Registry No. **1a**, 922-67-8; **1b**, 623-47-2; **2a**, 51326-24-0; **3a**, 70288-54-9; **3b**, 70288-55-0; **4a**, 70288-56-1; **4b**, 70288-57-2; **5b**, 70288-58-3; **6a**, 70288-59-4; **7a**, 13155-85-6; **8a**, 42132-17-2; **9a**, 3604-36-2; *cis*-cyclooctene, 931-87-3; *trans*-cyclooctene, 931-89-5; *cis*-cyclodecene, 935-31-9; norboradiene, 121-46-0; cyclopentadiene, 542-92-7; cyclopentene, 142-29-0; aluminum chloride, 7446-70-0.

Synthesis of [5.1]Metacyclophane

Neville Finch* and Charles W. Gemenden

Research Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, New Jersey 07901

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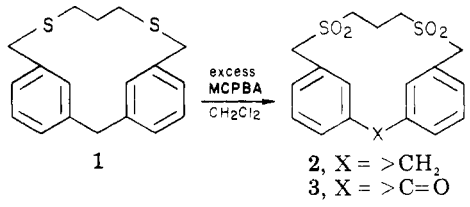
In an earlier publication[1] we mentioned the synthesis of [5.1]metacyclophane **10**, which we now describe. Vögtle[2] recently published the first syntheses of both [4.1]- and [5.1]metacyclophane by use of the sulfone pyrolysis method.

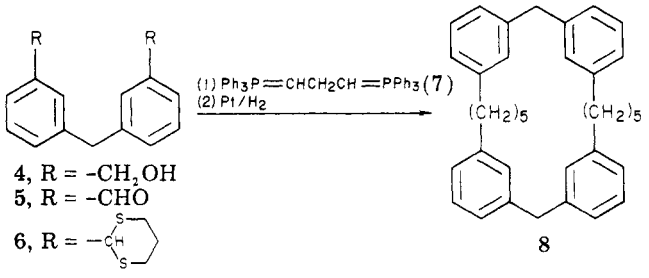
Syntheses of [*n*.1]metacyclophanes have not been commonplace due to the lack of a general method such as that developed by Boekelheide for the [2.2]metacyclophanes.[3] However, while the sulfone pyrolysis procedure developed by Vögtle[2] and Staab[4] promises to meet the requirement of general applicability, it appears to be limited with regard to the amounts of cyclophanes which can be produced. The bis(sulfone) **2** was available to us by oxidation, with excess peracid, of the bis(sulfide) **1** (see Scheme I). Despite the structural similarity to the bis(sulfone) **3** used successfully by Vögtle,[2] we were unable to induce thermal cracking of the bis(sulfone) **2** in a preparatively useful manner. Other routes suitable for the preparation of multigram quantities of [5.1]metacyclophane **10** were therefore explored.

As quite strained olefins had been synthesized by intramolecular Wittig reactions,[5] this reaction was the first approach we considered. More particularly, bis Wittig reactions had been widely used to prepare other types of macrocyclic compounds.[6] The dialdehyde **5** was readily prepared by Jones oxidation from the previously described bis(carbinol) **4**.[1] Reaction of this dialdehyde **5** with the bis(ylide) **7** obtained from 1,3-trimethylenebis(triphenylphosphonium) bromide[7] and 2 equiv of butyllithium yielded, after catalytic reduction of the product, not the desired product of intramolecular bridging, i.e., the [5.1]metacyclophane **10**, but the intermolecularly bridged dimeric product **8**. The structure of this product was evident by the strong molecular ion peak in the mass spectrum at *m/e* 472 (see Scheme II).

Other methods of inserting the three-carbon bridge were considered. The bis(dithiane) **6** could be readily prepared from the dialdehyde **5**. Although attempts to react the dilithio derivative of the bis(dithiane) **6** with a variety of 1,3-dihalopropanes were unsuccessful, a stepwise procedure was successful in providing the bridged dithiane **9**. Reaction of the lithio derivative with 1,3-bromochloropropane yielded the 3-chloropropyl dithiane contaminated with traces of starting material and presumably the dialkylated product. The crude monoalkylated material was treated

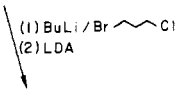


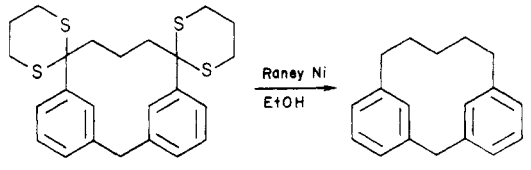
1 2, X = $>CH_2$ 3, X = $>C=O$



4, R = $-CH_2OH$
5, R = $-CHO$
6, R =

8





9 10

with lithium diisopropylamide (LDA) in THF. The crystalline-bridged dithiane **9** could be isolated by filtration through neutral III alumina. The overall yield of **9** for the two steps from the dithiane **6** was 30%, which, for the formation of this type of macrocycle, was considered satisfactory. Desulfurization of the bridged dithiane **9** with Raney nickel yielded [5.1]metacyclophane **10**, which was purified by preparative GLC and crystallized from methanol/pentane to yield a product with mp 53–54 °C. The spectral data obtained were similar to those reported by Vögtle,[2] but a direct comparison of the samples or spectra was not made.[8]

The yield on the desulfurization step was surprisingly poor (15%), but no attempt was made to study this process or employ other methods of removing dithioketals and then reducing the resulting diketone to **10**. The process though lends itself well to scale up and promises to be a route by which multigram quantities of [5.1]metacyclophane **10** can be obtained.

Experimental Section

General Procedures. Melting points were determined in a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were obtained on a Varian A60 spectrometer in $CDCl_3$, unless otherwise stated, infrared spectra on a Perkin-Elmer 21 or 521 spectrophotometer, mass spectra on an AEI MS902 spectrometer at 70 eV, and ultraviolet spectra on a Cary 14 instrument.

2,6-Dithia[7.1]metacyclophane 2,2,6,6-Tetraoxide (2). 2,6-Dithia[7.1]metacyclophane[1] (2 g, 0.0067 mol) was dissolved in CH_2Cl_2 (50 mL). With stirring, *m*-chloroperbenzoic acid (5 g, 0.0286 mol) was added portionwise during 30 min, which caused a gentle reflux. As the mixture cooled, a solid separated, which was collected. The filtrate was washed (10% aqueous $KHCO_3$) and dried ($MgSO_4$), and the solvent was removed. The residue

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(8) Professor Vögtle did not respond to our letter or comment on the 100-MHz spectrum of **10** contained therein.

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was combined with the previously collected solid and refluxed in methanol. Upon re-collection, the solid, the tetraoxide **2**, had mp 266–268 °C and represented an almost quantitative yield: NMR (CF_3CO_2H) δ 7.64–7.28 (m, 6), 7.12 (s, 2), 4.48 (s, 4), 4.12 (s, 2), 3.38–2.82 (t, 4), 2.42–1.58 (m, 2); IR (Nujol) 1603 (w), 1590 (w), 1298 (s), 1149 (s), 1112 (s), 1108 (s), 700 (m) cm^{-1}; MS *m/e* 365 (M^+). Anal. Calcd for $C_{18}H_{20}O_4S_2$: C, 59.33; H, 5.53. Found: C, 58.98; H, 5.43.

Pyrolysis[9] of **2** in gram quantities in high vacuum at 550–600 °C did not yield detectable amounts of [5.1]metacyclophane **10**.

3,3′-Methylenedibenzaldehyde (5). 3,3′-Methylenedi(benzyl alcohol)[1] (**4**) (51.6 g, 0.226 mol) was dissolved in acetone and the solution cooled to × −50 °C. Jones' reagent[10] (125 mL) was added during 1 h with cooling and stirring. The mixture warmed to −30 °C during the subsequent 1.5 h. Following usual workup, the ethereal extract was washed (with brine), dried ($MgSO_4$), and concentrated in vacuo. The residue (50.3 g, 0.225 mol, 99%) was the dialdehyde **5**: NMR δ 9.97 (s, 2), 7.68–7.25 (m, 8), 4.1 (s, 2).

3,3′-Methylenedibenzaldehyde Dithioketal (6). The dialdehyde **5** described above (10.1 g, 0.045 mol) was dissolved in toluene (700 mL). 1,3-Propanedithiol (13.7 g, 0.126 mol) and *p*-toluenesulfonic acid (0.3 g) were added. The mixture was refluxed 16 h with a Dean–Stark trap. The toluene was removed in vacuo. The residue was dissolved in $CHCl_3$, washed (20% aqueous KOH, 1 N HCl, water), and dried ($MgSO_4$), and then the $CHCl_3$ was removed in vacuo. The residue was recrystallized from $MeOH/CH_2Cl_2$ to give the dithiane **6**: mp 157–159 °C (14.6 g, 0.036 mol, 80%); NMR (Me_2SO) δ 7.4–7.0 (m, 8), 5.36 (s, 2), 3.94 (s, 2); IR (Nujol) 1596 (m), 1584 (w), 1270 (m), 746 (s), 710 (s) cm^{-1}. Anal. Calcd for $C_{21}H_{24}S_4$: C, 62.37; H, 5.98. Found: C, 62.56; H, 6.08.

[5.1.5.1]Metacyclophane (8). The dialdehyde **5** (3.3 g, 0.0147 mol) was dissolved in tetrahydrofuran (100 mL) under N_2. The ylide **7** was prepared from 1,3-trimethylenebis(triphenylphosphonium) bromide[7] (10.4 g, 0.0143 mol) and *n*-butyllithium (18.4 mL of a 1.6 N solution, 0.0294 mol) in tetrahydrofuran (150 mL) under N_2. The two solutions were added dropwise with stirring under N_2 to tetrahydrofuran (100 mL) during 2 h. The mixture was refluxed overnight. The tetrahydrofuran was removed in vacuo. The residue was dissolved in water and extracted (ether). The ethereal extracts were washed (brine), dried ($MgSO_4$), and concentrated to dryness. The residue (5.7 g) was dissolved in ethyl acetate and hydrogenated over 10% Pt/C at room temperature and atmospheric pressure. The catalyst and ethyl acetate were removed. The residue was put on to neutral III alumina (100 g). Elution by hexane yielded a crystalline compound **8**: mp 126–127 °C (recrystallized from ether) (0.24 g, 0.508 mmol, 3% yield); NMR δ 7.34–6.98 (m, 12), 6.88 (br, s, 4), 3.94 (s, 4), 2.70–2.30 (t, 8), 1.84–1.00 (m, 12); IR (Nujol) 1604 (m), 1590 (m), 778 (s), 738 (s), 700 (s) cm^{-1}; MS *m/e* 472 (M^+). Anal. Calcd for $C_{36}H_{40}$: C, 91.47; H, 8.53. Found: C, 91.43; H, 8.48.

[5.1]Metacyclophane-1,5-dione Bis(trimethylene dithioketal) (9). The dithiane **6** (8.55 g, 0.021 mol) was dissolved in tetrahydrofuran (600 mL). The solution was cooled to −60 °C under N_2, and *n*-butyllithium (20 mL of a 1.6 M solution, 0.032 mol) added dropwise. The mixture was stirred for 1 h, and then 1-bromo-3-chloropropane (3.90 g, 0.025 mol) in tetrahydrofuran (70 mL) was added dropwise. After 2 h the mixture was allowed to warm to room temperature and stirred overnight. The tetrahydrofuran was removed in vacuo. The residue was dissolved in $CHCl_3$. The chloroform solution was washed (1 N HCl, water) and dried ($MgSO_4$), and $CHCl_3$ was removed in vacuo to yield an oil (10.3 g, 101% yield based on product). TLC on silica GF eluted by benzene indicated the presence of a small amount of the dithiane **6** and a single slightly faster moving major component: NMR δ 7.82–7.50 (m, 2), 7.40–6.80 (m, 6), 5.08 (s, 1), 3.96 (s, 2), 3.32 (t, 2), 3.10–2.36 (m, 8), 2.36–1.40 (m, 8).

A portion of the above oil (1 g, 0.002 mol) was dissolved in dry tetrahydrofuran (100 mL). This solution was added, under N_2, dropwise with stirring to LDA (from diisopropylamine (0.424 g, 0.004 mol) and *n*-butyllithium (2 mL of a 1.6 M solution 0.003 mol)) in tetrahydrofuran (400 mL) at −60 °C. After 2 h the reaction mixture was allowed to warm to room temperature and stirred for 2 days. The tetrahydrofuran was removed in vacuo. The residue was dissolved in chloroform. The chloroform solution was washed (1 N HCl, water) and dried ($MgSO_4$), and $CHCl_3$ was removed in vacuo. The residue was chromatographed on neutral III alumina. Elution by pentane/benzene (1:1) yielded the crystalline cyclized dithiane **9** (270 mg, 0.6 mmol, 30% yield). Recrystallization provided the analytical sample (155 mg) of **9**: mp 225–227 °C (recrystallized from $MeOH/CH_2Cl_2$); NMR δ 7.84–7.50 (m, 2), 7.40–7.20 (m, 4), 7.02 (br s, 2), 4.08 (s, 2), 2.88–2.54 (m, 8), 2.14–1.66 (m, 8), 1.36–0.80 (m, 2); IR (Nujol) 1596 (w), 1584 (w), 1420 (s), 904 (m), 782 (s) cm^{-1}; MS *m/e* 444 (M^+). Anal. Calcd for $C_{24}H_{28}S_4$: C, 64.85; H, 6.35. Found: C, 64.61; H, 6.49.

[5.1]Metacyclophane (10). The bridged dithiane **9** (1.3 g, 0.00293 mol) was refluxed in ethanol (250 mL) with Raney nickel (approximately 8 g) for 24 h. The Raney nickel was removed and the filtrate concentrated in vacuo. The residue (294 mg) was purified by preparative GLC on Chromosorb (HP) 60/80 with a Dexsil GC300 coating at 200 °C. The main fraction (t_R 4.7 min) was crystalline (102 mg, 0.43 mmol, 15% yield). It was recrystallized to give [5.1]metacyclophane: mp 53–54 (crystallized from pentane/MeOH); NMR[11] (100 MHz, Varian XL100) δ 7.20–6.84 (m, 6), 6.64 (s, 2), 4.00 (s, 2), 2.54–2.42 (m, 4), 1.60–1.24 (m, 4), 1.12–0.80 (q, 2); IR (Nujol) 1600 (w), 1580 (w), 758 (m), 702 (m) cm^{-1}; MS *m/e* 236 (M^+). Anal. Calcd for $C_{18}H_{20}$ C, 91.47; H, 8.53. Found: C, 91.13; H, 8.83.

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Registry No. **1**, 59054-34-1; **2**, 70445-70-4; **4**, 59054-28-3; **5**, 70445-71-5; **6**, 70445-72-6; **7**, 63591-90-2; **8**, 70445-73-7; **9**, 70445-74-8; **10**, 67638-65-7; 1,3-trimethylenebis(triphenylphosphonium) bromide, 7333-67-7; 1-bromo-3-chloropropane, 109-70-6; 2-(3-chloropropyl)-2-[3-(3-(1,3-dithian-2-yl)benzyl)phenyl]-1,3-dithiane, 70445-75-9.

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Trifluoroacetylation of Amino Acids and Peptides by Ethyl Trifluoroacetate

Thomas J. Curphey

Department of Pathology, Dartmouth Medical School, Hanover, New Hampshire 03755

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Although the trifluoroacetyl group has not found general use as an N-protecting group in peptide synthesis, it has nevertheless continued to prove useful in certain special circumstances. For example, we recently capitalized on its ready enzymatic removal to develop a new synthesis of azaserine,[1] a compound of interest as an antitumor agent and pancreatic carcinogen. Methods for the introduction of the trifluoroacetyl group into amino acids and peptides include reaction with trifluoroacetic anhydride alone[2] or in trifluoroacetic acid solution,[3] reaction with aqueous *S*-ethyl trifluorothioacetate in mildly alkaline medium,[4] reaction with phenyl trifluoroacetate in phenol,[5] and re-

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