

ISOQUINOLINE SYNTHESSES FROM
DINITRILES

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by

IAN FREDERICK BARNARD

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JOSEPH KENYON RESEARCH LABORATORIES
UNIVERSITY OF SURREY
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ABSTRACT

o-Cyanobenzyl cyanide does not form an imidate with methoxide but undergoes dimeric addition and cyclization to 1-amino-4-cyano-3-(o-cyanobenzyl)isoquinoline. A better yield of this product is obtained from the action of sodamide in formamide on the dinitrile but with this reagent a secondary reaction occurs by attack of the formamido anion, generated in the reaction, on the dinitrile, to afford a mixture of cis- and trans-1-amino-3-formamidoisoquinoline.

o- α -Dicyanostilbene, from the piperidine catalysed condensation of o-cyanobenzyl cyanide with benzaldehyde, suffers nucleophilic addition across the aryl nitrile group on treatment with sodamide in formamide to yield 1-amino-4-cyano-3-phenylisoquinoline. Analogous 1-alkoxy isoquinolines are obtained by reacting the stilbene with catalytic amounts of alkoxides in the corresponding alcohols but, in the reactions examined, the yield decreases with increasing basicity of the alkoxide. The 3,4-dihydroisoquinoline is an intermediate which can be isolated by rigorously excluding oxygen from the system.

Hydrazine does not add across the nitrile groups of o- α -dicyanostilbene but effects cleavage of the olefinic

group to yield o-cyanobenzyl cyanide and benzaldehyde.

Hydroxylamine, on the other hand, forms the acyclic bis-amidoxime which, whilst stable in base, suffers cleavage of the ethylenic group in mild acid and cyclises to homophthalimide dioxime.

Nucleophilic addition of o-cyanobenzyl cyanide to o- α -dicyanostilbene is achieved in the presence of methoxide, the product being a substituted isoquinoline.

Reexamination of the reaction between o-cyanobenzyl cyanide and benzaldehyde in the presence of methoxide has led to determination of the structure of the major product, an adduct of two molecules of the dinitrile and one of the aldehyde.

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Part II of this thesis was typed by Mrs. K. Warren who is sincerely thanked.

The assistance and support my wife has given throughout the period of this work are affectionately noted and particular thanks are due for the typing of Part I of this thesis.

I.F.B.

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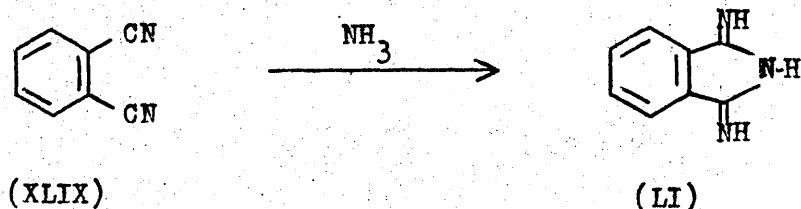
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INTRODUCTION

The greater electronegativity¹ of the nitrogen over the carbon atom imparts considerable polarity to the nitrile group in the sense $\overset{+}{\text{C}} \equiv \text{N}$. The nitrile group therefore, characteristically undergoes nucleophilic addition at the electropositive carbon.

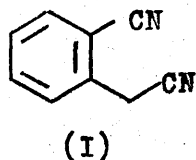
The wide range of reactivities shown by nitriles demonstrates that the polarization of the cyano group is greatly influenced by the moiety to which it is attached. Conversely, the nitrile group, which is strongly electron attracting both inductively² and mesomerically³, can have a decisive effect on the behaviour of the rest of the molecule.

With the introduction of a second nitrile group into a molecule, the above considerations still clearly apply, but in addition, where the two nitrile groups are suitably proximate, nucleophilic addition to one or both cyano groups can lead to synthesis of nitrogen heterocycles. Thus, for example, phthalonitrile (XLIX) affords 1,3-diiminoisoindoline (LI) when heated with methanolic ammonia under pressure⁴.



It is with this aspect of dinitrile chemistry that the present work is concerned.

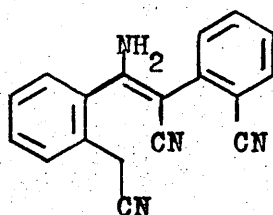
The two cyano groups in o-cyanobenzyl cyanide (I) are in different electronic environments. A difference in their reactivity could therefore be anticipated. Further, their spatial relationship is such that addition across them would yield a six-membered ring. Interesting products should therefore result from treatment of this dinitrile with nucleophiles.



Indeed, with ammonia, the dinitrile (I) afforded 1,3-diamino-isoquinoline (IV)⁵ whilst with hydroxylamine, different products were obtained depending on the reaction conditions. Isolation of 1-amino-3-hydroxylaminoisoquinoline (LVIII)⁵ suggested that in basic conditions, the alkyl nitrile of (I) was more susceptible to nucleophilic attack than the aryl. In mildly acidic media, however, homophthalimide dioxime (LV)⁶ was obtained. The explanation of this would appear to be that protonation of the aryl nitrile enhanced its reactivity such

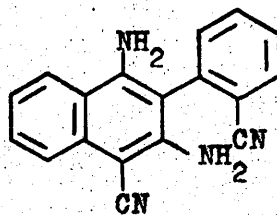
that the rates of attack by hydroxylamine on both nitrile groups were comparable.

Hydrazine also gave an isoquinoline product⁷ with (I) but Johnson and Nasutavicus⁸ found that the stronger base, ethoxide, afforded a product (m.p. 270°), of the dimeric addition of the dinitrile (I), the structure of which was given as (LII).



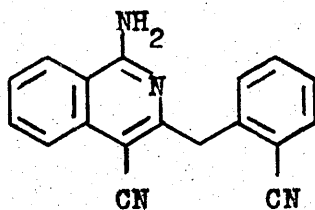
(LII)

Extending the duration of the reaction, a second product (m.p. 225°) having the same composition as (LII) was isolated, for which, from i.r. evidence, the structure (LIII) was proposed



(LIII)

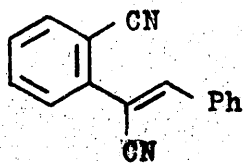
Now, it was found that treatment of the dinitrile (I) with methoxide gave a small yield of a compound (m.p. 223-224°) which was also obtained as the major product (XIV) from the reaction of (I) with sodamide in formamide.



(XIV)

From m.p. and spectral similarities it is believed that Johnson and Nasutavicus' second product had, in fact, the structure (XIV).

The behaviour of *o*-cyanobenzyl cyanide (I) with alkoxide and sodamide showed that the inductive effect of the nitrile group caused the methylene group (which was also benzylic) to be sufficiently acidic for strong bases to abstract a proton. Under more vigorous conditions, weaker bases can also remove this proton. Thus Gabriel and Eschenbach⁹ achieved the piperidine catalysed Knoevenagel condensation of the dinitrile (I) with benzaldehyde to yield *o*- α -dicyano-stilbene (II).



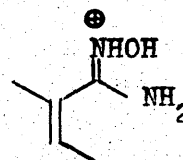
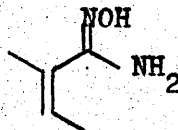
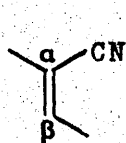
(II)

The trans-stilbene (II) is itself, a dinitrile potentially capable of forming 6-membered heterocycles. Comparison of its behaviour with that of *o*-cyanobenzyl cyanide (I) with nucleophiles is interesting because it again has the two nitrile groups in different chemical environments but, unlike the dinitrile (I), contains no acidic hydrogen atoms.

With ammonia, the dinitrile (II) afforded no tractable product¹⁰ but with sodamide in formamide, the product was 1-amino-4-cyano-3-phenylisoquinoline (XX). Under typical Nef¹¹ imidate synthesis conditions, the ethoxy analog, (XL), of (XX) was obtained. The corresponding 3,4-dihydroisoquinoline (XXXIX) was isolated as an intermediate and from the investigations made, it would seem that oxidation to the fully aromatic structure (XX) proceeds by the reverse of the mechanism established for the acid catalysed hydrogenation of conjugated double bonds in some biochemical systems¹².

The dinitrile (II) resisted hydrolysis in acid but in alkaline solution cleavage of the carbon-carbon double bond occurred, i.e., the Knoevenagel condensation of *o*-cyanobenzyl cyanide (I) with benzaldehyde was reversed. This result was not so surprising because the electron withdrawing effect of the nitrile group would be expected to activate the ethylenic group towards nucleophilic attack. However, the tendency for the dinitrile (II) to cleave, introduced complications to attempted addition of basic nucleophiles in aqueous media. No addition product was obtained with hydrazine, the reaction medium being too basic for the olefinic group to persist. But the weaker base, hydroxylamine, gave the acyclic bisamidoxime (LVI) which, whilst quite stable in basic solutions was readily cleaved by mild acid to afford homophthalimide dioxime (LV). A reasonable explanation of these results is that the nitrile group withdraws electrons more powerfully

than the amidoxime group but in acid, protonation of the amidoxime group renders the electropositive β -carbon highly electron attracting, with the result that the weak nucleophile, water, can attack.



Sufficiently activated for attack by OH^\ominus on β -carbon.

Not sufficiently activated for attack by OH^\ominus on β -carbon.

Highly activated. H_2O can attack β -carbon.

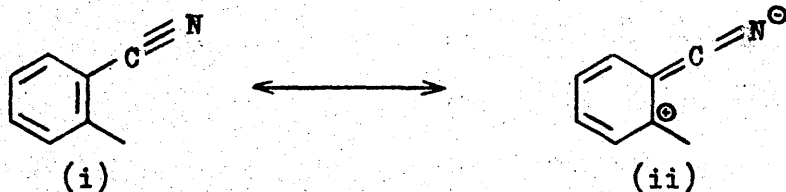
Nucleophilic attack on α - β -dicyanostilbene (II)

preferentially occurred across the aryl nitrile or the olefinic group. Except in the case of hydroxylamine, the α , β -unsaturated nitrile group resisted addition. The same order of reactivity was found for the methoxide catalysed addition of α -cyanobenzyl cyanide (I) to the dinitrile (II) in which the α , β -unsaturated nitrile moiety took no part.

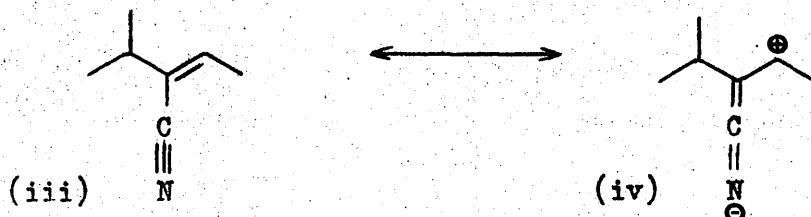
A natural extension of the work already described was the reexamination of the reaction of the dinitrile (I) with benzaldehyde in the presence of alkoxide^{10b}. Previously the expected condensation product (II) was obtained in small yield but the major product was not fully investigated. In the present work this product was found to be the result of addition of two molecules of the dinitrile (I) and one molecule of benzaldehyde. Elucidation of its structure showed that its mode of formation was consistent with the relative cyano group

reactivities already found for the dinitriles (I) and (II).

From the products obtained by nucleophilic attack on the dinitriles (I) and (II), the general order of reactivity of the cyano groups emerged as alkyl $>$ aryl $>$ α, β -unsaturated. The electrophilicity of the carbon of the alkyl nitrile group is only slightly lowered, relative to that of HCN, due to the small + I effect of the alkyl group. Phenyl and vinyl groups exert an approximately equally small - I effect with the result that from these considerations alone, a reverse order of reactivity to that found would be predicted. However, the magnitudes of the inductive effects of alkyl, phenyl and vinyl groups are insignificant compared with that of the nitrile group and it therefore seems reasonable to assume that resonance effects are largely responsible for the observed differences in the nitrile group reactivities. Clearly, the resonance concept cannot be applied to the alkyl nitrile group, but conjugation of the aryl nitrile group with the aromatic ring allows contributions to the total electronic distribution by resonance structures such as (ii), where a carbon atom other than that of the nitrile group bears the formal positive charge. The effect of such resonance is to reduce the electrophilicity of the carbon of the nitrile group and hence its reactivity towards nucleophiles.



The same structures apply to the aryl nitrile of (II) whilst canonical forms such as (iv) can contribute to the electronic distribution for the α, β -unsaturated nitrile.



That resonance effects do operate in the sense given above is supported by i.r.. Resonance electron donation such as expressed by the forms (ii) and (iv) considerably alters the bond order of the nitrile group and this is reflected in the i.r. as a lowering of the nitrile stretching frequency¹³. Thus the greater the resonance contribution, the lower the frequency and the lower the reactivity of the nitrile group. The observed frequencies are given in Table I.

TABLE I

Dinitrile	Nitrile group stretching frequency (cm^{-1}).		
	Alkyl	Aryl	α, β -unsaturated
(I)	2250	2226	
(II)		2223	2212

It is seen that the frequencies of the nitrile groups in Table I (and hence the extent of resonance electron donation to the nitrile groups) are in the same order as the observed reactivities.

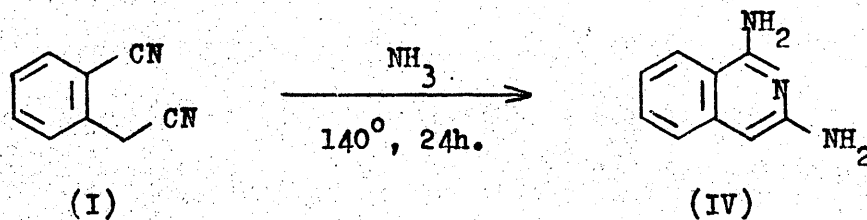
PART I

DISCUSSION

CHAPTER I

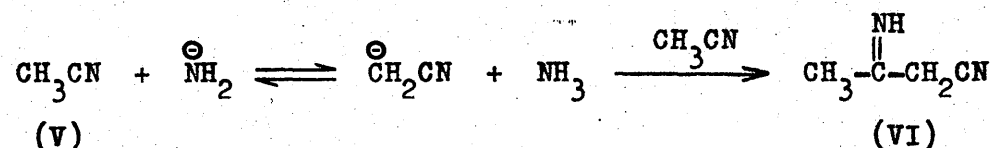
REACTION OF o-CYANOBENZYL CYANIDE WITH SODAMIDE IN FORMAMIDE.

Ziegler's method for the preparation of amidines¹⁴ from nitriles with sodamide has been successfully extended¹⁵⁻¹⁷ to the preparation of imidines (III) from dinitriles in a few cases where direct reaction of the dinitrile with ammonia was difficult. As vigorous conditions were necessary for the addition of ammonia to o-cyanobenzyl cyanide (I) and the product was 1,3-diaminoisoquinoline (IV)⁵, the aromatised tautomer of the expected imidine, it was of interest to determine whether (I) reacted smoothly under less vigorous conditions with sodamide.

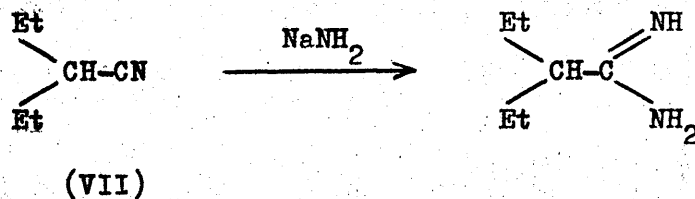


The amide anion, (NH_2^\ominus), as well as being a powerful nucleophile, is also a strong base and consequently undergoes reactions of the type $\text{NH}_2^\ominus + \text{B-H} \rightleftharpoons \text{NH}_3 + \text{B}^\ominus$. The strength of the amide anion as a base has resulted in a loss of generality

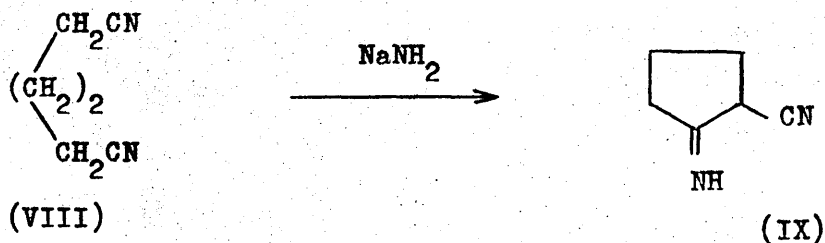
of the Ziegler method for amidine formation. The electron withdrawing effect of the nitrile group imparts slight acidity to a proton on the α -carbon of a nitrile. In some cases this acidity has been sufficient for the amide anion to abstract this proton with the result that a dimeric addition takes place to the exclusion of amidine formation. Acetonitrile (V) exhibits this behaviour¹⁸ and so gives the β -iminonitrile (VI).



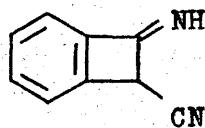
In general it has been found¹⁹ that nitriles containing two α -hydrogens undergo this dimerisation while those with one α -hydrogen, for example diethylacetonitrile (VII), react smoothly with sodamide to yield the amidine.



Similar dimerisation to that found with acetonitrile could be expected with dinitriles containing activated α -hydrogens while for suitable dinitriles, intramolecular addition to yield cyclic products was possible. Thus adiponitrile (VIII) was found to give the cyclic β -iminonitrile (IX)²⁰.

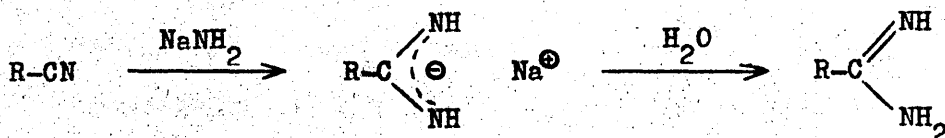


o-Cyanobenzyl cyanide (I) contains a highly activated methylene group being both benzylic and in the α -position to a nitrile group. Sodamide with this dinitrile could be expected to readily form the anion rather than add across the nitrile groups. Indeed, the failure to isolate any of the diamine (IV) from the reaction showed this to be the case. Further, intramolecular cyclisation analogous to that found for adiponitrile would lead to the structure (X).

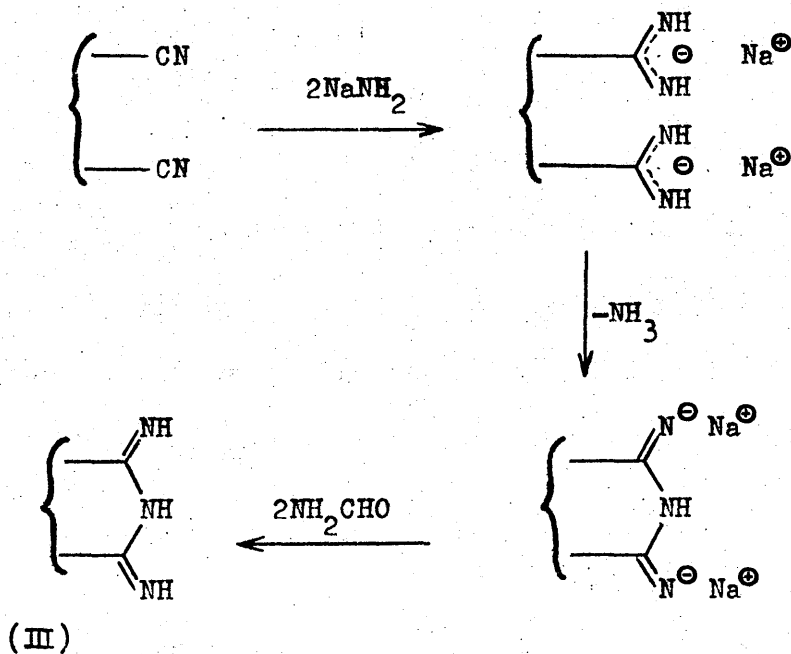


This was not obtained as a product suggesting that the formation of the 4-membered ring was energetically unfavourable compared with dimerisation. Identification of the reaction products showed that the reaction proceeded via a dimeric addition intermediate to more stable cyclised products.

In Ziegler's original method, a nitrile was reacted with a slurry of sodamide in an inert solvent (benzene, diethyl ether, etc.) to yield the sodium salt of the amidine from which the free base was liberated (usually in disappointingly low yield) by addition of water.

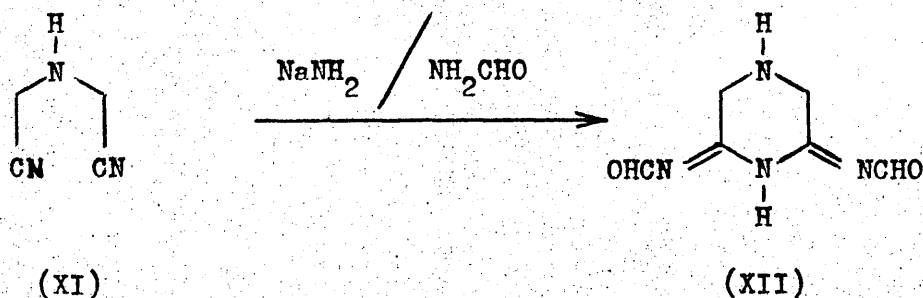


Elvidge and coworkers¹⁵⁻¹⁷ found that the free imidine could be obtained directly by using formamide as cosolvent for sodamide and the dinitrile. Here, the initially formed imidine salt was sufficiently basic to abstract protons from the formamide solvent.

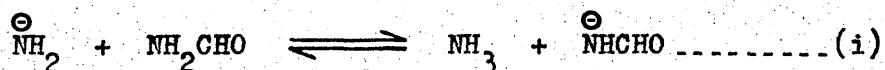


For this reason, formamide was preferred to the inert solvents in the present reaction.

A limitation in the usefulness of formamide as solvent for such reactions was noted when the product from the reaction of iminodiacetonitrile (XI) with sodamide in formamide was identified as 2,6-diformimidopiperazine (XII)¹⁷.

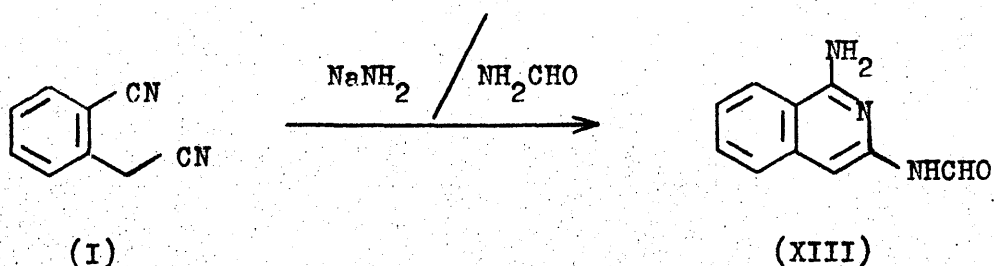


To explain this product it was necessary to propose the equilibrium



Addition of the formamide anion across the nitrile groups with cyclization and elimination of ammonia gave the product (XII).

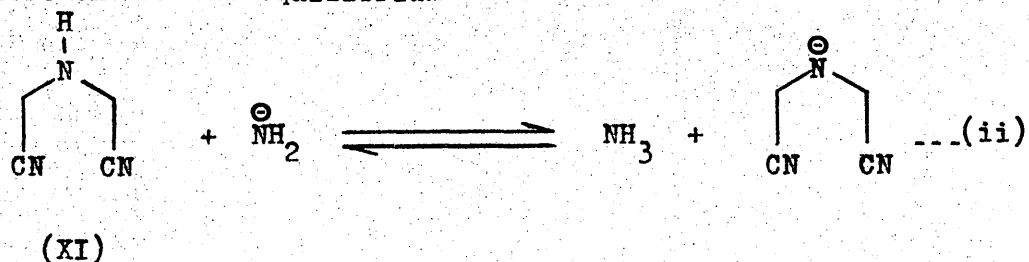
The same equilibrium (i) was necessary to explain the isolation of 1-amino-3-formamidoisoquinoline (XIII) as one of the products from (I) in the present reaction.



Even at $\text{ca. } 10^\circ$ a solution of sodamide in formamide slowly evolves ammonia so it is clear that in time, the loss of this volatile component will force the equilibrium (i) far to the right, reducing the concentration of amide anion to insignificant proportions. Thus successful attack of the amide anion on a dinitrile is limited in formamide, to those reactions

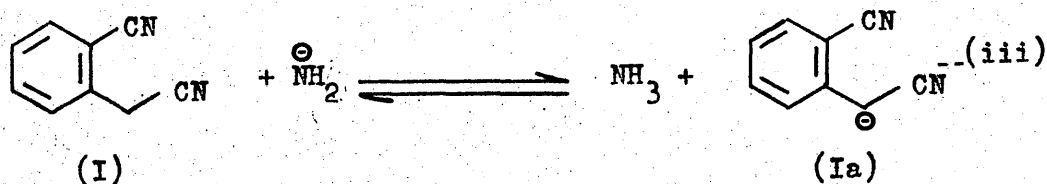
where the rate of attack by NH_2^- is fast relative to the establishment of the equilibrium (i).

In the reaction with iminodiacetonitrile (XI), where (XII) was the only isolated product, it would seem that achievement of the equilibrium



was slow compared with equilibrium (i) and what little further reaction of the dinitrile anion as did take place led to polymerisation.

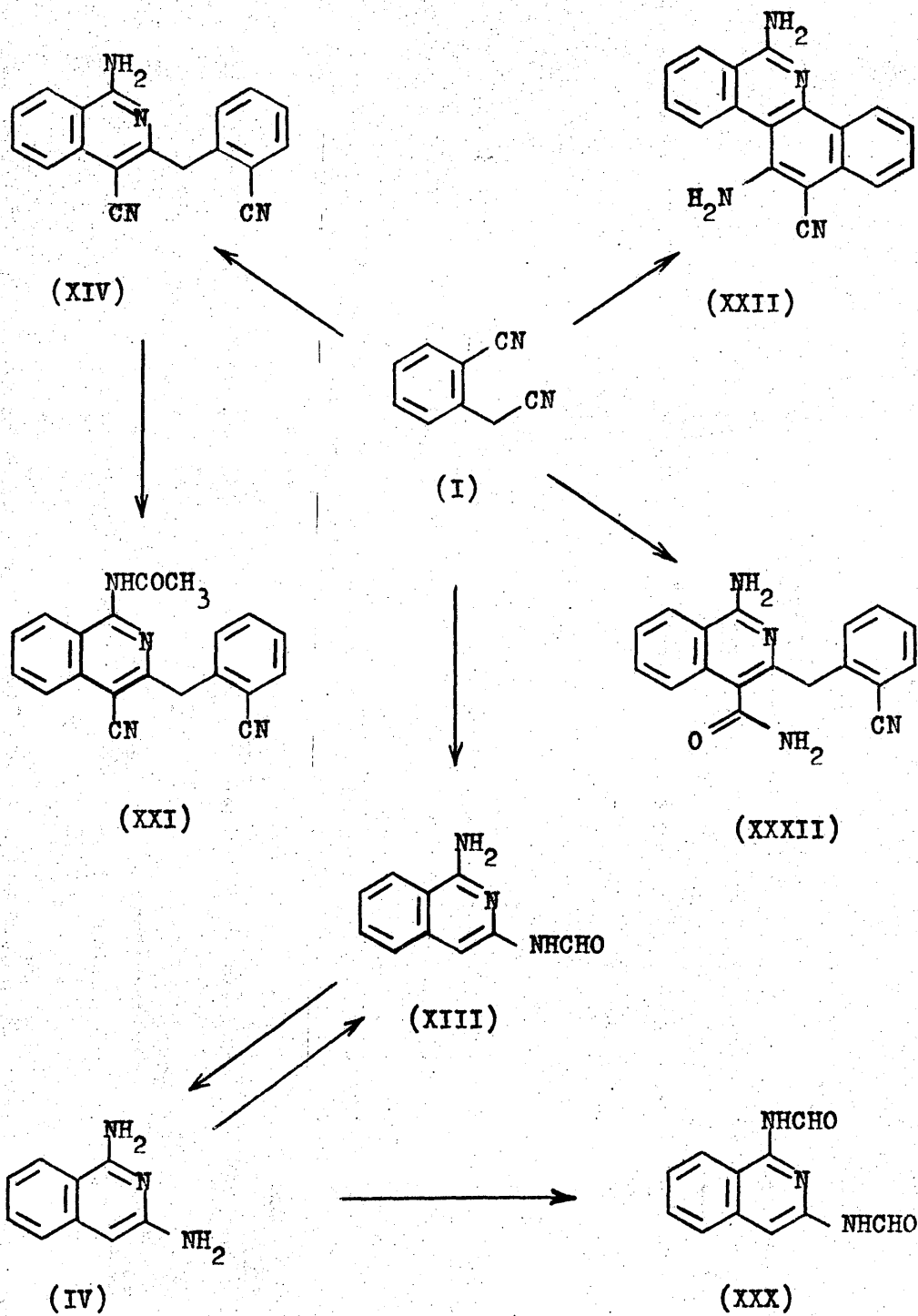
In the reaction of (I) however, products resulting from anionic dimerisation were isolated in reasonable yield which suggested that the equilibrium



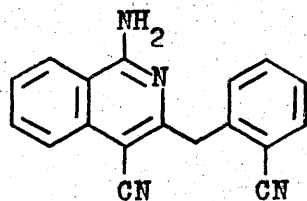
was fairly rapidly established relative to equilibrium (i) and that the subsequent dimerisation was facile.

SCHEME I

Products from the Reaction of *o*-Cyanobenzyl Cyanide with Sodamide in Formamide.

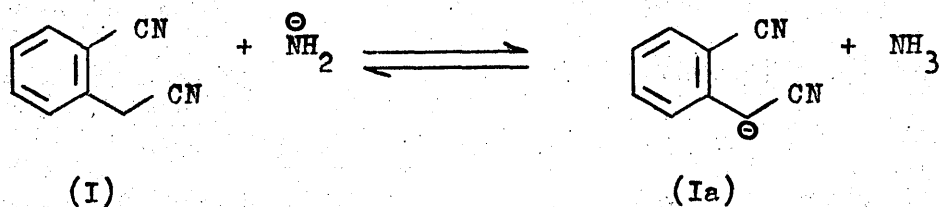


STRUCTURAL IDENTIFICATION OF THE PRODUCTS.

i) 1-Amino-4-cyano-3-(o-cyanobenzyl)isocouinoline (XIV).--

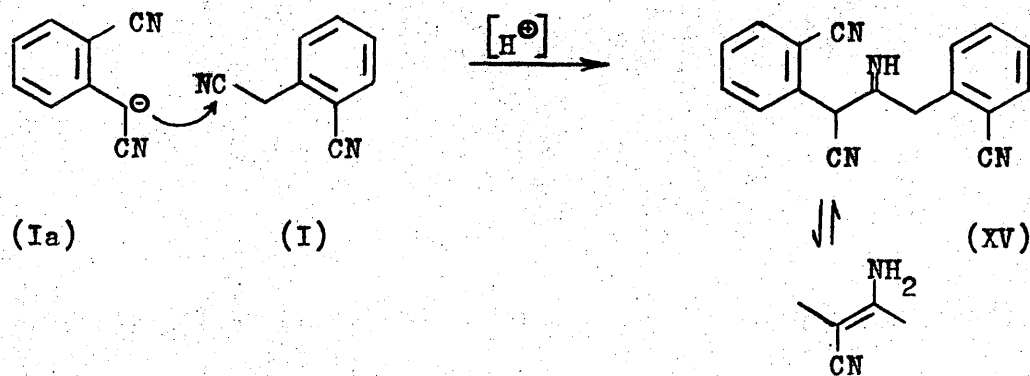
(XIV)

When o-cyanobenzyl cyanide (I) was treated with sodamide in formamide at room temperature, colourless prisms of a product A, $C_{18}H_{12}N_4$, separated from the solution. As the molecular weight of this compound was confirmed by mass spectrometry to be exactly twice that of (I), it was clear that the starting material had undergone dimeric addition, as the result of sodamide functioning as a base and abstracting a proton from (I) to form the anion (Ia).

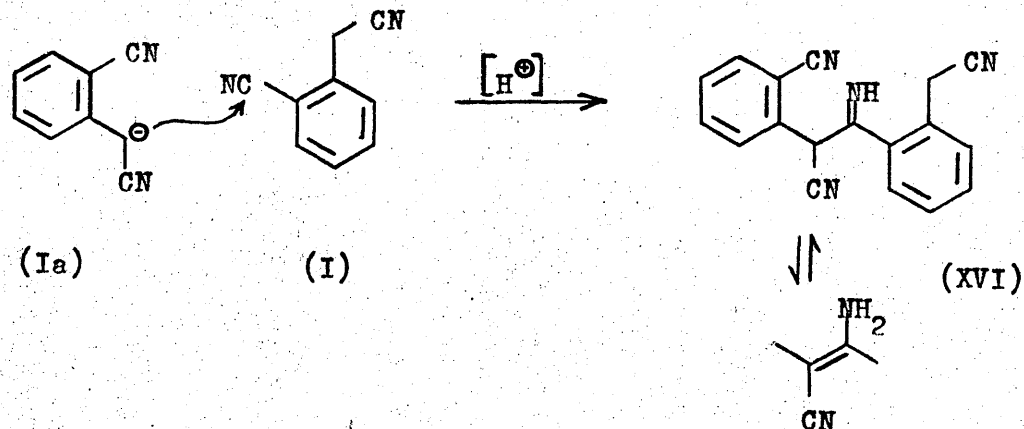


Attack by (Ia) across the alkyl nitrile of a molecule of (I) would lead to the structure (XV), while attack on the aryl nitrile of (I) would form (XVI).

Attack on the alkyl nitrile :



Attack on the aryl nitrile :

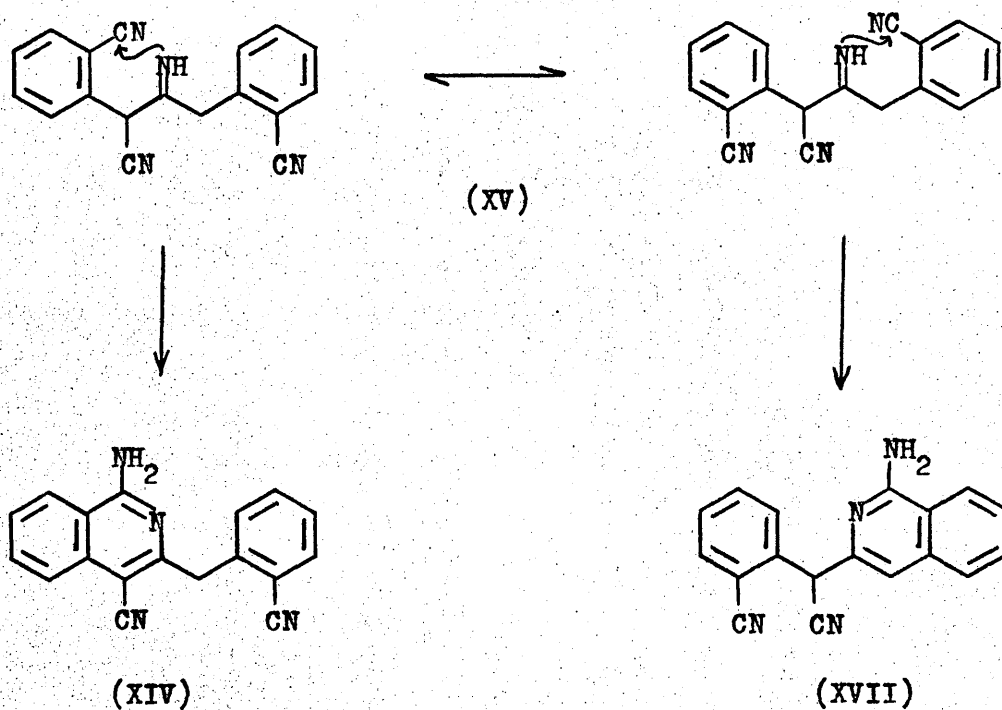


The i.r. spectrum of A showed that neither of the structures (XV) and (XVI) was correct for A. Although absorptions corresponding to asymmetric and symmetric stretching vibrations of a primary amino group were observed at 3450 and 3348 cm^{-1} , nitrile stretching frequencies at 2226 and 2206 cm^{-1}

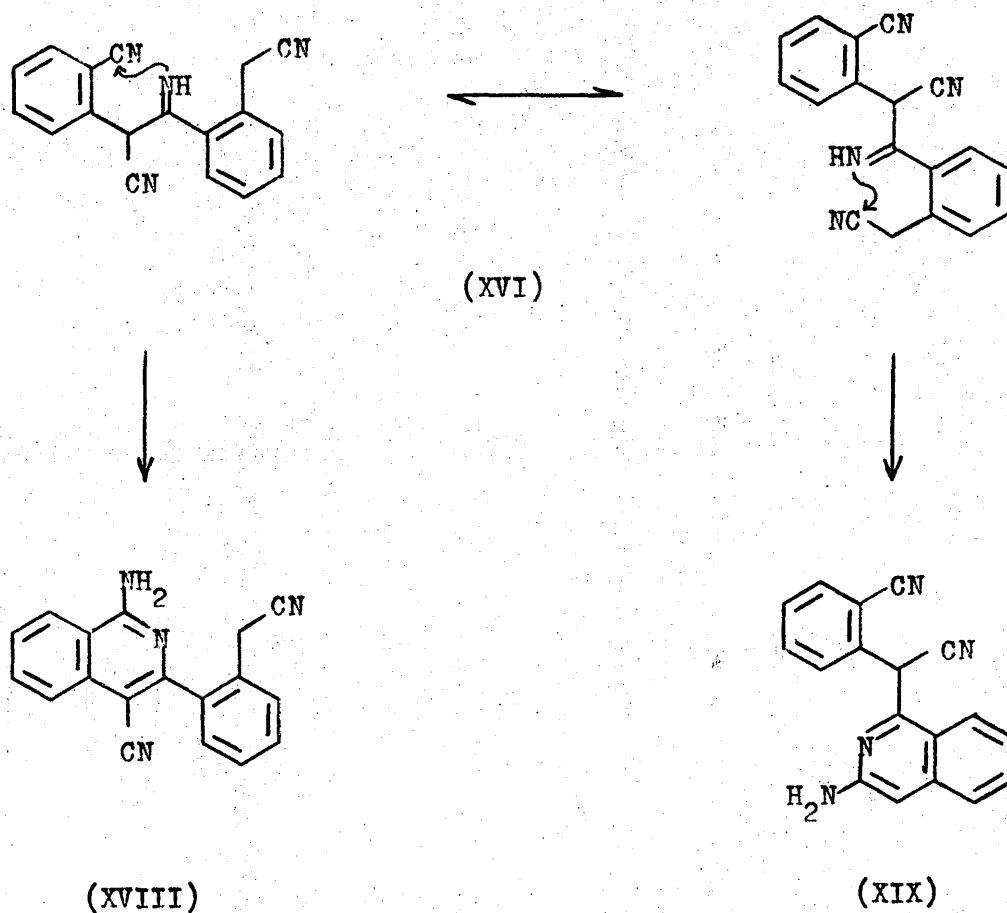
indicated the presence of only two nitrile groups in the molecule. A strong absorption at 1653 cm^{-1} could most reasonably be assigned to a ring skeletal vibration and a broadened peak at 3200 cm^{-1} was attributed to the stretching mode of an intermolecularly bonded NH_2 group. A similar bonded NH_2 peak is observed in the spectrum of (IV)⁵. It was therefore apparent that cyclization had occurred after addition. Both structures (XV) and (XVI), in basic conditions, could be expected to undergo cyclization. The resulting structures are given in Scheme II.

SCHEME II

i) Possible Structures for A from Cyclization of (XV).



ii) Possible Structures for A from Cyclization of (XVI).



Saturated alkyl nitriles typically absorb¹³ in the region 2260-2240 cm^{-1} and the alkyl nitrile of (I) absorbs within this range at 2250 cm^{-1} . While there are factors which cause the frequency of alkyl nitriles to lie below this range²¹, they are not relevant to the structure (XVIII) which should therefore absorb at a frequency close to that found for (I). As the observed frequencies for the nitrile groups of A occurred

well below 2240 cm^{-1} , structure (XVIII) was discounted as possible for A.

Table II gives the p.m.r. spectrum of A with assignments which indicated structure (XIV).

TABLE II

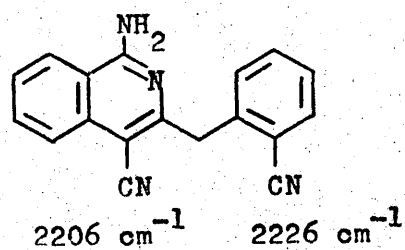
Solvent : d_6 Dimethyl sulphoxide.

<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
5.58	singlet	2	methylene CH_2
2.8-1.9	complex	7	ring protons
2.13	broadened singlet ^{a)}	2	NH_2
1.66	doublet (showing finer splitting), J_0 <u>ca.</u> 8.5 Hz	1	8-H

a) Removed on addition of D_2O .

It was immediately obvious that both structures (XVII) and (XIX) were incompatible with the p.m.r. spectrum as neither could account for the 2-proton methylene signal at 5.58τ . It was concluded that the product A was 1-amino-4-cyano-3-(o-cyanobenzyl)-isoquinoline, (XIV).

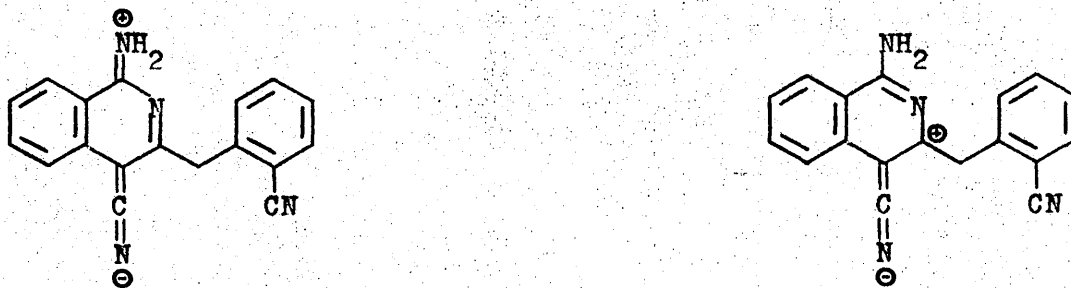
The i.r. absorption frequencies for the nitrile groups of (XIV) are assigned as below.



The 2226 cm^{-1} frequency lies in the typical range for aryl nitriles; 2240-2220 cm^{-1} whereas the second frequency is abnormally low. The explanation for this would appear to be the same as that given by Baldwin²² for the low frequencies observed for the nitrile absorptions of β -amino- α , β -unsaturated nitriles. Thus significant contributions to the structure from charge-separated resonance forms (Scheme III) are thought to effect the observed lowering of the nitrile frequency in (XIV).

SCHEME III

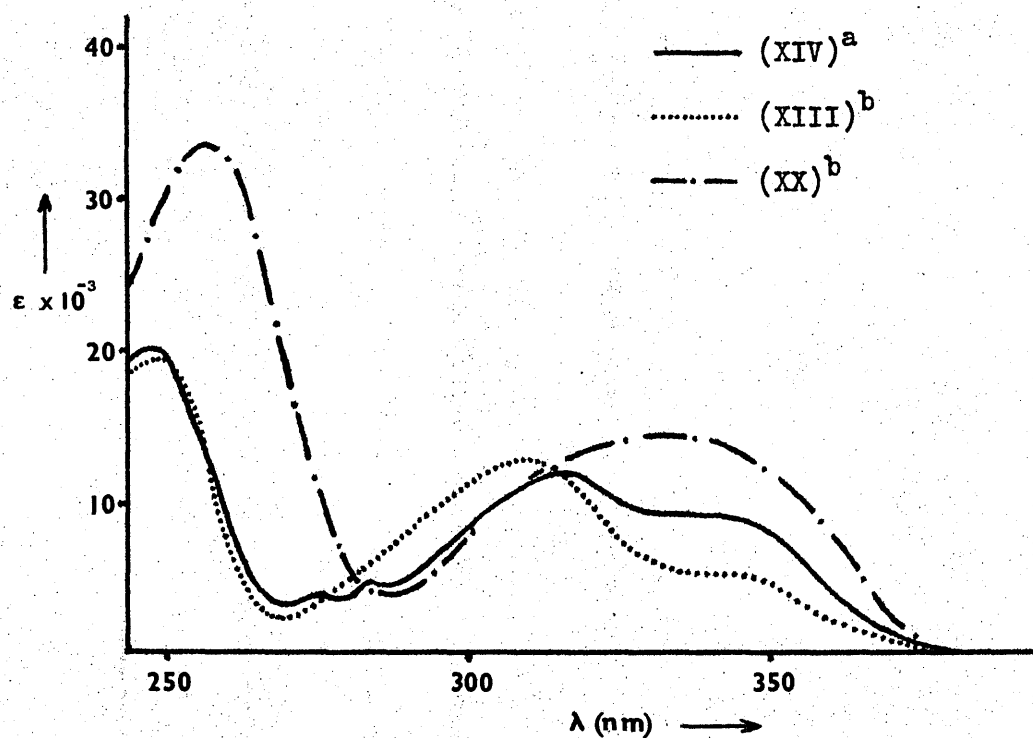
Charge-separated resonance forms of the Structure (XIV).



The u.v. absorption curve for A (Fig.I) confirmed the isoquinoline structure (XIV) by its correspondence to the absorption envelopes of similarly substituted isoquinoline compounds.

FIGURE I

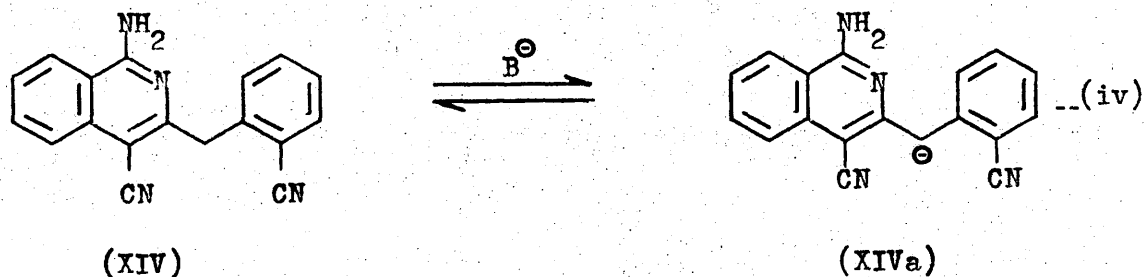
U.v. absorption curves for (XIV) and known, related isoquinolines.



a) in tetrahydrofuran.

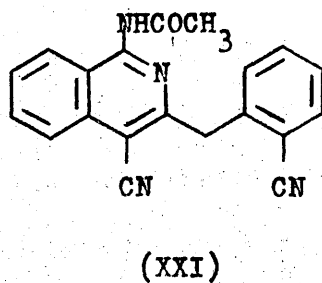
b) in ethanol.

Compound (XIV) contains an active methylene group and in basic solution could be expected to be in equilibrium with its anion (XIVa).



That this anion did not attack another molecule of (I) was attributed to steric interference. Internal cyclisation of (XIVa) across either of the nitrile groups required the formation of a strained 4-membered ring and was apparently energetically unfavourable. Consequently (XIV) reacted no further and as the strong base NH_2^\ominus gradually converted to NH_3 during the reaction, the equilibrium (iv) evidently moved to the left until the reaction solution was saturated with (XIV) and precipitation of the product occurred.

Additional evidence for the presence of a primary amino group in (XIV) was obtained by the preparation of the monoacetyl derivative (XXI).



The i.r. spectrum of (XXI) showed a broadened single absorption at 3280 for the NH stretching frequency of a bonded secondary amide, two nitrile stretching frequencies at 2222 and 2212, the amide I band at 1674 as a shoulder on the strong isoquino-line skeletal vibration at 1663 and the amide II band at 1523 cm^{-1} . The p.m.r. spectrum confirmed the structure (XXI) and is given in Table III.

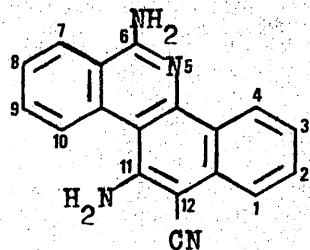
TABLE III

P.m.r. spectrum of (XXI).

Solvent: d_6 Dimethyl sulphoxide.

<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
7.94	singlet	3	acetyl $-\text{CH}_3$
5.36	singlet	2	methylene $-\text{CH}_2$
2.8-1.8	complex	7	ring protons
1.65	doublet (showing finer splitting), J_0 ca. 8.5 Hz	1	8-H
-0.8	broad singlet ^{a)}	1	NH

a) Removed on addition of D_2O .

ii) 12-Cyano-6,11-diaminobenzo(c)phenanthridine (XXII).-

(XXII)

After collection of (XIV), addition of water to the reaction filtrate caused the precipitation of a small yield of yellow needles of a product B, which was shown by mass spectrometry and elemental analysis to have the same molecular formula, $C_{18}H_{12}N_4$, as (XIV).

The i.r spectrum of B showed NH stretching absorptions at 3448, 3426, 3356 and 3344 and a single nitrile stretching absorption at 2189 cm^{-1} . These spectral observations suggested that addition of NH_3 to a nitrile in (XIV) had occurred, followed by a cyclization and elimination. However, a sensible structure cannot be arrived at in this way and, additionally, the p.m.r. spectra of B (Table IV) preclude structures for B derived from (XIV).

TABLE IV

P.m.r. spectra of (XXII).

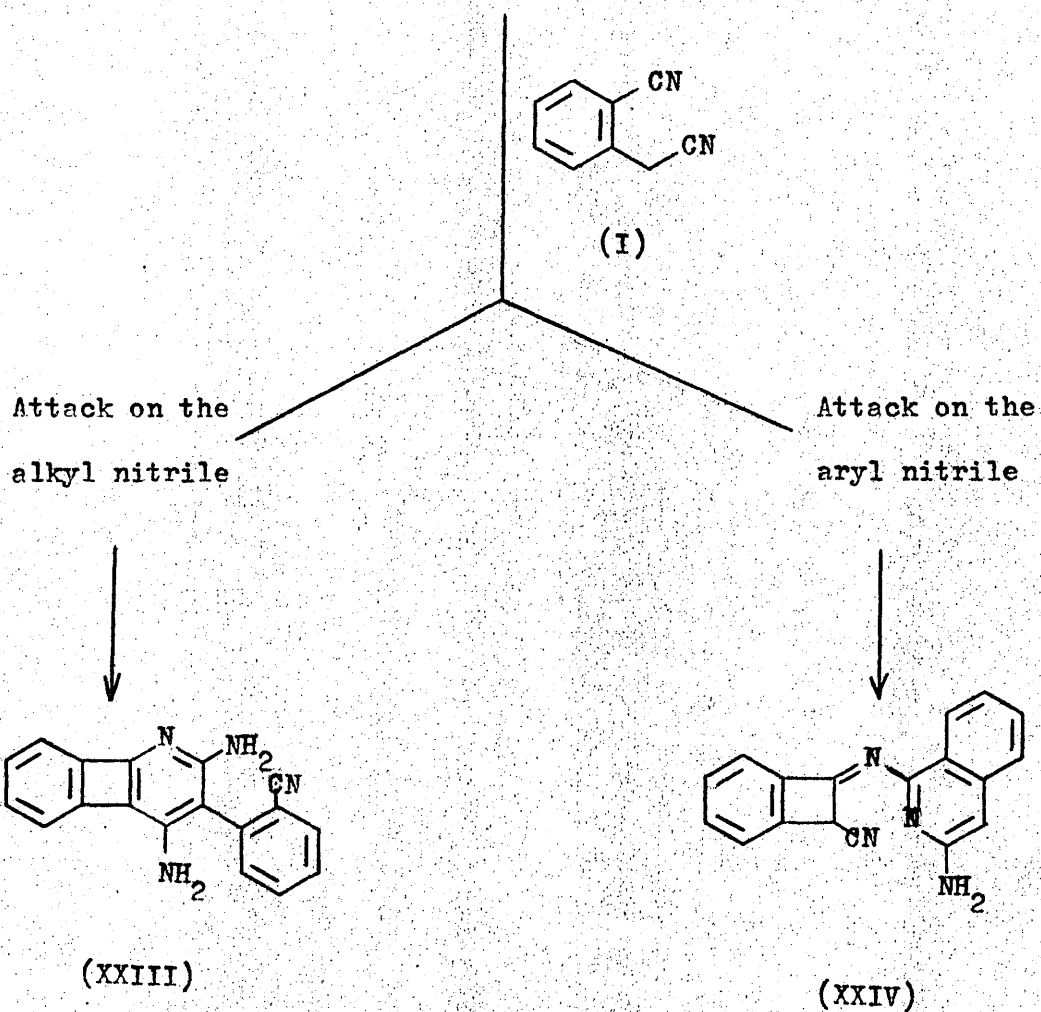
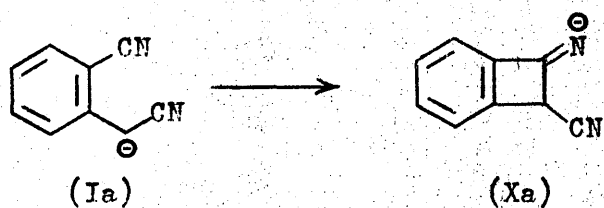
i) Solvent : Dimethyl sulphoxide.

<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
3.60	broad singlet	2	11-NH ₂
2.8-2.0	complex	7	1,2,3,8 and 9-H and 6-NH ₂
1.55	double doublet, \underline{J}_o ca.8.5, \underline{J}_m ca.3 Hz	1	7-H
1.04	doublet (showing finer splitting), \underline{J}_o ca.8.5 Hz	1	4-H
0.93	double doublet, \underline{J}_o ca.8.5, \underline{J}_m ca.3 Hz	1	10-H

ii) Solvent : Dimethyl sulphoxide/D₂O.

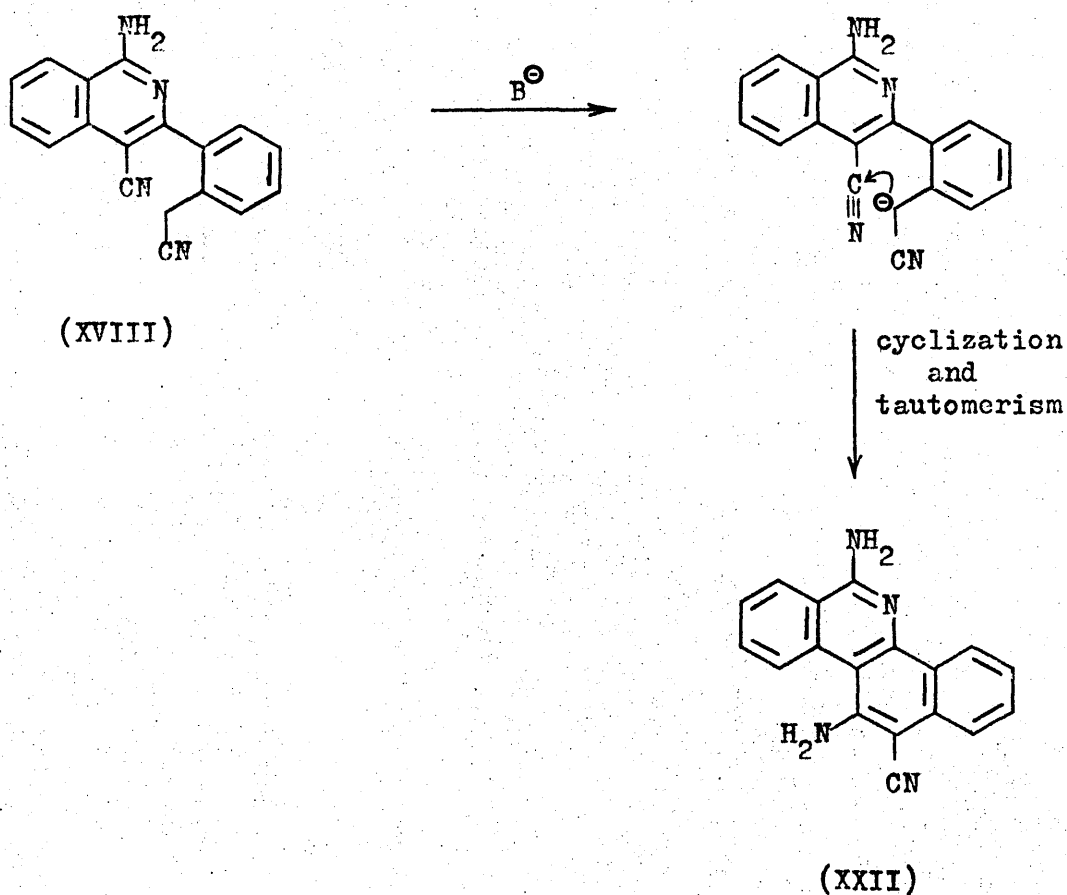
2.8-2.0	complex	5	1,2,3,8 and 9-H
1.57	double doublet	1	7-H
1.05	doublet (showing finer splitting), \underline{J}_o ca.8.5 Hz	1	4-H
0.95	double doublet, \underline{J}_o ca.8.5, \underline{J}_m ca.3 Hz	1	10-H

Another possibility for the formation of B was that (I) had undergone cyclization to the anion (Xa) and subsequently attacked another molecule of (I) across the alkyl or aryl nitrile. Such reaction would have led to either (XXIII) or (XXIV).



Compound (XXIII) was discounted because the nitrile group in this structure should have given rise to a stretching frequency in the i.r. lying inside the range $2240-2220\text{ cm}^{-1}$ while the observed frequency for B was at 2189 cm^{-1} . The p.m.r. spectrum of B showed four labile protons: (XXIV) has only three and so was not the structure of B.

Examination of the possible structures for A (p. 25) revealed that one of them, (XVIII), could easily cyclise further in basic medium.



The structure (XXII) is compatible with the p.m.r. spectrum of B (Table IV). In addition, the NH frequencies observed in

the i.r. spectrum at 3448, 3356 and 3426, 3344 cm^{-1} correspond to the asymmetric and symmetric stretching frequencies of the two NH_2 groups. The same reasoning as that given to explain the low nitrile frequency of (XIV) (p. 28) applies to the low nitrile frequency of (XXII).

The u.v. envelopes of 1,2-benzophenanthridine (XXV) and chrysene (XXVI) are very similar²³ (fig. II) so structure (XXII) could be expected to have a light absorption envelope which corresponded with that of a similarly substituted chrysene. An acceptable model for (XXII) was therefore 6-acetyl-12-aminochrysene (XXVII)²⁴ and there is indeed a reasonable correspondence between the absorptions of these two compounds (fig. III). The difference of ca. 20 cm^{-1} between the absorption maxima of the two compounds is possibly due to the greater bathochromic effect of the acetyl over the nitrile group as observed in the pair, acetophenone and benzonitrile²⁵.

The low yield of (XXII) relative to that of (XIV) can be explained by considering the alkyl nitrile to be more susceptible to nucleophilic attack than the aryl nitrile of (I). As the formation of (XXII) and (XIV) are competing reactions, the rate of production of (XIV) would then be greater than that of production of (XXII).

FIGURE II²³

Ultraviolet absorption spectra of 1,2-benzophenanthridine (XXV) (—) and chrysene (XXVI)(----) in ethanol.

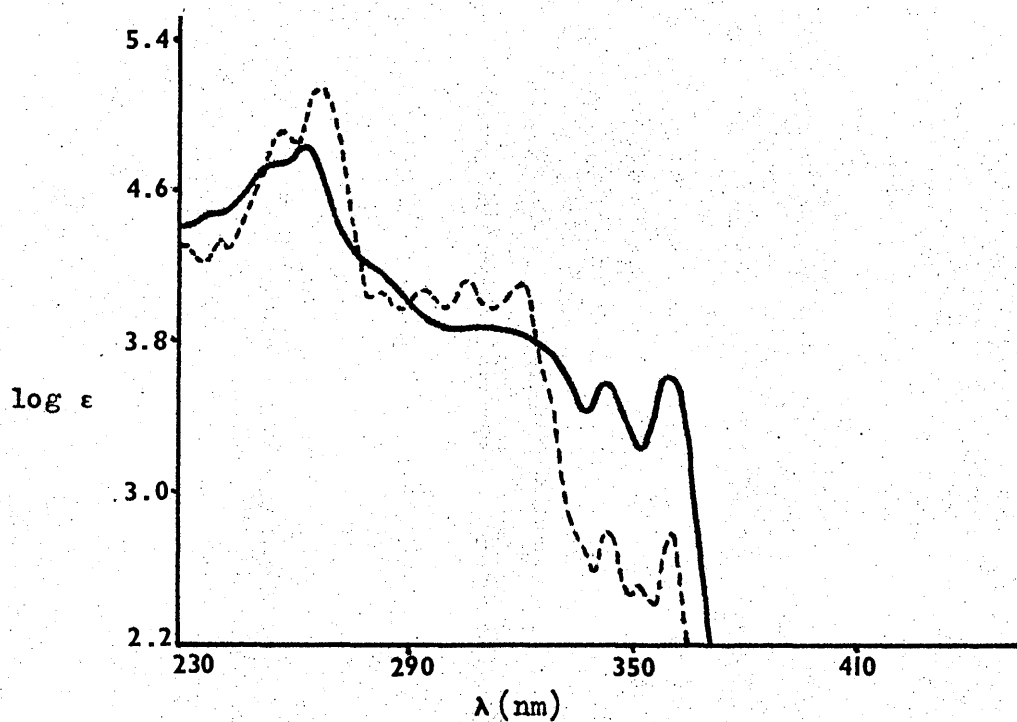
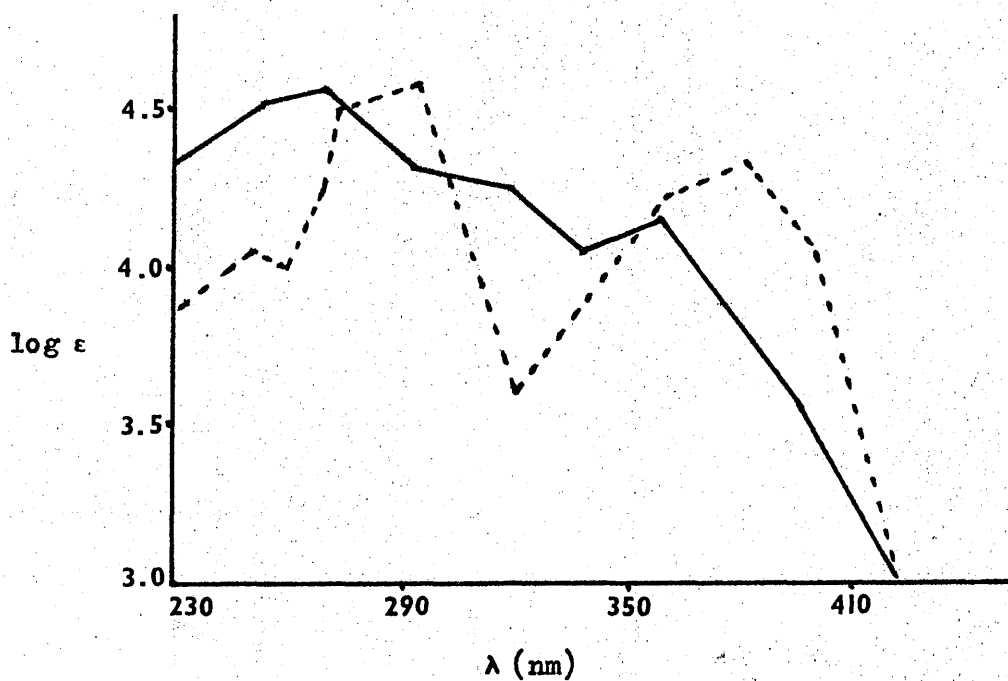
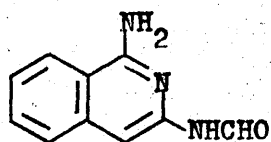


FIGURE III

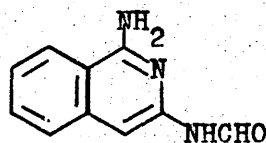
Ultraviolet absorption spectra of 12-cyano-6,11-diaminobenzo(c)-phenanthridine (XXII)(—) and 6-acetyl-12-aminochrysene (XXVII)²⁴ (----) in ethanol.



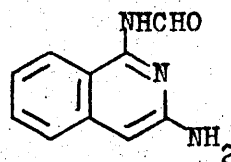
iii) 1-Amino-3-formamidoisoquinoline (XIII).-

(XIII)

Addition of more water to the reaction filtrate after isolation of the products (XIV) and (XXII) yielded a colourless product C, $C_{10}H_9N_3O$ which on base hydrolysis gave the known 1,3-diaminoisoquinoline (IV). Compound C was therefore a monoformyl derivative. After successive recrystallisations, C was obtained as a mixture of clusters of small needles and long splinters which showed separate m.p.s of $207-208^\circ$ and 217° . An unusual degree of complexity was observed in both the i.r. and p.m.r. spectra. Exactly the same spectral characteristics were observed for the product C, prepared by the monoformylation of (IV). Whilst it could be expected that, in at least one of these two very different preparations, a single monoformyl derivative might be produced, nevertheless it was possible that each gave a mixture and that successive recrystallisations were not separating the two compounds, 1-amino-3-formamido- and 3-amino-1-formamido-isoquinoline, (XIII) and (XXVIII).



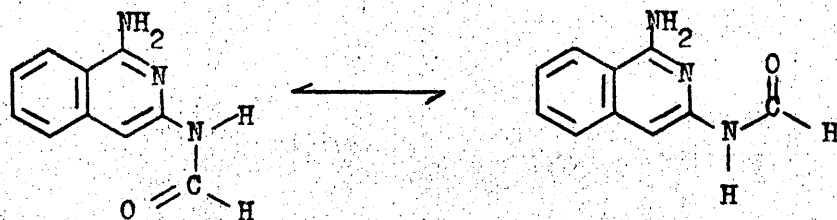
(XIII)



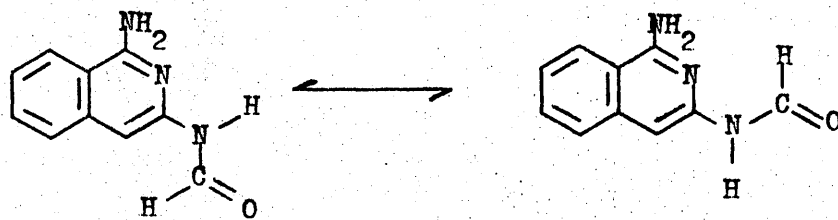
(XXVIII)

The p.m.r. spectrum of C (fig. IV) shows amino group signals at 3.05 and 3.24 τ of unequal intensity. This suggested either a mixture of the monoformyl derivatives (XIII) and (XXVIII), or possibly, a mixture of cis- and trans-isomers of one monoformyl derivative. Now the 1-amino and 3-amino signals in the p.m.r. spectrum of 1,3-diaminoisoquinoline (IV) in dimethylsulphoxide occur at 3.58 and 4.77 τ respectively⁵. Structure (XXVIII) was therefore unlikely because neither of the observed amino group signals for C corresponded with the expected 3-amino signal position.

The structure of C was fully determined by comparison of the p.m.r. spectra of C and formanilide (XXIX). The unexpected complexity of the p.m.r. spectrum of (XXIX) was satisfactorily explained, by Randall and coworkers²⁶, as a consequence of the existence of cis- and trans-formamido isomers in the solution. Extension of this concept to (XIII) gives the isomers



cis-(XIII)

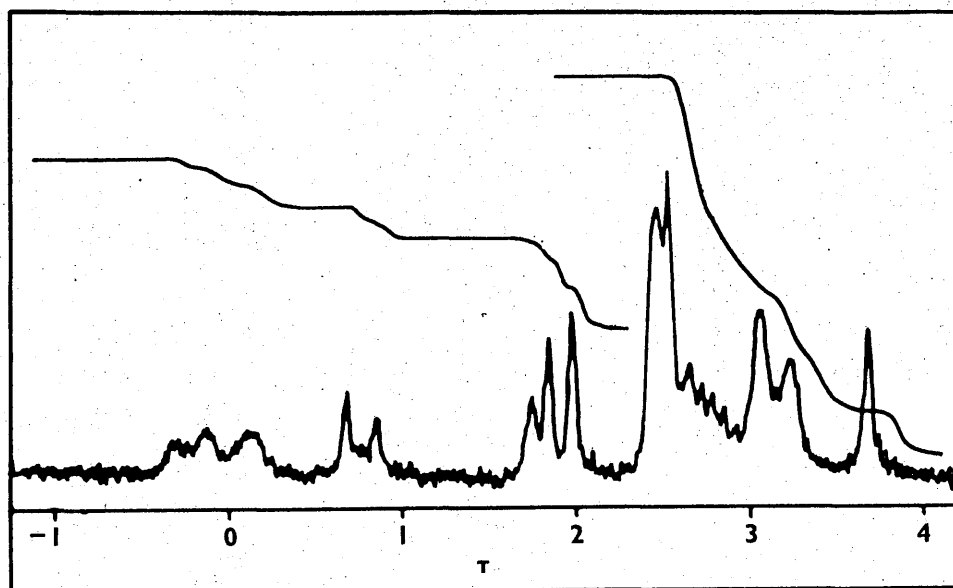


trans-(XIII)

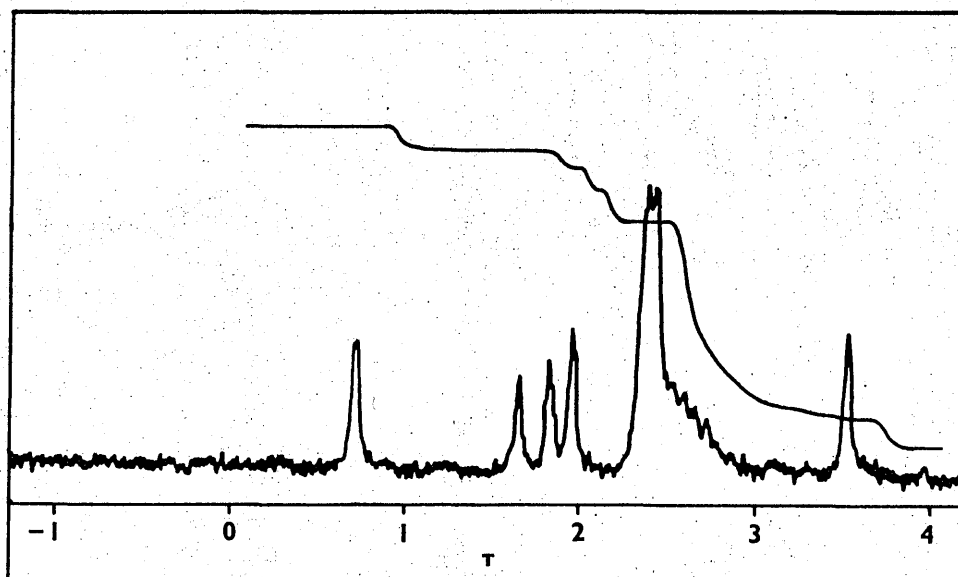
FIGURE IV

Proton magnetic resonance spectra of 1-amino-3-formamido-isoquinoline (XIII).

a) Solvent : d_6 dimethylsulphoxide.



b) Solvent : d_6 dimethylsulphoxide-deuterium oxide.



Randall et al. found that the trans-formyl and-NH protons of (XXIX) were coupled with a large coupling constant ($J=11.2$ Hz) and their signals occurred at lower field than the corresponding cis-protons which showed only a small coupling (J ca.0.2 Hz). These features were immediately obvious in the spectrum of (XIII), the coupling of the formyl protons disappearing in dimethylsulphoxide / deuterium oxide solvent. In addition, the carbonyl group in the cis-form would be expected to deshield the 4-proton whereas in the trans-form, the 4-proton would be expected at higher field near the value (4.10 τ) observed for (IV)⁵. The positions of the two 4-protons were as predicted, that in the cis-isomer under the aromatic complex (2.9 to 2.3) and that from the trans-isomer at higher field 3.67 τ . The amino group of the trans-isomer was assigned the lower field signal of the two by comparison of the integrals with those of peaks already assigned.

Best agreement between calculated and observed p.m.r. results was obtained by considering C as (XIII) existing in ca. 60% of the trans-form. The results are given in Table V.

The p.m.r. spectrum showed the presence of cis- and trans-forms of (XIII) in solution and the complexity of the i.r. spectrum of a nujol mull of (XIII) was strong evidence for the same isomerism existing in the condensed phase. In particular, the two strong absorptions at 1675 and 1650 cm^{-1} were most readily assigned as the amide I bands of the two isomers. Isomerism also provided a reason for the observed double

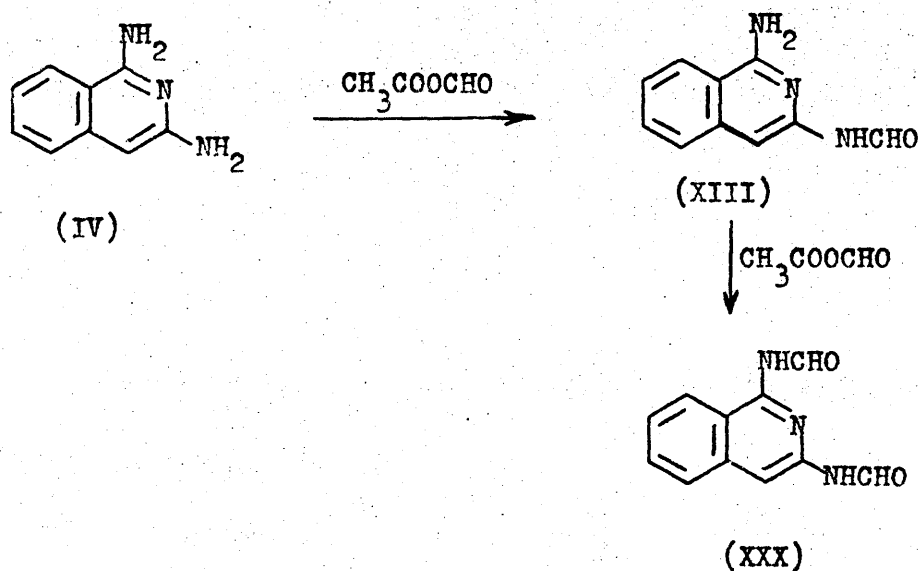
melting point and crystal form.

TABLE V

Signal assignments for the p.m.r. spectrum of (XIII) in d_6 dimethylsulphoxide and comparison of the found and calculated integral values for a mixture of 60% trans- and 40% cis-isomers.

<u>Assignment</u>	<u>τ</u>	<u>Multiplicity</u>	<u>Found Intensity</u>	<u>Calc. Intensity</u>
<u>trans</u> 4-H	3.67	singlet	0.6	0.6
<u>cis</u> NH ₂	3.23	broad singlet	0.8	0.8
<u>trans</u> NH ₂	3.05	broad singlet	1.0	1.2
<u>cis</u> 4,5,6 & 7-H and <u>trans</u> 5,6 & 7-H	2.9-2.3	complex	3.6	3.4
<u>cis</u> & <u>trans</u> 8-H	1.89	doublet (showing finer splitting), J_o ca. 8.5 Hz	1.0	1.0
<u>cis</u> formyl H	1.74	broad singlet	0.4	0.4
<u>trans</u> formyl H	0.76	doublet, J 11.2 Hz	0.7	0.6
<u>cis</u> NH	0.13	broad singlet	0.4	0.4
<u>trans</u> NH	-0.22	broad doublet, J 11.2 Hz	0.5	0.6

Under more vigorous conditions than those used to obtain (XIII) from (IV), 1,3-diformamidoisoquinoline (XXX) was obtained.



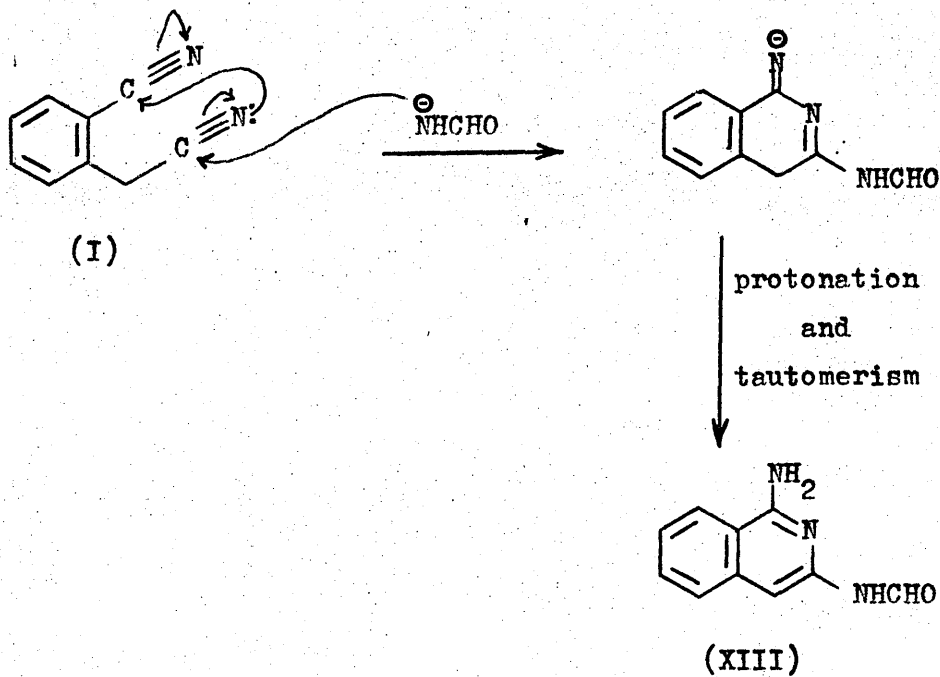
Again, the complexity of the p.m.r. spectrum of (XXX) indicated cis-trans-isomerism but the number of possible isomers for this diformamido product and the overlapping of signals made assignment of the individual signals largely impossible.

The identification of C as (XIII) established three points : i) The equilibrium (i)(p. 20) was reasonably established during the course of the reaction.

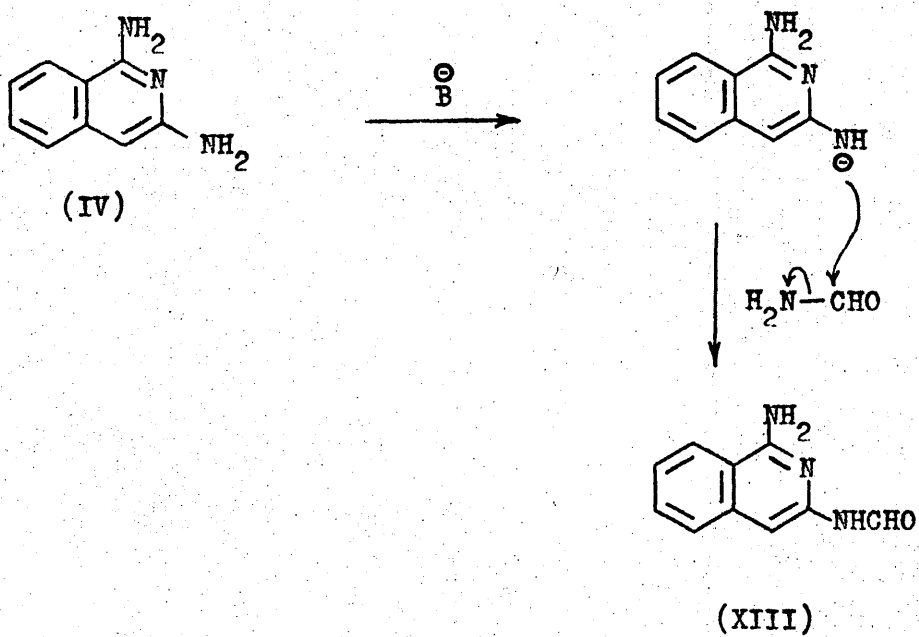
ii) The formamido anion was not sufficiently basic to remove the α -hydrogen of (I) and so cause dimerisation.

iii) The formamido anion was sufficiently strong a nucleophile to attack the alkyl nitrile of (I) and in so doing confirmed that the alkyl nitrile was more susceptible to nucleophilic attack than the aryl.

The above assertions rest on the mechanism of formation of (XIII) being

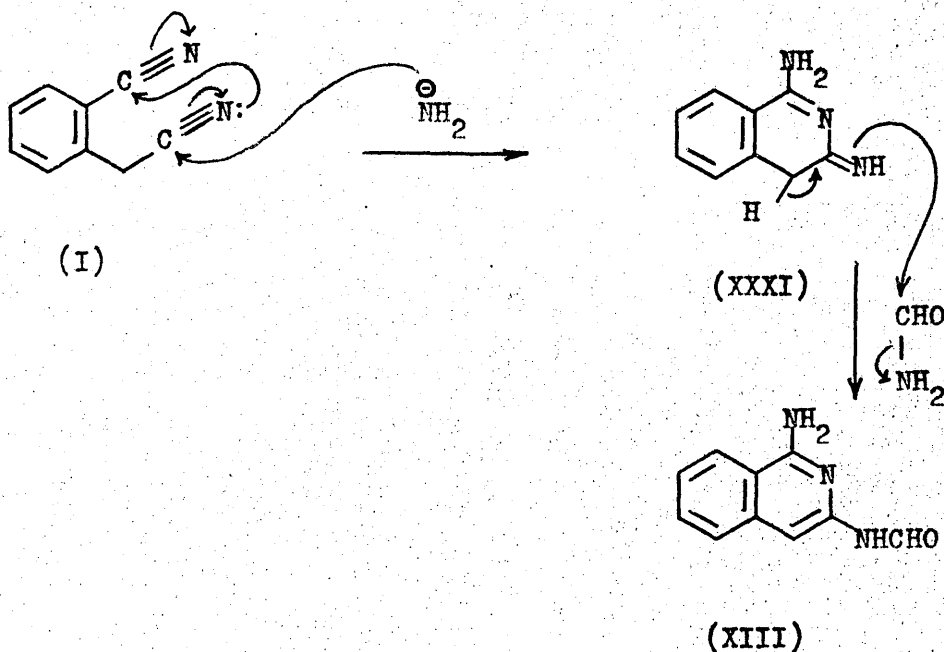


That (XIII) was not obtained by attack of (IV) on the formamide solvent under basic conditions



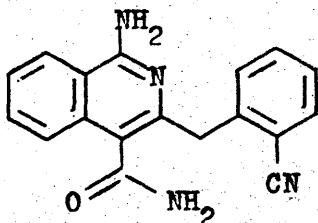
was demonstrated by recovering (IV) unchanged after reaction with sodamide in formamide for 6 hours at room temperature.

The only other possibility was that attack of the amide anion on (I) gave the amino-imine (XXXI) which rather than tautomerise to (IV) attacked a formamide molecule to yield (XIII):



This mechanism was believed unlikely as it would have to compete with the facile tautomerism of (XXXI) to (IV) and so at least some of compound (IV) should have been obtained. However, none was isolated.

iv) 1-Amino-4-carbamoyl-3-(o-cyanobenzyl)isoquinoline (XXXII).--



(XXXII)

On one occasion, after collection of the precipitated product (XIV), addition of water to the reaction filtrate caused the separation of colourless plates of the incidental hydrolysis product (XXXII), $C_{18}H_{14}N_4O$. A single nitrile stretching frequency in the i.r. spectrum at 2224 cm^{-1} showed that it was the 4-nitrile of (XIV) which had been hydrolysed to amide. The structure (XXXII) was confirmed by the p.m.r. spectrum which is given with assignments in Table VI.

From the p.m.r. spectral results it was clear that the amide C-N bond exhibited partial double bond character²⁷, restricting rotation so that the two amido protons gave rise to separate signals. The proton cis to the carbonyl group was deshielded and absorbed at lower field than the trans-proton (cf. (XIII)). On deuteration of the compound by exchange with deuterium oxide, the signal from the cis-proton disappeared as expected but even on addition of a trace of base (triethylamine) a vestige of the trans-signal remained.

It seemed possible that specific solvation of (XXXII) in dimethylsulphoxide resulted in steric crowding

such that this proton was resistant to exchange.

TABLE VI

P.m.r. spectrum of (XXXII). Solvent : d_6 Dimethylsulphoxide.

<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
5.56	singlet	2	methylene CH_2
3.24	approx. double doublet	1	Ar-H
2.96 ^{a)}	singlet	2	NH_2
2.8-2.3	complex	5	ring protons
2.16	approx. double doublet	1	5-H
1.76	doublet (showing finer splitting), J_0 ca. 8.5 Hz	1	8-H
0.65 ^{b)}	broad singlet	1	<u>trans-NH</u>
-0.18 ^{a)}	broad singlet	1	<u>cis-NH</u>

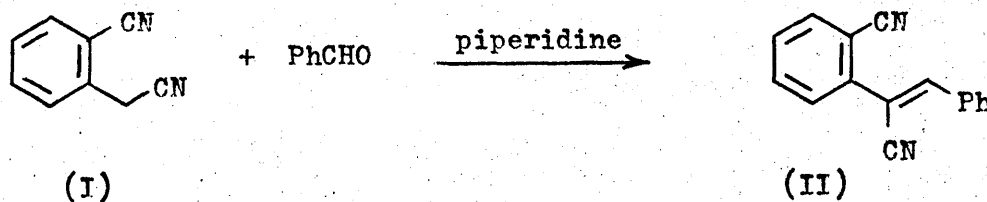
a) Removed on deuteration.

b) Partially removed on deuteration.

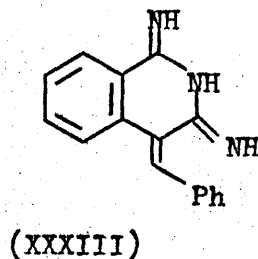
CHAPTER II

REACTION OF o- α -DICYANOSTILBENE WITH AMMONIA AND WITH SODAMIDE IN FORMAMIDE.

The ease of abstraction of a proton from the α -carbon to the nitrile results in o-cyanobenzyl cyanide (I) undergoing Knoevenagel condensations with aldehydes. Thus (I) condenses with benzaldehyde, in the presence of a base catalyst, to yield o- α -dicyanostilbene (II)⁹.



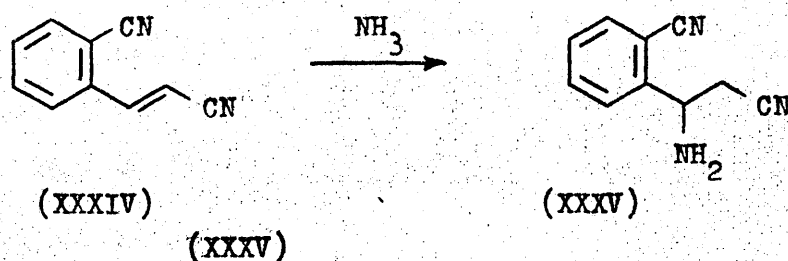
Addition of ammonia across both nitrile groups of (II) with subsequent cyclization and elimination of ammonia would form the imidine (XXXIII).



The reaction of methanolic ammonia with (II) under pressure was reported^{10a} as giving inconclusive results, the reaction proceeding almost completely to an intractable tar. When this reaction was reexamined under less vigorous conditions, equally disappointing results were obtained. In all cases, the reaction yielded either tar, or a mixture of tar and starting material.

As the dinitrile (II) did not contain labile α -hydrogens to the nitrile groups, it could not undergo dimerization analogously to (I) by reaction with sodamide in formamide. It was therefore feasible that, under mild conditions, sodamide in formamide should react cleanly with (II) to give the imidine (XXXIII), by addition of the amide anion (NH_2^-) across the nitrile groups.

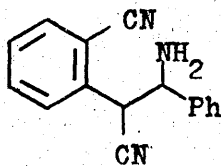
Now, Elvidge and Jones²⁹ found that treatment of *o*-cyanocinnamitrile (XXXIV) with methanolic ammonia in a Carius tube gave largely intractable material but also a poor yield of a product (XXXV) which resulted from addition of ammonia, not across either nitrile group, but across the carbon-carbon double bond.



Isolation of (XXXV) suggested that conjugation with a nitrile group and the benzene ring, rendered the olefinic

group of (XXXIV) more susceptible than either nitrile group to nucleophilic addition. However, the validity of this supposition could only be determined by identification of the major reaction, leading to tar. The vigorous conditions employed in the reaction may have caused polymerization of a product initially formed by addition of ammonia across either or both nitrile groups.

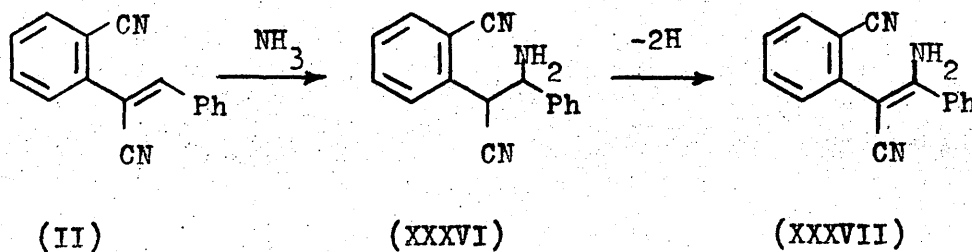
The presence of an α, β -unsaturated nitrile moiety in (II) meant that behaviour similar to that observed for compound (XXXIV) could be expected. Hence an alternative product to the imidine (XXXIII), from the reaction of (II) with sodamide in formamide, was the compositional isomer (XXXVI).



(XXXVI)

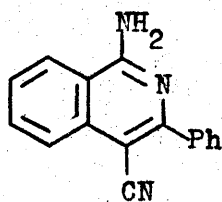
When (II) was treated with sodamide in formamide at room temperature, the product, D, which separated as colourless needles from solution after several days, had a composition $C_{16}H_{11}N_3$. This corresponded to addition of NH_3 and loss of $2H$. The mass spectrum confirmed that the molecular weight was 245 and as this was two less than the molecular weight of (XXXIII) or (XXXVI), the reaction had afforded neither of the predicted products. Evidently the primary product of addition of ammonia had undergone dehydrogenation in the basic medium. Whilst the imidine (XXXIII) could not reasonably eliminate a hydrogen

molecule, the isomer (XXXVI) might have done so to yield the stilbene (XXXVII).



An i.r. spectrum (nujol mull) of D showed absorptions at 3546, 3357 and 3218 cm^{-1} corresponding to NH_2 asymmetric and symmetric stretching and bonded NH stretching vibrations respectively. But the appearance of only one nitrile stretching absorption at 2193 cm^{-1} and a strong absorption at 1642 cm^{-1} , most readily assigned as an aromatic ring skeletal vibration, ruled out (XXXVII) as the structure of D.

A further possible structure for D, compatible with the i.r. data, was (XX).



(XX)

This also adequately accounted for the low nitrile frequency in the i.r. spectrum of D. The explanation is that already given for (XIV) (see p. 28).

The presence of an NH_2 group was confirmed by the broad 2-proton singlet at 4.15 τ in the p.m.r. spectrum. This signal was removed on shaking the solution with deuterium oxide. The remaining 9 protons gave rise to a complex multiplet (unchanged after D_2O shake) between 2.7 and 1.7 τ .

Confirmation that (XX) was the correct structure for D was provided by the similarity of the u.v. absorption curve to that for 4-cyano-1-ethoxy-3-phenylisoquinoline (LX) (Ch. VI). The absorption maxima with extinction coefficients are given in Table VII.

TABLE VII

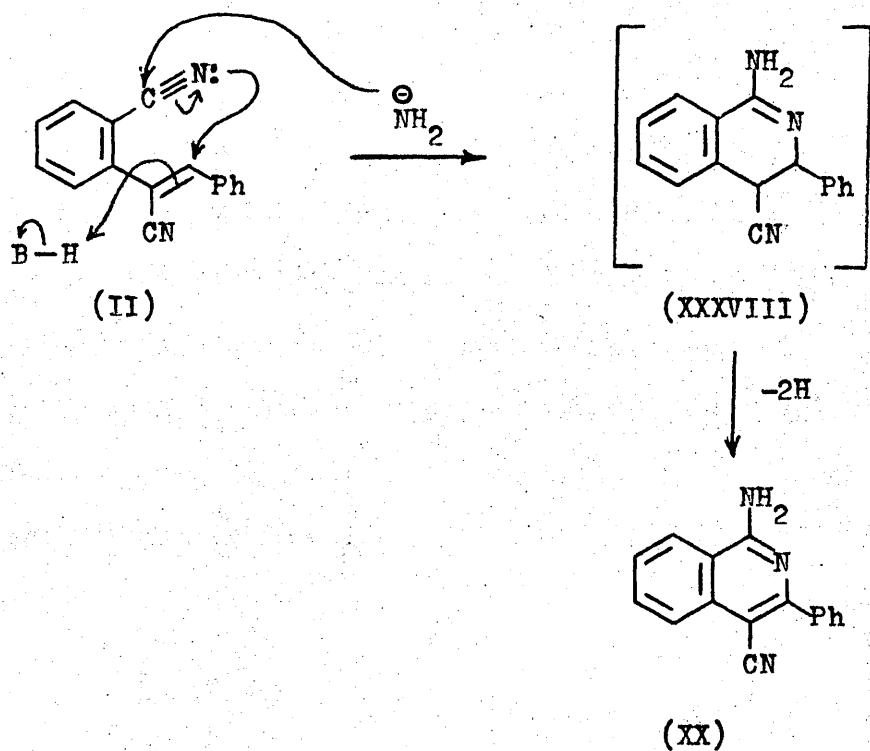
Compound	λ max(nm) ($\epsilon \times 10^{-3}$)		
(XX)	217 (33.9)	257 (33.4)	330 (14.4)
(LX)	217 (34.3)	256 (33.2)	309 (16.0)

It was therefore concluded that the product, D, was 1-amino-4-cyano-3-phenylisoquinoline (XX).

It was obvious that the aryl nitrile and the carbon-carbon double bond of (II) had been attacked in the formation of the product (XX). But from this product alone it was not possible to determine at which of these two sites on (II), initial attack by amide anion (NH_2^-) had occurred. Evidence

was obtained by examination of the reaction of (II) with methoxide in methanol. This reaction, which is discussed in Chapter VI, was shown to proceed via initial attack by methoxide on the aryl nitrile of (II) to give the dihydro intermediate (XXXIX) which dehydrogenated to (XL).

Methoxide and amide anion are similarly reactive nucleophiles, the latter being somewhat the stronger. Consequently, it was reasonable to assume a common mechanism for their reaction with (II). By analogy, therefore, the mechanism of formation of (XX) from (II) was believed to involve initial attack on the aryl nitrile of (II) by amide anion, followed by base-catalysed dehydrogenation. Despite stringent precautions to exclude oxygen from the reaction and work-up, none of the dihydro intermediate (XXXVIII) was isolated.

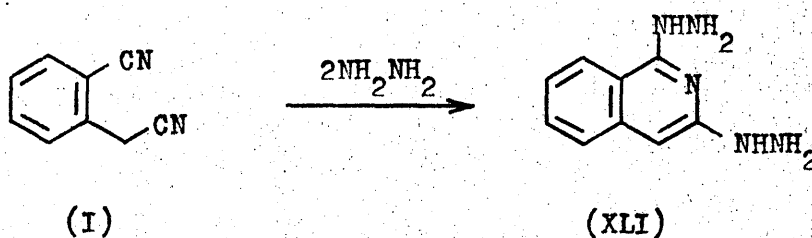


CHAPTER III

REACTION OF o-α-DICYANOSTILBENE WITH HYDRAZINE.

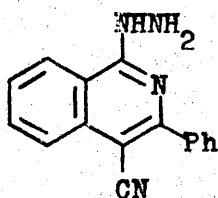
The successful reaction of o-α-dicyanostilbene (II) with sodamide (Ch. II) encouraged examination of the behaviour of other nitrogen bases towards this dinitrile.

Hydrazine, whilst unreactive in the cold, had been found sufficiently nucleophilic to yield 1,3-dihydrazinoiso-quinoline (XLI) when, in excess, it was heated under reflux in aqueous ethanol with o-cyanobenzyl cyanide (I) for several hours⁷.



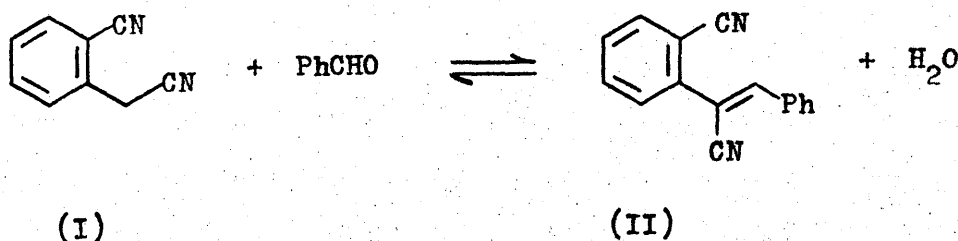
It was possible that under similar conditions, hydrazine would add to the dinitrile (II).

If hydrazine were to attack (II) in the same way as did sodamide, the product of such reaction would be 4-cyano-1-hydrazino-3-phenylisoquinoline (XLII).

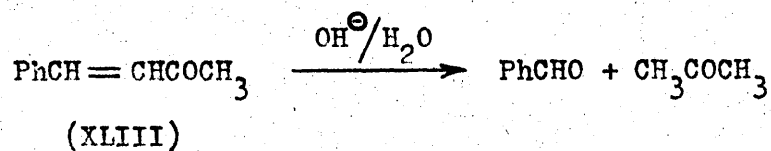


(XLII)

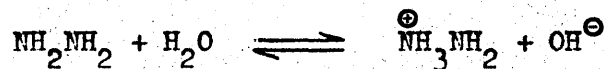
However, when the dinitrile (II) and hydrazine (4 mol) in aqueous ethanol were heated under reflux for 4 hours, o-cyanobenzyl cyanide (I) (74%) was obtained. The dinitrile (II) had evidently undergone cleavage across the olefinic function and the reaction had demonstrated the reversibility of the Knoevenagel condensation of the dinitrile (I) with benzaldehyde.



Reversal of the condensation of an active methylene with a carbonyl compound, is not uncommon. Generally, the condensation product, $\text{PhCH}=\text{CXY}$, is susceptible to base catalysed hydrolytic cleavage if at least one of X and Y is electro-negative. Thus, for example, benzylideneacetone (XLIII) gives, on alkaline cleavage, benzaldehyde and acetone³¹.



the appreciable basicity of hydrazine, was the nucleophile.



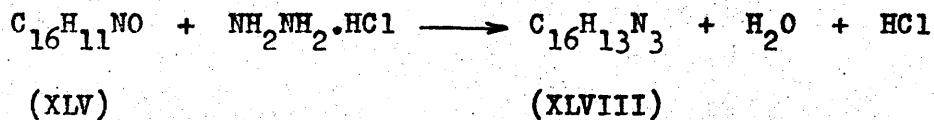
$$K_{25^\circ} = 8.5 \times 10^{-7}.$$

That hydrazine was not essential for the cleavage of (II), was demonstrated by achieving the carbon-carbon double bond rupture on boiling (II) in aqueous ethanolic sodium carbonate.

It has been shown³² that addition of acid to the reaction solution inhibits the cleavage of activated olefins. Accordingly, it was hoped that by heating the dinitrile (II) with hydrazine hydrate (2 mol) and hydrazine dihydrochloride (2 mol) under reflux, sufficient acid would have been added to the reaction medium to retard the cleavage reaction while at the same time allow hydrazine to add across the nitrile groups of (II). Certainly, when this reaction was performed, retardation of the olefinic cleavage was evident, as, after 28 hours, starting material (21%) was recovered. But isolation of the products (I) (35%) and (XLVI) (31%), (both yields calculated on reacted starting material), showed that cleavage persisted to the exclusion of attack across the nitrile groups.

It has been stated³⁵, without elaboration, that activated olefins from condensation reactions, give Michael adducts with hydrazine hydrochloride. On the other hand, the product (XLVIII), obtained when benzalcyanoacetophenone (XLV) was treated with aqueous ethanolic hydrazine hydrochloride

alone³⁴, was clear evidence that, in this case at least, condensation of the carbonyl group of (XLV) with hydrazine was the only reaction to ensue.



Nevertheless, it was considered worthwhile to treat the dinitrile (II) with hydrazine dihydrochloride alone. The attempt was abortive, as starting material (95%) was recovered after boiling an absolute ethanolic solution of (II) with hydrazine dihydrochloride (5 mol) for 48 hours. The slight solubility of hydrazine dihydrochloride in absolute alcohol could have resulted in too low a concentration of nucleophile in solution for reaction to proceed at a significant rate. Consequently, the reaction was repeated with sufficient added water to completely dissolve the salt at reflux temperature. But again, after 24 hours, starting material was recovered quantitatively.

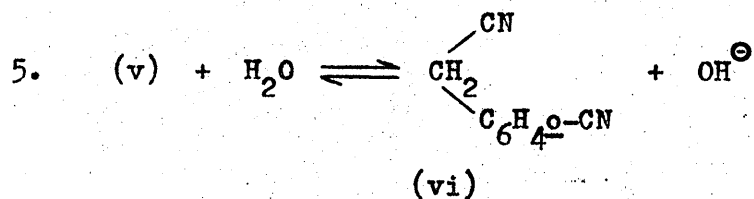
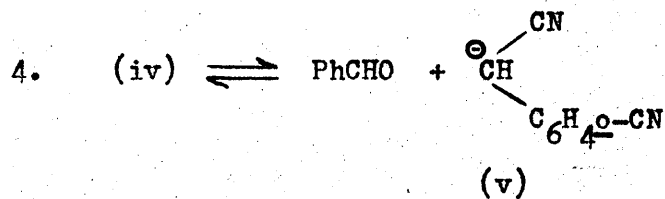
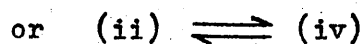
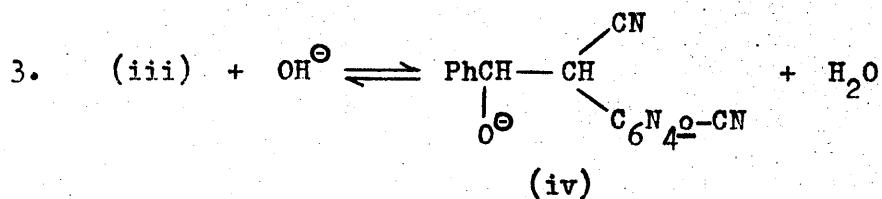
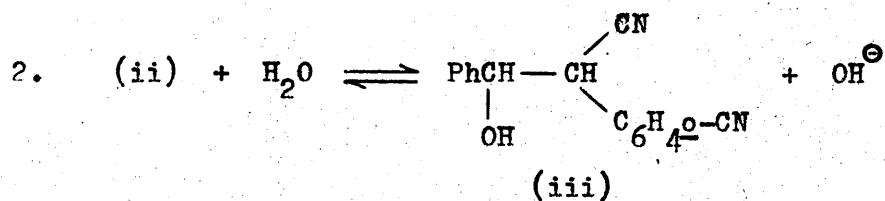
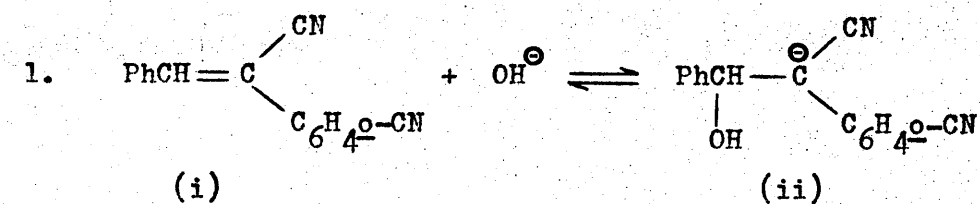
With the failure of acidic solutions to afford any reaction, further attempts to react the dinitrile (II) with hydrazine in basic media were made. There still remained the possibility that by minimising the proportion of water in the reaction medium, the cleavage reaction could be retarded and attack by hydrazine on the nitrile groups of (II) could be achieved. A 10 molar excess of hydrazine hydrate in absolute ethanol under reflux again afforded the product (I) (81%) after 2 hours. This result was somewhat surprising as

o-cyanobenzyl cyanide (I) itself had been found to react with hydrazine under these conditions³⁰. However, using hydrazine hydrate as both solvent for (II) and reagent, the product (XLI) (88%) was obtained after 2 hours at 95°.

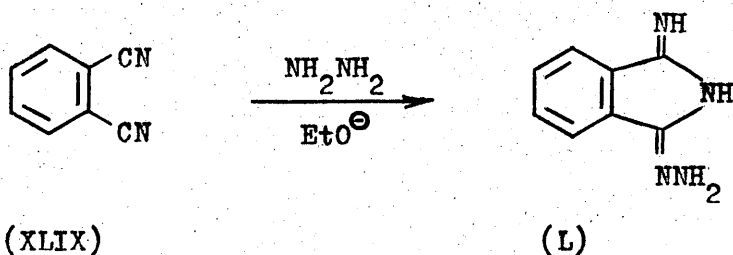
Lowering the proportion of water in the reaction still further by using 95% hydrazine, resulted in cleavage of the dinitrile (II) even in the cold. At the same time, the observation that o-cyanobenzyl cyanide (I) was not attacked by hydrazine in the cold but required a temperature of ca. 80° for the product (XLI) to be obtained, led to an alteration in the experimental procedure in an attempt to achieve rapid attack by hydrazine on the nitrile groups of (II). It was hoped that by adding the dinitrile (II) in small portions to 95% hydrazine at 80° and heating the solution under reflux (ca. 140°) for 1 hour, the initial conditions would be sufficiently energetic for nitrile addition to occur at a competitive rate to olefinic cleavage. Disappointingly, no product of such attack was obtained, but isolation of the product (XLI) (64%) showed that cleavage had occurred.

SCHEME IV

Mechanism for the hydroxide catalysed cleavage of o-α-dicyanostilbene (II).



It had been found³⁶ that, whereas phthalonitrile (XLIX) was unreactive towards hydrazine hydrate in boiling ethanol, addition of sodium ethoxide as catalyst caused an immediate vigorous reaction with formation of 3-hydrazono-1-iminoisoindoline (L).

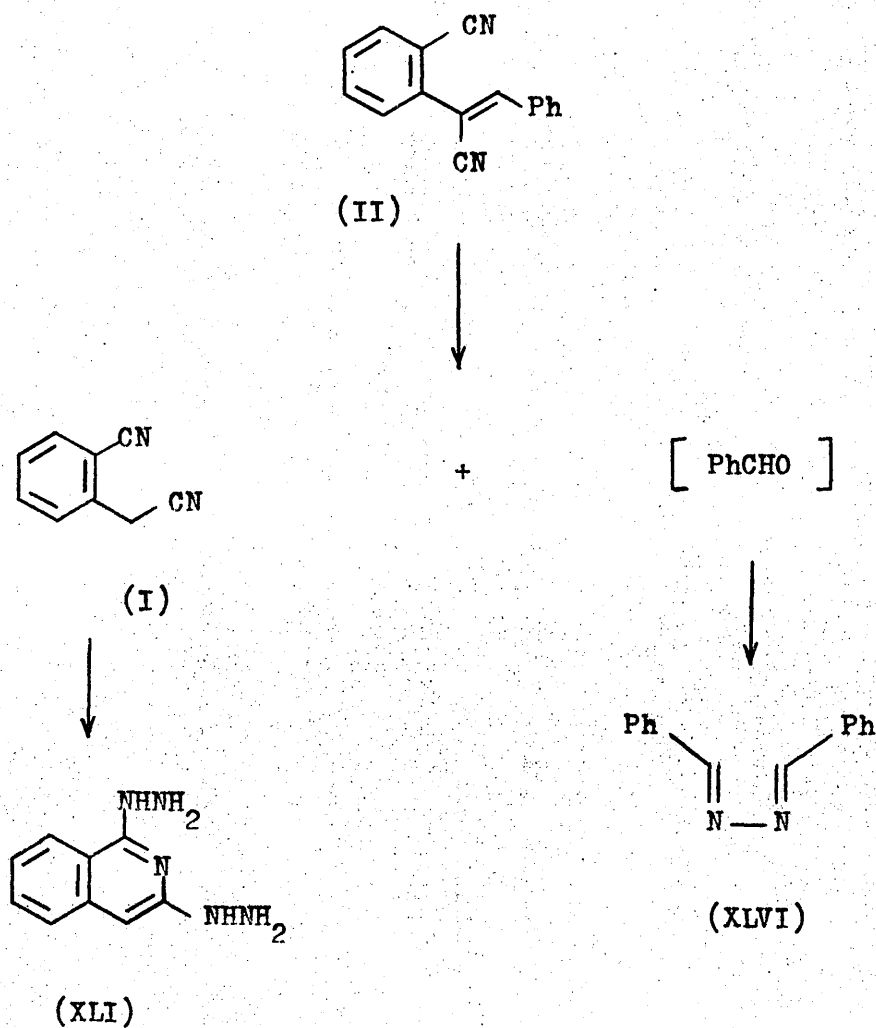


A final attempt to effect hydrazine attack on the nitrile groups was therefore made by adding the dinitrile (II) in small portions to 95% hydrazine at 50° to which a catalytic amount of sodium methoxide had been added, and heating the solution at 60° for 2 hours. Again, the cleaved product (XLI) (37%) was obtained together with a trace amount of a product E, m.p. 241°-243°, of which there was only sufficient to obtain an i.r. and a mass spectrum. A parent peak of 327 in the mass spectrum made it difficult to envisage the product as resulting solely from hydrazine addition to the dinitrile (II), though absorptions in the i.r. at 3340, 1644 and 1615 cm⁻¹ and absence of nitrile absorption were good evidence that attack by hydrazine on the nitrile groups had occurred. Perhaps a more reasonable suggestion for the formation of E was that *o*-cyanobenzyl cyanide (I), formed in the reaction, underwent dimerization, in the presence of the strong base, methoxide, (c.f. reaction of

(I) with sodamide), and the product thus formed reacted further with hydrazine to yield the unidentified compound E.

SCHEME V

Products from the reaction of α - α -dicyanostilbene (II) with hydrazine.



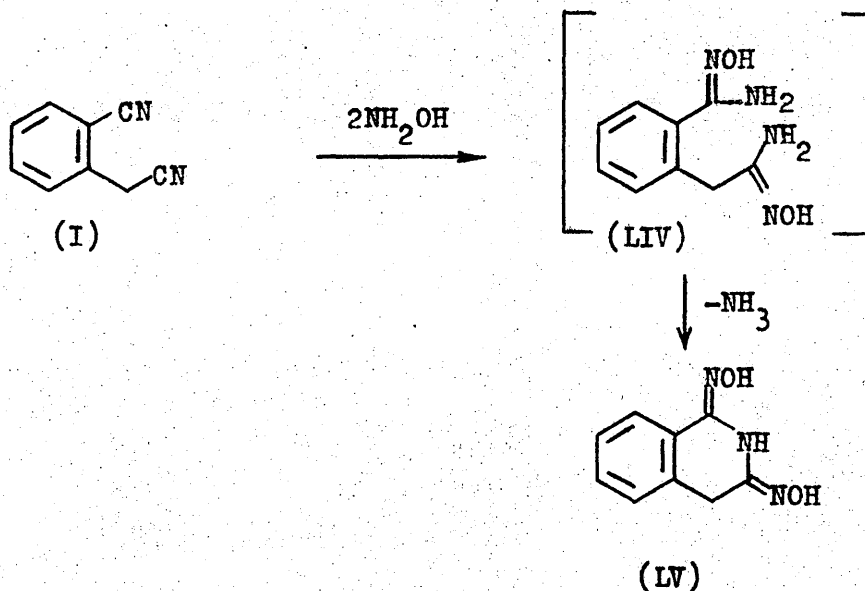
CHAPTER IV

REACTION OF o- α -DICYANOSTILBENE WITH HYDROXYLAMINE.

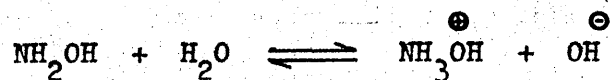
The results described in the previous chapter, concerning the reaction of hydrazine with o- α -dicyanostilbene (II), clearly indicated the instability of the ethylenic function of this dinitrile in basic media. It was obvious that cleavage of the carbon-carbon double bond of (II) could be expected in attempted nucleophilic additions of other nitrogen bases across the nitrile groups of (II). Further, achievement of nucleophilic attack across the nitrile groups of the compound (II) was the more difficult because conjugation of both the nitrile groups to unsaturated moieties, lowered their susceptibility to nucleophilic attack. The problem was, therefore, to employ reagents which maintained high nucleophilic power under conditions which retarded ethylenic cleavage.

Now, it is known that hydroxylamine is an exceptionally powerful nucleophile towards nitriles³⁸. Recent confirmation of this generalization was found in the reaction of o-cyanobenzyl cyanide (I) with hydroxylamine under mild

acid conditions⁶, in which both nitriles were attacked to form the (non-isolated) bisamidoxime intermediate (LIV) which rapidly cyclised to the dioxime (LV).



However, despite this high nucleophilicity, hydroxylamine is a weak base, weaker than hydrazine, and as it had already been confirmed (p. 57) that reduction in the basicity of the reaction medium retarded olefinic cleavage of (II), it was believed that conditions could be found for successful addition of hydroxylamine across the nitrile groups of (II) without the olefinic function of (II) being ruptured.



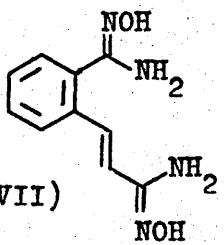
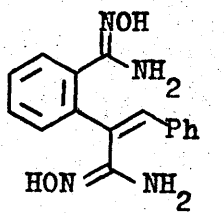
$$K_{25}^{\circ} = 6.6 \times 10^{-9}$$

Indeed, when the dinitrile (II) was heated under reflux with hydroxylamine (4 mol) in aqueous ethanol for

27 hours, the product F, which separated as colourless prisms on cooling, had a composition, $C_{16}H_{16}N_4O_2$, corresponding to the addition of 2 moles of hydroxylamine. A mass spectrum confirmed that the M.W. was 296, and absence of nitrile stretching frequencies in an i.r. spectrum was evidence that both nitrile groups of the compound (II) had been attacked. In addition, absorption frequencies at 3420 and 3330 (NH_2); 3245br (OH); 1675, 1640 (aryl amidoxime I and II bands²⁹), and 1668, 1630 cm^{-1} (α,β -unsaturated amidoxime I and II bands) provided good evidence that the product F was the bisamidoxime (LVI).

Further evidence that structure (LVI) was correct for F was furnished by the similarity of the u.v. absorption curves for the bisamidoxime (LVII) of o-cyanotranscinnamonnitrile²⁹ and the product F (Table VIII).

TABLE VIII

Bisamidoxime	λ max (nm)	$\epsilon \times 10^{-3}$
a)  (LVII)	310 222	8.4 15.6
b)  (LVI)	321 230	7.0 13.2

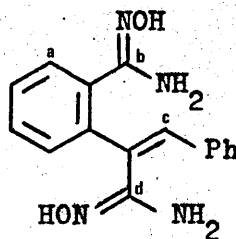
a) in methanol.

b) in ethanol.

A p.m.r. spectrum of F in dimethylsulphoxide

(Table IX) confirmed the bisamidoxime structure (LVI) for F.

TABLE IX



(LVI)

Solvent : Dimethylsulphoxide.

<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
4.73	broad singlet	1	c-H
4.37	broad singlet	2	b-NH ₂
3.14	broad singlet	2	d-NH ₂
3.0-2.6	multiplet	9	b-NOH and 8 ring protons
2.4	multiplet	1	a-H
0.64	broad singlet	1	d-NOH

Solvent : Dimethylsulphoxide / deuterium oxide.

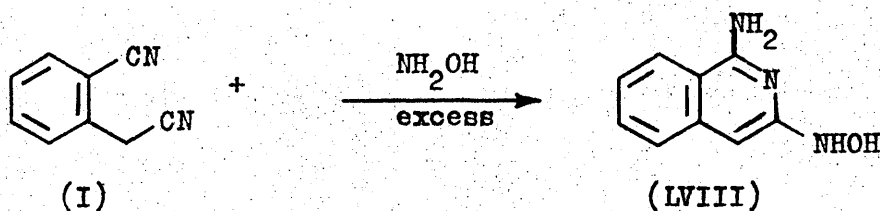
4.73	broad singlet	1	c-H
3.0-2.5	multiplet	8	8 ring protons
2.35	multiplet	1	a-H

The protons of the α , β -unsaturated amidoxime group of (LVI) were believed to be deshielded to a greater extent than those of the aryl amidoxime group owing to their proximity to the two aromatic rings. Additionally, the aryl amidoxime group lay in the shielding region of the carbon-carbon double bond whereas the protons of the α , β -unsaturated amidoxime group would be deshielded by the olefinic function.

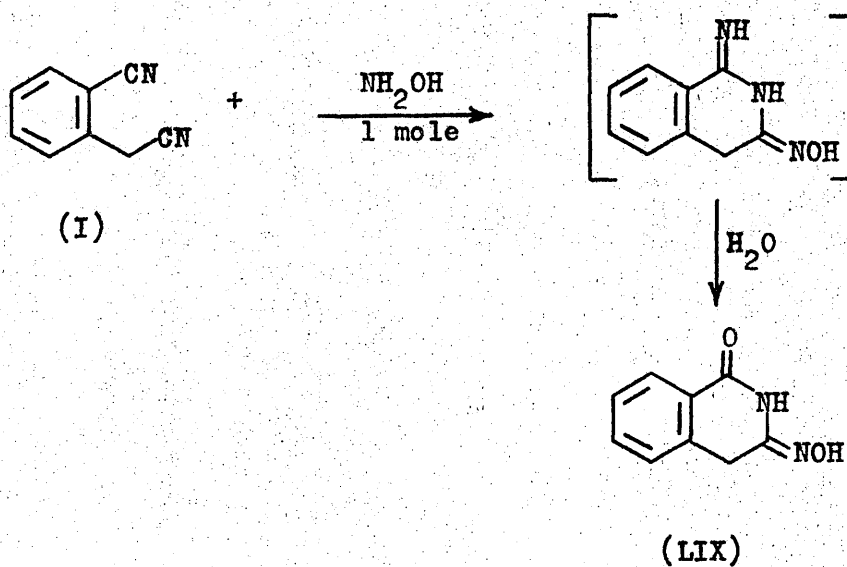
Reduction in the reaction time brought about a corresponding decrease in yield of the bisamidoxime (LVI) and, as in no case was a product from hydroxylamine attack on only one nitrile group of (II) isolated, it was believed that the rates of addition of hydroxylamine to each nitrile group were comparable.

It was hoped that by increasing the reaction time, a cyclic product would be obtained by a condensation between the amidoxime groups of (LVI). When an aqueous ethanolic solution of the dinitrile (II) and hydroxylamine (3 mol) in the presence of an excess of sodium hydrogen carbonate was heated under reflux for 12 hours, kept overnight (18 hours) at ca. 15° , and heated under reflux for a further 6 hours, almost colourless flakes of a product G (30%) were obtained. The product G had a composition $C_9H_8N_2O_2$, and a mass spectrum confirmed the M.W. as 176. It was apparent that cleavage of the olefinic group of (II) had occurred and, in the light of the previous reaction which yielded the bisamidoxime (LVI), this result was initially puzzling. The possibility existed that the excess of sodium hydrogen carbonate had increased the

polarity of the reaction medium and that such conditions enhanced the carbon-carbon double bond cleavage to yield initially benzaldehyde and *o*-cyanobenzyl cyanide (I) which then reacted with hydroxylamine to yield the product G. But Elvidge and coworkers^{29,6} had already shown that in the presence of excess hydroxylamine under conditions similar to those in the present reaction, *o*-cyanobenzyl cyanide (I) afforded 1-amino-3-hydroxyaminoisoquinoline (LVIII), i.e. not the product G.



However, earlier work³⁹ had shown that reaction of the dinitrile (I) with hydroxylamine (1 mol) gave homophthalimide-3-oxime (3-hydroximino-1-oxo-1,2,3,4-tetrahydroisoquinoline) (LIX).



Now this structure (LIX) had the correct composition for the product G and the i.r. absorptions of G at 3200br (OH); 1644s and 1582 (imidoxime I and II bands); and 1665s cm^{-1} (lactam C=O) were compatible. Hence it seemed that in the present reaction, the dinitrile (II) had first undergone olefinic cleavage to the product (I) and benzaldehyde. Rapid reaction of benzaldehyde with hydroxylamine to the oxime had then lowered the hydroxylamine concentration, to approximate the conditions under which formation of (LIX) was preferred to (LVIII).

Doubts that the product G was identical with the compound (LIX) arose from comparison of the melting points. Whereas the monoxime (LIX) was obtained as colourless needles, m.p. 158° , the colourless flakes of G showed high stability to heat up to ca. 230° at which temperature they decomposed without melting.

As acid hydrolysis of G gave the known homophthalimide (LXII), the only reasonable alternative to the structure (LIX) for G was homophthalimide-1-oxime (LXI). A p.m.r spectrum of G (Table X) confirmed this view whilst a comparison of the p.m.r. spectra of G, homophthalimide (LXII) and the dioxime (IV) (Table XI), provided convincing evidence that the product G had the structure (LXI). The shift to lower field of the 8-proton relative to the other ring protons in all three compounds was due to the deshielding effect of the substituent in the 1-position. From the observed signals for the 8-proton of the compounds (LXII)

and (LV) it was evident that the carbonyl group exerted a greater deshielding effect on the 8-proton than did the oxime group. The closeness of the 8-proton signal values of the product G and the dioxime (LV) implied that the oxime group of G was in the 1-position i.e. that structure (LXI) was correct for the product G.

TABLE X

P.m.r. spectrum of the product G : Homophthalimide-1-oxime (LXI).

Solvent : Dimethylsulphoxide.

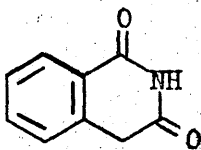
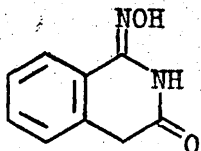
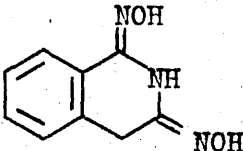
<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
6.16	singlet	2	4-CH ₂
3.0-2.4	complex	3	ring protons
2.15	doublet (showing finer splitting), <u>J ca. 8.5 Hz</u>	1	8-H
0.38	broad singlet	1	<u>NH</u>
-0.94	singlet	1	1- <u>NOH</u>

Solvent : Trifluoroacetic acid.

5.64	singlet	2	4-CH ₂
2.7-1.8	complex	4	ring protons

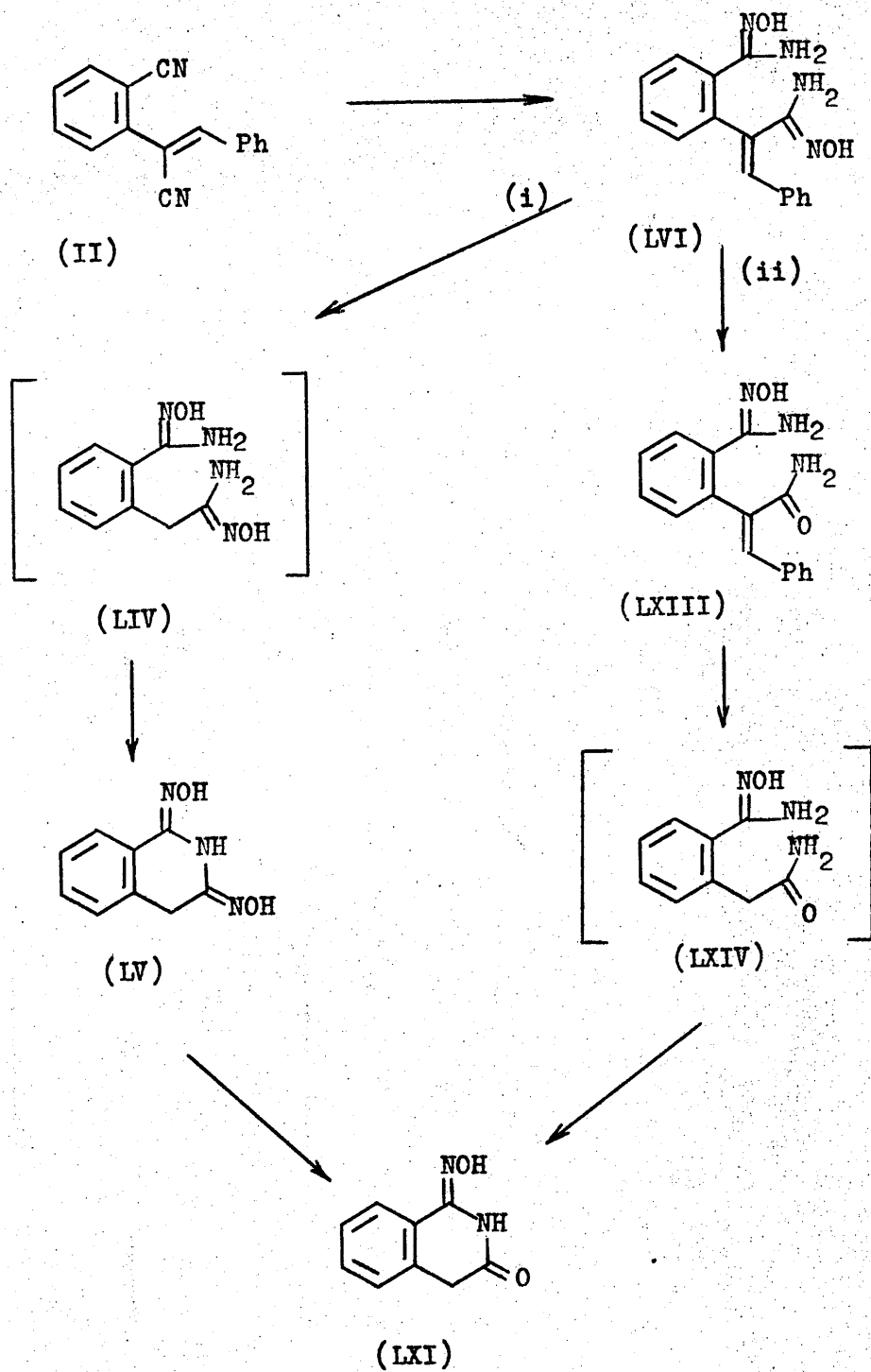
TABLE XI⁶

P.m.r. results for homophthalimide (LXII), homophthalimide-1-oxime (LXI) and homophthalimide dioxime (LV) in dimethylsulphoxide.

Compound	Signal positions (τ)				
	4-CH ₂	8-H	NH	1-NOH	3-NOH
 (LXII)	5.98	1.96	-1.2	-	-
 (LXI)	6.16	2.15	0.38	-0.94	-
 (LV)	6.215	2.17	1.41	-0.70	0.015

When the reaction time was reduced, the bisamidoxime (LVI) was obtained in good yield and so this product was clearly an intermediate in the formation of (LXI). Two pathways for the conversion of (II) to (LXI) were then envisaged (Scheme VI).

SCHEME VI



The bisamidoxime (LVI) itself, was found to be very stable in basic solutions. It was recovered in 84% yield after being boiled in aqueous ethanolic sodium carbonate for 3 hours. Starting material was recovered from several attempts to obtain the product (LXI) by treating the bisamidoxime (LVI) with hydroxylamine and excess sodium hydrogen carbonate at reflux temperature in aqueous ethanol. Even after 36 hours, 50% of unreacted bisamidoxime was recovered, although the gradual decrease in yield of starting material as the reaction time was increased did suggest that the expected conversion was slowly taking place. But the stability of the bisamidoxime (LVI) under these conditions was somewhat greater than would be expected from consideration of either of the above reaction pathways. From these it could reasonably be argued that conversion of (LVI) to (LXI) should proceed at least as rapidly as (II) to (LXI). However a possible reason for this not being so was thought to be the considerable dilution of the reagents occasioned by the low solubility of the bisamidoxime relative to the dinitrile (II), in ethanol.

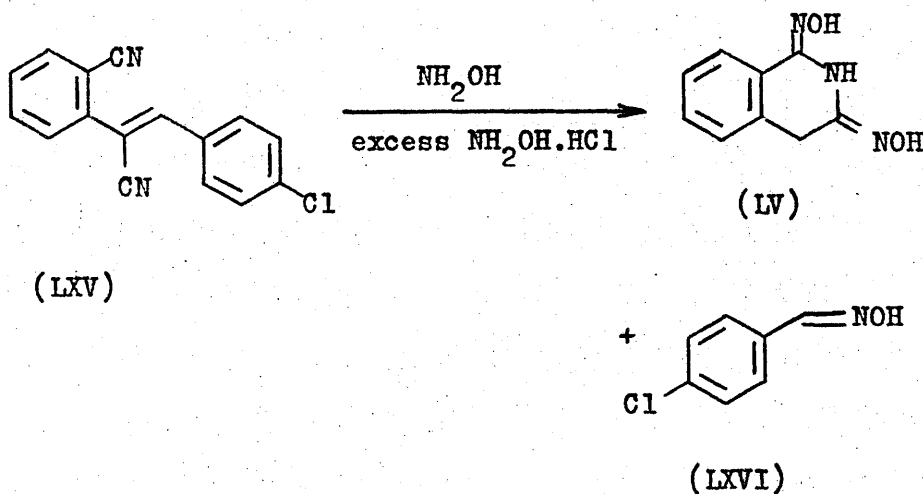
Neither of the intermediates (LV) or (LXIII) (Scheme VI) was isolated but (LV) was a known compound. Attempts to achieve its partial hydrolysis to (LXI), under similar conditions to those for the conversion of (II) to (LXI), failed. Formation of (LXI) under basic conditions was therefore believed to proceed via pathway (ii). However, when the dinitrile (II), hydroxylamine (2 mol) and hydroxylamine hydrochloride (2 mol) in aqueous ethanol were heated under

reflux for 3 hours, the yellow prisms (60%) which separated on cooling were identified as the dioxime (LV). When the reaction time was increased to 30 hours, hydrolysis of the dioxime occurred to yield the monoxime (LXI) (51%). In addition, when the bisamidoxime (LVII) and hydroxylamine hydrochloride (1 mol) in aqueous ethanol were heated under reflux for 3 hours, the dioxime (LV) (37%) was again obtained together with a quantity of tar. These results clearly indicated that the route for the reaction of the dinitrile (II) with hydroxylamine under mild acid conditions was the pathway (i) in Scheme VI.

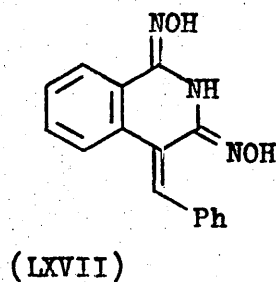
Contrary to the behaviour of the dinitrile (II), the bisamidoxime (LVI) suffered olefinic cleavage rapidly in acidic media and only very slowly in basic media. This was explained by the low electron withdrawing effect of the amidoxime group which resulted in low activation of the carbon-carbon double bond in the compound (LVI) towards nucleophilic cleavage in neutral or basic media. On the other hand, in acidic media, protonation of the amidoxime group made it powerfully electron withdrawing, with the result that the ethylenic group became highly polarized and therefore readily susceptible to addition of water and subsequent cleavage.

In those reactions where cleavage occurred to yield either of the products (LV) and (LXI), the secondary product, benzaldoxime should obviously have been obtained from reaction of initially formed benzaldehyde with the

excess hydroxylamine in the reaction media. From none of these reactions was this product isolated, a possible reason for which was thought to be the instability of this oxime in the reaction medium. However, when the p-chloro-analogue (LXV) (from reaction of o-cyanobenzyl cyanide (I) with p-chlorobenzaldehyde) of the dinitrile (II), in aqueous ethanol, was heated under reflux with hydroxylamine (2 mol) and hydroxylamine hydrochloride (2 mol) for 4 hours, the dioxime (LV) (45%) and p-chlorobenzaldoxime (LXVI) (57%) were obtained.

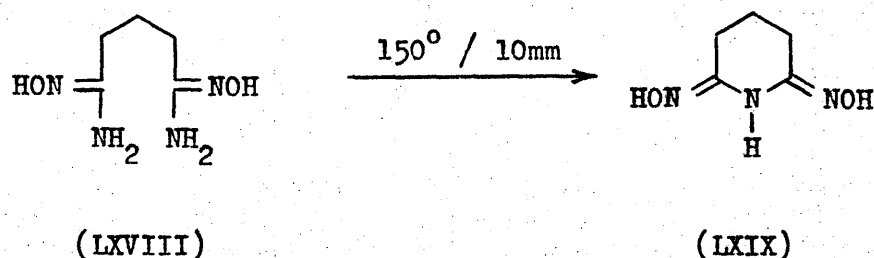


It was hoped that by subjecting the bisamidoxime (LVI) to higher temperatures, the uncleaved cyclic product (LXVII) could be obtained.



Accordingly, the bisamidoxime (LVI) was heated under reflux for 3 hours in dioxan. The solution became deep red but only starting material (84%) was recovered.

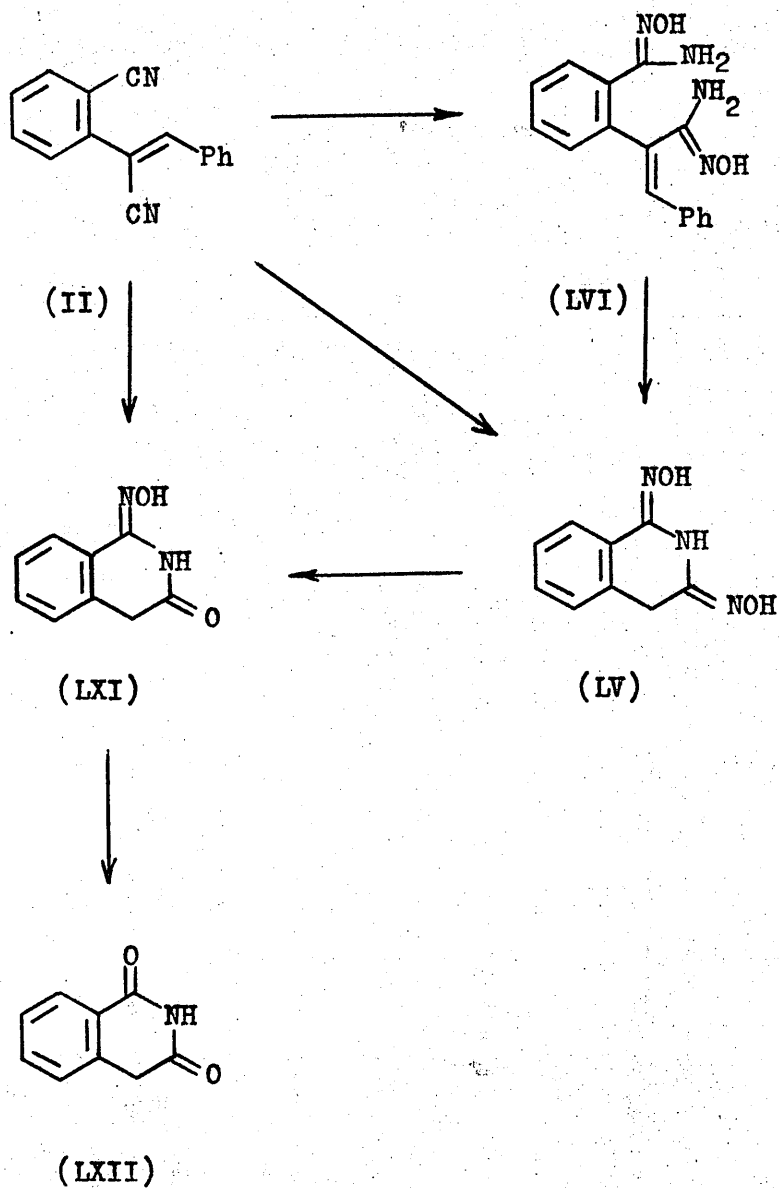
Cyclization to the dioxime (LXIX) had been readily achieved by sublimation of the bisamidoxime (LXVIII) of glutaronitrile⁴⁰.



An attempt was therefore made to achieve cyclization of the bisamidoxime (LVI) to the cyclic product (LXVII) by sublimation. However, the compound (LVI) was found to be stable under a vacuum of 0.05mm to a temperature of at least 200°.

SCHEME VII

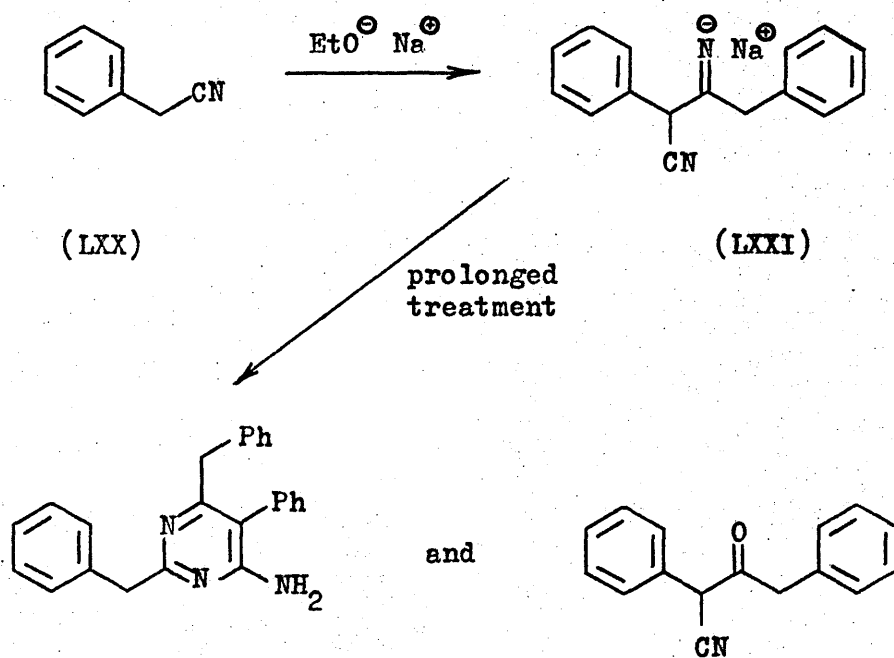
Products from reaction of o- α -dicyanostilbene (II) with hydroxylamine.



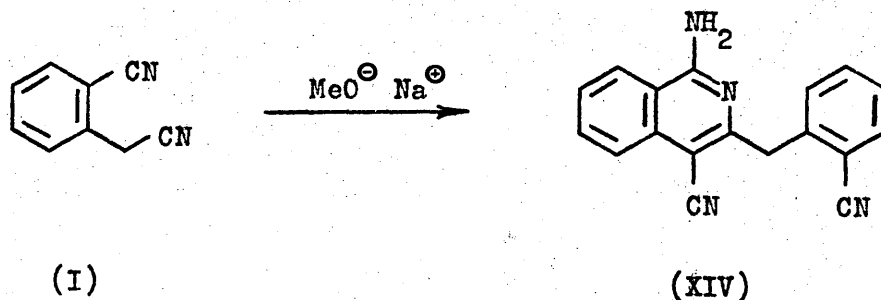
CHAPTER V

REACTION OF α -CYANOBENZYL CYANIDE WITH METHOXIDE IN METHANOL.

Alkoxides have been found sufficiently basic to generate the carbanion of nitriles containing a hydrogen atom on the α -carbon to the nitrile group. Thus Atkinson and Thorpe⁴² obtained the dimeric imine salt (LXXI) on treating benzyl cyanide (LXX) with sodium ethoxide in ethanol.



Accordingly, treatment of o-cyanobenzyl cyanide (I) with methoxide in methanol should yield 1-amino-4-cyano-3-(o-cyanobenzyl)isoquinoline (XIV), already obtained from the action of sodamide on this dinitrile.



Whilst sodium methoxide in methanol did react with o-cyanobenzyl cyanide (I) to give the predicted product (XIV), the rate of formation of the product was markedly slower than that found using sodamide in formamide as the basic medium (Chapter I). Indeed, only a 9% yield of (XIV) was obtained when the dinitrile (I) was heated under reflux with sodium methoxide in methanol for 8 hours.

The large difference in the ability of amide (NH₂[⊖]) and methoxide (MeO[⊖]) to achieve dimerization of o-cyanobenzyl cyanide (I) resulted perhaps from their very different effective basicity. They were not used in the same solvent and, moreover, several workers^{43,44} have shown that methoxide is heavily solvated in methanol, causing a lowering of the effective basicity of this anion.

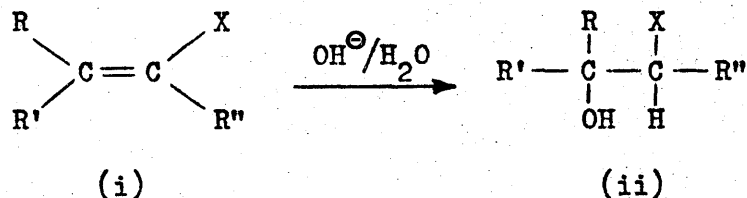
The solvent effect on the rate of the present

reaction was well illustrated when the dinitrile (I), in a 1:1 solution of methanol in dimethylsulphoxide, was heated under reflux for 3 hours with a catalytic amount of sodium methoxide. The yield of the product (XIV) was 44%.

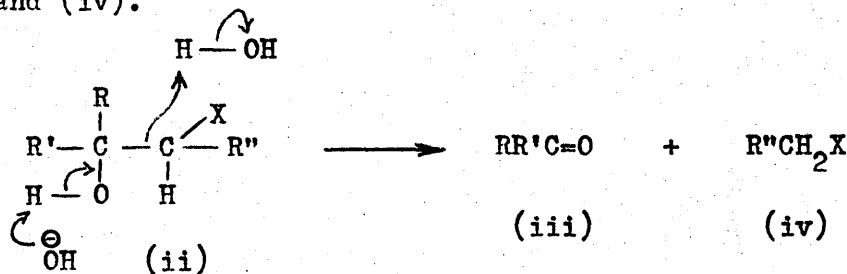
CHAPTER VI

REACTION OF α - α -DICYANOSTILBENE WITH ALKOXIDE IN ALCOHOL.

Base-catalysed addition of water to suitably activated olefins has already been discussed (Ch. III).

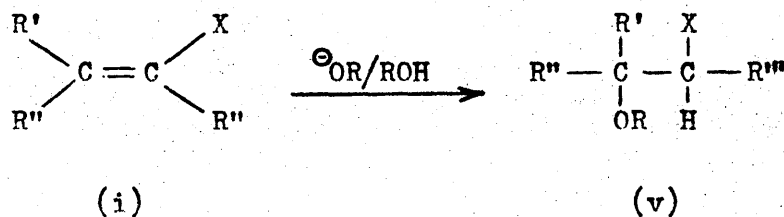


It is the presence of the ionizable hydrogen atom on the hydroxyl group in the adduct (ii) which generally results in the reaction proceeding to the cleavage products (iii) and (iv).

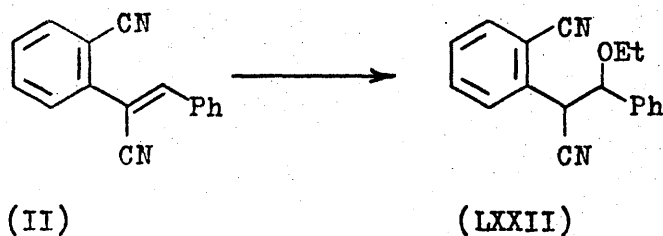


In contrast, whilst the analogous alkoxide-catalysed addition of alcohols to activated alkenes has been established as a general reaction, the resulting

adducts (v) do not contain an ionizable hydrogen atom of the type in (ii) and no cleavage of these adducts by alkoxide alone has been reported⁴⁵.

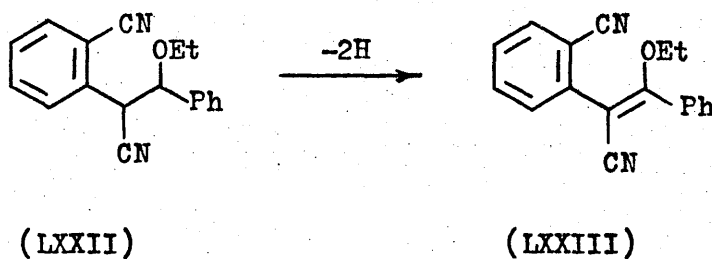


Now, as cleavage of the double bond in o-α-dicyanostilbene (II) was facile (Ch. III) with hydroxide, it could be anticipated that treatment of this dinitrile with sodium ethoxide in ethanol would yield the adduct (LXXII).

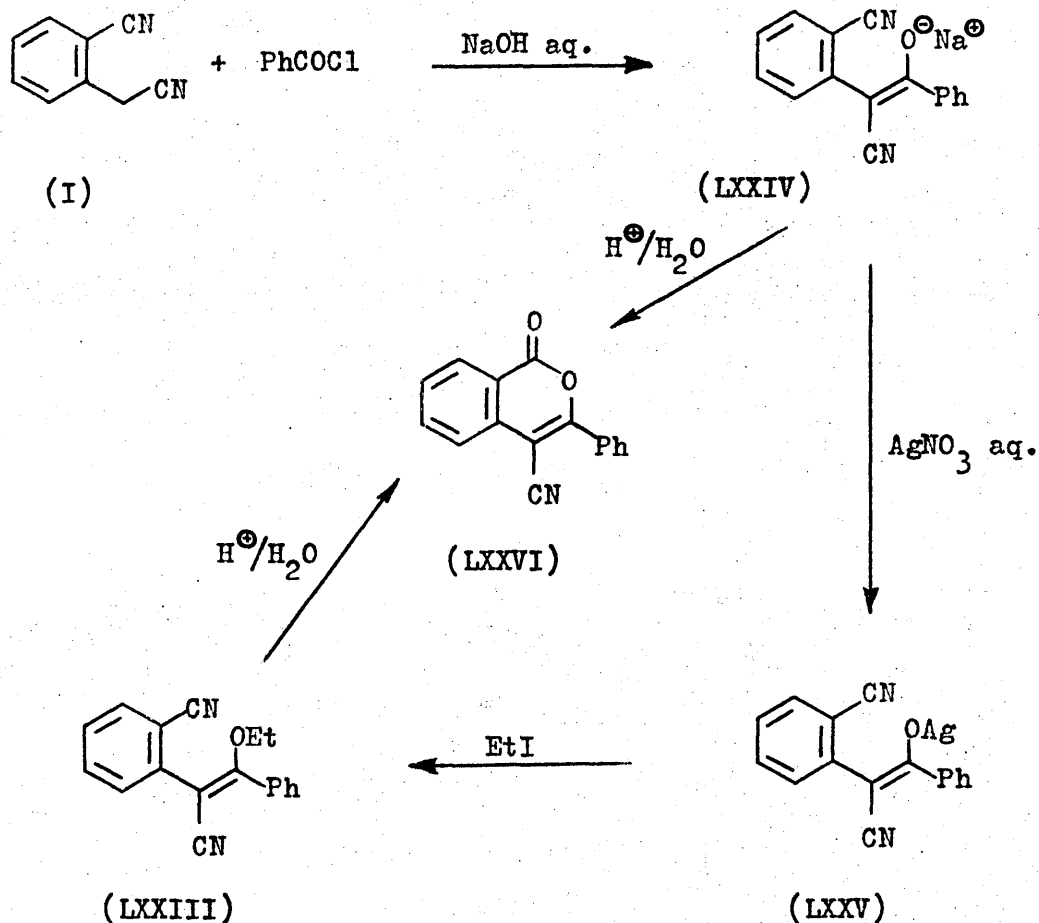


However, this adduct was not obtained when a solution of o-α-dicyanostilbene (II) and a catalytic amount of sodium ethoxide in absolute ethanol was heated at 60° for 4 hours. Mass spectrometry showed that the colourless product H, m.p. 132.5°, had a molecular weight (274) which was 2 units less than expected. In agreement the composition, by combustion, was found to be C₁₈H₁₄N₂O. So evidently the product had been formed by addition of ethanol to, and loss of two hydrogen atoms from, the dinitrile (II). A possible

structure was (LXXIII), but this was soon dismissed because there was only one nitrile stretching mode (at 2218 cm^{-1}) in the i.r. spectrum of H and the melting point of H differed from that reported⁴⁶ for the stilbene (LXXIII) ($115\text{--}116^\circ$).

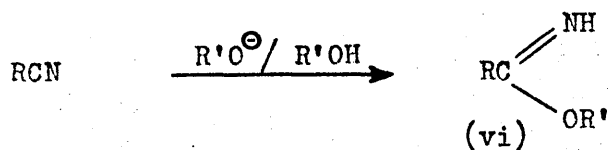


Some of the compound (LXXIII) was prepared according to Gabriel and Posner's method, and its assigned structure confirmed by analysis, mass spectrometry, the two i.r. nitrile stretching modes at 2225 and 2204 cm^{-1} , and its conversion with acid into the known isocoumarin (LXXVI)⁴⁶, also obtained by addition of dilute acid to the sodium salt (LXXIV).



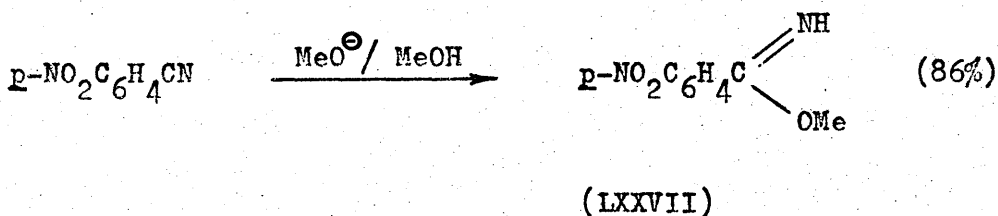
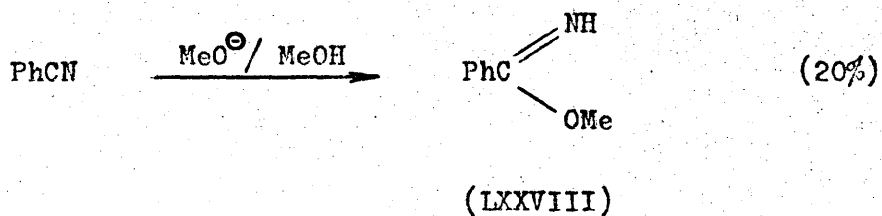
That the product H had not been obtained by ethoxide attack on the carbon-carbon double bond of the dinitrile (II) was then evident. A possible alternative was that the product H had resulted from ethoxide attack on the aryl nitrile group of the compound (II).

Imidate formation (vi), discovered by Nef¹¹,

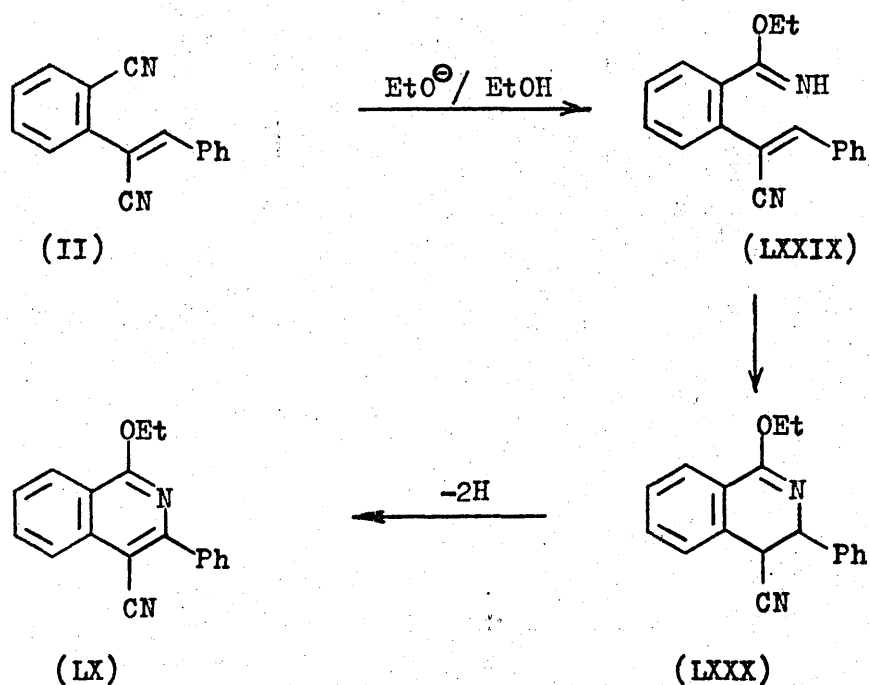


is promoted by the presence of electron-withdrawing substituents

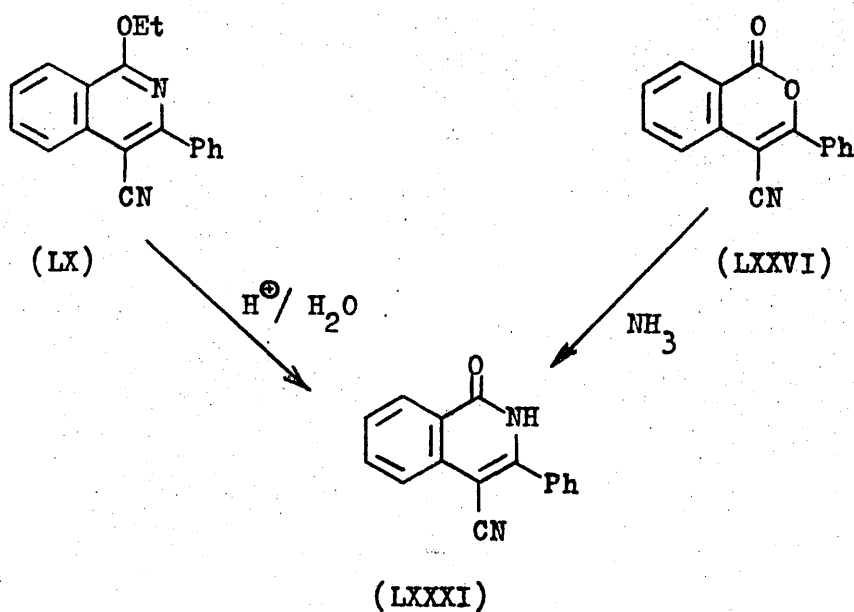
in the nitrile, although significant imidate yields have been obtained from nitriles lacking such groups. Thus, whilst *p*-nitrobenzonitrile gave the imidate (LXXVII) in 86% yield, benzonitrile itself afforded 20% of the imidate (LXXVIII)⁴⁷.



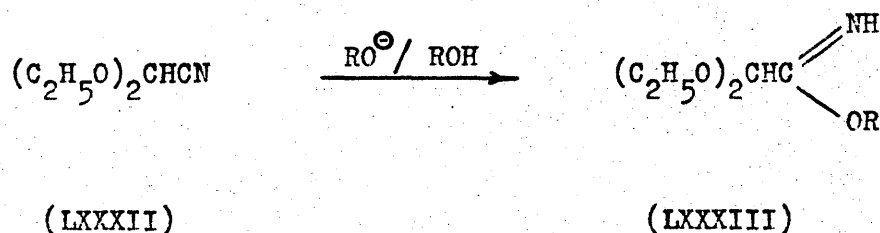
It was not unreasonable therefore to expect the dinitrile (II) and ethoxide to form the imidate (LXXIX). If cyclization ensued to give (LXXX), followed by dehydrogenation, then the substituted isoquinoline (LX) would result, and this structure appeared to be compatible with the characteristics found for the compound H. In particular, the p.m.r. spectrum of H in carbon tetrachloride (Table XV) showed signals attributable to ethoxy and aromatic protons only.



That H was the isoquinoline (LX) was then shown by its acid hydrolysis in 78% yield to 4-cyano-3-phenylisocarbostyryl (LXXXI), identical (i.r. and m.p.) with authentic material obtained by the action of ammonia on 4-cyano-3-phenylisocoumarin (LXXVI)⁴⁸.



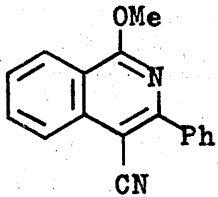
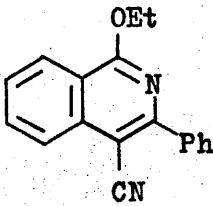
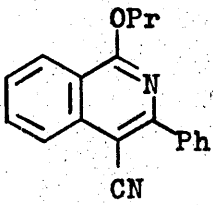
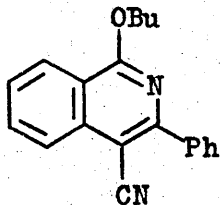
Schaefer and Peters⁴⁷ found that when diethoxyacetonitrile (LXXXII) was treated with primary alkoxides in alcohol, the yield of imidate (LXXXIII) decreased only slightly as the alcohol varied from C₁ to C₄. In addition, secondary alcohols did not show a large decrease in yield compared with that from their primary isomers.



It was of interest to determine whether the same constancy in yield held for the reaction of o-a-dicyanostilbene (II) as the alcohol was varied.

The dinitrile (II) was reacted for 4 hours at 60° with each of the alcohols : methanol, ethanol, propanol, butanol and isopropanol in the presence of a catalytic amount of the corresponding sodium alkoxide. A crystalline product was obtained in every case except with isopropanol which gave only tar. The products with yields and melting points are given in Table XII.

TABLE XII

<u>Alcohol / Alkoxide</u>	<u>Product</u>	<u>Yield %</u>	<u>m.p.</u>
MeOH / MeO [⊖]	 (XL)	61	152°
EtOH / EtO [⊖]	 (LX)	24	132.5°
PrOH / PrO [⊖]	 (LXXXIV)	20	110°
BuOH / BuO [⊖]	 (LXXXV)	12	108.5°
iPrOH / iPrO [⊖]	—	—	—

The products (XL), (LXXXIV) and (LXXXV) were all found to have the appropriate compositions and M.W.s. That they were all alkoxy homologues of the isoquinoline structure (LX) was established by the close similarity of their u.v. spectra in 96% ethanol (Table XIII).

TABLE XIII

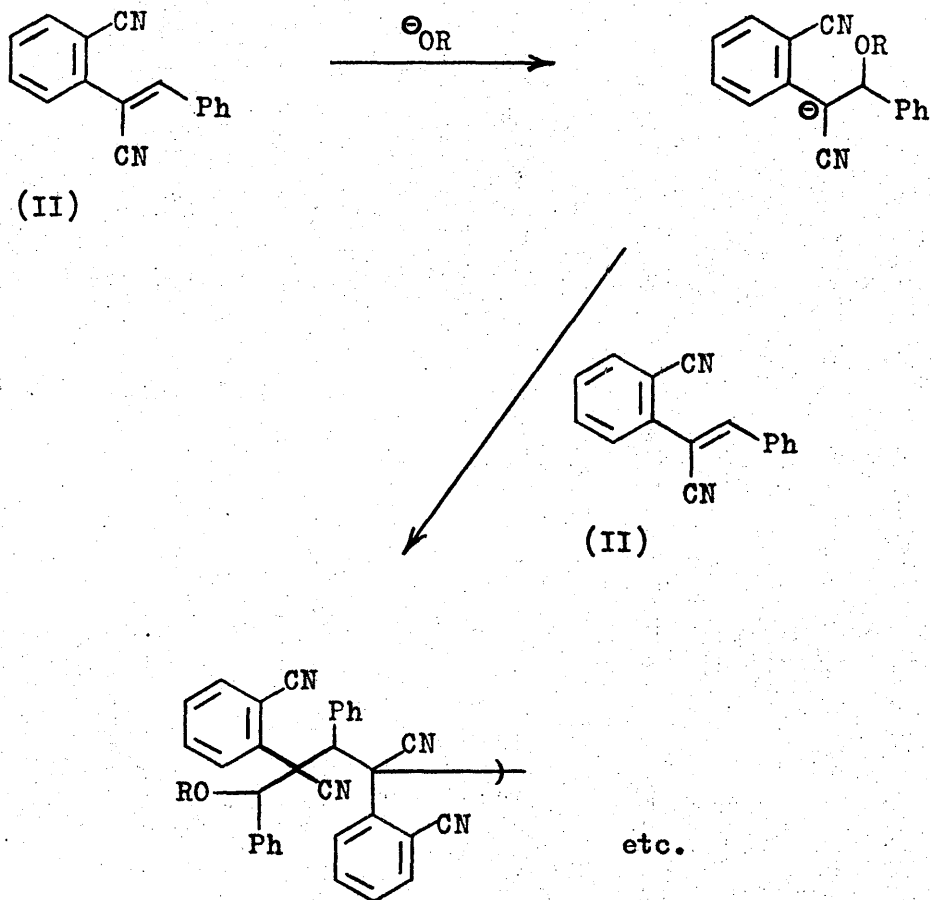
Compound	λ max (nm)				
	$(\epsilon \times 10^{-3})$				
(XL)	217 (30.8)	256 (29.0)	308 (13.4)	325sh (10.4)	337sh (6.0)
(LX)	217 (34.3)	256 (33.2)	309 (16.0)	325sh (12.6)	339sh (6.9)
(LXXXIV)	217 (32.4)	256 (31.0)	309 (14.6)	325sh (11.8)	339sh (6.2)
(LXXXV)	217 (31.4)	256 (30.3)	309 (14.5)	325sh (11.5)	340sh (6.1)

The results given in Table XII showed that the yield of product decreased as the basicity of the alkoxide increased. This trend at first seemed to conflict with the findings of Schaefer and Peters. However, studies of alkoxide catalysed addition of alcohols to activated alkenes showed that the relative reactivities increased with increasing basicity of the alkoxide^{49,50}.



A reasonable explanation of the results in Table XII therefore appeared to be that in the reaction of o-a-dicyano-stilbene (II) with alkoxide in alcohol, attack by alkoxide on the aryl nitrile group competed with attack by the same nucleophile across the olefinic group. But whereas the reaction rate remained almost constant for attack on the aryl nitrile group, the rate of attack on the carbon-carbon double bond increased according to the sequence (i) as the alkoxide varied.

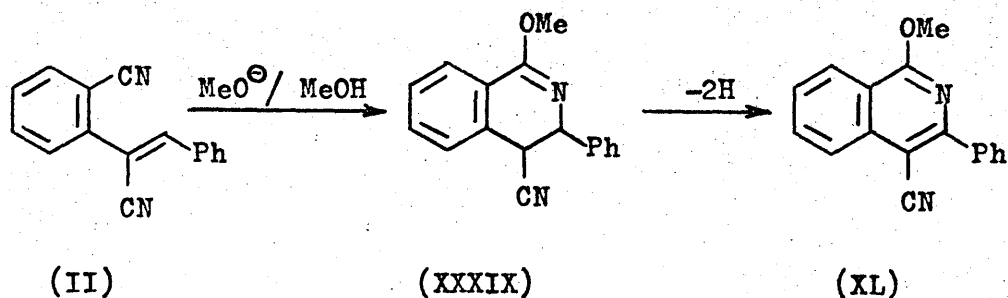
Disappointingly, no adduct from attack across the olefinic group of (II) was isolated from any of the reactions. But it was observed that the more to the right the alkoxide lay in the sequence (i), the greater the quantity of tar obtained from the reaction. This suggested that initial attack on the olefinic group of (II) resulted in polymerisation rather than formation of the expected adduct.



An example of polymerisation of this kind has been reported⁵⁰.

Although the structure of the product from reaction of the dinitrile (II) with alkoxide in alcohol had been satisfactorily determined as a substituted isoquinoline, its immediate precursor in the proposed reaction sequence was the corresponding dihydroisoquinoline. There was no clear reason why this intermediate should not have been the final product from the reaction. Because the reaction between the

dinitrile (II) and methoxide in methanol had afforded the highest yield of product, this reaction was reexamined in an attempt to obtain the compound (XXXIX) as a stable product.



The reaction was repeated as before but with precautions taken to exclude oxygen. The first crop of colourless crystals from recrystallisation of the reaction product from methanol under nitrogen was shown by mass spectrometry to be a mixture of two components of M.W. 262 and 260. This was encouraging evidence that the mixture comprised the compounds (XXXIX) and (XL). Compelling evidence for the presence of the dihydroisoquinoline (XXXIX) was afforded by the appearance of a pair of doublets, assignable to H-3 and H-4, in a p.m.r. spectrum of the mixture in deuteriochloroform (Fig. V). By comparison of this spectrum with that of the compound (XL) in deuteriochloroform (Fig. VI), in which the methoxy signal occurred at 5.77 τ , the signal at 6.12 τ in Fig. V could be assigned to the methoxy protons of (XXXIX). The ratio of the intensities of the signals at 6.12 and 5.80 τ in Fig. V gave the proportion of the two components of the mixture at 68% (XXXIX) and 32% (XL).

FIGURE V

Proton magnetic resonance spectrum of a mixture of (XXXIX) and (XL) (in deuteriochloroform) obtained from reaction of o-a-dicyanostilbene (II) with methoxide in methanol under nitrogen.

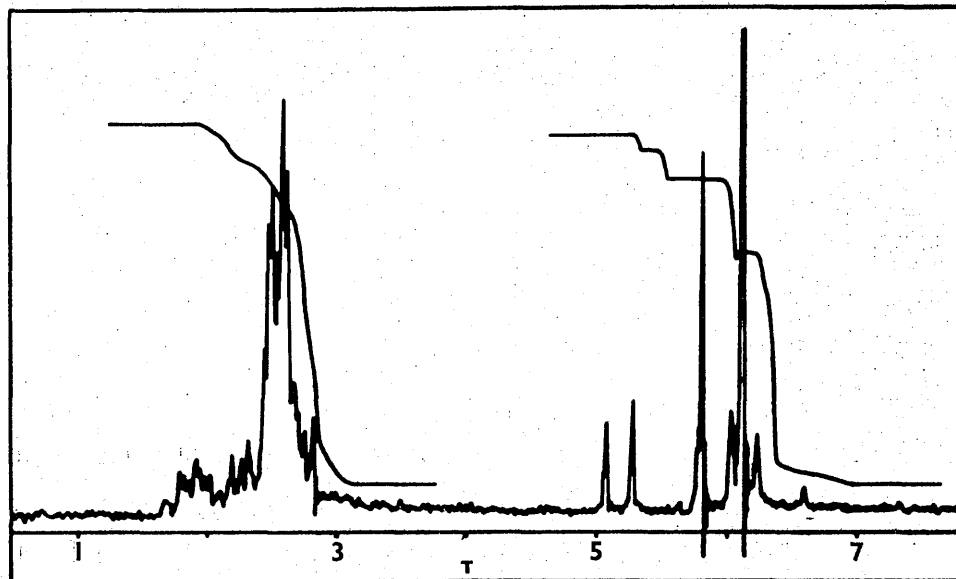
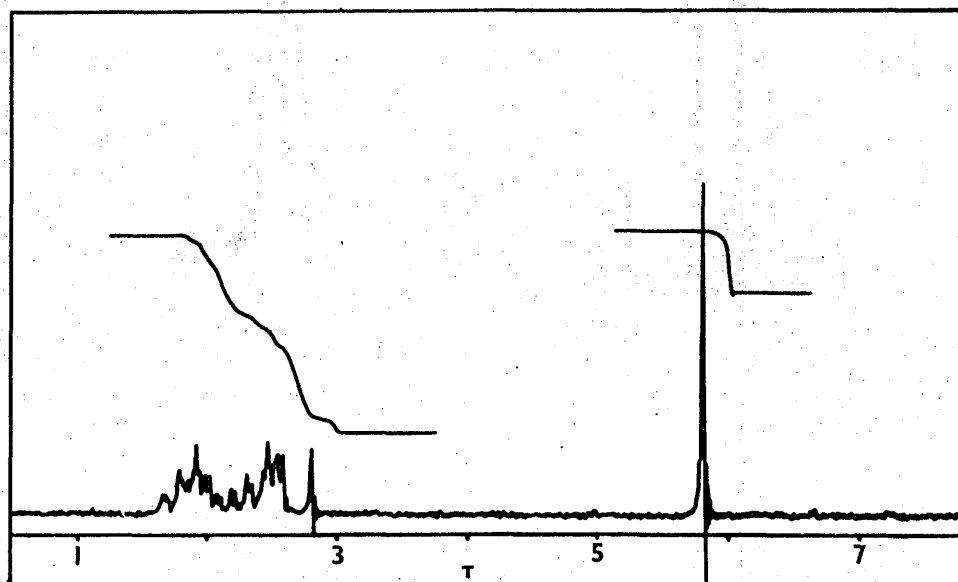


FIGURE VI

Proton magnetic resonance spectrum of 4-cyano-1-methoxy-3-phenylisoquinoline (XL) in deuteriochloroform.



The signals from (XXXIX) are tabulated below (Table XIV).

TABLE XIV

P.m.r. results for 4-cyano-1-methoxy-3-phenyl-3,4-dihydro-isoquinoline (XXXIX) in deuteriochloroform.

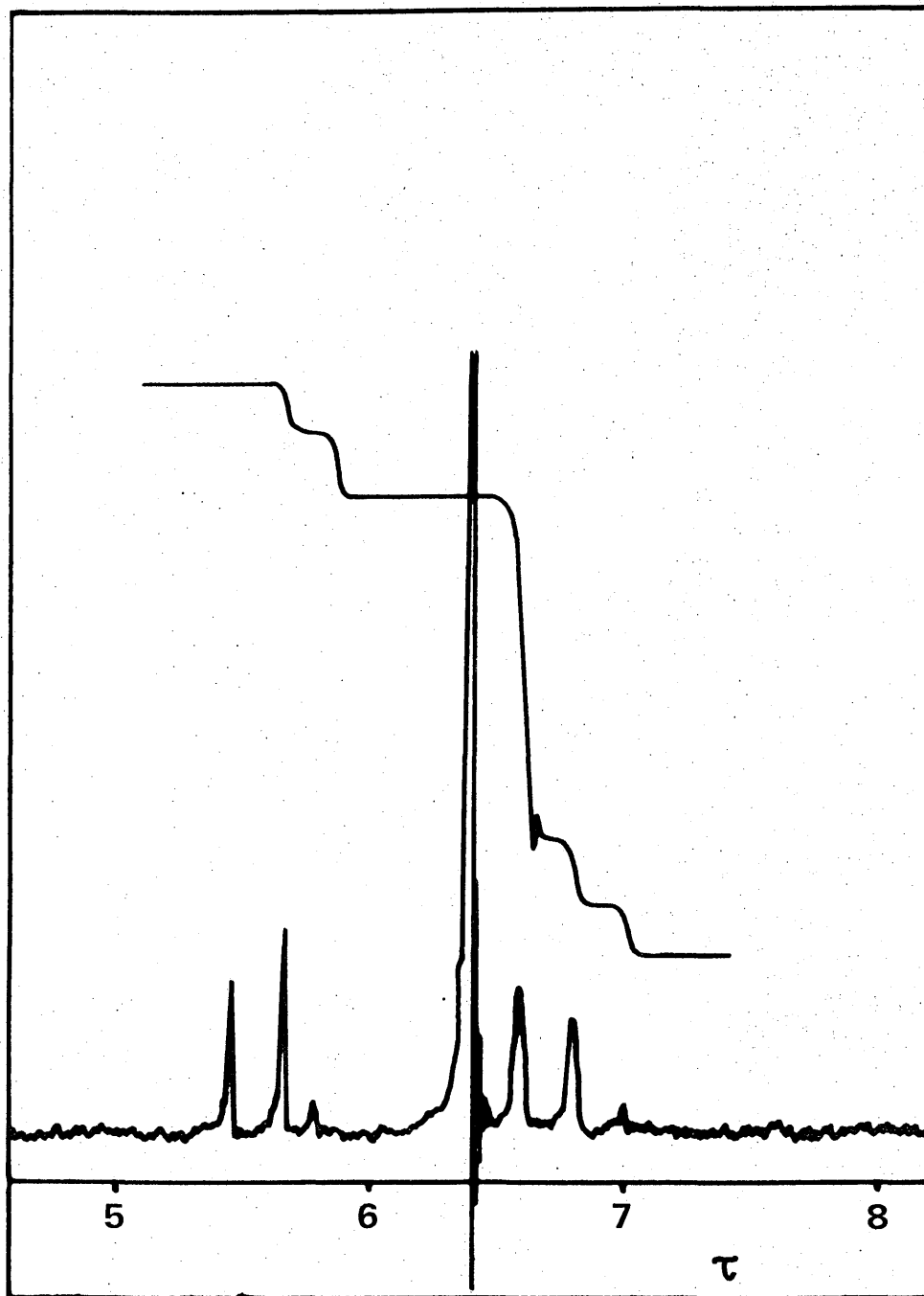
<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
6.12	singlet	3	-OCH ₃
6.14	doublet, <u>J</u> 12.0 Hz	1	3-H
5.17	doublet, <u>J</u> 12.0 Hz	1	4-H
2.8-2.0	complex	9	ring protons

The higher-field doublet was assigned to the 3-proton because it exhibited line broadening (Fig. V) which could be explained by quadrupolar effects due to the adjacent nitrogen⁵¹.

As the dihydroisoquinoline (XXXIX) had been obtained from the reaction of o-α-dicyanostilbene (II) with methoxide in methanol when efforts to exclude oxygen had been made but not when the reaction was performed in air, it seemed clear that the conversion of (XXXIX) to (XL) was the result of aerial oxidation. However, a small second crop from the re-crystallisation of the reaction product was obtained, which was the dihydroisoquinoline (XXXIX). This could be recrystallised from methanol in air to yield analytically pure, cubic crystals of the dihydroisoquinoline (XXXIX) which, in benzene, gave the p.m.r. spectrum shown in Fig. VII.

FIGURE VII

Proton magnetic resonance spectrum of the dihydroisoquinoline
(XXXIX) (in benzene).



The stability of (XXXIX) to oxygen alone was also demonstrated by the fact that the p.m.r. spectrum in Fig. V was unchanged after the solution had been refluxed in oxygen for 45 minutes.

Further experiment established that the oxidation was catalysed by alkali. The solution of (XXXIX) in benzene, which had given the p.m.r. spectrum in Fig. VII, was evaporated and the residue redissolved in methanol to which a catalytic amount of freshly prepared sodium methoxide had been added. The solution was heated under reflux for 45 minutes with oxygen passing through it. The yellow solution was then evaporated to dryness and the products extracted from the sodium methoxide into benzene. The solvent was removed from the benzene extract and the glassy residue dried over phosphorus pentoxide. The dried residue was redissolved in benzene and the p.m.r. spectrum of the solution was taken. A new signal at 6.27 τ was good evidence for the presence of the oxidation product (XL). (The methoxy protons of this compound in benzene gave a signal at 6.25 τ .) Additional proof of formation of (XL) was obtained by evaporating the benzene solution, rinsing the residue with methanol and filtering. Needles remained which upon recrystallisation were shown by m.p. and i.r. to be the product (XL).

TABLE XV

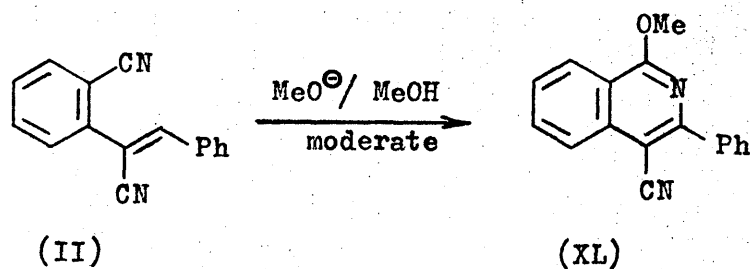
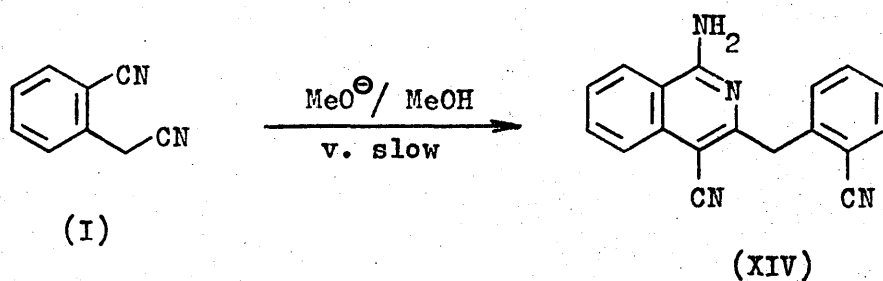
P.m.r. results [for ca. 8% solutions in a) carbon tetrachloride, b) deuteriochloroform and c) dimethylsulphoxide].

Compound	Signal(τ)	Multiplicity	Intensity	Assignment
(LXXIII) ^b	8.83	triplet, \underline{J} 6.8 Hz	3	$-\text{OCH}_2\text{CH}_3$
	6.17	quartet, \underline{J} 6.8 Hz	2	$-\text{OCH}_2\text{CH}_3$
	2.7-2.1	complex	9	ring protons
(LXXVI) ^b	2.7-1.8	complex	8	ring protons
	1.68	doublet (showing finer splitting), \underline{J} 7.8 Hz	1	8-H
(LX) ^a	8.50	triplet, \underline{J} 7.0 Hz	3	$-\text{OCH}_2\text{CH}_3$
	5.34	quartet, \underline{J} 7.0 Hz	2	$-\text{OCH}_2\text{CH}_3$
	2.9-1.5	complex	9	ring protons
(LXXXI) ^c	2.7-2.0	complex	8	ring protons
	1.73	double doublet, \underline{J}_o 7.2 Hz, \underline{J}_m 1.7 Hz	1	8-H
	-2.22	broad singlet	1	NH
(XL) ^a	5.82	singlet	3	$-\text{OCH}_3$
	2.7-1.7	complex	9	ring protons
(LXXXIV) ^a	8.89	triplet, \underline{J}_{AB} 6.8 Hz	3	$-\text{O}(\text{CH}_2)_2\text{CH}_3$
	8.08	sextet (showing finer splitting)	2	$-\text{OCH}_2\overset{\text{C}}{\text{CH}_2}\overset{\text{B}}{\text{CH}_2}\overset{\text{A}}{\text{CH}_3}$
	5.45	triplet, \underline{J}_{BC} 6.2 Hz	2	$-\text{OCH}_2\text{C}_2\text{H}_5$
	2.8-1.7	complex	9	ring protons
(LXXXV) ^a	8.98	distorted triplet, \underline{J} 6.8 Hz	3	$-\text{O}(\text{CH}_2)_3\text{CH}_3$
	8.8-7.8	complex	4	$-\text{OCH}_2(\text{CH}_2)_2\text{CH}_3$
	5.39	triplet, \underline{J} 6.1 Hz	2	$-\text{OCH}_2\text{C}_3\text{H}_7$
	2.7-1.6	complex	9	ring protons

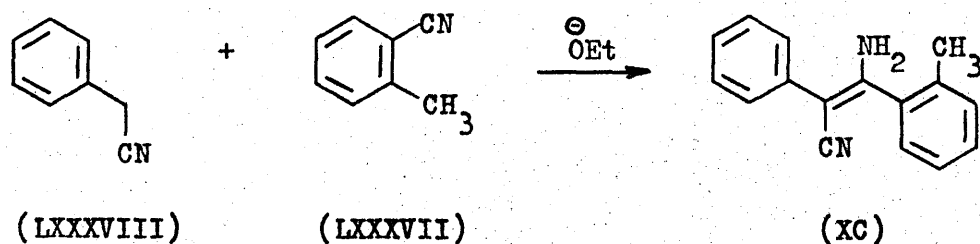
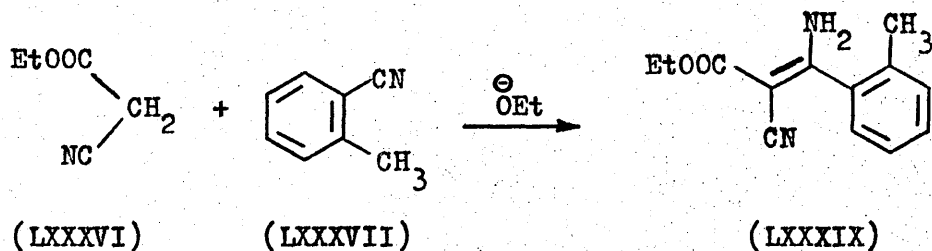
CHAPTER VII

REACTION OF o-CYANOBENZYL CYANIDE WITH o- α -DICYANOSTILBENE IN THE PRESENCE OF METHOXIDE.

The dimerisation of o-cyanobenzyl cyanide (I) to the product (XIV) where methoxide was the catalytic base, proceeded at a slow rate (Ch. V). In contrast, an appreciable yield of the product (XL) was obtained from the nucleophilic attack by methoxide on the aryl nitrile of o- α -dicyano-stilbene (II) (Ch. VI).



It could be supposed therefore that the outcome of attempted codimerisation of the two dinitriles (I) and (II) would merely be the formation of the product (XL) with the dinitrile (I) spectating. But the work of others showed that this result was not inevitable. In particular, Atkinson and coworkers⁵², having found that the reaction of ethyl cyanoacetate (LXXXVI) with *o*-toluonitrile (LXXXVII) in the presence of ethoxide, required vigorous conditions, were surprised at the greater ease with which benzyl cyanide (LXXXVIII) added to the nitrile (LXXXVII) under ethoxide catalysis.



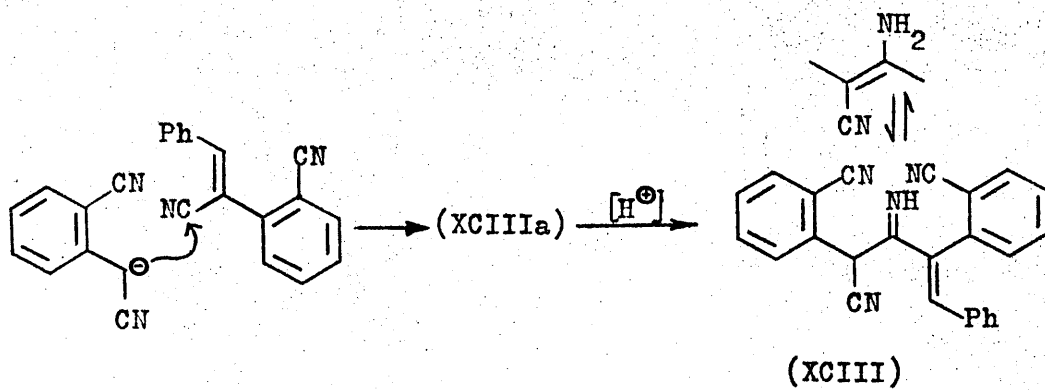
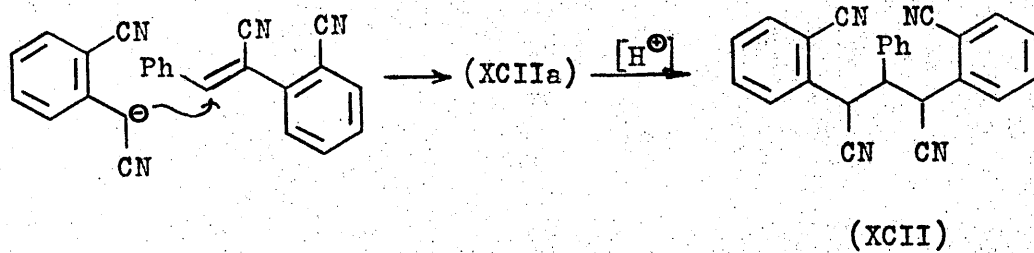
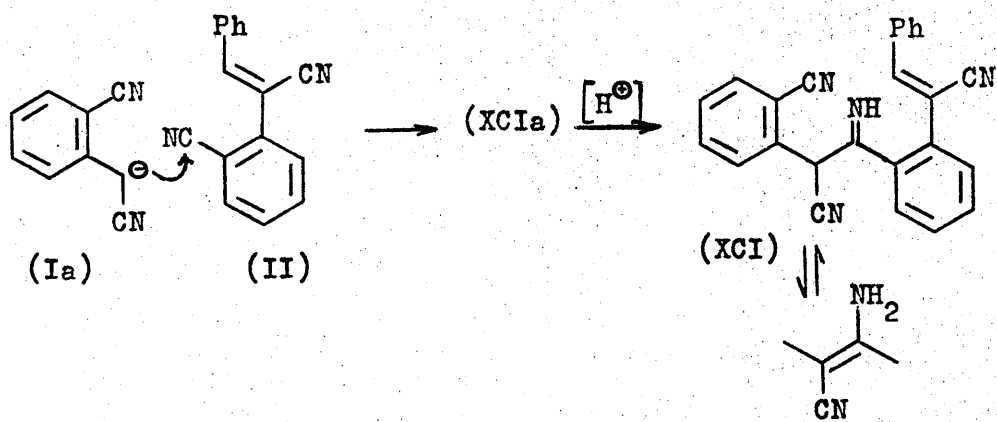
Apart from the unusual ease of formation of the product (XC), a salient point of this reaction was the preference shown by the anion of (LXXXVIII) for attack on the aryl nitrile of (LXXXVII) rather than on the saturated nitrile of a neutral

molecule of (LXXXVIII). Were the two dinitriles (I) and (II) to behave similarly, a product of their addition in the presence of methoxide could be expected.

When equimolar quantities of o-cyanobenzyl cyanide (I) and o- α -dicyanostilbene (II) were heated at 60° for 4 hours in methanol to which a catalytic amount of sodium methoxide had been added, colourless needles of the product (XL) (25%) were, in fact, obtained. But in addition, colourless cubes of a compound J (33%) were isolated as the major product. The M.W. of J was found by mass spectrometry to be 372 and as the composition of J agreed with the formula, $C_{25}H_{16}N_4$, it was clear that this product resulted from the addition of o-cyanobenzyl cyanide (I) to o- α -dicyanostilbene (II).

The three possible modes of attack by the anion (Ia) of o-cyanobenzyl cyanide (I) on o- α -dicyanostilbene (II), and the respective products are shown in Scheme VIII.

SCHEME VIII



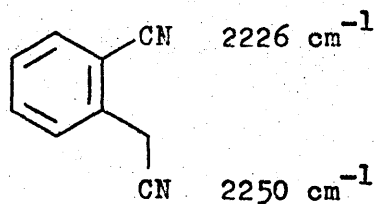
Structure (XCII) containing no amino group, was immediately discounted on examination of i.r. and p.m.r. spectra of J (p. 109).

Only two nitrile stretching frequencies (2215 and 2210 cm^{-1}) were observed in the i.r. of the product J. Now both structures (XCI) and (XCIII), which would preferentially exist in the enamine form, contained three nitrile groups. For structure (XCI) to show only two nitrile stretching modes it was necessary to assume quenching of the β -amino- α , β -unsaturated nitrile frequency. This assumption seemed tenuous when it was recalled that the stretching mode of the similarly conjugated β -ethoxy nitrile in structure (LXXIII) (Table XVI) was observed, although at a lower frequency than that expected for normal α , β -unsaturated nitrile groups. However, even accepting the assumption, the observed frequencies were too low for either to be assigned to the aryl nitrile of (XCI). The aryl nitrile groups of several related compounds (Table XVI) gave absorptions which were always very close to 2225 cm^{-1} and it was difficult to envisage a mechanism which could effect significant lowering of the aryl nitrile frequency of (XCI) from this value.

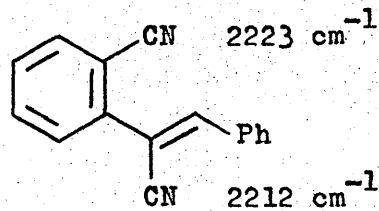
For structure (XCIII), the two aryl nitrile frequencies could be expected to be unresolved, but, again, have a common value very close to 2225 cm^{-1} .

TABLE XVI

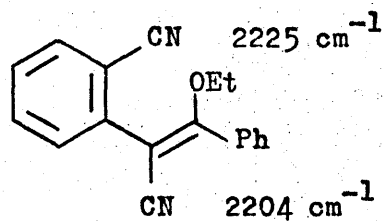
Nitrile stretching frequencies of related dinitriles.



(I)



(II)

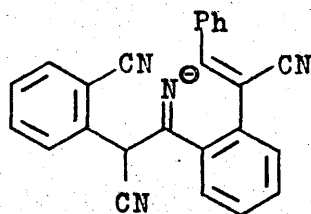


(LXXIII)

As none of the above three structures could be easily reconciled with the observed spectral data, the possibility of intramolecular cyclization of their respective anions (XCIIa), (XCIIIa) and (XCIIIIa) was considered. This approach afforded six possible structures for J (Scheme IX), starting from the three initial anions.

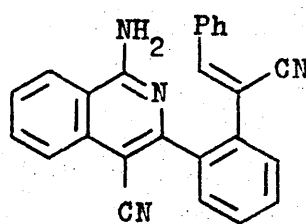
SCHEME IX

1.



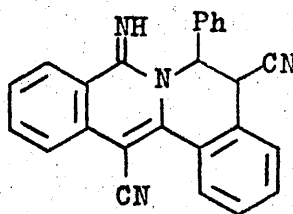
(XCIa)

i) Cyclization across the
aryl nitrile



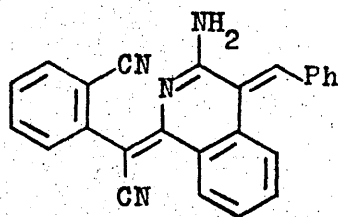
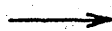
(XCIV)

ii) Cyclization across the
olefinic group



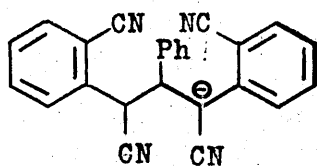
(XCV)

iii) Cyclization across the
 α,β -unsaturated nitrile



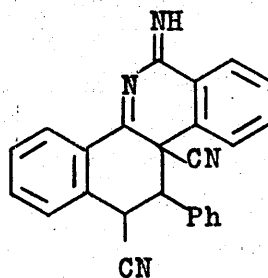
(XCVI)

2.



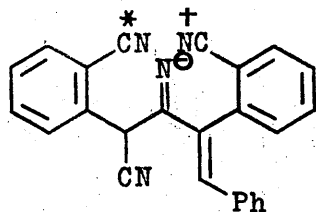
(XCIIa)

Cyclization across the
aryl nitrile



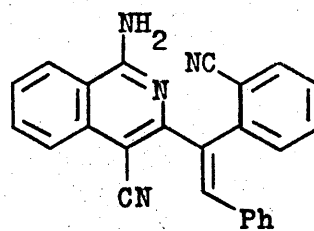
(XCVII)

3.



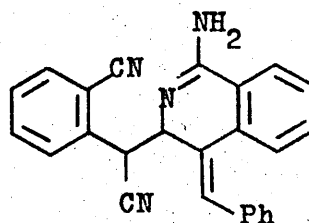
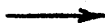
(XCIIIa)

i) Cyclization across the
aryl nitrile*



(XCVIII)

ii) Cyclization across the
aryl nitrile[†]



(XCIX)

From the p.m.r. results for J in acetonitrile (p. 110) it was unnecessary to consider the structures (XCV) and (XCVII) further. A broad two-proton singlet at 3.54 τ which was removed by addition of deuterium oxide to the solution was good evidence for the presence of an amino group. Furthermore, a p.m.r. spectrum of a compound possessing either structure (XCV) or (XCVII) would be expected to show a pair of doublets in the region of 6 τ corresponding to two vicinally coupled protons.

It was clear that identification of the products from ozonolysis of J would establish which of the remaining possible structures was correct. From this degradation, the isolation of benzaldehyde verified the presence of a benzal moiety in the molecule. Disappointingly, intractable material was the only other major product of the reaction and no further reliable structural information about J could be obtained.

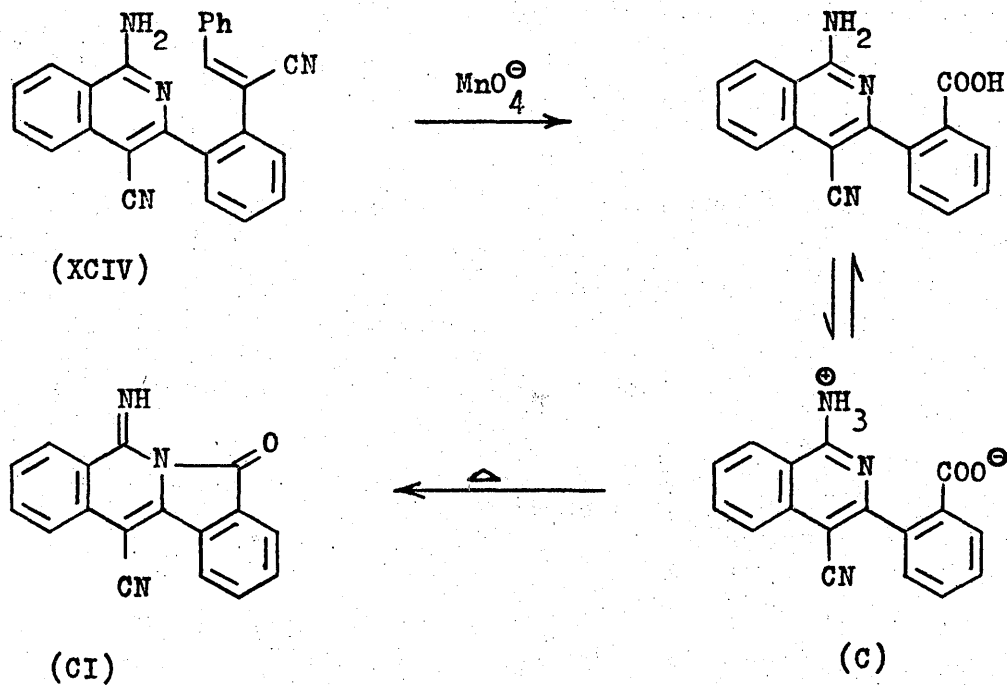
Rather surprisingly, in the light of the behaviour of J with ozone, the oxidative cleavage of J by permanganate proceeded smoothly to afford colourless prisms of an hygroscopic product K, $C_{17}H_{11}N_3O_2$, which, on heating, readily lost a molecule of water to yield bright yellow prisms of L, $C_{17}H_9N_3O$, the M.W. of which was confirmed as 271 by mass spectrometry.

By establishing the structure of L as (CI), it was possible to deduce that K had the structure (C) and that (XCIV) was the correct structure for J as none of the other

possible structures (XCVI), (XCVIII) and (XCIX) could, on oxidation, yield (C) and subsequently (CI).

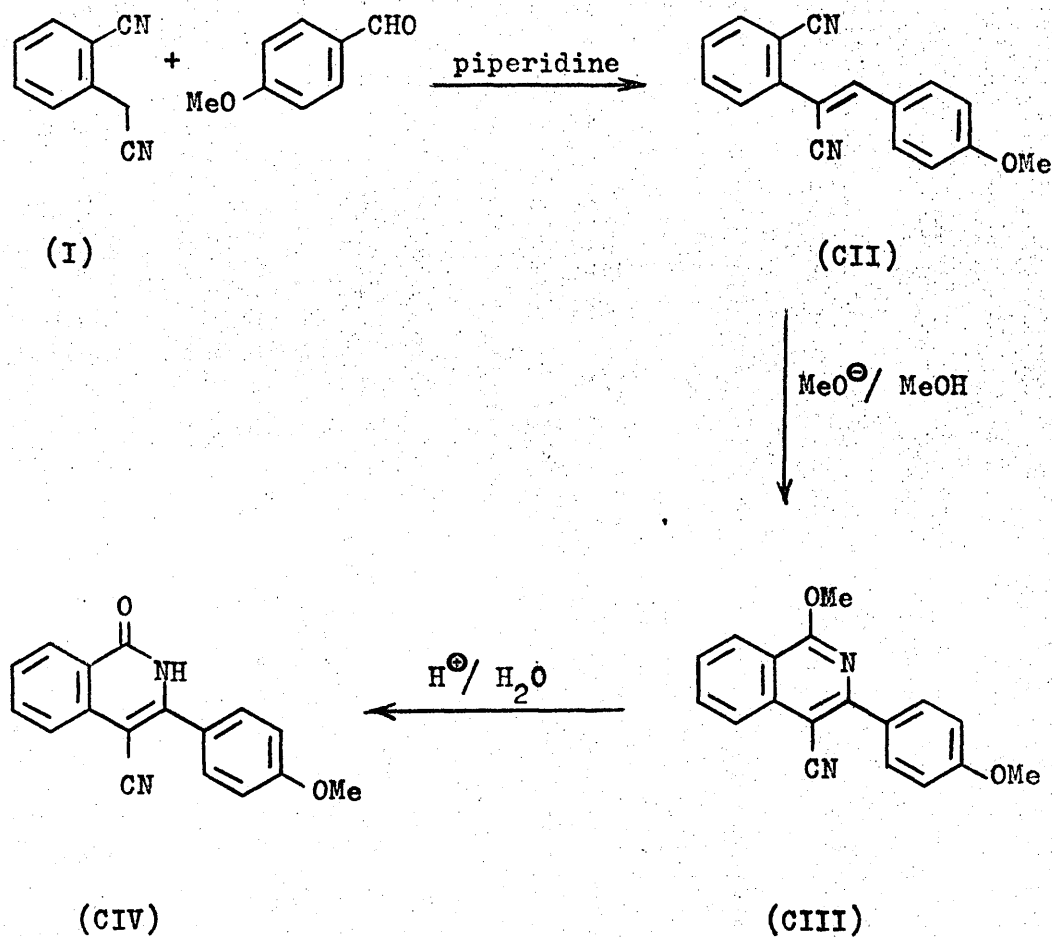
SCHEME X

Products from the permanganate oxidation of (XCIV).



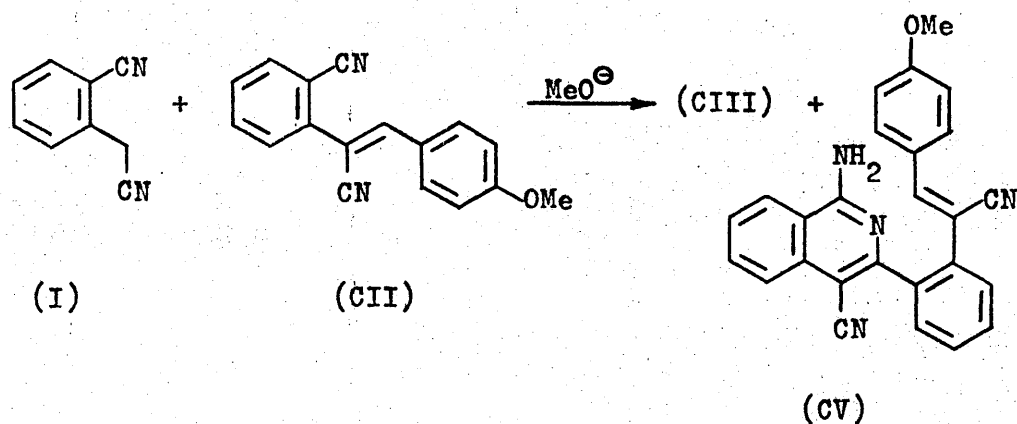
In the formation of (XCIV), the anion (Ia) behaved as had the methoxide nucleophile (p. 98) and attacked the aryl nitrile of the dinitrile (II). However, the imino anion thus formed, rather than cyclise across the double bond of (II), then added to the remaining aryl nitrile in a fashion reminiscent of the mechanism of formation of the dimeric product (XIV) from *o*-cyanobenzyl cyanide (I) (p. 98). It would seem that in these two cases, steric factors determined the mode of cyclization.

Condensation of *o*-cyanobenzyl cyanide (I) with anisaldehyde afforded the *p*-methoxy analogue (CII) of *o*- α -dicyanostilbene (II). Treatment of (CII) with methoxide in methanol afforded the substituted isoquinoline (CIII), acid hydrolysis of which yielded the isocarbostryl (CIV).



In a reaction to effect methoxide catalysed addition of *o*-cyanobenzyl cyanide (I) to the dinitrile (CII), the

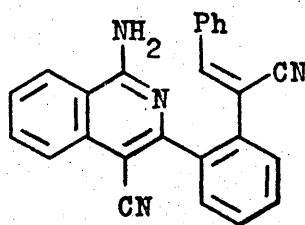
compound (CIII) and the addition product (CV) were obtained.



This reaction therefore proceeded analogously to that of *o*-cyanobenzyl cyanide (I) and *o*- α -dicyanostilbene (II) in the presence of methoxide.

SPECTRAL DATA

(i)



(XCIV)

I.r. (nujol mull).

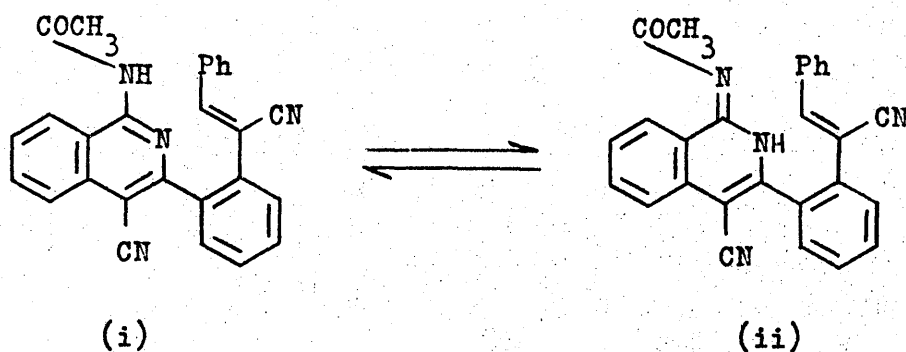
3485, 3368	NH ₂ asymmetric and symmetric stretching
3215	bonded NH stretching
2215, 2210	2 x C≡N stretching
1630s cm ⁻¹	<u>isoquinoline</u> skeletal vibration

P.m.r. (solvent : acetonitrile).

<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
3.54	broad singlet ^a	2	NH ₂
2.8-1.8	complex	14	olefinic and ring protons

^a removed on addition of deuterium oxide.

(ii) Monoacetyl derivative of (XCIV).

I.r. (nujol mull).

Variable absorption intensities in the NH and C=N stretching regions were good evidence for the existence of the tautomers (i) and (ii) in the solid state.

3226	NH (i) stretching
3175	NH (ii) stretching
2223 and 2213	2 x C=N stretching
1722	amide I band (ii)
1685 cm ⁻¹	amide I band (i)

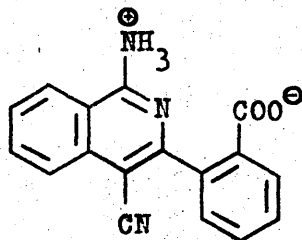
P.m.r. (solvent : d_6 dimethylsulphoxide).

<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
7.80	singlet	3	CH_3
2.8-1.8	complex	13	olefinic and ring protons
1.64	doublet (showing finer splitting), J_0 ca. 8.5 Hz	1	8-H
-0.91	broad singlet ^a	0.8	NH (i)

^a removed on addition of deuterium oxide to the solution.

The intensity of 0.8 proton found for the NH signal was attributed to the presence of the two tautomers (i) and (ii). The signal from the NH proton in (ii) was not observed. Possibly it occurred under the 13 proton complex but perhaps more reasonably the signal was too broad and low to be recorded.

(iii)

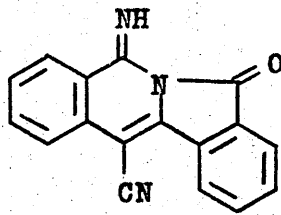


(c)

I.r. (nujol mull)

The hygroscopic nature of this compound made it difficult to measure the i.r. spectrum. The spectra from a number of attempts showed variations. However, the observations were not inconsistent with the given structure. All spectra showed a single nitrile stretching frequency at 2216 cm^{-1} .

(iv)



(CI)

I.r. (nujol mull).

3303	NH stretching
2221	C≡N stretching
1735 cm ⁻¹	γ-lactam carbonyl stretching

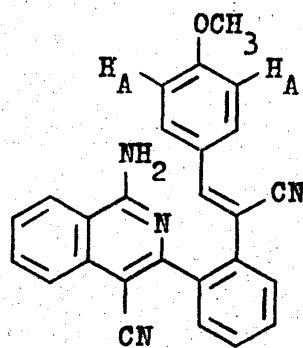
P.m.r. (solvent : deuteriochloroform).

<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
2.7-1.8	complex	6	ring protons
1.7-1.3	complex	2	4- and 8-protons
-0.53	broad singlet ^a	1	NH

^a removed on addition of deuterium oxide.U.v. (solvent : 96% ethanol).

Light absorption by this bright yellow compound extended above 400 nm which was consistent with its highly conjugated structure.

(v)



(CV)

I.r. (mujol mull).

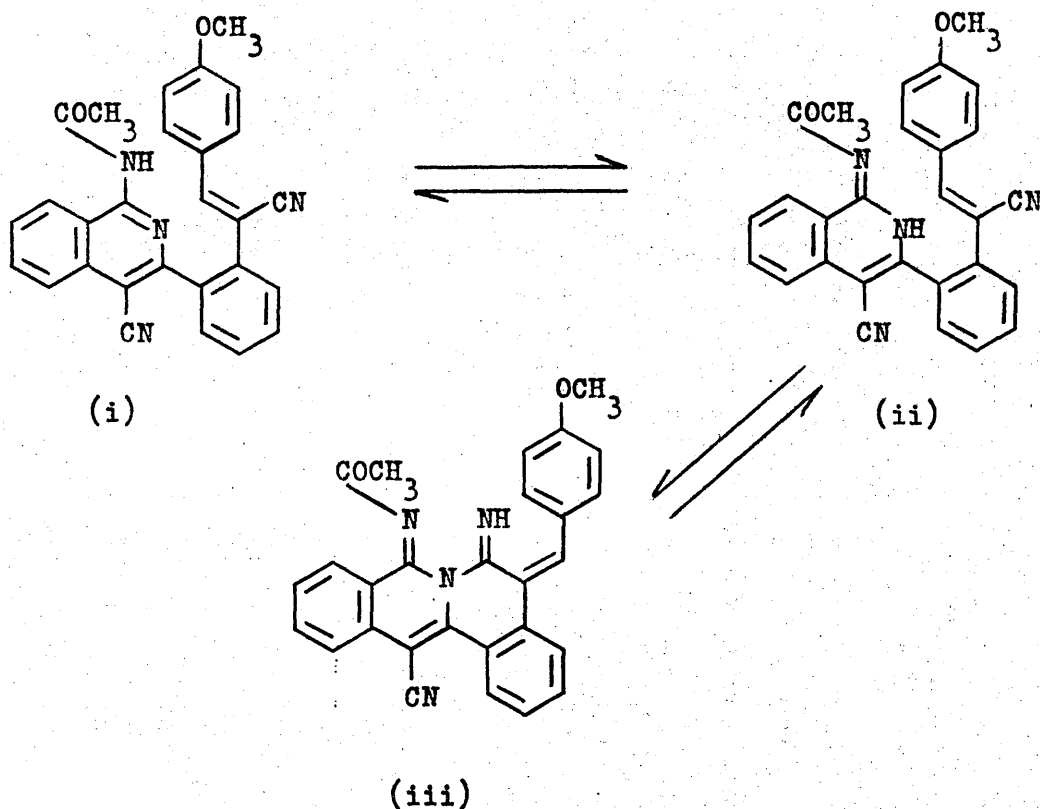
3497 and 3301	NH ₂ asymmetric and symmetric stretching
3096	bonded NH stretching
2215 and 2204	2 x C≡N stretching
1645s	<u>isoquinoline</u> skeletal vibration
1255s cm ⁻¹	aryl ether C - O - C stretching

P.m.r. (solvent : deuteriochloroform).

<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
6.23	singlet	3	-OCH ₃
4.22	broad singlet ^a	2	NH ₂
3.25-3.05	quasi doublet	2	H _A
2.84	singlet	1	= ^H
2.6-1.9	complex	10	ring protons

^a removed on addition of deuterium oxide.

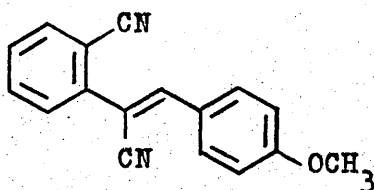
The presence of the methoxy group in the molecule caused a fortuitous separation in the ring proton signals making identification of the olefinic proton possible.

(vi) Monoacetyl derivative of (CV).

Recrystallisation of the product of acetylation of (CV) from 96% ethanol afforded yellow prisms from the warm solution and colourless prisms when the solution was cooled below 20° . It was found that, by appropriately controlling the temperature at which crystallisation occurred, the yellow and colourless prisms could be interconverted. This behaviour indicated tautomerism and, since the composition of the colourless prisms was found to be $C_{28}H_{20}N_4O_2$, it was believed that the two differently coloured prisms were tautomers of the monoacetyl derivative of (CV). On heating, the colourless

prisms gradually became yellow and finally melted at 210° , the melting point found for the yellow prisms. Differences in the i.r. spectra identified the yellow prisms as a mixture of the tautomers (i) and (ii) and the colourless prisms as the tautomer (iii) : the colourless prisms showed a single sharp absorption at 3420 corresponding to an imino NH stretching mode, a single nitrile stretching frequency at 2212 and an imide carbonyl stretching frequency at 1709 cm^{-1} ; the yellow prisms displayed broad NH stretching absorptions between 3300 and 3100, two nitrile stretching frequencies at 2225 and 2210 and a slightly broadened amide I band at 1690 cm^{-1} . The absorptions for the yellow prisms were consistent with the tautomer (i) but the broadened NH absorptions and a shoulder at 1709 on the carbonyl stretching mode at 1690 cm^{-1} suggested the presence of a small amount of the tautomer (ii).

(vii)

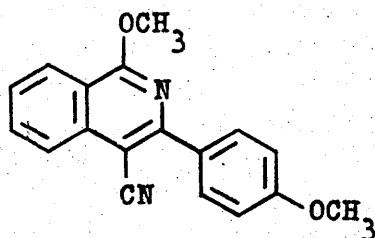


(CII)

P.m.r. (solvent : carbon tetrachloride).

<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
6.14	singlet	3	$-\text{OCH}_3$
3.1-2.4	complex	4	ring protons
2.35	singlet	1	olefinic H
2.3-1.9	complex	4	ring protons

(viii)



(CIII)

P.m.r. (solvent : carbon tetrachloride).

<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
6.14	singlet	3	-OCH ₃
5.75	singlet	3	1-OCH ₃
3.2-1.7	complex	8	ring protons.

CHAPTER VIII

REACTION OF o-CYANOBENZYL CYANIDE WITH BENZALDEHYDE IN THE PRESENCE OF METHOXIDE.

Several bases have been found to catalyse Knoevenagel condensations successfully. Typically, amines, alkoxides or sodamide have been used. Thus piperidine catalyses the condensation of o-cyanobenzyl cyanide (I) with benzaldehyde to afford o- α -dicyanostilbene (II) in 70% yield⁹. But on attempting the same condensation using ethoxide in ethanol, Jones^{10b} obtained, as the major product, a quite different, insoluble product which he failed to characterise because of its lack of reactivity. This reaction, relevant to the work described in the previous chapters, was reexamined.

Initially, ethoxide in ethanol was used but it was found that methoxide in methanol gave a cleaner reaction and the same products so the latter reagents were used in all subsequent experiments.

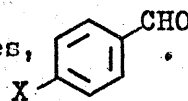
Heating equimolar quantities of the dinitrile (I) and benzaldehyde at 60° for 4 hours in methanol, to which a catalytic amount of sodium methoxide had been added, gave a

major product M (25%). This was insoluble in common solvents and only moderately soluble in hot 2-ethoxyethanol, 1,4-dioxan and tetrahydrofuran (THF). The colourless material from THF was obtained, after being dried at 40°/0.05mm, as fine cream prisms of the hemisolvate $C_{25}H_{18}N_4O \cdot \frac{1}{2}C_4H_8O$. Mass spectrometry confirmed the M.W. of M as 390 and, by a THF fragmentation pattern, the inclusion of this solvent in the material. Under more vigorous conditions of drying, pale yellow prisms of the unsolvated material were obtained.

The poor solubility of M caused difficulties in the investigation of its structure. Attempts to overcome these were made by reacting the dinitrile (I) with *p*-substituted benzaldehydes. In each of the three cases tried, the reaction proceeded analogously to that with benzaldehyde. The major products, homologues of M, are listed with compositional data in Table XVII.

TABLE XVII

Major products from the methoxide catalysed reaction of *o*-cyanobenzyl cyanide (I) with *p*-substituted benzaldehydes,



<u>X</u>	<u>Product</u>	<u>Appearance</u>	<u>Composition</u>	<u>m/e</u>
H	M	pale yellow prisms	$C_{25}H_{18}N_4O$	390
OMe	N	pale yellow prisms	$C_{26}H_{20}N_4O_2$	420
Cl	O	yellow prisms	$C_{25}H_{17}N_4ClO$	424
OBu	P	pale yellow prisms	$C_{29}H_{26}N_4O_2$	462

Whilst products N and O were rather more soluble than M, a marked improvement in solubility characteristics was found for the p-butoxy homologue, P, which was even moderately soluble in ethanol. However, these homologues showed a tendency to form sparingly soluble clathrates with solvents, behaviour reminiscent of the parent compound with THF already mentioned. On one occasion, attempted recrystallisation of M from dioxan failed because solvated material precipitated almost quantitatively from the hot solution before filtration. Similar behaviour was observed for the products N and O, and recrystallisation of P from ethanol could not be achieved for the same reason. Again, P, which was readily soluble in cold acetone, crystallised out again almost immediately : after being air-dried for 14 hours, the prisms were found to be hemi-solvated with acetone. But despite these difficulties, reproducible spectra were obtained thus allowing reliable structural deductions to be made.

When the spectra of the four products M, N, O and P were compared, the following common features emerged :

- I.r.
- i) broad general absorption between 3500 and 3000 cm^{-1} (NH stretching).
 - ii) a single nitrile stretching frequency between 2230 and 2226 cm^{-1} (aryl CN).
 - iii) strong multiple absorption between 1650 and 1610 cm^{-1} (C=N stretching).
- U.v. no red-end absorption maxima above 350nm suggesting a structure involving not more than two fused

aromatic rings (anthracene absorbs at 375nm^{53}).

- M.s.
- i) the only intense daughter ion peak at m/e 313 corresponded to the loss of $-\text{C}_6\text{H}_4\text{X}$ from the parent (confirmed by metastable peak).
 - ii) the parent ion increased by 3 mass units after samples were milled with deuterium oxide. This implied the presence of 3 labile protons.

P.m.r. (solvent : d_6 dimethylsulphoxide)

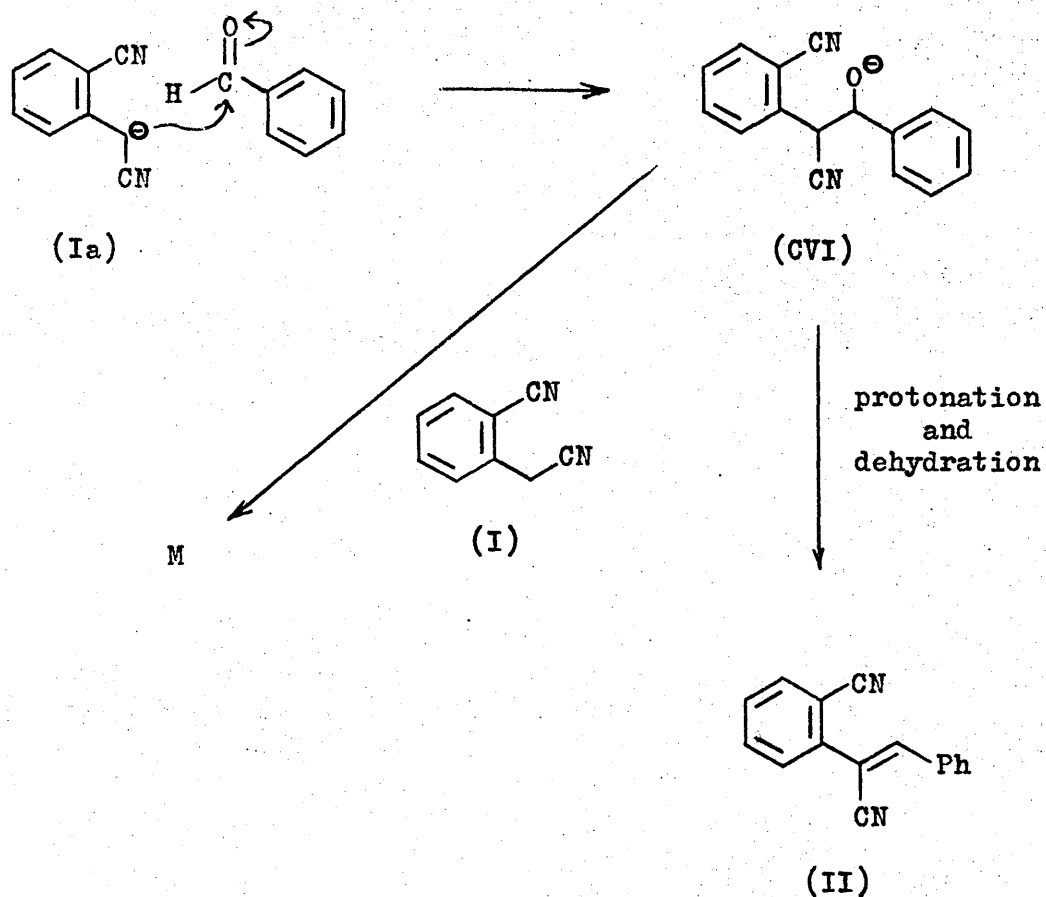
- i) three 1-proton NH signals at low field ($<2.4\tau$) (removed on addition of deuterium oxide) confirmed the mass spectral finding of 3 labile protons. The low chemical shifts suggested imino or amide groups rather than amino groups.
- ii) two 1-proton singlets at ca.5.70 and 5.65 τ showed the presence of two non-equivalent methine protons.

The product M clearly resulted from the combination of two molecules of the dinitrile (I) and one molecule of benzaldehyde. Complications in Knoevenagel condensations have been reported^{54,55} to arise from the further attack by the anion of the active methylene compound on the 1:1 condensation product. It has already been shown (Ch. VII) that in the present case such attack leads to the formation of the product (XCIV). Water would be present (from the initial condensation) so it was conceivable that alkaline hydrolysis of (XCIV) had occurred to yield the product M. But the compound (XCIV) was found to resist alkaline hydrolysis and, in any event, the possible structures for M which would have ensued could not

be reconciled with the spectral data given above. Furthermore, the observation that the present reaction afforded M in virtually unchanged yield when carried out under conditions of continuous dehydration^{10b}, contradicted any mechanism involving condensation and subsequent hydrolysis.

Starting material (72%) was recovered from an attempted methoxide catalysed addition of the compound (XIV) (Ch. I) to benzaldehyde. This result excluded the possibility that formation of M involved (XIV) as an intermediate. By considering the initial step to be self-addition of the dinitrile (I) to yield a dimeric intermediate which, rather than cyclise to (XIV), attacked the carbonyl carbon of benzaldehyde, other possible structures for M were obtained, but these were inconsistent with the spectral data. Notably, they all possessed an amino group which should have given rise to a broadened 2-proton singlet in the p.m.r. spectrum in the τ 4 region (cf. 1,3-diaminoisoquinoline spectrum)⁵.

The conclusion was, therefore, that the reaction proceeded via attack of the anion (Ia) on benzaldehyde to afford the anion (CVI) which either protonated and dehydrated to the stilbene (II) (a minor reaction product), or, reacted further with o-cyanobenzyl cyanide (I) to yield the product M.



Clearly, the anion (CVI) could cyclise to the imidic tautomer which could itself then attack the dinitrile (I) or alternatively the anion (CVI) might be protonated and then be attacked by the anion (Ia). However the resulting amino-iso-quinoline structures were discounted by the p.m.r. results for the reasons already given.

It remained to consider the possible structures for M derived from attack by the anion (CVI) on the dinitrile (I). Of the several structures obtained in this way, only one, (CVII) (X=H) could be reconciled with the p.m.r. spectral data (Table XVIII) so this structure was therefore believed correct for M.

SCHEME XI

Mechanism for the formation of the products (CVII).

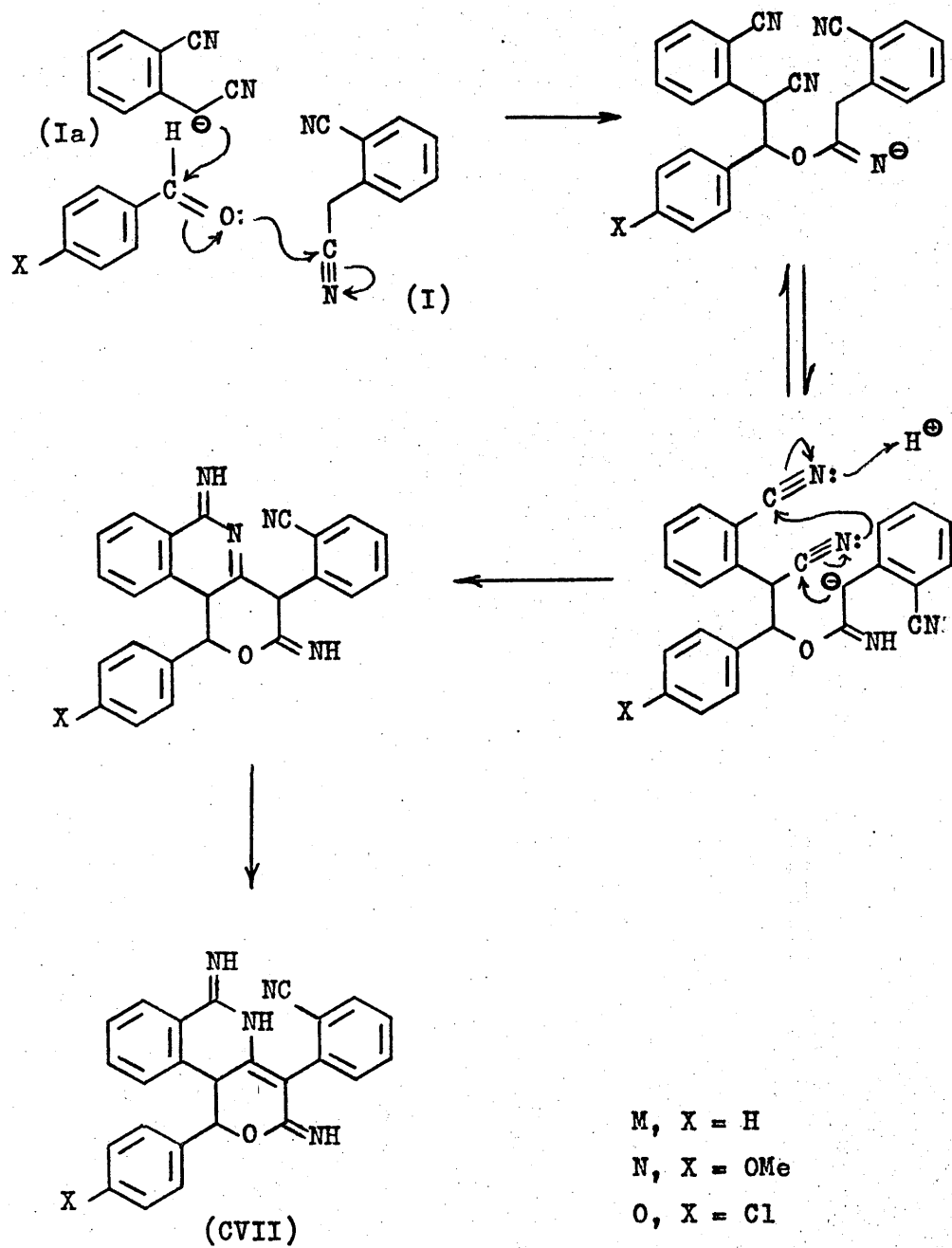
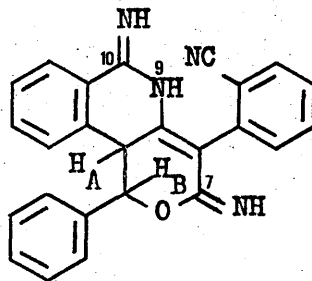


TABLE XVIII

P.m.r. results for the product M with assignments for structure (CVII) (X = H).



(CVII) (X = H)

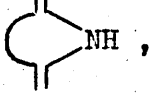
Solvent : d_6 dimethylsulphoxide.

<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
5.67	singlet	1	H_A
5.65	singlet	1	H_B
3.0-2.4	complex	11	ring protons
2.25	broad singlet ^a	1	7-NH
2.15-1.8	complex	2	ring protons
1.37	broad singlet ^a	1	10-NH
-2.03	broad singlet ^a	1	9-NH

^a removed on addition of deuterium oxide.

The assignments in Table XVIII were made on the following grounds : i) Buckling of the dihydropyran ring causes the dihedral angle between H_A and H_B to approximate 90° thus explaining the observed absence of coupling between these two adjacent protons.

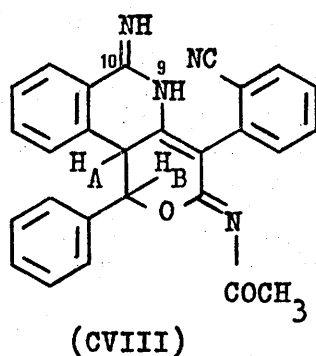
ii) The imidic nitrogen would be the most basic site with the consequence that the 7-NH could be reasonably assigned to the highest NH signal.

iii) It is known⁵⁶ that in the systems, , electron density is reduced about the endocyclic nitrogen. The acidic ring NH in (CVII) could therefore be assigned to the lowest observed NH signal.

The p.m.r. results (Table XIX), for the monoacetyl derivative, (CVIII), of M, confirmed the above assignments.

TABLE XIX

P.m.r. results for the monoacetyl compound (CVIII).

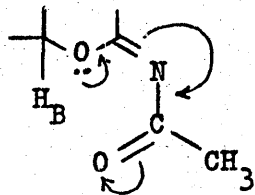


Solvent : d_6 dimethylsulphoxide.

<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
7.99	singlet	3	acetyl CH_3
5.60	singlet	1	H_A
4.78	singlet	1	H_B
3.2-1.7	complex	13	ring protons
-0.84	broad singlet ^a	1	10-NH
-1.56	broad singlet ^a	1	9-NH

^a removed on addition of deuterium oxide.

Disappearance of the highest field NH signal showed, as expected, that acetylation had occurred at the most basic nitrogen. Increased resonance electron withdrawal by the acetyl group (cf. >NH) would cause the observed downfield shift of H_B .



The compounds (CVII) were unaffected by hot dilute mineral acids in which they were insoluble. No useful products resulted from treatment with concentrated mineral acids. However, when the compound N, (CVII, X = OMe), was heated under reflux in 50% aqueous trifluoroacetic acid, the material dissolved to give a yellow solution which, on cooling, afforded colourless needles of a product $C_{27}H_{21}N_3O_4$. Loss of a molecule of water during thermogravimetric analysis indicated that this was a monohydrate, $C_{26}H_{19}N_3O_3 \cdot H_2O$, and the appearance of a parent peak at m/e 421 in a mass spectrum confirmed that the true molecular formula was $C_{26}H_{19}N_3O_3$. The p.m.r. spectra - in two solvents - (Table XX) verified the conversion of the product N to the lactone (CIX).

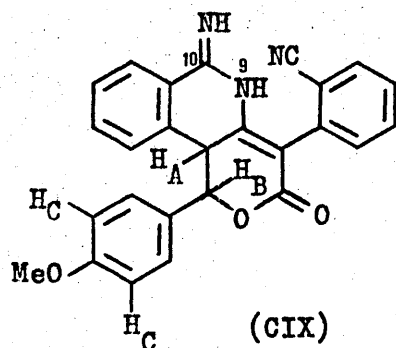


TABLE XX

P.m.r. results for the lactone (CIX).

i) Solvent : d_6 dimethylsulphoxide .

<u>Signal (τ)</u>	<u>Multiplicity</u>	<u>Intensity</u>	<u>Assignment</u>
6.29	singlet	3	OCH_3
5.83	singlet	1	H_A
5.40	singlet	1	H_B
3.09	doublet (showing finer splitting), J_o ca. 10 Hz	2	H_C
2.9-1.7	complex	10	ring protons
-0.4	v. broad singlet ^a	2	2 x NH

^a removed on addition of deuterium oxide.

ii) Solvent : deuteriochloroform.

6.25	singlet	3	OCH_3
5.37	singlet	1	H_A
5.34	singlet	1	H_B
3.14	doublet (showing finer splitting), J_o ca. 10 Hz	2	H_C
2.8-2.1	complex	10	ring protons
1.44	broad singlet	1	<u>syn-</u> and
1.33	broad singlet	1	<u>anti-10-NH</u>
-0.9	v. broad singlet	1	9-NH

The signals from the two NH protons of (CIX) merged to a broad singlet in d_6 dimethylsulphoxide, indicating that exchange between these two protons in this solvent was fast on the n.m.r. time scale. However, the exchange rate in deuteriochloroform was clearly reduced since separate signals were observed. The appearance of the higher-field signal as a broadened doublet was attributed to syn- and anti-forms of the imino group.

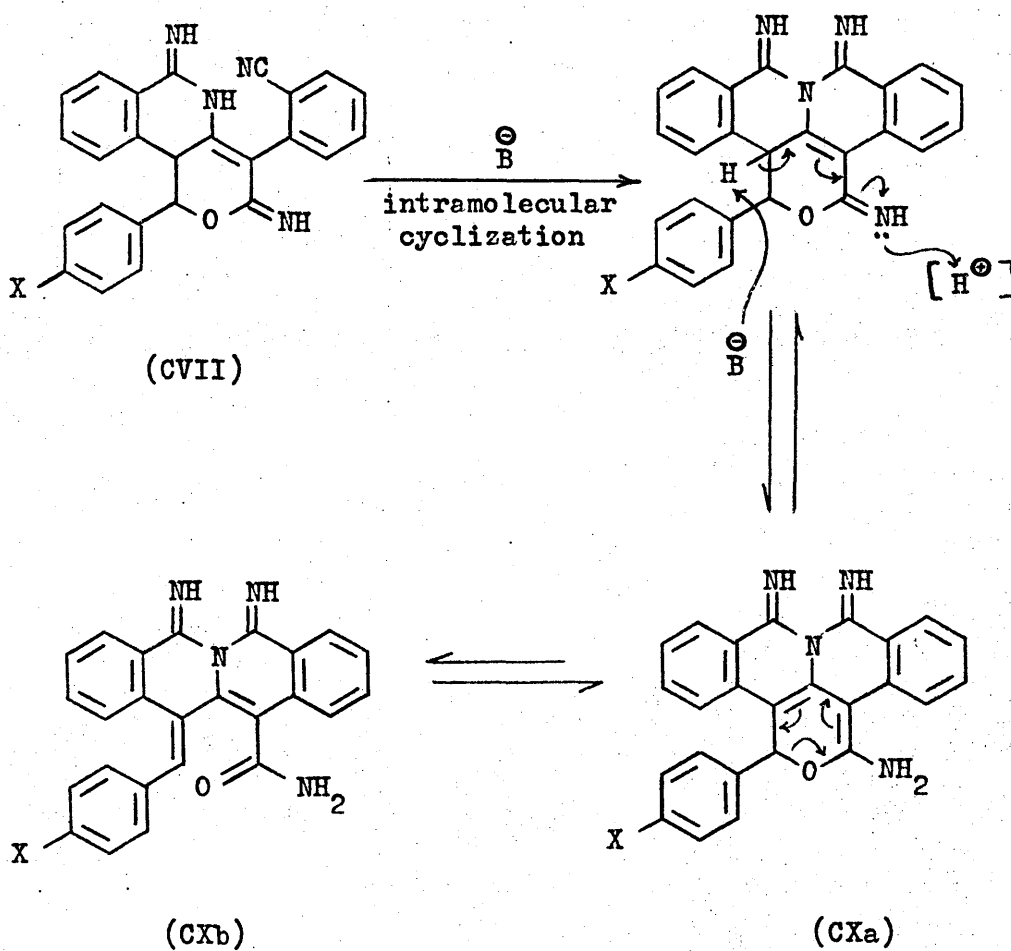
In accord with the structure (CIX) an i.r. spectrum showed the persistence of the nitrile stretching frequency at 2230 cm^{-1} and a δ -lactone carbonyl stretching frequency at 1730 cm^{-1} .

Treatment of the compounds M, N, O and P with dilute sodium hydroxide gave fine, bright yellow prisms of Q, R, S and T respectively. Closely corresponding u.v. absorption curves showed these products to be homologues. Extension of the light absorption to 404nm and the absence of a nitrile stretching frequency in their i.r. spectra, suggested that intramolecular cyclization across the nitrile group in the compounds (CVII) had occurred to yield these products. The composition of Q, $C_{25}H_{18}N_4O$, was identical to that of M and whilst initially the mass spectrum of Q appeared to suggest a M.W. two mass units less (i.e. 388), enhanced intensity of the peak at 390 over the predicted intensity from isotopic abundance tables³⁰ together with a metastable at 386 corresponding to the fragmentation

390 \rightarrow 388, confirmed that the M.W. was, in fact, 390. The same features were observed in the mass spectra of R, S and T and the presence of an intense peak at 313 in all four spectra, which could only be assigned to the loss of C_6H_4X from the parent ion (confirmed by metastable peak), supported the above conclusion.

The solubilities of these yellow products were lower than those of the compounds (CVII). However, the p-butoxy product, T, was sufficiently soluble in d_6 dimethylsulphoxide for a p.m.r. spectrum to be obtained. This spectrum showed signals of unequal intensity from two butoxy groups. From the areas of the signals it was clear that a slightly broadened singlet at 4.12 τ and two low-field broadened singlets (1.53 and 0.73 τ) were associated with the more intense butoxy signals whilst two very low-field broad singlets (-1.91 and -2.60 τ) were associated with the less intense butoxy signals. The remaining signals gave rise to a complex pattern in the aromatic region (3.7 to 1.7 τ).

On the above evidence, treatment of the compounds (CVII) with base was believed to form products having the structure (CX), which in solution, at least, existed predominantly in the tautomeric form (CX_a).



- Q, X = H
 R, X = OMe
 S, X = Cl
 T, X = OBu

The broad singlets at 1.53 and 0.73 were assigned to non-equivalent amido protons in (CXa) whilst those at -1.91 and -2.60 were assigned to the corresponding protons in (CXb). The remaining labile protons evidently gave rise to signals under the aromatic complex as presumably did the olefinic

proton in (CXb). The signal at 4.12 τ was assigned to the methine proton in (CXa) and its slight broadening was believed to arise from the slow tautomerism (CXa) \rightleftharpoons (CXb).

The i.r. spectra of the compounds Q, R, S and T were similar and absorptions at ca. 3420, 3340 (NH₂ stretching) and ca. 1660s (amide I band) were not inconsistent with the presence of an amido group.

Small yields of the products Q, R, S and T were obtained directly from the reaction of the dinitrile (I) with the appropriate *p*-substituted benzaldehyde in the presence of methoxide. It was clear that methoxide achieved the conversion (CXII) \longrightarrow (CX) as effectively as hydroxide. Slightly higher yields of (CX) could be obtained by extending the duration of the reaction or increasing the concentration of methoxide, but both these reactions were very dirty, presumably due to self-condensation reactions of the excess benzaldehyde and from methoxide attack on the minor stilbene product.

PART II

EXPERIMENTAL

TELEPHONE MESSAGE

For

From

Received by

Time

Date

OMAR

Fr...



11

Fig 2-4. GC 10

Gas Chromatography

Pye GC 10. gas chromatograph with flame ionisation detector. Separations were performed on glass columns 1.5m x 6mm od. The columns were operated with nitrogen carrier gas flow of 40cm³ min⁻¹

10% Carbowax 20M.

Polar

polyethylene glycol av ml wt 20000

OV1 non polar

OV17 semi polar.

NOTES

Analytical and Spectral Data:

Melting points were determined on a Kofler micro hot stage using standardised thermometers. Mixed melting points were determined using a Gallenkamp melting point apparatus.

Microanalyses were performed either by Dr. Alfred Bernhardt, Microanalytisches Laboratorium, W. Germany, or by the Microanalytical Service, Chemistry Department, University of Surrey, Guildford.

A Stanton Instruments Ltd. Thermobalance was used to obtain thermogravimetric analyses.

Mass spectra were obtained using an Associated Electrical Industries MS 12 Spectrometer (ionization energy, 70 eV).

Ultraviolet data were obtained using a Unicam SP 800 B Spectrophotometer. Unless otherwise stated, the solvent used was 96% ethanol. When tetrahydrofuran was used as solvent, it was first redistilled under nitrogen. The following abbreviations are used after the absorption values: infl, inflection; sh, shoulder.

For routine infra red absorption spectra, a Unicam SP 200 spectrophotometer was used whilst, for more precise measurements, spectra were taken on a Grubb Parsons Spectromaster or a Perkin-Elmer 157G Grating Spectrophotometer. The spectra are those of the compounds as nujol mulls unless otherwise stated. The following abbreviations are used after the absorption values: s, strong; br, broad; w, weak; sh, shoulder.

The proton magnetic resonance results were obtained using either a Perkin-Elmer 60 MHz N.M.R. Spectrometer operating at a sample temperature of 34° or a Bruker WH 90 FT N.M.R. Spectrometer. Tetramethylsilane (t.m.s.) was used as internal standard with all solvents.

Reagents and Solvents:

With the exception of those mentioned separately, all reagents were supplied by B.D.H. Chemicals Ltd., Poole, England or by Fisons Scientific Apparatus Ltd., Loughborough, England.

Whenever used, nitrogen was first dried by passing through concentrated sulphuric acid.

Ethanol, unless otherwise stated, means the 96% aqueous azeotrope.

Benzaldehyde was distilled under nitrogen before use. Other aldehydes were used as supplied.

p-Butoxybenzaldehyde was supplied by Eastman Kodak Co., Rochester, N.Y.

o-Toluonitrile was supplied by Fluka AG, Switzerland. This material was converted to o-cyanobenzyl chloride⁵⁷ which was then treated with sodium or potassium cyanide to afford o-cyanobenzyl cyanide⁵⁸.

P.m.r. data for these three compounds were obtained from reference 5.

Purified o-cyanobenzyl cyanide (m.p. 77°) was obtained from the crude product prepared in the above manner either by several recrystallisations from aqueous ethanol (charcoal) or by cold-finger sublimation at 90°/15mm.

o- α -Dicyanostilbene⁹ was purified to constant melting point (125°) before use. Spectral data for this compound are given below:

I.r. ν_{\max} , 2223, 2212, 1595, 1576w, 1289w,
1248w, 1205w, 1188w, 1075w, 946, 770,
756, 686 cm^{-1} .

U.v. λ_{\max} (nm) ($\epsilon \times 10^{-3}$): 212 (30.4), 227sh (15.4),
250sh (7.9), 306 (23.0).

P.m.r. At 60MHz, the p.m.r. spectrum of the compound in deuteriochloroform was observed as a complex pattern of signals between 2.7 and 1.9 τ .

CHAPTER IX

PRODUCTS FROM THE REACTION OF o-CYANOBENZYL CYANIDE WITH SODAMIDE IN FORMAMIDE.

Notes: Formamide was deoxygenated by passing dry nitrogen through it for 45 min.

The reaction was performed under nitrogen and with light excluded.

(i) 1-Amino-4-cyano-3-(o-cyanobenzyl)isoquinoline (XIV).-

o-Cyanobenzyl cyanide (I) (8.25g) was dissolved with warming in formamide (80ml). The solution was cooled to room temperature and an ice-cold solution of powdered 85% sodamide (6g) in formamide (100ml) was added in small portions. The reaction solution immediately became light tan in colour and was stirred at room temperature for 2h. The product, which had begun to separate after 1h, was collected, washed with a little formamide, boiled in ethanol to remove occluded formamide, dried, and recrystallised from tetrahydrofuran to yield colourless prisms of (XIV)

(1.57g, 18%), m.p. 223-224° (Found.: C, 76.1; H, 4.2; N, 19.6.

$C_{18}H_{12}N_4$ requires C, 76.1; H, 4.2; N, 19.7%), m/e 284.

ν_{\max} (cm^{-1}) : 3450, 3348, 3200br, 2226, 2206, 1653s, 1619, 1580

1558, 1511, 1491, 1408, 1195, 788, 775, 759, 682. U.v. p29.

(ii) Monoacetyl derivative (XXI). - The preceding product (0.71g) was ground and added to acetic anhydride (5ml) in glacial acetic acid (5ml) and heated under gentle reflux for 35min. The hot reaction solution was poured onto ice (30g) and the oil which formed soon solidified when scratched. Crystallisation from tetrahydrofuran gave colourless prisms of (XXI) (0.74g, 91%), m.p. 233-235^o (decomp.) (Found : C, 73.8; H, 4.3; N, 17.3.

$C_{20}H_{14}N_4O$ requires C, 73.6; H, 4.3; N, 17.2%), m/e 326. ν_{max} (cm^{-1}) : 3280, 2222, 2212, 1674, 1663s, 1573, 1523, 1340, 1308, 1019, 782, 765, 755, 677. λ_{max} (nm) ($\epsilon \times 10^{-3}$) : 240 (35.2), 279infl. (6.9), 285 (8.1), 294 (8.8), 306 (10.6), 335 (10.6), 349sh. (7.5).

(iii) 12-Cyano-6,11-diaminobenzo(c)phenanthridine (XXII). - Water (ca. 300ml) was added to the reaction filtrate from (i) till turbid. The green solid which separated was collected after 1h, washed with a little ethanol and recrystallised from ethanol (charcoal) to give yellow needles of (XXII) (0.25g, 3%), m.p. 285^o decomp.

(Found : C, 76.6; H, 4.2; N, 20.1. $C_{18}H_{12}N_4$ requires C, 76.1; H, 4.2; N, 19.7%), m/e 284. ν_{max} (cm^{-1}) : 3448, 3426, 3356, 3344, 2189, 1620, 1570, 1560, 1523, 1507, 1409, 768. λ_{max} (nm) ($\epsilon \times 10^{-3}$) : 220 (23.3), 234 (23.0), 254 (32.4), 271 (35.2), 293 (19.8), 303infl. (19.0), 319 (17.2), 360 (14.0), 394sh (6.2).

(iv) 1-Amino-3-formamidoisoquinoline (XIII) .- After collection of

(XXII), the reaction filtrate from (iii) was again made turbid by the addition of water (ca. 300ml) and the pale yellow product which separated was recrystallised from ethanol (charcoal) to yield colourless needles and splinters of (XIII) (1.54g, 14%), double m.p. 207-208° and 217°. The mixed crystalline form and double m.p. persisted after successive recrystallisations from ethanol (Found : i) C, 64.5; H, 4.9; N, 23.1; ii) C, 64.4; H, 4.9; N, 23.5. $C_{10}H_9N_3O$ requires C, 64.2; H, 4.8; N, 22.5%), m/e 187. ν_{max} (cm^{-1}): 3475, 3388 (NH_2 asym. and symm. stretch), 3260s (amide NH stretch). 3160br (bonded NH stretch), 1675s, 1650s (amide I bands), 1619s, 1602, 1562, 1523, 1510, 1408 1327, 1290s, 1199, 995, 795s, 787s, 739, 678.

(v) Hydrolysis of (XIII) to 1,3-diaminoisoquinoline (IV).- The compound (XIII) (0.1g) was dissolved in ethanol (5ml) and 2N sodium hydroxide (20ml) and the reaction heated under reflux for 1h. Evaporation of alcohol from the solution precipitated yellow solid which was collected, washed thoroughly with water and recrystallised from aqueous methanol to yield yellow prisms of (IV) (0.06g, 71%), m.p. 232-233° (lit.⁵ 231.5-232.5°) undepressed by admixture with authentic specimen. The i.r. spectrum of a nujol mull of the product was identical to that of (IV) prepared by reaction of ammonia with (I).

(vi) 1-Amino-4-carbamoyl-3-(o-cyanobenzyl)isoquinoline (XXXII) .- Repetition of the reaction of (I) with sodamide in formamide under the same conditions again gave (XIV) (0.77g, 9%). Addition of

water (ca. 300mls) to the reaction filtrate failed to precipitate (XXII) on standing for 1h. The cream product which separated after 12h was collected and recrystallised from ethanol (charcoal) to give colourless plates of (XXXII) (0.92g, 10%), decomp. 256° (Found : C, 71.6; H, 4.6; N, 18.5 . $C_{18}H_{14}N_4O$ requires C, 71.5; H, 4.6; N, 18.5%), m/e 302. ν_{\max} (cm^{-1}) : 3472, 3381 (NH_2 asymm. and symm. stretch), 3196br (bonded NH stretch), 2224 ($C\equiv N$ stretch), 1685s (amide I), 1620s, 1605, 1572 (amide II), 1524, 1414, 1361, 1332, 1299, 1266s, 1250, 1156, 799, 763, 746, 678. λ_{\max} (nm) ($\epsilon \times 10^{-3}$) : 222 (42.0), 252 (16.2), 277sh (3.8), 285sh (5.8), 312 (12.6), 342infl (6.0).

Formylation of 1,3-diaminoisoquinoline .- Acetic formic anhydride²⁸ was prepared by adding 100% formic acid (1ml) to acetic anhydride (2ml) at 0° , heating the mixture at 50° for 15min and immediately cooling in ice.

(vii) 1-Amino-3-formamidoisoquinoline (XIII) .- Cold acetic formic anhydride (3ml) was added dropwise to a solution of (IV) (0.24g) in 100% formic acid (5ml) at ice-water temperature and the reaction was stirred at 0° for 2h. Water (20ml) was added and the solution neutralised with aqueous sodium carbonate. The product which separated was collected, washed with water and crystallised from ethanol (charcoal) to yield colourless needles of (XIII) (0.22g, 79%). The product had identical i.r. spectrum and double m.p. to those of (XIII) prepared in (iv) above.

(viii) 1,3-Diformamidoisoquinoline (XXX) .- When the above formylation reaction was repeated at room temperature for 6h, the almost colourless product which began to separate from the amber solution after 4.5h was collected and a second crop obtained by addition of water (10ml) to the filtrate. The combined crops were recrystallised from tetrahydrofuran-ethanol (charcoal) to yield colourless fine needles of (XXX) (0.2g, 62%) m.p. 262-263 (decomp.) (Found : C, 61.4; H, 4.1; N, 19.5. $C_{11}H_9N_3O_2$ requires C, 61.4; H, 4.2; N, 19.5%), m/e 215. ν_{\max} (cm^{-1}) : 3220 br, 3140br, .3080br, (NH stretch); 1690s, 1670s (amide I bands); 1633, 1525, 1460s, 1430, 1406, 1380, 1365, 1340s, 1280, 1259s, 1235, 1150, 1128, 810br, 750, 707, 689, 660. λ_{\max} (nm) ($\epsilon \times 10^{-3}$) : 240 (37.9), 277sh (7.0), 290 (11.6), 301 (12.1), 347 (6.1).

CHAPTER X

PRODUCTS FROM THE REACTION OF o- α -DICYANOSTILBENE WITH AMMONIA

AND WITH SODAMIDE IN FORMAMIDE.

(i) 1-Amino-4-cyano-3-phenylisoquinoline (XX) .- In formamide (40ml), outgassed by passing dry nitrogen through it for 40min, sodamide powder (0.5g) was dissolved slowly with stirring and cooling. With the temperature maintained at ca. 20^o, o- α -dicyanostilbene(II) (1.15g) was added in small portions to the colourless solution. After 15 min. stirring at room temperature, the added dinitrile had dissolved and the solution had become golden brown. Light was excluded and the solution was stirred under nitrogen for 1h. The golden brown solution was stoppered and placed in the refrigerator. After 6 days, appreciable precipitation of colourless product had occurred. The solid was collected under nitrogen and on drying it became pale lilac in colour. Recrystallisation from diethyl ether gave colourless needles. A second crop, shown by i.r. to be the same product, separated from the reaction filtrate and was collected. It was found stable in air and was recrystallised from ethanol. The combined yield of colourless needles was 0.3g, 24%. M.p. 173-174^o (Found : C, 78.3; H, 4.4; N, 17.3 . C₁₆H₁₁N₃ requires C, 78.4; H, 4.5; N, 17.1%), m/e 245. ν_{\max} (cm⁻¹) : 3546, 3357, 3218br, 2193, 1642s, 1615,

1550, 1545s, 1348, 1250w, 1150w, 780w, 760, 700, 683, U.v. p. 52.

(ii) Reaction of o- α -dicyanostilbene(II) with ammonia .- The dinitrile(II) (1.0g) was placed in a Carius tube cooled in ice. Ammonia (ca. 7ml) in methanol (10ml) was added and the tube sealed. Heating at temperatures below 100^o did not cause significant reaction whilst at higher temperatures gross decomposition occurred.

CHAPTER XI

PRODUCTS FROM THE REACTION OF o - α -DICYANOSTILBENE WITH HYDRAZINE.

Notes: Reactions were performed under nitrogen and solvents were first deoxygenated by passing nitrogen through them. In all cases when starting material was recovered or o -cyanobenzylcyanide (I) or 1,3-dihydrazinoisoquinoline (XLI) was obtained as product, its identity was confirmed by m.p. and i.r. comparison with that of authentic material.

(i) Reaction of o - α -dicyanostilbene (II) with hydrazine .-

(a) The dinitrile (II) (1.73g) was dissolved in hot ethanol (100ml), and hydrazine hydrate (1.5g, 4mol) in water (40ml) was added. The amber solution was heated under reflux for 4h, cooled in ice and kept overnight at 5°. Some darkening of the solution occurred but no product separated. Evaporation of the solution to ca. 40ml under reduced pressure then afforded fawn plates (0.74g, 74%) which on recrystallisation from ethanol gave (I) as colourless plates (0.34g, 34%). The dark reaction filtrate yielded only tar from which no crystalline product could be obtained.

(b) The dinitrile(II) (1.73g) was dissolved in hot ethanol (100ml), hydrazine hydrate (0.75g, 2mol) and hydrazine dihydrochloride (4.61g, 2mol) in water (40ml) were added, and the solution heated under reflux for 28h. Cooling the solution in ice afforded needles which, after recrystallisation from ethanol, were identified as starting material (0.37g, 21%). Reduction of the reaction filtrate to ca.40ml under reduced pressure, filtration through charcoal and cooling gave further product. Recrystallisation of this product from ethanol (charcoal)-water yielded colourless plates of (I) (0.30g, 35%). The reaction filtrate was made turbid by the addition of water and the solid which separated was collected, dried, dissolved in benzene and loaded on to an alumina column (100-200mesh) (50g). The first fraction from elution with the same solvent gave yellow prisms (0.38g, 31%), m.p. 92° , m/e 208, of benzalazine (XLVI) (m.p. lit.³⁷ 93°), treatment of which with 2,4-dinitrophenylhydrazine in dilute hydrochloric acid afforded the dinitrophenylhydrazone of benzaldehyde.

(c) Hydrazine dihydrochloride (3.9g, 5mol) was ground and stirred with refluxing absolute ethanol (50ml). The dinitrile(II) (1.73g) was added and the solution heated under reflux for 48h. On cooling, starting material (1.64g, 95%) was recovered.

(d) The dinitrile(II) (1.73g) was dissolved in hot ethanol (100ml). Hydrazine dihydrochloride (7.88g, 10mol) in water (30ml) was added and the solution heated under reflux for 24h. On cooling, starting

material (1.7 g, 98%) was recovered.

(e) The dinitrile(II) (1.73g) was dissolved in a hot solution of hydrazine hydrate (3.75g, 10mol) in absolute ethanol. The solution was heated under reflux for 2h, reduced to half volume and cooled in ice. The dark amber colour of the solution indicated some decomposition, but no product separated. Addition of water (50ml) caused the crystallisation of almost colourless flakes of the dinitrile(I) (0.86g, 81%). The filtrate became very dark and no further crystalline product was obtained from it.

(f) The dinitrile(II) (1.73g) was dissolved in warm hydrazine hydrate (50ml). Oily droplets (o-cyanobenzyl cyanide) appeared in the bright yellow solution but dissolved as the temperature was raised to 95°. After heating for 2h at this temperature, the amber solution was cooled in ice. Slow precipitation of pale yellow product was achieved by bubbling nitrogen through the cold solution for 2h. Recrystallisation from benzene gave pale yellow prisms of the product (XLI) (1.25g, 88%) m.p. and mixed m.p. 136° (decomp.).

(g) The dinitrile(II) (0.5g) was dissolved in 95% hydrazine (20ml) at 15° and the flask was stoppered. After 4 days, half the solution was evaporated under reduced pressure over concentrated sulphuric acid to yield a black tar. Evaporation of an ether (charcoal) extract gave brown solid which when recrystallised from ethanol(charcoal)-water gave colourless flakes of the dinitrile (I).

Water (15ml) was added to the remaining half of the reaction solution, and the product which separated was recrystallised from ethanol (charcoal)-water to give colourless flakes of the dinitrile(I) (total yield, 0.15g, 48%).

(h) The dinitrile(II) (0.7g) was added in small portions to 95% hydrazine (20ml) at 80°. The temperature of the golden solution was raised to reflux temperature (ca. 140°) and the solution heated under reflux for 1h. Addition of water (20ml) to the solution at ice-water temperature precipitated reasonably pure pale yellow prisms of the product (XLI) (0.37g, 64%). The dark filtrate was discarded.

(i) Sodium methoxide (0.1g Na in 5ml MeOH) was added to 95% hydrazine (25ml) and the solution heated to 50°. The dinitrile(II) (1.15g) was added in small portions and the deep red solution was maintained at 60° for 2h. The solution was cooled in ice, water (20ml) was added and a product slowly separated over 1h. Recrystallisation from benzene-petroleum ether (b.p. 60-80°) gave a first crop of fine yellow prisms (0.01g), m.p. 241-243°, m/e 327, and ν_{\max} 3340, 1644, 1615, 1570, 1525s, 1262, 1233, 943, 762, 701, 676 cm^{-1} . A second crop of almost colourless flakes was identified as the dinitrile(I) (0.26g, 37%).

(ii) Reaction of o- α -dicyanostilbene(II) with sodium carbonate .- The dinitrile(II) (0.38g) was dissolved in a hot solution of sodium carbonate (1.06g) in water (20ml) and ethanol (30ml), which was heated under reflux for 1h. Water (20ml) was added to the amber solution and the solid which separated was collected, boiled with

water (to dissolved sodium carbonate impurity) and collected by hot filtration. The bright yellow prisms (0.04g, 13%) were identified by m.p. and i.r. as the product Q, $C_{25}H_{16}N_4O$, described later (Ch.XVI). Acidification of the reaction filtrate and addition of Brady's reagent precipitated benzaldehyde as the 2,4-dinitrophenylhydrazone (0.17g, 36%, from glacial acetic acid).

CHAPTER XII

PRODUCTS FROM THE REACTION OF o - α -DICYANOSTILBENE WITH HYDROXYLAMINE.

Note: Whenever mentioned, "1 mole hydroxylamine" implies 1 mole hydroxylamine hydrochloride plus 1 mole sodium hydrogen carbonate.

(i) The bisamidoxime (LVI) from o - α -dicyanostilbene (II). -The dinitrile (II) (4.60g, 0.02mol) was dissolved in hot ethanol (140ml) and water (50ml). A solution of hydroxylamine hydrochloride (5.56g, 0.08mol) and sodium hydrogen carbonate (6.72g, 0.08mol) in water (35ml) was added and the solution heated under reflux for 27h. Evaporation of the reaction solution to half volume under reduced pressure gave the product (LVI) on cooling. One recrystallisation from ethanol (charcoal) yielded colourless prisms of (LVI) (3.88g, 66%) which decomposed without melting at ca. 230° (Found : C, 64.5; H, 5.4; N, 18.9.

$C_{16}H_{16}N_4O_2$ requires C, 64.9; H, 5.4; N, 18.9%), m/e 296, u.v. p. 65, ν_{max} : 3420, 3330, 3245br, 1675, 1668, 1640, 1630, 1575, 1504, 1348, 1222, 1205, 1168, 1156, 1098, 920, 778, 733, 700, 670. cm^{-1} .

The bisamidoxime (LVI) with iron (III) chloride gave a violet colour which gradually turned black.

The same product (LVI) was obtained when the following changes in the reaction conditions were made :

- (a) The reaction was terminated after 24h. (Yield of (LVI), 62%)
- (b) The reaction was terminated after 18h and only 3 moles of hydroxylamine were used (Yield of (LVI), 52%).
- (c) Aqueous dioxan used as solvent and the reaction terminated after heating under reflux for 3h (Yield (LVI), 30%).
- (d) Excess sodium hydrogen carbonate (4mol) was used and the reaction terminated after 23h (Yield (LVI), 61%).

The bisamidoxime (LVI) was found to be stable under the following conditions:

(a) The bisamidoxime (LVI) (0.5g) was dissolved in a hot solution of sodium carbonate (0.18g) in ethanol (50ml) and water (30ml) and the solution was heated under reflux for 3h. On cooling, colourless prisms of (LVI) separated and a second crop of impure bisamidoxime (LVI) was obtained by reduction of the filtrate volume. After recrystallisation from ethanol (charcoal), the yield of (LVI) was 0.42g, 84%.

(b) The bisamidoxime (LVI) (0.5g, $1.7 \times 10^{-3}\text{mol}$) was dissolved in hot ethanol (150ml) and a solution of hydroxylamine

hydrochloride (0.12g , $1.7 \times 10^{-3}\text{mol}$) and sodium hydrogen carbonate (0.42g , $5.1 \times 10^{-3}\text{mol}$) in water (30ml) was added. The solution was heated under reflux for 3h , evaporated to one third volume under reduced pressure and cooled in ice. Starting material was recovered (0.45g , 90%).

(c) The reaction (b) was repeated but the solution was heated under reflux for 25h . Recrystallisation from ethanol (charcoal) of the orange product gave colourless prisms of (LVI) (0.32g , 64%).

(d) The reaction (b) was repeated but the solution was heated under reflux for 36h . Again, recrystallisation of the orange product from ethanol (charcoal) gave colourless prisms of (LVI) (0.25g , 50%).

(e) Starting material (0.42g , 84%) was recovered when the bisamidoxime (LVI) (0.5g) was boiled for 3h in dioxan (80ml).

(f) The bisamidoxime (0.3g) was heated under a vacuum of 0.05mm in an attempt to obtain the cyclic product (LXVII) by sublimation. No sublimation occurred as the temperature was raised to 200° and the bisamidoxime (LVI) was recovered unchanged.

(ii) Homophthalimide dioxime (LV) from o- α -dicyanostilbene (II) .-

The dinitrile (II) (1.15g , 0.005mol) was dissolved in hot ethanol (40ml) and a solution of hydroxylamine (1.39g , 0.02mol) and sodium hydrogen carbonate (0.84g , 0.01mol) in water (15ml) was added. The solution became yellow immediately and was heated under reflux

for 3h. Some product had separated and was collected. Cooling in ice yielded a second crop, and a third crop was obtained by reducing the filtrate to ca. half volume. The combined crops were recrystallised from aqueous ethanol to give yellow prisms of the dioxime (LV) (0.58g, 60%) identified by comparison of m.p., i.r. spectrum and mass spectrum with those of an authentic sample.

(iii) Homophthalimide dioxime (LV) from the bisamidoxime (LVI) .-

The bisamidoxime (LVI) (0.5g) was dissolved in hot ethanol (150ml) and hydroxylamine hydrochloride (0.12g, 1mol) in water (10ml) was added. The yellow solution became fluorescent as it was heated under reflux for 3h. The volume was reduced to ca. 40 ml and the yellow product (0.12g, 37%) which separated on cooling was recrystallised from aqueous ethanol and identified as the dioxime (LV) as in (ii) above.

When the reaction was repeated at 15° for 27h, starting material (LVI) (0.37g, 74%), together with a small yield of the dioxime (LV) (0.03g, 9%), was obtained.

(iv) Homophthalimide-1-oxime (LXI) from o- α -dicyanostilbene(II) .-

(a) The dinitrile (II) (1.5g) was dissolved in hot ethanol (55ml) and hydroxylamine hydrochloride (1.36g) and sodium hydrogen carbonate (5g) in water (30ml) were added. The solution was heated under reflux for 12, kept overnight (18h) at ca.15° and heated under reflux for a further 6h. The product which separated on cooling

gave, after three recrystallisations from ethanol (charcoal), almost colourless flakes of the monoxime (LXI) (0.35g, 30%) which decomposed at 230° (Found : C,61.1; H,4.6; N,15.8. $C_9H_8N_2O_2$ requires C,61.4; H,4.6; N,15.9%), m/e 176. ν_{max} : 3200br, 1665s, 1644s, 1582, 1412, 1350, 1330, 1133, 1098, 988s, 957, 935, 860, 830, 791, 762, 720 cm^{-1} . λ_{max} (nm) ($\epsilon \times 10^{-3}$) : 220(11.8), 259(9.0), 293(1.5). The product (LXI) gave no colour change with iron(III) chloride.

(b) The dinitrile (II) (2.30g, 0.01mol) was dissolved in hot ethanol (70ml) and hydroxylamine hydrochloride (2.78g, 0.04mol) and sodium hydrogen carbonate (1.68g, 0.02mol) in water (35ml) were added. The yellow solution was heated under reflux for 30h, reduced to half volume under reduced pressure and cooled in ice. The orange product which separated was recrystallised from ethanol (charcoal) to give almost colourless flakes of the monoxime (LXI) (0.9g, 51%), identified by m.p. and i.r. comparison with the product in (a) above.

(v) Acid hydrolysis of homophthalimide-1-oxime (LXI) to homophthalimide (LXII) .- The monoxime (LXI) (0.1g) was heated under reflux for 1h in 3N-hydrochloric acid (30ml). The product which separated on cooling was recrystallised from water (charcoal) to yield colourless needles of homophthalimide (LXII) (0.065g, 71%). The product from this reaction and an authentic specimen had identical i.r. spectra and both decomposed with a characteristic dark green colour at $205-210^{\circ}$. (Lit. ^{37b} 233°).

(vi) Reaction of p-chlorobenzalhomophthalic acid dinitrile (LXV) with hydroxylamine .- The dinitrile (XLV) (1.32g, 0.005mol) was dissolved in hot ethanol (50ml) and hydroxylamine hydrochloride (1.39g, 0.02mol) and sodium hydrogen carbonate (0.84g, 0.01mol) in water (20ml) were added. The yellow solution was heated under reflux for 4h. The product (LV) which separated on cooling was collected and the filtrate evaporated to dryness under reduced pressure. The residue was washed thoroughly in water and extracted with ether (2x10ml). The solid which remained was shown (i.r.) to be the dioxime (LV). The ether extract was dried over magnesium sulphate and evaporated to dryness. The crude p-chlorobenzaldoxime (LXVI) (0.45g, 57%) was recrystallised from benzene-petroleum ether (b.p. 60-80°) to yield yellow needles, m.p. 105° (lit. ⁴¹ 107°), m/e 155. The combined fractions of the dioxime (LV) were recrystallised from aqueous ethanol to give yellow prisms (0.43g, 45%).

(vii) Attempted base hydrolysis of homophthalimide dioxime (LV) to the monoxime (LXI) .-

(a) The dioxime (LV) (0.19g, 10^{-3} mol) was added to a hot solution of hydroxylamine hydrochloride (0.14g, 2×10^{-3} mol) and sodium hydrogen carbonate (0.17g, 2×10^{-3} mol) in 96% ethanol (15ml) and water (15ml). The yellow solution was heated under reflux for 6h, salt which had precipitated was removed, and the filtrate left to stand for three days. The yellow product which separated was recrystallised from ethanol(charcoal)-water to afford yellow prisms of starting material (0.13g, 68%), identified by m.p. and i.r..

(b) The dioxime (LV) (0.20g) was dissolved in hot 96% ethanol (15ml) and sodium hydrogen carbonate (0.5g) in water (20ml) was added. The solution, after heating under reflux for 1h, gave no precipitate when cooled in ice so water (10ml) was added and the dirty solid which separated over three days was recrystallised from ethanol(charcoal)-water to afford starting material (0.11g, 55%), identified as in (a) above. No further crystalline product was obtained from the reaction filtrate.

CHAPTER XIII

PRODUCTS FROM THE REACTION OF o-CYANOENZYL CYANIDE WITH METHOXIDE IN METHANOL

Reaction of o-cyanobenzyl cyanide(I) with methoxide in methanol .-

(a) o-Cyanobenzyl cyanide (I) (1.42g, 0.01mol) was dissolved in methanol (20ml) under nitrogen and a solution of sodium methoxide (0.54g, 0.01mol) in methanol (10ml) was slowly added with stirring. With the temperature maintained at ca. 15°, the solution was stirred under nitrogen for 3h. Evaporation of the deep red solution to half volume under reduced pressure afforded pale lilac plates. A second crop was obtained by further concentration of the filtrate. Recrystallisation of the combined product from methanol (charcoal)-water gave colourless flakes of starting material (0.67g, 47%) identified by m.p. and i.r.. Evaporation of the reaction filtrate still further afforded a quantity of black tar which was discarded.

(b) o-Cyanobenzyl cyanide(I) (0.5g) was dissolved in methanol (10ml) and a solution of sodium methoxide (0.04g Na in 3ml MeOH) was added. The solution became greenish yellow immediately and was maintained at 60° for 3h under nitrogen. The deep green solution became deep red on standing at ca. 15° overnight. The colour was

discharged on neutralisation of the solution by dropwise addition of 3N-hydrochloric acid. Addition of water (20ml) precipitated an almost colourless product which was shown by i.r. to be starting material. Sublimation of the product at 90°/15mm gave colourless prisms of o-cyanobenzyl cyanide (I) (0.31g, 62%), which had a m.p. of 77° undepressed on admixture with authentic material.

(c) The procedure in (ii) was repeated using a 2 molar excess of sodium methoxide (0.16g Na in 5ml MeOH). The reaction was appreciably dirtier and a reduced yield (0.10g, 20%) of starting material (I) (identified by m.p., i.r.) was obtained on sublimation of the crude reaction product.

(d) o-Cyanobenzyl cyanide (I) (1.42g) was dissolved in methanol (20ml) and sodium methoxide (0.05g Na in 5ml MeOH) was added. The yellow solution darkened as the reaction was maintained for 8h under nitrogen at reflux temperature. Cooling in ice afforded pale yellow prisms which on recrystallisation from tetrahydrofuran (charcoal) gave colourless prisms of 1-amino-4-cyano-3-(o-cyanobenzyl)isoquinoline (XIV) (0.13g, 9%) identified by identity of m.p. and i.r. spectrum with those of authentic material.

(e) o-Cyanobenzyl cyanide (I) (0.5g) was dissolved in dimethylsulphoxide (5ml) under nitrogen. Sodium methoxide (0.05g Na in 5ml MeOH) was added and the golden solution heated to reflux temperature. The solution became dark brown on heating under reflux for 2h. Addition of water (10ml) and cooling afforded

product which on washing with water and ethanol was obtained as very pale yellow prisms of (XIV) (0.22g, 44%) (by i.r.). Recrystallisation from tetrahydrofuran gave (XIV) as colourless prisms (0.15g, 30%), m.p. 223^o, m/e 284.

CHAPTER XIV

PRODUCTS FROM THE REACTION OF o- α -DICYANOSTILBENE WITH ALKOXIDE IN ALCOHOL.

(i) 4-Cyano-1-methoxy-3-phenylisoquinoline (XL) .- o- α -Dicyano-
stilbene (II) (4.60g) was dissolved in methanol (100ml) at 60°. Sodium methoxide solution (0.2g Na in 20ml MeOH) was added and the solution was heated at 60° for 4h. The product, which separated from the dark orange solution overnight, crystallised from methanol as colourless needles (3.2g, 61%), m.p. 152° (Found : C, 78.6; H, 4.8; N, 10.7. C₁₇H₁₂N₂O requires C, 78.5; H, 4.6; N, 10.8%), m/e 260. ν_{\max} : 2220, (C≡N stretching), 1615 (C=N stretching), 1576, 1569, 1506, 1345, 1280, 1329w, 1202 (aromatic ether C-O stretching), 1170w, 1156, 1095, 1074, 1027w, 972, 872, 777, 765, 706 and 675 cm⁻¹ (aromatic C-H bending). U.v. p.89. When the reaction was scaled down to quarter quantities the same yield (61%) was obtained.

(ii) 4-Cyano-3,4-dihydro-1-methoxy-3-phenylisoquinoline (XXXIX) .- The dinitrile (II) (1.15g) was dissolved in freshly distilled methanol (30ml) outgassed with dry nitrogen and heated to 60°. With nitrogen passing through the solution, an outgassed solution of sodium

methoxide (0.07g Na in 5ml MeOH) was added and the reaction was heated at 60° for 4h. No solid separated on cooling the stoppered solution overnight so the volume was reduced under nitrogen to ca. 15ml whereupon pale yellow crystals (0.75g) separated. Re-crystallisation from methanol under nitrogen afforded a first crop (0.16g) of colourless crystals, shown by p.m.r. (see text) to be a mixture of 68% (XXXIX) and 32% (XL). A second crop, obtained during a further recrystallisation from methanol, gave colourless cubes of (XXXIX) (0.15g), m.p. 122°, m/e 262. (Found : C, 77.6; H, 5.3; N, 10.7. $C_{17}H_{14}N_2O$ requires C, 77.9; H, 5.3; N, 10.7%). ν_{\max} : 2250 (C≡N stretching), 1650s (C=N stretching), 1600, 1580, 1500, 1450s, 1355, 1322, 1319s, 1300, 1278, 1198 (ether C-O stretch), 1145, 1090, 1050, 970, 869; 784, 755, 740, 700, 688, 668 cm^{-1} (aromatic C-H bending). λ_{\max} (nm) ($\epsilon \times 10^{-3}$) : 211(26.5), 247 (7.0), 262sh (4.4).

(iii) 4-Cyano-1-ethoxy-3-phenylisoquinoline (LX).— The dinitrile (II) (2.0g) was dissolved in absolute ethanol (90ml) at 60°. Sodium ethoxide solution (0.1g Na in 5ml EtOH) was added and the solution heated at 60° for 4h. On standing at 5° overnight, the brown solution afforded crystalline product which was recrystallised from ethanol to yield colourless needles of (LX) (0.56g, 24%), m.p. 132.5 (Found : C, 78.6; H, 5.1; N, 10.0. $C_{18}H_{14}N_2O$ requires C, 78.8; H, 5.1; N, 10.2%), m/e 274. ν_{\max} : 2218 (C≡N stretching), 1620 (C=N stretching), 1580s, 1568, 1511, 1427s, 1339s, 1286, 1185 (aromatic ether C-O stretching), 1163, 1109, 1093, 1072, 1030, 1022, 891; 775, 758, 688 and 679 cm^{-1} (aromatic C-H bending). U.v. p.89.

Attempts to obtain further product from the reaction filtrate yielded only tar.

(iv) 4-Cyano-3-phenyl-1-propoxyisoquinoline (LXXXIV) .- The dinitrile (II) (1.0g) was dissolved in propanol (40ml) at 60°. A solution of sodium propoxide (0.07g Na in 10ml PrOH) was added and the solution heated at 60° for 4h. No product separated from the solution when left to stand at 5° overnight. The product which was obtained when the volume was reduced under partial vacuum to ca. 15ml was re-crystallised from ethanol (charcoal) to yield colourless needles of (LXXXIV) (0.25g, 20%), m.p. 110° (Found : C, 79.3; H, 5.7; N, 9.8. $C_{19}H_{16}N_2O$ requires C, 79.2; H, 5.6; N, 9.7%), m/e 288. ν_{max} : 2220 (C≡N stretching), 1620 (C=N stretching), 1576s, 1562, 1505s, 1425s, 1380, 1345s, 1183 (aromatic ether C-O stretching), 1152w, 1088, 1073, 1029w, 970, 898w, 868w; 777, 762, 699 and 671 cm^{-1} (aromatic C-H bending). U.v. p.89. Further concentration of the reaction filtrate yielded tar from which no crystalline product could be extracted.

(v) 1-Butoxy-4-cyano-3-phenylisoquinoline (LXXXV) .- The dinitrile (II) was dissolved in butanol (50ml) at 60°. A solution of sodium butoxide (0.07g Na in 5ml BuOH) was added and the solution was heated at 60° for 4h. No solid product separated when cooled at 5° overnight and the reaction volume was reduced under partial vacuum to ca. 15ml. A small amount of tarry product separated from the syrupy solution and was collected, triturated with a little ethanol and filtered to yield a small crop of yellow crystals which on recrystallisation from ethanol (charcoal) afforded colourless needles of (LXXXV) (0.15g, 12%),

m.p. 108. 5° (Found : C, 79.4; H, 6.1; N, 9.2. $C_{20}H_{18}N_2O$ requires C, 79.5; H, 6.0; N, 9.3%), m/e 302 v_{max} : 2230 (C≡N stretching), 1618 (C=N stretching), 1580, 1558, 1510, 1431s, 1358, 1339s, 1309w, 1286w, 1243w, 1188 (aromatic ether C-O stretching), 1100, 1080, 1039w, 955, 874w, 808w, 789w; 772, 718 and 686 cm^{-1} (aromatic C-H bending). U.v. p.⁸⁹. Further concentration of the reaction filtrate afforded a considerable amount of tar from which attempts to extract crystalline product failed.

(vi) Reaction of o- α -dicyanostilbene (II) with sodium isopropoxide in isopropanol.- The dinitrile (II) (1.0g) was dissolved in isopropanol (45ml) at 60°. A solution of sodium isopropoxide (0.07g Na in 5ml isopropanol) was added and the reaction heated at 60° for 4h. The reaction solution afforded no product on cooling overnight and concentration of the filtrate gave tar from which no crystalline product could be obtained.

(vii) Preparation of the sodium salt (LXXIV)⁴⁶ . - o-Cyanobenzyl cyanide (I) (6g) and benzoyl chloride (8g) were warmed on a steam bath until a melt was just obtained. On addition of aqueous 10% sodium hydroxide (120ml) with vigorous shaking, an exothermic reaction ensued and the solution became bright yellow. The reaction temperature was kept below 40° for 0.5h and a small quantity of solid matter was removed by filtration. The yellow crystalline paste which separated on cooling the solution for 2h was collected and re-crystallised from warm water to yield almost colourless needles which when redissolved in water and filtered through charcoal, gave a

colourless solution. The salt (LXXIV) was not isolated, because the aqueous solution was used directly in the preparation of (LXXV) and (LXXVI) (below).

(viii) Preparation of the silver salt (LXXV)⁴⁶ .- The aqueous sodium salt (LXXIV) was added to aqueous silver nitrate. The product (LXXV) precipitated as dense colourless prisms which darkened on exposure to light. The product was collected and dried without further purification and used in the preparation of (LXXIII) (below).

(ix) α -(o-Cyanophenyl)- β -ethoxycinnamionitrile (LXXIII)⁴⁶ .- The reasonably pure silver salt (LXXV) (1.3g) was slurried with sodium dried ether (20ml) and iodæthane (1.5ml) was added. The mixture was heated under reflux for 40min., silver iodide removed by hot filtration and the filtrate evaporated to dryness. The viscous residue slowly crystallised and was recrystallised from ethanol (charcoal) to give colourless needles of (LXXII) (0.5g, 50%) m.p. 115-116° (Lit.⁴⁶ 115-116°) (Found : C, 79.0; H, 5.2; N, 10.2. Calculated for C₁₈H₁₄N₂O : C, 78.8; H, 5.1; N, 10.2%), m/e 274. ν_{\max} : 2225 (aryl C≡N stretching), 2204 (α, β -unsaturated C≡N stretching); 1608 and 1519 (C=N and C=C stretching); 1490w, 1450s, 1318s, 1296w, 1275, 1252w, 1163s (ether C-O stretching), 1108, 1077w, 1015, 970w, 940w, 902w, 845; 775, 768 and 710 cm⁻¹ (aromatic C-H bending). λ_{\max} (nm) ($\epsilon \times 10^{-3}$) : 205 (24.2), 225sh (17.9), 274 (10.5), 305sh (6.7).

(x) 4-Cyano-3-phenylisocoumarin (LXXVI) .-

(a) From the sodium salt (LXXIV)⁴⁶ .- The product (LXXVI) precipitated as colourless needles when the aqueous sodium salt (LXXIV) was added to 3Nhydrochloric acid. One recrystallisation from ethanol gave needles, m.p. 208° (Lit.⁴⁶ 204-205°) (Found : C, 77.7; H, 3.6; N, 5.5. Calculated for C₁₆H₉NO₂ : C, 77.7; H, 3.6; N, 5.7%), m/e 247 ν_{\max} : 2230 (C≡N stretching), 1749s (δ -lactone C=O stretching), 1612, 1348, 1329, 1240, 1154, 1100, 1012; 760, 697, 686, 672w (aromatic C-H bending). λ_{\max} (nm) ($\epsilon \times 10^{-3}$): 2212 (27.2), 226sh (17.3), 232infl (15.6), 240infl (13.8), 305 (16.8), 330sh (12.3), 348sh (5.8). The same product (LXXVI), identified by m.p. and i.r., was obtained when the aqueous sodium salt (LXXIV) was added to a cold, saturated aqueous boric acid solution.

(b) From acid hydrolysis of (LXXVIII) .- The dinitrile (LXXVIII) (0.26g) was dissolved in a hot solution of 3Nhydrochloric acid (20ml) and concentrated hydrochloric acid (0.5ml) and the solution was heated under reflux for 1.5h. The product which separated on cooling was recrystallised from ethanol to give colourless needles of (LXXVI) (0.14g, 56%), having m.p., and i.r. and u.v. spectra identical with those of the product in (a) above.

(xi) 4-Cyano-3-phenylisocarbostril (LXXXI)⁴⁸ .-

(a) From acid hydrolysis of (LX) .- The compound (LX) (0.2g) was dissolved in acetone (15ml) and 3Nhydrochloric acid (10ml). Concentrated hydrochloric acid (1ml) was added and the reaction heated

under reflux for 1h. Colourless crystals separated as the reaction proceeded and after cooling in ice, the product was collected and recrystallised from ethanol to yield colourless needles of (LXXXI)

(0.14g, 78%), m.p. 270° (Found : C, 78.2; H, 4.2; N, 11.3.

Calculated for $C_{16}H_{10}N_2O$: C, 78.1; H, 4.1; N, 11.4%), m/e 246⁺

ν_{\max} : 3160br (bonded NH), 2230 (C=N stretching), 1665s (δ -lactam C=O stretching), 1614, 1500, 1458s, 1383, 1347, 1285w, 1273w, 1170w, 1150, 884; 775w, 764, 701 and 690 cm^{-1} (aromatic C-H bending).

λ_{\max} (nm) ($\epsilon \times 10^{-3}$) : 215 (36.2), 233infl. (19.3). 244infl. (18.2), 310 (15.8), 325sh (12.9) 340sh (6.4). Under the same conditions, acid hydrolysis of (XL) gave a product (78%) identical (m.p. and i.r. spectrum) with the product (LXXXI) obtained by acid hydrolysis of (LX).

(b) From the action of ammonia on 4-cyano-3-phenylisocoumarin (LXXVI)⁴⁸.- The isocoumarin (LXXVI) (1.0g) was heated in a sealed tube with ethanol (12ml) and liquid ammonia (ca. 7ml) at ca. 140° for 18h. The product which separated on cooling was collected and recrystallised from ethanol to yield colourless needles (0.62g, 62%) which had a m.p. and i.r. spectrum identical with those obtained for 4-cyano-3-phenylisocarbostyryl (LXXXI) in (a) above.

CHAPTER XV

PRODUCTS FROM THE REACTION OF o-CYANOBENZYL CYANIDE WITH
o- α -DICYANOSTILBENE IN THE PRESENCE OF METHOXIDE.

(i) Reaction of o-cyanobenzyl cyanide (I) and o- α -dicyanostilbene (II)
in the presence of methoxide.- o-Cyanobenzyl cyanide (I) (5.68g,
 4×10^{-2} mol) was dissolved in methanol (120ml) to which sodium methoxide
(0.2g Na in 20ml MeOH) had been added. o- α -Dicyanostilbene (II) (9.20g,
 4×10^{-2} mol) was added and the solution maintained at 60° for 4h. Crude
prisms of (XCIV), which had separated on cooling the dark brown solution
overnight, were collected and immediately, needles of (XL) crystallised
in the filtrate. Slight reduction in volume of the filtrate and
cooling afforded a crop of prisms of (XCIV) and needles of (XL).
Further reduction in volume of the filtrate under partial vacuum gave a
black gum from which no solid product could be extracted. Re-
crystallisations from ethanol (charcoal) gave a) colourless needles
of (XL) (2.60g, 25%), identified by m.p., mixed m.p. and i.r. spectrum
and b) colourless prisms of (XCIV) (4.85g, 33%), m.p. 207° (Found : C
80.3; H, 4.4; N, 15.1. $C_{25}H_{16}N_4$ requires C, 80.7; H, 4.3; N, 15.1%).
m/e 372. ν_{\max} : 3485, 3368, 3215, 2215, 2210, 1630s, 1617, 1575, 1548,
1508, 1345, 1152, 929, 874, 778, 769, 736, 691, 682 cm^{-1} . λ_{\max} (nm)
($\epsilon \times 10^{-3}$) : 220(39.0), 255(26.2), 305(24.6), 344sh(12.0), 360sh(6.4).

(ii) Monoacetyl derivative of (XCIV) .- The compound (XCIV) (3.0g) was finely ground and dissolved in acetic anhydride (20ml) and glacial acetic acid (20ml) and the solution heated under reflux for 45min. The hot pale orange solution was poured on to ice (80g) and the oil which formed was caused to solidify by scratching, to give an almost colourless product, recrystallisation of which from tetrahydrofuran afforded colourless prisms of the monoacetyl derivative of (XCIV) (2.4g, 72%), m.p. 219° (Found : C, 78.0; H, 4.3; N, 13.6. $C_{27}H_{18}N_4O$ requires C, 78.3; H, 4.4; N, 13.5%), m/e 414. λ_{max} (nm) ($\epsilon \times 10^{-3}$) (solvent : tetrahydrofuran) : 251 (31.8), 305 (25.2), 338sh (15.6), 352sh (8.9). ν_{max} : 3226, 2223, 2213, 1685, 1619, 1601w, 1576, 1568, 1510, 1344, 1280w, 1240, 1042w, 1009w, 951w, 774, 769, 693, 678 cm^{-1} .

(iii) Ozonolysis of the monoacetyl derivative of (XCIV) .- The acetyl derivative (2.07g, 0.005 mol) from ii) above was stirred in A.R. glacial acetic acid (100ml) at 10° . When most of the solid was dissolved, an approximately 3M excess of ozone was passed through the solution over 30min. Zinc dust (4g) was carefully added to the cold reaction mixture followed by cold water (100ml). The dark solution and sludge were stirred at 10° for 2h. Upon removal of the metallic sludge, addition of water (70ml) to the filtrate precipitated a dirty flocculant solid which on recrystallisation from methanol (charcoal) gave a small yield (10mg) of yellow needles m.p. 149° , m/e 273 and a quantity of tarry material. The reaction filtrate was steam distilled, the distillate affording benzaldehyde, isolated as the 2,4-dinitrophenylhydrazone (0.71g, 50%) identified by m.p. (237°), mixed m.p. and i.r. comparison with authentic material. Attempts to obtain further product from the distillation residue were abortive.

(iv) Permanganate oxidation of (XCIV) .- The compound (XCIV) (0.93g, 2.5×10^{-3} mol) was dissolved in pyridine (20ml) with stirring. With the flask cooled in ice, potassium permanganate (0.79g, 5×10^{-3} mol) in water (15ml) was slowly added. An immediate exothermic reaction was noted and manganese dioxide was precipitated. After 10min all the permanganate was consumed (no pink in spot on filter paper). The reaction was acidified with dilute hydrochloric acid (10ml 3N, 0.5ml conc.) and the manganese dioxide converted to soluble manganous salts by passage through the solution of sulphur dioxide for 15min. The colourless product in the bright yellow solution was collected, washed with boiling water to dissolve any benzoic acid present, and recrystallised from tetrahydrofuran-96% ethanol to yield colourless prisms of (C) (0.45g, 63%). Drying the product over phosphorous pentoxide below 40° gave colourless anhydrous prisms which, when analysed encapsulated, were found to have the composition C, 70.5; H, 3.7; N, 14.6. $C_{17}H_{11}N_3O_2$ requires C, 70.6; H, 3.8; N, 14.5%. The anhydrous prisms readily gained weight on exposure to air to yield a hydrate of variable composition. I.r. spectra of (C) varied according to the state of hydration and possibly intermolecular association of the sample. General broadening of absorptions was observed in the 3500 to 3000 and 1700 to 1600 cm^{-1} regions but constant absorptions were observed at : 2500, 2216, 1680s, 1620s, 1583s, 1334, 768 cm^{-1} . In absolute ethanol there were U.v. λ_{max} at 218, 256, and 333 nm. The mass spectrum of (C) was identical to that of (CI) except for overloading of the peak at 18 (water).

On heating the colourless prisms gradually converted to bright

yellow prisms of (CI), which did not melt at a sharp temperature but lost their crystalline form at ca. 270° to form an amorphous mass. A quantity of (CI) was prepared by heating (C) (0.2g) in an oil bath at 210° for 1h. The yellow product was recrystallised twice from benzene to yield bright yellow prisms of (CI) (0.14g, 75%) which again lost their crystalline form at ca. 270° (Found : C, 75.6; H, 3.3; N, 15.6. $C_{17}H_9N_3O$ requires C, 75.3; H, 3.3; N, 15.5%), m/e 271.

ν_{\max} : 3303, 2221, 1735s, 1649, 1610, 1598, 1313, 1296, 1180, 1153br, 1100, 1025, 970, 874, 773, 761, 698 cm^{-1} . λ_{\max} (nm) ($\epsilon \times 10^{-3}$): 220 (36.0), 237 (31.0), 257sh (19.7), 286 (5.9), 318 (8.9), 335inf. (8.1), 360sh (6.8), 392 (5.5), 416sh (3.2).

(v) Condensation of o-cyanobenzyl cyanide (I) with anisaldehyde to yield the stilbene (CII) .- (Preparation according to the method of Gabriel and Eschenbach⁹) o-Cyanobenzyl cyanide (10g), anisaldehyde (11.9g) and piperidine (10 drops) were heated at $140-150^{\circ}$ for 1.25h. The hot product, a dark oil, was dissolved in hot ethanol (200ml). On cooling, the product separated as pale yellow crystals which on recrystallisation from ethanol (charcoal) gave colourless needles of (CII) (11.4g, 62%), m.p. 115.5° (Found : C, 78.4; H, 4.8; N, 10.7. $C_{17}H_{12}N_2O$ requires C, 78.5; H, 4.6; N, 10.8%, m/e 260. ν_{\max} : 2228, 2212, 1612, 1593s, 1567, 1522, 1488, 1432, 1319, 1271s, 1181s, 1165, 1030, 958, 949w, 934, 832, 762, 753 cm^{-1} . λ_{\max} (nm) ($\epsilon \times 10^{-3}$) : 216 (18.4), 240sh (12.4), 260sh (4.8), 336 (24.3).

(vi) Preparation of the substituted isoquinoline (CIII) .- The dinitrile

(CII) (0.5g) was dissolved in methanol (20ml). Sodium methoxide (0.05g Na in 5ml MeOH) was added and the reaction maintained at 60° for 4h. The product which separated from the dark solution on cooling, was recrystallised from ethanol (charcoal) to yield colourless needles of (CIII) (0.2g, 38%), m.p. 168° (Found : C, 74.6; H, 5.0; N, 9.5. $C_{18}H_{14}N_2O_2$ requires C, 74.5; H, 4.8; N, 9.7%), m/e 290. ν_{max} : 2225, 1609, 1576, 1558w, 1524, 1505, 1348, 1307, 1284w, 1251, 1201, 1172, 1145w, 1092, 1031, 975, 876w, 867w, 836, 815, 790w, 769, 735w, 702w, 673 cm^{-1} . λ_{max} (nm) ($\epsilon \times 10^{-3}$): 218 (32.3), 234sh (20.6), 255 (13.6), 284 (20.6), 316 (18.5), 350sh (6.3).

(vii) Acid hydrolysis of (CIII) to the isocarbostyryl (CIV). - The substituted isoquinoline (CIII) (0.45g) was heated under reflux in acetone (45ml) and hydrochloric acid (10ml 3N and 4ml conc.) for 2h. The product which separated as the hydrolysis proceeded was collected and recrystallised from tetrahydrofuran to yield fine colourless needles of (CIV) (0.38g, 89%) m.p. 307° (Found : C, 73.7; H, 4.3; N, 10.3. $C_{17}H_{12}N_2O_2$ requires C, 73.9; H, 4.4; N, 10.1%), m/e 276. ν_{max} : 3170, 3050, 2225, 1664s, 1608s, 1522, 1501, 1450, 1345, 1298, 1260s, 1183, 1146, 1034, 882w, 870w, 845, 817, 788, 770, 701w, 684 cm^{-1} . λ_{max} (nm) ($\epsilon \times 10^{-3}$) : 216 (32.0), 235sh (13.4), 254 (11.1), 271sh (7.6), 317 (15.2).

(viii) Reaction of o-cyanobenzyl cyanide (I) and the stilbene (CII) in the presence of methoxide. - o-Cyanobenzyl cyanide (I) (2.20g) was dissolved in methanol (50ml) to which sodium methoxide (0.1g Na in 20ml MeOH) had been added. The stilbene (CII) (4.0g) was added in small

portions and the solution maintained at 60° for 4h. Cooling the dark reaction solution in ice gave crystals which on recrystallisation from ethanol (charcoal) were obtained as colourless needles of (CIII) (1.65g, 37%), identified by m.p. and i.r. comparison with a sample prepared in (vi) above. On standing, the reaction filtrate afforded a second crop, recrystallisation of which from tetrahydrofuran-ethanol (charcoal) gave almost colourless prisms of (CV) (1.62g, 26%), m.p. 217° (Found : C, 77.6; H, 4.5; N, 14.0. $C_{26}H_{18}N_4O$ requires C, 77.6; H, 4.5; N, 14.0%), m/e 402. ν_{max} : 3497, 3301, 2215, 2204, 1645s, 1604, 1591, 1577, 1550, 1512s, 1430, 1311, 1255s, 1180s, 1032, 832, 771, 759 cm^{-1} . λ_{max} (nm) ($\epsilon \times 10^{-3}$) : 219 (44.8), 232infl (33.7), 256sh (23.8), 325 (32.2).

(ix) Monoacetyl derivative of (CV) .- Compound (CV) (0.3g) was finely ground and heated under gentle reflux in glacial acetic acid (4ml) and acetic anhydride (5ml) for 15min. The hot pale yellow solution was poured on to ice (30g) and the oil which formed soon solidified on being scratched. The almost colourless product nearly completely dissolved in hot ethanol but a small quantity of bright yellow prisms remained and dissolved with difficulty only on boiling. The boiling solution was colourless but charcoal was added and after filtration, the cool filtrate afforded colourless prisms (0.29g). A second crop of bright yellow prisms (0.03g) was collected from the filtrate after it had stood overnight.

The colourless prisms were warmed in acetonitrile. Some dissolution occurred but the bulk of the prisms became bright yellow and dissolved only with difficulty on boiling to give a colourless solution.

Cooling the filtered solution afforded a crop of mixed colourless and yellow prisms which were redissolved in boiling ethanol to give a colourless solution. Yellow prisms crystallised from the warm solution and were collected. The filtrate, when cooled below 20° afforded colourless prisms. Total yield 0.25g, 75%.

Data for the colourless prisms : m.p. : Became yellow on heating, finally melting at 210° (Found : C, 75.8; H, 4.4; N, 12.5. $C_{28}H_{20}N_4O_2$ requires C, 75.7; H, 4.5; N, 12.6%), m/e 444. ν_{max} : 3420, 2212, 1709s, 1610, 1598, 1566, 1555, 1505, 1328, 1303, 1288, 1260br, 1176, 1026, 827, 770, 759, 669 cm^{-1} .

Data for the yellow prisms : m.p. 210°. ν_{max} : 3300 to 3100br. multiple absorption, 2225, 2210, 1709sh, 1690br, 1614, 1604, 1586, 1572, 1560br, 1509br, 1425, 1339, 1309, 1260, 1245br, 1176, 1026, 827, 759, 755, 671 cm^{-1} . The yellow prisms could be recovered from ethanolic solutions by inducing crystallisation above 20°. Crystallisation below 20° afforded the colourless prisms (by m.p., i.r.).

CHAPTER XVI

PRODUCTS FROM THE REACTION OF o-CYANOBENZYL CYANIDE WITH
BENZALDEHYDE IN THE PRESENCE OF METHOXIDE.

Notes: In agreement with Chapter VIII, the following
notation is employed in this Chapter:

<u>Compound</u>	<u>Structure Number</u>
M	(CVII), X = H
N	(CVII), X = Ome
O	(CVII), X = Cl
P	(CVII), X = OBU
Q	(CX) , X = H
R	(CX) , X = Ome
S	(CX) , X = Cl
T	(CX) , X = OBU

Compounds having structure (CVII) became deeper yellow
and then charred on heating. Decomposition of the
compounds was complete by 290°.

Compounds having structure (CX), except T, were stable to
heat up to ca.250° at which temperature they began to char.

(i) Reaction of o-cyanobenzyl cyanide (I) with benzaldehyde in methoxide and methanol .-

(a) The dinitrile (I) (20g) was dissolved in warm methanol (150ml), and sodium methoxide (0.2g Na in 25ml MeOH) added, followed by benzaldehyde (15g). The yellow solution was heated at 60° for 4h. Some solid began to separate from the dark brown solution after 2h. and more was obtained on cooling the flask in ice. Recrystallisation from tetrahydrofuran (THF) (charcoal) and drying at 40°/0.05 mm gave fine cream prisms of hemisolvated M (6.7g, 25%) (Found : C, 75.8; H, 5.1; N, 13.4. $C_{25}H_{18}N_4O \cdot \frac{1}{2}C_6H_6O$ requires C, 76.1; H, 5.2; N, 13.2%), m/e 390 (96%), 313 (100%), 251*. The sample after being mulled with D₂O gave m/e 393 (10%), 392 (14%), 391 (10%), 390 (4%), 316 (77%), 315 (100%) 314 (59%), 313 (14%), 253*. ν_{max} 3500-3000, 2226, 1650-1610br, 1570, 1540, 1309, 1277, 1254, 1216w, 1165w, 1047w, 1030w, 880br, 765, 756, 697, 682 cm⁻¹. λ_{max} (nm) ($\epsilon \times 10^{-3}$) (solvent:THF) 276(4.3), 284(4.3), 348(14.7).

The reaction filtrate slowly afforded a second crop of crude product, more of which was obtained by reducing the filtrate to half-volume. Further attempts to obtain solid product gave an intractable tar. The crude product was boiled in ethanol and filtered hot. The filtrate was boiled with charcoal, refiltered and allowed to cool. The colourless needles (2.16g, 7%) which separated were identified (m.p., i.r.) as o- α -dicyanostilbene (II) (cf. p.135). The residue, from the ethanol filtration, was recrystallised from THF to afford very fine yellow prisms (0.14g, 0.5%) identical (i.r., m.s.) with the product Q obtained in (ii) below.

(b) Repeating the procedure in (a) above but using sodium ethoxide and ethanol in place of sodium methoxide and methanol, the reaction became darker, and reduced yields of the same products were obtained (M, 10%; (II), 6%; Q, 0.3%).

(c) Under less vigorous conditions the reaction in (a) above was much cleaner but none of the product Q was obtained and the yield of M was reduced. Thus at 25° for 4h. the reaction afforded M (15%) and II (8%) whilst at 5° for 4h, the yield of M was 3% and of (II), 6%.

(ii) Treatment of the compound M with hydroxide .- The compound M (0.5g) was heated under reflux in 2N-sodium hydroxide for 2h. Evolution of ammonia was not detected and the solid did not dissolve but became bright yellow. Recrystallisation from THF afforded very fine bright yellow prisms of the hemihydrate of Q (0.48g, 92%) (Found: C, 75.8; H, 4.8; N, 13.7. $C_{25}H_{18}N_4O \cdot \frac{1}{2}H_2O$ requires C, 75.2; H, 4.8; N, 14.0%), m/e 390 (11%), 389 (20%), 388 (59%), 386*, 313 (100%), 251* ν_{max} 3440, 3370, 3220, 1655s, 1642s, 1610, 1584, 1571, 1540, 1522, 1435, 1346, 1284, 1259, 1150, 1119, 1020, 888, 814, 755, 747, 699 cm^{-1} ..

(iii) Acetylation of the compound M .- The compound M (3.90g) was finely ground and added to acetic anhydride (25ml) and glacial acetic acid (30ml). The mixture was heated under reflux for 2h. and cooled. Bright yellow solid was collected and recrystallised from benzene-petroleum ether (b.p. 60-80°) to afford yellow prisms of the monoacetyl derivative (3.80g, 88%). The prisms did not melt but charred at ca. 270° and finally decomposed at ca. 290° (Found : C, 75.2; H, 4.7;

N, 12.8. $C_{27}H_{20}N_4O_2$ requires C, 75.0; H, 4.6; N, 13.0%), m/e 432 (27%), 430 (18%), 390 (36%), 388 (38%), 356 (31%), 355 (100%), 313 (83%).

There were meta stable peaks at 351* (432- CH_3CO), 350* (430- CH_3CO), 292* (432- C_6H_5), 276* (355- CH_3CO), 251* (390- C_6H_5). ν_{max} 3180, 2230, 1716, 1650s, 1590s, 1550, 1396, 1315, 1218, 1200s, 1150, 1015, 992, 790, 771, 760, 735, 700, 694 cm^{-1} .

(iv) Attempted oxidation of the compound M with permanganate .- The compound M (0.39g, 0.001 mol) was stirred with pyridine (20ml) at 10°. Potassium permanganate (0.32g, 0.002 mol) in water (10ml) was added and the mixture stirred at 10° for 2h. No reaction was observed, so a further quantity of permanganate (0.32g) in water (10ml) was added and, with nitrogen passing over, the solution was heated under reflux for 1h. Although the permanganate had been consumed and manganese dioxide had precipitated, the colourless prisms (0.31g, 79%), recovered from the yellow solution after passage of sulphur dioxide, were found to be starting material (by m.p., i.r.).

(v) Reaction of o-cyanobenzyl cyanide (I) with anisaldehyde in methoxide and methanol .-

(a) The dinitrile (I) (20g) was dissolved in warm methanol (150ml) and sodium methoxide (0.2g Na in 25ml MeOH) was added, followed by anisaldehyde (19g). The yellow solution was heated at 60° for 4h. The product, collected after cooling the flask in ice, was recrystallised from THF to afford pale yellow prisms of N (8.9g, 29%) (Found : C, 74.1; H, 4.9; N, 13.2. $C_{26}H_{20}N_4O_2$ requires C, 74.3; H, 4.8; N, 13.3), m/e

420 (100%), 313 (94%), 233.5*. ν_{\max} 3500-3000 multiple absorption, 2226, 1640s, 1610s, 1570, 1540, 1510, 1309, 1253, 1179, 1032, 824, 765, 756, 737, 683 cm^{-1} . λ_{\max} (nm) ($\epsilon \times 10^{-3}$) (solvent : THF) 277 (6.2), 285 (6.0), 348 (16.0). τ (d_6 DMSO) 6.30(3, singlet), 5.72(1, singlet), 5.66 (1, singlet), 3.3-1.7 (13, complex), 1.17(1, br singlet), -2.14(1, br singlet). In a spectrum of the compound in trifluoroacetic acid, the two methine proton signals occurred at 4.96 and 4.79 τ .

Continued work-up of the reaction as in (ia) above afforded

(1). Colourless prisms of the stilbene (CII) (2.1g, 6%, from ethanol) identical (m.p., i.r.) to the product (CII) from the piperidine catalysed condensation of the dinitrile (I) with anisaldehyde (p.168).

(2). Very fine yellow prisms of R(0.9g, 3%, from THF) (Found : C, 74.1; H, 4.8; N, 13.2. $\text{C}_{26}\text{H}_{20}\text{N}_4\text{O}_2$ requires C, 74.3; H, 4.8; N, 13.3%), m/e 420 (7%), 419 (19%), 418 (58%), 416*, 313 (100%), 233.5*. ν_{\max} 3440, 3360, 3200, 1645s, 1640s, 1611, 1584, 1573, 1541, 1522, 1348, 1290, 1250, 1170, 1040, 1023, 860, 825br, 787, 760, 748, 680 cm^{-1} . λ_{\max} (nm) ($\epsilon \times 10^{-3}$) (solvent THF) 275infl (18.6), 302 (16.2), 347infl (11.0), 384 (16.2), 404 (16.6).

The same product R(95%)(by i.r., m.s.) was obtained from treatment of N with 2N-sodium hydroxide under reflux.

(b) When the reaction was continued for 24h. at 60 $^{\circ}$, the solution became very dark and the yield of N (10%) was reduced, partly

by conversion to R which was obtained in slightly increased yield (5%).
 Attack by methoxide on the stilbene (CII) gave the product (CIII)
 (3%), identical as regards m.p. and i.r. spectrum with the compound (CIII)
 already described (p.168).

(c) Repeating the reaction for 4h. at 60° using one mole of
 sodium methoxide gave a very dirty reaction from which small yields
 of R(1 - 8%) and (CIII) (1 - 2%) were isolated.

(vi) Acid hydrolysis of the compound N .- The compound N(1.00g)
 was dissolved in 50% aqueous trifluoroacetic acid (20ml) and heated
 under reflux for 4h. The yellow solution was poured on to ice (100g)
 and the yellow crystals which formed were recrystallised from methanol
 (charcoal)-water to yield colourless needles of the monohydrated lactone
 (CIX) (0.65g, 62%), m.p. 194-195° (Found : C, 71.3; H, 4.5; N, 9.6.
 $C_{26}H_{19}N_3O_3 \cdot H_2O$ requires C, 71.1; H, 4.8; N, 9.6%), m/e 421. Thermo-
 gravimetric analysis of the monohydrate gave a weight loss of 3.7%
 (90-120°). Loss of one mole of water requires a weight loss of 4.1%.
 ν_{max} 3400-3000, 2230, 1730, 1660br, 1610, 1511, 1335br, 1304, 1253, 1211,
 1178, 1035br, 939, 821, 763, 754 cm^{-1} . λ_{max} (nm) ($\epsilon \times 10^{-3}$) 227 (34.6),
 279infl (7.4), 285 (8.9), 310 (11.1), 345infl (7.1).

(vii) Reaction between-o-cyanobenzyl cyanide (I) and p-
chlorobenzaldehyde with methoxide and methanol .- The dinitrile (I)
 (5.5g) was dissolved in methanol (35ml) and sodium methoxide (0.05g, Na
 in 5ml MeOH) added. p-Chlorobenzaldehyde (5g) was added and the
 solution heated at 60° for 4h. The solid which had separated from the

cooled solution was recrystallised from THF to afford fine yellow prisms of the product O (1.25g, 15%) (Found : C, 70.5; H, 4.1; N, 13.0; Cl, 8.3. $C_{25}H_{17}N_4ClO$ requires C, 70.7; H, 4.0; N, 13.2; Cl, 8.4%), m/e 426 (22%, P+2), 425 (18%, P+1), 424 (62%, P), 313 (100%), 231*.

ν_{max} 3500-3000, 2228, 1650-1610s, 1575br, 1543, 1504, 1479, 1311, 1280, 1257, 1216, 1167, 1092, 1014, 868br, 816, 769, 759 cm^{-1} . λ_{max} (nm) ($\epsilon \times 10^{-3}$) (Solvent:THF) 276 (4.8), 284 (5.0), 348 (15.9). $\tau(d_{6,DMSO})$ 5.63(2, singlet), 3.2 to 1.6 (13, complex), 1.24(1, br singlet), -2.15(1, br singlet).

Further product was obtained by reducing the reaction filtrate to half-volume. Cooling a hot ethanol (charcoal) extract afforded colourless prisms (0.13g, 1%) identical (m.p., i.r.) with the p-chloro-substituted stilbene (LXV) described in (viii) below. Recrystallisation from THF of the ethanol-insoluble residue yielded fine bright yellow prisms S (0.10g, 1%), m/e 426 (3%, P+2), 425 (7%, P+1), 424(22%, P), 422 (48%), 420*, 313 (100%), 231*. ν_{max} 3420, 3350, 3195, 3120, 1650s, 1638s, 1608, 1580, 1568, 1540, 1523, 1345, 1290, 1276, 1262, 1086, 1020, 860, 815, 758, 747 cm^{-1} .

(viii) Piperidine catalysed condensation of o-cyanobenzyl cyanide (I) with p-chlorobenzaldehyde .- The dinitrile(I) (6.00g), p-chlorobenzaldehyde (7.46g) and piperidine (12 drops) were heated at 150° for 1.75h. The hot dark liquid was dissolved in hot ethanol (120ml) and the solution was cooled. The yellow solid which separated was collected, dried, dissolved in benzene (100ml) and passed over alumina (200g, 100-200 mesh), using benzene (600ml) for elution.

The first and last fractions of very crude material were discarded and the very pale yellow prisms, obtained by removal of the solvent from the intermediate fractions, were recrystallised from ethanol (charcoal) to afford colourless prisms of p'-chloro-o- α -dicyano-stilbene (LXV) (6g, 54%), m.p. 137^o (Found : C, 72.8; H, 3.6; N, 10.5. $C_{16}H_9N_2Cl$ requires C, 72.6; H, 3.4; N, 10.6%), m/e 264.

ν_{max} 2226, 2220, 1608, 1587, 1495, 1411, 1281, 1093, 1080, 1013, 932, 825, 774 cm^{-1} . λ_{max} (nm) ($\epsilon \times 10^{-3}$) 254 (4.8), 309 (20.8).

(ix) Reaction of o-cyanobenzyl cyanide (I) with p-butoxybenzaldehyde using methoxide and methanol .- The dinitrile (I) (8.65g), p-butoxybenzaldehyde (10g) and sodium methoxide (0.1g Na in 10ml MeOH) were dissolved in methanol (60ml) and the solution was heated at 60^o for 4h. Yellow crystalline solid separated from the dark solution and was collected. Further product was obtained by reducing the volume of the filtrate. The combined yields were boiled in ethanol and filtered hot. Treatment of the filtrate with charcoal and cooling afforded very pale yellow needles (1.36g, 6%) m.p. 85-87^o. ν_{max} 2228, 2218, 1592, 1520, 1311, 1275, 1260, 1181, 1039, 1005, 832, 755 cm^{-1} . λ_{max} (nm) ($\epsilon \times 10^{-3}$) 216 (19.0), 240sh (12.8), 260sh (5.4), 337 (25.2). By the similarities in their i.r. and u.v. spectra, the product was shown to be the p-butoxy-homologue of the stilbene (CII) (p.168). Recrystallisation of the residue from THF yielded pale yellow prisms of P (1.85g, 13%) (Found : C, 75.1; H, 5.9; N, 12.1. $C_{29}H_{26}N_4O_2$ requires C, 75.3; H, 5.6; N, 12.1%), m/e 462 (100%), 313 (67%), 212^{*}. ν_{max} 3500-3000, 2230, 1640s, 1615s, 1575br, 1540, 1507, 1308, 1250, 1175, 1030br, 870br, 820, 760, 735, 682 cm^{-1} . λ_{max} (nm) ($\epsilon \times 10^{-3}$) (solvent:THF) 277

(6.0), 285 (5.8), 348 (15.0). τ (d_6 DMSO) 9.12 (3, distorted triplet), 8.9-8.0 (4, complex), 6.06 (2, triplet showing finer splitting), 5.72 (1, singlet) 5.66 (1, singlet), 3.4-1.7 (13, complex), 1.22 (1, br singlet), - 2.16 (1, br singlet). On addition of D_2O , the signals at 1.22 and -2.16 τ were removed and the complex between 3.4 and 1.7 τ then had an intensity corresponding to 12 protons.

(x) Treatment of the compound P with hydroxide .- The compound P (0.30g) was heated under reflux in ethanol (15ml) and 2N-sodium hydroxide (20ml). After 20 min, all the solid had dissolved to give a bright yellow solution. Heating was continued for 1h. Evaporation of most of the ethanol caused the precipitation of yellow product which was collected, washed thoroughly with water and recrystallised from THF to afford bright yellow prisms of T (0.28g, 93%), m.p. 243-245 $^{\circ}$, m/e 462 (18%), 460 (80%), 458 * , 313 (100%), 212 * . ν_{max} 3420, 3340, 3180, 3135, 1655s, 1640s, 1610, 1582, 1568, 1534, 1509, 1342, 1287, 1278, 1265, 1246, 1220, 1169, 1148, 1068br, 1020, 852, 825, 809, 781, 743, 672 cm^{-1} . λ_{max} (nm) ($\epsilon \times 10^{-3}$) (solvent : THF) 275inf1 (19.0), 302 (16.7), 347 (11.4), 384 (16.6), 404 (17.0). τ (d_6 DMSO) 9.4 - 8.1 (7, complex), 6.28 (1.2, br triplet), 6.06 (0.8, br triplet), 4.12 (0.65, singlet), 3.7 - 1.7 (14, complex), 1.53 (0.61, br singlet), 0.73 (0.57br singlet), -1.91 (0.40, br singlet), - 2.60 (0.35, br singlet).

(xi) Attempted alkaline hydrolysis of the compound (XCIV) .- The compound (XCIV) (0.3g) was heated under reflux for 1h in methanol (30ml) and 2N-sodium hydroxide (7ml). On cooling in ice, the yellow solution afforded pale yellow product which on recrystallisation from

methanol (charcoal) was obtained as colourless prisms (0.2g, 67%) of starting material (by m.p., i.r.).

(xii) Attempted methoxide catalysed condensation of the compound (XIV) with benzaldehyde .- The compound (XIV) (0.28g) was dissolved in hot methanol (25ml) containing sodium methoxide (0.05g in 5ml MeOH). To the refluxing solution, benzaldehyde (0.15g) in methanol (5ml) was added dropwise. The colourless solution, which smelt strongly of benzaldehyde after it had been heated under reflux for 2h, was cooled in ice to afford colourless prisms of starting material (0.20g, 72%) (by m.p., i.r.).

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