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**I. A Temperature Dependent NMR Study of
6,6-Dicarbethoxy-5,5-Dideuteodi-Benzo-[a,c]-[1, 3]-Cycloheptadiene
II. The Synthesis of Four Deuterated Analogs of 6,
6-Dicarbethoxydibenzo-[a,c]-[1,3]-Cycloheptadiene**

Patrick F. Jonas

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I. A TEMPERATURE DEPENDENT NMR STUDY
OF 6,6-DICARBETHOXY-5,5-DIDEUTERO-DI-
BENZO-[a,c]-[1,3]-CYCLOHEPTADIENE

II. THE SYNTHESIS OF FOUR DEUTERATED
ANALOGS OF 6,6-DICARBETHOXYDIBENZO-
[a,c]-[1,3]-CYCLOHEPTADIENE

by

Patrick F. Jonas

A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
Degree of Master of Arts
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Western Michigan University
Kalamazoo, Michigan
August 1984

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Patrick F. Jonas, M.A.

Western Michigan University, 1984

The kinetics of conformational interchange of 6,6-dicarbethoxydi-
benzo- a,c - 1,3 -cycloheptadiene and of its 5,5-dideuterated analog
were studied using variable temperature NMR techniques. The free energy
of activation for conformational interchange of the parent compound was
found to be $9.02 \text{ kcal mol}^{-1}$ and that of the 5,5-dideuterated analog to
be $9.42 \text{ kcal mol}^{-1}$. Values of the entropy of activation were found to
be -19.91 e. u. and -18.12 e. u. respectively. The spectra were recor-
ded on a Nicolet NMC-360 wide bore spectrometer and the data collected
treated as an AB spin system.

The 4,8-dideutero, 4,5,5,8-tetradeutero and 5,5,7,7-tetradeutero
analogs of the parent compound were also synthesized. Involved in the
synthetic procedures is a method for a greatly improved yield in the
synthesis of diphenide over what has been previously reported in the
literature.

ACKNOWLEDGEMENTS

I wish to thank my mother, Rosemary C. Jonas, who instilled in me as a youth a sense of curiosity and the need to know why. To my wife, Whitney, whose love and faith in me helped immensely and made all of this possible. To Benny for his help in the interpretation of the NMR spectra. To all of them this work is dedicated in love.

My special thanks goes to Dr. Don C. Iffland who presented a scientific problem, a possible solution and unending technical assistance along the way. My thanks also to Dr. Robert Harmon and to Dr. George Lowry for serving on the committee and for their technical assistance.

And lastly I wish to thank Stephen Spanton of Analytical Services, Pharmaceutical Products Division, Abbott Laboratories for his running of the temperature dependent NMR spectra.

Patrick F. Jonas

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I. A TEMPERATURE DEPENDENT NMR STUDY OF 6,6-DICARBETHOXY-5,5-DIDEUTERODIBENZO - (A,C)-(1,3)-CYCLOHEPTADIENE. II. THE SYNTHESIS OF FOUR DEUTERATED ANALOGS OF 6,6-DICARBETHOXYDIBENZO - (A,C)-(1,3)-CYCLOHEPTADIENE

WESTERN MICHIGAN UNIVERSITY

M.A. 1984

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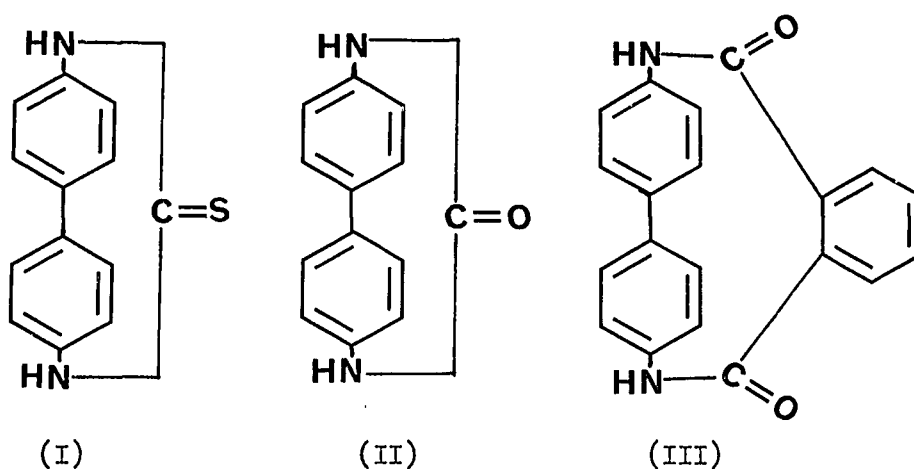
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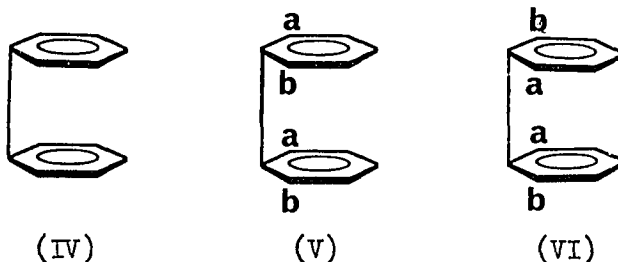
INTRODUCTION

Often a new discovery will result from erroneous observations and subsequent study. Prior to 1907 it was believed that the benzene rings in a biphenyl molecule were essentially coplanar. It was known that 4,4'-diaminobiphenyl would readily condense with carbon disulfide,¹ phosgene,² or phthalic anhydride³ to which the discovering chemists assigned the cyclic structures (I), (II) and (III) respectively.



Strakosch¹ recognized that these compounds might really exist as a disubstituted system but was unable to prove this due to the insolubility of these compounds for molecular weight determinations. But it was in that year of 1907 that Kaufler⁴ determined the molecular weight of the phthalic anhydride product and demonstrated it to be a monosubstituted, non-cyclic compound. In the course of these studies he noticed that 4,4'-diaminobiphenyl reacted as readily as,

and in some cases even much more readily than the disubstituted amine 2,2'-diaminobiphenyl and concluded that the amino groups of the former compound must be closer together than had originally thought to be. He therefore proposed the clam-like structure (IV) for biphenyl⁵ that was readily accepted and received experimental support.^{6,7,8}



If this were the actual case, however, then the clam-like structure should give both cis (V) and trans (VI) isomers with appropriate ortho (and/or meta) substituents. In 1922 Christie and Kenner⁹ successfully resolved the active isomers of 6,6'-dinitrodiphenic acid which at first gave further support to Kaufler's theory. Because of conflicting evidence in the literature this discovery would later rebuke the theory. Turner and Le Fevre¹⁰ demonstrated in 1926 that these isomers were not really cis-trans isomers but were, in fact, structural isomers and that ring closure of the amino groups of 4,4'-diaminobiphenyl could not be accomplished. Thus, a new type of optical activity was discovered— one that depended not upon the presence of a chiral atom but rather upon the structural aspects of the molecule itself.

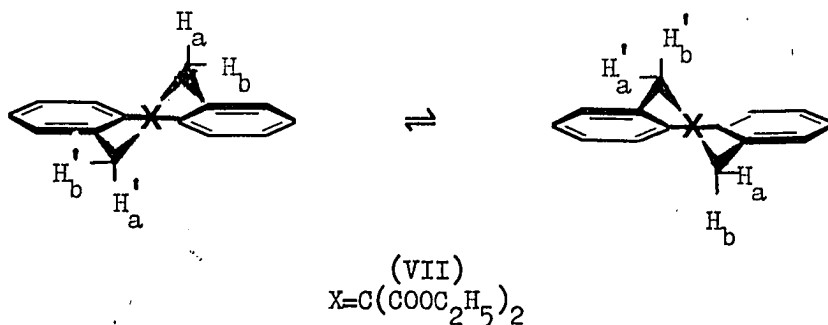
Later work^{12,13,14,15,16} rapidly followed demonstrating that the compounds (I), (II) and (III) were actually monosubstituted prod-

ucts rather than the originally proposed cyclic structures. This was accomplished mainly by the demonstration of a free amino group in the molecules.

From this point the stereochemistry of biphenyl compounds was more aggressively studied. Numerous substituted biphenyls, differing in both the degree and the type of substitution, were synthesized and studied. Attention ultimately turned to the synthesis of optically active biphenyls whose optical activity depended solely upon a 2,2'-three atom bridge. Numerous attempts were made^{17,18,19,20} but were not successful.

In 1956 Iffland and Siegel²¹ reported the synthesis of the first optically active bridged biphenyl. Its optical activity rested solely upon the presence of a 2,2'-three carbon bridge. Later, these workers determined that this compound, 6,6-dicarbethoxydibenzo-[a,c]-[1,3]-cycloheptadiene (VII), had a half time for racemization of 80 minutes at 32.5° Celsius in cyclohexane. This would correspond to a free energy of activation of approximately 23.3 kcal mol⁻¹ which should allow for the resolution of the individual antipodes.²³

The compound (VII) is capable of configurational inversion by intramolecular rotation about the bond between the benzene rings.



The diastereotopic benzylic protons H_a , H_b , H'_a and H'_b form a doublet of doublets centered at approximately 3.6 in a NMR spectrum taken at low temperatures (below approximately 0° Celsius).

As the temperature is increased the line widths of the doublet of doublets broaden with the outer two signals broadening faster than the inner two. The outer two signals eventually disappear and the inner two signals coalesce into a broad singlet (around room temperature).

These changes may be correlated to the rate of intramolecular inversion of the biphenyl molecule. At low temperatures the molecule exhibits a slow inversion rate such that the diastereotopic benzylic protons are quite distinguishable from each other as a pair of doublets. As the temperature is increased the rate of inversion increases such that these protons become less distinguishable from each other and a single doublet of broad lines arises. Finally, at higher temperatures, the benzylic protons are exchanging rapidly enough that they give rise to an averaged state- the doublet gradually narrows to a singlet.

The rest of the NMR spectrum is what would be normally expected: a triplet at approximately 1.26 due to the methyl groups of the esters; a quartet at approximately 4.16 due to the methylene groups of the esters; and a singlet at approximately 7.36 due to the protons on the aromatic rings.

Sutherland and Ramsey²⁴ were the first to study the rate of conformational interchange of this compound (VII) by NMR methods treating it as an AB spin system and found a free energy for it of 13.7 kcal

mol^{-1} . This value is grossly different from that of $23.3 \text{ kcal mol}^{-1}$ and, even more disturbing, is that a compound with a free energy for inversion of $13.7 \text{ kcal mol}^{-1}$ should not have sufficient optical stability to allow for conventional isolation. A molecule of this nature with demonstrated optical activity should have a barrier to rotation of approximately 20 kcal mol^{-1} or greater to be resolvable.²⁵ A barrier to rotation of at least 16 kcal mol^{-1} may lead to first order asymmetric transformations.²⁶

The compound (VII) was again studied in 1975 by Quarfoot,²⁷ who arrived at comparable energy of inversion values and concluded that treatment of the spin system as an AB type system was not the correct choice for NMR analysis.

Carter, Dahlqvist and Berntsson²⁸ made a study of the compound in 1977. They prepared the optically active compound essentially using the procedure of Iffland and Siegel²² but purified the material in the cold by TLC and column chromatography. They reported:

"We have attempted unsuccessfully to repeat the polarimetric work [of Iffland and Siegel] and have been able to show by means of thin layer chromatography in the cold, mass spectral analysis and polarimetry that an optically active impurity (as yet unidentified) is the most probable cause of the discrepancy."

In their NMR study they modified Heidberg's²⁹ density matrix bandshape equations to a coupled AB spin system by superimposing two AB quartets upon it. In this way they treated the spin system as a modified AB spin system. They obtained a free energy for inversion value of $11.3 \pm 0.2 \text{ kcal mol}^{-1}$. Treatment of the spin system by these workers as an $AA'BB' \rightleftharpoons A_4$ system at higher temperatures, using

DNMR3 bandshape analysis,²⁷ gave essentially the same results.

Because the values obtained among various workers for each method are so closely aligned with each other it is difficult to believe that the discrepancy lies within the techniques of the workers but rather it is more plausible to believe that the discrepancy lies within:

1. The use of polarimetry as a reliable tool to determine the rate of racemization,
2. The theory that a bridged biphenyl must have an energy of inversion of approximately 20 kcal/mol in order to be isolated,
3. The method of synthesis of the optically pure sample, or
4. The theoretical treatment of the spin system using NMR spectroscopy.

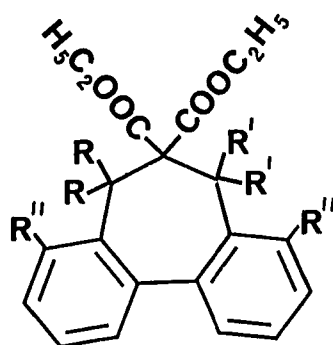
Because of the simplicity and the great reliance placed upon polarimetry it seems doubtful that the use of this tool could be held accountable. Iffland and Siegel,²² and later Quarfoot,²⁷ took great care in the final deamination step in order to minimize any racemization of the final compound. In the case of Iffland and Siegel elemental analysis of the compound was very close to the theoretical prediction. Carter's²⁸ report that the presence of an impurity as the probable cause of error must be taken lightly. He was not successful in identifying the impurity, nor is it reasonable to believe that an impurity of 0.05% would have such a dramatic effect upon the results. The impurity would necessarily have to have a relatively fast rate of racemization and a very large specific rotation.

It was thus decided that some investigation into the NMR method may resolve this discrepancy. The choice of quantitative treatment of

the spin system is not a clear one in that the system appears to go through an AB - AA'BB' - A_4 transition as the temperature is increased. If the system is truly an AA'BB' spin system then the observed spectra may show more line broadening through incomplete resolution than if the spin system was truly an AB type. This line broadening at higher temperatures would be interpreted, in an analysis as an AB spin system, as an increase of the rate of conformational change.

The selective quieting of one of the pairs of benzylic protons by deuteration may provide valuable information if the system is then treated as an AB spin system. It is also conceivable that an unexpected line broadening due to a more complicated spin system involving long range coupling with 3,3' protons is possible but probably less than that due to an erroneous treatment of an AA'BB' spin system as an AB spin system. Thus, deuteration of the 3,3' positions may also be helpful.

A literature search showed that no compounds of this nature had been synthesized nor studied. Thus, the project solidified into the synthesis and NMR study of compounds (VII) thru (XI).



VII $R = R' = R'' = H$

VIII $R = D, R' = R'' = H$

IX $R = R' = H, R'' = D$

X $R = H, R' = R'' = D$

XI $R = R' = D, R'' = H$

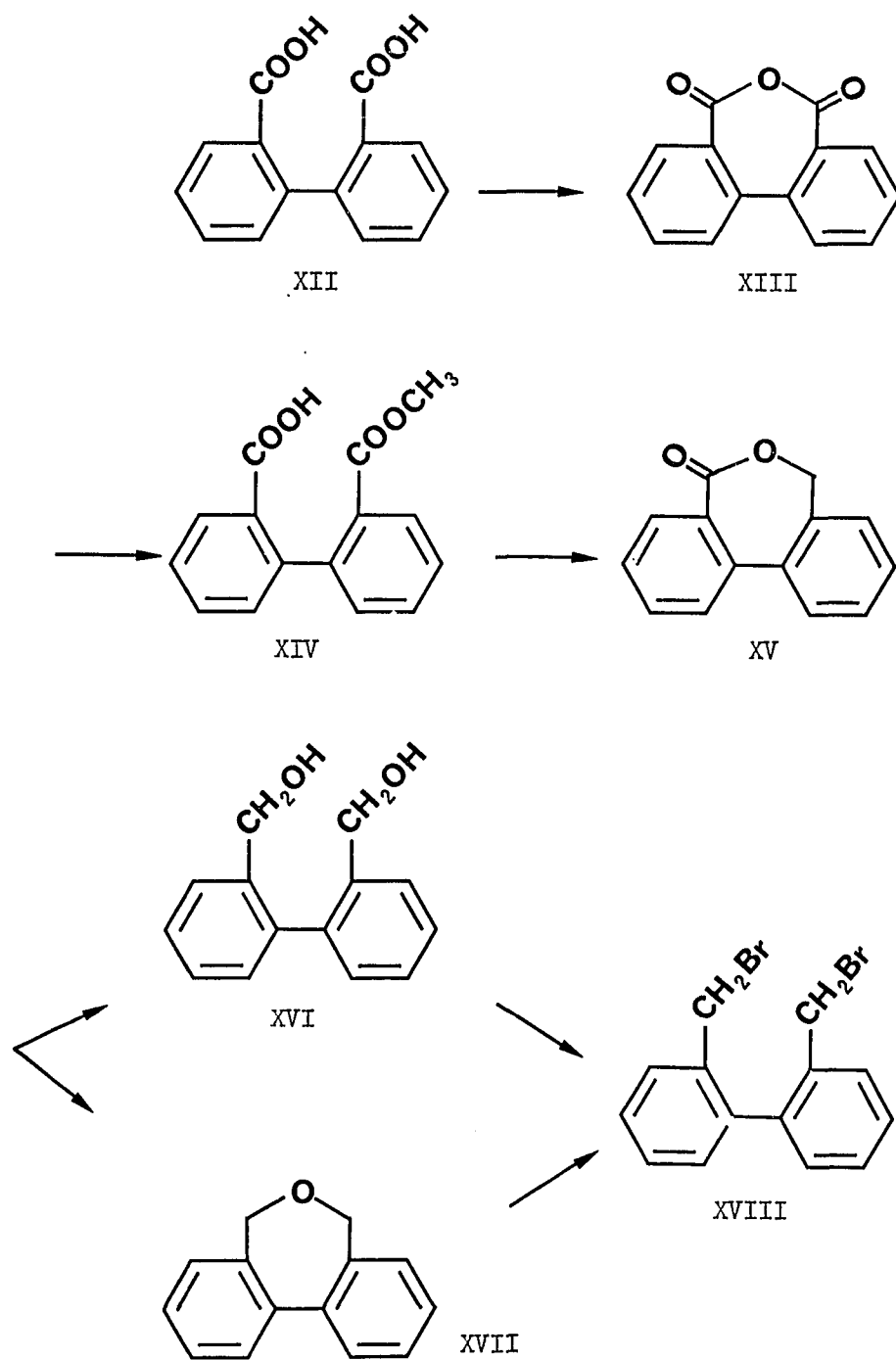
EXPERIMENTAL

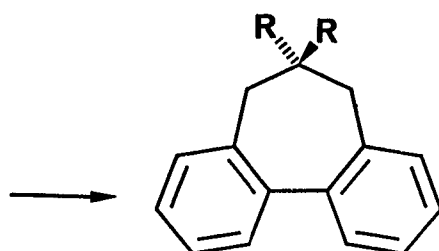
All melting and boiling points are given in degrees Celsius and are corrected. Melting points were determined by the capillary method.

Nuclear Magnetic Resonance spectra used in the synthetic work were recorded on either a Varian A60 or a Jeol PMX60 spectrometer. The spectra used in the temperature dependent studies were recorded on a Nicolet NMC360 wide bore spectrometer operating at a standing frequency of 361.065865 MHz. Data were simultaneously collected and later analyzed using the NMCCAP curve analysis/deconvolution program. The temperature in the temperature dependent studies was recorded as $\pm 0.1^\circ$. In all NMR spectra TMS was used as an internal standard and the samples were approximately a 10 % solution in the solvent given. Chloroform- d_1 was the solvent used in the temperature dependent studies. All shift positions are given in terms of δ units.

SCHEME 1.

Synthesis of (\pm) -6,6-dicarbethoxydibenzo-
[a,c]-[1,5]-cycloheptadiene (VII)

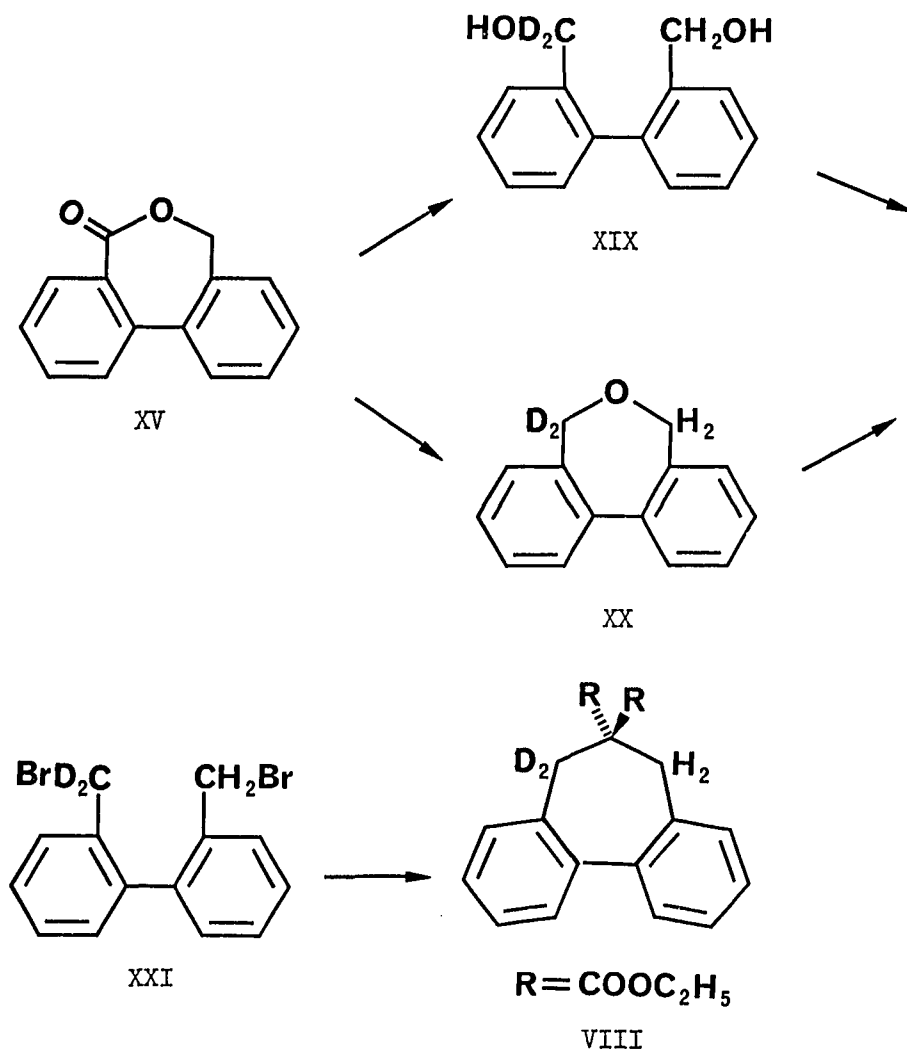




VII

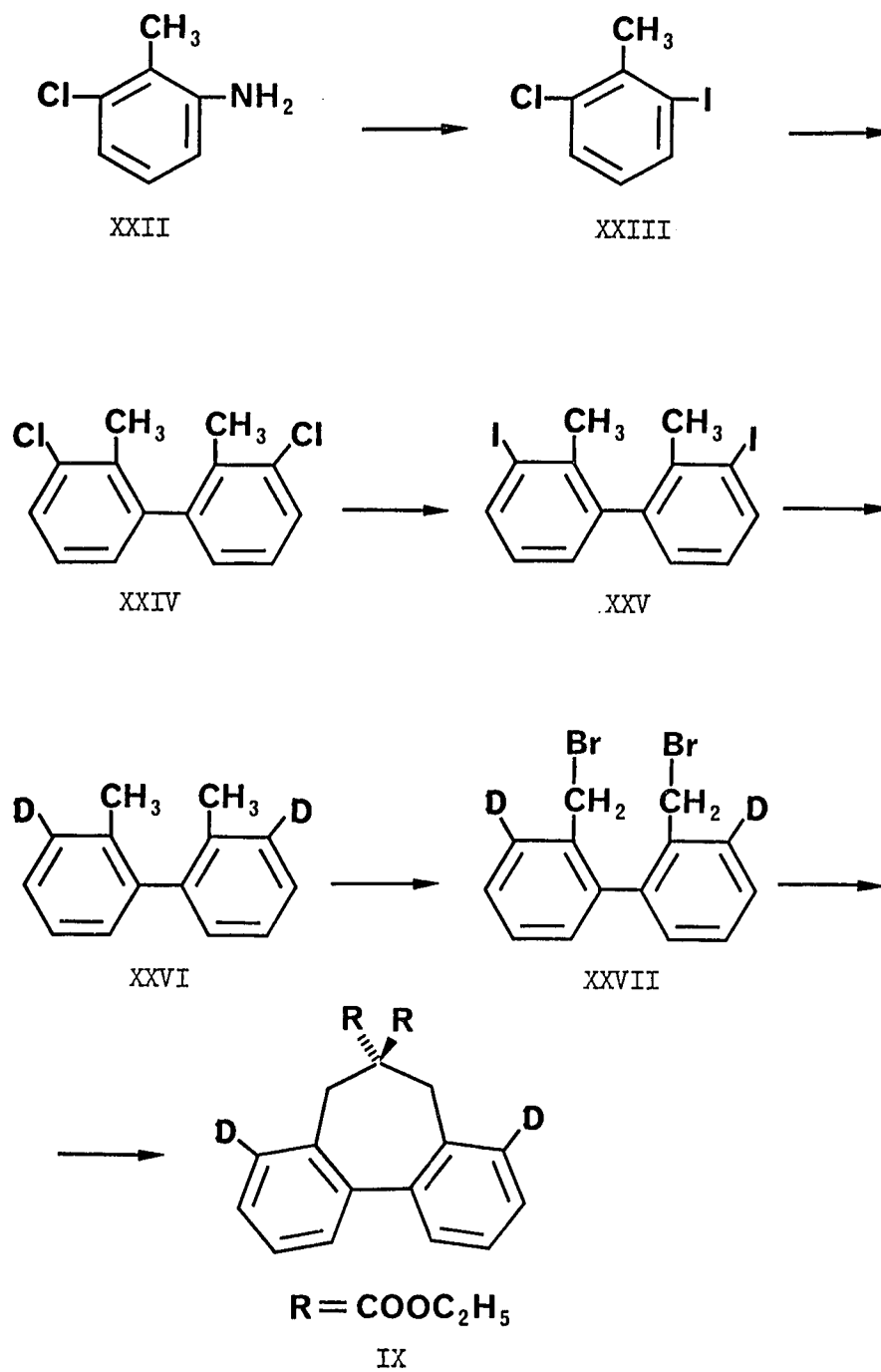
SCHEME 2.

Synthesis of (\pm) -6,6-dicarbethoxy-5,5-dideutero-dibenzo-[a,c]-1,3-cycloheptadiene (VIII)

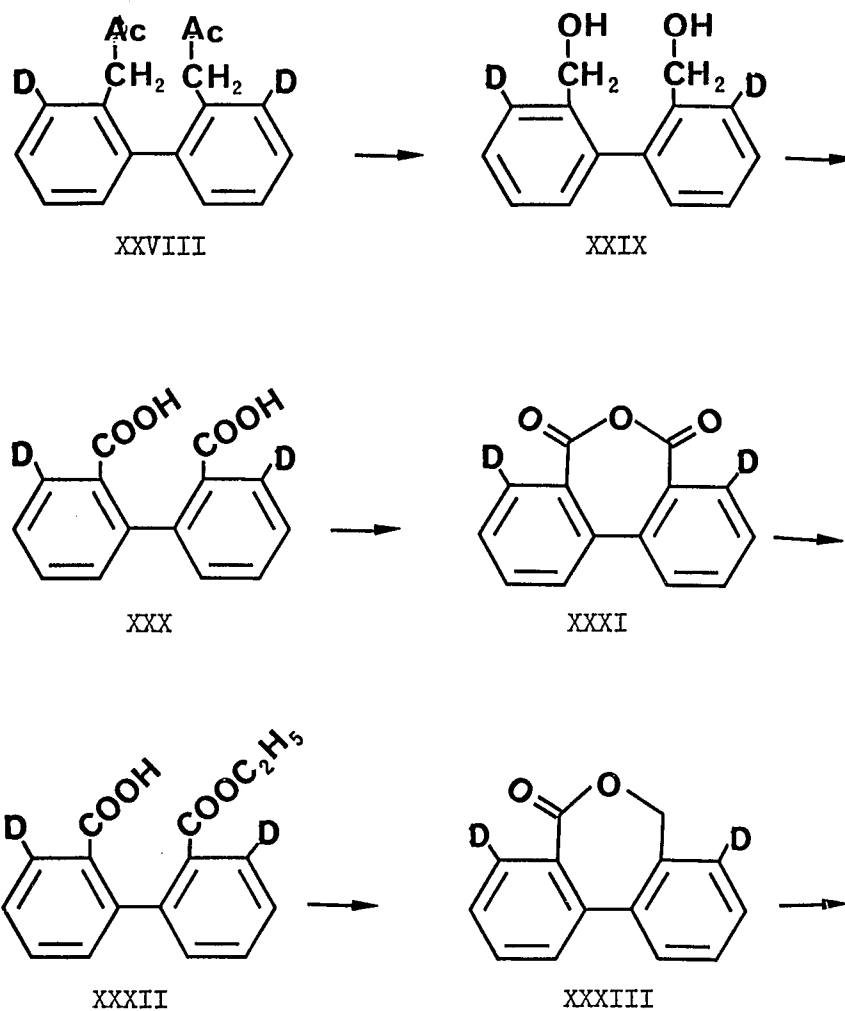


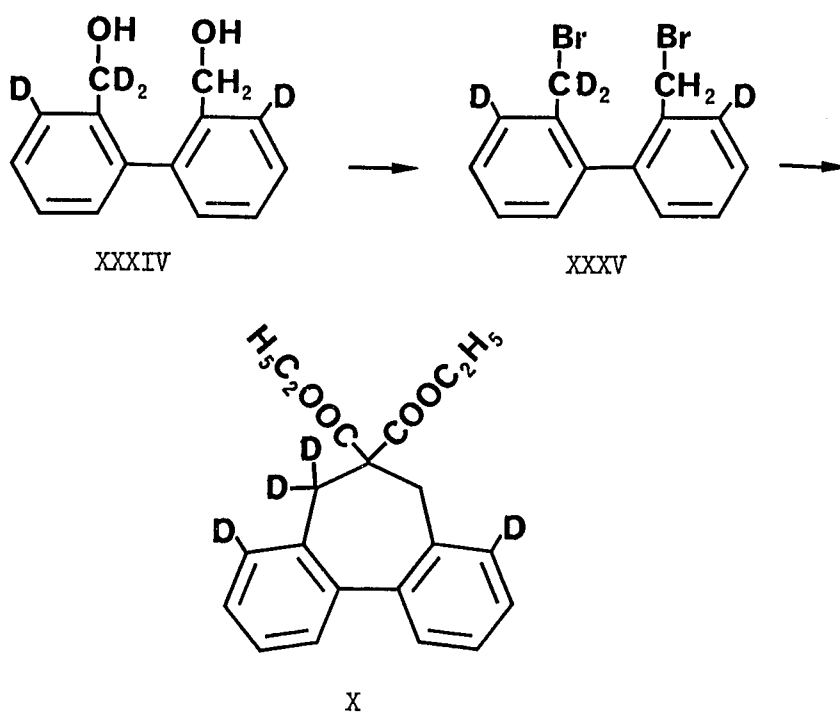
SCHEME 3.

Synthesis of (+)-6,6-dicarbethoxy-4,8-dideutero-dibenzo-[a,c]-[1,3]-cycloheptadiene (IX)



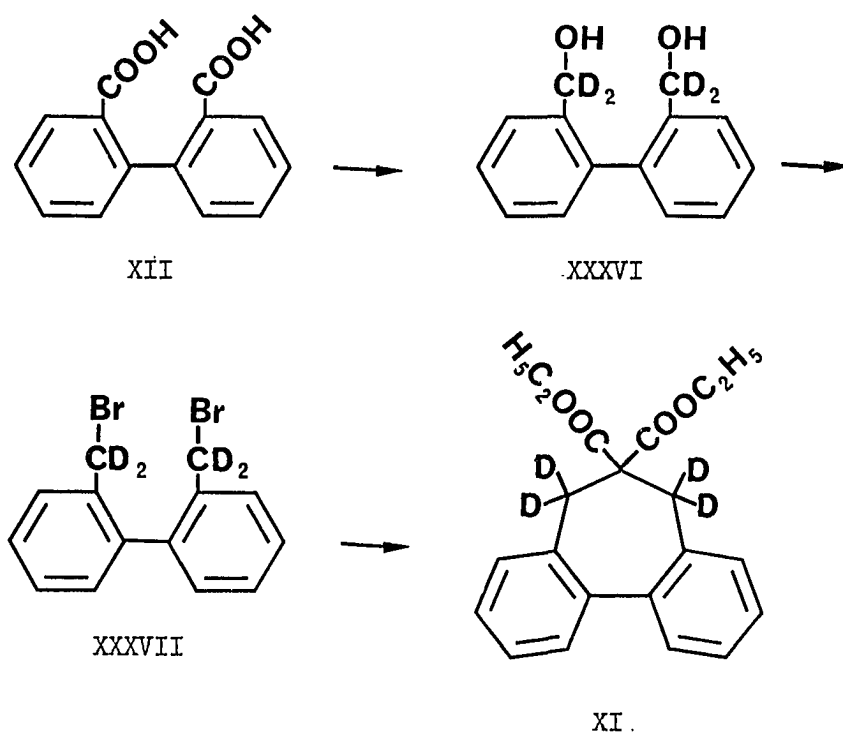
Synthesis of (\pm)-6,6-dicarbethoxy-4,5,5,8-tetra-deuterodibenzo-[a,c]-[1,3]-cycloheptadiene (X)





SCHEME 5.

Synthesis of (\pm)-6,6-dicarbethoxy-5,5,7,7-tetra-deuterodibenzo- a,c - 1,3 -cycloheptadiene (XI)



SYNTHESIS OF (+)-6,6-DICARBETHOXYDIBENZO-
[a,c]-[1,3]-CYCLOHEPTADIENE (VII)

Synthesis of diphenic anhydride (XIII)³⁰

Diphenic acid (XII) was purified by dissolving it in a sodium hydroxide solution at pH 14, clarifying the solution with Norite and precipitation of the acid by the addition, with cooling, of concentrated hydrochloric acid. This process was repeated a second time to produce a product that was white and had a melting point range of 228-230°. [lit.: mp 230-232.5°].³⁰

Into a round bottom flask containing 150 ml of acetic anhydride was added 100.3 g (0.41 mol) of the purified acid (XII). The mixture was then magnetically stirred and refluxed for a period of 1.5 hours. The acid gradually dissolved upon heating and after approximately 0.5 hour of refluxing fine needles began to appear. After refluxing for an additional 1.0 hour the heat source was removed and the reaction mixture was allowed to cool to room temperature whereupon it completely solidified into a mass of long, fine needles. The needles were collected on a Buchner funnel, washed with a small amount of cold acetic anhydride and allowed to air dry in a fume hood overnight. Recrystallization from glacial acetic acid gave 89.5 g (0.40 mol) of the desired anhydride (XIII). Yield: 98%. mp 215.5-216.5°. [lit.: mp 217°].³⁰

Synthesis of monomethyl diphenate (XIV)³¹

Into a round bottom flask containing 250 ml of absolute methan-

ol was added 68.43 g (0.31 mol) of diphenic anhydride (XIII). The mixture was then refluxed on a steam bath for 6 hours after which most of the methanol was removed by simple distillation at atmospheric pressure. The resulting mass was transferred to a crystallizing dish and vacuum dried overnight in a desiccator. A beaker of concentrated sulfuric acid was also placed in the desiccator to absorb and to react with any vaporized methanol. The following day the hard, white crystalline mass was ground into a fine powder and dried as before for an additional 24 hours. There was obtained 75.41 g (0.29 mol) of the desired compound (XIV). This compound was used in subsequent reactions without further purification. Yield: 97 %. mp 110-111° [lit.: mp 106-108°].³¹

¹H-NMR (CDCl₃) 3.56 (s, COOCH₃), 7.38 (6H, m, ArH), 8.02 (2H, m, 3,3' ArH), 11.48 (s, COOH)

Attempted synthesis of diphenide (XV) using sodium borohydride^{32,33}

Into a round bottom flask was placed 6.14 g (0.02 mol) of monomethyl diphenate (XIV) and 150 ml of dry ether. After dissolving the acid-ester there was added 30 ml (0.4 mol) of thionyl chloride and 2.5 ml (0.03 mol) of pyridine. The resulting solution was refluxed for 3 hours and then allowed to cool to room temperature. It was then filtered through a Buchner funnel and the ether evaporated under reduced pressure to give a golden brown oil. The intermediate ester-acid chloride was not purified but used directly in the subsequent reaction.

The oil was dissolved in 50 ml of p-dioxane and 1.49 g (0.04

mol) of solid sodium borohydride added cautiously and in small portions. The resulting solution was then heated on a steam bath for 0.2 hour. The solvent was removed under reduced pressure and the residue was dissolved in 250 ml of a 7 % potassium hydroxide solution in ethanol. After refluxing for 1 hour the solution was concentrated to a volume of approximately 50 ml and extracted with three 25 ml portions of diethyl ether. The combined ether extracts were washed with three 25 ml portions of water and dried with anhydrous magnesium sulfate. Evaporation of the filtered ether solution under reduced pressure gave 0.04 g of a white solid, mp 102-108°. This corresponded to the melting point of 2,2'-bis(hydroxymethyl)-1,1'-biphenyl.³⁰ ¹H-NMR showed the compound to be the diol. Yield: 0.9 % or 0.2 mmol.

The ether extracted alkaline solution was made acidic with concentrated hydrochloric acid to a pH of approximately 2 and heated on a steam bath for 0.2 hour. After cooling to room temperature it was extracted with three 25 ml portions of ether and the combined ether extracts first washed with three 10 ml portions of water and then dried with anhydrous magnesium sulfate. Upon removing the ether there was obtained 5.38 g of a white solid, mp 220-229°. ¹H-NMR showed the sample to be composed of 97 % diphenic acid and 3 % of monomethyl diphenate by weight. On a molar basis, 93 % of the starting material was recovered as one of these three compounds.

The synthetic procedure was repeated twice using purified thionyl chloride, solvents dried over 4Å molecular sieves, sodium borohydride from a fresh bottle and various reaction times. In all three cases the results obtained were essentially the same except for the

relative amounts of the products obtained. No diphenide could be detected in any of the products.

Attempted synthesis of diphenide (XV) using diborane³⁴

Diborane was generated under a flow of dried nitrogen by the dropwise addition of 3.6 g (0.1 mol) of sodium borohydride, dissolved in 100 ml of diglyme, to a solution of 25 ml (0.2 mol) of boron trifluoride etherate dissolved in 25 ml of diglyme. As the diborane formed it was passed from the diborane generating flask into a hydroboration flask cooled in an ice bath. The hydroboration flask contained 32.80 g (0.13 mol) of monomethyl diphenate (XIV) dissolved in 200 ml of tetrahydrofuran. Relative stoichiometric amounts were employed such that a molar excess of the monoester was used in order to limit reduction to the carboxylic acid and not to the ester.

After all of the sodium borohydride had been added, the diborane generating flask was heated on a water bath for one hour at a temperature of approximately 75°. The flow of nitrogen was maintained during this time in order to insure complete transfer of the diborane to the hydroboration flask.

The diborane generating flask was then allowed to cool to room temperature and finally disconnected from the system. The hydroboration flask was then slowly warmed to approximately 25° and kept at this temperature with stirring for 1 hour.

Twenty milliliters of water was then added dropwise to the hydroboration flask resulting in the production of a large amount of gas and heat. As a result the flask had to be cooled in an ice bath from

time to time. Thirty milliliters of 3 N sodium hydroxide was then added dropwise followed by the dropwise addition of 30 ml of 30 % hydrogen peroxide in order to oxidize the organoborane.

The resulting solution was then stirred for 1 hour and subsequently acidified to pH 2 with concentrated hydrochloric acid. After cooling in an ice bath the solution was extracted with four 100 ml portions of ether. The combined ether extracts were dried with anhydrous magnesium sulfate and filtered. Removal of the ether under reduced pressure gave 30.12 g of a white solid. $^1\text{H-NMR}$ showed the solid to be composed of 67 % diphenic acid and 33 % monomethyl diphenate. This represents a recovery of 95 % of the starting material. Further extraction of the acidified aqueous layer produced an additional 0.01 g of material.

Repetition of this procedure with 10.26 g (0.040 mol) of monomethyl diphenate produced essentially the same results.

Attempted synthesis of diphenide (XV) using lithium borohydride³⁵

Under a nitrogen atmosphere 2.11 g (8.2 mmol) of monomethyl diphenate (XIV) was dissolved in 40 ml of tetrahydrofuran. The resulting solution was cooled in an ice bath and 0.15 g (0.01 mol) of lithium borohydride, dissolved in 15 ml of tetrahydrofuran, added dropwise. After addition was complete the reaction was refluxed on a steam bath for 4 hours.

It was then cooled in an ice bath and 30 ml of water was added followed by the addition of 30 ml of 2N hydrochloric acid. The acid-

ified solution was then refluxed for 0.5 hour, cooled and extracted with three 50 ml portions of ether. The combined ether extracts were washed twice with 15 ml of a 2 % sodium bicarbonate solution. After washing the ether solution with 15 ml of water it was dried with anhydrous magnesium sulfate. The solution was then filtered and the ether removed to give 1.99 g of a white solid, mp 109-111°. ¹H-NMR showed the material to be essentially all unreacted starting material.

All aqueous layers were combined and extracted three times with 75 ml of ether. The combined ether layers were dried with anhydrous magnesium sulfate, filtered and the ether evaporated to give 0.07 g of a white solid, mp 109-112°. A total of 97 % of the starting material was thus recovered.

The reaction was repeated using a five-fold excess of lithium borohydride and refluxing for 24 hours. ¹H-NMR showed that no reduction had taken place.

Synthesis of diphenide (XV) using lithium triethylborohydride³⁶

Under a nitrogen atmosphere 2.56 g (0.10 mol) of monomethyl diphenate was dissolved in 15 ml of dry tetrahydrofuran. The solution was cooled in an ice bath and 40.0 ml of a 0.84 M solution of lithium triethylborohydride (0.028 mol) was added dropwise with stirring. The ice bath was removed and the reaction was refluxed on a steam bath for 1 hour. Most of the tetrahydrofuran was removed by simple distillation and to the resulting mushy material was added 20 ml of water.

After stirring for 0.2 hour 10 ml of 30 % hydrogen peroxide was

added dropwise. The reaction was then heated to approximately 45° and kept at this temperature for 0.5 hour. Twenty milliliters of a 6 N hydrochloric acid solution was then added and the reaction refluxed for an additional 0.5 hour. After cooling 50 ml of ether was added to dissolve any solid material and the layers were separated. The aqueous layer was extracted twice with 50 ml portions of ether and the combined ether layers washed once with 50 ml of a 2% sodium bicarbonate solution. After washing once with 50 ml of water the ether solution was dried with anhydrous magnesium sulfate. Removal of the ether gave 2.04 g of white crystals. Recrystallization from ether gave 2.00 g (0.010 mol) of diphenide. The yield was almost quantitative. mp 131-132°. [lit.: 132-133° ³², 136-136.5° ³⁷ and 132° ³⁸]. ¹H-NMR (CDCl₃) 3.95 (s, ArCH₂), 7.64 (m, ArH)

Synthesis of 2,2'-bis(hydroxymethyl)-1,1'-biphenyl (XVI)

To a cooled solution of 9.01 g (0.24 mol) lithium aluminum hydride in 200 ml of dry ether was added dropwise and under a nitrogen atmosphere 20.12 g (0.10 mol) of diphenide (XV) dissolved in 100 ml of dry ether. The reaction was allowed to stir 1 hour before the excess hydride was destroyed by the addition of 30 ml of water. Thirty milliliters of 2 N hydrochloric acid was then added and, after vigorous stirring for 0.5 hour the layers were separated. The aqueous layer was extracted twice with 50 ml of ether and the combined ether layers dried with anhydrous magnesium sulfate. After filtration the ether was evaporated to give a white solid. Recrystallization from petro-

added dropwise. The reaction was then heated to approximately 45° and kept at this temperature for 0.5 hour. Twenty ml of a 6N hydrochloric acid solution was then added and the reaction refluxed for an additional 0.5 hour. After cooling 50 ml of ether was added to dissolve any solid material and the layers separated. The aqueous layer was extracted twice with 50 ml of ether and the combined ether layers washed once with 50 ml of a 2 % sodium bicarbonate solution. After washing once with 50 ml of water the ether was dried with anhydrous magnesium sulfate. Removal of the ether gave 2.04 g of white crystals. Recrystallization from ether gave 2.00 g (0.010 mol) of pure diphenide. The yield was almost quantitative. mp $131-132^{\circ}$. [lit.: $132-133^{\circ}$ ³², $136-136.5^{\circ}$ ³⁷ and 132° ³⁸].

$^1\text{H-NMR}$ (CDCl_3) 3.95 (s, ArCH_2), 7.64 (m, ArH)

Synthesis of 2,2'-bis(hydroxymethyl)-1,1'-biphenyl (XVI)

To a cooled solution of 9.01 g (0.24 mol) lithium aluminum hydride in 200 ml of dry ether was added dropwise and under a nitrogen atmosphere 20.12 g (0.10 mol) of diphenide (XV) dissolved in 100 ml of dry ether. The reaction was allowed to stir for 1 hour before the excess hydride was destroyed by the addition of 30 ml of water. Thirty ml of 2N hydrochloric acid was then added and, after vigorous stirring for 0.5 hour, the layers were separated. The aqueous layer was extracted twice with 50 ml of ether and the combined ether layers dried with anhydrous magnesium sulfate. After filtration the ether was evaporated to give a white solid. Recrystallization from petro-

leum ether gave 19.88 g (0.090 mol) of the diol (XVI) as white needles. Yield: 90 %. mp 109-110°. [lit.: mp 111-112°].³⁹ ¹H-NMR (CDCl₃) 3.50 (s, OH), 4.28 (s, ArCH₂), 7.27 (m, ArH).

Synthesis of 5,7-dihydrodibenz-[c,e]-oxepin (XVII)

If in the procedure for the synthesis of 2,2'-bis(hydroxymethyl)-1,1'-biphenyl (XVI) above the addition is reversed and the lithium aluminum hydride solution is added to a solution of diphenide (XV) the dehydrated diol is formed. In this way 12.06 g (0.057 mol) of diphenide (XV) was converted to 10.78 g (0.055 mol) of the oxepin (XVII). Yield: 96 %. mp 71-72°. [lit.: mp 71.5-72°].⁴⁰ ¹H-NMR (CDCl₃) 4.34 (s, ArCH₂), 7.33 (m, ArH).

Synthesis of 2,2'-bis(bromomethyl)-1,1'-biphenyl (XVIII)⁴¹

Route A: From 2,2'-bis(hydroxymethyl)-1,1'-biphenyl (XVI). To 100 ml of 48 % hydrobromic acid cooled in an ice bath was added 8 ml of concentrated sulfuric acid. The resulting solution was cooled to approximately 2° and 9.21 g (0.043 mol) of the diol (XVI) was added. The resulting solution was then refluxed for 3 hours and, after cooling, poured into 250 ml of water. The precipitate which formed was collected, washed with water and dried in a vacuum desiccator overnight. It was then dissolved in benzene and decolorized with Norite. The volume of benzene was reduced and, after cooling overnight in a refrigerator, the crystals which formed were collected and vacuum dried. Subsequent further reduction in the volume of benzene pro-

duced more crystals. The combined collection of crystals was recrystallized from carbon tetrachloride to give 12.92 g (0.038 mol) of the purified dibromide (XVIII). Yield: 88 %. mp 88-89°. [lit.: mp 92-95°³⁹ and 82-83°⁴¹]. ¹H-NMR (CDCl₃) 4.24 (q, CH₂Br), 7.42 (m, ArH)

Route B: From 5,7-dihydrodibenzo-[c,e]-oxepin (XVII)

Following the above procedure 9.82 g (0.50 mol) of the oxepin was converted to 14.68 g (0.04 mol) of the desired compound. Yield: 80 %. mp 88-89°. The ¹H-NMR spectra corresponded well to that of the previously prepared compound and the melting point of a mixture of the two compounds remained unchanged.

Synthesis of (±)-6,6-dicarbethoxydibenzo-[a,c]-[1,3]-cycloheptadiene (VII)^{22,39}

To five ml of absolute ethanol there was added 0.34 g (0.01 g. at. wt.) of freshly cut sodium metal. After all of the sodium had reacted 2.25 ml (14.8 mmol) of diethyl malonate dissolved in 11 ml of ether was added all at once. The reaction mixture was stirred for 0.25 hour during which time it became cloudy. The resulting solution was then added with stirring to 2.26 g (6.64 mmol) of 2,2'-bis(bromomethyl)-1,1'-biphenyl (XVIII) dissolved in 15 ml of dry ether. The reaction was then refluxed for 3 hours after which it was filtered and the solvents removed under reduced pressure.

The resulting solid was recrystallized twice from absolute ethanol and vacuum dried overnight to give 1.44 g (4.25 mmol) of the desired compound (VII) as white crystals. Yield: 64 %. mp 63-64.5°.

[lit.: mp 64-66°]^{22,39}

¹H-NMR (CCl₄) 1.20 (t, CH₃), 3.01 (broad s, ArCH₂), 4.14 (q, COOCH₂), 7.25 (m, ArH). Mass Spectra M⁺ at 338 m/e. TLC: System A single spot at R_f=0.64; System B single spot at R_f=0.11

SYNTHESIS OF (+)-6,6-DICARBETHOXY-5,5-DIDEUTERO-
DIBENZO-[a,c]-[1,3]-CYCLOHEPTADIENE (VIII)

Synthesis of 2-(hydroxy- α,α -dideuteromethyl)-2'-hydroxymethyl-1,1'-biphenyl (XIX)

Following the procedure for the synthesis of the non-deuterated compound (XVI) 5.28 g (0.02 mol) of diphenide (XV) was reduced with 0.59 g (0.01 mol) of 99.98 %-d₄ lithium aluminum deuteride. Upon clean up there was obtained 5.17 g (0.02 mol) of the desired compound. The yield was essentially quantitative. mp 109-110°. ¹H-NMR (CDCl₃) 3.49 (s, OH), 4.28 (s, ArCH₂), 7.26 (m, ArH)

Synthesis of 5,5-dideutero-7,7-dihydrodibenz-[c,e]-oxepin (XX)

The procedure for the synthesis of the non-deuterated analog (XVII) was followed reducing 6.48 g (0.03 mol) of diphenide (XV) with 0.72 g (0.02 mol) of 99.98 %-d₄ lithium aluminum deuteride. There was obtained 5.96 g (0.03 mol) of the desired compound (XX). The yield was essentially quantitative. mp 71-72°. ¹H-NMR (CDCl₃) 4.33 (s, ArCH₂), 7.32 (m, ArH)

Synthesis of 2-(bromo- α,α -dideuteromethyl)-2'-bromomethyl-1,1'-biphenyl (XXI)

Route A: From 2-(hydroxy- α,α -dideuteromethyl)-2'-hydroxymethyl-1,1'-biphenyl (XIX).

Following the procedure for the synthesis of the non-deuterated compound (XVIII) 4.82 g (0.02 mol) of the starting material (XIX)

gave 6.80 g (0.02 mol) of the desired compound (XXI). The yield was essentially quantitative. mp 88.5-89.5°. $^1\text{H-NMR}$ (CDCl_3) 4.24 (q, CH_2Br), 7.40 (m, ArH)

Route B: From 5,5-dideutero-7,7-dihydrodibenz- $[\text{c},\text{e}]$ -oxepin (XX). Following the procedure for the synthesis of the non-deuterated compound (XVIII) from the oxepin (XVII), 5.43 g (0.03 mol) of (XX) gave 7.85 g (0.02 mol) of the desired dibromide (XXI). Yield: 67 %. mp 88.5-89.5°. The $^1\text{H-NMR}$ was very similar to that of the product using route A. A mixed melting point produced no change in the melting point.

Synthesis of (\pm) -6,6-dicarbethoxy-5,5-dideuterodibenzo- $[\text{a},\text{c}]-[1,3]$ -cycloheptadiene (VIII)

Following the procedure for the synthesis of the non-deuterated analog (VII), 2.00 g (5.85 mmol) of (XXI) gave 1.32 g (3.87 mmol) of the desired compound (VIII). Yield: 66 %. mp 64-65.5°. $^1\text{H-NMR}$ (CCl_4) 1.20 (t, CH_3), 3.00 (broad s, ArCH_2), 4.11 (q, COOCH_2), 7.28 (m, ArH). Mass spectra M^+ at 340 m / e. TLC: System A single spot at $R_f=0.64$; System B single spot at $R_f=0.10$.

SYNTHESIS OF (+)-6,6-DICARBETHOXY-4,8-DIDEUTERO-
DIBENZO-[a,c]-[1,3]-CYCLOHEPTADIENE (IX)

Synthesis of 2-chloro-6-iodotoluene (XXIII)²⁷

To a solution of 700 ml of concentrated hydrochloric acid and 700 ml of water cooled in an ice bath was added 250.1 g (1.8 mol) 3-chloro-2-methylaniline (XXII). The temperature of the solution was kept between 0 and 4° while 146.8 g (2.1 mol) of solid sodium nitrite was added in portions with vigorous stirring. Addition of the sodium nitrite required approximately 0.75 hour and stirring was subsequently continued for an additional 0.5 hour.

To the cold solution was then added 25.4 g (0.4 mol) of urea in order to destroy any unreacted nitrous acid. After stirring the mixture for 0.25 hour 296.5 g (1.8 mol) of potassium iodide, dissolved in a minimal amount of water, was added dropwise. The reaction was allowed to slowly warm to room temperature and then steam was applied in order to raise the temperature to approximately 35°. By this time the reaction had partitioned into an upper reddish-brown aqueous phase and a lower black organic phase. The addition of approximately 10 g of solid sodium bisulfite caused the upper layer to lighten in color. The layers were separated and the aqueous phase was extracted three times with 100 ml portions of benzene. The combined organic layers were then first washed twice with 150 ml of an aqueous 5 % sodium bicarbonate solution and then with two 150 ml portions of water. After removing most of the benzene by simple distillation at

atmospheric pressure the remaining material was fractionally distilled to give the following fractions:

<u>fraction</u>	<u>bp range</u>	<u>pressure</u>	<u>weight</u>
1	82-96°	3 mm	1.42 g
2	96-99.5°	2 mm	2.56 g
3	99.5-100°	2 mm	43.56 g
4	100-101°	2 mm	68.98 g
5	101°	2 mm	74.42 g
6	101°	2 mm	33.00 g
7	101°	2 mm	12.68 g

¹H-NMR showed that fractions 3 through 7 were the desired product and, upon combining these fractions, there was obtained 232.64 g (0.92 mol) of the desired compound (XXIII). Yield 52 %. [lit.: bp at 132-133° and 25mm⁴³; 99-100° and 5mm⁴⁴]. ¹H-NMR (CDCl₃) 2.52 (s, CH₃), 6.87 (m, ArH).

Synthesis of 3,3'-dichloro-2,2'-dimethyl-1,1'-biphenyl (XXIV)²⁷

In a round bottom flask containing 226.5 g (0.9 mol) of 2-chloro-6-iodotoluene (XXIII) was added 113.0 g (1.8 mol) of electrolytic grade copper dust and 28 g of acid washed ignited sand. A mechanical stirrer with a stainless steel blade was used to stir the mixture while an air cooled condenser was used to condense any volatile material. The reaction was heated in a high temperature silicone oil bath to approximately 235° and maintained at this temperature for 72 hours.

After cooling the reaction was filtered through a plug of glass wool and the solid material washed once with 50 ml of benzene. The combined organic material was decolorized with Norite and subsequently filtered through diatomaceous earth. The benzene was removed by simple

distillation at atmospheric pressure and finally under reduced pressure. The remaining material was then fractionally distilled to give the following fractions:

<u>fraction</u>	<u>bp range</u>	<u>pressure</u>	<u>weight</u>
1	68-72°	5 mm	2.86 g
2	72-76°	5 mm	0.42 g
3	129-131°	1.7 mm	0.99 g
4	131-135°	1.5 mm	42.46 g
5	135-138°	1.5 mm	50.64 g

The condenser used in the distillation had to be heated from time to time in order to melt any solid which had collected in it during the distillation of fractions 4 and 5. Upon cooling these two fractions solidified and were subsequently recrystallized twice from ethanol and dried in a vacuum dessicator overnight. There was thus obtained 89.64 g (0.36 mol) of the desired compound (XXIV).

Yield: 40 %. mp 76-77°. [lit.: bp 133-139° at 2 mm and mp 75-76°].⁴²

¹H-NMR (CDCl₃) 2.10 (s, CH₃), 7.19 (m, ArH)

Synthesis of 3,3'-diiodo-2,2'-dimethyl-1,1'-biphenyl (XXV)²⁷

Tetrahydrofuran (750 ml) was dried by refluxing it overnight with approximately 10 g of lithium aluminum hydride. It was then distilled under an atmosphere of dried nitrogen collecting the material distilling at 65.5-66.5° and subsequently storing it over calcium hydride. In this way approximately 650 ml of tetrahydrofuran was purified.

Under an atmosphere of nitrogen was placed 6.14 g (0.25 mol) of magnesium turnings and a small crystal of iodine. Heat was then momentarily applied to the flask. After cooling to room temperature

200 ml of the purified ether was added and the mixture was heated to reflux. A solution of 29.85 g (0.12 mol) of 3,3'-dichloro-2,2'-dimethyl-1,1'-biphenyl (XXIV) in 100 ml of tetrahydrofuran was then added dropwise at such a rate as to keep the reaction at reflux. The reaction was refluxed for 2 hours and then 0.24 g (1.2 mmol) of aluminum isopropoxide was added. After refluxing 24 hours an additional 0.24 g of aluminum isopropoxide was added. The reaction was then refluxed for an additional 3 days.

The solution was added dropwise through glass tubing to a solution of 65.24 g (0.26 mol) of iodine dissolved in 75 ml of tetrahydrofuran. It was stirred for 3 hours and then 100 ml of water followed by 18.42 g (0.10 mol) of sodium bisulfite were added. After the volume had been reduced to 100 ml the resulting solution was extracted with three 100 ml portions of benzene. The combined benzene extracts were washed with two 50 ml portions of water and dried with anhydrous sodium sulfate. The solution was clarified with Norite, filtered through diatomaceous earth and the benzene was evaporated.

The resulting mushy crystals were recrystallized from benzene/methanol (1:1) to give 16.05 g (0.04 mol) of the desired compound (XXV). Yield: 33 %. mp 118.5-123.0°. [lit.: mp 113-118°].⁴²

Repetition of this experimental procedure with 45.22 g (0.18 mol) of the starting material (XXIV) gave upon workup 29.31 g (0.07 mol) of the desired compound. Yield 39 %. mp 118-123°.

Synthesis of 3,3'-dideutero-2,2'-dimethyl-1,1'-biphenyl (XXVI)

Into a 250 ml three necked flask fitted with a condenser and an

addition funnel was placed 0.53 g (0.02 mol) of magnesium metal. The apparatus was set up as to allow it to be swept with dried nitrogen (also removed of carbon dioxide with Ascarite) or to be evacuated by a vacuum pump. Nitrogen was passed through the system as it was simultaneously heated to vaporize any water. The nitrogen flow was stopped and the system evacuated with the vacuum pump. This process was repeated three times in order to provide a system essentially free of water and carbon dioxide.

Under nitrogen 20 ml of diethyl ether (dried over sodium metal) was introduced via a syringe followed by the dropwise addition of 5.68 g (0.01 mol) of 3,3'-diiodo-2,2'-dimethyl-1,1'-biphenyl (XXV) dissolved in 50 ml of diethyl ether. The reaction started almost immediately and, after all of the solution of (XXV) had been added, the reaction was allowed to stir for 3 hours. The diethyl ether was then removed under reduced pressure and the apparatus cooled in an ice bath. Five ml (0.3 mol) of 99.996 % d_2 water dissolved in 10 ml of dry tetrahydrofuran was added dropwise via a syringe. (The tetrahydrofuran was prepared by the addition of 0.2 ml of the deuterated water to 75 ml of tetrahydrofuran and subsequent drying over 4\AA molecular sieves. This process was repeated twice.) The reaction was stirred for 1 hour at room temperature and then the solvents were removed under reduced pressure.

The resulting solid was recrystallized from ethanol to give 2.06 g (0.01 mol) of the desired compound (XXVI). The ethanol solution, upon being reduced in volume, gave an additional 0.26 g (1.4

mmol) of the desired compound (XXVI). The total amount obtained was 2.32 g (0.01 mol). The yield was essentially quantitative. mp 17.5-18.5°. $^1\text{H-NMR}$ (CDCl_3) 2.45 (s, ArCH_3), 6.77 (m, ArH)

Synthesis of 2,2'-bis(bromomethyl)-3,3'-dideutero-1,1'-biphenyl (XXVII)

To a solution of 3.58 g (0.02 mol) of 3,3'-dideutero-2,2'-dimethyl-1,1'-biphenyl (XXVI) dissolved in 40 ml of carbon tetrachloride was added 4.91 g (0.03 mol) of N-bromosuccinimide. The reaction was heated to reflux whereupon 0.26 g (1.1 mmol) of dibenzoyl peroxide was added. The refluxing continued for 12 hours whereupon another 0.26 g (1.1 mmol) of dibenzoyl peroxide was added. After refluxing an additional 12 hours the reaction was cooled to room temperature, filtered and washed once with 25 ml of a 5 % sodium bisulfite solution. The organic layer was dried with anhydrous magnesium sulfate and evaporated to dryness on a rotovap. Recrystallization from carbon tetrachloride gave a first crop of 3.96 g (0.01 mol) of the desired compound (XXVII). Concentration of the mother liquor gave, upon cooling, a second crop of 0.21 g (0.6 mmol) for a total of 4.17 g (0.01 mol) of the desired compound (XXVII). Yield 50 %. mp 89.5-91.5°. $^1\text{H-NMR}$ (CDCl_3) 4.29 (q, CH_2Br), 7.42 (m, ArH)

Synthesis of (\pm)-6,6-dicarbethoxy-4,8-dideuterodibenzo-[a,c]-[1,3]-cycloheptadiene (IX)

The procedure for the synthesis of the non-deuterated compound (VII) was followed except that 1.71 g (5.0 mmol) of 2,2'-bis(bromomethyl)-3,3'-dideutero-1,1'-biphenyl (XXVI) yielded 1.06 g (3.1 mmol)

of the desired compound (IX). Yield 62 %. mp 65-67°. $^1\text{H-NMR}$ (CDCl_3)
1.21 (t, CH_3), 3.02 (q, ArCH_2), 4.16 (q, COOCH_2), 7.27 (m, ArH)
TLC: System A single spot at $R_f=0.65$; System B single spot at $R_f=0.10$.

SYNTHESIS OF (\pm)-6,6-DICARBETHOXY-4,5,5,8-TETRA-
DEUTERODIBENZO-[a,c]-[1,3]-CYCLOHEPTADIENE (X)

Synthesis of 2,2'-bis(acetoxymethyl)-3,3'-dideutero-1,1'-biphenyl (XXVIII)

Into 30 ml of dry acetone was dissolved 13.82 g (0.04 mol) of 2,2'-bis(bromomethyl)-3,3'-dideutero-1,1'-biphenyl (XXVII). This solution was then added dropwise to a solution of 8.33 g (0.085 mol) of anhydrous potassium acetate heated to approximately 85°. After addition was complete the reaction was heated on a steam bath overnight. It was then cooled to room temperature, filtered and the acetic acid which formed removed under high vacuum. The residue was shaken with a mixture of water and ether (20 ml and 50 ml respectively) and the aqueous layer extracted twice with 50 ml portions of ether. The combined ether layers were washed twice with water (25 ml) and dried over anhydrous magnesium sulfate. After filtering of the solution the ether was removed on a rotovap to leave an oil which was fractionally distilled to give the following fractions:

<u>fraction</u>	<u>bp range</u>	<u>pressure</u>	<u>weight</u>
1	208-212°	15.6 mm	0.47 g
2	212-214°	15.4 mm	2.33 g
3	214-215°	15.4 mm	2.93 g
4	215°	15.4 mm	5.64 g

Fractions 2 through 4 were combined to give 11.37 g (0.038 mol) of the desired compound (XXVIII). Yield 95 %. $^1\text{H-NMR}$ (CDCl_3) 2.42 (s, CH_3), 5.01 (q, CH_2), 7.44 (m, ArH)

Synthesis of 2,2'-bis(hydroxymethyl)-3,3'-dideutero-1,1'-biphenyl (XXIX)

To a solution of 75 ml of 50 % aqueous potassium hydroxide was added 75 ml of ethanol and 5.23 g (0.017 mol) of 2,2'-bis(acetoxymethyl)-1,1'-biphenyl (XXVIII). Water and ethanol were added alternately in order to solubilize all of the material. The mixture was then refluxed on a steam bath for 6 hours, cooled in an ice bath and neutralized with 0.1 N hydrochloric acid. The volume of the reaction mixture was reduced to approximately 40 ml and shaken with a mixture of water and ether (50 ml of each). The aqueous layer was extracted twice with 50 ml portions of ether and the ether layers washed first with two portions of a 5 % sodium bicarbonate solution (25 ml) and then twice with water (25 ml).

The ether solution was then dried with anhydrous magnesium sulfate, filtered and the ether removed on a rotovap. The resulting crystals were recrystallized from hexanes to give 3.56 g (16.5 mmol) of the desired compound (XXIX). mp 110-111°. Yield 95 %. $^1\text{H-NMR}$ (CDCl_3) 3.54 (s, CH_2OH), 4.26 (s, ArCH_2), 7.27 (m, ArH)

Synthesis of 3,3'-dideuterodiphenic acid (XXX)

Under an atmosphere of nitrogen 5 ml of dry dimethylformamide was cooled to 0° and there was added 1.90 g (5.05 mmol) of pyridinium dichromate and 0.43 g (1.98 mmol) of 2,2'-bis(hydroxymethyl)-3,3'-dideutero-1,1'-biphenyl (XXIX). The mixture was stirred at 0° for 6 hours and then poured into 50 ml of water. The solution was made acidic with concentrated hydrochloric acid and the precipitate collec-

ted on a Buchner funnel. The aqueous layer was extracted four times with 50 ml portions of ether and the combined ether layers were passed through a 1 cm plug of anhydrous magnesium sulfate. The ether was removed on a rotovap and the resulting solid was purified by dissolving it in 2N sodium hydroxide, treatment with Norite and filtering through diatomaceous earth. The product was precipitated upon the addition of concentrated hydrochloric acid, collected and washed with water. After drying in a vacuum desiccator overnight there was obtained 0.35 g (1.44 mmol) of the desired compound (XXX). mp 228.5-230.5°. Yield 72 %.

$^1\text{H-NMR}$ (CDCl_3) 7.30 (m, ArH), 11.41 (s, COOH)

Repetition of the above procedure with 2.89 g (13.3 mmol) of the starting material (XXIX) gave 2.44 g (9.98 mmol) of the desired compound (XXX). mp 228.5-230.5°. Yield: 75 %. The $^1\text{H-NMR}$ was identical to the one of the above prepared compound and a mixed melting point showed no change.

Synthesis of 3,3'-dideuterodiphenic anhydride (XXXI)

The procedure for the synthesis of the non-deuterated analog (XIII) was followed. In this manner 2.68 g (11.0 mmol) of 3,3'-dideuterodiphenic acid (XXX) gave upon recrystallization from glacial acetic acid 2.40 g (10.6 mmol) of the desired anhydride (XXXI). Yield: 97 %. mp 218-218.5°. $^1\text{H-NMR}$ (CDCl_3) 7.54 (m, ArH).

Synthesis of monomethyl 3,3'-dideuterodiphenate (XXXII)

The procedure for the synthesis of the non-deuterated analog

(XIV) was followed. Using this procedure 2.27 g (10.02 mmol) of the anhydride (XXXI) gave 2.54 g (9.84 mmol) of the desired compound (XXXII). Yield 98 %. mp 112.5–113.5°. $^1\text{H-NMR}$ (CDCl_3) 3.60 (s, OCH_3), 7.28 (m, ArH), 11.36 (s, COOH).

Synthesis of 3,3'-dideuterodiphenide (XXXIII)

The procedure for the synthesis of the non-deuterated analog (XV) was followed using lithium triethylborohydride. Following this procedure 2.54 g (9.84 mmol) of the starting material (XXXII) gave 1.89 g (8.90 mmol) of the desired compound (XXXIII). Yield: 97 %. mp 131–131.5°. $^1\text{H-NMR}$ (CDCl_3) 3.92 (s, ArCH_2), 7.62 (m, ArH).

Synthesis of 2-(hydroxy- α,α -dideuteromethyl)-2'-hydroxymethyl-3,3'-dideutero-1,1'-biphenyl (XXXIV)

The procedure for the synthesis of the non-deuterated analog (XVI) was followed. Using this procedure 1.75 g (8.24 mmol) of (XXXIII) gave upon reduction with 0.20 g (4.8 mmol) of lithium aluminum deuteride and subsequent purification 1.75 g (8.00 mmol) of the desired compound (XXXIV). Yield 97 %. mp 110–111°. $^1\text{H-NMR}$ (CDCl_3) 3.47 (s, OH), 4.24 (s, CH_2), 7.23 (m, ArH).

Synthesis of 2-(bromo- α,α -dideuteromethyl)-2'-bromomethyl 3,3'-dideutero-1,1'-biphenyl (XXXV)

Following the procedure for the synthesis of the aromatically non-deuterated compound (XVIII), 1.70 g (8.00 mmol) of the starting material (XXXIV) gave 1.46 g (4.25 mmol) of the desired compound

(XXXV). Yield: 53 %. mp 89.5-91.5°. $^1\text{H-NMR}$ (CDCl_3) 4.28 (q, CH_2Br), 7.40 (m, ArH).

Synthesis of (\pm)-6,6-dicarbethoxy-4,5,5,8-tetradeuterodibenzo-[a,c]-1,3-cycloheptadiene (X)

Following the procedure for the synthesis of the non-deuterated compound (VII), 1.39 g (4.05 mmol) of the dibromo compound (XXXV) gave 0.86 g (2.52 mmol) of the desired compound (X). Yield 62 %. mp 64.5-66°. TLC: System A one spot at $R_f=0.61$; System B one spot at $R_f=0.08$. $^1\text{H-NMR}$ (CCl_4) 1.18 (t, CH_3), 3.01 (broad s, ArCH_2), 4.11 (q, COOCH_2), 7.25 (m, ArH).

SYNTHESIS OF (\pm)-6,6-DICARBETHOXY-5,5,7,7-TETRA-
DEUTERODIBENZO-[a,c]-1,3-CYCLOHEPTADIENE (XI)

Synthesis of 2,2'-bis(hydroxy- α,α -dideuteromethyl)-1,1'-biphenyl (XXX
(XXXVI))

To 0.14 g (3.2 mmol) of lithium aluminum deuteride dissolved in 25 ml of ether there was added dropwise a solution of 0.65 g (2.69 mmol) of diphenic acid (XII) dissolved in 25 ml of ether. After addition was complete the reaction was refluxed for 0.5 hour. The reaction was then cooled in an ice bath and 20 ml of a 1N aqueous hydrochloric acid solution was added dropwise. The reaction was extracted three times with 25 ml of ether and the combined ether extracts dried with anhydrous magnesium sulfate. After filtering the ether was removed on a rotovap. The resulting crystals were recrystallized from benzene to give 0.56 g (2.64 mmol) of the desired compound (XXXVI). Yield: 98 %. mp 111-112°. $^1\text{H-NMR}$ (CDCl_3) 3.48 (s, OH), 7.24 (m, ArH).

Synthesis of 2,2'-bis(bromo- α,α -dideuteromethyl)-1,1'-biphenyl
(XXXVII)

The procedure for the synthesis of the non-deuterated analog (XVIII) was followed. Using this procedure 0.56 g (2.59 mmol) of (XXXVI) gave 0.51 g (1.48 mmol) of the desired compound (XXXVII). Yield: 55 %. mp 89-90°. $^1\text{H-NMR}$ (CDCl_3) 7.36 (m, ArH).

Synthesis of (\pm)-6,6-dicarbethoxy-5,5,7,7-tetradeutero-[a,c]-1,3-cycloheptadiene (XI)

Following the procedure for the synthesis of the non-deuterated analog (VII), 0.49 g (1.42 mmol) of (XXXVII) gave 0.31 g (0.90 mmol) of the desired compound (XI). Yield: 63 %. mp 66-67.5°. $^1\text{H-NMR}$ (CCl_4) 1.21 (t, CH_3), 4.10 (q, COOCH_2), 7.24 (m, ArH).

DISCUSSION

Results of Synthesis Procedures

The individual synthetic routes employed to the selectively deuterated/non-deuterated compounds were essentially analogous to each other and straightforward. The largest problem appeared in the selective reduction of monomethyl diphenate. Since a wide range of reducing reagents are available with differing reductive capabilities it was logical to have pursued the synthetic routes that were chosen.

A study of the literature showed that compound (XV), diphenide, had previously been prepared by one of three methods:

1. The intramolecular Cannizzaro reaction of 2,2'-diphenyl-dialdehyde^{32,33,38}
2. The reduction of diphenic acid with lithium aluminum hydride³⁷
3. The reduction with sodium borohydride of the ester-acid chloride or diacid chloride of diphenic acid.³²

Method 1 was not used since the dialdehyde was not available commercially and since its synthesis would involve the use of ozone for the ozonolysis of phenanthrene. At that time it was felt that the use of ozone would present a safety hazard that could be avoided by the use of an alternate route.

Method 2 was rejected since the reaction at best would involve a degree of statistics and could possibly involve the ultimate separation of three different products.

As reported in the experimental section method 3 did not pro-

duce the desired results. Scrupulously purified materials and reduction times of 0.2 hour, 2 hours and 24 hours were all employed without success.

The use of lithium borohydride (or diborane) to selectively reduce an ester in the presence of a carboxylic acid (or a carboxylic acid in the presence of an ester in the case of diborane) has been employed in the synthesis of (R) and (S)-mevalanolactone.^{43,44} Surprisingly, application of these procedures in this problem did not, however, give the desired results. No attempt was made to study further these attempted reductions beyond what is reported here.

The use of lithium triethylborohydride provided a clean and fast route to the desired diphenide and may well be the method of choice for the selective reduction of acid-esters. The reduction reaction and subsequent purification steps took from 6 to 8 hours and produced diphenide in a yield of 97 % and high purity. Lithium triethylborohydride is sold under the name Super-Hydride by Aldrich Chemical Company.

Subsequent steps leading to the appropriate bridged biphenyls were straightforward and readily accomplished by means already published.^{22,27}

NMR Results

The use of NMR as a tool in the study of conformational changes of molecules has enjoyed much success. By its usage coupled with line shape analysis rate constants for many conformational changes may be determined.^{45,46,47,48,49}

The large difficulty in using this procedure, however, is the choice of the nature of the spin system and the subsequent mathematical treatment of the experimental data. Since the theoretical quantum-mechanical treatment of Alexander's^{50,51} work involving an AB spin system is beyond the present ability of this author it was used without question as is. This method was employed by Quarfoot²⁷ in his study of the same non-deuterated bridged biphenyl system. This method relates the average residence time τ of the system to the experimental values of the coupling constant J_{AB} , the chemical shift difference δ_{AB} , and the line widths at half-height ω . The value of the line width at half height ω_0 is obtained at a temperature where exchange is essentially non-existent.

Using Alexander's formulation, at low temperatures where exchange is slow the average residence time can be found by application of the equation

$$\tau = \frac{1 \pm J_{AB} / \sqrt{\delta_{AB}^2 + J_{AB}^2}}{\pi (\omega - \omega_0)} \quad (1)$$

As the temperature is increased the exchanging becomes more rapid

and, at the point where a broad singlet is formed, τ_c can be found by use of the equation

$$\tau_c = \frac{\sqrt{2}}{\pi \sqrt{\delta_{AB}^2 + 6J_{AB}^2}} \quad (2)$$

This equation, however, is valid only if the line width at half-height in the absence of exchange is negligible compared to the line width at coalescence.^{52,53} Use of this equation involves a systematic error due to approximations used in its derivation.⁵⁴

Above the temperature of coalescence the value of τ may be calculated using equation 3.^{53,55}

$$\tau = \frac{2(\omega - \omega_0)}{\pi \delta_{AB}^2} \quad (3)$$

A value of τ may then be easily transformed into a value of the rate constant for inversion by use of the simple expression²⁷

$$k_{INV} = 1/\tau \quad (4)$$

Since the rate constant for the inversion may be related to the free energy of activation by use of the Absolute Reaction Rate Theory the following relationship should hold true^{56,57,58}

$$k = \frac{K k_B T}{h} \exp\left(-\frac{\Delta G^\ddagger}{RT}\right) \quad (5)$$

Since $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$ (6)

$$k = \frac{K k_B T}{h} \exp\left(-\frac{\Delta H^\ddagger}{RT}\right) + \exp\left(-\frac{\Delta S^\ddagger}{R}\right) \quad (7)$$

In equations 5, 6 and 7 the following expressions are used: K is the transmission coefficient; k_B is Boltzmann's constant; T is the ab-

solute temperature; h is Planck's constant; ΔH^\ddagger is the enthalpy of activation; R is the gas constant; ΔS^\ddagger is the entropy of activation. Substituting known values into equation 7 gives rise to a new equation

$$\log_{10}\left(\frac{k}{T}\right) = 10.319 - \left(\frac{1}{T}\right)\left(\frac{\Delta H^\ddagger}{4.574}\right) + \left(\frac{\Delta S^\ddagger}{4.574}\right) \quad (8)$$

If the transmission coefficient has a value of unity then a plot of $\log_{10}(k/T)$ versus $1/T$ will have as its slope $-\Delta H^\ddagger/4.574$ and its y-intercept $10.319 + \Delta S^\ddagger/4.574$.

The values experimentally obtained in the temperature dependent NMR studies of compounds (VII) and (VIII) are listed in Tables I and II. Figures I and II are graphings of these values using equation 8. The least squares regression analysis program ACTENG was used.⁵⁹ All errors in values were obtained by assuming the largest possible errors of the instrument used.

As would be expected the intensities of the signals for the four benzylic protons of the non-deuterated compound (VII) are essentially twice the intensities of the signals for the two benzylic protons of the deuterated compound (VIII). Both compounds showed very similar spectral patterns at corresponding temperatures with regard to each of the other signals. However, some interesting aspects of the spectra were noted.

Quarfoot, in his studies of the non-deuterated compound (VII), observed that the relative inner/outer ratio of peak intensities of the benzylic proton signals were quite different between the experimental and the calculated values. In a chloroform solution he found the experimental/calculated ratio to be 1.58 and referred to similar

TABLE 1.

NMR Data of Compound (VII)
(Benzylic Protons)

Temperature	Line Frequencies (Hz)	ω (Hz)	ω_o (Hz)	k
-30.1°	1028.85 1042.19 1170.05 1183.37	5.63	4.24	2.92
-15.1°	1032.37 1045.72 1166.72 1180.07	5.97	3.30	3.15
-4.9°	1031.47 1044.76 1165.88 1179.18	7.75	3.15	9.58
+0.1°	1031.47 1044.76 1165.65 1178.87	9.14	3.30	12.50
+24.9°	1049.60 1163.89	45.84	2.14	91.04
+40.3°	1095.13	74.91	1.34	153.27

$$\Delta H_{INV}^{\ddagger} = 9.02 \text{ kcal mol}^{-1} \quad \text{Std. dev.} = 1.14 \text{ kcal mol}^{-1}$$

$$\Delta S_{INV}^{\ddagger} = -19.91 \text{ e.u.} \quad \text{Std. dev.} = 3.05 \text{ e. u.}$$

TABLE 2..

NMR Data of Compound (VIII)
(Benzylic Protons)

Temperature	Line Frequencies (Hz)	ω (Hz)	ω_o (Hz)	k
-30.1°	1029.00	5.85	4.83	2.13
	1042.34			
	1170.17			
	1183.51			
-15.1°	1031.66	6.15	3.45	5.63
	1045.01			
	1170.17			
	1183.51			
+0.1°	1031.36	9.01	2.11	14.29
	1044.74			
	1166.49			
	1179.86			
+24.0°	1049.94	58.13	1.80	117.65
	1160.04			
+40.1°	1101.97	78.02	1.20	161.29

$$\Delta H_{INV}^{\ddagger} = 9.42 \text{ kcal mol}^{-1} \quad \text{Std. dev.} = 0.79 \text{ kcal mol}^{-1}$$

$$\Delta S_{INV}^{\ddagger} = -18.12 \text{ e. u.} \quad \text{Std. dev.} = 1.80 \text{ e. u.}$$

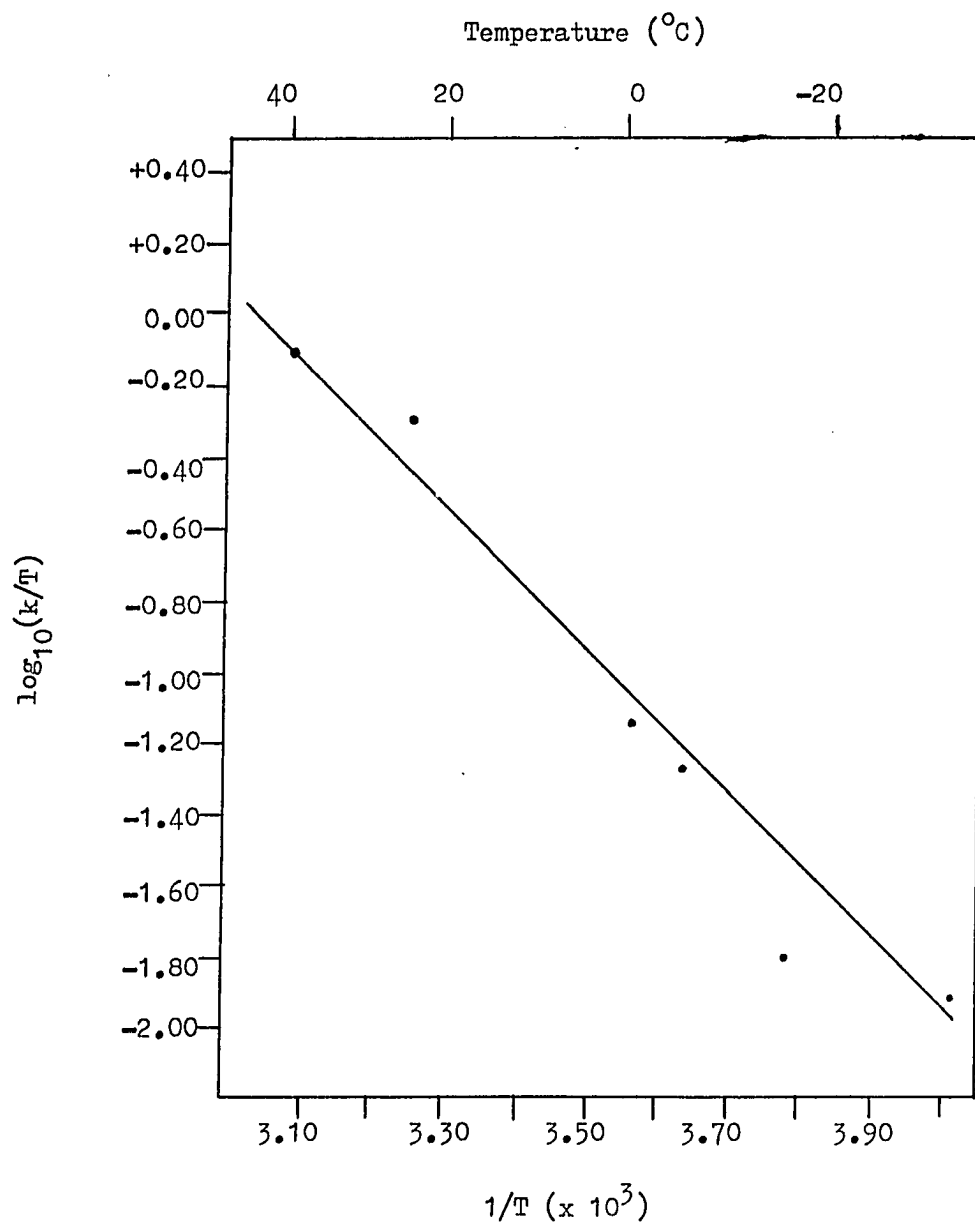


Figure 1.

NMR Kinetic Data of Compound VII

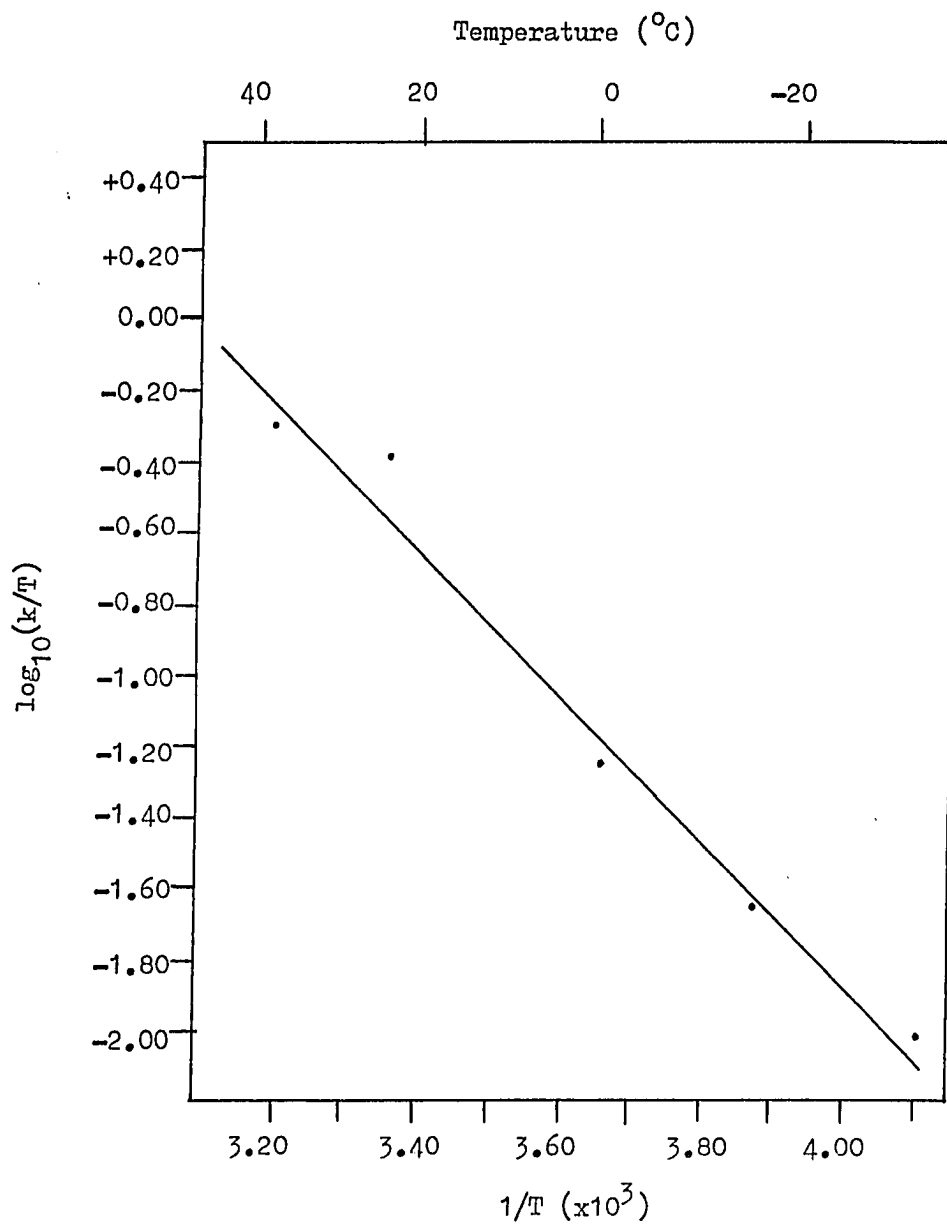


Figure 2.

NMR Kinetic Data of Compound VIII

correlations in the literature.⁶⁰ In the present study, however, it was observed that the experimental inner/outer peak intensity ratio had a consistent value of approximately 1.22 and that this value corresponded well with the calculated value of 1.23.

This value of 1.23 also corresponds well to that expected from an AB spin system. As an example, for compound (VII) at -15.1° , the ratio of the intensities of the stronger inner peaks to the intensities of the weaker outer peaks has a value of $2.81/2.31 = 1.22$. The value of the ratio of the separation of the inner peaks to the separation of the outer peaks is $121.00 \text{ Hz} / 147.70 \text{ Hz} = 0.82$ which is consistent with an AB spin system. The spectra then, at least at low temperatures, indicate an AB spin system is involved.

With regards to the aromatic portion of the spectra there is an observable increase in the complexity of the signal with increasing temperature. These signals for compound (VIII) are shown in Figure III for temperatures shown. The increasing rate of rotation about the pivot bond would understandably give rise to the observed rise in spectral complexity.

One distinct difference from that of the study of Quarfoot²⁷ involves the temperature at which coalescence of the benzylic proton signals occur. Quarfoot first observed the appearance of a doublet from a quartet at a temperature of 0.0° . In this study the compound still exhibited a quartet at 0.1° . At a temperature of 15.6° Quarfoot observed that a singlet had formed while in this study at 24.9° the doublet was still observed. In his studies Quarfoot accurately determined the temperature of coalescence by repeated experiments at different tempera-

tures.. This was not done in this study and therefore values obtained using equations (2) and (3) were not used in this study.

No evidence was seen that would demonstrate long range coupling between the 4 and 5 or the 7 and 8 protons. The temperature dependent study of the other compounds (IX), (X) and (XI) was not possible due to limitations of time and funds. In Figures I and II the values calculated using equation (2) are enclosed in a square while those values calculated using equation (3) are enclosed in a circle.

It is obvious from these figures, then, that a discontinuity exists when the different equations (1), (2) or (3) are used to calculate τ . As mentioned earlier assumptions made during their derivations are the probable cause of these discrepancies.⁵⁴ Scattering of the data about the individual lines may be due not only to instrumental error but also due to factors such as change in the viscosity of the solutions or the degree of solvation and/or pressure within the NMR tube.²⁷ Since a molecule with an inversion energy of less than 20 kcal mol⁻¹ would not be expected to be optically stable enough to be isolated in one of its antipodes, the use of NMR in this technique is seriously questionable. Since the molecule appears to exhibit an $AB \rightarrow AA'BB' \rightarrow A_4$ transformation in the spin system observed the choice of treatment solely as an AB spin system cannot be a correct one. Carter²⁸ has shown that the system cannot be treated as an $AA'BB'$ system either. It is reasonable then that the system must be treated as a complex changing system. Such a system could not be found in the literature and is beyond the present ability of this author to develop.

TABLE 3.

Values of ΔH^\ddagger and ΔS^\ddagger for
Compounds (VII) and (VIII)

Compound (VII):

Quarfoot²⁷ $\Delta H^\ddagger = 9.66 \text{ kcal mol}^{-1}$
 $\Delta S^\ddagger = -18.56 \text{ e.u.}$

Carter²⁸ $\Delta H^\ddagger = 11.3 \text{ kcal mol}^{-1}$
 $\Delta S^\ddagger = 15.3 \text{ e.u.}$

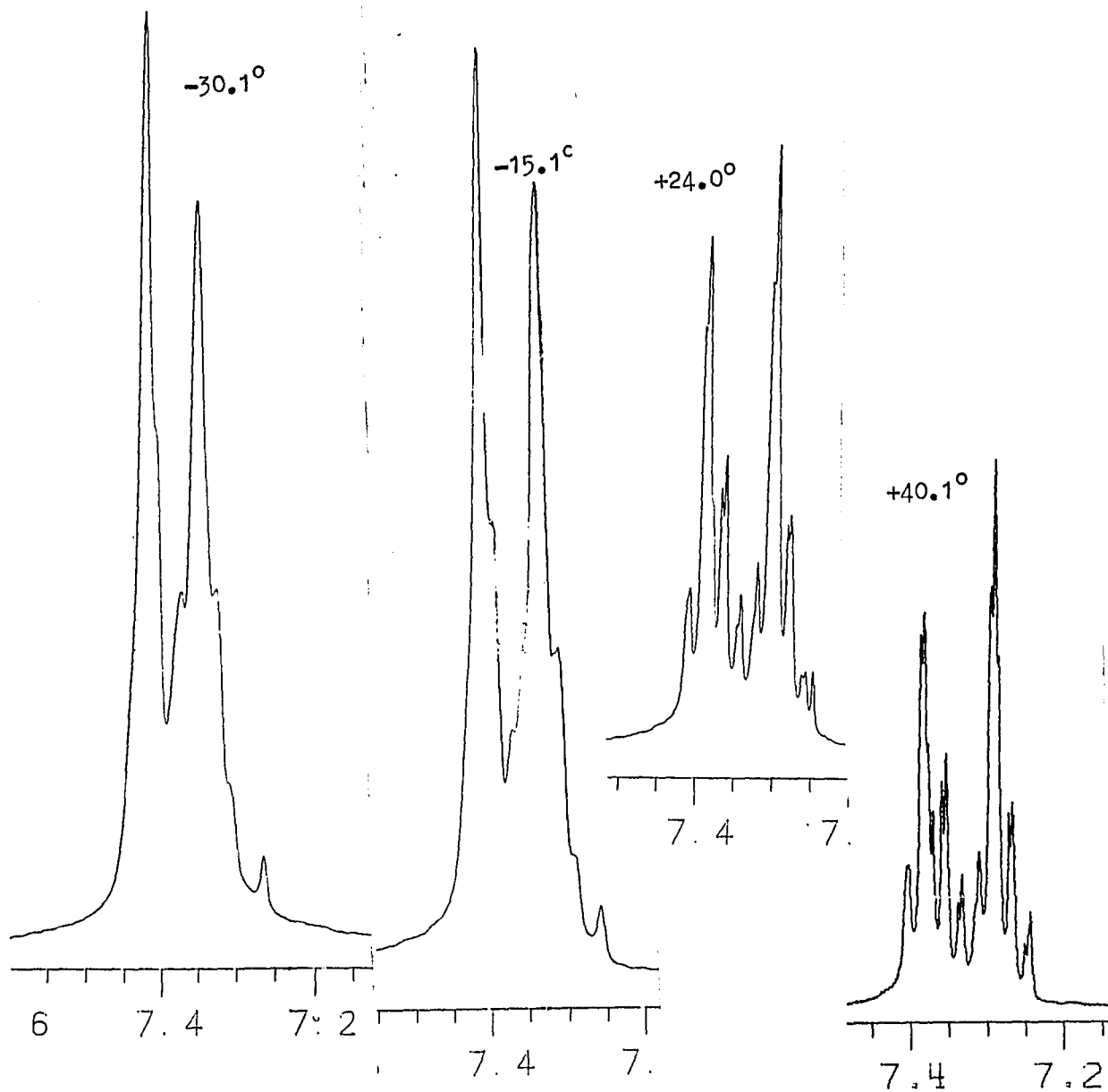
This study $\Delta H^\ddagger = 9.02 \text{ kcal mol}^{-1}$
 $\Delta S^\ddagger = -19.91 \text{ e.u.}$

Compound (VIII):

This study $\Delta H^\ddagger = 9.42 \text{ kcal mol}^{-1}$
 $\Delta S^\ddagger = -18.12 \text{ e.u.}$

FIGURE 3.

NMR Spectra of the Aromatic Protons of Compound (VIII)
Intensities are not related.



SUMMARY

The kinetics of conformational inversion of (+)-6,6-dicarbethoxy-dibenzo-[a,c]-[1,3]-cycloheptadiene and of its 5,5-dideuterated analog were studied using variable temperature NMR techniques. Recording the spectra on a Nicolet NMC-360 wide bore spectrometer the resulting data were treated as an AB spin system. Values obtained for the free energy of activation for inversion were $9.02 \text{ kcal mol}^{-1}$ for the parent compound and $9.42 \text{ kcal mol}^{-1}$ for the 5,5-dideuterated analog. Values obtained for the entropy of activation were -19.91 e. u. and -18.12 e.u. respectively.

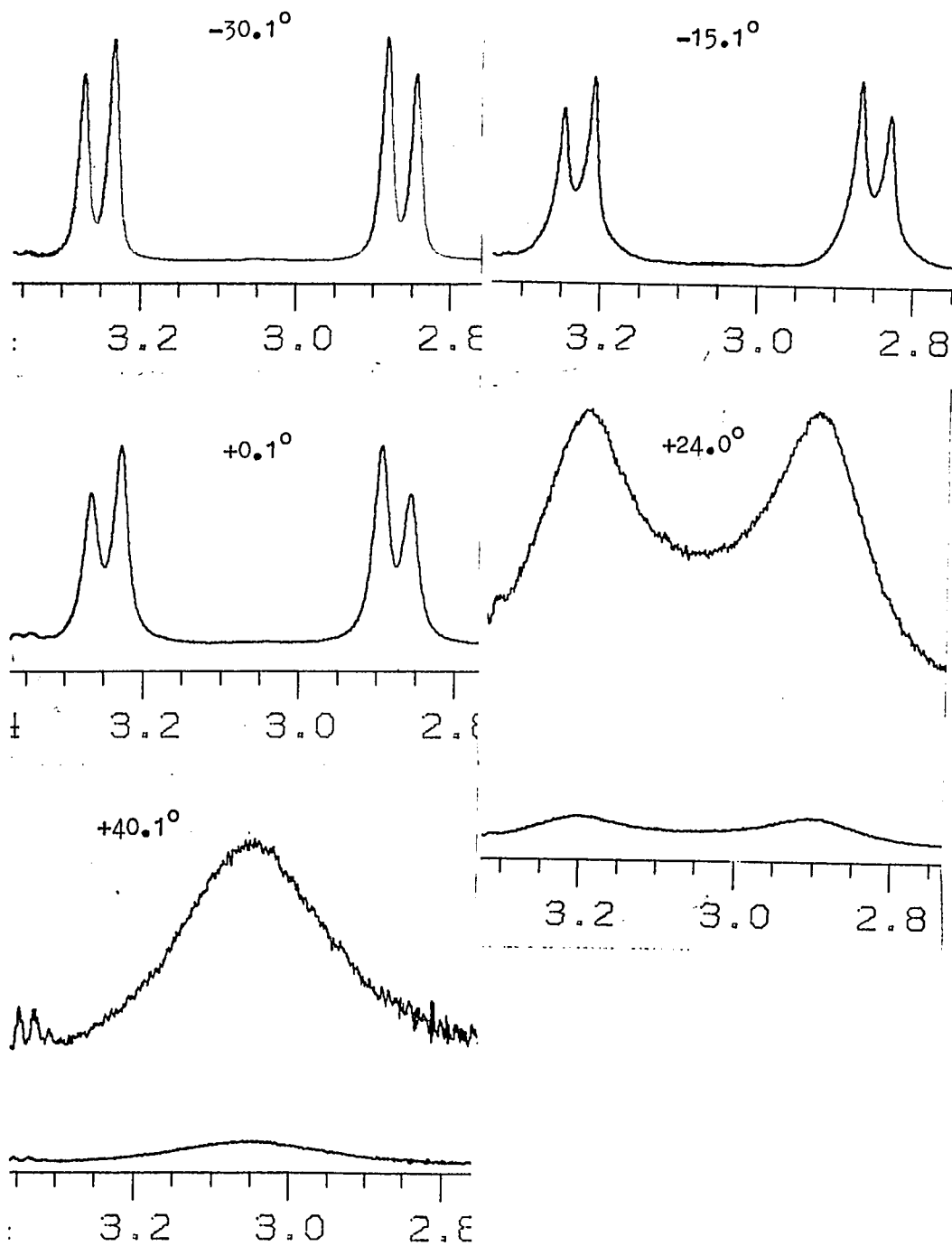
The spectra demonstrated a definite AB spin system at lower temperatures by means of a study of the inner/outer peak heights. It was concluded that since the spectra over all temperatures studied demonstrate a more complex spin system than that of a simple AB spin system that the use of NMR in this study is not a correct one at present.

The 4,8-dideutero, 4,5,5,8-tetradeutero and 5,5,7,7-tetradeutero analogs of the parent compound were also synthesized. The synthetic routes chosen involved the synthesis of 19 previously unreported compounds and the synthesis of diphenide in a greatly improved yield is also described.

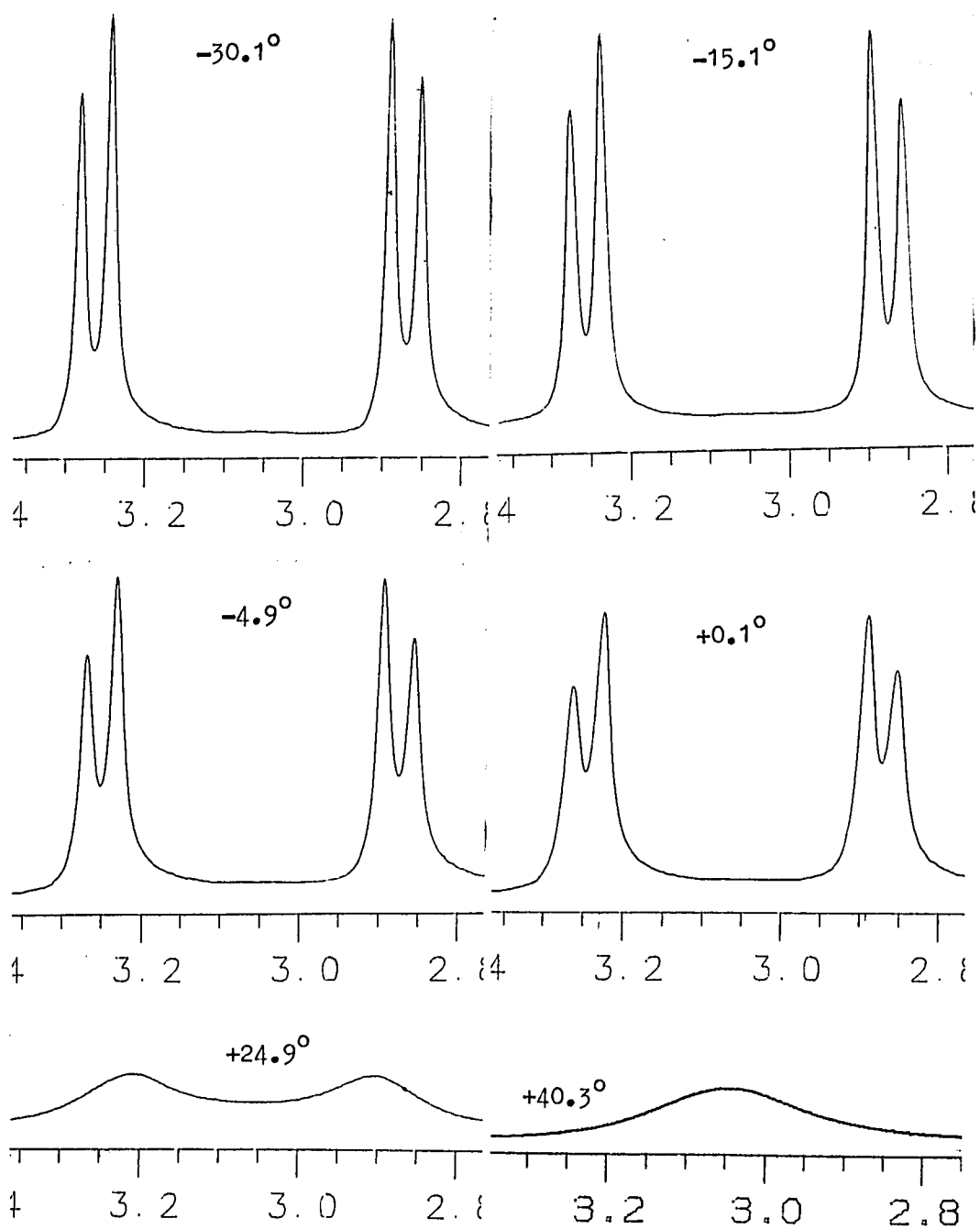
APPENDIX

NMR Spectra of the benzylic protons of Compound VIII

Amplitudes are not relative.



NMR Spectra of the benzylic protons of Compound VII
Amplitudes are not relative.



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