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PREPARATIONS AND PROPERTIES OF TETRAKIS[2.2.2.2]PARACYCLOPHANE DERIVATIVES

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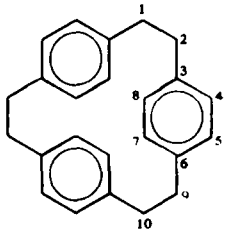
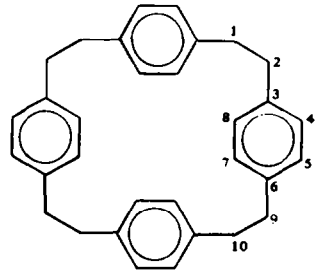
Abstract—Nuclear substituted tetrakis[2.2.2.2]paracyclophane (4°-PCP, II) derivatives were prepared and the NMR spectral properties investigated. Acetylation of II gave acetyl-4°-PCP (IV) which was converted to carboxy-4°-PCP (V) and to acetoxy-4°-PCP (VIII). Esterification of V gave carbomethoxy-4°-PCP (VI). VIII was hydrolized to hydroxy-4°-PCP (IX). Nitration of II with N_2O_5 gave nitro-4°-PCP (X) in good yield. Fuming nitric acid in acetic acid-acetic anhydride as a nitration reagent gave VIII together with X. Further acetylation of IV gave diacetylated derivatives (VII).

IN OUR PREVIOUS PAPER,[1] we reported electrophilic substitutions on a benzene ring of tris[2.2.2]paracyclophane (3°-PCP, I). The chemical and physical properties of 3°-PCP showed that 3°-PCP would afford an appropriate model to investigate the interactions (especially transannular) of three *normal* benzene rings fixed at a definite angle and distance.

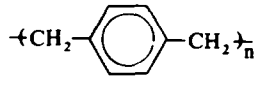
From molecular (Dreiding) models, one may conclude that tetrakis[2.2.2.2]paracyclophane (4°-PCP, II) and higher polyparacyclophanes (III) are more flexible than 3°-PCP. Therefore 4°-PCP or higher paracyclophanes seem to be better models for investigating higher order conformational problems or inclusion problems than 3°-PCP.* In this paper we report preparations and properties of some 4°-PCP derivatives.



I



II



$n \geq 5$

III

* Probably the rotation of a benzene ring of 3°-PCP around the $CH_2—C_3—C_6—CH_2$ axis is considerably restricted by the π-hydrogen, or hydrogen-hydrogen repulsions, while for 4°-PCP and higher polyparacyclophanes, these steric repulsions are not so important. The sizes of holes in molecules are estimated to be 2 Å, 3·5 Å and 5 Å for 3°-PCP, 4°-PCP and 5°-PCP (III, n = 5), respectively from the molecular model by assuming that a benzene ring is 3·4 Å thick. Therefore, 4°-PCP and higher polyparacyclophanes have the possibility of forming inclusion compounds like α-cyclodextrin.[2]

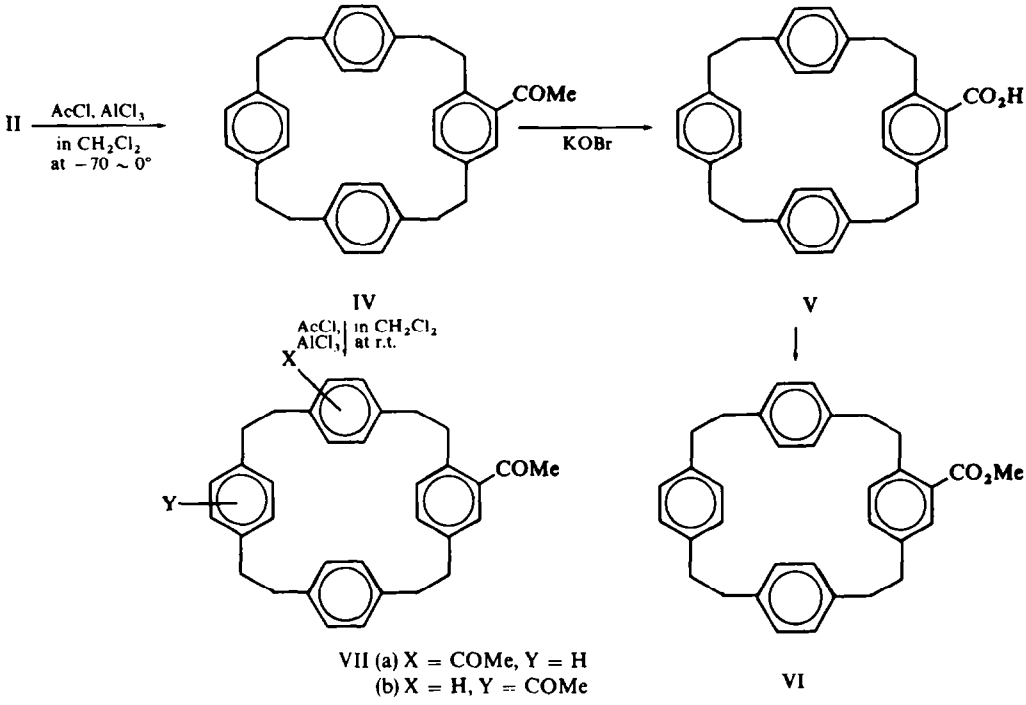
RESULTS AND DISCUSSION

Preparation of tetrakis[2.2.2.2]*paracyclophane* (II)

Although it was reported by Errede[3] that 4°-PCP (II) was obtained by the polymerization of *p*-xylylene in very low yield, we have succeeded in preparing II from *p*-xylylene chloride or 4,4'-bis(chloromethyl)bibenzyl by a modified Wurts reaction[4] using tetraphenylethylene and powdered sodium, yields of II amounted to 6% and 7% from *p*-xylylene chloride and 4,4'-bis(chloromethyl)bibenzyl, respectively.

Acetylation of 4°-PCP *and derived compounds*

Acetylation of 4°-PCP with AcCl and $AlCl_3$ in CH_2Cl_2 at $-70 \sim 0°$ for 2·5 hr gave 93% yield of acetyl-4°-PCP (IV) together with a small amount of diacetylated material (VII).



VII (a) X = COMe, Y = H
(b) X = H, Y = COMe

VI

Further acetylation of IV with AcCl and $AlCl_3$ in CH_2Cl_2 at room temperature for 2·5 hr gave diacetylated tetrakis[2.2.2.2]paracyclophanes (VII) in quantiative yield. VII has 13 isomeric forms if the benzene rings do not freely rotate,* but any pure isomer could not be isolated in this stage.

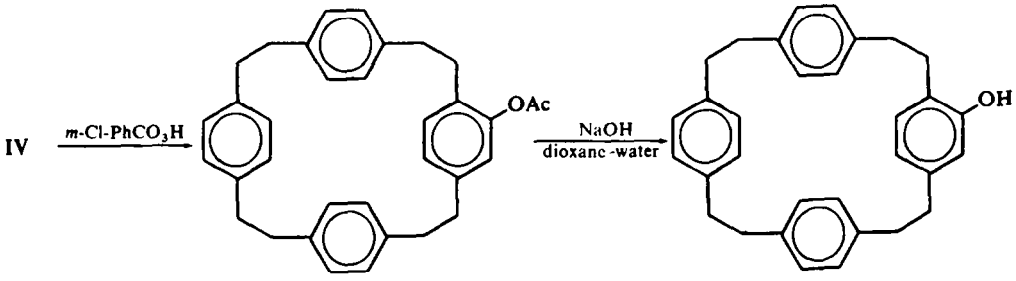
The bromoform reaction of IV gave carboxy-4°-PCP (V) in 52% yield. V was insoluble in aqueous alkaline solutions in a marked contrast to carboxy-3°-PCP[1] or to any of common aromatic carboxylic acids.

Treatment of V with CH_2N_2 in ether gave carbomethoxy-4°-PCP (VI) in quantitative

* Three of the isomers are molecules having two acetyl groups in the same benzene ring. Optical isomers are not included. If optical isomers are counted, 20 isomers are possible and if the benzene rings freely rotate, only 8 isomers remain.

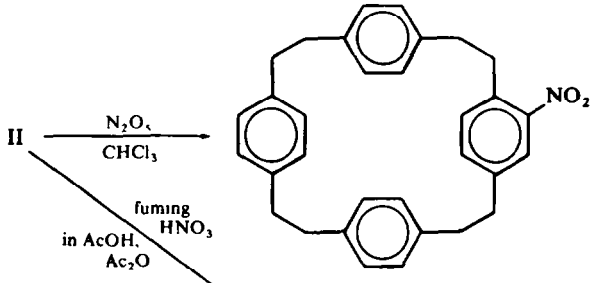
yield. Esterification of V in refluxing MeOH in the presence of a small amount of $HClO_4$ for 3 days also gave VI but only in 25% yield.

The Baeyer–Villiger oxidation of IV with *m*-chloroperbenzoic acid in $CHCl_3$ in the presence of a catalytic amount of H_2SO_4 for 2-days at room temperature gave acetoxy-4°-PCP (VIII) in 64% yield which was hydrolyzed in alkaline dioxane–water (70:30) to hydroxy-4°-PCP (IX) in 72% yield.



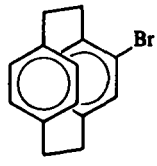
VIII IX

Nitration

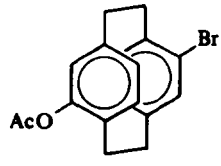


X + VIII X

Nitration of II with dinitrogen pentoxide in $CHCl_3$ gave nitro-4°-PCP (X) in 63% yield. When fuming HNO_3 in AcOH–Ac_2O was used as a nitration reagent, acetoxy-4°-PCP (VIII) was obtained as one of major products in 10% yield* together with X (15% yield).



XI

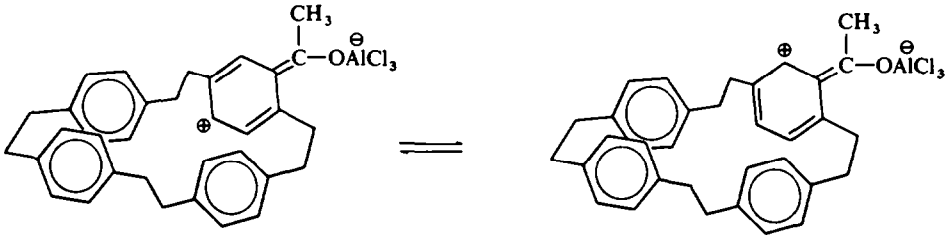


XII

* Nitration of 4-bromo[2.2]paracyclophane(bromobis[2.2]paracyclophane, bromo-2°-PCP, XI) with fuming HNO_3 in AcOH was reported by Cram *et al.* to give pseudo-*p*-bromoacetoxy-2°-PCP (XII) but only in 0·61% yield.[5]

Effect of acetyl group of acetyl-4°-PCP on further acetylation

Acetylation and diacetylation of II could be controlled by the reaction temperature. This may indicate that an acetyl group in one benzene ring of 4°-PCP apparently deactivates not only the acetylated benzene ring but also the other three rings toward further acetylation probably because of formation of an $AlCl_3$ complex of type XIII* which reduces the electron density of the three other benzene rings *via* a spatial (field) effect.



XIIIa XIIIb

NMR spectra of tetrakis[2.2.2.2]*paracyclophane derivatives*

NMR chemical shifts (60 MHz) of tetrakis[2.2.2.2]paracyclophane derivatives are listed in Table 1. 4°-PCP showed two sharp singlets for the aromatic protons and aliphatic protons. Introduction of a substituent into one of the benzene rings of 4°-PCP caused considerable change in aromatic line shape.† This change is due to remarkable

TABLE 1. NMR SPECTRA[a] OF TETRAKIS[2.2.2.2]PARACYCLOPHANE DERIVATIVES

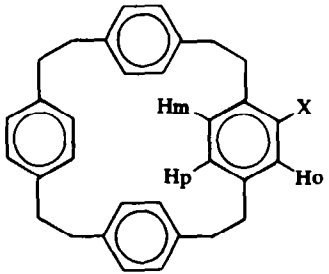
X	Aromatic protons (τ-value)	Ethylene protons	Other protons
H	3·35 (16H, s)	7·16 (16H, s)	
NO_2	2·43 (1H, br s) 3·17–3·40 (12H, m) 3·52 (2H, br s)	6·8–7·4 (16H, m)	
COMe	2·86 (1H, br s) 3·2–3·45 (14H, m)	6·8–7·3 (16H, m)	7·84 (3H, s)
CO_2H	2·18 (1H, br s) 3·0–3·6 (14H, m)	6·5–7·3 (16H, m)	
CO_2Me	2·41 (1H, br s) 3·2–3·45 (12H, m) 3·57 (2H, brs)	7·0–7·3 (16H, m)	6·20 (3H, s)
OCOMe	3·2–3·5 (14H, m) 3·60 (1H, br s)	6·8–7·5 (16H, m)	7·88 (3H, s)
OH[b]	3·15–3·4 (13H, m) 3·48–3·78 (2H, m)	7·0–7·3 (16H, m)	6·2 (1H, br s)
$(CO_2H)_2$[c,d]	2·30 (2H, m) 3·1–3·6 (12H, m)	6·5–7·6 (16H, m)	
$(COMe)_2$[d]	2·78 (2H, m) 3·1–3·7 (12H, m)	6·7–7·3 (16H, m)	7·74 (6H, s)

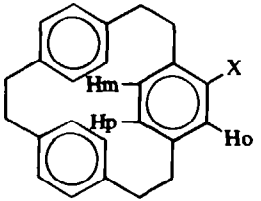
[a] With 1% TMS as internal standard, 5–10% in CCl_4 except OH and $(CO_2H)_2$. Abbreviations are: s, singlet; m, multiplet; br, broad.
[b] Measured in $CDCl_3$. [c] Measured in acetone-d_6. [d] Mixture of isomers.

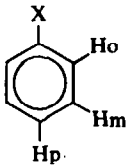
down and/or upfield shifts of *o*-, *m*- and *p*-protons with respect to a substituent. These shifts together with those of 3°-PCP derivatives, benzene derivatives and *p*-xylene derivatives are listed in Table 2. The effect of the substituents on proton chemical shifts observed for 3°-PCP derivatives was similar to that observed for *p*-xylene derivatives. But for 4°-PCP derivatives, appreciable changes in chemical shifts were

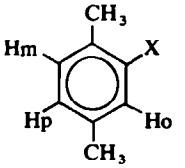
* See, ref 6.
† Aliphatic signals were also changed (Table 1), but could not be simply assigned to the structure.

TABLE 2. COMPARISON OF THE SUBSTITUENT CHEMICAL SHIFT VALUES [a] FOR *ortho*, *meta* AND *para* PROTONS IN TETRAKIS[2.2.2.2]PARACYCLOPHANES WITH THOSE OF SUBSTITUTED TRIS[2.2.2]PARACYCLOPHANES, SUBSTITUTED BENZENES AND SUBSTITUTED *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	−0·92	0·17	0·17	−0·73	0·03	−0·07	−0·95	−0·20	−0·33[c,d]	−0·71	−0·24	−0·13[j]
COMe	−0·49			−0·40			−0·67	−0·27	−0·27[e]	−0·49	−0·15	−0·15
CO_2H	−1·17			−1·04			−0·63	−0·10	−0·17[e]	−0·88	−0·15	−0·15
							(−0·8)					
CO_2Me	−0·95	0·22	0·22	−0·71			−0·72	−0·10	−0·20[f,g]	−0·66	−0·08	−0·08
OH	0·40	−0·04	0·22				0·54	0·17	0·46[c,f−h]	0·55	0·13	0·45
OAc	0·25						0·21	0·02[i]		0·20	−0·07	0·10

[a] The chemical shift from the aromatic resonance of the parent hydrocarbon (τ 3·35 for tetrakis[2.2.2.2]paracyclophane, τ 3·38 for tris[2.2.2.2]paracyclophane, τ 2·73 for benzene and τ 3·05 for *p*-xylene) in ppm. [b] ref 1. [c] H. Spiesecke and W. G. Schneider, *J. Chem. Phys.* **35**, 731 (1961); [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] J. L. Garnett, L. J. Henderson, W. A. Sollich and G. V. D. Tiers, *Tetrahedron Letters* 516 (1961); [g] R. R. Fraster and R. N. Renaud, *J. Am. Chem. Soc.* **88**, 4365 (1966); [h] J. C. Schug and J. C. Deck, *J. Chem. Phys.* **37**, 2618 (1962); [i] G. W. Smith, *J. Mol. Spec.* **12**, 146 (1964); [j] P. R. Wells, *Australian J. Chem.* **17**, 967 (1964)

observed. For nitro-4°-PCP, the *o*-proton (to the nitro group) was observed at lower field (by 0·92 ppm) and the *m*- and the *p*-protons were observed at higher field by 0·17 ppm and 0·17 ppm, respectively, than the protons of the parent hydrocarbon, in contrast to nitro-*p*-xylene where all three protons were found at lower field than those of *p*-xylene. Moreover, the magnitude of the downfield shift of the *o*-proton observed for nitro-4°-PCP was larger than that observed for nitro-*p*-xylene by 0·23 ppm. Practically the same situation was observed for carbomethoxy-4°-PCP and carboxy-4°-PCP. For 4°-PCP, an electron withdrawing substituent was generally observed to cause a definite extra shielding effect on the *o*-proton and an extra deshielding effect on *m*- and *p*-protons. Electron releasing substituents, showed no general trend for the compounds measured in this study.

EXPERIMENTAL

Tetrakis[2.2.2.2]*paracyclophane* (*II*)

Starting from p-*xylylene chloride.* To a violet solution of 1 g of tetraphenylethylene* in 1 l of dry THF containing 10 g of powdered Na was added with refluxing and stirring a solution of 25 g of *p*-xylylene chloride in 200 ml of dry THF at such a rate that the violet colour of the solution was never completely disappeared. After addition (2 ~ 14 days), the mixture was filtered and the filtrate evaporated. A residual white cake (12·3 g) was chromatographed on silica gel. After 4,4'-dimethylbibenzyl and the mixture of tris[2.2.2]paracyclophane (I) (1·7 g, 11%, after purification) and a small amount of *p*-di-(β-*p*-tolylethyl)benzene were eluted with petroleum ether, tetrakis[2.2.2.2]paracyclophane (II) was eluted with petroleum ether containing a small amount of benzene. Repeated recrystallization from benzene-n-hexane (10:90) gave 0·92 g (6·2%) of pure II as colourless crystals.

Starting from 4,4'-*bis*(*chloromethyl*)*bibenzyl.* Starting from 10 g of 4,4'-bis(chloromethyl)bibenzyl, 0·52 g (7%) of II was obtained: m.p. 185° (lit[3] 179–182); mass spectrum, 416 (Molecular peak); MW in $CHCl_3$ determined by means of vapor pressure osmometer was 418 (Calc. MW = 416·6); IR (KBr), 3070, 3035, 2990, 2920, 2840, 1511, 1439, 822, 813, 587, 569 cm^{-1}; UV (cyclohexane) λ_{max} mμ (ε) 253 (830), 260 (1220), 265 (1570), 267 (sh, 1440), 274 (1335).

Acetyltetrakis[2.2.2.2]*paracyclophane* (IV).

A mixture of 600 mg (4·5 mmole) $AlCl_3$, 150 mg (1·9 mmole) of AcCl and 25 ml CH_2Cl_2 was cooled to −70°. To this stirred mixture was added dropwise a solution of 441 mg (1·06 mmole) of II in 10 ml of CH_2Cl_2. After addition, the mixture was allowed to warm to 0°. When the colour of the solution changed from yellow to reddish orange (2·5 hr), the solution was poured into ice-conc-HCl and extracted with CH_2Cl_2 (3 ×). The combined organic layer was washed with water, $NaHCO_3$ aq. water and then with sat NaCl aq. and dried (Na_2SO_4). On evaporation, a residue was obtained which was chromatographed on silica gel. Elution with benzene gave 451 mg (0·98 mmole, 93%) of acetyltetrakis[2.2.2.2]paracyclophane (IV). Further elution with benzene gave 16 mg (0·032 mmole, 3%) of diacetyltetrakis[2.2.2.2]paracyclophanes (VII).

Recrystallization of IV from CH_2Cl_2-petroleum ether (30:70) gave white crystals: m.p. 141·6–142·1°; IR (KBr), 3020, 2940, 2860, 1685, 1520, 1440, 1360, 1260, 820, 810 cm^{-1}; UV (cyclohexane) λ_{max} mμ (ε), 242 (7000), 265 (1900), 274·5 (1600) 293 (1200); mass spectrum *m/e* (relative intensity), 458 (12), 442 (21), 441 (61), 207 (24), 146 (22), 145 (54) 105 (33), 104 (100). (Calc. for $C_{34}H_{34}O$: C, 89·04; H, 7·47; O, 3·49. Found: C, 88·72; H, 7·67; O, 3·41%).

Carboxytetrakis[2.2.2.2]*paracyclophane* (V)

To a stirred solution of 62 mg (0·135 mmole) of IV in 5 ml dioxane was added dropwise a solution of 210 mg (1·31 mmole) of Br_2 and 290 mg (6·8 mmole) of KOH in 5 mol of water with external ice cooling. After addition, the mixture was allowed to warm to room temp and stirred for 7 hr. The mixture was poured into $NaHSO_3$ aq., neutralized with HCl and ether extracted. The other extract was washed with water and

* An additional amount of tetraphenylethylene was added, if necessary, during the reaction.

with sat NaCl aq. and dried (Na_2SO_4). On solvent evaporation, the residue was absorbed on silica gel. After elution of IV with benzene, 32 mg (0·07 mmole, 52%) of carboxytetrakis[2.2.2.2]paracyclophane (V) was eluted with ether. V was a white solid m.p. 118–133° (from 50% petroleum ether CH_2Cl_2): IR (KBr), 3500–2400 (broad), 3010, 2930, 2850, 1685, 1510, 1440, 1400, 1280, 805 cm^{-1}.

Carbomethoxytetrakis[2.2.2.2]*paracyclophane* (VI)

To V in ether was added CH_2N_2 in ether with stirring until yellow colour did not fade. Evaporation of ether gave practically pure carbomethoxtetrakis[2.2.2.2]paracyclophane (VI) as white crystals (m.p. 124·6–125·5° from benzene–hexane) in quantitative yield; mass spectrum *m/e* (relative intensity), 474 (M^+, 6), 442 (10), 207 (12), 162 (10), 119 (10), 117 (7), 105 (17), 104 (100), 103 (11); IR (KBr), 3010, 2925, 2860, 1725, 1445, 1270, 1205, 1080, 810 cm^{-1}. Esterification of V in refluxing MeOH in the presence of a catalytic amount of $HClO_4$ for 3 days also gave VI but in 25% yield.

Acetoxytetrakis[2.2.2.2]*paracyclophane* (*VIII*)

A solution of 89 mg (0·55 mmole) of *m*-chloroperbenzoic acid in 0·5 ml of CH_2Cl_2 was placed in a 50 ml three necked flask covered with aluminium foil. A solution of 100 mg (0·22 mmole) of IV and a few drops 10% H_2SO_4 Ac_2O in 1 ml CH_2Cl_2 was added to the solution with stirring at 0°. After addition, the mixture remained at room temp for 2 days, then diluted with ether washed with water, $NaHCO_3$ aq water, and sat. NaCl aq and dried. The ether layer was evaporated and the residue absorbed on column of silica gel. Elution with 50% benzene–petroleum ether gave 65 mg (0·14 mmole, 64%) of acetoxytetrakis[2.2.2.2]paracyclophane (VIII) as white crystals: m.p. 138–139°; mass spectrum *m/e* (relative intensity), 474 (M^+, 12), 433 (16), 432 (45), 223 (19), 209 (12), 207 (37), 200 (11), 120 (30), 105 (38), 104 (100), 91 (16); IR (KBr), 3020, 2930, 2860, 1760, 1515, 1450, 1420, 1370, 1220, 1200, 820, 810 cm^{-1}.

Hydroxytetrakis[2.2.2.2]*paracyclophane* (IX)

A solution of 160 mg (0·337 mmole) of acetate VIII and 90 mg (2·25 mmole) of NaOH in 70% aqueous dioxane was heated at about 80° overnight. The mixture was diluted with cold HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, sat NaCl aq and evaporated. The residue was crystallized from $CHCl_3$. Crude crystals were collected and chromatographed on silica gel. Elution with CCl_4–C_6H_6 gave 105 mg (0·243 mmole, 72%) of hydroxytetrakis[2.2.2.2]paracyclophane (IX) as white crystals: m.p. 169·2–169·5° (from 50% hexane-$CHCl_3$); mass spectrum *m/e* (relative intensity), 432 (M^+, 37), 327 (14), 223 (38), 209 (22), 208 (17), 207 (72), 120 (32), 105 (40), 104 (100); IR (KBr). 3650–3140 (broad), 3040, 2940, 2870, 1525, 1450, 1430, 1190, 820, 810 cm^{-1}.

Diacetyltetrakis[2.2.2.2]*paracyclophanes* (VII)

To a stirred mixture of 133 mg (1·00 mmole) of $AlCl_3$, 35·6 mg (0·45 mmole), AcCl and 12·5 ml of CH_2Cl_2 was added a solution of 148 mg (10·32 mmole) of IV in 6 ml CH_2Cl_2 at 0°. After addition, the mixture was warmed to room temp and stirred for 2·5 hr. The mixture was poured into ice-HCl and ether extracted (3 ×). The combined ether extract was washed with dilute HCl, water, $NaHCO_3$ aq, water, sat NaCl aq, and dried. On evaporation, a residue was obtained and chromatographed on silica gel. Elution with 10% ether–benzene gave a quantitative yield of diacetoxy tetrakis[2.2.2.2]paracyclophanes (VII) (160 mg): IR (KBr) 3020, 2930, 2860, 1690, 1515, 1440, 1355, 1265, 815 cm^{-1}.

Nitrotetrakis[2.2.2.2]*paracyclophane* (X)

Nitration with dinitrogen pentoxide. To a stirred solution of 1·54 g (3·70 mmole) of II in 50 ml of $CHCl_3$ (alcohol free) was added dropwise a cold solution of 3·7 g (34 mmole) of N_2O_5[7] in $CHCl_3$ at 0°. After addition, the mixture was warmed to room temp and kept for 5 hr. The mixture was diluted with ether and washed with water, $NaHCO_3$ aq, water, sat NaCl aq and dried. On solvent evaporation, the residue was chromatographed on silica gel. First elution with 5% benzene–petroleum ether gave 739 mg (48%) of unreacted hydrocarbon. Further elution with 10% benzene–petroleum ether gave 554 mg (1·20 mmole, 33%) of nitrotetrakis[2.2.2.2]paracylophane (X) (63% based on II consumed): m.p. 151–151·3° (from the mixture of n-hexane and CH_2Cl_2); IR (neat), 3030, 2940, 2880, 1535, 1445, 1420, 1350, 815 cm^{-1}; UV (cyclohexane) λ_{max} mμ (ε), 261 (sh, 5400), 266 (5700), 274 (5200), 312 (sh, 2000). (Calc. for $C_{32}H_{31}NO_2$: C, 83·24; H, 6·90. Found: C, 83·26; H, 6·77%).

Nitration with fuming nitric acid. To a stirred solution of 947 mg (2·27 mmole) of II in a mixture of 100 ml Ac_2O and 30 ml AcOH was added dropwise a mixture of 0·2 ml of fuming HNO_3 and 4 ml Ac_2O at 40°.

After addition, the mixture was stirred for 2·5 hr, poured into ice–water, neutralized with $NaHCO_3$ aq and ether extracted. The ether extract was washed with water, sat NaCl aq and dried. On evaporation, the residue was chromatographed on silica gel. Elution with 10% benzene-petroleum ether gave 160 mg (0·347 mmole, 15%) of X. Further elution with 50% benzene–petroleum ether gave 111 mg (0·234 mmole, 10%) of acetoxytetrakis[2.2.2.2]paracyclophane (VIII) which was identical with the sample prepared from the Baeyer–Villiger oxidation of IV.

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