomethyl-16-methyl-13-nitro[2.2]metacyclophane(**11**): pale yellow prisms (toluene), mp 283–285°C; ¹H NMR (CDCl₃) δ 0.84 (3H, s), 2.88 (2H, s), 2.76–3.28 (8H, m), 7.38 (2H, s), 8.00 (2H, s); IR (KBr) 2930, 1558, 1510, 1340, 1320, 1189, 1080, 882, 830, 790, 740, 720; MS, m/e 437, 439, 441 (M⁺). Anal. Calcd for C₁₈H₁₇Br₂NO₂: C, 49.23; H, 3.90; N, 3.19. Found: C, 49.86; H, 3.88; N, 3.56.

When **7** was treated under shielding from light, and worked up as described above, the expected **10** was obtained in 91% yield.

With an Equivalent of NBS. A mixture of 281 mg (1 mmol) of **7**, 214 mg (1.2 mmol) of NBS, and 30 mg of benzoyl peroxide in 200 ml of carbon tetrachloride was refluxed for 12 h. After the reaction mixture was cooled to room temperature, the precipitate was removed by filtration. The filtrate was evaporated in vacuo to give a mixture of **8a** and recovered **7**.

Hydrolysis of 8a. The mixture of **8a** and **7** described above was added into a suspension of 121 mg (7.12 mmole) of silver nitrate in 10 ml of water and 50 ml of acetone. After the reaction mixture was refluxed for 20 h, it was poured into a large amount of

water. The organic layer was extracted with chloroform, dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel using chloroform as an eluant to give 130 mg (62% from **7**) of 16-hydroxymethyl-8-methyl-5-nitro [2.2] metacyclophane (**9**) and 40 mg (20%) of **7**.

16-Hydroxymethyl-8-methyl-5-nitro [2.2] metacyclophane (**9**); pale yellow needles, mp 182–184°C; IR (KBr) 3300, 2950, 1510, 1340, 1310, 1180, 1080, 1000, 900, 778, 753, 720 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.52 (1H, t, $J=6$ Hz), 0.64 (3H, s), 2.60–3.32 (8H, m), 2.90 (2H, d, $J=6$ Hz), 6.94–7.24 (3H, m), 7.96 (2H, s); MS, m/e 297 (M^+). Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.44; H, 6.37; N, 4.64.

Bromination With Excess NBS. After a mixture of 281 mg (1 mmol) of **7**, 445 mg (2.5 mmol) of NBS, and 30 mg of benzoyl peroxide in 200 ml of carbon tetrachloride was refluxed for 4 h, it was treated and worked up as described above to afford 350 mg (80%) of 8,16-bis (bromomethyl)-5-nitro [2.2] metacyclophane (**8b**) as pale yellow prisms (benzene), mp $>300^\circ\text{C}$; ^1H NMR (CDCl_3) δ 2.75–3.32 (8H, m), 2.88 (2H, s), 2.92 (2H, s), 7.17–7.24 (3H, m), 8.05 (2H, s); MS, m/e 437, 439, 441 (M^+); IR (KBr) 3100, 2970, 1590, 1580, 1515, 1460, 1450, 1350, 1330, 1220, 1190, 915, 805, 785, 750 cm^{-1} . Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{Br}_2\text{NO}_2$: C, 49.23; H, 3.90; N, 3.19. Found: C, 49.24; H, 3.95; N, 3.48.

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