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The Synthesis of 2, 11-Dithiabenzo - [3.3] - Paracyclophane and an Octadeutero Derivative

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UNION COLLEGE - GRADUATE STUDIES

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The Synthesis of 2,11-Dithia-benzo-[3.3]-paracyclophane and an Octadeutero Derivative

A thesis presented to the Committee on Graduate Studies and the Department of Chemistry of Union College, Schenectady, New York, in partial fulfillment of the requirements for the degree of Master of Science.

by Paul M. Begley III MS 1976

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(Student's signature)

Approved by William B Martin, Jr.
Thesis advisor

Approved by Carol Flinn
Committee on Graduate Studies

Date June 1976

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Submitted in partial fulfillment
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ABSTRACT

The purpose of this work was the synthesis of 2, 11 - dithia-benzo- [3.3] -paracyclophane and its octadeutero derivative 2,11-dithia- 3,3, 5, 6, 8, 9, 10, 10-octa-deutero-benzo - [3.3] paracyclophane. A comparison of their nuclear magnetic resonance spectra as well as their mass spectra will unequivocably provide proof of their successful synthesis.

DEDICATION

I wish to thank Dr. William B. Martin, whose knowledge, guidance and cooperation have been greatly appreciated. It has been a rewarding and educational experience to have worked with him.

I also wish to thank my wife, Carol, whose patience, understanding and encouragement over the years have helped us to successfully accomplish our goal.

This thesis
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Paul M Begley

to the
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is approved by

William B Martin, Jr

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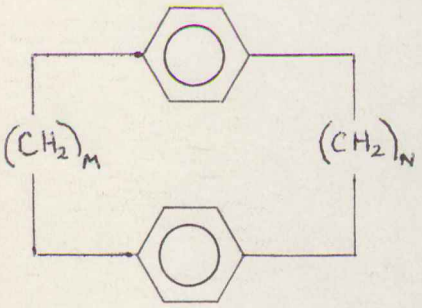
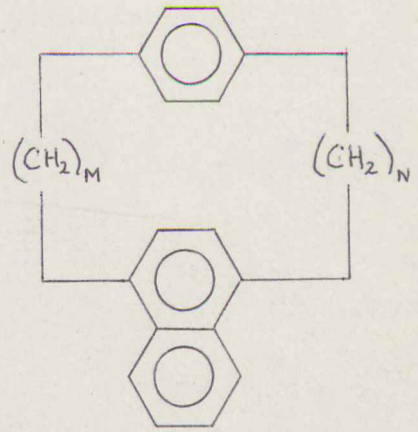
INTRODUCTION

The reason for undertaking the study of one of the paracyclophanes(I) stems from the synthetic work and electron - spin resonance (ESR) studies on radical anions of this series by Professor W. B. Martin, Jr. [1,2,3] In particular, publication of some research in benzoparacyclophanes (II) awaits an unequivocal assignment of presumably small coupling constants in the benzene moiety of the benzoparacyclophane radical anion.



I

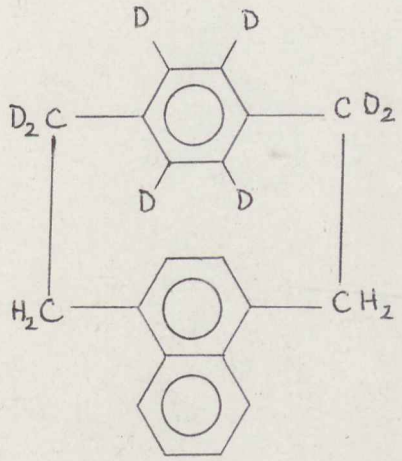


II

This assumption of small coupling assignments in the benzene portion of the molecule is based on the idea that better accommodation of the odd electron would be expected in the naphthalene portion of this sandwich-like compound. Such assignment has already been made by Gerson and Martin based on

ENDOR (electron nuclear double resonance spectroscopy) and ESR spectra of benzo- [2.2]-paracyclophane. Confirmation is possible by substitution in specific locations of deuterium for hydrogen.

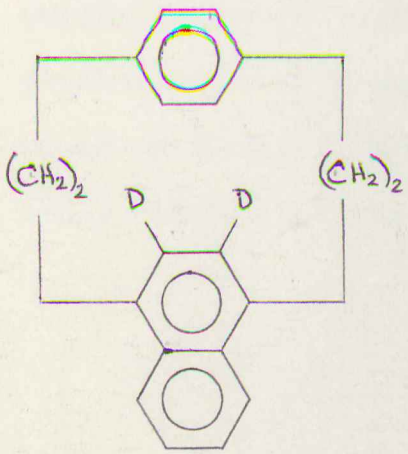
This present work deals with the partial preparation of 2, 2, 4, 5, 7, 8, 9,9-octadeutero-benzo - [2.2] - para-cyclophane (III) in which all of the hydrogens in the benzene moiety including the four benzylic hydrogens have been replaced with deuterium.



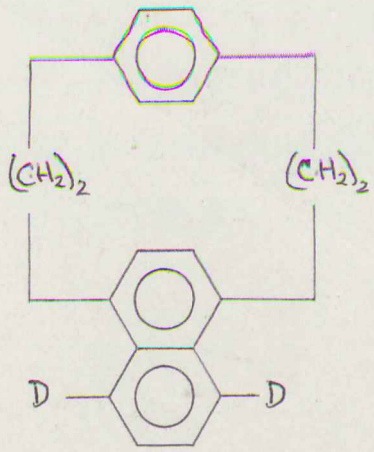
III

Comparison of the ESR spectra of the non-deuterated and deuter-ated benzo - [2.2] - paracyclophanes will hopefully confirm the previous hypothesis concerning small coupling constants for the benzene moiety. If, indeed, such assignments are proven correct, the next step would involve measuring the coupling constants of the naphthalene portion of the molecule in order to map the electron densities in the orbital bearing the single electron in its radical anion. Such future work would involve

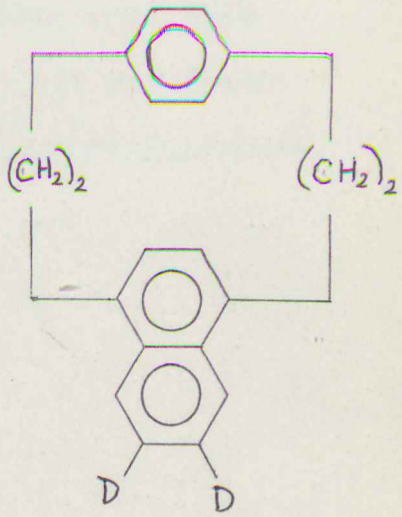
the synthesis of various benzo - [2.2] - paracyclophanes in which certain naphthalenic hydrogens have been isotopically labeled (IV, V, VI).



IV



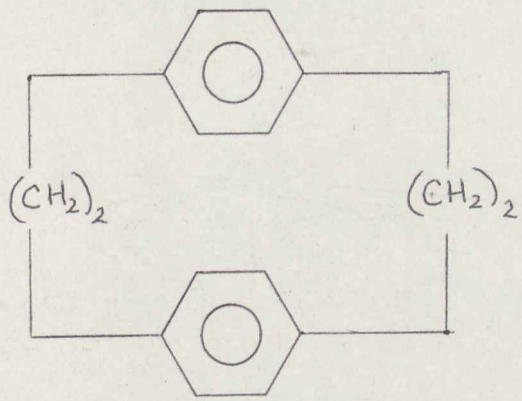
V



VI

HISTORICAL

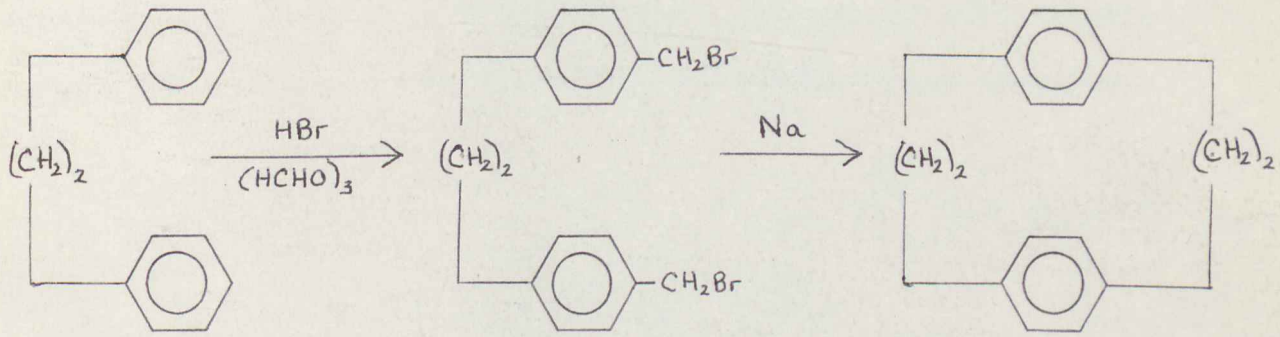
The first reported paracyclophane was discovered by Brown and Farthing[4] in 1949 while examining polymers prepared by low-pressure pyrolysis of p-xylene. They noticed that extraction of the polymer with chloroform yielded a mixture of low molecular weight compounds containing traces of an acetone insoluble fraction having a m.p. 285° whose novel structure was determined by x-ray diffraction to be that of [2.2]-paracyclophane (VII) which they named "di-p-xylene".



VII

Brown and Farthing attempted to prepare this novel compound by standard organic chemical methods but were unsuccessful. It was not until two years later that the first successful synthesis of a paracyclophane was reported by Cram and Steinberg.[5] Since that time Cram and various co-workers have published a series of over 47 articles in the Journal of the American Chemical Society dealing with paracyclophane chemistry.

Paracyclophane, as originally defined by Cram and Steinberg in 1951, is a class of compound(I) in which "two benzene rings are rigidly held in a face to face position by methylene bridges in the para positions".[5] The first member of the paracyclophane series synthesized by Cram was the [2.2]- paracyclophane (VII) discovered by Brown and Farthing and mentioned previously. The synthetic method employed was an intramolecular Wurtz reaction of the dibromide IX, with reduction and linear polymerization of the dibromide occurring as side reactions. The dibromide was prepared by the bromomethylation of the corresponding hydrocarbon(VIII).

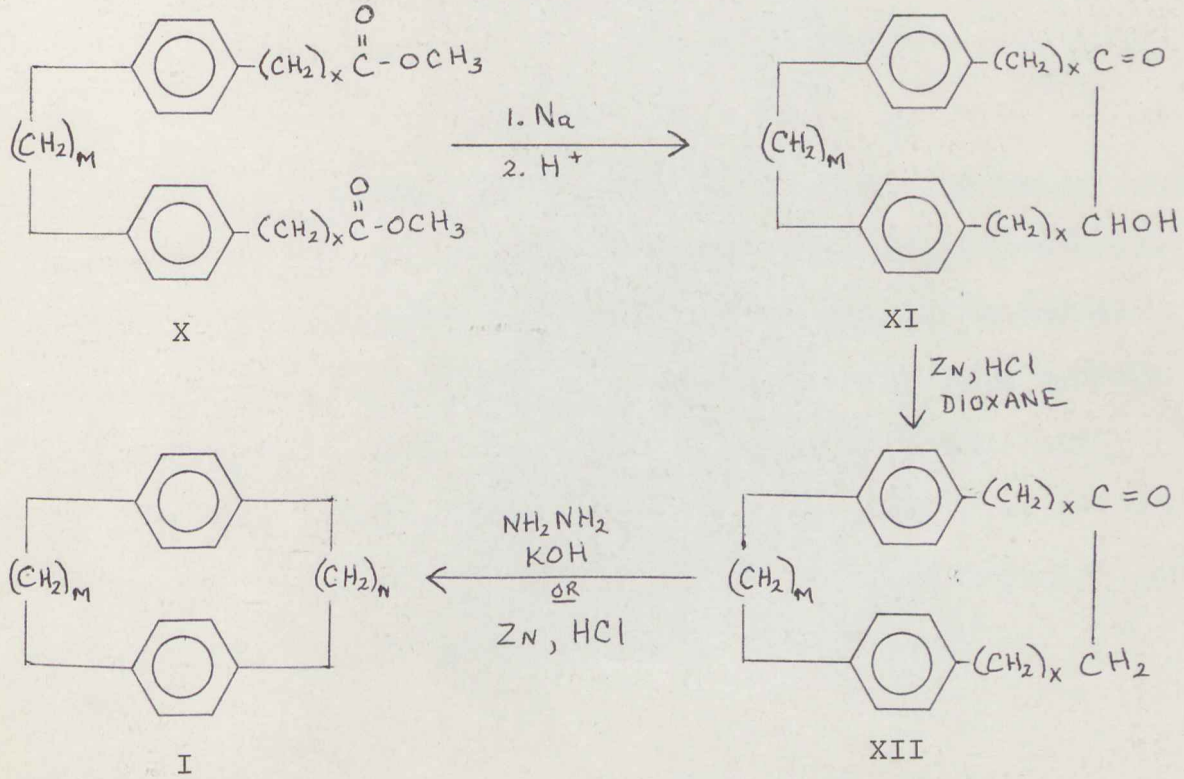


VIII IX VII

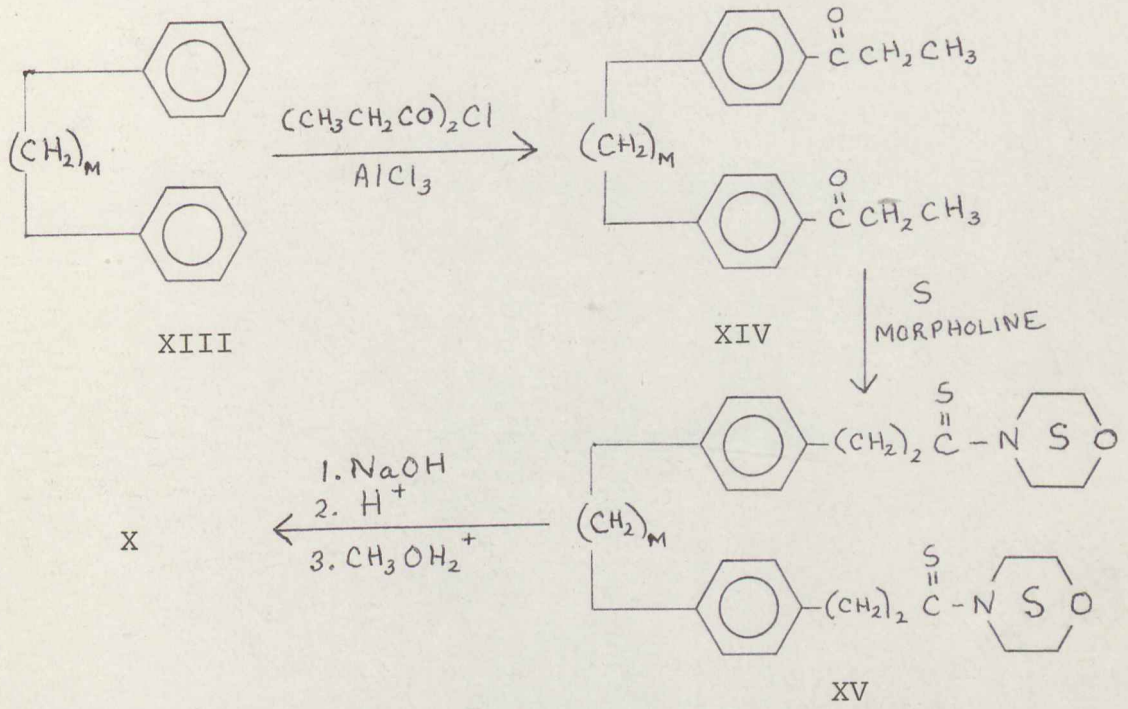
Hydrocarbon VIII was prepared by the action of magnesium on benzyl chloride. This snythetic route was utilized by Cram in preparing various other paracyclophanes containing at

least one two-membered methylene bridge such as [2.3] - and [2.4] - paracyclophanes. This reaction is, however, limited to compounds in which both bromide functions are of the benzyl type. While this method did indeed give the desired product, yields were extremely low and this prompted the search for a better synthetic method.

Another synthetic method for the preparation of paracyclophanes which does not require the presence of at least one two-membered methylene bridge involves the reduction of an appropriate cyclic acyloin (XI) to its corresponding ketone(XII), followed by further reduction of the ketone to the corresponding paracyclophane (I). The cyclic acyloin is synthesized in good yield by treatment of the appropriate diester(X) with highly dispersed sodium to effect an acyloin condensation reaction.[6]

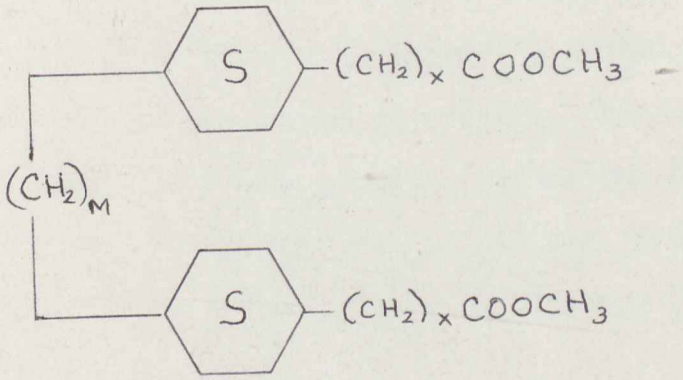


For instance the diester X with x = 2 is prepared by dipropionylation of the appropriate hydrocarbon XIII to give XIV followed by the Schwenk modification of the Willgerodt reaction [7,8] to produce the thiomorpholide XV, which upon hydrolysis and esterification gives X (where x = 2).



This synthetic pathway, while more useful than the Wurtz reaction, is still limited in that the acyloin ring closure fails on esters of the phenylacetic type due to the activated α-hydrogens which preferentially react in Claisen-type condensation reactions. [9,10] Thus, this synthetic pathway will work provided x in the diester X is greater than or equal to two. This limits the scope of the synthesis to paracyclophanes containing one methylene bridge of at least six carbons.

Cram was able to improve this synthetic method even further by discovering that if the benzene rings of X are hydrogenated prior to acyloin ring closure, the resulting dicyclohexyl compounds (XVI) can be closed to give an acyloin ultimately convertible to a paracyclopane. This can be illustrated with n=m=4 assuming m=4 and x=1 in compound XVI.

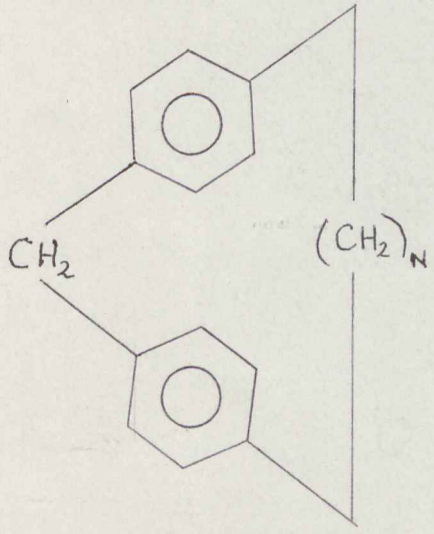


XVI

This method obviously is applicable to the synthesis of compounds having polymethylene bridges of this size or larger, but smaller only to a limit imposed apparently by steric factors which prohibit ring closure.[13] The synthesis of [3.3]- paracyclophane was carried out via this hydrogenation pathway in a 1% over-all yield from saturated diester. This yield is indicative of the unfavorable steric situation found for the

ring closing step and compares with the yields for analogous sequences in the preparation of the two next larger cycles as follows: Compound I with m=3, n=4, yield 6%; I with m=n=4, yield 22%. [14]

The general synthetic scheme involving an acyloin condensation of either the aromatic diester (X) or the dicyclohexyl compound (XVI) is important in the synthesis of the more symmetrical paracyclophane (I with n or m =2 to 6) in which the sandwich-like geometry of the aromatic rings places the π - orbitals of each ring fairly parallel. Cram also showed this synthetic route to be applicable to rather unsymmetrical, clam-shaped compounds in which one of the two bridges carries one methylene and the other 7, 8, 9, 10, 11 and 12 methylene groups (XVII).

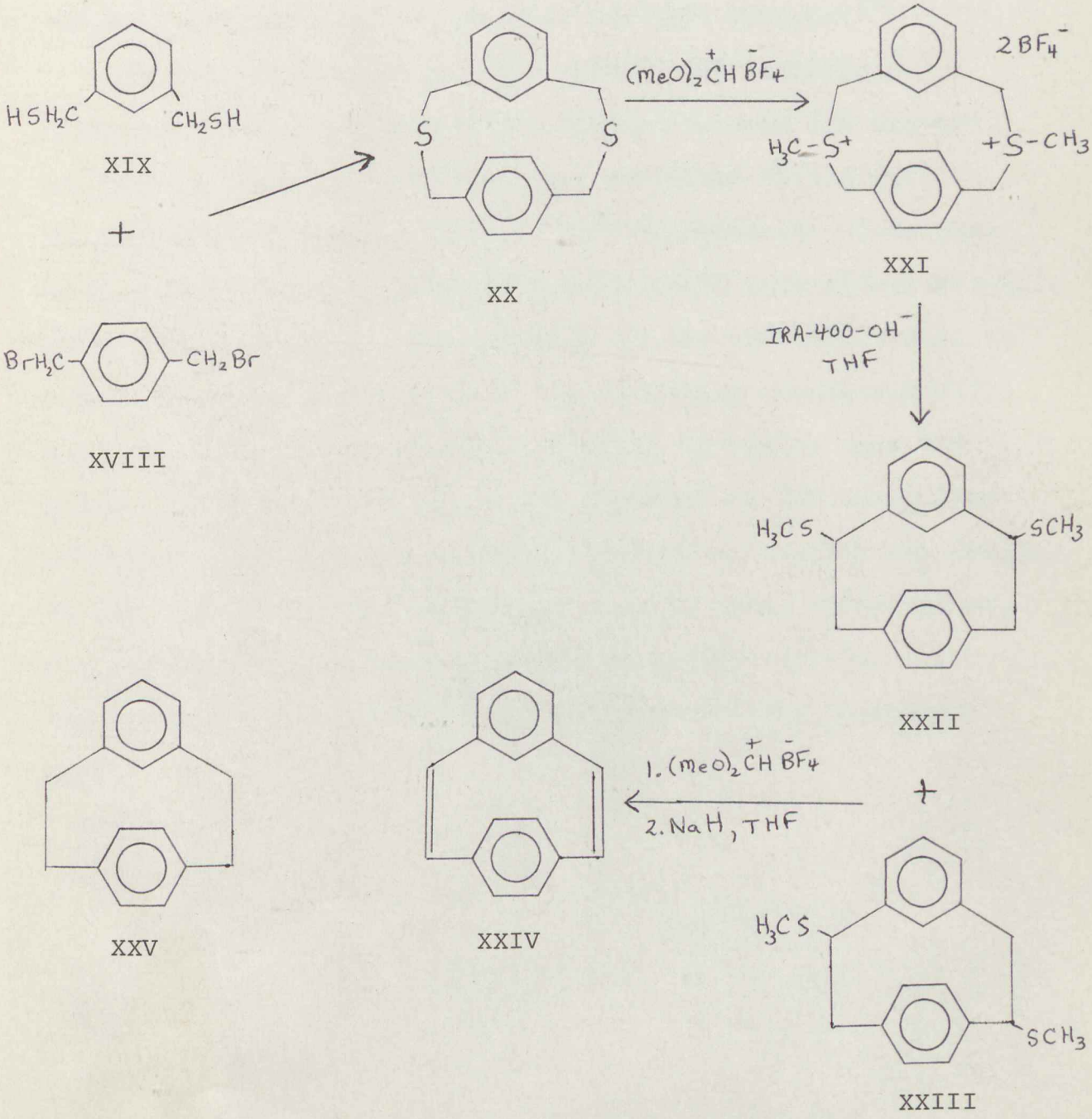


XVII

The smallest cycle preparable through use of the acyloin reaction on a diester carrying two aromatic rings was [1.8] - paracyclophane. The smallest cycle preparable through use of the acyloin reaction on a diester carrying two cyclohexane rings was [1.7] -paracyclophane.[15]

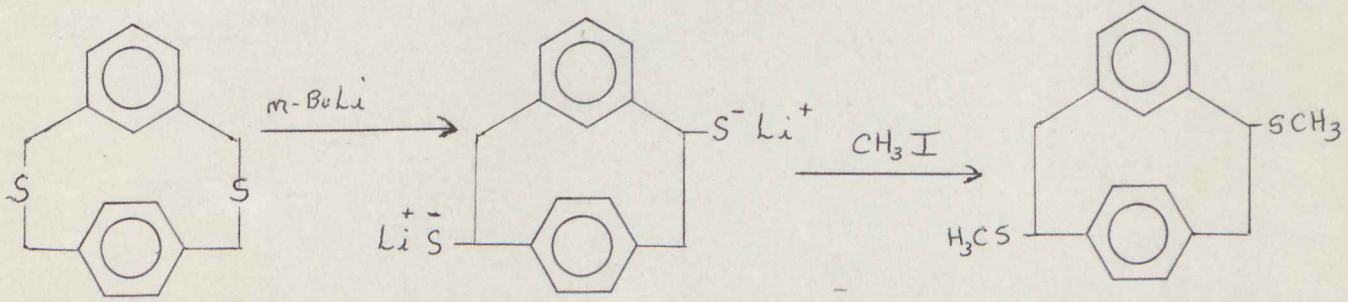
A two-step sequence of a Stevens rearrangement followed by a Hofmann elimination provides a convenient synthetic route for transforming 2, 11-dithia - [3.3] -metaparacyclophanes to [2.2] -metaparacyclophane- 1.9-dienes and ultimately to [2.2]-metaparacyclophane. The requisite 2,11-dithia- [3.3] -metaparacyclophanes are readily available in good yield by the condensation of p-xylylene dibromides with m-xylylene dimercaptans or, alternately, by the condensation of m-xylylene dibromides with p-xylylene dimercaptans.[16,17] As an example of this synthetic route, condensation of p-xylylene dibromide(XVIII) with 1,3-bis-(mercaptomethyl)-benzene (XIX) gave 2,11-dithia - [3.3] - metaparacyclophane (XX) in 43% yield. Treatment of XX with dimethoxycarbonium fluoroborate gave the corresponding bis(sulfonium) fluoroborate(XXI) in essentially quantitative yield. The stevens rearrangement was carried out by stirring a solution ofXXI in tetrahydrofuran with an ion exchange resin (IRA-400-OH) at room temperature for 84 hours. The product was a mixture of two isomers, XXII and XXIII, formed in an overall yield of 45%. For the Hofmann elimination the

mixture was again methylated with dimethoxycarbonium fluoroborate and then treated with sodium hydride in tetrahydrofuran. This gave [2.2] -metaparacyclophane-1,9-diene(XXIV) in 72% yield. Quantitative hydrogenation over platinum gave the known [2.2]-metaparacyclophane(XXV).



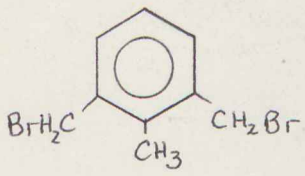
This synthetic route to cyclophanes utilizing a Stevens rearrangement followed by a Hofman elimination ran into problems when it was noticed that the Stevens rearrangement step is tempermental in certain cases and the yields obtained are sensitive to both the nature of the base used and its concentration, as well as to the starting thiocyclophane. Paracyclophanes could not be made via this process.[17]

Further investigations by Mitchell and Boehelheide[18] indicated some mechanistic similarities between the Stevens and Wittig rearrangements and they attempted Wittig rearrangements on various dithia-[3,3]-cyclophanes. Treatment of 2,11-dithia-[3.3]-metacyclophane(XXVI) with either n-butyllithium or lithium diisopropylamide in dry tetrahydrofuran at 0°C followed by methylation of the resulting thiolate(XXVII) gave the [2.2]-metacyclophane (XXVIII) in better than 94% yield. [2.2]-paracyclophane was prepared in 24% yield from its corresponding dithia compound whereas no product was obtained via the Stevens rearrangement. In all cases investigated, the Wittig rearrangement occured more rapidly and was more convenient to conduct than the analogous Stevens rearrangement.



XXVI XXVII XXVIII

The most recent synthetic route for the preparation of cyclophanes involves the previously discussed formation of dithiacyclophanes, but in this synthetic scheme the dithiacyclophanes are irradiated in the presence of trimethyl phosphite to provide a convenient, high yield, single-step synthesis of cyclophanes.[19] For example, the condensation of 2,6-bis-(bromomethyl)-toluene (XXIX) with 1,3-bis-(mercaptomethyl) benzene (XXX) gave XXXI in 38% yield. Irradiation by ultraviolet light of a very dilute solution of XXXI in trimethyl phosphite at room temperature for 48 hours gave the corresponding metacyclophane(XXXII) in 49% yield.



XXIX

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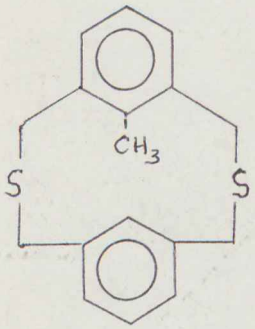
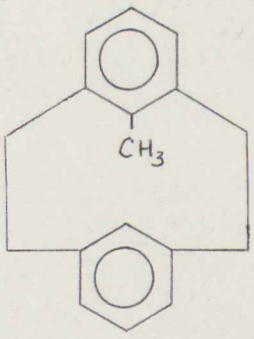
XXX



XXXI



XXXII

Gerson and Martin[3] successfully prepared [2.2] -para- cyclophane via the photochemical extrusion of sulfur from the corresponding 2,11 dithia- [3.3] -paracyclophane. This method will be the one utilized in our attempt to synthesize 2,2,4,5,7,8,9,9-octadeutero-benzo- [2.2] -paracyclophane (III).

FIGURE # 1

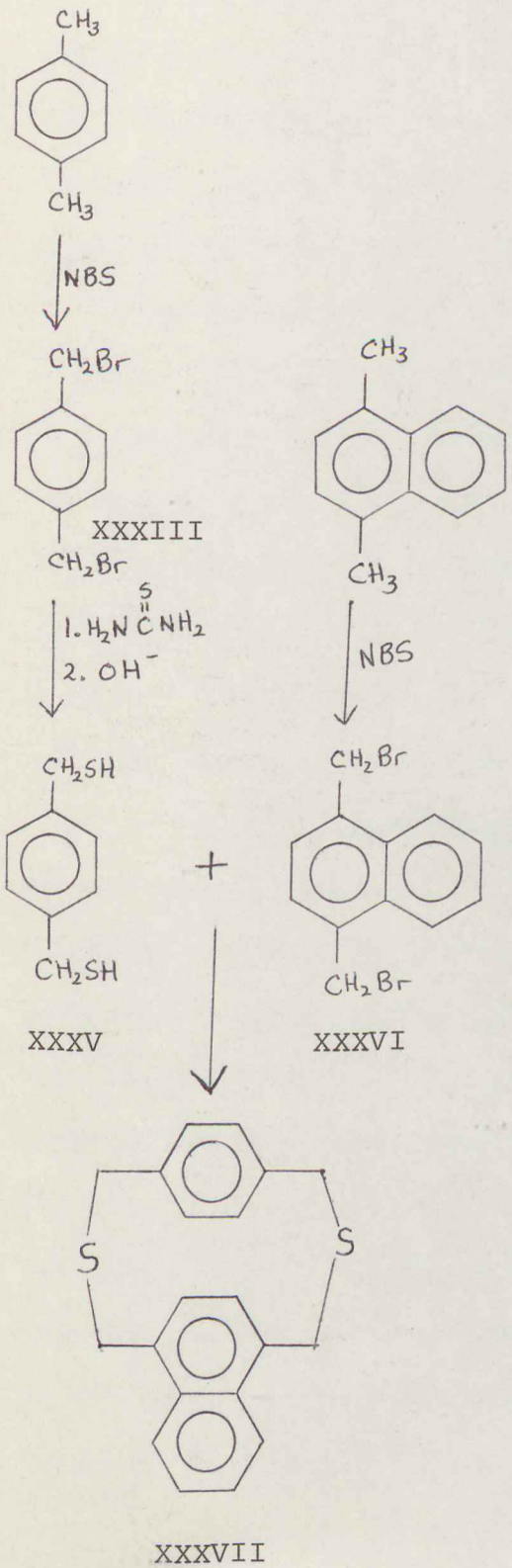
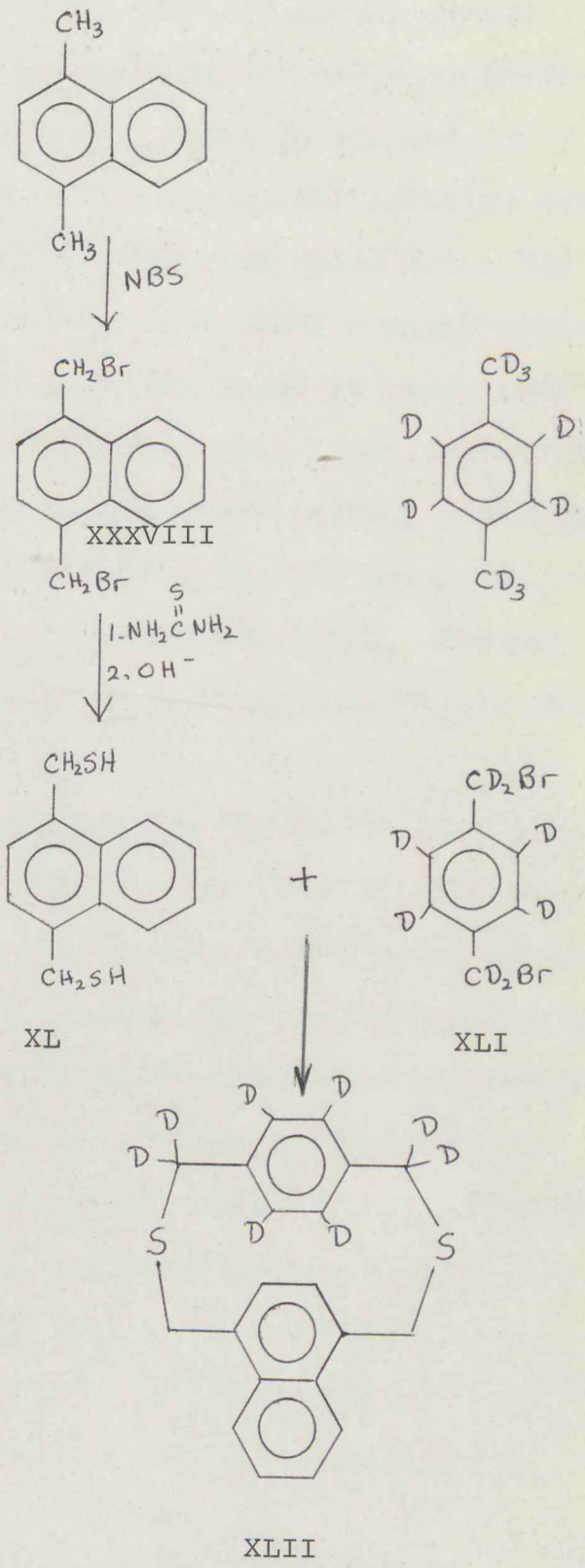


FIGURE # 2



EXPERIMENTAL

1. 1,4-bis(Bromethyl)-benzene (XXXIII).[20] -To a solution of 5.33 g. (0.0503 mole) p-xylene in 50 ml of carbon tetrachloride were added 23.28 g.(0.131 mole of N-bromosuccinimide [21] and the mixture was heated to reflux. After 30 minutes, a vigorous reflux occured for several minutes. The solution was refluxed an additional hour and then filtered while hot. The filtrate was distilled to dryness in vacuo using a Buchi roto-vapor-R apparatus, yielding 7.90 g.(0.030 mole) of crude 1,4-bis (bromomethyl)-benzene (XXXIII) (60%). The crude product was recrystalized from ligroin and filtered after setting overnight at room temperature. This yielded 4.47 g.(0.0169 mole) of crystals (34%), m.p. 138-143°(literature, 142-144°). The nmr spectrum (Figure #3) gave a singlet at 4.64 ppm(4H,-CH_2-), and a singlet at 7.48 ppm (4H, ArH).

2. 1.4-bis-(Mercaptomethyl)-benzene (XXXV).[22] To a hot solution of 2.60 g.(0.034 mole) thiourea in 25 ml of ethanol were added portionwise with stirring 4.47 g.(0.017 mole) of 1,4-bis-(bromethyl)-benzene (XXXIII). After addition was complete, the mixture was refluxed an additional 30 minutes; the solution was then concentrated to half volume and cooled yielding 6.42g. (0.015 mole) of 1,4-bis-(isothiouroniummethyl)-benzene dibromide (XXXIV) (88%). A mixture of 6.42 g.(0.015 mole) of XXXIV in a solution of 26 g. potassium hydroxide in 71 ml of water was boiled under reflux for five hours. The mixture was cooled, 30 ml of 9M aqueous sulfuric acid was added and the whole

extracted with ether. The ether extract was washed with water, dried over sodium sulfate and concentrated to yield 2.31g. (0.0136 mole) of a crystaline solid(80%). The solid was recrystalized from a benzene-cyclohexane mixture to yield 1.3g. (0.0076 mole) of 1,4-bis-(mercaptomethyl)-benzene(XXXV) (45%), m.p. 44-46°

3. 1,4-bis-(Bromomethyl)-naphthalene (XXXVI).[23] To a solution of 4.94 g. (0.032 mole) of 1,4-dimethylnaphthalene (Fluka AG, Buchs SG, purum, #146195-113) in 79 g. of carbon tetrachloride was added 11.43 g.(0.064 mole) of n-bromosuccinimide [21] and 0.6 g. of benzoyl peroxide. The mixture was refluxed 40 hours and the resulting solution was filtered hot and the filtrate cooled in the refrigerator. After 24 hours, the mixture was filtered yielding 3.2 g.(0.010 mole) of crude product (31%), m.p. 180-184°. The nmr spectrum (Figure #4) showed the following peaks: a singlet at 5.14 ppm(4H), a split multiplet centered at 8,35 and 7.75 plus a third obscured peak at 7.65 ppm. Recrystalization from benzene and then ligroin yielded 1.94 g(0.0062 mole) of 1,4-bis-(bromomethyl)-naphthalene (XXXVI), m.p. 192-193°(Literature 191-191.5°)[23]

In a larger scale preparation, using 20.0 g.(0.128 mole) of 1,4-dimethylnaphthalene (Aldrich Chemicals,D17,030-5) and 50.2g. (0.282 mole) of N-bromosuccinimide a yield of 25.5 g.(0.081 mole) of light yellow crystals (63.3%). This crude product was

recrystalized to yield 9.5 g.(0.030 mole) of white crystals, m.p. 178-185°(XXXVIII).

4. 2,11-Dithia-benzo-[3.3]-paracyclophane(XXXVII).[24] A solution of 1.048 g.(0.0062 mole) of 1,4-bis-(mercaptomethyl)-benzene (XXXV) and 1.936g.(0.0062 mole) of 1,4-bis-(bromomethyl)-naphthalene(XXXVI) in 250 ml of tetrahydrofuran was added dropwise over a 72 hour period to a vigorously stirred solution of 0.54 g.(0.133 mole) sodium hydroxide dissolved in 12 ml of water and 1.5 liters of methanol. The sodium hydroxide solution was preheated to 55-60° and held at this temperature throughout the addition. After addition was completed, the mixture was held an additional three hours at 55-60° and then filtered while warm. The filtrate was distilled to dryness in vacuo using a Buchi rotovapor-R apparatus. The resulting white solid was extracted several times with warm benzene, the combined fractions filtered and the filtrate distilled to dryness in vacuo yielding 1.743 g.(0.0064 mole) of crude product. The crude product was recrystalized by first dissolving in a minimum amount of hot chloroform with subsequent addition of pentane until turbidity developed. Slow crystal formation yielded a first crop of 0.555 g.(0.0020 mole) of clear crystal platelets(33%), m.p. 187-191°(XXXVII). Recrystalization with chloroform-pentane yielded platelets of

m.p. 193-195° The nmr spectrum (Figure #5) showed the following peaks: An AB quartet centered at 4.13 ppm and 4.60 ppm (4H), a singlet at 3.95 ppm(4H), a singlet at 6.45 ppm(2H), a singlet at 6.85 ppm (2H), a singlet at 6.98 ppm(2H), and an AB octet centered at 7.63 and 8.19 ppm(4H).

The mass spectrum (Figure #6) at 70 eV gave the following m/e(rel intensity)values: 322(73.81),217(3.26), 185(100), 171(17.97), 155(66.66), 141(13.52), 104 (15.83), and 91(23.64).

Analysis* Calculated for $C_{20}H_{18}S_2$: C,74.53; H,5.59; S,19.88. Found: C, 74.37; H,5.67; S,19.76.

5. 1,4-bis-(Mercaptomethyl)-naphthalene(XL).[22] To a hot solution of 4.50 g.(0.059 mole) of thiourea in 50 ml of ethanol was added portionwise with stirring 9.0g.(0.029 mole) of 1,4-bis-(bromomethyl)- naphthalene (XXXVIII). After addition was complete, the mixture was refluxed an additional 50 minutes, the solution was concentrated to half volume and cooled yielding 19.2 g.(0.041 mole) of 1,4-bis-(isothiouroniummethyl) naphthalene dibromide(XXXIX). A mixture of 19.2 g.(0.040 mole) of XXXIX and 140 ml of 6.6 N aqueous potassium hydroxide was boiled under reflux for five hours. The mixture was cooled, 60 ml of 9M sulfuric acid was added and the whole extracted with ether. The ether extract was washed with water, dried over sodium sulfate and concentrated to yield 4.84 g.(0.022 mole)

*Analysis by Galbraith Laboratories in Tennessee

of 1,4-bis-(mercaptomethyl)-naphthalene(XL) (75.8%), m.p. 82-84°.

6. 1.4-bis-(Bromomethyl)-benzene-d_8(XLI).[23] To a solution of 4.70 g. (0.041 mole) of p-xylene-d_{10} (Aldrich Chemicals, 17,592-7) in 45 ml of carbon tetrachloride was added 18.7 g.(0.105 mole) of N-bromosuccinimide[21] and the mixture was heated to reflux. After 15 minutes a vigorous reflux occured for several minutes. The solution was refluxed an additional 50 minutes and filtered while hot. The filtrate was distilled to dryness in vacuo using a Buchi rotovapor-R apparatus. Recrystalization from ligroin yielded 6.6 g. (0.024 mole) of crude product, m.p. 110-130(60%). Several recrystalizations with ethanol yielded 2.0 g.(0.0074 mole) of 1,4-bis-(bromomethyl)-benzene-d_8 (XLI) (17.9%),m.p. 141-145°.

7. 2,11-Dithia-3,3,5,6,8,9,10,10-octadeutero- benzo-[3.3] - paracyclophane (XLII). [24] A solution of 1.0804 g. (0.0049 mole) of 1,4-bis-(mercaptomethyl)- naphthalene (XL) and 1.3359 g.(0.0049 mole) of 1.4-bis-(bromomethyl)-benzene-d_8(XLI) in 185 ml of tetrahydrofuran was added dropwise over a 25 hour period to a vigorously stirred solution of 0.49g. (0.012 mole) sodium hydroxide dissolved in 15 ml of water and 1.3 liters of methanol. The sodium hydroxide solution was pre-heated to 57-62° and held at this temperature throughout the addition. After addition was completed, the mixture was

filtered while warm and the filtrate distilled to dryness in vacuo. The resulting white solid was extracted several times with warm benzene, the combined fractions filtered and the filtrate distilled to dryness in vacuo yielding 1.55 g.(0.0055 mole) of crude product. The crude product was redissolved in a small amount of benzene and transferred onto an alumina column and eluted with benzene. The first 20 ml portion contained no solute, but the second and third portions did contain solute. These solutes were combined and recrystalized from a chloroform/pentane solution. Slow crystal formation yielded white crystals of XLII, m.p.186-188 °. The mass spectrum (Figure #7) at 70 eV gave the following m/e(rel intensity) values: 330(60.57), 217(2.81), 185(100), 171(14.93), 156(41.18), 142(10.74), 130(9.03), 112(19.81), and 98(20.71)

The nmr spectrum (Figure #8) showed the following peaks: an AB quartet centered at 4.08 ppm and 4.55 ppm (4H), a singlet at 6.79 ppm(2H), and an AB octet centered at 7.08 and 8.1 ppm(4H).

FIGURE #3

NMR in d_6-acetone
1,4-bis-(Bromomethyl)-benzene

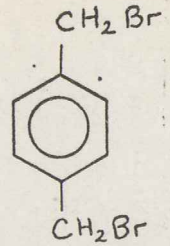
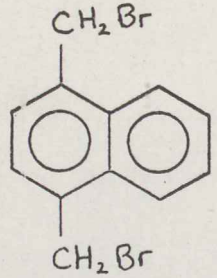
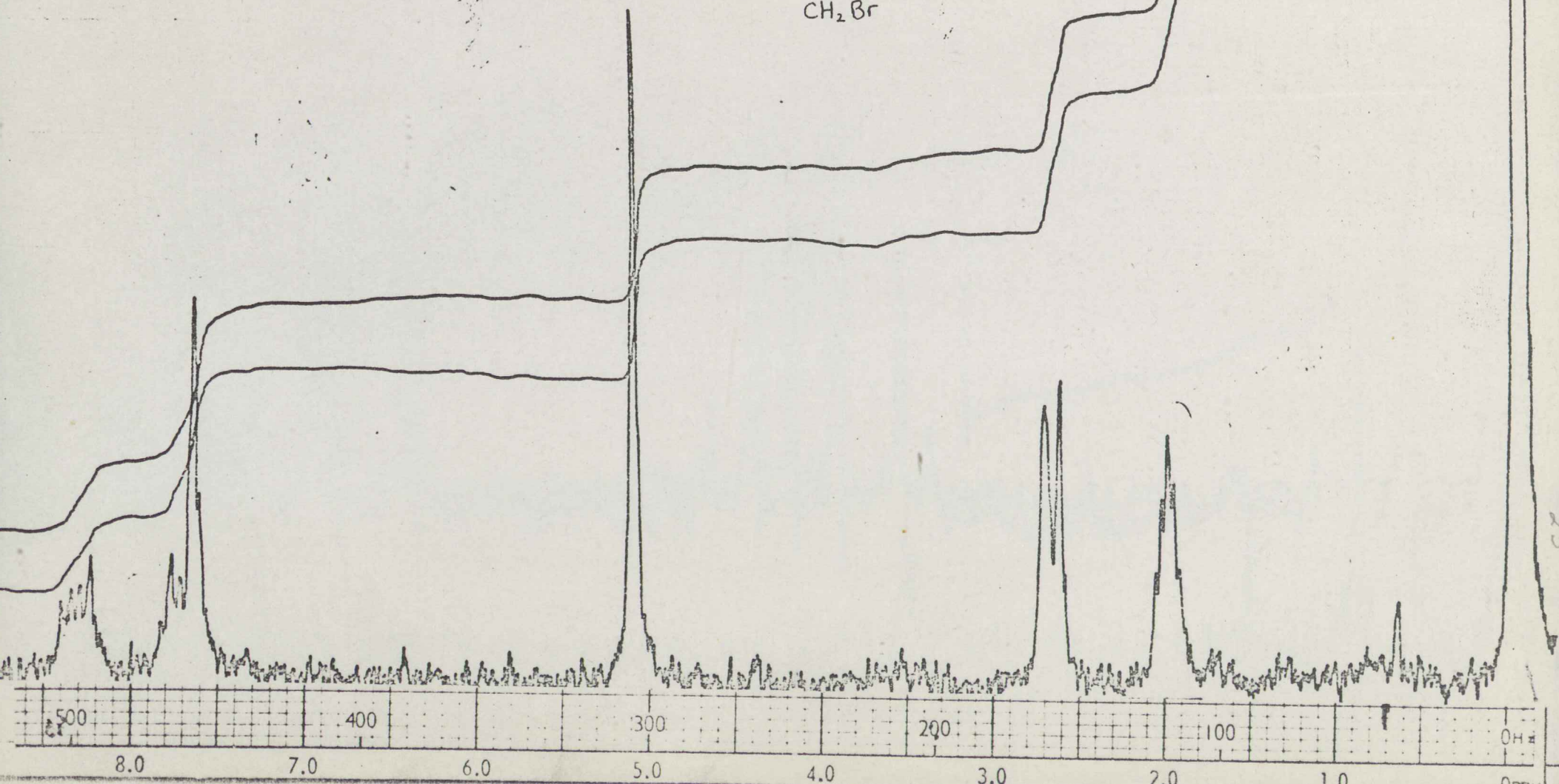


FIGURE #4

NMR in d_6-acetone
1,4-bis-(Bromomethyl)-naphthalene





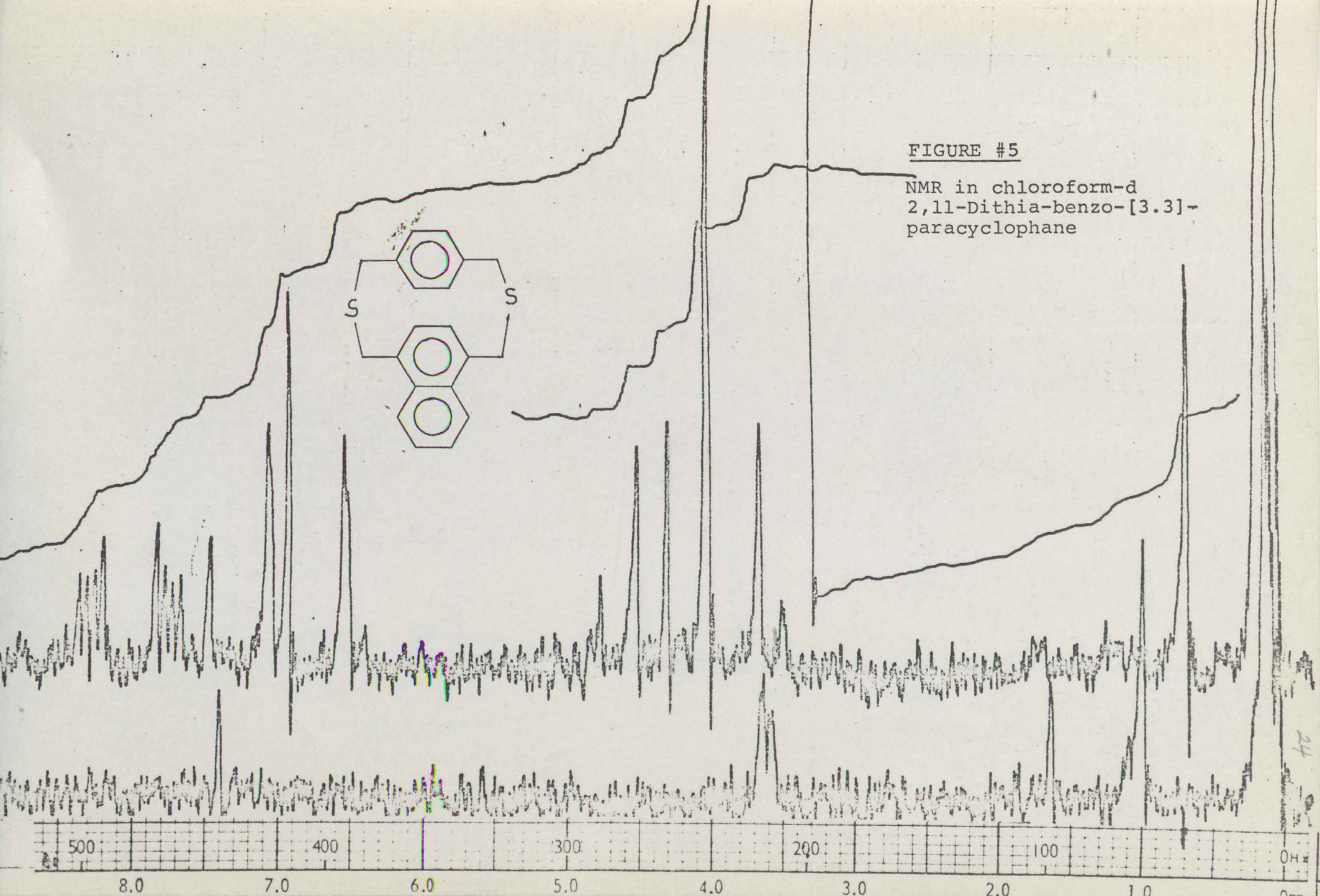


FIGURE #5

NMR in chloroform-d
2,11-Dithia-benzo-[3.3]-
paracyclophane

FIGURE #6

Mass spectrum of 2,11-Dithia-benzo-[3.3]-paracyclophane

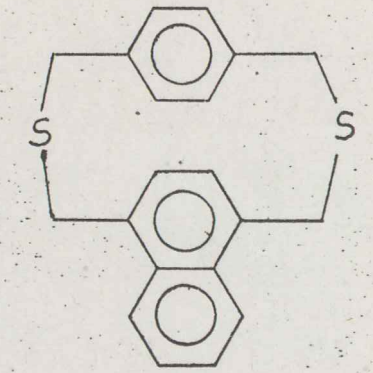
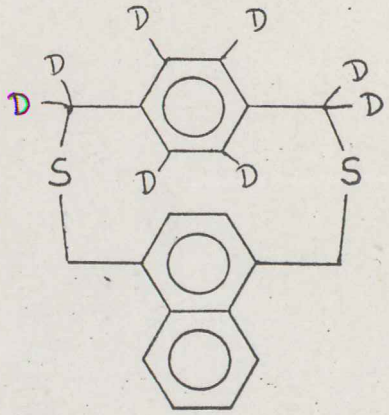


FIGURE #7

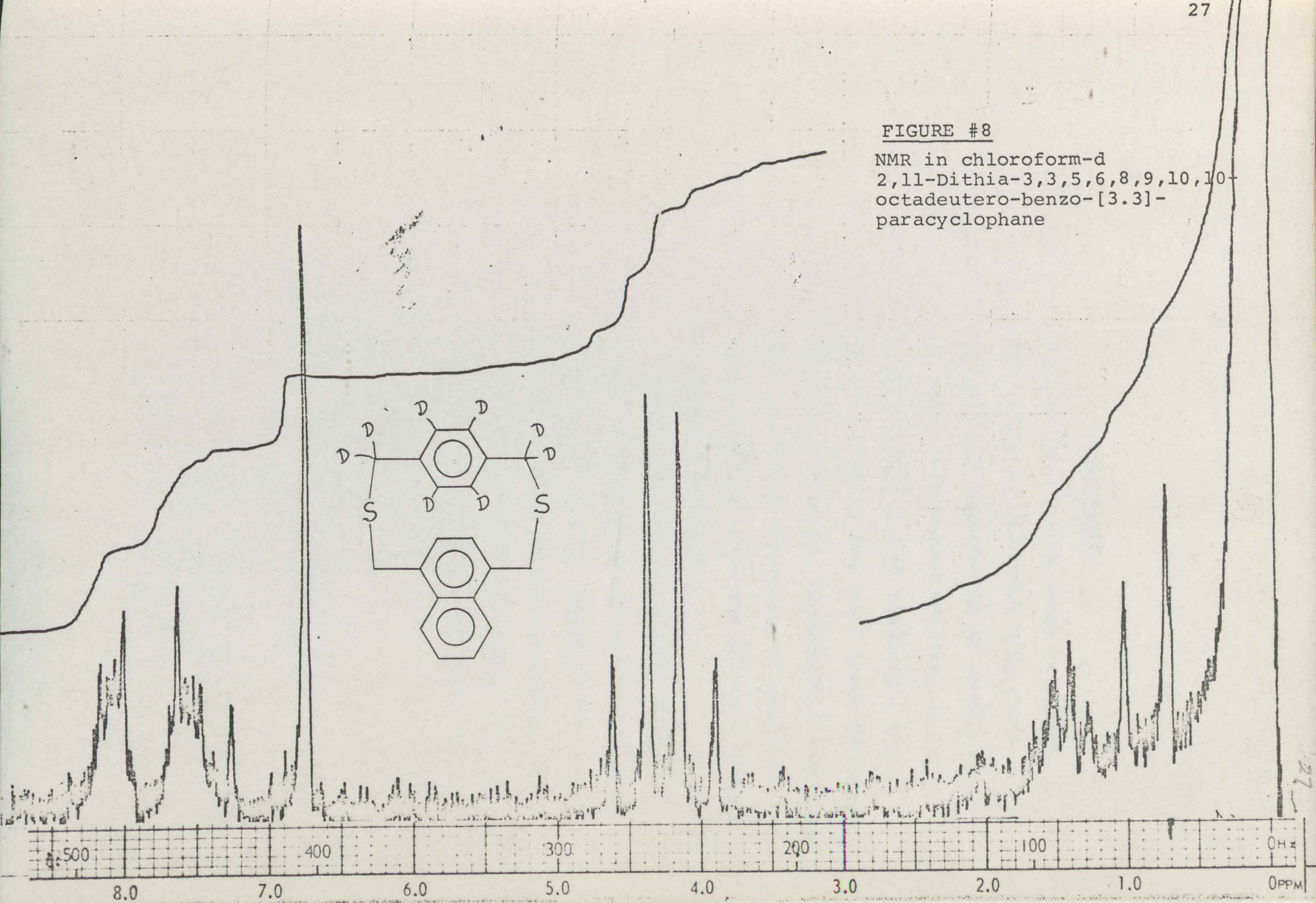
Mass spectrum of 2,11-Dithia-3,3,5,6,8,9,10,10- octadeutero-benzo-[3.3[-paracyclophane



SPEC# 2000 LM DITHIOBENZOPARACYCLOPHANE-D8/MARTIN STEP MASS=1, I/B/S = 1%

FIGURE #8

NMR in chloroform-d
2,11-Dithia-3,3,5,6,8,9,10,10-
octadeutero-benzo-[3.3]-
paracyclophane



DISCUSSION

Alkylbenzenes clearly offer two main areas to attack by halogens: The aromatic ring and the alkyl side chain. Aromatic bromination is generally regarded as an electrophilic attack of bromine, or a Lewis acid-bromine complex, on the aromatic ring to produce successively a pi complex, a sigma complex, and, after loss of a proton, the final bromo derivative. This electrophilic substitution reaction, so typical of aromatic rings, involves first the ionization of bromine to generate the attacking electrophilic particle, here the positive bromine ion. Acid catalysts such as ferric bromide or aluminum bromide attach themselves to a bromine molecule to form the $FeBr_4^-$ ion and a positive bromine ion. The electron deficient bromine ion can then react with the electron rich cloud of the aromatic ring to form a carbonium ion with subsequent abstraction of a hydrogen ion from this carbonium ion by some base, such as $FeBr_4^-$. Thus, the mechanism of electrophilic aromatic bromination can be illustrated as follows [25,26]

1. $Br_2 + FeBr_3 \rightleftharpoons FeBr_4^- + Br^+$
2. $Br^+ + C_6H_6 \longrightarrow C_6H_6Br^+$
3. $C_6H_6Br^+ + FeBr_4^- \rightarrow C_6H_5Br + HBr + FeBr_3$

While the aromatic ring of alkylbenzenes undergoes the electrophilic substitution reactions characteristic of such aromatic nucleii, the alkyl side chain should undergo the free-radical substitution reactions characteristic of alkanes. Under the influence of ultraviolet light, elevated temperatures or free radical imitiators (peroxides) bromine converts alkanes into bromoalkanes or alkylbromides. Unlike the first step in electrophilic aromatic substitution which involves the generation of a bromine ion, the first step in free-radical bromination involves the absorbtion of energy (heat or light) by a bromine molecule with subsequent cleavage of bromine into atoms or free-radicals. The bromine free-radical thus formed abstracts a hydrogen from the alkane yielding an alkyl radical which then reacts with bromine to give the alkylbromide and a bromine free-radical to carry on the reaction. Thus, the mechanism of free-radical bromination can be summarized as follows:

1. $Br_2 \xrightarrow{\text{heat or light}} 2Br\cdot$ — Chain-initiating step

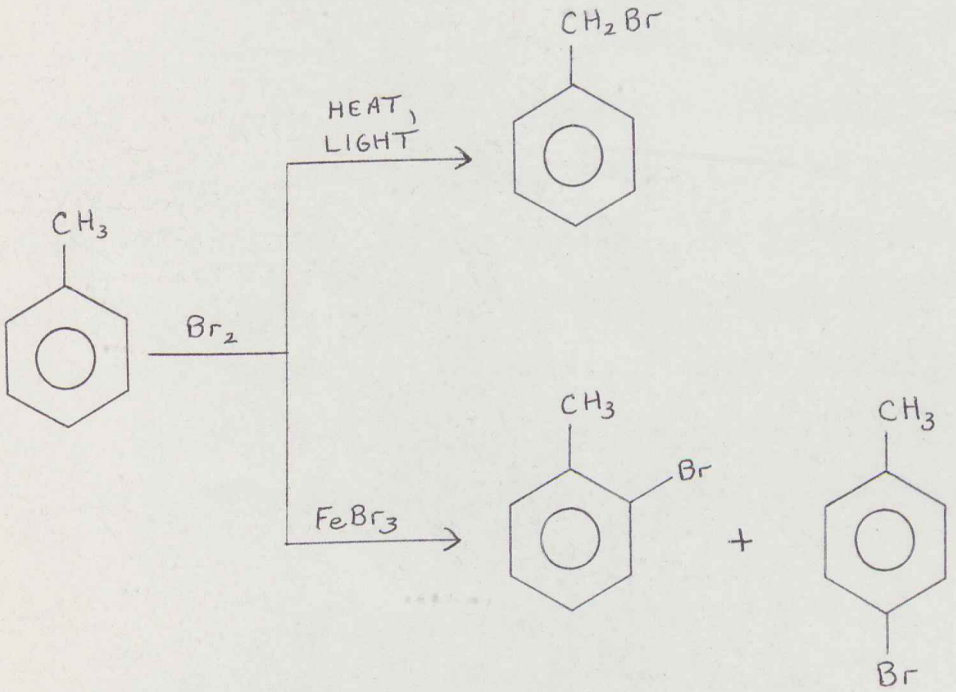
2. $Br\cdot + RH \rightarrow HBr + R\cdot$
3. $R\cdot + Br_2 \rightarrow RBr + Br\cdot$

} Chain-propagating steps

4. $Br\cdot + Br\cdot \longrightarrow Br_2$
5. $R\cdot + R\cdot \longrightarrow R\text{-}R$
6. $R\cdot + Br\cdot \longrightarrow RBr$

} Chain-terminating steps

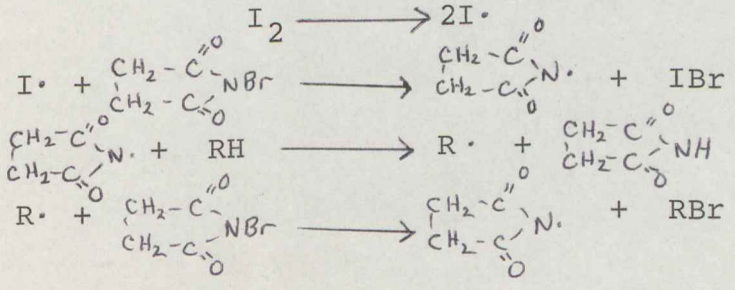
In view of these facts, one might expect that the position of attack in arenes, whether it be attack on the aromatic ring or the alkyl side chain, would be governed by the type of attacking particle involved and therefore ultimately by the reaction conditions employed. Bromination of the alkyl side chain requires conditions under which bromine atoms are formed, that is, high temperature or light. Bromination of the aromatic ring, on the other hand, involves ionization of halogen which is promoted by acid catalysts like ferric bromide:



The first reaction in the present synthetic scheme involves the free radical substitution of bromine to p-xylene to

form 1,4-bis(bromomethyl) benzene. N-bromosuccinimide was chosen as the brominating agent for a number of reasons: 1. bromination with NBS is more convenient than with molecular bromine, 2. molecular bromine is a much more hazardous material than N-bromosuccinimide, 3. milder reaction conditions can be employed, and 4. bromination with N-bromosuccinimide offers the opportunity for better yield of product.

Ziegler and his co-workers[27] were the first to point out the utility of N-bromosuccinimide (NBS) as a reagent for allylic bromination. Two years later, Bloomfield [28,29] proposed a radical chain mechanism for the allylic bromination with NBS where the succinimide radical acts as the hydrogen abstracting species. For many years, the attractive simplicity of the Bloomfield mechanism (succinimide radical process) complimented by results of various selectivity studies led to the general acceptance of this mechanism and was even broadened to encompass benzylic bromination.[29]



In 1953, however, Goldfinger [30,31] proposed an alternate scheme utilizing the bromine atom as the hydrogen abstracting and chain carrying species. In more recent years, studies have provided strong support for the Goldfinger mechanism (bromine radical process):

$$I_2 \longrightarrow 2I\cdot$$

$$I\cdot + Br_2 \longrightarrow IBr + Br\cdot$$

$$Br\cdot + RH \longrightarrow HBr + R\cdot$$

$$HBr + \text{N-bromosuccinimide} \longrightarrow Br_2 + \text{succinimide}$$

$$R\cdot + Br_2 \longrightarrow RBr + Br\cdot$$

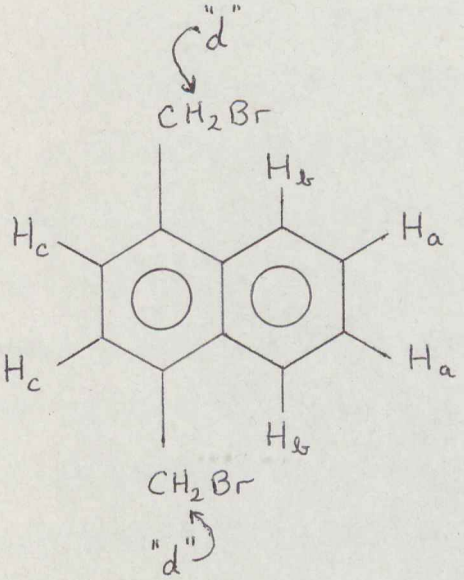
Pearson and Martin[32] determined the relative reactivities of a series of substituted toluenes toward NBS, NBTFS(N-bromotetraflourosuccinimide), NBTMS(N-bromotetramethylsuccinimide), and molecular bromine in benzene solution at 80° and found all values of reaction constants to be identical. The identity

of the rho values indicates the same radical serves as hydrogen abstractor in every case. Supporting evidence can be found in the data of Wilberg and Slaugh[33] who discovered that reactions involving NBS and molecular bromine exhibit essentially the same kinetic isotype effect in the removal of α-hydrogens from toluene. Thus, only bromine atoms can be the abstracting species. Incremona and Martin[29] compared the relative selectivities of NBS and molecular bromine obtained from competitive allylic bromination studies and found them to be nearly identical. This provides strong evidence that the operative mechanism in NBS allylic bromination is one involving the bromine atom as the chain carrying species. The NBS acts to provide a low steady-state concentration of Br_2 in a mechanism similar to the one previously mentioned for benzylic bromination. Studies by Hedaya, Hinman and Kibler[34] indicate that the succimidyl radical is highly unstable with respect to the dimer, succinimide or NBS and thus the generation of succinimide radicals necessary for the Bloomfield mechanism may be quite a difficult process. Thus, although considerable controversy still exists as to the nature of the chain carrying species in free-radical brominations utilizing NBS, most recent evidence indicates that a bromine radical is the hydrogen abstracting species in benzylic bromination and strongly suggests a similar mechanism for allylic bromination.

The first attempt at preparing the bis(bromomethyl) derivative of p-xylene resulted in a crystalline product which melted at 95-100° some 40-45 degrees lower than the desired product. In this initial preparation the first carbon tetrachloride filtrate was washed twice with 5% aqueous sodium hydroxide. It is possible that hydroxide ion could have reacted with the incompletely brominated monobromide or the dibromide product in a nucleophilic substitution reaction to yield various undesired products such as 1,4 dihydroxymethyl benzene, 4-hydroxy methyl toluene, or 1-hydroxymethyl-4-bromomethyl benzene. It is possible that a greater excess of NBS than used was required for the dibromination. No analysis was run on this low melting product but this could be done in future work.

A procedural modification was made in a subsequent reaction in which the sodium hydroxide wash was eliminated and a 30 percent excess of NBS was utilized. These changes permitted the successful preparation of the desired 1,4-bis(bromomethyl) benzene compound as indicated both by the melting point and by the NMR spectrum (Figure #3). There were four hydrogens of aromatic nature (7.48 ppm) and four of benzylic nature(4.64 ppm). The yield for this reaction was 60% of crude product and 34% pure 1,4-bis-(bromomethyl)-benzene (XXXIII).

The same procedure was applied to 1,4-dimethyl-naphthalene and the results were quite gratifying. Yields of 31% and 23.4% pure 1,4-bis-(bromomethyl)-naphthalene XXXVI and XXXVIII) were obtained in two separate reactions. The NMR spectrum(Figure #4) showed four hydrogens of benzylic nature (5.14 ppm), two hydrogens of aromatic nature(7.66 ppm) and an AB octet centered at 8.33 and 7.72 ppm integrating to four hydrogens. As can be seen in Figure #4, the singlet at 7.66 ppm partially obscures the upfield half of the octet. The assignment of bands to the various hydrogens can be visualized as follows:



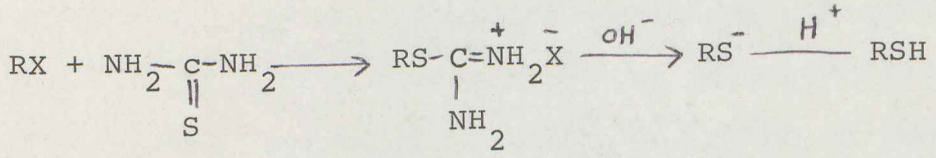
The "a" aromatic hydrogens are furthest downfield and are

split once by the "b" hydrogen ortho to it, and again by the "b" hydrogen meta to it. The ortho splitting is greater than the corresponding meta split. This splitting pattern yields the four bands noted. The "b" hydrogens centered at 7.72 ppm are split in like manner by one ortho and one meta "a" hydrogen into four bands. This yields the AB octet. The "c" hydrogens not being split appear as a singlet at 7.66 ppm and the four benzylic hydrogens, "d", appear as a singlet at 5.14ppm. The melting point of 192-193° compared favorably with the literature value of 191-191.5°

Far more exciting was the preparation of the octadeutero-bis-(bromomethyl)-benzene(XLI) by similar methods in a yield of 60% crude product and 17.9% pure 1,4-bis-(bromomethyl) benzene -d_8 (XLI). The melting point of the product 141-145° matched that of the non-deuterated material(XXXIII).

The next materials needed for the synthetic process toward the [2.2] -paracyclophane derivatives were the dithiols (XXXV and XL). 1,4-bis-(mercaptomethyl)-benzene(XXXV) was successfully prepared by reacting the 1,4-bis-(bromomethyl) benzene (XXXIII) with thiourea to yield the isothiouronium salt(XXXIV) which upon treatment with alkali is cleaved to dimercaptyl anion which upon treatment with the acid yielded the desired dimercaptan(XXXV). The mechanism is a nucleophilic substitution reaction with sulfur as the attacking species in the following

simplified mechanistic pathway



An 80% yield was obtained via this method. By the same method, 1,4-bis(mercaptomethyl)-naphthalene (XL) was prepared in 75.8% yield.

As our synthesis worked out, we showed that it was possible to prepare 2,11-dithia-benzo [3.3] -paracyclophane by either the naphthalene moiety having the two bromomethyl groups and the benzene portion having the mercaptomethyl groups or vica versa.

The non-deuterated 2,11-dithia-benzo-[3.3] -para-cyclophane (XXXVII) was prepared via a dilute solution cyclization reaction between 1,4-bis-(mercaptomethyl)-benzene(XXV) and 1,4-bis-(bromomethyl)-naphthalene (XXXVI) in alkali conditions. The basic medium abstracts a hydrogen from the mercaptan and the RS-species attacks the carbon of the alkyl halide. In dilute solution, the other mercaptan group can react in like manner with the remaining alkyl bromide group. A 33% yield of fairly pure product m.p. 187-191° was obtained. The

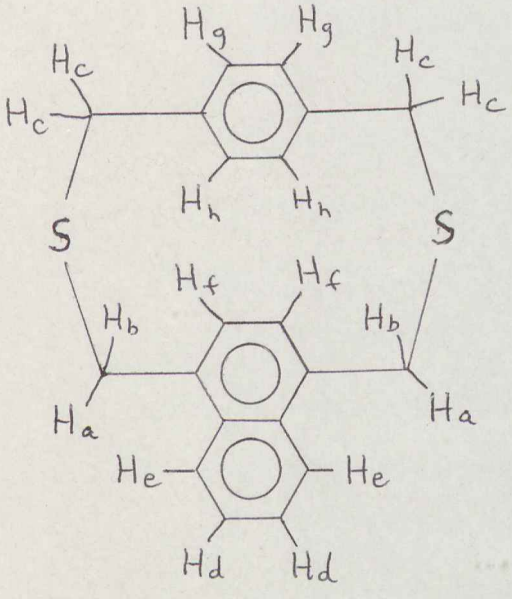
NMR spectra (Figure #5) and the mass spectra(Figure #6) will be discussed later.

The octadeuterated 2,11-dithia-benzo- [3.3] -para-cyclophane(XLII) was prepared by reacting, in like manner, 1,4-bis-(mercaptomethyl) naphthalene (XL) and 1,4-bis-(bromo-methyl)-benzene-d_8(XLI). The melting point of the deuterated compound 186-188° matched that of the non-deuterated material discussed above. The mass spectra(Figure #7) and the NMR spectra (Figure #8) will be discussed later.

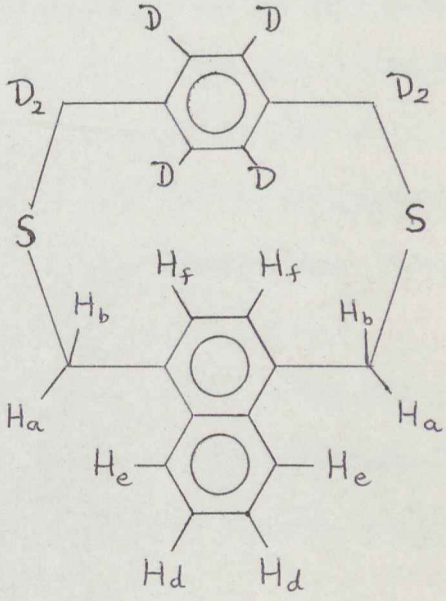
A photolysis was run with a Hanovia lamp and water jacketed quartz apparatus. A procedure used earlier by Professor Martin[3] with freshly distilled trimethyl phosphite as a solvent and sulfur-scavenger was employed. Unfortunately, the non-deuterated dithia-benzo- [3.3]-paracyclophane produced no crystals after irradiation, concentration and chromatographic separation. The benzo- [2.2]-paracyclophane melts at 115-116°. More work remains to be done on this final irradiation step. This procedure has also been used successfully by J. Bruhin[35] to produce substituted [2.2] - paracyclophanes, and suddenly the procedure failed to work for him. Professor Martin encountered no problem in his work at Basel in successfully producing d_8 - [2.2] -paracyclophane itself. The variables which need to be tested are: 1. the use of quartz versus pyrex vessels, 2. the use of completely oxygen-free nitrogen bubbling through the reaction solution, and 3. the nature and

reliability of the lamp itself. Further work is to proceed shortly on this reaction.

A comparison of the NMR spectra(Figures #8 and5) between the deuterated and non-deuterated dithia-benzo-[3.3]-para-cyclophane yields some interesting and exciting results. The AB quartet pattern in the alliphatic portion of the spectra is present in both compounds. This means that this splitting pattern must be attributed to the "a" and "b" hydrogens of XLIII and XLIV.



XLIII



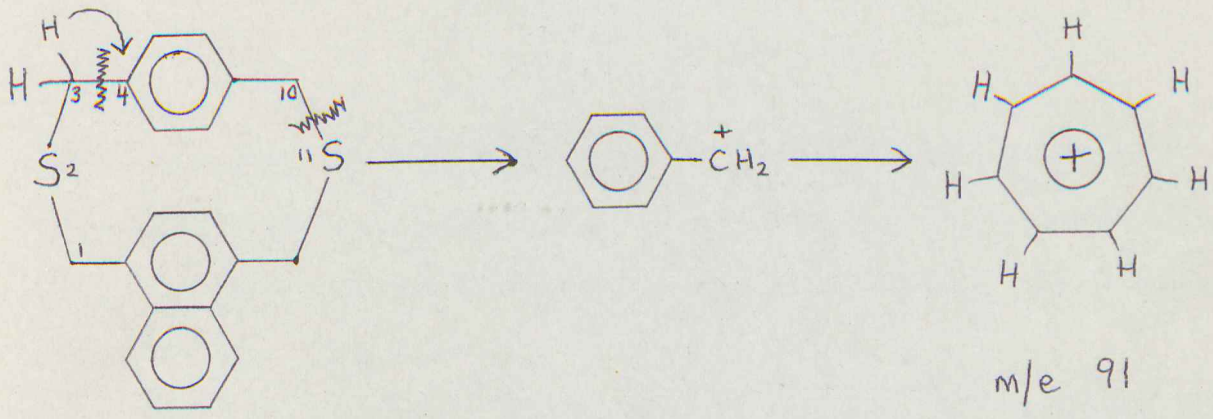
XLIV

The large singlet at 3.98 ppm in the non-deuterated spectrum but absent in the deuterated one must be assigned to hydrogens "c" of figure XLIII. The comparison of the aromatic peaks is even more conclusive as to the actual identity of the compounds. The AB octet appearing furthest downfield in both spectra is assigned to the "d" and "e" hydrogens on the benzo moiety of compounds XLIII and XLIV. The quartet centered at 8.10 ppm is assigned to the "e" hydrogens since α-hydrogens absorb at higher ppm values than do β-hydrogen. The peak at 6.79 and 6.85 ppm in Figures 8 and 5, respectively, is attributed to the "f" hydrogens on the naphthalene ring and is present in both compounds. The peaks appearing at 6.45 ppm and 6.98 ppm in the non-deuterated compound and not present in its deuterated counterpart must be assigned to the "h" and "g" hydrogens on the benzene ring, respectively. The "h" hydrogens are shielded by an induced magnetic field set up by the circulating electrons in the naphthalene ring and thus appear further downfield. Thus, the absence of certain peaks in the deuterated compound as compared to the non-deuterated one allows unequivocal proof of molecular structure.

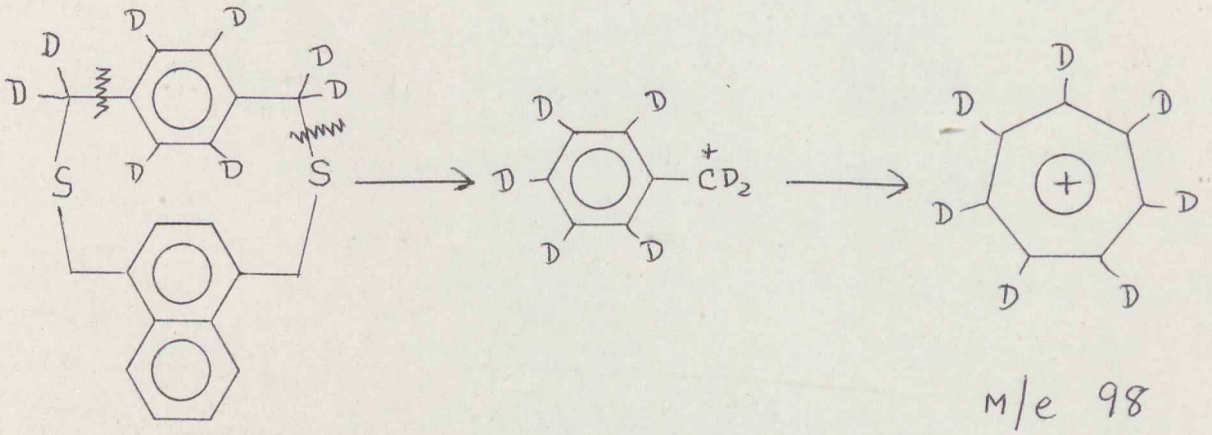
Comparison of our NMR data with peak assignments made by Cram and his coworkers[36] on benzo - [2.2]-paracyclophane forces us to disagree with Cram on two of his assignments. Cram assigned the "f" naphalenic hydrogens to a higher ppm value than the "g" benzenic hydrogens since "naphthalenic hydrogens

absorb at lower fields."[36] Our work has shown that removal of the "g" hydrogens eliminates the downfield peak and therefore must be assigned to these benzenic hydrogens.

The most novel and stimulating finding from this work is that of deuterium transfer in certain mass spectra cleavages. To our best current knowledge, no one to date has demonstrated the nature of hydrogen abstraction and transfer by radicals at cleavage centers. However, as one might prefer to predict a minimum structural change, it would follow that cleavage at a benzene anyl carbon would involve transfer of a neighboring benzyl hydrogen. In our particular compound, cleavage of the C_3-C_4 bond with subsequent transfer of a neighboring benzyl hydrogen followed by cleavage of the C_{10}-S_{11} bond would yield a resonance-stabilized benzyl ion or, more likely, the tropylium ion:



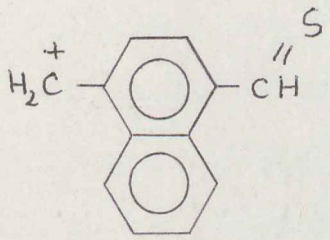
Indeed, this peak does occur at m/e 91 in the mass spectrum of the non-deuterated compounds(Figure #6). A similar splitting pattern of the deuterated material should yield, if our assumption of a benzylic hydrogen transfer is correct, a deuterated tropylium ion:



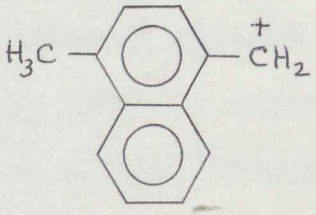
This peak does indeed occur a m/e 98 in the mass spectrum of the deuterated compound(Figure #7). Thus, we have demonstrated that benzylic deuterium transfer does indeed occur in certain mass spectra cleavages.

The parent peaks of both the deuterated and non-deuterated materials matched the expected molecular weights of 330 and 322, respectively. Other important peaks can be assigned the

following fragments:

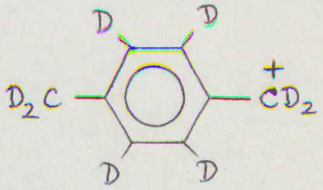


M/e 185



M/e 155

M/e 104



M/e 112

CONCLUSION

The successful synthesis of two novel compounds previously unreported in the literature was accomplished, namely, 2,11-dithia-benzo-[3.3] - paracyclophane and its deuterated counterpart 2,11-dithia- 3,3,5,6, 8,9,10,10-octadeutero-benzo-[3.3]-paracyclophane. A comparison of NMR spectra allowed an unequivocable assignment of absorption peaks to various aromatic and aliphatic hydrogens. Some of our findings are in conflict with previously reported results of other workers. A major finding concerning deuterium transfer in certain mass spectra cleavages demonstrated the nature of hydrogen transfer by radicals at cleavage centers. Benzylic deuterium and hydrogen transfer does occur in certain mass spectra cleavages.

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