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STRAINING STRAINED MOLECULES - 1.
THE SYNTHESIS OF THE FIRST CYCLOPHANE WITHIN A CYCLOPHANE - [2,2]PARACYCLO ([2,2]METACYCLOPHANE)

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The cyclophanes are an interesting group of strained molecules that have been the subject of extensive study.[1] In recent years they have taken bizarre forms as multi-bridged,[2] multi-stepped[3] and multi-layered[4] derivatives have been synthesized. Such studies have shown that both [2,2] meta- and [2,2] paracyclophanes contain considerable strain energy (11.9 and 31.4 kcal/mole respectively)[5] and that the benzene rings adopt boat conformations in both types of molecules.[6] As a consequence such molecules show unusual pmr spectra in which the aromatic protons are shielded to varying degrees.[2-4,7] This shielding would appear to depend, at least in part, on the deformation of the ring.[8] We therefore thought it would be interesting to further strain [2,2]metacyclophane by constraining two such units into a [2,2]paracyclophane, and have thus synthesized the first cyclophane within a cyclophane - **1**.

Wittig rearrangement[9] of 6,15-dimethyl-2,11-dithia[3,3]metacyclophane[10] **2**, followed by methylation gave a 95% yield of mixed isomers of **3** which were converted cleanly to anti-5,13-dimethyl[2,2]metacyclophane **4** in better than 85% yield by reduction[11] with Li in liq NH_3. Bromination of **4** with NBS in CCl_4 gave the dibromide **5**, m.p. 218-220° (lit[13] 206°) which, using the thiourea method,[14] gave the dithiol **6**, m.p. 128-130° (cyclohexane). Coupling[9] of **5** and **6** produced two dithiacyclophanes **7** and **8** in about 35% yield in ratio (5=1). The less soluble isomer could be obtained pure, m.p. 301-302° (dec) and was assigned the gross structure

7 on the basis of its pmr spectrum, (see table) analysis and mass[15] spectrum. The more soluble isomer has not yet been obtained free of **7**, and structure **8** seems the more probable. Repeat of the Wittig rearrangement - Li/NH_3 reduction sequence on **7** gave c.a. 25% product cyclophane **1**, white needles from cyclohexane, dec 310°, M^+ at m/e 468, together with the ring opened products **4** and  . Similar treatment of **8** gave a more soluble isomer **9**. Additional structural proof was supplied by oxidation of **1** and **9** to the very recently reported[13] pyrenophane **10** by $FeCl_3$ and then DDQ in refluxing toluene. The pmr spectra are given in table 1 below:

TABLE I - PMR SPECTRA ($CDCl_3$) τ - Values - 90 MHz

Compd.	EXT Ar-H	INT Ar-H	para-CH_2	meta-CH_2 (centres)
7	3.13	5.83	6.34	7.03, 7.94
8	3.01	5.78	6.33	6.93, 7.88
4	3.17	5.88	7.68 (CH_3)	7.02, 7.95
2,2-PCP	3.54	-	6.97	- (PCP = paracyclophane)
1	3.49	5.89	7.10	7.26, 8.12
9	3.39	6.01	7.09	7.25, 8.16

The shielding of the external aryl protons of **1** and **9** is clearly greater than for [2,2]metacyclophane **4** or the thiacyclophanes **7** and **8** but not as great as for [2,2]paracyclophane itself. This would seem reasonable since it could be expected that the meta-CH_2CH_2-bridges could take up some of the deformation that the ring experiences in [2,2]PCP themselves-indeed the pmr spectra indicates that these bridges are shielded somewhat with respect to 4. Surprisingly, the internal aryl protons are not much affected or differentiated. Molecular models indicate that the metacyclophanes distort greatly, and keep the internal protons away from the opposite cyclophane rings, however, the true reason must probably await an X-ray structure determination. We plan further to study the transannular effects present in these interesting molecules.

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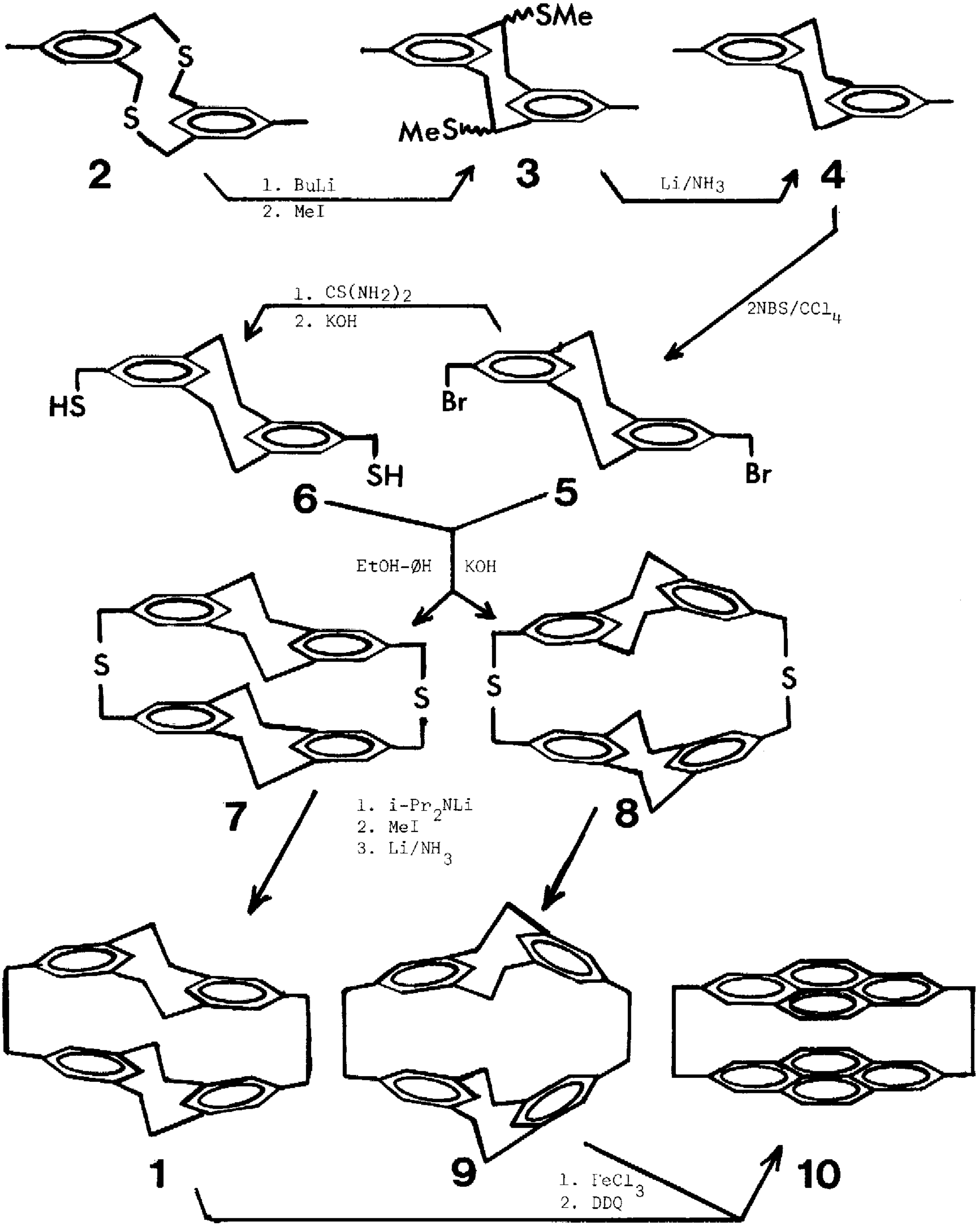
SMe
MeS
2
1. BuLi
2. MeI
3
Li/NH3
4
2NBS/CCl4
1. CS(NH2)2
2. KOH
HS
SH
Br
Br
6
5
EtOH-ØH
KOH
S
S
S
S
7
8
1. i-Pr2NLi
2. MeI
3. Li/NH3
1
9
1. FeCl3
2. DDQ
10

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8. Whereas it is clear that when a proton is pushed into the cavity of the π-electron cloud of a benzene ring it is shielded, it is not so obvious why bringing two benzene rings face to face should shield the external protons. This may be a consequence of ring deformation, i.e. less "aromatic" deshielding. See D. J. Cram and R. C. Helgeson, *J. Amer. Chem. Soc.*, **88**, 3515 (1966).

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11. We have found Li in NH_3-ℓ to be easier to use on the large scale than Raney Nickel, and Birch reduction of the benzene rings, observed[12] with Na/NH_3-ℓ is largely avoided.

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15. Even under chemical ionisation only fragment ions of **7** and **8** could be observed.