Macro Rings. XXXV. Transannular Directive Influences in Electrophilic Substitution of Monosubstituted [2.2]Paracyclophanes[1,2]

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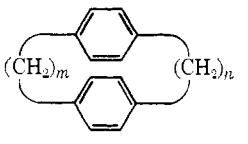
Abstract: The patterns of electrophilic substitution of the monosubstituted [2.2]paracyclophanes have been examined. The isolated yields (minimal) of products were as follows.[3] Acetylation (methylene dichloride–aluminum chloride) of 4-bromo[2.2]paracyclophane (I) gave 6% pseudo-*o*- (II), 41% pseudo-*p*- (III), and 17% *p*- (IV) (indirect detection) bromoacetyl derivatives. Nitration of I in acetic acid gave 5% pseudo-*o*- (IX), 4% pseudo-*p*- (X), 3% pseudo-*m*- (XI), and 2% *p*- (XII) bromonitro derivatives. Small amounts of pseudo-*p*-bromoacetoxy derivative XIV and of a substance derived by adding the elements of nitronium acetate to I (possibly compound XVIa) were also isolated. When treated with base, the latter substance gave pseudo-*gem*-bromonitro derivative (XIII). Iron-catalyzed bromination in methylene dichloride of 4-carbomethoxy[2.2]paracyclophane (XVII), of 4-carboxy-[2.2]paracyclophane (XVIII), or of 4-acetyl[2.2]paracyclophane (XXII) gave substituted pseudo-*gem* materials as sole products. Bromo ester XIX was obtained in 89% yield, bromo acid XX in 63%, and bromoacetyl compound VI in 59% yield. Iron-catalyzed bromination of 4-nitro[2.2]paracyclophane in methylene dichloride gave bromonitro derivatives in the following yields: pseudo-*gem* (XIII), 70%; pseudo-*ortho* (IX), 3%; pseudo-*para* (X), 6%; pseudo-*meta* (XI), 8%. Iron-catalyzed bromination in methylene dichloride of 4-cyano[2.2]paracyclophane (XXIII) gave 16% pseudo-*ortho* (XXIV), 28% pseudo-*para* (XXV), and 26% pseudo-*meta* (XXVI) bromocyano derivatives. Compatibility of structural assignments based on nmr spectra of these compounds was demonstrated through many interconversions. Iron-catalyzed bromination in methylene dichloride or noncatalyzed bromination in acetic or trifluoroacetic acid of 4-methyl[2.2]paracyclophane (XXX) gave predominantly *o*- and *p*-bromomethyl derivatives XXXI and XXXII, respectively. The ratios of yields of these isomers varied depending on medium, and on whether XXX contained deuterium in the position *para* to the methyl group. From the change in ratio, with the isotope being substituted, primary isotope effects were estimated for *para* substitutions: $k_H/k_D \geqslant 3.7$ (methylene dichloride–iron); $k_H/k_D \geqslant 3.9$ (trifluoroacetic acid); and $k_H/k_D \geq 1.5$ (acetic acid). The *para* product (XXXII) from deuterated starting material contained no deuterium when bromination was carried out in acetic acid, but did contain 45% of one atom of deuterium in the unsubstituted ring from bromination in trifluoroacetic acid or in methylene dichloride with an iron catalyst. These patterns of substitution reactions, when not random, are correlated in terms of a rate-limiting and product-determining step in which the proton being substituted is transferred from a σ complex to the strongest base in the proximity. In very nonbasic solvents the most basic position of the transannular ring accepts the proton in substitution of 4-methyl- and 4-bromo[2.2]paracyclophanes. Substituents that carry basic oxygen such as carbomethoxy, carboxy, acetyl, or nitro direct entering substituents pseudo-*gem* by accepting the leaving group.

Previous investigations of electrophilic substitution of the [*m.n*]paracyclophanes have centered mainly on activation–deactivation influences, either as a result of ring size, or the presence of a substituent in one of the two rings. For example, in diacetylation of [6.6]-paracyclophane, one substituent goes in each ring with random orientation,[4a] and no transannular activation or deactivation effects were appparent. However, as the two benzene rings were brought closer together by decreasing the values of *m* and *n*, the presence of one electron-withdrawing substituent in one ring deactivated both rings toward further electrophilic attack.[4b-e,g] For the hydrocarbons themselves, the smaller the values of *m* and *n*, the faster electrophilic substitution occurred.[4c] Electrophilic substitution of paracyclophanes with electron-releasing groups orient *ortho* and *para* in the ring bearing the substituent, which sub-



[*m*, *n*] paracyclophane

(1) The authors wish to thank the National Science Foundation for a grant used in support of this research. H. J. R. also wishes to acknowledge a Woodrow Wilson Fellowship (1964–1965) and a U. S. Rubber Co. tuition grant for 1967.

(2) Some of this material appeared in preliminary form: H. J. Reich and D. J. Cram, *J. Am. Chem. Soc.*, 90, 1365 (1968).

(3) The colloquial nomenclature is self-evident: pseudo-*gem* denotes two transannularly adjacent positions on the benzene rings; pseudo-*ortho*, pseudo-*meta*, and pseudo-*para* specify *ortho*, *meta*, and *para* relationships displaced from the usual homoannular into a transannular context.

(4) (a) D. J. Cram and J. Abell, *J. Am. Chem. Soc.*, 77, 1179 (1955); (b) D. J. Cram and R. W. Kierstead, *ibid.*, 77, 1186 (1955); (c) D. J. Cram, W. J. Wechter, and R. W. Kierstead, *ibid.*, 80, 3126 (1958); (d) M. Sheehan and D. J. Cram, unpublished observation; (e) D. J. Cram and H. P. Fischer, *J. Org. Chem.*, 30, 1815 (1965); (f) D. J. Cram, R. H. Bauer, N. L. Allinger, R. A. Reeves, W. J. Wechter, and E. Heilbronner, *J. Am. Chem. Soc.*, 81, 5977 (1959); (g) D. J. Cram and A. C. Day, *J. Org. Chem.*, 31, 1227 (1966).

Table I. Patterns of Electrophilic Substitution for Monosubstituted [2.2]Paracyclophanes

Run no.	Directing group	Entering group	Reagent	% yield of products[a] Pseudo *gem*	Pseudo *ortho*	Pseudo *para*	*meta*	*para*
1	Br	$COCH_3$	CH_3COCl–$AlCl_3$	(<0.7)[b]	6 (9)[b]	41 (58)[b]	(<12)[b]	17 (11–23)[b]
2	Br[c]	Br[c]	Br_2–Fe[c]		16[c]	26[c]	6[c]	5[c]
3	Br	NO_2	HNO_3–CH_3CO_2H	(1.4)[d]	5	4	3	2
4	CO_2CH_3	Br	Br_2–Fe	89				
5	CO_2H	Br	Br_2–Fe	63				
6	$COCH_3$	Br	Br_2–Fe	59				
7	NO_2	Br	Br_2–Fe	70	3	6	8	
8	CN	Br	Br_2–Fe		16	28	26	

[a] Isolated yields unless otherwise indicated. [b] Yields based on nmr and isomer equilibration. [c] Data taken from ref 6b. [d] Isolated as adduct of starting material, and elements of nitronium acetate; treatment with base gave pseudo-*gem* material.

stitutes faster than the transannular ring, as in the nitration of 4-acetamido[2.2]paracyclophane[4f] and diazonium coupling of 4-hydroxy[2.2]paracyclophane.[4g] Dinitration[4f,5] and dibromination[4g,5] of [2.2]paracyclophane have been reported without firm assignment of structures to the products. Gorham and Yeh[5] were the first to halogenate, metalate, alkylate, and cyanate [2.2]paracyclophane.

This paper reports an investigation of the transannular directive influences of substituents in one ring on the position of entry of new substituents into the second ring of [2.2]paracyclophane. Central to the investigation is the problem of structure determination of the large number of disubstituted [2.2]paracyclophanes synthesized. The primary tools used were nmr and mass spectra. These spectral results are reported and discussed in a separate but adjacent paper.[6a] These primary structural assignments are supplemented and confirmed by a large number of interconversions of disubstituted compounds by classical reactions in which one functional group is converted into another, and by thermal isomerization through the diradical intermediate.[6c] Interconversions of the classical variety are reported here, along with degradative experiments that demonstrate that the central nucleus has maintained its integrity during the substitution reactions.

Results

Monosubstituted [2.2]Paracyclophanes. The most useful entries into ring-substituted [2.2]paracyclophanes are by iron-catalyzed bromination,[4g,5b] aluminum chloride catalyzed acetylation,[4e,7,8] nitration,[7,9] and aluminum chloride catalyzed ethylation.[8] These reactions can be regulated to give predominantly monosubstituted products that serve as starting materials for functional group interconversions through conventional reactions. All of the monosubstituted compounds used here have been previously reported, except 4-methyl[2.2]paracyclophane.[10]

Acetylation of 4-Bromo[2.2]paracyclophane (I) (Run 1). In the absence of acetyl chloride, aluminum chloride catalyzes the rearrangement of [2.2]paracyclophane to [2.2]metaparacyclophane,[11] and more than minimum conditions during acetylation lead to ring-opened products.[4e] Acetylation in dichloromethane of bromo compound I proceeded slowly at −40° and rapidly at −25° to give, after chromatography and fractional crystallization of the crude product, the three isomeric bromoacetyl compounds, II, III, and IV. The approximate yields for the pseudo-*para*[3] and *para* isomers were determined by partial separation of the material into pure components and analysis of the residues by nmr integration procedures (Table I). The crystallization residue nmr spectrum showed indications of the presence of the pseudo-*meta* isomer. The methyl absorptions in the nmr of the five known isomeric bromoacetyl[2.2]paracyclophanes fall into three groups, that of the pseudo-*ortho*, that of the pseudo-*gem*, and those of the other three.[6a] A more complete isomer distribution was obtained by subliming the acetylation product to give a 93% yield of ketones. A portion of this product was thermally isomerized[6c] to an equilibrium mixture of each of the pairs of isomers. From the nmr integrations of the methyl peaks before and after isomerization and the known equilibrium constants for the isomerizations[6c] the yields of the five compounds were calculated (Table I) and found to be in reasonable agreement with the isolated ones. Unfortunately, the high equilibrium constant for V $\rightleftarrows$ VI (K = 5.75) allowed only an estimation of the upper limit for the pseudo-*meta* (V) yield.

As starting material for an attempt to see if deuterium was transferred from ring to ring during acetylation, the pseudo-*p*-deuteriobromo derivative VII was prepared by monometalation of pseudo-*p*-dibromo compound VIII[6b] and deuteration with deuterium oxide. Acetylation of VII (87% of one atom of deuterium) for 2.5 min at −25° gave 60% reaction, the recovered starting material (1.21 atoms of deuterium per molecule) from which showed extensive deuterium scrambling and disproportionation. These reactions appear to occur at a much faster rate than the acetylation reaction, and this fast reaction prevented a determination of the immediate fate of the leaving group in the substitution reaction carried out under these conditions.

Nitration of 4-Bromo[2.2]paracyclophane (I) (Run 3). Of several nitrating mixtures and conditions examined, use of fuming nitric acid in acetic acid at 80° for 1.5

(5) (a) W. F. Gorham, Canadian Patent 638,335 (1962); (b) Y. L. Yeh, U. S. Patent 3,155,172 (1962); (c) Y. L. Yeh, U. S. Patent 3,349,124 (1967); (d) Y. L. Yeh, Canadian Patent 705,457 (1965); (e) Y. L. Yeh, Canadian Patent 772,189 (1967); (f) Y. L. Yeh, U. S. Patent 3,155,712 (1964); (g) Y. L. Yeh and W. F. Gorham, *J. Org. Chem.*, in press.

(6) (a) H. J. Reich and D. J. Cram, *J. Am. Chem. Soc.*, 91, 3534 (1969); (b) H. J. Reich and D. J. Cram, *ibid.*, 91, 3527 (1969); (c) H. J. Reich and D. J. Cram, *ibid.*, 91, 3517 (1969).

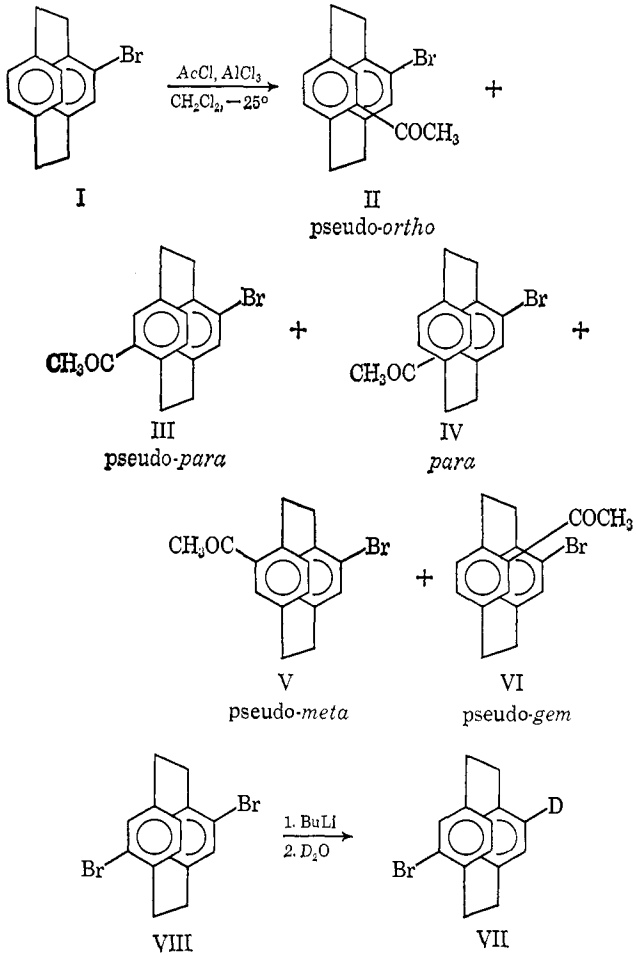
(7) D. J. Cram and N. L. Allinger, *ibid.*, 77, 6289 (1955).

(8) W. F. Gorham, U. S. Patent 3,117,168 (1964).

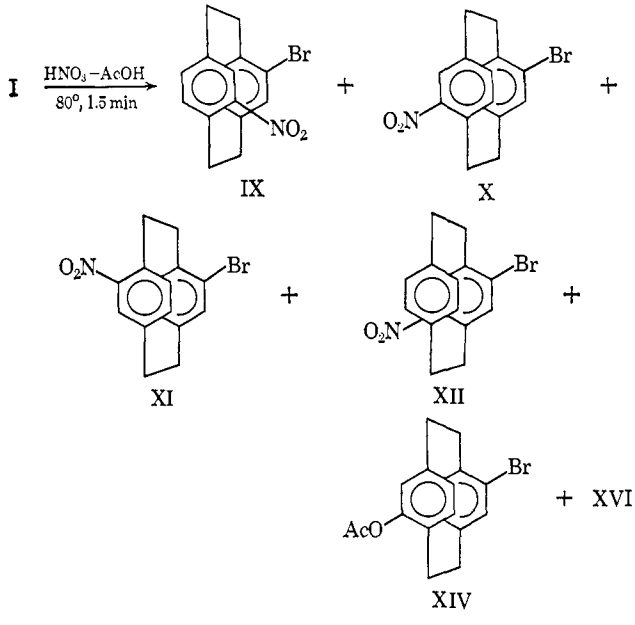
(9) B. E. Norcross, D. Becker, R. I. Cukier, and R. M. Schultz, *J. Org. Chem.*, 32, 220 (1967).

(10) The authors are indebted to D. T. Hefelfinger for these experiments.

(11) D. J. Cram, R. C. Helgeson, D. Lock, and L. A. Singer, *J. Am. Chem. Soc.*, 88, 1324 (1966).

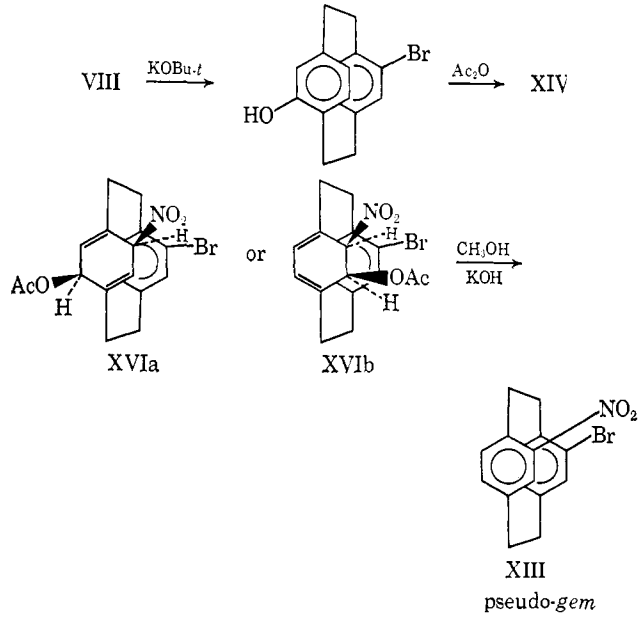


min gave the highest yield of simple nitration products. Chromatography of the complex mixture led to isolation of six discrete substances, and detection of many more. Four of these were the simple monosubstitution products, IX, X, XI, and XII, identified by their nmr spectra,[6a] and by thermal conversion of IX to X,[6c] and of XIII to XI.[6c] Significantly, no pseudo-*gem*-bromonitro derivative (XIII) was isolated from the reaction mixture, although it would have been detected readily in the chromatograph. Table I reports the yields, but

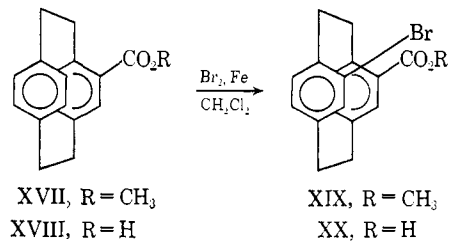


the difficulty of separation makes these very approximate and minimal.

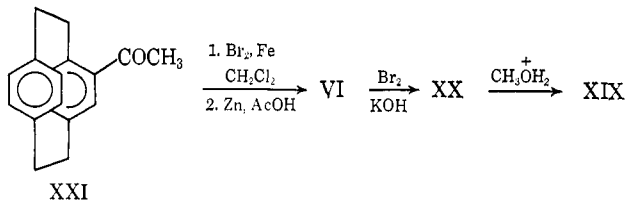
The fifth compound isolated was pseudo-*p*-bromoacetoxy derivative, XIV, identical with the acetylation product of the higher melting bromohydroxy compound (XV) prepared by treatment of pseudo-*p*-dibromo compound VIII with potassium *t*-butoxide.[4g] Other phenol acetates were present in various chromatographic fractions (nmr spectral detection). The sixth compound isolated (XVI) possessed an elemental analysis equivalent to the addition of the elements of nitronium acetate to I. Its nmr spectrum was complex, exhibiting vinyl proton absorption (two hydrogens) at τ 4.2 to 5.2, methylcarbonyl protons at τ 8.05 (three hydrogens), and aromatic absorption at τ 2.8 to 3.1 (three hydrogens). The infrared spectrum had a characteristic aliphatic ester carbonyl band at 1727 cm^{-1} and nitro absorption at 1548 and 1372 cm^{-1}. The essential clue to its structure was provided by its facile conversion, upon treatment with base, to pseudo-*gem*-bromonitro derivative, XIII. Of a number of possible structures for compound XVI, XVIa and XVIb are formulated.

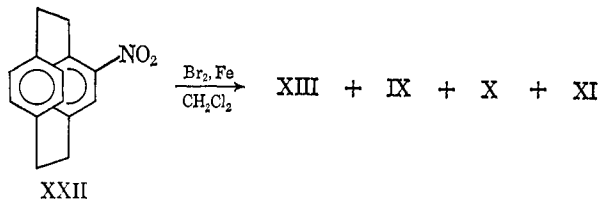


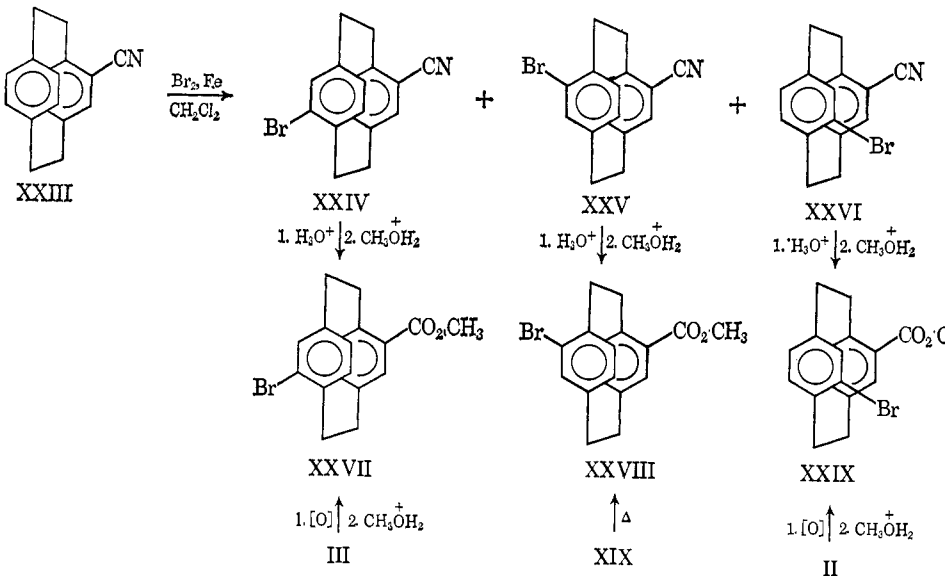
Bromination of 4-Carbomethoxy[2.2]paracyclophane (XVII) (Run 4) and of 4-Carboxy[2.2]paracyclophane (XVIII) (Run 5). Iron-catalyzed bromination of ester XVII in methylene dichloride gave an 89% yield (Table I) of pseudo-*gem*-bromo ester, XIX. Less than 2% of other isomers was present. The nmr spectrum of XIX unequivocally led to its structure.[6a] Confirmation was obtained by thermal isomerization of the



substance to give the pseudo-*meta* isomer.[6c] Similar bromination of acid XVIII followed by esterification of the crude product gave a 63% yield of the pseudo-*gem*-







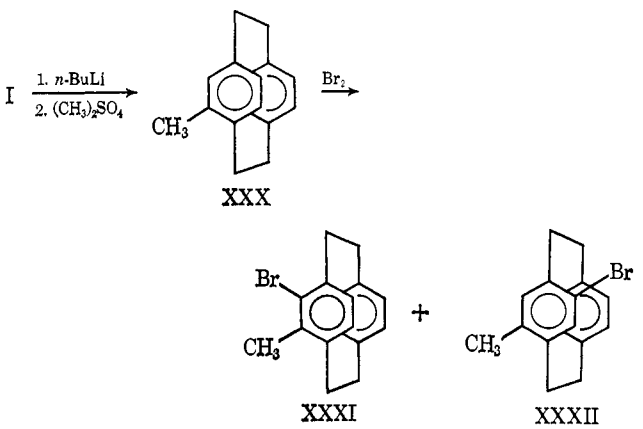
bromo ester, XIX, identical with material prepared as above. Isomeric bromo esters were not detected in the product of the bromination.

Bromination of 4-Acetyl[2.2]paracyclophane (XXI) (Run 6). Treatment of acetyl derivative XXI with bromine and iron in methylene dichloride gave products resulting from bromination of both the methyl and aryl groups. Reduction of the reaction mixture with zinc in acetic acid provided an isolated yield of 59% pseudo-*gem*-bromoacetyl compound, VI, and much recovered starting material. Analysis by nmr and vpc indicated the presence of less than 1% of the isomeric bromoacetyl compounds in the crude product. When submitted to the bromoform reaction, VI gave pseudo-*gem*-bromo acid, XX, which when esterified gave XIX. Both the α-bromination and cleavage steps of the haloform reaction proceeded with more difficulty than the same reactions with the other isomers of VI. Saponification of ester XIX also proceeded only under drastic conditions. The depressed reactivity of these pseudo-*gem* compounds is probably a steric phenomenon. The pseudo-*gem*-bromo ester XIX and bromoacetyl compound VI were both isomerized thermally[6c] to the corresponding pseudo-*meta* derivatives.[6c]

Bromination of 4-Nitro[2.2]paracyclophane (XXII) (Run 7). Under dry conditions in methylene dichloride, the iron-catalyzed bromination of nitro compound XXII gave by chromatographic separation a 70% yield of pseudo-*gem*-bromonitro compound XIII, 3–8% yields (see Table I) of the other pseudo isomers (IX, X, and XI), and a trace of dibrominated material. In carbon tetrachloride the reaction was harder to control, and although a 46% yield of XIII was formed, up to 30% dibrominated product was also produced. The higher specificity in methylene dichloride compared to carbon tetrachloride is probably due to the heterogeneity in the latter solvent. The structures of IX, X, XI, and XIII were established from their nmr spectra,[6a] and confirmed through equilibrations of IX and X, and of XI and XIII.

Bromination of 4-Cyano[2.2]paracyclophane (XXIII) (Run 8). Iron-catalyzed bromination of cyano compound XXIII gave almost equal amounts of pseudo-*p* (XXIV) and pseudo-*m* (XXV), and somewhat less pseudo-*o* (XXVI) bromocyano derivative (Table I for yields). No pseudo-*gem* derivative was detected. Compounds XXIV, XXV, and XXVI were hydrolyzed to the corresponding acids, which were esterified. The resulting methyl esters were compared with those prepared from the bromoacetyl compounds. The expected identities were observed. The nmr structural assignments[6a] of compounds XXIV, XXV, XXVI, II, III, and V were all shown to be compatible.

Bromination of 4-Methyl[2.2]paracyclophane (XXX). Compound XXX was prepared by metalation of bromo compound I with *n*-butyllithium followed by alkylation



with dimethyl sulfate.[10] Iron-catalyzed bromination in methylene dichloride and uncatalyzed bromination in acetic and trifluoroacetic acids gave predominantly a

Table II. Kinetic Isotope Effects in Bromination of 4-Methyl[2.2]paracyclophane (XXX) and its *para*-Deuterated Analog (XXXIII)[a] at 25°

Run no.	Starting material	Medium	Time, min	Conversion, %[b]	Product ratio[c] % *ortho*	Product ratio[c] % *para*	k_H/k_D[d]
9	XXX	CH_2Cl_2–Fe–Br_2	<0.03	47	57.8	42.2	⩾3.67
10[e]	XXXIII[a]	CH_2Cl_2–Fe–Br_2	<0.03	34	30.2	69.8	
11	XXX	CH_3CO_2H–Br_2	90	25	40.5	59.5	⩾1.51
12[f]	XXXIII[a]	CH_3CO_2H–Br_2	93	21	32.0	68.0	
13	XXX	CF_3CO_2H–Br_2	2.5	86	58.8	41.2	⩾3.94
14[g]	XXXIII[a]	CF_3CO_2H–Br_2	2.5	49	30.2	69.8	

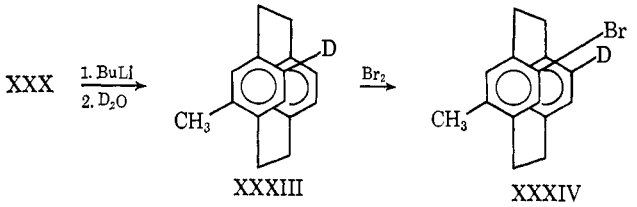
[a] 95% of one atom of deuterium (mass spectra). [b] Based on vpc analysis for starting material. [c] Based on vpc analysis of products, % *ortho* + % *para* = 100%. [d] Calculated through use of eq 1. [e] The *para*-bromination product XXXII contained 0.45 of one atom of deuterium in the unsubstituted ring. The *ortho*-bromination product XXXI contained 0.83 atom of deuterium in the substituted ring and <0.05 in the unsubstituted ring. [f] The *para* product XXXII contained 0.05 atom of deuterium in the unsubstituted ring. [g] The *para* product contained 0.44 atom of deuterium in the unsubstituted ring. The *ortho* product had 0.93 atom of deuterium in the substituted ring and <0.05 in the unsubstituted ring.

mixture of *o*-bromomethyl- (XXXI) and *p*-bromomethyl-[2.2]paracyclophanes (XXXII) in the proportions reported in Table II. The structural assignments of XXXI and XXXII were made on the basis of their nmr spectra.[6a]

Kinetic hydrogen–deuterium isotope effects were estimated through changes in the balance of isomers XXXI and XXXII when deuterated and nondeuterated starting materials were used in bromination. For these experiments, *para* isomer XXXII was monometalated with *n*-butyllithium and quenched with deuterium oxide to give XXXIII containing 0.95 atom of deuterium per molecule, of which 0.92 atom was found in the substituted ring (see below). The per cent conversion to brominated material and balance of isomers of products were determined by vpc. Table II records the conditions and results. When XXXIII was employed, a marked increase in the amount of the *ortho* derivative (XXXI) was observed in all three solvents. Equation 1 was used to estimate the kinetic isotope effect (k_H/k_D) for substitution in the *para* position. This approximate

$$\frac{k_H}{k_D} = \frac{(\%\,para/\%\,ortho)_{XXX}}{(\%\,para/\%\,ortho)_{XXXIII}} \qquad (1)$$

isotope effect was then used to correct for the 8% hydrogen present in the *para* position of XXXIII. A second iteration gave the final minimum[12] k_H/k_D values reported in Table II. The isotope effects appeared to vary with experimental conditions. For example, a run in acetic acid carried to 93% conversion gave $k_H/k_D \geqslant 2.7$, compared to 1.5 for the run reported in Table II. A duplicate run in methylene dichloride–iron medium yielded an isotope effect of ⩾3.9.



XXXIII XXXIV

Recovered starting material and products from runs 10, 12, and 14 were purified by preparative vpc and submitted to mass spectral analysis. Compounds XXX, XXXI, and XXXII cleanly produced molecular ions, *p*-xylylene, and substituted *p*-xylylene fragments in the mass spectrometer,[6a] allowing determination of the deuterium content of each ring. In all three solvents the starting material showed no change in its isotopic substitution, and XXXI had the expected 0.9 atom of deuterium still in the substituted ring, and no deuterium in the unsubstituted ring. The *para* isomer (XXXII) from run 12 contained <5% deuterium, but from runs 10 and 14, XXXII showed 0.44 of one atom of deuterium in the xylylene fragment, indicating that at least 44% of the *para*-substitution product had structure XXXIV. The method of analysis did not, however, allow proof of the *position of deuteration* in the unsubstituted ring, but there is little doubt on mechanistic grounds that the deuterium is pseudo-*gem* to the bromine (XXXIV).

(12) The presence of small amounts of other isomeric bromomethyl-[2.2]paracyclophanes with vpc retention times similar to that of XXXII would lower the observed isotope effects determined by this method.

Discussion

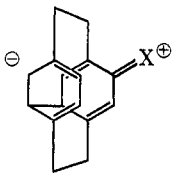
The first part of the discussion demonstrates the lack of correlation of transannular directive influence with transannular resonance effects. In the second the directive influences are shown to correlate with the basicity of positions and groups pseudo-*gem* to the position of substitution. A mechanistic hypothesis for operation of transannular directive influences follows. The kinetic isotope effects and transannular deuterium transfer in bromination are then discussed in terms of the hypothesis. Finally, the hypothesis is put in the context of results and theories that have been developed previously for the mechanisms of aromatic substitution.

Lack of Correlation of Transannular Directive Influences with Transannular Resonance Effects. Table I collates the yield data for electrophilic substitution of the monosubstituted [2.2]paracyclophanes. A ground-state electrostatic model based on transannular resonance interactions does not predict the product pattern obtained for the reactions of Table I. Canonical structures such as A for electron-donating substituents and B for electron-distributing substituents are formulated, and the predicted and observed results do not correspond (Chart I).

The lack of correlation between observed directive influences and the charge distribution predicted by canonical structures such as A and B does not mean that the predicted charge distribution does not exist. Rather this lack of correlation suggests that a ground-state electrostatic model does not apply, and that other models should be examined.

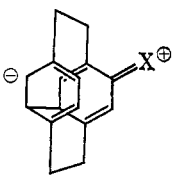
Correlation of Transannular Directive Influences with Basicity of Positions and Groups Pseudo-*gem* to Position

Chart I



A

A: Preferred site(s) of electrophilic substitution. Predicted: pseudo-*meta* and pseudo-*gem*. Observed: bromination, acetylation, and nitration of bromo compound gave predominantly pseudo-*ortho* and pseudo-*para*.

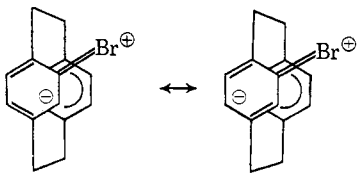


B

B: Preferred site(s) of electrophilic substitution. Predicted: pseudo-*ortho* and pseudo-*para*. Observed: bromination of carbomethoxy, acetyl, and carboxy compounds gave only pseudo-*gem;* bromination of nitro compound gave predominantly pseudo-*gem*, and pseudo-*meta* ~ pseudo-*para;* bromination of cyano compound gave pseudo-*meta* ~ pseudo-*para*.

of Substitution. The data of Table I provide these conclusions. (1) Bromination and acetylation of bromo compound give predominantly pseudo-*ortho* and pseudo-*para* substitution. (2) Bromination of carbomethoxy, carboxy, acetyl, and nitro compounds gives pseudo-*gem* material in all but the last case, essentially exclusively. (3) Nitration of bromo compound and bromination of cyano compound occurred with little transannular directive influence visible.

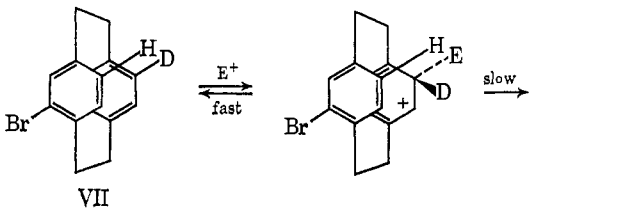
The correlation that emerges from generalizations 1 and 2 is that *predominant substitution occurs pseudo-gem to the most basic positions or substituents in the already substituted ring*. Thus, in bromo compound I, the most basic positions of the substituted ring are *ortho* and *para* to the bromine, and bromination and acetylation predominantly occur in the pseudo-*ortho* and pseudo-*para* positions. In the nitro- and carbonyl-substituted compounds the most basic position is the



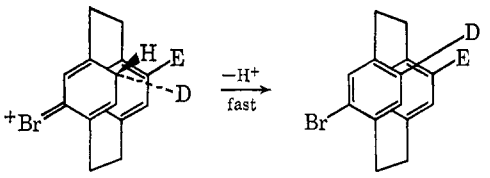
intraannular resonance structures of I

oxygen of the substituent, and substitution occurs pseudo-*gem*. This correlation suggests that the directive effects observed involve participation of a neighboring internal base in the product-determining step of the substitution reaction.

Mechanism for Operation of Transannular Directive Influences. The mechanism indicated for operation of these directive influences involves rapid and reversible formation of σ complexes, followed by rate-determining proton transfers to acceptor sites on the originally substituted ring. The geometry of [2.2]paracyclophane is suited for such proton transfer,[13a] and the aromatic nuclei are expected to be of at least comparable base strength to methylene dichloride, bromide ion, or aluminum tetrachloride anion. The proximity of the rings hinders approach by these external bases and should favor intramolecular processes. This mechanism is formulated for pseudo-*para* substitution of deuterated bromo compound, VII. In the over-all



VII

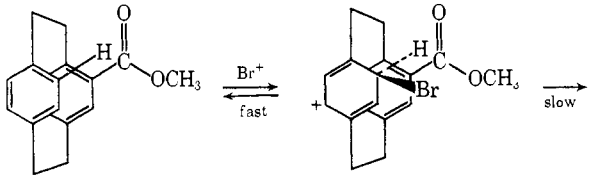


pseudo-*para*

scheme the electrophile attacks the face of the unsubstituted ring, a proton is transferred from ring to ring, and the proton departs from the face of the originally substituted ring. Thus, electrophiles enter and depart from the system by the least hindered paths. As can be seen by the formulation of mechanism, if the position being substituted contains deuterium, this deuterium should migrate to the position in the product pseudo-*gem* to the position just substituted. Unfortunately, the experiment designed to test this mechanism was circumvented by the starting material undergoing reaction of hydrogen–deuterium exchange and disproportionation much faster than the acylation reaction. Deuterium transfer was observed, however, during bromination of 4-methyl[2.2]paracyclophane.

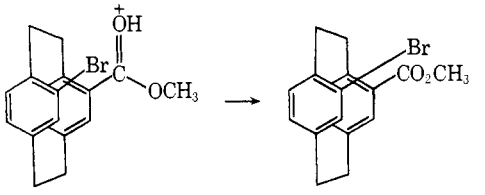
That this mechanism competes with others is shown by the almost random substitution observed in the nitration of bromo compound I in acetic acid–fuming nitric acid. Possibly this medium contains bases stronger than the transannular ring, and protons are removed from the sites of reaction without proton transfer from ring to ring.

The most striking example of transannular directive influences is found in the exclusive or predominant pseudo-*gem* directing effects of the basic oxygen-containing functional groups in the bromination reactions. Molecular models of the 4-carbomethoxy, 4-carboxy-, 4-acetyl-, and 4-nitro[2.2]paracyclophanes place the oxygens of the functional group in a position ideal for accepting a proton from the σ-complexed pseudo-*gem* position. The mechanism is formulated for the ester compound.



XVII

σ complex

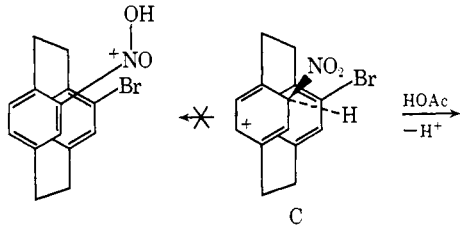


XIX

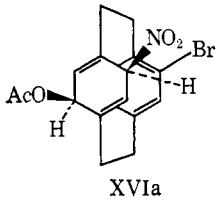
(13) (a) P. K. Gantzel and K. N. Trueblood, *Acta Cryst.*, 18, 958 (1965); (b) E. M. Arnett, *Progr. Phys. Org. Chem.*, 1, 223 (1963).

The orientation observed during bromination of the 4-cyano derivative is entirely different. Thus, the pseudo-*meta* and pseudo-*para* positions underwent substitution with equal ease, the pseudo-*ortho* position with more difficulty, and the pseudo-*gem* not at all. These results point to the conclusion that aside from the large steric effect inhibiting substitution at the pseudo-*gem* position and the smaller one at the pseudo-*ortho* position, no transannular effects are operative. The linear geometry of the cyano group precludes its acting as a neighboring group for removing a proton from the σ-complexed pseudo-*gem* adduct, and therefore no pseudo-*gem* material is formed. The random selection at the pseudo-*meta* and pseudo-*para* positions of the cyano compound provides a model for resonance and inductive effects in the nitro, acetyl, ester, and carboxy functions, and greatly strengthens the hypothesis that these latter groups act as neighboring bases in rate-limiting and product-determining proton transfer reactions. Additional support for these conclusions is found in the fact that the pattern of non-pseudo-*gem* products of bromination of the nitro compound resembles that of the cyano compound. Almost equal amounts of pseudo-*meta* and pseudo-*para* and less pseudo-*ortho* products were observed. The lower directing capacity of the nitro compound compared to that of the carbonyl compounds is attributed to its lower basicity. Thus, the pK_a of the conjugate acid of nitrobenzene is -11, whereas that of methyl benzoate is -7.8, of benzoic acid is -7.3, of acetophenone is -6.2, and of benzonitrile is -10.5.[13b]

The basic oxygen-containing functional groups might play the converse role of complexing the electrophiles and donating them to the pseudo-*gem* position. Although this possibility cannot be ruled out, it seems improbable on a steric basis. Molecular models show substantial compression in the intermediate resulting from electrophile transfer (electrophiles larger than protons) from the functional group to the inside of a pseudo-*gem* σ complex. In the nitration of bromo compound I, attack at the pseudo-*gem* position does occur, but apparently proton loss is not competitive with attack of acetic acid on the σ complex, C. The isolation of compound XVIa (or XVIb) from the reaction mixture also demonstrates that facile 1,3-tautomerism in the σ complex formed between a nitronium ion and an aromatic uncleus is not the cause for the irreversibility of the nitration reaction in general. Such a process could occur with C to give pseudo-*gem* product, but does not. Apparently, even the special route of proton transfer to the carbon atom carrying the bromine in C and from there to the oxygen of the nitro group is slow compared to nucleophile capture.



C



XVIa

Kinetic Isotope Effects and Transannular Deuterium Transfer in Bromination of 4-Methyl[2.2]paracyclophane. Kinetic isotope effects (k_H/k_D) of $\geqslant 3.4$, $\geqslant 3.9$, and $\geqslant 1.5$ were observed for bromination of *p*-protio and *p*-deuterio methyl derivatives in methylene dichloride–iron, trifluoroacetic acid, and glacial acetic acid, respectively (Table II). These substantial isotope effects demonstrate that proton loss from the σ complex is the slow step in all three media. This conclusion supports the mechanism for substitution proposed in the last section.

Bromination of XXXIV in acetic acid gave *p*-bromomethyl product containing $<5\%$ deuterium. Clearly, little transannular deuterium transfer accompanied this reaction. Acetic acid successfully competes with the other benzene ring as base. Under the more acidic conditions of runs 9, 10, 13, and 14, however, the large isotope effect and appearance of deuterium in the unsubstituted ring of *para* substitution (but not of *ortho* substitution) product clearly require a mechanism involving rate-determining ring-to-ring proton transfer, as proposed for runs 1 and 2 on the basis of product analyses.

Compatibility between Transannular Directive Effect Hypothesis and Past Results and Theories. Analogy exists for some of the results and notions of this investigation. The participation of basic functional groups in directing nitrating and halogenating agents to the *ortho* position in simple benzene derivatives has been discussed.[14] The only reference found to the concept of participation of a functional group by assisting proton removal was that of Hammond, *et al.*,[15a] who explained the high *ortho* substitution observed in nitration of nitrobenzene with this concept. This suggestion was later withdrawn[15b] when further work demonstrated that the cyano group exhibited the same property.

Because of the structural similarities between the *peri* relationship in naphthalenes and the pseudo-*gem* relationship in [2.2]paracyclophane, it seemed possible that similar neighboring directive influences might operate. However, the literature[16] reveals no evidence for substantial preference for the 8 over the 5 position in nitration, chlorination, or bromination of 1-nitro, 1-carbomethoxy, 1-carboxy, or other 1-naphthyl derivatives.

In the brominations of methyl, bromo, acetyl, carbomethoxy, and carboxy compounds, high substrate selectivities were observed. For example, dibromination of [2.2]paracyclophane itself gave less than 1% each of the mono and tribromo derivatives.[6b] This selectivity probably reflects a combination of trans-

(14) (a) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier Publishing Co., New York, N. Y., 1965, p 75; (b) D. E. Pearson, R. D. Wysong, and C. V. Breder, *J. Org. Chem.*, **32**, 2358 (1967); (c) P. Haberfield and D. Paul, *J. Am. Chem. Soc.*, **87**, 5502 (1965).

(15) (a) G. S. Hammond, F. J. Modic, and R. M. Hedges, *ibid.*, **75**, 1388 (1953); (b) G. S. Hammond and K. J. Douglas, *ibid.*, **81**, 1184 (1959).

(16) (a) V. Grignard, G. Dupont, and R. Locquin, "Traité' de Chimie Organique," Vol. XVII, Masson et Cie., Paris, 1949, pp 1–544; (b) P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution: Nitration and Halogenation," Academic Press, Inc., New York, N. Y., 1959, p 174.

and intraannular effects coupled with effects associated with the low catalyst concentrations present. Olah, *et al.*,[17] have reported increased substrate selectivity with dilution. In the bromination of the nitro- and cyanoparacyclophanes difficulty in avoiding higher bromination was encountered since considerably higher catalyst concentration was required for these unreactive substrates.

Kinetic isotope effects during bromination with a variety of reagents of all but highly hindered aromatic systems tend to range between 1 and 1.5.[17,18] Systems such as tri-*t*-butylbenzene gave substantial isotope effects,[18b,c] as were observed in the present study. The steric hindrance to external bases that must accept the proton coupled with the relief of strain at loss of bromine is probably the cause of these isotope effects. Both features would tend to enhance k_{-1} and depress k_2.

$$Br^+ + HAr \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\sigma \text{ complex}}{HAr^+Br} \xrightarrow{k_2} ArBr + H^+$$

Acetylation reactions of the type used in this work frequently exhibit substantial isotope effects, which indicates that proton transfer can be rate limiting, particularly when aluminum chloride is the catalyst.[19] In contrast, nitration rates of simple systems have been found consistently to have little dependence on which isotope of hydrogen served as leaving group.[18b,20] Only in the highly hindered 2,4,6-tri-*t*-butylnitrobenzene and similar systems have primary isotope effects been found,[20e] and one is not observed in the same system minus the nitro group.[18b] The hypothesis developed here utilizes the notion that transannular directive influences depend on proton loss from the σ complex as the rate-limiting step. The presence of these directive influences in the bromination and acetylation reactions and the absence in the nitration correlates with the literature reports that primary kinetic isotope effects are observed frequently in the first two but are seldomly found in the last reaction.

Experimental Section

General Comments (Unless Specified Otherwise). Melting points are uncorrected, and all solvents are reagent grade. Nmr measurements were made with a Varian A-60 spectrometer on dilute solutions (5–20%) in deuteriochloroform using tetramethylsilane as internal standard. Infrared spectra were run in chloroform solution on a Beckman IR-5 spectrophotometer. The mass spectra were obtained with an AEI Model MS-9. Vapor phase chromatography (vpc) was carried out on an F & M Model 720 instrument using 3 ft × 0.25 in. columns packed with 20% SE 30 on 60–80 Firebrick at a flow rate of 60 cc/min. Thin layer chromatograms were run using Brinkmann silica gel G or aluminum oxide G coated on glass or Pyrex plates with appropriate cyclohexane–ethyl acetate mixtures as eluent. Iodine vapor was used to spot the plates. Silica gel for column chromatography was Baker chromatographic grade; alumina was Woelm neutral.

Starting Materials. The monosubstituted [2.2]paracyclophanes were prepared as before and exhibited the following melting points: 4-bromo, mp 136–138°, lit.[5b] 132–134°; 4-acetyl, mp 109–110°, lit.[7] 110–111°; 4-carboxy, mp 224–225°, lit.[7] 223.5–224.5°; 4-carbomethoxy, mp 139–140°, lit.[5a] 135–138°; 4-nitro, mp 153–155°, lit.[7] 155.5–156.5°; 4-cyano, mp 122–124°, lit.[5b,21] 123–124°. The preparation of 4-methyl[2.2]paracyclophane[10] is presented below.

Acetylation of 4-Bromo[2.2]paracyclophane (I). A. Preparative Run 1. A solution of I (18.85 g, 0.0658 mol) in 600 ml of dichloromethane was cooled to −55°. Acetyl chloride (10 ml, 0.116 mol) and 19.75 g (0.148 mol) of aluminum chloride were dissolved in 240 ml of dichloromethane at 25° and added rapidly with vigorous stirring to the cold solution. After stirring for 3 min below −20°, the reaction was quenched by pouring it into 1 l. of dilute hydrochloric acid–ice mixture. Ether was added until the organic portion was lighter than water. After washing with 1 *N* hydrochloric acid, saturated sodium bicarbonate solution, and saturated sodium chloride solution the organic portion was dried, and the solvent was removed. The product was chromatographed on 2 kg of silica gel (activated by heating at 120° for 13 hr) using ether–pentane mixtures as eluent. At 7–10% ether–pentane (4 l.) 1.0 g of a yellow solid, identified as a mixture of dibromides by infrared spectrum and vpc retention time, was eluted. Further elution with 10% ether–pentane yielded 1.15 g of pseudo-*o*-bromoacetyl derivative II (5.6% yield), pure by nmr. Sublimation and two recrystallizations from ether–pentane gave an analytical sample, mp 143.5–144.5°.

Anal. Calcd for $C_{17}H_{18}BrO$: C, 65.66; H, 5.21. Found: C, 65.74; H, 5.25.

Elution with a further 20 l. of 10% ether–pentane gave a total of 16.2 g of pale yellow solid which appeared to be a mixture of several compounds. Several crystallizations from chloroform–methanol and ether resulted in isolation of 5.92 g of pseudo-*p*-bromoacetyl derivative III, mp 165–167°. Two more recrystallizations from ether gave mp 169–170°.

Anal. Calcd for $C_{17}H_{18}BrO$: C, 65.66; H, 5.21. Found: C, 65.71; H, 5.27.

From the mother liquors of the crystallization of pseudo-*p*-bromoacetyl derivative were obtained 1.3 g of *p*-bromoacetyl derivative IV after several recrystallizations from ether–pentane and ethyl acetate–ethanol. Two more recrystallizations from ether gave an analytical sample, mp 122.5–123.5°.

Anal. Calcd for $C_{17}H_{18}BrO$: C, 65.66; H, 5.21. Found: C, 65.76; H, 5.11.

It was not practical to crystallize the pseudo-*p*- and *p*-bromoacetyl[2.2]paracyclophanes apart completely. Mixtures of the two which appeared to be free of other impurities in the nmr spectrum were analyzed by integration of the aromatic protons, and compared to the spectra of the pure compounds. In this way mixtures totalling 4.7 g were shown to contain 2.5 g of pseudo-*para* isomer and 2.2 g of *para* isomer. Total yields were thus 8.4 g (41%) of pseudo-*para* and 3.5 g (17%) of *para* bromoacetyl compound.

B. Analytical Run. An acetylation of I was carried out at one-tenth the scale of run A (1.88 g of I, 1.0 ml of acetyl chloride, 1.97 g of aluminum chloride in 85 ml of dichloromethane at −25° for 3 min). The crude product, containing less than 1% starting material by vpc analysis, was sublimed at 120° (0.01 mm) to give 1.998 g of crude product (93% yield). This material was dissolved in 10 ml of dichloromethane and two 1-ml portions were taken out. One portion was placed in a tube and solvent was allowed to evaporate. The tube was flushed with nitrogen, evacuated, and heated at 200° for 46 hr (approximately ten half-lives for the isomerization).[6c] The second portion was placed in an nmr tube and solvent was allowed to evaporate. Both samples were then dissolved in deuteriochloroform, and the methyl region of the nmr spectrum was integrated (Table III). Use of these data and the equilibrium constants for pseudo-*gem* ⇄ pseudo-*meta* and pseudo-*para* ⇄ pseudo-*ortho* allowed calculation of the following yields: pseudo-*para*, 58%; pseudo-*ortho*, 9%; pseudo-*gem*, less than 0.7%; pseudo-*meta* + *para*, 23%; pseudo-*meta* (maximum), 12%.

Pseudo-*p*-deuteriobromo[2.2]paracyclophane (VII). A suspension of 0.5 g (1.37 mmol) of pseudo-*p*-dibromo derivative VIII[6b] in 12

(17) G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, *J. Am. Chem. Soc.*, **86**, 1039, 1044 (1964).

(18) (a) E. Berliner and K. E. Schueller, *Chem. Ind.* (London), 1444 (1960); (b) P. C. Myhre, *Acta Chem. Scand.*, **14**, 219 (1960); (c) E. Baciocchi, G. Illuminati, G. Sleiter, and F. Stegel, *J. Am. Chem. Soc.*, **89**, 125 (1967); (d) J. E. Dubois and R. Uzan, *Tetrahedron Letters*, 309 (1965); (e) E. Helgstrand, *Acta Chem. Scand.*, **19**, 1583 (1965).

(19) (a) F. R. Jensen and G. Goldman in "Friedel-Crafts and Related Reactions," Vol. III, Interscience Publishers, Inc., New York, N. Y., 1964, p 1017; (b) D. B. Denny and P. P. Klemchuk, *J. Am. Chem. Soc.*, 80, 6014 (1958); (c) G. A. Olah, S. J. Kuhn, S. H. Flood, and B. Hardie, *ibid.*, **86**, 2203 (1964).

(20) (a) W. M. Lauer and W. E. Noland, *ibid.*, **75**, 3689 (1953); (b) G. A. Olah, S. J. Kuhn, and S. H. Flood, *ibid.*, **83**, 4571, 4581 (1961); (c) L. Melander, *Arkiv Kemi*, **2**, 211 (1950); (d) T. G. Bonner, F. Bowyer, and G. Williams, *J. Chem. Soc.*, 2650 (1953); (e) P. C. Myhre, M. Beug, and L. L. James, *J. Am. Chem. Soc.*, **90**, 2105 (1968).

(21) L. A. Singer and D. J. Cram, *ibid.*, **85**, 1080 (1963).

Table III

	Pseudo-*meta* + pseudo-*para* + *para* (τ 7.57)	Pseudo-*ortho* (τ 7.48)	Pseudo-*gem* (τ 7.37)
Product prior to heating, %	89.6	9.6	<0.75
Product after heating, %	57.3	40.4	<2.3

ml of ether containing 2.0 mmol of *n*-butyllithium (1.2 ml of 1.7 *N* hexane solution) was stirred at 25° under nitrogen for 40 min, and 0.5 ml of deuterium oxide was added. The reaction mixture was stirred 10 hr, and worked up by washing with water and sodium bicarbonate solution and drying over sodium sulfate. The product was crystallized from ether (after removal of the bulk of the insoluble dibromide and [2.2]paracyclophane) to give 0.2 g of material consisting of 10% [2.2]paracyclophane, approximately 1% VIII, and the remainder VII. A sample of this deuterated material was purified by vpc and analyzed by mass spectrometry. Comparison with the mass spectra of undeuterated material showed the presence of 13.6% nondeuterated *p*-xylylene fragment (*m/e* 104), 12.0% nondeuterated molecular ion (*m/e* 286, 288), less than 1% deuterium on the bromo-*p*-xylylene fragment (*m/e* 182, 184), and no detectable dideuteration in any of these fragments. These results clearly indicate specific deuteration on the unsubstituted ring. The position of the deuterium is inferred from the structure of the starting material, and from the nmr spectrum of the product, which shows a clean doublet of doublets for the pseudo-*gem* proton and hence no *para* coupling. The nmr spectrum of I is reported elsewhere.[6a]

Acetylation of Pseudo-*p*-deuteriobromo[2.2]paracyclophane (VII). A solution of 0.2 g of VII prepared above was acetylated in 21 ml of dichloromethane with 0.16 g (2.04 mmol, 0.145 ml) of acetyl chloride and 0.285 g (0.214 mmol) of aluminum chloride at −30° for 3 min. The mixture was quenched to give a crude product containing 40% monosubstituted material (4-bromo- and 4-acetyl-[2.2]paracyclophanes) and 60% disubstituted material (bromoacetyl- and dibromo[2.2]paracyclophanes) by vpc analysis. Chromatography on 25 g of silica gel allowed separation of ketonic material from the 4-bromo- and pseudo-*p*-dibromo[2.2]paracyclophanes. Mass spectral analysis of the recovered 4-bromo[2.2]-paracyclophane (purified by preparative vpc) showed the isotopic composition for the fragments given in Table IV. These

Table IV

	d_0	d_1	d_2	d_3
p-Xylylene ion, %	48.1	40.8	11.1	
2-Bromo-*p*-xylylene ion, %	55.8	32.5	11.6	
Molecular ion, %	25.6	37.5	21.6	13.9

data demonstrate the occurrence of substantial amounts of scrambling of the starting material under the reaction conditions. Products were not analyzed.

Pseudo-*o*-bromocarbomethoxy[2.2]paracyclophane (XXIX). Bromine (0.22 ml, 0.65 g, 4.05 mmol) was added at 0° to a solution of 1.5 g of potassium hydroxide in 4.5 ml of water over a period of 10 min. A solution of 300 mg (0.91 mmol) of pseudo-*o*-bromoacetyl-[2.2]paracyclophane (II) in 4.5 ml of pure dioxane was added slowly to the hypobromite solution, and the mixture was allowed to warm to room temperature during 2 hr. Aqueous sodium bisulfite solution (1%, 50 ml) was added, and the aqueous portion was extracted twice with chloroform. Acidification with 5 *N* hydrochloric acid and extraction with 1:1 chloroform–ethyl acetate followed by washing and drying of the organic extract gave 240 mg of crude acid. The crude acid was esterified by refluxing for 2 days with 25 ml of 1,2-dichloroethane, 3 ml of methanol, and 0.25 ml of sulfuric acid. Ether (70 ml) was added, and the organic layer was washed with 10% sodium hydroxide solution, saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. Drying of the solution followed by removal of solvent gave crude ester which was chromatographed on 30 g of silica gel using 10% ether–pentane as eluent. The product was crystallized from ether–pentane to give 169 mg of pseudo-*o*-bromocarbomethoxy[2.2]-paracyclophane (XXIX), mp 72–73.5°. A further crystallization from ether gave an analytical sample, mp 73–74°.

Anal. Calcd for $C_{18}H_{17}BrO_2$: C, 62.62; H, 4.96. Found: C, 62.87; H, 5.06.

Pseudo-*p*-bromocarboxy[2.2]paracyclophane. Conversion of pseudo-*p*-bromoacetyl[2.2]paracyclophane (III) to the acid by the above procedure followed by two recrystallizations from acetic acid gave a sample of pseudo-*p*-bromocarboxy[2.2]paracyclophane with mp 292–292.5°.

Anal. Calcd for $C_{17}H_{15}BrO_2$: C, 61.64; H, 4.56. Found: C, 61.77; H, 4.45.

Decarboxylation of Pseudo-*p*-bromocarboxy[2.2]paracyclophane. A mixture of 300 mg of acid, 300 mg of copper powder, and 10 ml of quinoline (Matheson Coleman and Bell, refined) were refluxed for 1.5 hr. Ether was added and the reaction mixture was filtered. Extraction with 10% sodium hydroxide and acidification of the extract gave 0.11 g of starting material, mp 290°. The organic portion was washed with saturated sodium bicarbonate and sodium chloride solutions. Drying and removal of solvent gave 0.2 g of a tan solid. Recrystallization of this material from ether–methanol gave 30 mg of 4-bromo[2.2]paracyclophane (I), mp 134–137° (lit.[6b] 132–134°). The infrared spectrum was identical with that of authentic I.

Pseudo-*p*-bromocarbomethoxy[2.2]paracyclophane (XXVII). Esterification of a sample of pseudo-*p*-bromocarboxy[2.2]paracyclophane by the same procedure as for the pseudo-*ortho* isomer followed by sublimation of the crude product at 105° (0.04 mm) and recrystallization from tetrahydrofuran–ether gave an analytical sample, mp 159–160°.

Anal. Calcd for $C_{18}H_{17}BrO_2$: C, 62.62; H, 4.96. Found: C, 62.74; H, 5.07.

***p*-Bromocarbomethoxy[2.2]paracyclophane.** A haloform reaction, esterification, and purification as described for pseudo-*o*-bromoacetyl[2.2]paracyclophane converted the *para* isomer to *p*-bromocarbomethoxy[2.2]paracyclophane, mp 156–157°.

Anal. Calcd for $C_{18}H_{17}BrO_2$: C, 62.62; H, 4.96. Found: C, 62.77; H, 5.11.

Nitration of 4-Bromo[2.2]paracyclophane (I) (Run 3). I (10 g, 35 mmol) was dissolved in 250 ml of acetic acid at 75°, and 25 ml of 90% nitric acid was added with stirring. After 1.5 min the temperature had risen to 85°, and the brown solution was poured onto ice. After extraction with ether, the organic portion was washed repeatedly with water, then with saturated sodium chloride solution and dried. After removal of solvent the product was chromatographed on 1 kg of silica gel. Elution with 10 l. of pentane gave 0.34 g of a mixture of I and small amounts of dibromides.

Elution with 10 l. of 2% ether–pentane and 3 l. of 3% ether–pentane gave a mixture of bromonitro derivatives. The initial fractions consisted mainly of a mixture of pseudo-*para*, pseudo-*meta*, and *para* isomers, from which the bulk of the pseudo-*para* isomer could be separated by crystallization from dichloromethane–ether. Recrystallization of the mother liquors from acetone gave *p*-bromonitro[2.2]paracyclophane (XII) reasonably pure. Rechromatography on alumina (activity III) at low ratios of compound to packing (1:400) allowed separation of completely pure *p*-bromonitro compound (XII). Later fractions of the alumina rechromatographs gave pseudo-*m*-bromonitro material (XI) contaminated by small amounts of pseudo-*para* isomer (X). The tail of the bromonitro band in the original chromatograph consisted of pseudo-*ortho* isomer mixed with some pseudo-*para*. After removal of the bulk of the pseudo-*para* by crystallization, the pseudo-*ortho* isomer was obtained pure by rechromatography on silica gel. Ultimately, the following materials were isolated: (1) pseudo-*para* (X), 407 mg (4% yield), mp 214–216°, recrystallization of 373 mg from dichloromethane–ether gave 329 mg, mp 215–216° (*Anal.* Calcd for $C_{16}H_{14}BrNO_2$: C, 57.84; H, 4.25. Found: C, 58.00; H, 4.27); (2) compound XII (*para*), 240 mg (2.1%), mp 161.5–164.5°, two recrystallizations from acetone–ether and sublimation gave an analytical sample, mp 164–166° (*Anal.* Calcd for $C_{16}H_{14}BrNO_2$: C, 57.84; H, 4.25. Found: C, 57.81; H, 4.46); (3) compound XI (pseudo-*meta*), 345 mg (3.1%), containing small amounts (approximately 5%) of pseudo-*p*-bromonitro material (a mixture melting point with a pure sample (mp 118–120°) prepared by isomerization[6c] of pseudo-*gem*-bromonitro[2.2]paracyclophane was 116–118.5°); (4) compound IX (pseudo-*ortho*), 568 mg (5%), mp 221–222.5°, recrystallization from ether–pentane gave 375 mg, mp 222.5–224° (*Anal.* Calcd for $C_{16}H_{14}BrNO_2$: C, 57.84; H, 4.25. Found: C, 58.04; H, 4.48).

Elution of the original chromatograph with 4 l. of 6% ether–

pentane gave only small amounts of yellow oils. Elution with 4 l. of 10% ether–pentane gave what appeared to be a mixture of several phenol acetates (nmr spectra). The major component of the mixture could be separated by crystallization from ether–pentane and rechromatography of the mother liquors on silica gel. A total of 72 mg (0.61%) of pseudo-*p*-bromoacetoxy[2.2]paracyclophane (XIV), essentially pure by nmr analysis, was isolated. Recrystallization from ether gave an analytical sample, mp 181.5–182.5°, identical with the acetate prepared from the high-melting bromophenol synthesized previously[4g] (see below).

Anal. Calcd for $C_{18}H_{17}BrO_2$: C, 62.62; H, 4.96. Found: C, 62.80; H, 5.02.

Elution with 3 l. of 20% ether–pentane and 3 l. of 35% ether–pentane gave yellow oils whose nmr spectra had absorption in the vinyl region (τ 4–5) and acetate methyl region (τ 8), but attempts to isolate pure compounds failed. However, elution with 2 l. of 50% ether–pentane gave material from which 190 mg of XVI, mp 146–148°, could be isolated by crystallization from ether and rechromatography on silica gel. Two recrystallizations of this sample from ether gave an analytical sample, mp 148.5–150.5°.

Anal. Calcd for $C_{18}H_{18}BrNO_4$: C, 55.11; H, 4.62. Found: C, 55.10; H, 4.64.

Further elution with solvents of increasing polarity gave increasing amounts of yellow oils having nmr absorption in the aromatic vinyl, and acetate methyl regions, but no pure compounds could be isolated.

Compound XVI was hydrolyzed to pseudo-*gem*-bromonitro compound (XIII) as follows. To a solution of 0.17 g of potassium hydroxide in 5 ml of methanol was added 33 mg of compound XVI, and the mixture was refluxed for 30 min. Water and ether were added, and the organic portion was washed with water, saturated sodium bicarbonate solution, and saturated sodium chloride solution. After drying the solution, the solvent was removed. The residue (28 mg) was crystallized from dichloromethane–ether to give 10 mg of pseudo-*gem*-bromonitro[2.2]paracyclophane (XIII), mp 235.5–236.5°.

Anal. Calcd for $C_{16}H_{14}BrNO_2$: C, 57.84; H, 4.25. Found: C, 57.75; H, 4.23.

Pseudo-*p*-bromoacetoxy[2.2]paracyclophane (XIV). Exactly 30 mg of the higher melting bromohydroxy[2.2]paracyclophane (mp 181.5–184.5°) prepared previously[4g] was dissolved in 2 ml of pyridine and 2 ml of acetic anhydride, and left at 25° for several days. Ether and water were added, and the organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution. The solvent was removed, and the residue was crystallized from chloroform–ether to give 30 mg of pseudo-*p*-bromoacetoxy compound (XIV), mp 182.5–183.5°, with sample isolated from the nitration product of 4-bromo[2.2]paracyclophane, mmp 182–183°. The nmr spectra of the high and low melting bromohydroxy[2.2]paracyclophanes clearly require the pseudo-*para* and pseudo-*meta* structures,[6a] respectively, as suggested previously.[4g]

Bromination of 4-Carbomethoxy[2.2]paracyclophane (XVII) (Run 4). A solution of 4.6 g (29 mmol) of bromine in 50 ml of carbon tetrachloride was prepared, and 10 ml of this solution, 50 ml of dichloromethane, and 170 mg of iron were stirred for 0.75 hr. Dichloromethane (100 ml) and 7 g (26.3 mmol) of XVII were added, and the remainder of the bromine solution was added over a period of 1 hr at 25°. After stirring the mixture for another hour, 10% sodium bisulfite solution was added, and the organic portion was washed with water, 5% sodium carbonate solution, and saturated sodium chloride solution. A vpc chromatogram showed the presence of 10% starting material. After drying the solution and evaporating the solvent, the product was crystallized twice from 1:1 tetrahydrofuran–ether to give 3.7 g of pseudo-*gem*-bromocarbomethoxy[2.2]paracyclophane (XIX), mp 159.5–160.0°. The combined mother liquors were chromatographed on 600 g of silica gel. Elution with 10% ether–pentane gave 0.75 g of starting material (XVII). There was a very slight overlapping with the product, which was eluted with 10–15% ether–pentane. This product was crystallized from tetrahydrofuran–ether; first crop, 2.83 g, mp 159–160°; second crop, 0.44 g, mp 159–160°; third crop, 0.15 g, nmr identical with that of the other crops and no trace of any other isomers. The mother liquors from this crystallization yielded a further 0.11 g of XIX after rechromatography. The total yield of pure pseudo-*gem*-bromocarbomethoxy[2.2]paracyclophane was 7.23 g (89% yield after correcting for recovered starting material). Small amounts of acids (0.15 g) were also obtained from the chromatograph, but were not examined closely. A small amount of the product was recrystallized from dichloromethane–ether to give an analytical sample, mp 159.6–160.0°.

Anal. Calcd for $C_{18}H_{17}BrO_2$: C, 62.62; H, 4.96. Found: C, 62.50; H, 4.90.

A portion of the crude product from a bromination of XVIII (carried out as above except that the solvent was carbon tetrachloride) was submitted to vpc analysis at 190° on a 5 ft × 0.125 in. column packed with 5% SE-30, 0.5% Atpet 80 on 80–100 Chromosorb W, HMDS treated, using an Aerograph 200 instrument. Under these conditions the pseudo-*p*-, pseudo-*m*-, pseudo-*o*-, and *p*-bromocarbomethoxy isomers have a retention time of 7.9 min, whereas that of the pseudo-*gem* isomer is 8.6 min. Comparison of the vpc trace of the reaction product with that of standard mixtures of pseudo-*gem* isomer with 1.0 and 2.0% pseudo-*ortho* isomer and 0.5 and 1.0% pseudo-*meta* isomer showed the presence of approximately 1.8% contaminant in the product. This value is only approximate since about 1.5% thermal isomerization[6c] of the pseudo-*gem* isomer occurred on the vpc column.

Bromination of 4-Carboxy[2.2]paracyclophane (XVIII) (Run 5). A mixture of 25 ml of dichloromethane, 0.5 g (1.98 mmol) of XVIII, and 0.1 g of iron filings was refluxed while 0.116 ml (0.34 g, 2.1 mmol) of bromine in 6 ml of carbon tetrachloride was added dropwise. After refluxing for 3 hr, 35 ml of 1,2-dichloroethane was added, and the solvent was distilled until the boiling point was 82°. Methanol (3 ml) and 0.5 ml of sulfuric acid were added, and the mixture was refluxed for 3 days. The usual isolation procedure gave a product whose nmr spectrum was identical with that of pure pseudo-*gem*-bromocarbomethoxy[2.2]paracyclophane. The crude product was sublimed to yield 560 mg (82%), mp 160–165°. This material was crystallized from dichloromethane–ether to give 430 mg (63%) of pseudo-*gem*-bromocarbomethoxy[2.2]paracyclophane (XIX), mp 158–159.5°; mmp with product from the bromination of 4-carbomethoxy[2.2]paracyclophane was 158.5–160°.

Bromination of 4-Acetyl[2.2]paracyclophane (XXI) (Run 6). To a stirred mixture of 0.1 g of iron filings and 10 ml of dichloromethane was added 5 ml of a solution of 2.8 g (17.6 mmol, 0.94 ml) of bromine in 30 ml of carbon tetrachloride. After stirring for 15 min, 2.0 g (8 mmol) of XXI was added, and the remainder of the bromine solution was added over a period of 1 hr while the solution was refluxed. After refluxing for 0.5 hr longer, the reaction mixture was washed twice with dilute sodium bisulfite solution, once with saturated sodium chloride solution, and then dried. After removal of solvent the residue was dissolved in 30 ml of glacial acetic acid at 90–95°, and 3.0 g of zinc dust was added in small portions with vigorous stirring over a period of 5 min. The mixture was cooled, ether and water were added, and the organic portion was washed with water, 5% sodium carbonate solution, and saturated sodium chloride solution. After drying and removal of solvent, the product was chromatographed on 200 g of silica gel and 120-ml fractions were collected. The eluent was mixtures of ether and pentane: fractions 1–5, 5%; 6–9, 7%; 10–16, 10%; 17–23, 12%; 24–36, 15%; and 37–43, 25%. Fractions 16–22 contained 0.908 g (45%) of starting material (XXI) containing less than 0.4% monobrominated acetyl[2.2]paracyclophane by vpc analysis. Fractions 26–37 contained 0.890 g of a white crystalline solid. This material was crystallized from dichloromethane–ether to yield 0.687 g of pseudo-*gem*-bromoacetyl[2.2]paracyclophane (VI), mp 181–182.5°. A further crystallization from the same solvent gave an analytical sample, mp 181–182.5°.

Anal. Calcd for $C_{18}H_{17}BrO$: C, 65.66; H, 5.21. Found: C, 65.68; H, 5.30.

The mother liquor from the first crystallization above gave a second crop of 127 mg, mp 181–182°. Thus, the total yield of VI was 59% after correcting for recovered starting material. The mother liquor of this crop contained 53 mg of solid. The nmr spectrum of this material had two peaks in the methyl region with intensities 0.96 (peak A) and 0.04 (peak B). Chemical shifts of these peaks and of the known paracyclophane methyl ketones[6a] in deuteriochloroform (tetrachloroethylene) in hertz from tetramethylsilane are: peak A, 157 (152.5); peak B, 146 (141); 4-acetyl[2.2]paracyclophane, 146 (140.5); pseudo-*gem*-bromoacetyl-[2.2]paracyclophane, 156 (152); pseudo-*o*-bromoacetyl[2.2]paracyclophane, 152 (147); pseudo-*p*-bromoacetyl[2.2]paracyclophane, 144 (141); pseudo-*m*-bromoacetyl[2.2]paracyclophane, 146 (141); *p*-bromoacetyl[2.2]paracyclophane, 146 (141.5).

The vpc chromatogram of this residue showed a peak for 4-acetyl[2.2]paracyclophane (XXI) comprising 2.8% of the total area of the two peaks in the trace. If this is taken to be percentage by weight (controls were not run), then the mole per cent was 3.7%, as compared to 4% for the minor component as determined by nmr integration, which can thus be assigned entirely to XXI. If 2.8% of the residue is XXI, this amounts to 1.5 mg or 0.17% of the

total bromoacetyl[2.2]paracyclophane fraction. Any isomeric bromoacetyl compound must be present in considerably smaller quantity than this, provided it did not cocrystallize with the pseudo-*gem* isomer. This is probably a good assumption since the pseudo-*gem* compound is the least soluble of the known bromoacetyl[2.2]-paracyclophanes.

Oxidative Hydrolysis of Pseudo-*gem*-bromoacetyl[2.2]paracyclophane (VI). The usual procedure for the haloform reaction (see above) gave only trace amounts of acid. When a twofold excess of reagents was used, and the mixture stirred at room temperature for 24 hr instead of 2 hr, only 19 mg of base-insoluble material remained (from 150 mg of pseudo-*gem*-bromoacetyl[2.2]paracyclophane). The crude acid was esterified as for the pseudo-*ortho* isomer. From the alkaline extract there was obtained 74 mg of unreacted acid. The crude ester was chromatographed on 10 g of silica gel using 10% ether–pentane as eluent to give 30 mg of white solid. Crystallization from ether yielded 19 mg of pseudo-*gem*-bromocarbomethoxy[2.2]paracyclophane, mp 159–160°; with authentic material obtained from the bromination of 4-carbomethoxy[2.2]paracyclophane mmp 159.5–160.5°.

Bromination of 4-Nitro[2.2]paracyclophane (XXII) (Run 7). A mixture of 3 ml of dichloromethane, 0.25 ml (4.9 mmol) of bromine, and 0.1 g of iron filings was stirred for 1 hr. Freshly distilled dichloromethane (40 ml), 2.0 g (7.9 mmol) of XXII, and 0.20 ml of bromine were added. The reaction mixture was refluxed for 0.5 hr, after which a vpc of a portion of the reaction mixture showed that approximately 4% of XXII was left. A further 0.016 ml of bromine was added; the reaction mixture was refluxed for 20 min more, and was quenched by adding 10% sodium bisulfite solution. Ether was added, and the organic portion was washed with water, dried, and chromatographed on 300 g of silica gel, taking 100-ml fractions. Eluent for fractions 1–21 was 1% ether–pentane; 22–69, 2%; 70–79, 4%; 80–87, 6%; and 88–140, 10%. Fractions 32–44 contained 443 mg of a mixture of pseudo-*p*- and pseudo-*m*-bromonitro[2.2]paracyclophanes. This material was triturated with 20 ml of ether. The ether was decanted, two small crops of insolubles were collected, and the mother liquors were crystallized from ether–pentane to give 152 mg of pseudo-*m*-bromonitro[2.2]paracyclophane (XI), mp 117–118.5°. This material was separated from a small amount of insolubles, and recrystallized from ether–pentane to give 100 mg, mp 117–118.8°. The mother liquors were combined and recrystallized to give 104 mg of additional XI, mp 115–117°, for a total yield of 204 mg (8%). A mixture melting point with previously prepared XI (isomerization of pseudo-*gem* isomer[6c]) was 116–118°. The insoluble materials were combined and recrystallized from dichloromethane–ether to give 130 mg of pseudo-*para* isomer, X, mp 214.5–216°. A mixture melting point with material from the nitration of 4-bromo[2.2]paracyclophane was 214–215°. A second crop of 30 mg was obtained for a total yield of 6% pseudo-*para* isomer. Fractions 45–71 contained 103 mg of nitro-, bromonitro-, and dibromonitro[2.2]paracyclophanes (by vpc analysis). Fractions 72–81 contained 103 mg of crude pseudo-*o*-bromonitro-[2.2]paracyclophane (IX). This material was sublimed and recrystallized from ether–pentane to give 59 mg (2.3%), mp 219–221°, with material from nitration of 4-bromo[2.2]paracyclophane mmp 219.5–222°. Fractions 84–140 contained 1.88 g of pseudo-*gem*-bromonitro[2.2]paracyclophane (XIII). Recrystallization from dichloromethane–ether yielded 1.57 g, mp 235–236.5°; with a sample prepared by hydrolysis of compound XVI mmp 234.5–236.5°. A second crop of 250 mg, mp 234.5–236.5°, brought the total yield of pseudo-*gem* material to 70%. The residue from the above separation scheme amounted to 0.304 g.

Bromination of 4-Cyano[2.2]paracyclophane (XXIII) (Run 8). A mixture of 3 ml of dichloromethane, 0.35 ml (1.1 g, 6.9 mmol) of bromine, and 0.1 g of iron filings was stirred for 1 hr at 25°. Dichloromethane (47 ml, freshly distilled over molecular sieves), 2.0 g (8.6 mmol) of XXIII, and 0.15 ml of bromine were added and the solution was refluxed for 4 hr, when a vpc chromatogram indicated approximately 30% reaction. At intervals, portions of 0.2 ml, 0.2 ml, and 0.1 ml of bromine were added, until vpc analysis showed the reaction mixture to contain 4% of starting material, 1% dibrominated material, and the remainder monobromination products. The reaction was then quenched with 10% sodium bisulfite solution, ether was added, and the organic portion was washed with 10% sodium bisulfite solution and saturated sodium chloride solution. After drying the solution, the solvent was removed and the residue was recrystallized twice from dichloromethane–ether to give 483 mg of pseudo-*p*-bromocyano[2.2]paracyclophane (XXIV), mp 221.5–222.5°. The mother liquors were chromatographed on 300 g of silica gel, taking 100-ml fractions, and using 4% ether–pentane as eluent for fractions 1–48 and 6% ether–pentane for fractions 49–78. Fractions 22–38 (1.237 g) were recrystallized from dichloromethane–ether to give 287 mg of XXIV, mp 216–219°. This sample was combined with the 483 mg of pseudo-*para* isomer isolated above and recrystallized to yield 675 mg of XXIV, mp 221.5–223.5°; with material prepared by monocyanation of pseudo-*p*-dibromo[2.2]paracyclophane[6b] mmp 221.5–223.5°. The mother liquors from fractions 22 to 38 were recrystallized from ether–pentane to give 668 mg of pseudo-*m*-bromocyano[2.2]paracyclophane (XXV), mp 122.5–125°. A second recrystallization gave an analytical sample, mp 125.5–126.5°.

Anal. Calcd for $C_{17}H_{14}BrN$: C, 65.40; H, 4.52. Found: C, 65.55; H, 4.68.

Fractions 42–62 (0.494 g) were sublimed and recrystallized from ether–pentane to give 360 mg of pseudo-*o*-bromocyano[2.2]paracyclophane (XXVI), mp 179–182°; with material prepared by monocyanation of pseudo-*o*-dibromo[2.2]paracyclophane[6b] mmp 179.5–184°. The mother liquors were combined, chromatographed, sublimed, and recrystallized as above to give a further 72 mg of pseudo-*p*-, 35 mg of pseudo-*m*-, and 80 mg of pseudo-*o*-bromocyano[2.2]paracyclophanes. Total yields were 747 mg (28%) of pseudo-*p*-, 703 mg (26%) of pseudo-*m*-, and 440 mg (16%) of pseudo-*o*-bromocyano[2.2]paracyclophanes. The residues contained 0.20 g of unresolved material.

Hydrolysis of Pseudo-*m*-bromocyano[2.2]paracyclophane (XXV). A mixture of 150 mg of XXV was refluxed for 10 days with 10 ml of hydrochloric acid and 15 ml of acetic acid. The reaction mixture was diluted with water and extracted with ether. The ether solution was washed with water, and then with 10% sodium hydroxide solution, which was acidified. The precipitated acid was extracted with ether, washed with water, and dried. The crude acid was esterified as in other cases. The crude ester had an nmr spectrum identical with material prepared by isomerization of pseudo-*gem*-bromocarbomethoxy[2.2]paracyclophane,[6c] mp 92–93.5°. Crystallization of the sample prepared here did not give sharp-melting material, apparently because of the presence of small amounts of pseudo-*para* isomer.

Hydrolysis of Pseudo-*p*-bromocyano[2.2]paracyclophane (XXIV). A mixture of 300 mg (0.96 mmol) of XXIV, 10 ml of hydrochloric acid, and 15 ml of glacial acetic acid was refluxed for 3 days. The reaction mixture was poured into 200 ml of water, and extracted with 200 ml of ethyl acetate. The organic layer was washed with water and then extracted with 10% sodium hydroxide solution, which was washed once with chloroform and acidified. The precipitated acid was dissolved in 250 ml of ethyl acetate. This solution was washed with water and saturated sodium chloride solution, and dried. Solvent was removed to give 180 mg of acid which was directly esterified by the procedure used for the pseudo-*ortho* isomer. The crude ester (149 mg) was crystallized twice from ether–pentane to give pseudo-*p*-bromocarbomethoxy[2.2]paracyclophane (XXVII) whose nmr spectrum, melting point (158–159°), and mixture melting point (157–158°) were essentially identical with those of XXVII prepared from acetyl compound III (see above).

Hydrolysis of Pseudo-*o*-bromocyano[2.2]paracyclophane (XXVI). Hydrolysis of 320 mg of XXVI by the same procedure as above, except that the nitrile was refluxed for 5 days, gave 230 mg of acid, which was esterified. The crude product of the esterification had an nmr spectrum identical with that of pseudo-*o*-bromocarbomethoxy[2.2]paracyclophane (XXIX) prepared from the bromoacetyl compound II (see above).

4-Methyl[2.2]paracyclophane (XXX).[10] To 500 ml of anhydrous ether under a positive pressure of dried nitrogen was added 46 ml of 1.5 *M* *n*-butyllithium (60 mmol) in hexane (Foote Mineral Co.). This solution was cooled to 0° and 10.47 g (36.5 mmol) of 4-bromo-[2.2]paracyclophane (I) was added directly. The reaction was allowed to come to room temperature and stirred for 30 min (pale yellow color developed). The reaction mixture was then cooled to 0° and 6.86 ml (73 mmol) of dimethyl sulfate in 40 ml of ether was added over 10 min. After stirring for 2 hr, concentrated aqueous ammonia was added to destroy excess methylating agent. The reaction mixture was washed with water, sodium bicarbonate, and saturated sodium chloride solution, and chromatographed on 50 g of alumina with pentane eluent. Exactly 7.87 g of white solid was obtained which showed the following composition by analytical vpc: XXX, 92%; [2.2]paracyclophane, 4%; I, <1%; dimethyl[2.2]-paracyclophane, 1%. When 1 g of the above mixture was subjected to preparative vpc on SE-30 gum rubber on Firebrick (6 ft × 0.75 in. i.d., 180°, 15 psi He), 0.70 g of XXX, mp 150–152°, was obtained (68% yield).

Anal. Calcd for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 91.89; H, 8.05.

Fractional crystallization of the chromatographic product from ether–pentane yielded 4-methyl[2.2]paracyclophane containing ~1% of [2.2]paracyclophane which was used for the brominations.

Preparative Bromination of 4-Methyl[2.2]paracyclophane (XXX). One drop of bromine, 50 mg of iron powder, and 10 ml of dichloromethane were refluxed for 1 hr. Dichloromethane (100 ml) and 2.85 g of XXX (12.8 mmol) were added, and 2.00 g (12.5 mmol) of bromine in 30 ml of carbon tetrachloride was added dropwise over 0.5 hr. Analysis (vpc) showed complete reaction. Ether was added, and the organic layer was washed with dilute sodium bisulfite solution and saturated sodium chloride solution. The solvent was removed, and the product was filtered through 50 g of alumina with pentane as eluent. The product was crystallized from dichloromethane–ether to give 1.17 g and a second crop of 0.7 g. These were combined and recrystallized from dichloromethane–ether to give 1.2 g (31% yield) of *p*-bromomethyl[2.2]paracyclophane (XXXII), mp 159–160°. A second crystallization of this material afforded an analytical sample of XXXII, mp 160.5–161.5°.

Anal. Calcd for $C_{17}H_{17}Br$: C, 67.78; H, 5.69. Found: C, 67.80; H, 5.83.

Further crystallization of the mother liquors from ether–pentane gave 1.0 g of *o*-bromomethyl[2.2]paracyclophane contaminated by *para* isomer (15% by vpc analysis).

***p*-Deuteriomethyl[2.2]paracyclophane (XXXIII).** To 17 ml of ether under dry nitrogen was added 7 ml of a solution of 1.7 *N* *n*-butyllithium (11.9 mmol) in ether. The solution was cooled to 0° and 2.5 g (8.3 mmol) of *p*-bromomethyl[2.2]paracyclophane (XXXII) was added. The ice bath was removed, and the reaction mixture was stirred for 1 hr at 25°. One milliliter of deuterium oxide (99.8%) was added slowly, and the product was dissolved in ether. The solution was washed with water and dried, and solvent was removed. Analysis (vpc) showed the presence of <2% [2.2]-paracyclophane or XXXII. The crude product was crystallized from dichloromethane–ether to yield 598 mg of XXXIII, mp 146–148.5°. Mass spectral analysis of a sample purified by vpc showed that the product had <0.01, 0.92, and 0.96 atom of deuterium in the *p*-xylylene, 2-methyl-*p*-xylylene, and molecular ions, respectively.

Analytical Brominations of 4-Methyl[2.2]paracyclophane (XXX) and *p*-Deuteriomethyl[2.2]paracyclophane (XXXIII). In Acetic Acid (Runs 11 and 12). Exactly 21.0 mg of XXX (or XXXIII) was dissolved in 15 ml of acetic acid, and 0.005 ml of bromine was added. After stirring at 25° for 90 min, the reaction was quenched by addition of 10% sodium bisulfite solution and 50 ml of 1:1 ether–pentane, and 1.00 ml of an internal standard solution (102.0 mg of pseudo-*p*-dimethyl[2.2]paracyclophane[6b] in 10.0 ml of carbon tetrachloride) was added. The solution was washed three times with water, and once with 5% sodium bicarbonate solution and saturated sodium chloride solution. The solution was dried, solvent was removed, and the residue was dissolved in 1 ml of acetone and analyzed by vpc (Aerograph 200 at 205°; 10 ft × 0.125 in. o.d. column packed with 5% Carbowax 20M on 80–100 Chromosorb W); yield (vpc) was approximately 65%.

In Trifluoroacetic Acid (Runs 13 and 14). Exactly 21.0 mg of XXX (or XXXIII) was dissolved in 10 ml of trifluoroacetic acid which had been flushed with nitrogen for 0.5 hr (4-methyl[2.2]paracyclophane gives a purple color and decomposes rapidly when dissolved in trifluoroacetic acid in the presence of air, but the solution is stable under nitrogen). A solution of 0.003 ml of bromine in 5 ml of trifluoroacetic acid (under nitrogen) was added with stirring during 2 min. The reaction mixture was stirred for 0.5 min longer and then quenched and worked up as above; yield (vpc), approximately 80%.

In Dichloromethane (Runs 9 and 10). Use of the preparative bromination procedure, even with the reaction time shortened to 0.5 min, gave deuterium scrambling of the bromination products. A solution of 0.05 ml of bromine in 5 ml of dichloromethane was stirred with 0.05 g of iron dust for 0.5 hr, and 0.5 ml of this solution was added to a well-stirred solution of 21.5 mg of XXX (or XXXIII) in 10 ml of dichloromethane followed in 1–2 sec by 3 ml of an aqueous solution containing 10% ammonia and 5% sodium bisulfite. The product was isolated as above to give a vpc yield of approximately 65%.

Analyses. The retention times of XXX, pseudo-*p*-dimethyl-[2.2]paracyclophane, XXXII, and XXXI were 8.8, 10.7, 23.6, and 26.2 min, respectively. Because of the large difference in retention time between internal standard and products, the yields quoted are not highly accurate, but the conversions and relative amounts of XXXI and XXXII reported in Table II are reproducible to ±2%. Identical flame ionization detector responses were assumed for XXXI and XXXII.

The mass spectral samples for deuterium analyses were purified by preparative vpc (3 ft × 0.25 in. column, 20% SE-30 on Firebrick at 207°). Complete separation between XXXI and XXXII was not achieved under these conditions so that the samples of XXXII contained some XXXI (5–20%). This could be corrected for since XXXI could be obtained pure.