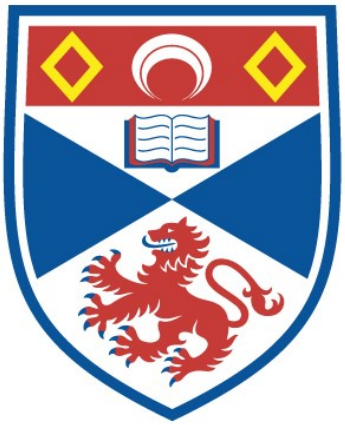
INTERNAL ROTATION ABOUT C-C AND C-N BONDS

Sally-Anne Hamlin

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1978

INTERNAL ROTATION ABOUT C-C AND C-N BONDS

being a Thesis

presented by

SALLY-ANNE HAMLIN, B.Sc.

to the

UNIVERSITY OF ST.ANDREWS

in application for

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SUMMARY

A study of the historical and more recent work on rotation about carbon-carbon and carbon-nitrogen bonds was the basis for the further investigation of three series of compounds:

1. 2,2′ - disubstituted biphenyls,
2. N-benzyl-N-tosyl substituted anilines,
3. substituted quinone-anils.

From this work it was established that, in certain compounds, the free energy ($\Delta G^{\neq}$) for hindered rotation cannot be discussed solely in steric terms but that electronic influences should also be considered.

In the substituted aniline series, it was concluded that a Hammett type correlation existed between the electronegativity of the substituents *para* to the amino group and the value of $\Delta G^{\neq}$. This correlation was extrapolated to explain the electronic influence of the substituents *ortho* to the amino group. Consideration was paid to the possibility that, for the *ortho* substituents, steric factors may outweigh electronic factors.

An attempt was made to extend this correlation to explain the electronic influence of 2′- and 4′-substituents upon the $\Delta G^{\neq}$ values and rates of racemization of substituted biphenyls. However, it was found that the simple Hammett correlation was not followed and that, for the racemization studies, the entropy of activation ($\Delta S^{\neq}$) became a significant factor.

The values of $\Delta G^{\ddagger}$ for hindered rotation were obtained from the analysis of 100MHz n.m.r. spectra. The validity of these $\Delta G^{\ddagger}$ values was discussed with respect to their accuracy and with respect to the effect of entropy. The synthetic routes used to obtain the three series of compounds were also discussed.

The discussion of the synthetic routes includes the attempted preparations of a number of quinone-anils via the condensation of 2,6-di-t-butyl-1,4-benzoquinone with 4-substituted 2-benzylanilines. This was complicated by the production of impure samples of 2-benzylaniline and 2-benzyl-4-chloroaniline. The synthesis of 2-benzyl-4-nitroaniline was not reproducible.

The condensation reaction resulted in a number of products. These were separated by crystallization techniques and identified by high pressure liquid chromatography, I.R. spectroscopy, ^{13}C and proton n.m.r. The structure of a new compound based on a dihydroindole containing one spiro carbon joined to a substituted quinone ring is proposed.

CONTENTS

DECLARATION

I declare that this thesis is based on the results of experiments carried out by me, that it is my own composition, and has not previously been presented for a Higher Degree.

The work was carried out in the Department of Chemistry of the University of St.Andrews, under the supervision of Dr.R.K.Mackie since 1st October, 1975, the date of my admission as a research student.

CERTIFICATE

I hereby certify that Sally-Anne Hamlin, B.Sc., has spent twelve terms at research work under my supervision, has fulfilled the conditions of the Resolution of the University Court 1967, No.1, and is qualified to submit the accompanying thesis in application for the degree of Doctor of Philosophy.

R. K. Mackie,
Research Supervisor.

ACKNOWLEDGEMENTS

I would like to thank Dr. Ray Mackie for all his help, encouragement and infinite patience over the last three years. I must also thank Professors Lord Tedder and P.A.H.Wyatt for use of the research facilities in the department during this time.

I am greatly indebted to the technical staff of the Department, particularly Mrs.M.Smith, (n.m.r. spectra), Mr.C.Millar (mass spectra), Mr.J.R.Bews (microanalyses) and Mrs.S.Smith (microanalyses). I am also grateful to Mrs.D.Milner and Dr.B.Sagar for their help in the production of this thesis.

Finally, I must thank my colleague, friend and, (more recently), husband Tony Sagar for all his help and support, without which this thesis would never have been written.

DEDICATION

To all the members of my large and much loved family.

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1. INTRODUCTION

1.1 The Historical Background

Restricted rotation in carbon-carbon and carbon-nitrogen bonds is an old and well documented phenomenon. In 1872, the first work on sterically hindered reactions was carried out by A.W.Hofmann in a study of the synthesis of aromatic monoamines[1]. Information relating to sterically hindered reactions then increased very rapidly, the most extensive and significant results being obtained in studies of the esterification of carboxylic acids, as first carried out by V.Meyer in 1894[2].

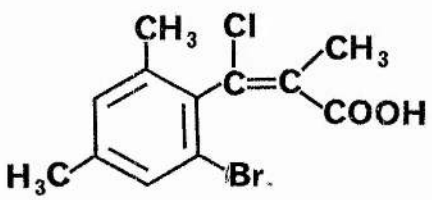
The next development in the field of steric hindrance was in 1922 with the discovery, by G.H.Christie and J.Kenner, of optical activity in 2,2',6,6'-tetrasubstituted biphenyls[3]. This work was carried out in order to resolve the argument relating to the actual conformation of the biphenyl molecule and proved that the benzene nuclei of the two phenyl residues in biphenyl were co-planar.

Once again this led to a rapid increase in information relating to the phenomenon of steric hindrance. Extensive studies were made on the rates of racemization of multi-substituted biphenyls, their dependence upon the "size" of the ortho-substituents and the effect upon the pivot bond and ortho-substituents of substitution in other parts of the molecule[4]. This work led to the first reliable classification of groups in order of "size", this being:-

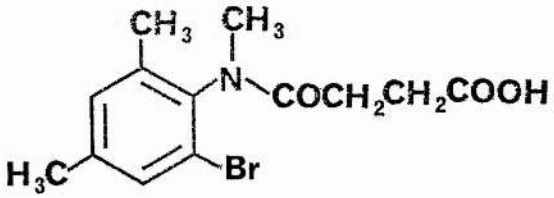
$$Br > CH_3 > Cl > NO_2 > COOH > OCH_3 > F > H \ .$$

This sequence was in some agreement with the "interference values" calculated from x-ray data[5]. The work also showed that substitution at the 3′ position of the biphenyl system had a strong effect on the rate of racemization.

Further work by M.Rieger and E.H.Westheimer proposed that the decrease in the rate of racemization of 2,2′,3′-trisubstituted biphenyls was due to the "buttressing effect" of the 3′-substituent[6]. This "buttressing effect" was explained as an interference by the 3′-substituent such that the 2′-substituent was forced further into the plane of the 2-substituent hence increasing the steric hindrance. Substitutionin the 5′ position had a similar, if smaller, effect. It was also interesting to note that the sequence for the degree of influence of the 3′-substituents was not the same as the sequence of "size" found for the 2,2′-substituents, being:- $NO_2 > Br > Cl > CH_3 > OCH_3$ [7]. Also, in other compounds which exhibited optical activity, for example substituted styrenes (I) and amines (II), the order of effectiveness of groups to hinder racemization was different again.



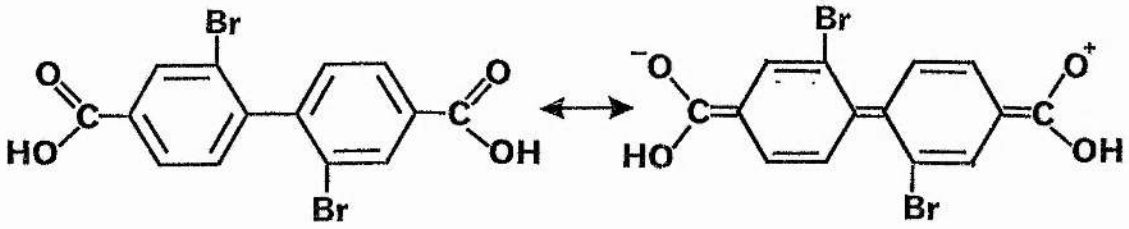
I



II

However, in all these examples the effects being studied were steric rather than electronic. Other factors may affect

rates of racemization, for example, the possibility of resonance or hydrogen bonding. An illustration of resonance affecting the rate of racemization was shown by the comparison of 2,2′-dibromo-4,4′-diaminobiphenyl and 2,2′-dibromobiphenyl-4,4′-dicarboxylic acid. The former cannot be resolved whereas the latter showed optical activity. This was attributed by M.Calvin to the possibility of a resonance stabilized form of the molecule (scheme I)[8].



Scheme I

Thus the study of the racemization of optically active biphenyls created the foundations for a now rapidly expanding field of study.

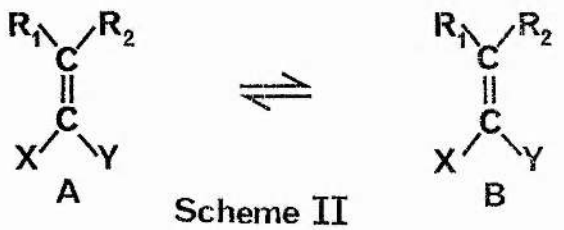
1.2 Current fields of study in sterically hindered carbon-carbon and carbon-nitrogen bonds.

The work on sterically hindered rotation in multi-substituted biphenyls, as carried out by R.Adams and H.C.Yuan, had one major limiting factor[9]. This was that, to be able to study the racemization of optical isomers, the isomers had first to be isolated and in most cases, the separation of isomers was not practicable unless the half-lives of racemization were of at least several hours duration at working temperatures.

However, with the advent of modern instrumentation, a wide range of methods are now available for the measurement of the "internal barriers", as described by E.B.Wilson Jr. [10]. The methods include the use of the dipole moment, electron diffraction, U.V., I.R., Raman and n.m.r. spectroscopy, the dispersion of sound, microwave intensity and microwave splitting. The main advantage of these methods is that they can be used to study very fast intramolecular movements and by combining these methods a wide range of rates of equilibration can be studied.

Of these methods, one of the most useful is dynamic nuclear magnetic resonance (d.n.m.r.) spectroscopy. Processes with activation energies of between 5 and 20 Kcal.mole^{-1} can be studied and this covers a wide range of rotations, isomerisations and inversions. It also overlaps with the energy range for processes which can be studied by direct equilibration.

A simple example is shown by considering scheme II.



Scheme II

If $R_1 = R_2$ then A and B are chemically identical. However, in the n.m.r. spectrum, if X and Y are different then R_1 and R_2 are not equivalent. (This is because in A, R_1 is cis to X

and trans to Y and in B, R_1 is trans to X and cis to Y; this change in environment is detected in the n.m.r. spectrum). Rotation about the double bond gives rise to an "exchange" of R_1 and R_2. If the rotation is "slow" on the n.m.r. timescale, (that is $k_r \ll \pi \Delta\nu / \sqrt{2}$, where $\Delta\nu$ is the chemical shift difference without exchange), then two separate signals are seen for R_1 and R_2. If the rotation is "fast" on the n.m.r. timescale then only one signal is seen for R_1 and R_2 with an intermediate chemical shift, (fig.1).

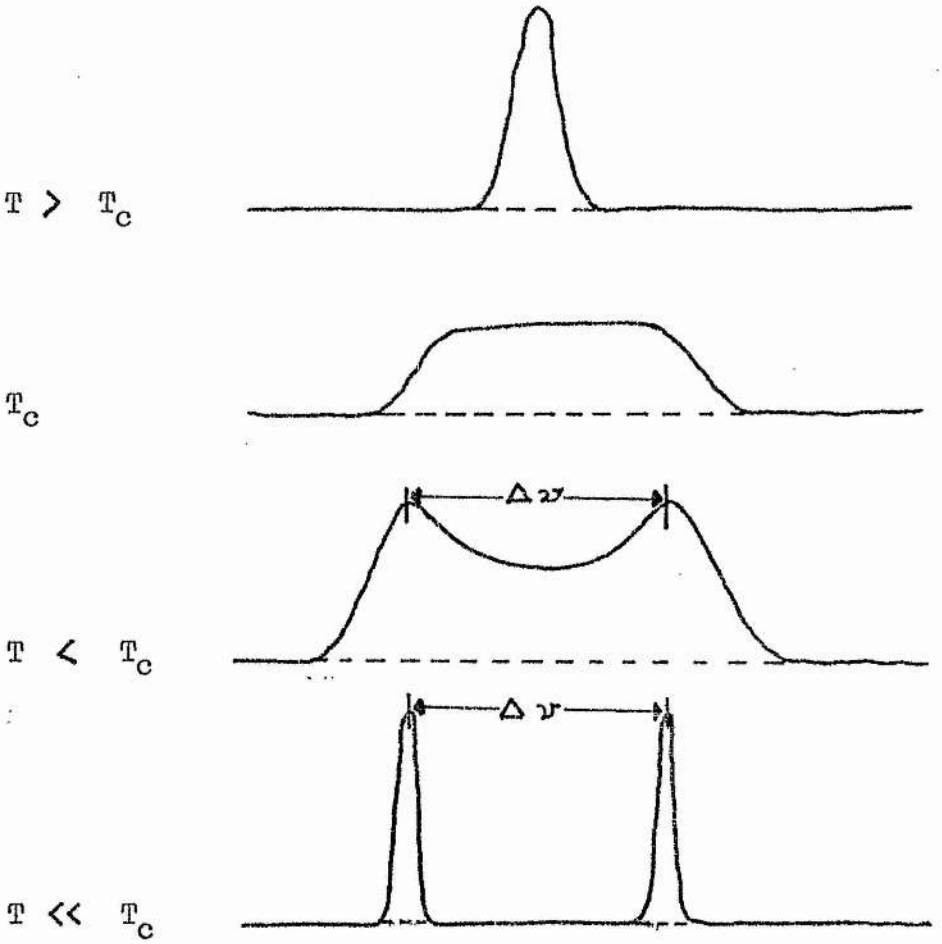


fig.1.

(Uncoupled AB case) T_c = temperature of coalescence

If free rotation can be induced thermally then, by studying the n.m.r. spectra from "slow" to "fast" rotation, the rate constant k_r can be elucidated. Also, the activation parameters $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ can be found from k_r by three methods, these being the use of approximation equations, the graphical evaluation of spectral parameters and the computer matching of measured and calculated spectra. Each method has its practical applications and limitations, however these will not be discussed at this juncture.

Also, although d.n.m.r. spectroscopy is most commonly used in the study of proton containing compounds, other nuclei with nuclear spin = $\frac{1}{2}$, for example, ^{13}C, ^{31}P and ^{19}F can be studied. Thus it can be seen that d.n.m.r. spectroscopy has very wide applications in both organic and inorganic chemistry. However, a full discussion of the range of these applications is out with the scope of this present work and therefore this introduction will be limited to a few selected examples. (Recent comprehensive reviews are available including that of T.H.Siddall and W.E.Stewart, and those of S.Sternhall[11, 12, 13]).

Three types of compound were selected for close study. These were substituted biphenyls, substituted anilines and related compounds, and nitrogen-aryl imines.

There are many examples of substituted biphenyls in which the rates of rotation about the pivot bonds are suitable for investigation by d.n.m.r. spectroscopy. A summary of those studied recently is shown in Table 1.

TABLE 1.

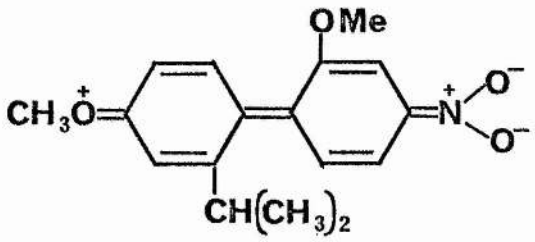
Biphenyl	$\Delta G^{\ddagger}$ kcal.mole^{-1}	T_c/°C	Compd. No.	Ref.
2,2′-di-CH_2-O-C(=O)-CH_3	20.2	127	1	14 15
2,2′-di-$CH(CH_3)_2$	> 26.1	> 200	2	15
2,2′-di-$C(OH)(CH_3)_2$	> 24.5	> 190	3	15
2-$CH(CH_3)_2$-2′-$COOCH_3$			4	16
2-$CH(CH_3)_2$-2′-OCH_3	19.2 ± 0.1	86	5	17
2-$CH(CH_3)_2$-2′-OCH_3-4′-OCH_3	18.5 ± 0.1	74	6	17
2-$CH(CH_3)_2$-2′-OCH_3-4′-NO_2	19.2 ± 0.1	86	7	17
2-$CH(CH_3)_2$-2′-OCH_3-4-OCH_3	18.3 ± 0.1	70	8	17
2-$CH(CH_3)_2$-2′-OCH_3-4,4′ di-OCH_3	17.9 ± 0.1	61	9	17
2-$CH(CH_3)_2$-2′-OCH_3-4-OCH_3-4′-NO_2	18.0 ± 0.1	65	10	17
2-$CH(CH_3)_2$-2′-OCH_3-4-NO_2	18.8 ± 0.1	79	11	17
2-$CH(CH_3)_2$-2′-OCH_3-4-NO_2-4′-OCH_3	17.6 ± 0.1	58	12	17
2-$CH(CH_3)_2$-2′-OCH_3-4,4′-di-NO_2	19.1 ± 0.1	82	13	17
2-$CH(CH_3)_2$-2′-OH	19.3 ± 0.2	77	14	18
2-$CH(CH_3)_2$-2′-OH-4′-NO_2	19.1 ± 0.2	76	15	18
2-$CH(CH_3)_2$-2′-OH-5′-NO_2	18.7 ± 0.2	65	16	18
2-$CH(CH_3)_2$-2′-OH-4-NO_2	17.7 ± 0.2	57	17	18
2-$CH(CH_3)_2$-2′-OH-5-NO_2	17.6 ± 0.2	55	18	18

In the unsubstituted 2,2′-diisopropylbiphenyl, (compound 2), it is seen that the $\Delta G^{\ddagger}$ is too high for evaluation by d.n.m.r. methods. (The steric hindrance due to the two isopropyl groups is too large for free rotation about the 1,1′-carbon-carbon bond to be thermally induced within the working temperature range). . For the related compound where the single protons of the isopropyl groups are replaced by hydroxyl functions, (compound 3), the value of $\Delta G^{\ddagger}$ is also too high for study by d.n.m.r. methods. However, the study of methyl 2-isopropylbiphenyl-2′-carboxylate has shown that the evaluation of $\Delta G^{\ddagger}$ by d.n.m.r. methods is possible although this has not yet been carried out.

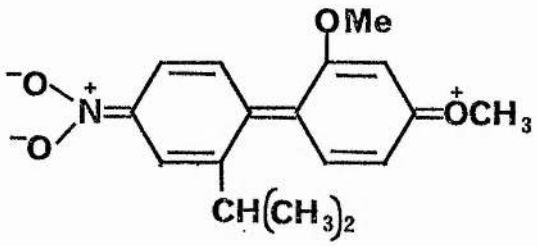
Therefore M.Ōki and co-workers carried out two systematic studies on a series of substituted biphenyls, (compounds 5-18). The biphenyls were studied by d.n.m.r. using the coalescence pattern of the isopropyl group in the 2-position. (Restricted rotation about the 1,1′-carbon-carbon bond renders the two methyl functions of the isopropyl group non-equivalent because of the induced unsymmetrical conformation). Various other groups were substituted in the 2′,4,4′,5 and 5′ positions to give a comparison of electronic effects.

In the series formed by the substitution of methoxy and nitro groups, (compounds 5-13), two effects were described as influencing the value of $\Delta G^{\ddagger}$, these being through

conjugation and bond-bending effects. An example of through conjugation affecting the value of $\Delta G^{\neq}$ is shown by compounds 10 and 12. M.Ōki and G.Yamamoto ascribed this to the contribution of canonical forms, (III, IV), which stabilized the planar transition state.



III



IV

An example of bond-bending affecting the value of $\Delta G^{\neq}$ was shown by a comparison of compounds 6 and 7. M.Ōki and G.Yamamoto stated that through resonance stabilization was of the same order in both compounds and therefore the difference seen in $\Delta G^{\neq}$ was due solely to bond-bending. The effect was rationalised as being due to the electron-donating methoxy group increasing the π-electron density at the 1-1′ carbons of the pivot bond and hence easing

out-of-plane bending of the bond[19,20]. This resulted in reduced steric interactions of the 2,2′ substituents and a corresponding decrease in $\Delta G^{\neq}$.

However, M.Ōki and G.Yamamoto also noted that the electron-withdrawing nitro-group would have the reverse effect on out-of-plane bonding. Therefore in considering the overall effect on $\Delta G^{\neq}$ a summation of these effects must be considered.

In the series formed by the substitution of hydroxyl and nitro-groups, (compounds 14-18), intramolecular O-H···π interaction was stated to be the main effect in influencing the value of $\Delta G^{\neq}$. In compound 14, the relatively high value of $\Delta G^{\neq}$ was attributed to stabilization of the ground state. This was considered as being due to O-H···π interaction enhanced by the perpendicular alignment of the two benzene rings caused by the steric requirements of the isopropyl group.

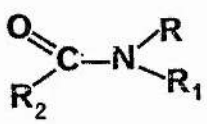
In compounds 17 and 18 the relatively low values of $\Delta G^{\neq}$ as compared to the values of $\Delta G^{\neq}$ for compounds 15 and 16 were attributed to the influence of the nitro group upon the hydroxyl group. This was rationalized as being due to stronger O-H···π interaction in compounds 15 and 16 because of the nitro-group being in the same ring as the hydroxyl-group, therefore increasing the acidity of the hydroxyl proton. Conversely, substitution of the nitro-group in the ring with the isopropyl group at the 2-position

would decrease the π-electron basicity and hence decrease the O-H····π bond interaction.

Thus it can be seen that a combination of many electronic effects may influence the value of $\Delta G^{\ddagger}$ arising from restricted rotation about the 1,1′-carbon-carbon bond of biphenyls. However, no systematic study appeared to have been carried out on the influence of the bulk of substituents substituted in the 2,2′-positions.

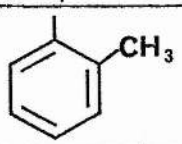
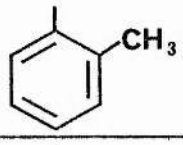
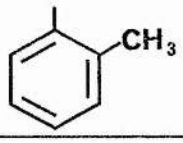
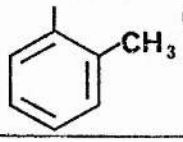
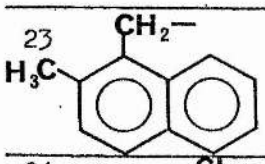
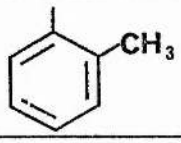
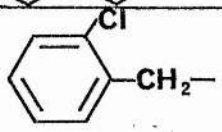
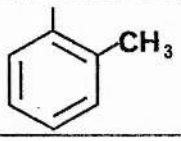
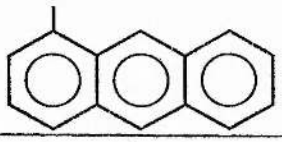
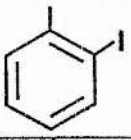
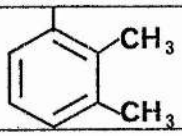
Therefore it was decided that an attempt should be made to synthesise a series of unsymmetric biphenyls, substituted only in the 2,2′-positions. One of the 2 or 2′ -substituents would contain a potentially non-equivalent methylene group, the coalescence of which would be studied by d.n.m.r. However, due to practical difficulties, very few of these compounds could be prepared successfully and so the series was very limited. Therefore the work was continued in the study of a series of substituted anilines.

Restricted rotation about the aryl-nitrogen bond in anilides and related compounds is analogous to that seen in biphenyls and has been studied extensively. (Recent work has been comprehensively reviewed by W.E.Stewart and T.H.Siddall[21]). The focus of this work has been the effect of the size of the substituents R, R_1 and R_2, (V),



V

TABLE 2

Cmpd. No.	R	R_1	R_2	$\Delta G^{\ddagger}$ / kcal mole^{-1}	T_c / °C	Ref.
19	$C_6H_5CH_2$-		CH_3	20.1	142	21,22
20	$C_6H_5CH_2$-		C_6H_5	18.5	99	21,22
21	$C_6H_5CH_2$-		$(C_2H_5)_3C$-	19.6	117	23
22	$C_6H_5CH_2$-		$(C_6H_5)_2(CH_3)C$-	20.1	121	23
23			CH_3	22.8	168	23
24			CH_3	20.0	110	23
25	$C_6H_5CH_2$-		CH_3	22.6	143	23
26	$C_6H_5CH_2$-		CH_3	21.4	154	23
27	$C_6H_5CH_2$-		CH_3	22.8	167	23

upon the values of $\Delta G^{\ddagger}$ for the restricted rotation around the aryl-nitrogen bond. A small number of examples selected for discussion are shown in Tables 2 and 3.

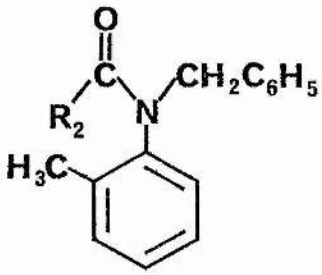
TABLE 3

Compound No.	Compound[a]	$\Delta G^{\ddagger}$ / kcal mole^{-1}	T/°C
28	$4\text{-}CH_3C_6H_4S(O)_2N(CH_2C_6H_5)(2\text{-}CH_3C_6H_4)$	16.0	51
29	$CH_3S(O)_2N(CH_2C_6H_5)(2\text{-}CH_3C_6H_4)$	14.8	21

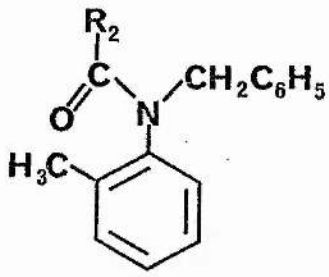
[a] Ref. 21, 22.

Comparison of the $\Delta G^{\ddagger}$ values for compounds 19, 23 and 24 shows that increasing the size of the substituent R will affect the rotation about the aryl-nitrogen bond only if the increase in the size of R is very large. In contrast, comparison of the $\Delta G^{\ddagger}$ values for compounds 19, 25, 26 and 27 shows that moderate increases in the size or rigidity of the ortho substituent of R_1 significantly increases the hindrance to rotation. This well demonstrates the analogy to biphenyl rotation, even to the extent of the buttressing shown by compound 27.

The consideration of the effect of the substituent R_2 upon the aryl-nitrogen bond is more complicated than for R and R_1. T.H.Siddall and W.E.Stewart state that restricted rotation around the aryl-nitrogen bond of most N-substituted anilides is only seen for the endo isomer, (VI, VII)[23]. They rationalize this statement on the grounds that the steric



exo isomer **VI**



endo isomer **VII**

hindrance due to the R_2 group in the exo isomer would be very large in comparison to that exerted by the carbonyl group in the endo isomer. Therefore, if the barrier to rotation about the amide bond is comparatively low, (as it is in most cases), the endo isomer will predominate and rotation about the aryl-nitrogen bond will be the only effect seen.

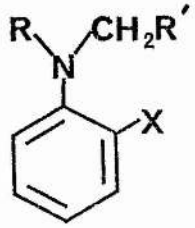
From this argument it follows that the R_2 group cannot have a direct, steric influence upon rotation about the aryl-nitrogen bond. However, the R_2 group may cause a distortion of the amide bond which in turn may ease the barrier to rotation about the aryl-nitrogen bond. This effect is illustrated by comparison of the $\Delta G^{\ddagger}$ values for compounds 19, 20, 21 and 22.

Another steric effect may be seen if substituted amides are compared with their related, substituted sulphonamides. The work of R.M.Moriaty has shown that the barrier to rotation about the N-SO_2R bond is low in comparison to that about the N-COR bond of amides[24,25,26]. Thus, by

this free rotation, it is possible for the sulphonyl-group to reduce the steric interaction with the 2 and 6 positions of the aryl ring, hence decreasing the barrier to aryl-nitrogen bond rotation. The steric interaction of the sulphonyl-group may also be reduced by virtue of the longer nitrogen-sulphur bond as compared to the carbon-sulphur bond. However, the effect may be reduced by the longer sulphur-oxygen bond as compared to the carbon-oxygen bond. Comparison of the $\Delta G^{\ddagger}$ values for compounds 19, 28 and 29 demonstrates the lowering of the rotational barrier.

A study carried out by D.M.Smith and co-workers on a series of N-benzyl- and N-(4-nitrobenzyl)-2-nitroanilides further demonstrated the effect of N-substituents on restricted rotation about the aryl-nitrogen bond[27]. In particular, the series showed markedly lower values for the temperature of coalescence for sulphonamides as compared to the anilides.

However, comparison of the temperatures of coalescence for this nitrated series with those of a similar series derived from 2-toluidine also showed that the former were consistently lower in value (VIII, Table 4)[22]. (Only comparison of coalescence temperatures was possible as the values of $\Delta G^{\ddagger}$ were not calculated for the nitro series).



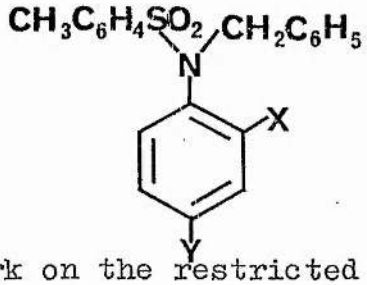
VIII

TABLE 4

R	T_c / °C.		
	R′ = C_6H_5 X = NO_2	R′ = 4-$NO_2C_6H_4$ X = NO_2	R = C_6H_5 X = CH_3
4-$CH_3C_6H_4SO_2$-	5± 1 ($(CD_3)_2CO$)	0 ± 1 ($(CD_3)_2CO$)	51 ± 2 (C_6H_5N)
CH_3SO_2-	9± 1 ($CDCl_3$)	18 ± 1 ($CDCl_3$)	21 ± 2 (C_6H_5N)
C_6H_5CO-	68 ± 1 ($CDBr_3$)	72 ± 1 ($CDBr_3$)	98·5± 2 ($PhNO_2$)
CH_3CO-	114 ± 1 ($CDBr_3$)	112 ± 1 ($CDBr_3$)	142 ± 2 ($PhNO_2$)

This phenomenon had not been expected and denied explanation on purely steric grounds. The presence of some form of electronic effect was postulated which encouraged further investigation.

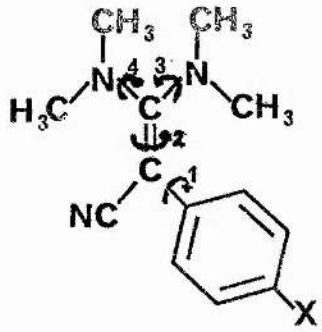
Therefore, in order to study possible steric and electronic effects, a series of substituted N-benzyl-N-tosylanilines (IX) were prepared with substituents in the 2-position and the 2,4-positions of the aryl ring.



IX

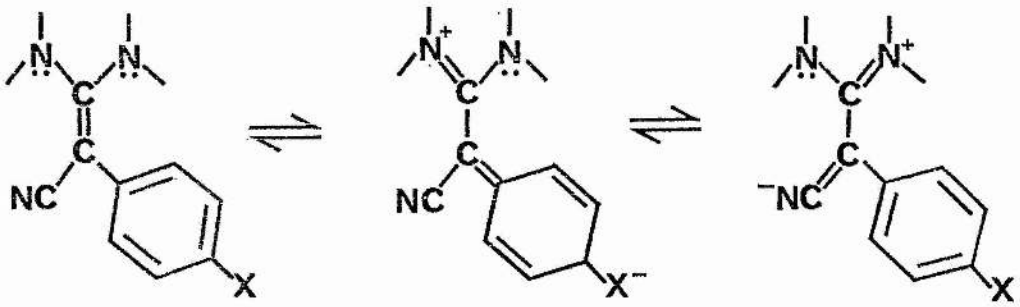
Further work on the restricted rotation about aryl-nitrogen bonds has been carried out by H.Kessler and co-

workers. H.Kessler had shown that for a series of 1,1-bis(dimethylamino)-2-aryl-2-cyanoethanes (X) restricted rotation about the carbon-nitrogen bonds, carbon-carbon double bond and the carbon-aryl bond was temperature dependent[28].



X

He also found that rotation about the carbon-aryl bond, (process 1, X), was dependent upon the nature of the substituent X, the greater the electron withdrawing power of X, the greater the barrier to rotation. This effect was rationalized in terms of resonance (scheme III), it being noted that, as the barrier to rotation about the carbon-aryl bond (process 1,X) increased, so the barrier to rotation about the carbon-carbon double bond (process 2,X) decreased.



Scheme III

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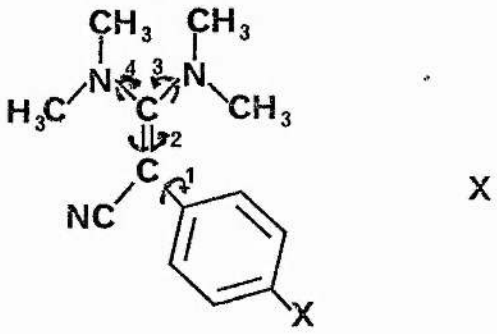

X

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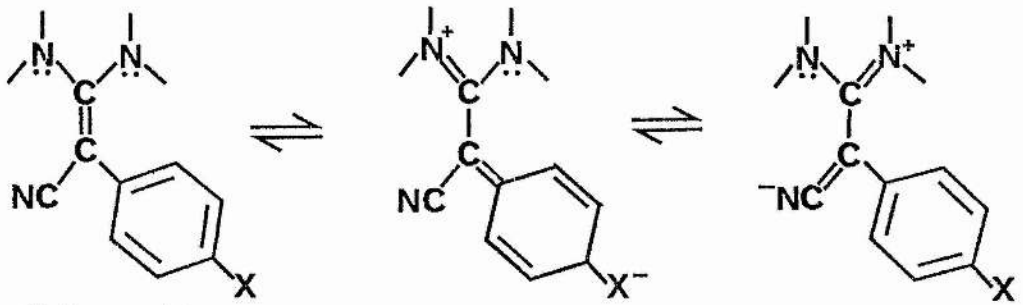
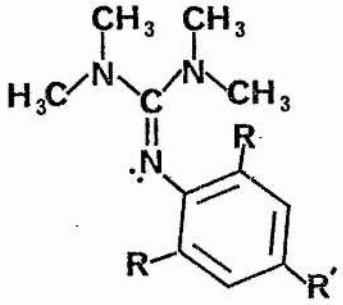


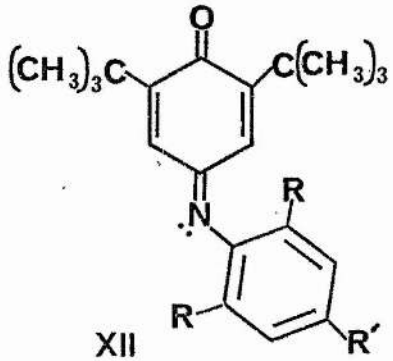
Scheme III

A plot of the kinetic data against the Hammett constants for the substituents, X, showed a linear correlation.

H.Kessler also studied the isomerization about the nitrogen-aryl bond in certain imines (XI, XII)[29,30].

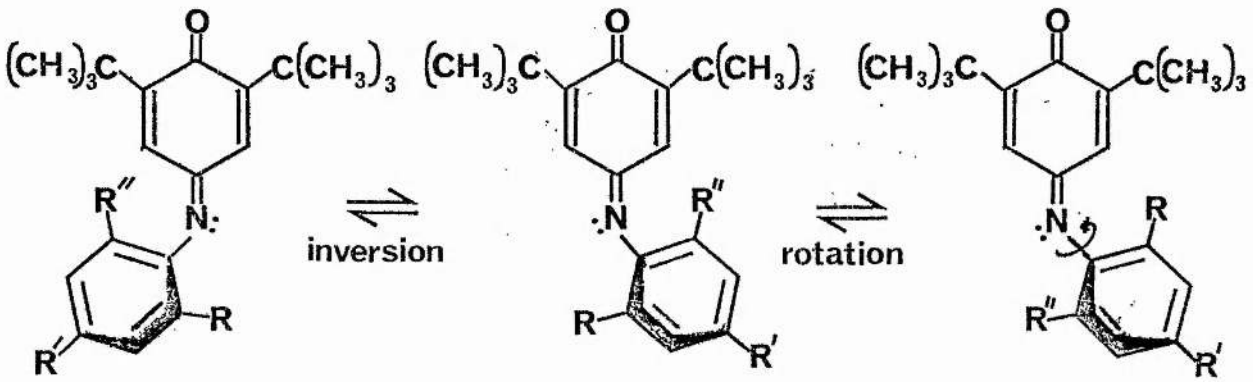


XI



XII

This isomerization could occur by two processes, these being rotation about the aryl-nitrogen bond and an inversion process at the nitrogen (scheme IV).



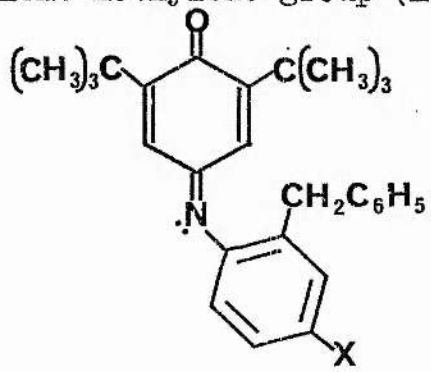
Scheme IV

In unsymmetrical imines of type XI, Kessler found that the isomerization proceeded via the inversion mechanism, the barrier to rotation being higher than that for inversion[31].

He also surmised that N-aryl rotation was sterically hindered in the ground state and electronically hindered in the transition state.

In imines of type XII, Kessler found that the values of $\Delta G^{\neq}$ for the isomerization decreased as the size of R increased[32]. He also showed that the isomerization process was hindered by electron-repelling substituents[32a]. He then argued that because the isomerization process was enhanced by larger substituents, the predominant process of isomerization was inversion, not rotation. However, further work by H.Kessler appeared to contradict these findings with lower values of $\Delta G^{\neq}$ for the rotation process and an increase in the values of $\Delta G^{\neq}$ for the inversion process with increasing size of R [30].

Therefore it was proposed that a series of unsymmetrical quinone-anils should be synthesised, containing a potentially non-equivalent methylene group (XIII).



XIII

The substituent X would be varied in order to study possible electronic effects upon the aryl-nitrogen bond rotation.

Thus, by studying restricted rotation in biphenyls, substituted anilines and substituted quinone-anils an attempt was made to clarify the possible influences of substituents via electronic and steric effects.

2. DISCUSSION OF THE SPECTROSCOPIC RESULTS.

2.1 Methods used to achieve the Analysis

The AB quartet coalescence may be analysed using a combination of two equations. The first is Eyring's rate equation in the form $k_r = K\left[\frac{k\,T_c}{h}\right] e^{-\Delta G^{\ddagger}/RT_c}$ [33]. k_r is the rate constant for the equilibration of the methylene protons between the equivalent and non-equivalent states, K is the transmission co-efficient, T_c is the temperature of coalescence and k, h and R the standard constants. The second equation is $k_r = \frac{\pi}{\sqrt{2}}\left[(\nu_A - \nu_B)^2 + 6J_{AB}^2\right]^{\frac{1}{2}}$ derived by S.Alexander[34], from a density matrix treatment for an exchanging AB system. Combination of these two equations, insertion of the standard values $k = 1.3806 \times 10^{-23}$ JK^{-1}, $h = 6.626 \times 10^{-34}$ J sec, $R = 1.9872$ cal K^{-1} $mole^{-1}$ and a transmission co-efficient (K) of one gave

$$\Delta G^{\ddagger} = 4.577\, T_c \left[9.972 + \log \frac{T_c}{\left[(\nu_A - \nu_B)^2 + 6J_{AB}^2\right]^{\frac{1}{2}}}\right]$$

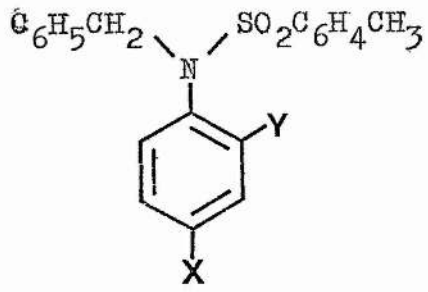
This formula is then used in the evaluation of the value of $\Delta G^{\ddagger}$ (in kcal $mole^{-1}$) for each compound studied.

Some question exists as to what value should be used for the transmission co-efficient, K. F.G.Riddell and J.H.Lehn, in their treatment of data for cyclohexane inversion, used a value of the transmission co-efficient, $K = \frac{1}{2}$[35]. However, the cyclohexane inversion is thought by J.E.Anderson and J.C.D.Brand to entail passing through a metastable boat and/or skew boat conformation[36]. Therefore, the isomerisation is thought to occur in two stages and hence the value of $K = \frac{1}{2}$.

In comparison, S.Glasstone, K.J.Laidler and H.Eyring propose that in systems where vibrational motion is rapid in comparison with motion along the reaction path, then K is of the order of unity[37]. R.H.Fowler and E.A.Guggenheim in their discussion of the traditional methods of applying the Eyring equation also assume K to be of the order of unity[38]. More recently, F.W.Cagle Jr., and H.Eyring used a value of unity for K in their calculations of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for certain sterically hindered biphenyls and related compounds[39]. They base their use of K being unity upon the argument that a substituted biphenyl possessing sufficient free energy to pass through the activated state will continue rotating until the energy in the reaction co-ordinate is dissipated into other degrees of freedom. They also state that similar results from the liquid and vapour phases further support their argument.

Therefore, in our treatment of the data, K was taken as being unity with the proviso that this should be noted in the event of comparison of these results with those of other workers.

Values for $\Delta G^{\ddagger}$ were evaluated for two different types of compound. The first type of compound formed a series of N-benzyl-N-tosyl-2-substituted anilines and N-benzyl-N-tosyl-2,4-disubstituted anilines.

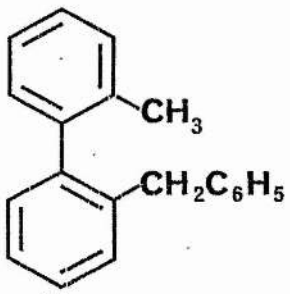


(1) X = H (a) Y = CH_3
(b) Y = I
(c) Y = Br
(d) Y = Cl
(e) Y = F
(f) Y = OCH_3
(g) Y = COOH
(h) Y = $COOCH_3$
(i) Y = NO_2

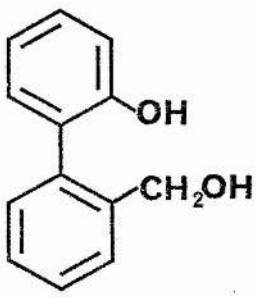
(2) Y = CH_3 (a) X = CH_3
(b) X = Cl
(c) X = OCH_3
(d) X = NH_2
(e) X = NO_2

The second type of compound was represented by three 2,2'-disubstituted biphenyls.

3a



3b



3c

The data used in the evaluation of $\Delta G^{\neq}$ and the final values of $\Delta G^{\neq}$ are shown in Tables 5, 6 and 7.

TABLE 5

Compound	Solvent concentration	$(\nu_A - \nu_B)/_{Hz}$	J_{AB} / Hz	T_c /K ± 2.0	$\Delta G^{\ddagger}$ /kcal mole^{-1} [kJ mole^{-1}]
1a	d_6 DMSO / 10% w/v	23.5 ± 4.0	14.5 (est)*	323.0	16.0 ± 0.3 [66.9 ± 1.3]
1b	$(CD_3)_2CO$/ 10% w/v	19.1 ± 1.0	14.3 ± 0.5	348.0	17.4 ± 0.3 [72.8 ± 1.5]
1c	d_6 DMSO / 10% w/v	11.9 ± 2.3	14.5 ± 0.2	318.0	15.9 ± 0.3 [66.5 ± 1.3]
1c	$(CD_3)_2CO$/ 10% w/v	6.7 ± 1.1	14.6 ± 0.2	303.0	15.1 ± 0.3 [63.2 ± 1.3]
1c	$CDCl_3$ / 150 mg/ml	17.2 ± 0.7	14.5 ± 0.2	321.0	16.0 ± 0.3 [66.9 ± 1.3]
1c	$CDCl_3$ / 50 mg/ml	24.5 ± 1.0	14.6 ± 0.2	324.5	16.1 ± 0.3 [67.4 ± 1.3]
1d	$(CD_3)_2CO$/ 10% w/v	2.6 ± 2.0	14.6 ± 0.2	280.5	14.0 ± 0.3 [58.6 ± 1.1]
1e	$(CD_3)_2CO$/ 10% w/v			Below 213.0	
1f	$(CD_3)_2CO$/ 10% w/v	57.9 ± 0.6	15.0 ± 0.5	253.0	12.2 ± 0.2 [51.1 ± 1.0]
1g	$(CD_3)_2CO$/ 10% w/v			Below 205.0	
1h	$(CD_3)_2CO$/ 10% w/v			Below 213.0	
1i‡	$(CD_3)_2CO$/ 10% w/v	32.8 ± 1.0	14.2 ± 0.4	281.5	13.8 ± 0.3 [57.7 ± 1.2]

*See section 2.3 p.40.

‡ Sample prepared by J.Machin and D.M.Smith[27].

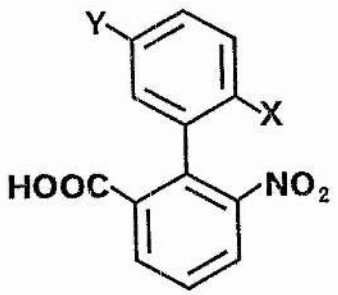
TABLE 6

Compound	Solvent concentration	$(\nu_A - \nu_B)/_{Hz}$	J_{AB} / Hz	T_c /K	$\Delta G^{\neq}$ /kcal mole^{-1} [kJ mole^{-1}]
2a	d_6 DMSO / 10% w/v	58.0 ± 1.0	15.0 ± 1.0	324.0 ± 2.0	15.8 ± 0.3 [66.1 ± 1.3]
2b	d_6 DMSO / 10% w/v	41.0 ± 4.0	13.0 ± 1.0	324.0 ± 2.0	16.0 ± 0.3 [66.9 ± 1.3]
2c	d_6 DMSO / 10% w/v	53.0 ± 1.0	14.0 ± 0.4	342.0 ± 2.0	16.8 ± 0.3 [70.3 ± 1.4]
2d	d_6 DMSO / 10% w/v	52.4 ± 0.8	13.9 ± 0.2	350.0 ± 4.0	17.1 ± 0.6 [71.6 ± 2.5]
2e	$(CD_3)_2CO$/ 10% w/v	75.5 ± 1.5	13.7 ± 0.5	300.0 ± 2.0	14.5 ± 0.3 [60.7 ± 1.2]

TABLE 7

Compound	Solvent concentration	$(\nu_A - \nu_B)/_{Hz}$	J_{AB} / Hz	T_c /K ± 2.0	$\Delta G^{\neq}$ /kcal mole^{-1} [kJ mole^{-1}]
3a	d_6 DMSO / 10% w/v	88.0 ± 0.4	15.2 ± 0.4	362.0	18.1 ± 0.4 [75.7 ± 1.5]
3b	d_6 DMSO / 10% w/v	9.5 ± 0.2	15.4 ± 0.5	409.0	20.5 ± 0.4 [85.8 ± 1.7]
3c	$(CD_3)_2CO$+ D_2O / 10% w/v	17.8 ± 0.2	14.2 ± 0.4	273.0	13.5 ± 0.3 [56.5 ± 1.1]

Comparison of the values of $\Delta G^{\neq}$ for rotation about C′ - C pivot bonds in 2-benzyl-2′-nitro-biphenyl and 2-benzyl-2′-methylbiphenyl showed that there was a difference of 2.4 k cal mole^{-1}, (47°). This marked lowering of the value of $\Delta G^{\neq}$ due to the nitro group was of the same order as seen in the comparison of nitro- and methyl-substituted anilines, (Table 4). R.Adams and H.C.Yuan have shown that, for a series of optically active 2′-substituted-2-nitro-biphenyl-6-carboxylic acids, the methyl group hinders rotation, (and hence racemization), to a greater extent than the nitro group[9]. However, when they attempted to compare their results from racemization with the "size" of the group as calculated from x-ray data, the results for the nitro and the methyl groups were anomalous, (Table 8).



XIV

TABLE 8

X	Y	T / °C	$t_{\frac{1}{2}}$ / mins.	ave. interface A°
Br	CH_3	118	3240	0.36
CH_3	H	118	179	0.18
Cl	CH_3	118	154	0.26
NO_2	H	118	125	0.27
COOH	H	118	91	0.09
CH_3O	H	25	9.4	0.04
F	H	No optically active acid obtained		0.01

Thus the order of "size" of the substituents based on racemization was:-

$$Br \gg CH_3 > Cl > NO_2 > COOH > CH_3O > F,$$

but in the order of size based on x-ray data the positions of the nitro and the methyl groups were reversed. Therefore, it was considered that the influence of the nitro and the methyl groups in the present work could not be explained solely on steric grounds. This therefore made necessary the postulation that some electronic effect must be present. However, as the number of simple 2,2′-substituted biphenyls prepared was very limited, the comparison was extended to include the series of substituted anilines.

If the values of $\Delta G^{\ddagger}$ for the anilines 1a to 1i are studied, the Y-substituents can be ordered in the extent to which they restrict rotation. This order is very similar

to that found by R.Adams and H.C.Yuan from their racemization data.

$$I > Br \cong CH_3 > Cl \equiv NO_2 > CH_3O > F, COOH, COOCH_3.$$

The striking exceptions are that, in the order obtained for the anilines, bromine and methyl are virtually equivalent and the carboxylic acid function is much lower in the series than methoxy, being of the same order as fluorine.

In studying this series of 2-substituted anilines, the possible steric and electronic effects had to be considered jointly. However, in the series of 2,4-disubstituted anilines, the group Y was kept constant, thus eliminating the variable steric factor and enabling the purely electromic influence of the group in the 4-position to be studied.

Comparison of the values of $\Delta G^{\neq}$ for the anilines 1a, and 2a to 2e shows that the X-substituents can also be ordered in the extent to which they restrict rotation.

$$NH_2 \equiv CH_3O > Cl \equiv H \equiv CH_3 >> NO_2$$

This series correlates to the electronegativity of the groups and indicates that electron donating or repelling groups lead to high barriers to rotation while electron accepting or attracting groups lead to low barriers.

Using this information, it is then possible to return to the series of 2-substituted anilines and explain the apparently anomalous results for the nitro and the methyl

groups. The nitro group is a strong electron acceptor and therefore when in the 2-or 4-positions should lead to a low barrier to rotation. In contrast to this, the methyl group is electron-repelling and therefore should lead to a high barrier to rotation when in the 2-or 4-positions.

However, this then leads to another apparent anomaly in that the values of $\Delta G^{\neq}$ for the 4-chlorosubstituted, the 4-methylsubstituted and the unsubstituted anilines, (compounds 1a, 2a and 2b), are all of the same order. This can be explained on the basis that the methyl group is an electron-repeller only by induction and therefore has considerably less influence than the nitro group which may accept electrons by a resonance mechanism. Thus, when in the 4-position, the electron-repelling power of the methyl group could be insufficient to noticeably influence the value of $\Delta G^{\neq}$. In contrast, when the methyl group is in the 2-position and adjacent to the carbon-nitrogen pivot bond, a noticeable effect on the value of $\Delta G^{\neq}$ should be expected.

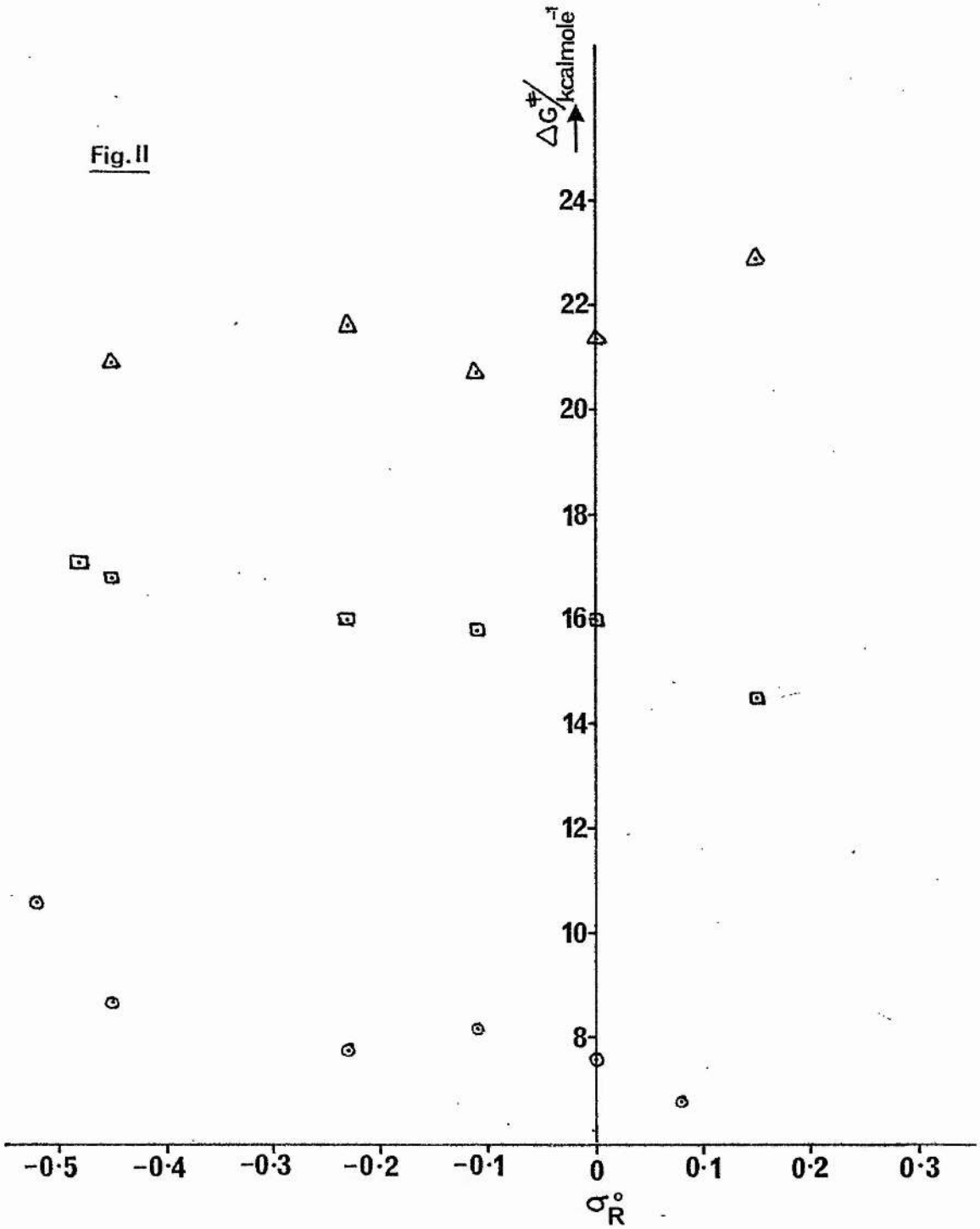
In considering the 4-chlorosubstituted aniline a further complication arises in that the chloro-function may be an electron-donator by a resonance effect but an electron-attractor by an inductive effect. By the previous arguments it would be expected that the inductive effect would be limited by the distance from the 4-position to the carbon-nitrogen pivot bond and so the resonance effect should

predominate. However, as the values of $\Delta G^{\neq}$ for the 4-chlorosubstituted and the unsubstituted anilines are the same, it appears that in this example the electron-donating resonance effect is sufficiently weak to be countered by the electron-attracting induction effect.

Continuing the comparison of the values of $\Delta G^{\neq}$ for the 2-substituted anilines with the substituted biphenyls, it is also possible to explain the relative differences for the bromo-substituted and the carboxylic acid substituted anilines on an electronic basis. Thus it can be reasoned that the electron-repelling power of the methyl group raises the barrier while, if the electron-attracting power of the bromine predominates over its donating effect, it lowers the barrier. Then the net effect seen is that of the 2-methyl-substituted and the 2-bromosubstituted anilines having equivalent $\Delta G^{\neq}$ values.

On a similar basis it can be argued that the strongly electron-accepting carboxylic acid function will lower the barrier to rotation, while the electron-donating methoxy group will raise the barrier. Thus, when electronic influences predominate as in the aniline series, the $\Delta G^{\neq}$ values for the 2-carboxylic acid substituted aniline is much lower than for the corresponding 2-methoxy-substituted aniline, whereas, in the multi-substituted biphenyls of R.Adams and H.C.Yuan, the steric influences predominate and hence the order of the carboxylic acid function and the methoxy group are reversed.

Fig. II



⊙ = 4-substituted benzaldehydes

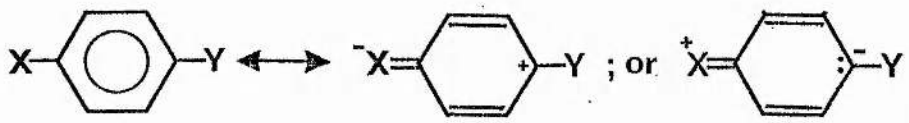
⊡ = 4-substituted N-benzyl-N-tosyl-2-methylanilines

△ = 4′-substituted 2′-methoxy-2-nitrobiphenyl-6-carboxylic acids

Plots of $\Delta G^{\neq}$ (kcal mole^{-1}) v. σ_R° to compare Electronic Effects of 4-substituents.

However, in the preceding arguments the electronic influence of the X-substituents has only been discussed qualitatively. It is therefore desirable that some form of quantitative correlation between the groups and their $\Delta G^{\ddagger}$ values should be derived. An example of this is the correlation between the values of $\Delta G^{\ddagger}$ and a Hammett type parameter, σ_R^o, (fig. II).

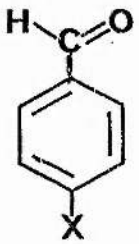
The parameter σ_R^o is defined by R.W.Taft as being the σ parameter for a series in which neither +R or -R substituent effects, from the 4-position, are enhanced or retarded by quinoidal resonance effects[40]. (Scheme V).



Scheme V

(Where X is the 4-substituent and Y the group used to detect the effects). The values of σ_R^o used were those quoted by R.W.Taft and were evaluated from I.R. data by A.R.Katritzky and co-workers[41].

Included in the plot of $\Delta G^{\ddagger}$ against σ_R^o is data for a series of 4-substituted benzaldehydes, (fig.II, XV, Table 9). T.Drakenberg studied these benzaldehydes using ^{13}C n.m.r. and it is apparent that his results show a similar trend to that exhibited by the substituted anilines[42].



XV

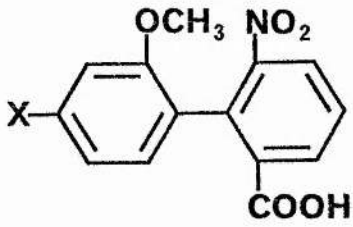
TABLE 9

Substituent X	$\Delta G^{\neq}$ at T_c / k cal mole^{-1}	T_c/°C	σ^{o}_{R}
$N(CH_3)_2$	10.6	-40	-0.52
OCH_3	8.7	-80	-0.45
CH_3	8.2	-90	-0.11
H	7.6	-105	0.00
Cl	7.8	-100	-0.23
CF_3	6.8	-120	0.08

Thus, the overall hypothesis for the substituted aniline is that, electron accepting groups stabilize the transition state by reducing the accumulation of negative charge at the carbon of the carbon-nitrogen pivot bond. Conversely, electron donating groups destabilize the transition state by increasing the accumulation of negative charge at the carbon of the carbon-nitrogen bond.

However, when a correlation is attempted between the $\Delta G^{\neq}$ values for 4'-substituted 2'-methoxy-2-nitro-biphenyl-6-carboxylic acids and the σ^{o}_{R} values, the obvious trend is in the opposite direction to that seen for the anilines and the benzaldehydes, (fig. II, XVI, Table 10)[9,43].

This is not unexpected, as the results of M.Ōki and G.Yamamoto discussed previously have shown that the electron withdrawing methoxy and nitro groups stabilize the transition state of similar substituted biphenyls.



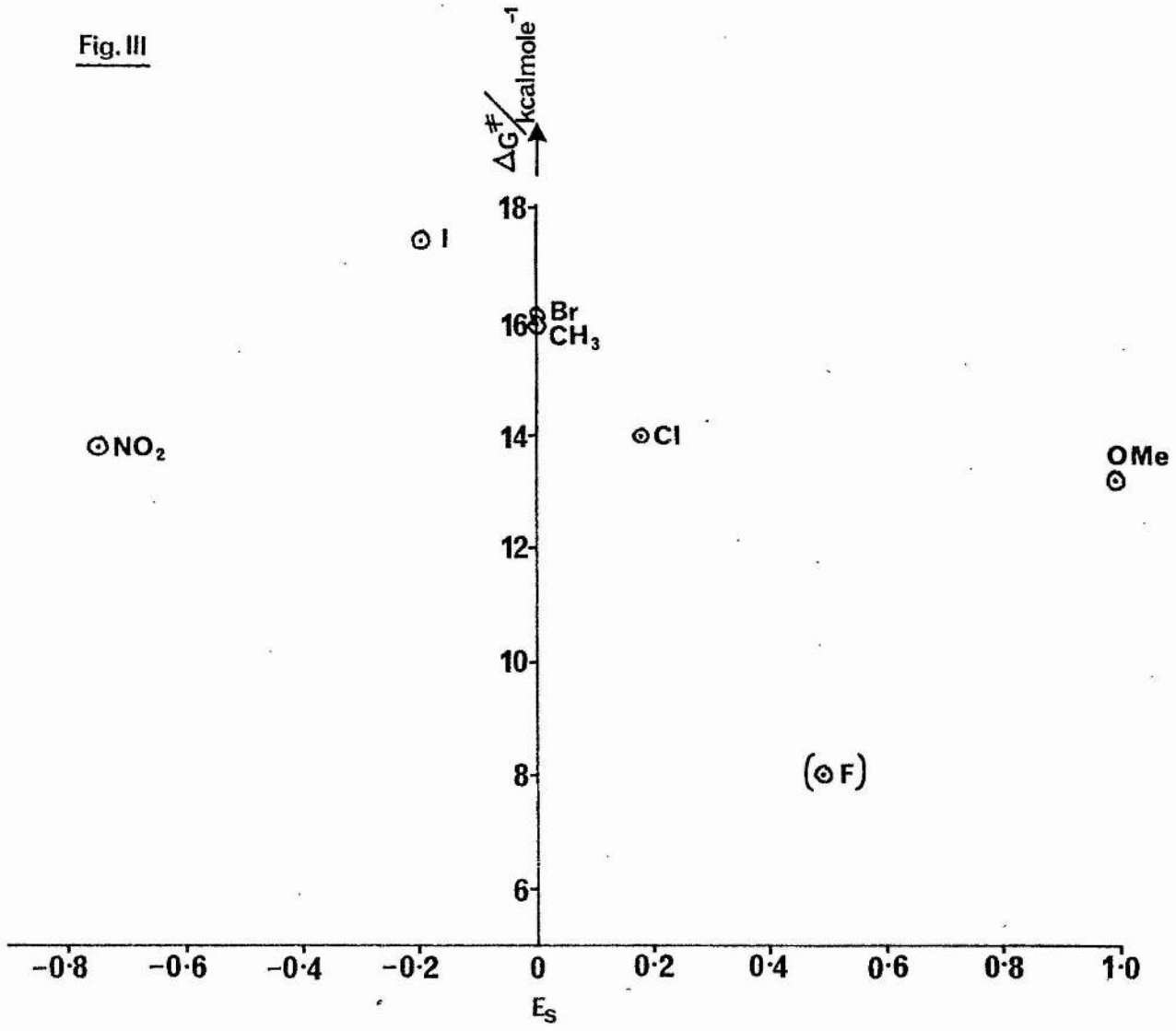
XVI

TABLE 10

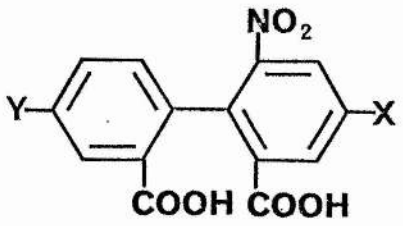
Substituent X	$t_{\frac{1}{2}}$ / min.	$\Delta G^{\neq}$ / k cal mole^{-1}	σ_R^o
H	9.4	21.4	0.00
OCH_3	3.6	20.9	-0.45
CH_3	2.6	20.7	-0.11
Cl	12.0	21.6	-0.23
NO_2	115.0	22.9	0.15

In contrast, work by J.W.Brooks, M.M.Harris and K.E.Howlett on a series of nitrodiphenic acids has shown that the rate of racemization decreases as the number of substituted nitro groups increases[44], (XVII, Table 11). However, it is also seen that although the enthalpy of activation, E_a, remains constant, the entropy of activation, $\Delta S^{\neq}$, increases in negativity.

Fig. III



Plot of $\Delta G^{\neq}$ (kcal mole^{-1}) v. E_s for 2-substituted N-Benzyl-N-Tosyl Anilines.



XVII

TABLE 11

X	Y	T / ^{o}C	$10^{4}k$ / sec^{-1}	E_A / kcal $mole^{-1}$	$\Delta S^{\neq}$ / e.u.
H	H	87.6	8.05	22.6	-12.2
NO_2	H	91.0	3.42	22.6	-14.7
NO_2	NO_2	94.0	1.90	22.6	-16.3

Thus it is apparent that in the case of substituted biphenyls, the simple hypothesis relating the electron withdrawing power to the value of $\Delta G^{\neq}$ cannot be applied.

One further attempt was made to assess the steric effect of the 2-substituent, in the substituted anilines, by the correlation of the values of $\Delta G^{\neq}$ with a substituent constant E_s (fig. III). The values of E_s are those quoted by R.W. Taft Jr., and are derived from the hydrolysis of 2-substituted benzoates[45]. As was expected, no direct correlation was found and so further indicated that the degree of hindrance was not due solely to steric influences.

In conclusion, it has been shown that, for a series of N-benzyl-N-tosyl-2,4-disubstituted anilines, a direct

correlation exists between the values of $\Delta G^{\neq}$ and the electronegativity of the 4-substituent. It has also been shown that this correlation can be extrapolated to explain the influence on the values of $\Delta G^{\neq}$ of the 2-substituent, in a series of N-benzyl-N-tosyl-2-substituted anilines, in electronic terms. However, no such simple explanation can be applied to substituted biphenyls.

2.2 Preparation of samples

Two factors had to be considered in the preparation of the samples for variable temperature n.m.r. spectra. The first was the solubility of the compound in the solvent at both high and low temperatures. The second was whether the solvent used had any effect on the spectrum obtained as solvent effects have been observed in previous work[18,46].

Three solvents were used in preparing the samples, these being deuteriacetone, deuteriochloroform and deuteriodimethylsulphoxide [d_6DMSO]. In general, deuteriacetone (f.p.-64°)[47] was used for compounds which had a coalescence point near or below room temperature and d_6DMSO (b.p. 189°)[48] was used for compounds with a coalescence point above room temperature. These solvents proved satisfactory for all compounds except N-benzyl-N-tosyl-2-fluoroaniline, N-benzyl-N-tosylanthranilic acid and methyl N-benzyl-N-tosylanthranilate. The coalescence of these compounds were so low that the samples either preciptatedout or froze

before the coalescence temperature was reached.

Another compound for which determination of the coalescence temperature proved difficult was 2-amino-2′-hydroxymethylbiphenyl. A series of variable temperature n.m.r. spectra were taken but the chemical shift of the hydroxyl group was found to be temperature dependent. This resulted in the peak due to this group moving through the splitting pattern of the methylene protons. The hydroxyl proton also coupled with the methylene protons at the lower temperatures. Analysis of the resulting confusion of peaks was not possible. Simplification of the spectrum by the addition of deuterium oxide was considered but was not carried out as the compound was not part of a full series and so was of doubtful relevance.

Two other biphenyls for which coalescence temperatures could not be obtained were 2′-(2-nitrophenyl)-benzyl-bromide and 2′-hydroxymethyl-2-nitrobiphenyl. The 100MHz n.m.r. spectrum of 2′-(2-nitrophenyl)-benzylbromide in d_6DMSO showed that the methylene protons were an AB quartet at room temperature. Therefore variable temperature spectra of the sample were taken but the sample decomposed before the coalescence temperature was reached. The 100MHz n.m.r. spectrum of 2′-hydroxymethyl-2-nitrobiphenyl in deuteriochloroform showed that the methylene protons were a singlet at room temperature. The 100MHz n.m.r. spectra of the sample in deuteroacetone and d_6DMSO showed that the methylene protons were a doublet at room temperature due to

their coupling with the hydroxyl proton. Variable temperature spectra were taken in d_6DMSO but at -70° the sample precipitated out, the methylene protons still appearing as the doublet seen at room temperature.

All the solutions for the n.m.r. spectra were of approximately 10% w/v in concentration. However, to ensure that the concentration of the samples did not affect the n.m.r. spectra obtained, a test compound was selected, (N-benzyl-N-tosyl-2-bromoaniline), and n.m.r. spectra were taken at different concentrations. The results of the analyses of these n.m.r. spectra showed that the values obtained for $\Delta G^{\ddagger}$ agreed to within the experimental error.

A similar test was carried out to investigate the effect of the solvents on the n.m.r. spectra. N.m.r. spectra of the test compound, (N-benzyl-N-tosyl-2-bromoaniline), were run in deuterioacetone, deuteriochloroform and d_6DMSO. The values obtained for $\Delta G^{\ddagger}$ from the samples in deuteriochloroform and d_6DMSO agreed to within the experimental error. The value for $\Delta G^{\ddagger}$ obtained from the sample in deuterioacetone showed a difference of 6% as compared with the values for $\Delta G^{\ddagger}$ from the sample in deuteriochloroform and d_6DMSO. No obvious reason could be found for this anomalous behaviour. Also, the test was only carried out with one compound and so this behaviour may not be typical of the complete series. However, all the results gave values for $\Delta G^{\ddagger}$ of the same order of

magnitude. Therefore, although the results obtained from samples run in deuterioacetone may display some solvent effects, these were of insufficient importance to deny a qualitative (rather than quantitative) comparison with the other values obtained for $\Delta G^{\ddagger}$.

2.3 The Accuracy of the Measurements Used in Evaluating $\Delta G^{\ddagger}$.

In using the formula

$$\Delta G^{\ddagger} \text{ (in kcal mole}^{-1}) = 4.577\ T_c \left[9.972 + \log \frac{T_c}{\left[(\nu_A - \nu_B)^2 + 6J_{AB}^2 \right]^{\frac{1}{2}}} \right]$$

three variables were obtained from the 100MHz n.m.r. spectra. These were the temperature of coalescence, T_c, the coupling constant between the two methylene protons, J_{AB}, and the chemical shift difference, $(\nu_A - \nu_B)$, (Tables 5, 6, 7).

The temperature of coalescence was taken as being the point at which the two inner peaks of the AB quartet were no longer distinct from one another, (as discerned by eye). This was carried out using 100MHz spectra at approximately 5° intervals initially, and subsequent 2° intervals once the correct temperature region had been found. The temperature was recorded by means of a thermocouple inserted into the n.m.r. probe. The accuracy of the thermocouple gave an error of $\pm 0.2^{\circ}$ in the temperature reading; however, the accuracy of extrapolating T_c by eye was only $\pm 2^{\circ}$, (with the exception of the measurements for compound 2d, Table 6). Therefore, any measurable instrumental error

was considered negligible.

The coupling constant, J_{AB}, was taken from the 100Hz or 250Hz expansion of the 100MHz n.m.r. spectra by direct measurements. This was carried out by taking the distances between the first and second peaks of the quartet and then the third and fourth peaks of the quartet for every temperature at which a spectrum was obtained. In general, this resulted in ten to twelve values for J_{AB} of which an average was taken to obtain the final value for J_{AB}. By this method the error in the values for J_{AB} was within the range $\pm 0.2 \rightarrow 0.5$Hz, (except for compounds 2a and 2b, Table 6).

The chemical shift difference, $(\nu_A - \nu_B)$ was also taken from the 100 or 250Hz expansion of the 100MHz n.m.r. spectra by direct measurements. This was carried out by taking the distances between the fourth and first peaks of the AB quartet and the third and second peaks of the AB quartet. The two differences were then multiplied together and the square root taken of the product to give $(\nu_A - \nu_B)$. (This is summarised by the formula, $\nu_A - \nu_B = \left[(\nu_4 - \nu_1)(\nu_3 - \nu_1)\right]^{\frac{1}{2}}$). This process was carried out at every temperature for which a 100Hz or 250Hz expansion was obtained. A graph was then plotted of $(\nu_A - \nu_B)$ against temperature to give a straight line from which $(\nu_A - \nu_B)$ at T_c was extrapolated. The error in the values of $(\nu_A - \nu_B)$ were also determined graphically and were in the range $\pm 0.2 - 1.5$Hz, (excepting

compounds 1a, 1e and 2b, tables 5 and 6).

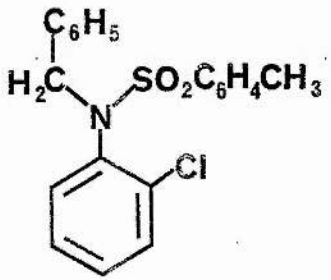
The graphical determination of ($\nu_A - \nu_B$) at T_c was necessary because ($\nu_A - \nu_B$) was temperature dependent. This phenomenon has been noted previously by G.J.Bishop, B.J.Price and I.O.Sutherland in their work on tetrasubstituted hydrazines, and by M.Ōki and G.Yamamoto in their work on substituted biphenyls[17,49].

There was one exception to these methods of evaluating J_{AB} and ($\nu_A - \nu_B$), this being N-benzyl-N-tosyl-2-methylaniline. The 100MHz n.m.r. spectrum of the compound d_6DMSO at room temperature was an AB quartet of which only the two central peaks could be readily distinguished from background noise. As the temperature was increased to the coalescence the total pattern became very indistinct.

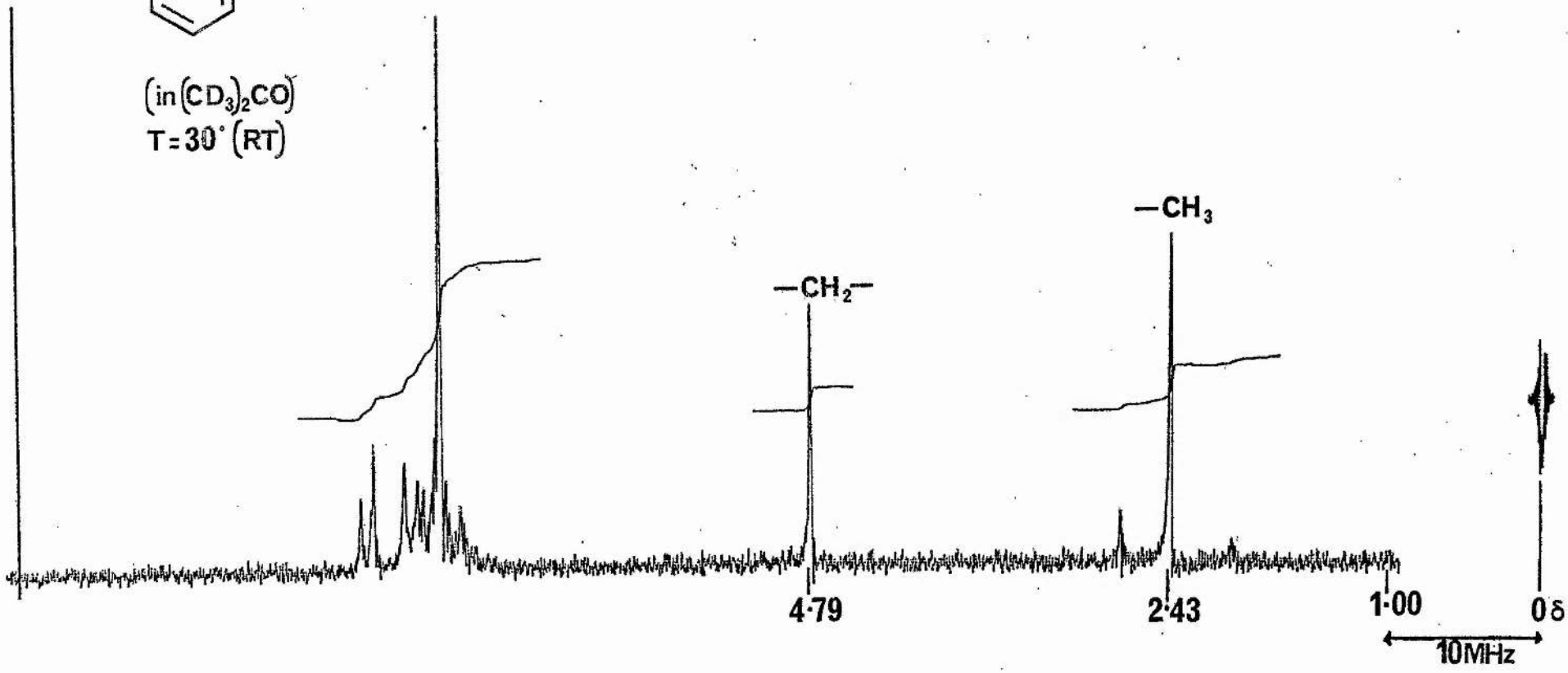
Therefore, an approximate value of J_{AB} was estimated from consideration of the values of J_{AB} for other, related, compounds. The positions of the two outer peaks of the AB quartet were then extrapolated from the known positions of the two central peaks and the use of the estimated value of J_{AB}. This resulted in frequencies for the four peaks of the AB quartet and ($\nu_A - \nu_B$) was then calculated by the method described previously. This resulted in an approximate value of ($\nu_A - \nu_B$), the inaccuracy of the calculation being reflected in the large error quoted.

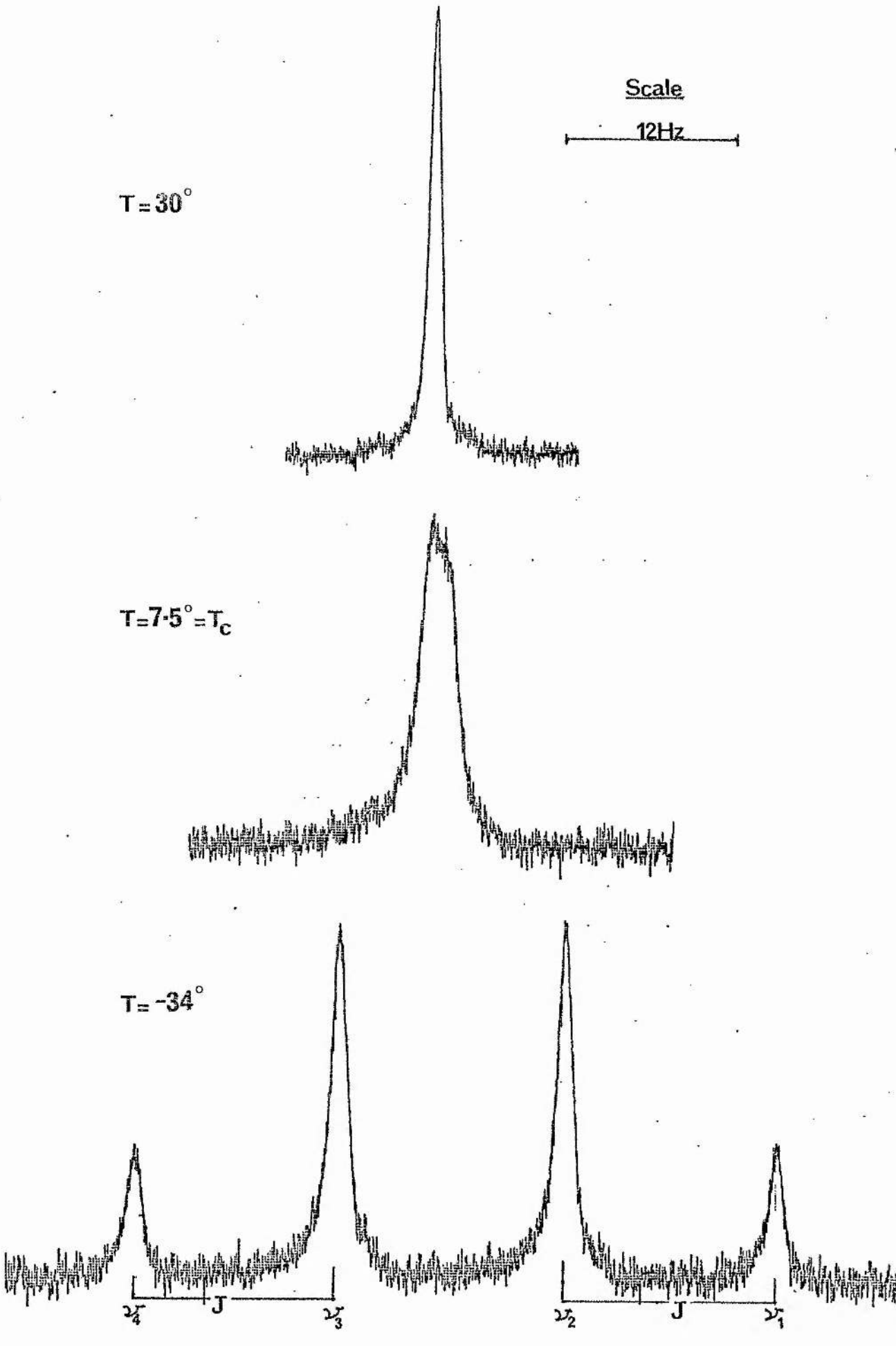
However, in the calculation of $\Delta G^{\ddagger}$, ($\nu_A - \nu_B$) and J_{AB} only occurred in a log term which was then added to

Fig. IV The 100 MHz NMR Spectrum of N-Benzyl-N-Tosyl-2-Chloroaniline and the 100Hz Expansion of the $-CH_2-$ Peak at Various Temperatures.



(in $(CD_3)_2CO$)
T = 30° (RT)




Scale
12Hz
T = 30°
T = 7·5° = Tc
T = -34°
J
J

a constant. Thus the errors from ($\nu_A - \nu_B$) and J_{AB} were small in the final calculation of $\Delta G^{\ddagger}$. In comparison to this, the error from T_c, which occurred in both the log term and the complete formula, was large. Thus, the overall error in calculating $\Delta G^{\ddagger}$ arose from the error in the estimation of T_c. A typical example of a set of spectra are shown at fig. IV.

2.4 The Consideration of Entropy

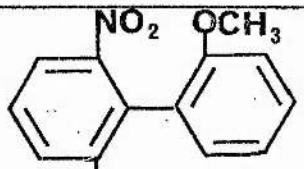
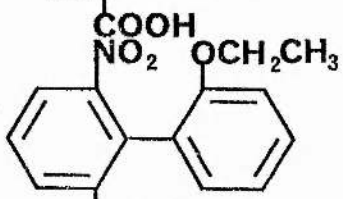
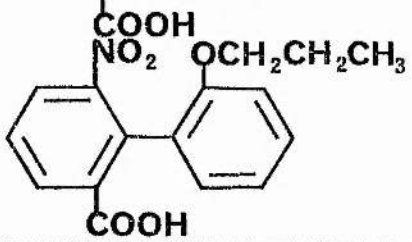
The free energy of activation, $\Delta G^{\ddagger}$, can be considered as arising from a combination of the enthalpy of activation, $\Delta H^{\ddagger}$, and the entropy of activation, $\Delta S^{\ddagger}$. This relationship is summarised in the equation, $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T \Delta S^{\ddagger}$. Thus it can be seen that $\Delta G^{\ddagger}$ contains a temperature dependent term. In comparison, the Arrhenius activation energy, E_A, does not contain a temperature dependent factor and so is often used in preference to $\Delta G^{\ddagger}$ when a comparison of activation energies is made.

However, the values found for E_A, (as determined by the normal method of a log plot of the rate constants k_r against the reciprocal of temperature), often show a wide range of values for the same process. An example of this is the evaluation of E_A for the rotation about the nitrogen-carbon bond in dimethylformamide where values ranging from 7 to 28 k cal $mole^{-1}$ have been found[15]. The reason for this is that the errors in the k_r values increase away from the coalescence temperature and the evaluation of k_r was only

possible over a small temperature range. Therefore, unless accurate measurements can be taken and over a wide range of temperatures, the comparison of E_A values is not meaningful and $\Delta G^{\ddagger}$ should be used.

However, the $\Delta G^{\ddagger}$ does contain terms for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. Also, as the $\Delta S^{\ddagger}$ term is combined with a temperature factor, changes in $\Delta S^{\ddagger}$ may have a large effect on the overall value of $\Delta G^{\ddagger}$. In some cases this has been shown to be true as in the work carried out by F.W.Cagle Jr., and H.Eyring on some optically active, sterically hindered biphenyls and related compounds[39]. To take one example, a comparison was made for the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for three substituted biphenyls (see Table 12).

TABLE 12

No.	Compound	Solvent	$\Delta H^{\ddagger}$ / k cal g mole^{-1}	$\Delta S^{\ddagger}$ / e.u.
I		absolute ethanol	19.3	- 9.19
II		absolute ethanol	20.1	- 9.38
III		absolute ethanol	20.0	-10.5

It is seen that as the chain length of the alkoxy group increases so the $\Delta S^{\ddagger}$ becomes more negative while the

values for $\Delta H^{\ddagger}$ remain comparatively constant. Thus, any increase seen in the values of $\Delta G^{\ddagger}$ would be due to the $\Delta S^{\ddagger}$ term rather than the $\Delta H^{\ddagger}$ term. D.M.Hall and M.M.Harris have also tabulated values of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for a large number of optically active biphenyls and biphenyl-like compounds which demonstrates the effect upon $\Delta G^{\ddagger}$ of changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ [50].

However, all these results were obtained using data arising from the rate constants for the racemisation processes. This method is a very accurate way of determining values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ and so comparison of these values can be considered meaningful. In contrast, the evaluation of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ using variable temperature n.m.r. spectra, (especially in extrapolations using the method of approximation equations), gives comparatively inaccurate values for these terms. A.Allerhand and H.S.Gutowsky have stated that, for the method using variable temperature n.m.r. spectra, systematic errors affect $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ far more than $\Delta G^{\ddagger}$, especially when measurements can only be made over a small range of temperatures[51].

Also, more recent work has shown that for many compounds that undergo fast rotation, inversion or isomerization processes, (as compared to the slow processes involved when racemization is studied), the $\Delta S^{\ddagger}$ term is so small as to be considered negligible[52,53].

Therefore, although extrapolation of values for $\Delta H^{\ddagger}$

and $\Delta S^{\neq}$ by graphical methods or computer line shape analysis from the data obtained was considered, it was decided that they would be too inaccurate or too small to be meaningful. Also, the scope of this work was limited to a qualitative comparison of data for similar compounds and so accurate quantitative values were unnecessary.

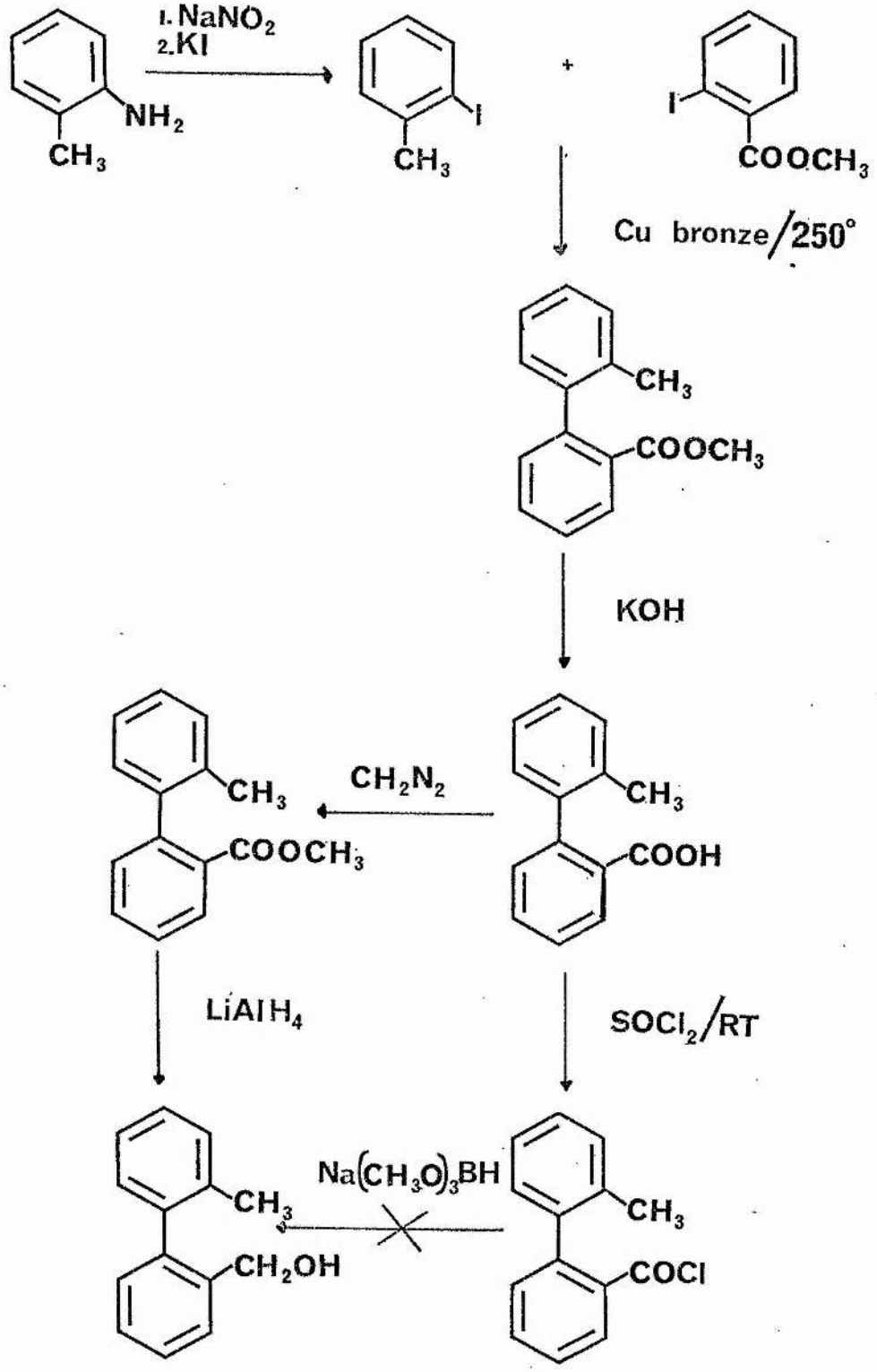
3. DISCUSSION OF THE SYNTHETIC ROUTES

3.1 Biphenyls

Several synthetic routes were attempted in the preparation of the substituted biphenyls. The major problem encountered in the preparation of unsymmetrical 2,2′-disubstituted biphenyls was the low yields of product obtained. For example, in the preparation of 2-methylbiphenyl-2′-carboxylic acid by the Ullmann reaction, only 1.1% of the desired product was obtained[54]. This was due to the preferential formation of the symmetrical diphenic acid. As the unsymmetrical biphenyl was normally the starting compound for a synthetic route, the low yields seriously curtailed further reactions. Direct synthesis of the unsymmetrical 2,2′-disubstituted biphenyls by diazotisation also gave low yields. Therefore a number of synthetic routes used 2-nitrobiphenyl-2′-carboxylic acid as a starting compound as this could be prepared from biphenyl-2-carboxylic acid with a relatively high yield, (47%)[55].

Further difficulties were experienced in the attempted reductions of the functional groups of the substituted biphenyls, particularly when using metal hydrides. In the preparation of 2′-hydroxymethyl-2-methylbiphenyl from 2-methylbiphenyl-2′-carboxylchloride using sodium trimethoxyborohydride no product could be isolated. A sample of 2′-hydroxymethyl-2-methylbiphenyl was prepared from methyl 2-methylbiphenyl-2′-carboxylate using lithium

Scheme VI

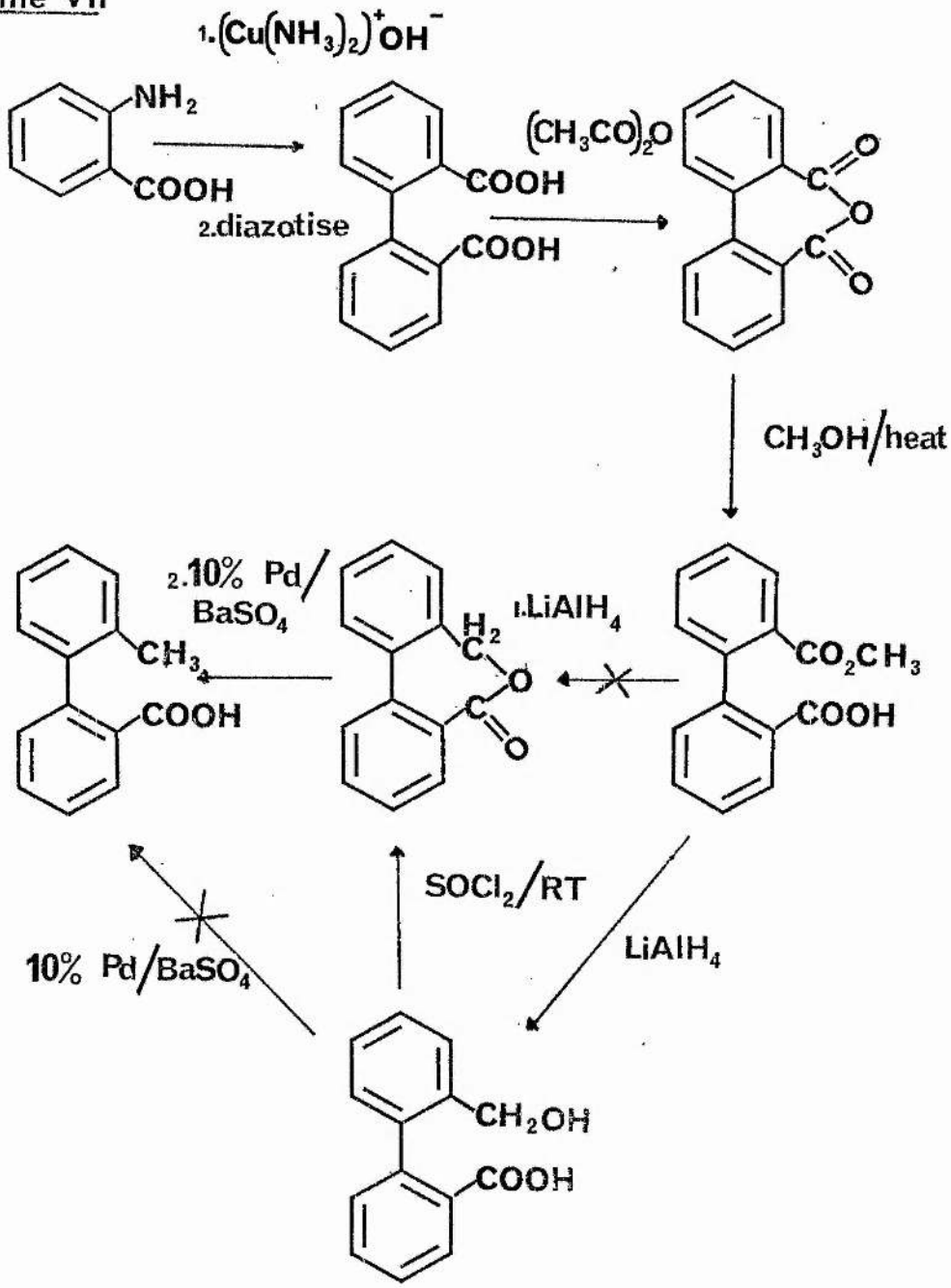

1. NaNO2
2. KI
NH2
CH3
I
CH3
+
I
COOCH3
Cu bronze/250°
CH3
COOCH3
KOH
CH3
COOH
CH2N2
CH3
COOCH3
LiAlH4
SOCl2/RT
Na(CH3O)3BH
CH3
CH2OH
CH3
COCl

aluminium hydride but analysis and mass spectroscopy indicated that the sample was impure. However, analysis of the n.m.r. spectrum was possible, (Scheme VI).

As the preparation of 2-methylbiphenyl-2'-carboxylic acid by the Ullman reaction gave such a low yield, a second method to prepare this compound was attempted. The monomethyl ester of diphenic acid was prepared in good yield and this was then to be used in a two step reduction[56,57,58]. The first stage was to be the reduction of the monomethyl ester of diphenic acid by lith ium aluminium hydride to diphenide. This reaction was attempted but the only product isolated was a trace of 2-hydroxymethylbiphenyl-2'-carboxylic acid. Comparison of a melting point of the sample with a literature melting point indicated that the sample was impure. Therefore identification of the product was based on n.m.r. and IR spectra. The mass spectrum was inconclusive as to the molecular weight of the compound, the molecular ion peak appearing at 210 rather than at 228. However, according to the literature 2-hydroxymethylbiphenyl-2'-carboxylic acid may be readily converted to diphenide by loss of water[59]. Therefore, various methods of dehydrating the 2-hydroxymethylbiphenyl-2'-carboxylic acid were attempted.

However, heating the acid under vacuum in the presence of a desiccant and refluxing in xylene in the presence of toluene-4-sulphonic acid both proved unsuccessful. A small sample of the diphenide was obtained by the action of thionyl chloride on the acid. This reaction was then

Scheme VII


1.(Cu(NH3)2)+OH−
NH2
COOH
2.diazotise
COOH
COOH
(CH3CO)2O
O
O
O
CH3OH/heat
2.10% Pd/BaSO4
1.LiAlH4
H2
CH3
COOH
CO2CH3
COOH
SOCl2/RT
LiAlH4
10% Pd/BaSO4
CH2OH
COOH

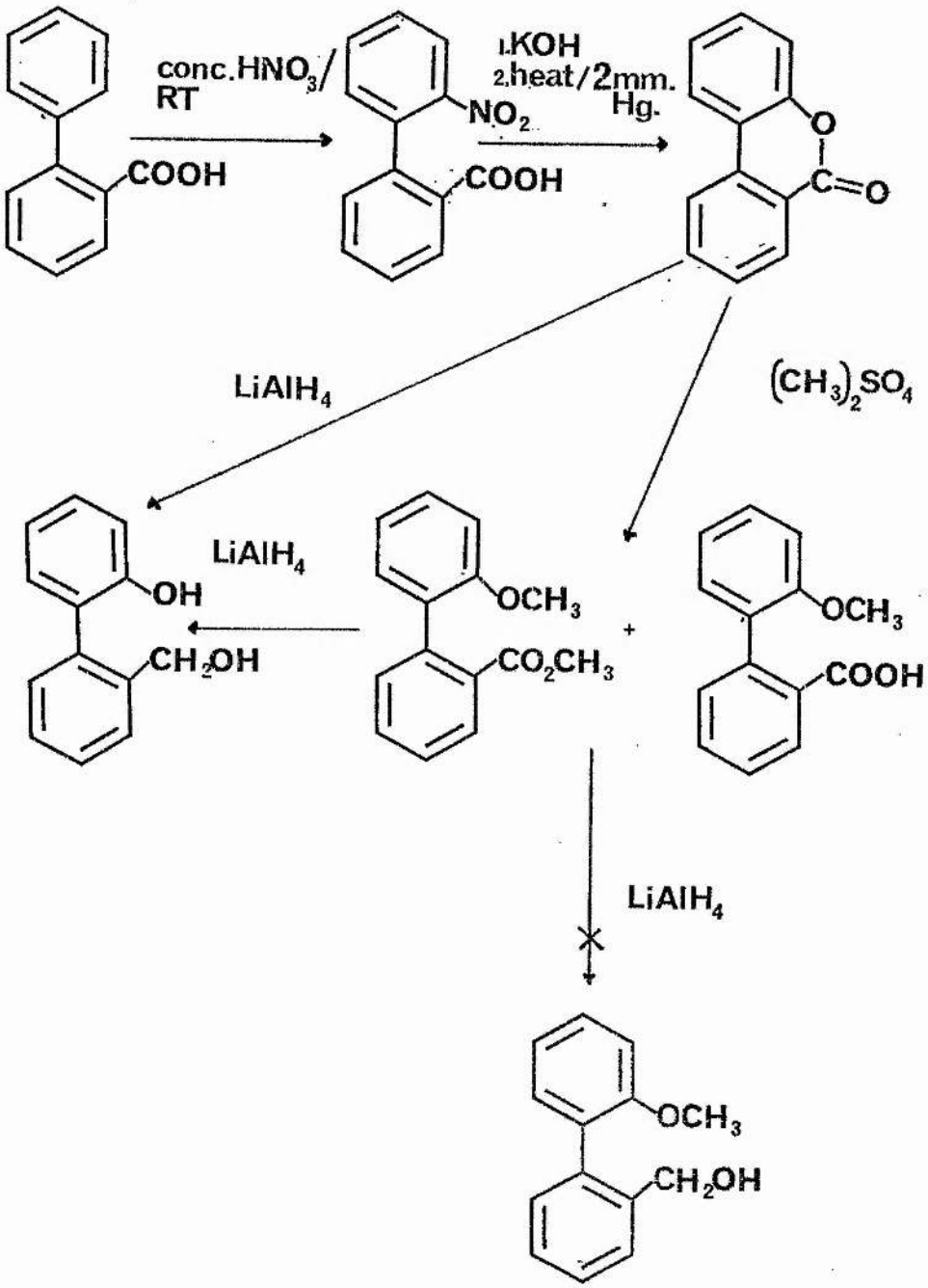
carried out on a larger scale but the product obtained was a highly impure mixture. Further purification of this mixture proved unsuccessful and spectral data proved inconclusive as to its exact composition, (Scheme VII).

Isolation of the diphenide having proved to be difficult, an attempt was made to carry out the second stage of the two step reduction using a sample of 2-hydroxymethylbiphenyl-2-carboxylic acid. Hydrogenation using 5% palladium on barium sulphate gave only unchanged starting material. Therefore, the hydrogenation was attempted using a stronger catalyst, (palladium on charcoal). A product was obtained from this reaction but the n.m.r. spectrum indicated that hydrogenation had only occurred in the biphenyl system. All attempts to continue this synthetic route were then abandoned.

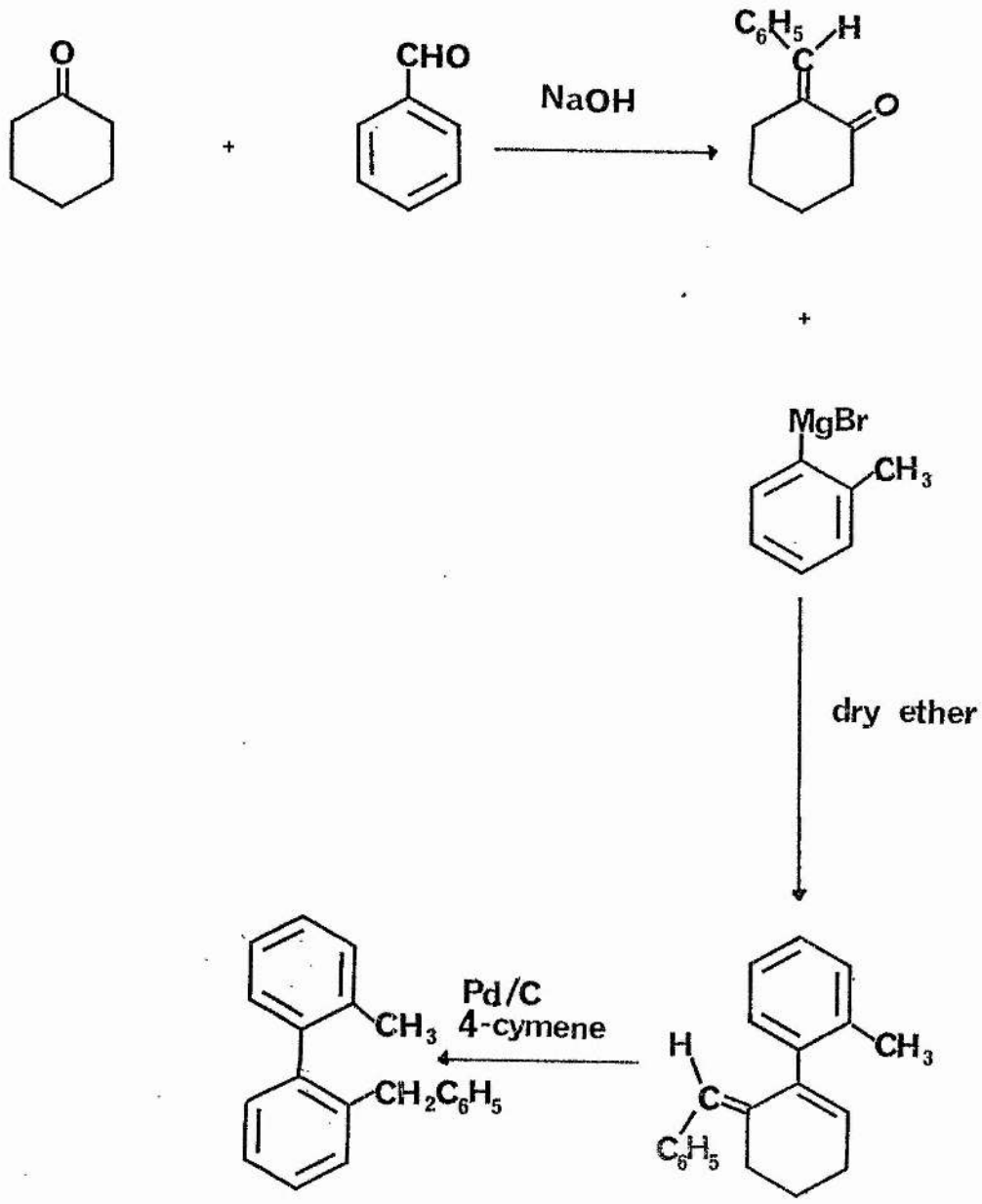
Another example of the difficulties experienced in using lithium aluminium hydride was the attempted preparation of 2′-hydroxymethyl-2-methoxybiphenyl from 2-methoxybiphenyl-2′-carboxylic acid. The reduction was attempted using a standard method but the only product obtained was 2-hydroxy-2′-hydroxymethylbiphenyl. Thus the 2-methoxybiphenyl-2′-carboxylic acid was demethylated as well as being reduced, (Scheme VIII).

However, two other synthetic routes attempted did lead to the successful preparation of unsymmetrical biphenyls. The first route involved the preparation of 2-benzalcyclohexanone[60]. This product was then reacted with a Grignard

Scheme VIII


conc.HNO3/
RT
COOH
NO2
COOH
1.KOH
2.heat/2mm.
Hg.
O
C=O
LiAlH4
(CH3)2SO4
LiAlH4
OH
CH2OH
OCH3
CO2CH3
+
OCH3
COOH
LiAlH4
OCH3
CH2OH

Scheme IX


O
CHO
NaOH
C_6H_5
H
C
O
+
+
MgBr
CH_3
dry ether
Pd/C
4-cymene
CH_3
$CH_2C_6H_5$
H
C
C_6H_5
CH_3

compound prepared from 2-bromotoluene to give 2-tolyl-3-benzalcyclohexanone. The final stage was the dehydrogenation of 2-tolyl-3-benzalcyclohexanone to give 2-methyl-2′-benzylbiphenyl[61]. This was the only product prepared by this synthetic route, (Scheme IX).

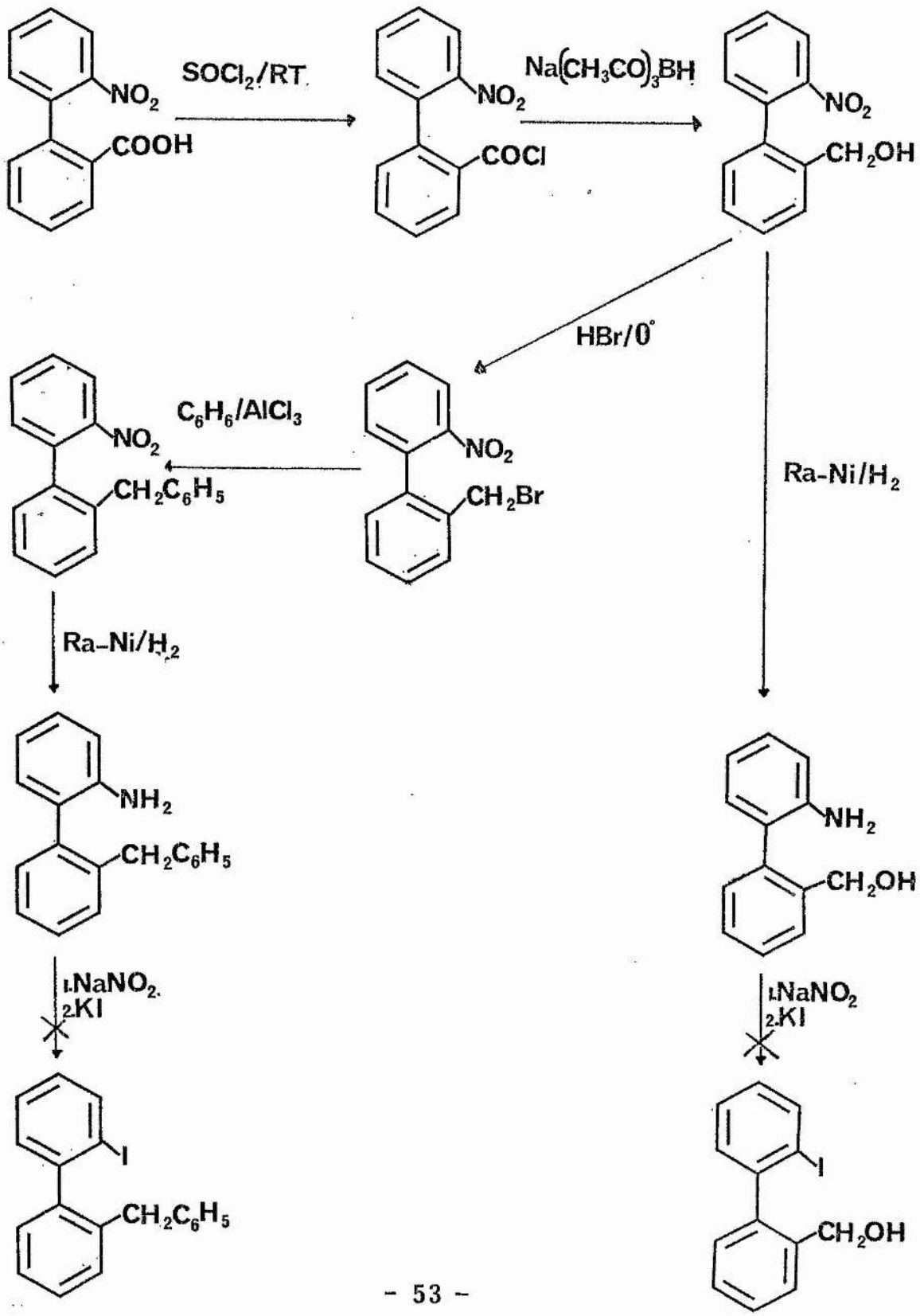
The second synthetic route was based upon 2-nitrobiphenyl-2′-carboxylic acid. Two methods were attempted to prepare this starting material. The first method was by an Ullmann reaction using 2-iodonitrobenzene and methyl 2-iodobenzoate[62]. However, the yield of 2-nitrobiphenyl-2′-carboxylic acid was low (19%). The second method of preparation of this starting material was carried out by stirring biphenyl-2-carboxylic acid in concentrated nitric acid at room temperature and gave the higher yield (47%) of 2-nitrobiphenyl-2′-carboxylic acid quoted previously[55].

A series of reactions were then carried out and samples of 2′-hydroxymethyl-2-nitrobiphenyl, 2-amino-2′-hydroxymethylbiphenyl, 2′-(2-nitrophenyl)-benzylbromide, 2′-benzyl-2-nitrobiphenyl and 2-amino-2′-benzylbiphenyl were successfully prepared. Diazotisation of the two amino compounds was attempted but was unsuccessful, (Scheme X)

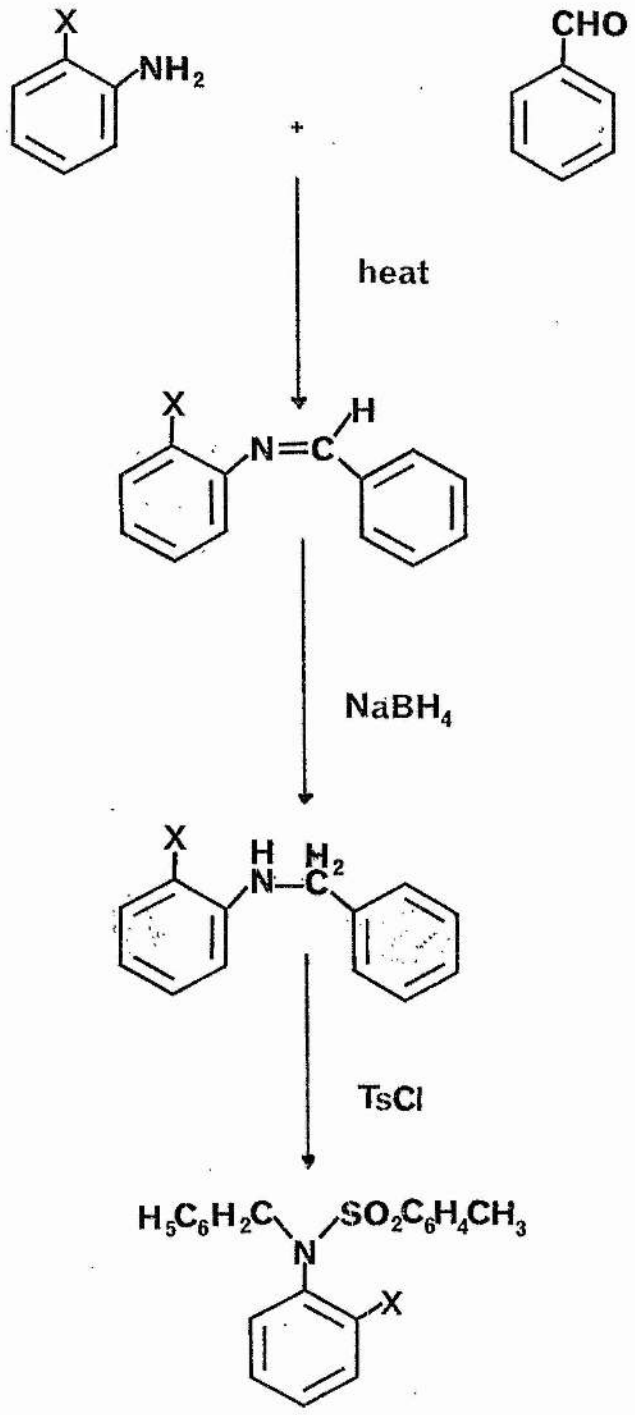
3.2 N-Benzyl-N-Tosyl substituted anilines

Two synthetic routes were used to prepare a series of N-benzyl-N-tosyl substituted anilines. The first route involved the preparation of the N-benzylidene-substituted aniline followed by reduction with sodium borohydride to

Scheme X


SOCl2/RT
Na(CH3CO)3BH
HBr/0°
C6H6/AlCl3
Ra-Ni/H2
Ra-Ni/H2
1.NaNO2
2.KI
1.NaNO2
2.KI
NO2
COOH
COCl
CH2OH
CH2Br
CH2C6H5
NH2
I

Scheme XI



X=Cl,I.

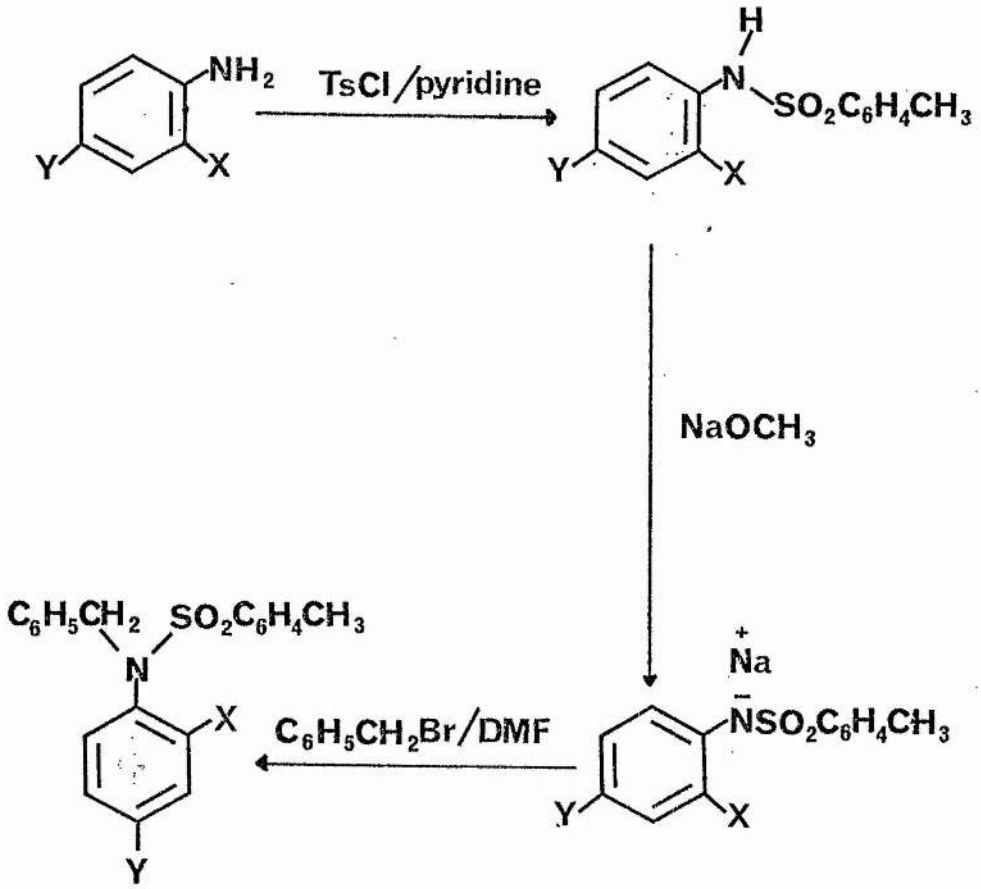
give the N-benzyl substituted aniline[63,64]. The N-benzyl substituted aniline was then tosylated to give the final product, (Scheme XI).

The main difficulties were again found to be in the reduction step using sodium borohydride. Only in the preparation of the N-benzyl-2-iodoaniline could a reasonably pure product be isolated and only in low yield (25%). In general, the reduction did not go to completion so that unchanged starting material was present and gave rise to oils. Therefore the crude oils from the reduction stage were used as the starting material for the tosylations. N-benzyl-N-tosyl-2-iodoaniline and N-benzyl-N-tosyl-2-chloroaniline were prepared by this method but in low yields, these being 13% and 14% respectively. An attempt was made to prepare N-benzyl-N-tosyl-2-bromoaniline by this method but gave only intractable oils.

The second synthetic route used proved more successful. This route involved the tosylation of a substituted aniline followed by formation of its sodium salt and subsequent benzylation[27,65], (Scheme XII).

However, difficulties were encountered in the tosylation of methyl anthranilate and 4-amino-3-methylbenzoic acid. The attempted tosylation of methyl anthranilate gave N-tosyl-anthranilic acid as the only product. Therefore this product was benzylated and then various methods of methylation were attempted to obtain the desired methyl N-benzyl-N-tosyl-anthranilate. Refluxing the N-benzyl-N-tosylanthranilic acid in dry methanol saturated with hydrogen chloride and

Scheme XII



Y = H, X = CH_3, Br, OCH_3, F, COOH, $COOCH_3$.

X = CH_3, Y = CH_3, Cl, NO_2, NH_2.

in dry methanol with concentrated sulphuric acid both proved unsuccessful. However, a sample was obtained by the action of diazomethane but in low yield (13%). The low yield was thought to be partly due to the insolubility of the acid in methanol at the low temperature required for the reaction.

An additional problem in the tosylation of methyl anthranilate was that the end product formed a gum which was difficult to purify. The attempted tosylation of 4-amino-3-methylbenzoic acid also gave a gum-like product which could not be purified by crystallisation, distillation or chromatography. As a pure sample of 4-(N-tosylamino)-3-methylbenzoic acid could not be isolated, the benzylation was carried out on the crude gum. This gave another gum from which an oil was extracted. A small amount of this oil very slowly solidified but, when attempts were made to purify the solid, it reverted to the oil. However, a sample of the crude sample was found to contain sufficient 4-(N-benzyl-N-tosylamino)-3-methylbenzoic acid for analysis of the n.m.r. spectrum.

3.3 Quinone-anils

The problems encountered in the attempted condensation of 2,6-di-t-butyl-1,4-benzylquinone and 4-substituted-2-benzylanilines were twofold. Firstly, preparation of the starting materials, in particular 2-benzyl-4-nitroaniline, proved to be more difficult than was anticipated. Secondly,

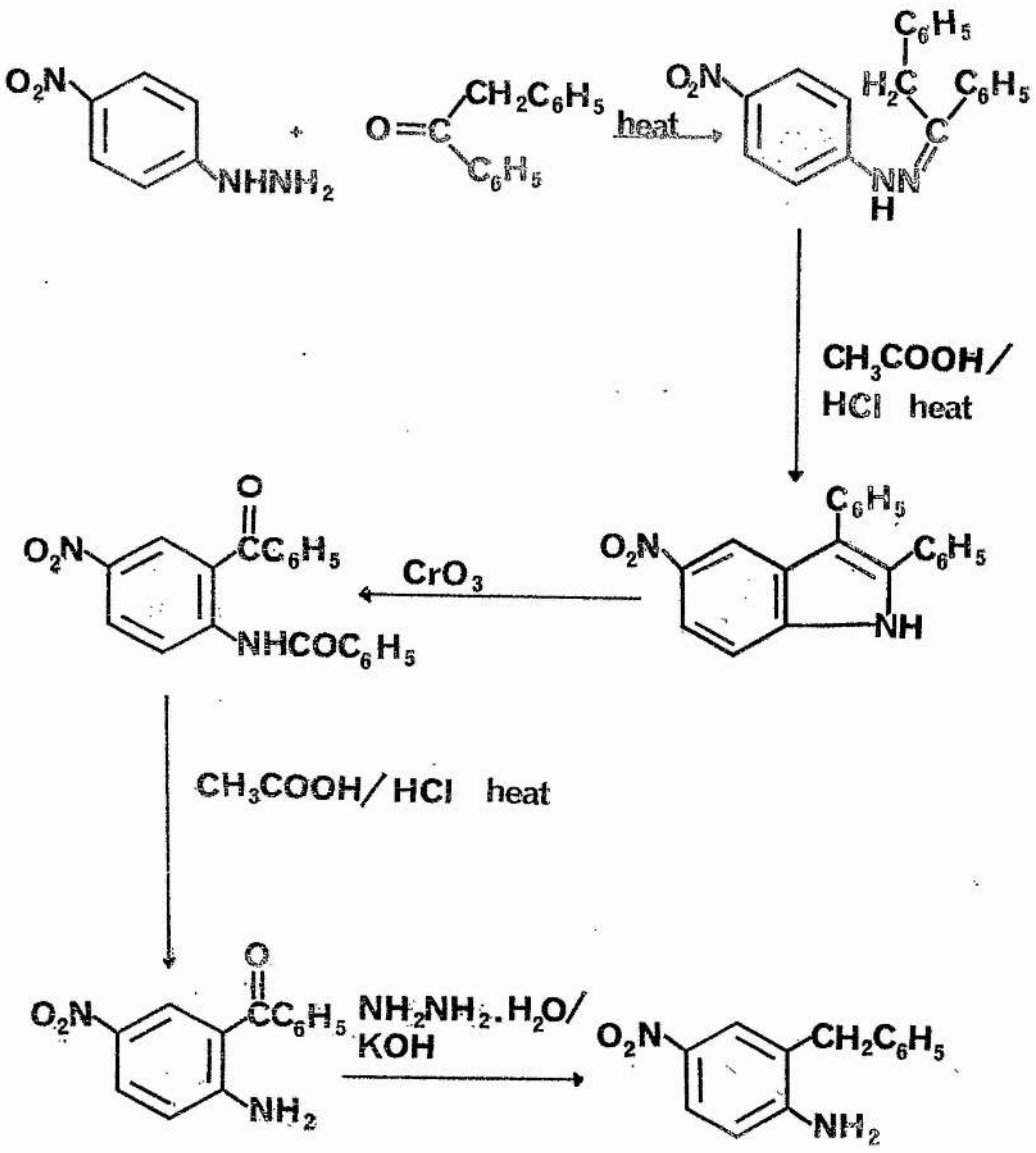
the actual condensation proved more difficult than was suggested in the literature and gave rise to different products from those expected[30].

The general method attempted for the preparation of the 4-substituted-2-benzylanilines was by the reduction with sodium and hot ethanol of the corresponding amino-benzophenone[65]. This was only completely successful in the preparation of 2-benzyl-4-methylaniline. Samples of 2-benzylaniline and 2-benzyl-4-chloroaniline were prepared by this method but analysis of the N-acetyl derivatives showed that they were impure.

An attempt was made to prepare 2-amino-5-nitrobenzophenone by the action of benzoyl chloride and anhydrous zinc chloride upon 4-nitroaniline. However, the only pure compound that could be isolated from the reaction mixture was unchanged starting material. Therefore an alternate synthetic route was devised. This involved the preparation of 2,3-diphenyl-5-nitroindole from benzylphenyl-(4-nitrophenyl)-hydrazone followed by oxidation of the indole to give 2-benzamido-5-nitrobenzophenone[67,68]. This compound was then hydrolysed to give 2-amino-5-nitrobenzophenone.

The complete synthetic route was carried out once successfully, (Scheme XIII). An attempt was then made to reduce the 2-amino-5-nitrobenzophenone using sodium and hot ethanol. This was unsuccessful and so a second method of reduction using the Huang-Minlon reaction was carried out[69]. This method was successful but in very low yield, (6%), and

Scheme XIII



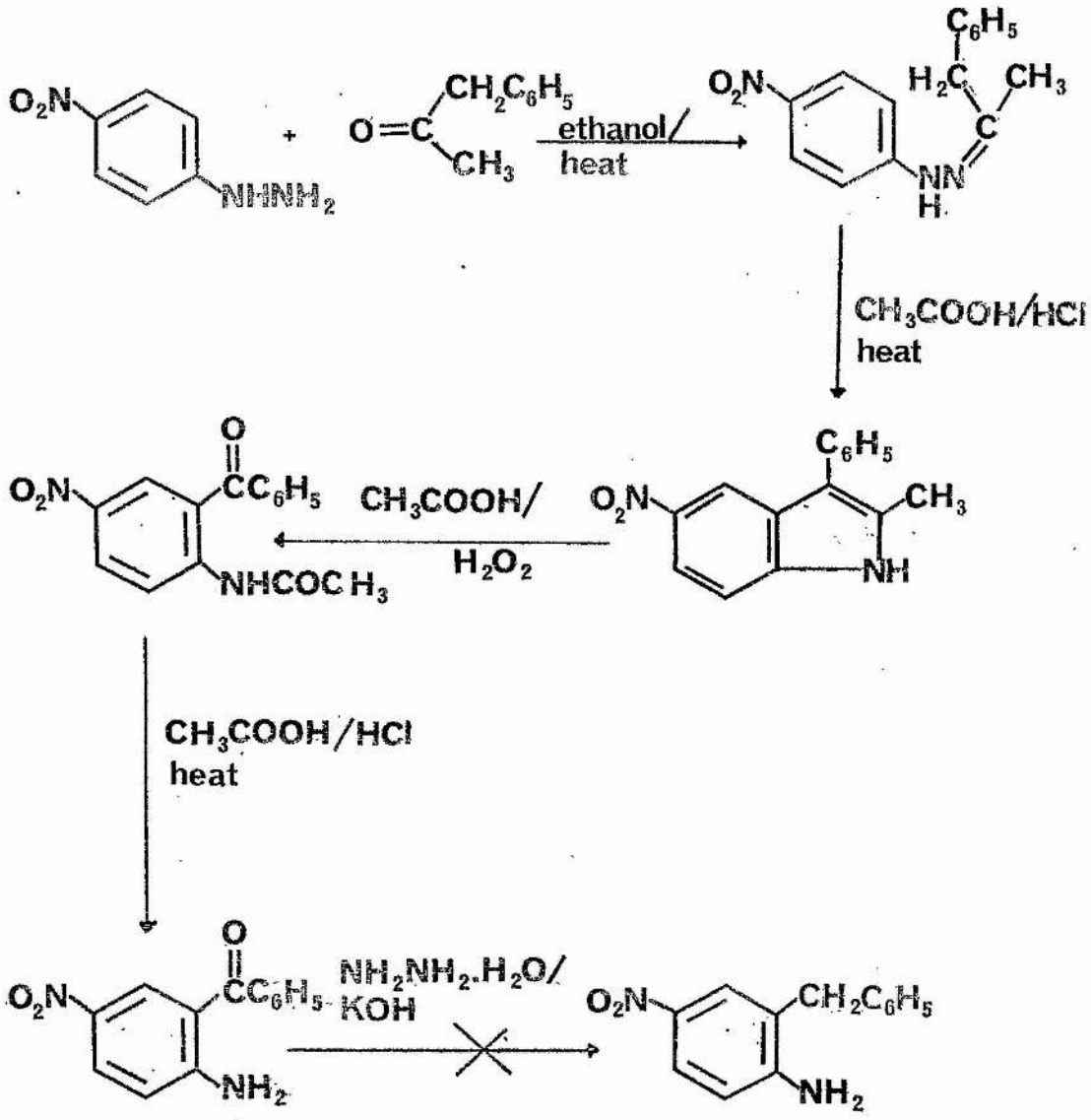
Synthesis of 2-Benzyl-5-Nitroaniline from Benzylphenylketone (failed at first step second attempt).

so an attempt was made to repeat the synthesis of the 2-amino-5-nitrobenzophenone.

At this stage an unexpected problem arose in that the preparation of the initial benzylphenyl-(4-nitrophenyl)-hydrazone could not be repeated. The reaction was prepared as before but with twice the amount of reactants used in the previous reaction. The two solids were then heated but on reaching 90° a sudden, strong exthothermic reaction took place, the temperature reaching 200° before the reaction could be controlled. An attempt was made to extract and purify a product but only a tar was obtained. A second attempt was made to repeat the reaction but on a smaller scale. This was unsuccessful as the violent exothermic reaction occurred once more with subsequent tar formation. A third attempt was made to repeat the reaction using fresh commercial samples of recrystallised starting materials. This and all subsequent attempts were unsuccessful.

Therefore attempts were made to prepare the hydrazone in solution. Refluxing equimolar amounts of the hydrazine and the ketone in ethanol or methanol, with or without catalytic quantities of concentrated sulphuric acid, gave only unchanged starting materials. Refluxing equimolar amounts of the hydrazine and the ketone in dry benzene, with or without catalytic quantities of concentrated sulphuric acid, resulted in tar formation. (The reactants were not fully soluble in benzene so that the conditions

Scheme XIV



Synthesis of 2-Benzyl-5-Nitroaniline from Methylphenylketone (failed at final step).

were analogous to the "dry" reaction, hence the tar formation).

At this stage the synthetic route was modified by substituting benzylmethylketone for benzylphenylketone, (Scheme XIV). (This change was irrelevant to the overall product of the synthesis as the intermediate amido-compound was hydrolysed to free amine before the reduction step). Benzylmethyl-(4-nitrophenyl)hydrazone was made in high yield (89%) by refluxing 4-nitrophenylhydrazine and benzylmethylketone, (in slight excess), in ethanol and was then used to prepare 2-methyl-5-nitro-3-phenylindole as in the previous synthetic route[70].

Difficulties were then encountered in the oxidation of the indole to the substituted benzophenone. According to the literature, 2,3-disubstituted indoles can be oxidised by the action of sodium metaperiodate[71]. Therefore, the oxidation was attempted using a sodium metaperiodate solution made by the addition of sodium hydroxide to periodic acid. This was unsuccessful and so a second attempt was made using a sodium metaperiodate solution made directly from the salt. This was also unsuccessful and was due to precipitation of the indole during the addition of the aqueous sodium metaperiodate. Therefore the oxidation was attempted in benzene with potassium metaperiodate using 18 crown 6 ether as a solvating agent. The indole remained in solution but was not oxidised. It

appeared that as well as reducing the solubility of the indole the nitro group was also deactivating the indole to periodate oxidation. A small-scale oxidation using chromic oxide was then attempted but gave an intractable tar. The oxidation was eventually achieved using peracetic acid and 2-acetamido-5-nitrobenzophenone was obtained in good yield, (53%).

The 2-acetamido-5-nitrobenzophenone was then hydrolysed to give the free amine and attempts were then made to reduce this to 2-benzyl-4-nitroaniline. Having successfully prepared a small sample of 2-benzyl-4-nitroaniline by the Huang-Minlon reaction an attempt was made to repeat the reduction on a larger scale. However, work-up of the reaction mixture gave only tarry oils. A small-scale reduction was also attempted using sodium and hot ethanol but gave only tar. Work on this synthetic route was then discontinued.

The samples of 2-benzylaniline, 2-benzyl-4-chloroaniline and 2-benzyl-4-methylaniline which had been prepared were then condensed with 2,6-di-t-butyl-1,4-benzoquinone. In the literature this was carried out by mixing equimolar amounts of the aniline with the quinone, adding a few drops of glacial acetic acid and heating to 100^{o} for 4 hours[30]. This method was attempted but analysis of the product by thin layer chromatography indicated that this was composed of unchanged starting materials. Refluxing

equimolar amounts of the aniline and the quinone in dry benzene with toluene-4-sulphonic acid was also unsuccessful. Equimolar amounts of 2-benzylaniline and 2,6-di-t-butyl-1,4-benzoquinone were then refluxed overnight in dry xylene with toluene-4-sulphonic acid.

Thin layer chromatography of the product showed three spots. Two of these spots corresponded to the two starting materials, but the third spot, which had the largest r.f. value, indicated the presence of a different compound. The mixture was purified by column chromatography and a product obtained which was shown by analysis to correspond to the molecular formula $C_{27}H_{31}NO$. The mass spectrum had a molecular ion of m/e **385**. This confirmed the molecular formula as $C_{27}H_{31}NO$.

This molecular formula corresponded to that of the expected quinone anil. However, both the n.m.r. and the IR spectra indicated that this was not the product. The IR spectrum indicated the presence of an >N-H stretching frequency. The 60MHz n.m.r. spectrum showed two singlets, both integrating to one proton, at $\delta(CDCl_3)$ 4.55 and $\delta(CDCl_3)$ 3.95. The normal pattern expected for the methylene protons of the benzyl group is either a singlet (integrating to two protons), if the two protons are equivalent or an AB quartet if the two protons are non-equivalent. It was thought that the two singlets seen in the 60MHz n.m.r. spectrum might be part of an AB quartet in which the outer peaks had been lost in baseline noise.

Therefore, a 100MHz n.m.r. spectrum was run at variable temperature to determine whether the two singlets would coalesce at higher temperatures. The two singlets did not coalesce and the sample eventually decomposed at 180°.

As the previous spectral evidence was still ambiguous as to the structure of the compound ^{13}C n.m.r. spectra were taken in the normal mode and in the off resonance decoupled mode.

Analysis of the ^{13}C n.m.r. spectral data (Table 13) showed that the compound contained six CH_3 groups, twelve CH groups and nine quaternary carbon atoms. From chemical shift considerations, the six CH_3 groups were identified as being the methyl groups in the two t-butyl substituents. Of the CH groups, eleven were identified as benzenoid ring and quinonoid ring carbons. This left one CH group with a chemical shift typical of an sp^3 hybridised carbon atom.

Of the quaternary carbon atoms, one $\delta(CDCl_3/CHCl_3)$ 185.45 could be attributed to the >C=O in the quinonoid ring. Five could be attributed to other carbons in the benzenoid and quinonoid rings and two to the carbons of the t-butyl groups. This left one quaternary carbon which had a chemical shift typical of an sp^3 hybridised carbon atom.

This data established the presence of the substituted quinone ring. However, the absence of any triplet in the off-resonance modespectrum indicated that the methylene

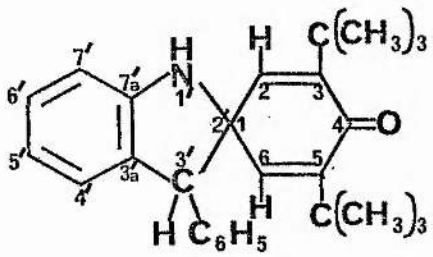
TABLE 13.

^{13}C in $CHCl_3/CDCl_3$

Peak No.	Peak Ht.	Chemical shift (ppm)	Multiplicity in off-resonance mode.
27	115	28.82	q
26	96	29.45	q
25	27	34.26	s
24	24	34.63	s
23	32	59.07	d
22	15	68.15	s
20	33	110.48	d
19	37	119.29	d
18	45	125.89	d
17	41	127.43	d
15	99	128.03	d
14	45	128.41	d
13	96	128.97	d
12	26	129.26	s
8	16	136.61	s
7	35	139.43	d
6	41	142.58	d
5	17	146.41	s
4	15	147.38	s
3	13	149.47	s
2	8	185.45	s

group of the benzyl substituent was not present. Also, the expected quinone-anil structure could not account for the one CH group and the one quaternary carbon atom which appeared upfield in the spectrum.

Therefore a structure was proposed based on a dihydroindole containing one spiro carbon through which the substituted quinone ring was joined to the indole.



XVIII

We propose that the product has structure XVIII spiro-[3,5-di-t-butylcyclohexa-2,5-diene-1,2'-(1',3') dihydro-3'-phenylindole] -4-one. The two singlets at $\delta(CDCl_3)$ 4.55 and $\delta(CDCl_3)$ 3.95 seen in the 60MHz spectrum are the two protons on the nitrogen and the 3' carbon of the five membered indole ring. The structure XVIII also explains the >NH stretching frequency seen in the IR spectrum and the absence of a mass peak for benzyl in the mass spectrum. The structure XVIII has the same molecular formula as that of the quinone-anil and so has the same molecular weight and analytical composition.

In identifying the structure of the spiro compound only the product from the condensation with the 2-benzyl-aniline was used. Therefore, further work was carried out

to try and expand the identification to include the condensation with the 4-substituted 2-benzylanilines. The product of the condensation of 2,6-di-t-butylbenzoquinone and 2-benzyl-4-chloroaniline was very impure, (as seen from the analysis), and so this product was selected for further purification.

The condensation using 2-benzyl-4-chloroaniline was repeated and a red oil was obtained. Thin layer chromatography of the oil on a silica plate eluted with a 1:1 mixture of 60:80 petrol ether and benzene showed three spots. Two of these spots corresponded to starting materials. The oil was then chromatographed on a silica column. This resulted in three fractions A, B and C which eluted successively from the column. Fraction B was further purified by a method of fractional crystallisation. All fractions were analysed by h.p.l.c.

The results of this analysis showed that fraction A was a mixture of the spiro compound and the quinone-anil. Of fraction B the products of the first and second recrystallisations were virtually pure spiro compound. The product of the third recrystallisation was a mixture of the spiro compound and the quinone anil. The product of the fourth recrystallisation showed some spiro compound was present but that the mixture was predominantly the quinone-anil. The residue of the fourth recrystallisation was a mixture of the spiro compound, the quinone-anil and some 2,6-di-t-butyl-1,4-benzoquinone. Fraction C contained

2,6-di-t-butyl-1,4-benzoquinone, 2-benzyl-4-chloroaniline and some quinone-anil.

All these results were only qualitative as detection of the products was carried out by U.V. spectrometry and the extinction co-efficients of the pure products would be required to obtain quantitative results.

However, U.V. spectra were taken of the first and fourth recrystallisations of fraction B as these were the purest samples of spiro compound and quinone-anil available. The spectra were run in cyclohexane and the approximate extinction co-efficients calculated from the absorbance at 254 nm. This gave extinction co-efficients of $\log \epsilon = 4.2$ for the spiro compound and $\log \epsilon = 4.07$ for the quinone-anil.

Thus it was shown that the condensation of 2,6-di-t-butyl-1,4-benzoquinone and 4-substituted-2-benzylanilines gave rise to a more complicated reaction than was expected. The condensations using 2-benzyl-4-chloroaniline, 2-benzyl-4-methylaniline and 2-benzylaniline all gave spiro compounds as products. Only the condensation with 2-benzyl-4-chloroaniline was shown to give quinone-anil as a product.

An attempt was made to extend the series by study of the condensation reaction using 2-benzyl-4-nitroaniline. This would have shown the effect of an electron - with - drawing group para - to the amino-function. However, this

was not possible as 2-benzyl-4-nitroaniline could not be made.

As the separation of single products from the mixtures was very difficult, the mechanism of formation of the spiro compound remained ambiguous. Also, the possibility that the quinone-anil could isomerise to the spiro compound under the rigorous purification procedures used could not be neglected. The work was discontinued at this stage, but further research into the subject is envisaged.

4. EXPERIMENTAL

4.1 Biphenyls

Preparation of 2-benzalcyclohexanone[60].

A mixture of benzaldehyde (21.2g, 0.20M), cyclohexanone (21.8g, 0.22M) and 100 ml 1M sodium hydroxide was stirred and heated under reflux for 3 hours. The mixture was allowed to cool and stand at room temperature overnight, then extracted with methylene chloride. The combined methylene chloride extracts were washed with water, water and a few drops of glacial acetic acid, dried over sodium sulphate, concentrated and distilled in vacuo to give 18.2g of a pale yellow oil, b.p. 140° at 15 mm. Hg. [Lit. b.p. 173-183° at 10 mm. Hg.] The pale yellow oil solidified very readily and was recrystallised from 40:60 petrol ether and gave 17.2 g (46%) of pale yellow crystals, m.p. 54-55°. [Lit. m.p. 54°.] [60]

$\delta(CDCl_3)$, 7.5 (1H,s), 7.25 (5H,s), 2.85 (2H, broad m), 2.50 (2H, broad m), 1.90 (4H, broad m).

Preparation of 2-tolyl-3-benzalcyclohexene[61].

Magnesium (3.6g, 0.15M) was covered with 25 ml dry ether and 2-bromotoluene (25g, 0.15M) dissolved in 175 ml dry ether was added dropwise maintaining the ether at gentle reflux. After addition was complete the reaction mixture was refluxed for a further 2 hours. The reaction mixture was then cooled in ice and a solution of benzalcyclohexanone

(16.8g, 0.9M) in 75 ml dry ether was added dropwise with constant stirring. After addition was complete the reaction mixture was refluxed for 4 hours and then allowed to stand at room temperature overnight. The reaction mixture was decomposed by pouring onto ice and hydrochloric acid, then extracted into ether. The ether extract was washed with water and aqueous sodium bicarbonate then dried over sodium sulphate and concentrated to give 10.5g of a dirty yellow oil.

The dirty yellow oil was chromatographed on alumina with 40:60 petrol ether to give 4.5g of a yellow oil. The yellow oil was distilled and a fraction (3.3g (14%) b.p. 170-172° at 0.8 mm. Hg.), was collected and used, without further purification, in the next stage of the reaction sequence.

Preparation of 2-benzyl-2'-methylbiphenyl[61].

2-Tolyl-3-benzalcyclohexanone (3.3g, 0.013M) was dissolved in 50 ml p-cymene and palladium on charcoal (0.33g, 10%) was added. The mixture was refluxed overnight. The mixture was cooled and concentrated to give a yellow oil which was distilled and a fraction (2.5g, b.p. 146° at 0.8 mm. Hg.) was collected.

The yellow oil was chromatographed on alumina with 40:60 petrol ether and the resulting solid recrystallised from ethanol to give 1.52g (45%) of white crystals, m.p. 52°.

Found 93.0% C, 7.1% H, $C_{20}H_{18}$ requires
93.0% C, 7.0% H.

δ (CCl_4) 7.10 (13H,m); 3.65 (2H,s); 1.90 (3H,s).

m/e 258 (35%), 243 (19), 179 (30), 166 (100).

Preparation of 2-nitrobiphenyl-2′-carboxylic acid[62].

A mixture of 2-iodonitrobenzene (20.33g, 0.08M) and methyl 2-iodobenzoate (20.33g, 0.08M) was heated to 230° then copper bronze powder (20.33g, 0.32M) was added portionwise over 1 hour; the temperature was maintained between 230° and 250°. The resulting mixture was cooled, extracted into acetone and concentrated to give a brown tar. The tar was boiled in 3M sodium hydroxide then diluted with water. A dark brown precipitate of 2,2′-dinitrobiphenyl was formed and filtered off. The filtrate was poured into 50% hydrochloric acid which gave a dark brown, gum-like precipitate. The precipitate was dissolved with concentrated aqueous ammonia and then reprecipitated with 50% hydrochloric acid. The dirty yellow precipitate was filtered off and recrystallised twice from chloroform to give 3.65g (19%) of pale yellow crystals, m.p. 166°. [Lit. m.p. 168°] [62].

δ ($CDCl_3$) 11.80 (1H,s); 8.1 (2H, broad m); 7.45 (6H, broad m).

Preparation of 2-nitrobiphenyl-2′-carboxylchloride[72].

Thionyl chloride (2 ml) was added to 2-nitrobiphenyl-2′-carboxylic acid (1.0g, 0.004M) in a distilling flask, fitted with a drying tube. The mixture was allowed to stand

at room temperature overnight. Excess thionyl chloride was removed by distillation at reduced pressure. Dry ether was added and the process of distillation repeated until all the excess thionyl chloride was removed. The resulting solution was stood over anhydrous sodium hydroxide, overnight at room temperature, in a vacuum dessicator. The solution solidified and was recrystallised from dry ether to give 0.98g (95%) of yellow crystals, m.p. 58 - 62°. [Lit m.p. 58 - 61°] [72].

Preparation of 2'-hydroxymethyl-2-nitrobiphenyl[73].

2-Nitrobiphenyl-2'-carboxylchloride (2.9g, 0.01M) was dissolved in dry dioxan (50 ml), and sodium trimethoxyborohydride (6.1g, 0.05M) in dry dioxan (25 ml) was added dropwise. During the addition the mixture was stirred in an ice-bath, the temperature being maintained between 10° and 20°. After the addition was complete the mixture was stirred in an ice-bath for a further 15 minutes and then at room temperature for 5 hours. The reaction mixture was acidified with dilute hydrochloric acid and then filtered to remove inorganic precipitate. Dioxan was removed by steam distillation and the residue extracted with benzene. The benzene extract was washed with water and with saturated sodium chloride, then dried and concentrated to give an orange oil. This was dissolved in a 1:1 mixture of benzene and carbon tetrachloride from which a waxy yellow solid separated. The solid was recrystallised from

1:1 benzene and carbon tetrachloride to give 1.7g (74%) of a yellow solid, m.p. 79 - 81°. [Lit. m.p. 80 - 82°] [73].

$\delta(CDCl_3)$ 8.0 (1H, broad m); 7.45 (7H, broad m); 5.05 (1H, t, J_{vr} = 6Hz); 4.20 (2H, d, J_{vr} = 6Hz).

Preparation of 2'-(2-nitrophenyl)-benzylbromide[73].

To ice-cold hydrogen bromide solution (7 ml, 48%) and concentrated sulphuric acid (0.8 ml) was added 2'-hydroxymethyl-2-nitrobiphenyl (0.9g, 0.004M) in small portions over 30 minutes, the temperature being maintained below 5°. The mixture was then allowed to warm to room temperature with stirring and refluxed for 2 hours to give an orange solution. This was cooled and extracted with benzene. The benzene extracts were washed with water, dilute sodium bisulphite and saturated sodium chloride, then dried and concentrated to give an orange oil which slowly crystallised. The product was recrystallised twice from a 1:1 benzene/carbon tetrachloride mixture to give 0.65g (56%) of a pale yellow solid, m.p. 76 - 78°. [Lit. m.p. 75 - 78°] [73].

$\delta(CDCl_3)$ 8.05 (1H, broad m); 7.55 (7H, broad m) 4.45 (1H, d, J_{vr} = 10Hz); 4.15 (1H, d, J_{vr} = 10Hz).

Preparation of 2-nitro-2'-benzylbiphenyl[74].

2'-(2-Nitrophenyl)-benzylbromide (0.6g, 0.002M) was added with stirring to dry benzene (15 ml) and freshly ground aluminium chloride (0.4g, 0.0003M).

The mixture was stirred for 10 hours and then allowed to stand at room temperature for two days. The mixture was tested for the presence of HCl, and, this being positive, was refluxed for 1 hour. The reaction was cooled and poured onto ice and hydrochloric acid. The benzene layer was separated, washed with dilute hydrochloric acid, 5% sodium carbonate solution and water, then dried and concentrated. This gave a yellow oil which crystallised very readily and was re-crystallised from ethanol to give 0.5g (87%) of white plate-like crystals, m.p. 98 - 100°. [Lit. m.p. 98 - 101°] [74].

δ (CCl_4) 7.75 (1H,m); 7.10 (12H, broad m),
3.95 (1H,d,J_{xy}= 12Hz); 3.60 (1H,d,J_{xy}, = 12Hz).

Preparation of 2-nitrobiphenyl-2'-carboxylic acid[55].

Biphenyl-2 -carboxylic acid (20g, 0.1M) was added with stirring to concentrated nitric acid (367 ml). Stirring was continued for 2 hours, during which time the white powder in suspension gradually turned yellow. The mixture was poured onto water (80 ml) and the yellow product filtered off. The precipitate was washed with water until the washings were neutral. The crude reaction product was then recrystallised from ethanol to remove 4-nitrobiphenyl-2'-carboxylic acid which was recovered as 4.84g (20%) of a nearly white solid, m.p. 214 - 218°. [Lit. m.p. 231°] [16].

The mother liquor was evaporated to dryness to give crude 2-nitrobiphenyl-2'-carboxylic acid which was recrystallised twice from chloroform to give 11.52g (47%) of a pale yellow solid, m.p. 162 - 164°. [Lit. m.p. 170°] [55].

δ($CDCl_3$) 11.85 (1H,s); 8.1 (2H, broad m); 7.45 (6H, broad m).

Preparation of 2′-hydroxymethyl-2-nitrobiphenyl.

2-Nitrobiphenyl-2′-carboxylchloride (1.4g, 0.005M), (prepared from 2-nitrobiphenyl-2′-carboxylic acid as recorded previously)[72], was treated with sodium trimethoxyborohydride, (by the method as recorded previously). 2′-Hydroxymethyl-2-nitrobiphenyl 0.4g (33%), m.p. 75 - 77°, was obtained but the yield was much reduced in comparison with the previous synthesis. [Lit. m.p. 80 - 82°] [73].

$\delta(CDCl_3)$ 8.0 (1H, broad m); 7.45 (7H, broad m); 5.05 (1H, t, J_{xy} = 6Hz); 4.20 (2H, d, J_{xy} = 6Hz).

Preparation of 2′- hydroxymethyl-2-nitrobiphenyl, (with sodium borohydride).

2-Nitrobiphenyl-2′-carboxylchloride (0.4g, 0.015M) was treated with sodium borohydride (2.1g, 0.055M) by the same method as used for sodium trimethoxyborohydride recorded previously. After completion of the reaction and the work-up an orange oil was obtained which gradually solidified. The solid was recrystallised from a 1:1 mixture of benzene and carbon tetrachloride to give 1.74g (50%) of a yellow waxy solid, m.p. 76 - 79°. [Lit. m.p. 80 - 82°] [73].

$\delta(CDCl_3)$ 8.0 (1H, broad m); 7.45 (7H, broad m); 5.05 (1H, t, J_{xy} = 6Hz); 4.20 (2H, d, J_{xy} = 6Hz).

Hydrogenation of 2′-benzyl-2-nitrobiphenyl.

2′-Benzyl-2-nitrobiphenyl, (0.9g, 0.003M), prepared as recorded previously[6], was dissolved in ethanol (5 ml) and Raney nickel (500 mg) in ethanol (10 ml), was added. The reaction mixture was degassed and then shaken in a hydrogen atmosphere for 24 hours. The catalyst was filtered off and the filtrate concentrated to give 0.14g (18%) of a yellow oil, identified as 2-amino-2′-benzylbiphenyl.

$\delta(CDCl_3)$ 7.25 (13H,m); 3.95 (2H,s); 2.80 (2H, broad s). The n.m.r. spectrum indicated reasonable purity. The preparation of an N-acetyl derivative was attempted using acetic acid and acetic anhydride but produced only a brown oil.

Attempted diazotisation of 2-amino-2′-benzylbiphenyl.

2-Amino-2′-benzylbiphenyl (0.12g, 0.0005M) was dissolved in concentrated hydrochloric acid (1 ml) and water (1 ml). Sodium nitrite (0.4g, 0.0006M) dissolved in water (1 ml) was added, with stirring, the temperature being maintained at 0°. Potassium iodide (0.33g, 0.002M) in water (1 ml) was added and the reaction mixture allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 1 hour then heated on a steam bath for 2 hours. The solution was then cooled and extracted with ether. The ether extract was washed with aqueous sodium bisulphite and water, then dried over

sodium sulphate and concentrated to give a yellowish oil. The oil gave a strong positive reaction when tested for iodine. The oil was chromatographed on a short alumina column with a 3:1 mixture of 40:60 petrol ether and benzene. Two fractions were collected but both proved negative when tested for iodine.

Hydrogenation of 2'-hydroxymethyl-2-nitrobiphenyl.

2'-Hydroxymethyl-2-nitrobiphenyl (1.5g, 0.0066M) dissolved in ethanol (15 ml) and Raney nickel (500 mg) in ethanol (10 ml) was added. The reaction mixture was degassed and shaken in a hydrogen atmosphere for 24 hours. After removal of the catalyst and ethanol, a yellow oil was obtained which, after pumping at 2 mm Hg, solidified to give a white powder, (1.1g, m.p. 76 - 80°). The product was recrystallised from a 1:1 mixture of benzene and 60:80 petrol and gave 0.9g (70%) of 2-amino-2'-hydroxymethyl-biphenyl, m.p. 80 - 81°.

Found 77.9% C, 6.3% H, 6.8% N, $C_{13}H_{13}NO$ requires 78.4% C, 6.6% H, 7.0% N.

$\delta(CCl_4)$ 7.0 (8H, m); 4.2 (2H, s); 3.2 (2H, broad s).

ν_{max} (nujol mull) 3460 cm^{-1}(NH_2); 3370 cm^{-1}(NH_2); 3240 cm^{-1}(OH).

m/e 199 (19%), 180 (100), 167 (16), 152 (29).

Attempted diazotisation of 2-amino-2'-hydroxymethylbiphenyl.

2-Amino-2'-hydroxymethylbiphenyl (1.0g, 0.005M) was dissolved in concentrated hydrochloric acid (3 ml) and water (3 ml). A white crystalline precipitate formed. Sodium nitrite (0.3g, 0.005M) in water (3 ml) was added with stirring, the temperature being maintained at 0°. The mixture formed a clear solution to which was added potassium iodide (0.83g, 0.005M) in water (3 ml). The reaction mixture was allowed to warm to room temperature, stirred at room temperature for 1 hour and then heated on a steam bath for 2 hours. The solution was allowed to cool and extracted with ether. The ether extract was washed with aqueous sodium bisulphite and water, then dried over sodium sulphate and concentrated to give an orange oil. The product was chromatographed on an alumina column with a 3:1 mixture of benzene and 40:60 petrol. Four fractions were obtained, all of which proved negative when tested for iodine.

The diazotisation was repeated but with the same result.

Preparation of 2-methylbiphenyl-2'-carboxylic acid[54].

2-Iodotoluene (28.84g, 0.13M), prepared by a standard method[75], and methyl-2-iodobenzoate (28.84g 0.11M) were intimately mixed with copper-bronze powder (57.68g, 0.9M). This mixture was heated gently to 130° when there was a sudden temperature rise to 210°. The reaction mixture was cooled to 200° and then maintained at 200° for 1 hour. The

reaction mixture was then heated to 250° and the temperature maintained at 250° for a further 5 hours. (Some slight refluxing was seen in the air condenser). The mixture was allowed to cool, transferred to a Soxhlet extractor and extracted overnight with ethanol. Concentration of the ethanolic extract gave a brown oil which was distilled in vacuo and gave two fractions. The first fraction gave 7.75g of an oil, b.p. 94 - 100° at 1 mm Hg. [Lit. b.p. 68° at 0.3 mm Hg][54]. The second fraction gave 27g of an oil, b.p. 120 - 142° at 0.7 mm Hg.

The first fraction was dissolved in ethanol and refluxed for 6 hours with potassium hydroxide (50 ml, 10%). The mixture was cooled and extracted with ether to remove 2,2'-dimethylbiphenyl. The alkaline solution was acidified with dilute hydrochloric acid and extracted with hot 60:80 petrol ether. The extract was dried over sodium sulphate and concentrated to give a white solid which was recrystallised from 60:80 petrol ether and gave 300 mg (1.1%) of 2-methylbiphenyl-2'-carboxylic acid, m.p. 105°. [Lit. m.p. 104 - 105°] [54].

$\delta(CDCl_3)$ 10.10 (1H, broad s); 8.0 (1H, broad m); 7.40 (7H, broad m); 2.05 (3H,s).

The experiment was repeated and further attempts made to extract more 2-methylbiphenyl-2'-carboxylic acid. The major product from all fractions was diphenic acid, m.p. 210 - 220°, (crude sample). [Lit. m.p. 233.5°] [76].

Attempted preparation of 2-methylbiphenyl-2′-carboxylchloride.

Thionyl chloride (1 ml) was added to 2-methylbiphenyl-2′-carboxylic acid (300 mg, 0.0014M) in a distilling flask, fitted with a drying tube. The mixture was stood overnight at room temperature and gave a dark purple solution. Excess thionyl chloride was removed by distillation at reduced vacuum and by successive distillations using dry ether. (During removal of the thionyl chloride the colour of the solution changed from purple, through pale green, to pale yellow which gradually darkened to orange). The residual orange oil was stood overnight over anhydrous sodium hydroxide in a vacuum dessicator. Orange crystals were formed and these were used in the next stage of the reaction without further purification.

Attempted preparation of 2′-hydroxymethyl-2-methylbiphenyl.

Crude 2-methylbiphenyl-2′-carboxylchloride (300 mg, 0.0013M) was dissolved in dry dioxan (2 ml). The solution was stirred in an ice-bath and a slurry of sodium trimethoxyborohydride (600 mg, 0.0047M) in dry dioxan (10 ml) was added dropwise. The mixture turned pale green. After the addition was complete, the mixture was stirred in the ice-bath for a further 15 minutes and then at room temperature for 6 hours. The reaction mixture was acidified with dilute hydrochloric acid and the resulting cloudy, pale yellow suspension filtered. Excess dioxan was removed by steam distillation and the residue extracted

with benzene. The benzene extract was washed with water, saturated sodium chloride solution, dried over sodium sulphate and concentrated to give a trace of a dark yellow oil. No crystallisation could be induced and further attempts at identification proving ambiguous, this synthetic route was abandoned.

Methylation of 2-methylbiphenyl-2'-carboxylic acid.

2-Methylbiphenyl-2'-carboxylic acid (0.47g, 0.0022M), was dissolved in ethanol (5 ml) and an ethereal solution of diazomethane, (prepared from p-tolylsulphonylmethyl-nitrosamide by a standard method[77]), was added dropwise until the solution remained a definite pale yellow, (approximately 10 ml). The reaction mixture was also tested for excess diazomethane with glacial acetic acid. The excess diazomethane was then removed with the solvent and by successive ether distillations. The product solidified and the white solid was used in the next stage without further purification. The crude product 0.4g (81%) was methyl 2-methylbiphenyl-2'-carboxylate, m.p. 88 - 94°.

$\delta(CDCl_3)$ 7.55 (8H,m); 3.55 (3H,s); 2.05 (3H,s).

Reduction of methyl 2-methylbiphenyl-2'-carboxylate.

To a slurry of lithium aluminium hydride (0.04g, 0.001M) in dry ether (5 ml) a solution of methyl 2-methyl-biphenyl-2'-carboxylate (0.4g, 0.0018M) in dry ether (10 ml)

was added dropwise with constant stirring. The reaction mixture was then refluxed for 4 hours, cooled and poured onto ice and water. The ether layer was separated and the aqueous layer extracted with more ether. The ether extracts were combined, dried and concentrated to give a white solid which was recrystallised from 60:80 petrol ether. This gave 0.23g (65%) of 2'-hydroxymethyl-2-methylbiphenyl, m.p. 82 - 84°.

$\delta(CDCl_3)$ 7.20 8H(broad m); 4.30 (2H,s); 3.55 (1H,s): 2.05 (3H,s).

Preparation of 2,2'-biphenyldicarboxylic acid[78].

Copper sulphate (250g, 1.0M) and sodium chloride (75g, 1.275M) were dissolved in hot water (1.25 l). The solution was mechanically stirred and a solution of sodium bisulphite (55g, 0.53M) and sodium hydroxide (36.32g, 0.91M) in water (415 ml) was added over 5-10 minutes. (A yellowish green precipitate formed but redissolved). The mixture was allowed to cool to room temperature and the white precipitate washed with water by decantation. The washed precipitate was added to sodium hydroxide (175 ml, 6M) in water (500 ml) in a 2L. beaker. The last portion of precipitate was washed in with more water (500 ml). The reaction mixture was stirred vigorously for 2-3 minutes; the suspension changing colour from green through ochre to a deep orange. The resulting heavy precipitate of cuprous hydroxide was

allowed to settle, the supernatant liquor removed by siphonation and the precipitate washed with water then left under water until required.

Anthranilic acid (50g, 0.365M) was placed in a 1L. beaker fitted with a mechanical stirrer and in an ice and salt bath. Water (150 ml) and glacial acetic acid (66.5g, 1.15M) were added. A solution of sodium nitrite (25.5g, 0.37M) in water (100 ml) was added dropwise over 1 hour, the temperature being maintained at 5°.

The last wash water covering the cuprous hydroxide was removed by siphonation and the 2L. beaker placed in an ice-bath. The cuprous hydroxide was stirred vigorously, then water (150 ml) and concentrated aqueous ammonia (135 ml, 2M) were added. The clear supernatent liquor from the diazonium reaction was added dropwise, beneath the surface of the reaction mixture, over 1 hour. After the addition was complete the reaction mixture was allowed to warm to room temperature and stirred for a further 30 minutes. The reaction mixture was then heated to boiling and carefully acidified to Congo Red with concentrated hydrochloric acid, while under constant stirring. The reaction mixture became a clear dark green with a dark brown precipitate of crude 2,2'-biphenyldicarboxylic acid. The reaction mixture was allowed to cool, the crude acid filtered off, washed with slightly acidic saturated ammonium chloride solution until free from cupric chloride and then washed with water.

The crude 2,2'-biphenyldicarboxylic acid was dissolved

in glacial acetic acid (200 ml) and hot water (500 ml) was added. Zinc dust (8.0g, 0.12M) was added and the mixture boiled for 6 minutes. Activated charcoal (2.0g, 0.17M) was then added and the mixture boiled for a further 2 minutes. The mixture was filtered under suction while hot to remove zinc and charcoal. The filtrate was heated to boiling and hot water (300 ml) added. The solution was allowed to cool and crystallisation induced by scratching. The mixture was allowed to stand at room temperature overnight, then the off-white solid filtered off, washed with water and air dried. The product 24.21g (28%) was 2,2′-biphenyldicarboxylic acid, m.p. 224 - 226°. [Lit. m.p. 233.5°][76].

Preparation of 2,2′-diphenicanhydride[56].

2,2′-Biphenyldicarboxylic acid (14.0g, 0.058M) and acetic anhydride (42 ml) were heated to reflux and refluxed for 1 hour. The reaction mixture was cooled with the immediate formation of a white precipitate. The precipitate was filtered off, washed with glacial acetic acid and dried to give 11.0g (85%) of 2,2′-biphenylanhydride, m.p. 215°. [Lit. m.p. 212°] [56].

$\delta(CDCl_3)$ 7.45 (8H, broad m).

ν_{max} (nujol mull) 1720 cm^{-1} (broad, C = O).

Preparation of the monoester of 2,2′-biphenyldicarboxylic acid [57].

Methanol (50 ml) was added to 2,2′-biphenylanhydride

(11.0g, 0.5M) and the mixture brought to reflux. After 35 minutes the mixture formed a clear solution which was then allowed to cool. The solution was concentrated to give a clear oil which eventually solidified. The white solid was recrystallised from methanol and water to give 11.92g (95%) of the monoester of 2,2′-biphenyldicarboxylic acid, m.p. 111°. [Lit. m.p. 110°] [57].

$\delta(CDCl_3)$ 7.95 (2H, broad m); 7.20 (6H, broad m); 3.50 (3H,s).

Attempted preparation of 2-methylbiphenyl-2′-carboxylic acid[58].

The monoester of 2,2′-biphenylcarboxylic acid (18.16g, 0.075M) was stirred in dry ether (150 ml) and a slurry of lithium aluminium hydride (1.94g, 0.5M) in dry ether (100 ml) added dropwise so as to maintain gentle reflux of the ether. The reaction mixture was then stirred at room temperature overnight. The reaction mixture was decomposed by pouring onto ice and concentrated hydrochloric acid. The ethereal layer was separated and the aqueous layer extracted with more ether. The ether extracts were combined, washed with dilute hydrochloric acid and water, then dried over sodium sulphate and concentrated to give an orange oil. The oil was allowed to stand overnight at room temperature when it formed very fine white crystals. The product was recrystallised twice from methanol to give 5.8g, (34%) 2-hydroxymethylbiphenyl-2′-carboxylic acid, m.p. 98 - 102°. [Lit. m.p. 146°] [59].

$\delta(CDCl_3)$ 9.30 (1H, broad s); 7.50 (8H,m); 5.00 (1H,s); 3.55 (2H,s).

ν_{max} (nujol mull) 3000 cm^{-1} (OH), 1700 cm^{-1} (C = O).

m/e 210 (100%), 196 (22), 180 (78), 163 (70), 151 (87), 76 (44).

Attempted dehydration of 2-hydroxymethylbiphenyl-2'-carboxylic acid.

Method 1. Heating under vacuum[59].

2-Hydroxymethylbiphenyl-2'-carboxylic acid (1.0g, 0.0044M) was placed in a drying pistol with phosphorus pentoxide as the dessicant. The pressure was reduced to 0.1 mm Hg and the sample gradually heated to 200°. The sample melted with some slight effervescence and a small amount of sublimation. The sample was then allowed to cool and recrystallised from methanol. 2-Hydroxymethylbiphenyl-2'-carboxylic acid, (0.9g, m.p. 99 - 102°) was recovered.

$\delta(CDCl_3)$ 10.35 (1H,s); 7.50 (8H,m); 5.00 (1H,s); 3.55 (2H,s).

ν_{max} (nujol mull) 3000 cm^{-1} (OH), 1700 cm^{-1} (C = O).

Method 2. Refluxing in xylene.

2-Hydroxymethylbiphenyl-2'-carboxylic acid (1.0g, 0.0044M) was dissolved in dry xylene (50 ml) and toluene-4-sulphonic acid (50 mg) was added. The mixture was refluxed overnight using a Dean and Stark condenser. Some clouding of the xylene was seen in the Dean and Stark

condenser. The mixture was allowed to cool and the xylene removed by distillation. The resulting solid was dissolved in ether, washed with water, then dried and concentrated to give a white solid which was recrystallised from methanol. 2-Hydroxymethylbiphenyl-2′-carboxylic acid, (0.9g, m.p. 99 - 102°), was recovered.

$\delta(CDCl_3)$ 9.80 (1H,s); 7.50 (8H,m); 5.00 (1H,s); 3.55 (2H,s).

ν_{max} (nujol mull) 3000 cm^{-1} (OH), 1700 cm^{-1} (C = O).

Method 3. Treatment with thionyl chloride.

2-Hydroxymethylbiphenyl-2′-carboxylic acid (1.0g, 0.0044M) was dissolved in thionyl chloride (5 ml) and stood at room temperature overnight. Excess thionyl chloride was removed by distillation at reduced pressure and successive stripping with dry ether. The resulting bright yellow solid was recrystallised from methanol. This gave 0.9g (97%) of dibenz[c,e]oxepin-5[7H]-one, m.p. 130°. [Lit. m.p. 130-131°][58].

$\delta(CDCl_3)$ 7.50 (8H,m); 4.00 (2H,s).

ν_{max} (nujol mull) 1700 cm^{-1} (C = O), 1680 cm^{-1} (C = O).

m/e 238, 207, 179.

Found 75.5%C 4.1%H $C_{14}H_{10}O_2$ requires 80.0%C 4.8%H.

The experiment was repeated on a larger scale using 4.5g (0.02M) 2-hydroxymethyl-2′-biphenylcarboxylic acid. After recrystallisation from methanol 4.1g of a beige micro-crystalline solid was obtained, m.p. 122 - 128°. Further recrystallisation gave no improvement of the melting-point.

$\delta(CDCl_3)$ 7.50 (8H,m); 5.00 (1H,s); 3.55 (2H,s).

ν_{max} (nujol mull) 1700 cm^{-1} (C = O), 1680 cm^{-1} (C = O).

m/e 270 (19%); 239 (25); 210 (100); 196 (15); 180 (11); 152 (16).

The complete synthesis was repeated starting from diphenic acid, but after the lithium aluminium hydride reduction 2-hydroxymethylbiphenyl-2'-carboxylic acid was the only product.

Attempted hydrogenation of 2-hydroxymethylbiphenyl-2'-carboxylic acid.

Method 1. Using 5% Palladium on barium sulphate catalyst.

2-Hydroxymethylbiphenyl-2'-carboxylic acid (1.28g, 0.0056M) was dissolved in ethanol (30 ml) and 5% palladium on barium sulphate (0.13g) was added. The mixture was degassed and then stirred for 3 days in a hydrogen atmosphere. The catalyst was then filtered off and the filtrate concentrated to give a white solid which was recrystallised from methanol. Starting material, 12g (94%) m.p. 102°, was recovered unchanged.

$\delta(CDCl_3)$ 7.50 (8H,m); 3.55 (2H,s); 2.05 (1H,s).

ν_{max} (nujol mull) 3000 cm^{-1} (OH), 1700 cm^{-1} (C = O).

Method 2. Using palladium on charcoal catalyst.

2-Hydroxymethylbiphenyl-2'-carboxylic acid (1.2g, 0.0053M) was dissolved in ethanol (30 ml) and palladium on charcoal (0.1g) was added. The mixture was degassed and then stirred in a hydrogen atmosphere for 2 days.

The catalyst was then filtered off and the filtrate concentrated to give a white solid which was recrystallised from methanol. This gave 0.9g of a white microcrystalline solid, m.p. 110-130°.

$\delta(CDCl_3)$ 7.25 (10H,m); 3·55 (2H,s); 2·05 (1H, s).

ν_{max} (nujol mull) 2510 cm^{-1}, 1720 cm^{-1} (C = O), 1625 cm^{-1}, (C = O).

Preparation of 3,4-benzocoumarin (biphenyl-δ-lactone).

2-Nitrobiphenyl-2'-carboxylic acid (6.0g, 0.025M), prepared from biphenyl-2-carboxylic acid as recorded previously, was dissolved in ethanol (50 ml). Potassium hydroxide (1.38g, 0.025M) dissolved in ethanol (50 ml) was added with stirring. A white precipitate formed which was filtered off and washed with small portions of cold ethanol and then dried to give 5.6g of crude potassium 2-nitrobiphenyl-2'-carboxylate. The dried product was ground to a fine powder and then placed in a sublimation tube. A white product sublimed at 220° at 0.02 mm Hg and was recrystallised from 60:80 petrol ether. This gave 2.55g (52%) of 3,4-benzocoumarin, m.p. 91-92°. [Lit. m.p. 92.5°] [55].

Found 79.4%C 4.0%H $C_{13}H_8O_2$ requires 79.6%C 4.1%H.

Preparation of 2-hydroxy-2'-hydroxymethylbiphenyl.

Lithium aluminium hydride (1.0g, 0.026M) was stirred in dry ether (100 ml) and treated dropwise over 20 minutes with

3,4-benzocoumarin (1.0g, 0.026M) in dry ether (120 ml) while stirring. The mixture was stirred at room temperature for a further 40 minutes then the excess lithium aluminium hydride decomposed by the addition of wet ether and then water, 10% sulphuric acid was added to decompose the aluminium complexes and dissolve aluminium hydroxide. The ether layer was separated and the aqueous fraction extracted with more ether. The combined ether extracts were washed with water then dried over sodium sulphate and concentrated to give a white solid which was recrystallised from ethanol. This gave 0.4g (77%) of 2-hydroxy-2′-hydroxymethylbiphenyl, m.p. 131 - 132°.

Found 77.9%C 5.9%H $C_{13}H_{12}O_2$ requires

78.0%C 6.0%H.

δ[$(CD_3)_2CO$] 8.10 (1H,s); 7.00 (8H,m); 4.45 (2H,s); 4.15 (1H, broad s).

Preparation of 2-methoxybiphenyl-2′-carboxylic acid and 2-methoxybiphenyl-methyl-2′-carboxylate[79].

3,4-Benzocoumarin (0.86g, 0.0044M), Sodium hydroxide (1.72g, 30%) and dimethylsulphate (1.6 ml) were shaken together for 1 hour. The reaction mixture was then extracted with ether to separate the methyl ester and the remaining solution acidified with dilute hydrochloric acid which gave a white precipitate. The white precipitate was filtered off and recrystallised from benzene to give 0.3g (30%) of 2-methoxybiphenyl-2′-carboxylic acid, m.p. 151-152°.

[Lit. m.p. 152 - 153°][79].

The ether extract was washed with water, dried over sodium sulphate and concentrated but gave only a trace of any product.

Attempted preparation of 2-hydroxymethyl-2'-methoxybiphenyl.

Lithium aluminium hydride (0.5g, 0.013M) was stirred in dry ether (50 ml) and treated dropwise over 20 minutes with a solution of 2-methoxybiphenyl-2'-carboxylic acid (1.0g, 0.0044M) in dry ether (50 ml). The reaction mixture was stirred for a further 40 minutes then the mixture decomposed by pouring into ice and water. 10% sulphuric acid (50 ml) was added and the reaction mixture was extracted with ether. The ether extract was washed with water, then dried over sodium sulphate and concentrated to give a white solid which was recrystallised from ethanol. This gave 0.6g (70%) of 2-hydroxy-2'-hydroxymethylbiphenyl, m.p. 130 - 131°.

$\delta(CDCl_3)$ 8.10 (1H, broad s), 7.00 (8H, m), 4.80 (1H, broad s), 4.45 (2H, s).

4.2 N-Benzyl-N-tosyl-2,4-substituted Anilines.

Preparation of N-benzylidene-2-iodoaniline[63].

2-Iodoaniline (2.14g, 0.01M) and redistilled benzaldehyde (1.04g, 0.01M) were dissolved in ethanol (5 ml) and warmed gently for 30 minutes. The reaction mixture was then cooled and the ethanol removed to give an orange oil.

The oil was dissolved in ether, washed with dilute acetic acid, then dried over sodium sulphate and concentrated to give a brown oil. This was vacuum distilled and gave two fractions. The first fraction gave 0.11g of a yellow oil, (b.p. 100 - 150° at 2mm Hg), which solidified on cooling. This was identified as unreacted 2-iodoaniline, m.p. 60 - 61°. [Lit. m.p. 60 - 61°] [80]. The second fraction gave 1.62g (53%) of N-benzylidene-2-iodoaniline, b.p. 178° at 2mm Hg. [Lit. m.p. 56 - 57°] [81].
$\delta(CDCl_3)$ 8.20 (1H,s), 7.50 (9H, broad m).

Attempted preparation of N-benzyl-2-iodoaniline[64].

N-Benzylidene-2-iodoaniline (1.62g, 0.005M) was dissolved in dry methanol, (25 ml). Sodium borohydride (0.4g, 0.01M) was slurried in dry methanol (25 ml) and added dropwise, over 2 minutes, to the stirred solution of N-benzylidene-2-iodoaniline. Stirring was continued at room temperature for 2 hours and the resulting clear solution was refluxed on a steam bath for 15 minutes. The solution was then cooled and poured onto water (50 ml). A yellow oil formed slowly. The mixture was extracted with ether and the ether extract washed with dilute hydrochloric acid at which point a white precipitate formed. The precipitate was filtered off and redissolved in 5M sodium hydroxide solution. The resulting solution was extracted with ether and the ether extract was washed with water, then dried over sodium sulphate and concentrated to give a

yellow oil. The oil was distilled in vacuo and 0.5g of starting material was recovered unchanged, b.p. 170 - 178° at 2mm Hg.

$\delta(CDCl_3)$ 8.20 (1H,s), 7.50 (9H, broad m).

The experiment was repeated using N-benzylidene-2-iodoaniline (2.0g, 0.0065M) and sodium borohydride (1.3g, 0.034M), which was added portionwise as a solid. The reaction then proceeded as before. Concentration of the final ether extract gave a pale yellow crystalline solid which was recrystallised from ethanol. This gave 500 mg (25%) of N-benzyl-2-iodoaniline, m.p. 50 - 54°.

$\delta(CDCl_3)$ 7.50 (9H, complex m), 4.60 (2H,s), 4.25 (1H,broad s).

ν_{max} (nujol mull) 1620 cm^{-1} (C = C).

Tosylation of crude oil from the attempted reduction of N-benzylidene-2-iodoaniline.

N-Benzylidene-2-iodoaniline (1.0g, 0.0033M) was dissolved in dry methanol (10 ml) and sodium borohydride (0.65g, 0.017M) was added portionwise as a solid over 2 minutes. The reaction mixture was stirred at room temperature for 2 hours, then refluxed on a steam bath for 15 minutes, cooled and poured onto water, (20 ml). A yellow oil formed slowly. The oil was extracted into ether and the ether extract washed with water, then dried over sodium sulphate and concentrated. The resulting yellow oil was dissolved in pyridine (5 ml) and toluene-4-sulphonylchloride (1.0g, 0.0056M) was added. The mixture was warmed on a steam bath for 30 minutes and then poured onto water (20 ml). The mixture was extracted with

ether, washed with dilute hydrochloric acid, dilute sodium hydroxide solution and water, then dried over sodium sulphate and concentrated to give a yellow oil. The oil was allowed to stand at room temperature for 25 weeks, after which time a small amount of solid had formed. The solid was filtered off and recrystallised four times from ethanol to give a white crystalline solid. This gave 200 mg. (13%) of N-benzyl-N-tosyl-2-iodoaniline, m.p. 124 - 126°.

Found 51.9%C, 4.0%H, 3.0%N, $C_{20}H_{18}INO_2S$ requires 51.8%C, 3.9%H, 3.0%N.

$\delta(CDCl_3)$ 7.80 (13H, broad m), 4.80 (2H,s), 2.45 (3H,s).

Preparation of N-benzylidene-2-chloroaniline.

2-Chloroaniline (2.55g, 0.02M) and benzaldehyde (2.12g, 0.02M) were dissolved in dry benzene (15 ml). The reaction flask was fitted with a Dean and Stark condenser and the reaction mixture heated to reflux temperature. The reaction was heated for 2 hours, after which time 0.4 ml (0.02M) water had been trapped in the Dean and Stark condenser. The reaction mixture was allowed to cool and the benzene removed. The resulting yellow oil was vacuum distilled. A fraction, (b.p. 129 - 131° at 0.3mm Hg), was collected and gave 2.88g (67%) of N-benzylidene-2-chloroaniline. [Lit. m.p. 33 - 34°] [82].

$\delta(CDCl_3)$ 8.15 (1H, s), 7.45 (9H, broad m).

Preparation of N-benzyl-2-chloroaniline.

N-Benzylidene-2-chloroaniline (2.88g, 0.013M) was dissolved in dry methanol (5 ml) and sodium borohydride (1.0g, 0.026M) was added portionwise. After the addition was complete the reaction mixture was refluxed for 15 minutes. The reaction mixture was then allowed to cool and concentrated to give a yellow oil. The oil was taken up in ether, washed with dilute hydrochloric acid and water, then dried over sodium sulphate and concentrated. Crystallisation of the resulting yellow oil could not be achieved and so the crude product (2.2g) was used in the next stage of the reaction without further purification.

$\delta(CDCl_3)$ 7.15 (9H, broad m), 4.60 (1H, broad s), 4.25 (2H,s).

Preparation of N-benzyl-N-tosyl-2-chloroaniline.

The crude N-benzyl-2-chloroaniline (2.2g, 0.01M) was dissolved in pyridine (11 ml) and toluene-4-sulphonyl-chloride (4.0g, 0.02M) was added. The reaction mixture was warmed on a steam bath for 30 minutes then allowed to cool and poured onto water. A yellow oil formed which was extracted into ether. The ether extract was washed with dilute hydrochloric acid, dilute sodium hydroxide and water, then dried over sodium sulphate and concentrated. The resulting oil crystallised very slowly and incompletely. The crystalline material was

filtered off and recrystallised twice from ethanol to give 500 mg. (14%) of white N-benzyl-N-tosyl-2-chloroaniline, m.p. 119 - 120°.

Found 64.4% C, 4.8% H, 3.6% N, $C_{20}H_{18}ClNO_2S$ requires 64.6% C, 4.9% H, 3.8% N.

$\delta(CDCl_3)$ 7.15 (13, broad m), 4.65 (2H,s), 2.40 (3H,s).

m/e 371 (16%), 294 (8), 215 (46), 155 (42), 139 (100), 110 (99).

Attempted preparation of N-benzylidine-2-bromoaniline.

2-Bromoaniline (11.6g, 0.05M) and benzaldehyde (5.3g, 0.05M) were dissolved in dry benzene (30 ml). The reaction flask was fitted with a Dean and Stark condenser and the reaction mixture heated to reflux temperature. The reaction was heated for 2 hours, after which time 0.9 ml. (0.05M) water had been trapped in the Dean and Stark condenser. The reaction mixture was allowed to cool and the benzene removed. The resulting 14.3g of yellow oil solidified on standing overnight at 0°. Recrystallisation from ethanol was attempted but the product formed an oil. Therefore the product was used in the next stage without further purification.

Attempted preparation of N-benzyl-2-bromoaniline.

The crude N-benzylidene-2-bromoaniline (14.3g) was dissolved in dry methanol, (100 ml). Sodium borohydride (1.9g, 0.05M), was added portionwise with stirring. A

strong effervescence was seen. After addition of the sodium borohydride was complete the reaction mixture was refluxed on a steam bath for 15 minutes. The reaction mixture was then cooled and poured onto water. The mixture was extracted with ether and the ether extract washed with water, then dried over sodium sulphate. This gave 8g. of a yellow oil which solidified very slowly on standing at 0^{o}. A trial tosylation was attempted on 1g. of the crude product but gave only an intractable oil. Tosylation of the remaining 7g. of crude product was attempted but also gave only an intractable oil. Therefore this synthetic route was abandoned.

A series of N-benzyl-N-tosyl-2-substituted anilines and N-benzyl-N-tosyl-2,4-disubstituted anilines were prepared. The following procedure for the preparation of N-benzyl-N-tosyl-2-bromoaniline was typical.

Preparation of N-tosyl-2-bromoaniline.

2-Bromoaniline (3.44g, 0.02M) and toluene-4-sulphonyl-chloride (3.85g, 0.022M) were dissolved in pyridine, (50 ml). The mixture was refluxed for 4 hours then cooled and poured onto water (50 ml). An oil separated slowly. The mixture was extracted with ether and the ether extract washed with dilute hydrochloric acid. The ether extract was then extracted with dilute aqueous sodium hydroxide and this extract acidified with dilute hydrochloric acid to precipitate the N-tosyl-2-bromoaniline. The white solid

was filtered off and recrystallised from ethanol to give 2.42g. (37%) of N-tosyl-2-bromoaniline, m.p. 93 - 94°.
$\delta(CDCl_3)$ 7.40 (9H, broad m), 2.30 (3H,s).

Preparation of N-benzyl-N-tosyl-2-bromoaniline.

N-Tosyl-2-bromoaniline (2.42g, 0.0074M) was dissolved in methanol (25 ml) and sodium (0.171g, 0.0074M) dissolved in methanol (10 ml) was added. The mixture was then evaporated to dryness at reduced pressure to give a white solid. The crude sodium salt was dissolved in dimethylformamide (25 ml) and benzyl bromide (1.80g, 0.011M) added. The mixture was stirred overnight at room temperature. The mixture was then poured onto crushed ice when a pinkish white precipitate formed. The precipitate was filtered off and recrystallised from methanol to give 2.4g (78%) of N-benzyl-N-tosyl-2-bromoaniline, m.p. 112 - 114°.

Found 57.8% C, 4.5% H, 3.3% N, $C_{20}H_{18}BrNO_2S$ requires
57.7% C, 4.4% H, 3.4% N.

$\delta(CDCl_3)$ 7.15 (13H, broad m), 4.70 (2H,s), 2.30 (3H,s).

The following compounds were prepared by the general method recorded previously:-

N-benzyl-N-tosyl-2-fluoroaniline as 7.35g (77%) of white, plate-like crystals, m.p. 132 - 134°.

Found 67.8% C, 5.1% H, 4.0% N, $C_{20}H_{18}FNO_2S$ requires
67.6% C, 5.1% H, 3.9% N.

$\delta(CDCl_3)$ 7.15 (13H, broad m), 4.65 (2H,s), 2.30 (3H,s).

N-benzyl-N-tosyl-2-methylaniline as 12.0g (77%) of white crystals, m.p. 130 - 131°. [Lit. m.p. 132°] [22].

Found 71.7% C, 6.3% H, 4.0% N, $C_{21}H_{21}NO_2S$ requires 71.8% C, 6.0% H, 4.0% N.

$\delta(CDCl_3)$ 7.55 (2H,d,$J_{}$ = 8Hz), 7.15 (2H,d,$J_{}$ = 8Hz), 7.05 (5H,s), 6.90 (H, broad m), 4.95 (1H,d,$J_{}$ = 16Hz), 4.10 (1H,d,$J_{}$ = 16Hz), 2.45 (3H,s), 2.20 (3H,s).

N-benzyl-N-tosyl-2-methoxyaniline as 10.0g (75%) of white crystals, m.p. 104 - 105°.

Found 68.6% C, 6.0% H, 3.7% N, $C_{21}H_{21}NO_3S$ requires 68.8% C, 5.8% H, 3.8% N.

$\delta(CDCl_3)$ 7.15 (13H, broad m), 4.70 (2H,s), 3.25 (3H,s), 2.40 (3H,s).

N-benzyl-N-tosyl-2,4-dimethylaniline as 7.7g (57%) of white crystals, m.p. 98°.

Found 72.2% C, 6.3% H, 3.7% H, $C_{22}H_{23}NO_2S$ requires 72.3% C, 6.3% H, 3.8% H.

$\delta(CDCl_3)$ 7.55 (2H,d,$J_{}$ = 8Hz), 7.15 (2H,d,$J_{}$ = 8Hz), 7.10 (5H,s), 6.60 (3H, broad m), 4.95 (2H,d,$J_{}$ = 14Hz), 2.45 (3H,s), 2.20 (3H,s), 2.00 (3H,s).

N-benzyl-N-tosyl-4-methoxy-2-methylaniline as 12.75g (77%) of white crystals, m.p. 92°.

Found 69.3% C, 6.1% H, 3.6% N, $C_{22}H_{23}NO_3S$ requires 69.3% C, 6.1% H, 3.7% N.

$\delta(CDCl_3)$ 7.55 (2H,d,J_{ortho} = 10Hz), 7.15 (2H,d,J_{ortho} = 10Hz), 7.10 (5H,s), 6.95 (1H,s), 6.90 (2H,s), 4.95 (1H,d,J_{ortho} = 12Hz), 4.10 (1H,d,J_{ortho} = 12Hz), 3.55 (3H,s), 2.30 (3H,s), 2.00 (3H,s).

N-benzyl-N-tosyl-2-methyl-4-nitroaniline as 5.4g (64%) of beige crystals, m.p. 124 - 126°.

Found 63.3% C, 5.1% H, 6.9% H, $C_{21}H_{20}N_2O_4S$ requires 63.6% C, 5.1% H, 7.1% H.

$\delta(CDCl_3)$ 7.50 (7H, complex m), 7.10 (5H, s), 4.50 (2H, very broad d), 2.50 (3H,s), 2.10 (3H,s).

N-benzyl-N-tosyl-4-chloro-2-methylaniline as 1.5g (42%) of beige crystals, m.p. 120 - 122°.

Found 65.2% C, 5.2% H, 3.5% N, $C_{21}H_{20}ClNO_2S$ requires 65.4% C, 5.2% H, 3.6% N.

$\delta(CDCl_3)$ 7.55 (2H,d,J_{ortho} = 11Hz), 7.20 (2H,d,J_{ortho} = 11Hz), 7.10 (5H,s), 6.80 (3H,broad m), 4.95 (1H,d,J_{ortho} = 15Hz), 4.10 (1H,d,J_{ortho} = 15Hz), 2.45 (3H,s), 2.0 (3H, s).

Attempted tosylation of methyl anthranilate.

Methyl anthranilate (4.52g, 0.03M) and toluene-4-sulphonylchloride (5.8g, 0.033M) were dissolved in pyridine (50 ml). The mixture was refluxed for four hours then cooled and poured onto water (50 ml). A very sticky gum formed. The gum was extracted with ether and the ether extract washed with acid and water. The ethereal solution was then extracted with dilute aqueous sodium hydroxide. The sodium hydroxide extract was acidified with dilute hydrochloric acid but gave only the intractable gum still smelling strongly of pyridine.

The experiment was repeated, but excess pyridine was removed by distillation before the reaction mixture was poured onto water. The mixture was extracted with ether and the ethereal extract washed with dilute hydrochloric acid and water. Extraction with dilute aqueous sodium hydroxide and subsequent acidification with dilute hydrochloric acid gave a tacky oil which very slowly solidified. The white solid was recrystallised with difficulty from ethanol to give 8.0g (91%) of a white solid shown to be N-tosylanthranilic acid, m.p. 92 - 115°.

$\delta(CDCl_3)$ 10.60 (1H, broad s), 7.40 (9H, broad m), 2.25 (3H,s).

Preparation of N-benzyl-N-tosylanthranilic acid.

N-Tosylanthranilic acid (8.0g, 0.028M) was dissolved with difficulty in methanol (100 ml) and sodium metal (0.6g, 0.026M) dissolved in methanol (30 ml) was added.

The solution was evaporated to dryness at reduced pressure to give a dirty white solid. The crude sodium salt was dissolved in dimethylformamide (100 ml) and benzyl bromide (4.56g, 0.027M) was added. The mixture was stirred at room temperature overnight. The mixture was poured onto crushed ice when a dirty white precipitate formed. The precipitate was filtered off and washed with water then dried. The dirty white solid was recrystallised with difficulty from ethanol to give 6.5g (61%) of N-benzyl-N-tosylanthranilic acid, m.p. 121 - 122°.

$\delta(CDCl_3)$ 10.6 (1H, broad s), 7.30 (13H, broad m), 5.20 (2H,s), 2.25 (3H,s).

Attempted methylation of N-benzyl-N-tosyl anthranilic acid.

Method 1. With methanol and hydrogen chloride.

Dry hydrogen chloride was passed through dry methanol (50 ml) until the methanol was saturated with hydrogen chloride, (approximately 4 hours). N-Benzyl-N-tosyl-anthranilic acid (1.5g, 0.004M) was added and the mixture refluxed for 2 hours. The mixture was then cooled and poured into water (25 ml), when a white precipitate formed. The precipitate was filtered off, washed with water and dried but gave 1.1g of unchanged starting material. The aqueous filtrate was then extracted with ether and the ether extract washed with very dilute aqueous sodium hydroxide and water. The extract was dried over sodium sulphate then concentrated. A further 0.4g of N-benzyl-

N-tosylanthranilic acid was recovered unchanged, m.p. 121 - 122°.
$\delta(CDCl_3)$ 10.6 (1H, broad s), 7.30 (13H, broad m),
5.20 (2H,s), 2.25 (3H,s).

Method 2. With methanol and concentrated sulphuric acid.

N-Benzyl-N-tosylanthranilic acid (1.5g, 0.004M) was dissolved in dry methanol (50 ml). Concentrated sulphuric acid (0.5 ml) was added and the solution refluxed for 4 hours. The reaction was cooled and diluted with water when a white precipitate formed. The precipitate was filtered off, washed with water and dried. The white solid was recrystallised from ethanol and gave 1.4g of unchanged N-benzyl-N-tosylanthranilic acid, m.p. 121 - 122°.
$\delta(CDCl_3)$ 10.6 (1H, broad s), 7.30 (13H, broad m),
5.20 (2H,s), 2.25 (3H,s).

Method 3. With diazomethane.

N-Benzyl-N-tosylanthranilic acid (1.5g, 0.004M) was dissolved in ethanol (100 ml). The solution was cooled to 0° when some precipitation of the N-benzyl-N-tosylanthranilic acid occurred. An ethereal solution of diazomethane, (prepared from p-tolysulphonylnitrosamide by a standard method[11]), was added, with stirring, until the mixture remained a definite pale yellow, (approximately 20 ml). The reaction mixture was tested for excess diazomethane with glacial acetic acid. The reaction mixture was diluted with water when a white precipitate formed. The precipitate was filtered off, washed and dried. Recrystallisation from

ethanol gave 1.4g of unchanged N-benzyl-N-tosylanthranilic acid, m.p. 121 - 122°.

$\delta(CDCl_3)$ 10.6 (1H, broad s), 7.30 (13H, broad m), 5.20 (2H,s), 2.25 (3H,s).

The aqueous filtrate was extracted with ether.

The ether extract was washed with water and very dilute sodium hydroxide, then dried over sodium sulphate and concentrated to give a white solid. Recrystallisation from ethanol gave 200 mg. (13%) of methyl N-benzyl-N-tosylanthranilate, m.p. 72 - 73°.

Found 67.0% C, 5.4% H, 5.5% N, $C_{22}H_{21}NO_4S$ requires 66.8% C, 5.4% H, 5.5% N.

$\delta(CDCl_3)$ 7.25 (13H, broad m), 5.20 (2H,s), 3.10 (3H,s), 2.25 (3H,s).

Attempted tosylation of 4-amino-3-methylbenzoic acid.

4-Amino-3-methylbenzoic acid (3.8g, 0.025M) and toluene-4-sulphonyl chloride (4.9g, 0.028M) were dissolved in pyridine (50 ml) and the solution refluxed for 4 hours. The solution was then cooled and poured into water (50 ml). This gave 7.5g of a gum which proved intractable to crystallisation. The experiment was repeated but excess pyridine was removed by distillation before dilution of the reaction mixture. The product was another intractable gum. Therefore the 7.5g of crude gum was used in the next stage of the reaction without further purification.

Attempted preparation of 4-(N-benzyl-N-tosylamino)-3-methylbenzoic acid.

The crude gum (7.5g) was dissolved, with difficulty, in methanol (500 ml), and sodium (0.58g, 0.025M) dissolved in methanol (25 ml) was added. A white precipitate formed immediately. The mixture was evaporated to dryness and the resulting white solid dissolved in dimethylformamide, (100 ml). Benzyl bromide, (4.28g, 0.025M) was added and the mixture stirred at room temperature overnight. The mixture was then poured onto ice and water when a sticky gum formed. An attempt was made to extract with ether but the gum was only slightly soluble. The ethereal extract was washed with water then dried over sodium sulphate and concentrated to give a yellow oil. The oil proved intractable to all attempts at recrystallisation.

The experiment was repeated, but excess dimethylformamide was distilled off before dilution with water. A sticky gum formed. The aqueous phase was removed by decantation and recrystallisation from ethanol was attempted. This gave 5g of a yellowish orange oil. The oil was allowed to stand at room temperature for three weeks. Some white solid gradually crystallised from around the edge of the oil, m.p. 79-113°. Recrystallisation of the white solid from ethanol was attempted but gave only a yellow oil. An n.m.r. spectrum indicated the presence of impure 4-(N-benzyl-N-tosylamino)-3-methylbenzoic acid.

$\delta(CDCl_3)$ 7.25 (12 H, broad m), 5.25 (2H,s), 2.45 (3H,s), 2.05 (3H,s).

Reduction of N-benzyl-N-tosyl-2-methyl-4-nitroaniline.

N-Benzyl-N-tosyl-2-methyl-4-nitroaniline (1.0g, 0.0026M), was dissolved in ethanol (10 ml) and hydrazine hydrate (1 ml, 99%) was added. Raney-Nickel (500 mg) was added to the pale yellow solution when effervescence was seen. The mixture was refluxed for 1 hour. The resulting colourless solution was filtered while hot to remove the catalyst. The filtrate was then cooled and poured into water (10 ml). A white precipitate formed which was filtered off, washed with water and dried. Recrystallisation from ethanol gave 0.7g (76%) of N-benzyl-N-tosyl-4-amino-2-methylaniline, m.p. 140 - 142°.

Found 69.2% C, 6.1% H, 7.5% N, $C_{21}H_{22}N_2O_2S$ requires 68.8% C, 6.1% H, 7.6% N.

$\delta(CDCl_3)$ 7.60 (2H,d,J_{γ} = 8Hz), 7.20 (2H,d,J_{γ} = 8Hz), 7.15 (5H,s), 6.25 (3H,s), 4.95 (1H,d,J_{γ} = 14Hz), 4.10 (1H,d,J_{γ} = 14Hz), 3.50 (2H,s), 2.45 (3H,s), 1.90 (3H,s).

4.3 Quinone-anils.

Attempted preparation of 2,6-di-t-butyl-1,4-benzoquinone.

Method 1. With peracetic acid[83].

2,6-Di-t-butylphenol (15.0g, 0.073M) was dissolved in glacial acetic acid (100 ml) and concentrated sulphuric acid (1 ml) was added. Hydrogen peroxide, (12 ml, 100%), was added over 10 minutes with stirring. Stirring was continued at room temperature for a further 15 minutes and

then the temperature was increased to 60° and maintained for 1 hour. The reaction mixture was cooled and poured onto ice and water. A deep orange precipitate formed. The precipitate was filtered off, washed with water until neutral and then dried over anhydrous sodium hydroxide. The orange solid was recrystallised from ethanol and water to give 8.8g of an orange crystalline solid. The solid was chromatographed on a silica column with a 2:1 mixture of 60/80 petrol ether and benzene. Starting product (8.0g) was recovered unchanged, m.p. 36°. [Lit. m.p. 37 - 38°] [84].

Method 2. With chromyl chloride[85].

Chromyl chloride (3.1g, 0.02M) was dissolved in dry carbon tetrachloride (100 ml), and 2,6-di-t-butylphenol (1.78g, 0.01M) in dry carbon tetrachloride (100 ml) was added, with stirring, over 1 hour. The mixture was stirred at room temperature for a further hour. The mixture was filtered and the thick brown oily precipitate was washed with dry carbon tetrachloride. The precipitate was then added to ice and water and stirred vigorously until all the brown precipitate had changed to a curdy greenish yellow precipitate. The mixture was extracted with ether and the ether extract washed with water, then dried over sodium sulphate. Concentration of the ether extract gave a reddish orange oil which slowly crystallised. The solid was recrystallised from ethanol and water to

give 0.5g (11%) of 2,6-di-t-butyl-1,4-benzoquinone, m.p. 64 - 65°. [Lit. m.p. 65°] [85].
$\delta(CDCl_3)$ 6.5 (2H,s), 1.40 (18H,s).

Method 3. With sodium nitrite and cuprous oxide[86].

2,6-Di-t-butylphenol (18.0g, 0.087M) was dissolved in ethanol (150 ml) and concentrated hydrochloric acid (12 ml) was added. The solution was cooled to -5° and sodium nitrite (6.6g, 0.078M) dissolved in water (30 ml) was added dropwise over 15 minutes. The mixture was stirred vigorously and the temperature maintained between 0 and -5° throughout the addition. A yellow precipitate formed. The mixture was stirred for a further 30 minutes and then poured onto ice and water. A yellow precipitate of 2,6-di-t-butyl-1,4-benzoquinone oxime (20.25g) was filtered off and dried and used, without further purification, in the next stage of the reaction.

2,6-Di-t-butyl-1,4-benzoquinone oxime (20.25g, 0.086M) was dissolved in 2-methoxyethanol (450 ml), acetone (45 ml) and hydrochloric acid (292.5 ml, 34%). Cuprous oxide (45.0g, 0.3M) was added and the mixture refluxed for 1 hour. The solution was cooled and then steam distilled. The distillate was extracted with ether. The ether extract was dried over sodium sulphate and concentrated to give an orange solid. The solid was recrystallised from ethanol and water to give 1.33g (7%) of 2,6-di-t-butyl-1,4-benzoquinone, m.p. 62°. [Lit. m.p. 65°] [85].
$\delta(CDCl_3)$ 6.5 (2H,s), 1.40 (18H,s).

Preparation of 2-benzoyl-4-methylaniline[87].

Benzoylchloride (19.68g, 0.14M) and anhydrous zinc chloride (9.2g, 0.068M) were heated to 120° with stirring and 4-methylaniline (5.99g, 0.056M) was added portionwise over 15 minutes. The mixture was heated to 220° and the temperature maintained until evolution of hydrogen chloride ceased, (1 - 2 hours). The mixture was cooled and extracted with hot water (200 ml) to remove benzoic acid. The mixture was then dissolved in glacial acetic acid (20 ml), concentrated sulphuric acid (26 ml) and water (14 ml) and refluxed overnight. The mixture was cooled and poured onto ice and water, then extracted with ether. The ether extract was washed with dilute aqueous sodium hydroxide and water, then dried over sodium sulphate. The ether extract was concentrated to give a yellow solid which was chromatographed on a silica column with chloroform. This gave 2.7g (23%) of 2-benzoyl-4-methylaniline, m.p. 65°. [Lit. m.p. 66°] [87].

$\delta(CDCl_3)$ 7.10 (8H, complex m), 5.90 (2H, broad s), 2.20 (3H,s).

Reduction of 2-benzoyl-4-methylaniline[66].

2-Benzoyl-4-methylaniline (1.5g, 0.007M) was dissolved in ethanol (10 ml) and the hot solution was added to small pieces of sodium (1.5g, 0.065M). When the reaction had moderated hot ethanol (12 ml) was added and the last sodium dissolved by heating and shaking. The reaction mixture was diluted with water (25 ml). The mixture was steam distilled

and the distillate extracted with ether. The ether extract was dried over sodium sulphate and concentrated to give a yellowish oil. The oil was vacuum distilled and gave 0.7g (51%) of 2-benzyl-4-methylaniline, b.p. 130° at 0.8 mm Hg.

$\delta(CDCl_3)$ 7.10 (5H,s), 6.65 (3H,m), 3.85 (2H,s), 3.20 (2H, broad s), 2.20 (3H;s).

A small sample of N-acetyl-2-benzyl-4-methylaniline, m.p. 166 - 168°, was prepared by a standard method.

Found 80.2% C, 7.3% H, 5.6% N, $C_{16}H_{17}NO$ requires 80.3% C, 7.2% H, 5.9% N.

Reduction of 2-aminobenzophenone[66].

2-Aminobenzophenone (5.0g, 0.025M) was reduced with sodium (5.0g, 0.22M) and hot ethanol as recorded previously. This gave 2.33g (51%) of 2-benzylaniline, b.p. 124° at 1.0 mm Hg. [Lit. m.p. 52°] [66].

$\delta(CCl_4)$ 7.10 (5H,s), 6.60 (4H, broad m), 3.85 (2H,s), 3.25 (2H, broad s).

A small sample of N-acetyl-2-benzylaniline, m.p. 124 - 126°, was prepared by a standard method.

Found 79.5% C, 6.4% H, 6.4% N, $C_{15}H_{15}NO$ requires 80.0% C, 6.7% H, 6.2% N.

Attempted reduction of 2-amino-5-chlorobenzophenone.

2-Amino-5-chlorobenzophenone (5.0g, 0.022M) was reduced with sodium (5.0g, 0.22M) and hot ethanol as recorded

previously. This gave 2.0g (42%) of 2-benzyl-4-chloroaniline, b.p. 140° at 2.0 mm Hg.

$\delta(CDCl_3)$ 7.20 (5H,s), 6.95 (3H,m), 3.90 (2H,s), 3.50 (2H, broad s).

A small sample of N-acetyl-2-benzyl-4-chloroaniline, m.p. 126 - 127°, was prepared by a standard method. Found 79.6% C, 6.6% H, 6.2% N, $C_{15}H_{14}ClNO$ requires 69.4% C, 5.4% H, 5.4% N.

Attempted preparation of 2-amino-5-nitrobenzophenone.

4-Nitroaniline (3.8g, 0.028M) was treated with benzoyl chloride (9.8g, 0.07M) and anhydrous zinc chloride (4.6g, 0.034M) as recorded previously. Concentration of the ether extract gave a black oil. The oil was chromatographed on silica with toluene and gave a fraction containing 2.7g of unchanged starting material. A second fraction was eluted with chloroform and gave 0.75g of an intractable reddish black tar.

Preparation of benzylphenyl-(4-nitrophenyl)hydrazone[67].

4-Nitrophenylhydrazine (5.0g, 0.33M) and benzylphenyl-ketone (7.0g, 0.036M) were heated together at 140° for 1 hour. The product solidified on cooling and was recrystallised from ethanol. Benzylphenyl-(4-nitrophenol) hydrazone was collected as 8.62g (80%) of an orangish red crystalline solid, m.p. 152 - 154°. [Lit. m.p. 158 - 160°] [67].

Preparation of 2,3-diphenyl-5-nitroindole[67].

Benzylphenyl-(4-nitrophenyl)hydrazone (8.0g, 0.024M) was dissolved in glacial acetic acid (200 ml) and concentrated hydrochloric acid (120 ml) then refluxed for 8 hours. The mixture was then cooled, diluted with water (200 ml) and extracted with ether. The ether extract was washed with aqueous sodium carbonate then dried over sodium sulphate and concentrated to give a crude brown solid (6.7g). The solid was recrystallised from ethanol and water to give 6.0g (80%) of pale yellow 2,3-diphenyl-5-nitroindole, m.p. 198 - 200°. [Lit. m.p. 211° previous sintering] [67].

Oxidation of 2,3-diphenyl-5-nitroindole[66].

2,3-Diphenyl-5-nitroindole (1.0g, 0.003M) was dissolved in glacial acetic acid (40 ml). The solution was treated dropwise with chromic oxide (0.6g, 0.006M) dissolved in water (1 ml), while stirring. A white precipitate formed which did not redissolve. The mixture was allowed to stand for 12 hours at room temperature, then diluted with an equal volume of water. A very pale yellow precipitate formed which was filtered off and dried. The solid was recrystallised from ethanol to give 0.93g (90%) of 2-benzamido-5-nitrobenzophenone as nearly white crystals, m.p. 197°. [Lit. m.p. 197 - 198°] [68].

Hydrolysis of 2-benzamido-5-nitrobenzophenone[68].

2-Benzamido-5-nitrobenzophenone (1.83g, 0.005M) was dissolved in glacial acetic acid (88 ml) and concentrated hydrochloric acid (88 ml). The solution was refluxed for 4 hours when it formed a clear orange solution. The solution was cooled and basified with concentrated aqueous ammonia. A yellow precipitate formed which was filtered off, washed with water and dried. The solid was recrystallised from ethanol and water to give 0.96g (80%) of ochre 2-amino-5-nitrobenzophenone, m.p. 159 - 161°. [Lit. m.p. 160 - 161°] [68].

Attempted reduction of 2-amino-5-nitrobenzophenone[66].

2-Amino-5-nitrobenzophenone (0.96g, 0.004M) was reacted with sodium (1.0g, 0.04M) in hot ethanol as recorded previously. Steam distillation of the final reaction mixture gave no product and so the reaction mixture was extracted with ether. The ether extract gave only an intractable brown tar.

Reduction of 2-amino-5-nitrobenzophenone[69].

2-Amino-5-nitrobenzophenone (0.6g, 0.003M) and hydrazine hydrate (0.6g, 98%) in diethyleneglycol (1.8 ml) were heated together to 100°. The solution was then allowed to cool while potassium hydroxide (0.6g, 0.01M) dissolved in diethyleneglycol (1 ml) was added. The mixture was heated cautiously initially then finally brought

to reflux at 200° and maintained at reflux for 3 hours. The reaction mixture was cooled and diluted with an equal volume of water. The mixture was extracted with ether and the ether extract was washed with water then dried over sodium sulphate and concentrated. The resulting yellow solid was recrystallised from ethanol to give 40 mg (6%) of bright yellow crystalline 2-benzyl-4-nitroaniline, m.p. 135 - 137°.

Found 68.3% C, 5.2% H, 12.3% N, $C_{13}H_{12}N_2O_2$ requires 68.4% C, 5.3% H, 12.3% N.

$\delta(CDCl_3)$ 8.05 (2H,m), 7.25 (5H,s), 6.60 (1H,s), 4.20 (2H, broad s), 3.95 (2H,s).

Attempted repeat preparation of benzylphenyl-(4-nitrophenyl) hydrazone.

4-Nitrophenylhydrazine (10.0g, 0.066M) and benzyl-phenylketone (14.0g, 0.072M) were heated together to 90° when a violent exothermic reaction took place. Subsequent work up of the reaction gave only an intractable brown tar.

Preparation of benzylmethyl-(4-nitrophenyl)hydrazone[70].

4-Nitrophenylhydrazine (6.12g, 0.04M) was dissolved in ethanol (200 ml), and benzylmethylketone (6.3g, 0.044M) was added. The solution was refluxed for 1 hour then cooled, when a yellow precipitate formed. The mixture was concentrated to give a yellow solid which was recrystallised from ethanol. Benzylmethyl-(4-nitrophenyl)hydrazone was

collected as 9.6g (89%) of yellow crystals, m.p. 172 - 173°.

$\delta(CDCl_3)$ 8.05 (2H,d,$J_{2,3}$ = 8Hz), 7.65 (1H, broad s), 7.20 (5H,s), 7.10 (2H,m), 3.60 (2H,s), 1.90 (3H,s).

Preparation of 2-methyl-5-nitro-3 phenylindole.

Benzylmethyl-(4-nitrophenyl)hydrazone (2.77g, 0.01M) was dissolved in glacial acetic acid (75ml) and concentrated hydrochloric acid (45 ml). The mixture was refluxed for 8 hours and then worked up as recorded previously. Concentration of the ethereal extract gave a dark brown solid which was recrystallised from glacial acetic acid. 2-Methyl-5-nitro-3phenylindole was collected as 2.35g (93%) of a yellowish brown solid, m.p. 196 - 197°. [Lit. m.p. 197 - 198°] [70].

$\delta((CD_3)_2CO)$ 10.40 (1H, broad s), 8.50 (1H,d,$J_{2,3}$ = 2Hz), 8.0 (1H,dd,$J_{2,3}$ = 8Hz and 2Hz), 7.50 (1H,d,$J_{2,3}$ = 8Hz), 7.45 (5H,s), 2.55 (3H,s).

Attempted oxidations of 2-methyl-5-nitro-3phenylindole.

Method 1. With periodic acid and sodium hydroxide[71].

2-Methyl-5-nitro-3phenylindole (1.26g, 0.005M) was dissolved in methanol (50 ml). To this was added a solution of periodic acid (2.735g, 0.12M) and sodium hydroxide (0.48g, 0.12M) in water (25 ml). A yellowish brown precipitate formed which did not redissolve. The mixture was stirred at room temperature for 8 hours and was then extracted with ether. The ether extract was washed with

water then dried over sodium sulphate and concentrated to a yellowish brown solid. The solid was recrystallised from ethanol to give 1.2g of unchanged starting material, m.p. 196 - 197°.

Method 2. With sodium metaperiodate[71].

2-Methyl-5-nitro-3-phenylindole (1.0g, 0.004M) was dissolved in methanol (50 ml), and sodium metaperiodate (1.92g, 0.009M) in water (25 ml) was added with stirring. A yellowish brown precipitate formed which did not redissolve. The mixture was stirred at room temperature for 8 hours and then extracted with methylene chloride. The methylene chloride extract was washed with water, then dried over sodium sulphate and concentrated to give a yellowish brown solid. The solid was recrystallised from ethanol to give 0.95g of unchanged starting material, m.p. 196 - 197°.

Method 3. With potassium periodate and 18 crown 6 ether.

2-Methyl-5-nitro-3-phenylindole (1.0g, 0.004M) was dissolved in benzene (75 ml), and potassium periodate (2.02g, 0.009M) was added. Two drops of 18 crown 6 ether were added and the mixture stirred at room temperature for 8 hours. The mixture was worked up as recorded previously and gave 0.9g of unchanged starting material, m.p. 196 - 197°.

Method 4. With chromic oxide[68].

2-Methyl-5-nitro-3-phenylindole (0.5g, 0.002M) was treated with chromic oxide (0.4g, 0.004M) as recorded previously. Concentration of the ether extract gave an intractable brown tar.

Oxidation of 2-methyl-5-nitro-3-phenylindole with peracetic acid.

2-Methyl-5-nitro-3-phenylindole (1.0g, 0.004M) was dissolved in glacial acetic acid (25 ml) and hydrogen peroxide (25 ml, 100%), was added. A reddish brown precipitate formed. Two drops of concentrated sulphuric acid were added and the reaction stirred at room temperature overnight. A yellow precipitate formed. The mixture was diluted with water (50 ml) and extracted with ether. The ether extract was washed with aqueous sodium bicarbonate then dried over sodium sulphate and concentrated to give a yellowish brown solid. The solid was recrystallised from ethanol to give 600 mg (53%) of 2-acetamido-5-nitrobenzophenone, m.p. 140 - 141°.

$\delta(CDCl_3)$ 11.10 (1H, broad s), 8.95 (1H,d,$J_{3'}$ = 9Hz), 8.30 (2H,d,J_{3}= 9Hz), 7.75 (5H,s), 2.25 (3H,s).

Hydrolysis of 2-acetamido-5-nitrobenzophenone[68].

2-Acetamido-5-nitrobenzophenone (500 mg, 0.0018M) was hydrolysed with glacial acetic acid (25 ml) and concentrated hydrochloric acid (25 ml) as recorded previously. The resulting brownish yellow solid was recrystallised from ethanol to give 350 mg (80%) of 2-amino-5-nitrobenzophenone, m.p. 162 - 163°. [Lit. m.p. 160 - 161°] [68].

$\delta((CD_3)_2CO)$ 8.45 (1H,d,$J_{3'}$ = 2Hz), 8.10 (2H,dd,$J_{3'}$ = 9Hz and 2Hz), 7.60 (2H, broad s), 7.55 (5H,s).

Attempted reduction of 2-amino-5-nitrobenzophenone.

2-Amino-5-nitrobenzophenone (3.83g, 0.0144M) and hydrazine hydrate (2.88g, 98%) were dissolved in diethylene glycol (30 ml) and heated to 40°. Potassium hydroxide (3.12g, 0.057M) in diethylene glycol (10 ml) was added. The mixture was gradually brought to reflux and continued refluxing at 140° for 1 hour. Water and hydrazine were then distilled off until the temperature reached 200°. The mixture was refluxed for a further 3 hours. The mixture was cooled, combined with the water and hydrazine distillate, then diluted with water (50 ml) when a blackish brown emulsion formed. Successive extractions of the emulsion were attempted with ether, chloroform and benzene. Work up of all extracts gave a blackish brown tarry oil. Thin layer chromatography on a silica plate eluted with a 1:1 mixture of benzene and 60:80 petrol ether showed a number of products but these proved inseparable by column chromatography. The experiment was repeated but gave only tarry oils.

Attempted condensation of 2,6-di-t-butyl-1,4-benzoquinone and 2-benzylaniline.

Method 1. In glacial acetic acid[30].

2-Benzylaniline (1.0g, 0.0055M) and 2,6-di-t-butyl-1,4-benzoquinone (1.2g, 0.0055M) were mixed with 3-4 drops of glacial acetic acid. The mixture was heated to 100° for 4 hours. The reaction product was diluted with water (10 ml) then extracted with ether. The ether extract was washed with

water then dried over sodium sulphate and concentrated to give a dark red oil. Thin layer chromatography on a silica plate with benzene showed only unchanged starting materials.

Method 2. Refluxing in dry benzene.

The red oil from the previous reaction was dissolved in dry benzene (10 ml), and toluene-4-sulphonic acid (150 mg) was added. The solution was refluxed for 6 hours when a small sample was tested by thin layer chromatography which indicated unchanged starting materials. Refluxing was continued overnight and the reaction then worked up as recorded previously. Thin layer chromatography indicated unchanged starting materials.

Condensation of 2,6-di-t-butyl-1,4-benzoquinone and 2-benzylaniline.

2,6-Di-t-butyl-1,4-benzoquinone (1.5g, 0.0068M) and 2-benzylaniline (1.25g, 0.0068M) were dissolved in dry xylene (25 ml), and toluene-4-sulphonic acid (50 mg) was added. The solution was refluxed overnight, then cooled and concentrated to give a dark red oil. The oil was dissolved in ether and washed with water, then dried over sodium sulphate and concentrated. Thin layer chromatography showed some starting materials present but also one spot which did not correspond to either starting material. The oil was chromatographed on a silica column with a 2:1 mixture of benzene and 60:80 petrol ether. The first fraction gave a red oil which crystallised on standing. The

solid was recrystallised from methanol to give 400 mg (15%) of a bright orange solid, m.p. 152 - 156°.

Found 84.1% C, 8.1% H, 3.6% N, $C_{27}H_{31}NO$ requires 84.3% C, 8.1% H, 3.3% N.

m/e MI. 385.

ν_{max}(nujol mull) 3350 cm^{-1} (N-H), 1660 cm^{-1} (C = O).

$\delta(CDCl_3)$ 7.05 (10H, broad m), 6.15 (1H,d,J_{ν} = 3Hz), 4.55 (1H,s), 3.95 (1H,s), 1.20 (9H,s), 0.90 (9H,s).

Condensation of 2,6-di-t-butyl-1,4-benzoquinone and 2-benzyl-4-methylaniline.

2-Benzyl-4-methylaniline (0.5g, 0.0021M) and 2,6-di-t-butyl-1,4-benzoquinone (0.46g, 0.0021M) were dissolved in dry xylene (10 ml) with toluene-4-sulphonic acid (25 mg). The mixture was refluxed overnight then worked up as recorded previously. The product was recrystallised from methanol to give 150 mg (20%) of an orange solid, m.p. 186°.

Found 83.5% C, 8.5% H, 3.2% N, $C_{28}H_{33}NO$ requires 84.2% C, 8.3% H, 3.5% N.

m/e MI. 399.

ν_{max}(nujol mull) 3340 cm^{-1} (N-H), 1660 cm^{-1} (C = O).

$\delta(CDCl_3)$ 7.00 (9H, broad m), 6.20 (1H,d,J_{ν} = 3Hz), 4.55 (1H,s), 3.90 (1H,s), 2.20 (3H,s), 1.25 (9H,s), 0.90 (9H,s).

Condensation of 2,6-di-t-butyl-1,4-benzoquinone and 2-benzyl-4-chloroaniline.

2-Benzyl-4-chloroaniline (0.5g, 0.0023M) and 2,6-di-t-butyl-1,4-benzoquinone (0.51g, 0.0023M) were dissolved in dry xylene (10 ml) with toluene-4-sulphonic acid (25 mg). The mixture was refluxed overnight then worked up as recorded previously. The product was recrystallised from methanol to give 100 mg (10%) of a reddish orange solid, m.p. 152°.

Found 82.7% C, 8.1% H, 3.3% N, $C_{27}H_{30}ClNO$ requires 77.3% C, 7.2% H, 3.3% N.

m/e M1.421, 419.

ν_{max}(nujol mull) 3330 cm^{-1} (N-H), 1655 (C = O).

$\delta(CDCl_3)$ 7.00 (9H, broad m), 6.20 (1H,d,J_{ν} = 3Hz), 4.55 (1H,s), 4.00 (1H,s), 1.20 (9H,s), 0.90 (9H,s).

Subsequent work indicated that the preceding compound was not a single product. (As explained in the previous section).

The condensation of 2,6-di-t-butyl-1,4-benzoquinone and 2-benzyl-4-chloroaniline was repeated and a red oil was obtained. Thin layer chromatography of the oil on a silica plate eluted with a 1:1 mixture of 60:80 petrol ether and benzene showed three spots. Two spots corresponded to starting materials. The oil was chromatographed on a silica column.

Ninety fractions, each of approximately 25 ml, were

collected. Fractions one to six were eluted with 40:60 petrol ether. Fractions seven to nineteen were eluted with a 1:3 mixture of 40:60 petrol ether and benzene. Fractions twenty to twenty-six were eluted with a 1:1 mixture of 40:60 petrol ether and benzene. Fractions twenty-seven to ninety were eluted with a 1:2 mixture of 40:60 petrol ether and benzene. Each fraction was chromatographed on a silica TLC plate with a 1:1 mixture of 60:80 petrol ether and benzene. This resulted in the combination of fractions two to six, (designated fraction A), ten to twenty-two, (designated fraction B), and fractions sixty-two to ninety-one, (designated fraction C).

The 60 MHz n.m.r. spectrum of fraction B showed that fraction B was still a mixture. Therefore a fractional crystallisation was carried out. The solid was recrystallised from ethanol to give orangish yellow crystals, m.p. 171-191°. The 60 MHz n.m.r. spectrum of this product showed it to be the spiro compound, [δ ($CDCl_3$) 4.55 (1H,s) 4.00 (1H,s)]. The mother liquor was allowed to evaporate and the residue, (a dark red oil), was recrystallised from 60:80 petrol ether to give a yellow solid, m.p. 162-171°. The 60 MHz n.m.r. spectrum of this product showed that it was still a mixture but with a predominance of the quinone-anil.

The second motherliquor was allowed to evaporate and the residue, (a dark red oil), was recrystallised from

60:80 petrol ether to give a dark red solid, m.p. 81-88°. The 60 MHz n.m.r. spectrum showed this was still a mixture. Finally, the residue of the previous recrystallisation was recrystallised from methanol to give a red solid, m.p. 92-93°. The 60 MHz n.m.r. spectrum showed that this product was nearly pure quinone-anil, [δ ($CDCl_3$) 3.90 (2H,s)] .

The products of the recrystallisations of fraction B still appeared to be mixtures. Therefore analysis of each product was carried out using h.p.l.c. and compared with similar analyses of fractions A and C. The analysis was carried out using a reverse phase column, the eluent a 60:40 mixture of acetonitrileand water with a flow rate of 2 ml per minute and the U.V. detector at 254 nm.

APPENDIX

Materials and Apparatus.

Infrared spectra were recorded using a Perkin Elmer 257 Grating spectrometer. Solids were recorded as nujol mulls and oils as liquid films. Ultra-violet spectra were recorded using a Pye Unicam SP800 spectrometer with cells of one cm. path length. Mass spectra were recorded using an AEI MS-902 spectrometer operating at 70 eV with a source temperature of 200°. Samples were introduced by means of a direct insertion probe.

Proton n.m.r. spectra were recorded at 60MHz on a Varian EM360 spectrometer and at 100MHz on a Varian HA100 spectrometer. The samples were run as 10% (w/v) solutions with tetramethylsilane as the internal reference except for high temperature spectra when hexamethyldisiloxane was used. When coupling constants were measured the sweep width of the spectrum was 100Hz. Carbon-13 n.m.r. spectra were recorded using a Varian CFT20 spectrometer.

Melting points were determined in open capillaries and are uncorrected.

Column chromatography was carried out on either activated alumina type H100/200 mesh or silica gel grade M60. Thin layer chromatography was done on silica (MN Kieselgel G) the layer of adsorbant being 0.25 mm. H.p.l.c. was carried out on a Pye Unicam LC3 system using an ultra-violet spectrophotometric detector and a chart recorder.

Concentrated nitric acid had a density of 1.42, concentrated hydrochloric acid 1.18 and concentrated aqueous ammonia 0.88.

Abbreviations.

n.m.r.	-	nuclear magnetic resonance.
I.R.	-	infra-red.
U.V.	-	ultra-violet.
h.p.l.c.	-	high pressure liquid chromatography.
t.l.c.	-	thin layer chromatography.
d_6-DMSO	-	deuterodimethylsulphoxide.
DMF	-	dimethylformamide.
TsCl	-	toluene-4-sulphonyl chloride (tosyl chloride).
s	-	singlet.
d	-	doublet.
dd	-	double doublet.
t	-	triplet.
q	-	quartet.
m	-	multiplet.

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