SYNTHESIS AND NUCLEAR MAGNETIC RESONANCE SPECTRA OF BENZIDINES AND SOME DERIVATIVES

BY

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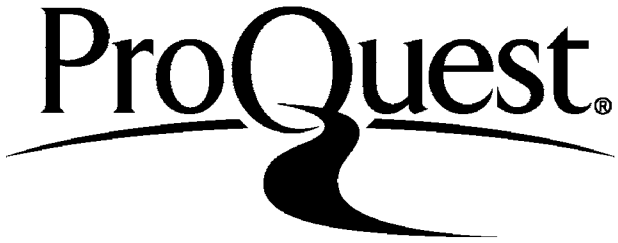

ABSTRACT

Benzidine, 2,2'-disubstituted and 2,6,2',6'- tetra substituted benzidines are usually prepared through the rearrangement of their corresponding hydrazobenzenes in acid medium. However, hydrazobenzenes which would lead to benzidines heavily substituted in the 2,6,2',6' positions were found to be difficult to rearrange or to give low yields when rearranged in concentrated acids. Best yields were obtained when sulfuric acid (2:1 by weight) at 85-90°C was used. Column chromatography was found to be the most satisfactory method of separating the rearrangement products (benzidine, diphenyline and semidine).

^1H N.m.r. spectra of the benzidines prepared throughout this work were done and the chemical shifts of the amino protons and of the ring protons in $CDCI_3$, in $CDCl_3$ with few drops of TFA and in neat D_2SO_4 were determined and discussed.

Many attempts were made to achieve optical resolution of 2,2'-di-t-butylbenzidine through the (+)-hydrogen tartrate, (+)-camphor-10-sulfonate salts, and the (-)-menthoxyacetyl derivative but without success. On the other hand, the optical activation of 2,2'-dibromo-6,6'-diethoxybenzidine gave only the (-) base through the (+)-camphor-10-sulfonate salt.

Temperature variable high resolution ^1H n.m.r. (220MHz) spectroscopy was employed to study the inversion process of the two enantiomeric forms by means of magnetic behaviour of the diastereotopic protons of the ethoxy group of 2,2'-dibromo-6,6'-diethoxybenzidine.

Schiff's bases derived from different benzidines and benzaldehydes were prepared and the substituent effect in both components on the rate of the reaction was studied. Moreover, ^1H n.m.r. spectra of these bases was extensively studied and the chemical shifts of the azomethine proton

and of the ring protons of the aldehyde and of the benzidine components were determined and discussed. The deshielding effect of the azomethine group CH=N on the chemical shifts of the benzylidene ring protons of these bases was determined for the first time.

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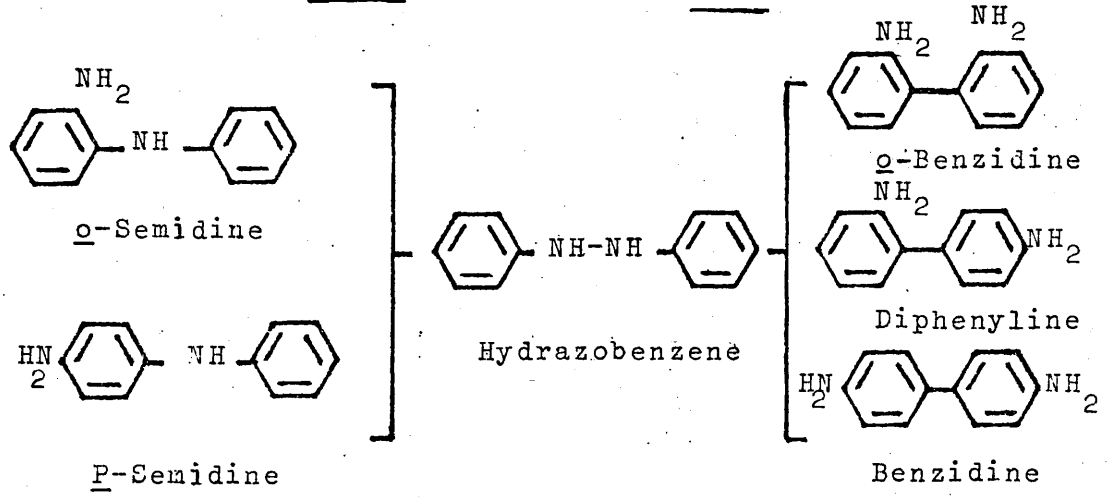
— INTRODUCTION —

INTRODUCTION

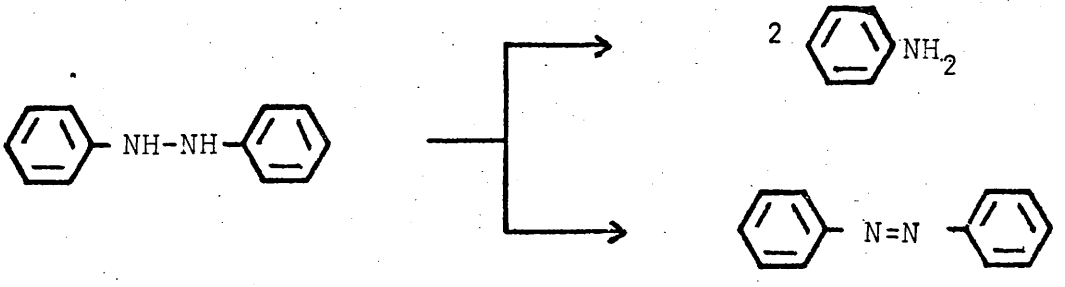
A. The Benzidine Rearrangement

Hydrazobenzene was discovered and its conversion into benzidine under the influence of acids was first discovered by Hofmann[1] in 1863. Benzidine was known already, Fittig[2] having identified it as a diaminobiphenyl. The positions of its amino groups were established later by Schultz[3]. Schmidt and Schultz[4] noted the formation, along with benzidine, of a minor proportion of a second diaminobiphenyl, so called diphenyline; and with Strasser[5] they determined the positions of its amino groups. The further investigation of these and related rearrangements is due chiefly to Jacobson[6] who in 1922 gave the historical background of benzidine syntheses and established the formation, not indeed from hydrazobenzene, but from many other benzenoid hydrazo compounds, of two other types of isomerization products. These were both aminobiphenylamines and are usually called ortho and para semidines.

Aromatic hydrazo compounds, on treatment with acids, yield either diaminobiphenyls or aminodiphenylamines by ortho and para coupling of the two arylamine residues of which the hydrazo compound can be considered to be composed. The possible products are 2,2'-, 2,4'-, 4,4'- diaminobiphenyls, respectively known as ortho-benzidines, diphenylines and benzidines, and 2- and 4- aminodiphenylamines, known as ortho-semidines and para-semidines.



Products of disproportionation reactions were observed in small amounts alongside these rearrangement products. They were formed by reduction of the hydrazo compound to the corresponding aniline (fission amine) and oxidation to the azo compound[7,8]. However, the amount of disproportionation depends mainly on the reaction medium, as well as on the reaction conditions such as temperature and concentration[7] In the case of 3,5,3',5' - tetrasubstituted hydrazo-benzenes, the disproportionation products are controlled in large measure by the steric size of the substituents; such factors as medium effect and the polar nature of the substituents play significant but comparatively minor roles[8].



When hydrazobenzene itself is rearranged, the formed mixture of isomers contains about 70% of the benzidine and 30% of the diphenyline, along with traces of other isomers detected chromatographically. However, some authors[8] gave results of 79% benzidine, 10.5% diphenyline, and 2.7% of both azobenzene and aniline when the rearrangement of hydrazobenzene was carried out in 2:1 sulphuric acid at 85-90°.

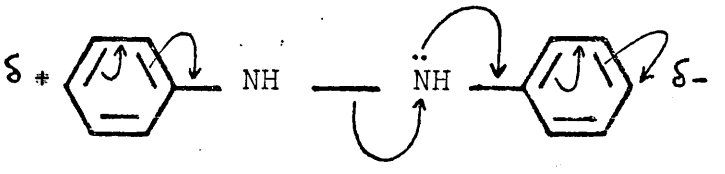
Although the mechanism of the benzidine rearrangement has engaged the attention of many workers, its course has not yet been fully clarified. The reagent in which the rearrangement is carried out is normally a strong acid; however, a case (β-hydrazonaphthalene) in which the benzidine rearrangement is brought about not only by acid but also by the agency of alkali has been mentioned by Meisenheimer and Witte[9]. No benzidine is formed in the catalytic reduction of azobenzene or hydrazobenzene, and this is perhaps an indication that hydrogen atom (as distinct from proton)

interchange is not of importance in the reaction, and that the rearrangements are prototropic and occur in proton-donor media as results of the action of an acid on a hydrazo compound[10].

Tichwinsky[11] was the first to draw attention to the fact that an acid converts a weak base into the salt of a strong base in the course of the migration, which, he stated, does not occur in benzene solution in the presence of hydrogen chloride.

Many workers published their views in which they assumed that the benzidine rearrangement proceeds through dissociation of the N-N bond of the salt of hydrazobenzene into radicals and their subsequent recombination [12,13,14]. However, Jacobson[6], who was against the dissociation theory, put forward his argument, after carrying out 63 examples of benzidine rearrangements of unsymmetrical hydrazo compounds, in which he proved that no symmetrical benzidines (A-A or B-B) were isolated from the rearrangement of an A-B hydrazobenzene. This proves conclusively that no mixing of the aromatic residues contained in a different molecules occurs and hence no dissociation of the hydrazobenzene molecule takes place.

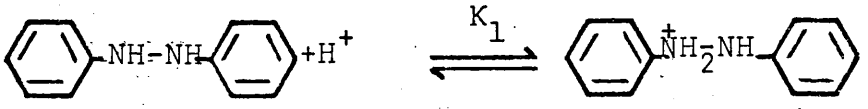
Ingold and Kidd[15] showed that this rearrangement is intramolecular and does not involve fission into two separate fragments, simply by conversion of a mixture of 2,2' - dimethoxy - and 2,2' - diethoxy - hydrazobenzene into the corresponding benzidines in which they obtained two components only; thus they concluded that before the nitrogen link is severed, the 4- and 4'- positions come within each other's sphere of influence in a molecule activated during the formation or decomposition of the corresponding hydrazinium cation.

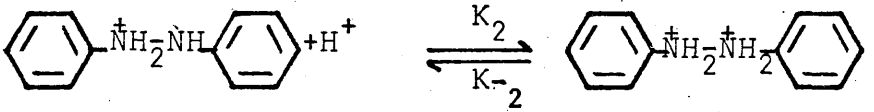


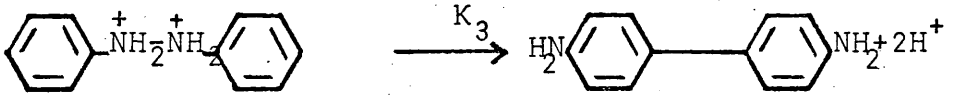
A general theory was proposed by Dewar[16] for the mechanism of benzidine rearrangement which was based on the formation of a protonated π - complex formed by transformation of the N-N bond into a π - bond between the rings provided that they are held in parallel planes, though with the possibility of relative rotation.

Hughes and Ingold[17] assumed first that the conjugative electron displacement from p- to p'- positions is an intermediate state in the formation of the univalent cation Ph $\overset{+}{N}H_2$-NHPh, but later[18] they agreed with Hammond and Shine[19] in their adduced evidence that the rearranging entity is the bivalent cation Ph $\overset{+}{N}H_2$- $\overset{+}{N}H_2$Ph.

From their experimental results, Hammond and Shine[19] concluded that the rearrangement of hydrazobenzene is second order in hydrogen ion as they obtained a constant of $K/[HCl]^2$ for various runs in which ionic strength was kept constant, and that it is the second conjugate acid of hydrazobenzene which undergoes rearrangement. The reaction involved may be formulated as follows:

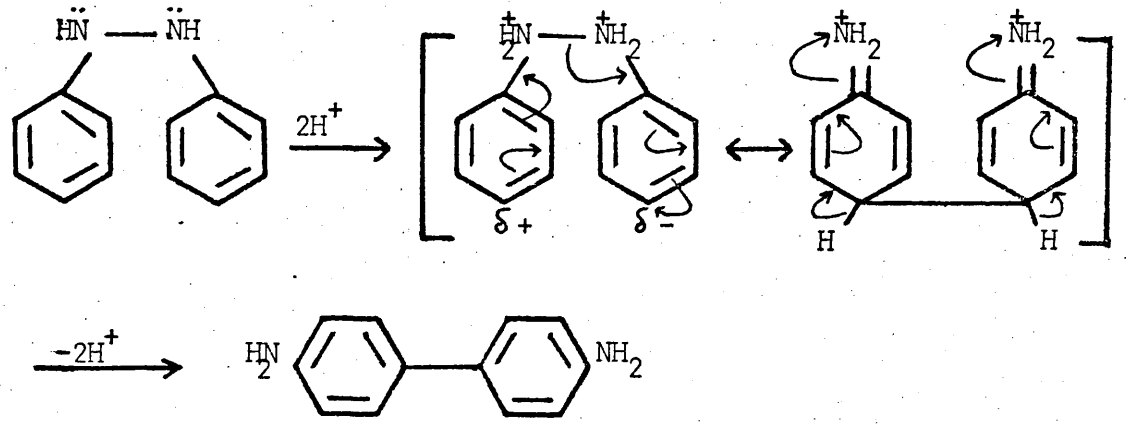
1. 

2. 

3. 

Moreover, they concluded also that the new bonds of the products of the rearrangement are partially formed before the old bond is broken in a manner similar to that suggested by Robinson[10] and Hughes and Ingold[17], and the geometrical difficulty of bringing nuclear carbon atoms close to each other in the transition state would be decreased by the stretching of the old bond due to electrostatic repulsion between the two positively charged nitrogen atoms.

Therefore, a conclusion regarding the mechanism of the benzidine rearrangement was reached and it is illustrated electronically as follows[16a,16b]:-



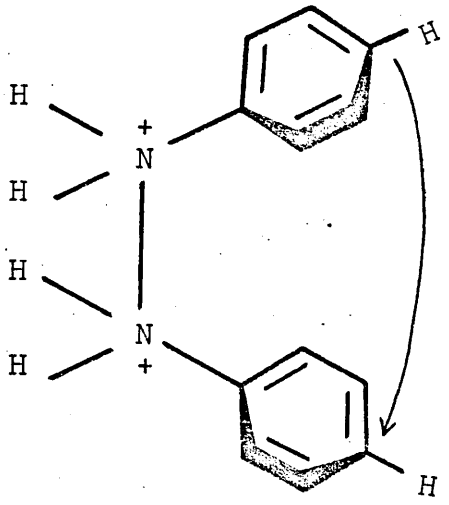
The syntheses and kinetic studies of the benzidine rearrangement in the hydrazobenzene series[16,19-22] and in the hydrazonaphthalene series[23], were done and similar conclusions and results were obtained: first-order reaction in hydrazo compound concentration, second-order reaction in the acid concentration, positive salt effect and the possibility of the rearrangement occurring in the solid state or thermally. The latter observation was supported and confirmed by Shine[24], who reported that thermal rearrangement is possible and that it is definitely intramolecular.

Attempts were made to isolate any cross-products from the benzidine rearrangement using C^{14} - compounds[25,26], but without success. This was regarded as additional evidence for intramolecularity of this rearrangement.

Searching the literature reveals that the polar-transition-state mechanism is the only theory proposed for the benzidine rearrangement that is consistent with the overall observations. This theory, which was incepted by Hughes and Ingold[17] in 1941 and has been modified since, notably by the incorporation of a suggestion by Hammick

and Mason[27] and finally by Hammond and Shine[19], assumes highly polar bonding along the reaction co-ordinate and a transition state containing at least two bonds, which are mainly, though not wholly, electrovalent. This circumstance allows the bond much greater lengths than are normal to bonds, and much lower bending force-constants, and hence very different angles from these of ordinary bonds. These geometrical and mechanical characteristics of the bonds permit shape-changes along the reaction co-ordinate which can be drastic enough, and yet energetically easy enough to fulfil without difficulty the drastic stereochemical demands of the rearrangement.

It seems unlikely that a simple electronic reorganization mechanism such as the one proposed for the Claisen rearrangement is applicable for the benzidine rearrangement. This formulation is objectionable because the benzene ring is thicker, 3.8Å, than it is long, 2.8Å; the N-N bond must be stretched appreciably, and the new bond between the carbon atoms must be formed at a considerable distance. The energy requirements for the rearrangement seem much too small for a process of this kind. Moreover, this mechanism would not account for the simultaneous formation of 2,4' - diaminobiphenyls.



Regarding the syntheses of benzidines, or in general benzidine rearrangement products, there are so many described in the literature that it is virtually impossible to list even a representative number of them Some benzidines were prepared by rearrangement under different conditions, or starting with compounds other than hydrazobenzenes, such as in the preparation of 2,6,2',6' - tetrabromobenzidine[28] and 2,2' - dichlorobenzidine[29]. However, some benzidines were prepared even in neutral solvents[23,24].

The effect of introducing a substituent into the ortho and/or para positions of the hydrazo compound seems to be of great importance in determining the expected products[27]. Hammick and Mason[27] studied the substituent effect on the rearrangement products and found that if the substituent is an electron attracting group, diphenylines are to be expected on rearrangement while semidines are predominant if the substituent is an electron donating group. They explain their conclusions on the basis of the ortho-para distance and the energy content of structures formed during the reaction, but these explanations and results were found not to fit the theory and mechanism proposed by Hammond and Shine[19], since they were postulating mono-protonation rather than diprotonation during the course of the rearrangement.

It might be expected that the rearrangement of any 3,5,3',5' - tetrasubstituted hydrazobenzenes to the corresponding benzidines should be hindered to a certain extent by the presence of a bulky groups occupying all ring positions ortho to the carbon atoms engaged in the formation of the new carbon - to - carbon bond. This hindrance, if sufficient to modify the normal electronic effects, might manifest itself by:

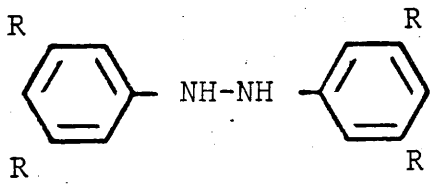
1 - An increase in the amount of diphenyline, which should be less hindered, at the expense of benzidine.

2 - Formation of semidine.

3 - Increased disproportionation of the hydrazobenzene 2 Ar NH-NH Ar $\longrightarrow$ Ar N = NAr + 2 Ar NH_2.

4 - More drastic conditions required to bring about reaction.

Carlin[7], concluded from his work on the rearrangement of tetrasubstituted hydrazobenzenes, where the substituents are chlorine, bromine and methyl, that 2:1 sulphuric acid (by weight) is the best medium yet found for the rearrangement, and that the tetramethylhydrazobenzene rearranges much more rapidly than the chloro and bromo analogues under similar conditions. He described the formation of 2,2'-diaminobiphenyl and the abnormally small benzidine - to - diphenyline ratios observed from the rearrangements of 3,5,3',5' - tetramethylhydrazobenzene (I), 3,5,3',5'-tetrabromohydrazobenzene (II) and 3,5,3',5'- tetrachlorohydrazobenzene (III), to the steric size



I R = CH_3

II R = Br

III R = Cl

of the substituents, and reached to a conclusion that if the factors which govern steric interference with the formation of biphenyl derivatives from hydrazobenzene are related to the van der Waals radii of the groups which appear in the ortho positions of the products and to the factors governing the relative ease of racemization of ortho substituted biphenyls, then bromine atoms and methyl groups should offer about an equal amount of steric interference with the benzidine and related rearrangements, and chlorine atoms and

amino groups should interfere to a somewhat lesser degree in that order. If this is true, then mechanical interference with the formation of rearrangement products of any of the substituted hydrazobenzenes I,II and III should decrease in the order: benzidine $\rangle$ diphenyline $\rangle$ 2,2' - diaminobiphenyl, an order which is reverse of that to be expected in the rearrangement of hydrazobenzene itself. If, however, the chlorine atom does not differ in size from the amino group as much as do the bromine atom and the methyl group, then the differences between the mechanical interference with benzidine formation, with diphenyline formation and with 2,2' - diaminobiphenyl formation should not be as great from III as from I or II. Thus on purely steric grounds, the benzidine: diphenyline: 2,2' - diaminobiphenyl ratios should be greater from the rearrangements of III than from I or II.

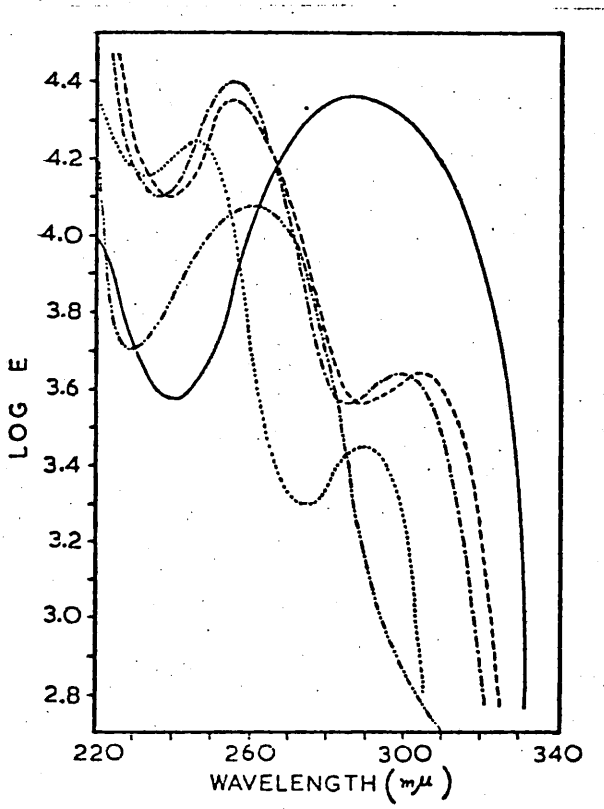
Examination of Carlin's results[7] showed that III gives the largest ratio; however, the diphenyline: 2,2' - diaminobiphenyl ratios are in the opposite order to that predicted on steric grounds, and the benzidine: 2,2' - diaminobiphenyl ratios remain essentially constant. Therefore, the steric size of the substituents in 3,5, 3',5' - tetrasubstituted hydrazobenzenes is by no means the sole factor in determining product ratios: In fact, this work lends support to the concept that a substituent whose polar nature is such that it would be expected to operate to increase the base strength of the present hydrazobenzene will also operate to increase its rate of rearrangement, a concept which was support by Dewar[16], who had pointed out that such reaction would probably be too rapid to be rate - determining.

Spectroscopic studies of benzidines

The electronic absorption spectra of benzidines have been measured as well as those of their derivatives and metal complexes. However, for the benzidines themselves they were studied under the name of substituted biphenyls. Many workers studied the effect of substituents on the

conjugation and coplanarity of biphenyl system[30], specially ortho-substituted ones (Section B, p.35).

Ultra-violet absorption spectra of benzidine[20], m -, o - tolidine[21], 2,6,2',6'- tetrabromo, 2,6,2',6'-tetrachloro and 2,6,2',6'- tetramethylbenzidine[7] were measured and studied in order to verify the correct constitution of these above compounds. 2,2'-Difluoro, 2,6,2'6'- tetrafluro, 2,2'-dichloro and 3,3'-dichlorobenzidine were studied spectroscopically and their spectra indicate that there is a hypsochromic or bathochromic shift on the introduction of a halogen atom(s) into the 2,2'- positions, or into the 3,3'- or 4,4'- positions respectively. This was attributable to the increase in the dihedral angle brought about by the introduction of halogen atom(s) in the ortho-position[31], Spectrum No. 1.



Spectrum No. 1. Ultraviolet absorption spectra of some 2,6,2',6', tetrasubstituted benzidines in 95% ethanol: (——) benzidine; (-·-·-·-) tetrafluorobenzidine; (-·-·-) tetrachlorobenzidine, (----) tetrabromobenzidine; (.....) tetramethylbenzidine[7].

Infra-red absorption spectra of benzidines were found to be difficult to investigate in the region 700-800cm^{-1} due to the N-H bending vibration[32].

Although many benzidines have been studied spectroscopically, the majority of them appear to have escaped such investigation. However, nuclear magnetic resonance studies of benzidines were found to be so few that they can be mentioned individually. Benzidine, O - tolidine and 3,3' - dimethoxybenzidine were measured by Sadtler Research Lab. inc., Philadelphia. 2,6,2',6' - Tetramethylbenzidine was recently studied by Nomura[33,34]. 3,3' - Dichlorobenzidine and 3,3' - dichloro - 6 - nitrobenzidine were studied and their chemical shifts were determined by Hickmott and Hudson[35].

N.M.R. Spectroscopy of Aromatic Amines

Amines ordinarily give rise to a single, sharp absorption line, a behaviour that indicates rapid chemical exchange of the amino hydrogen atoms. Aliphatic amines absorb in the region 0.3 - 2.2 p.p.m[36], and aromatic amines absorb in the region 2.9 - 4.8 p.p.m.[37]. These absorption values are shifted to higher field on dilution with inert solvents.

A proton on a nitrogen atom may undergo rapid, intermediate, or slow exchange. If the exchange is rapid, the NH proton (s) is decoupled from the nitrogen atom and from protons on adjacent carbon atom. The NH peak is therefore a sharp singlet, and the adjacent CH protons are not split by NH_2, as in the case of aliphatic amines. If the NH exchange is slow, the NH peak is broad because the electrical quadrupole moment of the nitrogen nucleus induces a moderately efficient spin relaxation and thus an intermediate lifetime for the spin states of the nitrogen nucleus (spin number = 1) which are changing at a moderate rate, and the proton responds by giving a broad peak. In this case, coupling of the adjacent protons may be observed [38].

A study of the chemical shifts of the amino protons of aniline and substituted anilines in carbon tetrachloride and in acetonitrile has been made by Dyall[39] who correlated the chemical shifts of amino protons of aromatic amines with Hammett substituent constants, whereby a linear correlation has been observed for the meta and para substituted anilines. Amino proton chemical shifts of many substituted anilines in cyclohexane were studied by Yonemoto and his co-workers[40], who correlated the chemical shift with Hammett σ-constants, with π - electron density on the nitrogen atom and with PKa of the protonated anilines in aqueous acid. They observed a small range of chemical shift of the amino protons of meta and para-substituted anilines in cyclohexane compared to a large shift in the ortho-substituted anilines. This was attributed to steric hindrance of the ortho-substituent to π - overlap which resulted in a small magnetic anisotropy and electric field effect. In addition, the overlapping of the van der Waals radii of the amino proton and the ortho-substituent and weak hydrogen bonding may also be responsible for this large shift.

If trifluoroacetic acid (TFA) is used as a solvent for aromatic amines, the protons of substituted aromatic ammonium ion absorb in the range 8.5 - 9.5 p.p.m.[36]. The absorptions are broad single peaks when insufficient excess acid is present to retard chemical exchange or broad triplets when a large excess of acid is present. There is a change of the amino protons of (0.5 - 1.0 p.p.m.) in (NH_3^+) downfield on changing from deuterochloroform to TFA. It is important to realize that only pronounced downfield shifts can be considered diagnostic in this respect, because small effects can be caused by the interaction of the TFA with other functional groups, and for this reason the addition of approximately equimolar amounts of TFA and deuterochloroform solutions may be preferable to the use of pure acid[37].

On the basis of the resonance theory, the trivalent nitrogen in the free aniline molecule can resonate with the phenyl group, with the result that the phenyl group shows a wide spread in spectral pattern because of the different charge density proper to each ring position. When acid is added to the base, the aniline molecule is converted into the anilinium ion accompanied by the fast proton exchange reaction. Thus the electronic configuration of the tetravalent nitrogen in the anilinium ion turns into a closed - shell one, and is incapable of sharing another pair of electrons, with the result that the charge densities at the positions in the ring become nearly uniform. The positive charge in the nitrogen, however, must retain the power to withdraw electron from its vicinal atoms. Thus the coalesced line of phenyl proton signals lies in a lower field than that of benzene by a few cycles[41].

Reynolds and Schaefer[42] studied the chemical shifts of the amino group of a series of substituted anilines relative to internal benzene in the solvents carbon tetrachloride and TFA. They observed that the ammonio group (NH_3^+) absorbs at 1-1.5 p.p.m. to lowfield from benzene as a very broad peak and that the π - overlap with the ring is destroyed by protonation.

N - Methyl protons in aromatic amines were found to absorb in the region 2.75 - 3.19p.p.m.[43,44] in deuterochloroform, and 2.15 - 2.90 p.p.m. in benzene solution[44]. However, upon protonation with TFA, a decreased shielding results in a downfield shift of the N - methyl protons resonance of ca. 0.3 - 1.3 p.p.m., depending on the type of amine[43].

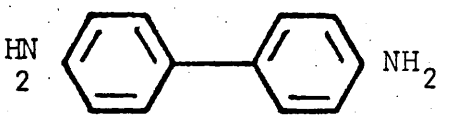
Ring - proton chemical shifts of substituted and N - substituted anilines have engaged the attention of several workers in order to investigate the effect of the amino group on the aromatic protons in neutral and in acidic

solvents[42,43,45,46]. In comparison with the aromatic protons of aniline (ortho, 6.51 p.p.m.; meta, 7.07 p.p.m. and para, 6.65 p.p.m.)[36], it has been shown that there are pronounced shifts of the aromatic protons to lower field in acid solution[42,43]. ortho - Protons in the substituted anilines absorb in the region 6.30- 7.75 p.p.m., while the meta - protons absorb in the region 6.70 - 9.18 p.p.m. and the para - protons absorb in the region 6.08 - 7.08 p.p.m.[45,46]. Protons in the meta position are affected by adjacent substituents but are not subject to the strong shielding and electronic effect by the amino group which is experienced by ortho and para protons respectively. Depending on the substituent, they may thus resonate over a wider range than ortho and para protons.

In the cases where more than one substituent is introduced into the aniline ring, the additivity rule has to be applied. However, it is considered that the additivity relationships are only an approximation, partially because, in many environments, the introduction of further groups may cause the alteration of some existing steric relationships and because of other factors.

Optical isomerism of Biphenyl System

The discovery of optical activity among biphenyl derivatives was due to a curious sequence of events arising out of Kaufler's attempt to explain the fact that benzidine exhibited certain properties which did not appear normal for a bicyclic molecule with coplanar rings. In 1907 Kaufler determined the molecular weight of several condensation products of benzidine[47] and dianisidine[48,49] with bifunctional reagents and several of these products were shown to be the 1:1 compounds. Kaufler concluded from the above evidence that the two amino groups in benzidine must be nearer together than was indicated by the ordinary formula IV and proposed a more or less rigid folded space formula V for biphenyls.



IV

V

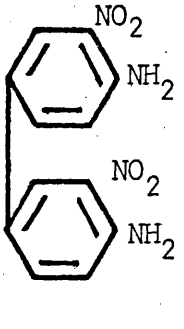
As further evidence for this conclusion, Kaufler pointed out that the diazotization of the second amino group of benzidine was more difficult than of the first amino group and also that after benzidine was tetrazotized, the second diazo group coupled with various dye intermediates with more difficulty than the first diazo group[50,51]. Furthermore, Kaufler suggested that such a structure offered a simple explanation of the para coupling in the conversion of hydrazobenzene to benzidine, the "Benzidine rearrangement".

Extensive investigation during the succeeding fifteen years tended to support such a hypothesis either by further efforts to join the amino groups of benzidine into a cyclic structure[52-56], or by adopting the Kaufler structure to explain the existence of some conventionally inexplicable isomers (nitration products of benzidine and tolidines) which were prepared by Cain and his co-workers[57-60], and by Brady and McHugh[61].

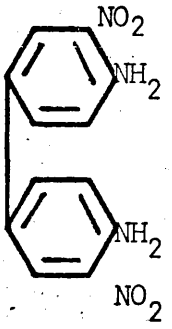
On the other hand, and in spite of the numerous experimental facts which supported Kaufler's view, other experiments intended to verify the folded formula failed to do so, and many attempts to repeat the previous or similar reactions of benzidine and substituted biphenyls to obtain the 1:1 or the cyclic structures resulted in failure[52,62-70].

Regarding the geometrical isomers which were prepared before, Le Féyre and Turner[71,72] proved that the most fully

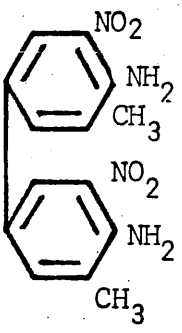
investigated of Cain's pairs of isomers, namely, the two dinitrobenzidines, VI and VII, were not stereoisomers but position isomers, and Cain's two pairs of isomers of dinitrotolidine[60,73], VIII and IX were also position isomers[74].



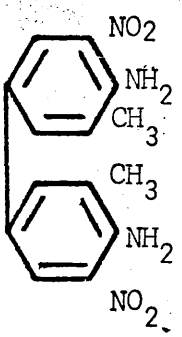
VI



VII



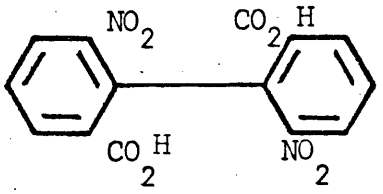
VIII



IX

Dipole moments of several biphenyls[75] and the dissociation constants of benzidine[76] indicated that the rings were coaxial and could not be inclined toward each other and the amino groups in benzidine were farther apart than Kaufler's formula suggested.

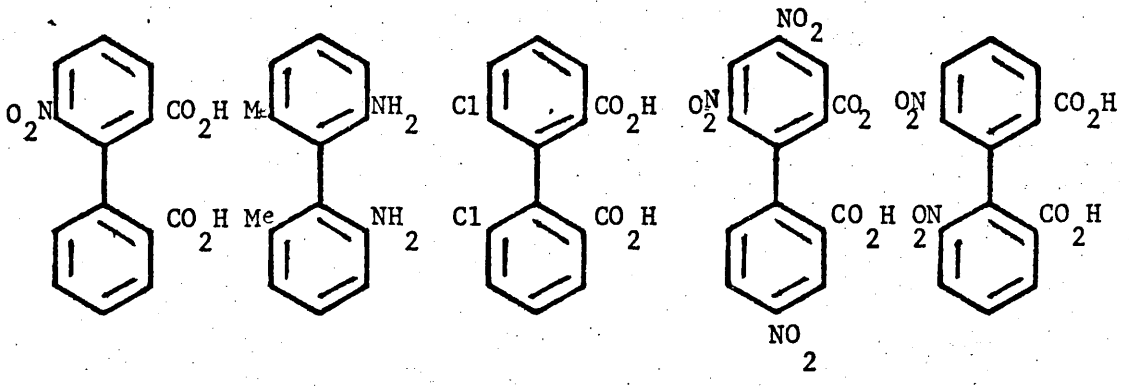
Subsequent studies of biphenyls entirely disposed of the folded structure. It was during a research on this problem that Christie and Kenner[77] in 1922 successfully resolved one of the dinitrodiphenic acids, X, into optically active forms.



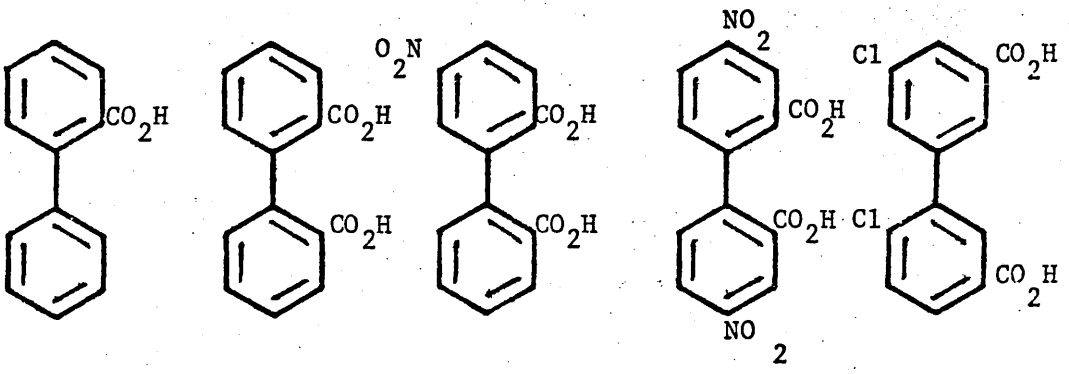
X

These experimental results remained unchallenged and opened an entirely new field of stereochemistry and led to an enormous number of attempts to resolve various biphenyl derivatives. It speedily became evident that some of them, such as those in series A, could easily be resolved, whereas others such as those in series B, resisted all attempts at resolution.

Series A



Series B



Inspection of these two sets of formulas reveals the difference between them. Each of those which have been resolved into active forms has three or four substituents in the 2,2',6,6' positions while those not resolved do not fulfil this condition. It becomes evident that regardless of the size of the O - substituents, resolution is impossible when the biphenyl system has a plane of symmetry in the conformation in which the two benzene rings are orthogonal to each other, and that in the dissymmetric biphenyls, the energy barrier to racemization is dependent on the bulk of the O - substituents. Most of the early examples of resolvable biphenyls contained four ortho-substituents. At first it seemed that at least three ortho-substituents were necessary to confer optical activity on a given biphenyl, but on the contrary, 2,2' - disubstituted and even 2 - mono - substituted biphenyls have been resolved into optically active forms, indicating that the size of the substituent, and not the number of the substituents, is of a major importance, as will be discussed later.

In 1926, Turner and Le Fevre[78], Bell and Kenyon[79], and Mills[80] postulated that the biphenyl molecule had its two aromatic nuclei collinear and also that the introduction of bulky ortho-substituents would prevent free rotation of the nuclei about the co-axis and at the same time produce a co-axial twist. Hence, the two benzene rings in 6,6' - dinitrodiphenic acid cannot be coplanor, due to impingement of the ortho-substituents, and the molecule is dissymmetric, Fig. 1.

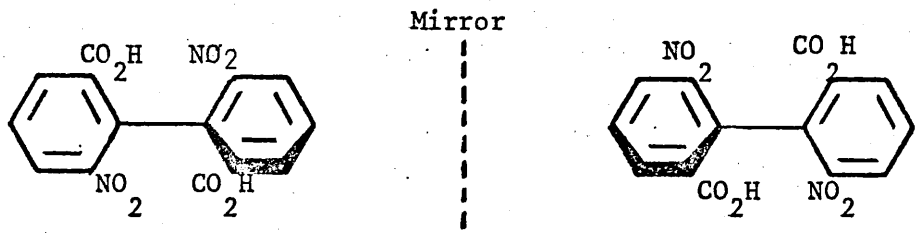
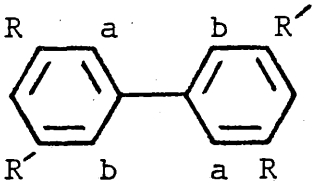


Fig.1. Not superimposable enantiomers: resolvable 6,6'-dinitrodiphenic acid

From the combined results of various investigations, it became evident that there was every reason to suppose that the biphenyl molecule had the two benzene nuclei coaxial, that the bonds by which groups were attached to the 2,2', 6 and 6' positions made equal angles with sides of the nuclei to which they attached and that considerable resistance was offered both by the main biphenyl structure and by the attached groups to any material deformation of such configuration. It is thus seen that in order that a substituted biphenyl can exhibit optically demonstrable molecular dissymmetry, first, the co-axis must not be an axis of symmetry of either benzene ring, including its substituents, and secondly, the substituents in positions 2,2' 6 and 6' must be such that rotation about the co-axis cannot bring about a planar configuration of the molecule as a whole[81].

It is clear that the energy barrier to racemization must depend on the bulk of the ortho-substituents; if these are very small, e.g. fluorine or methoxyl, racemization becomes so fast that the resolution fails. When one pair of small ortho-substituents and one pair of medium-sized ortho groups are juxtaposed, resolution becomes possible but the enantiomers are racemized on warming. When at least two of the four ortho-substituents are large, or if all four are at least medium-sized, optically stable enantiomers can be obtained[82]. The most obvious factors to be considered that result in preventing rotation in the 2,6,2',6'- tetra-substituted biphenyls are (1) the size of the 2,6,2',6' groups, (2) the electrical nature of these groups and (3) the influence of atoms or groups not in the 2,6,2',6' positions.

It is clear now, from the extensive experimental work already done on the preparation of the optically active biphenyls, that the size of the ortho-substituents plays an important role in the optical activity of the biphenyls as shown below:



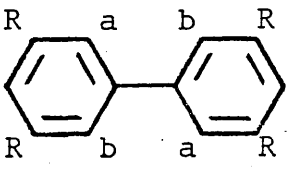
1- a=b=F , $R=CO_2H$, $R' = Cl$

2- $a=OCH_3$, b=F, R=H, $R' = CO_2H$

3- $a=b=OCH_3$, $R=CO_2H$, $R' = H$

4- $a=b=OCH_3$, $R = NH_2$, $R' = H$

Non-resolvable tetra-ortho-substituted biphenyls

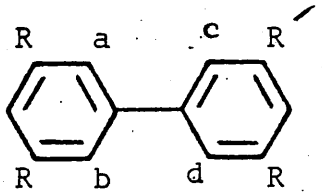


1- a=F , $b=CO_2H$, R=H

2- a=F , $b=NH_2$, $R=CH_3$

3- $a=OCH_3$, $b=CO_2H$, R=H

Moderately optical stable tetra-ortho-substituted biphenyls



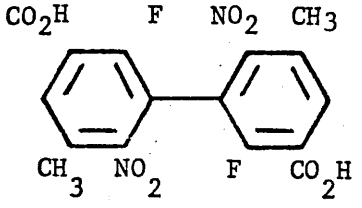
1- a=d=F , b=c=NO_2 , R=CO_2H, R´=CH_3

2 a=NO_2 , b=CO_2H , C=F, d=OCH_3, R=R´=H

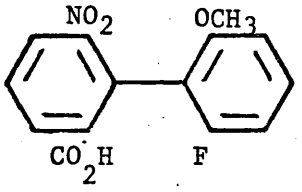
3- a=d=Cl , b=c=CO_2H, R=R´=H

Optically stable tetra-ortho-substituted biphenyls.

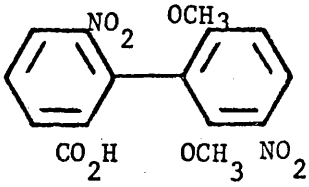
The capacity of the ortho-substituents to interfere with passage through the planar transition state seems to be Br $\rangle$ CH_3 $\rangle$ Cl $\rangle$ NO_2 $\rangle$ CO_2H $\rangle$ OCH_3 $\rangle$ F. It might be noted that this order roughly parallels the order of size of the groups (as determined by X-ray crystallographic measurements of van der Waals radii), whereas there is no parallel between group interference and polar properties[82]. To make certain that the size of the substituent is of primary importance and that no specific effect of the fluorine or methoxyl groups was involved, still larger groups along with the fluorine and methoxyl groups were introduced into the molecule. The active forms of XI do not racemize at room temperature[83]. In a similar manner, XII and XIII gave relatively stable active forms which racemize only slowly at higher temperature[84].



XI



XII



XIII

Similarly, investigations were carried out to estimate the steric and electronic effects of the substituents on the rate of racemization of the biphenyls, and it was found that the steric effect is of a major importance in this matter[85-89], and steric influences due to the polarity of the substituents probably produce no more than a secondary effect. In this connection it may be pointed out that the decrease of optical activity of biphenyls obeys the law of a first order reaction. Substituted biphenyls which had been resolved and of which mutarotating salts had been obtained were reviewed by Adams and Yuan[90] in 1933.

The further application to the biphenyl problem of values of atomic size, obtained by physical measurements, was a natural development. Atomic dimensions inferred from X-ray data on other compounds were used to demonstrate the probability of collision between the amino and methyl groups in 2,2' - dimethyl - 6,6' - diaminobiphenyl[91]. Data intended to permit definite predictions concerning the resolvability of any given biphenyl were first presented by Stanley and Adams[92]. They called the difference between the sum of the internuclear distances of the 2,2' substituents and the distance between the 2,2' ring carbon atoms[93] (2.90Å) the "interference value" and demonstrated that this value measured the relative degree of interference that might be expected in the molecule (Table I).

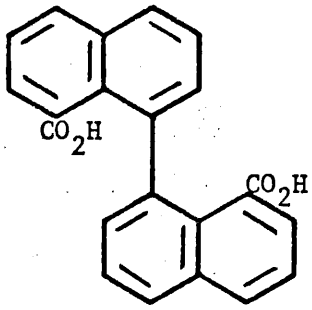
Table I: Distance in Å from the nucleus of the carbon atom of the benzene to centre of group atom.

C - H	0.94	C - CH_3	1.73
C - F	1.39	C - Cl	1.89
C - OH	1.45	C - NO_2	1.92
C - CO_2H	1.56	C - Br	2.11
C - NH_2	1.56	C - I	2.20

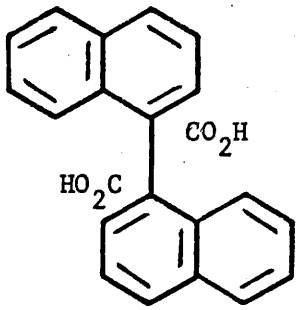
Where the interference value was negative, the compound could not be resolved; where positive, it could be resolved. Molecules with only a slight positive interference value racemized readily. The estimated interferences paralleled to a surprising degree the relative racemization rates of 2,6,2',6' - tetrasubstituted biphenyls as found experimentally but did not conform to the results obtained in the study of 2,6,2',-tri or 2,2' - disubstituted biphenyls. Therefore the method is purely empirical and is uniformly satisfactory only for 2,6,2',6'- tetrasubstituted biphenyls.

On the basis of the obstacle theory which was proposed by Bell and Kenyon[79], it should be possible merely by properly modifying the size of the 2,6,2',6' groups to prepare optically active biphenyls with widely varying degrees of stability to racemization. The racemization of active biphenyl derivatives or mutarotation of their salts may be explained on the basis of the theory of restricted rotation, in that thermal agitation causes the groups in the 2,6,2',6' positions to slip by each other and thus to result in complete rotation of the two nuclei.

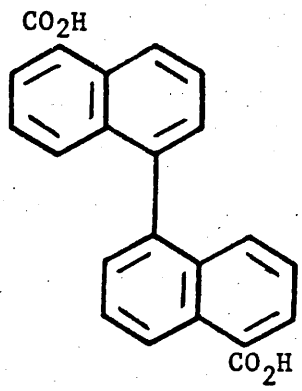
The possibility of optically active 2,2'-disubstituted biphenyls is of a particular interest, and several investigators simultaneously directed their attention to the solution of this problem. Theoretical possibilities of resolving the 2,2' - disubstituted biphenyls as a logical consequence of the obstacle theory were discussed[94] but without any experimental support: Adams and his co-workers were unable to resolve 4,4' - dicarboxy-1,1' - dianthraquinonyl[95] and diphenyl — 2,2'-disulfonic acid[85]. The resolution of optical isomers of XIV[96-98], which can be considered as a disubstituted biphenyls with the C-CO_2H groups in the 2- and 2'- positions, indicates that these groups are sufficiently large to interfere with the hydrogen atoms. However, it is very surprising that XIV is less optically stable than its isomer XV.



XIV



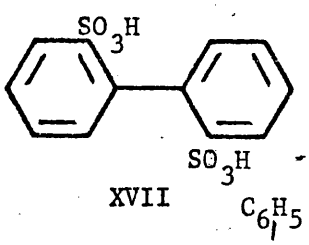
XV



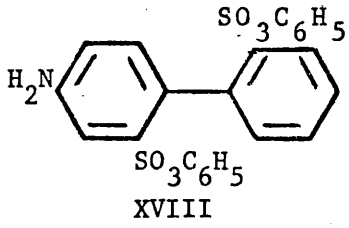
XVI

The discovery in 1954 that 1,1'-binaphthyl-5,5'-dicarboxylic acid (XVI)[99,100] which has no carboxylic acid group in the interfering positions was of comparable optical stability[101] with the 8,8'-acid stimulated many workers to investigate this problem more thoroughly. Harris and co-workers[102,103], who prepared and resolved many different substituted binaphthyls, have concluded that the rate of racemization can be influenced by the steric barrier to restricted rotation, by the gain in resonance energy in the transition state, by the entropy of activation, by the conformation of the transition state, and by the ground-state strain of the molecule.

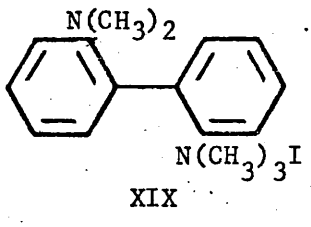
The optical resolution of several 2,2'-disubstituted biphenyls followed. These were XVII[104], XVII[105], XIX[106], XX[107], and the corresponding analog of XX with two methyl groups in place of phenyls attached to the carbon holding the hydroxyl[108] and XXI[109] and the corresponding dibromo compound[110]. The active forms of all these compounds are easily racemized substances.



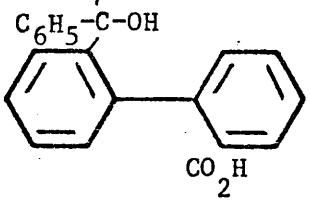
XVII



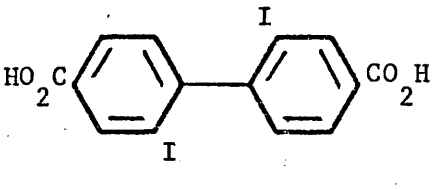
XVIII



XIX

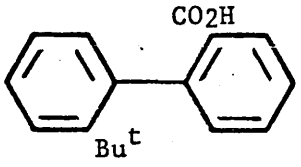


XX

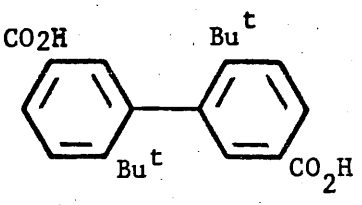


XXI

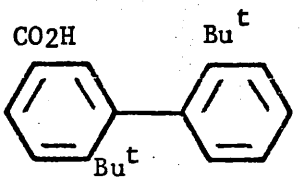
Later, several other disubstituted biphenyls were synthesized and resolved into active forms such as XXII, XXIII, XXIV[111], and the rate of racemization of XXII and XXV[112] was studied.



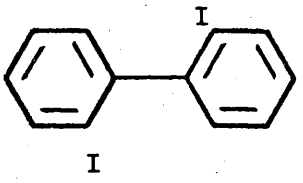
XXII



XXIII



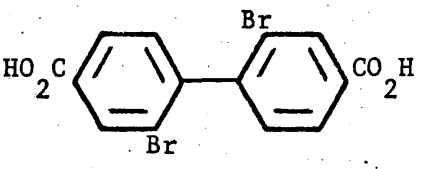
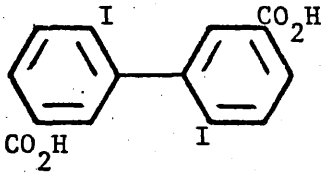
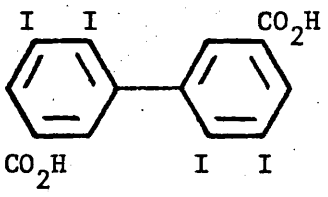
XXIV



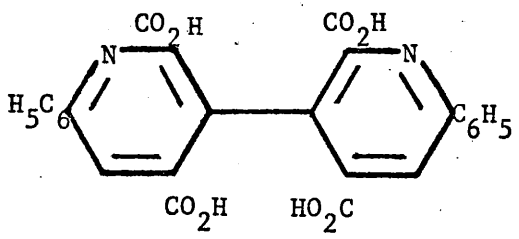
XXV

Perhaps the most conclusive evidence that the interference of the ortho substituents in the transition state of racemization is steric in origin comes from the elegant work of Westheimer and co-workers[113-116]. These investigators were able to estimate correctly the enthalpy of activation for racemization of three different di-ortho-substituted biphenyls from known-data on van der Waals radii and stretching and bending force constants of various bonds, as shown in table II.

Table II

Compound	Calc.Erac. KCal/mole	Found Erac. KCal/mole
 XXVI	18.2	19.0 (117)
 XXVII	21.4-23.6	21.0
 XXVIII	28.6-33.1	27.3

Whereas the variation of half-life caused by substituents in the 4'-position are all within a factor of 10, corresponding to relatively minor changes of activation energy of up to 1.5 KCal/mole[82], much more striking changes are brought about by substituents in the 3'-position. These changes are due to the so-called "buttressing effect". As a matter of fact, it is very obvious that in the transition state of racemization, the groups in the ortho-position bend away from each other. This means that the ortho-substituent is bent toward the 3'-position during racemization. If this motion is impeded by another substituent in the 3'-position, racemization is slowed down by a factor of between 10 and 2000 depending on the size of the 3'-substituent which can be arranged as follows: $NO_2 \rangle$ Br $\rangle$ CI $\rangle$ $CH_3 \rangle$ OCH_3. The buttressing effect can be taken into account in the calculations of the enthalpy of racemization, as in the case of compound XXIII; the agreement of the calculated enthalpy of racemization with the experimental value strengthens one's conviction that the effect of the 3'-substituent is indeed due to buttressing. The fact that compound XXIX racemizes with ease whereas biphenyls substituted with ortho-substituent of comparable size are quite difficult to racemize, may be attributed to the absence of a hydrogen atom on the pyridine nitrogen and the resultant complete lack of buttressing of the adjacent carboxyl group, provided that there is no buttressing due to the lone pair of electrons on the nitrogen atom[82].



XXIX

An extensive review regarding the chemical correlation, absolute configuration, stereochemistry and optical activity of many ortho-tetrasubstituted biphenyls was done by Mislow[118].

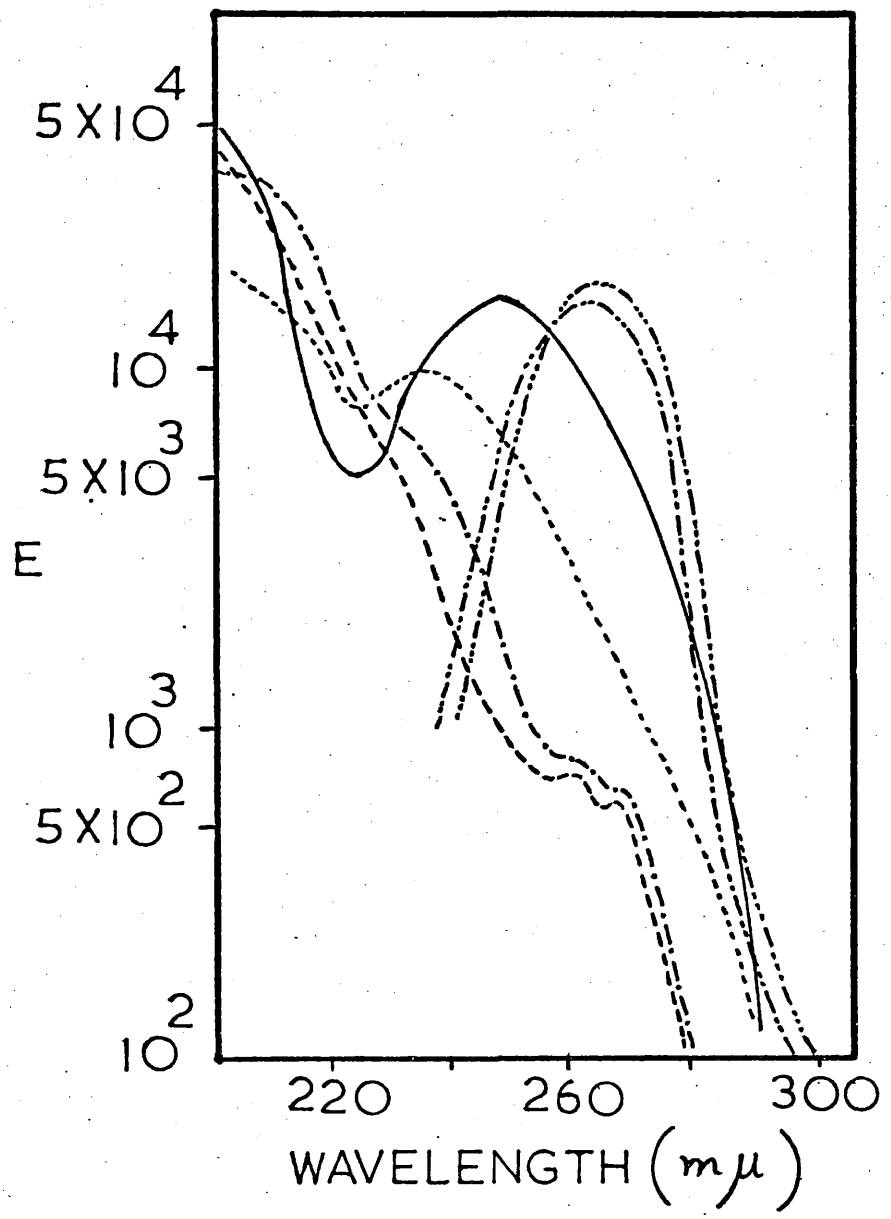
Spectroscopic Studies of Biphenyl (Electronic Spectra)

The UV spectrum of biphenyl itself shows a broad high-intensity band (E_{max}= 17,300) at approximately 249 mu in 96% ethanol[119]. This band has been attributed to resonance between the two aromatic nuclei and hence is sometimes termed the "conjugation band". The position of this band is not markedly different in various saturated hydrocarbons and alcohols as solvents. However, it varies considerably in other solvents; e.g., λmax in chloroform and in carbon tetrachloride is 249.5 and 256.5 mμ respectively[120]. There is extensive spectroscopic evidence of conjugation between the two rings in non ortho-substituted biphenyls[30,121-124].

The conjugation band of biphenyl is progressively shifted toward shorter wavelengths with concurrent decreases in the intensity as one and then two methyl groups are introduced into the O and O'- positions of the molecule. This hypsochromic shift is considered to be due to the increase of the dihedral angle between the two benzene rings caused by the steric interference of the substituents, which is considered to be relieved principally by further twist of the central bond (2-methylbiphenyl, λmax. 237 mμ, E max. 10,250[125], 2,2'-dimethylbiphenyl, $\lambda_{inf.}$ 227 mμ, $E_{inf.}$ 6,800[126], Spectrum No. 2.

This band is found to be absent in heavily ortho-substituted biphenyls [121,127], such as bimesityl, a phenomenon which at the time it was first observed, was reasonably attributed to the inability of such a molecule to be coplanar which results in the elimination of the π - π interaction across the central bond and in a spectrum similar to that of misitylene or isodurene.

According to the X-ray crystal analysis, Dhar[86] had pointed out that biphenyl in the crystal is a planar molecule with a dihedral angle of 0°. There is a slight difference between the position of the conjugation band in the planar



Spectrum No. 2. UV absorption spectra of disubstitued biphenyls in 95% ethanol. (——) biphenyl; (·····) 2-methylbiphenyl; (----) 2,2'-dimethylbiphenyl; (-·-·-·) 2,2'-dichlorobiphenyl; (-·-·-·-) 3,3'-dimethylbiphenyl; (-···-···-) 4,4'-dimethylbiphenyl[126].

biphenyl molecule in the crystal, 249.5-251 mμ and in biphenyl in n heptane solution, 247 mμ, which is assumed to be due to the difference between the preferred configurations of the molecule in the crystal and in the solution. From the comparison of the results of measurements of the infrared absorption spectra of biphenyl in solutions and in the pressed KBr disk, Dale[128] has inferred that biphenyl in solution is non-planar. By the use of the above assumed values of ν and ΔE for the references, from the value of λ_{max} of the conjugation band in the spectrum of the solution in n - heptane the value of the dihedral angle in the most preferred conformation of biphenyl in solution is estimated at 19-23° [126]. Other values are reported for this angle in biphenyl in different solvents[126,129-131], and a value of 41.6 ∓ 2° in the vapour phase was found by Bastiansen using a more accurate electron diffraction study (quoted by Suzuki[126]).

While the O - methyl substitution in the biphenyl molecule gives rise to a distinct hypsochromic shift of the conjugation band, the P - methyl substitution gives rise to a bathochromic shift of the band and the introduction of a second methyl group into the P' - position roughly doubles the magnitude of the shift as well as causing a considerable increase in the intensity of the band[132]. The m - methyl substitution exerts almost no distinct effect on the band; both the spectra of m - methyl and m,m' - dimethylbiphenyl resemble the biphenyl spectrum as shown in table III.

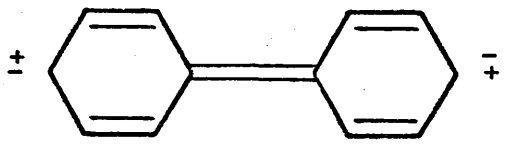
From table III, it appears that the spectrum of 2,6 - dimethylbiphenyl is closely similar to that of 2,2' - dimethylbiphenyl, exhibiting no distinct maximum of the conjugation band but an inflection at about 230 mμ in contrast with the spectrum of 2 - methylbiphenyl. 2,6 - Dimethylbiphenyl involves steric interference between two methyl groups and two hydrogen atoms while 2 - methylbiphenyl involves steric interference between only one methyl group and one hydrogen atom; hence the increased steric hindrance will result in the increase of the dihedral angle in the former compound in comparison with that in the latter.

TABLE III. THE CONJUGATION BANDS OF ALKYLATED BIPHENYLS[133]

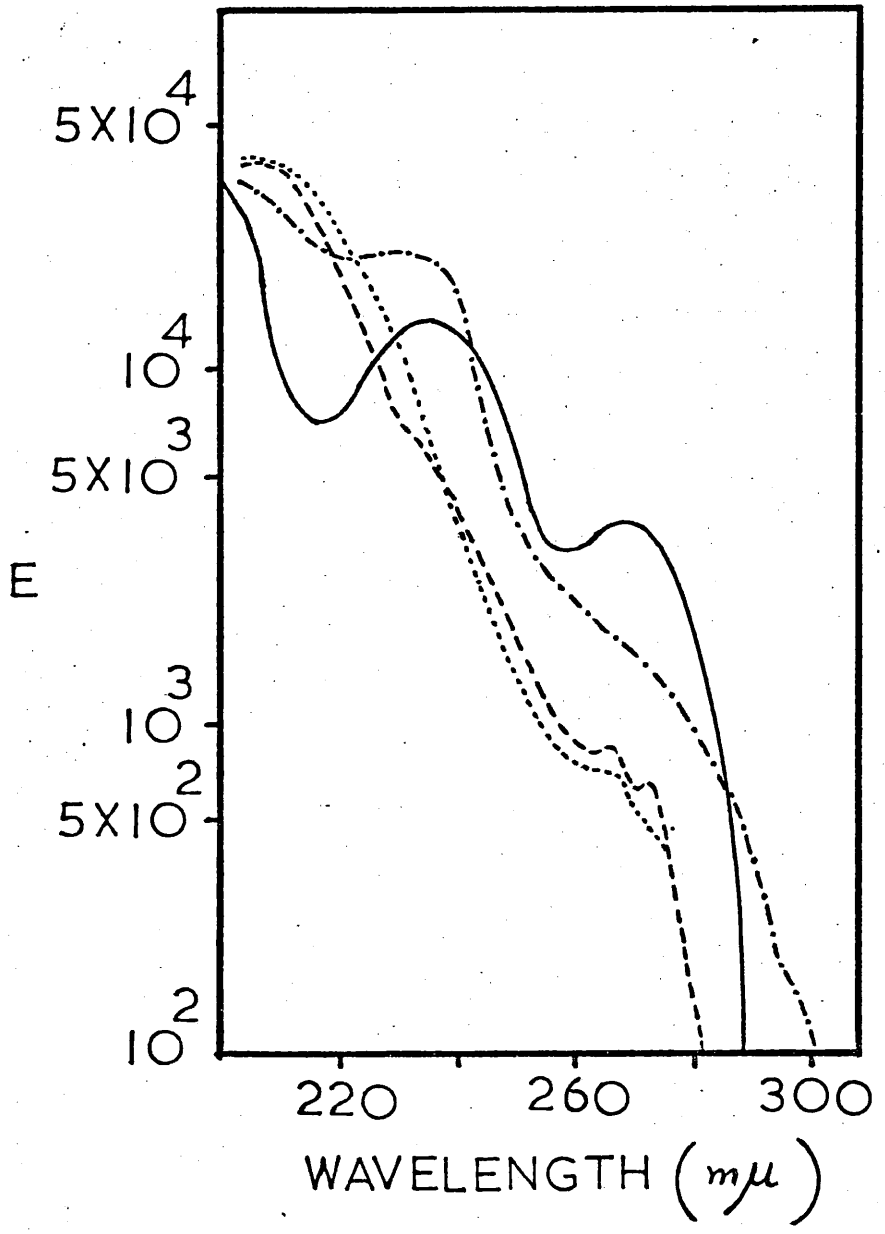
BIPHENYL	SOLVENT	λ_{MAX} mμ	E_{MAX}
UNSUBSTITUTED	ETHANOL	247.7	16 600
	HEPTANE	247.4	16 700
4-METHYL-	ETHANOL	253	19 000
3-METHYL-	LIGHT PET.(B.P. 100-120°)	249	16 300
2-METHYL-	ETHANOL	235	10 500
2-ETHYL-	ETHANOL	233	10 500
2-n- PROPYL-	ETHANOL	233	10 000
2-ISOPROPYL-	ETHANOL	233	11 000
2-n- BUTYL-	ETHANOL	233	10 500
4,4′-DIMETHYL-	ETHANOL	255.6	20 500
4,4′-DIETHYL-	ETHANOL	256.5	22 500
4,4′-DIISOPROPYL-	ETHANOL	256.5	23 500
3,3′-DIMETHYL-	LIGHT PET.(B.P. 100-120°)	250.5	16 100
2,2′-DIMETHYL-	ETHANOL	227	6 800
2,2′-DIETHYL-	ETHANOL	227	6 000
2,2′-DIISOPROPYL-	ETHANOL	227	5 500
2,6-DIMETHYL-	LIGHT PET.(B.P. 100-120°)	231	5 600
2,6,2′-TRIMETHYL-	LIGHT PET.(B.P. 100-120°)	230	4 000

The spectra of 2,6,2'- trimethyl-,2,6,2',6'- tetramethyl- and 2,4,6,2',4',6'- hexamethylbiphenyl show no sign of any contribution from the conjugation band, and are thus distinctly different from the spectra of 2,6 - and 2,2'-dimethylbiphenyl[133]. These highly methylated biphenyls involve necessarily steric interference between o and o'- methyl groups in a cis-like disposition. The spectrum of 2,2'- di- t- butylbiphenyl also shows no sign of any contribution from the conjugation band[133]. The spectra of these highly hindered biphenyls are rather similar to, but not completely quantitatively equivalent to, the additive absorption of two independent alkylbenzene chromophores. Probably the twist angle of the central bond is nearly 90° in these compounds.

The ortho-disubstituted and ortho-tetrasubstituted biphenyl spends most of its time in a conformation which deviates considerably from the planar, and therefore, by the Frank-Condon principle, the excited state must deviate from the planar also. As a result, the extended resonance structure shown below is greatly dampened and the conjugation band has disappeared[82].



The spectra of 2,2'- dihalogenobiphenyls show a progressive reduction in intensity and increasing hypsochromic shift of the conjugation band with the increasing size of the halogen atom in the sequence F,Cl,Br. The spectrum of 2,2'-diiodobiphenyl does not show a conjugation band and qualitatively resembles that of iodotoluene. Spectrum No. 3.



Spectrum No. 3. UV absorption spectra of 2,2'-dihalogenobiphenyl. (——) Difluoro; (----) Dichloro; (·····) Dibromo; (-·-·-) Diiodo in 95% ethanol[119].

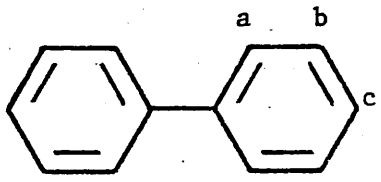
Table IV. The Conjugation band and interplanar angles of 2,2'- dihalobiphenyls[133].

Biphenyl	Conjugation band Solvent : ethanol λ max.mμ	Emax.	Interplanar angle Electron diffraction	Dipole moment	Calc. angle Cis.	Trans.
Biphenyl	249	17300	45 ∓ 10	-	42	
2,2'- Difluoro -	233.5	13800	60 ∓ 5	77	55	49
2,2'- Dichloro -	230	6600	74 ∓ 5	81	79	64
2,2'- Dibromo -	228	12000	75 ∓ 5	85	83	67
2,2'- Diiodo -	-	-	79 ∓ 5	84	91	72

The values of the interplanar angle shown in table IV correspond nearly to the cis-conformation in which the two ortho halogen atoms are in van der Waals contact. Moreover 2,2'-di-chlorobenzidine has been found by X-ray crystal analysis to assume in the crystalline state a cis-conformation in which the interplanar angle is about 72° [134]. Biphenyl derivatives substituted at ortho positions by bulky substituents such as amino, nitro, and carboxyl groups show spectra without a conjugation band and closely resembling those of the two halves of the molecule[135], suggesting the near-orthogonality of the substituted phenyl moieties.

N.M.R. Spectroscopy

The ^{1}H n.m.r. spectra of biphenyl and substituted biphenyls have not been as extensively studied as those of benzene and substituted benzenes. Aromatic protons of biphenyl itself show peaks in the range of (7.1 - 7.5 p.p.m.) in carbon tetrachloride[136].



a = 7.43 p.p.m.

b = 7.26 p.p.m.

c = 7.15 p.p.m.

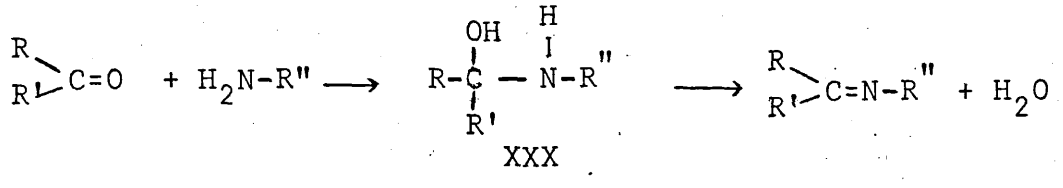
It was pointed out that the delocalization of the π-electrons of the biphenyl system is greatly affected by the substituents occupying the ortho positions to the central bond, and hence a significant change in the chemical shifts of aromatic protons was expected[137]. However, in the case of polymethylated biphenyls[138], it was found that the interaction of the methyl group with the neighbouring benzene ring is significant only for the methyl group in the ortho position and that it depends on the dihedral angle between the two benzene rings. This causes a change in the chemical shift of ortho - methyl group with respect to the meta-and para-methyl groups.

Tri- and tetra-ortho substituted biphenyls were thoroughly investigated by Nomura and Takeuchi[33,34,139]. They studied the substituent, inductive and solvent effects on these compounds, and found that the spectra of the substituted biphenyls resembled that of the parent hydrocarbon. Moreover, the two benzene rings of these biphenyls are mutually orthogonal because of large steric requirement of the tetra ortho-substituents and there is no mesomeric interaction between the two rings, and the inductive effect of one of the benzene rings in determining the chemical shifts of the protons of the other rings is negligible.

Symmetrical dihalobiphenyls were studied, their spectra were analyzed and the substituent effect was correlated with the coupling constants and chemical shifts[140]. It has been shown that the substituent effect correlates quite well with the electronegativity of the substituent.

C- Schiff's Bases

Under ordinary conditions aromatic aldehydes or ketones and aromatic amines react readily to give the imines. This reaction was first discovered by Schiff[141] and imines are often referred to as Schiff's bases.



(R=H, alkyl or aryl group, R' and R" = aryl group)

The reaction is acid catalyzed and generally carried out by heating the carbonyl compound and the amine together under reflux with an azeotroping agent if necessary, and separating water as formed. However, it is sometimes more convenient to work in a solvent such as absolute ethyl alcohol, dilute acetic acid or glacial acetic acid. Sometimes the reaction is aided by a trace of acid; in other cases the hydrochlorides of the amine can be used in the synthesis.

No attempt has been made to cover imines (Schiff's bases) where R is a group which does not contain carbon at the point of attachment, nor compounds containing the imino group as an internal part of heterocyclic system, nor ketenimines, $(R)_2$-C=C=N-R.

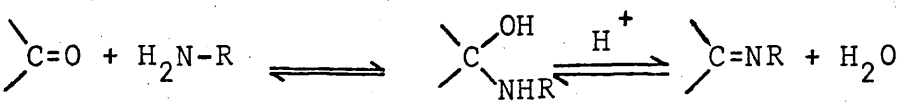
The synthesis of aromatic imines (azomethines) has engaged the attention of many workers in order to study their chemical and physical behaviour. The condensation of aniline and substituted anilines with benzaldehyde was carried out[142,143] and the aldol stage of the reaction was isolated.

Law[144] had successfully prepared a variety of substituted benzylideneanilines and reduced them electrolytically to the corresponding amine. Moving to highly substituted benzaldehydes, Lowy[145] prepared Schiff's bases from 2,4, 6-tri-nitrobenzaldehyde with aniline and several substituted anilines through the isolation of the intermediate aldol stage.

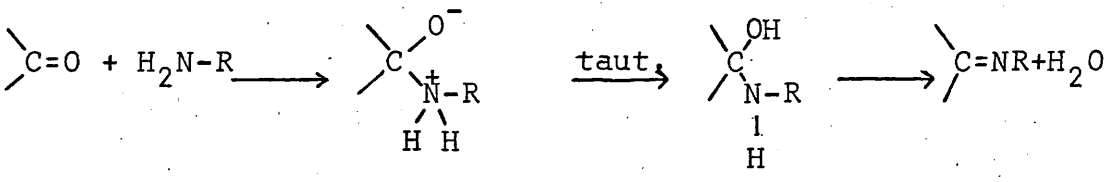
By using a cryoscopic method to follow the course of the reaction, Oddo[146] had observed that, for the nitroanilines, the rates of formation were in the order O- > M- > P- ; P- tolualdehyde reacted much faster than phenylacetaldehyde and cinnamaldehyde much more rapidly than either. The same author also noted that cinnamaldehyde reacted more rapidly than m- nitrocinnamaldehyde and the speed of reaction decreased in the series: cinnamaldehyde, anisaldehyde, vanillin and piperonal.

Most of the work that has been carried out in order to understand the mechanism of this reaction has been done using hydroxylamine or semicarbazide instead of an aromatic amine. Hammett[147] proposes, in the case of semicarbazide, that acids protonate the carbonyl group to give a carbonium ion which adds to the amine in a very fast reaction. By analogy, the rate-determining step then is the deprotonation of this intermediate which rapidly eliminates water to give the final product. Later, Jencks[148] had cogently shown that the carbonyl and the amine react rapidly to give the carbinolamine

XXX which dehydrated to the semicarbazone in the rate-determining step which is acid catalyzed.



However, a more comprehensive approach to this mechanism was discussed by Jencks[149,150] and a suitable mechanism was proposed for the formation of Schiff's bases at neutrality.

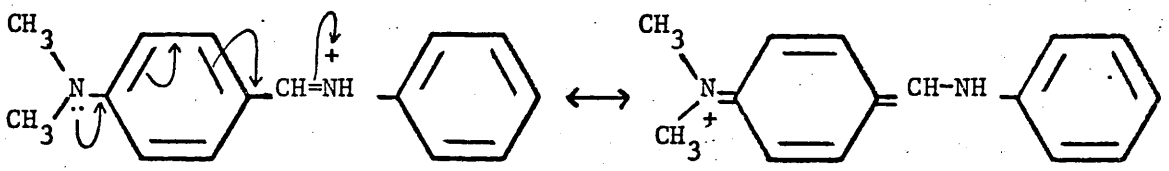


In the reaction of benzaldehyde, aniline and acid catalyst in benzene, it has been shown that the reaction is first order with respect to the aldehyde, amine and the catalyst[151]. Moreover, para-substitution of the benzaldehyde with electron-donating group decreases the reaction rate, while the reverse is true for similarly para-substituted anilines. This work agrees with both Hammett's and Jencks's mechanisms.

It was reported long ago that this reaction is a reversible reaction and the hydrolysis of the imines to the starting components is possible. Reddelien and Danilof[152] have reported that imines are readily decomposed by aqueous mineral acids but stable towards aqueous bases. Substituents on the benzylidene portion of N-benzylidene aniline have been found to facilitate hydrolysis when they are electron-donating groups while electron-withdrawing groups retard hydrolysis[153]. Similarly phenyl furyl ketimine hydrochloride hydrolyses more slowly than diphenyl ketimine hydrochloride, which is an agreement with a commonly observed rule that ketimine salts with more negative groups attached to the carbon of the imino group are more resistant to hydrolysis than those containing more

electron-donating groups[154].

An exception to this rule is N-4-dimethylaminobenzylidene aniline[155], which hydrolyzes more slowly than N-benzylidene aniline in dilute aqueous acid; this may be attributed mainly to the resonance stabilization of the protonated intermediate.



Culberson and co-workers[156] investigated the steric factors affecting the rate of hydrolysis. Later this work was extended to include aliphatic and alicyclic ketimines[157,158].

The mechanism of hydrolysis of imines has always been thought to proceed through the carbinol intermediate. Studying the kinetics of the acid-catalyzed hydrolysis of some imines in different acidic and basic media[159,160] showed that an intermediate forms and decomposes by an uncatalyzed and by an acid-catalyzed reaction path. The intermediate is present throughout the reaction only in a low steady-state concentration.

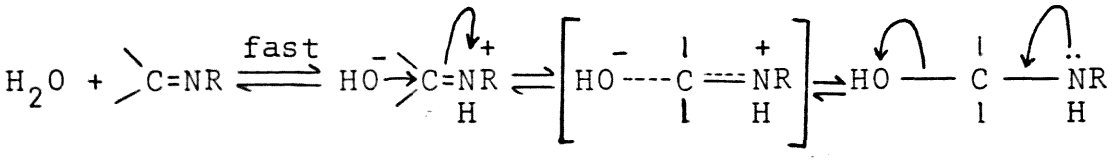
$$ArCH = NAr' + H^+ \underset{}{\overset{K_1}{\rightleftharpoons}} ArCH = \overset{+}{N}HAr' \quad \text{(Fast)}$$

$$ArCH = \overset{+}{N}HAr' + H_2O \underset{K_{-2}}{\overset{K_2}{\rightleftharpoons}} \underset{\underset{OH}{|}}{ArCH} - NHAr' + H^+ \quad \text{(Slow)}$$

$$\underset{\underset{OH}{|}}{ArCH} - NHAr' + H^+ \overset{K_3}{\rightleftharpoons} \underset{\underset{OH}{|}}{ArCH} - \overset{+}{N}H_2Ar' \quad \text{(Fast)}$$

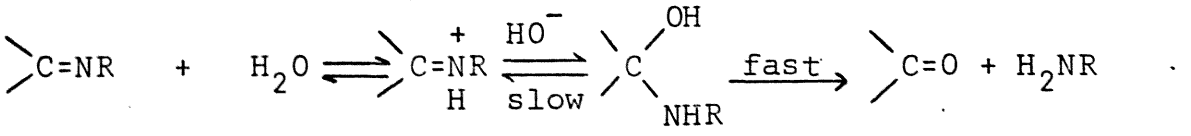
$$\underset{\underset{OH}{|}}{ArCH} - \overset{+}{N}H_2Ar' \underset{K_{-4}}{\overset{K_4}{\rightleftharpoons}} ArCHO + Ar'NH_2 + H^+ \quad \text{(Slow)}$$

The mechanism of catalysis of these reactions depends to some extent on the basicity of the amine. With derivatives of strongly basic amines, the predominant reaction pathway in basic solution involves a direct expulsion of hydroxide ion in the dehydration reaction, for which the electron pair of the amine provides the necessary driving force, and the attack of hydroxide ion on the protonated Schiff base in the reverse direction.



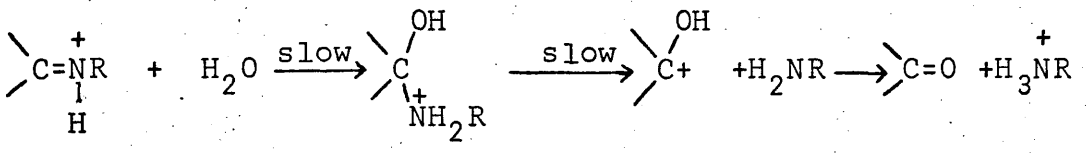
In contrast to Schiff's bases of more basic amines, benzylidene anilines show a base-catalyzed hydrolysis at high pH values, due to the direct attack of hydroxide ion on the relatively electrophilic $\rangle C{=}NR$ group of these compounds.

The effect of substituents (in the aldehyde component) in the hydrolysis is clearly not compatible with a rate-determining attack of water, which should be facilitated by electron-withdrawing substituents, but rather suggests that the reaction involves first protonation, and then attack of hydroxide ion on the protonated Schiff's base, as was first suggested, for the hydrolysis of benzylidene-aniline, by Willi[161].

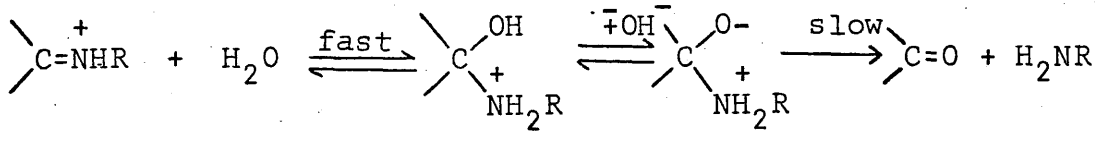


The effect of substituents (in the aldehyde component) on the protonation step, which is aided by electron-donating substituents, is evidently slightly larger than on the attack of hydroxide ion, which is hindered by electron-donating

substituents. As the pH is decreased and an appreciable fraction of the Schiff's base becomes protonated, the hydroxide ion reaction becomes insignificant and the attack of water on the protonated Schiff's base becomes the predominant reaction pathway.



In this pH region, the reaction shows the expected increase in rate with electron-withdrawing substituents. When the Schiff's base is completely protonated the rate levels off. At still lower pH values the rate drops again because of a change in the rate-determining step to rate-determining loss of amine from the aminoalcohol addition intermediate. The slowness of the



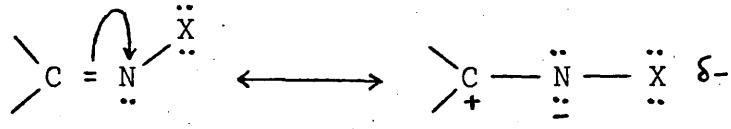
reaction in acid solution results from the requirement that a proton be removed from the oxygen atom of the aminoalcohol addition intermediate, in order to obtain sufficient driving force to expel the strongly basic amine. This pH region corresponds to that in which the attack of free nitrogen base on the carbonyl compound is rate-determining in similar reactions in the reverse direction[149]. More recently, the pH dependence of the kinetics of the hydrolysis of some Schiff's bases indicated that the rate-determining step in acid was the attack by water on the protonated base[162].

A comprehensive review of nearly all imines prepared and of all methods so far known used for their preparation was carried out by Spring[163] in 1940 and by Layer[164] in 1963.

Regarding the stereochemistry of imines, it was expected that since they are contain a double bond, geometric isomerism should be possible.

The first work on the attempted isolation of syn and anti isomers was carried out on N-salicylidene - p - carbmethoxyaniline[165]. These authors found that the above mentioned compound exists as yellow needles which melt at 145°, and after exposure to the light is converted into orange-red needles which melt at 259°. However, Anselmino[166] had pointed out earlier that the isolation of two forms of an imine could be the result of polymorphism, rather than of geometrical isomerism[167-169]. Dipole moment studies of many aliphatic and aromatic aldimines indicate that they exist only in the trans-configuration. The two forms of N-salicylidene-p-carbethoxyaniline obtained have the same polarities in benzene solution, and differences between them may be attributed to dimorphism rather than to geometrical isomerism[170].

Theilacker and Fauser[171] had concluded that the presence of electronegative group on the nitrogen of the imino group decreases the polarization that normally occurs by an electrostatic repulsion due to the adjacent negative changes in the following resonance structure.

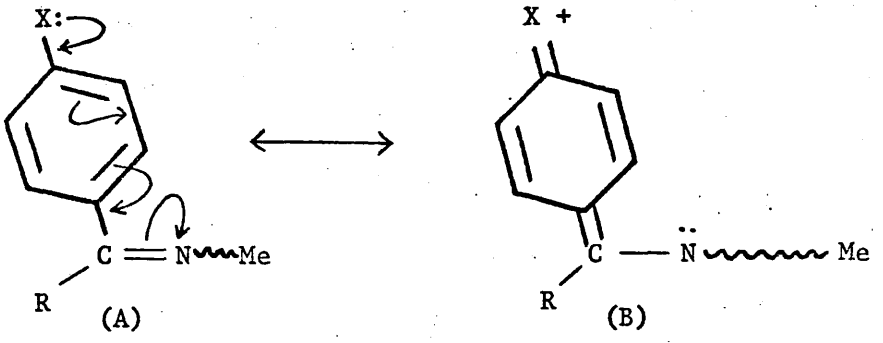


This would give the imino group more double bond character and would allow geometric isomers to be separable.

Substituted imines and the effect of structural changes on the interconversion of their stereoisomers was thoroughly discussed by Curtin and Hausser[172], who attempted to prepare the two isomers, namely cis and trans N-2-nitrofluorenylidene-

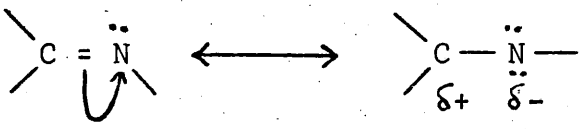
p-toluidine which had been prepared by Taylor and Fletcher[173], but instead they obtained one of these isomers which on recrystallization several times gave a material of higher melting point and whose composition is not correct for imine. However, on working on the rate of isomerization of Schiff's bases derived from p-nitro and p-chlorobenzophenone dichloride and methylamine, Curtin and Hausser[172] reported the capability of the imine to exist in syn and anti isomer forms. In cyclohexane, and at room temperature or above, these forms isomerize to an equilibrium mixture of syn and anti isomers very rapidly and the rate of isomerization could be followed and determined by ultraviolet spectroscopy.

Recently, Boyd et al[174], studied the equilibrium distribution of cis-trans ketimine isomers and found that the introduction of an ortho-substituent on the C-aryl group results in a very marked change in isomeric preference toward the trans-form. An electron-donating group on the para-position would tend to stabilize the coplanar conformation by increasing the delocalization energy A⟷B. This effect would increase the



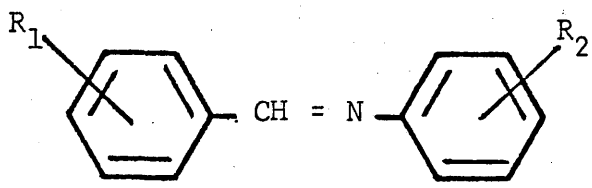
barrier to rotation around the C-aryl bond and move the equilibrium toward the cis-isomer. Thus in terms of both resonance energy and steric effects electron-donating substituents should favour the cis-imine in the order NMe_2 > OMe > H. On this basis electron-withdrawing substituents should have an opposite effect, i.e. destabilize the cis-isomer.

The fact that imines can not be isolated in both syn and anti forms must be due to the ease of free rotation about the C-N bond[164]. This probably arises from the fact that the electronegativity of the nitrogen compared to that of carbon cause a lowering of the double bond character of the imino linkage by a polarization of the C=N bond.



Imines were found to be affected by light and/or heat and the change in the colour of the compound due to the light or heat was referred to as phototropy or thermotropy respectively. These two concepts have engaged the attention of many workers[175,176]. However, it was found that the introduction of the negative bromine atom in salicylaldchyde inhibited to some extent the tendency toward forming phototropic anils, and when two bromine atoms were introduced the resulting anils no longer exhibited phototropy[177]. It is apparent that anils of aldehydes having the hydroxyl group para to the aldehyde group may be phototropic, as well as those with the hydroxyl group in the ortho-position. The anils from p-bromoaniline show phototropy, whether the hydroxyl group is ortho or para to the aldehyde group. Replacement of the ortho hydroxyl group by an ortho nitro group inhibits the phototropy. If the para bromine atom of the amine is replaced by chlorine, the resulting anil is not phototropic[177].

The coplanarity of Schiff's bases was discussed by Minkin and co-workers[178] who had considered the interaction of electronic and steric factors in the following benzylidene-anilines:



(1) $R_1=R_2$ = H
(2) R_1=H , R_2 = p-Cl
(3) R_1=H , R_2 = o-CH_3
(4) R_1=H , R_2 = m-CH_3
(5) R_1=H , R_2 = p-CH_3
(6) R_1=P-CH_3 , R_2 = H
(7) R_1=P-NO_2 , R_2 = H

Theoretical calculations predict the coplanarity of the azomethine molecule but experimental support for this view is lacking. The following observations and experiments were considered:-

a- Lowered intensity of the long-wave absorption band caused by $\pi \longrightarrow \pi^*$ transition.

b- Inability of crystal powders or solution to luminescence.

c- Absence of $n \longrightarrow \pi^*$ transition band.

d- Dipole moment measurements.

e- Lower cis-trans isomerization activity energy (13.5 - 17.5 KCal/mole) than that of stilbene (34-37 Kcal/mole) and alkylimine (25-27 KCal/mole).

f- Lower basicity of azomethine than that of pyridine and 2 - arylbenzazoles.

g- Low conduction of electronic influences in one nucleus upon the reaction centre in the other nucleus, and the tendency of the azomethine compounds to exist in a mesomorphic state.

The above experimental observations confirm that the azomethine molecule exists as a stable non-planar conformation in which the dihedral angle between the amino nucleus and the rest of the molecule is 40-60° and the substituents in the aldehyde nucleus have little effect. The suggestion was made of the possibility of finding atropoisomers which may account for specific features of their chemical and

physical properties. Moreover, the electronic spectra of different benzalanilines had been calculated and the nature of the electronic transitions and their connection with the molecular conformation of benzalaniline was discussed[178]. Later, Burgi and Dunitz[179] have shown, using X-ray analysis, that the aniline ring is twisted out of the C-N = C-C plane of the benzylideneaniline by 55° and the benzylidene ring is twisted in opposite sense by 10°. Moreover, they observed that the C-N single bond distance decreases with increase in electronegativity of the para-substituents in the aniline component.

Spectroscopic studies of Schiff's bases

Raman spectra of Schiff's bases were studied a long time ago and these compounds were found to give rise to a Raman line in the range 1650-1673 cm^{-1} [180-182].

Infrared absorption spectra of dialkyl ketimines showed absorption in the region 1639-1645 cm^{-1} for the azomethine group while the more conjugated diaryl ketamines absorb at higher wavelength, about 1602 cm^{-1} [183]. Aliphatic aldimines were found to absorb in the region 1665-1674 cm^{-1}, aliphatic-aromatic aldimines at 1648-1650 cm^{-1} [184] and aromatic aldimines at 1613-1638 cm^{-1} [185,186].

Substitution in one or both sides of the aromatic aldimines had a great effect on the intensity of the C=N band[187]. Imines derived from substituted phenols showed strong hydrogen bonding with the nitrogen atom of the azomethine group[188,189].

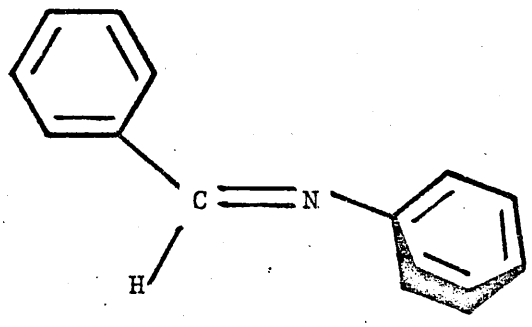
Ultra-violet absorption spectra of Schiff's bases have been studied by many workers[190-198]. The bands have the following positions and intensities in unsubstituted benzylideneaniline.

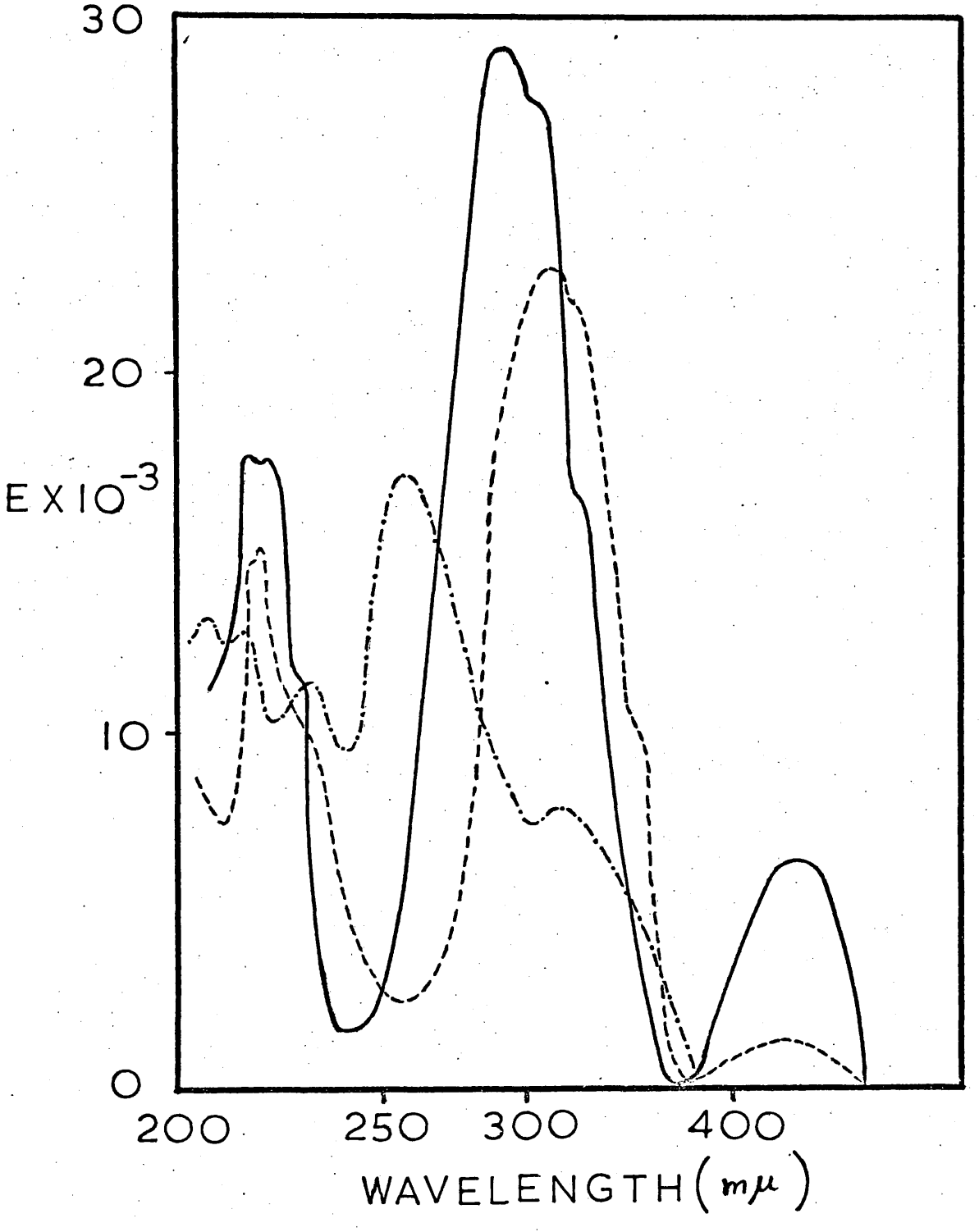
λ_{max} (mμ)	227	236	262	314
ε_{max}	12,000	9,900	17,300	6,900

The electronic spectra of Schiff's bases can not be explained by comparing their structures with stilbene-type planar structures, so an alternative structure was proposed by Ebara[199], with the benzene ring of the aniline part nearly perpendicular to the rest of the molecule. The same conclusion was reached by Brocklehurst[200] and by Smith[201] who showed that the azomethine molecule is not entirely planar and there is a twisting of the aniline ring out of the plane of the molecule due to the interference of the nitrogen doublet to a certain extent with the π- conjugation through the molecule; when this interference is removed through localization of the nitrogen doublet by nitrone formation or protonation, the azomethine molecule is constrained to assume a planar configuration and a normal stilbene spectrum results as shown in Spectrum No. 4.

Substituent effects on the UV absorption spectra for aliphatic[202] and aromatic azomethines[187,201,203-205] were determined and it is suggested that the effect on the aldehyde nucleus band is small, whereas marked shifts were obtained on the aniline nucleus band.

Theoretical studies of the coplanarity of aromatic azomethines, including linear combination of atomic orbitals - molecular orbital theory and atomic orbital theory[173,201,206], have been made and seem to confirm that the azomethine molecule exists in a stable, non-planar conformation in which the dihedral angle between the aniline nucleus and the rest of the molecule is 40-60°

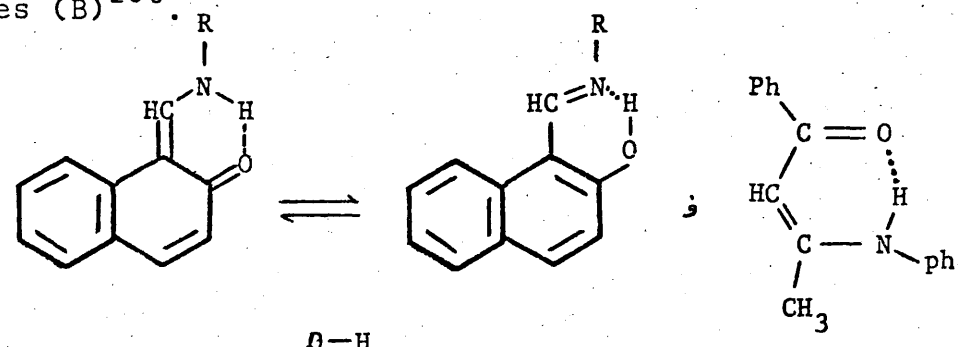




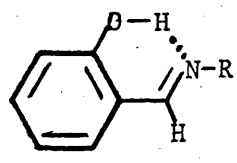
Spectrum No. 4. UV absorption spectra of stilbene (——); azobenzene (----) and benzylidene aniline (-·-·-) in 95% ethanol[179].

, Proton magnetic resonance spectroscopy has been used to determine the keto-enol tautomeric equilibria in imines derived from N^{15}-substituted anilines and β-diketones and substituted naphthols (A)[207] and imines derived from N^{15}-substituted anilines and different o-hydroxy aldehydes and ketones (B)[208].

A-



B-



Application of the proton magnetic resonance technique in the study of the conformation of azomethines was found to be very useful in calculating the dihedral angle[209] as well as in determining the degree of steric hindrance in some substituted azomethines[210]. Another recent application of this technique was in the protonated aldimine group in some natural products using trifluoroacetic acid at room temperature and chloroform acidified with equimolar amounts of trifluoroacetic acid at low temperature.[211]

There has been very little work on the nuclear magnetic resonance studies of aromatic azomethines ArCH = NAr'. N.m.r. studies of many aliphatic azomethines RCH=NR', were carried out [202,212-216] in order to investigate the isomerization equilibria as well as to confirm the structure of some related compounds[217]. Aliphatic-aromatic azomethines, ArCH = NR or RCH = NAr, were studied in order to determine their conformation in different solvents[184,218]. On the other hand, the aromatic azomethines have attracted the attention of few workers; however, several azomethines have been extensively studied and their n.m.r. spectra are well interpreted [186,219-221].

The chemical shift of the azomethine proton was found to be as follows:-

a-	Aliphatic azomethines	RCH = NR'	7.41 - 7.65 p.p.m.
b-	Aliphatic-aromatic azomethines	ArCH = NR RCH = NAr	8.07 - 8.19 p.p.m.
c-	Aromatic azomethines	ArCH = NAr'	8.27 - 9.54 p.p.m.
		Naph CH = NAr	8.69 - 9.30 p.p.m.

The above difference in the chemical shifts between aliphatic and aromatic azomethines is mainly attributed to the aromatic conjugation. The introduction of an electron-donating or of an electron-withdrawing group into the para position of the benzaldehyde ring brings about a small shift of the azomethine signal to a higher or to a lower field respectively. However, the introduction of any substituent into the para position of the aniline ring results in a very small shift; this was attributed to the distortion of the aniline ring from the plane of benzalamino skeleton (Fig.2), and consequently no great change takes place in the electron density and bond order of the azomethine (CH=N) bond[186].

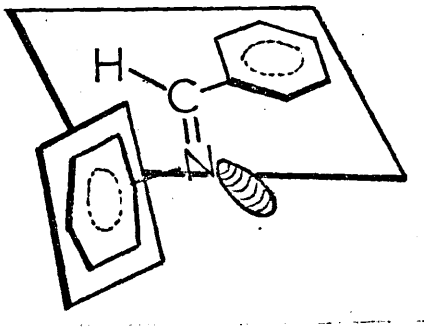


Fig.2. Non-planar structure of benzylideneaniline[186].

Aim of the work

In ^{1}H n.m.r. spectroscopy, aromatic amines show a characteristic downfield shift of their absorptions when their samples in $CDCl_3$ are treated with trifluoroacetic

acid or are examined in neat D_2SO_4. In view of these observations, it was aimed to extend these studies to include higher aromatic amines, namely, benzidines. Moreover, several new di- and tetra - o - substituted benzidines might be prepared in order to investigate their conformational stability either by separation of the corresponding optically active forms or by low temperature n.m.r. technique.

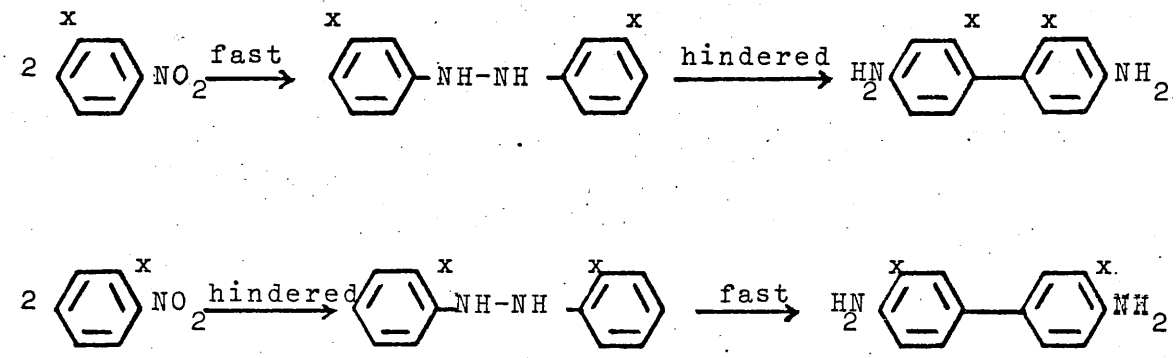
No attempt has previously been made to investigate the preparation and properties of Schiff's bases derived from benzidines and substituted benzaldehydes, and it was accordingly planned to prepare a series of such Schiff's bases in order to study their n.m.r. characteristics. In addition, it would be very useful to investigate in greater depth the effect of substitution in different positions of the molecule on the n.m.r. spectra as well as on the rate of condensation reaction.

– DISCUSSION –

Synthesis of Benzidines

1 - 2,2'-Dichloro- and 2,2'-dibromobenzidines were prepared by the action of zinc dust and sodium hydroxide on m-chloro- and m-bromo-nitrobenzene respectively.

A low yield of the benzidines is expected since the chlorine and bromine atoms are large enough to hinder the reaction, especially in the rearrangement step. However, 3,3'-dichloro and 3,3'-dibromobenzidines suffer more steric hindrance during the reduction and coupling step and therefore they need prolonged reflux to ensure complete reduction and coupling to form the hydrazo compounds before the acidic rearrangement to the corresponding benzidine.



In the literature, 3,3'-dichloro and 3,3'-dibromobenzidines were prepared by chlorination and bromination of N,N'-diacetylbenzidine respectively in acid medium. It seems that this method was suggested to avoid the preparation of the sterically hindered azo compound. However, during this work both the above mentioned benzidines were prepared by direct reduction and coupling of the corresponding o-halonitrobenzene with zinc and sodium hydroxide and the only modification applied to the general procedure was prolonged action of the reducing agent on the nitro compound to ensure that reduction and coupling (sterically hindered step) were as complete as possible.

Steric factors are operative to an extent depending upon the size of the substituent as well as its position, and some of the corresponding diphenylines were expected to be formed but in fact were not isolated.

2 - In the preparation of m-tolidine, both methods described by Carlin[22] and by Everitt (Ph.D. Thesis, London 1957) were applied and in both, the m-tolidine isolated had the m.p. 105-106°. Many attempts were made to prepare a sample with m.p. 87-88°, but without any success.

Several melting points are reported for m-tolidine; the majority of workers obtained the high melting form.

Schultz and Rohde, Chem. Zentr., 1902, II, 1447, m.p. 87-88°.

Jacobson and Fabin, Ber., 1895, 28, 2553; m.p. 106-107°.

Buchka and Schachbeck, Ber., 1889, 22, 838; m.p. 108-109°.

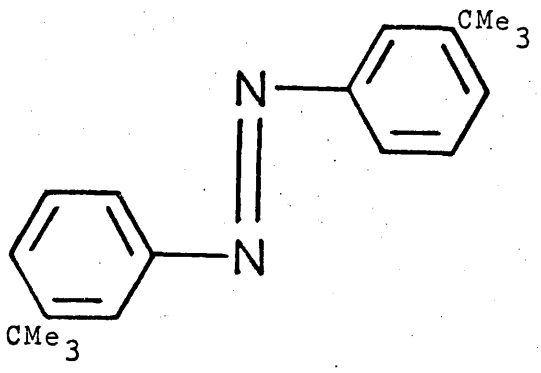
Carlin and Foltz, J. Amer. Chem. Soc., 1956, 78, 1992; m.p. 105-106°.

Loh, Ph.D. Thesis, London University (1955); m.p. 87°.

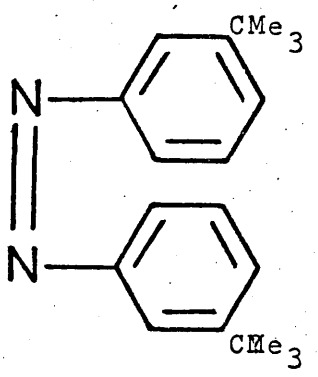
Furthermore, the m-tolidine prepared could not be crystallized from benzene as described by Everitt, and it was found that either water or light petroleum (b.P. 60-80°) was the best solvent for crystallization.

3 - 3,3'-Di-t-butylazobenzene was prepared by the action of zinc powder and alcoholic aqueous sodium hydroxide on m-nitro-t-butylbenzene as red-orange crystals, m.p. 106-107° (I). On partial evaporation of the mother-liquor, beautiful yellow crystals were collected, m.p. 59-60° (II).

First, it was thought that compound (II) was nothing but the cis-form of the stable trans-form of the azo compound (I).



trans-form



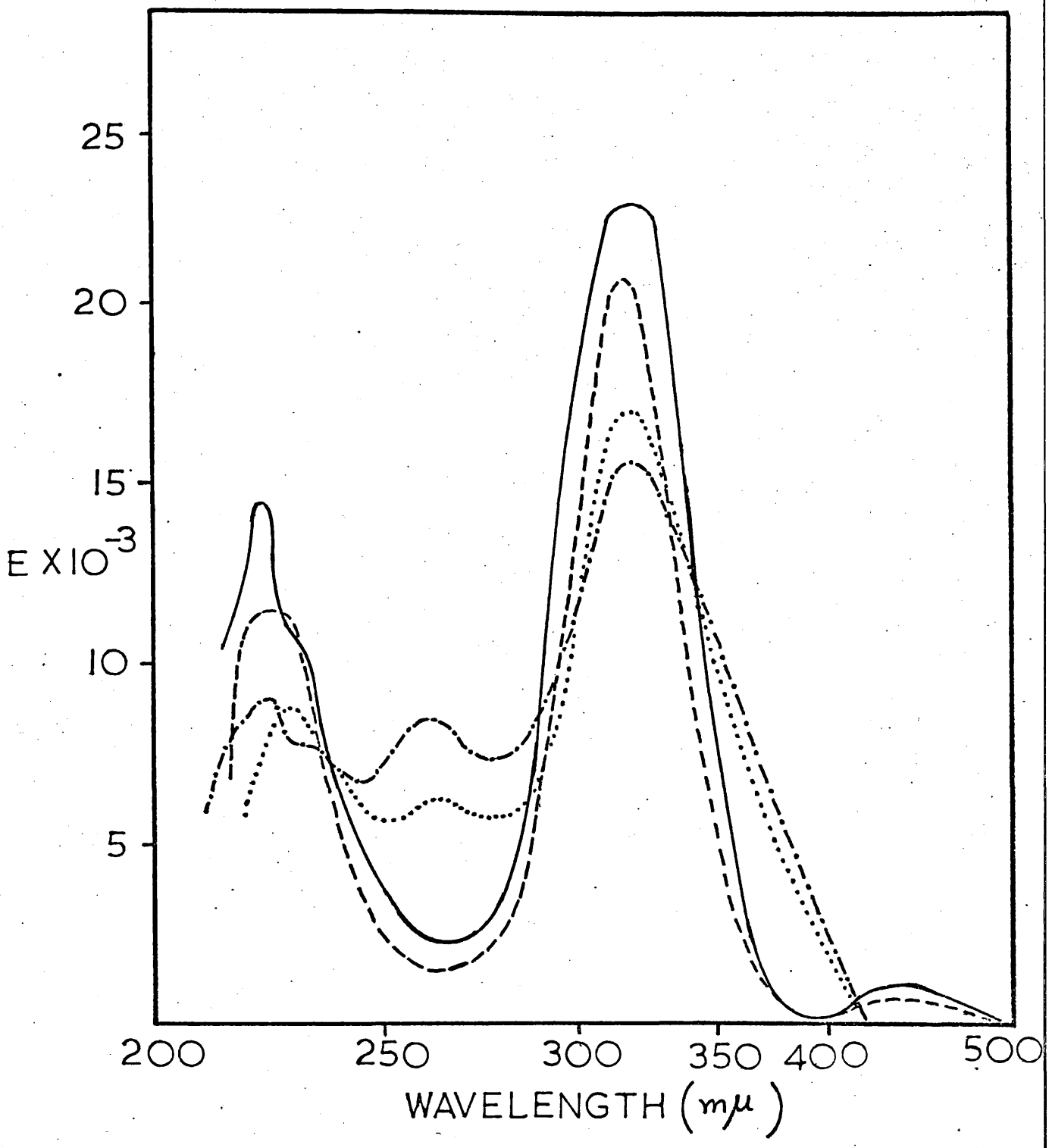
cis-form

IR spectra showed that there is a slight difference between I and II, but UV spectra showed some bands of the same positions but of different intensities (in 95% ethanol). However, the positions and intensities of the bands correspond closely to those for azobenzene and azoxybenzene respectively, Spectrum No. 5.

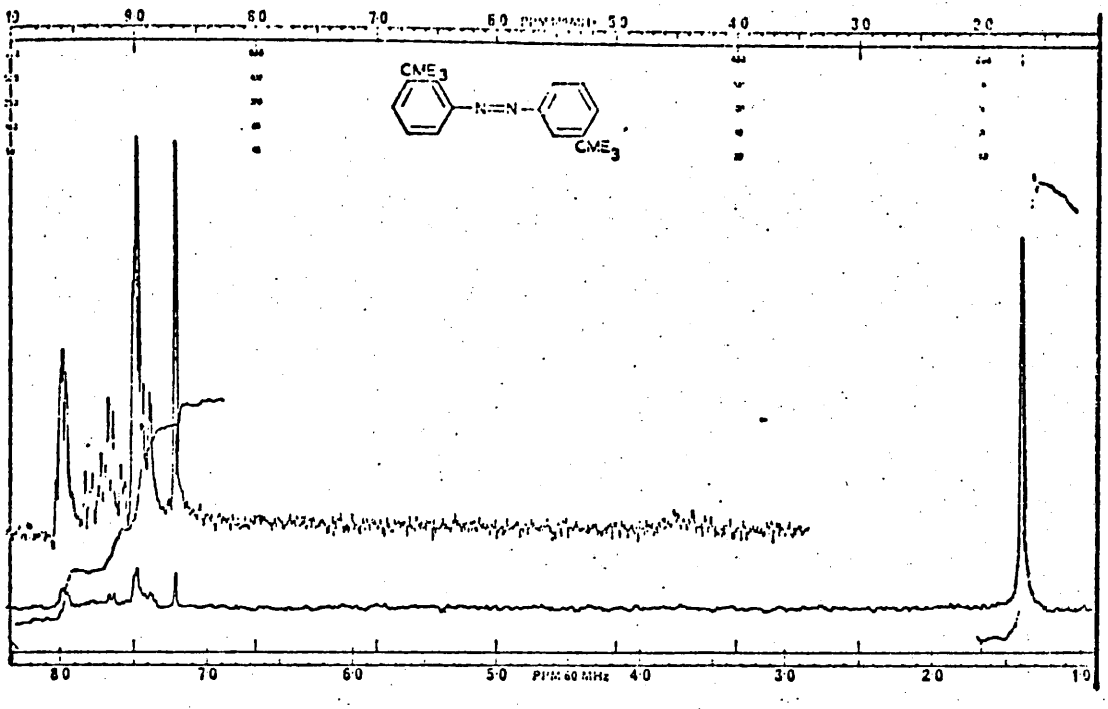
Compound I		Compound II	
λ_{max} (mμ)	E_{max}	λ_{max} (mμ)	E_{max}
437	700	324	18000
322	21500	258	6100
234	10900	230	9100

[1]HN.m.r. and mass spectra also indicate a similarity in the peaks for both compounds with a molecular weight for compound I = 294 and for compound II = 310, Spectra No. 6, 7, 8 and 9. Moreover, microanalysis of compound I agrees with that required for 3,3'-di-t-butylazobenzene, while that of compound II is very close to that of 3,3'-di-t-butylazoxybenzene. The product of m.p. 59-60° is thus 3,3'-di-t-butylazoxybenzene.

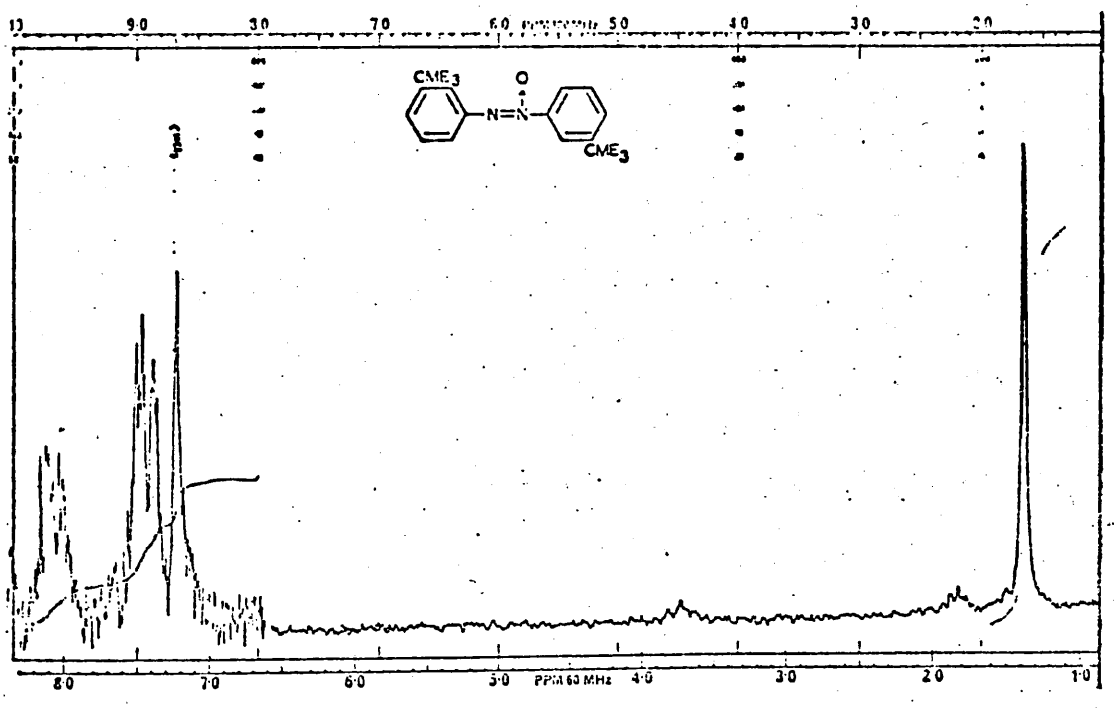
Reducing the azo compound with zinc dust-acetic acid afforded pale yellow-white crystals of the corresponding hydrazo compound which was found to be easily oxidized in the air and to change its colour rapidly; it was, therefore, rearranged immediately after filtration and drying.



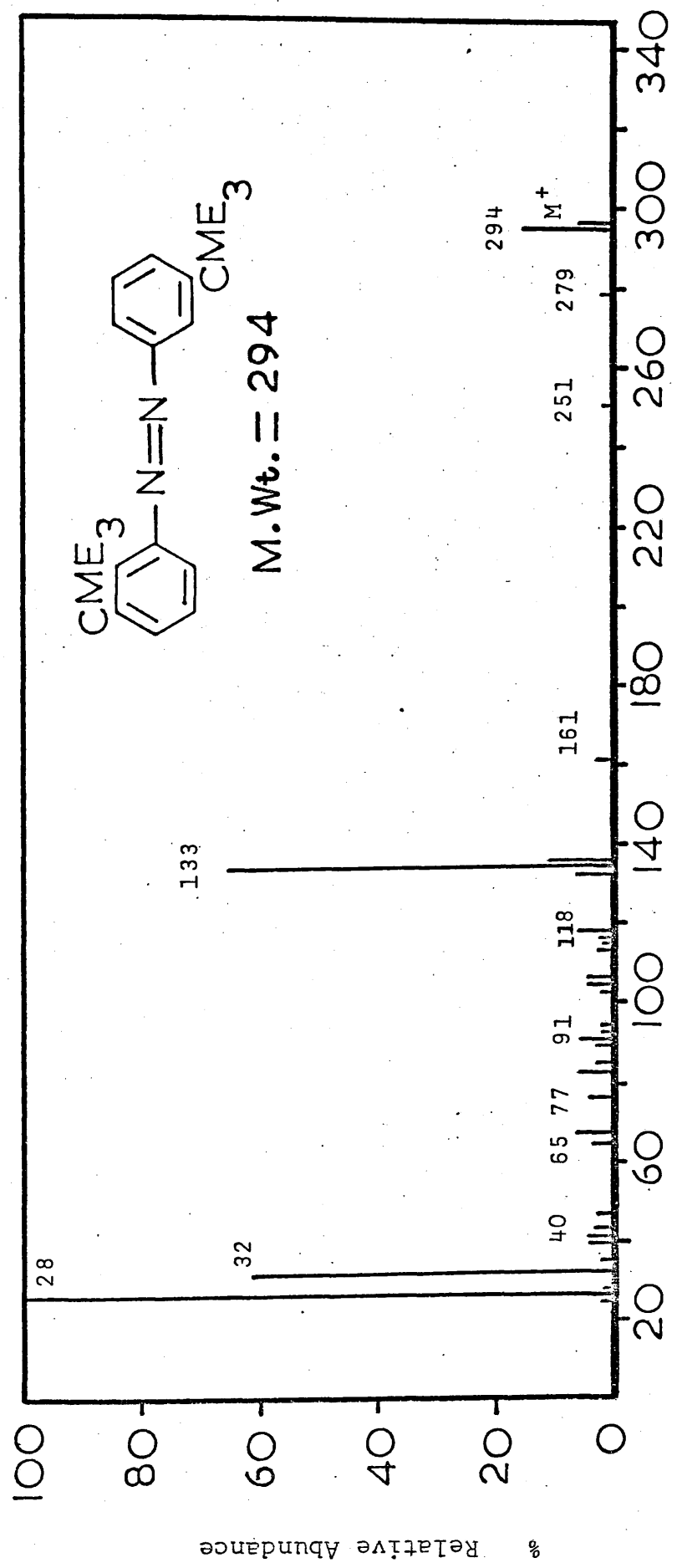
Spectrum No. 5. UV absorption spectra of azobenzene (——) ; 3,3'- di-t-butylazobenzene (----); azoxybenzene (±.-.-) and 3,3'- di-t-butylazoxybenzene (.....) in 95% ethanol.



Spectrum No. 6. ^{1}H N.m.r. spectrum, sweep width 500H_z.

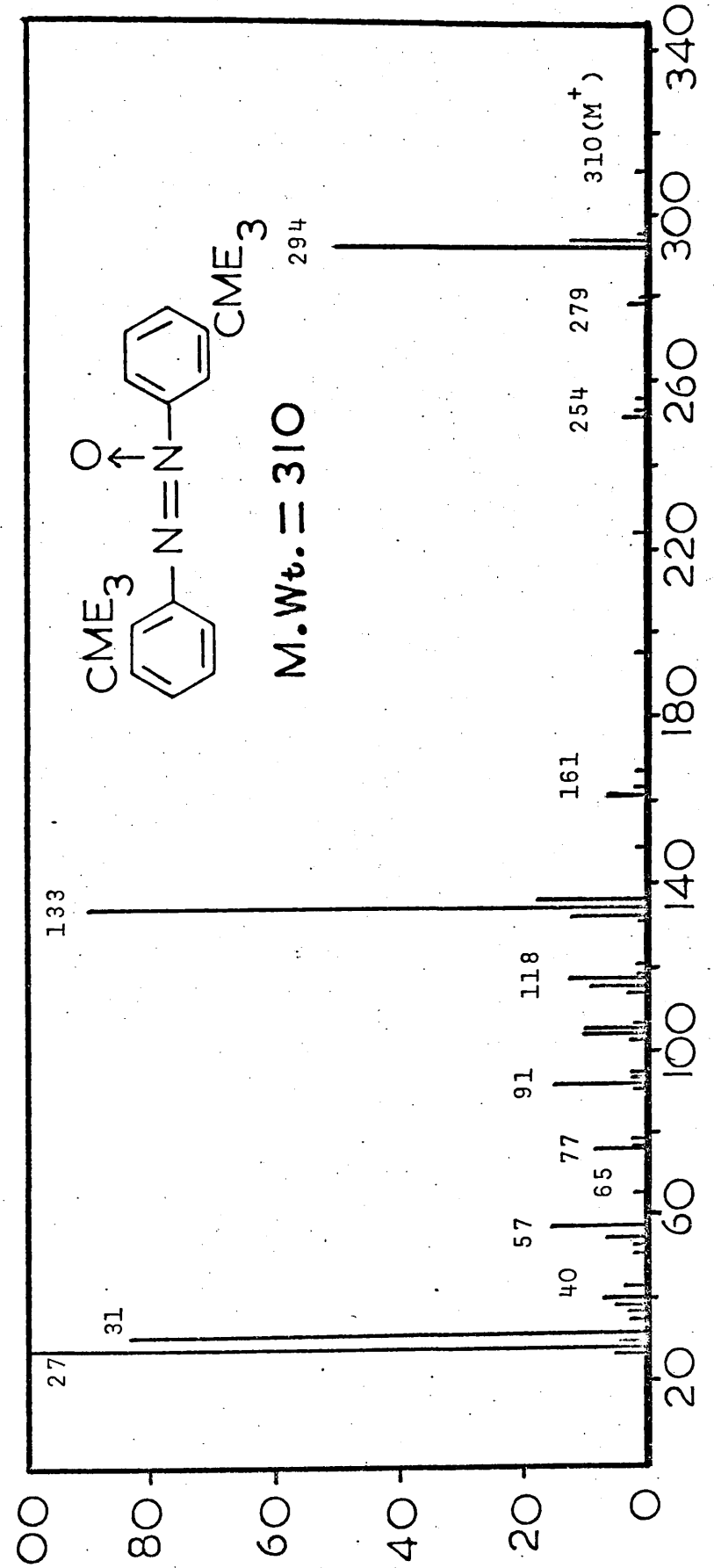


Spectrum No. 7. ^{1}H N.m.r. spectrum, sweep width 500H_z.



Spectrum No. 8. Mass spectrum of 3,3'- di-t-butylazobenzene, m.p. 106-107°.

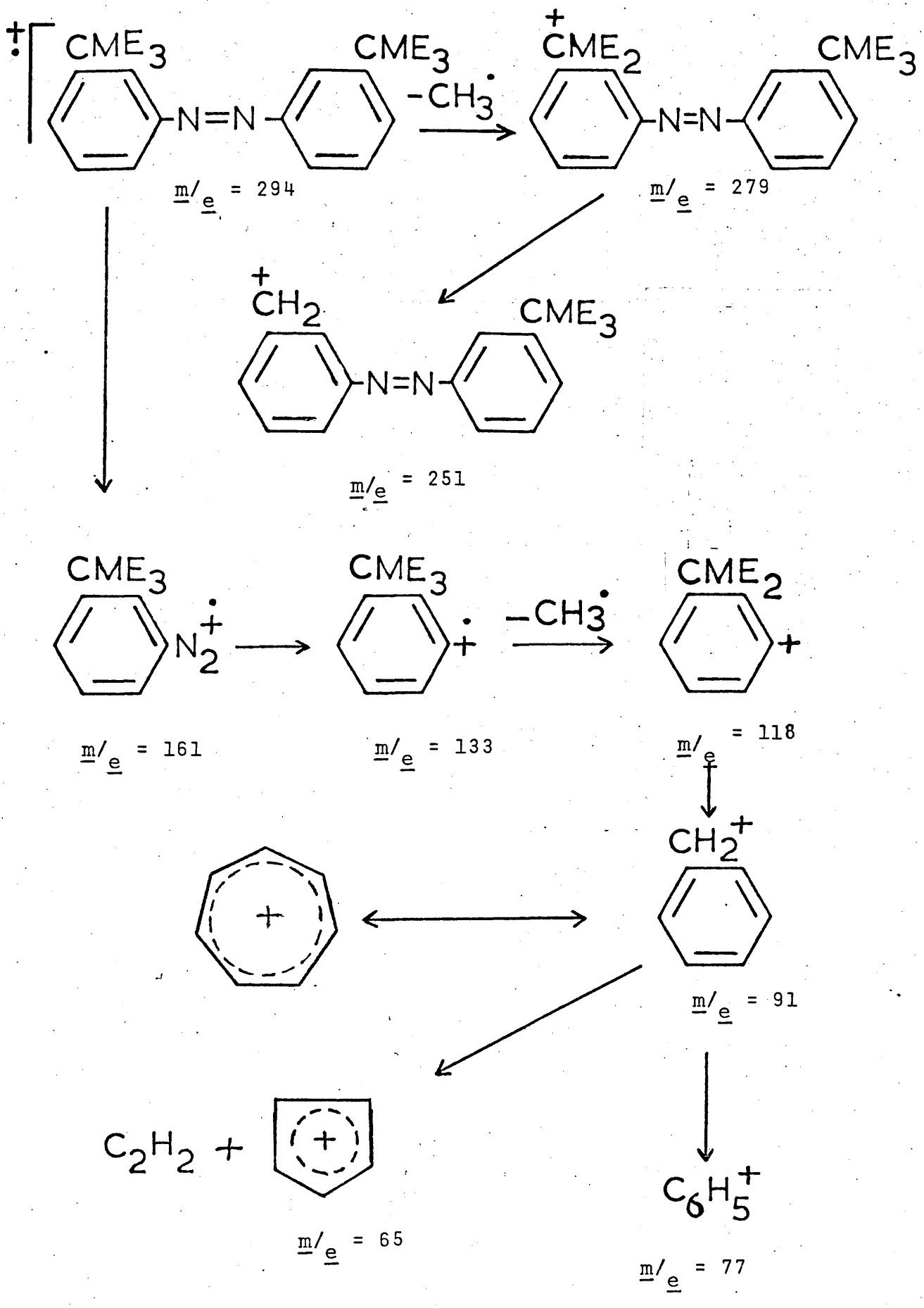
(Measured mass : 294.2100. Required mass: 294.2096).



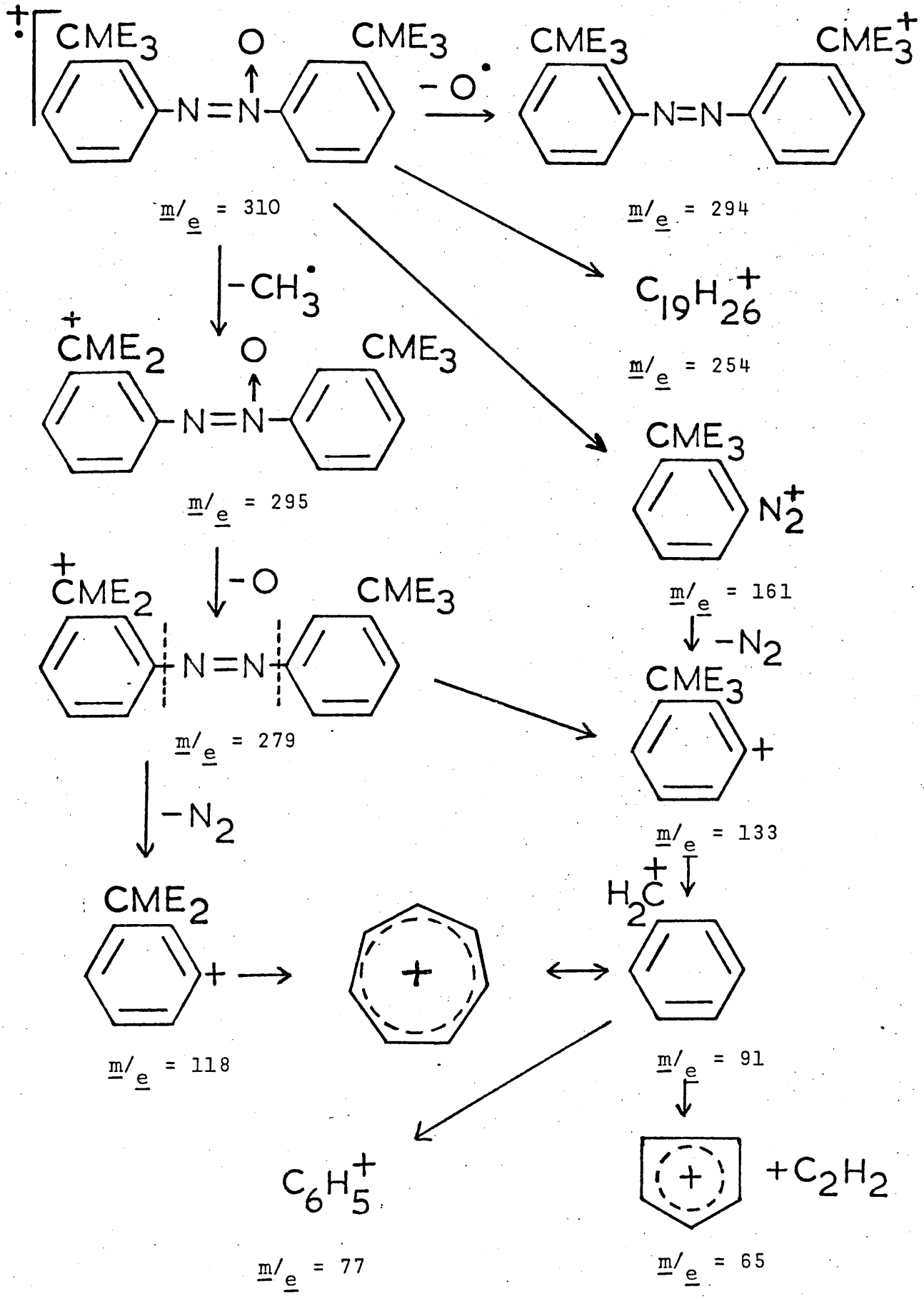
Spectrum No. 9. Mass spectrum of 3,3'- di-t-butylazoxybenzene, m.p. 59-60°.

(Measured mass: 310,2052. Required mass: 310.2045).

Mass spectrum fragmentation of 3,3'- di-t-butylazobenzene



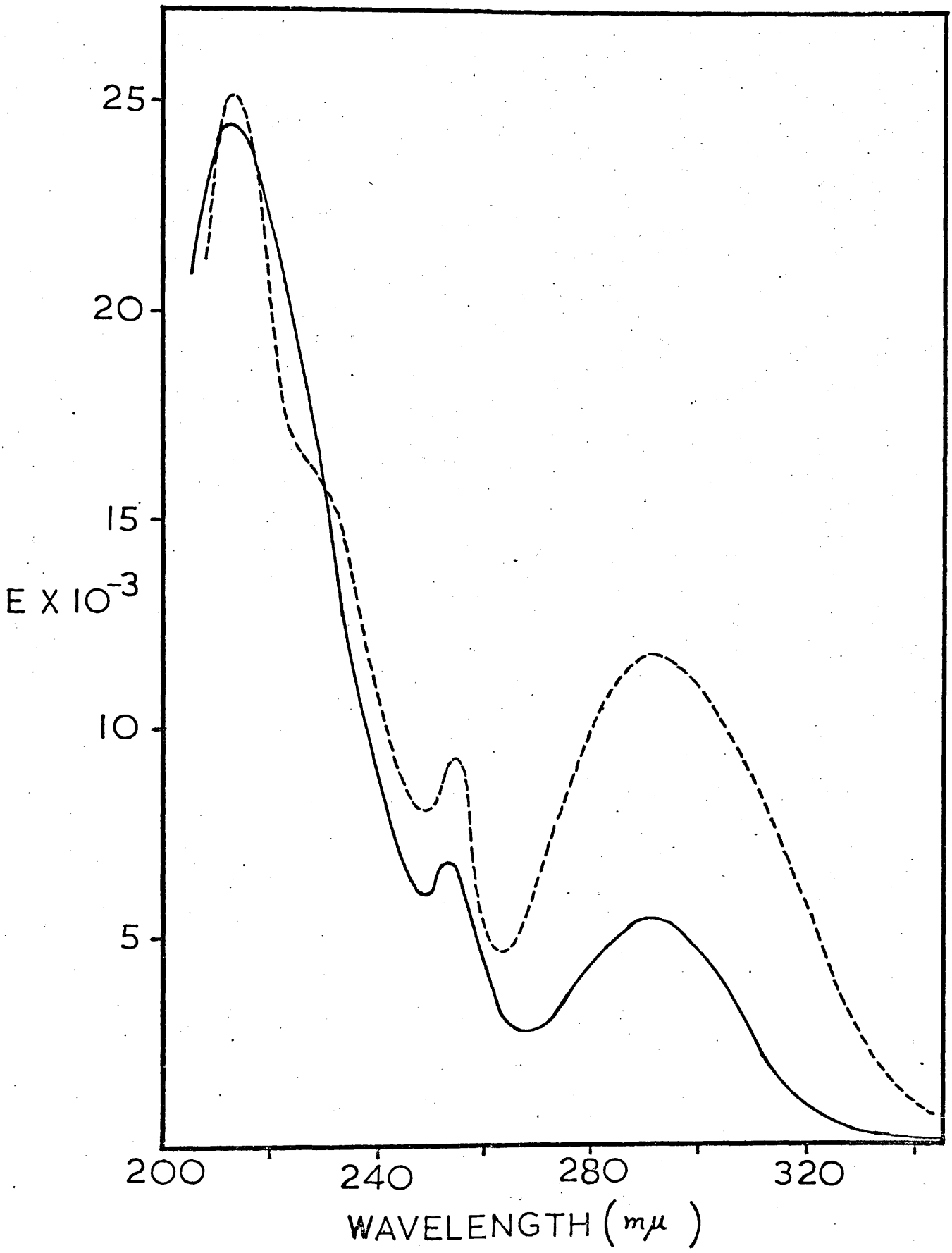
Mass spectrum fragmentation of 3,3'- di-t-butylazoxybenzene



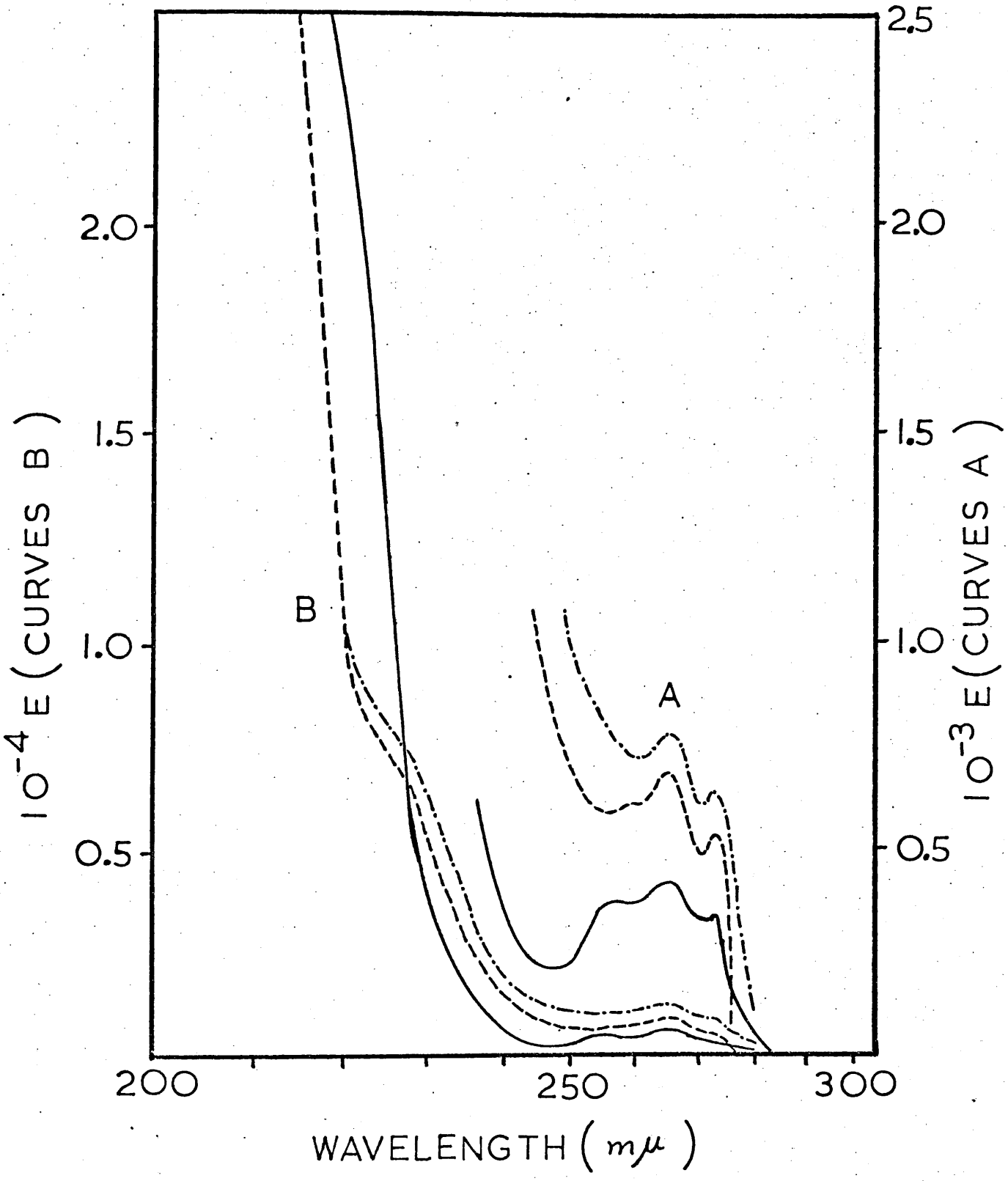
The corresponding benzidine, 2,2'-di-t-butylbenzidine, was obtained by the rearrangement of the hydrazo compound in 2:1 sulfuric acid at 85-90° for 15 minutes. There was no trace of any other expected compounds such as diphenylines in the isolated free base as indicated by the sharp melting point of the product. The ultraviolet absorption spectrum of the 2,2'-di-t-butylbenzidine (Spectrum No. 10) resembles that of the corresponding biphenyl (Spectrum No. 11) but with higher intensities. No conjugation band could be observed; this was mainly attributed to the absence of any conjugation between the two benzene rings due to the bulky tert. butyl groups in the ortho positions.

2,2'-Diisopropylbenzidine was prepared following the same method applied for 2,2'-di-t-butylbenzidine, and again a single product was isolated through the rearrangement process. The conjugation band was clearly observed in this compound as an inflection around 230 mμ, $E_{inf.}$ = 15,000 compared with that of the corresponding biphenyl at 227 mμ, $E_{inf.}$ = 7,000 (Spectra No. 10 and 11)[132].

4 - 2,6,2',6'-Tetrasubstituted benzidines were found to be much more sterically hindered than 2,2'-disubstituted benzidines and hence more drastic conditions are required to bring about the rearrangement of the corresponding hydrazo compounds. Carlin[7] had successfully suggested that 2:1 (by weight) sulfuric acid at 85-90° is the best medium for the rearrangement of the 3,5,3',5'- tetrasubstituted hydrazobenzenes into the corresponding benzidines. However, the problem here is not to overcome the difficulty of the rearrangement, but to find out an efficient method of separating the products from the isolated mixed crystalline bases, since this type of rearrangement results in more than two products.



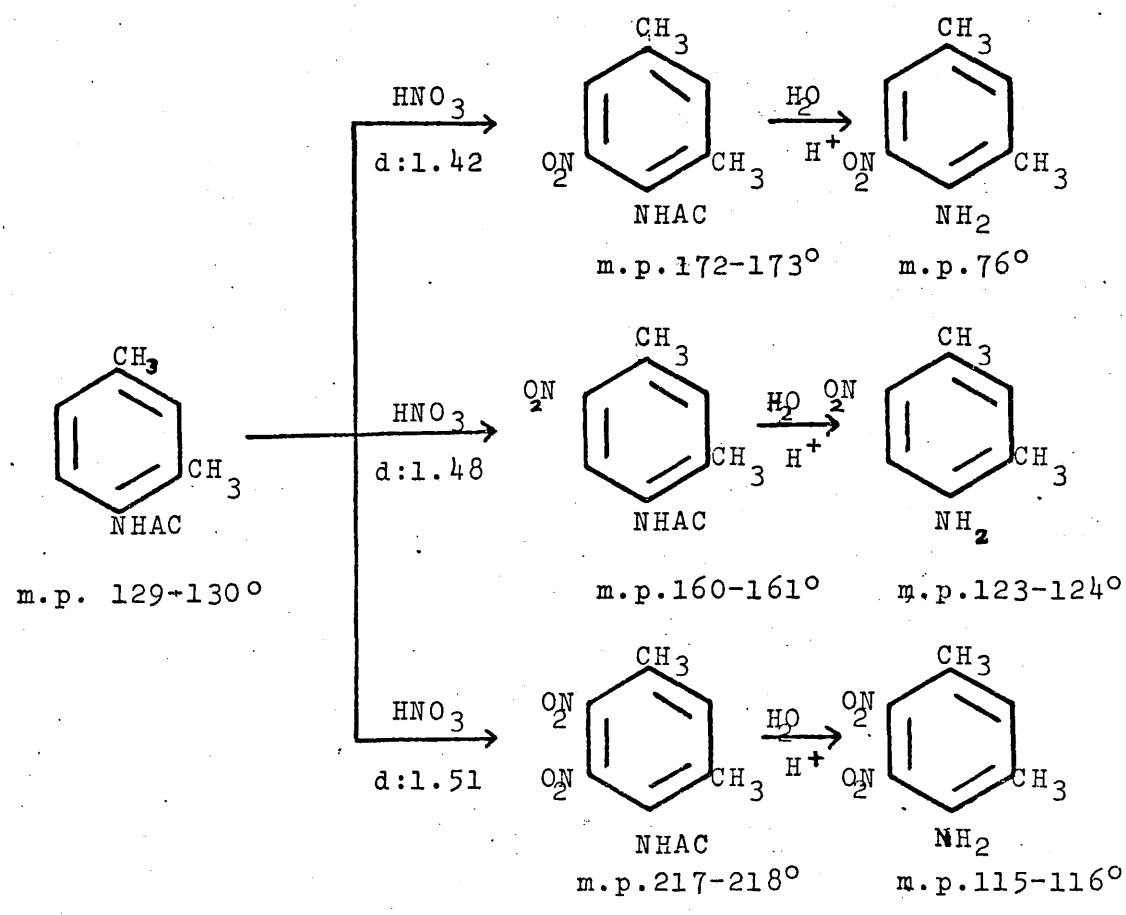
Spectrum No. 10. UV absorption spectra of 2,2'- di-t-butylbenzidine (——) ; 2,2'- di-iso-propylbenzidine (----) in 95% ethanol.



Spectrum No. 11. UV absorption spectra of 2,2'- diethylbiphenyl (-·-·-); 2,2'- di-iso-propylbiphenyl (----) and 2,2'- di-t-butylbiphenyl (——) in 95% ethanol[132].

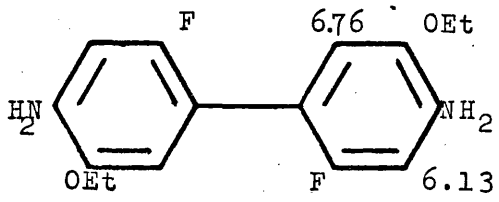
The method suggested by Carlin[7] to separate these products was the counter-current extraction method which was discovered by Craig[222]. An alternative and simple method which was applied during this work was column chromatography which will be discussed in details in the experimental part (Page 138). Column chromatography was found to be a simple method of obtaining satisfactory yields and to result in products with improved melting points.

5 - From the literature, it appeared that 5-nitro-4-m xylidine could be prepared by nitration of 4-m-acetxylidide using either nitric acid (d: 1.48)[223] or fuming nitric acid (d: 1.55-1.57)[224]. In fact, when the nitration was carried out with nitric acid (d: 1.48), the only compound which obtained was 6-nitro-4-m-xylidine as indicated from its melting point as well as that of its acetyl derivative, while using nitric acid (d: 1.51), the isolated product was nothing but 5,6-dinitro-4-m-xylidine[225]. The 5-nitro-4-m-xylidine was prepared by the nitration of 4-m-acetxylidide using only conc. nitric acid (d: 1.42).

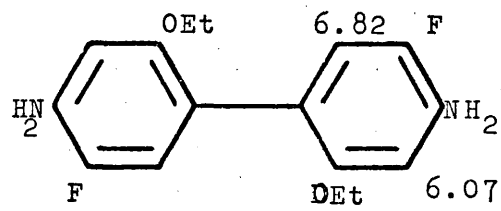


A modified method was used to diazotize 5-nitro-4-m-xylidine, which in fact was a combination of methods described by Willgerodt and Schmierer[223] and by Haller, Adams and Wherry[224], whereby an improved yield was obtained.

6 - Reduction and coupling of 2,5-difluoro-1-nitrobenzene to the corresponding azo compound using zinc powder and ethanolic sodium hydroxide afforded 2,2'-diethoxy-5,5'-difluoroazobenzene rather than the expected 2,5,2',5'-tetrafluoroazobenzene. The ^1H n.m.r. spectrum of the isolated azo compound showed three different protons (Spectrum No. 12), but the spectrum of the corresponding benzidine showed clearly absorptions due to two different protons, Spectrum No. 22, (two multiplets centered at 6.49 and 6.74 p.p.m.). Calculated chemical shifts of these two protons using the values given by Jackmann and Sternhell[37], were found to be as follows:

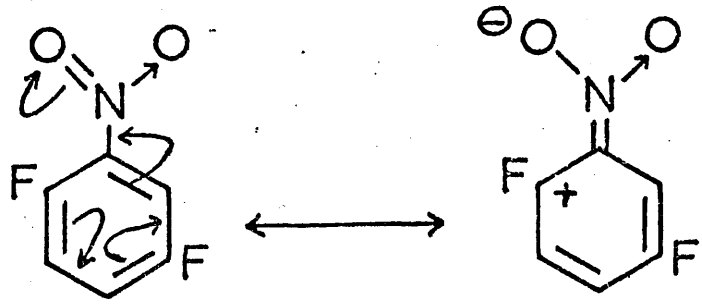


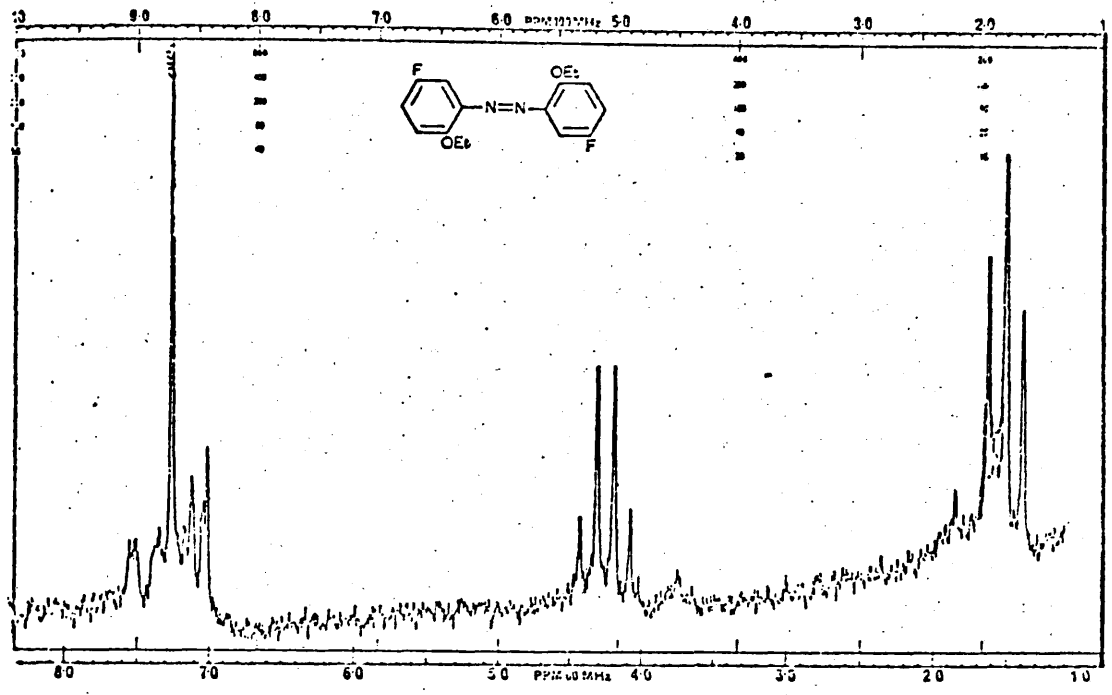
(A)



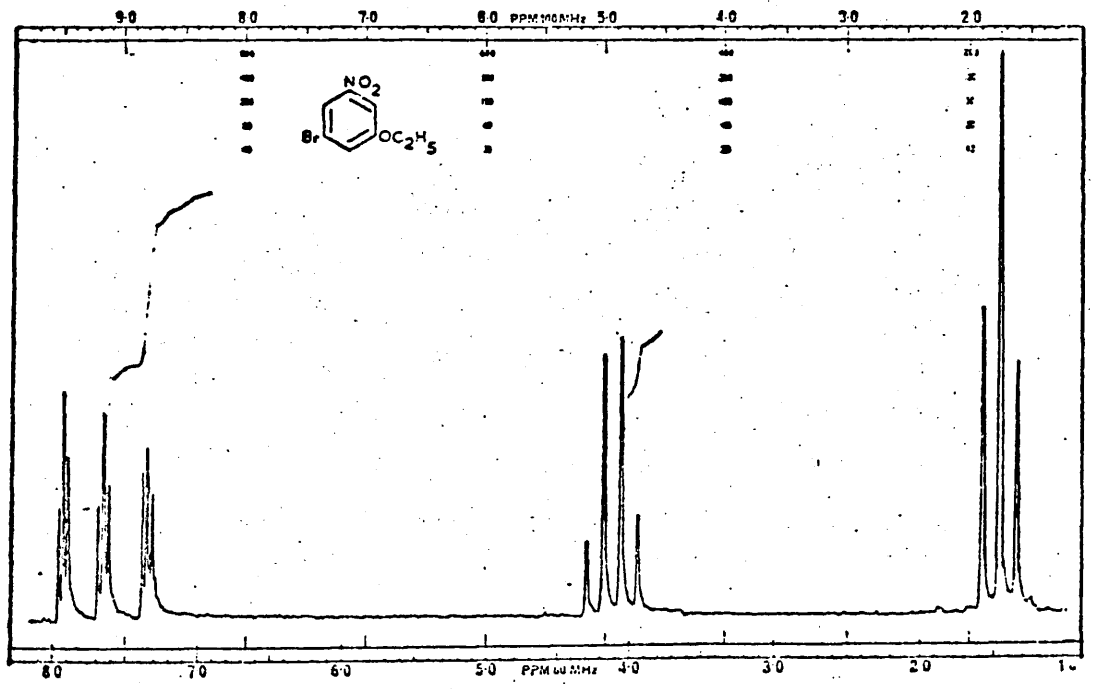
(B)

From the above calculated and observed chemical shifts, it is difficult to decide which compound is the right one, although compound (A) is the more consistent with the observed values of Spectrum No. 22. Furthermore, it is believed that a fluorine atom ortho to a nitro group is replaced very easily by a strong nucleophile (EtO^-) due to the delocaliiation of the π- bonds of the ring, which leaves the 2- positions with low charge density, while that of the 5- positions (meta) are unaffected (except inductively).



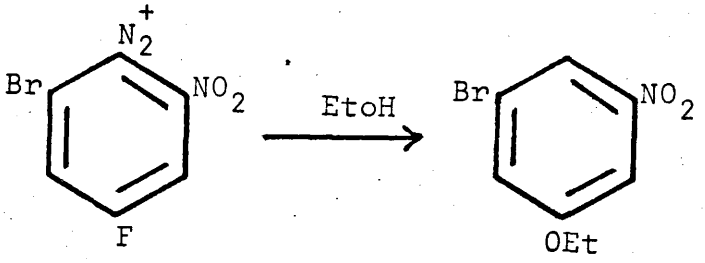


Spectrum No.12. ^1H N.m.r. spectrum, sweep width 500 H_z



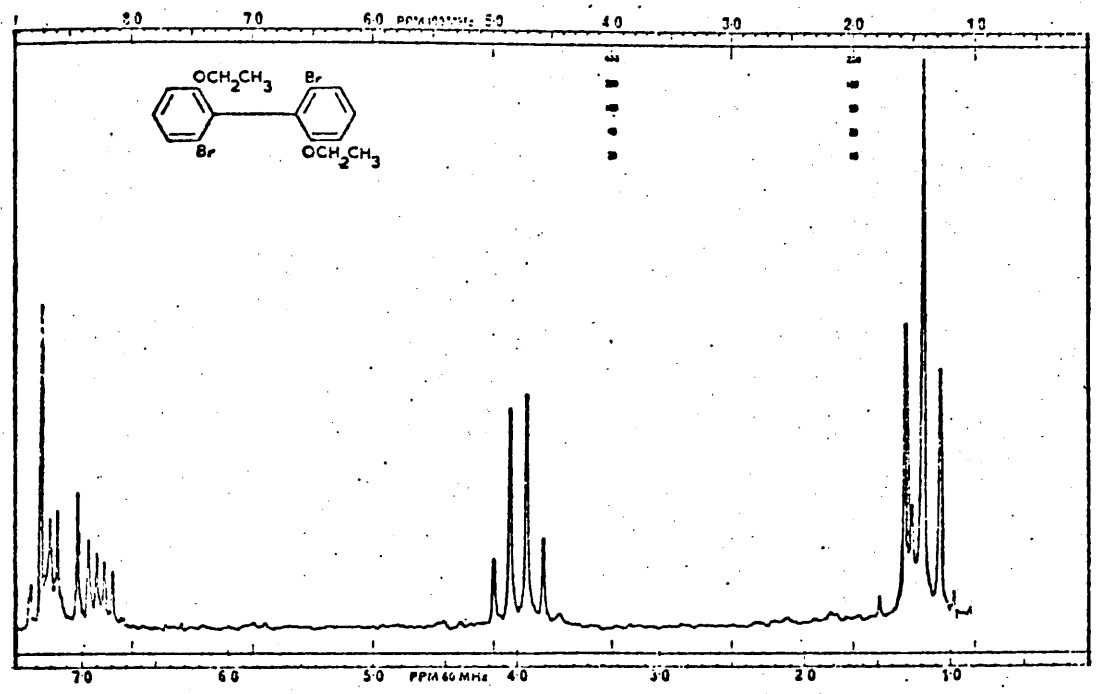
Spectrum No.13. ^1H N.m.r. spectrum, sweep width 500 H_z

. Similar behaviour was observed in the deamination of 2-nitro-4-fluoro-6-bromoaniline using sodium nitrite and concentrated sulfuric acid in ethanol as a solvent. The isolated substance was found to be 3-bromo-5-ethoxy-1-nitrobenzene rather than 3-bromo-5-fluoro-nitrobenzene as confirmed by its microanalysis as well as by its n.m.r. spectrum which revealed the presence of the ethoxy group absorption (a triplet for the methyl group and a quartet for the methylene group) Spectrum No. 13. This displacement is attributed to the diazonium group, N_2^+, which is an effective activator for nucleophilic substitution[226]. There are, however, many instances where a nitro or halo substituent, ortho or para to the diazonium group in a diazo salt is displaced during a reaction that is intended to alter only the diazonium group.

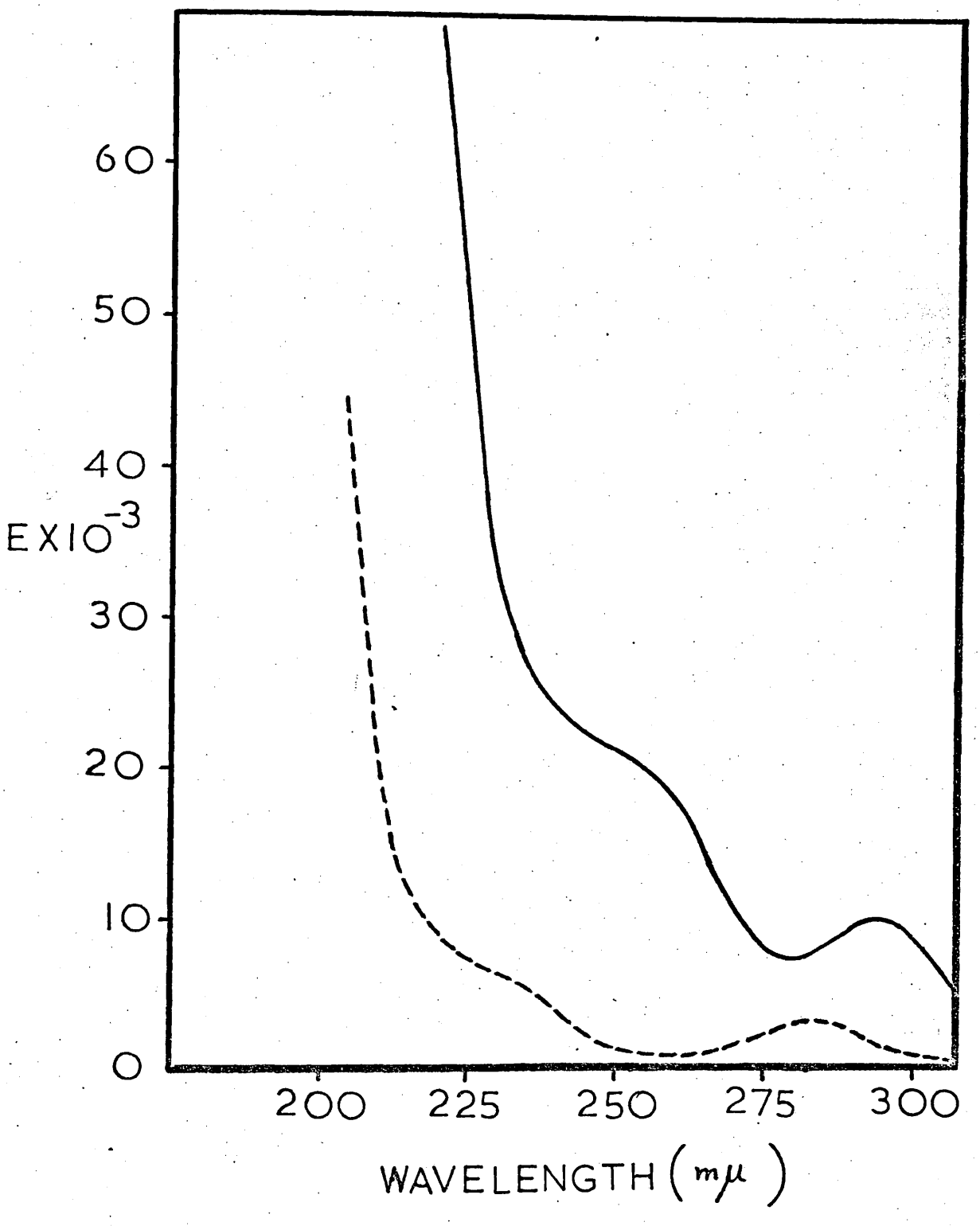


3-Bromo-5-ethoxy-1-nitrobenzene was reduced and coupled using zinc powder and alcoholic sodium hydroxide to the corresponding azo, hydrazo and then rearranged to the corresponding benzidine in 22% yield. 2,2'-Dibromo-6,6'-diethoxybiphenyl was prepared by diazotization of 2,2'-dibromo-6,6'-diethoxybenzidine in 74% yield.

The ^1H n.m.r. and UV spectra of the above mentioned new compounds (the benzidine and the corresponding biphenyl) were done (Spectra No. 14, 15, 23, and 24) and as expected, a multiplet absorption for the aromatic protons (6 protons) and a typical quartet for the methylene protons were clearly shown in the n.m.r. spectrum, while no conjugation band was observed in the region 220-250 mμ; which is mainly due to the presence of bulky groups in the 2,6,2',6'- positions.



Spectrum No.14. ^1H N.m.r. spectrum, sweep width 500 H_z



Spectrum No. 15. UV absorption spectra of 2,2'-dibromo-6,6'- diethoxybenzidine (——) and 2,2'- dibromo-6,6'- diethoxybiphenyl (----) in 95% ethanol.

^{1}H N.M.R. Studies of benzidines

The position of absorption of an aromatic proton depends on at least three factors:

1- The diamagnetic shielding which is the most important and depends on the electron density at the carbon atom to which the proton is attached.

2- Paramagnetic shielding as a result of the ring current whose magnitude will be greater for electron-donating substituent groups than for electron-withdrawing substituent groups.

3- Possibly diamagnetic anisotropic effect, which will be greatest at positions ortho to the substituent group.

In considering the chemical shifts occuring in many substituted benzidines that were prepared and studied throughout this work, the n.m.r. spectra of these benzidines were measured in $CDCl_3$ solution on a Varian HA 60 MHz spectrometer using TMS as an internal standard.

On treatment of these compounds with a few drops of trifluoroacetic acid (TFA) in $CDCl_3$ solution, a downfield shift in the absorption spectra occurs in all aromatic proton signals. The appearance of the amino group signal in the region 3.38-3.93 p.p.m. in all cases, even after the addition of TFA, is mainly due to the incomplete protonation of the amino group. In nearly all cases, however, the ammonium ion ($Ar\text{-}NH_3^+$) signal could not be detected as a distinct band, (8.5-9.5 p.p.m.)[36] because of the low concentration of TFA in the solvent (2-3 drops) and in many cases the salt separated from the solution as a solid or oily precipitate.

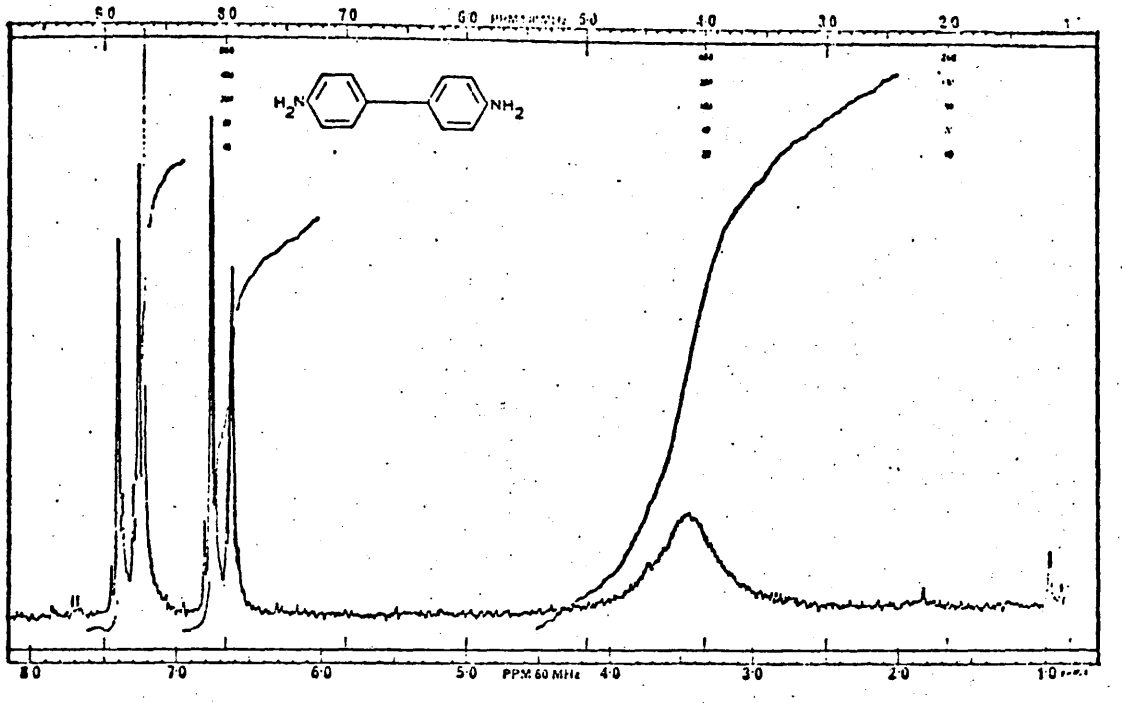
On using deuterated sulfuric acid (D_2SO_4) as a solvent, a more pronounced downfield shift was observed; this is due to the powerful protonating properties of this acid compared with those of TFA.

The n.m.r. spectrum of benzidine showed a double multiplet at 6.62-7.40 p.p.m. for the aromatic protons and a broad singlet at 3.45 p.p.m. for the amino protons, spectrum No.16, Table IV. Treating the benzidine solution with a few drops of TFA gives an upfield shift of 0.07 p.p.m. in the amino protons while on treating the benzidine with neat D_2SO_4 a downfield shift of 0.17 p.p.m. was observed, Table IV. In the following discussion, two different groups of protons are considered, namely the amino protons and the aromatic protons, and each group of protons will be discussed separately and in detail.

1- Amino protons

a- In $CDCl_3$:

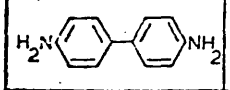
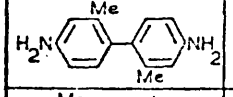
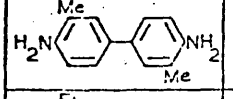
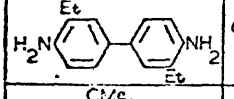
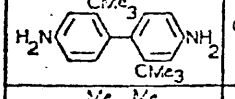
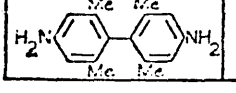
Benzidines substituted with an electron-releasing groups showed absorptions of the amino protons at nearly the same region, 3.38-3.55 p.p.m., Table IV, spectra No.17-20. Electron-withdrawing substituents cause the amino protons to absorb downfield, 3.62-3.81 p.p.m., spectrum No.21, compared with benzidine itself. However, if these electron-withdrawing groups are ortho to the amino group, the amino protons absorb further downfield, 4.48-4.88 p.p.m., Tables V and VI. This can be mainly attributed to the low electron density of the amino group as well as to the blocking action of the substituent ortho to the amino group. Table VII shows that there is no big difference in the position of the amino protons compared with that of benzidine itself when both



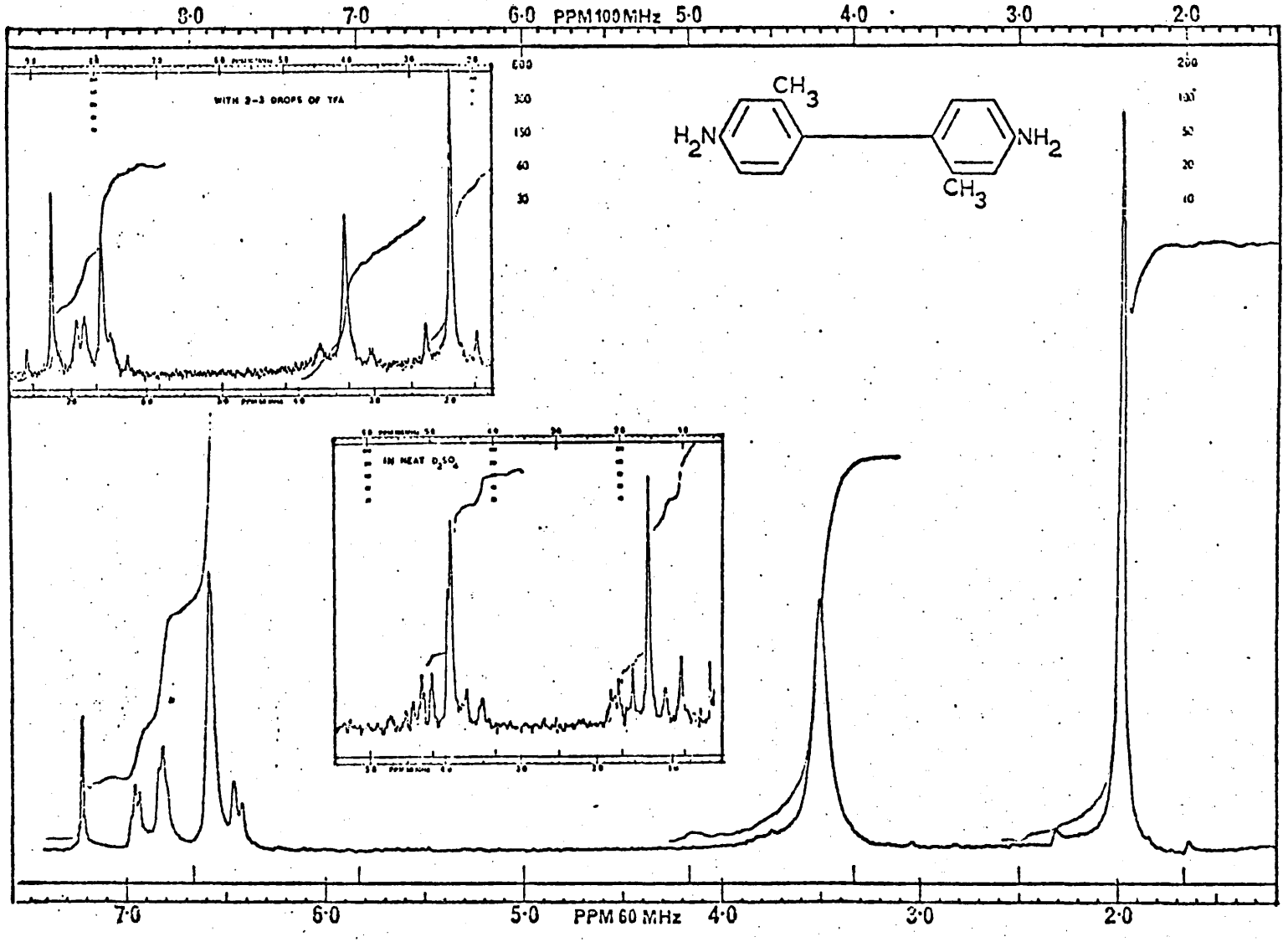
Spectrum No.16. ^1H N.m.r. spectrum, sweep width 500 H_z

Table IV. Chemical shifts of alkylated benzidines in p.p.m.,

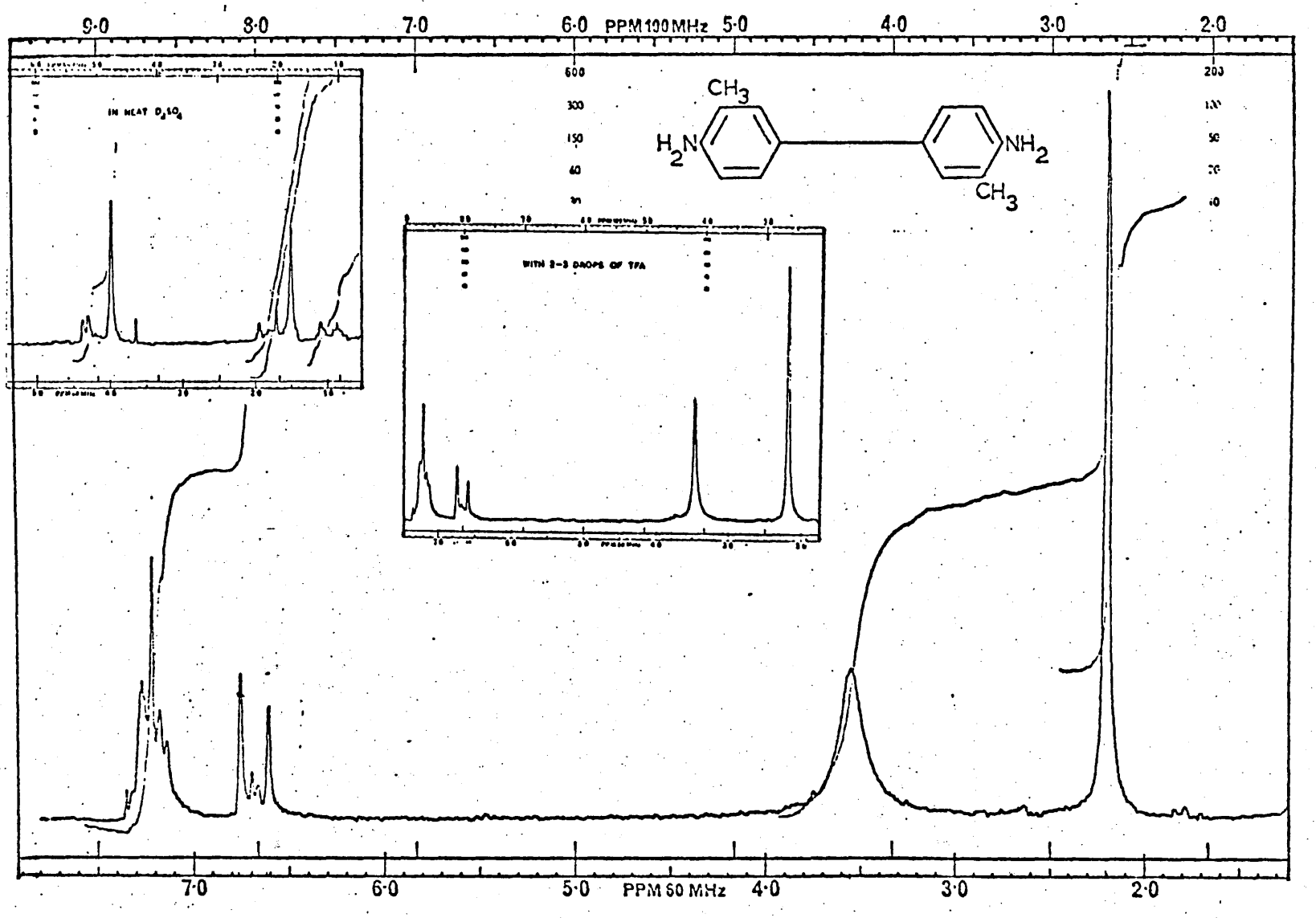
(S) singlet; (M) multiplet.

COMPOUND.	IN $CDCl_3$		IN $CDCl_3$ + 3 DROPS OF TFA				IN D_2SO_4			
	AROMATIC PROTONS	NH_2 GROUP	AROMATIC PROTONS	Δ_{Ar-H}	NH_2 GROUP	Δ_{NH_2}	AROMATIC PROTONS	Δ_{Ar-H}	NH_2 GROUP	Δ_{NH_2}
	6.62–7.40 M	3.45 S	6.62–7.40 M	0.00	3.38 S	−0.07	8.17–8.43 M	+1.29	3.62 S	+0.17
	6.47–6.95 M	3.52 S	6.60–7.58 M	+0.38	3.38 S	−0.14	7.00–8.60 M	+1.09	3.63 S	+0.11
	6.60–7.25 M	3.55 S	6.60–7.25 M	0.00	3.48 S	−0.07	7.28–8.73 M	+1.08	3.88 S	+0.33
	6.55–7.20 M	3.38 S	6.57–7.22 M	+0.02	3.45 S	+0.07	—	—	—	—
	6.78–7.35 M	3.43 S	7.03–7.66 M	+0.45	3.93 S	+0.50	7.80–8.30 M	+0.99	4.58 S	+1.15
	6.47 S	3.38 S	6.47 S	0.00	3.40 S	+0.02	7.70 S	+1.23	4.58 S	+1.20

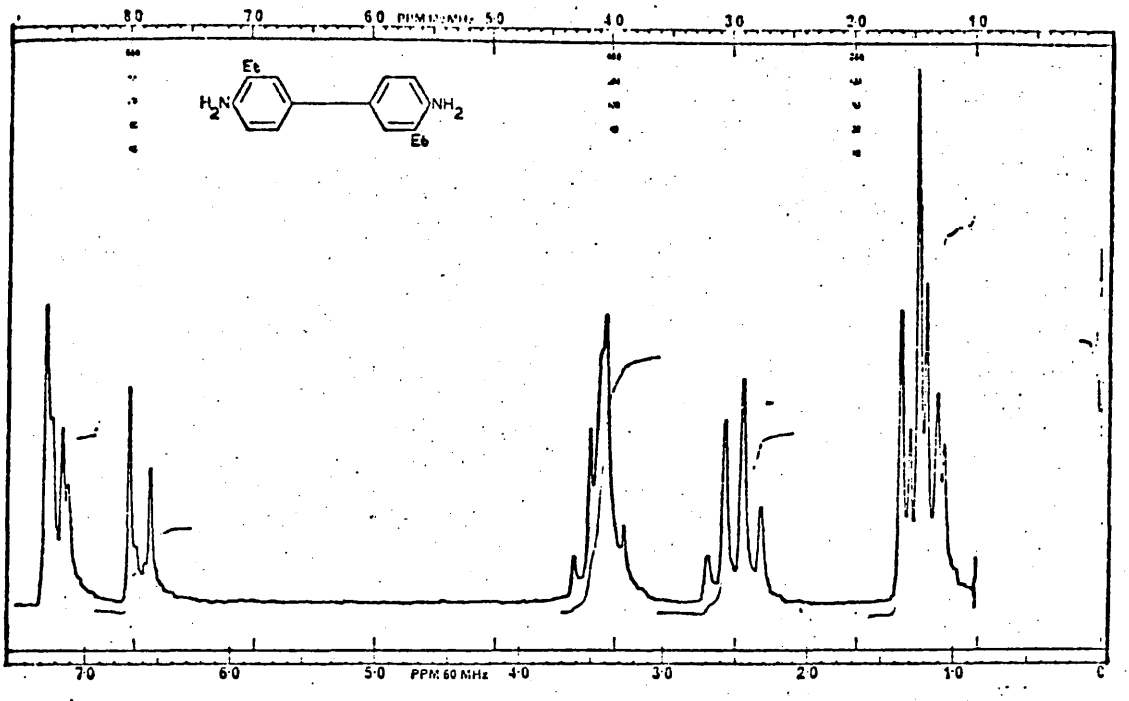
(Negative sign denotes upfield shift)



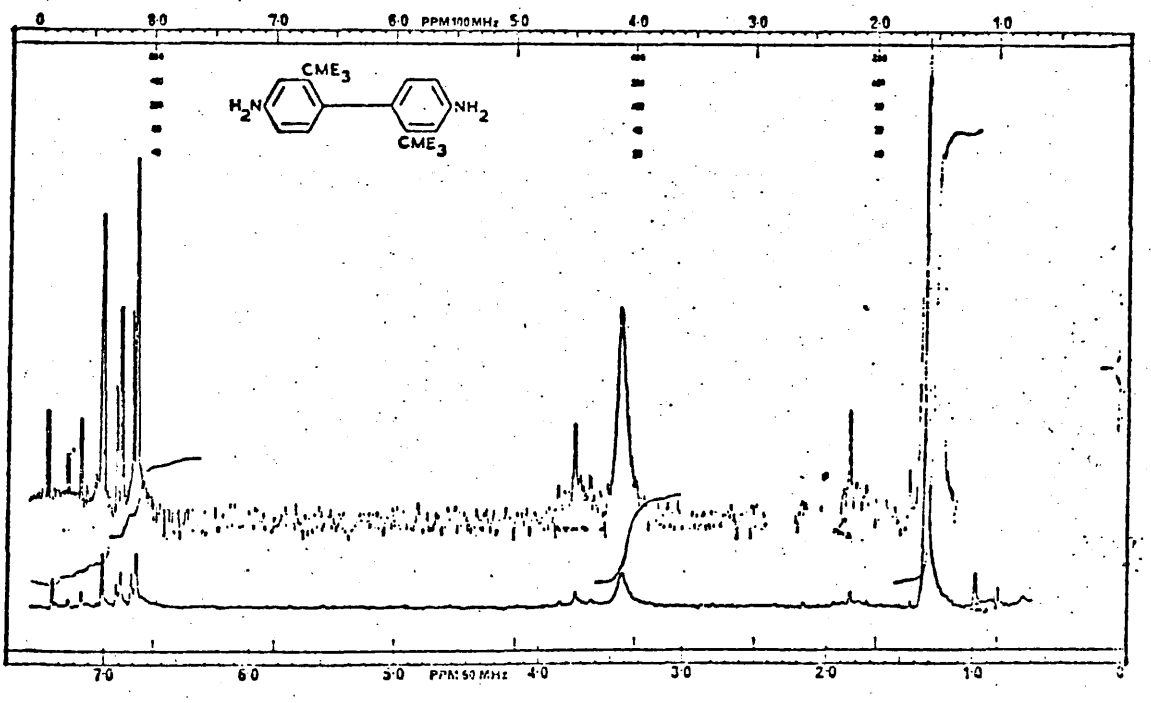
Spectrum No. 17. ^1H N.m.r. spectrum of m-tolidine in $CDCl_3$, in TFA and in D_2SO_4, sweep width 500 H_z



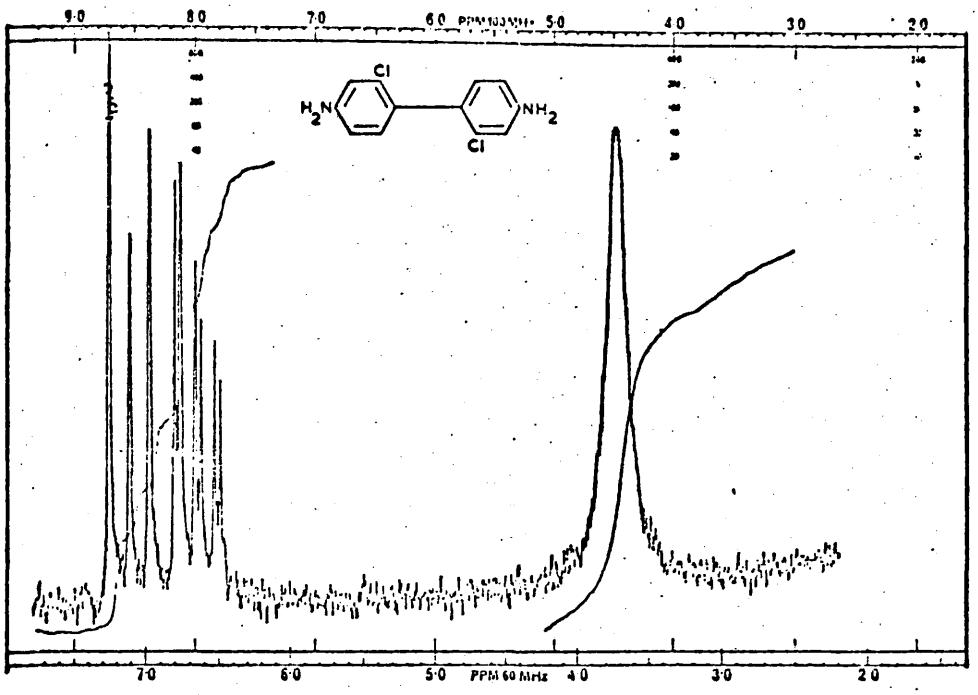
Spectrum No.18. ^1H N.m.r. spectrum of O-tolidine in $CDCl_3$, in TFA and in D_2SO_4, sweep width 500 H_z



Spectrum No.19. ^1H N.m.r. spectrum, sweep width 500 H_z

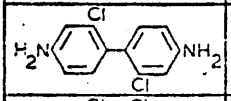
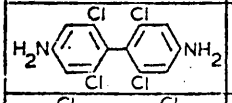
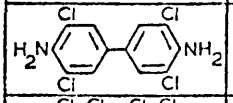
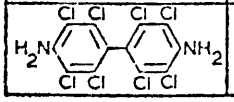


Spectrum No.20. ^1H N.m.r. spectrum, sweep width 500 H_z



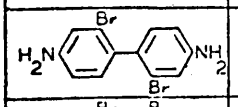
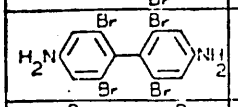
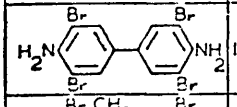
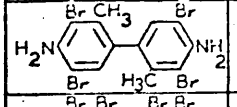
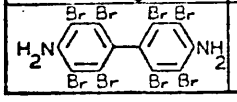
Spectrum No.21. ^1H N.m.r. spectrum, sweep width 500 H_z

Table V. Chemical shifts of chloro-benzidines in p.p.m., (S) singlet; (M) multiplet.

COMPOUND	IN $CDCl_3$		IN $CDCl_3$ + 3 DROPS OF TFA				IN D_2SO_4			
	AROMATIC PROTONS	NH_2 GROUP	AROMATIC PROTONS	Δ Ar-H	NH_2 GROUP	Δ NH_2	AROMATIC PROTONS	Δ Ar-H	NH_2 GROUP	Δ NH_2
	6.51 – 7.20 M	3.73 S	7.08–7.52 M	+0.49	3.93 S	+0.20	8.07– 8.25 M	+1.35	—	—
	6.70 S	3.81 S	6.72 S	+0.02	3.38 S	−0.43	8.10 S	+1.40	4.63 S	+0.82
	7.30 S	4.48 S	7.49	+0.19	3.93 S	−0.55	8.30 S	+1.00	4.65 S	+0.17
	—	4.88 S	—	—	3.93 S	−0.95	—	—	4.63 S	−0.25

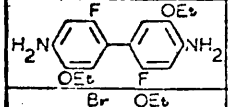
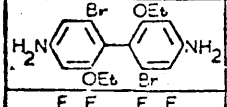
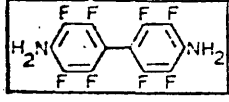
(Negative sign denotes upfield shift)

Table VI. Chemical shifts of bromo-benzidines in p.p.m., (S) singlet; (M) multiplet

COMPOUND	IN $CDCl_3$		IN $CDCl_3$ + 3 DROPS OF TFA				IN D_2SO_4			
	AROMATIC PROTONS	NH_2 GROUP	AROMATIC PROTONS	Δ Ar-H	NH_2 GROUP	Δ NH_2	AROMATIC PROTONS	Δ Ar-H	NH_2 GROUP	Δ NH_2
	6.47–7.00 M	3.62 S	6.57–7.10 M	+0.10	3.42 S	−0.20	8.03–8.55 M	+1.59	4.67 S	+1.05
	6.95 S	3.83 S	7.80 S	+0.85	3.93 S	+0.10	8.33 S	+1.38	4.63 S	+0.80
	INSOLUBLE	—	——	—	—	—	8.45 S	+1.05	4.63 S	—
	7.14 S	4.64 S	7.38 S	+0.24	3.93 S	−0.71	8.07 S	+0.93	4.65 S	+0.01
	—	3.78 S IN DMSO	——	—	—	—	——	—	—	—

(Negative sign denotes upfield shift)

Table VII. Chemical shifts of different substituted-benzidines in p.p.m., (S) singlet; (D) doublet; (M) multiplet

COMPOUND	IN $CDCl_3$		IN $CDCl_3$ + 3 DROPS OF TFA				IN D_2SO_4			
	AROMATIC PROTONS	NH_2 GROUP	AROMATIC PROTONS	Δ Ar-H	NH_2 GROUP	Δ NH_2	AROMATIC PROTONS	Δ Ar-H	NH_2 GROUP	Δ NH_2
	6.40–6.80 M	3.75 S	6.90–7.40 M	+0.55	3.75 S	0.00	7.66–8.32 M	+1.39	4.62 S	+0.87
	6.18–6.58 D	3.67 S	6.90–7.26 D	+0.60	3.50 S	−0.17	7.78–8.10 D	+1.56	4.66 S	+0.99
	——	3.55* S	——	—	4.85* S	+1.30	——	—	—	—

* IN ACETONE

(Negative sign denotes upfield shift)

electron-releasing and electron-withdrawing groups are in the molecule, 3.67-3.75 p.p.m., spectra No.22-24.

b- In $CDCl_3$ + 3 drops of TFA

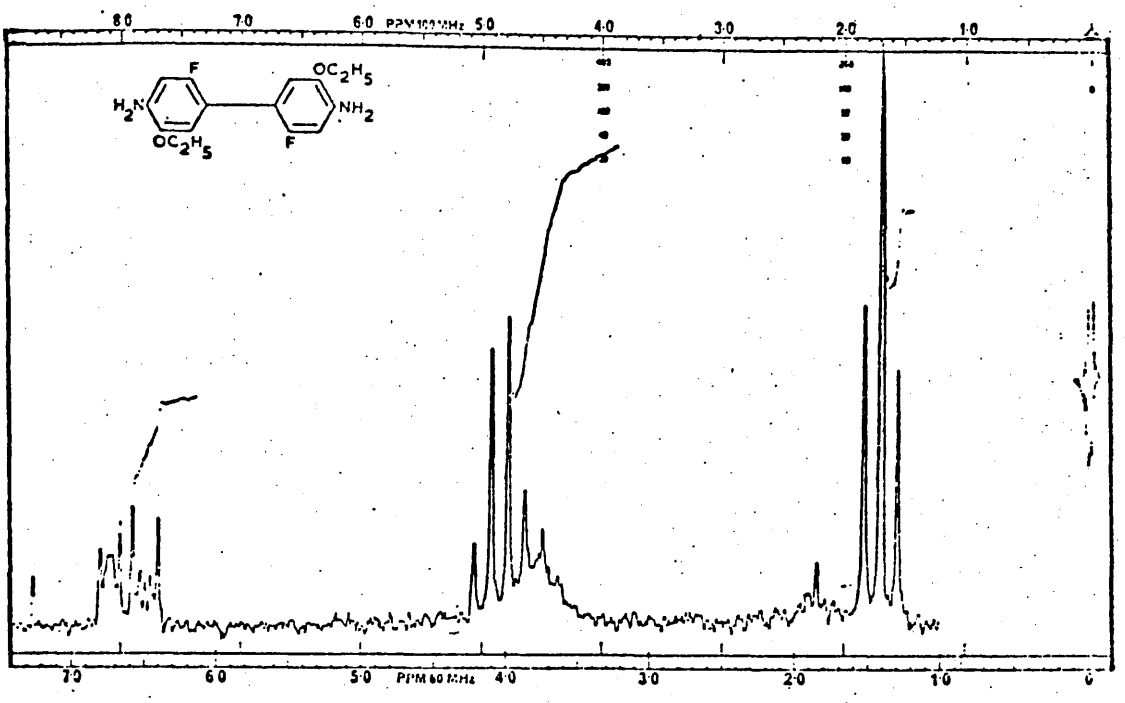
Amino protons of benzidine suffered an upfield shift of 0.07 p.p.m. when its chloroform solution was acidified with TFA. However, amino protons of some alkyl substituted benzidines were brought upfield while others suffered downfield shift. It seems that by no means these observations could be correlated or explained (whether upfield or downfield shift) on the basis of steric factors, electronic factors or solvent effect with the data available here, Table IV.

In the halogeno-benzidines, the only two cases where there is a downfield shift are in 2,2'-dichloro- and 2,6,2',6'-tetrabromobenzidine (Tables V and VI). In octafluorobenzidine, a large downfield shift of 1.30 p.p.m. was observed, but (it cannot be explained with the whole results since the solvent is not the same) in a different solvent, Table VII.

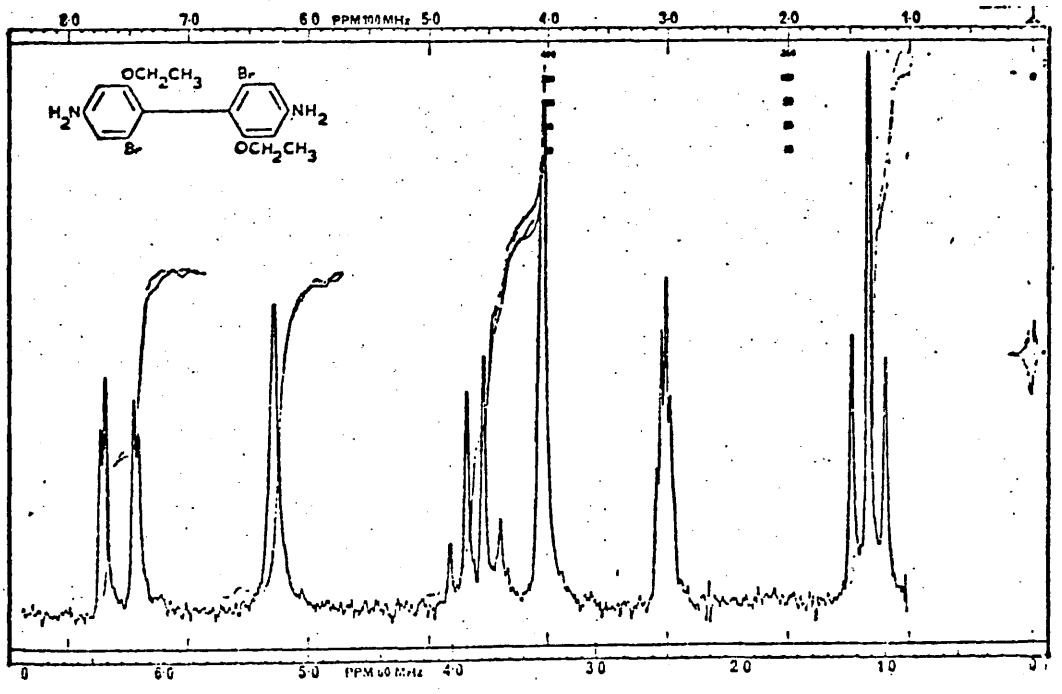
c- In neat D_2SO_4

Amino protons of all the benzidines studied, except octachloro-benzidine and 3,5,3',5'-tetrabromo- m- tolidine, suffered a downfield shift in neat D_2SO_4 in the range 0.11-1.20 p.p.m., Tables IV - VII. The only two compounds in which the amino protons were completely deuterated are 2,2'-dichloro- and octafluoro-benzidine as shown by the disappearance of the amino absorption signal.

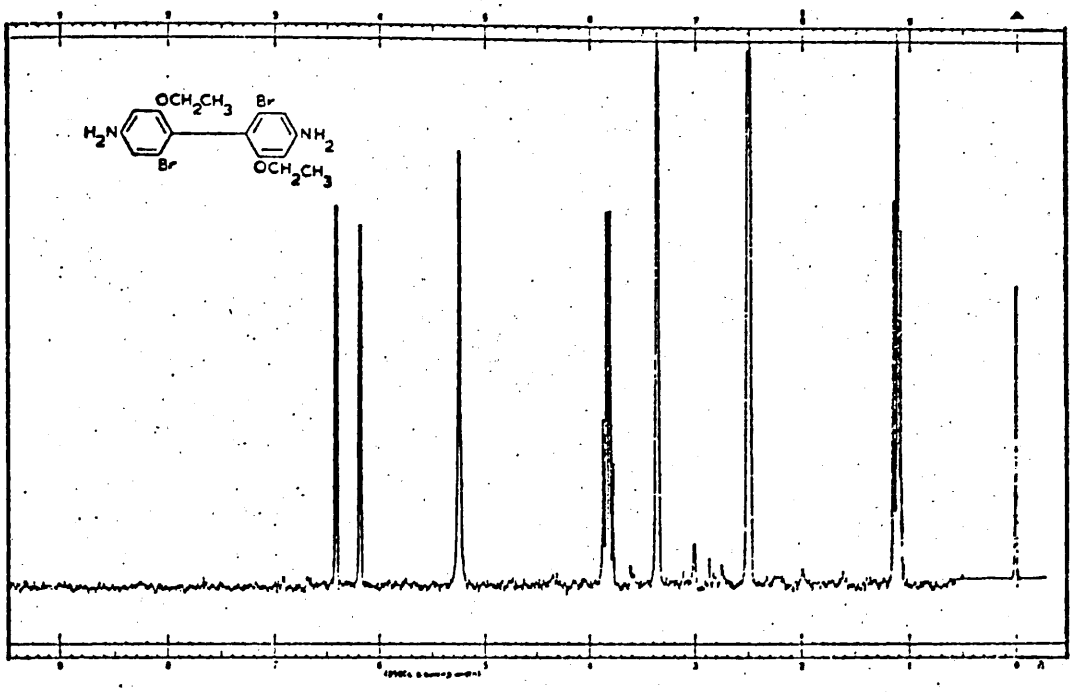
Studying the tables IV - VII showed that in some cases, the more substitution in the 2,6,2',6'-positions of the benzidine molecule, the greater



Spectrum No.22. ^1H N.m.r. spectrum, sweep width 500 H_z



Spectrum No.23. ^1H N.m.r. spectrum, sweep width 500 H_z in DMSO.



Spectrum No. 24 ^{1}H N.m.r. spectrum (220 MH_z), sweep width 2500, in DMSO

the downfield shift brought about by this solvent. However, there are a number of exceptions such as octachlorobenzidine and 2,2'-dimethylbenzidine.

2- Aromatic protons

a- In $CDCl_3$:

Aromatic protons of the benzidine molecule absorb in the region 6.62-7.40 p.p.m., Table IV. Some alkylated benzidines show only a small difference in range owing to the small effect exerted by the alkyl groups on the chemical shifts of the aromatic protons, 6.47-7.35 p.p.m., Table IV.

Ring protons of halogenated benzidines absorb in nearly the same region as alkyl-benzidines, 6.47-7.30 p.p.m., Tables V and VI. Benzidines substituted with the strongly electron-releasing OEt group, Table VII, absorb at comparatively higher field, 6.18-6.80 p.p.m.

b- In $CDCl_3$ + 3 drops of TFA:

Ring protons of some alkylated benzidines suffered a downfield shift on treatment of their samples in $CDCl_3$ with a few drops of TFA in the range 0.00-0.45 p.p.m., Table IV. No significant effect of TFA on the alkyl protons absorptions was detected, spectra No.17 and 18. In halogeno-substituted benzidines (chloro- and bromo-), a downfield shift of the aromatic protons absorptions was observed in the range 0.02-0.85 p.p.m., Tables V and VI.

A downfield shift in the aromatic protons signals of different substituted benzidines was observed in the range of 0.55-0.60 p.p.m., Table VII.

c- In neat D_2SO_4:

Upon dissolving the alkyl-benzidines in D_2SO_4, their aromatic proton were brought downfield in the range 0.99-1.29 p.p.m., Table IV. Chloro- and bromobenzidines showed a relatively larger downfield shift, 1.00-1.59 p.p.m., Tables V and VI. Substituted benzidines in Table VII, showed comparatively smaller downfield shifts with respect to their aromatic protons.

In almost all cases, the amino protons signal was found to appear even after the addition of TFA or D_2SO_4 to the chloroform solution of the benzidines. Moreover, no distinct signal for the ammonium group ($Ar-NH_3^+$) was observed, although it was reported that this group absorbs in the region 8.5-9.5 p.p.m.[36] This could be referred to the incomplete protonation of the amino group by the low concentration of TFA. Furthermore, a sharpening of the broad singlet of the amino protons was observed after treatment of the chloroform solution of the benzidine with TFA, spectra No.17 and 18. A reasonable explanation is that, it is due to the reduction of the rate of intermolecular exchange of the amino protons caused by the formation of the ammonium ion.

Aromatic protons of all the benzidines studied suffered a downfield shift of about 1.0-1.6 p.p.m. when dissolved in D_2SO_4, as well as the amino protons went downfield by about 0.17-1.2 p.p.m. Moreover, it was found that the downfield shift of the aromatic protons is inversely proportional to the number and size of the substituents ortho to the amino group.

General discussion

The surprising observation in this work, is the downfield shift of the amino protons in ortho-substituted benzidines with respect to the amino group, which is entirely different from that of Yonemoto and co-workers[40], for the ortho-sterically hindered anilines in cyclohexane. They observed an upfield shift of the amino protons and attributed this shift to the fact that less charge was delocalized from the amino group into the aromatic nucleus. The only explanation for this difference lies in the use of two different solvents. This downfield shift might be attributed to the steric effects which lower the protonation of the amino group by D_2SO_4, causing overlapping of the van der Waals radii of the substituents with that of the amino group and to the fact that the ammonium cation ($Ar\text{-}NH_3^+$) will exert an inductive effect on the benzene ring and therefore lower the electron density of the system, since it has been observed that the deshielding effect of a protonated nitrogen atom can be transmitted through several bonds in a conjugated system.[43]

Isobe and his co-workers[41] observed that by successive addition of the acid to the base, the total spread of the signals of the ring protons decreased gradually, and coalesced into a single signal when 60-80 mole percent was present. This observation was noticed to a lesser extent throughout this work when benzidines were treated with a few drops of TFA in $CDCl_3$ or dissolved in neat D_2SO_4, where the number of absorptions was reduced as well as the splitting disappearing, spectra No.17 and 18. This could be explained as follows:- When the acid is added to the base, the amine molecule is converted into the ammonium ion accompanied by the fast proton exchange reaction, thus the electronic configuration of the tetravalent nitrogen in the ammonium ion turns into a closed-shell one, and is incapable of sharing another pair of electrons, with the result that

the charge densities at the positions in the ring become nearly uniform[41]. The positive charge in the nitrogen, however, must retain a power to withdraw electron from its vicinal atoms. Thus the coalesced line of phenyl proton signals lies in a lower field than that of the benzene.

Attempting to correlate the degree of protonation of the benzidines studied with their basic strengths, it is important to point out that substitution in the benzidine nucleus controls to a certain extent the basic strength of the molecule either by inductive or mesomeric effect, assuming that no steric effect ortho to the amino group is operating. Electron-donating groups will result in more delocalization of charge within the ring, a lower electron-contribution from the amino group, and hence more electron availability on the nitrogen atom, i.e. greater basic strength than in the unsubstituted benzidine molecule to be expected, while electron-withdrawing groups result in an opposite sequence. Moreover, the information available throughout this work, simply by measuring the integral area of the remaining amino protons signal after acidification, agreed with the above theoretical estimations, assuming that both steric and inductive or mesomeric effects are operating at the same time.

Considering the benzidine molecule as a substituted biphenyl system, the steric effect of the substituents might exert a significant effect on the entire system in two different ways:

a- Effect of substituents ortho to the amino group.

b- Effect of substituents ortho to the biphenyl linkage on the dihedral angle between the two benzene rings.

The effect of the substituent ortho to the amino group, whether it is an electron-donating or electron-withdrawing on the degree of protonation is mainly due to steric factors and results in hindering the protonation process. The effect (b) is of great importance (Page 33). Since the benzene rings in the biphenyl system would have a maximum energy when the dihedral angle approaches to a minimum value, then the more substituents in the 2,6,2',6'- positions, the less conjugation between the two benzene rings and more deshielding effect of one ring by the other. This will cause a decreased delocalization of the π-electrons between the two benzene rings and consequently more electron density on the amino group, i.e. more basic strength and more upfield absorption for the aromatic protons and amino protons.

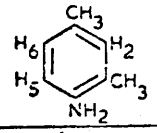
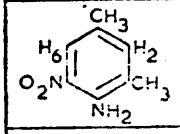
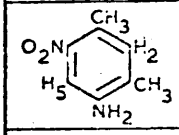
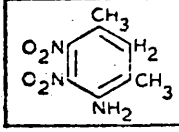
Steric interactions of biphenyl system have been studied by Brownstein[227] and by Hoffmann and co-workers.[228] They observed that some of the absorption bands in the 2-halobiphenyl hydrogen resonance spectra are at higher field than those of the parent biphenyl molecule and this was interpreted in terms of steric interactions between the halogen atom and the ortho-hydrogen atoms of the unsubstituted ring.

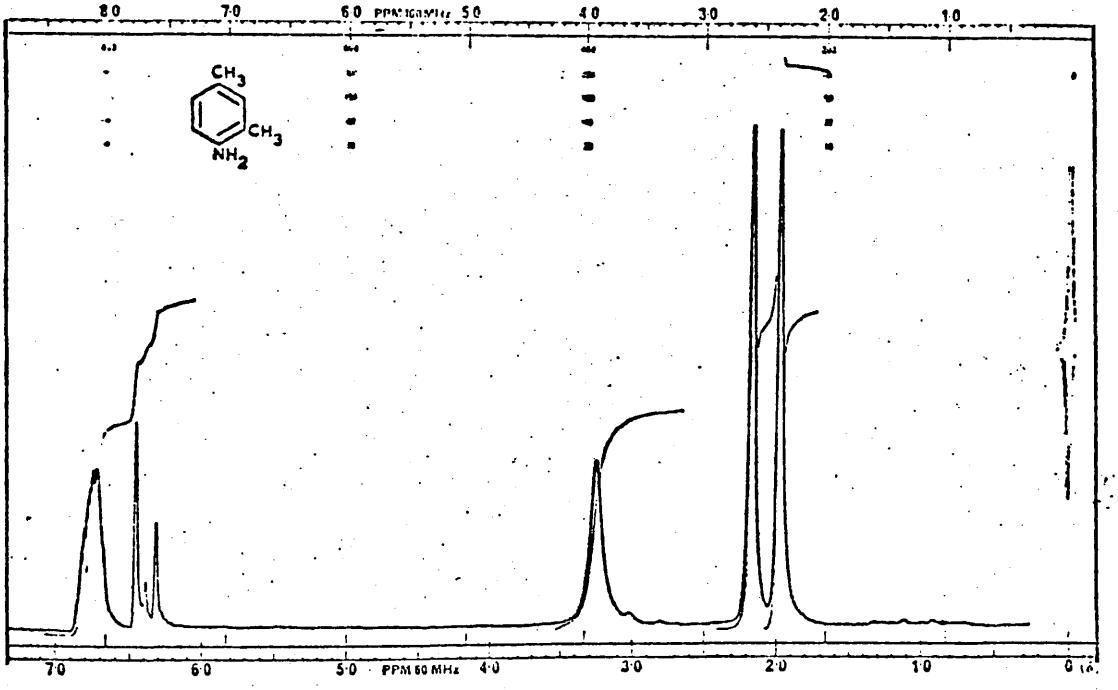
^{1}H N.m.r. Studies of some nitro-m-xylidines

Different nitro-substituted m-xylidines were prepared during this work in order to study their nuclear magnetic resonance properties in neutral and acidic media. The chemical shifts of the aromatic protons and the amino protons of the xylidines under investigation were measured on 60 MHz scale, then arranged in table VIII.

By studying the data in table VIII, the following conclusions were reached:

Table VIII. Chemical shifts of some m-xylidines in p.p.m., (S) singlet

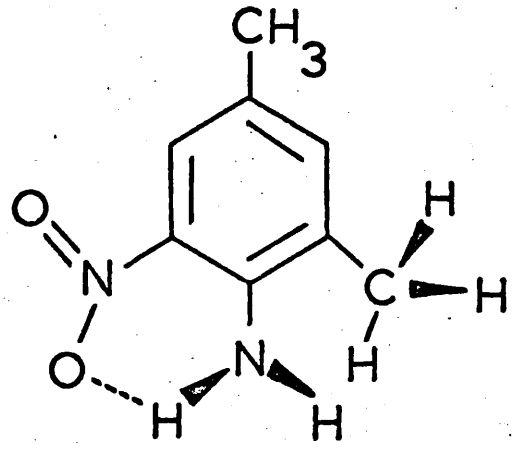
COMPOUND	OBSERVED CHEM. SHIFT IN $CDCl_3$			CALC. CHEM. SHIFT		OBSERVED CHEM. SHIFT IN $CDCl_3$ + 3 DROPS OF TFA	
	AROMATIC PROTONS		NH_2 GROUP	AROMATIC PROTONS		AROMATIC PROTONS	
	6.32 6.47 6.73	H_5 H_6 H_2	3.25 S	6.34 6.68 6.69	H_5 H_6 H_2	6.36 6.52 6.76	H_5 H_6 H_2
	7.07 7.76	H_2 H_6	5.99 S	7.02 7.63	H_2 H_6	7.18 7.78	H_2 H_6
	6.93 7.30	H_2 H_5	3.75 S	6.86 7.29	H_2 H_5	6.99 7.33	H_2 H_5
	7.17	H_2	5.95 S	7.19	H_2	7.20	H_2



Spectrum No.25. ^1H N.m.r. spectrum, sweep width 500 H_z

1- The aromatic protons absorption of the unsubstituted m-xylidine appear as three separate singlets at δ 6.32, 6.47 and 6.73 p.p.m. Moreover, amino protons signal was observed as a broad singlet at δ 3.25, spectrum No.25.

* **In addition, part of this large downfield shift may also be attributed to the hydrogen bonding between the O-nitro group and the amino protons which cause them to absorb further downfield. This explanation could be applied to case (4).**



the nitro group on the amino group. However, only the deshielding effect of the nitro group is operating.

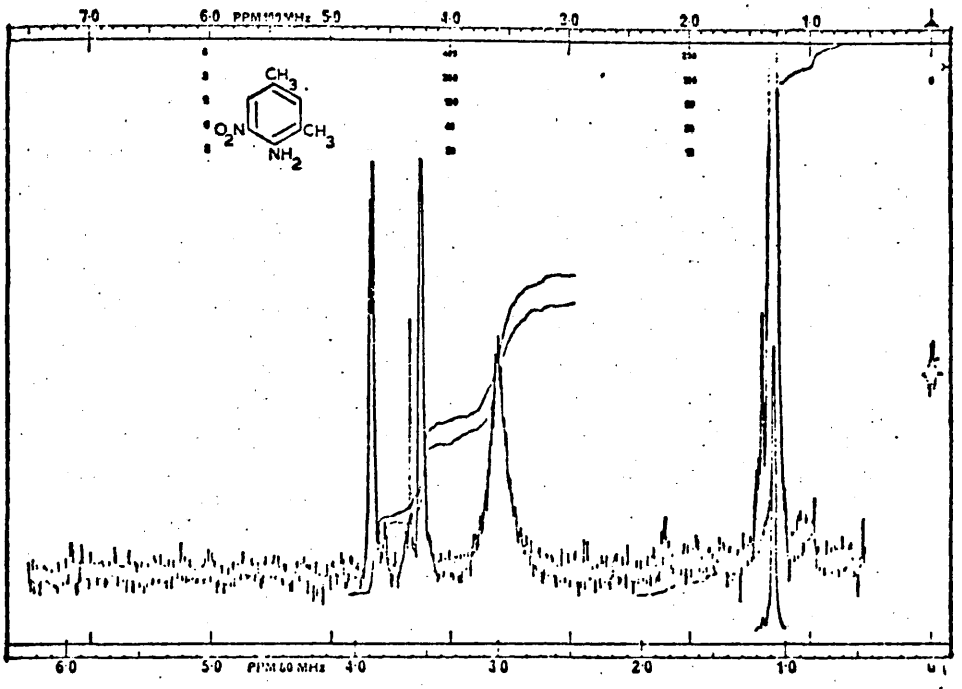
4- Amino protons of 5,6-dinitro-m-xylidine appear, as expected, relative downfield (δ = 5.95) because of the presence of nitro group ortho to the amino group, i.e. similar to (2), Spectrum No.28. Aromatic proton absorbs as a singlet at 7.17 p.p.m.

1- The aromatic protons absorption of the unsubstituted m-xylidine appear as three separate singlets at δ 6.32, 6.47 and 6.73 p.p.m. Moreover, amino protons signal was observed as a broad singlet at δ 3.25, spectrum No.25.

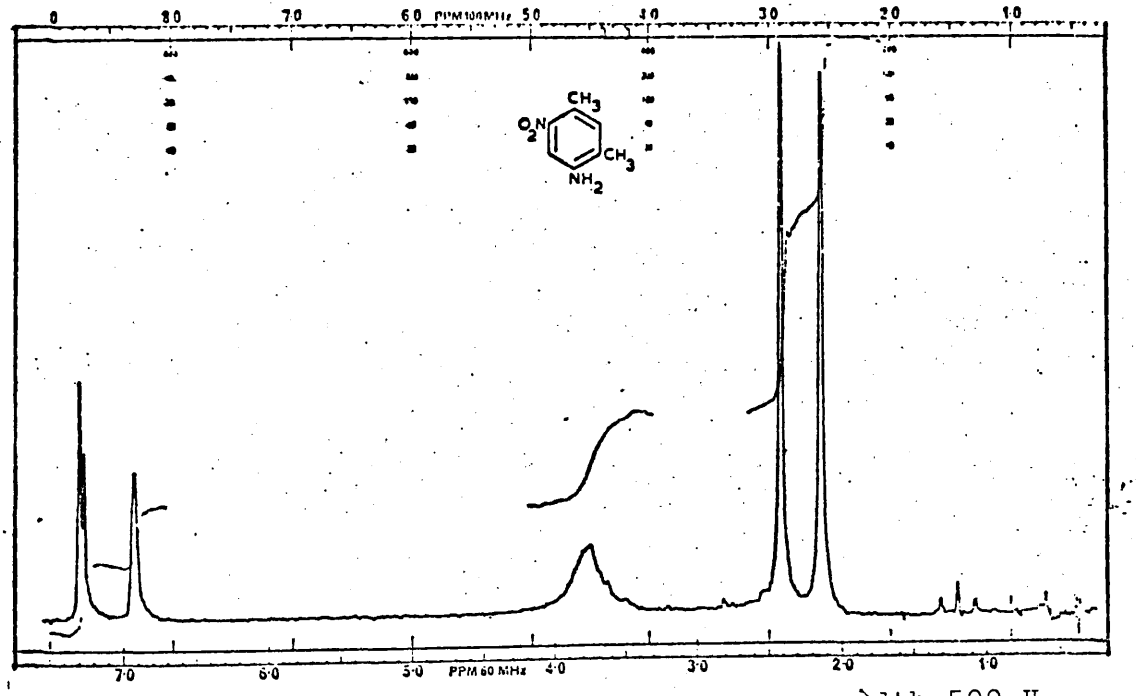
2- Introduction of a nitro group in the 5-position (o-) to the amino group causes a great downfield shift of the amino protons (δ = 5.99). The aromatic protons also deshielded and absorb at 7.07-7.76 p.p.m. as two singlets. This shift is reasonably attributed to the steric effect (as well as to the deshielding effect) of the ortho-nitro group which prevents the amino group being coplanar with the ring and being in resonance with the π- electrons, which results in more charge density being available on the nitrogen atom and therefore, the amino group signal appearing further downfield, Spectrum No.26.*

3- Amino protons of 6-nitro-m-xylidine absorb at higher field (δ = 3.75) relative to those of 5-nitro-m-xylidine, Spectrum No.27. Aromatic protons appear as two singlets at 6.93 and 7.30 p.p.m. This is mainly due to the absence of any steric effect exerted by the nitro group on the amino group. However, only the deshielding effect of the nitro group is operating.

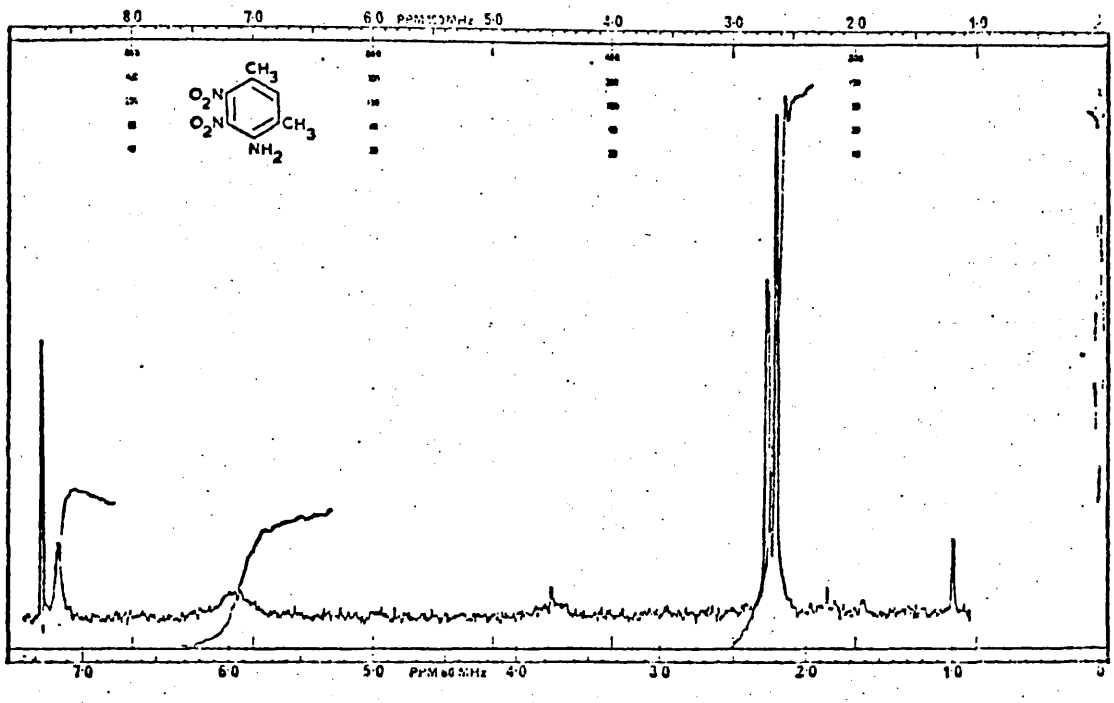
4- Amino protons of 5,6-dinitro-m-xylidine appear, as expected, relative downfield (δ = 5.95) because of the presence of nitro group ortho to the amino group, i.e. similar to (2), Spectrum No.28. Aromatic proton absorbs as a singlet at 7.17 p.p.m.



Spectrum No.26. 'H N.m.r. spectrum, sweep width 1000 H_z



Spectrum No.27. 'H N.m.r. spectrum, sweep width 500 H_z



Spectrum No.28. ^1H N.m.r. spectrum, sweep width 500 H_z.

On treating the chloroform solution of these xylidines with a few drops of TFA, no significant downfield shift was observed as compared with benzidines. Moreover, the observed chemical shifts were found to be in good agreement with the calculated chemical shifts, using the values of the substituents effects given by Jackman and Sternhell.[37]

Attempted optical resolution and optical activation of substituted benzidines :

a - 2,2'-Di-t-butylbenzidine

The attempted resolution of 2,2'-di-t-butylbenzidine into optically active forms was unsuccessful. Treatment of the benzidine with (+) - tartaric acid or with (+) - camphor-sulphonic acid failed to give stable salts. This was due to the difficulties in the isolation of the salt which was obtained as a thick oily substance. Attempts were therefore made to resolve this benzidine using (-) - menthoxyacetyl chloride; the resulting bis-acetyl derivative had m.p. 134-135°, $[\alpha]_{578}^{18}$ - 29.2°; $[\alpha]_{546}^{18}$ - 34.1°; $[\alpha]_{436}^{18}$ - 53.1° in chloroform. No other form could be obtained from the mother-liquor, and the following methods were applied to decompose the acetyl derivative but without success.

1 - Prolonged reflux in acetic acid - hydrochloric acid mixture.

2 - Prolonged reflux in concentrated sulphuric acid.

3 - Prolonged reflux in 20% HBr in alcoholic solution.

4 - Prolonged reflux in 25% NaOH solution.

b - 2,2'-Dibromo-6,6'-diethoxybenzidine

Attempts were made to resolve this benzidine into optically active forms through the (+) - camphorsulphonate salt, since it failed to resolve through the tartrate salt. Only one optical diastereoisomer could be obtained through the resolution process, as a light-brown crystalline substance, m.p. 309-310°, $[\alpha]_{578}^{24}$ + 20.1°; $[\alpha]_{546}^{24}$ + 23.6°; $[\alpha]_{436}^{24}$ + 53.3° in dimethylformamide. The evaporation of the mother-liquor gave the same optical form with nearly the same rotation, m.p. 309-310°, $[\alpha]_{578}^{24}$ + 20.5°; $[\alpha]_{546}^{24}$ + 25.1°; $[\alpha]_{436}^{24}$ + 56.2° in dimethylformamide.

The failure to isolate the two diastereoisomers from the solvent is attributed to an equilibrium process called epimerization. The epimerization process itself involves an equilibrium but since one diastereoisomer is continuously removed from the solution by filtration or mechanical separation, the equilibrium between the diastereoisomers is continuously disturbed and eventually the entire material is converted to the less soluble form. This combination of epimerization and precipitation is known as "second-order asymmetric transformation".

In the case (b), presumably the (+) - camphorsulphonate of one of the two enantiomers (Fig. 3) is more stable than that of the other, and the original mixture of equal parts of the (+) biphenyl (+) camphorsulphonate and (-) biphenyl (+) camphorsulphonate is equilibrated by passing the low energy barrier (planar form of the biphenyl) to a mixture containing one of the diastereoisomers in excess. Liberation of the free benzidine into active form was achieved through the alkaline hydrolysis of the salt as tiny needles, m.p. 217-218°, $[\alpha]_{578}^{15}$ - 2.65°, $[\alpha]_{546}^{15}$ - 5.33° ; $[\alpha]_{425}^{15}$ - 9.85° in acetone.

It is clear that this molecule is not planar but rather that the compound exists as a mixture of enantiomers which are interconverted readily by passage over a relatively low energy barrier.

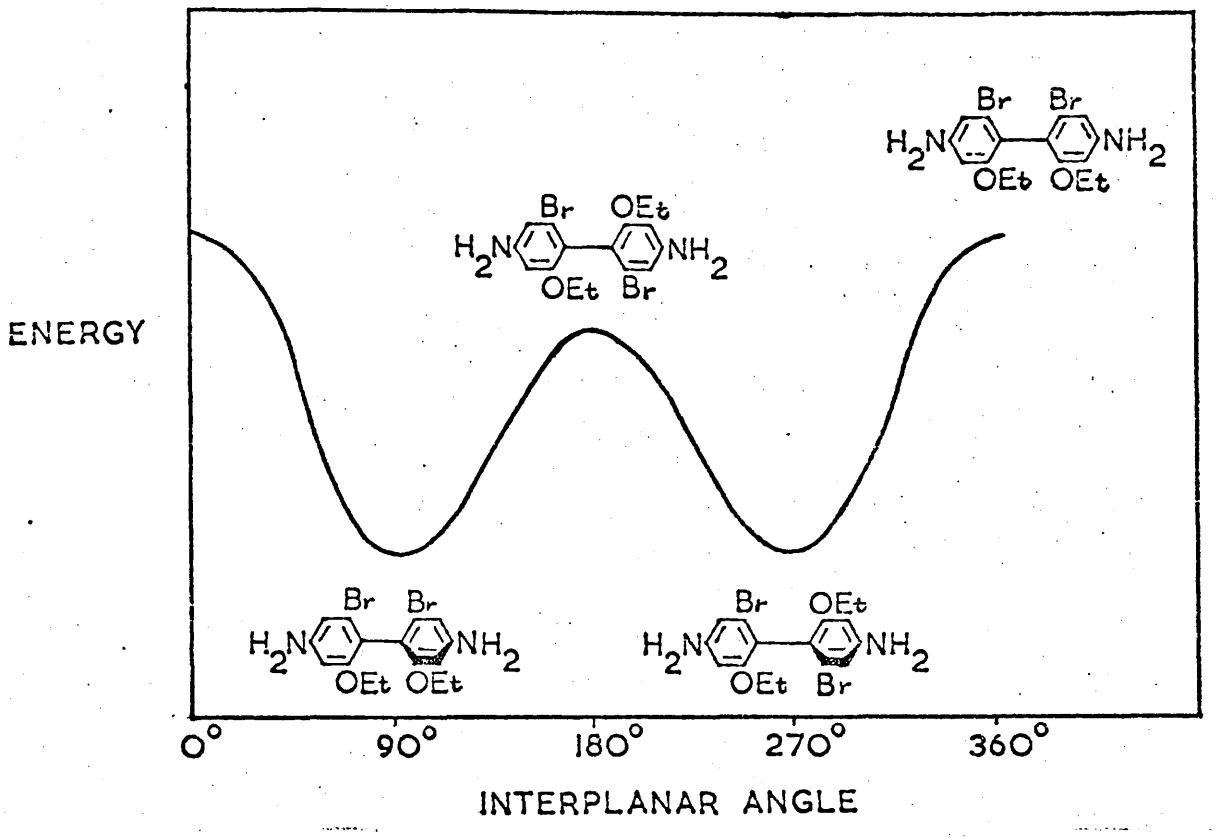
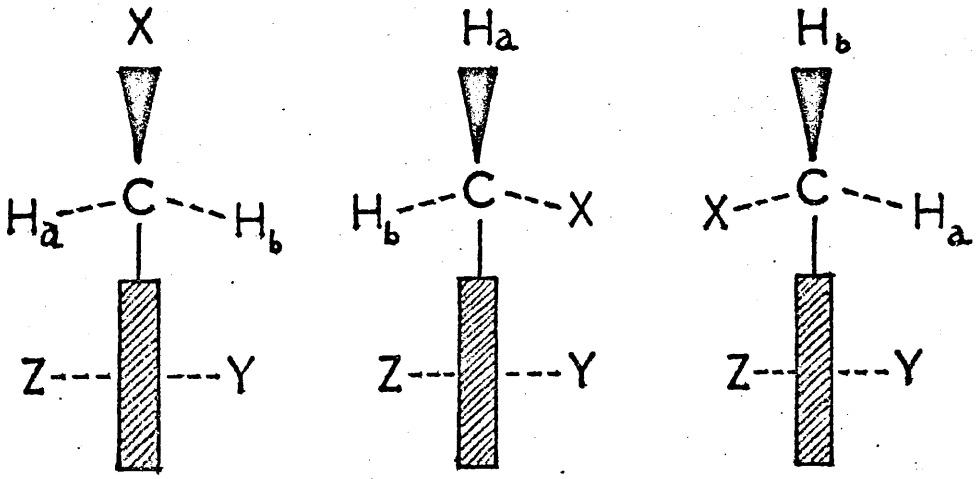


Fig. 3. Energy profile for 2,2'-dibromo-6,6'-diethoxybenzidine

High resolution n.m.r. studies of 2,2'-dibromo-6,6'-diethoxy-benzidine:

As a consequence of the steric requirements of O- substituents, the two aromatic rings of an O-substituted biphenyl are not coplanar. An O-substituent on one ring thus is located above the plane of the second, and if the second ring holds two different O- or m- groups, the substituent on the first ring is in an asymmetric environment. If that substituent contains a methylene group, its two protons are not necessarily magnetically equivalent (two diastereotopic hydrogens) even though the substituent rotates about the phenyl-substituent bond, for the conformers of the substituent about that bond (e.g. I_a-I_c) will not necessarily be equally populated and the environments of the two protons are different in each conformer[229].



I_a I_b I_c

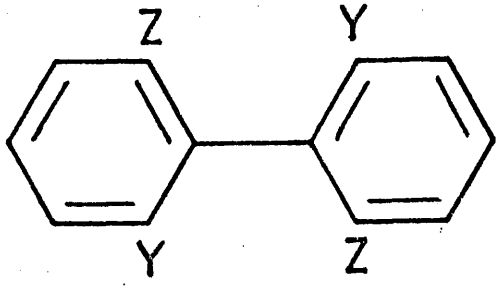
Non-equivalence of this type can only be observed provided rotation about the biphenyl bond is sufficiently slow, for such a rotation through 180° serves to exchange the environments of the two methylene protons. When

such rotational exchange is rapid compared to the chemical shift difference between both methylene protons, the same average environment is observed for both protons by n.m.r. technique, producing a single line (A_2) spectrum.

In particular, although the two CH_2 protons in many cases are diastereotopic, the non-equivalence is too small to be measured and an apparent A_2 spin system is observed[230]. This result might have been anticipated since the difference between the averaged environments of the two CH_2 protons is certain to be minute.[231] At lower temperatures, however, when the exchange is slow, the methylene proton absorptions are characteristics of the AB parts of ABC_3 spectra rather than the simple quartet which would be expected from A_2X_3 (or A_2B_3systems with chemical shifts and coupling constants of the order of magnitude usually found in the ethoxy group).[232]

In fact, the non-equivalence in many cases is not large enough to be measured, so an increased magnetic field results in observable non-equivalence. Moreover, it has been emphasized that conformational changes cannot be a significant factor[233].

The first example of such non-equivalence which results from biphenyl asymmetry was reported by Meyer and Meyer[229], although the corresponding phenomenon when the asymmetric environments is provided by a tetrahedral carbon holding three dissimilar groups is well known[230, 234].



II

II_a Y= CH_2OH ; Z= C_2H_5

II_b Y= CO_2CH_3; Z= C_2H_5

II_c Y= CH_2OCOCH_3; Z=H

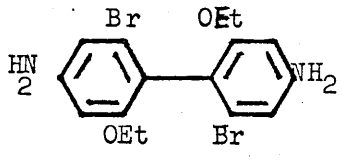
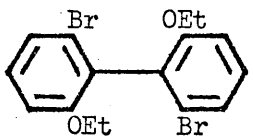
II_d Y= CH_2OH ; Z= CH_3

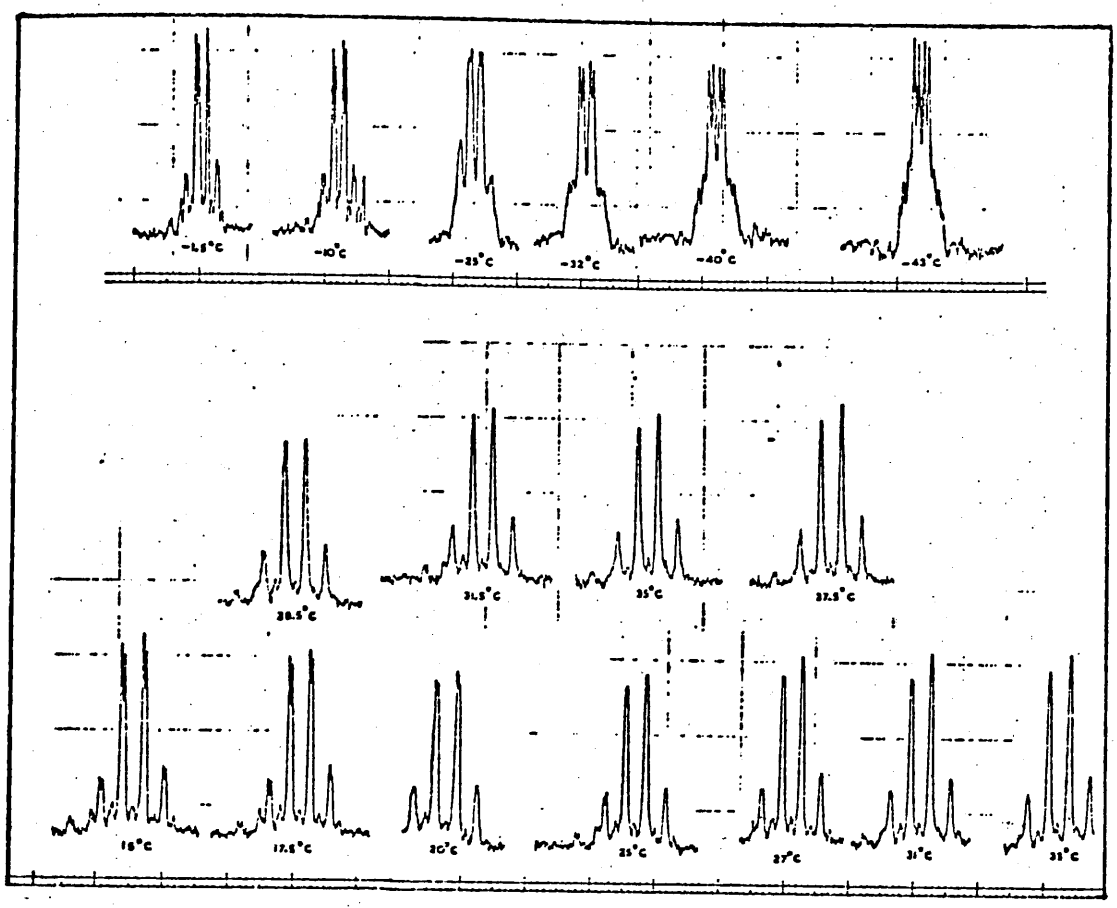
II_e Y= CH_2OH ; Z= CD_3

The biphenyls II_a-II_e were studied and their spectra were analyzed in order to observe the non-equivalence of the methylene protons which appear as an AB quartet at about 4.0-4.15 ppm. with coupling constant of 11.6-12.6 cps[229]. Other aromatic compounds containing non-equivalent methylene protons have been also studied such as ethyl-4-t-butylpipecolate[235] (δ = 4.15; J_{AB} = 11 cps) and several 10-carbethoxy-1,1-dimethyl decalins[232] (δ = 4.0-4.22; J_{AB} = 10.8-11.1 cps).

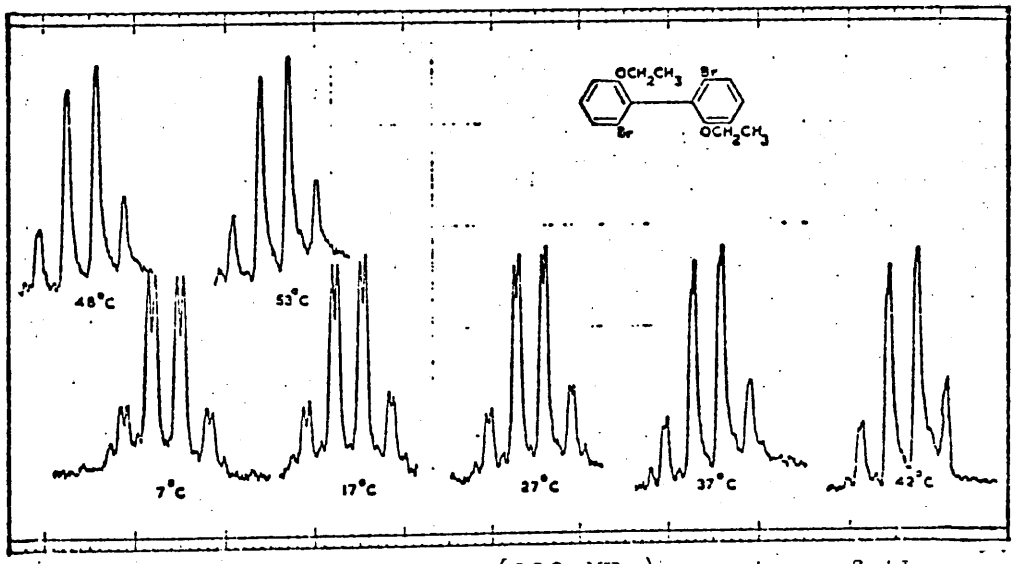
In the present work, 2,2'-dibromo-6,6'-diethoxybenzidine and its corresponding biphenyl were studied by high resolution n.m.r. (220 MHz) and at different temperatures in order to observe the non-equivalent methylene protons of the ethoxy group and to estimate approximately the coalescence temperatures of these compounds, spectra No.29 and 30.

Table IX: Chemical shifts and coalescence temperatures of 2,2'-dibromo-6,6'-diethoxybenzidine and the corresponding biphenyl.

Compound	δ_{CH_2} P.P.M.	$\Delta\nu_{AB}$	Coalescence temp. ^oC	Solvent
	3.91-4.00 (q)	1	30	acetone-d_6
	4.07-4.17 (q)	1	50	acetone-d_6



Spectrum No.29. ^1H N.m.r. (220 MH_z) spectra of the methylene protons of 2,2'-dibromo-6,6'-diethoxybenzidine at different temperatures (acetone-d_6).



Spectrum No.30. ^1H N.m.r. (220 MH_z) spectra of the methylene protons of 2,2'-dibromo-6,6'-diethoxybiphenyl at different temperatures (acetone-d_6).

Binsch,[236] has mentioned an approximate equation for calculating the coalescence temperature by measuring the $\Delta\nu$ from the spectrum. However this equation may give rise to an enormous error.

$$K_{coal.} = \pi\Delta\nu/\sqrt{2}$$

Indeed while the $-OCH_2$ resonance of all the compounds studied is of the typical methylene pattern at relatively high temperatures, a splitting of each signal into two peaks was clearly observed at lower temperatures as shown in the high resolution n.m.r. spectra of these compounds, spectra No.29 and 30. It seems reasonable that these ethoxy groups are attached to asymmetric structures and the magnetic non-equivalence thus arises from the location of the methylene group in an asymmetric environment.

From table IX, it is clear now that the failure of resolving the optically active forms of the 2,2'-dibromo-6,6'-diethoxybenzidine is mainly due to the low coalescence temperature at which the two enantiomers are interconverting into one another. Moreover, the corresponding biphenyl seems to be more stable than the benzidine, which is attributed to the low energy barrier of the benzidine compared to that of the biphenyl.

Thus the high resolution n.m.r. technique provides a means of studying the process by which an optically active biphenyl would be racemized, without requiring a resolved sample. Further it is applicable to systems, such as the 0,0'-disubstituted biphenyls mentioned before, which are difficult to study by the polarimetric method because their half-lives are too short to permit any optical resolution.

In general, only when barriers to interconversion are above about 18-20 KCal/mole are stereoisomers stable enough for isolation. For detection by n.m.r., barriers of about 10 KCal/mole are sufficient and even lower barriers are detectable in some instances[237].

Magnetic non-equivalence phenomenon was later observed by Snyder and his co-workers[238-240] in substituted ethanes and in some simple acyclic systems[233] through the study of the solvent effect on the chemical shifts and coupling constants of these compounds. However, they concluded that their data demonstrate a small, but real, solvent dependence of the coupling constants.

The high resolution n.m.r. (220 MHz) and temperature-variable n.m.r. spectra which were run by P.C.M.U., at Harwell, Berks., are gratefully acknowledged.

Preparation of the Schiff's bases

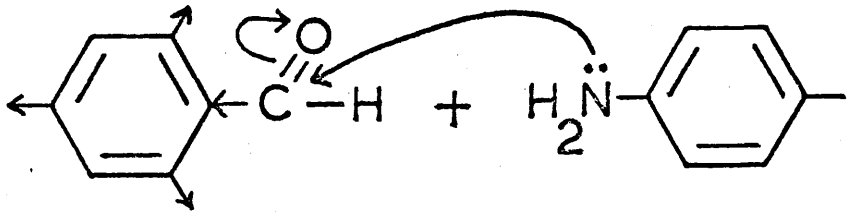
Two factors can be involved in considering the substituent effect on the yield of Schiff's bases derived from benzidines and aromatic aldehydes:

a- Steric effect.

b- Electronic effect.

As shown in table X, the depression in the yield of Schiff's bases due to steric factors was obvious, and the extent of depression depends on the position of the substituent in relation to the reaction centre and on the size of the substituent.

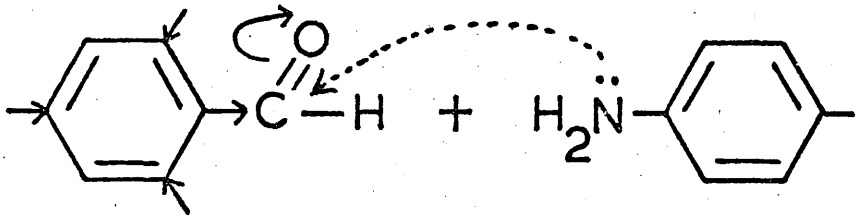
If the percent yield of the Schiff's base derived from benzidine and benzaldehyde is taken as a standard, since there are no steric and electronic effects operating, it was found that ortho substitution in the aldehyde nucleus results in decreasing the yield sterically, e.g. O-bromobenzaldehyde. At the same time, if the substituent is an electron-withdrawing group, it increases the yield by decreasing the electron density on the carbonyl group which becomes a strong electrophile, and consequently facilitates the reaction (condensation) by the attack of the lone pair of electrons on the nitrogen atom of the amino group, e.g. O-nitro-benzaldehyde.



On comparing the yield of O-nitro- and P-nitro-benzaldehyde with benzidine in order to estimate the

steric effect, it seems that the overall effect (steric and electronic) in the former is 2% while no effect could be detected in the latter. Moreover, introduction of two nitro groups in the ortho positions of the benzaldehyde decreases sharply the yield by 23%, and introduction of one bromine atom decreases it by 14%. This could be mainly attributed to the steric factor which plays an important role in hindering the reaction, although facilitating it electronically.

In the cases where there are electron-donating groups in the benzaldehyde nucleus, if they occupy the position ortho to the aldehyde group, they definitely hinder the reaction; further they will result in an increase in the electron density on the carbonyl group which eventually becomes a weak electrophile to the attacking by the lone pair of electrons of the amino group. The yield is therefore further reduced.



There is no large depression in the yield of the Schiff's base derived from 2,4,6-trimethylbenzaldehyde and benzidine (15%), which demonstrates a relatively small steric effect of the two methyl groups as well as a small electronic effect. As expected, the reaction of 3,4,5- and 2,4,6-trimethoxybenzaldehyde with benzidine cause less depression in the yield than that of the trimethyl analogues, i.e. 6% and 10%

respectively. In the case of 2,4,6-trimethoxy compound, this can be ascribed to the smaller size of the methoxy group relative to that of the methyl group.

The substitution in the benzidine nucleus could be regarded the same as for the aldehyde from the steric point of view, decreasing the yield if the substituent is in the ortho position to the amino group. However, electronically, electron-withdrawing groups result in decreasing the reaction rate while electron-releasing groups accelerate it, taking into consideration the resonance of the nitrogen electrons with the benzene ring which results in decreasing the availability of the charge on amino group and decreasing the reaction rate as well.

Generally, accurate estimation of the percent yield is a difficult target and could not be achieved easily and accurately, so all reported results may be considered as approximate values, taking into consideration the solubility problem of some reactants and products, the small scale of the preparation and the mechanical loss during filtration and collection which can be considered as a constant. It is important to point out that all Schiff's bases were prepared under nearly the same conditions.

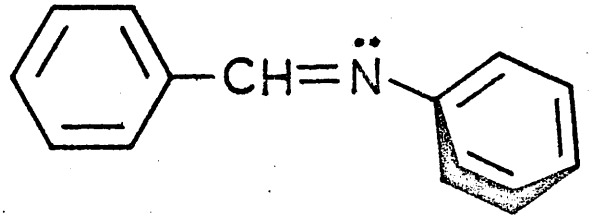
^{1}H N.m.r. spectra of Schiff's bases

The n.m.r. spectra of the Schiff's bases prepared throughout this work were measured in $CDCl_3$ solution on a Varian HA 60 MHz spectrometer using TMS as the lock signal. The results are shown in tables XI, XII and XIII.

a- Azomethine proton (-CH=N)

The azomethine proton signal appeared as a sharp singlet in the range 8.31-9.03 p.p.m. The effect of the substituent in the aldehyde component on the chemical shift of the azomethine proton is greater than that of the substituent in the benzidine component, Table XI.

Due to the rotation of the aniline ring of the Schiff's base from the plane of the remaining molecule, the substituent effect in the benzidine ring appears to be considerably smaller and consequently the substituent cannot exert any appreciable electronic effect upon the azomethine group. This can be reasonably understood by accepting the previous non-planar structure for the anil molecule in which an aniline ring cannot conjugate with a benzal-amino π-system (Page 50).

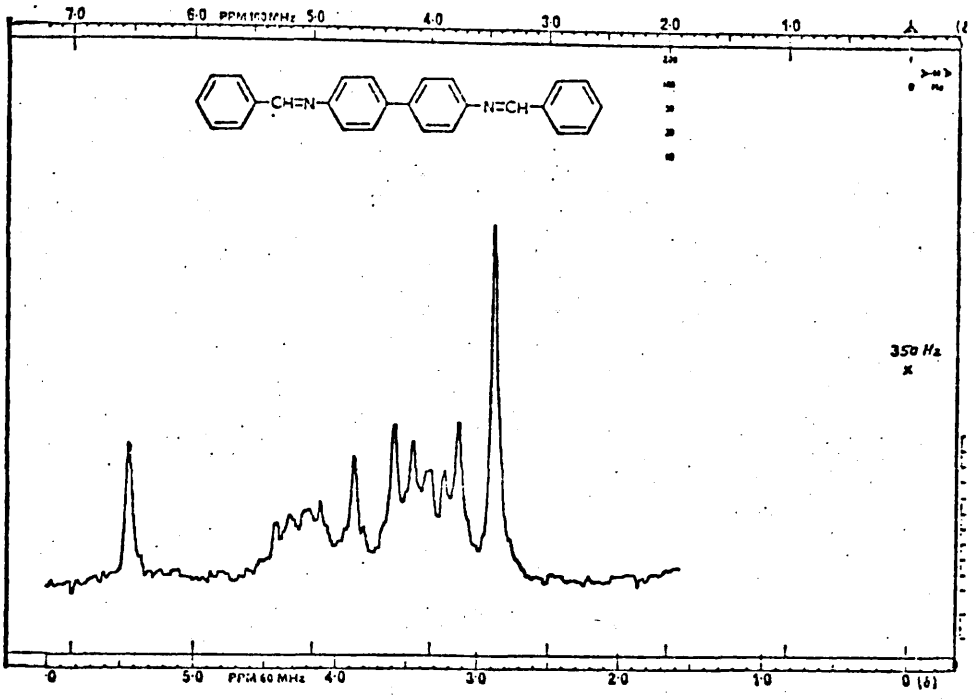


From Table XI, it is clear that the azomethine proton signal is not much affected by the different substituents in the benzidine component, while it is greatly affected by varying the substituents in the benzaldehyde component.

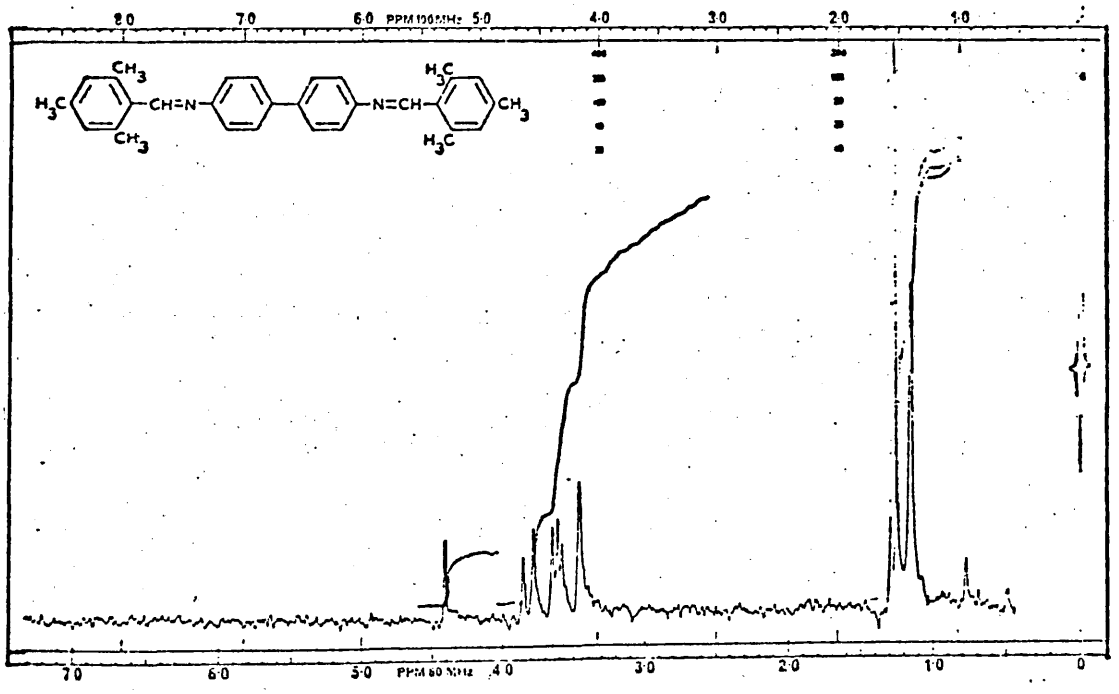
The azomethine proton signal of the Schiff's base derived from benzaldehyde and benzidine appears at 8.55 p.p.m., spectrum No.31. Introduction of an electron-releasing group in the 2,4,6-positions of the benzaldehyde ring causes a large downfield shift of the azomethine proton signal, 8.83-8.87 p.p.m., spectra No.32-34, while leaving the O- positions unsubstituted (e.g. 3,4,5- trimethoxy) cause an upfield shift of the proton signal, 8.42 p.p.m., spectrum No.35. Moreover, introduction of an electron-withdrawing group decreases the electron density at the CH=N group and, therefore, causes a significant deshielding of the proton signal to a lower field, 8.61-9.03 p.p.m., spectra No.36-43.

Studying the above results, Table XI, showed that O-substituents in the aldehyde ring have a marked deshielding effect even when they are electron releasing (cf. 2,4,6- and 3,4,5- trimethoxy). Larger downfield shift with O-nitro, 9.03 p.p.m., compared to the P-nitro, 8.61 p.p.m., indicates very clearly that only the steric effect is responsible for this deshielding despite the nature and polarity of the substituent.

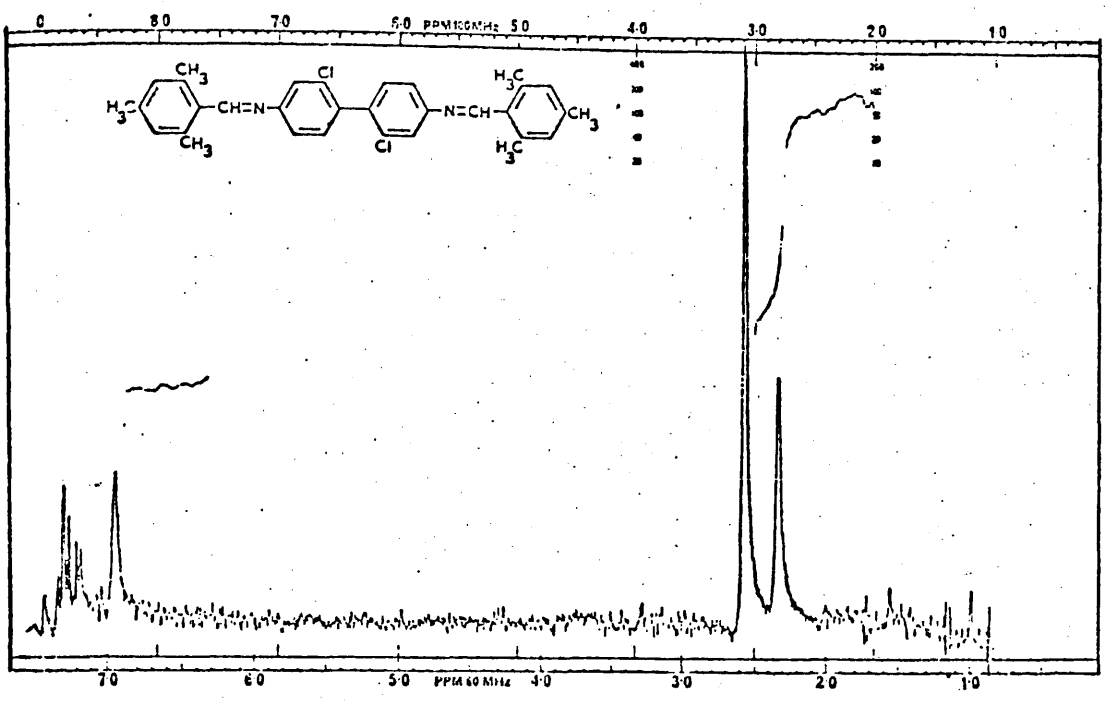
Bürgi and Dunitz[179] found that the aldehyde ring in azomethines is twisted out of the CH=N-C plane by only a small amount (10° in benzylideneaniline). This angle is insufficient to affect conjugation and, if it is maintained in the presence of small O-substituents, will leave the azomethine proton within the deshielding influence of the substituent. With the large spherically symmetrical substituents bromine and methyl, rotation of the CH=N group is to be expected and the observed downfield shifts in compounds with O-bromo and O-methyl can be



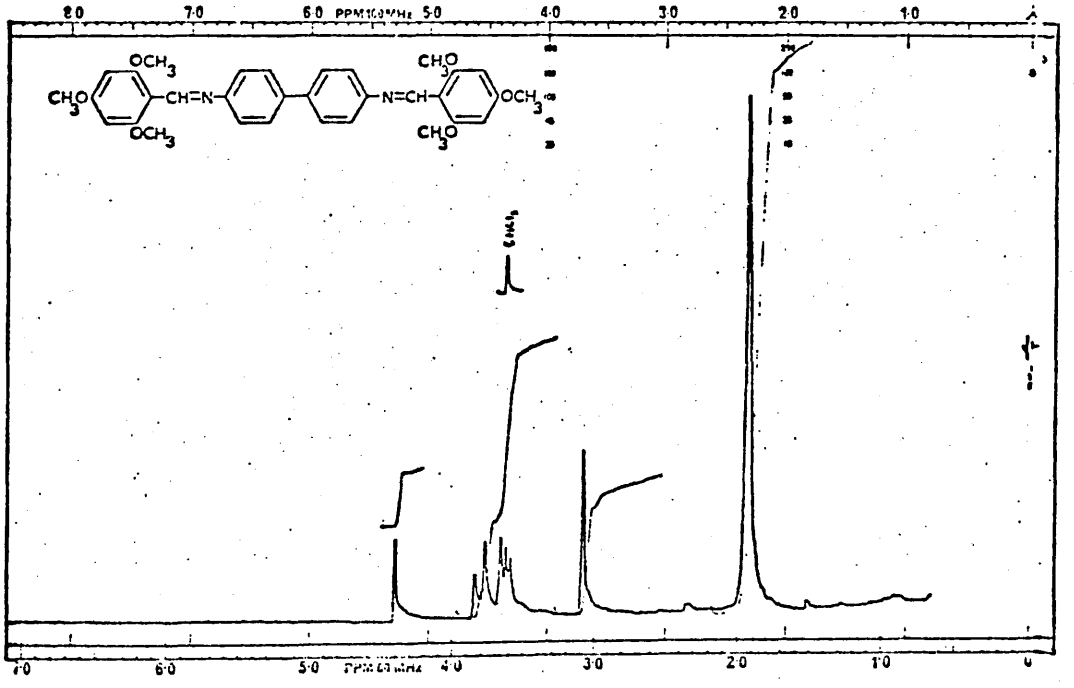
Spectrum No.31. ^1H N.m.r. spectrum, sweep width 250 H_z



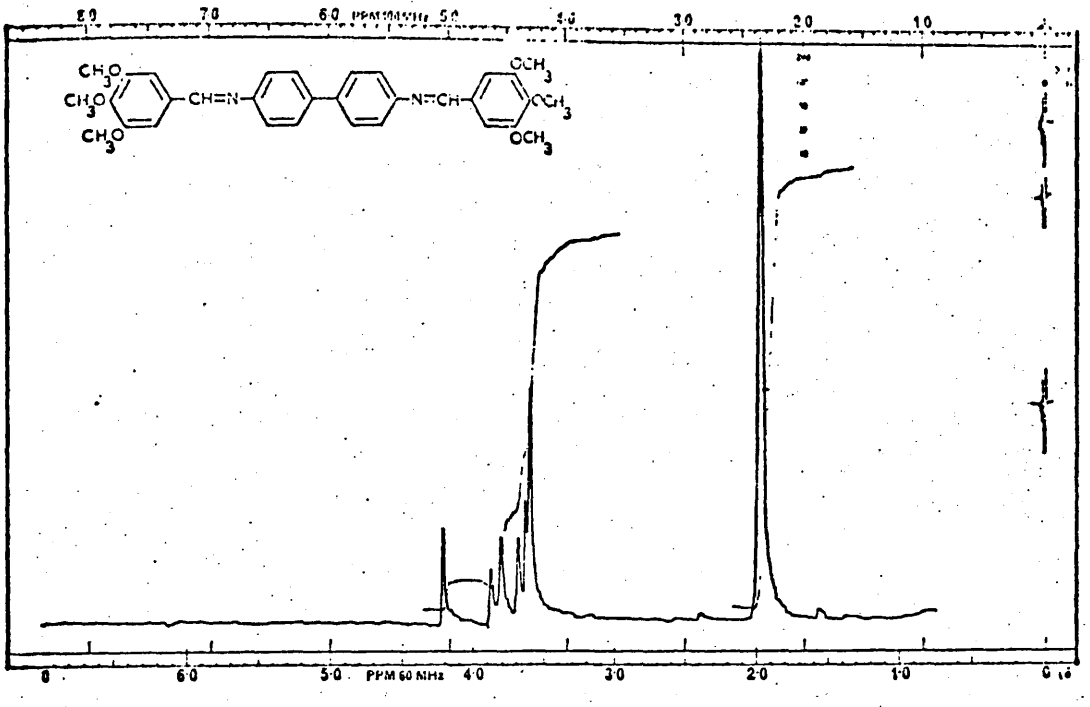
Spectrum No.32. ^1H N.m.r. spectrum, sweep width 500 H_z.



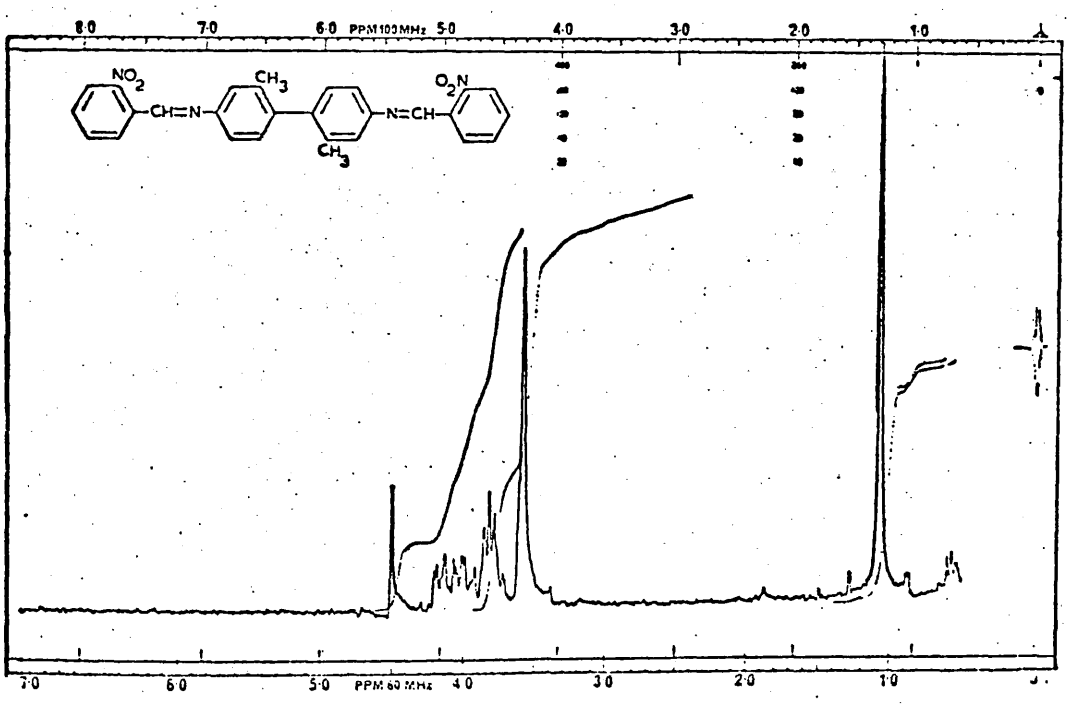
Spectrum No.33 ^1H N.m.r. spectrum, sweep width 500 H_z



Spectrum No.34. ^1H N.m.r. spectrum, sweep width 1000 H_z



Spectrum No.35. ^1H N.m.r. spectrum, sweep width 1000 H_z



Spectrum No.36. ^1H N.m.r. spectrum, sweep width 1000 H_z

Table X. Percent yield of the Schiff's bases (based on benzidine).

THE BENZIDINE	Ph-CHO	O-NO_2	O-Br	P-NO_2	2,6-DI-NO_2	2,4,6-TRI-Me	2,4,6-TRI-OMe	3,4,5-TRI-OMe
UNSUBSTITUTED	100	98	86	100	77	85	90	94
2,2'-DIMETHYL-	94	90	79	100	71	81	87	88
3,3'-DIMETHYL-	97	93	83	98	69	80	84	85
3,3'-DIETHYL-	84	70	58	89	54	72	74	75
2,2'-DICHLORO-	91	89	84	95	77	82	85	87
2,2'-DIBROMO-	89	85	80	90	69	80	81	83
3,3'-DICHLORO-	82	72	70	84	51	69		
3,3'-DIBROMO-	75	70	66	79	47	65		
2,6,2',6'-TETRACHLORO-				76				
2,6,2',6'-TETRABROMO-				60			71	75
2,6,2',6'-TETRAMETHYL-							77	83
2,2'-DIBROMO-6,6'-DIETHOXY-				91				
2,2'-DIFLUORO-5,5'-DIETHOXY-								71
2,3,5,6,2',3',5',6'-OCTAFLUORO-				43				

Table XI. Chemical shifts of the azomethine proton (CH=N) in p.p.m.

THE BENZIDINE	Ph-CHO	O-NO_2	O-Br	P-NO_2	2,6-DI-NO_2	2,4,6-TRI-Me	2,4,6-TRI-OMe	3,4,5-TRI-OMe
UNSUBSTITUTED	8.55	9.03	8.92	8.61	8.87	8.83	8.80	8.42
2,2'-DIMETHYL-	8.53	9.00	8.93	8.65	8.93	8.83	*	8.44
3,3'-DIMETHYL-	8.40	8.85	8.82	8.50	8.85	8.80	8.70	8.31
3,3'-DIETHYL-	8.40	8.85	8.93	8.53	8.83	8.80	8.70	8.35
2,2'-DICHLORO-	8.53	9.01	8.90	8.62	*	8.87	*	8.43
2,2'-DIBROMO-	8.52	9.01	8.90	8.60	*	8.83	*	8.40
3,3'-DICHLORO-	8.41	8.94	8.90	8.57	*	*		
3,3'-DIBROMO-	8.42	*	8.82	8.54	8.90	8.82		
2,6,2',6'-TETRACHLORO-				8.60				
2,6,2',6'-TETRABROMO-				8.63			8.80	8.40
2,6,2',6'-TETRAMETHYL-							8.82	8.45
2,2'-DIBROMO-6,6'-DIETHOXY-				8.60				
2,2'-DIFLUORO-5,5'-DIETHOXY-								8.40
2,3,5,6,2',3',5',6'-OCTAFLUORO-				8.80				

* INSOLUBLE IN CHLOROFORM

Table XII. Chemical shifts of aromatic protons of the aldehyde component in p.p.m.

(S) singlet; (D) doublet; (T) triplet- (M) multiplet.

THE BENZIDINE	Ph-CHO	O-NO_2	O-Br	P-NO_2	2,6-DI-NO_2	2,4,6-TRI-Me	2,4,6-TRI-OMe	3,4,5-TRI-OMe
UNSUBSTITUTED	7.40-8.05 M	7.65-8.42 M	7.40-8.33 M	8.00-8.41 M	7.68-8.33 M	6.93 S	6.16 S	7.18 S
2,2'-DIMETHYL-	7.40-8.01 M	7.45-8.40 M	7.33-8.33 M	8.02-8.43 M	7.63-8.40 M	6.93 S	*	7.18 S
3,3'-DIMETHYL-	7.40-8.01 M	7.40-8.35 M	7.30-8.37 M	7.98-8.40 M	7.63-8.32 M	6.93 S	6.17 S	7.17 S
3,3'-DIETHYL-	7.40-8.01 M	7.42-8.38 M	7.43-8.43 M	8.00-8.42 M	7.57-8.30 M	6.93 S	6.15 S	7.17 S
2,2'-DICHLORO-	7.45-8.03 M	7.43-8.45 M	7.39-8.33 M	8.01-8.45 M	*	6.95 S	*	7.18 S
2,2'-DIBROMO-	7.44-8.02 M	7.62-8.40 M	7.57-8.33 M	7.99-8.42 M	*	6.93 S	*	7.17 S
3,3'-DICHLORO-	7.40-8.05 M	7.50-8.48 M	7.43-8.40 M	8.08-8.45 M	*	*		
3,3'-DIBROMO-	7.44-8.08 M	*	7.40-8.44 M	8.04-8.47 M	7.67-8.45 M	6.97 S		
2,6,2',6'-TETRACHLORO-				7.99-8.43 M				
2,6,2',6'-TETRABROMO-				8.02-8.45 M			6.17 S	7.17 S
2,6,2',6'-TETRAMETHYL-							6.17 S	7.17 S
2,2'-DIBROMO-6,6'-DIETHOXY-				7.97-8.40 M				
2,2'-DIFLUORO-5,5'-DIETHOXY-								7.17 S
2,3,5,6,2',3',5',6'-OCTAFLUORO-				8.08-8.47 M				

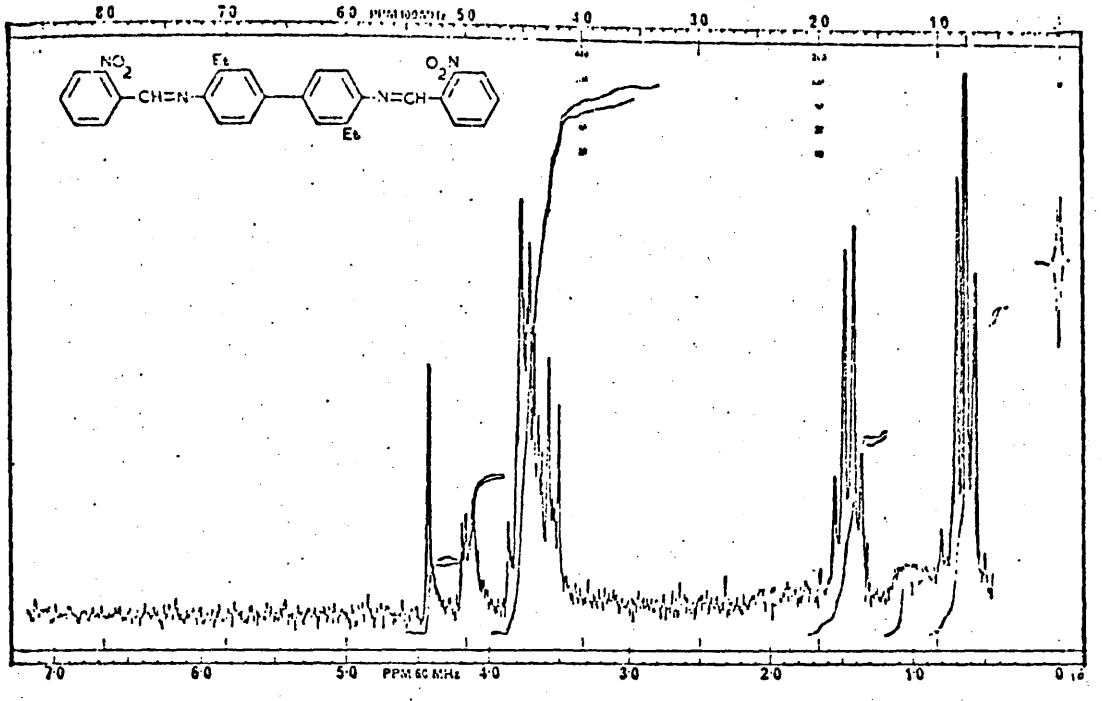
* INSOLUBLE IN CHLOROFORM

Table XIII. Chemical shifts of aromatic protons of the benzidine component in p.p.m.

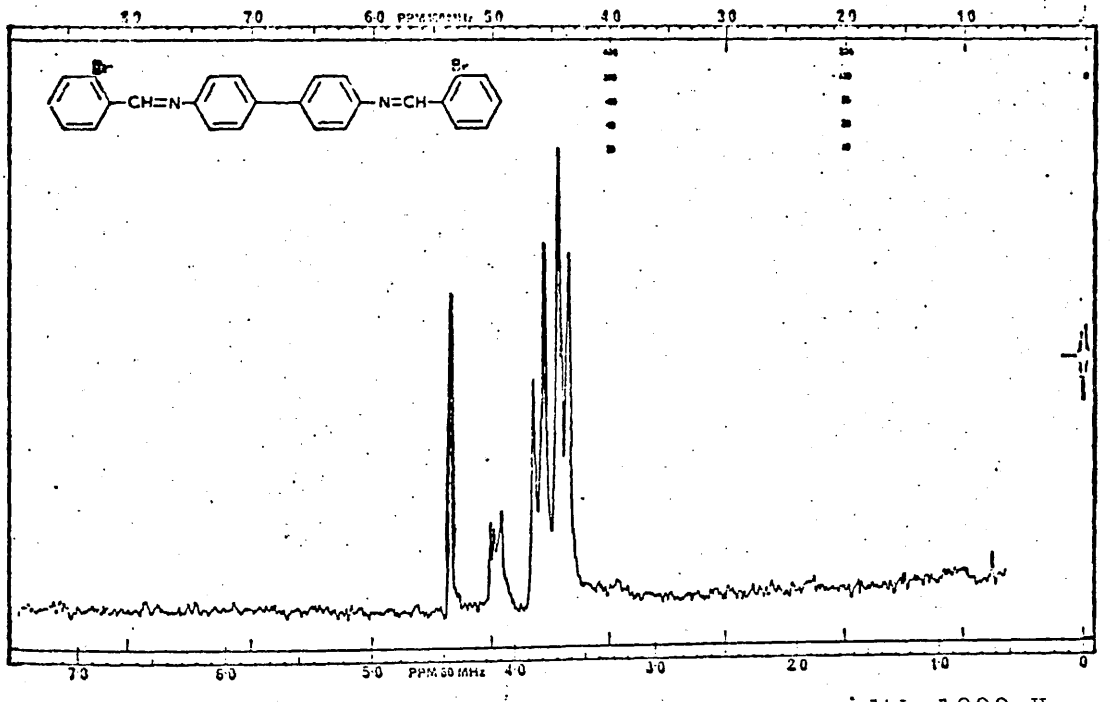
(S) singlet; (D) doublet; (T) triplet; (M) multiplet.

THE BENZIDINE	Ph-CHO	O-NO_2	O-Br	P-NO_2	2,6-DI-NO_2	2,4,6-TRI-Me	2,4,6-TRI-OMe	3,4,5-TRI-OMe
UNSUBSTITUTED	7.25-7.50 M	7.25-7.45 M	7.25-7.40 M	7.25-7.42 M	7.28-7.57 M	7.17 - 7.72 M	7.17 - 7.67 M	7.33-7.73 T
2,2'-DIMETHYL-	7.12 S	7.17 S	7.18 S	7.18 S	7.15 S	7.10 S	*	7.13 S
3,3'-DIMETHYL-	6.92-7.07 D	7.00-7.17 D	6.98-7.23 T	7.08-7.25 D	7.20-7.50 M	7.03-7.50 M	6.92-7.45 T	6.88-7.50 T
3,3'-DIETHYL-	6.92-7.05 D	7.00-7.33 M	7.02-7.18 M	7.00-7.53 M	7.07-7.40 M	7.03-7.50 M	6.87-7.47 T	6.87-7.51 T
2,2'-DICHLORO-	7.22-7.38 M	7.25-7.37 M	7.10-7.32 M	7.17-7.33 M	*	7.17-7.41 M	*	7.27-7.42 T
2,2'-DIBROMO-	7.20-7.44 M	7.32-7.33 D	7.20-7.46 M	7.27-7.56 M	*	7.20-7.49 D	*	7.27-7.53 T
3,3'-DICHLORO-	7.02-7.43 M	7.13-7.18 D	7.13-7.38 M	7.02-7.23 M	*	*		
3,3'-DIBROMO-	7.03-7.47 M	*	7.02-7.33 M	7.02-7.22 M	7.20-7.50 M	7.23-7.73 M		
2,6,2',6'-TETRACHLORO-				7.33 S				
2,6,2',6'-TETRABROMO-				7.58 S			7.47 S	7.50 S
2,6,2',6'-TETRAMETHYL-							6.98 S	7.02 S
2,2'-DIBROMO-6,6'-DIETHOXY-				6.81, 7.13 S				
2,2'-DIFLUORO-5,5'-DIETHOXY-								6.97-7.25 D
2,3,5,6,2',3',5',6'-OCTAFLUORO-								

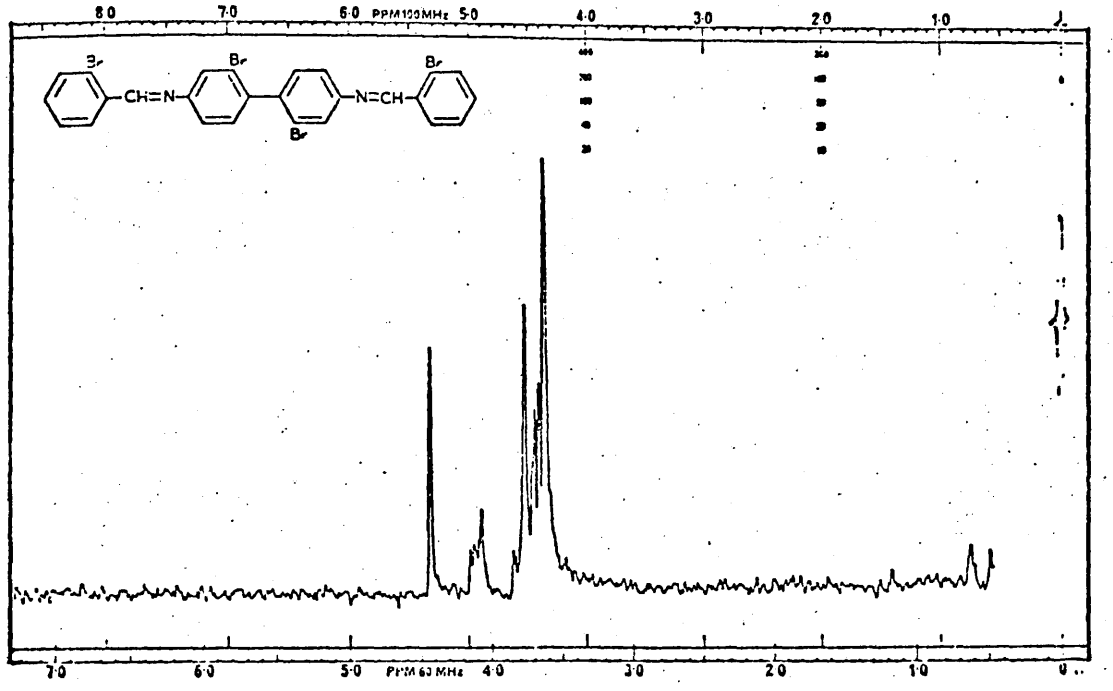
* INSOLUBLE IN CHLOROFORM



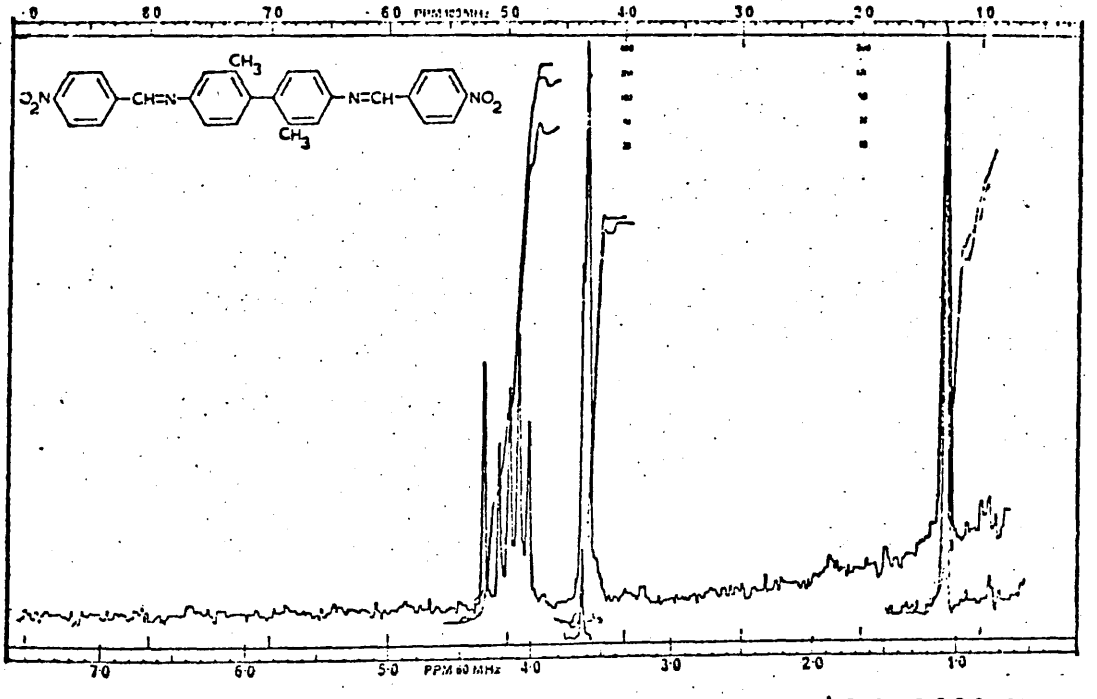
Spectrum No.37. ^1H N.m.r. spectrum, sweep width 1000 H_z



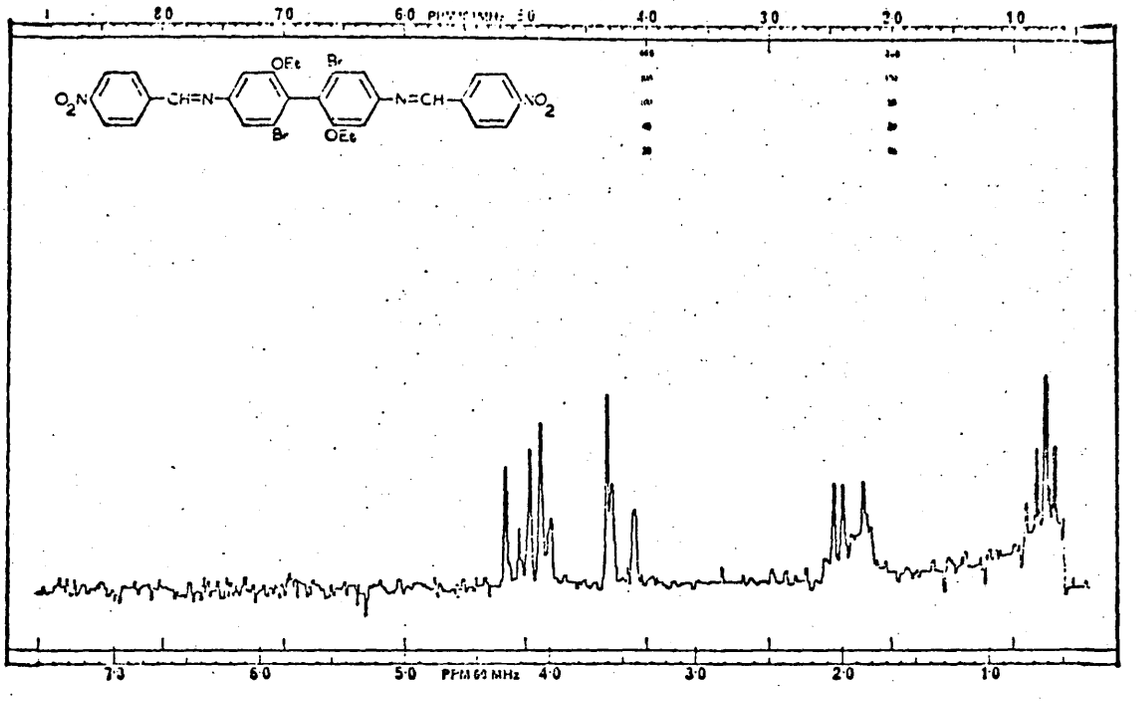
Spectrum No.38. ^1H N.m.r. spectrum, sweep width 1000 H_z



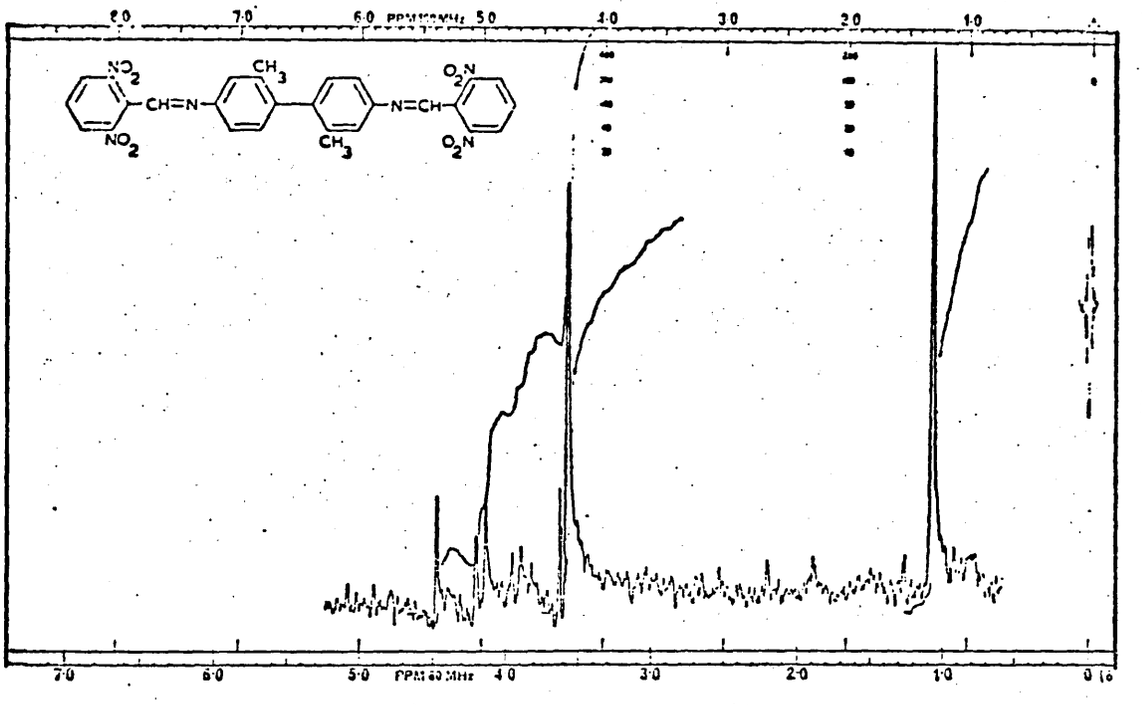
Spectrum No.39. ^1H N.m.r. spectrum, sweep width 1000 H_z



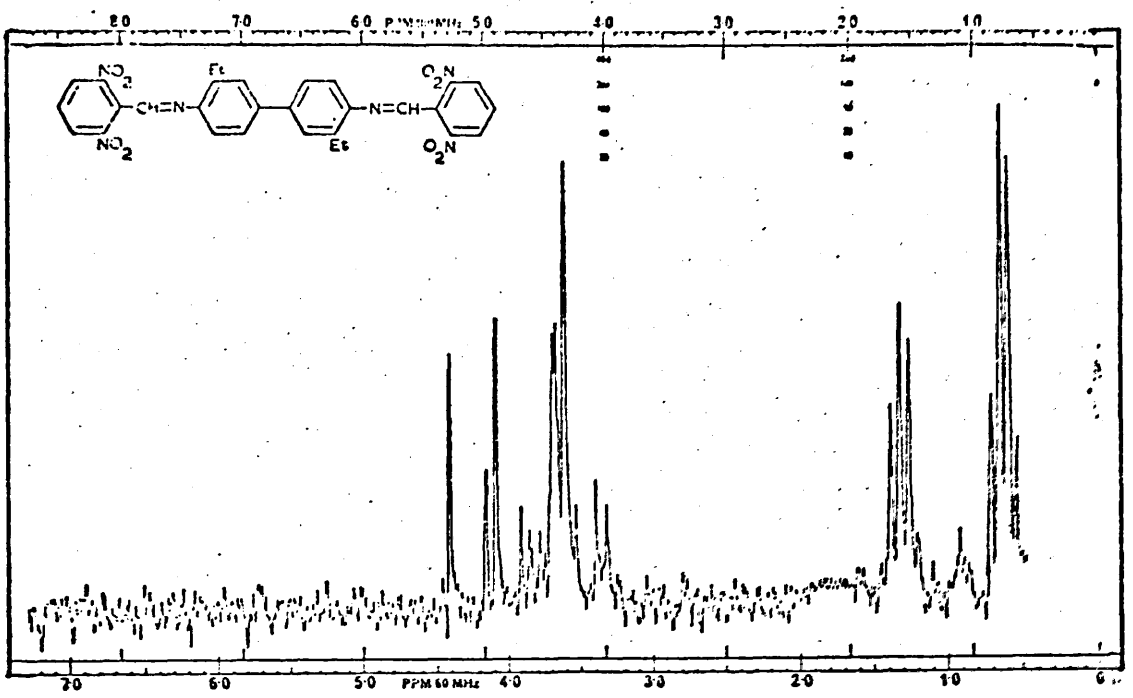
Spectrum No.40. ^1H N.m.r. spectrum, sweep width 1000 H_z.



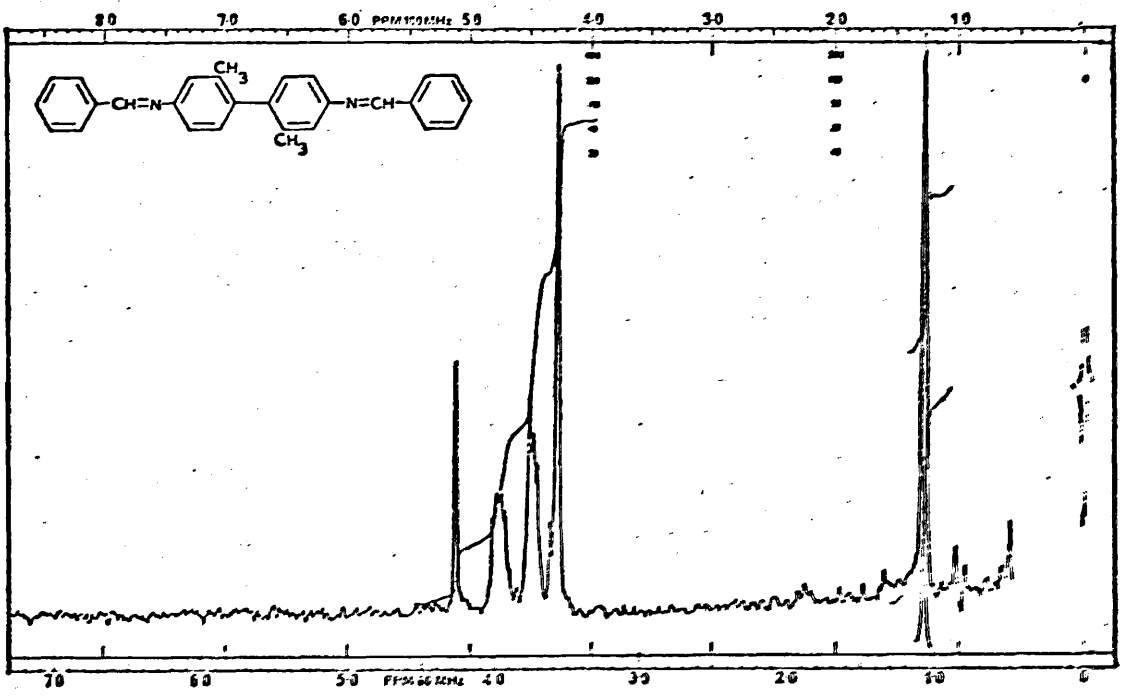
Spectrum No.41. ^1H N.m.r. spectrum, sweep width 1000 H_z



Spectrum No.42. ^1H N.m.r. spectrum, sweep width 1000 H_z.



Spectrum No.43. ^1H N.m.r. spectrum, sweep width 1000 H_z



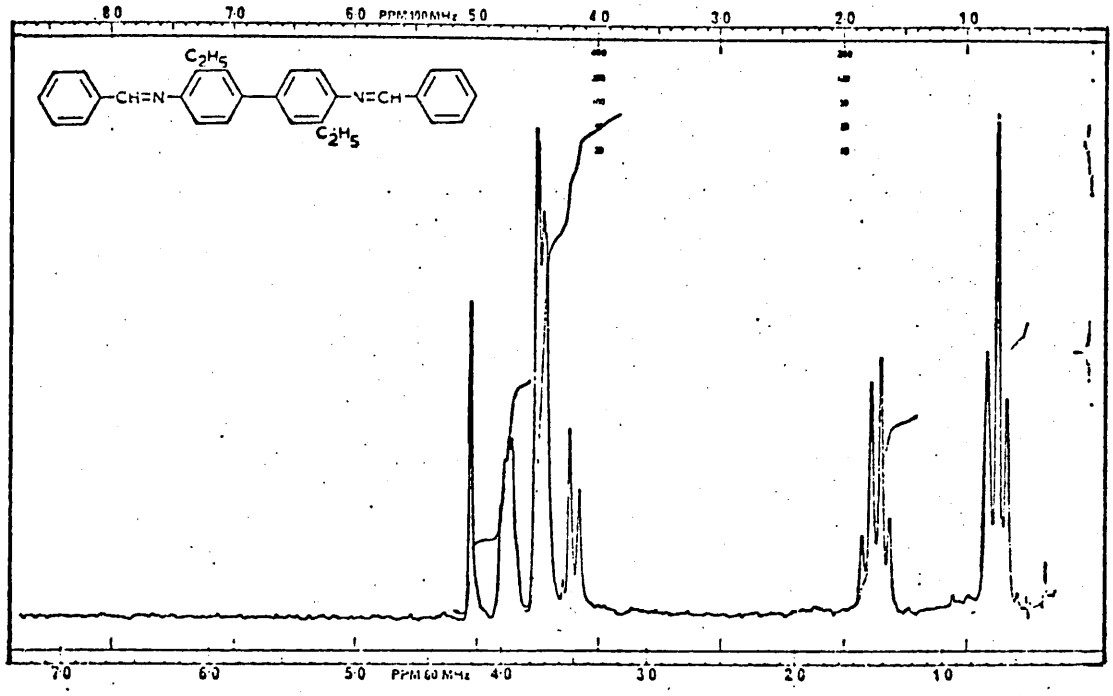
Spectrum No.44. ^1H N.m.r. spectrum, sweep width 1000 H_z

correlated with the size and direction of the inductive effects of these substituents.[241]

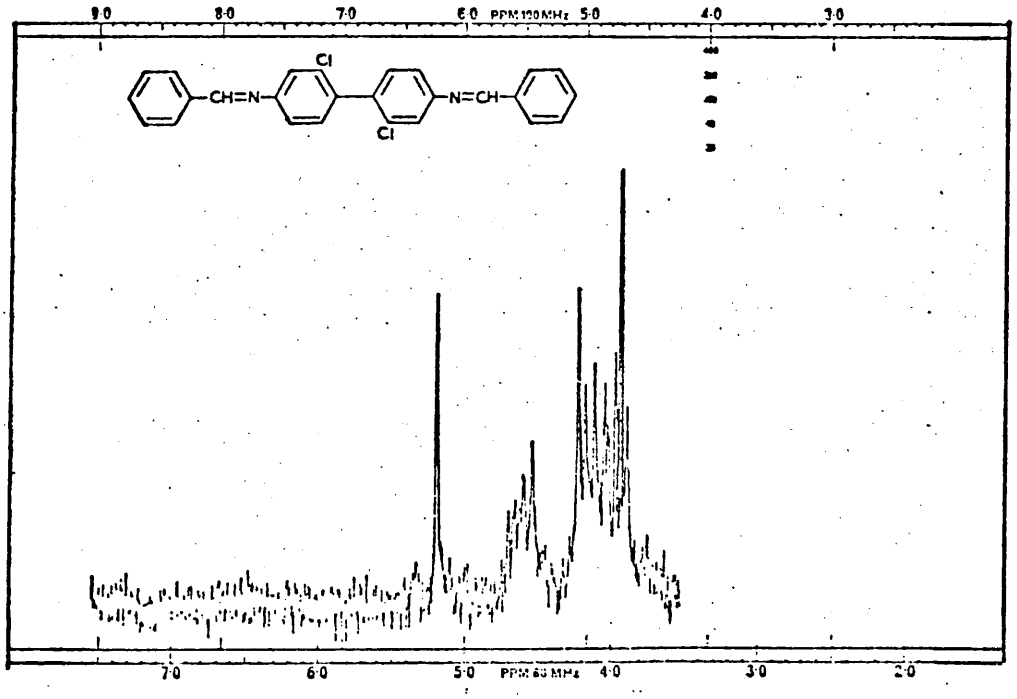
From Table XI, it is observed that one O-nitro group in the aldehyde ring is more deshielding than two O-nitro groups. It seems likely that twisting of the nitro group is important, and may happen preferentially as long as only one group is present. The azomethine proton will then be strongly deshielded by its proximity to N and O. The steric effect of two O-nitro groups is almost certainly large enough to cause twisting of the CH=N group as well (beyond the initial 10°) and the azomethine proton is thus further removed from the local deshielding influence, resulting in less deshielding shift.

b- Ring protons of the aldehyde component

The chemical shifts of the aromatic protons of the benzylidene component were found to be greatly affected by the substituents in the aldehyde ring. All electron-withdrawing substituents cause a downfield shift, 7.40-8.42 p.p.m., relative to that of the Schiff's base derived from benzaldehyde and benzidine, 7.40-8.05 p.p.m., Table XII. However, on the other hand, electron-releasing substituents cause an upfield shift, 6.16-7.18 p.p.m. It was found that no effect was observed due to the substituents in the benzidine component, as indicated by comparing the chemical shifts of ring protons of azomethines that derived from a certain aldehyde and different substituted benzidines, which were found to absorb in nearly the same region, spectra No.44-46. This is mainly attributed to the distortion of the benzidine component from the rest of the molecule and the non-planar structure of the Schiff's base.



Spectrum No.45. ^1H N.m.r. spectrum, sweep width 1000 H_z



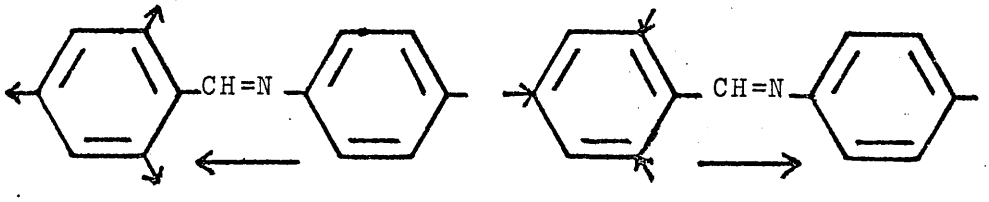
Spectrum No.46. ^1H N.m.r. spectrum, width 1000 H_z

Searching the n.m.r. literature and tables reveals that no attempt has been made previously to determine the effect of the azomethine group (CH=N) on the chemical shifts of aromatic protons, so by careful analysis of the n.m.r. spectra of the Schiff's bases prepared during this work, it was found that CH=N group causes a downfield shift by the following values relative to benzene:

ortho- protons = 0.60-0.71 p.p.m.
meta- protons = 0.11-0.19 p.p.m.
para- protons = 0.21-0.28 p.p.m.

c- Ring protons of the benzidine component

The effect of the substituents in the benzidine component on the chemical shifts of the ring protons of the benzidine was found to be of greater importance than that of the substituents in the benzaldehyde part, table XIII. However, a small effect might be expected for substituents in the benzaldehyde part to cause a downfield or upfield shift in the benzidine protons according to whether the substituent is an electron-withdrawing or electron-releasing group respectively.



(A) (B)

If the substituent(s) in the benzaldehyde part is electron-withdrawing group, the migration of the electrons will be in the direction of the

benzylidene part and the benzidine part will appreciably suffer an electron deficiency, causing its protons to absorb at lower field (A), while electron-releasing groups cause the migration of the electrons toward the benzidine part and thus a small upfield shift would be expected (B).

-EXPERIMENTAL-

GENERAL STATEMENTS

The following general statements apply wherever relevant to the text, unless specifically stated.

1. Melting points were determined in an oil bath and all are corrected.

2. N.M.R. spectra were determined for deuterochloroform solvent either at 60 MHz on a Varian A60 instrument or at 220 MHz by the Physico-Chemical Measurements Unit at Harwell, Berks. Chemical shifts were measured on the δ - scale relative to TMS as internal standard (δ = 0).

3. Ultra-violet absorption spectra were determined for ethanol solution either with Perkin-Elmer 124 automatic recording spectrophotometer or with Unicam SP. 500 manual spectrophotometer. Quartz cells were employed throughout.

4. Mass spectra were measured by Physico-Chemical Measurements Unit at Harwell, Berks.

5. Measurements of the optical activity were carried out on Carl-Zeiss photoelectric precision polarimeter.

6. Microanalyses were performed either by Dr. A. Bernhardt and his staff in West Germany or by the micro-analysis laboratory in Bedford College, London.

m - Tolidine

(R.B. Carlin and R.C. Odioso, J.Amer.Chem.Soc., 1954, 76, 2345).

A vigorously stirred mixture of zinc dust (120 g) and m - nitrotoluene (68g, 0.5 mole) in methyl alcohol (300 ml.) was treated dropwise with 30% aqueous sodium hydroxide (250 ml.) and the mixture was boiled for 3 hours. Most of the methyl alcohol was removed by distillation and the solids were collected by filtration and extracted with hot ethyl alcohol. The extracts were concentrated and treated first with concentrated aqueous ammonia (50 ml.) and then with hydrogen sulphide until the red colour of the solution disappeared. The pale yellow crude m - hydrazotoluene was recrystallized from light petroleum (b.p. 40 - 60°) and obtained as pale yellow prisms, (14.5g, 28%), m.p. 37-38° (lit., 37.5-38°; 28%).

A solution of m - hydrazotoluene (10g, 0.047 mole) in 95% ethyl alcohol (200 ml.) was treated with concentrated hydrochloric acid (20 ml.) and boiled for 1 hour; the mixture which contained crystals of m - tolidine hydrochloride was concentrated by distillation and the crystals (9g, 66%) were collected by filtration. A solution of these crystals in the minimum volume of water was cooled in an ice bath, stirred and slowly neutralized with aqueous ammonia. The white gummy precipitate was dissolved in light petroleum (b.p. 40-60°); after being kept for a day at 0°, the solution deposited a colourless oil which crystallized upon scratching with a glass rod to a microcrystalline solid, m.p. 101-103°. Recrystallization from water gave m - tolidine, m.p. 105-106° (lit. 103-104°).

Attempts were made to prepare the form of m - tolidine with m.p. 87-88°, previously described, but the only form obtained was that of the higher melting point which could not be recrystallized from any solvent but water.

2,2 - Dichlorobenzidine

(J.C. Cain and P. May, J.Chem.Soc., 1910, 720).

m - Chloronitrobenzene (100g, 0.64 mole), ethyl alcohol (130 ml) and sodium hydroxide (152g) in water (225 ml) were put into a 2-litre three-necked round bottom flask which was fitted with a mechanical stirrer and two double surface condensers and the mixture was boiled under reflux on a water-bath with vigorous stirring. Zinc dust (152g) was added as fast as the vigorous reaction allowed (50 min.). Heating was continued for another hour, so that the total time was about two hours. The reaction mixture was diluted with some ethyl alcohol and, while still hot, decanted from zinc into the hydrochloric acid (480 ml of concentrated acid + 160 ml of water) in a large beaker which was cooled in ice; the remaining sludge was extracted three times with small amounts of hot ethyl alcohol and the extracts added to the rest. Hydrochloride crystals which separated upon cooling in ice were filtered off in a large sentered glass funnel.

Recrystallization from water containing some hydrochloric acid and decolourization with activated charcoal gave the hydrochloride salt as white crystals which were filtered and dried on dish on a water bath (31g, 30%). The hydrochloride was dissolved in boiling water, and the free base was precipitated with ammonia, filtered and recrystallized from aqueous ethyl alcohol giving prisms, m.p. 167-168^{o} (lit., 165^{o}).

2,2' - Dibromobenzidine

(S. Gabriel, Ber., 1876, 9, 1405).

m - Bromonitrobenzene (100g, 0.5 mole), ethyl alcohol (120 ml.) and sodium hydroxide (125g) in water (210 ml.) were put into a three-necked round bottom flask which was fitted with a mechanical stirrer and two double surface condensers, and the mixture was boiled under reflux on a water-bath with

stirring. Zinc dust (125g) was added as fast as the vigorous reaction allowed (50 min.). Heating was continued for another hour so that the total time was about two hours. The reaction mixture was diluted with some ethyl alcohol and while still hot decanted from the zinc into the hydrochloric acid (395 ml. of concentrated acid + 135 ml. of water) contained in a large beaker which was cooled in ice; the remaining sludge was washed three times with small amounts of hot ethyl alcohol and all the washings were added to the rest. Hydrochloride crystals which separated upon cooling in ice were filtered off on a large sentered glass funnel. Recrystallization from water containing some hydrochloric acid, and decolourization with activated charcoal gave the hydrochloride as white crystals which were filtered and dried on a dish on a water bath (22g, 28%). The hydrochloride was dissolved in boiling water, and the free base was precipitated with ammonia, filtered and recrystallized from aqueous ethyl alcohol giving needles, m.p. 151-152° (lit., 151.5-152°).

P - Nitro-t-butylbenzene

(D. Craig, J. Amer.Chem.Soc., 1935, 57, 195).

A mixture of concentrated nitric acid (90g, 1 mole) and concentrated sulfuric acid (199g) was added to t-butylbenzene (134g, 1 mole) contained in a 1 litre beaker with efficient agitation and cooling to 20-30° during 1.1 hour. The mixture was then agitated for 1 hour at 40°. The product was separated and washed free from acid with dilute sodium hydroxide solution. Distillation without efficient fractionation gave unreacted t-butylbenzene (5g) and mixture of mononitro-t-butylbenzenes (162g) which on fractionaldistillation using a suitable column gave a fraction consisting mainly of o-nitro-t-butylbenzene (15g, 21%), b.p. 114-116°/$_{10mm}$, (lit., 143-145°/$_{45mm}$, 23%). An intermediate fraction was collected at 118-127°/$_{10mm}$, (20g) and finally a fraction consisting mainly of p-nitro-t-butylbenzene (122g, 74%) distilled at 127-131°/$_{10mm}$ as a pale yellow liquid, (lit., 155-158°/$_{30mm}$, 77%).

P - Amino-t-butylbenzene

(V. Vassiliadis and A.T. Peters, J.Chem.Soc., 1959, 3928).

A mixture of ethyl alcohol (500 ml.), concentrated hydrochloric acid (18 ml.) and iron powder (120g) was boiled under reflux for 15 min. to activate the iron; to the boiled and stirred mixture, p-nitro-t-butylbenzene (81g, 0.45 mole) was added during one hour; after being kept under reflux for a further 5 hours, the mixture was made alkaline with sodium carbonate solution and filtered. Most of the ethyl alcohol was removed from the filtrate, water was added and the mixture was extracted with benzene; the benzene extract was dried and the benzene evaporated. Dilute hydrochloric acid was added to the residue and the mixture was extracted with benzene to remove unchanged p-nitro-t-butylbenzene. The dilute hydrochloric acid solution was neutralized with aqueous ammonia and the amine was extracted with benzene; the extract was dried and the benzene evaporated. P-Amino-t-butylbenzene was distilled under reduced pressure as a pale yellow oil (46.5g, 70%), b.p. 98-102°/$_{8mm}$, (lit., 110-112°/$_{12mm}$, 71.2%).

The above reduction was carried out using the method described by (U.J.H. Mayer, Ph.D. Thesis, London, 1960) and an excellent yield was obtained, 95%.

P - Acetylamino-t-butylbenzene

(M.S. Carpenter, W.M. Easter & T.F. Wood, J.Org.Chem., 1951, 16, 586).

A mixture of p-amino-t-butylbenzene (46g, 0.31 mole), glacial acetic acid (30 ml, 0.6 mole), acetic anhydride (30 ml, 0.31 mole) and zinc powder (0.2g) was introduced into a 500 ml. round bottom flask fitted with a water condenser and was boiled under reflux for 30 min. The mixture was poured, while hot, into about 600 ml. of cold water, cooled in an ice bath and filtered. The acetyl derivative recrystallized from aqueous ethyl alcohol as leaflets (55.6g, 94%), m.p. 171-172° (lit., 170-171°).

3-Nitro-4-acetylamino-t-butylbenzene

(M.S. Carpenter, W.M. Easter and T.F. Wood, J.Org.Chem., 1951, 16, 586).

Nitric acid (d:1.51, 120 ml.) was added to a solution of glacial acetic acid (530 ml.) and acetic anhydride (450 ml), keeping the temperature at 5-10°. P-Acetylamino-t-butylbenzene (54g, 0.28 mole) was added in small portions at temperature -10 to +10°. The mixture was poured onto ice and extracted with benzene and the extract washed with water, then with 5% sodium hydroxide solution until the washings were free from colour, then with water to neutrality. The solvent was removed and the residue was recrystallized from ethyl alcohol giving bright yellow crystals (59g, 92%), m.p. 104-106° (lit., 103-106°, 100%).

3-Nitro-4-amino-t-butylbenzene

(M.S. Carpenter, W.M. Easter and T.F. Wood, J.Org.Chem., 1951, 16, 586).

3-Nitro-4-acetylamino-t-butylbenzene (57g, 0.28 mole) was dissolved in boiling ethyl alcohol (100 ml) in a 500 ml round bottom flask fitted with a water condenser. To this solution, 50% potassium hydroxide solution (40g) was added and the contents were boiled under reflux for about 30 min., then poured while hot into about ½ litre of ice-cold water. The orange-red crystals were filtered and washed with cold water. Recrystallization from aqueous ethyl alcohol gave orange-red needles (45.5g, 100%), m.p. 103-105° (lit., 102-105°, 100%).

3-Nitro-t-butylbenzene

(M.S. Carpenter, W.M. Easter and T.F. Wood, J.Org.Chem., 1951, 16, 586).

3-Nitro-4-amino-t-butylbenzene (48g, 0.25 mole) in ethyl alcohol (240 ml.) and concentrated hydrochloric acid (82 ml.) were put into a 1 litre round bottom flask fitted with a water condenser. The mixture was boiled under reflux and a solution

of sodium nitrite (34g) in water (50 ml) was added as rapidly as the heat of reaction would permit. The mixture was refluxed for a further one hour and then subjected to steam distillation. The oil which distilled with water was separated, washed with 5% sodium hydroxide solution, then with water to neutrality and dried ($CaCl_2$). 3-Nitro-t-butylbenzene was obtained as a yellow-red oil (30g, 65%), b.P. 96-98°/2.5mm (lit., 97-99/2.5mm, 67.4%).

3,3'-Di-t-butylazobenzene

3-Nitro-t-butylbenzene (20g, 0.11 mole), sodium hydroxide (23.5g), zinc dust (30g), water (50 ml) and ethyl alcohol (167 ml) were put into a 500 ml round bottom flask fitted with a water condenser. The mixture was boiled under reflux with stirring on a water-bath for 9 hours; the deep orange-red colour became slightly pale yellow. The reaction mixture was filtered while hot and the filtrate was kept at 0° for overnight. Orange-red crystals were separated (11.5g, 70%). On recrystallization from ethyl alcohol, bright orange-red crystals, m.p. 106-107° were obtained. Partial evaporation of the mother-liquor afforded a yellow substance, which after recrystallization from ethyl alcohol gave bright yellow crystals, m.p. 59-60°, and appeared to be a different compound. The high melting point substance was found to be the azo compound as indicated by its elemental microanalysis.

(Found : C, 81.7 ; H, 8.7 ; N, 9.6 ; m/e 294 (M^+).
$C_{20}H_{26}N_2$ requires C, 81.6 ; H, 8.8 ; N, 9.5% ; M, 294).

The yellow crystalline compound, m.p. 59-60°, was found to be 3,3' - di-t-butylazoxybenzene, as indicated by its micro-analysis, and by comparing its UV spectrum with that of azoxybenzene (Spectrum No.5)

(Found : C, 78.0 ; H, 8.5 ; N, 9.6 ; m/e 310 (M^+).
$C_{20}H_{26}N_2O$ requires C,77.7 ; H, 8.4 ; N, 9.4% ; M, 310).

2,2'-Di-t-butylbenzidine

To a stirred suspension of zinc dust (10g) in a boiling solution of 3,3'-di-t-butylazobenzene (8g, 0.027 mole) in ethyl alcohol (40 ml.), a solution of sodium hydroxide (5g) in water (15 ml.) was added dropwise at such a rate that the solution boiled vigorously. Partial crystallization of the hydrazo compound occurred occasionally, and ethyl alcohol was added as required to bring it into solution. The solution is still coloured and therefore it is necessary to add more zinc dust in 1-g quantities until the colour disappeared completely. The mixture was rapidly filtered through a preheated Buchner funnel into 30 % acetic acid (65 ml.) to which sodium bisulfite (0.5g) had been added. The insoluble sludge from the reaction mixture was twice stirred and boiled with 10 ml portions of ethyl alcohol, and the extracts were filtered into the acetic acid solution. The solution in the flask was cooled in an ice-bath (5°), and the solids were collected by filtration as pale yellow-white crystals (7.8g, 96%), m.p. 85-86°. This hydrazo compound is easily oxidized in the air to the corresponding azo compound, therefore it was immediately rearranged to the corresponding benzidine.

3,3'-Di-t-butylhydrazobenzene (7.8g, 0.026 mole) was treated with 2:1 sulfuric acid (120 ml) which had been preheated to 85-90°, and the mixture was stirred and maintained within that temperature range for fifteen minutes. The mixture was diluted with water, cooled and filtered. The insoluble material consisted of 3,3'-di-t-butylazobenzene (1.1g, 14%), m.p. 106-107°.

The sulfuric acid filtrate was neutralized slowly with cold aqueous ammonia solution and the solid compound which separated upon filtration was recrystallized twice from benzene-light petroleum (b.P. 80-100°) as tiny needles (1.3, 17%), m.p. 199-200° (Found : C, 80.9 ; H, 9.55 ; N, 9.3. $C_{20}H_{28}N_2$ requires C, 81.1 ; H, 9.5; N, 9.5%).

2,6-Dibromo-4-nitroaniline

(R. Meyer, W. Meyer and K. Taeger, Ber., 1920, 53, 2034).

P - Nitroaniline (50g, 036 mole) was dissolved in methyl alcohol (300 ml.) in a 1 litre beaker. Bromine (116g, 0.72 mole) was added dropwise with stirring, whereby immediately the bromo compound separated. After the addition of bromine was completed, the solid precipitate was filtered, washed well with water and dried. Recrystallization from aqueous ethyl alcohol gave yellow needles (101g, 92%), m.p. 202-203° (lit., 202°, 93%).

3,5-Dibromo-1-nitrobenzene

(R.B. Carlin and W.O. Forshey, J.Amer.Chem.Soc., 1950, 72, 793).

In a 500 ml round bottom flask fitted with a water condenser, a mixture of 2,6-dibromo-4-nitroaniline (60g, 0.2 mole), ethyl alcohol (320 ml) and concentrated sulfuric acid (37 ml) was introduced. While the mixture was boiled and stirred, pulverized sodium nitrite (35g) was added in portions as rapidly as the foaming would permit. Boiling was continued for 30 min. after the sodium nitrite addition was complete. The mixture was allowed to cool, and the solids were collected by filtration then washed well with water. Recrystallization from ethyl alcohol gave orange needles (53g, 90%), m.p. 105-106° (lit., 106°, 91%).

3,5,3',5'-Tetrabromoazobenzene

(R.B. Carlin and W.O. Forshey, J.Amer.Chem.Soc., 1950, 72, 793).

To a stirred, boiling suspension of zinc dust (24g) in a solution of 3,5-dibromo-1-nitrobenzene (30g, 0.107 mole) in ethyl alcohol (120 ml), a sodium hydroxide solution (30%, 60 ml) was added as rapidly as foaming would permit (about 10 min.).

The mixture was boiled under reflux for an hour after the base had been added; then about 75% of the ethyl alcohol was removed by distillation, and the residue was diluted with water and allowed to cool. The solids were removed by filtration, dried and extracted with portions of boiling toluene until the extracts were no longer coloured. On concentrating the toluene extracts to 100ml and cooling, the solution deposited orange needles (20.8g, 79%), m.p. 244-245° (lit., 245-247°, 80%).

3,5,3',5'-Tetrabromohydrazobenzene

(R.B. Carlin and W.O. Forshey, J.Amer.Chem.Soc. 1950, 72, 793).

To a stirred, boiling suspension of finely powdered 3,5,3',5'-tetrabromoazobenzene (20g) in ethyl alcohol (200 ml) and glacial acetic acid (10 ml) contained in a 500 ml round bottom flask fitted with a condenser, zinc dust (20g) was added in small portions until the soluble azo compound disappeared and the solution became nearly colourless. The mixture was cooled and filtered, and the filtrate was poured cautiously into about 250 ml of boiling water. The sludge from the filtration was extracted with two portions of boiling ethyl alcohol and the extracts were also poured into the boiling water. Boiling was continued until sufficient agglomeration of the precipitated hydrazo compound had occurred to permit its filtration. The mixture was cooled and the hydrazo compound was collected as tiny needles (19.6g, 98%), m.p. 180-181° (lit., 179.5-181°, 95%).

2,6,2',6'-Tetrabromobenzidine

(R.B. Carlin and W.O. Forshey, J.Amer.Chem.Soc., 1950, 72, 793).

A sample of 3,5,3',5'-tetrabromohydrazobenzene (15g) was treated with 2:1 sulfuric acid (450 ml) which had been preheated to 85-90°, and the mixture was stirred and maintained within that temperature range for 5 hours, then cooled and filtered through

a sintered glass funnel to remove the oxidized azo compound, which after washing with water and recrystallizing from ethyl alcohol, had m.p. 243-245° (1.2g, 8%). The sulfuric acid filtrate was cooled and neutralized slowly with cold 40% aqueous sodium hydroxide, and the organic material which separated was filtered and dissolved in benzene. The benzene solution was dried and allowed to flow through a 2-inch column of activated alumina to remove the highly coloured tar. The pale yellow solution was then concentrated to about 50 ml and treated with light petroleum (b.P. 80-100°) at the boiling point until small needles began to appear. On cooling, the solution gave 7.1g of mixed crystalline bases. Concentration of the filtrate gave a red oil, which was crystallized from aqueous ethyl alcohol and identified as 3,5-dibromoaniline m.p. 54-56°, acetyl derivative m.p. 225-227°.

Column chromatography technique was used to separate the mixed crystalline bases, as will be described later; satisfactory yields and improved melting points were obtained as shown below:

a) 2,6,2',6'-Tetrabromobenzidine, recrystallized from benzene-light petroleum (b.P. 80-100°) as short needles (2.2g), m.p. 251-252° (lit., 249-250°).

b) 2,4,2',6'-Tetrabromodiphenyline, recrystallized from benzene-light petroleum (b.P. 80-100°) as crystals (3.6g), m.p. 184-185° (lit., 183-184°).

2,6-Dichloro-4-nitroaniline

(B. Flurscheim, J.Chem.Soc., 1908, 1772).

P-Nitroaniline (41g, 0.3 mole) was dissolved in glacial acetic acid (123g) and concentrated hydrochloric acid (246g). The solution is cooled in an ice-bath and continually stirred while excess of chlorine gas was bubbled through for about

30 minutes. The solid yellow precipitate was filtered, washed well with water and recrystallized from ethyl alcohol as long bright yellow needles (58g, 95%), m.p. 189-190° (lit., m.p. 189-190°).

3,5-Dichloro-1-nitrobenzene

(R.B. Carlin and W.O. Forshey, J.Amer.Chem.Soc., 1950 72, 793).

To a stirred boiling mixture of 2,6-dichloro-4-nitroaniline (40g, 0.19 mole), ethyl alcohol (400 ml) and concentrated sulfuric acid (30 ml) contained into 1-litre round bottom flask fitted with a condenser, sodium nitrite (27g) was added in portions as rapidly as foaming would permit. Boiling was continued for 30 minutes after the sodium nitrite addition was complete. The mixture was allowed to cool and the solids were collected by filtration and washed well with water. Recrystallization from ethyl alcohol gave yellow needles (30.3g, 82%), m.p. 64-65° (lit., 62-64°, 84%).

3,5,3',5'-Tetrachloroazobenzene

(R.B. Carlin and W.O. Forshey, J.Amer.Chem.Soc., 1950, 72, 793).

To a stirred, boiling suspension of zinc dust (15g) in a solution of 3,5-dichloro-1-nitrobenzene (14g, 0.073 mole) in ethyl alcohol (100 ml) contained in 500 ml round bottom flask fitted with a condenser, 30% sodium hydroxide solution (35 ml) was added as rapidly as foaming would permit (about 10 min.) The mixture was boiled under reflux for one hour after the alkali had been added; then about 75% of the ethyl alcohol was removed by distillation, and the residue was diluted with a little water then allowed to cool. The solids were removed by filtration, dried and extracted with portions of boiling toluene until the extracts were no longer coloured. On concentrating the toluene extracts to 60 ml and cooling, orange needles were obtained (10.2g, 82%), m.p. 194-195° (lit., 194-195°, 85%).

3,5,3',5'-Tetrachlorohydrazobenzene

(R.B. Carlin and W.O. Forshey, J.Amer.Chem.Soc., 1950, 72, 793).

To a stirred, boiling suspension of finely powdered 3,5,3',5'-tetrachloroazobenzene (10g, 0.031 mole) in ethyl alcohol (100 ml) and glacial acetic acid (5 ml) contained in 250 ml round bottom flask fitted with a condenser, zinc dust (10g) was added in small portions until the insoluble azo compound disappeared and the solution became nearly colourless. The mixture was cooled and filtered, and the filtrate was poured into about 150 ml of boiling water. The sludge from the filtration was extracted with two portions of boiling ethyl alcohol and the extracts were also poured into the boiling water. Boiling was continued until sufficient agglomeration of the precipitated hydrazo compound had occurred to permit its filtration. The mixture was cooled, filtered and the hydrazo compound was collected as pale yellow prisms (9.4g, 94%), m.p. 138-139° from light petroleum (b.P. 60-80°), (lit., 131-132°, 96%).

2,6,2',6'-Tetrachlorobenzidine

(R.B. Carlin and W.O. Forshey, J.Amer.Chem.Soc., 1950, 72, 793).

A sample of 3,5,3',5'-tetrachlorohydrazobenzene (8g) was treated with 2:1 sulfuric acid (300 ml) which had been preheated to 85-90°, and the mixture was stirred and maintained within that temperature range for eighteen hours, then cooled and filtered through a sintered glass funnel to remove the oxidized azo compound which after washing with water and recrystallizing from ethyl alcohol (0.71g, 8.7%) m.p. 192-194°. The sulfuric acid filtrate was cooled and neutralized slowly with cold 40% aqueous sodium hydroxide, and the organic material which separated was filtered and dissolved in benzene. The benzene solution was dried and allowed to flow through a 2-inch column of activated alumina to remove the highly coloured tar. The pale yellow solution was then concentrated to about 40 ml and

treated with light petroleum (b.P. 80-100°) at the boiling point until small needles began to appear. On cooling, the solution deposited 5.9g of mixed crystalline bases. Concentrating of the filtrate gave a red oil from which a small amount of 3,5-dichloroaniline separated as white needles, m.p. 50-52°, acetyl derivative m.p. 187-188°.

Column chromatography technique was used to separate the mixed crystalline bases, as will be described later, a satisfactory yields and improved melting points were obtained as shown below:

a) 2,6,2',6'-Tetrachlorobenzidine, recrystallized from benzene - light petroleum (b.P. 80-100°) as bright short needles (1.25g), m.p. 218-220° (lit., 212.5-213.5°).

b) 2,4,2',6'-Tetrachlorodiphenyline, recrystallized from benzene - light petroleum (b.P. 80-100°) as tiny crystals (1.9g), m.p. 144-145° (lit., 141-141.5°).

Separation of the benzidine rearrangement products by column chromatography.

In the separation of the benzidine rearrangement products of 3,5,3',5'-tetrabromo, 3,5,3',5'-tetrachloro and 3,5,3',5'-tetramethylhydrazobenzene in 2:1 sulfuric acid at 85-90°, Carlin and Forshey, (loc.cit.), used the countercurrent extraction procedure which is suggested by Craig (J.Biol.Chem., 1944, 155, 519) as a nearly quantitative stoichiometric accounting method. Owing to the unclear description of this method, an attempt was made to apply column chromatography as an alternative method.

Activated alumina (15-20g) was used for each 1g of the mixed bases; the column was packed well and benzene was run down and then the mixed bases dissolved in the minimum amount of benzene. Benzene was used as an eluent, which was collected continuously from the column in quantities of 10 ml each; these were concentrated by evaporation and treated with light petroleum (b.P. 80-100°) at the boiling point until small needles began to appear. Almost all the crystalline compound

obtained by elution with benzene was found to be the corresponding benzidine. When the eluent no longer gave a precipitate with light petroleum, ethyl acetate was used instead of benzene and on evaporation of the solvent replacing by benzene and treating with light petroleum (b.P. 80-100°) at the boiling point, a powdered compound was collected and found to be the corresponding diphenyline. It was found that the compounds separated were purer than those separated by the counter-current extraction procedure as indicated by the considerable improvement in their melting points.

4-Nitro-m-xylene

(W.R. Boon, J.Chem.Soc., 1949, S231).

m-Xylene (50g, 0.47 mole) was added slowly with stirring to a mixture of fuming nitric acid (d: 1.51, 250 ml) and glacial acetic acid (250 ml) in a large beaker at 0°. After two hours the mixture was poured onto ice and extracted with ether. The extract was washed first with 5% sodium hydroxide solution then with water to neutrality and dried; the ether was evaporated and the residue was steam distilled. The distillate was then extracted with ether and the extract dried with calcium chloride, filtered and evaporated. On distillation under reduced pressure the residue gave a small amount of unchanged m-xylene together with 4-nitro-m-xylene as a pale yellow liquid (52g, 77.5%), b.P. 116/120°/$_{10mm}$ (lit., 125-126°/$_{20mm}$, 79%).

4-Amino-m-xylene

(T. Wherry, J.Amer.Chem.Soc., 1920, 42, 1840).

Into a 2-litre three-necked round bottom flask provided with a separating funnel and two water condensers, a solution of stannous chloride (170g) in concentrated hydrochloric acid

(240g) was introduced. 4-Nitro-m-xylene (40g, 0.26 mole) was added from the separating funnel in small portions while the mixture was heated to start the reaction. After the addition was completed, the mixture was heated on a steam bath for one hour, diluted with water, cooled, then made alkaline with 10% sodium hydroxide solution and distilled with steam. The distillate was extracted with ether, dried and the ether was evaporated. 4-Amino-m-xylene was obtained as a pale yellow liquid (25g, 78%), b.P. 96-98°/$_{10mm}$ (lit., 220-221°/$_{760mm}$).

4-Acetylamino-m-xylene

(C. Willgerodt and F. Schmierer, Ber., 1905, 38, 1472).

A mixture of 4-amino-m-xylene (43g, 0.35 mole), glacial acetic acid (42 ml, 0.7 mole), acetic anhydride (35 ml, 0.35 mole) and zinc powder (0.2g) was introduced into a 500-ml round bottom flask provided with a water condenser. The mixture was boiled under reflux for 30 min., then poured while hot into about 600 ml of cold water, cooled in an ice bath and filtered. Recrystallization from ethyl alcohol gave crystals (58g, 100%), m.p. 130-131° (lit., 127-128°).

5-Nitro-4-acetylamino-m-xylene

(S. Gabriel and R. Stelzner, Ber., 1896, 29, 303).

4-Acetylamino-m-xylene (41g, 0.25 mole) was added to concentrated nitric acid (210g) in small portions with stirring and the temperature was maintained in a range 0-10°. The mixture was poured in ice-water, allowed to stand for one hour and filtered. The solids were washed well with water, dried and recrystallized from ethyl alcohol giving yellow needles (47.5g, 91%), m.p. 171-173° (lit., 172-173°).

An attempt was made using fuming nitric acid (d:1.48) to prepare the above mentioned compound, but instead, 6-nitro-4-acetylamino-m-xylene was obtained as yellow needles, m.p. 159-160° (lit., 160°) which on hydrolysis gave the 6-nitro-4-xylidine m.p. 125-126° (lit., 123°) (Noelting and Collin, Ber., 1884, 17, 265).

Another attempt was also made using fuming nitric acid (d: 1.51) and the resulting compound was 5,6-dinitro-4-acetylamino-m-xylene, which was obtained as long needles m.p. 217-219° (lit., 217°) and gave on hydrolysis the corresponding amine, m.p. 115-116° (lit., 115°), (Blanksma, Rec.trav.chim, 1909, 28, 93).

5-Nitro-4-amino-m-xylene

(S. Gabriel and R. Stelzner, Ber., 1896, 29, 303).

In a 500 ml round bottom flask provided with a water condenser, a mixture of 5-nitro-4-acetylamino-m-xylene (70g, 0.42 mole) and concentrated hydrochloric acid (140) was boiled under reflux for about 3 hours. It was necessary to add small amounts of ethyl alcohol to the mixture to bring the solids into solution. The mixture was poured into about one litre of ice-cold water, cooled in ice and filtered. The solids were washed well with water and recrystallized from ethyl alcohol giving red-orange needles (54g, 96%), m.p. 75-76° (lit., 76°).

5-Nitro-m-xylene

(H.L. Haller, E.Q. Adams and E.T. Wherry, J.Amer.Chem.Soc., 1920, 42, 1840).

A mixture of ethyl alcohol (400g) and concentrated sulfuric acid (200g) was added to 5-nitro-4-amino-m-xylene (60g, 0.36 mole) and the mixture was cooled to 0-5°. A concentrated solution of sodium nitrite (45g in minimum quantity of water) was added slowly within that range of temperature, after that, the

the solution was boiled under reflux for 3 hours and then distilled with steam. 5-Nitro-m-xylene was collected by filtration of the distillate and recrystallized from ethyl alcohol giving yellow needles (41g, 76%), m.p. 74-75°.

3,5,3',5'-Tetramethylhydrazobenzene

(R.B. Carlin, J.Amer.Chem.Soc., 1945, 67, 928).

To a stirred suspension of zinc dust (25g) in a boiling solution of 5-nitro-m-xylene (10g, 0.066 mole) in ethyl alcohol (40 ml) contained in 250 ml round bottom flask provided with a water condenser, a solution of 30% sodium hydroxide (65g) was added dropwise. The alkali was added at such a rate that the solution boiled vigorously. Partial crystallization of the azo and hydrazo occurred occasionally, and ethyl alcohol was added as required to bring these compounds into solution. When all the alkali had been added, the solution was still coloured, and therefore it is necessary to add more zinc dust in 1g quantities until the colour disappeared completely. The mixture was rapidly filtered through a large preheated Buchner funnel into 30% acetic acid (150 ml) to which about one gram of sodium bisulfite had been added. The insoluble sludge from the reaction mixture was twice stirred and boiled with 20 ml portions of ethyl alcohol, and the extracts were also filtered into the acetic acid solution. The mixture in the filter flask was cooled to 10°, and the solids were collected by filtration and immediately dissolved in boiling light petroleum (b.P. 60-80°), filtered while hot and permitted to cool. Upon filtration and drying, long needles were collected (7.1g, 88%), m.p. 125-126° (lit., 125°, 92%).

2,6,2',6'-Tetramethylbenzidine

(R.B. Carlin and W.O. Forshey, J.Amer.Chem.Soc., 1950, 72, 793).

A sample of 3,5,3',5'-tetramethylhydrazobenzene (7g) was treated with 2:1 sulfuric acid (120 ml) which had been preheated to 85-90°, and the mixture was stirred and maintained within that temperature range for 5 minutes. The mixture was diluted with water, cooled and filtered. The insoluble material consisted of 3,5,3',5'-tetramethylazobenzene which on washing with water and recrystallization from ethyl alcohol gave red-orange needles (0.9g, 12%), m.p. 138-139° (lit., 137.5-139°, 7.7%).

The sulfuric acid filtrate was cooled and neutralized slowly with cold 40% aqueous sodium hydroxide. The solid substance which separated upon filtration (5.75g) was dissolved in benzene. The benzene solution was dried and allowed to flow through a 2-inch column of activated alumina to remove the highly coloured tar. The pale yellow solution was then concentrated to about 25 ml and submitted to a column chromatography method to separate its components, as described before and the following compounds were separated:

a) 2,6,2',6'-Tetramethylbenzidine, recrystallized from benzene - light petroleum (b.P. 80-100°) as long needles (1.1g), m.p. 167-168° (lit., 167-168°).

b) 2,4,2',6'-Tetramethydiphenyline, recrystallized from benzene - light petroleum (b.P. 60-80°) as short needles (1.8g), m.p. 147-148° (lit., 146.5-147.5°).

Mixed bases (0.3g) of wide range melting point were also obtained from the column and could not be separated further.

2,5-Dibromo-3,6-difluoro-1-nitrobenzene

1,4-Dibromo-2,5-difluorobenzene (20g, 0.074 mole) was treated with fuming nitric acid (d: 1.51, 100g) and the mixture was introduced into a 500 ml round bottom flask provided with a water condenser. The mixture was heated on a water bath for 2 hours then poured into ice-water, allowed to stand for 1 hour, filtered and washed well with cold water. On recrystallization from benzene-light petroleum (b.P. 60-80°), it gave yellow crystals (12.3g, 53%), m.p. 125-126°.

(Found : C, 23.2 ; H, 0.5; Br, 50.3 · $C_6H_1Br_2F_2NO_2$ requires C, 22.7 ; H, 0.3; Br, 50.5%).

2,3,5,6,2',3',5',6'-Octabromobenzidine

2,6,2',6'-Tetrabromobenzidine (1g) was dissolved in glacial acetic acid (5 ml) in a small conical flask. Bromine solution (4g) was added dropwise with constant stirring while the contents were heated to about 50°. Upon cooling, a yellow crystalline compound separated and was filtered, washed well with water and recrystallized from ethyl alcohol as pale-yellow crystals (1.1g, 70%), m.p. 319-320°.

(Found : C, 17.5 ; N, 3.2 ; Br, 78.6 · $C_{12}H_4Br_8N_2$ requires C, 17.65; N, 3.4 ; Br, 78.3%).

3,5,3',5'-Tetrabromobenzidine

(W. Schlenk, Annalen, 1908, 363, 313) ·

Benzidine hydrochloride (10g) was suspended in concentrated hydrochloric acid (200 ml) in a 500 ml round bottom flask. Bromine (35g, 12 ml) was added dropwise with stirring to the reaction mixture, which became black after all the bromine has been added. The reaction mixture was allowed to stand for two days at room temperature then bromine (6g) was added and the mixture allowed to stand for

one day. A concentrated solution of stannous chloride was added to the mixture, shaken gently and filtered, the residue was washed with dilute hydrochloric acid to remove any unbrominated benzidine. The solid was dried and recrystallized from xylene as pale-brown needles (13.7g, 71%), m.p. 287-288° (lit., 288°).

3,5,3',5'-Tetrachlorobenzidine

(W. Schlenk, Annalen, 1908, 363, 313).

Benzidine hydrochloride (10g) was suspended in concentrated hydrochloric acid (200 ml) in a 500 ml round bottom flask. Dry chlorine gas was bubbled through the mixture for about 30 minutes. After the reaction mixture had been allowed to stand for 3 hours, it was poured into concentrated stannous chloride solution, stirred and filtered. The residue was dried well and recrystallized from a mixture of toluene (2 vol.) and ethyl alcohol (1 vol.) as tiny needles (8.2g, 66%), m.p. 227-228° (lit., 226-227.5°).

3,5,3',5'-Tetrabromo-m-tolidine

(W. Schlenk, Annalen, 1908, 363, 313).

m-Tolidine hydrochloride (5g) was suspended in concentrated hydrochloric acid (100 ml) in a 250 ml round bottom flask. Bromine (21g) was added dropwise with stirring to the reaction mixture which became yellow-orange colour after all the bromine had been added. The reaction mixture was allowed to stand for two days at room temperature then bromine (3g) was added and the mixture was allowed to stand for one day. A concentrated solution of stannous chloride was added to the mixture, shaken gently and filtered. The solid compound was dried and recrystallized twice from xylene as yellow crystals (5.77g, 62%), m.p. 231-232° (lit., 229-230°).

2,5-Difluoro-1-nitrobenzene

(F. Weygand, Chem.Ber., 1951, 84, 101).

A mixture of fuming nitric acid (d: 1·51, 60 ml) and concentrated sulfuric acid (120 ml) was added dropwise to 1,4-difluorobenzene (55g) contained in a 1 litre beaker at 0°. The addition was at such a rate that the temperature did not exceed 10°. After the addition was completed, the reaction mixture was poured into ice water then extracted with ether and the extract was dried and evaporated. 2,5-Difluoro-1-nitrobenzene was collected as orange-red liquid (50g, 85%), b.P. $82\text{-}84^{\circ}/_{12mm}$, (lit., $86\text{-}87^{\circ}/_{15mm}$).

2,2'-Diethoxy-5,5'-difluoroazobenzene

A vigorously stirred suspension of 2,5-difluoro-1-nitrobenzene (10g) and zinc dust (14g) in ethyl alcohol (40 ml) was heated to the boiling point in a 250 ml round bottom flask provided with a water condenser. Sodium hydroxide solution (40 ml of 30%) was added to the boiling mixture as rapidly as the foaming would permit. The mixture was boiled for an hour after the base had been added; then filtered while hot and the filtrate was permitted to cool, whereby the solution deposited red-orange crystals (6.7g, 69%), m.p. $119\text{-}122^{\circ}$. This azo compound yielded long red needles, m.p. $129\text{-}130^{\circ}$, after two recrystallizations from ethyl alcohol. Instead of the expected azo compound, which is 2,5,2',5'-tetrafluoro-azobenzene, another azo compound was obtained and found to be 2,2'-diethoxy-5, 5'-difluoroazobenzene as proved by micro-analysis and the nuclear magnetic resonance spectrum.

(Found : C, 63.2 ; H, 5.3 ; N, 9.4 . $C_{16}H_{16}F_2N_2O_2$

requires C, 63.6 ; H, 5.3 ; N, 9.3%).

2,2'-Diethoxy-5,5'-difluorohydrazobenzene

To a boiling, stirred suspension of finely powdered 2,2'-diethoxy-5,5'-difluoroazobenzene (15g) in ethyl alcohol (200 ml) and glacial acetic acid (12 ml), zinc dust was added in successive small portions until further additions caused no more fading of the colour of the solution. The zinc dust was removed by a rapid filtration and the light yellow solution was poured quickly with stirring into 1-litre of hot water. After the mixture was cooled and the solid was collected by filtration, rapid crystallization from light petroleum (b.P. 60-80°) gave compact needles (14.2g, 94%), m.p. 80-81°.

(Found : C, 62.9 ; H, 5.85 ; N, 9.5 . $C_{16}H_{18}F_2N_2O_2$ requires C, 63.15 ; H, 5.9 ; N, 9.2%).

2,2'-Difluoro-5,5'-diethoxybenzidine

With vigorous stirring, a sample of finely ground 2,2'-diethoxy-5,5'-difluorohydrazobenzene (15g) was added in small portions to 2:1 (by weight) sulfuric acid (330 ml) which was preheated to 85-90°. The mixture was stirred and maintained in the same temperature range for 3 hours. Solid lumps were crushed from time to time as they formed. The rearrangement mixture was cooled and filtered through a sintered glass funnel, and the tan solid (13.4g) was washed many times with water, dried and washed with ether and the resulting solid was a tan powder (12.7g). Removal of the ether from the washings left an orange-red solid which on slow recrystallization from ethyl alcohol caused separation of 2,2'-diethoxy-5,5'-difluoroazobenzene (0.52g) in the form of long red needles, m.p. 124-125°.

The tan, ether-insoluble solid was boiled with 20% aqueous sodium hydroxide for 30 min., the mixture was cooled, filtered and washed thoroughly with water and the solid was dried well then recrystallized from light petroleum (b.P. 60-80°) as long needles (9.8g, 65%), m.p. 110-111°.

(Found : C, 63.1 ; H, 6.15 ; N, 9.5. $C_{16}H_{18}F_2N_2O_2$ requires C, 63.15; H, 5.9 ; N, 9.2%).

P-Fluoroacetanilide

(O. Wallach and F. Heusler, Annalen, 1888, 243, 219).

In a 500 ml round bottom flask provided with a water condenser, P-fluoroaniline (100g, 1 mole) and redistilled acetic anhydride (112g, 1.1 mole) were boiled under reflex for about 90 minutes. The mixture was poured with stirring while hot into ice-water, filtered then washed free from acid and recrystallized from aqueous ethyl alcohol as long needles (128g, 93%), m.p. 154-155° (lit., 154°).

2-Nitro-4-fluoroacetanilide

(A modified method of J.H. Wilinson and I.L. Finar, J. Chem.Soc., 1948, 288).

A nitrating agent was prepared by adding fuming nitric acid (d: 1.51, 133 ml) to a mixture of acetic anhydride (345 ml) and glacial acetic acid (405 ml) in a large beaker, and at such a rate that the temperature did not rise above 20°. P-Fluoroacetanilide(128g) was added with stirring to the nitrating agent in small portions and the temperature was kept at 10-20°. The mixture was stirred for 1 hour after the addition of the anilide was completed, then poured into ice-water, filtered, washed free from acid and recrystallized from aqueous ethyl alcohol as compact yellow plates (127g, 77%), m.p. 71-72° (lit., 71°).

2-Nitro-4-fluoroaniline

(J.H. Wilkinson and I.L. Finar, J. Chem.Soc., 1948, 288).

In a 500 ml round bottom flask provided with a water condenser, 2-nitro-4-fluoroacetanilide (76g) was dissolved in concentrated hydrochloric acid (150 ml) and the mixture was boiled under reflux after a sufficient amount of ethyl alcohol had been added to bring the solid anilide into solution. The mixture was boiled under reflux for 2 hours, then poured while hot into ice-water, filtered and washed free from acid. Upon recrystallization from aqueous ethyl alcohol, orange-red crystals were obtained (54.7g, 92%), m.p. 95-96° (lit., 93-94°, 96%).

2-Nitro-4-fluoro-6-bromoaniline

In a 1-litre beaker, 2-nitro-4-fluoroaniline (75g, 0.48 mole) was dissolved in a suitable quantity of glacial acetic acid. Bromine (192g, 1.2 mole) was added from a separatory funnel mounted at the top of the beaker at such a rate that the mixture was kept at a temperature range of 60-70° using a hot plate. The mixture was stirred at that temperature range for 1 hour after all the bromine has been added then poured into ice-water, filtered and washed free from bromine. After recrystallization from ethyl alcohol, yellow-orange crystals were obtained (107g, 95%), m.p. 77-78°.

(Found : C, 30.6 ; H, 1.6 ; N, 12.1 . $C_6H_4BrFN_2O_2$

requires C, 30.6 ; H, 1.7 ; N, 11.9%).

3-Bromo-5-ethoxy-1-nitrobenzene

2-Nitro-4-fluoro-6-bromoaniline (75g) was dissolved in a mixture of ethyl alcohol (300 ml) and concentrated sulfuric acid (63 ml) contained in a 1-litre three-necked round bottom flask provided with a mechanical stirrer and a water condenser. The mixture was boiled under reflux with stirring and sodium

nitrite (55g) was added through the condenser as rapidly as the foaming would permit. The mixture was refluxed for a further 1 hour then cooled in an ice-bath and filtered. The organic substance was extracted from the residue with hot ethyl alcohol as orange solid. After three recrystallizations from 95% ethyl alcohol, pale yellow-orange needles were obtained (39g, 51%), m.p. 67°.

The expected compound, which is 3-bromo-5-fluoro-1-nitrobenzene could not be isolated, but instead 3-bromo-5-ethoxy-1-nitrobenzene was obtained as proved from the microanalysis and n.m.r. spectrum.

(Found : C, 39.1 ; H, 3.4 ; N, 5.7 . $C_8H_8BrNO_3$

requires C, 39.0 ; H, 3.25; N, 5.7%).

3-Fluoro-5-bromo-1-nitrobenzene

(J.I. Cadagon and G.A. Molina, J.Chem.Soc., Perkin I, 1973, 541).

2-Nitro-4-fluoro-6-bromoaniline (20g) in tetrahydrofuran (100 ml) was added dropwise during 1-2 hours to a boiling solution of pentyl nitrite (26 ml) in tetrahydrofuran (150 ml) contained in 500 ml round bottom flask provided with a water condenser. The solution was boiled under reflux for a further 3 hours, then the solvent was removed by distillation using rotary evaporation and the pentyl alcohol by distillation under reduced pressure. The expected nitro compound was collected as a yellow oil (1.4g, 7.5%), b.P. 102-105°/8mm. This poor yield was due to the polymerization of the contents of the flask during the distillation process, leaving a residue of dark red polymer.

(Found : C, 32.4 ; H, 1.3 ; Br, 36.5 . $C_6H_3BrFNO_2$

requires C, 32.7 ; H, 1.4 ; Br, 36.3%).

The azo compound from the above nitro compound, namely 3,3'-difluoro-5,5'-dibromoazobenzene, had been prepared by the usual method used throughout this work, as orange-yellow

crystals (75%), m.p. 106-107°.

(Found : C, 38.5 ; H, 1.5 ; N, 7.5 . $C_{12}H_6Br_2F_2N_2$
requires C, 38.5 ; H, 1.6 ; N, 7.5%).

3,3'-Dibromo-5,5'-diethoxyazobenzene

A vigorously stirred suspension of 3-bromo-5-ethoxy-1-nitrobenzene (10g) and zinc dust (13g) in ethyl alcohol (80 ml) was heated under reflux in a 250 ml round bottom flask provided with a water condenser. 30% Sodium hydroxide solution (20 ml) was added to the reaction mixture as rapidly as the foaming would permit. The solution was boiled for a further 1 hour then filtered rapidly and the filtrate was kept at 0° for one day. Upon filtration and two successive recrystallizations from ethyl alcohol, orange-red needles were obtained (6.4g, 74%), m.p. 109-110°.

(Found : C, 44.6 ; H, 3.9 ; Br, 36.9 . $C_{16}H_{16}Br_2N_2O_2$
requires C, 44.9 ; H, 3.7 ; Br, 37.3%).

3,3'-Dibromo-5,5'-diethoxyhydrazobenzene

To a stirred, boiling suspension of finely powdered 3,3'-dibromo-5,5'-diethoxyazobenzene (20g) in ethyl alcohol (200 ml), glacial acetic acid (15 ml) was added and the mixture was brought to boiling under reflux in a 500 ml round bottom flask provided with a water condenser. To this mixture, zinc dust was added in small successive portions until further additions caused no more fading of the colour of the solution. The zinc dust was removed by rapid filtration, and the light yellow solution was poured quickly with stirring into 1-litre of hot water. After the solution was cooled, pale yellow solid was collected by filtration, which on recrystallization from light petroleum (b.P. 60-80°) gave powdered solid

(19.1g, 96%), m.p. 101-102°.

(Found : C,44.8 ; H, 4.05 ; Br, 37.1 . $C_{16}H_{18}Br_2N_2O_2$
requires C,44.65 ; H, 4.2 ; Br, 37.2%)

2,2'-Dibromo-6,6'-diethoxybenzidine

With vigorous stirring, a sample of finely ground 3,3'-dibromo-5,5'- diethoxyhydrazobenzene (17g) was added in small portions to 2:1 (by weight) sulfuric acid (400 ml) which was preheated to 85-90°. The mixture was stirred and maintained in the same temperature range for 3 hours, then cooled and filtered through a sintered glass funnel to remove the oxidized azo compound, which after washing with water and recrystallizing from ethyl alcohol gave orange-red needles (0.2g, 1.2%) m.p. 110°.

The sulfuric acid filtrate was cooled in an ice-bath and neutralized with aqueous ammonia and the organic material which separated was collected by filtration and washed many times with water. Upon recrystallization from ethyl alcohol, light-brown needles were obtained (3.7g, 22%), m.p. 217-218°.

(Found : C, 44.8 ; H, 4.0 ; Br, 37.0 . $C_{16}H_{18}Br_2N_2O_2$
requires C, 44.65; H. 4.2 ; Br. 37.2%).

UV Spectrum , λ max = 216 mμ Emax = 33,120
λ max = 255 mμ Emax = 9,510
λ max = 294 mμ Emax = 5,220 in 95% ethanol

2,2'-Dibromo-6,6'-diethoxybiphenyl

2,2'-Dibromo-6,6'-diethoxybenzidine (0.8g) was dissolved in concentrated hydrochloric acid (3 ml) contained in a small beaker placed in a bath of acetone and solid CO_2 at -25° to 20°. Sodium nitrite solution (1g in the least possible amount of water) was added to the benzidine solution while the mixture was stirred. The final diazo solution contained a slight yellow precipitate, but was poured without filtering into mechanically stirred hypophosphorous acid (15 ml) contained

in a beaker immersed in the same bath. Freshly prepared cuprous oxide (0.1-0.2g) was added from time to time to catalyse the reaction. Effervescence occurred, and after 30 minutes of stirring, vigorous frothing occurred with separation of more solid. After frothing had subsided, the solid was filtered, washed with water, cold 10% sodium hydroxide, then again with water, and dried. The crude product was dissolved in benzene and allowed to flow through a column of activated alumina, whereby a pale yellow filtrate was obtained, which upon dilution with equal volume of light petroleum (b.P. 40-60°) and evaporation to dryness gave light yellow-orange crystals (0.54g, 74%), m.p. 114-115°.

(Found : C, 47.9 ; H, 4.0 . $C_{16}H_{16}Br_2O_2$ requires C, 48.0 ; H, 4.0%).

4-Nitrocumene

(E.C. Sterling and M.T. Bogert, J.Org.Chem., 1939, 4, 20).

Cumene (100g, 0.83 mole) was added gradually to a mixture of concentrated nitric acid (83g) and concentrated sulfuric acid (125g) contained in a 500-ml beaker with constant stirring at a temperature range of 40-50°. After the addition of cumene was completed, the mixture was stirred for a further one hour at room temperature then poured into ice water and the organic substance was extracted with benzene. The benzene extract was dried over calcium chloride, then filtered and the solvent evaporated. The residue was distilled under reduced pressure and 4-nitrocumene (110g, 80%) was collected at 124-125°/11 mm (lit., 128-129°/12mm, 77%).

4-Aminocumene

(E.C. Sterling and M.T. Bogert, J.Org.Chem., 1939, 4, 20).

Into a 1 litre round bottom flask equipped with a reflux condenser, 4-nitrocumene (100g, 0.6 mole) and granulated tin (110g) were introduced. Concentrated hydrochloric acid (240 ml) was added slowly through the top of the condenser with frequent cooling and shaking of the flask to ensure thorough mixing. After the addition of the acid was completed, the mixture was heated on a water bath for about 1 hour, then cooled down and a solution of sodium hydroxide (180g) in water (300 ml) was added gradually to the reaction mixture with cooling and the mixture was subjected to steam distillation. The organic substance was extracted from the distillate with ether, and the ether was dried with anhydrous potassium carbonate, filtered and evaporated. 4-Aminocumene was collected as a pale yellow liquid (70g, 88%), b.P. 224-225° (lit., 222.5°, 77%).

4-Acetylaminocumene

(M.S. Carpenter, W.M. Easter and T.F. Wood, J.Org.Chem. 1951, 16, 586).

Acetic anhydride (83g) was added gradually to 4-aminocumene (110g, 0.82 mole) contained in a 500 ml round bottom flask fitted with a water condenser and the mixture was boiled under reflux for one hour. The mixture was cooled and benzene (200 ml) was added then the solution washed free from acid. The resulting solution was added to 28% ammonia solution (100 ml) and agitated for one hour during which time the temperature was raised to 55°. The benzene layer was removed, washed to neutrality and the benzene was evaporated and the remaining solid residue was recrystallized from light petroleum (b.P. 80-100°) as waxy plates (136g, 95%), m.p. 106-107° (lit., 105-106°).

3-Nitro-4-acetylaminocumene

(M.S. Carpenter, W.M. Easter and T.F. Wood, J.Org.Chem., 1951, 16, 586).

Nitric acid (d: 1.51, 54 ml) was added to a mixture of glacial acetic acid (220 ml) and acetic anhydride (200 ml) while the temperature was kept below 20°. P-Acetylaminocumene (89g, 0.5 mole) was added in small portions at temperature range -10° to 10°. The mixture was stirred at room temperature for 1 hour after the addition of the acetyl has been completed, then poured into ice water, filtered, washed thoroughly with water and dissolved in benzene (250 ml) and filtered. The filtrate was evaporated to dryness and the remaining residue was recrystallized from aqueous ethanol as yellow needles (107, 97%), m.p. 82-83° (lit., 80-81°, 81%).

3-Nitro-4-aminocumene

(M.S. Carpenter, W.M. Easter and T.F. Wood, J.Org.Chem., 1951, 16, 586).

3-Nitro-4-acetylaminocumene (133g, 0.6 mole) was dissolved in boiling ethanol (150 ml) contained in a 500 ml round bottom flask fitted with a water condenser. To this solution, 50% potassium hydroxide solution (100 ml) was added and the contents were boiled under reflux for about 15 minutes, then poured while hot into about 1.5 litre of ice-cold water. The dark oil layer was removed and the solid was filtered, washed thoroughly with cold water, and recrystallized from aqueous ethanol as orange-red crystals (88g, 100%) m.p. 41-42°.

3-Nitrocumene

(M.S. Carpenter, W.M. Easter and T.F. Wood, J.Org.Chem., 1951 16, 586).

3-Nitro-4-aminocumene (135g, 0.75 mole) was introduced into a solution of ethanol (600 ml) and concentrated hydrochloric acid (295g) contained in a 1 litre round bottom flask

fitted with a water condenser. While the mixture was boiled under reflux, a solution of sodium nitrite (103g) in water (160 ml) was added during 35 minutes. The mixture was boiled under reflux for a further 30 minutes then subjected to steam distillation and the oil which passed over with the filtrate was extracted with benzene, dried and evaporated. 3-Nitrocumene was collected (89g, 72%), b.p. 98-100°/$_{5mm}$ (lit., 92°/$_{3.5mm}$).

3,3'-Diisopropylhydrazobenzene

To a stirred, boiling suspension of zinc dust (60g) in a solution of 3-nitrocumene (33g, 0.2 mole) in ethyl alcohol (300 ml), sodium hydroxide solution (46g in 95 ml water) was added as rapidly as foaming would permit. The mixture was boiled under reflux with stirring for about 8 hours, whereby the deep orange-red colour became pale yellow. The reaction mixture was filtered while hot and the filtrate was kept at 0° for several hours. The solids were filtered, dried and immediately recrystallized from light petroleum (b.P. 60-80°) as pale yellow crystals (20.4g, 76%), m.p. 97-98°.

(Found : C, 80.8 ; H, 8.9 ; N, 10.2 . $C_{18}H_{24}N_2$
requires C, 80.6 ; H, 8.9 ; N, 10.5%).

The corresponding azo compound, namely 3,3'-diisopropylazobenzene, was obtained by boiling a sample of the hydrazo compound in ethyl alcohol for about 15 minutes then filtering and permitting to cool. Red-orange crystals were separated, m.p. 124-125°.

(Found : C, 81.1 ; H, 8.0 ; N, 10.6 . $C_{18}H_{22}N_2$
requires C, 81.2 ; H, 8.3 ; N, 10.5%).

2,2'-Diisopropylbenzidine

3,3'-Diisopropylhydrazobenzene (10g, 0.037 mole) was treated with 2:1 sulfuric acid (170 ml) which had been preheated to 85-90°, and the mixture was stirred and maintained within that temperature range for fifteen minutes. The mixture

was diluted with water, cooled and filtered. The insoluble material consisted of 3,3'diisopropylazobenzene (0.72g, 8%), m.p. 124-125°.

The sulfuric acid filtrate was neutralized slowly with cold aqueous ammonia solution and the solid compound which separated was filtered, washed thoroughly with water, dried and recrystallized several times from benzene-light petroleum (b.P. 60-80°) as short needles (3.7g, 37%), m.p. 237-238°.

(Found : C,80.5 ; H, 8.8 ; N, 10.6 . $C_{18}H_{24}N_2$ requires C,80.6 ; H, 8.9 ; N, 10.5%).

3,3'-Dichlorobenzidine

(P. Cohn, Ber., 1900, 33, 3551).

A vigorously stirred mixture of zinc dust (75g) and o-chloronitrobenzene (50g, 0.32 mole) in ethyl alcohol (130 ml) was treated dropwise with aqueous sodium hydroxide solution (71g in 113 ml of water) as fast as the vigorous reaction allowed. The mixture was heated under reflux for about 8 hours on a water-bath, then diluted with a little ethyl alcohol and decanted from the zinc into hydrochloric acid (240 ml of concentrated acid + 80 ml of water) in a large beaker which was cooled in ice; the remaining sludge was extracted with small amounts of hot ethyl alcohol and the extracts added to the rest.

Hydrochloride crystals which separated upon cooling in ice were filtered off and recrystallized from water, containing some hydrochloric acid, as white crystals (12g, 23%). The free amine was precipitated from a boiling solution of the hydrochloride salt in water, using ammonia solution, filtered and recrystallized from ethyl alcohol as pale brown-yellow needles, m.p. 133-134° (lit., 132-133°).

3,3'-Dibromobenzidine

(Levinstein, D.R.P. 97101; Chem.Zentr., 1898 II, 522).

A vigorously stirred mixture of zinc dust (65g) and o-bromonitrobenzene (50g, 0.25 mole) in ethyl alcohol (100 ml) was treated dropwise with aqueous sodium hydroxide solution (65g in 105 ml of water) as fast as the vigorous reaction allowed. The mixture was heated under reflux for about 10 hours on a water-bath, then diluted with a little ethyl alcohol and decanted from the zinc into hydrochloric acid (200 ml of concentrated acid + 70 ml of water) in a large beaker which was cooled in ice; the remaining sludge was extracted with small amounts of hot ethyl alcohol and the extracts added to the rest. Hydrochloride crystals which separated upon cooling in ice were filtered off and recrystallized from boiling water, containing some hydrochloric acid, as white crystals (8.3g, 21%). The free amine was precipitated with ammonia solution from a boiling aqueous solution of the hydrochloride salt, filtered and recrystallized from benzene-light petroleum (b.P. 60-80°) as long pale brown needles, m.p. 103-104° (lit., 103-104°).

Attempted resolution of 2,2'-di-t-butylbenzidine

The benzidine (0.74g) was dissolved in sodium-dried benzene (50 ml) contained in a 250 ml round bottom flask. L-Menthoxyacetyl chloride (1.17g) was added dropwise to the solution together with trimethylamine (10 drops). The solution was vigorously shaken for about 10 minutes then diluted with light petroleum (b.P. 60-80°) and the solid which separated was filtered and dried. The solid which isolated (0.67g), m.p. 251-252° was proved to be the trimethylamine hydrochloride.

(Found : C, 52.5 ; H, 12.0 ; N, 9.9 . Calculated for $C_6H_{16}ClN$ C, 52.3 ; H, 11.7 ; N, 10.2%).

The filtrate was left to evaporate at room temperature

whereby long needles were collected (1.47g), m.p. 134-135°.

(Found : C, 76.3 ; H, 10.1 . $C_{44}H_{68}N_2O_4$

requires C, 76.7 ; H, 9.9%).

The specific angles of rotation for this bis-(menthoxyacetyl) derivative in chloroform were determined as follows: (C, 0.1317g/$_{5ml}$).

Wavelength mμ	$[\alpha]^{18}$
578	-29.21°
546	-34.08°
436	-53.06°
405	-56.96°

Attempts to decompose this anilide to the corresponding free active amine by both acidic and basic media failed.

Attempted resolution of 2,2'-dibromo-6,6'-diethoxybenzidine

The benzidine (2.94g) and (+)-camphor-10-sulphonic acid (3.63g) were dissolved in warm ethyl alcohol (150 ml). The first crop which separated overnight at room temperature (3.29g), m.p. 302-304° had $[\alpha]_{578}^{25}$ + 15.1°; $[\alpha]_{546}^{25}$ + 18.2°; $[\alpha]_{436}^{25}$ + 42.4° in dimethylformamide, (C, 0.0496g/$_{5ml}$). Evaporation of the mother-liquor gave a second crop (2.22g), m.p. 303-305° and had $[\alpha]_{578}^{24}$ + 15.9°; $[\alpha]_{546}^{24}$ + 18.7°; $[\alpha]_{436}^{24}$ + 48.6° in dimethylformamide, (C, 0.0535g/$_{5ml}$).

Recrystallization of the first crop from ethyl alcohol gave salt with m.p. 309-310° and $[\alpha]_{578}^{24}$ + 20.1°; $[\alpha]_{546}^{24}$ + 23.6°; $[\alpha]_{436}^{24}$ + 53.3° (C, 0.0572g/$_{5ml}$), while recrystallization of the second crop from the same solvent gave salt with m.p. 309-310° and $[\alpha]_{578}^{24}$ + 20.5°; $[\alpha]_{546}^{24}$ + 25.1°; $[\alpha]_{436}^{24}$ + 56.2° in dimethylformamide, (C, 0.0489g/$_{5ml}$).

A portion of the pure first crop, on decomposition with cold 20% sodium hydroxide solution, gave the corresponding active benzidine which had m.p. 217-218° and $[\alpha]_{578}^{24}$ - 2.6°; $[\alpha]_{546}^{24}$ - 5.2°; $[\alpha]_{436}^{24}$ - 9.4°in acetone (C, 0.0964g/$_{5ml}$). On recrystallization from ethyl alcohol, the isolated benzidine had m.p. 218° and $[\alpha]_{578}^{23}$ - 1.98°; $[\alpha]_{546}^{23}$ - 4.71°; $[\alpha]_{436}^{23}$ - 6.94°in acetone, (C, 0.1009g/$_{5ml}$). On the other hand, the free benzidine obtained from the decomposition of the second crop had m.p. 218° and $[\alpha]_{578}^{24}$ - 2.69°; $[\alpha]_{546}^{24}$ - 5.38°; $[\alpha]_{436}^{24}$ - 9.94°in acetone, (C, 0.1091g/$_{5ml}$).

Attempts were made to obtain the highest angle by changing the concentration, since it was found that the solution becomes darker on increasing the concentration of the base which reduces the angle of rotation to lower values. The most suitable concentration to obtain the highest angle was found to be 0.1178g/5ml acetone as shown below:

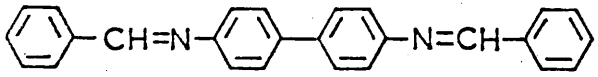
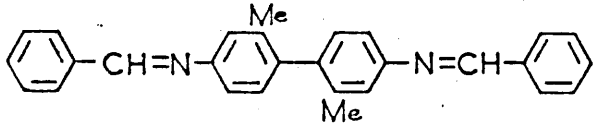
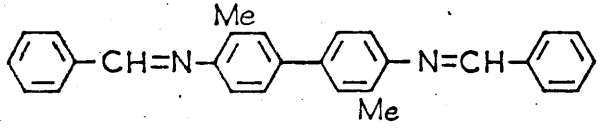
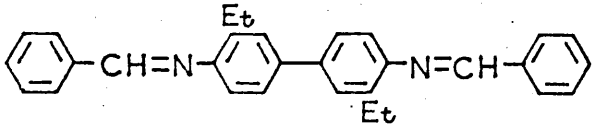
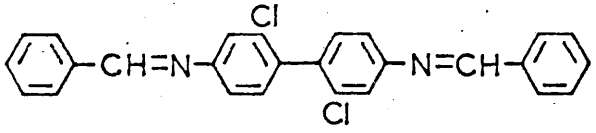
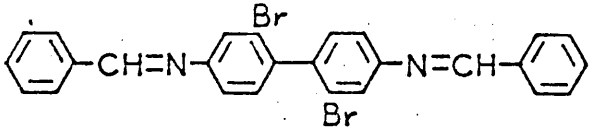
	$[\alpha]^{15}$			
Wavelength mμ	c=0.1098g	c=0.1178g	c=0.1292g	c=0.1838g
578	-2.52°	-2.65°	-2.58°	-1.36°
546	-5.23°	-5.33°	-5.26°	-2.45°
436	-9.65°	-9.85°	-9.70°	-4.35°

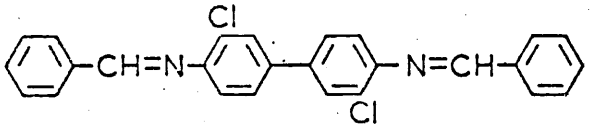
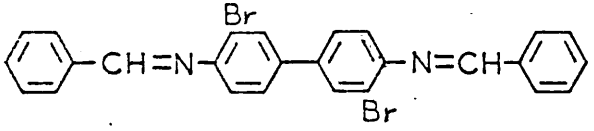
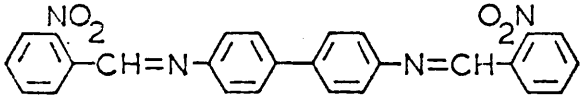
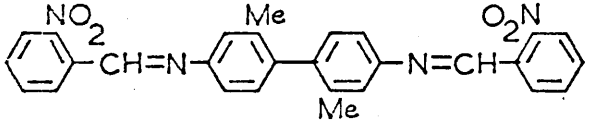
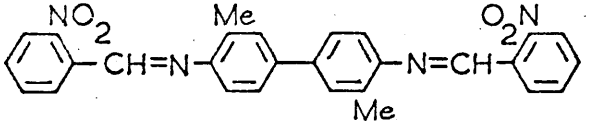
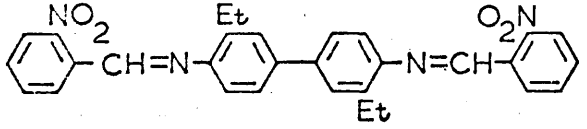
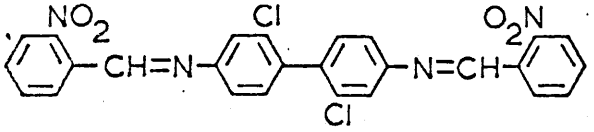
Preparation of the Schiff's bases

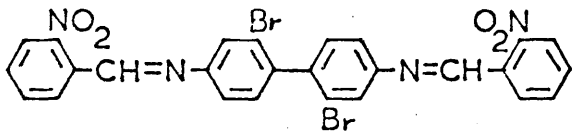
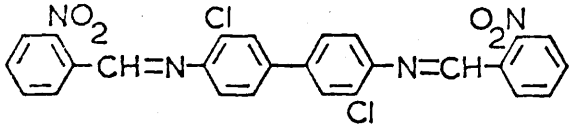
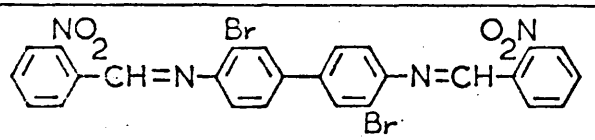
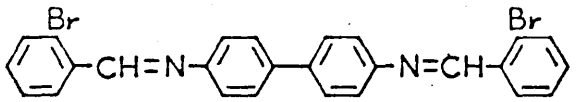
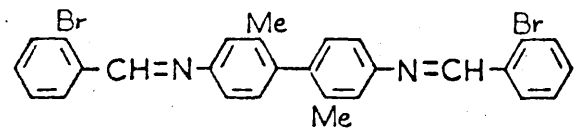
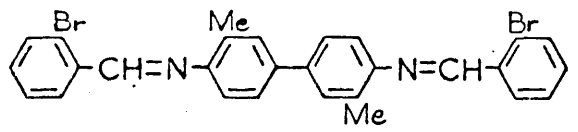
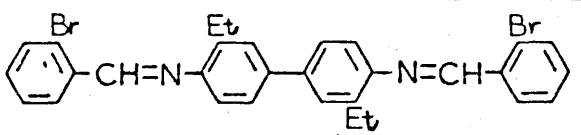
General procedure :

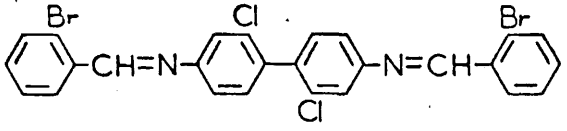
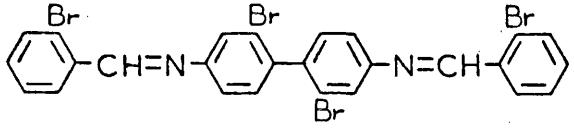
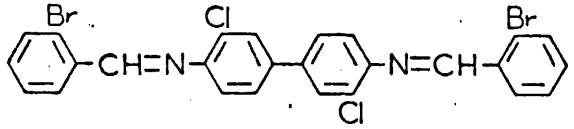
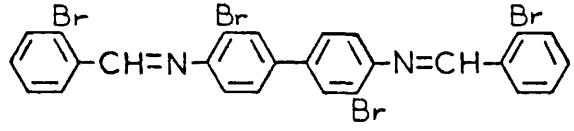
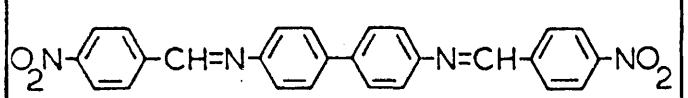
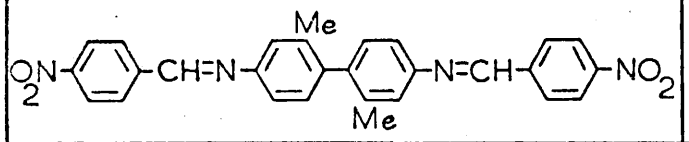
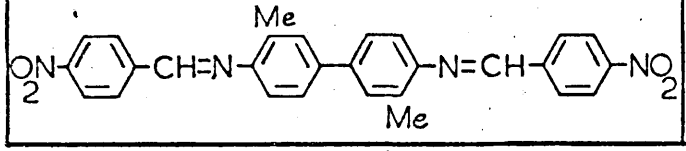
The benzidine (1 mole) and the aldehyde (2 moles) were dissolved in a suitable amount of absolute ethyl alcohol and the mixture was heated to the boiling point for 5-20 minutes (depending on the steric factors) then left to cool to room temperature. The solid which deposited after a few hours was filtered, dried and recrystallized several times to a constant melting point either from toluene, xylene or from a mixture of the above mentioned solvents and light petroleum (b.P. 80-100°). Properties and analysis of the Schiff's bases prepared are listed in Table XIV.

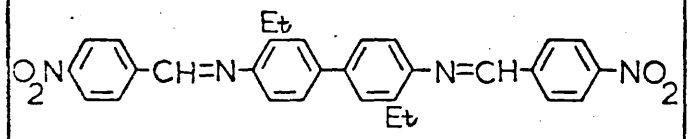
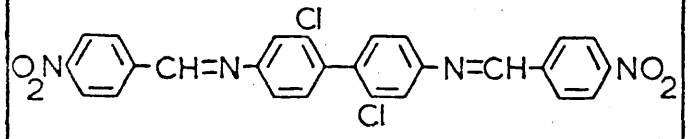
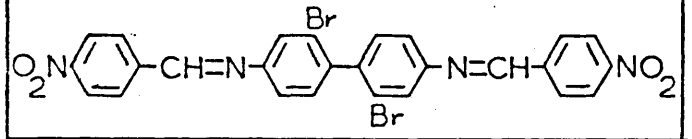
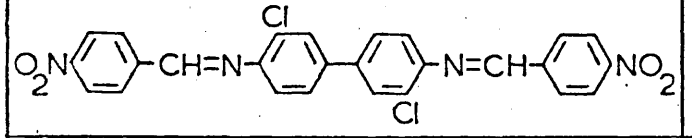
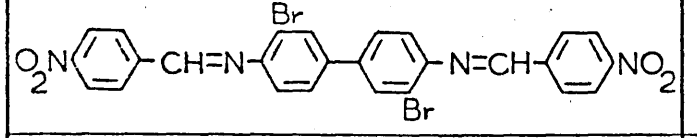
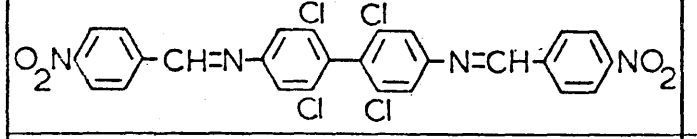
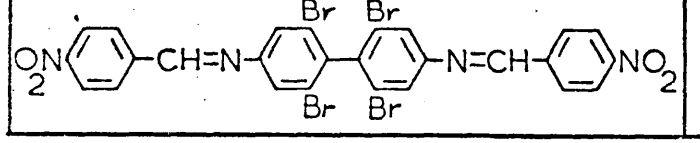
TABLE XIV. PROPERTIES & ANALYSIS OF THE SCHIFF'S BASES

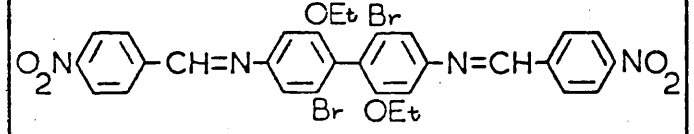
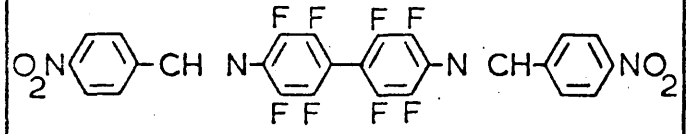
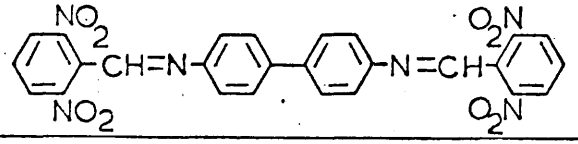
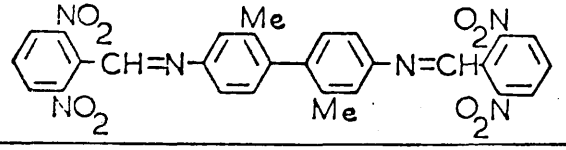
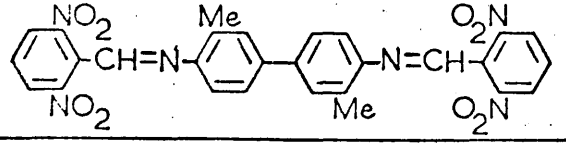
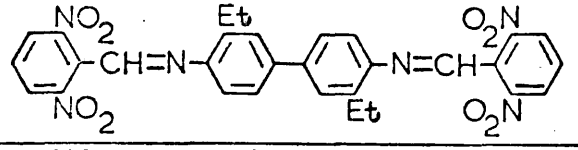
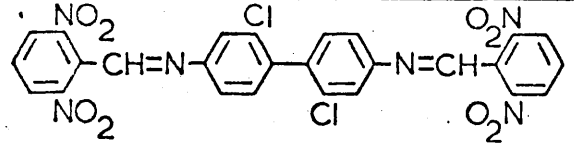
COMPOUND	M.P.°	COLOUR & SHAPE OF COMPOUND	% YIELD	FOUND %			FORMULA	REQUIRED %		
				C	H	N		C	H	N
	234–235	YELLOW CRYSTALS	100	86.8	5.6	7.7	$C_{26}H_{20}N_2$	86.7	5.6	7.8
	171–172	TAN NEEDLES	94	86.6	6.3	7.1	$C_{28}H_{24}N_2$	86.6	6.2	7.2
	153–154	YELLOW NEEDLES	97	86.6	6.3	7.0	$C_{28}H_{24}N_2$	86.6	6.2	7.2
	129–130	BROWN CRYSTALS	81	86.8	6.9	6.6	$C_{30}H_{28}N_2$	86.5	6.7	6.7
	199–200	YELLOW NEEDLES	91	72.5	4.3	6.4	$C_{26}H_{18}Cl_2N_2$	72.7	4.2	6.5
	221–222	TAN NEEDLES	89	59.9	3.8	5.5	$C_{26}H_{18}Br_2N_2$	60.2	3.5	5.4

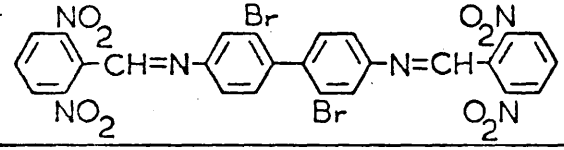
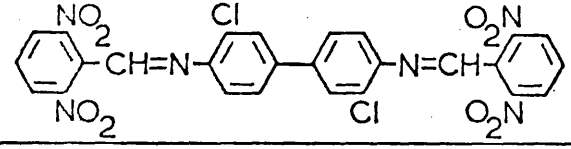
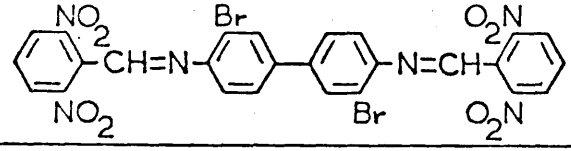
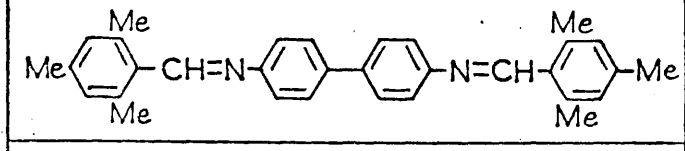
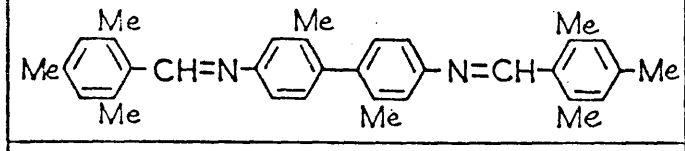
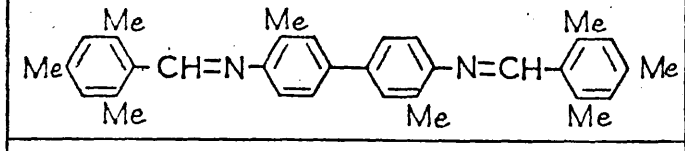
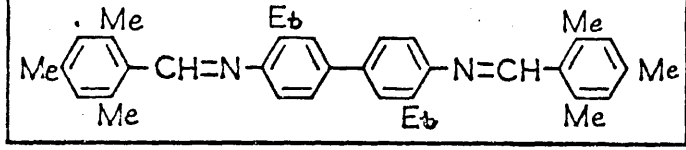
COMPOUND	M.P.°	COLOUR & SHAPE OF COMPOUND	% YIELD	FOUND %			FORMULA	REQUIRED %		
				C	H	N		C	H	N
	164–165	YELLOW CRYSTALS	82	72.6	4.2	6.6	$C_{26}H_{18}Cl_2N_2$	72.7	4.2	6.5
	174–175	ORANGE NEEDLES	75	60.1	3.7	5.4	$C_{26}H_{18}Br_2N_2$	60.2	3.5	5.4
	227–228	GOLDEN NEEDLES	98	69.1	4.0	12.6	$C_{26}H_{18}N_4O_4$	69.3	4.0	12.4
	153–154	BROWN CRYSTALS	90	70.5	4.7	11.8	$C_{28}H_{22}N_4O_4$	70.3	4.6	11.7
	217–218	ORANGE NEEDLES	93	70.6	4.6	11.8	$C_{28}H_{22}N_4O_4$	70.3	4.6	11.7
	143–144	YELLOW NEEDLES	70	71.3	5.2	11.3	$C_{30}H_{26}N_4O_4$	71.2	5.1	11.1
	179–180	YELLOW NEEDLES	89	60.0	3.3	10.7	$C_{26}H_{16}Cl_2N_4O_4$	60.1	3.1	10.8

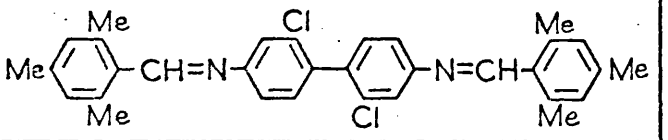
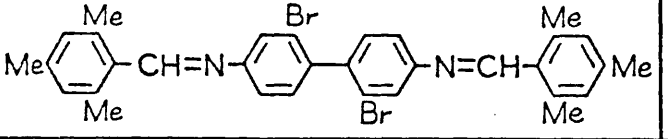
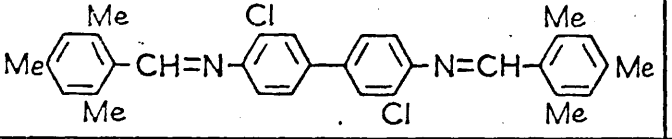
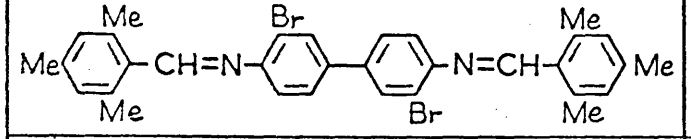
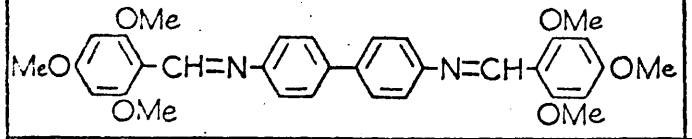
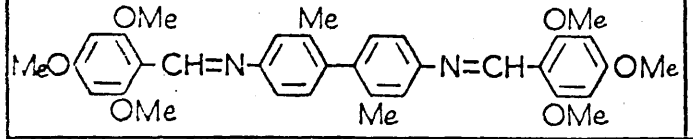
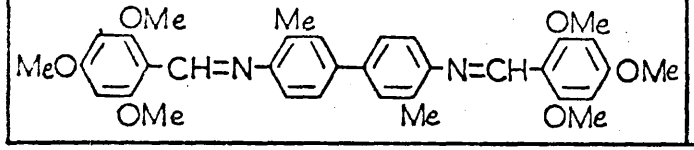
COMPOUND	M.P.°	COLOUR & SHAPE OF COMPOUND	% YIELD	FOUND %			FORMULA	REQUIRED %		
				C	H	N		C	H	N
	171–172	ORANGE–BROWN NEEDLES	85	51.4	2.5	9.1	$C_{26}H_{16}Br_2N_4O_4$	51.3	2.8	9.2
	223–224	ORANGE–RED CRYSTALS	76	60.3	3.2	10.8	$C_{26}H_{16}Cl_2N_4O_4$	60.1	3.1	10.8
	229–230	ORANGE–BROWN CRYSTALS	70	51.1	2.7	9.3	$C_{26}H_{16}Br_2N_4O_4$	51.3	2.8	9.2
	189–190	YELLOW CRYSTALS	86	60.1	3.4	5.7	$C_{26}H_{18}Br_2N_2$	60.2	3.5	5.4
	133–134	YELLOW CRYSTALS	79	61.5	4.0	5.2	$C_{28}H_{22}Br_2N_2$	61.5	4.0	5.1
	162–163	YELLOW CRYSTALS	83	61.2	3.9	5.1	$C_{28}H_{22}Br_2N_2$	61.5	4.0	5.1
	215–216	BROWN NEEDLES	58	63.0	4.5	4.9	$C_{30}H_{26}Br_2N_2$	62.7	4.5	4.9

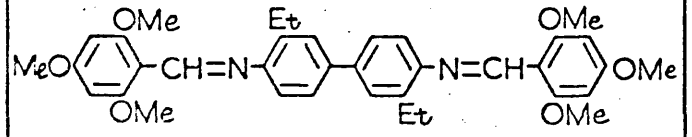
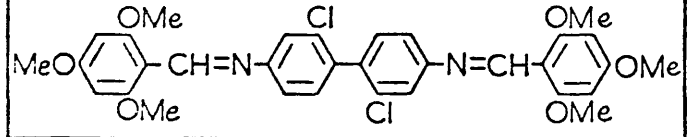
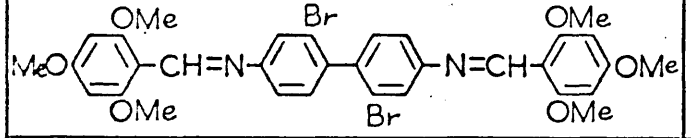
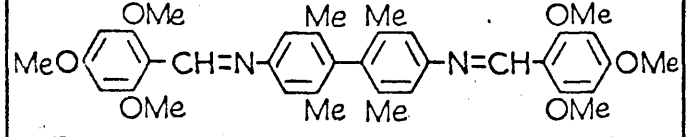
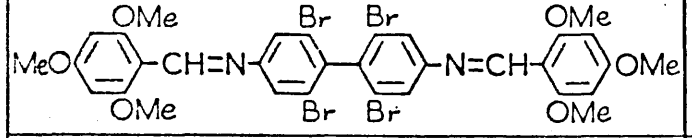
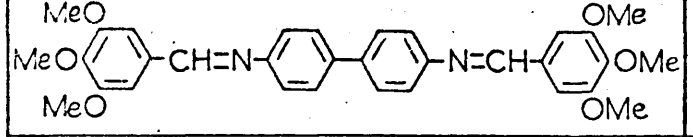
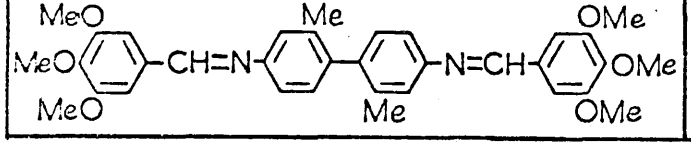
COMPOUND	M.P. °C	COLOUR & SHAPE OF COMPOUND	% YIELD	FOUND %			FORMULA	REQUIRED %		
				C	H	N		C	H	N
	173–174	YELLOW CRYSTALS	84	53.1	2.7	4.6	$C_{26}H_{16}Br_2Cl_2N_2$	53.2	2.7	4.7
	167–168	PALE YELLOW CRYSTALS	80	45.9	2.5	4.0	$C_{26}H_{16}Br_4N_2$	46.2	2.4	4.1
	228–229	BROWN CRYSTALS	71	53.0	2.8	4.9	$C_{26}H_{16}Br_2Cl_2N_2$	53.2	2.7	4.7
	230–231	YELLOW NEEDLES	66	46.1	2.5	4.2	$C_{26}H_{16}Br_4N_2$	46.2	2.4	4.1
	242–243	YELLOW CRYSTALS	100	69.5	4.0	12.1	$C_{26}H_{18}N_4O_4$	69.3	4.0	12.4
	224–225	YELLOW NEEDLES	100	70.0	4.6	11.5	$C_{28}H_{22}N_4O_4$	70.3	4.6	11.7
	244–245	ORANGE NEEDLES	98	70.2	4.7	11.5	$C_{28}H_{22}N_4O_4$	70.3	4.6	11.7

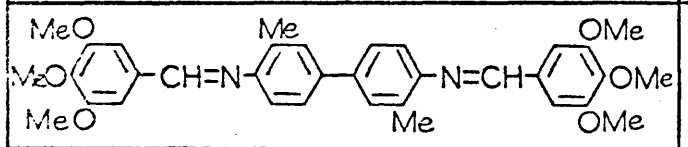
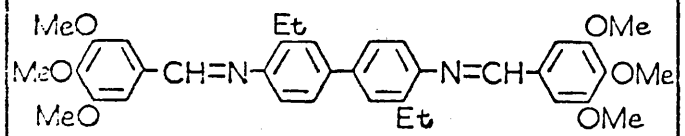
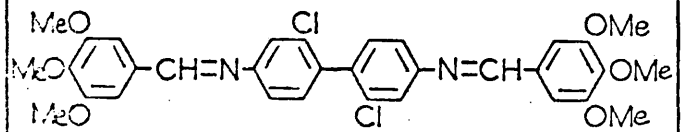
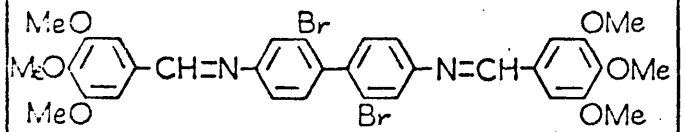
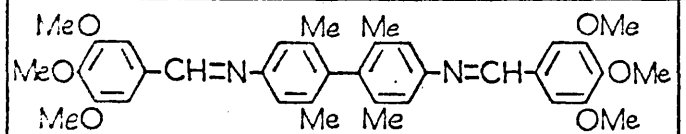
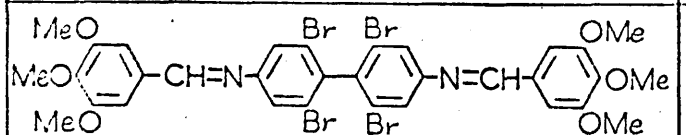
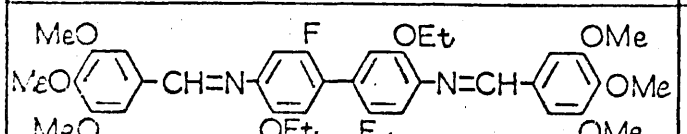
COMPOUND	M.P. °C	COLOUR & SHAPE OF COMPOUND	% YIELD	FOUND %			FORMULA	REQUIRED %		
				C	H	N		C	H	N
	197–198	ORANGE NEEDLES	89	71.4	5.1	11.1	$C_{30}H_{26}N_4O_4$	71.2	5.1	11.1
	224–225	YELLOW NEEDLES	95	60.0	3.2	10.9	$C_{26}H_{16}Cl_2N_4O_4$	60.1	3.1	10.8
	220–221	YELLOW CRYSTALS	90	51.4	2.7	9.4	$C_{26}H_{16}Br_2N_4O_4$	51.3	2.6	9.2
	215–216	YELLOW NEEDLES	84	59.9	3.0	11.1	$C_{26}H_{16}Cl_2N_4O_4$	60.1	3.1	10.8
	205–206	ORANGE CRYSTALS	79	51.1	2.7	9.5	$C_{26}H_{16}Br_2N_4O_4$	51.3	2.6	9.2
	304–305	YELLOW NEEDLES	76	53.2	2.3	9.6	$C_{26}H_{14}Cl_4N_4O_4$	53.1	2.4	9.5
	314–315	YELLOW NEEDLES	60	40.4	1.8	7.4	$C_{26}H_{14}Br_4N_4O_4$	40.7	1.8	7.3

COMPOUND	M.P. °C	COLOUR & SHAPE OF COMPOUND	% YIELD	FOUND %			FORMULA	REQUIRED %		
				C	H	N		C	H	N
	260–261	YELLOW NEEDLES	91	51.8	3.3	7.9	$C_{30}H_{24}Br_2N_4O_6$	51.7	3.5	8.0
	227–228	YELLOW NEEDLES	43	52.3	1.6	9.5	$C_{26}H_{10}F_8N_4O_4$	52.5	1.7	9.4
	216–217(d.)	RED ORANGE CRYSTALS	77	57.6	2.8	15.7	$C_{26}H_{16}N_6O_8$	57.8	3.0	15.5
	203–204 (d.)	ORANGE YELLOW NEEDLES	71	59.4	3.6	14.8	$C_{28}H_{20}N_6O_8$	59.2	3.5	14.8
	225–226 (d.)	RED CRYSTALS	69	59.3	3.4	14.8	$C_{28}H_{20}N_6O_8$	59.2	3.5	14.8
	165–166	RED CRYSTALS	54	60.2	4.3	14.0	$C_{30}H_{24}N_6O_8$	60.4	4.0	14.1
	211–212(d.)	RED CRYSTALS	77	51.1	2.6	13.7	$C_{26}H_{14}Cl_2N_6O_8$	51.2	2.3	13.8

COMPOUND	M.P. °	COLOUR & SHAPE OF COMPOUND	% YIELD	FOUND %			FORMULA	REQUIRED %		
				C	H	N		C	H	N
	205-206 (d.)	RED CRYSTALS	69	44.9	1.9	12.1	$C_{26}H_{14}Br_2N_6O_8$	44.7	2.0	12.0
	229-230 (d.)	RED CRYSTALS	51	51.2	2.1	13.6	$C_{26}H_{14}Cl_2N_6O_8$	51.2	2.3	13.8
	218-219	BROWN NEEDLES	47	44.6	2.1	12.2	$C_{26}H_{14}Br_2N_6O_8$	44.7	2.0	12.0
	211-212	YELLOW NEEDLES	85	86.3	7.6	6.2	$C_{32}H_{32}N_2$	86.5	7.2	6.3
	163-164	TAN CRYSTALS	81	86.3	7.5	5.7	$C_{34}H_{36}N_2$	86.4	7.6	5.9
	204-205	YELLOW CRYSTALS	80	86.5	7.7	5.8	$C_{34}H_{36}N_2$	86.4	7.6	5.9
	173-174	YELLOW NEEDLES	72	86.3	8.1	5.4	$C_{36}H_{40}N_2$	86.4	8.0	5.6

COMPOUND	M.P. °C	COLOUR & SHAPE OF COMPOUND	% YIELD	FOUND %			FORMULA	REQUIRED %		
				C	H	N		C	H	N
	166–167	YELLOW CRYSTALS	82	74.8	5.9	5.3	$C_{32}H_{30}Cl_2N_2$	74.9	5.8	5.4
	176–177	TAN CRYSTALS	80	63.8	4.9	4.7	$C_{32}H_{30}Br_2N_2$	63.7	5.0	4.7
	236–237	YELLOW CRYSTALS	69	74.7	5.8	5.2	$C_{32}H_{30}Cl_2N_2$	74.9	5.8	5.4
	240–241	YELLOW CRYSTALS	65	63.7	5.1	4.6	$C_{32}H_{30}Br_2N_2$	63.7	5.0	4.7
	238–239	PALE–YELLOW CRYSTALS	90	71.3	6.0	5.2	$C_{32}H_{32}N_2O_6$	71.1	5.9	5.2
	159–160	ORANGE–YELLOW CRYSTALS	87	72.1	6.2	5.0	$C_{34}H_{36}N_2O_6$	71.8	6.3	4.9
	214–215	ORANGE–YELLOW CRYSTALS	84	72.1	6.4	5.1	$C_{34}H_{36}N_2O_6$	71.8	6.3	4.9

COMPOUND	M.P.°	COLOUR & SHAPE OF COMPOUND	% YIELD	FOUND %			FORMULA	REQUIRED %		
				C	H	N		C	H	N
	208–209	YELLOW CRYSTALS	74	72.5	6.7	4.7	$C_{36}H_{40}N_2O_6$	72.6	6.7	4.7
	158–159	RED–ORANGE CRYSTALS	85	62.9	4.8	4.7	$C_{32}H_{30}Cl_2N_2O_6$	63.0	4.9	4.6
	163–164	YELLOW–ORANGE CRYSTALS	81	55.2	4.2	4.1	$C_{32}H_{30}Br_2N_2O_6$	55.1	4.3	4.0
	216–217	YELLOW–ORANGE NEEDLES	77	72.7	7.0	4.3	$C_{36}H_{40}N_2O_6$	72.6	6.7	4.7
	276–277	PALE YELLOW CRYSTALS	71	44.7	3.1	3.4	$C_{32}H_{28}Br_4N_2O_6$	44.8	3.3	3.3
	185–186	YELLOW CRYSTALS	94	71.1	6.0	5.2	$C_{32}H_{32}N_2O_6$	71.1	5.9	5.2
	184–185	PALE YELLOW CRYSTALS	88	71.8	6.5	4.8	$C_{34}H_{36}N_2O_6$	71.8	6.3	4.9

COMPOUND	M.P.°	COLOUR & SHAPE OF COMPOUND	% YIELD	FOUND %			FORMULA	REQUIRED %		
				C	H	N		C	H	N
	182–183	YELLOW CRYSTALS	85	72.1	6.4	5.0	$C_{34}H_{36}N_2O_6$	71.8	6.3	4.9
	151–152	YELLOW–ORANGE NEEDLES	75	72.4	6.6	4.5	$C_{36}H_{40}N_2O_6$	72.6	6.7	4.7
	176–177	PALE YELLOW CRYSTALS	87	62.9	4.9	4.6	$C_{32}H_{30}Cl_2N_2O_6$	63.1	4.9	4.6
	168–169	PALE YELLOW CRYSTALS	83	55.3	4.3	4.1	$C_{32}H_{30}Br_2N_2O_6$	55.0	4.3	4.0
	206–207	YELLOW NEEDLES	83	72.7	6.9	4.4	$C_{36}H_{40}N_2O_6$	72.6	6.7	4.7
	225–226	YELLOW CRYSTALS	75	44.6	3.1	3.4	$C_{32}H_{28}Br_4N_2O_6$	44.8	3.3	3.3
	178–179	YELLOW CRYSTALS	71	64.7	5.8	4.2	$C_{36}H_{38}F_2N_2O_8$	65.1	5.7	4.2

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