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PREPARATIONS AND PROPERTIES OF TRIS[2,2,2]PARACYCLOPHANE DERIVATIVES

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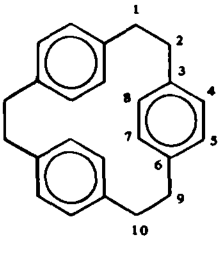
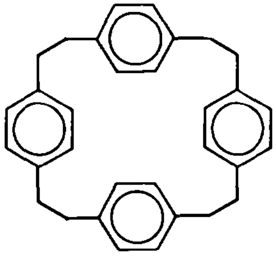
Abstract—Six nuclear monosubstituted tris[2.2.2]paracyclophane (cyclic trimer of *p*-xylylene, abbreviated as 3°-PCP) derivatives have been prepared and spectral properties of these compounds are described. Acetylation, nitration and bromination of tris[2.2.2]paracyclophane (I) led to the corresponding monosubstituted derivatives. Reduction of nitrotris[2.2.2]paracyclophane (IV) gave aminotris[2.2.2]paracyclophane (V). The bromoform reaction of acetyltris[2.2.2]paracyclophane (VI) afforded carboxytris[2.2.2]-paracyclophane (VII), which was esterified to carbomethoxytris[2.2.2]paracyclophane (VIII). The NMR spectra of 3°-PCP derivatives are described. The effect of the substituent on aromatic proton chemical shifts observed for 3°-PCP's showed close similarity to that observed for substituted *p*-xylenes. Electronic spectra of I, IV and VI in CH_2Cl_2 were measured. Electronic spectrum of VI was superimposable with an expected one from that of acetyl-*p*-xylene combined with that of *p,p'*-dimethyldibenzyl. Analyses of these spectral data indicate that benzene rings are rather normal. Thus, a conclusion may be drawn that 3°-PCP would afford an appropriate model to investigate chemical and/or physical (especially transannular) properties of three "normal" benzenes fixed at definite angle and distance.

The chemistry of cyclophanes[1] is largely concerned with the biscyclophanes* and little work has been done on triscyclophanes or higher cyclophanes. In the literature, only the formation of tris[2.2.2]paracyclophane (3°-PCP) (I)[2] and tetrakis[2.2.2.2]-paracyclophane (4°-PCP) (II)[3] was described and derivatives of these compounds are not known. The importance and interest of the polycyclophanes† is not a simple extension of the chemistry of biscyclophane but that a polycyclophane should be a good model to investigate a higher order conformation problem or an inclusion



I



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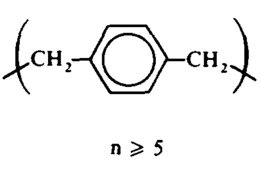

III

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* We tentatively use conventional nomenclature, biscyclophanes, triscyclophanes, tetrakiscyclophanes, etc. or polycyclophanes for bridged aromatic compounds having two, three or four benzene rings, etc., respectively.

† The name [2.2.2]*Paracyclophane* has been proposed for this compound, where numbering is to start at the bridge carbon as is shown in I. See, Ref. 1*a*.

problem. Interaction between 'normal' benzenes* in a polycyclophane may be another interesting study.† In this paper, we report the preparation and properties of some derivatives of tris[2.2.2]paracyclophane.

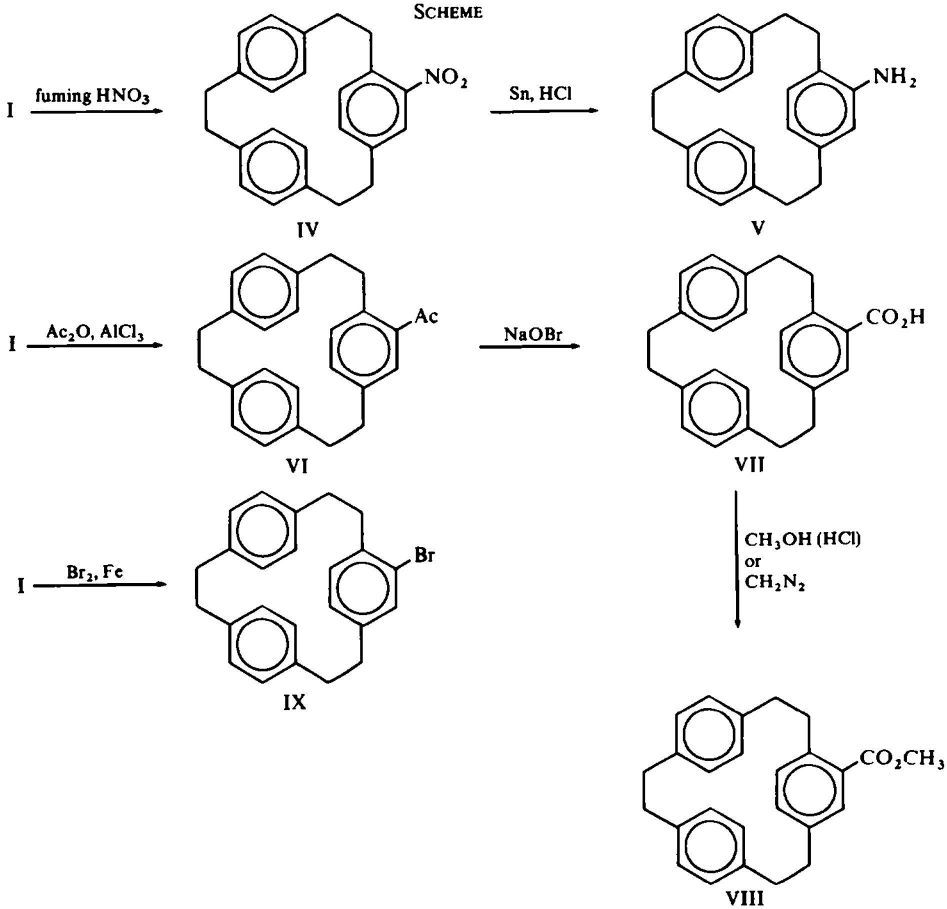
RESULTS AND DISCUSSION

Preparation of tris[2.2.2]paracylophane (I). Although preparation of I by the Wurtz reaction from *p*-xylylene chloride or *p*-xylylene bromide in 4% yield has been reported,[3] we prepared I in a remarkably improved yield from *p*-xylylene chloride by the modified Wurtz reaction using powdered sodium and tetraphenylethylene.[1e]

Electrophilic substitution on benzene ring of I

Nitration, acetylation and bromination of I were carried out under usual conditions.

SCHEME



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* In [2,2]paracyclophane, which was extensively investigated, the benzene rings were found to be nonplanar so that they could not be taken as normal, though a very strong interaction between benzene rings was often observed.

† Our preliminary experiments indicated that introduction of the second electronegative substituent led to unexpected transannular products in marked contrast to the present monosubstitution. The results will be published.

Nitration of I gave 53% (74% based on I consumed) of nitrotris[2.2.2]paracyclophane (IV), 11% (15% based on I consumed) of dinitrated materials of undetermined structure, and 28% of the unreacted hydrocarbon. Some nitro-acetoxy-3°-PCP's were also found. Reduction of IV gave 41% of the corresponding amine (V).

Acetylation of I gave 34% (61% based on I consumed) of acetyltris[2.2.2]paracyclophane (VI) and 44% of the unreacted hydrocarbon. No diacetylated derivatives were detected. The bromoform reaction of VI gave 46% of carboxytris[2.2.2]-paracyclophane (VII). The sodium salt of VII was water-soluble.† Treatment of VII with diazomethane gave carbomethoxytris[2.2.2]paracyclophane (VIII) in 92% yield. Esterification of VII with methanol-hydrochloric acid also gave VIII but in 44% yield.

Iron-catalysed bromination of I gave the corresponding monobromide as well as the dibromides. Monobromotris[2.2.2]paracyclophane (IX) was isolated by means of gas chromatography (PEG). The mass spectrum of IX showed two molecular peaks of expected *m/e* values and its IR spectrum showed the characteristic absorption of aromatic C-Br bond at 1035 cm^{-1}.

NMR spectra of 3°-PCP *derivatives.* NMR chemical shift of 3°-PCP derivatives are listed in Table 1. Aromatic protons of tris[2.2.2]paracyclophane were observed as a sharp singlet. Its methylene protons also appear as a singlet. ‡ However, introduction of a substituent into one of the benzene rings of 3°-PCP caused a splitting of both aromatic protons and methylene protons. The splitting is due to remarkable down- or upfield shift of *o*-, *m*- and *p*-protons with respect to a substituent. In Table 2, comparison was made between chemical shift of aromatic protons of 3°-PCP derivatives and those of bis[3.3]paracyclophane,[1c] benzene derivatives or *p*-xylene derivatives. Apparently, the effect of a substituent on proton chemical shift observed for 3°-PCP's showed close similarity to that observed for *p*-xylenes. For nitrotris[2.2.2]-paracyclophane, IV, only one proton was observed in lower field, in contrast to nitrobenzene where three protons were found in lower field (Table 2), and the extent of the downfield shift for nitro-3°-PCP was considerably (*ca* 0·2 τ) less than that of *o*-protons observed for nitrobenzene. A similar situation was observed for acetyltris-[2.2.2]paracyclophane, VI, in comparison with acetophenone. Though the behavior could not be fully understood, a probable interpretation is that some extra shielding effect is operating in these systems.§ For aminotris[2.2.2]paracyclophane, V, two protons were observed in higher field and the extent to which these protons shifted upfield was considerably less than that observed for aniline as shown in Table 2. In this case some extra deshielding effect may be operating. However, for carboxytris-[2.2.2]paracyclophane, VII, some enhanced deshielding effect was observed in comparison with the corresponding *p*-xylene derivative.

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† To the contrast, the Na salt of carbocytetrakis[2.2.2.2]paracyclophane is scarcely soluble in water. Preparations and properties of tetrakis[2.2.2.2]paracyclophane derivatives will be published.

‡ Tetrakis[2.2.2.2]paracyclophane or higher paracyclophane, have a sharp singlet absorption of aromatic protons, in good agreement with the absorption of aromatic protons of tris[2.2.2]paracyclophane. But as for the absorption of methylene protons, an appreciable difference was observed. 4°-PCP and higher paracyclophanes have the broad singlet absorption of methylene protons in contrast to 3°-PCP. The difference should be closely correlated with some conformational change of higher order which is not yet clear.

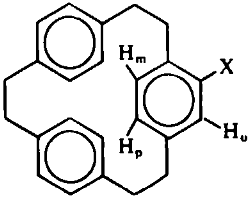
§ The electronic spectra indicate that no remarkable electron shift between benzene rings take place on the basis of almost superimposable λ *vs* ε curves obtained from acetyl-3°-PCP and acetyl-*p*-xylene. The present downfield shifts are in good agreement with those of nitro-*p*-xylene.

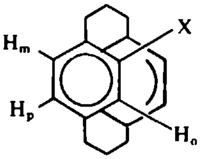
Table 1. NMR spectra[a] of tris[2.2.2]paracyclophane derivatives

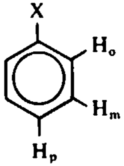
X	Aromatic protons [τ-value]	Ethylene bridge protons	Other protons
H	3·38 (12H, s)	7·07 (12H, s)	
NO_2	2·65 (1H, d), 3·2–3·45 (10H, m)	6·5–7·25 (12H, m)	
NH_2	3·3–3·5 (10H, m), 3·84 (1H, d), 3·98 (1H, br s)	7·0–7·3 (12H, m)	6·47 (2H, br s)
$COCH_3$	2·98 (1H, br s), 3·3–3·5 (10H, m)	6·4–7·3 (12H, m)	7·65 (3H, s)
CO_2H[b]	2·34 (1H, br s), 3·15–3·4 (10H, m)	6·4–7·15 (12H, m)	−1·90 (1H, br s)
CO_2CH_3	2·67 (1H, br s), 3·3–3·6 (10H, m)	6·7–7·3 (12H, m)	6·12 (3H, s)
Br	3·03 (1H, br s), 3·35–3·5 (7H, m), 3·60 (2H, br s)	6·9–7·2 (12H, m)	

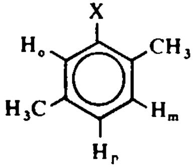
[a] With 1% tetramethylsilane as internal standard, 5–10% in CCl_4 except CO_2H. Abbreviations are: s, singlet; br s, broad singlet; d, doublet; m, multiplet. [b] Measured in $CDCl_3$.

Table 2. Comparison of the substituent chemical shift values[a] for ortho, meta and para protons in tris[2.2.2]paracyclophanes with those of bis[3.3]paracyclophanes substituted benzenes and p-xylenes









X	H_o	H_m	H_p	H_o^b	H_m^b	H_p^b	H_o	H_m	H_p	H_o	H_m	H_p
NO_2	−0·73	0·03	−0·07	−0·80			−0·95	−0·20	−0·33[c,d]	−0·71	−0·24	−0·13[f]
NH_2	0·60		0·46				0·77	0·13	0·40[e]			
$COCH_3$	−0·40			−0·45			−0·67	−0·27	−0·27[e]	−0·49	−0·15	−0·15
CO_2H	−1·04						−0·63 (−0·8[h])	−0·10	−0·17[e]	−0·88	−0·15	−0·15
CO_2CH_3	−0·71			−0·66			−0·72	−0·10	−0·20[d,g]	−0·66	−0·08	−0·08
Br	−0·35	0·22	0·22	−0·23			−0·22	−0·09	−0·03[c]			

[a] Defined as the chemical shift from the aromatic resonance of the parent hydrocarbon (τ 3·38 for tris[2.2.2]paracyclophane, τ 3·40 for bis[3.3]paracyclophane, τ 2·73 for benzene and τ 3·05 for p-xylene) in parts per million. [b] reference 1c, [c] H. Spieseke and W. G. Schneider, *J. Chem. Phys.* **35**, 731 (1960), [d] T. Schaefer and W. G. Schneider, *Ibid.* **32**, 1218 (1960), [e] P. L. Corio and B. P. Dailey, *J. Am. Chem. Soc.* **78**, 3043 (1956), [f] P. P. Wells, *Austral. J. Chem.* **17**, 467 (1964), [g] J. L. Garnett, L. J. Henderson, W. A. Sollich and G. V. D. Tiers, *Tetrahedron Letters* 516 (1961). [h] G. W. Smith, *J. Mol. Spec.* **2**, 146 (1964).

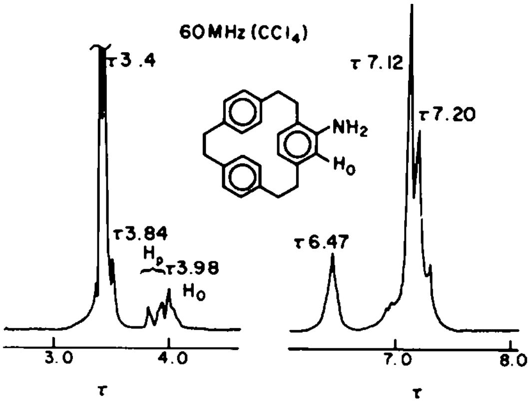


FIG. 1. Pmr spectrum of amino-3°-PCP in carbon tetrachloride.

Coupling constants of aromatic protons. Since the NMR absorptions of *o*-, *m*- and *p*-protons in respect to the substituent on 3°-PCP were observed in higher or lower field, it now became possible to determine the coupling constants between these protons. The NMR chart of the decoupling experiment is shown in Fig 2 taking nitro-3°-PCP for example. Thus a coupling constant of 2·0 Hz was observed between *o*-proton and another low field proton. This coupling constant is consistent with that

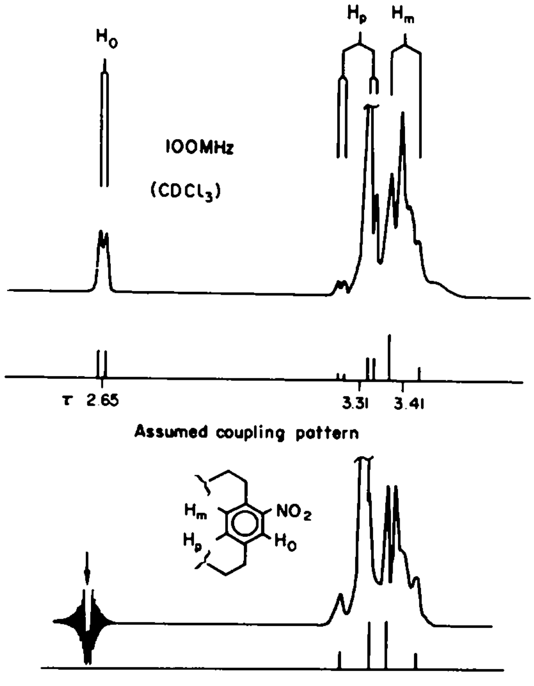


FIG. 2. The spin decoupling experiment of nitro-3°-PCP with 100 MHz.

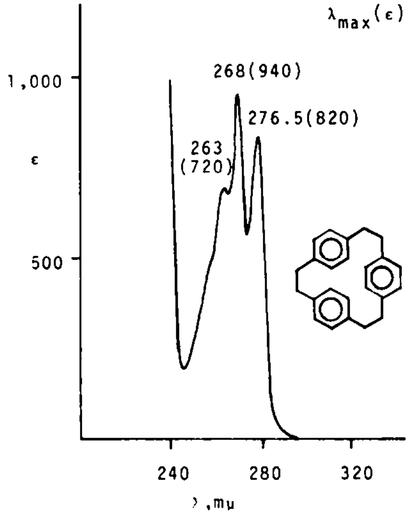


FIG. 3. (a) 3°-PCP (I).

commonly accepted for *meta* coupling[4] (i.e. coupling between *ortho* and *para* protons in question). This indicates that the *para* proton appears at the lower field, in accord with the assignment of chemical shift cited above. Another coupling constant, J_0 (between *meta* and *para* protons in question) was estimated to be *ca* 8 Hz in a good agreement with the commonly accepted *ortho* coupling constant.

Electronic spectra of 3°-PCP *derivatives*. Electronic spectra of I, IV and VI are shown in Figs 3a–c. Electronic spectra of reference compounds are also shown in

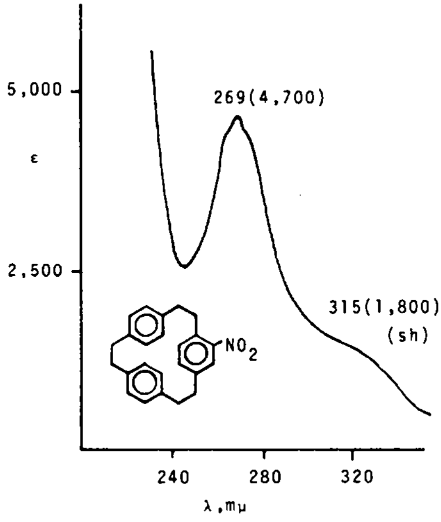


FIG. 3. (b) nitro-3°-PCP (IV).

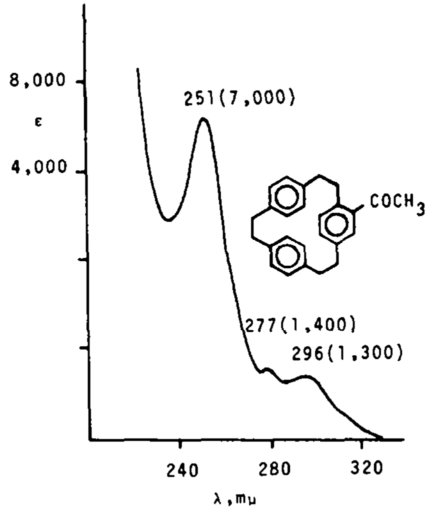


FIG. 3. (*c*) acetyl-3°-PCP (VI).

Figs 3d and e. Investigation of the electronic spectrum of acetyl-3°-PCP indicates that the spectrum is the superposition of *p,p*′-dimethyldibenzyl absorption (277 mμ) and acetyl-*p*-xylene absorption (251 and 296 mμ). Additivities were also observed to hold for electronic spectra of other 3°-PCP derivatives. These spectral data indicate that the benzene rings are normal. Thus, 3°-PCP would afford an appropriate model to investigate chemical and/or physical (especially transannular) properties of three "normal" benzene rings fixed at a definite angle and distance.

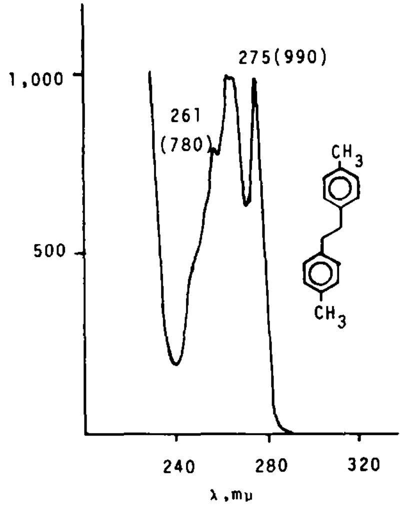


FIG. 3. (*d*) *p,p*′-dimethyldibenzyl.

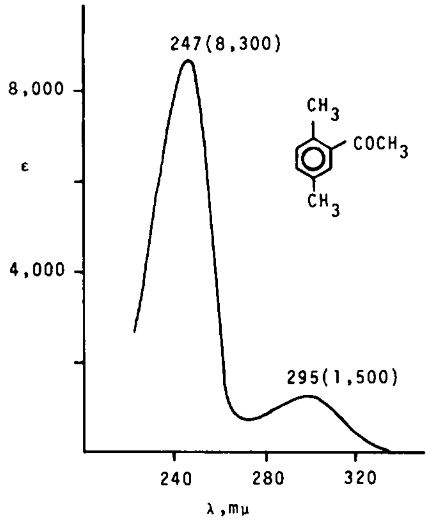


Fig. 3. (*e*) acetyl-*p*-xylene.

EXPERIMENTAL

Tris[2.2.2]*paracyclophane* (I)

Powdered Na (10 g) was added to a soln of tetraphenylene (1 g) in 1 l. dry THF and the mixture was heated under reflux with efficient stirring. After the intense violet color of the Na. adduct had developed, a soln of *p*-xylylene chloride (25 g) in 200 ml dry THF was added at such a rate that the violet color never completely disappeared. When the addition was complete (*ca* 2 days), the mixture was filtered. On evaporating the filtrate a solid (12·3 g) was obtained and chromatographed on silica gel with light petroleum. I was obtained together with higher paracyclophanes, *p,p*'-dimethyldibenzyl and *p*-di(2-*p*-tolylethyl)benzene. Repeated recrystallisation of crude I from n-hexane gave 1·7 g of pure I (11·4%, m.p., 168°), mass spectrum *m/e* (relative intensity) 312(44), 118(32), 117(100), 115(59), 105(90), 104(83), 91(54), 77(35); IR(KBr) 3020, 2925, 2850, 1515, 1440, 795, 780 cm^{-1}.

Acetyltris[2.2.2]*paracyclophane* (VI).

To a stirred mixture of I (0·5 g; 1·6 mmole) and $AlCl_3$ (0·438 g, 3.3 mmole) in 4 ml CS_2, a soln of Ac_2O (158 mg, 1·55 mmole) in 1 ml CS_2 was added dropwise in 1 hr. After additional stirring for 2 hr, the mixture was poured into the mixture of ice water (15 g) and conc HCl (5 ml) and the mixture was extracted with chloroform. The chloroform extract was washed with water, sat $NaHCO_3$ aq, water, and then with sat NaCl aq. The soln was dried and concentrated to about 0·5 ml and chromatographed on silica gel. First elution with light petroleum gave 218 mg of the recovered hydrocarbon (44%) and further elution with benzene gave 119 mg (34%) of VI, (61% based on I consumed). On recrystallization from light petroleum, VI melted at 80–81°, mass spectrum *m/e* (relative intensity) 354(19), 145(31), 105(100), 104(42); IR (neat) 3020, 2959, 2860, 1680, 1520, 1445, 1355, 1280, 1260, 800, 785 cm^{-1}.

Bromotris[2.2.2]*paracyclophane* (IX)

A soln of I (250 mg; 0·8 mmole) and Br_2 (142 mg; 0·89 mmole) in 17 ml CH_2Cl_2 was mixed with Fe powder (3·4 g) and the mixture was stirred under reflux for 4 hr.[1c] The soln was then washed with $NaHSO_3$ aq, water, and sat NaCl aq and dried. The solvent was distilled off and the residue chromatographed on an alumina column. Elution with 20% benzene–light petroleum gave a mixture of I, IX and dibromotrisparacyclophanes. The monobromo- and dibromo derivatives were separated by means of gas chromatography (PEG 20M). IX was obtained as white crystals (m.p. 88·5–89°, from light petroleum), mass spectrum *m/e* (relative intensity) 392(M + 2, 12), 390(M, 12), 311(21), 205(12), 193(18), 133(30·8), 117(14), 105(15), 104(100), 103(21); IR (neat 3050, 3010, 2920, 2850, 1515, 1490, 1440, 1035, 790, 780 cm^{-1}.

Nitrotis[2.2.2]*paracyclophane* (IV)

To a stirred soln of I (1 g, 3·2 mmole) in Ac_2O (20 ml) and AcOH (20 ml), a soln of fuming HNO_3 (0·4 ml) in Ac_2O (5·2 ml) was added dropwise at room temp during 5 min. After additional stirring for 10 min, the mixture was poured into 50 g crushed ice. On allowing the ice to melt, the crude mixture was extracted with ether. Then the ether layer was washed with sat $NaHCO_3$ aq, water, and sat NaCl aq and dried. The ether soln was concentrated and chromatographed on silica gel. Elution with 10% benzene–light petroleum gave 280 mg (28%) of the unreacted hydrocarbon. Further elution with 20% benzene–light petroleum afforded 609 mg (53%) (74% based on I consumed) of practically pure IV as a yellow oil which was crystallized after two months (m.p. 67–68°) and further elutions with benzene gave 136 mg (11%) of dinitro derivatives (15% based on I consumed) and 66 mg and 76 mg of unidentified materials, both of which had characteristic absorptions of the nitro (1550, 1370 cm^{-1}) and acetoxy groups (1740 cm^{-1}). The mass spectrum of IV *m/e* (relative intensity) 357(6), 340(7), 238(8), 223(10), 195(6), 119(7), 105(29), 104(100), 103(15), 91(18); IR (neat) 3020, 2930, 2860, 1530, 1500, 1445, 1350, 805, 785 cm^{-1}.

Aminotris[2.2.2]*paracyclophane* (V).

To a mixture of IV (80 mg; 0·224 mmole) and granulated tin (162 g), conc HCl (1 ml) and EtOH (1·5 ml) was added. With occasional shaking, the mixture was warmed on a water bath. After the mixture became homogeneous (5 hr), it was poured into conc HCl and extracted with ether to remove unreacted IV. The aqueous layer was neutralized with $NaHCO_3$ aq and the crude amine (V) was extracted with ether. The ether soln was washed with water and sat NaCl aq. After drying, the ether soln was evaporated and absorbed on a column of silica gel made up in light petroleum. Elution with benzene–light petroleum afforded *ca* 30 mg (41%) of V, m.p. 153–5° (CCl_4); mass spectrum *m/e* 327 (molecular peak); IR (neat) 3500, 3400, 3030, 2925, 2860, 1625, 1520, 1500, 1450, 1410, 800 and 785 cm^{-1}.

Carboxytris[2.2.2]*paracyclophane* (VII).

To a stirred soln of VI (80 mg, 0·226 mmole) in dioxan (5 ml), a soln of Br_2(230 mg) and KOH (576 mg) in 5 ml of water was added at 0°. After addition, the mixture was allowed to warm up to room temp, and stirred for an additional 5 hr. The mixture was poured into $NaHSO_3$ aq and NaOH and the aqueous soln was washed with ether to remove unreacted VI and then acidified with HCl. A resulting white ppt was extracted with ether and the ether extract was washed with sat NaCl aq and dried. Evaporation of ether gave practically pure VII (42 mg; 46%). On recrystallization from ether, VII melted at 183–185°, IR spectrum (neat) 3500–2500 (broad), 3020, 2925, 2850, 1680, 1520, 1440, 1290, 1260, 910, 800, 780 cm^{-1}.

Carbomethoxytris[2.2.2]*paracyclophane* (VIII)

Esterification with methanol and hydrochloric acid. A mixture of VIII (39 mg; 0·11 mmole) MeOH (30 ml) and three drops HCl was refluxed for 12 hr. The mixture was poured into water and extracted with ether. The ether extract was washed with $NaHCO_3$ aq, water and NaCl aq. After drying, the soln was concentrated and absorbed on a silica gel column. Elution with benzene gave VIII (17·7 mg; 44%) as a colorless oil, mass spectrum *m/e* (relative intensity) 370 (M, 25), 338(46), 234(20), 105(26), 104(100); IR (neat) 3025, 2940, 2870, 1725, 1525, 1450, 1265, 1200, 1075, 805, 785 cm^{-1}.

Esterification with diazomethane. To a ether soln of VII (9·1 mg, 0·026 mmole) an ether soln of diazomethane was added until the yellow color of diazomethane persisted. The mixture was concentrated and chromatographed on a silica gel column. Elution with benzene gave VIII (8·7 mg, 92%) as a colorless oil.

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