A thesis entitled

HETEROCYCLIC SYNTHESSES

FROM SOME GLUTARONITRILES

submitted by

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in part fulfilment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in the

UNIVERSITY OF SURREY

September 1973
ACKNOWLEDGEMENTS

This work was carried out under the supervision of Professor J.A. Elvidge, to whom I would like to express my gratitude for his constant advice and encouragement.

I would also like to thank the technical staff of the University of Surrey for their assistance, in particular Mr. J. Bloxidge and Mr. J. Delderfield for recording the p.m.r. and mass spectra respectively.
ABSTRACT

The dehydrogenation of 3-phenyl-2,6-diphenyliminopiperidine has been studied under a variety of conditions, leading to a new synthesis of 2,3'-bipyridyls and to a new synthetic route to 2,6-diaminopyridines from readily available glutaronitriles. A novel 3-aryloxypiperidine intermediate has been isolated from the dehydrogenation of 3-phenyl-2,6-diphenyliminopiperidine with 3,3',5,5'-tetrachloro-4,4'-diphenoquinone. Methyl homologues of 3-phenyl-2,6-diphenyliminopiperidine have been prepared and their reactions under dehydrogenating conditions studied, to help confirm the structure of the 2,3'-bipyridyl. A high yield synthesis of 2,6-di-imino-3-phenylpiperidine has been found but its dehydrogenation proved unsuccessful.

Investigation of α-alkylideneglutaronitriles and their condensations with amines has opened up a further route to the preparation of 2,6-di-aminopyridines.

The reactions of 3-phenyl-2,6-diphenyliminopiperidine under dehydrogenating conditions, together with spectra of fixed-bond analogues have helped to further elucidate its fine structure.

Glutaronitriles have been condensed with diamines to produce three-unit materials but none of these afforded macrocyclic or polymeric materials when further condensations were attempted. Ethylene-diamine afforded an imidazoline on condensation
with glutaronitriles in addition to the expected three-unit product, while o-phenylenediamine underwent an analogous reaction in which the sole product was a benzimidazole. No reaction could be achieved between glutaronitrile and 1,3-di-iminoisoindoline, the only products of the reaction being a mono amide of tricyanophenine and phthalocyanine.

Condensations between glutaronitriles and active methylene compounds have been carried out and extended to the formation of methine-linked macrocyclic products, but attempts to dehydrogenate the two- and three-unit products have been unsuccessful.

The mass-spectra of the glutaronitriles, di-iminopiperidines, and diaminopyridines prepared in this thesis are discussed in detail.

Nucleophilic additions to nitriles and the cyclization of dinitriles, particularly with amines and active methylene compounds, have been reviewed up to the completion of this work in 1969.
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CHAPTER 1

HISTORICAL INTRODUCTION
The ability of nitriles to form addition compounds with nucleophilic reagents derives from the reduced electron density at the carbon atom of the cyano group (1).

\[ \text{S}^+ \text{S}^- \rightarrow \text{C} \equiv \text{N} \]  

Thus many nitriles will add hydroxylamine\(^1\) to form amidoximes, and will add thiols\(^2\) to form thioamides. In such uncatalyzed reactions, attack is by a lone pair of the heteroatom, followed by proton transfer and, in some cases, double bond migration, e.g. (2).

\[ R-\text{C} \equiv \text{N} \xrightarrow{\text{HO-N-H}} \left\{ \begin{array}{c} R-\text{C} = \text{N}^\ominus \\ \text{HO-N-H} \end{array} \right\} \]

\[ R-\text{C} \equiv \text{N} \xrightarrow{\text{HO-N-H}} \left\{ \begin{array}{c} R-\text{C} = \text{N} \\ \text{HO-N-H} \end{array} \right\} \]

Amines in general will add to nitriles when the reactivity of the latter is increased by the presence of strongly acidic or basic compounds, the action of which is either to
increase the polarization in the nitrile group\(^3\),

\[
R'-\text{C} = \text{N}^\Theta + \text{R'} \quad \xrightarrow{\text{NH}_2-R'} \quad R'-\text{C} = \text{NH}^\Theta + \text{NH-R'}
\] (3)

or to convert the attacking reagent into a more powerful nucleophile\(^3\)(4).

\[
R' - \text{NH}_2 + :B \quad \xleftrightarrow{B} \quad R'-\text{NH}^\Theta + B^\oplus \\
R'-\text{C} = \text{N}^\Theta + B^\oplus \quad \xrightarrow{B} \quad R'-\text{C} = \text{NH}^\Theta + :B
\] (4)

Addition and Condensation Reactions of Nitriles with Bases

Nitriles are susceptible to attack by bases or nucleophiles in two ways. Firstly, there may be attack at the nitrile carbon (as above), resulting in addition (5);

\[
\begin{array}{c}
\text{C} \quad \text{C} = N \\
\text{H} \quad \text{H} \\
\end{array} \quad :B \quad \xrightarrow{B} \quad \begin{array}{c}
\text{C} \quad \text{C} = N^\Theta \\
\text{H} \quad \text{H} \quad \text{B}
\end{array}
\] (5)

or such as shown\(^2\)(6) where the product depends on the work-up.
where $M^+$ is a metal ion, $X$ is usually an electron withdrawing group, e.g. $NO_2$, $CN$; where $M^+$ is $Li^+$, in the case of lithium alkyls, $X$ may be $H$, electron withdrawing substituents, however, accelerate the reaction.

Secondly, there may be attack at an $\alpha$-hydrogen, resulting in proton removal and formation of a carbanion (7),

\[
\begin{align*}
  \begin{array}{c}
    \text{-C-C=\text{N}} \\
    \text{H}
  \end{array} & \xrightarrow{\text{B}} \begin{array}{c}
    \text{\Theta-C=\text{N}} \\
    \text{+BH}
  \end{array}
\end{align*}
\]  

(7)

which can then add to another molecule of nitrile as in (8).
In the latter case, it is immediately obvious that a variety of products may be expected. Thus the dimer product from (8) may add to a further molecule of nitrile, subsequently yielding a pyrimidine.\textsuperscript{5a,6a,7} Similarly, phenylacetonitrile dimer, 2,4-diphenyl-3-iminobutyronitrile (9), affords 4-amino-2,6-dibenzyl-5-phenylpyrimidine\textsuperscript{5a,6a,4,7,8} (10).
Alternatively if the α-methylene group of the nitrile is sufficiently highly activated, as in malononitrile, \( \text{N} = \text{C} - \text{CH}_2 - \text{C} \equiv \text{N} \), this may condense with the imino group of the dimer previously formed. Thus, malononitrile dimer, 2-cyano-3-iminoglutaronitrile (11) affords 2,4-dicyano-3-(cyanomethyl)glutacononitrile (12).

\[
\begin{align*}
\text{HC} & + \text{CN} \quad \xrightarrow{\text{BH}} \quad \text{HC} - \text{C} = \text{NH} \\
\text{CN} & \quad \text{CH}_2 & \quad \text{CN} \\
\text{CN} & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \text{CN}
\end{align*}
\]

(11)

\[
\begin{align*}
\text{HC} - \text{C} = \text{C} - \text{CN} & + \text{NH}_3 \\
\text{CN} & \quad \text{CH}_2 & \quad \text{CN} \\
\text{CN} & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \text{CN}
\end{align*}
\]

(12)

Such condensation reactions would appear to make the addition of a base to certain nitriles an extremely ambiguous proposition.

**Addition Reactions of Nitriles Involving Hydrogen Halides**

Hydrogen halides are particularly important as acid catalysts for reactions of the cyano group, and in many cases, especially with hydrogen chloride, they are specific catalysts.
The Pinner reaction (preparation of imino ether salts), Hoesch reaction (preparation of ketimine salts), Gattermann reaction, and Stephen reaction (preparation of aldimine salts), are carried out in the presence of hydrogen halides, and do not occur with other protogenic or Lewis acids in the absence of hydrogen halides. The products of the reaction of nitriles with hydrogen halides, which may be formed under the experimental conditions, are often formulated as either imidoyl halide salts \(^\text{11}\) (13), or nitrilium salts \(^\text{12}\) (14).

\[
\begin{align*}
[R-C\equiv NH_2]^+X^- & \\
(R-C\equiv NH)[HX_2]^+ & \\
(13) & \\
(14)
\end{align*}
\]

where \(X = \text{Cl, Br, or I}\).

In the presence of hydrogen halides some nitriles polymerize to produce 1,3,5-triazines \(^\text{13}\), probably by cyclic electron transfer \(^\text{13a}\) (15).
Nitriles having electron-withdrawing α-substituents undergo this reaction readily, due to the comparatively low electron density at the nitrile carbon atom increasing the electrophilic reactivity of the nitrile.

The addition of a proton to the nitrile nitrogen atom "opens up" the triple bond, and hence considerably increases the ability of the cyano group to react with electron donating compounds. The reaction of nitriles with water, alcohols, amines, thiols, and other nucleophilic reagents, is probably preceded by the formation of nitrile-hydrogen halide addition products (16). Nucleophilic attack by the freed base, or by free base originally present in the reaction, at the electron deficient carbon atom then takes place (17).

\[ \text{R'} \overset{\oplus}{\text{NH}_3} + \text{R}-\text{C} \equiv \text{N} \rightleftharpoons \text{R'} - \text{NH}_2 + \text{R}-\text{C} \equiv \text{N} \cdots \text{HX} \rightleftharpoons \text{R}-\text{C} = \text{NH} \]

(16)

\[ \text{R}-\text{C} = \text{NH} \overset{\oplus}{\text{X}} \rightarrow \text{R}-\text{C} = \text{NH} \overset{\oplus}{\text{HX}} \rightarrow \text{NH} + \text{HX} \]

(17)
NUCLEOPHILIC ADDITION TO DINITRILES

Dinitriles with nucleophilic reagents similarly can form diaddition products e.g. bis-amidines. However, in some cases, cyclization of the initial product takes place. The elimination of a molecule of ammonia from a diamidine yields an imidine.

\[ \text{HN} = \text{C} \text{N} \text{H}_2 \text{H}_2 \text{N} \text{C} = \text{NH} \rightarrow \text{HN} = \text{C} \text{N} \text{C} = \text{NH} \]

The elimination of an alcohol or thiol from a di-iminoether yields an alkoxyimino dehydroheterocycle, e.g. (19).

\[ \text{HN} = \text{C} \text{O} \text{Bu} \rightarrow \text{HN} = \text{C} \text{C} \text{O} \text{Bu} \]

Such internal cyclizations have been reported for derivatives formed from 1,2-, 1,3-, and 1,4-dinitriles, and it is thus a convenient synthetic route to 5, 6, and some 7 membered nitrogen heterocycles.

ADDITIONS TO 1,2-DINITRILES

The reactions of saturated, unsaturated, and aromatic 1,2-dinitriles with amines, alcohols, thiols,
haloacids, and carbanions have been extensively studied. Succinonitriles (20), 1,1,2,2-tetracyanoethanes (21), maleinitriles (22), fumaromt riles (23), and phthalonitriles (24) are cyclized by

![Chemical structures](image)

(a) $R = R' = H$
(b) $R = Me, R' = H$
(c) $R = R' = Me$
(d) $RR' = -(CH_2)_2-$
(e) $R = Me, R' = SH$
(f) $R = Ph, R' = H$

(a) $RR' = -C(\text{Me})_2-$
(b) $R = R' = H$

(a) $RR' = -(\text{CH}_2)_4-$
(b) $R = R' = Ph$
(c) $R = Ph, R' = CN$

(a) $R = H$
(b) $R = Ph$
ammonia (20, 15a, 18, 22, 18e, 24, 19), methylamine (24, 20), aniline (20, 18a, 21, 22, 18b), n-butylamine (24, 22), diethylamine (24, 20), morpholine (24, 20), hydroxylamine (20, 17, 24, 25), hydrogen sulphide (20, 17, 24, 24), thiols (20, 17), haloacids, (hydrogen bromide and hydrogen iodide), (20, 26, 21, 24, 22, 27, 23, 26a, 24, 28), and carbanions (20, 29, 24, 30), affording 5-membered heterocycles.

In most cases the uncyclized di-addition product has not been isolated, and so it appears that the addition and cyclization stages follow rapidly or are even concerted, as e.g. a) in the uncatalysed attack of an amine on succinonitrile (25),

\[
\begin{align*}
&\text{R} &\text{R'} \quad \text{N}^+\text{C} \quad \text{C} \quad \text{N}^\ominus \quad \text{R} \quad \text{R'} \\
&\text{H} &\quad \text{H} \\
&\text{NH}_2 &\quad \text{NH}_2
\end{align*}
\]

b) in the attack of a carbanion on maleinitrile (26)

\[
\begin{align*}
&\text{Ph} \quad \text{H} \quad \text{C} \quad \text{N} \quad \text{C} \quad \text{N} \quad \text{R} \quad \text{R'} \\
&\text{C} \quad \text{N} \quad \text{NH}_2 &\quad \text{NH}_2
\end{align*}
\]

*The references (20) etc. refer to reaction with dinitriles (20) etc..
and, c) in the addition of hydrogen bromide to phthalonitrile (27).

\[
\begin{align*}
\text{C}_7\text{H}_5\text{N} & \rightarrow \text{C}_7\text{H}_5\text{N}^+ \text{Br}_2^- & \rightarrow \text{C}_7\text{H}_5\text{N}^+ \text{Br}_2^- \text{Br}^- \\
\text{Ph} & \rightarrow \text{Ph} - \text{CH}_2 - \text{CN} & \rightarrow \text{Ph} - \text{N} - \text{CN} \\
\text{NH} & \rightarrow \text{NH} + \text{NH}_3 \\
\end{align*}
\]  

(27)

In the reactions (25) and (26), the first cyclic product can condense with a second molecule of an amine or an active methylene compound, with elimination of ammonia, e.g. (28).

\[
\begin{align*}
\text{C}_7\text{H}_5\text{NH} & \rightarrow \text{C}_7\text{H}_5\text{N}^+ \text{Br}_2^- \\
\text{NH} & \rightarrow \text{NH} + \text{NH}_3
\end{align*}
\]  

(28)

In most instances both the mono imino compound and the disubstituted compound can be isolated, as required. A product of the reaction between phthalonitrile and ammonia is 1,3-di-iminoisoindoline (29), a precursor of phthalocyanine pigments.

\[
\begin{align*}
\text{Ph} - \text{N} - \text{CN} & \rightarrow \text{Ph} - \text{N} - \text{NH} \\
\text{CN} & \rightarrow \text{CN}
\end{align*}
\]  

(29)
Phthalocyanine itself (30) is formed when 1,3-di-iminoisoindoline is refluxed in a hydrogen donor solvent, e.g., tetralin, whilst metal phthalocyanines are readily produced by gentle heating of 1,3-di-iminoisoindoline with metal salts, a process employed for printing cloth.

\[
\begin{align*}
4 \times \begin{array}{c}
\text{N} \\
\text{H} \\
\text{N} = \text{N}
\end{array} & \rightarrow \\
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array}
\end{align*}
\]

Under decidedly more vigorous conditions, phthalonitrile forms metal complexes of phthalocyanine when heated with metals or metal salts. The last reaction strictly requires the presence of a reducing agent to obtain the best yields. Thus with sodium in boiling amyl alcohol, phthalonitrile gives disodium phthalocyanine (31) in 70% yield.

\[
\begin{align*}
4 \times \begin{array}{c}
\text{C} \\
\text{N} \\
\text{C} \\
\text{N}
\end{array} & \xrightarrow{\text{2Na, Amyl alcohol, 135°C}} \\
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array}
\end{align*}
\]
Demetallation readily occurs when disodium phthalocyanine is dissolved in sulphuric acid and reprecipitated with ice.

Similarly, maleinitriles form metal complexes of tetrazaporphins (32), when refluxed in n-propanol with magnesium n-propoxide and a trace of iodine.

\[
\begin{align*}
R & = R' = H \\
R & = \text{Me, } R' = H \\
R & = R' = \text{Me} \\
R, R' & = -(\text{CH}_2)_4- \\
R & = R' = \text{Ph} \\
R & = R' = \text{NO}_2- \\
\end{align*}
\]

Tetrazaporphins (porphyrazines) have also been prepared by the reaction of 1,2-dicyanonaphthalene (33), 2,3-dicyanonaphthalene (34), 2,3-dicyanothiophen (35), 2,3-dicyanothionaphthen (36), 2,3-dicyanopyridine (37), and 2,3-dicyanopyrazine (38) with metal salts.
Macrocyclic pigments analogous to phthalocyanine, but containing some methine links have been prepared from intermediates derived from phthalonitrile, both by the Grignard reaction, 30b,40 by use of lithium alkyls, 30d and by the Thorpe reaction. Thus, phthalonitrile and an equivalent proportion of methylmagnesium iodide, or two proportions of methyl lithium, affords magnesium tetrabenztriaza-porphin, 30a,40 which is readily demetallated by acid to the parent macrocycle (39).
The mono-imine, 1-dicarboxymethylene-3-imino-isoindoline (41), prepared by hydrolysis of the product (40) from the reaction of phthalonitrile with diethyl sodiomalonate, under various conditions, yields mainly tetrabenzdiazaporphine (42), tetrabenzmanazaporphine (43), or tetrabenzporphine (44), in each case contaminated with the other pigments.
Polymerization of the nitrile groups in 1,2-dinitriles in the presence of free radical initiators has recently been described. The products are conjugated backbone polymers \( 41 \) (45), and tetrazaporphin derivatives, e.g. (46) and (47).

\[ \text{Ph} = \text{Ph} \quad \text{di-t-Bu peroxide} \quad N_2, 330^\circ, 2 \text{hr.} \]

\[ (45) \]

\[ \text{Ph} = \text{Ph} \quad + \quad \text{Ph} \quad \text{di-t-Bu peroxide} \quad N_2, 280^\circ, 5 \text{hr.} \]

\[ (46) \]
The method also affords excellent yields of phthalocyanine (30) from phthalonitrile under relatively mild conditions.

The reaction of 1,2-dinitriles with amines, and the hope of obtaining new macrocycles with properties resembling those of phthalocyanine, led to the preparation of the hemiporphyrines, e.g. cyclo-1,3':1',3-[2,6:2',6'-di-(pyridylenedi-imino)]-di-isoindoline, (51). These cross-conjugated macrocycles are prepared from 1,2-dinitriles or the corresponding imidines by condensation with meta-arylene diamines.

The two- and three-unit intermediates, 1-(2-amino-6-pyridyl)imino-3-iminoisoindoline (48), 2,6-di-(1-imino-3-isoidolinylideneamino)pyridine (49), and 1,3-di-(2-amino-6-pyridyl)iminoisoindoline (50), can all be isolated under various conditions, and then treated further to realize the macrocycle. This pyridine macrocycle (51) readily
forms metal chelates by the replacement of the two inner hydrogen atoms.
Analogous macrocycles (56) and their metal chelates have been reported when 3,5-diamino-1,2,4-triazoles (52) are treated with phthalonitriles (53), 1,2-dicyanodiphthalic anhydride (54), and 2,3-dicyan-5,6-diphenylpyrazine (55).

\[
\begin{align*}
\text{(52)} & \quad \text{H}_2\text{N} - \text{N} - \text{NH}_2 \\
\text{R} & = \text{H} \\
\text{R} & = \text{Ph} \\
\text{R} & = \text{p-NO}_2\text{C}_6\text{H}_4
\end{align*}
\]

\[
\begin{align*}
\text{(53)} & \quad \text{CN} - \text{CN} \\
\text{R}' & = \text{H} \\
\text{R}' & = \text{NO}_2
\end{align*}
\]

\[
\text{(56)}
\]

\[
\begin{align*}
\text{The bidentate 1,3-benzene (57), 2,4-toluene (58), 2,7-naphthalene (59), 2,8-acridine (60), and 3,5-pyridine (61) macrocycles have also been prepared by similar condensations of 1,3-diminoisoindoline with the corresponding diamine, and metal complexes (62) of the benzene macrocycle, cyclo-1,3':1',3'-[1,3:1',3'-di-(phenylenediimino)]di-isoindoline (57a) have been described.}
\end{align*}
\]
The tridentate ligand, three-unit compound (49) forms metal complexes (63), which can be used as templates for further reaction with 1,3-di-iminoisoindoline, yielding the tetradeptate macrocycle, cyclo-1,3':1',3-(1,3-isoindolenedi-imino-2',6'-pyridylenedi-imino)di-isoindoline, (64) possessing three-quarters of the phthalocyanine ring.
Unfortunately this macrocycle seems to be inherently unstable, and, in solution, it decomposes in 2 days.

The comparable 4'-substituted-1',3'-phenylene-di-imino-macrocycles (67), consisting of three isoindole units and one benzene unit, are however, more stable. The parent, cyclo-1,3':1',3-\((1,3\text{-isoindolylenedi-imino-1',3'-phenylenedi-imino-di-isoindoline, (67a) may be prepared from the three-unit adduct such as (65) (readily available from 1,3-di-iminoisoindoline and \(m\)-phenylenediamine in cold ethanol\(^{47}\) ) by heating with a further quantity of 1,3-di-iminoisoindoline, and the substituted macrocycles (67b-d) by heating the three-unit compounds (66) with 1,3-di-iminoisoindoline.

\[ \text{(65)} \]

\[ \text{(66)} \]

\[ \text{(67a)} \] \( R = H \)

\[ \text{(67b)} \] \( R = \text{Me} \)

\[ \text{(67c)} \] \( R = \text{OMe} \)

\[ \text{(67d)} \] \( R = \text{Cl} \)
The mixed hemiporphorazines, cyclo-1,3':1',3-\[1,3:1',4'-di-(phenylenedi-imino)\]di-isoindoline (68), cyclo-1,3':1',3-(1,4-naphthylenedi-imino-1',3'-phenylenedi-imino)di-isoindoline (69), and cyclo-1,3':1',3-(1,3-phenylenedi-imino-2',6'-pyridylenedi-imino)di-isoindoline (70), have been claimed to be formed by heating the three-unit compound, 1,3-di-(1-imino-3-isoindolinylideneamino)benzene, (56,R=H) with the corresponding arylene diamines.
The structures (68) and (69) for the products are, however, in need of confirmation because molecular models suggest that they would be extremely highly strained, so much so that their existence appears doubtful.

The three-unit compounds (71) when heated to 150-250° in high boiling solvents, e.g. nitrobenzene, α-chloronaphthalene, or tetralin, are reported to lose a molecule of ammonia, yielding, the three-unit macrocycles (72).

\[
\text{where } R = N, N^+Cl, N^+Me
\]

It would seem much more reasonable to suppose that dimerization occurred.
The addition of carbanions to 1,2-dinitriles has recently been extended to the formation of methine linked macrocycles related to the hemiporphyrizines. m-Phenylenediacetonitrile, and 2,6-dicyanomethylpyridine form 1',3'-phenylenedicyanomethylene- and 2',6'-pyridylenedicyanomethylene-three-unit compounds (73a) and (73b) respectively, when treated with two molar equivalents of phthalonitrile. However, no macrocyclic products were obtained when these three-unit compounds (73) were treated with a further molar equivalent of the respective dicyanomethyl compound. As a by-product of the preparation of the three-unit compound (73a), the macrocycle cyclo-1,3':1',3'-((1,3-isoindolenedi-imino-1',3'-phenylenedicyanomethylene)di-isoindoline (74) was obtained in small yield.

![Chemical structures](image-url)
The three-unit compounds (73) when treated with m-phenylenediamines apparently afford macrocycles (75), and uncyclized four-unit compounds (76), as shown by mass-spectral investigation of the products.

Pyromellitonitrile (77) when heated with cuprous chloride and urea, yields poly-(copper phthalocyanine) (78).
The reaction between pyromellitoniitrile (77) and diamines has also led to polymeric products. Using molar equivalents of tetraniitrile and diamine, linear precursors (79) or (80) of macrocyclic polymers are formed.

\[
\begin{align*}
(79) & : \quad \text{N} & & \text{N} & & \text{N} = \text{R} \\
& & \text{NH}_2 & & \text{NH}_2 & \}
\] \\
& n \]

where \( R = \begin{array}{c}
\text{phenyl} \\
\text{benzene}
\end{array} \), \( -\text{(CH}_2)_6- \).

Condensation of these products with a further molar equivalent of diamine, or reaction between pyromellitoniitrile and two molar equivalents of the diamine yield polymers, probably having poly-(hemiporphorazine) structures (81).

\[
\begin{align*}
(81) & : \quad \text{R} \quad \text{N} & & \text{N} & & \text{N} = \text{R} \\
& & \text{NH} & & \text{NH} & \}
\] \\
& \text{R} \quad \text{N} & & \text{N} & & \text{N} = \text{R} \\
& \text{R} \quad \text{N} & & \text{N} & & \text{N} = \text{R} \\
& & \text{NH} & & \text{NH} & \}
\] \\
& \text{R} \quad \text{N} & & \text{N} & & \text{N} = \text{R} \\
& & \text{NH} & & \text{NH} & \}
\]
The addition of base to a 1,4-dinitrile would, by analogy with the reaction of 1,2-dinitriles, lead to di-addition products which may condense to give seven-membered heterocycles. This is the case only very rarely, e.g. the hydrolysis of adiponitrile (82, R=H) yields adipimide (83, R=H).

No analogous reactions with ammonia or amines have been reported. Treatment of adiponitriles (82) and o-phenylenediacetonitrile (85) with strong base, e.g. sodium ethoxide, yield 1-cyano-2-iminocyclopentanes (84), and the highly reactive species, 1-cyano-2-iminoindane (86), respectively.

\[ \text{(82)} \xrightarrow{\text{H}_2\text{O}} \text{(83)} \]

\[ \text{where } R = H \]
\[ R = \text{CO}_2\text{Et} \]
However, with hydrogen bromide or iodide in acetic acid, o-phenylenediacetonitrile (85) affords 2-amino-4-halo-1H-3-benzazepine (87), after neutralization.

\[
\begin{array}{c}
\text{CN} \hspace{1cm} \text{CN} \\
(85)
\end{array}
\xrightarrow{\text{HX}}
\begin{array}{c}
\text{CN} \hspace{1cm} \text{CN} \\
(87) \\
\text{where } X = \text{Br, I}
\end{array}
\]

Similarly, 2,3-bis(cyanomethyl)naphthalene (88) treated with haloacid, on neutralization, yields 2-amino-4-halo-1H-naphtho[2,3-d]azepine (89).

\[
\begin{array}{c}
\text{CN} \hspace{1cm} \text{CN} \\
(88)
\end{array}
\xrightarrow{\text{HX}}
\begin{array}{c}
\text{CN} \hspace{1cm} \text{CN} \\
(89) \\
\text{where } X = \text{Br, I}
\end{array}
\]

The unsymmetrical 1,2-bis-(cyanomethyl)naphthalene (90) treated similarly, however, yields a mixture of amino-halo-1H-naphtho[1,2-d]azepines (91).
Cis- and trans-o-cyanocinnamonic nitriles (92) and (93) yield no seven-membered ring products when treated with a variety of amines.

Treatment of 2,2'-dicyanobiphenyl (94) with hydrogen bromide in benzene gives 7-bromo-5-imino-5H-dibenz[c,e]azepine hydrobromide (95), whilst with hydrogen bromide in acetic acid the product, after neutralization, is 6,7-dihydro-5-imino-5H-dibenz[c,e]azepine-7-one (96).
No imidines of seven-membered heterocycles have been reported apart from the condensed imidine derivative, 8-amino-5-bromo-13H-benzo[e]-isoquinolin[3,4-b]azepine (98), formed by the action of hydrogen bromide on 1,2-di-(2-cyanophenyl)-propionitrile (97).
Dinitriles linked by a carbon chain of more than four carbon atoms form di-addition products with nucleophilic reagents.

With a strong base, e.g. sodium ethoxide, proton abstraction occurs, and the carbanion formed then adds to a nitrile group. Intramolecular condensation is possible under high dilution conditions and leads to cyclic products. Intermolecular condensation necessarily leads to polymeric products.

\[
\begin{align*}
(CH_2)_n & \longrightarrow CH_2 \\
& \downarrow \quad \downarrow C N \quad C N \\
& \downarrow \quad (CH_2)_n \\
& \quad CH-CN \\
H N & \quad CH-CN
\end{align*}
\]

\[
\begin{align*}
(CH_2)_n & \longrightarrow CH-CN \\
& \downarrow \quad \downarrow C N \quad CH-CN \\
& \downarrow \quad (CH_2)_n \\
& \quad C=N H \quad C=N H \\
& \quad NC-CH-(CH_2)_n
\end{align*}
\]

Polymer, formed by intermolecular condensation (99), is the usual product in concentrated solution because the chances of the nitrile group and the carbanion in the same molecule reacting
together are remote. The intramolecular product (100) is formed only under high dilution conditions, by slow addition of the dinitrile to the catalyst. Even under such conditions when \( n = 7,8 \) or 9, the main product, although cyclic, is dimeric (101), formed by intermolecular, and then intramolecular condensation. A "highly" hindered base is used as catalyst such as lithium diethylamide, \((\text{Et})_2\text{N}^-\text{Li}^+\), in order to favour proton abstraction over its addition to the nitrile group.
ADDITIONS TO 1,3-DINITRILES

The ease of formation of five-membered heterocyclic products when 1,2-dinitriles undergo nucleophilic attack, and the relative difficulty of formation of seven-membered heterocyclic products when 1,4-dinitriles are so treated, suggests that the governing factors in the formation of the heterocycles are the stability of the heterocycle, the distance apart of the reactive nitrile groups, and the geometry between those groups. Thus apart from the formation of adipimide from adiponitrile, only unsaturated 1,4-dinitriles have been cyclized to azipinic derivatives.

Nucleophilic attack on a 1,3-dinitrile may give rise to a six-membered heterocyclic product, and if this ring is aromatic or potentially aromatic, by tautomerism, then it will undoubtedly be stable. Saturated 1,5-dinitriles, however, may give rise to dihydropyridines, or their tautomers. In this thesis the formation and stability of these compounds is investigated.

(a) Additions to Unsaturated 1,3-Dinitriles

o-Cyanophenylacetonitriles (102), and glutacononitriles (103), readily form addition-condensation products with water (102*, 103), ammonia (102),

*The references (102) etc. refer to reaction with dinitriles (102) etc..
amines (aniline, 2-chloroaniline, ethylamine, morpholine, benzylamine, isopropylamine, di-isopropylamine, naphthylamine, diethylamine, dioctylamine) (\textsuperscript{62} \& \textsuperscript{62}), hydroxylamine (\textsuperscript{102} \& \textsuperscript{61,63}), and haloacids (hydrogen bromide, hydrogen iodide), (\textsuperscript{62} \& \textsuperscript{64}). No cyclizations with carbanions have been reported.

\[
\text{R}^1\text{R}^2\text{N}^+ \quad \text{R}^3\text{R}^4\text{N}^- \quad \text{CN}^-
\]

Where

- R = H
- R\text{Me}
- R = Et
- R = CH\text{Me} \quad R' = H
- R = CH\text{MeCH} \quad R' = H
- R = H

- R' = H
- R' = NH\text{H}_2
- R' = CN
- R' = CN
- R' = CO\text{Et}

Except where an imide is formed, the products are aromatic. Thus o-cyanophenylacetonitrile (\textsuperscript{102a}) affords 1,3-diaminoisoquinoline (\textsuperscript{104}) when treated with ammonia, \textsuperscript{61,62,57,61} and 1-amino-3-hydroxylaminoisoquinoline (\textsuperscript{105}) when treated with hydroxylamine. \textsuperscript{63,58,65} With water, the product is homophthalimide \textsuperscript{57,59} (\textsuperscript{106}).

\[
\text{H}_2\text{N}^+\text{N}^+\text{NH}_2
\]

(\textsuperscript{104})

\[
\text{H}_2\text{N}^+\text{N}^+\text{NH}_2\h_{\text{OH}}
\]

(\textsuperscript{105})

\[
\text{O}^+\text{NH}^-
\]

(\textsuperscript{106})
Following these initial additions and cyclizations, there may be condensations involving nearby functional groups. Thus ethyl-3-cyano-3-(2-cyanophenylbutyrate) \(^6c\) (107) affords 5-bromo-8-oxo-7,8,9,10-tetrahydro-benzo[\(c\)]1',8'-naphthyridine (108), and 1,2-di-(2-cyanophenyl)propionitrile (109) affords 8-amino-5-bromo-13H-benzo[\(e\)]isoquinolin-[3,4-b]azepine (110).

\[
\begin{align*}
\text{CN} & \quad \text{CN} & \quad \text{CN} & \quad \text{CO}_2\text{Et} \\
(107) & \rightarrow & & \text{HN} \\
\text{Br} & \quad \text{N} & \quad \text{Br} \\
(108) & & & \\
\text{CN} & \quad \text{CN} & \quad \text{CN} & \quad \text{CN} \\
(109) & \rightarrow & & \text{NH}_2 \\
\text{Br} & \quad \text{N} & \quad \text{N} & \quad \text{NH}_2 \\
(110) & & & 
\end{align*}
\]

Glutacononitriles (or 1,3-dicyanopropenes) (103) are reported to react with amines affording pyridines, but no details are given of the products.

When treated with aqueous acids, glutacononitriles yield 2,6-dihydroxypyridines (111) or their tautomers, glutaconimides (112).
The aromatic products obtained by condensation of haloacids or alcohols with the sodium salts of the highly acidic 1,1,3,3-propene tetracarbonitriles (113) have been fully described. These are 2-amino-3,5-dicyano-6-halo-4-substituted pyridines (114).

When the pentanitrite (113; R=CH₂CN) (readily obtained by treatment of malonitrile with sodium ethoxide) is treated as follows, a 2,7-naphthyridine (115) is produced.
Surprisingly no solid products could be isolated when (116) was treated with hydrogen bromide and the product neutralized. Also only 3-phenyl-4-cyanoisocoumarin (118) could be isolated when (117) was similarly treated.

Only a mono-amidine (119 or 120) was obtained when (116) was treated with methanolic ammonia.
(b) **Additions to Saturated 1,3-Dinitriles**

(i) **Nucleophilic Addition Reactions**

Nucleophilic additions to saturated 1,3-di-nitriles were first studied by Biedermann in 1899. He treated glutaronitrile (121) with equivalent proportions of hydroxylamine hydrochloride and sodium carbonate at 60 - 70° for ten hours, in a closed flask, and reported the product to be a mixture of glutaramidoxime (122), which crystallized from water as a monohydrate, m.p. 233°, and glutarimidoxime [2,6-di-(hydroxyimino)-piperidine] (123), m.p. 193°.

![Chemical structures](image)

He reports confirmation of the products by making derivatives, viz. s-N,N'-diacetylglutaramidoxime (124), 1,3-di-[3-(5-methyloxadiazolyl)]propane (125), 2,6-di(acetyloximino)piperidine (126, R=Me), and 2,6-di(benzoyloximino)piperidine (126, R=Ph).
He also treated glutaronitrile with two equivalents of hydroxylamine, at room temperature, but found only one equivalent was consumed: he formulated the product as γ-cyanobutyramidoxime (127), m.p. 103°.

However, it seems that some of Biedermann's products were not as claimed. Tiemann suggested in 1891 that the product (127) was really 2-hydroxyimino-6-iminopiperidine (128).
Garny in the same year also reinterpreted some of Biedermann's work. Garny treated one molecule of glutaronitrile with one molecule of hydroxylamine and half a molecule of sodium carbonate in aqueous alcohol at 60 - 70° for eight hours in a closed flask and obtained crystals, m.p. 233°, which he, like Biedermann, called glutaramidoxime (122). Evaporation of the filtrate afforded 2-hydroxyimino-6-oxopiperidine (129), m.p. 196°, and not glutarimidoxime \([2,6\text{-di-(hydroxyimino)}\text{-piperidine}]\) (123), as claimed by Biedermann. The nature of the product was confirmed by conversion into glutarimide (2,6-dioxopiperidine) (131), m.p. 152°, with nitrous acid, and by an alternative preparation from a sample of Biedermann's glutaramidoxime (122) (which as will be seen, is, in fact, glutarimidoxime \([2,6\text{-di-(hydroxyimino)}\text{-piperidine}]\) (123)) with one molecule of nitrous acid.

Surprisingly, Knott, in 1947, suggested that Biedermann's uncyclized product (127) was, in fact, 6-amino-2-hydroxyamino-2,3-dihydropyridine (130),

\[
\begin{align*}
\text{(129)} & \quad \text{(130)}
\end{align*}
\]
i.e. a tautomer of the structure (128) which had been suggested by Tiemann. Elvidge, Linstead, and Salaman, in 1959, treated glutaronitrile with one molecule of hydroxylamine hydrochloride and half a molecule of sodium carbonate in 50% aqueous ethanol at 60 - 70° for sixteen hours, and obtained glutarimidoxime [2,6-di-(hydroximino)piperidine] (123), m.p. 228-230°, undepressed in admixtures with the product (m.p. 233-24°) from glutaronitrile with hydroxylamine hydrochloride (two molecules) and sodium carbonate (one molecule) in 50% aqueous alcohol at 90° overnight, and with the product (m.p. 240-1°) from glutarimidine (2,6-di-iminopiperidine) (137) and hydroxylamine hydrochloride (two molecules) refluxed in methanol for one and a half hours. The dioxime (123), treated with nitrous acid, yields 2-hydroxyimino-6-oxopiperidine (129), m.p. 156-7°.
It therefore seems certain that Biedermann's glutaramidoxime \(^2\) was, in fact, glutaramidoxime \([2,6\text{-di-(hydroxyimino)piperidine}]\) \(^1\), and that his glutaramidoxime \(^1\) was, in fact, 2-hydroxyimino-6-oxopiperidine \(^9\) as originally suggested by Garny.

Pinner (1890) \(^6\) first described the addition of alcohols to glutaronitrile, obtaining bisiminooether dihydrochlorides \(^1\).

\[
\begin{align*}
\begin{array}{c}
\text{CN} & \text{CN} \\
\uparrow & \downarrow \\
\text{HCl} & \text{ROH}
\end{array}
\end{align*}
\rightarrow
\begin{align*}
\begin{array}{c}
\text{RO} & \text{NH} & \text{OR} \\
\text{NH} & \text{NH}
\end{array}
\end{align*}
\quad (132)
\]
\[
\begin{align*}
\text{R} = \text{Me, Et, i-Bu.}
\end{align*}
\]

The reactions with methanol and ethanol were so violent that dilution with dry ether was necessary, and the products were unstable. \(\text{o,o'}\)-Di-(isobutyl)glutarisoamide dihydrochloride \((132, R=\text{Bu}^1)\) was more stable and decomposed only at about \(110^\circ\) to glutarimide \((131)\). The iminoether \((132, R=\text{Bu}^1)\) was hydrolysed by water to di-isobutyl-glutarate \((133)\), and it reacted with aqueous ammonia to give glutaramide \((134)\).
When the iminoether salt (132, R=\text{Bu}^+) was kept for several days with alcoholic ammonia, glutaramidine dihydrochloride (133) was obtained together with a double salt. This last approximated in composition to equimolecular amounts of glutaramidine dihydrochloride and glutarimidine hydrochloride (2,6-di-iminopiperidine hydrochloride) (136)

Dissolution of the double salt in water caused elimination of ammonium chloride, and afforded crude glutarimidine (2,6-di-iminopiperidine) (137), which could not be separated from ammonium chloride because of their similar solubilities in
water and ethanol. Evaporation of an alcoholic solution of the crude imidine yielded glutaramidine dihydrochloride (135), which crystalized as a dihydrate. Treatment of the amidine (135) with acetic anhydride afforded \( \text{O,O\textsuperscript{-}} \text{diacetylgutarisoamide} \) (138).

\[
\text{H}_2\text{N} = \text{C} = \text{NH} \quad \text{(137)}
\]

\[
\text{AcO} = \text{C} = \text{NH} \quad \text{OAc} \quad \text{(138)}
\]

Pinner \(^{16}\) also reacted his iminoether (132, \( R=\text{Bu}^1 \)) with aliphatic primary amines in alcohol, and suggested that the products, isolated as their platinichlorides, were \( s-N,N' \)-dialkylglutarimidines (2,6-dialkyliminopiperidines) (139), or their tautomers, 2,6-di-(alkylamino)3,4-dihydropyridines (140).

\[
\text{R} \quad \text{N}=\text{C}=\text{NH} \quad \text{R} \quad \text{(139)}
\]

\[
\text{R} = \text{Et} \quad \text{HN} = \text{C} = \text{NH} \quad \text{R} \quad \text{(140)}
\]

With an excess of an aliphatic secondary amine in alcohol, he describes the products as 2,6-di-(dialkylamino)-3,4-dihydropyridines (141).
isolated either as their platinichlorides (142),
or as a dibromide hydrobromide (143).

Elvidge, Linstead, and Salaman reacted glutaronitriles with methanolic ammonia at 80-100\(^\circ\) and obtained glutarimidines (2,6-di-iminopiperidines) (137, 144), also characterised as the picrate.
Glutarimidine (2,6-di-iminopiperidine) (137), itself was found to be readily hydrolysed, atmospheric moisture attacking an ethanolic toluene solution to afford 2-imino-6-oxopiperidine (145). Boiling water hydrolysed glutarimidine in one and a half hours to glutaramide (134), and cold water, at 0° for twenty four hours, to glutarimide (131).

α-Phenylglutarimidine (2,6-di-imino-3-phenylpiperidine) (144) with hydroxylamine hydrochloride in boiling methanol afforded 2,6-di(hydroxyimino)-3-phenylpiperidine (146). Mild degradation of the dioxime with nitrous acid yielded a monoxime, presumably the "hindered" isomer 2-hydroxyimino-6-oxo-3-phenylpiperidine (147), whilst hot dilute nitric acid smoothly gave α-phenylglutarimide (2,6-dioxo-3-phenylpiperidine (148).
Glutarimidine (2,6-di-iminopiperidine) (137) was found to react smoothly with aniline, in boiling ethanol, affording 2,6-diphenyliminopiperidine (149),

![Chemical structure](image)

but no condensation products were obtained with 2-aminopyridine, 2,6-diaminopyridine, or 1,3-di-imino-isoindoline.

2,6-Diphenyliminopiperidine (149) was also successfully prepared by heating glutaronitrile with two molecules of aniline hydrochloride to 230°, followed by neutralization. Hydrolysis of 2,6-diphenyliminopiperidine (149) in aqueous dioxan gave N,N'-diphenylglutaramide (150).

![Chemical structure](image)

α-Phenylglutarimidine (2,6-di-imino-3-phenylpiperidine) (149) reacted with aniline in two stages.
When equimolar proportions of the reactants were refluxed in ethanol a monophenyliminopiperidine was obtained, assigned the "unhindered" structure (151), i.e. 2-imino-3-phenyl-6-phenyliminopiperidine. Refluxing in a large excess of aniline overnight, however, afforded 3-phenyl-2,6-diphenyliminopiperidine (152), also obtained by refluxing the monoimine (137) in aniline overnight.

Bruylants, and his co-workers in Belgium, from 1921, studied the reaction of glutaronitrile (121) with Grignard reagents. Initially they considered the products to be acyclic addition products, e.g. (153),

\[ \text{CN} + \text{RMgX} \rightarrow \text{CN} \quad \text{(121)} \]

where \( R = \text{Ph, PhCH}_2 \)

\[ X = \text{Br, Cl} \]

(153)
and polymers of glutaronitrile, e.g. (154), which were usually hydrolysed to ketones (155) under the conditions of isolation.

\[
\text{(154)} \quad \text{(155)}
\]

In 1926, Bruylants and Dewaels re-examined the reaction between glutaronitrile (121) and benzyl magnesium chloride, obtaining 2,2-dibenzyl-2-imino-piperidine (156).

Arya, in 1951, confirmed Bruylants and Dewaels results.

\[
\begin{align*}
\text{(121)} & \quad \text{RMgX} \\
\text{(156)} & \quad \text{H}_2\text{O}
\end{align*}
\]

where \( R = \text{PhCH}_2 \) and \( X = \text{Cl} \).
Arya also studied the Thorpe reaction on glutaronitrile (121). The sodium salt of benzyl cyanide afforded 2-cyanophenylmethylene-6-imino-piperidine (157), m.p. 158°, which formed a hydrochloride, m.p. 175°, when treated with dry hydrogen chloride, and which was readily hydrolysed by acid or alkali to 2-cyanophenylmethylene-6-oxo-piperidine (158).

\[
\begin{align*}
(157) & \\
(158)
\end{align*}
\]

(ii) **Electrophilic Addition of Haloacids**

Howard, in 1957, and Osborn, in 1958, cyclized glutaronitrile (121, R=H) and \(\alpha\)-phenyl-glutaronitrile (121, R=Ph) with hydrogen bromide, and the products, after neutralization were 2-bromo-6-iminopiperidine (159, R=H), and 6-bromo-2-imino-3-phenylpiperidine (159, R=Ph), respectively.

\[
\begin{align*}
&\text{CN} &\text{CN} &\text{CN} \\
\text{R} &\text{HBr} &\text{Na}_2\text{CO}_3
\end{align*}
\]
Glutaronitrile (121) behaves differently with hydrogen chloride, and affords a dimer, $^{73}$ (160). In the presence of thiolactic acid, 2-imino-6-thioxopiperidine, (161) is formed after neutralization.

(iii) Formation of Pyridine Derivatives

In preliminary attempts to dehydrogenate 2,6-diphenyliminopiperidine (149), α-phenylglutarimididine (2,6-di-imino-3-phenylpiperidine) (144), and 3-phenyl-2,6-diphenyliminopiperidine (152), no evidence for the formation of substituted diaminopyridine was obtained in experiments involving dry distillation, heating with palladized charcoal in boiling nitrobenzene or boiling diethylene glycol diethyl ether, and treatment with chloranil or tetrachloro-o-benzoquinone in ethanol.

Takata $^{74}$ has prepared 2,6-di-imino-3-methylpiperidine (163a) and 2,6-di-imino-3,5-dimethylpiperidine (163b) from α-methylglutaronitrile (162a) and α,α'-dimethylglutaronitrile (162b), respectively,
by reaction at room temperature for two days with sodamide in formamide. He also reports the dehydrogenation of these imidines with palladium catalyst at 300° for eleven hours in diphenylether, obtaining 2,6-diamino-3-methylpyridine (164a) and 2,6-diamino-3,5-dimethylpyridine (164b).

\[
\begin{align*}
R &= \text{Me}, R' = \text{H} \quad (162a) \\
R &= \text{R'} = \text{Me} \quad (162b)
\end{align*}
\]

The same author has also obtained 2,7-didimino-1,2,3,4,5,6,7,9-octahydro-1,8-naphthyridines (166), from pimelonitriles (165), by treatment with sodamide in formamide, but no attempts at dehydrogenation are mentioned.

\[
\begin{align*}
R &= \text{Me}, R' = \text{H} \quad (166)
\end{align*}
\]

The reaction of hydroxyglutaronitriles with nucleophiles has been studied, because, under the conditions of the reaction, water may be eliminated and substituted pyridines formed. Lespieau, in
1923, and later Kurtz, Schwarz, and Disseln-kotter, in 1960, treated 3-hydroxyglutaronitrile (167) with hydrogen bromide, and reported the product, after neutralization, to be 3-bromoglutaronitrile. This is most surprising because in 1958 Middleton and his co-workers suggested the product was 2-amino-6-bromopyridine (168). This conclusion was verified by Johnson, et al. in 1962:

\[
\begin{align*}
\text{HO} & \\
\text{CN} & \text{CN} \\
\end{align*}
\xrightarrow{1) \text{HBr, } 2) \text{NaHCO}_3}
\begin{align*}
\text{H}_2\text{N} & \text{Br} \\
\end{align*}
\]

(167) \hspace{2cm} (168)

The 3-substituted-3-hydroxyglutaronitriles (169) reacted with hydrogen bromide or hydrogen iodide in the same way, affording the corresponding 3-substituted pyridine derivatives (170).

\[
\begin{align*}
\text{HO} & \\
\text{CN} & \text{CN} \\
\end{align*}
\xrightarrow{1) \text{HBr or HI, } 2) \text{NaHCO}_3}
\begin{align*}
\text{H}_2\text{N} & \text{X} \\
\end{align*}
\]

(169) \hspace{2cm} (170)

where \( R = \text{Me, Et, Ph} \)

\( X = \text{Br, I} \)

Analogously 3-hydroxy-2-methylglutaronitrile (171) with hydrogen bromide afforded equimolar proportions of 6-amino-2-bromo-3-methylpyridine (172) and
Johnson et al. also found that 3-hydroxyglutaronitrile affords 2,6-dihydroxypyridine (111) and glutacononitrile (103, R=R'=R''=H) when mixed with phosphorous pentoxide. Kekulé is stated to have been the first to realize that β-hydroxyglutaramide (174) can yield glutacononimide (112), and that the latter is a tautomer of 2,6-dihydroxypyridine (111).

Johnson, in 1965, patented a process for producing 2,6-diaminopyridines from 3-hydroxyglutaronitriles. He found that the glutaronitriles (175) when heated at about 120–180° for five hours with amines in the presence of hydrogen bromide...
afforded the 2,6-diaminopyridines (176).

Polycyclization of low melting polyacrylonitrile and polymethacrylonitrile fibres has been carried out and found to yield thermally stable polymers. Houtz was the first to ascribe a polycyclic, ladder, structure to heat-treated polyacrylonitrile fibre. Burlant and Parsons, and Topchiev represent the reaction as an intramolecular cyclization (177) followed by dehydrogenation to (178) which is isomeric with structure (179).
CHAPTER 2

AROMATIZATION OF 2,6-DI-IMINOPiperidines
Dehydrogenation of 2,6-di-iminopiperidines, which are readily available from glutaronitriles, appeared likely to provide a convenient new route to 2,6-diaminopyridines and so worthy of investigation. Amino substituted pyridines are potentially valuable heterocycles for the synthesis of drugs and dyestuffs and could have useful biological activity in themselves.

The dehydrogenation of the parent compound, 2,6-di-iminopiperidine (137)* has not been reported. It suffers from the disadvantage that it readily disproportionates on heating above about 100° to give ammonia and glutaronitrile.

\[
\begin{align*}
\text{HN} & \quad \leftrightarrow \quad \text{NH}_3 + \\
& \quad + \\
\text{CN} \quad \text{CN}
\end{align*}
\]

(137) (121)

Introduction of a phenyl substituent into the 3-position, as in (144), was likely to help dehydrogenation by stabilizing the compound against disproportionation, possibly by conferring some piperidine structure (e.g. 180) to the compound.

*The preferred fine structures of the di-imino-piperidines have not been assumed but they will be represented solely by the di-imino structures at this stage.
and by helping to stabilize any intermediate dihydropyridine (181) formed, and by increasing the conjugation and stability in the required substituted pyridine (182).

![Chemical structures](image)

The 2,6-diphenylimino derivatives (149) and (152) which on dehydrogenation should afford 2,6-dianilino-pyridines, were expected to be favourable compounds for initial study because of their greater resistance to disproportionation and to hydrolysis, and their greater solubility in organic solvents.

![Chemical structures](image)

Diphenylimino derivatives from other imidines are known to dehydrogenate spontaneously; viz. cis-hexahydro-1,3-di-iminoisoindoline (183, R=H) on treatment with
aniline yielded not cis-hexahydro-1,3-diphenylimino-isoindoline (183, \( R = \text{Ph} \)) but tetrahydro-1,3-diphenyl-iminoisoindoline (184),

![Chemical structure](183) ![Chemical structure](184)

where \( R = \text{H or Ph} \)

and similarly dimethylsuccinimidine (2,5-di-imino-3,4-dimethylpyrrolidine) (185) on treatment with aniline yielded 3,4-dimethyl-2,5-diphenylimino-\( \Delta^3 \)-pyrrolidine (186).

![Chemical structure](185) ![Chemical structure](186)

However although first attempts to dehydrogenate 2,6-di-imino-3-phenylpiperidine (144), 2,6-diphenyliminopiperidine (149), and 3-phenyl-2,6-diphenyliminopiperidine (152) by distillation, by heating with palladized charcoal in nitrobenzene or in diethylene glycol diethyl ether, and by treatment in ethanol with chloranil or tetrachloro-\( \alpha \)-benzoquinone failed, 3-phenyl-2,6-diphenyliminopiperidine (152) was found to undergo a reaction under dehydrogenating conditions.
(B) DEHYDROGENATION OF 3-PHENYL-2,6-DIPHENYLIMINO-PIPERIDINE (152).

a) Preparation of the compound (152)

α-Phenylglutaronitrile (187) was prepared by the method of Koelsch from a Michael condensation of phenylacetonitrile and acrylonitrile, and its constitution confirmed by ultra-violet (u.v.), infra-red (i.r.), and proton magnetic (p.m.r.) spectroscopy.

\[
\begin{align*}
\text{Ph-CH}_2-CH_2-CN & \quad + \quad \text{CH}_2-CH-CN \\
\text{CN} & \quad \rightarrow \quad \text{Ph} \\
\text{CN} & \quad \text{CN}
\end{align*}
\]

(187)

In the p.m.r. spectrum the five aromatic protons gave a sharp singlet at \( \tau 2.64 \), the methine proton gave rise to an approximate triplet at \( \tau 6.05 \), and a four proton multiplet centred at \( \tau 7.66 \) arose from the two methylene groups.

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{CN} & \quad \text{CN}
\end{align*}
\]

(187)

The mass spectrum exhibited a parent ion at \( m/e 170 \) and a fragmentation pattern that confirms the structure and will be discussed in detail later (p231).

Better yields of α-phenylglutaronitrile were obtained by condensing phenylacetonitrile and acrylonitrile in boiling nitrobenzene while adding portions of potassium cyanide, as catalyst, during
the course of the reaction.

3-Phenyl-2,6-diphenyliminopiperidine (152) was prepared by thermal condensation of \( \alpha \)-phenylglutaronitrile (187) and aniline hydrochloride at 285°.

\[
\text{Ph} \quad \text{Ph} \quad \text{CN} \quad \text{CN} \quad + \quad 2 \times \text{PhNH}_3\text{Cl} \quad \longrightarrow \quad \text{Ph} \quad \text{Ph} \\
\text{N} \quad \text{N} \quad \text{H} \quad \text{Ph} \quad \text{Ph} \quad + \quad \text{NH}_4\text{Cl} + \text{HCl} \\
\text{(187)} \quad \text{(152)}
\]

It was found difficult to crystallize, but was obtained as fine needles from ethanol after being purified by preparative thin-layer chromatography (t.l.c.) on silica gel, eluting with methanol.

The i.r. spectrum showed absorptions at 332, 320 (NH), 164 (C=NC), 161, 159.5 (C=C), 157 (secondary amine), 151.5 (amidine band), 150 (C=C), 148.5, 144.5 (CH\(_2\)), 141 (-CH\(_2\)-C=N-) \text{mm}^{-1}. The pattern between 165 and 140 \text{mm}^{-1} is characteristic of all of the 2,6-diphenyliminopiperidines described in this thesis.

The u.v. spectrum again exhibited a characteristic pattern having absorptions at 226, 287, 300 nm.

Its p.m.r. spectrum shows the typical broadening of the signals that we have found for all of these piperidines. It contains fifteen aromatic protons in a multiplet at \( \gamma \) 2.20-3.60, a diffuse NH proton signal at \( \gamma \) 5.60, a methine proton split
into an approximate triplet at $\tau \approx 5.94$, and four methylene protons in a complex multiplet between $\tau 7.20$-8.20. The broadening which occurs in this spectrum is not due to impurities because all of the signals sharpen up when trifluoroacetic acid is added or used as sole solvent. The broadening is probably due to the slow inversion of the N-H bond, which after protonation in trifluoroacetic acid is fixed in a rigid environment. Addition of three drops of trifluoroacetic acid to the deuteriochloroform solution caused a large change in the spectrum. The aromatic protons were partially resolved into two multiplets at $\tau 2.48$ (four protons), and $\tau 2.80$ (eleven protons), the methine proton was at $\tau 5.60$, the NH proton was still visible at $\tau 5.80$, and the methylene protons were partially resolved into two multiplets centred at $\tau 7.35$ (two protons), and $\tau 7.95$ (two protons). No further change in the spectrum occurred on standing, but addition of further trifluoroacetic acid (10% in all) sharpened and resolved the peaks into an aromatic multiplet at $\tau 2.70$ (fifteen protons), a methine proton resolved as a double doublet at $\tau 5.90$, a methylene group (H$^{4,5}$) at $\tau 7.02$, and a methylene group (H$^{2,3}$) at $\tau 7.60$.

The mass spectrum revealed a parent ion $m/e 339$, as required, and a fragmentation pattern which confirms the structure and will be discussed.
b) **Dehydrogenation of 3-phenyl-2,6-diphenyliminopiperidine (152) with nitrobenzene.**

The dehydrogenation of 3-phenyl-2,6-diphenyliminopiperidine (152) was attempted using nitrobenzene as the hydrogen acceptor. This strong dehydrogenating agent has advantages over most others in that it is a liquid having great solubilising power, and that the final reduction products will be aniline and water which can be removed by distillation, and which will not interact with starting material or products to produce any constitutional changes.

Stoichiometric quantities of 3-phenyl-2,6-diphenyliminopiperidine (152) and nitrobenzene were refluxed in o-dichlorobenzene as solvent. After 18 hrs., t.l.c. confirmed that the reaction had ceased, and yellow crystals were obtained after evaporation, extractive crystallization, and column chromatography. T.l.c., eluting with benzene-ethyl acetate (19:1),
revealed a single spot ($R_f$ 0.65).

The i.r. spectrum of the product did not contain the characteristic strong band at about $168 \text{ mm}^{-1} \text{ (C=}\text{N)}$ associated with the imidine group, but instead contained only bands attributable to aromatic compounds, viz. 345,160,158,152.5,151,145.5, 143.5,141 mm$^{-1}$.

Its u.v. and visible spectrum ($\lambda_{\text{max}}$403 nm, in hexane) showed an extremely large bathochromic shift relative to 3-phenyl-2,6-diphenyliminopiperidine ($\lambda_{\text{max}}$299 nm, in hexane). Now a large bathochromic shift would naturally be expected if the dehydrosation product was an aromatic planar molecule, but the size of the shift was much more than would have been expected for the required 2,6-dianilino-3-phenylpyridine (188).

The latter would be expected to have a maximum absorption in the ultra-violet of about 340-350 nm in hexane. Hence an aromatic system has been formed having more extensive conjugation than in 2,6-dianilino-3-phenylpyridine (188).
The mass spectrum exhibited a very intense molecular ion at m/e 581 and a fragmentation pattern characteristic of a very stable aromatic compound in that it gave numerous multiply charged ions, suggestive of several aromatic rings. The large parent ion was followed by a few fragments of low relative intensity, and the only other major peak in the spectrum came from a doubly charged molecular ion at 2e 290.5. Triply and quadruply charged molecular ions were also visible in this spectrum which was run under normal accelerating conditions. The fragments that were visible were due to loss of Ph, PhNH, and C_{17}H_{13}N_{2}. Now a parent ion of 581 requires that an odd number of nitrogen atoms be present in the molecule. Hence this dehydrogenation product is likely to be formed by the linkage of two molecules of 2,6-dianilino-3-phenylpyridine (188) with loss of one molecule of aniline. The elemental analysis confirms this conclusion and thus one arrives at a molecular formula of C_{40}H_{31}N_{5}. The mass spectral loss of the C_{17}H_{13}N_{2} fragment is due to splitting off an anilinophenylpyridyl fragment (e.g. 189).

![Diagram of the molecular ion](189)
The products most likely to be formed in the nitrobenzene-dehydrogenation reaction, having the required molecular formula, are listed below.

\[
\text{(190)}
\]

\[R_1 = Ph, R_2 = \text{Ph, } R_3 = R_4 = H\]

\[R_1 = \text{Ph, } R_2 = R_3 = H\]

\[R_3 = R_4 = \text{Ph, } R_1 = R_2 = H\]

\[
\text{(191)}
\]

\[a) R_1 = \text{Ph, } R_2 = H\]

\[b) R_2 = \text{Ph, } R_1 = H\]

\[
\text{(192)}
\]

\[a) R_1 = \text{Ph, } R_2 = H\]

\[b) R_2 = \text{Ph, } R_1 = H\]
The p.m.r. spectrum, while adding further substance to the conclusions so far drawn, failed to help distinguish between the possible alternatives proposed. The spectrum consisted of a complex multiplet at $\tau 2.20-3.50$, and one exchangeable proton at $\tau -1.30$. The multiplet integrated for thirty protons and must therefore be due to the twenty eight aromatic and two NH protons. The low field position of the third NH proton is presumably due to hydrogen-bonding.

c) Chemical identification of the dehydrogenation product.

(i) Acetylation

The dipyridylaniline (190), having only two secondary amino groups, would be expected to give a di-N-acetyl derivative, whereas the bipyridyls (191) and (192) might be expected to give tri-N-acetyl derivatives provided steric hinderance is not too great.

Acetylation was carried out employing a large excess of acetic anhydride under vigorous conditions in a Carius tube at 190° for 24 hrs. A white crystalline compound was obtained after preparative t.l.c. and recrystallizations.

The product had a typical i.r. spectrum for a N-acetyl derivative, the NH stretching frequency band at $345 \text{ mm}^{-1}$ having disappeared and been replaced by a strong carbonyl stretching band at $167.5 \text{ mm}^{-1}$. 

85
The u.v. spectrum contained an inflection at 293 nm as its longest wavelength absorption. A hypsochromic shift relative to the dehydrogenation product was not unexpected because it seemed likely that the acetyl groups would force the molecule out of a coplanar configuration.

The p.m.r. spectrum revealed a complex multiplet at δ2.00-3.40 having a relative intensity of about 10 and three singlets at δ7.95, 8.00, and 8.06 of relative intensity 1:1:1. These three signals have originated from the N-acetyl groups in three different environments. In the different solvent system, deuteriochloroform-benzene (1:1), these equal intensity singlets were observed at δ7.99, 8.10, and 8.13, slight solvent shifts having occurred.

The mass spectrum also confirmed that the acetylation product was a tri-N-acetyl derivative. The parent ion appeared at m/z 707, and successive loss of three molecules of keten, CH$_2$=C=O (i.e. loss of 42), by hydrogen rearrangement (193) afforded

\[
\begin{align*}
&\left[\begin{array}{c}
N \quad \text{C} \quad = \quad \text{O} \\
\text{H} \quad \text{CH}_2
\end{array}\right]^+ \\
\rightarrow \\
&\left[\begin{array}{c}
N \\
\text{H} \quad \text{C} \\
\text{H}_2
\end{array}\right]^+ + \left[\begin{array}{c}
\text{O} \\
\text{C} \\
\text{H}_2
\end{array}\right]
\end{align*}
\]
the base peak corresponding to the parent ion of the dehydrogenation product, at $m/\varepsilon = 581$. The successive loss of the neutral keten molecules was verified by three large metastable peaks at $m/\varepsilon = 625.3$, 583.8, and 541.7. Further fragmentation was relatively insignificant and resembled that obtained with the dehydrogenation product itself, apart from a few small fragments attributable to retention of a proportion of the acetyl groups by smaller fragments of the molecule, as would be expected.

The elemental analysis further identified the compound as a tri-acetyl derivative having molecular formula $C_{46}H_{37}N_5O_3$.

That the acetyl derivative is a tri-(N-acetyl) derivative eliminates the dipyridylaniline structure (190). From models it seems that the tri-N-acetyl derivative (194) would be sterically overcrowded. However, the overcrowding would be around the periphery of the molecule and a large proportion of the conjugation in the parent 2,4'-bipyridyl (192) would still be retained.

The envelope drawn encloses the part of the molecule where the stereochemistry in the parent compound and the derivative remains essentially unaltered. Thus the very large hypsochromic ultraviolet shift cannot be accounted for by a 2,4'-bipyridyl structure.
When we consider the 2,3'-bipyridyl (191) possibility and its tri-N-acetyl derivative we have to consider the effect of hydrogen bonding determining the steric positioning in the molecules. Thus (195) will probably be preferred to conformation (196) because the latter will be slightly non-planar and so less conjugated. The hydrogen-bonded structure (195) is in excellent agreement with the p.m.r. spectrum in which one NH proton was at low field (\( \tau -1.30 \)). In the tri-N-acetyl derivatives this hydrogen bond no longer exists. Both conformations (197) and (198), corresponding to the previous two, would necessarily be non co-planar.
The molecular overcrowding that occurs in the region between the pyridine nuclei in conformations (197) and (198) causes a much greater reduction in conjugation and thus a correspondingly greater
hypsochromic shift in the ultra-violet because the effect is at the centre of the chromophore, rather than near the periphery.

The acetylation results thus eliminated the dipyridylaniline structure (190) and strongly supported a 2,3'-bipyridyl structure (191), the less hindered hydrogen-bonded conformer (195a) being preferred for the parent compound.

(ii) Bromination

In order to distinguish between the 2,3'-bipyridyl (191) and other possible structures (see p. 67) bromination was carried out in chloroform under mild conditions. The hope was that bromination might occur only at the active $\beta$-positions in the pyridine nuclei, and at the $p$-positions of the anilino moieties. Provided that was achieved, then the degree of bromination would at once indicate the most likely structure for the compound because the possibilities differed in the number of $\beta$-positions available.

Employing four molecules of bromine to one of the dehydrogenation product in chloroform at 0° a yellow solid was obtained after evaporation and trituration. Column chromatography in benzene and examination of the fractions by mass spectroscopy indicated that a complex mixture of brominated products had arisen. This was unexpected and in
order to simplify matters the fractions were combined and treated with a further eight molecular proportions of bromine in chloroform, first at 0° and then at 50°. Column chromatography, eluting with benzene-cyclohexane (10:1), then revealed only two major non-polar components.

(a) Less-polar component

The less-polar component analysed for \( \text{C}_4\text{H}_2\text{N}_5\text{Br}_7 \), the bromine being non-ionic.

The i.r. spectrum was typical of a brominated aromatic compound with skeletal vibrations at 161, 160, 157.5, 155, 154, 151.5, 151 mm\(^{-1}\). There was also absorption at 345 mm\(^{-1}\) attributable to NH.

The p.m.r. spectrum showed a downfield signal from one proton at \( \gamma \)-3.50 and a complex multiplet at \( \gamma \)1.43-2.85 (twenty three protons). The multiplet evidently arose from twenty one aromatic protons and two NH protons. The downfield proton indicated that the product was derived from the hydrogen-bonded 2,3'-bipyridyl structure (195).

The mass spectrum was particularly informative. It confirmed the molecular formula, having a parent ion (for minimum isotopic weights) at \( m^+ \)1127, and isotopic peaks with the correct intensities for a heptabromide. The fragmentation pattern was dominated by successive losses of bromine (Br\(^-\)), by losses of
bromine (Br*) and concomitant gain of hydrogen (H*) from an external source in the mass spectrometer, by a large initial loss of hydrogen bromide (HBr°), and by doubly charged ions of the parent and all of the major fragments.

The heptabromide had its longest wavelength absorption in the ultra-violet at 375 nm (in hexane) which indicated a reduction in conjugation relative to the parent compound. This is probably the result of the large bromine substituents twisting the molecule out of plane. In the 2,3’-bipyridyl structure (191) there is one active β-position on a pyridine ring (2,6-diaminopyridine brominates in the β-positions extremely readily under mild conditions \cite{86}), and three anilino residues — which might each be tri-brominated (c.f. aniline itself \cite{87}). The formation of a hepta-bromo derivative could be rationalized by assuming that the anilino residues were not fully brominated, presumably due to steric hindrance. If the three anilino moieties had each been di-brominated then the product would be (199). In the absence of evidence to distinguish between the isomers (199a,b) the less hindered structure (199a) is preferred. Molecular models confirmed that the third site for bromination on each anilino moiety was sterically hindered and thus no further bromination was to be expected under mild conditions.
Considering the 2,4'-bipyridyl structure (192), a hepta-bromo derivative could be interpreted to mean that the three very well separated anilino residues were only dibrominated and one free \( \beta \)-position on a pyridine ring was also brominated i.e. structures (200a,b). From molecular models it would appear possible to insert at least one further bromine atom on one or other of the two anilino residues attached to the same pyridine nucleus (200a,b).

As the hepta-bromo derivative was by far the easiest bromo derivative to obtain under various brominating conditions, and it was produced in greatest yield, the 2,3'-bipyridyl structure (191) seems to fit the results better than the 2,4'-bi-
(b) **More-polar component**

The more-polar component obtained by column chromatography of the bromination product, analysed for $C_{40}H_{25}N_5Br_6$: again the bromine was all covalently bound. The i.r. spectrum was not unlike that of the heptacromide, with bands at 345, 160, 158, 155, 154, and 151 mm$^{-1}$. 

pyridyl structure (192).

(200a) 

(200b)
The longest wavelength absorption in the u.v. spectrum (394 nm in hexane) indicated only a slight decrease in conjugation relative to the parent compound (403 nm in hexane), but a moderate bathochromic shift has occurred with respect to the heptabromo derivative (375 nm in hexane). The small hypsochromic shift on hexabromination indicates no appreciable loss in planarity of the molecule and thus no steric hindrance.

The p.m.r. spectrum showed a signal at $\gamma$-3.20 indicative of a hydrogen-bonded NH proton. There was also a complex multiplet at $\gamma$1.00-3.20 from twenty four protons comprising twenty two aromatic and two NH protons.

The mass spectrum confirmed the molecular formula, having a parent ion at $^{79}M$ = 1,049 (for $^{79}$Br) with isotopic peaks with the correct intensities for a hexabromide. The fragmentation pattern showed that there was mainly loss of bromine (Br$^+$), hydrogen bromide (HBr$^-$), and of bromine (Br$^+$) with concomitant hydrogen (H$^+$) acquisition. There were also doubly charged peaks.

The one extra bromine in the heptabromide (199a) must be that which causes the molecule to buckle out of plane slightly and shift the u.v. maximum down to 375 nm. The most overcrowded bromine atoms in the heptabromide (199a) are the $o$-substituted bromine atom on the "central" anilino
moiety, and the \(\beta\)-substituted bromine on a pyridine nucleus. The former bromine seems likely to be the most difficult to introduce from steric considerations though naturally the relative reactivities of the two sites towards electrophillic attack, as previously discussed, is also important.

The structure (201) is therefore tentatively assigned to the hexabromide. In the absence of evidence to distinguish between the isomers (201a,b) the less hindered structure (201a) is preferred.

\[
\begin{align*}
\text{Bromination under very mild conditions in} \\
\text{chloroform at } 0^\circ \text{ with vigorous stirring and employing} \\
\text{slow addition of four molar proportions of bromine} \\
\text{afforded two further products as well as a small}
\end{align*}
\]
amount of heptabromide. These were separated by column chromatography, using benzene-petroleum ether (10:1) as eluant.

The less-polar component analysed for \(C_{40}H_{27}N_5Br_4\), and the more-polar for \(C_{40}H_{28}N_5Br_3\), neither containing ionic bromine. Their i.r. spectra were similar to the previous bromides, the major absorptions being at 345, 160.5, 158.5, 156.5, 154.5, 152, 151, and 149 mm\(^{-1}\) for the tetrabromide, and at 346, 160, 158, 156, 154, 152, 151, 149.5, and 148 mm\(^{-1}\) for the tribromide.

Their u.v. spectra were very similar to that of the parent 2,3'-bipyridyl (191) (403 nm in hexane), the tetrabromide having longest wavelength absorption at 402 nm, and the tribromide at 403 nm (both in hexane), indicating no departure from planarity in these derivatives.

The p.m.r. spectra indicated one downfield proton at \(\tau-0.10\) in the tetrabromo and one at \(\tau0.35\) in the tribromo derivative. The other protons gave complex multiplets at \(\tau1.98-3.20\) and \(\tau2.00-3.50\) respectively.

The mass-spectra confirmed the molecular compositions, the parent ions being strong peaks at \(m/ɛ 893\) and 815 for the tetra- and tri-bromide respectively, accompanied by the expected isotopic peaks. A similar fragmentation pattern was given by these bromides to that from the hepta- and hexa-
-bromo derivatives,

The tetrabromide is tentatively assigned the structure (202), and the tribromide is probably (203) or (204), the former being favoured by mass-spectral analysis.
All four of the foregoing bromides have a fairly intense peak in their mass spectra at $m_e = 579$. This fragment is probably due to the parent ion successively loosing bromine ($\text{Br}^+$) and acquiring ($\text{H}^+$) from an external source and also loosing ($\text{HBr}^+$) forming (205).

Now the parent 2,3'-bipyridyl (191) does not exhibit this peak so that loss of hydrogen ($\text{H}_2^+$) from the molecular ion, which would afford this very stable ion (205), is evidently not a feasible process. Hence it is likely that all four bromoderivatives possess $\beta$-bromopyridine atoms, and that the new ring is formed on electron bombardment by facile elimination of hydrogen bromide ($\text{HBr}^+$) between the $\beta$-bromopyridine and an NH proton. The necessary groups can become adjacent through rotation about the bond between the pyridine nuclei, as in (206).
In attempts to obtain a fully substituted product, bromination was carried out using a large excess of bromine (twelve fold excess) and warming the reaction to 80° for half an hour. Column chromatography revealed the presence of several highly brominated derivatives, but the major components appear, from their mass-spectra, to have been further dehydrogenated. Their u.v. spectra were all very similar, having multiple long wavelength absorptions at about 390, 398, and 406 nm. The excess of bromine in the reaction mixture obviously acts as a dehydrogenating reagent, probably via a bromination–dehydrobromination mechanism. The products are likely
to be compounds of the dipyridopyrrole series, similar to the ion (205) formed by electron bombardment, but containing varying amounts of bromine.

(iii) Attempted synthesis of bromo bipyridyls

(a) Condensation of \( \alpha \)-phenylglutaronitrile and \( p \)-bromoaniline hydrochloride

It was hoped that the tetrabromide (202) could be prepared by another route to verify its structure and help verify the structures of the other bromo derivatives. Preparation of a tri-\( p \)-bromoanilino-2,3'-bipyridyl (207) was attempted via 2,6-di-(\( p \)-bromophenylimino)-3-phenylpiperidine (208) by condensing \( \alpha \)-phenylglutaronitrile with \( p \)-bromoaniline and \( p \)-bromoaniline hydrochloride. The product should
have been different from the tribromide (203) already prepared but it should have been possible to mono-brominate it in the free pyridine β-position to give the tetrabromide (202).

The condensation of α-phenylglutaronitrile and p-bromoaniline hydrochloride at 240° under nitrogen returned 85% of the dinitrile unchanged. From a similar condensation at 300°, fractions of fine pale yellow solid were obtained after column chromatography of the neutralized reaction product and elution of the first broad band [benzene, then benzene-chloroform (1:1)] in a series of small fractions. All of the fractions gave solutions with a strong blue-fluorescence in most organic solvents, and t.l.c. [eluting with benzene-petroleum ether (2:1)] showed that the fractions had very similar retention factors (Rf 0.46). The fractions also had similar i.r. and u.v. spectra, all having bands at 345, 159, 157, 152, 150, 145, and 141 nm⁻¹, and 261, 280, 333, 377, 396 nm in cyclohexane, and 251, 279, 333, 377, and 390 nm in ethanol. The more-polar components of the reaction product remaining on the column were eluted with methanol. Mass spectra of materials so recovered revealed that a complicated reaction had taken place affording dehydrogenation-condensation products. Dehydrobromination had probably occurred, as well as exchange of chlorine and bromine atoms. Thus the products exhibited similar spectral
properties to those of the dehydrobrominated product obtained when the 2,3'-bipyridyl (191) was treated with a large excess of bromine, (c.f. very similar multiple absorptions in the 350-400 nm region in the ultra-violet). Vacuum sublimation of the reaction mixture afforded a yellow solid having identical properties to that eluted as the first band by column chromatography.

Mass spectral and ultra-violet examination of the second yellow band eluted with benzene-chloroform (1:1) showed that 2',6,6'-tri-p-bromoanilino-5,5'-di-phenyl-2,3'-bipyridyl (207) was also formed in the reaction, and examination of the polar fractions (eluted with methanol) revealed that 2,6-di-(p-bromo-phenylimino)-3-phenylpiperidine (208), the originally required product, was also formed.

(b) Condensation of 2,6-di-imino-3-phenylpiperidine (144) and p-bromoaniline

In a further attempt to prepare the tri-bromo-2,3'-bipyridyl (207), via 2,6-di-(p-bromophenylimino)-3-phenylpiperidine (208), 2,6-di-imino-3-phenylpiperidine (144) was heated with two molar proportions of p-bromoaniline at temperatures between 100° and 200°. When evolution of ammonia had ceased t.l.c. showed several products had been formed. Crystallization from ethanol failed to afford a pure compound, a brown solid being obtained which t.l.c. again showed to be a mixture.
(iv) Attempted reactions at the free β-position of the 2,3'-bipyridyl (191)

(a) Nitrous acid

The 2,3'-bipyridyl (191) was treated with nitrous acid in chloroform-ethanol (1:1) at 5° in an effort to obtain a 3-nitroso derivative as given by 2,6-diaminopyridine. T.l.c. showed that at least five products had been formed but none could be isolated pure and none apparently had the unhindered 2,3'-bipyridyl structure because the maximum wavelength absorption of any was 280 nm. Nitrosation on the nitrogen atoms of the anilino groups had probably occurred, and this would buckle the molecule, reducing its conjugation.
(b) Phenyl diazonium chloride

Treatment of the 2,3'-bipyridyl (191) with phenyl diazonium chloride at 5°, followed by five minutes at 70°, afforded an intense green colour, but the bipyridyl was returned in 90% yield and no product could be isolated from the reaction mixture apart from a trace of phenol.

(v) Preparation of blocked 3-phenyl-2,6-diphenylimino-piperidines

(a) Introduction

Further evidence that the product obtained on dehydrogenation of 3-phenyl-2,6-diphenyliminopiperidine (152) was a 2,3'-bipyridyl (191) was sought from dehydrogenation experiments on 3-phenyl-2,6-diphenyliminopiperidines having a methyl substituent in the 4- or the 5- position. Provided analogous dehydrogenations took place, the 4-substituted piperidine (209) could only form a 2,3'-bipyridyl, whilst the 3-substituted piperidine (210) might give a 2,4'-bipyridyl.

![Chemical structures](209) ![Chemical structures](210)
(b) Preparation of 3-methyl-5-phenyl-2,6-diphenyliminopiperidine (210)

Phenylacetonitrile and methacrylonitrile were condensed together in refluxing nitrobenzene with potassium cyanide as catalyst affording 2-methyl-4-phenylglutaronitrile (211).

\[
\begin{align*}
\text{Ph} & \text{CH}_2 + \text{CH}_2\text{C}=\text{CCH}_3 & \rightarrow & \text{Ph} & \text{CHCHCH}_3
\end{align*}
\]

(211)

Its mass spectrum exhibited a parent ion at \( m/\varepsilon 184 \) and a cracking pattern, discussed later (p.232), which uniquely identified the compound. The p.m.r. spectrum consisted of a five proton singlet at \( \gamma 2.61 \) arising from the aromatic protons, a single proton double doublet \( (J_{1,3} 9\text{Hz.}, J_{1,4} 8\text{Hz.}) \) centred at \( \gamma 5.97 \) from \( H^1 \), a single proton double doublet of quartets \( (J_{2-5,6,7} 7\text{Hz.}, J_{2-3} 8\text{Hz.}, J_{2-4} 9\text{Hz.}) \) at \( \gamma 7.03 \) arising from \( H^2 \), a two proton doublet of double doublets \( (J_{2-4} 9\text{Hz.}, J_{2-3} 8\text{Hz.}, J_{1-3} 9\text{Hz.}, J_{1-4} 8\text{Hz.}) \)

\[
\begin{align*}
\text{C} & \text{H}_2 & \text{C} & \text{C} & \text{H}_2 & \text{CH}_3 \\
\text{Ph} & \text{CN} & \text{CN} & \text{CN} & \text{CN} & \text{CN}
\end{align*}
\]

(211)
at $\tau \ 7.85$ from $H^{3,4}$, and a doublet ($J_{2-5,6,7}$ $7\text{Hz.}$) of three proton intensity at $\tau 8.67$ due to $H^{5,6,7}$. The complexity of the spectrum is due to the two asymmetric centres in the molecule.

2-Methyl-4-phenylglutaronitrile (211) and aniline hydrochloride were condensed together thermally at 280°. The yellow solid obtained after neutralization was examined by t.l.c. and found to contain one major product and several impurities. Column chromatography, eluting with benzene and collecting the first major band, afforded 3-methyl-5-phenyl-2,6-diphenyliminopiperidine (210). Crystallization was found to be impossible, but a solid, which analysed correctly, was obtained by preparative t.l.c. and elution with methanol.

\[
\begin{align*}
\text{Ph} & \quad \text{CH}_3 \\
\text{CN} & \quad \text{CN} \\
+ 2\times \text{NH}_3 \text{Cl} & \quad \Theta \\
\text{Ph} & \quad \Theta \\
\text{Condensation} & \quad (211) \\
\text{Ph} & \quad \text{CH}_3 \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
+ \text{NH}_4 \text{Cl} & \quad (210) \\
+ \text{NaCl} & \quad + \text{H}_2\text{O}
\end{align*}
\]

The i.r. spectrum showed the lines expected for a diphenyliminopiperidine, viz. 335, 320, 164, 163, 159.5, 157, 153.5, 152, 151, 150, 149, 145, and 142 mm$^{-1}$. The u.v. spectrum was similar to that of 3-phenyl-2,6-diphenyliminopiperidine (152) having absorptions at 228, 286, and 298 nm.
The lines in the p.m.r. spectrum were broadened, but this seems typical of diphenylimino-piperidines. The intensity corresponded to sixteen protons in the \( \tau 2.30-4.00 \) region, consisting of fifteen aromatic protons and one exchangeable proton (NH), one proton \( (H^1) \) at \( \tau 6.10 \), three protons at \( \tau 7.80 \) (\( H^2,3,4 \)), and three protons (\( H^5,6,7 \)) at \( \tau 8.80 \).

The positions of the signals compare closely with those from the precursor, 2-methyl-4-phenylglutaronitrile (211), and the broadening is probably due to mixtures of isomers or to conformational motion.

The mass spectrum revealed a parent ion \( m/e 353 \), as required, and a fragmentation pattern which confirms the structure, and will be discussed in detail later (p.237).
(c) Attempted dehydrogenation of 3-methyl-5-phenyl-2,6-diphenyliminopiperidine (210)

3-Methyl-5-phenyl-2,6-diphenyliminopiperidine (210) was treated under various dehydrogenating conditions with nitrobenzene, chloranil, and 3,3',5,5'-tetrachloro-4,4'-diphenoquinone. In each case either an excellent yield of starting material was recovered or more polar derivatives were formed, as shown by t.l.c.. Thus the hydrolysis products 3-methyl-2-(or 6-)-oxo-5-phenyl-6-(or 2-)-phenyliminopiperidine (212), and 3-methyl-2,6-dioxo-5-phenylpiperidine (3-methyl-5-phenyl-glutarimide) (213) were detected mass spectrometrically (parent ions at m/z 278 and 263 respectively).

\[
\begin{align*}
\text{(212)} & \\
\text{where} & \\
a) \ X = N-Ph, \ Y = O & \\
b) \ X = O, \ Y = N-Ph
\end{align*}
\]

No dehydrogenation product having either a pyridine or a bipyridyl structure was isolated.

Catalytic dehydrogenation using palladium or
rhodium on alumina might have afforded the pyridine, as might bromination-dehydrobromination using bromine in chloroform under mild conditions.

(d) Preparation of 4-methyl-3-phenyl-2,6-diphenyliminopiperidine. (209)

Phenylacetonitrile and crotononitrile were condensed together in a modified Michael reaction at 0° using sodium ethoxide as catalyst to give 3-methyl-2-phenylglutaronitrile (214).

\[ \text{Ph} \quad \text{CH}_2 \quad \text{CH} \quad \text{CN} \quad + \quad \text{CH}_3 \quad \text{CH} \quad \text{CN} \quad \rightarrow \quad \text{Ph} \quad \text{CH}_3 \quad \text{CH} \quad \text{CN} \quad \text{CN} \]

(214)

Its p.m.r. spectrum was complicated by the molecule having two asymmetric centres. Five aromatic protons resonate at \( \tau 2.64 \) (multiplet), a single proton at \( \tau 6.18 \) (multiplet) (\( H^1 \)), three protons at \( \tau 7.60 \) (multiplet) (\( H^{2,3,4} \)), and three protons at \( \tau 8.76 \) (multiplet) (\( H^{5,6,7} \)).
The mass spectrum confirmed the structure (parent ion $m/z$ 184) and will be discussed in detail later (p.233).

3-Methyl-2-phenylglutaronitrile (214) and aniline hydrochloride were heated together and the product subjected to preparative t.l.c. and elution with methanol. A pinkish solid was obtained. The mass and p.m.r. spectra showed it to be a mixture, mainly of 4-methyl-3-phenyl-2,6-diphenyliminopiperidine (209) with a hydrolysis product. Separation was not effected by crystallizations from ethanol, ethanol-water, or iso-propanol. However, treatment of the product with picric acid in ethanol, followed by evaporation, crystallization, and column chromatography, gave excellent separation of the two products, whilst picric acid remained on the column. (1) The less-polar component was identified as 4-methyl-3-phenyl-2,6-diphenyliminopiperidine (209) by its elemental analysis, i.r. (338, 325, 164, 159.5, 158.5, 152.5, 152, 150, 149, 144.5, and 142 mm$^{-1}$.) and u.v. (287, 299 nm) spectra.

The p.m.r. spectrum was typically broadened and showed a sixteen proton multiplet at $\tau$ 2.40-3.60 (fifteen aromatic and one NH proton), a single proton signal at $\tau$ 6.28 (H$^1$), and a signal from three protons at $\tau$ 7.70 (H$^2,3,4$), and three protons at $\tau$ 8.98 (H$^5,6,7$).
The mass spectrum confirmed the structure, there being a parent ion at $m/e$ 353. Detailed discussion is given later (p. 237).

(2) The more-polar component was identified as the hydrolysis product 4-methyl-6-oxo-3-phenyl-2-phenyliminopiperidine (215) by its elemental analysis, u.v. spectrum ($224, 280$ nm), and mass spectrum (parent ion $m/e$ 278) (discussed in detail on p. 238).
Dehydrogenation of 4-methyl-3-phenyl-2,6-diphenyliminopiperidine (209)

Treatment of 4-methyl-3-phenyl-2,6-diphenyliminopiperidine (209) with nitrobenzene in refluxing o-dichlorobenzene followed by preparative t.l.c., eluting with benzene-ethyl acetate (19:1), revealed several products as well as a substantial recovery of the diphenyliminopiperidine (209). The second yellow fraction afforded a very small amount of solid which, on examination by u.v. (230*, 263, 287*, 337 nm) and mass-spectroscopy (parent ion m/e 351) is tentatively assigned the structure 2,6-dianilino-4-methyl-3-phenylpyridine (216). Its retention factor (R_f 0.62) was close to that of 2,6-dianilinopyridine (236) (R_f 0.60) in benzene-ethyl acetate (19:1).

Examination of the least polar fraction by u.v. spectroscopy suggested that it was a bipyridyl.
Certainly it had a high degree of conjugation ($\lambda_{\text{max}} 230^*, 260^*, 302, 376$ nm). The hypsochromic shift relative to the $2,3'$-bipyridyl (191) resembled that for the heptabromide (199a) and could be due to the two 4-methyl substituents reducing the planarity of the molecule somewhat. The mass spectrum revealed a strong parent ion at $m/e 609$ corresponding to $2',6,6'$-trianilino-4,4'-dimethyl-5,5'-diphenyl-2,3'-bipyridyl (217). The compound was further characterized by its i.r. spectrum ($345, 160, 158, 152, 151, 144$, and $141$ mm$^{-1}$), and retention factor ($R_f 0.91$) in benzene-ethyl acetate (19:1), the latter being very close to that for the $2,3'$-bipyridyl ($R_f 0.90$) in the same eluant. That the product failed to crystallize was probably due to its being a mixture of isomers, arising from restricted rotation in the molecule. The methyl group at the crowded 4'-position adjacent to aromatic moieties in the 3'- and 5'-positions of the bipyridyl is responsible for the
restricted rotation, as models can clearly show.

Thus 4-methyl-3-phenyl-2,6-diphenyliminopiperidine (209) has been successfully dehydrogenated to a bipyridyl while 3-methyl-5-phenyl-2,6-diphenyliminopiperidine (210) has not. This supports the other evidence that the dehydrogenation of 3-phenyl-2,6-diphenyliminopiperidine (152) gives 2',6,6'-trianilino-5,5'-diphenyl-2,3'-bipyridyl (191).
d) Dehydrogenation of 3-phenyl-2,6-diphenyliminopiperidine (152) with quinones

(i) Chloranil

To find whether reactive quinones would dehydrogenate 3-phenyl-2,6-diphenyliminopiperidine (152), chloranil (218) was employed in n-pentanol at 150°, under nitrogen. The 2,3'-bipyridyl (191) and tetrachloroquinol (219) were isolated from the dark reaction mixture by column chromatography.

When 3-phenyl-2,6-diphenyliminopiperidine (152) was treated with chloranil in cold dry benzene an immediate reaction took place and the solution turned green. No dehydrogenation products could be readily isolated however. Refluxing for two hrs. turned the solution purple, and t.l.c. then revealed several products, 3-phenyl-2,6-diphenyliminopiperidine (152), tetrachloroquinol (219), and a small amount of the 2,3'-bipyridyl (191) being isolated pure.

\[
\begin{align*}
\text{(152)} & \quad + \quad \text{(218)} & \quad \rightarrow & \quad \text{Ph} & \quad \text{N} & \quad \text{Ph} \\
\text{Ph} & \quad \text{N} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{N} & \quad \text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{(191)} & \quad + & \quad \text{PhNH}_{2}
\end{align*}
\]

\[
\begin{align*}
\text{(219)}
\end{align*}
\]
(ii) 3,3',5,5'-Tetrachloro-4,4'-diphenoquinone

3,3',5,5'-Tetrachloro-4,4'-diphenoquinone (220) is reported to be a quinone of moderate dehydrogenating ability, and to be sterically favourable to the formation of dehydrogenation intermediates. It was prepared from p,p'-biphenol (221) by chlorination, and then oxidation of the 3,3',5,5'-tetrachloro-4,4'-biphenol (222) with fuming nitric acid.

\[
\text{OH} \\
\text{Cl}_2 \\
\text{glacial H\textsubscript{2}OAc} \\
\text{OH} \\
\]

\[
\text{OH} \\
\text{Cl}_2 \\
\text{fuming H\textsubscript{2}NO\textsubscript{3}} \\
\text{glacial H\textsubscript{2}OAc} \\
\text{O} \\
\text{Cl}_2
\]

When 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220) was employed in benzene under dry, anerobic conditions a trace of 2,3'-bipyridyl (191) was obtained, but the major product was a brownish solid. This was best purified by reprecipitation with water from ethanol or with petroleum ether (60-80°) from benzene. When subjected to column chromatography (eluting with solvents of varying polarity between petroleum ether and methanol), t.l.c., and preparative t.l.c. (again eluting with a wide range of solvents), it appeared to be
resolved into three components, viz. 3-phenyl-2,6-
diphenyliminopiperidine (152), 3,3',5,5'-tetrachloro-
4,4'-biphenol (222), and the 2,3'-bipyridyl (191) in the approximate relative proportions 1:10:4 respectively. However the ultra-violet spectrum of the brownish solid was not exactly a summation spectrum of these components, there being weak absorption at 340 nm and no absorption in the 400 nm region (see Fig.1). Moreover the p.m.r. spectrum did not agree with the brownish solid being a mixture containing the starting piperidine (152). This was because there were no signals in the \( \gamma 5.80-6.00 \) region as from the methine proton at C-3 in (152). In each of the 3-phenyl-2,6-diphenyliminopiperidines (152), (209), and (210) examined in this work, this methine proton has always appeared within this range. The spectrum in deuterochloroform was otherwise similar to that of the starting material (152) in that it showed the typical broadening of the signals. There were signals from aromatic protons at \( \gamma 2.02-3.22 \), signals at \( \gamma 3.70-4.30 \) from exchangeable protons (as shown by disappearance when trifluoroacetic acid was added) and non-aromatic protons at \( \gamma 6.60-7.85 \). The ratios of the aromatic to non-aromatic to exchangeable protons were 21:4:2. The spectrum can be interpreted on the basis of the 3-aryloxypiperidine structure (223) (theoretical ratios 19:4:2) if
**Fig. 1**

Key:
- the reaction product (223)
- the 2,3'-bipyridyl (191)
- the biphenyl (222)
- the 2,6-diphenyliminopiperidine (152)
- the quinone (226)
the aromatic signal is assumed to be enhanced by
a small amount of aromatic impurity.

\[
\begin{align*}
\text{CDCl}_3 & \quad \text{CDCl}_3 - \text{CF}_3 \text{CO}_2 \text{H} \\
\text{Integral Assignment} & \quad \text{Integral Assignment} \\
\tau 2.02-3.22 & \quad 2.00-3.20 \\
\text{21H} & \quad 21H \\
\text{19H Aromatic} & \quad \text{19H Aromatic} \\
\tau 3.70-4.30 & \quad 2H \\
\text{Exchangeable} & \quad \text{Exchangeable} \\
\tau 6.60-7.35 & \quad 6.25-7.38 \\
\text{4H} & \quad 4H \\
\end{align*}
\]

3-(3',3',5,5'-tetrachloro-4,4'-biphenyloxy)-3-phenyl-2,6-diphenyl-
iminopiperidine.

(223)

The i.r. and u.v. spectra would naturally be very
similar to the sum of the spectra from 3-phenyl-
-2,6-diphenyliminopiperidine (152) and 3,3',5,5'-tetrachloro-4,4'-biphenol (222). In the u.v., a low
intensity increase in the longest wavelength
absorption could be expected, due to the 3-aryloxy
substituent, as observed.

i.r. (152), \( \nu_{\text{max}} \): 332, 320, 164, 161, 159.5, 157, 151.5, 150,
148.5, 144.5, 141 mm\(^{-1}\).

i.r. (222), \( \nu_{\text{max}} \): 368, 358, 338, 160.5, 156, 148, 142, 133 mm\(^{-1}\).

i.r. (223), \( \nu_{\text{max}} \): 355, 345, 163.5, 159, 157.5, 154.5, 151.5, 150,
148.5, 144.5, 141 mm\(^{-1}\).

u.v. (152), \( \lambda_{\text{max}} \): 226, 287, 300 nm.

u.v. (222), \( \lambda_{\text{max}} \): 217, 267, 288* nm.

u.v. (223), \( \lambda_{\text{max}} \): 223, 279, 289*, 340* nm.
Mass spectroscopy provides some further evidence. With an inlet temperature of 160° at both 70eV and 15eV accelerating potentials, no molecular ion corresponding to the proposed 3-aryl-oxypiperidine (223) was detected. Instead there was a very stable ion at $m/e$ 337 corresponding to 2,6-dianilino-3-phenylpyridine (188) and a series of peaks from $m/e$ 322 to 328, having the correct ratios of isotopic abundance for a molecule containing four chlorine atoms, corresponding to 3,3',5,5'-tetrachloro-4,4'-biphenol (222). From the mass-spectrum alone it might have been thought, in the first instance, that the product was a mixture of these two compounds. However, such a mixture would not have given the observed p.m.r., u.v., and i.r., spectra. Moreover the product behaved as a single substance on vacuum sublimation. It appears therefore that the compound is disrupted in the electron beam to yield the pyridine (188) and the quinol (222).

At an early stage it was considered that the brownish compound might be a charge-transfer complex, akin to a quinhydrone. It seemed that it might be derived from 3-phenyl-2,6-diphenyliminopiperidine (152) and the quinone (220) or from the products of hydrogen-transfer, 2,6-dianilino-3-phenylpyridine (188) and the quinol (222). The idea was subsequently discounted on the i.r. and u.v. evidence.
Nevertheless, the idea gave rise to experimental work which does seem worth recording: this was a brief study of the mass spectrometric behaviour of a simple charge-transfer complex, quinhydrone (224).

\[
\begin{align*}
\text{(225)} & \quad \text{(226)} & \quad \text{(224)} \\
\end{align*}
\]

The mass spectrum exhibited only a very small parent ion at \( m/\varepsilon \) 218 but strong peaks at \( m/\varepsilon \) 108 and 110. These last two peaks correspond to quinone (225) and quinol (hydroquinone) (226), respectively. When the spectrum is run ten minutes after insertion of the sample on the probe, at 100\(^\circ\), a single parent ion at \( m/\varepsilon \) 110 and a fragmentation pattern corresponding to the hydroquinone (226) alone are observed. This is due to quinone being reduced, probably by the water vapour present in the sample and in the air, following the thermal degradation of quinhydrone (224) into quinone and hydroquinone.

The product obtained from the reaction of 3-phenyl-2,6-diphenyliminopiperidine (152) and 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220) behaved
quite differently on electron bombardment and prolonged heating in the mass spectrometer. At an inlet temperature of 70° the spectrum obtained immediately was that of the biphenol (222) and the pyridine (188) in the ratio of 100:1 respectively. On slowly increasing the temperature of the probe to 120° during 50 minutes a range of spectra were obtained in which the ratio of the ions due to the biphenol and the pyridine varied in intensity. At 120° the ratio was 18:100 in favour of the pyridine.

<table>
<thead>
<tr>
<th>Inlet temp</th>
<th>Time lapse before</th>
<th>Spectrum obtained, relative running spectrum intensity of major fragments (containing $^{35}$Cl at m/e 322, 337, 397</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>0 min.</td>
<td>100 : 1 : 0</td>
</tr>
<tr>
<td>80</td>
<td>3 &quot;</td>
<td>100 : 9 : 0.08</td>
</tr>
<tr>
<td>85</td>
<td>5 &quot;</td>
<td>100 : 21 : 0.2</td>
</tr>
<tr>
<td>95</td>
<td>8 &quot;</td>
<td>100 : 37 : 0.4</td>
</tr>
<tr>
<td>100</td>
<td>12 &quot;</td>
<td>100 : 45 : 0.7</td>
</tr>
<tr>
<td>105</td>
<td>15 &quot;</td>
<td>100 : 60 : 1.1</td>
</tr>
<tr>
<td>110</td>
<td>20 &quot;</td>
<td>100 : 97 : 2.0</td>
</tr>
<tr>
<td>120</td>
<td>50 &quot;</td>
<td>18 : 100 : 10</td>
</tr>
</tbody>
</table>

Now the 3-aryloxy-piperidine structure (223) would fit these facts very well if one of two possibilities occurred on electron bombardment. The first would be a thermal rearrangement, producing the pyridine (188) and the biphenol (222), the latter being ionized first due to its relatively
higher volatility at lower temperatures, and as the temperature is raised the volatility of the pyridine increases and it too is then ionized. The second possibility is that fragmentation into the pyridine (188) and the biphenol (222) may occur on electron bombardment such that the biphenol entity is formed preferentially as a positive ion and thus gives rise to the relatively stronger signals, whilst the pyridine entity is produced mainly as a neutral species. As the temperature increases the latter is volatilized progressively and ionized and the pyridine spectrum appears. At the same time there is a gradual decline in the intensity of the biphenol spectrum and appearance and relative increase of a new series of tetra-chloro-containing peaks at $m/e$ 397 to 403, corresponding to 4-anilino-4'-hydroxy-3,3',5,5'-tetrachlorobiphenyl (227). This may be formed from the biphenol by attack of aniline or of an anilino anion eliminated in the main reaction.

\[ \text{Reaction:} \]

\[
\begin{align*}
\text{HO-Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{OH} \quad \text{Cl} \\
\text{Cl} & \quad \text{NH} \quad \text{Ph} \\
\text{Cl} & \quad \text{HO} \\
\end{align*}
\]

(222)  (227)
At an inlet temperature of 260° the mass spectrum of the product from the piperidine (152) and the quinone (220) contains molecular ions corresponding not only to the pyridine (188) and the quinol (222), but also to the 2,3'-bipyridyl (191). The latter may be a small amount of product carried over from the preparation through the various purification stages, or it may be formed by an essentially thermal process at the high temperature of the mass-spectrometer source.

In any event the most probable structure for the product formed in the reaction between 3-phenyl-2,6-diphenyliminopiperidine (152) and 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220) is the 3-aryloxypiperidine (223).

e) Mechanism for the formation of the 3-aryloxypiperidine (223) from 3-phenyl-2,6-diphenyliminopiperidine (152) and 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220).

The necessity of dry conditions in benzene suggests a radical mechanism for this reaction. There may then be combination between the radicals to give (223) or the quinone radical may scavenge a further H⁺ from the substrate radical (228) to give, after prototropic rearrangement, the quinol (222) and the pyridine (188).
Heat in dry benzene

(152) + (220) → (223)
f) **Mechanism for the formation of the 2,3'-bi-pyridyl** (191) **from** (152) **with nitrobenzene**

This reaction occurs only at elevated temperature and would appear to be essentially the condensation of a Schiff base with an active methylene compound.
The compound (152) is probably basic enough to catalyse the condensation. After this, one can propose that dehydrogenation occurs, either thermally or by hydrogen transfer. A partially reduced ter- or quater-phenyl would dehydrogenate thermally, very readily, and the above condensation product (229) is analogous to these. If the dehydrogenation is by transfer, then one of the accessible allylic hydrogens will be picked off with its bonding pair by the oxidant, e.g. nitrobenzene or a quinone.

Repetition of the oxidation process with (230) will lead to (231) which by prototropic rearrangement yields (191):-
(i) **Proof for the mechanism**

In an effort to help establish a mechanism it was considered worthwhile investigating a 2,6-dianilino pyridine under dehydrogenating and other conditions to see if any 2,3'-bipyridyl could be obtained.

The $\beta$-position in a 2,6-dianilinopyridine (232) should be activated towards electrophilic attack. It might therefore act as a nucleophile and displace
aniline from a further molecule of 2,6-dianilino-pyridine at elevated temperature:

However, 2,6-dianilino-3-phenylpyridine (188) was not available from interaction of aniline with 2,6-dichloro-3-phenylpyridine (234), the final product being 2-anilino-5-phenylpyridine (235).
2,6-Dianilinopyridine (236) itself was nevertheless available from 2,6-dichloropyridine (237) by heating with aniline in the presence of copper sulphate.

\[
\begin{align*}
\text{C} & \text{C} \\
\text{PhNH}_2 & \Rightarrow \\
\text{HN} & \text{NH} \\
\text{Ph} & \text{Ph} \\
\end{align*}
\]

(237) \quad \text{PhNH}_2 \quad (236) \quad \text{Ph}

Various attempts were made to produce a 2,3'-bipyridyl (233, R=H) from 2,6-dianilinopyridine (236) including treatment under the successful dehydrogenation conditions employed for 3-phenyl-2,6-diphenyliminopiperidine (132), viz. refluxing with nitrobenzene in o-dichlorobenzene, with chloranil (218) in benzene and in n-pentanol, with 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220) in benzene, ethanol, and dioxan, heating at 215° in 1,2,4-trichlorobenzene under nitrogen, and dry distillation. In all of the experiments 2,6-dianilinopyridine (236) was recovered in yields not less than 80%. No other products, apart from a trace of aniline, were identified, although t.l.c. showed small amounts of other substances in the reaction mixture. T.l.c., u.v. and mass spectroscopic results definitely show that no 2,3'-bipyridyl (233, R=H) was formed in the reaction.

It is concluded, therefore, that either the
dehydrogenation-condensation does not proceed via a 2,6-dianilinopyridine intermediate, or that the β-phenyl group makes a very significant mechanistic difference.

g) Bromination - dehydrobromination of 3-phenyl-2,6-diphenyliminopiperidine (152).

Although dehydrogenation of 3-phenyl-2,6-diphenyliminopiperidine (152) had afforded an aromatic product, the original search for a method of preparing 2,6-dianilino-3-phenylpyridine (188) from the piperidine still continued.

Bromination followed by dehydrobromination was considered to be a reasonable alternative to dehydrogenation. It appeared that (152) should readily undergo free radical bromination having two allylic β-positions in the piperidine ring. One position is also benzylic, but the double activation may well be compensated here by steric hindrance.

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{H} & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{H} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

\[(152)\]
However, because the product from benzylic bromination would have two large substituents, viz. a phenyl group and a bromine atom, on one carbon atom, dehydrobromination should occur readily to relieve the steric compression and yield the aromatic product, 2,6-dianilino-3-phenylpyridine (188).

Bromination was carried out using equimolar quantities of 3-phenyl-2,6-diphenyliminopiperidine (152) and N-bromosuccinimide (238) in boiling carbon tetrachloride, using azobisisobutyronitrile (239) as the free radical initiator. Five products were visible when the reaction mixture, after removal of precipitated succinimide, was examined by t.l.c. Preparative t.l.c., using benzene, carbon tetrachloride, ethyl acetate (5:1:1) as eluant, separated the three major products extremely well. The least polar component had \( \lambda_{\text{max}} \) 260, 356 nm and was evidently a monobrominated 2,6-dianilino-3-phenylpyridine (240 or 241) from its analysis and mass spectrum (for parent ion containing \( \text{mass} = 415 \) (discussed in detail on p. 239).
It was contaminated with a small amount of a dibrominated 2,6-dianilino-3-phenylpyridine as seen from the mass spectrum. One of these two bromine atoms must be on an anilino moiety, and the lack of any tri-brominated product suggests that the bromine atoms are substituents on the two anilino moieties. The monobrominated product is thus probably (240) and the dibrominated product (242).
The second fraction from the preparative t.l.c. was shown to be 2,6-dianilino-3-phenylpyridine (188), by its analysis, i.r. spectrum (340, 325, 160, 158, 154, 150, 146, 130, 115 mm⁻¹), u.v. spectrum (273, 290, 349 nm), p.m.r. spectrum (complex multiplet 72.00-3.20), and mass spectrum (parent ion m 337, and doubly charged ion 2e 168.5) (discussed in detail on p.239).

\[
\begin{array}{c}
\text{Ph} \\
\text{N} \quad \text{N} \\
\text{H} \\
\text{Ph} \\
\end{array}
\quad \text{O} \quad \text{N} \quad \text{N} \\
\text{Br} \\
\begin{array}{c}
\text{Ph} \\
\text{N} \quad \text{N} \\
\text{H} \\
\text{Ph} \\
\end{array}
\]

The third fraction was a mono-brominated 3-phenyl-2,6-diphenyliminopiperidine as shown by the mass spectrum (parent ion m 417, losses of Br⁻ and HBr°) (discussed in detail on p.238). The u.v. absorption (226, 320 nm) was at an unexpectedly long wavelength and it is possible that dehydrobromination was slowly occurring and a summation spectrum was being observed.
h) Mechanisms for the bromination and dehydrobromination reactions involving 3-phenyl-2,6-diphenyliminopiperidine (152) and N-bromosuccinimide (238)

The bromination probably takes place as follows:

\[
\begin{align*}
\text{Initiation:} & \\
(CH_3)_2-C-N=N-C-(CH_3)_2 & \xrightarrow{\text{heat}} 2(CH_3)_2-C^* + N_2 \\
\text{(239)} & \\
\text{Propagation:} & \\
\text{Br} & \\
\text{(238)} & \\
& (243)
\end{align*}
\]
Termination involves combination of radicals involved in the propagation steps.

No 2,3'-bipyridyl (191) was formed in the reaction, indicating an entirely different course for the aromatization from that using a quinone or nitrobenzene, as has been suggested above. Thermal condensation obviously does not occur during the bromination reaction which takes place quickly under mild conditions, and in dilute solution.

The dehydrobromination would be expected to occur readily due to the active allylic hydrogen atoms and the aromatization of the product.

\[
\begin{align*}
\text{Br} & \quad \text{Ph} \\
\text{Ph} & \quad \text{N} \quad \text{H} \quad \text{Ph} \\
\text{N} & \quad \text{Ph} \\
\text{N} & \quad \text{Ph} \\
\end{align*}
\]

(243)

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{Ph} & \quad \text{N} \\
\text{H} & \quad \text{H} \quad \text{H} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

(188)
Further bromination can then take place, probably affording the p-bromoanilino- and di-p-bromoanilino- substituted pyridines (240) and (242).

\[ \text{Ph} \quad \text{Ph} \quad \text{Ph} \]

(188) \quad (240) \quad (242)

Dehydrogenation of 3-phenyl-2,6-diphenylimino-piperidine (152) by aerial oxidation

Following the successful preparation of 2,6-dianilino-3-phenylpyridine (188) by bromination-dehydrobromination of 3-phenyl-2,6-diphenyliminopiperidine (152) under mild conditions, and having found the pyridine to be quite stable, some further efforts were made to prepare it by dehydrogenation of the piperidine. It had been noted that solutions of 3-phenyl-2,6-diphenyliminopiperidine in chloroform and in ethanol decomposed on standing for several weeks, affording several products, two of which were now identified, one as a hydrolysis and the other as a dehydrogenation product. They were found to be
6-oxo-3-phenyl-2-phenylimminopiperidine (244), and 2,6-dianilino-3-phenylpyridine (188) respectively from their ultra-violet and mass spectra.

\[
\text{Ph} \quad \text{N} \\
\text{H} \\
\text{Ph}
\]

(244)

\[
\text{Ph} \quad \text{HN} \\
\text{N} \\
\text{Ph} \quad \text{Ph}
\]

(188)

u.v.(244) \( \lambda_{\text{max}} 231, 278 \text{ nm}, \) mass spectrum, parent \( m^e 264 \).

u.v.(188) \( \lambda_{\text{max}} 273, 290, 349 \text{ nm}, \) mass spectrum, parent \( m^e 337 \).

j) **Attempted dehydrogenation of 3-phenyl-2,6-di-phenyliminopiperidine (152) with sulphur**

Heating the piperidine (152) with flowers of sulphur for 1 hr. at 180° produced some hydrogen sulphide, but no new aromatic product could be detected by t.l.c. or u.v. spectroscopy.

k) **Dehydrogenation of 3-phenyl-2,6-diphenyliminopiperidine (152) with sulphur and 10% rhodium on charcoal**

When the piperidine (152) was heated with flowers of sulphur and a 10% rhodium on charcoal
catalyst at 180° for 1 hour, a small amount of 2,6-dianilino-3-phenylpyridine (188) as well as some 2,3'-bipyridyl (191) was extracted from the reaction mixture. The former (188) was readily identified by its spectral properties.

Thus the mass spectrum exhibited an intense molecular ion at \( m/e 337 \) and fragments due to loss of Ph', PhNH\(^2\), and PhNH'. Its i.r. and u.v. spectra were diagnostic of a substituted pyridine (\( \nu_{\text{max}} 340, 325, 160, 158, 154, 150, 146, 130, 115 \text{ mm}^{-1} \)), (\( \lambda_{\text{max}} 273, 290, 349 \text{ nm} \)).

1) **Dehydrogenation of 3-phenyl-2,6-diphenyliminopiperidine** (152) with **10% rhodium on charcoal**

Refluxing 3-phenyl-2,6-diphenyliminopiperidine (152) with 10% rhodium on charcoal in \( \alpha \)-methyl naphthalene for five minutes whilst blowing a stream of nitrogen through the liquid yielded one major product identified by its u.v. (273, 290, 349 nm.), mass spectrum (parent ion \( m/e 337 \)), and its retention
factor (Rf 0.62, in benzene-ethyl acetate (19:1)), as 2,6-dianilino-3-phenylpyridine (188).

A minor component was tentatively identified by its mass spectrum alone as 3-cyclohexyl-2,6-di-
cyclohexylaminopiperidine (245) (parent, \( m/z \) 361, fragments due to loss of H, 
\[
\text{NH-} \quad \text{NH}_2
\]

Obviously some 3-phenyl-2,6-diphenylimino-
piperidine (152) has been successfully dehydrogenated to the pyridine (188) while a small proportion has been simultaneously hydrogenated under the influence of the rhodium catalyst.

![Chemical Structures](image)

A trace of the 2,3'-bipyridyl (191) was produced in the reaction. The proportion of 2,3'-bipyridyl produced was increased somewhat by refluxing the reactants for half an hour.

The reaction involves simultaneous removal of
two cis-hydrogen atoms from the piperidine (152), on the surface of the rhodium catalyst, and this reaction presumably takes place at a faster rate than the thermal condensation of the piperidine (152) to the 2,3'-bipyridyl (191).
(C) ATTEMPTED DEHYDROGENATION OF 2,6-DI-IMINO-3-PHENYL-PIPERIDINE (144).

a) Preparation of the compound (144)

In order to investigate whether a similar, though less stable, system to 3-phenyl-2,6-diphenyl-iminopiperidine (152) could be dehydrogenated, 2,6-di-imino-3-phenylpiperidine (144) has been prepared by two methods.

(i) A Pinner type addition of ammonia to α-phenylglutaronitrile, using liquid ammonia in an autoclave at 80°, under autogeneous pressure for 18 hrs., afforded the di-iminopiperidine (144) in poor yield.

(ii) Treatment of α-phenylglutaronitrile with sodamide in formamide at room temperature gave, after 18 hrs. an excellent yield of the di-iminopiperidine (144).

Its i.r. spectrum, \( \nu \) max 320 (NH), 167 (C=\( \equiv \)), 160 (aromatic), 154 mm\(^{-1}\), and u.v. spectrum, \( \lambda \) max 253 nm, were as expected.
The imidine (144) is very poorly soluble in deutereochloroform, and most other solvents at room temperature, and the p.m.r. spectrum observed is diffuse. In trifluoroacetic acid, however, the p.m.r. spectrum is sharp and exhibits a line from five aromatic protons at 2.50, a single proton triplet (H$^1$) at 5.51, a two proton signal at 6.50 (H$^4$,5) which approximates to a triplet, and a two proton signal 7.32 (H$^{2,3}$) which approximates to a quartet. The mass spectrum confirmed the structure (parent m/z 187) (and will be discussed on p.235).

b) Attempted dehydrogenation

Treatment of 2,6-di-imino-3-phenylpiperidine (144) with nitrobenzene in boiling o-dichlorobenzene (under the conditions that dehydrogenated 3-phenyl-2,6-di-phenyliminopiperidine (152) to the 2,3'-bipyridyl(191)) afforded mainly the starting materials and α-phenyl-glutaronitrile together with a small amount of a semi-solid. Column chromatography of the last afforded traces of solid having absorption in the
u.v. characteristic of an aromatic compound ($\lambda_{\text{max}}$ 336 nm in CHCl$_3$).

The experiment was repeated under less drastic conditions using n-butanol as solvent, and a very small amount of the same material was isolated. This product was never obtained in sufficient amount to characterize. Its u.v. absorption and swift elution on alumina with benzene strongly suggests that the compound was aromatic and thus a dehydrogenation product.

The very poor solubility of the imidine in most solvents prevented an effective study of its behaviour under dehydrogenating conditions.
CHAPTER 3

SYNTHESSES OF 3-ALKYL SUBSTITUTED
2,6-DIANILINOPYRIDINES
At this stage it seemed worthwhile investigating whether other 2,6-diaminopyridines apart from the 3-phenyl derivative (188) could readily be synthesised using substituted glutaronitriles.

The condensation of glutaronitriles with amines to 2,6-diaminopyridines has previously been investigated. Another simple method might be found via a glutaronitrile having a substituent alkylidene group (246). Cyclization with an amine could proceed directly to the pyridine (248), or acid catalysis might be necessary to cause the exocyclic double bonds in the alkylidene di-iminopiperidine (247) to rearrange to a pyridine ring.
In order to see whether this was a feasible scheme, the syntheses of 2-alkylidene glutaronitriles and their cyclization with amines were briefly investigated.

(B) PREPARATION OF 2-ALKYLIDENE GLUTARONITRILES

(i) From α-carboxyglutaronitrile (252)

We have attempted to form 2-alkylidene glutaronitriles by Knoevenagel type condensations between ketones and α-carboxyglutaronitrile (252), with concomitant loss of CO$_2$ and H$_2$O. The method has not been particularly successful, due to the difficulties found in obtaining the correct conditions for the condensation without incurring cyclization of the product.

Cyanoethylation of ethyl cyanoacetate with acrylonitrile in nitrobenzene using aqueous potassium cyanide as catalyst afforded α-carbethoxyglutaronitrile (249).

\[
\begin{align*}
\text{CN} & \quad + \quad \text{CO}_2\text{Et} \quad \rightarrow \quad \text{CN} \quad + \quad \text{CN} \\
(249)
\end{align*}
\]

The p.m.r. spectrum of the product was wholly consistent with this structure as were the mass spectrum, molecular ion $m/z$ 166, and infra red spectrum 228 (C=CN), 174 (C=O) mm$^{-1}$. 
A second product from the reaction was identified from its mass spectrum, molecular ion $m/z$ 219, as ethyl bis-(2-cyanoethyl)cyanoacetate (250).

Hydrolysis of the carbethoxy group of $\alpha$-carbethoxyglutaronitrile (249) required carefully controlled conditions to avoid affecting the nitrile groups, and was achieved with alcoholic potassium hydroxide, the product being potassium glutaronitrile-2-carboxylate (251).
The p.m.r. spectrum in deuterium oxide confirmed the structure:

\[ \text{H}^1 \text{H}^2 \text{H}^3 \text{CO}_2 \text{K} \]

\[ \text{CN} \quad \text{CN} \]

\[ (251) \]

The methine proton is exchangeable and is thus not observed in D$_2$O.

Careful treatment of the potassium salt with hydrochloric acid then afforded \( \alpha \)-carboxyglutaronitrile (252). The mass spectrum of the product confirmed the structure and is discussed in detail later (p.234).

\[ \text{CO}_2 \text{K} \quad \text{CO}_2 \text{H} \]

\[ \text{CN} \quad \text{CN} \quad \text{CN} \quad \text{CN} \]

\[ (251) \quad (252) \]

Condensations of \( \alpha \)-carboxyglutaronitrile with cyclopentanone, cyclohexanone, and methyl n-propyl ketone were attempted under various Knoevenagel conditions, viz. in benzene with piperidine, piperidine + pyridine (1:1), ammonium acetate + acetic acid, and in glacial acetic acid with ammonium acetate. No reactions involving elimination of the carboxy group took place.
(ii) Direct method

(a) 2-Ethylidene glutaronitrile (253)

2-Ethylidene glutaronitrile (253) was prepared by reacting crotononitrile (prepared in situ from allyl cyanide) and acrylonitrile under strongly alkaline conditions.

The product exhibited the required molecular ion, m/e 120, in its mass spectrum and a fragmentation pattern which confirmed the structure. The p.m.r. spectrum also agreed with the proposed structure.

Two i.r. absorptions due to the conjugated and unconjugated nitrile groups were apparent (223, 227mm⁻¹).

A further compound isolated from the reaction was identified as the dicyanoethylation product,
γ-cyano-γ-vinylpimelonitrile (254), which exhibited only one nitrile absorption in the i.r. \( (227 \text{ mm}^{-1}) \) and gave a parent ion at \( m/e 175 \) in the mass spectrometer.

\[
\begin{align*}
\text{CN} & \quad \text{CN} & \quad \text{CN} \\
(254)
\end{align*}
\]

(b) 1,3-Dicyano-4-methyl-hept-3-ene (256)

β-n-Propyl crotononitrile (255) was synthesized from cyanoacetic acid and methyl n-propyl ketone by a Knoevenagel reaction.

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{CH}_3 & \quad \text{C-CH}_2\text{-CH}_2\text{-CH}_3 \\
\text{CN} & \quad 0
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_2 & \quad \text{CH}_2 & \quad \text{CH}_3 \\
\text{CN} & \quad (255)
\end{align*}
\]

Its i.r. spectrum confirmed the presence of an \( \alpha,\beta \)-unsaturated cyano group, at \( 222 \text{ mm}^{-1} \). Other absorptions occurred at 163, 146, 144, 138.5, 84, and 80 \( \text{mm}^{-1} \). Its mass spectrum contained a parent ion at \( m/e 109 \) and a fragmentation pattern confirming the structure. The p.m.r. spectrum contained a low field singlet from the proton \( H^1 \) at \( \gamma 4.90 \), a three proton triplet at \( \gamma 9.10 \) assigned to \( H^{2-4} \), and a seven proton complex multiplet from \( \gamma 7.50-8.80 \).
assigned to H₅₋1₁.

(255) was treated with acrylonitrile under the very strongly alkaline conditions afforded by tetramethylammonium hydroxide.

The product obtained, in low yield, was assigned the structure (256) based on its mass spectrum (molecular ion $m/z 162$), i.r. spectrum (two absorptions due to conjugated and unconjugated nitrile groups, at 227 and 230 mm⁻¹), and other absorptions at 161.5, 154, 136, 86, 80, and 71 mm⁻¹.
PREPARATION OF 3-ALKYLIDENE-2,6-DIPHENYLIMINOPIPERIDINES

(i) From 2-ethylidene glutaronitrile (253)

Thermal condensation between 2-ethylidene glutaronitrile (253) and aniline hydrochloride at 240° gave 3-ethylidene-2,6-diphenyliminopiperidine (257). Crystallization of this proved difficult but was accomplished from dry isopropanol.

\[
\begin{align*}
\text{CN} & \quad \text{CN} & \quad \overset{2\times \text{PhNH}_3\text{Cl}}{\text{CH-CH}_3} & \quad \overset{\text{PhNH}_3\text{Cl}}{\text{CH-CH}_3} \\
\text{(253)} & & \text{(257)}
\end{align*}
\]

Its i.r. spectrum was characteristic of the diphenyliminopiperidines prepared previously, apart from a small absorption at 347 mm\(^{-1}\) which could be attributed to Ar-NH in a tautomer (347, 335, 164 mm\(^{-1}\)). The u.v. spectrum also identified the compound as a substituted di-iminopiperidine (230, 285 nm). The mass spectrum revealed a parent ion at \(m/e 289\) as expected. The p.m.r. spectra obtained from this compound were most informative. A solution in deutereochloroform gave a rather broadened spectrum, but this was similar to the p.m.r. spectra obtained for the previous diphenyliminopiperidines in
deuteriochloroform. However, there was present in the spectrum a small triplet at $\tau_{8.80}$, which, from its position, must be due to a methyl group coupled to two equivalent protons, which were just visible as a quartet at $\tau_{6.45}$. This suggested that the piperidine (257) was contaminated with its isomeric 2,6-dianilino-3-ethylpyridine (258). One drop of trifluoroacetic acid added to the deuteriochloroform solution of the sample sharpened up the spectrum and intensified the triplet ($\tau_{8.80}$) and quartet ($\tau_{6.45}$) signals. From the integral, the ratio of aromatic to non-aromatic protons was approximately 10:9. The p.m.r. spectrum was subsequently obtained for a fresh solution in trifluoroacetic acid. This spectrum was noticeable for its broadness and for the drift occurring. The latter is characteristic of temperature changes occurring in the solution. One hour later the spectrum was more intense but it was still broadened and drifting. After one further hour the spectrum was greatly intensified, and was resolved. The aromatic protons absorbed at $\tau_{2.60}$, there was a quartet at $\tau_{5.42}$, a broad signal centred at $\tau_{6.75}$, another at $\tau_{7.65}$, an approximate doublet at $\tau_{8.25}$, and a sharp triplet at $\tau_{8.55}$. After being kept overnight, the solution showed little change in the spectrum and an equilibrium position appeared to have been reached at the probe temperature ($34^\circ$). Warming the aged sample and then
allowing it to cool before running, a spectrum did not change the spectrum significantly. A freshly recrystallized sample of the reaction product was examined by p.m.r. in methanol. It exhibited a small triplet at $\tau 8.84$ which grew relatively larger with respect to time. A further fresh sample in deuteriochloroform, which had been purged with nitrogen, was examined as quickly as possible (3 minutes after dissolution). The spectrum so obtained was broadened but contained only the slightest trace of a triplet in the $\tau 8.55$ region.

It thus seems apparent that the piperidine (257) was the product of the reaction, and that it can exist in an "exocyclic double bonded" structure as long as it is free from any trace of acid. Acid catalysis allows the double bonds to rearrange and conjugate, giving the pyridine (258) but unexpectedly there appears to be an equilibrium set up between the piperidine and the pyridine.

\[\text{Piperidine (257)} \rightleftharpoons \text{Pyridine (258)}\]
Thin layer chromatography of a sample aged in trifluoroacetic acid afforded two main spots having \( R_f \) values of 0.1 and 0.65. Both materials exhibited parent ions of \( m/e \) 289 in the mass spectrometer but their fragmentation patterns differed distinctly, the less polar component being more stable to electron bombardment. The u.v. spectra of the two materials confirmed that the less polar material was indeed a substituted pyridine (258) having a long wavelength absorption at 336 nm while that of the polar material was 285 nm, identifying it as a substituted 2,6-diphenyliminopiperidine (257).

(ii) From 1,3-dicyano-4-methyl-hept-3-ene (256)

Thermal condensation, on a very small scale, between 1,3-dicyano-4-methyl-hept-3-ene (256) and aniline hydrochloride at temperatures between 200° and 300°C failed to give any recognizable product.
CHAPTER 4

FINE STRUCTURE OF 2,6-DIPHENYLIMINOPIPERIDINES
Having studied the aromatization of di-imino-piperidines it was necessary to define, as precisely as possible, the fine structure of these compounds to explain the ease or difficulty in forming the corresponding pyridines. The relative ease of dehydrogenation of 3-phenyl-2,6-diphenyliminopiperidine (152) compared with 2,6-di-imino-3-phenylpiperidine (144), and 2,6-diphenyliminopiperidaine (149) may be due, to some extent, to a contribution from a resonance tautomer containing an endocyclic double bond, e.g. (259) or (260). There was no n.m.r. evidence for the other tautomers (261a or b).

More definitive evidence of fine structure might be obtained from a study of the long wavelength u.v. absorptions of model compounds.
(B) **FIXED BOND STRUCTURE**

The synthesis of a fixed bond product of the type (262) was therefore envisaged.

![Chemical Structure](image)

In efforts to prepare the di-$N$-methylanilino-di-hydropyridine (262, $R=\text{Ph}$, $R'=\text{Me}$), glutaronitrile was treated with methyl aniline under various conditions of base catalysis. Only one product could be obtained before hydrolysis products were formed. The product was tentatively identified, from its mass spectrum (molecular ion $m/e 201$), as the "two unit" condensation product (263).

![Chemical Reaction](image)

Its i.r. spectrum ($340, 167 \text{ mm}^{-1}$, NH stretch and C=N stretch respectively) supported the view that an exocyclic imino group was present. The compound's poor solubility in all solvents, made purification
extremely difficult. The u.v. absorptions were at 245 and 297 nm for a solution in ethanol.

One of the hydrolysis products formed on prolonged reaction was identified as 2-N-methyl-anilino-6-oxo-Δ\(^{1}\)-piperidine (264) from its mass spectrum (molecular ion \(m/z\) 202), its i.r. spectrum (320, 172, 166 mm\(^{-1}\)), and its longwavelength u.v. absorption at 276 nm in ethanol.

![Structures](image)

Glutarimide (131) was the major product from the reaction when glutaronitile and methyl aniline were refluxed for 24 hrs. with sodium ethoxide as catalyst.

A further attempt to form a dihydropyridine was by the condensation of glutaronitrile and dimethylamine in liquid ammonia at 162°C under autogeneous pressure. A viscous oil was obtained which could not be solidified. The u.v. spectrum of the product exhibited a considerable amount of conjugation, absorbing at 269*, 293, and 311 nm, and this could be assigned to the 2,6-di-(NN-dimethyl-amino)-3,4-dihydropyridine structure (265), particularly
as the i.r. spectrum exhibited neither C=\text{N} nor N-H absorptions.

\[
\text{CN} \quad \text{CN} \quad \xrightarrow{2 \times (CH_3)_2NH} \quad \begin{array}{c}
\text{CH}_3 \\
\text{N} \\
\text{CH}_3 \\
\text{N} \\
\text{CH}_3
\end{array}
\]

(265)

Similar reactions were carried out with morpholine and diethylamine but no reaction products could be identified, glutaronitrile being returned in over 90\% yield in both cases.

It therefore appears that 2,6-dii-minopiperidine (137), 2,6-diphenyliminopiperidine (149), and their 3-phenyl derivatives (144) and (152) are mixtures of tautomeric forms (266) and (267) having considerable contributions from the imino-amino structures (267a,b) because the addition product (263) absorbs at a very similar longwavelength in the u.v. to that of (151) and (152).
The 3-phenyl group contributes little to the light absorption.

\[ \text{HN}-\text{N}-\text{N}-\text{Me} \quad \text{(263)} \]
\[ \lambda_{\text{max}} 297 \text{nm} \]

\[ \text{HN}-\text{N}-\text{N}-\text{H} \quad \text{(151)} \]
\[ \text{HN}-\text{N}-\text{N}-\text{NH} \quad \text{(151)} \]
\[ \lambda_{\text{max}} 290 \text{nm} \]

\[ \text{HN}-\text{N}-\text{N}-\text{H} \quad \text{(151)} \]
\[ \lambda_{\text{max}} 298 \text{nm} \]

There is no evidence at all for any dihydropyridine (268) contribution to the structure of any of the 2,6-di-iminopiperidines prepared.

\[ \text{HN}-\text{N}-\text{N}-\text{NH} \quad \text{(268)} \]
CHAPTER 5

AZA LINKED MACROCYCLES
(A) INTRODUCTION

The condensation of glutaronitriles with aniline under basic conditions to yield a three-unit product suggests the possibility of forming polymers or, if the stereochemistry is right, macrocyclic ring products analagous to those previously obtained by condensation of diamines with phthalonitrile. Naturally the macrocycles would be non-aromatic. However this might be advantageous towards their formation as there would be no requirement for a strictly planar ring.

(B) CONDENSATIONS OF α-PHENYLGLUTARONITRILE (187)

(i) With p-phenylenediamine

(a) Three-unit intermediate

Two molecules of α-phenylglutaronitrile and one molecule of p-phenylenediamine were condensed together under strongly basic conditions in 2-ethoxyethanol. The yellow solid formed could not be purified by recrystallization or sublimation but it was tentatively identified by its mass spectrum (parent ion \( m/e \) 448) as a three-unit condensation product from the reaction. It is likely that this product is a mixture of positional isomers, the most abundant of which is probably the less hindered three-unit compound (266).
The product has a u.v. spectrum with absorption at 248, 304, and 341 nm and an i.r. spectrum having absorptions at 340 (broad), 164 (broad), and 160 (broad) mm⁻¹, and no C=N absorption. These both help to confirm the postulated structure (266).

(b) **Attempted preparation of a macrocycle**

No macrocyclic compound could be isolated after treatment of the three-unit material (266) with a further molecule of p-phenylenediamine under strongly basic conditions. There seemed no reason why the macrocyclic compound (267) should not have been a product of the reaction. Molecular models showed that the molecule was not unduly strained or hindered in any way.
(C) CONDENSATIONS OF GLUTARONITRILE (121)

(i) With m-phenylenediamine

(a) Three-unit intermediate

Glutaronitrile was substituted for \( \alpha \)-phenyl-glutaronitrile in the condensation to eliminate the possibility of mixtures of positional isomers being formed and thus making purification of any product simpler. m-Phenylenediamine and glutaronitrile afforded a three-unit addition product (268) when treated in the correct proportions with a strong base. (268) was identified by its mass spectrum (parent ion \( m/e \) 296), its u.v. spectrum (\( \lambda_{\text{max}} \) in dimethyl formamide 300, 326* nm), and its i.r. spectrum containing absorptions at 370 (broad),
340 (broad), 165, 164, 160, and 158 \text{ mm}^{-1}, \text{ and no } \text{C=N} \text{ absorption.}

(b) \textbf{Attempted preparation of a macrocycle}

Attempted condensation of the three-unit compound (268) with a molecule of \textit{m}-phenylenediamine afforded no trace of the macrocycle (269), as indicated by mass spectrometry of the reaction product.
(ii) **With ethylenediamine**

(a) **Attempted preparation of the two-unit intermediate**

Equimolar quantities of glutaronitrile and ethylenediamine when treated with sodium ethoxide in hot ethanol afforded two products. One was isolated as white crystals. The mass spectrum of this crystalline product contained a parent ion at \( m/e \) 180 which indicates that two molecules of ethylenediamine and one of glutaronitrile have condensed together with the elimination of ammonia. Structures (270), (271), and (272) can be envisaged. The u.v. spectrum was indicative of an N-alkyl-glutarimidine, \( \lambda_{\max} \) 243, 267 nm. An alternative, (271) is rejected for the reason that simple imidazolines show only end absorption in the u.v., up to 240 nm. The i.r. spectrum of the crystals contained no \( C=S \) stretch, but there was strong double absorption at 335 and 324 \( \text{mm}^{-1} \) indicative of a hydrogen bonded primary \( \text{NH}_2 \) group. Other i.r. absorptions occurred at 163, 161, 150, 128, and 98 \( \text{mm}^{-1} \) but these are not diagnostic.

The p.m.r. spectrum of the compound does not readily distinguish between the above three structures. It shows the two \( \text{NH} \) protons as a singlet at \( \tau \) 6.22 and the methylene protons in only two groups at \( \tau \) 6.44 (singlet, 6H), and \( \tau \) 7.70
(multiplet, 8H). This spectral evidence is consistent with the structure (270).

![Chemical structures](image)

The mass spectrum shows no fragment associated with a loss of an imidazole residue, hence structure (271) is eliminated. The fragmentation pattern confirms the structure as (270). A P-1 peak larger than the parent ion suggests a primary amine while losses of 30 and 44 mass units, corresponding to -CH₂NH₂ and -CH₂CH₂NH₂ respectively, confirm the presence of the free -CH₂CH₂NH₂ group. A major fragmentation occurs affording the base peak at m/z 97. This can be attributed to the
fragment (273) formed by a prototropic shift. This fragmentation is confirmed by a metastable peak (m* 180→97) at e 52.3. Other major fragments at e 84 (m* 180→84 at e 39.2) can be assigned to (274), that at e 95 (m* 150→95 at e 60.15 and m* 136→95 at e 66.37) to (275), that at e 150 (m* 180→30 at e 5.00) to (276), and that at e 109 (m* 150→109 at e 79.15) to (277).

The second product of the reaction, isolated by precipitation with water, gave a parent ion at e 197 in the mass spectrum, indicative of a product from one molecular proportion of glutarodinitrile and two molecular proportions of diamine. The u.v. maxima at 240 and 298 nm suggested that this three-unit condensation product existed in the
amino-imino form, this presumably resulting from internal hydrogen-bonding as indicated in (278). The i.r. spectrum showed $\gamma_{\text{max}}$ 350, 340, 162, 144, 134.5 mm$^{-1}$, and no C=NN absorption.

No simple two-unit addition product (279) was obtained from this reaction.

(b) Preparations of a three-unit intermediate

Reaction under the same conditions as (a) above but employing two molar proportions of glutaronitrile gave two products. These were identified as (270) and (278) by their u.v., i.r., and mass spectra.
The same two products were obtained in about the same ratio, when two molecules of ethylenediamine and one molecule of glutaronitrile were treated together with a strong base.

(c) **Attempted preparation of a macrocycle**

No macrocyclic product (280) could be isolated from the reaction of the three-unit product (278) and one further molecule of glutaronitrile under strongly basic conditions.

(iii) **With o-phenylenediamine**

The base catalysed condensation of one molecule of glutaronitrile and two molecules of o-phenylenediamine gave mainly a single product (281), analogous to the ethylenediamine product (270), and readily identified from its mass spectrum (parent...
ion $m/e$ 276) and its u.v. spectrum ($\lambda_{\text{max}}$ 241, 273*, 275, 281, 290 nm in ethanol).

\[
\begin{align*}
\text{CN} & \quad + \quad 2 \times \quad \text{NH}_2 \\
\text{CN} & \quad \rightarrow \quad \text{N} \quad \text{N} \\
\text{NH}_2 & \quad \text{NH}_2
\end{align*}
\]

(v) With 2,6-diaminopyridine

No product could be isolated from the reaction of glutaronitrile with 2,6-diaminopyridine using either (2:1) or (1:1) molar proportions respectively. The diamine was always returned in at least 90% yield.

(v) With 2,8-diaminoacridine

The condensation under strongly basic conditions of glutaronitrile and 2,8-diaminoacridine afforded very insoluble products. Among these could be identified, from its mass spectrum (parent ion $m/e$ 303), a two-unit addition product (282).
An extension of conjugation, as shown by a longer wavelength absorption in the u.v., was apparent in dimethyl formamide ($\lambda_{\text{max}}$ 452 nm) (2,8-diaminoacridine in dimethyl formamide has $\lambda_{\text{max}}$ 408 nm). Further condensations of glutaronitrile or of 2,8-diaminoacridine with (282) in attempts to prepare three-unit or macrocyclic materials were unsuccessful due to the poor solubility of (282). It is significant that 2,8-diaminoacridine condenses with glutaronitrile whereas 2-aminopyridine or 2,6-diaminopyridine apparently did not. In both of the last two compounds the amino groups are relatively unreactive as nucleophiles, yet both compounds add readily to phthalonitrile!
(D) REACTION OF GLUTARONITRILE WITH 1,3-DI-IMINOISOINDOLINE

The reaction between equimolar quantities of glutaronitrile and 1,3-di-iminoisoindoline under base catalysed conditions formed phthalocyanine and a pale yellow crystalline material. The i.r. spectrum of this compound clearly showed the presence of a nitrile group ($\nu_{\text{max}} 224\,\text{mm}^{-1}$), while absorptions at $\nu_{\text{max}} 342, 324$, and $312\,\text{mm}^{-1}$ indicated free and bonded NH$_2$ stretching frequencies, and absorptions at $\nu_{\text{max}} 165, 163$, and $158\,\text{mm}^{-1}$ probably corresponded to amide carbonyl and aryl ring stretching frequencies. The u.v. spectrum ($\lambda_{\text{max}} 274\,\text{nm}$) shows that little conjugation is present in the molecule. Elemental analysis and mass spectroscopy (parent ion $m/e 402$) indicated a molecular formula of C$_{24}$H$_{14}$N$_6$O. The p.m.r. spectrum exhibited only aromatic and exchangeable protons in the ratio of 1 : 3 : : downfield protons : upfield protons, at $\tau 0.80$ and $\tau 2.10$ respectively, and ruled out the presence of methylene groups in the compound. Hence glutaronitrile had not reacted and did not comprise any part of the product, yet one or more nitrile groups were indicated. The latter must have arisen from ring opening of the 1,3-di-iminoisoindoline.

Tricyanocyaphenine has previously been isolated
from attempted self-condensation of di-iminoisoindoline in boiling 2-methoxyethanol. The composition of the present product and the spectral characteristics suggest it is the mono amide of tricyanocyaphenine (283)

It is to be noted that the three phenyl substituents cannot be co-planar with the triazine ring, so that the u.v. absorption maximum (274 nm) is not shifted from that of 1,3,5-triazine itself.
CHAPTER 6

METHINE LINKED MACROCYCLES
The reactions of phenylacetonitrile with succinonitrile and with phthalonitrile have been investigated by Fitt and by Linstead and Barker respectively. Two- and three-unit methine linked condensation products (284) and (285) were obtained in each case.

\[
\begin{align*}
&\text{(284)} \\
&\text{(285)}
\end{align*}
\]

Extension of the reaction to disubstituted benzenes has been examined by Barker and Maron with a view to being able to carry the reactions through to a macrocycle.

The reaction of glutaronitrile with active methylene containing compounds has been studied with the same objective. Any product so formed would not be fully conjugated but may be capable of being oxidised to a conjugated or cross-conjugated macrocycle.
Now, if \( R = \) or \( R' \), the final stages above would not be feasible.

Exploratory reactions were carried out using glutaronitrile rather than \( \alpha \)-phenylglutaronitrile to avoid the complication of obtaining positional isomers.

(B) MODEL REACTIONS

(i) With phenylacetonitrile

The addition reaction between one molecule of phenylacetonitrile and one molecule of glutaronitrile was accomplished under mild conditions using base catalysis. The cyclic product, 2-(cyanophenylmethylidene)-6-iminopiperidine (157) was obtained in 83% yield.
The structure was confirmed by its i.r. spectrum, imino bond vibrations occurring at 359, 345, 336, and 332 mm$^{-1}$, and an extremely strong conjugated C$\equiv$N stretch at 220 mm$^{-1}$. ($\nu_{\text{max}}$ 359, 345, 336, 332, 220, 166, 162.5, 162, 160, 157.5, 155, 154, 149.5, 147, 143.5, 142 mm$^{-1}$), its u.v. spectrum, ($\lambda_{\text{max}}$ 232, 318 nm), by its mass spectrum (parent ion, $m/z$ 211), and from its p.m.r. spectrum (\(\delta\) 6.90-8.60, m, 6H, H$_{1-6}$, \(\delta\) 2.00-3.40, m, 7H, aromatic protons and H$_{7,8}$).
The condensation of two molecules of phenyl-acetonitrile and one molecule of glutaronitrile under basic conditions could be followed spectroscopically. Initially, almost immediately on heating, the two-unit addition product (157) was formed. There was then a progressive change until, after 20 hours, the light absorption became constant. The three-unit condensation product 2,6-di(cyano-phenylmethylidene)piperidine (286) could then be isolated.

\[
\text{CN} \quad \text{+} \quad 2 \times \text{CH}_2 \quad \xrightarrow{\text{Condensation}} \quad \text{CN} \quad \text{H} \quad \text{C} \quad \text{N} \quad \text{+NH}_3 \\
\text{Ph} \quad \text{Ph} \quad \text{Ph} \\
(286)
\]

The additional conjugation in 2,6-di(cyano-phenylmethylidene)piperidine (286) (\( \lambda_{\text{max}} \) 246, 335 nm) caused a bathochromic shift of 17 nm in the position of the maximum as compared with that of the two-unit product (157). The i.r. spectrum (\( \gamma_{\text{max}} \) 359, 336, 272, 220, 164, 162, 160, 157.5, 149.5, 147, 143.5, 142 mm\(^{-1}\)) was entirely consistent with the structure. Final confirmation of the structure was afforded by the mass spectrum which exhibited a parent ion at m/z 311.
When the two-unit product (157) was condensed with an excess of aniline, the major product was 2,6-di(cyanophenylmethylidene)piperidine (286), presumably formed by a disproportionation and recombination process. Only a small amount of the expected three-unit condensation product (287) was present, identified by its mass spectrum (parent ion $m/e$ 289), its i.r. spectrum ($\nu_{\text{max}}$ 359, 339, 220, 167, 162, 160, 152, 150, 145, 142 $\text{cm}^{-1}$), and its u.v. spectrum ($\lambda_{\text{max}}$ 237, 286, 338 nm).

(ii) With acetone

\[ \text{\(\alpha\)-Phenylglutaronitrile and an excess of acetone reacted together under strongly basic conditions giving the three-unit condensation product 2,6-di-acetonylidene-3-phenylpiperidine (288), identified by its mass spectrum (parent ion $m/e$ 269).} \]
Its i.r. spectrum showed a strong hydrogen bonded secondary N-H stretch at 340-320 mm$^{-1}$, $\alpha,\beta$-unsaturated ketone at 167 mm$^{-1}$ and a secondary N-H bend at 157 mm$^{-1}$. It exhibited a u.v. spectrum with a maximum longwavelength absorption at 300 nm.

(iii) With ethyl cyanoacetate

The reaction between glutaronitrile and ethyl cyanoacetate under base catalysed conditions afforded the three-unit condensation product 2,6-di(cyano-ethoxycarbonylmethylidene)piperidine (289).

\[
\begin{align*}
\text{CN} &+ \text{CH}_2\text{CN} \rightarrow \text{CN} \text{CN} \text{CN} + \text{NH}_3 \\
\text{CO}_2\text{Et} & \text{CO}_2\text{Et} \text{CO}_2\text{Et}
\end{align*}
\]

(289)

It absorbed in the u.v. at 280, 343 and 400 nm in dimethyl formamide, and in the i.r. at 336 mm$^{-1}$ (broad) (hydrogen bonded NH stretch), 222 mm$^{-1}$ ($\alpha,\beta$unsaturated C=\text{N}$), 163 mm$^{-1}$ ($\alpha,\beta$unsaturated C=O), and 158 mm$^{-1}$ (NH bend). Its formula was established from the mass spectrum (parent ion m/e 303).
(i) With p-dicyanoxlylene

Reaction of glutaronitrile with p-dicyanoxlylene using the corresponding molar proportions of reactants under basic conditions gave the two three-unit condensation products (290) and (291).

\[
\begin{align*}
\text{CN} & \quad \text{CH}_2 & \quad \text{CN} \\
\text{CN} & \quad \text{CH}_2 & \quad \text{CN} \\
\text{CN} & \quad \text{CH}_2 & \quad \text{CN} \\
\text{CN} & \quad \text{CH}_2 & \quad \text{CN}
\end{align*}
\]

(290)

\[
\begin{align*}
\text{CN} & \quad \text{CH}_2 & \quad \text{CN} & \quad \text{CN} \\
\text{CN} & \quad \text{CH}_2 & \quad \text{CN} & \quad \text{CN} \\
\text{CN} & \quad \text{CH}_2 & \quad \text{CN} & \quad \text{CN} \\
\text{CN} & \quad \text{CH}_2 & \quad \text{CN} & \quad \text{CN}
\end{align*}
\]

(291)
The three-unit product (290) was identified by its mass spectrum (parent ion $m/e$ 389), u.v. spectrum ($\lambda_{\text{max}}$ in dimethyl formamide, 295, 327, 450 nm), and i.r. spectrum ($\nu_{\text{max}}$ 359, 351, 336, 224.5, 220, 173, 171, 169, 162, 156.5, 155.5, 151 and 141 mm$^{-1}$).

Compound (291) was identified by its mass spectrum (parent ion $m/e$ 344), u.v. spectrum ($\lambda_{\text{max}}$ 334, 480 nm), and i.r. spectrum ($\nu_{\text{max}}$ 359, 335, 220, 171, 169.5, 162, 157, and 152 mm$^{-1}$).

The three-unit products (290) and (291) were further condensed with glutaronitrile and p-dicyanoxylylene respectively under strong basic conditions and the macrocycle (292) was obtained.
The macrocycle (292) was identified by its mass spectrum (parent ion \( m^+ = 466 \)), u.v. spectrum (\( \lambda_{\text{max}} \) in dimethyl formamide 288, 330, 468 nm), and i.r. spectrum (\( \nu_{\text{max}} \) 359, 349, 336, 320, 220, 172.5, 171, 164, 161.5, 156, and 151.5 mm\(^{-1}\)).

(ii) With \( m \)-dicyanoxylylene

Reaction of glutaronitrile with \( m \)-dicyanoxylylene under basic conditions gave corresponding three-unit condensation products (293) and (294).
The three-unit products (293) and (294) were identified by their mass spectra, having parent ions at $m^+ 389$ and 344 respectively. Their i.r. spectra were very similar to those of the $p$-isomers (290) and (291) showing absorptions at 359, 351, 335, 224.5, 220, 170, 162, 156.5, 151 and 141 mm$^{-1}$ for (293) and at 363, 359, 345, 335, 220, 170, 162, 160, and 156.5 mm$^{-1}$ for (294).

The three-unit condensation products (293) and (294) were further condensed with glutaronitrile and $m$-dicyanoxylylene respectively under strong basic conditions and the macrocycle (295) was obtained.
Identification of the macrocycle (295) was obtained from its mass spectrum which contained a parent ion at m/e 466. Its i.r. spectrum (γmax 362, 359, 347, 335, 220, 171, 162, 157, 154, and 151.5 mm⁻¹) was consistent with this structure.

(D) ATTEMPTED DEHYDROGENATION OF MACROCYCLES AND INTERMEDIATES

(i) 2-(Cyanophenylmethylidene)-6-iminopiperidine (157)

2-(Cyanophenylmethylidene)-6-iminopiperidine (157) was treated under the same conditions that caused 3-phenyl-2,6-diphenyliminopiperidine (152) to undergo dehydrogenation. However, reactions with nitrobenzene in boiling o-dichlorobenzene and with 3,3',5,5'--tetrachloro-4,4'-diphenoquinone in dry benzene produced no new products. With N-bromosuccinimide in dry carbon tetrachloride the main product was 2,6-di(cyanophenylmethylidene)piperidine (286).

(ii) 2,6-Di(cyanophenylmethylidene)piperidine (286)

Treatment of 2,6-di(cyanophenylmethylidene)piperidine (286) with nitrobenzene in o-dichlorobenzene and with 3,3',5,5'-tetrachloro-4,4'-diphenoquinone produced no reaction. With N-bromosuccinimide, however, a small amount of a monobrominated derivative (296) was formed. It had a maximum
longwavelength absorption in the u.v. of 315 nm, a mass spectrum containing a parent ion at m/z 389, and an i.r. spectrum having absorptions at 359, 343, 335, 326, 272, 220, 171, 162, and 151 mm\(^{-1}\).

![Chemical Structure (286) and (296)](image)

There was insufficient material to proceed to the dehydrobromination reaction.

(iii) 2,6-Di(cyano-p-cyanomethylphenylmethylidene)piperidine (290)

The three-unit condensation product (290) was treated with N-lithioethylene diamine under nitrogen at 100°C. Hydrogen was evolved, and the product exhibited an extension of conjugation over the reactants, having a longwavelength u.v. absorption at 468 nm. It was, however, found to be difficult to purify and it was not identified.
CHAPTER 7

EXPERIMENTAL
Preparation of α-phenylglutaronitrile (187). - (a) A mixture of freshly distilled phenylacetonitrile (117g) and freshly distilled acrylonitrile (53g) was agitated in an ice bath and treated with a solution of sodium ethoxide (1ml) (from sodium (1g) in dry ethanol (20ml)). An exothermic reaction took place and the temperature was held below 50°. Further aliquots of sodium ethoxide (4x1ml) were added at intervals until the temperature fell and was not raised by addition of further catalyst. The mixture was neutralized with acetic acid, and washed with water (3x500ml), and distilled under reduced pressure (1mmHg) affording a fraction as a colourless, viscous oil (46g), b.p. 163° at 1 mmHg (Found: C, 77.6; H, 5.9; N, 16.5. Calc. for \( \text{C}_{11}\text{H}_{10}\text{N}_{2} \): C, 77.6; H, 5.9; N, 16.5 %); \( v_{\max} \) 473, 445, 430, 410, 365, 354, 302, 292, 260, 249, 223, 196, 187, 179.5, 174.5, 166, 160, 159, 158, 154, 149.5, 145, 142 mm\(^{-1}\); \( \delta \) 2.64 (s; H\(_{1-5}\)), 6.05 (t; \( J = 7.8 \) Hz; H\(_{6}\)), 7.66 (m; H\(_{7-10}\)); \( M^+ \) 170.

(b) Freshly distilled phenylacetonitrile (117g) and freshly distilled acrylonitrile (53g) were added dropwise over a period of 40 min to a well stirred, refluxing mixture of nitrobenzene (500ml), water (5ml) and potassium cyanide (1g). Further aliquots of potassium cyanide (7x0.5g) were added at 5min intervals during the reaction. The mixture was
refluxed for a further 30 min. After cooling, the dark brown solution was washed with saturated aqueous sodium carbonate solution (3×100 ml), water (3×100 ml), 2N-hydrochloric acid (3×100 ml), and finally water (3×100 ml). The organic residue was distilled at 15 mmHg to remove nitrobenzene and unreacted phenylacetonitrile and then at 1 mmHg affording α-phenylglutaronitrile (187) (113 g) as a colourless, viscous liquid, b.p. 163-164° at 1 mmHg (Found: C, 77.5; H, 6.0; N, 16.5. Calc. for C_{11}H_{10}N_2: C, 77.6; H, 5.9; N, 16.5 %); $\gamma_{\text{max}}$ 473, 445, 430, 410, 365, 354, 302, 292, 260, 499, 223, 196, 187, 179.5, 174.5, 166, 160, 159, 158, 154, 149.5, 145, 142 mm⁻¹; ω 2.64 (s; H1-5), 6.05 (t; J6-7,8 7Hz; H6), 7.66 (m; H7-10); M⁺ 170.

Preparation of 3-phenyl-2,6-diphenyliminopiperidine (152). - α-Phenylglutaronitrile (187) (85 g) and aniline hydrochloride (130 g) were heated together, under dry nitrogen, with stirring. The internal temperature was slowly raised to 240° when an exothermic reaction took place. The temperature was maintained at 285° for 15 min while ammonium chloride sublimed and the melt thickened, turning from green to red. The melt was cooled, triturated with water (20 ml), and dissolved in ethanol (11). Sodium hydroxide (40 g) in water (21) was added and the mixture was
extracted with chloroform (3x500ml). The chloroform solution was dried over magnesium sulphate and distilled to dryness at 15mmHg. The residue was triturated with dry ether and preparative t.l.c. (eluting with methanol) was carried out. The first broad yellow band was collected and on evaporation the product was obtained as pale yellow needles (62g), m.p. 159-162° after crystallizations from aqueous ethanol, isopropanol, and ethanol, raised to 162-163° after 6 further crystallizations from ethanol (Found : C, 81.2; H, 6.3; N, 12.3%. Calc. for C₂₃H₂₁N₃ : C, 81.4; H, 6.4; N, 12.3%); \( \lambda_{\text{max}} \) (in ethanol) 226, 287, 300 nm; \( \lambda_{\text{max}} \) (in hexane) 299 nm; \( \gamma_{\text{max}} \) 332 and 320 (NH), 164 (C=N), 161, 159.5 (C=O), 157 (-NH-), 151.5 (amidine), 150 (C=O), 148.5, 144.5, 141 mm⁻¹; \( \gamma \) (in CDCl₃) 2.90 (m; \( H^{1-15} \)), 5.60 (s; \( H^{16} \)), 5.94 (t; \( J_{17-18,19} 7\text{Hz}; H^{17} \)), 7.70 (m; \( H^{18-21} \)); \( \gamma \) (in CDCl₃ - 3 drops TFA) 2.48 (m; \( H^{1-4} \)), 2.80 (m; \( H^{5-15} \)), 5.60 (s; \( H^{16} \)), 5.80 (t; \( J_{17-18,19} 6\text{Hz}; H^{17} \)), 7.35 (m; \( H^{20,21} \)), 7.95 (m; \( H^{18,19} \)); \( \gamma \) (CDCl₃ - 10% TFA) 2.70 (m; \( H^{1-15} \)), 5.90 (dd; \( J_{17-18} 6\text{Hz}; J_{17-19} 6\text{Hz}; H^{17} \)), 7.02 (t; \( J_{20,21-18,19} 6\text{Hz}; H^{20,21} \)), 7.60 (at; \( J_{18,19-17} 6\text{Hz}; J_{18,19-20,21} 6\text{Hz}; H^{18,19} \)); \( M^+339 \).

**Preparation of 2',6,6'-trianilino-5,5'-diphenyl-2,3'-bipyridyl (191).** - 3-Phenyl-2,6-diphenyliminopiperidine (152) (6g) was dissolved in dry o-dichlorobenzene
(100ml), treated with nitrobenzene (14ml), and refluxed under dry nitrogen for 18 hr, when t.l.c., eluting with benzene-ethyl acetate (19:1), confirmed that the reaction had ceased. Evaporation of the solvent under vacuum (10 mmHg) and washing with dry ether afforded the product as yellow needles (2.8g), m.p. 202-203° after crystallizations from ethyl acetate. T.l.c., eluting with benzene-ethyl acetate (19:1), revealed a single spot with Rf 0.65. The product was also isolated by dissolving the semi-solid residue remaining after evaporation of the solvent in dry benzene (25ml) and chromatographing on alumina. Elution of the yellow band with dry benzene-dry light petroleum ether (2:1) and evaporation afforded yellow needles (2.5g), m.p. 203° after crystallization from ethyl acetate (Found; C, 82.7; H, 5.3; N, 12.0. C₄₀H₅₁N₅ requires C, 82.6; H, 5.4; N, 12.0 %); λ_max (in ethanol) 242, 288, 315, 397 nm; λ_max (in hexane) 403 nm; ν_max 345, 160, 158, 152.5, 151, 145.5, 143.5, 141 mm⁻¹; τ-1.30 (s; H₃¹), 2.85 (m; H₁⁻₃⁰); M⁺ 581.

Preparation of 5,5'-diphenyl-2',6,6'-tri-(N-phenylacetamido)-2,3'-bipyridyl (195). - 2',6,6'-Trianilino-5,5'-diphenyl-2,3'-bipyridyl (191) (0.5g) and acetic anhydride (5ml) were heated in a Carius tube at 190° for 24 hr. Removal of the solvent under reduced
pressure and column chromatography of the pale pink solid obtained, eluting with dry benzene, and collecting the first major fraction, afforded small white plates, m.p. 211°, after recrystallization from ether-petroleum ether (1:1) (Found: C, 78.0, H, 5.2; N, 9.7. \( \text{C}_{46}\text{H}_{37}\text{N}_{5}\text{O}_{3} \) requires C, 78.1; H, 5.2; N, 9.9 %); \( \lambda_{\text{max}} \) 243, 293 nm; \( \gamma_{\text{max}} \) 312,167.5, 159.5, 157, 150, 146.5, 143, 140 mm\(^{-1}\); \( \tau \) (in CDCl\(_3\)) 2.85 (m; H\(_{1-28}\)), 7.95 (s; H\(_{29-31}\)), 8.00 (s; H\(_{32-34}\)), 8.06 (s; H\(_{35-37}\)); \( M^+ \) 707.

**Bromination of 2',6,6'-trianilino-5,5'-diphenyl-2,3'-bipyridyl (191).** - (a) The compound (191) (0.58g) was dissolved in chloroform (10ml) and cooled to 0°. Bromine (0.64g) in chloroform (5ml) was added, dropwise, over a period of 5min to the cold solution which was then allowed to warm to room temperature and stand for lhr. Evaporation of the solvent in vacuo, and trituration with dry ether yielded a yellow solid. Column chromatography, slowly eluting with dry benzene-dry cyclohexane (2:1) and collecting the effluent in aliquots (20ml) yielded, on evaporation, fractions as yellow crystals. Mass spectroscopic investigation of the fractions indicated that a complex mixture of brominated products had been formed. The fractions were combined and treated with a further eight molecular
proportions of bromine (1.28g) in chloroform (10ml) at 0° over a period of 30min when the temperature was raised to 50° for 15min. Column chromatography, eluting with dry benzene-dry cyclohexane (10:1) afforded fractions which were evaporated. The first 9 fractions were shown to be identical, and they were further purified by preparative t.l.c utilising multiple elution with dry benzene-dry cyclohexane (10:1) yielding the heptabromo product, 3-bromo-2',6,6'-tri-(2,4-dibromoanilino)-5,5'-diphenyl-2,3'-bipyridyl (199) as yellow needles (0.43g), m.p. 219-220° after crystallizations from benzene and from ethyl acetate (Found: C, 42.1; H, 2.1; N, 6.1; Br, 49.2. C₄₀H₂₄N₅Br₇ requires C, 42.4; H, 2.1; N, 6.2; Br, 49.3%); \( \lambda_{\text{max}} \) (in ethanol) 250*, 305, 330*, 380 nm; \( \lambda_{\text{max}} \) (in hexane) 249*, 305, 330*, 375 nm; \( \gamma_{\text{max}} \) 345, 161, 160, 157.5, 155, 154, 151.5, 151 mm⁻¹; \( \tau \) -3.50 (s; H₂₄), 2.14 (m; H¹⁻²³); M⁻ 1,127.

Fractions 11 to 14 were shown to be identical, and further purification by preparative t.l.c by multiple elution with dry benzene-dry petroleum ether (10:1) yielded the hexabromo product, 3-bromo-2'-(4-bromoanilino)-6,6'-di-(2,4-dibromoanilino)-5,5'-diphenyl-2,3'-bipyridyl (201) as long yellow needles (0.07g), m.p. 204-205° after crystallizations from benzene and from ethyl acetate (Found: C, 45.3; H, 2.2; N, 6.5; Br, 45.2. C₄₀H₂₅N₅Br₆ requires C, 45.5; H, 2.4; N, 6.65; Br, 45.43%); \( \lambda_{\text{max}} \) (in hexane) 249, 301, 326*,
394 nm; \( \nu_{\text{max}} \) 345, 160, 158, 155, 154, 151 mm\(^{-1} \); \( \tau \) 3.20 (s; \( H^25 \)), 2.10 (m; \( H^{1-24} \)); \( M^+ \) 1,049.

(b) This compound (191) (0.58 g) was dissolved in chloroform (10 ml) and cooled to 0\(^\circ\). Bromine (0.64 g) in chloroform (5 ml) was added, dropwise with vigorous stirring, over a period of l hr to the cold solution. The solution was evaporated in vacuo, and the residue triturated with dry ether to afford a yellow solid. Column chromatography, eluting with dry benzene-dry petroleum ether (10:1) and collecting the effluent from the first broad yellow band in aliquots (20 ml) yielded, on evaporation, fractions as yellow crystals. Fraction 1 was shown to be identical to the heptabromo derivative (199). Fractions 3 to 6 were shown to be identical, and further purification by preparative t.l.c using multiple elution with dry benzene-dry petroleum ether (10:1) yielded the tetrabromo product, 3-bromo-2',6,6'-tri-(4-bromoanilino)-5,5'-diphenyl-2,3'-bipyridyl (202) as yellow needles (0.09 g), m.p. 194-197°, after crystallization from ethyl acetate (Found: C, 53.3; H, 2.8; N, 7.6; Br, 35.3. \( C_{40}H_{27}N_2Br_4 \) requires C, 53.55; H, 3.0; N, 7.8; Br, 35.6%); \( \lambda_{\text{max}} \) (in ethanol) 250, 286, 295, 330*, 390 nm; \( \lambda_{\text{max}} \) (in hexane) 402 nm; \( \nu_{\text{max}} \) 345, 160.5, 158.5, 156.5, 154.5, 152, 151, 149 mm\(^{-1} \); \( \tau \) 0.10 (s; \( H^27 \)), 2.59 (m; \( H^{1-26} \)); \( M^+ \) 893.
Fractions 8 to 20 were shown to be identical to one another, and further purification by preparative t.l.c by multiple elution with dry benzene-dry cyclohexane (10:1) yielded the tribromo product, 2'-anilino-3-bromo-6,6'-di-(4-bromoanilino)-5,5'-diphenyl-2,3'-bipyridyl (203) as yellow needles (0.01g), m.p. 200-202° after crystallization from ethyl acetate (Found: C, 58.4; H, 3.3; N, 8.3; Br, 28.8. C₄₀H₂₈N₅Br₃ requires C, 58.7; H, 3.45; N, 8.55; Br, 29.3 %); \( \lambda_{\text{max}} \) (in hexane) 249, 298, 330*, 403 nm; \( \gamma_{\text{max}} \) 346, 160, 158, 156, 154, 152, 151, 149.5, 148 mm⁻¹; \( \tau \) 0.35 (s; H²₈), 2.75 (m; H¹-27); \( M^+ \) 815.

(c) This compound (191) (0.58g) was dissolved in chloroform (10ml) and cooled to 0°. Bromine (1.92g) in chloroform (10ml) was added and the mixture warmed to 80° for 30min. The solution was evaporated in vacuo, yielding a yellow solid on trituration with dry ether. Column chromatography, eluting with dry benzene-dry cyclohexane (10:1), yielded, on evaporation, fractions as yellow crystals. Mass spectrometry indicated that the fractions were highly brominated derivatives, but the major components appeared to have been further dehydrogenated.
Attempted preparation of 2,6-di-(4-bromophenylimino)-3-phenylpiperidine (208). - (a) α-Phenylglutaronitrile (187) (8.5g) and p-bromoaniline hydrochloride (21g) were heated together, under dry nitrogen, with stirring. The internal temperature was slowly raised to 240°. No exothermic reaction set in but the temperature was maintained for 15min while ammonium chloride sublimed. The melt was cooled, triturated with water (5ml), and dissolved in ethanol (100ml). Sodium hydroxide (4g) in water (200ml) was added and the mixture was extracted with chloroform (3x 50ml). The chloroform solution was dried over magnesium sulphate and the solvent removed at 15mmHg. The residue was distilled under vacuum (10⁻¹mmHg) and α-phenylglutaronitrile (187) (7.2g) was returned in 85% yield.

(b) The experiment was repeated as above but the internal temperature of the melt was raised to 300° for 15min. Following removal of the chloroform under vacuum the residue was triturated with dry ether yielding a yellow solid. Column chromatography slowly eluting with dry benzene, then dry benzene-chloroform (1:1), collecting the effluent from the first broad yellow band in small aliquots (20ml) yielded, on evaporation, fractions as pale yellow solids. T.l.c, eluting with dry benzene-dry petroleum ether (2:1), showed that the fractions were essentially identical (R_f 0.46) and had the following
spectral properties; \( \lambda_{max} \) (in ethanol) 251, 279, 333, 377, 390 nm; \( \lambda_{max} \) (in cyclohexane) 261, 280, 333, 377, 396 nm; \( \nu_{max} \) 345, 159, 157, 152, 150, 145, 141 mm\(^{-1}\).

Vacuum sublimation of the combined fractions (6.5g) from the first yellow band produced a yellow solid identical in composition to the combined fractions.

The second yellow band, eluted from the column with dry benzene-chloroform (1:1) was evaporated to give a yellow product, in small yield (2mg), identified as the tribromo derivative, 2',6,6'-tri-(4-bromoanilino)-5,5'-diphenyl-2,3'-bipyridyl (207); \( \lambda_{max} \) (in ethanol) 250*, 287, 526, 394 nm; \( \lambda_{max} \) (in hexane) 403 nm; \( M^+ \) 815.

The third broad yellow band was eluted from the column with methanol. Evaporation gave a pale yellow solid (0.38g) identified as 2,6-di-(4-bromo-phenylimino)-3-phenylpiperidine (208) from the R\(_f\) 0.71 value (t.l.c, methanol) and the mass spectrum \( M^+ \) 505.

**Attempted condensation of p-bromoaniline with 2,6-di-imino-3-phenylpiperidine (144).** - p-Bromoaniline (9.2g) and 2,6-di-imino-3-phenylpiperidine (144) (18.7g) were heated together with stirring at temperatures between 100° and 200°. When evolution of ammonia
had ceased t.l.c (using methanol) showed several products had been formed. Crystallization from ethanol gave a brownish solid which t.l.c again showed to be a mixture. The only identified products were the starting materials and $\varphi$-phenyl-glutaronitrile (187).

**Reaction of the 2,3'-bipyridyl (191) with nitrous acid.** - The 2,3'-bipyridyl (191) (0.58g) was treated with sodium nitrite (0.35g) in water (2ml) and hydrochloric acid (2ml) at 5° in chloroform-ethanol (1:1) (20ml). T.l.c, eluting with benzene, showed that at least five products were formed. None could readily be isolated in a pure state.

**Reaction of the 2,3'-bipyridyl (191) with phenyl-diazonium chloride.** - The 2,3'-bipyridyl (191) (0.58g) was treated with a solution of phenyl diazonium chloride (prepared from aniline (2.0g)) at 5° in chloroform-ethanol (1:1) (20ml), followed by 5min at 70°. An intense green colour developed. Careful evaporation of the solvent afforded only the 2,3'-bipyridyl (0.51g) and a trace of phenol.

**Preparation of 2-methyl-4-phenylglutaronitrile (211).** - Phenylacetonitrile (117g) and methacrylonitrile (67g) were refluxed together for 1hr in nitrobenzene (500ml)
while potassium cyanide (1g) was added as catalyst. Further portions of potassium cyanide (5x0.5g) were added during the period of the reaction. After cooling, the solution was washed with saturated aqueous sodium carbonate solution (3x100ml), water (3x100ml), 2N-hydrochloric acid (3x100ml), and finally water (3x100ml). The organic residue was distilled under reduced pressure (15mmHg) to remove nitrobenzene and unreacted phenylacetonitrile and then at 7mmHg affording 2-methyl-4-phenylglutaronitrile (211) (74g) as a colourless, viscous liquid, b.p. 140-142° at 7mmHg (Found: C, 78.0; H, 6.3; N, 15.0. C\textsubscript{12}H\textsubscript{12}N\textsubscript{2} requires C, 78.3; H, 6.5; N, 15.2 %); \(\nu_{\text{max}}\) 370, 365, 307, 302, 297, 291, 226, 197, 189, 181, 172, 160, 150, 146 mm\(^{-1}\); \(\gamma\) 2.61 (s; H\(^1\)), 5.97 (dd; \(J_{6-7}\) 9Hz; \(J_{6-8}\) 8Hz; H\(^6\)), 7.03 (ddq; \(J_{9-7}\) 9Hz; \(J_{9-8}\) 8Hz; \(J_{9-10,11,12}\) 7Hz; H\(^9\)), 7.85 (ddd; \(J_{7-6}\) 9Hz; \(J_{7-9}\) 9Hz; \(J_{8-6}\) 8Hz; \(J_{8-9}\) 8Hz; H\(^7\)), 8.67 (d; \(J_{10,11,12-9}\) 7Hz; H\(^{10,11,12}\)); \(M^+\) 184.

Preparation of 3-methyl-5-phenyl-2,6-diphenylimino-piperidine (210). - 2-Methyl-4-phenylglutaronitrile (211) (46g) and aniline hydrochloride (65g) were heated together at 280° under dry nitrogen with stirring. The mixture was held at this temperature for 15min while ammonium chloride sublimed. The melt was cooled, triturated with water (10ml) and dissolved
in ethanol (500ml). The solution was neutralized with sodium hydroxide (20g) in water (1l) and the mixture extracted with chloroform (3x250ml). The chloroform solution was dried (over magnesium sulphate) and distilled to dryness under reduced pressure (15mmHg). Trituration with dry ether afforded a yellow solid. T.l.c., eluting with methanol, showed one major product and several impurities. Column chromatography, eluting with benzene, collecting the first main band, yielded, on evaporation, a fine yellow solid. Crystallization was not successful from ethanol or isopropanol but preparative t.l.c., eluting with methanol, afforded the product (210) (47.1g) as a yellow solid (Found: C, 81.3; H, 6.4; N, 11.7. C_{24}H_{23}N_{3} requires C, 81.6; H, 6.5; N, 11.9%); 
\[ \lambda_{\text{max}} 228, 286, 298 \text{ nm}; \nu_{\text{max}} 335, 320, 164, 163, 159.5, 157, 153.5, 152, 151, 150, 149, 145, 142 \text{ mm}^{-1}; \Gamma 3.15 (\text{m; } \text{H}^{1-16}), 6.10 (\text{m; } \text{H}^{17}), 7.80 (\text{m; } \text{H}^{18-20}), 8.80 (\text{m; } \text{H}^{21-23}); \text{M}^{+} 353.\]

**Attempted dehydrogenation of 3-methyl-5-phenyl-2,6-diphenyliminopiperidine (210) with nitrobenzene.** - 3-Methyl-5-phenyl-2,6-diphenyliminopiperidine (210) (6.25g) was refluxed with nitrobenzene (14ml) in o-dichlorobenzene (100ml) under dry nitrogen for 24hr. The solvent was evaporated under reduced pressure (10^{-1}\text{mmHg}) and the residue washed with dry ether affording the
starting material (210) (5.3g), in 85% yield, identified by its spectral properties; \( \lambda_{\text{max}} \) 228, 286, 298 nm; \( \nu_{\text{max}} \) 335, 320, 164, 159, 157, 153.5, 152, 150, 149, 145, 142 \( \text{cm}^{-1} \); \( M^+ \) 353; and small amounts (0.08g) of 3-methyl-2-oxo-5-phenyl-6-phenyliminopiperidine (212) identified by its mass spectrum, \( M^+ \) 278 and (0.01g) of 3-methyl-2,6-dioxo-5-phenylpiperidine (213) identified by its mass spectrum, \( M^+ \) 263.

T.l.c, eluting with benzene-ethyl acetate (19:1), confirmed that no aromatic products were formed in the reaction.

**Attempted dehydrogenation of 3-methyl-5-phenyl-2,6-diphenyliminopiperidine (210) with chloranil.** - 3-Methyl-5-phenyl-2,6-diphenyliminopiperidine (210) (3.43g) was treated with chloranil (2.46g) in dry benzene under dry nitrogen and the mixture was refluxed for 2hr. The solvent was evaporated under vacuum (15mmHg) and t.l.c, eluting with benzene-ethyl acetate (19:1), showed that no aromatic products were formed in the reaction. Preparative t.l.c, eluting with benzene-ethyl acetate (19:1), suggested that the starting material (210) was returned in good yield, 87%. This was confirmed by the product's spectral properties which were identical to those of the starting material (210).

**Preparation of 3,3',5,5'-tetrachloro-4,4'-biphenol (222).** - 4,4'-Biphenol (221) (19g) was refluxed in glacial
acetic acid (100ml) and chlorine (29g) was bubbled in. The mixture was cooled and evaporated under reduced pressure (10⁻¹ mmHg) affording the product as white crystals (31g) after recrystallization from ethanol; \( M^+ 322 \) (for \(^{35}\)Cl).

Preparation of 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220). - 3,3',5,5'-Tetrachloro-4,4'-biphenol (222) (22g) was treated with fuming nitric acid (10ml) in glacial acetic acid (100ml). The mixture was cooled and the reddish brown precipitate filtered off and washed with water and ethanol; \( M^+ 320 \) (for \(^{35}\)Cl).

Attempted dehydrogenation of 3-methyl-5-phenyl-2,6-diphenyliminopiperidine (210) with 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220). - 3-Methyl-5-phenyl-2,6-diphenyliminopiperidine (210) (3.43g) was refluxed with 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220) (3.22g) in dry benzene for 30min. The solvent was evaporated under reduced pressure (15mmHg) and t.l.c, eluting with benzene-ethyl acetate (19:1), showed that the starting material (210) had been returned in excellent yield (95%).

Preparation of 3-methyl-2-phenylglutaronitrile (214). - Phenylacetonitrile (117g) was treated with crotonaldehyde, prepared in situ from allyl cyanide (67g),
sodium (5g) and ethanol (100ml) in a modified
Michael reaction at 0° for lhr. The solution was
washed with water (3x100ml) and the organic residue
was distilled at 15mmHg to remove unreacted
materials. Further distillation under reduced pressure
(4mmHg) afforded 3-methyl-2-phenylglutaronitrile (214)
(86g) as a faintly yellowish, viscous, liquid,
b.p. 168-169° at 4 mmHg (Found: C, 78.2; H, 6.4;
N, 15.0. C_{12}H_{12}N_2 requires C, 78.3; H, 6.5; N, 15.2%);
\( \gamma_{\text{max}} 302, 295, 223, 160, 150, 145 \text{ mm}^{-1}; \quad \tau 2.64 (m; H^{1-5}),
6.18 (m; H^{6}), 7.60 (m; H^{7-9}), 8.76 (m; H^{10-12}); M^+ 184.

Preparation of 4-methyl-3-phenyl-2,6-diphenylimino-
piperidine (209). - 3-Methyl-2-phenylglutaronitrile (214)
(46g) and aniline hydrochloride (65g) were heated
together at 280° for 15min while ammonium chloride
sublimed. The melt was dissolved in ethanol (500ml),
diluted with water (11), and neutralized to Congo
red with sodium hydroxide (20g). Extraction with
chloroform (3x250ml) and drying (over magnesium
sulphate) was followed by preparative t.l.c, eluting
with methanol. A pinkish solid was obtained which
was recrystallized from ethanol, ethanol-water, and
isopropanol, but which was not a single material.
Final purification was achieved by treating the
solid with an excess of picric acid in ethanol
and warming, followed by evaporation of the solvent
under reduced pressure, and column chromatography, eluting with dry ether. Excellent separation of fractions was obtained and picric acid was retained at the top of the column. The first component eluted was the diphenyliminopiperidine (209). It was obtained as fine yellow crystals m.p. 162-4° from ethanol (Found: C, 81.4; H, 6.5; N, 11.9. C_{24}H_{23}N_{3} requires C, 81.6; H, 6.5; N, 11.9 %); λ max 287, 299 nm; ν max 338, 325, 164, 159.5, 158.5, 152.5, 152, 150, 149, 144.5, 142 mm⁻¹; τ 3.00 (m; H₁⁻₁₆), 6.28 (m; H¹⁷), 7.70 (m; H¹₈⁻₂₀), 8.98 (m; H²¹⁻²₃); M⁺ 353.

The second component eluted during the column chromatography was identified as 4-methyl-6-oxo-3-phenyl-2-phenyliminopiperidine (215). It was obtained as a pale yellow solid, m.p. 178-180° from ethanol (Found: C, 77.3; H, 6.2; N, 9.8. C_{18}H_{18}N_{2}O requires C, 77.7; H, 6.5; N, 10.1 %); λ max 224, 280nm; M⁺ 278.

Dehydrogenation of 4-methyl-3-phenyl-2,6-diphenyliminopiperidine (209) with nitrobenzene. - The diphenyliminopiperidine (209) (6.25g) was heated under reflux with nitrobenzene (14ml) in o-dichlorobenzene (100ml) under dry nitrogen for 24hr. The solvent was evaporated under reduced pressure (10mmHg) and the sticky residue washed with dry ether. T.l.c, eluting with benzene-ethyl acetate (19:1), revealed several
products had been formed and a large proportion of the starting material (4.85g) remained unreacted. Preparative t.l.c., eluting with benzene-ethyl acetate (19:1), and examining the least-polar fractions suggested that the first fraction (R_f 0.91, the 2,3'-bipyridyl (191) has R_f 0.90 in the same solvent) was the required bipyridyl, 2',6,6'-trianilino-4',4'-dimethyl-5,5'-diphenyl-2,3'-bipyridyl (217). Attempts to crystallize the sample were not successful. It was obtained as a pale yellow solid, m.p. 198-204° (Found: C, 82.4; H, 5.7; N, 11.4.
C_{42}H_{35}N_{5} requires C, 82.75; H, 5.75; N, 11.5 %);
\( \lambda_{\text{max}} 230^*, 260^*, 302, 376 \text{ nm} \); \( \gamma_{\text{max}} 345, 160, 158, 152, 151, 144, 141 \text{ mm}^{-1} \); \( M^+ 609 \).

The second yellow fraction (R_f 0.62, 2,6-dianilinopyridine (236) has R_f 0.60 in the same solvent) afforded a small amount of solid identified as 2,6-dianilino-4-methyl-3-phenylpyridine (216);
\( \lambda_{\text{max}} 230^*, 263, 287, 337 \text{ nm} \); \( M^+ 351 \).

Dehydrogenation of 3-phenyl-2,6-diphenyldiminopiperidine (152) with quinones. - (i) Chloranil.
a) 3-Phenyl-2,6-diphenyldiminopiperidine (152) (3.29g) was refluxed with chloranil (2.46g) in n-pentanol at 150° under dry nitrogen for 30min. The solvent was removed under reduced pressure (10mmHg) and the residue separated by column chromatography,
eluting with benzene-ethyl acetate (19:1), followed
by chloroform and finally methanol. The 2,3'-bi-
pyridyl (191) was isolated from the first fraction
eluted.

The tetrachloroquinol (219) was eluted with methanol and was identified by its mass spectrum, \( M^+ 246 \).

b) 3-Phenyl-2,6-diphenyliminopiperidine (152) (3.29g) was treated with chloranil (2.46g) in cold dry benzene under dry nitrogen. An immediate reaction took place and the solution turned green. T.l.c of the reaction mixture, eluting with benzene-ethyl acetate (19:1), showed that no dehydrogenation products had been formed. The mixture was refluxed for 2hr and the resulting purple solution was examined by preparative t.l.c, eluting with benzene-ethyl acetate (19:1). A small amount of the 2,3'-bipyridyl (191) and larger amounts of the tetrachloroquinol (219), and the starting material (152) were the only products isolated in a pure state.

(ii) 3,3',5,5'-Tetrachloro-4,4'-diphenoquinone (220),

3-Phenyl-2,6-diphenyliminopiperidine (152) (3.29g) was refluxed with 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220) (3.22g) in dry benzene under anaerobic
conditions for 15 min. The solvent was evaporated under reduced pressure (15 mmHg) and t.l.c, eluting with benzene-ethyl acetate (19:1), showed that a trace of the bipyridyl (191) had been formed. The major product was a brownish solid which was best purified by precipitation with water or petroleum ether from ethanol or benzene respectively. Crystallization was not effected with methanol, ethanol, ethanol-water, ethanol-ether, chloroform-ether, isopropanol, isopropanol-water, benzene, or benzene-petroleum ether. The crude solid was subjected to column chromatography, eluting with a series of solvents of increasing polarity from petroleum ether to methanol, and the 2,3'-bipyridyl (191), 3-phenyl-2,6-diphenyliminopiperidine (152), and the tetrachlorobiphenol (222) were identified in the relative proportions 4:1:10, respectively.

Preparative t.l.c, after multiple elution with benzene-ethyl acetate (19:1), afforded only the same three materials (191), (152), and (222) in the same proportions as above.

Vacuum sublimation at 10⁻¹ mmHg produced a pale brown solid identical in spectroscopic properties to the material being sublimed, suggesting the material was a single compound (Found: C, 63.2; H, 3.7; N, 6.2; Cl, 21.4. C₂₅H₂₅N₃O₂Cl₄ requires C, 63.5; H, 3.8; N, 6.35; Cl, 21.5 %); λ_max 223, 279, 289*, 340* nm; ν_max 320, 163, 160, 157.5, 154, 152, 150,
$147, 146, 141 \text{ mm}^{-1}$; $\chi$ (in CDCl$_3$) $2.62 \text{ (m; H}_1-19)$,
4.00 (s; H$_{20}^{21}$), 7.20 (m; H$_{22}^{25}$); $\chi$ (in CDCl$_3$-T.F.A.)
2.60 (m; H$_1-21$), 6.80 (m; H$_{22}^{25}$); $M^+$ (not observed) $\rightarrow$
337 + 322, 324, 326, 328, 330.

**Preparation of quinhydrone (224).** - p-Benzoinquinone
(225) (10g) was treated with sodium thiosulphate
(15g) in ethanol (100ml). The reaction was warmed
for 5min and green plates of the product, m.p.
171°, were filtered off and washed with ethanol;
$M^+$ 218.

**Preparation of 2,6-dianilinopyridine (236).** - 2,6-Di-
chloropyridine (237) (16g) was refluxed with aniline
(50ml) in the presence of copper sulphate (2g)
for 12hr. The solution was washed with water
(3x100ml) and excess aniline was evaporated under
reduced pressure (10 mmHg). The residue was chromat-
ographed on a column of alumina, eluting with
benzene. The first major yellow band was collected
and on evaporation afforded the product as fine,
colourless plates (12g), m.p. 201-202°, after
crystallization from ether-petroleum ether (1:1);
$\lambda_{\text{max}}$ (in ethanol) 242*, 268, 283, 335 nm; $\lambda_{\text{max}}$ (in
hexane) 238, 266, 280*, 325 nm; $\gamma_{\text{max}}$ 340, 325, 160,
159.5, 159, 150, 146 mm$^{-1}$; $M^+$ 261.
Reactions of 2,6-dianilinopyridine (236).

i) Attempted self-condensation with nitrobenzene. - 2,6-Dianilinopyridine (236) (2.6g) was refluxed with nitrobenzene (7ml) in o-dichlorobenzene (50ml) under nitrogen for 24hr. The solvent was evaporated under reduced pressure (10^-1 mmHg). T.l.c, eluting with benzene-ethyl acetate (19:1), showed that no reaction had occurred.

ii) Attempted self-condensation with chloranil. - a) 2,6-Dianilinopyridine (236) (2.6g) was refluxed with chloranil (2.5g) in n-pentanol at 150° under dry nitrogen for 30min. The solvent was removed under reduced pressure (10^-5 mmHg) and t.l.c showed that 2,6-dianilinopyridine (236) was returned in good yield (88%).

b) 2,6-Dianilinopyridine (236) (2.6g) was refluxed with chloranil (2.5g) in dry benzene under dry nitrogen for 2hr. T.l.c showed that 2,6-dianilinopyridine (236) was returned in good yield (93%).

iii) Attempted self-condensation with 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220). - 2,6-Dianilinopyridine (236) (2.6g) was refluxed with 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220) (3.2g) in various solvents including benzene, ethanol, and dioxan. No new condensation products could be identified by t.l.c.
iv) Attempted thermal self-condensation. - a). 2,6-Dianilinopyridine (236) (0.26g) was heated at 215° for 2hr in 1,2,4-trichlorobenzene under nitrogen. No new products were formed when the reaction mixture was investigated by t.l.c.
b). 2,6-Dianilinopyridine (236) (0.26g) was dry distilled at atmospheric pressure. The distillate was identical with the starting material (236) as shown by t.l.c. A trace of aniline was also detected.

Bromination - dehydrobromination of 3-phenyl-2,6-diphenyliminopiperidine (152). - 3-Phenyl-2,6-diphenyliminopiperidine (152) (3.39g) and N-bromosuccinimide (1.64g) were refluxed together for 30min in carbon tetrachloride (100ml) with azobisisobutyronitrile (239) (0.1g) as the radical initiator. Succinimide precipitated out, was filtered off, and the solvent was removed under reduced pressure (15mmHg). The residue was examined on t.l.c, by eluting with benzene-ethyl acetate (19:1). Five products were noted and on preparative t.l.c, eluting with benzene-carbon tetrachloride-ethyl acetate (5:1:1), the three major products were isolated.

The least polar component was identified as a monobromo-2,6-dianilino-3-phenylpyridine (240) containing a little of the dibromo derivative (242); $\lambda_{\text{max}}$
226, 320 nm; \( M^+ 415 \) and \( M^+ 493 \).

The second fraction was identified as 2,6-dianilino-3-phenylpyridine (188); \( \lambda_{\text{max}} 273, 290, 349 \) nm; \( \gamma_{\text{max}} 340, 325, 160, 158, 154, 150, 146 \) nm\(^{-1}\); \( \gamma (m; 2.60); M^+ 337 \).

The third fraction was identified as a monobromo-3-phenyl-2,6-diphenyliminopiperidine (243); \( \lambda_{\text{max}} 226, 320 \) nm; \( M^+ 417 \).

**Aerial oxidation of 3-phenyl-2,6-diphenyliminopiperidine (152).** - 3-Phenyl-2,6-diphenyliminopiperidine (152) (1g) was dissolved in ethanol (50ml) and allowed to stand for 12 weeks. Evaporation of the solvent and preparative t.l.c., eluting with benzene-ethyl acetate (19:1), afforded two products, 2,6-dianilino-3-phenylpyridine (188); \( \lambda_{\text{max}} 273, 290, 349 \) nm; \( M^+ 337 \); and 6-oxo-3-phenyl-2-phenyliminopiperidine (244); \( \lambda_{\text{max}} 231, 278 \) nm; \( M^+ 264 \).

A similar experiment performed by dissolving 3-phenyl-2,6-diphenyliminopiperidine (152) (1g) in chloroform (50ml) afforded the same products (188) and (244).

**Catalytic oxidation of 3-phenyl-2,6-diphenyliminopiperidine (152).** - 3-Phenyl-2,6-diphenyliminopiperidine (152) (1g) was heated with flowers of sulphur (0.5g) for 1hr at 180°. Hydrogen sulphide was evolved but
t.l.c, eluting with benzene-ethyl acetate (19:1), showed that no aromatic products had been formed.

3-Phenyl-2,6-diphenyliminopiperidine (152) (1g) was heated with flowers of sulphur (0.5g) and 10% rhodium on charcoal (0.5g) at 180° for 1hr. Chloroform extraction and evaporation of the solvent followed by t.l.c, eluting with benzene-ethyl acetate (19:1), showed that two aromatic products were formed. These were identified as 2,6-dianilino-3-phenylpyridine (188); \( \lambda_{\text{max}} 273, 290, 349 \text{ nm}; M^+ 337; \) and the 2,3'-bipyridyl (191); \( \lambda_{\text{max}} 242, 288, 315, 397 \text{ nm}; M^+ 581. \)

3-Phenyl-2,6-diphenyliminopiperidine (152) (1g) was refluxed with 10% rhodium on charcoal (0.5g) in \( \alpha \)-methylnaphthalene (10ml) under a stream of dry nitrogen for 5min. The major product after separation by preparative t.l.c, eluting with benzene-ethyl acetate (19:1), was 2,6-dianilino-3-phenylpyridine (188); \( \lambda_{\text{max}} 273, 290, 349 \text{ nm}; M^+ 337. \) A minor component from the reaction was identified as 2,6-di-(cyclohexylamino)-3-cyclohexylpiperidine (245) by its mass spectrum, \( M^+ 361. \) A trace of the 2,3'-bipyridyl (191) was also formed in the reaction.

The experiment was repeated as above but refluxing was continued for 30min. Preparative t.l.c, eluting with benzene-ethyl acetate (19:1), showed that an increased proportion of the 2,3'-bipyridyl (191) was formed.
Preparation of 2,6-di-imino-3-phenylpiperidine (144). -
(a) \( \alpha \)-Phenylglutaronitrile (187) (48.3g) was treated with liquid ammonia (100ml) in methanol (300ml) at 80\(^\circ\) in an autoclave for 18hr. The solution was evaporated under reduced pressure (15mmHg) and the product obtained as large hexagonal plates (22g), m.p. 200-201\(^\circ\) after crystallization from ethanol (Found: C, 70.7; H, 6.7; N, 22.3. Calc. for \( \text{C}_{11}\text{H}_{13}\text{N}_{3} \): C, 70.6; H, 6.9; N, 22.5\%); \( \lambda_{\text{max}} \) 253, 261* nm; \( \nu_{\text{max}} \) 340, 320, 168.5, 167, 160, 155, 153, 150, 146, 142 mm\(^{-1}\); \( \gamma \) (in T.F.A) 2.50 (s; \( \text{H}^{1-5} \)), 5.51 (t; \( \text{J}_{6-7,8} \) 8Hz; \( \text{H}^{6} \)), 6.50 (t; \( \text{J}_{9,10-7,8} \) 6Hz; \( \text{H}^{9,10} \)), 7.32 (dt; \( \text{J}_{7,8-6} \) 8Hz; \( \text{J}_{7,8-9,10} \) 6Hz; \( \text{H}^{7,8} \)); \( M^{+} \) 187.

(b) \( \alpha \)-Phenylglutaronitrile (187) (4.8g) was treated with sodamide (2g) in formamide (20ml) at 20\(^\circ\) for 18hr under nitrogen. A precipitate formed and was filtered off and washed with formamide, ethyl acetate and dry ether. The imidine was obtained as white crystals (4.7g) m.p. 200-202\(^\circ\) after crystallization from ethanol; \( \lambda_{\text{max}} \) 253, 261* nm; \( M^{+} \) 187.

Attempted dehydrogenation of 2,6-di-imino-3-phenylpiperidine (144) with nitrobenzene. - 2,6-Di-imino-3-phenylpiperidine (144) (4g) was suspended in dry o-dichlorobenzene (100ml), treated with nitrobenzene (14ml) and refluxed under dry nitrogen for 18hr. The solvent was evaporated under vacuum (10\(^{-1}\)mmHg).
The residue was composed of starting material (144), α-phenylglutaronitrile (187), and a less polar material. Column chromatography, eluting with dry benzene, afforded an intractable white semi-solid material. This could not be purified further and was not identified. The reaction was repeated under less drastic conditions using n-butanol as solvent. Preparative t.l.c, again afforded a small amount of the same material which could not be crystallized.
Preparation of α-carbethoxyglutaronitrile (249). - Ethyl cyanoacetate (45.2g), potassium cyanide (1g), water (1ml) and nitrobenzene (200ml) were refluxed together and acrylonitrile (21.2g) was added drop-wise over 40min to the stirred solution. Further portions of potassium cyanide (8x0.25g) were added during this period. Refluxing was continued for a further 30min and then the solution was cooled, washed with saturated sodium chloride solution (4x50ml), 2N-hydrochloric acid (3x50ml), a further portion of sodium chloride solution (50ml) and water (3x50ml). The residue was distilled under vacuum and an almost colourless fraction was collected, b.p. 144-154° at 3mmHg. Redistillation afforded a mobile, colourless liquid (33g), b.p. 155-156° at 4mmHg. (Found: C, 58.0; H, 5.9; N, 16.7. \( \text{C}_8\text{H}_{10}\text{N}_2\text{O}_2 \) requires C, 57.8; H, 6.0; N, 16.9%). \( \nu_{\max} \) 228, 174 mm\(^{-1}\); \( \tau \) 5.76 (q; \( J_6,7-8,9,10 \) 8Hz; \( H^6,7 \)), 6.30 (t; \( J_{1,4,5} \) 6Hz; \( H^1 \)), 7.55 (m; \( H^2-5 \)), 8.73 (t; \( J_{8,9,10-6,7} \) 8Hz; \( H^8-10 \)); \( M^+ \) 166.

A second material from the reaction was the di-cyanoethylation product, ethyl bis-(2-cyanoethyl)-cyanoacetate (250) which crystallized out from the high distillation residue, \( M^+ \) 219.

Preparation of potassium glutaronitrile-2-carboxylate (251). - Potassium hydroxide (5.6g) in ethanol (50ml) was added drop-wise over 20min to a stirred solution
of 2-carbethoxyglutaronitrile (249) (16.6g) in ethanol (50ml). After stirring for 3hr and standing overnight a white solid was filtered off, the filtrate concentrated to 20ml and further solid filtered off. The combined precipitate was quickly washed with ethanol (5ml) and then with dry ether (5ml). The off-white solid (12g) was dried and stored under vacuum; \( \tau (D_2O) 7.38 (t; J_{2,3-4,5} 6Hz; H^2,3), 7.80 (t; J_{4,5-2,3} 6Hz; H^4,5) \).

**Preparation of 2-carboxyglutaronitrile (252).** - Potassium glutaronitrile carboxylate (251) (17.6g) was dissolved in water (50ml) and cooled to 0°. Concentrated hydrochloric acid (3ml) was added drop-wise with vigorous stirring. The aqueous solution was extracted with nitromethane (3x20ml) and dried with magnesium sulphate. The organic extract was distilled under reduced pressure (15mmHg) to remove the solvent, and the product (252) crystallized out on standing affording colourless needles (10.7g) (Found: C, 52.7; H, 4.0; N, 20.0. \( C_8H_6N_2O_2 \) requires C, 52.2; H, 4.3; N, 20.3%); \( \nu_{\text{max}} 320, 270, 220, 171, 149 \text{ mm}^{-1} \); \( M^+ 138 \).

**Reaction of 2-carboxyglutaronitrile (252) with ketones under Knoevenagel conditions.** - 2-Carboxyglutaronitrile (252) (1.4g) was refluxed for 12hr with cyclo-pentanone (1.7g) in benzene (20ml) with piperidine
(0.5ml) as catalyst. No reaction occurred involving Knoevenagel condensation. The experiment was repeated using the mixed catalyst piperidine (0.5ml) and pyridine (0.5ml) and using ammonium acetate (1g) in glacial acetic acid (20ml), but no products could be identified.

The experiments were repeated on cyclohexanone (2g) and methyl n-propyl ketone (1.8g) without success.

Preparation of 2-ethylidene glutaronitrile (253). - A mixture of allyl cyanide (67g) and acrylonitrile (53g) was added dropwise during 3hr to a stirred solution of t-butanol (250ml) and tetramethylammonium hydroxide (16ml of a 25% aqueous solution) whilst keeping the temperature at 10°. The solution was stirred for a further 1hr at 10°, then for 3hr at 20° and left to stand overnight. Dilute hydrochloric acid was added dropwise until the solution was acid to Congo red. It was taken up in 1,2-dichloroethane, shaken with water (25ml) and the 1,2-dichloroethane layer was separated and evaporated under reduced pressure (15mmHg) on a steam bath. The residual oil was distilled under reduced pressure (0.4mmHg) affording a colourless oil (68g) b.p. 105-120° at 0.4mmHg. This fraction was redistilled affording a colourless oil (48g) b.p. 120-122° at 0.6mmHg (Found: C, 69.8; H, 6.5; N, 23.1.
\[ \text{C}_7\text{H}_8\text{N}_2 \] requires C, 70.0; H, 6.65; N, 23.23%; \( \nu \max \) 227, 223, 166, 146, 141 mm\(^{-1}\); \( \tau \) 3.40 (q; \( \nu \) 6, 7, 8 Hz; \( \nu \) 5), 7.43 (s; \( \nu \) 1-4), 8.0 (d; \( \nu \) 5, 6, 7, 8-5 Hz); \( \text{M}^+ \) 120.

The distillation residue afforded \( \gamma \)-cyano-\( \gamma \)-vinylpimelonitrile (254) (0.8g) as colourless crystals; \( \nu \max \) 227, 164.5, 146 mm\(^{-1}\); \( \text{M}^+ \) 175.

**Preparation of 3-ethylidene-2,6-diphenyliminopiperidine (257).** - 2-Ethylideneglutaronitrile (253) (1g) and aniline hydrochloride (2.4g) were heated together to 240° with stirring. The melt turned red and stiffened, as a mass of ammonium chloride was formed. Trituration with water (2ml) was followed by dissolution in ethanol (20ml). Aqueous 10% sodium hydroxide solution (6ml) was added, followed by water (25ml). The solution was chloroform extracted (3x25ml) and the extract dried with magnesium sulphate and evaporated under reduced pressure (15mmHg). The residue was treated with dry ether and the yellow solid was washed with dry ether. Recrystallization was best achieved from dry isopropanol affording a pale yellow solid (0.8g) (Found: C, 78.6; H, 6.5; N, 14.5. \( \text{C}_{19}\text{H}_{19}\text{N}_3 \) requires C, 78.85; H, 6.55; N, 14.6%); \( \lambda \max \) 230, 285 nm; \( \nu \max \) 347, 335, 164, 146, 141 mm\(^{-1}\); \( \tau \) 3.00 (m; \( \text{H}^{10-19} \)), 3.40 (\( \text{H}^5 \)), 5.60 (\( \text{H}^9 \)), 6.45 (q; \( \text{H}^{3',4'} \)), 7.40 (m; \( \text{H}^{1-4} \)), 8.00 (\( \text{H}^6-8 \)), 8.80 (t; \( \text{H}^{5'-7'} \)); \( \tau (\text{CF}_3\text{CO}_2\text{H}) \) 2.60 (m;
Preparation of $\beta$-n-propylcrotonitrile (255). - Cyanoacetic acid (85g) and methyl n-propyl ketone (86g) were refluxed together for 3hr in benzene (250ml) with piperidine (5ml) as catalyst. Water (18ml) was collected in a Dean and Stark apparatus, and CO$_2$ was evolved during the reaction. The solvent was distilled off under vacuum (15mmHg) and the residue distilled at 15mmHg affording a pale yellow, viscous oil (255) (32g), b.p. 86-88° at 15 mmHg (Found: C, 76.8; H, 9.8; N, 12.6. $C_7H_{11}N$ requires C, 77.05; H, 10.1; N, 12.85 %); $\nu_{max}$ 222, 163, 146, 144, 138.5 mm$^{-1}$; $\gamma$ 4.90 (s; H$^1$), 8.15 (m; H$^2-8$), 9.10 (t; J 9,10,11-4,5 6Hz; H$^9-11$); $M^+$ 109.

Preparation of 1,3-dicyano-4-methylhept-3-ene (256). - A solution of $\beta$-n-propylcrotonitrile (255) (10.9g) and acrylonitrile (5.3g) was added dropwise to a stirred solution of t-butanol (25ml) and tetramethylammonium hydroxide (1.6ml of a 25% aqueous solution) over a period of 3hr while maintaining the temperature at 10°. The solution was stirred for a further 1hr at 10°, then 3hr at 20°, and left to stand for 16hr. The solution was neutralized to Congo red with dilute hydrochloric acid, taken up in 1,2-dichloroethane, shaken with water (25ml) and
the 1,2-dichloroethane layer was separated and evaporated under reduced pressure (15mmHg) on a steam-bath. The residual oil was distilled under reduced pressure (0.1mmHg) and a small yield of the product (256) was obtained as a pale yellow oil (4.2g), b.p. 120-123° at 0.1mmHg (Found: C, 73.8; H, 8.55; N, 17.1. \( \text{C}_{10}\text{H}_{14}\text{N}_2 \) requires C, 74.05; H, 8.65; N, 17.3 %); \( \nu_{\text{max}} \) 230, 227, 161.5, 154, 136 mm\(^{-1} \); \( \text{M}^+ \) 162.

**Thermal condensation of 1,3-dicyano-4-methylhept-3-ene (256) with aniline hydrochloride.** - 1,3-Dicyano-4-methylhept-3-ene (256) (1.6g) was heated with aniline hydrochloride (2.6g) at temperatures between 200° and 300° for 30min periods with stirring. Ammonium chloride sublimed and the melt thickened but no exothermic reaction took place. The melt was dissolved in ethanol (20ml) and neutralized with sodium hydroxide (0.65g) in water (10ml). Chloroform extraction (3x25ml) and evaporation of the solvent left a viscous liquid which proved to be extremely difficult to purify. No recognizable products apart from the starting material (256) were detected.
Preparation of 6-imino-2-N-methylanilino-ΔH'-piperidine (263). - Glutaronitrile (9.4g) and N-methylaniline (21.4g) were refluxed together with sodium (0.5g) in ethanol (50ml) under nitrogen for 3hr. The solution was poured into water and filtered. The precipitate was washed with ethanol (5ml). Column chromatography, eluting with benzene, and collecting the first yellow fraction afforded 6-imino-2-N-methylanilino-ΔH'-piperidine (263) (2.7g) as a yellow solid which would not crystallize; \( \lambda_{\text{max}}^{245} \), 297 nm; \( \gamma_{\text{max}} \) 340, 167, 160, 150, 146, 141 mm\(^{-1}\); M\(^+\) 201.

The experiment was repeated with the refluxing time extended to 12hr. Column chromatography again afforded 6-imino-2-N-methylanilino-ΔH'-piperidine (263) (2.1g) and a second fraction was identified as 2-N-methylanilino-6-oxo-ΔH'-piperidine (264) (0.4g); \( \lambda_{\text{max}} \) 276 nm; \( \gamma_{\text{max}} \) 320, 172, 166 mm\(^{-1}\); M\(^+\) 202.

Prolonging the refluxing period to 24hr followed by column chromatography of the product afforded glutarimide (131) (4.8g) as the major product; M\(^+\) 113.

Preparation of 2,6-di-(N,N-dimethylamino)-3,4-dihydropyridine (265). - Glutaronitrile (18.8g) was treated with dimethylamine (18g) in methanol (150ml) at 162° in an autoclave at autogeneous pressure for 24hr. The solvent and excess dimethylamine were distilled off under reduced pressure (15mmHg).
The residue was a colourless, viscous liquid (15g) which could not be solidified. It was identified as 2,6-di-(N,N-dimethylamino)-3,4-dihydropyridine (265); $\lambda_{\text{max}}$ 269*, 293, 311 nm; $\nu_{\text{max}}$ 166, 164, 146, 141 mm$^{-1}$; M$^+$ 167.

Reaction of glutaronitrile with morpholine. - Glutaronitrile (1.9g) and morpholine (1.8g) were refluxed in ethanol (10ml) containing sodium (0.1g) under nitrogen for 12hr. The mixture was poured into water (25ml) and neutralized with dilute hydrochloric acid. The solution was extracted with chloroform (3x25ml) and the solvent distilled off under vacuum (15mmHg) affording a viscous liquid. Distillation under high vacuum (10$^{-1}$mmHg) afforded morpholine and glutaronitrile.

Reaction of glutaronitrile and diethylamine. - Glutaronitrile (9.4g) and diethylamine (14.6g) were refluxed together with sodium (0.5g) dissolved in ethanol (50ml) under nitrogen for 12hr. Following neutralization with hydrochloric acid (0.6ml) and chloroform extraction (3x25ml) the organic fraction was distilled. The starting materials were returned in high yield.
Preparation of 1,4-di-(6-imino-5-phenyl-2-piperidinylidene-aza)benzene (266). - α-Phenylglutaronitrile (187) (3.4g) and p-phenylenediamine (1.1g) were refluxed together with 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g) under nitrogen for 3 hr. The solution was poured into water (100ml) and the precipitate collected and washed with ethanol (5ml). The yellow solid (266) (2.1g) could not be crystallized nor would it sublime; $\lambda_{\text{max}}$ (in dimethylformamide) 248, 304, 341*nm; $\gamma_{\text{max}}$ 340, 164, 160 mm$^{-1}$; $M^+$ 448.

Attempted preparation of the p-aza macrocycle (267). - The three-unit compound (266) (0.45g) was refluxed with p-phenylenediamine (0.11g) in 2-ethoxyethanol (10ml) containing sodium 2-ethoxyethoxide (from sodium 0.02g) under nitrogen for 12 hr. Precipitation with water afforded a yellow solid, identical to the starting material (266).

Preparation of 1,3-di-(6-imino-5-phenyl-2-piperidinylidene-aza)benzene (268). - Glutaronitrile (1.88g) and m-phenylenediamine (1.1g) were refluxed together in 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g) under nitrogen for 3 hr. The solution was poured into water (100ml) and the precipitate collected and washed with ethanol (5ml). The yellow solid (268) (1.2g) could
not be crystallized; $\lambda_{\text{max}}$ (in dimethylformamide) 300, 326 nm; $\nu_{\text{max}}$ 370, 340, 165, 164, 160, 158 mm$^{-1}$; $m^+$ 296.

**Attempted preparation of the m-aza macrocycle (269).**
- The three-unit compound (268) (0.3g) was refluxed with m-phenylenediamine (0.11g) in 2-ethoxyethanol containing sodium 2-ethoxyethoxide (from sodium 0.02g) under nitrogen for 12hr. Precipitation with water afforded a yellow solid, identical to the starting material (268).

**Reaction of glutaronitrile with ethylenediamine.**
- (a) Glutaronitrile (1.9g) and ethylenediamine (1.2g) were refluxed in ethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g) under nitrogen for 3hr. The solution was cooled and filtered affording white crystals of a three-unit imidazole product (270) (0.8g) after recrystallization from ethanol (Found: C, 59.8; H, 8.8; N, 31.0. C$_9$H$_{16}$N$_4$ requires C, 60.0; H, 8.9; N, 31.1 %); $\lambda_{\text{max}}$ 243, 267 nm; $\nu_{\text{max}}$ 335, 324, 163, 161, 150 mm$^{-1}$; $\tau$ 6.22 (s; H$^{15,16}$), 6.44 (s; H$^{1-6}$), 7.70 (m; H$^{7-14}$); $M^+$ 180. The filtrate from the reaction was poured into water (100ml) and the yellow precipitate filtered off and washed with ethanol (5ml). Crystallization was not achieved and the product was obtained as a yellow solid (0.5g) identified as 2-(2-amino-
ethylamino)-6-(2-aminooethylamino)-Δ^4-piperidine (278)
(Found: C, 54.5; H, 9.5; N, 35.2. C_{9}H_{19}N_{5} requires
C, 54.8, H, 9.65; N, 35.55 %); \( \lambda_{\text{max}} \) 240, 298 nm;
\( \gamma_{\text{max}} \) 350, 340, 162, 144, 134.5 mm\(^{-1}\); M\(^{+}\) 197.

(b) Glutaronitrile (3.8g) and ethylenediamine (1.2g)
were refluxed together in 2-ethoxyethanol (20ml)
containing sodium 2-ethoxyethoxide (from sodium 0.2g)
under nitrogen for 5hr. The solution was cooled
affording white crystals (1.5g) identical with (270);
\( \lambda_{\text{max}} \) 243, 267nm; M\(^{+}\) 180.
The filtrate was poured into water (100ml) and
the precipitate collected and washed with ethanol
(5ml). The yellow solid (0.3g) could not be
crystallized but was identified as (278) by its
spectral properties; \( \lambda_{\text{max}} \) 240, 298 nm; M\(^{+}\) 197.

(c) Reaction between glutaronitrile (1.9g) and
ethylenediamine (2.4g) in boiling 2-ethoxyethanol
(20ml) containing sodium 2-ethoxyethoxide (from
sodium 0.2g) under nitrogen for 5hr afforded the
same products as above (270) and (278) in about
the same proportions (1.6g) and (0.3g) respectively.

Attempted preparation of the macrocycle (280). -
The three-unit condensation product (278) (2.0g) was
refluxed with glutaronitrile (0.94g) in 2-ethoxy-
ethanol (10ml) containing sodium 2-ethoxyethoxide
(from sodium 0.1g) under nitrogen for 24hr. The
solution was cooled and poured into water (20ml)
affording a yellow solid (1.8g) identical to the starting material (278)

Reaction of glutaronitrile with \( \text{o-phenylenediamine} \).- Glutaronitrile (1.9g) and \( \text{o-phenylenediamine} \) (4.3g) were refluxed together under nitrogen for 3hr in 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g). The solution was cooled and poured into water (50ml) affording a yellow solid (2.8g), identified as the three-unit condensation product (281) (Found: C, 73.6; H, 5.6; N, 20.0. \( \text{C}_{17}\text{H}_{16}\text{N}_{4} \) requires C, 73.9; H, 5.8; N, 20.3%); \( \lambda_{\text{max}} \) 241, 273*, 275, 281, 290 nm; \( \text{M}^{+} \) 276.

Reaction of glutaronitrile with 2,6-diaminopyridine.- Glutaronitrile (1.9g) and 2,6-diaminopyridine (1.1g) were refluxed together in 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g) under nitrogen for 12hr. The cooled solution was poured into water (50ml) and the white precipitate filtered off and washed with ethanol (5ml). It was identical with the starting material 2,6-diaminopyridine; \( \text{M}^{+} \) 109.

The experiment was repeated using equimolar quantities of glutaronitrile (0.94g) and 2,6-diaminopyridine (1.09g). Precipitation into water again afforded over 90% return of the starting material 2,6-diaminopyridine.
Reaction of glutaronitrile with 2,8-diaminoacridine.

Glutaronitrile (1.9g) and 2,8-diaminoacridine (4.2g) were refluxed together in 2-ethoxyethanol (100ml) containing sodium 2-ethoxyethoxide (from sodium 1g) under nitrogen for 8hr. The solution was cooled and a dark yellowish solid (1.4g) filtered off. It could not be recrystallized. Mass spectral examination identified one of its components as 2-amino-8-(6-imino-2-piperidinylidene-amino)acridine (282); \( \lambda_{\text{max}} \) (in dimethylformamide) 452 nm; \( M^+ \) 303.

Further condensation of the two-unit addition product (282) (0.3g) with glutaronitrile (0.1g) was attempted in 2-ethoxyethanol (10ml) containing sodium 2-ethoxyethoxide (from sodium 0.01g). After 24hr the starting material (282) (0.28g) was returned.

The two-unit addition product (282) (0.3g) was refluxed with 2,8-diaminoacridine (0.21g) in 2-ethoxyethanol (10ml) containing sodium 2-ethoxyethoxide (from sodium 0.01g) under nitrogen for 24hr. Only starting materials could be identified in the reaction mixture.

Reaction of glutaronitrile with 1,3-di-iminoisoindoline.

Glutaronitrile (1.9g) and 1,3-di-iminoisoindoline (2.9g) were refluxed together in 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g) for 3hr under nitrogen. The solution was cooled and phthalocyanine (0.4g) was
filtered off; $\lambda_{\text{max}}$ 702, 667, 635, 604, 575, 555 nm.
The filtrate deposited further pale yellow crystals (1.2g) on standing. The product was recrystallized from ethanol and identified as the monoamide of tricyanocycophenine (283) (Found: C, 71.4; H, 3.4; N, 20.8. C$_{24}$H$_{14}$N$_{6}$O requires C, 71.6; H, 3.5; N, 20.9%); $\lambda_{\text{max}}$ 274 nm; $\gamma_{\text{max}}$ 342, 324, 312, 224, 165, 163, 158 mm$^{-1}$; $\tau$ 0.80 (m; 1H), 2.10 (m; 3H); $M^+$ 402.
Preparation of 2-(cyanophenylmethylidene)-6-imino-piperidine (157). - Glutaronitrile (1.9g) and phenylacetonitrile (1.2g) were refluxed together in ethanol (20ml) containing sodium ethoxide (from sodium 0.2g) under nitrogen for 1hr. The solution was neutralized with dilute hydrochloric acid and washed with water (3x20ml). The organic residue was distilled under reduced pressure (15mmHg) to remove solvent, affording white crystals (2.6g), m.p. 160° after recrystallization from ethanol (Found: C, 73.9; H, 6.1; N, 19.9. C_{13}H_{13}N_{3} requires C, 73.95; H, 6.15; N, 19.9 %); \( \lambda_{\text{max}} \) 232, 318 nm; \( \nu_{\text{max}} \) 359, 345, 336, 332, 220, 166, 162.5, 162, 160, 157.5, 155, 154, 149.5, 147, 143.5, 142 mm\(^{-1}\); \( \tau \) 2.70 (m; H\(_1-7\)), 7.75 (m; H\(_8-13\)); \( M^+ \) 211.

Preparation of 2,6-di-(cyanophenylmethylidene)piperidine (286). - Glutaronitrile (1.9g) and phenylacetonitrile (2.4g) were refluxed together in 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g) under nitrogen. The reaction was followed spectroscopically, and immediately on heating the two-unit addition product (157) was formed. After refluxing for 20hr the longwavelength absorption of the reaction mixture was constant and the solution was neutralized with dilute hydrochloric acid and poured into water (50ml). The yellow precipitate was collected, washed with ethanol and recrystallized
from ethanol affording yellow prisms (3.6g) of 2,6-di-(cyanophenylmethylidene)piperidine (286) (Found: C, 81.0; H, 5.5; N, 13.4. C_{21}H_{17}N_{3} requires C, 81.0; H, 5.5; N, 13.5%); \( \lambda_{\text{max}} \) 246, 335 nm, \( \gamma_{\text{max}} \) 359, 336, 272, 220, 164, 162, 160, 157.5, 149.5, 147, 143.5, 142 mm\(^{-1}\); \( M^{+} \) 311.

Reaction of 2-(cyanophenylmethylidene)-6-iminopiperidine (157) with aniline. - 2-(Cyanophenylmethylidene)-6-iminopiperidine (157) (2.1g) was refluxed with aniline (1ml) in 2-ethoxyethanol (10ml) containing sodium 2-ethoxyethoxide (from sodium 0.1g) under nitrogen for 5hr. The solution was poured into water (25ml) and the precipitate filtered off and washed with ethanol (5ml), and recrystallized from ethanol affording 2,6-di-(cyanophenylmethylidene)piperidine (286) (2.2g); \( \lambda_{\text{max}} \) 246, 335 nm; \( M^{+} \) 311. The mother liquor from the recrystallization was evaporated affording a yellow solid, identified as the three-unit condensation product, 2-cyanophenylmethylidene-6-phenyliminopiperidine (287) (0.4g), which was dissolved in dimethylformamide and precipitated with water; \( \lambda_{\text{max}} \) 237, 286, 338 nm; \( \gamma_{\text{max}} \) 359, 339, 220, 167, 162, 160, 152, 150, 145, 142 mm\(^{-1}\); \( M^{+} \) 289.

Preparation of 2,6-diacetonylidene-3-phenylpiperidine (288). - \( \alpha \)-Phenylglutaronitrile (187) (1.9g) and an
excess of acetone (5g) were refluxed together in 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g) under nitrogen for 3hr. The solution was poured into water (50ml) and the precipitate filtered off and washed with ethanol affording 2,6-diacetonylidene-3-phenylpiperidine (288) (1.7g) as a white solid (Found: C, 75.9; H, 7.0; N, 5.1. C_{17}H_{19}NO_2 requires C, 75.8; H, 7.05; N, 5.2 %); \( \lambda_{\text{max}} \) 330 nm; \( \gamma_{\text{max}} \) 330, 167, 157 mm\(^{-1}\); \( M^+ \) 269.

Preparation of 2,6-di-(cyanoethoxycarbonylmethylidene)-piperidine (289). - Glutaronitrile (1.9g) and ethyl cyanoacetate (4.5g) were refluxed together under nitrogen for 5hr in 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g). The reaction mixture was poured into water and the yellow precipitate of 2,6-di-(cyanoethoxycarbonylmethylidene)piperidine (289) (3.7g) filtered off and washed with ethanol (Found: C, 59.1; H, 5.5; N, 13.5. C_{15}H_{17}N_3O_4 requires C, 59.4; H, 5.6; N, 13.85 %); \( \lambda_{\text{max}} \) (in dimethylformamide) 280, 343, 400 nm; \( \gamma_{\text{max}} \) 336, 222, 163, 158 mm\(^{-1}\); \( M^+ \) 303.

Condensation of glutaronitrile and p-dicyanoxylylene. - (a) Glutaronitrile (1.9g) and p-dicyanoxylylene (6.3g) were refluxed together in 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium
0.2g) under nitrogen for 5hr. The solution was poured into water affording 2,6-di-(cyano-(4-cyanomethylphenyl)methylidene)piperidine (290) (5.3g) (Found: C, 77.0; H, 4.9; N, 17.9. C_{25}H_{19}N_{5} requires C, 77.1; H, 4.9; N, 18.0%; \( \lambda_{\text{max}} \) (in dimethylformamide) 295, 327, 450 nm; \( \gamma_{\text{max}} \) 359, 351, 336, 224.5, 220, 173, 171, 169, 162, 156.5, 155.5, 151, 141 mm\(^{-1}\); \( M^+ \) 389.

(b) Glutaronitrile (3.8g) and p-dicyanoxylylene (3.2g) were refluxed together in 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g) under nitrogen for 5hr. The reaction mixture was poured into water (50ml) and the yellow precipitate filtered off and washed with ethanol (5ml) affording 1,4-di-(cyano-(6-imino-2-piperidinylidene)methyl)benzene (291) (4.2g) (Found: C, 69.5; H, 5.7; N, 24.4. C_{20}H_{20}N_{6} requires C, 69.5; H, 5.8; N, 24.45%); \( \lambda_{\text{max}} \) 334, 480 nm; \( \gamma_{\text{max}} \) 359, 335, 220, 170, 169.5, 162, 157, 152 mm\(^{-1}\); \( M^+ \) 344.

Preparation of the cyanomethylene-p-macrocyle (292).
- (a) 2,6-Di-(cyano-4-cyanomethylphenylmethylidene)piperidine (290) (3.9g) was treated with glutaronitrile (1g) in boiling 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g) under nitrogen for 24hr. The reaction mixture was poured into water (50ml) and the brown precipitate
was washed with ethanol (5ml). The precipitate was dissolved in boiling dimethylacetamide and precipitated with water, filtered off and washed with hot ethanol, affording the cyanomethylene-p-macrocycle (292) (2.1g) (Found: C, 76.9; H, 4.5; N, 18.0. C₃₀H₂₂N₆ requires C, 77.2; H, 4.7; N, 18.1%); λ_max (in dimethylformamide) 288, 330, 468 nm; υ_max 359, 349, 336, 320, 220, 172.5, 171, 164, 161.5, 156, 151.5 mm⁻¹; M⁺ 466.

(b) 1,4-Di-(cyano-(6-imino-2-piperidinylidene)methyl)-benzene (291) (3.44g) was treated with p-dicyanoxylylene (1.6g) in boiling 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g) under nitrogen for 24hr. The reaction mixture was poured into water (50ml) and the brown precipitate was washed with ethanol (5ml). The precipitate was dissolved in boiling dimethylacetamide and precipitated with water, filtered off and washed with hot ethanol, affording the cyanomethylene-p-macrocycle (292) (2.9g) (Found: C, 77.0; H, 4.6; N, 17.8. C₃₀H₂₂N₆ requires C, 77.2; H, 4.7; N, 18.1%); λ_max (in dimethylformamide) 288, 330, 468 nm; υ_max 358, 349, 336, 321, 220, 172, 171, 164, 161, 156, 151.5 mm⁻¹; M⁺ 466.

Condensation of glutaronitrile and m-dicyanoxylylene.
- (a) Glutaronitrile (1.9g) and m-dicyanoxylylene (6.3g) were refluxed together in 2-ethoxyethanol
(20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g) under nitrogen for 5hr. The solution was poured into water (50ml) and the yellow precipitate filtered off, washed with ethanol (5ml) affording 2,6-di-(cyano-(3-cyanomethylphenyl)methylidene) piperidine (293) (4.6g) (Found: C, 76.9; H, 4.8; N, 17.8. C_{25}H_{19}N_{5} requires C, 77.1; H, 4.9; N, 18.0%); \( \lambda_{\text{max}} \) (in dimethylformamide) 293, 332, 440 nm; \( \gamma_{\text{max}} \) 359, 351, 335, 224.5, 220, 170, 162, 156.5, 151, 141 nm\(^{-1}\); \( M^+ \) 389.

(b) Glutaronitrile (3.8g) and \( m \)-dicyanoxylylene (3.2g) were refluxed together in 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g) under nitrogen for 5hr. The solution was poured into water (50ml) and the yellow precipitate filtered off, washed with ethanol (5ml) affording 1,3-di-(cyano-(6-imino-2-piperidinylidene)methyl)benzene (294) (3.9g) (Found: C, 69.3; H, 5.5; N, 24.2. C_{20}H_{20}N_{6} requires C, 69.75; H, 5.8; N, 24.45%); \( \lambda_{\text{max}} \) (in dimethylformamide) 290, 334, 462 nm; \( \gamma_{\text{max}} \) 363, 359, 345, 335, 220, 170, 162, 160, 156.5 nm\(^{-1}\); \( M^+ \) 344.

Preparation of the cyanomethylene-\( m \)-macrocycle (295).-(a) 2,6-Di-(cyano-(3-cyanomethylphenyl)methylidene)piperidine (293) (3.9g) was treated with glutaronitrile (1g) in boiling 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g) under
nitrogen for 24hr. The reaction mixture was poured into water (50ml) and the brown precipitate washed with ethanol (5ml). The precipitate was dissolved in boiling dimethylacetamide and precipitated with water, filtered off and washed with hot ethanol, affording the cyanomethylene macrocycle (295) (1.5g) (Found: C, 76.6; H, 4.5; N, 17.8. C$_{30}$H$_{22}$N$_6$ requires C, 77.2; H, 4.7; N, 18.1 %); $\lambda_{\text{max}}$ (in dimethylformamide) 290, 330, 452 nm; $\gamma_{\text{max}}$ 362, 359, 347, 335, 220, 171, 162, 157, 154, 151.5 mm$^{-1}$; M$^+$ 466.

(b) 1,3-Di-(cyano-(6-imino-2-piperidinylidene)methyl)-benzene (294) (3.44g) was treated with m-dicyanoxylidene (1.6g) in boiling 2-ethoxyethanol (20ml) containing sodium 2-ethoxyethoxide (from sodium 0.2g) under nitrogen for 24hr. The reaction mixture was poured into water (50ml) and the brown precipitate washed with ethanol (5ml). The precipitate was dissolved in boiling dimethylacetamide and precipitated with water, filtered off and washed with hot ethanol, affording the cyanomethylene macrocycle (295) (1.8g) (Found: C, 76.7; H, 4.4; N, 17.6. Calc. for C$_{30}$H$_{22}$N$_6$: C, 77.2; H, 4.7; N, 18.1 %); $\lambda_{\text{max}}$ (in dimethylformamide) 289, 330, 452 nm; $\gamma_{\text{max}}$ 363, 359, 348, 336, 220, 171, 162, 157, 154, 151.5 mm$^{-1}$; M$^+$ 466.

Attempted dehydrogenation of 2-(cyanophenylmethyldiene)-6-iminopiperidine (157). (a) With nitrobenzene. - 2-(Cyanophenylmethyldiene)-6-iminopiperidine (157) (2.1g)
was refluxed with nitrobenzene (2ml) in o-dichlorobenzene (20ml) under nitrogen for 18hr. The solvent was removed under reduced pressure (10⁻¹mmHg) and the residue crystallized from ethanol affording the starting material (157) (1.7g); \(\lambda_{\text{max}}\) 233, 318 nm; \(M^+\) 211.

(b) With 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220). - 2-(Cyanophenylmethylidene)-6-iminopiperidine (157) (2.1g) was treated with 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220) (3.2g) in boiling dry benzene (50ml) for 30min. The solvent was evaporated under reduced pressure (15mmHg) and the residue examined by u.v. spectroscopy. The starting material (157); \(\lambda_{\text{max}}\) 232, 318 nm; and 3,3',5,5'-tetrachloro-4,4'-biphenol (222); \(\lambda_{\text{max}}\) 217, 267, 288* nm; were the only products identified. This was confirmed by mass spectrometry; (157) \(M^+\) 211; and (222) \(M^+\) 322.

(c) With N-bromosuccinimide. - 2-(Cyanophenylmethylidene)-6-iminopiperidine (157) (2.1g) was treated with N-bromosuccinimide (3g) in dry carbon tetrachloride (50ml) and refluxed for 30min with azobisisobutyronitrile (239) (0.2g) as radical initiator. Succinimide was precipitated and filtered off and the solvent was removed under reduced pressure (15mmHg). The residue was crystallized from ethanol affording 2,6-di-(cyanophenylmethylidene)piperidine (286) (0.8g); \(\lambda_{\text{max}}\) 246, 335 nm; \(M^+\) 311.
Attempted dehydrogenation of 2,6-di-(cyanophenylmethylidene)piperidine (286). - (a) With nitrobenzene.
- 2,6-Di-(cyanophenylmethylidene)piperidine (286) (3.1g) was refluxed with nitrobenzene (2ml) in o-dichlorobenzene (20ml) under nitrogen for 18hr. The solvent was removed under reduced pressure (10⁻¹mmHg) and the residue crystallized from ethanol affording the starting material (286) (2.7g); \( \lambda_{\text{max}} 246, 335 \text{ nm} \); \( M^+ 311 \).

(b) With 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220).
- 2,6-Di-(cyanophenylmethylidene)piperidine (286) (3.1g) was treated with 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220) (3.2g) in boiling dry benzene (50ml) for 30min. The solvent was evaporated under reduced pressure (15mmHg) and the residue examined by u.v. spectroscopy. The starting material (286); \( \lambda_{\text{max}} 246, 335 \text{ nm} \); and 3,3',5,5'-tetrachloro-4,4'-biphenol (222); \( \lambda_{\text{max}} 217, 267, 288* \text{ nm} \); were the only products identified. This was confirmed by mass spectrometry; (286) \( M^+ 311 \) and (222) \( M^+ 322 \).

(c) With N-bromosuccinimide. - 2,6-Di-(cyanophenylmethylidene)piperidine (286) (3.1g) was treated with N-bromosuccinimide (3g) in dry carbon tetrachloride (50ml) and refluxed for 30min with azobisisobutyronitrile (239) (0.2g) as radical initiator. Succinimide was precipitated and filtered off and the solvent was removed under reduced pressure (15mmHg).
The residue was crystallized from ethanol affording the starting material (286) (2.5g). The mother liquor from the crystallization was evaporated to dryness affording a yellow solid which was washed with ethanol and identified as the monobromo derivative (296) (0.2g); $\lambda_{max}$ 315nm; $\gamma_{max}$ 359, 343, 335, 326, 272, 220, 171, 162, 151 m$^{-1}$; $\Delta^+$ 389.

**Attempted dehydrogenation of 2,6-di-(cyano-(4-cyanomethylphenyl)methylidene)piperidine (290) with N-lithioethylenediamine.** - N-Lithioethylenediamine was prepared by treating dry ethylenediamine (6g) with lithium (1.6g), under nitrogen at 100°. 2,6-Di-(cyano-(4-cyanomethylphenyl)methylidene)piperidine (290) (4.7g) was slowly added to the solution under nitrogen at 100°. Hydrogen was evolved and the reaction was continued for 3hr. The reaction mixture was poured into water (50ml) and neutralized with hydrochloric acid. The precipitate was filtered off and washed with ethanol. It could not be crystallized and was not identified; $\lambda_{max}$ (in dimethylformamide) 468 nm.
NOTES ON THE EXPERIMENTAL

(i) Thin Layer Chromatography (t.l.c). This was carried out on glass plates (20x5cm) carrying a layer (0.1mm) of silica-gel (Merck G). The chromatograms were developed by spraying with potassium permanganate (0.35g) in water-2N-sulphuric acid (3:1) (100ml) and examined under ultra-violet light (low pressure mercury ultra-violet lamp, 125 watt).

(ii) Preparative Thick Layer Chromatography (preparative t.l.c). This was carried out on glass plates (50x20cm) carrying a layer (2mm) of silica-gel (Merck PF254+366).

(iii) Ultra-violet Spectra. These were recorded on a Unicam SP800 instrument using 96% ethanol unless stated.

(iv) Infra-red Spectra. These were recorded as liquid films or as Nujol mulls on a Unicam SP200 instrument.

(v) Proton Magnetic Resonance Spectra (p.m.r). These were recorded for deuteriochloroform solutions at 60 MHz on a Perkin-Elmer R.10 spectrometer, unless otherwise stated. Chemical shifts are reported on the \( \tau \) scale and coupling constants in Hz. The abbreviations used for describing the multiplicity of the signals are shown in the table.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tr>
<td>s</td>
<td>singlet</td>
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<tr>
<td>d</td>
<td>doublet</td>
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</table>
In the p.m.r data reported in the experimental sections the subscripts refer to features of the structural diagrams in the discussion.

(vii) **Mass Spectra.** These were determined on an M.S. 12 instrument (70e/v) operating with a source temperature slightly higher than the melting point of the sample.

(viii) **Melting Points.** These were determined on a Kofler hot-stage apparatus.
CHAPTER 8

MASS SPECTRA
Glutaronitriles

where $R_1=\text{Ph}$, $R_2=\text{H}$, $R_3=\text{H}$.

- $R_1=\text{Ph}$, $R_2=\text{H}$, $R_3=\text{Me}$
- $R_1=\text{Ph}$, $R_2=\text{Me}$, $R_3=\text{H}$
- $R_1=\text{H}$, $R_2=\text{H}$, $R_3=\text{H}$
- $R_1=\text{CO}_2\text{Et}$, $R_2=\text{H}$, $R_3=\text{H}$
- $R_1=\text{CO}_2\text{H}$, $R_2=\text{H}$, $R_3=\text{H}$

The glutaronitriles generally showed strong parent ions and fragmentation occurred most readily adjacent to the $\beta$-carbon atom. When $R_1=\text{Ph}$, the fragment (297) ($m/z=116$) was prominent and usually the base peak: further fragmentation gave (298) ($m/z=89$).

Loss of HCN from the molecular ion was always a major fragmentation, affording (299) which probably rearranges to (300) which, in turn, fragments to (301).
McLafferty rearrangements with cleavage on either side of the $\beta$-carbon atom are also important fragmentations, eliminating the fragments (302) or (303).
Fragmentation pattern of α-phenylglutaronitrile (187)
Fragmentation pattern of 2-methyl-4-phenylglutaronitrile (211)
Fragmentation pattern of 3-methyl-2-phenylglutaronitrile (214)
Fragmentation pattern of α-carboxyglutaronitrile (252)
2,6-Di-imino-3-phenylpiperidine (144)

This imidine showed strong parent and \((P-1)\) ions. Eliminations of ethylene and phenylethylene giving \((304)\) and \((305)\) were important fragmentations, as was loss of HCN giving \((306)\).

Elimination of \(-\text{NH} = \text{C} = \text{NH}\) giving \((307)\) and the presence of a prominent peak at \(m/31\) are diagnostic of the structure:

The fragment at \(m/31\) is assigned to \((N_2H_2)^+\) which is unexpected but probably involves the migration.
of \(-\text{NH}_2\) to the \(=\text{NH}\) group via a 3-membered-ring-
transition-state of the molecular ion followed 
by loss of \(\text{CNH}_2^+\) in a similar fashion to the 
fragmentation of guanidine (308).

\[
\begin{array}{c}
\text{H}_2\text{N'} - \text{C} - \text{NH}_2 \\
\mid \\
\text{NH}
\end{array}
\]

(308)
2,6-Diphenyliminopiperidines

where $R_1=\text{Ph, } R_2=\text{H, } R_3=\text{H}$.

"Ph, "H, "Me.

"Ph, "Me, "H.

All exhibited strong parent and (P-l) ions. A major fragmentation was by loss of (309) or (310), especially of $R_1, R_2$, or $R_3=\text{H}$ giving (311) or (312).

Losses of Ph, PhNH, PhNC, PhNHC, and $R_2$ or $R_3$ if $=\text{Me}$, were all important fragments. A less abundant ion was formed by loss of NH from the parent giving (313).
6-Oxo-2-phenyliminopiperidines.

![Chemical Structure Image]

where \( R=H \)

\( R=\text{Me} \)

Both materials exhibited strong parent and \((P-1)\) ions. Losses of \(\text{Ph}, \text{PhNH}, \text{PhNHC}, \text{NH}, \text{CO}, \text{CONH}, \) and \(R\) if \(R=\text{Me}\) were all recorded as were losses of \(\text{RCH} = \text{CH}_2\) and \(\text{PhCH} = \text{CHR}\) especially when \(R=H\).

3-Bromo-3-phenyl-2,6-diphenyliminopiperidine.

![Chemical Structure Image]

Exhibited strong parent and \((P-1)\) ions. The major initial fragmentations were by loss of \(\text{Br}^*\) and \(\text{HBr}^0\) from the parent ion. The fragment ion at \(m/e \text{337}\) formed by loss of \(\text{HBr}\) was aromatic in nature as there was a doubly charged peak at \(2e \text{168.5}\). The aromatisation by loss of \(\text{HBr}\) showed that the bromine atom was on the piperidine nucleus rather than a phenylimino residue. The 3-position is most likely to be substituted from a mechanistic point of view.
2,6-Dianilino[pyridines

where \( R_1=H, \ R=H \)
\( R_1=\text{Ph}, \ R=H \)
\( R_1=\text{Ph}, \ R=\text{Br} \)

Exhibited strong parent and doubly charged molecular ions \( 2^P\text{e} \). The main fragmentation was by loss of \( R \) if \( R=\text{Br} \). Losses of \( \text{Ph}, \ \text{PhNH} \), and \( R-\phi-\text{NH} \), were the only other fragments of any size. The molecule was obviously very stable and aromatic in nature.
An exhaustive study has been carried out on the dehydrogenation of 3-phenyl-2,6-diphenylimino-piperidine (152). When the reaction was carried out with nitrobenzene it was shown to afford 5,5'-diphenyl-2',6,6'-trianilino-2,3'-bipyridyl (191). The 2,3'-bipyridyl has been characterized spectroscopically and through its tri-N-acetyl (195) and various bromo derivatives (199), (201), (202), and (203). A 4,4'-dimethyl analogue (217) has also been prepared suggesting that this is a general reaction for the preparation of similar 2,3'-bipyridyls. Dehydrogenation of (152) with other reagents also gave the 2,3'-bipyridyl (191) but using the hindered quinone, 3,3',5,5'-tetrachloro-4,4'-diphenoquinone (220), an intermediate 3-aryloxy adduct (223) was also isolated and characterized. Dehydrogenation of the piperidine (152) catalytically with 10% rhodium on charcoal afforded 2,6-dianilino-3-phenylpyridine (188) as did the bromination-dehydrobromination reaction carried out on (152) with N-bromosuccinimide. Thus a route is available to those dianilinopyridines difficult to prepare by conventional routes.

The dehydrogenation of 2,6-di-imino-3-phenyl-piperidine (144) was attempted unsuccessfully under various conditions.

The single stage conversion of alkylideneglutanaronitriles to dianilinopyridines has been demonstrated using 2-ethylideneglutanonitrile (253) which was
condensed with aniline to give 3-ethylidene-2,6-diphenyliminopiperidine (257). The piperidine (257) tautomerised to 2,6-dianilino-3-ethylpyridine (258) on addition of trifluoroacetic acid.

The fine structure of 3-phenyl-2,6-diphenyliminopiperidine (152) is now more clearly understood. A tautomeric mixture of isomers exists consisting mainly of the dehydropiperidines (259) and (260) as well as some contribution from the piperidine (152). There is no evidence for any dihydropyridine (261b).

Dehydropiperidine (263) and dihydropyridine (265) analogues have been prepared and their u.v. absorptions have helped confirm the tautomeric composition in the piperidine (152). The spectroscopic evidence
for the predominance of the dehydropiperidine structures (259) and (260) is backed-up by chemical evidence in that 3-phenyl-2,6-diphenylimino-piperidine (152) has now been found to dehydrogenate readily under the right conditions.

Other aza-linked two- and three-unit addition and condensation products have been prepared by reacting glutaronitriles with amines, and the possibility of forming polymeric or macrocyclic materials by condensation with diamines was investigated. It was found that, whereas three-unit materials (266) and (268) could be prepared using both m- and p-phenylenediamines, no macrocyclic material could be isolated. The condensations of ethylenediamine and o-phenylenediamine with glutaronitrile afforded intramolecularly condensed three-unit condensation products identified as the piperidinoimidazoles (270) and (281).
No reaction could be induced between glutaronitrile and 1,3-di-iminoisoindoline, the only products isolated being from the indoline itself, viz. phthalocyanine and a monoamide (283) of tricyano-cyaphenine. Aminopyridines and analogues reacted less readily with glutaronitriles and only 2-aminopyridine and 2,8-diaminoacridine afforded products. The pyridine nitrogen atom obviously has a deactivating effect on the reactivity of the amino groups.

Thorpe condensation of glutaronitriles with active methylene groups with a view to forming methine linked macrocycles was investigated. The condensations were found to take place, under alkaline conditions, much more readily than the condensations of glutaronitriles with amines. Model two- and three-unit compounds, and three-unit products from m- and p-dicyanoxylylene, have been prepared. Further condensation of the dicyanoxylylene three-unit products (290), (291), (293), and (294) gave the corresponding macrocycles (292) and (295).
Attempts were made to dehydrogenate the two- and three-unit condensation products (157), (286), and (290) but these were not successful.

The mass spectra of the glutaronitriles have been analyzed and general fragmentation patterns identified.

Further reactions might be carried out to form methine linked macrocycles containing aza or thia groups capable of chelating to a metal e.g. with 2,6-dicyanomethylpyridine and 2,5-dicyanomethylthiophen.
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