SYNTHESES AND CONFORMATIONAL STUDIES OF NOVEL AROMATIC COMPOUNDS

by

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B. Sc., University of Leiden, 1972

M. Sc., University of Leiden, 1977

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT

OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

ACCEPTED
FACULTY OF GRADUATE STUDIES

in the Department

of

Chemistry

DATE _____

we accept this dissertation as conforming

to the required standard

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March 1982

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ABSTRACT

The synthesis of *anti*-15-phenyl-16-methyldihydropyrene, a molecule having an aromatic π-electron cloud within and more or less perpendicular to another π-system, has been achieved. ^{1}Hmr data indicate the phenyl ring to be freely rotating and, furthermore, the *ortho* protons of the phenyl substituent to be the most shielded aryl protons known today. No interaction could be detected between the two π-electron systems of the aforementioned dihydropyrene, either by UV or ESR (ENDOR) spectroscopy.

Ring current shielding calculations, based on the Johnson-Bovey tables, have been performed for the phenyl protons of this dihydropyrene using one to four current loops in the annulene skeleton. A four current loop model was shown to give a fair correlation between calculated and observed shielding values.

Four new 2,11-dithia[3.3]metacyclophanes with one or two internal phenyl substituents have been synthesized and shown to undergo a dynamic process of phenyl ring twisting. Although these thiacyclophanes were obtained as *syn* and *anti* conformers, only one conformer was found for the dithiacyclophane with both a phenyl group and a hydrogen atom as internal substituents. Based on an X-ray crystallographic structure determination, this thiacyclophane was shown to exist in the crystalline state as the *syn* conformer. The phenyl substituent underwent a similar dynamic process as described above. This fluxional process was also found in three new [2.2]metacyclophanes

with internal phenyl substituents.

The barrier to the fluxional process in these systems has been determined using the coalescence temperature method. The twisting process of the internal phenyl substituent in the metacyclophanes is thought to be restricted by the non-bonded interaction between the *ortho* protons of the phenyl group and the methylene bridge protons.

Furthermore, it was shown that 2,11-dithia[3.3]metacyclophane (internal hydrogens) possessed the *syn* conformation in the solid state as well as in solution. Based on this observation many simple dithia[3.3]metacyclophanes have been reassigned the *syn* conformation.

A search for new synthetic methods to eliminate sulfur from thiametacyclophanes, in order to prepare the labile metacyclophanedienes was in so far unsuccessful that no improvements over existing methods were found.

EXAMINERS:

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ACKNOWLEDGEMENT

I would like to thank my supervisor, Dr. R.H. Mitchell, for his guidance and encouragement throughout the course of this work.

The support from members of the department is also gratefully appreciated.

GLOSSARY OF TERMS AND ABBREVIATIONS

^{13}Cmr	carbon-13 magnetic resonance (spectrum)
DIBAL	diisobutylaluminium hydride
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
^{1}Hmr	proton magnetic resonance (spectrum)
HOAc	acetic acid
ir	infrared absorption spectroscopy
Me	methyl
ms	mass spectrum
$NaBH_4$	sodium borohydride
NBS	N-bromosuccinimide
NMP	1-methyl-2-pyrrolidinone
Ph	phenyl
ppm	parts per million
THF	tetrahydrofuran

PART I

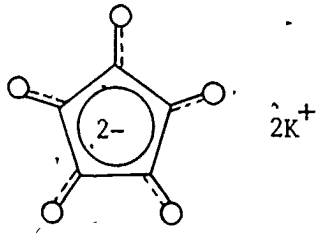
SYNTHESIS AND CONFORMATIONAL BEHAVIOUR OF A DIHYDROPYRENE AND SOME METACYCLOPHANES WITH INTERNAL PHENYL SUBSTITUENTS

CHAPTER ONE

INTRODUCTION

1.1 *Aromaticity: not a fragrant concept at all.*

If asked "what was the first aromatic compound ever isolated", most chemists would probably answer "benzene", crediting Faraday's detection of benzene[1] as a pyrolysis product of oil in 1825. Yet slightly earlier, dipotassium croconate 1, an aromatic compound of a totally different sort, was prepared by Gmelin[2].



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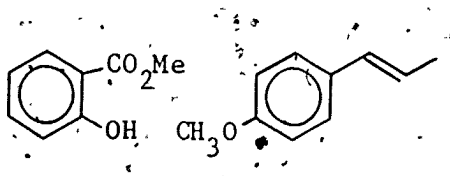
However, benzene has to be credited for the development of the concept of aromaticity[3].

The designation "aromatic" was first applied to a group of natural products such as methyl salicylate 2 (oil of winter green), anethole 3 (aniseed), vanillin 4 (vanilla beans) but also compounds like menthol 5 (peppermint oil) or camphor 6 (camphor laurel), on account of their characteristic odours or flavours.

When it was recognized (Kekulé (1865)[4]) that many of these substances were derivatives of benzene, the classification acquired a structural significance and the "aromatic" series implied "benzene and its derivatives".



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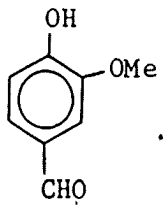

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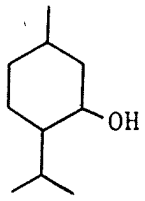

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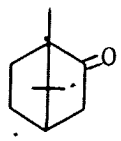

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Soon, however, the concept of aromatic character changed into a chemical criterion and became identified with the unique stability of the phenyl group and its preference for reacting by substitution rather than addition. As a consequence it was the properties of the transition state which were chiefly considered.

Although some justification of benzene-like stability was gained in the principle of the aromatic sextet[5] (1925), the necessary theoretical basis was provided by Hückel[6] in the early 1930's in terms of the Molecular Orbital (MO) theory. His conclusions have been summarized in the now familiar Hückel rule which states that *monocyclic systems with (4n+2)π-electrons will be aromatic, whereas those with (4n)π-electrons will not.* More recently the periphery modification of Platt[7] and the polycyclic modification of Volpin[8] have been put forward to broaden the existing Hückel rule.

MO theory also provided a way to calculate resonance energies, a property of the ground state of the molecule. This resonance energy, defined as the difference between the total π-electron energy of a given conjugated molecule and of a corresponding hypothetical reference structure, has often been utilized, with variable success, for understanding and predicting aromatic stability[9]. Redefinition of the

reference energy by Dewar[10] in 1965, led to what is now known as Dewar resonance energies, considered to be the best "aromaticity" values available.

Later modifications of resonance energy (RE) calculations (based on different definitions of the hypothetical reference energy) were made by Hess and Schaad[11] (RE from π-bond energies), Herndon[12] (RE from Kekulé structures) and independently by Aihara[13] and the Zagreb group[14] (RE from graph theory). The use of graph theory for resonance energy calculations has an advantage over Dewar's method in that it can be applied to ions and radicals. A graph theoretical approach has also been used by Herndon (RE from photoelectron spectra[15] or bond orders[16]) and Randic[17] (enumeration of conjugated circuits). It should be pointed out that all these different methods for calculating resonance energies make use of or compare their values with the ones obtained by Dewar. A close fit is then considered to be proof of the validity of the new method.

Aromatic compounds are not only characterized by their resonance energy but also by, for instance, the anisotropy of their diamagnetic susceptibility and changes in bond lengths and charge distribution related to the delocalization of the π-electrons.

So there has thus been a continuous process of transforming the meaning of aromaticity from the chemical definition, which emphasizes the energy content of the molecule in the excited state, to the physical viewpoint, which underlines the properties of the molecules in the ground state.

1.2 *Ring Currents as a Criterion for Aromaticity.*

Since the calculation of resonance energies is strongly dependent on the chosen degree of accuracy and on the personal selection of standards, the idea of defining aromaticity by the physical concept of ring currents found wide application.

The introduction of this concept can be attributed to the free electron model of Pauling[18] who calculated the diamagnetic anisotropy of benzene on the hypothesis[19] that the abnormally large diamagnetic susceptibility in the direction perpendicular to the basal plane arises from the Larmor precession of the six π-electrons in orbits including many nuclei. This idea was later used by Pople[20] to explain the NMR deshielding of the benzene ring proton with respect to the ethylene proton. According to this model, an applied magnetic field (H^o), perpendicular to the plane of a benzene ring, will induce a circulation of the π-electrons, called a diamagnetic ring current. This ring current will then generate a second magnetic field (H^c), opposed to H^o (figure 1), which will have the effect of increasing the magnetic field outside the plane of the ring (deshielding), while the apparent field inside the ring is decreased (shielding). This simple ring current model led to a new definition of aromaticity as being *the ability to sustain a magnetically induced ring current of π-electrons*[21].

Ring current effects on proton shifts have played a crucial part in elucidating the chemistry of the annulenes[22]. Initially, the only neutral annulene known was benzene 7 ([6]annulene), as the severely

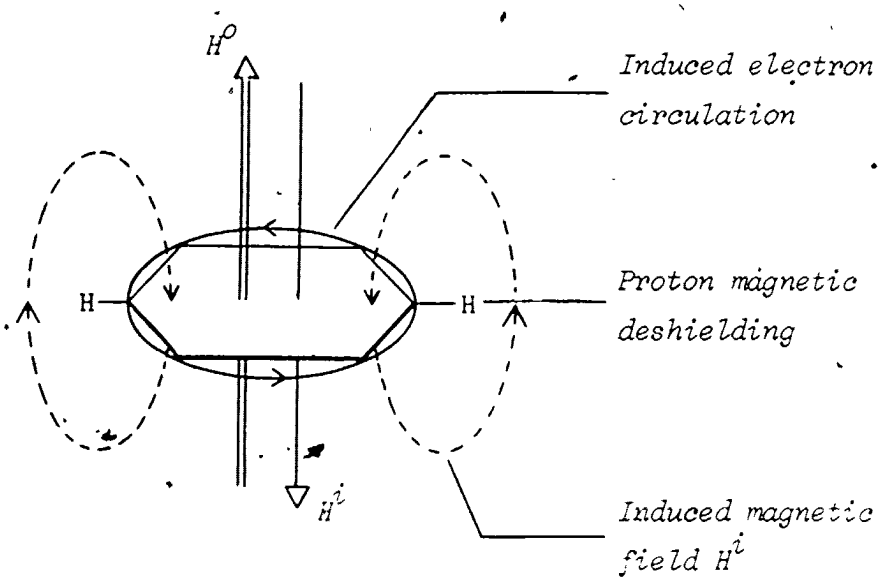
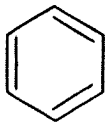


FIGURE 1. Magnetically induced electron circulation and proton magnetic deshielding in benzene.

non-planar cyclooctatetraene 8 ([8]annulene) may be excluded from consideration. More annulenes soon became available[23] and at first their proton shifts[24] seemed to disagree with simple ring current theory. However, gross discrepancies disappeared when the conformational mobility of some of these compounds was realized and low temperature spectra were obtained where necessary. The higher homologs of benzene, the [4n+2]annulenes, have very low field absorptions for outer ring protons, and very high field absorptions for inner protons, as compared to the normal value of $\delta 5.70^*$ for the non-aromatic [8]annulene 8 (see table 1). The only exceptions to this rule are the

*All δ values in ppm from tetramethylsilane (TMS) as internal standard.



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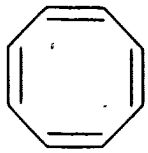
[6]annulene



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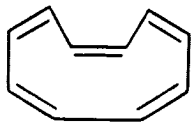
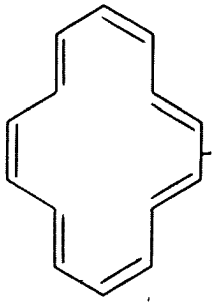
[8]annulene



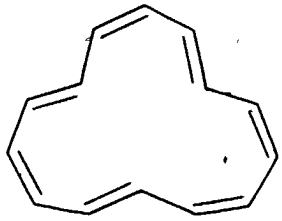
9A

9B

[10]annulenes



10A



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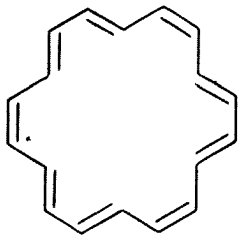
[14]annulenes



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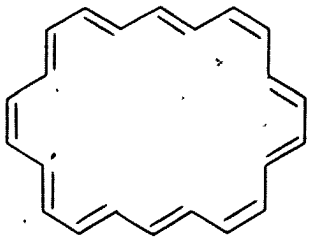
[18]annulene



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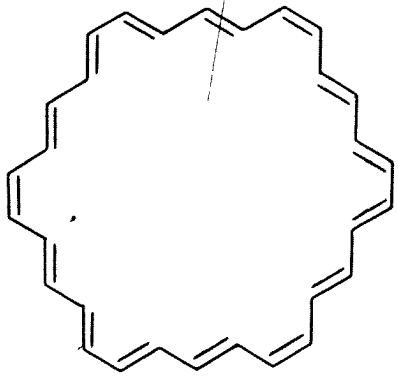
[22]annulene



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[30]annulene

TABLE 1: ^{1}Hmr δ values of [4n+2]annulenes and [8]annulene.

Annulene	Inner H	Outer H	Reference
[6] - 7		7.27	25
[8] - 8		5.70	26
[10] - 9A	------- 5.67[a]	-------	27f
[10] - 9B	------- 4.14[a]	-------	27f
[14] - 10A	-0.61[b]	7.88[b]	29a
[14] - 10B	3.55[c]	6.82[c]	29a
[18] - 11	-2.88[d]	9.25[d]	29
[22] - 12	-0.40, -1.20[e]	9.65 - 9.30[e] 9.10 - 8.50[e]	30
[30] - 13	no ^{1}Hmr obtained		32

[a]Spectrum taken at -40°C. [b]Spectrum taken at -126°C.
[c]Spectrum taken at -155°C. [d]Spectrum taken at -60°C.
[e]Spectrum taken at -90°C.

[10]annulenes[27]. Spectroscopic evidence led to the proposed structures 9A and 9B for the two isolated isomers of [10]annulene[27f]. This assignment turned out to be consistent with theoretical calculations[28]. Considering the higher [4n+2]annulenes, controversy still exists about the ground state structure of [18]annulene 11[31], whereas [26]annulene has not been prepared yet. Unfortunately, the"aromaticity" of [30]annulene 13 could not be tested by ^{1}Hmr[32].

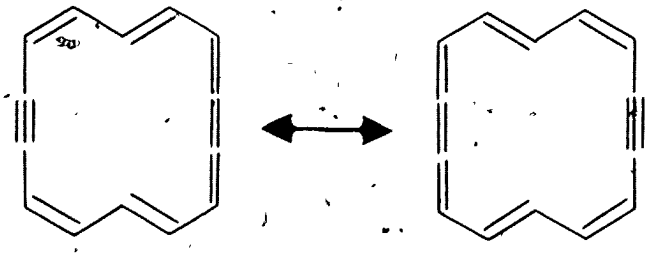
Although the [4n+2]annulenes, possessing 14 to 22 carbon atoms, are fluxional (see table 2), they all show a diamagnetic ring current effect, *i.e.*, the outer protons absorbing to low field, the inner protons to high field. Compounds exhibiting this phenomenon are now

TABLE 2. Free energy of activation and coalescence temperature for the ring inversion processes of some [4n+2]annulenes, as obtained by ^{1}Hmr.

Annulene	$\Delta G^{\neq}$ (kJmol^{-1})	T (*coal.*)	Reference
[14] - 10A	42.4 (0°C)	- 44°C	29a
[14] - 10B	30.1 (0°C)	*ca.* -110°C	29a
[18] - 11	60.1 (0°C)	41°C	29b
[22] - 12	53.6 (20°C)	20°C	30

called *diatropic*, while those with the reversed, paramagnetic ring current are called *paratropic*[33].

Since the degree of π-electron delocalization is related to the planarity of the conjugated system, stronger "ring currents" are expected in more rigid annulenes. One such group are the dehydroannulenes, prepared by Sondheimer[23] and Nakagawa[34], where the acetylene unit(s) increases the rigidity of the π-system.



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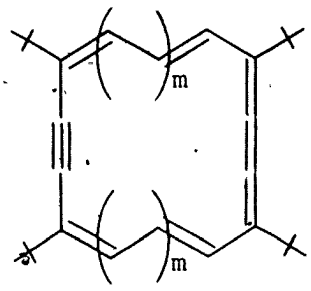
An interesting example is 1,8-didehydro[14]annulene 14[35] for which identical Kekulé structures can be drawn, as in the case of benzene. The rigidity of 14 is indicated by the high field ^{1}Hmr absorption of its inner protons: δ-5.48. This implies a much larger

"ring current" for 14 than for the flexible [14]annulene 10A. Nakagawa has reported an efficient synthesis of the tetra substituted derivative of 14 as well as the higher homologs of the didehydro-[4n+2]annulenes 15[36]. Unlike the various [4n+2]annulenes (table 1),



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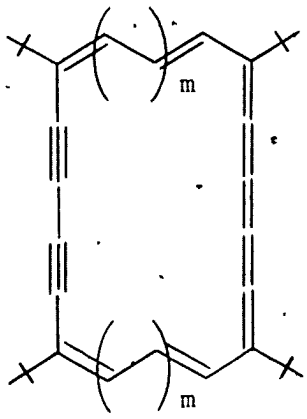

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all these didehydro- and tetradehydroannulenes have essentially the same geometry. This makes it possible to study the effect of increasing the value of n in aromatic (4n+2)π-electron systems, keeping the geometry largely unchanged. It can be seen from the ^{1}Hmr data (see table 3) that the diamagnetic shielding of the inner protons becomes progressively less as the value of n increases. However, the ring current is still evident in the didehydro[30]annulene 15 (m=5). This observation increases the uncertainty about the prediction[10a,37] that bond length equalization, a criterion for π-electron delocalization, is going to fail for large polyenes (somewhere between 22- and 26-membered rings).

Other constraints, apart from the acetylene-cumulene type bonds, for increasing the planarity of the annulene rings, have been put forward by Vogel[39] and Boekelheide[40].

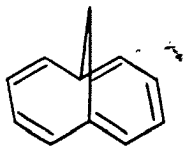
TABLE 3. ^{1}Hmr δ values of some didehydro- and tetradehydro-[4n+2]annulenes.

Didehydro-annulenes 15	Inner H	Outer H	Reference
[14] m=1	-4.39	9.42	38
[18] m=2	-3.61	9.82, 9.32	38
[22] m=3	-0.83	9.16, 8.76	38
[26] m=4	*ca.* 1.9	8.23, 7.93	38
[30] m=5	3.5	7.5	38
Tetradehydro-annulenes 16			
[18] m=1	-4.89	9.86	38
[22] m=2	-3.44	10.16, 9.67	38

Vogel[41] noticed that, if the conformational mobility of the [10]annulene ring (9A and 9B) is locked by a bridging methylene group, the resulting molecule 17 does exhibit aromatic character, whereas the open form is extremely reactive[27] and not diatropic at all (table 1). The ^{1}Hmr chemical shift data for some of these methano bridged annulenes are given in table 4.

These annulenes also constitute a group of compounds well suited for the correlation of the diamagnetic ring current of a $(4n+2)\pi$ system with changes in geometry of the carbon framework. The stepwise bending of the carbon periphery of the *syn*-bridged [14]annulenes can be monitored by the increased shielding of the outer ring protons in the series 23 - 27 (see table 4)*. From these data it is apparent that

*For X-ray data of methano bridged annulenes see reference 42.



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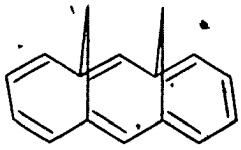

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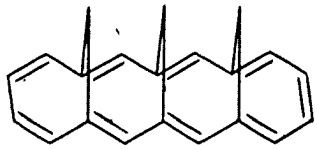

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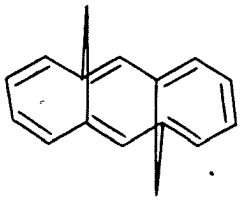

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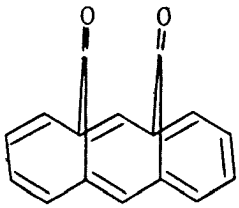

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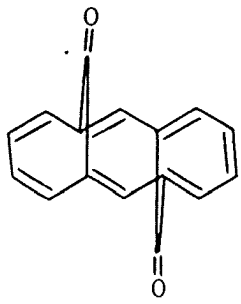

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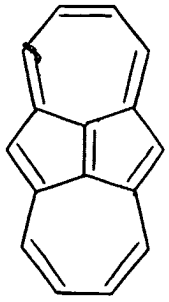

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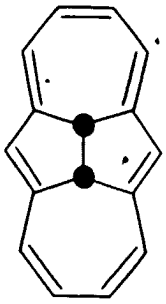

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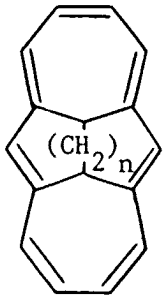
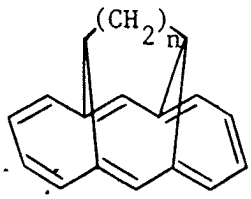
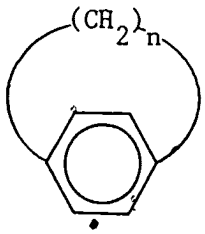




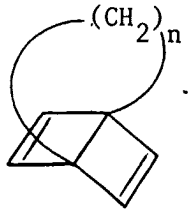
25 (n=1)
26 (n=2)
27 (n=3)

the relatively high degree of bending, achieved in this series, does not reduce the extent of π-electron delocalization significantly.

The same approach of a systematic departure from planarity has been used for the benzene ring in cyclophanes[43]. For instance, for the [n]paracyclophanes 28 and 29, although aromatic[44], an out of plane bending of the benzene ring has been reported of 9° and 17° respectively[45]. Even the [6]paracyclophane 30, in spite of a calculated



28: (n=8)
29: (n=7)
30: (n=6)
31: (n=5)



32: (n=4)
33: (n=3)

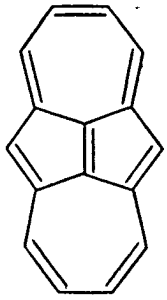
deviation of 22° from coplanarity of the benzene ring[46], is still "aromatic" by the ring current criterion[47]. The Dewar isomers of [4]- and [3]paracyclophane (32[48] and 33[49] respectively) have also been isolated, but no isomerization to the corresponding paracyclophanes has been detected. So it seems that the still elusive [5]paracyclophane 31 will form the crossover boundary between stability of benzene and Dewar benzene valence isomers, and therefore define the limit of aromaticity in the [n]paracyclophane series[50].

Comparison of *syn*-18 and *anti*-20 of the dimethano[14]annulenes shows a decrease in diatropicity for 20, as judged from the chemical shift values of the ring and bridge protons. X-ray data[42b] indicate bond length alternation for the carbon framework of 20, not because of deviation from planarity, but mainly due to the increased torsion angles (up to 75°) which prevent effective *p*-orbital overlap. However, for the comparable dioxo compound 22 no bond length alternation or increased torsion angles can be detected[42c], so that, based on geometrical parameters, *anti*-22 is *aromatic*. On the other hand, ^{1}Hmr data show an increased shielding for the ring protons of 22 compared to 21 (same increase in shielding can be noticed in going from 18 to 20), which, together with chemical behaviour[52e], implies an *olefinic*

nature for 22. This is a problem reminiscent to the controversy about the [18]annulene 11 structure[31].

Vogel's methano bridged [10]annulene 17 is not the only rigid, 10 π-electron system known. Recently, the tricyclic [10]annulene 41 has been prepared, and chemical, as well as ^{1}Hmr data indicate it to be aromatic[51].

Boekelheide[53], in his synthesis of *trans*-15,16-dimethyldihydropyrene 38, used an ethano bridge, instead of methylene bridges,



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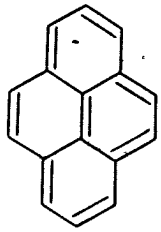

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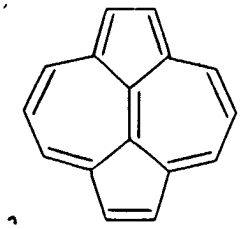

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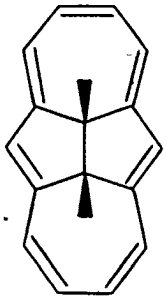

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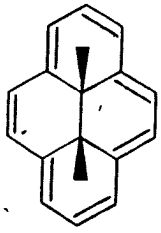

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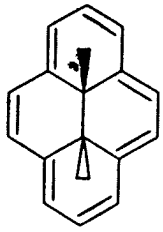

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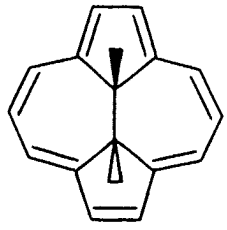

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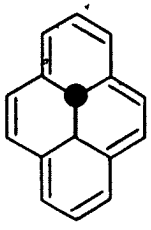

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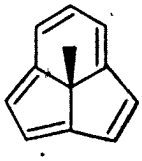

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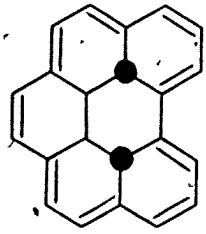

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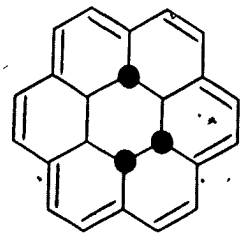

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TABLE 4. ^{1}Hmr δ values of bridged [4n+2]annulenes.

Annulene	Inner H	Outer H	Reference
[10] - 17	-0.5	7.5 - 6.8	41
[14] - 18	0.9,-1.2	8.0 - 7.0	52a
[18] - 19	1.32, 0.53,-0.45	7.70 - 6.70	52b
[14] - 20	2.48, 1.88	6.33 - 6.20	52c
[14] - 21	---	8.53 - 7.81	52d
[14] - 22	---	7.78 - 6.85	52e
[14] - 23	---	8.95 - 8.30	58
[14] - 24	-1.82	8.17 - 7.82	52f
[14] - 25	-0.61,-1.16	7.88 - 7.55	52g
[14] - 26	0.52,-0.96	7.86 - 7.12	52h
[14] - 27	0.55,-0.11	8.10 - 6.95	52i
[14] - 34	---	8.08 - 7.90	58
[14] - 35	---	8.72 - 7.38	58
[14] - 36			59
[14] - 37	-2.06	8.74 - 7.50	55
[14] - 38	-4.25	8.67 - 7.98	53
[14] - 39	-4.53	8.77 - 8.04	57
[14] - 40	-5.49	8.58 - 7.89	54
[10] - 41	-1.67	7.92 - 7.53	51
[18] - 42	-2.58,-2.86	9.10 - 7.47	56
[18] - 43	-6.44,-6.82,-7.88	9.48 - 9.40	56

to constrain the [14]annulene in a more or less planar structure; this type of bridging is based on the geometry of pyrene 34. Within this system, the internal hydrogens of *trans*-15,16-dimethyldihydropyrene 40[54] appear in the ^{1}Hmr at δ-5.49, the highest value obtained so far for the [14]annulenes. However, the absolute record for any type of neutral annulene is held by hexahydrocoronene 43[56], where two of the

internal hydrogens resonate as high as δ-7.88.

Spectroscopic[58] and theoretical[17] findings suggest that pyrene 34 and the two symmetrical isopyrenes 23 and 35, can be described as planar, vinyl-bridged [14]annulenes with perimeter type conjugation and, thus, as precursors of the annulenes 36 - 39. There exists, therefore, a remarkable geometrical parallel between these three types of bridged [14]annulenes. The anthracene perimeter of *cis*-36 is slightly bent[60] (saucer shaped), comparable to the curved shape of *cis*-dimethyldihydropyrene 37, whereas the C-*14* peripheries of *trans*-38[61] and *trans*-39[57] are both planar. A comparison of the ^{1}Hmr chemical shift data for 36 - 37 and 38 - 39 (table 4) show that all three systems sustain a diamagnetic ring current equally well. However, Vogel's system (methano bridged annulenes like 18) is probably only suitable for *cis*-type [14]annulenes, since the *trans* isomer of 36, if synthesized, will be a very reactive species (*c.f.*, *anti*-20).

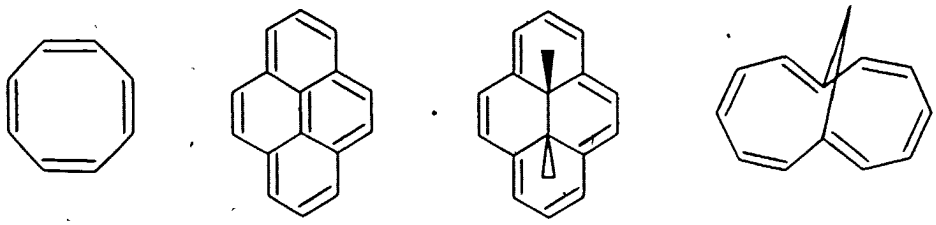
Compared with these [4n+2]annulenes, the [4n]annulenes show a complete opposite magnetic effect, *i.e.*, the outer protons absorb to high field, the inner protons to low field. This implies a paramagnetic ring current[62], flowing in the opposite direction to the diamagnetic ring currents found in the [4n+2]annulenes. In principle, it should be possible to convert a [4n+2]annulene into a (4n)π-system by adding or subtracting two electrons (and *vice versa*). This change in total π-electrons should lead then to opposite ring currents in the neutral and charged species, and manifests itself from chemical shift values.

This type of transformation was first realized with cyclooctatetraene 8[63] (a [4n]annulene). However, the ^{1}Hmr of the dianion was almost identical to the neutral species, indicating that the deshielding effect of the diamagnetic ring current is balanced by the shielding due to the excess electron density. Also the paramagnetic ring current of 8 is impaired due to the non-planar (tub-shaped) structure of 8.

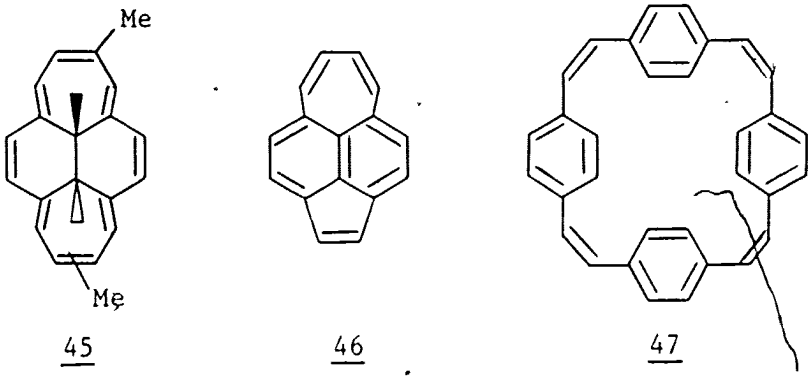
As was indicated before, *trans*-dimethyldihydropyrene 38 has a planar perimeter and is therefore an excellent candidate for testing the postulated ring current reversal. In fact the conversion of the neutral [14]annulene 38 to its dianion 38^{2-} involves the transformation of a strongly diatropic to a strongly paratropic system, as indicated by the shift of the internal methyl protons: from δ-4.25 to δ21.00[64].

As examples for the reversed case, where a paratropic [4n]annulene is changed into a diatropic (4n+2)π-system, one can use 1,7-methano[12]annulene 44[65a] and the bridged [16]annulene 45[67]. The crystal structure of 44 shows it to be nearly planar, but with complete bond alternation, due to increased torsion angles[66]. On the other hand, compound 45 is expected to have a puckered perimeter[67]. However, their respective dianions are diatropic (see table 5). For instance, the bridge methylene protons of 44 undergo an upfield shift from δ6.04 in the neutral molecule to δ-6.44 in the dianion[65b].

Since a two-electron reduction of a [4n+2]annulene generates a paratropic species, further reduction to the tetraanion should then



8 34 38 44



45 46 47

provide the next higher homolog of the [4n+2]annulene, and therefore restore the diatropicity of the system. This effect can clearly be seen from the dianion and tetraanion of pyrene 34 (table 5). The added electron density in the tetraanion 34^{4-}, however, increases the shielding of the ring protons and therefore opposes the effect of the diamagnetic ring current. Acepleiadylene 46, which, like pyrene 34, can be described as a vinyl-bridged [14]annulene[70], shows a similar pattern for its dianion and tetraanion.

An interesting example of a peripheral ring current can be found in the di- and tetraanion of [2$_4$]paracyclophanetetraene 47[71]. Whereas the neutral molecule 47 shows chemical shifts typical for aromatic and olefinic protons, the dianion 47^{2-} shows absorption of the internal benzene protons at δ-7.07. This implies a destruction of the

TABLE 5. ^{1}Hmr δ values of annulenes and their dianions and tetraanions.

Annulene	Inner H	Outer H	Reference
[8] - 8	---	5.70[a]	63
[10] - 8^{2-}	---	5.70[a]	63
[12] - 44	6.04	5.54 - 5.12	65b
[14] - 44^{2-}	-6.44	7.16 - 6.28	65b
[14] - 38	-4.25	8.67 - 7.98	64
[16] - 38^{2-}	21.00	-3.19 - 3.96	64
[16] - 45	4.81	4.50 - 0.59	67
[18] - 45^{2-}	-5.91,-5.99	8.53 - 6.68	67
[14] - 34	---	8.08 - 7.90	58
[16] - 34^{2-}	---	2.22 - 0.01	58
[18] - 34^{4-}	---	5.68 - 4.40	68
[14] - 46	---	8.33 - 6.89	69
[16] - 46^{2-}	---	1.53, -2.05	69
[18] - 46^{4-}	---	5.96 - 3.56	69
47	7.37	7.37 , 6.48	71
[26] - 47^{2-}	-7.07	9.56 , 9.26	71
[28] - 47^{4-}	12.76	4.48 , 2.09	71

[a]Signals of 8 and 8^{2-} are only 0.005 ppm apart[63]; δ5.70 taken from reference 26.

π-electron delocalization in the benzene rings of 47 in favor of a perimeter conjugation in the dianion. Further reduction to the tetraanion 47^{4-} generates a paratropic species that can be considered as a [28]annulene, with the internal benzene protons resonating at δ12.76.

The concept of a π-electron ring current in planar conjugated systems has clearly been of value in interpreting ^{1}Hmr spectra. From

the data, obtained in the field of annulene chemistry, it can be concluded that, in general, diatropicity gives a good *qualitative* picture of the aromaticity of the system considered. However, diatropicity is not the only magnetic property of conjugated (aromatic) systems that has been related to "aromaticity".

Dauben, for instance, proposed the diamagnetic susceptibility exaltation[72] as a criterion for aromaticity. Although this method is related to a theoretically well defined quantity, the London diamagnetism, it is still empirical in character. Closely related is the Faraday effect, proposed as a measure for aromaticity by Labarre[73]. Yet another ring current related approach is the determination of bond alternation from ^{1}Hmr coupling constants, based on the correlation between *ortho* coupling constants and π-bond orders of benzenoid hydrocarbons[74]. However, partly due to the simple experimental procedure, the use of ^{1}Hmr chemical shift values as an indication of aromaticity strongly outnumbers any of the above mentioned methods.

1.3 *Quantitative Aspects of the Ring Current Concept.*

Ever since Elvidge and Jackman[21], in 1961, proposed to use the ^{1}Hmr chemical shift as a *quantitative* measure of the ring current, and consequently of aromaticity, much effort has been put into deriving a mathematical equation that would relate the ring current to the other, frequently used, aromaticity criterion, the resonance energy. Although the existence of such a relation has been questioned[73b,75], Haddon[76] recently showed that, indeed, for [4n+2]-

annulenes, a direct analytical relationship exists between ring current (RC), ring area (S) and resonance energy (RE).

$$RC = \frac{3S}{\pi^2} \cdot RE \qquad (1)$$

Later, a slight modification of this formula was published by Aihara[77]. This author also found a simple relationship to exist between the London diamagnetism, *i.e.*, the contribution of ring currents to the magnetic susceptibility, and the resonance energy[78].

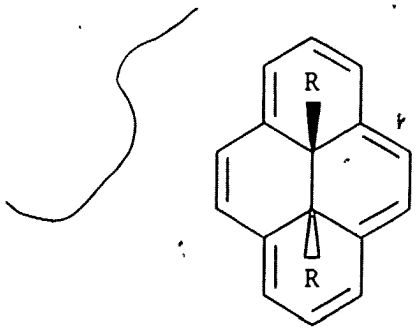
In order to obtain a quantitative assessment of the ring current[79], it is necessary to calculate the induced diamagnetic field (H' in figure 1), due to the π-electron circulation, at any position in and around a molecule. A semi-empirical approach, based on the free electron model of Pople[20], has been described by Waugh and Fessenden[80] (1957). They calculated the secondary field for benzene by assuming two circular current loops placed above and below the plane of the ring. This method has been put into graphical and tabular form by Johnson and Bovey[81]. In 1972, Haddon[82] pointed out that the use of line currents has distinct advantages over the Johnson Bovey method when applied to annulenes, for the carbon skeletons of annulenes larger than benzene are most often not circular at all. A further unique feature of Haddon's approach is that individual ring current intensities are not calculated, or even assumed, but are, instead, deduced from a statistical comparison with experimental ^{1}Hmr shifts.

A quantum mechanical formulation of the ring current for benzene,

based on the London theory[83], was developed by McWeeney[84] (1958). Later extension of this theory[85], to include protons located outside the plane of the benzene ring, led to the Haigh - Mallion tables[86] (1972), which have a similar format to the earlier ones by Johnson and Bovey.

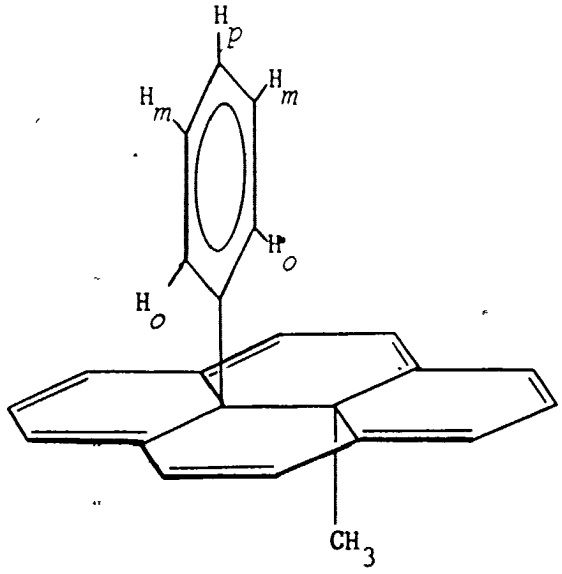
Although the Johnson - Bovey (JB) method and the Haigh - Mallion (HM) approach agree qualitatively with each other, in a quantitative sense there are some distinct differences. The JB tables overestimate the proton deshielding in or near the plane of the benzenoid hydrocarbons[74,87], while there is now sufficient evidence to show that the HM tables, although quite good in the deshielding region[87c], underestimate the proton shielding above the plane of a benzene ring[85,88].

Boekelheide[89] has shown that the ^{1}Hmr and ^{13}Cmr shift data for the alkylated dihydropyrenes 38, 48 and 49, correlate fairly well with the JB calculations. These comparisons, however, have been made under the assumption of a fixed conformation for the alkyl side chain in solution, which is not very likely.



38: R = CH_3
48: R = CH_2CH_3
49: R = $CH_2CH_2CH_3$
50: R = Ph

Our interests, therefore, went out towards a dihydropyrene with a more rigid substituent in the π-cavity, compared to the flexible alkyl chains in 48 and 49. We thought that a phenyl group would serve our purpose very well, better than, *e.g.*, a tertiary butyl group or acetylene unit. The reason is that the phenyl group will give us three types of hydrogens at different levels above the plane of the dihydropyrene ring, whereas the other groups will only give one type of hydrogen at a fixed distance from the ring. Since it is possible that a molecule like 50, with two internal phenyl substituents, may have a different ring current intensity compared to 38, due to a change in geometry or magnetic effects by the phenyl groups, we decided to leave one methyl substituent in place. This would give us then the asymmetrically substituted dihydropyrene 51, where the internal methyl group serves as a reference to other substituted dihydropyrenes (*e.g.*, 38, 48, 49) and the internal phenyl as a probe for the mapping of the



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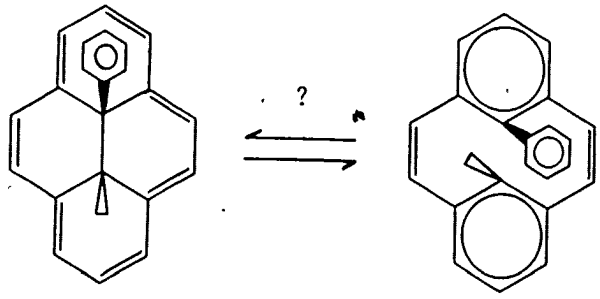
ring current effect above the ring of these dihydropyrenes. Apart from a synthetic challenge, it would also be of interest to see if there is any interaction between the π-cloud of the dihydropyrene ring and the π-cloud of the phenyl substituent, which is within and more or less perpendicular to the first one.

CHAPTER TWO

RESULTS AND DISCUSSION

2.1 *Possible synthetic Approach.*

Since dihydropyrene 51 is the valence isomer of the metacyclophanediene 51A, it is not surprising that synthetic routes to the dihydropyrene derivatives have evolved through [2.2]metacyclophanes and [2.2]metacyclophanedienes.

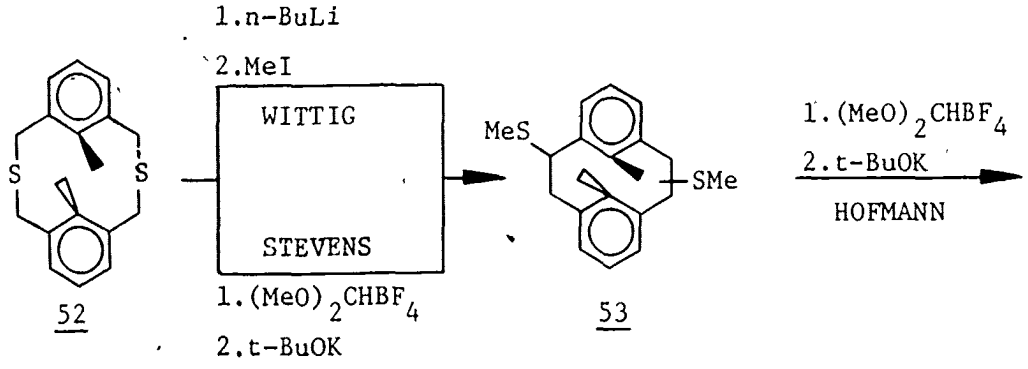


51 51A

From the time of Pellegrin[90] (1899) until the late 60's the only useful synthesis of [2.2]metacyclophanes was via the Wurtz reaction, involving dimerization of *m*-xylylenedibromides by means of alkali metals. Even with improved methods[91] this coupling reaction proceeds in yields of only 20-30%, and furthermore, no useful methods were available for converting the so obtained [2.2]metacyclophanes into the corresponding dienes[92].

The breakthrough came in 1969, when Vögtle introduced the concept of preparing dithiacyclophanes followed by oxidation and extrusion of sulfur dioxide as a method of synthesizing *anti*-[2.2]metacyclophanes[93]. However, Mitchell and Boekelheide[94] should be credited with the first

useful synthesis of *anti*-[2.2]metacyclophanedienes, which spontaneously valence tautomerize to the *trans*-15,16-dihydropyrenes. Their approach involved the Stevens rearrangement of a dithiacyclophane followed by a Hofmann elimination. Later, the Wittig rearrangement was put forward as an alternative method for the ring contraction of dithiacyclophanes[95]. A representative outline of these synthetic routes is shown in scheme 1.

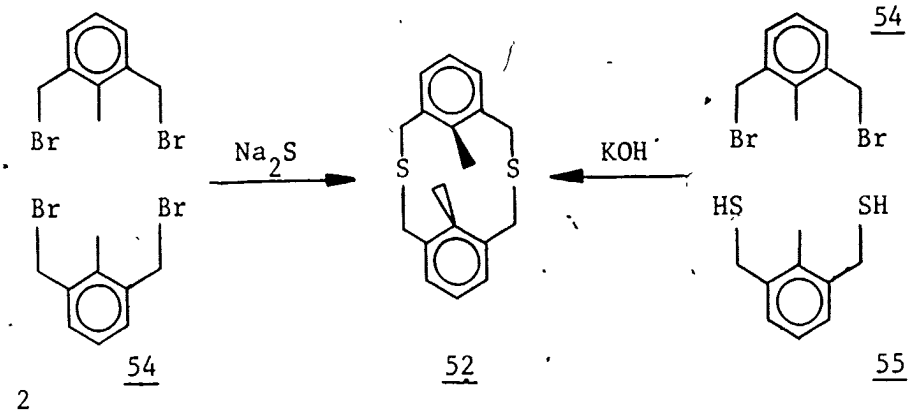


52 53

SCHEME 1 38A 38

For the synthesis of dithiacyclophanes two routes are used extensively: the sodium sulfide coupling[94,96] of a dibromide and the cyclization between a dibromide and a dithiol[95,97] (see scheme 2).

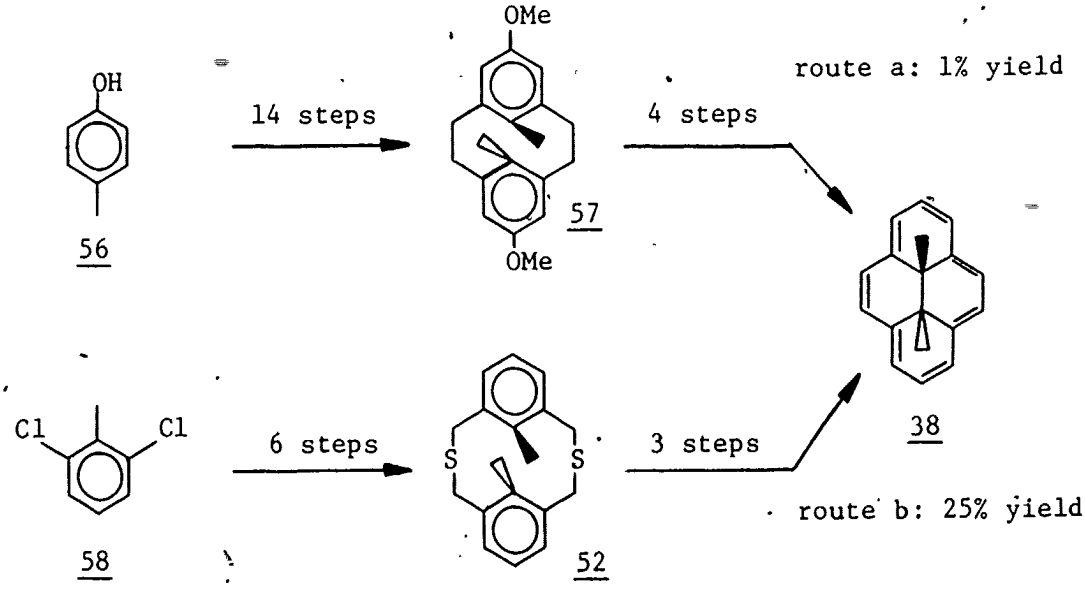
To highlight the importance of the dithiacyclophanes and the subsequent ring contraction steps in the synthesis of dihydropyrenes, a comparison has been made in scheme 3 between the first synthesis of *trans*-15,16-dimethyldihydropyrene 38 via a stepwise Wurtz coupling (route a)[53,98] and that via the thiol-bromide cyclization (route b)[97].



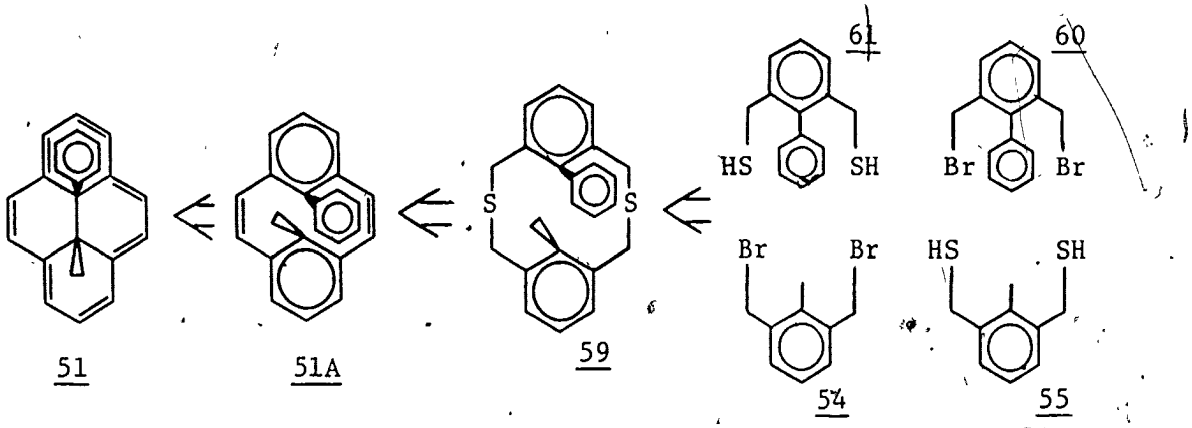
SCHEME 2

Apart from increased yields, the dithiacyclophane route has the further advantage that now for the first time *syn*- and *cis*-isomers respectively of [2.2]metacyclophanes and dihydropyrenes became accessible, because of the existence of *anti*- and *syn*-isomers in the thiacyclophanes. The thiol-bromide coupling made it also possible to obtain asymmetrically substituted [2.2]metacyclophanes and dihydro-pyrenes, of which our target molecule 51 is an example.

We therefore propose the synthetic pathway outlined in scheme 4



SCHEME 3

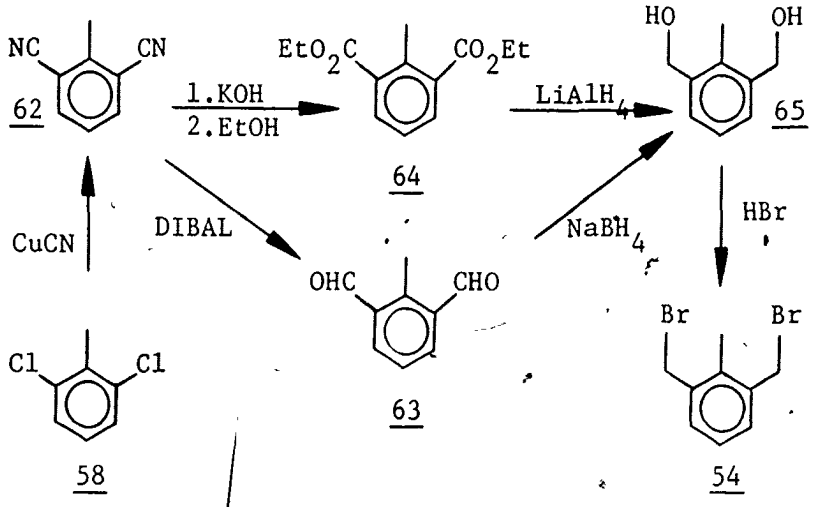


SCHEME 4

as our route towards the synthesis of *trans*-15-phenyl-16-methyldihydropyrene 51. We predicted that a higher yield of 59 would be obtained using thiol 61 and bromide 54 rather than bromide 60 and thiol 55, because in the attacking nucleophile 61 the sulfur atoms are farther removed from the very bulky phenyl substituent than are the methylene carbons (the electrophile) in bromide 60. This increased distance between the phenyl substituent and the reactive center should then decrease the steric inhibition to coupling between 54 and 61 as compared to the coupling between 55 and 60.

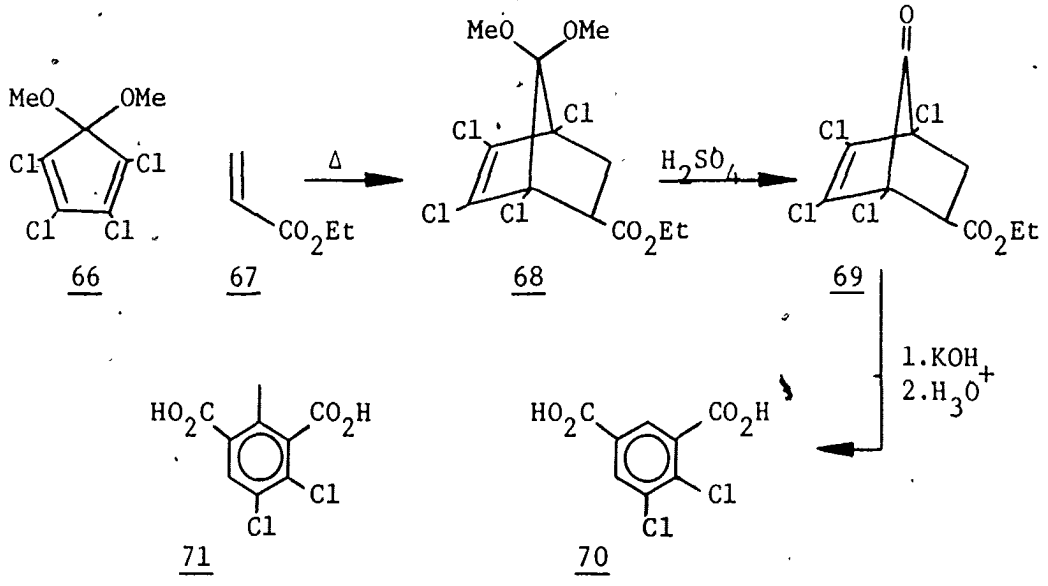
2.2 *Synthesis of 2,6-Bis(bromomethyl)toluene 54.*

The bromide 54 was obtained via three different routes. The first two routes, both starting from dichloride 58, differ only in the conversion of the dicyanide 62. In one case di(isobutyl)aluminium hydride (DIBAL) was used to obtain 63[97] whereas the other route involved basic hydrolysis followed by esterification with ethanol to yield diester 64[92a]. The conversion of dialcohol 65 to 54 proceeded much easier by using 48% aqueous HBr than by using PBr_3.



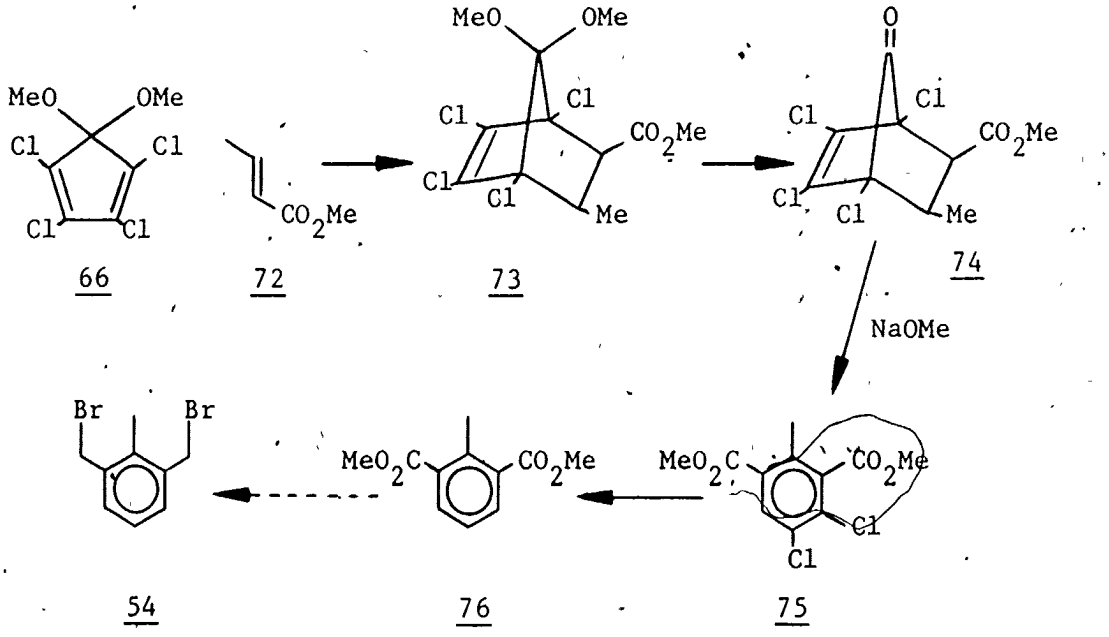
The third route towards the synthesis of dibromide 54 involved a novel approach of starting with non-aromatic precursors and constructing a 1,2,3-trisubstituted benzene by a Diels-Alder reaction.

Early work by Hoch[99] suggested that isophthalic acid derivative 70 was available by the sequence illustrated below. However, identification of the acid 70 was somewhat tenuous. The structure was mainly assigned by its melting point (305-306°C) as phthalic acids tend to melt below 200°C and the 4,6-dichloroisophthalic acid was known to

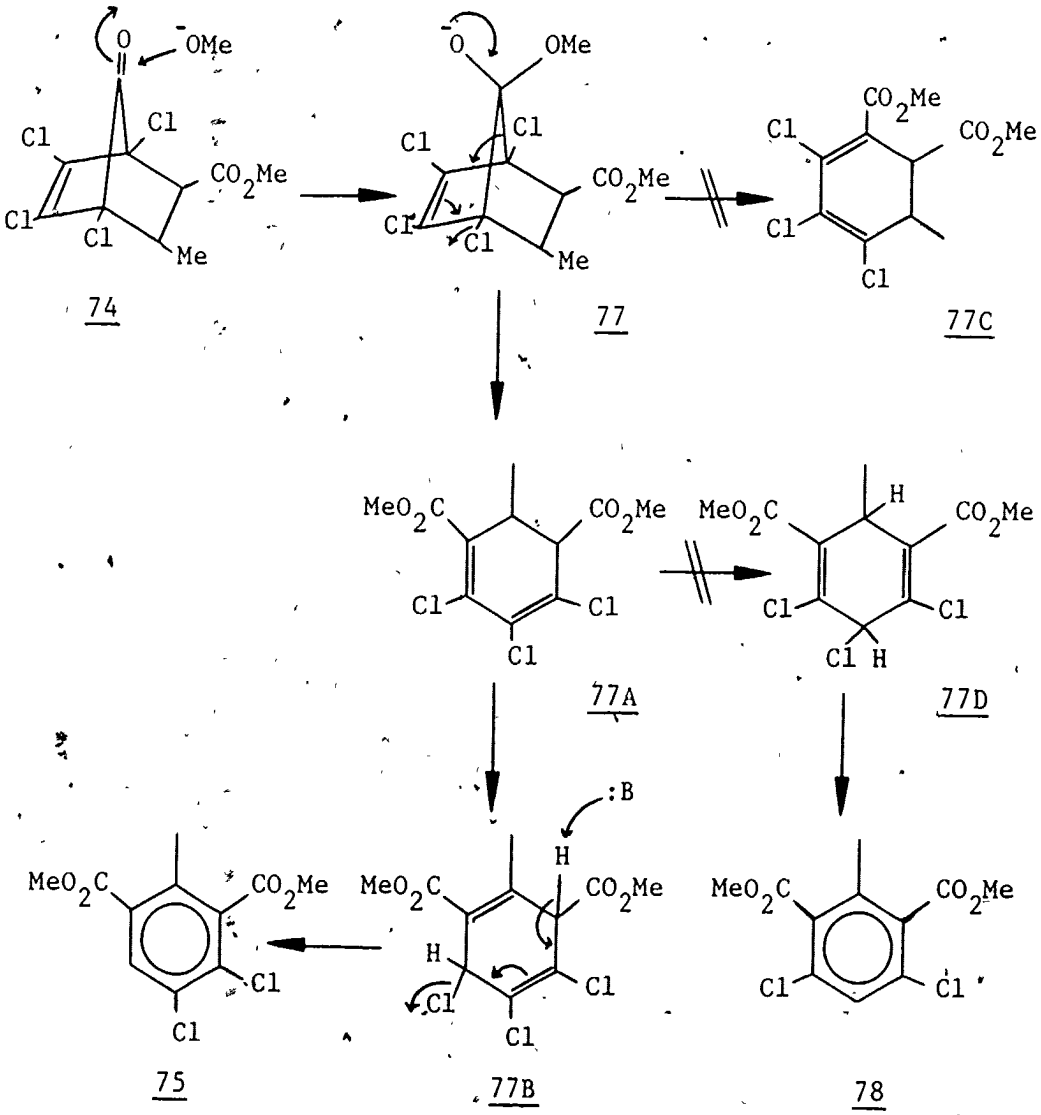


melt at 286°C.

In view of the simplicity and economy of this sequence further investigation by our group[100] was warranted. It was reasoned that by using methyl crotonate 72 instead of ethyl acrylate 67 the desired diacid 71 would be obtained. Indeed, cycloaddition of 66 (prepared in 86% yield by addition of MeOH/KOH to hexachlorocyclopentadiene[101]) and 72 gave a 60% yield of the Diels-Alder adduct 73 as a mixture of *endo* and *exo* isomers. Subsequent treatment with conc. sulfuric acid gave an almost quantitative conversion to the ketone 74 from which the diacid 71 could be obtained. However, treatment of ketone 74 with sodium methoxide in methanol gave directly the desired diester 75 in 70% yield. The removal of both chlorine atoms in 75 proceeded nearly quantitatively with Raney nickel (W-7). The dimethyl ester 76 can then be subjected to the same sequence of reactions as in the case of the diethyl ester 64 to yield 54.



The proposed mechanism for the rearrangement of 74 to 75 is outlined in scheme 5. As can be seen, intermediate 77 can open to give either 77A or 77C. However, it was established by the phthalein test[102] that the final product was not a phthalic acid derivative which shows that the preferred way of ring opening occurs via 77A. From this point two possible allylic rearrangements can take place to give either 77B or 77D, which would then aromatize to give 75 or 78 respectively. The



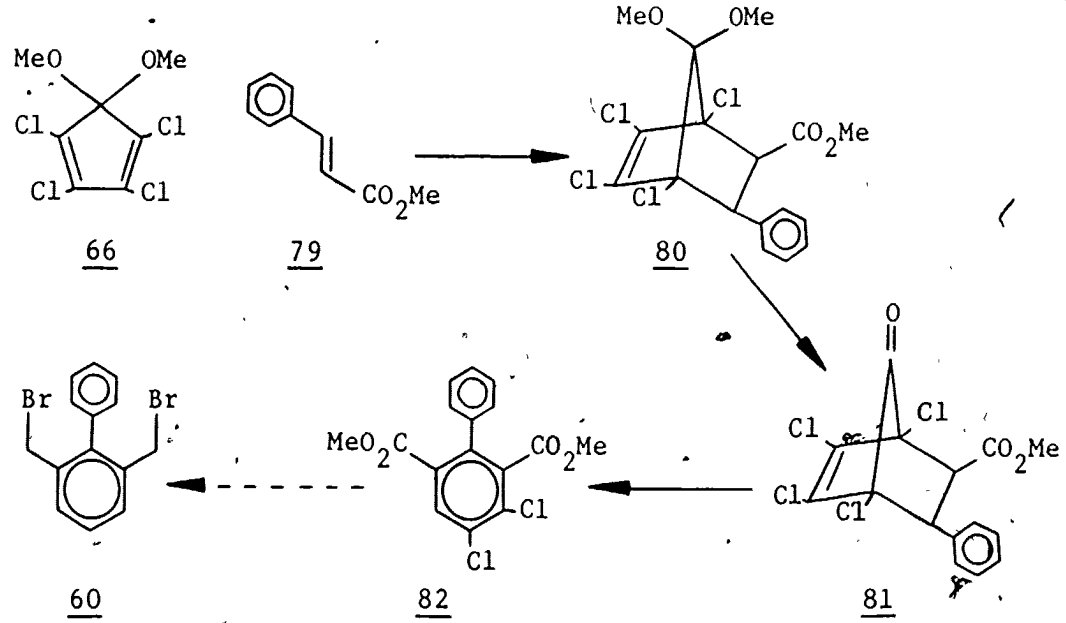
SCHEME 5

^{1}Hmr of the final product showed a one proton singlet at δ7.98, two singlets at δ3.88 and δ3.84 for the methyl esters and another singlet at δ2.43 for the methyl group. This, together with the ^{13}Cmr that clearly showed six different aromatic carbons, indicated 75 to be the final product since the symmetrical 78 will only give one signal for the methyl esters in the ^{1}Hmr and only four aromatic carbons in the ^{13}Cmr. This, therefore, indicates a mechanistic pathway via 77A and 77B as seen in scheme 5.

2.3 *Synthesis of 2,6-Bis(bromomethyl)-1,1'-biphenyl 60.*

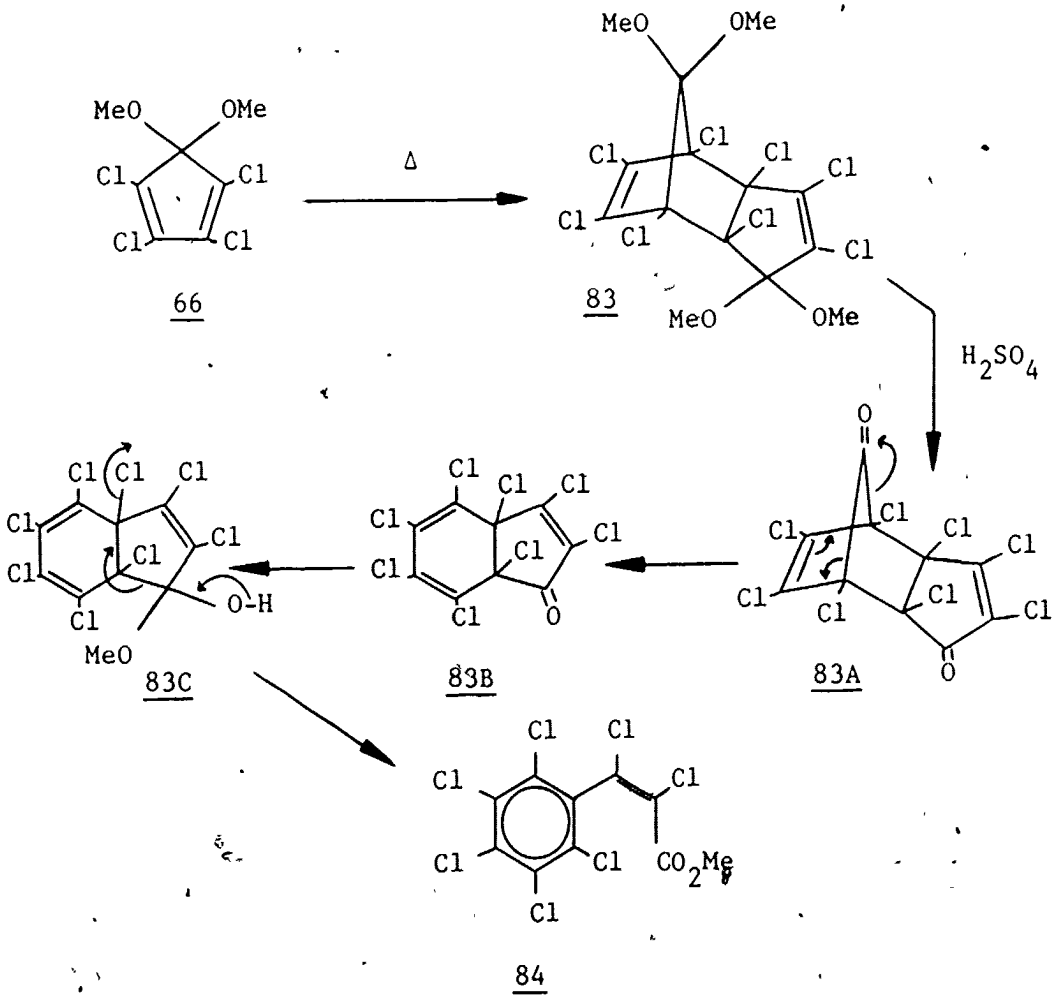
Although bromide 60 was a known compound we attempted first to find a better route than the literature[103].

Since the above described cycloaddition of 66 and methyl crotonate 72, followed by ring opening of the adduct, turned out to be an economic way of preparing 75, we thought that the biphenyl ester 82 could be obtained in a similar fashion by using methyl cinnamate 79



instead of 72 as dienophile. Conversion of 82 to bromide 60 will then be trivial (see conversion of 75 to 54).

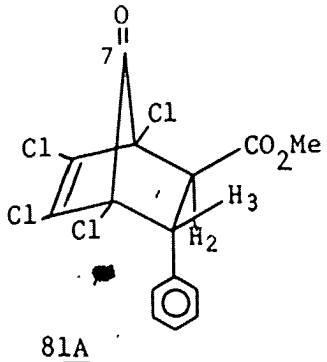
Thus heating of diene 66 and dienophile 79 for four days at *ca.* 160°C afforded 80. Since purification of 80 was problematic it was directly converted to ketone 81 by means of conc. sulfuric acid. This was then purified by column chromatography over silica gel. The first compound eluted from the column was a white solid that easily recrystallized from methanol to give colorless crystals in 20-30% yield, mp 112-113°C. This compound was assigned structure 84 based



on the following spectroscopic data. The ^{1}Hmr showed only one singlet at δ3.70. This, together with a C=O stretch at 1730 cm^{-1} and a C=C stretch at 1610 cm^{-1} in the ir spectrum, indicates an α,β-unsaturated methyl ester. A strong absorption in the ir spectrum at 715 cm^{-1} is indicative for C-Cl stretch. The presence of chlorine is corroborated by its mass spectrum where the weak molecular ion at *m/e* 400 ($^{35}Cl_7$) showed the characteristic isotope pattern for a heptachloride; the fragmentation pattern is consistent with the loss of seven chlorine atoms each showing the correct isotope pattern.

A rationale for the formation of 84 can be found in the possible self-condensation of 66 where one molecule serves as a diene and another molecule as a dienophile. This then leads to the Diels-Alder adduct 83 (depicted as *endo*-adduct) which, on treatment with conc. sulfuric acid can give ketone 83A. Loss of carbon monoxide, followed by formation of hemiketal 83C can give, after elimination of hydrogen chloride, the fully aromatized heptachloro ester 84.

The second compound isolated from the reaction mixture of 66 and 79 was obtained in 40-50% yield (mp 158-159°C) and assigned structure 81A. This compound showed the standard isotope pattern for four



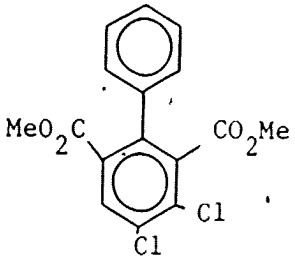
81A

chlorine atoms in its mass spectrum with the molecular ion at *m/e* 378 ($^{35}Cl_4$). The ^{1}Hmr for 81A consisted of a multiplet at δ7.43-7.11 for the five aromatic hydrogens, a doublet at δ4.77 (J=9.5 Hz) for H-3, a singlet at δ3.79 for the methyl ester and another doublet at δ3.74 (J=9.5 Hz) for H-2. In the ^{13}Cmr the C-7 carbonyl appeared at δ187.1 and the ester carbonyl carbon at δ166.7.

According to the ^{1}Hmr as well as the ^{13}Cmr only one isomer of 81 is present. Since *trans*-methyl cinnamate 79 was used in the cycloaddition with 66, the Diels-Alder adducts 80 and 81 therefore should also have both substituents in a *trans* arrangement. It is known[104] that a phenyl group is sterically more demanding than a carbomethoxy group. This then leads us to the indicated stereochemistry of 81A, where the phenyl substituent is placed in the *endo* position.

Having established the structure of ketone 81 as being 81A, it was then treated with sodium methoxide in methanol in order to give the expected biphenyl 82. Although, after column chromatography, the ^{1}Hmr of the first fraction indicated the presence of the desired compound 82, by showing three singlets at δ8.02, δ3.56 and δ3.53 in the ratio of 1:3:3 plus a multiplet around δ7.4, the main product, however, was assigned the structure 85 on the basis of its ^{1}Hmr, ^{13}Cmr and mass spectrum. The ^{1}Hmr of 85 showed the expected multiplet at δ7.42-7.11 for the aromatic protons, but furthermore there were two 1H doublets (J=8.5 Hz) at δ4.69 and δ3.48 respectively and three 3H singlets at δ3.75, δ3.64 and δ3.50. The ^{13}Cmr showed three methyl carbons (quartet), two methine carbons (doublet), a carbonyl carbon at δ191.5 and a carbonyl ester at δ168.0. In the mass spectrum, the molecular ion at *m/e*

370 ($^{35}Cl_2$) showed an isotope pattern for two chlorine atoms. A strong signal at *m/e* 208 occurs in the mass spectrum of 85 and supports the proposed structure, since this mass number corresponds with the retro Diels-Alder fragment 2,5-dichloro-3,4-dimethoxycyclopentadienone 86.



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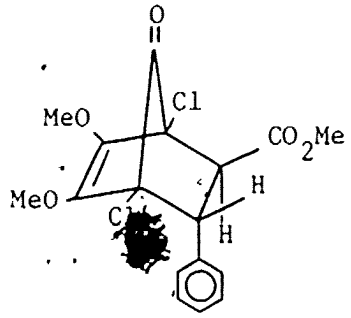

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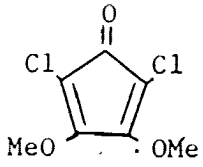
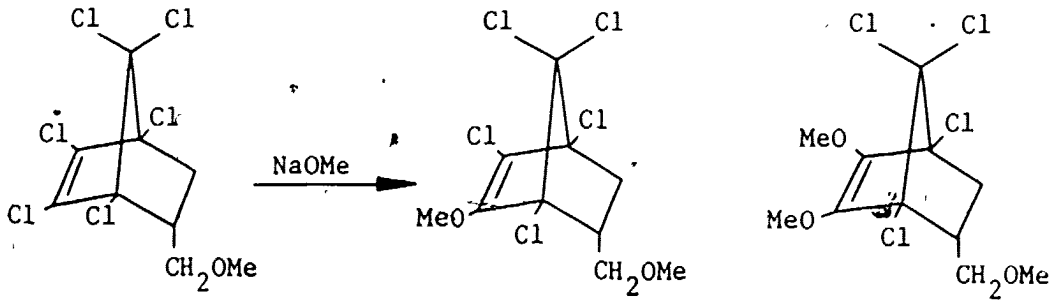
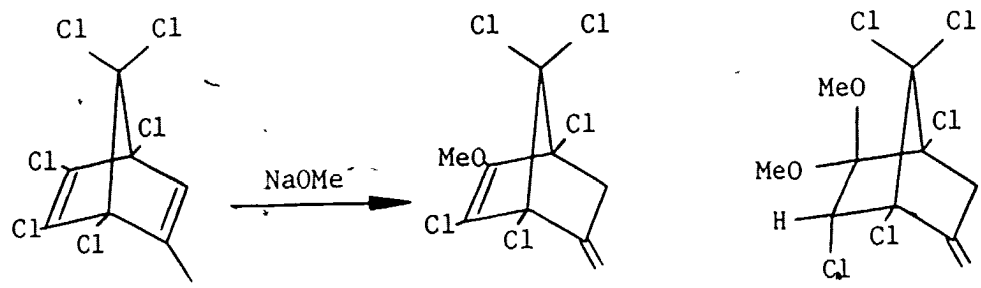


86

The apparent substitution of the vinylic chlorine atoms in 81A by methoxy groups is not unprecedented in norbornene systems. Davies, for instance, reported that treatment of 87 with sodium methoxide yielded a mixture of the mono- and di-substituted norbornenes 88 and 89[105]. The same reaction with 90 as substrate gave a 1:1 mixture of 91 and 92[106]. However, the existence of a structure like 92 for our new compound 85 is not likely since this would give one extra proton



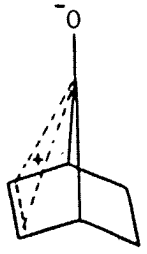
87 88 89



90 91 92

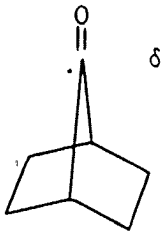
signal. Further, the geminal dimethoxy group would not be stable towards strong acid whereas 85 was recovered unchanged after acid treatment.

Mechanistically these reactions of 87 and 90 can occur via an addition-elimination mechanism. However, homoconjugation between the double bond and the carbonyl in norbornenone systems like 81A can invoke the participation of a non-classical ion like 93 in the substitution of the vinylic chlorides by methoxy groups. This type of conjugation is of course not possible in 87 and 90.



93

Spectroscopic evidence[107] for the non-classical structure 93 can be found in ^{13}Cmr where a strong upfield shift of the carbonyl carbon, in going from 94 to 95, is indicative for a structure like 93.



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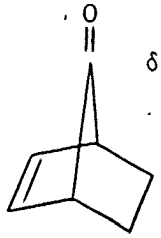
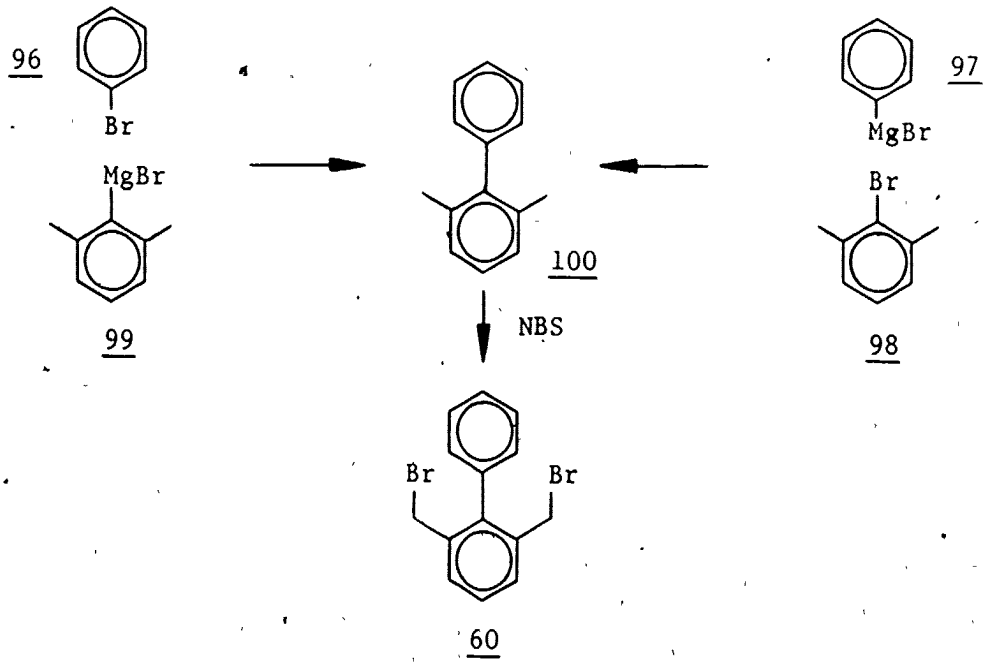


95

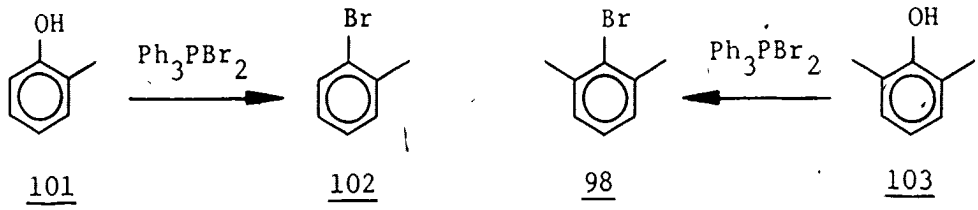
Thus a mechanism for the 1,2-substitution in 81A is much easier to envisage by using a non-classical structure like 93 than by using a direct addition-elimination mechanism, as proposed for 87 and 95[105]. So we can conclude that spectroscopic and chemical data, as well as mechanistic considerations, are in support of the proposed structure 85

Since the Diels-Alder approach for the synthesis of bromide 60 did not give the anticipated products an alternative synthesis involving biphenyl 100 was planned, which should give 60 on bromination with



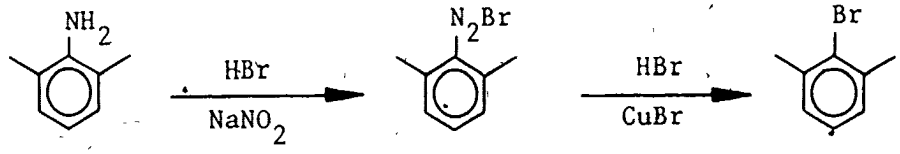
N-bromosuccinimide (NBS). A Grignard coupling between 96 and 99 or between 97 and 98 could be expected to give the biphenyl 100. Because of steric reasons the first coupling would probably be preferred.

Naphthols[108b,c] and phenols[108a] have been converted directly to the corresponding bromides by the action of triphenylphosphine dibromide (Ph_3PBr_2), even *o*-cresol 101 gave a 72% yield of the bromide 102 via this method[108b]. However, reacting 2,6-dimethylphenol 103 with Ph_3PBr_2, either in DMF or NMP or neat, did not yield the required bromide 98.



101 102 98 103

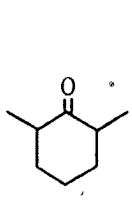
Bromide 98 was subsequently obtained by the diazotization[109] of 2,6-dimethylaniline 104. The conversion of diazonium salt 105 with 48% aqueous HBr and CuBr gave a 62% yield of bromide 98. This was then



104 105 98

converted to the Grignard reagent 99 and coupled with bromobenzene 96. Although biphenyl 100 was formed, the yield (<10%) necessitated that a more practical route to 100 be devised.

Vögtle[103] had previously synthesized bromide 60 by reaction of 2,6-dimethylcyclohexanone 106 with phenyllithium to give alcohol 107



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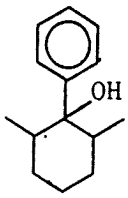

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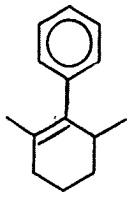

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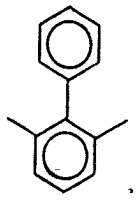

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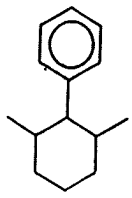


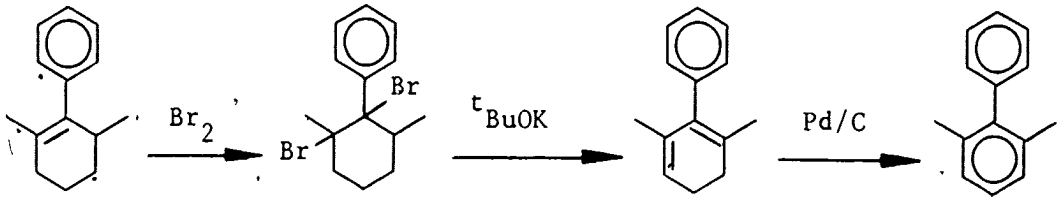
109

which was then dehydrated by phosphoric acid, and then dehydrogenated with 10% palladium on charcoal to give biphenyl 100 in a claimed 44% overall yield.

However, we found this sequence required some modification. Thus cyclohexanone 106 with the Grignard reagent 97 (prepared from bromobenzene 96) gave alcohol 107. Subsequent dehydration of 107 proved to work better with *p*-toluenesulfonic acid than with phosphoric acid to yield the cyclohexene derivative 108. Both products, 107 and 108, were purified by vacuum distillation. Vögtle's next step, however, turned out to be problematic. Dehydrogenation of 108 using palladium on charcoal (10% or 30%) gave in our hands always a mixture of compounds containing 100, based on the strong singlet at δ1.96 in its ^{1}Hmr and a molecular ion at *m/e* 182 in its mass spectrum. The mass spectrum also showed a molecular ion at *m/e* 188. This, together with multiplets at δ2.75-2.45 and δ0.80-0.50 in the ^{1}Hmr, led us to the conclusion that the second compound in the mixture was in fact the cyclohexyl derivative 109. This implies that a disproportionation has taken place in the dehydrogenation of 108, where some part of the molecules serve as hydrogen donors while others function as acceptors.

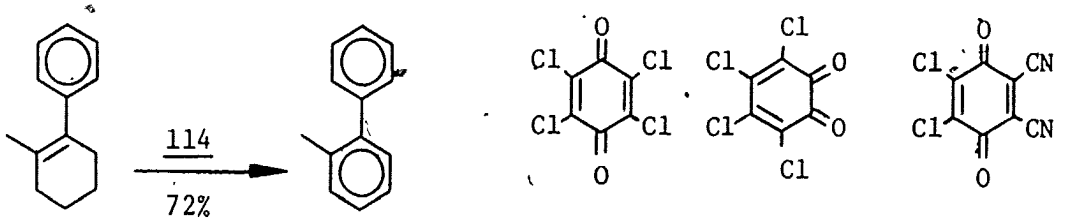
Since we were unable to separate 100 from 109, either by chromatography or distillation, we looked for different methods to oxidize 108 to 100.

The tendency of 108 to aromatize should increase upon the incorporation of an extra double bond in the cyclohexene unit. This was accomplished by the addition of bromine to 108 to form the dibromide 110 followed by dehydrobromination with potassium t-butoxide. The so obtained cyclohexadiene derivative 111 aromatized with 10% palladium on charcoal and gave us, after column chromatography, biphenyl 100 in 54% yield.



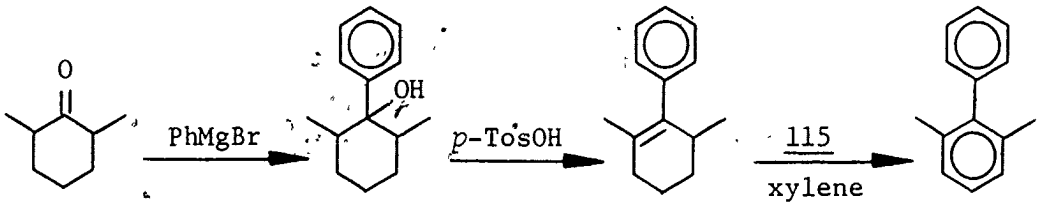
108 110 111 100

An even better yield of 100 was obtained when a quinone was used as an oxidizing agent for 108. It has been reported that 112 gave a 72% yield of 113 on dehydrogenation with *p*-chloranil 114 in refluxing xylene[110a]. We thus first tried dehydrogenation of 108 to 100 with quinone 116 (DDQ), the most powerful quinone reagent in routine use[110b]; this occured smoothly in refluxing benzene. Economic reasons, however,



112 113 114 115 116

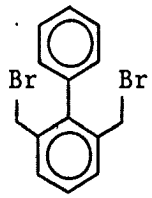
made us choose *o*-chloranil 115 for use on large scale. This quinone, although it has a greater reactivity than *p*-chloranil 114, has a lower oxidation potential than 116 and thus gave a reaction which was too slow in benzene but acceptable in xylene. Thus by using the reaction sequence indicated in scheme 6 we were able to increase the overall yield of 100 from the reported 44%[103] to 64%.



106 107 108 100

SCHEME 6

Conversion of biphenyl 100 to the desired bromide 60 proceeded smoothly by adding N-bromosuccinimide in portions to a refluxing solution of 100 in carbon tetrachloride in the presence of catalytic amounts of benzoyl peroxide. However, recrystallization of 60 from methanol, as reported by Vögtle[103], gave only a 20% yield of bromide 60. The bulk of the crude material had been converted to the corresponding dimethyl ether 117 as indicated by its ^{1}Hmr that, apart from



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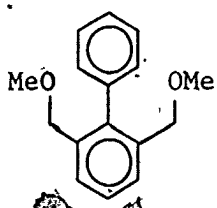
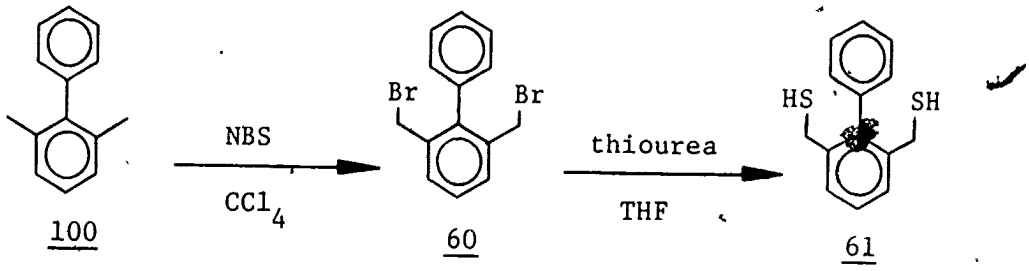


117

the usual aromatic protons at δ7.40, showed two singlets in the ratio of 2:3 at δ4.11 and δ3.20 respectively. A molecular ion at *m/e* 242 in its mass spectrum was further proof for the existence of 117. Recrystallization from cyclohexane solved this problem and bromide 60 was subsequently obtained in 61% yield (mp 116-117°C). Therefore the low yield reported by Vögtle[103] (34%) for the NBS bromination of 100 may be explained by the formation of 117 during the recrystallization of 60 from methanol.

The normal procedure of converting bromide 60 into thiol 61 is by the action of thiourea in boiling ethanol followed by basic hydrolysis of the intermediate isothiouronium salt[97]. Following this sequence Vögtle[103] obtained a 43% yield of thiol 61. However, keeping in mind the easy substitution of the bromine atoms of 60 by methanol to form 117, we decided to use tetrahydrofuran (THF) instead of ethanol as the solvent for the conversion of 60 into 61. This way we obtained thiol 61 in 94% yield (mp 66-68°C).

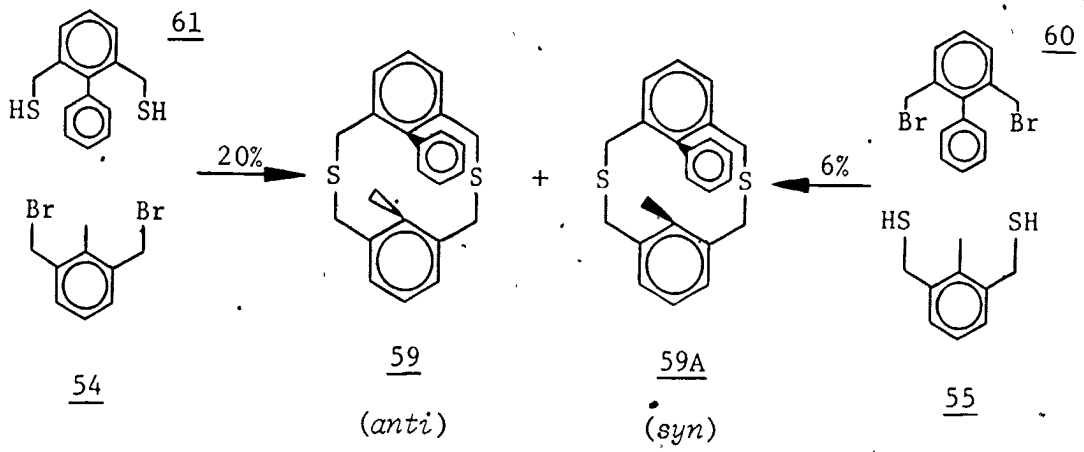


100 60 61

Thus, starting from 2,6-dimethylcyclohexanone 106 we have considerably improved the synthesis of dithiol 61 from the reported[103] 6% to a 37% overall yield.

2.4 *Synthesis of trans-15-Phenyl-16-methyldihydropyrene 51**.

Coupling of bromide 54 and thiol 61 under high dilution conditions at room temperature, using potassium hydroxide in ethanol-benzene, gave, after chromatography over silica gel, a 20% yield of the desired dithiacyclophane as a mixture of *anti*-59 and *syn*-59A in the ratio of 7 : 1 (based on ^{1}Hmr)[111].



To verify our statement (page 28) that the coupling between bromide 54 and thiol 61 would be more successful than the coupling of thiol 55 and bromide 60, we proceeded to attempt the coupling of 55 and 60 under the same conditions as described above. This time, however, the yield of the dithiacyclophane was only 6%, again as a mixture of *anti*-59 and *syn*-59A in the same ratio as obtained above. This proves that steric hindrance in the approach of the thiolate

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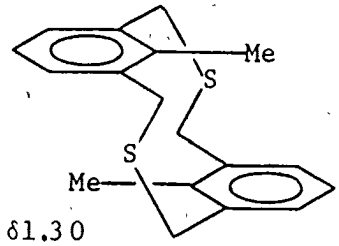
* The Chemical Abstract now calls 51: *trans*-10b-phenyl-10c-methyl-10b,10c-dihydropyrene

nucleophile towards the methylene electrophile (of the bromide) is far less by using thiol 61 and bromide 54 than by using bromide 60 and thiol 55.

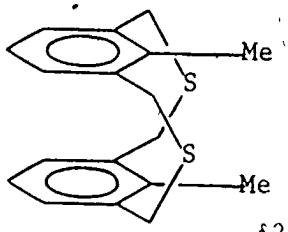
The yield of the dithiacyclophanes 59 and 59A could be further increased by coupling the bromide and thiol in refluxing ethanol instead of at room temperature. This yielded 59 and 59A in the ratio of 4 : 1 (based on ^{1}Hmr) in about 40% overall yield. The separation of the *anti*- and *syn*-isomer 59 and 59A was quite tedious. Repeated column chromatography over silica gel gave pure *anti*-59 which, after recrystallization from benzene, yielded colorless crystals, mp 165°C. Those fractions from the column chromatography that showed (by ^{1}Hmr) the presence of both isomers 59 and 59A with more of the *syn*-isomer 59A, were again chromatographed over silica gel to increase the yield of pure 59A. This was then repeatedly recrystallized from benzene/hexane to give 86 mg (0.6%) of pure *syn*-59A as colorless crystals, mp 170°C. Both isomers, 59 and 59A, showed a molecular ion at *m/e* 362 in their mass spectra and gave correct elemental analyses. The structure assignment of the pure *anti*- and *syn*-isomers 59 and 59A is based on their ^{1}Hmr as compared with the ^{1}Hmr of the *anti*- and *syn*-dimethyldithiacyclophanes 52 and 52A[97] which are not spontaneously interconvertible[1,12]. In the ^{1}Hmr, the protons of the internal methyl groups of 52 show an upfield shift due to the ring current of the opposite aromatic ring and appear as a singlet at δ1.30, whereas the internal methyl protons of 52A are comparable with those of thiol 55 and appear at δ2.54. In addition, the aromatic protons of 52 show the normal



δ1.30

52

(*anti*)



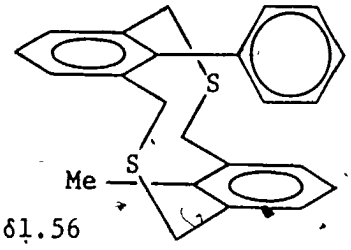
δ2.54

52A

(*syn*)

anti-metacyclophane pattern at δ7.4-7.0, whereas the aromatic protons of 52A are shifted upfield to δ6.66, a common consequence of superimposing two parallel aromatic rings[113]. The *syn*-conformation of 52A was later confirmed by X-ray crystallography[114].

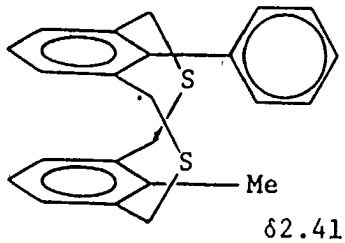
In the ^{1}Hmr for 59, we find a singlet at δ1.56 for the internal methyl protons whereas the aromatic protons of the thiacyclophane are in the range of δ7.46-7.02. The ^{1}Hmr of 59A shows a singlet at δ2.41 for the methyl protons whereas the aromatic protons are shifted



δ1.56

59

(*anti*)



δ2.41

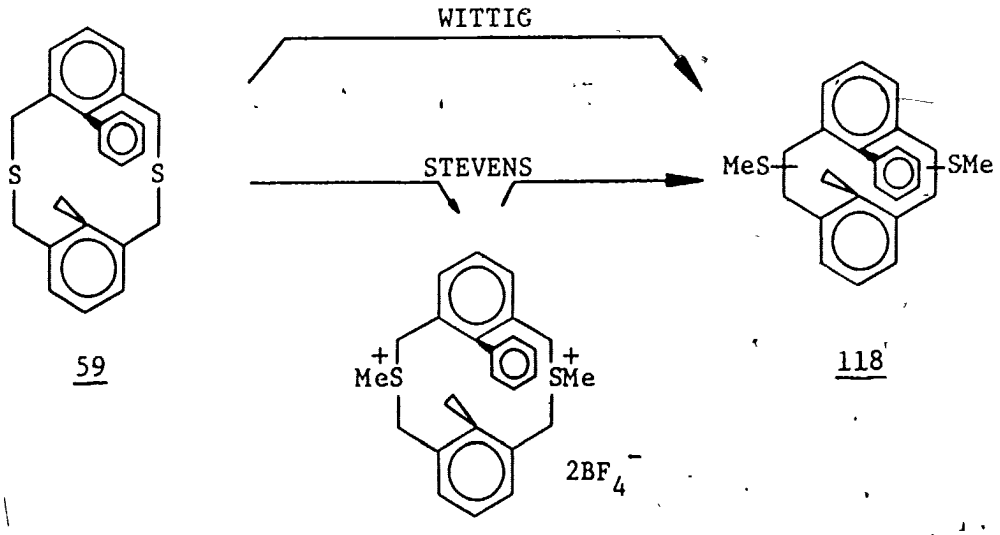
59A

(*syn*)

upfield to δ6.99-6.75 as compared to 59. Thus comparison of these data with the ones given for thiacyclophanes 52 and 52A makes the assignment of the *anti*-conformation to 59 and the *syn*-conformation to 59A straightforward. It may be argued that the internal methyl group of 59A should experience a strong upfield shift because of the neighbouring phenyl substituent. However, from data that will be discussed in Chapter 3, we know that the phenyl group is not rigid but undergoes a partial rotation around the biphenyl bond. Therefore the methyl group experiences only a minor shielding by the phenyl substituent.

The next step towards the synthesis of dihydropyrene 51 is the ring contraction of thiacyclophane 59. This was done by the Wittig[95] as well as the Stevens rearrangement[94], the latter giving better results.

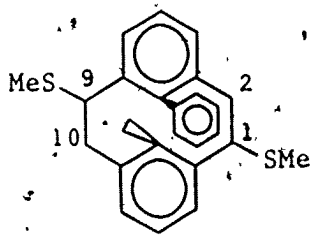
Thus Wittig rearrangement of thiacyclophane 59 in dry THF using lithium diisopropylamide or n-BuLi, at 0°C or room temperature, followed by the addition of methyl iodide gave 118 as a mixture of isomers in



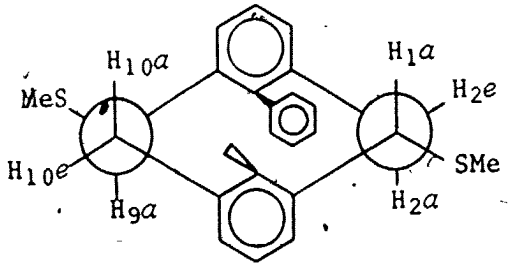
59 118

59S

37% yield. Alternatively, treatment of 59 with dimethoxycarbonium fluoroborate[115] gave the Stevens salt 59S as a white powder in 96% yield. This salt 59S underwent a Stevens rearrangement upon treatment with potassium t-butoxide in dry THF and gave a 64% yield of 118, again as a mixture of isomers. For its use in the Hofmann elimination reaction the mixture of isomers corresponding to 118 need not be separated. However, careful chromatography of 118 over silica gel gave the principal component in a pure state. Recrystallization from hexane afforded colorless needles, mp 157-158°C; its mass spectrum gave a molecular ion at *m/e* 390. This isomer has been assigned structure 118A based on its ^{1}Hmr signals for the methylene-methine bridges of the [2.2]metacyclophane. Because we are dealing with the *anti*-confqrmation for 118A, based on the upfield shift of the internal methyl protons at δ0.87, the bridge protons are arranged in pseudoaxial or pseudoequatorial positions. Therefore; from the magnitude of the two coupling constants (J=4 Hz, J=11.5 Hz) found in both methine proton signals (H-1 and H-9) we can safely deduce that both thiomethyl groups are in the pseudoequatorial position. As a consequence, two of

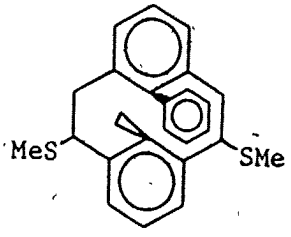


118A

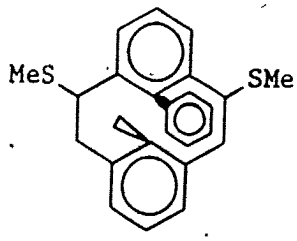


118A

the aromatic protons are strongly deshielded by these neighbouring sulfur atoms. The technique of double resonance was used to probe the coupling pattern for the bridge protons. This way, we were able to separate the six 1H signals into two sets of coupled spin systems. Although the assignment of axial and equatorial protons in each set, based on the splitting patterns, is trivial, the correct assignment of H-1 and H-9 had to await the characterization of another isomer of 118, which we assigned structure 118B. Isomer 118B was obtained as a mixture of isomers from the same chromatography experiment that yielded 118A. Rechromatographing, followed by recrystallization from hexane, gave us 2 mg (0.3%) of 118B as white crystals, mp 162-163°C. Since the ^{1}Hmr showed only three 2H signals for the bridge protons, it was obvious that we were dealing with a symmetrical structure like 118B or 118C where both thiomethyl groups are again in the pseudo-equatorial position, as indicated by coupling constants.



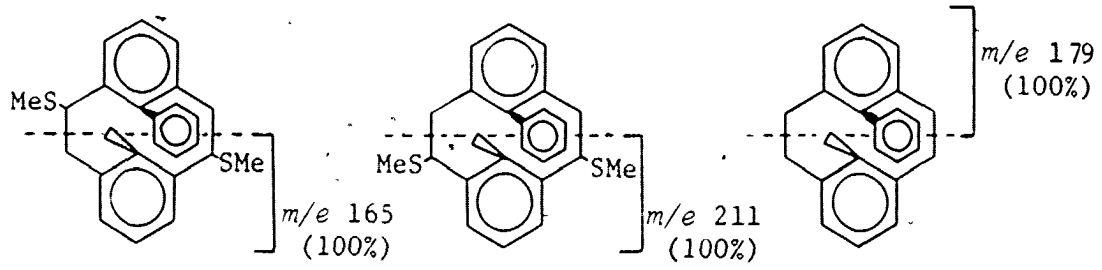
118B



118C

From mass spectral data of 118A and the desulfurized isomer 119, we can deduce that the preferred fragmentation pathway for these phenyl substituted [2.2]metacyclophanes is by symmetrical splitting of the

bridges as indicated by the dashed line for 118B. Thus, in the mass spectrum of 118B we find, apart from a molecular ion at *m/e* 390, a strong signal (100%) at *m/e* 211 corresponding to the fragment shown in 118B (see scheme 6). This implies that we are dealing with structure 118B instead of 118C.



118A 118B 119

SCHEME 6

Now, by simply comparing the chemical shifts of the methine protons H-1 and H-9 in 118A with H-1 in 118B, we can confidently assign the low field signal of the bridge protons in 118A to H-1 (δ4.26, see figure 2 and table 6). The assignment of some of the aromatic protons has been done by comparison between 118A, 118B and 119, and is straightforward, keeping in mind the deshielding effect of a neighbouring sulfur atom. The previously mentioned [2.2]metacyclophane 119 was obtained from 118A by desulfurization with Raney Nickel (W-7)[116]. Recrystallization from hexane gave colorless crystals of 119 (98%), mp 147°C. Its mass spectrum showed a molecular ion at *m/e* 298. No efforts were made to solve the ABCD spin system for the bridge methylene protons in 119 (see figure 2).

The mixture of isomers 118 was subjected to a Hofmann elimination

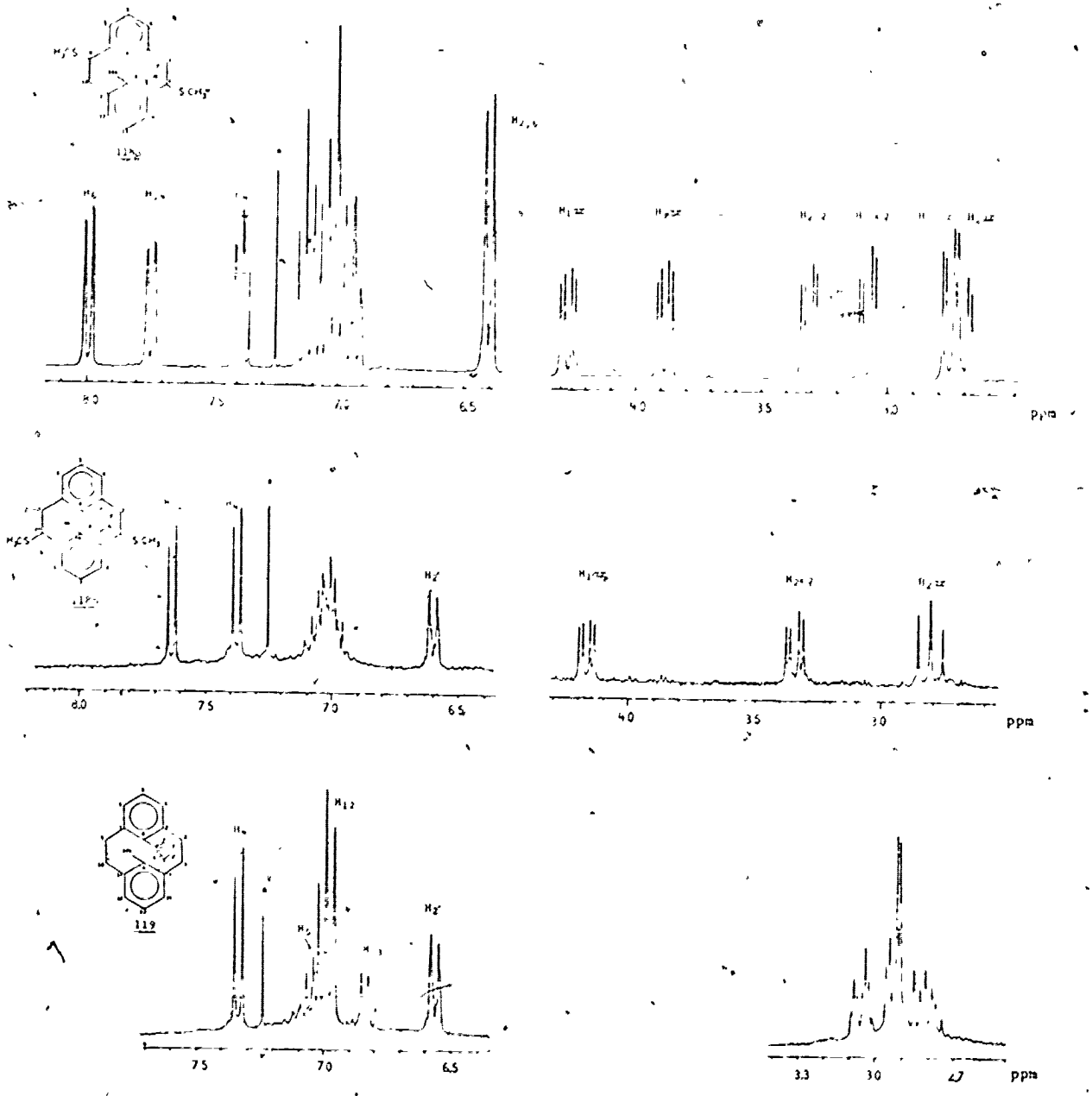
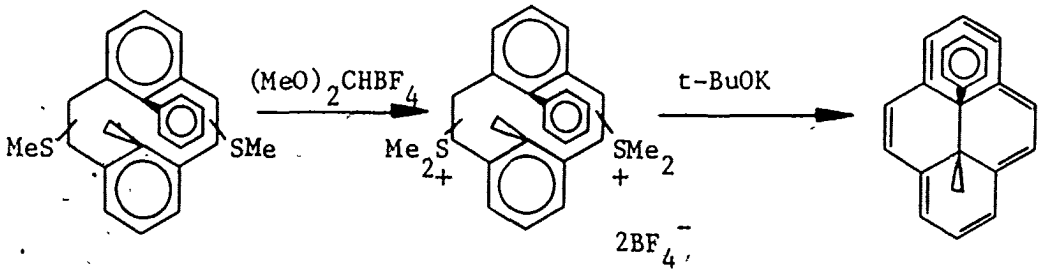


FIGURE 2. ^{1}Hmr (250 MHz) of 118A, 118B and 119; internal methyl and thiomethyl protons are not shown. Solvent (*) is $CDCl_3$.

TABLE 6. ^{1}Hmr ($CDCl_3$, 250 MHz) δ values and coupling constants (J) for assigned protons of 118A, 118B and 119.

Proton	118A	J (Hz)	118B	J (Hz)	119	J (Hz)
H-4	7.39	J_{4-5} =7.4	7.38		7.34	J_{4-5} =7.1
H-5		J_{4-6} =1.5			7.04	
H-6	8.00	J_{5-6} =7.4				
H-12			7.64		6.97	J_{12-13}=7.4
H-13		J_{13-14}=7.4			6.82	
H-14	7.75	J_{12-14}=1.5				
H-2'	6.40		6.60		6.57	
H-1(*ax*)	4.27	J_{1a-2e}=4.4	4.17	J_{1a-2e}=4.4		
H-2(*eq*)	3.31	J_{1a-2a}=11.0,	3.34	J_{1a-2a}=11.0		
H-2(*ax*)	2.72	J_{2a-2e}=12.5	2.81	J_{2a-2e}=12.5		
H-9(*ax*)	3.88	J_{9a-10e}=4.4			3.09-2.75	
H-10(*eq*)	3.08	J_{9a-10a}=11.0				
H-10(*ax*)	2.74	$J_{10a-10e}$=12.9				
SCH_3-1	2.15		2.14		-	
SCH_3-9	2.18		-		-	
CH_3-16	0.88		0.92		0.84	

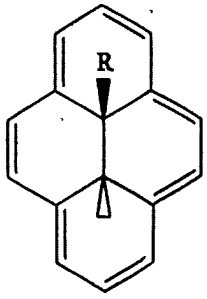
by, firstly, methylation with dimethoxycarbonium fluoroborate to give in 67% yield the *anti*-bis(sulfonium) salt, 120 which was then reacted with potassium t-butoxide in dry THF. This gave, after isolation and



118 120 51

purification, pure *trans*-15-phenyl-16-methyldihydropyrene 51 in 41% yield[117]. Recrystallization from cyclohexane gave dark green crystals, mp 159-160°C. The structure of 51 was confirmed by elemental analysis, ^{1}Hmr and by its mass spectrum that showed a molecular ion at *m/e* 294 (16%) with peaks at 279 (30%) and 217 (22%), indicating the loss of a methyl or a phenyl group respectively, plus a peak at 202 (100%) which indicated the loss of both substituents leaving the stable pyrene 34 nucleus behind.

Our compound 51 is not the first dihydropyrene with different internal substituents at the C-15 and C-16 positions. Boekelheide[118] reported the synthesis of 121, 122 and 123, where one substituent is kept as methyl while the other position is taken by a linear four atom chain. In the ^{1}Hmr, the internal methyl group absorbs at δ-4.25 for 122 and at δ-4.30 for 121 and 123. Since the internal methyl group of 38 absorbs at δ-4.25, we can safely deduce from this that increasing the length of the substituent, with or without a remote functionality, does not noticeably alter the ring current effect and therefore the geometry of the dihydropyrene skeleton. It may be argued that the



38: R = CH_3
51: R = Ph
121: R = $CH_2CH_2CH_2CH_3$
122: R = $CH_2CH_2CH{=}CH_2$
123: R = $CH_2CH_2OCH_3$

steric requirements close to the annulene ring will be the same for a methyl group as for a n-butyl group so that no distortion of the annulene skeleton is expected by changing from 38 to 121. On the other hand, incorporation of a phenyl group, as in 51, may lead to some distortion because of the closer proximity of the *ortho* protons to the annulene perimeter. However, the ^{1}Hmr of 51 shows the internal methyl protons to absorb at δ-4.30 so that we can conclude that also for 51 a normal dihydropyrene ring current is present.

The outstanding feature of the ^{1}Hmr of 51 is the appearance of the *ortho* protons of the phenyl substituent at δ2.80, the most shielded aryl protons known today. Also the *meta* protons (δ5.87) and *para* proton (δ6.20) are shifted upfield, with respect to normal aryl protons, because of the dihydropyrene ring current. The ^{1}Hmr (250 MHz) of 51 also shows two AB_2 and one AB spin system for the annulene ring protons (the ^{1}Hmr (250MHz) of 51 and 38 are compared in figure 3 and table 7). The upfield triplet (δ8.15) was assigned to H-9. This is reasonable when one assumes a geometry for 51 more or less identical with 38, which means that the phenyl group is not perpendicular to the plane of the annulene ring but slightly tilted towards H-9. This will induce, on average, a greater shielding for H-9 than for H-2. By using selective homo- and heteronuclear decoupling techniques, we were able to assign all the proton and carbon signals for 51 (for ^{13}Cmr of 51 see figure 4 and table 8). In general, nonproton-bearing carbons are exempted from being assigned by single-frequency decoupling. However, these carbons are often subjected to long-range ^{13}C-H couplings. Selective irradiation of a particular proton not only removes the one-bond

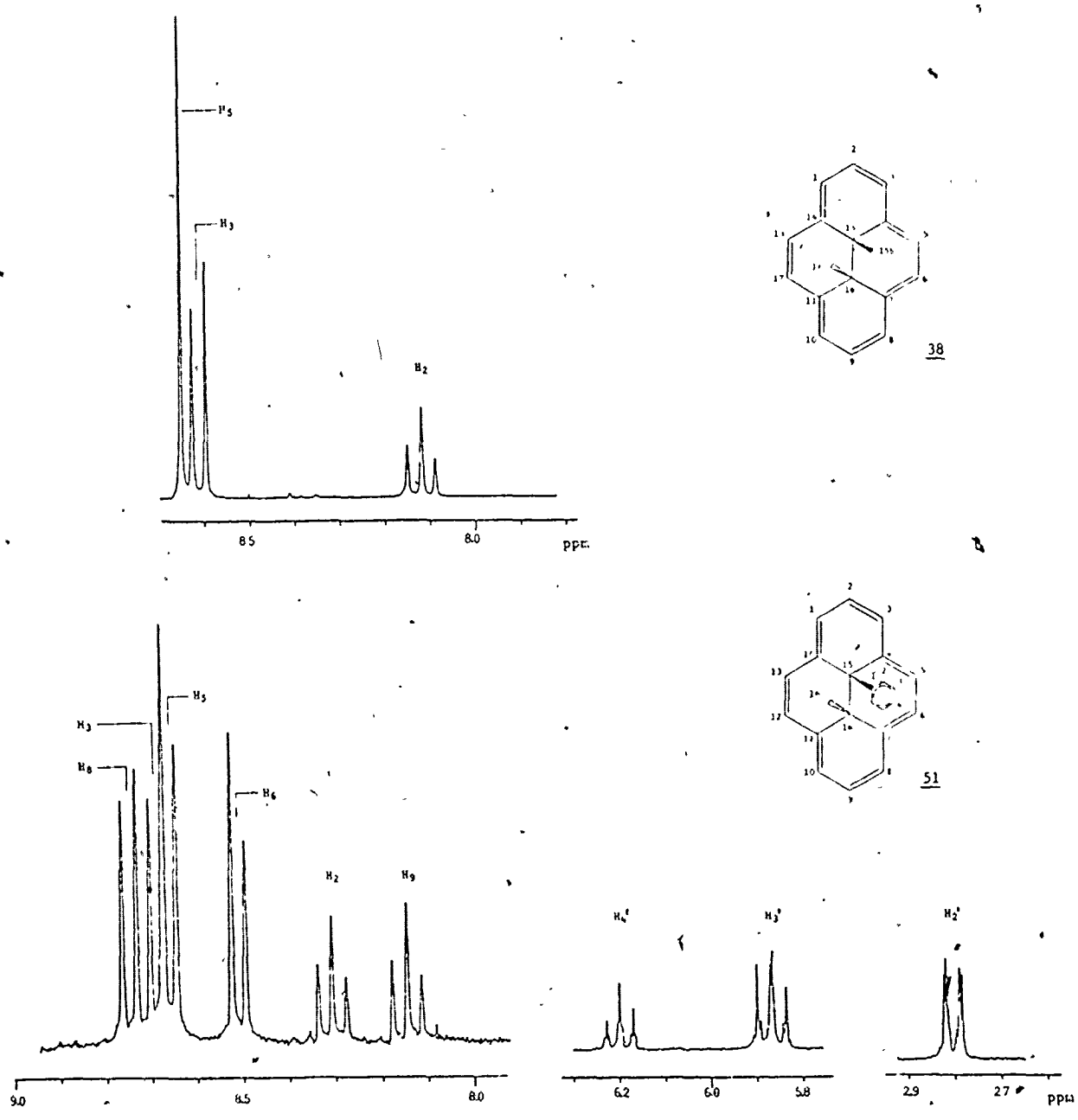
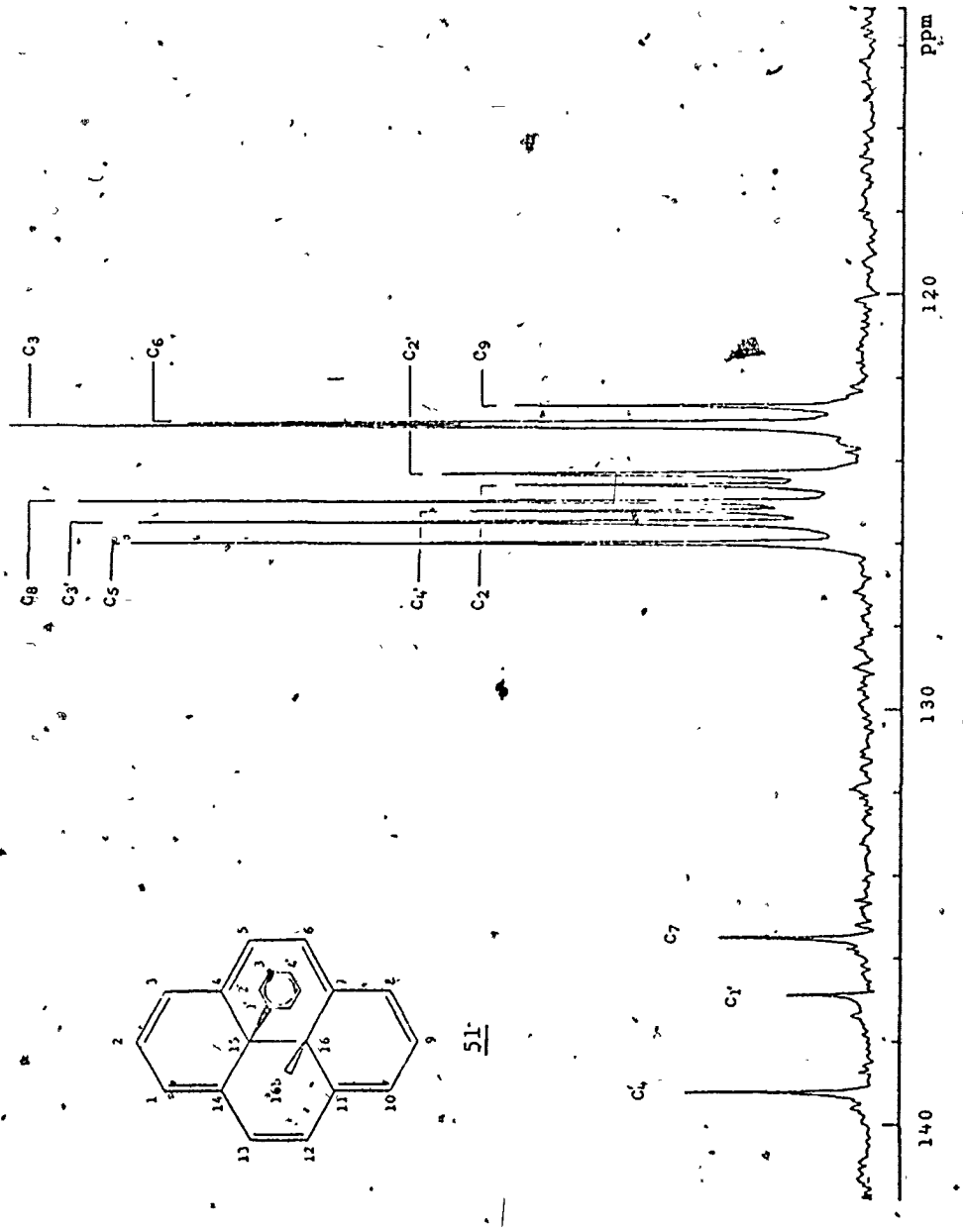


FIGURE 3. ^{1}Hmr (250 MHz) of dihydropyrene 38 and 51; internal methyl protons are not shown.



51

FIGURE 4. ^{13}Cmr (62.9 MHz) of dihydropyrene 51; only the aromatic region is shown.

TABLE 7. ^{1}Hmr ($CDCl_3$, 250 MHz) δ values and coupling constants (J) for dihydropyrene 51 and 38[a].

Proton	51	J (Hz)	38	J (Hz)
H-2	8.31	J_{2-3}=7.85	8.12	J_{2-3}=7.69
H-3	8.69		8.61	
H-5	8.66	J_{5-6}=7.63	8.65	
H-6	8.51		8.65	
H-8	8.75	J_{8-9}=7.81	8.61	
H-9	8.15		8.12	
CH_3-16b	-4.30		-4.24	
H-2'	2.80		--	
H-3'	5.87		--	
H-4'	6.20		--	

[a] δ values and coupling constants obtained by computer simulation, where necessary.

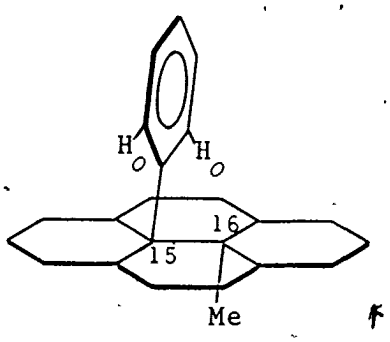
TABLE 8. ^{13}Cmr δ values[a] for dihydropyrene 51 and 38.

Carbon	51[b]	38[c]
C-2	124.4	122.9
C-3	122.9$_5$	123.3
C-4	139.0	136.7
C-5	125.8	123.3
C-6	122.9	123.3
C-7	135.3	136.7
C-8	124.8	123.3
C-9	122.5	122.9
C-15	36.6	30.1
C-16	29.1	30.1
C-16b	14.9	14.1
C-1'	136.7	--
C-2'	124.1	--
C-3'	125.3	--
C-4'	125.0	--

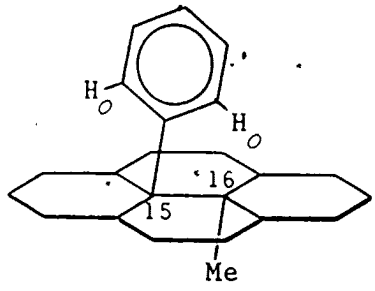
[a] δ $CDCl_3$ =77.0 ppm taken as reference point.
[b] Operating frequency: 62.9 MHz.
[c] Values taken from ref. 89 and corrected for δ $CDCl_3$ =77.0 ppm, operating frequency: 25.2 MHz.

coupling but also all long-range couplings to carbon in which this proton is involved. The result is a line narrowing and therefore an increase in intensity for those quaternary carbons that exhibit long-range coupling with the irradiated proton. This way, we were able to assign carbons C-4 and C-7 as indicated in figure 4.

In the ^{1}Hmr of 51 (figure 3) only one signal for the *ortho* protons of the phenyl group is present; this situation does not change between +100 °C and -100°C. On this basis, a structure like B, where the plane of the phenyl ring is parallel to the C_{15}-C_{16} bond, can be ruled out because the two *ortho* protons (H_o) would experience two different magnetic environments, which would lead to



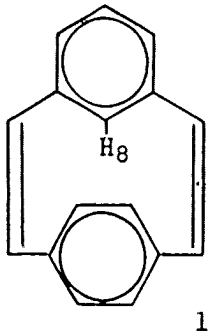
A



B

separate chemical shifts for both protons. Therefore a situation like structure A, where the plane of the phenyl ring is perpendicular to the C_{15}-C_{16} bond, or a freely rotating phenyl group, is more in line with the observation of only one signal for both *ortho* protons in the ^{1}Hmr. However, we believe that the phenyl group undergoes free rotation for the following reasons.

Again assuming the same geometry for 51 as for 38 than, by using the X-ray data of 38[61], and taking the standard benzene bond lengths and bond angles for the phenyl group, we calculate the minimum distance of H_o to the mean plane of the annulene ring as 1.77 Å. From the ^{1}Hmr of [2.2]metaparacyclophane-1,9-diene 124[119] we know that the *meta*-bridged benzene ring undergoes a fast ring inversion rendering the four protons of the *para*-bridged benzene ring into a singlet. Only below -100°C two separate signals are observed for these protons (coalescence temperature: T_c = -96°C). During this easy process of ring inversion ($\Delta G_c^{\neq}$ = 34.7 kJmol^{-1}), H-8 penetrates into the aromatic π-electron cloud of the *para*-bridged benzene ring. The crystal structure of 124[120] showed the two benzene rings to be inclined



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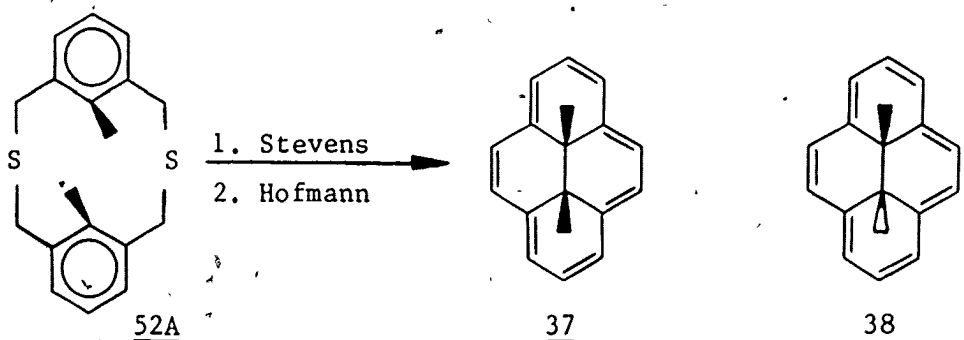
towards each other at an angle of 41°. In this position, the distance of H-8 to the plane of the *para*-bridged benzene ring is 2.16 Å. Now if the *meta*-bridged ring is brought perpendicular to the *para*-bridged ring, but without otherwise distorting bond angles or bond lengths, this distance becomes 1.59 Å. Thus, taking collectively into account our calculated value of 1.77 Å for the distance of the *ortho* hydrogens to the plane of the ring in 51, the easy process of conformational flipping for 124 and the invariability of the ^{1}Hmr of 51 between

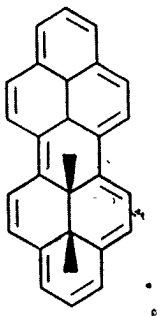
+100°C and -100°C, we conclude that the phenyl substituent in dihydropyrene 51 is freely rotating.

Having successfully synthesized *trans*-15-phenyl-16-methyldihydropyrene 51, we turned our attention towards the preparation of the *cis*-isomer 128. This dihydropyrene 128 should be accessible by a similar route as the one used for the synthesis of *trans*-51, the only difference being that *syn*-59A instead of *anti*-59 has to be used. Mitchell and Boekelheide[55] reported that Stevens rearrangement of *syn*-52A, followed by Hofmann elimination, gave 37 (as well as 38), the first example of a *cis*-substituted dihydropyrene. The formation of both 37 and 38 from 52A implies that a



52A (*syn*) 37 38

conformational inversion has taken place during the Stevens rearrangement of 52A. This is in accord with the postulated diradical mechanism for this type of rearrangement of sulfonium ylids[121]. However, no inversion took place during the Stevens rearrangement in the recently reported[122] syntheses of the annelated *cis*-dimethyldihydropyrenes 125 and 126. On the other hand, Wittig rearrangement of *syn*-52A gave almost 100% inversion[95], so that after Hofmann



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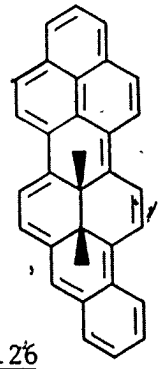

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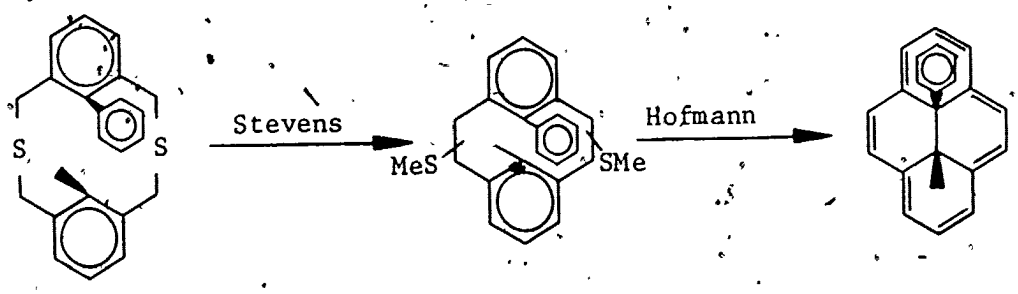
elimination, only *trans*-38 will be obtained. We therefore subjected *syn*-59A to the sequence of Stevens rearrangement and Hofmann elimination, hoping to isolate *cis*-128. Thus, reaction of 59A with dimethoxycarbonium fluoroborate gave 88% of the sulfonium salt which on treatment with potassium t-butoxide gave 11 mg (24%) of rearranged product 127 that, based on ^{1}Hmr, closely resembled 118 (no separation of



59A

(*syn*)

127

128

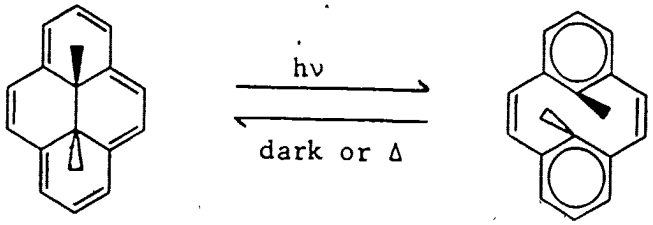
(*cis*)

isomers was attempted). This implies that an inversion from *syn* to *anti* has taken place during the rearrangement of 59A. However, subsequent treatment of the bis(sulfonium) salt of 127 with potassium t-butoxide in dry THF (Hofmann elimination) at 0°C did not yield

any identifiable products. Decreasing the temperature of the Hofmann elimination to -30°C did not change this result. Since the amount of pure *syn*-59A was limited, subsequent tries were done with 1 : 1 mixtures of 59 and 59A. However, the outcome was invariably the same: only *trans*-51 was obtained, no *cis*-dihydropyrene 128 could be detected.

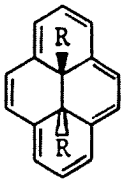
2.5 *Photoisomerization of 51.*

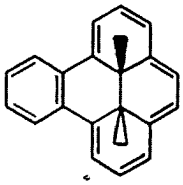
One of the interesting aspects of dimethyldihydropyrene 38 is its reversible photochemical valence tautomerization into the [2.2] metacyclophane-1,9-diene 38A[123a]. This can be viewed as a specialized

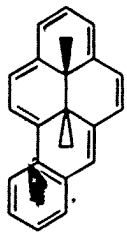


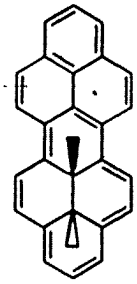
38 38A

example of the more general *cis*-stilbene to 4a, 4b-dihydrophenanthrene isomerization[124]. The tautomerization between 38 and 38A, as well as in many derivatives of 38, has been well studied by Blattmann and Schmidt[125]. Apart from 38, this type of tautomerization has also been found in 48[123b] and 49[123c] and in the benzannelated 129[126] whereas for 130[127] and 131[122] no diene could be detected on irradiation with visible light. The dark reaction is very sensitive to the nature of the internal substituent and is, for instance, six times faster for 48 than for 38[123c]. However, the correlation of the rate to the bulk of the internal substituent is not consistent, for the rate of the dark





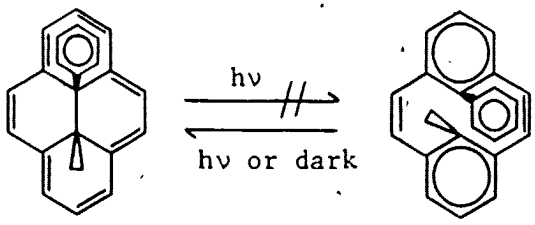




48 : R = CH_2CH_3
49 : R = $CH_2CH_2CH_3$

129 130 131

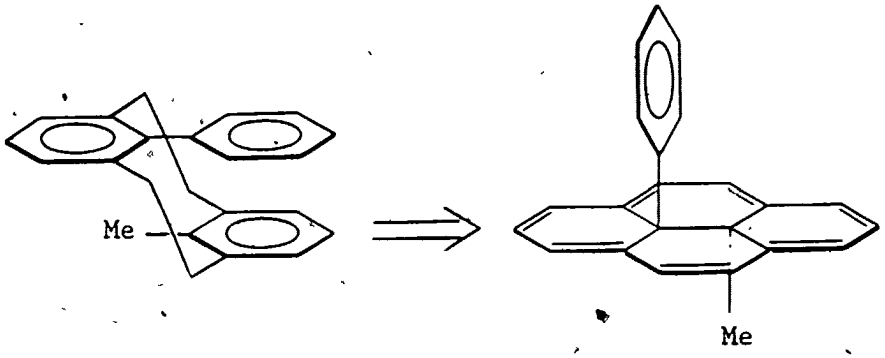
reaction for 49 lies intermediate between 38 and 48[123c]. Since the protons of the open form (the diene) do not overlap with those of its isomeric dihydropyrene, ^{1}Hmr can be used to monitor this process of valence tautomerization. However, irradiation of a solution of 51 in C_6D_6 with a tungsten lamp (General Electric, model MG,650 Watt) did not result in any change in the ^{1}Hmr of 51. Based on the mechanism



51 51A

of the Hofmann elimination, diene 51A will be formed first and will then rapidly isomerize to 51. And indeed, column chromatography in the dark of the Hofmann elimination product gave, in the first fraction, a mixture of 51 and 51A as based on ^{1}Hmr. The presence of 51A is indicated in the ^{1}Hmr by a singlet at δ1.70 for the internal methyl protons, an AB quartet (J=13 Hz) at δ6.69 and δ6.35 for the bridge olefinic protons and by further signals around δ7.05-6.45.

Efforts to separate 51A from 51 were unsuccessful because of the easy isomerization of 51A to 51. Irradiation of this mixture of 51 and 51A with visible light (30 seconds) led to a quantitative conversion of 51A to 51 based on the complete disappearance of the above mentioned signals in the ^{1}Hmr. Since the phenyl group in 51A



51A 51

is not able to rotate freely as in 51, we can state that 1) the relief of steric interaction of the bulky substituents with the metacyclophane ring in 51A, 2) the loss of strain energy of the twisted double bonds and 3) the gain of a planar (14) π-electron system more than offsets the loss of delocalization energy of the two benzene rings in 51A on isomerization to 51.

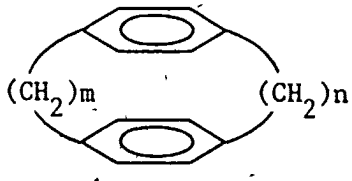
2.6 *Possible Interaction between the π-cloud of the Phenyl Substituent and the π-cloud of the Annulene Ring in 51.*

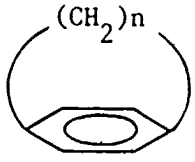
The interaction of non-conjugated π-electron systems has attracted great theoretical and experimental interest[128-132]. It is clear that in neutral molecules experimental evidence for such interactions should be sought in spectral and ionization properties.

As was already reported by Cram[133], the face to face crowding of the benzene rings in [m.n]paracyclophanes resulted in a shift to longer wavelength (bathochromic), accompanied by a loss of fine structure, in the electronic spectrum of these compounds as compared to the open chain analog 136. For instance, [4.4]paracyclophane 132 still showed the same features in its UV spectrum as the open form 136, whereas for [4.3]paracyclophane 133, a bathochromic shift and a marked decrease in fine structure were already noticeable. This shift in wavelength and loss of fine structure became even more pronounced in 134 and 135.

These phenomena can be attributed, in part, to the concommitant bending of the benzene rings upon shortening the bridges, since [8]paracyclophane 28 showed a minor bathochromic shift and loss of fine structure[44a] as compared to the higher [n]paracyclophanes. This trend continues for 29[44b] and 30[47]; the bathochromic shifts, however, are smaller than in the case of the [m.n]paracyclophanes.

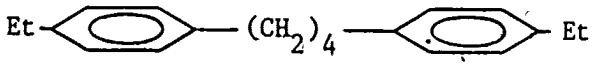
The same wavelength shift and structure loss can be seen in the UV spectrum of 137, as compared to 138, where the endo carbomethoxy group restricts the rotation of the two phenyl groups[134].



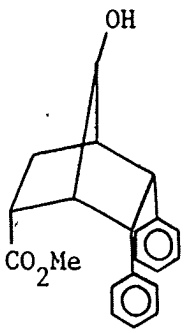


28: n=8
29: n=7
30: n=6

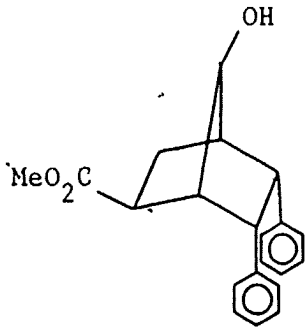
132: m=n=4
133: m=4,n=3
134: m=n=3
135: m=n=2



136

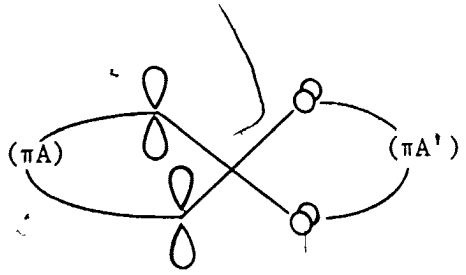


137

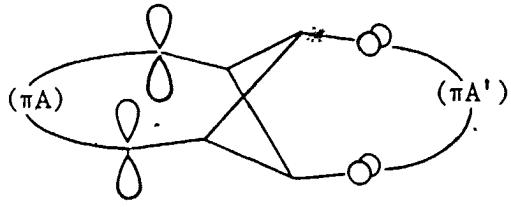


138

The more interesting cases, however, are those where the two π-systems are perpendicular and in close proximity to each other, since this is in fact the situation we encounter in our dihydropyrene 51. Two ways of obtaining mutually perpendicular π-electron systems are via spiro systems like A or via tricyclic systems like B. In



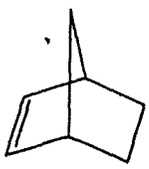
A



B

"spiropolyenes" like A, the orbital interaction is through-space[129] and this leads to a new kind of homoconjugation called spiro-conjugation[130]. This type of interaction manifests itself in the electronic spectra of spiro compounds where normally a bathochromic shift is observed as compared to the non-spiroannelated compound.. A similar through-space orbital effect is evident in norbornadiene 139 which also shows a bathochromic shift in its UV spectrum as compared to the monoene 140.

139

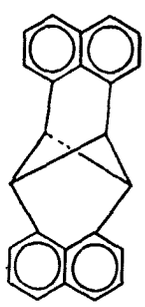


140

Gleiter[131] explained the strong bathochromic shift in the UV spectrum of 141 (λmax: 300 nm)[132b], as compared to 142 (λmax: 220 nm)[132a], by a strong through-bond interaction between the π-orbitals of the double bond and the σ-bonds of the cyclobutane ring. The strong bathochromic and hyperchromic shift observed for 143, as reported by Mitchell and Sondheimer[135], can therefore be explained by a similar type of through-bond interaction. Thus, in case there is an inter-

141

142



143

action between the two perpendicular π-systems of 51, we may expect a shift to longer wavelength in the electronic spectrum with a possible loss of fine structure as compared to the spectrum of dimethyldihydropyrene 38. In figure 5, the spectra of 51 and 38 have been depicted whereas in table 9 a comparison of the absorption maxima and extinction

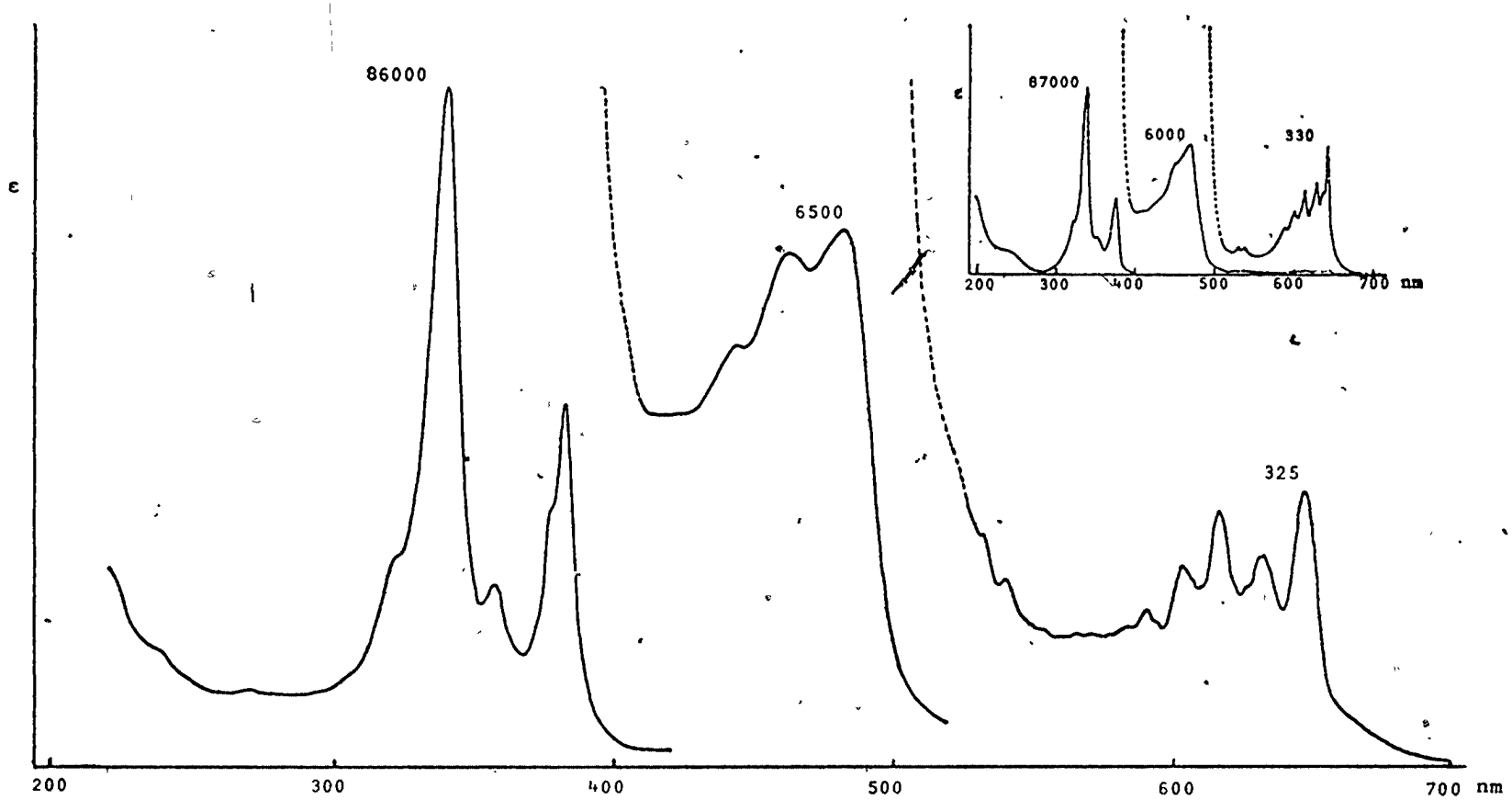
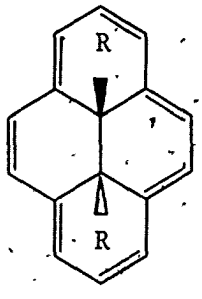


FIGURE 5. Ultraviolet and visible absorption spectra of *trans*-15-phenyl-16-methyldihydropyrene 51 (large spectrum) and *trans*-15,16-dimethyldihydropyrene 38 (insert; spectrum taken from reference 98b).

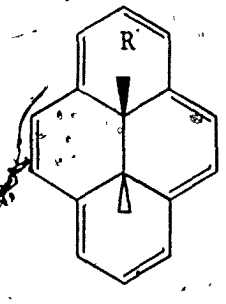
TABLE 9. UV $\lambda_{max}^{cyclohexane}$ (nm) and ε for some *trans*-dihydropyrenes.

38[98b]		48[123b]		49[123c]		121[118a]		122[118b]		123[118b]		51	
λ	ε	λ	ε	λ	ε	λ	ε	λ	ε	λ	ε	λ	ε
						238	6.300	237	5.700				
						273	780	275	680	275	770		
				331	20.500	324	34.000	320	37.500	324	31.000		
337.5	87.000	345	61.000	345	67.500	340	100.000	341	96.300	337	67.000	341	86.000
		349	63.900	348	67.500	343	110.000	345	10.500	346	98.000		
		367	18.400	366	20.500	358	25.000	358	33.000	357	25.000	357.5	24.000
377	37.000	386	28.180	386	31.000	379	43.000	380	41.000	380	38.000		
		391	36.850	391	39.000	383	52.000	384	49.000			383	46.000
463	6.000	428	4.870	465	5.400	420	3.100	415	4.200	430	4.100	443	5.000
		493	4.620			441	4.300	439	3.800	481	5.700	461	6.200
						463	6.200	450	5.900			481	6.500
						478	6.500	475	6.100				
						485	6.300	483	5.700				
528	28	545	97	544	105	533	640	534	600	533	610	540	215
536	58	554	78	553	85	542	590	574	570	569	320	590	217
586	110	606	100	605	118	575	430	590	620	583	240	603	264
598	150	619	140	618	160	581	570	605	1.300	635	690	615.5	296
611	210	633	246	632	235	592	950	617	1.500	651	570	631	244
627	230	649	255	648	282	605	1.400	634	1.850			645.5	325
634	210	655	376	664	372	618	1.800	651	2.000				
641	330					634	1.900						
						647	2.100						
						652	2.100						

coefficients of a series of *trans*-dihydropyrenes has been made. From figure 5 we see that no loss of fine structure is evident for 51 as compared to 38. Furthermore, a comparison of the absorption maxima (table 9) shows that the whole spectrum of 51 is shifted *ca.* 4 nm to longer wavelength with the exception of the peak at 481 nm which is shifted 18 nm to longer wavelength as compared to the corresponding maximum in the spectrum of 38 (463 nm). This single shift may therefore be related to a possible interaction of the two π-clouds in 51. However, when we compare 51 with the other known asymmetrically substituted dihydropyrenes, *i.e.* 121, 122, and 123, we see (table 9) that these three compounds have a comparable absorption maximum in



38; R = CH_3
48: R = CH_2CH_3
49: R = $CH_2CH_2CH_3$



51: R = Ph
121: R = $CH_2CH_2CH_2CH_3$
122: R = $CH_2CH_2CH{=}CH_2$
123: R = $CH_2CH_2OCH_3$

their electronic spectra (481 - 485 nm) as the one already mentioned for 51 (481 nm). Therefore, the observed bathochromic shift of this peak (481 nm in 51) with respect to the one in the spectrum of 38 (463 nm) may be simply due to the increased size of the substituent rather than to π-π interaction, since 121, 122 and 123 do not have a chromophore close to the annulene ring system.

Another technique that may shed some light on the possible interaction between the two π-clouds of *trans*-15-phenyl-16-methyldihydro-

pyrene 51 is ESR spectroscopy. For this purpose, the radical anion $51^{\cdot -}$ was prepared by reduction of 51 with potassium metal using 1,2-dimethoxyethane (DME) as solvent. Since direct exposure of the DME solution of 51 to the surface of potassium may lead to a two electron reduction to form the dianion, the reduction was carried out in two steps. Firstly, generation of solvated electrons in DME and, secondly, reaction of 51 with these solvated electrons. Both steps have to be carried out at low temperature (-80°C). The ESR-spectrum obtained thereupon is shown in figure 6. Increasing the temperature stepwise from -80°C to +20°C did not alter the observed signal, *i.e.*, no fine structure could be detected. The overall triplet shape of the spectrum (figure 6) is due to electron spin coupling with H-2 and H-9 which should be of comparable magnitude (*ca.* 5.5 G*). This assignment was borne out by the large hyperfine splittings of 5.46 G and 5.48 G found for the H-2 protons of the radical anions of 38[136] and 40[137] respectively. Coupling constants to other hydrogens in these two systems were smaller than one. Unambiguous assignment of the 5.46 G coupling to H-2 in 38 was made by preparation of the radical anion of the 2,9-dideutero derivative of 38[136]. The featureless structure of the ESR spectrum of 51 is not too surprising when we consider the theoretical number of lines possible for $51^{\cdot -}$. Assuming a delocalization of the odd electron over both π-systems, a total of 23,328 lines can be found for $51^{\cdot -}$ whereas for $38^{\cdot -}$, only 525 lines are theoretically available. Even by ignoring interactions of the electron with the two substituents

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* hyperfine coupling constants are expressed in Gauss (G).

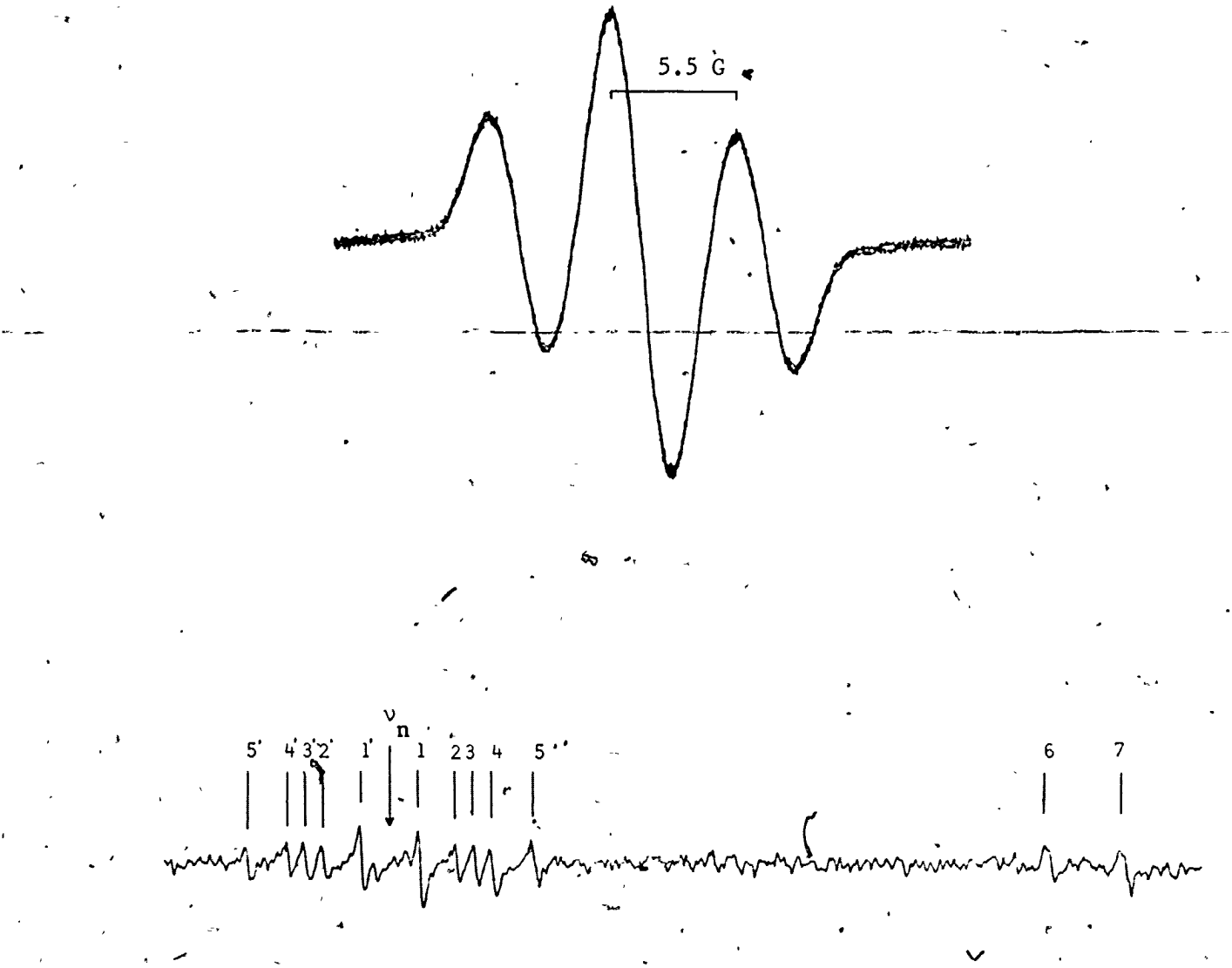


FIGURE 6. ESR (top) and ENDOR spectrum (bottom) for the radical anion of *trans*-15-phenyl-16-methyldihydropyrene 51. The numbers above the ENDOR spectrum refer to the frequencies listed in table 10. Both spectra recorded at -80°C on a Bruker ER 200 tt.

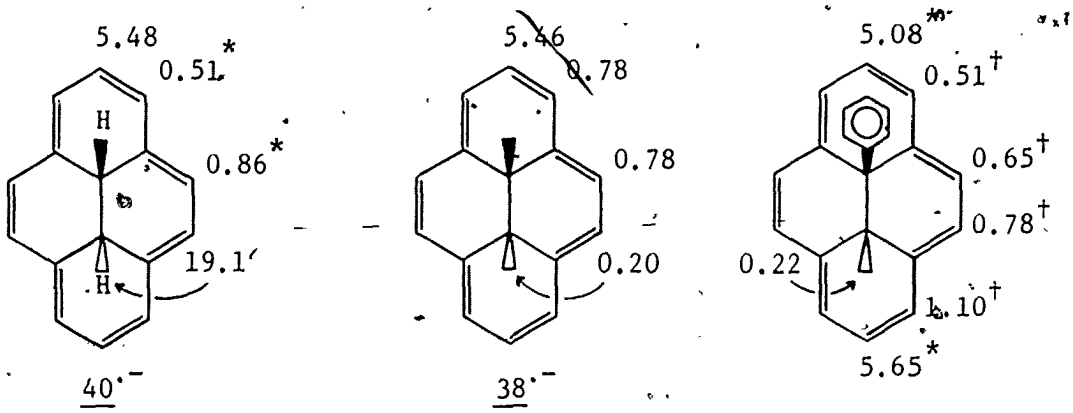
in $51^{\cdot -}$, we still calculate the number of lines in the ESR spectrum of $51^{\cdot -}$ to be more than four times as great as for $38^{\cdot -}$.

As in ^{1}Hmr, the technique of double resonance can be used to simplify ESR spectra. For this reason, the electron nuclear double resonance (ENDOR) spectrum of $51^{\cdot -}$ was recorded (figure 6). The ENDOR spectrum consists of a series of doublets centered around the free proton frequency (ν_n). The number of lines to highfield of ν_n is equal to the number of sets of equivalent protons that undergo interaction with the odd electron in the radical anion. As can be seen from figure 6, seven lines are recorded in the ENDOR spectrum of $51^{\cdot -}$ indicating seven different types of protons. In table 10, the observed ENDOR frequencies and coupling constants for $51^{\cdot -}$ are tabulated.

TABLE 10. ENDOR frequencies (MHz) and hyperfine coupling constants a_H (Gauss) for the radical anion of *trans*-15-phenyl-16-methyldihydropyrene 51.

ENDOR frequencies	Line position	a_H	Proton
12.82	5'		
13.26	4'		
13.44	3'		
13.63	2'		
14.03	1'		
14.35	ν_n		
14.66	1	0.22	CH_3
15.07	2	0.51	
15.26	3	0.65	H-3,5,6,8
15.44	4	0.78	
15.89	5	1.10	
21.47	6	5.08	H-2,7
22.27	7	5.65	

In scheme 7, a comparison has been made between the coupling constants found in the three known dihydropyrene radical anions 40$^{\cdot -}$, 38$^{\cdot -}$, and 51$^{\cdot -}$. A correct assignment of the observed coupling constants ~~for~~ 51$^{\cdot -}$ at this stage is not possible. From the ENDOR data, it is



SCHEME 7

immediately obvious that there is no direct spin density on the phenyl substituent. However, there is still the possibility of long-range proton hyperfine interaction between the odd electron in the annulene perimeter and the *ortho* proton of the phenyl substituent.

Two mechanisms have been invoked for obtaining spin density at a nucleus separated by two or more σ-bonds from some principal center containing a significant portion of the electron spin density. One such mechanism, called spin polarization, is purely a through-bond effect where spin density is induced through the bonding electrons. This mechanism decreases rapidly when the number of intervening σ-bonds increases. The second mechanism is that of spin delocalization (some-

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* a reverse assignment cannot be excluded

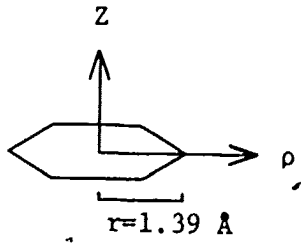
† values may be interchanged

times refered to as hyperconjugation) and is a through-space effect. For instance, the large coupling of 19.1 G found in 40$^{\cdot-}$ for the internal hydrogens has been explained by spin delocalization[137]. Since the *ortho* hydrogen of the phenyl group (H-1') is four bonds removed from the nearest electron center (C-4), the effect of spin polarization will be negligible. As for the possibility of spin delocalization from the annulene perimeter onto the *ortho* hydrogen, molecular models indicate a favorable arrangement between H-1' and C-3 or C-5. However, from MO calculations[136] as well as from the observed coupling constants for 51$^{\cdot-}$, we can infer a small spin density on carbons C-3 and C-5 as opposed to C-2 and C-4. Therefore, the effect of spin delocalization from C-3 (C-5) to H-1' will be even smaller than the observed coupling constants for H-3 and H-5. Our previously made assumption of a freely rotating phenyl group will decrease a possible spin delocalization even more. To make sure that no coupling constants smaller than 0.22 G were overlooked, an expanded ENDOR scan (1MHz width) was made around the free proton frequency. However, no extra coupling constants could be detected. We therefore conclude that there is no direct π-orbital overlap between the two π-systems in 51 and further that, probably because of rotation, no through-space delocalization of spin density onto the phenyl ring has taken place. However, to use the words of Russell[138], "It is considerably more reliable to make inferences based on the observation of long-range couplings rather than the lack of them". Thus both UV and ESR seem to support the idea that 51 consists of two non-interacting orthogonal π-electron systems.

2.7 *Assessment of Ring Current Models for 51.*

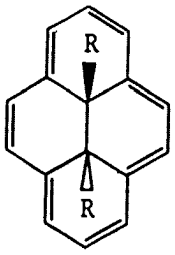
2.7.1 *Existing Models.*

The phenomenon of the aromatic ring current in NMR spectroscopy has been the subject of much interest and investigation since the original suggestion of a ring current shift in benzene by Pople[20]. The most widely used approach today, to explain ring current shifts, is that based on the classical current loop model of Johnson and Bovey (JB)[81a], probably because of the easy access to their tabulated shielding-deshielding contributions of the benzene ring[81b]. The JB model for benzene consists of a current loop with radius 1.39Å (standard benzene bond length). The parameters; Z and ρ, are used to determine any position in space around the benzene ring; Z denotes the vertical distance above the plane of the ring whereas ρ gives the in-plane distance from the center of this ring, both parameters are tabulated as 0.1 increments of the benzene ring radius (1.39Å)[81b].

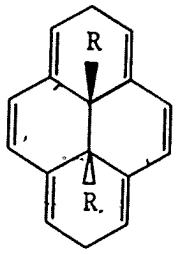


Boekelheide[89] adopted the JB model in his attempt to rationalize the observed chemical shifts of the alkyl protons and carbons in 38, 48 and 49. The dihydro derivatives 144, 145 and 146 were used as reference (no ring current present), since it is believed that the geometry of these compounds is almost the same as that for the

corresponding dihydropyrenes.

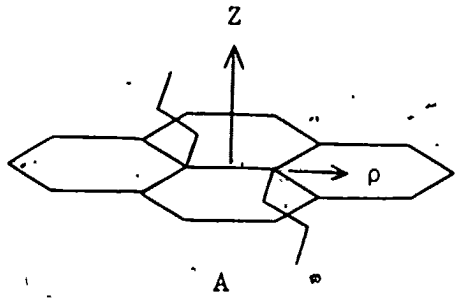


38: R = CH_3
48: R = CH_2CH_3
49: R = $CH_2CH_2CH_3$



144: R = CH_3
145: R = CH_2CH_3
146: R = $CH_2CH_2CH_3$

For the purpose of comparing the observed chemical shift difference $\Delta\delta$ with the calculated shielding contribution $\Delta\sigma$, due to the ring current, Boekelheide assumed the conformation of the alkyl side chain in 48 and 49 to be as shown in A. Furthermore, the variation of the in-plane distance ρ for the carbons and hydrogens of the side chain



A

was neglected. Although the plot of the observed shift difference $\Delta\delta$ versus Z (out of plane distance)* showed a similar curve as the theoretical graph (JB method), fairly large deviations (2-5 ppm) can be observed (see figure 7).

* Z measured from Dreiding models for 38, 48 and 49.

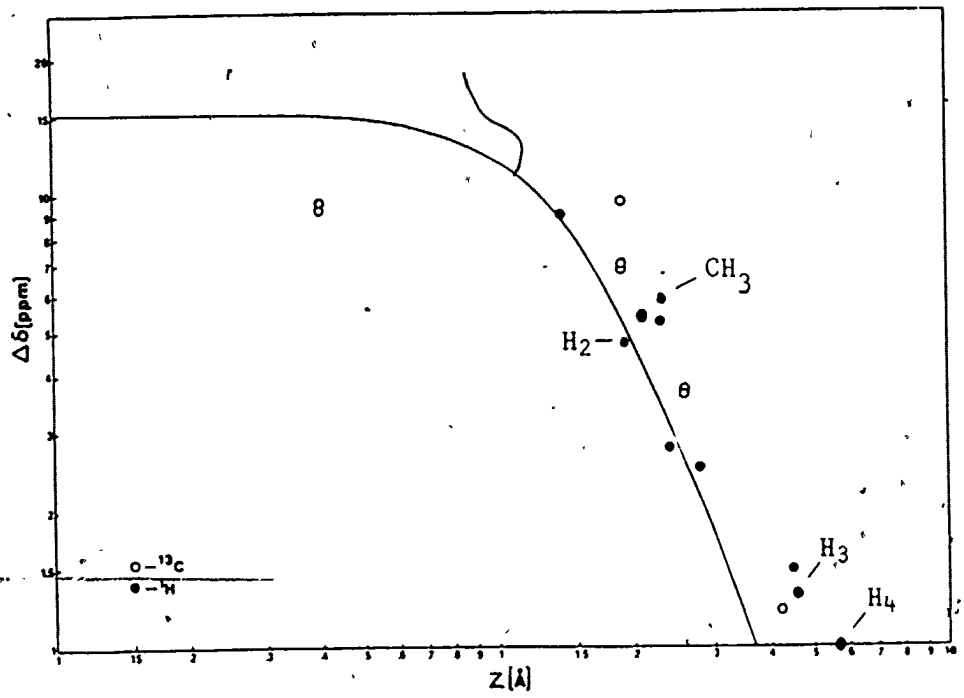


FIGURE 7. Correlation of the upfield shifts due to the ring current in 38, 48, 49 and 51 (the solid line represents the theoretical results of Johnson and Bovey for benzene; ref. 89).

Because of the above mentioned approximations in the assessment of the ring current of dihydropyrenes we hoped that by making allowance for the variation in ρ, our compound 51 with the non-flexible phenyl substituent, would serve as a better model.

2.7.2 *Single Current Loop Model for 51.*

The chemical shift of the aromatic protons of toluene (δ 7.20) was taken as reference for the phenyl protons of 51 in the hypothetical case that the aromatic ring current would be absent; local anisotropy effects on the phenyl protons will not be considered yet. Compound 144 was used as reference for the internal methyl protons of 51.

To calculate the out of plane distance (Z) and the in-plane distance

(ρ) for the different hydrogens above the plane of the annulene ring of 51, we used the data from the crystal structure of 38[61]. This gave us the basic annulene skeleton as well as the angle between the substituent and the plane of the ring (83.5°). The C_{15}-C_1 bond length was taken as 1.52Å whereas standard benzene bond lengths (1.39Å) and bond angles (120°) were used for the phenyl substituent; the C-H bond was taken as 1.1Å for benzene. Since we consider both substituents in 51 as freely rotating, the in-plane distance (ρ) was averaged over four positions for the phenyl hydrogens whereas six positions were used to describe the methyl group.

To compare the values of Δδ observed for 51 with Boekelheide's ring current model[89], we have added our values to figure 7; the numerical comparison between Δδ (observed) and Δσ (calculated) is made in table 11.

TABLE 11. Shielding calculations for the single current loop model of 51.

				ρ=0			
				R=1.39[a]	R=1.39	R=2.16	R=2.23
Prpton	δ(obs)[b]	δ(ref)	Δδ	Δσ	Δσ	Δσ	Δσ
H-2'	2.80	7.20[c]	-4.40	-4.67	-0.45	-3.74	-4.42
H-3'	5.87	7.20	-1.33	-0.60	-0.30	-1.19	-1.31
H-4'	6.20	7.20	-1.00	<-0.30	<-0.27	-1.01	-1.11
CH_3	-4.30	1.00[d]	-5.30	-3.55	-2.46	-7.59	-7.99

[a] ring radius R in Å; [b] all δ, Δδ and Δσ values in ppm; [c] toluene taken as reference; [d] δ(ref) taken from reference 89.

Although the calculated value of Δσ for the *ortho* protons (H-2') is very close to the observed value of δ-4.40, the strong deviation

between $\Delta\delta$ and $\Delta\sigma$ for the other protons makes reconsideration of this model obvious. For comparison $\Delta\sigma$ was calculated for the same ring current model but now with the in-plane distance included ($\rho \neq 0$). It is, of course, obvious that such a simple model must be far removed from actual size and shape of the current loop in the annulene ring, for a current loop with radius 1.39Å is situated far inside the perimeter of the annulene. Furthermore, the actual shape of this loop will probably resemble an ellipse rather than a circle. As was already mentioned in chapter 1, Haddon[76] reported that a direct relation exists between the ring current (RC) and the resonance energy (RE) of the aromatic system (equation 1). In the same paper[76] the ring current was shown to be proportional with the ring area (S) and inversely proportional with the number of π-electrons (N); E represents the total π-energy of the system (equation 2).

$$RC = \frac{3S}{\pi^2} RE \qquad (1)$$

$$RC = \frac{ES}{2N^2} \qquad (2)$$

Using the resonance energies calculated by Haddon[76], Aihara[13] or the Zagreb group[14] we found that by applying equation 1, the ring current for the [14]annulene is *ca.* 1.6 times greater than for benzene, whereas application of equation 2 gave a factor of 1.5-1.7, depending on the value taken for E[82].

A simple way of increasing the ring current is by expanding the radius of the current loop and subsequently expressing Z and ρ in

units of this new radius; the shielding contributions can then again be calculated from the JB tables.

Since the *para* proton (H-4') has a fixed position with respect to the annulene ring it can be used to calibrate the size of the ring current. As can be seen from table 11, a ring current with radius 2.16Å results in a calculated $\Delta\sigma$=-1.01, perfectly in line with the observed $\Delta\delta$=-1.00. However, the calculated shielding contributions ($\Delta\sigma$) for H-2' and H-3' are too small. Increasing the ring radius to 2.23Å (1.6 times the size of benzene) gave a near perfect match between $\Delta\sigma$ and $\Delta\delta$ for the phenyl protons. However, in this model the internal methyl protons are too strongly shielded ($\Delta\sigma$= -8.0). To obtain the correct shielding contribution of $\Delta\sigma$=-5.30 for the methyl protons a ring radius of 1.85Å had to be used. This, however, strongly underestimated the $\Delta\sigma$ values for the phenyl protons. Although minor changes in the ring radius resulted in major changes for the shielding contributions of H-2' and the methyl protons (see table 11), we were not able to find a set of $\Delta\sigma$ values that resembled the observed $\Delta\delta$ values for the four types of protons in 51.

2.7.3 *Multiple Current Loop Model for 51.*

Since a single current loop, placed in the center of the annulene ring, was not able to describe the observed shielding effects in 51 satisfactorily, we tried to improve our calculated values of $\Delta\sigma$ by summation over two or more circular current loops. We thought that two current loops, centered at C-15 and C-16 respectively, would give

a better description of the more elongated ring current in the annulene ring of 51. However, even variation of the ring radius of these loops between 1.39Å and 1.85Å did not yield a set of $\Delta\sigma$ values that was in agreement with the observed $\Delta\delta$ values.

Although the best ring current model for dihydropyrenes would be the line current model used by Haddon[82] this would also require a full mapping of the shielding-deshielding contributions around the ring. We, therefore, resorted to a simpler approximation.

Our next model is based on the observation by Pople[139] who showed that the proton chemical shifts of some polycyclic aromatic hydrocarbons could be calculated under the assumption that essentially the same current, equal to the benzene ring current, is induced in each benzene hexagon of the polycyclic system. The same approach was later used by Abraham[140] to calculate the observed proton chemical shifts in porphyrin systems.

We therefore placed four current loops in the annulene ring, each one located in the center of one of the four hexagons. For instance, for hexagon A, where five of the six carbons participate in the overall ring current (figure 8A), we approximated the contribution of the total ring current for this hexagon by a small circular current centered in hexagon A (figure 8B). The same approximations were used for the three remaining hexagons B, C and D (figure 8C).

For calculation purposes we further assumed the two substituents in 51 to be perpendicular to the plane of the annulene ring instead of making an angle of 83.5°; apart from this the same bond lengths and

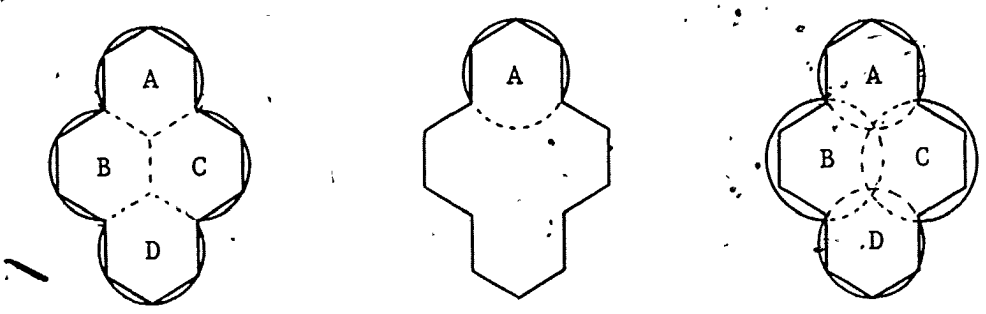


FIGURE 8. Four current loop model for ring current shielding calculations of dihydropyrene 51

bond angles were used as mentioned in section 2.7.2.

For our model we took the standard benzene ring current loop for the hexagons A and D (figure 8), whereas the ring radius for the current loops in B and C were simultaneously varied between 1.62Å and 1.72Å. The pertinent shielding calculations are reported in table 12:

TABLE 12. Shielding calculations for the four current loop model of 51.

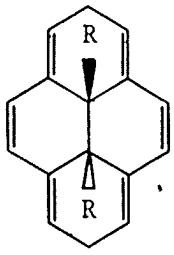
				$R_A=R_D=1.39$			
				R=1.62[a]	R=1.65	R=1.68	R=1.72
Proton	δ(obs)	δ(ref)[b]	Δδ	Δσ	Δσ	Δσ	Δσ
H-2'	2.80	7.20	-4.40	-2.97	-3.14	-3.30	-3.52
H-3'	5.87	7.20	-1.33	-1.48	-1.52	-1.57	-1.62
H-4'	6.20	7.20	-1.00	-0.99	-1.02	-1.07	-1.13
CH_3	-4.30	1.00	-5.30	-5.36	-5.52	-5.67	-5.92

[a] R stands for $R_B=R_C$ (Å), the ring radius of the current loop in hexagon B or C (see figure 8).

[b] δ(ref) as defined in table 11.

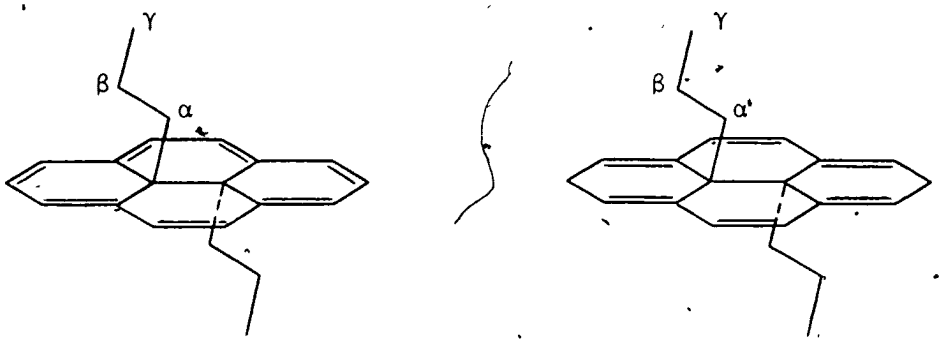
We believe that the combination of two benzene ring currents for the hexagons A and D ($R_A = R_D = 1.39$Å) and two current loops of radius 1.68Å each for the hexagons B and C ($R_B = R_C = 1.68$Å) gives the best description of the ring current in 51, although it may seem that the difference between $\Delta\sigma$ and $\Delta\delta$ for H-2' is too large. However, no corrections for local anisotropy contributions to δ (ref) have been made so far.

If we look at the chemical shifts for the ethyl-side chain in 145[89] we notice that the methyl protons absorb at δ0.63, whereas a



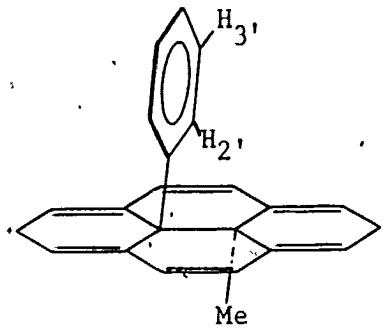
145: R = CH_2CH_3
146: R = $CH_2CH_2CH_3$

value of δ0.95 is normally found for the methyl protons in straight alkanes. This means that the ethyl side chain in 145 experiences an upfield shift of at least 0.3 ppm due to the local anisotropy of the double bonds. This effect is still noticeable in 146 where the methyl protons (γ) of the side chain absorb at δ0.82. Boekelheide[123c] interpreted the AA'XX' spin system of the α- and β-methylene protons of the n-propyl group in 49 either in terms of a preferred conformation or as restricted rotation about the carbon-carbon bond between the α- and β-methylene carbons. This interpretation was supported by the fact that the ^{1}Hmr of 49 did not show any temperature dependence over the range of -80° to +80°C.



49 146

If indeed these alkyl side chains in 48 and 49 have a preferred conformation like the one depicted above, we can say that the α-methylene protons will experience a smaller shielding from the double bonds in 145 or 146 than the *ortho* protons (H-2') of the phenyl group in the so far hypothetical molecule 147. This is because the *ortho* protons will be pushed farther over the double bonds in 147 during the rotation of the phenyl group than the comparable β-protons in



147

their "fixed" conformation as in 145 and 146. Since the γ-protons in

146 experienced a similar but smaller shielding from the double bonds we can say that also for the *meta* protons (H-3') in 147 a small up-field shift can be expected due to the olefinic system. We therefore believe that the reference chemical shift for H-2' and H-3' should be smaller than the δ7.20 value quoted in tables 11 and 12. However, it has to be seen if the chemical shift for H-2' in 147 will be as high field as δ6.20 which is the shift value that would give a very good match between Δδ and Δσ (table 12). It would therefore be of considerable help if compound 147 were available. Unfortunately, our efforts to synthesize 147 have been without success so far.

Although the ring current effect for protons has been well established and, in many instances, successfully applied, the picture is less clear for heavier elements like carbon. For instance, Boekelheide[89] concluded, based on his data represented in figure 7*, that "for the same position in space relative to the mean plane of delocalization of the aromatic π-electron cloud, the magnitude of the ring-current effect on chemical shifts is essentially the same for carbon-13 as for protons and follows the theoretical curve predicted by Johnson and Bovey". On the other hand, extensive investigation of the ^{13}Cmr of bridged annulenes led Günther[141] to a totally different conclusion. According to his opinion: "It is evident that the dominance of local atomic contributions to the shielding constant prevents the carbon nucleus from being a probe for ring current effects; this is,

* for a different graph of the data from figure 7 see reference 40.

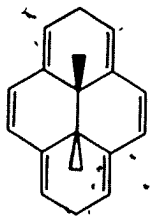
however, no disadvantage, since ^{1}Hmr will take care of ring currents and there is no need to duplicate these results".

In table 13 the ^{13}Cmr δ values are reported for the phenyl and methyl substituents of 51 together with values for possible reference compounds.

TABLE 13. ^{13}Cmr δ values for selected carbon atoms of 51 and possible reference compounds; calculated shielding (Δσ) for these carbon atoms of 51.

Carbon	δ(51)	δ(144)[a]	δ(148)[b]	δ(149)[b]	δ(150)[b]	δ(151)[b]	Δσ[c]
C-1'	136.7	-	137.8	144.3	148.8	150.9	-11.2
C-2'	124.1	-	129.3	128.1	126.6	125.4	- 5.1
C-3'	125.3	-	128.5	128.6	128.6	128.3	- 2.5
C-4'	125.0	-	125.7	125.9	126.1	125.7	- 1.9
CH_3	14.9	23.6	-	-	-	-	-10.5

[a]Reference 89; [b]reference 148; [c]based on four current loop model with $R_A=R_D=1.39$ Å and $R_B=R_C=1.65$ Å (figure 8).



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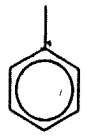

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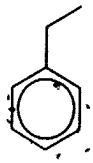

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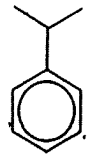

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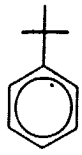

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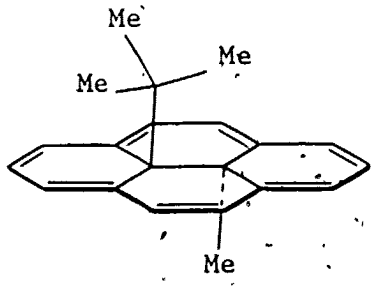
As can be seen from table 13, the calculated shielding contributions (Δδ) do not really match with the "observed" shift differences (Δδ); the best values for Δδ are obtained by taking ethylbenzene 149 as reference compound for the carbon chemical shift values of the phenyl ring of 51 in the absence of a ring current.

Although we are lacking a good reference model for our observed carbon chemical shift values of 51, we can state that the proton is indeed a far better nucleus to probe a possible ring current effect than the carbon. Our proposed four current loop model (figure 8) gives a good qualitative picture of the ring current in dihydropyrene 51 and is expected to be close to quantitative if reference compound 147 becomes available. A further test for this model would be the synthesis of dihydropyrene 152 where one substituent is a t-butyl group. This group is expected to undergo free rotation, for the same reason as the phenyl group does. Therefore, this t-butyl group does not suffer from the shortcomings of the linear alkyl chains in 48 and 49 which may or may not undergo free rotation. Furthermore, the protons of the t-butyl group will extend further over the dihydropyrene ring and are therefore even closer to the edge of the current loop in hexagons B and C (figure 8), the area where the shielding-deshielding contributions are changing fastest.



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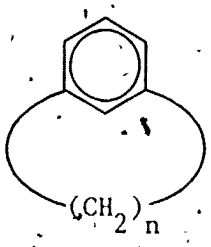
CHAPTER THREE

CONFORMATIONAL BEHAVIOUR OF METACYCLOPHANES.

3.1 *Introduction.*

The term 'cyclophane' was first introduced by Cram[143] in 1951 and was later defined[144] as a general name for a family of compounds containing any number of benzene rings joined by chains in the *para*, *meta* and/or *ortho* positions. An increasingly greater interest has arisen in these bridged molecules during recent years resulting in many bizarre new structures. To accommodate the need for a systematic way of naming all these new compounds a general nomenclature was developed[145] to name all bridged molecules containing any number and type of aromatic rings.



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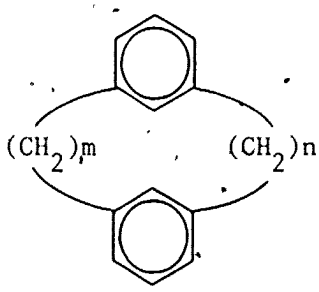

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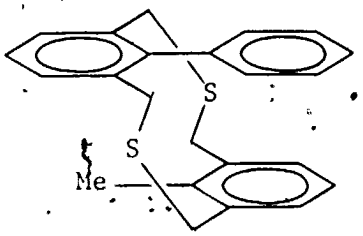
As far as metacyclophanes are concerned, the most common are the [n]metacyclophanes 153 and [m.n]metacyclophanes 154 (m≠n or m=n); both series show interesting conformational changes. Dithiametacyclophanes, used extensively as precursors for the corresponding metacyclophanes[146], show similar conformational processes. However, the

longer C-S bond, and therefore lower bending energy of a C-S-C bridge provides more conformational flexibility in the dithiametacyclophanes than in their metacyclophane counterparts, thus resulting in lower conformational energy barriers.

During the course of this work it was discovered that the phenyl substituent of the otherwise rigid thiacyclophanes 59 and 59A underwent a dynamic process of ring twisting[111].



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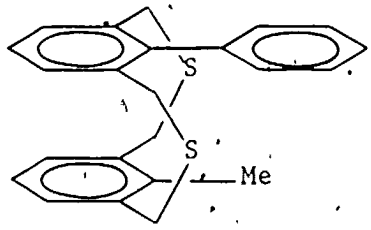
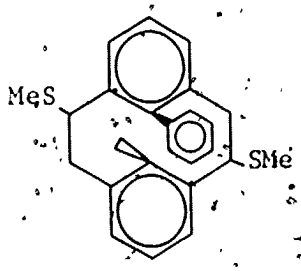
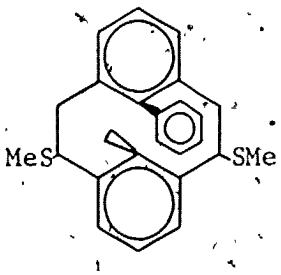


59A

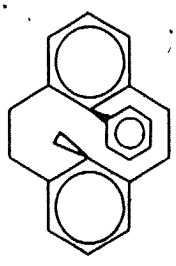
At low temperatures we were able to 'freeze out' this process on the NMR time scale. Subsequently it was found that this process of ring twisting of the phenyl substituent was also present in the more closely packed [2.2]metacyclophanes 118A, 118B and 119.



118A



118B



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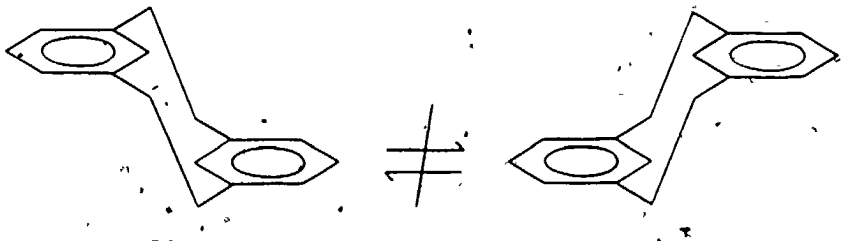
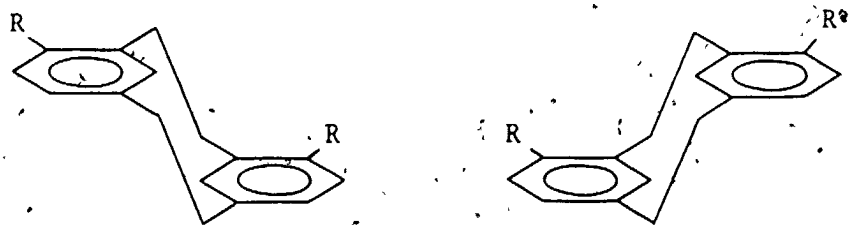
In the following sections we have limited the discussion of metacyclophanes to two main classes of compounds: [2.2]metacyclophanes[147] (section 3.2) and dithia[3.3]metacyclophanes (section 3.3).

3.2 [2.2]*metacyclophanes*.

The parent [2.2]metacyclophane 153, which was first synthesized by Pellegrin[90] in 1899, has been shown from ^{1}Hmr[148] and X-ray studies[149] to exist in a 'stepped'conformation (*anti*), in solution as well as in the solid state. Ring inversion between 153A and 153B can be ruled out since the methylene protons of 153 did not show any temperature dependence in the ^{1}Hmr between -80° and +190°C[150]. Further evidence of the rigid conformation of the [2.2]metacyclophane system was provided by the isolation of stable optical isomers[150] such as 154A and 154B.

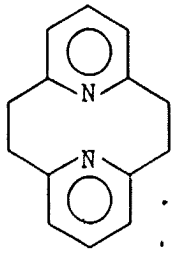


153A ≠ 153B



154A 154B

Since 153 does not show a ring inversion process, it is of course clear that any substituted [2.2]metacyclophane will therefore have the same rigid structure as the parent 153. However, if the benzene nuclei in 153 are replaced by pyridine rings as in 155 the rigidity of the [2.2]metacyclophane system is lost and an inversion process of the type 153A $\rightleftharpoons$ 153B must be assumed on the basis of the temperature dependent ^{1}Hmr[151a]. On the other hand, 156 showed again the rigid [2.2]metacyclophane structure[151b]. It was therefore concluded that



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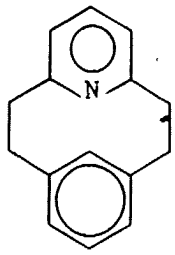

δ4.40

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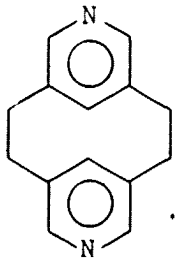


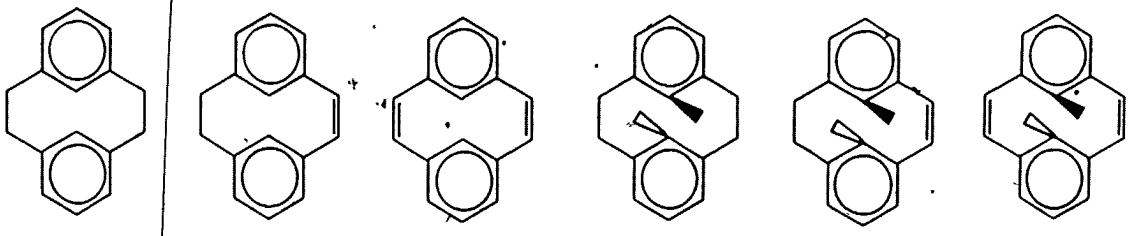
δ4.51

157

the space occupied by the lone pair of electrons on the nitrogen atom of pyridine is smaller than that occupied by a hydrogen atom attached to an aromatic nucleus. Further ^{1}Hmr studies have confirmed these results[152].

The internal protons of 153 absorb at δ4.25 whereas a value of *ca.* δ7.1 is found for m-xylene. This strong upfield shift (Δδ=2.85) was adequately explained[88c] by the ring current model of Johnson and Bovey[81a]. The internal protons of 156[151b] and 157[153] absorb at slightly lower field (δ4.40 and δ4.51 respectively), as might be expected for an electron withdrawing group.

For the methyl derivative 160[92a] we find the internal methyl protons at δ0.56, considerably shielded from those of 1,2,3-trimethylbenzene (δ2.15). The difference in shielding from their respective models of the internal protons in 153, Δδ=1.59, can be explained with the help of the X-ray data for 153[149] and 160[154]. These data show, firstly that the vertical distance between the benzene ring planes is greater in 160 than in 153 and, secondly, the distortion of the benzene ring into a boat shape is more pronounced for 160 than for 153. The methyl group in 160 will therefore be farther removed from the benzene ring than the internal proton is in 153. Also the extra distortion of the benzene ring may contribute to the smaller Δδ value found for 160 as compared to 153.



δ4.25	δ5.62	δ7.90	δ0.56	δ0.79	δ1.55
153	158[155]	159[54]	160	161[155]	162[97]

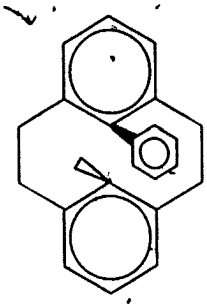
SCHEME 8

Introduction of a double bond into one or both of the bridges of 153 or 160, has a rather dramatic effect on the chemical shift of the internal protons as can be seen in scheme 8 (δ values refer to the

internal substituent). This deshielding effect, which is much greater for an internal hydrogen (153, 159) than for an internal methyl group (160, 162), has been explained[155] as an anisotropy effect of the double bond. However, from the crystal structure of 153[149], 158[156a] and 159[156b] we can see a decrease of the interplanar distance of the benzene rings together with a flattening of the stepped structure in going from 153 to 159.

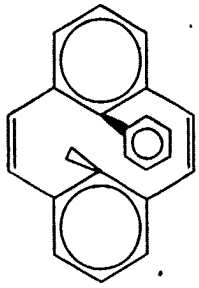
In 153 the internal proton is deeply immersed in the shielding zone of the opposite benzene ring whereas for 159 this proton is located right on the edge of the benzene ring (based on X-ray data), *i.e.*, the region of space where the magnetic field is changing rapidly. It is therefore possible that the internal proton moves from the shielding zone (as in 153) to the deshielding zone (as in 159) of the opposite benzene ring. Because of the bulky methyl groups no major flattening of the [2.2]metacyclophane ring can take place on going from 160 to 162. This implies that the position of the methyl group with respect to the opposite benzene ring does not change much in 160 and 162 which reflects the minor changes in the observed chemical shifts for 160-162 as compared to those for 153, 158 and 159.

Comparable shift variations for the methyl group can be seen in 119 (δ0.84) and 51A (δ=1.70). We therefore believe that not the anisotropy of the double bond alone but more the ring current of the opposite benzene ring, explains the observed deshielding of the internal protons of the [2.2]metacyclophanes upon introduction of double bonds.



δ0.84

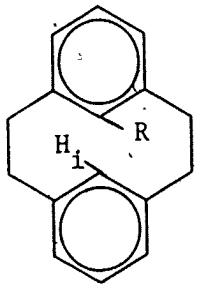
119



δ1.70

51A

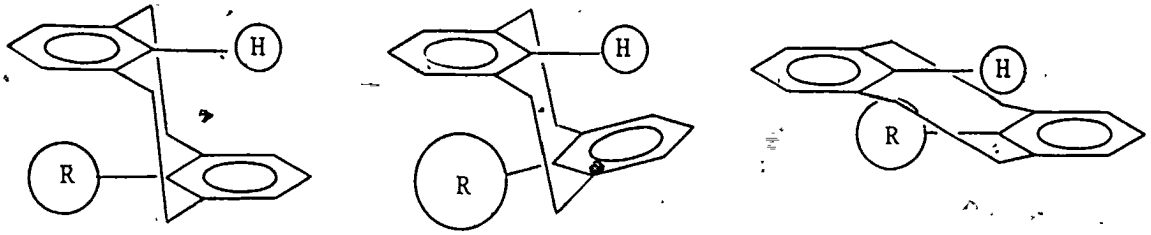
Changing one of the internal protons of 153 for a larger group has a pronounced effect on the chemical shift of the remaining H_i as can be seen from scheme 9.



	R	δH_i	reference
163:	F	4.37	93a
164:	Cl	3.94	93a
165:	CH_3	3.72	155
166:	Ph	3.57	157

SCHEME 9

From these data it can be deduced that, generally speaking, the bigger the R group the more H_i is pushed towards the π-cloud of the benzene nucleus resulting in an increased shielding. Based on the ^{1}Hmr data of the [2.2]metacyclophanes reported so far we can visualize three possible geometries for the metacyclophane ring system, these are depicted in scheme 10.



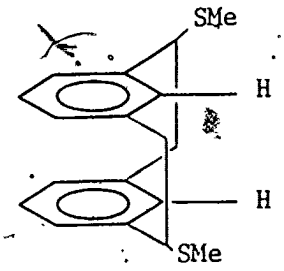
A B C

SCHEME 10

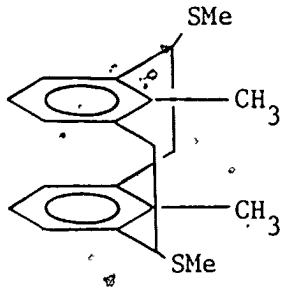
Which geometry, A, B, or C, would be preferred would then depend on the size of the R group as well as on the hybridization of the bridge carbons. With a large R-substituent, such as chlorine (164), methyl (165) or phenyl (166), geometry B will be preferred resulting in the observed upfield shifts of the internal protons as compared to the value of δ4.25 for 153. As was mentioned before, the internal protons for [2.2]metacyclophane-1-ene 158 and -1,9-diene 159 are considerably less shielded than for 153, which may reflect a structure like C.

Whereas the [2.2]metacyclophanes described so far, according to the spectroscopic findings, have the *anti* conformation with staggered benzene rings, the existence of a *syn* form for a [2.2]phane has also been detected. Mitchell and Boekelheide, for instance, have reported 167[97] and 168[55,94], the thiomethyl derivatives of the still elusive *syn* forms of 153 and 160 respectively.

The existence of both *syn* structures 167and 168 was based on ^{1}Hmr;

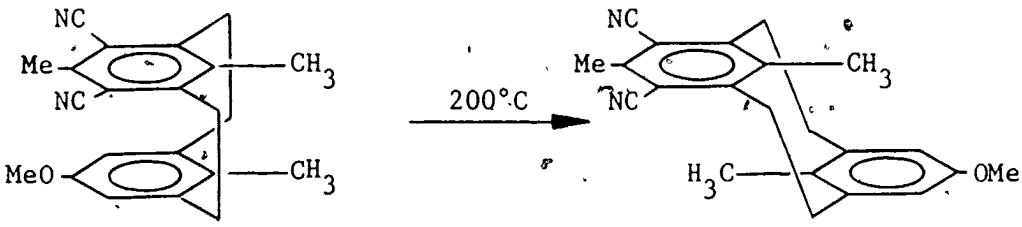


167



168

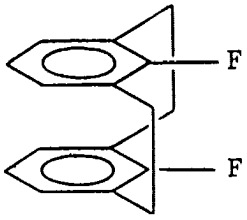
the internal protons of 167 absorbed at δ7.3 whereas a value of δ2.0 was found for the internal methyl protons of 168.



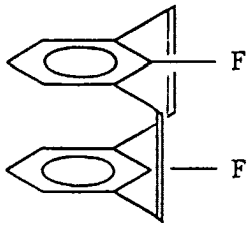
169A 169

Subsequently 169A, a *syn*-[2.2]phane without thiomethyl groups on the bridges, was synthesized[158] and shown to undergo a quantitative conversion to the *anti* form 169, indicating the greater stability of this type of conformation. As a last example of *syn*-[2.2]metacyclophanes the two difluoro compounds 170 and 171 deserve mentioning[159]. The assignment of the *syn* conformation for 170 and 171 is not obvious from ^{1}Hmr, and since ^{19}Fmr is not established yet in cyclophane chemistry, the authors resorted to dipole moment measurements to

solve this question.



170



171

Since the ring structure of [2.2]metacyclophanes has been shown to be rigid, the only dynamic behaviour in this class of compounds can be found in suitably substituted [2.2]phanes. Whereas for 160, 165 and 172-174 the internal methyl-, ethyl- and even n-propyl group did not give an indication in their ^{1}Hmr of hindered rotation, the ^{1}Hmr of the internal phenyl group in 119 showed a remarkable temperature dependence as shown in figure 9.

From the ^{1}Hmr of 119, as seen in figure 9, it is obvious that we are dealing with a dynamic process of ring twisting of the phenyl substituent. Molecular models show that a complete rotation of the phenyl group is unlikely. Since 119 will have a structure represented by A (scheme 10) only the *ortho* protons (H-2',6') of the substituent will experience a stronger shielding than normal from the opposite benzene ring. At -20°C this process of ring twisting is still fast enough to equilibrate both *ortho* protons resulting in only one signal in the ^{1}Hmr. The coalescence temperature (T_c) is reached at -59°C. Further cooling will slow down the ring twisting even more so that

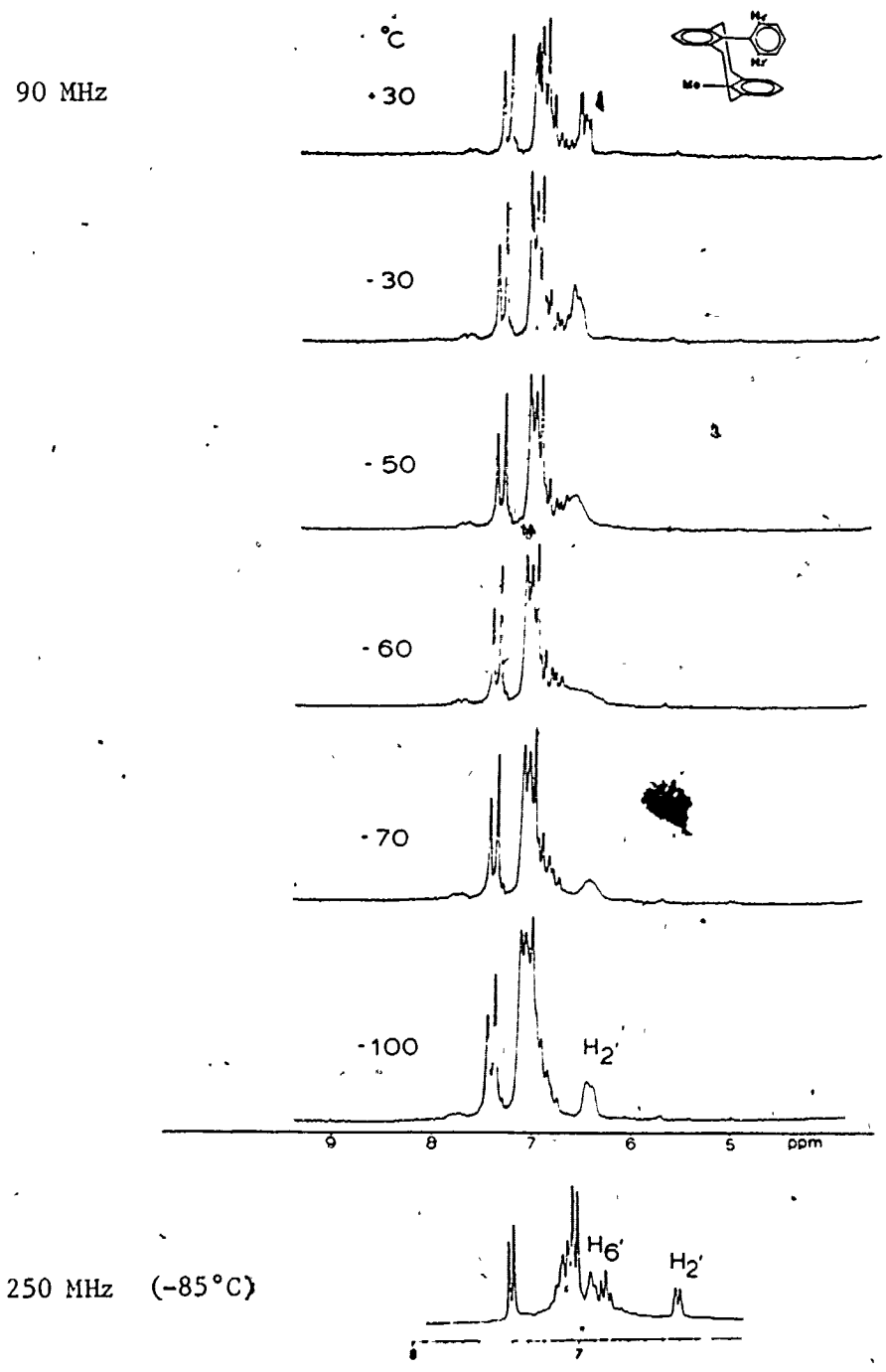
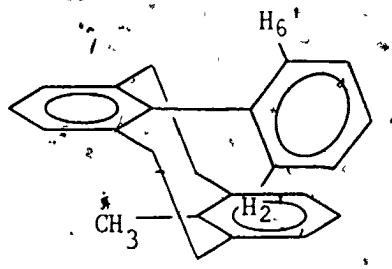


FIGURE 9. Variable temperature ^{1}Hmr ($CDCl_3/CD_2Cl_2$) of 119.

eventually two separate signals can be observed for H-2' and H-6'. The high field signal (H-2') is well separated in figure 9.



119

However, the signal due to H-6' is obscured by the aromatic protons of the metacyclophane skeleton. This problem was solved by obtaining a low temperature (-80°C) 250 MHz ^{1}Hmr which clearly showed both protons H-2' and H-6'.

To calculate the activation parameters for dynamic processes, like the one encountered for 119, either Line shape analysis or the T_c method can be used[160]. Reasonably accurate (±.1kJ/mol) $\Delta G_c^{\neq}$ values can be obtained by either method, even when the error in temperature estimation is up to 8°C. We have employed the T_c method for our calculations. The only two parameters necessary to derive $\Delta G_c^{\neq}$ at the coalescence temperature T_c are T_c (in °K) itself and the low temperature separation $\Delta\nu$ (in Hz) of the two exchanging protons. The free energy of activation at the coalescence temperature is then obtained from 161.

$$\Delta G_c^{\neq} = 2.3RT_c\,(10.32 + \log T_c - \log k_c) \qquad (3)$$

where

$$k_c = \frac{\pi}{\sqrt{2}}\Delta\nu \qquad (4)$$

Equation (4) is only valid for uncoupled equally populated exchanging sites, but is often used for more complex cases to obtain approximate values of $\Delta G_c^{\neq}$.

The correct exchange rate k_c for coupled (AB) nuclei is calculated as follows:

$$k_c = \frac{\pi}{\sqrt{2}} (\Delta\nu^2 + 6J^2)^{1/2} \qquad (5)$$

where J (in Hz) is the coupling constant between the two exchanging nuclei. Since the coupling between H-2' and H-6' in 119 is only the order of 1-1.5Hz. and the shift difference $\Delta\nu$ for all our systems is greater than 35 Hz, the error, introduced by using equation (4) instead of (5) is negligible. At the slow exchange limit for 119 we find H-2' at δ6.42 and H-6' at δ6.93 (based on $\Delta\nu$ = 46.2 Hz obtained from 250 MHz spectrum and corrected for 90 MHz data).

A similar process of ring twisting is observed for the two isomeric thiomethyl derivatives 118A and 118B.

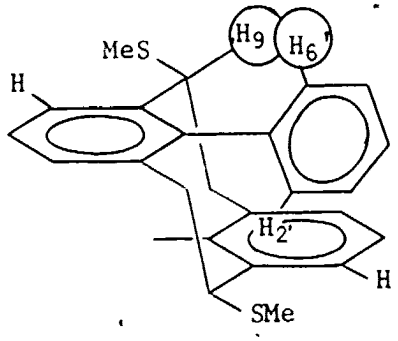
At the low temperature limit H-2' and H-6' for 118A absorb at δ6.26 and δ6.67 respectively. Because of solubility problems for 118B at low temperature (-85°C) the 'frozen' conformation was not obtained but the chemical shifts for H-2' and H-6' are estimated as δ6.42 and δ6.82, based on the similarity of the coalescence process of 118B with that for 118A. The activation parameters for 118A, 118B and 119, calculated via the T_c method are reported in table 14.

From these data we can see that 118A and 119 show an energetically

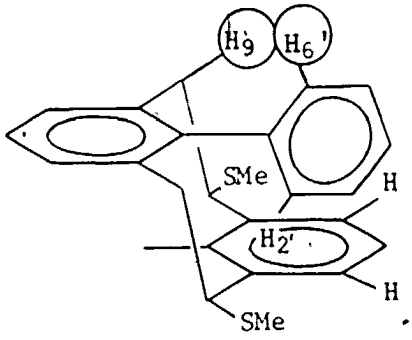
TABLE 14. Activation parameters for phenyl substituted [2.2]metacyclophanes.

Phanes	$\Delta G_c^{\neq}$ (kJ/mol)	T_c	Reference
118A	43.1	-63°C	this work
118B	40.0	-77°C	this work
119	43.5	-59°C	this work
166	54	0°C	157

similar behaviour, whereas 118B has a slightly lower activation energy for this process of ring twisting. An explanation can be found in the varying degrees of interaction between H-6' and H-9 as depicted below.



118A

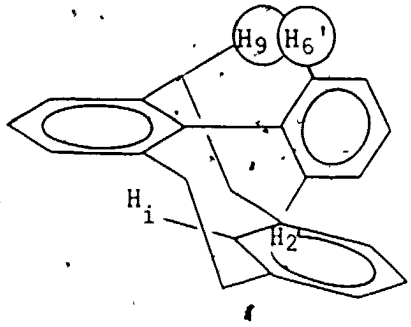


118B

The twisting of the phenyl ring is severely hindered by the interaction of the two *ortho* protons (H-2',6') with the two axial bridge protons H-2 and H-9. As we have shown before, the thiomethyl groups in 118A and 118B are placed in equatorial positions and are therefore subjected to a 1,3-diaxial interaction with the neighbouring aromatic proton. To relieve this non-bonded interaction the thiomethyl group will have to move out of the plane of the benzene ring thereby changing

the location of H-2 and H-9, whereas this effect works in opposite directions for the substituents in 118A, resulting in no net change compared to 119 (see table 14), in the symmetrically substituted 118B this out of plane bending of the thiomethyl groups increases the distance between H-2,9 and H-2',6' slightly. In geometric terms (page 96) this results in a small change from structure A towards the more elongated structure C (based on molecular models).

Recently Vögtle[157] reported that [2.2]phane 166 showed a similar process of ring rotation as the compounds mentioned above. The free energy of activation for this process is also reported in table 14. From this we see that for 166 we are dealing with a higher energy barrier than for 119. This implies an increased non-bonded interaction between H-2,9 and H-2',6'. Based on the δ3.57 value reported for the internal proton of 116 we did assign geometry B (page 96) to 166. Since the phenyl ring can undergo a larger bond rotation in a geometry like B than in A (page 96), H-2' will be pushed deeper in the π-cloud of the benzene ring and therefore be subjected to an increased shielding; this is supported by the observed shifts for H-2' (δ5.29) and H-6' (δ6.55) in the slow exchange range. As a result of the bending of the metacyclophane structure (geometry B as depicted for 166) the protons H-2,9 and H-2',6' are placed closer together, resulting in the higher $\Delta G_c^{\neq}$ value of 166 as compared to 119. Whether we are dealing with a free rotation of the phenyl group of 166 at higher temperatures, as implied by Vögtle[157], remains to be seen.



166

3.3 *2,11-Dithia[3.3]metacyclophanes.*

Insertion of a sulfur atom into the middle of the bridges of the [2.2]metacyclophane system leads to the 2,11-dithia[3.3]metacyclophanes. Whereas the former are rigid the latter can undergo several dynamic processes such as *syn-anti* isomerization (A ⇌ B), wobbling of the bridges* (C ⇌ D ⇌ E) or scissoring of the benzene rings.

The first observation of stable *anti* and *syn* isomers in this thiacyclophane series was reported by Vögtle[96b] for the dichloro compound 172, however, no separation of the individual isomers was mentioned. In the case of 52, Mitchell and Boekelheide[94] reported the isolation of *syn*-52A and *anti*-52 (page 46). Although the large size of the internal substituents of 52[112] and 172[96b] prevents

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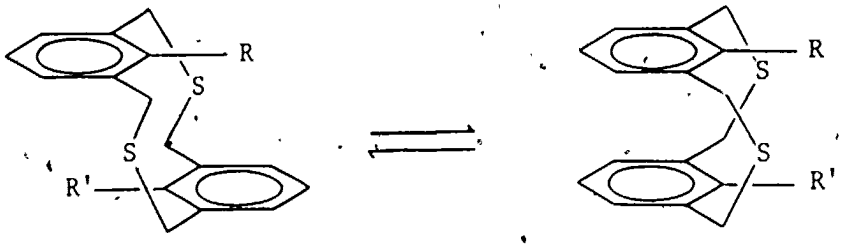
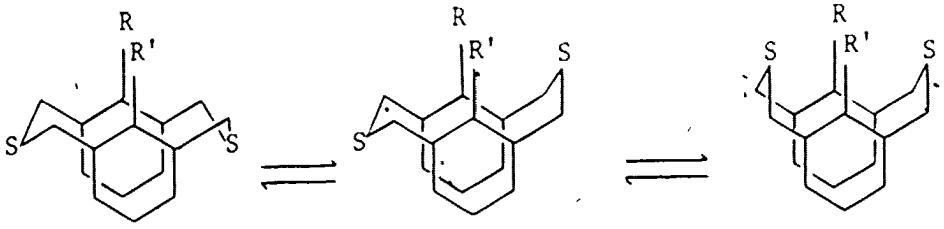
* Depicted for the *syn* conformation; bridge wobble in *anti* conformation leads mainly to ring scissoring (according to molecular models)

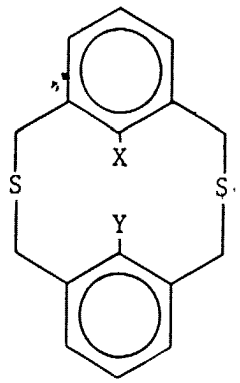


A (*anti*) B (*syn*)



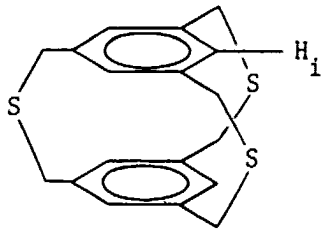
C D E

isomerization of the type A ⇌ B (no change in ^{1}Hmr up to ~180°C), the parent compound 173 has always been assumed to undergo a rapid interconversion of the *anti* and *syn* form based on the temperature independent ^{1}Hmr.[96,162]. The observed chemical shift for the internal protons of 173 (δ6.82, $CDCl_3$) was thus considered to be an average for all contributing conformers, though it was quite clear from these and subsequent papers[97,159] that the *anti* conformer of 173 was generally thought to be in excess. As a result of an investigation to attempt to resolve an apparent anomaly[54] of melting points of 173, we undertook an X-ray structure determination of this compound[163]. This showed that in the crystalline state 173 exists as the *syn*



	X	Y
52:	CH_3	CH_3
172:	Cl	Cl
173:	H	H
174:	CH_3	H

conformer. To determine the preferred conformation of 173 in solution suitable models for *syn*-173 and *anti*-173 have to be found. The *syn*-tris-bridged cyclophane 175, with the aromatic proton (H_i) at δ6.91[164] (δ6.90[165]), provides an excellent model for H_i of *syn*-173, whereas at that time 174, with H_i at δ5.59[112] (δ5.50[166]), was taken as a model for *anti*-173. Clearly H_i for 173 (δ6.82) is almost identical in chemical shift to that of 175. Also the remaining aryl hydrogens of



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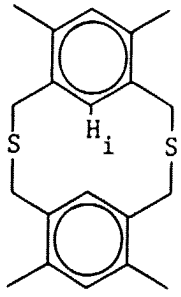


176

173 at δ6.91 are clearly shielded from normal benzene hydrogens. This evidence points to the fact that at room temperature 2,11-dithia[3.3]-

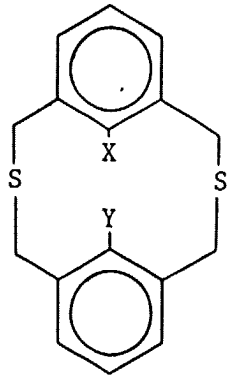
metacyclophane 173 exists in solution, as in the crystalline state, as the *syn*-conformer. We could not find evidence for participation of the *anti*-conformer. Related thiacyclophanes with internal protons have therefore been reassigned to the *syn*-conformer based on ^{1}Hmr data[163]. Although we were not able to detect any ring inversion ($\underline{A} \rightleftharpoons \underline{B}$) for 173 we did notice a collapse of the ^{13}Cmr signal due to the bridging methylenes at *ca.* -100°C in CD_2Cl_2. Unfortunately, however, we were not able to find a solvent in which 173 retained some solubility at lower temperatures, and hence could not determine whether a freezing out was occuring of the bridge wobbling process ($\underline{C} \rightleftharpoons \underline{D} \rightleftharpoons \underline{E}$). We believe that the freezing out of this wobbling was observed in the case of 176[162]. The internal protons (H_i) of 176 appeared at δ6.58 at -55°C, whereas the methylene protons showed a singlet (δ3.58) at room temperature and an AB quartet (δ3.65 and δ3.51) at -55°C (T_c=-41°C). Although the room temperature shift value for H_i of 176 was not reported we believe that it should be very close to the reported value of δ 6.63* for H_i of 173[162].

We therefore assume H_i of 176 to be temperature independent, which implies that no ring inversion has taken place. The 'freezing out' of the bridge wobble should be in favor of structure C since D as well as E experiences an 1,3-diaxial interaction between one of the methylene protons and a methyl substituent, structure C was also

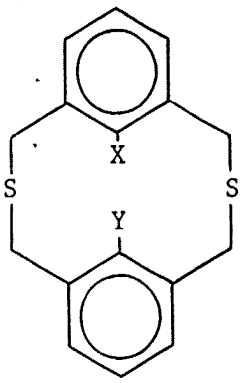
* Sato[162] recorded the ^{1}Hmr of 173 and 176 in d_8-toluene. His value of δ6.63 for H_i of 173 is therefore lower than our value of δ6.82 in $CDCl_3$; this behaviour in different solvents is normal[163].

found in the crystal structure of 173.

Prior to the structure determination of 173, Vögtle[96b, 103] had undertaken a large study of the size effect of internal substituents of 2,11-dithia[3.3]metacyclophanes on the conformational mobility of the ring system. Whereas the dichloro compound 172 consisted of distinct non-interconvertible *syn* and *anti* isomers, the smaller difluoro 177 was formed as a single isomer, later proven to be *syn*[159], that showed coalescence of the AB quartet of the bridge protons at 157°C. This collapsing of the bridge protons can be a result of either ring inversion (A ⇌ B) or a fast bridge wobble (C ⇌ D ⇌ E). We believe that the former situation is occuring. Cyclophanes 178 and 179 both showed a temperature independent ^{1}Hmr, however, for 180 coalescence of the bridge AB-system was reached at 185°C[96b]. We have reasons to believe that all three compounds 178-180, prefer the *syn* conformation. Firstly, for 181-185 H_i was reported[103] between δ7.45-7.26 indicating, on our arguments, a high preference for the *syn* conformation.



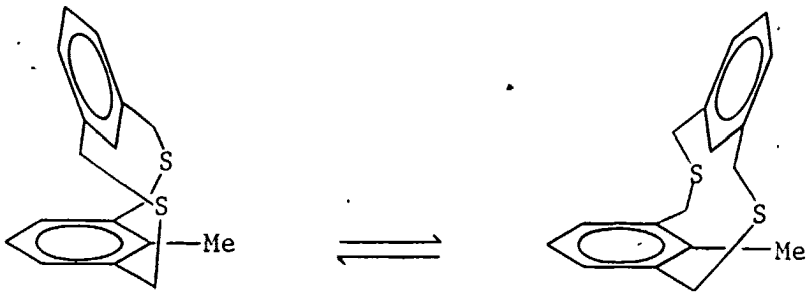
	X	Y
172:	Cl	Cl
177:	F	F
178:	H	Br
179:	H	Cl
180:	H	F



	X	Y
181:	H	NO_2
182:	H	CO_2H
183:	H	CO_2CH_3
184:	H	$CO_2CH(CH_3)_2$
185:	H	$CO_2C(CH_3)_3$
186:	H	OCH_3
187:	OCH_3	OCH_3
188:	F	OCH_3
189:	F	CH_3
190:	H	NH_2

Furthermore, for 186 H_i appeared between δ7.15-6.85 whereas the methoxyl group absorbed at δ3.70; no change with temperature was observed[112]. Based on the shift values of the methoxyl group of the *syn*- and *anti*-isomers of 187 (δ3.55 and δ3.25 respectively), 186 was also assigned the *syn* form. Secondly, the position of H_i for a *syn* conformation of 178-180 will be around δ6.8-7.3 which is also the area for the other aromatic protons of a *syn* cyclophane. Since the ^{1}Hmr of 178-180 were recorded at 60 MHz no separation between H_i and the other aromatic protons may have been possible. If, in the case of 180 we are dealing with a ring inversion (A ⇌ B) at higher temperatures, we expect H_i to shift upfield to obtain an averaged position for a *syn*- and *anti*-conformer. However, the high temperature ^{1}Hmr of 178-180 have been recorded in diphenyl ether so that any shift of H_i will be obscured by the solvent peak and/or spinning side bands. Reinvestigation of the ^{1}Hmr of 180 at higher field strength is recommended.

Whereas only the *syn* isomer was present for 188 (OCH_3 at δ3.58;



174

cf. 178), both isomers were found for 189, although the *syn* isomer was in excess (2:1)[112]. In the case of 189 there is no doubt that at elevated temperatures a fast ring inversion (A ⇌ B) is taking place (T_c=110°C), as judged from the coalescence of the methyl signals.

Taking all these data into account, the picture emerges that as long as one internal substituent in the 2,11-dithia[3.3]metacyclophanes is small (i.e., H or F) the *syn* conformation is favored independent of the size of the other internal substituent. The only obvious discrepancy to this observation is 190 where H_i appears at δ5.0 (also temperature independent). Anomalous behaviour is also found for 174, where H_i absorbs at δ5.59 and the internal methyl group at δ2.14[112]. If we compare this latter value with those for *anti*-189 (δ1.49) and *syn*-189 (δ2.42) it is tempting to assume a preferred *syn* conformation for 174. However, we believe that 174 behaves more like a pendulum, an inversion reminiscent to that of [2.2]metaparacyclophanediene 124. It would be interesting to know what conformation 174 adopts in the crystal state.

Although *syn-anti* inversion is not possible for thiacyclophane 59, because of the size of the internal substituents, it does undergo the same dynamic process of phenyl ring twisting (partial rotation) as observed in the [2.2]metacyclophanes 118A, 118B and 119.

Thus, in the ^{1}Hmr of *anti*-59 (figure 10) we see, on cooling, a collapse of the broad 'singlet' at δ6.74, representing the two *ortho* protons H-2' and H-6', followed by the appearance of two doublets at δ7.11 (H-6')* and δ6.62 (H-2') respectively. The upfield shift of H-2' is caused by the shielding of the opposite benzene ring of the thiacyclophane. The same process of phenyl ring twisting occurs also in *syn*-59A. At ambient temperature the five protons of the phenyl substituent form a broad singlet at δ7.37, indicative for a *syn* conformation. In the 'frozen' conformation (-50°C) we see (figure 11) the two *ortho* protons at δ8.29 (H-2') and δ6.72 (H-6'). The downfield shift for H-2' is probably caused by steric compression with the methyl group. Double resonance was used to assign the other phenyl ring protons in the low temperature 250 MHz ^{1}Hmr of *syn*-59A (see figure 11). Since we expect the two unhindered protons H-4' and H-5' to absorb around δ7.35 (a normal benzene value). The downfield shift of H-3' (δ7.60) corroborated the assignment of H-2'.

Prior to the synthesis of 59 and 59A, the only successful preparation of a thiacyclophane having an internal phenyl group also had a small co-substituent, a hydrogen atom, 191[103]. At that time, Vögtle[103] reported that compound 192, with two internal phenyl groups

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* Based on 250 MHz ^{1}Hmr of 59 at -55°C (see figure 10).

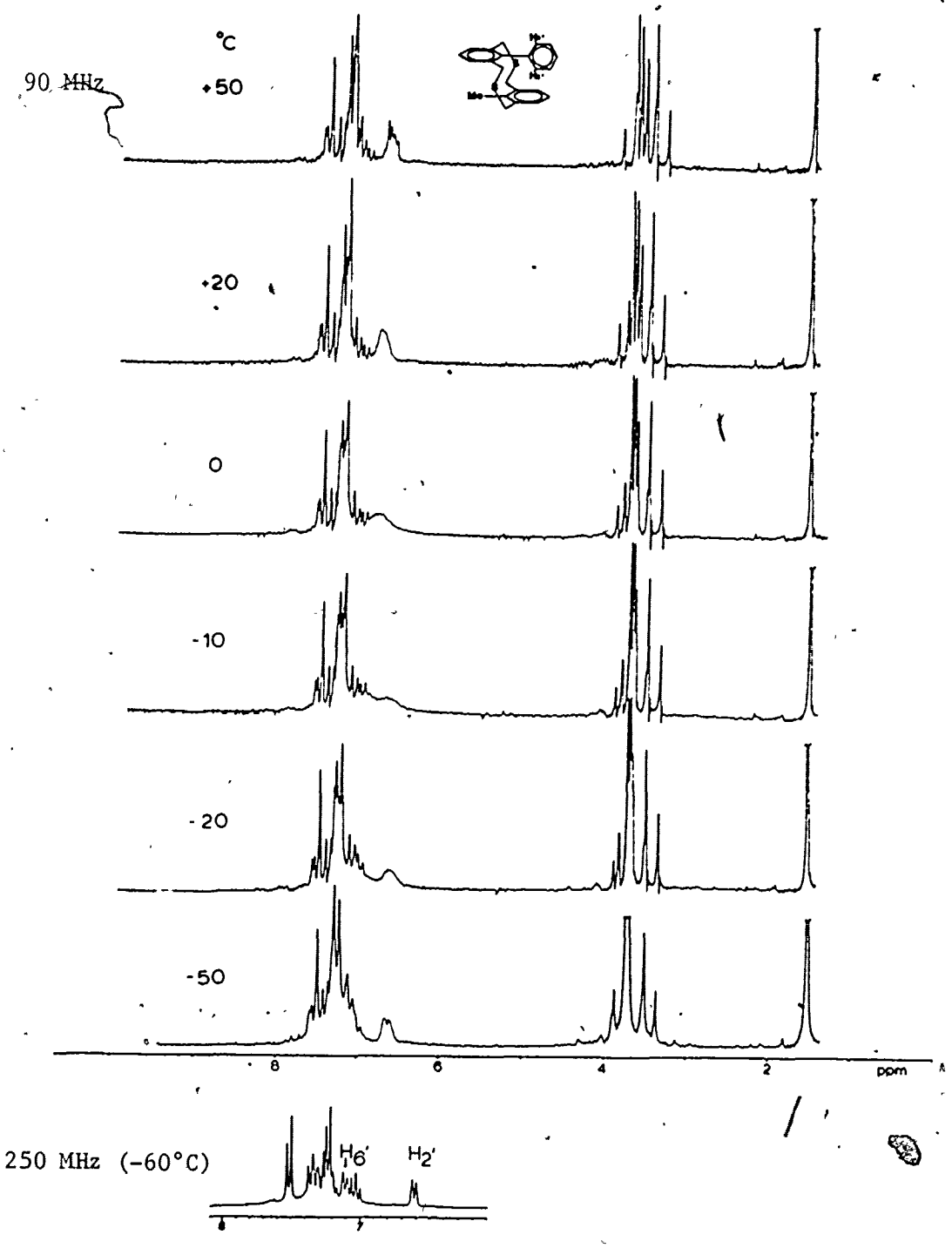


FIGURE 10. Variable temperature ^{1}Hmr ($CDCl_3$) of *anti*-59.

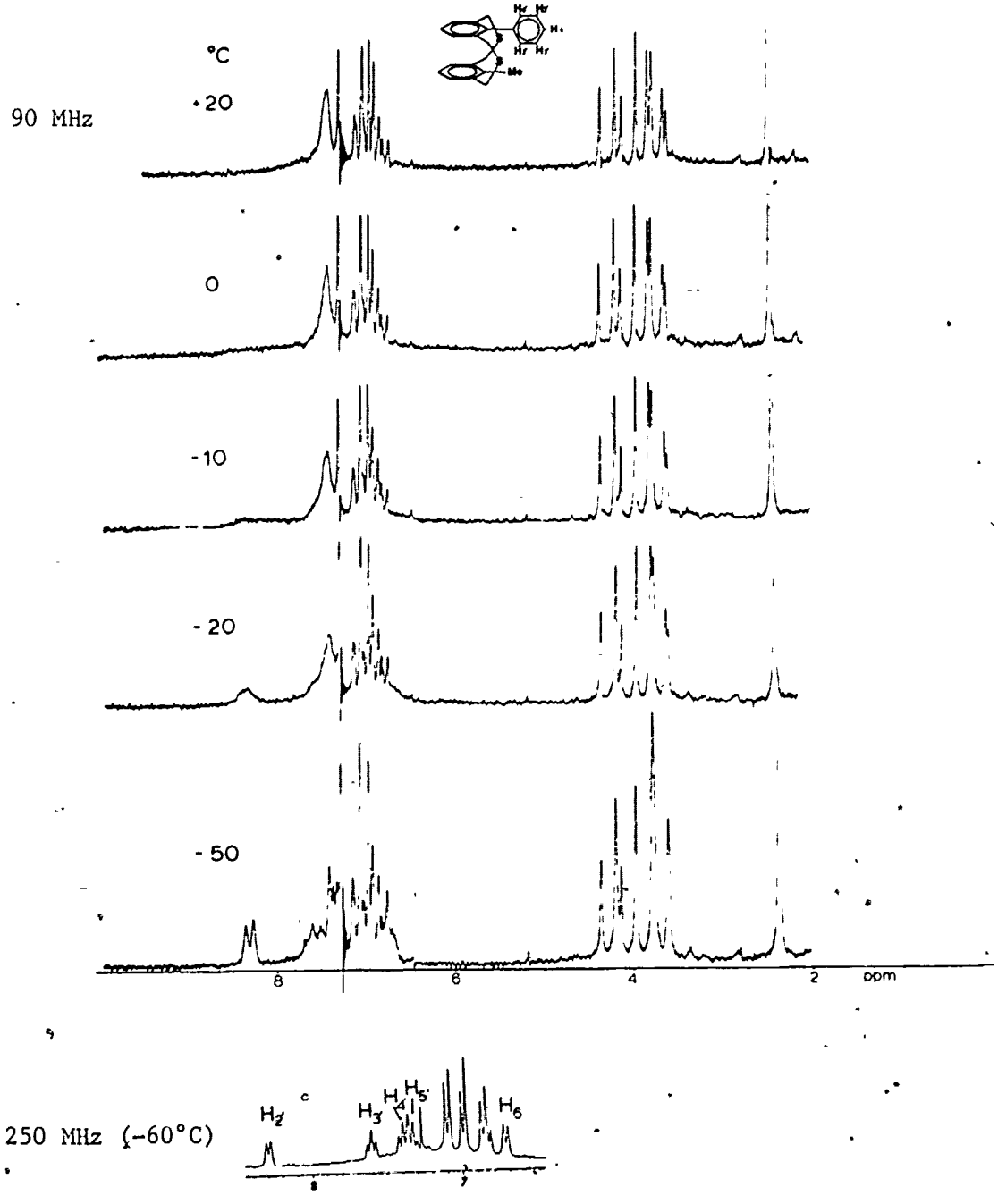
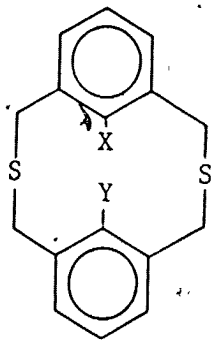


FIGURE 11. Variable temperature ^{1}Hmr ($CDCl_3$) of *syn*-59A.

could not be obtained from the cyclization of 2,6-bis(bromomethyl) biphenyl 60 and 2,6-bis(thiomethyl)biphenyl 61. However, we have successfully isolated *anti*-192 as well as *syn*-192A from this reaction, albeit in very low yields.

Recently, Kellogg[168] reported the use of cesium carbonate (Cs_2CO_3) instead of KOH, as base for the bromide - thiol coupling, leading to vast improvements in the yields of the cyclic dithia compounds. However, application of this method to the coupling of bromide 60 and thiol 61 did not give anticipated yield increase for 192.



	X	Y
59:	Ph	CH_3
191:	Ph	H
192:	Ph	Ph

The assignment of an *anti* and *syn* conformation to the thiacyclophane 192 was not as simple as for 59, where the internal methyl group made the characterization of *anti* and *syn* conformers straight forward. Both *anti*-192 and *syn*-192A showed, in their ^{1}Hmr, an AB quartet for the bridge methylene protons and an AB_2 system for the aromatic protons of the cyclophane ring (table 15). The only difference was that for 192A the aromatic protons of the phenyl substituent appeared more or less as a singlet at δ7.23*

* Based on 250 MHz ^{1}Hmr for 192 and 192A.

TABLE 15. 250 MHz ^{1}Hmr δ values and coupling constants (J) for the aromatic protons of the cyclophane rings of 59 and 192.

Phane	Proton	δ(ppm)	J(Hz)
anti-59	H-5	7.47	7.6
	H-6	7.29	
	H-14	7.20	7.5
	H-15	7.02	
syn-59A	H-5	6.92*	
	H-14	7.01*	
	H-6,15	6.77	7.7
anti-192	H-5	7.25	7.6
	H-6	6.96	
syn-192A	H-5	7.33	7.6
	H-6	6.99	

* a reversed assignment can not be excluded.

(*cf.* 59A), whereas for 192 these protons appeared in two separate regions, a broad singlet at δ7.03* (*ortho* Protons) and a multiplet at δ7.35-7.20*. These data indicate an *anti* conformation for 192 and a *syn* conformation for 192A. The above assignments were further supported by the likeness of the variable temperature ^{1}Hmr of 192 (figure 12) and 192A as compared to the ones for 59 (figure 10) and 59A (figure 11). In the 'frozen' conformation, the two *ortho* protons of the phenyl substituent of 192 absorbed at δ7.22* (H-6') and δ6.66 (H-2'), comparable to the values found for *anti*-59 (δ7.11 and δ6.62 respectively).

* Based on 250 MHz ^{1}Hmr for 192 and 192A.

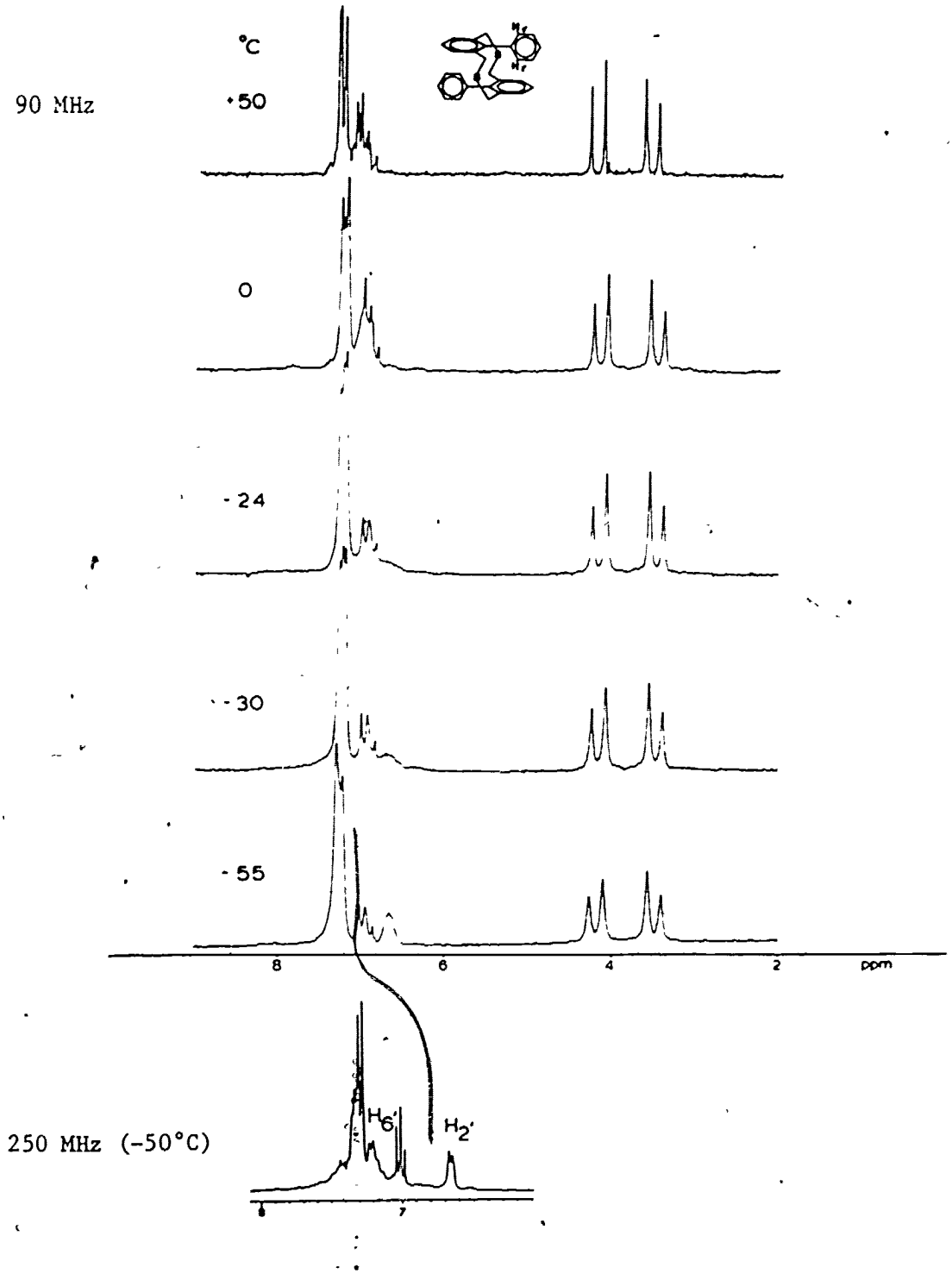
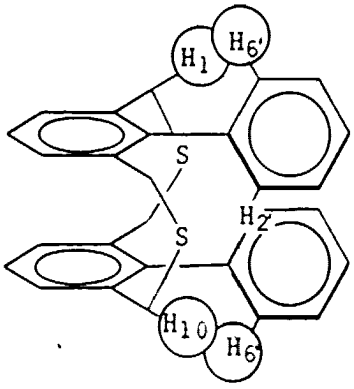


FIGURE 12. Variable temperature ^{1}Hmr (CCl_4) of *anti*-192.

In the low temperature ^{1}Hmr of 192A the two *ortho* protons absorbed at δ7.93 and δ6.62, similar shifts were observed for *syn*-59A (δ8.29 and δ6.72 respectively).



192A

Whereas for 59A the assignment of H-2' (δ8.29) and H-6' (δ6.72) is fairly simple, the picture is less clear for 192A. H-2' of 192A probably lies partly in the shielding zone of the other phenyl substituent and can therefore be assigned the shift δ6.62. The downfield shift of H-6' (δ7.93) can then be explained by steric compression with H-1,10. However, a reversed assignment (as in 59A) can not be excluded.

Undeniable proof of the *anti* conformation of 192 was obtained by X-ray determination of the crystal structure, which will, of course, also be the conformation in solution. From these X-ray data* it can been seen that the phenyl substituents have undergone a partial bond rotation of *ca.* 54°, furthermore, it is obvious that no full rotation of the phenyl group will be possible. The crystal structure

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* to be published.

also showed that the benzene rings of the cyclopnane skeleton are slightly overlapping; the angle C1'-C9-C18 is *ca.* 116°. The activation parameters for the dynamic process of ring twisting of the phenyl group in thiacyclophanes 59, 59A, 192 and 192A are given in table 16.

TABLE 16. Activation parameters for phenyl substituted dithia[3.3]metacyclophanes.

Phane	$\Delta G_c^{\neq}$ (kJ/mol)	T_c	Solvent
anti-59	55.1	- 5°C	$CDCl_3$
syn-59A	52.0	- 8°C	$CDCl_3$
anti-192	50.8	-24°C	CCl_4
syn-192A	42.7	-55°C	$CDCl_3/CD_2Cl_2$

We believe that a similar process of ring twisting occurs in these thiacyclophanes as in the previously mentioned [2.2]metacyclophanes 118A, 118B and 119, *i.e.* rotation is hindered by the non-bonded interactions between the *ortho* protons of the phenyl substituent and the bridge methylene protons, as shown below in figure 13 (only *anti* conformers shown).

In 191 (internal phenyl and hydrogen) the rotation of the phenyl substituent presents an interesting problem. Whereas for 59, 59A, 192 and 192A the *ortho* protons H-2' and H-6' can be seen clearly at low temperature, albeit at high field strength (250 MHz), this is not the

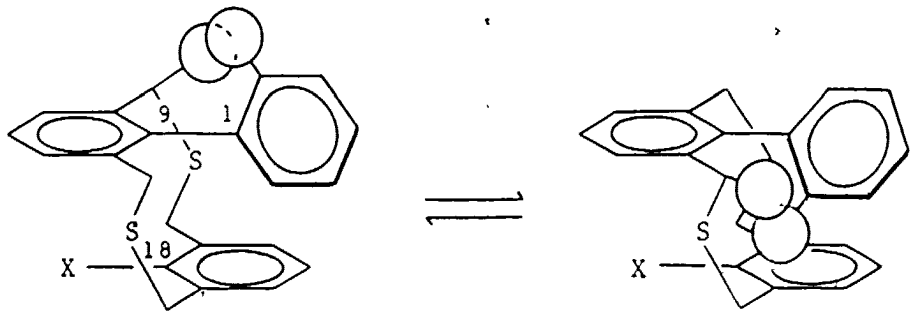

FIGURE 13. Dynamic process of ring twisting of the phenyl substituent of 2,11-dithia[3.3]metacyclophanes (only depicted for the *anti* conformer).

case for 191. Vögtle reported that 191 is not temperature dependent[103, 157, 169]. However, we observed that H-2' can be seen at δ6.70 and H-6' at *ca.* δ6.90, with H_i at δ5.49. As the temperature was lowered (figure 14) H-2' and H_i both steadily moved upfield reaching, at -100°C, δ5.82 and δ4.60 respectively. The shift difference (Δδ) between H-2' and H_i stayed constant (*ca.* 1.22 ppm) over the temperature range of +40°C to -110°C. The high field value of H_i can be explained by an *anti* as well as a *syn* conformation, since in both cases H_i is shielded by a benzene ring. We have, however, carried out an X-ray structure determination* on this compound which showed it to be the *syn* isomer.

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* to be published

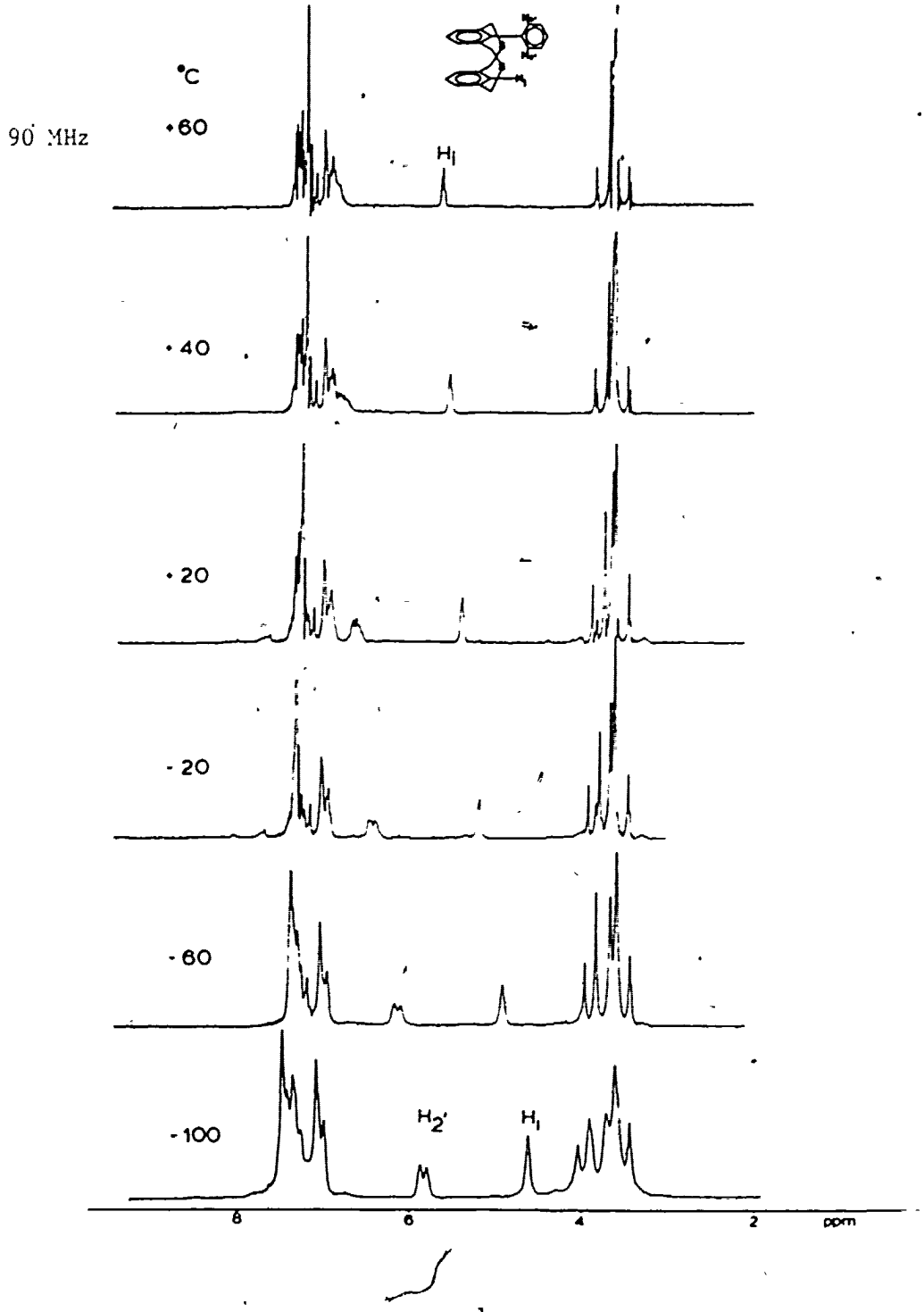
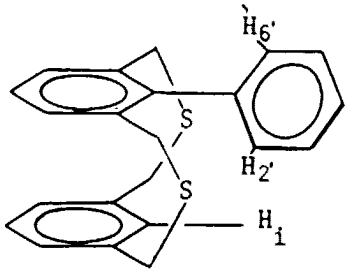


FIGURE 14. Variable temperature ^{1}Hmr ($CDCl_3/CD_2Cl_2$) of 191.

This, therefore, supports the observation that, as long as one internal substituent is small (H or F), the *syn* conformation is preferred over the *anti*.

We interpret the observed dynamic behaviour of 191 (figure 14) as being analogous to that for 95 or 192 (figure 13) except that at temperatures below +60°C the system is 'frozen' in one conformation. We believe that, as the temperature is lowered, the phenyl substituent rotates slightly thereby increasing the angle between the biphenyl rings (78.5° in crystal structure) and moving H-2' into the shielding region between the two phane rings. This probably also allows the dihedral angle between the two phane rings (20° in crystal structure) to increase such that H_i also gets progressively more shielded.



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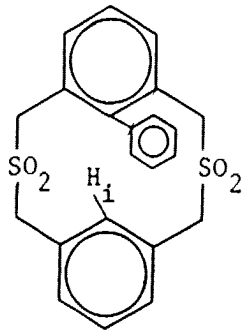


193

Above 40°C H-2' disappears in the aromatic multiplet so that no possible coalescence of these two protons can be observed. For the disulfone 193[157], however, H-2' (δ6.10) and H-6' (δ6.70) coalesced at 167°C ($\Delta G_c^{\neq}$ =91.3 kJ/mol). Since the internal proton H_i of 193 (δ5.9)[157] absorbs in the same region as H_i of 191 (δ5.49), one can argue that 193 also prefers the *syn* conformation and not the *anti* conformation, as assumed by Vögtle[157].

In conclusion, we have shown that the internal phenyl substituent of 2,11-dithia[3.3]metacyclophanes with the other internal substituent larger than hydrogen undergoes a twisting process (partial bond rotation), with respect to the phane ring, that can be 'frozen out' at low temperatures. We believe that this twisting process is restricted by the non-bonded interaction between the *ortho* protons of the phenyl group and the methylene bridge protons.

PART II

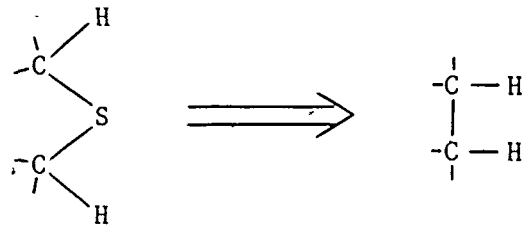
SULFUR ELIMINATIONS

CHAPTER ONE

INTRODUCTION

1.1 *The Pitfalls of the Hofmann Elimination in Cyclophane Chemistry.*

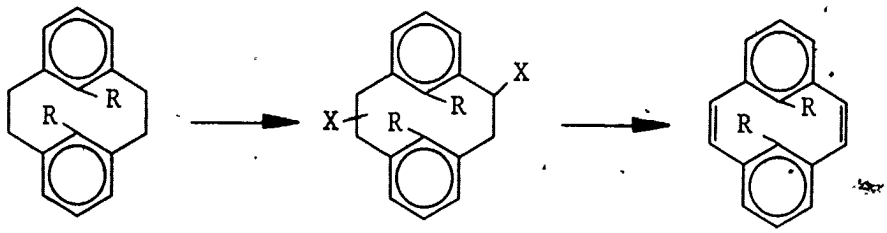
Thiacyclophanes are now regarded as being useful intermediates in the preparation of many novel conjugated aromatic systems[146]. One of the more important steps in such a synthesis of aromatic compounds is the transformation of a carbon-sulfur-carbon linkage in the thiacyclophanes to a carbon-carbon bond.



Whereas this sequence has now been achieved by a variety of methods[170] most of which extrude sulfur or a small neutral group containing sulfur, *e.g.* SO_2, the direct conversion of a C-S-C linkage to a carbon-carbon double bond is more difficult to achieve. This is particularly important in the metacyclophane series, since it is not possible to functionalize[92] the bridge methylenes of [2.2]metacyclophanes 194 directly which could lead to the desirable cyclophane-1,9-dienes 195 (precursors to the dihydropyrenes).

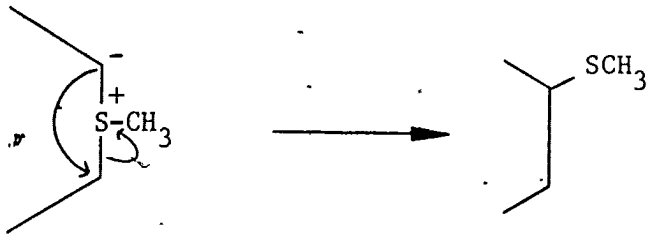
This problem was partially overcome when a method was found to ring contract a thiacyclophane and leave a substituent on the bridge. The latter could subsequently be eliminated to introduce the unsatura-

ration in the bridge and so give the desired diene 195.

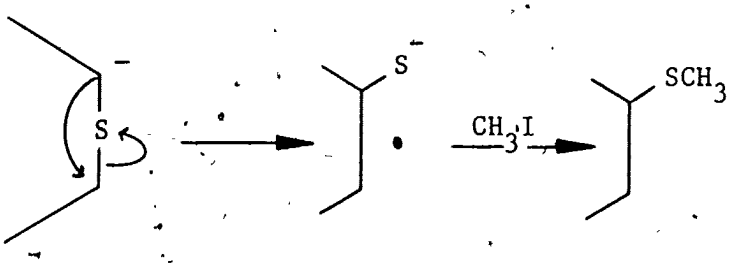


194 195

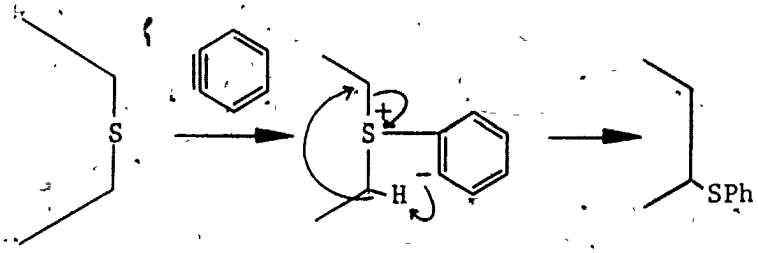
The ring contraction step was effected by means of firstly the Stevens rearrangement[94, 97], and subsequently by the more easy to carry out Wittig rearrangement[95] or benzyne induced Stevens rearrangement[171] both of which avoided the preformation of a sulfonium salt.



Stevens rearrangement

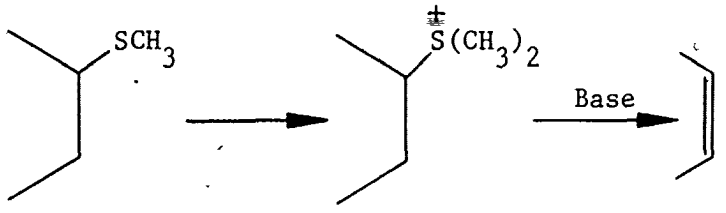


Wittig rearrangement



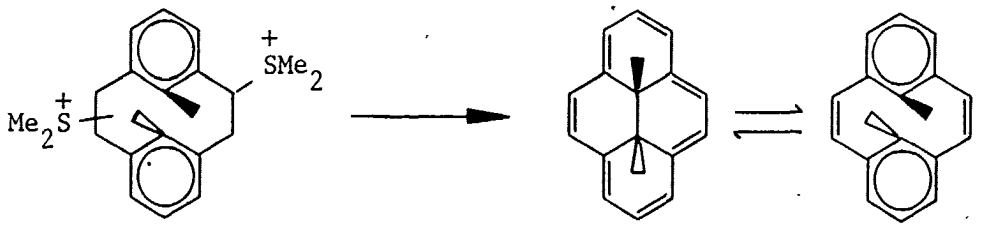
Benzyne-Stevens rearrangement

For the elimination of the remaining thio-substituent on the bridge a Hofmann elimination has most often been used.



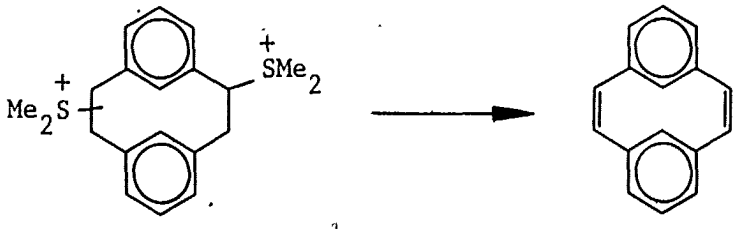
Hofmann elimination

Although this elimination works very well in some cases, the yield and nature of the product is strongly dependent on the geometry of the molecule under investigation, as well as the base-solvent system used[146]. For instance, mixed isomers of the bis(sulfonium) salt 196 with t-BuOK/THF at reflux gives an 85% yield of dihydropyrene 38[97],



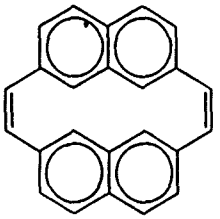
196 38 38A

whereas bis(sulfonium) salt 197, which is analogous to 196 but has internal hydrogen atoms instead of methyl groups, only gives 35% of [2.2]metacyclophane-1,9-diene 159 after treatment with t-BuOK/THF at 0°C[54].



197 159

Whereas in these simple systems the yields are at least fair, in more complex cases the yields have often been very poor. The erratic behaviour of the Hofmann elimination becomes quite obvious if we consider, for example, the naphthalenophanes. Reiss[172] has reported the synthesis of [2.2](2,7)naphthalenophane-1,11-diene 198, from the corresponding bis(sulfonium) salt, in 21% yield by using KOH in EtOH. The elimination was unsuccessful using NaH or potassium 2,6-di-t-butylphenoxide in THF (only products derived from a second Stevens rearrangement were obtained).



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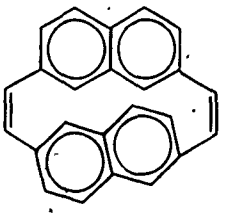

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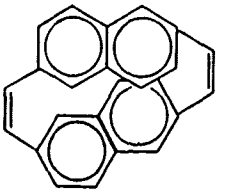
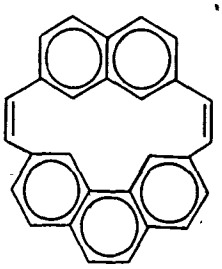


200

Boekelheide[173] reported the synthesis of the (2,6; 2', 7')naphthalenophanediene 199 in only 6% yield using KOH/EtOH. In contrast to these results stands the chiral (2,6)naphthalenophanediene 200 that has been prepared by Staab[174] in 41% yield from the sulfonium salt by using t-BuOK/THF. The Hofmann elimination failed completely in the synthesis of [2.2](3,6)phenanthro-(2,7)naphthalenophane-1,11-diene 201[175] (KOH/EtOH gave only a second Stevens rearrangement) and [2.2](2,7)pyrenophane-1,9-diene 202[176].

An alternative method to generate a C-C double bond in metacyclophanes would thus be of considerable use, particularly if it were found successful in one or more of these more difficult systems.



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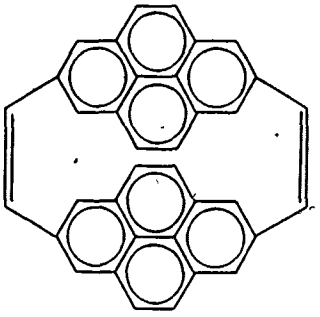

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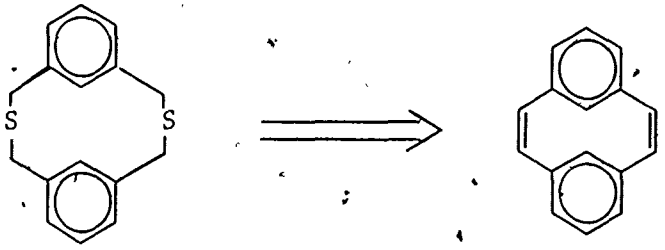
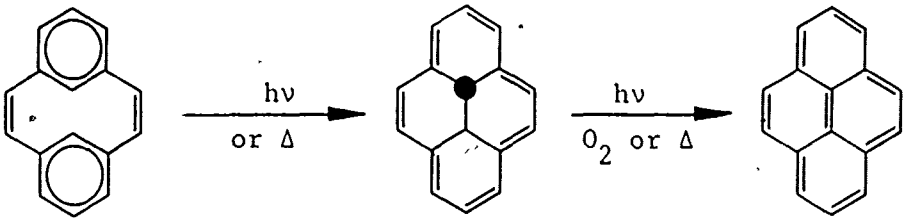
This part of the project thus had as its goal, the conversion of 2,11-dithia[3.3]metacyclophane 173 into the diene 159 by an alternate route to that used above.



173 159

This system was chosen to study first since the Hofmann elimination of the bis(sulfonium) salt 197 only gave a 35% yield of diene 159 and further because this diene 159 rapidly converted to pyrene 34 at temperatures above 60°C. Thus not only an alternative way of generating the double bonds of 159 was required which would improve the yield (>35%) but also the reaction must proceed at room temperature or less to prevent the valence tautomerization of diene

159 to the dihydropyrene 40. The latter rapidly forms pyrene 34



159 40 34

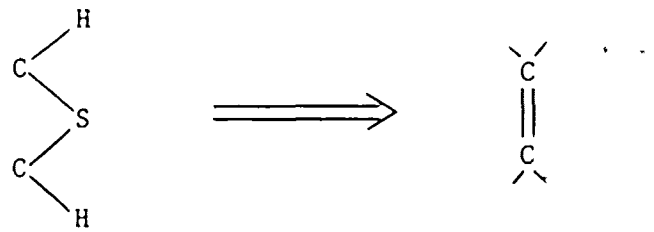
at higher temperatures or by oxidation[54]. It is then hoped that a successful method for the formation of diene 159 could be used in other problematic systems such as mentioned in reference 146.

CHAPTER TWO

SULFUR ELIMINATIONS WITH DOUBLE-BOND FORMATION

2.1 *Introduction.*

The objective of this project was to find an alternative to the well-known sequence of Stevens/Wittig rearrangement followed by the Hofmann elimination to change the C-S-C linkage in thiacyclophanes into a C-C double bond.

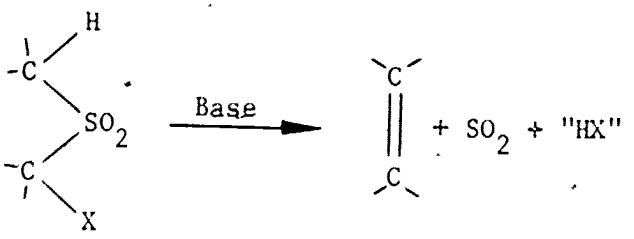


In the following pages a list of possibilities for the above mentioned conversion is given and the application of some of these reactions to metacyclophanes is discussed.

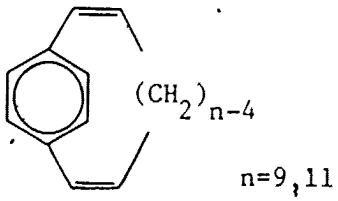
2.2 *Ramberg-Bäcklund Rearrangement.*

The halogen atoms of α-halosulfones, in contrast to halogen atoms α to other electron-withdrawing groups, show marked resistance to nucleophilic substitution[177]. However, the same α-sulfonyl halogen atoms are capable of facile intramolecular 1,3-elimination, leading to replacement of the sulfonyl group by a C-C double bond with loss of halide ion. This extrusion process, frequently referred to as the α-halosulfone[178] or Ramberg-Bäcklund rearrangement[179], has

found broad utility in olefin synthesis and can be depicted as follows:

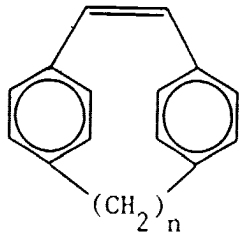
α-halosulfone: 

Application of this rearrangement in the cyclophane series has been successful in a few cases, e.g. in the synthesis of [n+1]paracyclophane-1,n-dienes 203[180] and [2.n]paracyclophane-1-enes 204[181].



n=9,11

203

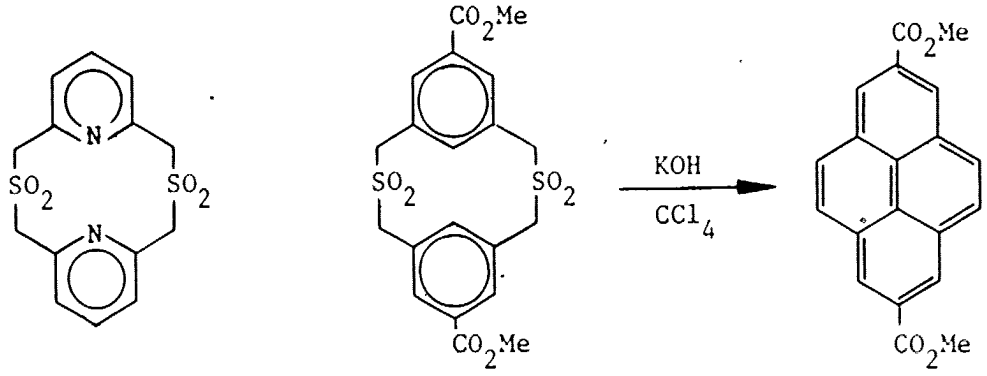


n≥5

204

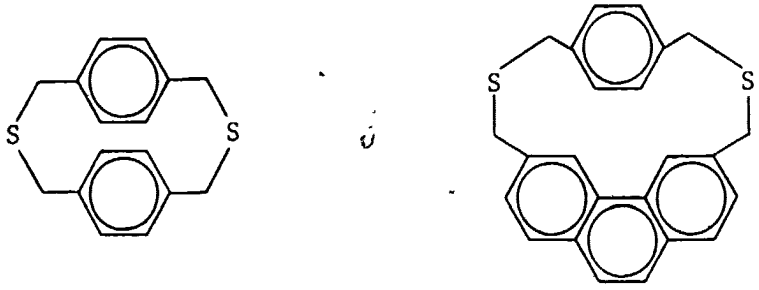
However, the reaction has proven unsatisfactory when applied to thiacyclophane systems having two C-S-C bridges, possibly because of, firstly, severe conformational restraints that impede the intramolecular displacement and, secondly, problems in the chlorination step of the sulfide where quite often the dichloride instead of the monochloride was obtained. For instance, pyridinophane 205 on treatment with KOH/CCl_4 (in situ generation of α-chlorosulfone[182]) failed to give the ring contracted product[183]. Similar results were obtained in other metacyclophane systems such as thiacyclophane 173[184].

Staab *et. al.*[185] were only marginally successful in ring contracting metacyclophane 206 via a modified Ramberg-Bäcklund rearrangement[182], where the yield of the pyrene derivative 207 was only 0.9%.



205 206 207

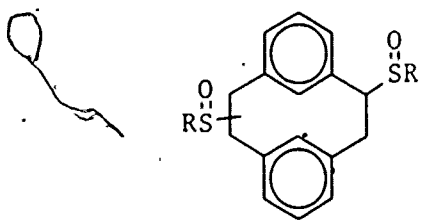
Mitchell[186] has reported the successful conversion of the C-S-C linkage in α-chlorosulfides to C-C double bonds without preparing the sulfones, as is required in the Ramberg-Bäcklund rearrangement. Although this method worked very well in open chain sulfides sub - sequent attempts with thiametacyclophane 173 and its para analog 208 did not yield pyrene 34 or [2.2]paracyclophane-1,9-diene respectively [187]. Reiss[188] was also unsuccessful in his attempts to ring contract thiacyclophane 209 to the diene system via this method.



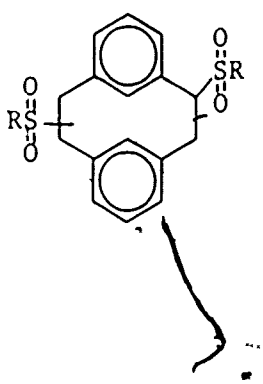
208 209

2.3 *Eliminations of Sulfoxides and Sulfones.*

Double bond formation by thermal elimination of sulfenic acids from sulfoxides was first reported by Cram[189] in 1960, and has, since then, found wide application in organic chemistry[190]. For instance, the previously mentioned [2.n]paracyclophane-1-enes 204 have also been prepared by the thermolysis of the corresponding methylsulfoxide derivatives[181]. Boekelheide[171], however, was the first to apply this procedure to [2.2]cyclophanes, prepared from the thiacyclophanes via the benzyne induced Stevens rearrangement. He found that sulfoxide 210 gave a 37% yield of pyrene 34 on pyrolysis in vacuum. We found, however, that the yield could be made quantitative by thermolysis of the methylsulfoxide 211 in xylene rather than pyrolysis of the phenylsulfoxide 210. Due to the high temperatures employed in these reactions only pyrene 34 and no diene 159 was obtained in the case of metacyclophanes 210 and 211.



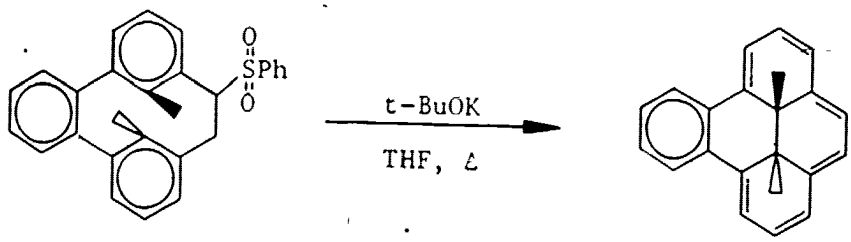
210: R = Ph
211: R = Me



213: R = Ph
214: R = Me
215: R = 2,4-DNP
216: R = CF_3

As an alternative to pyrolysis Mitchell and Yan[126a] investigated the base induced sulfinate elimination, first reported by Ingold[191], for the benzannelated example 212. This successfully gave the benzdi-

hydropyrene 129 in 85% yield using t-BuOK in THF.

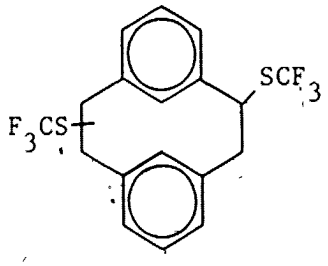


212 129

Thus we further investigated this approach. However, treatment of the [2.2]metacyclophane sulfones 213 and 214 with t-BuOH in THF either at room temperature or at reflux, did not give the expected diene 159. Even when using the strongly electron withdrawing 2,4-dinitrophenyl group (2,4-DNP) as in 215, no diene 159 could be detected. However, we found that the methylsulfone 214 with t-BuOK in DMF or DMSO at 55°C[192] yielded 41% of pyrene 34 (no reaction occured at room temperature).

Whilst this was disappointing it was reasoned that the trifluoromethylsulfone 216 would improve the reaction since trifluoromethylsulfinate should be a better leaving group than the ones already mentioned. However, Wittig rearrangement of 2,11-dithia[3.3]metacyclophane 173 followed by addition of trifluoroiodomethane (CF_3I) at -50°C (CF_3I: bp -22°C) gave only a very low yield of the trifluoromethylsulfide 217).

Moreover, oxidation to the sulfone 216 as well as direct elimination of the CF_3S group in 217 were unsuccessful. While it was known that CF_3I undergoes easy homolytic fission of the carbon-iodine bond both

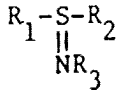


217

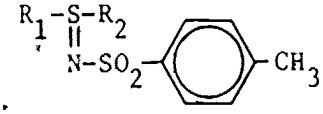
under thermal and photolytic conditions[193], the polarization of the carbon-iodine bond in CF_3I is not as obvious as it is for methyl iodide ($CH_3^{\delta+}-I^{\delta-}$), and hence may be responsible for the poor yield of the desired product 217.

2.4 *Sulfilimines.*

A further group of sulfur derivatives that have been used in pyrolytic double bond formations are the sulfilimines, also known as sulfimides. Their general structure can be represented by 218. Spectroscopic studies suggest that the sulfur-nitrogen bond in N-tosylsulfilimines 219 is of greater dipolar nature than the sulfur-oxygen bond in sulfoxides[194].



218



219

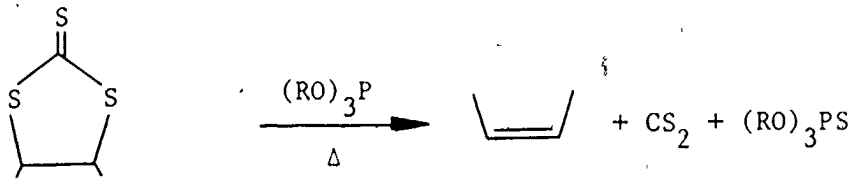
It was thus expected that sulfilimines such as 219 with a β-hydrogen would undergo a similar, and perhaps more facile, cis-elimination than sulfoxides.

Indeed, experiments showed that the pyrolysis of N-tosyl-

sulfilimines 219 was much more facile than the corresponding sulfoxides[195]. However, the temperature applied (>80°C) was expected to limit the usefulness of this method in the synthesis of metacyclophanediene 159.

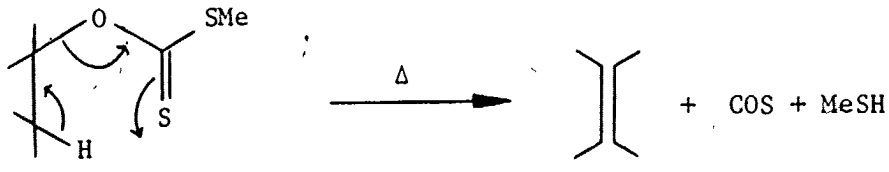
2.5 *Trithiocarbonates.*

It was pointed out by Corey and Winter[196] that reaction of the cyclic 1,2-trithiocarbonates 220 with trialkylphosphite gave alkenes via a stereospecific cis-elimination.



220

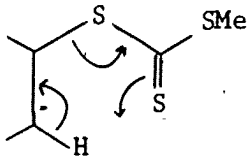
In contrast to these cyclic trithiocarbonates 220, the open chain derivatives have not been well studied either on thermolysis or on treatment with base. However, by analogy to the Chugaev reaction[197], where a methylxanthate 221 yields an olefin on pyrolysis, the



221

reaction of a trithiocarbonate 222 was thought worth investigating.

Thus Wittig rearrangement of 2,11-dithia[3.3]metacyclophane 173



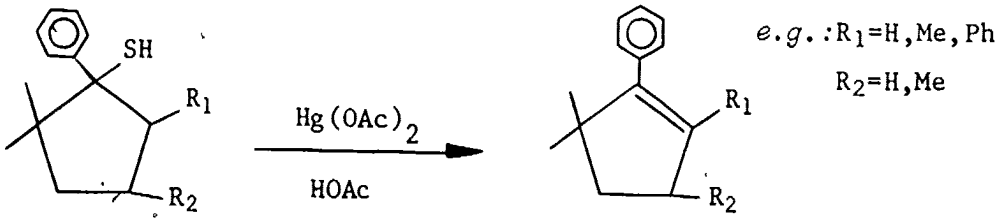
222

followed by addition of CS_2 and CH_3I respectively gave trithiocarbonate 225 in 63% yield. Then 225 was treated with t-BuOK in THF at 0°C, 25°C, and at reflux, also direct pyrolysis in xylene and in 2,6-lutidine were tried. However, no diene 159 or pyrene 34 could be detected in any of these experiments.

We also attempted a number of conversions not based on pyrolysis. These are listed below.

2.6 *Thiol Elimination by Mercuric Acetate.*

The successful elimination of a thiol group in a substituted cyclopentane 223, by the action of mercuric acetate in acetic acid, has been mentioned by de Mayo[198]. Good yields of the corresponding cyclopentene 224 were claimed. However, a reaction procedure or cross-reference was not mentioned, either in this paper or in any previous or subsequent papers.

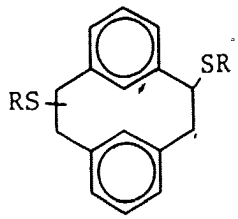


223 224

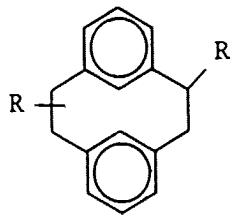
Treatment of dithiol 226 with mercuric acetate in THF or HOAc

(under N_2) at 10°C, 30°C or 80°C did not yield the expected diene 159 or pyrene 34.

Substitution of an ethylthio group in 229 for an acetate group 230 by the action of mercuric acetate in THF was mentioned in an earlier report[199].

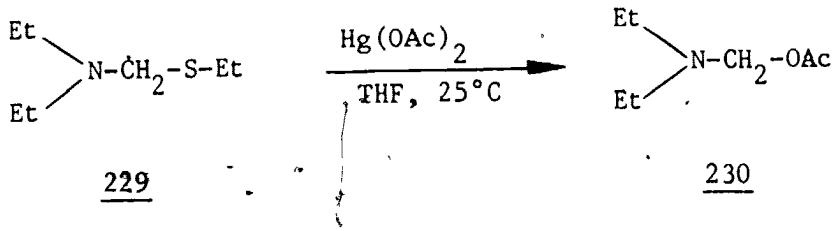


225 : R = C(S)SMe
226 : R = H
227 : R = Me
228 : R = Ph



231 : R = OAc
232 : R = Br
233 : R = Cl

However, when we reacted methylthio derivative 227 with mercuric acetate in THF at 25°C or at reflux no acetate 231 could be detected.



229 230

2.7 *Attempted Substitution of the Sulfur Group in 226 and 227 by Halogen or Oxygen.*

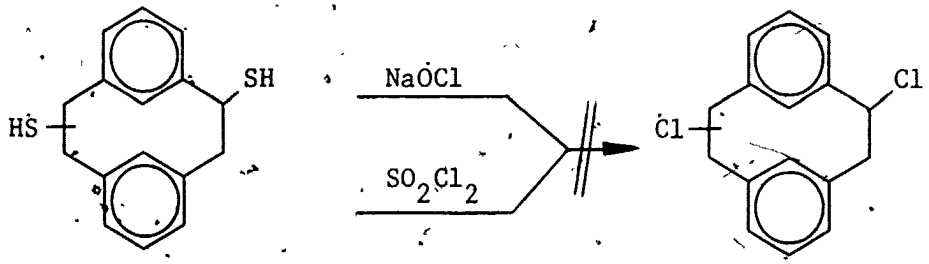
Dibromotriphenylphosphorane (Ph_3PBr_2) has been found to effect the cleavage of a variety of ethers under essentially neutral conditions

$$R\text{-}O\text{-}R' + Ph_3PBr_2 \longrightarrow R\text{-}Br + R' - Br + Ph_3OH$$

Unfortunately alkyl sulfides are essentially inert to this reagent. However, dibenzylsulfide gave a 51% yield of benzylbromide on treatment with Ph_3PBr_2[200]. The same reagent has also been used successfully for the conversion of primary and secondary thiols to the corresponding bromides[201].

However, our attempted conversion of dithiol 226 and methylthio derivative 227 into the metacyclophane bromide 232 by reaction with Ph_3PBr_2 did not give any products that could be identified. Treatment of dithiol 226 with triphenylphosphine and CCl_4, which is a known method for the substitution of a hydroxyl group by a chlorine[202], also failed to give the desired metacyclophane chloride 233.

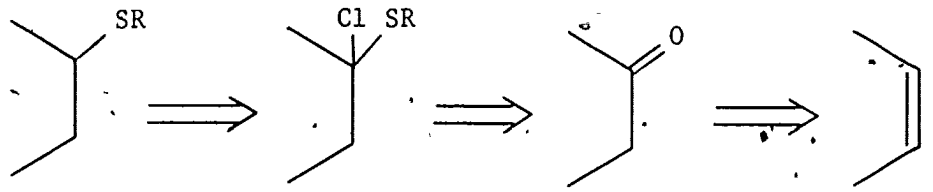
Heterocyclic thiols have been converted to the corresponding chlorides by a number of methods. For example, reaction with aqueous sodium hypochlorite[203] or treatment with sulfurylchloride[204]. However when these methods were tried on dithiol 226 no chloride 233 was obtained.



226 233

At this point we attempted a different approach in which the functionality of the system of the carbon bearing the sulfur substituent is changed, e.g. by conversion to a carbonyl. This would be

effected by means of an α-chlorosulfide, which, on subsequent



hydrolysis[205] or treatment with mercuric oxide in BF_3-etherate[206], might give the carbonyl group, from which several reactions might find success in forming the final double bond.

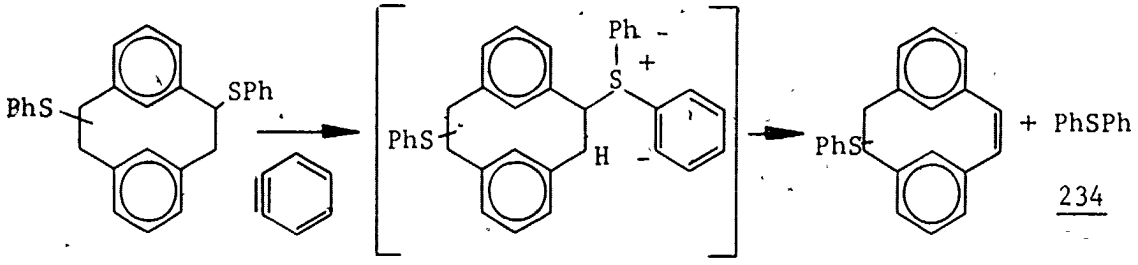
A very large number of sulfides have been converted to α-chlorosulfides by both N-chlorosuccinimides (NCS)[207] and sulfurychloride[208]. However, we were surprised to find that methylthio derivative 227 and phenylthio derivative 228 both failed to α-chlorinate with the above reagents.

2.8 *Possible Olefin Formation by Double Benzyne Stevens Rearrangement.*

It was noted that on treatment of 2,11-dithia[3.3]metacyclophane 173 with benzyne (benzyne induced Stevens rearrangement[171]) not only the expected phenylthio derivative 228 was formed but also diphenylsulfide 234. A possible explanation for the presence of diphenyl sulfide 234 can be that after the first benzyne Stevens rearrangement a second benzyne molecule reacts with one side of the ring contracted phenylthio derivative 228 to yield, after abstraction of a β-hydrogen from the bridge, diphenylsulfide 234 and an olefin.

To verify this hypothesis and test whether the olefinic product

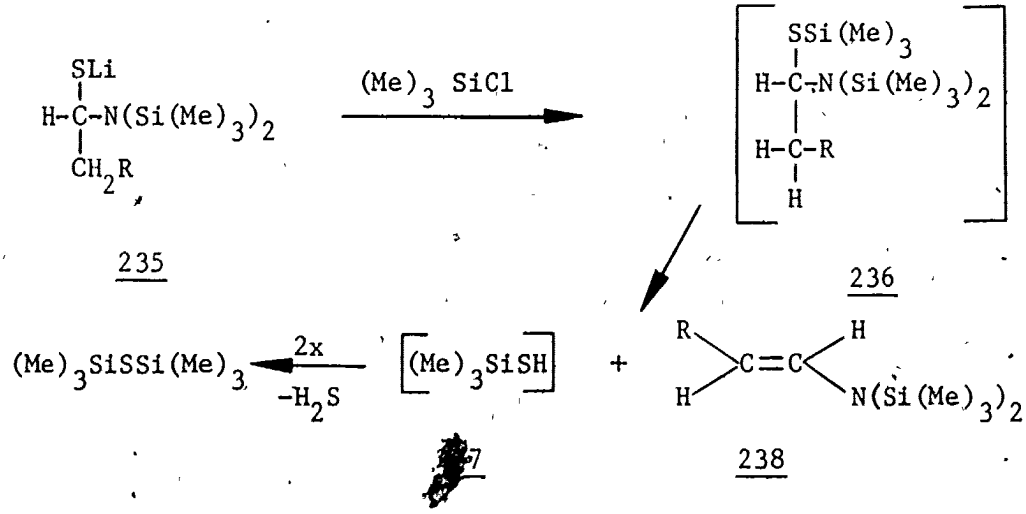
could be made more significant, phenylthio derivative 228 was tested with 2.2 equivalents of benzyne. Unfortunately, however, only a small amount of pyrene 34 could be detected.



228 234

2.9 *Elimination of Trimethylsilanethiol.*

Walter and Lüke[209], in their synthesis of masked enamines, reported that the addition of trimethylsilylchoride to the lithium salt 235 resulted in the spontaneous decomposition of the postulated intermediate 236 by elimination of unstable trimethylsilanethiol 237 with concommitant double bond formation to 238

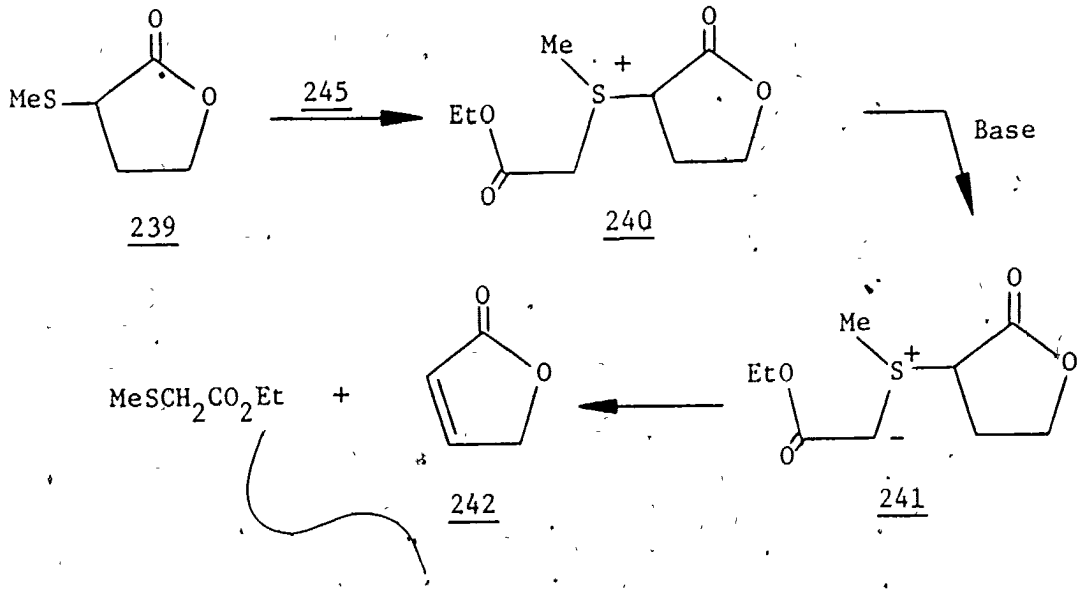


235 236 237 238

However, treatment of the lithium salt of dithiol 226 with trimethylsilylchloride led only to recovered dithiol 226.

2.10 *Elimination via Ester stabilized Sulfur Ylids.*

An elegant procedure to effect double bond formation by sulfide elimination was put forward by Vedesj[210]. This procedure involved the fragmentation of an ester stabilized sulfur ylid (*e.g.* 241) which was prepared by alkylation of a sulfide with trifluoromethane sulfonates (triflates[211]) of *e.g.* α-hydroxyesters, ketones or nitriles, followed by deprotonation of the resulting sulfonium salts (*e.g.* 240). Ylid fragmentation at room temperature then yielded the olefin. For instance lactone 239 gave sulfonium salt 240 on alkylation with triflate 245 (alkylation time: 2 days).



Subsequent treatment with base gave the ester stabilized ylid 241 from which the α,β-unsaturated lactone 242 was obtained in 94% yield (reaction time: 10 min.). Examples with phenylthio groups instead of a methylthio group as in 239 were also reported.

Thus the trifluoromethanesulfonate ester of ethylglycolate 245

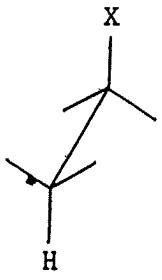
(representative of triflates derived from α-hydroxyesters) was conveniently prepared in 72% yield by slow addition of ethyldiazoacetate 244 to trifluoromethanesulfonic acid 243 in liquid SO_2 at -78°C.

$$\underset{\underline{243}}{CF_3SO_3H} + \underset{\underline{244}}{N_2CHCO_2Et} \longrightarrow \underset{\underline{245}}{CF_3SO_3CH_2CO_2Et}$$

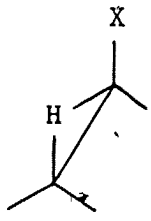
Alkylation of the metacyclophane sulfides 227 and 228 with triflate 245 was complete in 15 h. Subsequent treatment of these sulfonium salts with base (triethylamine or 1,5-diazabicyclo[5.4.0]-undec-5-ene (DBU)) should have given the ester stabilized sulfur ylids,which could then have undergone fragmentation, as indicated before, to form an olefin. However, none of the expected diene 159 or pyrene 34 could be detected, even when the reaction was warmed to 60°C.

2.11 *Some Mechanistic Considerations.*

Most examples of the elimination reactions discussed above are β-eliminations in which two groups are lost from adjacent atoms. There are two ways for this to happen.



246

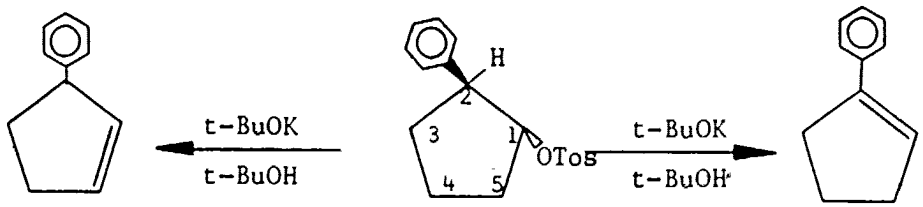


247

From a conformation such as 246 (anti-periplanar) *anti* elimination occurs, whereas from conformation 247 (syn-periplanar) *syn* elimination

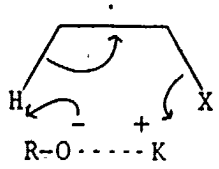
is the result.

It has been noted that the presence of free or ion-paired base can alter the mode of elimination (*anti* versus *syn*). For example, the case of cyclopentane 249, where the phenyl and tosylate group are *trans* to each other, there are two types of β-hydrogens, one of which is more acidic (H-2) and leads to 250 via *syn* elimination. Loss of the less acidic proton (H-5) will give the non-conjugated cyclopentene 248 via an *anti* elimination. With t-BuOK in t-BuOH (50°C) 92% of 250 and 8% of 248 were formed, which indicated a high preference for *syn* elimination in this system[213].



248 249 250

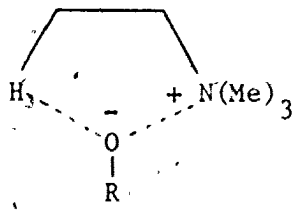
However, addition of the crown ether dicyclohexyl 18-crown-6 (this ether selectively removes K^+ from the $t\text{-BuO}^-K^+$ ion pair and thus leaves $t\text{-BuO}^-$ as a free base) changed the product composition to 70% of 248 and 30% of 250 which indicates a preference for *anti* elimination[213].



252

From this and other studies[214] the picture emerged that for neutral leaving groups (*e.g.* tosylate; halide) *syn* elimination is favored by ion-paired bases, via a transition state like 251 whereas the free base favors *anti* elimination.

For positively charged leaving groups (*e.g.* trimethylammonium) it was predicted[215] that free base should be more effective than ion-paired base in promoting *syn* elimination, because electrostatic interaction of the negatively charged base and the positive leaving group would put the base into a favorable position for attack on a *syn* β-hydrogen. This would lead to a transition state like 252. This view was corroborated by Saunders' work[216a].

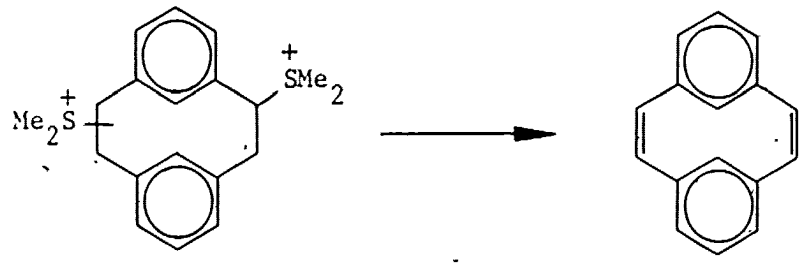


252

2.12 *Application of these Findings to the Metacyclophane System.*

Molecular model studies of sulfonium salt 197 showed us that an anti-periplanar arrangement was very unlikely, this would put the leaving group in the sterically more hindered pseudo-axial position. Therefore the Hofmann elimination of 197 was assumed to follow a *syn* pathway. Since we have a positively charged leaving group in 197,

syn elimination will be promoted by free base, Apart from adding a



197 159

crown ether, the free base concentration can also be increased by using DMSO instead of THF, since the former solvates cations more effectively than the latter. Still another way of increasing the free base concentration is by addition of a quaternary ammonium salt[216] that cannot itself undergo elimination.

Treatment of sulfonium salt 197 with t-BuOK in DMSO at room temperature yielded pyrene 34 in 43% yield. Addition of tetramethylammonium bromide did not improve the elimination. The effect of added ammonium salt was also negligible in the t-BuOK/THF system. Hofmann elimination of 197 in t-BuOK/THF with crown ether 18-crown-6, to promote the free base, was in so far successful that mainly cyclophanediene 159 was obtained, as opposed to the other reactions where pyrene 34 was formed instead. The yield, however, was only 10%.

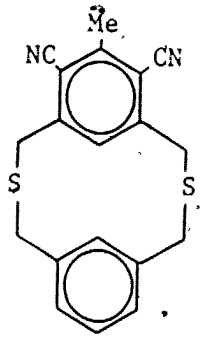
Unfortunately, no new or improved method for sulfur elimination with double bond formation was found during the course of this research.

CHAPTER THREE

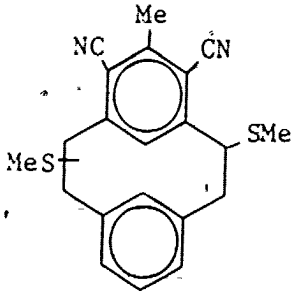
POSSIBLE FUTURE WORK

Since ring contraction of thiacyclophanes via Wittig or Stevens rearrangement, followed by reaction with methyl iodide, yields a mixture of thiomethyl isomers, it is possible that only certain of these isomers can successfully undergo the Hofmann elimination of the corresponding sulfonium salts.

It has been noticed[122] that the isomer ratio of the thiomethyl derivative 254 depends on the temperature at which the Wittig rearrangement of thiacyclophane 253 is executed.



253



254

If this variation in isomer ratio with reaction temperature turns out to be a general phenomenon for thiacyclophanes, separation of these isomers from the mixture followed by Hofmann elimination of the sulfonium salts then will give valuable information about, firstly, which isomer(s) eliminates preferentially and secondly, how to enrich the product mixture with this isomer(s).

EXPERIMENTAL

All melting points were determined on a Kofler hot stage and are uncorrected. The ^{1}Hmr spectra were determined in $CDCl_3$ (unless otherwise stated) on a Perkin-Elmer R12B (60 MHz), R32 (90 MHz) or Bruker WM-250 (250 MHz) spectrometer and are reported in ppm downfield from tetramethylsilane as internal standard. The variable-temperature ^{1}Hmr studies were carried out on a R32 (90 MHz) spectrometer, using $CDCl_3$, CD_2Cl_2, or $CDCl_3$:CD_2Cl_2 (1:1) as solvent for variable temperature (-100°C to +60°C) studies. ^{13}Cmr spectra were determined in $CDCl_3$ on a Nicolet TT-14 Fourier Transform spectrometer operating at 15.1 MHz or on a Bruker WM-250 operating at 62.9 MHz and are reported in ppm with $\delta CDCl_3$=77.0 ppm as reference point.

UV spectra were recorded on a Cary-17 spectrophotometer or a Beckmann DU-8 spectrophotometer.

Mass spectra were determined on a Hitachi Perkin-Elmer RMU-7E or Finnigan 3300 mass spectrometer at 70 eV using electron impact (EI) or chemical ionization (CI) (M^+ = molecular ion in mass spectra).

Microanalyses were performed by Canadian Microanalytical Service Ltd. (Vancouver, B.C.). All evaporations were carried out under reduced pressure on a rotary evaporator at *ca.* 40°C. All organic layers were washed with water (unless otherwise stated) and dried over anhydrous sodium sulfate or magnesium sulfate.

1. *2-Bromo-1,3-dimethylbenzene 98.*

(a) Diazotization of 2,6-dimethylaniline 104.

48% aq. HBr (35 ml, 310 mmol) was added slowly to 2,6-dimethylaniline 104 (15g, 123.8 mmol) at 0°C. Then a solution of sodium nitrite (8.54g, 123.8 mmol) in H_2O (15 mL) was added rapidly, with stirring, the temperature being kept below 10°C.

(b) Conversion of diazonium salt into 98.

The above prepared cold diazonium solution (see (a)) was added dropwise to a refluxing mixture of CuBr (9.77 g, 68.1 mmol) and 48% aq. HBr (8.4 mL, 74.3 mmol) over a period of 30 min. After cooling the mixture was extracted with benzene. The combined organic layers were washed, dried and evaporated. The residual dark red liquid was chromatographed over silica gel using pentane as eluant to yield 2-bromo-1,3-dimethylbenzene 98, 14g (62%), bp 205-206°C (lit.[217] bp 206°C) ^{1}Hmr, δ, (CCl_4, 60 MHz), 6.90 (s, 3H, Ar-H) and 2.34 (s, 6H, Ar-CH_3).

2. *2,6-Dimethyl-1-phenylcyclohexanol 107.*

A portion (1 mL) of a solution of bromobenzene (68.43g, 435.8 mmol) in dry THF (500 mL) was added to magnesium (10.7g, 440 mg-atom) in dry THF (100 mL) at 35°C under N_2.

A few drops of 1,2-dibromoethane were added to initiate the reaction and then the remainder of the solution of bromobenzene was added dropwise at a rate to maintain gentle reflux. After the addition the mixture was further heated at reflux for 30 min.

2,6-Dimethylcyclohexanone 106 (50g, 396 mmol) was then added dropwise to the hot Grignard reagent. After the addition, heating at reflux was continued for 9 h. The reaction mixture was then cooled and concentrated under reduced pressure. Benzene was added and the organic extracts were washed with dilute HCl and H_2O. The organic extracts were combined, dried and evaporated to give a clear yellow liquid. Vacuum distillation yielded colorless alcohol 107, 67.32g (83%), bp 158°C/18 Torr (Lit.[103] bp 134-135°C/15 Torr); ^{1}Hmr, δ, (CCl_4, 60 MHz), 7.25 (m, 5H, Ar-H), 1.56 (m, 9H, $-CH_2-$) and 0.57 (d, J=6Hz, 6H, $-CH_3$).

3. *(2,6-Dimethyl-1-cyclohexen-1-yl)benzene 108.*

p-Toluenesulfonic acid (1.4g, 8.14 mmol) was added to a solution of alcohol 107 (67.2g, 329.4 mmol) in toluene (25 mL). The mixture was heated at reflux for 6 h. with azeotropic removal of water (Dean-Stark apparatus).

Vacuum distillation yielded the cyclohexene 108 as a colorless liquid. 52.24g (85%), bp 64°C/0.5 Torr (Lit.[218] bp 91-92°C/1.5 Torr), ^{1}Hmr, δ, (CCl_4, 60 MHz), 7.07 (m, 5H, Ar-H), 2.40-1.20 (m, 7H, $-CH_2-$), 1.46 (s, 3H, $-C-CH_3$) and 1.80 (d, 3H, J=6Hz, $-CH_3$).

4. *2,6-Dimethyl-1,1'-biphenyl 100.*

(a) From the Grignard of 2-bromo-1,3-dimethylbenzene 98.

A portion (1 mL) of a solution of 98 (4g, 21.6 mmol) in dry THF (15 mL) was added to magnesium (530 mg, 21.8 mg-atom) in dry THF (15 mL)

at 35°C under N_2. Then a few drops of 1,2-dibromoethane were added to initiate the reaction and then the remainder of the solution of 98 was added dropwise at a rate to maintain gentle reflux. After the addition, the mixture was heated at reflux for an additional 2 h. at which time most magnesium had disappeared.

The mixture was then cooled to -78°C and a solution of bromobenzene (3.58g, 22.8 mmol) in dry THF (25 mL) was added dropwise, followed by Ni $(acac)_2$ (ca. 5 mg).

The reaction mixture was then allowed to warm to room temperature over 1 h. and subsequently was heated at reflux for 15 h. This mixture was then cooled and benzene was added and the organic extracts were washed with dilute aqueous HCl and H_2O. The organic layer was dried and evaporated to give a brown liquid which was chromatographed over silica gel using pentane as eluant.

From the methyl proton resonances in the ^{1}Hmr spectra (60 MHz) the presence of m-xylene (δ2.26, s, Ar-CH_3), 2-bromo-1,3-dimethylbenzene 98 (δ2.32, s, Ar-CH_3) and 2,6-dimethylbiphenyl 100 (δ2.00, s, Ar-CH_3) was indicated.

Vacuum distillation of this eluate then yielded two main fractions. The first (bp ca. 80°C/50 Torr) contained mainly m-xylene. The second fraction (0.53g) still showed, by ^{1}Hmr, some bromide 98 to be present together with the desired product (in the ratio by ^{1}Hmr 1:3). Subsequently 100 was obtained pure by the alternate route C described below.

(b) From (2,6-dimethyl-1-cyclohexen-1-yl) benzene 108 via bromination, dehydrobromination followed by dehydrogenation.

A solution of Br_2 (3g, 18.75 mmol) in CCl_4 (20 mL) was added dropwise to a solution of 108 (2g, 10.75 mmol) in CCl_4 (25 mL) at 0°C. The addition was stopped as soon as the bromine colour persisted. The reaction mixture was then washed successively with aqueous $NaHSO_3$ and H_2O, dried and evaporated to give a pale yellow liquid.

Dry THF (40 mL) and t-BuOK (2.4g, 21.4 mmol) were then added to this liquid and the mixture was heated at reflux for 4 h. under N_2.

After cooling, dichloromethane and dilute HCl were added to the reaction mixture. The organic layer was separated, washed, dried and evaporated to give a dark brown liquid. This was then chromatographed over silica gel using pentane dichloromethane (1:1) as eluant to give an orange liquid.

Benzene (25 mL) and 10% Pd/C (2g) were then added to this orange liquid. This mixture was heated at reflux for 12 h., while N_2 was bubbled through the solution. After cooling, the mixture was then filtered with celite and the filtrate was evaporated to give a brown liquid. Subsequent chromatography over silica gel using pentane as eluant yield biphenyl 100, 1.06g (54%), identical to the next sample (c).

(c) From (2,6-dimethyl-1-cyclohexen-1-yl) benzene 108 via direct dehydrogenation.

A solution of cyclohexene 108 (30g, 161.3 mmol) and *o*-chloranil 115

(95.2g, 387.2 mmol) in dry m-xylene (200 mL) was heated at reflux for 30 h. under N_2.

Tetrachlorohydroquinone was then removed by hot filtration and the filtrate was distilled under vacuum. The fraction with boiling range 60-80°C/ 2-3.10^{-1} Torr was then collected and subsequently chromatographed over silica gel, using pentane as eluant to give 2,6-dimethylbiphenyl 100 as a colorless liquid, 18.58g (63%), bp 66-70°C/2-3.10^{-1} Torr (Lit.[103] bp 128°C/14 Torr), ^{1}Hmr, δ, (90 MHz), 7.40-6.93 (m, 8H, Ar-H) and 1.96 (s, 6H, Ar-CH_3);ms peaks (EI) at m/e (relative intensity) 182 (M^+, 100), 181 (46), 167 (92), 166 (32), 165 (58) and 152 (20); ^{13}Cmr, δ, (62.9 MHz), 141.9 (C-1), 141.1 (C-1'),136.0 (C-2), 129.0, 128.4, 127.3 (C-3, C-2', C-3'), 127.0, 126.7 (C-4, C-4') and 20.8 (Ar-CH_3).

Note: For preparative purposes biphenyl 100 was obtained from 2,6-dimethylcyclohexane 106 without the isolation of alcohol 107 and cyclohexene 108. The overall yield was 64% based on the cyclohexane 106.

5. *2,6-Bis(bromomethyl)-1,1'-biphenyl 60.*

N-bromosuccinimide (37.2g, 209 mmol) and benzoylperoxide (5 mg) were added, in four equal portions, over a period of 2 h., to 2,6-dimethylbiphenyl 100 (18.5g, 101.6 mmol) in refluxing CCl_4 (125 mL) with concomitant irradiation (200W. lamp)

After the addition the mixture was irradiated under reflux for an additional 1.5 h. The reaction mixture was then cooled and the

succinimide was removed by filtration. The filtrate was evaporated and gave a tan colored solid. This was then stirred with pentane for 10 min; filtration yielded white bromide 60. Evaporation of the filtrate, followed by washing with pentane, was repeated to increase the yield of bromide 60, 21.2g (61%), a sample was recrystallized from cyclohexane as white crystals, mp 116-117°C, (Lit.[103] mp 116-117°C), ^{1}Hmr, δ, (CCl_4, 90 MHz), 7.37 (broad s, 8H, Ar-H) and 4.10 (s, 4H, $-CH_2Br$); ^{13}Cmr, δ, (62.9 MHz), 141.6, 136.4 (C-1, C-1'), 136.6 (C-2), 130.5, 129.2,128.2 (C-3, C-2', C-3'), 128.4, 127.9 (C-4, C-4') and 31.7 ($-CH_2Br$).

6. *2,6-Bis(mercaptomethyl)-1,1'-biphenyl* 61.

Thiourea (5.5g, 72.4 mmol) was added to a solution of 2,6-bis(bromomethyl)biphenyl 60 (10g, 29.4 mmol) in dry THF (200 mL). After the addition the mixture was heated at reflux for 3 h. under N_2. Then a solution of KOH (3.88g, 69.3 mmol) in H_2O (50 mL) was added to the hot mixture and heating at reflux was continued for another 3 h. The mixture was then cooled and acidified with 6M aqueous H_2SO_4, and the whole was extracted with benzene. The benzene extract was washed, dried and evaporated to give a pale yellow oil which solidified on standing. Subsequent chromatography of the solid over silica gel using pentane (400 mL) and pentane/ dichloromethane (200 mL, 9:1) as eluants yielded white dithiol 61, 6.82g (94%), mp 66-68°C. (Lit.[103] mp 64-66°C), ^{1}Hmr, δ, (90 MHz), 7.48-7.22 (m, 8H, Ar-H), 3.42 (d, 4H, J=5 Hz, $-CH_2SH$) and 1.55 (t, 2H, J=5 Hz, $-CH_2SH$); ^{13}Cmr, δ,

(62.9 MHz), 139.9 (C-2), 139.8, 137.9 (C-1, C-1'), 129.4, 128.4, 127.6 (C-3, C-2', C-3'), 128.4, 127.8 (C-4, C-4') and 26.9 ($-\underline{CH}_2SH$).

7. 9-Phenyl-18-methyl-2,11-dithia[3.3]metacyclophane 59.

A solution of the dithiol 61 (10g, 40.6 mmol) and the dibromide 54 (11.3g, 40.6 mmol) in nitrogen purged benzene (900 mL) was added dropwise to a well stirred solution of KOH (5.7g, 101.8 mmol) in nitrogen purged 95% EtOH (2500 mL) at 60°C under nitrogen. When the addition was complete (2.5d) the solution was cooled and concentrated. Dichloromethane and water were added to the residue as well as dilute aqueous HCl to neutralize the solution. The dichloromethane extract was washed, dried and evaporated. The residue was then preadsorbed on celite and chromatographed over silica gel using benzene/pentane (1:1) as eluant. The chromatography gave two fractions: The first consisted of a mixture of *anti* and *syn* thiacyclophanes 59 and 59A 5.7g (39%), while the second contained products of higher molecular weight.

Note: when the bromide-thiol coupling was done at room temperature lower yields of dimer 104 were obtained (20%).

(a) *anti*-9-phenyl, 18-methyl-2,11-dithia[3.3]metacyclophane 59.

The mixture of the *anti*- and *syn*-dithiacyclophanes 59 and 59A, obtained from the first fraction from the chromatography experiment above, was rechromatographed over silica gel using benzene/pentane (1:4) as eluant. The first fraction of this chromatography contained

the pure *anti*-isomer 59, while later fractions contained increasing amounts of the *syn*-isomer 59A.

The mixture of the *anti*- and *syn*-isomer obtained in these later fractions was repeatedly recrystallized from benzene to give pure crystals of *anti*-isomer 59. The crystals of 59 obtained by chromatography (see above) were also recrystallized from benzene. The combined yield of *anti*-isomer 59 was 2.66g (18%) of colorless crystals, mp 165°C, ^{1}Hmr, δ, (90 MHz), 7.46 ($\underline{AB}_2$, 2H, H-5), 7.35-7.13 (m, 6H, Ar-$\underline{H}$), 7.02 ($\underline{AB}_2$, 1H, H-15), 6.74 (br. s, 2H, H-2', 6'), 3.79 and 3.66 (AB quartet, 4H, J=14.3 Hz, -$\underline{CH}_2$-S-), 3.70 and 3.46 (AB quartet, 4H, J=13.6 Hz, -CH_2-S-) and 1.56 (s, 3H, Ar-$\underline{CH}_3$);
ms peaks (EI) at m/e (relative intensity) 362 (M^+, 9), 212 (15), 211 (24), 179 (100), 178 (49), 165(38), 152 (17), 149 (13), 148 (12), 135 (17), 134 (16), 118 (28), 117 (60), 91 (45) and 77 (23);
^{13}Cmr, δ, (1511 MHz), 143.0 (C-9), 137.9 (C-1'), 136.8 (C-18), 135.6, 134.9 (C-4, C-13), 130.7 (C-2'), 130.1, 129.9, 126.8 (C-5, C-14, C-3'), 127.0, ;26.8, 125.0 (C-6, C-15, C-4'), 32.5, 31.1 (C-1, C-3) and 15.8 (Ar-$\underline{CH}_3$).

Anal. Calcd. for $C_{23}H_{22}S_2$: C 76.19, H 6.11
Found : C 76.09, H 6.16

(b) *syn*-9-phenyl, 18-methyl-2,11-dithia[3.3]metacyclophane 59A.

The mixtures of *anti* and *syn* thiacyclophanes 59 and 59A that showed the *syn*-isomer to be the major component, obtained from chromatography or from recrystallization as described in (a), were

repeatedly recrystallized from a benzene/hexane mixture (1:9) to yield 86 mg (0.6%) of 59A as colorless crystals, mp 170°C, ^{1}Hmr, δ, (90 MHz), 7.37 (br. s, 5H, Ar-H), 6.99 (AB_2, 2H, J=7Hz, H-5 or H-14), 6.90 (AB_2, 2H, J=7Hz, H-5 or H-14), 6.75 (AB_2, 2H, J=7Hz, H-6, H-15), 4.19 and 3.68 (AB quartet, 4H, J=15Hz, $-CH_2-S-$), 3.93 and 3.64 (AB quartet, 4H, J=15Hz, $-CH_2-S-$) and 2.41 (s, 3H, Ar-CH_3);
ms peaks (EI) at m/e (relative intensity) 362 (M^+, 37), 211 (27), 179 (100), 178 (52), 165 (33), 149 (12), 148 (11), 134 (11), 117 (37), 115 (24), 91 (26) and 77 (15);
^{13}Cmr, δ, (15.1 MHz), 139.1 (C-9), 138.2, 134.2 (C-18, C-1'), 136.1, 135.2 (C-4, C-13), 131.7 (C-2'), 130.3, 129.4, 127.7 (C-5, C-14, C-3'), 128.2, 127.0, 125.8 (C-6, C-15, C-4'), 36.1, 34.9 (C-1, C-3) and 17.9 (Ar-CH_3).

Anal. Calcd. for $C_{23}H_{22}S_2$: C 76.19, H 6.11
Found : C 76.87, H 6.13

8. *Wittig rearrangement of anti-dithiacyclophane 59 to 118.*

n-BuLi (268.8 mg, 4.2 mmol) in hexane (4mL) was added by syringe to a stirred solution of dithiacyclophane 59 (648 mg, 1.79 mmol) in dry THF (45 mL) under nitrogen at room temperature. The initially colorless solution turned dark red and was stirred for an additional 5 min. Methyl iodide (0.5 mL, 8.0 mmol) was then added upon which the solution turned pale yellow. The mixture was then acidified with aqueous HCl and extracted with dichloromethane. The organic extract was washed with water, until neutral, dried and evaporated to give a

yellow oil. This was then chromatographed over silica gel using benzene as eluant to give 258 mg (37%) of 118 as a mixture of isomers.

9. Anti-Bis(sulfonium)salt 59S of anti-dithiacyclophane 59.

A solution of thiacyclophane 59 (1.76g, 4.86 mmol) in dry dichloromethane (50 mL) was added slowly with stirring to a suspension of dimethoxycarbonium fluoroborate (3.42g, 80% as oil, 16.8 mmol) in dry dichloromethane (5 mL) held at -30°C under a nitrogen atmosphere. When the addition was complete, the mixture was allowed to warm to room temperature and was stirred for another 4 h. Then ethyl acetate (35 mL) was added and the mixture was stirred for 5 h. This on filtration gave the bis(sulfonium)salt 59S as white powder (2.63g, 96%). This was employed directly in the next step.

10. Stevens Rearrangement of 59S to give 118.

Potassium t-butoxide (2.0g, 17.86 mmol) was added to a stirred suspension of sulfonium salt 59S (2.63g, 4.65 mmol) in dry THF (130 mL) under a nitrogen atmosphere. The mixture was then stirred for 1h. at room temperature after which aqueous HCl and dichloromethane were added. The organic layer was separated, washed with water, dried and evaporated. The yellow residue was then preadsorbed on silica gel and chromatographed over silica gel, using pentane as eluant to give 1.16g (64%) of 118 as a mixture of isomers.

(a) *anti*-1,9-Bis(methylthio)-8-phenyl-16-methyl[2.2]metacyclophane 118A.

The mixture of isomers 118 (747 mg, 192 mmol) was carefully rechromatographed over silica gel, using pentane as eluant, to separate the individual components. The first fractions provided a crystalline solid 118A which, after recrystallization from hexane, gave 182 mg (24%) of colorless needles, mp 157-158°C, ^{1}Hmr, δ, (90 MHz), 8.00 (dd, 1H, H=7Hz, J=1.5Hz, H-6), 7.70 (dd, 1H, J=6Hz, J=2Hz, H-14), 7.39 (dd, 1H, J=7Hz, H-4), 7.22-6.87 (m, 6H, Ar-H), 6.48-6.34 (m, 2H, H-2',6'), 4.26 (dd, 1H, J-4Hz, J=11.5Hz, H-1(ax)), 3.82 (dd, 1H, J=4Hz; H-9(ax)), 3.29 (dd, 1H, J=4Hz, J-11.5Hz, H-10(eq)), 2.70 (t, 2H, J=11.5Hz, J=11.5Hz, H-2(ax)), H-10(ax)), 2.16 (s, 3H, (S-CH_3)-9), 2.12 (s, 3H, (S-CH_3)-1) and 0.87 (s, 3H, Ar-CH_3);

ms peaks (EI) at m/e (relative intensity) 390 (M^+, 7), 225 (31), 179 (16), 178 (17), 165 (100), 149 (13), 147 (11), 115 (12), 91 (6) and 77 (7);

^{13}Cmr, δ, (62.9 MHz), 147.2 (C-8), 143.3 (C-16), 137.9 (C-1'), 137.1, 136.3, 135.9, 134.9 (C-3, C-7, C-11, C-15), 130.7 (C-2',6'), 126.7 (C-3',5'), 129.3, 128.4, 126.9, 126.4, 125.9, 124.8, 124.7 (C-4, C-5, C-6, C-12, C-13, C-14, C-4'), 53.2 (C-9), 52.9 (C-1), 43.2 (C-2), 42.5 (C-10), 16.2 (Ar-CH_3), 15.6 (1 S-CH_3) and 15.1 (9 S-CH_3).

Anal. Calcd. for $C_{25}H_{26}S_2$: C 76.87, H 6.71

Found : C 76.40, H 6.38

(b) *anti*-1,10-bis(methylthio)-8-phenyl-16-methyl[2.2]metacyclophane 118B.

Later fractions of the above mentioned chromatograph (see (a)) showed, based on ^{1}Hmr, an increase in a second isomer which we

assigned as 118B. These fractions were again chromatographed over silica gel using pentane as eluant to give 118B as a waxy solid. Repeated recrystallization from hexane gave 2 mg (0.3%) of 118B as white crystals, mp 162-163°C, ^{1}Hmr, δ, (90 MHz), 7.62 (d, 2H, J=8Hz, H-12), 7.36 (d, 2H, J=7Hz, H-4), 7.12-6.86 (m, 5H, Ar-H), 6.65-6.52 (m, 2H, H-2',6'), 4.15 (dd, 2H, J=4Hz, J=11Hz, H-1(ax)), 3.32 (dd, 2H, J=4Hz, J=12Hz, H-2(eq)), 2.77 (t, 2H, J=11Hz, J=12Hz, H-2(ax)), 2.11 (s, 3H, S-CH$_3$) and 0.93 (s, 3H, Ar-CH$_3$);
ms peaks (EI) at m/e (relative intensity) 390 (M^+, 29), 211 (100), 191 (21), 178 (22), 165 (32), 163 (21), 147 (37), 115 (14), 91 (11) and 77 (13);
^{13}Cmr, δ, (62.9 MHz), 146.5 (C-8), 143.6 (C-16), 137.8 (C-1'), 136.6, 135.7 (C-3, C-11); 131.2 (C-2'), 129.1, 126.7, 125.4 (C-4, C-12, C-3'), 126.8, 125.8, 125.2 (C-5, C-13, C-4'), 52.5 (C-1), 44.0 (C-2), 16.4 (Ar-CH$_3$) and 15.5 (-S-CH$_3$).

11. Hofmann Elimination of 118 to give anti-15-phenyl-16-methyl dihydropyrene 51.

A solution of the mixture of isomers 118 (1.03g, 2.64 mmol) in dry dichloromethane (10 mL) was added to a stirred suspension of dimethoxycarbonium fluoroborate (2.14g, 80% as oil, 10.6 mmol) in dry dichloromethane (5 mL) held at -30°C under nitrogen. When the addition was complete, the mixture was allowed to warm to room temperature and was stirred for another 4 h. Then ethyl acetate (35 mL) was added and stirring was continued for 0.5 h. The solvent was removed by

decantation and the oily residue was triturated with ethyl acetate effecting the separation of 1.05g (67%) of the bis(sulfonium) salt 120 as an off-white powder. This was employed directly in the next step.

Anhydrous potassium t-butoxide (0.79g, 7.05 mmol) was added to a stirred suspension of the bis(sulfonium) salt 120 (1.05g, 1.77 mmol) in dry THF (35 mL) under nitrogen. The mixture was then stirred for 1 h. at reflux. After cooling of the reaction mixture, benzene was added and the mixture was acidified with aqueous HCl. The organic layer was then separated, washed, dried and evaporated. The dark green residue was preadsorbed on celite and chromatographed over silica gel, using pentane as eluant, and gave 213 mg (41%) of 51. Recrystallization from cyclohexane gave dark green crystals, mp 159-160°C, ^{1}Hmr, δ, (90 MHz), 8.77-8.03 (m, 10H, Ar-H), 6.20 (t, 1H, J=7.5Hz, H-4'), 5.85 (t, 2H, J=7.5Hz, H-3'), 2.81 (d, 2H, J=7.5Hz, H-2') and -4.30 (s, 3H, -CH$_3$;

ms peaks (EI) at m/e (relative intensity) 294 (M^+, 16), 279 (30), 217 (22) and 202 (100);

UV, $\lambda_{max}^{cyclohexane}$ (ε) 341 nm (86.000), 357.5 (24.000), 383 (46.000), 443 (5.000), 461 (6.200), 481 (6.500), 540 (215), 590 (217), 603 (264), 615.5 (296), 631 (244) and 645.5 (325);

^{13}Cmr, δ, (62,9 MHz), 139.0 (C-4), 136.7 (C-1'), 135.3 (C-7), 125.8 (C-5), 125.3 (C-3'), 125.0 (C-4'), 124.8 (C-8), 124.4 (C-2), 124.1 (C-2'), 122.95 (C-3), 122.9 (C-6), 122.5 (C-9), 36.6 (C-15), 29.1 (C-16) and 14.9 (C-16b).

Anal. Calcd. for $C_{23}H_{18}$: C 93.84, H 6.16

Found : C 93.63, H 6.35

12. Raney Nickel Desulfurization of 118A.

A solution of 118A (182 mg, 0.466 mmol) in 100% ethanol (40 mL) containing W-7 Raney Nickel[116] (6g) was heated at reflux for 6 h. After removal of the catalyst and solvent, the residue was taken up in dichloromethane and chromatographed over silica gel. This gave 136.4 mg (98%) of *anti*-8-phenyl-16-methyl[2.2]metacyclophane 119. Recrystallization from hexane gave colorless crystals, mp 147°C, ^{1}Hmr, δ, (CCl_4, 90 MHz), 7.26-7.18 (d (AB_2), 2H; Ar-H), 7.0-6.6 (m, 7H, Ar-H) 6.51-6.38 (m, 2H, H-2',6'), 3.05-2.65 (m, 8H, $-CH_2-CH_2-$) and 0.79 (s, 3H, $Ar-CH_3$);

ms peaks (EI) at m/e (relative intensity) 298 (M^+, 7), 180 (21), 179 (100), 178 (21), 165 (9), 119 (16), 117 (10), 91 (7) and 77 (5);

^{13}Cmr, δ, (62.9 MHz), 146.8 (C-8), 143.0 (C-16), 138.9 (C-1'), 137.4, 136.3 (C-3, C-11), 130.8 (C-2'), 128.3, 127.2, 126.34 (C-4, C-12, C-3') 126.30, 125.8, 124.0, (C-5, C-13, C-4'), 37.0, 36.7 (C-1, C-2) and 15.8 ($Ar-CH_3$).

Anal. Calcd. for $C_{23}H_{22}$: C 92.57, H 7.43

Found : C 92.41, H 7.23

13. 9,18-Diphenyl-2,11-dithia-[3.3]metacyclophane 192.

A solution of the dithiol 61 (5.0g, 20.32 mmol) and the dibromide 60 (6.91g, 20.32 mmol) in deoxygenated benzene (900 mL) was added dropwise to a well stirred solution of potassium hydroxide (3.4g,

61 mmol) in deoxygenated 95% ethanol (1(00 mL) at reflux under nitrogen. When the addition was complete (3 days), the solvent was removed under reduced pressure. The residue was then acidified with aqueous HCl and extracted with dichloromethane (500 mL). The organic layers were combined and washed with water, dried and evaporated. The white residue was preadsorbed on silica gel and chromatographed over silica gel using pentane (1000 mL) and pentane/dichloromethane (9:1) as eluants. This yields 58 mg (0.6%) of 192 as a mixture of *syn*- and *anti*-isomers.

In a comparable experiment, dicesium carbonate (3 equivalents) was used as the base instead of potassium hydroxide. However, the yield of the *syn* and *anti* mixture of 192 was not improved, 43 mg (0.5%).

(a) *anti*-9,18-Diphenyl-2,11-dithia[3.3]metacyclophane 192.

The mixture of isomers 192, described above, was again preadsorbed, this time on celite, and chromatographed over silica gel using pentane as eluant. The first fractions were enriched in the *anti*-isomer. Recrystallization from dichloromethane gave 9 mg of *anti*-192 as colorless crystals, mp 248-249°C, [Lit.[157] mp 220-226°C], ^{1}Hmr, δ, (90 MHz), 7.34-7.19 (m, 12H, Ar-H), 7.15-6.86 (m, 6H, H-6, H-2'), 4.22 and 3.57 (AB quartet, 8H, J=15Hz; $-CH_2-S-$);

ms peaks (EI) at m/e (relative intensity) 424 (M^+, 4), 211 (6), 207 (6), 180 (19), 179 (100), 167 (2) and 165 (2);

^{13}Cmr, δ, (CD_2Cl_2, 15.1 MHz), 139.4 (C-9), 137.6 (C-1'), 135.7 (C-4), 133.2 (C-2'), 130.6, 127.7 (C-5, C-3'), 128.7, 127.4 (C-6, C-4') and 35.0 (C-1).

Anal. Calcd. for $C_{28}H_{24}S_2$: C 79.20, H 5.70

Found : C 79.11, H 5.79

(b) *syn*-9,18-Diphenyl-2,11-dithia[3.3]metacyclophane 192A

The later fractions of the above mentioned chromatography experiment (see (a)) showed, by ^{1}Hmr, enrichment in the *syn*-isomer. These *syn*-isomer enriched fractions were combined and evaporated to dryness. Dichloromethane (5 mL) was then added and the solid was dissolved by heating. Subsequent cooling to 0°C followed by filtration gave, after two repetitions, 2.5 mg of pure *syn*-192A, mp 174-176°C, ^{1}Hmr, δ, (90 MHz), 7.42 ($\underline{AB}_2$, 4H, J=7Hz, H-5), 7.29 (s, 10H, Ar-$\underline{H}$), 7.07 ($\underline{AB}_2$, 2H, J=7Hz, H-6), 3.74 and 3.58 (AB quartet, 8H, J=13Hz, -$C\underline{H}_2$-S-);

ms peaks (EI) at m/e (relative intensity) 424 (M^+, 26), 211 (39), 180 (35), 179 (100), 178 (33), 165 (42) and 152 (16);

^{13}Cmr, δ, (62.9 MHz), 141.7 (C-9), 136.8 (C-1'), 134.9 (C-4), 132.3, 130.7, 126.9 (C-5, C-2', C-3'), 127.2, 127.0 (C-6, C-4') and 32.7 (C-1).

14. 9-Phenyl-2,11-dithia[3.3]metacyclophane 191.

A solution of the dithiol 61 (429 mg, 2 mmol) and α,α'-dibromo-m-xylene (538 mg, 2 mmol) in nitrogen purged benzene (400 mL) was added dropwise to a well stirred solution of potassium hydroxide (320 mg, 5.7 mmol) in nitrogen purged 95% ethanol (500 mL) at 60°C under nitrogen. When the addition was complete (30 h), the solution

was stirred at 60°C for an additional hour. The solvent was then removed under reduced pressure. The residue was acidified with aqueous HCl and extracted with dichloromethane. The organic extract was washed with water until neutral, dried and evaporated. The residue was then preadsorbed on celite and chromatographed over silica gel using pentane (500 mL) and pentane-dichloromethane (200 mL, 9:1) as eluants.

Recrystallization from cyclohexane gave colorless crystals of the dithiacyclophane 191, 276 mg (40%), mp 144°C [Lit.[103] mp 134°C), ^{1}Hmr, δ, (90 MHz), 7.34-7.05 (m, 7H, Ar-H), 6.99-6.83 (m, 3H, Ar-H), 6.70 (br s, 1H, H-2'), 5.49 (s, 1H, H-18), 3.70 and 3.53 (AB quartet, 4H, J=13Hz, -CH_2-S-), 3.62 and 3.55 (AB quartet, 4H, J=16Hz, -CH_2-S-); ms peaks (EI) at m/e (relative intensity) 348 (M^+, 50), 211 (19), 180 (24), 179 (100), 178 (57), 165 (21), 135 (10), 104 (10), 91 (12) and 78 (9);

^{13}Cmr, δ, (62.9 MHz), 143.4 (C-9), 137.7 (C-1'), 139.6, 135.0 (C-4, C-13), 130.4, 126.5 (C-5, C-14), 130.1 (C-2'), 129.5 (C-6'), 128.6 (C-18), 128.3, 127.7, 127.4$_0$ (C-6, C-15, C-4'), 127.3$_0$ (C-3',5'), 35.3 and 34.2 (C-1, C-3).

Anal. Calcd. for $C_{22}H_{20}S_2$: C 75.82, H 5.78

Found : C 75.70, H 5.92

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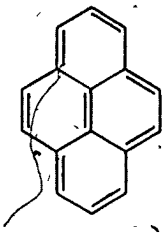
APPENDIX



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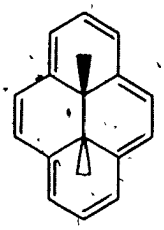

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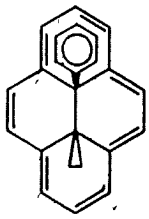

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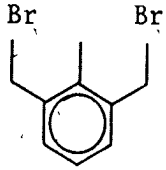

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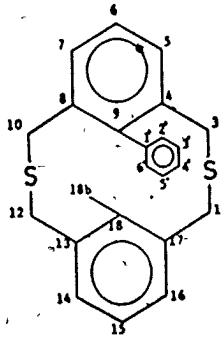

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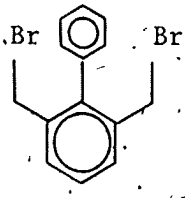

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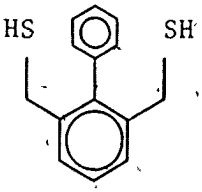

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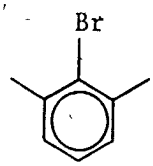

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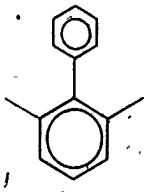

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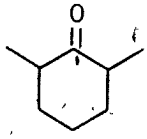

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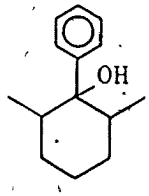

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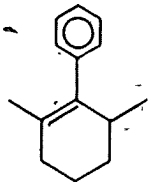

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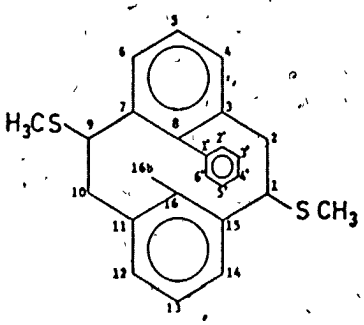

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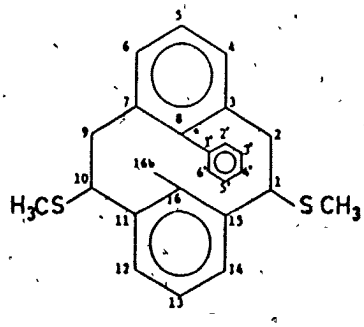

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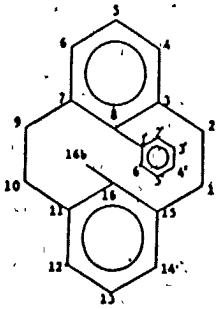

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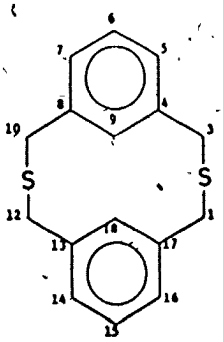

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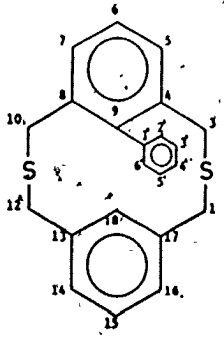

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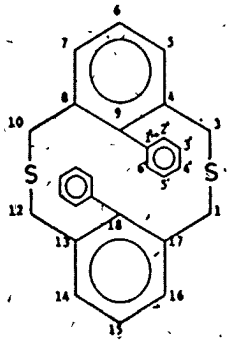

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1. The crystal and molecular structure of *syn*-2,11-dithia-[3.3]metacyclophane.
   Willem Anker, Gordon W. Bushnell, and Reginald H. Mitchell; Can. J. Chem., 57, 3080 (1979).

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