Aromatic Molecules Bearing Substituents within the Cavity of the π-Electron Cloud. A General Method for the Synthesis of *trans*-15,16-Dialkyldihydropyrenes[1,2]

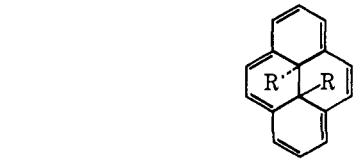
V. Boekelheide[3] and Thomas A. Hylton[4]

Contribution from the Department of Chemistry, University of Oregon, Eugene, Oregon 97403. *Received October 7, 1969*

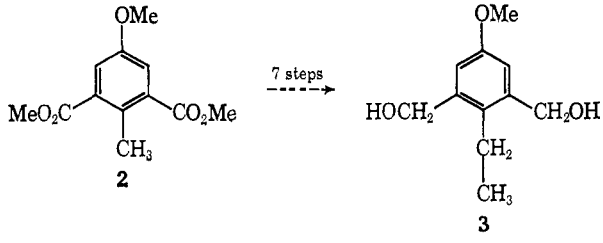
Abstract: A general method for the synthesis of *trans*-15,16-dialkyldihydropyrenes is described, and using this method, preparations of *trans*-15,16-diethyldihydropyrene (**1b**) and *trans*-15,16-di-*n*-propyldihydropyrene (**1c**) have been accomplished. Studies on the thermal rearrangement as well as the chemical and physical properties of these compounds are discussed.

The synthetic scheme for the preparation of *trans*-15,16-dimethyldihydropyrene (**1a**) depended on the aluminum chloride catalyzed rearrangement of 2,6-dibromo-*p*-cresol to 3,5-dibromo-*p*-cresol.[5] This rearrangement was discovered originally by Baddeley and Plant.[6] However, attempts to apply this two-step, bromination–rearrangement procedure to *p*-ethylphenol encountered difficulties that were not resolved.[7] Instead, the synthesis of *trans*-15,16-diethyldihydropyrene (**1b**) was accomplished by an alternate route.[8] The key steps in this alternate synthesis involved the transformation of 3,5-dicarbomethoxy-4-methylanisole (**2**) to 3,5-bis (hydroxymethyl)-4-ethylanisole (**3**). Aside from adding seven steps to the original scheme for the synthesis of dihydropyrenes, this variation is not suited as a general method for the synthesis of *trans*-15,16-dialkyldihydropyrenes (**1**). In this communication we describe a method that does have general application and which we have employed for the synthesis of both *trans*-15,16-diethyldihydropyrene (**1b**) and *trans*-15,16-di-*n*-propyldihydropyrene (**1c**).

Nitration of the appropriately substituted 4-alkylanisole (**4**) in acetic anhydride gives the corresponding 2-nitro-4-alkylanisole (**5**) in essentially quantitative yield. Catalytic hydrogenation over Raney nickel as catalyst yields the amine (**6**). Bromination of the amine gives exclusively the desired isomer, 2-amino-3,5-dibromo-6-alkylanisole (**7**). Deamination to give **8** occurs smoothly by diazotization of **7** in ethanol. The overall yield in the four-step conversion of 4-alkylanisoles to 3,5-dibromo-4-alkylanisoles was about 50%. These steps, as well as the subsequent ones leading to the *trans*-15,16-dialkyldihydropyrenes (**1**), are summarized in Scheme I.



1a, R = $-CH_3$
b, R = $-CH_2CH_3$
c, R = $-CH_2CH_2CH_3$



2 **3**

The reactions illustrated in Scheme I going from **8** through the various intermediates on to **1** and **17** parallel closely those described previously for the synthesis of *trans*-15,16-dimethyldihydropyrene (**1a**).[5] The yields in each case were comparable and the spectral properties of the products were similar. It is of interest that the yields in the Wurtz dimerization reaction (**12** to **13**) do not fall off with the increasing size of the internal substituents at positions 8 and 16. As discussed previously,[9] the geometry of the [2.2]metacyclophanes is such that the aromatic rings are in separate planes so that substituents at the 8 and 16 positions are not highly crowded.

As the internal substituents of the dihydropyrenes are lengthened from methyl to ethyl to *n*-propyl (**1a** to **1b** to **1c**) and so begin to extend through the cavity of the aromatic π cloud, the proton resonances of these substituents become of particular interest since they provide a map of the magnetic effects due to ring current. The nmr spectrum of *trans*-15,16-di-*n*-propyldihydropyrene (**1c**) is shown in Figure 1. If the proton reso-

(1) We express our appreciation to the National Science Foundation for their support of this investigation.
(2) For the preceding article in this series, see V. Boekelheide and E. Sturm, *J. Amer. Chem. Soc.*, 91, 902 (1969).
(3) Roche Memorial Foundation Fellow.
(4) Abstracted from the doctoral dissertation of T. A. Hylton, University of Oregon, 1969.
(5) V. Boekelheide and J. B. Phillips, *J. Amer. Chem. Soc.*, 89, 1695 (1967).
(6) G. Baddeley and J. Plant, *J. Chem. Soc.*, 525 (1943).
(7) R. J. Barnhard, M. S. Thesis, University of Oregon, 1965.
(8) V. Boekelheide and T. Miyasaka, *J. Amer. Chem. Soc.*, 89, 1709 (1967).
(9) W. S. Lindsay, P. Stokes, L. G. Humber, and V. Boekelheide, *ibid.*, 83, 943 (1961).

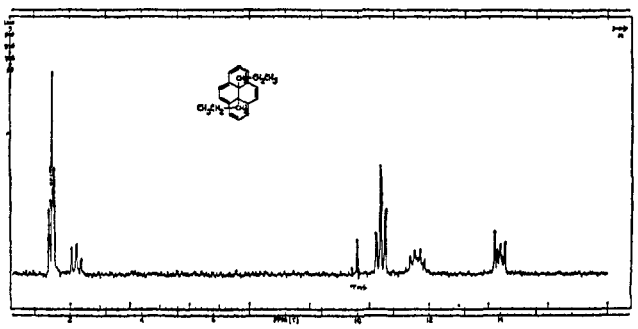


Figure 1. Nmr spectrum of *trans*-15,16-di-*n*-propyldihydropyrene in deuteriochloroform taken using a Varian HA-100 MHz spectrometer.

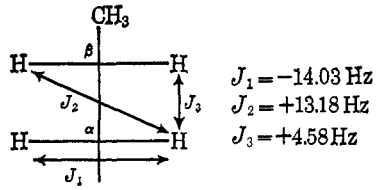


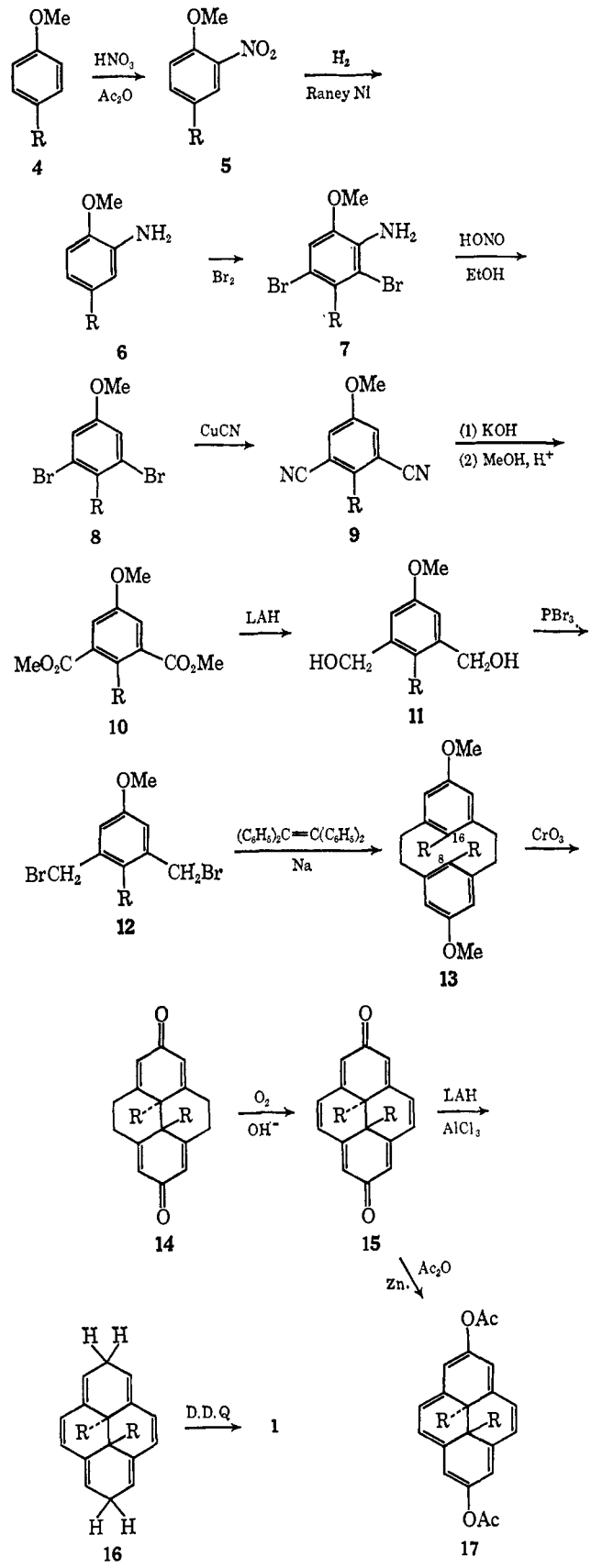
Figure 2. Coupling constants which permit a computer simulation of the high field region of the spectrum of **1c** as shown in Figure 1.

nances of the *n*-propyl group are analyzed with respect to the α, β, and γ carbons, it can be seen that the signal for the α-methylene protons appear as a multiplet centered at τ 14.03, that for the β-methylene protons at 11.82, and the signal for the γ-methyl protons as a triplet at 10.65. Thus, the diamagnetic ring current shielding effect shows a continual falloff as the internal protons are extended through the cavity and become more distant from the center of the ring. The peripheral ring protons of **1c** show the same pattern and essentially the same signals as the other dihydropyrenes. The nmr spectrum of **17** shows an almost identical pattern in the high field region.

The complex pattern of the nmr signals for the *n*-propyl group can be interpreted either in terms of a preferred conformation or as restricted rotation about the carbon–carbon bond between the α- and β-methylene carbons. The experimental spectrum in the high field region can be reproduced by a computer-simulated spectrum using the J values shown in Figure 2.[10] Examination of molecular models suggests a very high energy barrier for rotation about the carbon–carbon bond between the α- and β-methylene carbons and it is our belief that this is a true example of restricted rotation. This interpretation is supported by the fact that the spectrum shows no temperature dependence over the range of −80 to 80°.[11]

As a molecule having a planar $4n + 2$ π-electron peripheral system, it would be expected that *trans*-15,16-di-*n*-propyldihydropyrene (**1c**) would be aromatic and its nmr spectrum clearly indicates a strong diamagnetic ring current, one of the important criteria for aromaticity.[12] Because of the rigidity of the molecule and with its internal *n*-propyl protons providing a map for observing magnetic effects, **1c** was of particular interest for studying the change in physical properties with differing numbers of π electrons. Thus by converting **1c** to the corresponding dianion the number of π elec-

Scheme I



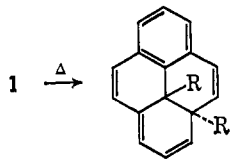
(10) We are very much indebted to Professor C. E. Klopfenstein for carrying out the computer simulation of this spectrum.

(11) The upper temperature range is limited by the fact that **1c** undergoes a thermal rearrangement at an appreciable rate at temperatures above 80° (*vide infra*).

(12) F. Sondheimer, I. C. Calder, J. A. Felix, Y. Gaoni, P. J. Garratt, K. Grohmann, G. di Maio, J. Mayer, M. V. Sargent, and R. Wolovsky, Special Publication No. 21, The Chemical Society, London, 1967, p 75.

trons is changed from 14 to 16, *i.e.*, from $4n + 2$ to a $4n$ π-electron system. As predicted, the nmr spectrum of the dianion of **1c** shows a very strong paramagnetic ring current.[13] The signals for the α-methylene protons of the internal *n*-propyl group appear at τ −11.24, the β-methylene protons at −2.59, and γ-methyl protons at +4.49, whereas the peripheral protons appear in the range of +12.56 to +13.14. This is a dramatic example of the reversal of ring current effects as the number of π electrons is changed from $4n + 2$ to $4n$.

In the original description of *trans*-15,16-diethyldihydropyrene,[8] it had been noted that the molecule underwent a thermal isomerization although the structure of the thermal isomer was not established due to lack of material. Later, it was found that *trans*-15,16-dimethyldihydropyrene (**1a**) also underwent a thermal rearrangement and the product in this case was shown to be the isomer **18a**, resulting from migration of an internal methyl to the periphery.[2] With both the *trans*-15,16-diethyldihydropyrene (**1b**) and *trans*-15,16-di-*n*-propyldihydropyrene (**1c**) now available by the present, more convenient route, their thermal rearrangement was investigated.



18

Although *trans*-15,16-dimethyldihydropyrene (**1a**) requires temperatures in the range of 190–210° for the thermal rearrangement to occur at an appreciable rate, it was found that both *trans*-15,16-diethyldihydropyrene (**1b**) and *trans*-15,16-di-*n*-propyldihydropyrene (**1c**) were readily isomerized by heating in boiling cyclohexane. In each case the rearrangement gave a single isomer in essentially quantitative yield. The physical properties of each of these thermal isomers parallel very closely those previously described for **18a**, and so the structures of these thermal rearrangement products are assigned as **18b** and **18c**, respectively.[14] As was indicated in our earlier study,[2] the mechanism for this thermal rearrangement has not been established but it is our opinion that it is probably a 1,5-sigmatropic shift of the internal alkyl group. Evidence bearing on this interpretation may be forthcoming from current studies using dihydropyrenes with optically active, internal substituents.

In this regard the mass spectra of **1b** and **1c** as well as those of their thermal isomers, **18b** and **18c**, are quite instructive. As a general rule the mass spectra of *trans*-15,16-dialkyldihydropyrenes show a small parent molecular ion peak, a much stronger peak for loss of one alkyl group, a still larger signal for loss of both alkyl groups, and further fragmentation corresponding to that observed for pyrene. The mass spectrum of *trans*-15,16-di-*n*-propyldihydropyrene (**1c**) is shown in Figure 3.

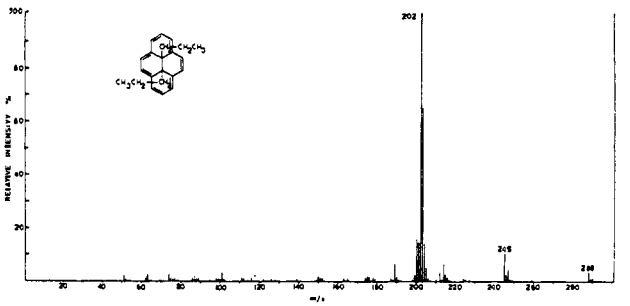
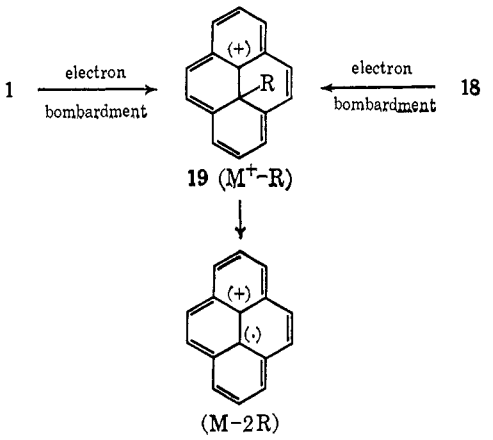


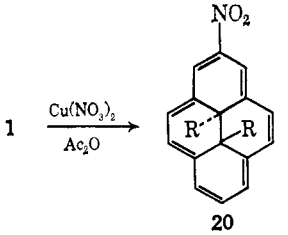
Figure 3. The mass spectrum of **1c** observed using a direct inlet at room temperature with a C.E.C.-110-21B double focusing mass spectrometer.

It is obvious that, if the first fragmentation of **18c** under electron bombardment is loss of the peripheral *n*-propyl group, the resulting ion **19c** will be the same as that from the fragmentation of **1c** by electron bombard-



ment. Thus, **1c** and **18c** have virtually identical mass spectra. Likewise, **1b** and **18b** have essentially identical mass spectra and show the same sort of fragmentation pattern. Similar observations have also been made in the dimethyl series, **1a** and **18a**, as reported previously.[2]

Although the chemical properties of *trans*-15,16-di-*n*-propyldihydropyrene (**1c**) have not been investigated extensively as yet, it has been shown that **1c** readily undergoes electrophilic substitution. Nitration of **1c**, for example, gives the corresponding 2-nitro derivative **20c** in high yield.



20

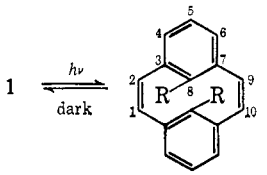
In our previous studies,[8,15] we have described the photoisomerization of *trans*-15,16-dimethyldihydropyrene (**1a**) and *trans*-15,16-diethyldihydropyrene (**1b**) to their corresponding valence tautomers, **21a** and **21b**. In the dark, the valence tautomers **21a** and **21b** revert

(13) The preparation of the dianion of **1c** and its spectral studies are described in R. H. Mitchell, C. E. Klopfenstein, and V. Boekelheide, *J. Amer. Chem. Soc.*, 91, 4931 (1969).

(14) In the previous report (ref 8) on the thermal rearrangement of *trans*-15,16-diethyldihydropyrene (**1b**), it was indicated that the thermal isomer underwent nitration to give *trans*-15,16-diethyl-2-nitrodihydropyrene. With the more abundant supplies now available we have reexamined this reaction and been unable to reproduce the nitration experiment. We conclude that our earlier report was in error on this point.

(15) H.-R. Blattmann, D. Meuche, E. Heilbronner, R. J. Molyneux, and V. Boekelheide, *J. Amer. Chem. Soc.*, 87, 130 (1965); *cf.* H.-R. Blattmann, Doctoral Dissertation, Eidg. Tech. Hochschule, Zurich, 1967.

back to the dihydropyrenes, **1a** and **1b**. The dark reaction follows first-order kinetics whose rate is remarkably sensitive to the nature of the internal substituents. Thus, at 30°, when the internal substituent is changed from methyl (**21a**) to ethyl (**21b**), the rate of the dark reaction becomes about sixfold faster. However, the correlation of the rate to the bulk of the internal substituent is not consistent, for the rate of the dark reaction for the di-*n*-propyl derivative (**21c**) lies intermediate between those of the diethyl and dimethyl derivatives (**21b** and **21a**). At present we have no explanation for this unusual relationship.[16] However, in the case of the 2-nitro derivatives of **21**, for which the rate of the dark reaction is very much faster than for the corresponding hydrocarbons, the relationship of the bulk of the internal substituent to the rate follows the same pattern.



21

The application of this general method for the synthesis of 15,16-dialkyldihydropyrenes having internal substituents with still longer hydrocarbon chains is under study.

Experimental Section[17]

4-Ethyl-2-nitroanisole (5, R = Et). CAUTION! THIS PROCEDURE IS POTENTIALLY HAZARDOUS. A solution of acetyl nitrate was prepared by cautiously adding 80 ml of concentrated nitric acid dropwise to 750 ml of acetic anhydride which was magnetically stirred and kept at −20 to −25° by means of a Dry Ice–acetone bath. To the solution was added 136 g (1.00 mole) of 4-ethylanisole dropwise over a period of at least 1 hr, keeping the temperature between −10 and 0°. The reaction could be monitored by examination of the aromatic region of nmr spectra taken directly on aliquots of the reaction mixture. Spectra taken 10 min after the completion of the addition of 4-ethylanisole showed only the nmr spectrum expected for the pure product. The resulting yellow solution was poured into 2.5 l. of water and stirred overnight. The heavier oily layer was separated, washed once or twice with water, and used directly in the following reaction. A small sample of the material was distilled to obtain a yellow liquid, bp 110–112° (0.3 mm) (attempted distillation of larger samples resulted in gassing and difficulty in maintaining low pressures); nmr (CCl_4) ABC multiplet at τ 2.0–2.8 (3 H, Ar*H*), singlet at 4.12 (3 H, $-OCH_3$), quartet at 3.38 (2 H, $-CH_2CH_3$, J = 8 cps), and a triplet at 8.78 (3 H, $-CH_2CH_3$, J = 8 cps); and ir (CCl_4) 6.52 and 7.80 μ (NO_2).

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.65; H, 6.17; N, 7.97.

2-Amino-4-ethylanisole (6, R = Et). The crude product from the preceding reaction was separated into 30-g portions and each was dissolved in 100 ml of methanol. These were placed in Parr bottles with 5 ml of freshly prepared W-2 Raney nickel catalyst and shaken under a hydrogen atmosphere at a pressure of 3 atm for 2 hr. The colorless solutions were decanted from the catalyst and a second group of aliquots was similarly treated, using the same catalyst from the previous reduction. After the entire batch had been reduced, the solutions were combined, filtered, and used directly in the following reaction. A sample of amine was obtained by evaporation of a small amount of the methanol solution. It crystallized from hexane, after decolorization of the solution with charcoal, to yield colorless crystals: mp 54.5–55.5° (lit.[18] mp 55°); nmr (CCl_4) multiplet at τ 2.3–2.8 (3 H, Ar*H*), singlet at 6.23 (3 H, $-OCH_3$), singlet at 6.42 (2 H, $-NH_2$), quartet at 7.54 (2 *H*, $-CH_2CH_3$, J = 8 cps), and a triplet at 8.84 (3 H, $-CH_2CH_3$, J = 8 cps).

2-Amino-3,5-dibromo-4-ethylanisole (7, R = Et). The solution of crude 2-amino-4-ethylanisole from the preceding reaction was diluted with methanol to a volume of 1.5 l. and cooled in an ice bath. The solution was stirred during the addition of 110 ml (320 g, 2.0 mol) of bromine over a period of 1.5 hr. The resulting slurry was concentrated and the crystalline residue was treated with excess 1 *N* sodium hydroxide solution. The oily amine was extracted with three 300-ml portions of ether which were then combined and washed successively with water and a saturated sodium chloride solution. After the ether extract dried over anhydrous sodium sulfate, it was concentrated to give a dark viscous oil which was used directly in the following reaction. A small sample was purified by crystallization from hexane to give white crystals: mp 65.5–66.0°; nmr (CCl_4) singlet at τ 3.17 (1 H, Ar*H*), singlet at 6.17 (3 H, $-OCH_3$), broad singlet at 5.81 (2 H, $-NH_2$), quartet at 7.08 (2 H, $-CH_2CH_3$, J = 8 cps), and a triplet at 8.88 (3 H, $-CH_2CH_3$, J = 8 cps).

Anal. Calcd for $C_9H_{11}Br_2NO$: C, 34.98; H, 3.59; Br, 51.72. Found: C, 35.09; H, 3.60; Br, 51.68.

3,5-Dibromo-4-ethylanisole (8, R = Et). In a 5-l. three-necked flask fitted with a stirrer and a large bulb-type condenser was placed a solution of the crude dibromoamine **7** (R = Et) from the preceding reaction in 1.5 l. of absolute ethanol, followed by a solution of 100 ml of concentrated sulfuric acid in 1 l. of absolute ethanol. To the stirred mixture was added 100 g (1.45 mol) of powdered sodium nitrite, after which the solution was boiled under reflux. Nitrogen evolution began slowly and was complete after 14 hr. Ethanol was removed by distillation, and the residue was extracted with 600 ml of ether. The ether solution was washed successively with water, 1 *N* sodium hydroxide solution, water, and a saturated sodium chloride solution. After the ether extract had been dried over anhydrous sodium sulfate, the solution was evaporated to give a black mobile oil which was distilled at reduced pressure to yield a pale yellow oil, bp 93–96° (0.1 mm). On a 1 molar scale the overall yield of **8** (R = Et) from 4-ethylanisole was 30–50%, but, on a small scale when the intermediates were purified, the yields were higher. A sample was purified by recrystallization from ethanol to give white crystals: mp 39.5–40°; nmr (CCl_4) singlet at τ 3.01 (2 H, Ar*H*), singlet at 6.29 (3 H, $-OCH_3$), quartet at 7.10 (2 H, $-CH_2CH_3$, J = 8 cps), and a triplet at 8.88 (3 H, $-CH_2CH_3$, J = 8 cps).

Anal. Calcd for $C_9H_{10}Br_2O$: C, 36.77; H, 3.43; Br, 54.36. Found: C, 36.59; H, 3.27; Br, 54.32.

3,5-Dicyano-4-ethylanisole (9, R = Et). A solution of 56 g (0.19 mol) of 3,5-dibromo-4-ethylanisole and 45 g (0.50 mol) of cuprous cyanide in 300 ml of N-methyl-2-pyrrolidinone was stirred and heated at 170–180° for 4 hr. The solution was allowed to cool and then poured into water. The resulting solid was collected by filtration and dried overnight under reduced pressure. The dried material was extracted by boiling with three 250-ml portions of chloroform. The solid which resulted from evaporation of the chloroform extracts was recrystallized from acetonitrile, after filtering the hot solution to remove undissolved material, to give 28 g (79%) of nearly colorless crystals, melting at 161.5–163°. The analytical sample was recrystallized from acetonitrile and sublimed at 150° at 0.05 mm to give colorless crystals: mp 163.5–164°; nmr ($CDCl_3$) singlet at τ 2.67 (2 H, Ar*H*), singlet at 6.05 (3 H, $-OCH_3$), quartet at 6.95 (2 H, $-CH_2CH_3$, J = 8 cps), and a triplet at 8.68 (3 H, $-CH_2CH_3$, J = 8 cps); and ir ($CHCl_3$) 4.47 μ ($-C\equiv N$).

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.02; H, 5.26; N, 15.09.

3,5-Dicarboxy-4-ethylanisole. A suspension of 23 g (0.12 mol) of 3,5-dicyano-4-ethylanisole and 30 g of potassium hydroxide in 150 ml of water was stirred and heated under reflux for 3 days. The solution was cooled and acidified with concentrated hydrochloric acid, and the resulting solid was collected by filtration, washed with water, and dried overnight at 65° (9 mm). The dried material was

(16) The details of these photoisomerization studies and the kinetics of the dark reaction will be published separately in the near future.

(17) Elemental analyses are by A. Bernhardt Microanalytical Laboratories. Ultraviolet and visible spectra were measured with Cary Model 14 or 15 spectrometers, infrared spectra with a Beckman I.R.-5 spectrometer, nmr spectra with Varian A-60 or HA-100 MHz spectrometers, and mass spectra with a C.E.C.-110-21B double-focusing mass spectrometer. We thank the National Science Foundation for funds used toward the purchase of the Varian A-60, the C.E.C.-110-21B, and the Joy liquid nitrogen machine.

(18) H. Oelschlager, *Chem. Ber.*, **89**, 2025 (1956).

dissolved in a hot mixture of 150 ml of ethanol and 800 ml of water. The solution was filtered, and the filtrate was concentrated to a volume of 500 ml. There separated 25 g (90%) of nearly colorless needles, mp 192–194°.

Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.82; H, 5.57.

3,5-Bis(hydroxymethyl)-4-ethylanisole (11, R = Et). To a stirred solution of 26.4 g (0.12 mol) of 3,5-dicarboxy-4-ethylanisole in 500 ml of tetrahydrofuran was added dropwise 400 ml of a 1 *M* solution of diborane in tetrahydrofuran. A gelatinous precipitate soon appeared, but it disappeared after the solution had been heated under reflux overnight. Water was added cautiously to the reaction mixtures to destroy excess reagent and to dilute the mixture. The solution was then extracted with chloroform. The extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to give 19.4 g (84%) of essentially pure crystalline diol. A small sample was recrystallized from a benzene–hexane mixture to give colorless needles, mp 80.5–81.5° (lit.[8] mp 80–81°).

2-Nitro-4-*n*-propylanisole (5, R = *n*-Pr). 4-*n*-Propylanisole (obtained in quantitative yield *via* catalytic hydrogenation of anethole) was nitrated with acetyl nitrate by the procedure described for the preparation of 4-ethyl-2-nitroanisole (**5**, R = Et). Because of a similar difficulty in maintaining low pressure during attempted vacuum distillation, the crude product was always used directly in the following reaction. A small sample was vacuum distilled to obtain a yellow liquid boiling at 107–110° at 0.3 mm (lit.[19] bp 164–169° (9 mm)); nmr ($CDCl_3$) ABC multiplet at τ 2.3–3.1 (3 H, Ar*H*), singlet at 4.07 (3 H, $-OCH_3$), multiplet at 7.43 (2 H, $-CH_2CH_2CH_3$), and a multiplet at 8.1–9.1 (5 H, $-CH_2-CH_2CH_3$).

2-Amino-4-*n*-propylanisole (6, R = *n*-Pr). Crude 2-nitro-4-*n*-propylanisole (**5**, R = *n*-Pr) was reduced by the procedure described for the preparation of 2-amino-4-ethylanisole (**5**, R = Et). Although the crude reduction product was used directly in the following reaction, a small sample was purified by recrystallization from hexane and sublimed *in vacuo* to give colorless thin plates melting at 51–52° (lit.[20] mp 53°).

The acetyl derivative melted at 91.5–92°.

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.56; H, 8.32; N, 6.85.

3,5-Dibromo-4-*n*-propylanisole (8, R = *n*-Pr). Crude 2-amino-4-*n*-propylanisole (**42c**) from the preceding reaction was brominated, and the crude dibromide deaminated by the procedures described for the preparation of the corresponding 4-ethyl compounds. Essentially pure 3,5-dibromo-4-*n*-propylanisole, bp 109–110° (0.1 mm), was obtained in overall yields of 30–50% based on the four steps from 4-*n*-propylanisole. A sample was crystallized from methanol to give colorless crystals: mp 28.5–29°; nmr (CCl_4) singlet at τ 3.01 (2 H, ArH), singlet at 6.30 (3 H, $-OCH_3$), a multiplet at 7.17 (2 H, $-CH_2CH_2CH_3$), and a multiplet at 8.3–9.1 (5 H, $-CH_2CH_2CH_3$).

Anal. Calcd for $C_{10}H_{12}Br_2O$: C, 38.99; H, 3.93; Br, 51.89. Found: C, 38.84; H, 3.98; Br, 51.88.

3,5-Dicyano-4-*n*-propylanisole (9, R = *n*-Pr). A solution of 81 g (0.26 mol) of 3,5-dibromo-4-*n*-propylanisole and 58 g (0.65 mol) of cuprous cyanide in 165 ml of N-methylpyrrolidinone was stirred and heated at 170–180° for 8 hr. The solution was allowed to cool and poured into 1.5 l. of ice water. The resulting solid was collected by filtration, washed with water, and dried overnight at 60° (9 mm). The dried material was powdered and extracted with three 400-ml portions of boiling chloroform, which were combined, filtered, and evaporated to give a brown oil which crystallized when cooled in ice. The product was recrystallized from methanol to give 36 g (68%) of white crystals: mp 78–79°; nmr ($CDCl_3$) singlet at τ 2.63 (2 H, ArH), singlet at 6.12 (3 H, $-OCH_3$), multiplet at 7.03 (2 H, $-CH_2CH_2CH_3$), and a multiplet at 8.1–9.1 (5 H, $-CH_2-CH_2CH_3$).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.16; H, 5.86; N, 13.99.

3,5-Dicarboxy-4-*n*-propylanisole. A suspension of 35.4 g (0.177 mol) of 3,5-dicyano-4-*n*-propylanisole and 50 g of potassium hydroxide in 200 ml of water was stirred and boiled under reflux for 13 days. The suspension of dinitrile only slowly dissolved during the first 10 days, after which time the reaction mixture was transferred to a new flask and an additional 10 g of potassium hydroxide was added. The resulting solution was cooled and filtered, and the filtrate acidified with concentrated hydrochloric acid to give a white precipitate. This was collected by filtration, washed with water, and dried for 24 hr at 80° (9 mm). The crude product (87 g, largely silica) was purified by extraction with ether in a Soxhlet apparatus. The diacid, which was essentially insoluble in ether, very slowly appeared in the lower solvent flask as a mass of tiny colorless needles which eventually were collected and dried to give 29.8 g (71%) of white crystals melting at 218–224°.

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.66; H, 5.86.

3,5-Dicarbomethoxy-4-*n*-propylanisole (10, R = *n*-Pr). A solution of 29.1 g (0.122 mol) of 3,5-dicarboxy-4-*n*-propylanisole and 30 drops of concentrated sulfuric acid in 250 ml of methanol was heated under reflux for 5 days. The solution was evaporated and the residue was dissolved in ether and extracted with 1 *N* sodium bicarbonate solution. The ether solution was washed with water, dried, and evaporated to give, after crystallization from hexane, 13.0 g (37%) of white crystals melting at 39.5–40.5°.

The aqueous bicarbonate extract from the work-up was acidified with concentrated hydrochloric acid and filtered to recover a solid containing unesterified, or partially esterified, acids. This was suspended in ether and treated with excess diazomethane to obtain an additional 15.4 g of diester for a total yield of 28.4 g (80%). The analytical sample was recrystallized from hexane to give white crystals melting at 40–41°.

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.72; H, 6.74.

3,5-Bis(hydroxymethyl)-4-*n*-propylanisole (11, R = *n*-Pr). 3,4-Dicarbomethoxy-4-*n*-propylanisole (28.4 g, 0.107 mol) was reduced by adding it as a solution in 100 ml of tetrahydrofuran to a suspension of 2.5 g of lithium aluminum hydride in 50 ml of tetrahydrofuran. After the addition the reaction mixture was heated under reflux overnight, then cooled in ice while excess reagent was decomposed cautiously with a minimum of water. The white inorganic precipitate was collected by filtration and extracted with ether in a Soxhlet apparatus for 36 hr. The ether extract was combined with the preceding tetrahydrofuran filtrate and concentrated to give a colorless solid. This was recrystallized from benzene to give 19.0 g (85%) of white needles melting at 119.5–120.5°.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.12; H, 8.67.

3,5-Bis(bromomethyl)-4-*n*-propylanisole (12, R = *n*-Pr). To a suspension of 19.0 g (0.090 mol) of 3,5-bis(hydroxymethyl)-4-*n*-propylanisole in 200 ml of benzene was added 10 ml of phosphorus tribromide. The solid dissolved quickly, and, after heating the solution under reflux for 1 hr, it was cooled and poured into 100 ml of ice water. The benzene layer was separated, washed successively with water, 1 *N* aqueous sodium bicarbonate solution and water, and then dried over anhydrous sodium sulfate and evaporated. The crystalline residue was recrystallized from methanol to give 25 g (83%) of white crystals melting at 89–91°.

Anal. Calcd for $C_{12}H_{16}Br_2O$: C, 42.88; H, 4.80; Br, 47.56. Found: C, 42.95; H, 4.90; Br, 47.58.

5,13-Dimethoxy-8,16-di-*n*-propyl[2.2]metacyclophane (13, R = *n*-Pr). A solution of 25.2 g (0.075 mol) of 3,5-bis(bromomethyl)-4-*n*-propylanisole in 1 l. of anhydrous tetrahydrofuran was added dropwise through a Hershberg funnel over 9 days to a solution of 1 g of tetraphenylethylene and 8 g of sodium shot in 2 l. of anhydrous tetrahydrofuran. The reaction was stirred by a high-speed stirrer in an apparatus described previously.[8] After about 5 days the dark red color of the reaction had faded appreciably, so an additional 1 g of tetraphenylethylene and 5 g of sodium shot were added to restore the color. Upon completion of the addition of the dibromide the reaction mixture was filtered and concentrated. The residue was dissolved in chloroform, which was then washed with water, dried, and evaporated to give 17.3 g of brown gummy residue. The metacyclophane was purified partially by chromatography with chloroform on 500 g of Woelm neutral alumina I. The first seven fractions (400 ml each) were combined and concentrated to give 5 g of a crystalline solid containing tetraphenylethylene as the major impurity. Rechromatography of the material with a mixture of hexane and benzene (3:1) on 500 g of silica gel resulted in an excellent separation of pure 5,13-dimethoxy-8,16-di-*n*-propyl[2.2]-metacyclophane. The metacyclophene fraction (3.1 g) was recrystallized from hexane to give 2.93 g (22.4%) of colorless crystals melting at 145–146°. An additional 0.099 g was left in the mother liquors, as determined by the yield of bisdienone **14** (R = *n*-Pr) obtained upon treatment of the residue from the mother liquor with chromic acid reagent. The total yield of metacyclophane **13**

(19) H. Thomas and W. Drauzburg, *Ber.*, 44, 2125 (1911).

(20) Y. Sugli, *J. Pharm. Soc. Jap.*, 50, 183 (1930); *Chem. Abstr.*, 24, 3505 (1930).

(R = *n*-Pr) was therefore 3.04 g (23.2%). Sublimation at 135° (0.01 mm) gave white crystals: mp 150.5–151.5°; nmr ($CDCl_3$) singlet at 3.31 (4 H, Ar*H*), singlet at 6.23 (6 H, $-OCH_3$), singlet at 7.16 (8 H, $-CH_2CH_2-$), and a complex multiplet at 8.6–9.7 (14 H, $-CH_2CH_2CH_3$).

Anal. Calcd for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15. Found: C, 81.85; H, 8.79.

2,7-Diketo-15,16-di-*n*-propyl-4,5,9,10,15,16-hexahydropyrene (14, R = *n*-Pr). Chromic acid reagent was prepared by dissolving 2.67 g of chromium trioxide in 5 ml of water, adding 2.13 g of concentrated sulfuric acid, and diluting the solution with water to a total volume of 10 ml. Then, to an ice-cold suspension of 2.824 g of **13** (R = *n*-Pr) in 140 ml of acetone, 3.32 ml of the chromic acid reagent was added dropwise with stirring. During the first 5 min a pale yellow precipitate separated. The solution was stirred an additional 10 min and then was diluted by addition of 500 ml of water. The aqueous mixture was extracted with methylene chloride and the methylene chloride extract was washed successively with water, a 5% aqueous sodium bicarbonate solution, and water. Concentration of the methylene chloride solution gave a solid residue which was recrystallized from a chloroform–methanol mixture to give 2.426 g (94%) of colorless crystals: mp 273–276° dec; nmr ($CDCl_3$) singlet at τ 3.60 (4 H, $-CH{=}CH-$), singlet at 7.32 (8 H, $-CH_2CH_2-$), complex multiplet at 8.0–8.6 (4 H, $-CH_2-CH_2CH_3$), and a complex multiplet at 8.9–9.5 (10 H, $-CH_2CH_2CH_3$).

Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.85; H, 8.13. Found: C, 81.81; H, 7.89.

***trans*-15,16-Di-*n*-propyldihydropyrene-2,7-quinone (15, R = *n*-Pr).** Air was bubbled through a suspension of 1.080 g of **14** (R = *n*-Pr) in 200 ml of hot absolute methanol containing 6.0 g of potassium hydroxide for 2 hr. The solution was then cooled in an ice bath and the solid precipitate was collected, yielding 757 mg of crude product. Acidification of the filtrate followed by concentration gave a slurry. This was taken up in chloroform, washed with water, dried, and concentrated. The resulting solid residue was combined with the crude product from the filtration and chromatographed over neutral alumina (Woelm, activity 3) using methylene chloride as eluent. The eluate fraction containing the first yellow band was concentrated and the resulting residue was recrystallized from a chloroform–hexane mixture to give 840 mg (79%) of yellow crystals: mp 282–284° dec; nmr ($CDCl_3$) singlets at τ 3.67 (4 H) and 3.75 (4 H, vinyl protons), and complex multiplets at 7.5–8.1 (4 H) and 8.4–9.4 (10 H, *n*-propyl protons); uv λ_{max}^{MeOH} 228 mμ (ϵ 27,100), 278 (42,100), 317 (13,600), 330 (16,500), and 345 (sh, 12,200).

Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.99; H, 6.96. Found: C, 82.79; H, 6.77.

2,7-Diacetoxy-*trans*-15,16-di-*n*-propyldihydropyrene (17, R = *n*-Pr). A suspension of 103 mg of **15** (R = *n*-Pr), 74 mg of triethylamine, and 130 mg of zinc powder in 4 ml of acetic anhydride was stirred at 0° for 1 hr. The mixture was filtered, and the filtrate was stirred for 0.5 hr with 100 ml of saturated sodium bicarbonate solution. The solution was then extracted with several portions of chloroform which were then combined, dried over anhydrous sodium sulfate, and evaporated. Chromatography of the residue with methylene chloride on 6 g of silica gel revealed three separate green bands. The fraction which contained the first green band was collected and evaporated to give 61 mg (47%) of green crystals, mp 148–150°. This was recrystallized from a methylene chloride–methanol mixture, which gave green crystals: mp 155–156°; ir ($CDCl_3$) λ_{max} 5.68 μ ($-C{=}O$); uv $\lambda_{max}^{C_6H_{12}}$ 330 mμ (sh ϵ 26,800), 348 (72,200), 360 (sh, 29,000), 385 (33,300), 497 (8350), 546 (28), 613 (25), 656 (972), and 667 (1860); nmr ($CDCl_3$) singlets at τ 1.43 (4 H) and 1.60 (4 H, Ar*H*), singlet at 7.52 (6 H, acetate), triplet at 10.57 (4 H, $-CH_2CH_2CH_3$), and a symmetrical sextet at 13.88 (6 H, $-CH_2CH_2CH_3$).

Anal. Calcd for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98. Found: C, 77.11; H, 6.86.

***trans*-15,16-Di-*n*-propyl-2,7,15,16-tetrahydropyrene (16, R = *n*-Pr).** To a suspension of 4.0 g of lithium aluminum hydride in 250 ml of anhydrous ether, cooled in an ice bath, there was added cautiously 14.0 g of aluminum chloride and the resulting mixture was boiled under reflux for 1 hr. The supernatant solution was decanted from the precipitate and stirred vigorously at room temperature while adding dropwise a solution of 400 mg of **15** (R = *n*-Pr) in 15 ml of benzene. When addition was complete, the mixture was stirred an additional 15 min before adding a saturated aqueous solution of sodium sulfate to decompose the excess hydride. The ether layer was separated and the precipitate extracted once again with ether. The combined ether extracts were dried and concentrated to give 380 mg of crude **16** (R = *n*-Pr). Analysis by nmr indicated the presence of about 10% of **1c**. Since the separation of **16** (R = *n*-Pr) and **1c** is quite difficult, the crude product is normally employed in the next step to prepare **1c**. However, by heating the crude sample of **16** (R = *n*-Pr) in boiling cyclohexane, thermal rearrangement of **1c** to **18c** occurs and now purification of **16** (R = *n*-Pr) is readily accomplished by crystallization from a chloroform–methanol mixture to give yellow needles: mp 201–203°; nmr ($CDCl_3$) singlet at τ 4.07 (4 H, $-CH{=}CH-$), triplet at 4.20 (4 H, $-CH_2CH{=}CH-$, J = 7 cps), triplet at 7.07 (4 H, $-CH_2-CH{=}CH-$, J = 7 cps), and a multiplet at 8.5–9.4 (14 H, *n*-propyl).

Anal. Calcd for $C_{22}H_{26}$: C, 90.98; H, 9.02. Found: C, 90.76; H, 9.20.

***trans*-15,16-Di-*n*-propyldihydropyrene (1c).** A solution of 245 mg of **16** (R = *n*-Pr) and 180 mg of 2,3-dichloro-5,6-dicyanoquinone (DDQ) in 100 ml of benzene was stirred in the dark at room temperature for 6 hr. The solution was then concentrated under reduced pressure and the residue was chromatographed over *Florisil* using hexane for elution. The green eluate gave 205 mg (84%) of dark green crystals. These, after recrystallization from hexane or from a chloroform–methanol mixture, gave dark green needles: mp 136.5–138.0°; uv $\lambda_{max}^{cyclohexane}$ 331 mμ (ϵ 20,500), 345 (67,500), 348 (67,500), 366 (20,500), 386 (31,000), 391 (39,000), 465 (5400), 544 (105), 553 (85), 605 (118), 618 (160), 632 (235), 648 (282), and 664 (372); nmr ($CDCl_3$) singlet at τ 1.33 (4 H, Ar*H* at 4, 5, 9, and 10), doublet centered at 1.33 (4 H, Ar*H* at 1, 3, 6, and 8, J = 7 cps), triplet at 2.05 (2 H, Ar*H* at 2 and 7, J = 7 cps), triplet at 10.65 (6 H, $-CH_2CH_3$, J = 7 cps), multiplet at 11.1–12.2 (4 H, $-CH_2CH_3$), and a multiplet at 14.03 (4 H, $-CH_2CH_2CH_3$); and mass spectrum, parent molecular ion at 288 with major fragmentation signals at m^+/e 245 and 202.

Anal. Calcd for $C_{22}H_{24}$: C, 91.61; H, 8.39. Found: C, 91.49; H, 8.51.

***trans*-15,16-Di-*n*-propyl-2-nitrodihydropyrene (20, R = *n*-Pr).** A mixture of 36 mg of **1c** and 50 mg of cupric nitrate in 2 ml of acetic anhydride was stirred at room temperature for 15 min. The excess acetic anhydride was hydrolyzed with water and the mixture was extracted with methylene chloride. After the methylene chloride extract had been washed successively with water, a saturated aqueous sodium bicarbonate solution, and water, it was dried and concentrated. The residue was taken up in a 1:2 methylene chloride–hexane mixture and chromatographed over Florisil. The purple eluate was concentrated and the residue recrystallized from a chloroform–methanol mixture to give 24 mg (58%) of deep purple crystals: mp 145.0–146.0°; ir $\lambda_{max}^{CHCl_3}$ 6.5 and 7.5 μ ($-NO_2$); uv $\lambda_{max}^{cyclohexane}$ 344 mμ (inflection, ϵ 32,400), 355 (44,700), 395 (13,900), 398 (13,900), 420 (21,900), 543 (10,000), 614 (2400), 643 (inflection, 258), 661 (258), 668 (302), and 683 (710); nmr (CCl_4) singlet at τ 0.55 (2 H, Ar*H* at 1 and 3), doublet at 1.15 (2 H, Ar*H* at 6 and 8, J = 8 cps), broad singlet at 1.38 (2 H, Ar*H* at 4 and 10), broad singlet at 1.43 (2 H, Ar*H* at 5 and 9), triplet at 1.93 (1 H, Ar*H* at 7, J = 8 cps), two overlapping triplets centered at 10.57 and 10.59 (6 H, $-CH_2CH_3$, J = 7 cps), multiplet centered at 11.6 (4 H, $-CH_2CH_3$), and a multiplet centered at 13.83 (4 H, $-CH_2-CH_2CH_3$).

Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95. Found: C, 79.15; H, 7.02.

Thermal Isomerization of *trans*-15,16-Diethyldihydropyrene (1b) to *trans*-13,15-Diethyldihydropyrene (18b). A solution of 120 mg of **1b** in 200 ml of cyclohexane was boiled under reflux until the green color had disappeared (66 hr). The solution was then concentrated and the oily residue was chromatographed over silica gel using hexane for elution. The main eluate fraction gave 108 mg (90%) of a yellow oil, which could not be induced to crystallize. The spectral data of the yellow oil [uv $\lambda_{max}^{cyclohexane}$ 253 mμ (sh, ϵ 22,100), 260 (23,100), 272 (15,400), 298 (3700), 310 (4650), 324 (3650), 387 (4800), and 404 (sh, 3400); nmr (CCl_4) multiplet at τ 2.8–3.2 (sharp signal at 3.10, 3 H, Ar*H*), multiplet at 3.50–4.30 (7 H, $-CH{=}CH-$), multiplet at 7.7–8.8 (4 H, $-CH_2CH_3$), and two overlapping triplets centered at 9.20 and 9.29 (3 H each, $-CH_2CH_3$)] are extremely similar to that of *trans*-13,15-dimethyldihydropyrene (**18c**).[2] The mass spectrum of **18b** shows a parent molecular ion m^+/e 260, with major fragmentation peaks at 231 and 202. The mass spectrum of **18b** is essentially superimposable with that of **1b**.

Anal. Calcd for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 92.02; H, 7.94.

Thermal Isomerization of *trans*-15,16-Di-*n*-propyldihydropyrene (1c) to *trans*-13,15-Di-*n*-propyldihydropyrene (18c). A solution of 68 mg of **1c** in 200 ml of cyclohexane was boiled under reflux

for 66 hr by which time all of the green color had been lost. The solution was concentrated and the residue was chromatographed over silica gel using hexane containing a trace of benzene. The yellow fraction gave a yellow solid which, after recrystallization from aqueous methanol, yielded 60 mg (88%) of yellow crystals: mp 110–111°; uv $\lambda_{max}^{cyclohexane}$ 252 mμ (sh, ε 22,000), 260 (23,500), 272 (15,200), 298 (3720), 311 (4500), 325 (3550), 388 (4680), and 404 (sh, 3350); nmr (CCl_4) multiplet at τ 2.9–3.2 (3 H, Ar*H*), a multiplet at 3.5–4.5 (7 H, –C*H*=C*H*–), and a complex multiplet from 7.6 to 9.5 (14 H, $-CH_2CH_2CH_3$); mass spectrum m^+/e 288 with major fragmentation peaks at 245 and 202. The mass spectrum of **18c** is virtually superimposable with that of **1c**. The aromatic and vinyl hydrogen region in the nmr spectrum of **18c** is quite analogous to that observed for 13,15-dimethyldihydropyrene (**18a**).[2]

Anal. Calcd for $C_{22}H_{24}$: C, 91.61; H, 8.39. Found: C, 91.54; H, 8.49.

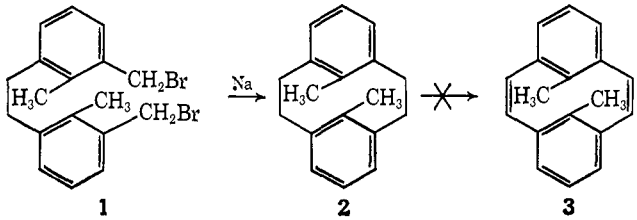
Syntheses of [2.2]Metacyclophan-1-enes. An Alternate Route to *trans*-15,16-Dialkyldihydropyrenes[1-4]

Heinz Blaschke, C. E. Ramey, Ian Calder, and V. Boekelheide

Contribution from the Department of Chemistry, University of Oregon, Eugene, Oregon 97403. *Received October 7, 1969*

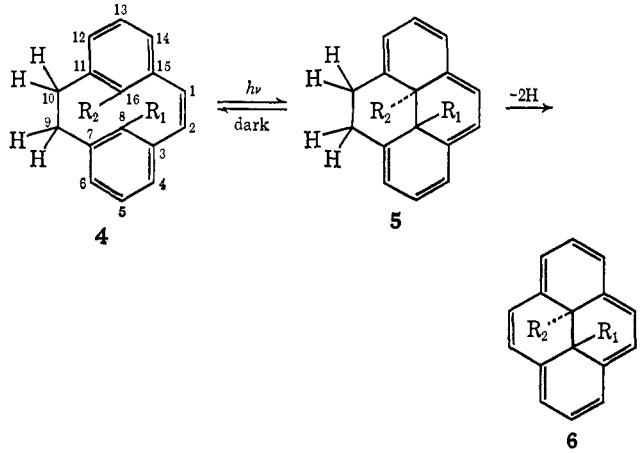
Abstract: It is shown that the cyclization of suitably substituted *cis*-stilbenes (**15**, **23**, and **24**) yields [2.2]metacyclophan-1-enes (**4**). Dehydrogenation of 8,16-dimethyl[2.2]metacyclophan-1-ene (**4**, $R_1 = R_2 = -CH_3$) readily yields *trans*-15,16-dimethyldihydropyrene (**6**, $R_1 = R_2 = -CH_3$).

The methods presently available for the synthesis of *trans*-15,16-dialkyldihydropyrenes are lengthy and difficult.[4] For a variety of reasons it would be desirable to have alternate routes that would be more flexible and, hopefully, simpler for the preparation of examples of this interesting class of compounds. In our initial publication in this series,[5] we described the Wurtz cyclization of 1,2-diphenylethane derivatives such as **1** to give 8,16-dimethyl[2.2]metacyclophanes (**2**).[6] However, attempts to introduce unsaturation into the bridging ethano groups were unsuccessful and it was not possible to obtain the corresponding [2.2]metacyclophane-1,9-diene (**3**), the valence tautomer of *trans*-15,16-dimethyldihydropyrene.



1 **2** **3**

The photoisomerization of *cis*-stilbenes to 4a,4b-dihydrophenanthrenes is a well-studied reaction.[7] Thus it would be expected that a *cis*-stilbene such as **4** would undergo photoisomerization to the corresponding tetrahydropyrene derivative **5**. Since aromatization of **5** to give the corresponding 15,16-dihydropyrene derivative **6** only requires the loss of two hydrogen atoms, it would be anticipated that this would be a feasible, if not facile, reaction and would thus provide a new route to *trans*-15,16-dialkyldihydropyrenes.



4 **5** **6**

To test this hypothesis it was necessary to find a method of synthesis for [2.2]metacyclophan-1-enes (**4**). Since the Wurtz procedure is probably the most generally applicable one for preparing [2.2]metacyclophanes,[8] we turned our attention to the possibility of carrying out a Wurtz cyclization with an appropriately substituted *cis*-stilbene such as **15**. Although the presence of the *cis* double bond increases the possibility of side reactions, it also provides a more rigid molecule with conformations favorable to ring closure.

Our first studies were directed toward the synthesis of **4** ($R_1 = R_2 = -H$). This was accomplished by the reaction sequence shown in Scheme I. The starting

(1) We thank the National Science Foundation and the Office of Naval Research (Contract Nonr-2771(OR), NR-055-468) for their support of this investigation.

(2) For a preliminary communication on this work, see H. Blaschke and V. Boekelheide, *J. Amer. Chem. Soc.*, **89**, 2747 (1967).

(3) Abstracted in part from the doctoral dissertation of C. E. Ramey, University of Oregon, 1968.

(4) This is paper XX in our series on "Aromatic Molecules Bearing Substituents within the Cavity of the π-Electron Cloud." For the preceding article, see V. Boekelheide and T. A. Hylton, *J. Amer. Chem. Soc.*, **92**, 3669 (1970).

(5) W. S. Lindsay, P. Stokes, L. G. Humber, and V. Boekelheide, *ibid.*, **83**, 943 (1961).

(6) These were formerly named 4,12-dimethyl[2.2]metacyclophanes and have now been renamed to follow the nomenclature suggested by B. H. Smith, "Bridged Aromatic Compounds," Academic Press, New York, N. Y., 1964, p 8.

(7) For a recent report on this reaction as well as earlier references, see K. A. Muszkat and E. Fischer, *J. Chem. Soc., B*, 662 (1967).

(8) See ref 6, p 88.