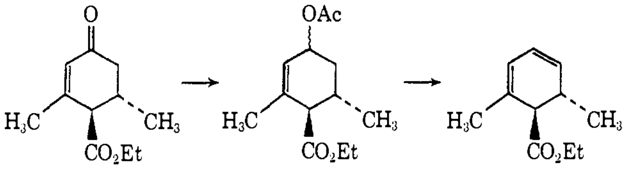
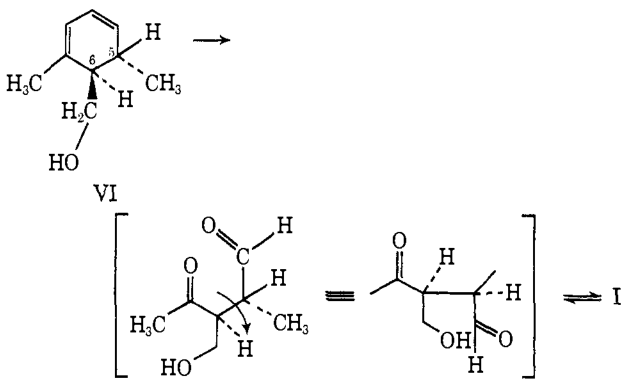
to tetrahydrofuran derivatives based on coupling constants,[4] and the desire to obtain quantities of compound I for further studies, we undertook the synthesis of compound I in a manner which decisively bears on its stereochemistry. The results are summarized below.

The readily available 3,5-dimethyl-4-carbethoxycyclohex-2-en-1-one (III)[5] was subjected to reduction with sodium borohydride and subsequent acetylation (Ac_2O–pyridine, 0°, overnight) to provide the allylic acetate mixture IV[6] in 75% yield (bp 93–97° (0.05 mm)). Pyrolytic elimination of acetic acid at 450° (0.1 mm) gave a mixture of three dienes[7] in 95% yield from which the major isomer V [40%; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 262 nm (log ϵ 4.44)] was separated by preparative glc. Reduction of V with lithium aluminum hydride afforded the homoannular dienol VI[8] [$\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 262 nm (log ϵ 4.13); bp 80–83° (0.1 mm)] in 95% yield.



III IV V

Ozonolysis of VI (CH_2Cl_2, −78°, Zn, HOAc) produced *dl*-botryodiplodin presumably *via* intermediate VII. It is seen that the trans relationship of the hydrogens at C_5 and C_6 in alicyclic structure VI is translated into a syn relationship in rotamer VII and thence into a cis relationship in the heterocyclic structure I. The stereochemical relationship of the nonanomeric centers is thus defined.[9] The nmr spectra of synthetic (see Figure 1) and natural botryodiplodin[10] measured at 250 MHz[11] in CCl_4 were identical, except for slight differences in the ratio of anomers. The acetate derived from the synthetic material also displayed spectral properties identical with those of natural botryodiplodin acetate.



VI

VII

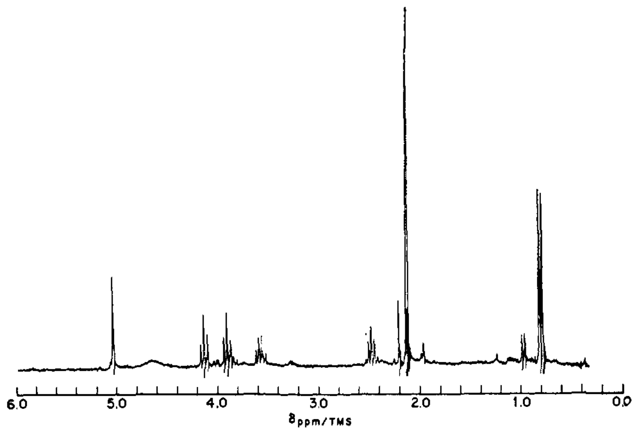


Figure 1. 250-MHz spectrum of synthetic botryodiplodin.

We are currently preparing analogs of I, by ozonolysis of appropriately substituted unsaturated alcohol derivatives, in order to define the structural features necessary for anti-cancer activity.

Acknowledgment. We thank the Research Corporation and the Chemistry Department of Carnegie-Mellon University for financial support of this work.

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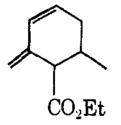
[4] J. D. Stevens and H. G. Fletcher, Jr., *J. Org. Chem.*, 33, 1799 (1968).

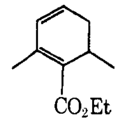
[5] E. C. Horning, M. O. Denekas, and R. E. Field, "Organic Synthesis," Collect. Vol. III, John Wiley, New York, N. Y., 1955, p 317.

[6] All new compounds had ir, nmr (250 MHz), elemental analysis, and/or high-resolution mass spectra compatible with the structures proposed.

[7] Two isomeric products, shown to be i and ii, were also formed in this reaction, probably as a result of competitive rearrangement to a tertiary allylic acetate and subsequent loss of acetic acid.



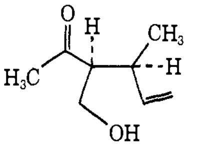
i



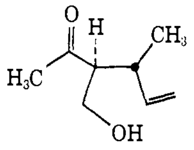
ii

[8] The stereochemistry of VI is trans as shown, this assignment resting on its mode of synthesis and the value of the vicinal coupling constant (*via* triple resonance) between the aliphatic ring hydrogens (1.1 Hz).

[9] A referee has raised the question of epimerization in the enolizable intermediate VII. We believe that this possibility can be discounted because we have shown that pure diastereomers iii and iv give *only* botryodiplodin and 3-*epi*-botryodiplodin, respectively, upon ozonolysis.



iii



iv

[10] We wish to thank Professor Arsenault for a sample of natural botryodiplodin.

[11] The 250-MHz nmr spectra of all compounds in this study were taken at the National Institutes of Health Facility for Biomedical Studies (Grant No. RR20092), located at Carnegie-Mellon University.

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Received June 13, 1973

Construction of Additional Bridges across [2.2]Paracyclophane[1]

Sir:

The synthesis of the highly strained [2.2.2](1,3,5)-cyclophane (**1**) has been reported.[2] The key step involved an elegant reaction in which three three-atom bridges were contracted to three two-atom bridges. We report here the synthesis, and a novel reaction of [2.2.2](1,2,4)cyclophane (**2**), as well as the synthesis of

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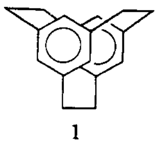
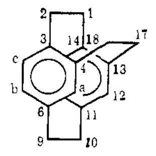
[1] This work was supported by a grant from the National Science Foundation (GP 4395).

[2] V. Boekelheide and R. A. Hollins, *J. Amer. Chem. Soc.*, 92, 3512 (1970).



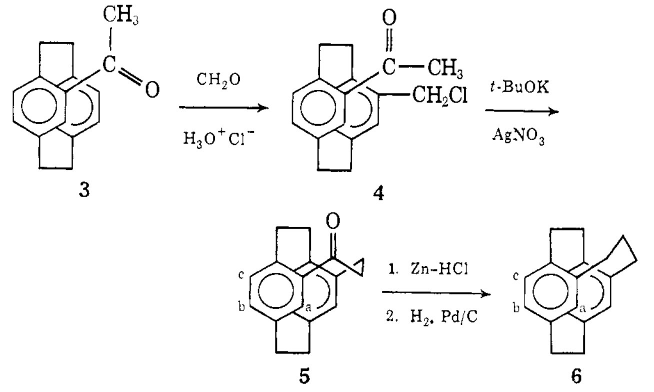
1



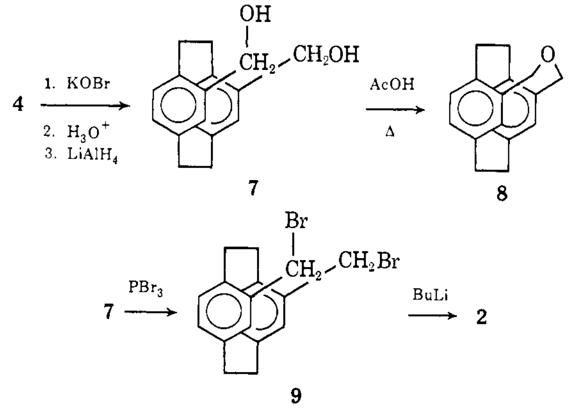
2

other tris-bridged cyclophanes. The key reaction in these syntheses makes use of the unusual ability of the acetyl group of 4-acetyl[2.2]paracyclophane (3) to direct entry of a chloromethyl group into the transannular ring at the position (pseudo-geminal) closest to the acetyl group.

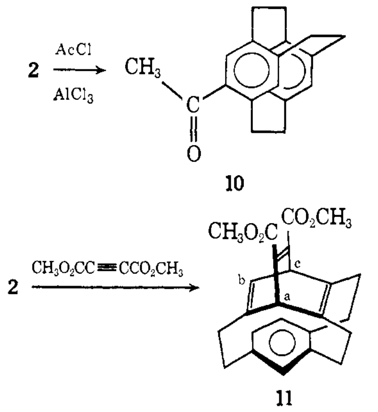
Earlier work demonstrated that acetyl, carboxyl, carbomethoxyl, and nitro groups in the 4 position of the [2.2]paracyclophane nucleus directed bromine substitution to occur nearly exclusively in the 13 position to give the pseudo-geminal disubstituted hydrocarbon.[3] Isotope and medium effect studies indicated that this directing effect involved a mechanism in which proton transfer from the σ complex to the oxygen of the transannularly located group was rate determining and product controlling.[3] We report that addition of finely divided, crystalline 3[3] to a solution of paraformaldehyde in concentrated hydrochloric acid (55°, 3.5 hr) gave (55%) 4-acetyl-13-chloromethyl[2.2]paracyclophane (4)[4] after recrystallization from acetone, mp 213–215°, and a trace of bischloromethylated material of unassigned structure. Apparently even in this medium, the product-controlling and rate-limiting step involved an intramolecular proton transfer from the σ complex to the acetyl's oxygen. Treatment of 4 with 1.1 equiv of potassium *tert*-butoxide and 1.1 equiv of silver nitrate in tetrahydrofuran (25°, 4.5 hr) gave (84%) ketone 5,[4] mp 193–194°. Reduction of 5 with first zinc–hydrochloric acid followed by hydrogen–Pd/C gave 78% of tris-bridged hydrocarbon 6,[4] mp 135–137°. Molecular models (CPK) of 6 indicate the molecule to be highly strained and suggest that the conformation drawn is the more stable.



Oxidation of 4 with bromine and potassium hydroxide in dioxane–water (80°, 1 hr) gave a mixture of hydroxy acid, aldehydo acid and diacid, reduction of which, without separation, with lithium aluminum hydride (refluxing tetrahydrofuran, 4 days) gave (72%) 4,13-bishydroxymethyl[2.2]paracyclophane[4] (7), mp 208–210°. When heated in glacial acetic acid (50°, 12 hr), diol 7 dehydrated to give (72%) bridged ether 8,[4] mp 199–200°. Phosphorus tribromide in dichloromethane (−20°, 0.5 hr) converted (81%) 7 to 9,[4] mp 133–135° dec. Slow addition of butyllithium at −60° to 9 in tetrahydrofuran gave (68%) hydrocarbon 2,[4] mp 168–169° (from ether–cyclohexane). The pmr spectra of the aromatic protons of 2 and 4–9 are consistent with the assigned structures and are inconsistent with alternative structures in which the points of attachment of the side chains or the new bridges are pseudo-ortho to one another (see below).



Aromatic behavior of tris-bridged compound 2 is found in its acetylation to give (72%) 10,[4] mp 144–145°. Cyclohexatriene-like behavior of [2.2]paracyclophane is found in its addition of 2 mol of the "super" dienophile, dicyanoacetylene.[5] Tris-bridged hydrocarbon 2 when heated with a large excess of dimethyl acetylenedicarboxylate (neat, 170°, 1 hr) gave (61% based on the amount of 2 consumed) the bridged-barrelene derivative 11. Prolonged heating of the mixture did not produce the bis adduct, but did destroy 11. Repeated attempts to induce [2.2]paracyclophane to react with dimethyl acetylenedicarboxylate gave only starting materials. Thus the extra bridge of 2 makes the substance a better enophile, probably because more strain is relieved in 2 → 11 than could be realized should [2.2]paracyclophane undergo a similar reaction.



The points of attachment of the new substituents and bridges were determined from their pmr spectra.[4c] The aromatic protons of diol 7 appeared as a doublet (τ 3.52 (2 H)) and broad singlet (τ 3.71 (4 H)). The aromatic protons of 8 gave an essentially identical spectrum. The aromatic protons of dibromide 9 provided two doublets (τ 3.60 (4 H), 3.70 (2 H)). Absent

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(3) (a) H. J. Reich and D. J. Cram, *J. Amer. Chem. Soc.*, **90**, 1365 (1968); (b) *ibid.*, **91**, 3505 (1969).

(4) (a) Carbon and hydrogen analyses were within 0.30% of theory. (b) A 70-eV mass spectrum exhibited a molecular ion. (c) The pmr spectrum in $CDCl_3$ was consistent with the assigned structure (100 MHz).

(5) E. Ciganek, *Tetrahedron Lett.*, 3321 (1967).

in the spectrum of **7**, **8**, and **9** is a downfield signal at about τ 3.1–3.2, characteristic of [2.2]paracyclophane protons pseudo-geminal to $-CH_2-X$ substituents (X = OH, Cl, Br).[6] Thus **7**, **8**, and **9** do not contain protons pseudo-geminal to CH_2-X substituents, and the CH_2-X substituents themselves must be pseudo-geminal to one another. Since reactions link compounds **2** and **4–9**, the points of attachment of the substituents or new bridges all must be pseudo-geminal to one another. Although molecular models (Fisher–Hirschfelder–Taylor) can be made of [2.2]paracyclophanes containing extra *three*-atom bridges attached at pseudo-ortho positions, an extra *two-atom* bridge can only be assembled which spans the pseudo-geminal positions. The extra bridge of **2** contains two methylene groups, and should they be attached to pseudo-ortho positions, the compound would be extraordinarily strained.

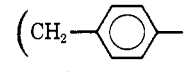
The pmr spectra contained other interesting features. Those of **3** and **4** were typical of [2.2]paracyclophane derivatives,[6] including a close doublet (τ 3.15 (1 H)) assigned to the proton ortho to the carbonyl-containing substituent.[6] In the spectrum of **5**, this proton was not moved downfield. The downfield shift of this proton in **3** and **4** appears associated with carbonyl conformations that are eliminated in **5** by the constraints of the additional bridge of which the carbonyl is a part. The usual meta coupling[6] between H_a and H_b of **5** was not detectable. In the pmr spectrum of **2** the aromatic protons were upfield of those in [2.2]paracyclophane (τ 3.63).[7] In **2**, H_a appeared as a doublet (τ 3.95 ($J_{a,b}$ = 1.9 Hz)), and H_b and H_c gave an AB quartet (τ 3.63 and 3.83, respectively ($J_{b,c}$ = 8.2 Hz)). On the basis of its meta coupling H_b was assigned the downfield signal. In **6**, the chemical shifts of the corresponding protons followed a different pattern. Thus, H_a was furthest downfield (τ 3.57 (d, $J_{a,b}$ = 1.9 Hz)) and H_b and H_c gave an AB quartet (τ 3.85 for H_b and 3.65 for H_c ($J_{b,c}$ = 8.1 Hz)). Again H_b was assigned on the basis of its meta coupling, and in **6**, H_b gave the upfield signal. Molecular models (CPK) indicate that in **2** the rings are tilted so that C-5 and C-12 and their H_a protons are close to one another. In **6**, the relative positions of the aromatic rings and their protons are more similar to those of [2.2]paracyclophane itself.

The aromatic protons of **11** (τ 3.15–3.48) were shifted downfield relative to those of **2**, but were upfield of normal aromatic protons or of those of 3-carboxy[7]-paracyclophane (τ 2.8).[8] The barrelene bridgehead proton H_c and the olefinic proton H_b are coupled ($J_{b,c}$ = 10 Hz), the former giving a signal at τ 5.92 and the latter at 4.64. The other bridgehead proton H_a gave a doublet at τ 5.96 ($J_{a,b}$ = 2 Hz), not far from the signal of the proton of C-1 of barrelene (τ ~5.4).[9] Proton H_b was far upfield of its counterpart in barrelene (τ ~3.3).[9]

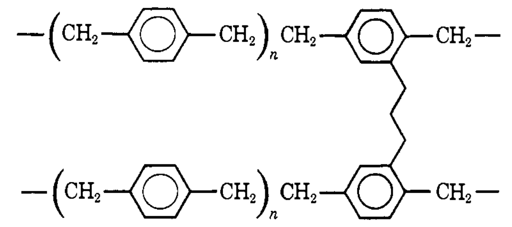
The differences in shape between **2** and **6** are also reflected in differences in their uv spectra. The spectrum of **6** (ethanol) was nearly superimposable on that of [2.2]paracyclophane, which gave[10] λ_{max} (ϵ) at 227 nm (18,000), 291 (200), and 302 (160, shoulder). The uv spectrum of **2** (ethanol) gave λ_{max} (ϵ) at 223 nm (12,000), 291 (440), and 305 (220, shoulder). The ultraviolet spectrum of adduct **11** (ethanol) gave λ_{max} (ϵ) at 220 nm (>20,000), 284 (1200), 291 (1130), and 323 (730). The band at 284 nm correlates with that observed for [7]paracyclophane[8,11] at 284 nm (1000), and for the mono-TCNE adduct of [2.2]paracyclophane at 284 nm (1100),[5] possibly indicating similar deformations of the benzene rings in the three systems.

The carbonyl stretching frequencies (μ) in the ir spectra of **3** (5.95), **4** (5.95), **5** (5.96), and **10** (5.98) indicate the carbonyl groups are at least partially conjugated with the rings. Compounds **3** and **4** also exhibit bands at 10.75 and 11.20 μ, characteristic of [2.2]paracyclophanes.[10]

At about 500° in the gas phase, [2.2]paracyclophane gives *p*-xylylene, which when condensed on cold surfaces produces a film of linear polyparaxylylene.[12] If our tris-bridged cyclophanes, **6** or **8**, behave similarly, a highly cross-linked polymer could be produced. Possibly pyrolysis and condensation of an appropriate mixture of **6** and [2.2]paracyclophane will give a film (**12**), cross-linked to a desired degree, much as the addition of *p*-divinylbenzene to styrene provides cross-linked polystyrene. This possibility is being examined.



polyparaxylylene



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(6) H. J. Reich and D. J. Cram, *J. Amer. Chem. Soc.*, **91** 3534 (1969).

(7) D. J. Cram and R. C. Helgeson, *ibid.*, **88**, 3515 (1966).

(8) N. L. Allinger and T. J. Walter, *ibid.*, **94**, 9267 (1972).

(9) H. E. Zimmerman, G. L. Grunewald, R. M. Paufler, and M. H. Sherwin, *ibid.*, **91**, 2330 (1969).

(10) D. J. Cram, N. L. Allinger, and H. Steinberg, *ibid.*, **76**, 6132 (1956).

(11) H. D. Wolf, V. V. Kane, R. H. Levin, and M. Jones, Jr., *ibid.*, **95**, 1680 (1973).

(12) (a) W. F. Gorham, *J. Polym. Sci., Part A-1*, **4**, 3027 (1966); (b) *Chem. Eng. News*, **43**, 35 (Feb 22, 1965); (c) *ibid.*, **43**, 41 (Mar 1, 1965).

(13) National Science Foundation Trainee Fellowship, 1969–1973.

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Contribution No. 3170
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Received May 19, 1973

Di-π-methane Interaction *vs.* Group Migration

Sir:

During the past several years we have been interested in intramolecular photochemical reaction between nonconjugated benzene rings. In the course of this work, photochemical interaction between rings separated by two, three, and four atoms[1] has been systematically investigated; however, similar attention has not been directed toward the parent reaction in this series, namely, that in which the interacting benzene rings are attached to the same carbon atom. This latter type of

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(1) (a) J. A. Ross, W. C. Schumann, D. B. Vashi, and R. W. Binkley, *Tetrahedron Lett.*, 3283 (1971); (b) W. C. Schumann, D. B. Vashi, J. A. Ross, and R. W. Binkley, *J. Org. Chem.*, 37, 21 (1972); (c) R. W. Binkley and W. C. Schumann, *J. Amer. Chem. Soc.*, **94**, 1769 (1972); (d) R. W. Binkley and W. C. Schumann, *ibid.*, **94**, 8743 (1972).