[4.2]- and [4.3]-Metacyclophanes

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[4.2]Metacyclophanes may conveniently be prepared *via* carbene insertion into appropriately protected [2.2]- and/or [3.2]-metacyclophanediones. Thus, starting from [2.2]metacyclophane-1,10-dione propylene thioacetal (1) [4.2]metacyclophane (6) was obtained (28%, three steps). For the synthesis of [4.3]metacyclophanes, [4.2]metacyclophane-2,12-dione (5) served as a key compound. Regioselective carbene insertion into (5) yielded [4.3]metacyclophane-2,13-dione (7) which was transformed into [4.3]metacyclophane (8) [7% starting from (1)]. The ring inversion barriers of (6) (60 kJ mol^{-1}, 308 K) and (8) (<38 kJ mol^{-1}, 138 K) were estimated by ^{1}H n.m.r. spectroscopy.

RECENTLY we reported the synthesis of [3.2]- and [3.3]-metacyclophanes *via* carbene insertion † into [2.2]metacyclophane-1,10-dione.[1,2] We now describe a route to the synthetically poorly explored [4.2]- and [4.3]-metacyclophane systems which are of interest for a comparative conformational study of [*m.n*]metacyclophanes.

The only compound described possessing the [4.2]-metacyclophane skeleton is 2,3-dimethyl[4.2]metacyclophan-1-ene prepared from 2,2-dimethyl[3.2]metacyclophanylmethanol by a Wagner–Meerwein type rearrangement.[3] This route, however, is restricted to the synthesis of certain derivatives and hence lacks general applicability. On the other hand for [4.3]metacyclophanes no synthesis has been described so far.

RESULTS AND DISCUSSION

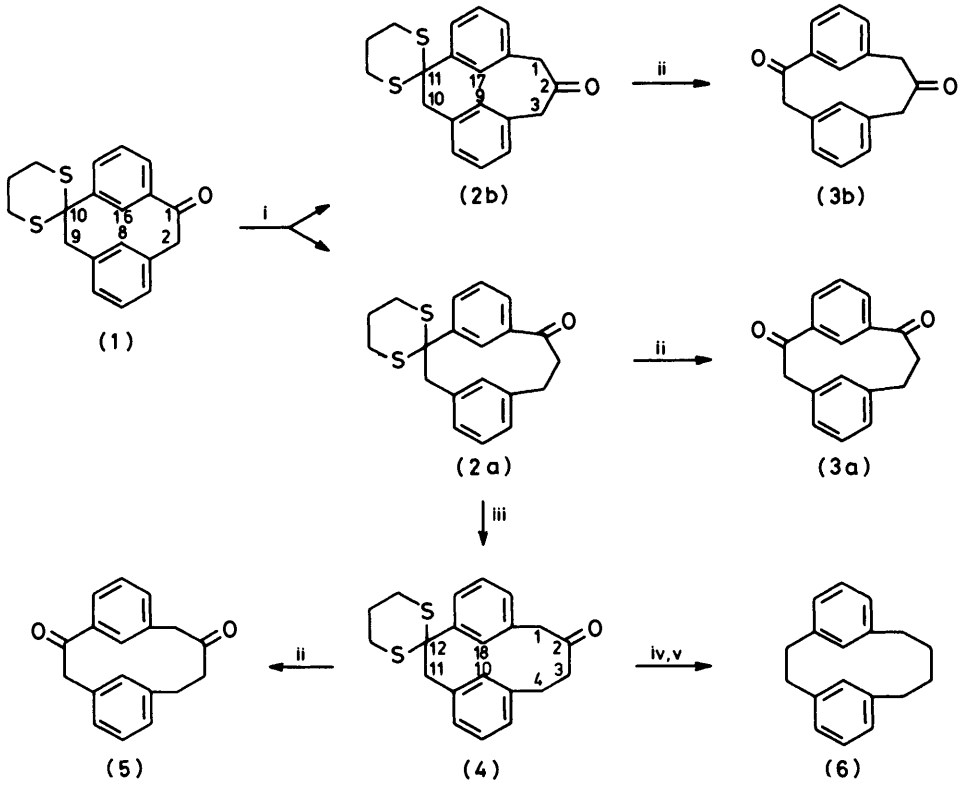
Any attempt to prepare [4.2]metacyclophanediones starting from the [3.2]metacyclophanediones (3a) or (3b) by ring enlargement with diazomethane failed because of the higher reactivity of the carbonyl group in the C_2 bridge of the latter. Thus under mild conditions only [3.3]metacyclophanes were formed while under forcing conditions a complex mixture of higher homologues was obtained.[1] This competition, however, can be overcome if the more reactive carbonyl group of (3a) or (3b) is blocked by a protecting group. As a precursor for the [4.2]metacyclophane synthesis we used the monopropylene thioacetal of [2.2]metacyclophane-1,10-dione (1) easily available either by partial oxidative saponification of the pertinent bis[propylene thioacetal][4,5] or by reaction of [2.2]metacyclophane-1,10-dione with one equivalent of propane-1,3-dithiol. If the thioacetal (1) is treated with ethereal diazomethane in propan-2-ol–chloroform two [3.2]metacyclophanes, (2a) and (2b), are formed and can be separated by p.l.c. The substitution pattern of (2a) and (2b) unequivocally follows from the chemical transformation into the known compounds (3a) and (3b)[1] with aqueous *N*-bromosuccinimide. Under the conditions employed, carbene exclusively adds to a very reactive carbonyl group as present in a C_2 bridge while a carbonyl group in a C_3 bridge turns out to be far less reactive. This is due to the difference in the relief of steric strain by ring enlargement and has been discussed elsewhere.[1] In the [3.2]metacyclophanones (2a) and (2b) the carbonyl groups of the C_2 bridge are appropriately protected, so that under more rigorous conditions (methanol-catalyzed, 30-fold excess of diazomethane) a second equivalent of diazomethane is added to (2a) yielding the [4.2]metacyclophane (4) (61%) accompanied by small amounts of isomeric oxirans. The second possible isomer of (4) could not be detected. In contrast to (2a), (2b) resisted any ring enlargement reaction with diazomethane.

Alternatively, compound (4) can be synthesized directly from compound (1) if more forcing reaction conditions are employed the by-products [oxirans and the inert compound (2b)] being separated by p.l.c. The position of the oxo-function in (4) follows from the ^{1}H n.m.r. spectrum of the bridges at 323 K. It exhibits one AA'BB' system and two singlets indicating an apparent C_s symmetry (see Experimental section).

Compound (4) served as an intermediate in the synthesis of [4.2]metacyclophane-2,12-dione (5) and the parent hydrocarbon [4.2]metacyclophane (6). Removal of the protecting group with *N*-bromosuccinimide in aqueous tetrahydrofuran yielded the diketone (5). Treatment of compound (4) with propane-1,3-dithiol and subsequent desulphurisation with Raney nickel gave [4.2]metacyclophane (6) [28% starting from (1)]. Although the signals of the ^{1}H n.m.r. spectrum due to the bridges of (6) at room temperature are broad and somewhat unstructured, at 233 K they sharpen and the C_2 symmetry becomes obvious (C_2 bridge: AA'BB'; C_4 bridge: AA'BB'CC'DD'). Conversely, at 323 K the AA'BB' system of the C_2 bridge becomes a singlet while for the C_4 bridge an A_4B_4 system is observed (see Experimental section). From the coalescence temperature (T_c 308 K) and the ^{1}H n.m.r. parameters of the AA'BB' spin system ($\Delta\nu$ 200 Hz) the ring inversion barrier was estimated to be 60 kJ mol^{-1}.

The different reactivities of the two oxo-functions in [4.2]metacyclophane-2,12-dione (5) offer the opportunity to prepare [4.3]metacyclophanes selectively. On treatment of (5) with diazomethane in propan-2-ol–chloroform two fractions were obtained (p.l.c.). The slower zone

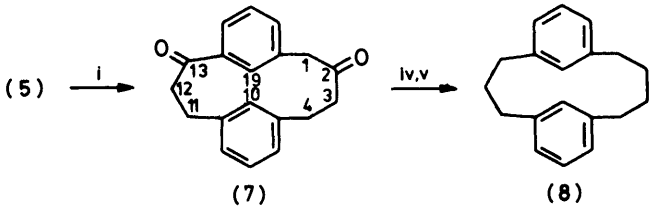
† The term 'carbene insertion' refers to the net reactions. Mechanistically the rate-determining step leads to an ionic tetracovalent intermediate. The comments given in ref. 1 are also valid for the reactions discussed herein.



SCHEME 1 *Reagents:* i, CH_2N_2–propan-2-ol; ii, *N*-bromosuccinimide–water; iii, CH_2N_2–methanol; iv, propane-1,3-dithiol; v, Raney nickel

turned out to be homogenous. The ^1H n.m.r. spectrum shows an apparent C_s symmetry and the protons of the bridges exhibit two AA'BB' spin systems and one singlet (see Experimental section). This evidence is compatible with [4.3]metacyclophane-2,13-dione (7), rapidly interconverting between its enantiomers.

The second fraction obtained consisted of at least four compounds (g.c.–mass spectrometry), *i.e.* starting material (5), [4.3]metacyclophane-2,12-dione and two isomeric oxirans. A preparative separation of this mixture has not been attempted.



SCHEME 2 *Reagents:* see Scheme 1

Analogously to compound (6), [4.3]metacyclophane (8) was obtained *via* desulphurisation of the appropriate thioacetal with Raney nickel [overall yield 7%, six steps starting from (1)]. The ^1H n.m.r. spectrum of (8) at room temperature exhibits sharp signals and an apparent C_{2v} symmetry. On lowering the temperature to 193 K (CD_2Cl_2) the resonance absorptions due to the aliphatic moieties become broad but no splitting of signal bands is observed. Assuming the shift difference of the axial and equatorial protons at C-1 (and C-4) in (8) and (6) (120 Hz) to be similar, the ring inversion barrier of (8) is estimated to be <38 kJ mol^{-1}.

A conformational analysis of the compounds synthesized will be given in connection with a comparative study of [*m.n*]metacyclophanes.[6]

EXPERIMENTAL

M.p.s were taken with a Kofler-Reichert hot-stage apparatus. For ^1H n.m.r. spectra (250 MHz, Fourier transform mode) a Bruker WM 250 instrument was used (deuteriochloroform and 20 °C if not stated otherwise, tetramethylsilane as internal standard). I.r. spectra were run with a Perkin-Elmer 377 spectrometer in spectroscopic grade carbon tetrachloride (Uvasol, Merck). Mass spectra were taken with a Varian MAT CH7 instrument (70 eV). For electronic absorption spectra in spectroscopic grade cyclohexane (Uvasol, Merck) a Cary 15 spectrometer was used (1-cm cuvettes, ambient temperature). P.l.c. was performed on Kieselgel HF_{254} (Merck). G.l.c. analysis was performed with a Varian Aerograph 1 400 [5 ft × 1/8 in column of 2% OV 17 on Anakrom ABS (Analabs) at 210 °C]. For preparation of ethereal diazomethane (1—1.6 mol l^{-1}, by titration) see ref. 1. Ether refers to diethyl ether.

[3.2]*Metacyclophane*-1,11-*dione* (2a) *and* [3.2]*Metacyclophane*-2,11-*dione* 11-*Propylene Thioacetals* (2b).—To a solution of compound (1) [4,5] (200 mg, 0.61 mmol) in chloroform (7 ml) and propan-2-ol (2.5 ml) ethereal diazomethane (1M; 3 ml, 3 mmol) was added in one portion at 0 °C. After 2.5 h at 0 °C excess of diazomethane was trapped

with acetic acid. The solvent was evaporated off under reduced pressure and the residue chromatographed (p.l.c., benzene). This yielded (2a) (115 mg, 54%) and (2b) (34 mg, 16%); overall yield 70%.

Compound (2a) had m.p. 143—147 °C (from ether); $\nu_{max.}$ 1 685 cm^{-1} (CO); δ 8.33 (d, 1 H, 13-H), 7.74 (d, 1 H, 15-H), 7.58 (t, 1 H, 14-H), 7.29 (t, 1 H, 6-H), 7.25 (d, 1 H, 5-H or 7-H), 7.14 (d, 1 H, 7-H or 5-H), 6.75 (' t ', 1 H, 17-H), 5.05 (' t ', 1 H, 9-H), 3.38 and 2.65 (AXq, 2 H, *J* 12.8, 10-H), 3.10, 3.05, 2.66, and 2.38 (ABCD m, 4 H, 2-H and 3-H), 2.96, 2.74, 2.50, 2.29, and 1.97 (ABCDEF m, 6 H, H of dithian moiety); $\lambda_{max.}$ 288 (ε 1 320), 250s (5 460), and 220s nm (22 400) (Found: C, 70.7; H, 6.0; S, 18.5%; M^+, 340. $C_{20}H_{20}OS_2$ requires C, 70.5; H, 5.9; S, 18.8%; *M*, 340). *Compound* (2b) had m.p. 149—153 °C (from ether); $\nu_{max.}$ 1 707 cm^{-1} (CO); δ 8.05 (d, 1 H, 13-H), 7.47 (t, 1 H, 14-H), 7.25 (d, 1 H, 15-H), 7.25 and 7.15 (m, 3 H, 5-H, 6-H, and 7-H), 6.32 (' t ', 1 H, 17-H), 5.02 (' t ', 1 H, 9-H), 3.63 and 3.47 (ABq, 2 H, *J* 15.3, 1-H or 3-H), 3.53 and 3.46 (ABq, 2 H, *J* 14.8, 3-H or 1-H), 3.34 and 2.57 (AXq, 2 H, *J* 12.8, 10-H), 3.03, 2.76, 2.56, 2.47, and 2.00 p.p.m. (ABCDEF m, 6 H, H of dithian moiety); $\lambda_{max.}$ 325s (ε 80), 315 (200), 305 (270), 296 (280), 268 (1 020), and 235s nm (7 800) (Found: C, 70.4; H, 6.0; S, 18.7%; M^+, 340).

[3.2]*Metacyclophane*-1,11-*dione* (3a).—To (2a) (50 mg, 0.15 mmol) in tetrahydrofuran (2 ml) and water (0.2 ml) was added within 5 min *N*-bromosuccinimide (140 mg, 0.8 mmol) in acetone (2 ml) and water (0.2 ml). After 20 min water (20 ml) and ascorbic acid (20 mg) were added. Usual work-up [1] yielded after p.l.c. (benzene containing 0.3% v/v ethyl acetate) (3a) (20 mg, 55%), m.p. 125—128 °C; identical (^{1}H n.m.r., mass spectrum) with the material reported.[1]

[3.2]*Metacyclophane*-2,11-*dione* (3b).—By the same procedure as described for (3a), (3b) (26 mg, 50%) was obtained from (2b) (70 mg). It had m.p. 109—112 °C and was identical (^{1}H n.m.r., mass spectrum) with the material reported.[1]

[4.2]*Metacyclophane*-2,12-*dione* 12-*Propylene Thioacetal* (4).—(*a*) *From compound* (2a). Compound (2a) (105 mg, 0.3 mmol) dissolved in chloroform (8 ml) and methanol (4 ml) was treated with ethereal diazomethane (1.4M; 8 ml, 11.2 mmol) and the mixture allowed to stand at 0 °C for 22 h. Work-up followed by p.l.c. (benzene) gave compound (4) (65 mg, 61%), m.p. 184—186 °C (from ether); $\nu_{max.}$ 1 720 cm^{-1} (CO); δ(323 K) 8.12 (d, 1 H, 14-H), 7.53 (t, 1 H, 15-H), 7.23 (d, 1 H, 16-H), 7.17—7.08 (m, 3 H, 6-H, 7-H, and 8-H), 6.54 (' t ', 1 H, 18-H), 5.39 (' t ', 1 H, 10-H), 3.51 (s, 2 H, 1-H), 3.07 (s, 2 H, 11-H), 2.76 and *ca.* 2.5 (AA'BB' m, 4 H, 3-H and 4-H), *ca.* 2.6 and 1.94 p.p.m. (A_4B_2 m, 6 H, H of dithian moiety); $\lambda_{max.}$ 323s (ε 24), 305s (100), 274 (1 010), 267 (1 200), and 261s nm (1 020) (Found: C, 71.2; H, 6.2; S, 17.9%; M^+, 354. $C_{21}H_{22}OS_2$ requires C, 71.1; H, 6.3; S, 18.1%; *M*, 354).

(*b*) *From compound* (1) *without isolation of intermediates.* To compound (1) (60 mg, 0.18 mmol) dissolved in chloroform (3 ml) and methanol (2 ml) ethereal diazomethane (1.6M; 4 ml, 6.4 mmol) was added at 0 °C. Work-up after 25 h and p.l.c. (benzene) gave compound (4) (25 mg, 38%) accompanied by compound (2b) (10 mg, 16%).

[4,2]*Metacyclophane*-2,12-*dione* (5).—Compound (4) (80 mg, 0.22 mmol) dissolved in tetrahydrofuran (2 ml) and water (0.2 ml) was immersed in an ice-bath. Then *N*-bromosuccinimide (210 mg, 1.2 mmol) in acetone (2 ml) and water (0.2 ml) was added within 4 min. After the mixture had been maintained for 15 min at 0 °C aqueous ascorbic acid was added. Extraction with ether yielded after p.l.c. (benzene containing 0.3% v/v ethyl acetate) compound (5) (35 mg, 60%), m.p. 144—148 °C (from ether); $\nu_{max.}$ 1 717 and 1 695 cm^{-1} (CO); δ 7.28 (d, 1 H, 14-H or 16-H), 7.25 (t, 1 H, 15-H), 7.14 (d, 1 H, 16-H or 14-H), 7.05 (' t ', 1 H, 10-H or 18-H), 7.00 (' t ', 1 H, 18-H or 10-H), 6.99 (t, 1 H, 7-H), 6.86 (d, 1 H, 6-H or 8-H), 6.79 (d, 1 H, 8-H or 6-H), 4.05 (s, 2 H, 11-H), 3.64 (s, 2 H, 1-H), 2.96 and 2.48 p.p.m. (AA'BB' m, 4 H, 3-H and 4-H); $\lambda_{max.}$ 350s (ε 105), 335s (155), 320s (190), 298s (625), 283 (890), 278s (880), and 234 nm (9 300) (Found: C, 81.5; H, 6.2%; M^+, 264. $C_{18}H_{16}O_2$ requires C, 81.8; H, 6.1%; *M*, 264).

[4.2]*Metacyclophane* (6).—A solution of compound (4) (65 mg, 0.18 mmol) in acetic acid (2 ml) was treated with propane-1,3-dithiol (0.05 ml and boron trifluoride–diethyl ether (0.02 ml). After 24 h at room temperature the mixture was diluted with water (10 ml) and then extracted with chloroform; the extract was washed with aqueous sodium hydrogen carbonate and water and then evaporated to dryness. The residue was taken up in tetrahydrofuran (3 ml) and Raney nickel T1 [7] was added. Desulphurisation was complete after the mixture had been heated for 5 h under reflux. The slurry was filtered off and the solvent evaporated from the filtrate. The resulting oil was distilled (Kugelrohr, 110—130 °C, 0.03 Torr). This yielded compound (6) (32 mg, 74%), m.p. 43—45 °C (from methanol); δ(323 K) 7.20 (t, 2 H, 7-H and 15-H), 7.05 [d, 2 H, 6-H and 16-H (or 8-H and 14-H)], 6.92 [d, 2 H, 8-H and 14-H (or 6-H and 16-H)], 5.72 (' t ', 2 H, 10-H and 18-H), 2.71br (s, 4 H, 11-H and 12-H), 2.47br and 1.32br (A_4B_4 m, 8 H, 1-H, 4-H, 2-H, and 3-H); δ(233 K) 7.25, 7.08, 6.97, and 5.74 (ABCX m, 8 H, ArH, assignment as at 323 K), 3.14 and 2.34 (AA'BB'm, 4 H, J_{AB} −12.5, $J_{A'B} = J_{AB'}$ 2.9, $J_{AA'}$ 4.9, $J_{BB'}$ 12.6, 11-H and 12-H), 2.72, 2.26, 1.61, and 1.02 (AA'BB'CC'DD'm, 8 H, J_{AB} −14, $J_{AC} \sim J_{AD}$ 3.0, J_{BC} 13, J_{BD} 2.8, J_{CD} −13 1-H, 4-H, 2-H, and 3-H); $\lambda_{max.}$ 274 (ε 360), 270 (370), 266s (440), 264 (470), 258s (370), 252s (270), and 220s nm (16 300) (Found: C, 91.3; H, 8.6%; M^+, 236. $C_{18}H_{20}$ requires C, 91.5; H, 8.5%; *M*, 236).

[4.3]*Metacyclophane*-2,13-*dione* (7).—A solution of compound (5) (100 mg, 0.38 mmol) in chloroform (6 ml) and propan-2-ol (3 ml) was treated with ethereal diazomethane (1M; 6 ml, 6.0 mmol) and the mixture allowed to stand for 16 h at 0 °C. Work-up and p.l.c. (benzene containing 0.3% v/v ethyl acetate) yielded compound (7) (52 mg, 50%) as the slower fraction and a mixture (30 mg) of compound (5), [4.3]metacyclophane-2,12-dione, and two oxirans (g.c.-mass spectrometry). *Compound* (7) had m.p. 85—88 °C (from diethyl ether); $\nu_{max.}$ 1 717 and 1 685 cm^{-1} (CO); δ 7.59 (d, 1 H, 15-H), 7.17 (m, 2 H, 16-H and 17-H), 7.13 (' t ', 1 H, 19-H), 6.93 (' t ', 1 H, 10-H), 6.76 (t, 1 H, 7-H), 6.64 (d, 1 H, 6-H or 8-H), 6.60 (d, 1 H, 8-H or 6-H), 3.61 (s, 2 H, 1-H), 3.19 and 2.98 [AA'BB' m, 4 H, $J_{AA'} \sim -14$, J_{AB} 6.8, $J_{AB'}$ 6.4, $J_{BB'} \sim -12$, 11-H and 12-H (or 3-H and 4-H)], 2.84 and 2.67 [AA'BB' m, 4 H, $J_{AA'}$ −13, J_{AB} 7.6, $J_{A'B}$ 4.1, $J_{BB'}$ −12.3, 3-H, and 4-H (or 11-H and 12-H)]; $\lambda_{max.}$ 345s (ε 34), 315s (115), 297 (850), 288 (950), and 242 nm (6 850) (Found: C, 81.8; H, 6.6%; M^+, 278. $C_{19}H_{18}O_2$ requires C, 82.0; H, 6.5%; *M*, 278).

[4.3]*Metacyclophane* (8).—The hydrocarbon (8) was obtained from compound (7) following the procedure given for compound (6). Starting from compound (7) (48 mg, 0.17 mmol) compound (8) (26 mg, 60%) was obtained. *Compound* (8) had m.p. 28—31 °C (from methanol); δ 7.16

(t, 2 H, 7-H and 16-H), 7.04 [d, 2 H, 6-H and 17-H (or 8-H and 15-H)], 6.90 [d, 2 H, 8-H and 15-H (or 6-H and 17-H)], 6.11 (' t ', 2 H, 10-H and 19-H), ~2.5 and 2.13 (A_4B_2 m, 6 H, 11-H, 13-H, and 12-H), *ca.* 2.5 and 1.52 (A_4B_4 m, 8 H, 1-H, 4-H, 2-H, and 3-H); (no splitting of ^1H n.m.r. bands in CD_2Cl_2 down to 193 K); $\lambda_{max.}$ 273 (ε 290), 270 (340), 266s (400), 263 (440), 258s (350), 220s (13 300), and 215s nm (15 500) (Found: C, 91.0; H, 8.9%; M^+, 250. $C_{19}H_{22}$ requires C, 91.1; H, 8.9%; *M*, 250).

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REFERENCES

[1] D. Krois, and H. Lehner, *J. Chem. Soc., Perkin Trans. 1*, 1982, 477.
[2] For the nomenclature of phanes see F. Vögtle and P. Neumann, *Tetrahedron*, 1970, **26**, 5847.
[3] R. W. Griffin, jun. and R. A. Cobrun, *J. Org. Chem.*, 1967, **32**, 3956.
[4] D. Krois, E. Langer, and H. Lehner, *Tetrahedron*, 1980, **36**, 1345.
[5] H. W. Gschwendt, *J. Am. Chem. Soc.*, 1972, **94**, 8430.
[6] D. Krois, and H. Lehner, *Tetrahedron*, in the press.
[7] X. A. Dominguez, I. C. Lopez, and R. Franco, *J. Org. Chem.*, 1961, **26**, 1625.