Calcd for $C_{16}H_{12}O_4$, parent ion *m/e* 268.073; found 268.071.

Preparation of V. Into a pressure bottle was placed 0.09 g (0.43 mmol of III, 25 mL of benzene, and a Teflon stirring bar. The solution was cooled to −78 °C and excess I was condensed in. The bottle was capped and the reaction flask was heated to 90 °C and stirred overnight. The flask was then cooled and vented and the solvent was removed under reduced pressure. The crude product was dissolved in 5 mL of hexane and poured into a column of alumina. Elution with hexane removed butadiene polymer. This was followed by elution with 15% EtOAc/hexane to move the desired product from the column. The eluent was evaporated to yield 0.10 g (90%) of V (greenish crystals), whose spectral (UV, NMR) properties were identical with those of an authentic sample (Aldrich), mp 165–166 °C (lit. mp 166–167 °C).[4]

2-Methoxy-V was prepared as above by the reaction of 0.10 g (0.42 mmol) of 6-methoxy-III and excess 9.7 g (200 mmol) of I to yield 0.11 g (91%) of V (yellow crystals), mp 195 °C (lit. mp 200 °C):[28] NMR δ 9.2 (d, 1 H, J = 4 Hz), 8.3–8.0 (m, 4 H), 7.8–7.65 (m, 3 H), 7.3 (d, 1 H, J = 4 Hz), 4.0 (s, 3 H); IR C═O 1670 cm^{-1}, C═C 1625; UV 2236 Å (ϵ 1.93×10^4), 2555 (1.71×10^4), 2903 (9.5×10^3), 3010 (8.25×10^3), 4408 (1.69×10^3).

3-Methoxy-V was prepared as above by the reaction of 0.05 g (0.21 mmol) of 7-methoxy-III and excess 9.7 g (200 mmol) of I to yield 0.045 g (75%) of 3-methoxy-V (yellow crystals), mp 145 °C: NMR δ 9.5 (d, 1 H, J = 10 Hz), 8.3–7.9 (m, 4 h), 7.75–7.6 (m, 2 H), 7.3 (dd, 1 H, J = 10 and 3 Hz), 7.1 (d, 1 H, J = 3 Hz), 3.9 (s, 3 H); IR C═O 1670 cm^{-1}, C═C 1620; UV 2241 Å (ϵ 3.22×10^4), 2456 (2.13×10^4), 2530 (1.99×10^4), 3037 (2.95×10^4), 3841 (4.02×10^3). Calcd for $C_{19}H_{12}O_3$, parent ion *m/e* 288.079; found 288.076.

4-Methoxy-V was prepared as above by the reaction of 0.025 g (0.11 mmol) of 8-methoxy-III and excess 9.7 g (200 mmol) of I to yield 0.026 g (88%) of 4-methoxy-IV (red-orange crystals), mp 212 °C (lit. mp 220 °C):[29] NMR δ 9.22 (d, 1 H, J = 10 Hz), 8.7 (d, 1 H, J = 10 Hz), 8.3–8.18 (m, 3 H), 7.8–7.5 (m, 3 H), 6.9 (d, 1 H, J = 8 Hz), 3.98 (s, 3 H); IR C═O 1670 cm^{-1}, C═C 1590; UV 2184 Å (ϵ 2.71×10^4), 2461 (1.32×10^4) 2800 (8.69×10^3), 3007 ($1.51 \times 10^{4)},$ 4322 (1.22×10^3).

2,3-Dimethoxy-V was prepared as above by the reaction of 0.116 g (0.43 mmol) of 6,7-dimethoxy-III and excess 9.7 g (200 mmol) of I to yield 0.11 g (80%) of 2,3-dimethoxy-V (yellow crystals), mp 237 °C dec: NMR δ 9.2 (s, 1 H), 8.3–8.1 (m, 3 H), 7.94 (d, 1 H, J = 9 Hz), 7.8–7.65 (m, 2 H), 7.08 (s, 1 H), 4.1 (s, 3 H), 4.0 (s, 3 H); IR C═O 1660 cm^{-1}, 1650, C═C 1620; UV 2250 Å (ϵ 1.71×10^4), 2450 (1.11×10^4), 2571 (9.3×10^3), 2902 (5.9×10^3), 3025 (5.9×10^3), 3290 (2.27×10^3), 4225 (2.41×10^3). Calcd for $C_{20}H_{14}O_4$, parent ion *m/e* 318.089; found 318.087.

Acknowledgment. This investigation was supported by Grant No. 1R01-CA-19444-01 awarded by the National Cancer Institute, DHEW.

Registry No.—I, 106-99-0; II, 106-51-4; III, 569-15-3; 6-methoxy-III, 63216-06-8; 7-methoxy-III, 63216-07-9; 8-methoxy-III, 63216-08-0; 6,7-dimethoxy-III, 63216-09-1; IV, 21889-09-8; 2-methoxy-V, 63216-10-4; 3-methoxy-V, 63216-11-5; 4-methoxy-V, 16277-48-8; 23-dimethoxy-V, 63216-12-6, 1,4-dimethoxyphenanthrene, 63216-13-7; *p*-methoxystyrene, 637-69-4; *m*-methoxystyrene, 626-20-0; *o*-methoxystyrene, 612-15-7; 3,4-dimethoxystyrene, 17055-36-6; styrene, 100-42-5.

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A General Synthesis of 1-, 2-, 3-, and 4-Substituted Benz[*a*]anthracene-7,12-diones

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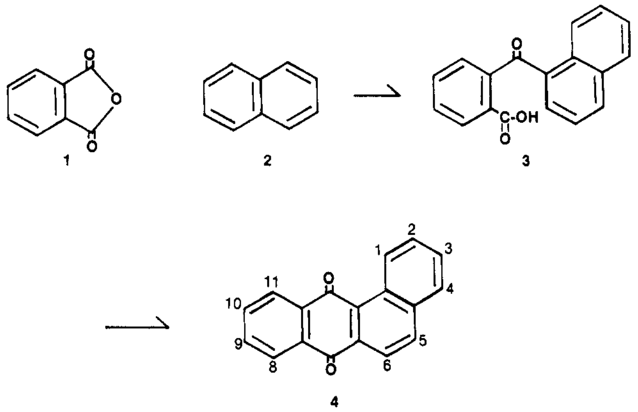
Various 1-, 2-, 3-, and 4-substituted derivatives of benz[*a*]anthracene-7,12-dione (4) have been prepared by reaction of ring-substituted styrenes and 1,4-naphthoquinone (5) in the presence of chloranil. Comparative reactions done with and without chloranil demonstrated that chloranil had a positive effect upon the yield of the substituted benz[*a*]anthracene-7,12-diones. The preparation of 1,4-dimethylbenz[*a*]anthracene-7,12-dione in yields comparable with those obtained for the monosubstituted diones demonstrated that certain steric problems of the Diels–Alder reaction could be overcome. Spectral data are discussed.

The current interest in the metabolites of benz[*a*]anthracene and 7,12-dimethylbenz[*a*]anthracene as potential carcinogens has prompted study into synthetic methods to prepare these compounds. Recent preparations of substituted benz[*a*]anthracenes and 7,12-dimethylbenz[*a*]anthracenes (DMBAs) have been based upon multistep syntheses using substituted naphthalenes and phthalic anhydrides in a Friedel–Crafts acylation, followed by cyclization of the re-

Scheme I



sulting keto acid **3** to the dione product[1,2] (Scheme I). This classical route for preparing 1-, 2-, 3-, and 4-substituted benz[*a*]anthracene-7,12-diones required substituted naphthalenes that often led to problems in orientation. Diels–Alder reactions between 1,4-naphthoquinone (**5**) and the appropriate styrenes were recently used[3] to prepare benz[*a*]anthracene-7,12-dione (BAD) and its 5-methyl derivative (5-MeBAD). This Diels–Alder reaction does not suffer from the problems inherent in the Friedel–Crafts method and, if general, provides a simple alternative. We now wish to report the generalization of this reaction to the formation of 1-, 2-, 3-, and 4-substituted BADs from which the corresponding benz[*a*]anthracenes could be prepared in one step[4] and the substituted DMBAs in two steps.[5]

The formation of these diones from 1,4-naphthoquinone and ring-substituted styrenes, represented by **6**, requires two dehydrogenations after the Diels–Alder adduct formation (Scheme II). The presence of 1,4-naphthalenediol in the reaction mixture, identified by TLC, suggested that 1,4-naphthoquinone served as the oxidizing agent. Addition of chloranil, with its higher oxidation potential[6] than **5**, aided the formation of the dione **9**.

Results and Discussion

For comparison, two solutions of equimolar amounts of styrene plus 1,4-naphthoquinone in toluene were set in an oil bath at 85–90 °C. One of these was treated with an equimolar amount of chloranil. The chloranil-treated reaction showed the presence of benz[*a*]anthracene-7,12-dione (BAD) by thin-layer chromatography (TLC) within 4 h. Comparable amounts of BAD appeared in the TLC analyses of the chloranil-free solution only after 2–4 days at 85 °C. When neither reaction exhibited any quantity of naphthoquinone by TLC, workup of the mixtures yielded 12% BAD in the unmodified reaction and 33% BAD in the chloranil-treated one.

Reaction of equimolar amounts of 2-chlorostyrene, **5**, and chloranil in a small volume of benzene for 6 days at 85 °C led to a 44% yield (method B) of 4-chlorobenz[*a*]anthracene-7,12-dione (4-ClBAD). In contrast, when an extra equivalent of **5** was used instead of the chloranil, the yield of 4-ClBAD was only 14%. This reaction mixture contained many components, three of which possessed parent ions in their mass spectra at m/e 292, 294, and 296. This suggested the presence of 4-chlorobenz[*a*]anthracene-7,12-dione (m/e 292), a "dihydro" intermediate (**8**, X = Cl) (m/e 294), and a "tetrahydro" intermediate (**7a**, X = Cl) (m/e 296). The diol tautomer **7a** was suggested for the "tetrahydro" component because of the lack of fragmentation attributable to CO loss, as would be expected for **7**.

The favorable yields produced by the addition of chloranil to the 2-chlorostyrene/1,4-naphthoquinone reaction prompted the use of chloranil in the preparation of the substituted BADs listed in Table I. With the exception of the 4-methoxy compound, the similarity in the yields suggested that the ring substituents did not have a profound effect upon the reactivity when chloranil was present. The low yield of 1-ClBAD was not unexpected because of the steric interaction between the chlorine atom and the quinone carbonyl in this approach of 3-chlorostyrene. The alternate attack should be energetically preferred and lead to a high proportion of 3-ClBAD.

Even these steric problems can be overcome in some cases. 1,4-Dimethylbenz[*a*]anthracene was prepared in 29% yield from 2,5-dimethylstyrene, **5**, and chloranil (method A). The one styrene approach leading to product exhibits steric interactions similar to those present for the formation of the 1-ClBAD, yet the yield of the reaction was comparable with that for the other substituted BADs.

Yields were further improved by oxygenation of the crude reaction mixtures,[7] as was done in method B. This treatment resulted in a much higher yield for the 4-ClBAD when compared with the other substituted BADs that were not oxygenated, and preliminary results indicated a 20% increase (13–16%) in the yield of 4-OMeBAD upon oxygenation.

The spectral characteristics of the diones synthesized were consistent with their assigned structures. Large parent ions were found in the mass spectra of all compounds except the 1-chloro isomer, which possessed a large (M − Cl) fragment.

Proton magnetic resonance spectra were particularly useful in establishing the positions of substitution in the angular benzene ring. Brown and Thomson[8] showed that the resonance signal of the proton in the one position of BAD occurred at δ 9.72 (CDCl$_3$), further downfield than that of any other proton. The position of this resonance and the effect of substitution upon its splitting pattern gave information useful in assigning the position of substitution.

In the cases of the 4-chloro-, 4-bromo-, and 4-fluorobenz[*a*]anthracene-7,12-diones, this proton signal appeared

Scheme II

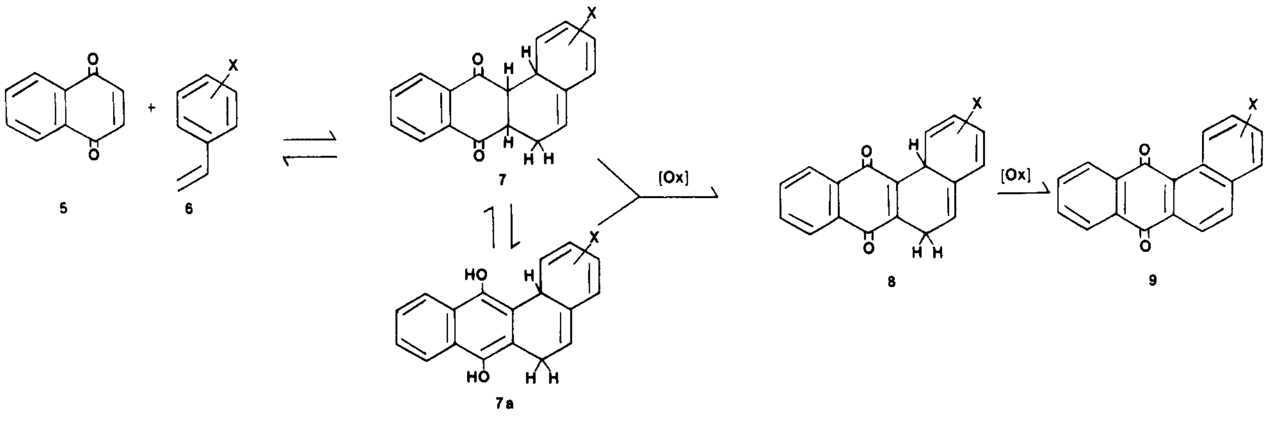


Table I. Substituted Benz[*a*]anthracene-7,12-diones Prepared from 1,4-Naphthoquinone and Substituted Styrenes

Reactant styrene	Registry no.	Product dione	Registry no.	Method	Scale, mol	Yield, mg (% theoretical)	Mp, °C	Lit. mp °C
2-F[a]	394-46-7	4-F	2712-26-7	A	0.005	300 (20%)	198–199	199–200[b]
4-Me[a]	622-97-9	2-Me	58024-07-0	A	0.010	600 (29%)	188.5–190.0	189–190[c]
2-Br[a]	2039-88-5	4-Br	63715-52-6	A	0.010	780 (30%)	234.5–235.5	230–232[c]
3-Cl[e]	2039-85-2	3-Cl	63715-53-7	A	0.010	680 (30%)	216–217	215–216[f]
3-Cl[e]		1-Cl	63715-54-8	A	0.010	50 (4%)	199–200	*g*
4-Cl[e]	1073-67-2	2-Cl	49600-94-4	A	0.010	720 (33%)	232–233	232–233[h]
2-Cl[e]	2039-87-4	4-Cl	63715-55-9	B	0.010	966 (44%)	232–233	226–227[i]
2-OMe[a]	612-15-7	4-OMe	16277-48-8	A	0.010	374 (13%)	219–220	220–221[j]
2,5-DiMe[k]	2039-89-6	1,4-DiMe	63715-56-0	A	0.010	630 (29%)	213–214	*g*

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Table II. Characteristic Infrared Bands from the Fingerprint Region of Spectra of Substituted Benz[*a*]anthracene-7,12-diones (KBr)

Compd	IR bands (1000–700 cm^{-1})
4-BrBAD	900, 848, 784, 741, 712
4-ClBAD	990, 848, 785, 742, 711
4-FBAD	991, 848, 788, 743, 713
4-OMeBAD	850, 787, 781, 743, 718
2-ClBAD	857, 712
3-ClBAD	991, 881, 800, 712
1-ClBAD	850, 845, 752, 713, 701
2-MeBAD	870, 778, 712
1,4-DiMeBAD	840, 708

as a doublet (J = 9 Hz). In the cases of the 1-chloro- and the 1,4-dimethylbenz[*a*]anthracene-7,12-diones, the absence of the δ 9.72 signal confirmed the one-proton assignment. The 2-chloro isomer showed a singlet in this region, while the 2-methylbenz[*a*]anthracene-7,12-dione yielded a quartet (J = 1 Hz).

Although all of the BADs prepared contained infrared bands at 1655 and 1590 cm^{-1}, the infrared spectra of the 4-substituted isomers exhibited unique absorptions in the ranges of 782–788, 741–744, and 710–718 cm^{-1} (see Table II). In no other spectrum were all of these peaks present. The strength and sharpness of these peaks suggested their use for the differentiation of the 4-substituted BADs from the other isomers.

The ultraviolet spectra were distinct, but of no practical use for determining the position of substitution (see Table III). All of the monosubstituted BADs except the 4-methoxy isomer possessed a major absorption in the 283–287-nm range.

The overall success of this diene synthesis suggests that this method could be a general one for reaction of ring-substituted styrenes with 1,4-naphthoquinone. The results of ongoing investigations will be reported in the near future.

Experimental Section

All melting points were determined using a Fisher-Johns hot-stage apparatus and were uncorrected. Mass spectra were taken on a Finnegan 3300 mass spectrometer equipped with a Finnegan 6000 MS data system. A Cary 17 UV–vis spectrophotometer was used for the UV spectra. Proton magnetic resonance spectra were taken on a Varian XL-100 spectrometer using $CDCl_3$ (0.5% Me_4Si) as solvent, while the IR spectra were obtained on a Perkin-Elmer 467 spectrophotometer.

Method A. To 5–8 mL of toluene were added 0.01 mol (or 0.005 mol) of 1,4-naphthoquinone (recrystallized from alcohol) and equimolar amounts of the substituted styrene and chloranil. The mixture was placed in an 85–90 °C oil bath for ~1 week. When monitoring by thin-layer chromatography on silica gel GF plates, using benzene as development solvent, showed little or no naphthoquinone remaining, the reaction was stopped and the colored reaction mixture was chromatographed on Silicar CC-7 (Mallinckrodt) by elution with hexane, followed by 1:1 benzene–hexane. The progress of the components through the column was followed by long wavelength UV (λ 366 nm), with the diones exhibiting an orange or red-orange color. The BADs isolated in this manner were recrystallized from either benzene or benzene–ethanol.

Method B. The same as method A except that benzene was used as solvent and the reaction was heated in a 75–80 °C oil bath for 1 week. The mixture was then reduced to dryness on a rotary evaporator and 50 mL of a 5% solution of alcoholic potassium hydroxide (95% ethanol) was added to the resultant dark material. The flask was fitted with a reflux condenser and oxygen bubbled through for 24 h. The mixture was then neutralized with concentrated HCl and the crude product extracted with ether. After drying and removal of the ether by evaporation, the residue was chromatographed as in method A.

Acknowledgment. This research was supported by the National Cancer Institute under Contract No. N01-CO-25423 with Litton Bionetics.

Registry No.—5, 130-15-4.

Supplementary Material Available: Complete proton magnetic resonance spectra (9 pages). Ordering information is given on any current masthead page.

Table III. Ultraviolet Absorption Data of Substituted Benz[*a*]anthracene-7,12-diones (95% Ethanol)

Compd	λ_{max}, nm (log ϵ)				
4-BrBAD	286 (4.48)	254 (4.23)	248 (4.28)	233 (4.35)	217 (4.55)
4-ClBAD	284 (4.51)	254 (4.27)	247 (4.30)	232 (4.38)	217 (4.61)
4-FBAD	284 (4.58)	253 (4.27)	247 (4.29)		217 (4.55)
4-OMeBAD	300 (4.39)	247 (4.34)			218 (4.65)
2-ClBAD	283 (4.50)	253 (4.34)	248 (4.37)	237 (4.36)	217 (4.63)
3-ClBAD	287 (4.48)	254 (4.30)	250 (4.30)	238 (4.29)	218 (4.49)
1-ClBAD	284 (4.51)	255 (4.25)	245 (4.31)		215 (4.56)
2-MeBAD	287 (4.52)	253 (4.42)	248 (4.45)		218 (4.68)
1,4-DiMeBAD	300 (4.52)	248 (4.39)			221 (4.57)

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Preparations of Optically Active [8][8]- and [8][10]Paracyclophanes with Known Absolute Configurations[1]

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(+)-(*S*)-[8][8]Paracyclophane (**4**) was prepared from (+)-[8]paracyclophane-10-carboxylic acid (**6d**) whose absolute configuration was correlated to (+)-(*S*)-[2.2]paracyclophane-4-carboxylic acid (**20**). Preparations and absolute configurations of (−)-(*R*)-[8][10]paracyclophane (**5**) and related optically active paracyclophane derivatives are also reported.

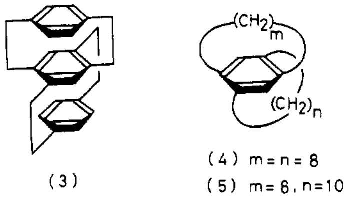
As part of our continuing efforts to study the chiroptical properties and the biological transformations[2] of high-symmetry chiral (gyrochiral)[3] molecules,[4] the first successful syntheses of (+)-twistane (D_2 symmetry) (**1**),[5] (+)-twist brendane (C_2 symmetry) (**2**),[3] and (−)-[3]chochin (D_2 symmetry)[6] (**3**), all with known absolute configurations, have been reported from our laboratory (Chart I).

[3]Chochin (**3**) and [*m*][*n*]paracyclophane (**4** and **5**)[7] (D_2 symmetry with $m = n$, and C_2 symmetry with $m \neq n$) bear the twisted central benzene nucleus as a common structural unit, and our preceding papers[8] reported the preparation of unusually strained [8][8]paracyclophane (**4**) and [8][10]paracyclophane (**5**). This contribution reports the preparations of (+)-[8][8]paracyclophane (**4**) and (−)-[8][10]paracyclophane (**5**) together with the determination of their absolute configurations.

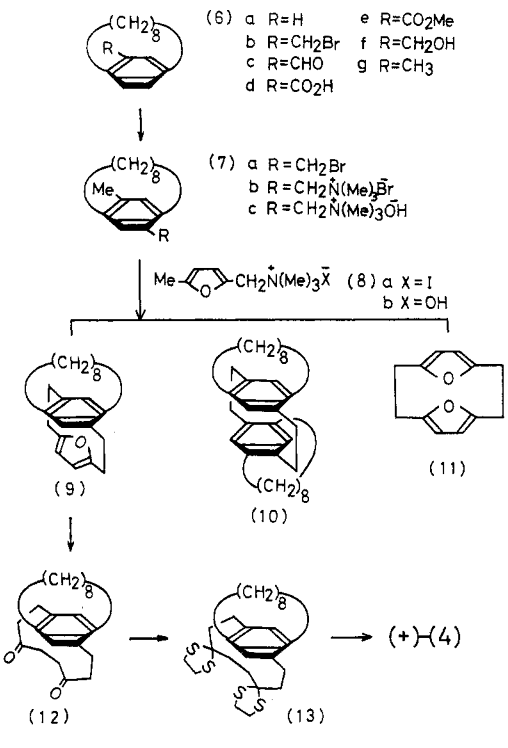
Results and Discussion

Preparation of (+)-[8][8]Paracyclophane (4) (Scheme I).[9] Bromomethylation[10] of [8]paracyclophane (**6a**)[11] afforded the 10-bromomethyl derivative **6b** which was treated with the sodium salt of 2-nitropropane[10] in ethanol to yield the aldehyde **6c**. Permanganate oxidation of the aldehyde **6c** in acetone gave (±)-[8]paracyclophane-10-carboxylic acid (**6d**), the optical resolution of which was accomplished by working with (+)-1-(*β*-naphthyl)ethylamine as the resolving agent. The (+)-carboxylic acid **6d**, $[\alpha]^{18}_{D}$ +18°, was converted to the methyl ester **6e** whose hydride reduction afforded the alcohol **6f**. Conversion to the bromide **6b** with phosphorus tribromide followed by reduction with lithium aluminum hydride furnished (+)-10-methyl[8]paracyclophane (**6g**), $[\alpha]^{19}_{D}$ +4.6°, which was further bromomethylated to the bromide **7a**.

Chart I.



Scheme I



Construction of the second [8] bridge was carried out via the benzene–furan "hybrid" [2.2]paracyclophane **9**. The quaternary ammonium bromide **7b** ($[\alpha]^{20}_{D}$ −5.4°) prepared from the bromide **7a** was mixed with 5-methylfurfuryltrimethylammonium iodide (**8a**),[12] and the mixture was treated with silver hydroxide to give a mixture of Hofmann bases which was pyrolyzed in refluxing toluene. Since a preliminary experiment had revealed the rather labile character of the hybrid [2.2]-paracyclophane **9**, the pyrolysate was chromatographed on neutral alumina in a cold room (5 °C). Elution with hexane gave the doubly [8]-bridged [2.2]paracyclophane **10** ($[\alpha]^{20}_{D}$ −25°, 2.5% yield) which was followed by the hybrid [2.2]par-