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Substituent Effects on Chemical Shifts and Geminal Coupling Constants of Benzylic Protons.

by

Roger N. Renaud

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University of Ottawa.

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Roger N. Renaud
Candidate

R.R. Fraser
Associate Professor in Chemistry
Research Director

PREFACE

The elucidation and confirmation of the structures of organic compounds have been a constant problem in organic chemistry. Recently, the improvement of already known physical methods of analysis and the development of new ones have made this task much easier. Modern ultraviolet and infrared spectrometers have contributed a great deal to this task. In the last few years, the technique of mass spectrometry has developed to the extent that it has become an important method of structural analysis. However, to-day nuclear magnetic resonance spectroscopy is probably the most important of the existing spectroscopic methods. In addition to its use for the determination of molecular structures, it is also used to investigate such phenomena as stereoisomerism, tautomeric equilibrium, relaxation processes, reaction rates, hydrogen bonding and complex formation.

The subject of this thesis is an investigation of the potential use of nuclear magnetic resonance in one small area of conformational analysis, specifically to elucidate the conformation of benzylic protons in compounds of the general formula $X-C_6H_4-CH_2-Z$. To this end we have examined the effects of various substituents X on both the chemical shifts and the geminal coupling constants in the methylene groups of four series of molecules containing different Z groups.

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ABSTRACT

Four series of rigid molecules were synthesized, namely, 6-substituted-phthalides, 5-substituted-3-phenylphthalans, 2-substituted-5H-dibenzo[a,d]cycloheptenes and 2-substituted-10,11-epoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptenes. The nuclear magnetic resonance spectrum of each compound was measured and the benzylic proton absorptions analyzed. The chemical shifts, geminal coupling constants and in some cases the vicinal and the long range coupling constants obtained from these analyses were plotted against the Hammett σ values in each series. The ρ values obtained from these plots show that the chemical shifts of the benzylic protons depend partially on the conformation of the methylenic protons with respect to the benzene ring. Other factors also contribute to the observed ρ values. The ρ values for the geminal coupling constants depend entirely on the orientation of the two protons with respect to the benzene ring.

Evidence on the conformation of 10,11-epoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene was provided by variable temperature NMR measurements and an examination of Dreiding models. It is concluded that the epoxy group occupies a quasi-equatorial conformation. Assignments of configuration of the protons in position 5 with respect to the epoxy group in 2-methoxy-10,11-epoxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene were made from a determination of their intramolecular nuclear Overhauser effects.

INTRODUCTION

The observation of hyperfine structure in optical atomic spectra by Pauli (1) opened the way to a most important method of structural analysis. It was found that nuclei which possess a magnetic moment are space quantized in the presence of a magnetic field. Transitions between the various quantized states can be obtained by applying an r.f. magnetic field with a frequency equal to the energy separation of any two states. At the correct frequency one obtains a nuclear magnetic resonance (NMR) spectral line. The first nuclear resonance effect was observed in 1945 by Purcell, Torrey and Pound (2) in detecting hydrogen resonance absorption in paraffin wax, and by Bloch, Hansen and Packard (3) who observed the hydrogen resonance in water. However, the most important discovery for practical purposes of NMR was made (4,5,6,7) when it was observed that the resonance position for a given nucleus depends on its chemical environment; in other words, a nucleus, behaving essentially as a magnetic probe, can be used to investigate local magnetic effects inside a molecular system. As the local magnetic field near a particular nucleus depends on its chemical environment, this effect was given the name of "chemical shift".

A second important property of nuclear magnetic resonance spectra is that the strength of any given signal depends on the number of equivalent nuclei in the compound under examination and is independent of the nature of chemical environment.

A third parameter of importance is the fine structure associated with individual resonances. This was first observed by Proctor and Yu (8) for ^{121}Sb resonance in $NaSbF_6$. Also Gutowsky and McCall (9) showed that fine structure may arise in any molecule containing two or more nuclei which resonate at different field strengths. In the case of nuclei of different isotopic species or having different chemical shifts, equally spaced multiplet lines may be obtained from mutual interactions between the different nuclei within the same molecule. The magnitude of the splitting is known as the "coupling constant" or, more completely, as the "electron coupled nuclear spin-spin interaction constant".

Therefore, an NMR spectrum can give very important information about the structure of a molecule. The power of the method is largely due to the fact that three different parameters (the chemical shift, the signal intensity and the spin-spin splitting)all contribute directly to the structure determining process. The parameters will be discussed separately.

The Chemical Shift

A nucleus within a molecule is surrounded by its valence electrons, as a result of which the actual field H at any nucleus is not the same as the applied field H_o. Therefore, the effective field is given by

$$H_{eff} = H_o(1-\sigma) \qquad (1)$$

where σ is the screening constant which depends only on the electronic environment. The degree of screening determines the amount by which the applied field has to be increased to reach the correct field H at the nucleus which will satisfy the resonance condition

$$\nu = \frac{\gamma H}{2\pi} \qquad (2)$$

Theoretical calculations of the screening constant were first made by Lamb (10) who estimated the diamagnetic shielding of a nucleus possessing a spherical electron distribution. However, the expression derived by Lamb cannot be used for the calculation of a screening constant of a nucleus in a polyatomic molecule since the electron density no longer has spherical symmetry.

Ramsey (11) derived an expression for σ in the case of an isolated molecule. The expression can be divided in two general terms. The first term,which is similar to the Lamb formula and gives a positive contribution to the shielding coefficient, is called the diamagnetic term. The second term gives a negative contribution to the shielding coefficient and is called the paramagnetic term. The calculation of σ from the Ramsey equation is not generally possible since the evaluation of the second term requires a knowledge of excited state wave-functions.

Saika and Slichter (12) have proposed a division of σ into local contributions to the different terms in Ramsey equation, which is represented as follows:

$$\sigma = \sigma_d+\sigma_p+\sigma_o \tag{3}$$

where σ_d is the diamagnetic shielding of the nucleus, which is proportional to the magnetic field produced at the nucleus by the moment induced through the rotation of the electrons about the nucleus, σ_p is the paramagnetic shielding, which arises from the hindrance to the Larmor precession produced by the lack of symmetry within the molecule, and σ_o is the combined effect of diamagnetic and paramagnetic atomic currents on other atoms.

The division proposed by Saika and Slichter does not take account of the possible effects of interatomic currents in which electrons flow from one atom to another. For instance, this effect can be very important in aromatic compounds.

In the case of a proton, the situation is unique in that the proton does not have any low-energy excited states. Therefore, the paramagnetic term is less important than for other nuclei. Furthermore, the total electron density at a hydrogen is so small that circulations in other parts of the molecule can have great significance. For example, the low-field shifts of the ring protons in aromatic systems and the high-field shifts of acetylenic protons arise from the effect of σ_p and σ_d respectively. Electronic perturbations arising at a proton are numerous and are still not all known. They can be summarized as follows.

1. The electrical charge of the nucleus in question: this charge can arise from hybridization, inductive and mesomeric effects. It is generally known that the chemical shift of a proton is proportional to the density of π electrons (14,15,16,17).

2. Anisotropy due to the neighboring electronic system (σ or π bonds): the effect of a σ bond (13) is much less important than the effect due to a π bond. Generally speaking, atoms such as N, O, S or groups such as C=O, C=C, C≡N, N→O, NO_2 or the current due to an aromatic ring are the main contributors.

3. Neighboring electronic charge effects: Buckingham (18) has presented a theoretical development of a formula relating the screening constant of a proton and the electrical field E of the system.

4. Intermolecular effects: hydrogen bonding (19,20), van der Waals forces (21) and solvent effects are included in this category. Generally, the most important of the intermolecular effects is the contribution due to the solvent, since usually NMR spectra are obtained in solutions. The solvent contribution may be subdivided as follows (22):

$$\sigma_{solvent} = \sigma_b+\sigma_a+\sigma_w+\sigma_E+\sigma_H \qquad (4)$$

where σ_b is proportional to the bulk magnetic susceptibility of the medium, σ_a is the anisotropy in the magnetic susceptibility of the solvent molecules, σ_w is the van der Waals forces between the solute and the solvent, σ_E is the polar effect of neighboring solvent molecules, and σ_H is the hydrogen bond interaction between the solute and the solvent molecules.

Due to the multiplicity of intramolecular and intermolecular phenomena to which the screening of a proton is very sensitive, care must be taken before attributing observed shifts to any of these effects (23).

Signal Intensity

The intensities of well separated signals are a direct measure of the relative number of nuclei contributing to the signals. This is of considerable importance in chemical-structure identification and quantitative analysis. Intensities can be estimated either by area measurements or measurements of peak heights, however, it is generally preferable to use area measurements since the area is less critically dependent on the rf power (H_1). Indeed, as H_1 is increased, the area tends to become constant, whereas the peak height approaches zero. The intensity of the bands can be measured with respect to one another in the same sample or referred to a standard. For this latter purpose, the entire spectrometer must have adequate stability, linearity and reproducibility; measurements have to be made at the same radiofrequency.

Proton-Proton Coupling

The nucleus possesses a spin I and a quantized angular momentum $\frac{h}{2\pi}\sqrt{I(I+1)}$. If a group of such nuclei is placed in proximity, their spins may interact so that different combinations of the allowed spin-states differ in total energy.

A suitable theory has been developed by Ramsay (24) in which the indirect coupling between two nuclei, N and N', is written as the sum of three terms.

$$J_{NN'} = J_{NN'}(1) + J_{NN'}(2) + J_{NN'}(3) \qquad (5)$$

$J_{NN'}(1)$ arises from the interaction of the orbital electronic currents with the nuclear magnetic moments. $J_{NN'}(2)$ is due to dipole-dipole interaction between the nuclear magnetic moments and the spins of the electrons which are not in the S-states. $J_{NN'}(3)$ is similar to a term introduced by Fermi (25) to account for the hyperfine structure in atomic spectra. It is due to the interaction between the spins of the electrons in the S-states and the nuclear magnetic moments. It is sometimes referred to as the "contact term" since it depends on the properties of the electrons at the nucleus. Since $J_{NN'}(1)$ and $J_{NN'}(2)$ are relatively small for most molecules, the major contribution arises from $J_{NN'}(3)$. An important feature of the above breakdown of indirect nuclear spin-spin coupling constants is that all the terms are proportional to the product of the magnetogyric ratios of the two nuclei ($\gamma_N\gamma_{N'}$).

For two nuclei, N and N', separated by n bonds, the coupling constants is often symbolized as $^{n}J_{NN'}$. It is therefore convenient to divide proton-proton coupling constants into three categories:

1. Geminal couplings or the spin-spin interaction between protons attached to the same atom.

2. Vicinal couplings or the spin-spin interaction between protons attached to contiguous atoms, i.e., across three bonds (H-C-C-H or H-C=C-H).

3. Long range couplings or the spin-spin interaction across four or more bonds.

Geminal Proton-Proton Coupling Constants ($^{2}J_{HH}$).

The first detailed theory of geminal proton-proton coupling was based on valence bond calculations (26). This theory predicted a positive coupling constant in methane and a dependence of the coupling on the $\overset{\curvearrowright}{H \diagdown C \diagup H}$ angle, with the coupling decreasing as the angle increased from 109° 28' in methane to 120° in ethylene. This was in reasonable agreement with the available data at that time. However, when the sign of the coupling constant in a saturated CH_2 fragment was shown conclusively to be negative, these ideas were no longer tenable.

Recently a molecular orbital theory was developed for these couplings (27). Even though the accuracy of the calculations is uncertain, the qualitative predictions are of great use. These predictions are:

1. Increasing the $\overset{\rightarrow}{\mathrm{H}\diagdown_{\mathrm{C}}\diagup\mathrm{H}}$ angle increases the S character of the orbitals and this gives a positive contribution to the coupling. This interaction predicts that the coupling would become more positive as the $\overset{\rightarrow}{\mathrm{H}\diagdown_{\mathrm{C}}\diagup\mathrm{H}}$ angle increases from methane to ethylene. Furthermore, in small ring compounds the $\overset{\leftrightarrow}{\mathrm{H}\diagdown_{\mathrm{C}}\diagup\mathrm{H}}$ angles are also larger than the tetrahedral value, and again the coupling should become more positive, which is precisely what is observed.

2. A substituent which withdraws electrons at the α-position to the CH_2 group will give a positive contribution to the geminal coupling constant. A positive coupling in formaldehyde was predicted by the theory and verified experimentally shortly after (27).

3. A substituent which withdraws electrons at the β-position to the CH_2 group will give a negative contribution to the geminal coupling constant.

4. A π-electron system next to a CH_2 group will generally give a negative contribution to the geminal coupling constant. Both valence bond and molecular orbital calculations indicate this shift to be greatest when the H-H axis is perpendicular to the nodal plane of the π-electrons (28). Many examples of this effect are available in a review article (29).

Vicinal Proton-Proton Coupling Constants ($^3J_{HH}$)

A theory of vicinal proton-proton coupling was developed by Karplus (30,31,32) using a valence-bond approach. The four conclusions which emerged are:

1. The vicinal coupling depends on the dihedral angle ϕ (32) between the two C-H bonds and is expressed by

$$^3J_{HH} = A + B \cos \phi + C \cos 2\phi \qquad (6)$$

with $A \approx 4.22$ c/s, $B \approx -0.5$ c/s and $C \approx 4.5$ c/s for a C-C bond between two sp^3 carbons. Therefore, the coupling will be small when $\phi = 90°$ and large when $\phi = 0°$ and $180°$.

2. The electronegativity of a neighboring substituent causes a perturbation which modified the hybridization on a carbon atom. For $CH_2 = CHX$, the electronegativity effect of a substituent is given by

$$^3J_{cis\ HH} = J_o(1 - 0.60\ \Delta X) \qquad (7)$$

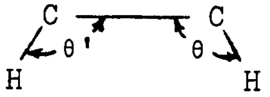
$$^3J_{trans\ HH} = J_o(1 - 0.25\ \Delta X) \qquad (8)$$

and for CH_3CH_2X, the expression is

$$^3J_{HH} = J_o\ (1 - 0.07\ \Delta X) \qquad (9)$$

where ΔX is the electronegativity difference between the substituent and the hydrogen and J_o represents $^3J_{HH}$ for ethane itself.

3. The coefficients in equation (6) are modified when there is a change in the H-C-C bond angles θ and θ'



$$A \sim 4.22 - 0.10\,(\theta + \theta' - 220)$$

$$B \sim 0.5 \;\; - 0.05\,(\theta + \theta' - 220)$$

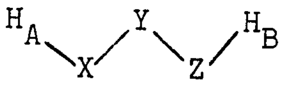
$$C \sim 4.5 \;\; - 0.12\,(\theta + \theta' - 220)$$

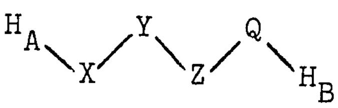
Therefore, ${}^3J_{HH}$ decreases as the angles increase.

4. The vicinal coupling decreases as the C-C bond length increases.

It is in fact impossible to separate these factors since they are not completely independent. A change in the hybridization on a carbon atom leads necessarily to changes in bond angles, bond lengths and dihedral angles.

Long Range Proton-Proton Coupling Constants

Coupling across more than three bonds is generally designated as "long range coupling". Both experimental data (33,34,35) and theoretical considerations (33,34,36) suggest strongly that significant spin-spin interactions across more than three bonds are confined to certain arrangements of nuclei and bonds. Protons separated by four bonds (34) or five bonds (34,37) in a planar zig-zag arrangement, usually referred to as 

or 

configuration where X, Y, Z and Q can be C=C, C=O, O or N, are generally appreciably coupled regardless of the nature and hybridization of the intervening atoms. Important long range couplings have also been observed in acetylenes, allenes and cumulenes (34).

Double Resonance

Although the method of double resonance is only one of many special techniques used in NMR, it has proven to be important in the work that follows. For this reason a brief review is given here.

The widest application of double resonance technique is to simplify the measurement of complicated spectra. The aim is to remove the effect of undesirable spin coupling by the application of a second rf field H_2 in addition to the field used for observation, generally referred to as H_1. This second field disturbs one group of nuclei and leads to saturation of their energy levels so that they become effectively decoupled from the remaining nuclei. This technique was developed by Bloch (38), Royden (39) and Bloom (40).

Double-irradiation has various applications which are usually classified according to the strength of the field H_2. With a large amplitude of the field H_2, studies of chemical shifts can be made on complicated spectra. The correct assignment of spin-spin coupling can be established by selective decoupling of given nuclei and by noting the collapse of other spin multiplets. It is possible to use double resonance to measure the chemical shifts of protons that are obscured by overlapping features either from other protons in the molecule or by solvent resonance. The proton that is obscured must be coupled to other protons whose resonances are observable. Broadening of lines can also be removed by this technique.

Spin-decoupling by double irradiation is suited for the determination of the signs of coupling constants. The method is relatively simple for weakly coupled spin systems such as APX, however, this method is not applicable with strongly coupled systems where there is mixing between different product spin functions. Freeman and Anderson (41) have shown that application of a weak second radiofrequency field H_2 provides information of the ordering of energy levels and relative signs of coupling constants. This weak field can be described as double resonance since no spin decoupling occur but only a perturbation in the spin system. It was found that the frequency sweep technique of recording has advantages over the field sweep technique with low values of H_2. Thus ω_2 remains on resonance for a particular line or group of lines being perturbed, while ω_1 is swept to record the spectrum. Many strongly coupled systems were resolved by this technique such as AB, ABC systems. Even hidden or weak signals are detectable by this method.

Nuclear Overhauser Effect

In addition to the normal enhancement of the signal intensity due to the collapse of a multiplet in the presence of a second rf field, a further enhancement by several fold is sometimes observed because of a nuclear Overhauser effect (42). It was shown by Bloembergen (43) and by Abragam (44) that the main source of spin-lattice relaxation T_1 with most organic compounds is the direct intramolecular dipole-dipole interaction mechanism in the absence of paramagnetic species and in a magnetically inert solvent. The intramolecular relaxation between two nuclei A and B is given by

$$\frac{1}{T_1{}^{AB}} = \frac{\hbar^2 \gamma_A{}^2 \gamma_B{}^2 \tau}{d^6} \qquad (10)$$

where $T_1{}^{AB}$ is the contribution to T_1 for nuclei A or B, τ is the correlation time for random molecular rotation, d is the internuclear distance between A and B, and the other symbols have their usual significance.

If several nuclei are present, the contribution to T_1 is the sum of all the nuclear dipole-dipole interactions:

$$\frac{1}{T_1{}^{A}} = \frac{1}{T_1{}^{AB}} + \frac{1}{T_1{}^{AC}} \cdots\cdot \qquad (11)$$

If A and B are both protons, a maximum of 50% enhancement of the A nuclei signal intensity can be observed on irradiation of B nuclei if only B nuclei are contributing to the relaxation of A nuclei. If other nuclei contribute also to the relaxation of A nuclei, then the effect will be less.

The intramolecular nuclear Overhauser effect has been shown by Anet and Bourn (45) to have a great potential in stereochemical and conformational problems since the effect of relaxation of one nucleus on another is strongly dependent on the distance between these nuclei.

Correlation between δ and Hammett σ values

Many attempts have been made to correlate chemical shifts within a series of similar compounds with specific substituent properties such as electronegativity (46,47), dipole moment (48) and Hammett σ constants (46). In this thesis only the correlation between the effect of substituents on the chemical shift (abbreviated to SCS) of benzylic protons and the Hammett sigma values of the substituents at the para position will be discussed.

Spiesecke and Schneider (46) have treated critically the extent to which a correlation of this type can be used for monosubstituted benzenes. Hammett σ constants are derived from kinetic data and would be expected to be related to the change in electron distribution on formation of a transition state rather than just to some property of an unperturbed ground-state molecule. Furthermore, these constants are obtained using disubstituted benzenes and would therefore not be strictly applicable to the monosubstituted derivatives. Finally, other factors than the electron density around the nuclei contribute to the shielding of hydrogen i.e. diamagnetic, anisotropic and paramagnetic contributions. However, these contributions are not considered to correlate with chemical reactivity parameters.

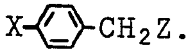
Despite these objections, it is observed that para-proton chemical shifts in monosubstituted benzenes show a fairly good linear correlation with the Hammett σ constants, whereas the meta-protons show a very poor correlation (46). The same type of correlation was also found on protons not directly bound to the aromatic ring. Klinck and Stothers (49) found a rough correlation between the chemical shifts of the formyl protons in a series of aromatic aldehydes and the corresponding Hammett σ constants. In addition, similar correlations have been observed for para-substituted phenols (50), anisoles (51), phenylacetylenes (52), toluenes (53), phenylbicycloheptenes (54), dihydrocinnamic acids (55), benzonorbornenes (56) and finally for the system $R-C_6H_4-T-H$ where T = 0, 1 or 2 atoms (57,58).

Several attempts have been made to interpret proton chemical shifts of substituted benzenes in terms of the inductive and resonance effects (59,60,61,62). The Π electron density distribution is altered by the resonance effect and this is relayed to the protons on the ring or in the side chain by polarization of the intervening sigma electrons. However, Dewar and coworkers (63,64,65) rejected the importance of the σ-inductive effect of the substituent at atoms separated by more than one bond from the atom to which the substituent is attached, and suggested that the long-range interactions are due to the field and the mesomeric (FM) effects. On the other hand, Wittstruck and Trachtenberg (55) examined the shifts of a series of cinnamic and dihydrocinnamic acids and observed that the contribution to the chemical shifts of side-chain hydrogen from the electric field is either zero or very small and, to a first approximation, the contribution from the anisotropy of the phenyl ring is independent of the nature of the substituents. They concluded therefore that perturbation in the chemical shifts of the β-protons are caused mainly by inductive and resonance effects rather than by electric field and magnetic field effects. Recently, Fraser and coworkers (66,67), while working on para-substituted benzyl derivatives of the type $X-C_6H_4-CH_2-Z$, found that the ρ derived from a $\tau = \rho\sigma$ correlation varied from -0.21 to +0.01 (Table I) depending on the nature of Z. The variation was attributed to the change in conformation of the methylenic protons with respect to the plane of the benzene ring. This conclusion was supported by the fact that the two methylene protons in a sulfoxide series ($Z = SOC_6H_5$) are magnetically non-equivalent and each proton has a different ρ value (figure 1).

The observed ρ values could not be explained according to the already mentioned effects. Therefore, it was concluded that either a hyperconjugative interaction between the benzylic hydrogen and the Π system of the aromatic ring or the paramagnetic shielding term in the Ramsay formula (68) is responsible for the variations in chemical shifts. Accordingly, the effect should be maximal when the benzylic C-H bond is colinear with the adjacent p orbital (a) and minimal when perpendicular to it (b).

Table I

Rho values of SCS-Hammett σ plots for



Z	$-\rho^a$	VdW^b	r^a	s^a	n^c
H	0.21	1.2	.926	.04	9
CH_3	0.20	1.5	.938	.03	9
CH_2COOH	0.20	-	.990	.01	4
COOH	0.18	-	.995	.01	4
CN	0.18	-	.937	.04	7
OH	0.20	1.4	.968	.03	6
$OCOCH_3$	0.17	1.4	.989	.01	5
OCH_3	0.15	1.4	.960	.02	6
OTHP	0.15;0.15	1.4	.960;.985	.01;.02	8
Cl	0.11	1.8	0.975	.01	5
$SOCH_3$	0.12;0.09	1.85	.943;.978	.02;.02	5
SO_2CH_3	0.16	1.85	.984	.02	5
SC_6H_5	0.07	1.85	.908	.02	5
SOC_6H_5	0.21;-0.01	1.85	.952;.810	.05;.01	5
$SO_2C_6H_5$	0.16	1.85	.984	.02	5
Br	0.01	1.95	.544	.02	5

[a] ρ, r and s represent the slope in p.p.m/σ, the correlation coefficient and the standard deviation as derived from a least squares treatment of the data (137).

[b] Values of the van der Waal's radius of the atom attached to the methylene group are quoted from reference 109.

[c] n is the number of compounds studied in each series.

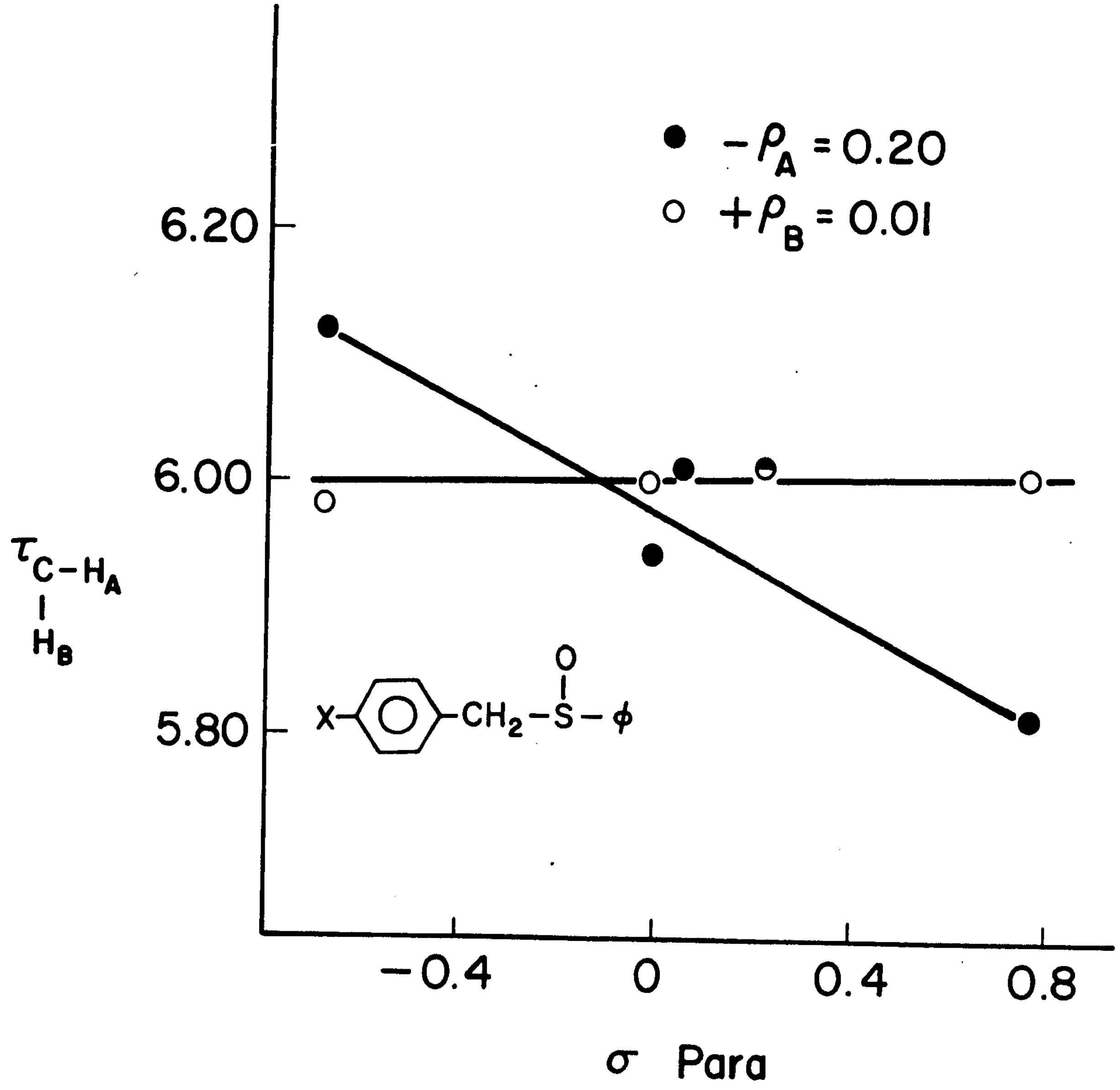
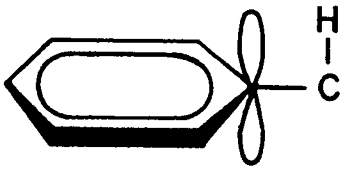
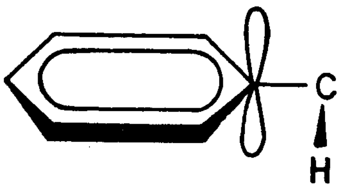


Figure 1. A Hammett plot of each diastereotopic proton shifts of *para*-substituted benzyl phenyl sulfoxides.



(a)



(b)

Correlation between $^2J_{HH}$ and Hammett σ values

The geminal coupling constants in the system $X-C_6H_4-CH_2-Z$ were demonstrated by two groups of workers (69,70) to follow a correlation with the Hammett σ values. The relationship between the geminal coupling constant and the σ value of the substituent X was expressed by the equation

$$\frac{J - J_o}{J_o} = \rho_G \sigma \qquad (12)$$

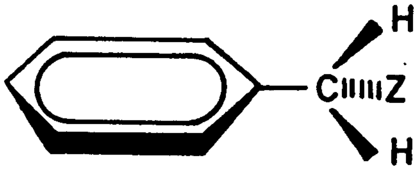
where J_o is the geminal coupling constant for the unsubstituted benzyl compound and ρ_G is the measure of the sensitivity of the ground-state property J to σ. Therefore, ρ_G values of -1.5 for <u>para</u>-substituted benzyl ether (69), -1.1 for dibenzylsulfites (71), 0.0 for toluenes (72,73) and 0.0 for benzylphenyl sulfoxides (69) were obtained. The effect was less for the <u>meta</u>-substituted series. From these results, the following conclusions were made (69).

1. $^2J_{HH}$ is more sensitive to the resonance effect than the inductive effect of the substituents (ρ values being greater for the <u>para</u>-substituted series than for the <u>meta</u>-substituted series).

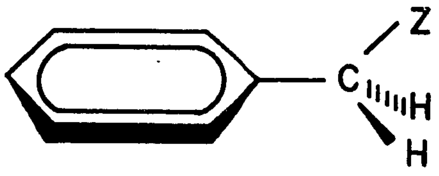
2. The change in $^2J_{HH}$ depends only on the electronic effect of the substituent, since it is known that the replacement of a hydrogen atom by a substituent at the para or the meta position does not increase the steric effect (74).

3. The direction of the effect of the substituent is in accord with its hyperconjugative effect.

4. The hyperconjugative effect is largest in conformation c̲ and zero in conformation d̲, an effect which was first predicted theoretically on the basis of molecular orbital theory (27) and valence bond theory (75).



(c)



(d)

The object of this thesis is to investigate the validity of these conclusions, especially the geometric dependence of the chemical shifts and the geminal coupling constants on the Hammett σ values using rigid molecules of known stereochemistry. The models chosen are 6-substituted-phthalides, 5-substituted-3-phenylphthalans, 2-substituted-5H-dibenzo[a,d] cycloheptenes and 2-substituted-10,11-epoxy-10,11-dihydro-5H-dibenzo[a,d] cycloheptenes.

Synthetic Scheme

The synthesis of complex molecules demands a great deal of planning which not only includes the starting and the final compounds but also all the possible intermediates and the different reagents involved in the complete synthesis. This can be achieved with a basic knowledge of the available reactions, the relative reactivities of the different substituents, the stabilities of the intermediates, the mechanisms of many reactions and, very often, the stereospecificity of the reactions. Even though a good knowledge of chemistry is important, some basic rules must be followed before attacking any synthetic problem. Corey (76) has proposed a few important considerations which are summarized as follows:

1. The desired molecule must be dissected in a way that the individual units can be reunified by simple reactions.

2. A logical selection must be made among all the possible routes by rejection of the least promising ones.

3. The starting material must be relatively cheap and readily available.

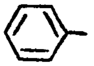
4. Proper control groups must be used to prevent undesirable reactions and to direct newly introduced units.

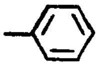
5. Known chemical reactions must be used whenever possible, unless a new one greatly simplifies the synthetic process.

6. Above all, the reactions must be as short and simple as possible.

These recommendations, when applied to the synthesis of a series of *para*-substituted aromatic compounds, should simplify the problem.

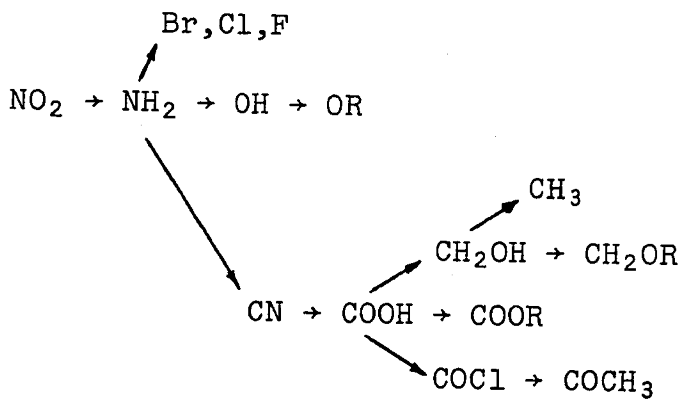
Two main approaches must be considered for the synthesis of a series of molecules of the type XZ where X is a variable substituent and Z is a constant substituent:

route *a*: X is added to  Z

route *b*: Z is added to X 

In route *a*, Z does not have to be the final substituent but must direct the attack of X at the proper position on the ring. The nature of X must be such that it serves as the starting group for the preparation of a series of compounds without affecting the nature of Z. In aromatic chemistry, many electrophilic reactions are known to have some selectivity toward the para position as long as Z is a good electron donating group. Unfortunately, this is not always easy and thus a very good knowledge of electrophilic substitution reactions is necessary. The best choice for X is a nitro group since it can sometimes be introduced specifically at the para position of monosubstituted benzenes and can serve as the starting point for the preparation of many other compounds.

This is illustrated as follows:



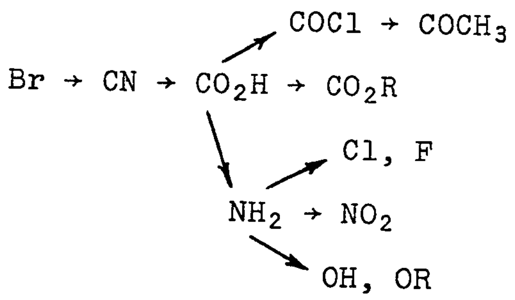
Even though route _b_ is more complex than route _a_, there are known chemical reactions leading to _para_-substituted compounds which are very selective. Two subroutes are possible:

subroute _i_ : X is kept constant while Z is built up to the final product.

subroute _ii_: X is varied while Z is kept constant at the starting material, at some intermediates or at the final product.

The best known selective reaction through subroute _i_ is the Friedel-Crafts reaction as long as X is an electron donating group such as CH_3, OCH_3, halogens etc. Therefore, bromine can serve as the starting substituent X for the preparation of a series of compounds by this route.

This is illustrated as follows:



It is sometimes much simpler and cheaper to do the series through the subroute ii than to prepare the series from a unique starting substituent X.

These possible routes were considered for the synthesis of the series of rigid molecules needed in this thesis. The phthalides and the 3-phenylphthalans were best prepared following route a while 5H-dibenzo[a,d] cycloheptenes and their epoxide derivatives could only be obtained by route b.

EXPERIMENTAL

The NMR spectra were run either on a Varian HA-100, a Varian HR-60-EL or a Varian T-60 spectrometer. All spectra, unless otherwise noted, were taken in deuteriochloroform solution and are reported on the τ value scale. The proton decoupling experiments were performed by the frequency sweep mode using the standard technique (77). The N.O.E. effects were performed on an HA-100 spectrometer using a sample of 2-methoxy-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptene in deuteriochloroform. The sample was degassed and sealed under vacuum before use. The technique employed has been described elsewhere (78). The experiments were performed by Dr. R.R. Fraser and Mr. J. Maxwell.

Exact analyses of the HA-100 spectra were carried out on an IBM-360 model 65 computer using the LAOCN-3 program of Bothner-By and Castellano (80,110). Agreement between the experimental (average of five spectra) and theoretical line positions was better than 0.1 Hz.

The IR spectra were recorded either on a Beckman IR-8 or on a Perkin-Elmer Infracord spectrometer. The wavenumber scale was calibrated after each measurement. The spectra were taken neat, in chloroform solution or as potassium bromide pellets. The absorptions were recorded in units of cm^{-1} and only the characteristic bands are reported.

All melting points were corrected.

6-Substituted Phthalides

The 6-substituted phthalides were prepared according to procedures in the literature. The yields and melting points are shown in Table II.

5-Substituted-3-Phenylphthalans

3-Phenylphthalan (IX)

Procedure a. - 3-Phenylphthalide (85) (2.0g) in anhydrous ether (50 ml) was reduced with aluminum hydride to 3-phenylphthalans following the procedure developed by Eliel and coworkers (86) for the reduction of 2-t-butoxy-tetrahydrofuran. The crude oily product obtained was purified by bulb to bulb distillation and the fraction distilling at 155° (0.25 mm) was identical with an authentic sample (87). The yield was 1.2g (67%).

Procedure b.

o-Hydroxymethylphenyl-phenyl carbinol (X) - o-Benzoylbenzoic acid (1g) dissolved in 15 ml of anhydrous THF was reduced to X with diborane generated as described by Schmitt and coworkers (88). The sticky colorless o-hydroxymethylphenyl-phenyl carbinol obtained was not purified but was used as such in the next step.

3-Phenylphthalan (IX)

To a solution of the crude diol (X) in ether (25 ml) was added freshly powdered fused potassium bisulfate (32g). After

TABLE II

6-Substituted Phthalides

Substituents	Yield %	M.P. °C	
		observed	lit. (ref.)
H (I)	82	72.5- 73.5	73 (81)
NO_2 (II)	64	144-145.5	145 (82)
NH_2 (III)	78	181-182	182 (81)
OH (IV)	70	200-201	201-202 (83)
OCH_3 (V)	74	119-120	119.5-120 (83)
Cl (VI)	85	111.5-112.5	112 (83)
CN (VII)	28	194-195	195 (83)
F[a] (VIII)	4	102-103	--

[a] The fluoro derivative was prepared as described in the literature for the preparation of 5-fluorophthalide (84). The microanalysis was not done since there was just enough material for an NMR analysis.

evaporation of the ether, the temperature was gradually raised to 160° and kept at that temperature for 1 h. Then the cold solid mass was extracted with ether and the dark brown solution was filtered through a column containing magnesium sulfate and aluminum oxide. The oil obtained after removal of the solvent was distilled under reduced pressure. The fraction collected at 145° (0.2 mm) was also identical with an authentic sample (87).

(5-Nitro-2-hydroxymethyl)phenyl-phenyl carbinol (XI)

Diborane reduction of 4-nitro-2-benzoylbenzoic acid (3.2g) (89,90) was done as described for the preparation of X. An oil was obtained in 96% yield (3.3g) which slowly crystallized on standing to a light brown solid melting at 85-87°; i.r. (film): 3490 (OH), 1530, 1355 (NO_2); n.m.r. (DMSO): 1.80 (1H doublet, proton at C-6), 2.02 (1H quartet, proton at C-4), 2.54 (1H doublet, proton at C-3), 2.86 (5H singlet, aromatic), 3.82 (1H doublet, hydroxyl proton of CHOH), 4.04 (1H doublet, methine), 4.52 (1H triplet, hydroxyl proton of CH_2OH), 5.44 (2H octet, methylene).

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.02; N, 5.21

Found: C, 64.68; H, 5.25; N, 5.24

5-Nitro-3-phenylphthalan (XII)

A solution of compound XI (6.8g) in ether was dehydrated as described for the preparation of the parent compound IX (procedure b). A solid melting at 55.5-56.5° was obtained in a yield of 87% (5.8g); i.r. (KBr): 1522 and 1350 (NO_2), 1048 (C-O-C); n.m.r.: 1,82 (1H quartet, proton at C-6), 2.14 (1H doublet, proton at C-4), 2.66 (6H multiplet, aromatic), 3.81 (1H multiplet, methine), 4.70 (2H octet, methylene).

Anal. Calcd. for $C_{14}H_{11}NO_3$; C, 69.70; H, 4.57; N, 5.81

Found; C, 69.67; H, 4.74; N, 5.65.

5-Amino-3-phenylphthalan (XIII)

5-Nitro-3-phenylphthalan (2.7g) dissolved in methanol (25 ml) was reduced at room temperature in presence of 0.2g of 10% palladium-on-charcoal catalyst under hydrogen at a pressure of four atmospheres. The theoretical volume of hydrogen was absorbed in 5 h. Removal of the catalyst by filtration followed by evaporation of the methanol gave a dark brown oil. This crude material was treated with excess of dilute hydrochloric acid, filtered and then the filtrate was basified with dilute sodium hydroxide solution. A yield of 2.2g (93%) of a light brown amorphous solid melting at 84-85° was obtained. An analytical sample of the amine was prepared by recrystallization from water. Long colorless needles melting at 85.5-86° were obtained; i.r. (KBr): 3475 and 3385 (NH_2), 1032 (C-O-C); n.m.r.: 2.73 (5H singlet, aromatic), 2.98 (1H at C-7), 3.44 (1H quartet at C-6), 3.72 (1H doublet at C-4), 3.96 (1H broad singlet, methine), 4.83 (2H octet, methylene), 7.05 (2H broad singlet, NH_2).

5-Chloro-3-phenylphthalan (XIV)

To a solution of 5-amino-3-phenylphthalan (1.2g) in concentrated hydrochloric acid (1.5 ml) and water (1.5 ml) at 0°C was added dropwise a solution of sodium nitrite (0.42g) in water (1 ml) until a positive test with potassium iodide-starch paper was obtained. This cold solution was added in portions to a well-stirred solution of cuprous chloride in concentrated hydrochloric acid (3 ml) kept below 8°C. The mixture was allowed to warm up to room temperature, at which temperature the solid complex decomposed. After the reaction mixture had been stirred for 3 h, the chloro compound was extracted with ether, washed with 10% sodium hydroxide solution and dried ($MgSO_4$). The residue obtained after removal of ether in vacuo was distilled in a Späth bulb under reduced pressure to yield 0.45g (34.5%) of a yellow oil; i.r. (film): 1040 (C-O-C); n.m.r.: 2.69 (7H multiplet, aromatic), 3.00 (1H broad singlet at C-4), 3.88 (1H broad singlet methine), 4.77 (2H octet, methylene).

Anal. Calcd. for $C_{14}H_{11}ClO$: C, 72.88; H, 4.77; Cl, 15.41
Found: C, 73.21; H, 5.01; Cl, 15.02.

5-Cyano-3-phenylphthalan (XV)

5-Amino-3-phenylphthalan (2.1g) was diazotized as described for the preparation of XIV. The diazonium salt was added in small portions to a solution of cuprous cyanide, prepared as described by Vogel (91), at 90°C with vigorous shaking by hand during each addition. Then a condenser was attached to the flask and the mixture was heated for 15 minutes on a steam bath or until decomposition ceased. The mixture was filtered cold and the solid extracted with ether. The ethereal solution was washed with a 5% solution of sodium carbonate and dried ($MgSO_4$). Evaporation of the solvent in vacuo gave a red gummy solid which, after purification by sublimation and recrystallization from ethanol, afforded 1.0g (45.5%) of a colorless crystalline solid melting at 104.5-105.5°; i.r. ($CHCl_3$): 2260 (C≡N); 1040 (C-O-C); n.m.r.: 2.70 (8H multiplet, aromatic), 3.86 (1H broad singlet, methine), 4.71 (2H octet, methylene).

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.49; H, 5.21; N, 6.33.
Found: C, 81.56; H, 5.13; N, 6.04.

5-Hydroxy-3-phenylphthalan (XVI)

5-Amino-3-phenylphthalan (0.8g) dissolved in a solution of sulfuric acid (3 ml) in water (20 ml) was diazotized as described for the preparation of XIV. The diazonium salt was decomposed in a preheated water bath at 92° until the evolution of nitrogen ceased. The reaction mixture was extracted with ether and the ethereal layer was washed with a 5% sodium bicarbonate solution, followed by water, and dried ($MgSO_4$). The crude material obtained after removal of ether was purified by sublimation and recrystallization from water to give 0.27g (34.5%) of long colorless needles melting at 133-134°; i.r. ($CHCl_3$): 3225 (OH), 1020 (C-O-C); n.m.r.: 2.72 (5H multiplet, aromatic), 2.92 (1H doublet at C-7), 3.30 (1H quartet at C-6), 3.58 (1H doublet at C-4), 3.86 (1H broad singlet, methine), 4.71 (2H octet, methylene).

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.24; H, 5.66.

Found: C, 79.21; H, 5.86.

5-Methoxy-3-phenylphthalan (XVII)

To a stirred solution of 5-hydroxy-3-phenyl-phthalan (0.13g) in 5 ml of aqueous sodium hydroxide (10%) was added dropwise dimethyl sulfate (0.4 ml). Stirring was continued for 5 h after the addition. The still basic solution was extracted with ether and the organic layer was washed with water and dried ($MgSO_4$). The slightly orange solid obtained after removal of the solvent was purified by sublimation to give 0.11g (79%) of a colorless solid melting at 78.5-79.5°; i.r. (KBr): 1040 (C-O-C); n.m.r.: 2.70 (5H singlet, aromatic), 2.84 (1H doublet at C-7), 3.18 (1H quartet at C-6), 3.48 (1H doublet at C-4), 3.90 (1H broad singlet, methine), 4.79 (2H octet, methylene), 6.28 (3H singlet, methoxy).

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.60; H, 6.19.

Found: C, 79.50; H, 6.39.

2-Substituted-5H-Dibenzo[a,d]cycloheptenes

5H-Dibenzo[a,d]cyclohepten-5-one(XVIII)

This compound was prepared by bromination of the commercially available 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one with N-bromo-succinimide followed by dehydrobromination of the resulting 10-bromo derivative with triethylamine according to the procedure of Cope and Fenton (92).

5H-Dibenzo[a,d]cycloheptene(XIX)

The Huang-Minlon modification of the Wolff-Kishner reaction as described by Campbell and coworkers (93) was used to convert XVIII to XIX.

2-(4-Bromobenzoyl)benzoic acid(XX)

Compound XX was prepared from freshly crystallized phthalic anhydride and bromobenzene in presence of aluminum chloride as described by Groggins and coworkers (94). A colorless lustrous solid melting at 171-172° (lit. m.p. 170-171°) (94) was obtained from aqueous ethanol.

3-(4-Bromophenyl) phthalide(XXI)

2-(4-Bromobenzoyl) benzoic acid (24g) was reduced with a mixture of amalgamated zinc (95), concentrated hydrochloric acid (23 ml), water (8 ml) and toluene (12 ml) as reported by Bergmann and Loeventhal (96), to yield 11.7g (52%) of XXI melting at 129-130° (lit. m.p. 139-140°) (96).

2-(4-Bromobenzyl) benzoic acid (XXII)

The reduction of XXI (7.4g) was carried out with iodine (2.2g), red phosphorus (0.8g), acetic acid (20 ml) and water (1 ml) according to the method described by Bergmann and Loeventhal (96). The colorless solid (6.8g; 90%) melted at 134-135° (lit. m.p. 133-135°) (96).

2-(4-Bromobenzyl) benzyl alcohol (XXIII)

2-(4-Bromobenzyl) benzoic acid (11.4g) dissolved in dry tetrahydrofuran (100 ml) was reduced with diborane generated from ethereal boron trifluoride (35 ml) and sodium borohydride (8g) as described by Schmitt and coworkers (88). The excess diborane was destroyed with ethanol and the solvent evaporated in vacuo. Ether and water were added and the ethereal layer was washed with a 5% sodium bicarbonate solution followed by water, dried ($MgSO_4$) and then evaporated to dryness. The colorless oil which was obtained in a yield of 96% (10.4g) was not purified further; i.r. (film): 3290 (OH); n.m.r.: 2.70 (8H multiplet, aromatic); 5.42 (2H singlet, CH_2), 6.01 (2H singlet, CH_2-O), 7.63 (1H singlet, OH).

2-(4-Bromobenzyl) benzyl bromide (XXIV)

Compound XXIV was obtained from the reaction of XXIII with 48% aqueous hydrobromic acid following a procedure described by Leonard and coworkers (97). Colorless prisms melting at 73-74° were obtained in a yield of 85% from ethanol;

n.m.r.: 2.80 (8H multiplet, aromatic), 5.61 (2H singlet, CH_2), 5.90 (2H singlet, CH_2Br).

Anal. Calcd. for bromine: 47.05. Found: 47.04.

2-(4-Bromobenzyl) benzylcyanide (XXV)

A solution of XXIV (2.2g) and potassium cyanide (0.54g) in 95% ethanol (15 ml) was heated under reflux for 3 h. Dilution with water (25 ml), followed by extraction with ether and evaporation gave 1.8g (100%) of a slightly yellow oil; i.r. (film): 2260 (C≡N); n.m.r.: 2.7 (8H multiplet, aromatic), 6.0 (2H singlet, methylene), 6.45 (2H singlet, CH_2CN).

2-(4-Bromobenzyl) phenylacetic acid (XXVI)

A mixture of the crude nitrile XXV (1.9g), water (1.9 ml), sulfuric acid (1.9 ml) and acetic acid (3.0 ml) was heated at reflux temperature for 15 hr. Then the reaction mixture was poured into ice water. The solid that separated was collected by filtration, dissolved in a hot solution of sodium hydroxide (5%), filtered and reprecipitated with concentrated hydrochloric acid. After filtration, 1.9g (94%) of a nearly colorless amorphous solid melting at 161-162° (lit. m.p. 166°) (98) was obtained; i.r. ($CHCl_3$): 3000 (OH), 1680 (C=O); n.m.r.: 2.71 (9H multiplet, aromatic and OH), 5.94 (2H singlet, methylene), 6.34 (2H singlet, $CH_2\overset{O}{C}O$).

Anal. Calcd. for bromine: 26.22. Found: 25.85.

2-Bromo-5,11-dihydro, 10 H-dibenzo[a,d]cyclohepten-11-one (XXVII).

A mixture of compound XXVI (2g) and thionyl chloride (6 ml) was heated under reflux for 3 h. Then the excess thionyl chloride was removed in vacuo. The oily residue was dissolved in carbon disulfide (25 ml) and added dropwise during 2 h to a stirred suspension of aluminum chloride (5g) in carbon disulfide (100 ml) at room temperature. After 1 h of additional stirring, the mixture was poured on ice containing hydrochloric acid. The organic layer was washed with a 5% solution of sodium bicarbonate, with water, and then dried ($MgSO_4$). The brown solid obtained after evaporation of the solvent was sublimed as a light yellow solid (1.7g; 90%) melting at 101-102°, (lit. m.p. 106°) (99); i.r. ($CHCl_3$): 1675 (C=O); n.m.r.: 1.76 (1H doublet, aromatic proton at C-1), 2.70 (6H multiplet, aromatic), 5.79 and 5.82 (total of 4H, two singlets, $2CH_2$).

Anal. Calcd. for $C_{15}H_{11}BrO$: C, 62.72; H, 3.83; Br, 27.88.
Found: C, 62.72; H, 3.93; Br, 27.99.

2-Bromo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-11-ol(XXVIII)

To a solution of compound XXVII (1g) in absolute ethanol (25 ml) was added during a period of 10 minutes a solution of sodium borohydride (1.3g) in absolute ethanol (20 ml). The mixture was stirred at room temperature for 20 h and then enough water was added to decompose the complex. The solvent was removed in vacuo. Water (5 ml) was added to the residue which was then extracted with ether. The ethereal extract was dried ($MgSO_4$) and evaporated to dryness. A colorless solid (1g; 99%) melting at 99-103° (lit. m.p. 106°) (99) was obtained. The crude alcohol was not purified further and was used as such in the next step.

2-Bromo-5H-dibenzo[a,d]cycloheptene(XXIX)

A mixture of compound XXVIII (1g) and p-toluenesulfonic acid (0.05g) in toluene (40 ml) was heated to boiling and the azeotropic mixture was slowly collected for 3 h. Then the solution was washed with a solution of sodium bicarbonate (5%) and dried ($MgSO_4$). The solvent was evaporated to dryness and the residue recrystallized from ethanol to give 0.84g (79%) of colorless plates melting at 117-118°; n.m.r.: 2.70 (7H multiplet, aromatic), 3.00 (2H quartet, CH=CH), 6.33 (2H singlet, CH_2).

Anal. Calcd. for $C_{15}H_{11}Br$: C, 66.42; H, 4.06; Br, 29.52.
Found: C, 66.24; H, 4.01; Br, 29.35.

2-Cyano-5H-dibenzo[a,d]cycloheptene(XXX)

A stirred mixture of compound XXIX (0.6g), freshly prepared cuprous cyanide (0.36g) and N-methylpyrrolidone (23 ml) was refluxed for 3 h (99,100). To the resulting brown mixture was added a hot solution of ferric chloride (1.8g) and concentrated hydrochloric acid (0.5 ml) in water

(3 ml) (101). After the reaction mixture had been maintained at 60° for 20 minutes to decompose the complex, dilute hydrochloric acid was added and the organic material was extracted with four portions of 25 ml of toluene. The combined extracts were washed with a solution of sodium hydroxide (10%), followed by water. The organic layer was dried ($MgSO_4$) and evaporated to dryness in vacuo. The light brown solid residue obtained was purified by sublimation to give 0.38g (79%) of light yellow crystals melting at 102.5-103.5°; i.r. ($CHCl_3$): 2250 ($C\equiv N$); n.m.r.: 2.60 (7H multiplet, aromatic), 2.92 (2H quartet, CH=CH), 6.25 (2H singlet, CH_2).

Anal. Calcd. for $C_{16}H_{11}N$: C, 88.48; H, 5.07; N, 6.45.
Found: C, 88.40; H, 4.99; N, 6.27.

5H-Dibenzo[a,d]cyclohepten-2-carboxylic acid (XXXI)

To a solution of compound XXX (0.2g) in ethylene glycol monoethyl ether (3 ml) was added a solution of potassium hydroxide (0.7g) in water (0.5 ml). The resulting mixture was heated to 140° for 7 h with stirring. Then the solvent was removed by evaporation in vacuo. The residue was dissolved in water and the solution acidified with dilute sulfuric acid. The colorless solid that separated was collected by filtration and dried in air. The yield was 0.2g (92%) (m.p. 227-228°).

2-Carbomethoxy-5H-dibenzo[a,d]cycloheptene (XXXII)

Diazomethane in ether (102) was distilled into a solution of compound XXXI (0.1g) in ether until the yellow color persisted. After evaporation of the solvent in vacuo, the residue was purified by sublimation to give 0.09g (85%) of colorless crystals melting at 110-110.5°; i.r. ($CHCl_3$): 1700 (C=O); n.m.r.: 2.01 (1H singlet at C-1), 2.71 (6H multiplet, aromatic), 2.92 (2H singlet, CH=CH), 6.12 (3H singlet, CH_3), 6.23 (2H singlet, CH_2).

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.60; H, 5.60.

Found: C, 81.70; H, 5.56.

2-(4-Methoxybenzoyl) benzoic acid (XXXIII)

Compound XXXIII was prepared in 70% yield from phthalic anhydride, anisole and aluminum chloride as described for the preparation of compound XX. The amorphous solid obtained which melted at 140-142° (lit. m.p. 144-145°) (98) was not purified further.

2-(4-Methoxybenzyl) benzoic acid (XXXIV)

A mixture of compound XXXIII (8g), zinc powder (20g), ammonium hydroxide (200 ml), water (75 ml) and a few ml of cupric sulfate solution was well stirred at 100° for 2 days (103). The remaining zinc was removed by filtration and the filtrate was concentrated under reduced pressure to a volume of about 50 ml. The solid obtained by acidification with dilute hydrochloric acid was purified by sublimation. The yield was 6.8 (90%) of a colorless amorphous solid melting at 114-115° (lit. m.p. 111-112°) (98, 104).

Methyl-2-(4-methoxybenzyl) benzoate (XXXV)

A solution of the acid XXXIV (6g) in methanol (60 ml), benzene (50 ml) and sulfuric acid (0.5 ml) was heated to boiling for 40 h. Then the solution was concentrated to 25 ml under reduced pressure and water (100 ml) was added. The water layer was washed with ether and the combined organic layers were washed with a solution of sodium bicarbonate (10%), dried ($MgSO_4$) and evaporated to dryness in vacuo to give 5.4g (85%) of an oil which was not purified further (lit. b.p. 150-160°; 0.3 mm) (104).

2-(4-Methoxybenzyl) benzyl alcohol (XXXVI)

To a suspension of lithium aluminum hydride (2g) in anhydrous ether (30 ml) was added dropwise with stirring compound XXXV (5g) in anhydrous ether (30 ml). Stirring was continued for an additional 3 h after which time ethyl acetate and water were successively added. The ether layer was dried ($MgSO_4$) and the solvent removed in vacuo. The oil obtained slowly crystallized to a colorless solid melting at 41-42° (lit. b.p. 170-180°, 0.2 mm pressure) (104) in a yield of 4.1g (92%); i.r. (film): 3380 (OH), 2860, 1250 (CH_3O); n.m.r.: 2.89 (8H multiplet, aromatic), 5.42 (2H singlet, CH_2O), 6.03 (2H singlet, CH_2), 6.39 (3H singlet, CH_3O), 8.08 (1H singlet, OH).

2-(4-Methoxybenzyl) benzyl chloride (XXXVII)

Thionyl chloride (0.5 ml) was added dropwise to compound XXXVI and the resulting mixture was stirred at room temperature for 0.5 h. The excess thionyl chloride was removed in vacuo. The brown oily residue was purified by distillation in a Späth bulb at 140-145° (0.2 mm) (lit. b.p. 150-158°, 0.7 mm) (104) to give 1.5g (76%) of a colorless oil; n.m.r.: 2.83 (8H multiplet, aromatic), 5.42 (2H singlet, CH_2Cl), 5.90 (2H singlet, CH_2), 6.22 (3H singlet, CH_3O).

2-(4-Methoxybenzyl) benzyl cyanide (XXXVIII)

Compound XXXVIII was prepared as described for the preparation of compound XXV. The oil obtained by distillation in a Späth bulb slowly crystallized to give colorless plates melting at 71-72° (lit. m.p. 65°) (104) in nearly quantitative yield; i.r. ($CHCl_3$): 2250 (C≡N); 2860, 1245 (CH_3O); n.m.r.: 2.82 (8H multiplet, aromatic), 6.01 (2H singlet, CH_2), 6.22 (3H singlet, CH_3O), 6.42 (2H singlet, CH_2CN).

2-(4-Methoxybenzyl) phenylacetic acid (XXXIX)

The nitrile XXXVIII (1.2g) was hydrolyzed as described for the preparation of compound XXXI. A light yellow solid melting at 69-71° (lit. m.p. 70°) (104) was obtained in a yield of 1.1g (81%); i.r. ($CHCl_3$): 3000 (OH); 1701 (C=O), 2860, 1250 (CH_3O); n.m.r.: 1.52 (1H broad, OH), 2.92 (8H multiplet, aromatic), 6.00 (2H singlet, CH_2), 6.22 (3H singlet, CH_3O), 6.39 (2H singlet, $CH_2C{=}O$).

2-Methoxy-5,11-dihydro-10H-dibenzo[a,d]cyclohepten-11-one (XL)

The acid XXXIX (0.6g) was added in small portions with stirring over a period of 3/4 h to polyphosphoric acid (prepared by heating for 2 h a mixture of phosphorus pentoxide (26.7g) and phosphoric acid (17.2 ml) 85%). The heating and stirring was continued for an additional period of 2.5 h and the resulting dark viscous mass was poured on ice. The gummy brown precipitate obtained was filtered and dissolved in ether. The ethereal solution was washed with a solution of sodium bicarbonate (10%), washed with water, dried ($MgSO_4$) and evaporated to dryness in vacuo. The oily residue was distilled in a Späth bulb to give 0.41g (73.5%) of colorless crystals melting at 84.5-85.5° (lit. m.p. 82-84°) (104); i.r. ($CHCl_3$): 1660 (C=O), 2840, 1280 (CH_3O); n.m.r.: 2.39 (1H doublet, aromatic proton at C-1), 2.80 (6H multiplet, aromatic), 5.80 and 5.81 (two 2H singlets, $2CH_2$), 6.20 (3H singlet, CH_3).

2-Methoxy-5H-dibenzo[a,d]cycloheptene (XLI)

The reduction of compound XL and the dehydration of the resulting alcohol were done as described for the preparation of compound XXIX (2-bromo-5H-dibenzo[a,d]cycloheptene). Nearly colorless plates melting at 131-132° were obtained in a yield of 92%; i.r. ($CHCl_3$): 2850, 1260 (CH_3O); n.m.r.: 2.76 (5H multiplet, aromatic), 3.00 (2H singlet, CH=CH), 3.16 (2H multiplet, aromatic protons at C-1 and C-3), 6.25 (3H singlet, CH_3), 6.33 (2H singlet, CH_2).

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.49; H, 6.31

Found: C, 86.64; H, 6.17.

2-Methyl-5H-dibenzo[a,d]cycloheptene (XLII)

Compound XLII was prepared via the sequence of reactions used for the preparation of the 2-methoxy derivative starting with toluene instead of anisole. The yield was essentially the same at each step. Colorless plates melting at 137-138° were obtained from ethanol; n.m.r.: 2.80 (7H multiplet, aromatic), 3.00 (2H singlet, CH=CH), 6.31 (2H singlet, CH_2), 7.71 (3H singlet, CH_3).

Anal. Calcd. for $C_{16}H_{14}$: C, 93.20; H, 6.80.

Found: C, 93.32; H, 6.97.

2-Chloro-5H-dibenzo[a,d]cycloheptene (XLIII)

Procedure a.-

2-Chloro-5H-dibenzo[a,d]cyclohepten-5-one(XLIV)

Compound XLIV was synthesized as described for the preparation of compound XVIII (5H-dibenzo[a,d]cyclohepten-5-one) via bromination of 2-chloro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (prepared as described by Winthrop and coworkers (105)). A yield of 58.2% of long colorless needles melting at 153-155° was obtained from ethanol; i.r. ($CHCl_3$): 1646 (C=O); n.m.r.: 1.80 (2H multiplet, aromatic protons at C-4 and C-6), 2.50 (5H multiplet, aromatic); 2.80 (2H quartet, CH=CH).

Anal. Calcd. for chlorine: 14.76. Found: 14.72.

2-Chloro-5H-dibenzo[a,d]cycloheptene.

The Huang-Minlon modification of the Wolff-Kishner reaction on compound XLIV was done as described by Campbell and coworkers (93) to give XLIII melting at 100-101° in 15% yield (lit. m.p. 105-106°) (107).

Procedure b.-

2-Chloro-10,11-dibromo-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5-one (XLV)

A mixture of 2-chloro-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5-one (2.9g), N-bromosuccinimide (4.4g), benzoyl peroxide (0.1g) in carbon tetrachloride (25 ml) was heated under reflux for 2 h. The resulting mixture was filtered and the filtrate was washed with a 5% solution of sodium hydroxide, followed by water, and then dried ($MgSO_4$). The yellow solid obtained after the evaporation of the solvent in vacuo was recrystallized from ethanol to give 3.2g (67%) of orange crystals melting at 162-163°; i.r. ($CHCl_3$): 1652 (C=O); n.m.r.: 2.10 (2H multiplet, aromatic protons at C-4 and C-6), 2.70 (5H multiplet, aromatic), 4.48 (2H singlet, CHBr-CHBr).

2-Chloro-5H-dibenzo[a,d]cycloheptene

Compound XLV was chlorinated with a mixture of phosphorus pentachloride and phosphorus oxychloride as described by Looker (106) for the preparation of 5,5-dichloro-5H-dibenzo [a,d]cycloheptene. The crude dibromotrichloro compound obtained was thoroughly stirred with zinc dust and water under reflux for 24 h. The hot mixture was filtered through glass-wool and the solid material was washed with ether. The filtrate was extracted with ether and the combined ethereal solutions were dried ($MgSO_4$) and evaporated to dryness in vacuo. The residue was purified by sublimation and recrystallization from ethanol to give compound XLIII in 32% yield. The melting point was 100-101° (lit. m.p. 105-106) (107).

Procedure c.-

A mixture of compound XLV (0.3g), zinc dust (0.3g), calcium hydroxide (0.5g) and water (10 ml) was heated to reflux for 24 h. The resulting mixture was worked up as described in procedure b. Colorless plates melting at 100-101° were obtained in a yield of 41% (0.07g); n.m.r.: 2.71 (7H multiplet, aromatic), 2.99 (2H quartet, CH=CH), 6.32 (2H singlet, CH_2).

Anal. Calcd. for $C_{15}H_{11}Cl$: C, 79.47; H, 4.86; Cl, 15.67
Found: C, 79.60; H, 4.76; Cl, 15.58.

10,11-Dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptene (XLVI)

5H-Dibenzo[a,d]cycloheptene (1g) was added to a solution of m-chloroperbenzoic acid (1.2g) in chloroform (10 ml) and the mixture was stirred at room temperature for 20 h. The m-chlorobenzoic acid formed was removed by shaking with a 5% solution of sodium bicarbonate. The organic layer was dried ($MgSO_4$) and evaporated to dryness in vacuo. The crude residue was purified by recrystallization from ethanol (99%) and gave 0.59g (54%) of colorless plates melting at 144-145° (lit. m.p. 144-146°) (108); n.m.r.: 2.80 (7H multiplet, aromatic), 4.83 (1H doublet, axial proton of CH_2), 5.77 (2H singlet, $\mathrm{H{-}C\underset{O}{-}C{-}H}$) 6.69 (1H doublet, equatorial proton of CH_2).

Anal. Calcd. for $C_{15}H_{12}O$: C, 86.54; H, 5.77.

Found: C, 86.42; H, 5.95.

2-Substituted-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d] cycloheptenes

A series of 2-substituted-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptenes was synthesized in a yield of 50 to 60% from their olefinic derivatives and purified as described for the preparation of compound XLVI. The following is a list of the physical properties and elemental analysis of each member of the series:

-Br (XLVII): colorless plates melting at 113.5-115°; n.m.r.: 2.78 (7H multiplet, aromatic), 4.93 (1H doublet, axial proton of CH_2), 5.81 (2H quartet, $\text{H-}\underset{\text{O}}{\text{C-C}}\text{-H}$), 6.73 (1H doublet, equatorial proton of CH_2)

Anal. Calcd. for $C_{15}H_{11}BrO$: C, 62.72; H, 3.83; Br, 27.87.

Found: C, 62.86; H, 3.75; Br, 27.75.

-CH_3 (XLVIII): colorless plates melting at 151-152°; n.m.r.: 2.84 (7H multiplet, aromatic), 4.91 (1H doublet, axial proton of CH_2), 5.80 (2H quartet, $\text{H-}\underset{\text{O}}{\text{C-C}}\text{-H}$), 6.72 (1H doublet, equatorial proton of CH_2), 7.84 (3H singlet, CH_3).

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.49; H, 6.31.

Found: C, 86.45; H, 6.24.

-CN (IL): colorless needles melting at 175-176°; i.r. ($CHCl_3$): 2250 (C≡N); n.m.r.: 2.70 (7H multiplet, aromatic), 4.79 (1H doublet, axial proton of CH_2), 5.75 (2H quartet, $\text{H-}\underset{\text{O}}{\text{C-C}}\text{-H}$), 6.64 (1H doublet, equatorial proton of CH_2).

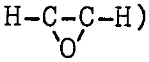
Anal. Calcd. for $C_{16}H_{11}NO$: C, 82.40; H, 4.72; N, 6.01.

Found: C, 82.25; H, 4.75; N, 5.84.

-CO_2CH_3(L): colorless plates melting at 146-147.5°; i.r. ($CHCl_3$): 1720 (C=O); n.m.r.: 2.60 (7H multiplet, aromatic), 4.79 (1H doublet, axial proton of CH_2), 5.71 (2H quartet, $\text{H-}\underset{\text{O}}{\text{C-C}}\text{-H}$), 6.62 (1H doublet, equatorial proton of CH_2), 6.18 (3H singlet, CH_3).

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.69; H, 5.26

Found: C, 76.69; H, 5.20.

$-OCH_3$ (LI): colorless plates melting at 138.5-139.5°; i.r. ($CHCl_3$): 2850, 1275 (CH_3O), n.m.r.: 2.90 (7H multiplet, aromatic), 4.96 (1H doublet, axial proton of CH_2), 5.82 (2H quartet,  $\underset{\diagdown \mathrm{O} \diagup}{\mathrm{H-C-C-H}}$), 6.20 (3H singlet, CH_3), 6.73 (1H doublet, equatorial proton of CH_2).

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.67; H, 5.88

Found: C, 80.47; H, 5.09.

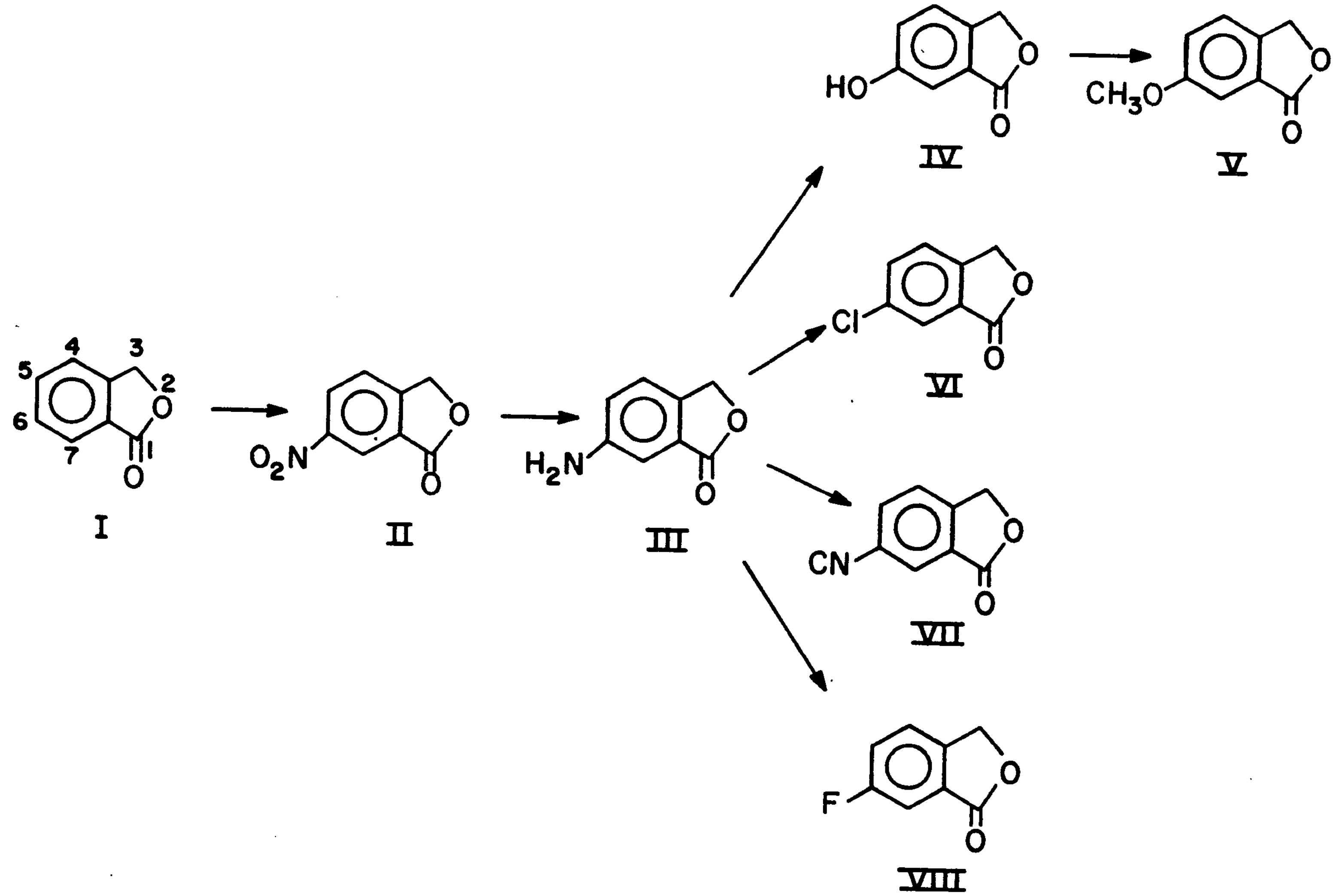
RESULTS AND DISCUSSION

1. Synthetic procedures

Three of the four series of compounds needed for NMR spectroscopic studies (the phthalide series was known) were synthesized following systematic sequences of logical schemes devised in the manner recommended by Corey (76).

The 6-substituted phthalides were prepared according to procedures already described in the literature. The scheme is shown in figure 2. The formation of two isomeric nitrophthalides is possible by nitration of phthalide itself. The electron withdrawing carbonyl group and the electron releasing methylene group favor the attack of the nitronium ion at the 4- or the 6-position of phthalide. However, nitration proved to be selective at the 6-position since only 1% of the 4-isomer was isolated. The lactone ring was very stable to strongly basic or acidic treatment, thus allowing the facile preparation of all the substituted phthalides. The yields were good except in the synthesis of the fluoro-derivative. Tirouflet (83) could not prepare 5-fluorophthalide by the Schiemann reaction, but a 59% yield of this compound is reported in the literature (84) by the same reaction. In our hands the Schiemann reaction of 6-aminophthalide gave a yield of only 4% of 6-fluorophthalide after laborious purification.

The 5-nitro-3-phenylphthalan was prepared following route <u>a</u> (page 23) even though nitration of 3-phenylphthalan was



<u>Figure 2</u>. Synthetic scheme of 6-substituted-phthalides.

not used. Hauser and coworkers (87) prepared 3-phenylphthalan as illustrated in figure 3. The procedure could not be used for the preparation of the 5-nitro-derivative since no identifiable compounds were isolated from the reaction between n-butyllithium and N,N-dimethyl-4-nitro-benzylamine. Pernot and Willemart (111) reported the preparation of 3-phenylphthalan in a yield of 75% by dehydration of 2-(hydroxymethyl) phenyl-phenyl carbinol with 50% phosphoric acid. When this reaction was repeated with 5-nitro-2-(hydroxymethyl) phenyl-phenyl carbinol, an oil was obtained in 60% yield which appeared to be impure 5-nitro-3-phenylphthalan by NMR spectroscopy. Subsequently, the dehydration of the nitro-diol compound was better done in a yield of 87% when the compound was well dispersed in solid potassium bisulfate and heated to 120° for 1 h. The other members of the series were easily prepared from the nitro compound since the dihydrofuran ring was very stable in basic and acidic medium. The general scheme is shown in figure 4.

Many synthetic routes are possible for the preparation of 2-substituted-5H-dibenzo[a,d]cycloheptenes. It should be mentioned that direct nitration of commercially available 5H-dibenzo[a,d]cyclohepten-5-one gives only the 3-nitro-derivative (93). Therefore, the problem was analyzed through a systematic disconnection of the molecule to find all the logical synthetic procedures to recombine the disconnected bonds. The molecule can be disconnected at four positions as illustrated in figure 5.

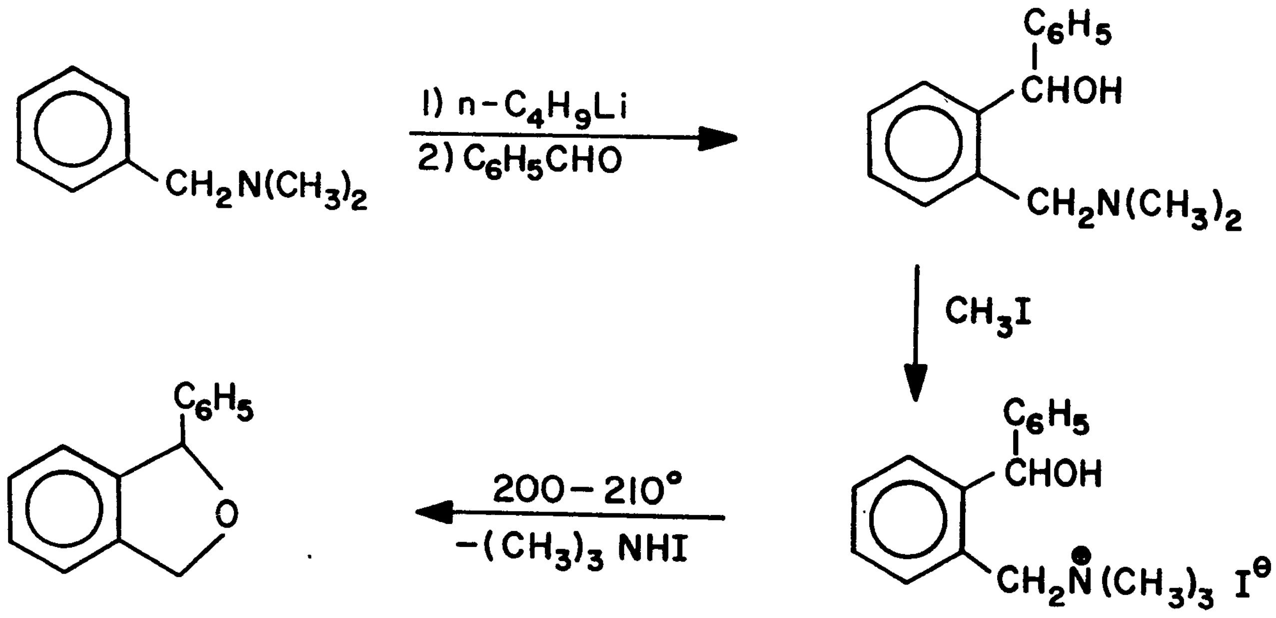


Figure 3. Preparation of 3-phenylphthalan.

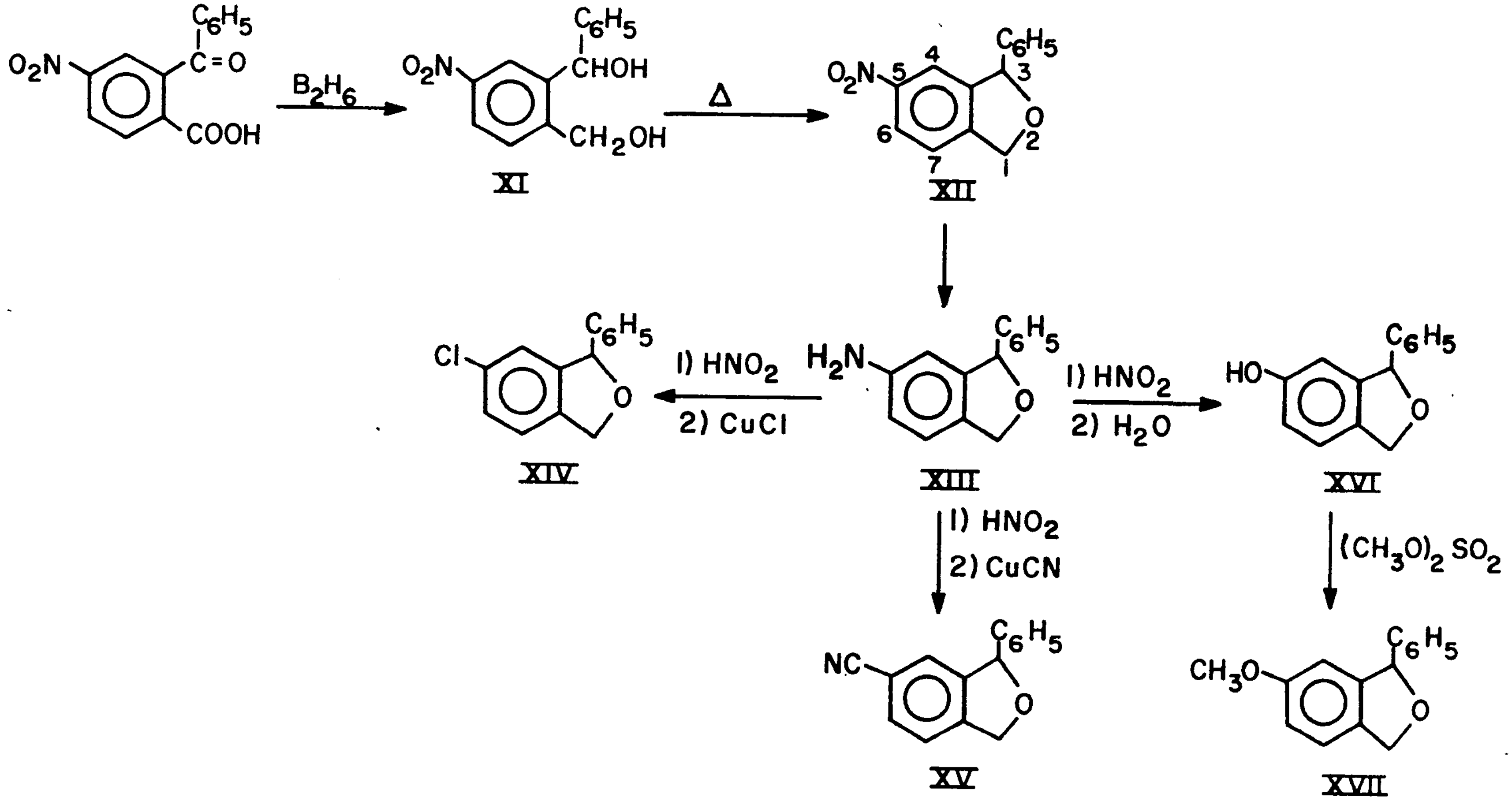


Figure 4. Synthetic scheme of 5-substituted-3-phenylphthalans.

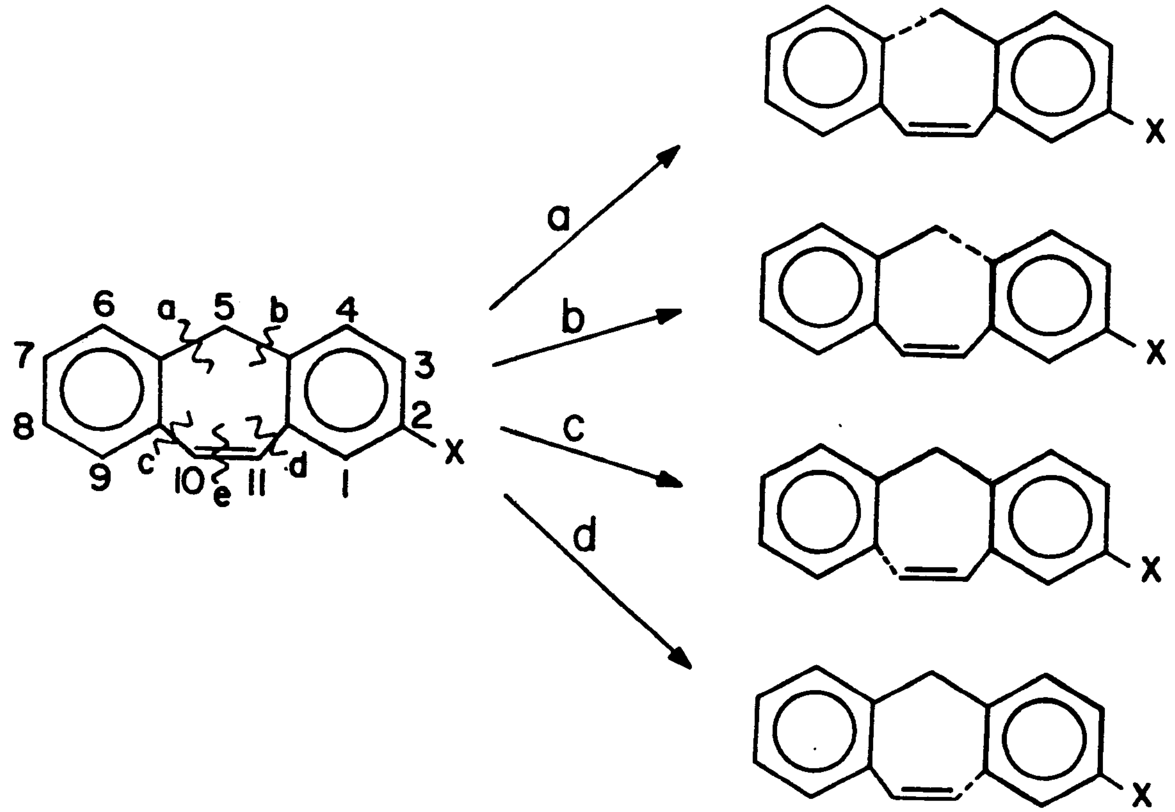


Figure 5. Disconnections of 2-substituted-5H-dibenzo[a,d]cycloheptenes.

A good method for ring closure to a carbocyclic compound is the dehydration or the dehydrochlorination of a carboxylic acid compound or its corresponding acyl chloride derivative in the vicinity of an active site of an aromatic group in presence of a Lewis acid such as aluminum chloride, polyphosphoric acid or sulfuric acid. This procedure can be used for the formation of the seven member ring in 5H-dibenzo[a,d] cycloheptene (figure 6).

The carboxylic acid intermediates in figure 6 have to be disconnected further to more easily accessible starting materials. There are six possible ways the 2-substituted-5H-dibenzo[a,d]cycloheptene molecule can be disconnected at two positions (figure 5), namely at a and b, c and d, a and c, a and e, b and e and finally at b and d.

Possible synthetic methods for the preparation of 2-nitro-5H-dibenzo[a,d]cycloheptene for each of these routes are:

1. Connections at a and b or at c and d.

Molecules which can be used for the formation of the seven membered ring by these two routes will still be intermediates since more disconnections will be necessary in order to start with accessible compounds. Because of these synthetic problems, they seem unsuitable as possible synthetic methods for the preparation of 2-substituted-5H-dibenzo[a,d]cycloheptenes.

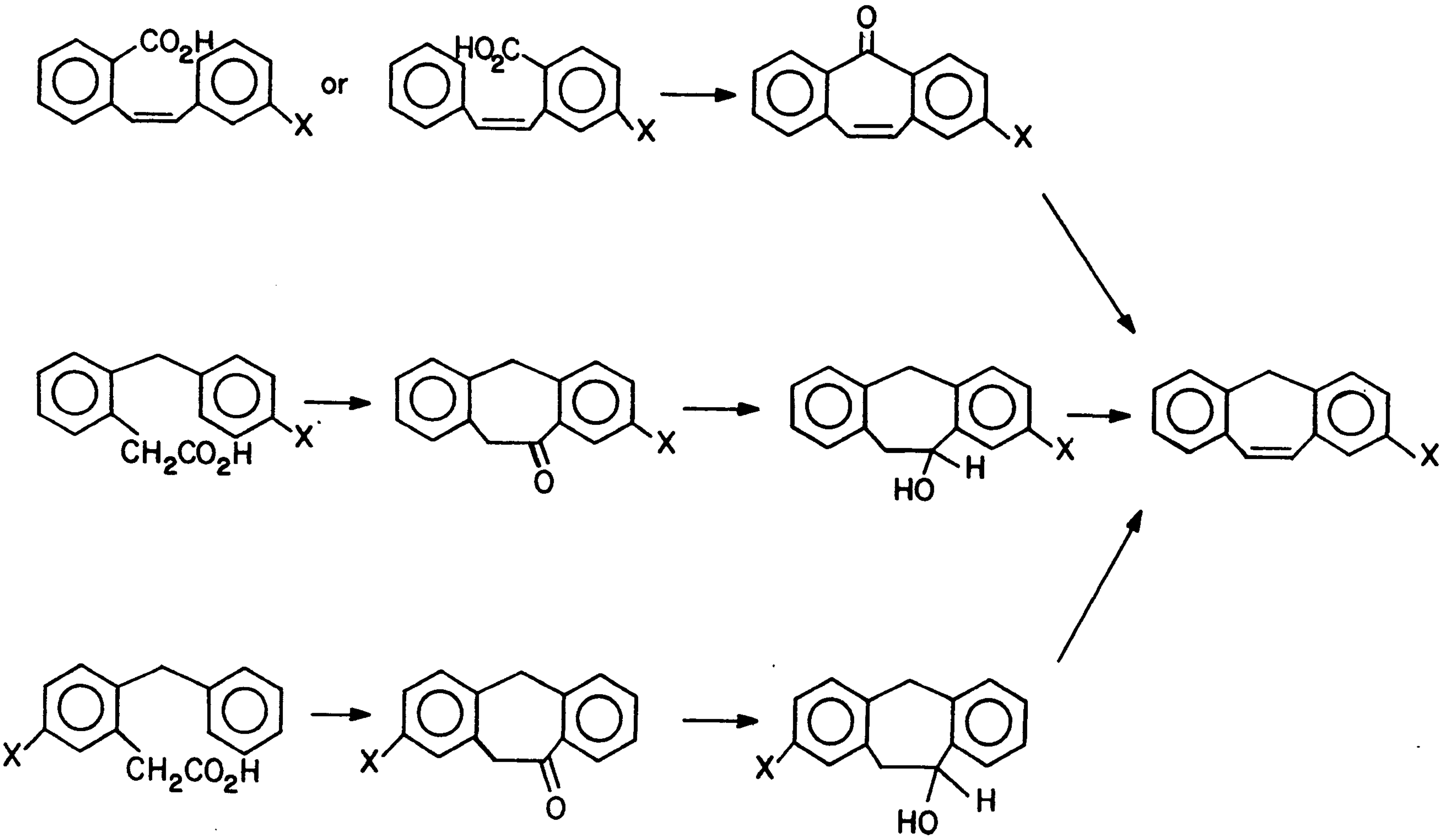


Figure 6. Suggested procedures for the formation of the seven member ring in 5H-dibenzo[a,d]cycloheptene.

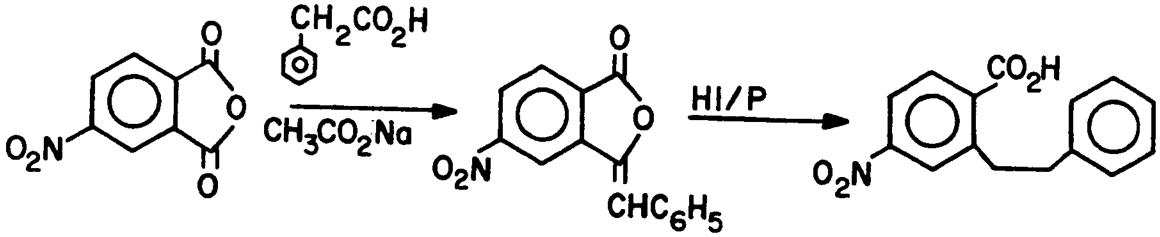
2. Connections at a and c.

This route is only possible if another disconnection is made at e. The chain can eventually be extended at C-11 by an Arndt-Eistert reaction or by a series of classical reactions on a carboxylic acid group to give α-substituted acetic acid.

The Friedel-Crafts reaction of 4-nitrophthalic anhydride on benzene (112) gives mainly 2-benzoyl-5-nitro-benzoic acid. There are different methods reported in the literature describing the reduction of a keto group to an aliphatic group, such as the Wolff-Kishner reaction, the use of aluminum isopropoxide at 250° (113), the Clemmenson reaction or zinc in basic aqueous solution (114). The Wolff-Kishner reaction on 2-benzoyl-5-nitrobenzoic acid gave only 4-phenyl-7-nitro-phthalazone (115), the reduction in presence of aluminum isopropoxide was not tried due to technical problems, and the two last reactions would certainly reduce the nitro group. Preparation of 5-nitro-2-benzylbenzoic acid was tried by a Friedel-Crafts reaction (116) of 6-nitrophthalide with benzene, but no nitro-acid could be isolated from this reaction. Therefore, this route was also discarded.

3. Connections at a and e.

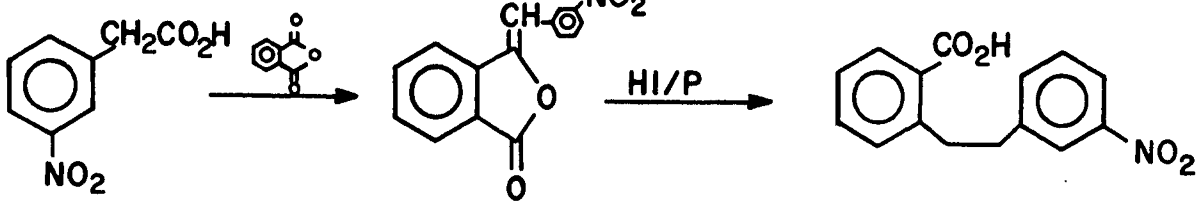
Campbell and coworkers (93) prepared 5H-dibenzo[a,d]cycloheptene following this route. The scheme for the preparation of the nitro derivative is as follows:



This synthesis is unattractive because two isomers are possible in the first step and only a 10% yield of 5-nitro-3-benzylidene-phthalide was obtained (117). This nitro compound can be prepared in a better yield by the reaction of benzaldehyde with 5-nitro-phthalide (82). The reduction of 5-nitro-3-benzylidene-phthalide with hydriodic acid and phosphorus gave no nitro acid or amino acid product. Nevertheless, this method should be applicable for the preparation of the bromo-derivative.

4. Connections at b and e.

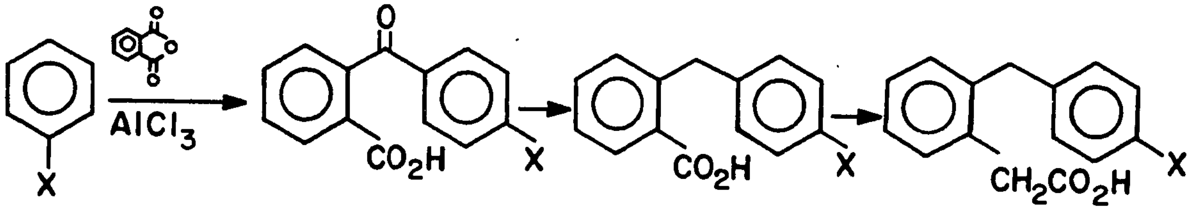
Winthrop and coworkers (105) described a method for the preparation of the parent compound by this route. The scheme for the preparation of the 2-nitro-derivative could therefore be as follows:



The nitro-derivative could not be synthesized by this route because of the reduction step with hydriodic acid and phosphorus, but the chloro-derivative was prepared in a fair yield.

5. Connection at b and d.

Rhone-Poulenc (98,99,104) used this route for the preparation of many 2-substituted-5,11-dihydro-10H-dibenzo[a,d]cyclohepten-11-one. The general scheme is as follows:



However, the method is only suitable for compounds having *para*-directing groups in the first step, such as methoxy, methyl or halogen.

Of all the possible routes described for the synthesis of 2-substituted-5H-dibenzo[a,d]cycloheptenes, none is suitable for the preparation of the 2-nitro-derivative. Therefore, the 2-bromo-derivative was the next best starting material for the synthesis of the series. The easiest route for the synthesis of the 2-bromo-5H-dibenzo[a,d]cycloheptene was through the connections at b and d, even though the chloro-derivative was obtained in good yield through the connections at *b* and *e*.

The next step in the preparation of a series of compounds via the bromide was its conversion to a nitrile using cuprous cyanide (page 25). The solvent effect was found to be of great importance in this reaction. Friedman and Schechter (101) obtained good yields of aromatic nitriles using DMF as solvent. However, a better yield of 2-cyano-5H-dibenzo[a,d] cycloheptene was obtained with N-methylpyrrolidone as solvent. Advantages of this solvent had previously been noted (100).

The carbomethoxy-derivative was easily obtained by hydrolysis of the nitrile, followed by esterification of the resulting carboxylic acid.

The method described by Snyder and coworkers (118) for the preparation of aromatic amines from carboxylic acids in the presence of hydroxylamine hydrochloride and polyphosphoric acid was not successful for the preparation of 2-amino-5H-dibenzo[a,d]cycloheptene from the corresponding acid.

The preparation of 2-methyl-5H-dibenzo[a,d]cycloheptene could not be done by the following sequence:

$$\mathrm{R\cdot CO_2CH_3} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{RCH_2OH} \xrightarrow[\mathrm{B^-}]{\mathrm{TsCl}} \mathrm{RCH_2OT_s} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{RCH_3}$$

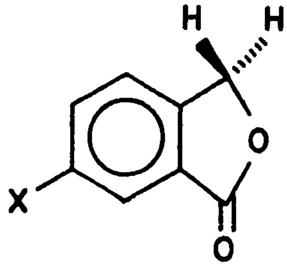
because the benzylic tosylate group reacted with the base present during its formation. The 2-methyl derivative was therefore prepared from toluene in the same manner as the methoxy derivative was prepared from anisole.

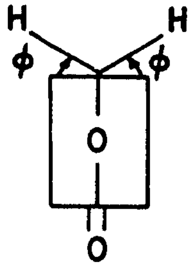
The validity of the conformational dependence of ρ vs σ for a series of benzylic protons would be ideally tested with a large number of substituted compounds in each series, but a compromise has to be made between the synthesis of a large number of compounds in one series or a limited number of compounds in several series within the time available. Miller and coworkers (58) suggest that at least ten representative compounds are needed to satisfy the basic requirements of being precise. However, five to seven substituted compounds in four series should be sufficient to determine whether or not the conformation of the benzylic protons has an effect on ρ. Should the results prove encouraging more detailed studies will ensue.

2. Stereochemistry

The configuration and the bond angles of each benzylic proton in relation to the π orbitals of the benzene ring in the four series of compound studied have to be known in order to determine the exact influence of stereochemistry on the chemical shifts and the geminal coupling constants of the benzylic protons.

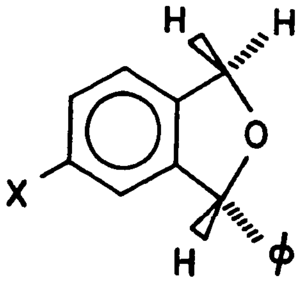
The two benzylic protons of phthalide are magnetically equivalent with their H-H axis perpendicular to the nodal plane of the π orbitals of the benzene ring. The angle ϕ between the C-H bond of the methylene group and the π orbitals of the benzene ring is assumed to be 30°.

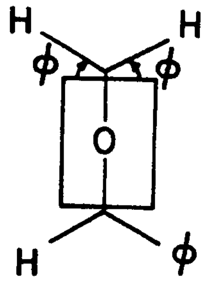




(SIDE VIEW)

On the other hand, the two benzylic protons in 3-phenylphthalan are magnetically non-equivalent due to the asymmetric center at position 3. The five-membered ring appears almost completely rigid (from examination of a model), and the bond angle between the benzylic C-H bonds and the π orbitals of the benzene ring can only vary by 10° or less. For this reason, the average H-H axis and bond angles are expected to be similar to those in the phthalide molecule.





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The determination of configuration of 5H-dibenzo[a,d] cycloheptene and its corresponding epoxide is more complicated. Evans and Lord (119) interpreted their infrared and Raman spectral measurements on cycloheptatriene as indicative of a quasi-aromatic ring, although a structure in which the CH_2 group is displaced slightly out of the molecular plane could not be excluded. Tulinsky and Davis (120) showed from an X-ray determination that the conformation of the p-bromophenacyl ester of 7,7-dimethyl-cycloheptatriene-3-carboxylic acid was in a boat conformation. This conformation was also supported by ter Borg and coworkers (121) from the observation of a 1,5-transannular hydrogen shift in cycloheptatriene. Anet (122) showed from N.M.R. studies at low temperature that cycloheptatriene is definitely nonplanar and found the activation energy for the inversion process to be 6.3 kcal/mole. Shimanouchi and coworkers (123) did an X-ray determination on

5H-dibenzo[a,d]cyclohepten-5-one and found that the seven-membered ring is in a boat conformation similar to cycloheptatriene. The benzene ring planes were estimated to be inclined to each others at an angle of about 39° (figure 7).

The conformation of 2-substituted-5H-dibenzo[a,d] cycloheptene (figure 8) should be, to a first approximation, the same as for the ketone shown in figure 7. The bond angles for the C-H_A and C-H_B bonds with respect to the nodal plane of the π orbitals of the benzene rings were measured on a Dreiding molecular model and were found to be approximately 50° and 10° respectively. The H-H axis was estimated to be at an angle of 73° with respect to the π orbitals of the adjacent benzene rings.

A variable temperature NMR study of 5H-dibenzo[a,d] cycloheptene has shown it to be a rapidly inverting structure on the NMR time scale. The inversion barrier for the two conformers was determined from observation of the two non-equivalent methylene protons at C-5 at low temperature. From the coalescence temperature (T_c = -71°C), the expression (124)

$$k_r = \frac{\pi\sqrt{\Delta\nu_{AB}^2 + 6J_{AB}^2}}{\sqrt{2}} \qquad (13)$$

the Eyring equation (125) and using a transmission coefficient of 1, the barrier could be calculated. At a temperature of -90°C, the methylene protons appeared as a quartet with $\Delta\nu_{AB}$ = 24.8 H_z and J_{AB} = 12.8 H_z. From all these parameters,

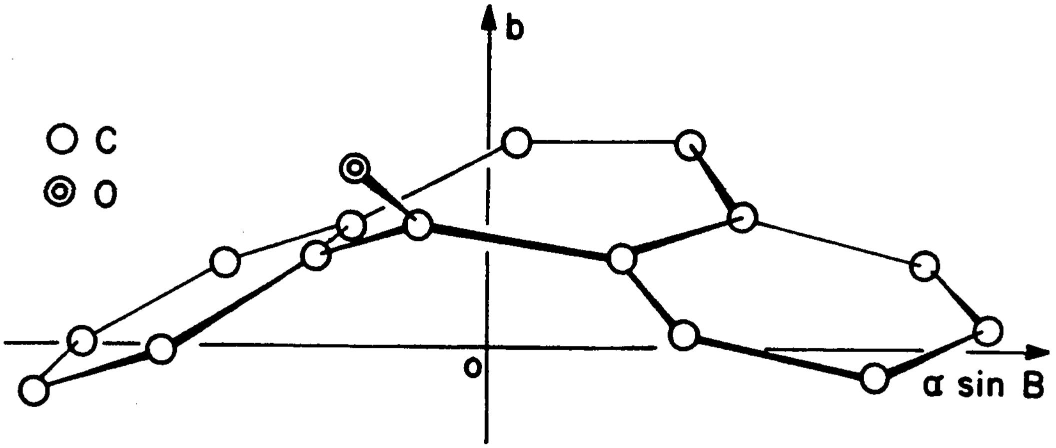


Figure 7. Conformation of 5H-dibenzo[a,d]cyclohepten-5-one

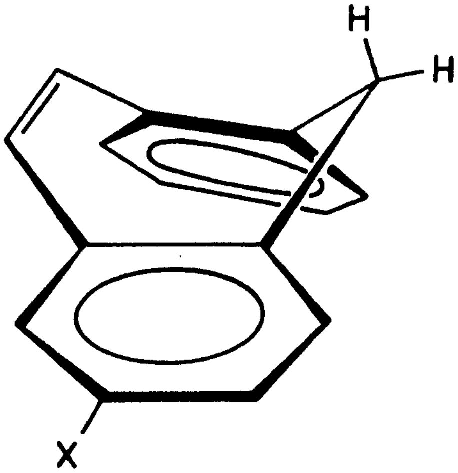


Figure 8. Conformation of 2-substituted-5H-dibenzo[a,d] cycloheptene.

the free energy of activation ($\Delta F^{\ddagger}$) was calculated to be 9.8 kcal/mole, a value comparable with other similar systems. For instance, a value of 15 kcal/mole was reported for 5,5-dimethoxy-5H-dibenzo[a,d]cycloheptene (126) in which inversion is sterically hindered by the substituents at the position 5.

Variable temperature measurements were also done on 3-methoxy-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptene in order to find if the quartet of the AB system for the non-equivalent methylene protons will be frozen into two AB systems at low temperature when the rate of inversion is slowed or will perhaps vary at higher temperature. No significant changes in the spectra were noticed over the temperature range of -90° to +140°. From this observation, it can only be said that the energy barrier for the inversion is too low to be measured on the N.M.R. time scale, too high or that there is only one dominant conformation. As the coalescence temperature could be measured for a variety of similar systems (122,126) in the range of temperatures used, the epoxide molecule likely has only one preferred conformation with the epoxide group in a quasi-axial or a quasi-equatorial position. Bauld and Rim (127,128) concluded from N.M.R. spectroscopic analysis that 5-hydroxy-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptene has a conformation in which the epoxide ring is quasi-axial. This conclusion was based on the observation of a coupling constant of 12.5 H_z between the two protons in the H-C-O-H fragment, in $CDCl_3$, which requires the two protons to be trans (129). In addition, an hydroxyl band at 3440 cm^{-1} in the infrared which was unaffected by dilution requires a bonded OH. However, a model of the molecule in this conformation shows that the interatomic distance between the epoxide oxygen and the proton of the OH group is only 0.6Å, a distance within which a strong van der Waals repulsion effect must occur. This van der Waals interaction also appears to be repulsive in the case where the OH is replaced by a proton (O---H distance = 1.56Å). Corroborative information on the conformation of the 2-methoxy-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d] cycloheptene was obtained by a study of nuclear Overhauser effects. The spectrum of this epoxide is illustrated in figure 9 and the results are shown in Table III.

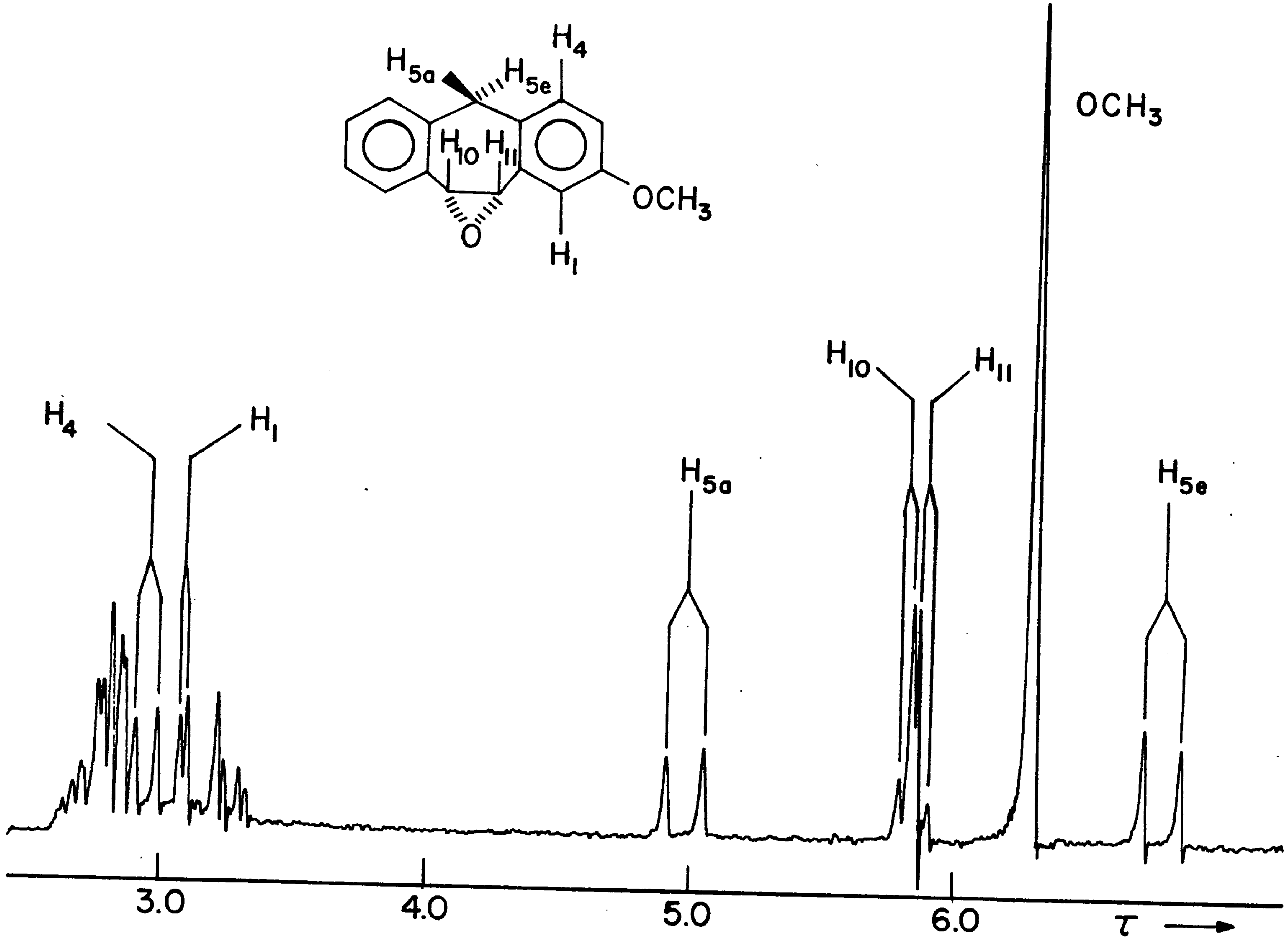
The following observations were obtained from the N.O.E. experiment:

1. The transannular signal intensity increase at the C-10 and C-11 protons of 3% during irradiation of the low field doublet and none during the irradiation of the high field doublet suggest that the low field doublet represents the proton closer to the epoxide protons and is therefore quasi-axial. This conclusion is also supported by the fact that a larger N.O.E. was observed at the high field doublet than at the low field one during irradiation of the C-4 proton.

In two molecules possessing similar geometries, the assignment of the low field proton to be quasi-axial was made by Lansbury and coworkers (130,131) from N.O.E., low-temperature and long-range coupling studies on 7-methoxy-7,12-dihydropleiadene and by Winstein and coworkers (132,133) from an N.M.R. study on 5-hydroxy-10,11,dihydro-cyclopropa[f] 5H-dibenzo[a,d] cycloheptene.

2. The 5% signal enhancement observed at the quasi-axial proton during irradiation of the C-11 proton, or vice-versa, suggests that these protons relax each other and therefore the epoxide group is quasi-equatorial. The internuclear distance between a C-11 proton quasi-equatorial and a C-5 proton quasi-axial was measured and found to be nearly 4Å (Table III) and no mutual relaxation between these protons would be expected at such a distance. Winstein (132,133) gave evidence that the cyclopropylmethylene group in his cyclopropa[f] dibenzo[a,d]cycloheptene molecule preferred a quasi-equatorial conformation.

The conformation of 2-methoxy-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptene is therefore that illustrated in figure 10.



gure 9. NMR spectrum of 2-methoxy-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptene.

TABLE III

Nuclear Overhauser effects in 2-methoxy-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptene

H_1	H_4	H_{5e}	H_{5a}	H_{10}-H_{11}	H_{11}	CH_3	Internuclear distance (Å)[c]	
[12][b]						*[a]	2.9	(2.9)
[20]					*		2.8	(2.4)
*					[11]		2.8	(2.4)
			[5]		*		3.3	(3.9)
			*	[3]			3.3	(3.9)
		*		[0]			4.7	(5.2)
	*	[16]					2.3	(2.3)
	*		[5]				3.4	(3.4)

a * refers to the proton irradiated.

b [%] refers to the % increase in integrated intensity of that proton.

c as measured from a Dreiding Molecular Model for a quasi-equatorial epoxide ring (In parentheses are the values for a quasi-axial epoxide ring).

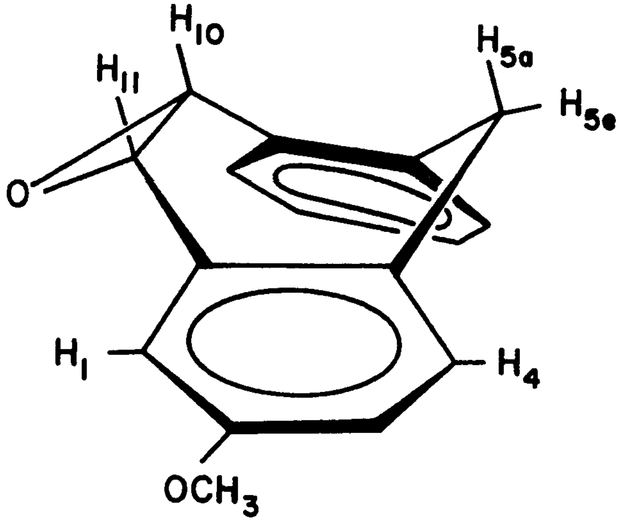


Figure 10. Conformation of 2-methoxy-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptene.

The only explanation which can be given for Bauld and Rim's finding is that their molecule possessed an equatorial epoxide group and an axial hydroxyl group which was retained in a trans conformation by hydrogen bonding to the C-C bond of the epoxide ring. Such bonding, while not previously known, might be possible in view of the known ability of a cyclopropane ring to form a hydrogen bond (134,135). This tentative rationalization requires further study.

3. Effects of substituents on the chemical shift of benzylic protons

The chemical shifts of the benzylic protons in four series of compounds substituted at the position para to a methylene group (figure 11) were determined. All spectra were taken in deuteriochloroform using 0.1 M concentration to avoid any intermolecular effects. No changes in the spectra were noticed from a 0.3 M solution down to a 0.1 M solution. Miller and coworkers (58) made a study on the solute-solvent and solute-solute interactions for para-substituted benzyl fluorides, chlorides and bromides in different solvents. Even though these halides showed a strong tendency to associate, they found that the chemical shifts at 0.1 M and at infinite dilution by extrapolation varied by less than 1 Hz. We feel confident that, since our solutes showed no tendencies towards association over the 0.3 to 0.1 M range, the values measured at 0.1 M concentrations can be used to represent shifts at infinite solution. The chemical shifts in τ values for each series were plotted against Hammett σ constants. The standard para σ values listed by McDaniel and Brown (136) were used. The ρ values were determined from a least-squares analysis (137) and the results are shown in figures 12, 13, 14, 15 and in Table IIIa, IIIb and IV.

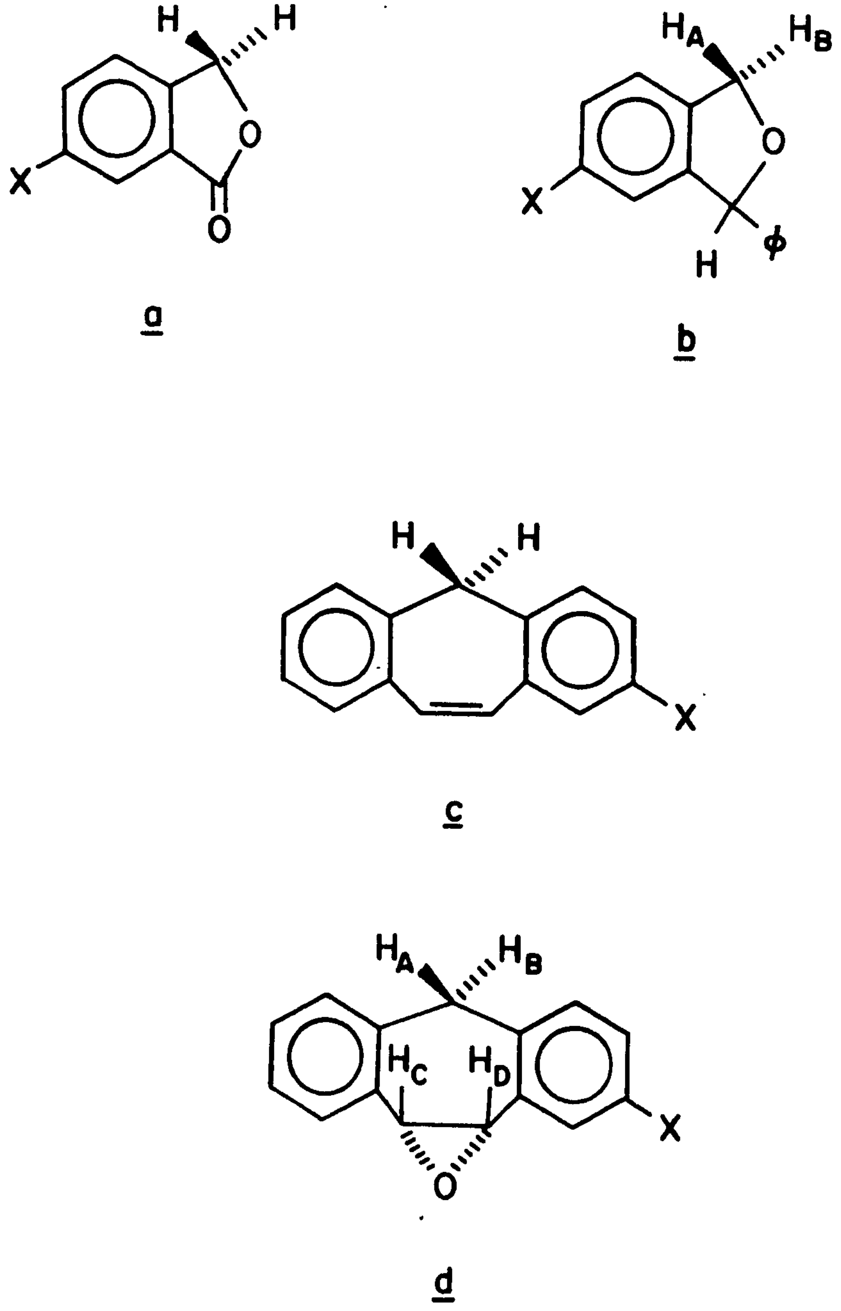


Figure 11. Structures of phthalide (a), 3-phenylphthalan (b), 5H-dibenzo[a,d]cycloheptene (c) and 10,11,dihydro-10,11,epoxy-5H-dibenzo[a,d] cycloheptene (d).

TABLE IIIa

Chemical shifts for the methylene protons of the 5-substituted-3-phenylphthalans.

Proton	Substituent	Shielding value*, τ
H_A	NO_2	4.741
	CN	4.773
	H	4.795
	OCH_3	4.861
	NH_2	4.894
H_B	NO_2	4.664
	CN	4.647
	H	4.668
	OCH_3	4.732
	NH_2	4.766

*Measured in deuteriochloroform.

TABLE IIIb

Chemical shifts for the methylene protons of the 2-substituted-5H-dibenzo[a,d]cycloheptenes.

Substituent	Shielding value*, τ
CN	6.25
CO_2CH_3	6.23
H	6.32
CH_3	6.31
OCH_3	6.33

*Measured in deuteriochloroform.

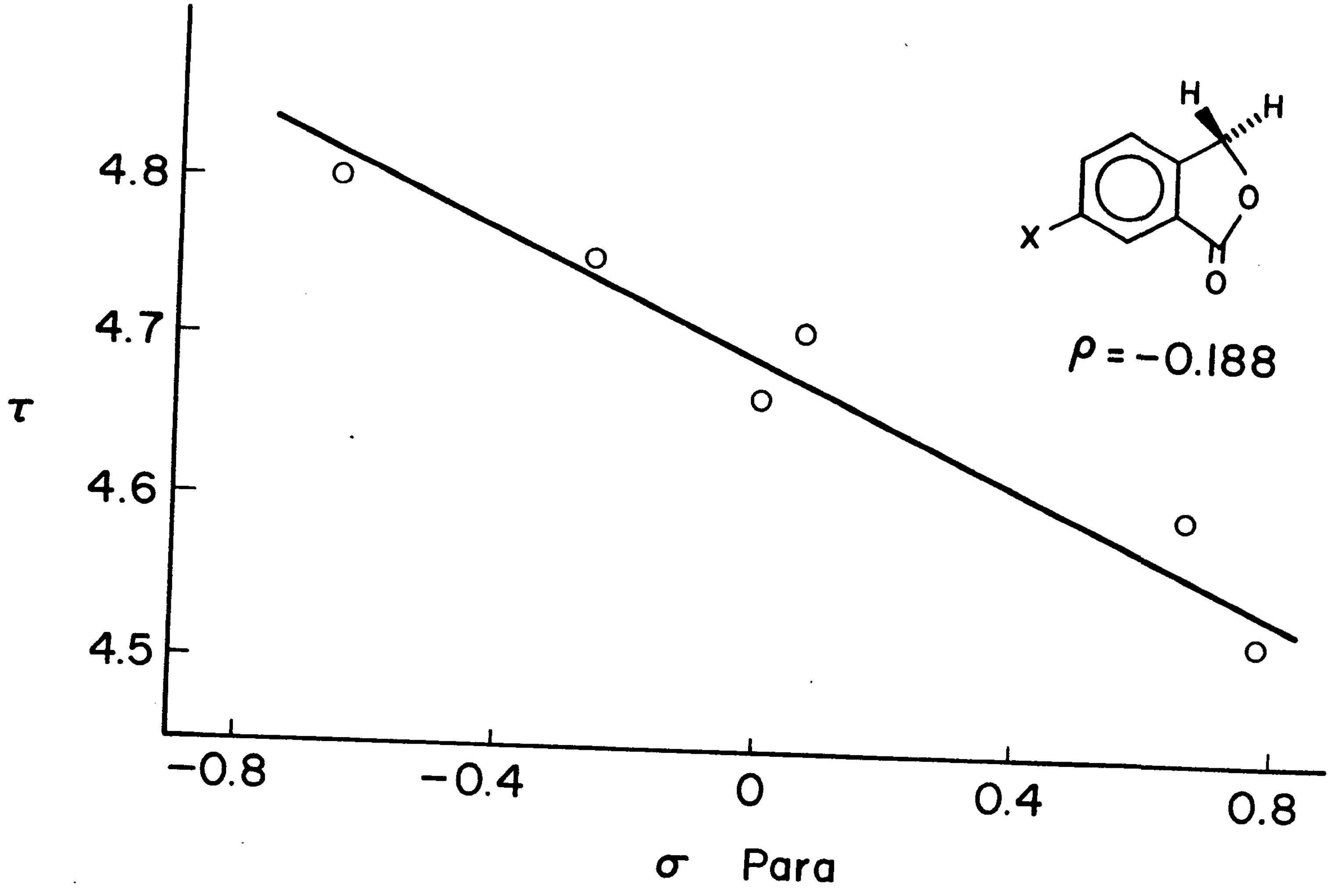


Figure 12. A Hammett plot of the benzylic proton shifts of 6-substituted phthalides.

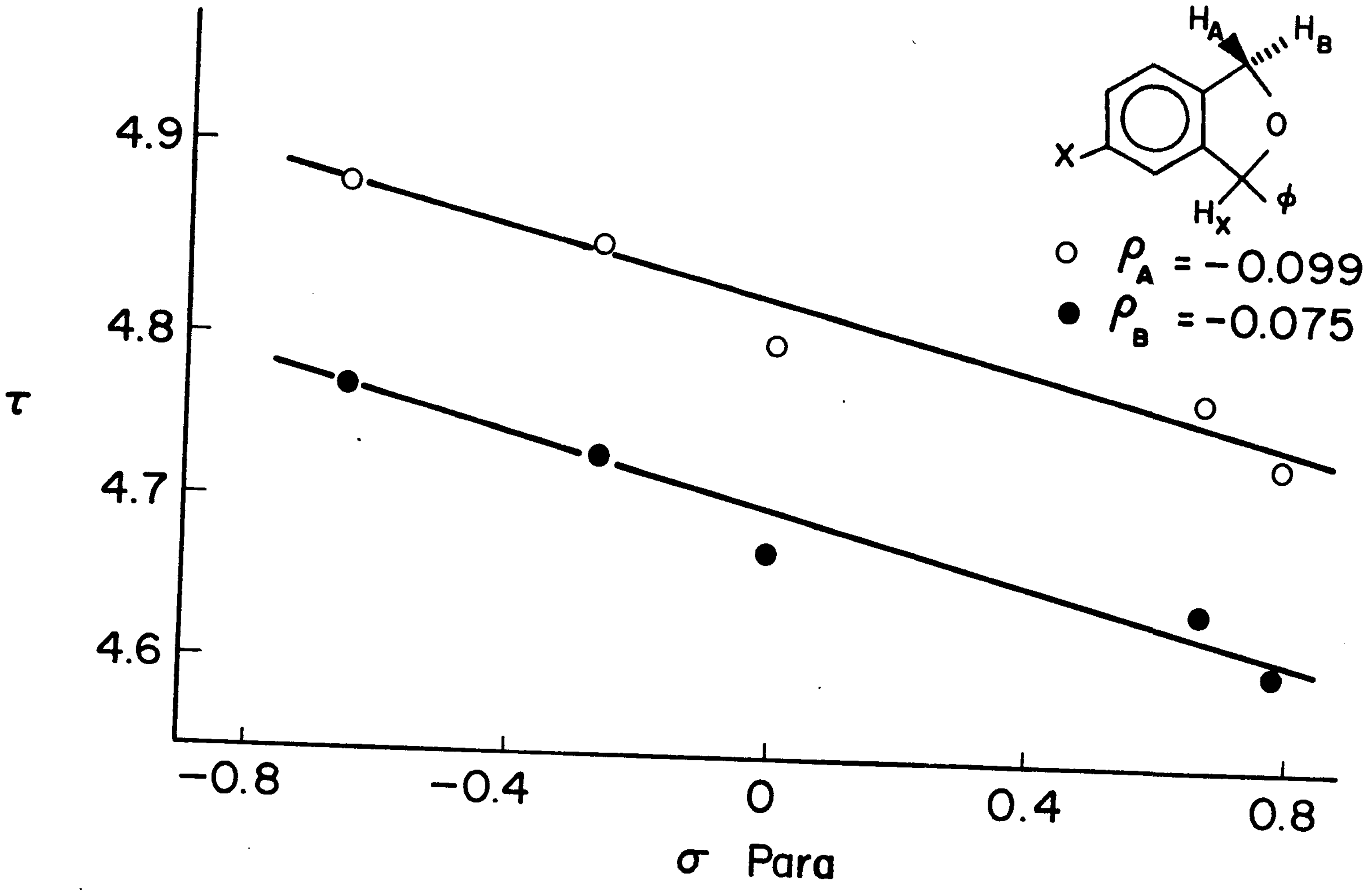


Figure 13. A Hammett plot of the benzylic proton shifts of 5-substituted-3-phenylphthalans.

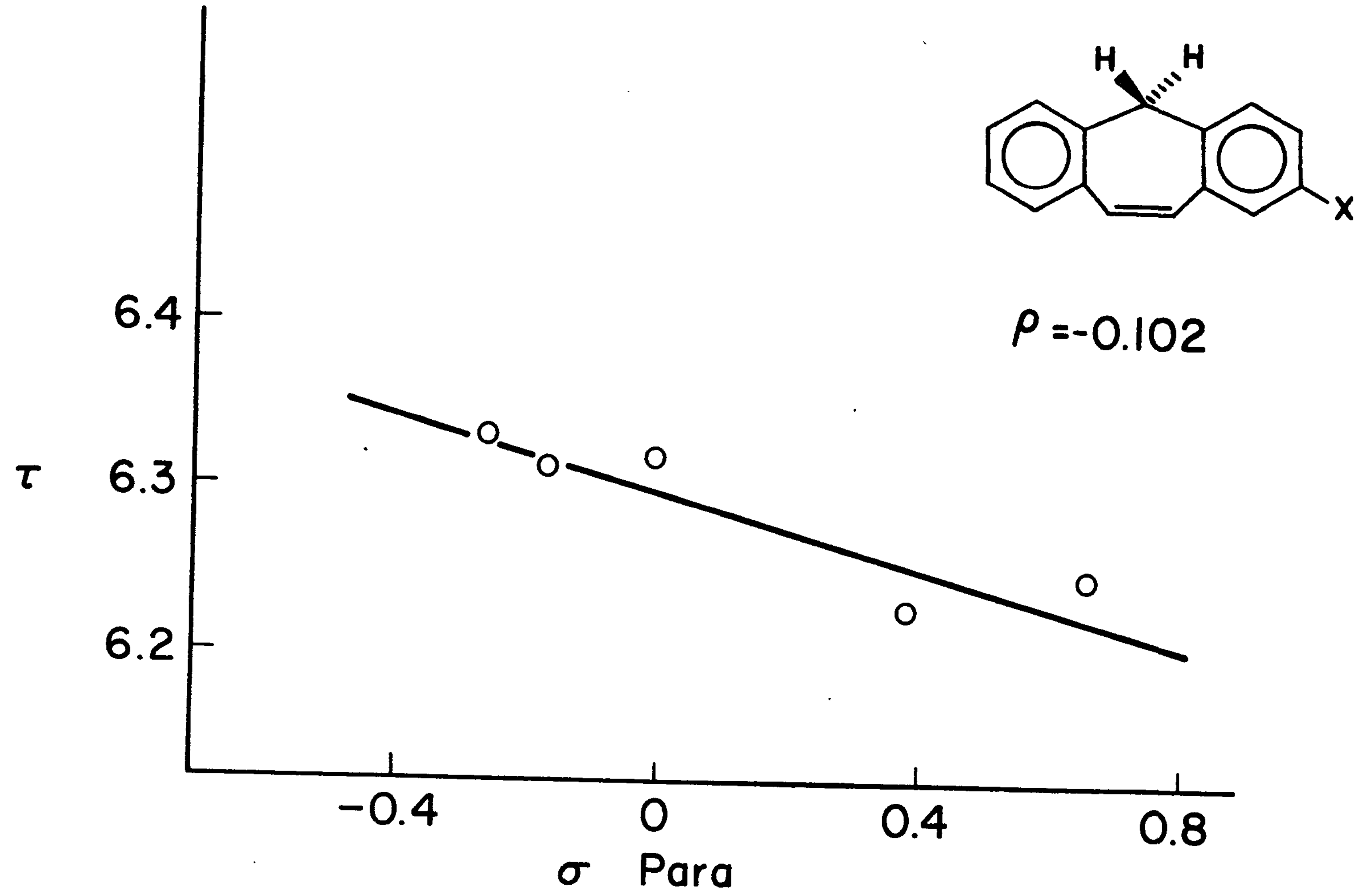


Figure 14. A Hammett plot of the benzylic proton shifts of 2-substituted-5H-dibenzo[a,d]cycloheptenes.

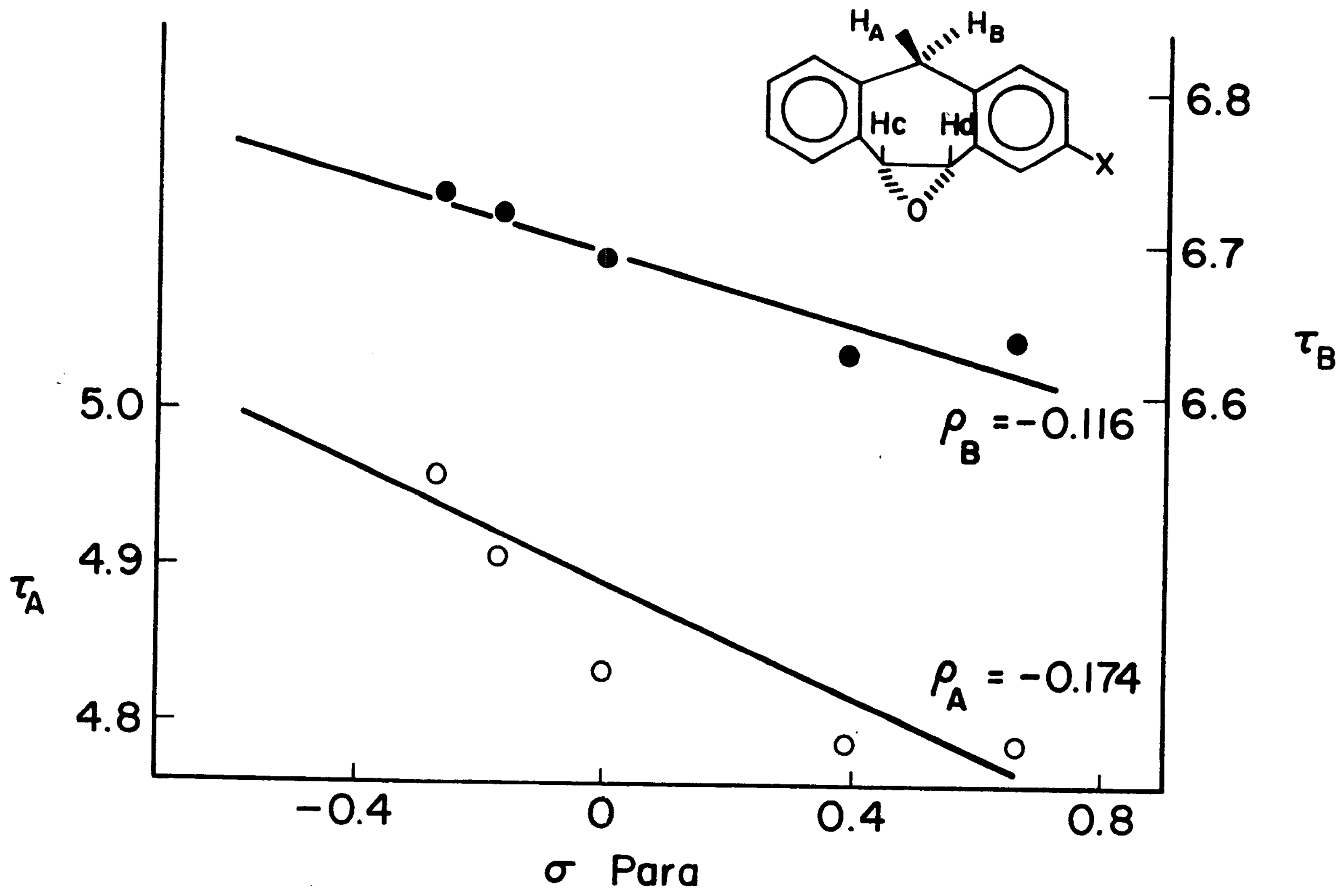


Figure 15. A Hammett plot of the benzylic proton shifts of 2-substituted-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d] cycloheptenes.

TABLE IV

Rho values of SCS-Hammett σ plots for series a, b, c and d

Series	Proton[a]	$-\rho$[b]	r[b]	s[b]	n[c]
a	-	0.188	0.941	0.036	6
b	H_A	0.099	0.959	0.021	5
	H_b	0.075	0.900	0.026	5
c	-	0.102	0.88	0.025	5
d	H_A	0.174	0.90	0.038	5
	H_B	0.116	0.92	0.022	5

a) see figure 11 for labelling of protons

b) ρ, r and s represent the slope in p.p.m./σ, the correlation coefficient and the standard deviation as derived from a least-squares treatment of the data.

c) n is the number of compounds studied in each series.

In all cases, correlation coefficients (r) better than 0.88 and standard deviations (s) less than 0.04 were obtained. The halogenated derivatives were not used in the calculation of ρ since previous experience has shown that consistent high field deviation from the best straight line are commonly encountered with these substituents (66,67).

It has been proposed by Fraser and coworkers (67), that the ρ value should be maximal for a system where the benzylic C-H bond is colinear with the adjacent π orbital, and should follow a $\cos^2\phi$ relationship (figure 16) if only hyperconjugative effects are operating. On this basis, ρ values for the benzylic protons for the four series, shown in Table V, were calculated from the angles ϕ measured from Dreiding models and the assumption of a maximum ρ value of -0.42. This maximum ρ value is estimated from the fact that the average ρ value for the methyl protons in <u>para</u>-substituted toluenes (57) is -0.21.

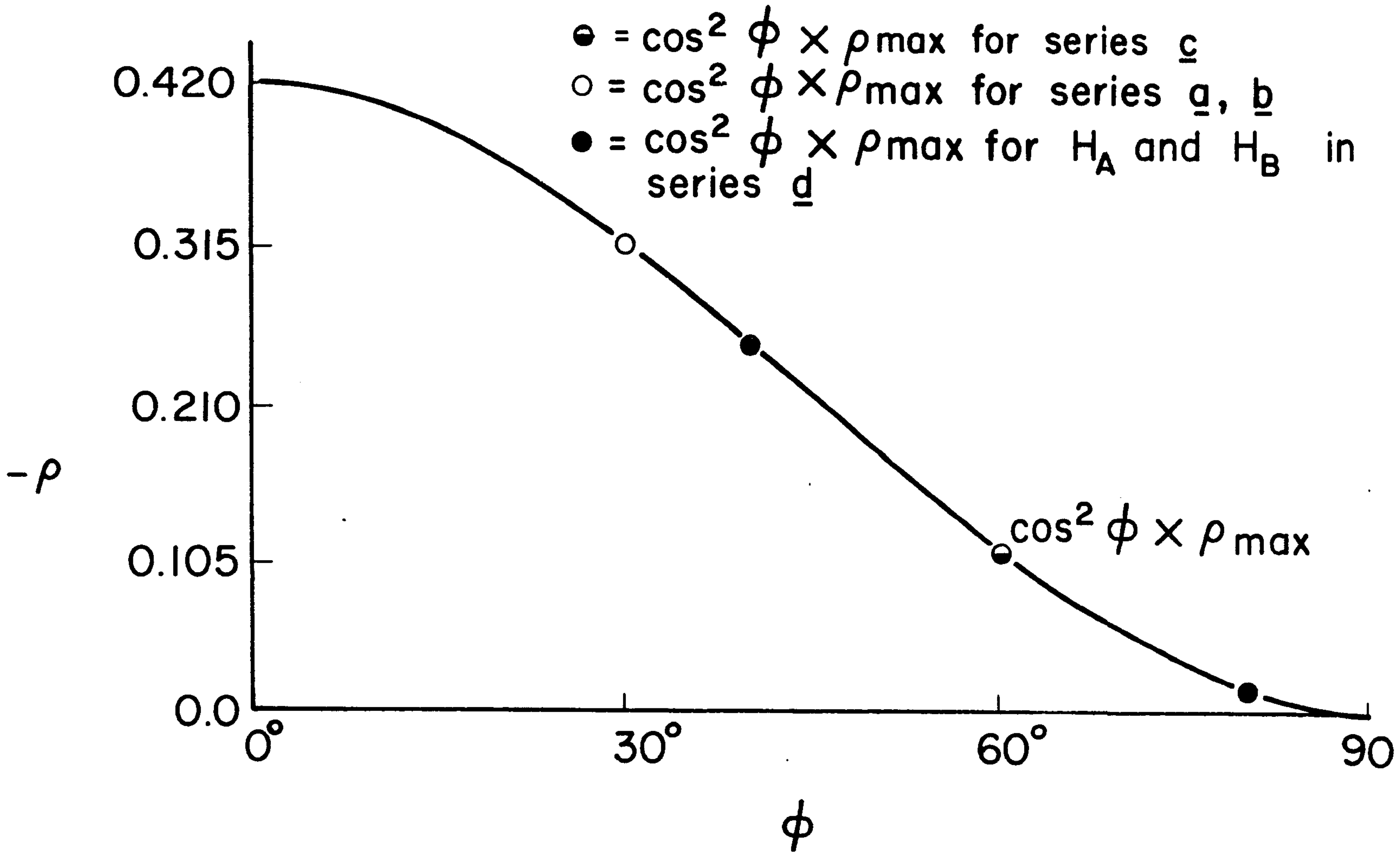


Figure 16. Calculated $\cos^2\phi$ relationship between ρ values from SCS and the conformation of the benzylic protons.

TABLE V

Calculated and Observed

ρ values of SCS-Hammett σ plots for

series a, b, c and d.

Series	C-H bond	Angle ϕ	$-\rho$ Calculated	$-\rho$ Observed
a	-	30	0.3	0.188
b	C-H_A	30	0.3	0.099
b	C-H_B	30	0.3	0.075
c	-	60	0.12	0.102
d	C-H_A	40	0.23	0.174
d	C-H_B	80	0.02	0.116

The ρ value for the equivalent benzylic protons in the phthalide series is lower than the calculated value from a $\cos^2\phi$ relationship (Table V) even though the correlation coefficient is good (Table IV). Both C-H bonds of the non-equivalent benzylic protons in the phthalans have the same angle with the π orbitals of the benzene ring as those in the phthalides but they show much lower ρ values. The same very low ρ value was obtained for the non-rigid system c but the correlation coefficient in this case is too low (58) to be considered reliable in this work. The conformation of the molecules in series d has been determined and accordingly the two fixed benzylic protons should give two different ρ values since both protons are magnetically and geometrically non-equivalent. Actually ρ values of-0.174 and-0.116 respectively for the quasi-axial and the quasi-equatorial protons were observed. However, these ρ values for H_A and H_B are respectively lower and higher than those calculated.

It is difficult to explain the actual importance of hyperconjugative effects on ρ,based on the results obtained. Other factors are certainly contributing to the variation of the effect of substituents on the chemical shift of the benzylic protons. It is reported in the literature (138,139) that the main factors influencing the chemical shift of protons are electronic transmission through the σ bonds, the localized π electrons, the contribution due to the ring current of the

π electrons and the solvent effect. The electronic contribution through the σ bond, being equal for the two benzylic protons, might partially explain the results obtained. For example, if the ρ value of -0.21 for toluene is due in part to a σ bond transmission and in part to a π bond transmission then the stereochemical dependence of ρ would be diminished. However, this explanation cannot account for the ρ value of zero observed in studies of two previous series (67). It would seem, therefore, that ring current and solvent effects may also be more important than was first thought.

Johnson and Bovey (140) calculated the theoretical shielding effect of side chain protons due to a ring current and evaluated elliptic integrals for points along the plane of the ring and along the hexagonal axis. Using his evaluation, the ring current is found to contribute to the shielding of the benzylic protons in the four series of compounds studied in this work. However, there remains to explain the effect of the substituents on this ring current. Wu and Dailey (141) and Figeys and Flammang (142) postulated that a change in the π electron density induced by the introduction of substituents in the benzene ring will be reflected by significant modifications in the ring current effect. However, Wittstruck and Trachtenberg (55) assumed that the variation of chemical shifts of the side-chain hydrogen from the anisotropy of the phenyl ring is, to a first approximation, independent of the nature of the substituent. Even though this approximation does not eliminate the possibility of a small variation of the ring current effect on the chemical shifts of the benzylic protons by a variation in the electronic nature of the substituents, it will be difficult at the moment to correlate this effect with the observed ρ values.

4. Solvent effects on the chemical shifts and on ρ

The effect of a change in solvent on the chemical shifts of the benzylic protons was studied for two series of compounds, namely: 6-substituted-phthalides (a) and 2-substituted-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptenes (d); the results are listed in Tables VI and VII. It is instructive to consider these results within the framework of the expression on page 5, i.e.

$$\sigma = \sigma_b + \sigma_a + \sigma_w + \sigma_E + \sigma_H \qquad (5)$$

The term σ_b (the bulk susceptibility of the medium) was not taken into account, because the shifts were determined using an internal standard. The contribution due to σ_a (the anisotropy in the susceptibility of the solvent molecules) can be ignored because the molecules of the solvents are not disc or rod-shapes, except for acetonitrile, and, therefore, the non-vanishing anisotropy effect should be small. The term σ_w (the van der Waals forces between the solute and the solvent) may be neglected here, because the data in Tables VI and VII refer to measurements in solution in which case the van der Waals contribution will be constant. It remains to know the importance of the terms σ_E (the polar effect of neighboring solvent molecules) and σ_H (the hydrogen bonding interaction between the solute and the solvent molecules).

Buckingham and coworkers (22) postulated that when a polar molecule is dissolved in a medium of dielectric constant

TABLE VI

The effect of solvent on the chemical shift of the benzylic protons in 6-substituted-phthalides, in τ values.

Substituent	Solvent				
	$CDCl_3$ $\varepsilon=5.1$	$(CH_2Cl_2)_2$ 10.5	CH_3COCH_3 21.4	CH_3CN 38.8	DMSO-d_6 47
NO_2	4.526	4.575 (+0.049)*	4.409 (-0.117)	4.542 (+0.016)	4.428 (-0.098)
CN	4.604	4.623 (+0.019)	4.465 (-0.139)	4.586 (-0.018)	4.477 (-0.127)
Cl	4.711	4.716 (+0.005)	4.588 (-0.123)	4.682 (-0.029)	4.584 (-0.127)
F	4.709	4.723 (+0.014	4.603 (-0.106)	4.688 (-0.021)	4.584 (-0.115)
H	4.668	4.698 (+0.030)	4.607 (-0.061)	4.698 (+0.030)	4.569 (-0.099)
OCH_3	4.757	4.785 (+0.028)	4.695 (-0.142)	4.745 (-0.012)	4.660 (-0.097)
NH_2	4.803	4.837 (+0.034)	4.807 (+0.004)	4.826 (+0.013)	4.801 (-0.002)

*The number in parenthesis is the shift from the value in deuteriochloroform.

TABLE VII

The effect of solvent in the chemical shift of the benzylic protons in 2-substituted-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptenes, in τ values.

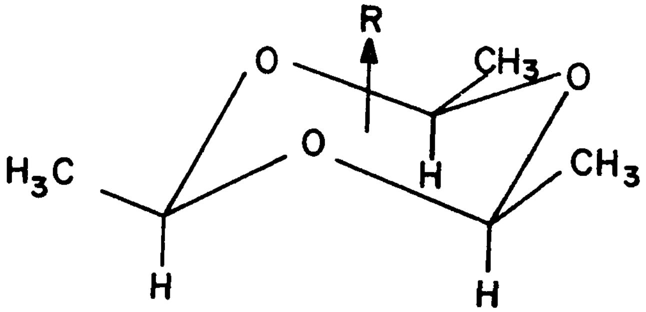
Proton	Substituent	Solvent	
		$CDCl_3$ ε=5.1	CH_3COCH_3 ε=21.4
H_A	CN	4.788	4.869(+0.081)*
	CO_2CH_3	4.791	4.871(+0.080)
	H	4.833	4.898(+0.065)
	CH_3	4.907	4.966(+0.039)
	OCH_3	4.960	5.023(+0.063)
H_B	CN	6.638	6.451(-0.187)
	CO_2CH_3	6.627	6.494(-0.123)
	H	6.691	6.619(-0.072)
	CH_3	6.720	6.660(-0.060)
	OCH_3	6.734	6.658(-0.076)

*The number in parenthesis is the shift from the value in deuteriochloroform.

ε,it polarizes its surrounding and this polarization leads to an electric field (the reaction field R) at the solute. Even molecules which do not have a permanent dipole moment may still produce a reaction field provided that the molecule possesses polar groups. They also pointed out that the magnetic shielding of the nuclei in a chemical bond should depend upon the component along the bond of the electrical field E.

$$\Delta\sigma_E = -k_E \cdot E \cdot \cos\phi - k'_E \cdot E^2 \qquad (14)$$

where k_E is a constant characteristic of an A-X covalent bond, along which E cos ϕ is the projection of the local electric field E and where σ_E is the variation in the screening of nucleus X. Therefore, when cos ϕ is positive, increasing the dielectric constant of the solvent will tend to shift proton signals from polar molecules to lower field. However, the prediction of the effect of the reaction field on chemical shift is more qualitative than quantitative. Diehl and Freeman (143) calculated the chemical shift displacements of the methyl and the methine protons in paraldehyde (I) from the reaction field theory.

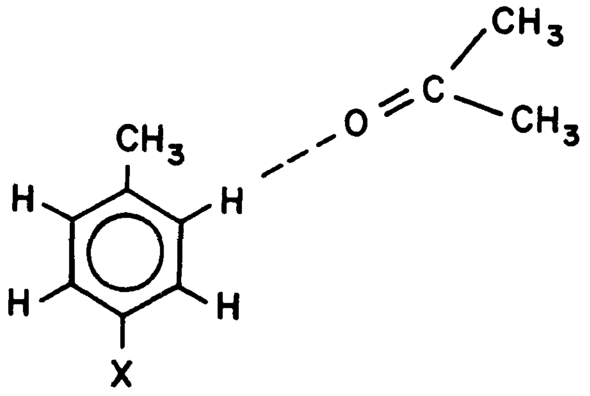


I

The reaction field R in I being directed along the C_{3v} axis of symmetry, the C-H methine protons should then be affected in full with cos $\phi = +1$, and their chemical shift would tend to be at lower field with increasing dielectric constant of the solvent, conversely, the methyl protons would be shielded when the dielectric constant increases because the projection of the reaction field along the C-H bond is now negative, with cos $\phi = -\frac{1}{9}$; the magnitude of the variation ought to be one ninth of that for the methine protons. Actually the individual slopes are -12.3 c/s per dielectric function unit (CH) and -5.5 c/s per dielectric function unit (CH_3). Becconsall and Hampson (144) tried to give an explanation for this discrepancy by postulating that the dielectric constant ε characteristic of the solvent is reduced by a faster random thermal reorientation of the solute molecule than the dielectric relaxation of the medium. This approach still does not give a good quantitative correlation. It can be concluded that the dielectric constant of the solvent has a large influence on the proton chemical shift of molecules possessing polar groups but no quantitative correlation can be made at the moment. The reaction field theory predicts qualitatively that the chemical shift displacements of the benzylic protons in the phthalides should increase or decrease gradually, depending on the cos ϕ element in equation 14, as the dielectric constant of medium increases. However, the results in Table VI show no correlation between the chemical shift of the benzylic protons and the dielectric constant of the medium. Furthermore, the chemical shifts of the benzylic protons in 5-amino-phthalide are nearly independent of the nature of the solvent. The situation is more complicated in the case of the series d since the benzylic protons are geometrically non-equivalent and the relative direction of the reaction field R with the direction of the C-H_A and C-H_B bonds is not known.

Schaefer and Schneider (139) attempted to find the factors controlling the observed solvent effects on the shielding of aromatic hydrogen nuclei by considering all the possible ways in which the solvent shielding interaction could operate. They concluded that the solute-solvent interaction through hydrogen bonding (σ_H) was an important interaction.

Weak hydrogen bond complexes of the type



were suggested as contributing to the variation of chemical shifts. Later experiments have established that aromatic compounds are capable of coordinating at an electron-deficient site within a solute molecule (145). A 1/1 complex between the solute and aromatic solvent molecules seems to exist per polar site provided that they are not too closely located. The relative orientation of both solute and solvent molecules in the associated complex was deduced from the sign of the shifts observed from the solute protons. Ledaal (146) proposed that only one common model exists for the geometry of benzene-solute collision complex. This common model has the dipole axis of the solute molecule located along the sixfold axis of symmetry of the benzene nucleus with the positive end of the polar function nearest, and the negative end farthest away from it. The nature of this association is illustrated in figure 17 for acetone in benzene.

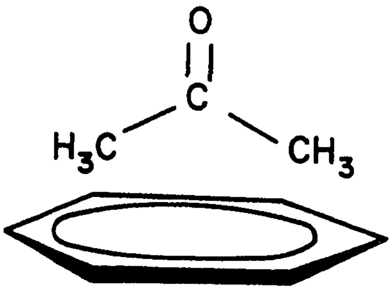


Figure 17. Geometry of benzene-acetone collision complex

The solvent-shift value (+23 H_z) observed for the methyl protons in acetone agrees with the shielding of a proton in the diamagnetic region of the ring current effect.

In this line of thought, it will be interesting to explain the results shown in Tables VI and VII. Practically the same chemical shifts were observed in series a in chloroform and in dichloroethane; meaning that the solute-solvent interaction is similar for both solvents. However, a marked downfield shift in acetone and in dimethylsulfoxide for all substituted phthalides, except for aminophthalide, was observed. Assuming that collision complexes of similar geometry as shown in figure 17 are formed between the aromatic and the acetone or dimethylsulfoxide molecules, then the preferred orientation of the carbonyl group of the acetone and the sulfoxide group in dimethylsulfoxide will be such that the electronegative oxygen will be away from the π orbitals of the benzene ring and the non-bonded electrons of the oxygen of the lactone ring. The exact position of the solvent molecule is not necessarily located along the sixfold axis of symmetry of the benzene nucleus in this case since the aromatic molecule possesses a lactone ring and a variable substituent at position 6. Furthermore, the configuration of the phthalides is such that complexing occurs with equal probability on either side since the two benzylic protons experienced the same solvent effect. Although the anisotropy of a carbonyl group is not well understood (147), it could produce the observed deshielding. A specific molecular interaction by hydrogen-bonding between the solvent and the amino group in 6-aminophthalide of the type NH---OS may cancel the above effect to account for the observed solvent independency on the chemical shift of the benzylic protons.

A possible collision complex between acetone and 10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptene is shown in Figure 18.

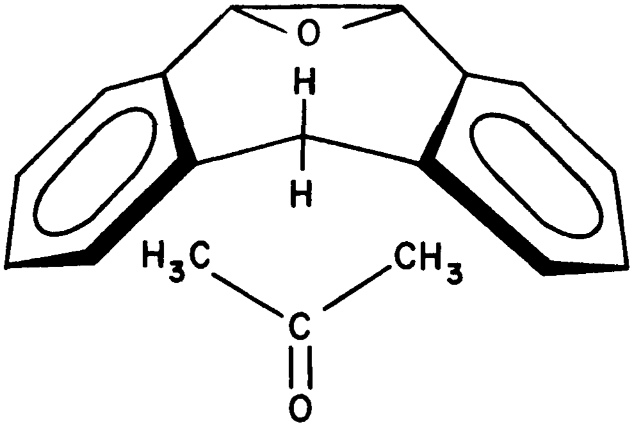


Figure 18. 10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptene-acetone collision complex.

The formation of a collision complex as shown in figure 17 and the mutual repulsion effect between the epoxide oxygen and the acetone oxygen may be combined to orient the acetone molecule in such a direction that the quasi-equatorial and the quasi-axial protons experienced respectively a down-field and a up-field shifts by the anisotropic effect of solvent (Table VII). It will be difficult to predict the exact solvent-solute orientation in such a complex system. Beside this complication, more than one solvent molecule may contribute to the observed experimental results.

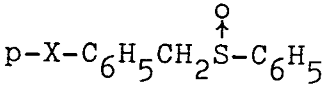
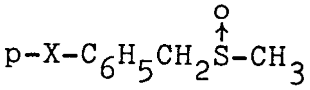
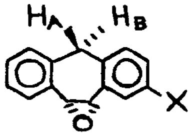
It remains to evaluate the effect of the solvent on ρ based on the results shown in Table VIII. In this table is also included findings by other workers (67).

The correlation coefficients and the standard deviations for series a and d were all dependable. No good correlation between the dielectric constants ε of the solvents and ρ was obtained. It appears therefore that the variation in ρ is largely influenced by specific solvent-solute interactions. This is not too surprising after an analysis of the solvent effect on the chemical shift. The most striking observation is the change in ρ values for the quasi-equatorial and the quasi-axial protons in series d. While the ρ value for the quasi-axial proton (H_A) is slightly reduced, the value for the quasi-equatorial proton (H_B) is tremendously increased from deuteriochloroform to acetone as solvent. It could be that the geometry and perhaps the strength of the collision complex between the solvent and the dibenzo system is influenced by the electronic properties of the substituent, and the quasi-equatorial proton is most affected.

Although these rationalizations can explain the data to a certain extent, the important observation is that the value of ρ has been dominated by the solvent effect. Recently, Miller and coworkers (58) tried to correlate SCS and σ in

TABLE VIII

The effect of solvent on ρ values.

Series*	ρ	r	s	Solvent (ε)
p-X-$C_6H_5CH_2OCH_3$	0.15			$CDCl_3$(5.1)
	0.23			DMSO-d_6(47)
 p-X-$C_6H_5CH_2\overset{\overset{O}{\uparrow}}{S}-C_6H_5$	0.00;0.22			$CDCl_3$
	0.22;0.33			DMSO-d_6
 p-X-$C_6H_5CH_2\overset{\overset{O}{\uparrow}}{S}-CH_3$	0.10;0.14			$CDCl_3$
	0.06;0.13			D_2O(80)
	0.22;0.33			DMSO-d_6
Phthalides, (a)	0.19	0.94	0.036	$CDCl_3$
	0.17	0.97	0.022	$ClCH_2CH_2Cl$(10.5)
	0.26	0.99	0.017	CH_3COCH_3(21.4)
	0.19	0.99	0.017	CH_3CN (38.8)
	0.24	0.98	0.028	DMSO-d_6
	0.17(H_A);0.12(H_B)	0.90;0.92	0.038;0.022	$CDCl_3$
	0.15(H_A);0.25(H_B)	0.87;0.99	0.039;0.018	CH_3COCH_3

*The results for the three first series were obtained from ref. 67.

the general system R-C_6H_5-T-H, where T = 0,1 or 2 atoms, in ca. 30 aryl systems in order to get information on the transmission of electronic effects, and concluded that the ρ values were meaningless because of an enormous still unknown solvent effect on ρ.

It can be concluded from these observations that many factors are influencing ρ, such as the ring current effect, the hyperconjugative effect and the solvent effect. Of these effects, the influence of the solvent can be a most important factor. One of the purposes of this thesis was to examine the dependence of ρ on the configuration of the benzylic protons. It has thus been demonstrated that such a dependence does not exert a major influence on ρ. Nevertheless, if specific solute-solvent interactions can be avoided by the use of "inert solvents", measurements in these solvents might still provide useful information on the electronic factors.

5. Effect of substituents on geminal proton-proton coupling constants

The results obtained by Fraser (69) and by Franck (70) on the effect of para-substituents on geminal coupling constants for freely rotating benzylic systems are to be investigated further in rigid systems having known conformations of the methylene group in relation to the plane of the benzene ring. The two systems studied were the series b (3-phenylphthalans) and d (10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptenes).

From Table IX, it can be seen that the substituent in the 3-phenylphthalans influences the magnitude of the geminal coupling constants. According to theory (27,28), a nitro group, for example, should enhance the hyperconjugative withdrawing power of the phenyl ring and produce a negative shift in J_{gem}. On the other hand, an amino group should produce a positive shift. However, the influence of the substituent in series d is nil or slightly in the opposite direction (Table X) since the electron-withdrawing cyano group caused a slightly more positive shift in J_{gem} than in the case of the electron-donating methoxy group. This behavior is explicable by the variation of the hyperconjugative effect with orientation of the adjacent π orbital as proposed by Pople and Bothner-By (27) and by Barfield and Grant (28). The hyperconjugative effect should be greatest for series b (most negative) and small for series d since in the former

TABLE IX

Geminal and long range coupling constants for the 3-phenylphthalan series (b)

Substituent	$-J_{AB}$*	J_{AX}*	J_{BX}*
NO_2	13.79	2.71	2.02
CN	13.60	2.57	2.03
Cl	12.44	2.60	2.09
H	12.13	2.57	1.91
OCH_3	11.43	2.51	1.99
OH	11.39	2.61	1.98
NH_2	11.35	2.53	1.88

*The signs are assumed to be negative for the geminal coupling constants and positive for the long range coupling constants (79).

TABLE X

Geminal and vicinal coupling constants for the 10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptene series (d)

Substituent	$-J_{AB}$*	J_{CD}*
CN	13.68	4.48
CO_2CH_3	13.71	4.40
Br	13.80	4.32
H	13.66	-
CH_3	13.77	4.45
OCH_3	13.96	4.41

*The signs are assumed to be negative for the geminal coupling constants and positive for the vicinal coupling constants (79).

the H-H axis is parallel to the π orbitals of the adjacent benzene ring and in the latter the angle between the H-H axis and the π orbitals of the benzene ring was measured to be 73° from Dreiding model.

It is also noteworthy from a comparison of the geminal coupling constants in Tables IX and X that the geminal coupling constants are lower for the series b than for the series d. Anteunis (148) has proposed that an increment of +1.8 H_z should be added to J_{gem} each time an α-oxygen or an α-nitrogen atom has one of its "lone pairs" of electrons parallel with a C-H bond. Cookson and Crabb (149) found the same tendency in methylene groups α to nitrogen or oxygen atoms in five and six membered ring compounds; the effect being larger in 5-membered ring than in the corresponding 6-membered ring compounds. This increase in J_{gem} is attributed to the eclipsing effect of the heteroatoms and the maximum contribution is ca. 3.35 H_z for an oxygen atom and 2.5 H_z for a nitrogen atom. Therefore, the observed geminal coupling constants in the phthalans result from a combination of the hyperconjugative effect and the eclipsing effect of the adjacent electrons on oxygen. The exact magnitude of this latter effect cannot be determined easily since the angle between the lone pair orbital of the oxygen atom and the C-H bonds of the adjacent methylene group is not known. The geminal coupling constants in series d are influenced only by a very slight hyperconjugative effect.

Fluorene, which has an ideal geometry for this effect, has a J_{gem} of -20 H_z (29).

The ρ values shown in Table XI and in figures 19 and 21 from correlation of coupling constants with the Hammett σ values are in agreement with the proposal made by Fraser and coworkers (page 20). The hyperconjugative effect should be maximal in series b, with a value of -1.9, because the H-H axis is parallel to the π orbitals of the adjacent benzene ring and very low in series d because the H-H axis is at an angle of 73° with respect to these orbitals. The positive ρ value of 0.3 observed in series d implies that ρ changes sign as the angle nears 90°. In order to obtain a sound conformational relation between ϕ and ρ, further rigid systems are needed. Nevertheless, it is possible to draw a theoretical curve (figure 22) for the $\cos^2\phi$ relationship with the two values obtained in this work (Table XI). From the graph, ρ will change sign when the H-H axis of the benzylic protons is around 66° with the π orbitals of the adjacent benzene ring and the minimum value will probably be +0.5. It is interesting to note that the results of Ripka and Applequist (73), when compared with our findings, agree in a qualitative sense. For a freely rotating CH_3 group, a $\cos^2\phi$ relation averages to 0.5 of the maximum. Thus, a ρ of approximately -0.95 would be expected for their series. They found a ρ value of ca. -0.5, but the accuracy of this value is extremely poor

TABLE XI

Rho values of the coupling constants J versus the Hammett substituent parameter σ for the 3-phenylphthalan series (b) and 10,11-dihydro-10,11-epoxy-5H-dibenzy[a,d]cycloheptene series (d)

Series	J	ρ	r	s	n*
b	AB	-1.89	0.98	0.25	6
	AX	0.09	0.81	0.05	5
	BX	0.10	0.76	0.06	5
d	AB	0.28	0.66	0.11	6
	CD	0.03	0.41	0.04	5

*n represents the number of compounds studied in each series

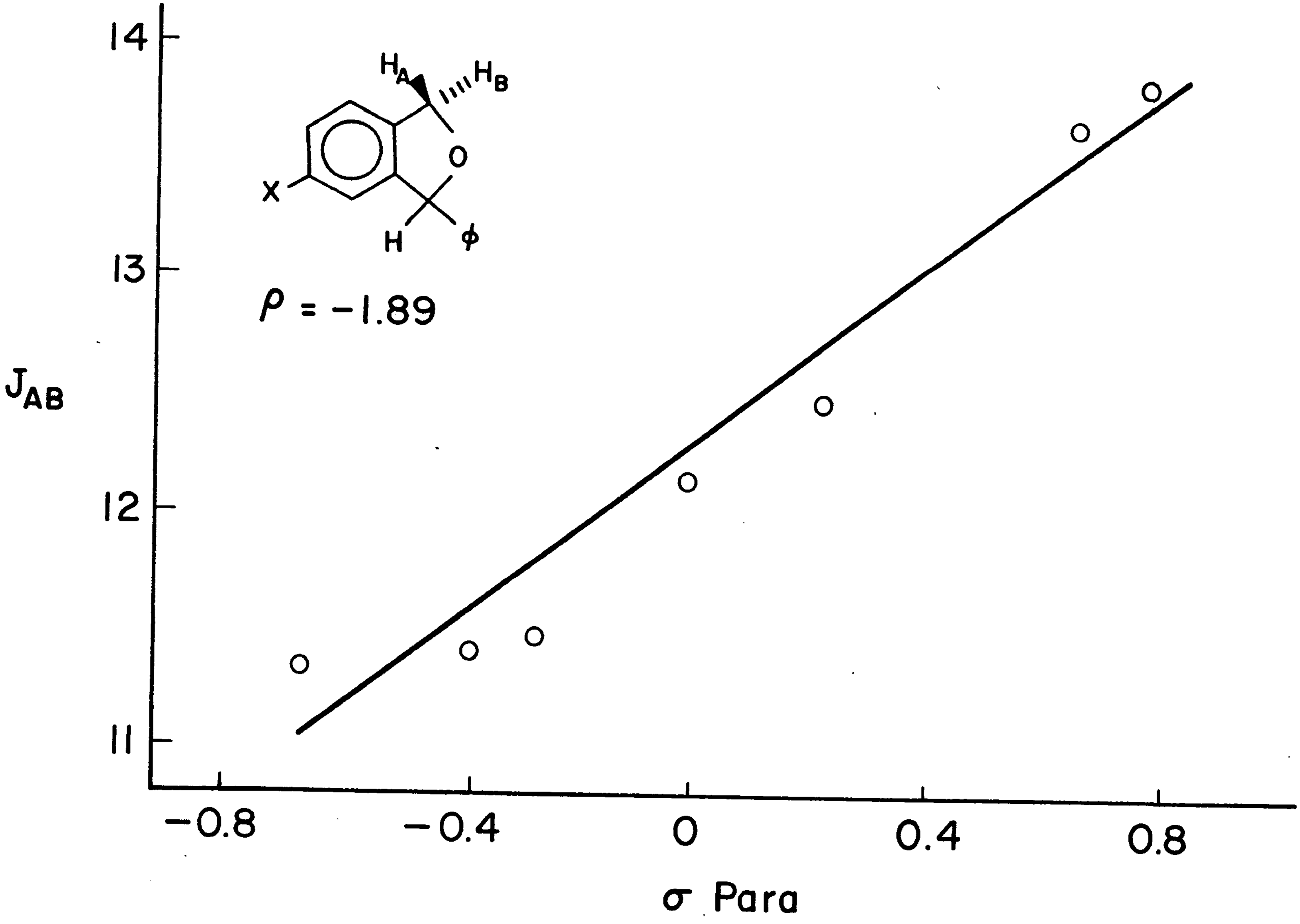


Figure 19. A Hammett plot of the geminal coupling constant in 5-substituted-3-phenyl-phthalans.

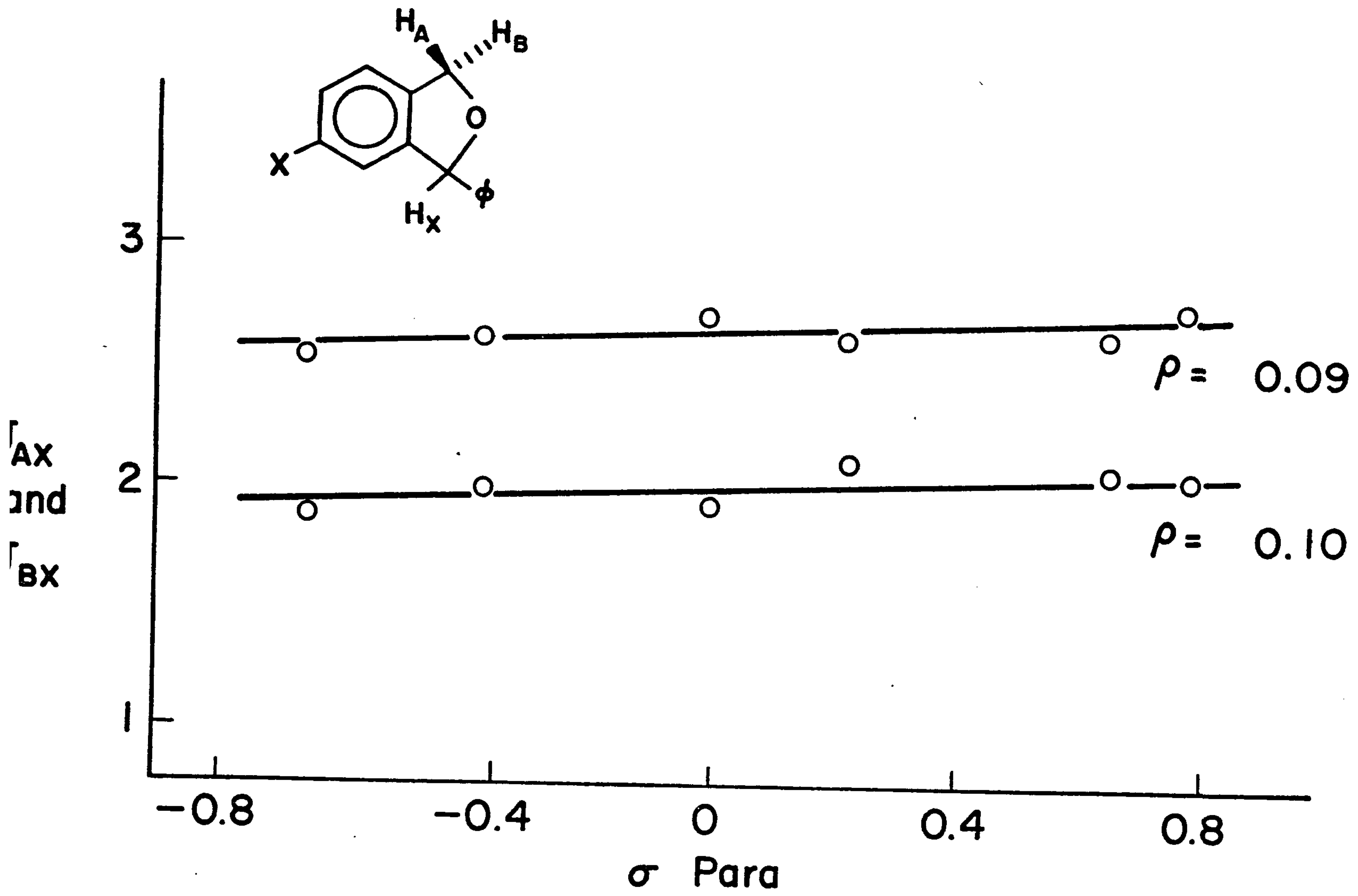


Figure 20. A Hammett plot of long range coupling constants in 5-substituted-3-phenyl-phthalans.

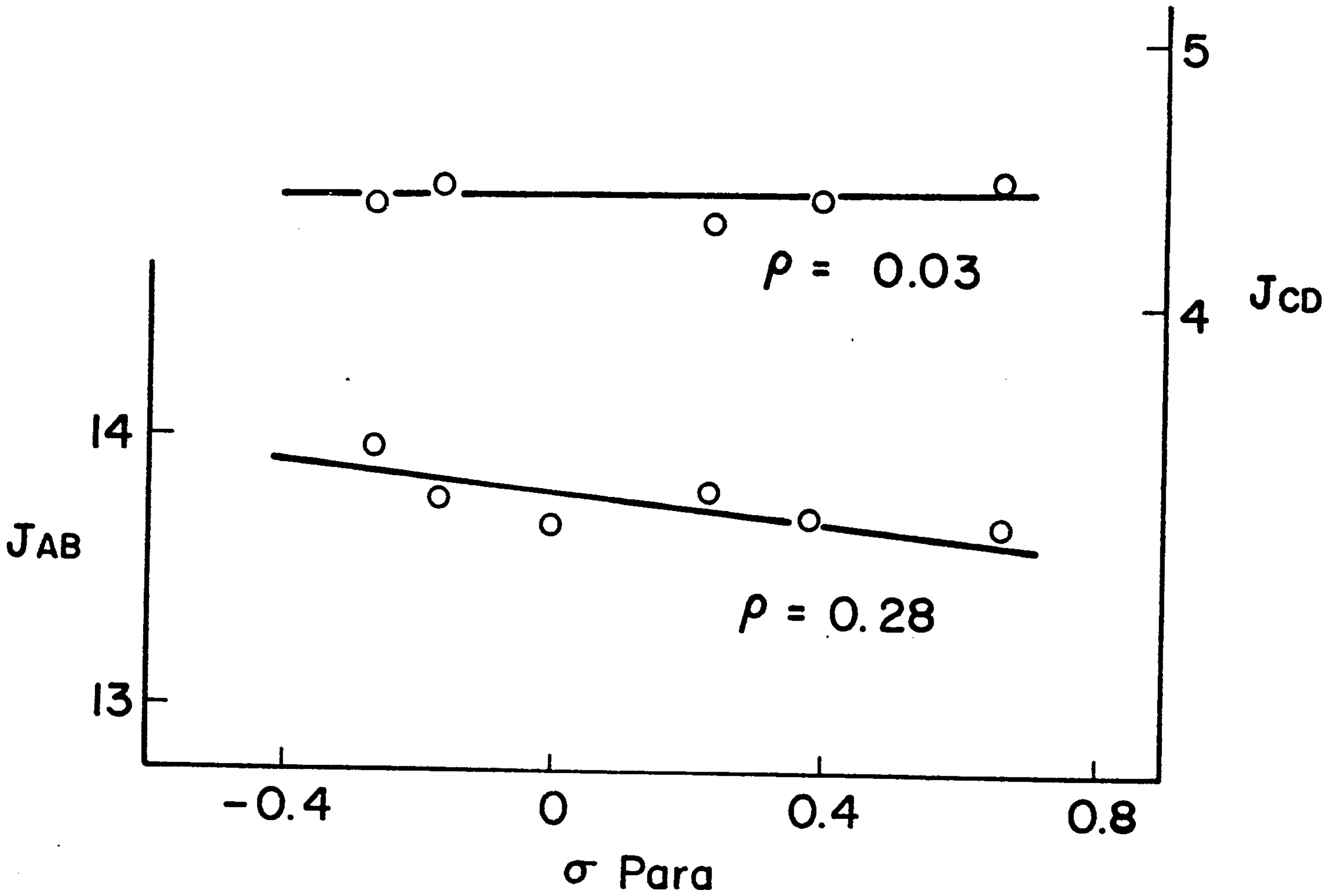


Figure 21. A Hammett plot of geminal coupling and vicinal coupling constants in 2-substituted-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptenes.

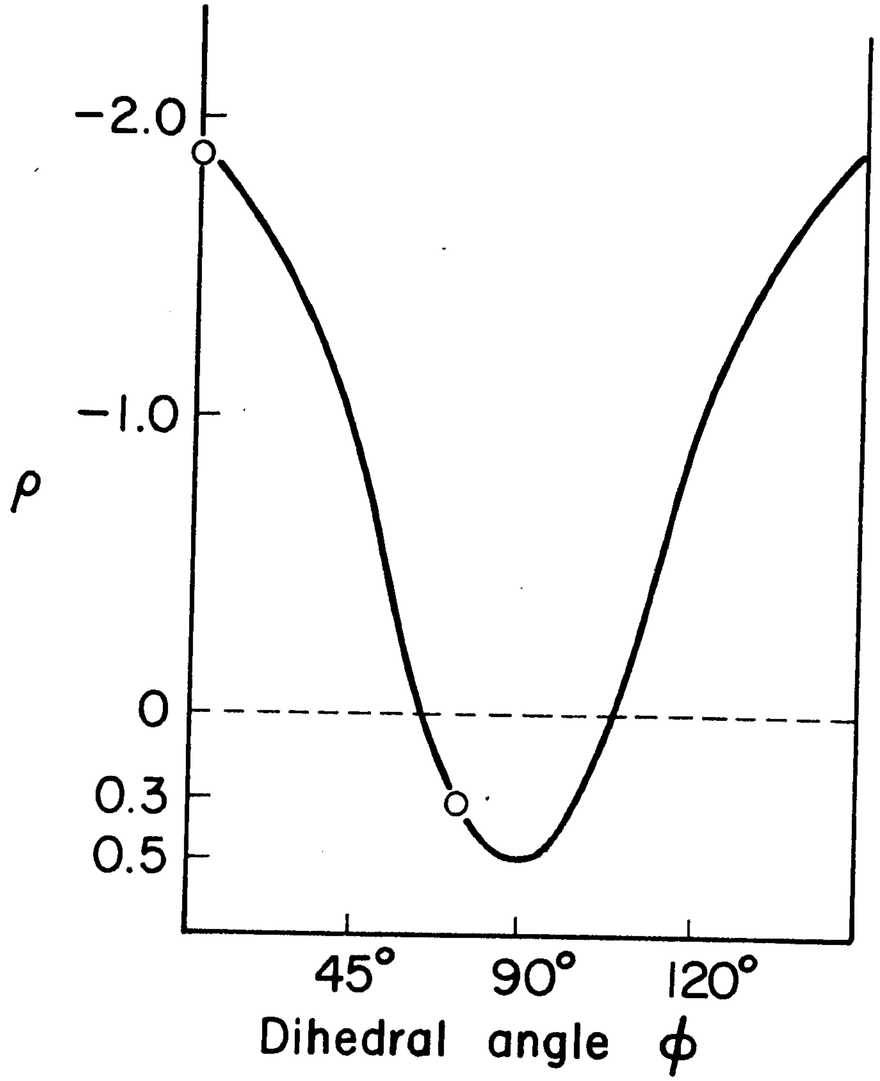


Figure 22. $\cos^2\phi$ relationship between ρ values of geminal coupling constants and the conformation of the benzylic protons.

due to errors in the measurement of J_{gem} by the H-D couplings.

The results obtained for the two rigid systems, b and d, support equally the molecular orbital (MO) and the valence bond (VB) calculations, but no distinction between a smooth $\cos^2\phi$ (27) and a double minimum (28) curve can be made at the moment. Therefore, quantitative conformational analysis based on the dependence of ρ upon conformation of the methylene group with respect to the adjacent π orbitals (69) is still questionable since only two series of rigid systems are known, but the results obtained are in the right direction and more work on the subject is recommended.

6. Effect of solvent on geminal coupling constants

The effect of solvent on the geminal coupling constants was studied in series d and the results are listed in Table XII. A small increase in J_{gem} was observed going from chloroform to acetone as solvent. This increase was greater for the most electron-releasing and electron-withdrawing substituents. Smith and Cox (150) postulated that a negative geminal coupling constant is expected to be made more negative by an increase in the dielectric constant of the medium. The observation shown in Table XII is opposite to this proposal since in acetone the geminal coupling constants were all less negative than in chloroform. Of more practical significance perhaps is the observation that ρ is not affected by the solvent and should, therefore, be a reliable criterion of conformation should further work support our findings.

TABLE XII

The effect of solvent on the geminal coupling constant of the benzylic protons in 2-substituted-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptenes.

Substituent	Solvent	
	$CDCl_3$(ρ=0.3)	CH_3COCH_3(ρ=0.4)
CN	-13.68	-13.11 (+0.57)*
CO_2CH_3	-13.71	-13.50 (+0.21)
H	-13.66	-13.57 (+0.09)
CH_3	-13.77	-13.59 (+0.18)
OCH_3	-13.96	-13.65 (+0.31)

*The number in parenthesis is the difference of the geminal coupling constants from the values in deuteriochloroform.

Conclusions

The proposal presented by many workers on the electronic transmission in aromatic compounds has been analyzed through the effect of para-substituents in benzylic compounds having rigid geometry. Both the chemical shifts and geminal coupling constants of the benzylic protons have been examined. Conformational studies were done on four series of rigid molecules.

It was found that correlations between the chemical shifts of benzylic protons and Hammett σ values depend not only on the hyperconjugative effects, as already proposed, but also on the ring current and the solvent effects. The formation of a collision complex between the solvent and the solute is seemingly an important factor. Therefore, it is suggested that a study of the geometry of these complexes must be made before that of a study on the conformation of the benzylic protons by the hyperconjugative effects.

The correlations between the Hammett σ values and the geminal coupling constants agreed with the proposal that the conformation of the benzylic protons follows a $\cos^2\phi$ relationship with the values of ρ. It was also determined that the solvent had a very low effect on the value of ρ.

This second method seems to be suitable for conformational studies on the benzylic protons, but the evidence given is far from being absolute and a need for further theoretical and experimental work is necessary.

CLAIMS OF ORIGINAL WORK

1. The synthesis of three new series of compounds, namely: 5-substituted-3-phenylphthalans, 2-substituted-5H-dibenzo[a,d]cycloheptenes and 2-substituted-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptenes, was accomplished. A total of twenty new compounds were prepared.

2. The conformation of 2-methoxy-10,11-dihydro-10,11-epoxy-5H-dibenzo[a,d]cycloheptene was determined.

3. The free-energy of activation for the flipping of the seven membered ring in 5H-dibenzo[a,d]cycloheptene was determined.

4. The chemical shifts of the benzylic protons of the system $X-C_6H_5-CH_2-Z$ were found to depend not only on the "hyperconjugative effect" but on other factors, possibly, the formation of solute-solvent collision complex and anisotropy effects.

5. The conformation of the benzylic protons of rigid systems were found to influence the J_{gem} vs σ relationship and the values of ρ were found to be nearly independent of the nature of the solvent.

6. A tentative $\cos^2\phi$ curve from this data on the conformation of the benzylic protons and ρ (J_{gem}-Hammett σ values plots) was constructed.

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VITAE

Roger N. Renaud was born in the city of Hull, Québec, Canada, in 1926. He studied successively at the "Collège Notre-Dame de Hull" and at the "Ecole Supérieure de Hull" for his primary and secondary education. A diploma in Industrial Chemistry was obtained in 1947 from the "Ecole Technique de Hull". Thereafter, as a permanent employee of the National Research Council of Canada at Ottawa, he collaborated on twenty publications of original work, mostly on the synthesis of labelled compounds with deuterium and carbon-13. While working at N.R.C., he obtained a B.Sc. diploma in 1957 and an M.Sc. diploma in 1966 from the University of Ottawa. He resumed graduate studies on a full-time basis in 1967.