Medium-sized Cyclophanes. Part 42.[1] Synthesis of [2.*n*]Metacyclophan-1-ones and [2.*n*]Metacyclophane-1,2-diones

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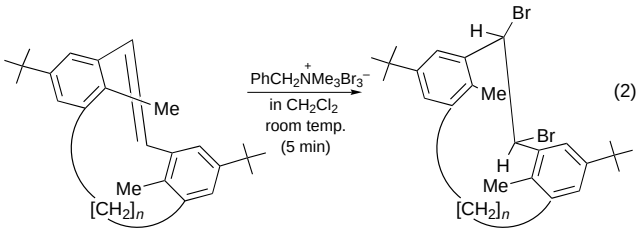
Acetolysis of 10-*endo*, 11-*exo*-dibromo-6,14-di-*tert*-butyl-9,17-dimethyl[3.2]metacyclophane *cis*-**3b** afforded the corresponding 10,11-diacetoxy derivative *cis*-**5b** with retention of configuration, whereas in the case of [4.2]metacyclophane *cis*-**3c** the same stereoselectivity was not observed: the diacetoxy derivatives **5** were converted into a 10,11-dione **10b** and a 11,12-dione **10c** *via* hydrolysis followed by Swern oxidation of dihydroxy derivatives **7b** and **7c**.

For many years various research groups have been attracted by the chemistry and spectral properties of the [2.2]MCP ([2.2]MCP = [2.2]metacyclophane) skeleton.[2,3] Its conformation, which has been elucidated by X-ray measurements,[4] is frozen into a chair-like non-planar form. Many attempts have been made directly to introduce functional groups into the methylene groups of [2.2]MCPs, but these have failed because of deviation of the benzyl carbon atom from the plane of the benzene ring.[5g]

Singler and Cram have reported that bromination of [2.2]paracyclophan-1-ene with bromine affords the corresponding *cis*-adduct.[6] Recently, we have reported that di-*tert*-butyl(dimethyl)[2.*n*]MCP-1-enes **1b**,**c** when treated with an equimolar amount of benzyltrimethylammonium tribromide (BTMA Br_3) in methylene dichloride[9a] afford the *cis*-adducts **3b**,**c** to the bridged double bond in 90 and 95% yield, respectively [eqn. (2)]. These results indicate the first success in the introduction of two bromo groups into the methylene groups of dimethyl[*n*.2]MCPs. We undertook the present work in order to extend the novel reaction mentioned above. We report here on the acetolysis of bromine adducts with silver acetate in acetic acid and the conversion into the 10,11-dione **10b** and 11,12-dione **10c** *via* hydrolysis followed by Swern oxidation of the dihydroxy derivatives **7**.



(2)

1b; *n* = 3
c; *n* = 4

cis-**3b**; *n* = 3
c; *n* = 4

Scheme 1

Acetolysis of 10-*endo*,11-*exo*-dibromo-6,14-di-*tert*-butyl-9,17-dimethyl[3.2]MCP *cis*-**3b** with silver acetate in acetic acid at 60 °C for 30 min afforded the corresponding 10-acetoxy derivative **4b** with complete retention of configuration in 90% yield. A prolonged reaction time (to 12 h) and higher reaction temperature (to 90 °C) furnished complete acetolysis to afford 10-*endo*,11-*exo*-diacetoxy-6,14-di-*tert*-butyl-9,17-dimethyl[3.2]MCP *cis*-**5b** with complete retention of configuration at the 10,11 positions in the bridged cyclophane ring.

In contrast, in the case of the [4.2]metacyclophane *cis*-**3c** the same stereoselectivity was not observed under either set of reaction conditions. Thus, 11,12-bis(*endo*-acetoxy)-7,15-di-*tert*-butyl-10,18-dimethyl[4.2]MCP *trans*-**5c** was obtained in 30 and 40% yields along with **4c** and *cis*-**5c**, respectively.

These results can be attributed to the nature of the cyclophane structure, like in the acetolysis of 1,2-dibromo[2.2]paracyclophane.[10a] The stereoselectivity of the acetolysis decreases with increasing the length of the methylene bridges and the distances between the two aromatic rings.

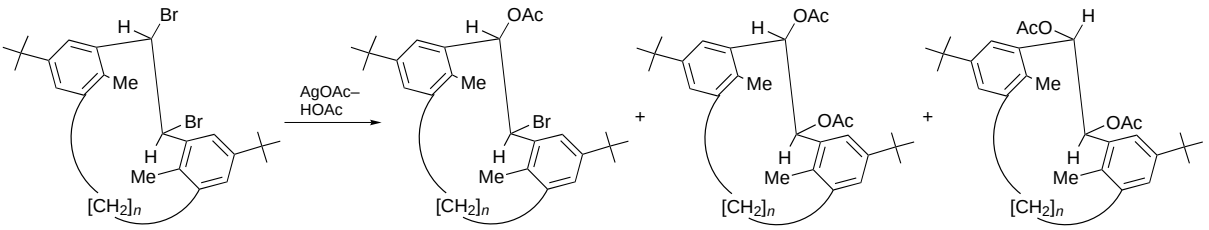
Acetates **4** and *cis*-**5** were easily converted into the corresponding alcohols **6** and *cis*-**7** by hydrolysis with alcoholic KOH at 50 °C for 15 min in almost quantitative yields.

Attempted oxidation of monools **6b** and **6c** with pyridinium chlorochromate[12] carried out in a methylene dichloride

Table 1 Acetolysis of *cis*-**3** with AgOAc in acetic acid[a]

Run	Substrate	Temp. (*T*/°C)	Time (*t*/h)	Products (%)
1	*cis*-**3b**	60	0.5	**4b** (90)
2	*cis*-**3b**	90	12	*cis*-**5b** (87)
3	*cis*-**3c**	60	0.5	**4c** (60), *trans*-**5c** (30)
4	*cis*-**3c**	90	12	*cis*-**5c** (50), *trans*-**5c** (40)

[a]Isolated yields are shown.



cis-**3b**; *n* = 3
c; *n* = 4

4b; *n* = 3
c; *n* = 4

cis-**5b**; *n* = 3
c; *n* = 4

trans-**5c**

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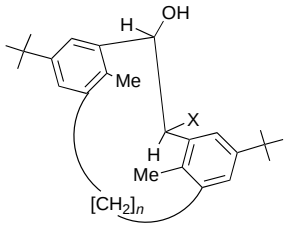
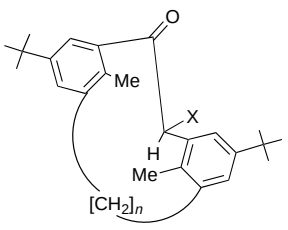


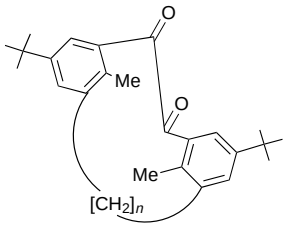
6b X = Br, *n* = 3
c X = Br, *n* = 4

cis-**7b** X = OH, *n* = 3
c X = OH, *n* = 4



8b X = Br, *n* = 3
c X = Br, *n* = 4

9b X = H, *n* = 3
c X = H, *n* = 4

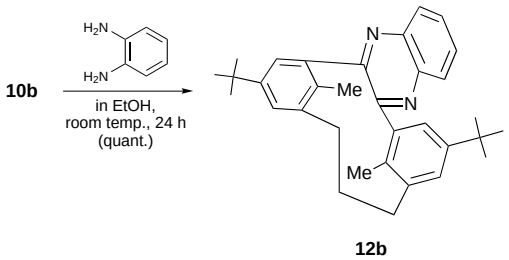


10b *n* = 3
c *n* = 4

solution at room temperature for 1 h led to the expected monoketones **8b** and **8c** as a single product in 61 and 90% yields, respectively. Monoketones **8b** and **8c** were easily converted into the corresponding **9b** and **9c** by reduction with zinc powder in acetic acid at 80 °C for 15 min.

In contrast, an attempted oxidation of the *cis*-diol cis-**7b** to the 11,12-dione **10b** with pyridinium chlorochromate carried out in a methylene dichloride solution under the same reaction conditions as described above failed. Only the cleavage reaction product, 1,3-bis(5-*tert*-butyl-3-formyl-2-methylphenyl)propane **11b**, was obtained in quantitative yield. This finding seems to support the strained nature of the diketone **10b** compared to the monoketones **8b** and **9b**, in spite of these having the same ring size.

Fortunately, Swern oxidation[13] of *cis*-**7b** succeeded in affording the desired [3.2]diketone **10b** in quantitative yield. However, **10b** was found to be labile during silica gel column chromatography, and on refluxing in hexane it gave only intractable mixtures. Thus, a trapping reaction of diketone **10b** with *o*-phenylenediamine was attempted, in which the crude diketone **10b** was treated with *o*-phenylenediamine in ethanol at room temperature for 24 h to afford in almost quantitative yield the desired [3.2]MCP **12b** having a quinoxaline skeleton (Scheme 3).



Scheme 3

Similarly, in the case of [4.2]MCP, Swern oxidation of the *cis*-diol *cis*-**7c** also succeeded in affording the desired diketone **10c** in 70% yield as stable colourless prisms. This finding seems to support the notion that the strain of the [3.2]diketone **10b** compared to the [4.2]diketone **10c** increases as the length of the methylene bridge decreases.

The low frequency in the IR spectrum (1700 cm^{-1} for **9b** and 1696 cm^{-1} for **9c**) in comparison with that of the reference compound, 5-*tert*-butyl-2,3-dimethylbenzyl 5-*tert*-butyl-2,3-dimethylphenyl ketone (1685 cm^{-1}), presumably and in analogy with the corresponding paracyclophane analogue,[10a,14] reflects expanded OCC bond angles rather than conjugation. Bathochromic shifts were observed in the cyclophane ketones **9b**,**c** and the diketone **10b**, which are ascribed to a transannular interaction between the two benzene rings and an increase in the strain of these systems.[15] The lack of an acetophenone-type chromophore in the UV spectrum of the MCP ketones confirms the non-planarity of the aromatic ring and carbonyl group.

In conclusion, we have demonstrated that acetolysis of 10-*endo*, 11-*exo*-dibromo-6,14-di-*tert*-butyl-9,17-dimethyl-[3.2]MCP *cis*-**3b** affords the corresponding 10,11-diacetoxy derivative **5b** with retention of configuration, whereas in the case of [4.2]MCP **3c** the same stereoselectivity is not observed. The present results of the stereoselective acetolysis of bromine adducts of [2.*n*]MCP-1-enes will open up new mechanistic aspects for cyclophane chemistry. Also, diacetoxy derivatives **5** were converted into the 10,11-dione **10b** and the 11,12-dione **10c** *via* hydrolysis followed by Swern oxidation of the dihydroxy derivatives **7**.

Further studies on the chemical properties of the monoketone **9** and diketone **10** are now in progress.

Techniques used: ^{1}H NMR, IR, mass spec.

References: 15

Schemes: 3

Fig. 1: UV absorption spectra of [*n*.2]MCP ketones **9b**, **9c** and reference compound **13** in cyclohexane

Fig. 2: UV absorption spectra of [*n*.2]MCP diketone **10c** and reference compound benzil **14** in cyclohexane

Table 2: ^{1}H NMR data for [2.*n*]MCP-1-ones **8**, **9** and [2.4]MCP-1,2-dione **10c**

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