A thesis

entitled

ACTIVE METHYLENE COMPOUNDS IN THE SYNTHESIS OF MACROCYCLES AND INTERMEDIATES

by

MICHAEL DEREK BARKER

in partial fulfilment of the requirements for the degree of Doctor of Philosophy at London University.

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ABSTRACT

An examination has been made of some possible ways of activating a methylene group so that it could be used to form methine-linked compounds and ultimately a methine-linked macrocycle.

It was shown that N-oxidation of picolines did not confer the required activity on the methyl groups. It was also shown that the methylene group of a 2-picolylphosphonate was similarly insufficiently active.

But it was found that the methylene group of an aromatic cyanomethyl compound was reactive and would undergo an addition-cyclisation reaction with phthalonitrile thus joining the aromatic ring *via* a cyanomethine link to an *iso*indoline system. A series of compounds was prepared from phenylacetonitrile and 2-pyridylacetonitrile, and metal complexes were obtained from some of the products from the latter compound.

Then the reactions were extended to the appropriate di(cyanomethyl)benzene and pyridine compounds. It was hoped that this would lead to the formation of the desired macrocycle. A number of intermediates were prepared, from which macrocycles might be obtained, but only one macrocycle was isolated and this was a di-cyanomethine-di-aza-linked macrocycle. Also good evidence was obtained that other di-cyanomethine-di-aza-linked macrocycles were prepared

but not isolated. Attempts to prepare tetra-cyanomethine-linked macrocycles were not successful here, but there are reasons for thinking that further study may be profitable.

A general survey of the intermediates prepared is included, with particular emphasis on their ultra-violet absorption properties, and a comparison of these with their analogues in the aza-linked series.

Finally a number of suggestions are made as to how the work described in this thesis could be continued.

ACKNOWLEDGEMENTS

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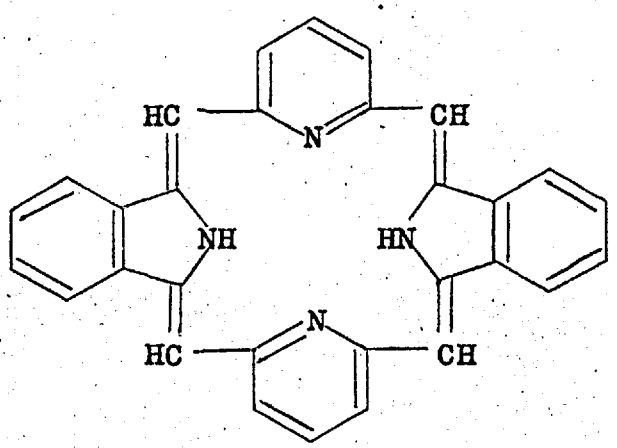
Introduction

This thesis describes an investigation of some possible methods of synthesising a new methine-linked macrocycle(I). Its aza-linked analogue(II) is already known. It was felt that the new macrocycle might be of interest and would be capable of complexing metals. It would also bear certain resemblances to other macrocyclic pigments such as the technologically valuable phthalocyanine(III) and to porphin(IV), the parent ring system on which the structure of naturally occurring pigments such as chlorophyll and haemin are based. The macrocycle(I) differs from the above pigments in that it has a cross-conjugated rather than a fully conjugated system, and this would be expected to give different light absorption properties.

The macrocycle(II) was prepared[2,17] by the reaction of 2,6-diaminopyridine with 1,3-di-iminoisoindoline(V) and also with 1-imino-3-thioisoindoline(VI). Other macrocycles have also been prepared by the reaction of other diamines in these ways[4,7]. A number of other reactions of amines with reactive imino groups have also been investigated[1,3,6,11]. In order to obtain a methine-linked macrocycle it was obviously necessary to have a compound containing an active methylene group for reaction with the imidine(V). A simple methyl



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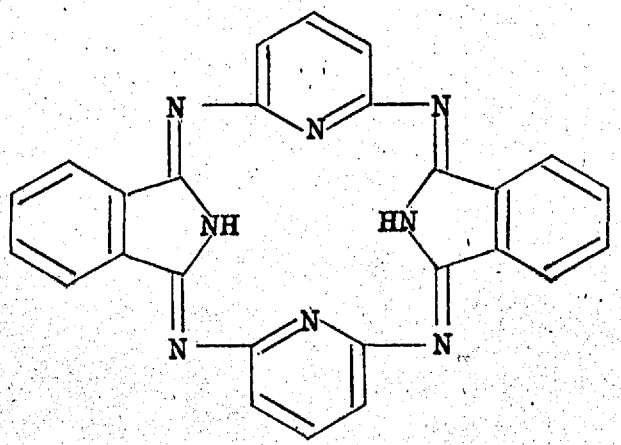

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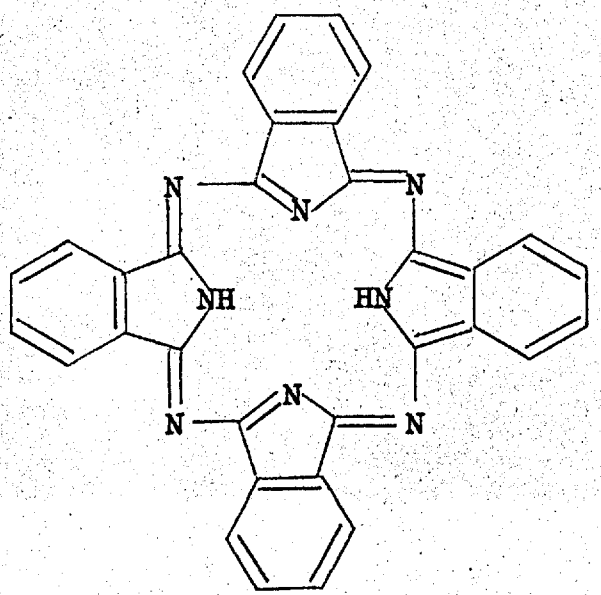

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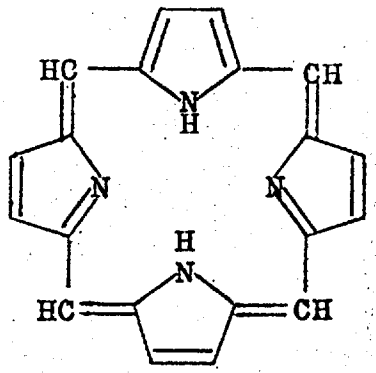

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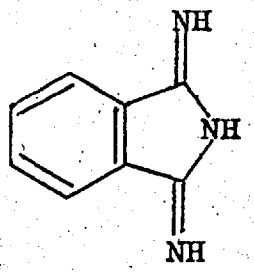

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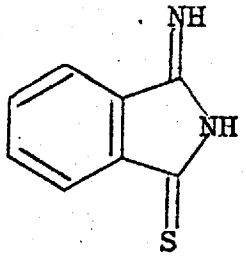

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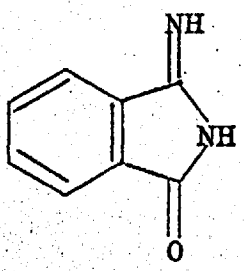

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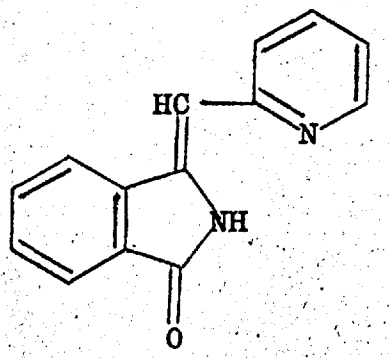

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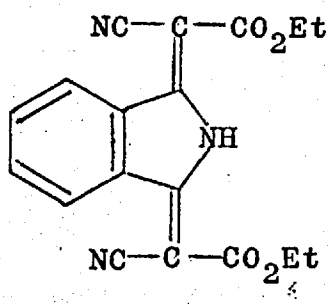

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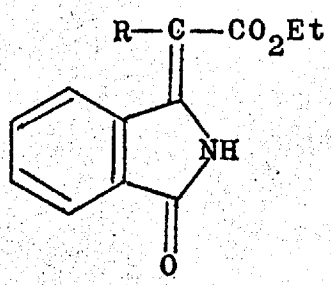

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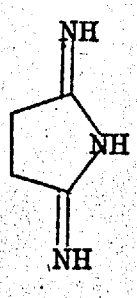

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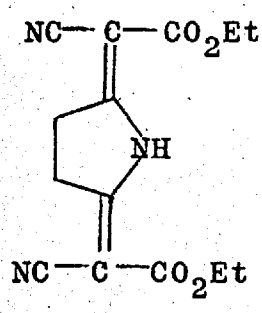


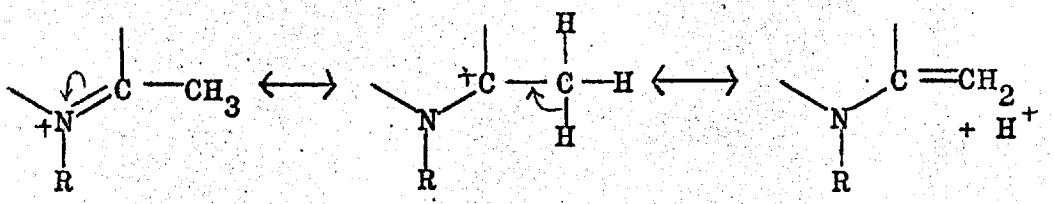
XII

group would hardly be reactive enough. This was demonstrated by the behaviour of 2-picoline with 1-imino-3-oxo*iso*indoline(VII). Only under the most vigorous conditions was there condensation to give 1-(2'-pyridylmethylene)-3-oxo*iso*indoline(VIII)[9]. Under the necessary conditions the imidine(V) is unstable. We have therefore sought methods of activating methylene groups in the appropriate pyridine and other compounds so that a macrocycle might be formed with di-imino*iso*indoline under moderate conditions.

First, one can consider the well established method of using a methylene group attached to an electron withdrawing group, which has the effect of making the protons of the methylene group more easily removed by base, thereby generating a reactive carbanion. The groups most commonly used for this purpose are the cyanide, ester and nitro groups, and examples of their use are legion throughout the chemical literature. However it is relevant at this point to mention just one or two reactions which have a direct bearing on the problem in hand. The imino compound(VII) has been shown to react with acetoacetic and malonic esters to yield the products(X; R=Ac and CO_2Et)[10]. The di-imine(V) reacted with ethyl

cyanoacetate to give the product(IX), and succinimidine (XI) also reacted with ethyl cyanoacetate to give the corresponding product(XII)[11]. An interesting variation on this theme is provided by the reaction of succinonitrile with ethyl cyanoacetate to give the same product(XII)[11], and with benzyl cyanide to give the product(XIII)[9]. These reactions show that synthesis of a suitable pyridine derivative could be expected to undergo similar reactions, which might lead to the desired macrocycle.

A further possibility is introduced when one is using pyridine compounds. This involves activation of an α (or γ) methyl group by quaternisation of the nitrogen atom. The production of a positive charge on the nitrogen atom tends to reduce the electron density at the α (and γ) carbon atoms (which effect is reflected in the p.m.r. spectrum) and this makes the methyl groups more reactive thus:

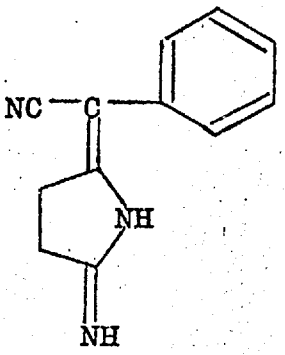


It has been demonstrated that activation of a 2-methyl group by formation of the quaternary salt is effective in the present context. Thus 1-ethyl-2,6-

lutidinium iodide condenses readily with the di-imine(V), to give the products(XIV) or (XV) according to the conditions used[8]. However this route cannot be directly applied to macrocycle synthesis since the two quaternising groups would have to be accommodated in the centre of the ring and the steric hindrance would surely prevent closure of the ring. Therefore use of this method is perhaps limited to cases where the quaternising groups can be readily removed.

The means of activation already mentioned were then tried. The use of picoline-1-oxides and their quaternary salts was shown to be unsuccessful. Then the effect of a phosphonate substituent on a 2-methylene group was examined. This is a relatively new method, and has been successfully used in condensations with ketones. Once again, only negative results were obtained when attempts were made to apply this to imino compounds.

Faced with this lack of success a model reaction was tried using benzyl cyanide as the source of an active methylene group. Immediately this approach gave positive results, cyanomethine linked compounds being readily obtained and a series of products were prepared. The reaction was then extended to the disubstituted benzene, and subsequently to the corresponding mono- and di-substituted pyridine derivatives. A new synthesis of



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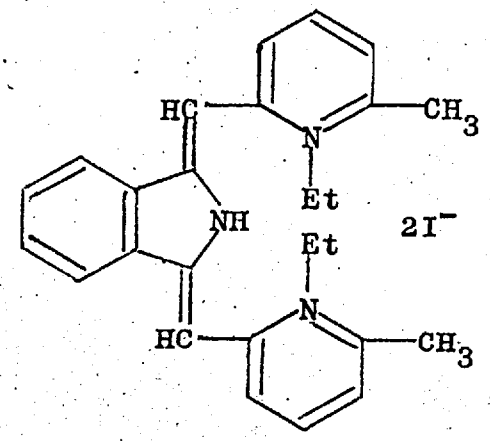

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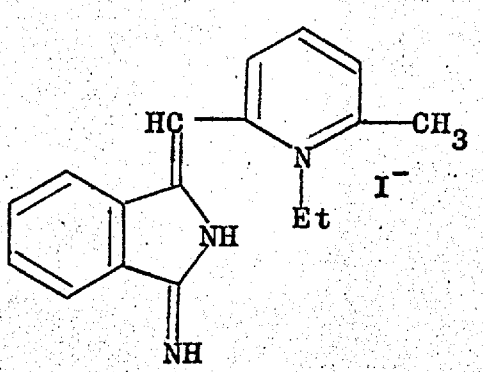


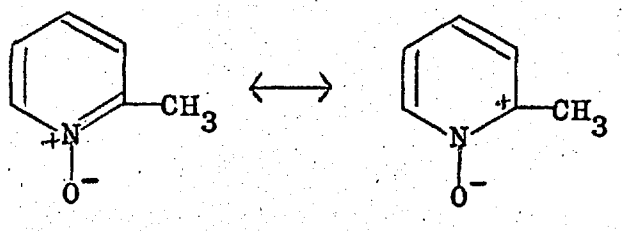
XV

the latter compound was worked out during this part of the work.

Chapter 1

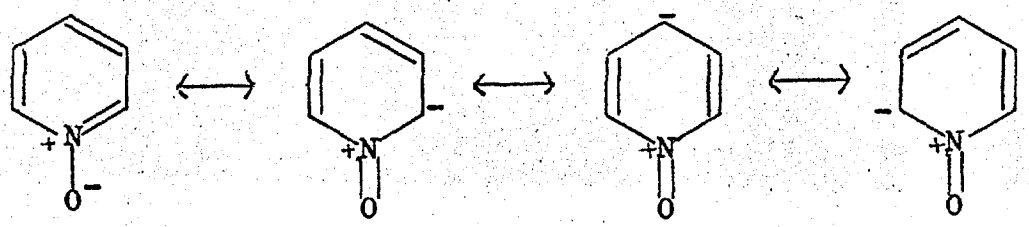
Picoline-1-oxides and their quaternary salts

Picoline-1-oxides were chosen as the starting point for the investigation as it was hoped that their dipolar character would lead to the activation of a 2-methyl group thus:



this being analogous to the manner of activation of a 2-methyl group in a quaternised pyridine. After condensation, reduction would remove the N-oxide group, leaving the pyridine.

All attempts at bringing about the condensation between 2-picoline-1-oxide and 1,3-di-iminoisoindoline failed to yield any evidence that reaction had occurred. However, it has been shown by Liston[12] that the dipole moment of pyridine-1-oxide is 4.28D as opposed to a calculated value of 6.6D. To explain this difference he proposed other contributing structures:



This explanation is supported by two pieces of evidence:

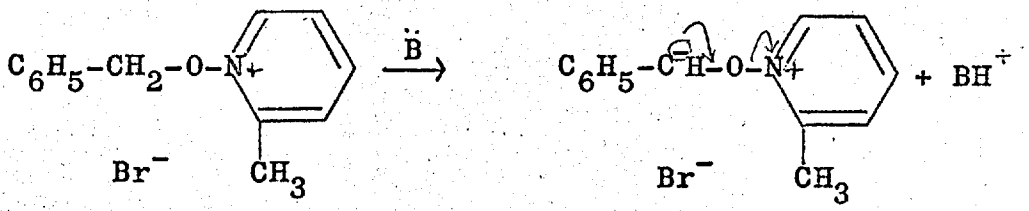
(i) Ochiai[13] nitrated pyridine-1-oxide in the 2- and 4- positions directly.

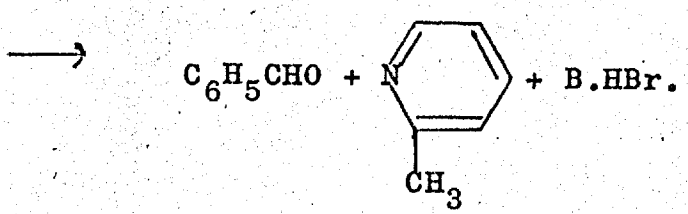
(ii) We have measured the proton magnetic resonance spectra of 2-picoline, 2-picoline-1-oxide and 2-picoline ethiodide and found that the methyl protons of the first two compounds have very similar τ values (7.42 and 7.45 respectively) which are higher than that (6.92) for the 2-methyl protons of 2-picoline ethiodide. If, as seems reasonable, the induced ring currents in the compounds make comparable contributions to the total shieldings, then it follows that the electron density at the methyl group must be similar in the first two compounds and less in the last. As 2-picoline is unreactive towards imino compounds (whereas 2-picoline ethiodide condenses with 1,3-di-imino<u>iso</u>indoline) it is not after all surprising that 2-picoline-1-oxide failed to condense.

2-picoline-1-oxide, unlike 2-picoline, did not condense with 1-imino-3-oxo<u>iso</u>indoline under similar conditions. The product isolated was phthalimide in 70% yield, showing the absence of a comparable reaction.

Synthesis of some quaternary picoline-1-oxides was carried out in the hope that making the molecule cationic would bring about activation of the methyl group. The 1-methoxy iodides of 2-, 3-, and 4-picolines were

prepared, but as that of 2-picoline was particularly unstable, the corresponding 1-benzyloxy bromide was prepared and used instead. When 1-benzyloxy-2-picolinium bromide was refluxed in a solvent with 1,3-di-imino-isoindoline, the product obtained was the isoindoline hydrobromide. This is presumably formed as follows[15,16]:





This decomposition also occurred when 1-methoxy-4-picolinium iodide was used, a hydrated hydriodide of 1,3-di-iminoisoindoline being isolated.

A possible solution to this difficulty was sought in the preparation of the 1-t-butoxy-picolinium salts, which would have no protons on the carbon adjacent to the oxygen. But attempts to prepare this type of compound met with no success.

A further attempt to avoid the above decomposition was made by using monothiophthalimide(VI), which is less basic than 1,3-di-iminoisoindoline, but which is known to condense with amines[17]. When this compound was

treated with 1-methoxy-4-picolinium iodide, a highly crystalline pale red-orange material was obtained. This was shown to be a 1:1 molecular complex between monothiophthalimide and 4-picoline-1-oxide. The p.m.r. spectrum showed a methyl group (τ7.60, cp 4-picoline-1-oxide τ7.64) and the 2-pyridyl protons (τ1.65, cp 4-picoline-1-oxide τ1.91). Also the integrals of the various signals were correct for the postulated structure. Comparison of the u.v. and i.r. spectra of the separate constituents with those of the complex provide further support e.g. monothiophthalimide has peaks (inter alia) at 230, 296 and 329 mμ. The complex similarly has peaks at 231, 296 and 329 mμ. The absorption of 4-picoline-1-oxide at 266 mμ is only detectable as an enhancement of ε values compared to monothiophthalimide. In the i.r. spectrum, the following maxima of monothiophthalimide are also visible in the complex: 1734, 1297, 1287, 1192, 1094, 798, 781, 704 cm^{-1}. Similarly those of 4-picoline-1-oxide visible in the complex are: 1485, 1247, 1211, 762 cm^{-1}. By reaction of 4-picoline-1-oxide and monothiophthalimide directly under mild conditions, the same complex was obtained.

1-methoxy-4-picolinium methosulphate was also synthesised. However this failed to react in any way with monothiophthalimide, 80% of the latter being

recovered even after refluxing for 24 hours in dioxan.

It was, therefore, concluded that 1-alkoxy-4-picolinium halides and related compounds were not suitable for this type of condensation with 1,3-di-iminoisoindoline or monothiophthalimide. However, as a result of this work and the proton magnetic resonance measurements which were made, it appeared that a qualitative measure of the reactivity of a substituent methyl group in a quaternised picoline could be obtained by comparison of its τ value with that of the corresponding value for the parent picoline.

The methyl group in the quaternary compounds appears at lower field than in the parent picoline e.g. $\Delta\tau$ for the picolines $\longrightarrow$ picoline ethiodides are 2-:0.50, 3-:0.36, 4-:0.41. This effect is caused by the electron drain from the aromatic system of electrons towards the positively charged nitrogen atom. This is also the cause of increased acidity of the protons in the methyl group, particularly in the cases of 2- and 4-picolines. It is therefore reasonable to suppose that the change in τ value is a guide to the increase in the acidity of the protons.

The effect is less pronounced in the case of 3-picoline since the methyl group of the parent picoline is less reactive than those of its 2- and 4- isomers and

the activating effect of quaternisation is also less than in the other two cases. By comparison of the τ values one would expect the reactivity of the 3-methyl group in 3-picolinium ethiodide to be about the same as that of the 2-methyl in 2-picoline.

An apparent anomaly was observed for the 1-benzyloxy-2- and -4-picolinium halides where the change in τ value of the nuclear methyl group from the parent picoline was very much smaller than was observed for the other quaternary salts. This must presumably be due to a different effect of the benzyloxy group on the electron densities round the ring compared with the other cases. But it is not easy to see why this should be so. Further experimental evidence would be necessary to provide a satisfactory explanation.

Experimental

SECTION A

Picoline-1-oxides

1. 2-, 3- and 4-picoline-1-oxides were prepared by the method of Boekelheide and Linn[19].

2. Reaction of 1,3-di-iminoisoindoline with 2-picoline-1-oxide

1,3-Di-iminoisoindoline and 2-picoline-1-oxide in equimolar amounts were refluxed together in a variety of solvents for up to 24 hrs., but the only material isolated from the reactions was 1,3-di-iminoisoindoline, identified by its m.p. and by mixed m.p. Even using excess 2-picoline-1-oxide as solvent produced no reaction.

3. Reaction of 1-imino-3-oxoisoindoline and 2-picoline-1-oxide

1-Imino-3-oxoisoindoline (0.7g, 0.0048 mole) was heated in 2-picoline-1-oxide (3g, 0.0275 mole) at 180-185° for 3 days. The solution became dark brown. As much as possible of the excess 2-picoline-1-oxide was distilled off under high vacuum (1 mm). The residue was taken up in n-butanol (5 mls) and a large excess of petroleum ether (60-80°) was added, giving a dark coloured precipitate (0.5g, 71.4%). This was identified, after recrystallisation from n-butanol, as phthalimide by m.p. and mixed m.p. with authentic phthalimide (Found: C, 65.21;

H, 3.65; N, 10.02. Calc. for $C_8H_5NO_2$: C, 65.30; H, 3.41; N, 9.55%)

SECTION B

1-Alkyl and -aryloxy-picolinium quaternary salts

1. Preparation of 1-methoxy-2-picolinium iodide (XVII)

2-Picoline-1-oxide (0.48g, 0.0044 mole) was kept in an excess of methyl iodide (2-3 mls) in the dark at room temperature overnight. A mass of crystals (0.75g, 67.5%) were produced, which were recrystallised from the minimum volume of acetone, keeping the temperature below 50°. White crystals of 1-methoxy-2-picolinium iodide (XVII) were obtained m.p. 80.5-81.5° (decomp.) (Found: C, 33.70; H, 3.91; N, 5.36. $C_7H_{10}INO$ requires C, 33.48; H, 3.98; N, 5.58%). This compound decomposed in the light at room temperature.

2. Preparation of 1-methoxy-3-picolinium iodide (XVIII)

3-Picoline-1-oxide (4g, 0.0367 mole) was dissolved in the minimum amount of acetone, and methyl iodide (10g, 0.0704 mole) added. The solution was kept at room temperature overnight in the dark. The pale yellow crystals were filtered off and recrystallised from acetone giving 1-methoxy-3-picolinium iodide (XVIII) m.p. 97.5° (Found: C, 33.93; H, 4.01; N, 5.23; I, 51.46. $C_7H_{10}INO$ requires C, 33.48; H, 3.98; N, 5.58; I, 50.60%).

3. Preparation of 1-methoxy-4-picolinium iodide (XIX)

4-Picoline-1-oxide (3g, 0.0275 mole) was dissolved in ethanol (10 mls) and methyl iodide (7g, 0.0492 mole) was added. The solution was kept at room temperature overnight in the dark. Addition of diethyl ether (20 mls) and cooling at 0° for 3 hrs. gave white crystals (2.87g, 41.6%). On recrystallisation from acetone/ether (1:3), 1-methoxy-4-picolinium iodide (XIX) was obtained, m.p. 108° (Found: C, 33.52; H, 3.77; N, 5.50; I, 50.41. $C_7H_{10}INO$ requires C, 33.48; H, 3.98; N, 5.58; I, 50.60%).

4. Preparation of 1-benzyloxy-2-picolinium bromide (XX)

1-Benzyloxy-2-picolinium bromide (XX) m.p. 112-114°, was prepared according to the method of Feely, Lehn and Boekelheide[15] in 77% yield (Found: C, 55.43; H, 5.04; N, 5.04 Br, 28.31. Calc. for $C_{13}H_{14}BrNO$: C, 55.65; H, 5.00; N, 5.00; Br, 28.58%).

5. Preparation of 1-benzyloxy-4-picolinium bromide (XXI)

4-Picoline-1-oxide (1g, 0.0092 mole) and benzyl bromide (2 mls, 2.88g, 0.0168 mole) were kept together in the dark at room temperature for 3 days. A dense white precipitate was produced. Recrystallisation from n-butanol yielded 1-benzyloxy-4-picolinium bromide (XXI), m.p. 108-109° (Found: C, 55.50; H, 5.05; N, 5.00; Br, 28.25. $C_{13}H_{14}BrNO$ requires C, 55.65; H, 5.00; N, 5.00; Br, 28.58%).

6. Preparation of 1-benzyloxy-4-picolinium iodide (XXII)

4-Picoline-1-oxide (1g, 0.0092 mole) and benzyl iodide (2.5 mls, 4.33g, 0.0199 mole) were dissolved in acetone (5 mls) and the solution kept at room temperature for 24 hrs. in the dark. The crystals were filtered off and recrystallised from ethanol/ether (1:3) to yield 1-benzyloxy-4-picolinium iodide (XXII), m.p. 102° (Found: C, 48.32; H, 4.45; N, 4.36. $C_{13}H_{14}INO$ requires C, 47.70; H, 4.28; N, 4.28%).

7. Preparation of 1-methoxy-4-picolinium methosulphate (XXIII)

(cp the method of Feely and Beavers[18])

4-Picoline-1-oxide (2.17g, 0.0200 mole) was treated with dimethyl sulphate (approx. 2 mls, 2.5g, 0.0198 mole). After a 15 min. induction period, the mixture became warm and then gradually cooled. After a further 15 mins., the mixture was heated on a steam bath for 1½ hrs. On cooling, the solution set to a crystalline mass. This was taken up in hot anhydrous acetone and cooled to 0°. The crystals were filtered off and washed with diethyl ether. After recrystallisation from acetone, white hygroscopic flakes of 1-methoxy-4-picolinium methosulphate (XXIII) (4.2g, 90%) were obtained m.p. 72° (Lit.[20] m.p. 69-73°) (Found: C, 40.54; H, 5.30; N, 6.11. Calc. for $C_8H_{13}NO_5S$: C, 40.85; H, 5.53; N, 5.96%).

8. Reaction of 1,3-di-iminoisoindoline with 1-benzyloxy-2-picolinium bromide

1,3-Di-iminoisoindoline (1.0g, 0.0069 mole) and 1-benzyloxy-2-picolinium bromide (1.93g, 0.0069 mole) were refluxed in dry methanol (40 mls) for 3½ hrs. The solution was cooled and a very small amount of solid filtered off. The filtrate was evaporated under reduced pressure to a small volume (2-3 mls) and treated with a large excess of diethyl ether. This yielded a yellow precipitate, which after filtration and drying, gave 1,3-di-iminoisoindoline hydrobromide (XXIV) (1.23g, 62.9%) as a yellow powder decomposing at about 300° (Found: N, 18.13; Br, 34.9. $C_8H_7N_3$.HBr requires N, 18.60; Br, 35.4).

The picrate was prepared from this compound and its identity with the picrate of 1,3-di-iminoisoindoline was shown by m.p. 290° and mixed m.p. 289-290°, and by analysis (Found: C, 44.61; H, 2.96; N, 22.25. Calc. for $C_{14}H_{10}N_6O_7$: C, 44.88; H, 2.68; N, 22.45%).

9. Reaction of 1,3-di-iminoisoindoline with 1-methoxy-4-picolinium iodide

1,3-Di-iminoisoindoline (1.05g, 0.0072 mole) and 1-methoxy-4-picolinium iodide (1.70g, 0.0068 mole) were refluxed in dry methanol (40 mls) for 3 hrs. The methanol was then evaporated under reduced pressure to a small

volume (5 mls). A yellow precipitate slowly formed. This was 1,3-di-iminoisoindoline hemihydriodide hemihydrate (0.79g, 52.5%) decomposing at about 150° (Found: C, 43.81; H, 3.85; I, 29.75. $C_8H_7N_3.\frac{1}{2}(HI.H_2O)$ requires C, 44.02; H, 3.90; I, 29.14%).

The derived picrate was identical with the picrate of 1,3-di-iminoisoindoline (m.p. 288° and mixed m.p. 288-298°) (Found: C, 44.90; H, 2.83; N, 22.15. Calc. for $C_{14}H_{10}N_6O_7$: C, 44.88; H, 2.68; N, 22.45%).

10. Reaction of monothiophthalimide with 1-methoxy-4-picolinium iodide

Monothiophthalimide (0.50g, 0.0031 mole) and 1-methoxy-4-picolinium iodide (0.72g, 0.0030 mole) were refluxed in dry methanol (20 mls) for 36 hrs. The methanol was removed under reduced pressure leaving a red mass, which was extracted with diethyl ether. The ether was evaporated to dryness, giving red crystals (0.60g, 72.3%). After recrystallisation from ethyl acetate large red crystals of a 1:1 molecular complex (XXV) between monothiophthalimide and 4-picoline-1-oxide (m.p. 134°) were obtained (Found: C, 61.68; H, 4.03; N, 9.86. $C_{14}H_{12}N_2O_2S$ requires C, 61.65; H, 4.41; N, 10.29%).

Monothiophthalimide (0.25g, 0.0015 mole) and 4-picoline-1-oxide (0.15g, 0.0014 mole) were refluxed together for 2 hrs. in dry methanol (10 mls). After

evaporation of the methanol and recrystallisation from ethyl acetate, the same 1:1 molecular complex of monothiophthalimide and 4-picoline-1-oxide was obtained m.p. 136° and mixed m.p. 135.5° (Found: C, 61.10; H, 3.95; N, 9.82. $C_{14}H_{12}N_2O_2S$ requires C, 61.65; H, 4.41; N, 10.29%).

11. Reaction of monothiophthalimide and 1-methoxy-4-picolinium methosulphate

Monothiophthalimide (0.50g, 0.0031 mole) and 1-methoxy-4-picolinium methosulphate (0.68g, 0.0029 mole) were refluxed for 24 hrs. in dry dioxan. There was no apparent reaction. The solution was evaporated to dryness under reduced pressure and the residue taken up in methanol (10 mls), reduced to about 2 mls and kept overnight at 0°. A mass of red crystals were produced, which yielded monothiophthalimide (0.40g, 80%) identified by m.p. and mixed m.p. with an authentic sample.

Spectroscopic Data

P.M.R. Spectra (5-10% solution in $CDCl_3$)

Compound	τ values[a]		
	Nuclear methyl[b]	2 and/or 6 pyridine-H	Other pyridine-H
2-picoline	7.42	1.45	3.00-2.26
3-picoline	7.69	1.56+1.53	2.95-2.43
4-picoline	7.67	1.55 (5.8)	2.92 (5.3)
2-picoline-1-oxide	7.45	1.66	2.71
3-picoline-1-oxide	7.66	1.91	2.91-2.81
4-picoline-1-oxide	7.64	1.91 (6.9)	2.91 (6.7)
2-picoline ethiodide	6.92	0.57 (7.0)	2.16-1.27
3-picoline ethiodide	7.33	0.79	1.71
4-picoline ethiodide	7.26	0.46 (6.4)	1.89 (6.8)
XX	7.47	1.61	2.85-2.56[c]
XXI	7.63	1.82 (6.5)	2.87 (7.0)
XXII	7.63	1.83 (7.0)	2.86 (7.0)
XVIII	7.30	0.63	1.92-1.45
XIX	7.24	0.40 (7.0)	1.83 (7.3)
XXIII	7.29	0.65 (7.0)	1.92 (7.0)

a. Figures in parentheses are J values in c.p.s., where they can be distinguished. These signals are all doublets.

b. All singlets.

c. Includes the aromatic protons of the benzyl group.

Other P.M.R. features

Compound	τ values	
	Ethyl CH_2 [d]	Ethyl CH_3 [e]
2-picoline ethiodide	5.10 (7.3)	8.32 (7.3)
3-picoline ethiodide	5.03 (7.0)	8.27 (7.3)
4-picoline ethiodide	4.97 (7.3)	8.25 (7.4)
	Benzyl CH_2 [f]	Benzyl aromatic protons
XX	5.50	2.85-2.56 [g]
XXI	5.51	2.64
XXII	5.53	2.63
	$-OCH_3$ [f]	$CH_3S\overset{\ominus}{O}_4$ [f]
XVIII	5.38	-
XIX	5.34	-
XXIII	5.48	6.29

d. All quartets, J values in parentheses.

e. All triplets, J values in parentheses.

f. All singlets.

g. Contains some pyridine aromatic protons.

Light absorption data

Compound	Solvent	λ max (mμ)	$\varepsilon \times 10^{-3}$
XVIII	H_2O	225	15.15
		264	4.63

XIX	H_2O	226.5	21.80
		254	4.83
	EtOH	256	5.05
XXIII	H_2O	227	7.57
		255	3.86
XX	H_2O	264	5.68
XXI	H_2O	225*	10.26
		249-256*	5.30
		262*	4.54
XXII	H_2O	225-6	25.22
		256*	5.63
		264*	4.21
XXIV	H_2O	228	27.18
		260	16.76
		310	3.70
		314	3.71
Monothiophthalimide	EtOH	230	26.72
		269	14,75
		289	16.67
		296	15.30
		329	9.97

XXV	EtOH	231	29.92
		276*	20.33
		287.5	21.93
		296*	19.72
		327	13.13

* inflexion

Infra red absorptions (cm^{-1}) (Nujol mull)

XVIII: 1614(m), 1591(w), 1493(m), 1319(m), 1281(s), 1164(m), 1142(m), 1119(m), 1095(m), 1013(m), 968(s), 940(w), 906(s), 864(w), 809(s), 731-727(m),

XIX: 1627(m), 1282(m), 1208(w), 1166(w), 1045(w), 982(w), 956(s), 945(s), 857(m), 846(m), 822(m), 766(w), 730(s), 691(m).

XX: 1622(s), 1561(m), 1501(s), 1305(w), 1272(m), 1223(m), 1162(s), 1119(m), 1065(w), 1056(m), 982(m), 955(m), 917(s), 894(m), 860(s), 816(w), 792(s), 776(s), 755(s).

XXI: 1627(s), 1505(s), 1284(w), 1275(m), 1224(w), 1215(w), 1200(w), 1162(m), 1101(m), 968(m), 952(m), 925(m), 912(m), 878(m), 865(s), 826(m), 810(s), 770(s), 750(s), 704(s).

XXII: 1625(s), 1499(s), 1282(s), 1220(m), 1202(m), 1159(m), 1039(m), 967(m), 946(m), 919(s), 866(s), 830(s), 823(s), 769(s), 752(s), 747(w), 704(s), 694(w).

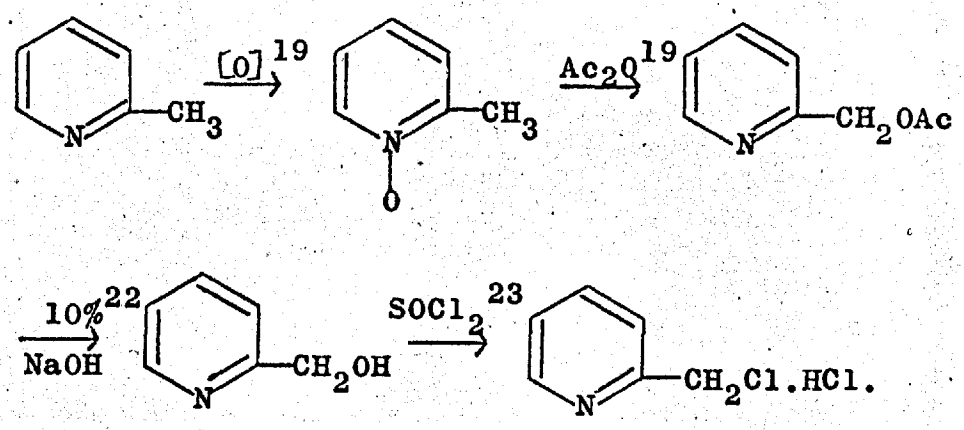
XXV: 1734(s), 1362(w), 1335(w), 1297(m), 1287(m), 1256(m), 1247(m), 1211(m), 1192(w), 1174(m), 1163(w), 1121(w), 1110(m), 1084(s), 1036(w), 1023(m), 856(m), 831(m), 804(m), 798(w), 781(s), 762(m), 741(m), 704(s).

Chapter 2

Di-n-butyl-2-picolyl phosphonate

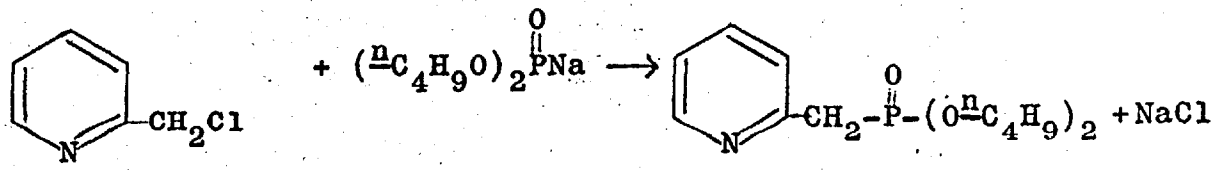
This chapter describes the preparation of a reactive methylene compound of the type $PyCH_2X$ where X is a phosphonate group. Wadsworth and Emmons[21] have demonstrated that compounds of the general formula $O=P(OR)_2CH_2R'$ would react smoothly with sodium hydride to give an anion which would then condense with ketones. The products were unsaturated compounds $(R'')_2C=CHR'$ formed by elimination of the phosphonate residue during the work-up. It seemed reasonable to extend this type of reaction to a phosphonate where R' = pyridine and 1,3-di-iminoisoindoline. For this purpose, di-n-butyl-2-picolyl phosphonate was synthesised.

The first stage of the synthesis involved the formation of 2-chloromethylpyridine by the scheme shown below:



The chloromethylpyridine was then treated with sodium

dibutylphosphite as in the Michaelis-Arbuzov reaction[24], yielding di-n-butyl-2-picolyl phosphonate by elimination of sodium chloride.



Having isolated the desired phosphonate, various attempts were made to condense the methylene group with 1,3-di-iminoisoindoline. In the first instance, the compounds were refluxed together in a solvent, but on working up the only material recovered was the phosphonate (as its picrate) in 70% yield. The use of sodium butoxide in refluxing butanol resulted in the formation of a 41% yield of phthalocyanine (identified by the presence of bands at 698 and 664 mμ in the visible spectrum). No other identifiable material was recovered.

In view of the effect of sodium butoxide, the use of sodium hydride was investigated instead, this being the base originally used in the work in ketones. It was found that addition of a solution of the phosphonate in dioxan to a suspension of sodium hydride in dioxan gave rise to immediate evolution of a gas (presumably hydrogen) indicating formation of the anion from the

phosphonate. 1,3-di-iminoisoindoline in dioxan was then added and the solution refluxed. However on working up a total of 77% of the 1,3-di-iminoisoindoline was recovered (as its picrate).

Some time later, after it had been shown that cyanomethyl compounds reacted readily with phthalonitrile as described later in this thesis, a reaction between the phosphonate and phthalonitrile in the presence of sodium ethoxide was attempted. A small yield (about 10%) of phthalocyanine was obtained, but no other identifiable product was isolated.

It must be concluded therefore, that the phosphonate is not suitable for this type of condensation reaction, in spite of the success of reactions of other phosphonates with ketones.

The spectral properties of the phosphonate are recorded in the experimental section. The p.m.r. spectrum gives rise to two points of interest. (a) The methylene group between the phosphorus atom and the pyridine ring appears as a doublet with a coupling constant of 22 c.p.s. This large splitting is due to the presence of the phosphorus atom, which has a spin of $\frac{1}{2}$, adjacent to the methylene group. (b) The two methylene groups of the two n-butoxyl groups which are α to the oxygen atom do not appear as a simple triplet. In each of these two

methylene groups the two constituent protons are not equivalent to each other. Consider one of these methylene groups, to which the phosphorus atom appears as an asymmetric centre, since the three other groups attached to it are different from each other. The effect of this is that the constituent protons of the methylene group are in different chemical environments from each other, and the normal rotations of the molecule do not average out this difference[34]. Hence their chemical shifts are different, and give rise to a basic spectrum of a double doublet. This is then split by the adjacent methylene group to give (in theory) twelve lines in all. In practice the signal is not resolved due to overlapping of some of the lines.

This type of effect has been observed for acetals[33], ethers[35], sulphites and sulphinic esters[36], and imidazolidines[37], but it does not seem to have been observed previously where a phosphorus atom provides the centre of dissymetry.

Experimental

1. 2-picoline-1-oxide

2-Picoline (60g) yielded 2-picoline-1-oxide (63g, 89%) by oxidation with hydrogen peroxide in glacial acetic acid[19].

2. 2-pyridyl-methyl acetate

2-Picoline-1-oxide (63g) was rearranged to 2-pyridyl-methyl acetate (66g, 76%) by refluxing acetic anhydride[19].

3. 2-hydroxymethylpyridine

2-Pyridyl-methyl acetate (66g) hydrolysed with 10% NaOH to yield 2-hydroxymethylpyridine (14.5g, 30%)[22].

4. 2-chloromethylpyridine hydrochloride

2-Hydroxymethylpyridine (14.5g) was treated with thionyl chloride (redistilled, 42g) yielding 2-chloromethylpyridine hydrochloride (21.2g, 97%)[23].

5. Di-n-butyl-2-picolyl phosphonate[24]

Petroleum ether (100-120°, sodium dried, 100 mls) was refluxed in a 250 mls three neck flask (equipped with mercury seal stirrer, condenser and funnel) with sodium metal (0.755g, 0.033 mole). Di-n-butyl phosphite (6.36g, 0.033 mole) was added dropwise over 30-40 mins. with stirring. After completion of addition, refluxing was continued for a further 4 hrs. 2-chloromethyl-pyridine hydrochloride (4.59g, 0.030 mole) was treated

with 5% sodium hydroxide solution (30 mls) and the resultant oil extracted with dry petroleum ether (100-120, 2×30 mls). The combined extract was dried over sodium sulphate, filtered and evaporated to a small volume under reduced pressure. A further 50 mls. of dry petroleum ether was added, and the solution again evaporated to a small volume to remove any last traces of moisture. This was repeated once more, to give a final total volume of solution of 10 mls. This was then added dropwise to the refluxing solution over 30-40 mins. The reaction mixture was then refluxed for a further 20 hrs. It was then allowed to cool and a white precipitate and a gum were evident. The cool reaction mixture was extracted with 1% sodium hydroxide solution (3×50 mls). The petroleum ether solution was dried over sodium sulphate, filtered and evaporated to a small volume under reduced pressure. Dry petroleum ether (60-80°, 100 mls) was added and the solution again evaporated. This was repeated with a further 100 mls of petroleum ether (60-80°). The last traces of solvent were removed under high vacuum (1 mm) yielding di-n-butyl-2-picolyl phosphonate (4.23g, 53%) as a yellow oil. This was redistilled in vacuo, giving an almost colourless oil b.p. 139°/0.8 mm, n_D^{21} 1.4845 (Found: C, 58.46; H, 8.51; N, 5.09. $C_{14}H_{24}NO_3P$ requires C, 58.95; H, 8.42;

N, 4.91%). It forms a picrate which, after recrystallisation from n-pentanol, has m.p. 122-123° (Found: C, 46.50; H, 5.42; N, 11.11. $C_{20}H_{27}N_4O_{10}P$ requires C, 46.73; H, 5.25; N, 10.90%).

The u.v. absorption spectrum of di-n-butyl-2-picolyl phosphonate in ethanol showed the following maxima (ε): 213(5,151), 249.5*(2,039), 256(2,920), 262(3,370), 268.5 mμ(2,530).

The principal maxima of the i.r. spectrum are: 750(m), 850(m), 905(m), 988(vs), 1026(vs), 1063(vs), 1119(w), 1122(w), 1150(w), 1199(m), 1254(vs), 1308(w), 1386(w), 1398(w), 1404(w), 1415(s), 1475(s), 1572(m), 1588(s), 2950(s) cm^{-1}.

The n.m.r. spectrum (10% in $CDCl_3$) was as follows:

Line position (τ)	Intensity	Multiplicity	Assignment
9.08	6	Doublet (J=6c.p.s.)	2 CH_3- of n-butyl
8.99-8.28	8	Complex	2 $-CH_2-CH_2-$ of n-butyl
6.56	2	Doublet (J=22c.p.s.)	$-P-CH_2-Py$
6.14-5.81	4	Complex	2 $-CH_2-O$
2.92-2.18	3	Complex	3-, 4- and 5-protons of pyridine

1.44	1	Doublet (J=5c.p.s.)	6-proton of pyridine

6. Reaction of di-n-butyl-2-picolyl phosphonate with 1,3-di-iminoisoindoline

Di-n-butyl-2-picolyl phosphonate (0.98g, 0.0035 mole) and 1,3-di-iminoisoindoline (0.50g, 0.0035 mole) were refluxed in dry n-butanol (50 mls) for 24 hrs. After cooling the solution was filtered from a small amount of dark blue material (probably phthalocyanine). The filtrate was evaporated under reduced pressure to a small volume (approx. 2 mls). No solid separated out, therefore an excess of petroleum ether (60-80°) was added. This yielded only 74 mg. of nondescript solid. Treatment of the filtrate with ethanolic picric acid gave the picrate of di-n-butyl-2-picolyl phosphonate (1.177g, 70%) m.p. 120° and mixed m.p. 121°.

7. Reaction of di-n-butyl-2-picolyl phosphonate and 1,3-di-iminoisoindoline in the presence of sodium butoxide

Sodium (0.08g, 0.0034 mole) was dissolved in dry n-butanol (50 mls). Di-n-butyl-2-picolyl phosphonate (0.99g, 0.0035 mole) was added to the solution which was then kept at R.T. for 5 mins. Then 1,3-di-imino-isoindoline (0.50g, 0.0035 mole) was added and the solution refluxed for 22 hrs. After cooling, filtration

of the solution yielded a purple solid (181 mg., 41%). A solution of this solid in 1-chloronaphthalene exhibited absorption maxima at 664 and 698 mμ showing that it was phthalocyanine. No other material could be isolated from the reaction mixture.

8. Reaction of di-n-butyl-2-picolyl phosphonate and 1,3-di-iminoisoindoline in the presence of sodium hydride

Sodium hydride (50% dispersion in mineral oil, 0.17g, 0.0035 mole) was suspended in sodium dried dioxan (20 mls). Di-n-butyl-2-picolyl phosphonate (0.98g, 0.0035 mole) in sodium dried dioxan (20 mls) was added to the suspension. Immediate evolution of a gas occurred which rapidly died down to a steady flow. After ½ hr., the solution was heated to 50°C for ½ hr. 1,3-Di-imino-isoindoline (0.50g, 0.0035 mole) in dioxan (20 mls) was then added and the solution heated to 50-60°C for 1½ hrs. It was then heated to reflux for 2 hrs. The solution became dark green. After cooling, the solution was filtered giving 0.21g of pale green hygroscopic solid (A). The filtrate was evaporated to a small volume under reduced pressure, and treated with diethyl ether giving a further 0.27g of pale green hygroscopic solid (B). The filtrate from this was treated with ethereal picric acid yielding 0.285g of a yellow-green picrate (C). Solid C

had an i.r. spectrum identical in every respect with the i.r. spectrum of an authentic sample of the picrate of 1,3-di-iminoisoindoline. A portion of solid B was dissolved in ethanol and treated with ethanolic picric acid giving a picrate which also showed itself to have an i.r. spectrum identical with that of the picrate of 1,3-di-iminoisoindoline. Solid A was dissolved in water, and the solution extracted with chloroform. The chloroform extract on treatment with ethanolic picric acid gave no precipitate initially, and after standing overnight gave only a very small amount of an unidentified picrate. The aqueous residue, after chloroform extraction, was treated with an aqueous solution of picric acid. This gave a picrate which again showed an i.r. spectrum identical with that of 1,3-di-iminoisoindoline.

9. Reaction of di-n-butyl-2-picolyl phosphonate with phthalonitrile

Sodium (0.039g, 0.0017 mole) was dissolved in dry ethanol (15 mls). Di-n-butyl-2-picolyl phosphonate (0.50g, 0.0018 mole) and phthalonitrile (0.23g, 0.0018 mole) were added and the mixture stirred at room temperature for 2 hrs. Colour developed only very slowly and stirring was continued for 20 hrs. at 55°. After cooling the reaction mixture was poured into water (150 mls) giving a blue precipitate. This was identified as phthalocyanine (0.019g)

by its u.v. spectrum. The residual filtrate was quite colourless and no other products of the desired type could be isolated.

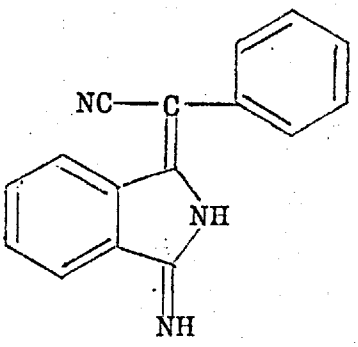
Chapter 3.

Model reactions with substituted benzenes

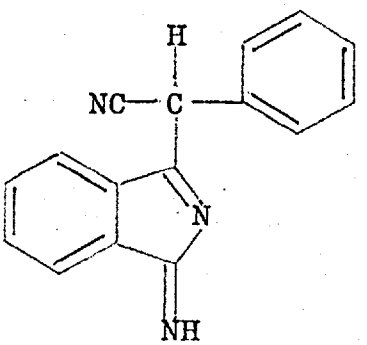
It was shown by Fitt[9] that benzyl cyanide will condense with succinonitrile in the presence of sodium ethoxide to give the substituted succinimidine (XIII). Further the reaction between benzyl cyanide and phthalonitrile has been investigated by Linstead *et al*[31], and was shown to give 1-phenylcyanomethylene-3-iminoisoindoline (XXVI). This type of reaction should provide a good synthetic method that could be extended to substituted pyridines, which could lead to the formation of the desired methine-linked compounds, after removal of the activating nitrile groups.

In the first instance the reaction between benzyl cyanide and phthalonitrile was reinvestigated in order to provide a more thorough proof of the structure of the compound prepared by Linstead. From reaction of equimolar amounts of the two reagents a 93% yield of the compound (XXVI) was obtained. This shows the following important features in its i.r. spectrum. (a) C≡N absorption at 2200 cm^{-1}, (b) C=N at 1660 cm^{-1}. This absorption moved to 1690 cm^{-1} in the hydrochloride and this is in accordance with the observed effect of protonation on C=N absorption[25, 26, 27], (c) C=C absorption at about 1600 cm^{-1}.

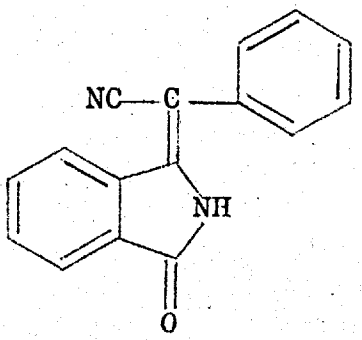
The p.m.r. spectrum provided valuable negative evidence,



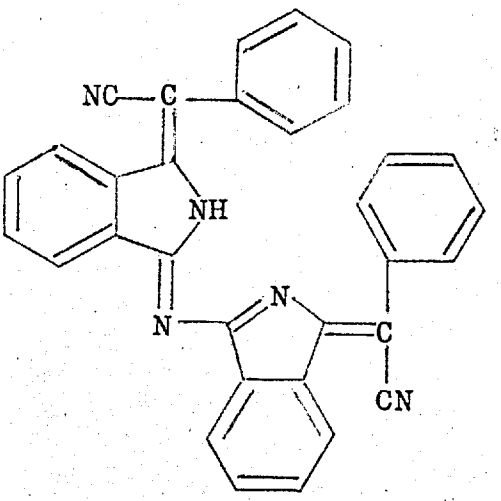
XXV1



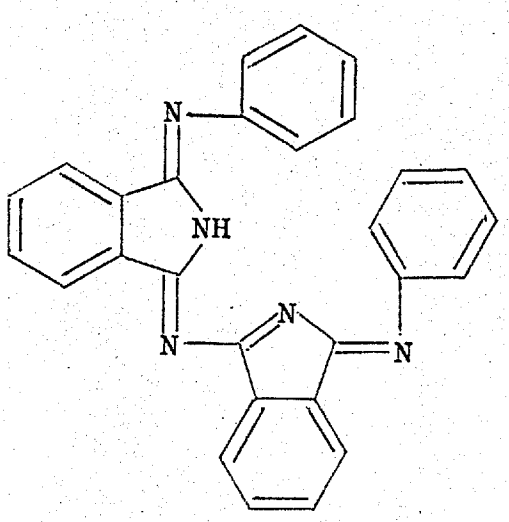
XXV1A



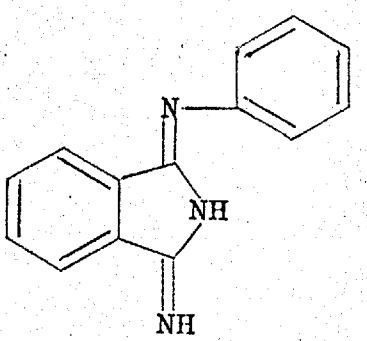
XXV111



XX1X

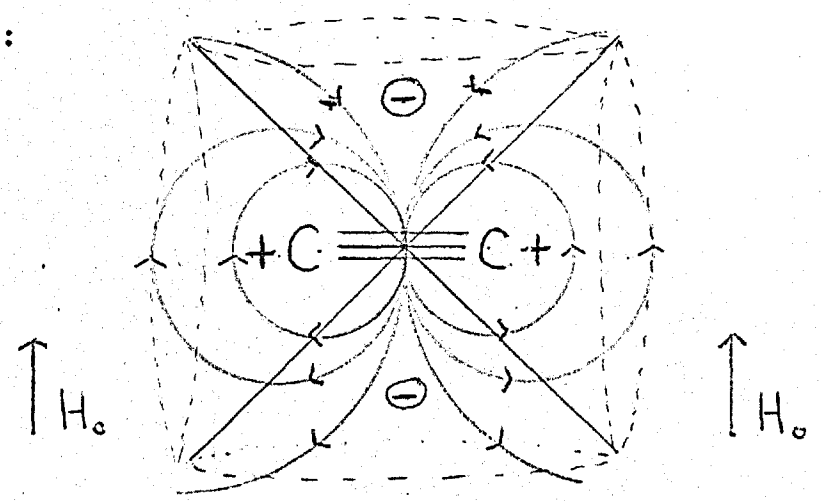


XXX



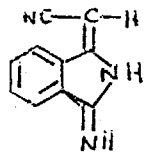
XXX1

in that the presence of a CH peak could not be detected, ruling out the possibility of structure (XXVIA). The only protons detected were aromatic and one of them appears at lower field than the rest; this is presumably due to the effect of the nitrile group on the proton nearest to it. This type of effect has been discussed[46,47] particularly with reference to the acetylenic triple bond. In that case, the applied field causes diamagnetic anisotropy of the electrons forming the triple bond, which in turn induces a magnetic field which reinforces or opposes the applied field according to the position in space. Consequently a proton in the vicinity is shielded or deshielded depending on its position relative to the triple bond, thus:

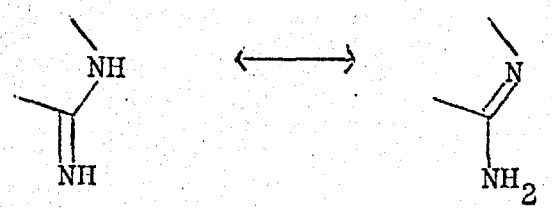


In the case of the acetylenic double bond, the 'cones of effect' are symmetrical, but for a nitrile group, which is dipolar, the cones will be displaced along the bond axis. The long-range effect of a nitrile group has been

observed in acrylonitrile[49] and in phthalylidene-cis- and -trans-acetonitriles and other cis-cinnamonitriles[48]. Thus it is reasonably certain that the observed effect is due to the nitrile group present in the molecule.

Further evidence for the position of the double bond is furnished by the ultra-violet spectrum. The longest wavelength absorption occurs at 365 mμ. Compare this with compounds of the type  which absorb up to about 320 mμ [50]. The increase of wavelength due to conjugation with a phenyl group is usually of the order of 45 mμ [51], which gives the predicted maximum wavelength of (XXVI) as about 365 mμ. Hence it suggests that the double bond lies between the aromatic rings producing an extended conjugated system.

There remain two structural features which are not yet absolutely determined. Firstly, the actual position of the C=N bond, i.e. whether it is in fact endo- or exo-cyclic. No evidence has been found that will show whether it is one form or the other, but it seems likely that a tautomeric equilibrium exists thus:

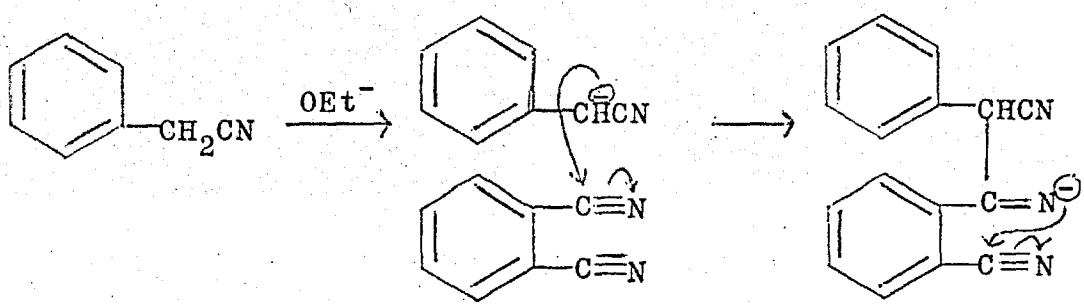


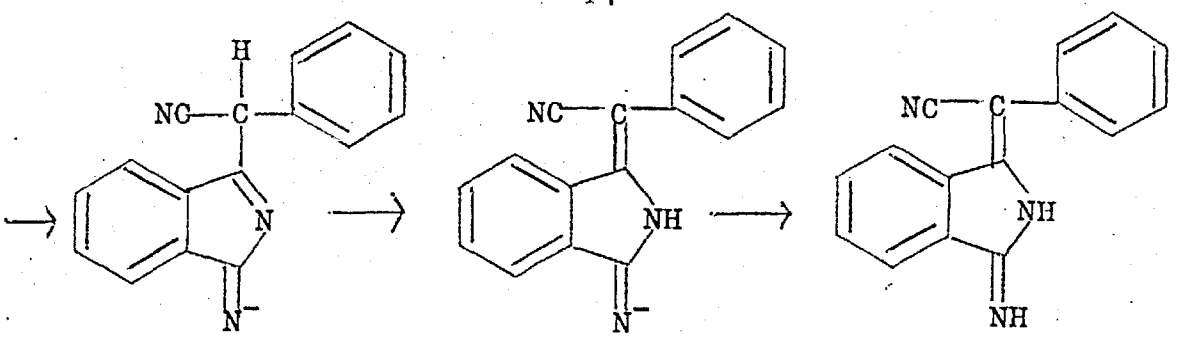
although the position of equilibrium may favour predominantly

one form only. This problem is further discussed in the chapter on the u.v. spectra of the compounds.

Secondly, the relative positions of the aromatic rings across the connecting double bond could be syn or anti. In order to elucidate this problem, the same reaction was carried out using phthalonitrile and pentafluorophenyl-acetonitrile, giving initially the compound (XXXll). This could not be obtained free from the oxo-compound (XXXlll), the latter however easily being obtained pure. The p.m.r. spectrum of (XXXlll) shows only the protons of the isoindoline ring and the presence of one of these affected by the cyanide group is again observed. This demonstrates conclusively that the cyanide group must be syn to the benzene ring of the isoindoline group, and therefore the two aromatic rings must be anti. Comparison of the u.v. spectra of the fluorinated and normal compounds suggests that there is no change in the geometry of the molecule between the two, and therefore the unfluorinated compound also has the anti arrangement.

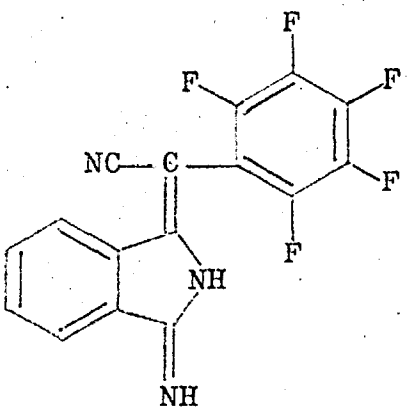
The mechanism of the addition reaction is probably as follows:



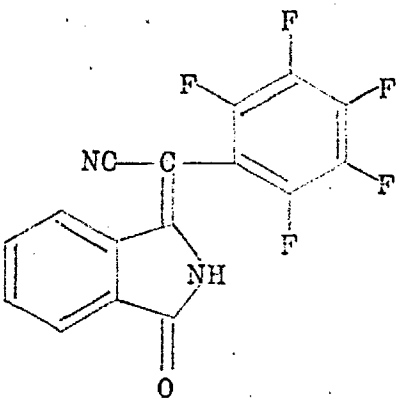


The imino-compound (XXVl) readily undergoes hydrolysis with dilute acid to the corresponding oxo-compound (XXVlll), and in the i.r. spectrum the C=N absorption at 1660 cm^{-1} is replaced by C=O absorption at 1720 cm^{-1}.

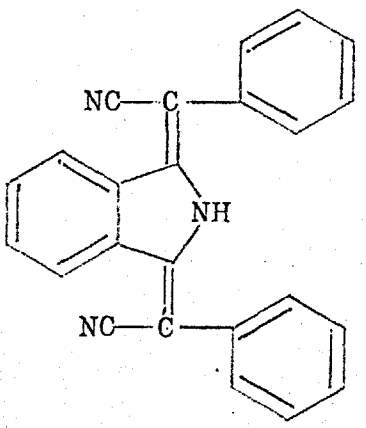
The imino-compound (XXVl) and its hydrochloride both undergo a self-condensation reaction when heated above 200°. A dark coloured residue is obtained which when pure is fine dark red needles. This new compound absorbs up to 495 mμ in the visible spectrum, indicating an increase in the length of the conjugated system. Analysis suggested the structure (XXlX) which is formed by elimination of one molecule of ammonia from two molecules of the imino-compound. This is confirmed by the mass spectrum which shows the molecular ion to have a mass of 473, which is correct for (XXlX). Peaks also occur at 243 and 229 which are due to rupture of the molecule into two parts at the single bond of the linking nitrogen atom. The other major peaks in the mass spectrum can all be explained in terms of fragments of structure (XXlX). This reaction is very similar to one observed by Clark[30] who prepared compounds



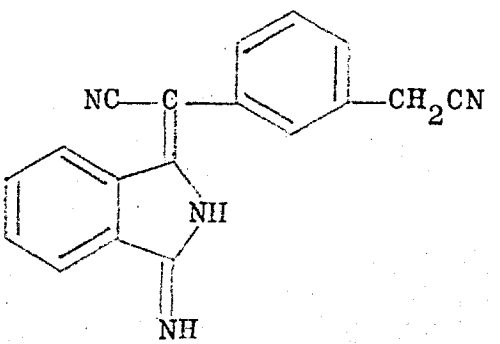
XXX11



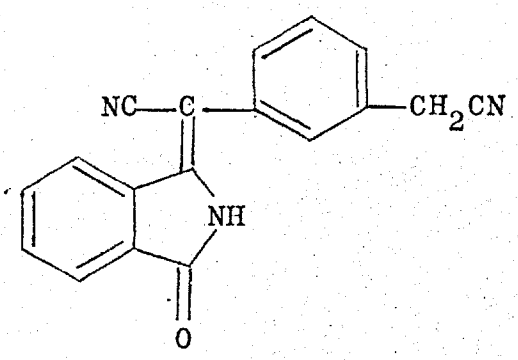
XXX111



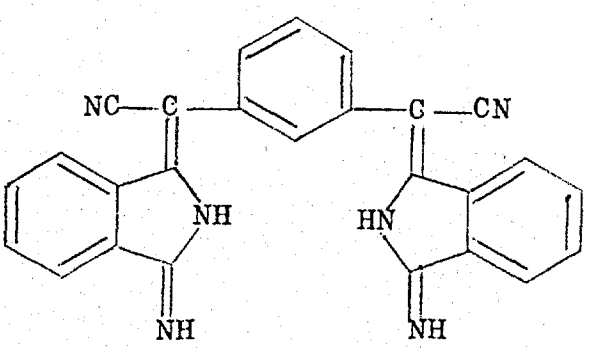
XXX1V



XXXV



XXXV1



XXXV11

such as (XXX) by the action of heat on (XXXl). Clark also succeeded in preparing 2:1 ligand to metal complexes of his compounds of the type (XXX). But attempts to prepare metal complexes from (XXlX) failed.

Compound (XXlX) is hydrolysed by aqueous ethanolic hydrochloric acid to give two molecules of 1-phenylcyanomethylene-3-oxo*iso*indoline, by fission at the linking nitrogen atom.

Next the reaction between phthalonitrile and two molar equivalents of benzyl cyanide was investigated. The aim of this was that following formation of the 'two-unit' compound, reaction should then occur between the imino group and the active methylene of another molecule of benzyl cyanide, eliminating ammonia and giving a 'three-unit' compound. In fact, using more vigorous conditions than previously, such a reaction did take place and 1,3-di(phenylcyanomethylene)isoindoline (XXXlV) was isolated in good yield (89%). This compound absorbs further into the visible spectrum (415 mμ) than the two-unit compound (365 mμ), showing a lengthening of the conjugated system. In the i.r. spectrum it shows (a) C≡N absorption at 2200 cm^{-1} (b) NH at 3300 cm^{-1} and (c) C=C at 1620 cm^{-1} (broad). It does not show any C=N absorption in the region 1640-1700 cm^{-1}.

The p.m.r. spectrum further supports the structure,

now showing two protons moved to low field by the presence of cyanide groups and a complex pattern of twelve other protons as expected from the structure.

The mass spectrum gives the expected value of the mass of the molecular ion as 345, and also shows a peak at 172.5 for the doubly charged molecular ion. The remainder of the breakdown pattern is in agreement with the structure (XXXIV).

Having successfully taken reactions with a mono-substituted benzene to their logical conclusion, the reactions of a disubstituted benzene, namely 1,3-di(cyano-methyl)benzene were investigated with a view to being now able to carry the reactions through to a macrocycle.

Initially the preparation of a 'two-unit' compound was carried out, equimolar amounts of the di(cyanomethyl) benzene and phthalonitrile reacting readily at room temperature to give 1-(3-cyanomethylphenylcyanomethylene) -3-iminoisoindoline (XXXV) in 81% yield. This compound was not isolated pure but was well characterised by its spectral properties. Its u.v. spectrum was substantially the same as that of (XXVI) but showed a bathochromic displacement of 14 mμ due to the $-CH_2CN$. In the i.r. the C≡N, C=N and C=C absorptions were again observed, and in the p.m.r. spectrum in addition to expected aromatic protons, a peak due to the CH_2 was observed at 6 τ.

Confirmation was provided by the mass spectrum which gives the mass of the molecular ion as 284.

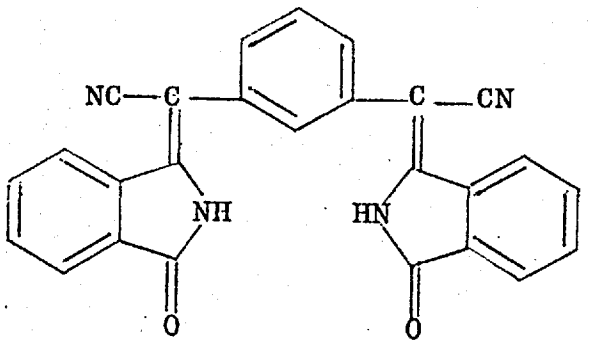
The imino-compound (XXXV) was readily hydrolysed by dilute aqueous ethanolic acid to give 1-(3-cyanomethyl phenylcyanomethylene)-3-oxoisoindoline (XXXVI), which was isolated pure. Its spectral properties were all as expected, including the exchange of C=O absorption for C=N in the i.r. and the presence of a CH_2 in the p.m.r. spectrum.

Having prepared a 'two-unit' compound, synthesis of a 'three-unit' compound was now attempted. In this case there are two possible 'three-unit' compounds, namely one derived from one molecule of phthalonitrile and two of the di(cyanomethyl)benzene, and the other from two molecules of phthalonitrile and one of the di(cyanomethyl)benzene. The synthesis of the latter was chosen since it was anticipated that each of the active methylene groups of the benzene would react with a molecule of phthalonitrile at room temperature, whereas formation of the other 'three-unit' material would, by analogy with benzyl cyanide require an elevated temperature. This might easily lead to higher reaction products which would have to be separated.

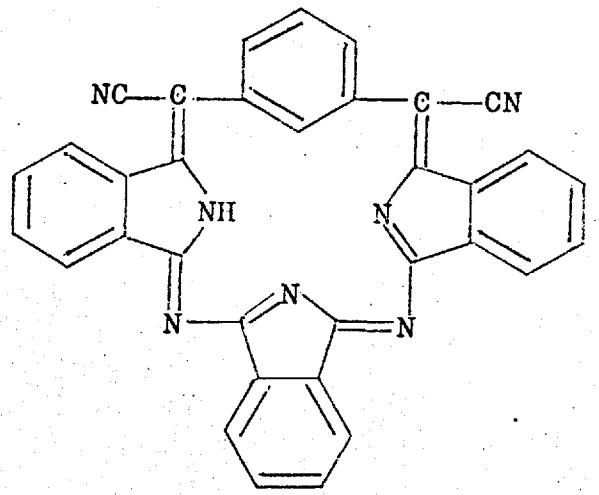
In the event, one molecule of 1,3-di(cyanomethyl) benzene and two molecules of phthalonitrile did react at room temperature giving the expected product, 1,3-di(cyano

(3-imino-1-isoindolinylidene)methyl)benzene (XXXVII) in 76% yield. This shows a lengthening of the conjugated system compared with (XXXV), there being a bathochromic shift of 25 mμ for the longest wavelength absorption in the visible spectrum. Also the i.r. spectrum is consistent with the expected structure, although it is of course not very different from that of (XXXV), But it does show an increase in the number of bands attributable to aromatic substitution. No suitable solvent for p.m.r. spectroscopy could be found, but the mass spectrum confirms the structure, giving the correct molecular weight of 412 and another peak at 206.

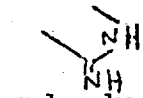
Compound (XXXVII) was not the only product isolated from the above reaction. A small amount of brick-red, highly insoluble solid was obtained. From the mass spectrum the molecular weight was determined as 523. Furthermore, an accurate mass determination of the molecular ion suggested that the molecular formula was $C_{34}H_{17}N_7$ from which it was proposed that the compound was the macrocycle (XXXIX) (10% yield based on phthalonitrile). It is easy to see that this could be formed by reaction of (XXXVII) with a further molecule of phthalonitrile, followed by cyclisation. The i.r. spectrum supports the structure. Apart from the usual absorptions due to NH and C≡N, it shows C=N at 20 cm^{-1} lower than has been found for the



XXXVIII



XXXIX

compounds having C=NH. Also the strong band at about 1530 cm^{-1} which seems to be particularly associated with the part-structure  (or its tautomer) is not present, and the bands due to carbon-carbon double bonds in the 1600 cm^{-1} region have become stronger and broader, which suggests perhaps an increase in the number of these present in the molecule.

The analogous compound having all aza-links (XL11) has previously been prepared[7], but the two compounds are not markedly similar. (XL11) absorbs 40 mμ farther into the visible spectrum and is at least sufficiently soluble in chloroform for the u.v. to be measured, whereas it is difficult to get a sufficiently concentrated solution of (XXX1X), even in o-dichlorobenzene.

Attempts were made to deliberately prepare (XXX1X) by reaction of (XXXV11) with 1,3-di-iminoisoindoline. However, in the first instance a long reaction time was allowed, and the precipitate which had appeared initially, had redissolved at the end of the reaction time. In a second experiment, the reaction solution was filtered at intervals until no further precipitate was formed. In this case a 5% yield of (XXX1X) was obtained, From the combined residual solutions about 65% of (XXXV11) could be recovered after the reaction and was identified by its u.v. and i.r. spectra.

The reaction temperature employed (120°) was about 20° below that at which 1,3-di-iminoisoindoline begins to decompose and it does not seem likely that yields could be increased by elevation of the temperature, particularly as formation of (XXXIX) occurs to a very small extent and then ceases. No evidence was found of phthalocyanine formation, thus ruling out a possible alternative reaction of the di-imine. Unfortunately sufficient time was not available to pursue this problem any further.

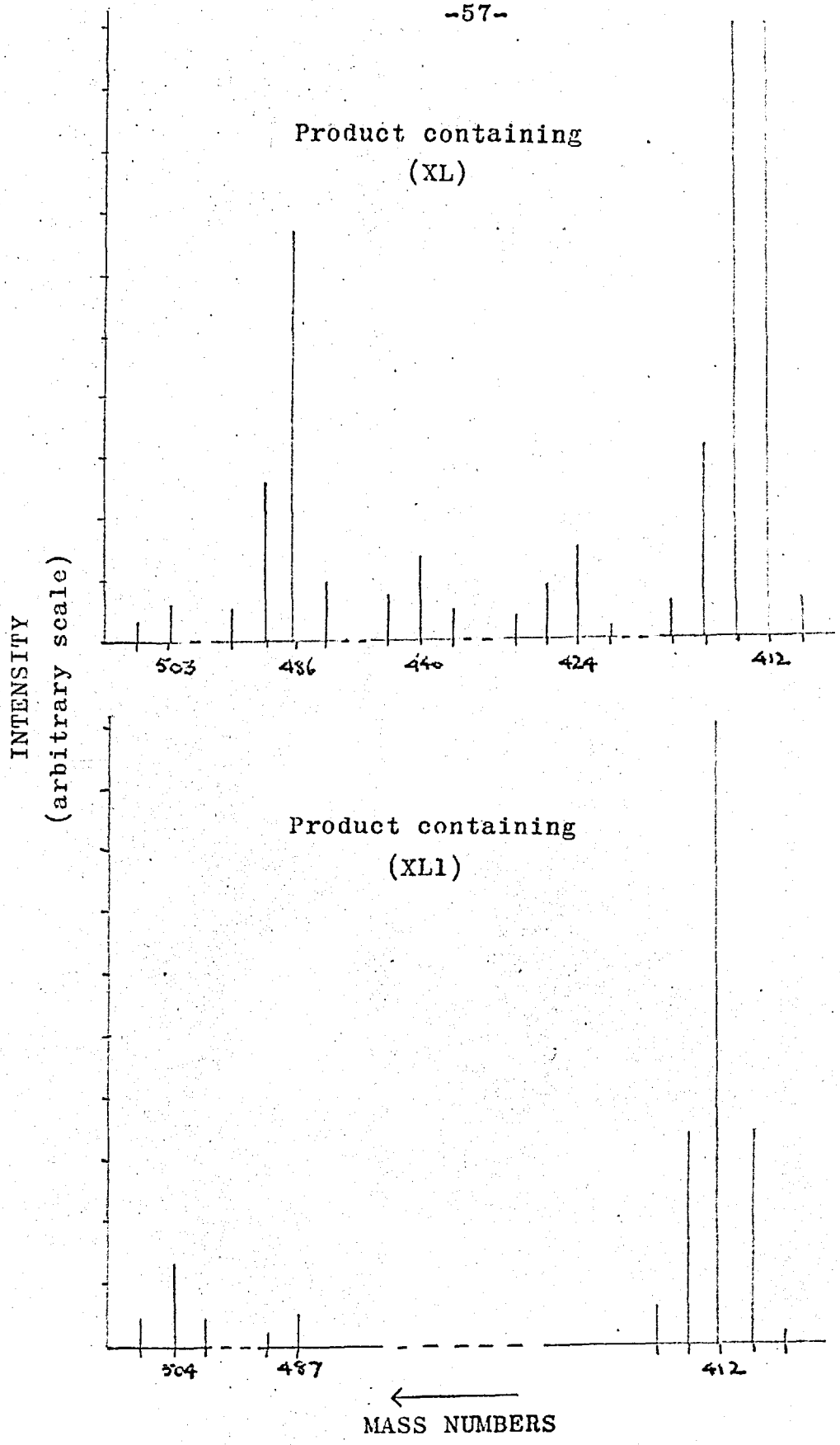
(XXXVII) was hydrolysed by dilute aqueous ethanolic acid to the corresponding oxo-compound, 1,3-di(cyano(3-oxo-1-isoindolinylidene)methyl)benzene (XXXVIII) whose spectral properties were in accordance with its structure, including its molecular weight, determined from the mass spectrum as 414. An interesting feature of its i.r. spectrum is that two C=O absorptions are apparent, at 1735 and 1710 cm^{-1}. It is not clear whether the two carbonyl groups are giving bands different from each other, or whether each carbonyl group is giving rise to two bands.

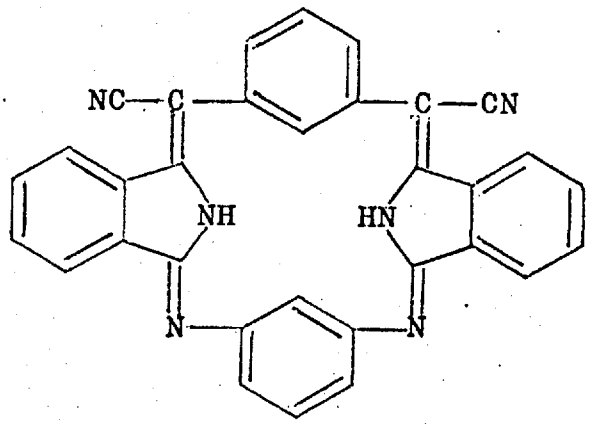
The next step in the main theme of this section was to attempt the conversion of (XXXVII) into macrocycles. Initially it was reacted with diamines, since compounds of the type of (XXXVII) have previously been reacted with diamines to give in that case entirely aza-linked macrocycles.

Now it is expected that macrocycles with two aza-links and two cyanomethine-links should be obtained.

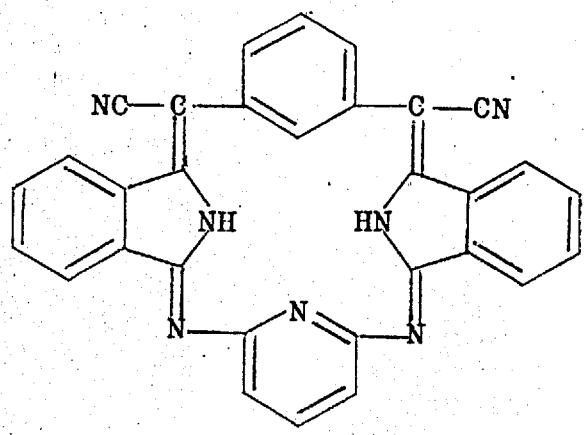
(XXXVll) was refluxed in dimethylacetamide with, separately, m-phenylenediamine and 2,6-diaminopyridine. In both cases a product was obtained, but analyses demonstrated that they were not pure. U.V. and i.r. spectra were of little use here, but the mass spectra of these impure products demonstrated quite clearly the presence in both cases of the expected macrocycle, (XL) and (XLl) respectively, since peaks at mass numbers 486 and 487 were easily detected (see overleaf). Further there were small peaks at mass numbers 17 higher in both cases, suggesting that the non-cyclic 'four unit' compound is also present. This shows that cyclisation does not occur particularly readily since both products were obtained by hot extraction of the crude reaction product with chlorobenzene, and any non-cyclic material present must have survived this.

These peaks at higher mass numbers are not conclusive proof of the presence of the non-cyclic compounds since very small peaks occur higher still but these are attributed to the presence of traces of metals complexed to the compounds. This effect is observed for all the three-unit compounds previously described, even when analytically pure. This is supported further by the fact

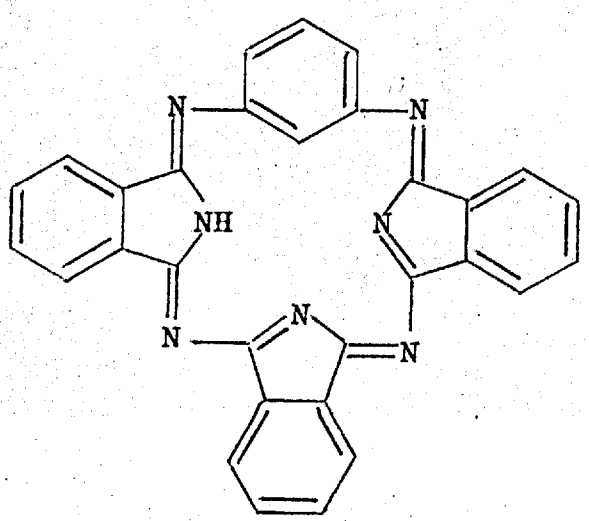

Product containing
(XL)
503
486
440
424
412
INTENSITY
(arbitrary scale)
Product containing
(XL1)
504
487
412
MASS NUMBERS



XL



XL1



XL11

that the analysts found small amounts of non-combustible residues remaining.

It seems most likely therefore that the macrocycles (XL) and (XL1) and their non-cyclic precursors were obtained, although none of them in their pure state.

An attempt was also made to condense (XXXV11) with 1,3-di(cyanomethyl)benzene in the presence of sodium hydride in dry dimethylformamide at 100°. A product was obtained in this case also, again impure, and the mass spectrum only indicated the presence of the starting material (XXXV11).

Lastly a similar condensation was attempted between (XXXV11) and 2,6-di(cyanomethyl)pyridine (whose preparation is described in Chapter 4) under the same conditions as above, with the same results. The mass spectrum did suggest the presence of a high molecular weight species of the right order, but the intensities were very low and not too much importance can be attached to this.

In view of the difficulty of reaction of (XXXV11) with diamines, it seems that if the totally cyanomethine-linked macrocycles are to be obtained, much more vigorous reaction conditions will be required.

Experimental

Notes

1. P.M.R. spectra were measured on a Varian A-60 spectrometer in 5-10% solutions of the stated solvent. Figures are quoted as τ values with relative intensity in parentheses.

2. I.R. spectra were measured on a Unicam S.P. 200 (Nujol mull). The quoted figures are not intended as a complete description of the spectra, but simply to give the approximate positions of those bands which are of some diagnostic importance.

3. U.V. spectra were measured on a Unicam S.P. 800. Solvents used were:- (a) Ethanol
(b) 0.2N-NaOH in ethanol
(c) 0.2N-HCl in ethanol
(d) Chloroform
(e) Dimethylformamide
(f) o-dichlorobenzene.

1. Preparation of 1-phenylcyanomethylene-3-iminoisoindoline (XXVI)

To a solution of sodium ethoxide (from sodium (0.98g, 0.043 mole)) in dry ethanol (50 mls), phthalonitrile (5.00g, 0.039 mole) and benzyl cyanide (5.00g, 0.043 mole) were added, which was swirled to dissolve the phthalonitrile. The solution was kept at room temperature for 15 mins.,

then refluxed for 15 mins. After being cooled, the solution was poured into water (50 mls). 2N-hydrochloric acid (22.1 mls) was added producing a dark yellow solid (8.57g). The ethanol was then evaporated from the filtrate giving a further precipitate (0.34g). The total yield of 1-phenylcyanomethylene-3-iminoisoindoline (XXVl) was 8.91g (93%). It was recrystallised from n-butanol (Found: C, 78.34; H, 4.55; N, 17.25. Calc. for $C_{16}H_{11}N_3$: C, 78.36; H, 4.49; N, 17.14%). It forms a hydrochloride (XXVll) which was recrystallised from methanol (Found: C, 67.89; H, 4.25; N, 14.45; Cl, 12.55. Calc. for $C_{16}H_{12}ClN_3$: C, 68.21; H, 4.26; N, 14.91; Cl, 12.61%).

I.R. (XXVl) 3470w (NH), 2200 (cyanide), 1660s (C=N), 1605w and 1590w (C=C), 1525s (amidine band), 1300w, 1215s, 1165w, 1145w and 1090 (aryl C-H), 770s, 745 and 700s (aryl C-H).

(XXVll) 3200w (NH), 2200 (cyanide), 1690s ($C=NH^+$), 1625, 1610w and 1595w (C=C), 1270w, 1240w, 1165, 1125w and 1105w (aryl C-H), 780, 760, 725 and 680 (aryl C-H).

P.M.R.(XXVl) in dimethylacetanide.

3.21 - 2.30 (8), 1.97 - 1.78 (1).

(XXVll) in dimethylsulphoxide.

2.53 - 1.89 (7), 1.56 - 1.21 (2).

2. Hydrolysis of 1-phenylcyanomethylene-3-iminoisoindoline (XXVl)

1-Phenylcyanomethylene-3-iminoisoindoline (5g, 0.02 mole)

was dissolved in ethanol (100 mls) and 2N-hydrochloric acid (20 mls) added. This caused some precipitation of the hydrochloride and more ethanol (100 mls) was added to give complete solution. The solution was refluxed on a water-bath for 4 hrs. The hot solution was then neutralised with 2N-sodium hydroxide. After being cooled, 1-phenylcyanomethylene-3-oxoisoindoline (XXVlll) separated as pale yellow crystals (2.88g, 75%) m.p. 236° after recrystallisation from ethanol/benzene (3:1) (Found: C, 78.38; H, 4.34; N, 11.13 Calc. for $C_{16}H_{10}N_2O$: C, 78.05; H, 4.07; N, 11.39%). From the mother liquors, 1.18g of (XXVl) was recovered.

I.R. 3250 (NH), 2200 (cyanide), 1720vs (carbonyl), 1610s and 1590 (C=C), 1300, 1255, 1200, 1165w, 1140, 1090 and 1020 (aryl C-H), 790w, 770, 695s and 690s (aryl C-H).

P.M.R. in dimethylsulphoxide.

2.47 (5), 2.22 - 2.03 (3), 1.52 - 1.33 (1).

3. The action of heat on 1-phenylcyanomethylene-3-iminoisoindoline

1-Phenylcyanomethylene-3-iminoisoindoline (5.0g, 0.02 mole) was heated to 230° for 1 hr. The colour changed from yellow-orange to dark red. After extractive crystallisation (Soxhlet) from benzene, dark red needles of 1-phenylcyanomethylene-3-(1-phenylcyanomethylene-3-isoindoleninyl)iminoisoindoline (XXlX) were obtained m.p.312° (Found: C, 80.79; H, 4.07; N, 14.83; $^{m}/_{e}$: M^+, 473;

M^{++}, 236.5. $C_{32}H_{19}N_5$ requires C, 81.17; H, 4.02; N, 14.80; $^{m}/_{e}$: M^{+}, 473, M^{++}, 236.5).

I.R. 2200 (cyanide), 1600bs (C=N and C=C), 1260, 1190, 1150, 1120w and 1095w (aryl C-H), 760s, 720w, 705w and 680 (aryl C-H).

4. Hydrolysis of (XXIX)

Compound (XXIX) (0.10g, 0.00021 mole) was suspended in a mixture of ethanol (75 mls) and conc. hydrochloric acid (75 mls) and the suspension heated on a steam-bath for 10 hrs. During this time the solid dissolved giving a pale yellow solution. After being cooled, the ethanol was removed under reduced pressure and the residue neutralised with solid sodium bicarbonate. This gave a yellow solid whose i.r. spectrum showed the presence of both C=O and C=N. The solid was redissolved in a mixture of ethanol (25 mls) and 2N-hydrochloric acid (25 mls) and heated on a steam-bath for a further 4 hrs. After removal of the ethanol and neutralisation of the residual aqueous solution, 1-phenylcyanomethylene-3-oxoisoindoline (XXVIII) (0.10g, 0.00041 mole, 95%) was obtained, having an i.r. spectrum identical with that of authentic (XXVIII). After recrystallisation from acetonitrile it had m.p. 237° (c.p. (XXVIII), 236°).

5. Reaction between phthalonitrile and pentafluorophenylacetonitrile

To a solution of sodium ethoxide (from sodium (0.11g, 0.00047 mole)) in dry ethanol (20 mls), pentafluorophenylacetonitrile (0.95g, 0.0047 mole) and phthalonitrile (0.59g, 0.0046 mole) were added. The solution was then stirred at room temperature for 18 hrs. Ethanolic hydrochloric acid (7N, 0.7 mls) was added to neutralise the solution which was then poured, with stirring, into water (300 mls). After 1 hr. the solution was filtered giving 0.54g of orange 1-pentafluorophenylcyanomethylene-3-iminoisoindoline (XXXll). It was found very difficult to free this from contamination with the oxo-compound and it was not obtained pure.

The filtrate from above after being kept at room temperature for 3 days deposited a solid. Filtration yielded 0.48g of 1-pentafluorophenylcyanomethylene-3-oxoisoindoline (XXXlll) m.p. 208-210° after recrystallisation from methanol/water (2:1) (Found: C, 57.49; H, 2.08; N, 8.29; F, 28.00. $C_{16}H_5F_5N_2O$ requires: C, 57.15; H, 1.49; N, 8.34; F, 28.28%).

I.R. (XXXlll) 3200ms (NH), 2200 (cyanide), 1720s (carbonyl), 1625, 1610w and 1595w (C=C), 1500s (fluorinated aromatic ring), 1220, 1140w, 1130, 1100w and 1070 (aryl C-H), 995s and 960s (C-F), 780, 760, 745 and 700 (aryl C-H).

P.M.R.(XXXIII) in $CDCl_3$.

2.35 - 2.04 (3), 1.47 - 1.28 (1).

6. Preparation of 1,3-di(phenylcyanomethylene)isoindoline - (XXXIV)

To a solution of sodium n-butoxide (from sodium (0.36g, 0.016 mole)) in dry n-butanol (50 mls), benzyl cyanide (3.66g, 0.031 mole) and phthalonitrile (2.00g, 0.016 mole) were added and the solution refluxed for 48 hrs. The n-butanol was evaporated under reduced pressure to a small volume and the residue taken up in ethanol (50 mls). This was poured with vigorous stirring into water (1 litre). Addition of 2N-hydrochloric acid to neutralise the solution produced a dark yellow-brown solid (4.81g, 89.2%). After several extractive crystallisations (Soxhlet) from methanol, bright yellow needles of 1,3-di(phenylcyanomethylene)isoindoline (XXXIV) were obtained m.p. 201° (Found: C, 83.70; H, 4.50; N, 12.05; $^m/_e$: M^+, 345; M^{++}, 172.5. $C_{24}H_{15}N_3$ requires: C, 83.49; H, 4.35; N, 12.17%; $^m/_e$: M^+,345; M^{++}, 172.5).

I.R. 3300b (NH), 2200ms (cyanide), 1620s and broad (C=C), 1270, 1235s, 1160 and 1115 (aryl C-H), 780, 765s, 760s, 700s and 690 (aryl C-H),

P.M.R.in $CDCl_3$.

2.62 - 1.82 (12), 1.37 - 1.15 (2).

7. Preparation of 1-(3-cyanomethylphenylcyanomethylene)-3-oxoisoindoline (XXXVI)

To a solution of sodium ethoxide (from sodium (0.071g, 0.0031 mole)) in dry ethanol (25 mls), 1,3-di(cyanomethyl) benzene (0.47g, 0.0030 mole) and phthalonitrile (0.36g, 0.0028 mole) were added. The solution was stirred at room temperature for 5 hrs. A yellow colour developed rapidly, finally going dark orange-brown. The reaction mixture was poured into water (200 mls) with vigorous stirring. A slight excess of 2N-hydrochloric acid was added, causing the finely divided precipitate to coagulate. There was obtained 0.675g (81%) of crude 1-(3-cyanomethylphenylcyanomethylene)-3-iminoisoindoline (XXXV). This crude solid (0.10g, 0.00035 mole) was refluxed in a mixture of ethanol (10 mls) and 2N-hydrochloric acid (10 mls) for 3 hrs. The ethanol was removed under reduced pressure, and the residual aqueous solution neutralised with 2N-sodium hydroxide. A yellow precipitate was produced which yielded 0.09g (86%) of orange powder. After recrystallisation from aqueous methanol 1-(3-cyanomethylphenylcyanomethylene)-3-oxoisoindoline (XXXVI) m.p. 252-253° was obtained (Found: C, 75.77; H, 4.11; N, 15.13. $C_{18}H_{11}N_3O$ requires: C, 75.80; H, 3.86; N, 14.73%).

I.R. (XXXV) 3400 (NH), 2200 (cyanide), 1665s (C=N), 1605 and 1590w (C=C), 1535s (amidine band), 1260, 1215s, 1170

and 1100 (aryl C-H), 790w, 765s and 685s (aryl C-H).

(XXXVI) 3400 (NH), 2200 (cyanide), 1720s (carbonyl) 1615ms (C=C), 1270w, 1215 and 1145 (aryl C-H), 770s, 730w and 695s (aryl C-H).

P.M.R.(XXXV) in pyridine

6.07

in acetone

5.99 (2), 2.62 - 1.57 (7), 1.47 - 1.28 (1).

(XXXVI) in pyridine

6.10

in dimethylsulphoxide

2.48 (4), 2.24 - 2.03 (3), 1.56 - 1.32 (1).

8. Preparation of 1,3-di(cyano(3-imino-1-isoindolinylidene) methyl)benzene (XXXVII)

To a solution of sodium ethoxide from (sodium (0.31g, 0.013 mole)) in dry ethanol (30 mls), 1,3-di(cyanomethyl) benzene (1.00g, 0.0064 mole) was added and dissolved by stirring. Then phthalonitrile (1.70g, 0.013 mole) was added and the solution stirred at room temperature for 20 hrs. It was then poured into water (500 mls) and 2N-hydrochloric acid (7 mls) was added. Filtration yielded 3.013g of red-brown solid. This was taken up in hot dimethylacetamide, leaving a small amount of insoluble material. This brick-red solid was the macrocycle (XXXIX) (0.23g, 10%). It was purified by recrystallisation (hot

extractor) from o-dichlorobenzene (Found: C, 77.84; H, 3.46; N, 18.54; $^{m}/_{e}$: M^{+}, 523 and molecular formula $C_{34}H_{17}N_{7}$. $C_{34}H_{17}N_{7}$ requires: C, 78.02; H, 3.25; N, 18.74%; $^{m}/_{e}$: M^{+}, 523).

The dimethylacetamide filtrate after cooling was diluted with water until no further precipitation occurred. Filtration gave 2.06g (76.5%) of 1,3-di(cyano(3-imino-1-isoindolinylidene)methyl)benzene (XXXVll) as a dark yellow solid. This was recrystallised from dimethylacetamide/methanol (Found: C, 72.51; H, 4.94; N, 19.46. $C_{26}H_{16}N_{6}$. $CH_{3}CON(CH_{3})_{2}$ requires: C, 72.14; H, 5.01; N, 19.63%. Found: $^{m}/_{e}$: M^{+}, 412. $C_{26}H_{16}N_{6}$ requires $^{m}/_{e}$:M^{+}, 412). I.R. (XXXVll) 3430w and 3300w (NH), 2200 (cyanide), 1660 (C=N), 1635 and 1575w (C=C), 1530s (amidine band), 1300, 1275, 1240, 1215, 1195w, 1170, 1105 and 1035 (aryl C-H), 815, 765s, 745w, 715 and 690s (aryl C-H).

(XXXlX) 3330w (NH), 2200 (cyanide), 1640s (C=N), 1605s and 1585 (C=C), 1255, 1180w, 1155, 1115, 1100 and 1025 (aryl C-H), 800w, 765, 720s and 690 (aryl C-H).

9. Preparation of 1,3-di(cyano(3-oxo-1-isoindolinylidene)methyl)benzene (XXXVlll)

1,3-Di(cyano(3-imino-1-isoindolinylidene)methyl)benzene (XXXVlll) (0.20g, 0.00048 mole) was suspended in a refluxing mixture of ethanol (15 mls) and 2N-hydrochloric acid (15 mls) for 2 hrs. Filtration and drying yielded 0.19g (93%) of

1,3-di(cyano(3-oxo-1-isoindolinylidene)methyl)benzene (XXXVIII) which was recrystallised from dimethylacetamide (Found: C, 75.32; H, 3.78; N, 13.67. $C_{26}H_{14}N_4O_2$ requires: C, 75.37; H, 3.38; N, 13.53%).

I.R. 3250s (NH), 2200 (cyanide), 1735vs and 1710vs (carbonyl) 1605s and 1590 (C=C), 1280w, 1230, 1205w, 1145, 1110w and 1095w (aryl C-H), 805w, 775, 715 and 705 (aryl C-H).

10. Reaction of (XXXVII) with diamines

(a) (XXXVII) (0.20g, 0.00049 mole) and m-phenylenediamine (0.054g, 0.00050 mole) were refluxed in dimethylacetamide (8 mls) for 18 hrs. After being cooled the solution was diluted with a large excess of water (100 mls). The precipitate was allowed to coagulate at room temperature for a few hours. Filtration gave 0.21g of a brown solid, which was extractively crystallised (hot extractor) from chlorobenzene.

(b) (XXXVII) (0.25g, 0.00061 mole) and 2,6-diaminopyridine (0.070g, 0.00064 mole) were refluxed in dimethylacetamide (10 mls) for 18 hrs. After being cooled, the solution was worked up as above to give 0.24g of brown solid, which was extractively crystallised (hot extractor) from chlorobenzene.

11. Reaction of (XXXVII) with 1,3-di(cyanomethyl)benzene

The dimethylformamide used in this and subsequent reactions was dried by the method of Thomas and Rochow[43].

Sodium hydride (53.3% dispersion in mineral oil, 0.019g, 0.00038 mole) was suspended in dry dimethylformamide (10 mls). (XXXVll) (0.15g, 0.00037 mole) and 1,3-di(cyanomethyl)benzene (0.058g, 0.00037 mole) were added and the solution stirred at 110° for 20 hrs. After being cooled, a large excess of water (150 mls) was added and filtration gave 0.14g of a brown solid, which was extractively crystallised (hot extractor) from chlorobenzene.

12. Reaction of (XXXVll) with 2,6-di(cyanomethyl)pyridine

Using sodium hydride (0.018g, 0.00036 mole), (XXXVll) (0.15g, 0.00037 mole) and 2,6-di(cyanomethyl)pyridine (0.057g, 0.00036 mole) in dry dimethylformamide (10 mls) the reaction was carried out as described in the preceding section. 0.16g of brown solid was obtained, which was extractively crystallised (hot extractor) from chlorobenzene.

U.V. spectra

Compound	Solvent	λmax (mμ)	$\varepsilon \times 10^{-3}$
(XXV1)	(a)	233	23.59
		294	9.71
		375	14.30
	(b)	284	11.74
		402	15.36
(XXV11)	(a)	274	10.70
		294^{+}	9.43
		365	17.25
(XXV111)	(a)	226	19.44
		295	10.24
		342	17.57
	(b)	288.5	10.02
		316-317^{+}	8.06
		394	22.90
(XX1X)	(a/d)(4:1)	344	38.71
		400^{+}	11.40
		495	13.59
(XXX111)	(a)	225^{+}	27.99
		228.5	28.49
		286	18.40
		293.5	18.51
		332	20.70
(XXX1V)	(a)	239.5	17.31

(XXXIV) (cont.)		260	11.77
		305.5	14.35
		415	26.50
	(b)	247+	22.00
		261	24.62
		276+	18.76
		307-309	13.07
		346+	8.80
		503	32.02
		536	40.86
(XXXV)*	(a)	239-240	21
		294	8
		387	16
	(b)	285	11
		418	19
	(c)	270	11
		353	17
(XXXVI)	(a)	275	8.93
		292.5	10.58
		341	18.61
	(b)	274+	9.50
		288-289	9.79
		390	15.17
(XXXVII)	(e)	296	14.34
		309+	13.49

(XXXVll) (cont.)		412	34.59
(XXXVlll)	(e)	291	19.76
		342	28.89
(XXXlX)	(f)	363	38.48
		458-462	9.48

+ Inflexion

* Not pure

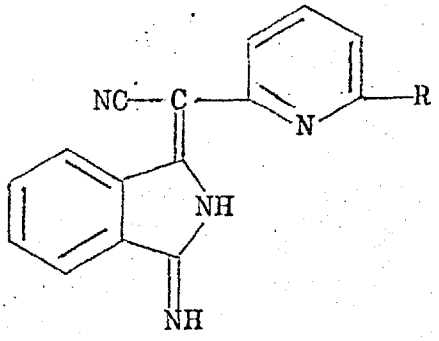
Chapter 4

Syntheses using substituted pyridines

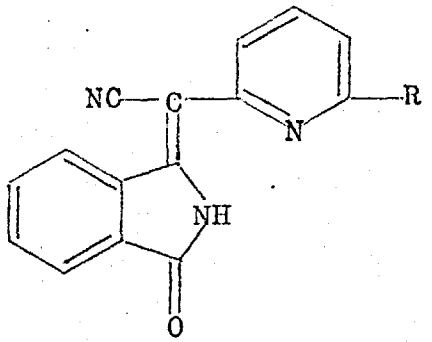
Having successfully completed a series of model reactions with benzene derivatives, it was now possible to extend these reactions to substituted pyridines which should lead eventually to the synthesis of the macrocycle (111) which was the ultimate aim of this work.

In order to obtain a complete comparison of the products from the two series of reactions, almost all the pyridine analogues of the compounds in the benzene series were prepared.

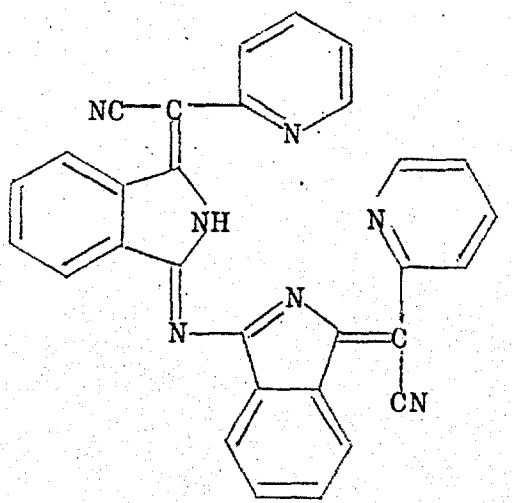
2-Pyridylacetonitrile was prepared by standard methods[28,29]. From this, by reaction with one molar equivalent of phthalonitrile at room temperature, 1-(2-pyridylcyanomethylene)-3-iminoisoindoline (XLV, R=H) was obtained in 73% yield. This showed the expected absorptions (NH, C≡N, C=N, C=C and pyridine) in the i.r. spectrum. The u.v. spectrum was very similar to that of its benzene analogue, but there was a bathochromic shift of some 27 mμ and an increase in ε values. The p.m.r. spectrum shows only aromatic protons, the 5-pyridyl proton being distinguishable at higher field than the main complex peak. It might have been thought that the 3-pyridyl proton should also appear on the high field side. But it has been shown[44] that a 2-vinyl group on a pyridine ring moves the



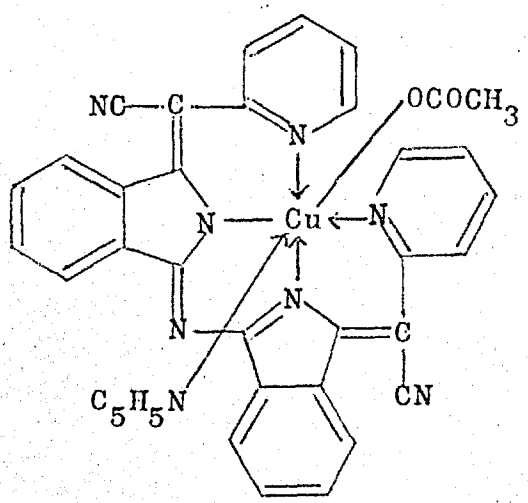
XLV



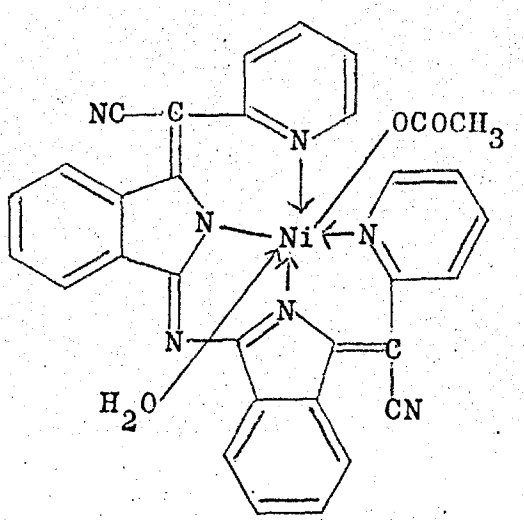
XLVI



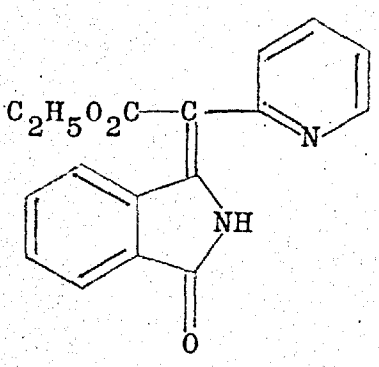
XLVII



XLVIII



XLIX



L

3-pyridyl proton to a lower position. The cyanide-affected proton and the 6-pyridyl proton are detectable on the low field side of the main peak.

This compound was easily hydrolysed by dilute aqueous acid to 1-(2-pyridylcyanomethylene)-3-oxoisoindoline (XLVI, R=H), whose i.r. demonstrated the exchange of C≡N for C=O. All the other spectral properties were as expected.

The compound (XLV, R=H) also underwent the self-condensation reaction with elimination of ammonia to give the condensed compound (XLVII), having an almost identical u.v. spectrum to that of its benzene analogue. Attempts were made to prepare metal complexes from this compound since it would be expected to have four nitrogen atoms in a suitable arrangement for chelation. It is however a somewhat unusual ligand in that it has one nitrogen atom that can form a covalent bond, and three that have only a lone pair to form a co-ordinate link.

With cupric acetate in pyridine solution crystals were obtained whose analysis suggested that it was a copper complex containing the ligand, one acetate group and a molecule of pyridine. Its structure is therefore probably the complex (XLVIII), an octahedral complex of Cu^{II}. The i.r. spectrum shows C≡N absorption demonstrating clearly the presence of the ligand in the complex. Also there is a strong band at 1700 cm^{-1} which can be attributed to the

acetate carbonyl group.

A similar complex (XL1X) was obtained from nickel acetate and (XLV11) in formamide/dimethylformamide solution, the difference being that in place of the pyridine molecule there is one of water. There is however a considerable difference in the observed u.v. spectra, the Cu complex absorbing up to 429 mμ in the visible region and the Ni complex up to 614 mμ. It may be that the Cu complex decomposed or dissociated in the dimethylformamide solution employed for the u.v. measurements because it does not seem reasonable that two such similar metal complexes should have such dissimilar u.v. spectra. The other alternative of course is that their stereochemistry differs in some way.

From dimethylformamide solution, cupric acetate and (XLV11) give a crystalline complex whose i.r. spectrum is identical with that of the Cu complex (XLV111). It cannot contain a pyridine molecule in this case, but could contain a water molecule instead. One would have expected this difference to be reflected in the i.r. spectra of the two compounds. This suggests that the copper complex (XLV111) might not in fact contain a pyridine molecule, but a water molecule. In that case the analytical results differ much more from the calculated figures than in the former case. The complex obtained from dimethylformamide

solution does not have a similar analysis to that of (XLVlll), nor does its analysis agree any better with figures calculated on the basis of its containing a water molecule. It seems that this difficulty cannot be resolved on the information available.

Attempts to prepare complexes of (XLVll) from salts of various other metals did not yield any compounds that could be designated as metal complexes. In some cases the u.v. absorption of the reaction solution suggested that the ligand had been hydrolysed at its nitrogen link, leaving a solution of 1-(2-pyridylcyanomethylene)-3-oxo-isoindoline.

Hydrolysis of (XLVll) occurs very readily with conc. hydrochloric acid in ethanol, and from the reaction mixture two molar equivalents of 1-(2-pyridylcyanomethylene)-3-oxoisoindoline were obtained.

In order to compare the ease of (a) a condensation reaction with phthalonitrile with (b) an elimination (of ammonia) reaction with isoindoline derivatives, attempts were made to prepare compounds (XLV, XLVl, R=H) from isoindoline derivatives. The reaction of 2-pyridyl-acetonitrile with 1,3-di-iminoisoindoline in the presence of sodium ethoxide in ethanol at room temperature gave only a 6.5% yield of (XLV, R=H). With sodium ethoxide in refluxing ethanol, 1-imino-3-oxoisoindoline gave a 15%

yield of (XLVI, R=H). However it was found that when the latter reaction was repeated in the absence of sodium ethoxide, the yield was raised to 47%, indicating that the base in fact considerably reduces the yield. It also shows that even under favourable conditions, the reaction with phthalonitrile, going in good yield at room temperature as it does, is very much easier than that with an isoindoline derivative.

An investigation was also made into the reaction between phthalonitrile and methyl 2-pyridylacetate to determine whether an ester group was as efficient an activating group as a nitrile in this context. Sodium ethoxide in ethanol was the reaction medium, and it was shown by p.m.r. spectrum that the product had completely exchanged the methyl ester for an ethyl ester. The yield of crude imino-compound was only 40% and it was not obtained pure. Mild hydrolysis of this crude material gave 1-(2-pyridylethoxy-carbonylmethylene)-3-oxoisoindoline (L) whose p.m.r., i.r. and u.v. spectra were entirely consistent with its proposed structure.

Attempts to obtain the corresponding product using sodium methoxide in methanol gave only products which were apparently mixtures of the methyl ester and the carboxylic acid. This occurred no matter how carefully the methanol was dried. In view of these difficulties, this line of

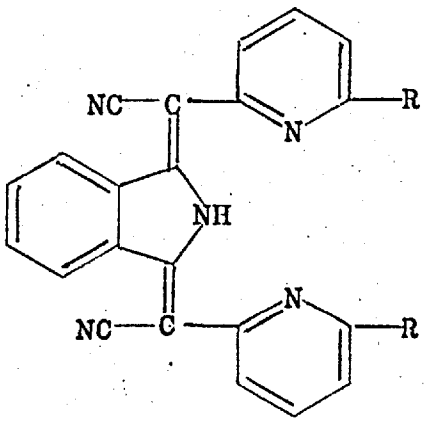
investigation was not pursued.

Reaction between phthalonitrile and two molecules of 2-pyridylacetonitrile was next attempted under the same conditions as had been used for benzyl cyanide. The expected product 1,3-di(2-pyridylcyanomethylene)isoindoline (L1, R=H) was obtained though only in 57% yield, which is considerably lower than the yield with benzyl cyanide. It might have been expected that the pyridyl compound should give a better yield by virtue of the electron-withdrawing effect of the pyridine nitrogen making the methylene group more reactive.

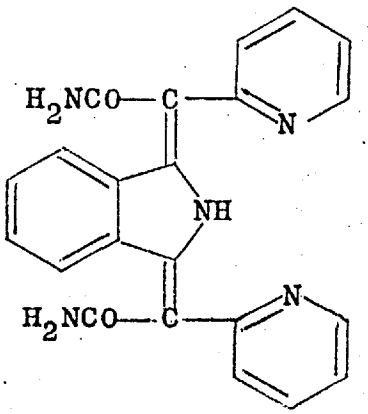
Nevertheless, the desired compound was obtained and its properties agreed with its proposed structure. The i.r. showed C≡N, C=C and pyridine absorption, but no C=N. In the p.m.r. spectrum there could be distinguished the two 5-pyridyl protons at higher field than the main peak, the 3-pyridyl protons being in the main peak due to the effect of the adjacent double bond as before. Two groups of protons (the 6-pyridyl and the cyanide-affected) were observed at lower field.

In the u.v. the absorption bands are bathochromically shifted nearly 100 mμ with respect to those of the 'two-unit' compound.

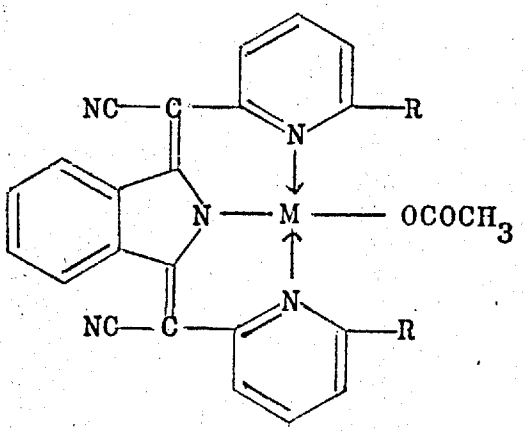
It was also shown that this compound could be prepared in two stages, firstly by synthesis *in situ* of the 'two-unit'



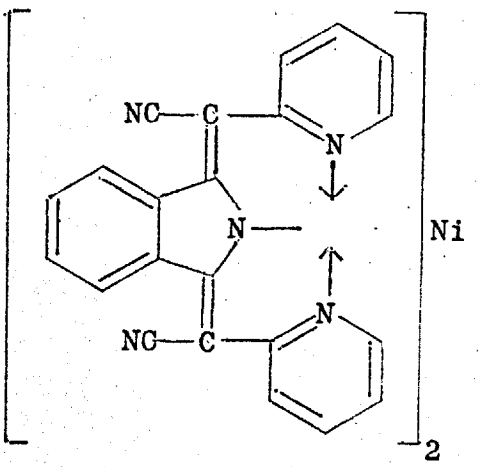
L1



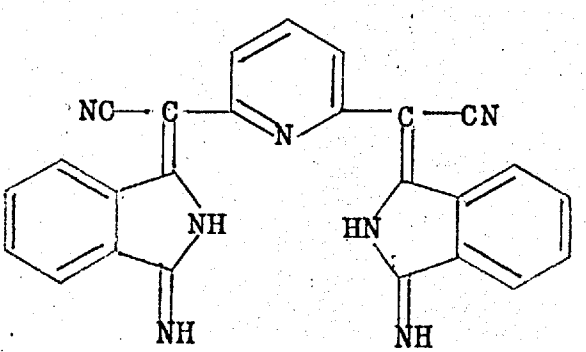
L11



L111



L1V



LV1

compound, and secondly by addition of an equimolar amount of 2-pyridylacetonitrile and elevation of the temperature.

Attempted hydrolysis of the nitrile groups of (L1, R=H) with refluxing 75% sulphuric acid led to the isolation of phthalic acid in 77% yield. But by using 95% sulphuric acid at a lower temperature it was possible to isolate the corresponding di-amide, 1,3-di(2-pyridylcarbamoylmethylene) isoindoline (L11). The i.r. spectrum indicated the presence of NH_2 at 3500 and 3400 cm^{-1}. Also the amide I and II bands appeared at 1655 and 1620 cm^{-1}. No C≡N absorption was detectable. The u.v. absorption in comparison with that of the dinitrile showed a hypsochromic shift of about 30 mμ, demonstrating the weaker auxochromic effect of the amide groups.

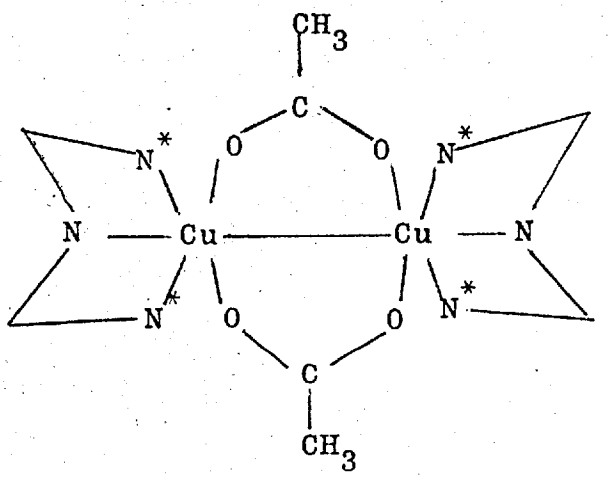
Hydrolysis of the di-amide with dilute sodium hydroxide gave a product which was probably the di-acid. Its u.v. spectrum was different from that of the di-amide. The i.r. spectrum lacked the amide I and II bands, but there were strong bands at 1635 and 1585 cm^{-1} possibly due to carboxylic acid and carboxylate anion.

Attempts to decarboxylate this compound using basic copper carbonate or copper powder in refluxing quinoline gave solutions which undoubtedly contained a copper complex, but whether it was of the di-acid or of the decarboxylated material was not discovered. No pure compound was isolated

from the reaction mixtures.

From the 'three-unit' compound (Ll, R=H) metal complexes were prepared. With cupric acetate the copper complex (Llll, R=H, M=Cu) was obtained as a monohydrate. The anhydrous complex was prepared by drying at 0.1 mm/100°.

The u.v. spectrum of this complex showed a considerable bathochromic shift (50 mμ) compared to that of (Ll, R=H), although the intensities were decreased by a factor of about 2. Presumably the acetoxy group is present in the anionic form; certainly there is no carbonyl absorption in the 1700 - 1800 cm^{-1} region (cf XLVlll). It has been shown[45] that cupric acetate dihydrate exists in the crystalline state as a dimer, with all the acetate groups bridging pairs of copper atoms. Also the copper complex of diazoaminobenzene exists as a dimeric all-bridged structure[58]. Cupric acetate shows carboxylate anion absorption bands at 1620, 1605 and 1450 cm^{-1} (all strong)[59]. It is possible therefore that the i.r. absorption of our new Cu complex at 1520 cm^{-1} is produced by the acetoxy group, although the second absorption band which is usually shown by the acetoxy group has not been located. It is possible that the structure is more complicated than that suggested by the formula (Llll). Thus the copper may be octahedral as in the dimeric structure:-



with the water held only as water of crystallisation. If it is assumed that this type of structure would have similar bond lengths to those in cupric acetate, then the difficulty arises of accommodating both the ligand molecules in the same plane. A scale drawing shows that the pyridine rings (represented by N^*) would overlap considerably if the Cu-Cu bond was of the order of 2.6A as it is in cupric acetate. In order to prevent this overlap, a Cu-Cu bond length of the order of 6A would be required. And this is surely much too great. The copper complex (Llll, R=H, M=Cu) is therefore probably monomeric.

It is interesting to note that the removal of the water has no effect on the i.r. spectrum at all, there being no disappearance of any peaks. However, this is not surprising because copper aquo complexes frequently fail to show any absorptions, in the NaCl region, due to water molecules[60].

With nickel acetate two different complexes were

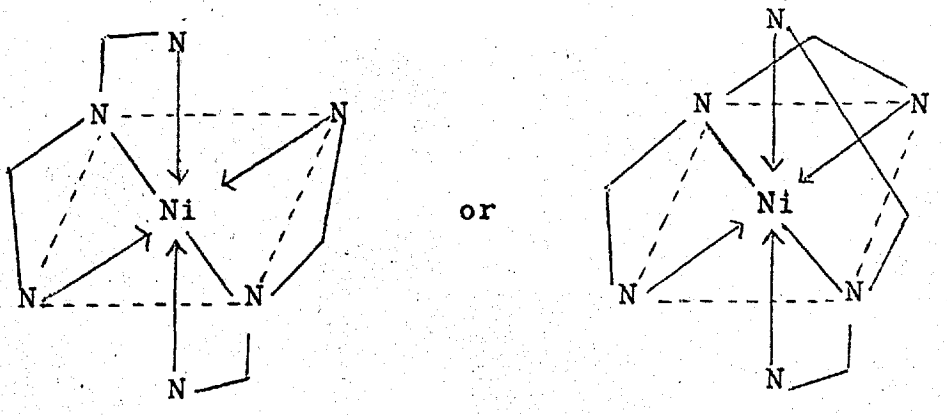
obtained. One of them (LIII, R=H, M=Ni) corresponds to the copper complex just described, having one acetate residue in it. The u.v. spectrum is very similar to that of the copper complex, but is bathochromically displaced by 13 mμ. In the i.r., again there is no acetoxy carbonyl in the 1700 - 1800 cm^{-1} region, but it is possible that absorptions at 1500 and about 1450 cm^{-1} are due to vibrations of the anionic acetate group. Nickel acetate, unlike copper acetate, is monomeric[61], and there seems no reason to doubt the monomeric structure of (LIII, R=H, M=Ni).

The second nickel complex obtained was shown to be a 2:1 ligand:nickel complex (LIV). It will be noted that the experimental conditions for formation of the two nickel complexes are almost identical (including the molar proportions). The difference is believed to lie in the fact that nickel acetate is appreciably less soluble in dimethylacetamide than in formamide. And consequently when the former was used, it is likely that it was not all dissolved and the excess was filtered off, thus producing relative quantities more favourable to the formation of the 2:1 complex.

The existence of the two complexes is not unexpected since the same situation occurred in the case of the aza-linked analogues[1]. In this latter case the 2:1 complex

was given a square planar structure about the Ni atom, which necessitated twisting one pyridine ring about its aza-link in each molecule of the ligand in order to accommodate two molecules.

For the complex (LlV) it seems more likely that it is in fact an octahedral complex of Ni^{II}, and this would give rise to the possibility of two isomers:



A B

No evidence has been found for the existence of two isomers, but if the complex is octahedral then form B would probably be more strongly favoured since the Ni atom would then be in the plane and at the centre of each ligand molecule.

If it is square planar, then undoubtedly an isomerisation of one of the pyridine rings from anti-isoindole to syn-isoindole would have to occur, and the conditions do not seem vigorous enough to bring this about. There seems to be little evidence either, as to why the 2:1 complex of

the aza-linked analogue should be regarded as square-planar rather than octahedral.

The possibility of this complex being tetrahedral has not been discussed as it seems unlikely since relatively few Ni^{II} complexes are in fact tetrahedral[58].

There was also obtained a zinc complex (Llll, R=H, M=Zn) which was of the 1:1 type, having an acetate group in the molecule. This complex is interesting because it shows an absorption in the i.r. at 1680 cm^{-1} which must surely be attributed to the carbonyl of the acetoxy group. This would suggest perhaps that the metal-acetate bond is more covalent in character than those of the previously described Cu and Ni complexes. It has a similar u.v. spectrum to these two complexes, but is apparently less stable since attempted recrystallisation from hot dimethylformamide gives back a mixture of the complex and the ligand.

The next series of syntheses to be investigated was that using 2-cyanomethyl-6-methylpyridine. This compound reacted in exactly the same way as 2-pyridylacetonitrile. Initially 1-(6-methyl-2-pyridylcyanomethylene)-3-iminoisoindoline (XLV, R=CH_3) was prepared. Its i.r. spectrum confirmed the presence of the expected functional groups, and its u.v. spectrum showed a slight bathochromic displacement compared to (XLV, R=H). Its p.m.r. spectrum is as expected, showing the $-CH_3$ in addition to aromatic protons.

Also there is of course no signal at low field from a 6-pyridyl proton. This compound formed a hydrochloride (LV), and also was easily hydrolysed to the corresponding oxo-compound (XLVI, R=CH_3).

A point worth noting was that a condensed compound corresponding to (XLVII) was not obtained from (XLV, R=CH_3) under the same conditions. In fact the starting material was recovered unchanged. It is possible that the 6-methyl groups produce sufficient steric hindrance to prevent two molecules from undergoing condensation. This effect was observed again in compounds described later.

It was thought that it might be possible to abstract a proton from the 6-methyl group of (XLV, R=CH_3) under the appropriate conditions and so form a reactive carbanion which would undergo self-condensation to a macrocycle. However, refluxing (XLV, R=CH_3) alone in basic solvents (pyridine or dimethylcyclohexylamine), in alcohols in the presence of the sodium alkoxide (butyl or nonyl alcohols) or in pyridine with phthalonitrile did not give any products that could be identified as the desired macrocycle. On one occasion the reaction in dimethylcyclohexylamine gave a small yield (about 10%) of an insoluble purple solid, which from the u.v. absorption in dimethylformamide, was not a phthalocyanine. Its molecular weight was determined as 517 from the mass spectrum. The i.r. spectrum showed

the presence of C≡N, demonstrating that the product originated from (XLV, R=CH_3), but its structure has so far defied elucidation. Nor has it been found possible to repeat this reaction, in spite of many attempts, under varying conditions.

Next, from phthalonitrile and two molar equivalents of 2-cyanomethyl-6-methylpyridine, the 'three-unit' compound 1,3-di(6-methyl-2-pyridylcyanomethylene)isoindoline (Ll, R=CH_3) was prepared. This compound showed all the expected spectral characteristics except that in the u.v. it shows a slight hypsochromic shift compared to (Ll, R=H) which is not the normal effect of substituent methyl groups. From scale diagrams of the molecule it is clear that the 6-methyl groups will interfere with one another and this will produce some strain in the molecule which will in turn reduce the degree of conjugation of the unsaturated system.

After the first purification of this compound a small amount of residue was obtained which in dimethylformamide solution had an identical u.v. spectrum with the unknown purple compound described above. Unfortunately this does not assist in determining the structure of this by-product.

Attempts were made to prepare a macrocycle from (Ll, R=CH_3) by reaction with a 'fourth unit' under various conditions. No reaction could be detected with 1,3-di-iminoisoindoline either in the absence or the presence of

sodium alkoxide. With phthalonitrile in the presence of sodium alkoxide, only starting material was identified from the reaction. So under these conditions, even with the molecule held in a favourable arrangement, the 6-methyl groups are not reactive.

As a last resort, the effect of metal complex formation was investigated, since the presence of the metal might cause a sufficient electron drain from the ligand to make the 6-methyl groups more reactive. Accordingly the monohydrate of the copper complex (Llll, R=CH_3, M=Cu) was prepared. This was similar to the previous copper complex (Llll, R=H, M=Cu) and when it was dried it lost a molecule of water with no change in the i.r. absorption spectrum. In the i.r. it shows absorptions at 1520 and 1330 cm^{-1} either or both of which might be due to the acetate group. As far as the structure of this complex is concerned, the same arguments apply as before, and it may have a bridged dimeric structure.

When this copper complex was refluxed with 1,3-diiminoisoindoline in 1-nitropropane, a small amount of a product was obtained. But the i.r. spectrum did not show any cyanide absorption (one of the most easily recognised absorptions of the ligand) showing that the ligand was not incorporated in the product. This product was also insoluble in dimethylformamide, and most probably was copper phthalo-

cyanine, formed by reaction of the 1,3-di-iminoisoindoline with itself.

The reaction was then repeated using 1-imino-3-thioisoindoline which does not so readily form phthalocyanine. In this case there was no evidence of any reaction having occurred and no product could be isolated.

It is possible that if the structure of the copper complex is of some more complicated bridged type, then this obstructs the formation of a macrocycle. It was not found possible to prepare complexes of this ligand with several other metals, and so this approach was abandoned.

Having failed to prepare a macrocycle from any of these 6-methyl substituted compounds, attention was turned to the possibility of using 2,6-di(cyanomethyl)pyridine which should react in the same way as 1,3-di(cyanomethyl)-benzene. This pyridine is not readily available. Only one preparation has been described before[41], from the dichloro- or dibromomethylpyridine and potassium cyanide in aqueous methanol. The yields quoted were not high, and even these were not attained on repetition. It seems that there must be a competing intermolecular quaternisation reaction which will occur under the basic conditions used. Consequently a better method was sought, and in the course of this it was decided that pyridine—2,6-dimethanol should be prepared in reasonable quantities. This compound has

been produced[19,52,53] either as a by-product or else by a several-stage synthesis involving rearrangement of N-oxides.

The possibility of reducing a diester of dipicolinic acid was considered since many examples of the lithium aluminium hydride reduction of pyridine carboxylic esters are known[54,55,56,57]. But frequently the yield from such reductions is low and in the case of diethyl dipicolinate was found to be about 5%[39]. This low yield may be due to the fact that pyridine-2,6-dimethanol is not very soluble in ether, the normal solvent for L.A.H. reductions. However, Brown et.al.[40] have developed a method for the reduction of esters in high yield by using sodium borohydride in diglyme (diethylene glycol dimethyl ether) in the presence of certain anhydrous metal halides.

Applied to the reduction of dimethyl dipicolinate this method gave a 76% yield of the dimethanol. Thus 2,6-lutidine can readily be converted to pyridine-2,6-dimethanol by permanganate oxidation[38], esterification[39] and subsequent reduction.

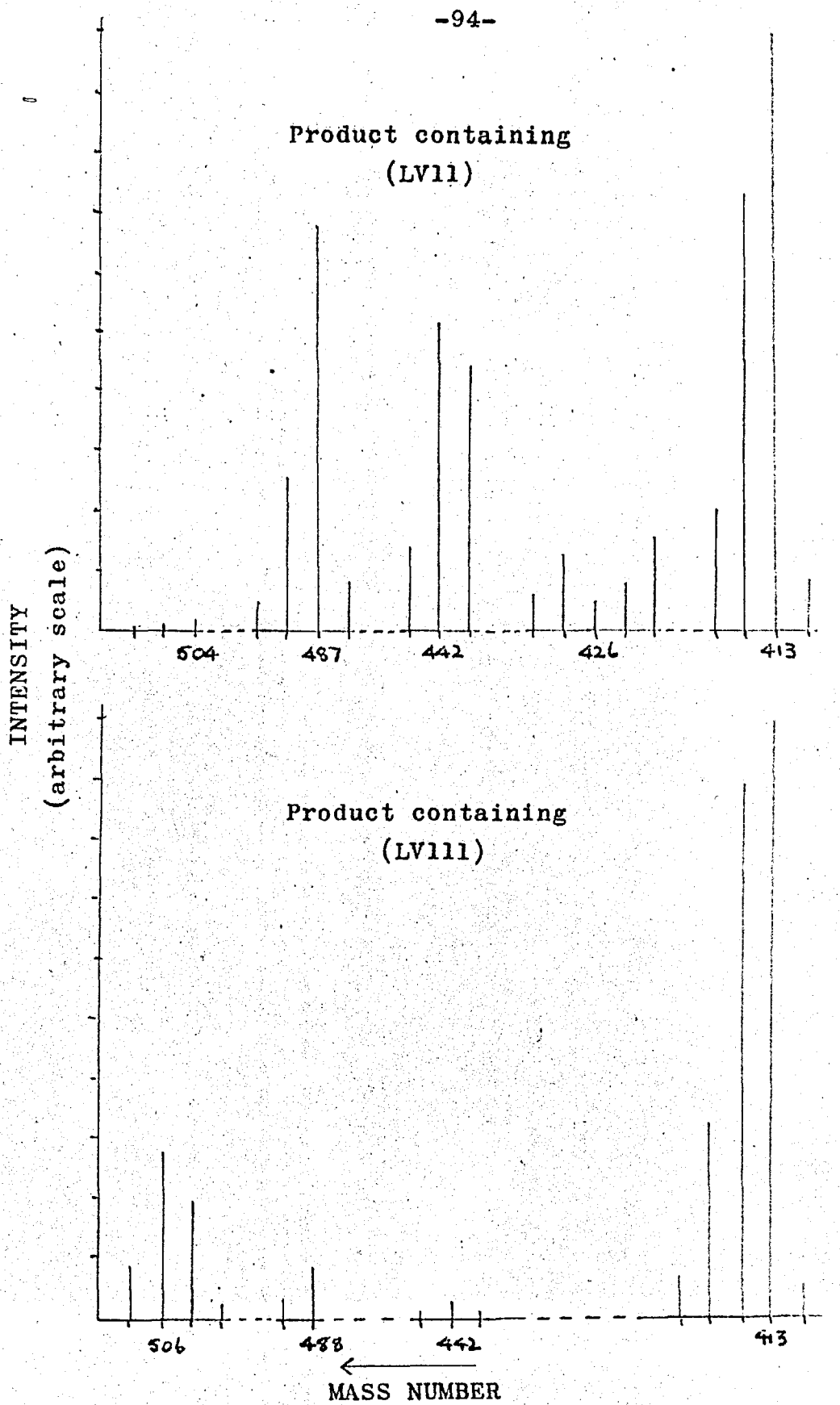
The dimethanol was easily converted by thionyl chloride to the corresponding di(chloromethyl)pyridine. This by the action of sodium cyanide in dimethylsulphoxide[42] (a non-aqueous neutral medium) was converted to 2,6-di-(cyanomethyl)pyridine in 54% yield. Thus a reasonably

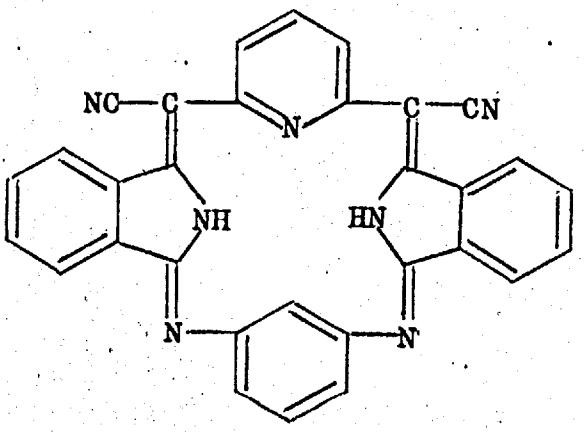
simple route from the easily accessible 2,6-lutidine was established.

Having obtained the necessary substituted pyridine, its reaction with two molar equivalents of phthalonitrile was investigated. As in the case of the benzene analogue, the reaction proceeds smoothly at room temperature and a 91% yield of 2,6-di(3-imino-1-isoindolinylidenecyanomethyl)-pyridine (LVl) was obtained. The i.r. spectrum shows the cyanide and C=N absorptions amongst others. Although this new compound is only cross-conjugated its u.v. spectrum shows a bathochromic shift compared to that of the 'two-unit' compound (XLV, R=H). The molecular weight is confirmed by the mass spectrum which shows that the parent peak has $^{m}/_{e}$ 413, and there is a doubly charged ion at 206.5.

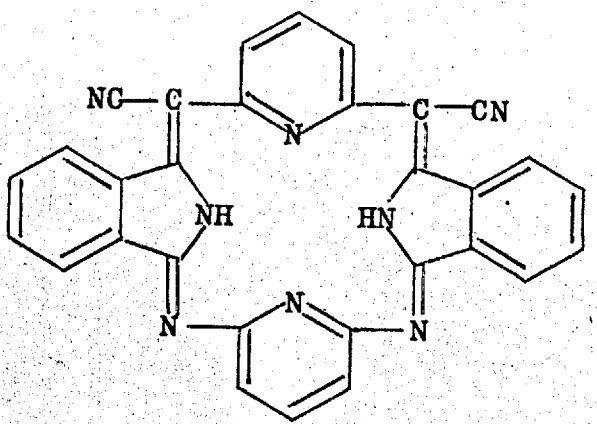
It is interesting to note that there is no evidence of a macrocyclic by-product corresponding to (XXXlX) in the benzene series.

Attempts to form macrocycles from (LVl) and diamines were made as for the corresponding benzene analogue, and almost identical results were obtained. No pure compounds were prepared, but the mass spectral results definitely showed the presence of compounds having the molecular weights of the macrocycles (LVll) and (LVlll) (see overleaf). Furthermore, in the mass spectrum of the product from reaction with 2,6-diaminopyridine the peak attributable

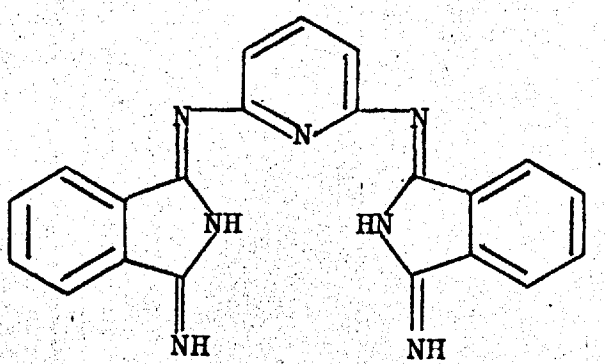

Product containing
(LV11)
504
487
442
426
413
INTENSITY
(arbitrary scale)
Product containing
(LV111)
506
488
442
413
MASS NUMBER



LV11



LV111



L1X

to the presence of the non-cyclic four unit compound was much more intense than any that had been observed for the corresponding peak in the other three cases.

The attempted condensation between (LVl) and 2,6-di(cyanomethyl)pyridine also failed and in this case no real evidence of any species of higher molecular weight was obtained.

It is interesting to compare these results with those of Baguley and Elvidge[17] who attempted to react the analogous aza-linked compound (LlX) with m-phenylenediamine to form an asymmetric macrocycle. They found that disproportionation and recombination occurred which resulted in the formation of the symmetrical 2,6-pyridine macrocycle. Similarly compound (LlX) with 2,6-diaminopyridine gave both the possible symmetrical, but not the asymmetrical, macrocycles.

Hence one concludes that these three unit di-imino compounds are not as reactive as might have been anticipated.

Experimental

Spectra were measured as previously (Chapter 3).

Solvents for u.v. were:- (a) Ethanol
(b) 0.2N-NaOH in ethanol
(c) 0.2N-HCl in ethanol
(d) Chloroform
(e) Dimethylformamide
(f) o-dichlorobenzene
(g) Benzene
(h) Dimethylacetamide

1. Preparation of 2-pyridylacetonitrile

Methyl 2-pyridylacetate (51.2g) on treatment with ammonia solution (d0.88, 80 mls) was converted to 2-pyridylacetamide (41.3g)[28]. By distillation of the amide from phosphorus pentoxide[29], and treatment of a benzene solution of the distillate with dry HCl gas, 2-pyridylacetonitrile hydrochloride (20g) was obtained.

2. Preparation of 1-(2-pyridylcyanomethylene)-3-iminoisoindoline (XLV, R=H)

(a) To a solution of sodium ethoxide (from sodium (1.21g, 0.053 mole)) in dry ethanol (70 mls), 2-pyridylacetonitrile hydrochloride (4.01g, 0.026 mole) was added and the mixture stirred until all the solid had dissolved. Then phthalonitrile (3.34g, 0.026 mole) was added and the solution was stirred for 4 hrs. at room temperature. The solution rapidly

became dark red, and a considerable precipitate was formed. The reaction mixture was poured into water (1 litre) with vigorous stirring. A yellow-orange precipitate of 1-(2-pyridylcyanomethylene)-3-iminoisoindoline (XLV, R=H) (5.39g, 73.5%) was obtained. This was recrystallised by dissolving it in ethanol at 50° (not higher) and evaporating the solution to small volume at room temperature (Found: C, 73.41; H, 4.26; N, 22.67. $C_{15}H_{10}N_4$ requires: C, 73.18; H, 4.07; N, 22.77%).

(b) To a solution of sodium ethoxide (from sodium (0.32g, 0.014 mole)) in dry ethanol (15 mls), 2-pyridylacetonitrile hydrochloride (1.04g, 0.0067 mole) was added and the solution stirred until all the solid had dissolved. Then 1,3-di-iminoisoindoline (1.00g, 0.0069 mole) was added and the solution stirred at room temperature for 5 hrs., after which time it had become a dark orange-red colour. The solution was poured with stirring into water (350 mls). An orange powder (0.11g) was obtained. This had u.v. and i.r. spectra identical with those of 1-(2-pyridylcyanomethylene)-3-iminoisoindoline from 2(a). The yield was 6.5%.

I.R. 3200 (NH), 2200 (cyanide), 1655s (C=N), 1610s, 1595s and 1560 (C=C and pyridine), 1260w, 1230s, 1180w, 1155w, 1115w, 1095w, 1055w and 1035 (aryl and pyridine C-H), 780s, 730 and 685 (aryl and pyridine C-H).

P.M.R. in $CDCl_3$

2.95 - 2.76 (1), 2.54 - 2.03 (5), 1.47 - 1.29 (2).

3. Preparation of 1-(2-pyridylcyanomethylene)-3-oxoisoindoline (XLVl, R H)

(a) 1-(2-Pyridylcyanomethylene)-3-iminoisoindoline (5.0g, 0.020 mole) was dissolved in a mixture of ethanol (100 mls) and 2N-hydrochloric acid (100 mls) and the solution heated on a steam-bath for 4½ hrs. A precipitate was formed. The ethanol was evaporated under reduced pressure and the residual solution made alkaline with aqueous ammonia (d0.88). After filtration, 1-(2-pyridylcyanomethylene)-3-oxoisoindoline (XLVl, R=H) (4.60g, 92.1%) was obtained as a yellow powder. After recrystallisation from acetonitrile it formed yellow needles, m.p. 257° (Found: C, 72.78; H, 3.62; N, 17.40. $C_{15}H_9N_3O$ requires: C, 72.88; H, 3.64; N, 17.00%).

(b) To a solution of sodium ethoxide (from sodium (0.16g, 0.0070 mole)) in dry ethanol (20 mls), 2-pyridylacetonitrile hydrochloride (0.50g, 0.0032 mole) was added and the mixture stirred until the solid had dissolved. Then 1-imino-3-oxoisoindoline (0.51g, 0.0035 mole) was added and the solution was refluxed for 1½ hrs. After being cooled, the solution was poured into water (250 mls). 1-(2-pyridylcyanomethylene)-3-oxoisoindoline (0.12g, 14.7%) was obtained, with u.v. and i.r. spectra identical with those of the product obtained above.

(c) To a solution of sodium ethoxide (from sodium (0.08g, 0.0035 mole)) in dry ethanol (20 mls), 2-pyridylacetonitrile hydrochloride (0.50g, 0.0032 mole) was added and the mixture stirred to dissolve the solid. Then 1-imino-3-oxoisoindoline (0.51g, 0.0035 mole) was added and the solution refluxed for 2 hrs. The solution went dark orange and ammonia was evolved. After being cooled, the reaction mixture was poured into water (250 mls) and 1-(2-pyridylcyanomethylene)-3-oxoisoindoline (0.37g, 46.9%) was obtained as an orange solid. After recrystallisation from acetonitrile it had m.p. 253-257° and mixed m.p. 255-257°, and the u.v. and i.r. absorptions were identical with those of authentic material.

I.R. 2200 (cyanide), 1730s (carbonyl), 1620, 1605w, 1590 and 1560w (C=C and pyridine), 1280w, 1195, 1170w, 1115w, 1095, 1060 and 1040w (aryl and pyridine C-H), 785s, 765s, 720 and 695s (aryl and pyridine C-H).

P.M.R. in $CDCl_3$

2.94 - 2.59 (1), 2.30 - 1.95 (5), 1.43 - 1.26 (2).

4. The effect of heat on 1-(2-pyridylcyanomethylene)-3-iminoisoindoline

1-(2-Pyridylcyanomethylene)-3-iminoisoindoline (4g, 0.016 mole) was heated to 215° for 2 hrs. with occasional stirring. Evolution of ammonia was detected and a purple solid (3.65g, 94.5%) was obtained. After extractive crystallisation (Soxhlet) from benzene 1-(2-pyridylcyano-

methylene)-3-(1-(2-pyridylcyanomethylene)-3-isoindoleninyl)-iminoisoindoline (XLVll) was obtained as needles m.p. 310° which were blood-red with a green reflex (Found: C, 75.75; H, 3.40; N, 20.66. $C_{30}H_{17}N_7$ requires: C, 75.78; H, 3.58; N, 20.63%).

I.R. 2200 (cyanide), 1615, 1600s, 1685s and 1560 (C=N, C=C and pyridine), 1260, 1190w, 1160, 1110, 1100w and 1040w (aryl and pyridine C-H), 800, 790, 770s, 740 and 710 (aryl and pyridine C-H).

5. Hydrolysis of (XLVll)

Compound (XLVll) (0.10g, 0.00021 mole) was suspended in a mixture of ethanol (100 mls) and conc. hydrochloric acid (20 mls) and the suspension heated on a steam-bath. After 1 hr. the solid had dissolved. Heating was continued for a further 4 hrs. After being cooled, the ethanol was removed under reduced pressure. Neutralisation of the aqueous residue with solid sodium carbonate gave 0.10g (0.00040 mole, 97%) of yellow solid having an i.r. spectrum identical with authentic 1-(2-pyridylcyanomethylene)-3-oxoisoindoline.

6. Preparation of metal complexes from (XLVll)

(a) Compound (XLVll) (0.10g, 0.00021 mole) was dissolved in hot, dry pyridine (about 20 mls) and the solution filtered. Cupric acetate monohydrate (0.042g, 0.00021 mole) was dissolved in hot, dry pyridine (about 5 mls) and the solution filtered. The filtrates

were mixed and kept at room temperature but no crystals formed. Therefore methanol (30 mls) was added and the solution kept overnight at room temperature. There were then obtained 31 mg of reddish crystals of the complex (XLVIII), m.p.> 350° (Found: C, 66.11; H, 3.55; N, 16,35; Cu, 9.64. $C_{32}H_{19}N_7O_2Cu.C_5H_5N$ requires: C, 65.73; H, 3.55; N, 16.58; Cu, 9.40. $C_{32}H_{19}N_7O_2Cu.H_2O$ requires: C, 62.47; H, 3.42; N, 15.94; Cu, 10.33%).

I.R. 2200 (cyanide), 1700s (carbonyl), 1600, 1575s, 1540s, 1300, 1290, 1270w, 1215, 1200, 1165w, 1140, 1110s, 1095, 1050, 1020, 880, 780s, 720, 710s.

(b) Compound (XLVII) (0.10g, 0.00021 mole) was dissolved in hot dimethylformamide (about 40 mls) and the solution filtered. Nickel acetate tetrahydrate (0.027g, 0.00011 mole) was dissolved in formamide (5 mls) and the solution filtered. The filtrates were mixed and kept at room temperature for 48 hrs. Filtration yielded 18 mg of dark coloured crystals of the complex (XLIX) m.p. > 350° (Found: C, 62.85; H, 3.53; N, 16.34; Ni, 9.54. $C_{32}H_{20}N_8O_3Ni$ requires: C, 62.98; H, 3.44; N, 16.07; Ni, 9.63%).

(c) Compound (XLVII) (0.10g, 0.00021 mole) was dissolved in hot dimethylformamide (about 40 mls) and the solution filtered. Cupric acetate monohydrate (0.024g, 0.00011 mole) was dissolved in warm dimethylformamide (5 mls) and the solution filtered. The filtrates were mixed and kept at

room temperature for 48 hrs. Filtration yielded 29 mg of a crystalline solid, which had an i.r. spectrum identical with that of the complex (XLVIII). However, it could not in this case be a pyridinate, and is of uncertain structure (Found: C, 65.06; H, 3.12; N, 13.93; Cu, 9.56%).

I.R. 2200 (cyanide), 1700s (carbonyl), 1600, 1575s, 1540s, 1300, 1290, 1270w, 1210, 1200, 1165w, 1140, 1110s, 1090, 1045, 1015, 880, 770s, 720, 710s.

(d) Attempted preparation of complexes from $FeCl_3.6H_2O$, CuBr, $CrCl_3.6H_2O$, $Fe(OAc)_2.OH$, $CoCl_2.6H_2O$, $FeSO_4$, $Mn(OAc)_2.4H_2O$, and $Pb(OAc)_2.3H_2O$ did not lead to the isolation of any identifiable complexes. In most cases some of the ligand was recovered, and in several cases the u.v. spectrum of the reaction solution suggested the presence of 1-(2-pyridylcyanomethylene)-3-oxoisoindoline, formed perhaps by hydrolysis of the ligand (XLVII).

7. Reaction of phthalonitrile with methyl 2-pyridylacetate

To a solution of sodium ethoxide (from sodium (0.17g, 0.0076 mole)) in dry ethanol (20 mls), methyl 2-pyridylacetate (1.19g, 0.0079 mole) and phthalonitrile (1.00g, 0.0079 mole) were added and the solution was stirred at room temperature for 4 hrs. It was then poured into water (500 mls) with vigorous stirring, whereupon 1-(2-pyridylethoxycarbonylmethylene)-3-iminoisoindoline (LA) (0.90g, 41%) precipitated as a yellow solid m.p. 83-93°.

The yellow solid (0.35g) was dissolved in 2N-hydrochloric acid (10 mls) and the solution heated on a steam-bath for 2 hrs. After being cooled, the solution was made alkaline with aqueous ammonia (d0.88). 1-(2-Pyridylethoxycarbonylmethylene)-3-oxoisoindoline (L) was obtained as a pale yellow solid (0.25g, 71.5%). After recrystallisation from aqueous methanol it had m.p. 134.5-136.5° (Found: C, 68.68; H, 4.87; N, 9.20. $C_{17}H_{14}N_2O_3$ requires: C, 69.39; H, 4.76; N, 9.52%).

I.R. (L) 3200w (NH), 1720s (carbonyl), 1695s (carbonyl), 1625, 1585, and 1565w (C=C and pyridine), 1315, 1275, 1230s, 1195, 1170w, 1110, 1085 and 1055 (aryl and pyridine C-H), 795w, 775, 760w, 715 and 695 (aryl and pyridine C -H).

P.M.R.(LA) in $CDCl_3$

8.71 (3), 5.60 (2), 3.95 (1), 2.53 - 1.67 (6), 1.15 (1).

(L) in $CDCl_3$

8.80 (3), 5.76 (2), 4.10 (1), 2.82 - 2.08 (6), 1.22 (1), -0.37 (1).

8. Preparation of 1,3-di(2-pyridylcyanomethylene)isoindoline (L1)

(a) To a solution of sodium butoxide (from sodium (0.90g, 0.039 mole)) in dry n-butanol (100 mls), 2-pyridylacetonitrile hydrochloride (4.00g, 0.026 mole) was added and the mixture stirred until all the solid had dissolved. Then phthalonitrile (1.68g, 0.013 mole) was added and the

solution was refluxed for 30 hrs. After the solution had been cooled, the precipitate was filtered off. Washing with water removed sodium chloride and left 1,3-di(2-pyridylcyanomethylene)isoindoline (L1) (2.59g, 57%)as a yellow-orange solid, m.p.) 350°. It was purified by extractive crystallisation (Soxhlet) from ethanol/benzene (1:1) (Found: C, 76.30; H, 3.90; N, 19.86. $C_{22}H_{13}N_5$ requires: C, 76.08; H, 3.75; N, 20.18%).

(b) To a solution of sodium ethoxide (from sodium (0.15g, 0.0067 mole) in dry ethanol (30 mls), 2-pyridylacetonitrile hydrochloride (0.50g, 0.0032 mole) was added, and the solution stirred for 5 mins. to dissolve the solid. Phthalonitrile (0.42g, 0.0033 mole) was added and this solution (A) stirred at room temperature for 4 hrs.

To a solution of sodium ethoxide (from sodium (0.077g, 0.0033 mole)) in dry ethanol (10 mls), 2-pyridylacetonitrile hydrochloride (0.50g, 0.0032 mole) was added and the suspension was swirled until the base had dissolved. This solution was then added to the preceding reaction solution (A) and the whole stirred at 45-60° for 17 hrs. Filtration gave 0.19g of orange solid. The filtrate was then refluxed for 24 hrs. A further 0.18g of orange solid was obtained. Refluxing was continued for 48 hrs., giving a further 0.16g. A total yield of 0.53g (47%) of 1,3-di(2-pyridylcyano-methylene)isoindoline was obtained, having u.v. and i.r.

spectra identical with those of the product (L1) above.

I.R. 2200 (cyanide), 1600s, 1585s and 1555s (C=C and pyridine), 1260, 1220, 1160 and 1120 (aryl and pyridine C-H), 785, 770s, 740s and 680 (aryl and pyridine C-H).

P.M.R. in N-methyl-2-pyrollidone (approximate-no internal standard)

2.83 - 2.58 (2), 2.50 - 1.92 (6), 1.58 - 1.37 (2), 1.30 - 1.03 (2).

9. Hydrolysis of 1,3-di(2-pyridylcyanomethylene)isoindoline

(a) 1,3-Di(2-pyridylcyanomethylene)isoindoline (0.50g, 0.0014 mole) was dissolved in 90$^{w}/_{w}$ sulphuric acid (36 mls). The solution was stirred at 60° for 5 hrs. After pouring onto ice, the pH of the solution was adjusted to 7 with solid sodium carbonate. Filtration yielded 0.59g of a yellow solid. This was treated with boiling chloroform to extract the organic material. Evaporation of the chloroform solution left a yellow-brown solid. After recrystallisation from ethyl acetate 1,3-di(2-pyridylcarbamoylmethylene)isoindoline (L11) (0.45g, 82%) was obtained, m.p. 212-213° (Found: C, 68.07; H, 4.72; N, 18.40; $^{m}/_{e}$: M^{+}, 383. $C_{22}H_{17}N_5O_2$ requires: C, 68.93; H, 4.44; N, 18.28%; $^{m}/_{e}$: M^{+}, 383).

I.R. 3500 and 3400w (NH_2), 3300 (NH), 1665s (carbonyl, Amide I), 1620s ($CONH_2$, Amide II), 1600s, 1585s and 1560s (C=C and pyridine), 1245s, 1150w, 1125, 1090w and 1005

(aryl and pyridine C-H), 800, 770, 745, 730 and 720 (aryl and pyridine C-H).

(b) 1,3-Di(2-pyridylcyanomethylene)isoindoline (0.71g, 0.0020 mole) was dissolved in a mixture of conc. sulphuric acid (7.5 mls) and water (7.5 mls). The solution was refluxed for 2 hrs., and then cooled. Crystals of phthalic acid (0.26g, 77%) were obtained. After recrystallisation from ethanol/petroleum ether (60-80°), the acid had m.p. 197-199° (decomp.) (Found: C, 57.98; H, 4.12; N, <0.3. Calc. for $C_8H_6O_4$: C, 57.84; H, 4.12%).

10. Hydrolysis of 1,3-di(2-pyridylcarbamoylmethylene)isoindoline

1,3-Di(2-pyridylcarbamoylmethylene)isoindoline was dissolved in a mixture of ethanol (30 mls) and 10% sodium hydroxide (30 mls) and the solution was refluxed for 2 hrs. The ethanol was evaporated under reduced pressure and the precipitate filtered off. This was redissolved in 2N-hydrochloric acid, and reprecipitated by careful addition of solid sodium bicarbonate to pH7. A yellow solid was obtained which was probably 1,3-di(2-pyridylcarboxymethylene) isoindoline. It absorbed in the u.v. at 460$^+$, 436, 417$^+$, 317 and 303 mμ. The i.r. spectrum showed peaks at 3400b, 1635s, 1585s, 1560, 1360w, 1325, 1260s, 1160, 1130, 1020w, 780 and 750.

11. Attempted decarboxylation of the product from above

Portions of the crude product (50 mg) from above with (a) basic copper carbonate (15 mg) and (b) copper powder (15 mg) were separately refluxed in quinoline (7 mls) for 45 mins. In both cases dark red solutions were obtained after filtration. The u.v. spectra of these solutions indicated the formation of copper complexes by the bathochromic shift of the major absorptions to the 500-550 mμ region. But no recognisable products were obtained from the reaction mixtures, and it is not known whether decarboxylation had occurred.

12. The copper complex of 1,3-di(2-pyridylcyanomethylene) isoindoline (Llll, R=H, M=Cu)

1,3-Di(2-pyridylcyanomethylene)isoindoline (0.25g, 0.00073 mole) and cupric acetate monohydrate (0.16g, 0.00079 mole) were ground up together and placed in a Soxhlet thimble. The mixture was extracted (hot extractor) with methanol for 48 hrs., cooled and filtered. Bright green crystals of the monohydrate of the copper complex (Llll, R=H, M=Cu) were obtained (0.15g, 40%), m.p. >350°. It was purified by hot extraction with methanol, and then Soxhlet extraction with chlorobenzene (Found: C, 59.43; H, 3.55; N, 14.17. $C_{24}H_{15}N_5O_2Cu.H_2O$ requires: C, 59.21; H, 3.52; N, 14.38%).

The anhydrous complex was obtained by drying at

100°/0.1 mm (Found: C, 61.17; H, 3.12. $C_{24}H_{15}N_5O_2Cu$ requires: C, 61.48; H, 3.20%).

I.R. 2200 (cyanide), 1600, 1570s, 1545, 1520s, 1340, 1295, 1225s, 1165, 1125, 785s, 720w, 695w and 680w.

13. The nickel complexes of 1,3-di(2-pyridylcyanomethylene)-isoindoline

(a) 1,3-Di(2-pyridylcyanomethylene)isoindoline (0.20g, 0.00059 mole) was dissolved in the minimum volume of hot dimethylacetamide (about 20 mls). Nickel acetate tetrahydrate (0.14g, 0.00058 mole) was dissolved in the minimum volume of hot dimethylacetamide (about 20 mls). The hot solutions were filtered and the filtrates mixed and kept at room temperature for 3 days. Purple crystals were formed. These were filtered off and washed with a little cold dimethylacetamide, and the 2:1 ligand:nickel complex (LIV) was obtained m.p.> 350° (Found: C, 70.47; H, 3.08; N, 18.70. $C_{44}H_{24}N_{10}Ni$ requires: C, 70.33; H, 3.20; N, 18.65%).

(b) 1,3-Di(2-pyridylcyanomethylene)isoindoline (0.10g, 0.00030 mole) and nickel acetate tetrahydrate (0.070g, 0.00030 mole) were separately dissolved in the minimum volumes of hot pyridine and the hot solutions filtered. The filtrates were mixed and kept at room temperature for 24 hrs. No crystals were produced; therefore the solution was evaporated to a small volume and methanol added. The

nickel-acetate complex (L111, R=H, M=Ni) then separated (0.10g) as red crystals with a green reflex m.p.> 350° (Found: N, 15.32; Ni, 12.00. $C_{24}H_{15}N_5O_2Ni$ requires: N, 15.10; Ni, 12.66%).

(c) 1,3-Di(2-pyridylcyanomethylene)isoindoline (0.20g, 0.00059 mole) was dissolved in the minimum volume of hot dimethylformamide and the hot solution filtered. Nickel acetate tetrahydrate (0.13g, 0.00057 mole) was dissolved in formamide (5 mls) and the solution filtered. The filtrates were mixed and kept at room temperature for 48 hrs. As no crystallisation occurred, the solution was evaporated under reduced pressure to about 2 mls. Crystals of the nickel complex (L111, R=H, M=Ni) slowly formed (0.096g) which had a u.v. spectrum identical with that of the product from section (b) above.

I.R. (L1V) 2200 (cyanide), 1595, 1575, 1560w, 1505s, 1325, 1280, 1215ms, 1180, 1125, 790, 770, 750w, 715w and 700w.

(L111, R=H, M=Ni) 2200 (cyanide), 1600, 1575w, 1560, 1500s, about 1460bs, 1330, 1290, 1220s, 1175, 1125ms, 795, 780, 755w, 715, 710 and 680.

14. The zinc complex of 1,3-di(2-pyridylcyanomethylene)-isoindoline (L111, R=H, M=Zn)

1,3-Di(2-pyridylcyanomethylene)isoindoline (0.10g, 0.00029 mole) and zinc acetate dihydrate (0.063g, 0.00029 mole) were dissolved separately in the minimum volumes of

hot dimethylformamide. The hot solutions were filtered and the filtrates mixed and kept at room temperature for 3 days. Crystals of the zinc complex (L111, R=H, M=Zn) (0.073g) m.p.> 350° were obtained which had a bright green reflex (Found: C, 61.91; H, 3.33; N, 14.95. $C_{24}H_{15}N_5O_2Zn$ requires: C, 61.22; H, 3.19; N, 14.88%).

I.R. 2200 (cyanide), 1680 (carbonyl?), 1605s, 1585, 1570s, 1555, 1520s, 1340, 1310, 1295, 1230s, 1185, 1175, 1125, 905, 875, 795s, 780s, 715, 705 and 695.

15. Preparation of 2-cyanomethyl-6-methylpyridine hydrochloride

Methyl 6-methyl-2-pyridylacetate (49g) was prepared by the method of Woodward and Kornfeld[32]. The ester was dissolved in aqueous ammonia (d0.88, 80 mls) and kept at room temperature for 3 days. The solution was evaporated under reduced pressure almost to dryness, and after recrystallisation from acetone 6-methyl-2-pyridylacetamide (38g, 85%) was obtained.

The amide was mixed with phosphorus pentoxide (41g) and the mixture heated under reduced pressure (water pump) to 300°. The oil which distilled was collected, dissolved in benzene and the solution treated with dry HCl gas. 2-Cyanomethyl-6-methylpyridine hydrochloride (11g, 26%) was obtained (Found: Cl, 21.05. Calc. for $C_8H_9ClN_2$: Cl, 21.07%).

16. Preparation of 1-(6-methyl-2-pyridylcyanomethylene) -3-iminoisoindoline (XLV, R=CH_3)

To a solution of sodium ethoxide (from sodium (0.46g, 0.020 mole)) in dry ethanol (50 mls), 2-cyanomethyl-6-methylpyridine hydrochloride (2.00g, 0.012 mole) was added and the mixture stirred until all the hydrochloride had dissolved. Phthalonitrile (1.52g, 0.012 mole) was then added and the solution stirred at room temperature for 4 hrs. The solution was then poured into water (400 mls) with vigorous stirring. By filtration, 1-(6-methyl-2-pyridylcyanomethylene)-3-iminoisoindoline (XLV, R=CH_3) (2.64g, 85.6%) was isolated, and recrystallised from aqueous methanol (Found: N, 21.18; $C_{16}H_{12}N_4$ requires: N, 21.54%).

It forms a hydrochloride (LV) which was recrystallised from ethanol (Found: C, 65.15; H, 4.72; N, 18.80; Cl, 11.63. $C_{16}H_{13}ClN_4$ requires: C, 64.76; H, 4.38; N, 18.89; Cl, 11.98%).

I.R. (XLV, R=CH_3) 3300w and 3150 (NH), 2200 (cyanide), 1655ms (C=N), 1620ms, 1595 and 1585 (C=C and pyridine), 1230, 1180, 1120w, 1095 and 1050 (aryl and pyridine C-H), 790, 765 and 680 (aryl and pyridine C-H).

(LV) 2200 (cyanide), 1665ms ($C=NH^+$), 1625s and 1570 (C=C and pyridine), 1285w, 1255, 1240w, 1170 and 1100 (aryl and pyridine C-H), 860 (pyridine), 800, 790, 780, 730 and 690 (aryl and pyridine C-H).

P.M.R. (XLV, R=CH_3) in $CDCl_3$

7.36 (3), 3.05 - 2.87 (1), 2.42 - 2.01 (5), 1.42 - 1.22 (1).

17. Attempted preparations of a macrocycle from (XLV, R=CH_3)

(a) Compound (XLV, R=CH_3) (0.20g) was refluxed in dry pyridine (30 mls) for 3 days. There was no evidence of any reaction occurring and no identifiable product could be isolated.

(b) Compound (XLV, R=CH_3) (0.10g) was refluxed in dimethylcyclohexylamine (30 mls) for 18 hrs. Filtration of the cool solution gave an unidentified purple solid (11 mg) which was not phthalocyanine. It had $^m/_e$ (M^+): 517 (Found: C, 77.14; H, 4.68%).

All attempts to repeat this reaction, including use of longer reaction times and illumination of the reaction mixture, failed.

(c) After sodium hydride (50% dispersion in oil, 0.011g, 0.0005 mole) had reacted with dry n-butanol (25 mls), compound (XLV, R=CH_3) (0.055g, 0.0002 mole) was added and the solution refluxed for 18 hrs. No product was identified.

(d) After sodium hydride (50% dispersion in oil, 0.011g, 0.0005 mole) had reacted with nonyl alcohol (redistilled, 25 mls), compound (XLV, R=CH_3) (0.052g, 0.0002 mole) was added and the solution refluxed for 18 hrs. No product

was identified.

(e) Compound (XLV, R=CH_3) (0.20g, 0.00077 mole) and phthalonitrile (0.20g, 0.0016 mole) were refluxed in dry pyridine (A.R., 5 mls) for 18 hrs. A very small amount of phthalocyanine, identified by its u.v. spectrum, was the only product obtained.

18. Effect of heat on 1-(6-methyl-2-pyridylcyanomethylene)-3-iminoisoindoline

1-(6-Methyl-2-pyridylcyanomethylene)-3-iminoisoindoline (0.60g) was heated to 200° for 2 hrs. It melted and became very dark in colour. After being cooled the solid was ground up and extracted (Soxhlet) with benzene. A u.v. spectrum of the solid that crystallised from benzene showed it to be identical with the starting material. The residual benzene solution also showed the same u.v. spectrum, indicating that no reaction had occurred.

19. Preparation of 1-(6-methyl-2-pyridylcyanomethylene)-3-oxoisoindoline (XLVI, R=CH_3)

1-(6-Methyl-2-pyridylcyanomethylene)-3-iminoisoindoline (0.60g, 0.0023 mole) was dissolved in a mixture of ethanol (15 mls) and 2N-hydrochloric acid (15 mls), and the solution was heated on a steam-bath for 4 hrs. After being cooled, the solution was made just alkaline with saturated sodium carbonate solution. A precipitate was formed of 1-(6-methyl-2-pyridylcyanomethylene)-3-oxoisoindoline (XLVI, R=CH_3)

(0.48g, 80%) which after recrystallisation from aqueous ethanol had m.p. 216-218° (Found: C, 73.25; H, 4.27; N, 15.96. $C_{16}H_{11}N_3O$ requires: C, 73.57; H, 4.21; N, 16.09%).

I.R. 2200 (cyanide), 1725s (carbonyl), 1620, 1590w and 1565 (C=C and pyridine), 1255w, 1190, 1170w, 1095 and 1060w (aryl and pyridine C-H), 800, 775, 730 and 700 (aryl and pyridine C-H).

P.M.R. in $CDCl_3$

7.37 (3), 3.02 - 2.81 (1), 2.52 - 1.97 (5), 1.55 - 1.34 (1).

20. Preparation of 1,3-di(6-methyl-2-pyridylcyanomethylene)-isoindoline (L1, R=CH_3)

To a solution of sodium butoxide (from sodium (1.03g, 0.044 mole)) in dry n-butanol (50 mls), 2-cyanomethyl-6-methylpyridine hydrochloride (5.00g, 0.030 mole) was added and the solution swirled until the particles of hydrochloride had dissolved. Phthalonitrile (1.90g, 0.015 mole) was then added and the solution refluxed for 18 hrs. The solution rapidly became dark red and ammonia was evolved. The mixture was cooled and filtered to yield 1,3-di(6-methyl-2-pyridylcyanomethylene)isoindoline (L1, R=CH_3) (3.13g, 56.3%) as a dark red powder. It was purified by continuous extraction (Soxhlet) with methanol and had m.p. 213-216° (Found: C, 76.35; H, 4.35; N, 18.85. $C_{24}H_{17}N_5$ requires: C, 76.78; H, 4.56; N, 18.65%).

I.R. 3300w (NH), 2200 (cyanide), 1610s, 1600s and 1560s (C=C and pyridine), 1255, 1230s, 1170, 1125, 1105w, 1040w and 1005 (aryl and pyridine C-H), 800s, 765s, 735, 710 and 685s (aryl and pyridine C-H).

P.M.R. in $CDCl_3$

7.58 (6), 3.04 - 2.83 (2), 2.44 - 2.23 (6), 1.37 - 1.17 (2).

It was found that after the first Soxhlet extraction a very small residue of purple solid remained. This was removed from the thimble by solution in hot dimethylformamide. The solution had maxima at 614, 562 and 520 mμ in the visible spectrum, which was identical with the spectrum of the purple material previously obtained.

21. Attempted preparation of a macrocycle from (L1, R=CH_3)

(a) Compound (L1, R=CH_3) (0.50g, 0.0013 mole) and 1,3-diiminoisoindoline (0.19g, 0.0013 mole) were dissolved in dry n-butanol (30 mls) and the solution refluxed for 17 hrs. No apparent reaction had occurred although there was a very slow evolution of ammonia. A small piece of clean sodium (circ. 15 mg) was added to the solution which was further refluxed for 24 hrs., but no identifiable product could be obtained.

(b) To a solution of sodium butoxide (from sodium (0.016g, 0.00070 mole)) in dry n-butanol (25 mls), compound (L1, R=CH_3) (0.25g, 0.00067 mole) and phthalonitrile (0.086g,

0.00067 mole) were added, and the solution was refluxed for 17 hrs. Evolution of ammonia was not detected. Cooling of the solution gave a solid having a u.v. spectrum identical with that of the starting material. The residual solution had the same u.v. spectrum.

(c) After sodium hydride (50% dispersion in oil, 0.034g, 0.0014 mole) had reacted with nonyl alcohol (redistilled, 25 mls), compound (Ll, R=CH_3) (0.25g, 0.00067 mole) and phthalonitrile (0.091g, 0.00071 mole) were added and the solution was refluxed for 3 days. There was no evidence of the formation of any macrocycle and no product was isolated.

(d) Compound (Ll, R=CH_3) (0.25g, 0.00067 mole), 1,3-di-iminoisoindoline (0.098g, 0.00068 mole), and cupric acetate monohydrate (0.14g, 0.00070 mole) were refluxed in dry n-butanol (30 mls) for 17 hrs. Cooling of the solution gave back 0.14g of solid which had the u.v. spectrum of the starting material.

22. The copper complex of 1,3-di(6-methyl-2-pyridylcyano-methylene)isoindoline (Llll, R=CH_3, M=Cu)

1,3-Di(6-methyl-2-pyridylcyanomethylene)isoindoline (0.25g, 0.00068 mole) and cupric acetate monohydrate (0.15g, 0.00075 mole) were separately dissolved in the minimum volumes of hot dimethylformamide and the hot solutions were filtered. The filtrates were mixed and kept at room

temperature for 3 days. Green crystals of the monohydrate of the copper complex (L111, R=CH_3, M=Cu) were obtained, m.p. >350° (Found: C, 60.91; H, 3.63; N, 13.48. $C_{26}H_{19}N_5O_2Cu.H_2O$ requires: C, 60.64; H, 4.08; N, 13.60%), which were dried at 80°/0.05 mm for 24 hrs. to give the anhydrous complex (Found: C, 63.43; H, 3.74; N, 14.04. $C_{24}H_{17}N_5OCu$ requires: C, 62.85; H, 3.83; N, 14.10%).

I.R. 2200 (cyanide), 1600b,ms, 1565w, 1525s, about 1460ms, 1330, 1210, 1190, 1135, 1120, 800s, 780, 695 and 680.

23. Attempted preparation of a nickel complex of 1,3-di-(6-methyl-2-pyridylcyanomethylene)isoindoline

(a) 1,3-Di(6-methyl-2-pyridylcyanomethylene)isoindoline (0.11g, 0.00026 mole) was dissolved in the minimum volume of hot dimethylformamide and the hot solution filtered. Nickel acetate tetrahydrate (0.076g, 0.00027 mole) was dissolved in formamide (5 mls) and the solution filtered. The filtrates were mixed and kept at room temperature. No crystals appeared, and the u.v. spectrum of the solution was identical with that of (L1, R=CH_3). The solution was then heated on a steam-bath for 10 hrs., and then allowed to stand at room temperature, but no change occurred.

(b) 1,3-Di(6-methyl-2-pyridylcyanomethylene)isoindoline (0.10g, 0.00025 mole) and nickel acetate tetrahydrate (0.075g, 0.00026 mole) were separately dissolved in the minimum volumes of hot pyridine. The hot solutions were filtered

and the filtrates mixed and kept at room temperature. No crystals formed and the u.v. of the solution was again identical with that of (L1, R=CH_3).

Similar attempts to prepare complexes from salts of Zn, Mn and Pb also failed.

24. Attempted preparation of a macrocycle from (L111, R=CH_3, M=Cu)

(a) Compound (L111, R=CH_3, M=Cu) (0.050g, 0.00009 mole) and 1,3-di-iminoisoindoline (0.015g, 0.0001 mole) were refluxed in 1-nitropropane (10 mls) for 18 hrs. Filtration gave 10 mg of a purple compound. This compound showed no cyanide absorption in the i.r. spectrum and was insoluble in dimethylformamide.

(b) Compound (L111, R=CH_3, M=Cu) (0.050g, 0.00009 mole) and 1-imino-3-thioisoindoline (0.017g, 0.0001 mole) were refluxed in 1-nitropropane (10 mls) for 18 hrs. There was no evidence of any reaction and no product was obtained.

25. Preparation of pyridine-2,6-dimethanol

Dipicolinic acid hydrate was prepared by the method of Soine and Buchdahl[38] from 2,6-lutidine.

The dipicolinic acid hydrate was converted to dimethyl dipicolinate by the method of Barnes and Fales[39].

Dimethyl dipicolinate (10g, 0.051 mole) and commercial sodium borohydride (2.4g, 0.063 mole) were stirred in dry diglyme($(CH_3OCH_2CH_2)_2O$) (15 mls). Then anhydrous magnesium

chloride (3.6g, 0.036 mole) was added[40] and the mixture stirred at room temperature for 30 mins. During this time an orange colour developed. The mixture was then heated to 85° for 4 hrs., and most of the colour discharged. After cooling, 2N-hydrochloric acid was added until all the solid had dissolved. The solution was made alkaline with sodium carbonate solution and evaporated to dryness. The solid residue was crushed and continuously extracted (Soxhlet) with chloroform. Evaporation of the extract gave a mixture of pyridine-2,6-dimethanol and residual di-ester. The solid was treated with water, and the insoluble di-ester filtered off. Evaporation of the aqueous filtrate gave pyridine-2,6-dimethanol (5.4g, 76%) which after two sublimations at 90°/0.1 mm and recrystallisation from ethyl acetate had m.p. 114° (Found: C, 60.68; H, 6.47; N, 10.70. Calc. for $C_7H_9NO_2$: C, 60.43; H, 6.47; N, 10.07%).

I.R. 3400 (OH), 1605 and 1580 (pyridine), 1230 (OH), 1165 and 1110 (pyridine C-H), 1090s (OH), 1030, 990, 830s and 780 (pyridine C-H).

P.M.R. in $CDCl_3$

5.40 (4), 2.83 - 2.10 (3).

26. Preparation of 2,6-di(cyanomethyl)pyridine

Pyridine-2,6-dimethanol was converted to 2,6-di(chloromethyl)pyridine by the method of Baker et al[41].

The dichloride was converted to the dinitrile by a method based on that of Smiley and Arnold[42].

Dry sodium cyanide (1.4g, 0.029 mole) was placed in a flask equipped with reflux condenser (with drying tube), stirrer and dropping funnel. Dry dimethylsulphoxide (5 mls) was added and the suspension stirred and heated to 100°. A solution of 2,6-di(chloromethyl)pyridine (2.0g, 0.011 mole) in dry dimethylsulphoxide (5 mls) was added dropwise over 10 mins. Stirring and heating were continued for a further 30 mins. The dark reaction mixture was allowed to cool. Chloroform (25 mls) was added and the mixture poured into saturated sodium carbonate solution (50 mls). The chloroform layer was run off, and the upper layer further extracted with chloroform (2 x 25 mls). The combined extracts were washed with saturated sodium carbonate solution (20 mls). The chloroform extract was dried (Na_2SO_4) and evaporated leaving a solution of the dinitrile in dimethylsulphoxide. As much as possible of the dimethylsulphoxide was distilled off at 100°/0.1 mm. The residue was taken up in ethanol (charcoal), and after evaporation of the ethanol solution to small volume, 2,6-di(cyanomethyl)pyridine (0.80g, 54%) crystallised out. After recrystallisation from methanol it had m.p. 95-97°(Lit. 97-98°)[41] (Found:N, 27.00. Calc. for $C_9H_7N_3$: N, 26.73%).

I.R. 2250 (cyanide), 1595 and 1580 (pyridine), 1270w and

1160w (pyridine C-H), 1100, 1000, 950w, 925, 800s and 720 (pyridine C-H).

P.M.R. in $CDCl_3$

6.07 (4), 2.59 (2), 2.20 (1).

27. Preparation of 1,3-di(3-imino-1-isoindolinylidene-cyanomethyl)pyridine (LVl)

To a solution of sodium ethoxide (from sodium (0.075g, 0.0033 mole)) in dry ethanol (30 mls), 2,6-di(cyanomethyl) pyridine (0.25g, 0.0016 mole) and phthalonitrile (0.41g, 0.0032 mole) were then added, and the solution was stirred at room temperature for 5 hrs. Then the reaction mixture was poured into water (100 mls) with stirring. After filtration, the dark yellow 1,3-di(3-imino-1-isoindolinylidenecyanomethyl)pyridine (LVl) (0.60g, 91%) was obtained. It was recrystallised from dimethylacetamide, giving yellow crystals containing one molecule of dimethylacetamide, decomp. above 300° (Found: C, 69.41; H, 4.93; N, 22.34. $C_{25}H_{15}N_7.CH_3CON(CH_3)_2$ requires: C, 69.60; H, 4.80; N, 22.40%. The mass spectrum gives $^m/_e$: M^+, 413; M^{++}, 206.5. $C_{25}H_{15}N_7$ requires: $^m/_e$: M^+, 413; M^{++}, 206.5).

I.R. 2200 (cyanide), 1655ms (C=N), 1630, 1610s, 1590w and 1575 (C=C and pyridine), 1530s and 1520s (amidine band), 1330s, 1250, 1240, 1210s, 1180, 1120w, 1100 and 1040 (aryl and pyridine C-H), 930, 890, 870 and 810s (pyridine C-H), 770s, 740, 715 and 690s (aryl and pyridine C-H).

28. Reaction of (LV1) with diamines

(a) (LV1) (0.20g, 0.00049 mole) and 2,6-diaminopyridine (0.055g, 0.00049 mole) were refluxed in dimethylacetamide (20 mls) for 18 hrs. After being cooled, the solution was diluted with water (150 mls). Filtration gave 0.24g of red-brown solid, which was extractively crystallised (hot extractor) from ethanol.

(b) (LV1) (0.20g, 0.00049 mole) and m-phenylenediamine (0.053g, 0.00050 mole) were refluxed in dimethylacetamide and the solution worked up as above to give 0.23g of dark brown powder which was extractively crystallised (hot extractor) from chlorobenzene.

29. Reaction of (LV1) with 2,6-di(cyanomethyl)pyridine

Sodium hydride (53.3% suspension in mineral oil, 0.015g, 0.00025 mole) was suspended in dry dimethylformamide. 2,6-di(cyanomethyl)pyridine (0.039g, 0.00025 mole) and (LV1) (0.10g, 0.00025 mole) were added and the solution stirred at 110° for 20 hrs. After being cooled, the solution was diluted with water (150 mls) and filtration gave 0.14g of brown solid, which was extractively crystallised (hot extractor) from chlorobenzene.

U.V. spectra

Compound	Solvent	λ max (mμ)	ε x 10^{-3}
(XLV, R=H)	(a)	233-234	24.07
		239	25.03
		273^{+}	9.84
		282.5	11.07
		296^{+}	8.96
		311	6.94
		326	8.17
		366	23.72
		381	25.13
		400^{+}	17.57
	(b)	253^{+}	12.27
		282	9.99
		312^{+}	7.68
		400^{+}	17.89
		422	22.07
(XLVI, R=H)	(a)	229	24.24
		233^{+}	22.37
		272-280	8.30
		311	8.05
		358	23.28
		370	23.44
		388^{+}	13.26
	(b)	290	9.80

(XLVl, R=H) (cont.)		303+	8.94
		398	15.61
	(c)	283	7.64
		315	7.15
		355	12.81
		365+	12.40
		390	6.05
(XLVll)	(g)	349	44.61
		444	10.47
		498	13.42
	(e)*	344	36.23
		392+	21.02
		505	10.64

* ϵ were diminishing.

(XLVlll)	(e)	308+	20.04
		405	34.10
		429+	27.57
(XLlX)	(e)	367	36.95
		428+	10.36
		462+	8.62
		564	14.42
		614+	11.44
(L)	(a)	223	24.33
		226	23.86
		281.5	13.01

(L) (cont.)		291	12.42
		331	15.14
		347^{+}	10.01
	(b)	269^{+}	11.92
		281.5	13.27
		292^{+}	12.51
		374	12.27
(L1, R=H)	(a/d)(4:1)	299^{+}	18.03
		310	25.55
		322	24.65
		350	5.75
		369.5	8.04
		393	9.96
		420	20.05
		447.5	35.90
		478	41.69
	(b)	246	28.95
		256^{+}	25.59
		270^{+}	18.39
		282^{+}	15.53
		309	15.48
		323	15.70
		389	5.64
		419	5.80
		447	15.07

(L1, R=H) (cont.)		478	26.20
		511	27.97
		541	33.16
(L11)	(a)	240	28.50
		256	24.86
		288	22.81
		298-300	21.22
		314+	16.23
		419	30.09
		444.5	32.07
	(b)	262	29.02
		288+	24.00
		299+	19.52
		316+	13.43
		391+	12.27
		414-418	21.13
		442-444	21.76
		470+	13.46
(L111, R=H, M=Cu)	(e)	314	14.00
		324	15.24
		340.5	17.19
		372	8.16
		392	6.70
		422+	5.27
		453	12.83
		483.5	25.35

(LIII, R=H, M=Cu) (cont.)		527	29.52
(LIII, R=H, M=Ni)	(e)	326^{+}	13.27
		346	17.22
		371	8.17
		390^{+}	5.14
		503	25.25
		540	39.22
(LIII, R=H, M=Zn)	(e)	312.5	12.48
		323	13.70
		336^{+}	9.34
		372	5.61
		394.5	6.41
		423	8.71
		450	17.37
		481.5	25.10
		527	15.46
(LIV)	(h)	331	30.39
		347.5	33.79
		382	16.44
		408^{+}	12.07
		481^{+}	29.09
		517	57.55
		553	53.67
(XLV, R=CH_3)	(a)	212	20.62
		233	23.31

(XLV, R=CH_3) (cont.)		273$^+$	11.36
		282-283	12.52
		297$^+$	9.33
		311	6.28
		325	7.17
		367	22.90
		381	25.64
		402$^+$	16.20
	(b)	253$^+$	13.20
		279	13.75
		285$^+$	14.15
		408	20.20
		418$^+$	20.09
(LV)	(a)	236	21.98
		280	11.43
		367$^+$	20.14
		382	24.30
		402	17.29
(XLVI, R=CH_3)	(a)	230	23.82
		275	10.44
		311	7.21
		363$^+$	23.07
		373	24.32
		395$^+$	13.67
	(b)	282	9.86

(XLVl, R=CH_3) (cont.)		400	22.77
	(c)	270	12.97
		277	12.97
		313$^+$	6.94
		362$^+$	18.88
		371	19.61
		394$^+$	10.65
(Ll, R=CH_3)	(a)	242	21.16
		258$^+$	17.66
		314	21.41
		324-325	19.20
		452	30.71
		474$^+$	25.61
	(b)	245	30.46
		272	25.74
		346	15.83
		512	33.88
		539	39.49
	(c)	313	16.62
		329$^+$	12.96
		451	28.84
(Llll, R=CH_3, M=Cu)	(e)	275$^+$	15.77
		315.5	14.82
		327$^+$	14.28
		342$^+$	11.40
		446	13.58

(L111, R=CH_3, M=Cu) (cont.)	484^{+}	11.88
	512^{+}	10.34
	550.5	11.40

$^{+}$ Inflexion

Chapter 5

Discussion of results

A. General

The synthesis of the macrocycle (111) (p.6), which was the ultimate aim of this work, has not been achieved. Nor has the synthesis of the corresponding compound having four cyanomethine links instead of four methine links. But there is good evidence that some di-cyanomethine-di-aza-linked macrocycles have been prepared (pp.56 and 93), although not isolated; and a synthetic method has been established for the preparation of the two and three unit compounds which might yet be used to synthesise the macrocycle, since a lack of time prevented an exhaustive investigation of the extension of the synthesis to produce the macrocycle. It is possible that the use of more vigorous reaction conditions would give the desired results.

In the beginning it was shown (Chap.1, p.5) that a 2- or 4-methyl group on a pyridine molecule is not made more reactive by the presence of an N-oxide group; and it was also shown that the quaternary salts derived from these N-oxides were unsuitable for reaction with isoindoline derivatives. The salts either decomposed, gave the wrong product or did not react at all.

A brief investigation of the activating effect of a phosphonate group (Chap.2, p.31) showed that, in this case,

the methylene group to which it was attached was not sufficiently activated to give the desired results.

Following this the re-investigation of the reaction between benzyl cyanide and phthalonitrile (p.42) led to the preparation of a series of compounds, all intermediates on the route to the synthesis of macrocycles. The scope of this part of the work included a comparison between the use of phthalonitrile and isoindoline derivatives (p.78). It was shown that phthalonitrile reacts more readily and gives better yields than isoindoline derivatives. The phthalonitrile reaction involves an addition and cyclisation, whereas with an isoindoline derivative, condensation with elimination of ammonia is necessary.

The difference in reactivity towards phthalonitrile between 2-pyridylacetonitrile and methyl 2-pyridylacetate was also compared (p.79). The reaction with the ester gave only about half the yield obtained when pyridylacetonitrile was used. So the cyanide group is a more effective activating group than the ester group here.

The self-condensation reaction of the imino 'two unit' compounds was observed (pp.48 and 76), as it had been for the aza-linked compounds (loc. cit.). Although Clark was able to prepare 2:1 ligand:metal complexes of his condensed compounds this was not possible with the present ones. An exception in the pyridine series, was compound (XLVII)

which formed 1:1 ligand:metal complexes (p.78).

The metal complexing properties of the pyridine 'three unit' materials were also investigated. Compound (L1, R=H) formed Cu, Zn and Ni complexes whose structures have already been discussed in the previous chapter (pp.83-86). Similarly compound (L1, R=CH_3) formed a Cu complex, but failed to form complexes with Ni, Zn, Mn and Pb (p.90). This may be connected with the steric hindrance between the 6-methyl groups (see scale diagram p.151) preventing the pyridine nitrogen atoms from approaching sufficiently closely. On the other hand the ionic sizes of the metals that failed to form complexes lie on both sides of that of Cu^{++}. The metal complexes that have been prepared might well be a rewarding field of investigation by X-ray crystallography. Tri-dentate ligands are not very common, and a comparison of the absolute structures might be very interesting and instructive.

It has also been shown in one case that the activating cyanide groups can be hydrolysed to amide groups (p.82), and probably thence to carboxylic acid groups. The brief investigation of the possibility of decarboxylating the product was inconclusive (p.82). It may be that a copper complex of the decarboxylated product could be obtained from a reaction using copper or a copper salt. But the isolation of the un-complexed decarboxylated product may

require a different method. Eaton and Cole[62] showed that decarboxylation can occur when a t-butyl perester is refluxed in a high boiling solvent. Other methods include the use of concentrated aqueous potassium hydroxide under pressure[63], heating the potassium salt with calcium oxide[64] and heating the ammonium salt in glycerol[65].

A good synthesis of 2,6-di(cyanomethyl)pyridine has been worked out (p.91), and it is possible that the method may have wider application, particularly where lithium aluminium hydride reduction of an ester is undesirable.

One macrocycle has been prepared, albeit unintentionally, and characterised (p.52). This is the di-cyanomethine-di-aza-linked macrocycle (XXIX) having one benzene and three iso-indole units. The tetra-aza-linked analogue had previously been prepared; and there is real evidence, in the form of the mass spectral results, that condensation between the 'three unit' compounds (XXXVII) and (LVI) on the one hand, and diamines on the other does take place to produce macrocycles (pp.56 and 93). So far these products have not been isolated pure, and the optimum reaction conditions probably have not been attained.

As far as reactions to produce the tetra-cyanomethine-linked macrocycles are concerned, the signs are less encouraging but on the other hand the reaction conditions used were less vigorous than those for the amine condensations

and it would undoubtedly be worthwhile to examine the possibility of using higher reaction temperatures.

Also it must not be forgotten that there is another possible route to the macrocycles via the other 'three unit' compound, namely (L1, R=CH_2CN). This route was not investigated, for the reason that the preparation of this 'three unit' compound would require elevated temperatures, thereby encouraging formation of higher reaction products and a complex reaction mixture. It is probable that if this compound could be prepared, macrocycle formation would be easier than for the route chosen. Perhaps by first preparing the two unit compound, and then condensing this separately with 2,6-di(cyanomethyl)pyridine, rather than attempting to form the three unit in one reaction, it might be possible to isolate the three unit product (L1, R=CH_2CN). From evidence provided by reaction of the other cyanomethyl compounds, this three unit product should condense readily with phthalonitrile.

B. Spectroscopic properties

(i) Infra-red. Most of the infra-red absorptions of the compounds were as expected, and require no further comment here. Two points are worth noting however. Firstly, all the imino 'two unit' compounds and the two di-imino 'three unit' compounds showed a strong absorption at about 1520 cm^{-1}, as well as that attributed to C=N at 1640 cm^{-1}. This

absorption at 1520 cm^{-1} disappears on hydrolysis to the oxo-compound and must surely be a vibration associated specifically with the amidine system. A few other cyclic amidines[7] show this band around 1520 cm^{-1}. Furthermore, Prevorsek[71] showed for a series of acyclic N,N'-disubstituted amidines, that there were three characteristic bands at 1644-1620 (strong), 1550-1531 (strong) and about 1340 (medium). There seems no doubt therefore that both acyclic and cyclic amidines exhibit at least two strong characteristic bands in the infra-red spectrum.

Secondly, there is a considerable variation in the position of the absorptions due to acetate groups in the metal complexes prepared. Complexes of (XLVII) showed a peak at 1700 cm^{-1} (p.101). The Zn complex (LIII, R=H, M=Zn) absorbed at 1680 cm^{-1} (p.110). The other metal complexes absorbed at about 1500 cm^{-1} (pp.108 and 109). It is probable that this variation in position reflects the varying nature of the acetate-metal bond from predominantly covalent to predominantly ionic.

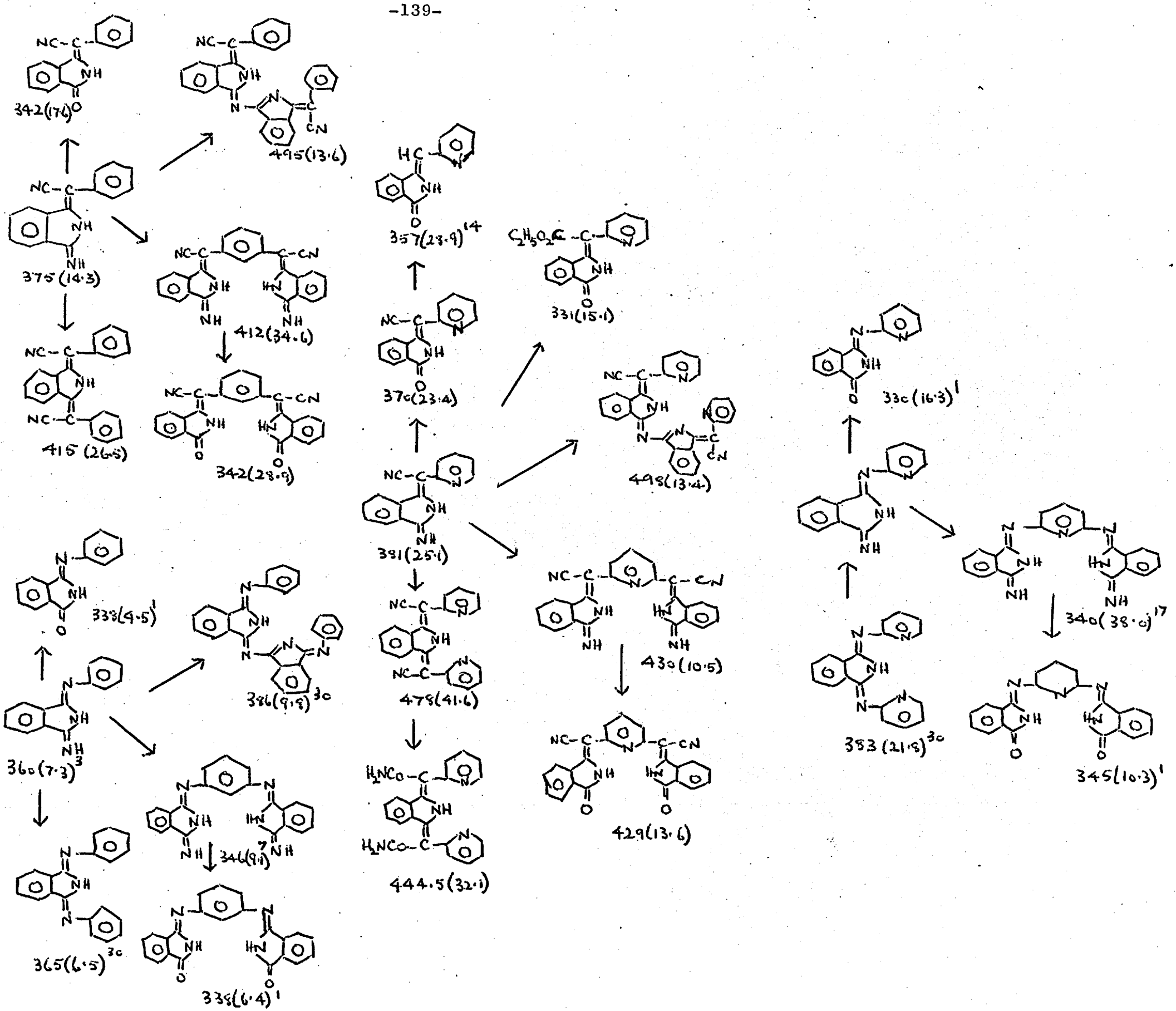
(ii) Proton magnetic resonance. The effect of the cyanide group on one of the aromatic protons has already been discussed (p.44). It can be seen from the scale diagram (p.151) that the isoindole 7-proton is nearer than any phenyl group proton to the deshielding zone of the cyano-group. By using the perfluorophenyl compounds as described

(p.46), it was confirmed that it is the isoindole 7-proton that gives rise to the characteristic low field signal.

A shielding rather than deshielding effect is observed when one compares the methylene absorptions of pyridine-2,6-dimethanol and 2,6-di(cyanomethyl)pyridine (pp.119 and 120). Since a cyanide group has a greater electron withdrawing effect than a hydroxyl, it might be expected that the methylene protons would appear at lower field in the cyano- than in the hydroxy-compound. However, the methylene protons lie approximately on the axis of the C≡N bond in the shielding region. This more than counteracts the deshielding due to the greater electron-withdrawing power of the cyanide over the hydroxyl group. The result is that the spectrum of the di(cyanomethyl) compound shows the methylene protons at higher field than those in the hydroxy compound.

(iii) Ultra-violet. These results are discussed in terms of the longest wavelength absorptions of the compounds since these are characteristic of the whole chromophore, whereas shorter wavelength absorptions are due to transitions in smaller parts of the chromophore.

A diagrammatic comparison of the electronic absorption properties of a number of the compounds prepared in this work and their aza-linked analogues (where known) is set out on p.139.It should be noted that the arrows serve only


342(17.4)
495(13.6)
375(14.3)
412(34.6)
415(26.5)
342(28.9)
357(28.9)14
331(15.1)
370(23.4)
498(13.4)
391(25.1)
479(41.6)
430(10.5)
444.5(32.1)
429(13.6)
338(9.5)1
386(9.8)30
360(7.3)3
346(9.1)7
365(6.5)30
338(6.4)1
330(16.3)1
353(21.8)30
340(38.6)17
345(10.3)1

to show general chemical relationships in the various groups and are not necessarily intended to indicate actual reactions that have been or could be carried out.

It can be seen that invariably a cyanomethine-linked compound absorbs at a longer wavelength than its aza-linked analogue. As might be expected, the difference is greater in the three unit compounds than in the two unit compounds. This difference may well be a reflection of a fundamental difference in the excited states of the two types of compound. It is not simply due to the two types existing in different tautomeric forms of the amino-imino system, since it persists in the fixed-bond three unit compounds. Nor can it be wholly due to the cyanide groups since 1-2'-pyridylmethylene-3-oxoisoindoline (prepared by Barnes[14]) absorbs at a longer wavelength (357 mμ) than the aza-analogue (338 mμ).

By a comparison of some cyanomethine- with some aza-linked compounds it is possible to draw some tentative conclusions regarding the fine structure of the two unit compounds. By preparation of compounds with fixed bond structures, Elvidge and co-workers[3,6] have shown that in general where there is an endo-cyclic double bond, the u.v. absorption is 20-40 mμ further into the visible region than where it is exo-cyclic. From this they deduced that the two unit compound 1-phenylimino-3-iminoisoindoline

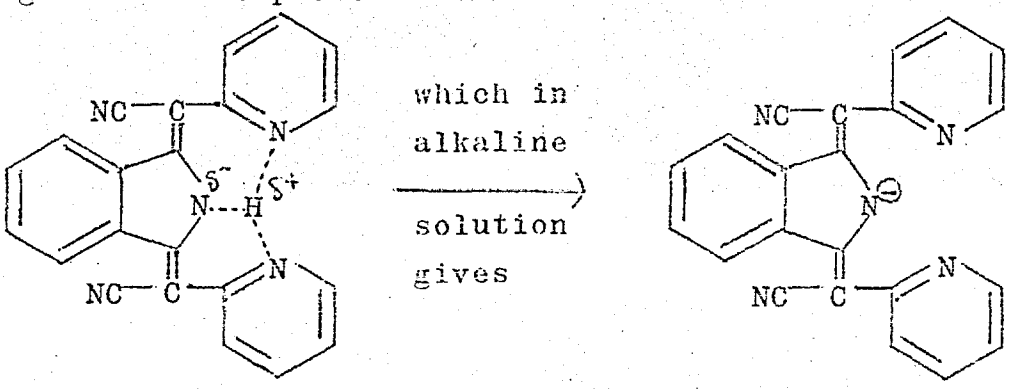
existed, at least in the ethanol solution used for u.v. measurement, as a mixture of the two tautomers because it shows absorption both in the 300-320 mμ region and in the 360 mμ region. This is supported by comparison with the three unit compound 2-methyl-1,3-diphenyliminoisoindoline[6] where both double bonds are of necessity exo-cyclic. This compound only absorbs 5 mμ further into the visible than the two unit compound. One expects that removal of any contribution from an endo-cyclic form will reduce the longest wavelength absorption, and this is slightly more than compensated by the addition of a phenyl group to the conjugated system.

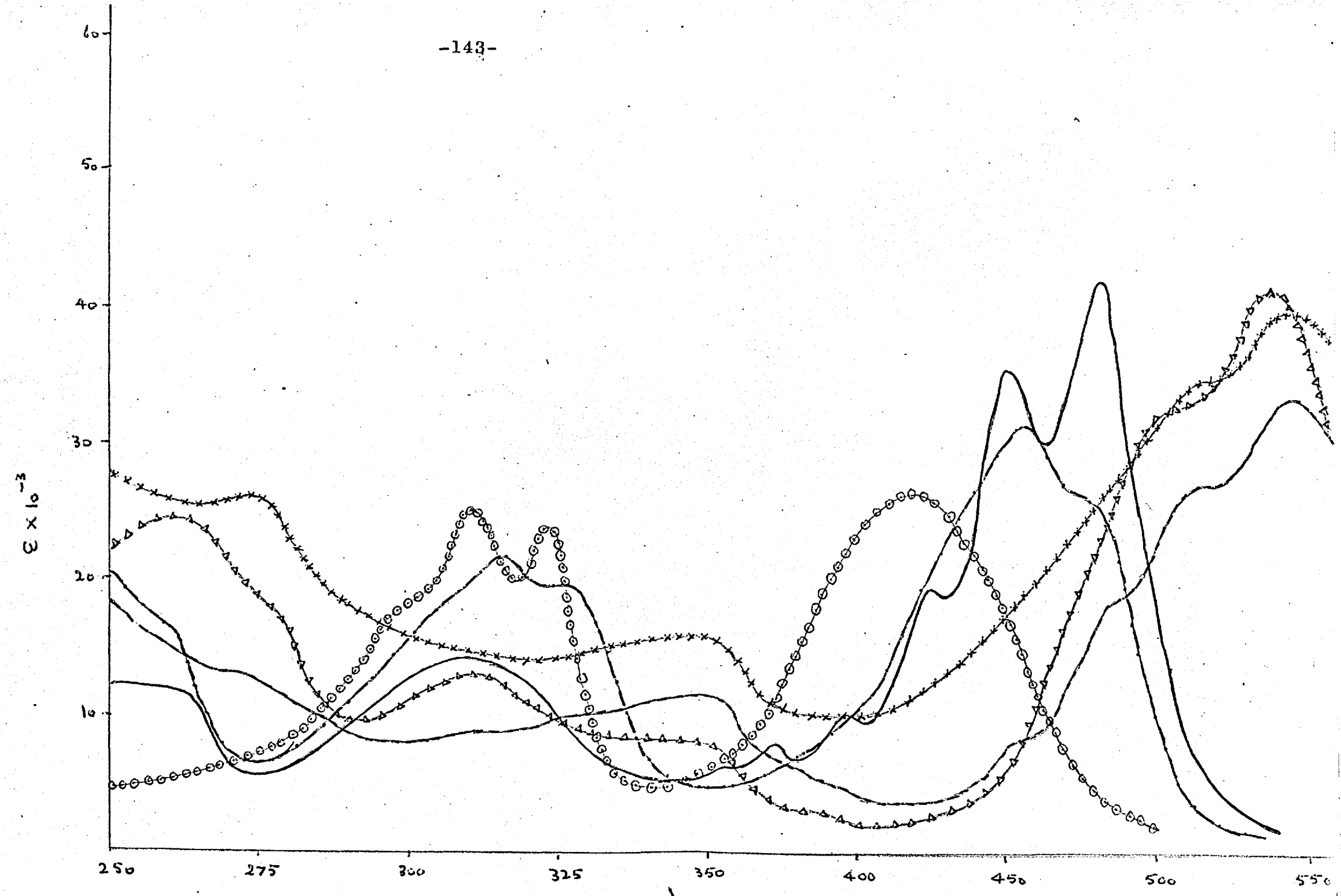
Now we turn to the cyanomethine linked compounds. In this case the three unit compound, 1,3-di(phenylcyanomethylene)isoindoline, absorbs 40 mμ further into the visible region than its two unit precursor. We can therefore deduce that in this case the longest wavelength absorption of the two unit material is due to the exo-cyclic tautomer, and the 40 mμ increase represents the increase in length of the conjugated system on addition of a phenyl group. If the endo-cyclic tautomer were present one would expect its absorption to appear in the region of 400 mμ and there is no evidence at all of a maximum or inflexion in that region.

This argument can be extended, with limitations as

will be seen later, to the pyridine series of compounds. It would be expected that the exo-cyclic double bond form would be favoured in this case anyway, since then the hydrogen of the amino-nitrogen can become hydrogen bonded to the pyridine nitrogen.

It is interesting to examine the corresponding compounds in the pyridine series in a little more detail. The longest wavelength band in the three unit structure shows a bathochromic shift of 97 mμ from the position of the band given by the two unit structures. This is a very much greater shift than in the benzene series. A comparison of the spectra of the benzene and pyridine three unit compounds in alkaline ethanol (p.143) shows that their absorptions are only 5 mμ apart, whereas in ethanol the difference is 63 mμ. In alkaline solution it is presumably the metal salt derived by replacement of the proton on the amino-nitrogen that gives rise to the spectrum. It therefore seems possible that the pyridine three unit material absorbs so far into the visible region because a partial charge separation is effected by the attraction of the pyridine nitrogens for the proton thus:





L1, R=H —— in ethanol - - - - in alkaline ethanol

L1, R=CH_3 -·-·- " xxxxxx " "

XXXIV ooooo " ΔΔΔΔΔΔ " "

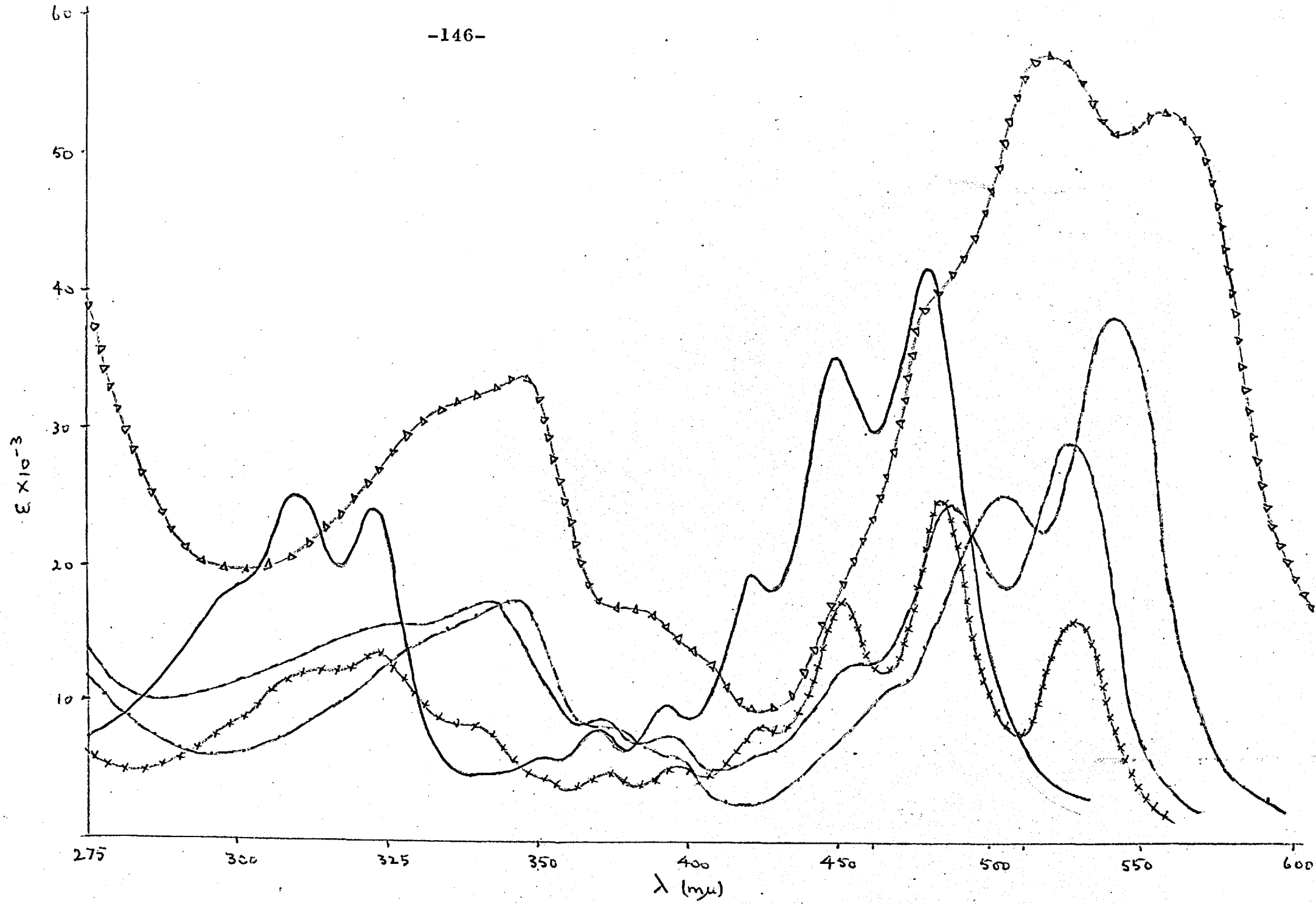
in which the negative charge can be delocalised. Hence the spectrum is part-way between that which would be expected, and that of the species having a full negative charge on the nitrogen atom.

Support for this view is obtained from the spectra of 1,3-di(6-methyl-2-pyridylcyanomethylene)isoindoline. In this compound it is thought that the two methyl groups will sterically hinder one another (see diagram) thus forcing the pyridine rings away from one another and therefore making it difficult to form the hydrogen bonds. The spectra both in ethanol and alkali more closely resemble those of its benzene analogue than those of its unsubstituted pyridine analogue.

Some other empirical observations can be made about the u.v. spectral properties. (a) The effect of hydrolysis of C=NH to C=O is to cause a hypsochromic shift of 20-30 mμ both in the aza-linked and the cyanomethine-linked series. (b) Hydrolysis of the two cyano groups of 1,3-di(2-pyridyl-cyanomethylene)isoindoline to amide groups also causes a hypsochromic shift of 34 mμ. (c) Comparison of the condensed compounds shows that the spectra of the two derived from cyanomethine-linked compounds are very similar to each other (only 3 mμ difference) and yet the longest wavelength bands are 110 mμ further into the visible than from an aza-linked compound. This can only partly be explained by

the effect of the different links. By comparison of other compounds in these series one could reasonably predict a difference of about 50 mμ. It must therefore be some difference of stereochemistry or fine structure.

The metal complexes (LIII, R=H, M=Cu, Ni and Zn) have spectra very similar to each other (see p.146). These complexes absorb about 60 mμ further into the visible than the uncomplexed ligand, and also about 60 mμ further than the Ni complex of the aza-linked analogue. This latter difference is much the same as the difference between the metal free ligands, and is presumably due simply to the difference in linking groups.



LI, R = H ——

LIII, R = H, M = Cu. - - - - -

" , M = Ni. - · - · - · -

" , M = Zn. × × × × × ×

LIV Δ Δ Δ Δ Δ

Chapter 6

Further work

It is suggested that these studies should be continued to determine whether the tetra-cyanomethine-linked macrocycles can be obtained by the routes investigated in the present work.

Various other syntheses can be envisaged. The influence of substitution in the pyridine could be studied. One variation would be to start from 3-hydroxypyridine, which readily undergoes the Mannich reaction with formaldehyde to give 2,6-di(hydroxymethyl)-3-hydroxypyridine[66]. This could be converted to the di(chloromethyl) compound, and then after methylation of the 3-hydroxy group, into the 2,6-di(cyanomethyl)-3-hydroxypyridine. The conversion of this into a macrocycle would make accessible a number of disubstitution products. At the same time, the actual formation of the macrocycle would presumably give rise to two isomeric products. This is because the substituent groups can be arranged *syn* or *anti* with respect to an axis drawn through the two pyridine nitrogen atoms of the molecule.

It follows that 3,5-dihydroxypyridine, whose preparation has been described[67,68], should undergo the Mannich reaction even more readily thus leading eventually to a tetra-substituted macrocycle.

Again, preparation of a suitably substituted pyrimidine

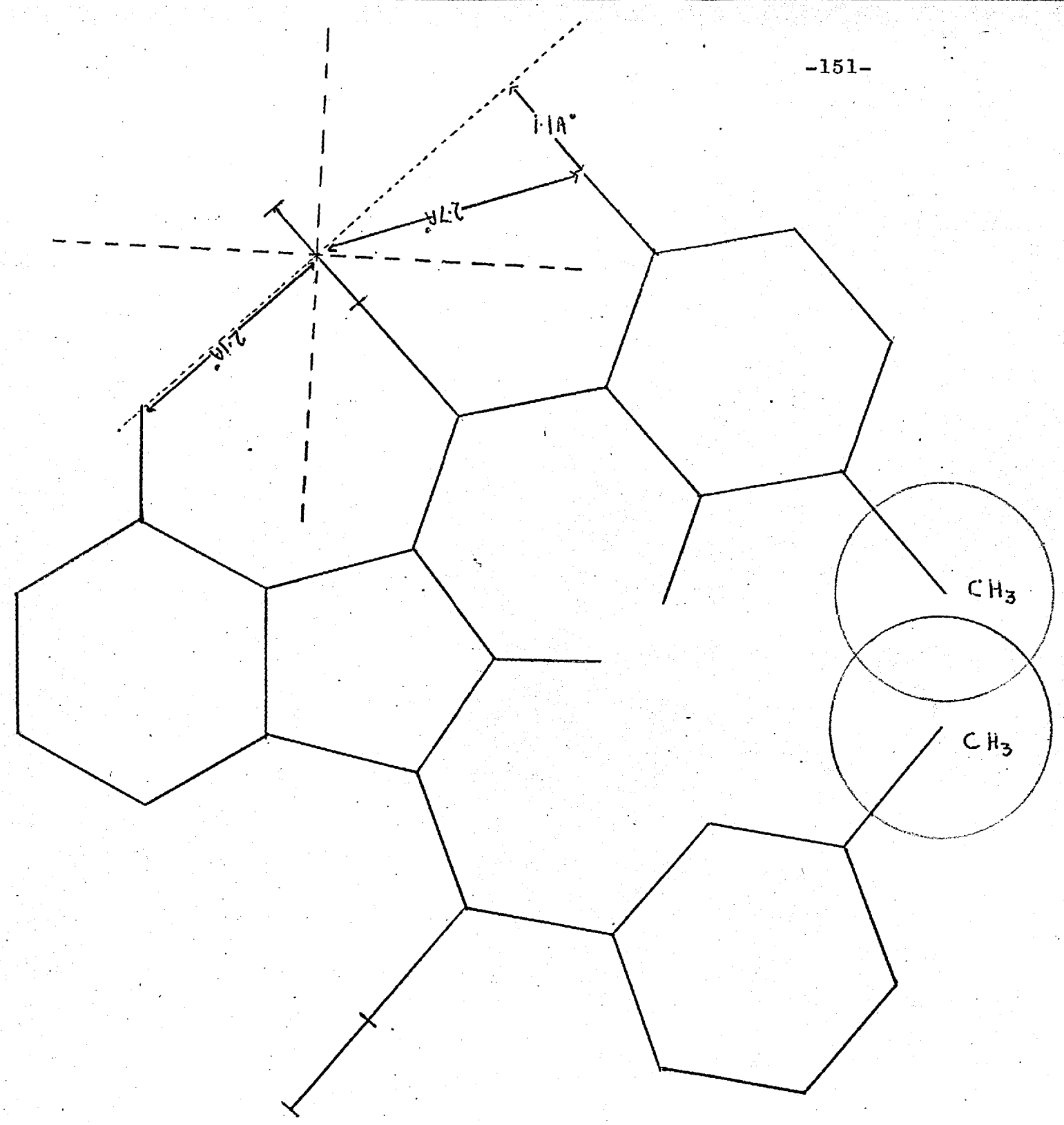
might be of interest. If a 2,4-di(cyanomethyl)pyrimidine could be converted to a macrocycle, then one nitrogen atom would be available on the outer ring of the macrocycle for examination of the effect of quaternisation of that nitrogen on the properties of the macrocycle. At least one possible relevant starting material, 4-hydroxy-2,6-di(hydroxymethyl)-5-methylpyrimidine, has been described[69] which might be converted to the analogous di(cyanomethyl) compound.

Turning to five-membered heterocycles, the case of thiophene is of immediate interest since thiophene itself is readily chloromethylated to 2,5-di(chloromethyl)thiophene[70], and also the chloro groups are readily replaced by acetate groups, and therefore surely also by cyanide groups to give 2,5-di(cyanomethyl)thiophene. A macrocycle prepared from this would be of particular interest since the unsaturated system would be fully conjugated rather than cross conjugated. This would provide a much closer analogy to compounds such as haem and phthalocyanine, and might be expected to support a ring current and therefore be aromatic in the same way as these latter compounds.

This idea can of course be extended to pyrrole, which should be analogous to thiophene. 2,5-Di(hydroxymethyl)-pyrrole has been described[72], and it is possible that this might be converted into the di(cyanomethyl) compound and thence to a macrocycle.

The other basic variation on the work described in this thesis would be the use of substituted phthalonitriles. It would be of interest to study the effect of substituents in two respects: (i) the effect on the properties of macrocycles and intermediates formed from them; and (ii) the effect on the cyclisation reaction which forms the isoindole ring. It might be that electron releasing substituents would reduce the partial positive charge on the nitrile carbon atom thus making it less susceptible to nucleophilic attack by the carbanion formed in the cyclisation reaction. On the other hand electron withdrawing substituents might aid the addition reaction.

The first diagram is not of an actual compound prepared, but a composite picture incorporating features from several of the compounds prepared. Bond angles and lengths are based on those of phthalocyanine[73] and compounds included in the Chemical Society tables[74].



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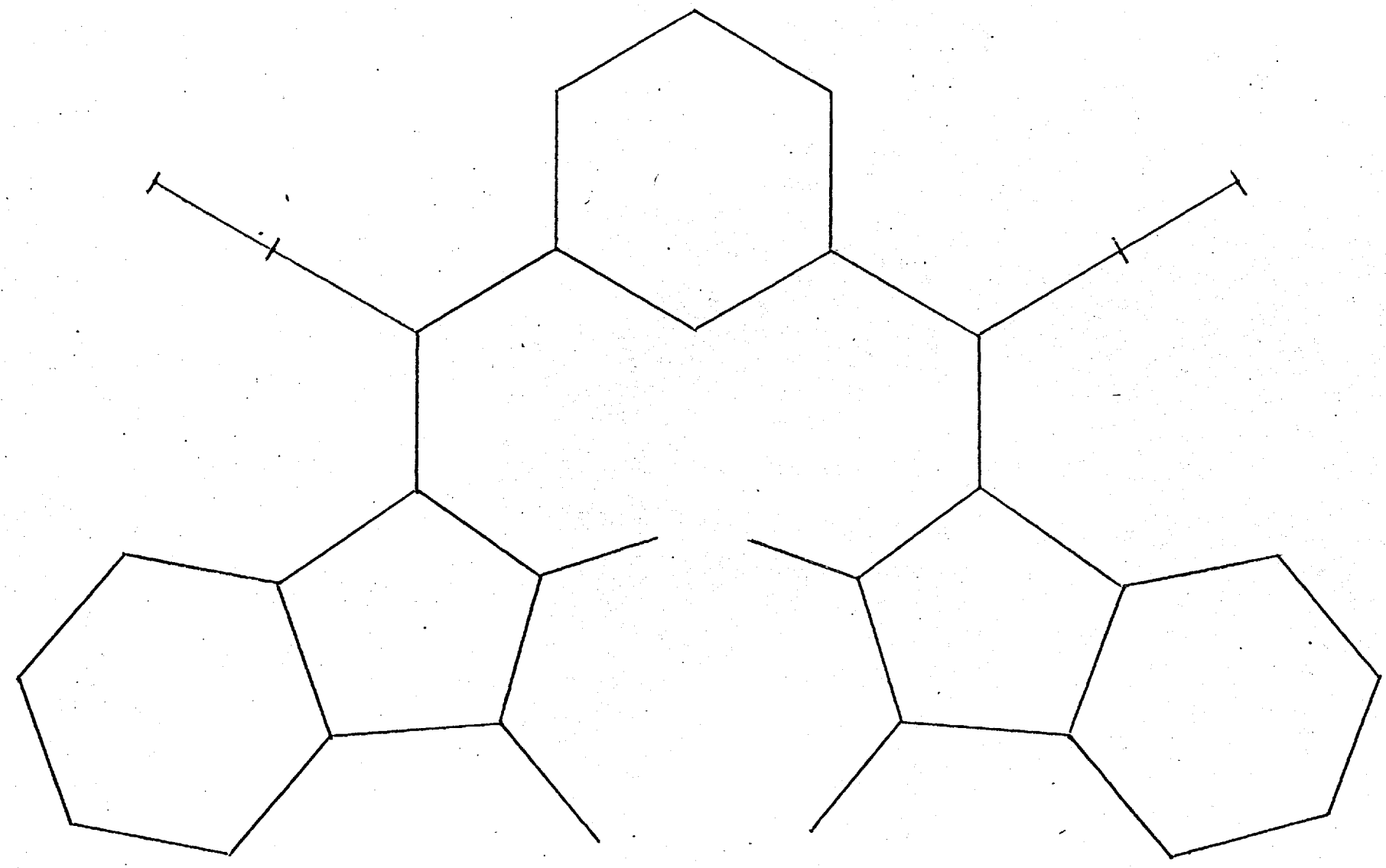

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