Macro Rings. XXXIX. Syntheses and Spectral Properties of the Aromatic Monosubstituted Derivatives of [3.3]Paracyclophane[1]

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Abstract: A series of 13 aromatically monosubstituted [3.3]paracyclophanes have been prepared for study of their spectral and π-base properties. Nitration, acetylation, and bromination of [3.3]paracyclophane (I) led to monosubstituted derivatives which, in turn, were converted to the other compounds. Reduction of 5-nitro[3.3]paracyclophane (II) gave 5-amino[3.3]paracyclophane (III) characterized as its acetyl derivative (IV). This same compound (IV) was prepared from 5-acetyl[3.3]paracyclophane (V) by a Schmidt rearrangement, and this cycle of reactions demonstrates that no rearrangements occurred during the original electrophilic substitutions of the [3.3]paracyclophane nucleus. Clemmenson reduction of acetyl derivative V gave 5-ethyl[3.3]paracyclophane (VI), whereas oxidative cleavage by the bromoform reaction provided 5-carboxy[3.3]paracyclophane (VII), methylation of which gave 5-carbomethoxy[3.3]paracyclophane (VIII). Treatment of 5-bromo[3.3]paracyclophane (IX) with cuprous cyanide in quinoline at 225° gave 5-cyano[3.3]paracyclophane (X). Metalation with butyllithium of bromo compound IX provided the lithio derivative, methylation of which with dimethyl sulfate gave 5-methyl[3.3]paracyclophane (XI). Oxidation of this lithio derivative with nitrobenzene provided 5-hydroxy[3.3]paracyclophane (XII) characterized as its methyl ether, 5-methoxy[3.3]paracyclophane (XIII), and acetyl derivative, 5-acetoxy[3.3]paracyclophane (XIV). In the nitration and acetylation reactions the first substituent entered the ring under conditions milder than usual. The presence of an acetyl group deactivated both rings toward further electrophilic attack in either ring. The nmr and mass spectral properties of the above compounds are reported. The 5-substituted [3.3]paracyclophanes, unlike the 4-substituted [2.2]paracyclophanes, exhibited normal chemical shifts for protons *ortho*, *para*, and pseudo-*gem* (proton closest to substituent in transannular ring) to the substituent. The protons pseudo-*gem* to the amino and bromo substituents were exceptions, and exhibited downfield shifts less than half as great as those found for the pseudo-*gem* protons in the corresponding 4-amino- and 4-bromo[2.2]paracyclophanes. These differences are interpreted in terms of the differences in geometry of the [3.3]- and [2.2]paracyclophanes. All of the substituted [3.3]paracyclophanes and the parent compounds gave strong parent peaks in their mass spectra. The parent hydrocarbon also gave peaks that correspond to a fragmentation to two entities, one equal to half the parent mass and the other to half the parent mass minus one. The substituted compounds fragmented similarly. The structures of these entities are discussed.

Earlier papers in this series reported a practical synthesis[2a] of [3.3]paracyclophane (I),[2b] and established that the substance was the strongest π base (toward tetracyanoethylene) of the [*m.n*]paracyclophanes. Transannular effects of substituents on the π-base character of monosubstituted [2.2]paracyclophanes were also found to correlate with σ_m values.[2d] Studies of the gross relative rates of acetylation of the more symmetrical of the [*m.n*]paracyclophanes indicated that the closer the two benzenes were held to one another, the faster the first substituent entered the molecule.[3a] However, for the more symmetrical [*m.n*]paracyclophanes, the presence of an electron-withdrawing group in one ring inhibited the introduction of a substituent into the second ring.[3b,c,e] For example, [2.2]- and [3.4]paracyclophanes could not be diacetylated,[3b,c] whereas introduction of a second acetyl group into monoacetylated [4.4]paracyclophane occurred slightly more slowly than the first.[3e] With [6.6]paracyclophane, acetylation of monoacetylated material occurred as fast as that of the hydrocarbon itself.[3d] Substituents in one ring of [2.2]paracyclophane exerted considerable influence on the position of entry of substituents into the second ring,[4a,b] but random orientation was observed in the [4.4]paracyclophane system.[3e] Transannular chemical shifts of the aromatic protons in the nmr spectra of many mono- and disubstituted [2.2]paracyclophanes were observed.[4c] The monocarboxylic acid derivatives of [2.2]paracyclophane[3b] and of [3.4]paracyclophane[3a] were resolved, but that of [4.4]paracyclophane was not resolvable at ordinary temperatures.[3e] Thermal reacemization of the acid of [3.4]paracyclophane occurred at 175° by rotation of the substituted benzene ring with respect to the other,[3a] but that of [2.2]paracyclophane was stable to 200° at which temperature racemization occurred by benzyl–benzyl bond scission and recombination.[4d] Ultraviolet,[5] infrared,[4c,5] nmr,[4c] and mass spectral studies[4c] of many of the parent hydrocarbons and their derivatives have been reported, and correlated with structure.

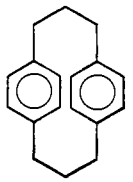
(1) The authors wish to thank the National Science Foundation for a grant used in support of this research. M. S. also wishes to thank the National Science Foundation for a Predoctoral Fellowship, 1965–1969.

(2) (a) D. J. Cram and R. C. Helgeson, *J. Am. Chem. Soc.*, **88**, 3515 (1966); (b) D. J. Cram, N. L. Allinger, and H. Steinberg, *ibid.*, **76**, 6132 (1954); (c) D. J. Cram and R. H. Bauer, *ibid.*, **81**, 5971 (1959); (d) L. A. Singer and D. J. Cram, *ibid.*, **85**, 1080 (1963).

(3) (a) D. J. Cram, W. J. Wechter, and R. W. Kierstead, *ibid.*, **80**, 3126 (1958); (b) D. J. Cram and N. L. Allinger, *ibid.*, 77, 6289 (1955); (c) D. J. Cram and R. W. Kierstead, *ibid.*, 77, 1186 (1955); (d) D. J. Cram and J. Abell, *ibid.*, 77, 1179 (1955); (e) D. J. Cram and R. A. Reeves, *ibid.*, **80**, 3094 (1958).

(4) (a) H. J. Reich and D. J. Cram, *ibid.*, **91**, 3505 (1969); (b) H. J. Reich and D. J. Cram, *ibid.*, **91**, 3517 (1969); (c) H. J. Reich and D. J. Cram, *ibid.*, **91**, 3527 (1969); (d) H. J. Reich and D. J. Cram, *ibid.*, **91**, 3534 (1969).

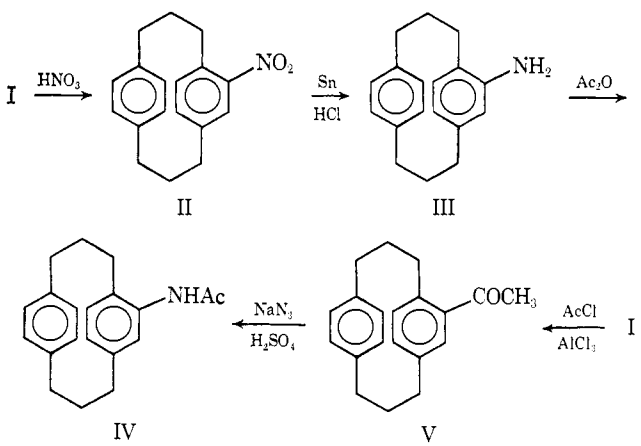
(5) D. J. Cram, R. H. Bauer, N. L. Allinger, R. H. Reeves, W. J. Wechter, and E. Heilbronner, *ibid.*, **81**, 5977 (1959).



I

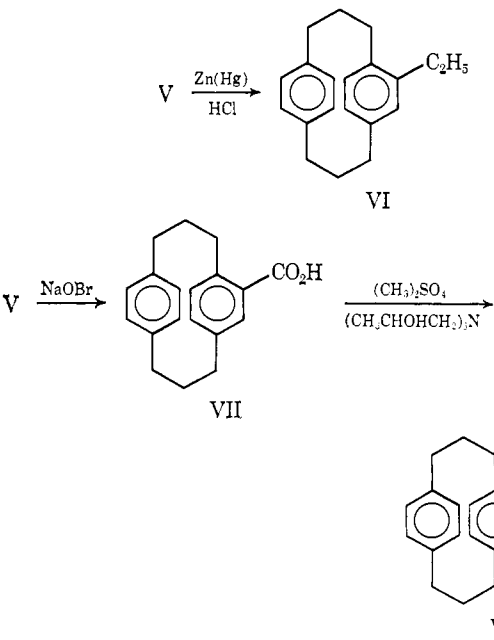
Although [3.3]paracyclophane (I) occupies a central structural position between the smallest symmetrical cycle ([2.2]paracyclophane) and the smallest symmetrical cycle that does not exhibit abnormal spectral and chemical properties ([4.4]paracyclophane),[5] it has been little studied because of its unavailability until recently.[2a] This paper reports the preparation of a series of aromatic monosubstituted [3.3]paracyclophanes and their nmr and mass spectral properties. The next paper[6] describes the results of an investigation of the π-base properties of the substances whose preparation is reported here. The first section describes the preparation of the compounds; the second, the nmr spectral properties; and the third, the mass spectral fragmentation patterns.

Products of [3.3]Paracyclophane Nitration and Acetylation, and Derived Compounds. Nitration of I with fuming nitric acid in acetic acid–acetic anhydride at 70° for 40 sec gave the best yield (41%) of 5-nitro[3.3]-paracyclophane (II) and left only about 1% of I unreacted. Higher temperatures or longer reaction times produced dinitrated material of undetermined structure. The [3.3]paracyclophane ring system being less strained seems less subject to oxidation during nitration than the [2.2]paracyclophane ring system. Reduction of II with tin–hydrochloric acid gave 5-amino[2.2]paracyclophane (III) in 72% yield. This amine was air unstable, and was acetylated with acetic anhydride to give 5-acetamido[2.2]paracyclophane (IV). Preparation of this same compound (IV) by an acetylation route established that the ring system underwent no rearrangements during substitution.



Treatment of a mixture of I and acetyl chloride in dichloromethane with aluminum chloride at −70 to −40° gave a 52% yield of 5-acetyl[3.3]paracyclophane (V). No amount of disubstituted material could be detected with reaction temperatures ranging from −70 to +25°. Thus, the presence of an acetyl group in one ring deactivates both rings toward further acylation. When subjected to the conditions of a modified Schmidt rearrangement,[7] acetyl compound V gave acetamido derivative IV (62%), identical in all respects with the sample prepared *via* the nitration route.

Clemmenson reduction of acetyl derivative V gave an 88% yield of 5-ethyl[3.3]paracyclophane (VI), and oxidative cleavage of V with sodium hypobromite gave 5-carboxy[3.3]paracyclophane (VII) in 96% yield. Methylation of VII gave (80%) 5-carbomethoxy[3.3]-paracyclophane (VIII).



Unlike 4-carbomethoxy[2.2]paracyclophane which underwent bromination readily in the pseudo-*gem* position, the [3.3] analog underwent bromination reluctantly to an unresolved mixture of products. Apparently, the special mechanism for proton transfer in the bromination of the smaller ester homolog[4a] is unavailable in the higher homolog due to the increased distance between the rings.

Brominated and Derived Compounds. Iron-catalyzed bromination of [3.3]paracyclophane (I) occurred extremely rapidly, and with 1 mol of bromine, 5-bromo-[3.3]paracyclophane (IX) was obtained in 76% yield. Polybromination occurred readily when more bromine was employed. Cyanation of IX with cuprous cyanide in refluxing quinoline gave a 63% yield of 5-cyano[3.3]-paracyclophane (X). When treated with *n*-butyllithium in ether at low temperature, IX formed the corresponding lithium derivative, methylation of which with dimethyl sulfate gave 5-methyl[3.3]paracyclophane (XI) in 58% yield. Treatment of the lithium derivative with nitrobenzene at −95°[8] gave a 51% yield of 5-hydroxy-[3.3]paracyclophane (XII) which like 4-hydroxy[2.2]-paracyclophane[9] could not be obtained as a sharp-melting compound. This compound was characterized by its methylation to give (60%) 5-methoxy[3.3]para-cyclophane (XIII), and acetylation (67%) to 5-acetoxy-[3.3]paracyclophane (XIV).

(6) M. Sheehan and D. J. Cram, *J. Am. Chem. Soc.*, **91**, 3553 (1969).

(7) P. A. S. Smith, *ibid.*, **76**, 431 (1954).

(8) P. Buck and G. Kobruck, *Tetrahedron Letters*, 1563 (1967).

(9) D. J. Cram and A. C. Day, *J. Org. Chem.*, **31**, 1227 (1966).

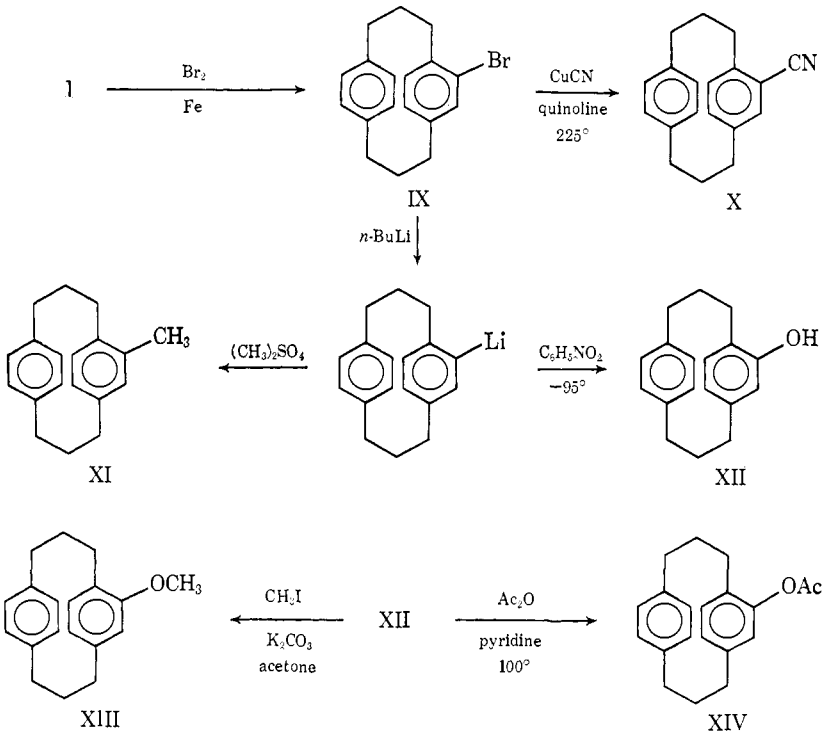
Table I. Nuclear Magnetic Resonance Spectra[a] of 5-Substituted [3.3]Paracyclophanes

Compound		Aromatic protons						Bridge protons						Other protons		
Substit	No.	No.	Pattern	τ, ppm	No.	Pattern	τ, ppm	No.	Pattern	τ, ppm	No.	Pattern	τ, ppm	No.	Pattern	τ, ppm
H	I	8	s	3.40				8	t	7.38[b]	4	m	8.07[c]			
NO_2	II	1	br s	2.60[d]	6	m	3.20	8	t	7.26[b]	4	m	7.86[c]			
NH_2	III	1	br s	4.28[d]	6	m	3.50[e]	8	m	7.42[b]	4	m	8.00[c]	2	br s	6.90[f]
$NHCOCH_3$	IV	1	br s	3.40[d]	6	m	3.30	8	m	7.30[b]	4	m	7.85[c]	1	br s	2.90[g]
$COCH_3$	V	1	br s	3.05[d]	6	m	3.35	8	t	7.40[b]	4	m	7.90[c]	3	s	7.64[h]
C_2H_5	VI	7	m	3.34				10	m	7.35[b]	4	m	7.93[c]	3	t	8.87[i]
CO_2CH_3	VIII	1	s	2.74[d]	6	m	3.41	8	t	7.35[b]	4	m	7.91[c]	3	s	6.18[j]
Br	IX	2	m	3.06[k]	5	d	3.48	8	m	7.46[b]	4	m	7.86[c]			
CN	X	1	br s	3.13[d]	6	m	3.35	8	m	7.32[b]	4	m	7.96[c]			
CH_3	XI	7	m	3.44				8	t	7.38[b]	4	m	7.93[c]	3	s	7.85[l]
OH	XII	7	m	3.43[m]	1	br s	3.75[d]	8	t	7.36[b]	4	m	7.88[c]			
OCH_3	XIII	4	s	3.25[n]	3	m	3.65[o]	8	t	7.27[b]	4	m	7.92[c]	3	s	6.21[j]
$OCOCH_3$	XIV	1	br s	3.58[d]	6	m	3.26	8	t	7.27[b]	4	m	7.93[c]	3	s	7.68[p]
1,4-Bis(*p*-tolyl)butane		8	s	2.95				6	s	7.68[q]	4	m	7.48[b]	4	m	8.36[c]

[a] Varian A-60 analytical nmr spectrometer, with 1% tetramethylsilane as internal standard, and deuteriochloroform as solvent, except IX, where tetrachloroethylene was employed. Abbreviations used are: s, singlet; br s, broad singlet; d, doublet; t, triplet; m, multiplet. [b] Benzylic protons. [c] Protons β to aryl. [d] Proton *ortho* to functional group. [e] See Figure 1 and Discussion. [f] Amino protons. [g] Amide protons. [h] Methyl protons of acetyl group. [i] Methyl protons. [j] Methoxyl protons. [k] *ortho* proton plus transannular proton (see Discussion and Figure 1). [l] Methyl protons. [m] Aromatic plus hydroxyl proton. [n] Aromatic protons in unsubstituted ring. [o] Aromatic protons in substituted ring. [p] Acetoxy methyl protons. [q] *para* methyl protons.

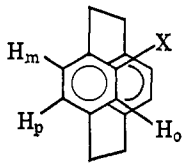
Spectral Properties of Monosubstituted [3.3]Paracyclophanes. Nuclear Magnetic Resonance Spectra. Table I records the nmr spectral bands observed for the 5-substituted [3.3]paracyclophanes, as well as those for the model compound, 1,4-bis(*p*-tolyl)butane and [3.3]paracyclophane itself,[2a] which are included for comparison purposes.

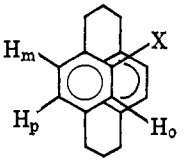
the spectra of the [3.3]paracyclophane derivatives were roughly the same as those of the respective benzene derivatives but only about one-half as large as those of the respective [2.2]paracyclophane derivatives. In the spectra of most of the [3.3]derivatives, the *para* shifts could not be separated from the bulk of the aromatic absorptions. For the amino and methoxyl derivatives,

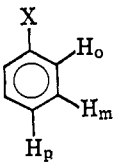


Introduction of a substituent into the aromatic ring of [3.3]paracyclophane caused considerable change in the aromatic proton resonance. Both *ortho* and *para* shifts were observed for a number of derivatives, and these shifts and those found in the analogously substituted [2.2]paracyclophane and benzene derivatives are recorded in Table II. For electron-donating substituents the magnitudes of the *ortho* shifts observed in however, *para* shifts of +0.60 and +0.20 ppm (relative to the singlet for the parent cycle at τ 3.40) were detectable. These shifts contrast with the complete absence of *para* shifts in the spectra of the monosubstituted [2.2]paracyclophanes.[4d] The absence of *para* and the enhancement of *ortho* shifts for [2.2]paracyclophane derivatives have been rationalized[4d] in terms of the distortion of the benzene rings from their normal

Table II. Comparison of the SCS Values[a] for *ortho*, *meta*, and *para* Protons in [3.3]Paracyclophane with Those of [2.2]Paracyclophane and Substituted Benzenes



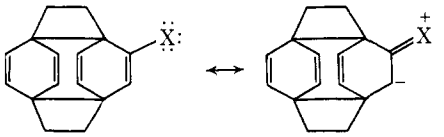




X	H_o[b]	H_m[b]	H_p[b]	H_o	H_m	H_p	H_o	H_m	H_p
OH	0.89			0.45		0.31	0.54	0.17	0.46[c-f]
OCH_3	0.77	−0.01	0.13	0.40	0.02	0.20	0.45	0.08	0.42[c,d]
OAc				0.18					
CH_3	0.35			0.16			0.17	0.09	0.19[g]
Br				−0.23			−0.22	−0.09	−0.03[c]
CN	−0.38			−0.30			−0.27	−0.10	−0.22[d]
$COCH_3$	−0.49			−0.45			−0.64[h]		
CO_2CH_3	−0.77			−0.66			−0.72	−0.10	−0.20[d,e]
NO_2	−0.83	−0.72	−0.39	−0.80			−0.95	−0.20	−0.33[c,i]

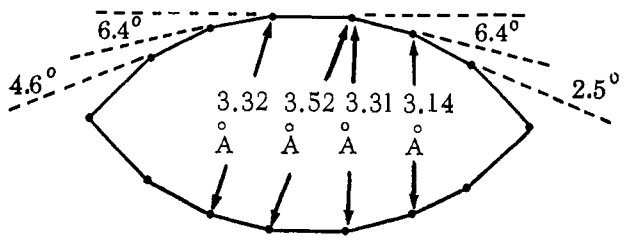
[a] Defined as the chemical shift from the aromatic resonance of the appropriate hydrocarbon (τ 3.63 from [2.2]paracyclophane, τ 3.40 for [3.3]paracyclophane, and τ 2.73 for benzene) in parts per million. [b] Reference 4d. [c] H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961). [d] R. R. Fraser and R. N. Renaud, *J. Am. Chem. Soc.*, **88**, 4365 (1966). [e] J. L. Garnett, L. J. Henderson, W. A. Sollich, and G. V. D. Tiers, *Tetrahedron Letters*, 516 (1961). [f] J. C. Schug and J. C. Deck, *J. Chem. Phys.*, **37**, 2618 (1962). [g] F. A. Bovey, F. P. Hood, IV, E. Pier, and H. E. Weaver, *J. Am. Chem. Soc.*, **87**, 2060 (1965). [h] N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, p 192. [i] T. Schaefer and W. G. Schneider, *J. Chem. Phys.*, **32**, 1218 (1960).

planar configuration.[10] This distortion dampens the resonance interaction between the substituent and the *para* position and probably increases the double-bond character at the *ortho* position. Weak transannular σ bonding was also envisioned between the two aromatic rings at the positions of closest contact (2.79 Å), the two sets of aromatic carbons attached to the methylene bridges (see A and B). This bonding tended to insulate the substituent from its *para* position, and enhanced electron delocalization between the substituent and its *ortho* position.

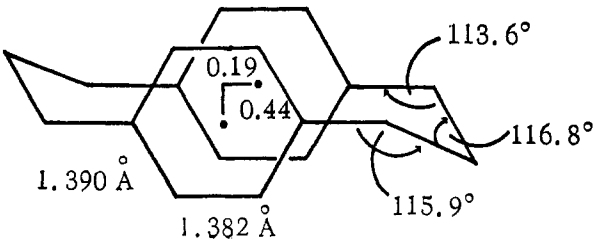


A B

The benzene rings of [3.3]paracyclophane are distorted from their planar configurations by only 6.4° as compared to 15° for [2.2]paracyclophane.[10b,c] The bridgehead carbon atoms are 0.35 Å further from one another in [3.3]- than in [2.2]paracyclophane, partly as a result of decentering of the two benzene rings in the larger cycle. As a result, structures such as A and B probably contribute little to the electron distribution of [3.3]paracyclophane, and the resulting *ortho*- and *para*-substituent shifts are close to normal.



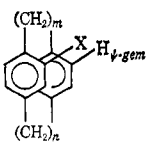
profile of crystal structure of [3.3]paracyclophane



face view of crystal structure of [3.3]paracyclophane

One of the unique features observed in the nmr spectra of the 4-substituted [2.2]paracyclophanes was that in a number of derivatives the proton pseudo-*gem* (the aromatic transannular position closest to the reference position) to the substituent was deshielded compared to the bulk of the aromatic protons.[4d] Proximity of this proton to the functional group was considered important for operation of this effect. The pseudo-*gem* positions in [3.3]paracyclophane are about 0.21 Å farther apart[10c] than in [2.2]paracyclophane, and therefore this pseudo-*gem* effect is expected to be much smaller than in the smaller cycle. Table III

Table III. Comparison of SCS Values[a] for Protons Pseudo-*gem* to 4-Substituent in [2.2]Paracyclophane and to 5-Substituent in [3.3]Paracyclophane



X	$m = n = 2$[b]	$m = n = 3$
Br	−0.80	−0.34
NH_2	−0.75[c]	−0.34
OH	−0.60	
CN	−0.38	
OCH_3	−0.37	
CH_3	−0.35	

[a] Defined as chemical shift from the aromatic resonance of the appropriate hydrocarbon (τ 3.63 for [2.2]paracyclophane and τ 3.40 for [3.3]paracyclophane) in parts per million. [b] Values taken from ref 4d. [c] This work.

(10) (a) C. J. Brown, *J. Chem. Soc.*, 3265 (1953); (b) P. Gantzel, C. L. Coulter, and K. N. Trueblood, *Angew. Chem.*, **72**, 755 (1960); (c) P. Gantzel and K. N. Trueblood, *Acta Cryst.*, **18**, 958 (1965).

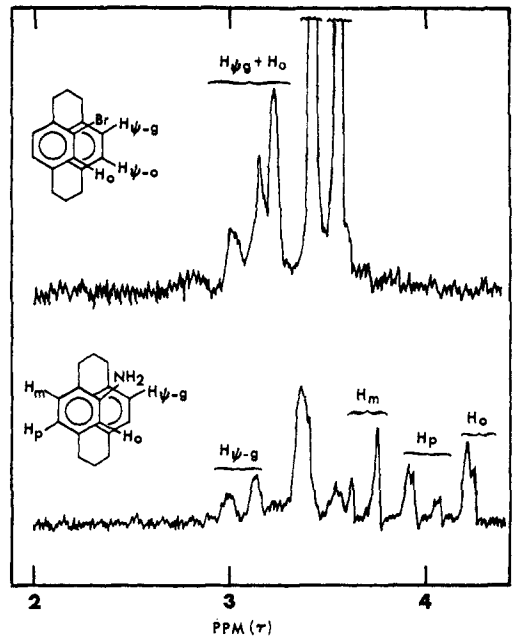
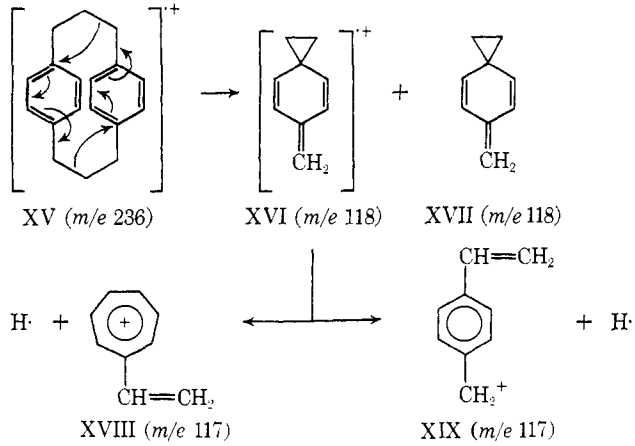


Figure 1. Aromatic proton nmr absorption spectra of 5-amino-[3.3]paracyclophane in deuteriochloroform and of 5-bromo[3.3]-paracyclophane in tetrachloroethylene, and the structural assignment.

compares the transannular deshielding shifts for the 4-substituted [2.2]paracyclophanes with those of the 5-substituted [3.3]paracyclophanes, and Figure 1 shows the aromatic proton resonance bands of 5-amino[3.3]-paracyclophane where this effect is clearly exhibited. The low-field broad doublet (J = 8 cps) gave an intensity of unity, and is split by its *ortho* proton and much less by its *meta* proton in the expected way. For 5-bromo-[3.3]paracyclophane the pseudo-*gem* proton resonance is complicated by overlap with the *ortho*-proton band, but the effect is still visible (Figure 1). Apparently, the rings are too far apart in [3.3]paracyclophane to produce a transannular deshielding effect for the protons pseudo-*gem* to the methoxy, cyano, methyl, and hydroxy groups, although such effects are visible in the spectra of the [2.2]paracyclophane derivatives.[4e]

Only in the spectra of the 5-amino-, 5-acetamido-, 5-ethyl-, 5-bromo-, and 5-cyano[3.3]paracyclophanes are the benzyl protons of the substituted ring sufficiently different from those of the unsubstituted to produce a more complicated multiplet than the triplet characteristic of these protons in [3.3]paracyclophane itself. Only in the spectrum of 5-amino[3.3]paracyclophane were two overlapping triplets distinguishable. Apparently, only this substituent produced a big enough chemical shift of the benzyl protons to produce a visible separation of bands.

Mass Spectra. Table IV records the principal m/e values (and the relative intensities) observed in the mass spectra of [3.3]paracyclophane and its 5-substituted derivatives. For all but the bromo and acetoxy derivatives, the parent molecular ion is the most intense peak in the spectrum (intensity = 100), and even with the derivatives, the parent molecular ion gives a high-intensity peak. Thus, the cycle is intrinsically stable toward fragmentation. The next most intense ion found in the spectra of the parent cycle and many of the derivatives was located at m/e 117, which corresponds to half of the molecular weight of [3.3]paracyclophane minus the mass of one hydrogen atom. A reasonable formulation of the origin of this fragment involves cleavage of the parent radical cation (XV) in both bridges between the methylenes α and β to the aryl groups to produce the same species, except that one is a radical cation of m/e 118 (XVI) and the other a neutral species of m/e 118 (XVII). Loss of a hydrogen atom from XVI could produce either carbonium ions XVIII or XIX, both with m/e 117. These conversions can be envisioned as being either stepwise or concerted. The hypothesis that the m/e 118 fragment also present at fairly high intensities in the spectrum comes from the molecular ion and that the

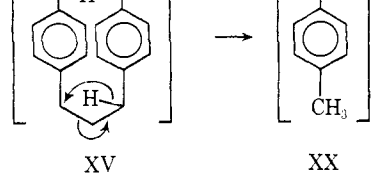


XV (m/e 236) XVI (m/e 118) XVII (m/e 118)

XVIII (m/e 117) XIX (m/e 117)

m/e 117 fragment comes from the m/e 118 fragment is supported by the presence of metastable ions at m/e 59.0 and 116.2, respectively. Similar side-chain cleavages of the type envisioned in this fragmentation scheme have been observed in alkylbenzenes.[11]

The remainder of the spectrum of the parent hydrocarbon can be rationalized in terms of bridge cleavages and hydrogen migrations. The intense ion at m/e 106 is undoubtedly the *p*-xylene radical cation (XX) resulting from two β cleavages and two hydrogen transfers.[12] A metastable ion at m/e 47.6 was observed in support of



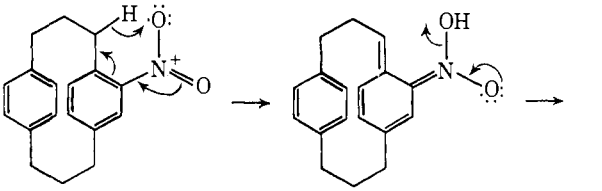
XV XX

this assignment. The ion in the spectrum at m/e 91 is prominent in the spectrum of *p*-xylene[13a] and other alkylated benzenes, and is presumably the tropylium radical cation.[13b]

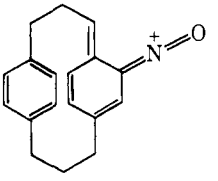
The mass spectra of the monosubstituted [3.3]paracyclophane derivatives were found to be generally similar to that of the parent hydrocarbon, with the exception that new fragments were observed attributable to cleavages characteristic of the functional groups.

(11) F. W. McLafferty, "Mass Spectrometry of Organic Ions," Academic Press, New York, N. Y., 1963, p 457.
(12) Reference 11, p 456.
(13) (a) S. Meyerson and P. N. Rylander, *J. Phys. Chem.*, **62**, 2 (1958); (b) P. N. Rylander, S. Meyerson, and H. M. Grubb, *J. Am. Chem. Soc.*, **79**, 842 (1957).

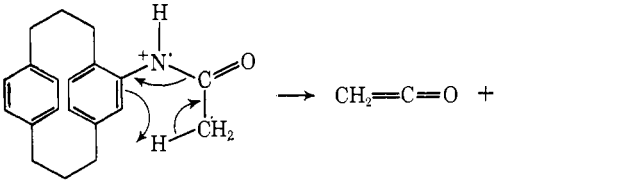
Furthermore, the major ions found in the spectrum of [3.3]paracyclophane were either enhanced or diminished depending on whether the substitutent was electron withdrawing or donating. For example, the intensities of the *m/e* 117 fragments in the spectra of the derivatives with electron-donating substitutents were less than half those of the other derivatives and of the parent hydrocarbon. New fragments appeared with *m/e* values of 117 plus the mass of the substituent plus or minus the mass of one hydrogen atom. This observation is not unexpected, since fragments containing rings substituted with electron donors should be more stable than those with unsubstituted rings, or rings substituted with electron-withdrawing substituents. Similar but less definitive trends were also found for the *m/e* 91 and 106 fragments.



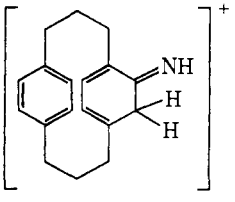
m/e 281 *m/e* 281



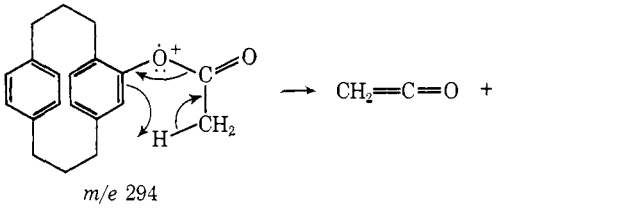
m/e 264



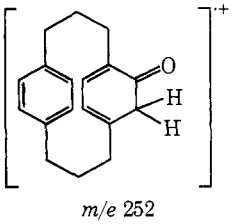
m/e 293



m/e 251



m/e 294



m/e 252

The characteristic loss of hydroxyl from *ortho*-alkylated nitrobenzenes[14] was evidenced in the spectrum of 5-nitro[3.3]paracyclophane by the presence of an intense ion at *m/e* 264. Also, the characteristic McLafferty rearrangements with subsequent loss of ketone for both the acetamido[15] and acetoxy derivatives were observed.

Experimental Section

General. Reagent grade dichloromethane, pyridine, ether, acetic acid, methanol, quinoline, carbon tetrachloride, and dioxane were employed as solvents. Reagent grade bromine, acetyl chloride, nitrobenzene, methyl iodide, anhydrous aluminum chloride, and potassium hydroxide were used without further purification. All melting points were taken on a Mel-Temp melting point apparatus and are uncorrected. Silica gel layers on glass plates were used in thin layer chromatography. The plates were developed in an iodine chamber. Analytical vapor phase chromatography (vpc) was performed on an F & M temperature program Model 720 machine. A 3-ft column, 0.25 in. in diameter, was used in all analytical work. All nmr spectra were taken on a Varian A-60 analytical nmr spectrometer, with 1% tetramethylsilane as an internal standard. Carbon tetrachloride, deuteriochloroform, and tetrachloroethylene were employed as solvents. The ir spectra were taken on a Beckman IR-5 recording spectrophotometer. The mass spectra were taken with a double focusing mass spectrometer (AIE MS-9) equipped with a heated inlet operated at 190°, ionizing current 100 μA; ionizing voltage 70 eV.

[3.3]Paracyclophane (I). Application of the reported preparation of I from [2.2]paracyclophane resulted in an average yield of 13% after vpc purification. This material after crystallization from acetone–methanol gave mp 104–105°.

5-Bromo[3.3]paracyclophane (IX). Iron powder (0.0015 g) was stirred with 1 ml of dichloromethane and 0.1875 ml of a solution of bromine (0.0768 g or 0.48 mol) in 2.5 ml of carbon tetrachloride for 2 hr at 25°. A solution of 0.100 g (0.424 mmol) of I in 10 ml of dichloromethane was then added in one batch and the resultant mixture was brought to reflux in the presence of air but in the absence of moisture. The remainder of the bromine–carbon tetrachloride solution (2.313 ml) was then added dropwise to the refluxing, stirred solution. After the addition, the mixture was stirred at room temperature for an additional 2 hr. The solution was then washed twice with dilute sodium bisulfite solution, once with water and saturated sodium chloride solution, and dried. The dichloromethane solution was then evaporated and the residue adsorbed on a column of 10 g of alumina (Woelm, activity I) made up in pentane. Elution with 5% ether–pentane produced only trace amounts of material. Elution with 10% ether–pentane produced 102 mg (76%) of IX, which when crystallized from hot ethyl acetate had mp 153–154°. Further elution with 20, 40, and 60% ether–pentane solutions produced no solid material. *Anal.* Calcd for $C_{13}H_{19}Br$: C, 68.58; H, 6.07. Found: C, 68.77; H, 6.27.

5-Acetyl[3.3]paracyclophane (V). A mixture of 0.468 g (3.5 mmol) of aluminum chloride, 0.270 ml (3.75 mmol) of acetyl chloride, and 25 ml of dichloromethane was placed in a flask equipped with a drying tube and cooled to −70°. To this stirred solution 0.500 g (2.12 mmol) of I in 10 ml of dichloromethane was added dropwise over a period of 10 min. The solution was then allowed to warm to −40° (20 min), during which time the color changed from yellow to red purple. The reaction was then quenched by pouring the solution into ice–hydrochloric acid (concentrated) and stirring until the mixture became colorless. The organic layer was separated and diluted with ether. The aqueous layer was washed once with ether and discarded. The organic layer and ether extract were combined and washed with water, saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. After drying, the solution was evaporated to about 0.5 ml and adsorbed on 50 g of silica gel made up in 5% ether–pentane. Elution with 5% ether–pentane produced traces of yellow oil. Elution with 15% ether–pentane produced 303 mg (51.5%) of V, which when crystallized from methanol–water had mp 64–65°. Further elution of the chromatograph with 20, 50, and 80% ether–pentane solutions produced only traces of yellow oils. *Anal.*

(14) S. Meyerson, I. Puskas, and E. Fields, *J. Am. Chem. Soc.*, **88**, 4974 (1966).

(15) For loss of ketone from acetanilide see J. L. Cotter, *J. Chem. Soc.*, 5477 (1964); 5742 (1965).

Table IV. Relative Intensities of the Peaks[a] in the Mass Spectra[b] (Partial) of 5-Substituted [3.3]Paracyclophane

	Substituent										
m/e	NO_2	CN	$COCH_3$	$OCOCH_3$	CO_2CH_3	Br	H	$NHCOCH_3$	C_2H_5	OH	OCH_3
91	95	42	51	33	50	57	64	20	12	39	19
105	39	57	54	10	53	58	35	26	29	14	8
106	31	46	23	10	20	45	80	27	12	52	4
115	51	23	26	14	31	30	20	8	5	18	100
117	100	73	63	33	74	100	93	43	49	42	24
118	33	38	31	13	48	40	77	14	18	20	10
119	25	30	26	9	32	38	41	22	29	14	5
120	26	5	3	7	5	3	7	30	6	12	
121	48			14			6	58		20	16
122				45						64	
128	17	8	4	5	13	10	2	9	6	6	3
129	17	15	10	6	14	10	6	11	8	7	3
130	45	19	9	4	16	23	30	38	8	9	2
131	36	24	34	15	51	41	27	78	27	19	9
132	27	4	7	11	12	7	17	49	26	14	4
133	21		6	19	6	1	3	69	14	26	11
134	10			34				13	33	44	7
135	24			12	3			1	4	17	16
136											51
137											4
142		16									
143	2	15	5	2	17	5	2	4	3		
144	7	3	4	8	16	4	7	9	9	2	6
145	6		19	3	4	3	6	7	16	10	2
146			23	5	6	2		12	14	4	
147			7	10	2			5	11	8	14
148			6	4	3			2	1	14	29
149					4			1		14	11
150					1					10	10
155		4									
156		29									
157		6	3		17	8		4			
158	3	2	2		8	8			6		
159			39		3			4	6		
160			43		4	2		7	1		
161			10		3			5			
162	1				8			4			
163					3			92	1		
164					16			11			
165	13			2	6	5	4	3			2
169		6									
170		3									
172	3		2		1			1			
173			18			2					
174			2		1			4			
175					7			74			
176					12	1		26			
177					14			4			
178	14		1		7	4	3				
182						8					
183						1					
184						11					
186						2					
187					1						
188					3			43			
189	4		1		19	2		7			
233		11									
234	2	3									
235	3		2		2	25	2		9		
236	7				1	7	100		2		
237	1					1	21				
238							2				
246		3									
250	9							38			
251	3							15			
252				100						100	
253				20						23	
254				2						2	
261		100									
262		22									
263		2	23		10			4			
264	56		5		5			7	100		
265	12							1	24		
266	5								3		100
267											22

Table IV (*Continued*)

m/e	Substituent: NO_2	CN	$COCH_3$	$OCOCH_3$	CO_2CH_3	Br	H	$NHCOCH_3$	C_2H_5	OH	OCH_3
268											2
278			100		5			6			
279			21		38			3			
280	1		2		8						
281	100										
282	22										
293				1	1			100			
294				34	100			22			
295				8	23			3			
296				1	3						
315						66					
316						18					
317						64					
318						18					
319						2					

[a] Ions of each spectrum were normalized to the spectrum's most intense ion set equal to 100. [b] Spectra were taken with double focusing AIE MS-9 mass spectrometer equipped with a heated inlet operated at 190°, ionizing current 100 μA, ionizing voltage 70 eV.

Calcd for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 86.49; H, 7.96.

5-Nitro[3.3]paracyclophane (II). A mixture of 200 mg (0.48 mmol) of I in 5 ml of acetic anhydride and 5 ml of acetic acid was stirred at room temperature until it became homogeneous (3 min). A 1.48-ml portion of a solution of 0.1 ml of fuming nitric acid in 2 ml of acetic anhydride was then added dropwise to the above stirred solution. The resulting solution was swirled on a steam bath for 40 sec and immediately poured over 25 g of crushed ice. After allowing the ice to melt, the crude product was extracted from the aqueous solution with three 20-ml portions of methylene chloride. The methylene chloride extracts were combined and washed with water, 5% sodium bicarbonate solution, water, and saturated sodium chloride solution. After drying, the orange solution was reduced and adsorbed on a column of 18 g of silica gel made up in pentane. Elution with pure pentane produced only traces of solid material. Elution with 1% ether–pentane gave 98 mg (41%) of II, which when crystallized from aqueous methanol had mp 151–151.7°. Elution with 2% ether–pentane gave a compound (one spot on tlc) whose mass spectrum indicate it to be a dinitro[3.3]paracyclophane derivative. Further elution with solvent mixtures up to pure ether gave a variety of semicrystalline orange solids (total weight *ca.* 30 mg). *Anal.* Calcd for $C_{18}H_{18}NO_2$: C, 76.84; H, 6.81. Found: C, 76.84; H, 6.90.

5-Acetamido[3.3]paracyclophane (IV) from 5-Nitro[3.3]paracyclophane (II). To a mixture of 25 mg (0.108 mmol) of II and 60 mg of granulated tin was added 0.3 ml of concentrated hydrochloric acid in three equal portions, with vigorous shaking after each addition. After the exothermic reaction had subsided, 0.5 ml of ethanol was added and the solution heated on a steam bath for 2 hr with occasional swirling. After cooling, excess aqueous sodium hydroxide solution (30%) was added and the resultant solution was extracted with ether. The ether extracts were combined and washed with water and a saturated sodium chloride solution. The ether solution was dried and evaporated, and the residue was adsorbed on column of 5 g of silica gel made up in pentane. Elution with ether–pentane solvent mixtures up to pure ether gave only traces of unreduced II. Elution with 1% methanol–ether gave 20 mg (72%) of a brown crystalline solid which was shown to be 5-amino[3.3]paracyclophane (III) by nmr and infrared spectroscopy. This air-unstable amine (III) was immediately converted to IV and characterized as such. To 20 mg (0.08 mmol) of III was added 2 ml of acetic anhydride, and the solution was swirled on a steam bath for 10 min. Water was then added and heating continued until there was only one liquid phase. The mixture was then extracted with ether, and the ether extracts were washed with water, saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. After drying the solution the solvent was evaporated to give 23 mg of crude product. Sublimation of the crude product (125°, 0.15 mm) gave 21 mg (80%) of 5-acetamido[3.3]paracyclophane (IV) as a white solid, mp 186–187.5° (sealed tube). *Anal.* Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90. Found: C, 81.96; H, 7.81.

5-Acetamido[3.3]paracyclophane (IV) from 5-Acetyl[3.3]paracyclophane (V). To a mixture of 200 mg (0.72 mmol) of V and 213 mg (1.3 mmol) of trichloroacetic acid maintained at 60° was added in one portion 0.1 ml of concentrated sulfuric acid. To the resultant orange solution was added 80 mg (1.25 mmol) of sodium azide in small portions over a 30-min interval. After an additional 30 min at 60° the mixture was diluted with 20 ml of ice water. The gummy precipitate which formed was then extracted with three 30-ml portions of ether. The ether extracts were combined and washed with water, 5% sodium bicarbonate solution, water, and saturated sodium chloride solution. After drying the solution, the solvent was removed to give 148 mg (66%) of crude product. Sublimation (125°, 0.10 mm) gave 130 mg (62%) of IV, mp 186–187°, undepressed upon admixture with an authentic sample of IV.

5-Ethyl[3.3]paracyclophane (VI). To 0.2 ml of 6 *N* hydrochloric acid in 2.5 ml of water was added 3.0 g of mossy zinc followed by 0.12 g of mercuric chloride. The mixture was then swirled for 10 min, and the supernatant liquid decanted. The amalgamated zinc was washed three times with distilled water, and a solution of 101 mg (0.36 mmol) of V in 6.6 ml of acetic acid was added followed by 9 ml of concentrated hydrochloric acid. About 5 ml of toluene was also added to form an organic layer, and the mixture was refluxed for 12 hr. At the end of this period the mixture was allowed to cool and *ca.* 100 ml of water was added. After separating the organic layer the aqueous layer was extracted with three 20-ml portions of ether. The toluene layer and ether extracts were combined and washed with water, saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. After drying, the solvent was reduced to *ca.* 2 ml and adsorbed on a column of 20 g of neutral alumina (Woelm, activity I) made up in pentane. Elution with 3% ether–pentane gave 85 mg (88%) of VI, which after sublimation had mp 94–95°. Further elution with solvent mixtures up to pure ether produced no solid material. *Anal.* Calcd for $C_{20}H_{24}$: C, 90.85; H, 9.15. Found: C, 90.93; H, 9.19.

5-Carboxy[3.3]paracyclophane (VII). To a stirred solution of 0.1 g (0.36 mmol) of V in 5 ml of freshly purified dioxane was added dropwise at 0° a solution of 0.31 g (20 mmol) of bromine and 0.75 g (47 mmol) of potassium hydroxide in 3 ml of water. The reaction mixture was then allowed to warm to room temperature and stirred for an additional 5 hr. The excess bromine was neutralized by adding a 1% sodium bisulfite solution until the color faded from yellow to clear. The reaction mixture was then diluted with 50 ml of water and extracted twice with ether to eliminate any unreacted V. The aqueous phase was then acidified with dilute hydrochloric acid, and the crude acid which precipitated was extracted with three portions of ether. The ether extracts were washed once with a saturated sodium chloride solution and dried. Removal of the solvent *in vacuo* gave 96 mg (96%) of VII, which when crystallized twice from acetic acid–water had mp 202–204°. *Anal.* Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.25; H, 7.35.

5-Carbomethoxy[3.3]paracyclophane (VIII). A mixture of 125 mg (0.5 mmol) of VII, 518 mg (1.35 mmol) of tris(2-hydroxypropyl)-amine, 314 mg (1.35 mmol) of dimethyl sulfate, and 5 ml of methanol was swirled on a steam bath for 10 min. After cooling, the mixture was diluted with water (*ca.* 50 ml) and extracted with ether. The ether extracts were combined and washed with water, saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. After drying, the solution was evaporated and adsorbed on a column of 10 g of silica gel made up in pentane. Elution

with 5% ether–pentane gave 100 mg (80%) of a colorless oil. Spectral and combustion analyses showed this oil to be the desired ester, VIII. All attempts to effect its crystallization were unsuccessful. *Anal.* Calcd for $C_{20}H_{22}O_2$: C, 81.59; H, 7.53. Found: C, 81.41; H, 7.50.

5-Cyano[3.3]paracyclophane (X). A mixture of 100 mg (0.317 mmol) of IX, 2 ml of reagent grade quinoline, and 32.6 mg (0.356 mmol) of cuprous cyanide was heated to 225° under nitrogen. A small amount of pyridine was added to cause refluxing, and the temperature was maintained at 225° for 24 hr. The reaction mixture was diluted with water and extracted with ether. The ether extracts were washed successively with 15% ammonia, water, 5 *N* hydrochloric aicd, saturated sodium bicarbonate, and saturated sodium chloride solution. After drying the solution, the solvent was removed, and the residue was chromatographed on 20 g of silica gel. Elution with 1% ether–pentane gave 5 mg of unreacted starting material. Elution with 4% ether–pentane gave 52 mg (63%) of X which, when recrystallized twice from ether, gave mp 149–150°. Further elution with solvent mixtures up to 80% ether–pentane produced no solid material. A satisfactory combustion analysis for X could not be obtained (three difference analyses from the same sample gave three widely different per cent carbon readings). The mass spectrum of X had the anticipated molecular ion at *m/e* 261, and the infrared spectrum exhibited a characteristic CN absorption at 2221 cm^{-1}.

5-Methyl[3.3]paracyclophane (XI). Under a nitrogen atmosphere 3 ml of a solution of 1.6 *M* butyllithium in hexane was stirred with 20 ml of dry ether at room temperature for 15 min. To this solution 100 mg (0.316 mmol) of IX was added in one batch, and stirring was continued under nitrogen at room temperature for 30 min. Dimethyl sulfate (0.5 ml) in 2 ml of dry ether was then added dropwise over a period of 15 min to the above solution (heat evolved). The reaction was then quenched with 3 ml of methanol, and washed consecutively with water, 5% sodium bicarbonate, water, and saturated sodium chloride solution. The solution was dried and evaporated, and the residue was chromatographed on 10 g of alumina (Woelm, activity I). Elution of the column with pentane gave 46 mg (58%) of XI, which after sublimation and recrystallization from pentane gave mp 99–100°. *Anal.* Calcd for $C_{19}H_{22}$: C, 91.14; H, 8.86. Found: C, 91.03; H, 8.57.

5-Hydroxy[3.3]paracyclophane (XII). Under a dry nitrogen atmosphere 3 ml of a solution of 1.6 *M* butyllithium in hexane and 40 ml of dry ether were stirred for 15 min at room temperature. To this solution was added 300 mg (0.95 mmol) of IX in one batch, and stirring was continued for 1 hr. The solution was then cooled to −95° (liquid nitrogen–dichloromethane slush), and 0.5 ml (4.9 mmol) of nitrobenzene in 6 ml of dry ether was added dropwise over a 10-min period. After the addition, the reaction was immediately quenched with 10 ml of methanol. The reaction mixture was allowed to warm to room temperature and was washed with water. The aqueous layer was then acidified and extracted with ether. The ether extracts and the original organic layer were then combined and washed with water and saturated sodium chloride solution. The solution was then dried and the solvent evaporated, leaving a dark orange residue. The residue was adsorbed on a column of 50 g of silica gel made up in pentane. Elution with 2% ether–pentane gave 100 mg of a mixture of nitrobenzene, [3.3]-paracyclophane, and 5-bromo[3.3]paracyclophane. Elution with 8% ether–pentane gave 122 mg (51%) of a yellow solid (XII). This material was recrystallized from ether–pentane, mp 148–152°. Repeated recrystallization of the material failed to improve the melting point. The substance was pure to tlc and analytical vpc, and nmr and mass spectra demonstrated the substance to be XII, which was characterized as its methyl ether and acetate (see below).

5-Methoxy[3.3]paracyclophane (XIII). A solution of 80 mg (0.318 mmol) of XII, 0.5 ml of methyl iodide, and 0.5 g of potassium carbonate, and 15 ml of acetone were stirred at reflux for 24 hr. Fresh additions of 0.2-ml portions of methyl iodide were added periodically. The reaction mixture was then diluted with 200 ml of water and extracted several times with ether. The ether extracts were combined and washed with water and saturated sodium chloride solution. After drying the solution, the solvent was evaporated, and the yellow residue was chromatographed on 10 g of silica gel. Elution with 2% ether–pentane gave 50 mg (60%) of XIII, which after sublimation and recrystallization from pentane gave mp 76.1–77.7°. *Anal.* Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.32. Found: C, 85.51; H, 8.23.

5-Acetoxy[3.3]paracyclophane (XIV). A solution of 40 mg (0.159 mmol) of XII in 2 ml of dry pyridine and 2 ml of acetic anhydride were stirred at 100° for 4 hr. After allowing to cool to room temperature, the reaction mixture was diluted with dilute hydrochloric acid and extracted with ether. The ether extracts were combined and washed consecutively with dilute hydrochloric acid, saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. After drying the solution, the solvent was evaporated, and the residue was chromatographed on 10 g of silica gel. Elution with 8% ether–pentane gave 31 mg (67%) of XIV, which after sublimation, had mp 62.3–63.3°. *Anal.* Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.64; H, 7.52.