SYNTHESIS AND SPECTROSCOPIC STUDIES OF SOME POLYCYCLIC HETEROCYCLIC COMPOUNDS

BY

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A THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY IN THE UNIVERSITY OF LONDON

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APRIL, 1979

TO MY MOTHER

BROTHERS AND SISTERS

ACKNOWLEDGEMENT

I would like to express my sincere thanks to Dr. D.M. Hall for her constant supervision and encouragement, which has made this work most enjoyable.

I should also like to express my gratitude to Professor G.H. Williams, Head of the Department of Chemistry, for offering me a place in his Department.

Measurement of the mass spectra, ^{1}H n.m.r. (220 MHz) spectra, and most of the ^{13}C n.m.r. (22.63 MHz) spectra by the Physico-Chemical Measurements Unit, Harwell, Berks., of some ^{13}C n.m.r. (22.63 MHz) spectra by the University of London Intercollegiate Research Service, King's College, and of ^{1}H n.m.r. (60 MHz) spectra by Mr. G. Howell, Bedford College, is hereby gratefully acknowledged.

I am greatly indebted to Miss M.F. Easton, Bedford College, for carrying out the micro-elemental analyses, and to Mr. R.K. Mitchell and Miss J. Betts, Bedford College, who have so generously furnished photographs of the structures of some of the compounds. Thanks are also due to Mrs. D. Storey for typing the manuscript.

Finally, I am very grateful to my brothers, Dr. John A. Behnam and Dr. Ramsey A. Behnam, for their financial support, without which this research could not have been conducted.

BASIL ABDUL-AHED BEHNAM

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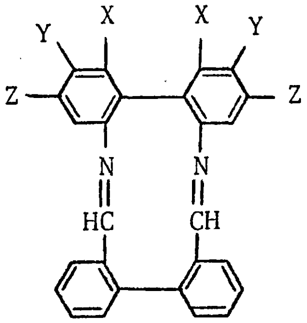
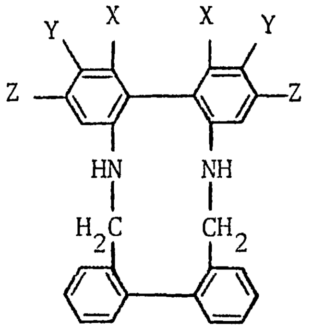
ABSTRACT

Four tetrabenzo[b,d,h,j][1,6]diazacyclododecines, series I, and their tetrahydro derivatives, series II, have been prepared.



Series I

(1) X = Y = Z = H
(2) Y = Z = H, X = CO_2CH_3
(3) X = Z = H, Y = OCH_3
(4) X = Y = H, Z = CO_2CH_3



Series II

(1) X = Y = Z = H
(2) Y = Z = H, X = CO_2CH_3
(3) X = Z = H, Y = OCH_3
(4) X = Y = H, Z = CO_2CH_3

^1H N.m.r. spectra (220 MHz) and ^{13}C n.m.r. spectra (22.63 MHz) of the compounds in both series were studied and assignments of the chemical shifts of most of the nuclei were made.

Temperature variable high resolution ^1H n.m.r. (220 MHz) was employed to study the behaviour of the methyl protons doublet in compounds (3) and (4) of series II, and the diastereotopic methylene protons in all compounds of series II. It is concluded from these results and from the ^{13}C n.m.r. spectra that compounds (1),(3) and (4) in series II must exist as two non-equivalent conformers.

The ultra-violet absorption spectra, in 95% ethanol, of the compounds in both series were determined. On the basis of these spectra and of the ^1H n.m.r. results it is concluded that the compounds in series I, must have the EE configuration.

Mass spectra of the four compounds in series II were measured by the Physico-Chemical Measurements Unit, Harwell. Fragmentation patterns are discussed in detail.

Lanthanide shift reagents, Eu(fod)$_3$ and Pr(fod)$_3$, were used extensively to help in the elucidation of the ^1H n.m.r. spectra (60 MHz) of the compounds in both series. It was found that the mole ratio of the shift reagent/substrate in compounds of series I is 1:1, and 2:1 in compounds of series II. Chirality was observed in compounds (2),(3) and (4) of series I in the presence of large amounts of Eu(tfc)$_3$ or Pr(tfc)$_3$ in $CDCl_3$ solutions. Compounds of series II are achiral under the conditions of the experiment.

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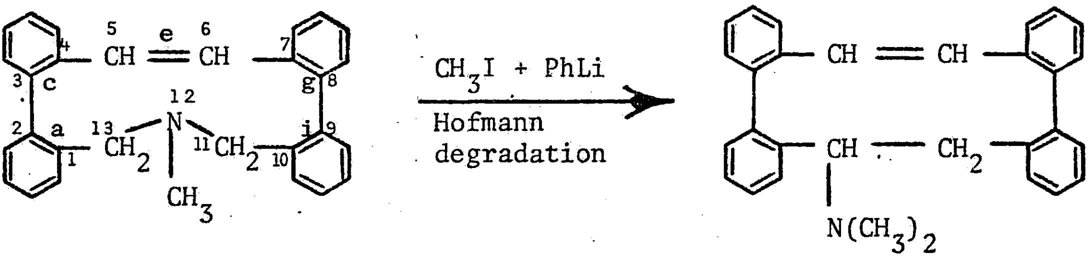
1. INTRODUCTION

1.1. The Historical Background of 2,2'-Bridged Biphenyls with 12-Membered Homo- and Hetero-Cyclic Bridging Rings

For roughly the past thirty years, 2,2'-bridged biphenyls have been extensively studied. They have yielded much information to interest stereochemists, for two important reasons: firstly, where the bridge consists of no more than four atoms, these compounds exist, in many cases, in only two conformations which are enantiomerically related; secondly, the energy barrier separating these conformations is frequently high enough to be conveniently measurable.[1]

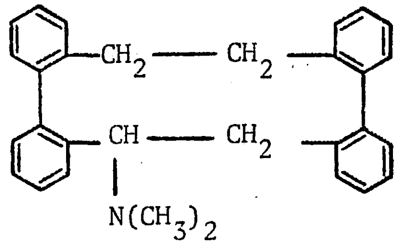
Several workers have realized that synthesizing 2,2'-bridged biphenyls with ten and higher-membered bridging rings presents considerable difficulties, as only a few of them are known at the present time. In 1955, Wittig and his co-workers[2] published an elegant and interesting paper concerned with some compounds containing 12-membered homocyclic bridging rings. They showed that both under the influence of phenyl-lithium as well as under the conditions of Hofmann degradation, the methiodide of *cis*-N-methyl-12-aza-1,2,3,4,7,8,9,10-tetrabenzocyclotrideca-pentaene-[*a*,*c*,*e*,*g*,*i*](I) gave *trans*-12-dimethylamino-1,2,3,4,7,8,9,10-tetrabenzocyclododeca-pentaene[*a*,*c*,*e*,*g*,*i*](II), m.p. 228-229°, in 65-73% yield. Likewise, the *trans*-isomer of (I) gave the *cis*-isomer of (II), m.p. 147-148°, in 65% yield.



(I)

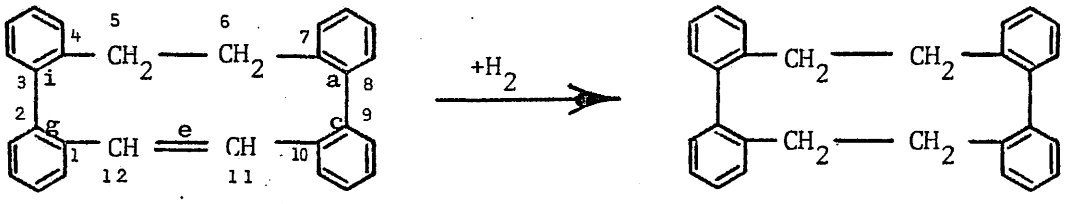
(II)

The cis-trans isomeric amines (II) were identified by their infra-red spectra. On hydrogenation over platinum, the higher melting amine (II) produced a dihydro-product (III) of m.p. 209-210° and the lower melting isomer produced one of m.p. 137-138°. It was found that the dihydro-derivative (III) of m.p. 137-138° converted into that of m.p. 209-210° during melting, whilst the opposite conversion could not be detected.



(III)

On the other hand the methiodide of the dihydroamine (III) (m.p. 137-138°) gave a hydroxide which underwent normal thermal decomposition with separation of water and trimethylamine. The residue, obtained after high vacuum sublimation and crystallisation in 78% yield, consisted of colourless optically uniform crystals of trans-1,2,3,4,7,8,9,10-tetrabenzocyclododeca-pentaene[a,c,e,g,i] (IV), m.p. 298.5-299°. It was suggested that the C=C- double bond has the trans-configuration in this hydrocarbon.



(IV) (V)

With the catalytic hydrogenation of (IV) in the presence of platinum in tetrahydrofuran, 1,2,3,4,7,8,9,10-tetrabenzocyclododeca-tetraene[a,c,g,i](V)* of m.p. 267-268° was formed by the absorption of one mole of hydrogen.

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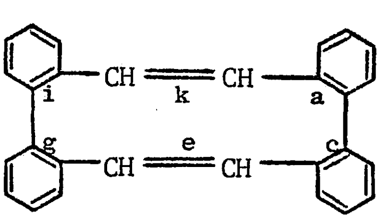
*Now called 9,10,19,20-tetrahydrotetrabenzo[a,c,g,i]cyclododecene.

The methiodide of the *cis*-amine (II) was submitted to Hofmann degradation, and after sublimation in high vacuum, a mixture of four hydrocarbons was obtained. By fractional crystallisation and selection of the crystals as well as by chromatographic separation using aluminium oxide, besides phenanthrene which was isolated in 19% yield, three isomeric hydrocarbons were separated with melting points 163-164^o (21%), 236.5-237^o (29%) and 297.5-298^o (10%).

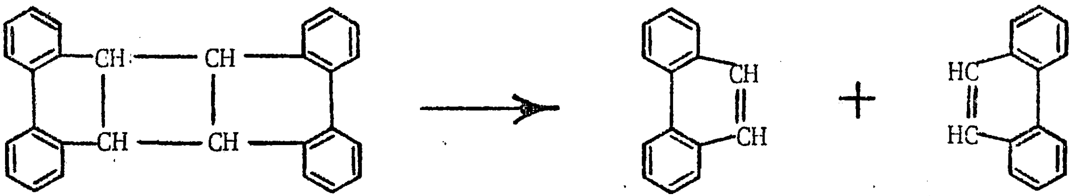
The hydrocarbon of m.p. 163-164^o, which fluoresced strongly violet with ultra-violet radiation, unlike its isomers, oxidised straight away with potassium permanganate to yield two moles of diphenic acid. With this, it is certain that the Hofmann degradation of the accompanying methiodide took the desired course and the sought for 1,2,3,4,7,8,9,10-tetrabenzocyclododecahexaene[*a*,*c*,*e*,*g*,*i*,*k*] (VI) emerged. As the isomeric compound of m.p.297.5-298^o was likewise oxidizable, even if more slowly, to two moles of diphenic acid with potassium permanganate in good yields, the same structural formula (VI) is given to it.



(VI)

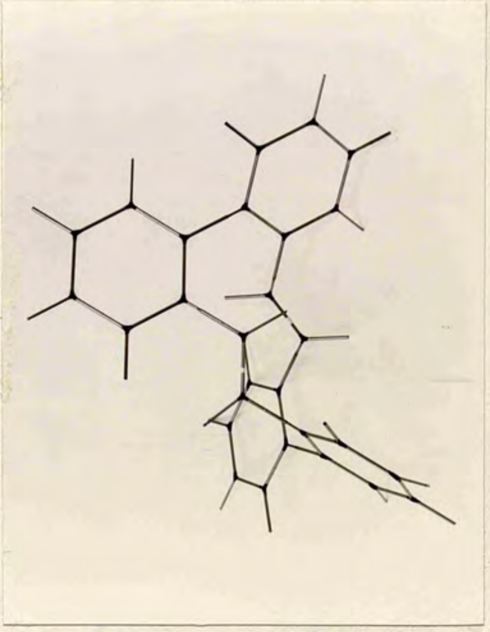
In agreement with this is the result of the catalytic hydrogenation with platinum as the catalyst. After absorption of two moles of hydrogen, both hydrocarbons (VI) produced the same compounds of m.p. 260-261^o. By heating to 240^o, this common hydrogenation product could be changed into a modification, which admittedly did melt a few degrees lower than the 1,2,3,4,7,8,9,10-tetrabenzocyclododeca-tetraene[*a*,*c*,*g*,*i*] (V), m.p. 267-268^o, obtained by hydrogenation of (IV), but it proved to be wholly identical with (V) on the basis of their ultra-violet and infra-red spectra. Observations of the Calotte models reveal that it is possible that the twisted benzene nuclei of the two biphenyl systems click into particular places. In this case "rotational polymorphism" becomes clear here due to the especially strong rotational obstacle.

While the two hydrocarbons of m.ps. 163-164° and 297.5-298° showed similar reactions with oxidative degradation and catalytic hydrogenation, which ensures their corresponding structure (VI), a suggestion was made that they must be stereo-isomers. The hydrocarbon (VI) of m.p. 163-164° and only this one, changed into the above mentioned isomer of m.p. 236.5-237°, when heated to about 180°. As this latter compound was neither affected by potassium permanganate nor hydrogenated, it can only be the bis-(*o*-phenylene)cyclobutane (VII). The ultra-violet spectrum of (VII), which largely matches that of 9,10-dihydrophenanthrene argues for the structure (VII) too. Another proof of the cyclobutane-derivative structure (VII) was that it decomposes completely on melting to give two moles of phenanthrene (VIII).

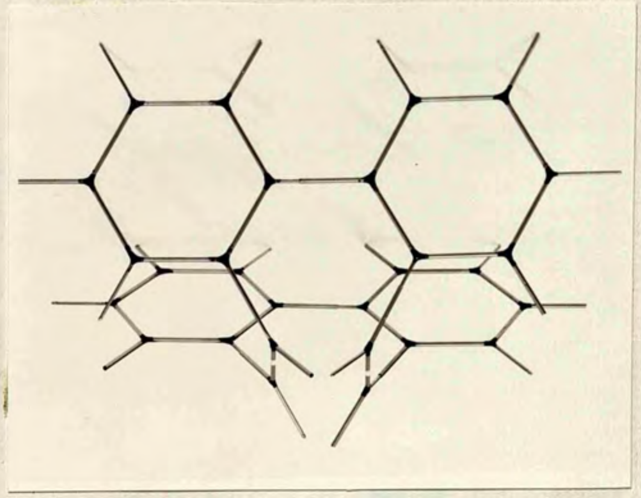


(VII) (VIII)

The infra-red and ultra-violet spectra of the two stereo-isomeric hydrocarbons (VI) gave strong evidence that the compound which melts at 163-164° represents the *trans-trans*-isomer (VIa). This was later shown by X-ray crystallography to be the *cis-trans*-isomer (VIc).[125,126] The stereoisomer of m.p. 297.5-298° represents the *cis-cis*-form (VIb). The m.p. was later raised to 306-306.5° and the configuration confirmed by X-ray crystallography.[127]

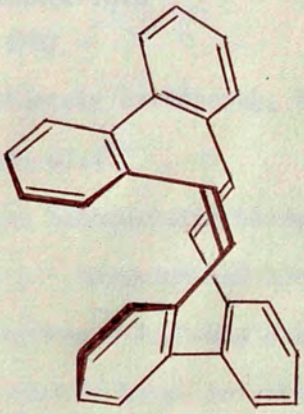


trans-*trans*-form
(VIa)



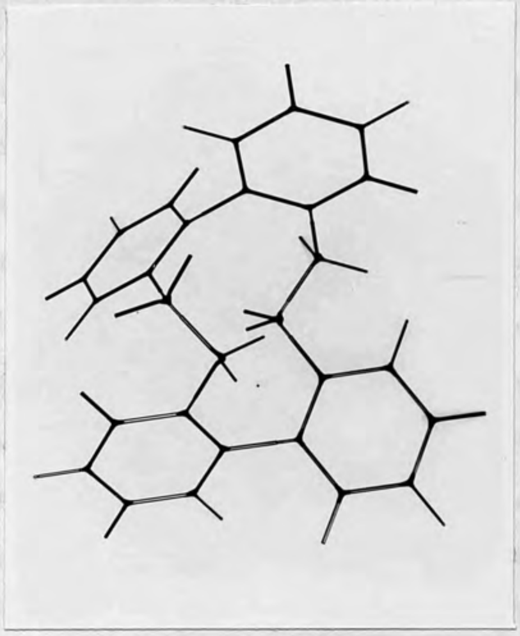
cis-*cis*-form
(VIb)

The true *trans*-*trans*-isomer was subsequently obtained[126,128] and found to have m.p. 302-303°; its configuration was also determined by X-ray crystallography[129].

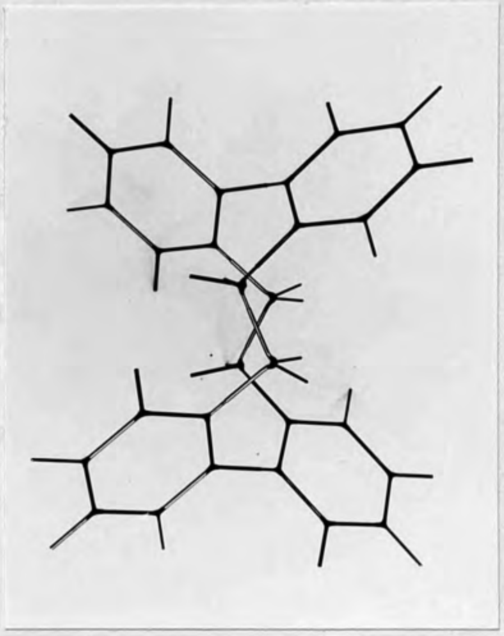


cis-*trans*-form
(VIc)

Voll and his co-workers[3] recently have reported that 9,10,19,20-tetrahydrotetrabenzo[*a*,*c*,*g*,*i*]cyclododecene (V) occurs in two diastereoisomeric forms. The X-ray crystal analysis has shown that the isomer of m.p. 260-261° is the meso-form (Va), in which the axes of both of the biphenyl units are approximately parallel. The dihedral angles between the planes of the benzene rings are 84.9°. On the other hand, the isomer which melted at 267-268° is the racemic form (Vb) which contains two independent molecules.



Meso-form
(Va)

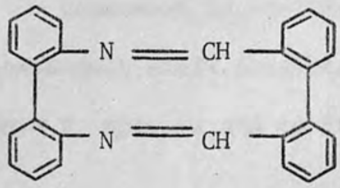


Racemic-form
(Vb)

The axes of the biphenyl groups are approximately orthogonal, the twist angles of the planes of the benzene rings are 63.4°.

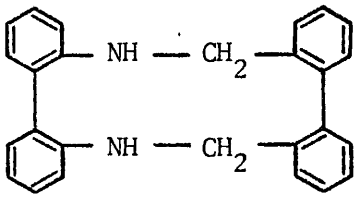
As far as bridged biphenyls with 12-membered heterocyclic bridging rings are concerned, little work has been published. Bergmann and his co-workers[4] have proved that the condensation of biphenyl-2,2'-dialdehyde and 2,2'-diaminobiphenyl proceeds to give the bis-Schiff base, tetrabenzo-[*b*,*d*,*h*,*j*][1,6]diazacyclododecine (IX) in quantitative yield as a single product with a m.p. above 300°.

A few years later, Bindra and Elix[5] confirmed that compound (IX) was obtained as a result of the above condensation, in quantitative yield with a m.p. 326°, and proved that the cyclic 12-membered ring is not planar.



(IX)

They added that the course of aromatic diamine-dialdehyde condensations is governed by the distance between the substituents and it appeared that a 12-membered ring is the minimum ring size necessary for the formation of a bis-Schiff base. When the ring size of the potential bis-Schiff base is less than twelve, only the hydride shift products are in fact observed. They also have confirmed the structure (IX) by reduction with sodium borohydride in methanol, to give 9,10,19,20-tetrahydrotetrabenzo-[b,d,h,j][1,6]diazacyclododecine (X), with m.p. 158°.



(X)

As it appears that 2,2'-bridged biphenyls with 12-membered heterocyclic bridging ring may be of particular theoretical interest, it seemed worthwhile to attempt to resynthesize compounds (IX) and (X) and to study in more detail their spectroscopic behaviour by means of ^{1}H- and ^{13}C-N.M.R., U.V. and I.R. Spectroscopy and by Mass Spectroscopy.

In ^{1}H-n.m.r. spectroscopy, bridged biphenyls show a complex multiplet in the aromatic region of the spectrum which cannot easily be analysed; therefore, attempts have been made to investigate in greater depth the effect of ring substitution, in different positions of the molecule, on the n.m.r. spectra as well as on the rate of the condensation reaction.

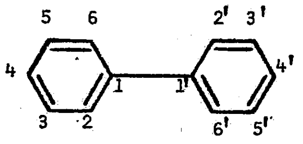
Lanthanide shift reagents and chiral lanthanide shift reagents have been used to help in elucidation of the n.m.r. spectra and to induce stereospecific chemical shifts.

1.2. Electronic Spectra

Electronic spectra arise from transitions between electronic states and are accompanied by simultaneous changes in the vibrational and rotational states. The transitions observed in the near ultra-violet and visible regions generally involve π-electrons with or without interaction with substituents containing other π-electron or n-electron systems, that is unshared pair of electrons associated with atoms such as nitrogen and oxygen. Relatively large energy differences (ΔE) are involved, and hence absorption occurs at rather large frequencies or relatively short wavelengths.

Empirical correlation between ultra-violet light absorption and molecular structure depends upon the fact that ultra-violet light absorption is characteristic of certain π-electron systems or chromophores rather than of the molecule as a whole. When two or more chromophores are present in the same molecule without conjugation, the overall absorption is almost additive. When two or more chromophores are in conjugation, the absorption band usually shifts to the longer wavelength region (bathochromic shift) and its intensity is frequently higher than those observed for the two separately.

The biphenyl molecule (XI) is collinear and the two benzene rings can rotate almost freely about the 1,1'-bond, e.g. Howlett[6] has calculated the energy barrier for the passage through the flat coplanar state to be only 3.9 kcal/mole.



(XI)

The biphenyl molecule was shown by X-ray crystal analysis to be coplanar in the crystalline state, with a 1,1'-bond of length 1.48 Å[7].

Trotter[8] has confirmed the above basic coplanar structure of biphenyl in the crystalline state, though according to him the 1,1'-bond length is 1.507 Å; the 2,2',6,6'-hydrogen bond angles are slightly deformed, the hydrogen atoms remaining in the plane of the rings[9].

The ultra-violet spectrum of biphenyl itself shows a broad high-intensity band at 249 nm, sometimes called "the conjugation band", with a maximal molecular extinction coefficient of 17,300 in 96% ethanol[10]. This band has been attributed to resonance between the two aromatic nuclei, the 1,1'-bond acquiring some double bond character. Since conjugation operates by overlapping of the π-orbitals of the two benzene rings, the presence of this band was once accepted as demonstrating the planarity of the biphenyl molecule in solution. The overlap of the π-orbitals is obviously maximal in the coplanar conformation but it still exists, becoming increasingly smaller, when the angle between the rings increases, and becomes zero only at 90°. At small interplanar angles there should be only a relatively slight loss of resonance and it seems that near-planarity should also produce effective conjugation.

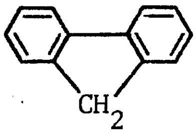
The introduction of substituents into the biphenyl molecule affects the spectrum in a way which depends on their position in the parent phenyl ring, as well as upon their own nature. Ortho-Substituents have a very large steric effect. If they are large enough the two benzene rings cannot become coplanar or rotate freely about the 1,1'-bond. Electronic spectra are very sensitive to the steric effects and introduction of one fluorine atom into the ortho-position of the biphenyl results in a considerable short-wave shift to λ_{max} 241.5 nm and reduction in extinction coefficient to ε_{max} 16,500 of the conjugation band[10]. The introduction of only two substituents into the sterically sensitive ortho-positions of the biphenyl molecule as with 2,2'-dimethylbiphenyl leads to failure to show the characteristic intense biphenyl absorption indicating a lack of conjugation between the two benzene rings owing to interference between the two methyl groups and the 2'- and 6'-hydrogen atoms.[11] On the other hand, as the interfering effect of the two hydroxyl groups in 2,2'-dihydroxybiphenyl is comparatively small, the ultra-violet spectrum of this compound shows the characteristics both of a conjugated biphenyl and of phenol, and is presumably an intermediate case.[11]

The biphenyl compounds in which the 2,2'-positions are joined together by rings of various sizes are of considerable interest. By joining the 2,2'-positions in biphenyl with a saturated bridge of two or more atoms, the two benzene rings can also be fixed at an inclined angle, and the resulting homocyclic or heterocyclic ring will be nonplanar, provided that normal bond lengths and angles obtain.

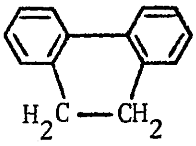
The interplanar angle, Θ, between the planes of the two benzene rings may be calculated for undistorted structures where the bridge consists of 2, 3 or 4 atoms. For compounds where the bridge consists of 5 or more atoms, the bridging ring is flexible, and many values of Θ are possible without any distortion from normal molecular dimensions.[1]

The simplest 2,2'-bridged biphenyl, fluorene (XII), in which the rings are joined through one methylene group, does not satisfy the above requirements since it is regarded as a strained planar structure and the two benzene rings are no longer collinear.[12,13]

Bridging the 2,2'-positions in biphenyl by two methylene groups (XIII) involves apparently no strain, the two benzene rings are collinear and the ultra-violet spectrum exhibits a typical high-intensity biphenyl band at λ_{max} 263.5 nm, ε_{max} 18,000 and a broad low-intensity band at the longer wavelength region. The appearance of these bands as absorption contributions from the separate unconjugated phenyl chromophores make it reasonable to think about a lesser interplanar angle, Θ, in this compound than in biphenyl itself.

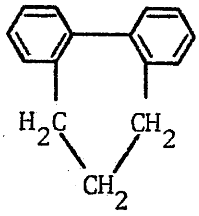


(XII)

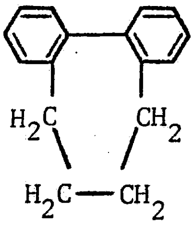


(XIII)

With the three-atom-bridge biphenyl (XIV), the ultra-violet absorption spectrum shows a shift of the biphenyl conjugation band to shorter wavelength (λ_{max} 247 nm) accompanied by a reduction in extinction coefficient (ε_{max} 15,700). On increasing the number of bridging carbon atoms to four, the compound formed (XV)^{14} exhibits a further perceptible short-wave shift of the conjugation band

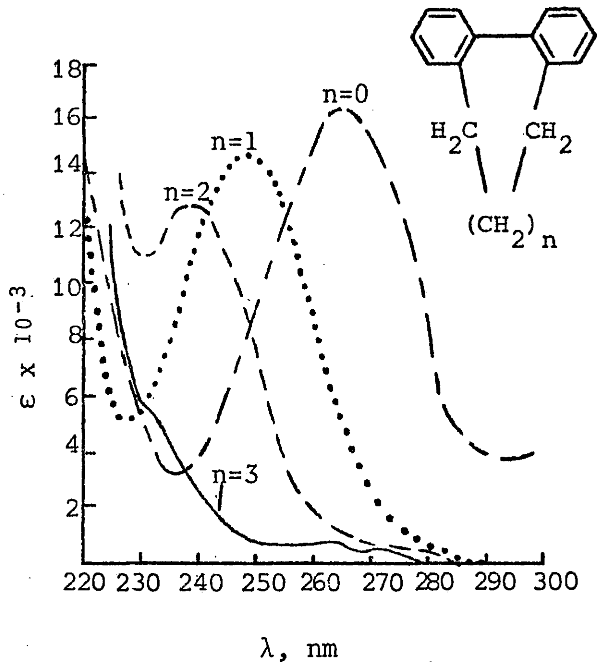


(XIV)



(XV)

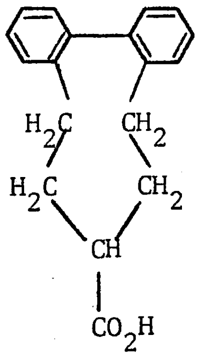
(λ_{max} 235 nm) and a marked reduction in extinction coefficient (ε_{max} 9,680) (Spectrum 1). The interplanar angle, Θ, between the



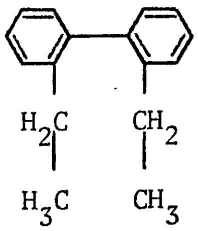
Spectrum No.1. Ultra-violet spectra of simple derivatives of biphenyls with homocyclic bridging rings, showing the effect of increasing ring size on the conjugation band. (Mislow, Hyden and Schaefer, 1962)[15]

planes of the benzene rings, increases rapidly with the increased size of the bridging ring, and there is sufficient electronic interaction between the two benzene rings to produce a separated conjugation band even when Θ is as large as 59° (for compound XV). Complete coplanarity of the benzene rings is evidently not required for the development of a conjugation band.

For biphenyl compounds with a 5-membered bridge at the 2,2'-positions, such as (XVI), the bridging ring is flexible, and many values of Θ are possible without any distortion from normal molecular dimensions. The ultra-violet absorption spectrum shows that the conjugation band is present as an inflection at short wavelength (λ_{infl} 231 nm, ε_{infl} 5,550). The long-wave features are clearly resolved and the spectrum of (XVI) is nearly superimposable on that of the open-chain analogue (XVII), this indicates severe reduction in conjugation.[15]

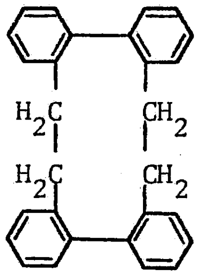


(XVI)

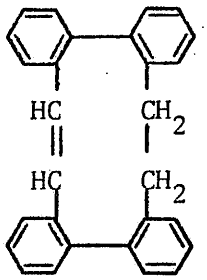


(XVII)

In biphenyls with the 12-membered ring at the 2,2'-positions, such as (XVIII), the bridging ring is flexible. On comparing its ultra-violet absorption spectrum with that of (XIX), one notices the strong decrease in the intensity of the band at λ_{max} 267 nm, which is ascribed to the loss of conjugation between the C=C- combination and the biphenyl system. The spectrum of (XVIII) is very similar

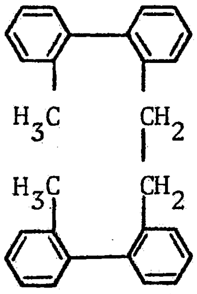


(XVIII)

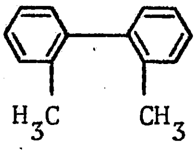


(XIX)

to the spectrum of its non-cyclic analogue (XX) and thus to that of



(XX)

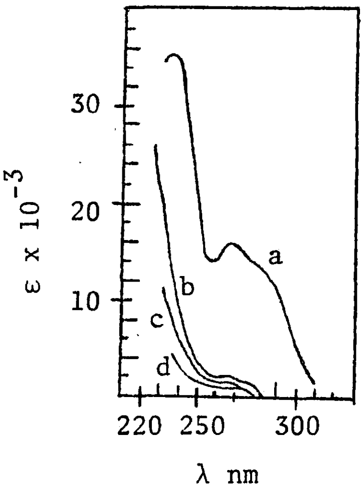


(XXI)

(XXI), [2] (Spectrum 2).

Spectrum No.2. Ultra-violet spectra of:

(a) Tetrabenzo-cyclododecapentaene (XIX)
(b) Tetrabenzo-cyclododecatetraene (XVIII)
(c) Tetrabenzo-dodecatetraene (XX)
(d) 2,2'-Dimethylbiphenyl (XXI)



1.3. Lanthanide Shift Reagents in Proton Magnetic Resonance Spectroscopy

1.3.1. Introduction

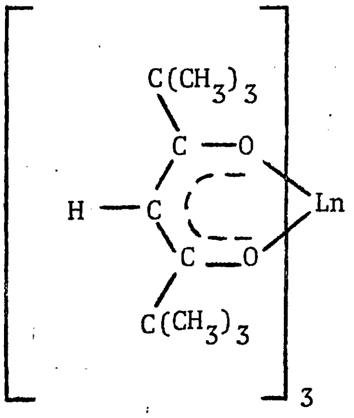
One of the most important recent developments in organic nuclear magnetic resonance spectroscopy is the discovery by Hinckley in 1969 that some paramagnetic lanthanide β-diketonates, "Shift Reagents", can be used to induce stereospecific chemical shifts in the n.m.r. spectra of organic molecules containing functional groups with lone pairs of electrons and thus to facilitate spectral analysis.[16] Quite often spectra of great complexity can be reduced to "first-order" without the loss of resolution. Thus multiplicities are discernible, non-equivalence is usually greatly amplified, and coupling constants are easily evaluated.

The direction of the shift, i.e. upfield or downfield, depends primarily upon the lanthanide complex used. Complexes of europium, erbium, thulium and ytterbium shift n.m.r. resonances to lower field while complexes of cerium, praseodymium, neodymium, samarium, terbium and holmium tend to shift resonances to higher field.[17]

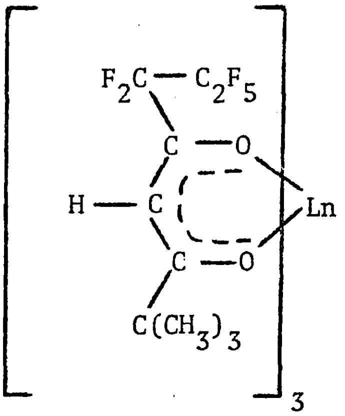
1.3.2. Historical background

The possibility of utilizing specific electron-nuclear interactions with paramagnetic ions to resolve accidental coincidences of n.m.r. spectra was realized in 1960 in an ^{17}O n.m.r. study of cation hydration. Since that time, there have been numerous reports of the perturbation properties of transition metal complexes on the proton magnetic resonance spectra of the ligands to which they are attached.[18] The Ni^{2+} and Co^{2+} acetylacetonates attracted most interest, although other transition metal complexes were also investigated. The ligands were usually attached by nitrogen- or oxygen-based functional groups. The induced shifts were often very small, and, owing to the relatively slow electron spin relaxation times of the transition metal ions, line broadening resulted in the loss of signal multiplicity from which much of the structural information is derived.

In 1969, Hinckley[16] reported the influence of the dipyridine adduct of tris(dipivaloylmethanato)europium (III), $Eu(dpm)_3$ (XXII, Ln = Eu), on the p.m.r. spectrum of cholesterol. Significant induced chemical shifts were found with acceptable levels of signal broadening. Shortly afterwards, Sanders and Williams[19] employed the chelate without the two molecules of pyridine and observed a fourfold increase in the magnitude of the induced shifts in the spectra of n-hexanol and of benzyl alcohol, presumably due to the lack of competition for co-ordination sites by pyridine.



(XXII)



(XXIII)

Another fairly early discovery was the fact that other lanthanide elements besides europium are useful in shift reagents. Thus Briggs et al.[20] reported that while Eu(dpm)$_3$ induces shifts to lower fields those induced by Pr(dpm)$_3$ are to higher fields with rather larger shifts than Eu(dpm)$_3$ and evidenced this with the resolved spectrum of n-pentanol.

Shift reagents are not limited to dpm chelates. Rondeau and Sievers[21] have reported that europium and praseodymium complexes of 1,1,1,2,2,3,3-heptafluro-7,7-dimethyl-4,6-octanedione, fod, of the type Ln(fod)$_3$ (XXIII), are superior shift reagents for weak Lewis bases such as ethers and esters. Eu(fod)$_3$ and Pr(fod)$_3$ are also superior in terms of solubility (which can be a problem with the dpm analogues[21,22]) but require greater care in handling since they are extremely moisture sensitive.

The initial reports of Hinckley[16] and Sanders and Williams[19] inspired considerable interest in the potential of lanthanide shift reagents. In 1970, only a few additional papers appeared, but in 1971 and 1972 the subject was one of the most active areas of chemistry and several hundred citations have now been published. A wide range of shift reagents has now been developed.

1.3.3. Mechanism of induced chemical shifts[18,23-26]

Incorporation of a paramagnetic metal ion into a substrate molecule by means of some kind of complexation or chelation modifies the external homogeneous magnetic field, at least in the close vicinity of the metal ion[23]. Paramagnetic ions are sources of secondary magnetic fields, which are usually anisotropic, their magnitude and direction varying with the direction of the primary field. The influence of the secondary magnetic fields falls away sharply with distance, and induced shifts will only be significant if the nucleus being observed is in close average proximity to the paramagnetic ion. This requirement is satisfied by the rapid equilibria involving organic compounds possessing Lewis base sites and lanthanide ions, which function as Lewis acids.[18]

The lanthanide induced shift (LIS) value is defined as the difference between the resonance frequency of a particular nucleus in the substrate (S) and the frequency of that nucleus in the adduct (lanthanide reagent-substrate, LS):

$$\Delta = \nu_S - \nu_{LS} \qquad \ldots\ldots \quad (1)$$

Δ is the observed induced shift, and since it represents the average of the signal for complexed and uncomplexed substrate (fast exchange of L and S with LS occurs on the n.m.r. time scale), Δ is proportional to the molar concentration of reagent (L) in solution. Thus a plot of Δ versus molar concentration of lanthanide shift reagent (LSR) is a straight line passing through zero.

In the lanthanide-substrate complex, interaction between the paramagnetic metal ion and the nuclei of the substrate causes changes in the chemical shift of the nuclei. Two types of interaction between metal cation and ligand have been proposed, the dipolar or pseudocontact and the Fermi contact interactions. The paramagnetic shift arising from these interactions can be expressed as:

$$\Delta\ \text{para} = \Delta\ \text{dip} + \Delta\ \text{contact} \qquad \ldots\ldots \quad (2)$$

With lanthanides the predominant magnetic interaction with protons is pseudocontact in nature. Dipolar or pseudocontact shift is caused by a dipolar interaction between the nucleus and the electron spin magnetization of the paramagnetic metal ion. The dipolar shift can be expressed as a function of the internal co-ordinates of the nucleus under consideration with the metal ion at the origin: r is the length of a vector joining the paramagnetic centre and the nucleus, Θ is the angle between this vector and the z-magnetic axis, and ω is the angle which the projection of $\vec{r}$ into the xy-plane makes with the x-magnetic axis (Figure 1). The equation for this dipolar shift in its most general form is:

$$\Delta\ \text{dip} = K_{ax}\left(\frac{3\cos^2\Theta - 1}{r^3}\right) + K_{nonax}\left(\frac{\sin^2\Theta\cos 2\omega}{r^3}\right) \qquad \ldots\ldots \quad (3)$$

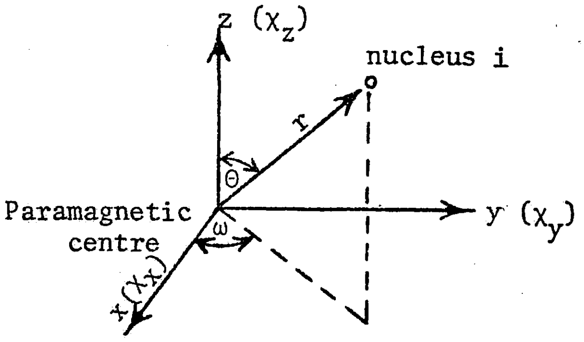


Figure No.1.
Co-ordinates r, Θ and ω of a nucleus i in the co-ordinate system x, y, z with the three principal components χ_x, χ_y and χ_z of the magnetic susceptibility.

The expression in the brackets are called the "geometric factors"; they are dependent on the geometry of the complex formed but independent of the lanthanide itself. The constants K_{ax} and K_{nonax} are functions of the magnetic anisotropy of the complex, determined by the electronic properties of the lanthanide in magnitude and sign. In the case of most common relaxation phenomena (where the tumbling time of the complex is much greater than the electron spin relaxation time) these constants may be expressed as functions of the three principal molecular magnetic susceptibilities χ_x, χ_y, χ_z, corresponding to the x, y, and z axes in Figure 1.

For an axially symmetrical field where $\chi_z \equiv \chi_{||}$ and $\chi_x = \chi_y \equiv \chi_{\perp}$, K_{nonax} becomes zero, and the non-axial term in equation (3) vanishes. Equation (3) reduces to equation (4). Equation (4) is valid for all i observed resonances of a substrate.

$$\Delta_i = K \frac{3\cos^2\Theta_i - 1}{r_i^3} \qquad \text{......} \quad (4)$$

Equation (4) is the McConnell-Robertson equation and is used in most calculations of lanthanide inducedshift (LIS) values. Δ_i is characteristic for a particular nucleus i; Θ_i and r_i depend on the geometry of the complex and can be calculated from an appropriate model of the complex for every nucleus i; the value of K is different for each complex studied as it involves the χ tensor, which is split into $\chi_{\perp}$ and $\chi_{||}$, the tensors perpendicular and parallel to the molecular axis. If one knows the topology of the complex (geometry of the substrate and position of the lanthanide ion), then the observed induced shifts should be proportional to the calculated geometrical factor. Thus from the induced shifts it should be, in principle, possible to determine the geometry of a rigid substrate. The expression (4), derived for axially symmetric complexes, will not necessarily be applicable to the wide range of complexes of lower symmetries.

According to McConnell-Robertson's theory, the pseudocontact shift arises from a failure of the dipolar interaction to average to zero owing to the metal ion's possessing an anisotropic χ tensor. However, Bleaney[27] proposes a theory in which K encompasses a different set of parameters. Rather than attributing pseudocontact shift to the anisotropic χ factors, he suggests that the dipolar induced shift is caused by anisotropy in the susceptibility which occurs in less than cubic geometries.

The Fermi-contact interaction involves direct delocalization and/or spin polarization of the unpaired electron via the molecular orbitals of the substrate ligand. As a result, the unpaired electron spin density is spread over a number of atomic sites in the ligand, thereby inducing a contact shift. Contact interaction may involve both π and σ bonds, although it falls off rapidly through a series of σ bonds except in conjugated systems, which facilitate delocalization of unpaired electrons. This interaction is independent of the $(3\cos^2\Theta_i - 1)$ term. For the case of a spin-only system, equation (5) has been derived to account for the contact shift:

$$\Delta_i^{con} = -A_i \frac{\gamma_e}{\gamma_N} \frac{g_e \beta S(S+1)}{3kT} \qquad \text{......} \quad (5)$$

In this equation γ_e and γ_N are the magnetogyric ratios of the electron and nucleus, respectively, S is the spin quantum number, β is the Bohr magneton, and k is Boltzmann's constant. In anisotropic systems A_i includes all possible orientations of the molecule tumbling freely in solution.

The distinction between contact and pseudocontact shift is important for a better understanding of the factors affecting the LIS. The assumption that lanthanides interact with ^{1}H nuclei by a pseudocontact mechanism is based on their high electropositive character and the shielding of unpaired electrons of the f-orbitals. As the lanthanides form complexes by electrostatic interaction, this precludes the operation of a contact mechanism of the same order of magnitude as those found with first-row transition-block metal complexes, but with even as little as 1% covalency contact shift should be observed. Therefore, even with lanthanides, a small degree of contact interaction is possible and is seen in deviations from the expression (4), particularly for protons attached to the carbons nearest the lone-pair-bearing atoms. Pseudocontact and contact interactions are distinguished in a graphical analysis using the log of expression (4). A similar deviation from an otherwise linear plot of log r_i against log Δ_i is reported by Demarco,[24] who attributes this to the presence of contact shift.

1.3.4. Distance-shift relationships[18,23,25,26]

Assuming the interaction of the lanthanide complexes is predominantly pseudocontact, the magnitude of the LIS of the ith nucleus is inversely proportional to the cube of the average distance from the metal ion [expression (4)]. Taking logarithms of both sides of equation (4) gives equation (6), in which K is a multi-term constant.

$$\log (\Delta_i) = -3 \log r_i + \log (3\cos^2\Theta_i - 1) + \log K \qquad \ldots\ldots \quad (6)$$

For most organic molecules, values of Θ_i for most of the nuclei lie between 0 and 30°, and changes in $(3\cos^2\Theta_i - 1)$ are therefore small compared with changes in log r_i. Under these conditions, a graph of log (Δ_i) against log r_i should approximate to a linear correlation with a slop of -3. In analyses of this kind, a ligand atom-lanthanide bond distance of 3-4 Å is usually assumed, and measurements from the estimated average position of the lanthanide nucleus to each nuclei are made using Dreiding molecular models. Consequently this approach enables relative distances of the nuclei from the metal ion to be estimated, which can contribute to structural information. This can be applied by altering the possible structural models of the molecule to obtain the best correlation of the distance-shift data.

The presence of more than one co-ordination site in the organic substrate complicates the interpretation of the measured shifts since these represent sums of the interactions with the LSR at each site, although some groups form stronger co-ordination complexes than others. At each co-ordination site, equilibrium constants, and hence pseudo-contacts, contribution differ and so result in different proportionality constants in expression (4).

By assuming expression (6) correct, a graphical analysis by this approach allows a distinction between the relative contributions of co-ordination at each site of a bifunctional molecule. This approach is only useful when co-ordination sites are far apart so that some protons are only affected by co-ordination at one site. The slope of -3 would be expected but it is not in fact obtained with these graphs, and this is attributed to errors in the distance measurement or to neglect of Θ_i. One generalized interpretation suggests that molecules which produce slopes greater than 3 are flexible, but those of slopes less than 3 are rigid.

1.3.5. Influence of the angular term

Deviations from the distance-shift correlations due to neglect of the geometric term are common and by including the term $(3\cos^2\Theta_i-1)$, improved correlations are obtained.

In certain cases the angle Θ_i may be sufficiently large for the direction of "normal shift" to be reversed. A plot of the $(3\cos^2\Theta_i-1)$ term against angle, as in Figure 2, shows how the LIS can be varied from positive to negative as the angle is altered.

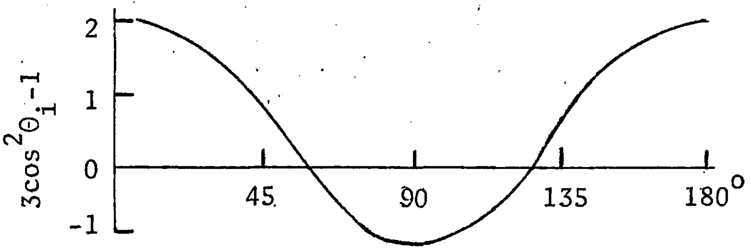


Figure No.2. The variation of $3\cos^2\Theta_i-1$ with the angle Θ

Thus with $Eu(dpm)_3$, the angle term $(3\cos^2\Theta_i-1)$ is positive for Θ_i values from 0 to 54.7° and from 125.3 to 180° and a positive Δ_i (shift to lower field) is observed, however when Θ_i has a value from 55 to 125° the angle term and Δ_i become negative (i.e., shifts to higher field are observed).[17] By altering the solvent or ligand of the LSR, the direction of the shift is often altered, as these factors can also affect the geometry of the complexed substrate. An alternative explanation for the reversal of the 'normal' direction of the LIS is attributed either to the presence of significant contact interaction, or to changes in magnetic susceptibility χ tensor, (although disagreement has been expressed with this latter reason) or to changes in the sign of crystal field coefficients. It is obviously advantageous not to neglect the term $(3\cos^2\Theta_i-1)$ also in cases of lower than axial symmetry.[25]

It is a characteristic feature of the geometrical factor that for $\Theta = 54.7°$ the sign of the shift is inverted. Figure 3 illustrates the geometrical effect on the LIS.

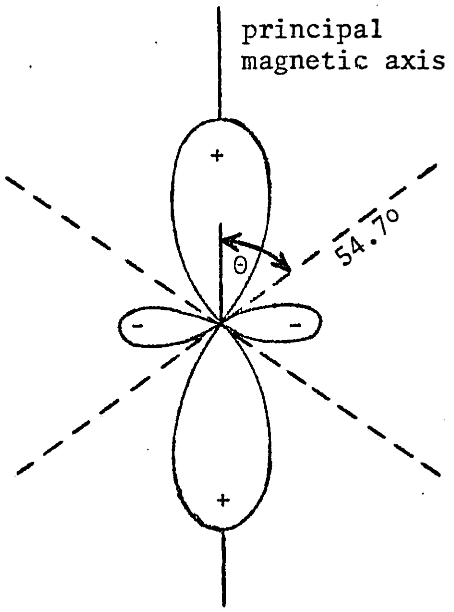


Figure No.3. The dipolar, axially symmetric field (point dipole); positive lobes signify induced downfield shifts, negative lobes upfield shifts for Eu(III); the reverse is true for Pr(III).

1.3.6. Effects of temperature

The use of variable-temperature studies in n.m.r. spectroscopy is now well established in solving problems involving rotamerism and conformational analysis.

Temperature-dependent shifts in the presence of LSRs have been observed. With monofunctional substrates it is found that shift magnitudes increase with decreasing temperature. Line broadening is also a consequence of reducing the temperature and has been attributed to reduced rates of interconversion of the free and complexed substrate. This suggestion is supported by the appearance of free and complexed substrate at temperatures below -80° in solutions of DMSO in CD_2Cl_2 containing $Eu(fod)_3$.

Linear relationships between the LIS and the inverse of the absolute temperature have been observed over the temperature range -30 to 90°, but in any single molecule all the protons may not always respond uniformly to temperature changes. Curved Arrhenius plots can be attributed to changes in the molecular configuration of the complexes with temperature, or, in the case of polyfunctional ligands, to a change in the site of co-ordination.[18]

With a chiral shift reagent Fraser, Petit and Saunders[28] found that the shift separation between enantiomers increases with increasing temperature.

1.3.7. Lanthanide metal ion

Transition-metal complexes could be used as shift reagents in n.m.r. spectroscopy if it were not for the excessive linewidth broadening these metal ions exhibit in solution. Europium(III), the most frequently selected lanthanide, is selected by virtue of its anomalously inefficient nuclear spin-lattice relaxation properties. It has a low-lying Russell-Saunders state and a diamagnetic $^7F_0$ ground state, which gives a very small separation of the highest and lowest occupied metal orbitals and which leads to inefficient relaxation; the excited $^7F_1$ state presumably contributes to the pseudocontact shift. Thus the presence of such metal ions as europium(III) in solution causes very little broadening in n.m.r. spectra.

Narrow bandwidths are exhibited by the lanthanides praseodymium (Pr), neodymium (Nd), samarium (Sm), and europium (Eu), and moderate broadening is found with ytterbium (Yb), but a notable exception to these characteristics occurs with gadolinium (Gd), which is used explicitly as a broadening probe. Europium and praseodymium are used most extensively and ytterbium also appears satisfactory for use, although it causes greater broadening.

A second factor in selection of the correct lanthanide as a LSR is the magnitude of the shift produced. The largest shifts are unfortunately exhibited by the metals which cause greatest broadening, e.g. terbium to thulium, and, therefore, the metals selected for use as LSRs are necessarily a compromise of these factors, with a greater consideration given to the broadening factor. Consequently, europium produces relatively small but adequate shifts and is the lanthanide used most extensively since the first paper was published by Hinckley.[16] This metal ion produces large enough shifts with sufficiently minimal broadening to allow gross multiplet adsorption bands to be resolved at relatively large shifts.

Praseodymium follows europium in its popularity, owing to two factors: (i) the shifts are larger than those caused by europium, in proton n.m.r.,[20] compensating for the slightly poorer broadening properties; (ii) praseodymium causes upfield shifts and is, therefore, a useful complementary reagent . A disadvantage of praseodymium and other shielding of LSRs, however, is the added complication of crossing over of resonances, which confuses analysis in some cases.

A series of papers,[29-32] largely by Beauté and Wolkowski, advocates the use of ytterbium and holmium[33] owing to their relatively greater shifting power (cf. europium), but these advantages are balanced by their greater bandwidths. Thulium has been used as a LSR,[34] but although shifts are greater than those caused by europium, drastic broadening again limits its application. The reference to a LSR as deshielding or shielding refers to its use under 'normal' conditions (as a β-diketonate complex), in fairly non-polar solvents and with angle Θ_i outside the 54.7 to 125.3^o limits. Finally, diamagnetic lanthanum is used[35] in LSR studies although the shifts produced are probably due to changes in shielding by bonded electrons and not indicative of any pseudocontact shift. The main use of lanthanum may, therefore, lie in taking accurate measurements of the LIS due to pseudocontact shift only, by subtracting shifts caused by the lanthanum complex from the LIS caused by a paramagnetic LSR.[36]

In an isostructural series, Δ_i is proportional to K, which in turn depends on the magnetic properties of the metal alone [eq. (4)], provided dipolar or pseudocontact interactions are solely responsible for the shifts. The results are shown in Figure 4.

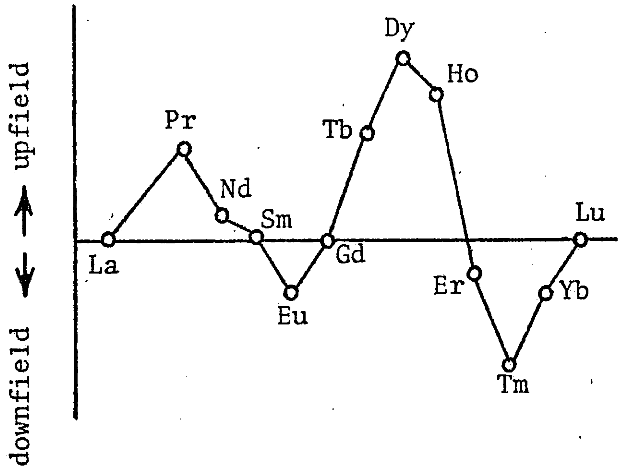


Figure No.4. Relative LIS for a typical dipolar-shifted nucleus in the region $-54.7 < \Theta < +54.7^{\circ}$ for different lanthanide ions.

1.3.8. Lanthanide shift reagent (LSR)[26]

Bulky ligands in the LSR are an advantage as this restricts mobility in the complex, preventing the susceptibility tensors being averaged out by a combination of different configurations.

The introduction of fluorine atoms on the β-diketonate ligand overcomes the solubility problem and has led to superior LSRs. One such complex, the 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato(fod) lanthanide, apart from having improved solubility, has a more acidic metal ion owing to the electron-withdrawing power of the fluorines. This greater Lewis acidity causes a stronger association with the substrate and thus extends its range to less basic groups; although the bond chemical shift is smaller for these fluorinated LSRs, the observed LIS is larger because of the stronger binding in the complex. However, an alternative method for comparing the shifting power of LSRs, by measuring their vinylic proton shifts, allows a comparison of the shifting power of various fluorinated LSRs with the non-fluorinated reagents.

$Eu(fod)_3 > Eu(pfd)_3 > Eu(fhd)_3 > Eu(dpm)_3$ where (pfd) represents 1,1,1,2,2-pentafluoro-6,6-dimethylheptane-3,5-dione and (fhd) represents 1,1,1-trifluoro-5,5-dimethylhexane-3,4-dione. Various LSRs appear to exhibit different degrees of Fermi contact interaction with aromatic substrates, and a series of the reagents with an increasing degree of Fermi contact interaction operating is reported:

$$\underset{\text{increasing Fermi contact interaction}}{\overrightarrow{Pr(fod)_3 < Yb(fod)_3 < Eu(dpm)_3 < Er(dpm)_3 < Eu(fod)_3}}$$

Finally, one disadvantage in using the fluorinated LSR is that the t-butyl resonance occurs in the 1-2 p.p.m. region when complexed, hence interfering with proton resonances in this region. On the other hand the t-butyl resonance of $Eu(dpm)_3$ occurs upfield of TMS in proton n.m.r. and is, therefore, not interfering with the spectra.

1.3.9. Application of LSR to simplify the p.m.r. spectra of monofunctional compounds.[18,26,37]

Only substrates having a sufficiently polar and exposed group (or atoms) to form a complex with the reagent can be subjected to investigation using shift reagents. Some general conclusions have been made concerning comparisons of co-ordinating ability of different functional groups. The following series of functional groups have been put in order of their ability to co-ordinate and cause a LIS:

phosphoryl > carbonyl > thiocarbonyl > thiophosphoryl
ethers > thioethers > ketones > esters
amines > hydroxyls > ketones > aldehydes > ethers > esters > nitriles
(for RCH_2X)

(Note: there are contradictions with respect to relative shifts, e.g. ketones and ethers).

This order reflects the 'binding' dissociation constant of the corresponding substrate-reagent adduct and to a smaller extent the geometry (distance and angle) of the protons with respect to the central metal ion, although factors such as steric hindrance cannot be ignored.

A. LIS of alcohols and phenols

Both $Eu(dpm)_3$ and $Eu(fod)_3$ have been used successfully on many occasions to simplify the p.m.r. spectra of alcohols. $Eu(fod)_3$ is a stronger Lewis acid and is therefore expected to form stronger complexes with strong Lewis bases. In addition, owing to the greater solubility of $Eu(fod)_3$ in CCl_4, larger induced shifts are expected for this reagent.

Phenols with pK_a values less than 10 cause decomposition of $Eu(dpm)_3$. The more acidic $Eu(fod)_3$ should be less unstable and might be more useful for phenols.

B. LIS of ketones and aldehydes

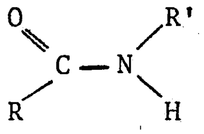
Carbonyl compounds complex much less strongly than hydroxyl compounds with LSR. $Eu(fod)_3$ does not appear to offer any advantage over $Eu(dpm)_3$ as a shift reagent for ketones, similar induced shifts being observed with both reagents for 3,5,5-trimethyl-3-(p-chlorophenyl)-cyclohexanone.

C. LIS of esters and lactones

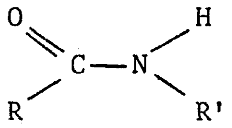
Esters are weaker Lewis bases than ketones toward LSR, the preferred co-ordination site being the carbonyl and not the ether oxygen.

D. LIS of amides and lactams

Co-ordination of LSR to amides and lactams involves the carbonyl oxygen rather than the nitrogen atom. Delocalization of the nitrogen lone pair of electrons under the electron-withdrawing influence of the carbonyl group gives rise to partial double-bond character of the C-N bond, and thus the existence of the Z and E rotamers (XXIV and XXV). LSR offer an attractive method for determining the rotamer ratios.



(XXIV) Z rotamer



(XXV) E rotamer

In the absence of steric hindrance, groups cis to the carbonyl experience a larger induced shift than their trans counterparts. This situation may be reversed when bulky groups are present.

Increase in the coalescence temperature of cis and trans amides on complexation with LSR has been attributed to the increased electron-withdrawing power of the complexed carbonyl and/or increased peak separations of the rotamers.

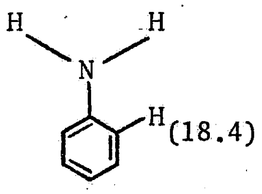
E. LIS of ethers and epoxides

Although ethers are generally regarded as very poor donors toward LSR, the work of Hart and Love[38] has shown that they may compete effectively with esters and ketones; e.g. for an equimolar mixture of tetrahydrofuran and acetone with $Eu(dpm)_3$ 90% complexing to the ether function is indicated. When the ether oxygen lone pair of electrons is delocalized into an extended π system, complexing becomes very weak.

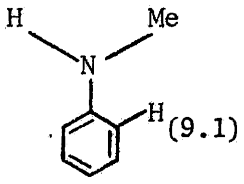
The efficacy of a number of europium chelates as LSR have been compared using di(n-butyl)ether. The ligand decafluoroheptanedione ($F_5C_2COCH_2COC_2F_5$) is a stronger Lewis acid than fod and has fewer interfering ligand proton absorptions. The corresponding europium complex has greater chloroform solubility and induces larger shifts in protons remote from the co-ordination site. The epoxide group is an ideal function for shift calculations because of its rigid nature.

F. LIS of amines

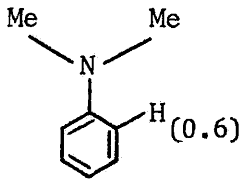
The amine function is usually more basic than the hydroxyl, and therefore large apparent shifts may be observed with shift reagents owing to the lower dissociation constant of the reagent-substrate adduct. The importance of steric effect is clearly demonstrated by the drastic fall in the magnitude of the induced shifts for the ortho protons along the series (XXVI) ⟶ (XXVII) ⟶ (XXVIII), despite the actual increase in basicity of 0.5 pK unit along the same series.



(XXVI)



(XXVII)



(XXVIII)

Considerable care must be exercised when interpreting the shifts induced in anilines and aniline analogues, because of the possibility of Fermi contact interactions. Large Fermi contact contributions occur in aniline and p-toluidine, the effect being most apparent for the Eu(fod)$_3$ reagent. By contrast, Pr(fod)$_3$ and Eu(dpm)$_3$ show little evidence for Fermi contact shifts, the results being interpretable in terms of dipolar interactions alone.

G. LIS of aza heterocyclic compounds

Much of the discussion regarding interactions of LSR with aza heterocyclics has been concerned with the controversy surrounding the relative contributions of the Fermi contact and dipolar contributions to the observed induced shifts. It has been shown that the induced shifts for the protons of pyridine and quinoline in complexes with Eu(dpm)$_3$ can be accounted for mainly in terms of dipolar interactions.

H. LIS of nitriles

Nitriles are very weak donors and only small LIS are observed. Eu(dpm)$_3$ has been used successfully to enable distinction between the cis- and trans-bicyclo[6,1,0]nonatriene derivatives (Figure 5) and their thermolysis products. The ketenimine group (=C=NR) is an even weaker donor than the nitrile.

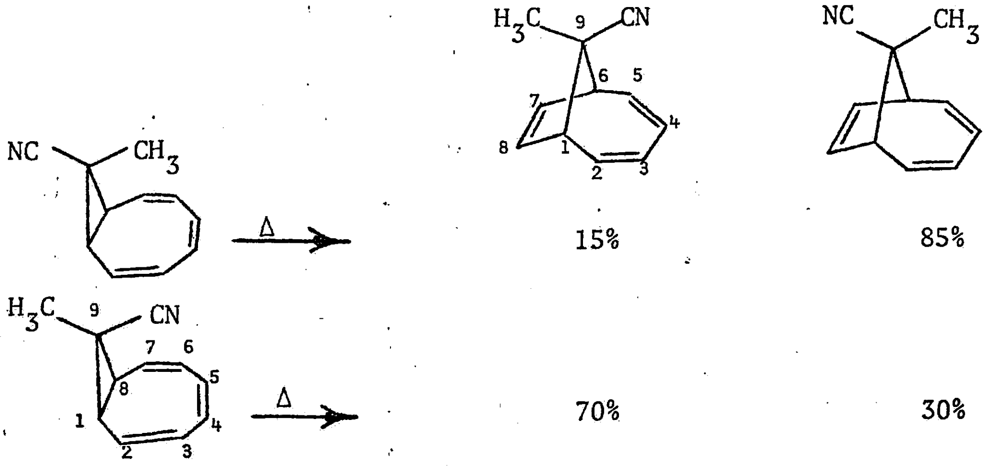


Figure No.5. The thermolysis products of cis- and trans-9-cyano-9-methyl-bicyclo[6,1,0]nona-2,4,6-triene.

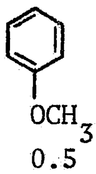
1.3.10. Interaction of LSR with polyfunctional molecules

The relative shifting (and complexing) abilities of functional groups can be determined by n.m.r., either by intermolecular (external) or intramolecular (internal) competition experiments; the former is done with a mixture of substrates,[38] the latter with a substrate containing more than one function. This latter case is of great interest in practical terms, since one frequently has to deal with polyfunctional substrates.

Double or higher complexation in polyfunctional molecules shows up in the absolute shift values observed [large LIS, if the different centres of complexation have comparable co-ordination binding constants, the induced shifts of the two or more Ln(III) being additive] or in a bend in the Δ versus LSR-concentration slope (at low LSR concentration the strongest basic function is dominant, when the strongest base site approaches saturation, the other(s) start to co-ordinate LSR too).[23]

The additivity of LIS can be exploited to determine complex populations in polyfunctional compounds by use of the LIS values of monofunctional standard model compounds.

Distinct nonadditivity indicates some special effects. In the series methoxy-, o-, m-, p-dimethoxybenzene a remarkable increase in the LIS (ratio LSR/S = 1/1, p.p.m.) is observed for the methoxyl groups in the ortho isomer only.



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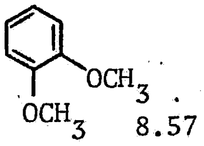

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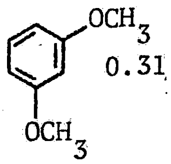
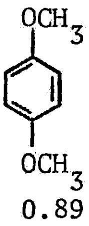
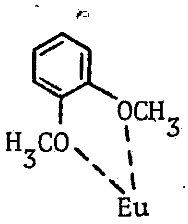


(XXXI)



(XXXII)



(XXXIII)

Clearly, (XXX) forms a strongly bonded bidentate complex (XXXIII). It was found[39] that the o-dimethoxy arrangement in (XXX) appears to have about twice the affinity for Eu(fod)$_3$ that an aromatic ester group has. (An isolated methoxy function co-ordinates poorly compared to the ester group).

The simplest way to make the case clear cut is to use a model compound with one, and only one, strongly Lewis-basic functionality.

1.3.11. Chiral shift reagents

Prior to the discovery of LSR, two principal methods have been used to distinguish enantiomers by n.m.r. In the first method, a derivatizing agent [(R)-o-methylmandeloyl chloride[40] or better, Moscher's (R)- or (S)-α-methoxy-α-trifluoromethylphenylacetic acid[41]] is used to convert optically active amines or alcohols into diastereoisomers, which show useful, but not particularly large, chemical shift differences generally of about a maximum of 0.15 p.p.m. The second method employs a solute-solvent interaction between a chiral solvent and each of the enantiomers to form loosely-bound diastereoisomers of slightly different chemical shifts ($\Delta\delta < 0.1$ p.p.m.). The splitting of the signals in the spectrum results from a different position of the substrate nuclei in the diastereomers with respect to the magnetic field produced by the ring current of the π-system of the solvent. Optically active 2,2,2-trifluoro-1-phenylethanol has been the most successful reagent for a variety of amines, esters and sulphur and phosphorus compounds.[42]

Since the discovery[16,19] that LSRs are capable of inducing simplification and enhancement of resolution in n.m.r. spectra of various Lewis bases, many new developments and refinements have been introduced. Whitesides and co-workers[43-45] and others[28,46-49] have reported that chiral LSRs shift the resonances of many enantiomeric organic Lewis bases to different extents. This finding provides a simpler method for the determination of enantiomeric purity than others employed. Since the magnitude of the LIS, $\Delta\delta$, has proved to be a sensitive probe of steric environment[16], it is expected that chiral shift reagents C_+ (where $_+$ denotes one optical isomer of the chelate) will produce diastereoisomeric shift difference, $\Delta\Delta\delta$, between the resonances of equivalent nuclei in an enantiomeric pair (R,S).[50]

The situation is described by equations (7) and (8), where

$$C_+ + R \rightleftharpoons (C_+R) \qquad \ldots\ldots \quad (7)$$

$$C_+ + S \rightleftharpoons (C_+S) \qquad \ldots\ldots \quad (8)$$

the association of C_+ with R and S forms two diastereomeric (and, in principle, n.m.r. distinguishable) adducts in solution. Because the interchange processes are rapid, the observed shifts are a time average of those for the complexed and free substrate. Thus $\Delta\Delta\delta$ and $\Delta\delta$ are dependent on the molar shift reagent/substrate ratio . The intensity of a signal, on the other hand, is proportional to the total mole fraction, n, of a given enantiomer. From the measurement of peak areas, the enantiomeric purity, E.P. can be readily calculated using equation (9).

$$\text{E.P.} = \frac{n_R - n_S}{n_R + n_S} \qquad (n_R \geqslant n_S) \qquad \ldots\ldots \quad (9)$$

The disappointing feature of the chiral LSR concerns the relative shifting of the R/S enantiomers, which is a function of both the differences in equilibrium constants and the actual geometries of the complexes.[18] It is difficult to predict which shift reagent will yield the best enantiometric shift differences for a given substrate.[45]

The successful application of the optically active shift reagent technique to the reactions of epimerization, racemization, asymmetric induction or to the determination of enantiomeric purity depends mainly on the use of a high-resolution spectrometer and an appropriate solvent, and on the asymmetric centre being relatively close to the complexation site.[51]

1.3.12. Substrate-lanthanide shift reagent interaction

Determination of relative lanthanide induced shift (LIS) values by plotting Δ versus the ratio molar concentration of shift reagent/ substrate (Figure 6 shows the plots of Δ vs L_t/S_t) would seem to be a reliable and rather easy procedure. However, it has been shown that the values obtained for the slope (at low LSR concentrations) differ for different substrate concentrations despite equal L_t/S_t ratios[52] (L_t and S_t are the molar concentrations of added LSR and substrate, respectively); this finding and the nonlinearity of the plot at L_t/S_t ratios higher than ~ 0.5 require explanation.

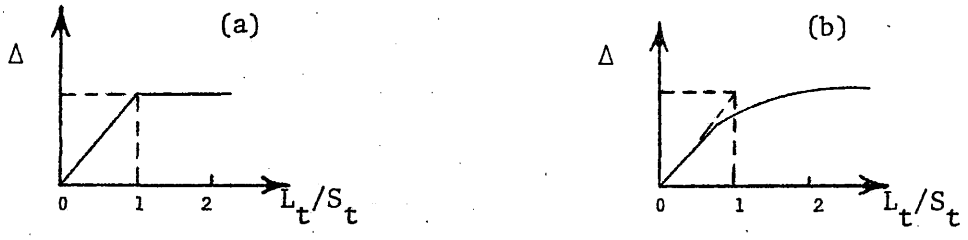


Figure No. 6. (a) Ideal and (b) typical Δ versus L_t/S_t plot; in (b) the plot should represent a straight line up to L_t/S_t ~ 0.5 allowing extrapolation of the Δ value for the 1:1 complex; S_t is kept contant, L_t is varied in the experiment.

For strong Lewis-base substrates (e.g. amines, alcohols) one can assume that at high concentrations of LSR a value for the LIS is obtained which does not change upon further addition of reagent, since no more lanthanide ions can be incorporated into the complex, all coordination sites being saturated. In the ideal case of a well defined 1:1 complex, a very sharp bend should show up in the plot (Figure 6). However, this is almost never true, thus indicating that a simple, one-step, 1:1 equilibrium is not, in fact, the only one involved. Besides the species L,S, and LS, the species LS_2 (1:2 stoichiometry) will be present in solution, also[23]. Nevertheless, almost all methods to obtain the intrinsic parameters of the reagent-substrate equilibrium are based on the assumption of a 1:1 complex.

The observed lanthanide-induced shift Δ for any particular nucleus is an average of the shifts for the complexed substrate and the uncomplexed one in the case of rapid exchange on the n.m.r. time scale. For a nucleus of a substrate molecule in the presence of a shift reagent forming 1:2 adducts the observed lanthanide-induced shift Δ is given by:

$$\Delta = \frac{[LS]}{S_t}\Delta_1 + \frac{2[LS_2]}{S_t}\Delta_2 \qquad \ldots\ldots \quad (10)$$

where S_t is the total substrate concentration and [LS], Δ_1 and $[LS_2]$, Δ_2 are respectively the equilibrium concentrations and limiting LISs of the 1:1 and 1:2 adducts.[53]

A two-step mechanism should provide a reasonable model for the equilibria involved in the complex mechanism:[23,54-57]

$$L + S \rightleftharpoons LS \;,\; K_1 = \frac{[LS]}{[L][S]} \qquad \ldots\ldots \quad (11)$$

$$LS + S \rightleftharpoons LS_2 \ , \ K_2 = \frac{[LS_2]}{[LS][S]} \qquad \ldots\ldots \ (12)$$

where L and S are the molar concentrations of the LSR and substrate, respectively, and [LS] the molar concentration of the complex formed in solution; the ratios of these species depends on K_1 and K_2, the binding constants. If $K_2 = 4K_1$ ...... (13) then the reagent has two equivalent and independent sites for substrate co-ordination.

In addition to adduct formation there are at least three other types of chemical interactions that are often present in shift reagent-substrate systems. These include the presence of another substrate, e.g. water impurity, complex formation between the substrate and the solvent molecules, e.g. hydrogen bonding to chloroform, and dimerization of the reagent.

The presence of an impurity binding to the reagent will add the equilibrium:

$$L + I \rightleftharpoons LI \ , \ K_i = \frac{[LI]}{[L][I]} \qquad \ldots\ldots \ (14)$$

which for n = 1 (n = number of equivalent and independent binding sites) will exist simultaneously with that described by equation (11). Therefore, the presence of other donor substrates as impurities can reduce the effective concentration of the LSR[58] if they form stronger co-ordination complexes than the substrate under study.

Interaction of the substrate with solvent molecules, A, adds the equilibrium:

$$S + A \rightleftharpoons SA \ , \ K_s = \frac{[SA]}{[S][A]} \qquad \ldots\ldots \ (15)$$

As a result of this interaction, substrate concentration is reduced and a smaller value of the slope is obtained.

For the case of reagent dimerization which adds [to equilibrium (11)] the equilibrium:

$$L + L \rightleftharpoons L_2 \;,\; K_d = \frac{[L_2]}{[L]^2} \qquad \ldots\ldots \quad (16)$$

It is assumed that the dimer does not co-ordinate substrate. A two-fold advantage exists in measurements at low concentrations of the LSR (a factor favouring the fluorinated LSRs which have greater 'shifting power') since (i) this minimizes the possibility of dimerization of the LSR and (ii) the bulk susceptibility changes caused by the metal ion are minimal.

The three interactions above [equations (14), (15) and (16)] were considered as existing separately. If present simultaneously the equations become rather involved.

The lowering of the LIS with different solvents is reported;[59] one explanation attributes this to competitive inhibition of weakly complexed substrates, particularly with donor solvents such as acetonitrile, pyridine, acetone and dimethyl sulphoxide. Therefore, the use of donor competing solvents should be avoided when using the tris-β-diketonate LSR. As the magnitude of LIS is geometry dependent and lanthanide complexes are predominantly electrostatic, the solvation spheres can influence this geometry so that different solvents may alter shifts.

As the LSR is only a weak Lewis acid, steric hindrance reduces the LIS either because of a smaller value of the equilibrium constant or a greater nucleus-cation distance or both.

1.3.13. Graphical interpretation of induced shifts

Although a large amount of information can be gleaned by a visual analysis of a series of spectra obtained from incremental additions of LSR, the information is more conveniently expressed in graphical form. The mathematical treatment to allow manual (graphical) evaluation of the experimental results with reasonable simplifications is outlined as follows[23].

Consider the equilibrium for a 1:1 complex [equation (11)], the observed LIS Δ of a given nucleus in the presence of a shift reagent is given by:

$$\Delta = \frac{X}{S_t}\,\Delta_1 \qquad \ldots\ldots \quad (17)$$

where X is the concentration of the LS complex, and the other symbols are as defined previously. $\Delta = \Delta_1$ for the pure LS complex.

The equilibrium binding constant is given as:

$$K_1 = \frac{[LS]}{[L][S]} = \frac{X}{(L_t - X)(S_t - X)} \qquad \ldots\ldots \quad (18)$$

where L_t is the total concentration of the reagent. S_t and L_t are determined by the experimental conditions chosen. By extraction of X from equation (18) and substituting X in equation (17) one obtains an expression where Δ is a function of Δ_1, K_1, S_t and L_t.

One experimental restriction to simplify matters is to use low reagent concentrations

$$S_t \gg L_t$$

in which case X will be small too (X is the LS concentration)

$$S_t \gg X$$

Upon introducing this condition, equation (18) becomes

$$K_1 = \frac{X}{(L_t - X)S_t} = \frac{X}{L_tS_t - XS_t}$$

extracting X,

$$X = \frac{K_1L_tS_t}{1 + S_tK_1}$$

and substituting in Δ [equation (17)] yields

$$\Delta = \frac{K_1L_t\Delta_1}{1 + S_tK_1} \qquad \ldots\ldots \quad (19)$$

Equations (18) and (19) are the basic equations for the two most important approaches to obtain intrinsic LIS parameters.

Approach 1. Δ versus L_t/S_t plot at constant S_t.

The most used graphical method is the one where the substrate concentration S_t is kept constant and the reagent concentration L_t is varied (the condition $S_t \gg L_t$ remaining valid). In practice, a n.m.r. sample of the substrate, is prepared, and the n.m.r. spectra are recorded for various concentrations of the reagent, which is added incrementally. The slope of the plot Δ versus L_t/S_t is assumed to give a measure of the "bound" or "limiting" shift.

To check the validity of this assumption we have to consider two limiting cases:

A. Strong binding of the substrate to the reagent: this means $K_1S_t \gg 1$ in equation (19), then equation (19) becomes

$$\Delta = \frac{K_1L_t\Delta_1}{S_tK_1} = \Delta_1\left(\frac{L_t}{S_t}\right) \qquad \ldots\ldots \quad (20)$$

Equation (20) corresponds to a straight line for the plot Δ versus $\frac{L_t}{S_t}$ passing through the origin, with slope equal to the limiting shift Δ_1.

For high $S_t (S_t \gg L_t)$ and good complexing (a large value for K_1) this method will yield correct results.

B. Weak binding of the substrate to the reagent: this means $K_1 S_t \ll 1$ in equation (19), then equation (19) becomes

$$\Delta = K_1 L_t \Delta_1$$

or

$$\Delta = K_1 \Delta_1 S_t \frac{L_t}{S_t} \qquad \ldots\ldots \quad (21)$$

Equation (21), too, corresponds to a straight line in the plot of Δ versus L_t/S_t, but the slope is not equal to Δ_1 any more. It is also dependent on the substrate concentration and the binding constant of the complex formed.

Approach 2. Plot of S_t versus $1/\Delta$ at constant L_t.

This approach was introduced by Armitage.[52,60] It offers the bonus that values for Δ_1 and K_1 are obtained as well.

We write equation (18) in the following form:

$$K_1 = \frac{X}{L_t S_t - S_t X - L_t X + X^2}$$

We have assumed $S_t \gg L_t$; therefore, X will be low and X^2 will be very small, therefore, negligible.

Rearranging equation (17) to extract X ($X = \Delta S_t/\Delta_1$) and substituting in K_1,

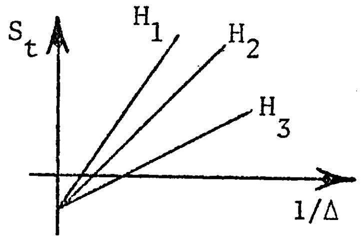
$$K_1 = \frac{\Delta}{\Delta_1 L_t - \Delta S_t - \Delta L_t}$$

rearranging to extract S_t yields

$$S_t = \Delta_1 L_t \left(\frac{1}{\Delta}\right) - \left(L_t + \frac{1}{K_1}\right) \qquad \ldots\ldots \quad (22)$$

Equation (22) predicts a straight S_t versus $1/\Delta$ plot with a slope of $L_t\Delta_1$ and a y-intercept of $-(L_t + 1/K_1)$, thus yielding values for both intrinsic parameters Δ_1 and K_1. A typical (idealized) plot is shown in Figure 7. The separate lines for all protons converge to the same intercept, which corresponds to a consistent value of K_1 obtained from any one of the protons.

Figure No. 7. Idealized S_t versus $1/\Delta$ plot for three nuclei of a particular substrate; at low L_t concentrations a straight line is expected; L_t is kept constant, S_t is varied in the experiment.



All previously derived equations [(11) and (17) - (22)] are valid for a "one step - 1:1 binding model". To account for the expected 1:2 complexing, also, the equations can be modified easily for the assumption of a "one step - 1:2 binding model" of the type,

$$2S + L \rightleftharpoons LS_2.$$

We write equation (10) in the following form:

$$\Delta = \frac{1}{S_t} (X\Delta_1 + 2y\, \Delta_2) \qquad \ldots\ldots \quad (23)$$

where y is the molar concentration of the LS_2 species. K_1 and K_2 are defined as follows [derived from the equilibrium (11) and (12)]

$$K_1 = \frac{[LS]}{[L][S]} = \frac{X}{(S_t - X - 2y)(L_t - X - y)} \qquad \ldots\ldots \quad (24)$$

$$K_2 = \frac{[LS_2]}{[LS][S]} = \frac{y}{X(S_t - X - 2y)} \qquad \ldots\ldots \quad (25)$$

In principle, X and y can be extracted from equations (24) and (25) and substituted in equation (23) to solve this four-parameter problem for Δ_1, Δ_2 and K_1, K_2.

Assuming the condition $S_t \gg L_t$ may be valid; then equations (23), (24), (25) assume the following form when $2y\Delta_2 \gg X\Delta_1$ is assumed for (23) and $S_t \gg X$, $S_t \gg 2y$ is assumed for (24) and (25):

$$\Delta = \frac{2y\Delta_2}{S_t} \qquad \ldots\ldots \quad (26)$$

$$K_1 = \frac{X}{S_t(L_t - X - y)} \qquad \ldots\ldots \quad (27)$$

$$K_2 = \frac{y}{XS_t} \qquad \ldots\ldots \quad (28)$$

Equation (28) upon rearrangement is

$$y = XS_tK_2$$

Equation (27) upon rearrangement is

$$X = K_1S_tL_t - K_1S_tX - K_1S_ty$$

Equation (28) substituted in (27) is

$$X = K_1S_tL_t - K_1S_tX - K_1S_tXS_tK_2 \qquad \ldots\ldots \quad (29)$$

Now X, extracted from (29) is

$$X = \frac{K_1S_tL_t}{1 + K_1S_t + K_1K_2S_t^2} \qquad \ldots\ldots \quad (30)$$

Equation (30) substituted in equation (28) becomes

$$y = \frac{K_1K_2S_t^2L_t}{1 + K_1S_t + K_1K_2S_t^2} \qquad \ldots\ldots \quad (31)$$

and equation (31) substituted in equation (26) becomes

$$\Delta = \frac{2\Delta_2}{S_t} \frac{K_1K_2S_t^2L_t}{1 + K_1S_t + K_1K_2S_t^2}$$

Now the assumption $S_t^2K_1K_2 \gg 1$ or K_1S_t is introduced, yielding

$$\Delta = 2\Delta_2 \frac{K_1K_2S_tL_t}{K_1K_2S_t^2}$$

rearranged becomes

$$\Delta = 2\Delta_2 \left(\frac{L_t}{S_t}\right) \qquad \text{......} \quad (32)$$

and rearranged again becomes

$$S_t = 2\Delta_2L_t \left(\frac{1}{\Delta}\right) \qquad \text{......} \quad (33)$$

Comparison of equations (32) and (33) with (20) and (22), respectively, demonstrates that for both complexation models (1:1, one step, and 1:2, two steps) the plots Δ versus L_t/S_t and S_t versus $1/\Delta$ yield straight lines, the Δ_1 in equations (20) and (22) being equal to $2\Delta_2$ in equations (32) and (33).

In the majority of cases, plots of induced shift versus the ratio of [LSR]/[substrate] are not linear over the entire range from zero to one for [LSR]/[substrate], although for one or two instances a linear relationship has been claimed.[18] Usually some curvature is apparent at both extremes of the plot, with a good linear correlation being noted for the range 0.2 - 0.6 mole ratio. Curvature at low LSR concentrations has been attributed to competition between the substrate and traces of water or acidic impurities for the LSR.[24,34] Curvature at high ratios of [LSR]/[substrate] has been ascribed to incomplete solution of the LSR and medium and association effects.[21,61]

1.4. Carbon-13 Magnetic Resonance Spectroscopy

For many years ^{1}H n.m.r. spectroscopy has been used in the structural determination of organic compounds. The advent of ^{13}C n.m.r. spectroscopy as a new tool has provided a valuable complementary technique. In 1957 the first reports[62,63] of successful determinations of n.m.r. of ^{13}C nuclei in natural abundance appeared and since then sufficient work has been done to indicate several features which offer new approaches to problems of chemical interest. There are many points to contrast between the two techniques.[64,65]

A. Chemical shift

It is generally found that ^{13}C chemical shifts are ca. 20 times larger in p.p.m. than ^{1}H chemical shifts. Whereas a precise chemical shift determination in proton spectra often requires a detailed analysis because this quantity is obscured by splitting due to spin-spin coupling, this complication does not arise in natural-abundance ^{13}C spectra. Broad-band noise-modulated proton decoupling simultaneously removes all heteronuclear ^{13}C - ^{1}H couplings. Hence each chemically non-equivalent carbon within the molecule gives rise to a separate line whose relative position corresponds to a chemical shift.

B. Line width

With modern instrumental methods, it is possible to have narrower resonance lines in ^{13}C n.m.r. spectra than with ^{1}H spectra. ^{1}H spectra are extensively spin-coupled, leading to broadened resonance bands for most protons. In ^{13}C n.m.r. the situation is more easily controlled and spin-spin splitting is not usually present.

C. Sensitivity

Isotope 13 has a nuclear spin of 1/2 (as does ^{1}H); however, the natural abundance of carbon-13 is 1.1%. On account of the much lower sensitivity of ^{13}C as compared to ^{1}H n.m.r. spectroscopy, sensitivity is a far worse problem. It is generally preferable to use solutions which are at least 1 M. The low sensitivity of ^{13}C spectroscopy creates additional problems by the use of large diameter tubes and Fourier transform spectroscopy to increase the sensitivity.

^{13}C n.m.r. spectra of organic compounds are usually recorded with simultaneous proton decoupling in order to eliminate spin-spin splitting and to take advantage of the signal enhancement provided by the nuclear Overhauser effect.[66] For the assignment of the resonance signals obtained in this way to the individual carbons in the molecule studied, "off resonance" decoupling is a straightforward technique to distinguish between the signals of quaternary carbons, CH-, CH_2–, and CH_3-groups. The differentiation within each group, however, is a more difficult task if chemically different carbons are expected to yield signals of equal intensity.

In general, however, it has not been possible to make a full assignment in complex organic molecules without the aid of spectral comparison of chemically related compounds. This can be achieved by introducing functional groups at various sites of a molecule or by specific labelling. For carbons bearing protons and in cases where synthetic methods are available, specific deuteration provides a useful alternative that leads to an unequivocal decision due to the observable ^{13}C-D spin-spin coupling. Clearly, deuteration fails if the desired synthesis is impossible or becomes too time consuming.

The lanthanide chemical shift reagents that are currently being used to "simplify" ^1H n.m.r. spectra of compounds containing coordinating functional groups can also be used in ^{13}C n.m.r. studies. Since ^{13}C resonances enjoy a far greater freedom from overlap than proton resonances, it is possible to aid ^{13}C n.m.r. spectral assignments by the use of these reagents.

Assigning the lines in a ^{13}C n.m.r. spectrum to individual carbon atoms in a molecule obviously requires the combined application of the above-mentioned techniques.[67]

The results which can be obtained directly from ^{13}C spectra are concerned, for the most part, with the chemical shift which has been called "the most important single parameter to be derived from the n.m.r. spectrum". For a specific nucleus A, the chemical shift depends on the field H_A experienced at that nucleus and which is given by:

$$H_A = H_O\,(1 - \sigma_A) \qquad \ldots\ldots \quad (34)$$

where H_O is the applied field. The total shielding constant σ_A can be approximated by a sum of three terms:[68]

$$\sigma_A = \sigma d + \sigma p + \sigma' \qquad \ldots\ldots \quad (35)$$

The diamagnetic contribution of σd is the Lamb term for the atom being considered; i.e., σd corresponds to the uniform circulation of the atomic electrons as if they were free. The paramagnetic term σp is a local correction due to the molecular environment and involves the mixing of ground and excited electronic states by the applied magnetic field (σp would be zero in an isolated atom). The term σ' represents the effect of the electron circulation on all other atoms and any interatomic ring currents which cannot be localized.

Several studies of ^{13}C n.m.r. of aromatic molecules have been reported.[69-77] For the alternant hydrocarbons, the carbon shieldings for the nuclei bonded to two other carbons only differ very slightly ($\leqslant$ 1 p.p.m.) from that of benzene, while the carbon nuclei at ring junctions absorb at appreciably lower field. For the non-alternant hydrocarbons, the aromatic nuclei absorb over a much wider range than for the alternants.[70] The two types of hydrocarbon exhibit clear differences. Since, theoretically, the significant distinction between the alternant and non-alternant hydrocarbons is that for the former the π-electron density at each carbon is very close to unity while for the latter large differences may result at various positions, it follows that ^{13}C shifts in aromatic systems may be governed by the π-electron distribution.

The results for the methyl-substituted benzene series[70,78] indicate two general features of aromatic ^{13}C shieldings. The more distinctive of these is a pronounced deshielding of ca. 9 p.p.m. at an aromatic carbon upon replacement of hydrogen by methyl. It is particularly interesting that this deshielding influence is approximately constant for a large variety of aromatic derivatives and only for cases in which there is substantial steric interference with the methyl group are marked changes in its magnitude found. The second feature which was recognised, although the differences are small, was that the indirect effects of a methyl group on the other aryl carbons are additive with successive methyl substitution on the ring provided the methyl groups are in meta- or para- positions. Thus, if the substituents are not ortho-, the aromatic ^{13}C shifts in polysubstituted cases are given by the algebraic sum of the effects observed for the monosubstituted benzenes. The agreement between observed and calculated values is often ~1 p.p.m. and, generally, the deviations are less than 2 p.p.m.[79] If the substituents are <u>ortho</u>-, larger deviations are usually found.

From the available data, shift values for the monosubstituted benzenes have been collected in Table 1.

From these results it is apparent that the carbon bonded to the substituent absorbs over the widest range, 66.8 p.p.m.; in contrast, the <u>meta</u>-carbons are the least affected by substitution, 3.2 p.p.m. The <u>ortho</u>- and <u>para</u>- carbons exhibit appreciable shifts, 19-25 p.p.m. for this assortment of substituents.

Since the carboxylic carbon in benzoic acid absorbs at 174.9 p.p.m.,[81] formation of the methyl ester produces a 9 p.p.m. upfield shift.[82] Substituents on the aryl ring are shown to affect the carboxyl shieldings very slightly, with significant changes occurring only in the <u>ortho</u>- substituted examples. The largest shift, + 4.4 p.p.m., is caused by an <u>ortho</u>-hydroxyl group, presumably, because of intramolecular hydrogen bonding.[83] The much smaller shifts caused by the other <u>ortho</u>-substituents indicate that these compounds are more sterically hindered.

Dhami and Stothers[84] have studied extensively a series of 40 substituted anisoles. The data for the <u>mono</u>-<u>para</u>-substituted anisoles confirm the existence of the additive nature of substituent effects on aryl carbon shieldings. While, in <u>ortho</u>-substituted systems, generally, it is found that the shielding effects of substituents on the aryl carbons are no longer additive, but it appears that the

Table No.1. Empirical parameters* for the calculation of chemical shifts in substituted benzenes.[80]

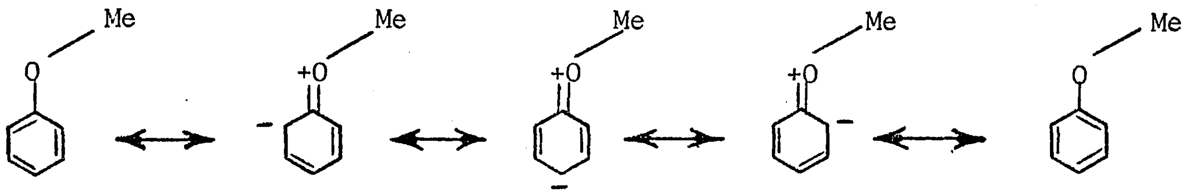
Substituent	Position			
	C-1	ortho	meta	para
H	0	0	0	0
CH_3	+ 9.3	+ 0.8	0	- 2.9
CH_2CH_3	+15.6	- 0.4	0	- 2.6
$CH(CH_3)_2$	+20.2	- 2.5	+ 0.1	- 2.4
$C(CH_3)_3$	+22.4	- 3.1	- 0.1	- 2.9
CF_3	- 9.0	- 2.2	+ 0.3	+ 3.2
C_6H_5	+13	- 1	+ 0.4	- 1
$CH=CH_2$	+ 9.5	- 2.0	+ 0.2	- 0.5
$C\equiv CH$	- 6.1	+ 3.8	+ 0.4	- 0.2
CH_2OH	+12	- 1	0	- 1
COOH	+ 2.1	+ 1.5	0	+ 5.1
$COO^{\ominus}$	+ 8	+ 1	0	+ 3
$COOCH_3$	+ 2.1	+ 1.1	+ 0.1	+.4.5
COCl	+ 5	+ 3	+ 1	+ 7
CHO	+ 8.6	+ 1.3	+ 0.6	+ 5.5
$COCH_3$	+ 9.1	+ 0.1	0	+ 4.2
$COCF_3$	- 5.6	+ 1.8	+ 0.7	+ 6.7
COC_6H_5	+ 9.4	+ 1.7	- 0.2	+ 3.6
CN	-15.4	+ 3.6	+ 0.6	+ 3.9
OH	+26.9	-12.7	+ 1.4	- 7.3
OCH_3	+31.4	-14.4	+ 1.0	- 7.7
$OCOCH_3$	+23	- 6	+ 1	- 2
OC_6H_5	+29	- 9	+ 2	- 5
NH_2	+18.0	-13.3	+ 0.9	- 9.8
$N(CH_3)_2$	+23	-16	+ 1	-12
$N(C_6H_5)_2$	+19	- 4	+ 1	- 6
$NHCOCH_3$	+11	-10	0	- 6
NO_2	+20.0	- 4.8	+ 0.9	+ 5.8
NCO	+ 5.7	- 3.6	+ 1.2	- 2.8
F	+34.8	-12.9	+ 1.4	- 4.5
Cl	+ 6.2	+ 0.4	+ 1.3	- 1.9
Br	- 5.5	+ 3.4	+ 1.7	- 1.6
I	-32	+10	+ 3	+ 1

---

* p.p.m. Relative to internal benzene standard; positive shifts downfield (based on TMS convention).

magnitude of the deviation from additivity is a crude measure of the steric hindrance to electronic interactions.

The interaction of the methoxyl oxygen with the benzene ring is altered in the highly substituted examples relative to that in the meta-, para-, and mono-ortho-substituted cases. For a compound in which there is no interference by substituents, several canonical forms can be written. The more important of these are shown as structures (XXXIV - XXXVIII).[85] The aromatic shieldings for anisole



(XXXIV) (XXXV) (XXXVI) (XXXVII) (XXXVIII)

are readily explicable in terms of the contributing forms (XXXV) - (XXXVII), since an increase in the electron density is expected at the ortho- and para- positions, and since these positions are considerably shielded in the anisole molecule relative to the value for benzene carbons.

The major contributions to any substituent effect must be related in some way to the ability of the substituent to alter the electronic structure at the site involved in the molecule under study. Contributions due to simple electrostatic effects arising from electronegativity differences in the substituent are transferred to the reaction site through simple inductive processes, field effects, and resonance or mesomeric phenomena. Attempts have been made to divide substituent effects into these various contributions and thereby find a common basis for the numerous substituent effect derived from a variety of chemical reactions or physical properties.

The ^{13}C chemical shifts of 14 monosubstituted benzenes and 14 4-substituted biphenyls have been determined by Schulman and his co-workers[86] and correlated by various linear free energy relationships. They concluded that electronic reorganisation in these molecules through resonance structures is of greater significance than that due to electrostatic field effects, as the field effects will alter the ^{13}C shifts in only a minimal way. They added that a significant substituent effect is transmitted all the way from the 4-carbon of biphenyls to the 4'-carbon, i.e., a substituent effect is transmitted through eight covalent bonds.

An early study of biphenyl at 8.5 MHz by Lauterbur[70] revealed a spectrum very similar to that of toluene, with no resolvable shifts between the o-, m- and p-carbons; a re-examination of the spectrum at 15.1 MHz has given more detailed information[87]. Suitably deuterated derivatives were employed to allow unambiguous assignments for naphthalene and biphenyl to be made. Alger et al.[88] concluded that the inclusions of the mobile bond-order and charge polarization effect (both σ- and π-electron charge densities) improved the theoretical treatment of aryl carbon shieldings.

Hasegawa and his co-workers[89] have studied the ^{13}C n.m.r. spectra of several alkyl biphenyls. For the meta- and para-alkylated biphenyls, the chemical shift of each aromatic carbon-13 is calculated according to the additivity rule. A satisfactory agreement obtained between the observed values of the ^{13}C chemical shifts and those predicted by the additivity calculations. They found, in all cases, that the hyperconjugative effect gives rise to a drastic lower-field shift for the ring carbon atoms bonded to the alkyl groups in the order of $CH_3 < CH_3CH_2 < CH(CH_3)_2 < C(CH_3)_3$. At the same time, an alternative higher-field shift of the next neighbouring carbon atoms of the alkyl groups is observed; that is, in the case of 4,4'-dialkylbiphenyl, the ring carbons at the meta-position reveal a chemical shift in the directions opposite to the chemical shift of the para-positions. They suggested that these results are probably due to the ortho-para-conjugation or to the inductive effect of the alkyl groups.

For the ortho-alkylated biphenyls, the substituents may cause a large steric effect; hence, the analysis of the spectra is much more difficult and the quantitative assignment using the additivity rule does not hold.

They added that the observed chemical shifts of aliphatic ^{13}C atoms for para- or meta-alkylated biphenyls agree with the values of the corresponding alkylated benzenes. In the case of ortho-alkylated biphenyls, such as 2,2'-dimethylbiphenyl and 2,2',6,6'- tetramethylbiphenyl, the chemical shifts of the methyl carbons shows a field shift higher by about 1 p.p.m. than that of toluene. The different shifts were suggested to be due to a space interaction between the two methyl groups, and this interaction may arise by an orbital overlap between the methyl groups, which were considered to approach one another to take the cis-conformation.

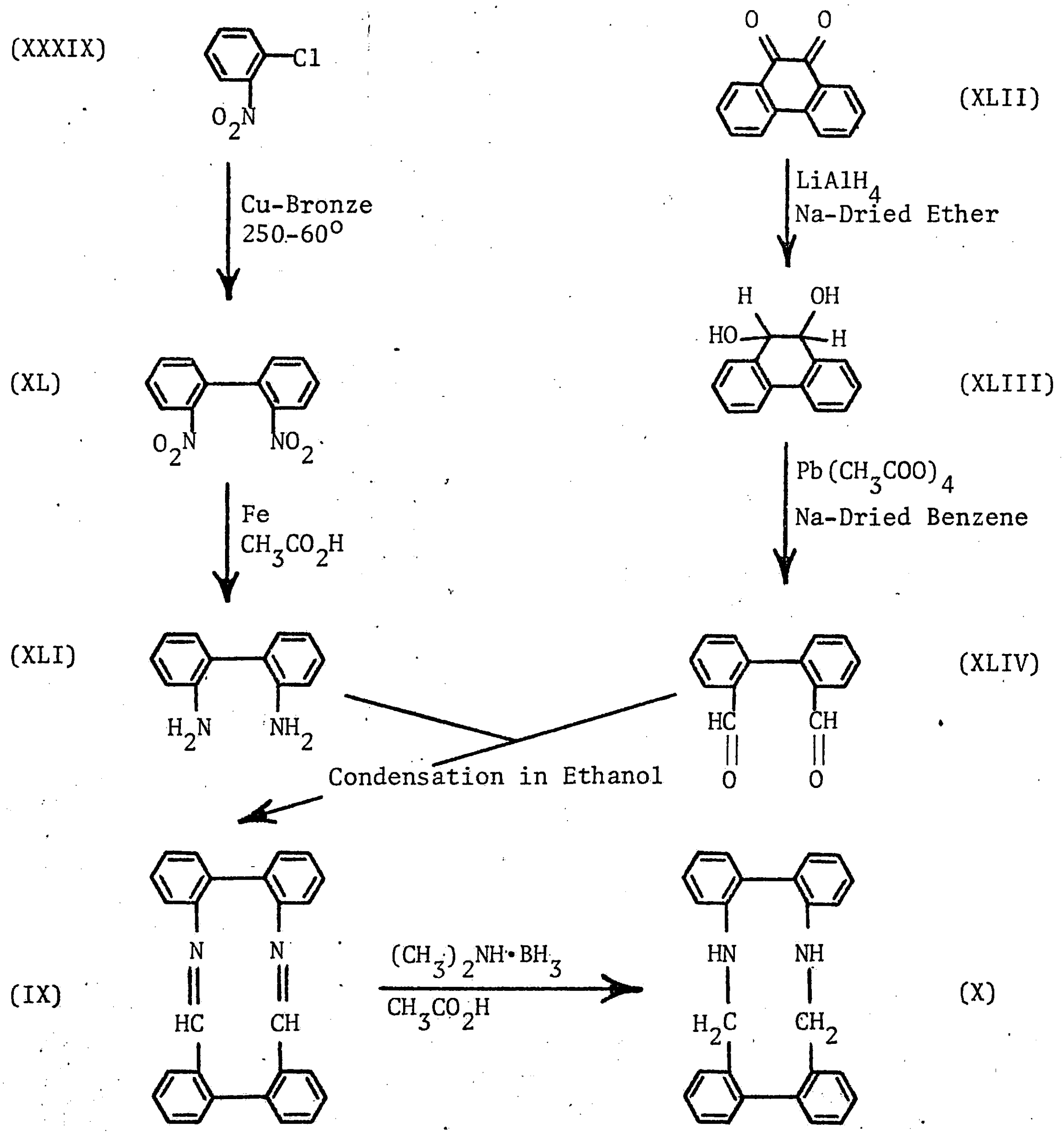
In a subsequent paper, Imanari and his co-workers[90] have studied the ^{13}C n.m.r. spectra of the ortho- and para-halogenobiphenyls. For the 4,4'-dihalobiphenyls, the observed chemical shifts of the C_1 and C_3 positions gave an excellent positive linear dependence on the absolute value of the electronegativity of the substituents.

Conversely, those for the C_2 and C_4 positions show a negative dependence. The plots of the C_4-position only revealed a remarkable deviation from the straight line, which may be due to the heavy atom effects of the halogen atoms. For the ortho-halobiphenyls, e.g., 2,2'-, and 2,6-dichlorobiphenyl and 2,2',6,6'-tetrachlorobiphenyl, the additivity calculation gave more or less satisfactory results for the ring carbons, except for the values of the bridgehead C_1 and C_1' positions. They suggested that this deviation, a remarkable high field shift, is due to the anisotropic effect of the ring current which is reduced by the large electronegativity of the halogen atoms. They also suggested that these anomalous discrepancies in the C_1-chemical shift may be considered to result from some interaction between the chlorine and $2P_z$ carbon atomic orbitals.

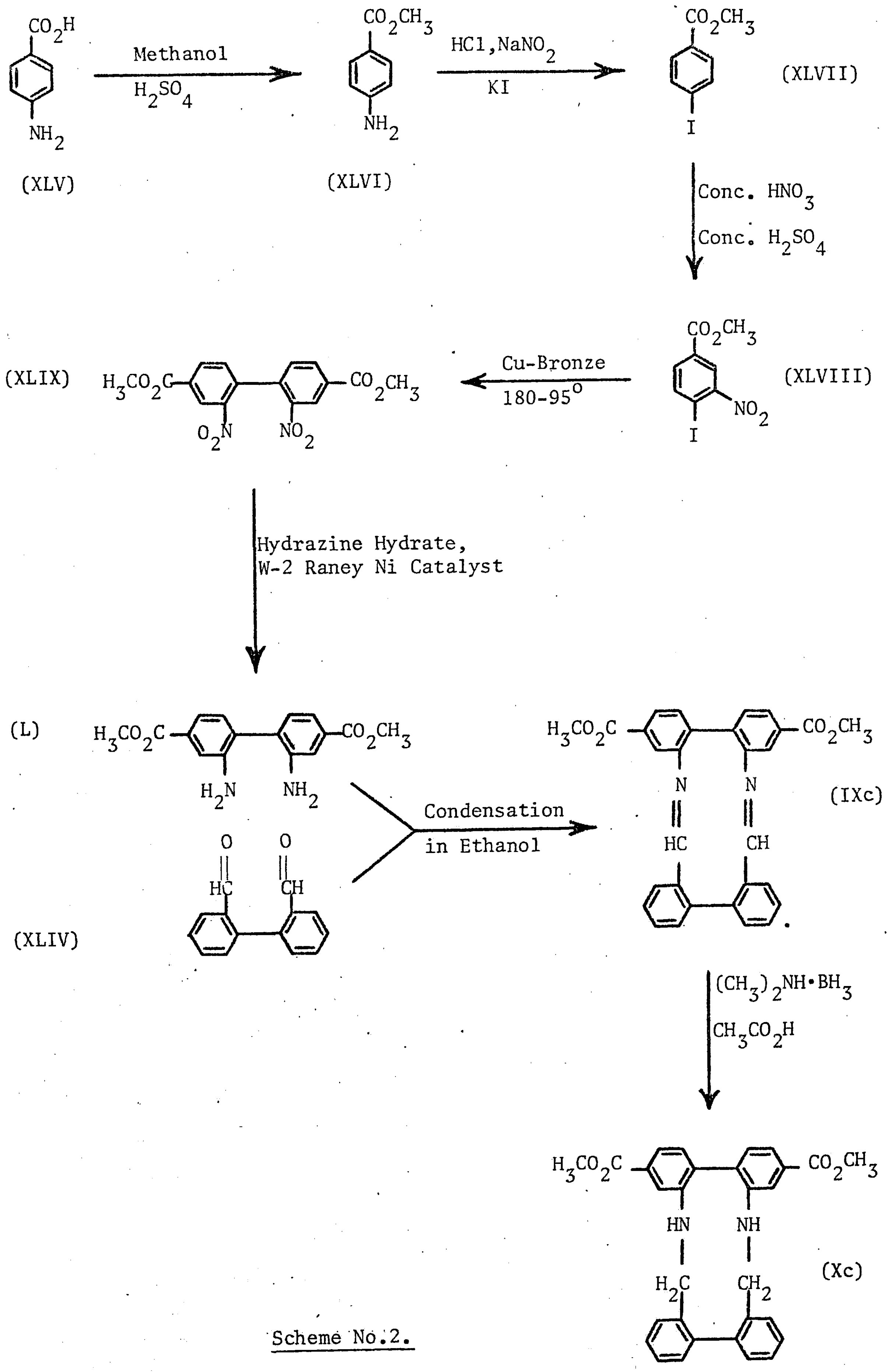
2. DISCUSSION

2.1. Synthesis of some 2,2'-Bridged Biphenyls with 12-Membered Hetero-cyclic Bridging Rings.

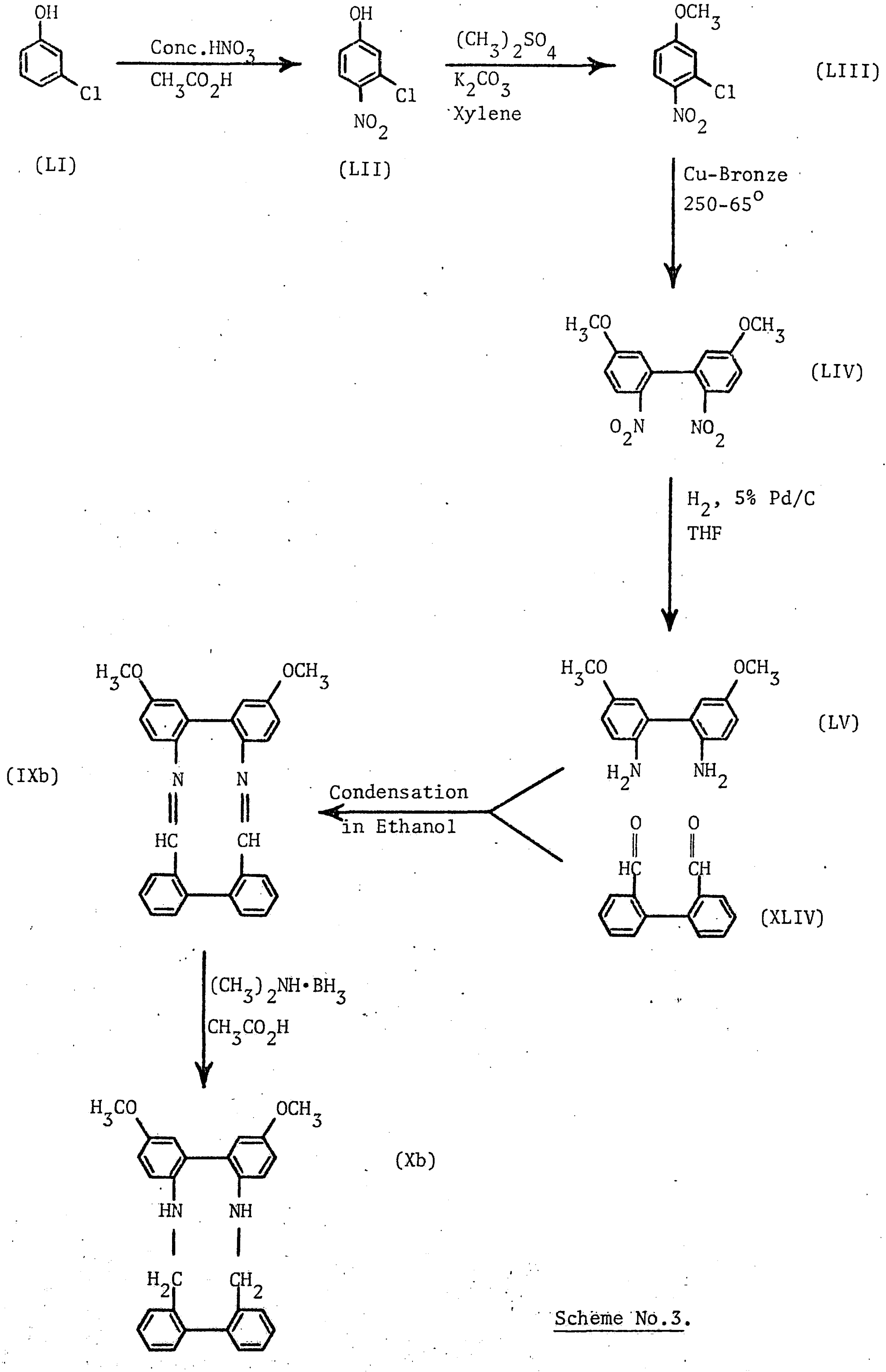
The synthesis are set out in Schemes 1 - 4.



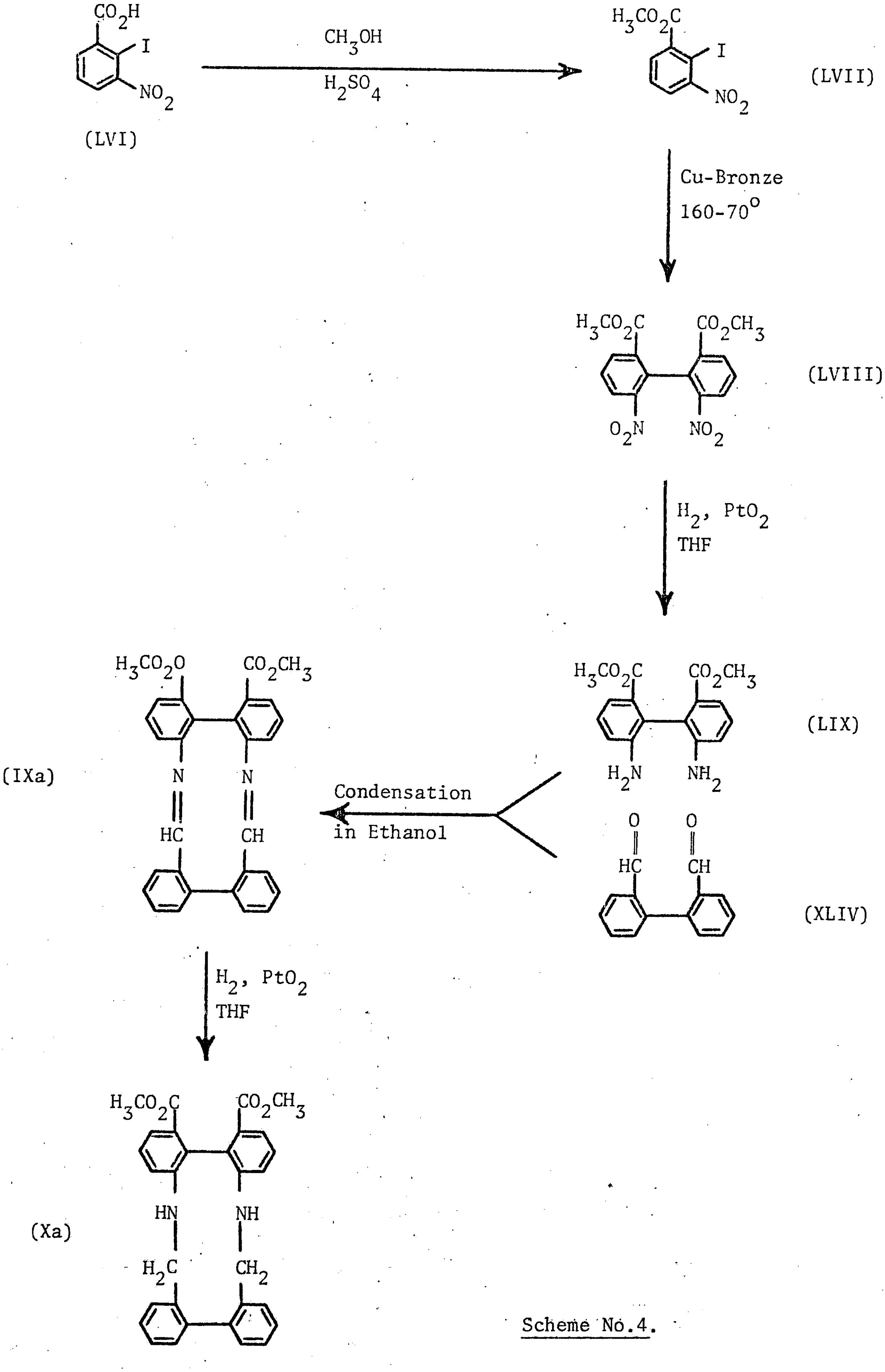
Scheme No.1.


(XLV)
Methanol
H_2SO_4
(XLVI)
$HCl, NaNO_2$
KI
(XLVII)
Conc. HNO_3
Conc. H_2SO_4
(XLVIII)
Cu-Bronze
180-95°
(XLIX)
Hydrazine Hydrate,
W-2 Raney Ni Catalyst
(L)
(XLIV)
Condensation
in Ethanol
(IXc)
$(CH_3)_2NH \cdot BH_3$
CH_3CO_2H
(Xc)
CO_2H
NH_2
CO_2CH_3
I
NO_2
H_3CO_2C
O_2N
H_2N
HN
NH
H_2C
CH_2

Scheme No.2.


OH
Cl
(LI)
Conc.HNO3
CH3CO2H
OH
Cl
NO2
(LII)
(CH3)2SO4
K2CO3
Xylene
OCH3
Cl
NO2
(LIII)
Cu-Bronze
250-65°
H3CO
OCH3
O2N
NO2
(LIV)
H2, 5% Pd/C
THF
H3CO
OCH3
H2N
NH2
(LV)
O
O
HC
CH
(XLIV)
Condensation
in Ethanol
H3CO
OCH3
N
N
HC
CH
(IXb)
(CH3)2NH·BH3
CH3CO2H
H3CO
OCH3
HN
NH
H2C
CH2
(Xb)

Scheme No.3.


(LVI)
CH$_3$OH
H$_2$SO$_4$
(LVII)
Cu-Bronze
160-70°
(LVIII)
H$_2$, PtO$_2$
THF
(LIX)
(XLIV)
Condensation
in Ethanol
(IXa)
H$_2$, PtO$_2$
THF
(Xa)

Scheme No.4.

In Scheme 1, the condensation of 2,2'-diaminobiphenyl (XLI) and biphenyl-2,2'-dialdehyde (XLIV) in absolute ethanol at room temperature furnished tetrabenzo[b,d,h,j][1,6]diazacyclododecine (IX), as colourless crystals, in 76% yield, and having the m.p. 312-313°. Bergmann *et al.*[4] and Bindra *et al.*[5] prepared (IX) with m.ps. above 300° and 326°, respectively. Many attempts were made to prepare a sample with m.p. 326°, but without any success. Also an attempt to isolate any isomeric component of (IX) by column chromatography was unsuccessful.

Compound (IX) upon reduction with sodium borohydride in methyl alcohol was reported[5] to yield 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j]-[1,6]diazacyclododecine (X) in 80% yield as colourless needles with m.p. 158°. Attempts were made to reduce (IX) by the method given by Bindra *et al.*,[5] but these failed to give (X). However, reduction of compound (IX) with dimethylamine borane in glacial acetic acid gave (X) in 89% yield and with the m.p. 174-176°. It was found that (X) is easily oxidised in the air and changes its colour rapidly from white to pale yellow to brown. The ease, speed and high yield with which this reduction proceeded is worthy of mention, the entire reaction occurring within a matter of a few minutes.

In Scheme 2, the condensation of dimethyl 2,2'-diaminobiphenyl-4,4'-dicarboxylate (L) and (XLIV) in absolute ethanol furnished dimethyl tetrabenzo[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate (IXc) in 83.5% yield. Compound (IXc) was found to occur in two crystalline forms; very pale yellow rods with m.p. 262-263°, and pale yellow diamond-shaped plates with m.p. 261-261.5° (see page 224). (IXc) was reduced easily, with dimethylamine borane in glacial acetic acid, to dimethyl 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate (Xc) in 89% yield. On crystallisation of the reduction product from ethanol, two crystalline forms were obtained; a large proportion of pale yellow triangular rods with m.p. 238-239°, and a small proportion of bright yellow hexagonal plates with m.p. 237-238° (see page 225). Attempts to prepare a quaternary salt from (Xc) using iodomethane in warm dry acetone and in dry benzene, separately, failed.

In Scheme 3, the preparation of 5,5'-dimethoxy-2,2'-dinitrobiphenyl (LIV) was reported by Kempter and Castle, (J. Heterocycl. Chem., 1969, 6, 523) who obtained it in 80% yield by the reaction of 3-iodo-4-nitroanisole and copper bronze at 140-170°. However, during this work (LIV) was prepared in 46% yield by heating 3-chloro-4-nitroanisole (LIII) with activated copper bronze at 250-265°. A dark black solid was obtained, purified (some) on silica gel column and eluted with chloroform. The first portion of eluate gave nearly colourless prisms with m.p. 149-149.5°, while the remaining portions gave coloured prisms (see page 228). The low yield obtained by this method in comparison to that obtained by Kempter and Castle is mainly due to the higher temperature at which reaction occurred in which some of the product (LIV) is decomposed.

Compound (LIV) was readily reduced. When hydrogenated over 5% palladinized charcoal at 45 p.s.i. at room temperature in tetrahydrofuran it gave 2,2'-diamino-5,5'-dimethoxybiphenyl (LV) in 77% yield. On the other hand, hydrogenation of (LIV) over Adams' platinum oxide at 46 p.s.i. at room temperature in glacial acetic acid furnished (LV) in only 11% yield. The figures of the micro-elemental analysis of (LV) have shown some discrepancies from the theoretical values. Out of fourteen analyses, only two sets of figures were found to be acceptably close to the theoretical one (see page 229). However, ^{1}H n.m.r. spectrum (60 MHz) of (LV) in $CDCl_3$ displayed a broad singlet at 3.37 p.p.m. (2 NH_2 protons which exchange with D_2O) and a sharp singlet at 3.76 p.p.m. (6H, methyl protons) as well as a singlet at 6.79 p.p.m. due to the aromatic protons. The mass spectroscopic determination of the molecular weight of (LV) had given the formula $C_{14}H_{16}N_2O_2$ (measured mass = 244.1211) [see Spectrum 20 , page 113]. The infra-red spectrum (hexachlorobutadiene mull) showed marked absorption at 3410 and 3330 cm^{-1} (NH_2). Also the condensation product (IXb) made from (LV) had a satisfactory analysis.

From the above spectroscopic studies of (LV) it is concluded that the compound is the right one despite the discrepancies encountered in its elemental micro-analysis.

The condensation of (LV) and (XLIV) in absolute ethanol furnished 3,6-dimethoxytetrabenzo[b,d,h,j][1,6]diazacyclododecine (IXb) in 95% yield. Reduction of (IXb) proceeded easily, with dimethylamine borane in glacial acetic acid, to give 3,6-dimethoxy-9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine (Xb) in 69% yield.

In Scheme 4, hydrogenation of (LVIII) over Adams' platinum oxide at 63.5 p.s.i. at room temperature in tetrahydrofuran gave dimethyl 2,2'-diaminobiphenyl-6,6'-dicarboxylate (LIX) in 76% yield. It was found that (LIX) had the m.p. 127-128°, changing after melting to a white solid which did not remelt even at 340°. Reduction of (LVIII) with hydrazine using W-2 Raney nickel catalyst was unsuccessful. A yellowish-green solid was obtained whose m.p. was above 300°.

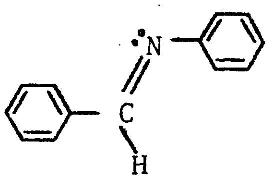
Condensation of (LIX) and (XLIV) in absolute ethanol furnished dimethyl tetrabenzo[b,d,h,j][1,6]diazacyclododecine-4,5-dicarboxylate (IXa) in 81% yeild. Hydrogenation of (IXa) went easily over Adams' platinum oxide at 48 p.s.i. at room temperature in tetrahydrofuran and gave dimethyl 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]-diazacyclododecine-4,5-dicarboxylate (Xa) in 73% yield. Attempts to reduce (IXa) with dimethylamine borane in glacial acetic acid failed to give (Xa).

Hydrogenation of 2,2'-dinitro-4,4',6,6'-tetramethylbiphenyl over Adams' platinum oxide at 44 p.s.i. at room temperature in a mixture of glacial acetic acid and absolute ethanol gave 2,2'-diamino-4,4',6,6'-tetramethylbiphenyl in 87% yield. In another method, when 2,2'-dinitro-4,4',6,6'-tetramethylbiphenyl was hydrogenated over W-2 Raney nickel at 600 p.s.i. and 200° in benzene for three hours, only 27% yield of the amino-compound was obtained. A considerable amount of brown sticky material was left unidentified. Attempts were made to condense 2,2'-diamino-4,4',6,6'-tetramethylbiphenyl and biphenyl-2,2'-dialdehyde in absolute ethanol, benzene or glacial acetic acid but failed to give the desired compound.

2.2. Electronic Absorption Spectra

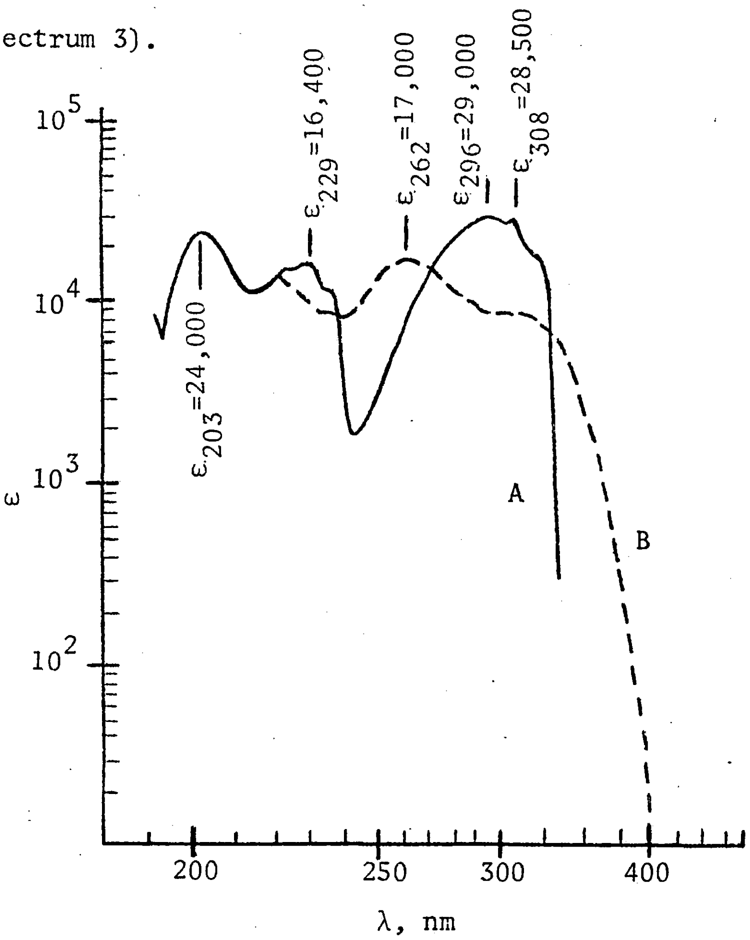
Schiff's bases contain the azomethine group $-HC=\ddot{N}-$, as in benzylideneaniline, and may be considered to have an electronic structure similar to that of stilbene, since the azomethine and vinyl groups are iso-π-electronic. One may therefore predict, at first consideration, similar absorption spectra for both molecules. Such expectations are not realized, however. The most striking difference between the spectra of trans-stilbene and benzylideneaniline is in the relative extinction coefficients of the long wavelength bands (Table 2).

Table No. 2. Comparison of the ultra-violet absorption spectra of trans-stilbene and benzylideneaniline.

Compound	$\lambda_{max,nm}$	ε_{max}	$\lambda_{max,nm}$	ε_{max}	$\lambda_{max,nm}$	ε_{max}	Solvent	Ref.
	203	24,000	229	16,400	296	29,000	Ethanol	91
					308	28,500		
	206.7	20,640						
	218	14,390						
	235	9,071	262	17,000	(310)	8,530	Ethanol	92,93
	227	12,000	262	17,300	314	6,940	Cyclohexane	94
	236	9,900						

Wavelengths enclosed in parentheses indicate a shoulder rather than a band maximum.

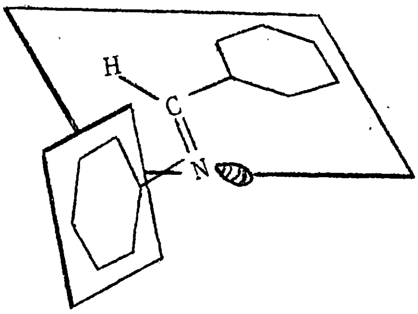
In the case of trans-stilbene, the band at λ_{max} 296 nm is the most intense one in the near ultra-violet region. This band occurs with markedly reduced intensity in the spectrum of benzylideneaniline, appearing as a shoulder at λ_{sh} 310 nm; such differences must reflect differences in their electronic structures (Spectrum 3).



Spectrum No.3. Ultra-violet absorption spectra of *trans*-stilbene (A) and benzylideneaniline (B) in ethanol.[95]

Ismailsky and Smirnov[96] recognized that while π-conjugation extends over the whole molecule in the case of stilbene, it is reduced in benzylideneaniline. They postulated that the unshared pair of electrons on the nitrogen atom can conjugate with the N-phenyl ring. This implies a non-coplanar molecular structure, since the N-phenyl group can only conjugate with the nitrogen lone pair if the N-phenyl ring is rotated out of the plane of the conjugated system consisting of the C-phenyl group, and the azomethine group. Bürgi and Dunitz[97,98] found that in the crystal the N-phenyl ring is twisted out of the Ph-CH=N-plane by 55°. This considerably reduces stilbene-like conjugation between the phenyl rings through the -CH=N- linkage. The benzylideneaniline molecule energetically favours a non-coplanar structure (Figure 8) rather than the planar configuration[94,99-105].

Figure No.8. Non-planar structure of benzylideneaniline.



El-Bayoumi and his co-workers[102] have studied the spectral changes of benzylideneanilines due to substitution, change of solvent, and protonation and interpreted the 315 and 262.5 nm bands as corresponding respectively to transitions involving the aniline part and the benzal part of the molecule. In a subsequent paper, El-Bayoumi and his co-workers[106] studied the absorption spectra of N-benzylimines and found that the 311 nm band observed for benzylideneaniline is absent in the spectra of N-benzylimines. This further supports its assignment as a locally excited transition which involves the aniline part of benzylideneaniline.

Room temperature ultra-violet absorption spectra of benzylideneanilines have shown them to exist in the anti-configuration, and photoisomerization studies[107] add supporting evidence that the sterically hindered syn-benzylideneanilines can be expected to isomerize rapidly to the anti-configuration except at low temperatures. Irradiation of a solution of benzylideneaniline at low temperature converts it reversibly to a photoisomer of different ultra-violet absorption, but no concrete evidence as to its structure has been presented. Kobayashi and his co-workers[108] have determined the ultra-violet spectra of photoisomers of many substituted benzylideneanilines in an EPA matrix (ether-isopentane-ethanol) at -196°C and showed that the imino arene ring of the photoisomer is about 90° rotated from the Ph-CH=N- plane around the N-Ph bond. However, it was not possible to determine whether or not the photoisomer has a syn-structure. They added that the photoisomers are stable in a matrix at -196°C for a long period and stable for several hours in solutions (EPA, methylcyclohexane, or acetone) at -72°C. Therefore, in a subsequent paper, Kobayashi *et al.*[103] have studied the configuration of the photoisomers by determining ^{1}H n.m.r. spectra of a number of benzylideneanilines at -75°C in acetone-d_6 solution and concluded that, as in the cases of stilbenes and azobenzenes, benzylideneanilines do have syn-isomers, which are stable only below -70°C and have not been isolated as such.

Before starting to discuss the ultra-violet absorption spectra of the heterocyclic 2,2'-twelve-membered-ring bridged biphenyls, it is of importance to discuss their geometries first. Dreiding molecular models of tetrabenzo[*b*,*d*,*h*,*j*][1,6]diazacyclododecine (IX) have shown that there are three distinct possibilities of geometrical isomerisms:

1 - Syn-syn-configuration where there are two conformational possibilities:

A - Where the two biphenyl units are flat, and the bridging ring is flexible (Figure 9). The molecule cannot have (S)- and/or (R)-configurations in the biphenyl units.

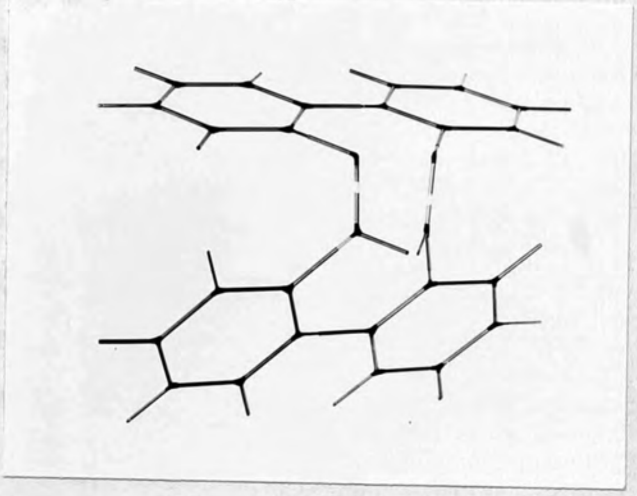


Figure No. 9. Syn-syn-configuration of (IX) with flexible bridging ring.

B - Where the bridging ring is rigid. The molecule has (S)- and (R)- configurations at the amine and aldehyde biphenyl units respectively, with angles of twist of about 75° for each (Figure 10).

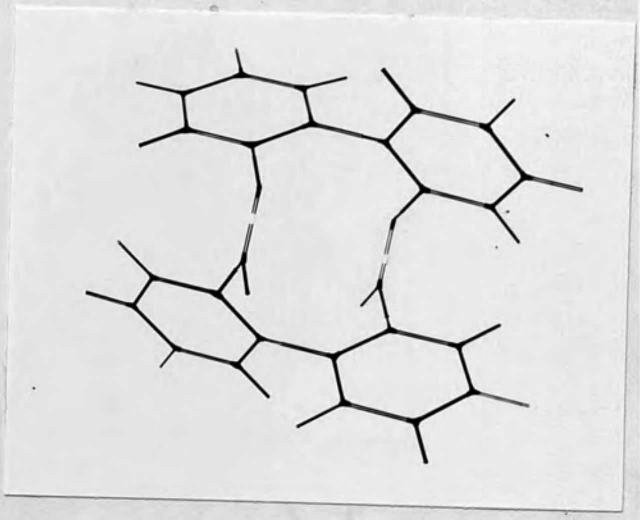


Figure No. 10. Syn-syn-configuration of (IX) with rigid bridging ring. (S)- and (R)- configurations at the amine and aldehyde biphenyl units, respectively.

2 - Anti-anti-configuration where the bridging ring is flexible and the molecule can have several conformations, and therefore, several values of Θ, the angle between the planes of the benzene rings, i.e. of

twist about the 1,1'-bond of each of the biphenyl skeletons. There are two extreme conformations, out of many the molecule may have, where in one of these two extreme conformations the N-phenyl ring in one half of the molecule is twisted out of the Ar-CH=N- plane by about 90°, while the C-phenyl ring in the same half of the molecule has zero twist. The reverse is true for the other half of the molecule. In the other extreme conformation, the situation is the same as stated above except the twisting of the N-phenyl and C-phenyl are in the reverse order for the same half of the molecule.

In these two extreme conformations with (R)- configuration at the amine and aldehyde biphenyl units (Figure 11), the angles of twist are about 53 and 55°, respectively. In changing the conformation from one to another, these angles of twist may increase to about 60 and 62°, respectively, as a maximum.

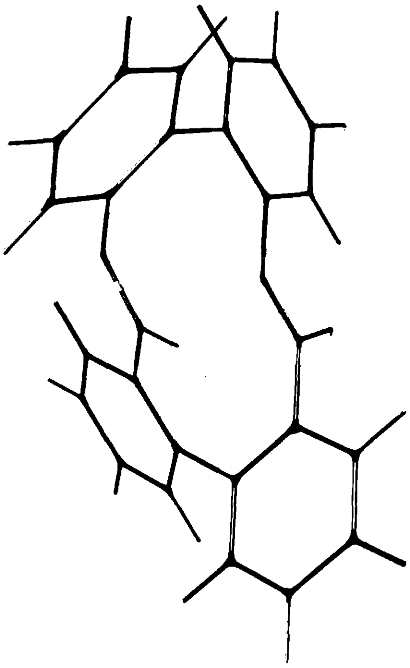


Figure No.11. Anti-anti-configuration of (IX) with flexible bridging ring. (R)-configuration at both biphenyl units.

3 - Syn-anti-configuration where the bridging ring is relatively rigid and the molecule can have only two conformations.

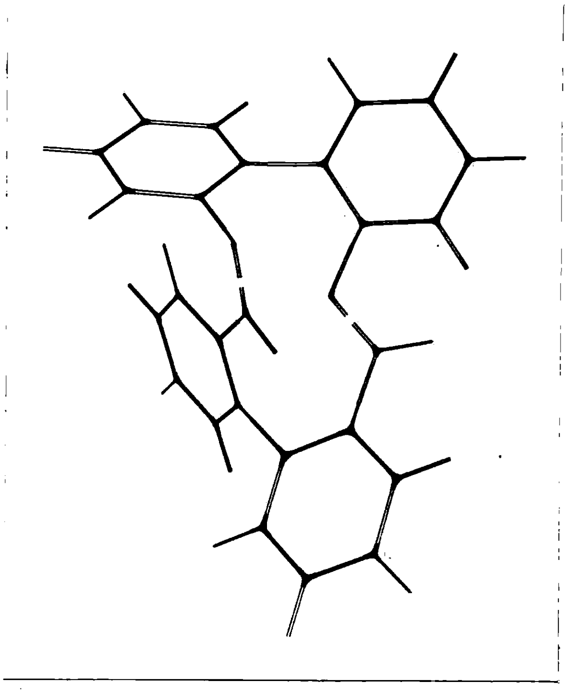


Figure No. 12.

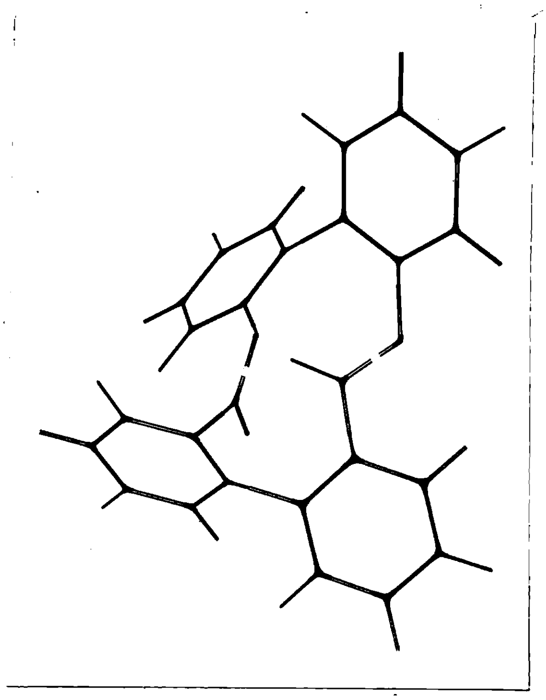


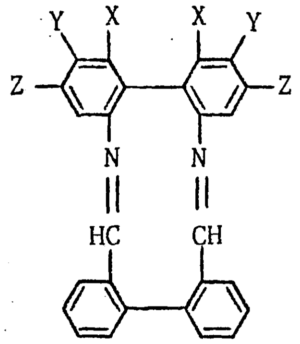
Figure No. 13.

Syn-anti-configuration of (IX) with relatively rigid bridging ring. (S)- and (R)-configurations at the amine and aldehyde biphenyl units, respectively.

Figure 12 has an (S)- and (R)- configurations along the 1,1'-bond of the biphenyl skeletons of the molecule with angles of twist of about 37 and 55^{o} at the amine and aldehyde biphenyl skeletons, respectively.

Figure 13 has the same (S)- and (R)- configurations, but the angles of twist at the amine and aldehyde biphenyl units are about 55 and 37^{o}, respectively.

Table No.3. Room temperature ultra-violet absorption spectra of:



Compound	Substituent										
	X	Y	Z	λ_{max},nm	ε_{max}	λ_{max},nm	ε max	λ_{max},nm	ε_{max}	λ_{max},nm	ε_{max}
IX	H	H	H	203	56,400	234	39,400	(249)	36,300	(300)	6,440
IXa	CO_2CH_3	H	H	205	57,600	227	49,700	(253)	34,200	300	10,800
IXb	H	OCH_3	H	203	56,400	235	43,200	(253)	33,100	300	9,890
IXc	H	H	CO_2CH_3	203	59,200	-	-	253	41,500	(290)	16,700

Solvent, 95% ethanol; values in parentheses denote inflections.

The spectrum of tetrabenzo[b,d,h,j][1,6]diazacyclododecine (IX) in 95% ethanol solution exhibited four main bands in the near ultraviolet region (Spectrum 4)*. The absorption data are summarised in Table 3 and are in good agreement with those obtained by Bindra and Elix,[5] and Bergmann et al.[4] (Table 4).

Table No. 4. Ultra-violet absorption spectrum of tetrabenzo-[b,d,h,j][1,6]diazacyclododecine.

λ_{max},nm	log ε_{max}	λ_{max},nm	log ε_{max}	Solvent	Reference
235	4.62	300	3.94	90% ethanol	5
		310	3.78	chloroform	4

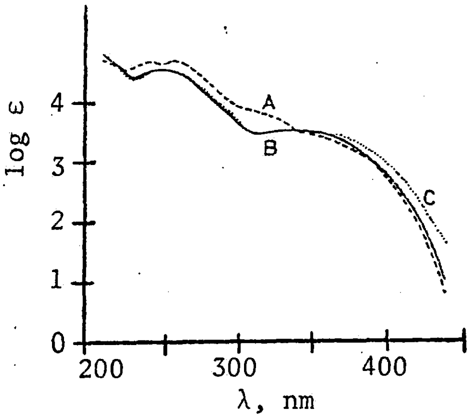
The longest wavelength band appeared as a structureless shoulder at ca. λ_{sh} 300 nm (ε_{sh} 6,440) and occurred at slightly longer wavelength than the corresponding band of the *trans*-stilbene (λ_{max} 296 nm, ε_{max} 29,000) and with considerably reduced intensity. On the other hand, this band occurred at shorter wavelength than the corresponding band of benzylideneaniline (λ_{sh} 310 nm, ε_{sh} 8,530) and with slightly lower intensity.

The marked difference in the intensity of this band in compound (IX) and in stilbene and the similarity in intensity in comparison with benzylideneaniline reflect the fact that π-conjugation is interrupted at the nitrogen atom and the unshared pair of electrons on the nitrogen atom can conjugate with the N-aryl ring. Such results are in favour of the non-coplanar molecular structure of tetrabenzo[b,d,h,j][1,6]diazacyclododecine and indicate that the N-aryl ring is nearly perpendicular to the benzal part (Ar-CH-) of the molecule; i.e. the two aromatic rings are weakly interacting with each other across -CH=N- linkage. This is

* Spectra 4, 6 - 9, 11, 13 and 14 are on pages 92 - 99.

in good agreement with Bindra and Elix[5] who confirmed that there is no extended conjugated system in (IX), and therefore, concluded that this cyclic twelve-membered ring is not planar.

The vestigial band corresponding to the inflection at λ_{inf} 249 nm (ε_{inf} 36,300) is probably due to a transition involving the benzal part of molecule (IX). The high intensity of this inflection must be due in part to overlapping by the longwave side of the biphenyl conjugation band, presumably occurring at λ_{max} 234 nm (ε_{max} 39,400) and the high intensity of the latter must be due in part to overlapping by the short-wave side of the band due to transition involving the benzal part of molecule (IX), and in part to the band at λ_{max} 235 nm (ε_{max} 9,071)[in benzylideneaniline] which is due to electronic transition involving the N-aryl ring of molecule (IX) and is hidden under the more intense transitions as shown in Spectrum 4. Intensities of transitions throughout are expected to be approximately twice as high as those of benzylideneaniline since two such chromophores are present in the molecule. In comparison with the locations of the suggested two bands at λ_{inf} 249 and λ_{max} 234 nm, Insole[109] has reported the ultra-violet absorption spectra of some unsaturated heterocyclic eight-membered-ring bridged biphenyls (Spectrum 5) and suggested that the broadness of the biphenyl conjugation band at λ_{max} 254.5 nm of (curve B) is due to the Ar-N=CH-Ar chromophore which is absorbing in this region as well.



Spectrum No.5. Ultra-violet absorption spectra of; (A) (S)-(+)-6,7-Diphenyldibenzo[e,g][1,4]-diazocine-3,10-dicarboxylic acid, (B) (S)-(+)-1,12-Dimethyl-6,7-diphenyldibenzo[e,g][1,4]-diazocine, and (C) 6,7-Diphenyldibenzo-[e,g][1,4]diazocine.

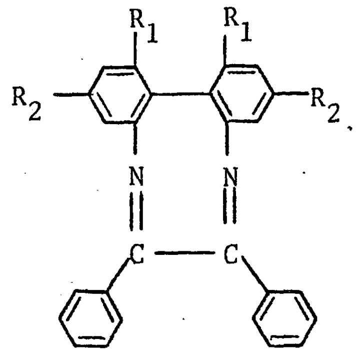
The absorption intensities of the bands obtained by Insole[109] (Table 5) are in good agreement with the intensities obtained in the present work. The suggested biphenyl conjugation band of (IX) at λ_{max} 234 nm has undergone hypsochromic displacement, 18 nm, in comparison with the band at λ_{max} 252 nm of 6,7-diphenyldibenzo[e,g]-[1,4]diazocine (curve C). This is due probably to the increase in the size of the bridging ring and to the flexibility of the cyclic 12-membered-ring of compound (IX).

The intense band at λ_{max} 203 nm (ε_{max} 56,400) may in part be due to the overtone transition corresponding to one benzene ring.[110]

The introduction of two carboxyl groups into the 4,5-positions of the parent compound (IX), produced a hypsochromic shift of 7 nm in the biphenyl conjugation band (Spectrum 6, Table 3). This suggests that the two carboxyl groups cannot be accommodated with ease into the 4,5-positions of the parent compound without producing some molecular distortion. Nevertheless, considerable biphenyl conjugation still persisted in spite of the large angle of twist. The high intensity of the shifted biphenyl conjugation band λ_{max} 227 nm (ε_{max} 49,700) must be due in part to overlapping by the long-wave side of the short-wave band at λ_{max} 205 nm, by the short-wave side of the vestigial band at λ_{inf} 253 nm, and to the hidden band at λ_{max} 235 nm (ε_{max} 9,071). It is therefore clear that the suggested biphenyl conjugation band at λ_{max} 234 nm in the parent compound (IX) does exist.

The introduction of two methoxyl groups into the 3,6-positions of the parent compound (IX), exerted almost no distinct effect on the positions of the biphenyl conjugation band λ_{max} 235 nm and the short-wave band at λ_{max} 203 nm (Spectrum 7, Table 3).

Table No. 5. Ultra-violet absorption spectra of:



Substituent									
R_1	R_2	λ_{max},nm	log ε_{max}	λ_{max},nm	log ε_{max}	λ_{max},nm	log ε_{max}	λ_{max},nm	log ε_{max}
H	CO_2H	244	4.68	259	4.70	(308)	3.92	(354)	3.49
CH_3	H	254.5	4.54	-	-	-	-	338	3.58
H	H	252	4.54	-	-	-	-	340	3.59
H	CO_2CH_3	244.5	4.68	259	4.71	(308)	3.92	(354)	3.49

Solvent, dioxan; values in parentheses denote inflections.

The long wavelength bands, λ_{max} 300 nm (ε_{max} 10,800) and λ_{max} 300 nm (ε_{max} 9,890), of the above two derivatives, respectively, have shown better resolved features with comparable intensity in comparison to the long wavelength band, λ_{inf} 300 nm (ε_{inf} 6,440), of the parent compound (IX). This probably indicates that this band is sensitive to substitution and supports the assignment to electronic transitions involving the N-aryl ring in the two compounds.

While the introduction of two carboxyl groups into the 2,7-positions of the parent compound (IX), a bathochromic shift of 19 nm in the biphenyl conjugation band is produced (Spectrum 8, Table 3). This is probably due to the resonance between the carboxyl group and the biphenyl nucleus. The long wavelength band λ_{inf} 290 nm (ε_{inf} 16,700) has suffered a hypsochromic shift of 10 nm and an increase in intensity in comparison to the parent molecule (IX) [(λ_{inf} 300 nm, ε_{inf} 6,440)]. The broadness of the band at λ_{max} 253 nm suggests that the benzal chromophore is also absorbing in this region.

There is a slight bathochromic shift in the spectra of the three substituted compounds in comparison to the parent molecule (IX) for the band at λ_{inf} 249 nm which is probably due to transitions involving the benzal part of the molecule.

From the above discussion, one may conclude that substituent effects on the ultra-violet spectra reveal an effect on the biphenyl conjugation band and show a comparable high intensity in the long-wave bands, probably corresponding to electronic transitions involving the N-aryl ring of the molecule. Such results are in favour of the non-coplanar structure of the compound (IX), including its derivatives, and indicate that the N-aryl ring is nearly perpendicular to the Ar-CH=N- plane.

^{1}H n.m.r. studies of these four compounds at room temperature, showed a singlet band for the two azomethine protons, therefore excluding the probability of their having the _syn_-_anti_-configuration. Since _syn_-benzylideneaniline has not been detected at room temperature, it is concluded that tetrabenzo[_b_,_d_,_h_,_j_][1,6]diazacyclododecine (IX) and its derivatives must have the _anti_-_anti_-configuration, in accordance with the above interpretation of the ultra-violet spectra.

With the 9,10,19,20-tetrahydro-derivative of (IX), Dreiding molecular models have shown that this compound and its derivatives possess a heterocyclic twelve-membered-ring of high flexibility. The interplanar angle between the two benzene rings along the 1,1'-bond cannot be accurately estimated from models, since these compounds must have more than one conformation corresponding to the minimum valence-angle strain. There are four configurational possibilities that these compounds might have according to the sense of twist of the biphenyl units.

1 - $(R)_N$ - $(R)_C$ - configuration, Figure 14 2 - $(S)_N$ - $(S)_C$ - configuration.	} enantiomers
3 - $(R)_N$ - $(S)_C$ - configuration, Figure 15 4 - $(S)_N$ - $(R)_C$ - configuration.	} enantiomers

where $(R)_N$, $(S)_N$ are the senses of twist of the biphenyl unit attached to the nitrogen atoms, and $(R)_C$, $(S)_C$ are the senses of twist of the biphenyl unit attached to the carbon atoms.

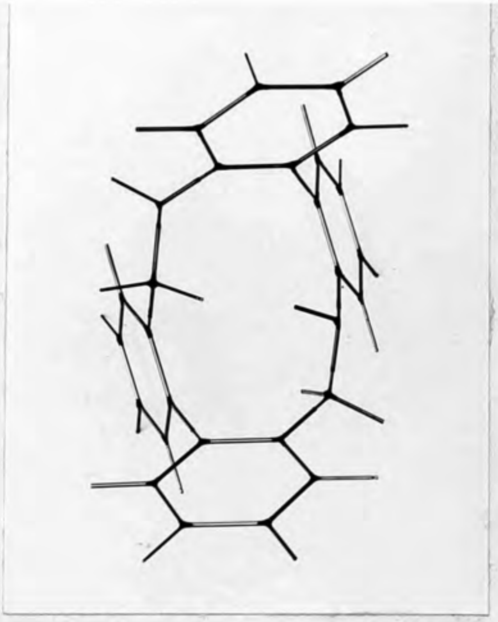


Figure No.14

(R)-configuration of (X) at both biphenyl units with highly flexible bridging ring.

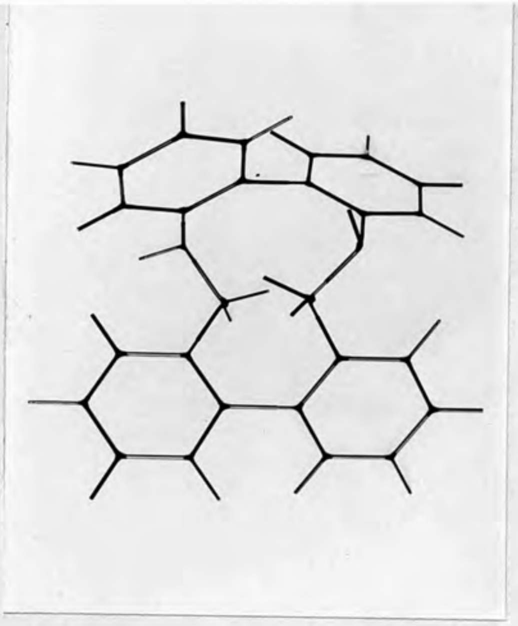


Figure No.15

(R)- and (S)-configurations of (X) at the amine and aldehyde biphenyl units, respectively, with highly flexible bridging ring.

The ultra-violet absorption spectrum of 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine (X) (Spectrum 9) showed a slight hypsochromic shift of the biphenyl conjugation band (λ_{inf} 230 nm, ε_{inf} 32,500) in comparison with λ_{max} 234 nm for (IX), probably due to the reduced conjugation between the two benzene rings across the 1,1'-bond. Comparing the intensity of this band with that of the biphenyl molecule (ε_{max} 17,000), its high intensity is presumably owing in part to overlapping by the long-wave side of the inflection at λ_{inf} 210 nm, and in part by the short-wave side of the vestigial band at λ_{inf} 245 nm (ε_{inf} 28,100) which is probably the intramolecular charge transfer band of the transition accompanied by a partial electron transfer from the amino group to the benzene ring of the Ph-$\ddot{N}$H-CH$_2$-group. The ultra-violet absorption spectrum of N-methylaniline (Spectrum 10) and its absorption data (Table 6) are given for comparison.

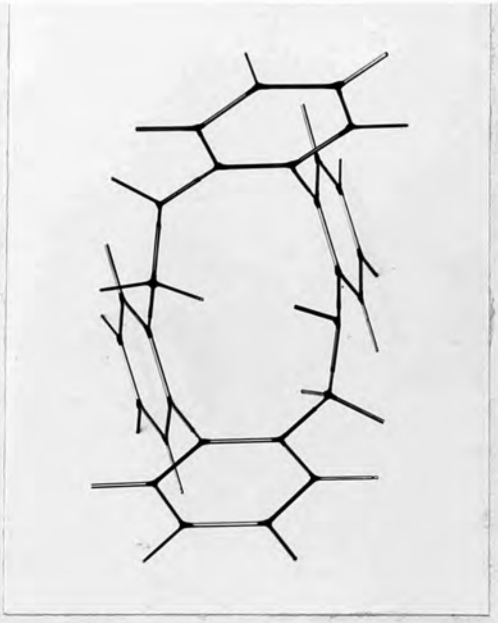


Figure No.14

(R)-configuration of (X) at both biphenyl units with highly flexible bridging ring.

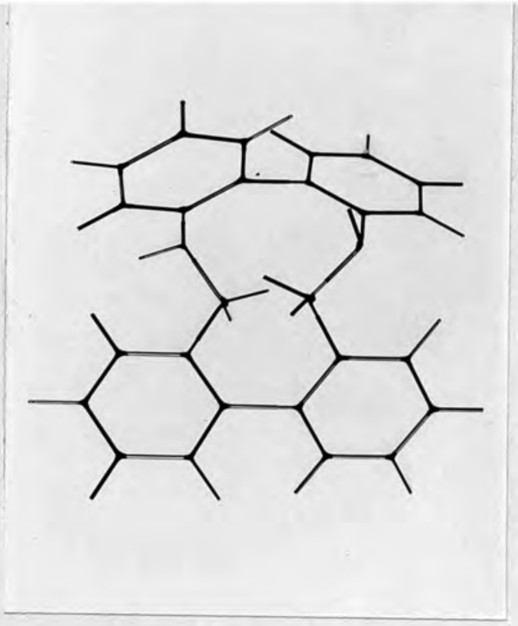
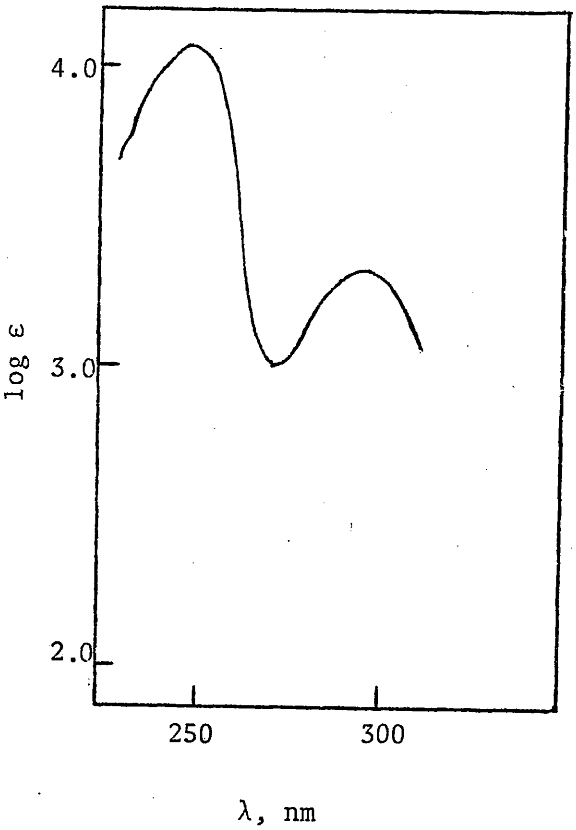


Figure No.15

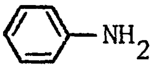
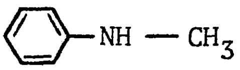
(R)- and (S)-configurations of (X) at the amine and aldehyde biphenyl units, respectively, with highly flexible bridging ring.

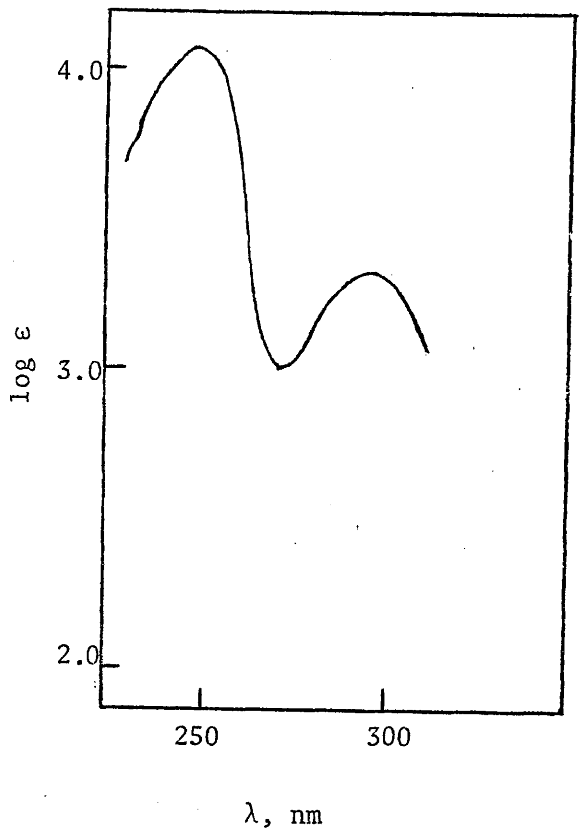
The ultra-violet absorption spectrum of 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine (X) (Spectrum 9) showed a slight hypsochromic shift of the biphenyl conjugation band (λ_{inf} 230 nm, ε_{inf} 32,500) in comparison with λ_{max} 234 nm for (IX), probably due to the reduced conjugation between the two benzene rings across the 1,1'-bond. Comparing the intensity of this band with that of the biphenyl molecule (ε_{max} 17,000), its high intensity is presumably owing in part to overlapping by the long-wave side of the inflection at λ_{inf} 210 nm, and in part by the short-wave side of the vestigial band at λ_{inf} 245 nm (ε_{inf} 28,100) which is probably the intramolecular charge transfer band of the transition accompanied by a partial electron transfer from the amino group to the benzene ring of the Ph-$\ddot{N}$H-CH$_2$-group. The ultra-violet absorption spectrum of N-methylaniline (Spectrum 10) and its absorption data (Table 6) are given for comparison.



Spectrum No.10. Ultra-violet absorption spectrum of N-methylaniline in 95% ethanol.[111]

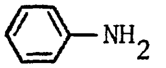
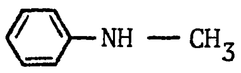
Table No.6. Ultra-violet absorption data of aniline and N-methylaniline

Compound	The α band		The CT band		Solvent	Ref.
	λ_{max},nm	log ε_{max}	λ_{max},nm	log ε_{max}		
	284.5	3.24	234	4.06	Ethanol	112
			243	ε_{max} 13,200	Isooctane	112,113
	294	ε_{max} 1,500			Ethanol	114



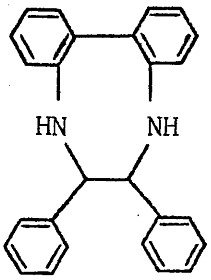
Spectrum No.10. Ultra-violet absorption spectrum of N-methylaniline in 95% ethanol.[111]

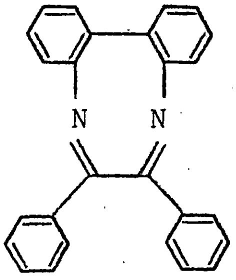
Table No.6. Ultra-violet absorption data of aniline and N-methylaniline

Compound	The α band		The CT band		Solvent	Ref.
	λ_{max},nm	log ε_{max}	λ_{max},nm	log ε_{max}		
	284.5	3.24	234	4.06	Ethanol	112
			243	ε_{max} 13,200	Isooctane	112,113
	294	ε_{max} 1,500			Ethanol	114

The longest wavelength band λ_{inf} 290 nm (ε_{inf} 7,830) appears as a shoulder and is probably the perturbed locally excited transition band corresponding to the benzene α-band. The high intensity of this shoulder in comparison to that of N-methylaniline λ_{max} 294 nm (ε_{max} 1,500) may be due in part to a small absorption contribution from the $-H_2C-C_6H_4-C_6H_4-CH_2-$ part of the molecule. For example, 2,2'-dimethylbiphenyl has absorption maxima of λ_{max} 270.8 nm (ε_{max} 600) and λ_{max} 263.5 nm (ε_{max} 800).[115] Also the shoulder at λ_{inf} 290 nm has suffered a hypsochromic shift of 10 nm in comparison to that of (IX) λ_{inf} 300 nm. This is in good agreement with the hypsochromic shift, 15 nm, of the longest wavelength band λ_{max} 323 nm (ε_{max} 2,500) of (LX) in comparison with that of (LXI) λ_{max} 338 nm (ε_{max} 2,950).[116]

(LX)

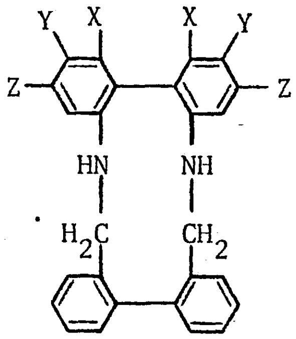




(LXI)

The short wavelength band λ_{max} 203 nm has an extra inflection at λ_{inf} 210 nm. These bands may in part be due to the overtone transition corresponding to one benzene ring. The absorption data summarized in Table 7 are partly in agreement with that obtained by Bindra and Elix[5] (Table 8).

Table No.7. Room temperature ultra-violet absorption spectra of:



Compound	Substituent												
	X	Y	Z	λ_{max},nm	ε_{max}	λ_{max},nm	ε_{max}	λ_{max},nm	ε_{max}	λ_{max},nm	ε_{max}	λ_{max},nm	ε_{max}
X	H	H	H	203	70,200	(210)	63,800	(230)	32,500	(245)	28,100	(290)	7,830
Xa	CO_2CH_3	H	H	200	63,500	(205)	59,300	-	-	(250)	18,400	334	4,890
Xb	H	OCH_3	H	204	76,100	(209)	70,400	(230)	35,300	(273) (245)	8,770 28,100	308	8,010
Xc	H	H	CO_2CH_3	203	63,600	(207)	60,400	241	50,250	(280)	12,600	340	7,610

Solvent, 95% ethanol; values in parentheses denote inflections.

Table No.8. Ultra-violet absorption spectrum of 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]-diazacyclododecine in 90% ethanol.

λ_{max},nm	log ε_{max}	λ_{max},nm	log ε_{max}	λ_{max},nm	log ε_{max}	Reference
217	4.64	230	4.54	(290)	4.00	5

Values in parentheses denote inflections.

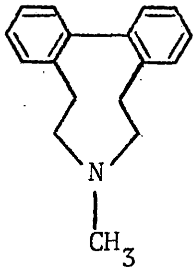
With the introduction of two carboxyl groups into the 4,5-positions of the parent compound (X), the ultra-violet absorption spectrum (Spectrum 11) shows a perceptible hypsochromic shift of the biphenyl conjugation band, so that it is no longer separated from the shortwave band by a minimum. The molecule is relatively free to increase the angle of twist between the two benzene rings across the 1,1'-bond in order to accommodate the substituents. Accordingly, the large bathochromic shift, 44 nm, of the long wavelength band λ_{max} 334 nm is a pertinent allowance for the electronic bathochromic effect of the two carboxyl groups attached at the 4,5-positions of the molecule.

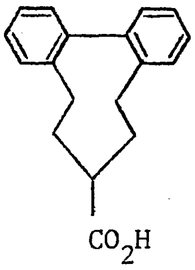
The vestigial band at λ_{inf} 250 nm (ε_{inf} 18,400) is probably the intramolecular charge transfer band corresponding to that at λ_{inf} 245 nm (ε_{inf} 28,100) in Spectrum 9. The slightly high intensity of this band is probably due in part to overlapping by the vestigial long-wave side of the conjugation band.

The inflection at λ_{inf} 273 nm (ε_{inf} 8,770) is believed to correspond to the hidden biphenyl band referred to as the H band,[112] and this revelation is probably due to the marked hypsochromic shift and reduction in intensity of the biphenyl conjugation band caused by larger deviation from planarity of the conformation of the conjugated biphenyl systems in (Xa) as compared with (X).

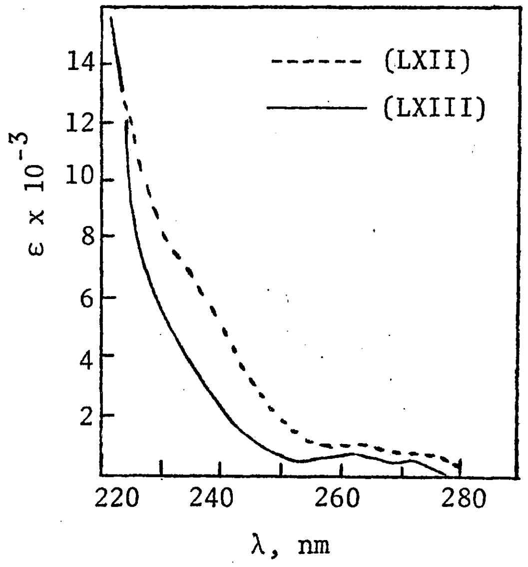
This H band at λ_{inf} 273 nm can be compared with the two inflections at λ_{inf} 266 nm (ε_{inf} 1,004) and λ_{inf} 274 nm (ε_{inf} 716) of (LXII),[117] and also with the two bands at λ_{max} 265 nm (ε_{max} 800) and λ_{max} 273 nm (ε_{max} 600) of (LXIII)[15] (Spectrum 12). The high intensity of the H band (ε_{inf} 8,770) must be due in part to overlapping by the long-wave side of the vestigial band at λ_{inf} 250 nm.

(LXII)





(LXIII)



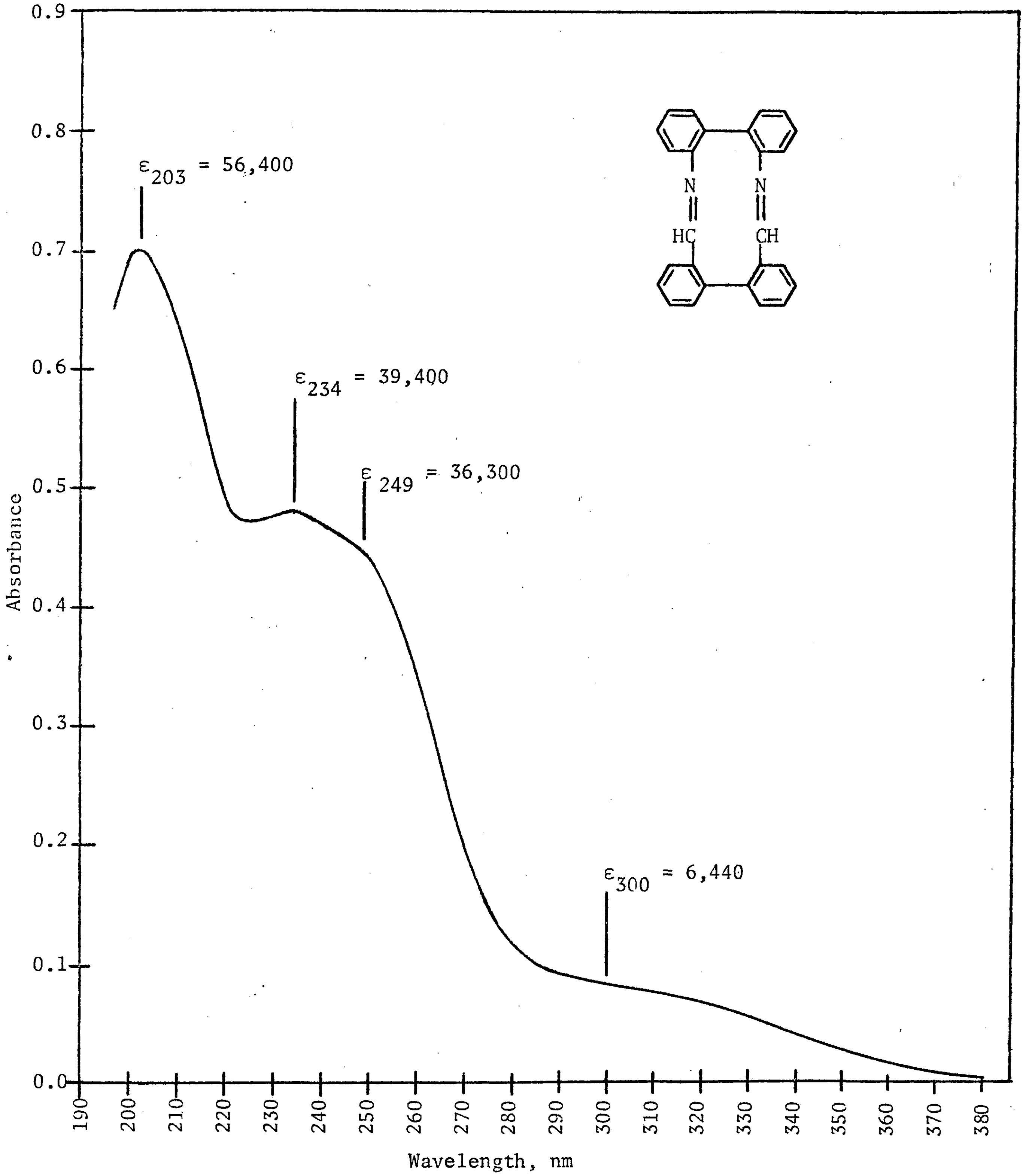
Spectrum No.12. Ultra-violet absorption spectrum of 1-methyl-2,3,8,9-tetrahydro-4,5:6,7-dibenzazonine (LXII) and 1,2,3,4-dibenzcyclonona-1,3-diene-7-carboxylic acid (LXIII) in 96% ethanol.[117]

The short wavelength bands at λ_{max} 200 (ε_{max} 63,500) and the inflection at λ_{inf} 205 (ε_{inf} 59,300) have suffered a slight hypsochromic shift and drop in intensity in comparison to the same bands of compound (X); λ_{max} 203 (ε_{max} 70,200) and λ_{inf} 210 (ε_{inf} 63,800).

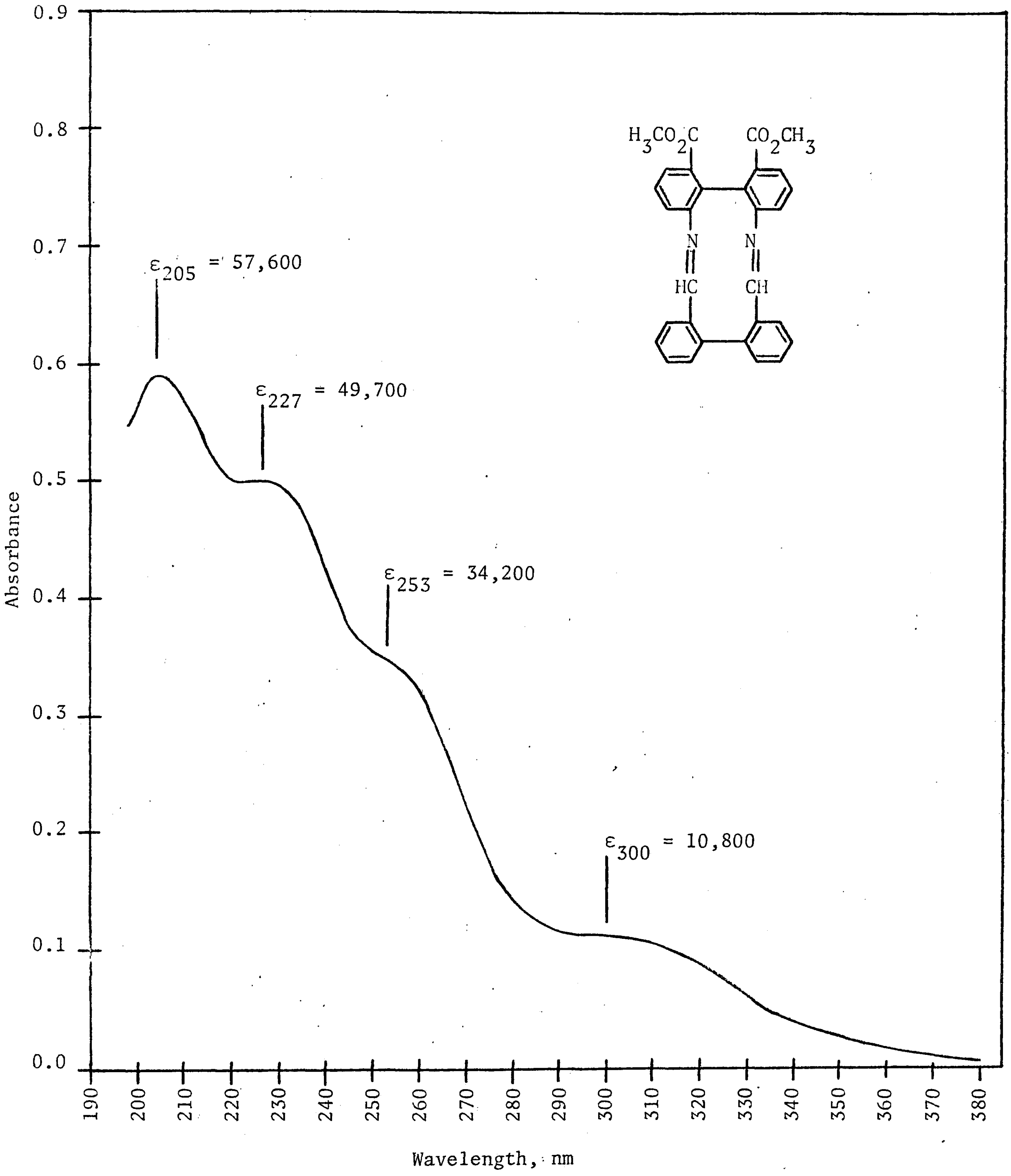
In compound (Xb), distortion of the molecule resulting from the accommodation of two methoxyl groups at 3,6-positions seems to be negligible, as the ultra-violet spectrum of (Xb) (Spectrum 13) is nearly superimposible on that of Spectrum 9 except that the long wavelength band at λ_{max} 308 nm has suffered a bathochromic shift, 18 nm, and the short wavelength bands (λ_{max} 204 and λ_{inf} 209 nm) show an increase in their intensities. The absorption data are summarized in Table 7. The biphenyl conjugation band λ_{max} 230 nm and the intramolecular charge transfer band λ_{inf} 245 nm are in the same positions as those in Spectrum 9 and have nearly similar intensities.

In compound (Xc), the biphenyl conjugation band λ_{max} 241 nm (ε_{max} 50,250) shows a bathochromic shift, 11 nm, and increased intensity in comparison to that of (X) (Spectrum 14). The intramolecular charge transfer band of the transition accompanied by a partial electron transfer from the amino group to the benzene ring of the $Ar{-}\ddot{N}H{-}CH_2{-}$group is probably hidden under the more intense the biphenyl conjugation band. The inflection at λ_{inf} 280 nm (ε_{inf} 12,600) is probably the H band, and of higher intensity than the inflection at λ_{inf} 273 nm (ε_{inf} 8,770) of compound (Xa), due in part to overlapping by the long-wave side of the biphenyl conjugation band. The absorption data are summarized in Table 7.

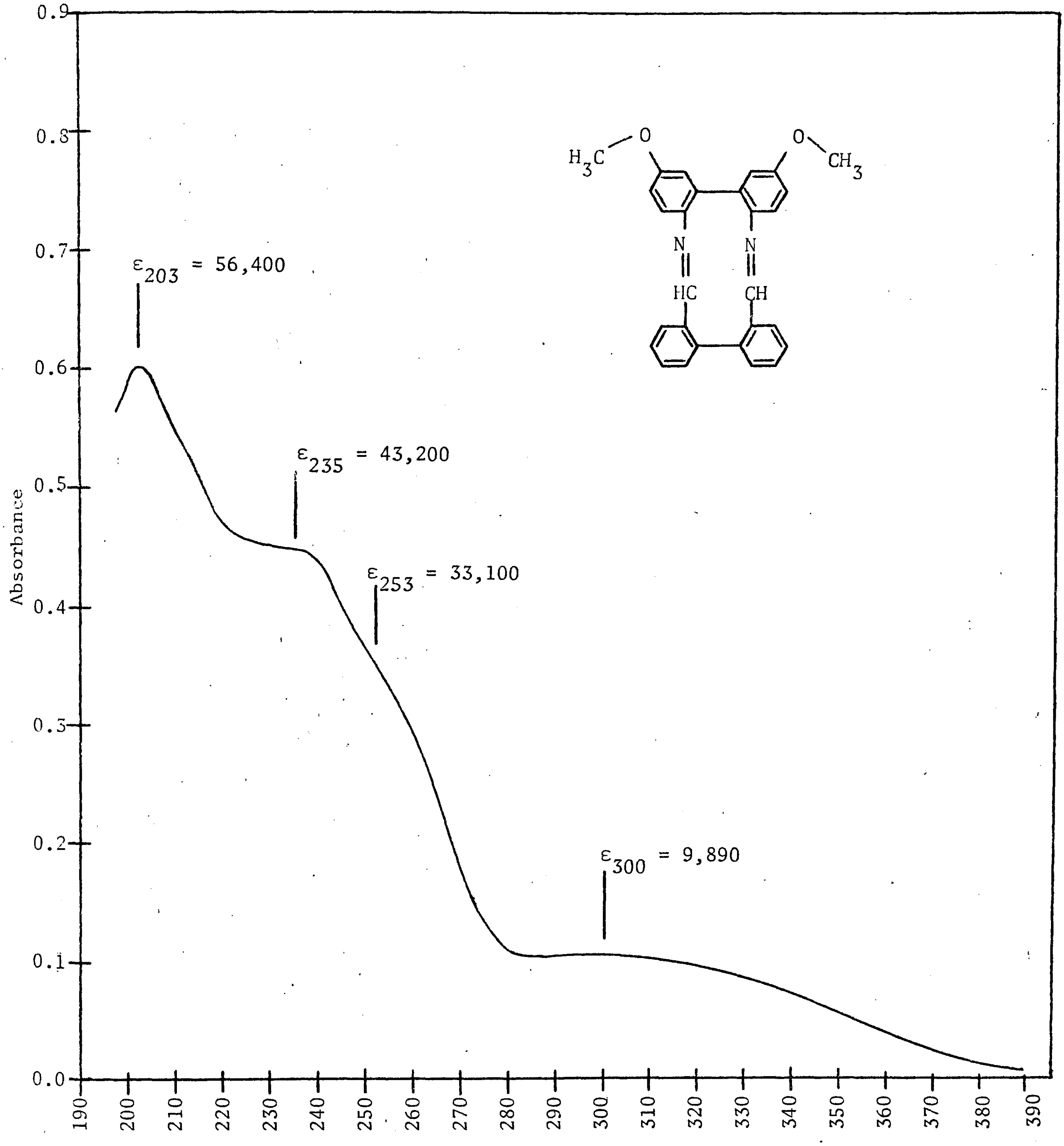
The long wavelength band λ_{max} 340 nm (ε_{max} 7,610) shows a large bathochromic shift, 50 nm, and a broad well resolved band of nearly the same intensity as that in Spectrum 9 (ε_{max} 7,830), while the short wavelength bands (λ_{max} 203, λ_{inf} 207 nm) show reduced intensity probably due in part to the bathochromic shift of the biphenyl conjugation band.



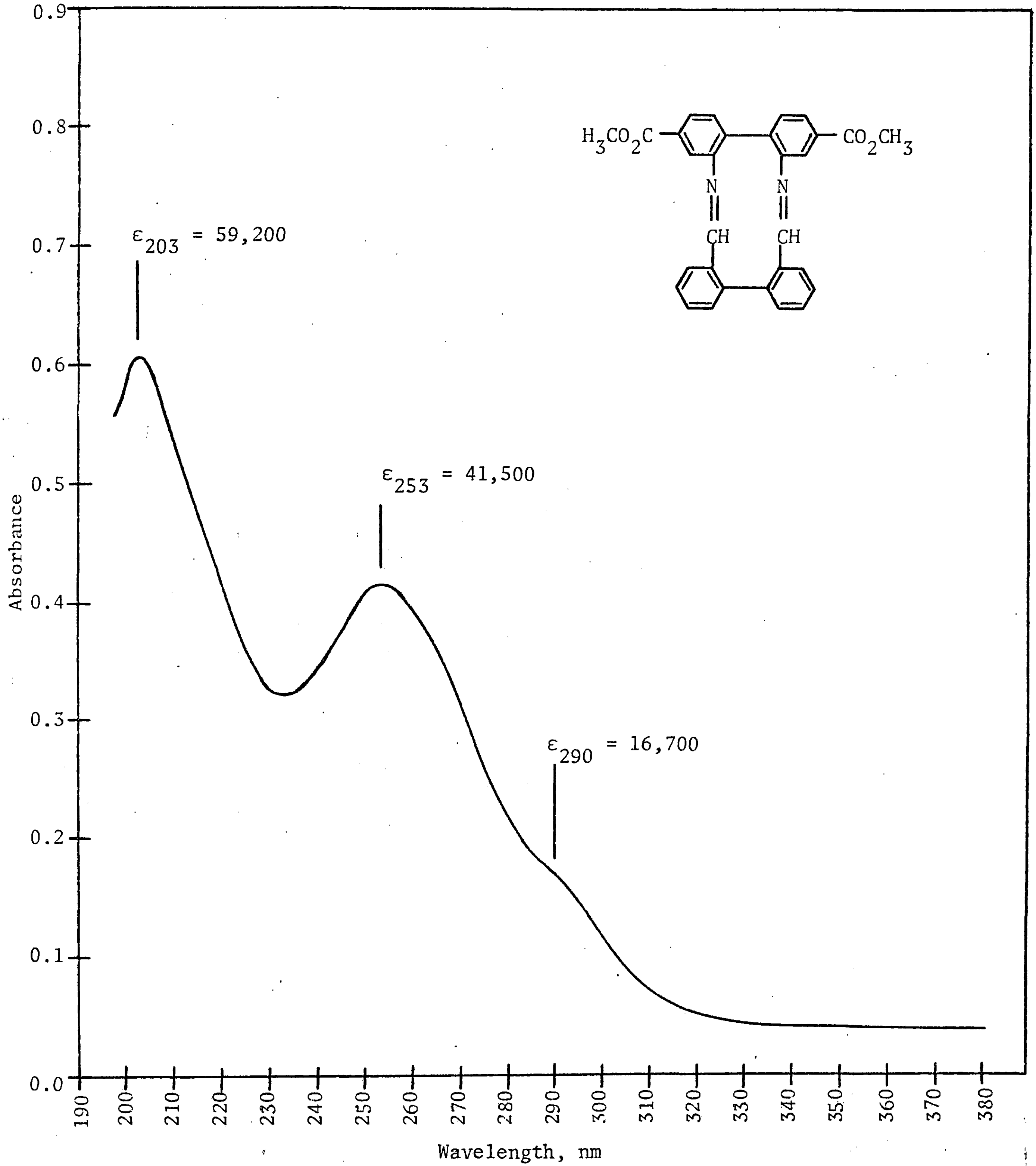
Spectrum No.4. Room-temperature ultra-violet absorption spectrum, in 95% ethanol, of tetrabenzo[b,d,h,j][1,6]diazacyclododecine (IX), 6.137 x 10^{-5} mole/litre.



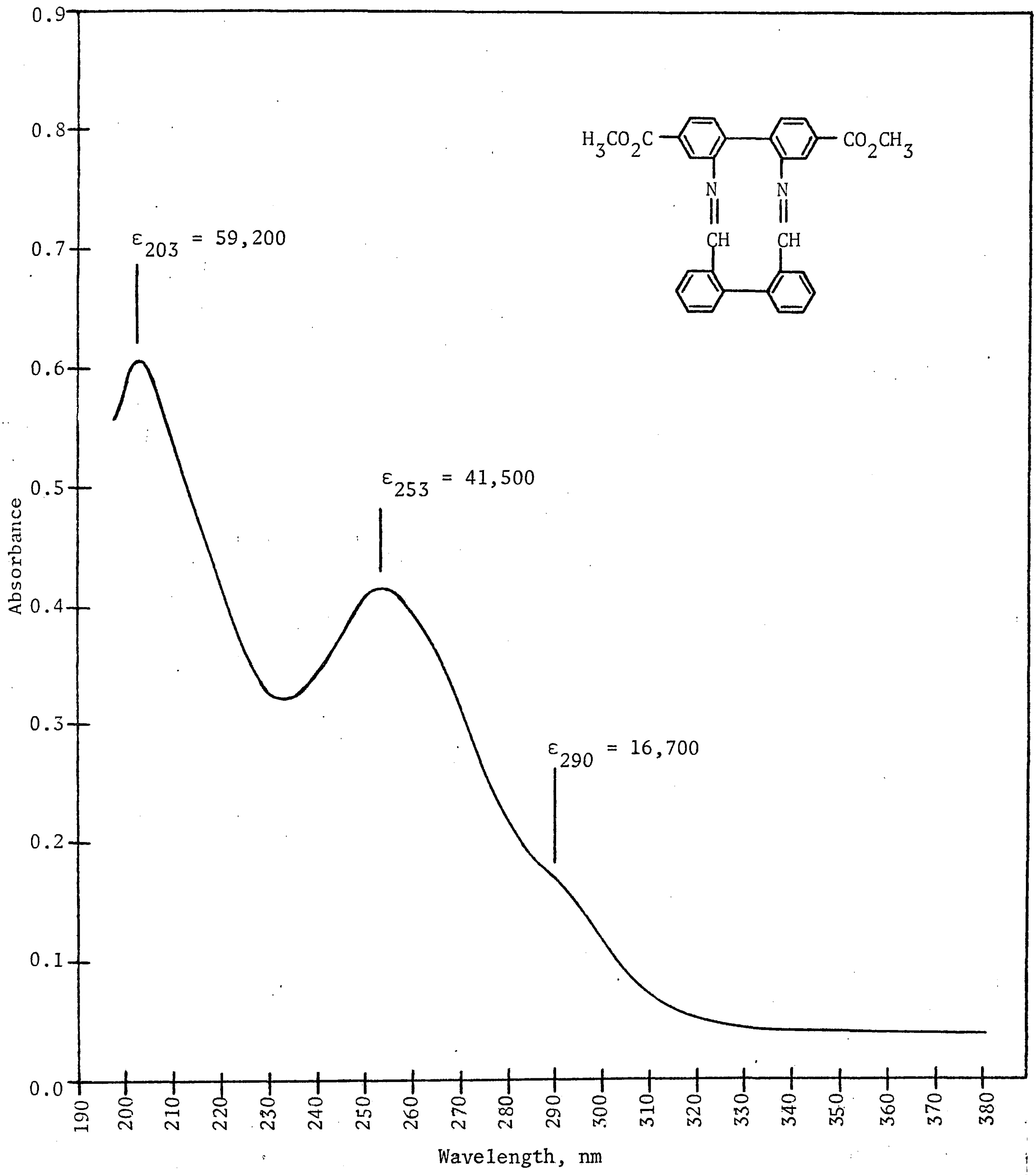
Spectrum No.6. Room-temperature ultra-violet absorption spectrum, in 95% ethanol, of dimethyl tetrabenzo[b,d,h,j][1,6]diazacyclododecine-4,5-dicarboxylate (IXa), 5.099 x 10^{-5} mole/litre.



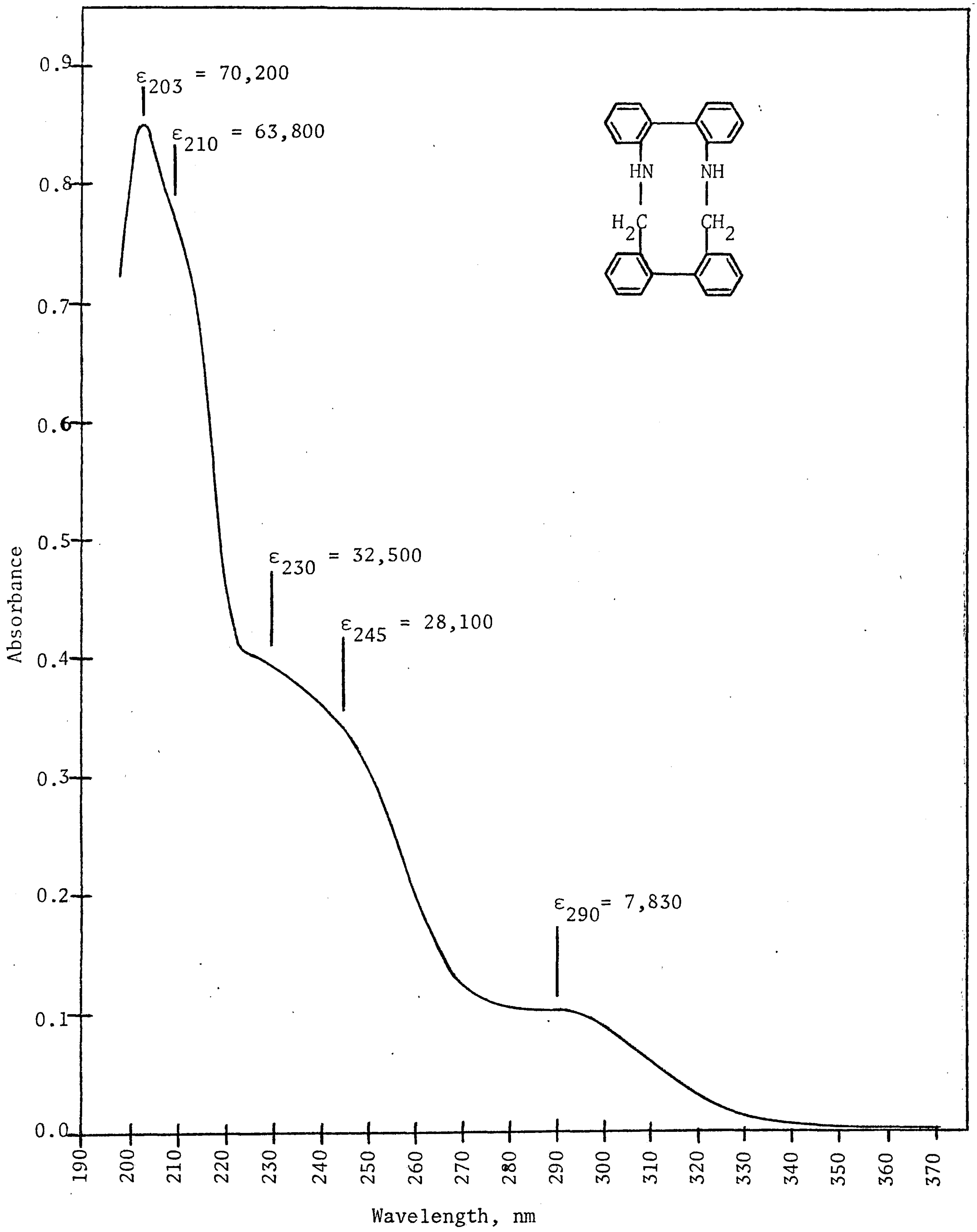
Spectrum No. 7. Room-temperature ultra-violet absorption spectrum, in 95% ethanol, of tetrabenzo[b,d,h,j][1,6]diazacyclododecine-3,6-dimethoxy (IXb), 5.257 x 10^{-5} mole/litre.



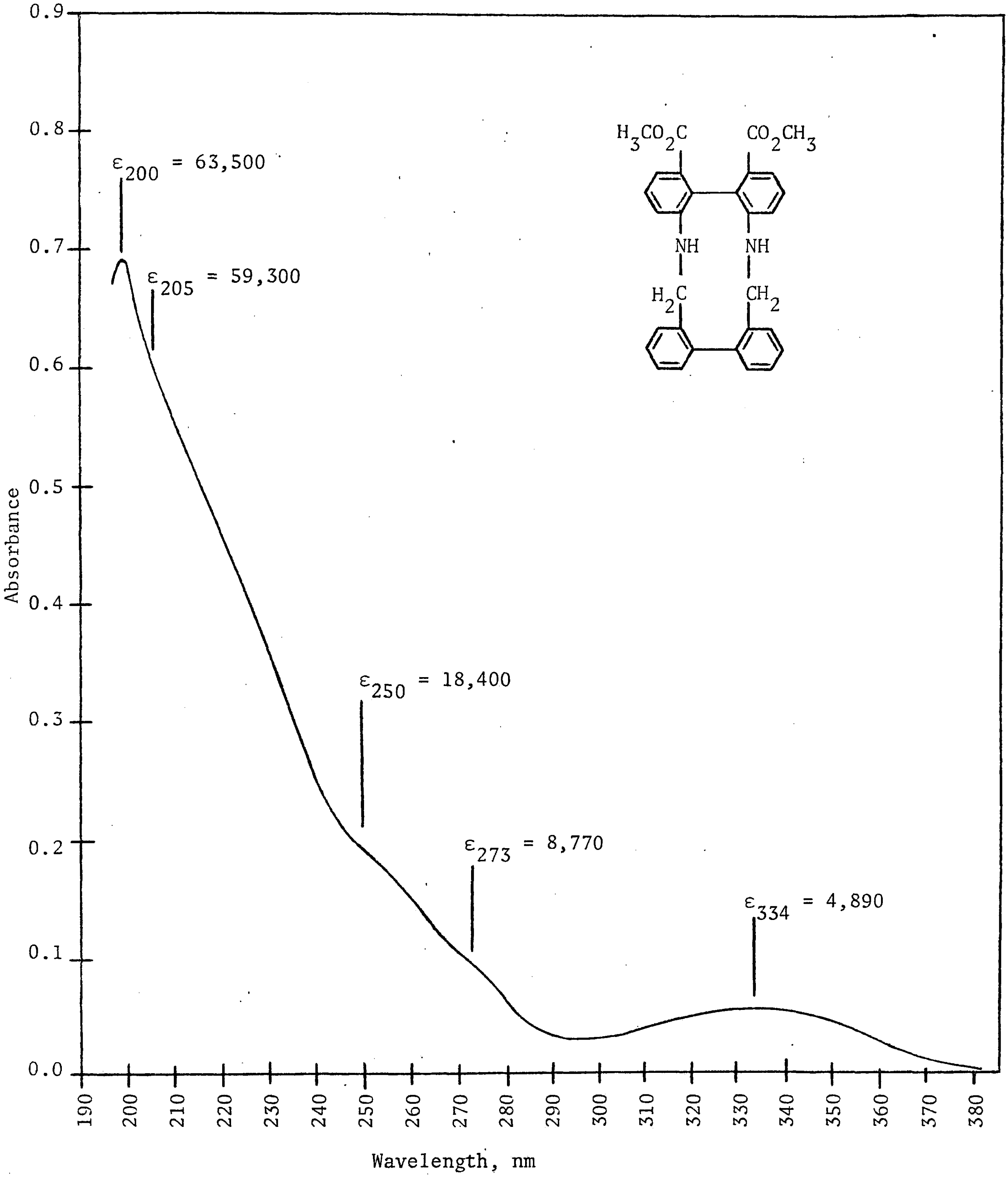
Spectrum No.8. Room-temperature ultra-violet absorption spectrum, in 95% ethanol, of dimethyl tetrabenzo[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate (IXc), 5.057×10^{-5} mole/litre.



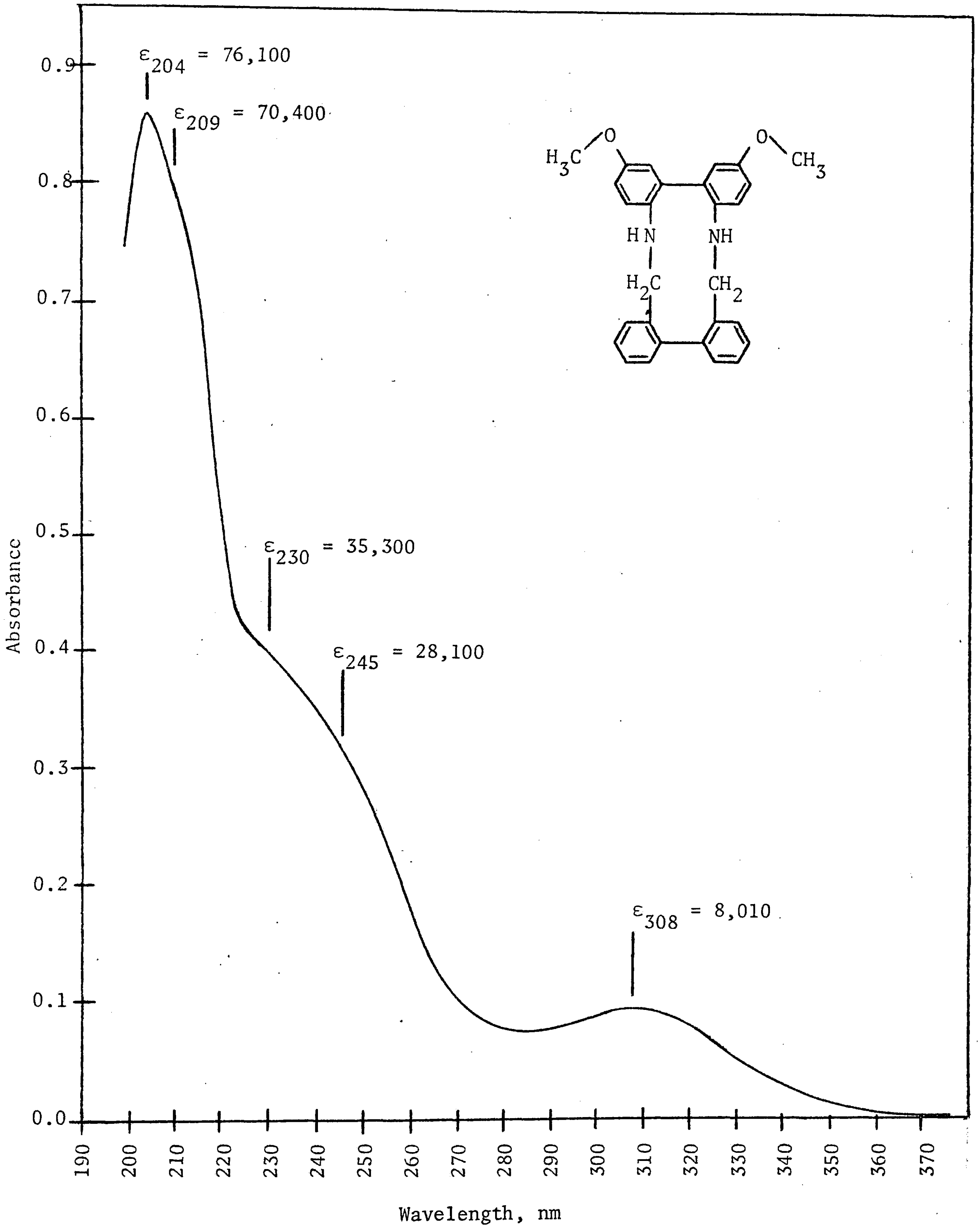
Spectrum No.8. Room-temperature ultra-violet absorption spectrum, in 95% ethanol, of dimethyl tetrabenzo[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate (IXc), 5.057 x 10^{-5} mole/litre.



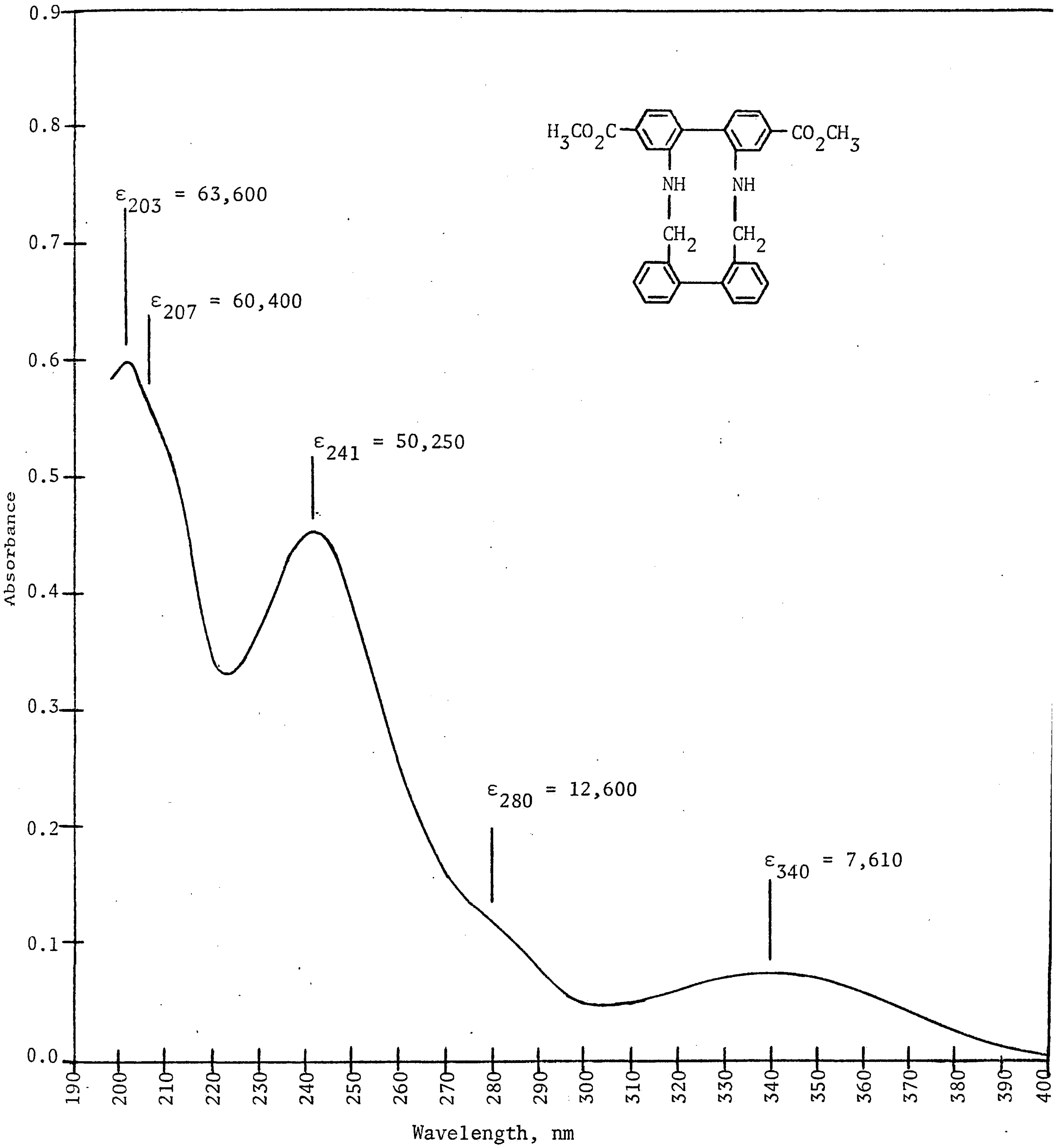
Spectrum No.9. Room-temperature ultra-violet absorption spectrum, in 95% ethanol, of 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j]-[1,6]diazacyclododecine (X), 6.069×10^{-5} mole/litre.



Spectrum No. 11. Room-temperature ultra-violet absorption spectrum, in 95% ethanol, of dimethyl 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine-4,5-dicarboxylate (Xa), 5.015 x 10^{-5} mole/litre.



Spectrum No.13. Room-temperature ultra-violet absorption spectrum, in 95% ethanol, of 3,6-dimethoxy-9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine (Xb), 5.680 x 10^{-5} mole/litre.



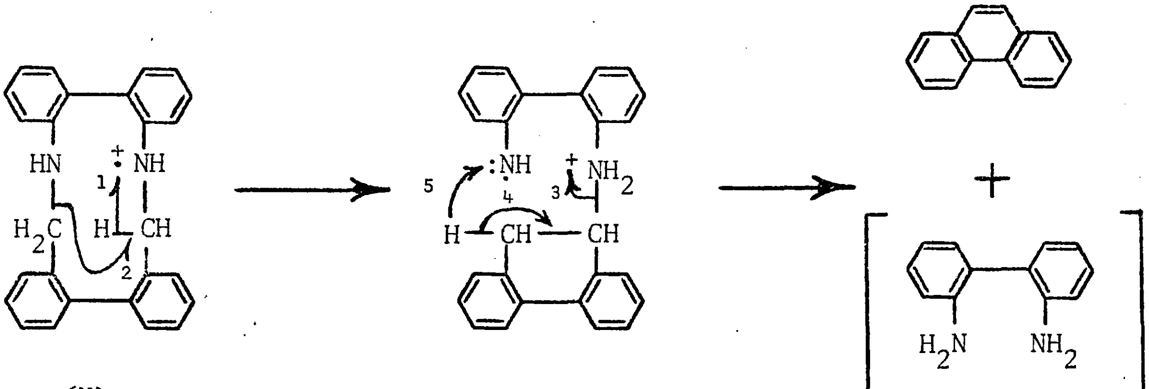
Spectrum No.14. Room-temperature ultra-violet absorption spectrum, in 95% ethanol, of dimethyl 9,10,19,20-tetrahydrotetrabenzo[b,d,j,h]-[1,6]diazacycldodecine-2,7-dicarboxylate (Xc), 4.597 x 10^{-5} mole/litre

2.3. Mass Spectra

The mass spectroscopic determination of the molecular weight of (X) had given the formula $C_{26}H_{22}N_2$ (measured mass = 362.1799; calculated mass = 362.1783) which fitted with the results obtained from elemental microanalysis (see page 217).

In the mass spectrum of this compound (Spectrum 15), the molecular ion peak appears at m/e = 362, formed by the loss of a non-bonded electron from one of the nitrogen atoms in structure (X). The peak at m/e = 363 is the characteristic isotope peak (M+1). The molecular ion is accompanied by a peak at m/e = 361 of lower intensity; its formation is due to the loss of one hydrogen atom.

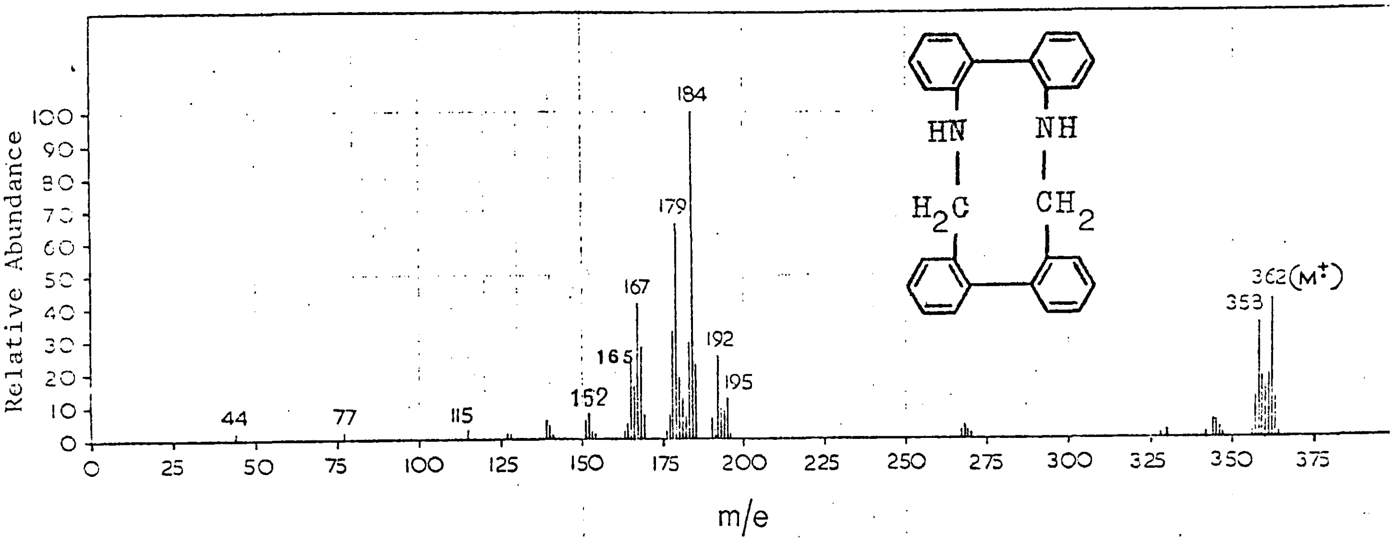
The main process in the fragmentation behaviour of this compound is elimination of phenanthrene as a neutral fragment with the formation of an odd-electron ion, the base peak, at m/e = 184. A possible scheme is depicted below:



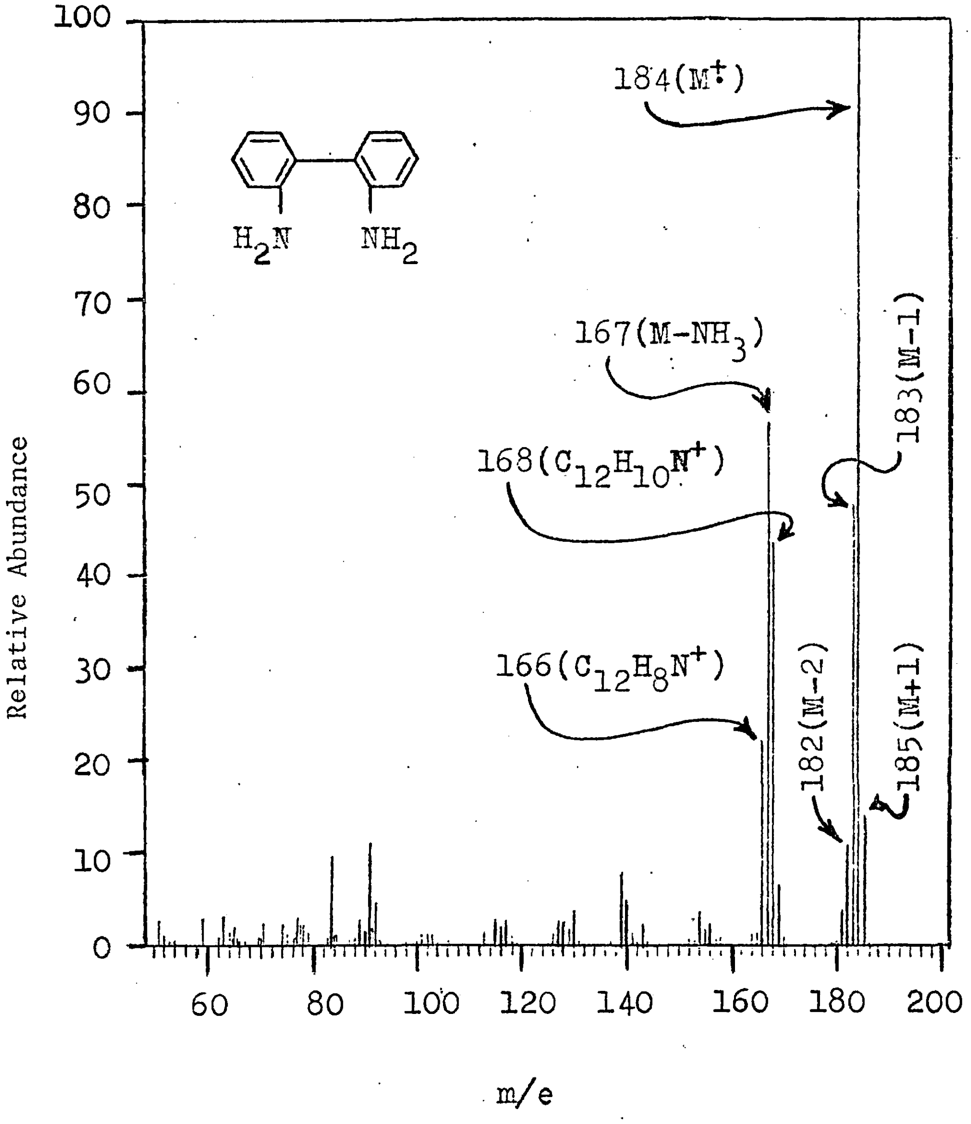
(X)

m/e = 184

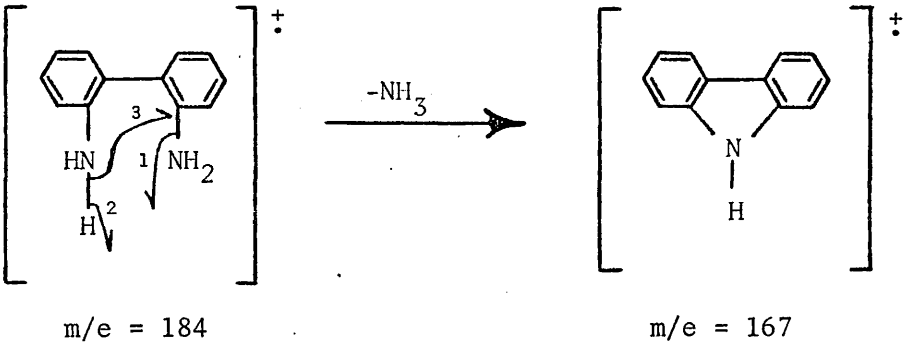
The odd-electron ion, m/e = 184, so formed decomposes further by the loss of ammonia as a stable neutral fragment to yield the carbazole ion peak at m/e = 167.



Spectrum No.15. Mass spectrum of 9,10,19,20-tetrahydrotetrabenzo-[b,d,h,j][1,6]diazacyclododecine (X).



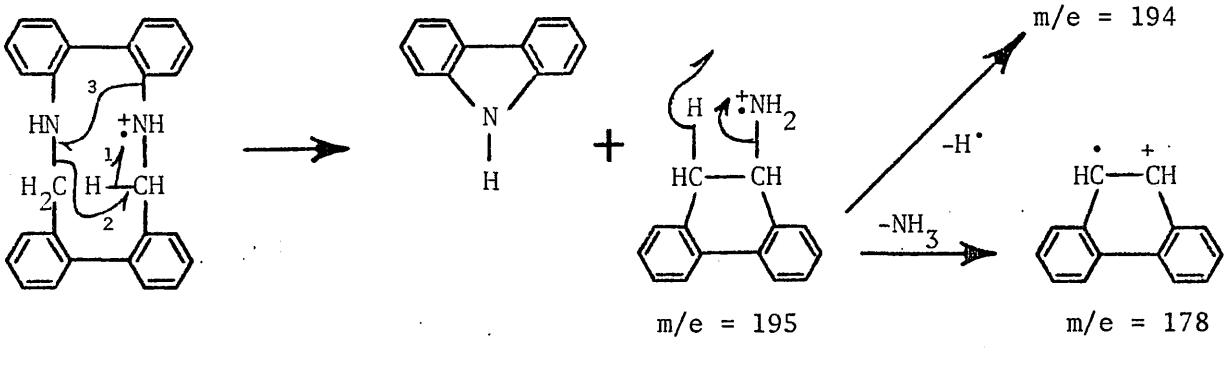
Spectrum No.16.
Mass spectrum of
2,2'-diaminobiphenyl.



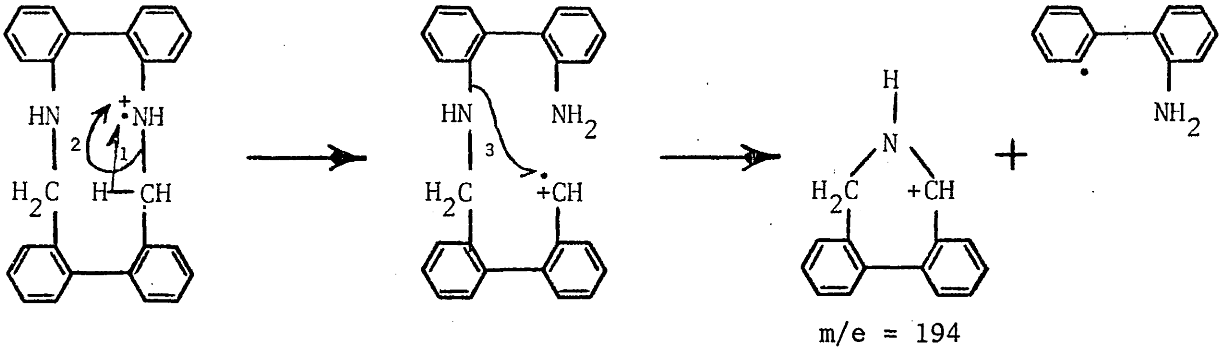
Loss of a hydrogen atom from each of the species of m/e = 184 and m/e = 167 corresponds to the ions of m/e = 183 and m/e = 166, respectively.

Spectrum 16 shows the mass spectrum of 2,2'-diaminobiphenyl.

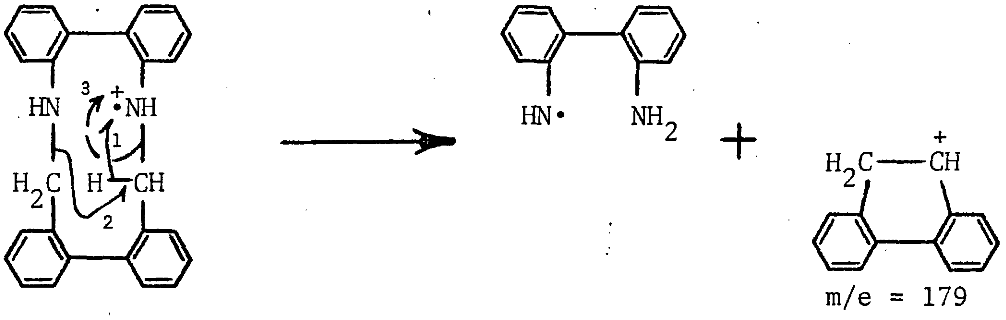
Elimination of carbazole as a neutral fragment from the molecular ion of (X) leads to the formation of an odd-electron ion of m/e = 195. Subsequent loss of ammonia may also produce the ion of m/e = 178.



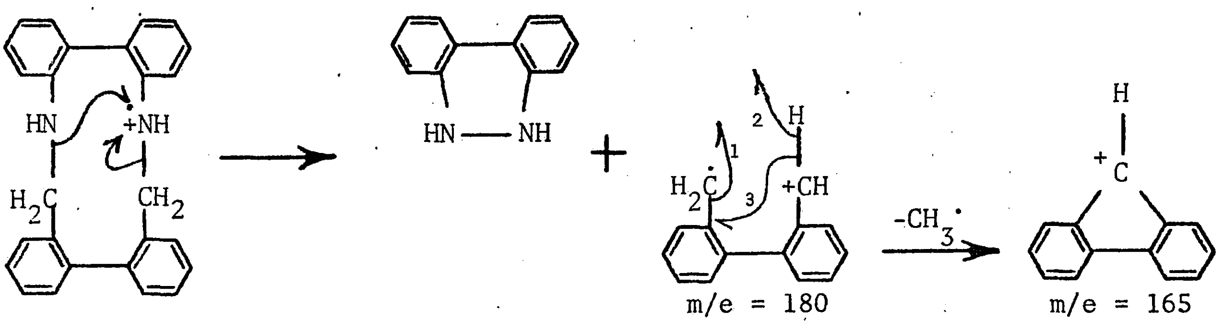
Loss of a hydrogen atom from the odd-electron ion of m/e = 195 produces an even-electron ion of m/e = 194. On the other hand, this even-electron ion of m/e = 194 could be formed by rearrangement of the molecular ion followed by loss of $C_{12}H_{10}N^{\bullet}$ radical. A possible route is as follows:



A fragment ion of m/e = 179 which occurs in the recorded mass spectrum has been assigned a structure derived from the following scheme:

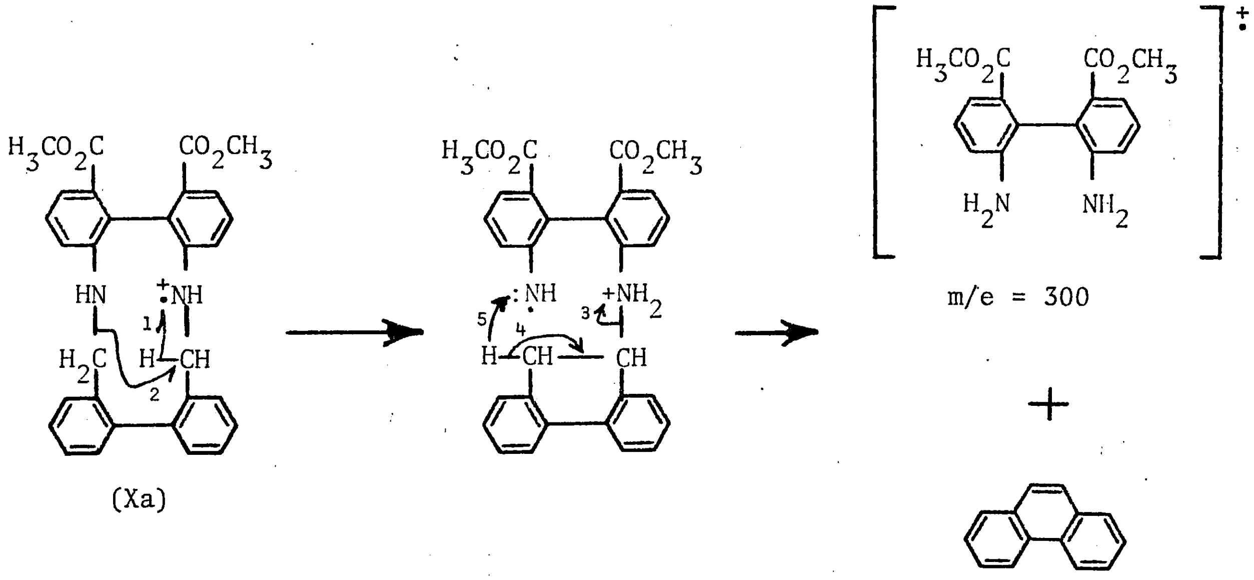


The origin of the fragment ion corresponding to the peak at m/e = 165 is probably related to the intermediate ion of m/e = 180 if a methyl radical should happen to be lost from it. A possible scheme could be as follows:



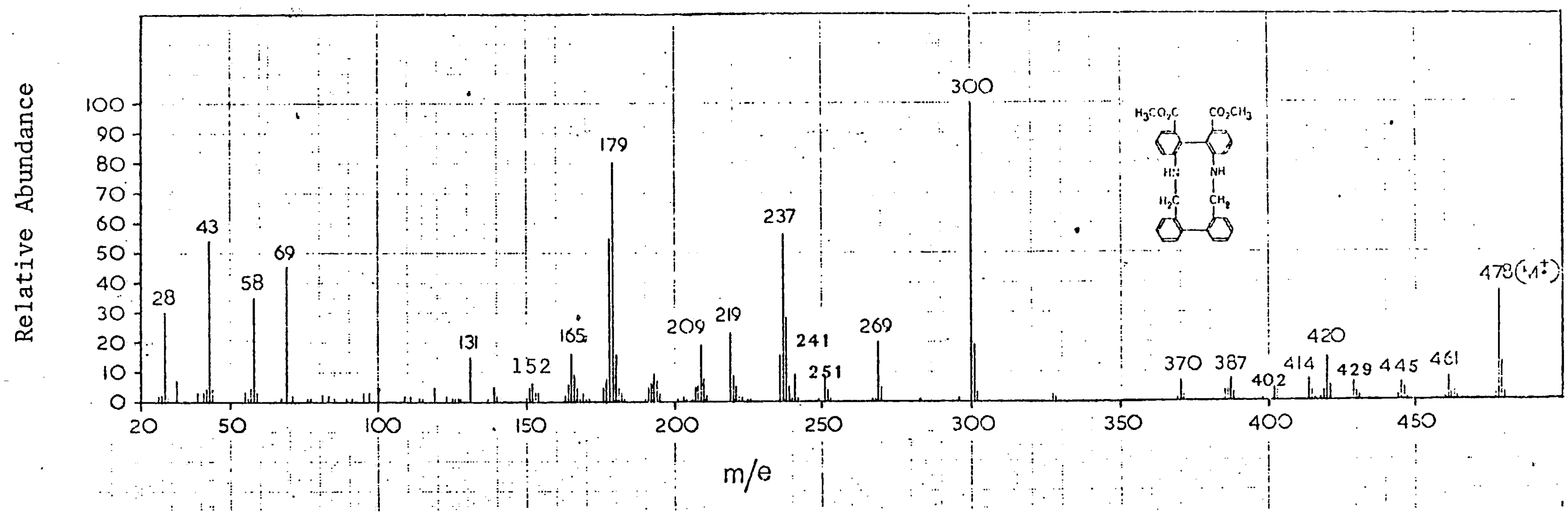
The complexity of the fragmentation processes becomes evident when one considers the fragmentation behaviour of (Xa). The mass spectroscopic determination of the molecular weight of this compound had given the formula $C_{30}H_{26}N_2O_4$ (measured mass = 478.1890; calculated mass = 478.1892).

In its mass spectrum (Spectrum 17), the molecular ion peak appears at m/e = 478. The lesser intensity peak at m/e = 477 is due to the loss of one hydrogen atom from the molecular ion. The base peak at m/e = 300 corresponds to the ejection of phenanthrene as a neutral fragment from the molecular ion.

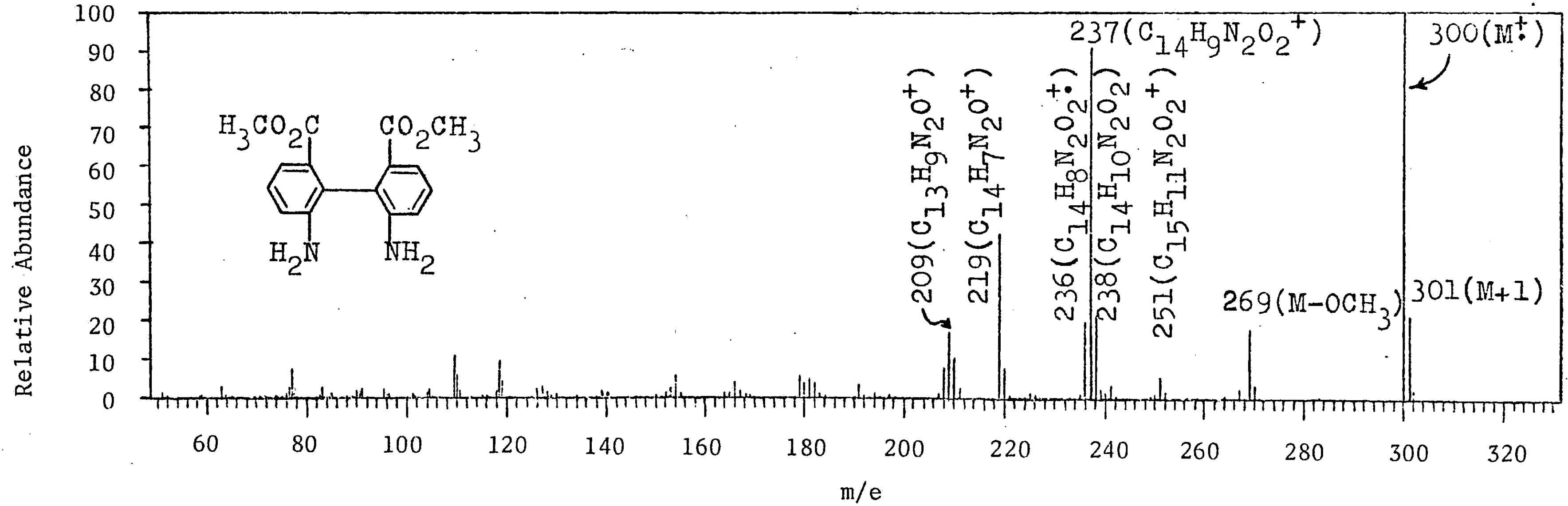


(Xa)

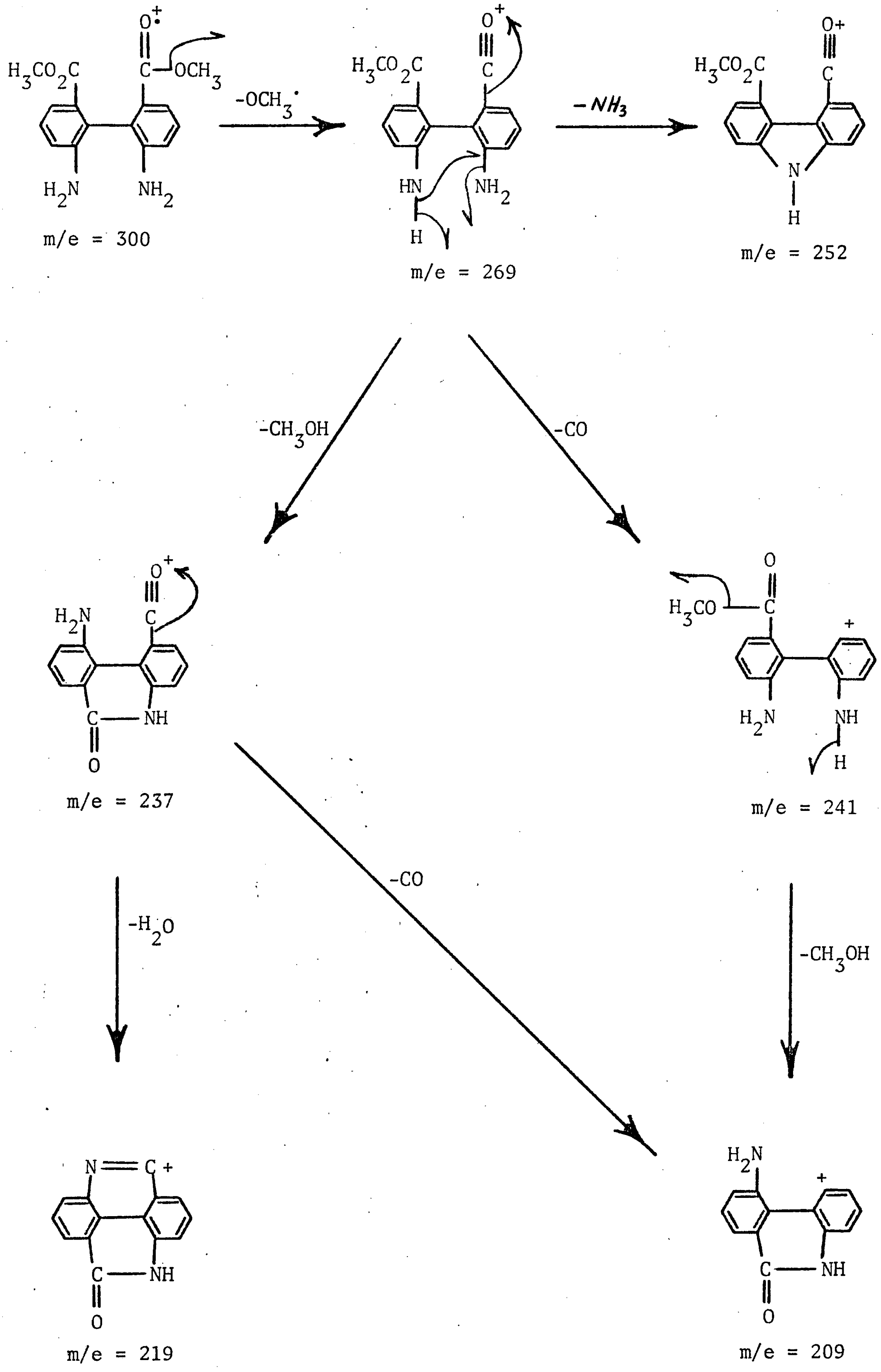
Loss of a methoxyl radical from the fragment ion of m/e = 300 will produce an even-electron ion of m/e = 269. Degradation with loss of ammonia or carbon monoxide as two stable neutral fragments from the fragment ion of m/e = 269 could produce two ions corresponding to the two peaks at m/e = 252 and m/e = 241, respectively.



Spectrum No.17. Mass spectrum of dimethyl 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine-4,5-dicarboxylate (Xa).



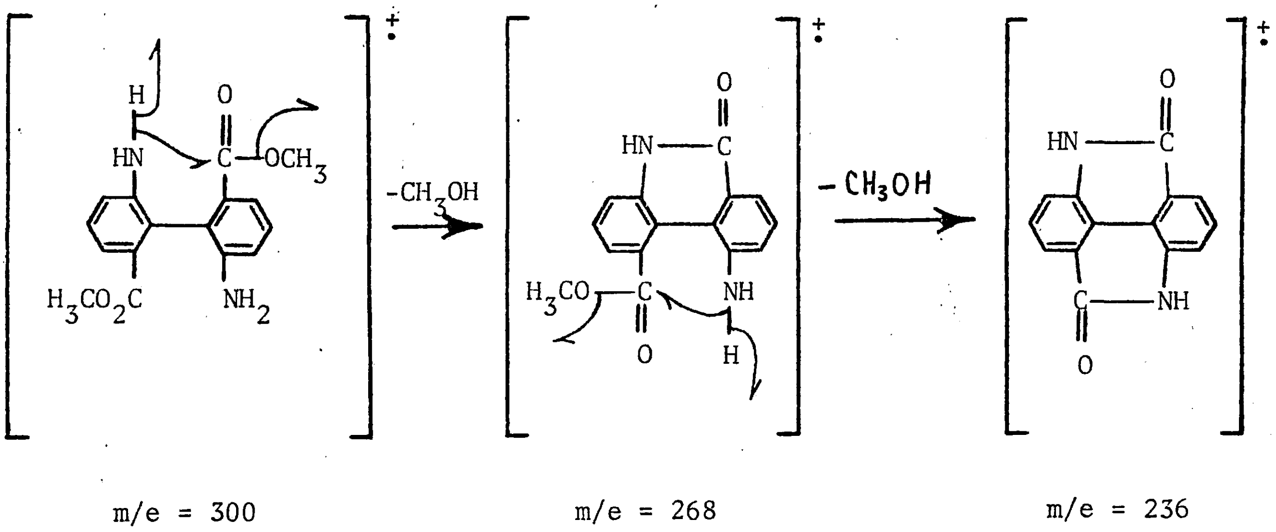
Spectrum No.18. Mass spectrum of dimethyl 2,2'-diaminobiphenyl-6,6'-dicarboxylate.


H3CO2C
C—OCH3
H2N
NH2
m/e = 300
-OCH3·
m/e = 269
-NH3
m/e = 252
-CH3OH
-CO
m/e = 237
m/e = 241
-H2O
-CO
-CH3OH
m/e = 219
m/e = 209

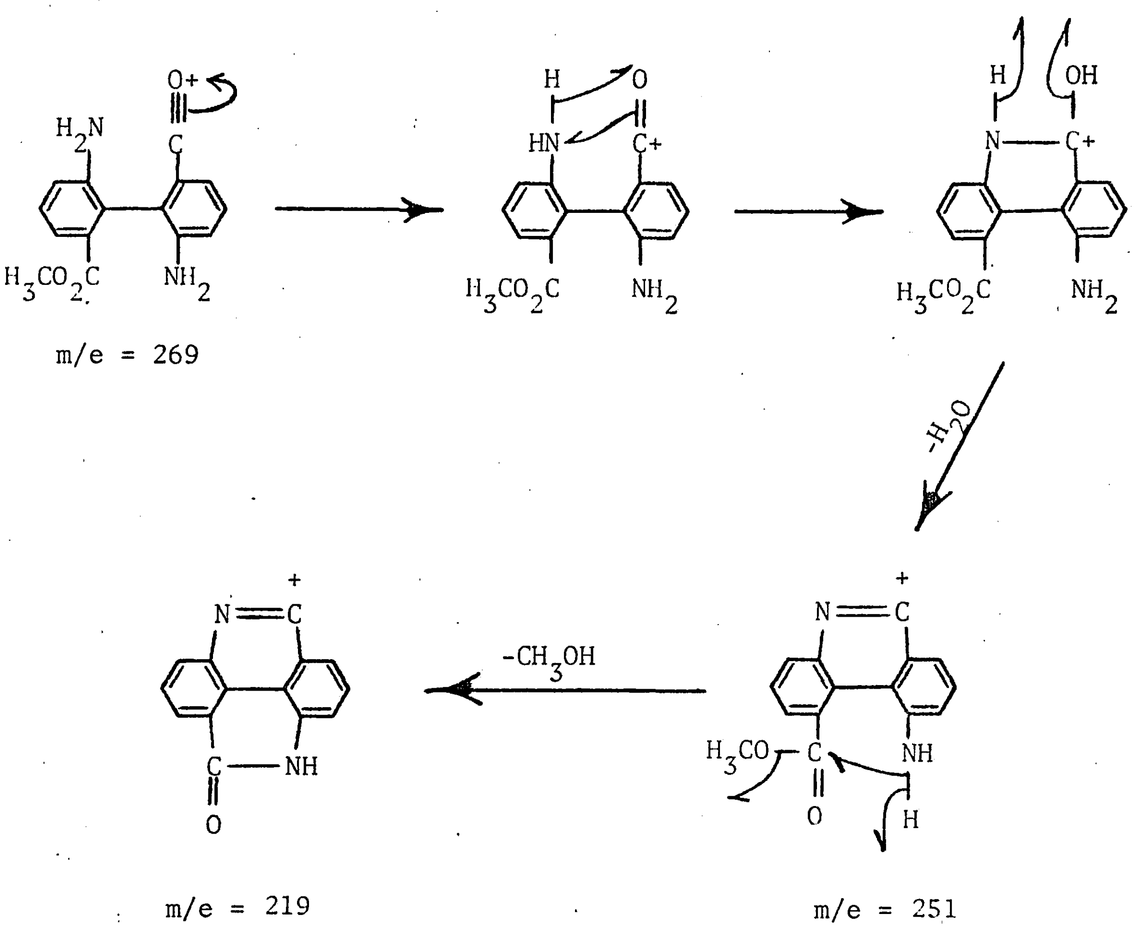
The route to a moderately intense peak at m/e = 237 has been formulated as a successive loss of methoxyl radical and methyl alcohol from an m/e = 300 precursor.

Further elimination of carbon monoxide or methanol as two stable neutral fragments from the fragment ions of m/e = 237 and m/e = 241, respectively, would produce an even-electron ion of m/e = 209.

On the other hand, successive loss of two methyl alcohol as neutral fragments from the base peak at m/e = 300 would result in the formation of an odd-electron ion of m/e = 236.



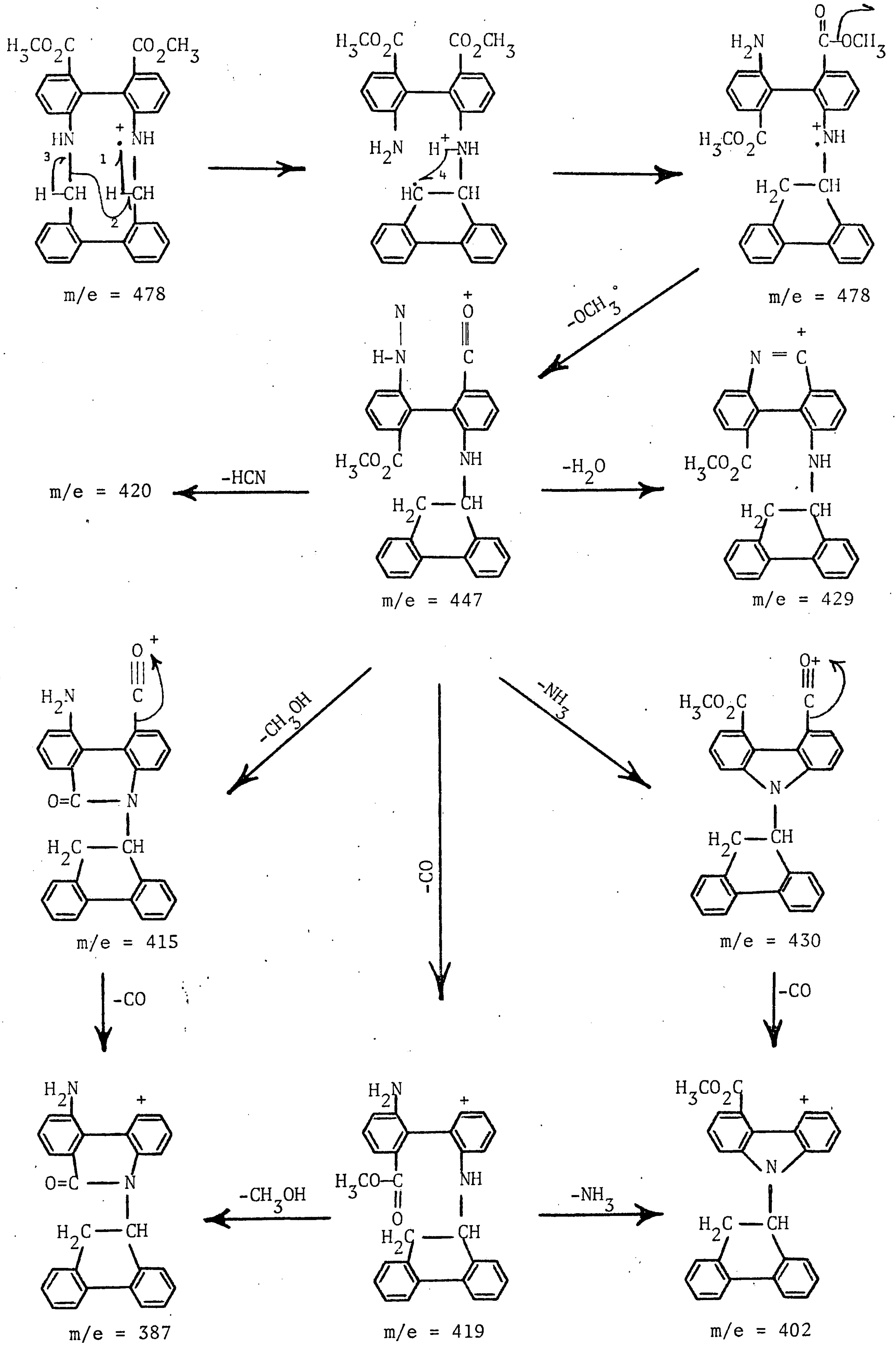
Rearrangement followed by elimination of a water molecule from the fragment ion of m/e = 269 would give an even-electron ion of m/e = 251. Further elimination of methanol as a stable neutral fragment would produce a fragment ion of m/e = 219, which might be formed, as well, by loss of a water molecule from the fragment ion of m/e = 237.



Spectrum 18 shows the mass spectrum of dimethyl 2,2'-diaminobiphenyl-6,6'-dicarboxylate.

Peaks at m/e = 195, 194, 180, 179, 178 and 165 are derived by similar routes to those mentioned in compound (X).

A useful peak at m/e = 447 is formed by rearrangement of the molecular ion and loss of a methoxyl radical. Although this even-electron ion is of low abundance, it forms probably as an intermediate ion for the formation of many other ions. The fragmentations pathway may be presented as follows:

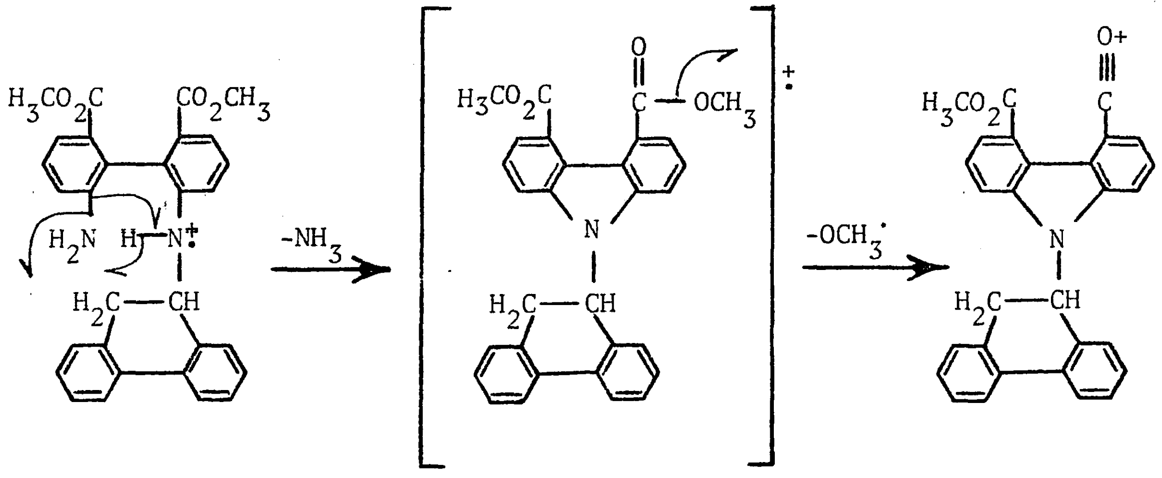

m/e = 478
m/e = 478
-OCH$_3$
m/e = 420
-HCN
m/e = 447
-H$_2$O
m/e = 429
-CH$_3$OH
-CO
-NH$_3$
m/e = 415
m/e = 430
-CO
-CO
m/e = 387
-CH$_3$OH
m/e = 419
-NH$_3$
m/e = 402

The origin of the two fragment ions corresponding to the peaks at m/e = 429 and m/e = 420 are probably related to the loss of a water molecule and HCN as neutral fragments from the intermediate fragment ion of m/e = 447, respectively.

Degradation with loss of ammonia and then carbon monoxide from the fragment ion of m/e = 447 should produce two even-electron ions corresponding to the two peaks at m/e = 430 and m/e = 402, respectively. Elimination of a methanol neutral fragment with subsequent loss of carbon monoxide from m/e = 447 would result in the formation of two even-electron ions of m/e = 415 and 387.

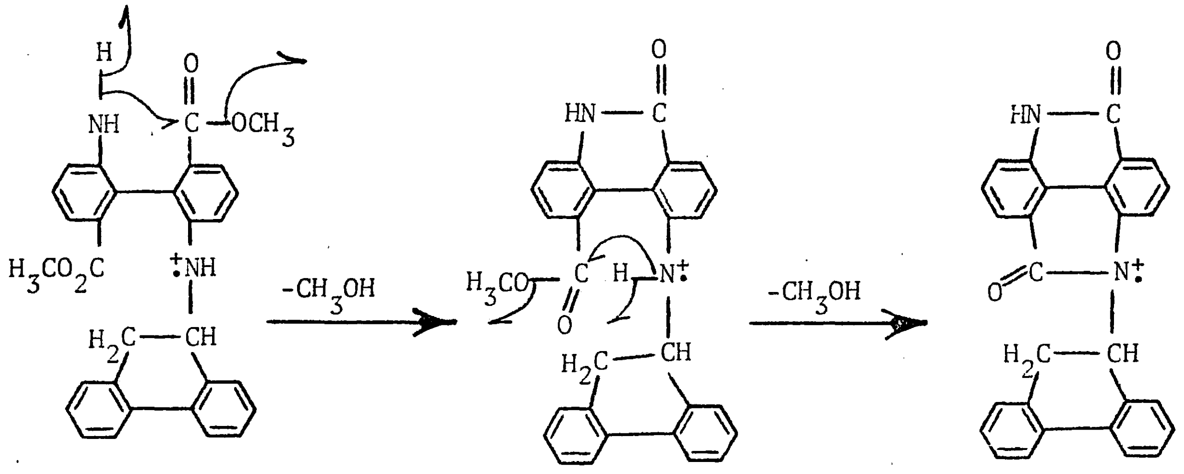
On the other hand, the ion of m/e = 419 is probably formed by loss of neutral carbon monoxide from the ion of m/e = 447. Further elimination of ammonia or methanol would produce two even-electron ions of m/e = 402 and m/e = 387, respectively.

Degradation with loss of ammonia and then a methoxyl radical from the molecular ion of m/e = 478 should produce two ions corresponding to the two peaks at m/e = 461 and m/e = 430.



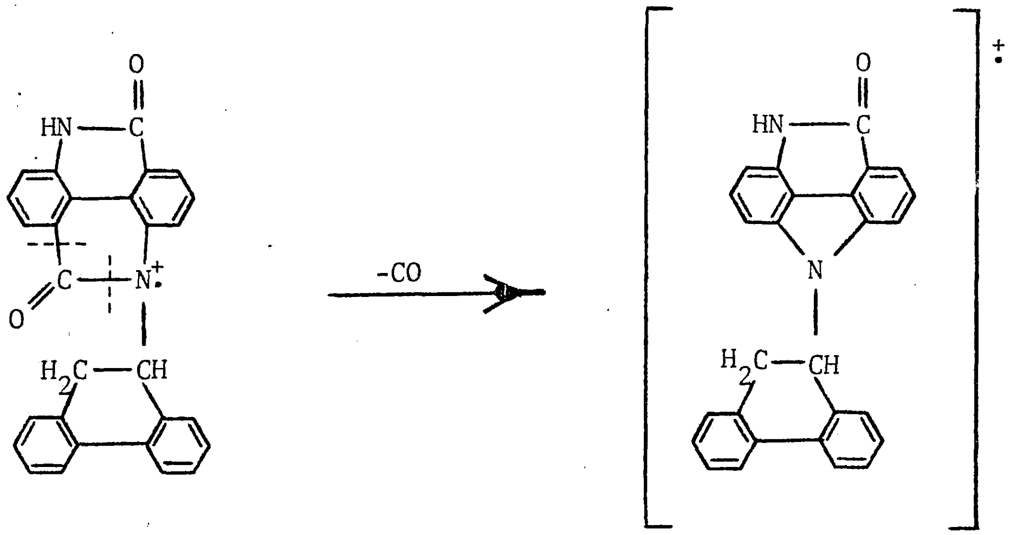
m/e = 478 m/e = 461 m/e = 430

Successive elimination of two molecules of methanol from the molecular ion should produce two fragment ions of m/e = 446 (which may lose a hydrogen atom to give an even-electron ion of m/e = 445) and m/e = 414.



m/e = 478 m/e = 446 m/e = 414

The peak at m/e = 386 could be produced from the loss of carbon monoxide as a neutral fragment from the fragment ion of m/e = 414.



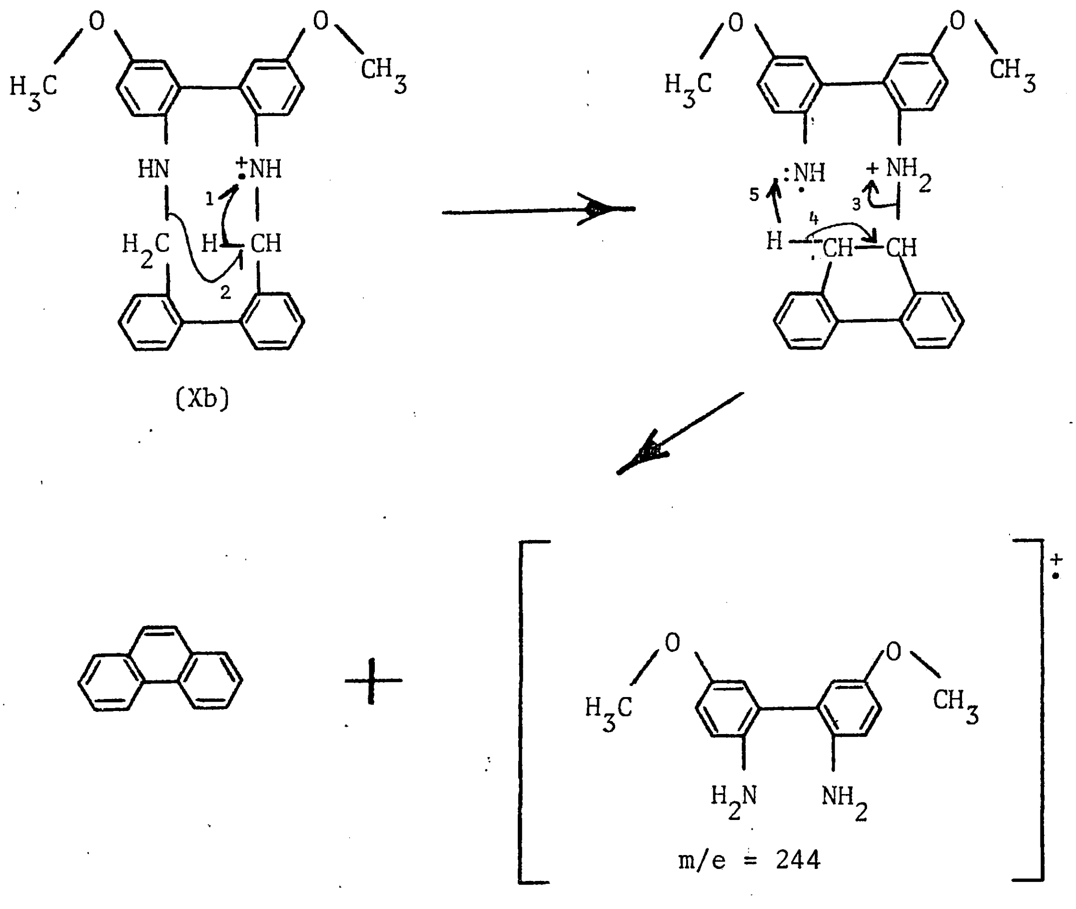
m/e = 414 m/e = 386

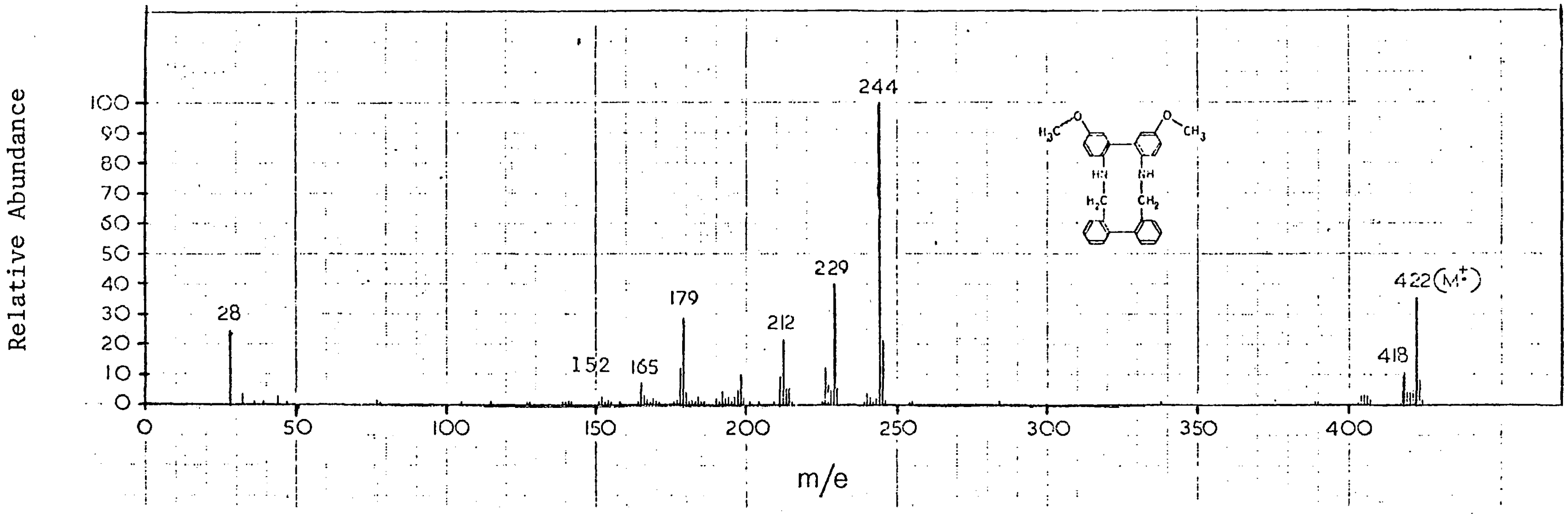
The mass spectrum (Spectrum 19) of (Xb) is relatively simple. The molecular ion peak appeared at m/e = 422. This ion was found to have the formula of $C_{28}H_{26}N_2O_2$ by accurate mass measurement:

Measured mass	Possible formula	Calculated mass
422.1990	$C_{28}H_{26}N_2O_2$	422.1994

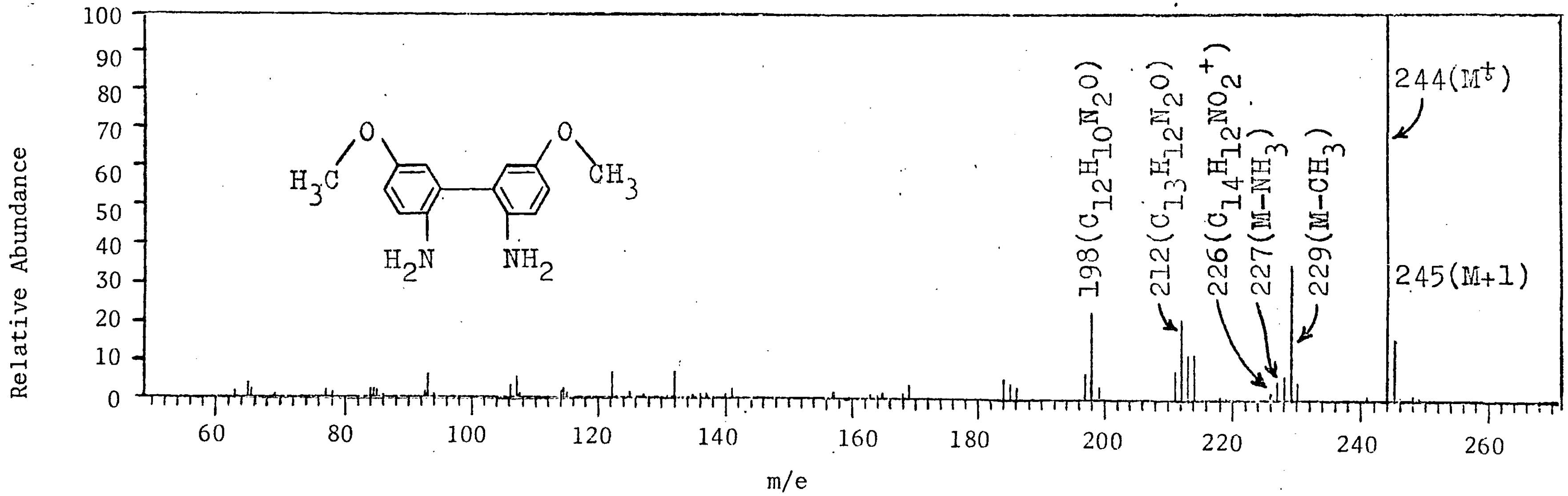
The peak at m/e = 421 is due to the loss of one hydrogen atom from the molecular ion, while the peak at m/e = 423 is the characteristic isotope peak (M+1).

Elimination of a phenanthrene molecule from the molecular ion produces the most abundant fragment ion of m/e = 244 "base peak".





Spectrum No.19. Mass spectrum of 3,6-dimethoxy-9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine (Xb).

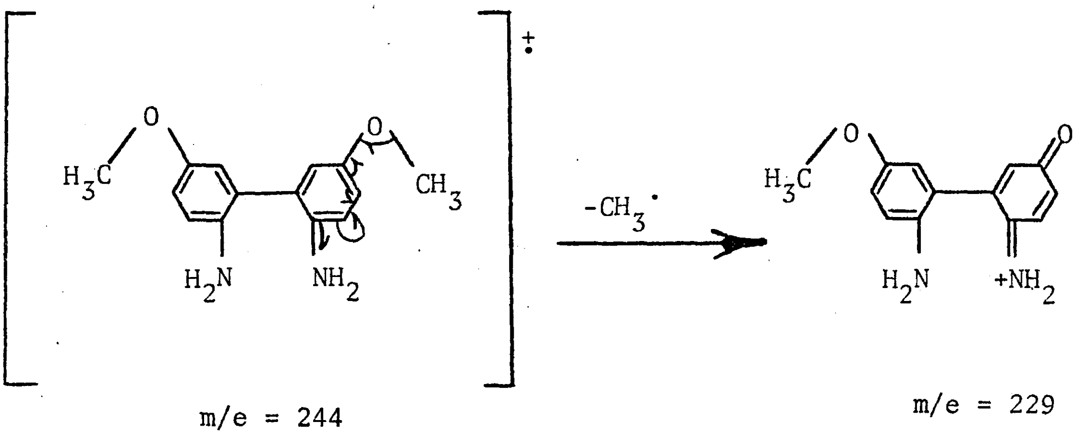


Spectrum No.20. Mass spectrum of 2,2'-diamino-5,5'-dimethoxybiphenyl

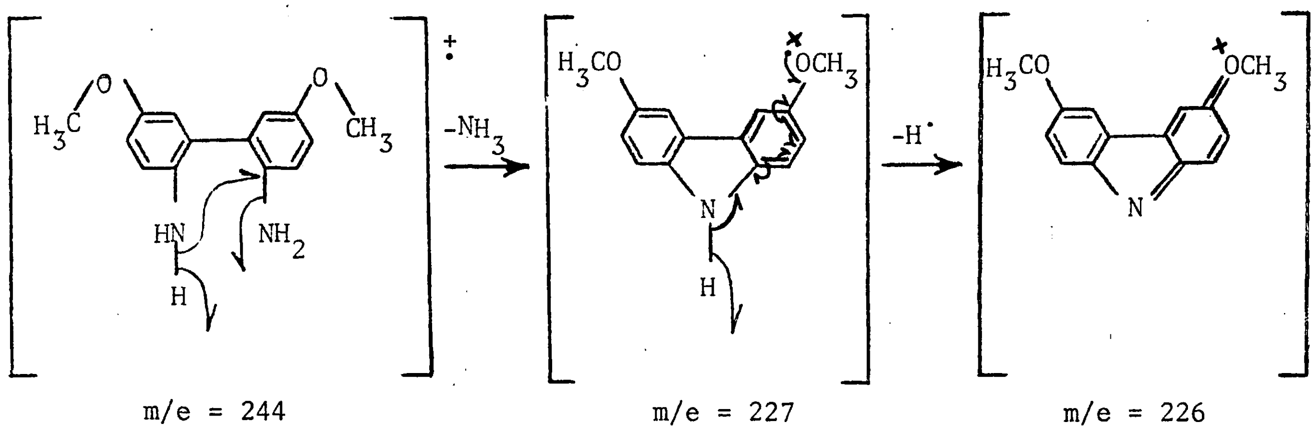
Accurate mass measurement of the base peak has given the following data:

Measured mass	Possible formula	Calculated mass
244.1215	$C_{14}H_{16}N_2O_2$	244.1212

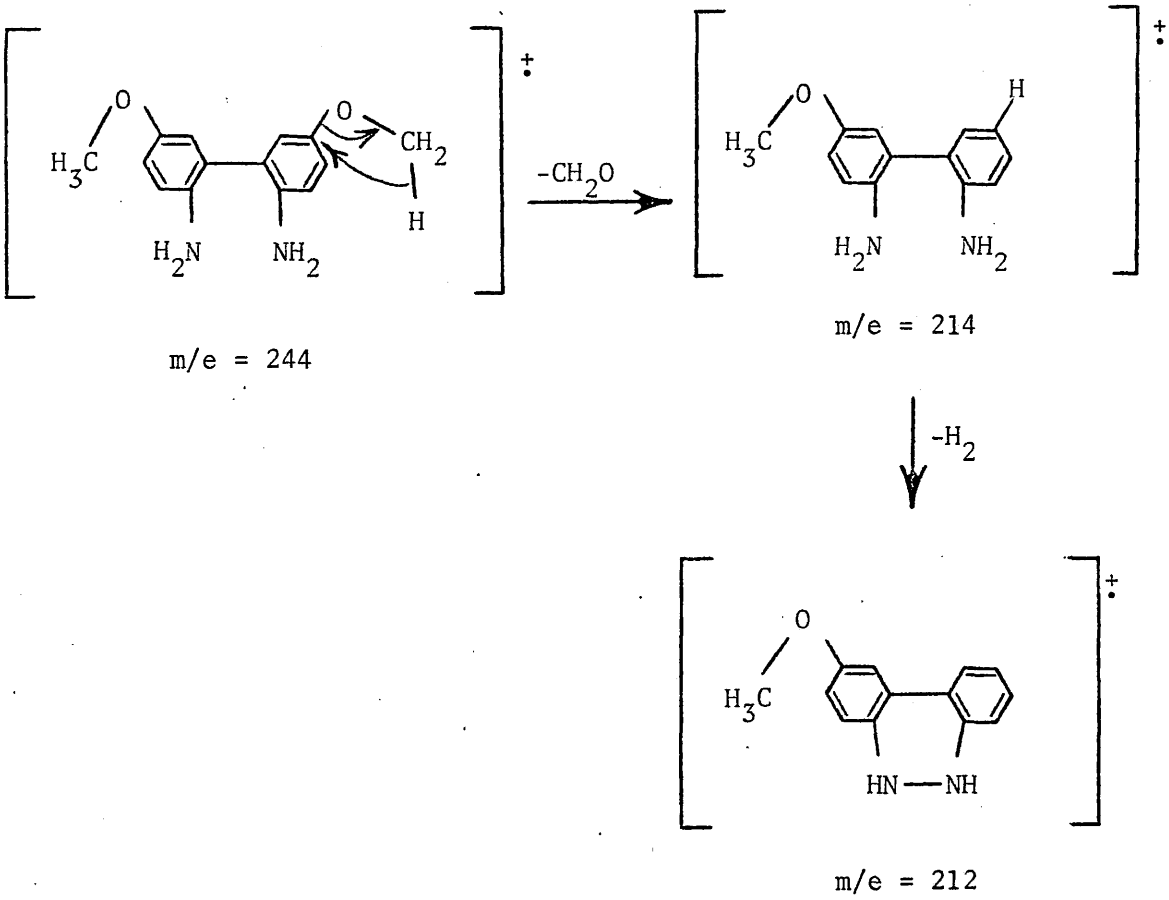
Loss of a methyl radical from the most abundant ion of m/e = 244 would produce a fragment ion of m/e = 229.



Degradation with loss of ammonia from the fragment ion of m/e = 244 should produce an ion corresponding to the peak at m/e = 227. Since an odd-electron ion is less stable, elimination of a hydrogen atom from the ion of m/e = 227 to produce the more stable even-electron ion at m/e = 226 is also possible.



The peak at m/e = 214 appears to be due to the loss of CH_2O from the fragment ion of m/e = 244. Loss of a hydrogen atom from the odd-electron ion of m/e = 214 produces an even-electron ion of m/e = 213.



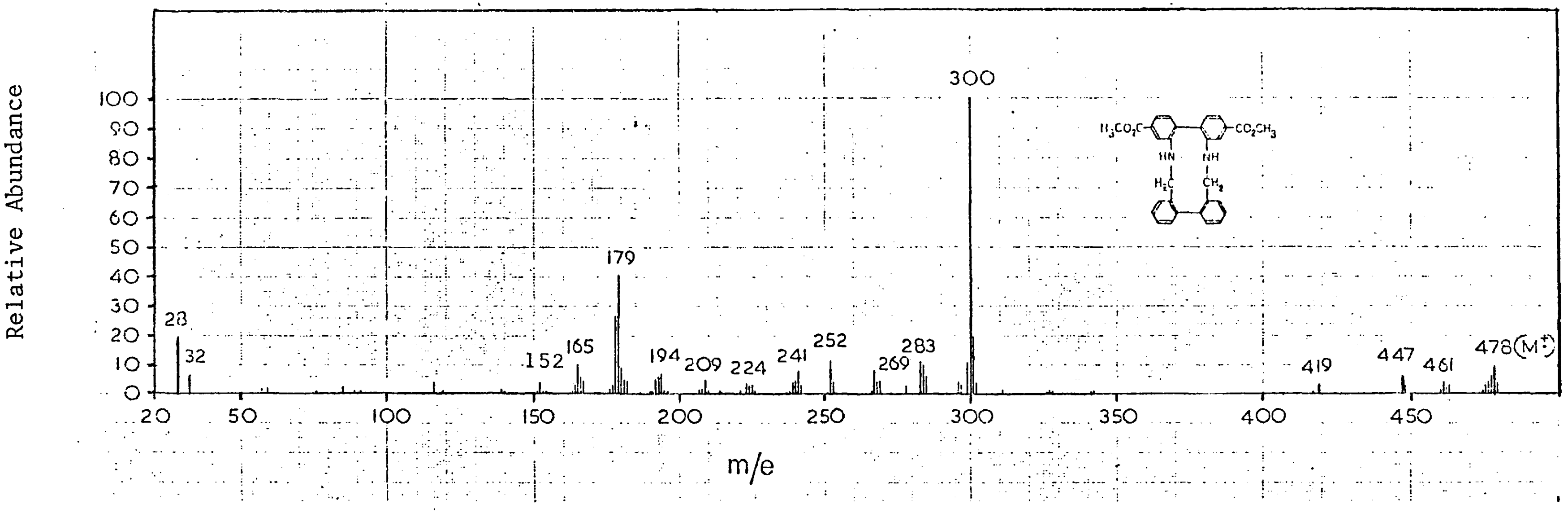
On the other hand, the fragment ion of m/e = 212 seems to be due to the loss of two hydrogen atoms from m/e = 214. Spectrum 20 shows the mass spectrum of 2,2'-diamino-5,5'-dimethoxybiphenyl.

The fragmentation paths to produce the ions of m/e = 195, 194, 180, 179, 178 and 165 are identical to those obtaining for compounds (X) and (Xa).

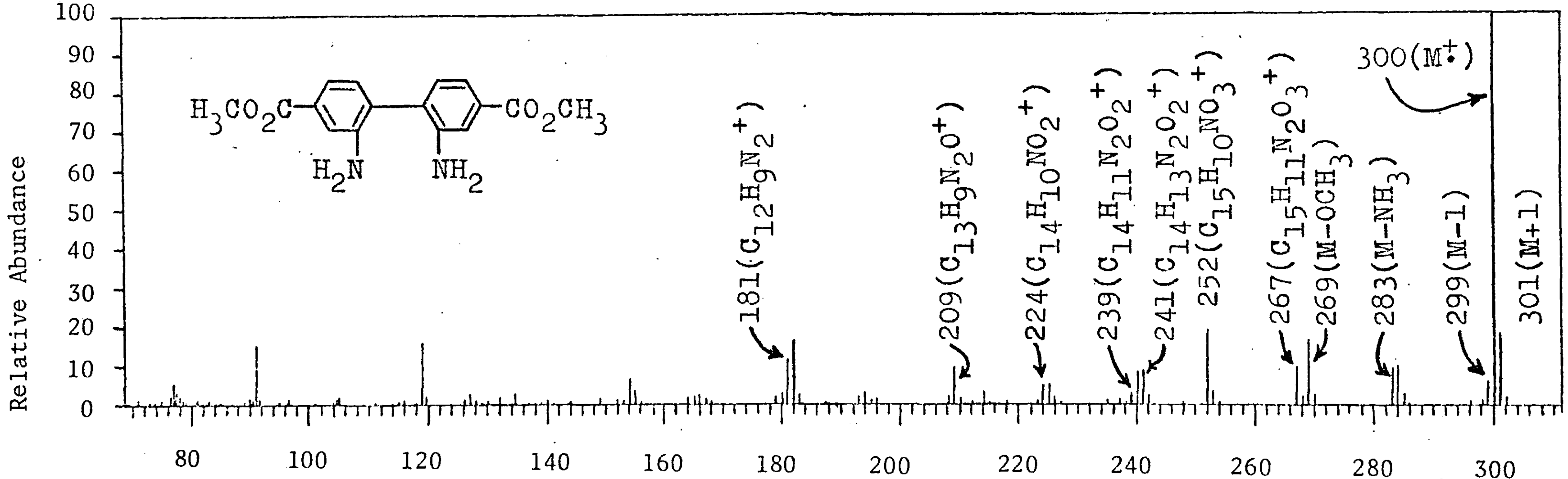
The mass spectrum of (Xc) is shown in (Spectrum 21). It can be seen by comparison with the mass spectrum of (Xa) (Spectrum 17) that the fragmentation patterns are basically very similar, but there is sufficient variation in the relative abundances of the fragment ions to differentiate between the two isomers. The molecular ion peak at m/e = 478 can be seen in both spectra, although it is very much smaller in Spectrum 21 than it is in Spectrum 17.

The mass spectroscopic determination of the molecular weight of (Xc) had given the formula $C_{30}H_{26}N_2O_4$ (measured mass = 478.1885; calculated mass = 478.1893). The peak at m/e = 477 is due to the loss of one hydrogen atom from the molecular ion, while the peak at m/e = 479 is the characteristic isotope peak (M+1).

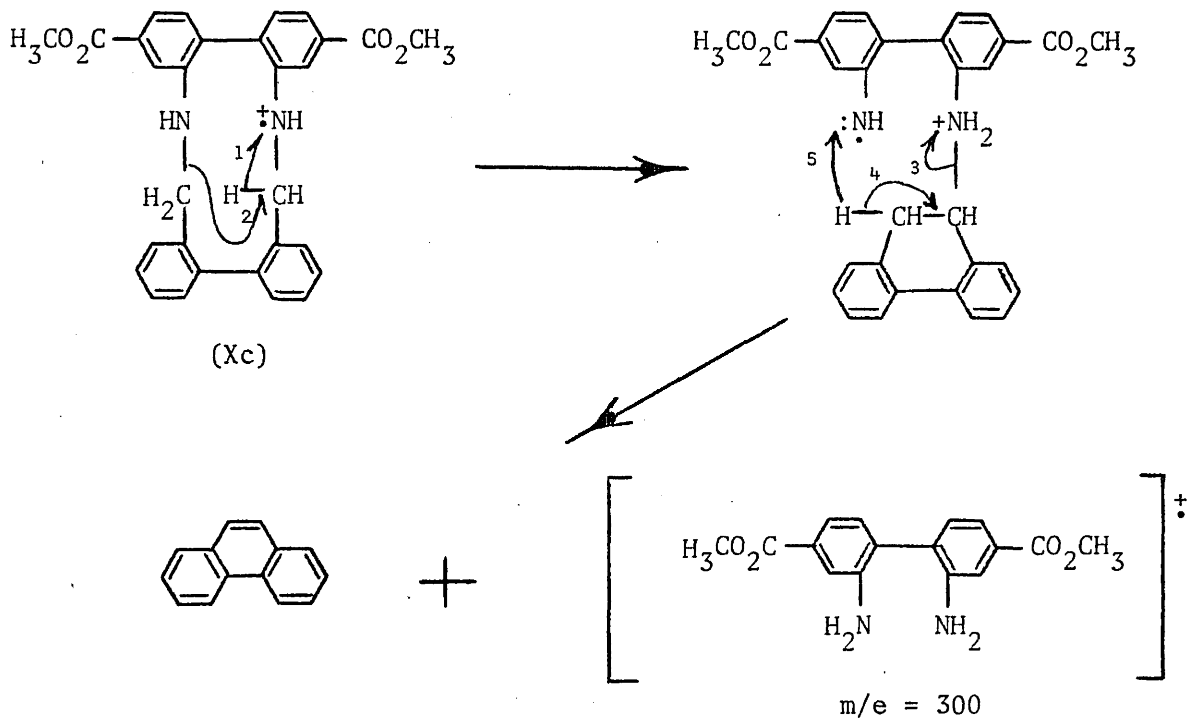
Rearrangement followed by elimination of a phenanthrene molecule as a neutral fragment from the molecular ion would produce the most abundant ion in the spectrum of m/e = 300.



Spectrum No.21. Mass spectrum of dimethyl 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate (Xc).



Spectrum No.22. Mass spectrum of dimethyl 2,2'-diaminobiphenyl-4,4'-dicarboxylate.



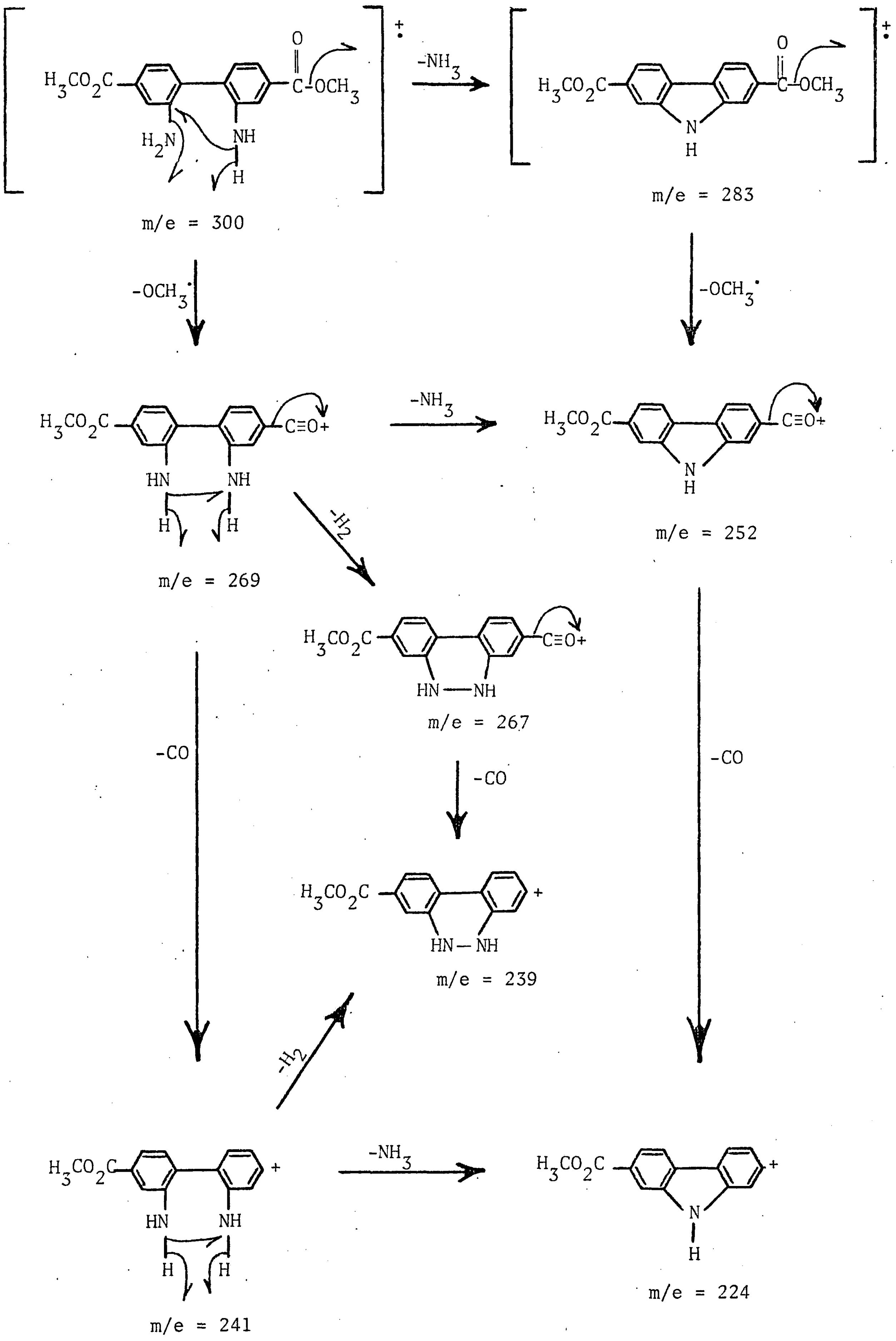
(Xc)

The even-electron ion of m/e = 269 could be derived from the most abundant ion of m/e = 300 by loss of methoxyl radical. Subsequent loss of two hydrogen atoms and/or carbon monoxide results in three peaks corresponding to three even-electron ions of m/e = 267 and m/e = 239 or m/e = 241, respectively. Degradation with loss of ammonia as a neutral fragment could lead to the formation of the even-electron ion of m/e = 252.

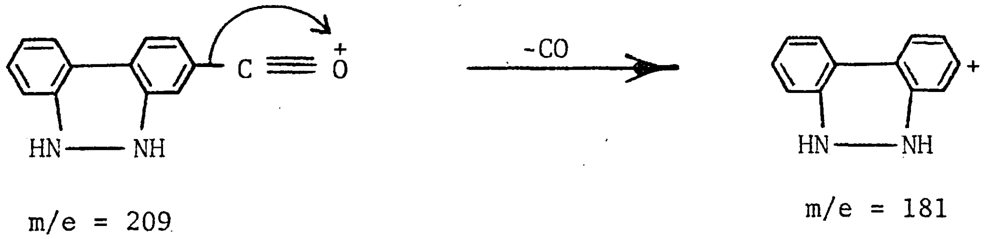
Loss of two hydrogen atoms or ammonia from m/e = 241 produces two ions of m/e = 239 and m/e = 224.

On the other hand, thermal degradation with loss of ammonia from the ion of m/e = 300 could produce an odd-electron ion of m/e = 283. Further elimination of methoxyl radical followed by loss of carbon monoxide as a neutral fragment would lead to the formation of two even-electron ions of m/e = 252 and m/e = 224, respectively.

It is possible that fragmentations might proceed as follows:


H3CO2C
C-OCH3
H2N
NH
H
m/e = 300
-NH3
m/e = 283
-OCH3
C≡O+
HN
m/e = 269
m/e = 252
-H2
HN—NH
m/e = 267
-CO
m/e = 239
m/e = 241
m/e = 224

The peak at m/e = 209 is produced by an unknown route, and is believed to have the following structure:



Elimination of carbon monoxide neutral fragment from the fragment ion of m/e = 209 produces an even-electron ion of m/e = 181. Spectrum 22 shows the mass spectrum of dimethyl 2,2'-diaminobiphenyl-4,4'-dicarboxylate.

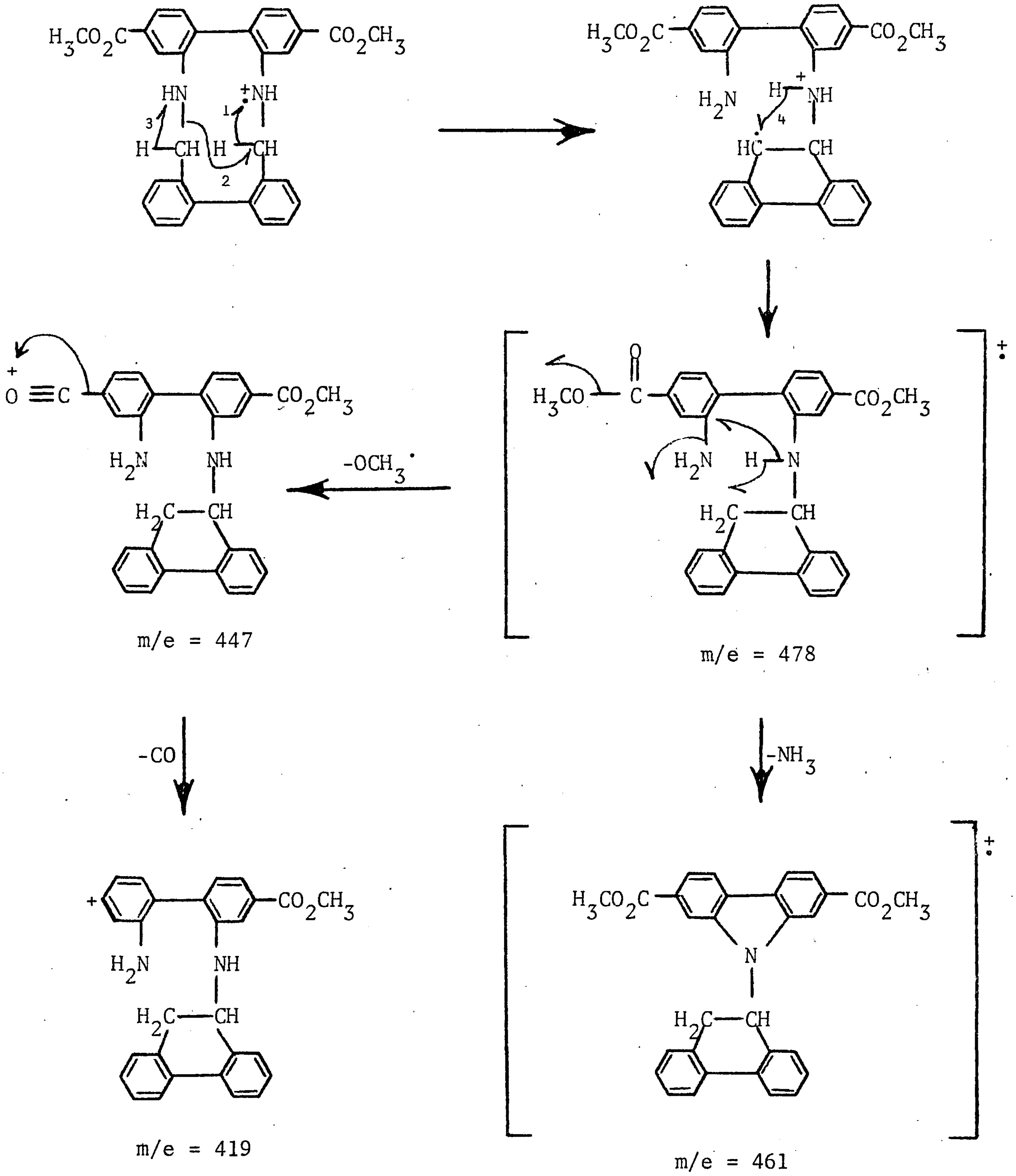
Rearrangement followed by loss of ammonia as a neutral fragment from the molecular ion produces an odd-electron ion of m/e = 461.

Successive elimination of methoxyl radical and then carbon monoxide neutral fragment from the molecular ion could lead to the formation of two even-electron ions of m/e = 447 and 419.

The fragmentation paths to produce the ions of m/e = 195, 194, 180, 179, 178 and 165 are identical to those obtaining for compounds (X), (Xa) and (Xb).

Finally, the simple fragmentation pattern of compound (Xc) in the region of m/e = 370 to m/e = 478 in comparison to that of (Xa) is due to the complete elimination of cyclization possibilities which can readily occur in compound (Xa).

The peaks at M-4 in the spectra of compounds (X), (Xb) and (Xc) may be due to traces of the unreduced compound in each case. There is no evidence of such impurity in the n.m.r. spectra of (X), (Xb) and (Xc) so that the amount must be very small; presumably the molecular ion of these unreduced compounds is rather stable and thus appears with a relatively high intensity.

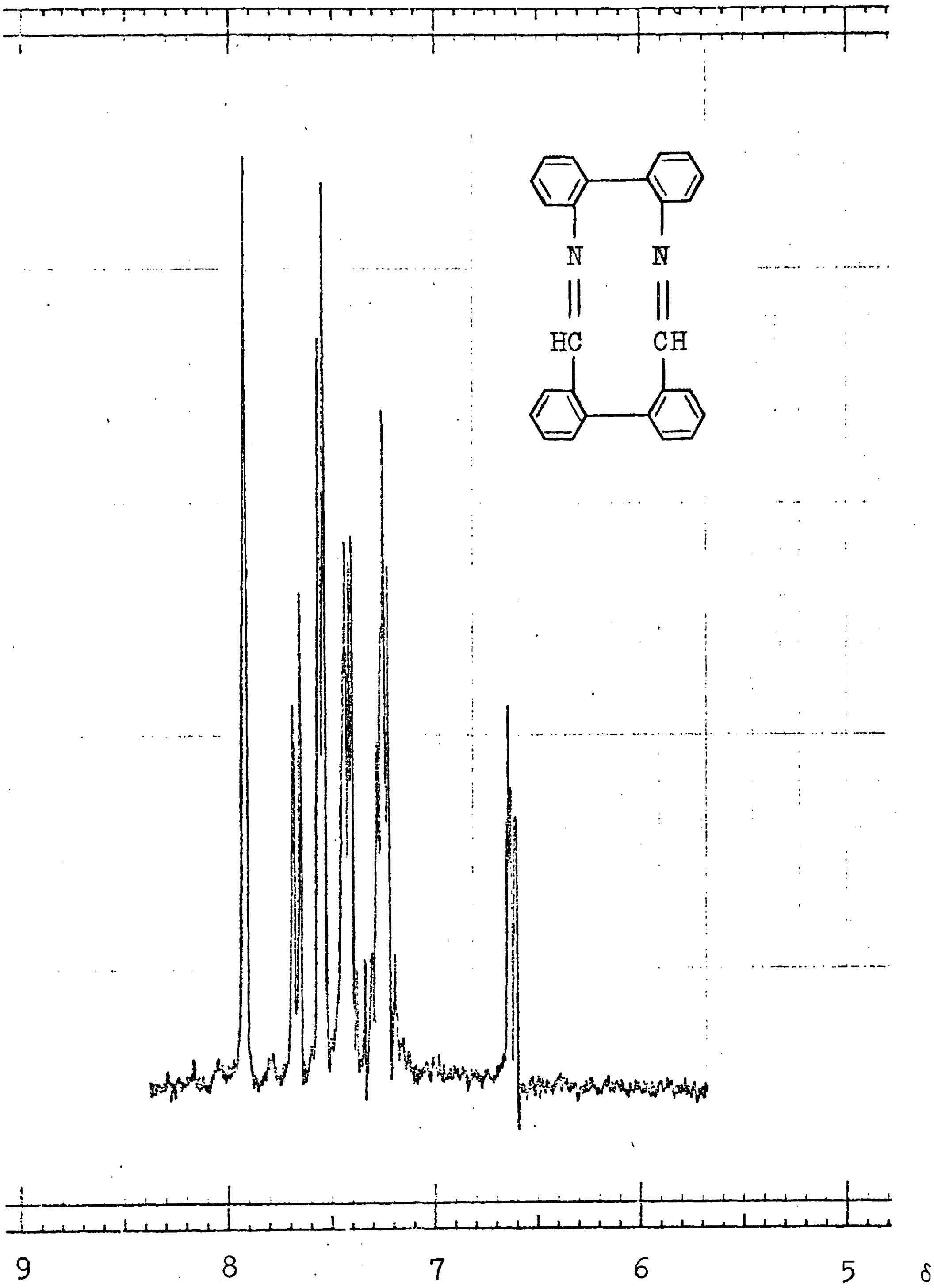


2.4. Proton Magnetic Resonance Spectra including Results Using Lanthanide Shift Reagents

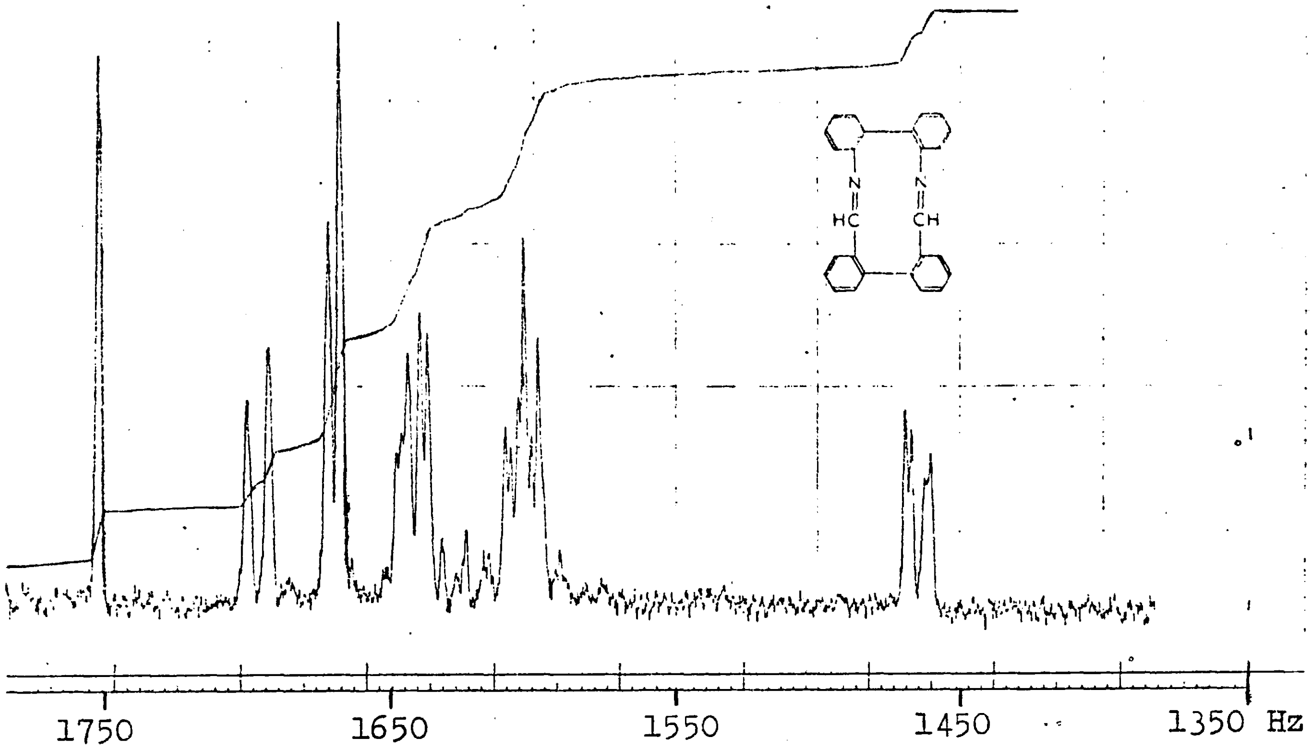
The ^{1}H N.m.r. spectra of the eight polycyclic heterocyclic compounds (IX - IXc and X - Xc) were determined at 60, 100 and 220 MHz in $CDCl_3$ solution using TMS as internal reference standard. The results are presented in the following order:

2.4.1. ^{1}H N.m.r. spectra of tetrabenzo[b,d,h,j][1,6]diazacyclododecine and its derivatives with substituents in ortho-, meta- or para- positions of the nitrogen biphenyl system

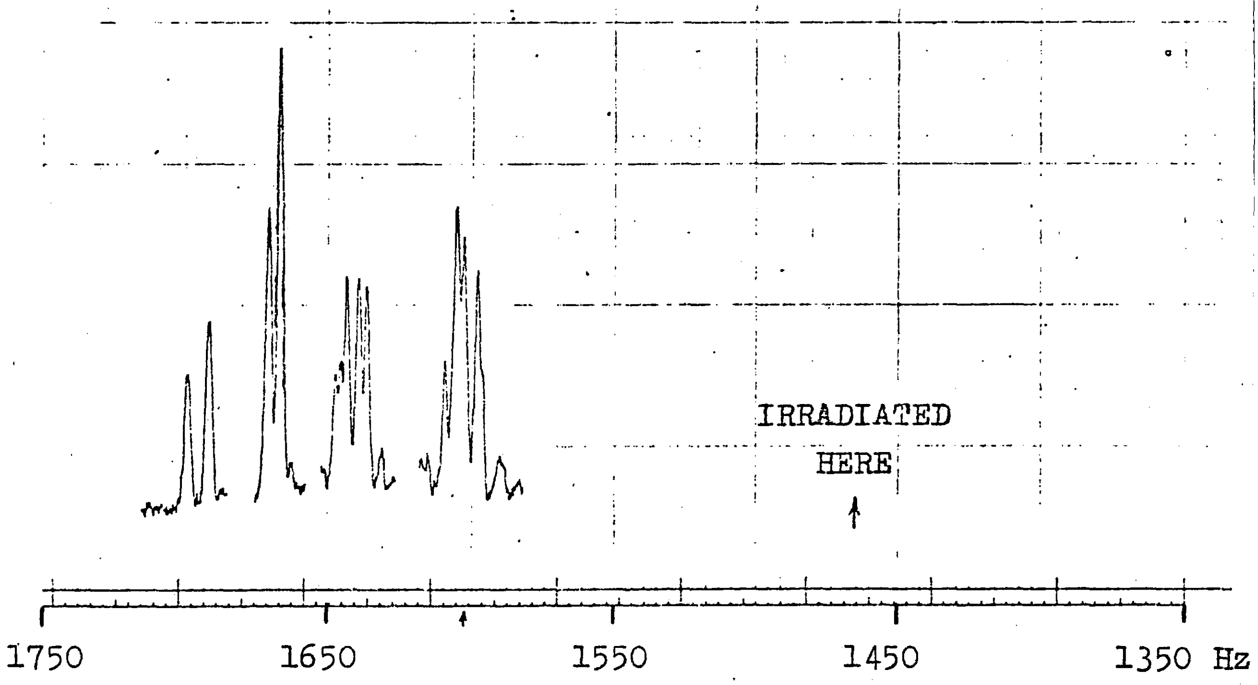
The ^{1}H N.m.r. spectrum of tetrabenzo[b,d,h,j][1,6]diazacyclododecine (IX) showed absorption only in the aromatic region (Spectrum 23). Expansion of the Spectrum 23 and integration of the peaks showed very clearly resonances corresponding to nine protons (Spectrum 24). The aromatic protons were separated very well and the splitting patterns of individual peaks can be recognised. Irradiating the multiplet at 6.61 - 6.65 p.p.m. revealed loss of meta-coupling at 7.20 - 7.32 p.p.m. (Spectrum 25).



Spectrum No.23. ^{1}H N.m.r. spectrum (220 MHz) of tetrabenzo[b,d,h,j][1,6]diazacyclododecine (IX) in CDCl$_3$.

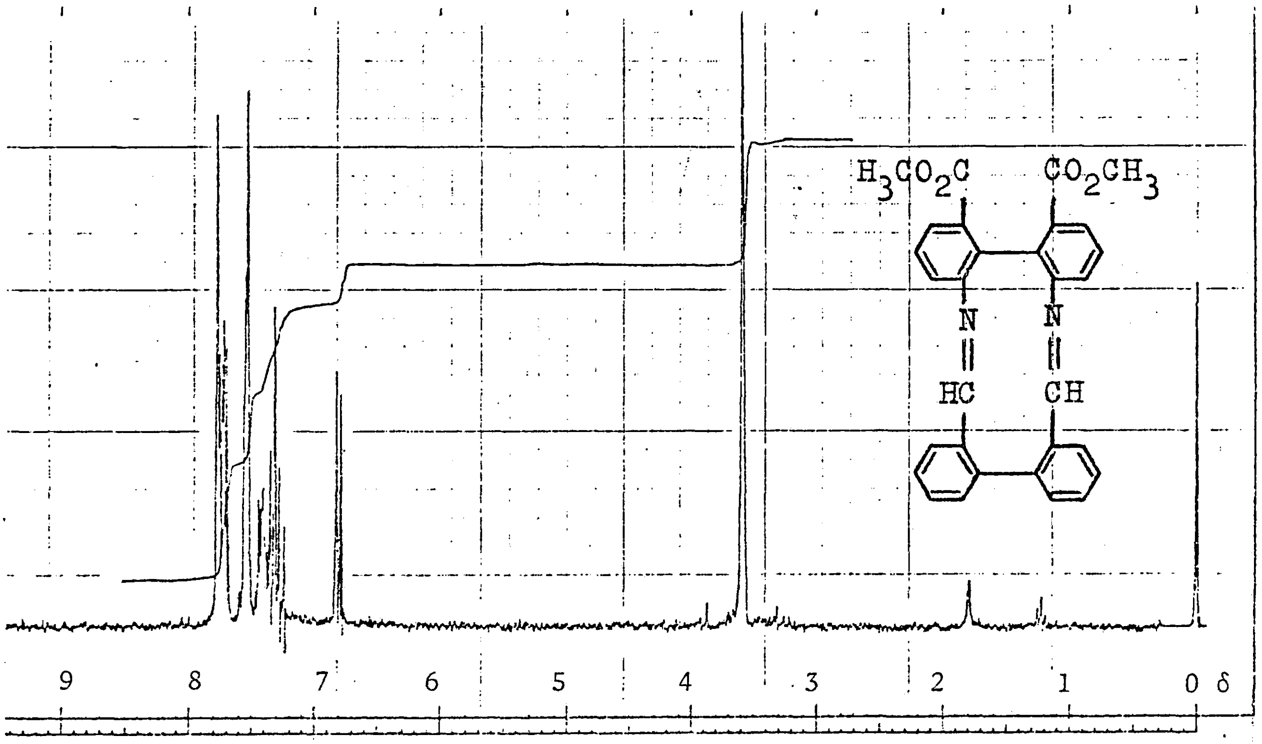


Spectrum No.24. Expanded ^{1}H N.m.r. spectrum (220 MHz) of tetrabenzo-[*b*,*d*,*h*,*j*][1,6]diazacyclododecine (IX) in $CDCl_3$, sweep offset by 1350 Hz, sweep width 500 Hz.

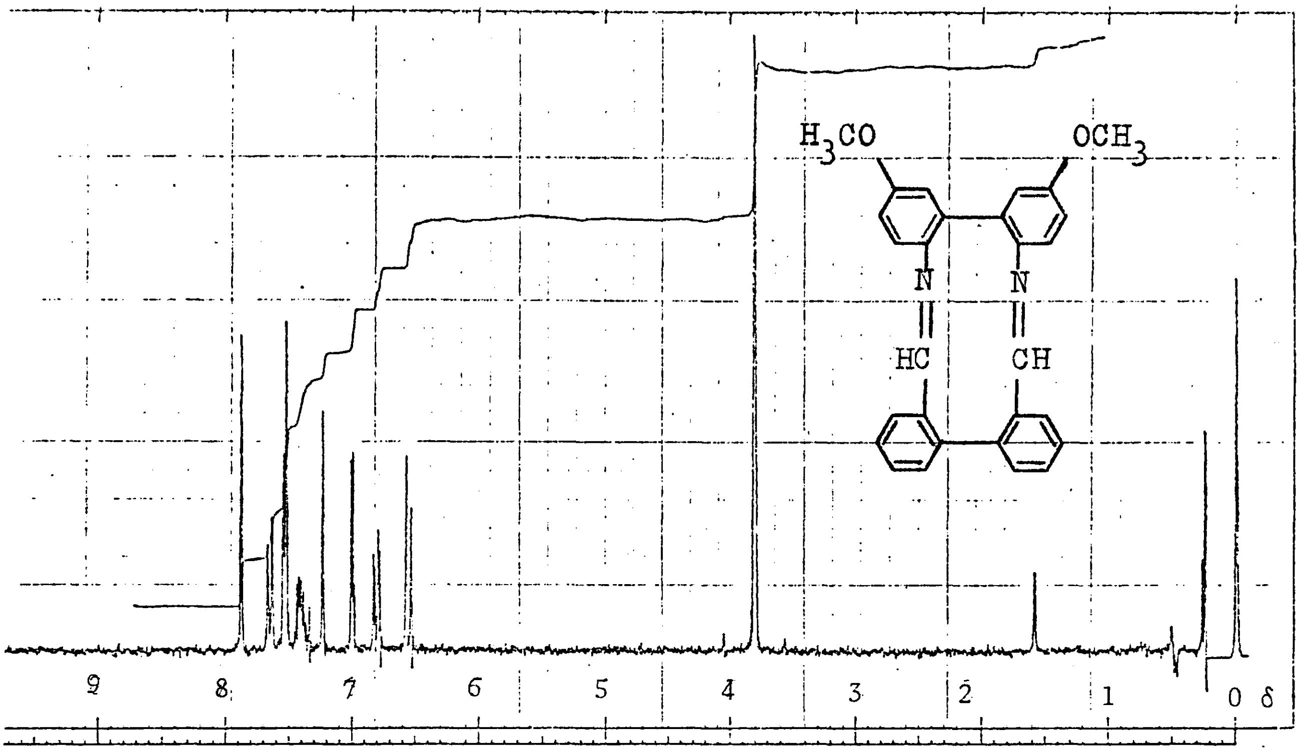


Spectrum No.25. Irradiated ^{1}H N.m.r. spectrum (220 MHz) of tetrabenzo-[*b*,*d*,*h*,*j*][1,6]diazacyclododecine (IX) in $CDCl_3$ at 6.61 - 6.65 p.p.m., sweep offset by 1350 Hz, sweep width 500 Hz.

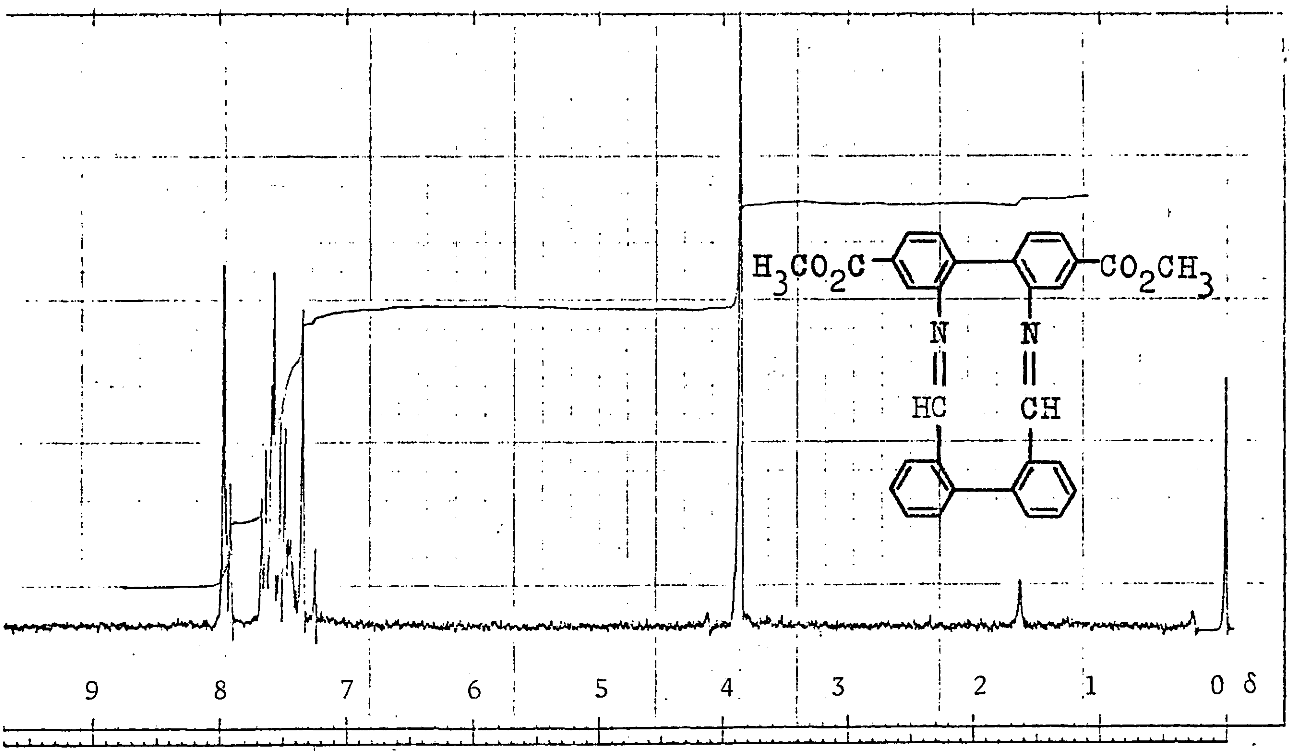
Unambiguous assignments of individual peaks are made with the aid of substituents effect in the ortho-, meta- or para-positions in the nitrogen biphenyl system of the molecule. ^{1}H N.m.r. spectra of these derivatives (IXa), (IXb) and (IXc) are shown in Spectra 26, 27 and 28, respectively. The chemical shifts data of tetrabenzo[b,d,h,j][1,6]diazacyclododecine (IX) and its derivatives (IXa), (IXb) and (IXc) are collected in Table 9.



Spectrum No.26. ^{1}H N.m.r. spectrum (220 MHz) of dimethyl tetrabenzo-[b,d,h,j][1,6]diazacyclododecine-4,5-dicarboxylate (IXa) in $CDCl_3$.

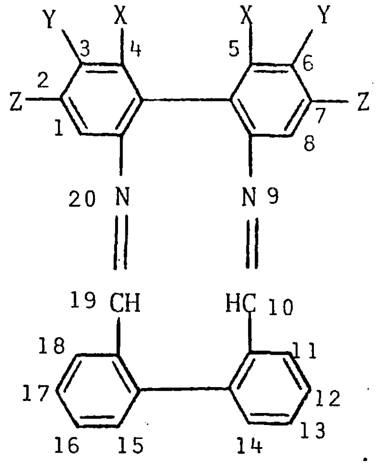


Spectrum No. 27. ^{1}H N.m.r. spectrum (220 MHz) of 3,6-dimethoxytetrabenzo[b,d,h,j][1,6]diazacyclododecine (IXb) in CDCl$_3$.



Spectrum No.28. ^{1}H N.m.r. spectrum (220 MHz) of dimethyl tetrabenzo-[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate (IXc) in CDCl$_3$.

Table No.9. Chemical shifts (δ; 220 MHz; Me_4Si; $CDCl_3$) of methyl, aldimine and aromatic protons of compounds (IX) - (IXc).



Compound	Substituent			Methyl Protons	Aldimine Proton	AROMATIC PROTONS						
						Amine Biphenyl Protons				Aldehyde biphenyl Protons		
	X	Y	Z	CH_3	CH=N	$H_{1,8}$	$H_{2,7}$	$H_{3,6}$	$H_{4,5}$	$H_{11,18}$	$H_{12,17}$	$H_{13,16}$ and $H_{14,15}$
IX	H	H	H	-----	7.93(s)	6.61-6.65(q)	7.20 ———	——— 7.32(m)	7.35-7.46(m)	7.66-7.70(d)	7.35-7.46(m)	7.55-7.58(d)
IXa	CO_2CH_3	H	H	3.59(s)	7.77(s)	6.78-6.82(d)	7.24-7.35(m)	7.70-7.75(d)	------------	7.68-7.73(d)	7.37-7.46(m)	7.52-7.55(m)
IXb	H	OCH_3	H	3.81(s)	7.88(s)	6.53-6.57(d)	6.78-6.83(q)	------------	6.99-7.01(d)	7.64-7.67(d)	7.34-7.46(m)	7.53-7.54(d)
IXc	H	H	CO_2CH_3	3.86(s)	7.96(s)	7.34(s)	-----------	7.90-7.94(m)	7.47-7.51(d)	7.63-7.66(d)	7.40-Hidden(m)	7.57-7.58(d)

(s) singlet (d) doublet (t) triplet (q) quartet and (m) multiplet

Studying the above results, Table 9, showed that the effect of the substituents in the nitrogen biphenyl system of the molecule produced changes in the chemical shifts of the ring protons of the same biphenyl unit which are in line with the conjugative effects of the substituents, whereas the effect on the chemical shifts of the ring protons of the carbon biphenyl system is nearly negligible. This shows that the Ph_N ring and the Ph_C ring joined by CH=N cannot lie in the same plane.

The aldimine proton signal in compounds (IX-IXc) appeared as a sharp singlet in the range 7.77-7.96 p.p.m. and resonated in the upfield region in comparison to the same signal of the compounds reported by Hall and her co-workers,[118] which resonated in the downfield region in the range 8.08-8.93 p.p.m. This is probably due to increased twisting of the N-Ph bond in compounds (IX-IXc) in comparison to those reported by Hall et al., resulting in less deshielding. An interesting point is observed in the case of compound (IXa) in which the aldimine proton signal has been shifted from 7.93 to 7.77 p.p.m. This is probably due to the steric effect of the two ortho-carboxyl groups which are certainly large enough to cause increased twisting of the nitrogen biphenyl system and the aldimine, CH=N, groups as well. Thus, the aldimine protons are removed from the local deshielding influence, resulting in slightly shielding shift.

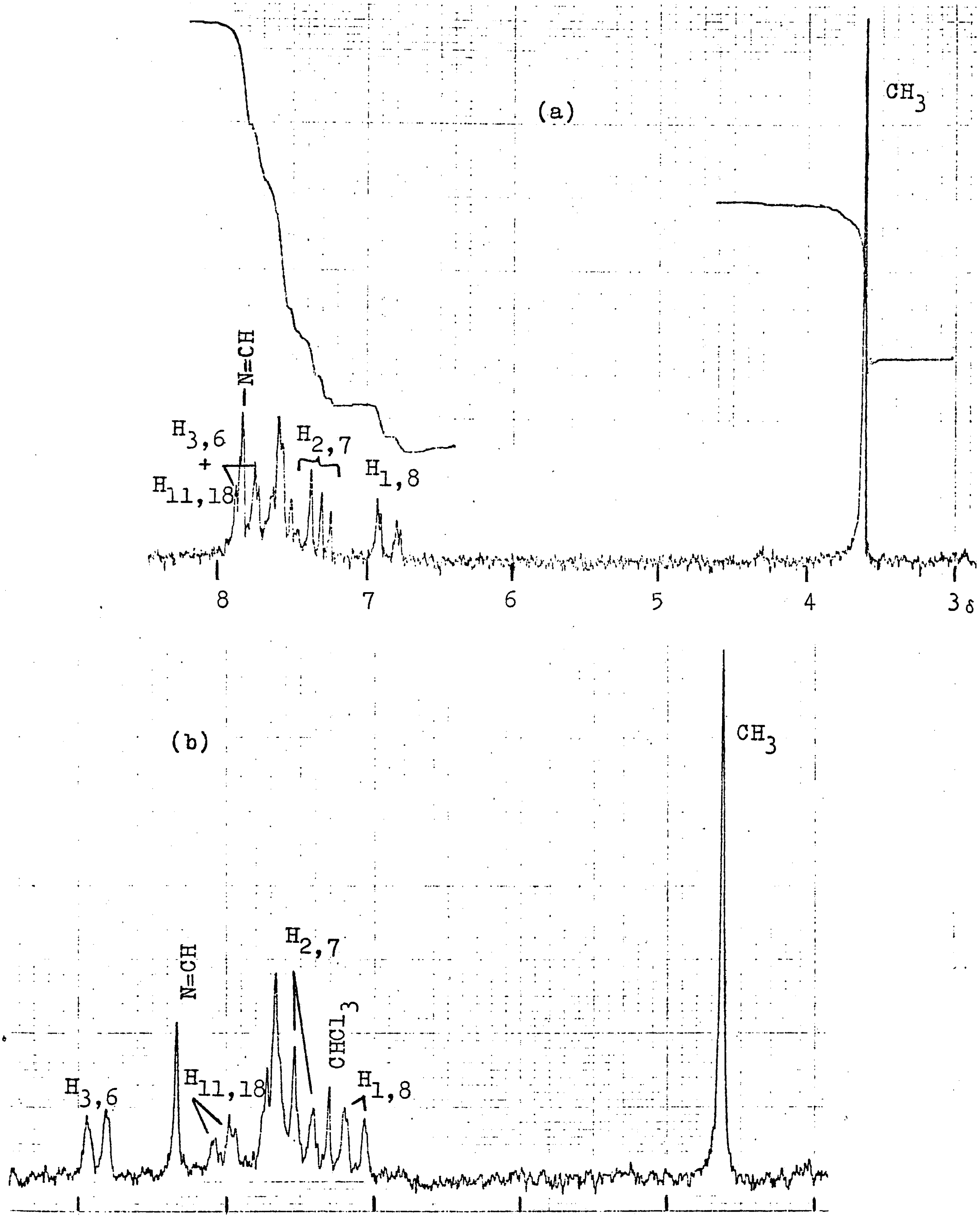
From the evidence discussed above, it may certainly be concluded that the quartet at 6.61-6.65 p.p.m. in compound (IX) arises from the two ring protons ortho- to nitrogen and not from the methine group as was suggested by Bergmann and his co-workers[4]. However, it is not apparent from models why this signal is so far upfield.

Lanthanide shift reagents, $Eu(fod)_3$ and $Pr(fod)_3$, were used to simplify the ^1H N.m.r. spectra. No detectable shifts could be observed on successive addition of $Eu(fod)_3$ or $Pr(fod)_3$ to a solution of tetrabenzo-

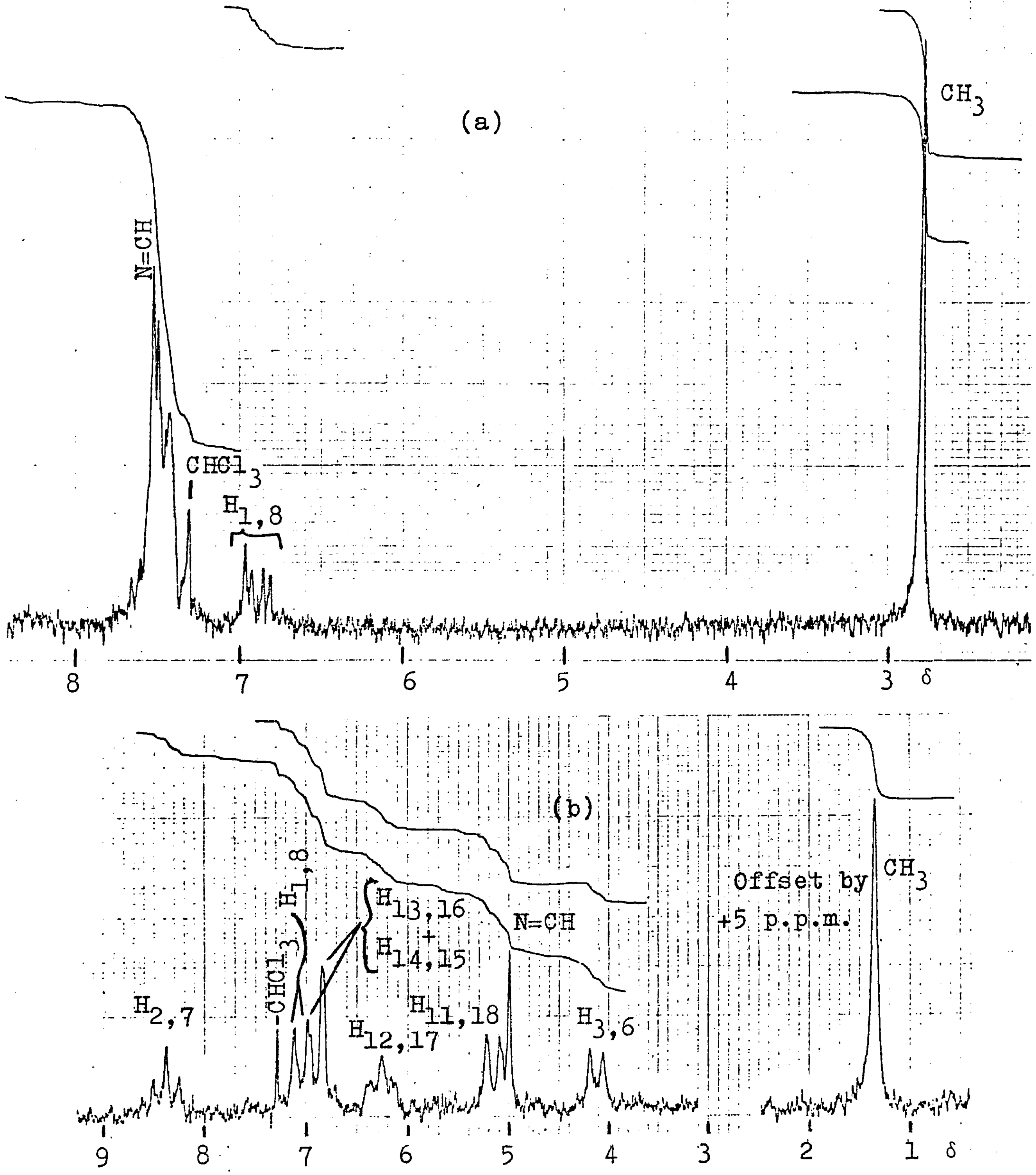
[b,d,h,j][1,6]diazacyclododecine (IX) in $CDCl_3$. Evidently the electron density at the nitrogen atoms, in this case, is insufficient for complexation with the shift reagents used here, individually.

The effect on the resonance positions of the different protons in compound (IXa) upon addition of increasing amounts of $Eu(fod)_3$ and $Pr(fod)_3$ is shown in Spectra 29 and 30, respectively. Increasing the amount of $Eu(fod)_3$ or $Pr(fod)_3$, however, has increasingly resolved the spectrum of (IXa) such that upon addition of 40.95 mg (3.989×10^{-5} mole) of $Pr(fod)_3$ to the solution dramatic changes occurred in the spectrum of (IXa)(Spectrum 30b). Most obvious of these changes was the shift of five well-resolved signals to the highfield regions of the spectrum.

Of greatest interest, however, are the downfield shifts observed for the aromatic hydrogen resonances $H_{1,8}$ and $H_{2,7}$ upon addition of $Pr(fod)_3$ to (IXa), (Spectrum 30a). This could be explained by a substantial alteration of geometry in the interaction of (IXa) with $Pr(fod)_3$. With such an alteration the dependance of shift on angle could become important enough to change the sign of the shift[119] (Figure 16).



Spectrum No.29. 60 MHz ^{1}H N.m.r. spectra of dimethyl tetrabenzo[b,d,h,j]-[1,6]diazacyclododecine-4,5-dicarboxylate (IXa) (5.40 mg, 1.138 x 10^{-5} mole) in $CDCl_3$ (0.5 ml) containing various amounts of $Eu(fod)_3$: (a) 0.00 mg; (b) 5.90 mg.



Spectrum No.30. 60 MHz ^{1}H N.m.r. spectra of dimethyl tetrabenzo-[b,d,h,j][1,6]diazacyclododecine-4,5-dicarboxylate (IXa) (5.40 mg; 1.138 x 10^{-5} mole) in CDCl$_3$ (0.4 ml) containing various amounts of Pr(fod)$_3$: (a) 1.76 mg; (b) 40.95 mg.

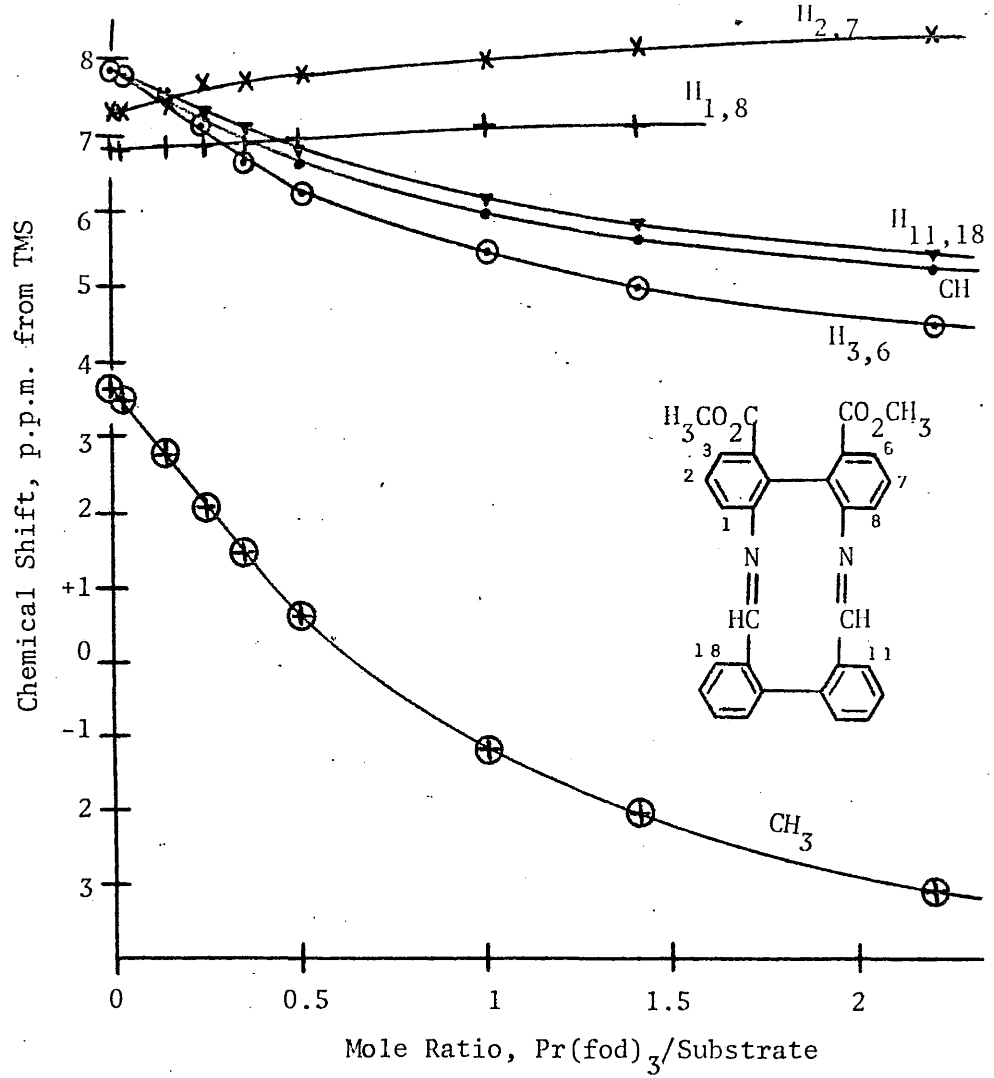


Figure No.16. Variation in the chemical shift of some of the protons in dimethyl tetrabenzo-[b,d,h,j][1,6]diazacyclododecine-4,5-dicarboxylate (IXa) upon addition of Pr(fod)$_3$ in CDCl$_3$.

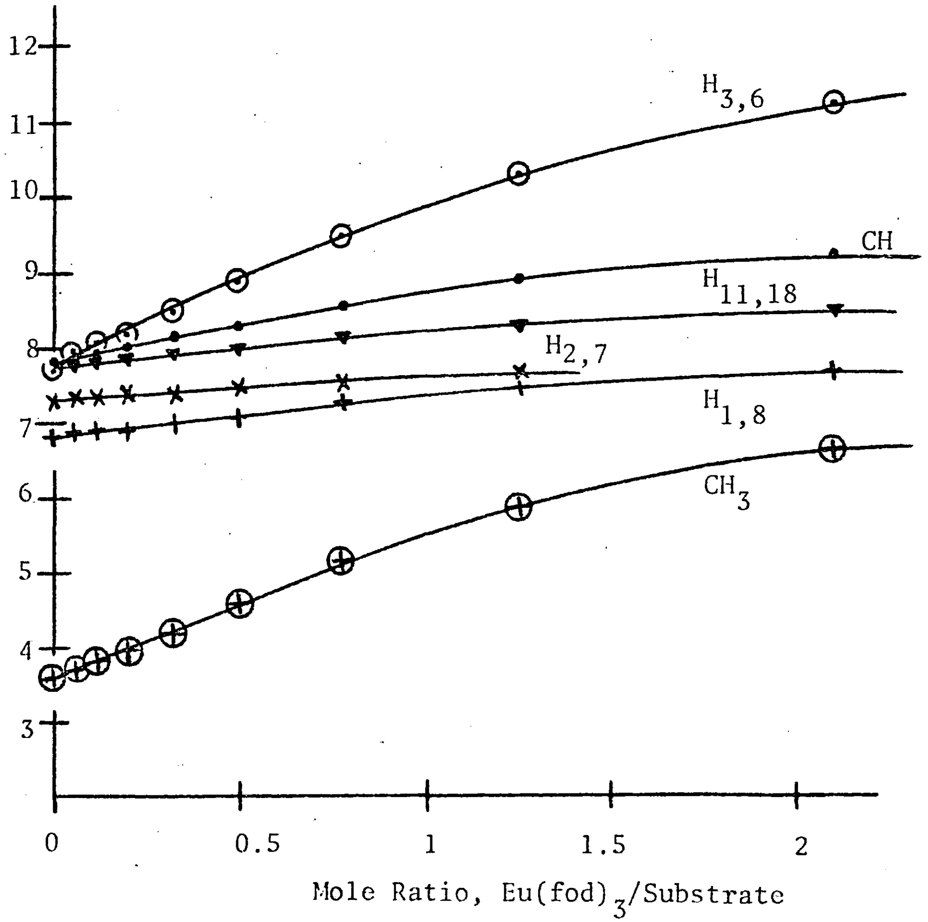


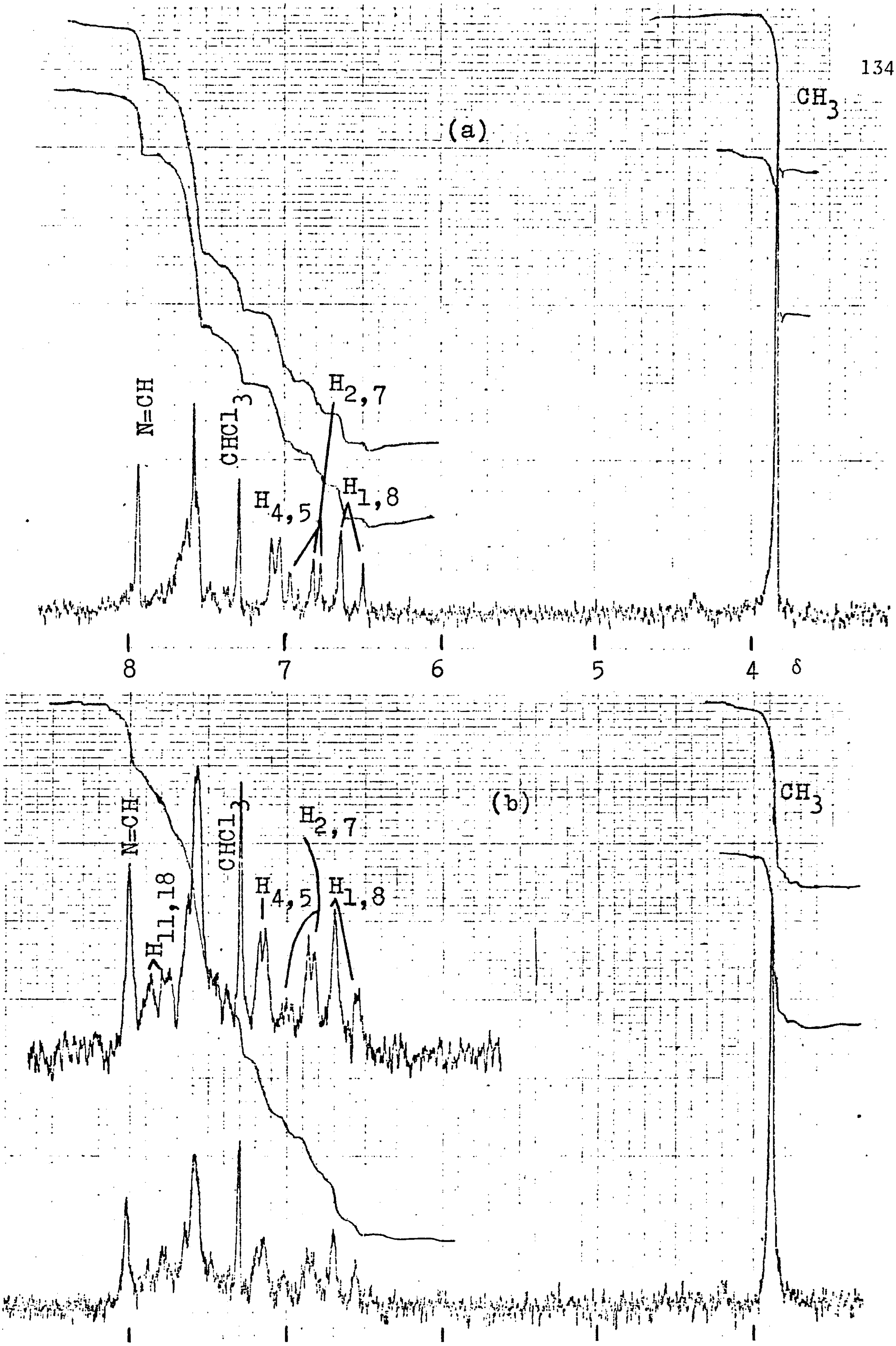
Figure No.17. Variation in the chemical shift of some of the protons in dimethyl tetrabenzo-[b,d,h,j][1,6]diazacyclododecine-4,5-dicarboxylate (IXa) upon addition of Eu(fod)$_3$ in CDCl$_3$.

Very weak association of compound (IXb) with $Eu(fod)_3$ and $Pr(fod)_3$ was observed. This behaviour can be justified by considering that the electron pairs of the oxygen atom are delocalized over the aromatic ring, not therefore being available for association with the shift reagent[120]. Upon addition of 10.46 mg (1.0081×10^{-5} mole) of $Eu(fod)_3$ to the solution of (IXb) only the aromatic proton $H_{11,18}$ was resolved (Spectrum 31b). On the other hand upon addition of 101.18 mg (9.857×10^{-5} mole) of $Pr(fod)_3$ to the solution of (IXb) [5.00 mg, 1.195×10^{-5} mole, (mole ratio of $Pr(fod)_3$/substrate = 8.25)], this large amount of $Pr(fod)_3$ failed to resolve any aromatic protons besides $H_{1,8}$; $H_{2,7}$; $H_{4,5}$ and $H_{11,18}$.

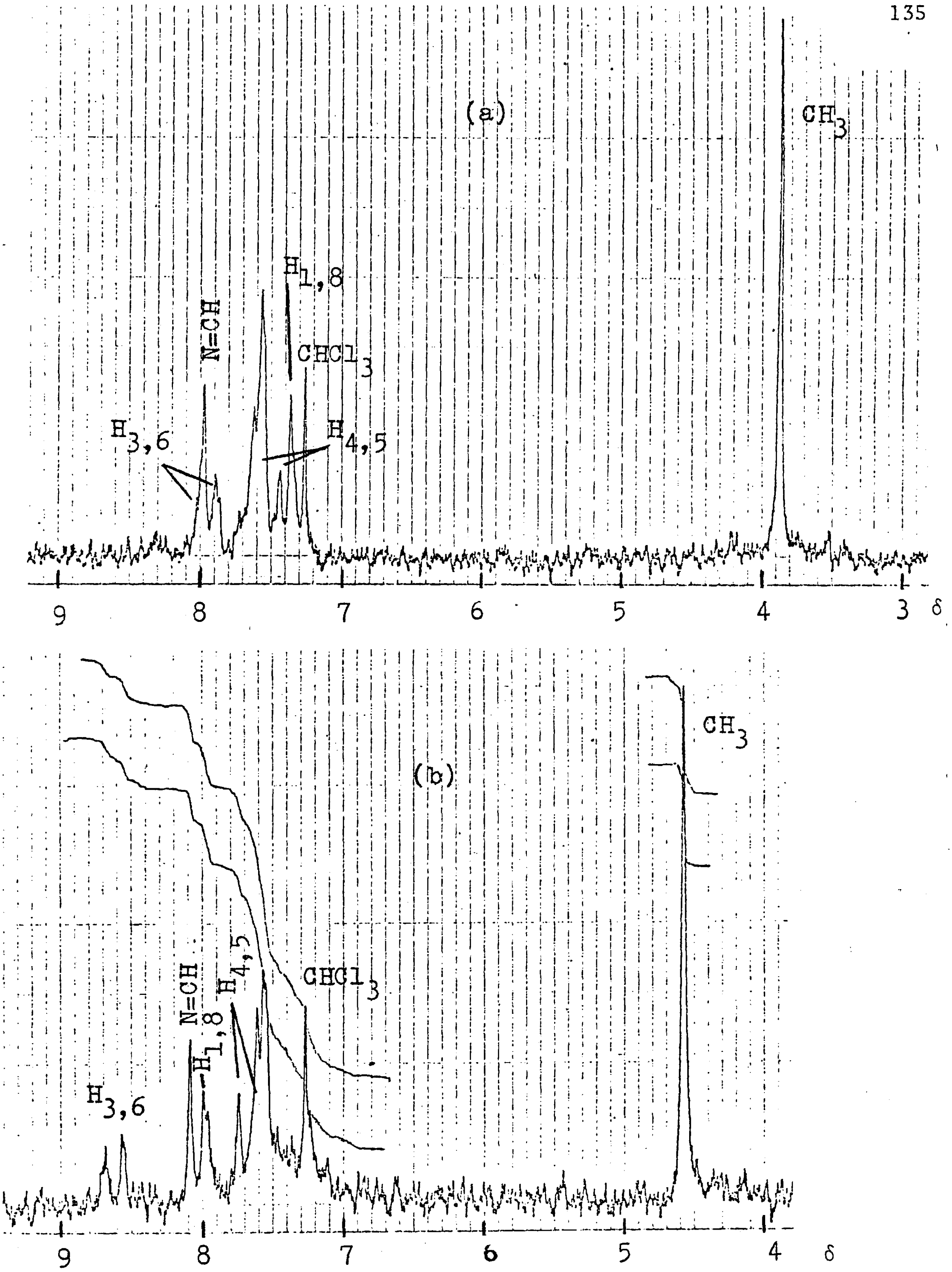
Spectra 32 and 33 illustrated the effect of adding successive quantities of $Eu(fod)_3$ and $Pr(fod)_3$ to the solution of compound (IXc) in $CDCl_3$, respectively. Four aromatic protons were resolved and confirmed the earlier assignments.

The assignments of the various protons resolved by lanthanide shift reagents were based on the analysis of their signal multiplicities and by making use of the fact that the pseudocontact shifts decrease with increasing spatial distance of the respective nuclei from the bonding site between shift reagent and substrate. Also the geometric factor, Θ, has been given considerable attention.

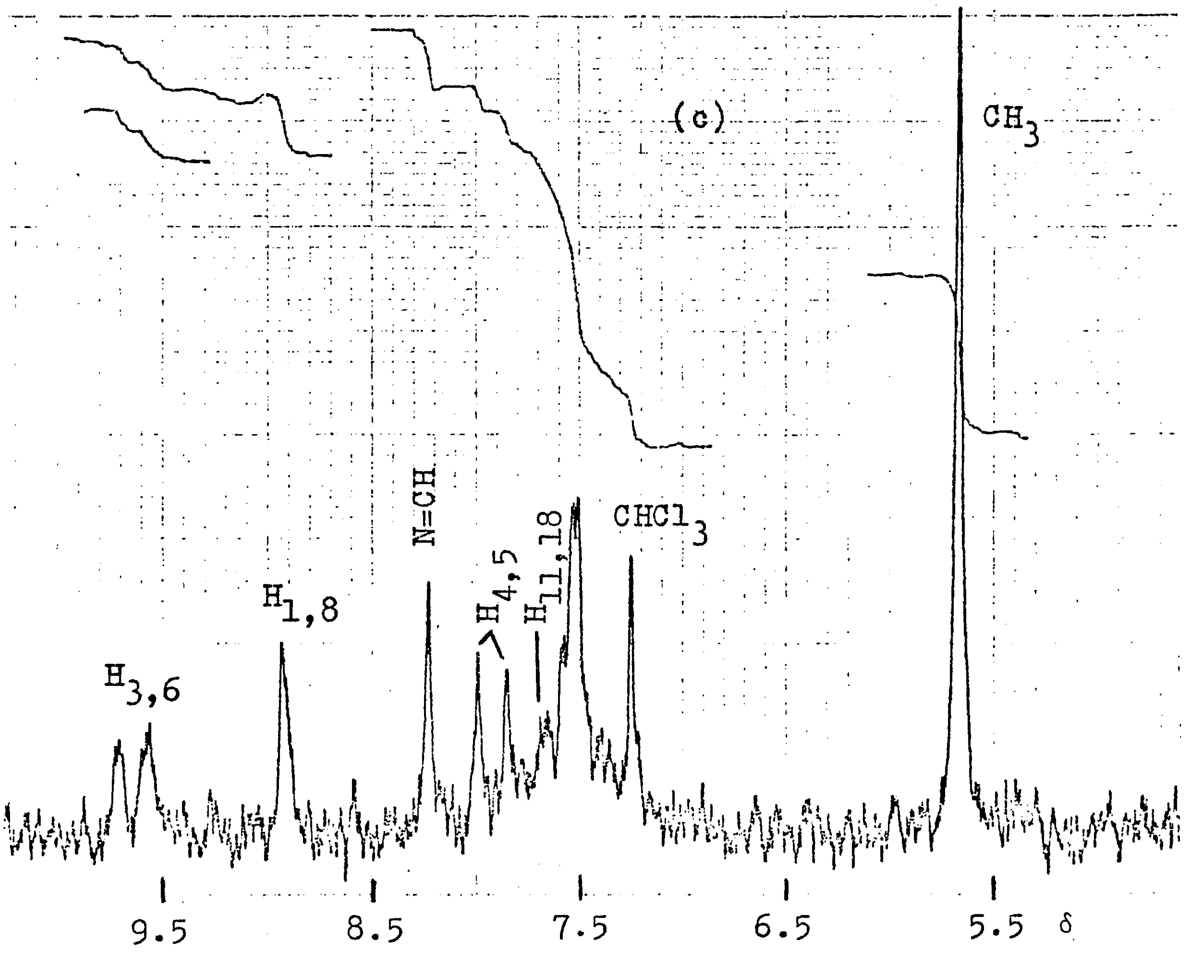
Figures 16, 17, 18 and 19 demonstrated an essentially linear dependence of the paramagnetic shifts on added $Eu(fod)_3$ and $Pr(fod)_3$ at lower concentration. The induced shift changes are proportional to the amount of shift reagent added to the solution up to a molar ratio of shift reagent to substrate of about 1:1, and then tend to a limiting value.

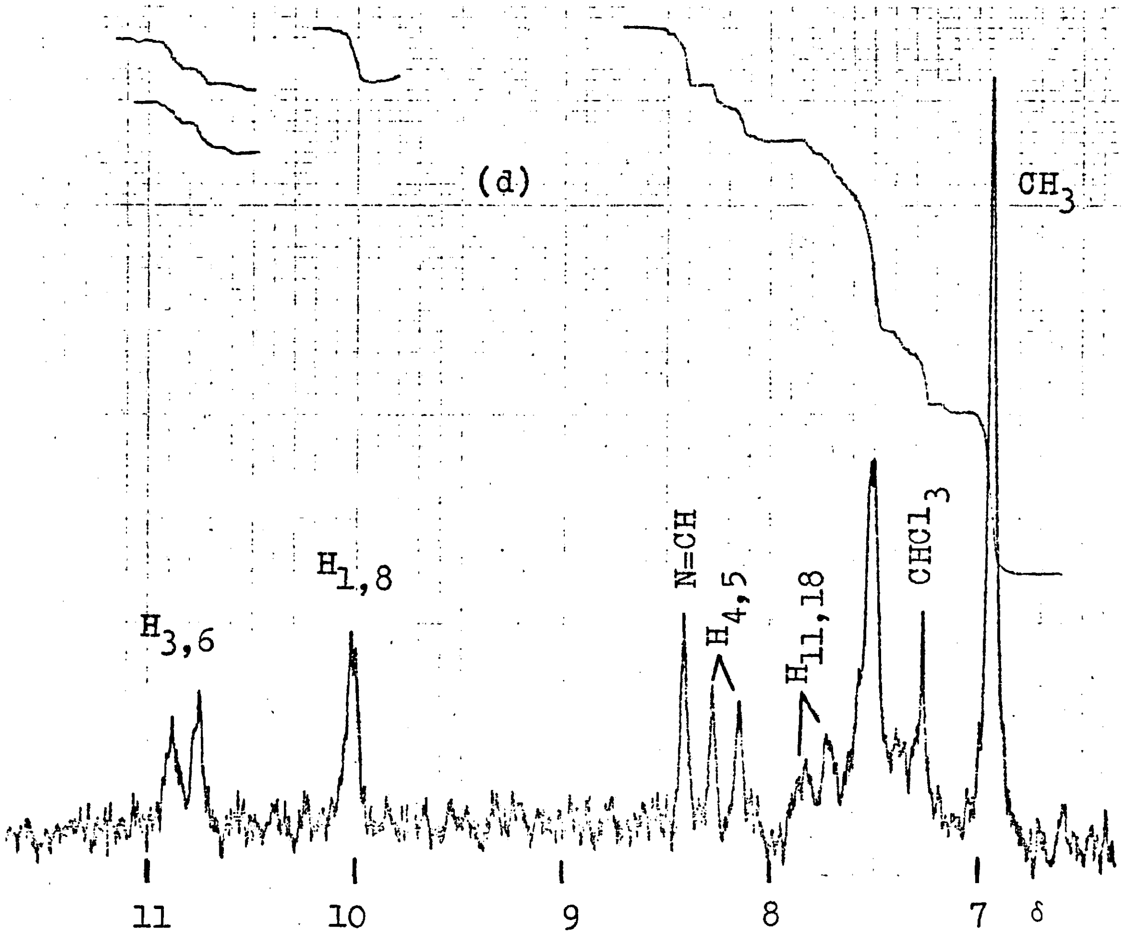


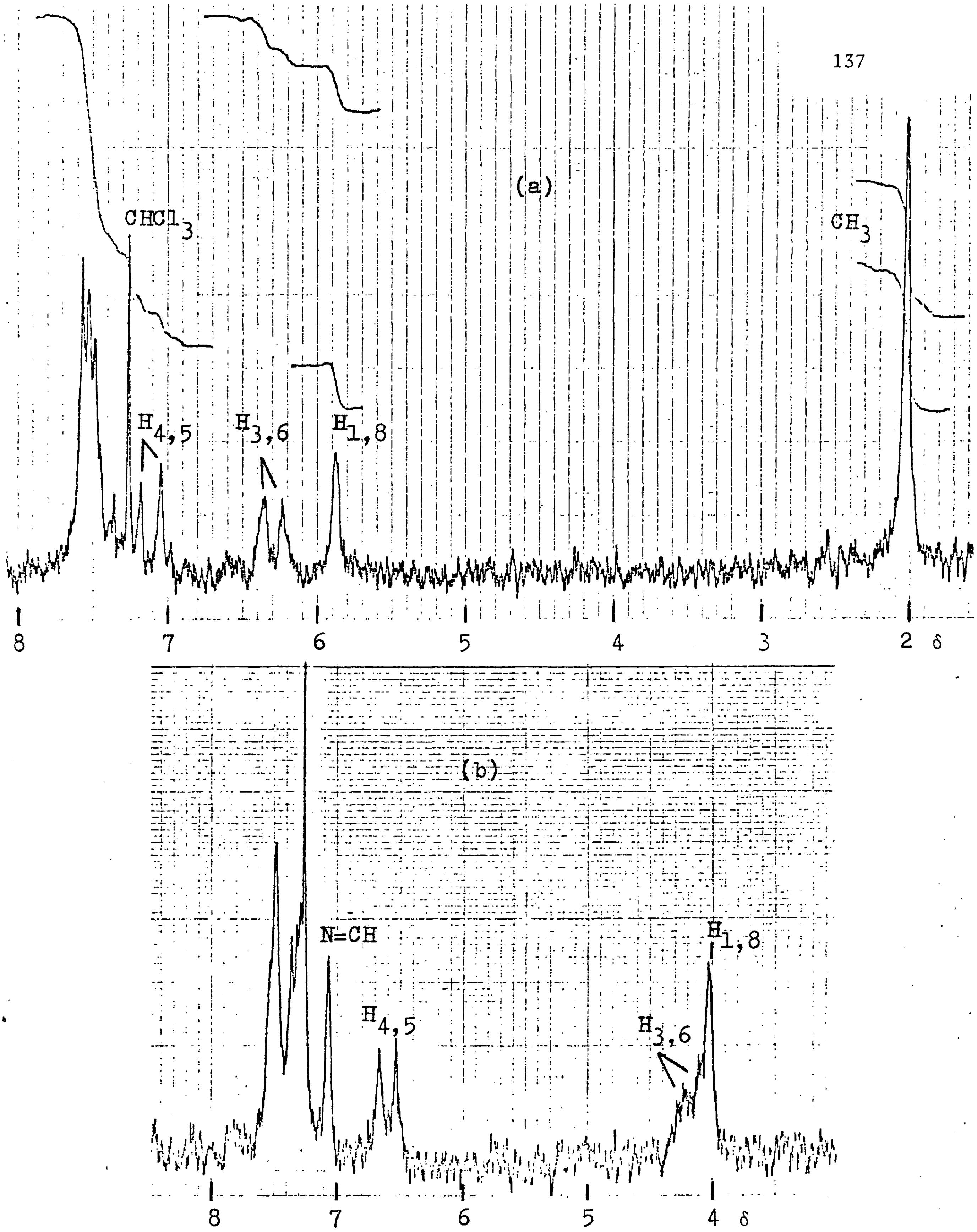
Spectrum No. 31. 60 MHz ^{1}H N.m.r. spectra of 3,6-dimethoxytetrabenzo-[b,d,h,j][1,6]diazacyclododecine (IXb) (5.30 mg; 1.266 x 10^{-5} mole) in CDCl$_3$ (0.6 ml) containing various amounts of Eu(fod)$_3$:
(a) 0.00 mg; (b) 10.46 mg.



Spectrum No.32. 60 MHz ^{1}H N.m.r. spectra of dimethyl tetrabenzo-[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate (IXc) (5.00 mg, 1.054 x 10^{-5} mole) in $CDCl_3$ (0.7 ml) containing various amounts of $Eu(fod)_3$: (a) 0.00 mg; (b) 5.87 mg; (c) 13.04 mg; (d) 22.83 mg.


(c)
CH$_3$
N=CH
H$_{1,8}$
H$_{3,6}$
H$_{4,5}$
H$_{11,18}$
CHCl$_3$
9.5
8.5
7.5
6.5
5.5
δ


(d)
CH$_3$
N=CH
H$_{1,8}$
H$_{3,6}$
H$_{4,5}$
H$_{11,18}$
CHCl$_3$
11
10
9
8
7
δ



Spectrum No.33. 60 MHz ^{1}H N.m.r.spectra of dimethyl tetrabenzo[b,d,h,j]-[1,6]diazacyclododecine-2,7-dicarboxylate (IXc) (5.00 mg, 1.054×10^{-5} mole) in $CDCl_3$ (0.7 ml) containing various amounts of $Pr(fod)_3$: (a) 7.88 mg; (b) 36.06 mg.

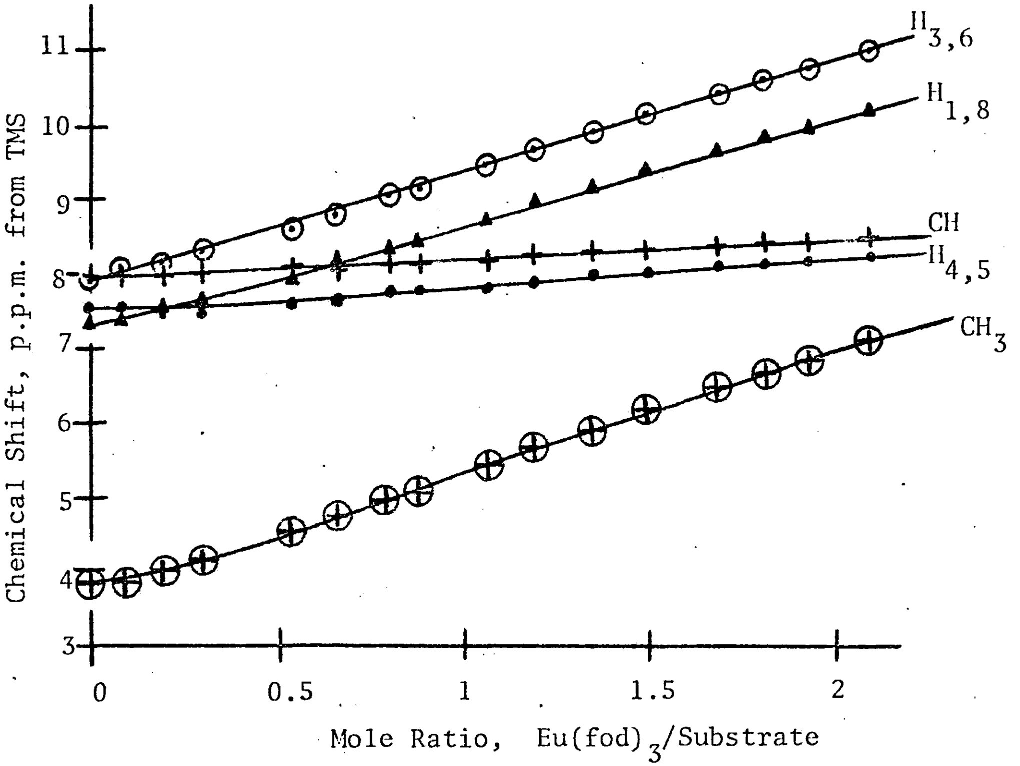
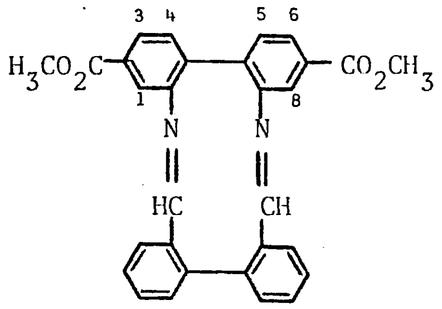


Figure No.18. Variation in the chemical shift of some of the protons in dimethyl tetrabenzo[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate (IXc) upon addition of Eu(fod)$_3$ in CDCl$_3$.



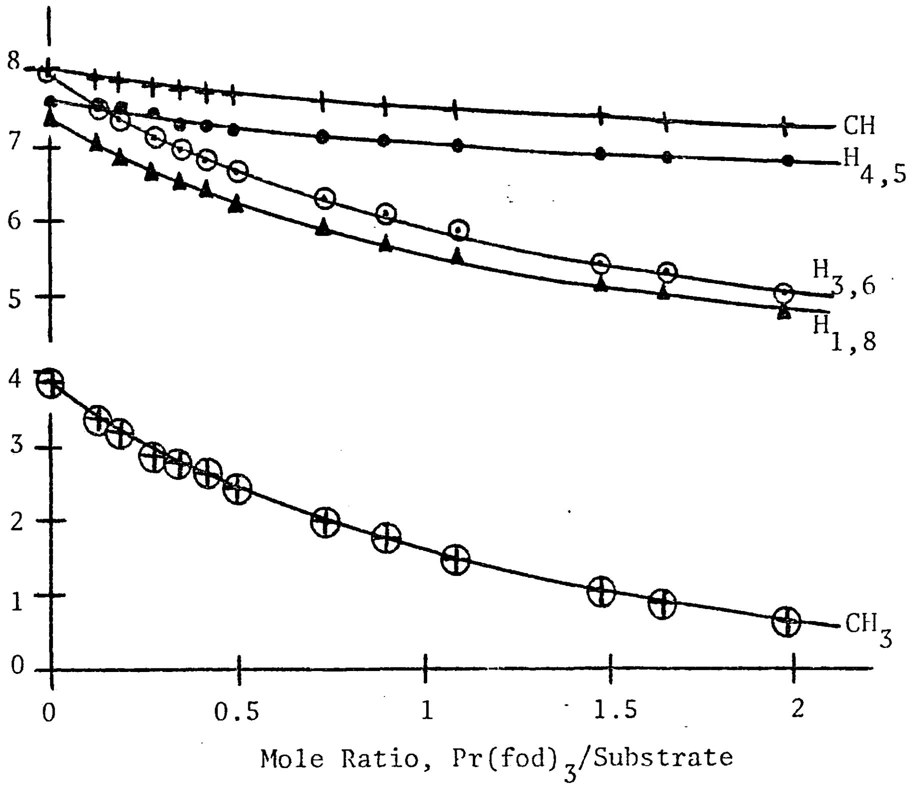
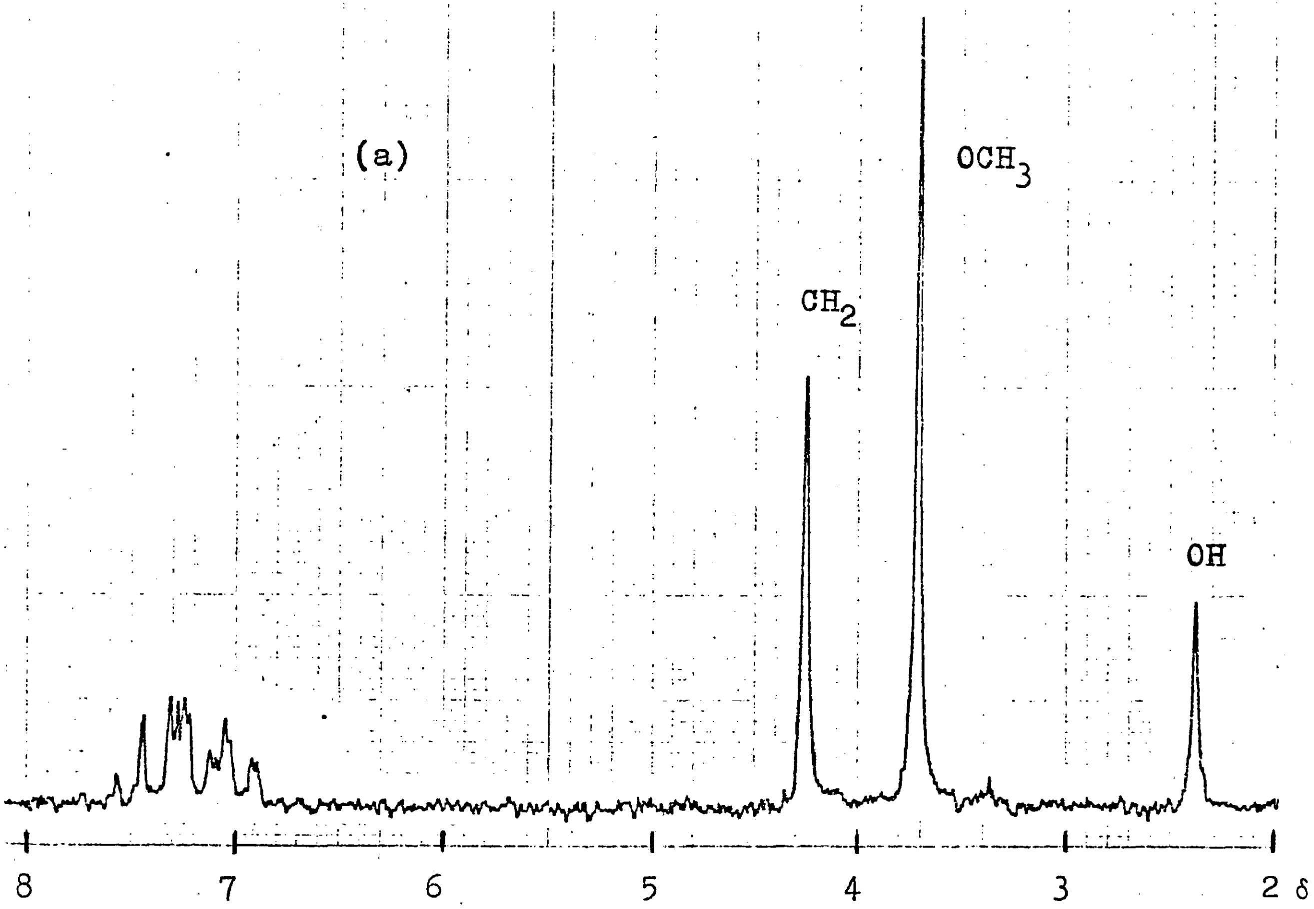
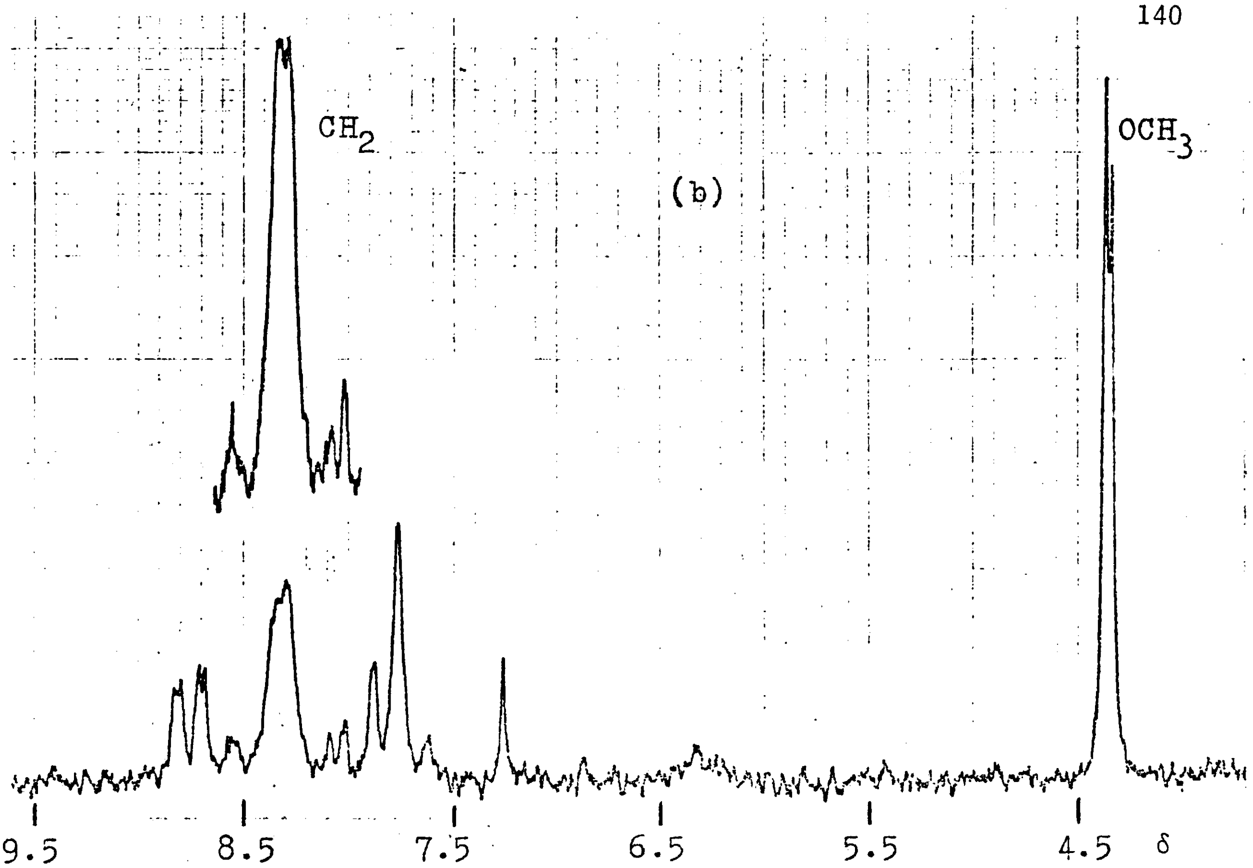
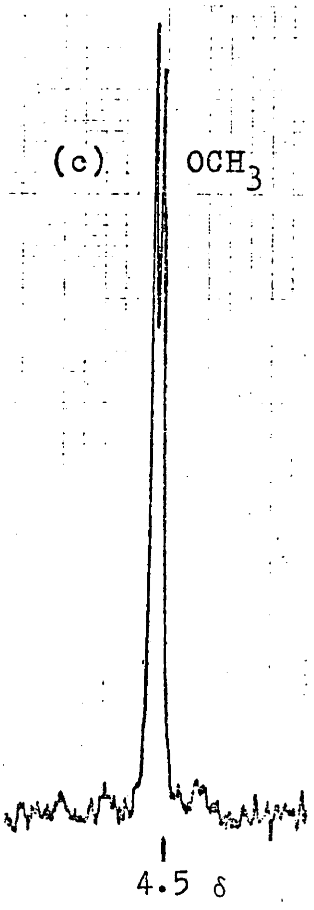


Figure No.19. Variation in the chemical shift of some of the protons in dimethyl tetrabenzo-[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate (IXc) upon addition of Pr(fod)$_3$ in CDCl$_3$.

Chiral lanthanide shift reagents tris[3-trifluoromethylhydroxymethylene-d-camphorato]europium (III), Eu(tfc)$_3$, and praseodymium (III), Pr(tfc)$_3$, have been used to determine whether or not the above compounds are chiral. 2,2'-bisHydroxymethyl-6,6'-dimethoxybiphenyl and dimethyl 6,6'-dimethoxybiphenyl-2,2'-dicarboxylate are used as two examples of the analysis. Upon addition of Eu(tfc)$_3$ to a solution of 2,2'-bishydroxymethyl-6,6'-dimethoxybiphenyl in CDCl$_3$, the CH$_2$ protons were shifted to lower field and appeared as an AB quartet having J_{AB} = 12 Hz (Spectrum 34b). This resolution of the methylene protons must result from their shift non-equivalence as diastereotopic protons. The methoxyl groups showed a non-equivalence of 0.04 p.p.m. (Spectrum 34c).

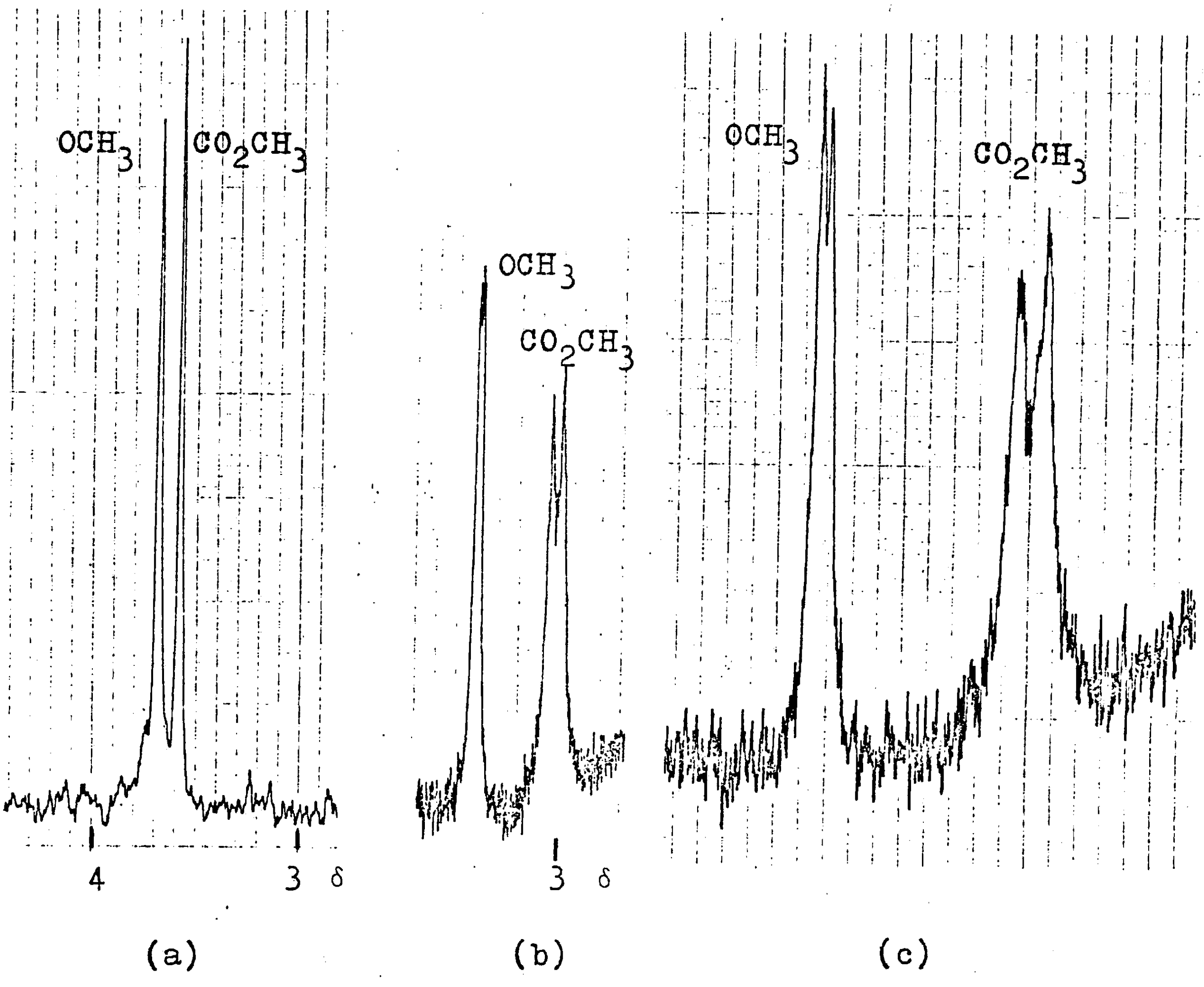






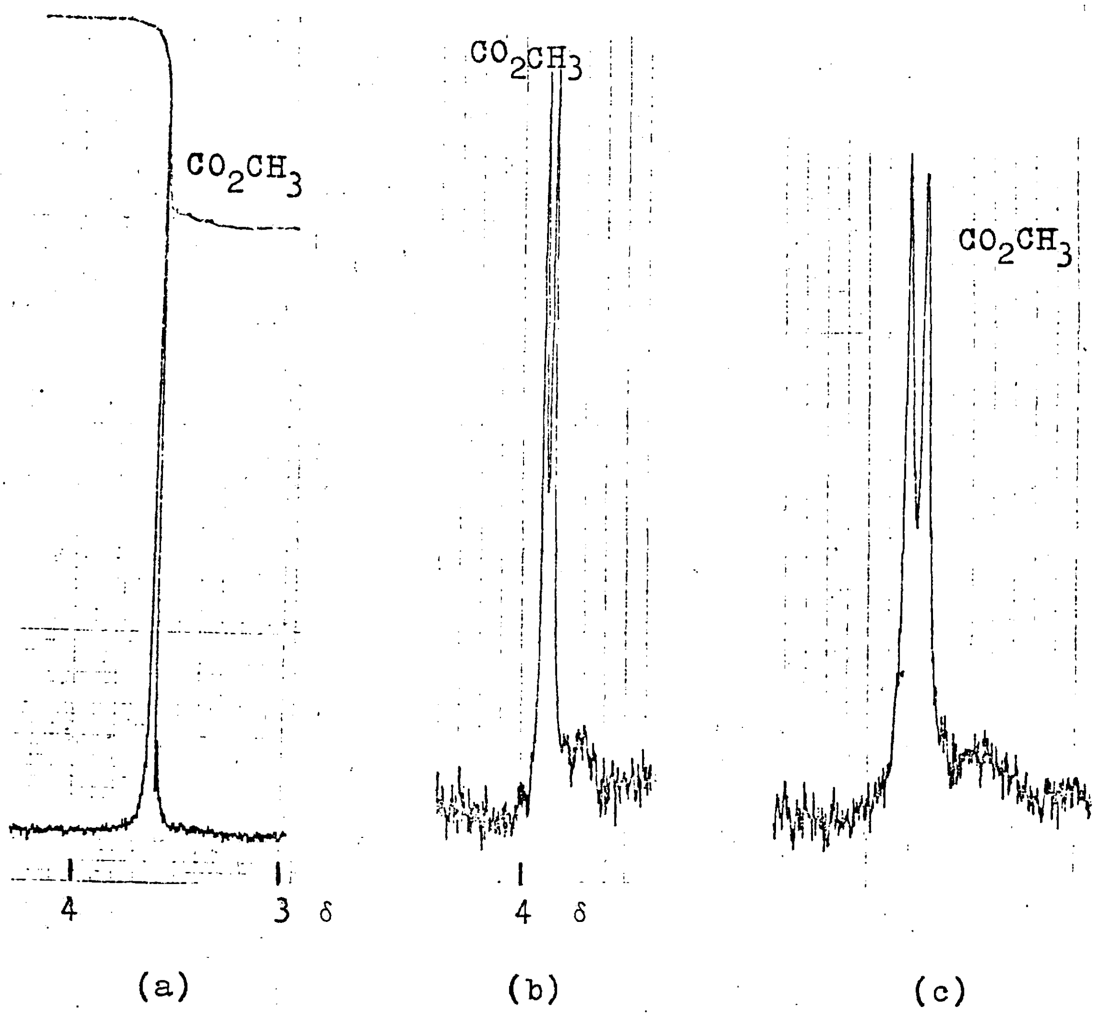
Spectrum No.34. 60 MHz ^{1}H N.m.r. spectra of 2,2'-bishydroxymethyl-6,6'-dimethoxybiphenyl (5.35 mg, 1.950 x 10^{-5} mole) in CDCl$_3$ (0.5 ml) containing various amounts of Eu(tfc)$_3$: (a) 0.00 mg; (b) 10.37 mg; (c) 18.75 mg "Resolved methoxyl resonances". Chemical shifts are referenced to TMS.

Addition of Pr(tfc)$_3$ to a solution of dimethyl 6,6'-dimethoxybiphenyl-2,2'-dicarboxylate in CDCl$_3$ also succeeded in effecting a resolution of the signals for the enantiotopic protons. The carbomethoxyl groups showed a non-equivalence of 0.05 p.p.m. while those of methoxyl groups showed a non-equivalence of 0.02 p.p.m. (Spectra 35b and 35c).



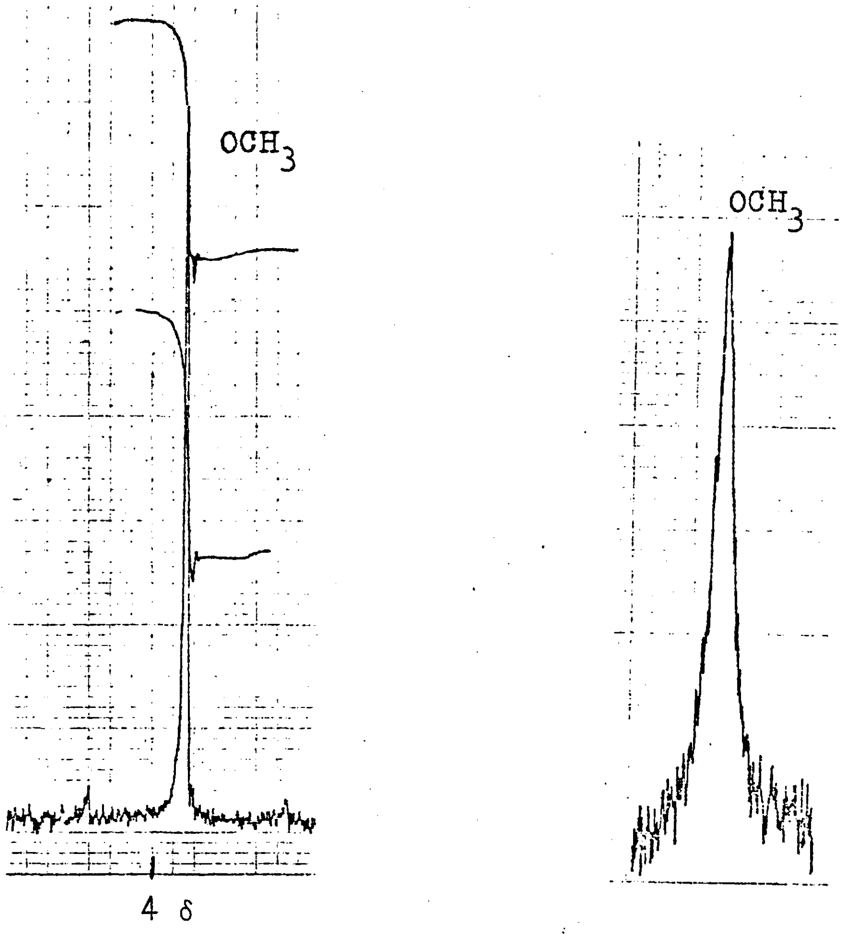
Spectrum No.35. Resolved methoxyl and carbomethoxyl resonances are observed (60 MHz) for the enantiomers of dimethyl 6,6'-dimethoxybiphenyl-2,2'-dicarboxylate (3.08 mg, 0.932 x 10^{-5} mole) in CDCl$_3$ (0.6 ml) containing various amounts of Pr(tfc)$_3$: (a) 0.00 mg; (b) 95.87 mg; (c) 114.82 mg "Expanded Spectrum".

Effects of $Eu(tfc)_3$ on the ^1H N.m.r. spectrum of compound (IXa) are illustrated in Spectra 36a, 36b and 36c. The enantiotopic carbomethoxyl groups showed a non-equivalence of 0.04 p.p.m.



Spectrum No.36. Resolved carbomethoxyl resonances are observed (60 MHz) for the enantiomers of dimethyl tetrabenzo[b,d,h,j][1,6]-diazacyclododecine-4,5-dicarboxylate (IXa) (5.60 mg, 1,180 x 10^{-5} mole) in $CDCl_3$ (0.4 ml) containing various amounts of $Eu(tfc)_3$: (a) 0.00 mg; (b) 105.42 mg; (c) 105.42 mg "Expanded Spectrum".

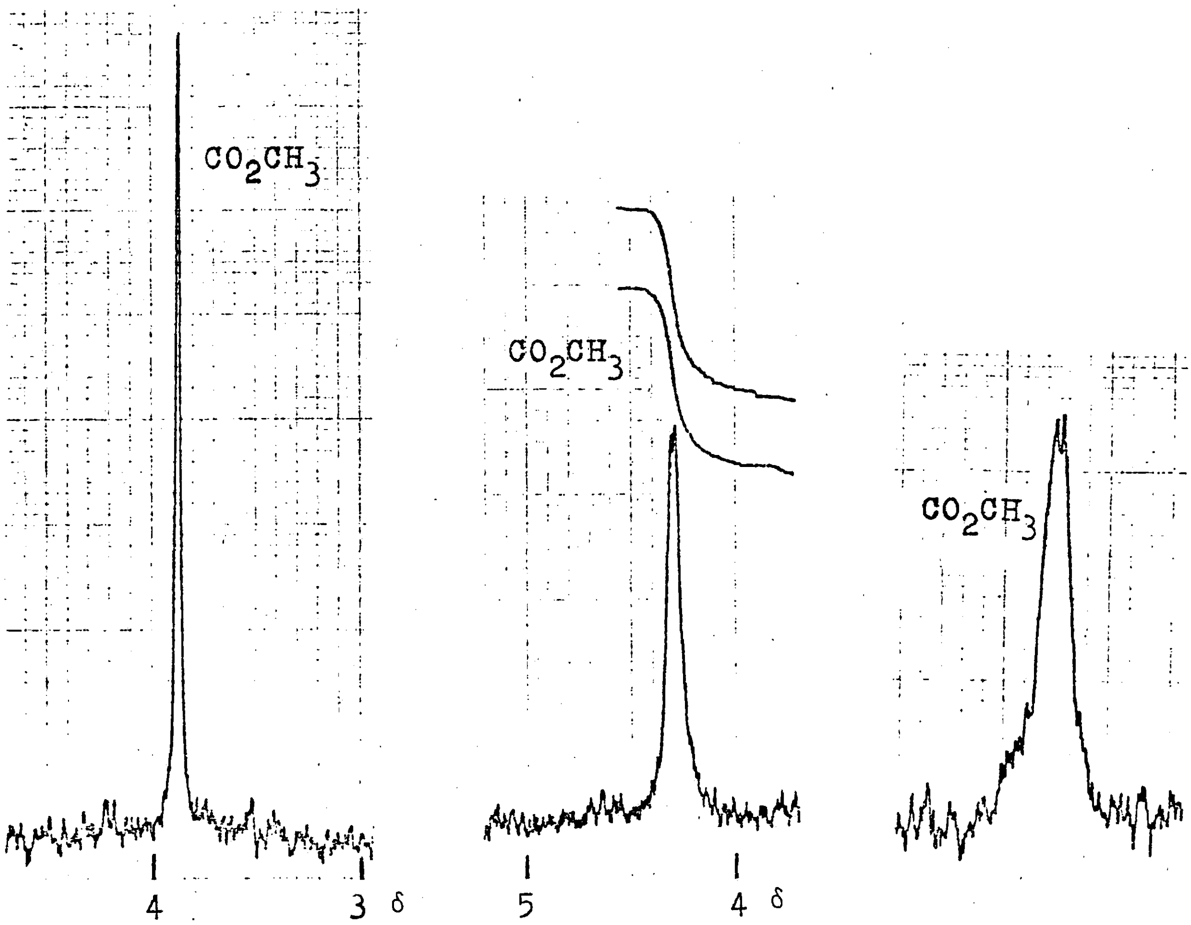
The enantiotopic methoxyl groups in compound (IXb) showed very poor shift non-equivalence (Spectra 37a and 37b) upon addition of Eu(tfc)$_3$. This is probably due to the weak association of Eu(tfc)$_3$ with the substrate.



(a) (b)

Spectrum No.37. Resolved methoxyl resonances are observed (60 MHz) for the enantiomers of 3,6-dimethoxytetrabenzo[b,d,h,j][1,6]-diazacyclododecine (IXb) (5.28 mg, 1.262 x 10^{-5} mole) in CDCl$_3$ (0.5 ml) containing various amounts of Eu(tfc)$_3$: (a) 0.00 mg; (b) 99.87 mg "Expanded Spectrum".

Non-equivalence of carbomethoxyl groups in compound (IXc) is also observed upon addition of Eu(tfc)$_3$(Spectra 38a, 38b and 38c). The magnitude of non-equivalence is 0.02 p.p.m.



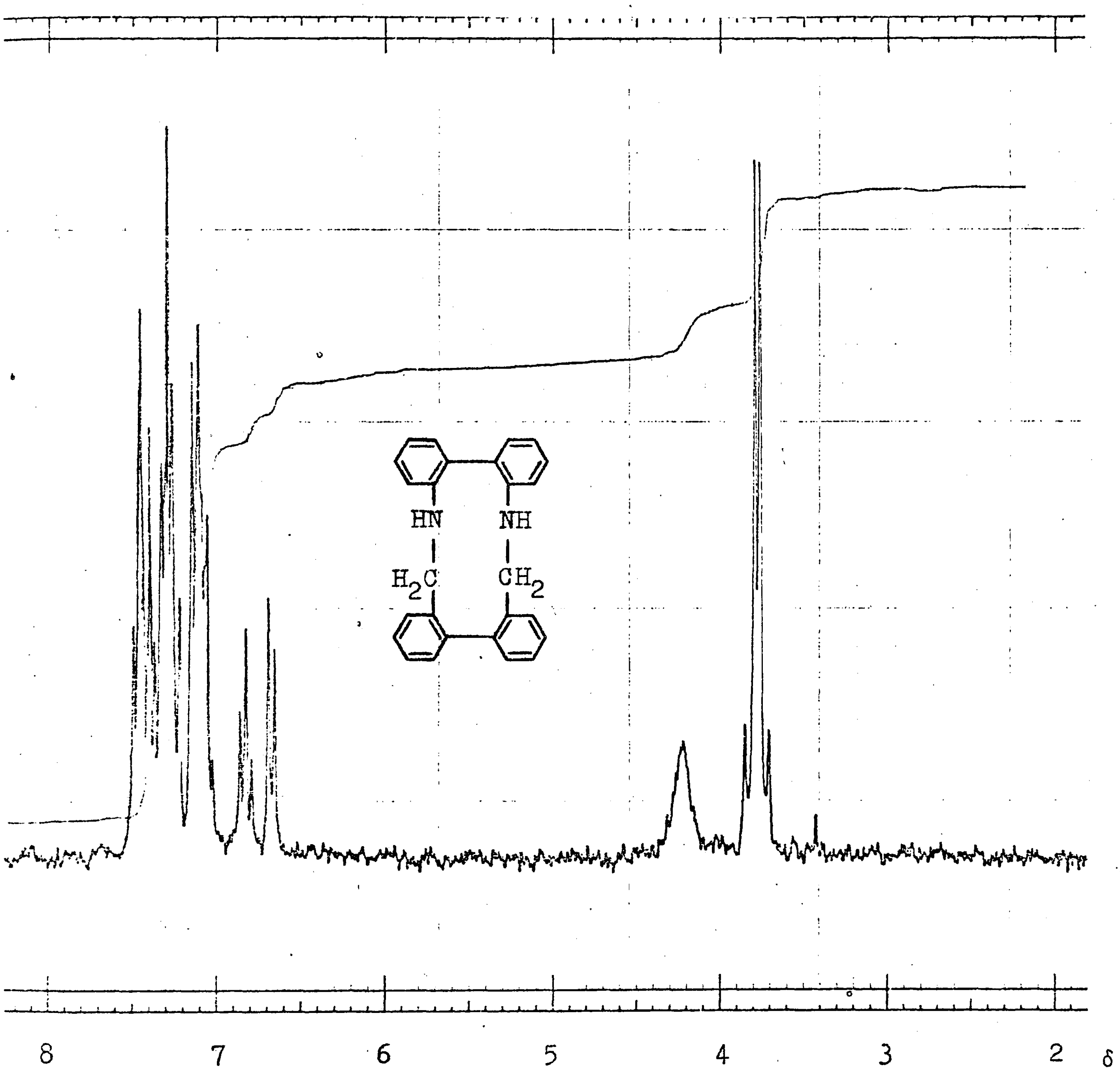
(a) (b) (c)

Spectrum No.38. Resolved carbomethoxyl resonances are observed (60 MHz) for the enantiomers of dimethyl tetrabenzo[b,d,h,j][1,6]-diazacyclododecine-2,7-dicarboxylate (IXc) (6.60 mg, 1.391 x 10^{-5} mole) in $CDCl_3$ (0.7 ml) containing various amounts of Eu(tfc)$_3$: (a) 0.00 mg; (b) 51.46 mg; (c) 69.50 mg. Expanded spectrum of (IXc)(4.20 mg; 0.885 x 10^{-5} mole) in $CDCl_3$ (0.7 ml).

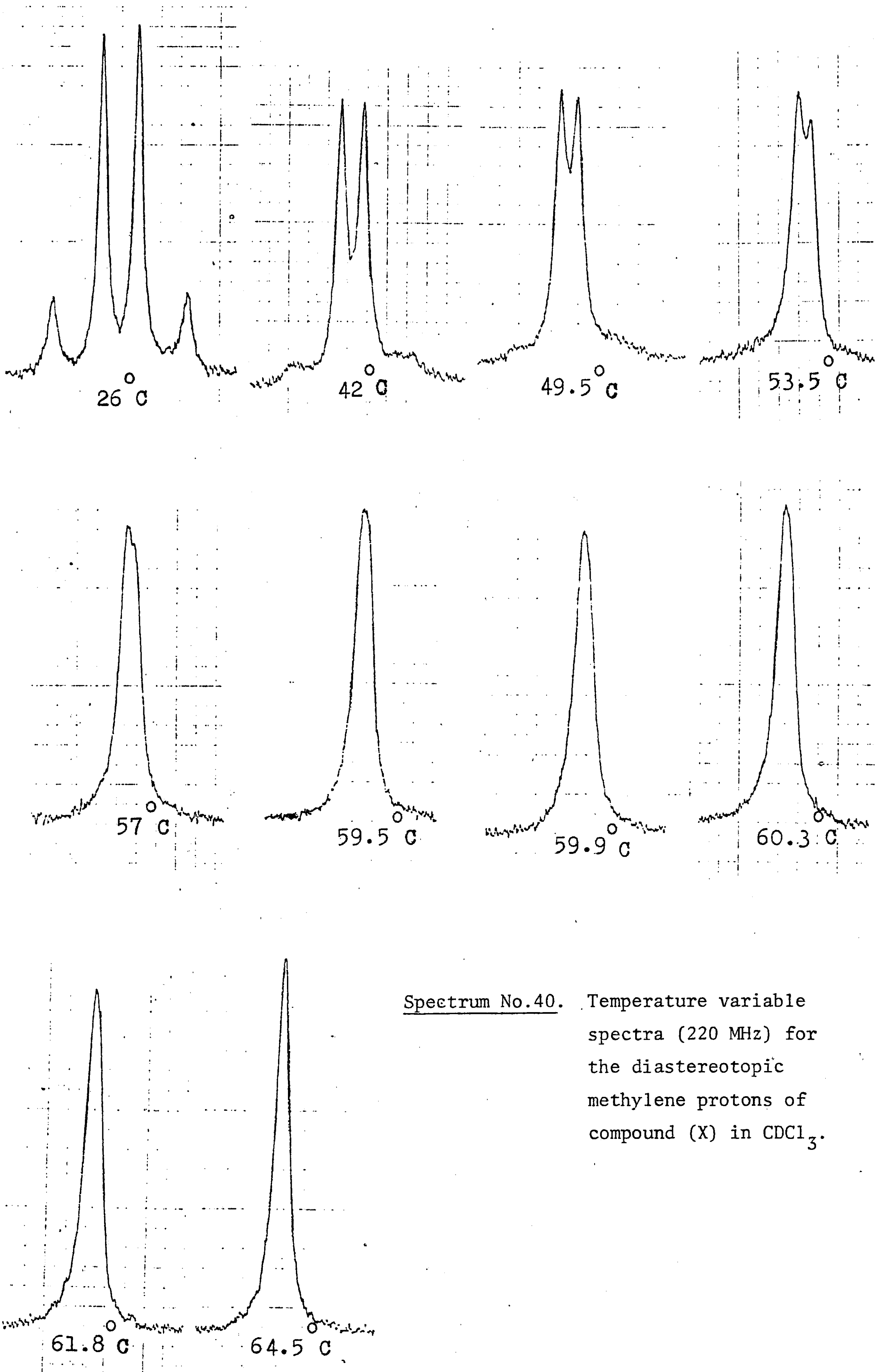
Non-equivalence was not observed among aromatic and aldimine protons in compounds (IXa), (IXb) and (IXc). Also magnitudes of non-equivalence among the above discussed compounds were found to be small, but proved that these compounds are chiral.

2.4.2. ^{1}H N.m.r. spectra of 9,10,19,20-tetrahydrotetrabenzo[*b*,*d*,*h*,*j*][1,6]diazacyclododecine and its derivatives with substituents in *ortho*-, *meta*- or *para*-positions of the nitrogen biphenyl system.

^{1}H N.m.r. spectrum at 220 MHz in $CDCl_3$ of (X) at 27° is shown in Spectrum 39 which displays a broad singlet at 4.22 p.p.m. (2 NH protons which exchange with D_2O) and a quartet at 3.78 p.p.m. (4 H, methylene protons) as well as a complex multiplet at 6.66 – 7.49 p.p.m. due to the aromatic protons. Each pair of methylene protons is diastereotopic. At low temperatures they appear as an AB quartet (J_{AB} = 12.25 Hz), becoming a doublet between 49.5 and 57° and coalescing to a singlet between 59.5 and 64.5° (Spectrum 40), when conformational inversion of the twisted biphenyl systems becomes rapid. At 60 MHz the quartet is no longer resolved.

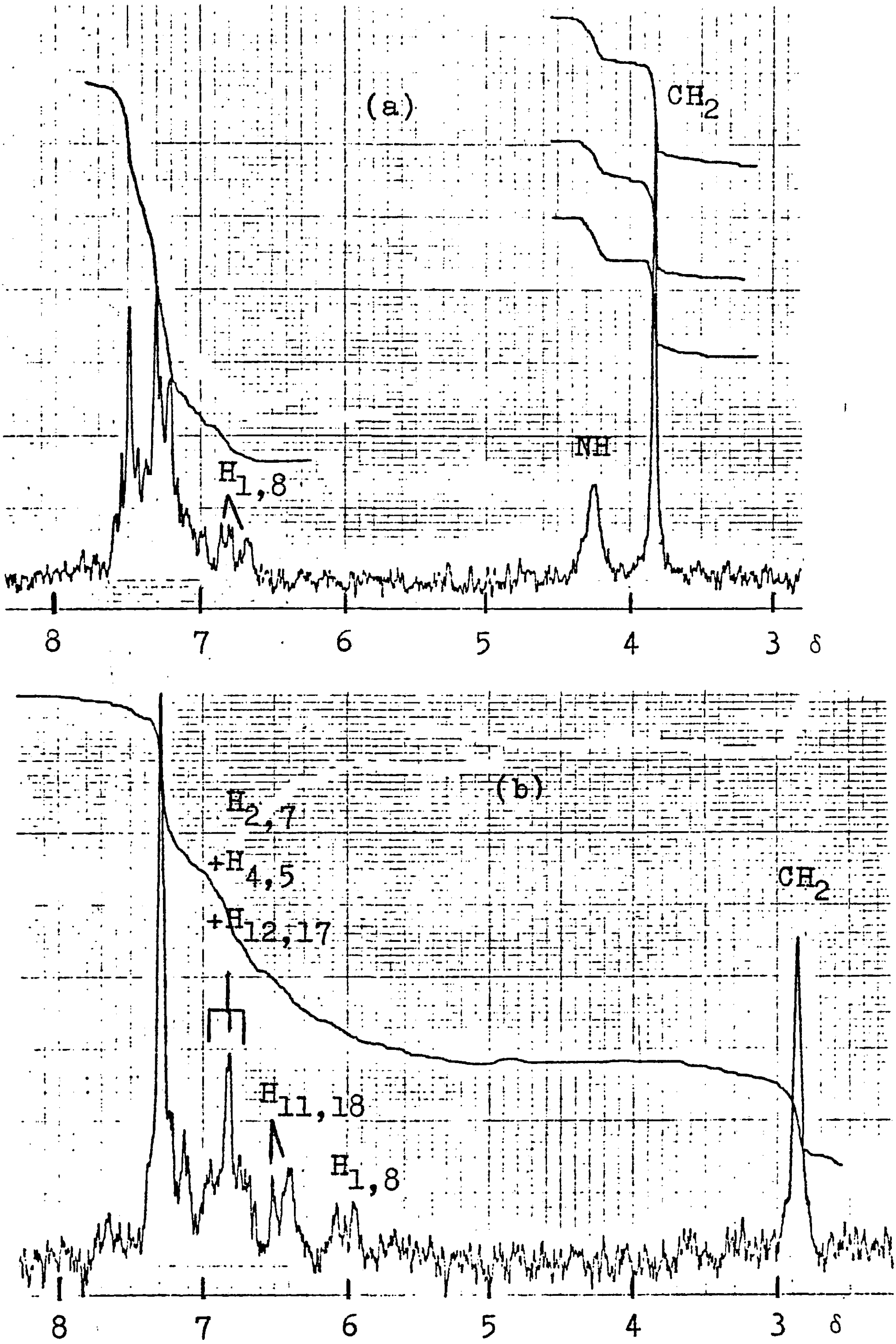


Spectrum No.39. ^{1}H N.m.r. spectrum (220 MHz) of 9,10,19,20-tetrahydrotetrabenzo[*b*,*d*,*h*,*j*][1,6]diazacyclododecine (X) in $CDCl_3$ at 27°C.



Spectrum No.40. Temperature variable spectra (220 MHz) for the diastereotopic methylene protons of compound (X) in $CDCl_3$.

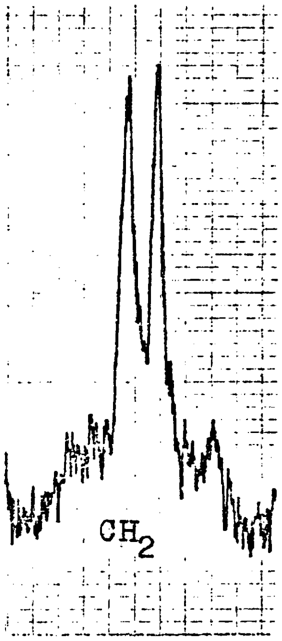
The addition of successive quantities of Pr(fod)$_3$ to a solution of (X) in CDCl$_3$ separates only H$_{1,8}$ and H$_{11,18}$ (Spectrum 41). No more peaks could be separated even when a total quantity of 172.64 mg of Pr(fod)$_3$ was added.



Spectrum No.41. 60 MHz ^{1}H N.m.r. spectra of 9,10,19,20-tetrahydrotetrabenzo-[b,d,h,j][1,6]diazacyclododecine (X) (5.40 mg, 1.490 x 10^{-5} mole) in CDCl$_3$ (0.7 ml) containing various amounts of Pr(fod)$_3$: (a) 0.00 mg; (b) 50.14 mg.

On the other hand, successive addition of Eu(fod)$_3$ to (X) in CDCl$_3$ shift $H_{1,8}$ and some of the other peaks to lower field, but it is not possible to assign any of them due to their overlapping with the rest of the aromatic protons. It is worth noting here that on addition 55.21 mg of Eu(fod)$_3$ to 5.97 mg of (X) in CDCl$_3$ (0.7 ml), the CH$_2$ protons appear as an AB quartet having J_{AB} = 12.2 Hz (Spectrum 42).

<u>Spectrum No.42.</u> 60 MHz ^{1}H N.m.r. spectrum of the methylene proton absorption of 5.97 mg of (X) in CDCl$_3$ (0.7 ml) in the presence of 55.21 mg of Eu(fod)$_3$.



Figures 20 and 21 show schematic representations of the quantitative study of the association of (X) with Pr(fod)$_3$ and Eu(fod)$_3$, respectively. Figure 21 shows that the stoichiometry for the adduct formation is 2:1 for the molar ratio of Eu(fod)$_3$/Compound (X).

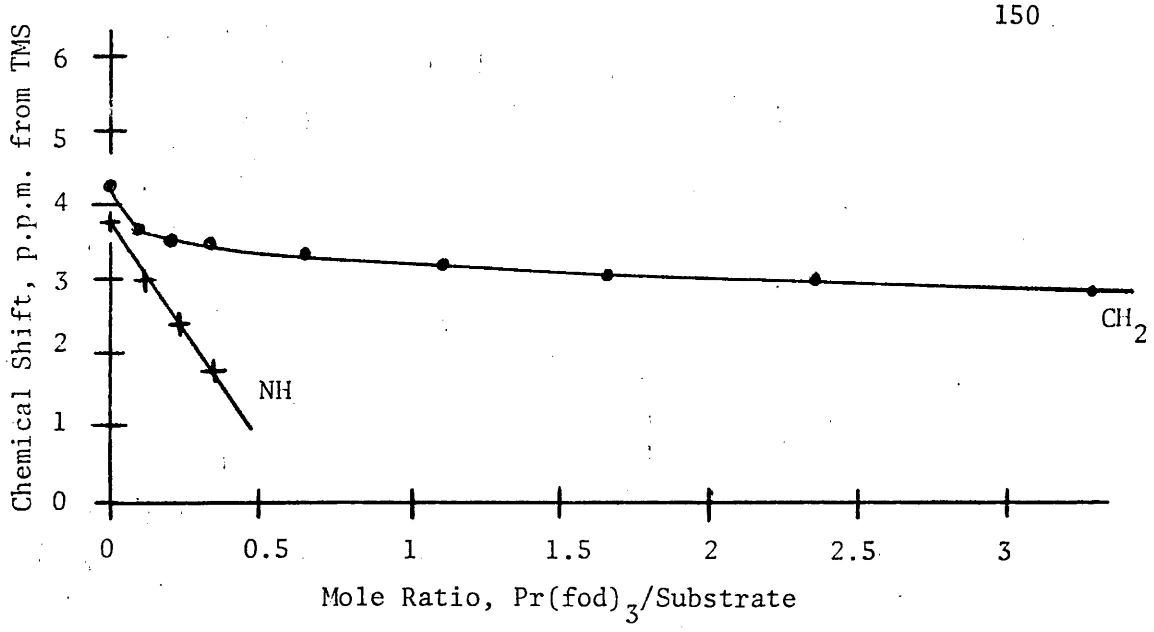


Figure No.20. Variation in the chemical shift of some of the protons in (X) upon addition of $Pr(fod)_3$ in $CDCl_3$.

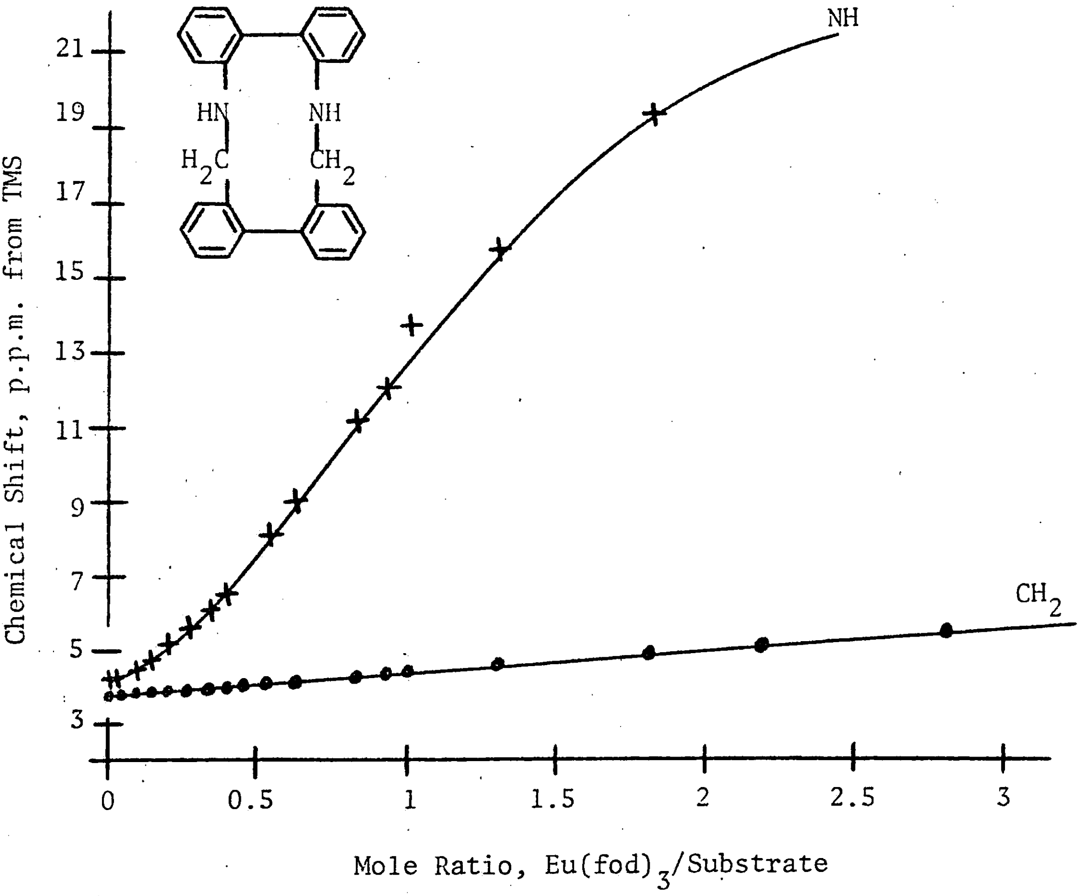
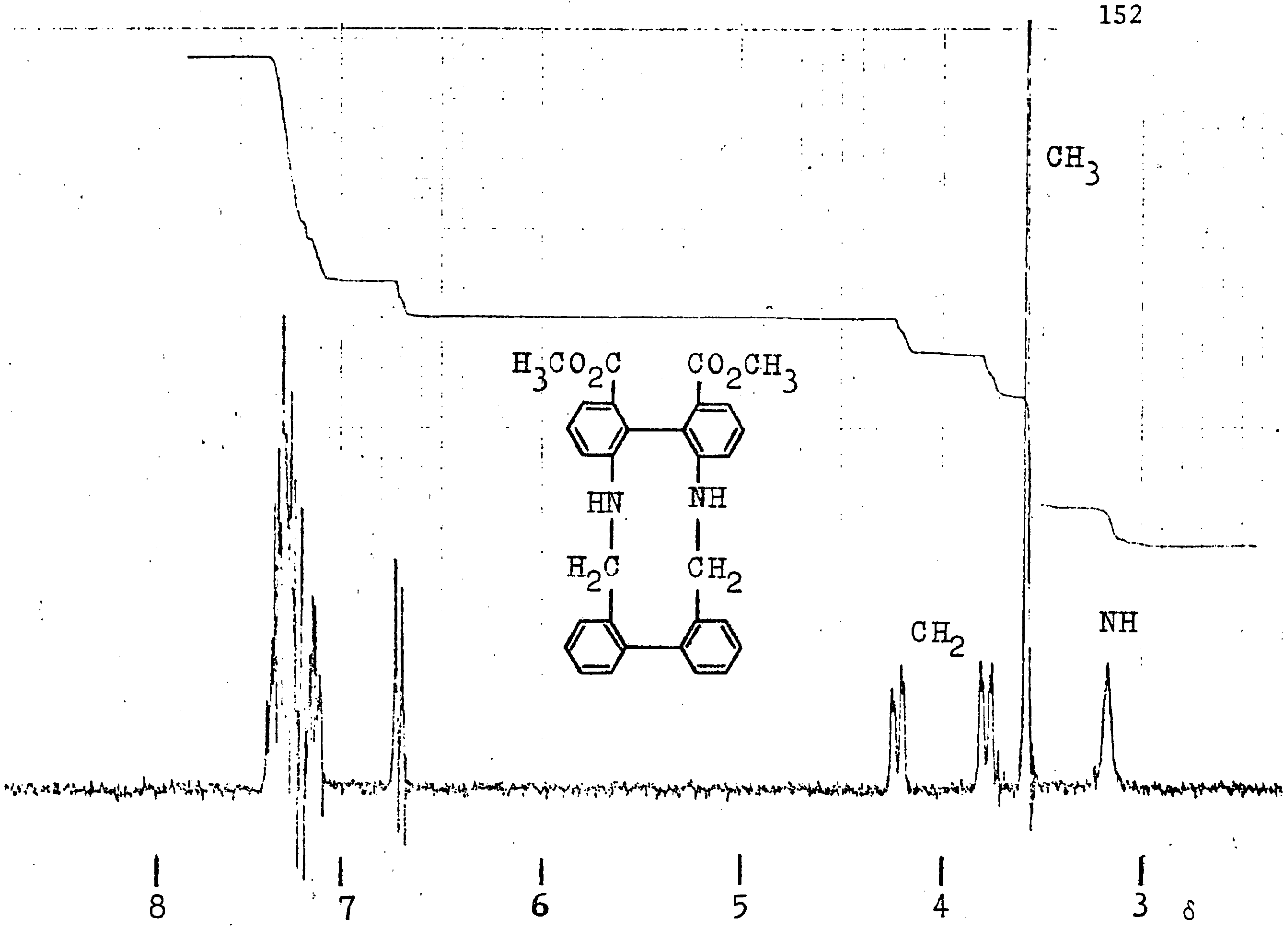


Figure No.21. Variation in the chemical shift of some of the protons in (X) upon addition of $Eu(fod)_3$ in $CDCl_3$.

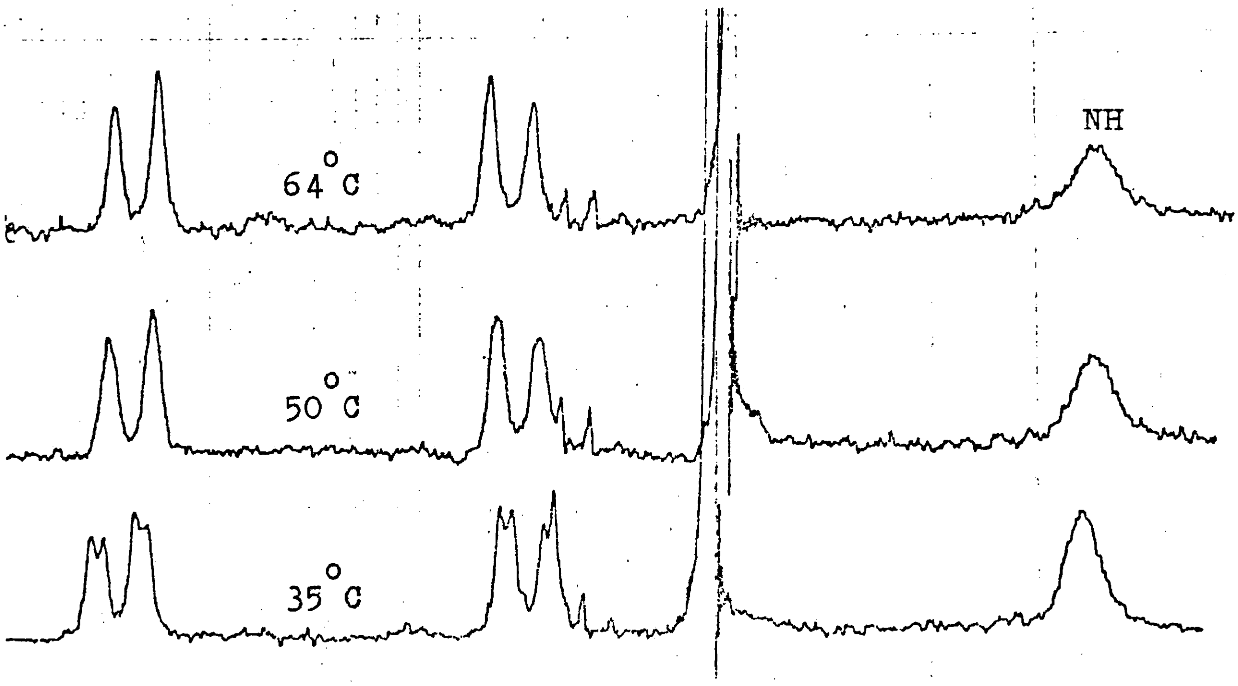
Spectrum 43 shows the 220 MHz ^1H N.m.r. spectrum of (Xa) in $CDCl_3$ which consists of a broad singlet at 3.17 p.p.m. (2 NH protons which exchange with D_2O), a sharp singlet at 3.57 (2 CH_3), an octet at 4.00 p.p.m. (4 H, methylene protons), a doublet at 6.72 p.p.m. (thought to arise from the two ring protons ortho to nitrogen) and a complex multiplet at 7.11 - 7.37 p.p.m. due to the aromatic protons. Each pair of methylene protons is diastereotopic. At 35° these protons appear as a double AB quartet and become a single quartet between 50 - 64° (Spectrum 44). Presumably the favourable conformation at lower temperatures has the CH_2 group in different environments.

The effect on the resonance positions of the different protons in (Xa) upon addition of increasing amounts of $Pr(fod)_3$ is shown in Spectrum 45. In the absence of $Pr(fod)_3$ (Spectrum 45a), only NH, CH_3, CH_2, $H_{1,8}$ and $H_{3,6}$ protons are readily assignable. Increasing the amount of $Pr(fod)_3$, however, increasingly resolves the spectrum of (Xa) such that, at a molar ratio of $Pr(fod)_3$ to (Xa) of 0.985, the spectrum of (Xa) becomes first order (Spectrum 45f). Most obvious of these changes is the shift of $H_{2,7}$ to the lower field regions of the spectrum. A possible explanation for the downfield shift for $H_{2,7}$ would be a substantial alteration of geometry in the interaction of (Xa) with $Pr(fod)_3$. With such an alteration the dependence of shift on angle could become important enough to change the sign of the shift.

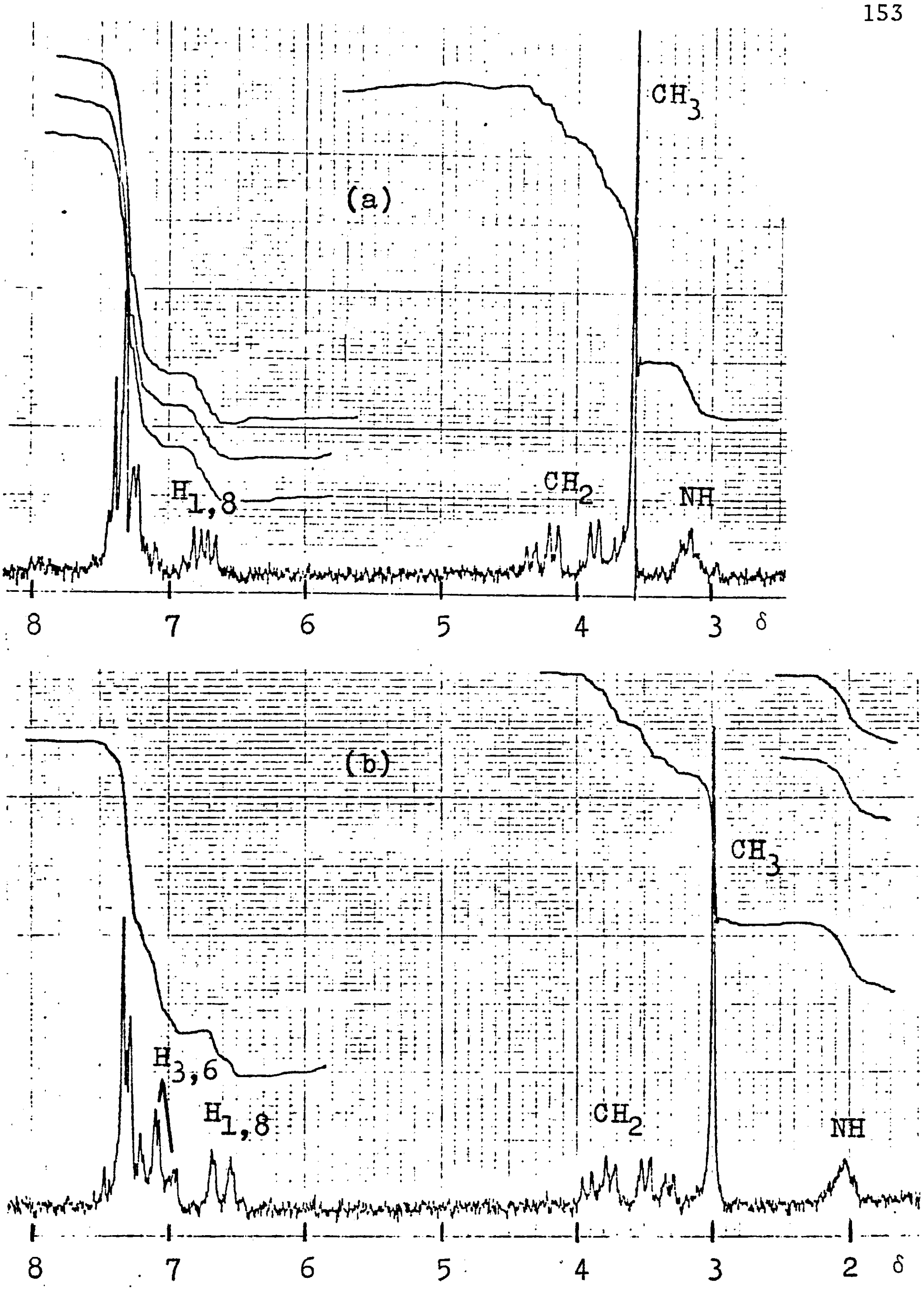
Proton assignments shown were based on observed splitting patterns and confirmed by distance-shift relationships.



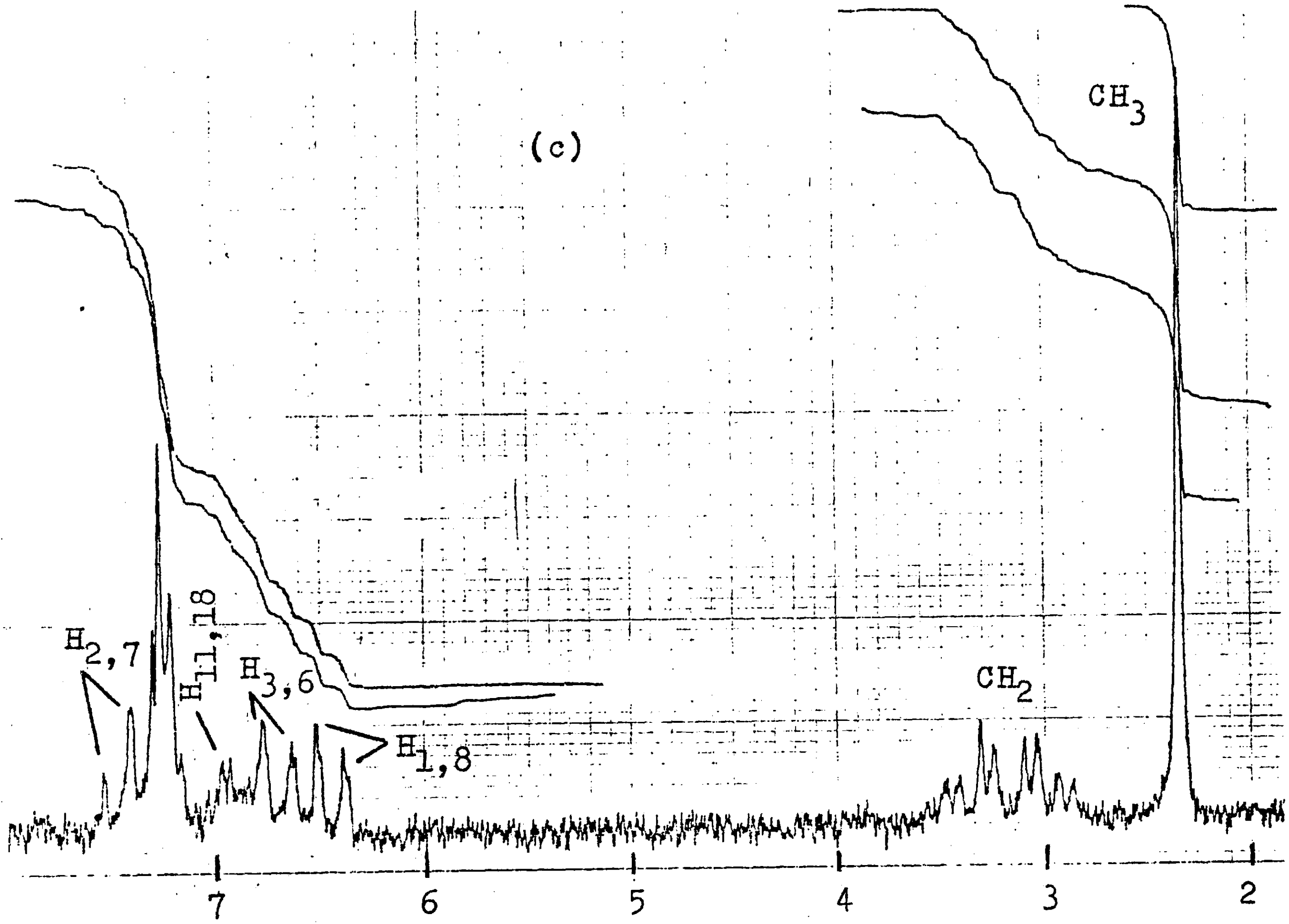
Spectrum No.43. ^{1}H N.m.r. spectrum (220 MHz) of dimethyl 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine-4,5-dicarboxylate (Xa) in CDCl$_3$.

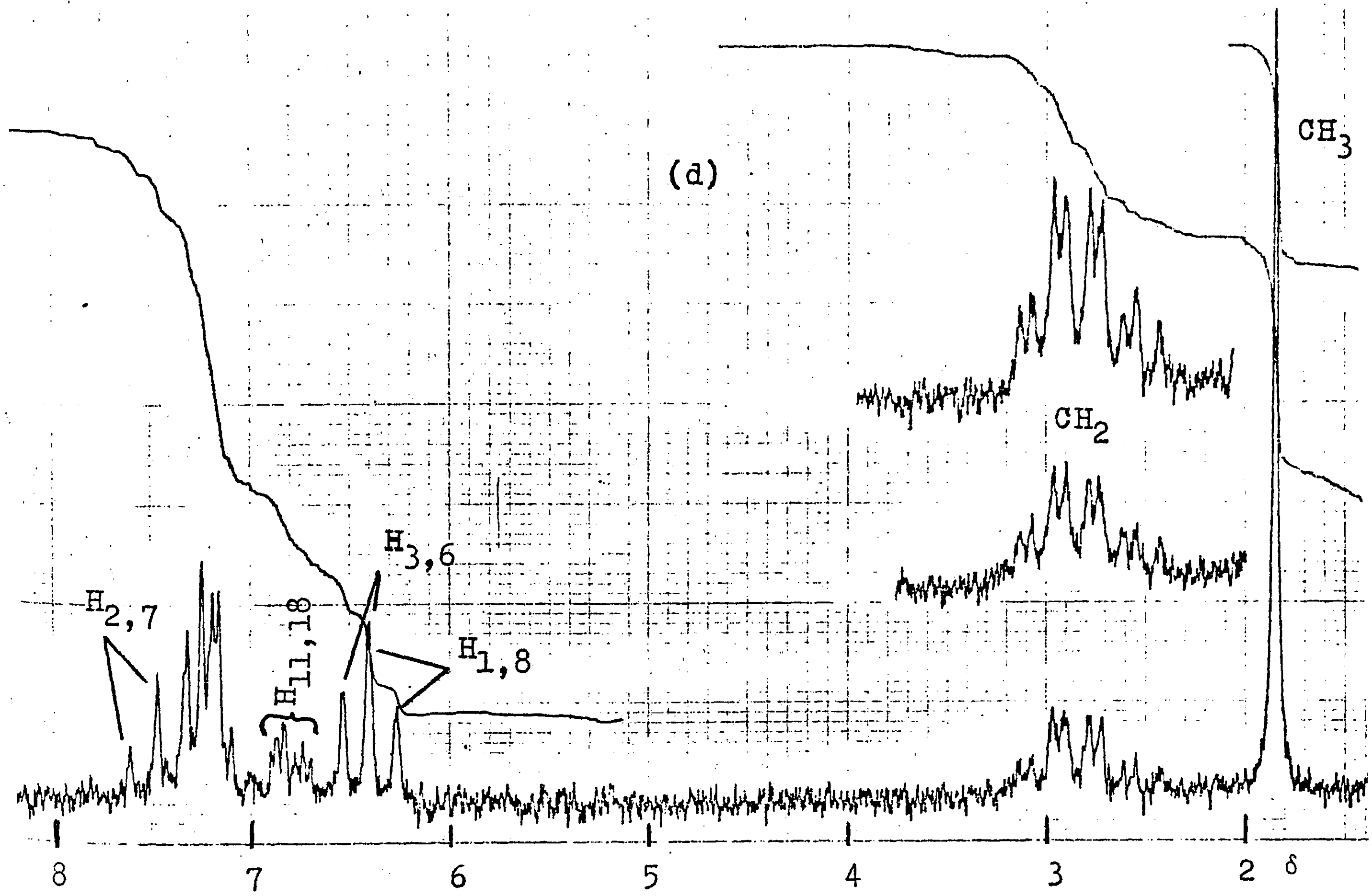


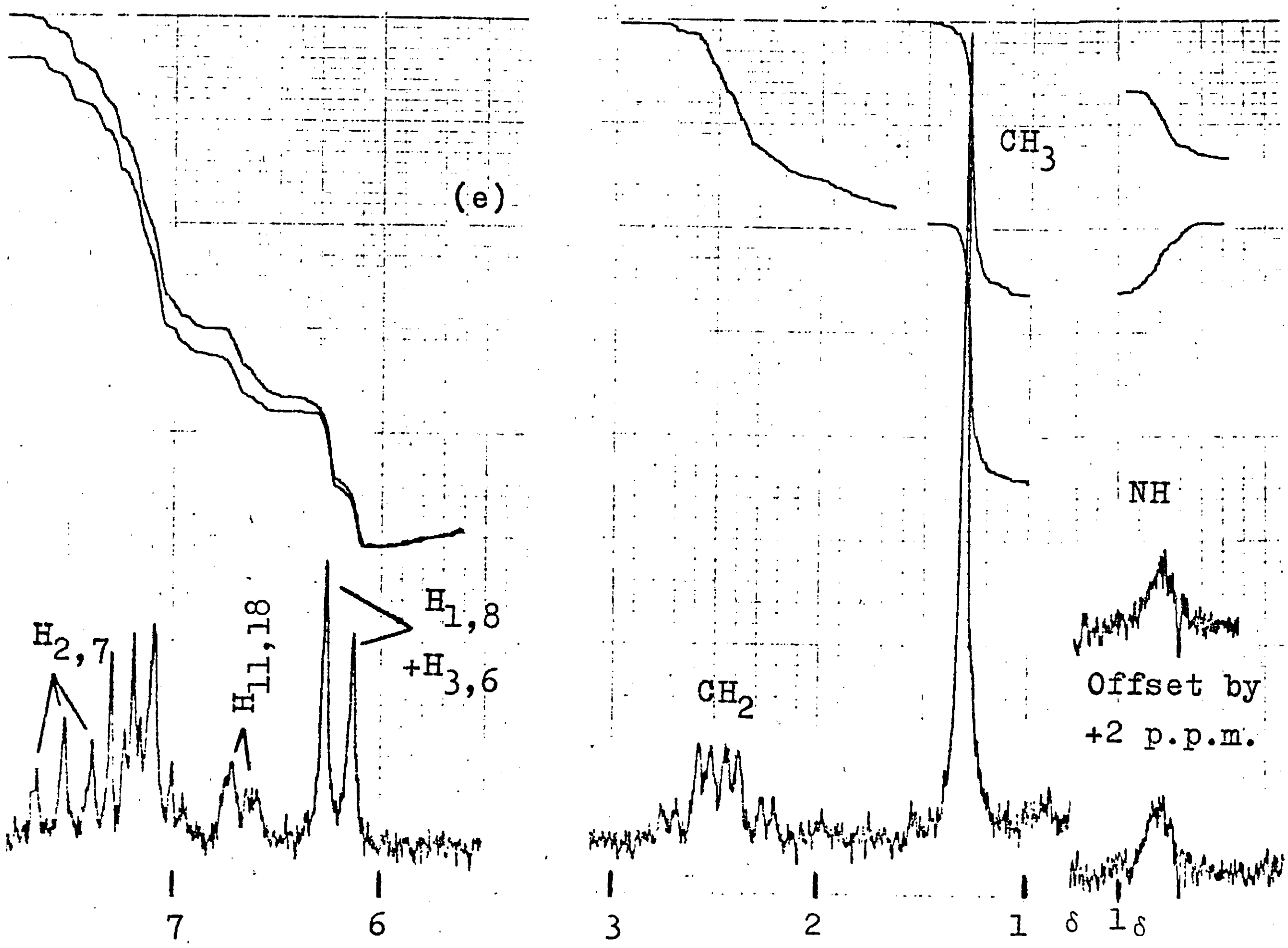
Spectrum No.44. Temperature variable spectra (220 MHz) for the diastereotopic methylene protons of compound (Xa) in CDCl$_3$.

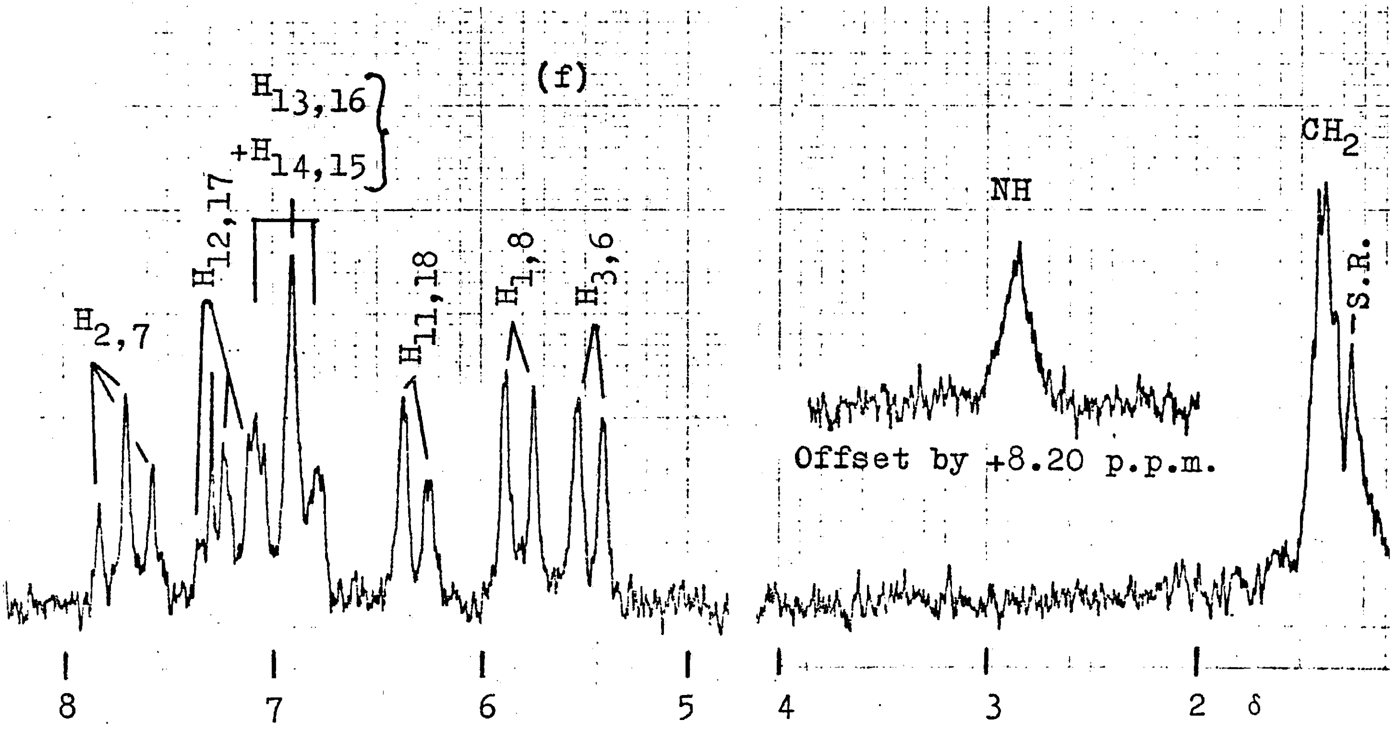


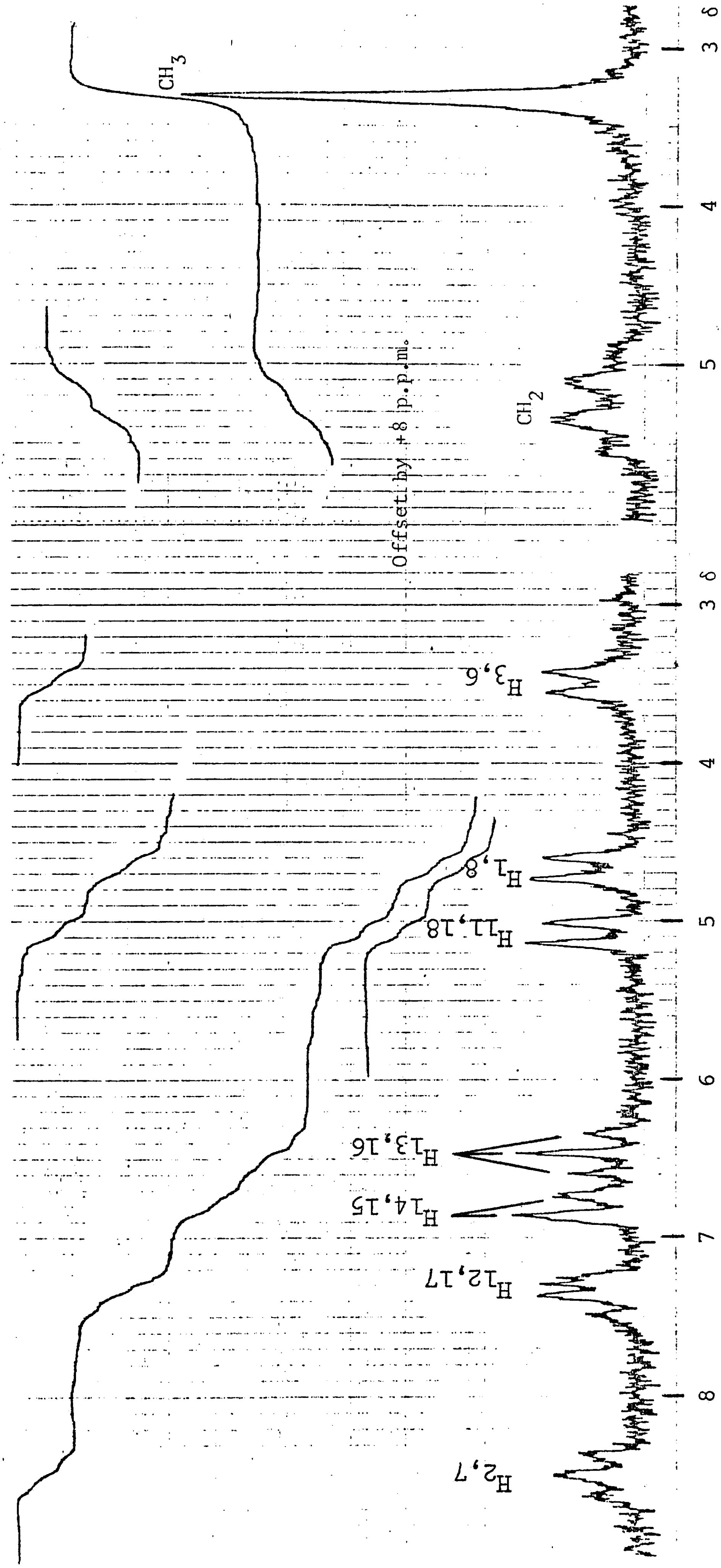
Spectrum No.45. 60 MHz ^{1}H N.m.r. spectra of dimethyl 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine-4,5-dicarboxylate (Xa) (5.40 mg, 1.128 x 10^{-5} mole) in $CDCl_3$ (0.4 ml) containing various amounts of Pr(fod)$_3$: (a) 0.00 mg; (b) 1.15 mg; (c) 2.53 mg; (d) 3.66 mg; (e) 5.21 mg; (f) 11.41 mg; (g) 90.92 mg.


(c)
CH3
CH2
H2,7
H11,18
H3,6
H1,8
7
6
5
4
3
2
δ


(d)
CH3
CH2
H2,7
H11,18
H3,6
H1,8
8
7
6
5
4
3
2
δ


(e)
$H_{2,7}$
$H_{11,18}$
$H_{1,8}$
$+H_{3,6}$
CH_2
CH_3
NH
Offset by
+2 p.p.m.
7
6
3
2
1 δ
1δ

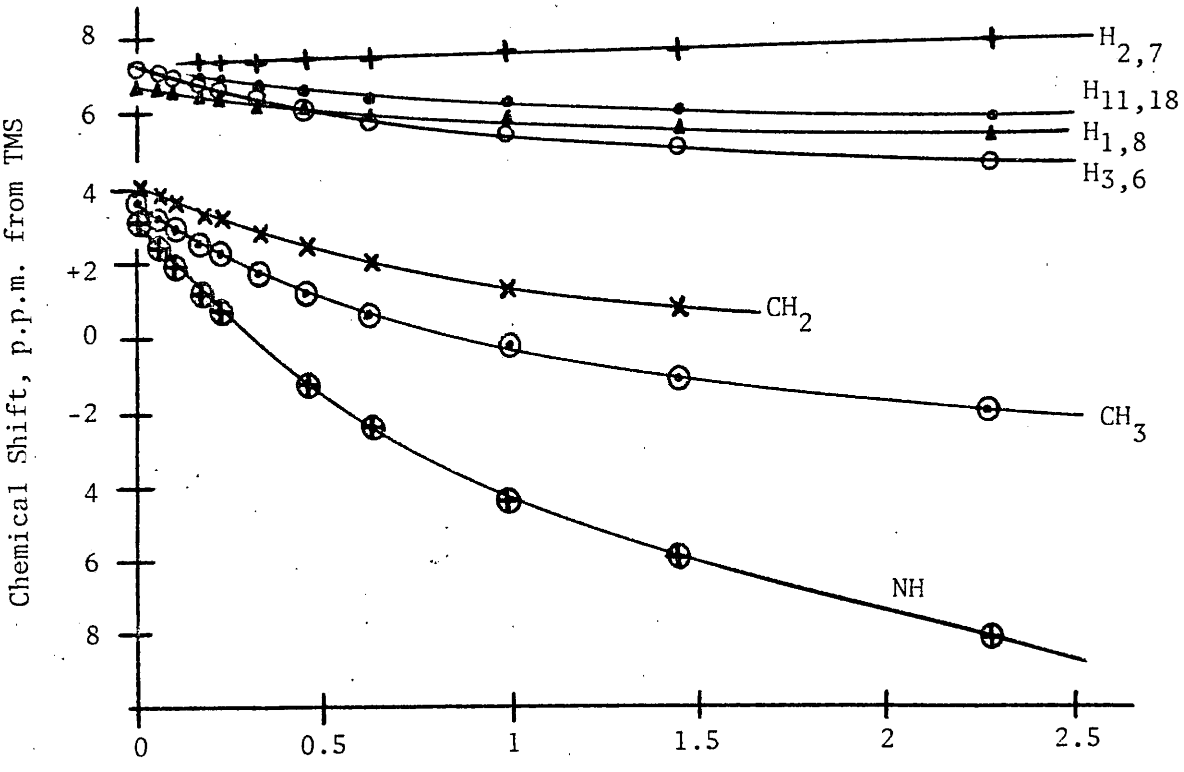

(f)
$H_{13,16}$
$+H_{14,15}$
$H_{2,7}$
$H_{12,17}$
$H_{11,18}$
$H_{1,8}$
$H_{3,6}$
NH
Offset by +8.20 p.p.m.
CH_2
S.R.
8
7
6
5
4
3
2 δ


CH$_3$
CH$_2$
Offset by +8 p.p.m.
3 δ
4
5
3 δ
4
5
6
7
8
H$_{3,6}$
H$_{1,8}$
H$_{11,18}$
H$_{13,16}$
H$_{14,15}$
H$_{12,17}$
H$_{2,7}$

(g)

Figure 22 shows schematic representations of the quantitative study of the association of (Xa) with Pr(fod)$_3$, and reveals that shifts for all solute protons are in the same direction, i.e., to higher field values except for $H_{2,7}$ where the shifts are in the opposite direction, i.e. lower field values. Also it shows that the stoichiometry for the adduct formation is 2:1 for the molar ratio of Pr(fod)$_3$/ Compound (Xa).

It is clear from the movement of NH and CH_3 that co-ordination occurs at both sides even at small concentration of shift reagent.



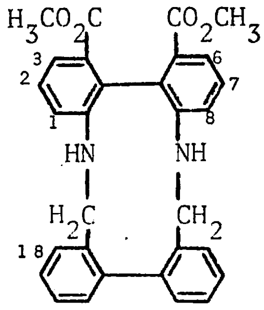
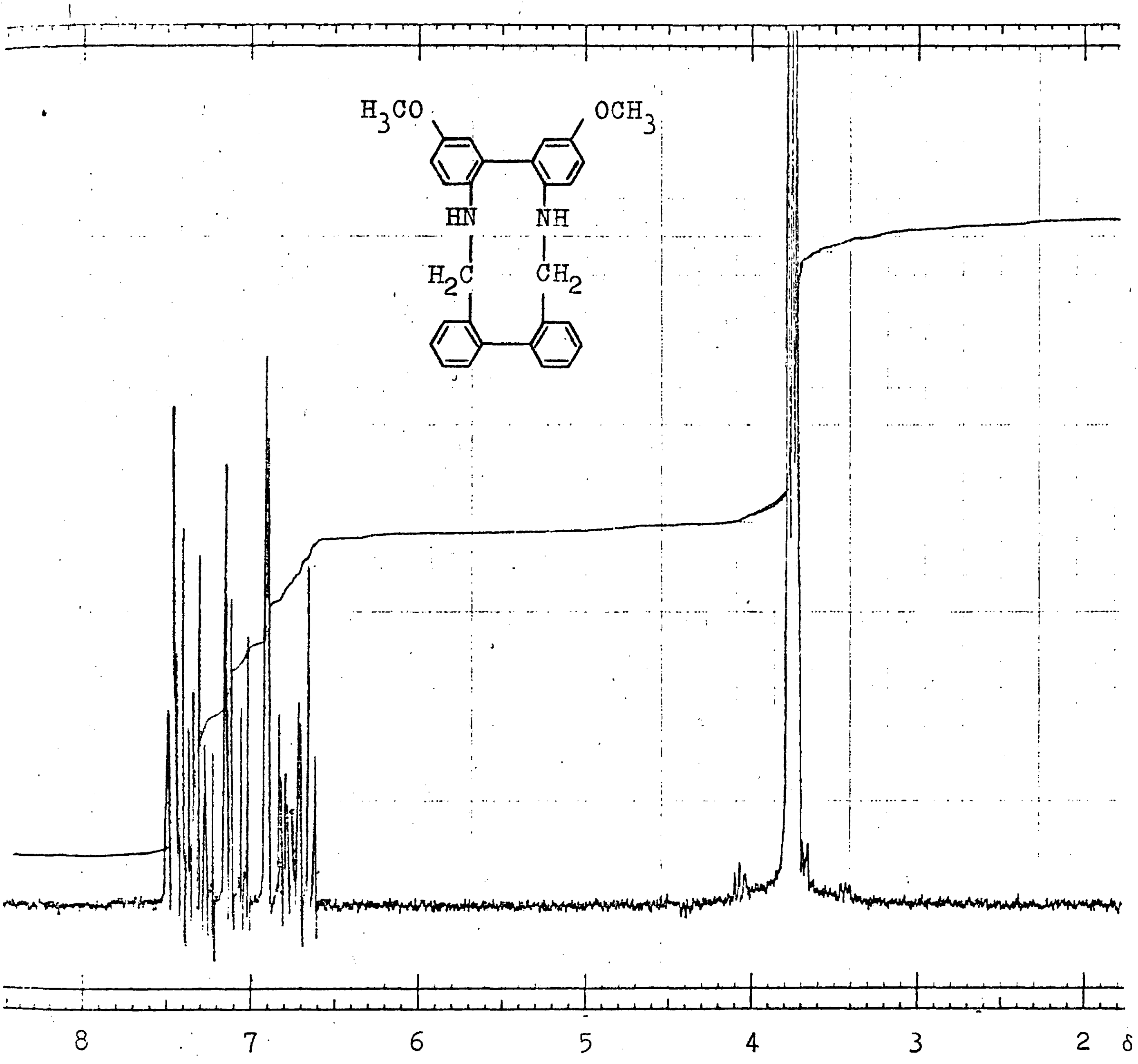


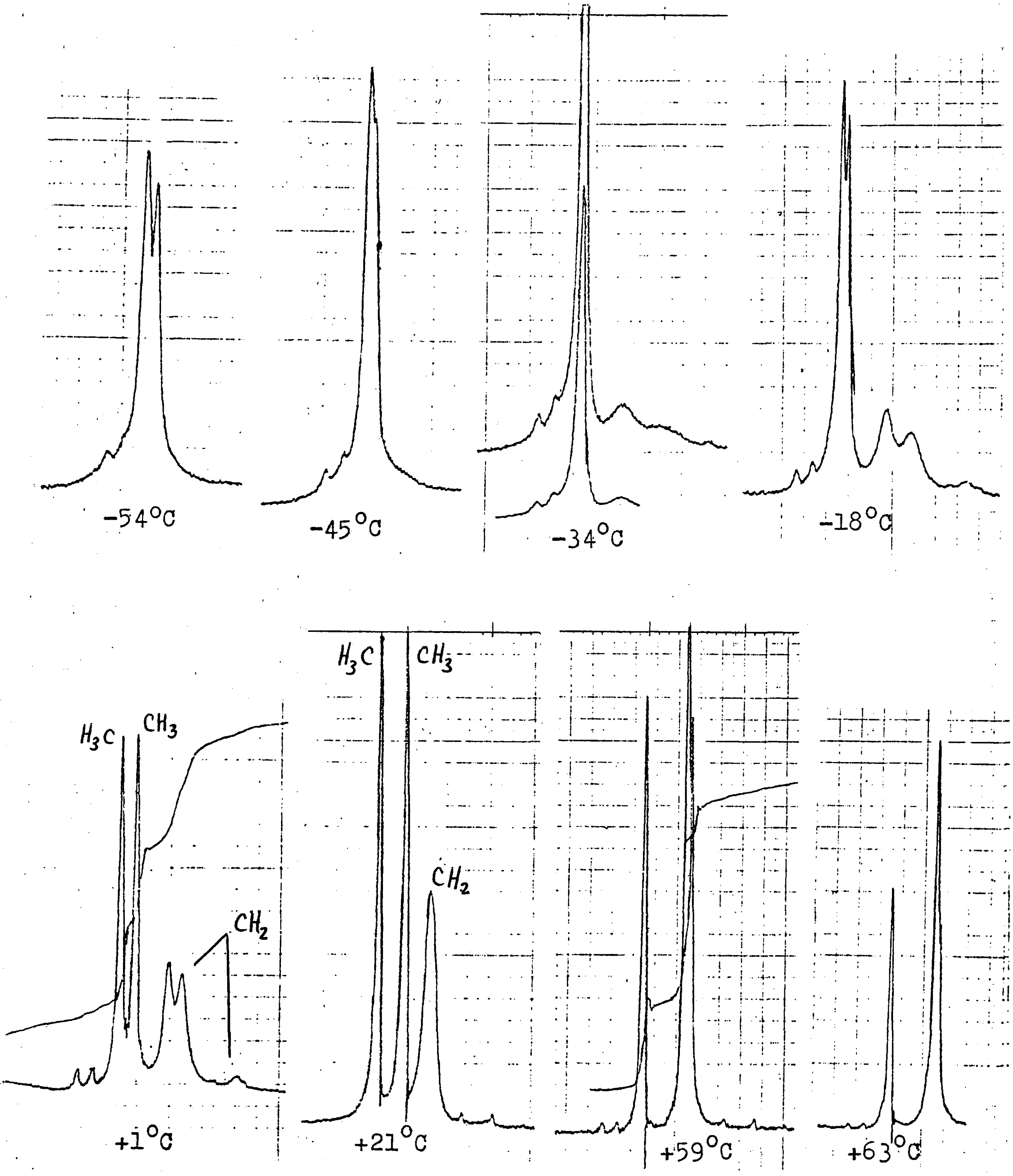
Figure No.22. Variation in the chemical shift of some of the protons in (Xa) upon addition of Pr(fod)$_3$ in $CDCl_3$.

Spectrum 46 shows the ^{1}H N.m.r. spectrum at 220 MHz in $CDCl_3$ of (Xb) at 21°. It reveals part of the methylene quartet at 3.74 p.p.m. (4 H, methylene protons), a doublet at 3.75 and 3.78 p.p.m. (6 H, methyl protons) and a complex multiplet at 6.62 - 7.48 p.p.m. due to the aromatic protons. The NH peak does not show in the spectrum because, it is believed, the solution was left for some time before running the spectrum. From the 60 MHz spectrum it appears as a broad singlet at 4.11 p.p.m. (2 NH protons which exchange with D_2O). The observed doublet for the methyl protons is more likely to come from two non-equivalent conformers. Each pair of methylene protons is diastereotopic. At low temperatures they appear as an AB quartet (J_{AB} = 12.8 Hz, one-fourth of the quartet is overlapped with the two methyl peaks), and coalescing to a singlet between 21 and 63° (Spectrum 47).

It is of interest to note that dramatic changes occur in the Spectrum 47. Most obvious of these changes is that the two methyl peaks move far away from each other as the probe temperature increases, while they move towards each other and form one peak as the temperature is decreased. This means that the two methyl groups are magnetically equivalent and non-equivalent at lower and higher temperatures, respectively.

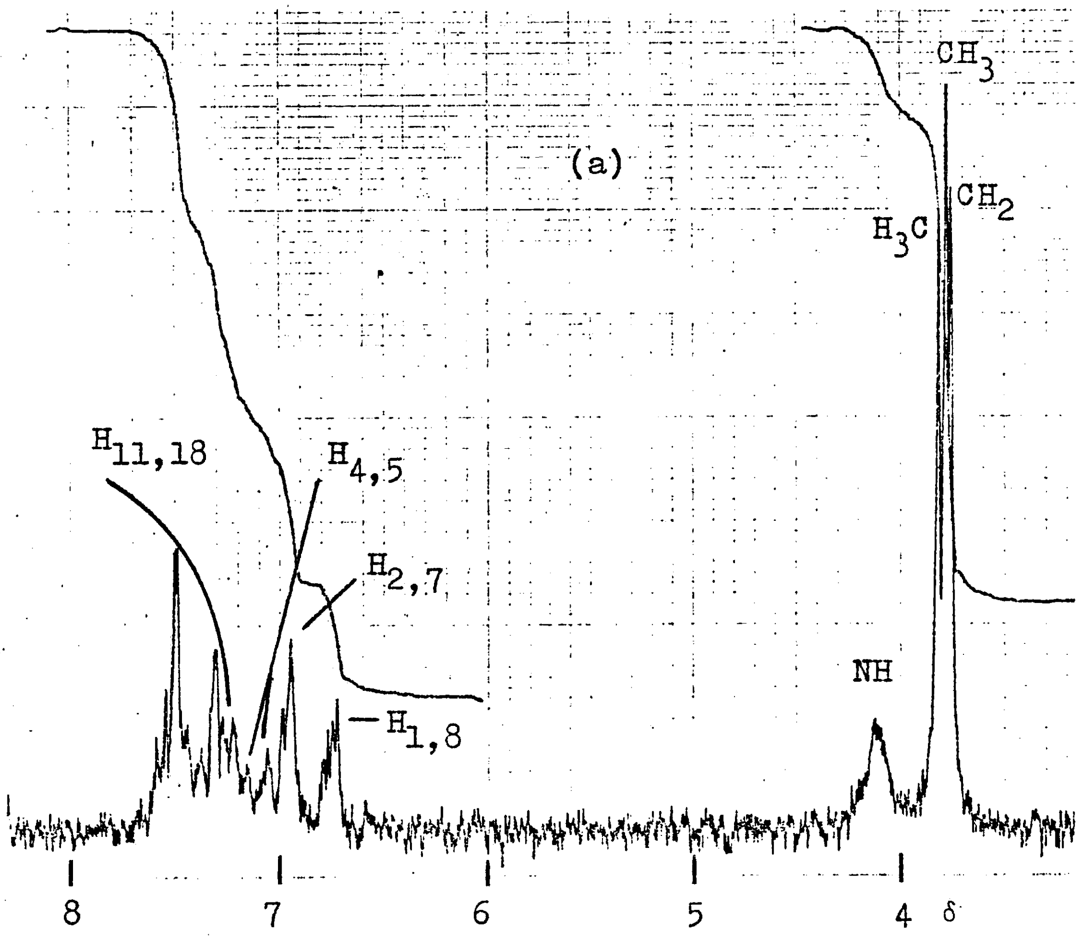


Spectrum No.46. ^1H N.m.r. spectrum (220 MHz) of 3,6-dimethoxy-9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]-diazacyclododecine (Xb) in $CDCl_3$ at 21°C.

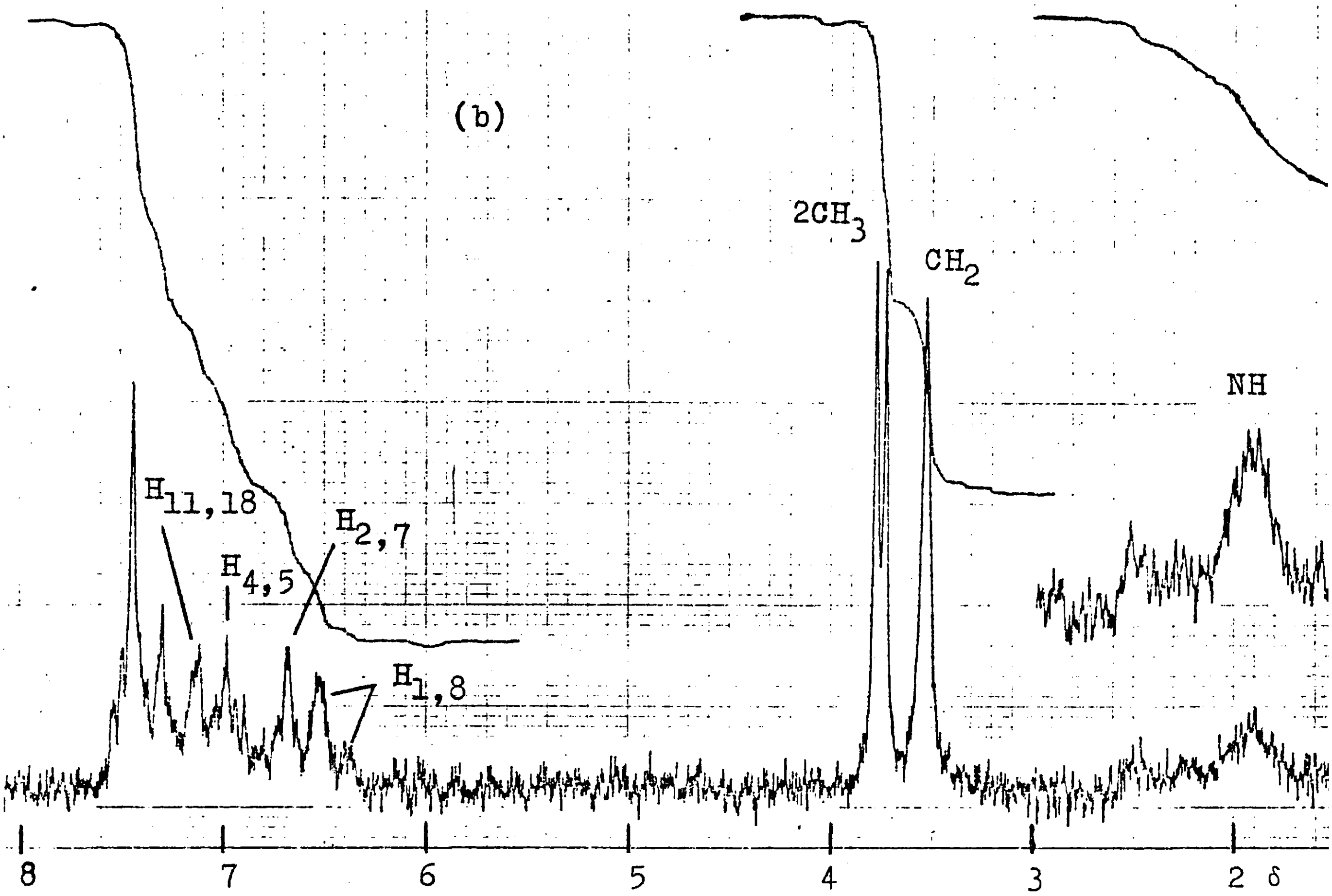


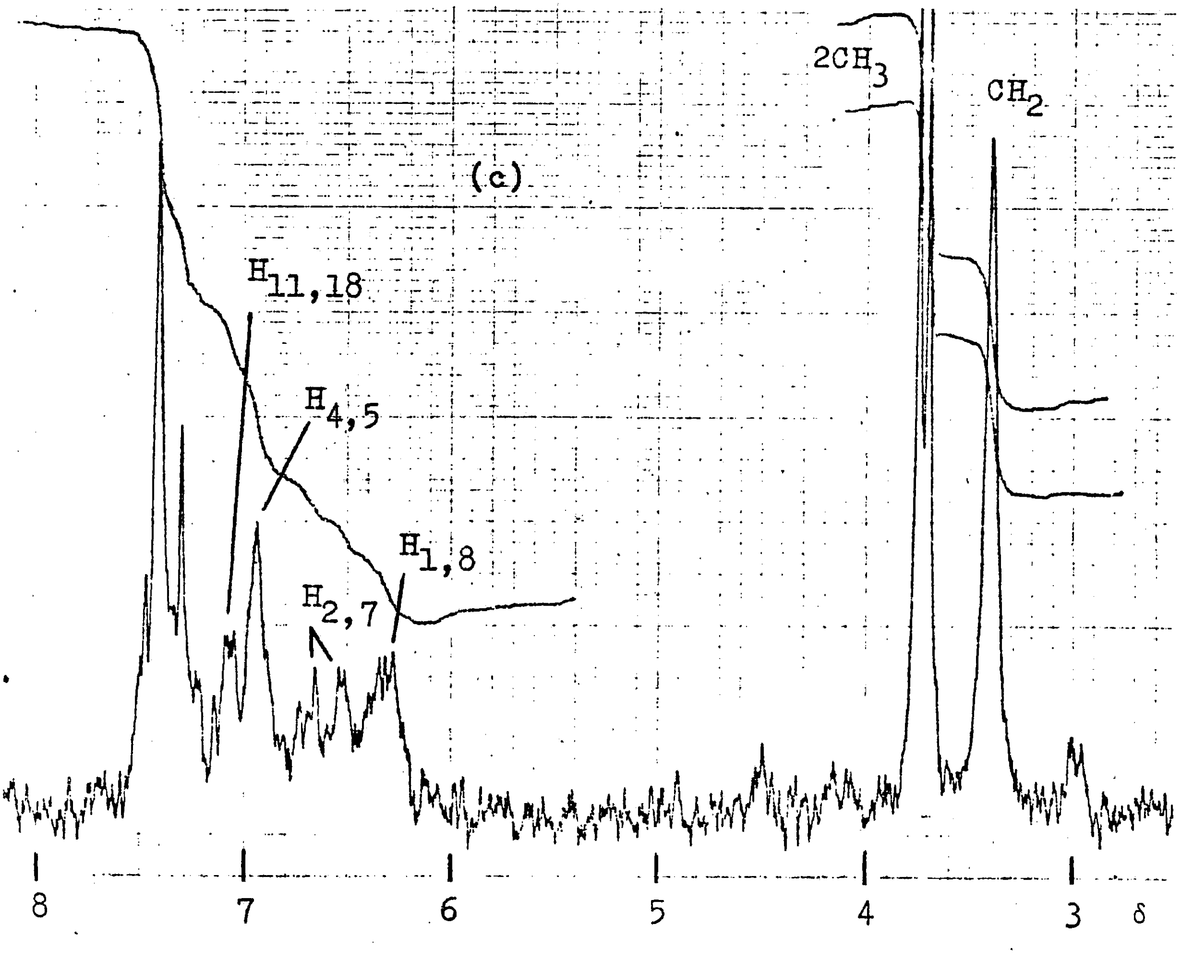
Spectrum No.47. Temperature variable spectra (220 MHz) for the methyl protons and the diastereotopic methylene protons of compound (Xb) in $CDCl_3$.

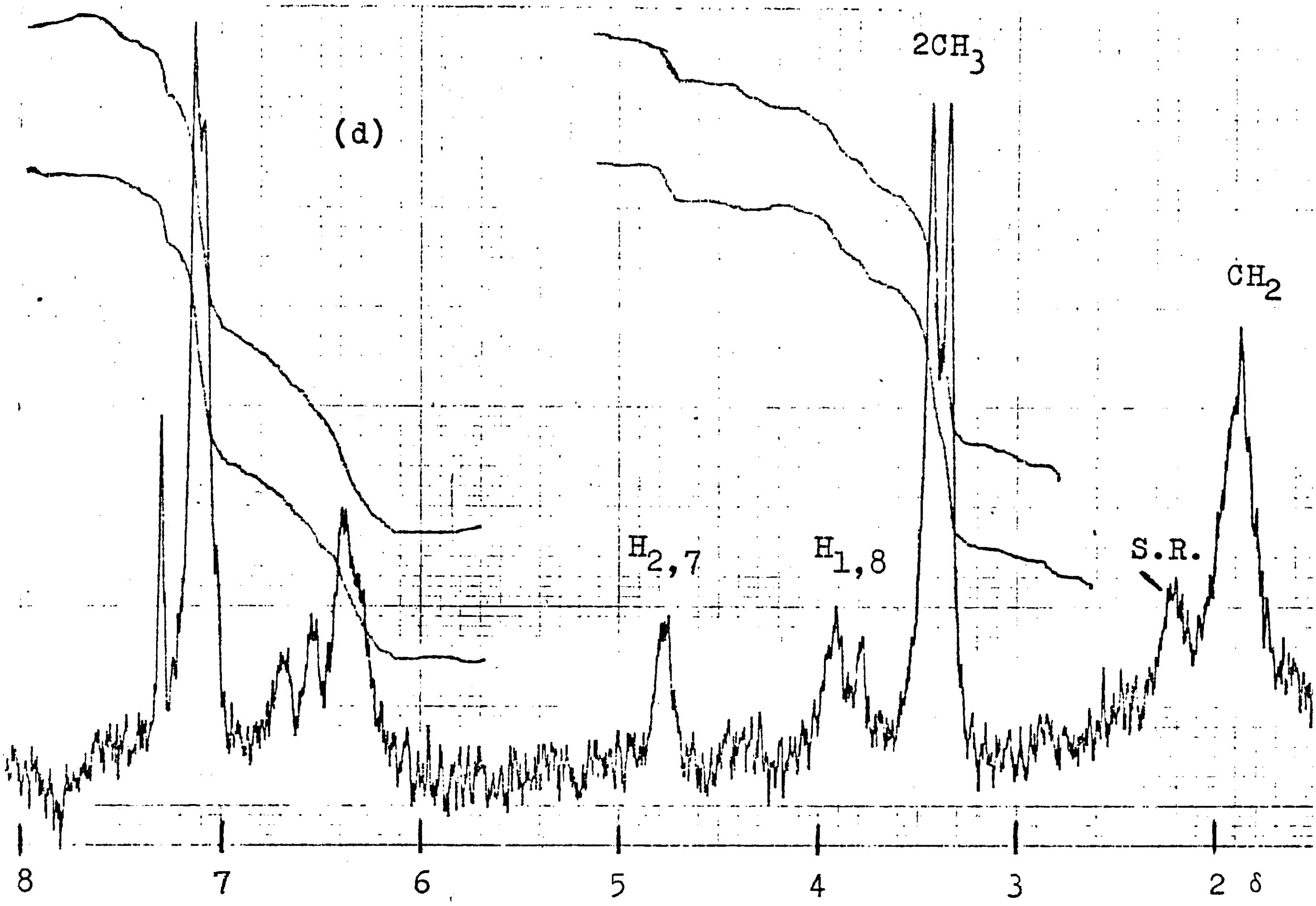
Upon addition of increasing amounts of $Pr(fod)_3$ to a solution of (Xb) in $CDCl_3$ (Spectrum 48), as is observed, four of the aromatic protons are resolved and moved to the upper field regions of the spectrum. Further addition of $Pr(fod)_3$ failed to resolve extra aromatic protons. As compared to the case in compound (Xa), where all of the aromatic protons are resolved, very weak association of (Xb) with $Pr(fod)_3$ was observed,this is probably due to delocalisation of the electron pairs of the oxygen over the aromatic rings.



Spectrum No. 48. 60 MHz ^1H N.m.r. spectra of 3,6-dimethoxy-9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine (Xb) (5.90 mg, 1.396×10^{-5} mole) in $CDCl_3$ (0.6 ml) containing various amounts of $Pr(fod)_3$: (a) 0.00 mg; (b) 1.38 mg; (c) 2.30 mg; (d) 36.47 mg.

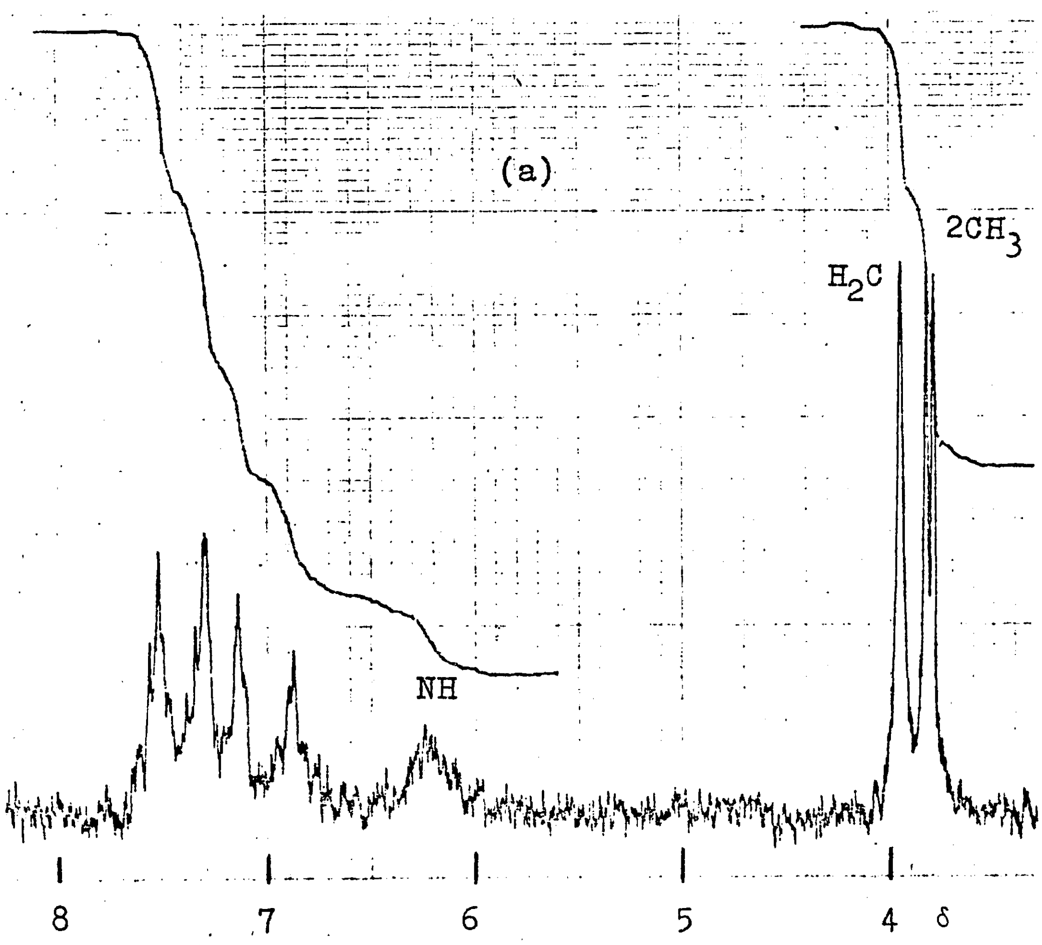

(b)
$2CH_3$
CH_2
NH
$H_{11,18}$
$H_{4,5}$
$H_{2,7}$
$H_{1,8}$
8
7
6
5
4
3
2 δ


(c)
$2CH_3$
CH_2
$H_{11,18}$
$H_{4,5}$
$H_{1,8}$
$H_{2,7}$
8
7
6
5
4
3 δ

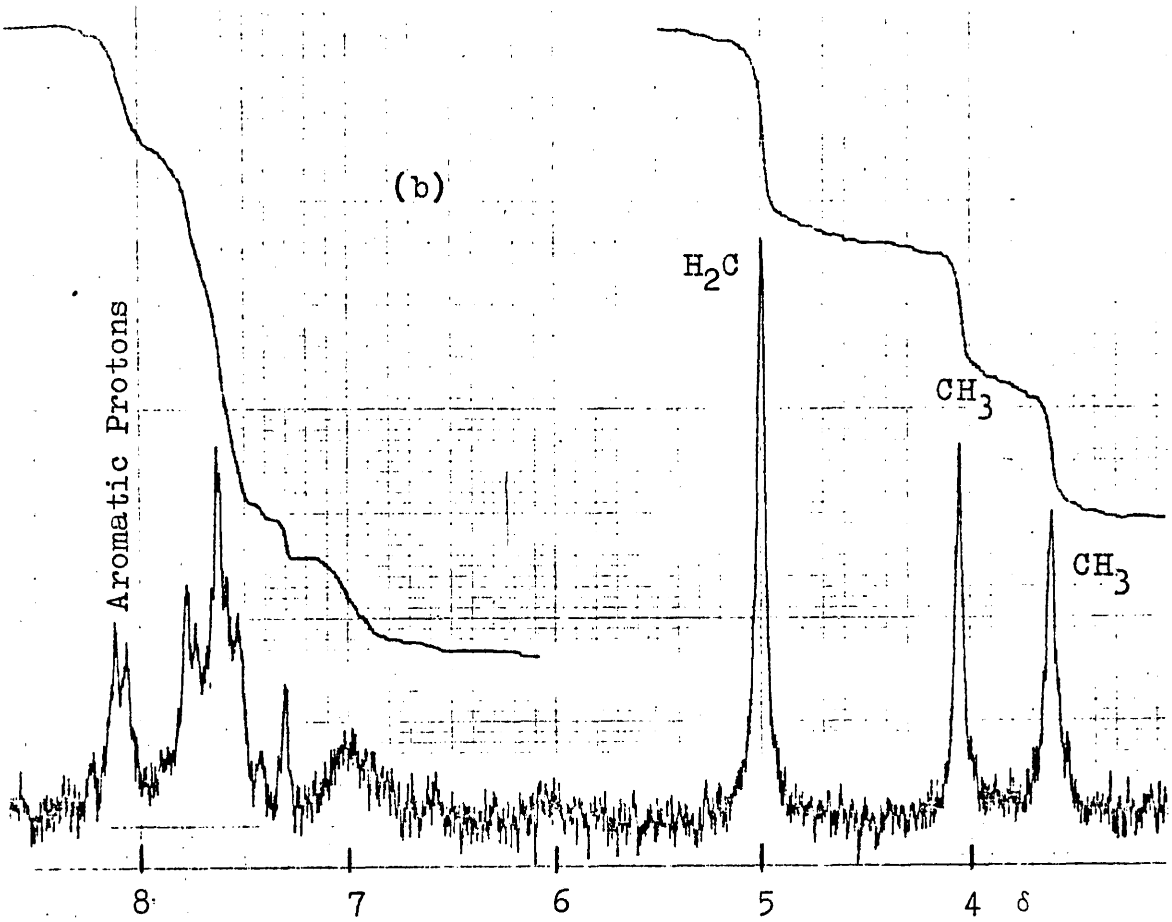


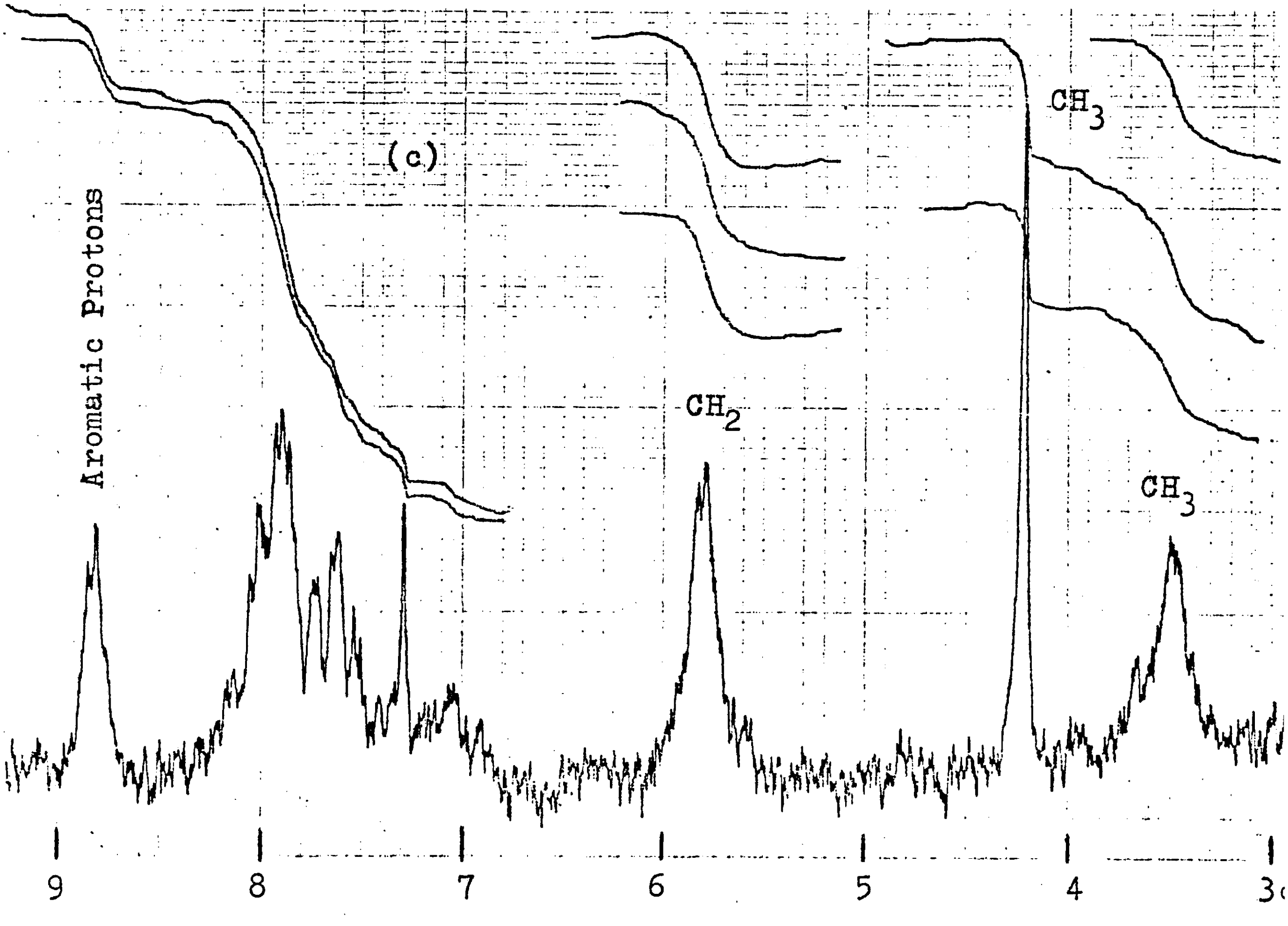
On the other hand, upon addition of increasing amounts of $Eu(fod)_3$ to a solution of (Xb) in $CDCl_3$ (Spectrum 49) the aromatic protons in the upper regions of the spectrum (i.e. $H_{1,8}$ and $H_{2,7}$) are shifted to the lower regions, but due to their overlapping with the rest of the aromatic protons their assignments together with the other aromatic protons become difficult.

An interesting phenomenon is observed here as the two methyl protons move in different directions of the spectrum. The upfield shift of one of the methyl doublets may be related, as well, to a substantial alteration of geometry in the interactions of this compound with Eu(fod)$_3$. With such an alteration the dependence of shift on angle could become important enough to change the sign of the shift. An alternative explanation based on a change in relative magnitudes of the magnetic susceptibility tensors seems unlikely.



Spectrum No.49. 60 MHz ^{1}H N.m.r. spectra of 3,6-dimethoxy-9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine (Xb) (5.90 mg, 1.396 x 10^{-5} mole) in CDCl$_3$ (0.6 ml) containing various amounts of Eu(fod)$_3$: (a) 1.35 mg; (b) 8.75 mg; (c) 19.35 mg.


(b)
Aromatic Protons
H$_2$C
CH$_3$
CH$_3$
8
7
6
5
4
δ


(c)
Aromatic Protons
CH$_2$
CH$_3$
CH$_3$
9
8
7
6
5
4
3

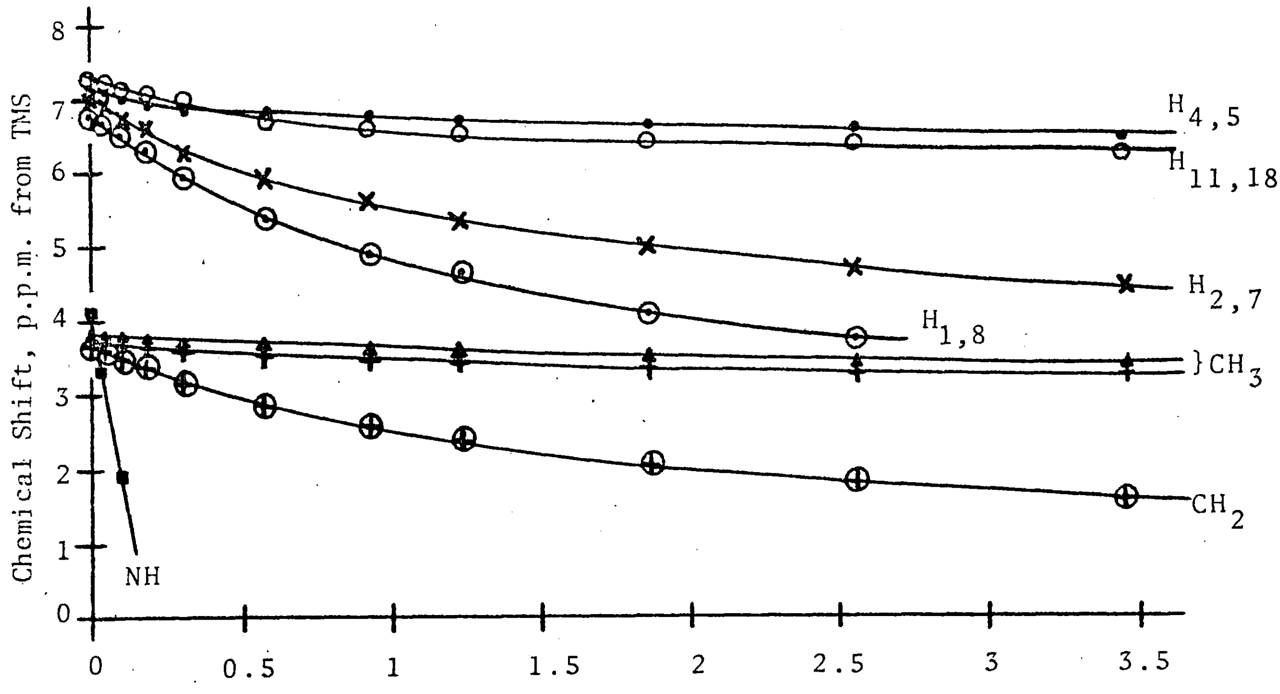
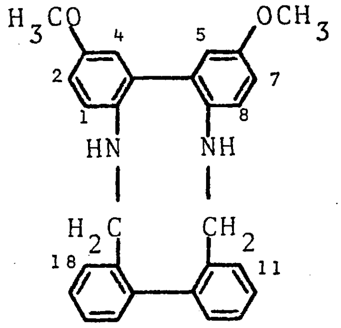


Figure No.23. Variation in the chemical shift of some of the protons in (Xb) upon addition of Pr(fod)$_3$ in CDCl$_3$.



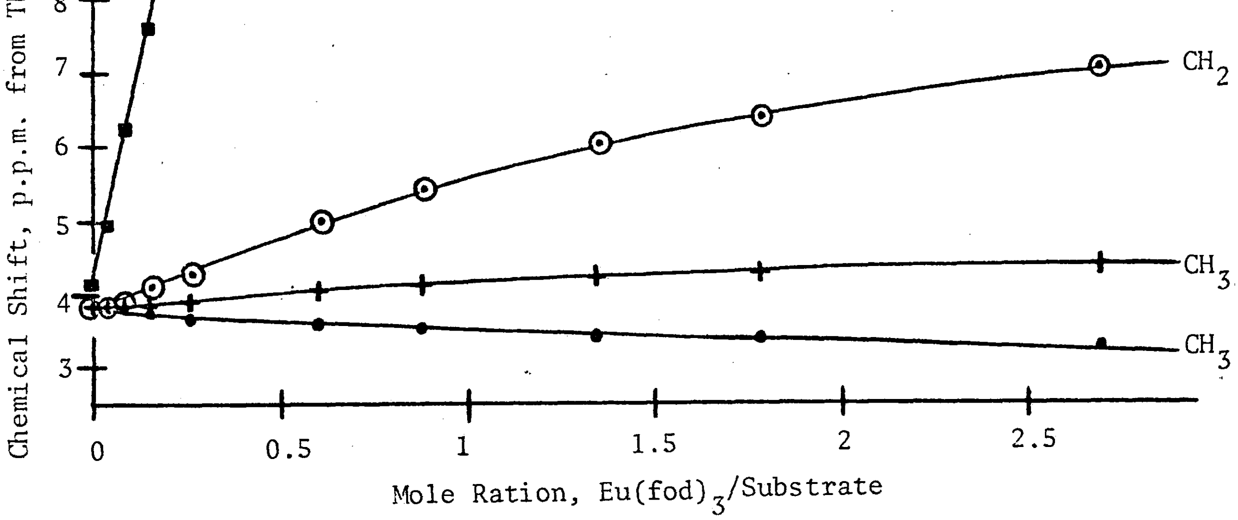
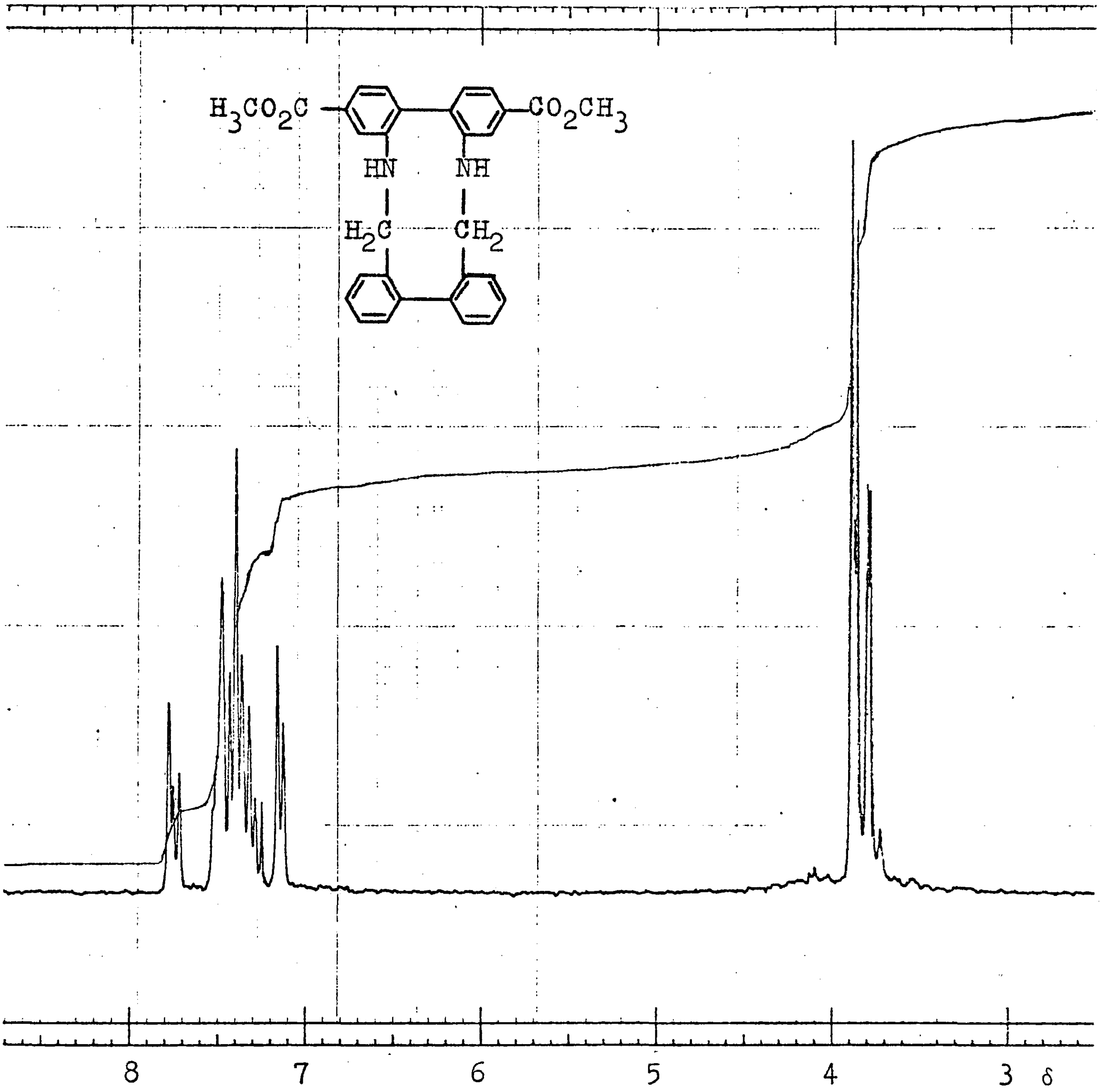


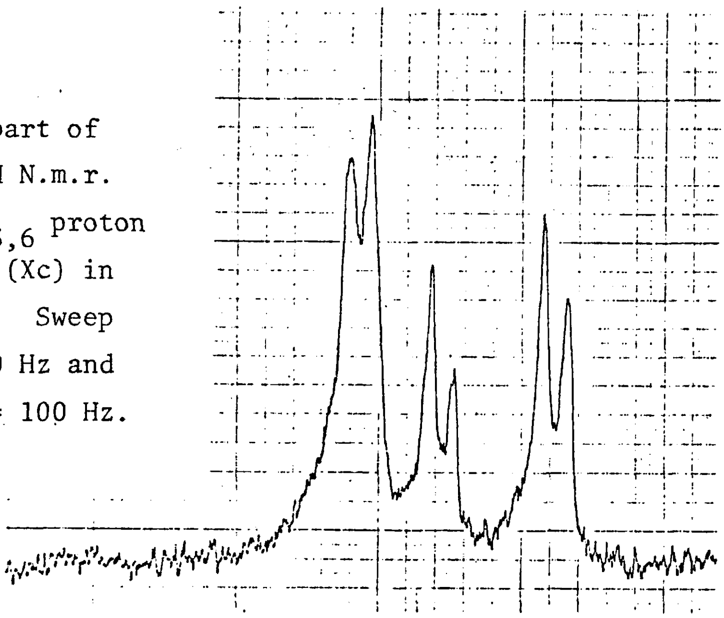
Figure No.24. Variation in the chemical shift of some of the protons in (Xb) upon addition of Eu(fod)$_3$ in CDCl$_3$.

Figures 23 and 24 show schematic representations of the quantitative study of the association of (Xb) with $Pr(fod)_3$ and $Eu(fod)_3$, respectively, and reveal that the stoichiometry for the adduct formation is 2:1 for the molar ratio of $Pr(fod)_3$ or $Eu(fod)_3$ to (Xb). Figure 23 shows that the induced shifts for all solute protons are in the same direction, i.e.,to the higher field values, while Figure 24 shows that the protons of one of the methyl groups is moving in the opposite direction relative to those of the other.

The ^1H N.m.r. spectrum at 220 MHz of (Xc) in $CDCl_3$ at 24° is shown in Spectrum 50 which reveals $^3/_4$ of the methylene quartet at 3.79 p.p.m. (4 H, methylene protons), a doublet at 3.86 and 3.89 p.p.m. (6 H, methyl protons) and a complex multiplet at 7.13 - 7.78 p.p.m. due to the aromatic protons. The peaks at 7.13 - 7.17 (d); 7.40 (s) and 7.72 - 7.78 (t) p.p.m. are believed to arise from the aromatic protons $H_{4,5}$; $H_{1,8}$ and $H_{3,6}$ respectively. On expansion of part of Spectrum 50, the peak at 7.72 - 7.78 (t) p.p.m. shows ortho- and meta-couplings (Spectrum 51). The NH peak does not show in Spectrum 50, because the solution was left for some time before running the spectrum. From 60 MHz spectrum NH appears as a broad singlet at 4.34 p.p.m. (2 NH protons which exchange with D_2O). The observed doublet for the methyl protons, as in case of (Xb), is more likely to arise from two non-equivalent conformers.

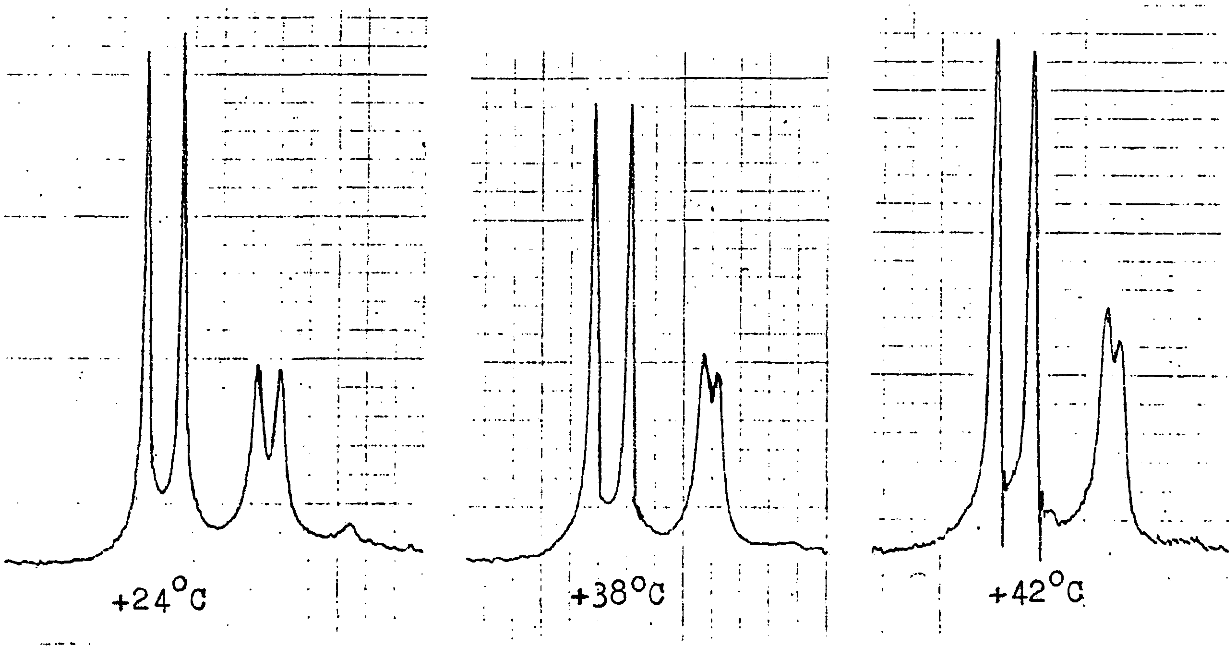


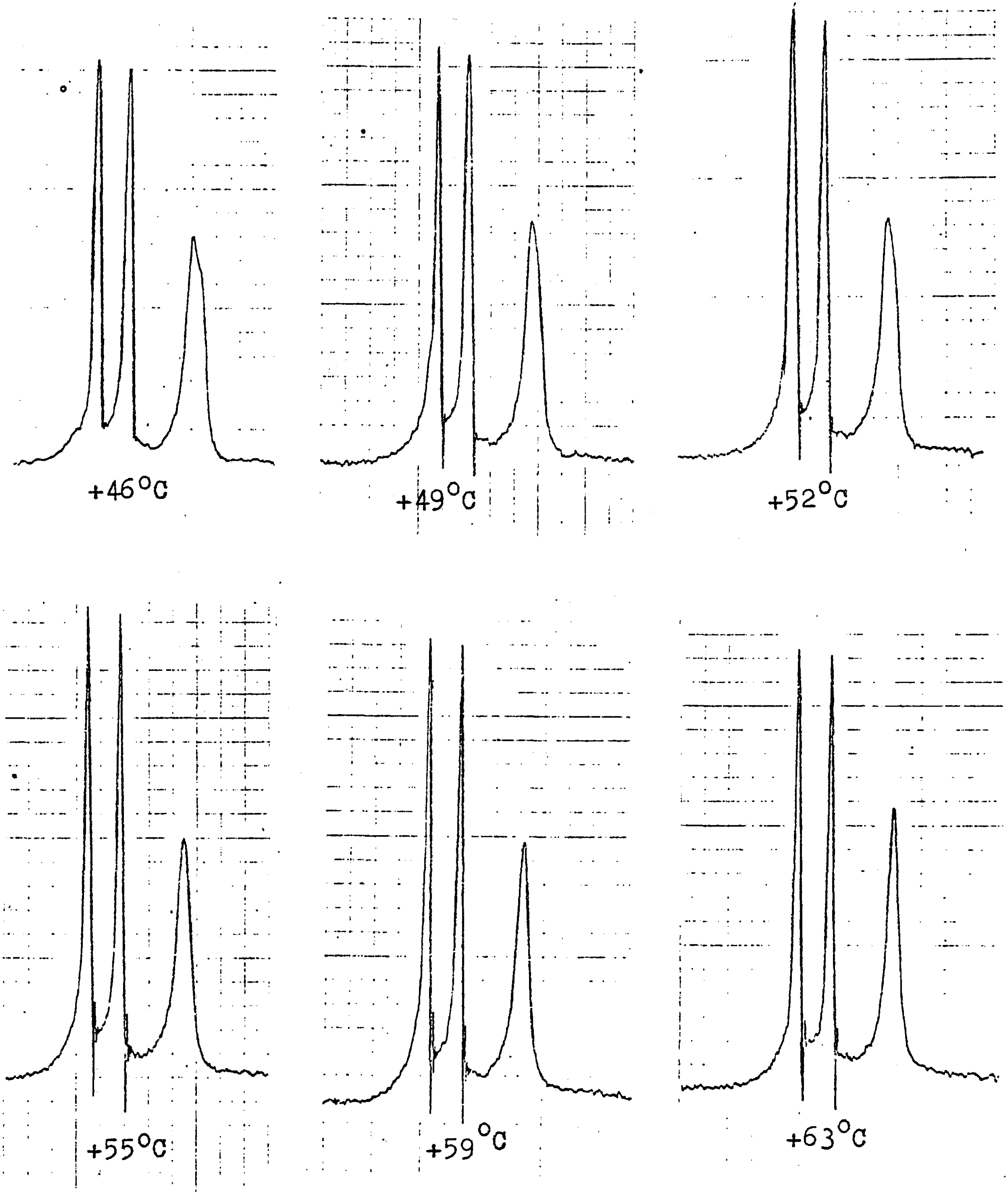
Spectrum No.50. ^{1}H N.m.r. spectrum (220 MHz) of dimethyl 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate (Xc) in $CDCl_3$ at 24°C.



Spectrum No.51. Expansion of part of the 220 MHz ^{1}H N.m.r. spectrum of $H_{3,6}$ proton absorption of (Xc) in $CDCl_3$ at 25°C. Sweep offset by 1650 Hz and sweep width = 100 Hz.

Each pair of methylene protons is diastereotopic. At low temperatures they appear as an AB quartet (J_{AB} = 12.45 Hz, one-fourth of the quartet is overlapped with the two methyl peaks), becoming a doublet between 38 and 42° and coalescing to a singlet between 46 and 63° (Spectrum 52), when conformational inversion of the twisted biphenyl systems becomes rapid.

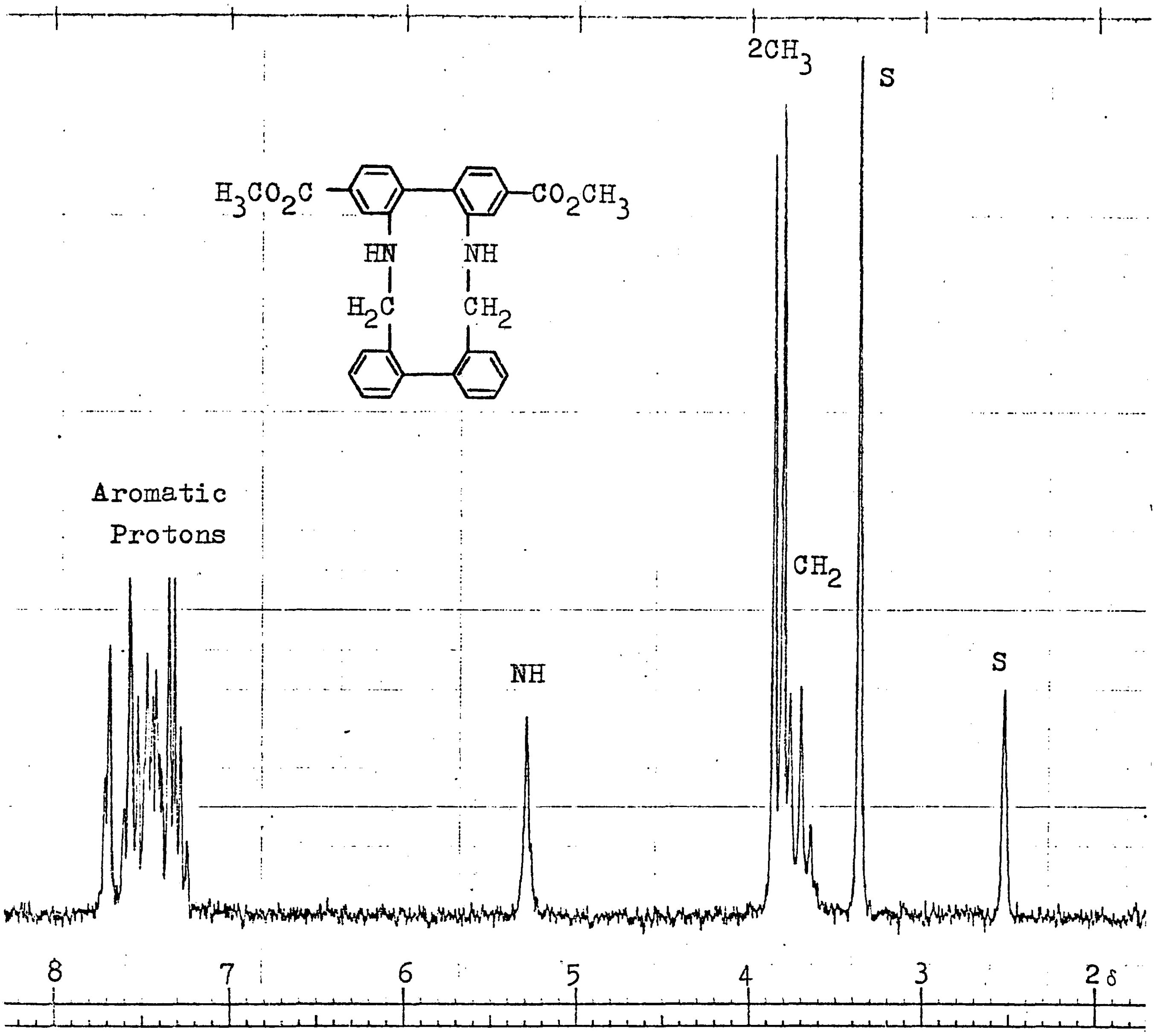




Spectrum No.52. Temperature variable spectra (220 MHz) for the methyl protons and the diastereotopic methylene protons of compound (Xc) in $CDCl_3$.

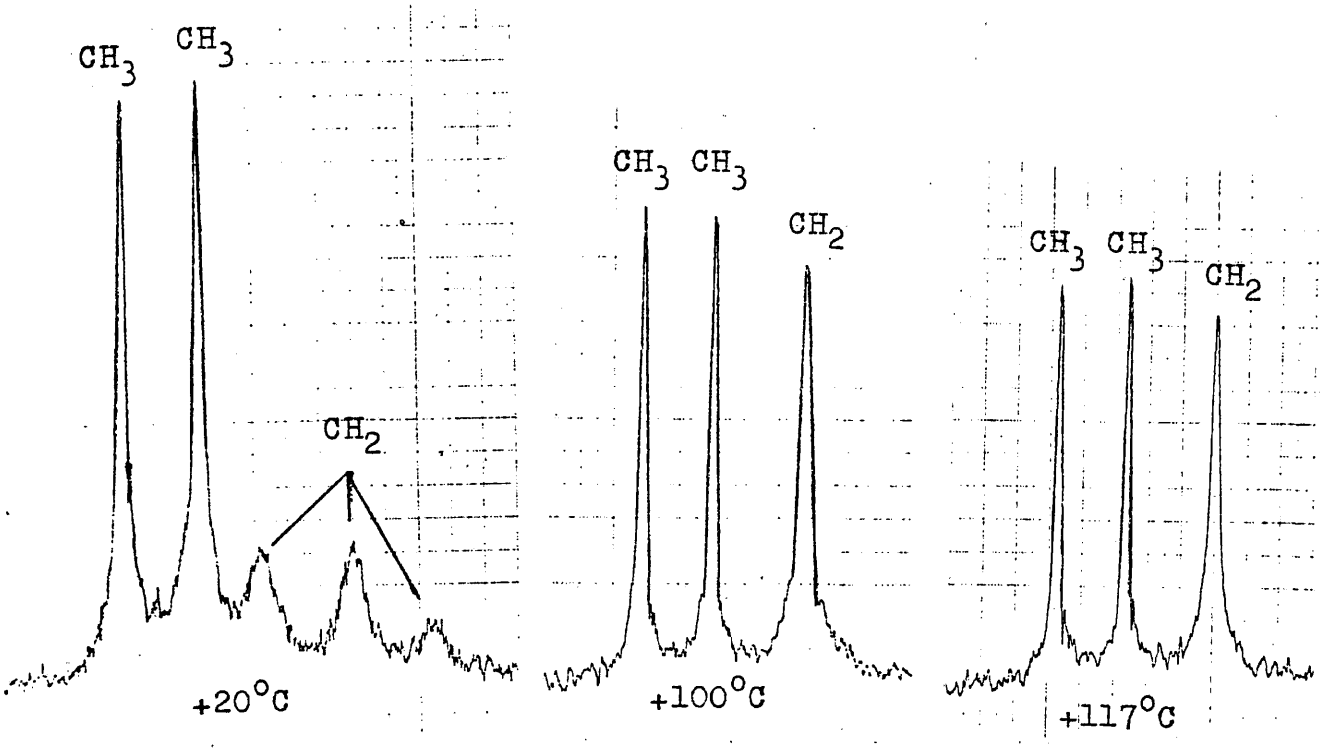
From the temperature variable spectra (Spectrum 52), it is quite clear that the two methyl peaks did not show any changes with temperature.

^{1}H N.m.r. spectrum (220 MHz) of (Xc) in [$^2H_6$] DMSO at 20^o also shows two peaks for the two methyl protons (Spectrum 53), and therefore, supports the previous conclusion that (Xc) does exist in two stable non-equivalent conformers.



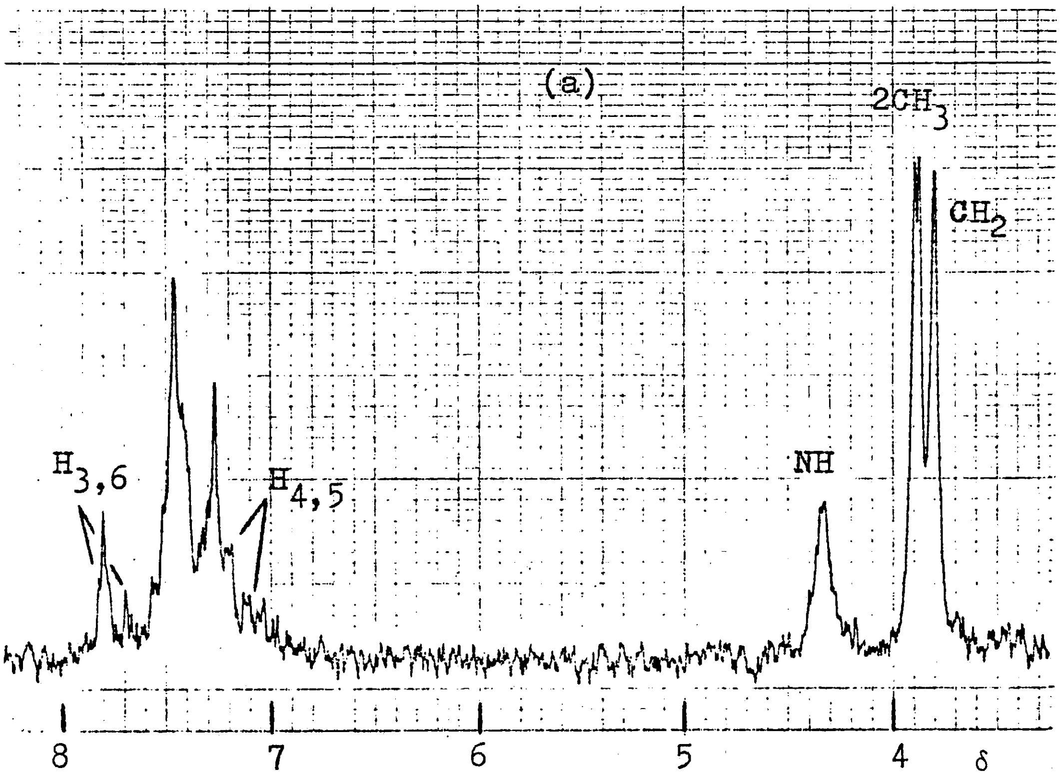
Spectrum No.53. ^{1}H N.m.r. spectrum (220 MHz) of dimethyl 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate (Xc) in [$^2H_6$] DMSO at 20^{o}C. Bands marked 'S' are due to solvent.

Studying the effect of increasing probe temperature on the two methyl peaks in [$^{2}H_{6}$] DMSO, it is found that the methyl peaks did not coalesce even when the probe is heated to 117^{o} (Spectrum 54).

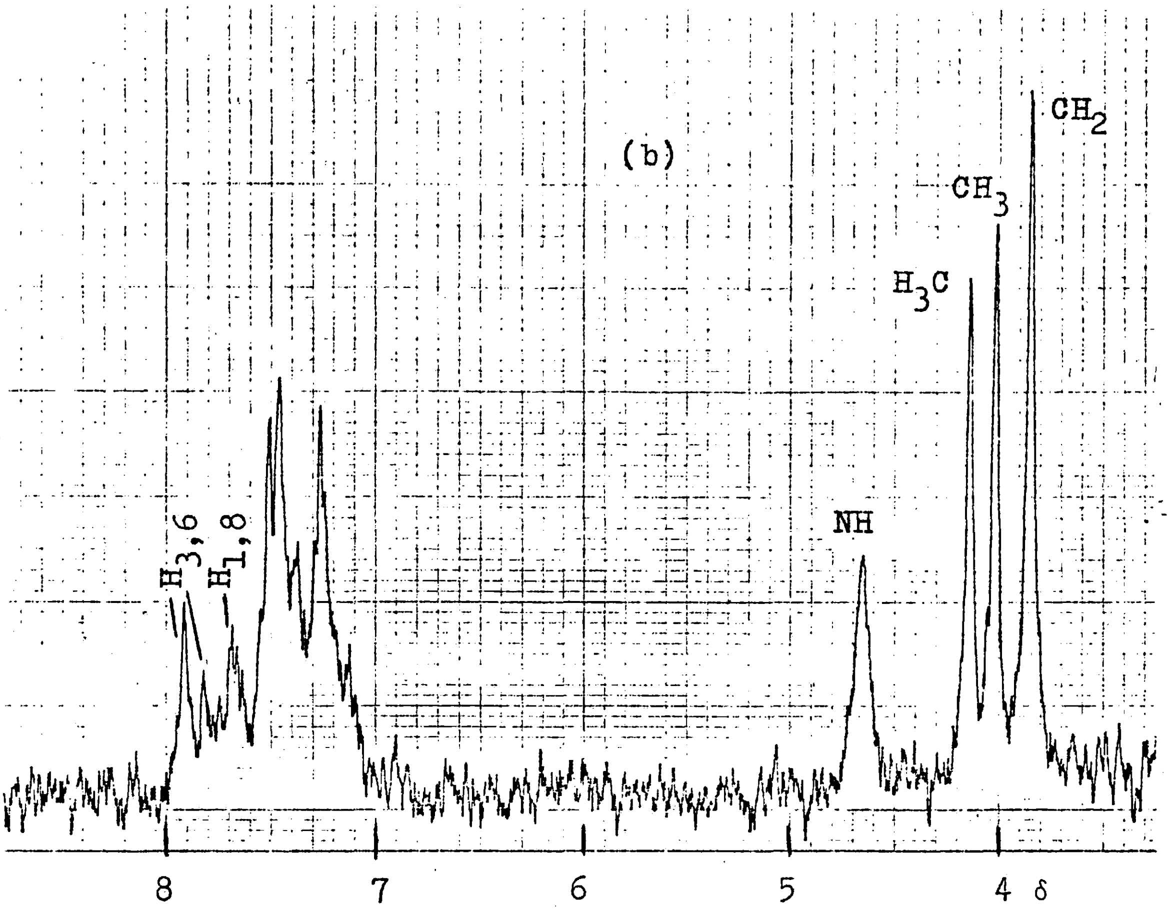


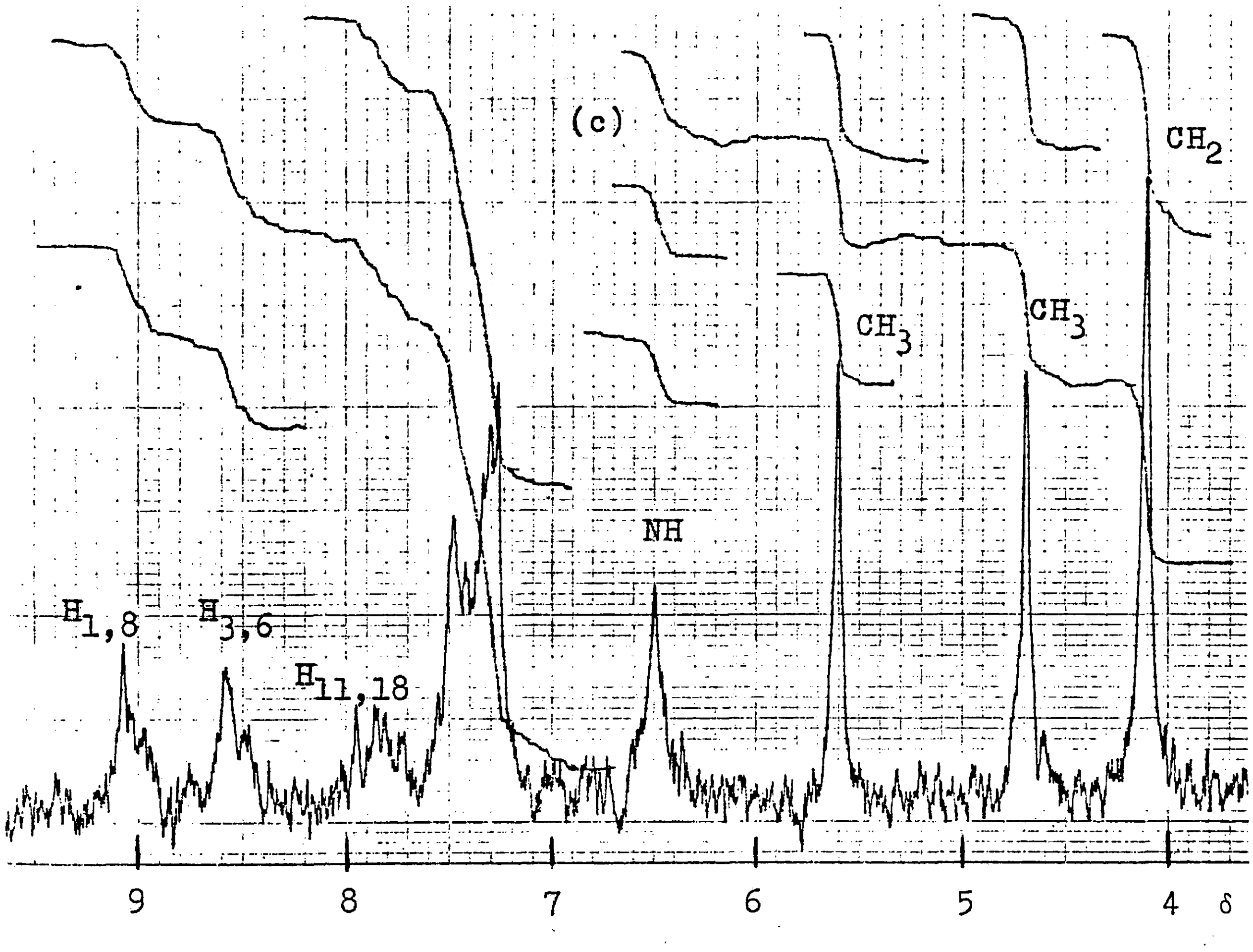
Spectrum No.54. Temperature variable spectra (220 MHz) for the methyl protons and the diastereotopic methylene protons of compound (Xc) in [$^{2}H_{6}$] DMSO.

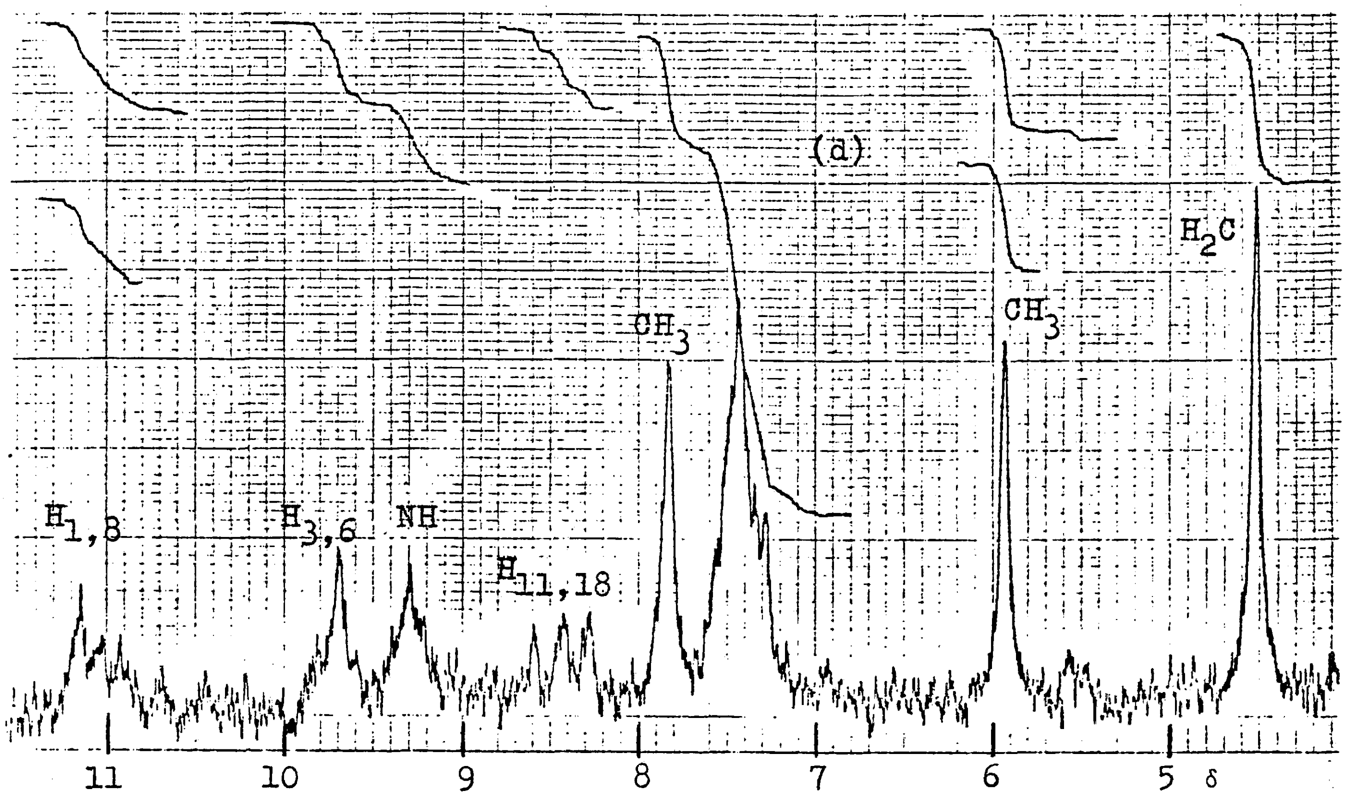
Spectrum 55 represents the ^{1}H N.m.r. spectra of the association of (Xc) with Eu(fod)$_3$ in CDCl$_3$ before and after addition of the shift reagent. Seven well-resolved peaks move to the lower field regions of the spectrum and can be assigned unambiguously on the basis of observed splitting pattern and distance-shift relationships.



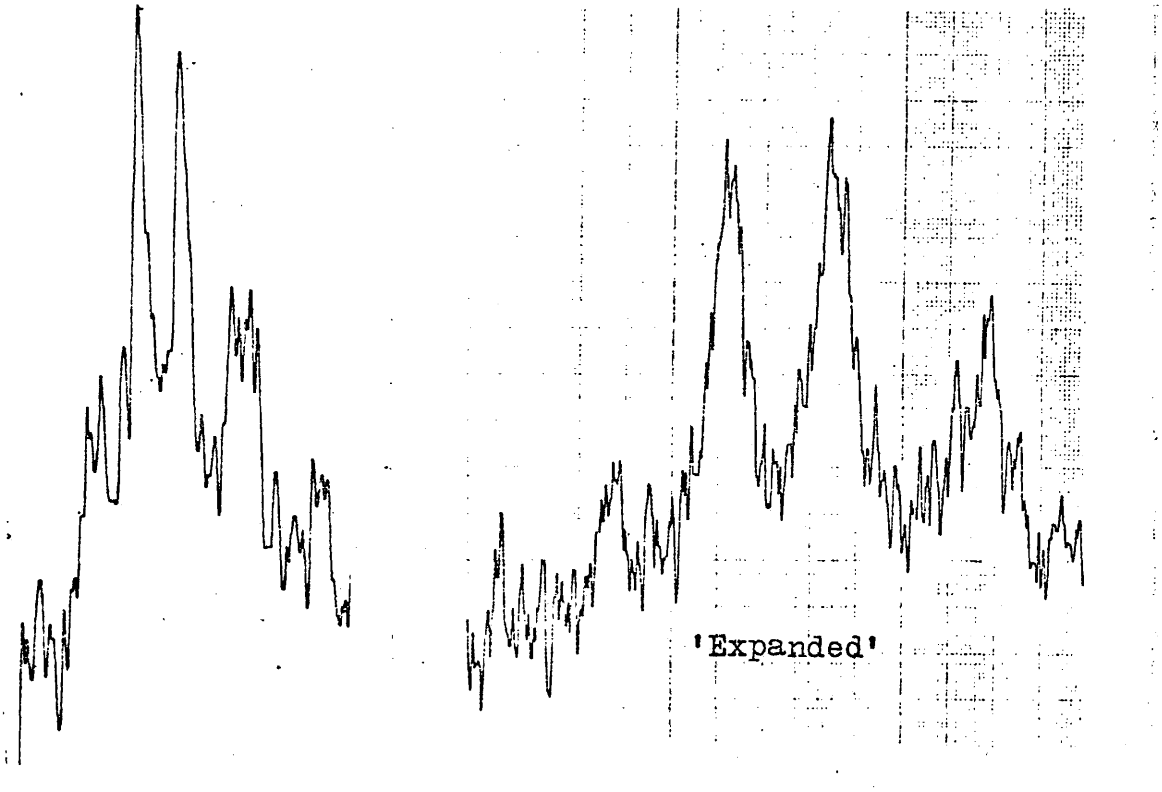
Spectrum No.55. 60 MHz ^{1}H N.m.r. spectra of dimethyl 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate (Xc) (5.40 mg, 1.128 x 10^{-5} mole) in CDCl$_3$ (0.7 ml) containing various amounts of Eu(fod)$_3$: (a) 0.00 mg; (b) 1.90 mg; (c) 7.98 mg; (d) 18.86 mg.


(b)
CH$_2$
CH$_3$
H$_3$C
NH
H$_{3,6}$
H$_{1,8}$
8
7
6
5
4 δ


(c)
CH$_2$
CH$_3$
CH$_3$
NH
H$_{1,8}$
H$_{3,6}$
H$_{11,18}$
9
8
7
6
5
4 δ



Upon addition of 107.89 mg of Eu(fod)$_3$, the methylene protons appear as an AB quartet (Spectrum 56).



Spectrum No.56. 100 MHz ^1H N.m.r. spectra of the methylene proton absorption of 5.40 mg of (Xc) in CDCl$_3$ (0.7 ml) in the presence of 107.89 mg of Eu(fod)$_3$.

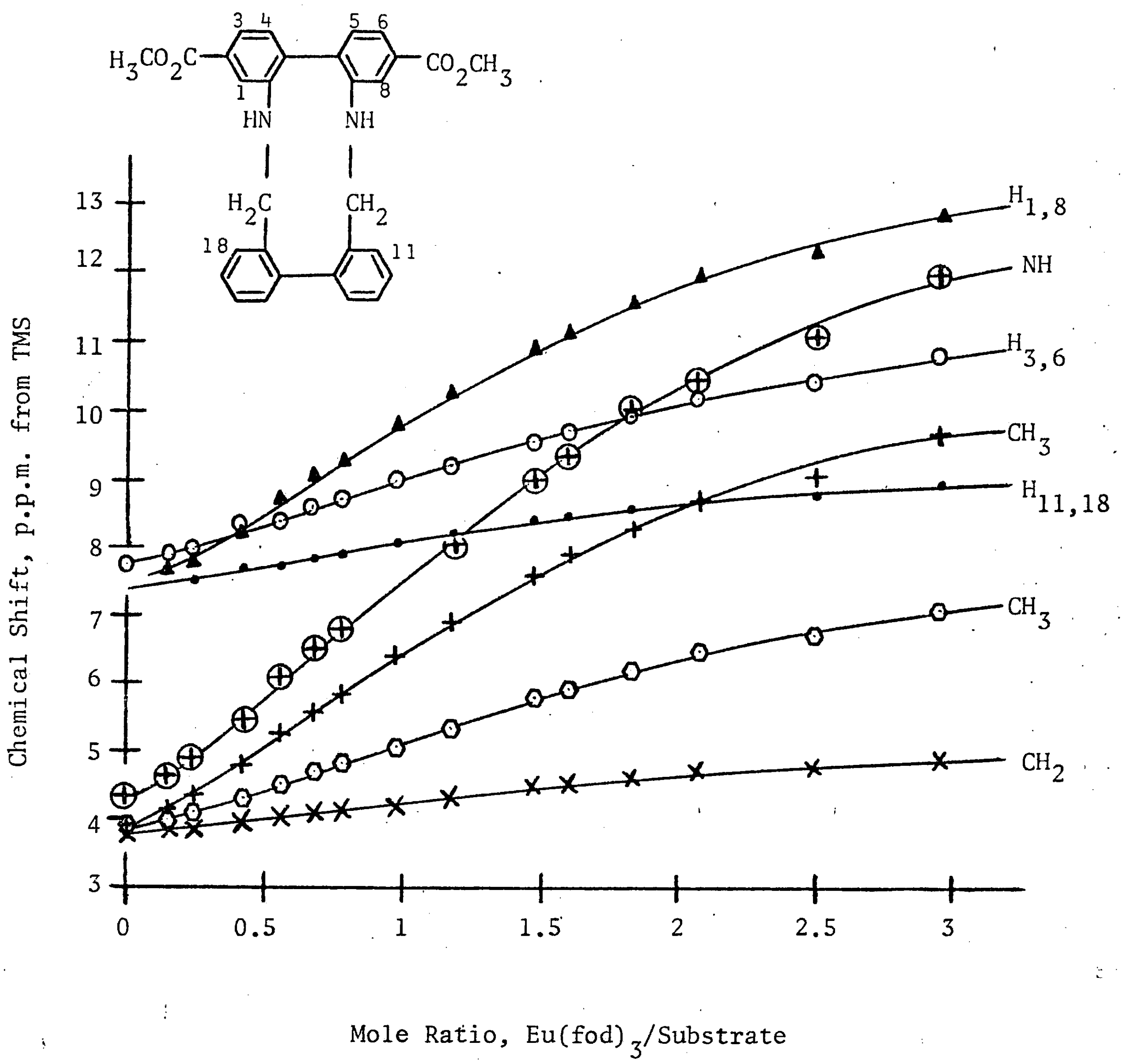


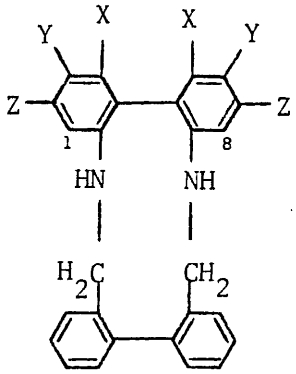
Figure No. 25. Variation in the chemical shift of some of the protons in (Xc) upon addition of Eu(fod)$_3$ in $CDCl_3$.

Figure 25 shows schematic representations of the quantitative study of the association of (Xc) with Eu(fod)$_3$ and reveals that the stiochiometry for the adduct formation is 2:1 for the molar ratio of Eu(fod)$_3$/(Xc). Also, the induced shifts for all solute protons are in the same direction, i.e. to the lower field values.

No enantiomeric shift differences could be detected on treatment of (X) with Eu(tfc)$_3$, (Xa) with Eu(tfc)$_3$ and Pr(tfc)$_3$, (Xb) with Pr(tfc)$_3$ and (Xc) with Eu(tfc)$_3$. It is difficult to conclude definitely at this stage that the above four compounds are achiral. In this connection, it is important to suggest that it may be necessary to try several other chiral shift reagents to achieve definite conclusions.

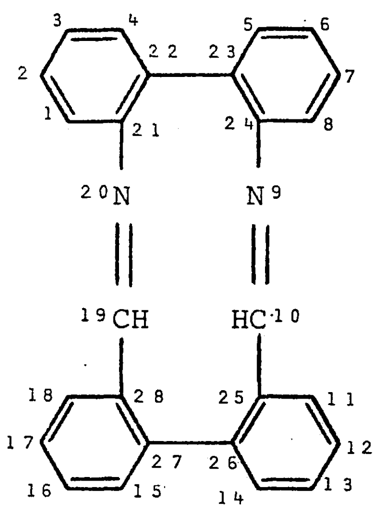
The chemical shift data of some of the protons of 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacycldodecine (X) and its derivatives (Xa), (Xb) and (Xc) are collected in Table 10.

Table No.10 Chemical shifts (δ; 60 and 220 MHz ; Me$_4$Si; CDCl$_3$) of methyl, methylene, secondary amine and some aromatic protons of compounds (X)-(Xc).

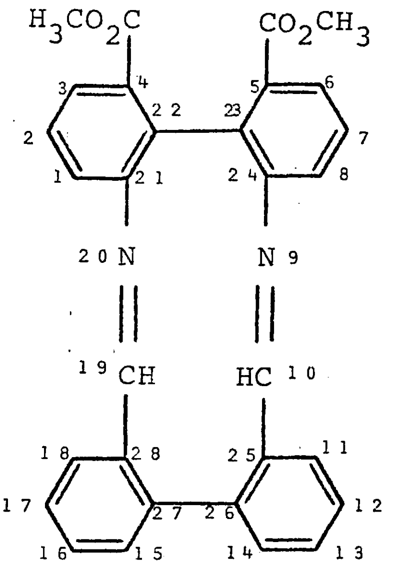


Compound	Substituent			Methyl Protons	Methylene Protons	Sec. Amine Protons	Aromatic Protons
	X	Y	Z	CH_3	CH_2	NH	$H_{1,8}$
X	H	H	H	----	3.78(q)	4.22(s)	6.66 - 6.86 (m)
Xa	CO_2CH_3	H	H	3.57(s)	4.00(o)	3.17(s)	6.69 - 6.74(d)
Xb	H	OCH_3	H	3.75(s) 3.78(s)	3.74(q)	4.11(s)	6.62 - 6.66 (d)
Xc	H	H	CO_2CH_3	3.86(s) 3.89(s)	3.79(q)	4.34(s)	7.40(s)

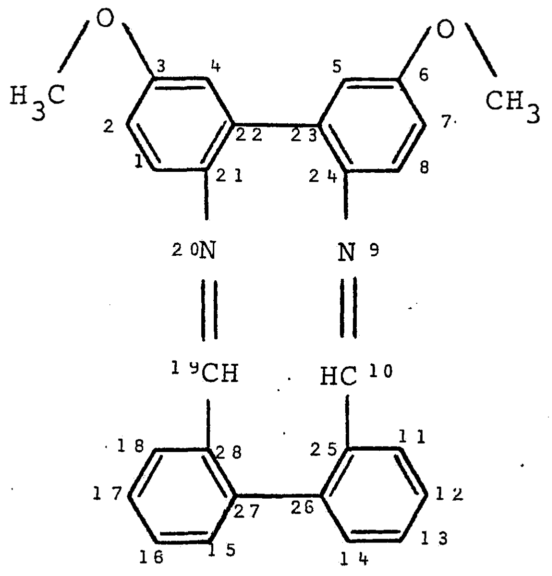
(s) singlet; (d) doublet; (q) quartet; (o) octet; (m) multiplet



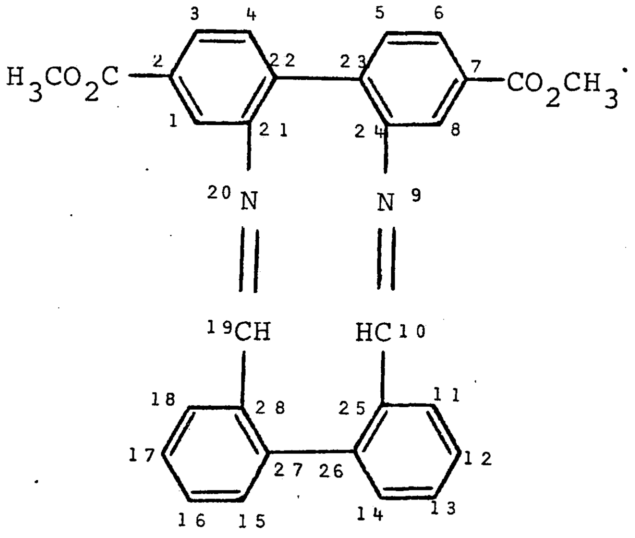
(IX)



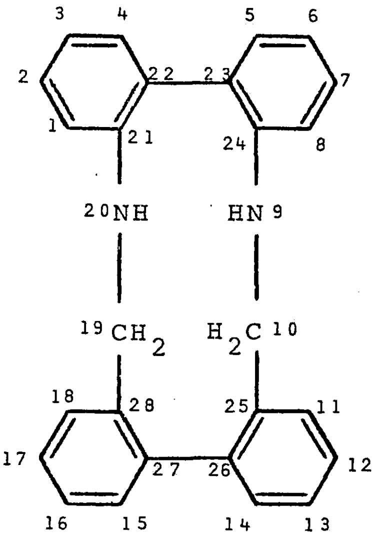
(IXa)



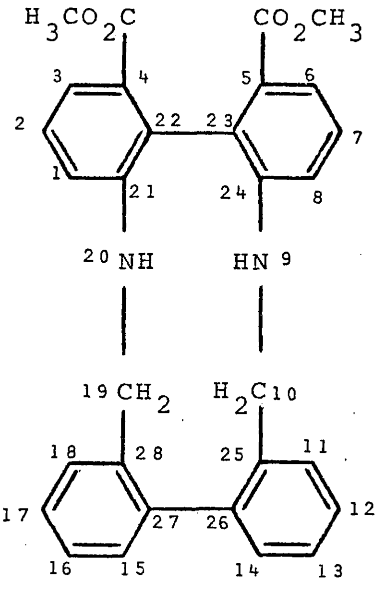
.(IXb)



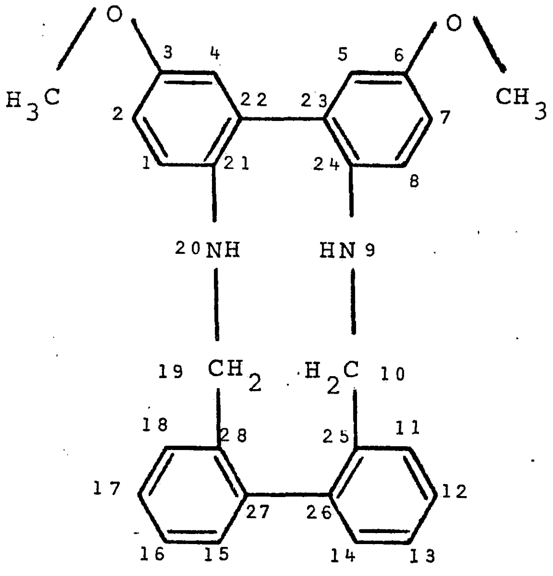
(IXc)


20NH
HN9
19CH$_2$
H$_2$C10

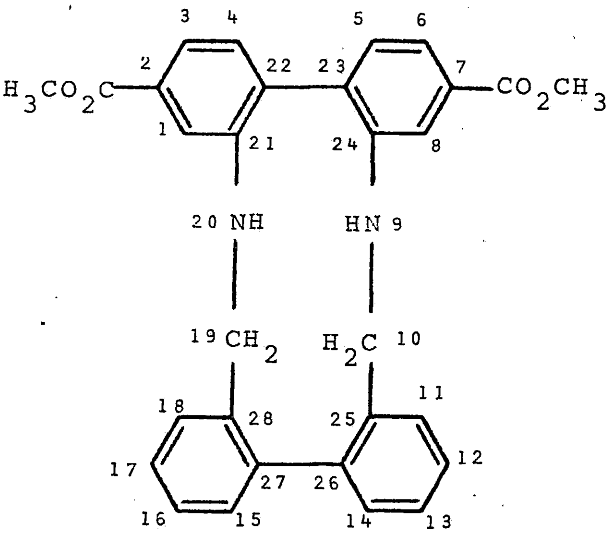
(X)


H$_3$CO$_2$C
CO$_2$CH$_3$
20 NH
HN 9
19 CH$_2$
H$_2$C10

(Xa)


O
H$_3$C
O
CH$_3$
20NH
HN 9
19 CH$_2$
H$_2$C 10

(Xb)


H$_3$CO$_2$C
CO$_2$CH$_3$
20 NH
HN 9
19 CH$_2$
H$_2$C 10

(Xc)

2.5. C-13 Magnetic Resonance Spectra

With the aid of complete proton decoupling it was possible to resolve all of the carbon resonances one from the other. It has also been possible by using off-resonance proton decoupling, substituent influences and spectral comparison of related compounds to make self-consistent and unambiguous assignments of nearly all of the resonances encountered.

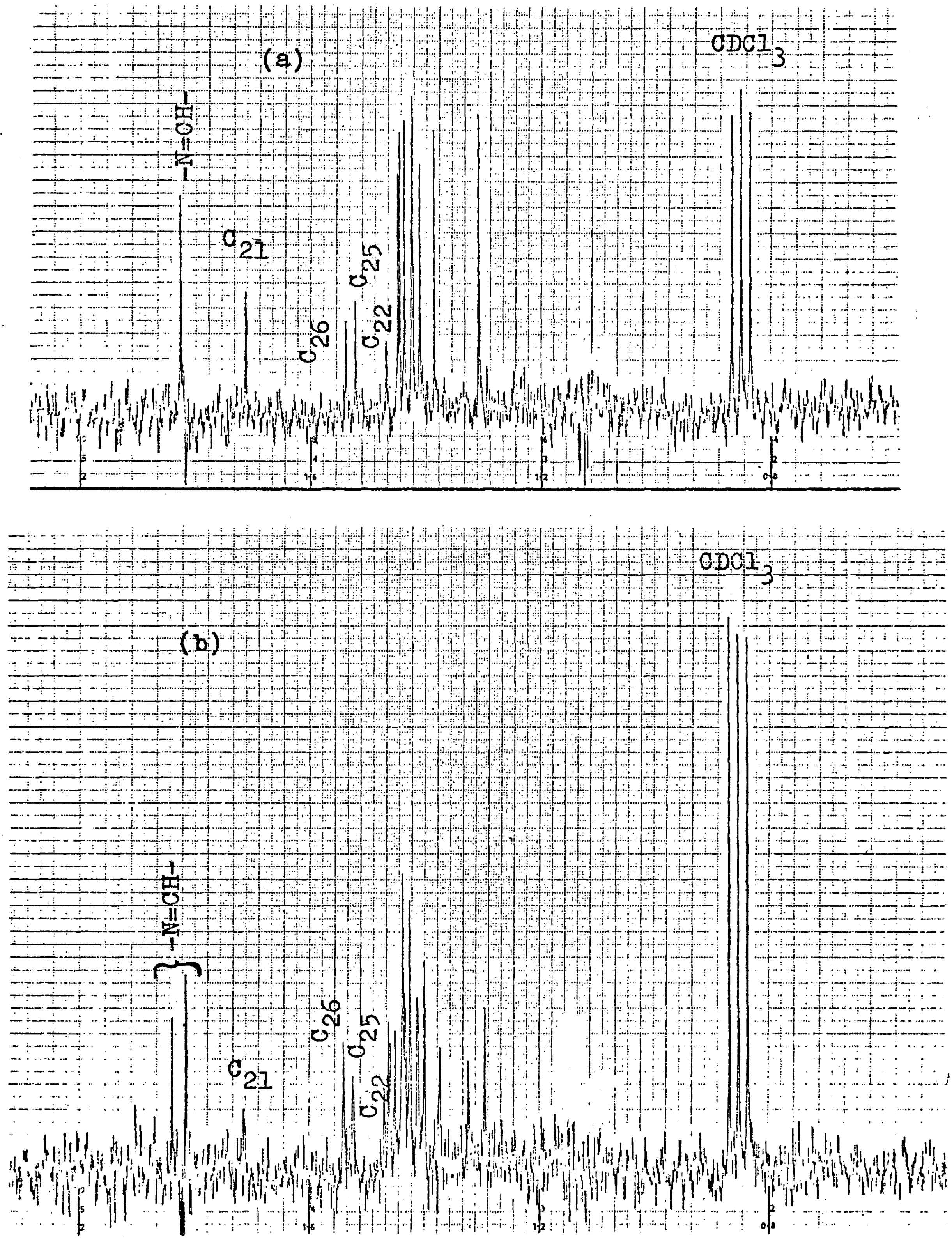
To facilitate the interpretation of the spectra, the eight compounds have been classified into two categories:

2.5.1. ^{13}C N.m.r. spectra of tetrabenzo[b,d,h,j][1,6]diazacyclododecine and its derivatives with substituents in *ortho*-, *meta*- or *para*-positions of the nitrogen biphenyl system.

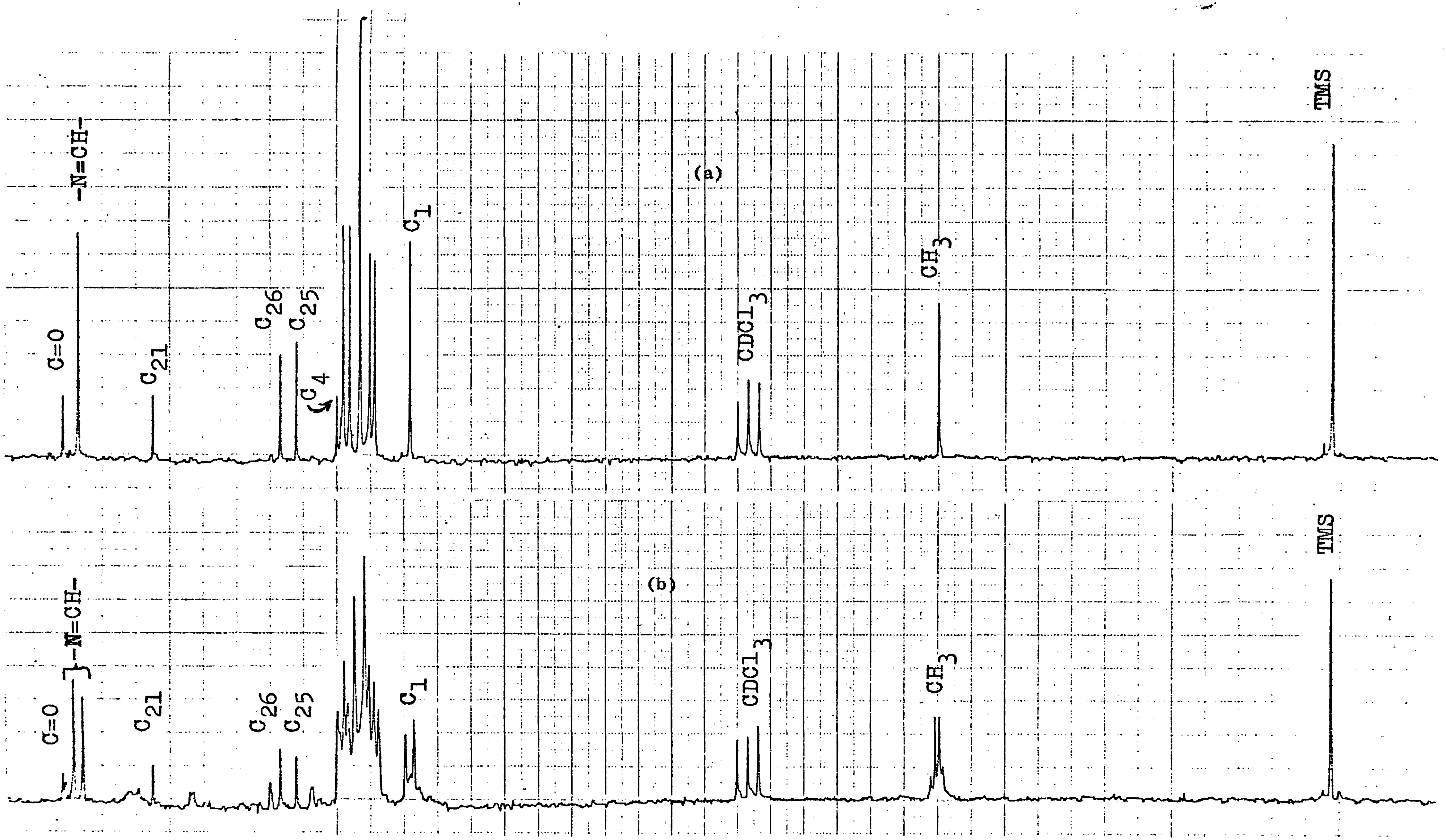
The complete proton decoupled ^{13}C n.m.r. spectra of compounds (IX - IXc) with their off-resonance proton decoupled spectra are given in Spectra 57 - 60. The observed chemical shifts for the aromatic carbons, aldimine, carbomethoxyl and methoxyl carbon nuclei for the same compounds are collected in Table 11. These results are discussed in turn in the following manner:

Methoxyl and carbomethoxyl carbon nuclei

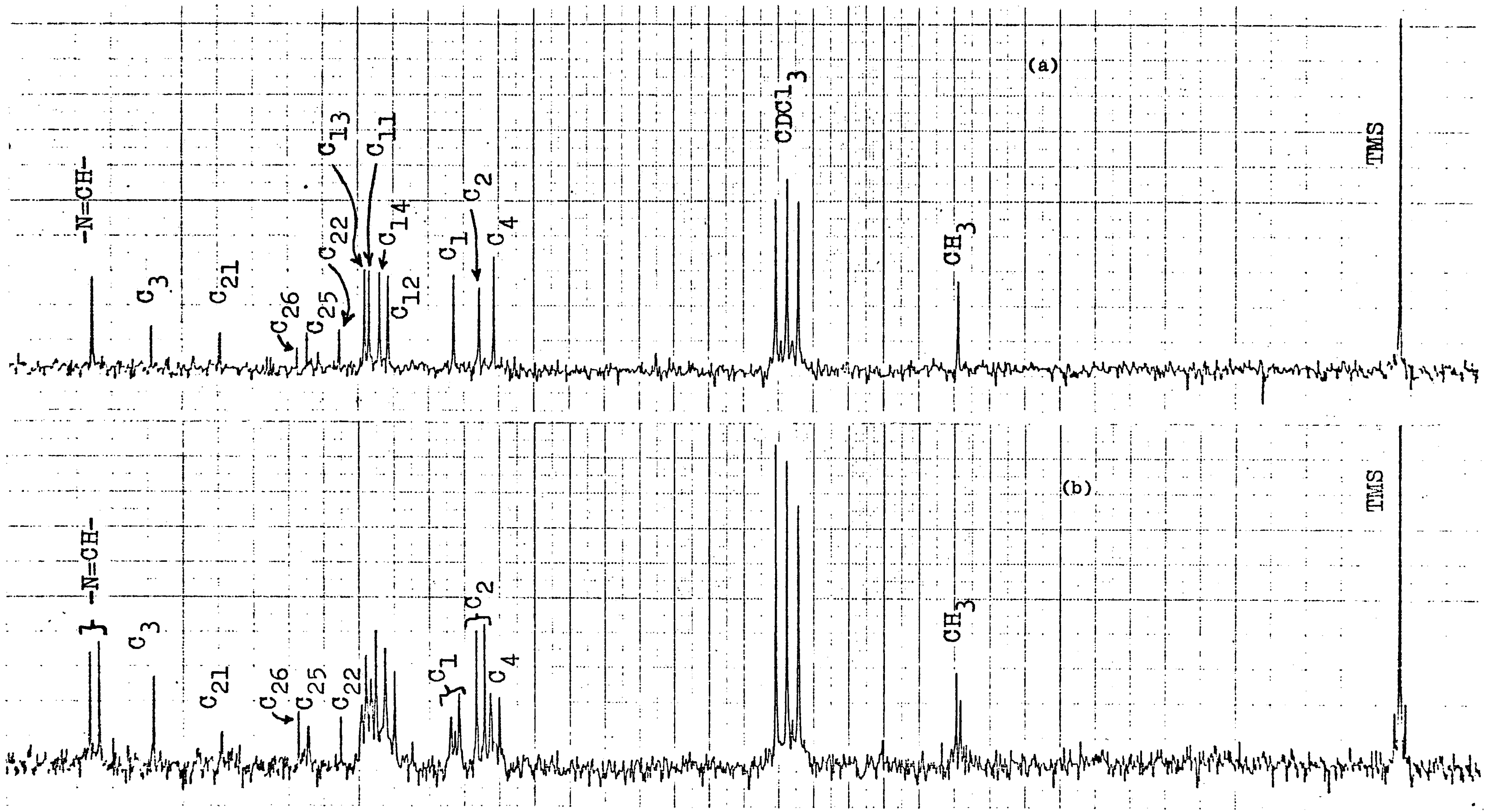
The assignment for the highfield methyl absorption of the methoxyl carbon is straightforward and unequivocal, as it appears as a quartet in the off-resonance proton decoupled spectrum. On the other hand, the carboxyl carbon absorbs at lowfield in a region relatively free of other signals. The small lowfield shift (1.2 p.p.m.) experienced by the carboxyl carbon in compound (IXa) relative to compound (IXc) can be attributed to reduced conjugation between the aromatic benzene ring and the carbomethoxyl group as a result of steric interference.



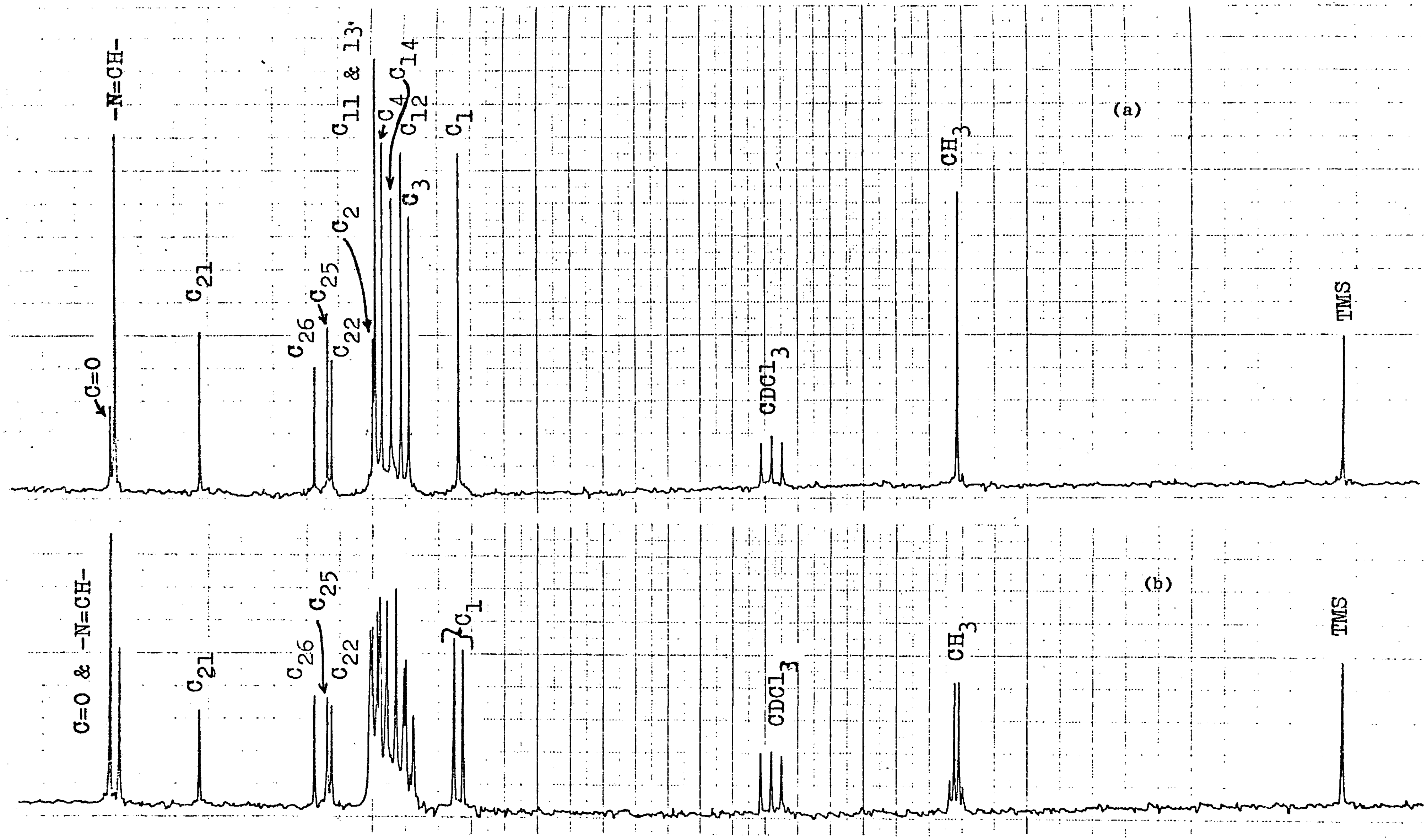
Spectrum No.57. 22.63 MHz ^{13}C F.T. n.m.r. spectra of tetrabenzo[b,d,h,j]-[1,6]diazacyclododecine (IX) in CDCl$_3$ (a) proton noise-decoupled; (b) off-resonance proton-decoupled.



Spectrum No.58. 22.63 MHz ^{13}C F.T. n.m.r. spectra of dimethyl tetrabenzo[b,d,h,j][1,6]diazacyclododecine-4,5-dicarboxylate (IXa) in $CDCl_3$ (a) proton noise-decoupled; (b) off-resonance proton-decoupled.

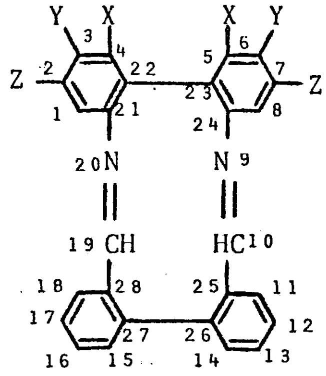


<u>Spectrum No.59</u>. 22.63 MHz ^{13}C F.T. n.m.r. spectra of 3,6-dimethoxytetrabenzo[*b*,*d*,*h*,*j*][1,6]-diazacyclododecine (IXb) in $CDCl_3$ (a) proton noise-decoupled; (b) off-resonance proton-decoupled.



Spectrum No.60. 22·63 MHz ^{13}C F.T. n.m.r. spectra of dimethyl tetrabenzo[b,d,h,j][1,6]-diazacyclododecine-2,7-dicarboxylate (IXc) in $CDCl_3$ (a) proton noise-decoupled; (b) off-resonance proton-decoupled.

Table No.11. The observed carbon-13 chemical shift of tetrabenzo[b,d,h,j][1,6]diazacyclododecine and its ortho-, meta- and para-derivatives in $CDCl_3$ relative to TMS, in p.p.m.



Compound	Substituent			Carbomethoxyl Group		Aldimine Group	Aromatic Carbons											
							Amine Biphenyl Carbons				Aldehyde Biphenyl Carbons				Quaternary Carbons			
	X	Y	Z	CH_3O	>C=O	-CH=N-	$C_{1,8}$	$C_{2,7}$	$C_{3,6}$	$C_{4,5}$	$C_{11,18}$	$C_{12,17}$	$C_{13,16}$	$C_{14,15}$	$C_{21,24}$	$C_{22,23}$	$C_{25,28}$	$C_{26,27}$
IX	H	H	H	---	---	164.65	118.2	129.8*	125.1	128.65*	130.5	127.4	130.8	128.5	154.4	132.5	137.3	138.85
IXa	CO_2CH_3	H	H	52.0	167.7	165.7	121.9	128.5	126.5	[131.5]	129.5	127.2	129.85	128.5	155.85	130.7	136.9	139.0
IXb	H	OCH_3	H	55.5	---	164.5	119.1	115.9⊕	[157.1]	114.1⊕	129.8	127.4	130.3	128.5	148.4	133.55	137.6	138.9
IXc	H	H	CO_2CH_3	52.1	166.5	165.85	119.5	[131.1]	126.2	129.85	130.7	127.3	130.8	128.6	154.4	136.6	137.2	138.9

Square brackets indicate carbons carrying additional substituents.

* It is possible that these assignments should be reversed.

⊕ It is possible that these assignments should be reversed.

It is quite clear from Table 11, that the absorption for the methoxyl carbon appears at somewhat higher field than that of a methoxyl group bonded directly to an aromatic ring, but it is difficult to account for this difference on the basis of the presently available data.

Aldimine carbon nuclei

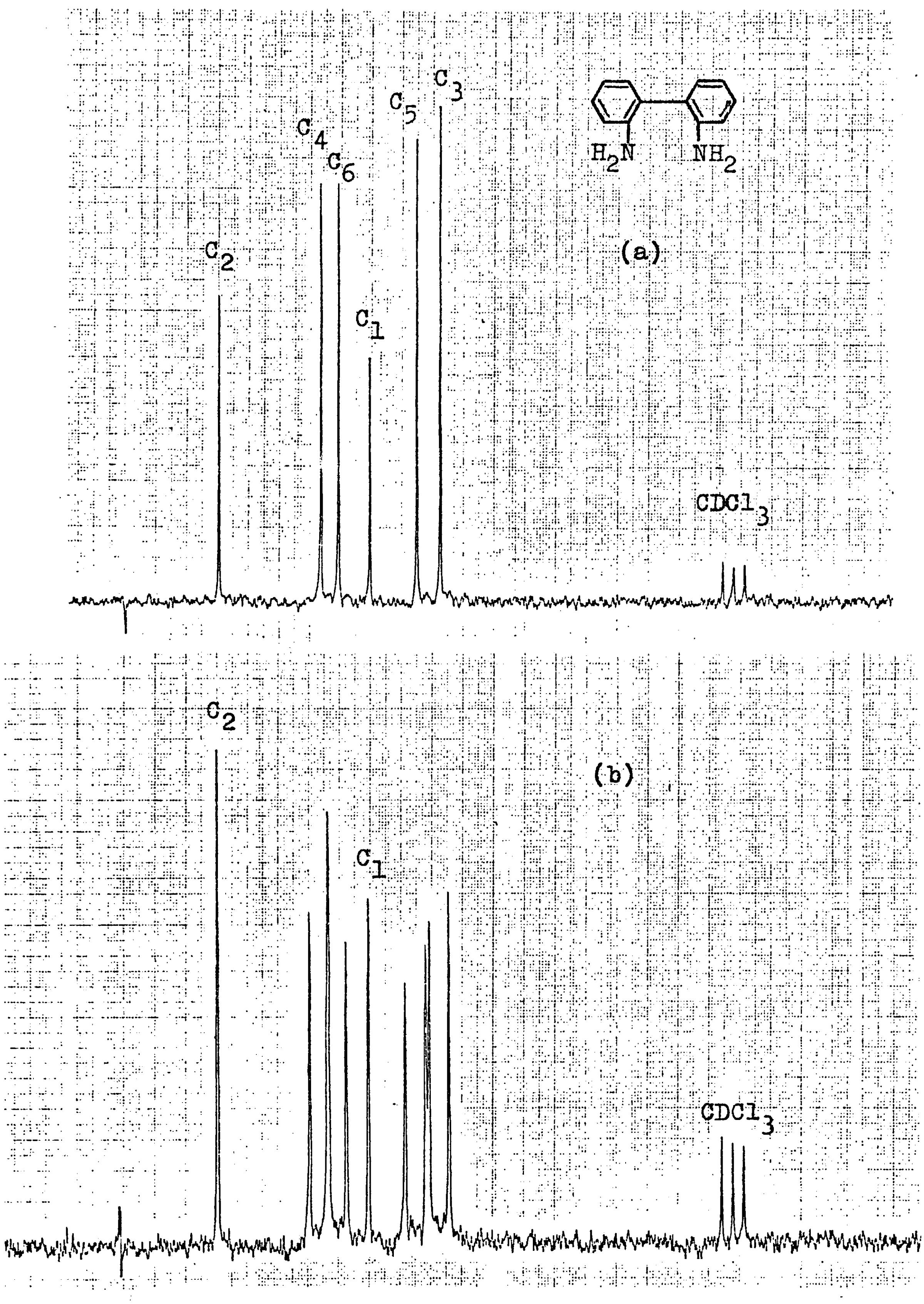
These are easily assigned by the off-resonance proton decoupled spectra, where a clean doublet is observed. The slight upfield shift experienced by the aldimine carbon in compound (IXb) and the small downfield shifts experienced by the same nuclei in compounds (IXa) and (IXc) relative to compound (IX) may be in line with the inductive effects of the substituents.

Aromatic carbon nuclei

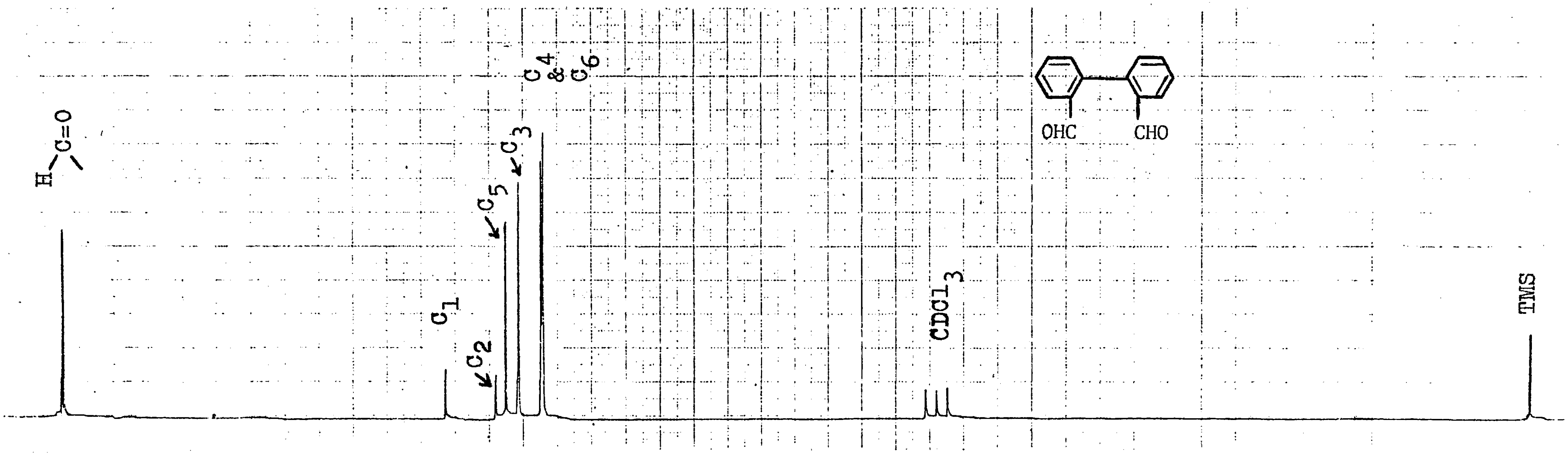
A distinction between the quaternary carbons and the others is straightforward, since the former give rise to single bands in the off-resonance proton decoupled spectra.

A complete assignment in complex molecules can generally not be achieved without utilizing the tool of spectral comparison. This is not possible, however, unless a series of closely related compounds is available.

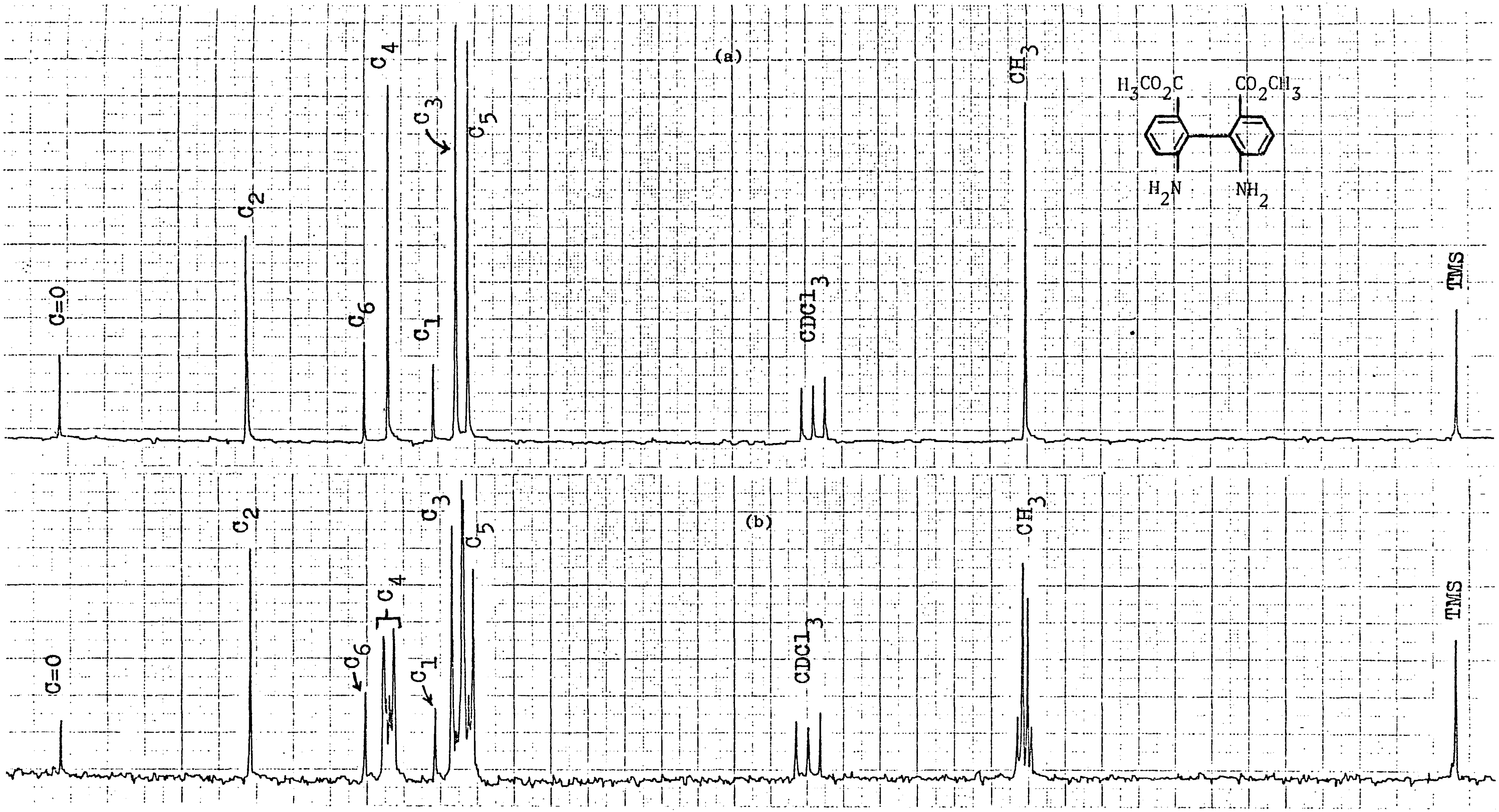
The complete proton decoupled ^{13}C n.m.r. spectra of 2,2'-diaminobiphenyl, biphenyl-2,2'-dialdehyde, dimethyl 2,2'-diaminobiphenyl-6,6'-dicarboxylate, 2,2'-dinitro-5,5'-dimethoxybiphenyl, dimethyl 2,2'-dinitrobiphenyl-4,4'-dicarboxylate, 2,2'-diaminobiphenyl-4,4',6,6'-tetramethyl and benzylideneaniline together with their off-resonance proton decoupled spectra are given in Spectra 61 - 67, respectively. From the obtained signal multiplicities in the off-resonance proton decoupled spectra (it is possible to discriminate between methyl, methylene, methine and quaternary carbons) and from the predictions of additivity calculations[79],



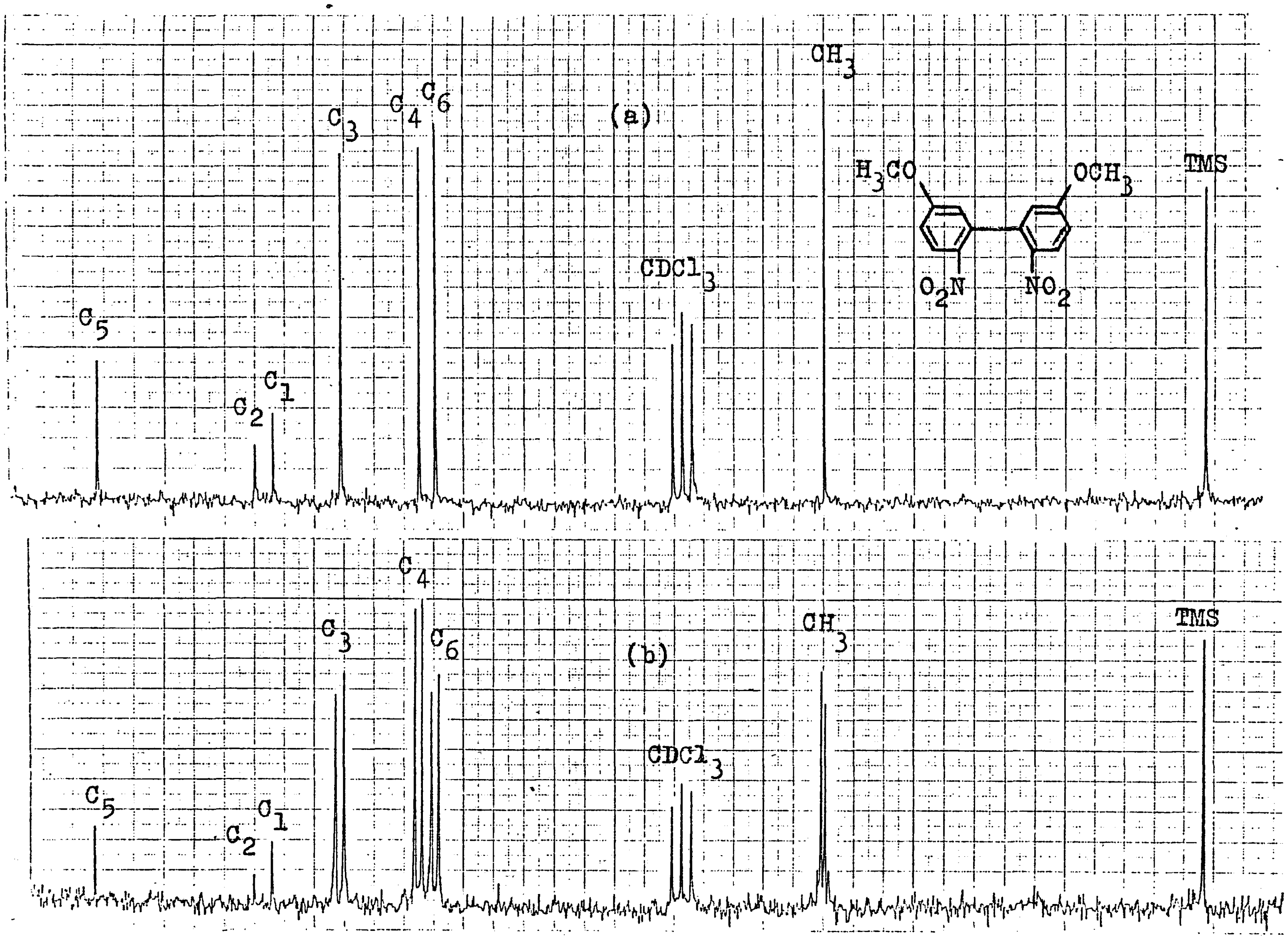
Spectrum No. 61. 22·63 MHz ^{13}C F.T. n.m.r. spectra of 2,2'-diaminobiphenyl in CDCl$_3$ (a) proton noise-decoupled; (b) off-resonance proton-decoupled.



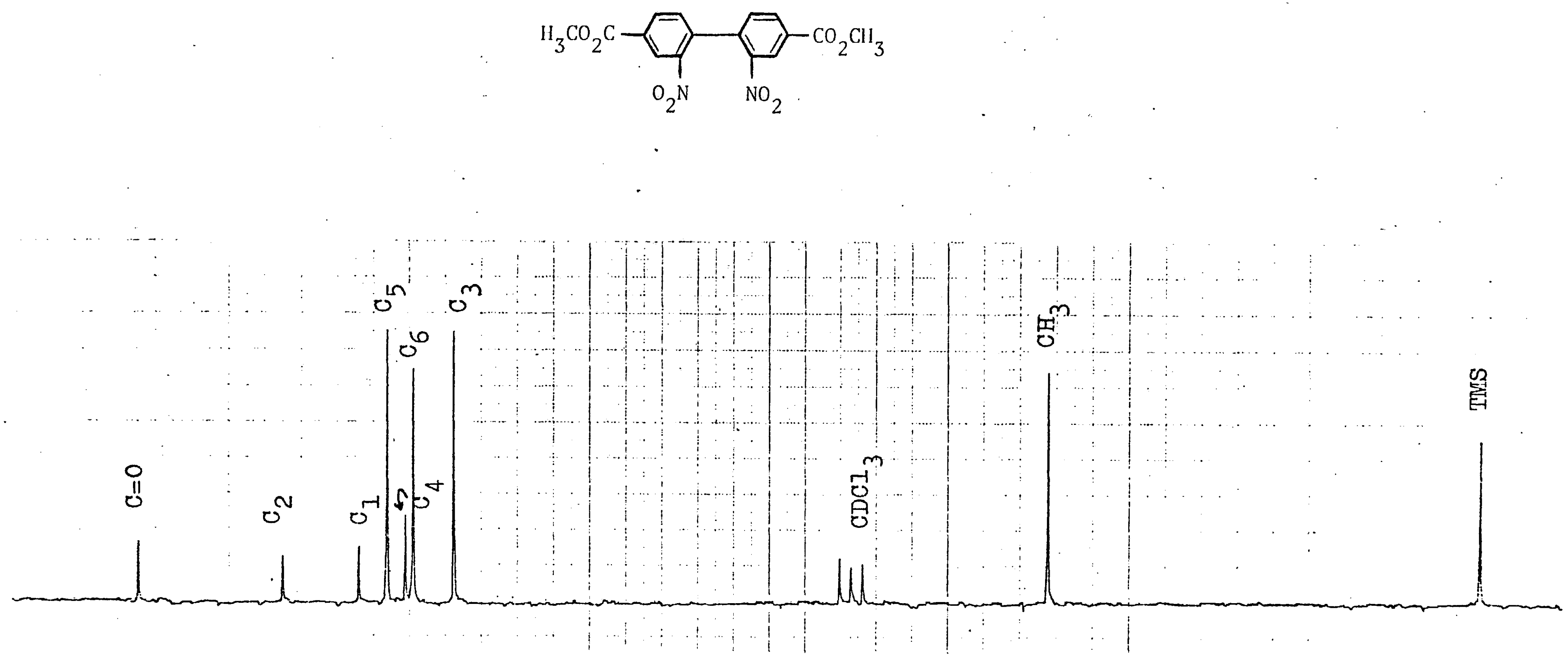
Spectrum No. 62. 22.63 MHz ^{13}C F.T. n.m.r. spectrum of biphenyl-2,2'-dialdehyde in $CDCl_3$ under proton noise-decoupling conditions.



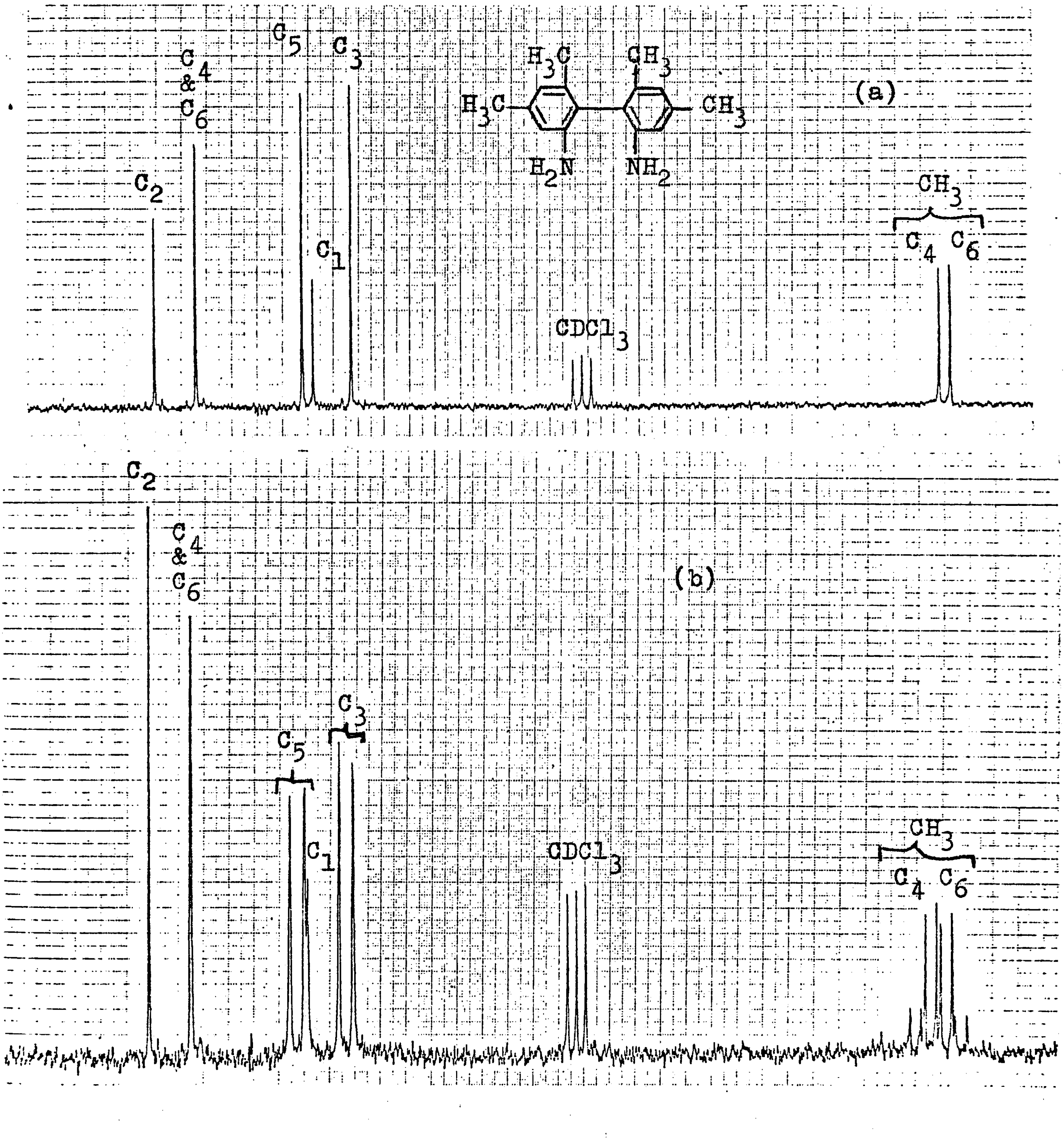
Spectrum No.63. 22·63 MHz ^{13}C F.T. n.m.r. spectra of dimethyl 2,2'-diaminobiphenyl-6,6'-dicarboxylate in $CDCl_3$ (a) proton noise-decoupled; (b) off-resonance proton-decoupled.



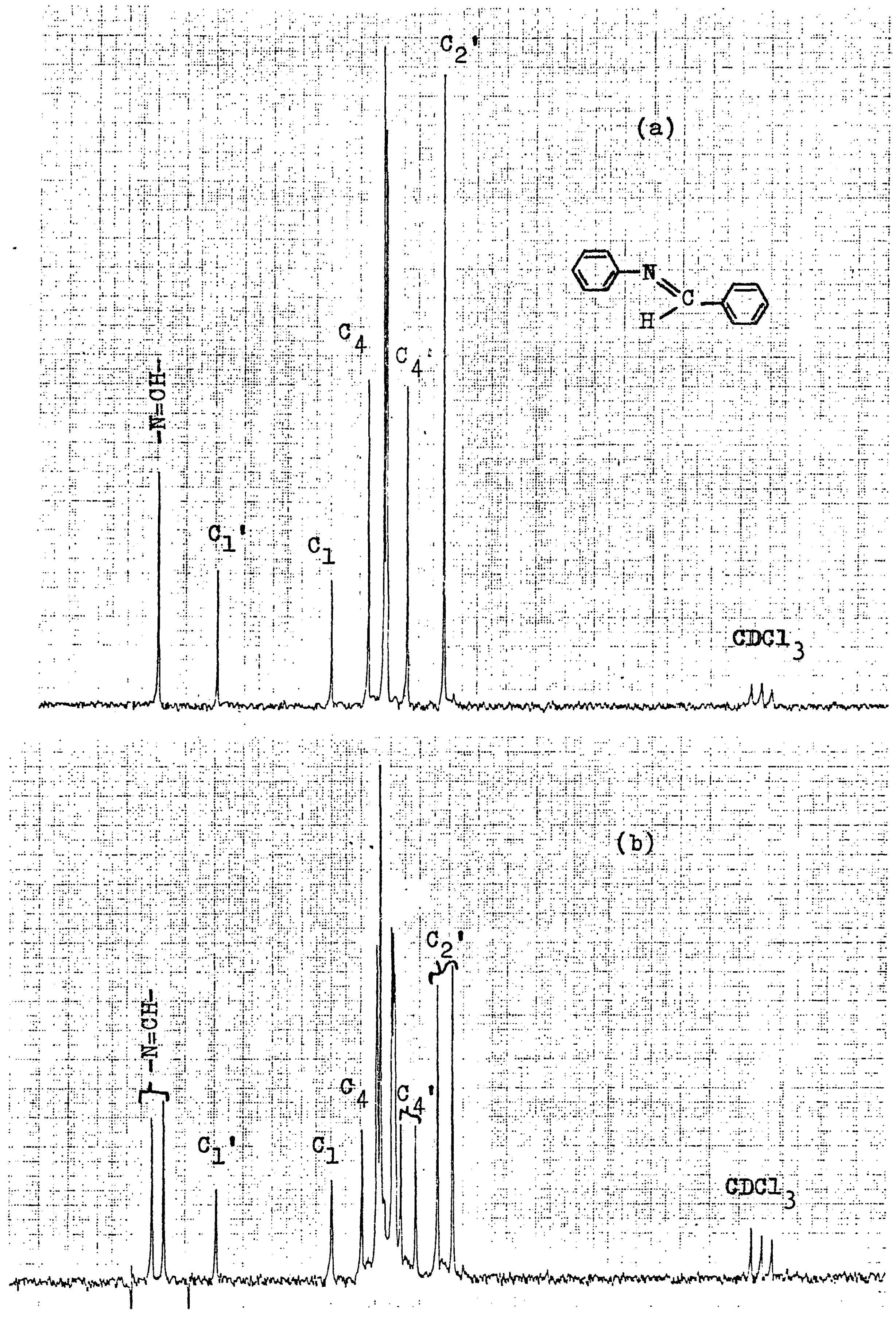
Spectrum No.64. 22·63 MHz ^{13}C F.T. n.m.r. spectra of 2,2'-dinitro-5,5'-dimethoxybiphenyl in $CDCl_3$ (a) proton noise-decoupled; (b) off-resonance proton-decoupled



Spectrum No.65. 22·63 MHz ^{13}C F.T. n.m.r. spectrum of dimethyl 2,2'-dinitrobiphenyl-4,4'-dicarboxylate in CDCl$_3$ under proton noise-decoupling conditions.

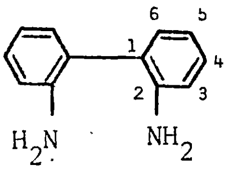
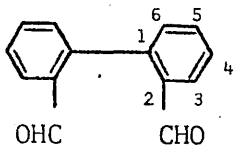
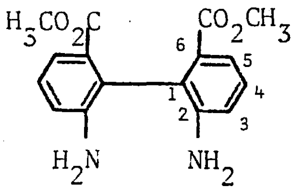
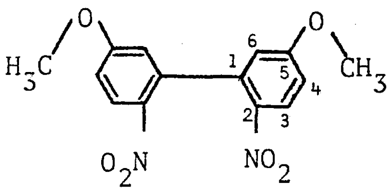
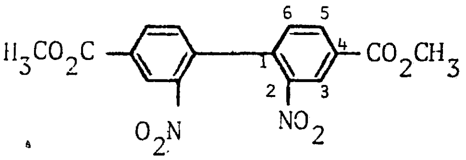
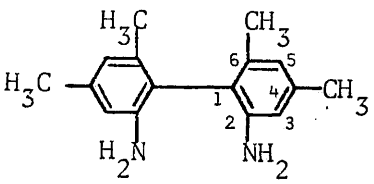
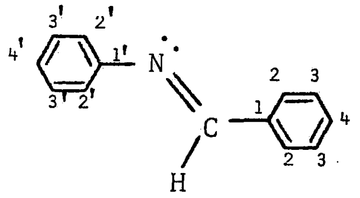


Spectrum No.66. 22·63 MHz ^{13}C F.T. n.m.r. spectra of 2,2'-diaminobiphenyl-4,4',6,6'-tetramethyl in $CDCl_3$ (a) proton noise-decoupled; (b) off-resonance proton-decoupled.



Spectrum No.67. 22.63 MHz ^{13}C F.T. n.m.r. spectra of benzylideneaniline in $CDCl_3$ (a) proton noise-decoupled; (b) off-resonance proton-decoupled.

Table No.12. The observed and calculated aromatic carbon-13 chemical shift of some substituted biphenyls and benzylideneaniline together with the chemical shift of the functional groups in $CDCl_3$ solutions relative to TMS, in p.p.m.

Compound	Carbon Position	Observed	Calculated*	Functional Group Observed
	1	124.5	129.3	
	2	144.1	146.8	
	3	115.4	116.8	
	4	130.9	129.0	
	5	118.45	119.7	
	6	128.6	128.9	
	1	141.2	142.9	Aldehyde $H_{>}C{=}O$
	2	134.6	136.6	
	3	131.7	130.4	
	4	128.8	128.9	
	5	133.4	135.2	190.9
	6	128.6	128.8	
	1	122.8	128.8	Carbomethoxyl
	2	145.1	146.3	OCH_3 >CO
	3	120.2	120.3	
	4	128.4	128.5	51.8 167.6
	5	118.8	119.2	
	6	131.3	130.2	
	1	137.5	136.4	Methoxyl
	2	140.2	138.3	
	3	127.5	123.9	OCH_3
	4	115.8	113.0	
	5	163.4	165.4	56.1
	6	113.4	112.9	
	1	137.65	139.9	Carbomethoxyl
	2	146.9	146.7	
	3	126.0	123.4	OCH_3 >C=O
	4	131.9	129.8	
	5	134.2	134.7	52.9 164.5
	6	131.0	127.9	
	1	119.4	124.5	Methyl
	2	144.4	148.7	
	3	113.5	112.3	CH_3
	4	137.8	138.4	
	5	121.1	117.6	C_4 21.3
	6	137.8	138.0	C_6 19.5
	1'	151.9 ⊕	---	
	1	136.2	---	
	2'	120.8	---	Aldimine
	2	128.7?	---	N=CH
	3'	128.7?	---	159.9
	3	129.0?	---	
	4'	125.8	---	
	4	131.1	---	

---

*The calculated C-13 chemical shifts in substituted biphenyls are based on the values of biphenyls and mono-substituted benzenes given by Stothers[122] and Schulman et al.[86]

⊕The assignments of the observed C-13 chemical shifts in benzylideneaniline are based on the values given by Inamoto et al.[123] and Ruxer et al.[124]

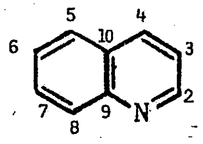
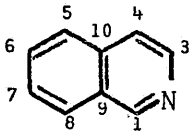
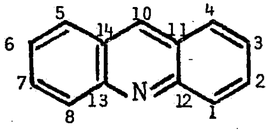
complete analyses for peak assignments were made unequivocally. The observed and the calculated values of the aromatic carbon-13 chemical shifts together with the observed chemical shifts of carbon-13 in those groups incorporated in these molecules are summarized in Table 12. The chemical shift data summarized in Table 12 are considered as a basis for discussing the diazacyclododecine compounds.

The difference of about 22 p.p.m. between two of the quaternary carbon signals in compound (IX) strongly supports the assignment of the lower field signal to $C_{21,24}$, α to nitrogen; while the β quaternary carbon, ($C_{22,23}$) in the amine biphenyl unit is shielded. The above assignments are in line with those given by Pugmire et al.[121] for quinoline, isoquinoline and acridine, Table 13.

The assignment of the bridgehead carbons ($C_{21,24}$) in compound (IXb) is in good agreement with the conjugative effect of the methoxyl substituent. It is interesting to note that the small upfield shift (-1.8 p.p.m.) experienced by $C_{22,23}$ in compound (IXa) compared with that in (IX) probably arises from the steric effects in terms of the repulsive forces between the closely spaced carbomethoxyl groups.

As mentioned earlier, the ultra-violet spectra and the ^{1}H n.m.r. spectra can be satisfactorily interpreted in terms of a non-planar structure for the Ph-N=CH-Ph part of the molecule in which the aniline ring cannot conjugate fully with the benzal-amino π-system. The bridgehead carbons $C_{25,28}$ and $C_{26,27}$ (β and γ to nitrogen, respectively) in the aldehyde biphenyl unit show downfield shifts in comparison to the bridgehead carbon $C_{22,23}$ (β to nitrogen) in the amine biphenyl unit, Table 11. It is clear now that the bridgehead carbon signals in the aldehyde biphenyl unit are not much affected by the different substituents

Table No. 13. ^{13}C shieldings of some polycyclic heterocycles in p.p.m. relative to TMS

Compound	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}
	-	151.1	121.7	136.2	128.5	127.0	129.9	130.3	149.1	128.9
	153.3	-	144.0	121.0	127.0	130.7	127.7	128.1	129.3	136.2
	$C_{1,8}$	$C_{2,7}$	$C_{3,6}$	$C_{4,5}$	C_{10}	$C_{11,14}$	$C_{12,13}$			
	129.7	128.5	125.7	130.5	136.1	126.7	149.3			

in the amine biphenyl unit in comparison to the shifted bridgehead carbon signals in the amine biphenyl unit.

In line with the above conclusion, it is found that the protonated carbons in the aldehyde biphenyl unit are not affected by the different substituents in the amine biphenyl unit as well. The assignments of the protonated carbon signals of $C_{11,18}$; $C_{12,17}$; $C_{13,16}$ and $C_{14,15}$ are based on their appearance as a doublet in the off-resonance proton decoupled spectrum and the fact that their chemical shifts parallel those obtained in biphenyl-2,2'-dialdehyde and benzylideneaniline, Table 12. Unequivocal assignments of the above protonated carbon signals, possibly, could be made using selective proton decoupling technique and/or specifically labelled materials would be required.

It is interesting to note that the aldimine group CH=N has significant deshielding effect (+ 1.8 p.p.m.) on the ortho-carbons $C_{11,18}$ of the rings attached to carbons. On the other hand, it has a pronounced shielding effect (-10.5 p.p.m.) on the ortho-carbons $C_{1,8}$ of the rings attached to nitrogens with significant shielding effect (-3.6 p.p.m.) on the para-carbons $C_{3,6}$, Table 11 (compound IX).

The assignment of the carbon bearing methoxyl group $C_{3,6}$ in compound (IXb) is straight forward and unequivocal because of the marked deshielding effect of the methoxyl group. This peak is the lowest field signal in the aromatic region and appears as a singlet in the off-resonance proton decoupled spectrum. Since an increase in the electron density is expected at the ortho- and para-positions, then the ortho-carbons $C_{2,7}$ and $C_{4,5}$ are markedly shielded, while the effect of methoxyl group on the meta-carbon $C_{1,8}$ is a small deshielding effect.

In compounds (IXa) and (IXc), the carbon bearing the carbomethoxyl group is deshielded and appeared as a singlet in the off-resonance spectra. The electron-withdrawing tendency of the carbomethoxyl group is evident from its deshielding effect on the *para*-carbon. Less deshielding effect is observed on the *ortho*-carbon, Table 11.

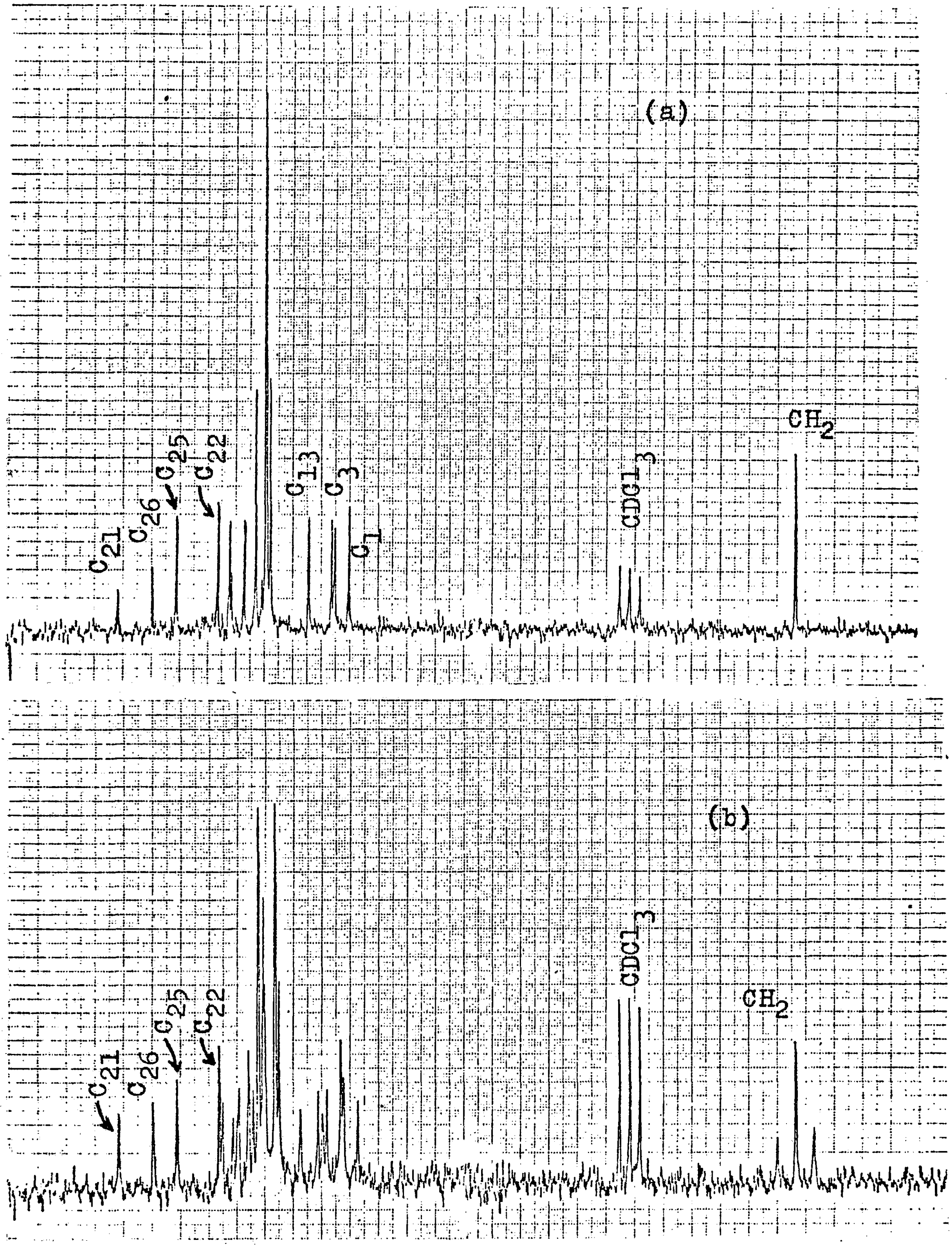
2.5.2. ^{13}C N.m.r. spectra of 9,10,19,20-tetrahydrotetrabenzo[*b*,*d*,*h*,*j*]-[1,6]diazacyclododecine and its derivatives with substituents in *ortho*-, *meta*- or *para*-positions of the nitrogen biphenyl system

The complete proton decoupled ^{13}C n.m.r. spectra of compounds (X - Xc) with their off-resonance proton decoupled spectra are given in Spectra 68 - 71. The observed chemical shifts for the aromatic carbons, carbomethoxyl, methoxyl and methylene nuclei for the same compounds are collected in Table 14. These results are discussed in turn in the following order:

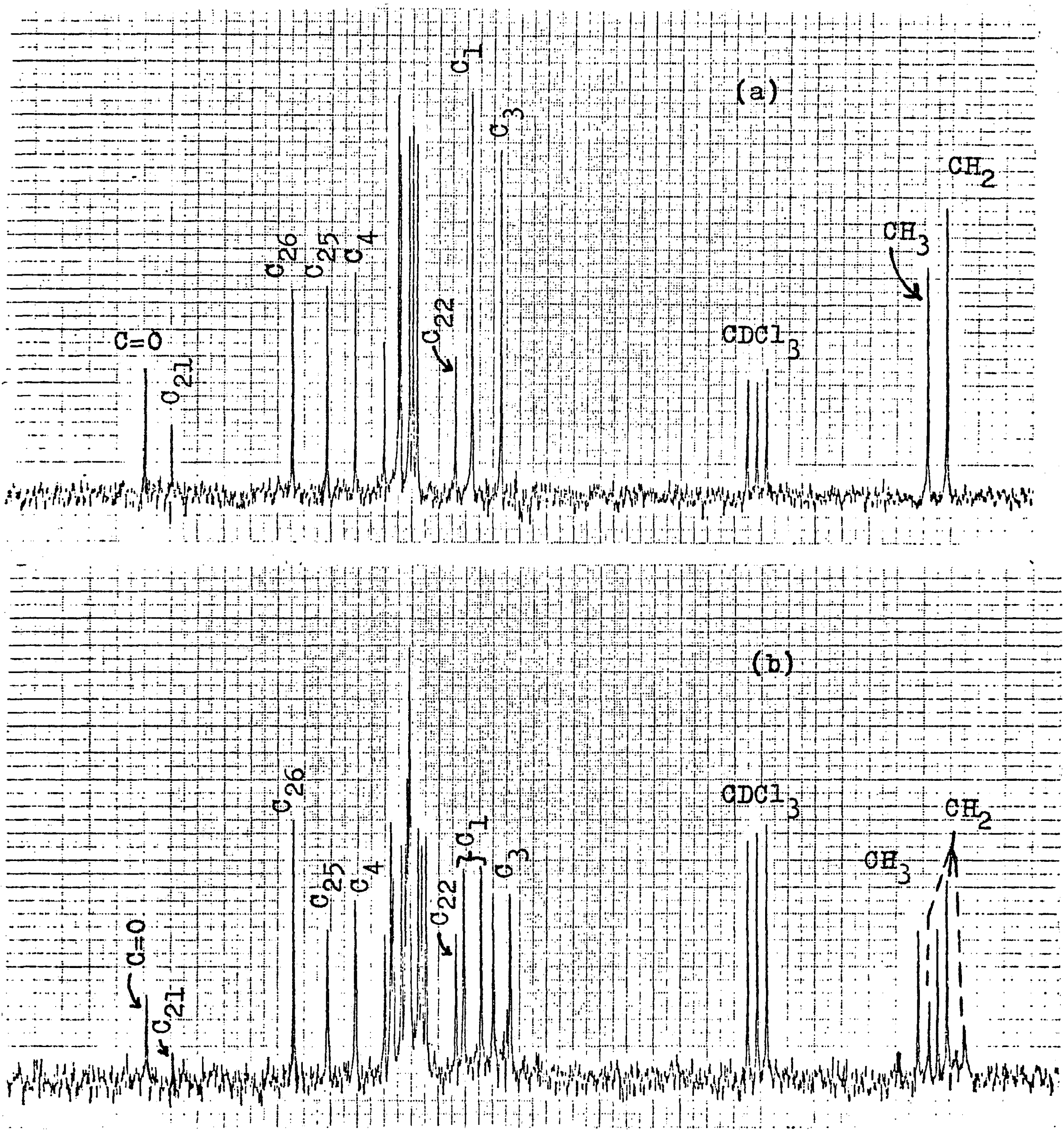
Methoxyl and carbomethoxyl carbon nuclei

Confident assignment of the highfield methyl absorption of the methoxyl and carbomethoxyl carbon nuclei could be made from its quartet splitting in the off-resonance proton decoupled spectra. The complete proton decoupled ^{13}C n.m.r. spectra of compounds (Xb) and (Xc) in $CDCl_3$ showed a doublet for the methyl carbon signal which is probably due to two non-equivalent conformers. The complete proton decoupled ^{13}C n.m.r. spectrum of compound (Xc) in [$^2H_6$] DMSO, Spectrum 72, still showed the doublet for the methyl carbon which supports the above suggestion.

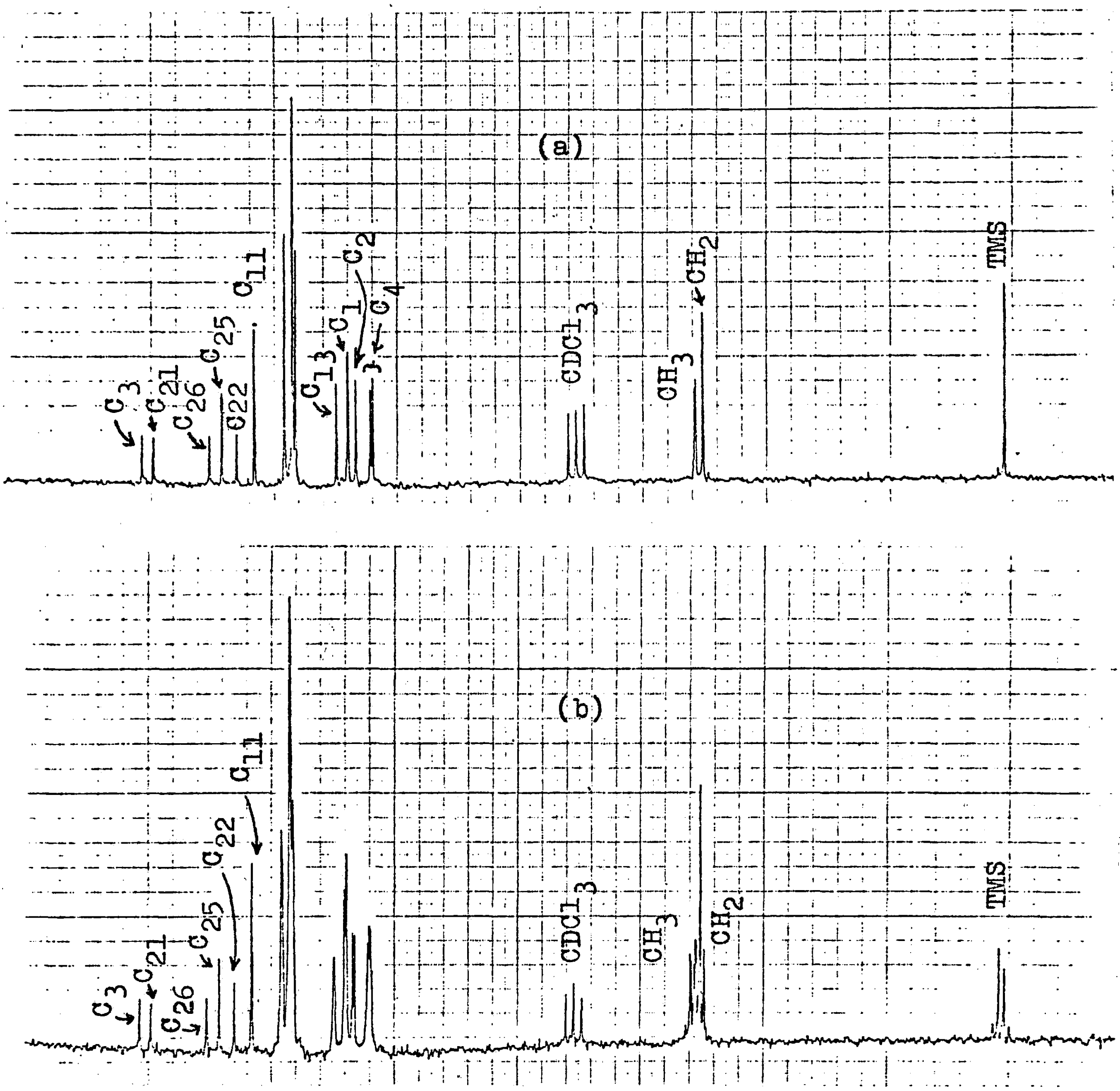
The carboxyl carbon in compounds (Xa) and (Xc) absorbed at lowfield in a region relatively free of other signals. Spectral



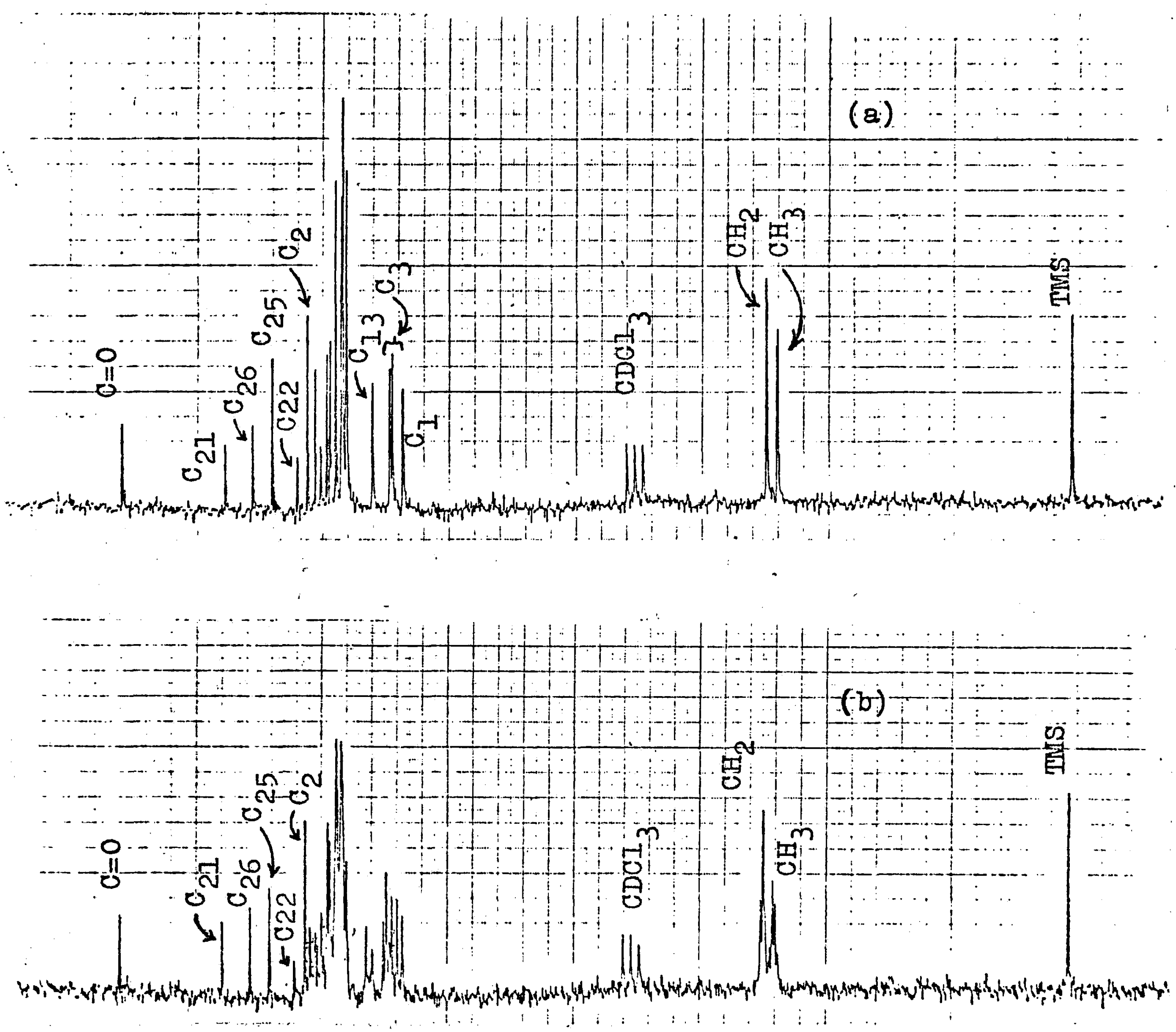
Spectrum No.68. 22·63 MHz ^{13}C F.T. n.m.r. spectra of 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine (X) in $CDCl_3$ (a) proton noise-decoupled; (b) off-resonance proton-decoupled.



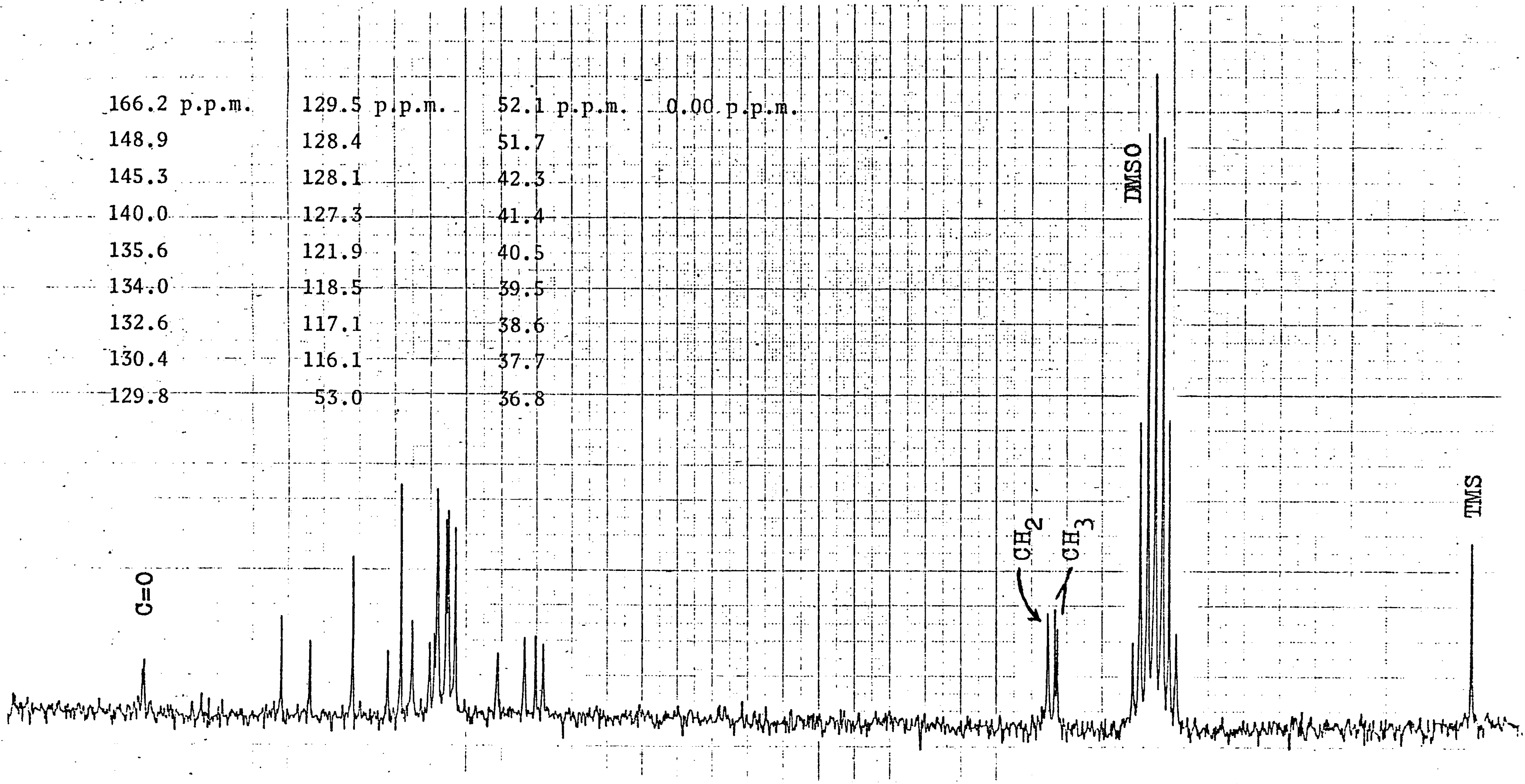
Spectrum No.69. 22.63 MHz ^{13}C F.T. n.m.r. spectra of dimethyl 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine-4,5-dicarboxylate (Xa) in $CDCl_3$ (a) proton noise-decoupled; (b) off-resonance proton-decoupled.



Spectrum No.70. 22·63 MHz ^{13}C F.T. n.m.r. spectra of 3,6-dimethoxy-9,10,19,20-tetrahydrotetrabenzo[*b*,*d*,*h*,*j*][1,6]diazacyclododecine (Xb) in $CDCl_3$ (a) proton noise-decoupled; (b) off-resonance proton-decoupled.

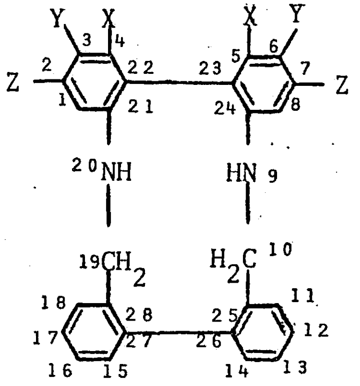


Spectrum No.71. 22·63 MHz ^{13}C F.T. n.m.r. specta of dimethyl 9,10,19,20-tetrahydrotetrabenzo[*b*,*d*,*h*,*j*][1,6]diazacyclododecine-2,7-dicarboxylate (Xc) in CDCl$_3$ (a) proton noise-decoupled; (b) off-resonance proton-decoupled.



Spectrum No.72. 22·63 MHz ^{13}C F.T. n.m.r. spectrum of dimethyl 9,10,19,20-tetrahydrotetrabenzo-[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate (Xc) in [$^2H_6$] DMSO under proton noise-decoupling conditions.

Table No.14. The observed carbon-13 chemical shift of 9,10,19,20-tetrabenzo[b,d,h,j][1,6]diazacyclododecine and its ortho-, meta- and para-derivatives in $CDCl_3$ relative to TMS, in p.p.m.



Compound	Substituent			Carbomethoxyl Group		Methylene Group	Aromatic Carbons											
							Amine Biphenyl Carbons				Aldehyde Biphenyl Carbons ⊕				Quaternary Carbons			
	X	Y	Z	CH_3O	>C=O	$-CH_2-$	$C_{1,8}$	$C_{2,7}$	$C_{3,6}$	$C_{4,5}$	$C_{11,18}$	$C_{12,17}$	$C_{13,16}$	$C_{14,15}$	$C_{21,24}$	$C_{22,23}$	$C_{25,28}$	$C_{26,27}$
X	H	H	H	---	---	53.7	116.5	129.5	118.5 118.9	128.0 128.6	132.9 133.2	131.1	122.0	127.4	148.9	134.9	140.7	144.1
Xa	CO_2CH_3	H	H	51.7	167.9	48.9	119.6	128.8	115.3	[132.5]	130.35	130.0	127.5	128.2	146.1	121.9	136.7	140.9
Xb	H	OCH_3	H	55.6 55.8	---	54.3	117.9	116.5	[155.0]	113.5 114.0	134.9	129.5	120.0	127.45 128.0*	152.9	138.1	140.8	143.0
Xc	H	H	CO_2CH_3	52.0 52.1	167.0	53.9	117.6	[134.4]	119.45 119.9	128.2 128.4	133.0	130.4 130.95	122.9	127.6	149.0	136.3	140.7	144.15

Square brackets indicate carbons carrying additional substituents.

* The intensity suggests that this signal corresponds to four carbon atoms rather than two.

⊕ These assignments are not conclusive.

comparison with substituted biphenyls, Table 12, and off-resonance spectra of compounds (Xa) and (Xc) gave unambiguous assignment of this singlet signal.

The complete proton decoupled ^{13}C n.m.r. spectrum of compound (Xc) in $[^2H_6]$ DMSO, Spectrum 72, showed a doublet for the carboxyl carbon.

Methylene carbon nuclei

Methylene carbon resonances could be distinguished both by their upfield absorption and by their triplet splitting in the off-resonance spectra. The significant upfield absorption of methylene carbon in compound (Xa) is probably due to conformational effect, where the CH_2 is no more under the influence of the local deshielding effect, thus, resulting in an upfield shift.

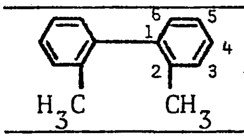
Aromatic carbon nuclei

The assignments of the aromatic carbons in compounds (X), (Xb) and (Xc) became more difficult due to the presence of extra signals in the aromatic region of their spectra, Spectra 68, 70 and 71, respectively. The extra carbon signals are more likely to come from two (or more) non-equivalent conformers.

Quaternary (bridgehead) carbons $C_{21,24}$; $C_{22,23}$; $C_{25,28}$ and $C_{26,27}$ in compounds (X - Xc) give singlet signals in the off-resonance proton decoupled spectra due to the absence of direct ^{13}C - ^1H coupling. Also, quaternary carbon signals are of lower intensity than protonated carbons. Therefore, confident assignments of all of the bridgehead carbons are made through the use of the above facts. In addition, spectral comparison supports the assignment of these signals. It is interesting to note that the observed upfield shifts in the quaternary carbons $C_{21,24}$; $C_{22,23}$; $C_{25,28}$ and $C_{26,27}$ in compound (Xa) probably arise from the steric effects in terms of the repulsive forces between the closely spaced carbomethoxyl groups.

The assignment of the protonated carbons in the aldehyde biphenyl unit is much more difficult than that encountered in compounds (IX - IXc). The observed doublet splitting in the off-resonance spectra and spectral comparison with that of 2,2'-dimethylbiphenyl, Table 15, provide some sort of help in assigning these signals.

Table No.15. The observed aromatic ^{13}C chemical shift of 2,2'-dimethylbiphenyl in p.p.m. from TMS

Compound	C_1	C_2	C_3	C_4	C_5	C_6
	141.9	135.9	130.4	129.9	126.4	127.8

The original data in p.p.m. in THF referenced to benzene^{89} and converted using $\delta_C^{C_6H_6}$ 128.7

It is of interest to mention here the significant downfield shift (+5.5 p.p.m.) observed for $C_{13,16}$ in compound (Xa) relative to the same carbon in compound (X). This discrepancy is difficult to account for on the basis of the presently available data.

The assignment of the carbon bearing methoxyl group $C_{3,6}$ in compound (Xb) is easy and unequivocal because of the pronounced deshielding effect of the methoxyl group. It appeared as a singlet in the off-resonance spectrum. It is important, however, to draw attention to the pronounced shielding at the <u>ortho</u>-positions, $C_{2,7}$ and $C_{4,5}$ indicative of electron release to the rings by methoxyl groups, while the <u>meta</u>-carbon $C_{1,8}$ is deshielded slightly.

In compounds (Xa) and (Xc), the carbon bearing the carbomethoxyl group is deshielded and appeared as a singlet in the off-resonance spectra. In compound (Xc), the carbons ortho to the carbomethoxyl function [$C_{1,8}$ and $C_{3,6}$] absorb at lower field due to the interaction of the carbomethoxyl groups with the amine biphenyl unit. Whereas, in compound (Xa), the carbon ortho to the carbomethoxyl function, $C_{3,6}$, experiences a significant upfield shift. This is probably due to steric inhibition of conjugation between the carbomethoxyl group and the aromatic ring.

Finally, it is worthwhile to suggest here that variable-temperature ^{13}C n.m.r. is the technique worth investigating next to help in the analysis of the different conformations the molecules (X), (Xb) and (Xc) might have.

In conclusion the results of ^{1}H and ^{13}C n.m.r. of compounds (X), (Xb) and (Xc) may be summarised. ^{13}C n.m.r. spectra of the above compounds have shown extra signals in the aromatic region. Also, the methyl signal in compounds (Xb) and (Xc) occur as a doublet in the ^{1}H and ^{13}C n.m.r. spectra. Temperature variable studies of the methyl protons doublet in compound (Xb) have shown that the two signals move apart on increasing the probe temperature and move towards each other and form one signal on decreasing the temperature. On the other hand, the methyl protons doublet in compound (Xc) are unaffected on increasing the probe temperature even when heated to +117°.

Shift reagents studies on compound (Xb) resulted in an upfield shift of the methyl doublet upon addition of $Pr(fod)_3$, while one signal of the doublet moved upfield on addition of $Eu(fod)_3$ and the other downfield. In compound (Xc), the doublet moved downfield upon addition of $Eu(fod)_3$, but one signal of the doublet moved faster than the other.

These observations suggested that compounds (X), (Xb) and (Xc) must occur as two or more non-equivalent conformers. More detailed studies are required, especially temperature variable and shift reagents studies on the ^{13}C n.m.r. spectra of these compounds.

3. EXPERIMENTAL

General Statements

The following general statements apply wherever relevant in the text, unless otherwise stated.

1. Melting points below 120° were determined in an oil bath. Those above 120° were determined on an Electrothermal melting point apparatus. Thermometers were calibrated against standard thermometers.

2. ^{1}H-N.M.R. spectra were determined for deuteriochloroform solutions either at 60 MHz on a Perkin-Elmer R12 instrument or at 100 and 220 MHz by the Physico-Chemical Measurements Unit at Harwell, Didcot, Oxfordshire. Chemical shifts were measured on the δ-scale relative to TMS as internal standard (δ = 0).

3. ^{13}C-Fourier Transform N.M.R. spectra were determined for deuteriochloroform solutions at 22.63 MHz, by the P.C.M.U., or by King's College, London, under the University of London Intercollegiate Research Services Scheme. Chemical shifts were measured on the δ-scale relative to TMS as internal standard (δ = 0).

4. Ultra-violet absorption spectra were determined for 95% ethanol solutions with the Perkin-Elmer 124 automatic recording spectrophotometer. Quartz cells were employed throughout.

5. Mass spectra were measured by the P.C.M.U.

6. Infra-red spectra were measured either with the Perkin-Elmer 457 or with the Unicam SP.200 spectrophotometers, with a mulling agent.

7. Microanalyses were performed by the micro-analytical laboratory in Bedford College, London, by Dr. F.B. Strauss at Oxford, or by Dr. A. Bernhardt in West Germany.

8. The general procedure employed for lanthanide shift reagents experiments was as follows:

   An accurately weighed amount (3.08 - 6.60 mg) of substrate was placed in a clean and dry n.m.r. tube. Dry $CDCl_3$ [0.4 - 0.7 ml, previously dried over preheated (120°C) 3 Å molecular sieves] was then added and the n.m.r. spectrum was recorded at 60 MHz on a Perkin-Elmer R12 instrument.

   Accurately weighed amounts of the Eu or Pr shift reagents were added in increments to the n.m.r. tube. After each addition of shift reagent, the n.m.r. tube was stoppered and vigorously shaken. In some cases, the n.m.r. tube was placed in a beaker of warm tap water (40°) to effect solution. The spectrum was recorded after each addition of shift reagent, and the chemical shifts of all the protons were recorded (in p.p.m. downfield from internal tetramethylsilane).

2,2'-Dinitrobiphenyl

(F.R. Shaw and E.E. Turner, J. Chem. Soc., 1933, 135)

o-Chloronitrobenzene (60 g, 0.381 mole) was briskly boiled in a wide boiling-tube kept at 250-260° in a metal bath while copper-bronze (40 g) was added gradually and stirred in (with a thermometer) during 20 minutes. Heating was continued for another 10 minutes, the mixture was allowed to cool somewhat and was extracted with hot o-dichlorobenzene. The solution was filtered hot, the solid residue washed with hot o-dichlorobenzene, and the total filtrate treated with light petroleum (b.p. 40-60°) until the solution went faintly cloudy. Filtration of the resulting cold suspension gave dark brown crystals. The dark brown crystals were recrystallized from glacial acetic acid and gave a brown crystalline product (26.5 g, 57%), m.p. 121-123°. A small portion of the product, after recrystallization once from ethanol, gave light brown prisms, m.p. 124-124.5° (lit.,[a] 124°).

2,2'-Diaminobiphenyl

(W.L. Mosby, J. Org. Chem., 1957, 22, 671)

A mixture of iron powder (60 g), water (30 ml) and glacial acetic acid (2 ml) was stirred mechanically in a two-necked flask (500 ml) and boiled under reflux for 15 minutes. 2,2'-Dinitrobiphenyl (24.4 g, 0.10 mole) was added in small portions, occasionally washed down with ethanol (a total of 10 ml). The resulting dark mixture was stirred and

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[a] F. Ullmann and J. Bielecki, Ber., 1901, 34, 2176

boiled under reflux for 5 hours, then cooled somewhat and 200 ml of benzene was added, and the heating and stirring were continued for another hour. The benzene layer was decanted while it was hot and the solids were washed well with additional hot benzene. The combined benzene extracts were dried over anhydrous potassium carbonate. After filtration and removal of solvent, the product obtained was crystallized from a mixed solvent containing 80% of ethanol and 20% of light petroleum (b.p. 60-80°) giving slightly coloured transparent prisms (14.84 g, 80.7%), m.p. 78.5-79°. Recrystallization a small portion of the product from light petroleum (b.p. 80-100°) gave white needles, m.p. 80-80.5° (lit.,[b] 80-81°).

Trans-9,10-dihydro-9,10-dihydroxyphenanthrene

(J. Booth, E. Boyland and E.E. Turner, J. Chem. Soc., 1950, 1188)

The preparation of diol was performed in two ways:

A. Portion-wise addition

The lithium aluminium hydride (1 g, 0.026 mole) in sodium-dried ether (200 ml) was stirred magnetically while the 9,10-phenanthrenequinone (4 g, 0.019 mole) was added in solid form (in small portions), occasionally being washed down with ether. After the addition, the mixture was heated under reflux for 4¾ hours and cooled. Water (50 ml) and 4N-sulphuric acid (50 ml) were added. When all the excess of lithium aluminium hydride had been decomposed, the aqueous layer was grey and the ethereal layer

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[b] S. Sako, Mem. Coll. Eng. Kyushu Imp. Univ., 1932, 6, 263; Chem. Zentr., I, 1937, 3791.

yellow. But when more ether was added, with shaking, green solid was formed. This green solid was decomposed by the acid, and more ether was added to dissolve the yellow substance formed. When the ethereal layer was clear it was separated, the aqueous layer was extracted with ether, and the combined ethereal layer and extract washed with 2N-sodium hydroxide. The ethereal layer was dried over sodium hydroxide pellets. Green substance was seen to collect at the bottom of the flask again. It was filtered off and ether removed. The crude diol obtained was crystallized from benzene and gave white large needles (1.463 g, 35.9%), m.p. 186-187°.

B. Soxhlet apparatus

The lithium aluminium hydride (2 g, 0.053 mole) was suspended in sodium-dried ether (400 ml) and the 9,10-phenanthrenequinone (8 g, 0.039 mole), previously dried over phosphorus pentoxide, was put in a Soxhlet thimble and extracted with the refluxing ether. A greenish-yellow precipitate was formed soon afterwards. Extraction was continued for 12 hours and the reaction mixture treated with water (50 ml) and 2N-sulphuric acid (120 ml) after cooling to room temperature. The ether solution was combined with the ethereal extract of the aqueous solution and washed several times with 2N-sodium hydroxide until free of green substance. When dried over sodium hydroxide pellets, the green substance was again formed and collected at the bottom of the flask. It was filtered off and the ether removed by distillation. The diol obtained was recrystallized from benzene giving large needles (5.09 g, 67 %), m.p. 186-187° (lit., needles, m.p. 185-187°; prisms, m.p. 194°).

The yield is based on the amount of quinone consumed in this preparation. A significant amount of 9,10-phenanthrenequinone (0.53 g) was left in the thimble.

Biphenyl-2,2'-dialdehyde

(D.M. Hall and B. Prakobsantisukh, *J. Chem. Soc.*, 1965, 6311)

The *trans*-9,10-dihydro-9,10-dihydroxyphenanthrene (8.5 g, 0.04 mole) was suspended in sodium-dried benzene (250 ml) and lead tetra-acetate (18.2 g, 0.04 mole) was added to the stirred suspension; stirring was continued at room temperature for 4 hours. After stirring, the white lead diacetate was filtered off and the yellow filtrate was evaporated to dryness under reduced pressure, giving an oily substance (7.4 g) which solidified on standing overnight. The solid obtained was recrystallized from a mixture of 30% sodium-dried ether and 70% light petroleum (b.p. 40-60°) giving large bright yellow plates (5.5 g, 65%), m.p. 62-63° (lit.,[c] 64-65°).

In another preparation, the crude dialdehyde (5.73 g) was purified by column chromatography. It was dissolved in a minimum amount of sodium-dried ether and passed through neutral alumina (60 g) using a mixture of 30% dry ether and 70% light petroleum (b.p. 40-60°) as eluent. The first portion of eluate gave colourless prisms (4.31 g) and had m.p. 63-64° when recrystallized from ether-light petroleum. The second portion of eluate yielded a few orange-yellow crystals, identified as 9,10-phenanthrenequinone, m.p. 204-207° (lit.,[d] 208.5-210°).

[c] R.G.R. Bacon *et al.*, *J. Chem. Soc.*, *Perkin I*, 1974, 2153

[d] R. Wendland and J. LaLonde, *Org. Synth.*, 1954, *34*, 76, Coll. Vol.4, 757

Tetrabenzo[b,d,h,j][1,6]diazacyclododecine

(E.D. Bergmann, I. Agranat and M.A. Kraus, *J. Org. Chem.*, 1967, 32, 600)

Biphenyl-2,2'-dialdehyde (1.05 g, 0.005 mole) and 2,2'-diaminobiphenyl (0.92 g, 0.005 mole) were dissolved separately in a minimum amount of absolute ethanol (20 ml for each) at room temperature and then mixed. Crystalline solid was observed soon afterwards. The solution was left to stand for two days and the solid obtained was filtered off and dried giving colourless crystals (1.728 g, 97%), m.p. 297-300°. Three crystallizations from benzene gave the desired product, m.p. 312-313°, 76% (lit.,[e] 326°).

The infra-red spectrum (Nujol) showed marked absorption at 1625 cm^{-1} (C=N).

Attempt to isolate the isomeric component of tetrabenzo[b,d,h,j][1,6]-diazacyclododecine by column chromatography

1.237 g of tetrabenzo[b,d,h,j][1,6]diazacyclododecine was dissolved in a minimum amount of chloroform, passed through a column of silica gel (60 g) and eluted with a mixture of sodium dried benzene (70%) and ethyl acetate (30%). Most of the column became mustard coloured. After collecting the mustard fraction, the solvents were evaporated under reduced pressure, 0.965 g of pale yellow crystals obtained. Recrystallisation from benzene (three times) gave colourless crystals, m.p. 312-313°.

Two zones were developed in the column after collecting the mustard fraction. The lower zone spread over a wide area which was pale

[e] A.P. Bindra and J.A. Elix, *Tetrahedron*, 1970, 26, 3749

yellow in colour, while the upper zone was brown in colour and of small area. The pale yellow zone was collected, solvents were evaporated under reduced pressure and 0.083 g of yellow crystals were obtained. Recrystallization from benzene gave colourless crystals, m.p. 304.5-305°.

The brown zone was collected later on and gave yellow crystals 0.141 g. When recrystallised from benzene gave off-white crystals, m.p. 286-292°.

The total amount of tetrabenzo[*b*,*d*,*h*,*j*][1,6]diazacyclododecine collected from the column was 1.189 g.

The n.m.r. spectra of the mustard fraction, m.p. 312—313°, and the off-white crystals, m.p. 286-92°, were identical and were also identical with the spectrum of tetrabenzo[*b*,*d*,*h*,*j*][1,6]diazacyclododecine before chromatographic separation.

9,10,19,20-Tetrahydrotetrabenzo[*b*,*d*,*h*,*j*][1,6]diazacyclododecine

(Method used by J.H. Billman and J.W. McDowell, *J. Org. Chem.*, 1961, *26*, 1437, for the reduction of Schiff bases)

A. Reduction with dimethylamine borane in glacial acetic acid

Tetrabenzo[*b*,*d*,*h*,*j*][1,6]diazacyclododecine (1.00 g, 0.0028 mole) was suspended in glacial acetic acid (2 ml) in a test-tube fitted with a thermometer and placed in a cold water bath. An equimolar amount plus 25% excess of the dimethylamine borane (0.412 g) was dissolved in glacial acetic acid (2 ml) and this solution added slowly to the Schiff base suspension keeping the temperature approximately at 20°. After the addition was complete, the colour changed from brown to colourless; glacial acetic acid (1 ml) was added, the reaction mixture was heated at 50-53° for 7 minutes, and allowed to cool. Cold distilled water was added slowly until precipitation was complete. The white precipiate was collected by suction filtration, washed with cold water and dried giving white solid (0.985 g, 97%), m.p. 168-172.5°. Crystallization from methyl alcohol gave pale yellow diamond-shaped plates m.p. 174-176°, 89%, which turned brownish on storing (lit.,[e] 158°).

Three reductions were performed successfully on the above mentioned compound.

The infra-red spectrum (Nujol) exhibited pronounced bands at 3310 and 3415 cm^{-1} (N-H). The C=N band is absent.

(Found: C, 86.2; H, 6.1; N, 7.6.

Calc. for $C_{26}H_{22}N_2$: C, 86.1; H, 6.1; N, 7.7%).

B. Reduction with sodium borohydride

(A.P. Bindra and J.A. Elix, Tetrahedron, 1970, 26, 3749)

Attempts to reduce tetrabenzo[b,d,h,j][1,6]diazacyclododecine by sodium borohydride in methyl alcohol failed to give the tetrahydro-derivative.

Methyl p-aminobenzoate

(E.R. Riegel and K.W. Buchwald, J. Amer. Chem. Soc., 1929, 51, 484)

p-Aminobenzoic acid (200 g, 1.46 mole) was dissolved in methyl alcohol (2 litres) in a 5-litre, round-bottomed flask. The flask was fitted with a reflux condenser and concentrated sulphuric acid (100 ml)

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[e] A.P. Bindra and J.E. Elix, Tetrahedron, 1970, 26, 3749

was added cautiously to the flask down the condenser, with occasional swirling. The solution was then boiled under reflux for 13 hours. About 1 litre of methyl alcohol was distilled off and the residual solution poured into 2.5 litres of cold water. The solution was stirred mechanically and neutralized by adding solid sodium bicarbonate, until the solution was alkaline to litmus. The creamy solid ester, which separated, was filtered off, washed with water and crystallized from ethyl alcohol giving fawn crystals (192.3 g, 87%), m.p. 111.5-112^o (lit., 112^o).

Methyl p-iodobenzoate

(Method of N.E. Searle and R. Adams, J. Amer. Chem. Soc., 1933, 55, 1651)

Finely powdered methyl p-aminobenzoate (138 g, 0.92 mole) was made into a thin paste with water. 6N-hydrochloric acid (750 ml) (450 ml of conc. HCl + 300 ml of H_2O) was added. The mixture was cooled with mechanical stirring to -6^o and diazotized with sodium nitrite (69 g, 1 mole) dissolved in water (150 ml). During the above dropwise addition, the temperature was kept between -3 and -6^o. To the diazotized solution, potassium iodide (250 g, 1.5 mole) dissolved in water (225 ml) was added dropwise with rapid stirring. The frothing reaction mixture was warmed in hot water and stirred with sodium metabisulphate solution to remove excess iodine. The product was filtered, washed thoroughly with water and dried. Crystallization from methyl alcohol gave sandy-orange crystals (193 g, 81%), m.p. 113-114^o (lit.,[f] 112-114^o).

[f] Chua Cheung King Ling, Ph.D. Thesis, London. Univ., 1962.

Methyl p-iodo-m-nitrobenzoate

(C.C. King Ling and M.M. Harris, J. Chem. Soc., 1964, 1825)

A solution of powdered methyl p-iodobenzoate (58 g, 0.22 mole) in conc. sulphuric acid (75 ml) was cooled, (ice-salt bath), with mechanical stirring to 0° and a mixture of conc. nitric acid (sp. gr. 1.42, 30 ml) and conc. sulphuric acid (sp. gr. 1.84, 30 ml) added dropwise, keeping the temperature between 5 and 6°. The first drop of nitrating mixture added turned the solution black and the reaction mixture became increasingly viscous until about 1/3 of the nitrating mixture had been added. Further addition was, however, accompanied by a decrease in viscosity and a gradual change of colour from black to reddish-brown. When all the nitrating mixture had been added, the reaction mixture was stirred for a further ½ hour and then allowed to stand in the ice + water for another 3 hours. The thick mixture was poured, with stirring, onto crushed ice. The yellow solid which separated was filtered, washed thoroughly with water, then treated with hot water at about 80° and filtered giving yellow-orange crystals. Recrystallisation from methyl alcohol gave large ochre needles (43 g, 63%), m.p. $103-104^{\circ}$ (lit., $104-106^{\circ}$).

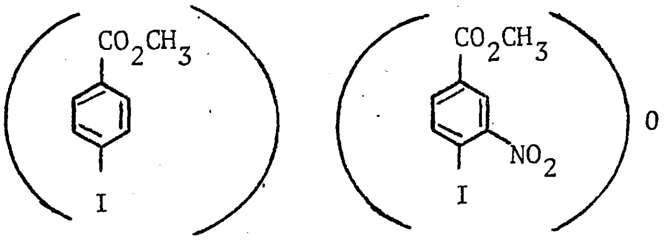
A considerable amount of by-product was obtained from the mother liquor, filtered off, washed thoroughly with cold water and dried giving yellow crystals 7.12 g, m.p. $147-149^{\circ}$. Recrystallization from methyl alcohol gave white silky needles (6.28 g), m.p. $164.5-165^{\circ}$ (decomp.) [lit., m.p. 182° (decomp.)]

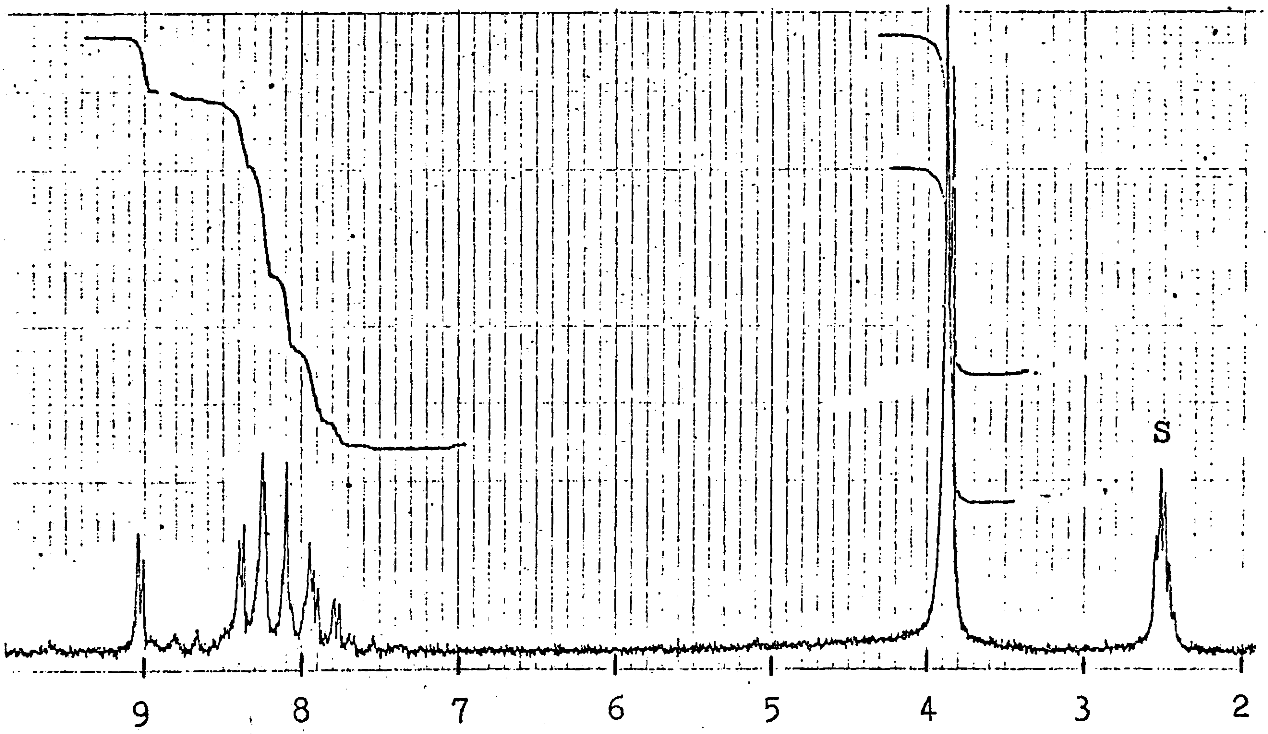
It was found that the m.p. of this by-product is not constant, but changeable from time to time depending on the rate of heating.

(Found: C, 32.8; H, 2.2; N, 1.9; O, 19.04; I, 42.81%).

From the above analysis, the possible molecular formula is $C_{16}H_{13}NO_7I_2$.

The n.m.r. spectrum of this by-product in [$^2H_6$]DMSO with tetramethylsilane as internal standard (Spectrum 73) has revealed seven aromatic protons and six protons in the upfield region of the spectrum. It is suggested that the compound might have a general structure like:





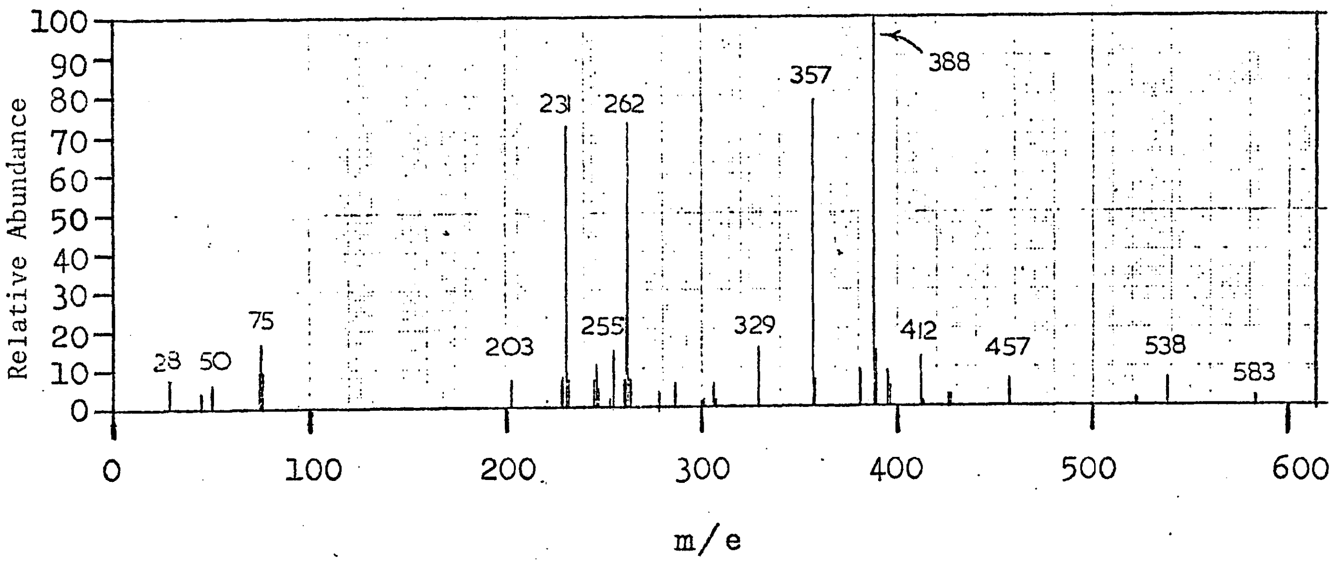
Spectrum No.73. ^{1}H N.m.r. spectrum of a by-product from nitration of methyl p-iodobenzoate in [$^2H_6$]DMSO. Band marked 'S' is due to solvent.

The infra—red spectrum (Nujol) exhibited pronounced bands at 1707 (C=O of aromatic ester), 1285 and 1117 (C-O of aromatic ester), and 1576 and 1300 cm^{-1} (NO$_2$ of aryl-nitrobenzoate).

However, the mass spectrum (Spectrum 74) of the by-product has shown that the molecular ion peak appeared to be at m/e = 583, which means that there are only five aromatic protons. This disproves the above suggestion made by considering the n.m.r. spectrum.

Accurate mass measurements of the molecular ion at m/e = 583 and the base peak at m/e = 388 have given the following data:

Measured masses	Possible formulae	Calculated masses
582.8611	$C_{16}H_{11}NO_7I_2$	582.8630
387.8452	$C_8H_6O_2I_2$	387.8462



Spectrum No. 74. Mass spectrum of a by-product from nitration of methyl p-iodobenzoate.

On examining a fresh mass spectrum of the by-product, it appeared that the sample is a mixture of a number of compounds with peaks beyond the mass of m/e = 583.

Consequently, assigning the structure of the by-product is abandoned at the present time, due to the disagreement between the results obtained by n.m.r. and mass spectroscopy.

Dimethyl 2,2'-dinitrobiphenyl-4,4'-dicarboxylate

(C.C. King Ling and M.M. Harris, *J. Chem. Soc.*, 1964, 1825)

Methyl 3-nitro-4-iodobenzoate (50 g, 0.163 mole) was melted in a hard glass tube immersed in a metal bath heated to 180°. The temperature inside the hard glass tube was brought to 175°. Copper bronze (40 g) was added, stirred in with a thermometer, at such a rate as to maintain the internal temperature between 180-195°, while the temperature of the bath was kept between 165-175°. When all the copper bronze had been added, the bath was raised to 190° for 15 minutes. The tube was then removed from the metal bath, allowed to cool to 100° and the reaction mixture extracted several times with boiling chloroform. The extracts were filtered hot through a Buchner funnel, and the filtrate evaporated to dryness under reduced pressure giving brown crystals. Recrystallization of the crude product from acetone-water (4:1) gave khaki coloured monoclinic crystals (23.7 g, 81%), m.p. 159-159.5° (lit., 159-161°).

Dimethyl 2,2'-diaminobiphenyl-4,4'-dicarboxylate

Reduction with hydrazine using W-2 Raney Ni as catalyst

(C.C. King Ling and M.M. Harris, *J. Chem. Soc.*, 1964, 1825)

W-2 Raney nickel catalyst was prepared according to the procedure given in *Organic Synthesis*, Collective Vol. III, p.181.

Dimethyl 2,2'-dinitrobiphenyl-4,4'-dicarboxylate (9 g, 0.025 mole) was dissolved in a mixture of 95% ethyl alcohol (580 ml) and toluene (100 ml) in a 1-litre, 3-necked, round-bottomed flask, fitted with a reflux condenser, a dropping funnel and a thermometer. The thermometer was fitted so that its bulb was immersed in the solution. The solution was heated on a water bath to ~ 70°. The flask was then removed from the water bath and two tea-spoonsful of W-2 Raney nickel were added to the solution. Hydrazine hydrate (100%; 40 ml) was added slowly from the dropping funnel at such a rate that the temperature of the reaction mixture remained between 63 and 67°, or to maintain a vigorous reaction (important). There was vigorous effervescence during the addition of the hydrazine hydrate, and the colour of the solution changed from bright yellow, through dark brown, to very pale yellow. More W-2 Raney nickel catalyst, one tea-spoonful, was added and the reaction mixture was boiled on a water bath for 15 minutes and was then filtered hot. The filtrate was concentrated to a small bulk by distilling off the solvent under reduced pressure. When the concentrated solution had cooled, the amine crystallized out as yellow long needles, and was filtered off and dried, giving 7.14 g. Recrystallization from benzene containing a little ethanol gave pale yellow rhombohedra (6.93 g, 92%), m.p. 174-175° (lit., 174-176°).

Dimethyl tetrabenzo[*b*,*d*,*h*,*j*][1,6]diazacyclododecine-2,7-dicarboxylate

It was found that dimethyl 2,2'-diaminobiphenyl-4,4'-dicarboxylate is not soluble in absolute ethyl alcohol at room temperature; therefore, the reaction was carried out as follows:-

Biphenyl-2,2'-dialdehyde (1.05 g, 0.005 mole), dimethyl 2,2'-diaminobiphenyl-4,4'-dicarboxylate (1.5 g, 0.005 mole) and absolute ethyl alcohol (60 ml) were heated under reflux for 3 hours. The clear reaction mixture was left to stand at room temperature for two days. Yellow crystals separated at the bottom of the flask, and were filtered off and dried, giving yellow diamond-shaped plates (2.3 g, 97%), m.p. 251-255°.

This compound was prepared four times. Recrystallization of the condensation product "yellow diamond-shaped plates" from a mixture of 60% dry benzene and 40% light petroleum (b.p. 60-80°) gave, on two occasions, very pale yellow rods, m.p. 259-261°, as a major crystalline form. Recrystallization of the rods once gave two crystalline forms; a large proportion of very pale yellow rods, m.p. 262-63°, and a small proportion of pale yellow diamond-shaped plates, m.p. 261-261.5°, 83.5%. On the other two occasions, pale yellow diamond-shaped plates, m.p. 261-261.5° , were obtained as a major crystalline form after one crystallization of the condensation product.

The infra-red spectrum (Nujol) exhibited strong bands at 1727 (C=O of aromatic ester) and 1632 cm^{-1} (C=N).

(Found: C, 76.1; H, 4.6; N, 5.6.

$C_{30}H_{22}N_2O_4$ requires: C, 75.9; H, 4.7; N, 5.9%).

Dimethyl 9,10,19,20-tetrahydrotetrabenzo [b,d,h,j] [1,6]diazacyclododecine-2,7-dicarboxylate

(Method of J.H. Billman and J.W. McDowell, J. Org. Chem., 1961, 26, 1437)

Dimethyl tetrabenzo[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate (0.5 g, 0.00105 mole) was suspended in glacial acetic acid (1.5 ml) in a test-tube fitted with a thermometer and placed in a cold water bath. An equimolar amount plus 33% excess of the dimethylamine borane (0.165 g) was dissolved in glacial acetic acid (1 ml) and this solution added slowly to the Schiff base suspension keeping the temperature approximately at 20°. After the addition was complete, the colour changed from orange-red to yellow and then to very pale green; glacial acetic acid (1 ml) was added, the reaction mixture was heated at 48-51° for 7 minutes, and allowed to cool. Cold distilled water was added slowly until precipitation was complete. The precipitate was collected by suction filtration, washed with cold water and dried giving pale yellow solid (0.473 g, 94%), m.p. 214-227°. Crystallization from ethyl alcohol gave two crystalline forms; a large proportion of pale yellow triangular rods, m.p. 238-239°, and a small proportion of bright yellow hexagonal plates, m.p. 237-238° (0.45 g, 89%).

Four reductions were performed successfully on the above mentioned compound on the same scale each.

(Found: C, 74.7; H, 5.4; N, 5.6.

$C_{30}H_{26}N_2O_4$ requires: C, 75.3; H, 5.5; N, 5.85%).

The infra-red spectrum (Nujol) showed marked absorption at 3395 and 3360 (N-H) and 1709 cm^{-1} (C=O of aromatic ester). The C=N band is absent.

Attempted quaternization of dimethyl 9,10,19,20-tetrahydrotetrabenzo-[b,d,h,j][1,6]diazacyclododecine-2,7-dicarboxylate

Attempt to prepare a quaternary salt from dimethyl 9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]-diazacyclododecine-2,7-dicarboxylate using iodomethane in warm dry acetone and in dry benzene, separately, failed. The n.m.r. spectrum of the product, in each case, was identical with that of the starting material.

3-Chloro-4- and 6-nitrophenols

A. Nitration with concentrated sulphuric acid and sodium nitrate

(H.H. Hodgson and F.H. Moore, J. Chem. Soc., 1925, 127, 1599)

m-Chlorophenol (24 g, 0.187 mole), liquified by ethyl alcohol (2 ml), was added slowly during 40 minutes to the mechanically stirred solution, kept at 20-21°, of concentrated sulphuric acid (sp. gr. 1.84, 40 g) and sodium nitrate (29 g, 0.341 mole) in water (70 ml). After being stirred for 2 hours, the mixture was diluted with water (140 ml). The yellowish-orange solid was filtered, washed with cold water and steam-distilled. The yellow oil in the distillate solidified on cooling, and after being filtered off, washed with cold water and dried, it gave 3-chloro-6-nitrophenol (0.795 g) as a yellow solid, m.p. 39-40° (lit., 41°).

The original filtrate and washings were added to the mixture in the distillation flask and steam-distilled. More 3-chloro-6-nitrophenol collected in the distillate as a yellow oil which solidified on cooling (5.8 g), m.p. 39-40°. The total yield of 3-chloro-6-nitrophenol was 20%.

3-Chloro-4-nitrophenol, which remained in the distillation flask as a brown solid, was filtered and dried. Crystallization from benzene containing some activated charcoal gave large pale brown needles (7.26 g, 22%), m.p. 120.5-121.5° (lit., 121-122°).

B. Nitration with concentrated nitric acid in glacial acetic acid

(H.E. Ungnade and I. Ortega, J. Org. Chem., 1952, 17, 1475)

m-Chlorophenol (10 g, 0.078 mole) dissolved in glacial acetic acid (10 ml), was added dropwise during 15 minutes to the mechanically stirred solution of concentrated nitric acid (sp. gr. 1.42, 11 ml) in glacial acetic acid (30 ml), kept within a temperature range of -17 and -11°. Stirring was continued for a further 2 hours after the addition was completed. The resultant reddish-brown mixture was poured on to 300 gm of ice, allowed to stand for 30 minutes, and steam-distilled. The yellow oil in the distillate solidified on cooling, and when filtered off, washed with cold water and dried it gave 3-chloro-6-nitrophenol (3.03 g, 22%), as a yellow solid, m.p. 39-40°.

3-chloro-4-nitrophenol, which remained in the distillation flask as a brown oil, was decolourized with activated charcoal and crystallized from water giving white needles (3.64 g, 27%), m.p. 120-121°.

3-Chloro-4-nitroanisole

(H.H. Hodgson and F.W. Handley, J. Chem. Soc., 1926, 542)

3-Chloro-4-nitrophenol (9.5 g, 0.055 mole) dissolved in xylene (70 ml) was stirred mechanically and heated under reflux on the water-bath in the presence of anhydrous potassium carbonate (12 g). Dimethyl sulphate (16 ml) was gradually added during 15 minutes and the whole mixture heated under reflux for 11 hours. The resultant thick pale yellow mixture was rendered strongly alkaline with sodium hydroxide (5 g) and steam-distilled; xylene passed over first and was followed by 3-chloro-4-nitroanisole as a viscous pale yellow liquid which solidified on cooling. After being filtered, washed with cold water and dried it gave pale yellow solid (9.415 g, 92%), m.p. 56-56.5°. Rapid crystallization from light petroleum (b.p. 60-80°) gave yellowish-green needles, m.p. 56-56.5° (lit.,[g] 56.5°).

[g] H.H. Hodgson and F.H. Moore, J. Chem. Soc., 1926, 157

5,5'-Dimethoxy-2,2'-dinitrobiphenyl

(F.E. Kempter and R.N. Castle, J. Heterocycl. Chem., 1969, 6(4), 523, who used 3-iodo-4-nitroanisole)

3-Chloro-4-nitroanisole (27 g, 0.144 mole) was melted in a hard glass tube immersed in a metal bath heated to 255°. The temperature inside the hard glass tube was brought to 250°. Copper bronze (20 g) was added during 30 minutes, stirred in with a thermometer, at such a rate as to maintain the internal temperature between 250-265°. When all the copper bronze had been added, the bath was raised to 275-280° for 15 minutes. The tube was then removed from the metal bath, allowed to cool to 100° and the reaction mixture extracted several times with boiling benzene. The extracts were filtered hot through a Buchner funnel, and the filtrate evaporated to dryness under reduced pressure. A dark black solid was obtained, and was washed with some ether and filtered with suction giving a light black solid (10.025 g, 46%), m.p. 144-146.5°. Recrystallization from ethanol gave nearly colourless crystals, m.p. 147-,48.5° (lit.,148-149°).

Column chromatography was used to purify some of the crude product (1 g). It was dissolved in a minimum amount of chloroform and passed through silica gel (28 g). Chloroform was used as an eluent, which was collected continuously from the column in quantities of 10 ml each; these were evaporated to dryness under reduced pressure and the solids were crystallized individually from benzene. The first portion gave nearly colourless prisms (0.179 g) and had m.p. 149-149.5°. The second and third portions gave brown prisms (0.506 g) and had m.p. 148-149°, while the fourth and last portion gave dark brown prisms (0.158 g) and had m.p. 147-148°.

2,2'-Diamino-5,5'-dimethoxybiphenyl

A. Reduction using 5% palladinized charcoal catalyst

(Method of D.C. Iffland and H. Siegel, *J. Amer. Chem. Soc.*, 1958, **80**, 1947)

A mixture of 5,5'-dimethoxy-2,2'-dinitrobiphenyl (1 g, 0.0033 mole), 5% palladinized charcoal catalyst (0.4 g) and tetrahydrofuran (50 ml) was shaken with hydrogen at 3 atmospheres in a hydrogenation apparatus at 13-17°. After the absorption of hydrogen ceased, the solution was filtered and the light green filtrate obtained was reduced to about 7 ml by vacuum evaporation, keeping the water-bath temperature under 30°. Cold distilled water was added to the reduced filtrate, and light green solid separated at the bottom of the flask; after being filtered, it was washed with cold water and dried giving (0.69 g, 86%), m.p. 99-102°. Crystallization from light petroleum (b.p. 80-100°) gave amber needles (0.62 g, 77%), m.p. 105-106°.

(Found:	1 -	C, 68.2;	H, 6.5;	N, 11.3
	2 -	C, 69.0;	H, 6.9;	N, 10.7
$C_{14}H_{16}N_2O_2$ requires		C, 68.8;	H, 6.6;	N, 11.5%).

B. Reduction using Adams' platinum oxide catalyst

A mixture of 5,5'-dimethoxy-2,2'-dinitrobiphenyl (2.0 g, 0.0066 mole), Adams' platinum oxide catalyst (0.1 g) and glacial acetic acid (230 ml) was shaken with hydrogen at 46 p.s.i. in a hydrogenation apparatus at 15°. After the absorption of hydrogen ceased, the solution was filtered and the brown filtrate obtained was evaporated to dryness under reduced pressure. The tarry material obtained was treated with dilute hydrochloric acid, the solution was filtered, and the filtrate was made alkaline to litmus. The preciptate was filtered, washed with water and dried giving dark brown solid (0.28 g, 17%), m.p. 100-103°. Crystallization from light petroleum (b.p. 80-100°) gave amber needles (0.17g, 11%), m.p. 105-6°.

3,6-Dimethoxytetrabenzo[b,d,h,j][1,6]diazacyclododecine

Biphenyl-2,2'-dialdehyde (0.525 g, 0.0025 mole), 2,2'-diamino-5,5'-dimethoxybiphenyl (0.611 g, 0.0025 mole) and absolute ethyl alcohol (35 ml) were heated under reflux for 1 hour. Yellow solid was observed soon. The reaction mixture was left to stand, at room temperature, overnight. The yellow diamond plates were filtered and dried giving (0.99 g, 95%), m.p. 286-287.5°. Recrystallization from sodium-dried benzene gave pale yellow prisms, m.p. 288.5-289.5°.

The infra-red spectrum (Nujol) exhibited a band at 1630 cm^{-1} (C=N).

(Found: C, 80.5; H, 5.3; N, 6.3.

$C_{28}H_{22}N_2O_2$ requires C, 80.35; H, 5.3; N, 6.7%).

3,6-Dimethoxy-9,10,19,20-tetrahydrotetrabenzo[b,d,h,j][1,6]diazacyclododecine

(Method of J.H. Billman and J.W. McDowell, *J. Org. Chem.*, 1961, *26*, 1437).

3,6-Dimethoxytetrabenzo[b,d,h,j][1,6]diazacyclododecine (0.50 g, 0.0012 mole) was suspended in glacial acetic acid (1.5 ml) in a test-tube fitted with a thermometer and placed in a cold water bath. An equimolar amount plus 25% excess of the dimethylamine borane (0.18 g) was dissolved in glacial acetic acid (1 ml) and this solution added slowly to the Schiff base suspension keeping the temperature approximately at 20°. The colour of the solution changed from orange to red to yellow and then became colourless. After the addition was complete, glacial acetic acid (1 ml) was added, the reaction mixture was heated at 45-47° for 10 minutes, and allowed to cool. Cold distilled water was added slowly until precipitation was complete. The precipitate was collected by suction filtration, washed with cold water and dried giving white solid (0.44 g, 87%), m.p. 158-161°. Crystallization from absolute ethyl alcohol gave pale yellow hexagonal plates, m.p. 164.5-165°, 69%.

The infra-red spectrum (Nujol) showed marked absorption at 3405 and 3275 cm^{-1} (N-H). The C=N band is absent.

(Found: C, 79.8; H, 6.3; N, 6.5.
$C_{28}H_{26}N_2O_2$ requires C, 79.6; H, 6.2; N, 6.6%).

Methyl 2-iodo-3-nitrobenzoate

(Method of E.R. Riegel and K.W. Buchwald, J. Amer. Chem. Soc., 1929, 51, 484)

2-Iodo-3-nitrobenzoic acid (50 g, 0.171 mole) was dissolved in methyl alcohol (1,500 ml) in a 5-litre, round-bottomed flask. The flask was fitted with a reflux condenser and concentrated sulphuric acid (sp. gr. 1.840, 70 ml) was added cautiously to the flask down the condenser, with occasional swirling. The solution was then boiled under reflux for 27 hours. A clear yellow solution was obtained and when it was poured into 2.5 litres of ice-water, yellow solid formed. This was filtered off, washed with cold water, slurried in ice-water, and the slurry was treated with solid sodium bicarbonate until it was alkaline to litmus. The ester was filtered off, washed thoroughly with cold water and crystallized from aqueous methyl alcohol giving yellow needles (50.7 g, 97%), m.p. 62-63° (lit.,[h] 64-66°).

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[h] D.C. Iffland and H. Siegel, J. Amer. Chem. Soc., 1958, 80, 1947

Dimethyl 2,2'-dinitrobiphenyl-6,6'-dicarboxylate

(D.C. Iffland and H. Siegel, *J. Amer. Chem. Soc.*, 1958, **80**, 1947 and P.F. Holt and A.N. Hughes, *J. Chem. Soc.*, 1960, 3216)

Methyl 2-iodo-3-nitrobenzoate (40 g, 0.111 mole) was melted in a hard glass tube immersed in a metal bath heated to 160°. The temperature inside the hard glass tube was brought to 155°. Copper-bronze (34 g) was added during 45 minutes, stirred in with a thermometer, at such a rate as to maintain the internal temperature between 160-170°, while the temperature of the bath was kept at 135-145°. When all the copper-bronze had been added, the bath temperature was raised to 210-220° for 15 minutes. The tube was then removed from the metal bath, allowed to cool to 100° and the reaction mixture extracted several times with boiling chloroform. The extracts were filtered hot through a Buchner funnel, and the filtrate evaporated to dryness under reduced pressure giving brown crystals. Recrystallization of the crude product from benzene gave pale yellow hexagonal plates (20.5 g, 87%), m.p. 129-130° (lit.,[i] 132-133°).

Dimethyl 2,2'-diaminobiphenyl-6,6'-dicarboxylate

A. Reduction using Adams' platinum oxide catalyst

(Method of D.C. Iffland and H. Siegel, *J. Amer. Chem. Soc.*, 1958, **80**, 1947)

A mixture of dimethyl 2,2'-dinitrobiphenyl-6,6'-dicarboxylate (4 g, 0.0111 mole), Adams' platinum oxide catalyst (1.40 g) and tetrahydrofuran (240 ml) was shaken with hydrogen at 63.5 p.s.i. in a hydrogenation apparatus at 13-15°. After the absorption of hydrogen

[i] J. Kenner and W.V. Stubbings, *J. Chem. Soc.*, 1921, **119**, 593.

ceased, the solution was filtered and most of the solvent was removed from the yellowish-green filtrate by vacuum evaporation, keeping the water-bath temperature under 30°. Cold distilled water was added to the residue, and yellowish-green solid separated at the bottom of the flask. This was filtered off, washed with cold water and dried, giving (3.0 g, 90%), m.p. 120-123°. Crystallization from ethyl alcohol gave pale yellow prisms, m.p. 127-128°, 76%, changing after melting to a white solid which did not re-melt even at 340°.

(Found: C, 63.9; H, 5.4; N, 9.2.
$C_{16}H_{16}H_2O_4$ requires C, 64.0; H, 5.4; N, 9.3%).

B. Reduction with hydrazine using W-2 Raney Ni catalyst

(Method of D. Balcom and A. Furst, *J. Amer. Chem. Soc.*, 1953, *75*, 4334 and R.E. Moore and A. Furst, *J. Org. Chem.*, 1958, *23*, 1504)

Attempts to reduce dimethyl 2,2'-dinitrobiphenyl-6,6'-dicarboxylate by hydrazine in presence of W-2 Raney nickel as a catalyst, using variable proportions of substrate to ethanol, failed to give the amino-compound. A yellowish-green solid was obtained, in all cases, whose m.p. was above 300°.

Dimethyl tetrabenzo[*b*,*d*,*h*,*j*][1,6]diazacyclododecine-4,5-dicarboxylate

Biphenyl-2,2'dialdehyde (0.525 g, 0.0025 mole) was added to the warm solution of dimethyl 2,2'-diaminobiphenyl-6,6'-dicarboxylate (0.751 g, 0.0025 mole) in absolute ethyl alcohol (50 ml). The resultant clear solution was shaken for 4 hours and left to stand at room temperature for 2 days. Yellow solid separated at the bottom of the flask, after being filtered and dried giving pale yellow tiny crystals (1.084 g, 91%), m.p. 272-274°. Recrystallization from absolute ethyl alcohol gave pale yellow tiny crystals, m.p. 276-277°, 81%.

The infra-red spectrum (Nujol) exhibited strong bands at 1727 (C=O of aromatic ester) and 1626 cm^{-1} (C=N).

(Found: C, 75.6; H, 4.7; N, 5.6.

$C_{30}H_{22}N_2O_4$ requires C, 75.9; H, 4.7; N, 5.9%).

Dimethyl 9,10,19,20-tetrahydrotetrabenzo[*b*,*d*,*h*,*j*][1,6]diazacyclododecine-4,5-dicarboxylate

A. Reduction using Adams' platinum oxide catalyst

(Method of D.C. Iffland and H. Siegel, *J. Amer. Chem. Soc.*, 1958, *80*, 1947)

A mixture of dimethyl tetrabenzo[*b*,*d*,*h*,*j*][1,6]diazacyclododecine-4,5-dicarboxylate (0.2 g, 0.00042 mole), Adams' platinum oxide catalyst (0.15 g) and tetrahydrofuran (100 ml) was shaken with hydrogen at 48 p.s.i. in a hydrogenation apparatus at 16-18.5°. After the addition of hydrogen ceased, the solution was filtered and the colourless filtrate obtained was reduced to about 3 ml by vacuum evaporation, keeping the water-bath temperature under 30°. Cold distilled water was added to the reduced filtrate, light grey solid separated at the bottom of the flask, after being filtered, washed with cold water and dried giving (0.170 g, 84%), m.p. 205-211°. Two crystallization from absolute ethyl alcohol gave colourless needles, m.p. 214-214.5°, 73%.

Two reductions were performed successfully.

The infra-red spectrum (Nujol) exhibited pronounced bands at 3395 and 3413 (N-H) and 1723 cm^{-1} (C=O of aromatic ester). The C=N band was absent.

(Found: C, 74.95; H, 5.8; N, 5.9.

$C_{30}H_{26}N_2O_4$ requires C, 75.3; H, 5.5; N, 5.85%).

B. Reduction with dimethylamine borane in glacial acetic acid

(Method of J.H. Billman and J.W. McDowell, J. Org. Chem., 1961, 26, 1437)

Attempts to reduce dimethyl tetrabenzo[b,d,h,j][1,6]diazacyclododecine-4,5-dicarboxylate by dimethylamine borane in glacial acetic acid failed to give the tetrahydro-derivative. A yellowish-green solid was obtained, in all cases, whose m.p. was 223-248°. The n.m.r. spectrum of the product obtained by this method was quite different from the n.m.r. spectrum obtained for the product from method (A), and was unchanged on treatment with D_2O (absence of NH groups).

Dimethyl 6,6'-dimethoxybiphenyl-2,2'-dicarboxylate

(D.M. Hall and E.E. Turner, J. Chem. Soc., 1951, 3072)

6,6'-Dimethoxydiphenic acid (5 g, 0.0165 mole) was dissolved in methyl alcohol (67 ml) in a 250 ml, round-bottomed flask. The flask was fitted with a reflux condenser and concentrated sulphuric acid (5 g) was added cautiously to the flask down the condenser, with occasional swirling. The solution was then heated under reflux for 6 hours. Off-white prisms were collected at the bottom of the flask, after being filtered, washed and dried, giving (5.24 g, 96%), m.p. 128-133°. Recrystallization from methyl alcohol gave white prisms (4.97 g, 91%), m.p. 136-137° (lit., 136.5-137.5°).

2,2'-Bishydroxymethyl-6,6'-dimethoxybiphenyl

(D.M. Hall and E.E. Turner, J. Chem. Soc., 1951, 3072)

The lithium aluminium hydride (0.9 g, 0.0237 mole) was suspended in sodium-dried ether (65 ml) contained in a 500 ml, 2-necked, round-bottom flask, fitted with a reflux condenser and a dropping funnel.

Dimethyl 6,6'-dimethoxybiphenyl-2,2'-dicarboxylate (3 g, 0.0091 mole) was added slowly, from a dropping funnel into a magnetically stirred solution, as a finely ground solid, each lot being washed into the reaction flask with ether (100 ml altogether). The addition was completed in 30 minutes boiling under reflux and the reaction mixture was left to reflux for another 30 minutes to ensure complete reduction. The excess of lithium aluminium hydride was decomposed very cautiously by adding sucessively wet ether, water (drop at a time) and dilute sulphuric acid. A fairly clear aqueous layer with white solid at the interface was obtained. The ether was distilled off from the reaction vessel, and the white solid was filtered off, washed with cold water and dried giving (2.35 g, 94%), m.p. 156-157°. Crystallization from ethyl alcohol gave white rods, m.p. 157-158° (lit., 158-159°).

2,2'-Diamino-4,4',6,6'-tetramethylbiphenyl

A. Reduction using Adams' platinum oxide catalyst

(Method of D.C. Iffland and H. Siegel, J. Amer. Chem. Soc., 1958, 80, 1947)

A mixture of 2,2'-dinitro-4,4',6,6'-tetramethylbiphenyl [j] (5 g, 0.0167 mole), Adams' platinum oxide catalyst (0.173 g), glacial acetic acid (60 ml) and absolute ethyl alcohol (150 ml) was shaken with hydrogen at 44 p.s.i. in a hydrogenation apparatus at 13-14°. After the addition of hydrogen ceased, the solution was filtered and the colourless filtrate obtained was evaporated to dryness under reduced pressure, keeping the

[j] P.M. Everitt, S.M. Loh and E.E. Turner, J. Chem. Soc., 1960, 4587.

water-bath temperature under 30°. The residue, which had m.p. 179.5-181°, was crystallized once from light petroleum (b.p. 60-80°) and gave brownish-creamy cluster crystals (3.51 g, 87%), m.p. 180-181.5°.

(Found: C, 79.9; H, 8.5; N, 11.7.

$C_{16}H_{20}N_2$ requires C, 79.9; H, 8.4; N, 11.7%).

B. Reduction using W-2 Raney nickel catalyst

(Method of I. Puskas, E.K. Fields and E.M. Banas, Amer. Chem. Soc., Div. Petrol. Chem. Prepr., 1972, 17(1), B56)

2,2'-Dinitro-4,4',6,6'-tetramethylbiphenyl (10 g, 0.0333 mole), benzene (100 ml) and two spatula tips of W-2 Raney nickel catalyst were placed in a 1-litre autoclave which was then evacuated, filled with hydrogen at 600 p.s.i., and heated at 200°C for 3 hours. The reaction mixture was cooled to room temperature, treated with ethyl alcohol and filtered. Solvent was removed from the filtrate under reduced pressure, keeping the water-bath temperature under 30°, and gave a brown sticky material. This was washed with a small amount of n-hexane and was crystallized from light petroleum, giving light grey cluster crystals (2.121 g, 27%), m.p. 180-181.5°.

A considerable amount (4.83 g) of brown sticky material was left unidentified.

Attempted preparation of 2,4,5,7-tetramethyltetrabenzo[b,d,h,j][1,6]-diazacyclododecine

Biphenyl-2,2'-dialdehyde (0.525 g, 0.0025 mole) and 2,2'-diamino-4,4',6,6'-tetramethylbiphenyl (0.601 g, 0.0025 mole) were dissolved separately in a minimum amount of absolute ethanol (10 and 15 ml, respectively) and then mixed. The mixture was boiled under reflux for

6.30 hours, cooled and the yellow solid was filtered off and dried giving (1.00 g, 96%), m.p. 200-215°.

The product failed to give a sharp m.p. (230-251°) after various attempts to crystallize it from a variety of organic solvents (e.g. methanol, ethanol, glacial acetic acid, benzene or a mixture of 70% sodium dried benzene and 30% light petroleum (b.p.60-80°). The product from the crystallization process was a yellow fine solid.

An attempt was made to purify the condensation product by column chromatography. The product (0.7 g) was dissolved in a minimum amount of chloroform passed through a column of silica gel (60 g) and eluted with a mixture of 94% sodium dried benzene and 6% ethyl acetate. 0.62 g of yellow solid, m.p. 240-260°, was collected from the column. The n.m.r. spectrum of the condensation product was not a promising one for the expected structure.

Attempts to prepare 2,4,5,7-tetramethyltetrabenzo[b,d,h,j][1,6]-diazacyclododecine in benzene or glacial acetic acid media also failed to give the desired compound.

Methyl 3-chloro-2-nitrobenzoate

(Method of E.R. Riegel and K.W. Buchwald, J. Amer. Chem. Soc., 1929, 51, 484)

3-Chloro-2-nitrobenzoic acid (7.3 g, 0.0362 mole) was dissolved in absolute methyl alcohol (190 ml) contained in a 500 ml, 2-necked, round-bottomed flask, fitted with a reflux condenser and a dropping funnel. Concentrated sulphuric acid (sp. gr. 1.840, 10 ml) was added cautiously to the flask from the dropping funnel during 10 minutes, with occasional swirling. The solution was then boiled under reflux for 18¾ hours. A colourless solution was obtained and when it was poured into 500 ml of ice-water, white solid formed. This was filtered off, washed with cold water, slurried in ice-water, and the slurry was treated with solid sodium bicarbonate until it was alkaline to litmus. The ester was filtered off, washed thoroughly with cold water and dried giving (7.44 g, 95%), m.p. 104.5-105.5°. Crystallization from methyl alcohol gave white square-ended rectangular rods, m.p. 104.5-105.5°.

(Found: C, 44.3; H, 2.8; N, 6.3.

$C_8H_6ClNO_4$ requires C, 44.6; H, 2.8; N, 6.5%).

Attempted preparation of dimethyl 2,2'-dinitrobiphenyl-3,3'-dicarboxylate

(Method of C.C. King Ling and M.M. Harris, J. Chem. Soc., 1964, 1825)

An attempt was made to prepare the above mentioned compound as follows:

Methyl 3-chloro-2-nitrobenzoate (17 g, 0.0788 mole) was melted in a hard glass tube immersed in a metal bath heated to 270°. The temperature inside the hard glass tube was brought to 265°. Copper bronze (17 g) was added during 20 minutes, stirred in with a thermometer, at such a rate as to maintain the internal temperature between 265-275°. When all the copper bronze had been added, the bath temperature was raised to 290-98° for 15 minutes. The tube was then removed from the metal bath, allowed to cool to 100° and the reaction mixture extracted several times with boiling chloroform. The extracts were filtered hot through a Buchner funnel, and the filtrate evaporated to dryness under reduced pressure giving dark brown sticky material. Crystallization of the product from benzene or passing it through a column of alumina eluted with a mixture of 70% sodium dried benzene and 30% ethyl acetate failed to give any solid; a dark brown sticky material was obtained instead.

6,7-Diphenyldibenzo[e,g][1,4]diazocine

(N.L. Allinger and G.A. Youngdale, J. Org. Chem., 1959, 24, 306)

This was prepared from 2,2'-diaminobiphenyl and benzil in glacial acetic acid. The condensation product was recrystallized from glacial acetic acid, and gave yellow triangular rods, m.p. 241-242, 70% (lit.,[k] m.p. 239-240°).

Attempted preparation of 5,6,7,8-tetrahydro-6,7-diphenyldibenzo[e,g]-[1,4]diazocine

Reduction with dimethylamine borane in glacial acetic acid

(Method of J.H. Billman and J.W. McDowell, J. Org. Chem., 1961, 26, 1437)

Due to the ease, speed and effectiveness of the reduction of tetrabenzo[b,d,h,j][1,6]diazacyclododecine by dimethylamine borane in glacial acetic acid medium, attempts to reduce 6,7-diphenyldibenzo[e,g]-[1,4]diazocine by dimethylamine borane were made. The compound proved to be rather inert to the reducing agent, as the bulk of the starting material was recovered unchanged.

3,8-Dimethyl-4,5-6,7-dibenzo-1,2-diazocine

(D.M. Hall, J.E. Ladbury, M.S. Lesslie and E.E. Turner, J. Chem. Soc., 1956, 3475)

This was prepared from 2,2'-diacetylbiphenyl and 100% hydrazine hydrate in ethyl alcohol. The product was crystallized from aqueous ethanol, and gave colourless prisms, m.p. 166-167°, 55% (lit., m.p. 167-168°).

[k] D.M. Hall, Hwang Huaun-Yong and B.Bhanthumnavin, J. Chem. Soc., Perkin Trans. II, 1973, 2131.

Attempted preparation of 1,2,3,8-Tetrahydro-3,8-dimethyl-4,5-6,7-dibenzo-1,2-diazocine

Reduction with dimethylamine borane in glacial acetic acid

(Method of J.H. Billman and J.W.McDowell, J. Org. Chem., 1961, 26, 1437)

Attempts to reduce 3,8-dimethyl-4,5-6,7-dibenzo-1,2-diazocine by dimethylamine borane in glacial acetic acid failed to give the tetrahydro-derivative. The compound proved to be rather inert to the reducing agent, as the bulk of the starting material was recovered unchanged.

2,7-Dinitrophenanthraquinone

(J.Schmidt and A. Kämpf, Ber., 1903, 36, 3738)

9,10-Phenanthraquinone (30 g, 0.1443 mole) was boiled under reflux with a mixture of red fuming nitric acid (sp. gr. ~ 1.50, 400 ml) and concentrated sulphuric acid (sp. gr. 1.84, 50 ml) for 30 minutes, and the cooled reaction mixture was poured into eight times the amount of water. The voluminous yellow precipitate, left to stand over-night, was separated by syphoning off and filtering off of the liquid and was dissolved in 4 litres of boiling glacial acetic acid. On cooling this solution, the 2,7-dinitrophenanthraquinone appeared in tiny yellow needles, filtered off and dried giving (19.30 g, 45%), m.p. 303-304° (lit., 300-303°).

The glacial acetic acid mother liquor was reduced to an eighth of its volumne. From this concentrated solution, 4,5-dinitrophenanthraquinone was separated, on cooling, as brown feathers. The amount varied from nil to 0.4 g, m.p. 200-210° (lit.,[1] 215-217°).

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[1] J. Schmidt, Ber., 1902, 35, 3121

Attempted reduction of 2,7-dinitrophenanthraquinone

A. Reduction with sodium borohydride in methanol

(Method of S.W. Chaikin and W.G. Brown, J. Amer. Chem. Soc., 1949, 71, 122).

Attempt to reduce 2,7-dinitrophenanthraquinone by sodium borohydride in methanol failed to give the dinitro-diol. A black solid was obtained and left unidentified.

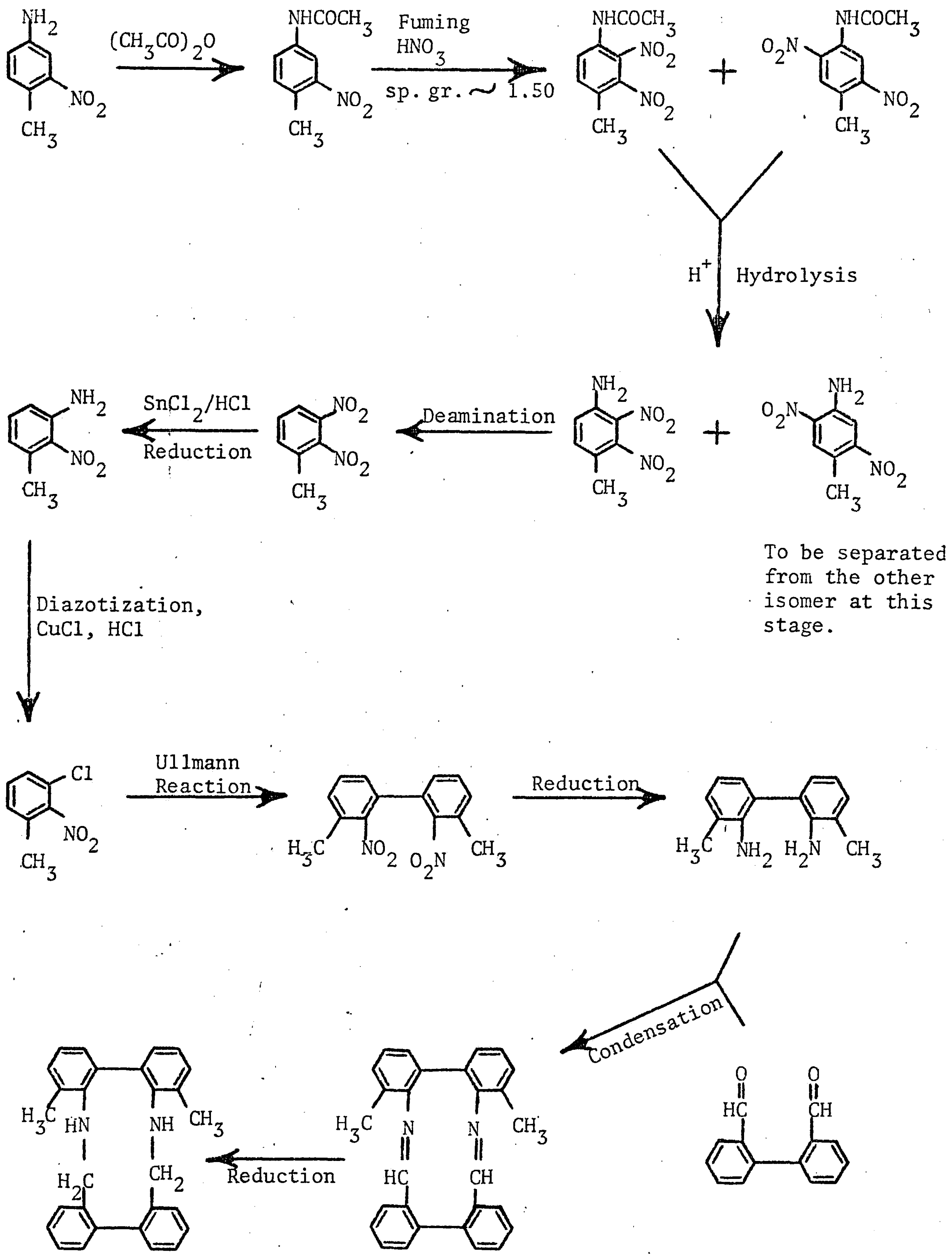
B. Reduction with sodium borohydride in the presence of aluminium chloride

(Method of H.C. Brown and B.C. Subba Rao, J. Amer. Chem. Soc., 1956, 78, 2582)

Attempt to reduce 2,7-dinitrophenanthraquinone by sodium borohydride in the presence of aluminium chloride in tetrahydrofuran failed to give the dinitro-diol. A crimson-red solid was obtained and left unidentified.

Attempts to prepare 1,8-dimethyl tetrabenzo[b,d,h,j][1,6]diazacyclododecine and its tetrahydro-derivative.

The following scheme showed the processes through which it was hoped to get the 12-membered ring compound with 1,8-substituents:



To be separated from the other isomer at this stage.

Scheme No.5.

2-Nitroaceto-p-toluidide

(R.A. Morton and A. McGookin, J. Chem. Soc., 1934, 901)

This compound was prepared by treatment of 2-nitro-p-toluidine with freshly distilled acetic anhydride in the presence of concentrated sulphuric acid. Yellow flakes were obtained in 83% yield, m.p. 144.5-145.5° (lit., 145°).

2,3- and 2,5-Dinitroaceto-p-toluidides

(R.A. Morton and A. McGookin, J. Chem. Soc., 1934, 901 and
H.J. Page and B.R. Heasman, J. Chem. Soc., 1923, 3235)

These were prepared by treatment of 2-nitroaceto-p-toluidide with fuming nitric acid (sp. gr. ~ 1.50) at a temperature kept below 0°. Yellow solid was obtained in 93% yield.

Attempts were made to separate the two isomers, at this stage, by dissolving the nitration product in boiling glacial acetic acid. On cooling, 2,3-dinitroaceto-p-toluidide crystallized first as colourless needles, m.p. 174 (lit. 175°). It was found that the amount of 2,3-dinitroaceto-p-toluidide separated, in each case, varied from 30-45%. The isolation of 2,5-dinitroaceto-p-toluidide from the mother-liquors was found to present considerable difficulties.

2,3- and 2,5-Dinitro-p-toluidines

(R.A. Morton and A. McGookin, J. Chem. Soc., 1934,901)

These were prepared on hydrolyzing a mixture of 2,3- and 2,5-dinitroaceto-p-toluidides in sulphuric acid medium; orange solid was obtained in 94% yield.

Several attempts were made to separate the mixture of dinitrotoluidines, using variable proportions of acetone/water solution. It was found that only a small quantity of pure 2,3-dinitro-*p*-toluidine, m.p. 123.5-124° (lit., 124°), can be separated by this method. In other attempts, recrystallization of the mixture from ethyl alcohol or benzene, also failed to separate the two isomers.

3-Amino-2-nitrotoluene

(H. Burton and J. Kenner, *J. Chem. Soc.*, 1921, *119*, 1047)

This compound was prepared by partial reduction of 2,3-dinitrotoluene with an absolute ethyl alcoholic solution of stannous chloride saturated with dry hydrogen chloride. The product crystallized from a mixture of equal proportions of dry benzene and light petroleum (b.p. 80-100°) giving deep red prisms, m.p. 105.5-107° (lit.,[m] 108°), 40%.

Conclusion

In order to carry out the whole synthesis fairly large quantities of 3-amino-2-nitrotoluene were required. It was found that several attempted separations of 2,3- and 2,5-dinitroaceto-*p*-toluidides, and of 2,3- and 2,5-dinitro-*p*-toluidines by various methods were tedious, time consuming, and gave only small amount of each isomer in pure state. Also, partial reduction of 2,3-dinitrotoluene with an absolute ethyl alcoholic solution of stannous chloride saturated with dry hydrogen chloride gave 40% yield, while Burton and Kenner obtained a 79% yield.

For the above reasons, the attempt to prepare 1,8-dimethyl tetrabenzo[*b*,*d*,*h*,*j*][1,6]diazacyclododecine and its tetrahydro-derivative was abandoned.

[m] R.A. Morton and A. McGookin, *J. Chem. Soc.*, 1934, 901

4. REFERENCES

1. D.M. Hall, 'Progress in Stereochemistry', eds. B.J. Aylett and M.M. Harris, Butterworth and Co., London, 1969, vol.4, p.1.
2. G. Wittig, G. Koenig, and K. Clauss, Annalen, 1955, 593, 127.
3. U. Voll, H. Burzlaff, and H.-J. Bestmann, Chem. Ber., 1976, 109, 1324.
4. E.D. Bergmann, I. Agranat, and M.A. Kraus, J. Org. Chem., 1967, 32, 600.
5. A.P. Bindra and J.A. Elix, Tetrahedron, 1970, 26, 3749.
6. K.E. Howlett, J. Chem. Soc., 1960, 1055.
7. J. Dhar, Indian J. Phys., 1932, 7, 43.
8. J. Trotter, Acta Cryst., 1961, 14, 1135.
9. G.B. Robertson, Nature, 1961, 191, 593.
10. G.H. Beaven and D.M. Hall, J. Chem. Soc., 1956, 4637.
11. B. Williamson and W.H. Rodebush, J. Amer. Chem. Soc., 1941, 63, 3018.
12. G.M. Brown and M.H. Bortner, Acta Cryst., 1954, 7, 139.
13. D.M. Burns and J.Iball, Nature, 1954, 173, 635.
14. A.C. Cope and R.D. Smith, J. Amer. Chem. Soc., 1956, 78, 1012.
15. K. Mislow, S. Hyden, and H. Schaefer, J. Amer. Chem. Soc., 1962, 84, 1449.
16. C.C. Hinckley, J. Amer. Chem. Soc., 1969, 91, 5160.
17. M.R. Peterson,Jr. and G.H. Wahl, Jr., J. Chem. Edn., 1972, 49, 790.
18. A.F. Cockerill, G.L.O. Davies, R.C. Harden, and D.M. Rackham, Chem. Rev., 1973, 73, 553 and references cited therein.
19. J.K.M. Sanders and D.H. Williams, J.C.S. Chem. Comm., 1970, 422.
20. J. Briggs, G.H. Frost, F.A. Hart, G.P. Moss, and M.L. Staniforth, J.C.S. Chem. Comm., 1970, 749.
21. R.E. Rondeau and R.E. Sievers, J. Amer. Chem. Soc., 1971, 93, 1522.
22. P. Bélanger, C. Freppel, D. Tizané, and J.C. Richer, J.C.S. Chem. Comm., 1971, 266.

23. O. Hofer, 'Topics in Stereochemistry', ed. N.L. Allinger and E.L. Eliel, Interscience, New York, 1976, Vol.9 p.111.

24. P.V. Demarco, T.K. Elzey, R.B. Lewis, and E. Wenkert, J. Amer. Chem. Soc., 1970, 92, 5734.

25. R.V. Ammon and R.D. Fischer, Angew. Chem. Internat. Edn., 1972, 11, 675.

26. B.C. Mayo, Chem. Soc. Rev., 1973, 2, 49.

27. B. Bleaney, J. Magnetic Resonance, 1972, 8, 91.

28. R.R. Fraser, M.A. Petit, and J.K. Saunders, J.C.S. Chem. Comm., 1971, 1450.

29. C. Beauté, Z.W. Wolkowski, and N. Thoai, Tetrahedron Letters, 1971, 817.

30. Z.W. Wolkowski, Tetrahedron Letters, 1971, 821.

31. B.L. Shapiro, J.R. Hlubucek, G.R. Sullivan, and L.F. Johnson, J. Amer. Chem. Soc., 1971, 93, 3281.

32. C. Beauté, Z.W. Wolkowski, and N. Thoai, J.C.S. Chem. Comm., 1971, 700.

33. L. Tomić, Z. Majerski, M. Tomić, and D.E. Sunko, Croat. Chem. Acta, 1971, 267

34. I. Armitage and L.D. Hall, Canad. J. Chem., 1971, 49, 2770.

35. E. Wenkert, D.W. Cochran, E.W. Hagaman, R.B. Lewis, and F.M. Schell, J. Amer. Chem. Soc., 1971, 93, 6271.

36. B. Bleaney, C.M. Dobson, B.A. Levine, R.B. Martin, R.J.P. Williams, and A.V. Xavier, J.C.S. Chem. Comm., 1972, 791.

37. J. Reuben, 'Progress in Nuclear Magnetic Resonance Spectroscopy', eds. J.W. Emsley, J. Feeney, and L.H. Sutcliffe, Pergamon, Oxford, 1973, vol.9, pt.1.

38. H. Hart and G.M. Love, Tetrahedron Letters, 1971, 625.

39. G.E. Wright and T.Y. Tang Wei, Tetrahedron, 1973, 29, 3775.

40. J.A. Dale and H.S. Mosher, J. Amer. Chem. Soc., 1968, 90, 3732.

41. J.A. Dale, D.L. Dull, and H.S. Mosher, J. Org. Chem., 1969, 34, 2543.

42. W.H. Pirkle and S.D. Beare, J. Amer. Chem. Soc., 1969, 91, 5150.

43. G.M. Whitesides and D.W. Lewis, J. Amer. Chem. Soc., 1970, 92, 6979.

44. G.M. Whitesides and D.W. Lewis, J. Amer. Chem. Soc., 1971, 93, 5914.

45. M.D. McCreary, D.W. Lewis, D.L. Wernick, and G.M. Whitesides, *J. Amer. Chem. Soc.*, 1974, *96*, 1038.

46. H.L. Goering, J.N. Eikenberry, and G.S. Koermer, *J. Amer. Chem. Soc.*, 1971, *93*, 5913.

47. H.L. Goering, J.N. Eikenberry, G.S. Koermer, and C.J. Lattimer, *J. Amer. Chem. Soc.*, 1974, *96*, 1493.

48. R.R. Fraser, M.A. Petit, and M. Miskow, *J. Amer. Chem. Soc.*, 1972, *94*, 3253.

49. N.A. Shaath and T.O. Soine, *J. Org. Chem.*, 1975, *40*, 1987.

50. C. Kutal, 'Nuclear Magnetic Resonance, Shift Reagents', ed. R.E. Sievers, Academic Press, New York, 1973, p.87.

51. K. Jankowski and A. Rabczenko, *J. Org. Chem.*, 1975, *40*, 960.

52. I. Armitage, G. Dunsmore, L.D. Hall, and A.G. Marshall, *J.C.S. Chem. Comm.*, 1971, 1281.

53. J. Reuben, 'Nuclear Magnetic Resonance, Shift Reagents', ed. R.E. Sievers, Academic Press, New York, 1973, p. 341.

54. J.W.M. de Boer, C.W. Hilbers, and E. de Boer, *J. Magnetic Resonance*, 1977, *25*, 437.

55. B.L. Shapiro, M.D. Johnston, Jr., R.L.R. Towns, A.D. Godwin, H.L. Pearce, T.W. Proulx, and M.J. Shapiro, 'Nuclear Magnetic Resonance, Shift Reagents', ed. R.E. Sievers, Academic Press, New York, 1973, p.227.

56. C.C. Hinckley, *Proc. Rare Earth Res. Conf.*, *10th* (Conf-730402-P1), 1973, *1*, 362.

57. C.C. Hinckley, W.A. Boyd, G.V. Smith, and F. Behbahany, 'Nuclear Magnetic Resonance, Shift Reagents', ed. R.E. Sievers, Academic Press, New York, 1973, p.1.

58. L. Tomić, Z. Majerski, M. Tomić, and D.E. Sunko, *J.C.S. Chem. Comm.*, 1971, 719.

59. J.K.M. Sanders and D.H. Williams, *J. Amer. Chem. Soc.*, 1971, *93*, 641.

60. I. Armitage, G. Dunsmore, L.D. Hall, and A.G. Marshall, *Canad. J. Chem.*, 1972, *50*, 2119.

61. A.F. Cockerill and D.M. Rackham, Tetrahedron Letters, 1970, 5149.

62. P.C. Lauterbur, J. Chem. Phys., 1957, 26, 217.

63. C.H. Holm, J. Chem. Phys., 1957, 26, 707.

64. G.C. Levy and G.L. Nelson, 'Carbon-13 N.M.R. for Organic Chemists', Wiley-Interscience, New York, 1972.

65. B.E. Mann, Prog. N.M.R. Spectroscopy, 1977, 11, 95.

66. H. Günther, H. Schmickler, and G. Jikeli, J. Magnetic Resonance, 1973, 11, 344.

67. F.W. Wehrli, 'Nuclear Magnetic Resonance Spectroscopy of Nuclei Other than Protons', eds. T. Axenrod and G. Webb, Wiley, New York, 1974.

68. M. Karplus and J.A. Pople, J. Chem. Phys., 1963, 38, 2803.

69. P.C. Lauterbur, Ann. New York Acad. Sci., 1958, 70, 841.

70. P.C. Lauterbur, J. Amer. Chem. Soc., 1961, 83, 1838.

71. P.C. Lauterbur, J. Amer. Chem. Soc., 1961, 83, 1846.

72. P.C. Lauterbur, J. Chem. Phys., 1963, 38, 1406.

73. P.C. Lauterbur, J. Chem. Phys., 1963, 38, 1415.

74. P.C. Lauterbur, J. Chem. Phys., 1963, 38, 1432.

75. H. Spiesecke and W.G. Schneider, J. Chem. Phys., 1961, 35, 731.

76. H. Spiesecke and W.G. Schneider, Tetrahedron Letters, 1961, 468.

77. J.B. Stothers, Quart. Rev., London, 1965, 19, 144.

78. W.R. Woolfenden and D.M. Grant, J. Amer. Chem. Soc., 1966, 88, 1496.

79. G.B. Savitsky, J. Phys. Chem., 1963, 67, 2723.

80. F.W. Wehrli and T. Wirthlin, 'Interpretation of Carbon-13 N.M.R. Spectra', Heyden, London, 1978, p.47.

81. G.A. Olah and A.M. White, J. Amer. Chem. Soc., 1967, 89, 7072.

82. K.S. Dhami and J.B. Stothers, Canad. J. Chem., 1967, 45, 233.

83. K.N. Scott, J. Amer. Chem. Soc., 1972, 94, 8564.

84. K.S. Dhami and J.B. Stothers, Canad. J. Chem. 1966, 44, 2855.

85. G.W. Buchanan, G. Montaudo, and P. Finocchiaro, Canad. J. Chem., 1974, 52, 767.

86. E.M. Schulman, K.A. Christensen, D.M. Grant, and C. Walling, J. Org. Chem., 1974, 39, 2686.

87. H.L. Retcofsky, J.M. Hoffman, Jr., and R.A. Friedel, J. Chem. Phys., 1967, 46, 4545.

88. T.D. Alger, D.M. Grant, and E.G. Paul, J. Amer. Chem. Soc., 1966, 88, 5397.

89. H. Hasegawa, M. Imanari, and K. Ishizu, Bull. Chem. Soc. Japan, 1972, 45, 1153.

90. M. Imanari, M. Kohno, M. Ohuchi, and K. Ishizu, Bull. Chem. Soc. Japan, 1974, 47, 708.

91. U.V. Atlas of Organic Compounds, Butterworths-Verlag Chemie, London, D10/76.

92. J.D. Margerum and J.A. Sousa, Appl. Spectros., 1965, 19, 91.

93. T. Kubota, M. Yamakawa, and Y. Mori, Bull. Chem. Soc. Japan, 1963, 36, 1552.

94. W.F. Smith, Tetrahedron, 1963, 19, 445.

95. U.V. Atlas of Organic Compounds, Butterworths-Verlag Chemie, London, C6/1 and D10/76.

96. V.A. Izmailsky and E.A. Smirnov, J. Gen. Chem. (U.S.S.R.), 1956, 26, 3389.

97. H.B. Bürgi and J.D. Dunitz, J.C.S. Chem. Comm., 1969, 472.

98. H.B. Bürgi and J.D. Dunitz, Helv. Chim. Acta, 1970, 53, 1747.

99. P. Brocklehurst, Tetrahedron, 1962, 18, 299.

100. V.I. Minkin, Yu. A. Zhdanov, E.A. Medyantzeva, Yu. A. Ostroumov, Tetrahedron, 1967, 23, 3651.

101. G. Wettermark, 'The Chemistry of the Carbon-Nitrogen Double Bond', ed. S. Patai, Interscience, New York, 1970, p.577.

102. M.A. El-Bayoumi, M. El-Aasser, and F. Abdel-Halim, J. Amer. Chem. Soc., 1971, 93, 586.

103. M. Kobayashi, M. Yoshida, and H. Minato, J. Org. Chem., 1976, 41, 3322.

104. A.C. Pratt, Chem. Soc. Rev., 1977, 6, 63,

105. N. Ebara, Bull. Chem. Soc. Japan, 1960, 33, 534; 1961, 34, 1151.

106. M. El-Aasser, F. Abdel-Halim, and M.A. El-Bayoumi, J. Amer. Chem. Soc., 1971, 93, 590.

107. E. Fischer and Y. Frei, J. Chem. Phys., 1957, 27, 808.

108. M. Kobayashi, M. Yoshida, and H. Minato, Chemistry Letters, 1976, 185.

109. J.M.Insole, J. Chem. Soc., (C), 1971, 1712.

110. J. Dale, Acta. Chem. Scand., 1957, 11, 650.

111. D.J. Cram and K.C. Dewhirst, J. Amer. Chem. Soc., 1959, 81, 5963.

112. H. Suzuki, 'Electronic Absorption Spectra and Geometry of Organic Molecules', Academic Press, New York, 1967, p.261.

113. H.H. Jaffé and M. Orchin, 'Theory and Applications of Ultra-Violet Spectroscopy', Wiley, New York, 1962.

114. R. Huisgen and H.-J. Koch,. Annalen, 1955, 591, 200.

115. G.H. Beaven, D.M. Hall, M.S. Lesslie, E.E. Turner, and G.R. Bird, J. Chem. Soc., 1954, 131.

116. N.L. Allinger and G.A. Youngdale, J. Org. Chem., 1959, 24, 306.

117. H-Y. Hwang; Ph.D. Thesis, University of London, 1971.

118. A.S. Al-Tai, D.M. Hall, and A.R. Mears, J.C.S. Perkin II, 1976, 133.

119. T.H. Siddall, J.C.S. Chem. Comm., 1971, 452.

120. P. Joseph-Nathan and V.M. Rodriguez, Rev. Latinoamer. Quim., 1974, 5, 12.

121. R.J. Pugmire, D.M. Grant, M.J. Robins, and R.K. Robins, J. Amer. Chem. Soc., 1969, 91, 6381.

122. J.B. Stothers, 'Carbon-13 N.M.R. Spectroscopy', Academic Press, New York, 1972, pp. 108 and 197.

123. N. Inamoto, K. Kushida, S. Masuda, H. Ohta, S. Satoh, Y. Tamura, K. Tokumaru, K. Tori, and M. Yoshida, Tetrahedron Letters, 1974, 3617.

124. J.M. Ruxer, A. Solladié-Cavallo, G. Solladié, and D.O. Olliero, Org. Magnetic Resonance, 1977, 10, 105.

125. H. Irngartinger, Chem. Ber., 1972, 105, 2068.

126. G. Wittig and G. Skipka, Annalen, 1973, 59; K. Grohmann, P.D. Howes, R.H. Mitchell, A. Monaham, and F. Sondheimer, J. Org. Chem., 1973. 38, 808.

127. I. Irngartinger, Chem. Ber., 1973, 106, 2786.

128. I. Agranat, M.A. Kraus, E.D. Bergmann, P.J. Roberts and O. Kennard, Tetrahedron Letters, 1973, 1265.

129. I. Irngartinger, Chem. Ber., 1973, 106, 2796.