Aromatic Molecules Bearing Substituents within the Cavity of the π-Electron Cloud. Synthesis of *trans*-15,16-Dimethyldihydropyrene[1,2]

V. Boekelheide and Joseph B. Phillips

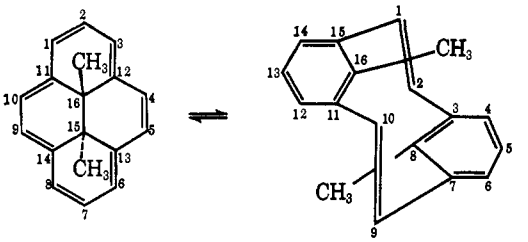
Contribution from the Department of Chemistry, University of Oregon, Eugene, Oregon. *Received October 19, 1966*

Abstract: A synthesis of *trans*-15,16-dimethyldihydropyrene (**1**) is described. By all of the common criteria, including both spectral properties and chemical reactivity, *trans*-15,16-dimethyldihydropyrene is an aromatic molecule. This is the first example of an aromatic molecule having substituents within the cavity of the π-electron cloud.

Although the concept of aromaticity has been commonly employed by organic chemists since the time of Kekulé, there is still no general agreement on a rigid definition of the term or the proper experimental test to determine its presence. However, Hückel's application of molecular orbital theory to aromatic molecules[3] has undoubtedly been one of the most important developments in our understanding of the concept. It has spurred an extraordinary synthetic effort in which appropriate molecules, ranging in size from three-membered rings[4] to very large rings,[5] have been shown to meet certain criteria of aromaticity. These successes of Hückel theory have emphasized the importance of having the proper number $(4n + 2)$ of π electrons if aromaticity is to occur.

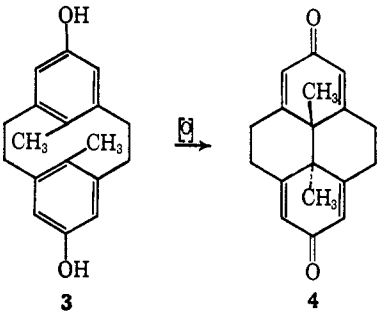
In considering the enormous value of Hückel molecular orbital theory, we were intrigued by the possibility of testing its validity by a different experimental approach. One of the predictions of Hückel theory is that the π electrons of the aromatic ring will be in a doughnut-shaped cloud above and below the plane of the ring. Presumably, the center or cavity of this π-electron cloud should be empty space. There seemed no inherent reason why, if Hückel theory were correct, molecules could not be constructed in which substituent groups would be located in this cavity of the π-electron cloud. A successful synthesis of such a molecule would provide strong support for Hückel theory as well as providing unusual test molecules for studying the interaction of the π-electron cloud with substituent groups.

Of the various hypothetical structures that might be considered for this purpose, our choice was limited to those having an aromatic ring sufficiently large to provide a cavity of adequate size for substituent groups and, secondly, those whose synthesis seemed reasonably feasible. In both respects, *trans*-15,16-dimethyldihydropyrene (**1**) seemed attractive and its synthesis was undertaken.



1 **2**

It was recognized at the beginning that structures **1** and **2** are valence tautomers and that one could not be certain which valence tautomer would predominate at equilibrium. However, from a synthetic point of view, the probability of such an equilibrium seemed to be of considerable help since a synthesis of the metacyclophane isomer **2** would, in fact, realize our objective. However, we were frustrated in our initial studies with [2.2]metacyclophanes by our inability to introduce the necessary side-chain unsaturation.[6,7] Because of these difficulties, our approach *via* the [2.2]metacyclophanes was altered to allow introduction of the central 15,16 bond at an earlier stage. It was proposed that this be done by phenolic oxidation of the appropriate metacyclophane (**3**) to give the corresponding bis-dienone **4**.



3 **4**

Thus, our first goal was the synthesis of 5,13-dihydroxy-8,16-dimethyl[2.2]metacyclophane (**3**).[8] From

(1) We express our deep appreciation to the National Science Foundation for their support of this work.

(2) For preliminary annnouncements regarding this work, see (a) V. Boekelheide and J. B. Phillips, *J. Am. Chem. Soc.*, **85**, 1545 (1963); (b) *Proc. Natl. Acad. Sci. U. S.*, **51**, 550 (1964); and (c) H. R. Blattmann, D. Meuche, E. Heilbronner, R. J. Molyneux, and V. Boekelheide, *J. Am. Chem. Soc.*, **87**, 130 (1965).

(3) E. Hückel, *Z. Elektrochem.*, **43**, 752 (1937).

(4) R. Breslow and C. Yuan, *J. Am. Chem. Soc.*, **80**, 5991 (1958).

(5) F. Sondheimer, *Pure Appl. Chem.*, **7**, 363 (1963).

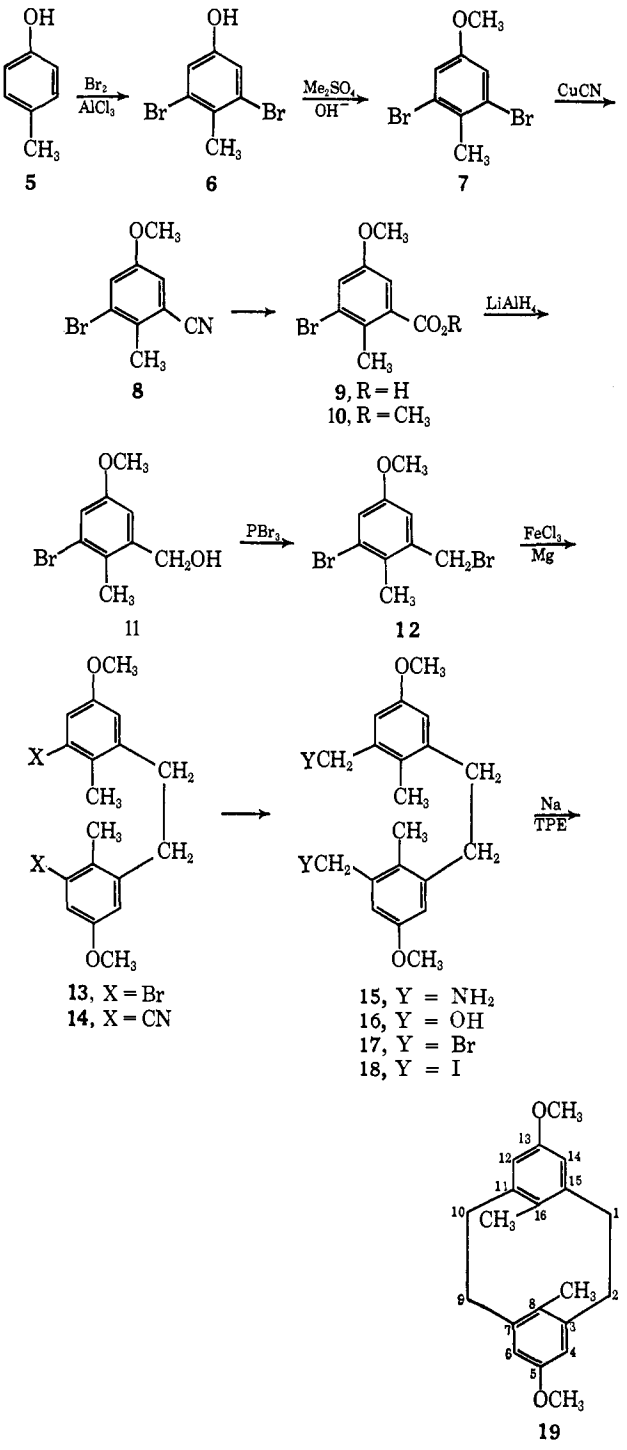
(6) D. J. Wilson, V. Boekelheide, and R. W. Griffin, Jr., *J. Am. Chem. Soc.*, **82**, 6302 (1960).

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

(8) B. H. Smith, "Bridged Aromatic Compounds," Academic Press, Inc., New York, N. Y., 1964, Chapter on Nomenclature, has pointed out the need for a systematic nomenclature and uniform numbering of bridged aromatic molecules. The numbering used in the present paper follows his recommendation and differs slightly from that used in our earlier papers.[6,7]

our previous studies on the synthesis of [2.2]metacyclophanes,[6,7] it was clear that the formation of such bridged rings occurs in higher yield if only one bond is being formed, and this seemed sufficiently critical to justify the longer synthetic route of this approach.[9] The steps which were carried through successfully in this approach to give 5,13-dimethoxy-8,16-dimethyl[2.2]metacyclophane (**19**) are outlined in Scheme I. The first step in

Scheme I



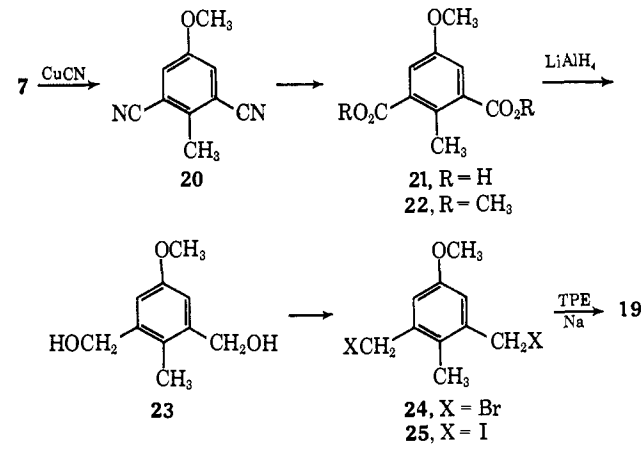
this scheme involved the conversion of *p*-cresol (**5**) to 2,6-dibromo-4-hydroxytoluene (**6**). The usual direct bromination product of *p*-cresol is 3,5-dibromo-4-hydroxytoluene; however, Baddeley and Plant have shown that heating 3,5-dibromo-4-hydroxytoluene with aluminum chloride at 130° effects an equilibration in which 2,6-dibromo-4-hydroxytoluene predominates.[10] We found that adding bromine to a mixture of *p*-cresol and aluminum chloride held at 130° yielded the equilibrium mixture from which the sodium salt of **6** could be separated directly by fractional crystallization. Treatment of the sodium salt of **6** with dimethyl sulfate then gave the methoxy derivative **7**.

When **7** was treated with cuprous cyanide using a 3:1 molar ratio, conversion to the mononitrile **8** occurred in good yield with relatively little of the dinitrile being formed. Hydrolysis of **8** gave the acid **9** which, after esterification to the ester **10**, was reduced with lithium aluminum hydride to give the carbinol **11** in excellent yield. Treatment of the carbinol **11** with phosphorus tribromide led to the dibromide **12** which on reaction with magnesium in the presence of ferric chloride produced the bibenzyl derivative **13**. This, in turn, was converted by treatment once again with cuprous cyanide in N-methylpyrrolidone to the dinitrile **14** in high yield.

Difficulties encountered in the hydrolysis of **14**, presumably due to steric hindrance, led us to an alternate procedure utilizing the reduction of **14** with lithium aluminum hydride, to give the diamine **15**. Reaction with nitrous acid gave the diol **16** and this, with phosphorus tribromide, reacted smoothly to yield the dibromide **17**. Initial attempts to effect the cyclization of **17** were unsuccessful. For this reason the dibromide **17** was converted to the corresponding diiodide **18** by treatment with sodium iodide in acetone. When the diiodide **18** was added to a mixture of finely divided sodium and tetraphenylethylene (TPE) in dry tetrahydrofuran, ring closure occurred smoothly in 55% yield to give the desired dimethoxymetacyclophane **19**. The over-all yield in this 14-step reaction sequence was 1.9%.

Subsequently it became necessary to prepare appreciable quantities of **19**, and later studies provided a shorter and more convenient route. This is summarized in Scheme II. In this case the dibromide **7** was converted

Scheme II



to the dinitrile **20** and this, by a sequence of reactions similar to those discussed before, gave the corresponding *m*-xylyl dibromide **24** and the *m*-xylyl diiodide **25**.

(9) R. W. Griffin, Jr., Ph.D. Thesis, University of Rochester, 1960, made a study of the dimerization of *m*-xylyl dibromides to [2.2]metacyclophanes in which he found that methoxyl-substituted *m*-xylyl dibromides underwent dimerization in much poorer yield than *m*-xylyl dibromide itself.

(10) G. Baddeley and J. Plant, *J. Chem. Soc.*, 525 (1943).

A careful study of the optimum conditions for the dimerization reaction with sodium and TPE in tetrahydrofuran showed that both halides were about equally useful in this reaction and could be converted consistently and reproducibly to the dimethoxymetacyclophane **19** in about 20% yield. Thus, by Scheme II, the conversion of *p*-cresol to the dimethoxymetacyclophane **19** was accomplished in ten steps with an over-all yield of 5.1%. The advantages and convenience of the approach following Scheme II made it practical to prepare the dimethoxymetacyclophane **19** in quantity.[11]

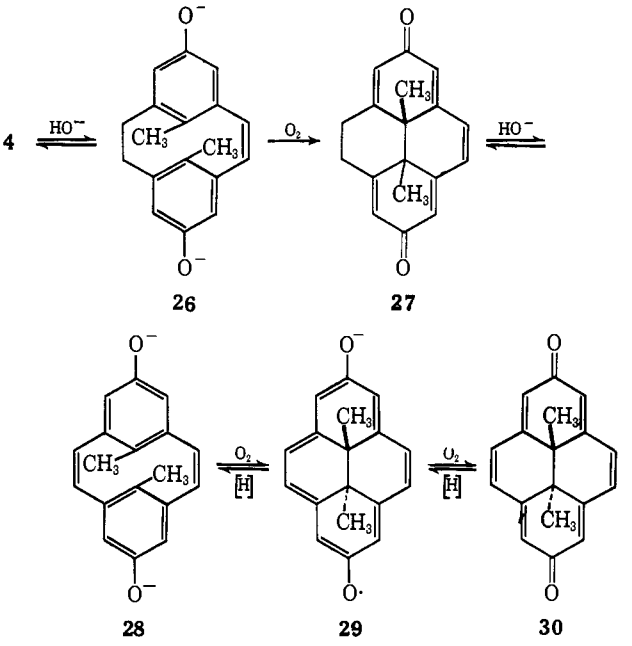
In our earlier studies on [2.2]metacyclophanes,[6] it had been discovered that methyl groups at the internal 8- and 16-position show a large shift (1.5 ppm) to higher field due to the fact that they are situated in space over the face of the opposite aromatic ring and so feel its induced ring current. This provides a very useful diagnostic tool for the presence of the [2.2]metacyclophane ring system. Thus, in addition to the usual analytical and molecular weight evidence, the structure of **19** is supported by the fact that the nmr signal for the 8- and 16-methyls occurs at τ 9.25, a shift to higher field of 1.57 ppm from that of the methyl group in toluene.

Initial attempts to cleave the methoxyl group of **19** were monitored by testing the reaction mixture with ferric chloride, but it was discovered that ferric chloride reacted directly with **19**. An investigation of several reaction conditions quickly showed that **19** undergoes a smooth reaction with anhydrous ferric chloride in dry chloroform to give the desired bis-dienone **4** in 93% yield. The fact that a phenolic oxidation–radical coupling was accomplished under these conditions and with phenolic ethers rather than phenols is quite surprising. We have not yet made a study to determine whether this procedure is general but, if so, it could have considerable synthetic usefulness.

On the other hand, we have found that other oxidizing agents will also bring about this reaction. Of these a chromic acid solution in acetone is particularly convenient and effects the conversion of **19** to **4** in quantitative yield at room temperature. In most instances this is the preferred procedure for this reaction.

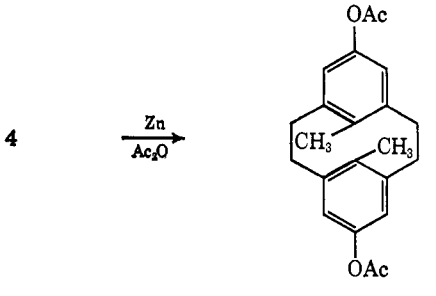
The bis-dienone **4** is a pale yellow compound whose internal methyls appear as a singlet in its nmr spectrum at τ 8.80, a shift downfield in accord with the loss of the [2.2]metacyclophane system. Although **4** might be expected to undergo a dienone–phenol rearrangement it is not sensitive to acid, being recovered from boiling hydrochloric acid unchanged.

In contrast, **4** was readily soluble in aqueous base. Although this seems surprising at first, it can readily be explained as a double enolization of **4** followed by valence tautomerism to give the dianion of the metacyclophane **26**. Actually, this change can be followed by observing the shifts in the nmr when **4** reacts with base in a deuterium oxide solution. Most significantly, the signal for the internal methyls at τ 8.80 disappears and is replaced by a new signal at τ 9.3, as would be expected for the metacyclophane structure **26**. Furthermore, it would be expected that **26** would readily undergo phenolic oxidation and, in fact, bubbling air through a basic, aqueous solution of **26** leads in good yield to the corresponding quinone **30**. The transient, green-violet color that appears during this oxidation suggests a pathway involving intermediates **27**, **28**, and **29**.



As would be expected, the oxidation steps leading to the quinone **30** are reversible. This was reported previously in a detailed study of the esr spectrum of the semiquinone **29**.[12] Treatment of the yellow quinone **30** with glucose in the presence of alkali gives the deep violet semiquinone **29** which, on further addition of glucose, loses color yielding the hydroquinone dianion **28**, a sequence of color changes exactly reversed by introduction of oxygen. Undoubtedly, the hydroquinone dianion **28** is in equilibrium with the corresponding dihydropyrene valence tautomer but, in this case, relief of charge repulsion shifts the equilibrium in favor of **28**.

Another instance of valence tautomerism between the bis-dienone **4** and the corresponding metacyclophane was encountered when **4** was subjected to reductive acetylation using zinc dust and acetic anhydride. The product, isolated in high yield, was 5,13-diacetoxy-8,16-dimethyl[2.2]metacyclophane (**31**).



31

Although the alkaline air oxidation of **4** is a useful and practical method for preparing the quinone **30**, there are some accompanying minor impurities due to overoxidation and formation of hydroxy derivatives. Alternatively, the reaction of **4** with N-bromosuc-

(11) We would like to express our deep appreciation to J. R. Geigy, A.G., Basel, for their kindness in carrying through the preparation of the dibromide **17** in their kilo laboratory and providing us with generous quantities of this substance.

(12) F. Gerson, E. Heilbronner, and V. Boekelheide, *Helv. Chim. Acta*, 47, 1123 (1964).

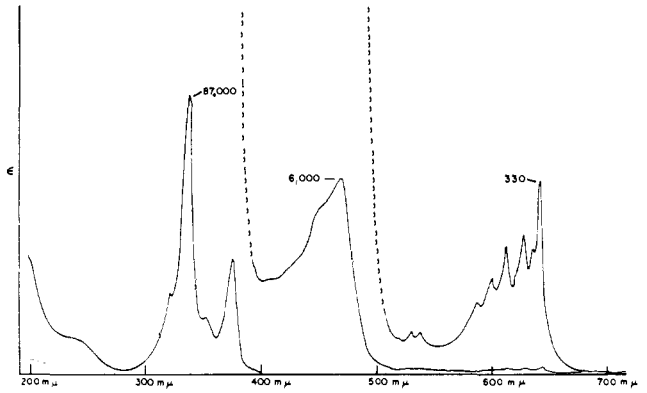
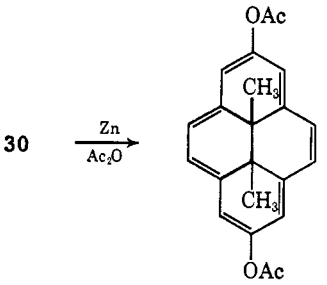


Figure 1. Ultraviolet and visible absorption spectrum of *trans*-15,16-dimethyldihydropyrene measured in cyclohexane using a Cary 14 spectrometer.

cinimide occurs smoothly to give the quinone **30** in 93% yield.

When the quinone **30** was treated with zinc dust in acetic anhydride, it was converted in 92% yield to the corresponding hydroquinone diacetate **32**, isolated as dark green needles, mp 204.5–205.0°. That the goal of preparing an aromatic molecule with methyl groups in the cavity of the π-electron cloud had been accomplished was immediately evident from the nmr spectrum of **32**. The signal for the 15,16 internal methyls occurs at τ 14.03, a shift to higher field of about 5 ppm and indicative of a strong ring current. The absorption spectrum of **32** shows four main bands at 337, 371, 466, and 643 mμ and is in very good agreement with the spectrum predicted from molecular orbital theory.[13a,b]



32

Our attention then turned to the preparation of the parent hydrocarbon **1**. Various methods of reducing the quinone **30** were investigated and a lithium aluminum hydride–aluminum chloride mixture proved to to be most useful. When the quinone **30** was treated with this mixture at −80°, the corresponding bis-triene **33** was formed in good yield. The structure assigned **33** is supported particularly by its nmr spectrum which shows the 4-, 5-, 9-, and 10-vinyl hydrogens as a singlet at τ 4.03, the 1-, 3-, 6-, and 8-vinyl hydrogens as a triplet at τ 4.25, the four allylic hydrogens as a triplet at τ 7.02, and the 15,16 internal methyls as a singlet at τ 9.05. Treatment of the bis-triene **33** with a palladium-on-charcoal catalyst in boiling benzene or cyclohexene rapidly effected dehydrogenation to give the desired hydrocarbon **1**.

(13) (a) Private communication from Professor E. Heilbronner, Eidg. Tech. Hochschule, Zurich, Switzerland; (b) private communication from Dr. H. E. Simmons, E. I. du Pont de Nemours and Co., Wilmington, Del.

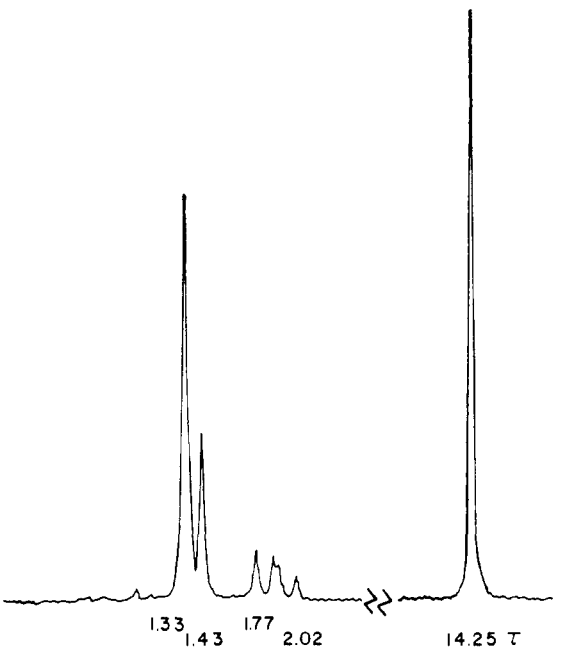
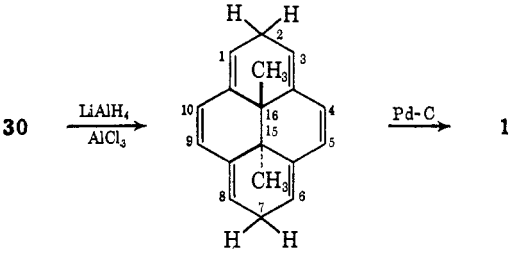


Figure 2. Nmr spectrum of *trans*-15,16-dimethyldihydropyrene measured in deuteriochloroform using a Varian A-60 spectrometer.

In the preparation of the bis-triene **33**, the chief impurity is the hydrocarbon **1** itself. Thus, there is an advantage in carrying out the dehydrogenation on the crude reaction product from the lithium aluminum hydride–aluminum chloride reduction of the quinone **30** rather than purifying the bis-triene **33**. The over-all



33

yield of **1** from quinone **30** by this procedure is about 75%. Also, the dehydrogenation step may be accomplished smoothly in very high yield using 2,6-dichloro-3,5-dicyanoquinone. When the reaction of the quinone **30** with the lithium aluminum hydride–aluminum chloride mixture is carried out at room temperature rather than −80°, the chief product is the hydrocarbon **1**, but the yield is lower than *via* the two-step procedure.

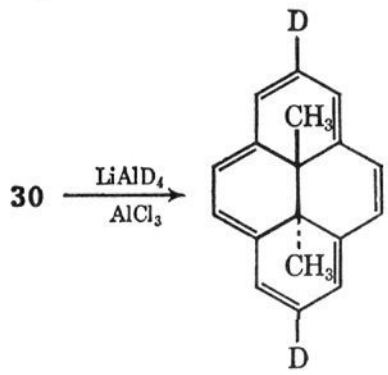
trans-15,16-Dimethyldihydropyrene forms dark, emerald-green needles, mp 119.0–119.5°. Its ultraviolet and visible absorption spectra are shown in Figure 1.

One of the most common tests for aromaticity is to determine whether a molecule develops a ring current in the presence of an outside magnetic field.[14] The nmr spectrum of *trans*-15,16-dimethyldihydropyrene (**1**) is shown in Figure 2 and provides clear evidence for a strong ring current. The internal methyl protons

(14) Although the ring current hypothesis has been widely used to interpret nmr spectra of aromatic molecules, J. I. Musher (*J. Chem. Phys.*, **43**, 4081 (1965)) has presented theoretical arguments against the concept. Regardless of whether one speaks of magnetic anisotropy or ring currents, though, there is clearly a correlation between chemical shifts of internal and external protons and the presence of an aromatic π-cloud.

show a remarkable shift to higher field appearing as a singlet at τ 14.25, whereas the peripheral aromatic protons show a downfield shift appearing below the normal region for benzene protons.

An assignment of the individual peripheral aromatic protons can readily be made. The 4-, 5-, 9-, and 10-protons exhibit no spin coupling and appear as a singlet at τ 1.33. The 1-, 3-, 6-, and 8-protons undergo spin coupling with the 2- and 7-protons giving a doublet at τ 1.33 and 1.43. The *peri* protons at the 2- and 7-positions then provide the multiplet at τ 1.77–2.02.[15] These assignments have been established by preparing the 2,7-dideuterio-*trans*-15,16-dimethyldihydropyrene (**34**). This was readily done by reducing the quinone **30** with a lithium aluminum deuteride–aluminum chloride mixture at room temperature. Examination of the aromatic region of the nmr spectrum of 2,7-dideuterio-*trans*-15,16-dimethyldihydropyrene (**34**) shows that the multiplet at τ 1.77–2.02 has disappeared, the 1-, 3-, 5-, and 7-protons appear as a singlet at τ 1.37, and the 4-, 5-, 9-, and 10-protons remain as a singlet at τ 1.33.



34

A second method for assessing aromaticity is the comparison of bond lengths of the molecule under consideration with the aromatic carbon–carbon bond length of benzene. Dr. A. W. Hanson has kindly made an X-ray crystallographic examination of 2,7-diacetoxy-*trans*-15,16-dimethyldihydropyrene (**32**).[16] In comparison with the standard value of 1.397 A for benzene,[17] the carbon–carbon bond lengths in the perimeter of **32** vary between 1.386 and 1.401 A, and so this criterion for aromaticity is fully met. As shown in Figure 3, molecular models indicate the perimeter of the dihydropyrene molecule should be essentially planar. Again, this is confirmed by the X-ray examination which shows the maximum deviation of a perimeter atom from a mean plane is no more than 0.027 A.

A third measure of aromaticity is that of diamagnetic susceptibility. Dauben and Laity have measured the perpendicular diamagnetic anisotropy of *trans*-15,16-dimethyldihydropyrene and found the value to be quite large, again providing strong evidence for the aromatic character of **1**.[18]

The classical criterion for aromaticity is that of whether a molecule undergoes substitution rather than

(15) This multiplet is an AB_2 case (see K. B. Wiberg and B. J. Nist, "The Interpretation of NMR Spectra," W. A. Benjamin, Inc., New York, N. Y., 1962, p 11) and can be fit by a calculated spectrum with J_{AB} = 7.5 cps. Actually, when the spectrum is taken at 100 Mc, this multiplet reduces to a simple triplet.

(16) A. W. Hanson, *Acta Cryst.*, **18**, 599 (1965).

(17) B. P. Stoicheff, *Can. J. Phys.*, **32**, 339 (1954).

(18) We are very much indebted to Professor H. J. Dauben and Mr. J. L. Laity for making these measurements. The procedure employed has been described by Professor Dauben (Abstracts, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., 1965, p 325). The details of the experiments with **1** will be described elsewhere.

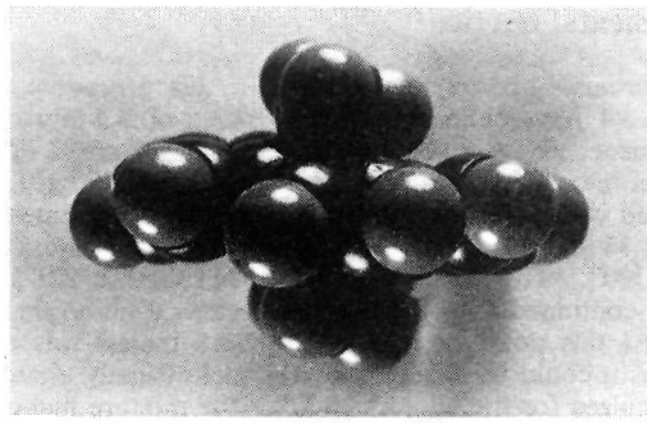


Figure 3. Fisher–Taylor–Hirschfelder model of *trans*-15,16-dimethyldihydropyrene.

addition reactions. *trans*-15,16-Dimethyldihydropyrene undergoes the typical electrophilic substitution reactions of nitration, deuteration, bromination, and Friedel–Crafts acylation, being somewhat more reactive than benzene.[19]

Thus, by all of the tests we have been able to apply, *trans*-15,16-dimethyldihydropyrene appears aromatic and is comparable in its properties to benzene. The feasibility of placing substituents within the cavity of an aromatic π-electron cloud has been demonstrated, and it is clear that many additions to this class of compounds will be forthcoming. The elegant work of Vogel and Roth has already provided a second example in the case of the 1,6-methanocyclodecapentaenes.[20]

Although, as pointed out earlier, *trans*-15,16-dimethyldihydropyrene (**1**) could readily give the corresponding metacyclophane (**2**) by valence tautomerism, such an equilibrium must lie almost completely in favor of the dihydropyrene isomer **1**. Certainly, none of our spectral data gives any indication of the presence of **2**. It is worth noting that the 14-π-electron system of **1** is preferable energetically to the metacyclophane system **2** containing two isolated benzene rings.

Even though **1** is the preferred valence tautomer, it was found that conversion to **2** is readily accomplished by visible light.[2c] Irradiation of **1** in pentane or methanol solution yielded mixtures containing both **1** and **2**. The formation of **2** can be followed readily using a spectrophotometer since a new absorption band appears in the region of 275 mμ while the absorption bands of **1** decrease in intensity. Similarly, in the nmr spectrum, irradiation of **1** causes a decrease in the signal of the internal 15- and 16-methyls at τ 14.25 and the appearance of a new signal at τ 8.48, corresponding to the 8- and 16-methyls of the metacyclophane **2**.

$$\mathbf{1} \underset{\text{dark}}{\overset{h\nu}{\rightleftharpoons}} \mathbf{2}$$

The photoisomer **2** is not stable on standing in the dark but rapidly reverts back to the dihydropyrene **1**. The dark reaction follows first-order kinetics and at 50° shows a half-life of about 2 hr. All of the derivatives of dihydropyrene which have been prepared thus far show this photoisomerization reaction, and a more detailed study of this behavior will be reported separately.

(19) J. B. Phillips, R. J. Molyneux, E. Sturm, and V. Boekelheide, *J. Am. Chem. Soc.*, **89**, 1704 (1967).

(20) E. Vogel and H. D. Roth, *Angew. Chem.*, **76**, 145 (1964).

Experimental Section[21]

2,6-Dibromo-4-hydroxytoluene (6). In this procedure the bromination of *p*-cresol and the rearrangement of 3,5-dibromo-4-hydroxytoluene, as described by Baddeley and Plant,[10] have been combined into one operation. Molten *p*-cresol (130 g, 1.2 moles) was added with vigorous stirring under a nitrogen atmosphere to 180 g (1.34 moles) of powdered, anhydrous aluminum chloride held at 100°. The temperature was then raised to 130°, and stirring was continued until the mixture became a homogeneous thin paste. At this point bromine (450 g, 2.8 moles) was added as rapidly as it could be absorbed by the melt, usually about 30 min being required for the addition. After the mixture had cooled to about 100°, water (500 ml) was added to the black viscous mass to decompose the aluminum chloride. Stirring and heating of the mixture on a steam bath was continued until there was clean separation into two phases, the black organic layer and the aqueous layer. With the temperature still at 70°, the black organic phase was separated and added to a hot solution prepared from 150 g of sodium hydroxide and 600 ml of water. When the resulting solution was allowed to stand at −5° for 24 hr, the sodium salt of 2,6-dibromo-4-hydroxytoluene separated as a crystalline mass and was collected using a sintered glass filter funnel. The crystals, after drying *in vacuo* at 50°, weighed 186 g (54%) and were sufficiently pure to be used directly in the preparation of 2,6-dibromo-4-methoxytoluene (7).

Acidification of an aqueous solution of a portion of the sodium salt gave a solid which, after recrystallization from cyclohexane, afforded white crystals, mp 105–107° (lit.[10] 107°), of the free phenol 6.

Treatment of a portion of the crystals of the phenol 6 with acetic anhydride gave the corresponding O-acetyl derivative. This was obtained, after recrystallization from methanol, as white needles, mp 86.5–87°.

Anal. Calcd for $C_9H_8O_2Br_2$: C, 35.10; H, 2.63. Found: C, 35.27; H, 2.83.

2,6-Dibromo-4-methoxytoluene (7). The crude sodium salt of 6 (640 g, 2.21 moles), as obtained from the previous experiment, was dissolved in a solution prepared from 30 g of sodium hydroxide in 1.5 l of water. Dimethyl sulfate (250 ml) was then added dropwise with stirring over a period of 1 hr while maintaining the temperature of the solution around 30° by addition of ice as necessary. After the addition was complete, the temperature of the suspension was raised to 90° with stirring, and finally the solution was boiled under reflux for 1 hr. Then the mixture was cooled to 50° and the organic layer was separated. Distillation of the organic layer using a Claisen flask gave 385 g (62%) of a colorless oil, bp 154° (15 mm). This crystallized on standing and, after recrystallization from methanol at −10°, gave white needles, mp 47–48°.

Anal. Calcd for $C_8H_8OBr_2$: C, 34.31; H, 2.88. Found: C, 34.62; H, 3.10.

2-Bromo-4-methoxy-6-cyanotoluene (8). To a stirred solution of 585 g (2.09 moles) of 2,6-dibromo-4-methoxytoluene (7) in 600 ml of N-methyl-2-pyrrolidone held at 160° there was added dropwise over a period of 3 hr a solution of 60 g (0.67 moles) of cuprous cyanide in 400 ml of N-methyl-2-pyrrolidone. Then the temperature was allowed to fall to 100°, a small Vigreux column was attached to the reaction flask, and most of the solvent (about 900 ml) was removed by distillation at 15-mm pressure. After the residual semisolid had cooled, 1.0 l. of acetone was added and the mixture was stirred for 15 min while boiling under reflux. The precipitate of cuprous bromide was collected and the filtrate was concentrated. Then 1.0 l. of ether was added and the organic layer was washed successively with dilute, aqueous hydrochloric acid and water. After the ethereal solution had been dried, it was concentrated, the residue was dissolved in 1.0 l. of petroleum ether (bp 30–60°), and the solution was allowed to stand overnight at −5°. The crystalline solid, which separated, was collected and washed on the filter with 50 ml of cold methanol. This, after drying, amounted to 140 g of a white solid in a satisfactory state for use in the preparation of 2-methyl-3-bromo-5-methoxybenzoic acid (9).

Concentration of the petroleum ether filtrate gave 410 g of a crystalline residue, consisting very largely of 2,6-dibromo-4-methoxytoluene (7). When this residue was recycled in the above reaction using 40 g of cuprous cyanide, an additional 73 g of product resulted plus recovery of 213 g of 7. A second recyclization of the 213 g of 7 using 31 g of cuprous cyanide yielded an additional 73 g of product with recovery of 133 g of 7. The combined product (286 g) was distilled (bp 146–152° at 15 mm) to give 270 g of a white, crystalline solid, mp 80–84°. The nmr spectrum of this solid indicated it to be a mixture of 7 and 8, probably a 1:1 complex. For the most part it was convenient simply to use this mixture in the next step, the preparation of 9. However, by repeated recrystallizations from petroleum ether at −10°, a pure sample of 8 was obtained as white crystals, mp 109–110°.

Anal. Calcd for C_9H_8NOBr: C, 47.81; H, 3.57; N, 6.20. Found: C, 47.72; 47.81; H, 3.43; 3.57; N, 6.35; 6.22.

2-Methyl-3-bromo-5-methoxybenzoic Acid (a). The product mixture (475 g) from the previous experiment was suspended in a solution of 600 g of potassium hydroxide in 1.5 l. of ethanol and heated on a steam bath with occasional stirring until evolution of ammonia ceased (about 4 days). The mixture was then concentrated under reduced pressure to about one-half volume and 2 l. of water was added. When the mixture was allowed to stand, the lower organic layer solidified. The aqueous layer was removed and extracted with 500 ml of ether. The ether extract was combined with the solid organic layer and reserved for work-up as described in part b below.

The aqueous layer was acidified by the addition with cooling of 1.0 l. of concentrated hydrochloric acid. The precipitate was collected, washed with water, and dried to give 178 g of crude acid. Recrystallization of this from a mixture of 100 ml of benzene and 400 ml of cyclohexane yielded 152.0 g of white needles, mp 161.0–161.5°.

Anal. Calcd for $C_9H_9O_3Br$: C, 44.10; H, 3.70. Found: C, 44.55; H, 3.61.

(b). The combined ether extract and solid organic layer from above was evaporated to dryness and the residue was taken up in 500 ml of hot petroleum ether. The insoluble, suspended material was removed by filtration and weighed 21 g. This was crystalline, mp 171°, and corresponds to the amide of 9. The petroleum ether filtrate on concentration followed by distillation of the residue gave 205 g of oil, bp 145–150° (15 mm), whose nmr spectrum showed it to be essentially pure 2,6-dibromo-4-methoxytoluene (7).

Methyl 2-Methyl-3-bromo-5-methoxybenzoate (10). A solution of 173 g (0.7 mole) of 2-methyl-3-bromo-5-methoxybenzoic acid (9) in 1.5 l. of methanol previously saturated with anhydrous hydrogen chloride was boiled under reflux for 5 hr (the ester began to separate as a separate phase after 3 hr). The suspension was then poured onto 1.5 kg of ice, and the mixture was stirred vigorously until the droplets of ester solidified. The solid was collected by filtration, redissolved in ether (1.5 l.), and washed with 200 ml of water. Concentration of the ether solution followed by distillation of the residue gave 141 g (78%) of a colorless oil, bp 164° (12 mm), which readily solidified. Recrystallization of a sample from methanol gave white prisms, mp 42.5–43.0°.

Anal. Calcd for $C_{10}H_{11}O_3Br$: C, 46.35; H, 4.28. Found: C, 46.09; H, 4.19.

2-Bromo-4-methoxy-6-hydroxymethyltoluene (11). A solution of 130 g of methyl 2-methyl-3-bromo-4-methoxybenzoate (10) in 1 l. of ether was added dropwise with stirring to a prepared solution of 25 g of lithium aluminum hydride in 1.5 l. of ether. The mixture was boiled under reflux for 5 hr and then stirred at room temperature overnight. The excess lithium aluminum hydride was destroyed by the addition of 90 ml of ethyl acetate, and then a cold solution of 150 ml of concentrated sulfuric acid in 500 ml of water was added. After the ether layer had been separated, it was washed with water, dried, and concentrated. The solid residue was dissolved in 600 ml of a hot 50% aqueous methanol solution and allowed to stand at −10° overnight. There separated 100.0 g of white needles, mp 69.0–69.5°. An additional 6.0 g of crystals resulted from concentration of the mother liquor followed by cooling to give a total of 106.0 g (92%) of 11.

Anal. Calcd for $C_9H_{11}O_2Br$: C, 46.77; H, 4.80. Found: C, 46.92; H, 4.63.

2-Bromo-4-methoxy-6-bromomethyltoluene (12). A solution of 25.0 ml of phosphorus tribromide in 50 ml of benzene was added with stirring over a period of 15 min to a solution of 98.0 g of 2-bromo-4-methoxy-6-hydroxymethyltoluene (11) in 500 ml of benzene, and the resulting mixture was boiled under reflux for 15 min. The solution was then cooled, decanted from inorganic residue, and

(21) Microanalyses are by Micro-Tech Laboratories and by Pascher and Pascher Laboratories. Ultraviolet and visible spectra were determined with a Cary Model 15 spectrometer, infrared spectra with a Beckman IR-5A spectrometer, and nmr spectra in deuteriochloroform as solvent with a Varian A-60 spectrometer. We express our thanks to the National Science Foundation for the funds allowing the purchase of the Varian A-60.

poured onto 1 kg of ice. After the resulting mixture had been stirred for 0.5 hr, the benzene layer was separated, dried, and concentrated. The solid residue was recrystallized from 700 ml of petroleum ether to give 109.0 g (90%) of white needles, mp 72–72.5°.

Anal. Calcd for $C_9H_{10}OBr_2$: C, 36.77; H, 3.43. Found: C, 36.58; H, 3.24.

2,2′-Dimethyl-3,3′-dibromo-5,5′-dimethoxybibenzyl (13). In a 5-l. flask a mixture of 122 g of 2-bromo-4-methoxy-6-bromomethyltoluene (**12**) and 5.5 g of magnesium in 650 ml of ether was warmed until ebullition indicated reaction was occurring. Then, 1.0 g of anhydrous ferric chloride was added with rapid stirring, causing the onset of a vigorous reaction. When the reaction had subsided somewhat, heating was begun and the suspension was boiled under reflux, still with vigorous agitation, until all of the magnesium had dissolved. After removal of most of the ether by distillation, 1.0 l. of benzene was added followed by the addition of 100 ml of 5 *N* hydrochloric acid. The benzene layer was separated and concentrated to a volume of 100 ml, and 500 ml of ether was added. After the solution was allowed to stand overnight at −10°, there separated 40.0 g (45%) of white crystals, mp 136–139°. Recrystallization of a sample from a chloroform–methanol mixture gave white plates, mp 143.5–144.0°.

Concentration of the ethereal mother liquor gave about 50 g of an oil which when treated with petroleum ether caused the separation of several grams of additional product.

Anal. Calcd for $C_{18}H_{20}O_4Br_2$: C, 50.49; H, 4.71. Found: C, 50.84; H, 4.72.

2,2′-Dimethyl-3,3′-dicyano-5,5′-dimethoxybibenzyl (14). A solution of 40.0 g of 2,2′-dimethyl-3,3′-dibromo-5,5′-dimethoxybibenzyl (**13**) and 25.0 g of cuprous cyanide in 250 ml of N-methyl-2-pyrrolidone was heated at 160° for 2 hr. After the solution had cooled, it was poured into 1.5 l. of a 5% ammonium hydroxide solution and allowed to stand at 5° overnight. The precipitate was collected, washed with water, and dried. It was then finely ground and extracted with three 500-ml portions of boiling chloroform. The chloroform extract was percolated through a small column of alumina and the eluate was concentrated to a volume of 250 ml. Then, 500 ml of benzene was added, and the entire solution was concentrated to a volume of 400 ml and allowed to cool. There deposited 24.5 g of white crystals. Concentration of the mother liquor to 50 ml followed by addition of 50 ml of ether caused the separation of an additional 2.5 g of crystals giving a total of 27.0 g (93%) of product. Recrystallization of a sample for analysis from a chloroform–methanol mixture gave white needles, mp 195–196°.

Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.74. Found: C, 74.98; H, 6.25; N, 8.59.

2,2′-Dimethyl-3,3′-di(aminoethyl)-5,5′-dimethoxybibenzyl (15). To a stirred suspension of 15.0 g of lithium aluminum hydride in 500 ml of boiling tetrahydrofuran there was added dropwise with stirring over a period of 8 hr a solution of 27.0 g of 2,2-dimethyl-3,3′-dicyano-5,5′-dimethoxybibenzyl (**14**) in 1.4 l. of tetrahydrofuran. After the solution had been heated with stirring for an additional 2 hr, the excess lithium aluminum hydride was destroyed by addition of ethyl acetate followed by addition of 75 ml of water. The inorganic precipitate was removed and washed with four 150-ml portions of tetrahydrofuran. The combined washings and filtrate were concentrated to 150 ml and diluted with an equal volume of water. The solid, which separated, was collected and recrystallized from methanol to give 23.1 g (83%) of fine white needles, mp 94.5–95.0°.

Anal. Calcd for $C_{20}H_{28}N_2O_2$: C, 73.13; H, 8.59; N, 8.53. Found: C, 73.31; H, 8.77; N, 8.59.

2,2′-Dimethyl-3,3′-di(hydroxymethyl)-5,5′-dimethoxybibenzyl (16). A solution of 23.1 g of 2,2-dimethyl-3,3′-di(aminomethyl)-5,5′-dimethoxybibenzyl (**15**) in 350 ml of acetic acid and 5 ml of water was cooled in an ice bath, and, when the mixture began to freeze, 30 ml of a saturated aqueous solution of sodium nitrite was added dropwise with stirring over a period of 1 hr. The reaction mixture was then slowly warmed to 70° over a period of 1 hr and held at this temperature for 15 min. Once again the solution was cooled to 10° and another 15 ml of the sodium nitrite was added. After the solution had been stirred at 10° for 2 hr, the temperature was slowly raised to 80°, 200 ml of water was added, and the entire mixture was concentrated on a steam bath under reduced pressure. The residue was taken up in 700 ml of ether and washed with 200 ml of water. Concentration of the ether solution left an oil whose infrared spectrum was in accord with that expected for the diacetate of **16**. This was hydrolyzed by dissolving it in 200 ml of a 10% ethanolic potassium hydroxide solution and boiling under reflux for 15 min. This solution was then concentrated and 500 ml of ice water was added. The resulting precipitate was collected, dried, and recrystallized from 150 ml of carbon tetrachloride containing 3 ml of methanol to give 17.2 g (74%) of white crystals, mp 117–118°. Recrystallization of a sample from benzene gave white needles, mp 118.0–118.5°.

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.62; H, 7.80.

2,2′-Dimethyl-3,3′-di(bromomethyl)-5,5′-dimethoxybibenzyl (17). A solution of 16.9 g of 2,2′-dimethyl-3,3′-di(hydroxymethyl)-5,5-dimethoxybibenzyl (**16**) and 20 ml of phosphorus tribromide in 1.5 l. of benzene was allowed to stand at room temperature before being boiled under reflux for 2 hr. The solution was then cooled, decanted from the inorganic residue, and shaken vigorously with 500 ml of ice water. After the organic phase was separated, it was concentrated under reduced pressure. The solid residue was recrystallized from 150 ml of dioxane to give 19.9 g (86%) of white crystals, mp 184–185°. A sample for analysis was recrystallized from benzene to give white needles, mp 185.5–186.0°.

Anal. Calcd for $C_{20}H_{24}O_4Br_2$: C, 52.65; H, 5.30. Found: C, 52.30; H, 5.28.

2,2′-Dimethyl-3,3′-di(iodomethyl)-5,5-dimethoxybibenzyl (18). To a solution of 9.7 g of 2,2′-dimethyl-3,3′-di(bromomethyl)-5,5′-dimethoxybibenzyl (**17**) in 1.0 l. of hot acetone there was slowly added with stirring 100 g of finely ground sodium iodide. The resulting suspension was boiled under reflux for 2 hr. After removal of most of the solvent under reduced pressure, 500 ml of ice water was added. The crystalline precipitate was collected and washed with water and cold methanol. Recrystallization from benzene then gave 11.1 g of white needles, mp 147° dec.

Anal. Calcd for $C_{20}H_{24}O_2I_2$: C, 43.65; H, 4.40. Found: C, 43.35; H, 4.56.

8,16-Dimethyl-5,13-dimethoxy[2.2]metacyclophane (19). A solution of 4.6 g of 2,2′-dimethyl-3,3′-di(iodomethyl)-5,5′-dimethoxybibenzyl (**18**) in 500 ml of tetrahydrofuran was added through a Hershberg dropping funnel over a period of 36 hr to a stirred suspension of 5.0 g of sodium granules in 100 ml of tetrahydrofuran containing 200 mg of tetraphenylethylene while the reaction mixture was kept at −80° under a nitrogen atmosphere. At the end of the addition the reaction mixture was filtered to remove excess sodium, and the filtrate was concentrated under reduced pressure. The residue was taken up in 500 ml of chloroform and washed with 200 ml of dilute hydrochloric acid. Concentration of the chloroform solution gave 2.55 g of solid residue. This, on sublimation at 150° at 0.01 mm, yielded 1.55 g of crystalline product. This was shown by nmr spectroscopy to be a mixture containing about 86% of **19** and 14% of tetraphenylethane. This mixture melted at 221–222° and was unchanged by recrystallization from various solvents. However, when the mixture was taken up in benzene and chromatographed over alkaline alumina (activity 1, Woelm), elution with chloroform effected good separation. The crystals from the main fraction were recrystallized from cyclohexane to give 1.37 g of white prisms, mp 212.5–213°. In its nmr spectrum, signals were observed at τ 3.37 (4 aryl H), 6.25 (6 methoxyl H), 7.15 (8 methylene H), and 9.25 (6 methyl H).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16; mol wt, 296. Found: C, 81.12; H, 8.20; mol wt (vapor-phase osmometry), 275.

2,6-Dicyano-4-methoxytoluene (20). A solution of 235 g of 2,6-dibromo-4-methoxytoluene (II) and 170 g of cuprous cyanide in 300 ml of N-methyl-2-pyrrolidone was heated at 170° for 3 hr with stirring. Precipitation of cuprous bromide occurred during the reaction. At the end of the reaction time, the mixture was allowed to cool but, while still warm, 1 l. of water was added cautiously with stirring. The solid that separated was collected and washed with water. This was followed by successive washings with dilute nitric acid, aqueous ammonia, and water. The yellow-brown solid was then extracted four times with 500-ml portions of hot acetone by swirling and decantation. Concentration of the combined acetone extracts gave a residue which was dissolved in boiling chloroform and percolated through alumina (50 g) to remove tarry impurities. After concentration of the chloroform filtrate to 500 ml, it was diluted by addition of 1.5 l. of hot methanol. The solution, on cooling, deposited 90.0 g of white needles, mp 175–176°. Concentration of the filtrate to a volume of 500 ml followed by cooling caused the separation of an additional 31 g of crystals (total yield 121 g, 85%).

Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.53; H, 4.79; N, 16.54.

2,6-Dicarboxy-4-methoxytoluene (21). A mixture of 116 g of 2,6-dicyano-4-methoxytoluene (**20**) in a solution prepared from 150

g of potassium hydroxide and 750 ml of water was boiled under reflux until complete solution occurred (about 24 hr). When the solution had cooled, it was carefully acidified with 300 ml of concentrated hydrochloric acid. The solid that separated was collected, washed with water, and dried. The crystals obtained in this way weighed 132 g (99%) and were sufficiently pure for use in the next step. Recrystallization of a sample from isopropyl alcohol gave fine, white needles, mp 220.5–221.0°.

Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80; Found: C, 57.05; H, 4.96.

2,6-Dicarbomethoxy-4-methoxytoluene (22). A solution of 130 g of 2,6-dicarboxy-4-methoxytoluene (**21**) in 1 l. of a saturated solution of methanolic hydrogen chloride was boiled under reflux for 5 hr. The solution was then poured onto 1 kg of cracked ice. With care, the ester will solidify and can be collected by filtration. Usually, though, it was more convenient to extract with ether, dry, and concentrate. Distillation of the residue gave 123 g (84%) of a colorless oil, bp 192° (15 mm), which solidified in the receiver to give crystals, mp 40–42°. A sample for analysis was recrystallized from petroleum ether (30–60°) at ice-bath temperatures to give white crystals, mp 41–42°.

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.33; H, 5.92.

2,6-Bis(hydroxymethyl)-4-methoxytoluene (23). A solution of 73 g of 2,6-dicarbomethoxy-4-methoxytoluene in 750 ml of ether was added dropwise with stirring to a solution of 35 g of lithium aluminum hydride in 1.5 l. of anhydrous ether. The mixture was boiled under reflux for 5 hr and then stirred at room temperature overnight. The excess lithium aluminum hydride was destroyed by adding ethyl acetate followed by aqueous sulfuric acid. The ether layer was separated, washed with water, dried, and then concentrated. The solid residue was recrystallized from 900 ml of a 60% aqueous methanol solution to give 46 g (83%) of white crystals, mp 140–142°. Recrystallization from benzene gave fine needles, mp 142–143°.

The solubility of 2,6-bis(hydroxymethyl)-4-methoxytoluene in ether is rather low and in some instances it precipitated out of solution during addition of the aqueous sulfuric acid. In these cases the entire precipitate was collected, placed in a Soxhlet extractor, and extracted with chloroform to obtain crystalline **23**. Since **23** is quite water soluble, care must be exercised in its handling.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.26; H, 7.72.

The **diacetate** of **23** was obtained from a cyclohexane–petroleum ether mixture as white needles, mp 54°.

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.81; H, 6.81.

2,6-Bis(bromomethyl)-4-methoxytoluene (24). A solution of 24.0 ml of phosphorus tribromide in 50 ml of benzene was added with stirring over a period of 15 min to a solution of 40 g of 2,6-bis(hydroxymethyl)-4-methoxytoluene (**23**) in 400 ml of benzene. The resulting mixture was boiled under reflux for 15 min, cooled, decanted from inorganic residue, and poured onto 1 kg of ice. After the resulting mixture had been thoroughly stirred, the benzene layer was separated and concentrated. The solid residue was recrystallized from cyclohexane to give 47.6 g (70%) of white crystals, mp 133–134°.

Anal. Calcd for $C_{10}H_{12}OBr_2$: C, 38.99; H, 3.93. Found: C, 38.95; H, 3.91.

2,6-Bis(iodomethyl)-4-methoxytoluene (25). A mixture of 50.0 g of 2,6-bis(bromomethyl)-4-methoxytoluene (**24**) and 200 g of sodium iodide in 2.0 l. of dry tetrahydrofuran was boiled under reflux for 2 hr. Most of the solvent was then removed by distillation under reduced pressure, and 1.5 kg of cracked ice was added. The resulting precipitate was collected by filtration, washed with water, and dried. The solid was then taken up in 200 ml of methylene chloride and percolated through a short column of Florisil to remove yellow impurities. The methylene chloride solution was concentrated to 100 ml and then diluted with 200 ml of *cold* methanol. There separated 48.0 g (74%) of white plates, mp 138° (143° dec).

Anal. Calcd for $C_{10}H_{12}OI_2$: C, 29.86; H, 2.99. Found: C, 30.04; H, 3.10.

Dimerization of 25 to Give 8,16-Dimethyl-5,13-dimethoxy[2.2]-metacyclophane (19). A solution of 30.0 g of 2,6-bis(iodomethyl)-4-methoxytoluene (**25**) in 1.0 l. of dry tetrahydrofuran was added through a Hershberg dropping funnel over a period of 70 hr to a stirred suspension of 20.0 g of sodium granules in 1.0 l. of tetrahydrofuran containing 2.0 g of tetraphenylethylene while the reaction mixture was kept at room temperature under a nitrogen atmosphere. At the end of the addition, the unreacted sodium was removed by filtration, the filtrate was concentrated to dryness under reduced pressure, and the residue was shaken with a mixture of 500 ml of methylene chloride and 500 ml of water. Sufficient hydrochloric acid was added to assist the separation of the two phases, and the methylene chloride layer was separated and percolated through a short column (30 g) of Florisil. The filtrate was concentrated under reduced pressure and then redissolved in 50 ml of hot carbon tetrachloride. The carbon tetrachloride solution, on cooling, deposited 4.1 g of crystals whose nmr spectrum indicated the presence of a mixture of the desired metacyclophane (**19**) and tetraphenylethane. When the carbon tetrachloride filtrate was concentrated to 20 ml and then diluted with 60 ml of hot cyclohexane, the resulting solution deposited a gummy residue, whose nmr spectrum indicated the absence of metacyclophane. Evaporation of the cyclohexane mother liquors gave a pale yellow solid which was subjected to sublimation at 150° (0.02 mm) to give an additional 1.6 g of the metacyclophane–tetraphenylethane mixture. The combined fractions (4.1 + 1.6 g) were taken up in benzene and chromatographed over alkaline alumina (activity 1, Woelm). The main fraction, on elution with chloroform, gave 2.19 g (20%) of white prisms, mp 211–212°. The nmr spectrum of these crystals was in accord with the previous preparation of the metacyclophane and showed it to be of good purity.

Following the main fraction described above, a second, slower moving substance was eluted from the alumina column with chloroform. Concentration of the eluate gave 500–800 mg (5–8%) of white crystals which, after recrystallization from benzene, yielded white needles, mp 247–248°; nmr, τ 3.62 (singlet, 8 H), 6.40 (singlet, 12 H), 7.24 (singlet, 16 H), and 8.50 (singlet, 12 H). The nmr data and the molecular weight of the compound are in accord with a tetramer structure, similar to those observed previously.[7]

Anal. Calcd for $C_{40}H_{48}O_4$: C, 81.04; H, 8.16; mol wt, 592.8. Found: C, 81.03; H, 8.16; mol wt (vapor-phase osmometry), 557.

Although the first experiments were conducted on the dimerization of the diiodide **25**, subsequent studies have shown that the procedure given above is equally successful with the corresponding dibromide **24**. The results of a rather extensive study of this dimerization reaction have shown the procedure given above to be most satisfactory, and the yield quoted is readily reproducible. In individual runs yields as high as 27.5% have been obtained, but these have not been reproducible.

Conversion of 19 to the Bis-dienone 4. A. Oxidation with Ferric Chloride. A solution of 1.10 g of 8,16-dimethyl-5,13-dimethoxy-[2.2]metacyclophane (**19**) and 3.5 g of anhydrous ferric chloride in 100 ml of dry chloroform was stirred at room temperature for 3 hr. A reddish-brown inorganic complex precipitated and was collected by filtration. The solid, so obtained, was suspended in 100 ml of chloroform and shaken with 20 ml of 3 *N* hydrochloric acid until solution occurred. The chloroform layer was separated, washed with water, and concentrated. The resulting red-brown solid (1.14 g) was treated with Norit in 100 ml of boiling ethanol. After removal of the Norit, the solution was concentrated to 20 ml and allowed to stand overnight in the cold. There separated 910 mg (92%) of pale yellow needles, mp 265° dec; $\lambda_{max}^{cyclohexane}$ 225 mμ (ε 27,000); nmr, τ 3.75 (singlet, 4 vinyl H), 7.20 (multiplet, 8 methylene H), and 8.80 (singlet, 6 methyl H).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81; mol wt, 266. Found: C, 81.38; H, 6.99; mol wt (vapor-phase osmometry), 271.

B. Oxidation with Chromic Acid.[22] The chromic acid reagent was prepared by adding a solution of 2.67 g of chromium trioxide in 5 ml of water to 2.13 g of concentrated sulfuric acid in the cold and then adding water to dilute the solution, giving a total volume of 10 ml. Then, 0.70 ml (1.87 mmoles) of the chromic acid reagent was added dropwise with stirring to a suspension of 800 mg (2.70 mmoles) of 8,16-dimethyl-5,13-dimethoxy[2.2]metacyclophane (**19**) in 20 ml of acetone. Precipitation of a pale yellow complex was nearly complete in 5 min, and stirring was continued another 10 min before decomposing the complex by addition of 100 ml of water. The mixture was then extracted with three 50-ml portions of methylene chloride, and the combined extracts were washed successively with a 5% aqueous sodium bicarbonate solution and water before drying concentration. The resulting residue was crystallized first from methanol and then from methylene chloride

(22) We are indebted to Dr. E. Sturm for the details of this experiment.

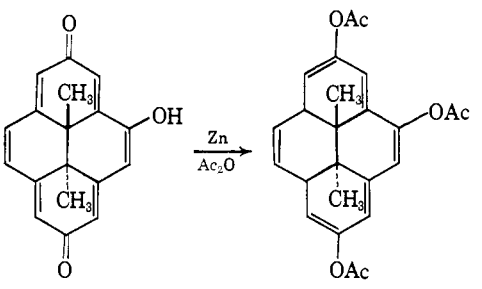
to give 680 mg (94%) of pale yellow needles, mp 265° dec, identical in all respects with the sample of **4** obtained from the ferric chloride oxidation (A). Although both procedures A and B give the bis-dienone **4** in high yields, the chromic acid oxidation (**B**) is easier to carry out and generally appears to be the preferred method.

Formation of *trans*-15,16-Dimethyldihydropyrene-2,7-quinone (30). A. Oxidation with N-Bromosuccinimide. To a solution of 860 mg (3.23 mmoles) of recrystallized bis-dienone **4** in 350 ml of dry carbon tetrachloride, there was added 1170 mg (6.50 mmoles) of N-bromosuccinimide and 15 mg of azobisisobutyronitrile as an initiator. When the mixture was boiled under reflux, it turned brown during the first 15 min and then during the next hour it became yellow. The mixture was concentrated under reduced pressure to dryness; the residue was taken up in methylene chloride and chromatographed over neutral alumina (Woelm, No. 3). The eluate fraction containing a bright yellow band was concentrated to give 760 mg (90.5%) of bright yellow needles, mp 252° dec (*in vacuo*); $\lambda_{max}^{cyclohexane}$ 268 mμ (ε 49,000), 277 (43,000), 312 (15,000), 325 (19,000), and 342 (13,000); nmr, τ 358 and 3.85 (singlets, 4 vinyl H), and 8.08 (6 methyl H).

Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.39; H, 5.42.

B. Air Oxidation in Alkaline Solution. To a mixture of 190 mg of bis-dienone **4** in 35 ml of methanol there was added a solution of 2.5 g of sodium hydroxide in 15 ml of water, and the resulting solution was stirred at room temperature for 12 hr. After concentration to remove most of the methanol, 50 ml of water was added, and the blue aqueous solution was extracted with methylene chloride. The methylene chloride extracts were combined, washed with water, dried, and concentrated. Sublimation of the residue followed by recrystallization of the sublimate gave 173 mg (91%) of bright yellow needles, mp 252° dec, identical in all respects with crystals obtained by procedure A.

A modification of this procedure can be made in which the solution is heated to 50–60° and oxygen is rapidly bubbled through the reaction mixture. In this case the reaction is complete in about 1 hr. However, the yield of quinone is variable and the intensity of the blue-green color of the aqueous layer increases. Thus, in a run employing 821 mg of the bis-dienone **4**, there was isolated 543 mg of the quinone **30**. However, acidification of the blue-green aqueous layer followed by extraction with ethyl acetate led to the isolation of 152 mg of a red solid, mp 270 dec. This substance was readily soluble in sodium carbonate, which suggested that it was a hydroxyquinone. Since attempts at recrystallization or purification were unsuccessful, 150 mg of the substance was dissolved in 5 ml of acetic anhydride containing 5 drops of triethylamine. Activated zinc dust was added in small portions over a 0.5-hr period causing the solution to turn a dark purple. The mixture was then poured into 25 ml of water, and the dark precipitate was extracted with chloroform. After the chloroform extract was washed with water, dried, and concentrated, the residue was taken up in benzene and chromatographed over Florisil. The eluate fraction containing the violet-green band was concentrated and the residue on crystallization from cyclohexane gave 57 mg of dark green crystals, mp 185–186°; $\lambda_{max}^{cyclohexane}$ 339 mμ (ε 88,000), 372 (40,000), 468 (9100), and 649 (2100); nmr, τ 1.40 (singlet, 2 H), 1.58 (singlet, 5 H), 7.42 (singlet, 3 H), 7.53 (singlet, 6 H), and 13.83 (doublet, 6 H). The spectral data show clearly the presence of the dihydropyrene system, and the nmr spectrum strongly suggests that the product is 2,4,7-triacetoxy-15,16-dimethyldihydropyrene (**36**). The red



35 **36**

solid precursor would thus be 4-hydroxy-15,16-dimethyldihydropyrene-2,7-quinone (**35**).

Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.92; H, 5.46. Found: C, 70.97; 70.98; H, 5.74, 5.60.

Nmr Spectrum of the Bis-dienone 4 in Alkaline Deuterium Oxide. A solution containing a small piece of sodium dissolved in 0.5 ml of deuterium oxide was introduced by syringe through a serum cap into an nmr tube containing 40 mg of the bis-dienone **4** under a nitrogen atmosphere. When solution was complete, the nmr spectrum was examined. The 15- and 16-methyl signal of **4** at τ 8.80 had disappeared and been replaced by a signal at τ 9.10 corresponding to the 8- and 16-methyls of **26**. The signals of the vinyl protons of **26** were gone and a new signal at τ 3.45 corresponding to the aromatic protons of **26** was present. There was no signal to be assigned to the vinyl hydrogens of **26** but, presumably, this signal is lost due to deuterium exchange. There was a signal at τ 7.15, though, indicating the presence of the bridging methylene protons. When the contents of the nmr tube were transferred to a methanol solution and oxygen was introduced, work-up of the reaction mixture as under procedure B above gave 35 mg of the quinone **30**.

8,16-Dimethyl-5,13-diacetoxy[2.2]metacyclophane (31). To a solution of 30 mg of the bis-dienone **4** in 5 ml of acetic anhydride containing 5 drops of triethylamine, zinc dust was added in small portions with stirring over a period of 0.5 hr. Ice water was added, and, when decomposition of the acetic anhydride was complete, the solution was extracted with chloroform. The residue (28 mg) after recrystallization from cyclohexane gave 19 mg of white crystals, mp 190–191°; nmr, τ 3.25 (singlet, 4 H), 7.20 (singlet, 8 H), 7.86 (singlet, 6 H), and 9.30 (singlet, 6 H). The signal at τ 9.30 is characteristic of the 8- and 16-methyls of [2.2]metacyclophanes.

Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.97; H, 6.86. Found: C, 75.26; H, 7.22.

2,7-Diacetoxy-*trans*-15,16-dimethyldihydropyrene (32). A solution of 50 mg of 15,16-dimethyldihydropyrene-2,7-quinone (**30**) in 5 ml of acetic anhydride containing 5 drops of triethylamine was cooled to 0°, and 150 mg of acetivated zinc dust was added in small portions with stirring over a period of 4 hr. The mixture was filtered and the filtrate added to 50 ml of ice water. The resulting green suspension was extracted with 150 ml of benzene; the benzene extract was washed with water and then concentrated under reduced pressure. Sublimation of the residue followed by recrystallization of the sublimate from carbon tetrachloride gave 61 mg (92%) of dark green needles, mp 210–211° (evacuated tube); $\lambda_{max}^{cyclohexane}$ 337 mμ (ε 97,400), 371 (38,900), 466 (10,250), and 643 (1840); nmr, τ 1.42 (singlet, 4 H), 1.63 (singlet, 6 H), 7.50 (singlet, 6 H), and 14.03 (singlet, 6 H).

Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.92, 76.12; H, 5.86, 5.91.

***trans*-15,16-Dimethyl-2,7,15,16-tetrahydropyrene (33).** The lithium aluminum hydride–aluminum chloride reagent was prepared by boiling a slurry of 4.0 g of lithium aluminum hydride in 240 ml of ether for 2 hr, adding 14.0 g of aluminum chloride, and boiling the resulting mixture an additional 2 hr before cooling it to −80°. A solution of 300 mg of the quinone **30** in a mixture of 70 ml of dry benzene and 150 ml of dry ether was then added dropwise with stirring over a period of 2 hr to the reagent mixture held at −80°. When the addition was complete the orange-tinted suspension was stirred at −80° for an additional 2 hr, before being allowed to warm to room temperature. The excess reagent was destroyed by addition of ethyl acetate, and then 50 ml of ice water was added. The organic layer was separated, washed with water, concentrated to a small volume, and chromatographed over Florisil using petroleum ether (30–60°) for elution. The deep yellow eluate fraction was concentrated and the crystalline residue was recrystallized from methanol to give 154 mg of yellow needles, mp 168–170°; $\lambda_{max}^{cyclohexane}$ 248 mμ (ε 62,000), 257 (81,500), 340 (67), 359 (79), 379 (90), and 402 (67); nmr, τ 4.03 (singlet, 4 H), 4.30 (triplet, 4 H, J = 3 cps), 7.03 (triplet, 4 H, J = 3 cps), and 9.00 (singlet, 6 H).

The chief side product in this preparation appeared as a deep green band during chromatography and corresponded to **1**. Thus, for the preparation of **1** both fractions from the chromatogram were combined and used in the dehydrogenation step.

***trans*-15,16-Dimethyldihydropyrene (1). A. By Catalytic Dehydrogenation.** The experiment described above for the preparation of **33** was repeated but, after chromatography, the yellow and green eluates were combined and concentrated to give 225 mg of crystalline residue. This was dissolved in 200 ml of freshly distilled cyclohexane, 300 mg of a 30% palladium-on-charcoal catalyst was added, and the mixture was boiled under reflux for 12 hr. After removal of the catalyst and solvent, the residue was sublimed at 100° (0.01 mm) to give 198 mg (75%) of dark green crystals. For analysis, a sample was taken up in petroleum ether (bp 30–60°) and chromatographed over neutral alumina (Woelm, No. 2). Concentration of the dark green eluate gave a crystalline residue

which, after recrystallization from methanol, was obtained as dark green plates, mp 119–120°; $\lambda_{max}^{cyclohexane}$ 337.5 mμ (ε, 87,000), 377 (37,000), 463 (6000), 528 (58), 536 (58), 586 (110), 598 (150), 611 (210), 627 (230), 634 (210), and 641 (330); nmr, τ 1.33 (6 H), 1.43 (2 H), 1.77–2.02 (2 H), and 14.25 (6 H).

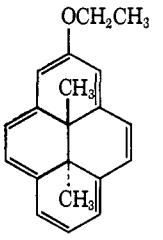
Anal. Calcd for $C_{18}H_{16}$: C, 93.06; H, 6.94. Found: C, 92.82; H, 7.13.

B. By Dehydrogenation of 33 with DDQ. A mixture of 50 mg of **33** and 100 mg of 2,6-dichloro-3,5-dicyanoquinone (DDQ) in 25 ml of benzene was boiled under reflux for 2 hr. The solution was concentrated to dryness; the residue was taken up in a pentane–ether mixture (20:1) and chromatographed over neutral alumina (Woelm, No. 1). The green eluate fraction was concentrated to dryness, and the residue was recrystallized from methanol to give 48 mg (100%) of dark green plates, mp 119–120°, identical with the specimen obtained by procedure A.

***trans*-15,16-Dimethyl-2,7-dideuteriodihydropyrene (34).** In order to prepare the deuterio derivative **34** in which the 2- and 7-positions could be assigned to the deuterium atoms with certainty, it was necessary to devise a procedure of converting the quinone **30** to dimethyldihydropyrene (**1**) without using catalytic dehydrogenation. This was found to be possible by carrying out the reduction of the quinone at room temperature with inverse addition. Thus, to a solution of 300 mg of quinone **30** in 10 ml of benzene, 300 ml of ether was added, and then at room temperature the lithium aluminum hydride–aluminum chloride reagent (described under the preparation of **33**) was added dropwise with stirring. The resulting mixture was allowed to stir overnight before decomposing the excess reagent by addition of water. The ether layer was separated, washed with water, and concentrated. The residue was taken up in petroleum ether and chromatographed over Florisil. Elution with a petroleum ether–ether mixture (20:1) led to the separation of two dark green bands. The first of these bands was collected and then chromatographed again over neutral alumina (Woelm, No. 1). Concentration of the main eluate fraction gave 84 mg (32%) of dark green plates, mp 119–120°, identical in all respects with samples of **1** described previously.

When this experiment was repeated using lithium aluminum deuteride in place of lithium aluminum hydride, the corresponding 2,7-dideuterio-*trans*-15,16-dimethyldihydropyrene (**34**) was obtained in comparable yield. In the nmr spectrum, **34** showed two incompletely resolved singlets (4 H each) at τ 1.33 and 1.37 and a sharp singlet at τ 14.28.

The second dark green band from the original chromatography was also purified by rechromatography over neutral alumina (Woelm, No. 2) using a petroleum ether–ether mixture (20:1). This gave 60 mg of a dark green oil which could not be induced to crystallize. It was unstable toward light and air. Its visible and ultraviolet spectrum showed absorption maxima at 351, 382, 462, and 615 mμ, clearly showing it to be a dihydropyrene derivative. Its nmr spectrum showed signals at 0.95–2.40 (multiplet, 9 H), 5.45 (quartet, 2 H), 8.34 (triplet, 3 H), and 13.97 (singlet, 6 H).



37

The nmr spectrum strongly suggests structure **37**, although the mode of its formation is not apparent.

Aromatic Molecules Bearing Substituents within the Cavity of the π-Electron Cloud. Chemical Properties of *trans*-15,16-Dimethyldihydropyrene[1,2]

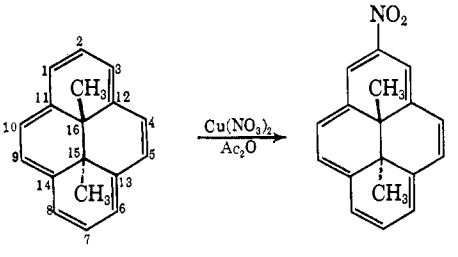
J. B. Phillips, R. J. Molyneux, E. Sturm, and V. Boekelheide

Contribution from the Department of Chemistry, University of Oregon, Eugene, Oregon. *Received October 19, 1966*

Abstract: It is shown that *trans*-15,16-dimethyldihydropyrene (**1**) undergoes bromination, deuteration, Friedel–Crafts alkylation and acylation, and nitration. These typical aromatic electrophilic substitution reactions occur more readily than with benzene, giving mono- and disubstitution products resulting from attack at the 2- and 7-positions.

In an accompanying paper,[2] the synthesis of *trans*-15,16-dimethyldihydropyrene (**1**) is described. All of the physical properties of **1** support the conclusion that this molecule is aromatic, having a 14-π-electron perimeter with methyl groups being inserted into the cavity of the π-electron cloud. The present investigation was undertaken to examine the chemical properties of *trans*-15,16-dimethyldihydropyrene to see whether it would exhibit the substitution reactions typically associated with benzene.

The first reaction to be investigated was nitration. Under the very mild conditions, cupric nitrate in acetic anhydride at 0°, previously used for nitration of azulene[3] and [3.2.2]cyclazine,[4,5] *trans*-15,16-dimethyldihydropyrene underwent nitration in essentially quan-



1 **2**

(1) We express our deep appreciation to the National Science Foundation for their support of this work.

(2) For the previous communication in this series, see V. Boekelheide and J. B. Phillips, *J. Am. Chem. Soc.*, **89**, 1695 (1967).

(3) A. G. Anderson, Jr., J. A. Nelson, and J. J. Tazuma, *ibid.*, **75**, 4980 (1953).

(4) R. J. Windgassen, W. H. Saunders, Jr., and V. Boekelheide, *ibid.*, **81**, 1459 (1959).

(5) V. Boekelheide and T. Small, *ibid.*, **83**, 462 (1961).