

STUDIES IN THE QUINOLIZINE SERIES.

by

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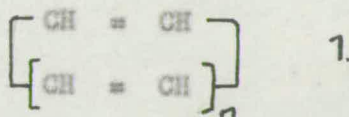
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INTRODUCTION.

INTRODUCTION.

Interest in cyclopolyolefins of the general structure (1) arises from their possible use in the verification of Hückels $(4n + 2)\bar{\pi}$ electron rule which predicts that monocyclic systems of alternate single and double bonds, having $(4n + 2)\bar{\pi}$ electrons, should exhibit a special stability.

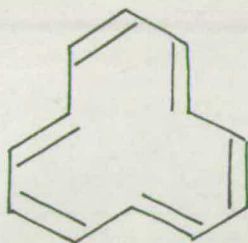


Baker² has shown that fully conjugated systems containing 10 - 18 carbon atoms, e.g. cyclododecahexaene (11), are not normally capable of existence, because of steric interference between the internal hydrogen atoms and the possibility of transannular bridging with the formation of polycyclic structures. Steric interference between the internal hydrogen atoms arises since a pre-requisite to conjugation in the system is planarity, and scale drawings by Mislow³ have shown that all cyclopolyolefins from C_8 to C_{28} must assume a buckled rather than a planar configuration to avoid repulsive interactions between hydrogen atoms situated inside the carbon periphery. Mislow also suggests that, owing to their buckled configuration, cyclopolyolefins between C_8 and

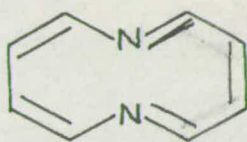
C_{28} will not possess sufficient aromatic character to be stable. However, as Baker^{2b} has pointed out, some compounds are known which are buckled, or possess C-C-C valence angles differing substantially from the optimum value of 120° and yet remain aromatic in character, e.g., di-p-xylylene and di-m-xylylene⁴. "Overcrowded" ring systems such as 3,4-5,6- dibenzophenanthrene also contain distorted benzene rings⁵. If, then, we concede that a bond angle in the cyclopolyolefin (1) could lie between 110° and 130° without seriously decreasing the resonance energy of the molecule, the steric interference of the central hydrogen atoms would be greatly reduced. Furthermore, if we assume a slight deviation from planarity to be possible, then members of the series below $C_{30}H_{30}$ should be capable of existence as stable molecules, although aromaticity may not be particularly obvious in them. Sondheimer's recent synthesis of a number of conjugated cyclopolyolefins has helped to confirm Baker's assumptions experimentally. Finally, Baker has suggested that the cyclopolyolefin, cyclooctadecanonaene $C_{18}H_{18}$, is the smallest cyclopolyene which will be both stable and show diminished unsaturation.

Various solutions have been suggested to avoid steric

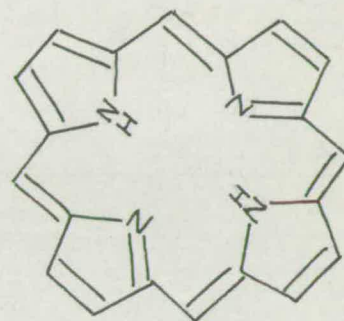
interference between the interior hydrogen atoms.



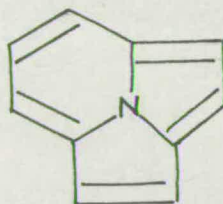
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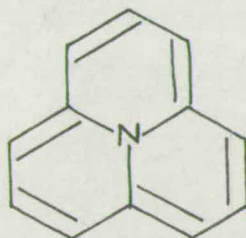
III.



IV.



V.

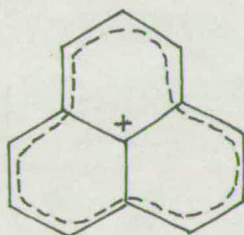


VI.

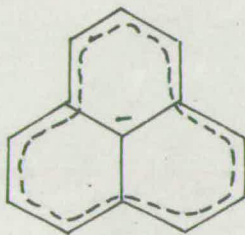
These include (a) the replacement of the inward-pointing CH groups by nitrogen atoms⁶ as, for example, in the hypothetical 1,6-diazacyclodecapentaene (III), (b) the replacement of pairs of interior hydrogen atoms by NH groups, as in porphin (IV) and related compounds, and (c) the replacement of three interior hydrogen atoms by a single trivalent atom such as nitrogen, thereby forming a compound such as cycl [3,2,2] azine⁷ (V).

The aim of the present research is to synthesise cycl [3,3,3] azine (VI). This system contains 12 π electrons (excluding the lone pair on the nitrogen atom which cannot be

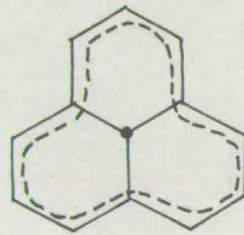
completely included in the cyclic molecular orbital) and, therefore, simple application of Hückel's rule predicts non-aromaticity. Nevertheless, 12 π electron systems of this type possess considerable stability as is shown, for example, by the synthesis of the phenalenyl cation by Pettit⁸. This system is remarkable since it can exist as the comparatively stable cation (VII), the free radical (VIII), and the anion¹⁰ (IX) which is isoelectronic with the desired compound (VI).



VII.



IX.

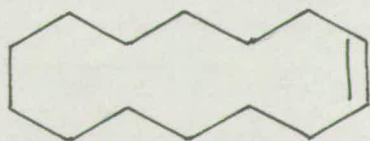


VIII.

Furthermore, theoretical work by Boekelheide et alia⁷, has shown that cycl [3,3,3] azine should show considerable stability and possess a resonance energy (after certain assumptions) higher than cycl [3,2,2] azine which has already been synthesised.

REVIEW OF CYCLOPOLYOLEFINS.

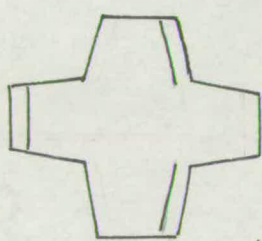
In recent years a substantial amount of work on cyclopolyolefins has been undertaken. The subject had received little attention since Willstätter's synthesis of cyclooctatetraene⁹, and certainly there was little chance that his synthesis could be extended to larger polyenes. The synthesis of cycloparaffins by Prelog¹⁰ and Stoll¹¹ (using the acyloin reaction) led Prelog¹² and his co-workers to examine the gas phase dehydrogenation of a series of cycloalkanes at 400°, using a palladium-charcoal catalyst. No cyclopolyolefins were obtained, however, and the reactions yielded only polycyclic benzenoid compounds which were formed, presumably, by trans-annular bridging. Attempts were also made by Prelog and Polyak¹³ to elucidate the mechanism of these reactions using C¹⁴ labelled starting materials. The starting material was cyclotetradecene (1), labelled at each end of the double bond, and although the compound yielded the same products as the corresponding cycloalkane, the radioactivity was equally distributed throughout the molecule.



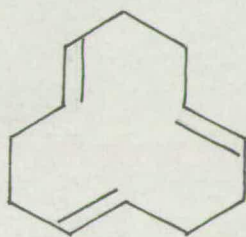
So far the mechanism of these trans-annular reactions remains

unknown.

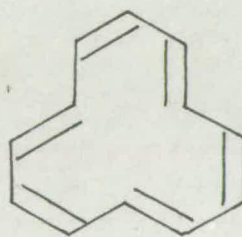
Wilke¹⁴ found that, with the aid of a mixed organo-metallic catalyst, butadiene could be converted, in excellent yield, to a mixture of cis-trans-trans (II) and trans-trans-trans (III) cyclododeca-1,5,9 triene. The introduction of two more double bonds into the molecule was relatively easy but it was not found possible to prepare cyclododecahexaene (IV) since the introduction of a sixth double bond is likely to involve an alteration in the carbon skeleton.



II.



III.

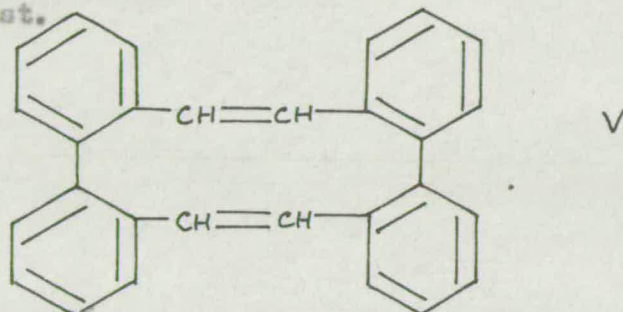


IV.

Although a compound of composition $C_{12}H_{12}$ was obtained, and it was unstable to air and heat, the compound's behaviour suggested that it was a homologue of cyclooctatetraene rather than the fully conjugated cyclopolyolefin.

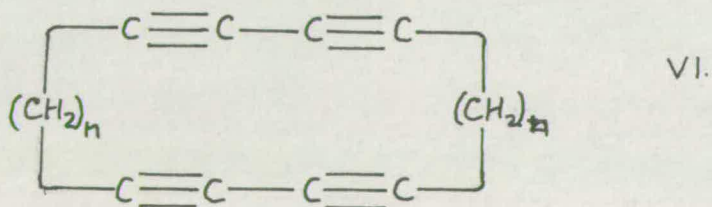
The idea that the introduction of a sixth double bond into the compound (III) would result in distortion of the carbon skeleton is supported by Wittig's¹⁵ synthesis of 1,2 - 3,4 - 7,8 - 9,10 tetrabenzocyclododecahexaene (V). Two stereoisomers,

corresponding to the strainless cis-cis and trans-trans forms, were obtained and models have shown that a strainless planar form could not exist.



Further work by Wittig¹⁶ led to the isolation of tetraphenylene, hexaphenylene and octaphenylene by the action of metal halides on 2,2'-^{Li}dithiodiphenyl. These molecules are not planar, due to the interference of adjacent ortho-hydrogen atoms, the benzene rings being twisted alternately above and below the two parallel planes containing the carbon atoms of the large ring.

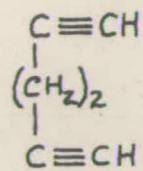
The most successful approach to the cyclic polyenes has undoubtedly been that of Sondheimer¹⁷ and his co-workers who have exploited their discovery, and the independent discovery by Eglinton and Galbraith¹⁸, that oxidation of α,ω -diacetylenes yields cyclic tetracetylenic compounds e.g., (VI) together with cyclic trimers, tetramers, pentamers and hexamers of the open chain compounds.



Sondheimer's original method¹⁷ was to couple the acetylenes in a mixture of cupric chloride, ammonium chloride and aqueous ethanol but, independently, he²⁶ and Eglinton and Galbraith¹⁸ discovered the use of cupric acetate in pyridine at high dilution. It is Sondheimer's use^{19,26} of this second reagent, with higher concentrations of the acetylenes, which has yielded the most satisfactory results. The structure of the products obtained has been confirmed by ultraviolet and infrared spectral analysis, and hydrogenation to cycloparaffins. Sondheimer²⁰ has also discovered that the diyne groups in the cyclic polyacetylenes derived from 1,5-hexadiyne may be rearranged by potassium *t*-butoxide to conjugated dienyne groups and that the resulting cyclic polyenyynes may be partially hydrogenated to the corresponding cyclic-polyenes. The rearrangement may be compared with that observed by Jones, Shaw and Whiting²¹, in which certain diacetylenic dicarboxylic acids undergo prototropic isomerisation when treated with 10% potassium hydroxide solution to yield conjugated dienyne dicarboxylic acids.

Using these reactions Sondheimer and his co-workers have made a number of cyclic polyenes and polyenyynes containing fewer, and more than, 30 carbon atoms. The main interest concerns those with less than 30 carbon atoms, for reasons which have been stated in the introduction. The first synthesis of a cyclic polyene and of the smallest which might be expected to

Scheme I.



1:5-Hexadiyne.

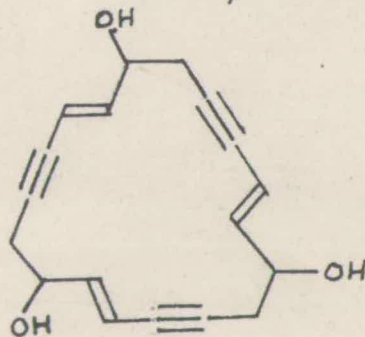
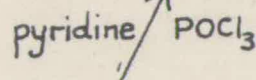
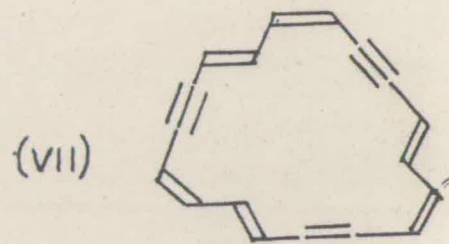
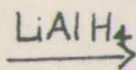
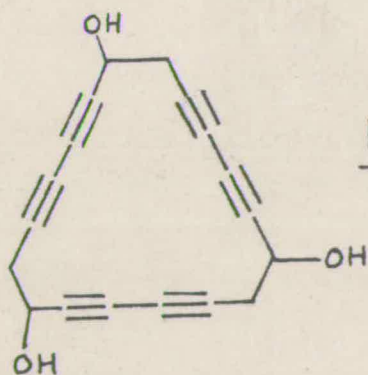
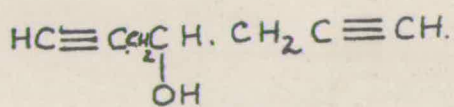
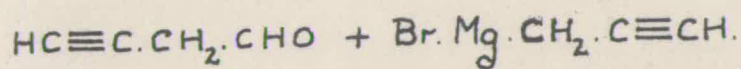
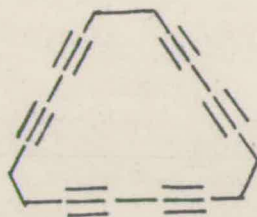
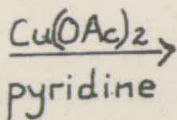
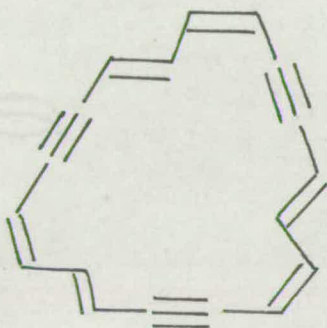
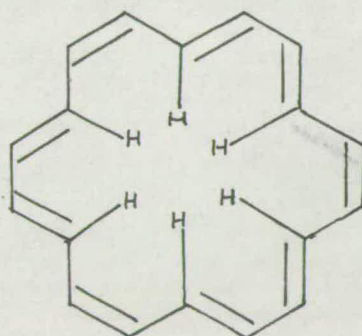


exhibit aromatic properties, according to Baker's theories, was achieved when Sondheimer^{22(a,b)} synthesised cyclooctadecanonaene (VII). This compound was synthesised by the partial hydrogenation over a "Lindlar"²⁴ catalyst of cyclooctadeca-1,7,13-(cis)-triene-3,9,15-(trans)-triene-5,11,17-triyn (VI) which had previously been prepared by two separate routes^{23(a,b)} as shown in Scheme 1 (opposite).



VII.



VIII.

The longest wavelength absorption maximum in the ultraviolet occurs at 456 μ which is identical to that shown by the corresponding open chain linear nonaene²⁵. This, coupled with the remarkable increase in intensity of the peak ca. 370 μ , indicated that the molecule is comparatively planar and the double bonds are in conjugation. It also contains 18 π electrons which corresponds to $n=4$ in Hückel's rule and the molecule exhibits reasonable stability, e.g., it can be sublimed and it remains unchanged up to 230^oc. but no typical aromatic substitution products can be

obtained. Compare this with its linear analogue which decomposes very rapidly at room temperature²⁵. Cyclooctadecanonaene is not as stable as a classical benzoid system, however, as it decomposes over the course of several weeks when allowed to stand in light and air.

From the cyclic tetramer obtained by the action of copper acetate in pyridine on 1,5-hexadiyne²⁶, Sondheimer isolated^{27,226}, by a similar series of reactions, the cyclic polyene cyclotetracosadecaene $C_{24}H_{24}$, a system containing $24\overline{\pi}$ electrons. This compound does not comply with Hückel's rule and was found to be considerably less stable than cyclooctadecanonaene. The corresponding pentamer, under the same conditions, gives the 30 membered ring system which does not exhibit the stability which might have been expected of it²⁸. The pentayne intermediate which is obtained at the last stage before the final reduction is reasonably stable but the pentadecaene is very unstable. Despite the fact that the ultraviolet absorption spectrum shows $\lambda_{\text{max}} 430 \text{ m}\mu$, which indicates incomplete conjugation, it is unlikely that this compound is an unfavourable stereoisomer as it was again obtained by another series of reactions. More recently, renewed attempts by Sondheimer²⁹ to prepare the cyclic polyene $C_{30}H_{30}$, using a modified reaction scheme, resulted in yellow oils which were unstable but showed ultraviolet peaks in

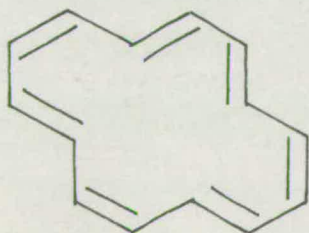
what was considered to be the correct positions. Since the corresponding linear acyclic analogues could be prepared, he suggests that both the cyclic polyenes $C_{30}H_{30}$ and $C_{20}H_{20}^{30}$ are unstable systems. Yet the fact that the polyene cyclotriacontapentadecaene is unstable, whereas cyclooctadecanonaene is relatively stable, is surprising especially as the degree of proximity between every internal hydrogen atom in cyclooctadecanonaene exists only between every alternate hydrogen atom in cyclotriacontapentadecaene. It is important, however, to mention that stability itself is not an independent measure of aromaticity.

Very recently a number of interesting new facts have appeared regarding the cyclopolyolefins $C_{18}H_{18}$, $C_{24}H_{24}$ and $C_{30}H_{30}^{22(b)31}$. Despite the predictions of Mislow³, which were re-iterated by Coulson and Golebiewski³², the experimental results showing the relative stability of $C_{18}H_{18}$ as compared with $C_{24}H_{24}$ and $C_{30}H_{30}$ have tended to support Baker's theories^{2(b)}. Indeed Coulson and Golebiewski's contention that $C_{18}H_{18}$ is not a planar molecule has been refuted by X-ray crystallographic work³³ which shows that this cyclic polyene possesses a centro-symmetric molecule (which incidentally rules out bond length alternation) and a carbon skeleton deviating from co-planarity by no more than 0.1 \AA . Furthermore, nuclear magnetic resonance spectroscopy has shown the ring system to be capable of sustaining an induced

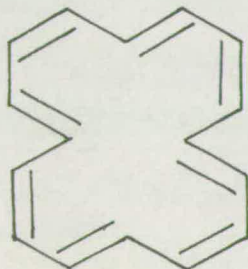
ring current and to bear certain resemblances to the porphyrins. This evidence strongly suggests that, within the present concepts of aromaticity, cyclooctadecanonene is aromatic in character.

The instability of $C_{24}H_{24}$ is not particularly surprising but that of $C_{30}H_{30}$ is. Perhaps this is due to the size of the molecule being such that it can no longer support itself in one plane and the consequent buckling destroys the stability of the ring.

Finally, Sondheimer has also achieved the synthesis of two systems containing fewer than 18 carbon atoms. The first synthesis³⁴ was that of cyclotetradecaheptaene $C_{14}H_{14}$ (IX) ($n=3$, in Hückel's rule). This substance cannot be planar and therefore complies with only one of Baker's requirements for aromaticity in cyclic polyenes. Since the substance is quite unstable, it provides a further experimental demonstration of the importance of planarity for aromaticity in conjugated cyclic polyolefins. The other synthesis³⁵ was that of cyclohexadeca-octaene $C_{16}H_{16}$ (X) and two derivatives. As expected, this cyclic polyene was also unstable.

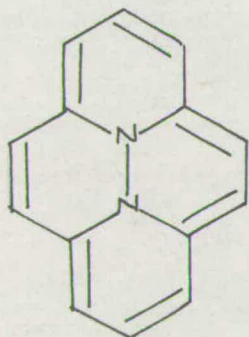


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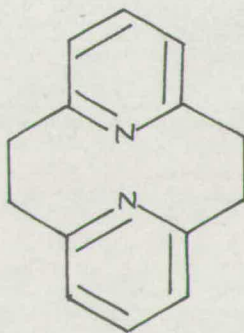


X.

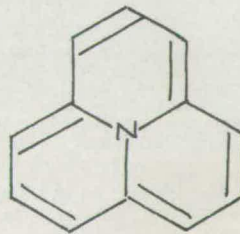
It has already been shown that, for conjugation, carbon-carbon angles close to 120° and an essentially planar system are necessary. Despite Sondheimer's success in preparing the higher conjugated polyolefins, it is obvious from the instability of compounds (IX) and (X) that the preparation of the lower cyclo-polyolefinic systems, and hence the testing of Hückel's rule for systems below $C_{18}H_{18}$ (i.e., below $n=3$), is unlikely. This is supported by Baker's conclusions^{2(a,b)} which have so far been borne out by Sondheimer's work. An indirect solution may be possible as the steric clash of interior hydrogen atoms, and the possibility of transannular bridging, are both avoided by replacing, e.g., in cyclotetradecaheptaene, the four interior hydrogen atoms by two trivalent nitrogen atoms to form 15:16-dihydro-15:16-diazapyrene (XI), or the replacement of the three hydrogen atoms in cyclododecahexaene by a nitrogen atom as in cycl [3,3,3] azine (XIII).



XI.

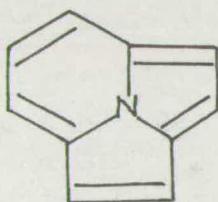


XII.



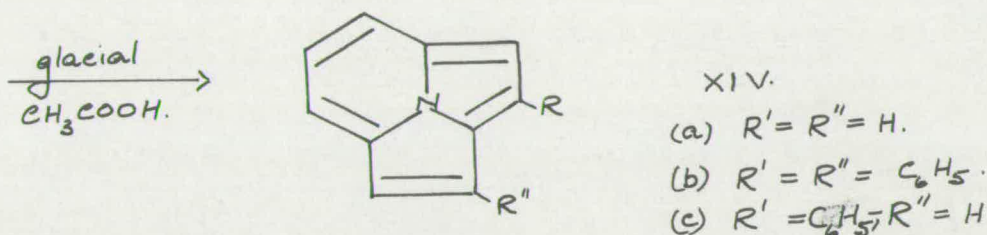
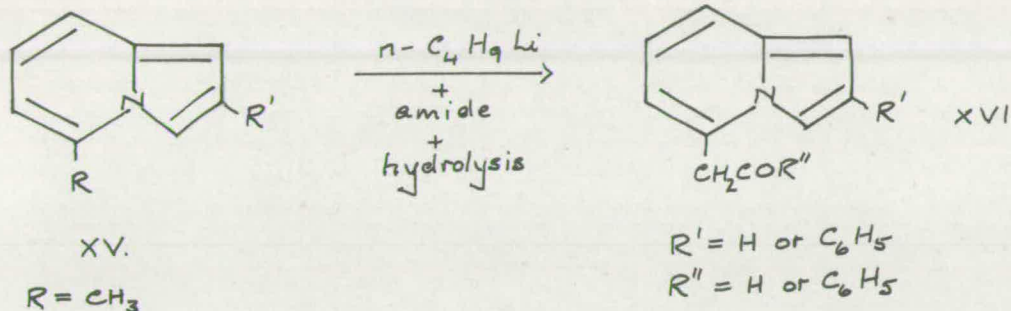
XIII.

Two groups of workers have pursued this type of approach: Baker has synthesised the tetrahydroderivative of compound (X1) i.e., di(pyridine-2:6-dimethylene) (X11) and the structure of this compound has been thoroughly examined and confirmed. One nitrogen atom appears to be above, and the other below, the rings. No report of the dehydrogenation of compound (X11) to compound (X1) has yet appeared. Boekelheide and his co-workers⁷ have recently synthesised cycl [3,2,2] azine (X1V) and some of its derivatives. This is the compound obtained by the replacement of the three internal hydrogen atoms of cyclodecapentaene by a single trivalent nitrogen atom.



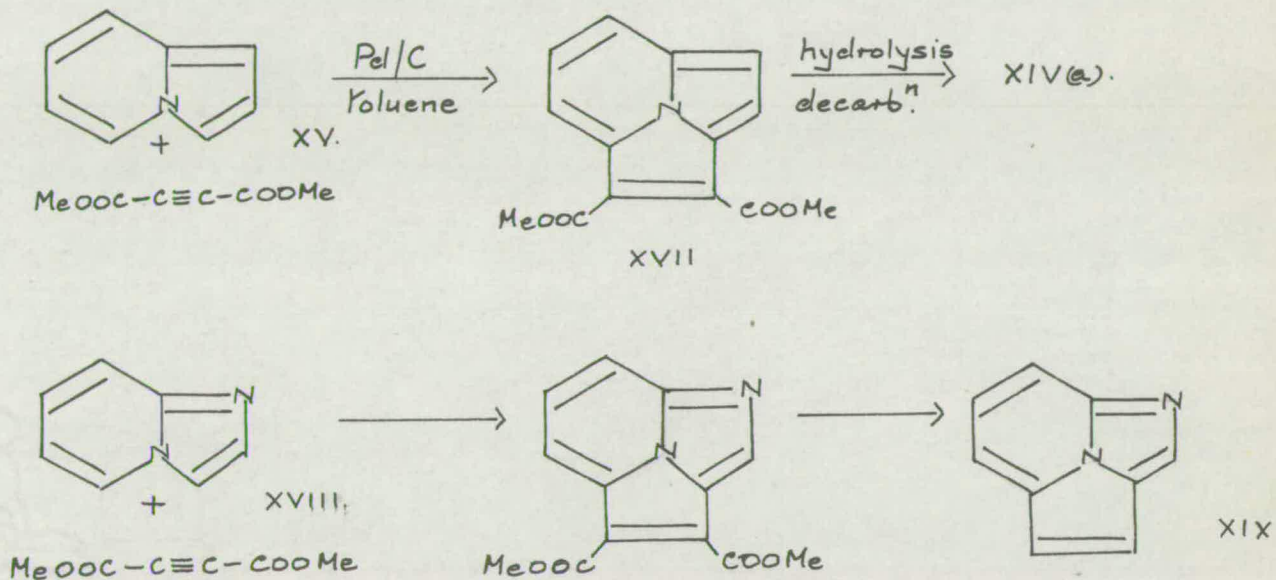
XIV.

Two separate routes from pyrrocolines have been used to synthesise this compound. The first started from 5-methyl-pyrrocoline (XV) which, on treatment with n-butyllithium and an N,N disubstituted amide followed by hydrolysis, gave either the aldehyde or ketone (XV1). These compounds on cyclodehydration⁴² gave cycl [3,2,2] azine or its phenyl substituted derivatives.



A simpler and better synthesis was discovered^{39,40} when the pyrrocoline (XV) was treated with dimethyl acetylenedicarboxylate in boiling toluene using 5% palladium on charcoal as the catalyst. This gave a 50% yield of cycl [3,2,2] azine after hydrolysis and decarboxylation. This reaction is related to those discovered by Diels⁴¹ and his co-workers who obtained quinolizines, etc., by treatment of a series of heterocyclic bases with dimethyl acetylenedicarboxylate. 2-phenyl-1-aza-cycl [3,2,2] azine (XIX) was obtained in a similar reaction with 2-phenyl-1-azapyrrocoline (XV111) but attempts to use other dienophiles in

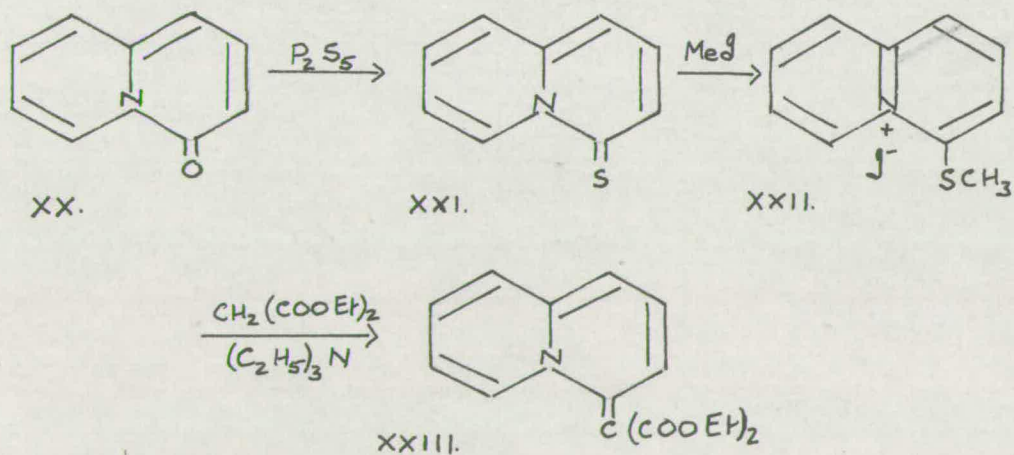
place of dimethyl acetylenedicarboxylate were unsuccessful, except in the case of the closely related methyl propiolate.



Since cyclodecapentaene obeys Hückel's rule ($n=2$), we have in cycl $[3,2,2]$ azine the first example of a large conjugated carbocycle held planar by bonding to an internal atom. Calculations⁷ (which must be made separately for each system in polycyclic molecules) have shown that both cycl $[3,2,2]$ azine and cycl $[3,3,3]$ azine (X111) should exhibit a degree of aromaticity, and experiment has confirmed this prediction for cycl $[3,2,2]$ azine. For example⁴³, the molecule is stable to heat and light, non-basic, and undergoes electrophilic substitution (nitration, bromination and Friedel-Crafts' reaction) but attempts

to induce the molecule to undergo nucleophilic substitution have not met with much success.

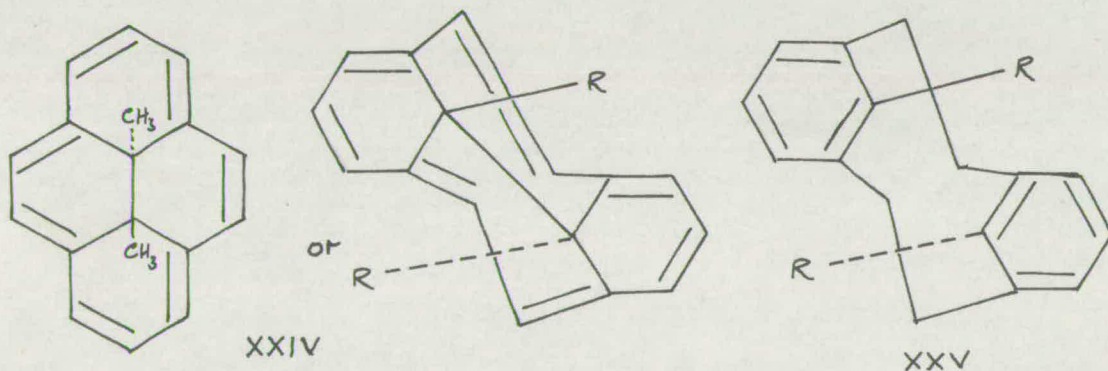
Boekelheide has also attempted the synthesis of cycl [3,3,3] azine (X111). In 1951 he and Lodge prepared³⁶ 4-quinolizone (XX) by the condensation of ethyl 2-pyridyl acetate and diethyl ethoxymethylenemalonate followed by hydrolysis and decarboxylation of the initial product, 1,3-dicarbethoxy-4-quinolizone. 4-Quinolizone was easily converted to 4-thioquinolizone (XXI) by the action of phosphorus pentasulphide. When 4-thioquinolizone was treated³⁷ with methyl iodide a quaternary salt, compound (XXII), was readily formed and treatment of this salt with diethylmalonate resulted in evolution of methylmercaptan and formation of compound (XXIII).



A synthesis of cycl [3,3,3] azine might have resulted if the same derivative could have been prepared from 6-methyl-4-quinolizone,

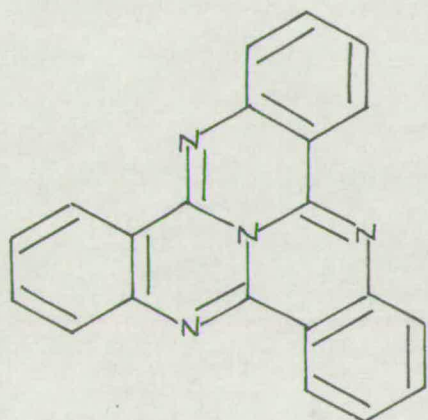
condensation between one of the carbethoxy groups and the 6-methyl group giving the third ring. However, 6-methyl-4-thioquinolizone could not be prepared despite numerous attempts³⁷ to replace the carbonyl oxygen atom by sulphur.

An attempt has also been made by Boekelheide³⁸ to prepare a derivative of cyclotetradecaheptaene (IX), in which each pair of internal hydrogen atoms was replaced by a saturated carbon atom. Models showed that a near planar system was still possible, in which case the periphery of the molecule could still be conjugated - formula (XXIV).

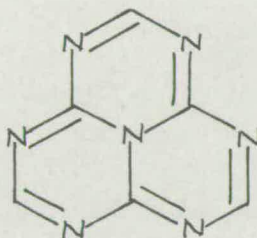


Although the saturated precursor, compound (XXV), and some derivatives could be prepared, attempted bromination - dehydrobromination⁴⁴ resulted either in recovery of starting materials or bromination only in the benzene rings.

Finally, two polyazaderivatives of cycl [3,3,3] azine have been synthesised. Tricycloquinazoline (XXVI) has been obtained by three separate reactions, namely (a) heating o-aminobenzaldehyde with compounds capable of yielding ammonia⁴⁵, (b) heating o-cyano-anilinium-p-toluene sulphonate⁴⁶ and (c) heating indazole with copper powder⁴⁷.



XXVI



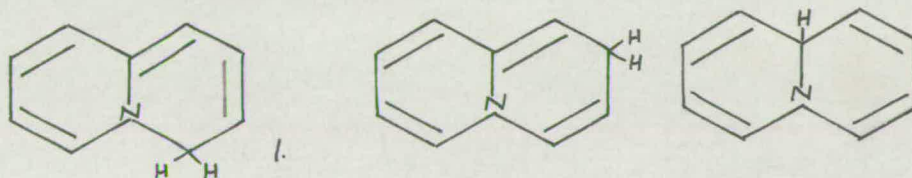
XXVII.

Tri-s-triazine (XXVII) has been shown⁴⁸ to be the nucleus of hydromelonic and cyameluric acids which have both been known for some time. Both these acids may be prepared from potassium thiocyanate.

OBJECT OF RESEARCH.

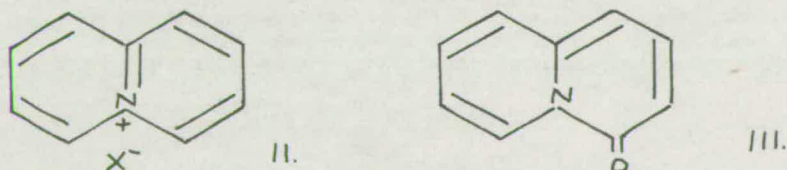
Three main synthetic routes have been pursued in the work described here. Clearly, to synthesise cycl [3,3,3] azine it is necessary to approach via the quinolizine series.

Structure (1) represents quinolizine itself which is unknown except as its derivatives and would be expected to be non-aromatic in character. (The numbering is that used in Chemical Abstracts).



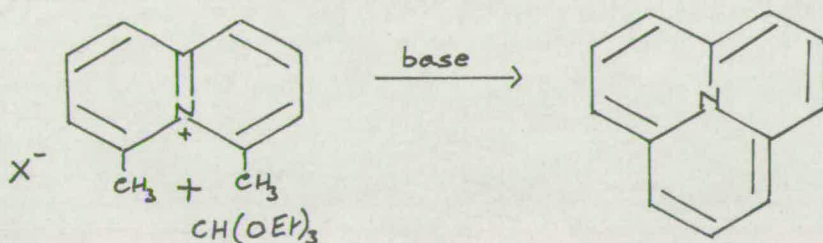
The quinolizines contain a bicyclic naphthalene ring system with a tertiary nitrogen atom in one of the bridgehead positions. As shown above, three tautomeric structures are possible.

The aromatic derivatives of quinolizine are of two main types, the dehydroquinolizinium salts (II) and the quinolizones (III), 4-quinolizone being illustrated here.



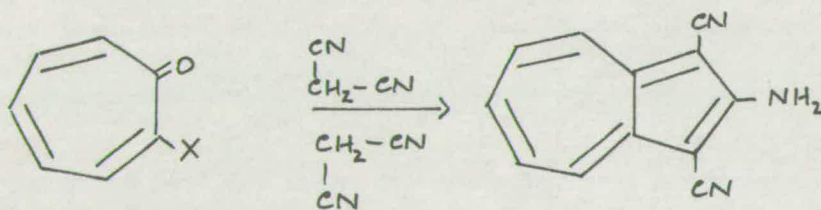
Route 1.

The first projected synthesis was to proceed from 4,6-dimethyldehydroquinolinizinium salts, which would be expected to react with formic acid, or its equivalent, to give cycl [3,3,3] azine, probably in one stage, e.g., 4-methyldehydroquinolinizinium salts have already been shown to possess a reactive methyl group which can be condensed with aldehydes.



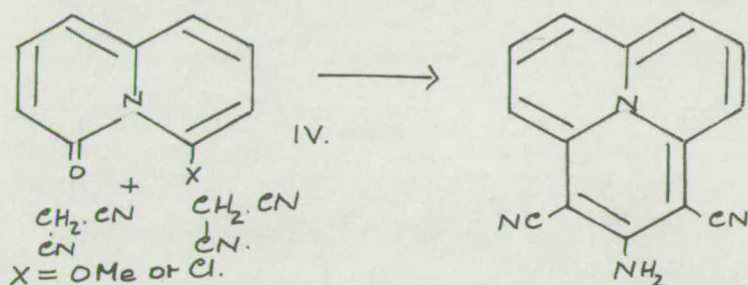
Route 11.

The second approach was based on Nozoe's synthesis⁴⁹ of azulenes from tropolones. He has reacted chlorotropolones and the methyl ethers of tropolones with malononitrile and ethyl cyanoacetate to provide the necessary 3-carbon chain across the positions previously occupied by the -OMe and C=O groups. e.g.,



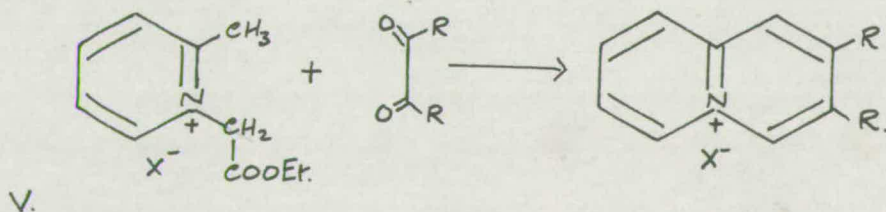
X = OMe or Cl.

Since the system present in the 6-hydroxy-4-quinolizones (IV, X=OH) is essentially similar to that present in tropolone, we might expect that a similar reaction, using compounds of type (IV), would yield derivatives of the cycl [3,3,3] azine system. e.g.,



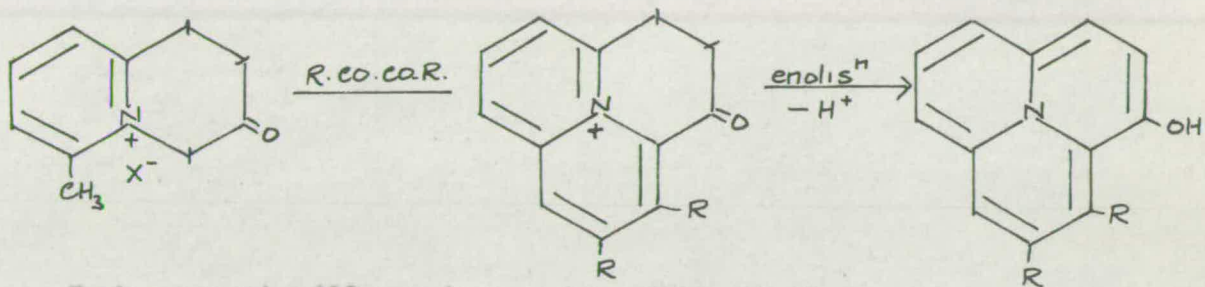
Route 111.

The final approach was to be based on a synthesis of dehydroquinolizinium salts, from N-ethoxycarbonylmethyl-2-methylpyridinium salts (V) and α -diketones, reported by Westphal, Jahn and Heffe⁵⁰. e.g.,



The methyl and N-methylene groups of 3-keto-6-methyl-1,2,-dihydroquinolizinium salts (VI) would possess a similar activity to those of compound (V) and might, therefore, condense with α -diketones to give, after enolisation and loss of proton, derivatives of hydroxy-

cycl [3,3,3] azine. e.g.,



Each approach will now be considered in detail.

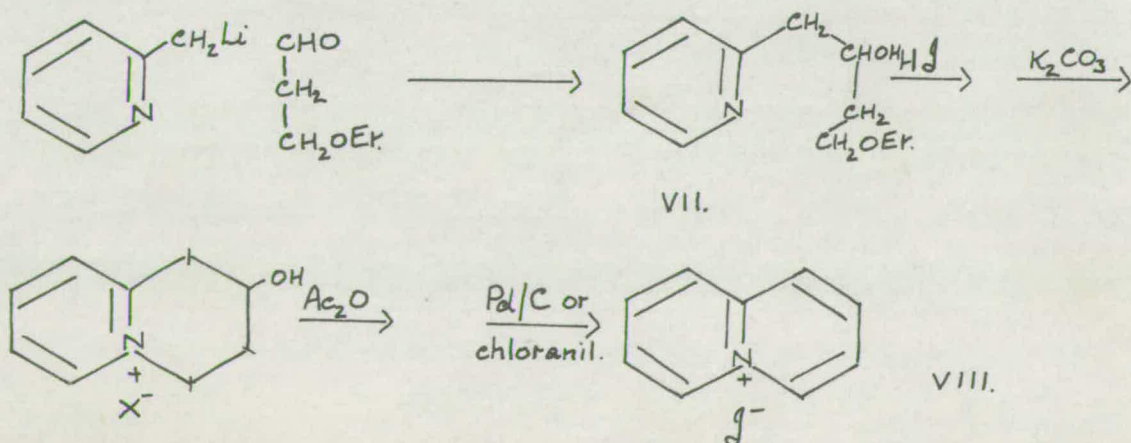
A. ATTEMPTS TO SYNTHESISE 4,6-DIMETHYLDEHYDROQUINOLIZINIUM
SALTS.

(1) Previous synthesis of dehydroquinolizinium
salts.

Boekelheide^{51,52}, and subsequently Glover and Jones⁵³, first reported the synthesis of the dehydroquinolizinium ion. The first synthesis of the ion had been accomplished earlier by Beaman and Woodward but had not been reported. Its occurrence as the nucleus of some alkaloids, e.g., sempervirine, had also been recognised⁵⁴ for some time.

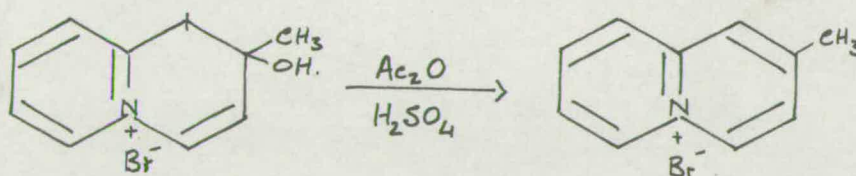
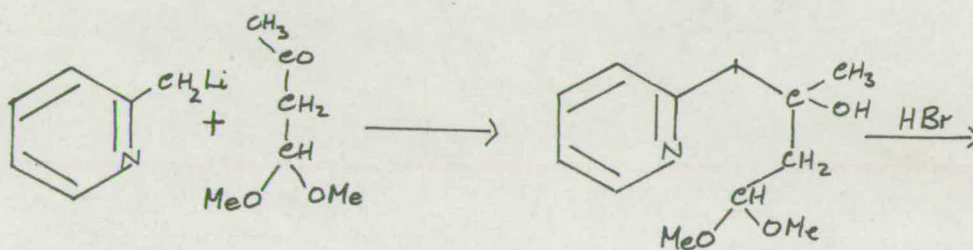
Both Boekelheide and his co-workers and Glover and Jones, followed a rather similar approach based on Beaman's synthesis.

Boekelheide's synthesis⁵¹ started from 2-picolyllithium which was allowed to react with β -ethoxypropionaldehyde to give the adduct (VII) which yielded the dehydroquinolizinium ion as the iodide (VIII) after subsequent cyclisation, dehydration and dehydrogenation.



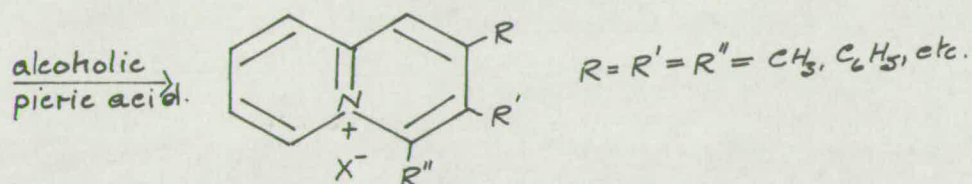
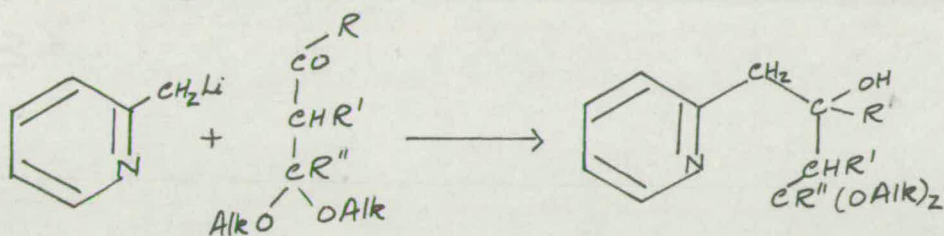
4-Methyldehydroquinolizinium salts were obtained by a similar method.

Nesmeyanov⁵⁶, and Richards and Stevens⁵⁸, used related methods to synthesise 2- and 3- alkyl and aryldehydroquinolizinium salts. Nesmeyanov, using the dimethyl acetals of various keto-aldehydes, found that the condensation products obtained from the acetals and picolylithium underwent easy cyclisation and dehydration to give 2- substituted dehydroquinolizinium salts.e.g.,



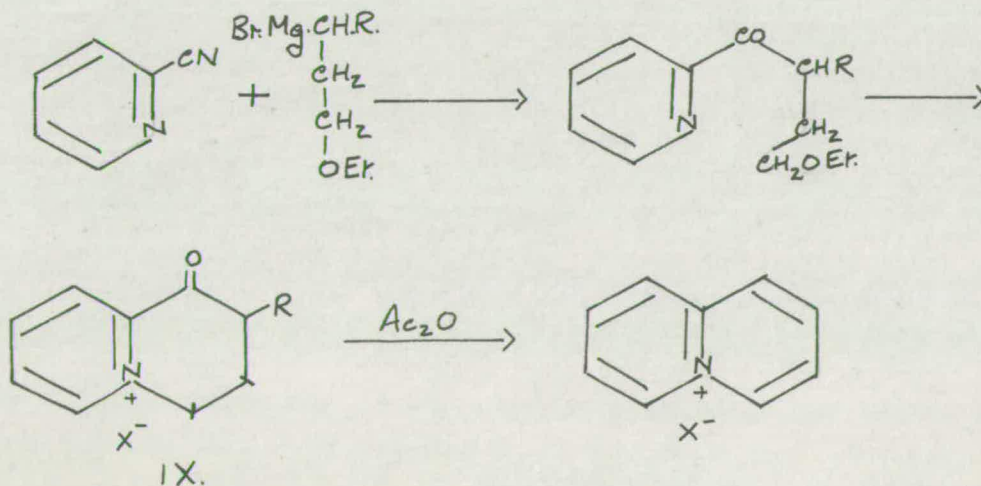
Richards and Stevens, using the enol-ether or the mono-acetal of a β -diketone, found that the products obtained, after this type of compound had been allowed to react with picolylithium, could be easily cyclised using alcoholic picric acid. This reduced the number of stages involved in the previous syntheses as

the dehydration was accomplished without isolation of the initial cyclic product. e.g.,



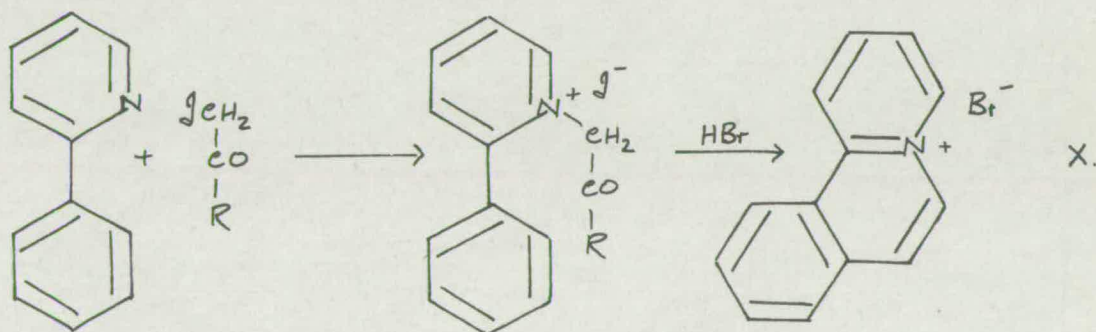
This method enabled the synthesis of 2,3, and 4-substituted dehydroquinolizinium salts to be achieved.

Glover and Jones ^{53(a,b)} prepared 1-keto-3,4-dihydro-2H-quinolizinium salts (IX) from 2-cyanopyridine and found that these salts could be converted, in one stage, into dehydroquinolizinium salts, using acetic anhydride alone. e.g.,



They also showed that, by varying the aliphatic precursor, a general synthesis of dehydroquinolizinium salts is available and their synthesis has already been extended to 1,2,3 and 4 substituted dehydroquinolizinium salts^{53(b),55}. This synthesis is capable of further extension by variation of the pyridine precursor.

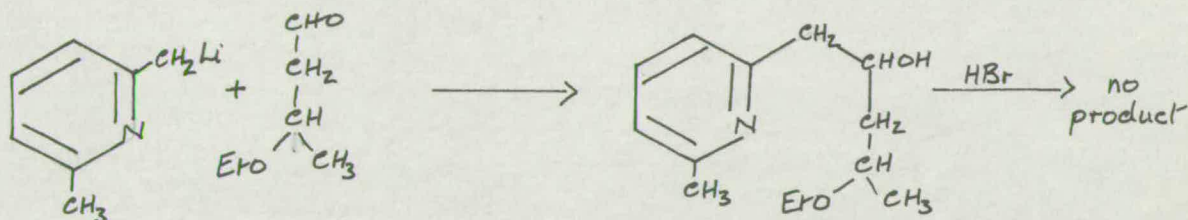
Benzodehydroquinolizinium salts, e.g., compound (X), have been prepared by Bradsher et alia who have made extensive use of cyclodehydration in their syntheses.



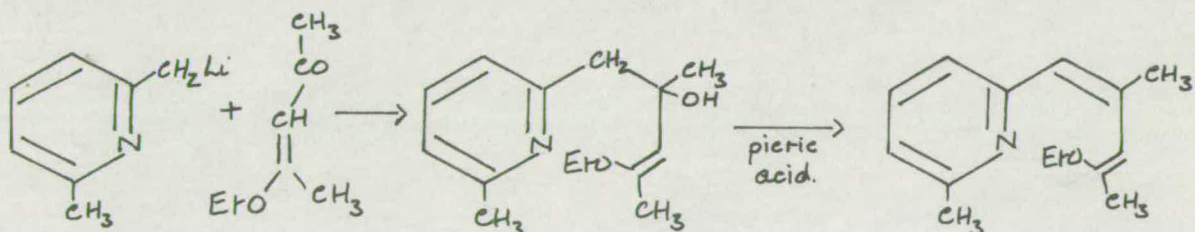
Boekelheide (in a personal communication to Glover and Jones^{53(b)}) has stated that he was unable to extend his method to the synthesis of 4,6-dimethyldehydroquinolizinium salts. Examination of molecular models shows that the formation of 4,6-dimethyldehydroquinolizinium salts is not sterically impossible although the methyl groups might be out of plane in the final molecule.

(11) Attempted syntheses of 4,6-dimethyldehydroquinolinizinium salts.

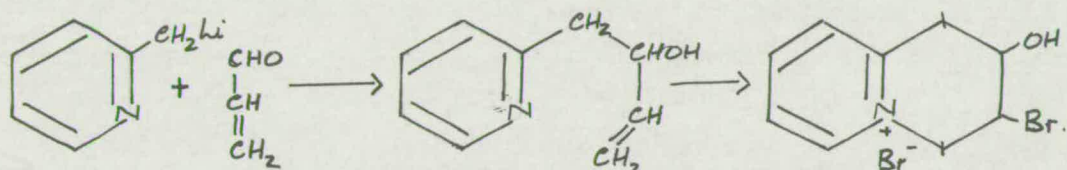
(a) When β -ethoxybutyraldehyde was allowed to react with monolithio-2,6-lutidine the expected initial adduct appeared to be formed but no cyclised material could be isolated using 48% hydrogen bromide as the cyclising agent, only starting material being recovered.



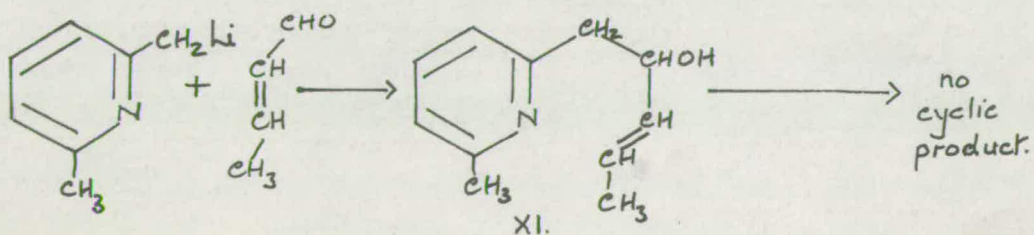
(b) A similar reaction using the enol ether of acetyl acetone was hardly more successful. Again the initial adduct was obtained but boiling hydrobromic acid had no effect on this material and treatment with alcoholic picric acid appeared to result only in dehydration of the uncyclised material.



(c) A report by Wischmann⁶¹ et alia whereby α,β -unsaturated aldehydes were condensed with 2-picolyllithium and the resultant alcohols cyclised by the addition of bromine in the cold to give 3-bromo-2-hydroxy-1,2-dihydro-3H,4H-quinolizinium bromide, led to an attempt to prepare 4,6-dimethyldehydroquinolizinium salts by an analogous method.

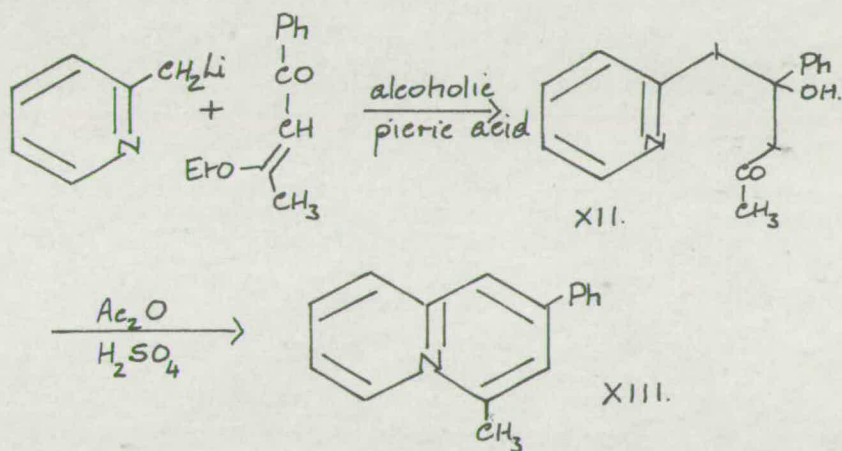


When the secondary alcohol (XI), obtained by the reaction of monolithio-2,6-lutidine and crotonaldehyde, was treated with bromine in carbon tetrachloride solution a sticky precipitate was obtained immediately. Crystallisation of this precipitate could not be effected despite the use of a variety of solvents, nor could the corresponding perchlorate be isolated (assuming the material to have been cyclised). All other attempts to isolate crystalline cyclic material or derivatives failed and attempts to characterise the oily product as various derivatives were not successful.



(iii) Attempts to prepare model compounds similar to the intermediates involved in Richards and Steven's synthesis.

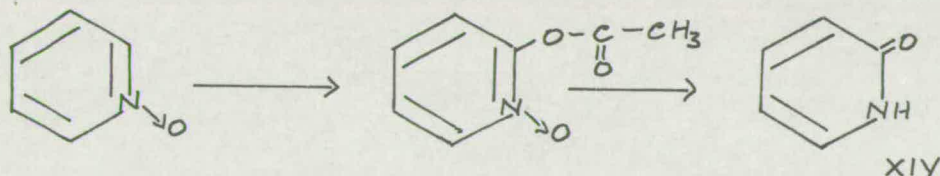
(a) In one of Richards and Steven's preparations, namely that using the enol ether of benzoylacetone, the cyclised product was not isolated initially, the reaction yielding instead the keto derivative (X11), presumably formed by the cleavage of the enol ether precursor. This keto derivative was subsequently cyclised using the acetic anhydride/sulphuric acid method to give compound (X111).



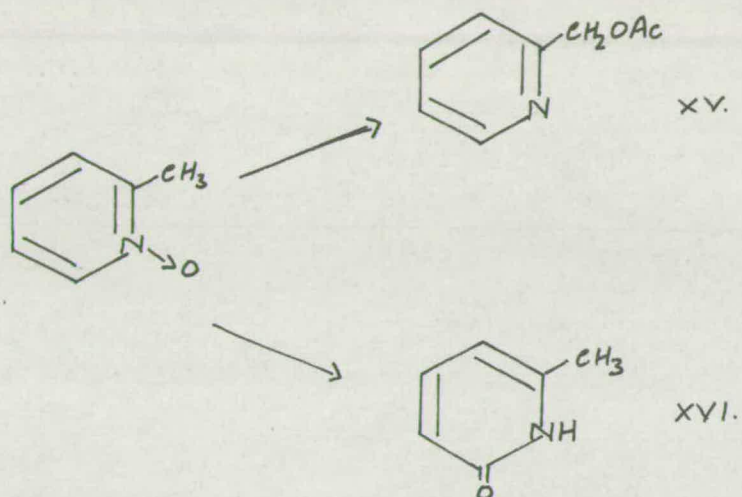
Since this keto compound was isolated it seems reasonable to suppose that similar intermediates are formed during the related cyclisations, especially since replacement of the phenyl group by a methyl group resulted in a straightforward reaction. If, then, a similar series of keto-alcohols to the intermediate isolated by Richards and Stevens could have been synthesised, this might have provided a convenient route to dehydroquinoliz-

inium salts. One of the limitations involved in such a scheme is the preparation of aliphatic precursors with a suitable functional group, e.g., aldehydes and β -diketones which enable an hydroxyl group to be present in the 1- or 2- position of the side chains. If the hydroxyl group could be introduced at a later stage a much wider range of suitable intermediates would become available. The reaction of acetic anhydride with pyridine-N-oxides suggested a possible route to compounds with an hydroxy group in the position 1 of the side chain.

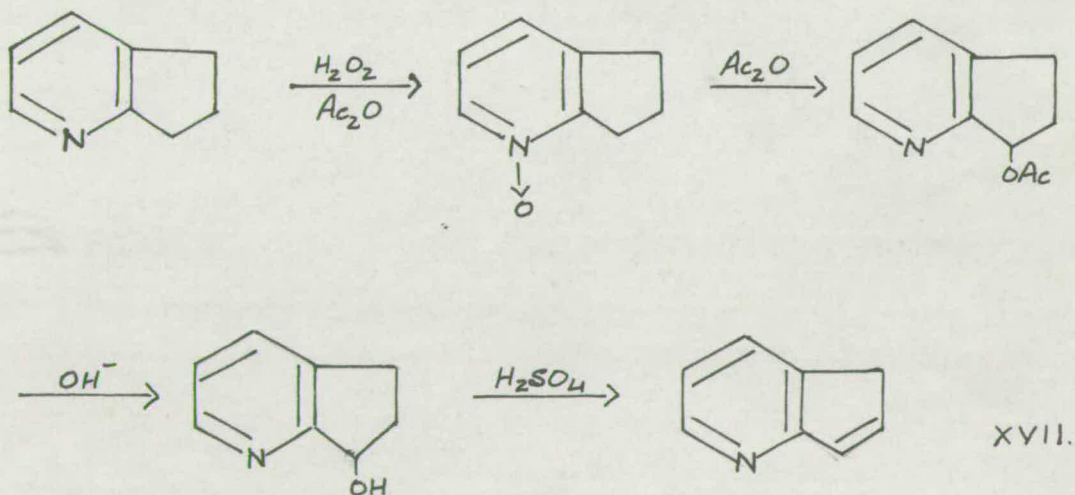
When pyridine-N-oxide is treated with acetic anhydride 2-pyridone (XIV) is obtained⁶⁴.



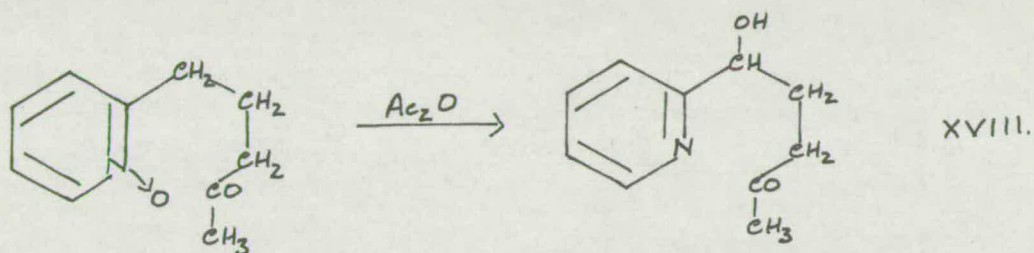
If alkyl groups are present in the 2- and 4- positions of the pyridine ring a rather different type of reaction takes place. For instance, 2-picoline-N-oxide yields mostly 2-acetoxymethylpyridine (XV) and only a little 6-methyl-2-pyridone is obtained⁶⁵ (XVI).



Robison⁶⁶, in his synthesis of 1,5-pyridene (XVII), has used this type of reaction to insert a secondary hydroxyl group at a neighbouring saturated carbon atom, as shown below:-

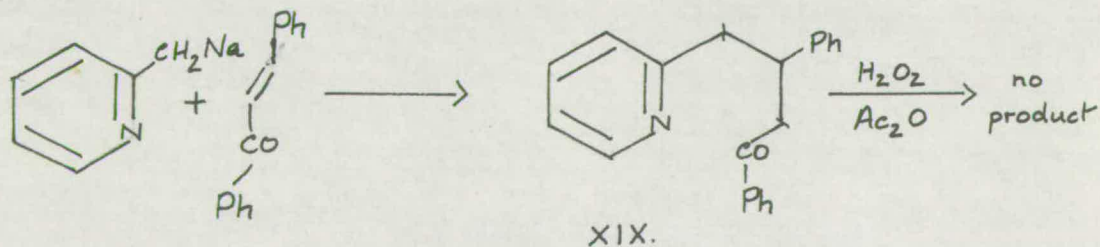


It was hoped that pyridine derivatives possessing saturated carbon atoms in the 1-position of the side chain might undergo a similar reaction and thus enable an hydroxyl group to be introduced in position 1. e.g., (XV111)



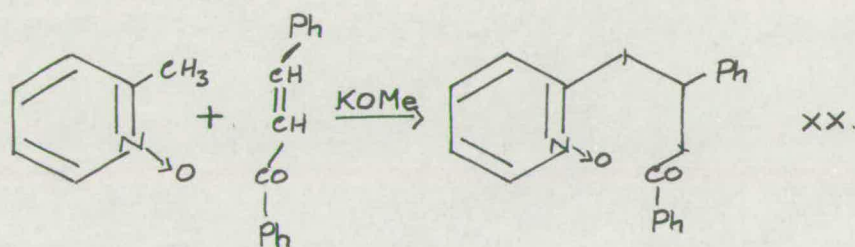
Subsequent cyclisation and dehydration would then yield dehydroquinolizinium salts and the method might then have been extended to 4,6-dimethyldehydroquinolizinium salts. Various attempts to prepare model compounds of type (XV111) were undertaken.

(1) The reaction of the sodium salt of α -picoline with benzylideneacetophenone yielded a white solid originally thought to be compound (XIX) i.e., 4-(2'-pyridyl)-1,3-diphenylbutan-1-one.



However, it was very insoluble in ethanol, has a high melting point (247-249°), and a most unsatisfactory analysis was obtained. The N-oxide could not be prepared, starting material being recovered.

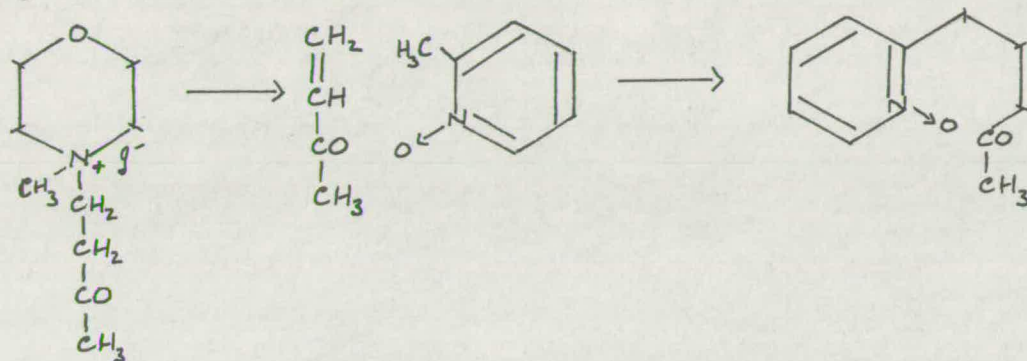
A similar experiment, using 2-picoline-N-oxide as starting material and potassium methoxide as catalyst, also gave high melting (294-296° c) relatively insoluble material which did not analyse for the expected compound (XX).



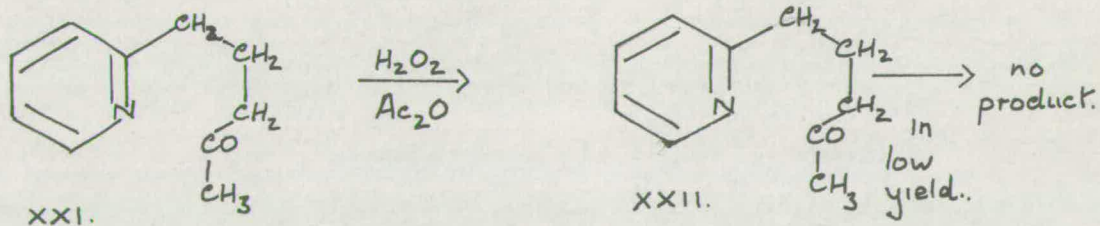
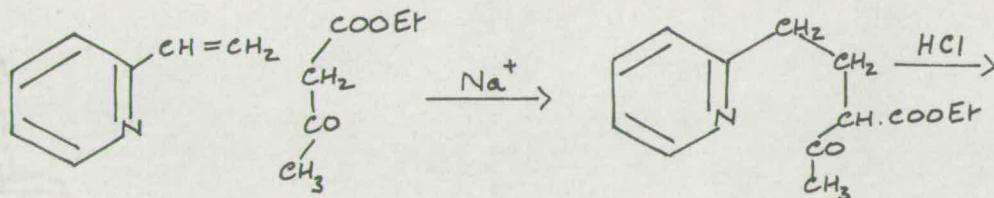
Weiss and Hauser⁶⁷ have already shown that, in this type of compound, continued reaction may occur between the methylene group alpha to the carbonyl group in the side chain and any unreacted α,β -unsaturated ketone. Although neither of the products mentioned above gave analyses closely similar to those of Weiss and Hauser's, it seems likely that this type of reaction has taken place here, resulting in formation of polymeric products.

An experiment using methylvinyl ketone and 2-picoline-N-oxide, with potassium methoxide as catalyst, was no more successful. Only a very small amount of an oily product was

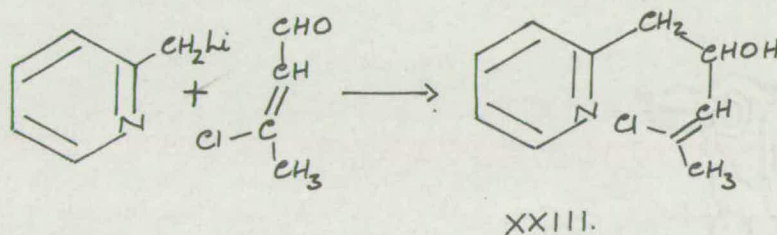
obtained and the experiment was quite unsuitable as a method of preparing the N-oxide.



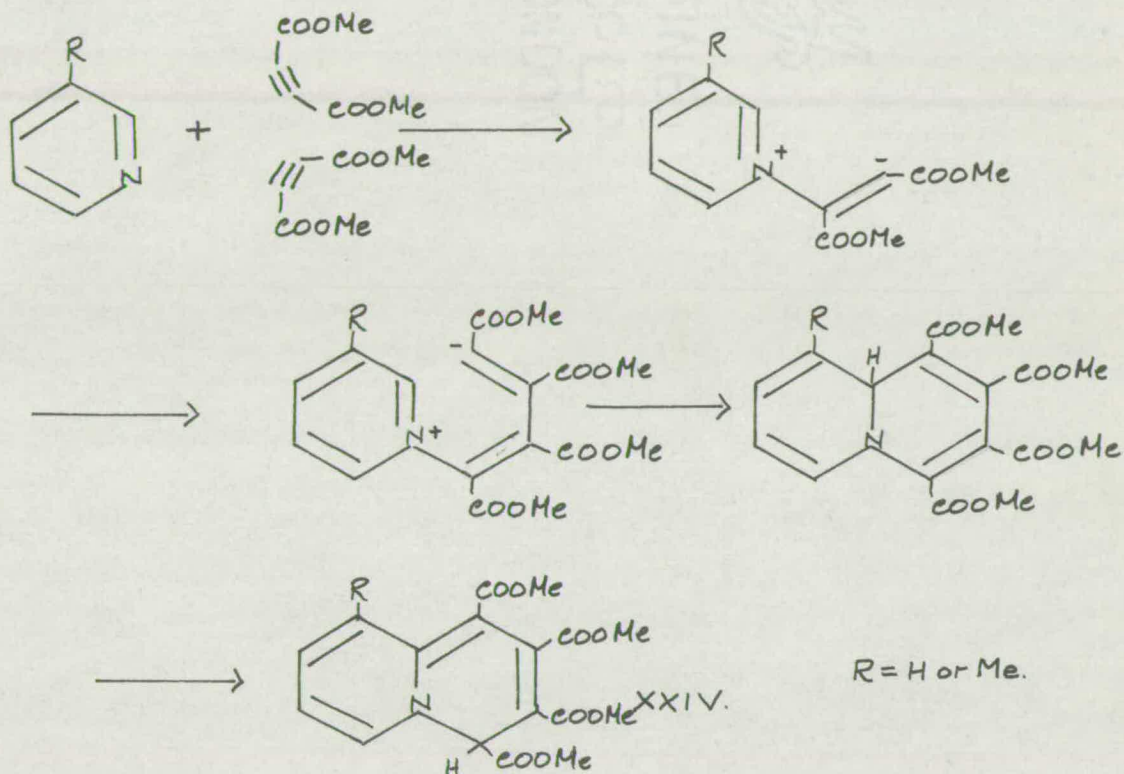
When 5-(2'-pyridyl-pentan-2-one) (XXI) was prepared from 2-vinylpyridine, it proved extremely difficult to prepare the N-oxide (XXII). The N-oxide was eventually prepared in extremely low yield and of doubtful purity. Attempts to prepare the 5-acetoxy compound or to obtain cyclised material from the intermediate (XXII) were not successful.



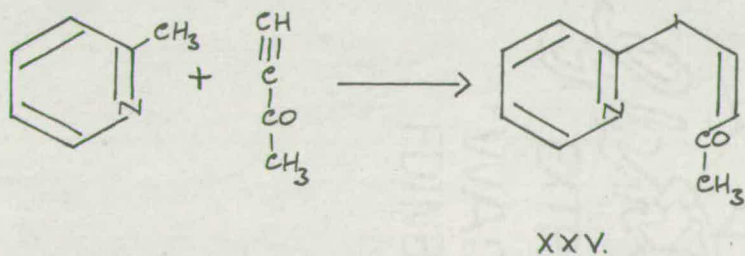
(b) Following the reported preparation⁶³ of β -chloro-crotonaldehyde in good yield by a new method, attempts were made to prepare an intermediate of type (XX111) i.e., where a chlorine atom has replaced the ether grouping in Richards and Stevens precursors. No satisfactory product could be isolated from the reaction of α -picolyl lithium and β -chlorocrotonaldehyde, and the products obtained always smelt strongly of α -picoline. To some degree this lack of success can be attributed to the instability of the β -chloro-crotonaldehyde.



(c) In the 1930's Diels and his co-workers made an extensive study of the reactions of dimethylacetylenedicarboxylate and pyridine and its homologues. Only recently has the structure of some of the products obtained been finally established with the aid of modern physical methods of analysis^{41,70}. It would appear that when pyridine or 3-picoline and dimethylacetylenedicarboxylate react together the sequence of reaction is as follows, to give compound (XXIV):



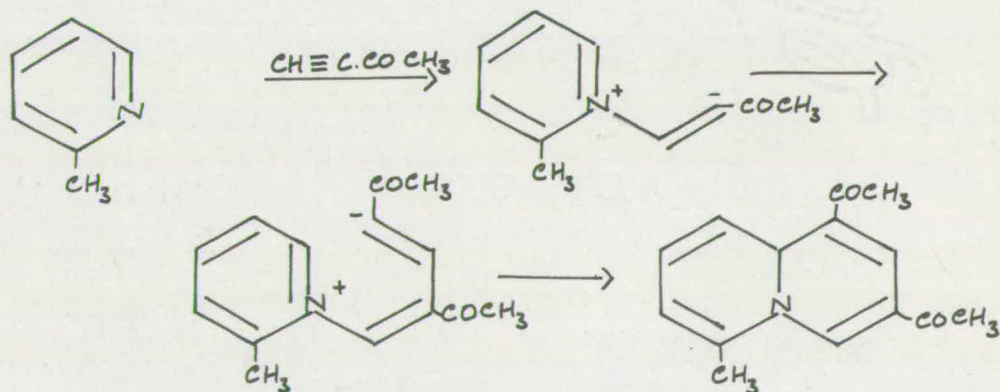
If reaction between 2-picoline and 1-butyne-3-one had occurred at the methyl group of 2-picoline, then a synthesis of an intermediate of type (XXV), capable of cyclisation to a dehydro-quinolizinium salt, might have resulted.



Against this is the fact that Diels and Pistor⁷³ have found that α -picoline and dimethyl acetylenedicarboxylate appear to give rise to the 6-methyl analogue of compound (XXIV) i.e., reaction at the N atom occurs.

Both 2-picoline itself and the sodium salt of 2-picoline were allowed to react with 1-butyne-3-one under a wide variety of conditions. In every case a very dark sticky material was obtained, either as a result of violent reaction when higher temperatures were used or, as in the case of the reactions in the cold, after standing up to three months at -20°C .

This was unexpected as 'normal' reactions between dimethyl acetylenedicarboxylate and heterocyclic bases have been cited under all these conditions^{41,70,71} and the alternative reaction shown below seemed most likely to occur if reaction with the methyl group failed and reaction occurred at the N atom.



The most probable explanation is that, instead of

DISCUSSION.

The work described in this section seems to suggest that synthesis of 4,6-dimethyl dehydroquinolizinium salts, although sterically possible, (from the examination of models) evidently requires very drastic conditions to induce cyclisation of the intermediates. Since the experiments described followed analogous routes to previously successful syntheses, the energy barrier to be surmounted must be very considerable and it is probable that the stability of any intermediate would be endangered, if not destroyed, by any conditions which would effect cyclisation.

While this is borne out by the experimental work, it is surprising that the model experiments involving the N-oxides were not more successful. In the case of the benzylideneacetophenone and methylvinyl ketone condensation with 2-picoline-N-oxide, formation of a prolonged side chain would probably prevent N-oxidation occurring due to steric difficulties. Yet there are cases known where bulky side chains have not prevented N-oxidation, e.g., Adams⁷² has prepared the N-oxide of 6-benzyloxy-2-methyl pyridine but the bulk of this side chain would not compare with that of the dimer or trimer, etc., which may have been formed.

The reasons for the N-oxides, when formed, failing to react with acetic anhydride are not at all clear as the acetic

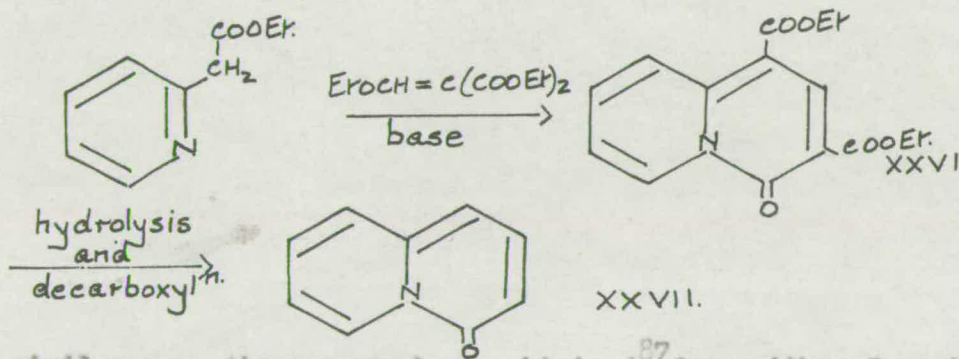
anhydride re-arrangement is well known and has been shown to occur in various systems.

Within present knowledge of experimental techniques it is unlikely that a satisfactory synthesis of 4,6-dimethyl dehydroquinolizinium salts can be evolved.

B. ATTEMPTS TO SYNTHESISE 6-HYDROXY-4-QUINOLIZONES.

(1) Previous syntheses of 4-quinolizones and 6-hydroxy-4-quinolizones.

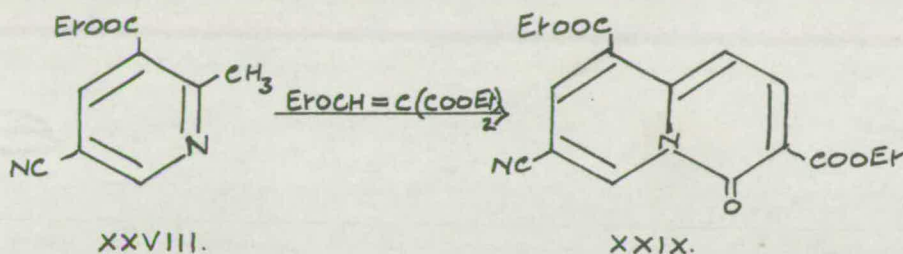
4-Quinolizone (XXV11) was first prepared³⁶ by the condensation of ethyl-2-pyridylacetate and diethyl ethoxymethylenemalonate, followed by hydrolysis and decarboxylation to remove the ester groups. e.g.:



In a similar way, the compound was obtained³⁷ from either 2-pyridylacetamide or 2-pyridylacetonitrile. 4-Quinolizones substituted in both rings have also been prepared³⁸ by this reaction and have been used in various attempts to synthesise cytosine.

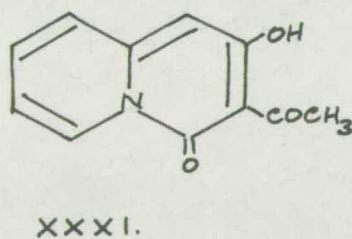
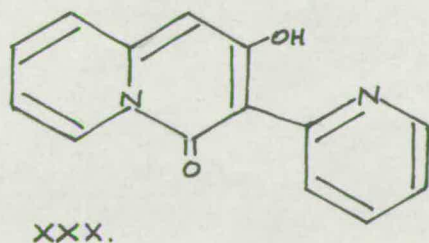
Although these earlier methods all started from pyridines containing an acetic acid side chain in the 2-position, it has been found that ethyl 5-cyano-2-methylnicotinate (XXV111) can be condensed with diethyl ethoxymethylenemalonate to give 7-cyano-3,9-

diethoxycarbonylquinolizone-4-one (XXIX). e.g.,



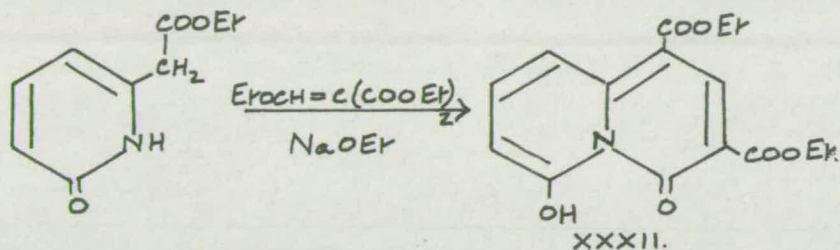
Using ethyl ethoxymethylenecyanoacetate instead of diethyl ethoxymethylenemalonate, the same workers also synthesised 1,3-diethoxycarbonyl-4-quinolizone imine which was found to be converted to 1,3-diethoxycarbonyl-4-quinolizone (XXVI) at its melting point.

4-Quinolizones have also been reported to be formed by self-condensation of 2-pyridylacetic ester, e.g., compound (XXX), and as a result of passing ketene into pyridine, e.g., compound (XXXI).

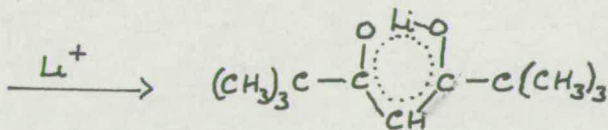
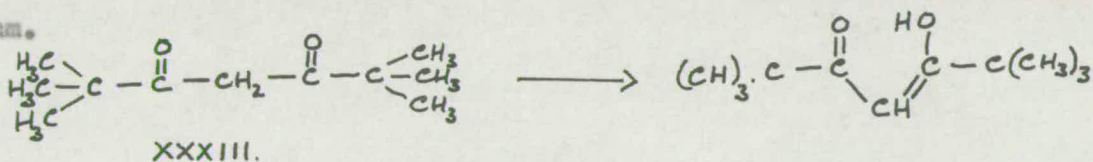


The first synthesis of a derivative of the 6-hydroxy-4-quinolizone system was reported by Adams and Reifschneider⁷⁴ who synthesised 1,3-diethoxycarbonyl-6-hydroxy-4-quinolizone (XXXII) by the condensation of ethyl 2-pyridone-6-acetate and diethyl

ethoxymethylenemalonate, using sodium ethoxide as catalyst.



Compound (XXXI) could not be reduced, using lithium aluminium hydride, to the corresponding dihydric alcohol as complexes formed immediately on addition of the lithium aluminium hydride solution. These metal complexes could not be broken down using 6% H_2SO_4 . It is interesting to note that stable lithium salts of a rather similar nature have been reported⁸⁹ to be formed when compound (XXXI) is treated with solutions containing lithium.



In each of the previous syntheses the starting materials have consisted of a heterocyclic compound and an aliphatic compound which were allowed to react together to produce the bicyclic system. When applied to the synthesis of 6-hydroxy-4-quinolizones the methods suffer from the disadvantage that a

lengthy preliminary synthesis of the heterocyclic compound is usually required and a synthesis of the quinolizine ring system from purely aliphatic starting materials would be a great advantage. To synthesise the 6-hydroxy-4-quinolizone system, one of the starting materials requires to be a 2-pyridone. By analogy with previous work, a suitably activated methyl or methylene group attached to the 6-position of the pyridone ring would be an essential feature. A large part of the work described in this section was devoted to attempted syntheses of suitably substituted 2-pyridones.

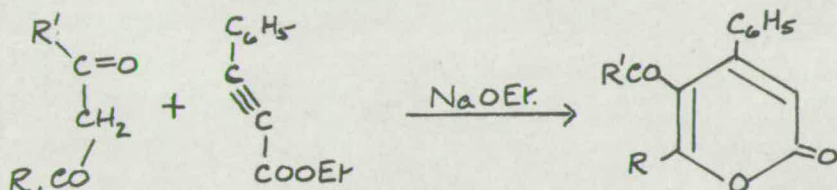
(ii) Attempted syntheses of 2-pyridones from diethyl acetonedicarboxylate and ethoxymethylene compounds.

While a large number of 2-pyridones are known, including many with substituents in the 6-position, there are few authentic reports of 2-pyridones containing a methylene group in the 6-position having been synthesised directly from aliphatic starting materials. Most of these have contained the grouping $-\text{CH}_2\text{Ph}$ in the 6-position which would be of little value in this work.

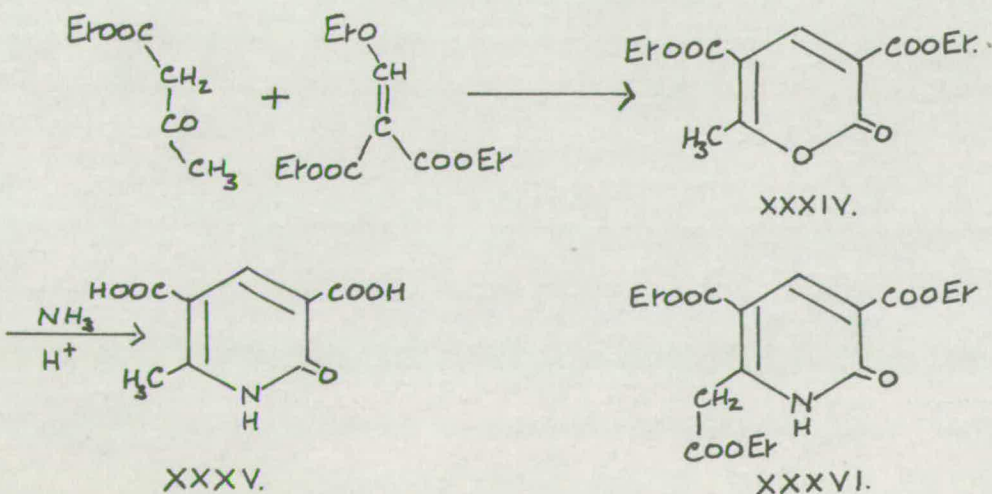
A more promising approach appeared to be via the 2-pyrone series. 2-Pyridones have been frequently prepared by treatment of 2-pyrones with ammonia. This reaction has been studied for over 70 years and has generally been found to proceed in good

yield under mild conditions. Work by Simonsen and Ruhemann suggested possible methods of synthesising 2-pyrones possessing a 6-side chain containing an activated methylene group.

Ruhemann⁷⁸ prepared 6-substituted-2-pyrones in good yield from ethyl phenyl propiolate and an acylacetic ester, or an acylacetone, in presence of sodium ethoxide. i.e.,

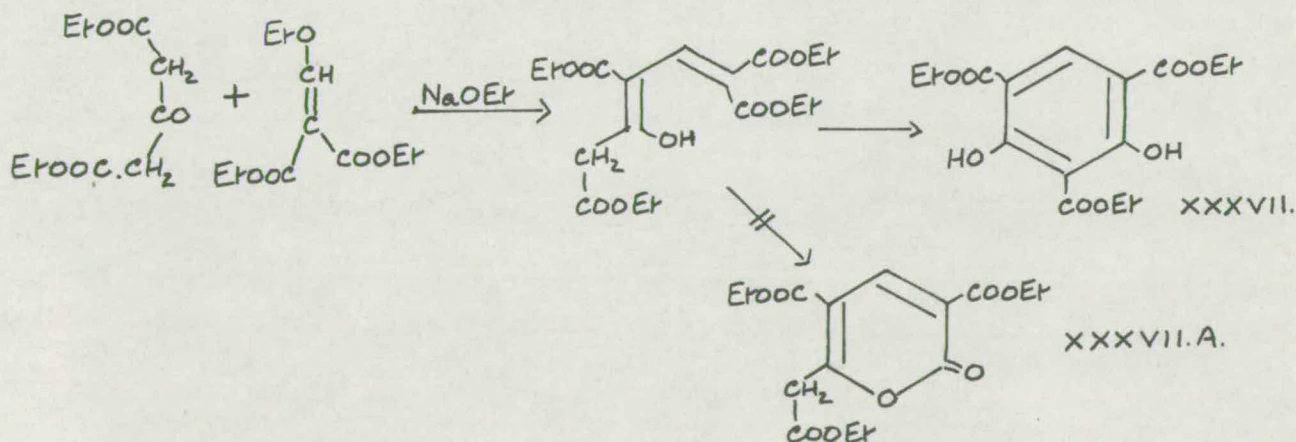


Similarly, Simonsen⁷⁷ obtained 3,5-diethoxycarbonyl-6-methyl-2-pyrone (XXXIV) by the Michael reaction of ethyl acetoacetate and diethyl ethoxymethylenemalonate. Better yields of the same pyrone were obtained using ethyl ethoxymethylenecyanoacetate as the second component. Treatment of the pyrone (XXXIV) with ammonia and hydrolysis then led to the pyridone (XXXV).



In either of these reactions, replacement of the keto-ester or β -diketone by diethyl acetonedicarboxylate ($\text{EtOOC}\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{COOEt}$) seemed likely to lead to the formation of a 2-pyrone possessing the grouping $-\text{CH}_2\cdot\text{COOEt}$ in the 6-position. Since this grouping possesses a suitably activated methylene group, conversion to the corresponding pyridone (XXXVI) would provide an excellent starting material for further syntheses.

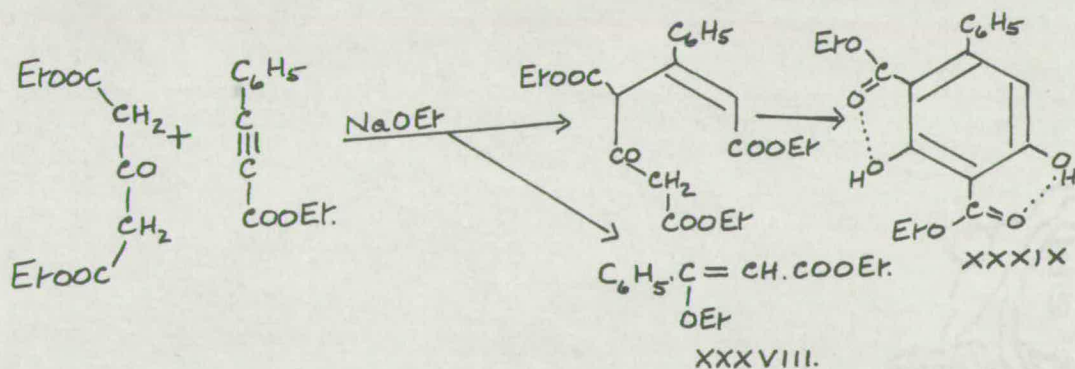
However, Errera⁷⁹ had shown earlier that diethyl acetonedicarboxylate and diethyl ethoxymethylenemalonate react to yield, not a pyrone but a derivative of resorcinol (XXXVII). This was presumably formed by Michael addition followed by a Dieckmann cyclisation instead of the expected lactonisation, to give compound (XXXVIIA).



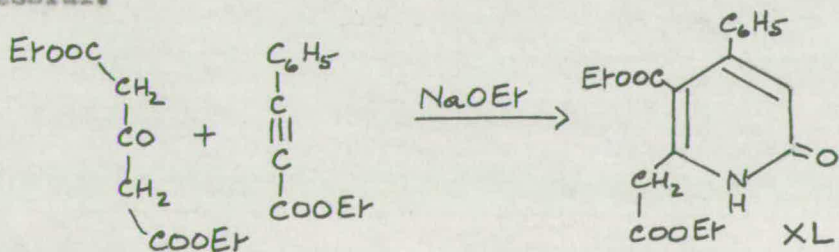
(a) Preliminary experiments based on Ruhemann's work, using diethyl acetonedicarboxylate and ethyl propiolate, were not successful. Despite the use of a variety of basic catalysts, no

crystalline products could be isolated from the attempted condensation of these two substances.

A similar experiment, using ethyl phenylpropiolate and diethyl acetonedicarboxylate, gave mainly ethyl β -ethoxycinnamate (XXXV111) together with a small yield of a colourless product (m.p.t. 157-9^o). The latter had an ultraviolet spectrum similar to that of compound (XXXV11) (Fig. 111) and its infrared spectrum indicated the presence of strongly hydrogen bonded (Chelated) ester group(s) (peak at 1672cm⁻¹). On the basis of this evidence and analysis, it was formulated as compound (XXXIX) indicating that a reaction analogous to that of Errera has occurred.

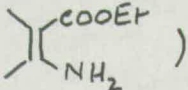


An attempt to prepare the pyridone (XL) directly from diethyl acetonedicarboxylate and phenylpropiolamide, was not successful.

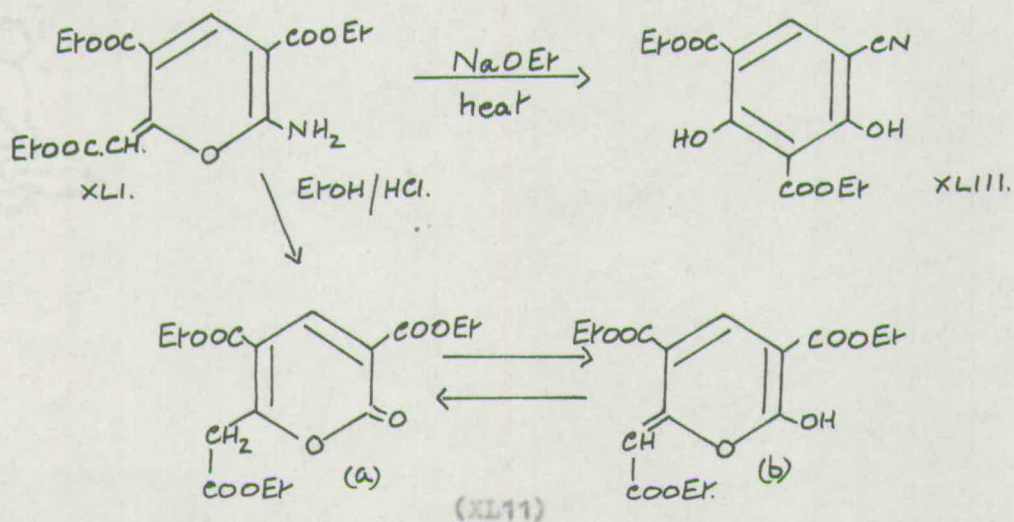


(b) The reaction of ethyl acetonedicarboxylate and various ethoxymethylene compounds was then examined. Despite Errera's earlier work which resulted in the synthesis of the resorcinol derivative (XXXV11) by this type of reaction, it was hoped that the Dieckmann cyclisation of the intermediate could be avoided and cyclisation to a 2-pyrone derivative achieved.

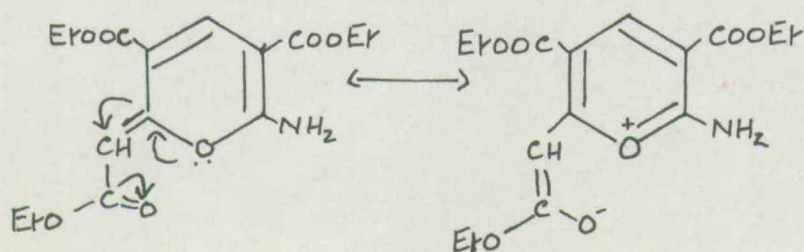
(1) The Michael reaction of diethyl acetonedicarboxylate and ethyl ethoxymethylenecyanoacetate in ethanol, using potassium hydroxide or sodium ethoxide as catalyst, yielded a yellow crystalline product (m.pt. 158-9°) whose infrared and ultraviolet spectra (Fig. 1V) showed clearly that it was neither a resorcinol derivative nor a 2-pyrone; analysis indicated an empirical formula $C_{15}H_{19}NO_7$.

That this compound had structure (XL1) was confirmed by its infrared spectrum and by its reactions. Treatment of the compound with ethanolic hydrogen chloride gave the pyrone (XL11) and a quantitative yield of ammonium chloride (c.f. ethyl β -amino crotonate) which reacts with ethanolic hydrogen chloride in a similar manner and contains the system  and boiling the compound with sodium ethoxide solution afforded compound (XL111). The infrared spectrum of compound (XL1) exhibited peaks at 3380 and 3220 cm^{-1} , indicative of a primary

amino group, and at 1680, 1700 and 1725 cm^{-1} .



The absorption at 1680 cm^{-1} has been attributed to the ester group (in position 3) which is hydrogen bonded to the 2-amino group. The ester carbonyl group at position 7 is likely to possess considerably more single bond character than that at position 5 because of the contribution of pyrylium betaine structures to the resonance hybrid and the absorption at 1700 cm^{-1} is therefore attributed to the ester carbonyl at position 7, leaving the absorption at 1725 cm^{-1} for the 5-ethoxycarbonyl group, which is normal for a conjugated ester. e.g.,



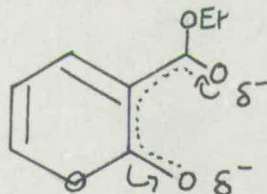
The structure of the products (XL111) and (XL11) was established as follows:

Compound (XL111) was identified by comparison of its ultraviolet spectrum (Fig.11) with the spectra obtained from compound (XXXV11) and (XXX1X), by its analysis and by its infrared spectrum which showed peaks at 2220cm^{-1} ($\text{C}\equiv\text{N}$ group), and 1670cm^{-1} (hydrogen bonded ester group(s)). The cyano-group proved very resistant to hydrolysis and an attempted conversion of compound (XL111) to compound (XXXV11) failed.

The structure of compound (XL11) was partially established by comparison of its ultraviolet spectrum (Fig.1) with that of the pyrone (XXX1V) obtained by Simonsen. Strong similarities were present but the spectrum of compound (XL11) possessed an extra peak near 395μ . This was attributed to enol formation ($\text{XL11a} \rightleftharpoons \text{XL11b}$) and was confirmed by the formation of a stable sodium salt on treatment of the pyrone with sodium carbonate solution, and by the formation of an unstable ammonium salt on treatment of a solution of the free pyrone with gaseous ammonia. Confirmation of the structure was obtained by analysis and comparison of the infrared spectra of compounds (XXX1V) and (XL11) (q.v.).

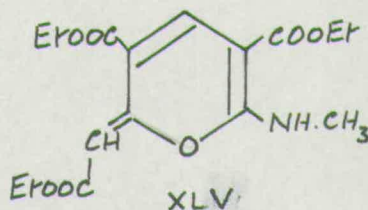
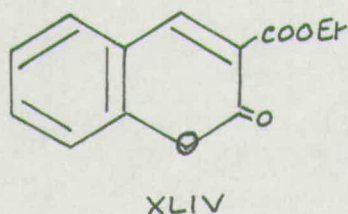
The infrared spectra of compounds (XXX1V) and (XL11)

both show an unusual feature. This is the peculiarly high absorption ($1785\text{-}1795\text{cm}^{-1}$) in the carbonyl region. Compound (XL11) exhibited peaks in the carbonyl region at 1715 , 1745 , 1748 and 1795cm^{-1} , and these were attributed to the carbonyl groups present in the 2-, 5-, 7- and 3-positions respectively. The pyrone (XXXIV) also showed carbonyl absorptions at 1715 , 1745 and 1785cm^{-1} . These results support the assignment of the 1748cm^{-1} frequency to the 7-ethoxycarbonyl group in compound (XL11). That the carbonyl group in the 2-position absorbs at 1715cm^{-1} and that in the 5-position at 1745cm^{-1} is supported by previous results⁶⁰. The abnormally high absorption frequency of the ester carbonyl in the 3-position, which is present in both compounds, appears to be due to the proximity of the 2-carbonyl group. This electronegative group would have an electrostatic effect on the carbonyl in the 3-position which, if it took the form shown below, might lead to



an increase in double bond character and hence to an elevation in its frequency of absorption. Some support for this assignment of the high absorption frequency to this carbonyl group comes from unpublished work in this department⁸⁰ where a similar

effect was found in the infrared spectrum of 3-ethoxycarbonyl-coumarin (XLIV) ($\nu_{\text{CO}} = 1715$ and 1770cm^{-1} in CCl_4).

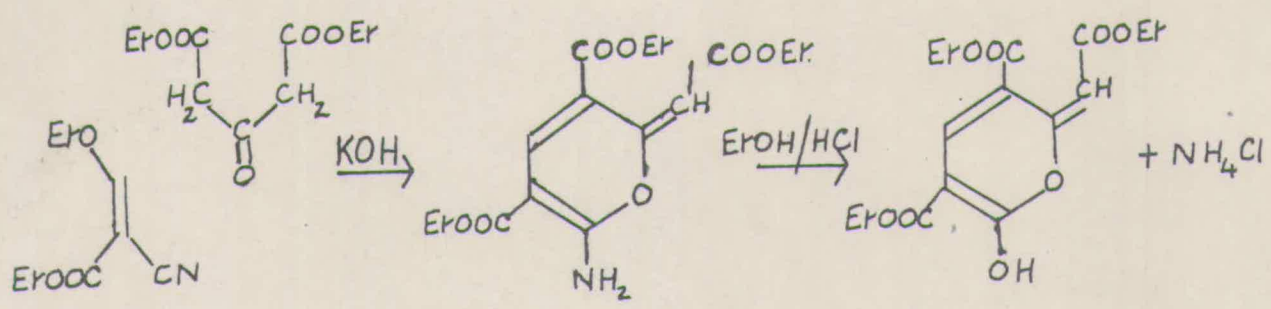


A similar effect, although not nearly so pronounced, has been noted in the infrared spectrum of compounds having similarly positioned electronegative groups^{81,82} e.g., ethylcyanoacetate.

Attempted N-methylation of compound (XLIV), using sodium ethoxide/methyl iodide, resulted in the formation of a yellow compound (mp $134-5^{\circ}\text{C}$) which appeared to be the expected material (XLV) from comparison of its ultraviolet spectra with that of compound (XLIV) (Fig. 1V), but a rather unsatisfactory analysis was obtained.

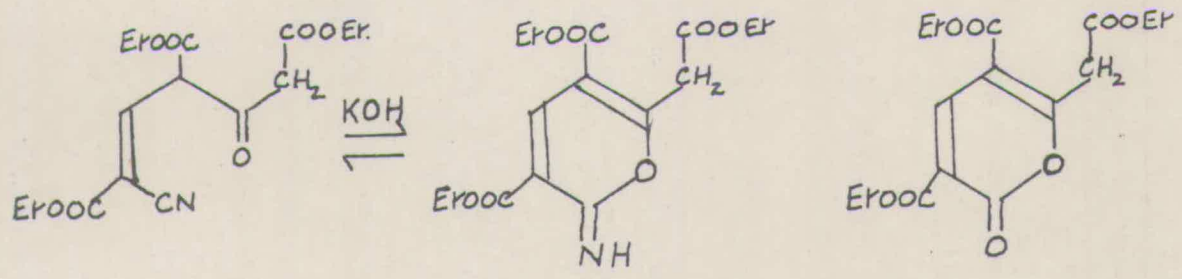
Further confirmation of the infrared assignments for, and hence for the structure of, compound (XLIV) was obtained when dibenzyl ketone and ethyl ethoxymethylencyanoacetate were allowed to react together in ethanol, in presence of potassium hydroxide, to yield compound (XLV). Since the infrared spectrum showed peaks at 3380 and 3250cm^{-1} (primary NH_2 stretching frequencies) with only a single carbonyl absorption at 1670cm^{-1} (3-carbonyl

Scheme II

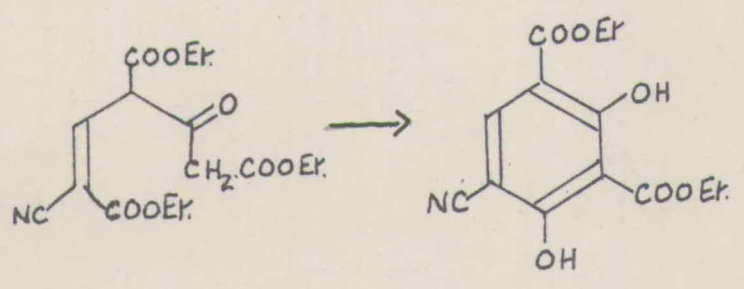


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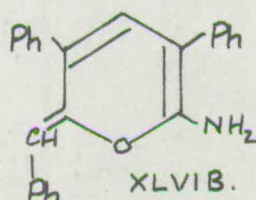
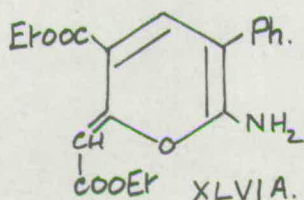
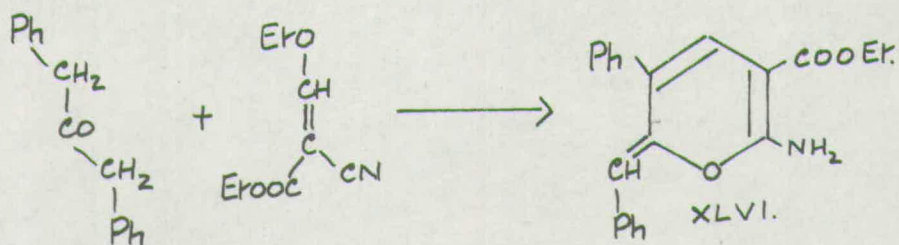
↓



↓ NaOEt/heat.



group, hydrogen bonded to NH_2), the assignment of the infrared frequencies in compound (XLV1) was supported.

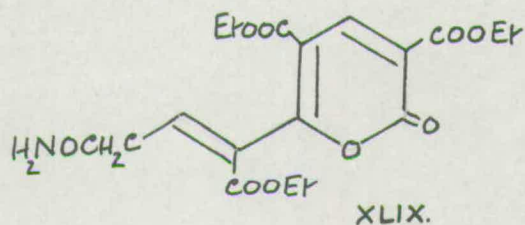
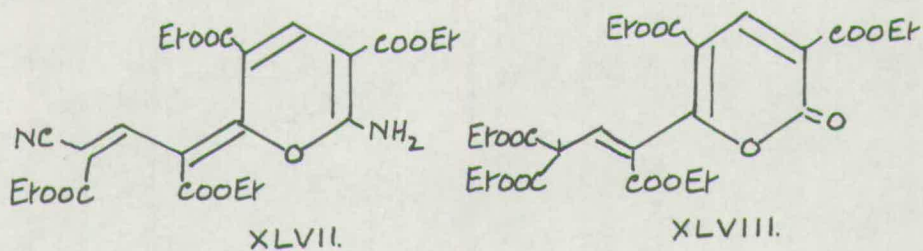


Unfortunately, attempts to condense α -cyanophenylacetaldehyde and diethyl acetonedicarboxylate or dibenzyl ketone, to give compounds (XLV1A) or (XLV1B) and hence completely confirm the infrared data, were wholly unsuccessful. The structure of compound (XLV1) was confirmed by comparison of its ultraviolet spectrum with that of compound (XL1) (Fig.1V) and by analysis.

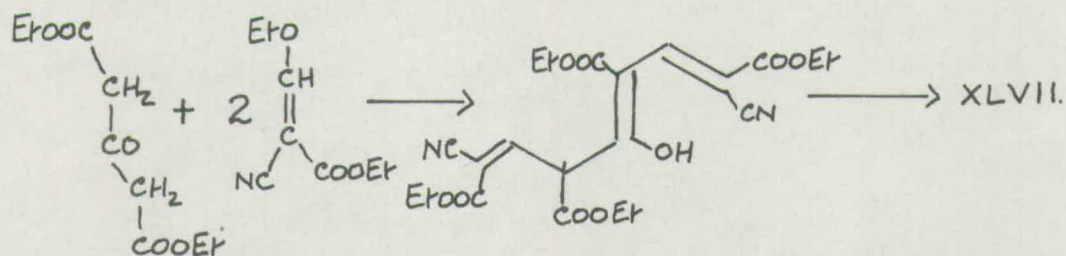
The interconversions of compounds (XL1), (XL111) and (XL11) are explained in Scheme 11.

(2) The reaction of diethyl acetonedicarboxylate with 2 moles of ethyl ethoxymethylenecyanoacetate, in anhydrous ethanol using sodium ethoxide as catalyst, yielded deep red

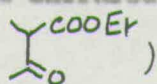
crystals (m.p. 158-9°, mixed m.p. with compound (XL1) showed depression) formulated as (XLV11).



This compound could not be formed by the reaction of a second molecule of ethyl ethoxymethylenecyanoacetate with compound (XL1). It would appear, then, that double Michael addition precedes cyclisation, i.e.,



The structure of compound (XLV11) follows from its analysis, from its ultraviolet spectrum (Fig. V), and from its infrared spectrum (q.v. Experimental). Treatment with ethanolic HCl gave ammonium chloride and two products both exhibiting high

carbonyl absorptions ($\sim 1780\text{cm.}^{-1}$) in the infrared, suggesting the possible presence of the system . Although satisfactory analyses could not be obtained for either compound, their infrared and ultraviolet spectra suggest that they probably have structures (XLV111) and (XL1X). Compared with the parent compound, both show hypsochromic shifts in the visible region, clearly owing to the reduction in the extent of conjugation present in the molecule. Structure (XLV111) was assigned to one compound as the basis of its infrared spectrum, analysis, and its solubility in sodium carbonate solution (c.f. the lower vinylogue (XL11)). Since the second compound, with postulated structure (XL1X), was separated from the first (XLV111) on the basis of its relative insolubility in sodium carbonate, it seems likely that the poor analyses obtained for the compounds may be due to contamination with each other.

In an attempt to prepare compound (XLV11), using potassium hydroxide as catalyst, a very small amount of a red crystalline compound (m.p. $235-7^{\circ}$) was obtained, together with the desired product. Although this compound's ultraviolet spectrum exhibited similarities to that of compound (XLV11), its analysis and infrared spectrum showed it to possess a different structure. Elemental analysis indicated an empirical formula $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_5$ which corresponds to compound (XLV11) less two ethoxycarbonyl groups, but the

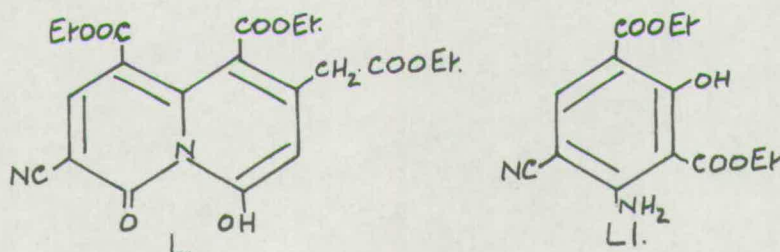
structure of this compound remains unknown. The infrared spectrum did indicate, however, that the β -ethoxycarbonyl group, hydrogen bonded to the amino group, was still present.

Attempted N-methylation of compound (XLV11), using diazomethane in ether, failed but yielded a red/blue compound which was also isolated from the mother liquors of a preparation of the original pyran (XL1), together with a little of the pyridone (XXXV1) which had been the original object of this work. Its m.p. was $160-2^{\circ}$ but mixed m.p.s. with both the pyran (XL1) and the propene derivative (XLV11) showed depressions. Analysis indicated an empirical formula of $C_{21}H_{26}N_2O_{10}$. The ultraviolet spectrum of the compound (Fig.V) indicated a close relationship with compound (XLV11). Since the analysis corresponds to compound (XLV11) with the addition of the elements of water, and the infrared spectrum has a peak near 3600cm.^{-1} , it was concluded this compound is a hydrate of compound (XLV11) but the mode of combination of the elements of water is unknown.

(3) A series of reactions was carried out with diethyl acetonedicarboxylate and ethoxymethylenemalononitrile, under similar conditions.

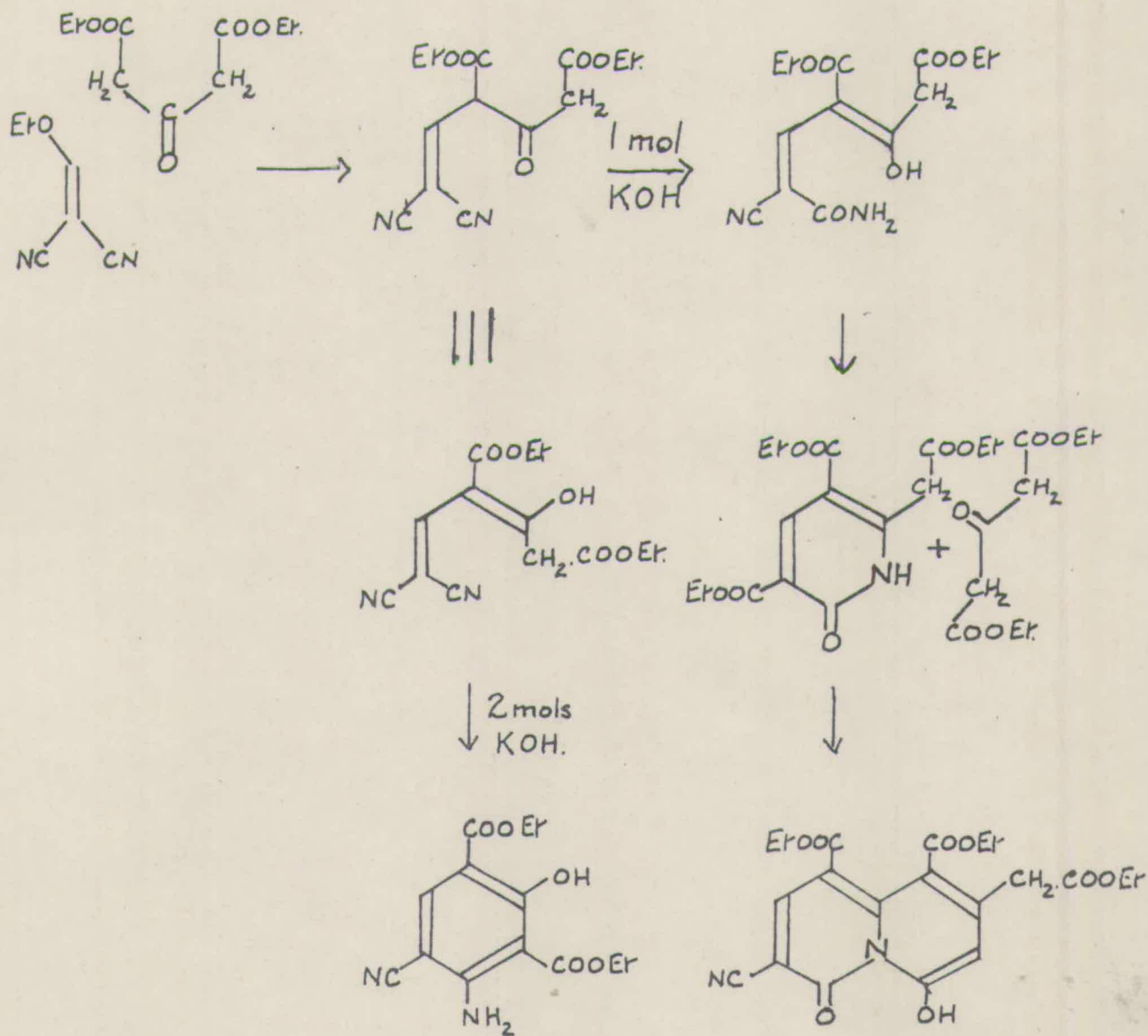
Using one mole of potassium hydroxide in alcohol as the catalyst, the reaction of diethyl acetonedicarboxylate and ethoxymethylenemalononitrile produced, in low yield, a yellow

compound (m.p. 164-6°) which fluoresced strongly in ultraviolet light. Comparison of the ultraviolet spectrum of this compound with that of known quinolizones (Figs. V1 & V11) indicated the presence of the quinolizone nucleus in the compound (peaks at 426, 266 and 230m μ , inflexion at 352m μ). This fact, combined with elemental analysis and the infrared spectrum, (peaks at 2240cm $^{-1}$ due to C \equiv N, and at 1755 and 1740cm $^{-1}$ attributed to the unconjugated and 1,8-ethoxycarbonyl groups respectively) led to the formulation of this compound as (L).



In a similar manner, but using 2 moles of potassium hydroxide as the catalyst, a colourless compound (m.p. 129-30°) was obtained. Since its ultraviolet spectrum was very similar to those of compounds (XXXV11), (XXX1X) and (XL111) (Figs. 11 & 111), it appeared to be closely related to these compounds. Analysis and infrared spectral examination (peaks at 3420, 3350cm $^{-1}$ due to NH₂ stretching frequencies, 2230cm $^{-1}$, due to C \equiv N, and 1700 and 1670cm $^{-1}$ attributed to -NH₂ and -OH hydrogen bonded ester groups respectively) established this compound's structure as (L1).

Scheme III



The low yield of compound (L) may be accounted for by continued condensation of the methylene group in the final molecule with further molecules of diethyl acetonedicarboxylate, or with ethoxymethylenemalononitrile, or by competing reactions which consume the intermediates. Scheme 111 attempts to account for the various reaction products.

(4) Numerous attempts to extend this interesting series of reactions, by using diethyl acetonedioxalate as the dicarbonyl component, were completely unsuccessful.

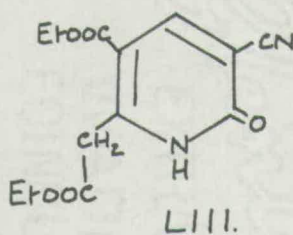
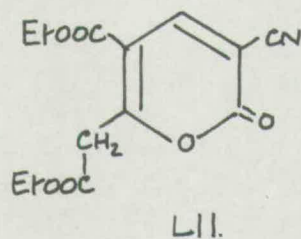
An attempt to utilise the possible reaction between diethyl β -ethoxymethyleneacetonedicarboxylate and cyanoacetamide (q.v.) was also unsuccessful.

(iii) The reported synthesis of compound (XXXV11A)
diethyl 6-ethoxycarbonylmethyl-2-pyrone-
3,5-dicarboxylate.

The synthesis of this compound by the condensation of diethyl acetonedicarboxylate and diethyl ethoxymethylenemalonate was reported by Mitra in 1938⁸⁴. He also reported the conversion of the pyrone (XXXV11A) into the corresponding pyridone (XXXV1). Repetition of this condensation produced a compound (m.p. 106-7°) which seemed to be identical with that (m.p. 104-5°) obtained by Errera⁷⁹ and already formulated as (XXXV11) on the basis of its ultraviolet and infrared spectra. The m.p. claimed by Mitra for the pyrone (XXXV11A) was 106° and it would therefore appear that

Mitra, unaware of Errera's earlier work, wrongly assigned structure (XXXV11A) to this compound. Mitra's claim to have synthesised the pyridone (XXXV1) by the action of ammonia on compound (XXXV11A) is also refuted on the grounds that this pyridone (m.p. 119-20^o) has now been synthesised unequivocally (see later) and its structure proved by degradation to known compounds. Mitra reported a m.p. of 223^o for this pyridone and it seems likely, since his analysis results were satisfactory, that the compound he obtained was, in fact, an isomer of the pyridone formed by replacement of one hydroxyl group in compound (XXXV11) by an amino group.

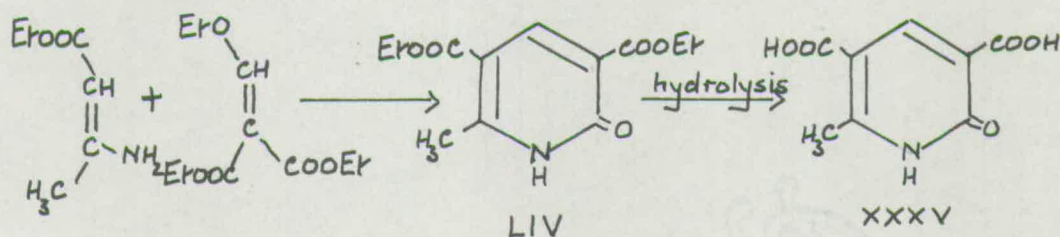
As a result of the reaction of diethyl acetonedicarboxylate and ethyl ethoxymethylenecyanoacetate, Mitra claimed to have synthesised the pyrone (L11) and reported its m.p. as 142^o (colourless needles). It is now clear, however, that this compound possesses structure (XL111). The compound derived from it by treatment with ammonia is not (L111) but probably also an aminophenol.



(iv) The synthesis of diethyl 6-ethoxycarbonyl-
methyl-2-pyridone-3,5-dicarboxylate and its
reactions with some ethoxymethylene compounds.

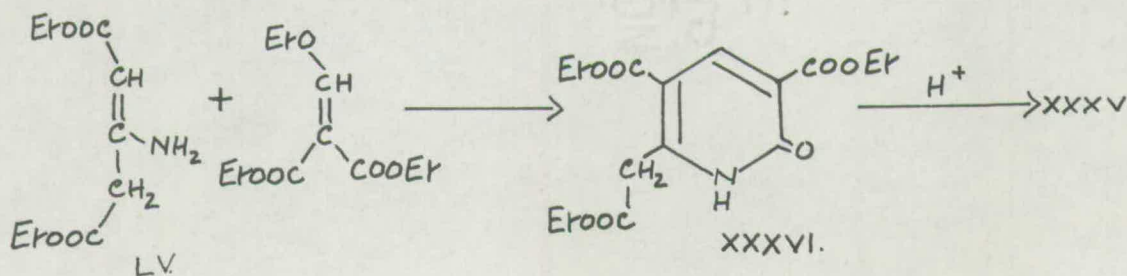
Since it was obvious that an indirect approach to the desired compound (XXXV1), via the 2-pyrone series, was unlikely to be very successful, an alternative synthetic route was examined.

Ethyl β -aminocrotonate and diethyl ethoxymethylene-malonate condense together, in basic conditions, to give diethyl 6-methyl-2-pyridone-3,5-dicarboxylate⁹⁰ (LIV).



The acid (XXXV) derived by hydrolysis of the ester (LIV) has also been obtained by Simonsen⁷⁷ and by Errera⁸⁵, using two further separate methods.

The corresponding β -amino compound (LV), derived from diethyl acetonedicarboxylate, would be expected to undergo an analogous reaction with diethyl ethoxymethylenemalonate to yield the pyridone (XXXV1) directly.



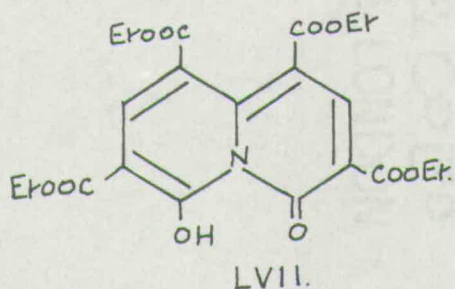
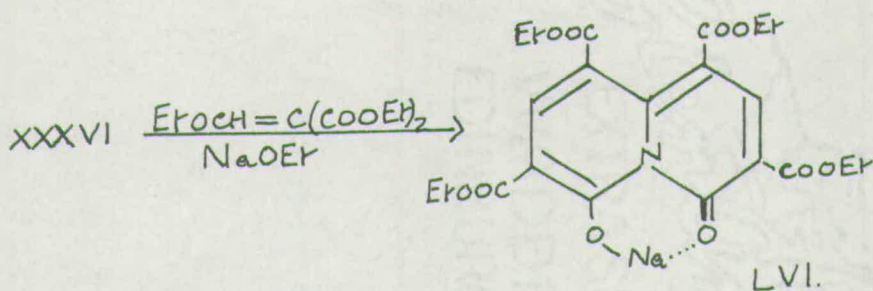
Treatment of diethyl acetonedicarboxylate in a large volume of ether, with anhydrous ammonia, gave the desired compound (LV) in 60% yield. It was a liquid which decomposed slowly at room temperature but, if used immediately, it was quite satisfactory for synthetic purposes.

Diethyl β -aminoglutaconate (LV), on treatment with diethyl ethoxymethylenemalonate, using sodium ethoxide as catalyst, afforded a 50% yield of diethyl 6-ethoxycarbonylmethyl-2-pyridone-3,5-dicarboxylate (XXXV1). The structure of this compound was established by acid hydrolysis and decarboxylation of the side chain to the known 6-methyl-2-pyridone-3,5-dicarboxylic acid (XXXV), m.p. 303-4° (Lit. m.p. 305°)⁹⁰, by elemental analyses, and by examination of the infrared spectrum (peaks at 1750, 1705 and 1660cm⁻¹, attributed to the carbonyl groups in the side chain, the 3- and 5-positions and the 2-position, respectively, and at 3300 and 1580cm⁻¹ secondary amine stretch and deformation frequencies respectively). The ultraviolet spectrum (Fig. V111), which had peaks at 328, 263 and 212 μ , also showed certain resemblances to the spectrum of 6-methyl-2-pyridone⁸⁶.

Following the synthesis of 6-hydroxy-4-quinolizones by Adams and Reifschneider⁷⁴, the pyridone (XXXV1) was allowed to react with diethyl ethoxymethylenemalonate, using sodium ethoxide as catalyst. No reaction could be induced in boiling ethanol but

heating in dimethylformamide at 100° for six hours, in the presence of solid sodium ethoxide, afforded a bright yellow compound which was strongly fluorescent in solution, both in ultraviolet light and day-light. Examination of the ultraviolet spectrum (Fig.V11) indicated the presence of the quinolizone nucleus (peaks at 450, 363, 274, 242 and 210 μ) but elemental analysis suggested that inorganic material must be present since a residue was reported. The presence of sodium was indicated when the emission spectrum of the compound was examined in the flame spectrometer. On this evidence the substance was formulated as compound (LV1).

No means could be found whereby the free hydroxyquinolizone (LV11) could be released. Treatment with chloroform and hydrogen chloride in the cold, grinding with 2N hydrochloric acid, or shaking with zinc uranylacetate, left the compound unchanged. Passage of the compound down a weak acid ion-exchange column also allowed the material to pass through unchanged. Treatment of the compound (LV1) with saturated ethanolic hydrogen chloride, however, yielded a colourless solid whose ultraviolet spectrum indicated that the quinolizone nucleus had been destroyed. This compound, when treated with alkali in ethanolic solution, underwent a series of colour changes, being colourless in acid solution, deep yellow near pH 8 and light yellow near pH 11.



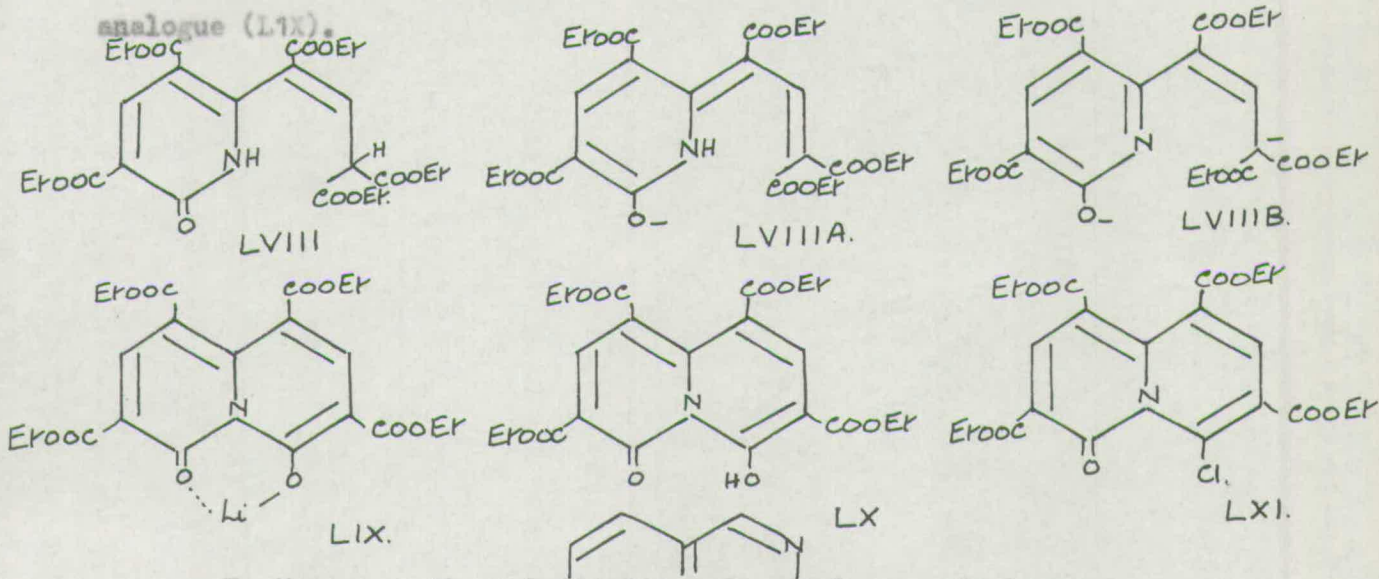
The structure of this compound is shown as (LV111) and follows from the similarity between the ultraviolet spectrum of this compound and that of the pyridone (XXXV1) (Figs. V111 & 1X) which suggested that the pyridone nucleus had remained intact, from the analysis results, and from the infrared spectrum which showed carbonyl absorptions at 1660, 1705, 1730 and 1750 cm^{-1} , attributed to the carbonyl groups in the 2-position and the 3- and 5- positions of the ring, to that in the α/β -unsaturated ester group in the side chain, and to the saturated ester carbonyls in the side chain respectively.

As shown in the formulae below (LV111 - LV111B) the colour changes have been explained by loss of a proton to give compound (LV111A) which has the longest conjugation path of the three molecules, followed by formation of the sodium salt (LV111B) and aromatisation of the pyridine ring by loss of a

further proton which reduces the conjugation in the molecule with consequent lightening of colour.

It was hoped that the property of compound (LV1) to chelate the sodium ion would be unique but repetition of the experiment, using lithium ethoxide, produced the lithium

analogue (LIX).



Furthermore, the substitution of certain organic bases, e.g., quinoline or isoquinoline for lithium or sodium ethoxide, led to the isolation of two complexes (e.g., LX) of the hydroxyquinolizone (LV11) with the organic bases. Clearly these compounds cannot be stabilised by chelation, which is presumably the way in which lithium and sodium ions are retained. Probably their existence depends on π -complex formation between the two heterocyclic nuclei. As is the case with the sodium derivative (LV1), these complexes and that with lithium, cannot be made to release the free hydroxyquinolizone (LV11).

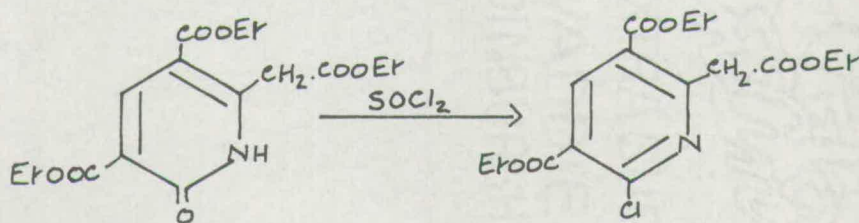
Treatment of the pyridone (XXXV1) with diethyl ethoxymethylenemalonate in the presence of potassium ethoxide, for reaction times similar to those used in the experiments with lithium and sodium ethoxide, yielded only the uncyclised pyridone (LV111). However, when longer reaction times were used the corresponding potassium salt to compound (LV1) was obtained. The pyridone (LV111) could be re-cyclised to compound (LV1), using sodium ethoxide as catalyst. Dimethylaniline and triethanolamine are not effective catalysts for the cyclisation and, since the amines would be less effective in forming $\bar{\pi}$ -complexes, this result supports the view that quinoline and isoquinoline do form $\bar{\pi}$ -complexes with the hydroxyquinolizone.

Since the free 6-hydroxy-4-quinolizone could not be obtained, it was hoped that treatment of the sodium or isoquinoline derivatives with an inorganic acid chloride might yield the 6-chloro-4-quinolizone (LX1) directly. Treatment of either of these compounds with thionyl chloride, phosphorus pentachloride or phosphorus oxychloride, in a variety of solvents and under different conditions, gave no identifiable product in reasonable yield. In only one case was a product isolated, and then in very small yield. This was obtained when the sodium derivative (LV1) was treated with phosphorus oxychloride but analysis showed the absence of chlorine and a residue was left after combustion. This material was of no synthetic value.

Tosylation of the 6-hydroxyl group was attempted in the hope that this would provide a compound of similar reactivity to a chloroquinolizone but, although a little sulphur containing material was obtained, using the isoquinoline or sodium derivatives as starting material, analysis indicated that this was not the compound required.

The attempted preparation of a 6-methoxy-4-quinolizone from the sodium salt (LV1) and methyl iodide was also quite unsuccessful.

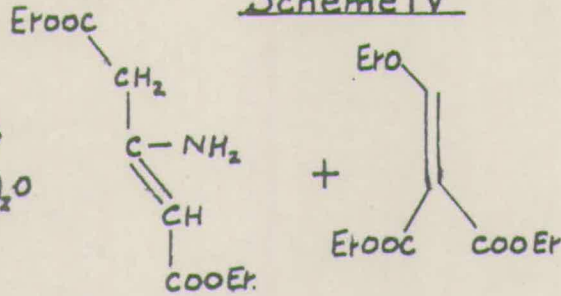
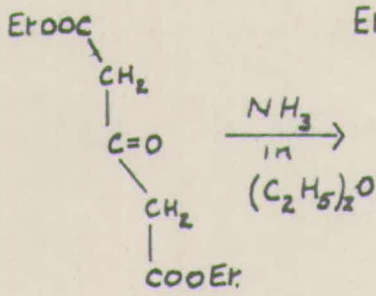
In an attempt to synthesise 6-chloro-4-quinolizones directly, compound (XXXV1) was treated with thionyl chloride and similar chlorinating agents in an effort to obtain the corresponding chloropyridines.



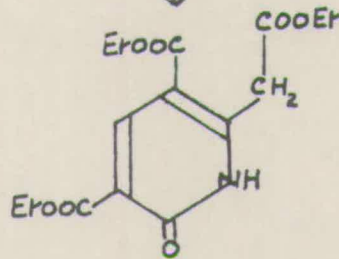
Surprisingly, no product could be isolated; the reaction invariably produced evil smelling intractable oils.

Finally, attempts to induce reaction between compound (XXXV1) and diethyl acetonedicarboxylate (c.f., compound (LV), Scheme 11) or diethyl oxalacetate were also unsuccessful.

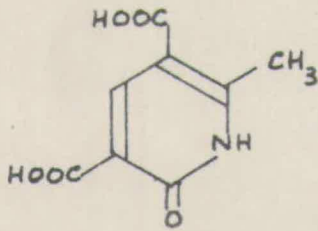
Scheme IV



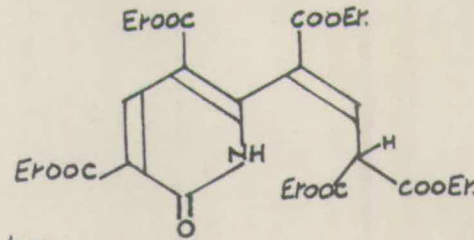
↓ NaOEt in EtOH.



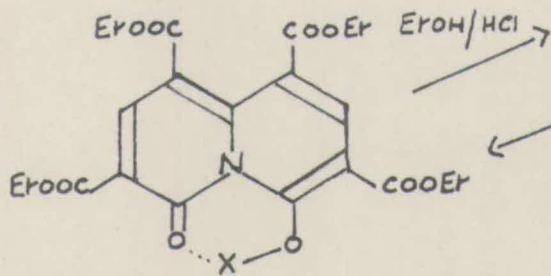
HCl



+ $\begin{array}{c} \text{EtO} \\ | \\ \text{C} \\ | \\ \text{EtOOC} \quad \text{COOEt} \end{array}$ (shorter reaction time)
 ↓ KOEt in D.M.F.



{ NaOEt, LOEt, KOEt } + $\begin{array}{c} \text{EtO} \\ | \\ \text{C} \\ | \\ \text{COOEt} \quad \text{COOEt} \end{array}$
 in D.M.F.



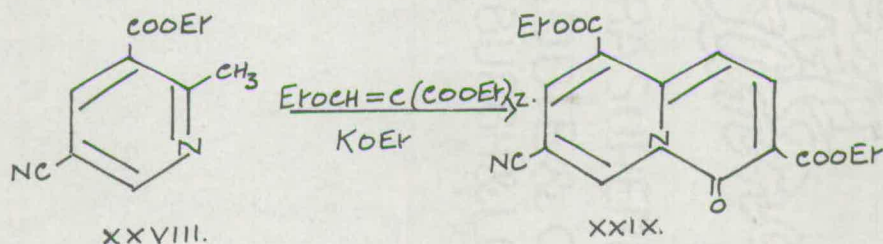
NaOEt in D.M.F.

X = Li, Na or K.

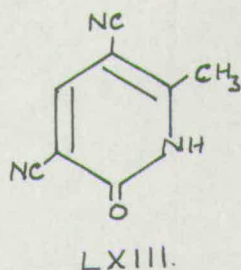
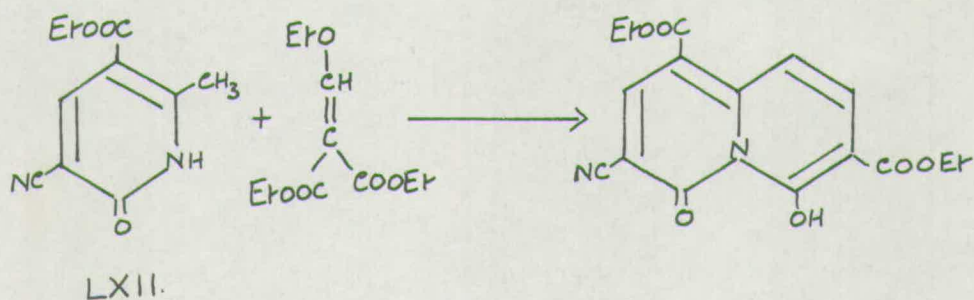
The reactions described with diethyl β aminoglutaconate are illustrated in Scheme 1V.

(v) Attempts to utilise other 2-pyridones as starting materials in the synthesis of 6-hydroxy-4-quinolizones.

(a) As mentioned in section (i), Govindachari et alia⁷⁵ have made use of the reactivity of the methyl group in ethyl 5-cyano-2-methyl nicotinate (XXVIII) to synthesise quinolizones. e.g., (XXIX).



The reactivity of the methyl group is enhanced by electron withdrawal, due to the ethoxycarbonyl and cyano groups, and hence the methyl group has evidently acquired a reactivity comparable to (e.g.) a methylene group adjacent to an ethoxycarbonyl group. If a similar compound in the 6-methyl-2-pyridone series could be obtained, it was hoped that an analogous reaction with diethyl ethoxymethylenemalonate would take place to give the corresponding 6-hydroxy-4-quinolizone. e.g.,

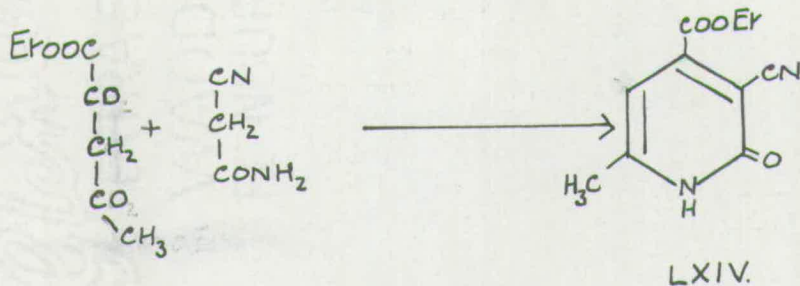


Ethyl 3-cyano-6-methyl-2-pyridone-5-carboxylate (LXII) has been prepared by Errera⁸⁵ and a recent synthesis of 3,5-dicyano-6-methyl-2-pyridone (LXIII) by Lukes and Kuthan⁹¹ was thought to be the source of an equally promising starting material.

Unfortunately, attempts to condense either compound (LXII) or (LXIII) with diethyl ethoxymethylenemalonate were unsuccessful. An attempt to make use of 2-chloro-3,5-dicyano-6-methylpyridine in a similar reaction was also unsuccessful. Only starting material was recovered from all three attempts.

(b) Bardhan⁹², in 1929, suggested that cyanoacetamide reacts with keto-form of β -diketones and not, in a Michael type reaction, with the enol form of the ketone. In the same paper he shows that ethyl acetylpyruvate and cyanoacetamide react together,

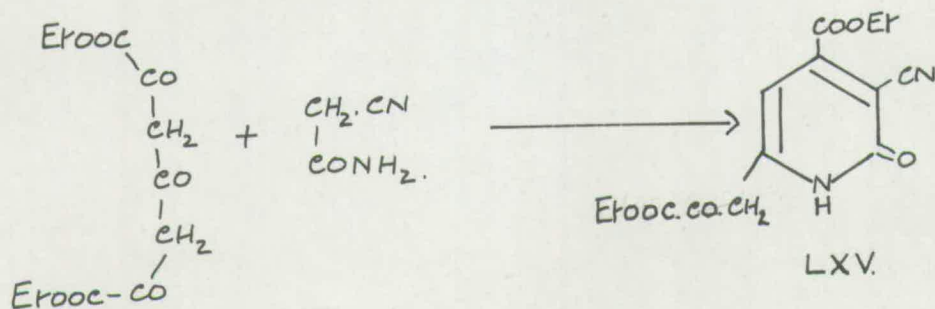
via the keto group adjacent to the ethoxycarbonyl group in the ester and via the methylene group in cyanoacetamide, to give the pyridone (LXIV) as the sole product. e.g.,



Supporting evidence is supplied by the analagous reaction of benzoylacetone, ω -propionylacetophenone and propionylacetone with cyanoacetamide.

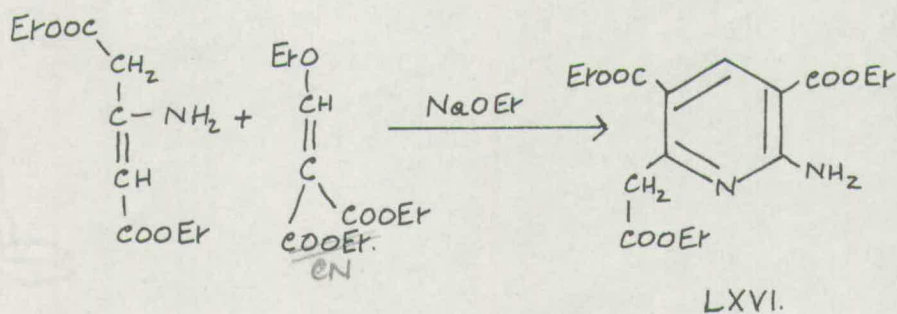
More recently this reaction of ethyl acetylpyruvate and cyanoacetamide has been shown⁹³ to yield the same product.

Diethyl acetonedioxalate might be expected to undergo the same type of reaction with cyanoacetamide to produce pyridones of structure (LXV). Such pyridones would possess a very reactive methylene group in the 6-position and might provide a useful starting material for further syntheses.



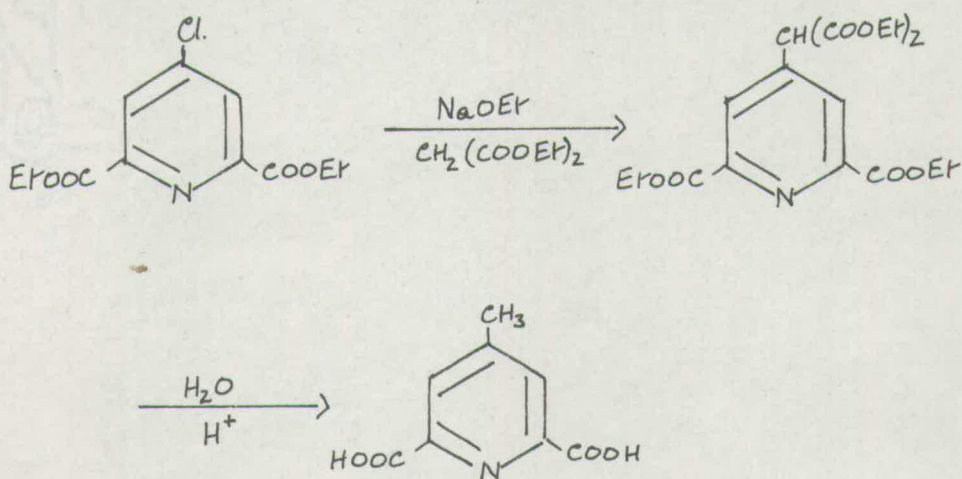
The reaction of cyanoacetamide and diethyl acetone-dioxalate was attempted using a variety of conditions but no product could be isolated. The reaction was also attempted, using ethyl malonamate (EtOOC. CH₂. CONH₂.) and malonamide (CH₂.(CONH₂.)₂) instead of cyanoacetamide, but was equally unsuccessful.

(b) The condensation of diethyl β-aminoglutaconate with ethyl ethoxymethylenecyanoacetate yielded compound (LXVI), identified by its infrared spectrum and analysis, but the yield was too low to be of any practical value. The main reaction product was a red oil from which was isolated a little of the red-blue hydrate which had previously been obtained in methylation attempts on compound (XLV11) and which was isolated from the mother liquors of a preparation of the aminopyran (XL1).



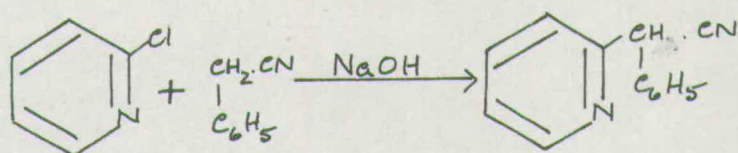
(vi) Attempts to prepare or utilise 2-chloro-pyridines as starting material for the synthesis of the quinolizone ring system.

The halogen atoms in 2-, 4- and 6-halopyridines undergo nucleophilic replacement by a variety of reagents. The simplest case is that in which the halogen atom is replaced by hydrogen but replacement by hydroxyl, mercapto, alkoxy, metallic and amino groups has also been effected. More important, however, from the present point of view, are reactions with carbanions. For example, the reaction⁹⁴ of diethyl 4-chloropyridine-2,6-dicarboxylate and sodio-malonic ester which, on hydrolysis and decarboxylation of the product, yields 4-methylpyridine-2,6-dicarboxylic acid. e.g.,



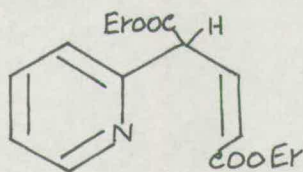
Despite a report by Kuhn and Richter⁹⁵ that this reaction could not be applied to 2-bromopyridine, Walter and McElvain⁹⁶ have

reported the reaction between sodiomalonic ester and 2-bromo-pyridine to give the expected ethyl-2-pyridylmalonate in small yield. Sodium hydroxide has been used to catalyse the reaction of 2-chloropyridine with phenylacetonitrile⁹⁷. e.g.,



The presence of an electron withdrawing group ortho or para to the 2- or 4-halogen atom in a halopyridine enhances the reactivity of the halogen atom. It is for this reason that 2-chloro-5-nitropyridine possesses such a reactive halogen substituent, as shown in several reactions⁹⁸.

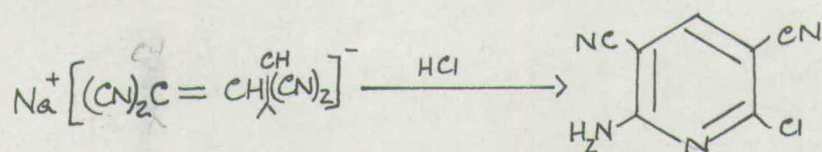
It was hoped that this known reactivity of the halogen atom in 2- and 4-halopyridines could be exploited to effect the syntheses of pyridines with side chains capable of cyclisation. Accordingly, the syntheses of a number of model compounds of the type (LXVII) was attempted in order that this hypothesis could be tested.



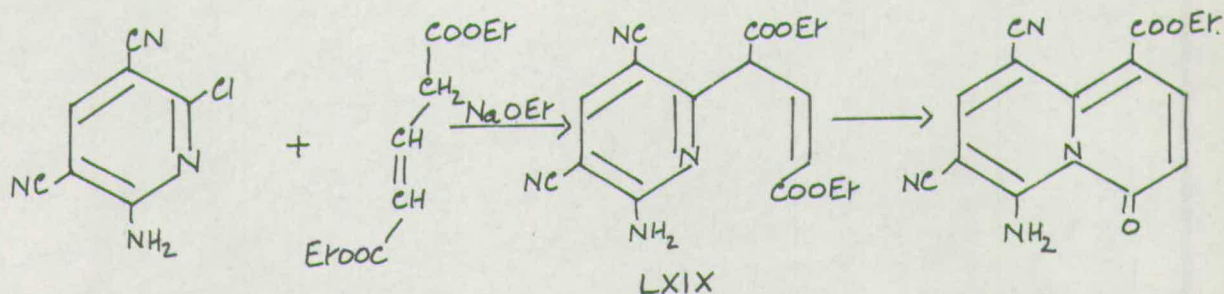
LXVII.

(a) 2-Chloropyridine was allowed to react with diethyl glutaconate, using sodium ethoxide as catalyst, but despite the use of a variety of conditions, no product could be isolated: it was assumed that the chlorine atom had not been replaced because it was insufficiently activated.

The recent publication of the syntheses of 2-chloro-3,5-dicyanopyridine derivatives appeared to offer a means of preparing an intermediate more likely to possess a suitably reactive halogen atom. It has been shown⁹⁹ that treatment of the sodium salt of 1,1,3,3-tetracyanopropene with hydrogen halides yields 2-amino-6-halo-3,5-dicyanopyridines (LXV111). e.g.,



The halogen atom in this molecule has been shown to be very reactive, being replaced by amino, alkoxy, arylsulphonyl and dicyanomethyl groups on reaction with the appropriate sodium salt. It therefore seemed possible that these dicyanohalopyridines, such as compound (LXV111), might undergo reaction with the sodium salt of diethyl glutaconate. e.g.,

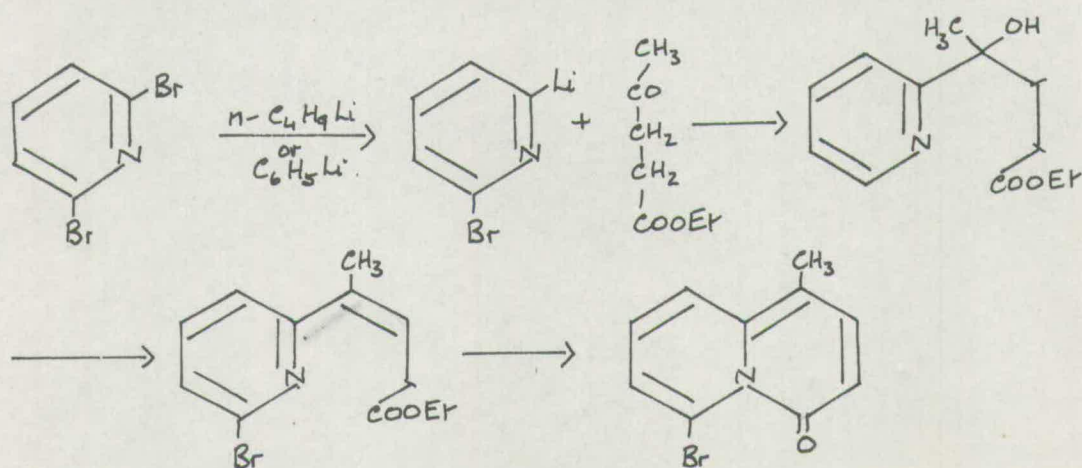


A number of attempts were made to condense together 6-amino-2-chloro-3,5-dicyanopyridine and diethyl glutaconate, using sodium ethoxide as catalyst, but in only one case was a product obtained. Examination of the infrared spectrum of this compound and elemental analysis showed that it was not the expected product (LXIX), nor was it 2-amino-3,5-dicyano-6-ethoxypyridine which seemed to be the most likely alternative. The product appeared to have the empirical formula $\text{C}_{16}\text{H}_{16}$ or $17\text{N}_5\text{O}_4$ and its structure is unknown.

Attempts were then made to replace the amino group in compound (LKV111) with another halogen atom (c.f. Ref. 100). This compound would also have been useful if synthesis of the quinoline had been achieved as it would have given a 6-halo-4-quinoline directly.

A number of attempts to diazotise the amino group using isosylnitrite and hydrochloric acid in tetrahydrofuran⁴⁹, or sodium nitrite and hydrochloric acid in the same solvent, were without success.

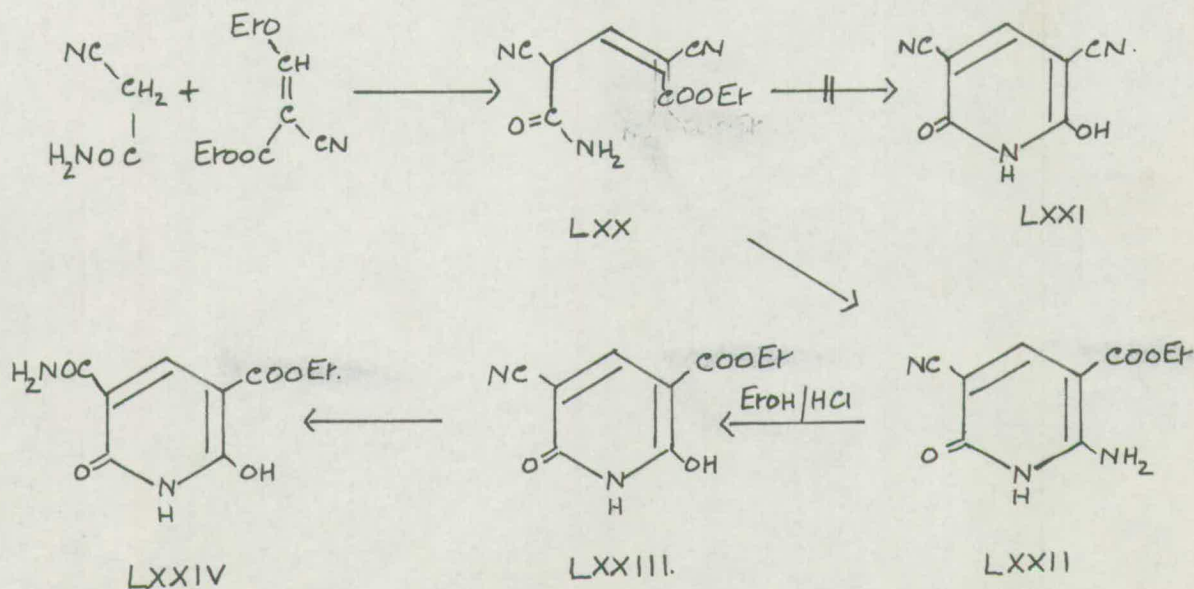
(b) Although 2-aminopyridine has been diazotised by the Craig procedure¹⁰¹ to give 2-bromopyridine, and there are numerous reports of various monoaminopyridines containing other substituents, there is only one report¹⁰² concerning the diazotisation of a diaminopyridine - namely 2,5-diaminopyridine - to give a dihalopyridine. This was accomplished by a Sandmeyer-type reaction. Since 2,6-dibromopyridine is not commercially available, and existing methods of formation require lengthy procedures or large and specialised apparatus¹⁰⁵, it was hoped that diazotisation of 2,6-diaminopyridine by Craig's procedure would yield 2,6-dibromopyridine. This compound could then be allowed to react with phenyl or butyl-lithium to give an organometallic compound which would react with a suitable keto-ester to give a 6-bromopyridine derivative capable of cyclisation. 2,6-Dibromopyridine reacts with Grignard reagents¹⁰⁴ and 2-bromopyridines have been shown capable of forming organolithium derivatives which then react in a manner analogous to the corresponding Grignard reagents¹⁰³.



It is known that 2,6-dibromopyridine forms only a mono-lithium derivative¹⁰⁰.

The diazotisation of 2,6-diaminopyridine in concentrated hydrobromic acid containing bromine yielded a colourless compound which was not the expected 2,6-dibromo compound but appeared to be a more highly brominated pyridine. No reaction could be induced between this compound and ethyl laevulinate, using n-butyllithium or phenyllithium, although a lithium derivative did appear to be formed in some experiments. Attempts to induce reaction between the sodium salt of diethyl acetonedicarboxylate and the above compound also failed.

(c) In another attempt to prepare an intermediate capable of conversion to a 2,6-dihalopyridine derivative, the reaction of cyanoacetamide and ethyl ethoxymethylenecyanoacetate was examined.

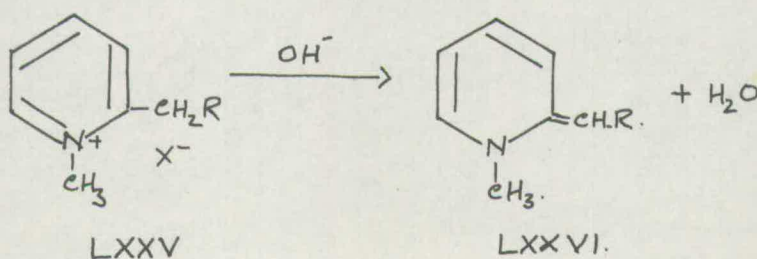


Two alternative cyclisations of the intermediate (LXX) are possible, one to give the hydroxypyridone (LXX1), the other to give the aminopyridone (LXX11).

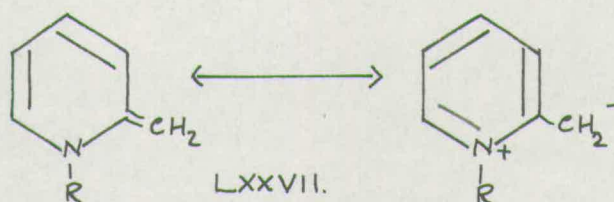
If the compound (LXX1) had been obtained, reaction with phosphorus oxychloride might have yielded 2,6-dichloro-3,5-dicyanopyridine which might then have reacted with diethyl glutaconate or diethyl acetonedicarboxylate (diethyl β -hydroxyglutaconate). The reaction, however, yielded compound (LXX11) whose structure was established by analysis and examination of its infrared spectrum. Attempts to convert this compound into compounds (LXX111) or (LXX1V), by treatment with ethanolic hydrogen chloride, were unsuccessful: the product yielded unsatisfactory analytical results for either compound.

(vi) Attempts to utilise pyridinium salts in the synthesis of 2-pyridones and quinolizones.

It has been known for some time that the reactivity of a 2- or 4-methyl group in the pyridine ring is greatly enhanced by the formation of the corresponding N-alkylpyridinium salt. Such quaternary compounds (e.g., (LXXV)) may lose a proton, on treatment with base, to give non-ionic bases. (e.g., (LXXVI)).

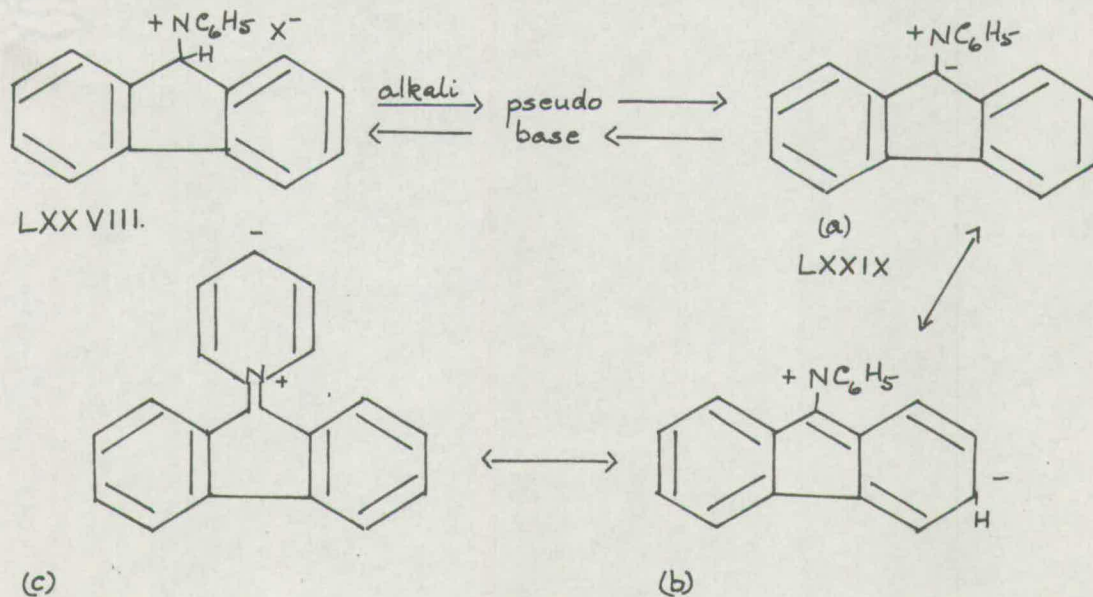


These compounds are highly reactive and their reactivity can be understood on the basis of the resonance structures (LXXVII), in which the unshared electron pair on the nitrogen atom is accessible at the methylene carbon atom. e.g.,



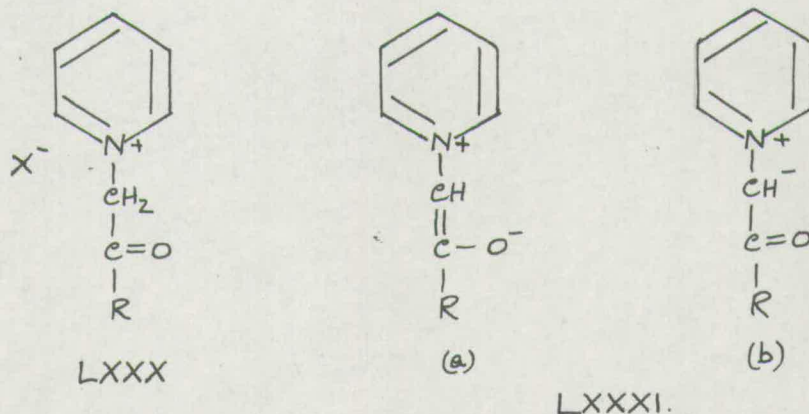
Any reaction at the nitrogen atom would cause loss of ring resonance energy and, consequently, reaction occurs exclusively at the methylene carbon atom.

Behaviour very similar to these examples is found in some types of 1-pyridinium derivatives. 9-Fluorenylpyridinium bromide (LXXVIII), on treatment with alkali, forms a deep blue compound considered to be an anhydro base of type (LXXIX)¹⁰⁶.



That the canonical structure (LXXIXa) predominates is shown¹⁰⁷ by the formation of a nitron derivative at the 9-position.

Resonance stabilisation is important, not only for C-betaines of type (LXXIX), but also for pyridinium derivatives in which the negative charge may be carried by an oxygen or by other nitrogen atoms in the molecule. Thus the enolbetaine (LXXXIa), obtained by the treatment of phenacylpyridinium halides (LXXX), may have contributions from structure (LXXXIb) as well as from structure (LXXXIa).

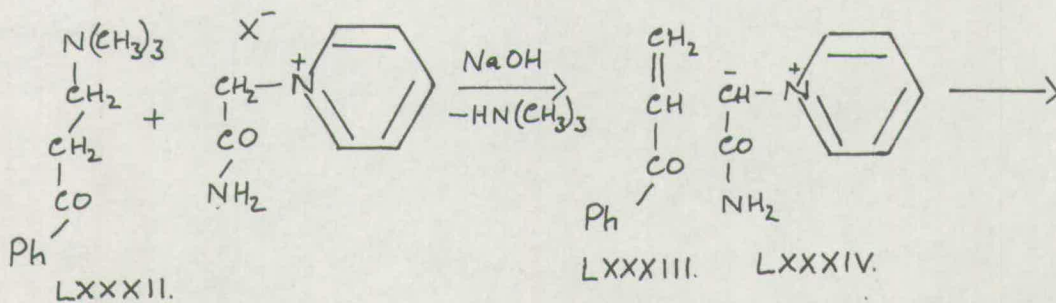


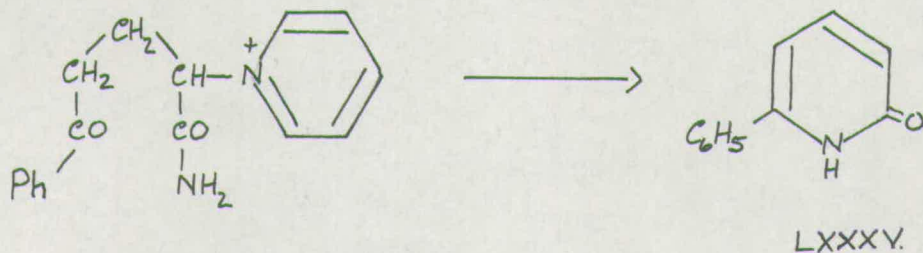
Where the contribution from a C-betaine structure of type (LXXXIb) predominates, the betaines are less stable, more easily oxidised and more reactive to aldehydes, nitroso compounds, picryl chloride, etc., than is the case where an enol betaine structure, e.g., (LXXXIa) predominates.

Generally speaking, the reactivity of an N-methylene group

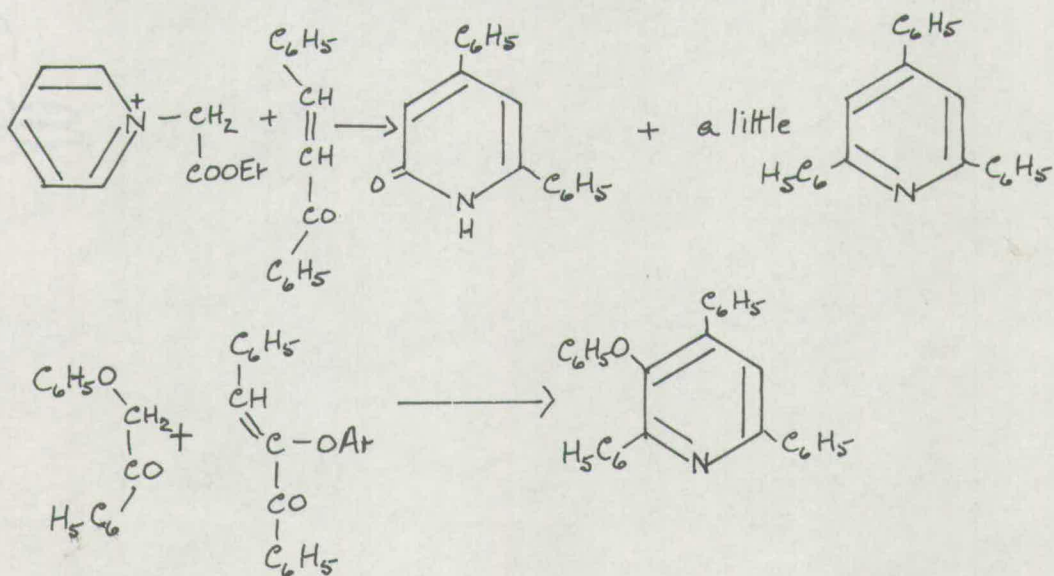
is greatly enhanced by the presence of an α -carbonyl group and pyridinium salts of this type, e.g., (LXXX) have been compared to β -diketones¹¹⁰, since the methylene group undergoes condensation with aldehydes, alkylation, acylation and coupling with diazonium salts, etc.

Recently pyridinium salts of the general type (LXXX) have been employed in a Michael reaction with Mannich bases¹¹¹ e.g., (LXXXII). Clearly, the Mannich base is the source of the acceptor, addition of alkali releasing both the vinyl ketone (LXXXIII) and the pyridinium betaine (LXXXIV), which then undergo Michael addition and subsequent cyclisation with elimination of pyridine, to form a 2-pyridone (LXXXV).



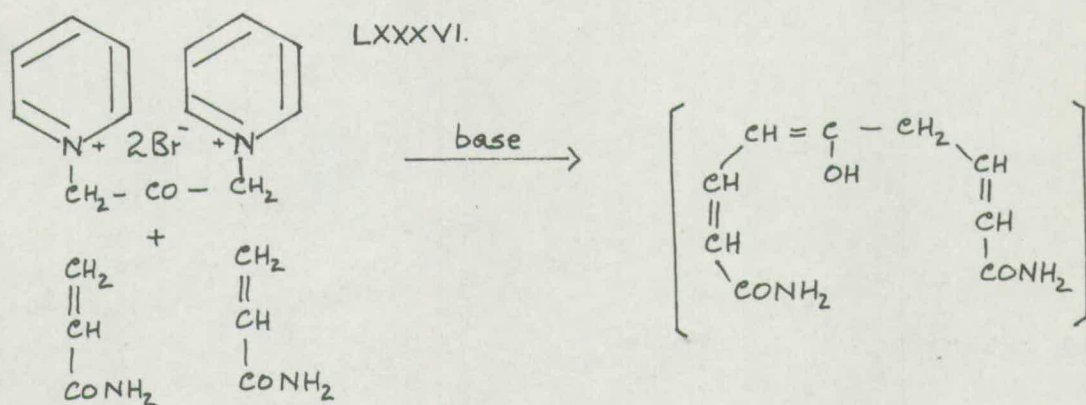


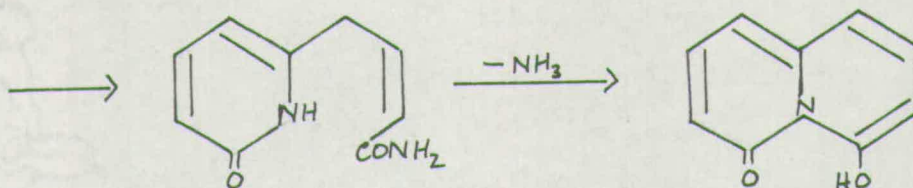
Kröhnke and Becher¹¹² have exploited and extended this synthesis by using pyridinium or isoquinolinium salts and α,β -unsaturated ketones as the starting materials. Using this method they have synthesised not only 2-pyridones but also substituted pyridines, azafluoranthenes, azaphenanthrenes, etc. They found that ammonium acetate in acetic acid was an excellent substitute reagent for the alkali hydroxides, as it removes the need for an amino group in the starting material.



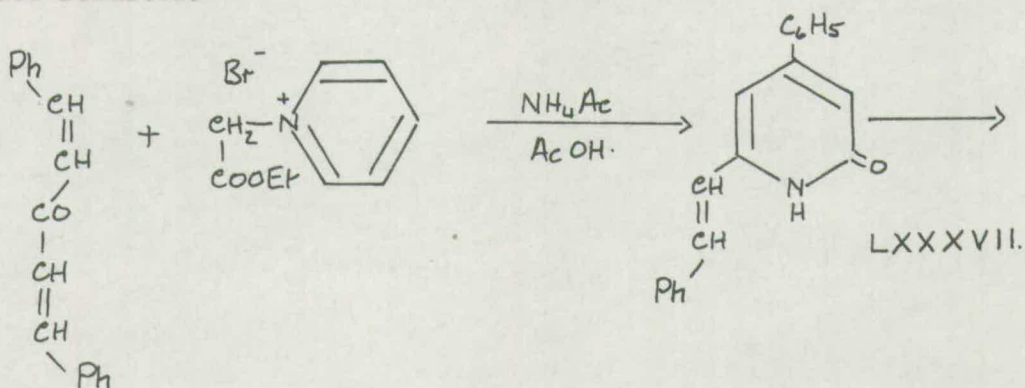
Since pyridinium salts appeared to offer a source of a wide variety of Michael addends possessing reactive methylene groups, a number of attempts were made to prepare compounds which could be used as models for further synthesis.

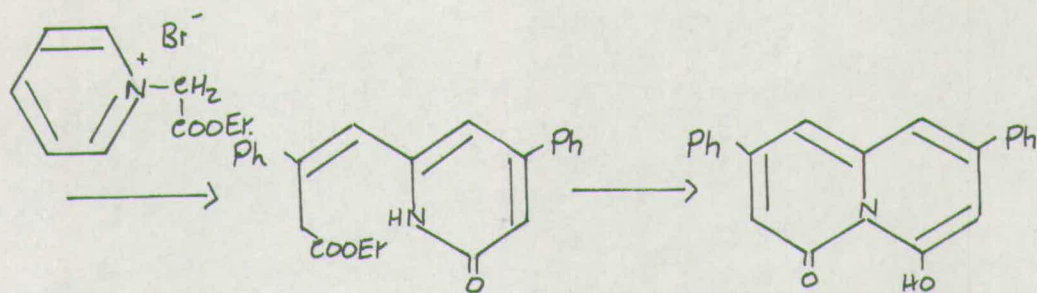
(a) Acetonyl-bis-pyridinium bromide (LXXXVI), first prepared by Kröhnke and Luderitz¹¹³, seemed to offer a particularly promising starting material as it seemed likely to possess two reactive methylene groups. A number of attempts were made to condense this compound with acrylamide, ethyl acrylate, acrylonitrile and ethyl cinnamate, using sodium hydroxide in methanol, ammonia in ethanol and ammonium acetate in acetic acid as catalysts, but no products could be isolated, only deeply coloured solutions being obtained. This was unfortunate as Michael addition might have led to a source of pyridones or pyridines capable of cyclisation to 6-hydroxy or 6-amino-4-quinolizones, e.g.



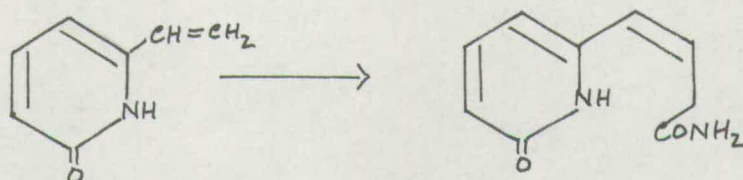
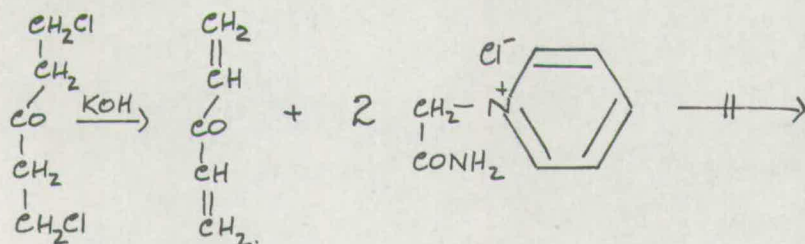


(b) Kröhnke's success in using α,β -unsaturated ketones and pyridinium salts as a means of synthesising pyridones prompted an attempt to extend this method still further. When dibenzylideneacetone and 1-(ethoxycarbonylmethyl)-pyridinium bromide were allowed to react together in presence of acetic acid and ammonium acetate, 6-styryl-4-phenyl-2-pyridone (LXXXVII) was obtained. However, a number of attempts to condense together this compound and a further molecule of the C-betaine, or to condense two molecules of the C-betaine directly with dibenzylideneacetone, were unsuccessful. Had this synthesis been successful, a convenient route to 2,8-diphenyl-6-hydroxy-4-quinolizone might have resulted.



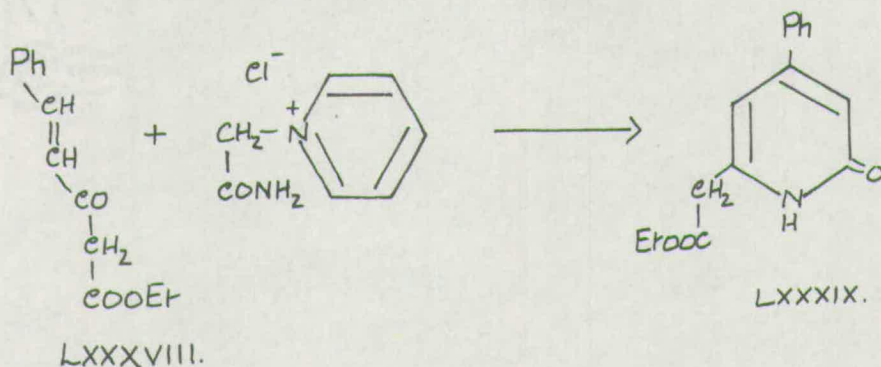


Attempts were made to achieve a similar synthesis of vinyl pyridones using 2,2'-dichlorodiethylketone (divinyl ketone) and 1-(aminocarbonylmethyl)-pyridinium chloride but these attempts completely failed to give any crystalline product. In one case a red oil was obtained in small yield; chromatography failed to purify it or to separate it into components.



(c) Another attempt to utilize pyridinium salts as precursors in pyridine and pyridone syntheses was directed towards the synthesis of 6-ethoxycarbonylmethyl-2-pyridones (LXXXIX) and was based again on Kröhnke's use of α,β -unsaturated ketones and pyridinium salts for Michael-type additions. Reaction of ethyl

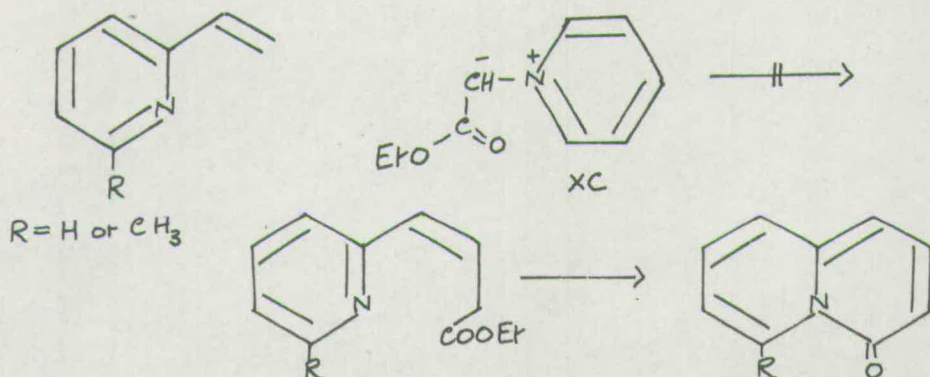
cinnamoylacetate (LXXXV111)¹¹⁵ with 1-(aminocarbonylmethyl)-pyridinium chloride would, it was hoped, lead directly to 6-ethoxycarbonylmethyl-4-phenyl-2-pyridone (LXXXIX).



Sodium hydroxide in ethanol and sodium acetate in acetic acid failed to bring about reaction and attempts to effect Michael addition of cyanacetamide to compound (LXXXV111) were also unsuccessful. No product could be isolated from any of these reactions; in most cases ethyl cinnamoylacetate was recovered.

(d) Notwithstanding the lack of reactivity to further Michael addition shown by the styrylpyridone (LXXXV11), 2-vinylpyridines and their derivatives were subjected to a series of reactions with pyridinium salts. The existing tendency of pyridine to react with nucleophilic reagents at the 2- and 4-positions, due to the electron deficiency induced by the ring nitrogen atom, would be expected to be extended to a double bond conjugated in the 2- or 4-position. This has already been confirmed¹¹⁴ by the addition of ethylsodioacetoacetate, diethyl-

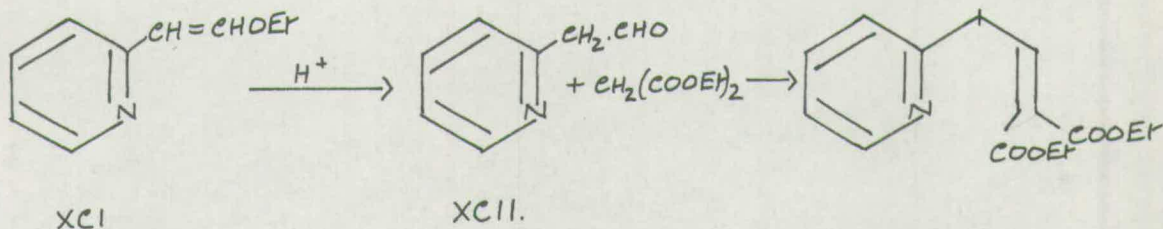
sodiummalonate, etc., to vinyl pyridines to give the α -pyridyl-ethyl-acetoacetate and malonate. If pyridinium salts could be used as the source of the nucleophilic reactant then, since they can be a source of C-betaines of type (XC), addition would result in pyridines with unsaturated side chains which might have cyclised to quinolizones.



2-Vinylpyridine and 6-methyl-2-vinylpyridine were allowed to react with 1-(ethoxycarbonylmethyl)-pyridinium bromide and 1-(bis-ethoxycarbonylmethyl)-pyridinium perchlorate under a variety of conditions but no product could be isolated in reasonable yield. However, 6-methyl-2-vinylpyridine and 1-(ethoxycarbonylmethyl)-pyridinium bromide, when allowed to react together in presence of sodium ethoxide, did yield a very small amount of oily product. This was rejected because examination of the oil in a gas/liquid chromatography unit showed that it contained three components. Since the oil had previously been purified on alumina, it was clearly difficult to separate into its components and the experiment was of no synthetic value.

Although it is not directly connected with the work being described in this particular section, it is convenient to mention here some reactions carried out with 2- β -ethoxyvinylpyridine (XC1).

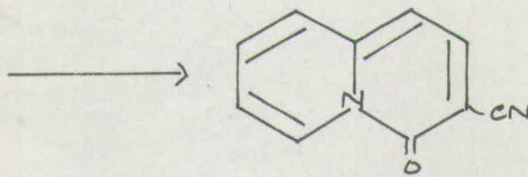
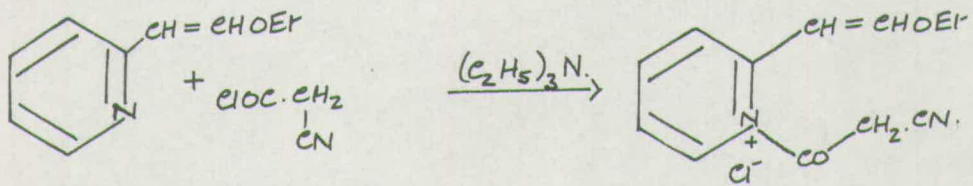
It was hoped, initially, that heating a solution of 2- β -ethoxyvinylpyridine with a little concentrated mineral acid would result in hydrolysis to 2-pyridylacetaldehyde (XC11). If diethylmalonate was present this aldehyde might then react with the diethylmalonate to produce a pyridine derivative (XC111) which could cyclise to a quinolizone.



Several attempts to carry out this reaction, using glacial acetic acid as the solvent and the minimum quantity of mineral acid, yielded only minute quantities of sticky material which could not be purified.

Finally, an attempt to prepare cyclic material by an intramolecular cyclisation of a pyridinium salt was also unsuccessful. 2- β -ethoxyvinylpyridine and cyanacetyl chloride were allowed to react together in presence of triethylamine. It was

hoped that quaternisation of the ring nitrogen and subsequent cyclisation would lead directly to a 4-quinolizone derivative (XCIV) but only a little sticky material was obtained which could not be recrystallised. Purification of the material by chromatography, using neutral alumina, was also unsuccessful.



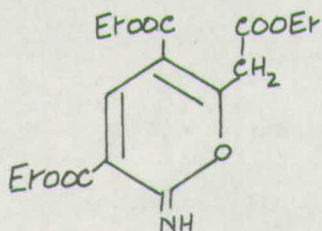
XCIV.

DISCUSSION.

In view of the complex nature of later reactions, it is perhaps not surprising that the experiments based on Ruhemann's work were not successful. The isolation of a resorcinol derivative from the reaction between ethyl phenylpropiolate and diethyl acetonedicarboxylate is perhaps indicative of the tendency towards Dieckmann cyclisation, where possible, rather than lactonisation to give a pyrone. Clearly, the methylene group in the intermediate formed by the initial addition of the two components is very reactive, owing to the presence of the ethoxy-carbonyl group, and undergoes reaction in preference to enolisation of the keto group and subsequent lactonisation. A side reaction appears to be attack of ethoxide ion on the acetylenic component of the mixture, as is shown by the isolation of ethyl β -ethoxycinnamate. Increasing the time of reaction or the severity of the reaction conditions, seems likely to increase the amount of this and other side reactions.

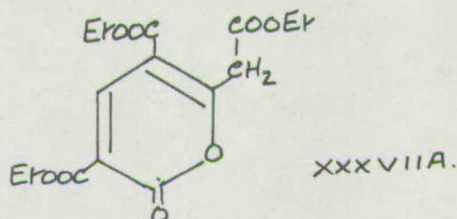
With regard to the experiments using diethyl acetonedicarboxylate and ethoxymethylene compounds, it is interesting to note that neither Errera nor Mitra report complex side reactions. Errera's work was repeated and his report confirmed. Mitra allowed a reaction time of 12 hours whereas the reaction time allowed in this work was only 1 hour. Since the reaction time

was so much shorter, the isolation of the aminopyran and its great ease of conversion into the resorcinol derivative (XL111) is specially interesting. If we consider the intermediate

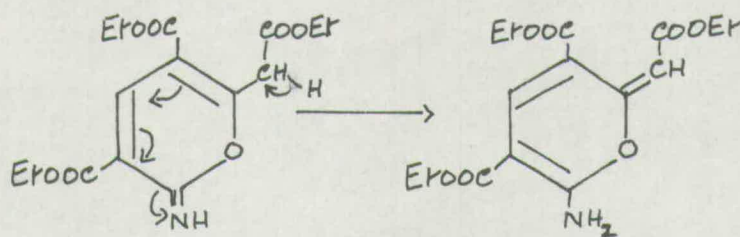


to be formed as a result of the initial condensation and subsequent cyclisation (Scheme 11), then attack of hydroxyl ion and elimination of NH_2^- would have given

rise to the pyrone (XXXV11A). This type of elimination must have occurred when Simonsen obtained compound (XXXIV) by the reaction of ethyl acetoacetate

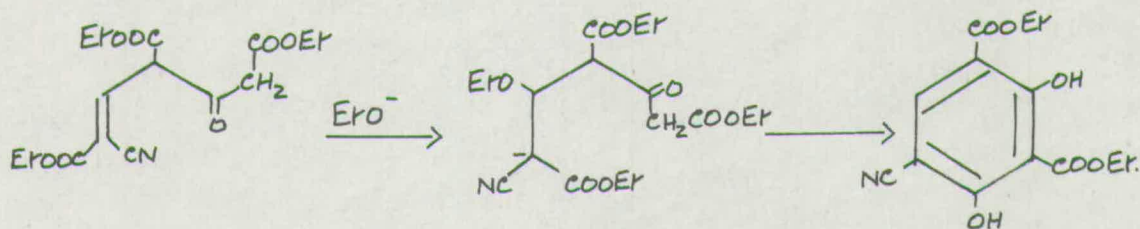


and ethyl ethoxymethylenecyanoacetate. However, the presence of the reactive methylene group at position 7 of the system permits tautomerisation to occur to give the aminopyran



This does not, however, explain the formation of the resorcinol derivative (XL111). To do this, it is postulated that the formation of the pyran from the initial adduct is reversible and that attack of ethoxide ion at the double bond

of the latter gives an intermediate in which free rotation is possible.



The methylene group and the ethoxycarbonyl group may then come into close proximity to each other, again permitting a Dieckmann cyclisation in preference to enolisation and lactonisation.

Cyclisation by intramolecular addition of an enolic hydroxyl group to a cyano group, while unusual, is not unknown. Apart from Simonsen's work with ethyl ethoxymethylenecyanoacetate, a recent synthesis of 2-amino-4,7-dimethyloxepine-3-carboxamide involves a similar cyclisation¹¹⁷.

The poor yield of the aminopyran (XL1) has already been mentioned. The isolation of the red hydrate and of the pyridone (XXXV1), (the latter presumably by partial hydrolysis of a $C \equiv N$ group to $CONH_2$ and subsequent cyclisation and elimination of water) are clear evidence for competing reactions which will consume the intermediates.

A partial hydrolysis of a $C \equiv N$ group to $CONH_2$ and subsequent cyclisation to a pyridone is postulated in Scheme 111 to account for the formation of the 6-hydroxy-4-quinolizone (L). Once again the low yield can be accounted for by the consumption of intermediates by competing reactions or by continued condensation at the methylene group in the 8-side chain, either with more diethyl acetonedicarboxylate or with ethoxymethylenemalononitrile.

An alternative reaction of the initial intermediate (Scheme 111), in presence of two moles of catalyst, permits cyclisation via a cyano group and the active methylene group to give the aminophenol (L1).

The failure of diethyl acetonedioxalate to yield crystalline products with ethoxymethylene derivatives is a little surprising as the methylene groups in this compound should be sufficiently reactive to take part in Michael additions. Since coloured oils were sometimes isolated, it is possible that the reaction is too complex to permit the isolation of a mono-adduct. The failure to isolate crystalline reaction products from the reaction of diethyl acetonedioxalate and cyanoacetamide, ethyl malonamate or malonamide, is also surprising. This may be due to additional reactions consuming the intermediates or the final products, and would again account for the production of coloured oils. Keto-esters of this

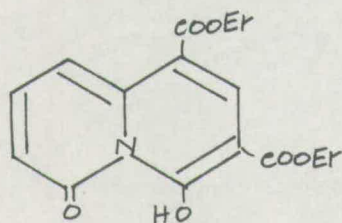
type are known to be very reactive in condensation with compounds such as cyanoacetamide^{93,118,119}.

The unusual features of the infrared spectra of the 3-ethoxycarbonyl-2-pyrones have already been discussed. Before any general conclusions can be drawn from these observations it will be necessary to synthesise a number of model compounds to show whether the effect is general or not.

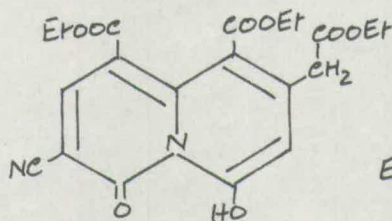
The structure of the salts and complexes of the 6-hydroxy-4-quinolizone (LV1) are of considerable interest. Adams and Reifschneider⁷⁴ had no difficulty in the isolation of 1,3-diethoxycarbonyl-6-hydroxy-4-quinolizone (XXX11), the compound being released in the free state simply on acidification. Not only that, but this compound was formed under very mild reaction conditions, as was compound (L). This is in sharp contrast to the relative difficulty in forming compound (LV1). Similarly, compound (L) is obtainable in the free state with great ease, whereas compound (LV1) cannot be obtained except as a salt or a complex.

However, Adams and Reifschneider did find that lithium was chelated by compound (XXX11) and they were unable to release the free compound again, even by continuous treatment with 6% sulphuric acid. As mentioned in the introduction to this

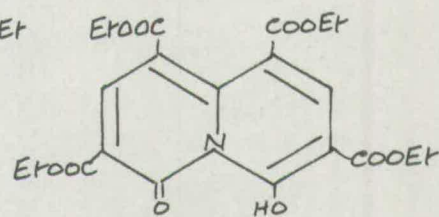
section, they compared this chelation of the lithium ion with a similar effect in compound (XXX111) which was found³⁹ to be capable of chelating the lithium ion. Guter and Hammond suggest that the specificity of compound (XXX111) for the lithium ion is due to the small size of the latter (0.60 \AA°) and have stated that other small ions, e.g., Be^{2+} , Sr^{4+} and Hf^{4+} , are also chelated by this compound. By inference, Adams and Reifschneider appear to consider that 1,3-diethoxycarbonyl-6-hydroxy-4-quinolizone acts in a similar manner, i.e., the chelation of the lithium ion is a direct consequence of the small size of this ion. It has been found that addition of an ethereal solution of compound (L) to an ethereal solution of lithium aluminium hydride does not result in chelation of the lithium ion. This fact, coupled with the isolation of lithium, sodium and potassium chelates of compound (LVI), suggests that the property of this type of compound to chelate ions of Group 1 is not a consequence of the mechanical size of the ions (the potassium ion (1.33 \AA°) is twice the diameter of the lithium ion (0.60 \AA°), and the sodium ion is 0.95 \AA° in diameter) but is closely related to the structure of any given compound.



XXX111.



L



LVI.

All three of these compounds possess electron withdrawing groups ortho or para to the C=O and C-OH groupings. An explanation in terms of the relative amount of electron withdrawal in each compound would require compound (L) to be intermediate in its chelating ability between compounds (XXXI) and (LV1). This is not the case, as compound (L) does not exhibit any obvious tendency to chelate Group 1 metals at all (we can consider the β -side chain to be essentially neutral, i.e., it will not add or withdraw electrons from the ring system). The effect of size has been ruled out and there is no obvious connection between the substituents in the ring system and the chelating power of the molecule. No explanation can be offered at present for this remarkable difference between the three compounds in their ability to chelate ions of Group 1.

In the case of the quinoline and isoquinoline salts the situation is a little more satisfactory. Compound (LV1) can be considered similar to picric acid in structure, i.e., electron withdrawing groups are situated ortho and para to an hydroxyl group. Weiss¹⁰⁸ has suggested that the formation of picric acid complexes is the result, not of the acidity of the hydroxyl group in picric acid, but of the ease with which picric acid can accept electrons from the aromatic component. This view has been supported by some experimental evidence¹⁰⁹ in which the complexes

have been shown to have a measureable conductivity in solution, i.e., they are essentially ionic in character and can be considered as charge-transfer complexes.

The quinoline and isoquinoline complexes with compound (LV1) can be considered as complexes in which the quinoline or isoquinoline act as electron donors, by virtue of the lone pair of electrons on the nitrogen atom, or of the whole $\bar{\pi}$ -electron orbital, and compound (LV1) acts as the acceptor in which the ethoxycarbonyl groups act as "electron sinks". It is also possible that proton transfer from the 6-hydroxyl group of the compound (LV1) to the quinoline or isoquinoline molecule has taken place. Some experimental support for the idea of a charge-transfer type of complex comes from the fact that the ultraviolet spectra of the isoquinoline complex shows lowering of the $\log_{10} \epsilon$ values with decreasing concentration. This suggests that the complexes are perhaps more dissociated at low concentrations. This difference in the spectra at different concentrations is not shown by the sodium chelate compound.

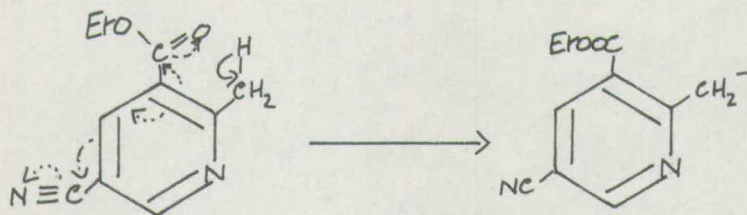
The ease with which the hydroxyquinolizone ring system is opened by concentrated acid, e.g., ethanolic hydrogen chloride, is in keeping with Adams and Reifschneider's experience.

Since Govindachari⁷⁵ has prepared a quinolizoneimine using

ethyl ethoxymethylenecyanoacetate and compound (XXV111), the failure to obtain crystalline material from the reaction of compound (XXXV1) and ethyl ethoxymethylenecyanoacetate may be due to cyclisation occurring via the $C \equiv N$ group and the $COOEt$ group of the cyanoacetate to give a mixture of a quinolizoneimine and a quinolizone. The tar obtained from the reaction was fluorescent.

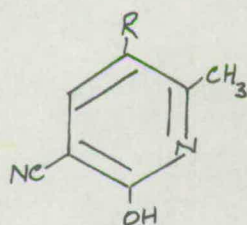
The failure of the reactions between the pyridone (XXXV1) and ethyl propiolate is also surprising. A number of examples are known of Michael addition of acetylenic esters to reactive methylene groups¹²⁰ and it seems strange that not even a simple addition product could be isolated.

Govindachari's success⁷⁵ in using 6-methylpyridines, activated by the presence of electron withdrawing groups ortho and para to the methyl group as Michael addends, was interesting.



The acidity of the methyl group has been greatly increased so

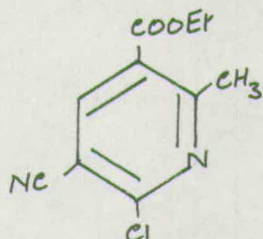
that a proton can be very easily lost to the basic catalyst and the resultant negative ion then behaves as a normal Michael addend. Since the pyridones used as starting materials in the attempts to utilise this reaction differ only in the presence of an hydroxyl group meta to the methyl group (or ortho to the ring nitrogen), it seems surprising, at first, that the reaction was not successful. The hydroxyl group, however, is also influenced by the electron withdrawing groups which are situated in the same relationship to it as to the methyl group.



R = COOEt in LXII
R = CN in LXIII.

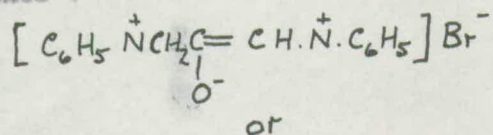
The hydroxyl group exhibits a more powerful electron releasing effect than a methyl group and hence will be activated preferentially, leaving the methyl group relatively unreactive. This would account for the failure to obtain Michael addition to the pyridones (LXII) and (LXIII). The original pyridone (XXXVI) is not affected in this way since the methylene group is much more strongly influenced by the close proximity of the 6-side chain ester carbonyl. The corresponding chloropyridine has been shown to possess a very reactive chlorine atom⁹¹ e.g., it is very easily replaced by hydrogen by reduction with a

palladium/barium carbonate catalyst.

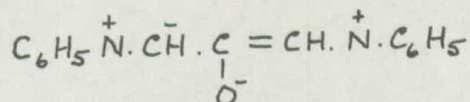


To some extent the experimental difficulties in the large scale preparation of diethyl glutaconate prevented a fuller examination of the reaction of this compound with halopyridines containing activated halogen atoms.

Since acetonyl-bis-pyridinium bromide failed to react with a number of Michael acceptors, including acrylonitrile, it is concluded that treatment of the bromide with alkali does not yield a C-betaine which is sufficiently reactive to undergo Michael addition. This is in keeping with Kröhnke and Luderitz's suggestion¹¹³ that treatment of this compound with alkali yields the betaines :



or



Enolbetaines are generally of much greater stability, and correspondingly lower reactivity, than C-betaines and the failure

of this compound to react with acrylonitrile, in presence of alkali, is a strong indication that C-betaine structures are not of great significance in its resonance forms.

The synthesis of 6-styryl-4-phenyl-2-pyridone was most promising as it was evident that a double bond in dibenzylideneacetone was sufficiently activated by the keto group to react with the C-betaine produced from 1-(ethoxycarbonylmethyl)-pyridinium bromide in a Michael addition. It seems, however, that in the resultant pyridone the styryl double bond is not sufficiently activated to permit further Michael addition.

The failure of the experiments with divinyl ketone may be due to the absence of the stabilising influence of the phenyl groups (c.f. dibenzylideneacetone).

The evident lack of reactivity to Michael addends shown by ethyl cinnamoylacetate (no reaction with cyanoacetamide or 1-(aminocarbonyl)-pyridinium chloride in presence of alkali), suggests that the reactivity of the double bond in this compound is far outweighed by the reactivity of the methylene group.

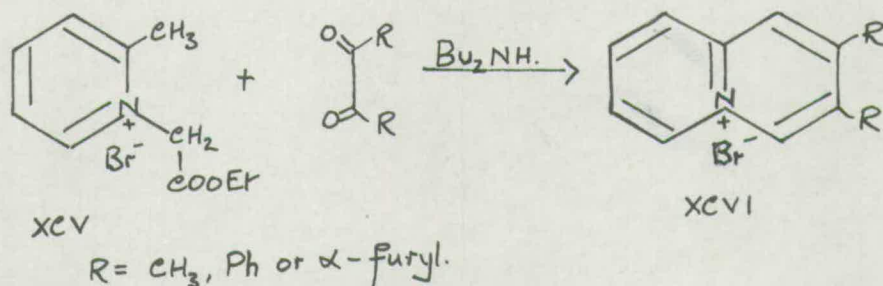
It seems unlikely, judging from the experimental results, that effective use can be made of vinylpyridines as intermediates in the syntheses of quinolizines.

The work in this section, while it has provided an

interesting series of reactions involving diethyl acetonedicarboxylate, ethyl ethoxymethylenecyanoacetate and ethoxymethylenemalononitrile, a synthesis of 6-hydroxy-4-quinolizones from aliphatic starting materials, a new type of chelate and salt-like compounds, and some indication of the difficulties in the syntheses of quinolizones by new routes, has been disappointing since it has not been possible to obtain products which could have been used as starting materials in an attempt to extend Hozoe's azulene synthesis to the synthesis of the cycl [3,3,3] azine system.

C. ATTEMPTS TO PREPARE THE CYCL [3,3,3] AZINE SYSTEM FROM 3-KETO-1,2-DIHYDRO-4H-QUINOLIZINIUM SALTS.

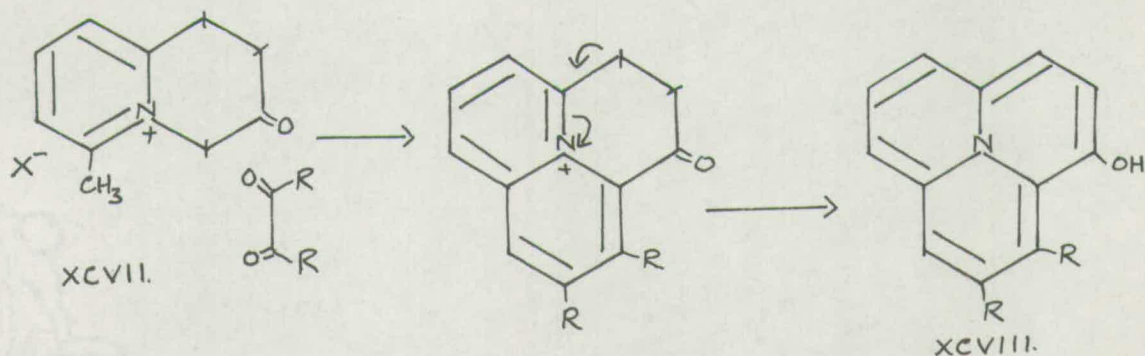
In a recently published paper⁵⁰ a new synthesis of 2,3-disubstituted-dehydroquinolizinium salts was reported. The method is one of remarkable simplicity and proceeds in good yield. Treatment of 2-methyl-pyridine with ethyl bromoacetate gave an 82% yield of N-(ethoxycarbonylmethyl)-2-methylpyridinium bromide (XCV). This compound, on heating in alcoholic solution with a 1,2-diketone, using dibutylamine as catalyst, gave a 2,3-disubstituted-dehydroquinolizinium bromide (XCVI). The corresponding compounds were formed when the N-ethoxycarbonylmethyl bromides of 2-ethylpyridine, 1-methylisoquinoline and quinaldine were treated in a similar manner.



This is the first report of a reaction in which advantage has been taken both of the reactivity of the 2-methyl group in the pyridinium ring and of the reactivity of the N-methylene group

itself, when adjacent to a carbonyl group.

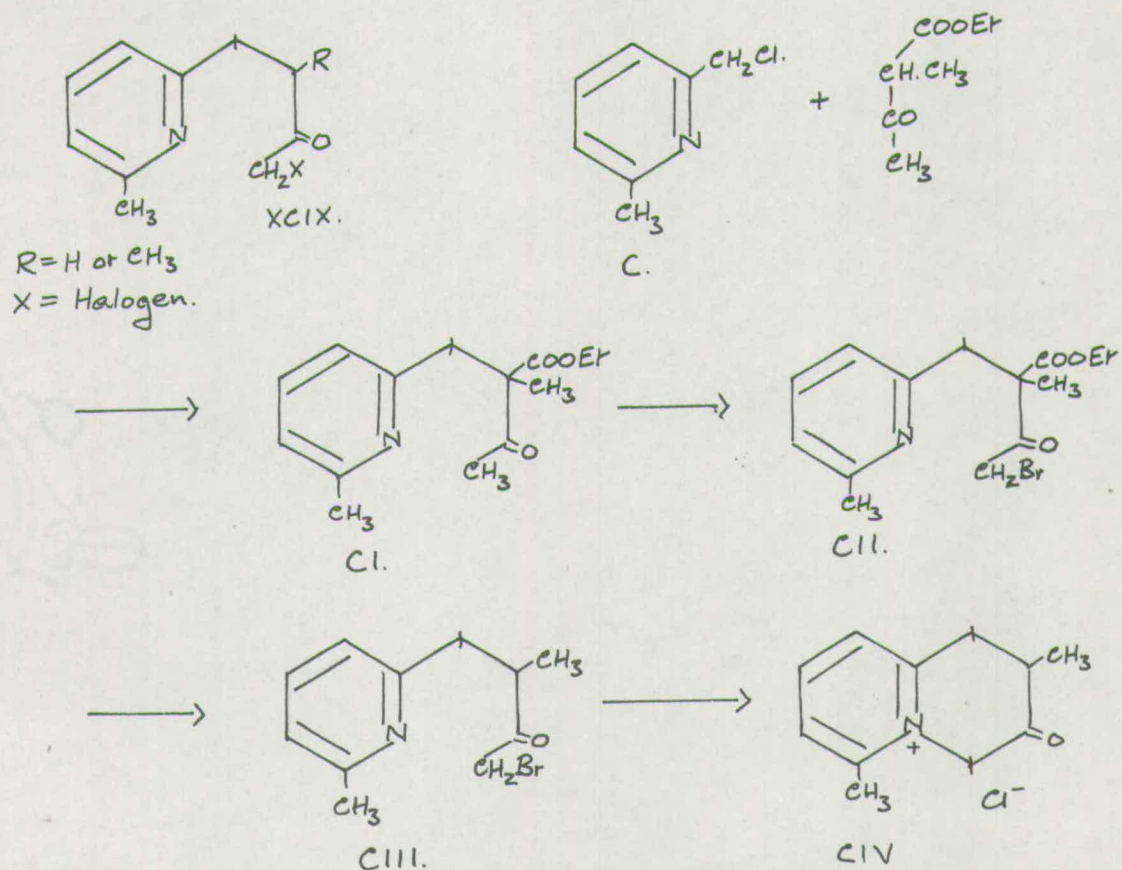
It was hoped to apply this type of reaction to a very direct synthesis of the cycl [3,3,3] azine system. If a suitably activated derivative of the quinolizine ring system could be prepared then an analogous reaction to that of Westphal et alia might be employed to effect the formation of the third ring. A suitable starting material would be compound (XCVII), the 3-keto-6-methyl-1,2-dihydro-4H-quinolizinium ion in which the 6-methyl group would be reactive and the N-methylene group in the 4-position is further activated by the presence of the 3-carbonyl group.



This compound is, therefore, closely analogous in structure to compound (XCV) and reaction with glyoxal, or a similar α -diketone, could reasonably be expected to result in the synthesis of compound (XCVIII) hydroxycycl [3,3,3] azine.

Three approaches to the starting material were attempted. It was necessary to synthesise a compound of structure (XCIX)

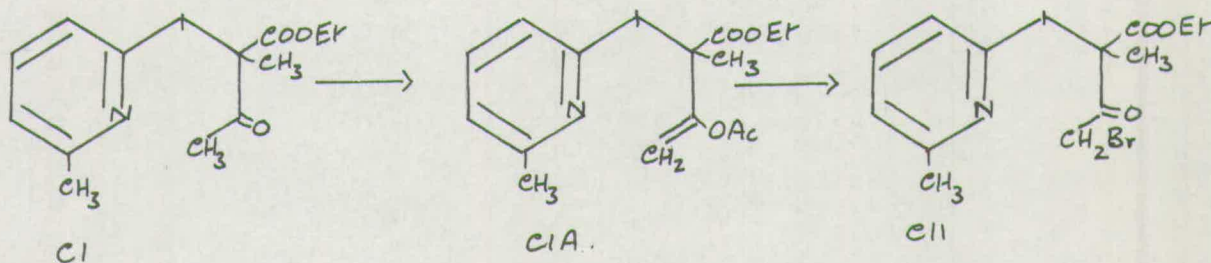
which could then be cyclised by intramolecular quaternisation at the ring nitrogen atom.



(a) The first synthesis attempted was the reaction of ethyl α -methylacetoacetate with 2-chloromethyl-6-methylpyridine (C). It was then hoped to brominate the terminal methyl group of the product (C1), remove the ethoxycarbonyl group and cyclise the bromo derivative (C111) to give the 2-methyl derivative (C1V) of the required compound.

Alternatively, preparation of the enolacetate (CIA) of

compound (C1) and subsequent bromination, using *N*-bromo-acetamide, might have yielded compound (C11) which could then have been converted to compound (C1V), as previously described.

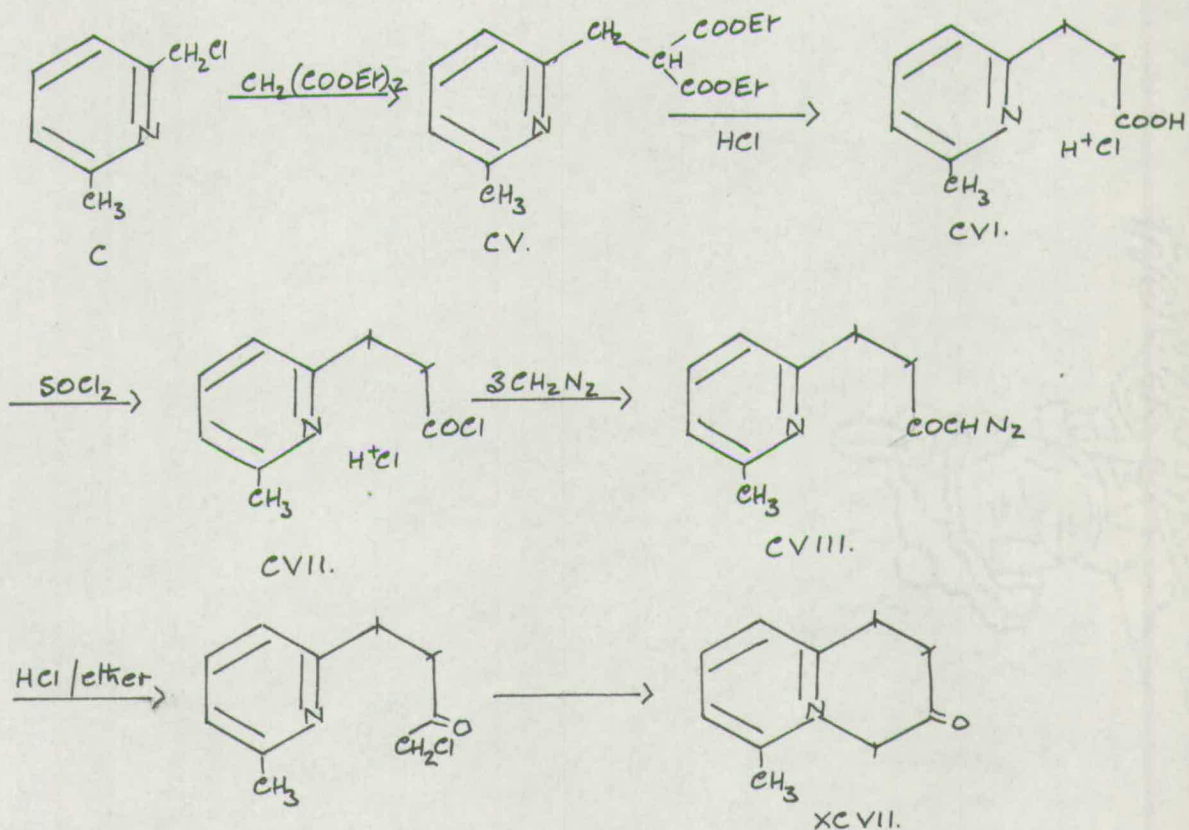


The choice of ethyl 2-methylacetoacetate instead of ethyl acetoacetate was intended to prevent bromination at the 2-carbon atom.

The reaction of 2-chloromethyl-6-methylpyridine and ethyl α -methylacetoacetate yielded oils whose picrates gave unsatisfactory analyses for the desired compound (C1).

(b) The same starting material, 2-chloromethyl-6-methylpyridine was used in the second approach. It was intended to prepare the acid chloride (CV11) by reaction with diethyl malonate and subsequent hydrolysis, decarboxylation and treatment with thionyl chloride. Treatment with diazomethane to give the diazoketone (CV111), reaction of this with hydrogen chloride and

cyclisation of the resulting chloromethylketones, would then have given the desired compound (XCVII).



The reaction of diethylsodicmalonate and 2-chloro-methyl-6-methylpyridine gave a 45% yield of the ester (CV). Hydrolysis of the diester and decarboxylation proceeded in high yield to give 2-(6-methyl-2-pyridyl) propionic acid hydrochloride (CVI). A large number of preliminary experiments indicated that preparation of the acid chloride hydrochloride (CVII) was not straightforward. The acid chloride hydrochloride (CVI) could not be prepared satisfactorily on a large scale and it was found best to perform a

number of small-scale experiments when preparing larger amounts of the compound. The most satisfactory preparation was that using thionyl chloride in the cold and standing overnight at room temperature, but the compound (CV11) was never prepared entirely free of some of the acid (CV1) used as starting material. As a result of this contamination, all the preparations of the diazo-ketone (CV111) contained varying quantities of the methyl ester of the acid which could not be removed. Nevertheless, addition of 1 mole anhydrous ethereal hydrogen chloride to the crude diazo-ketone, dissolved in anhydrous methylene chloride, resulted in a brisk evolution of nitrogen and precipitation of an ether-insoluble sticky, black oil. This was dissolved in methylene chloride, heated under reflux, and reduced to dryness, but no crystalline material could be isolated. Treatment with perchloric acid did not yield solid material either and it was found that the material was quite intractable, despite a number of attempts to induce crystallisation. The infrared spectrum of this compound indicated the presence of a considerable amount of the methyl ester hydrochloride, but there was no definite evidence of the presence of a quinolizinium salt.

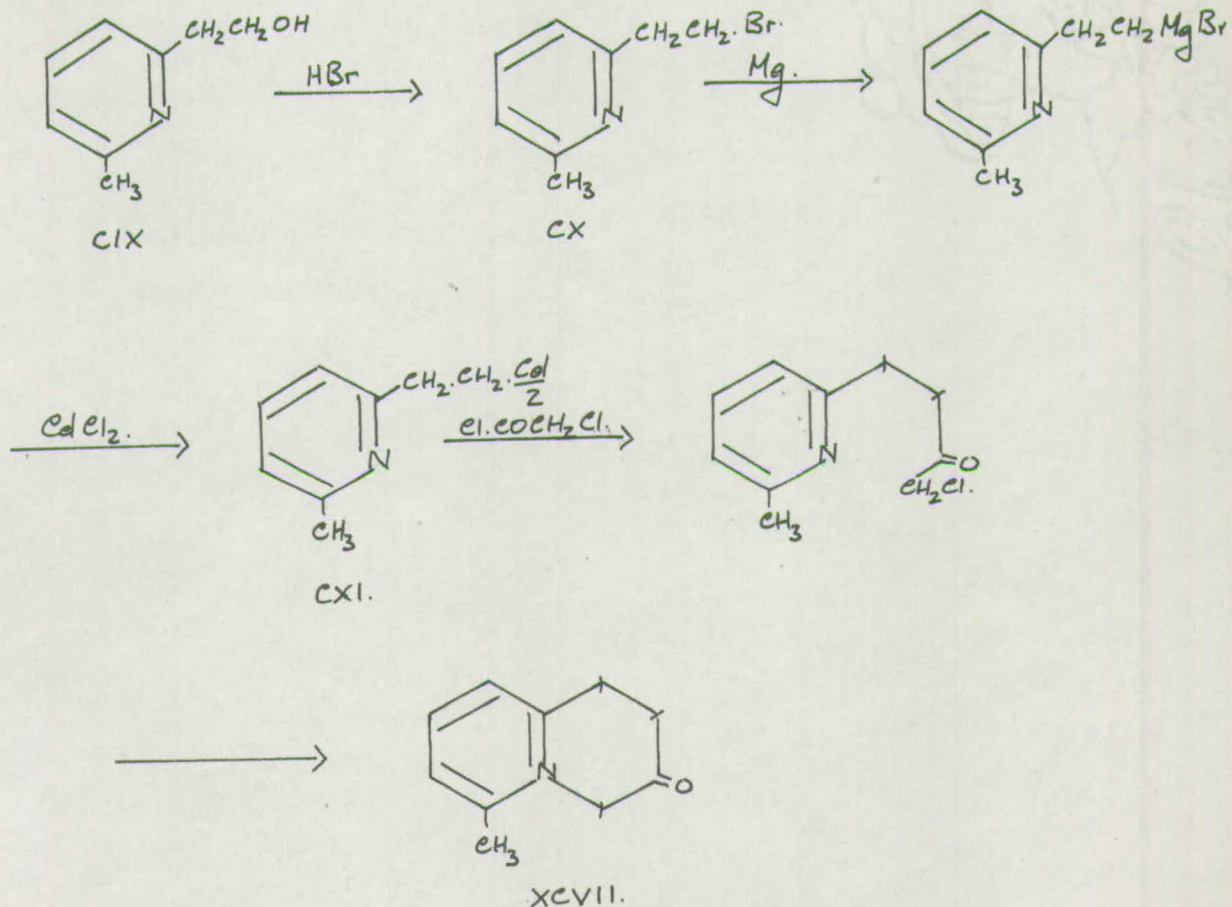
Although the acid chloride hydrochloride could not be analysed as it was extremely deliquescent, the formation of the acid chloride was indicated by infrared spectral examination which showed a strong peak at 1850 cm.^{-1} , indicative of the

presence of the carbonyl grouping in an acid chloride group, $\overset{\text{O}}{\parallel}\text{C}-\text{Cl}$. Similarly, the diazoketone was detected by the peaks at 2120, (81,116) and 1710cm^{-1} , and the methyl ester by a peak at 1740cm^{-1} .

To some extent the non-crystalline nature of the final product may be due to excessive contamination of the cyclic material by the methyl ester hydrochloride, but the failure of the product to form a crystalline perchlorate suggests that it may well contain no cyclic material in any substantial quantity. An attempt was made to separate the material into its components by ion-exchange chromatography but the only material obtained appeared to be purified methyl ester hydrochloride. No other material could be eluted from the column.

(c) The third method was an attempt to make use of the reaction between an organocadmium compound and an acid chloride.¹²¹ 6-Methyl-2-pyridyl ethanol (C1X) was converted to 2-bromoethyl-6-methylpyridine (CX) by refluxing with 48% aqueous hydrobromic acid. The bromo derivative was then converted to the Grignard reagent by the entrainment method¹²³ and treatment with anhydrous cadmium chloride afforded what appeared to be the corresponding cadmium derivative¹²² (CX1). Treatment of this cadmium derivative with chloroacetyl chloride in boiling benzene¹²¹ produced a vigorous reaction but infrared examination of the product, which was a brown mobile oil, indicated the absence of a carbonyl group. Treatment

of the oil with perchloric acid did not yield a product.



Discussion of this section is not possible as it has so far been found difficult to synthesize the starting material (or a simple derivative). The hypothesis which was postulated could not be tested yet it is felt that synthesis of a suitably substituted quinolizinium salt could be achieved after more extensive examination of this problem than has been possible to date.

Fig. 1

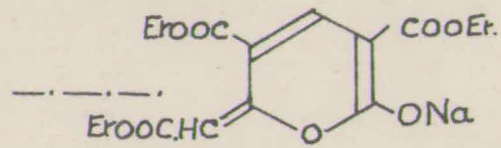
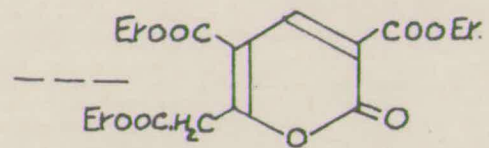
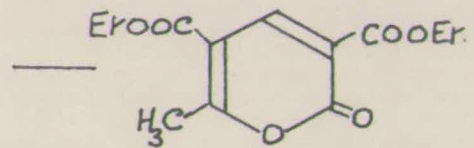
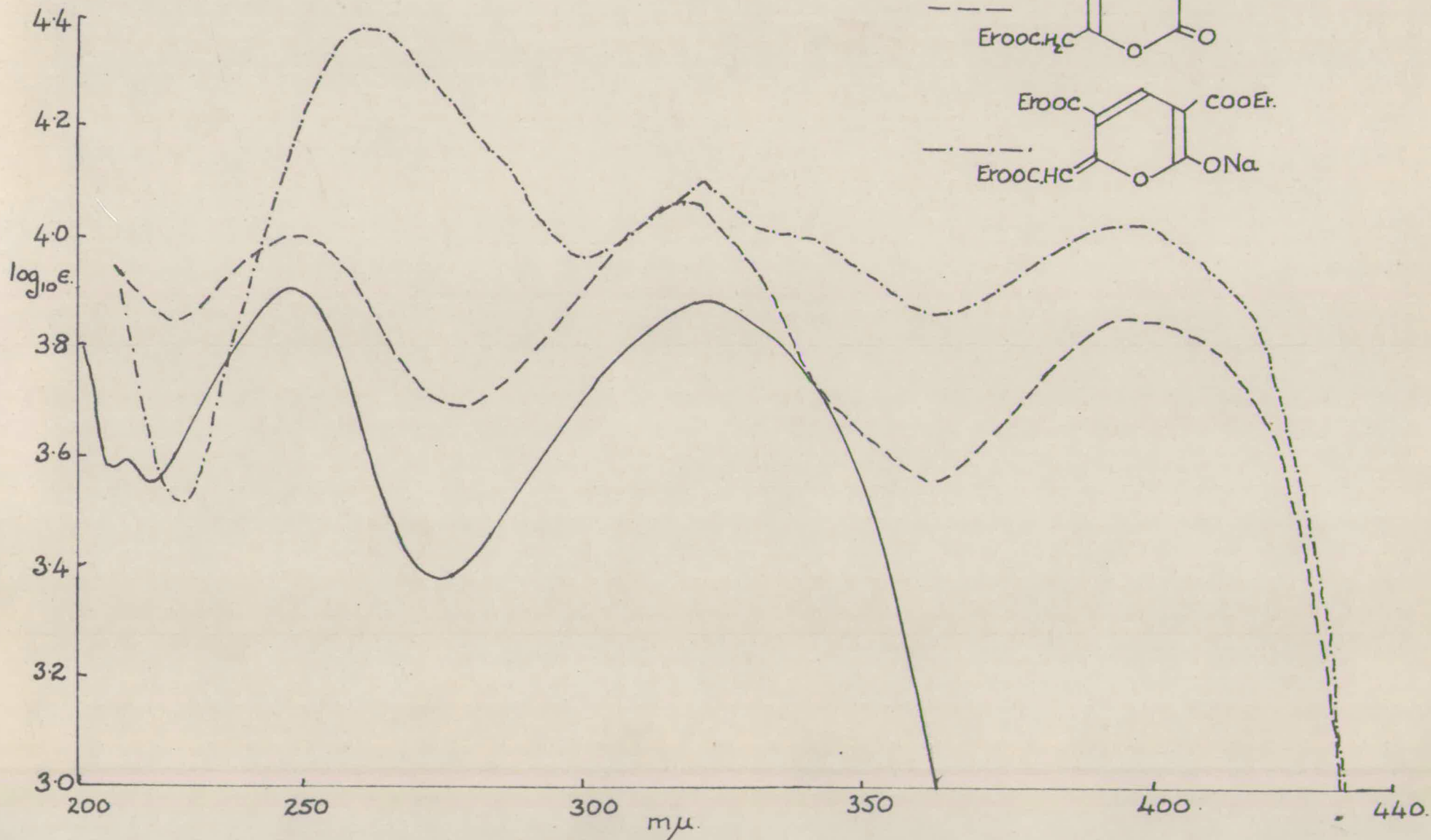


Fig. II

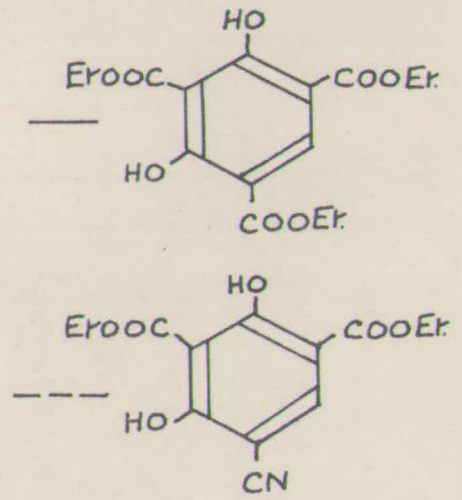
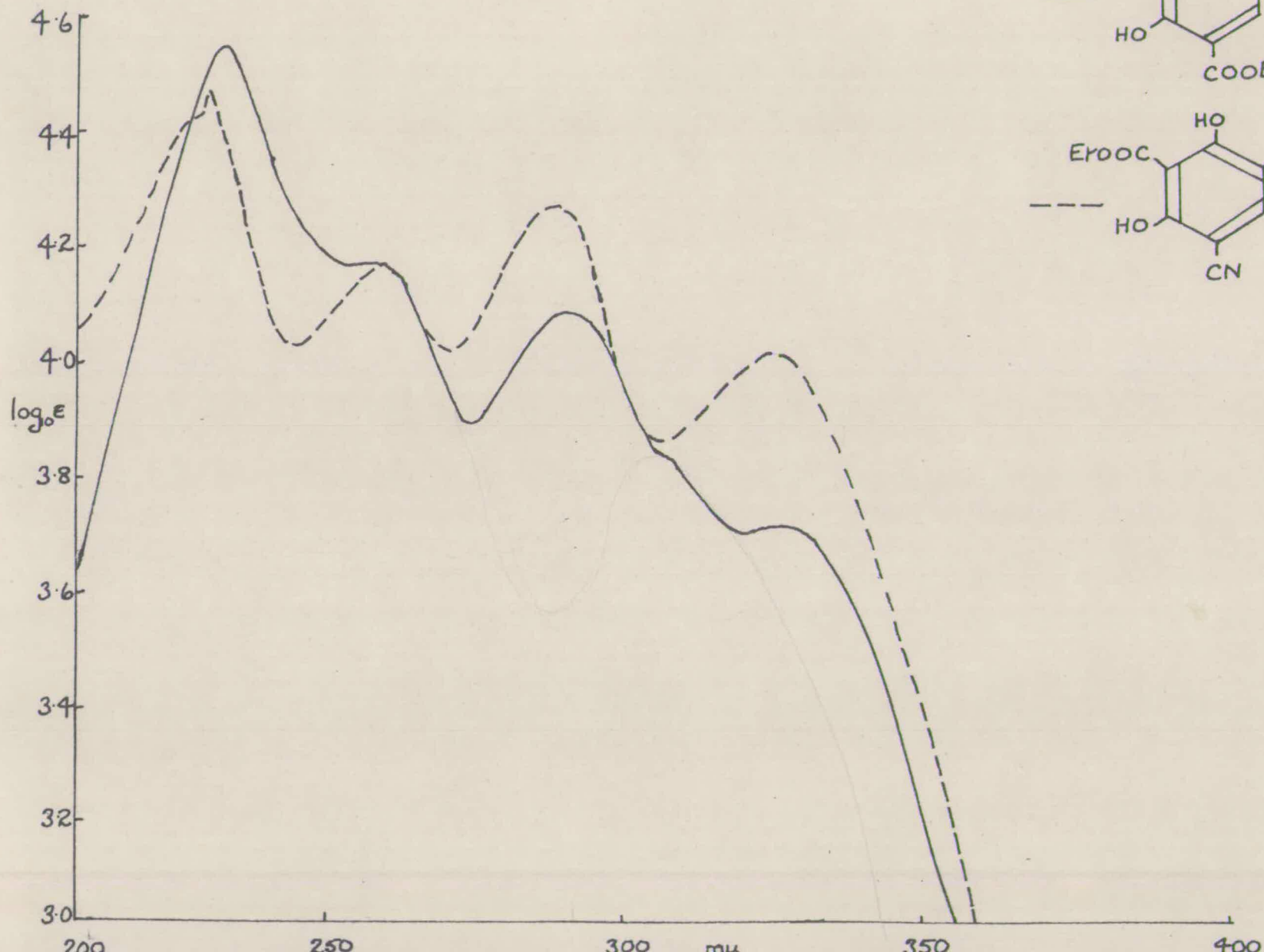


Fig. III

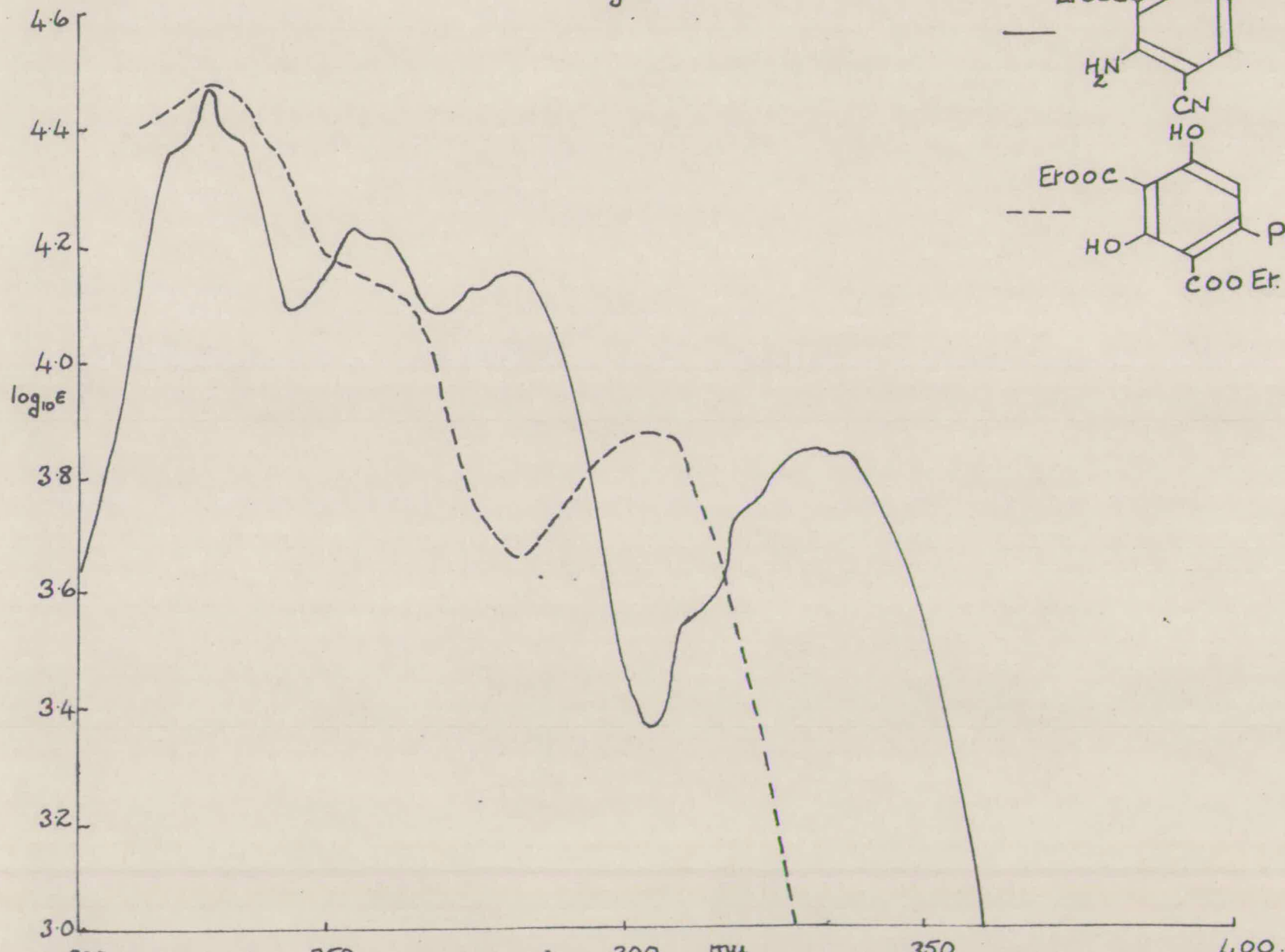


Fig. IV

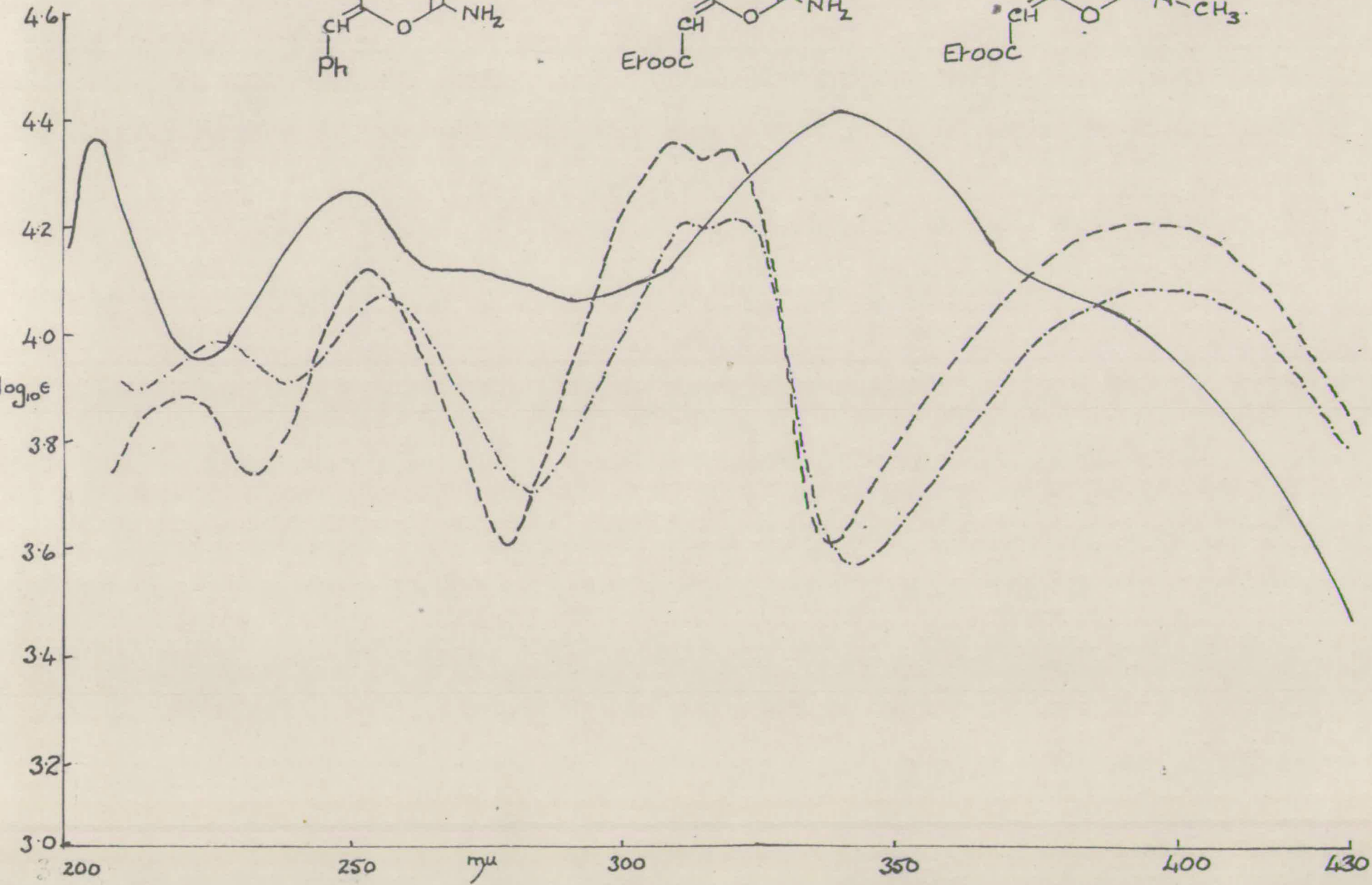
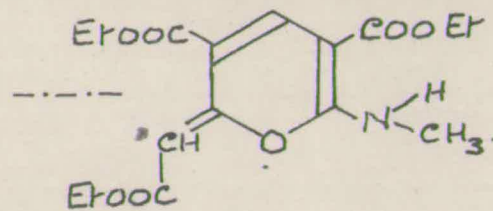
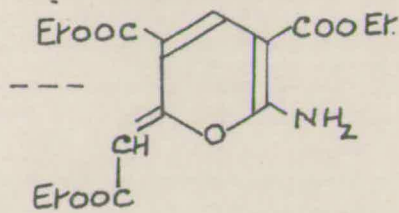
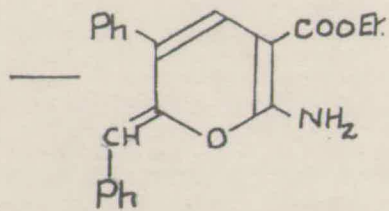


Fig. V

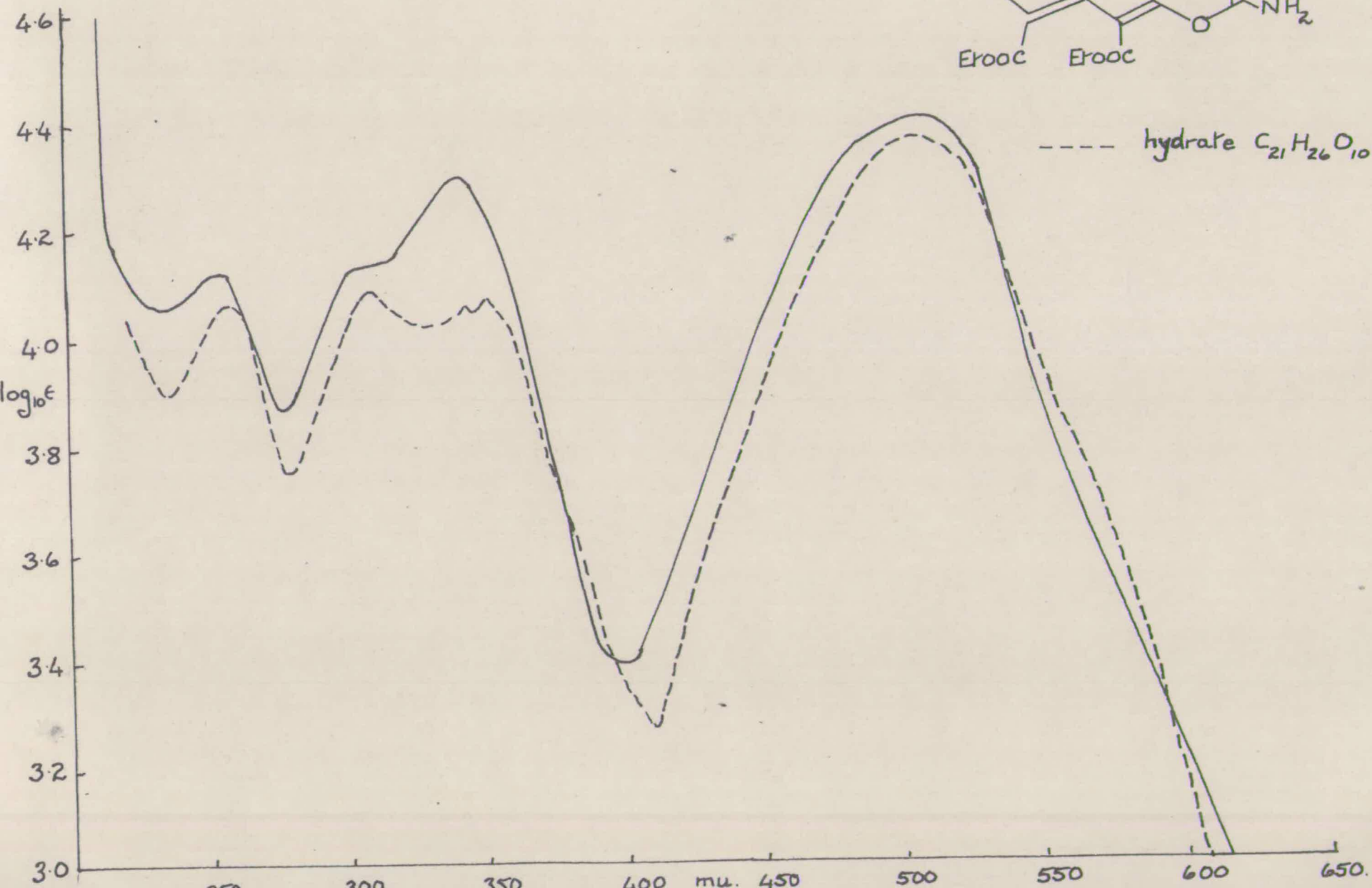


Fig VI

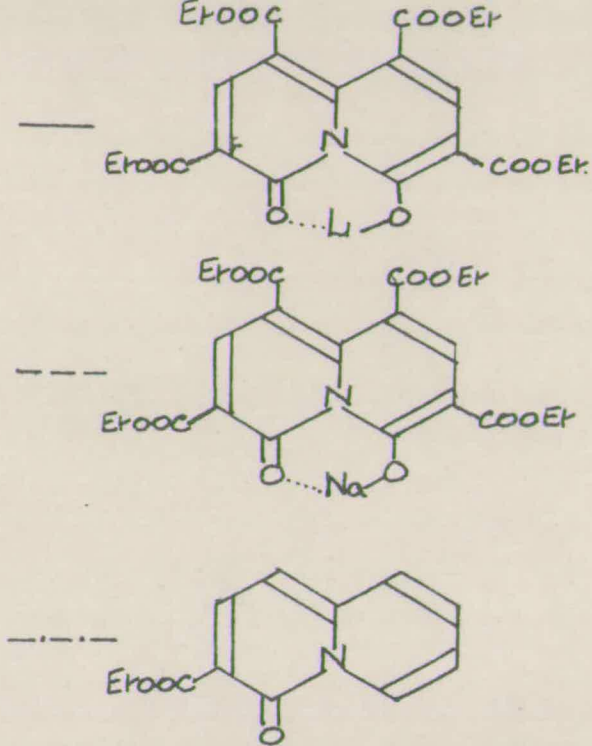
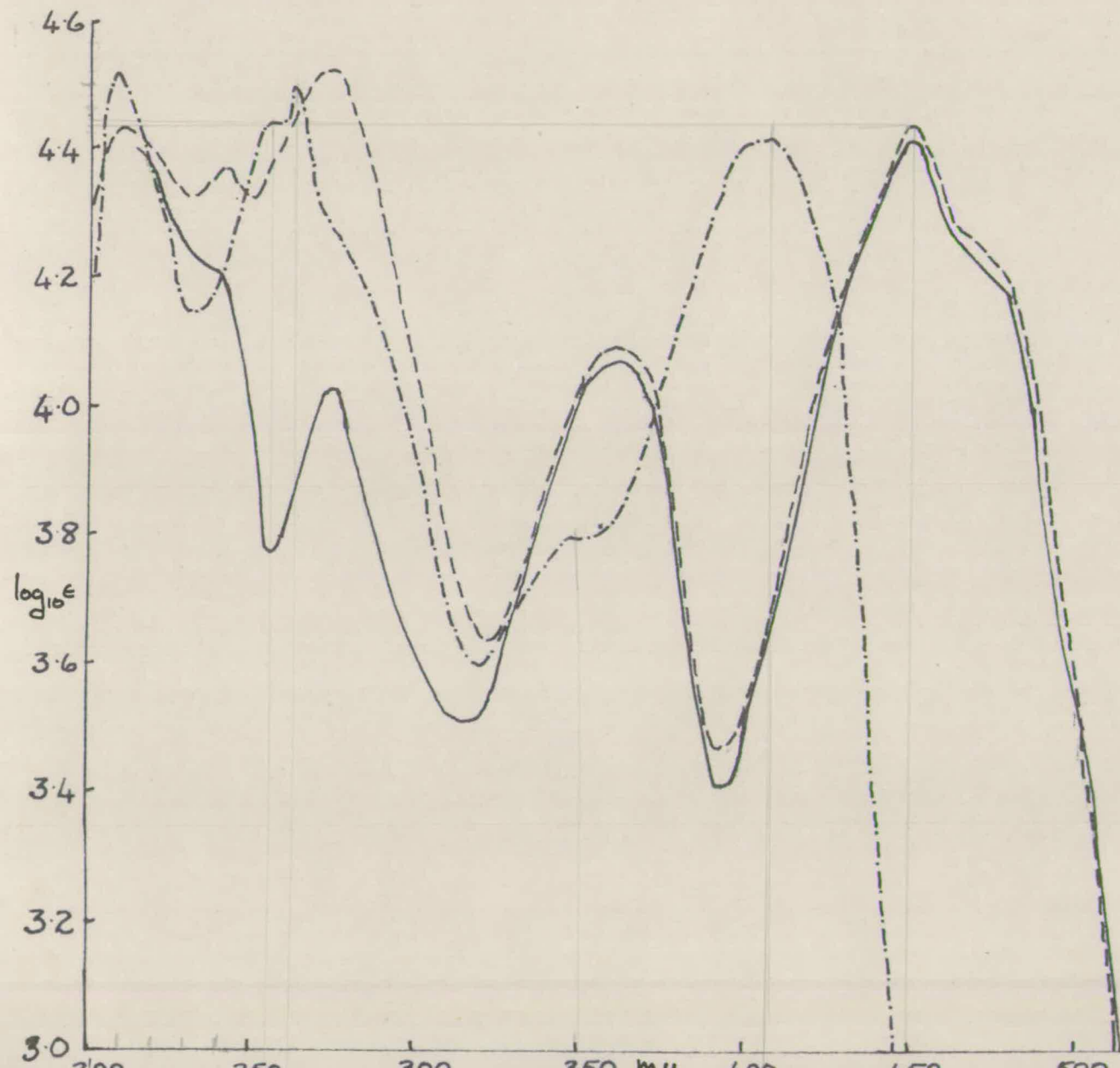
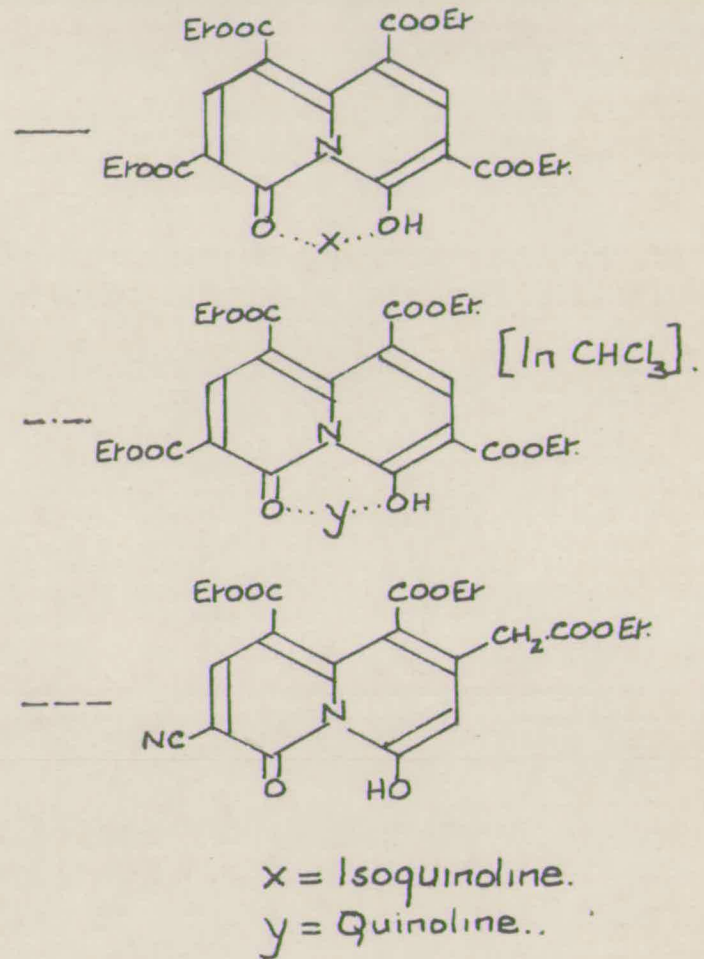
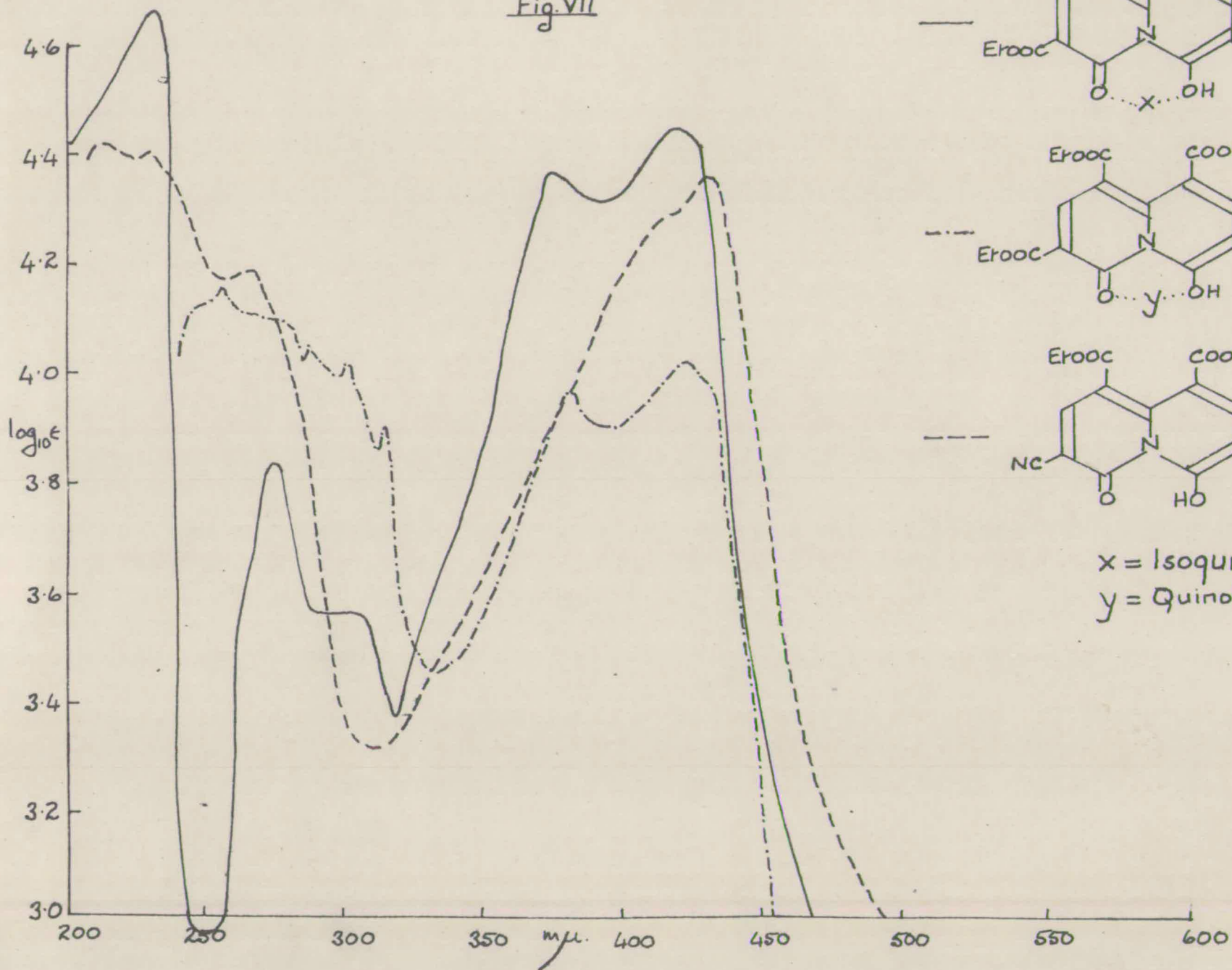


Fig. VII



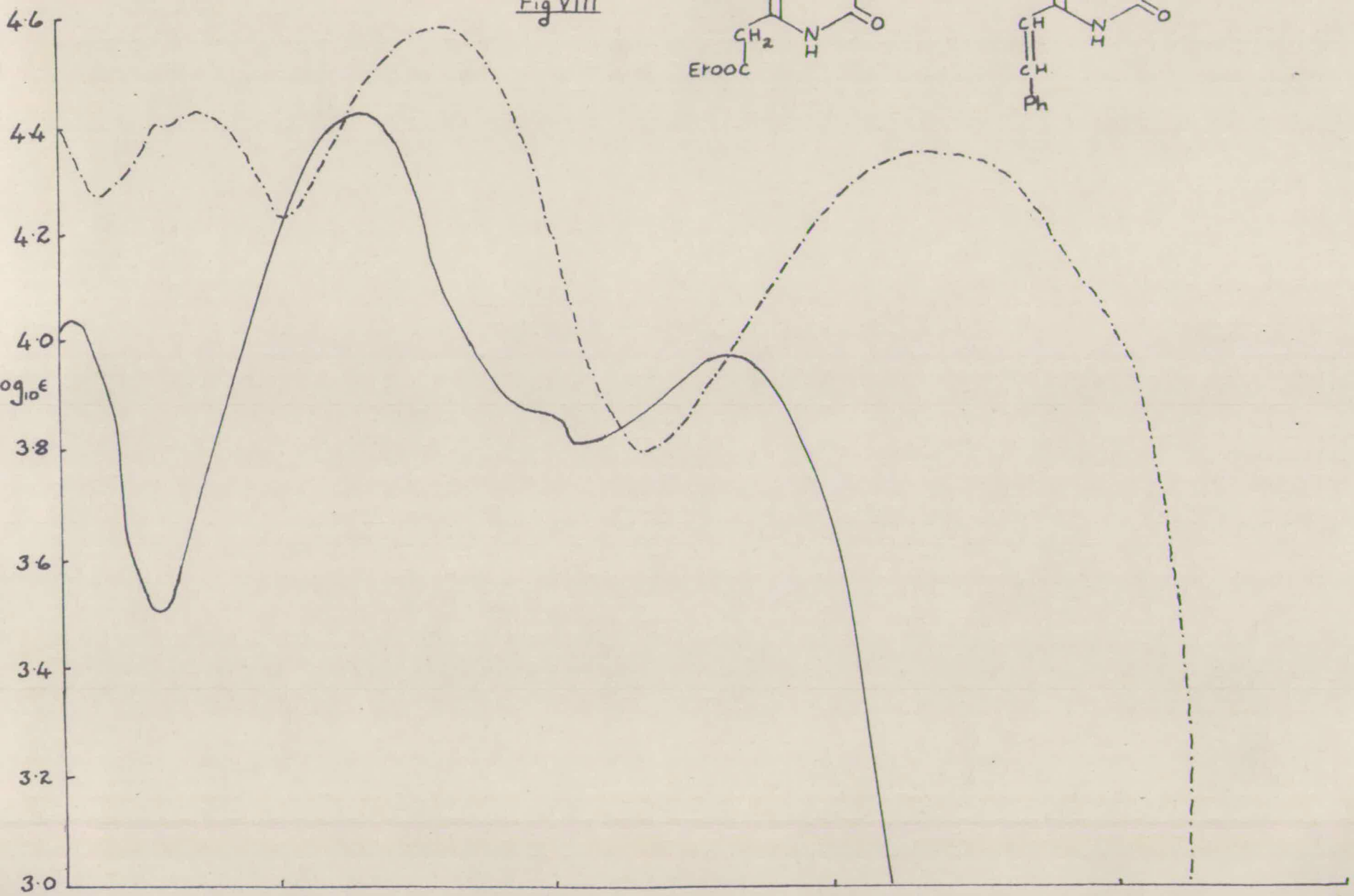


Fig VIII

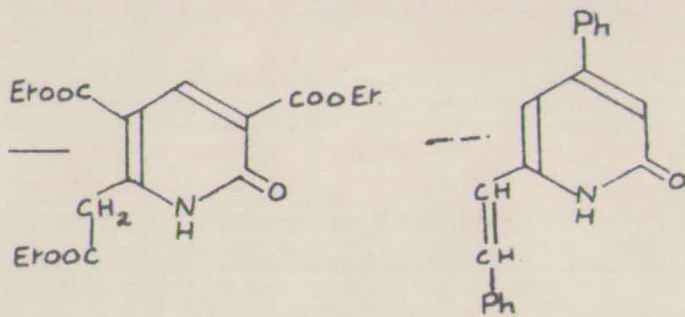
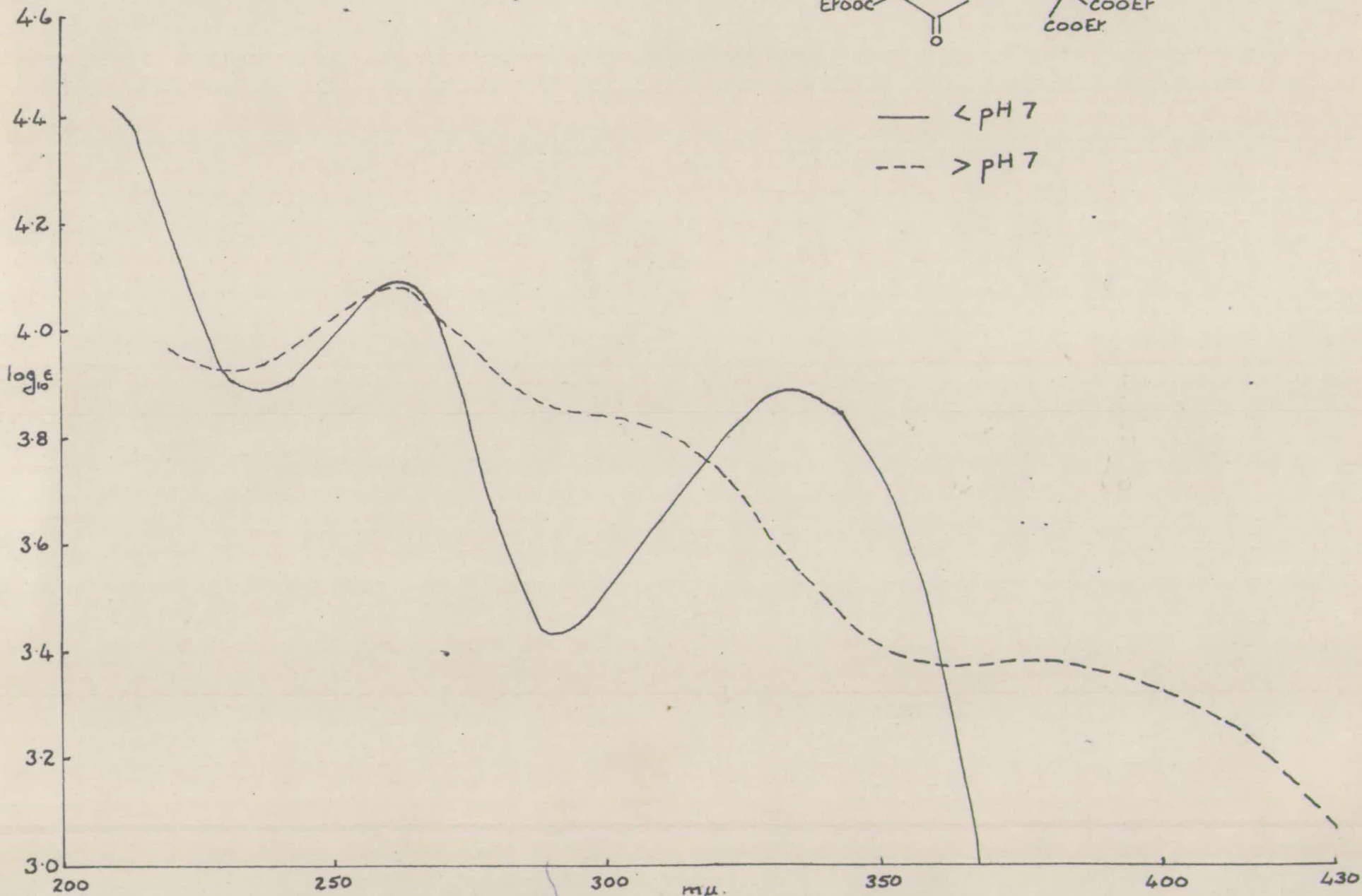
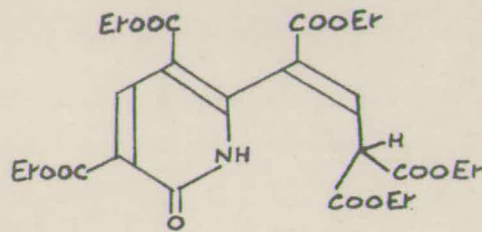


Fig IX



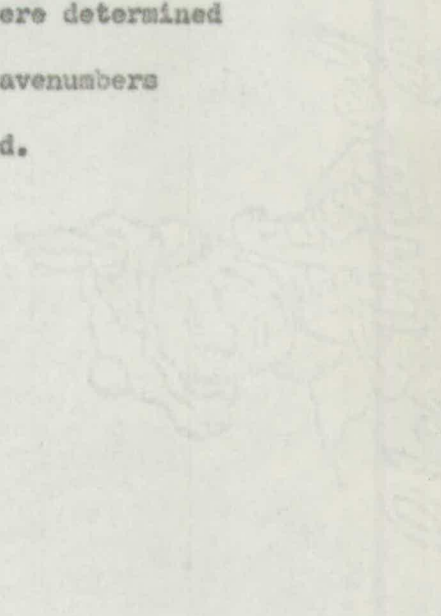
EXPERIMENTAL METHODS AND RESULTS.

Melting-points and boiling-points are uncorrected.

Analyses were carried out by Drs. Weiler and Strauss of Oxford.

Unless otherwise stated, extracts were dried over anhydrous sodium sulphate and ultraviolet spectra were determined in ethanolic solution.

Ultraviolet spectra were determined using a Unicam S.P.500 absorption spectrophotometer, and infrared spectra were determined using a Perkin-Elmer infrared spectrophotometer. Wavenumbers reported are for Nujol mulls, unless otherwise stated.



The preparation of β -ethoxybutyraldehyde.^{124.}

Ethanol (105 g.) containing 0.66 g. hydrogen chloride was mixed with 21 g. crotonaldehyde and the solution heated on a water bath for 14 hours at 50°. After cooling, the solution was neutralised with solid calcium hydroxide and the excess ethanol was removed "invacuo". Distillation of the residue gave 19 g. (33%) of the diethyl acetal as a colourless liquid, b.p. 82-3° at 15 mm. β -Ethoxybutyraldehyde-diethylacetal (19 g.) and 21 ml. 5% aqueous hydrochloric acid were shaken together for 30 minutes. The resultant homogeneous solution was extracted with ether, the extract was dried and the ether was removed by distillation. The residue yielded 7 g. (60% based on the diethyl acetal) of a pale yellow liquid, b.p. 46-48° at 10 mm. $n_D^{20} = 1.4074$ (Lit. $n_D^{20} = 1.4077$).

The reaction of monolithio-2,6-lutidine and β -ethoxybutyraldehyde.^{c.f. 52.}

An ethereal solution of monolithio-2,6-lutidine¹²⁶ was prepared from 0.80 g. lithium, 9.6 g. bromobenzene and 6.5 g. 2,6-lutidine in 50 ml. anhydrous ether. To this stirred solution, keeping the temperature of the mixture at 0°, was added 7 g. β -ethoxybutyraldehyde in 10 minutes. The solution was then stirred for 1 hour at room temperature, ice was added (100 g.), the ethereal layer was separated, and the aqueous phase was extracted with 3x30 ml. ether. The ether extracts were combined, washed, dried and distilled to yield a yellow oil (3 g.; 25%), b.p. 99-101° at 0.05 mm.

A picrate was obtained as yellow needles and recrystallised from ethanol, m.p. 270-1°.

Analysis. Found: C:46.3, H:3.6, N:15.5

Picrate of 4-ethoxy-1-(6-methyl-2-pyridyl)-pentan-2-ol.

$C_{19}H_{24}N_4O_8$ Requires: C:52.1, H:5.51, N:12.8.

Treatment of the foregoing product with 48% hydrobromic acid.

The oil (2.8 g.) was refluxed with 50 ml. 48% hydrobromic acid for 6 hours. After reflux the mixture was concentrated under reduced pressure, neutralised with 10% potassium carbonate solution and extracted with chloroform. The yellow chloroform extract yielded a red oil found to be unchanged starting material. (2.5 g.).

The reaction of monolithio-2,6-lutidine and acetylacetone enol ether.

Acetylacetone enol ether (5 g.) in 10 ml. ether (prepared by method C. ref. 125) was added slowly, with stirring, to 40 ml. ice-cold ethereal solution of monolithio-2,6-lutidine prepared from 0.65 g. lithium, 5.1 ml. bromobenzene and 5.3 g. 2,6-lutidine. After 10 minutes at 0° the mixture was stirred for 1 hour at room temperature, decomposed with 100 g. ice and the ethereal layer was separated. After extracting the aqueous phase with 3 30 ml. ether, the ethereal extracts were combined, washed and dried. On removal of the ether, distillation of the residual oil in a molecular still yielded 4.4 g. (40%) of a pale yellow oil (oil-bath temperature 130-140° and pressure 0.05 mm.). This was presumed to be 4-ethoxy-2-methyl-1-(6-methyl-2-pyridyl)-pent-3-en-2-ol. and was used for the next stage.

Treatment of the foregoing product with boiling ethanolic picric acid.

The oil (4.4 g.) was refluxed with 4.7 g. picric acid in 50 ml. ethanol for 4 hours and the crystalline material which deposited on cooling, was filtered off. Recrystallisation from aqueous ethanol yielded a very small amount of yellow plates, m.p. $208-12^{\circ}$. The ultraviolet spectrum of this compound showed none of the peaks associated with the dehydroquinolizinium nucleus, only a peak at $264 \text{ m}\mu$. being evident. This suggested that dehydration of the uncyclised material had resulted.

Repetition of the experiment under more vigorous conditions produced intractable tars.

The preparation of 1-(6-methyl-2-pyridyl)-pent-3-en-2-ol.¹²⁷

A solution of monolithio-2,6-lutidine was prepared from 400 ml. dry ether, 6.9 g. lithium, 79 g. bromobenzene and 53.5 g. 2,6-lutidine. After immersion of the solution in an ice-salt mixture the nitrogen supply was disconnected and 35 g. crotonaldehyde in 50 ml. dry ether was added during 20 minutes, with thorough stirring. Stirring was continued for a further 15 minutes and 100 ml. water, followed by 100 ml. conc. hydrochloric acid (S.G.1.17), were then added slowly.

The aqueous phase was then separated (ethereal phase rejected) and poured, with stirring, into a mixture of 300 g. sodium carbonate decahydrate and 100 ml. water where a deep yellow oil was precipitated.

The oil was taken up in 300 ml. chloroform and the sodium carbonate was washed with a further 4x200 ml. chloroform. Combination of the chloroform solutions, drying and removal of solvent gave 33.5 g. (38%) of a pale yellow oil, b.p. 92-6° at 0.1 mm.

No picrate or picrolonate could be obtained but an isocyanate was prepared. m.p. 110-11°.

<u>Analysis</u> (oil)	Found:	C:74.6,	H:8.7,	N:7.8.
$C_{11}H_{15}NO$	requires:	C:74.6,	H:8.5,	N:8.0.
(isocyanate)	Found:	C:72.6,	H:6.8,	N:9.5.
$C_{15}H_{20}N_2O_2$	requires:	C:73.0,	H:6.8,	N:9.5.

Attempted cyclisation of 1-(6-methyl-2-pyridyl)-pent-3-en-2-ol using bromine in carbon tetrachloride.^{61.}

1-(6-Methyl-2-pyridyl)-pent-3-en-2-ol- (2.0 g.) was dissolved in 20 ml. carbon tetrachloride and 2.0 g. bromine in 20 ml. of the same solvent was added dropwise, with stirring. As the bromine was added a pale yellow colour developed in the solution and an almost colourless oily precipitate was thrown out. After the addition was complete, the mixture was allowed to stand for 15 minutes, the carbon tetrachloride was decanted and the residue was taken up in the minimum amount of methanol (ca. 10 ml.). No crystallisation could be effected nor was attempted re-precipitation with perchloric acid and ether successful. The solvent was removed under reduced pressure and the oil was set aside but again a crystalline

precipitate was not obtained.

The experiment was repeated with the bromine addition over 30 minutes and subsequent stirring for 30 minutes. An oil was again obtained from which no picrate (using calcium picrate solution) nor perchlorate appeared to be formed. Hydrogen bromide gas was released on the addition of perchloric acid. 2N Sodium hydroxide, in excess, was added to destroy any molecular complex formed with bromine, and to release the original alcohol, but only a black, sticky tar was obtained. Extraction of this tar with chloroform (in which the original precipitate was insoluble) gave an almost black extract which, on washing with 2N hydrochloric acid, drying and removal of the solvent, yielded some dark blue glassy material which was rejected.

The original oily precipitate was soluble in most polar solvents, (e.g., methanol, ethanol, etc.) but could not be crystallised from them.

The reaction of the sodium salt of α -picoline with benzylideneacetophenone.

α -Picoline (2.5 g.) was stirred while 1.25 g. finely powdered sodamide¹²⁸ were added. Benzylideneacetophenone (6.5 g.) in 5 g. α -picoline (200% xs.) were then slowly added to the ice-cold mixture (xs. α -picoline ensures the formation of sodio-picoline). The contents of the flask were then allowed to attain room

temperature, over a period of 5 hours, and a dark brown, sticky, oil was precipitated during this time. Addition of water precipitated a colourless solid and caused complete solidification of the oil. The solid material was filtered off and recrystallised from ethanol to give fine white needles (2.7 g.) m.p. 247-9°. The recrystallisation was performed using a Soxhlet extractor.

<u>Analysis</u>	Found:	C:84.3,	H:6.0,	N:0.5.
$C_{21}H_{19}NO$	requires:(mono adduct)	C:83.7,	H:6.4,	N:4.7.
$C_{36}H_{31}NO_2$	" (dimer)	C:84.8,	H:6.1,	N:2.8.
$C_{51}H_{43}NO_3$	" (trimer)	C:85.33,	H:6.0,	N:2.0.

Treatment of the previous product with acetic acid and hydrogen peroxide.

The previous product, (1.0 g.) m.p. 247-9°, was treated with 8 ml. glacial acetic acid and 0.5 ml. 30% hydrogen peroxide for 18 hours at 70°. The resulting thick suspension was filtered, the mother liquor was reduced in volume, and the precipitate obtained was combined with the original precipitate. Both were found to consist of starting material. Repetition of the experiment, using more hydrogen peroxide or acetone as solvent, or refluxing the reaction mixture, yielded only starting material.

The reaction of 2-picoline-N-oxide and benzylideneacetophenone.¹²⁹

Benzylideneacetophenone (10.4 g.), 2-picoline-N-oxide (5.5 g.) and 25 ml. 5% potassium methoxide were refluxed together for 2.5 hours. The inky-blue solution was then allowed to stand for 16 hours at room temperature and the potassium methoxide was decomposed

with solid carbon dioxide. A colourless solid was obtained (3.7 g.) which was recrystallised from ethanol in a Soxhlet apparatus, to give fine white needles, m.p. 295-6°.

Analysis

Found: C:86.0, H:6.0, N:3.5, M:(Rast) 440.

$C_{21}H_{19}NO_2$ requires:(mono-adduct) C:79.4, H:6.1, N:4.4, M: 317.

Treatment of this compound with acetic anhydride on a boiling water-bath yielded only unreacted starting material. Addition of a little conc. sulphuric acid^{65(a)} to the reaction mixture yielded unworkable tars.

The preparation of 4-morpholino-2-butanone methiodide.¹³⁰

Analar acetone (30 ml.), morpholine hydrochloride (25 g.), paraformaldehyde (8.4 g.) and 5 ml. ethanol were refluxed together for 6 hours. On cooling, 40 ml. dry ether were added to the reaction mixture but, since crystallisation was not complete, 100 ml. 4N sodium hydroxide were added and the solution was saturated with solid potassium chloride, and extracted with ether. After drying, the ether extract yielded 21 g. (54%) crude product. Distillation of this oil yielded a little unchanged morpholine and 8 g. of a colourless liquid, b.p. 106-8° at 10 mm.

The liquid (8 g.) was slowly mixed with 8 g. methyl iodide to give 12 g. 4-morpholino-2-butanone methiodide.

The reaction of methyl vinyl ketone and 2-picoline-N-oxide.

4-Morpholino-2-butanone methiodide (12 g.), 2-picoline-N-oxide (4.5 g.) and 45 ml. 5% potassium methoxide were refluxed together for 3 hours. The red solution was then treated with excess of solid carbon dioxide to destroy the potassium methoxide, poured into 500 ml. water and extracted with ether. Removal of the dry ether yielded a reddish-brown oil which was purified by distillation in a molecular still (bath temperature 120° , pressure 0.5 mm.), to give 300 mg. product which solidified on cooling. The yield was too low to be of any synthetical value.

The synthesis of 1-(2¹-pyridyl)-4-pentanone.

Ethyl- β -(2¹-pyridyl)-ethylacetoacetate (12 g.) (prepared by the method of Doering and Weil¹³¹) were treated with 60 ml. of boiling 20% hydrochloric acid, for 4 hours, brought to pH 10 with sodium hydroxide and the solution was concentrated "in vacuo" until two phases appeared. Extraction with ether yielded 7.0 g. (84%) 1-(2¹-pyridyl)-4-pentanone as a fluorescent yellow oil. A picrate was obtained, m.p. $109-11^{\circ}$. (Lit.¹³¹ m.p. $110-11.5^{\circ}$).

Attempted preparation of 1-(2¹-pyridyl)-4-pentanone¹³²-N-oxide.

1-(2¹-pyridyl)-4-pentanone (7.0 g.) was dissolved in 27 ml. glacial acetic acid and 1.5 ml. 30% hydrogen peroxide was added. After heating at 80° , for 6 hours, a further 0.9 ml. 30% hydrogen peroxide were added and the mixture was heated for 12 hours at 80° .

Distillation of the reaction mixture yielded 4 g. starting material and the dark coloured residue was then distilled in a molecular still, to give 1.6 g. (20%) of a yellow liquid (bath temperature $\sim 155^{\circ}$, pressure 0.03 mm.).

A 2,4-dinitrophenylhydrazone was obtained from this oil and was recrystallised from alcohol to give yellow plates, m.p. $192-4^{\circ}$.

Analysis (2,4-dinitrophenylhydrazone).

	Found:	C:51.7,	H:4.8,	N:17.2.
				17.0.
$C_{16}H_{17}N_5O_5$	requires:	C:53.5	H:4.5	N:22.3.

The foregoing product (0.5 g.) was heated on the water-bath for 15 minutes with 2.5 ml. acetic anhydride and 1 drop conc. sulphuric acid. No perchlorate could be isolated from this mixture after treatment with perchlorate acid. Heating a similar mixture at 100° , for 30 minutes, gave an oil which did not yield a perchlorate either. Heating the starting material with acetic anhydride alone also gave an oil which did not yield a perchlorate.

The preparation of β -chlorocrotonaldehyde.⁶³

Phosphorus oxychloride (56.5 ml.) was added slowly to 55 g. ice-cold, mechanically stirred, dimethylformamide during 20 minutes and the mixture was then stirred for 30 minutes at room temperature. This mixture was again cooled on ice and 18.5 ml. acetone was added dropwise, during 20 minutes with continuous stirring. After main-

taining the resultant solution at 35-40° for 30 minutes, the solution was decomposed with 750 g. crushed ice and allowed to attain room temperature. This ice-cold solution was then continuously extracted with 500 ml. ether for 10 hours, after neutralisation with sodium bicarbonate. The ether extract, after drying, yielded 11 g. yellow liquid, b.p. 36-40° at 10 mm., which decomposed slowly at room temperature.

A 2,4-dinitrophenylhydrazone was obtained, m.p. 165-7° (alcohol).

Analysis (2,4-dinitrophenylhydrazone).

Found: C:42.2, H:3.2, N:19.6, Cl:12.3.

$C_{10}H_9ClN_4O_4$ requires: C:42.2, H:3.1, N:19.3, Cl:12.5.

The reaction of β -chlorocrotonaldehyde with α -picolylithium.

To the ice-cold, well stirred, solution of picolylithium obtained from 0.70 g. lithium, 7.85 g. bromobenzene and 4.7 g. α -picoline in 40 ml. dry ether. was added 8 g. freshly prepared β -chlorocrotonaldehyde, keeping the temperature at or below 0°. Stirring was continued for 1 hour at room temperature when ice was added to decompose the lithium salts, and the aqueous phase extracted with ether. Distillation of the dried ether extract yielded 8.9 g. of a liquid smelling very strongly of α -picoline. The α -picoline was removed as far as possible by distillation of

the mixture at 40° and 5 mm. pressure but only sticky picrates, which could not be recrystallised, were obtained from the residue. Distillation of the residue was thought inadvisable owing to the danger of dehydration of the product (if formed).

The reaction of 1-butyne-3-one and α -picoline. ^{41,70,71.}

In a typical experiment 3.2 g. α -picoline were dissolved in 15 ml. ether and to this ice-cold solution 2.3 g. 1-butyne-3-one was added. The mixture was then allowed to attain room temperature slowly. Distillation of the deep red mixture, either immediately or after times up to 3 months at -20°, invariably produced either a violent reaction (after a short reaction time) or an intractable oil (after e.g., 3 months). The use of the sodium salt of 2-picoline produced the same results. A reaction in which the components were mixed at -78°, and maintained at -20° for 3 months, yielded a tar whose infrared spectrum (thin film) showed the presence of a carbonyl group ($\nu_{\text{CO}} = 1700 \text{ cm.}^{-1}$) but no triple bond absorption was evident.

The reaction of diethyl acetonedicarboxylate and ethyl propiolate.

In a typical experiment diethyl acetonedicarboxylate (5.05 g.) and ethyl propiolate (4.9 g.) were added to sodium ethoxide (3.4 g.) in alcohol (20 ml.) at 0°. Some heat was evolved on the addition of the components but no product could be isolated if the mixture was worked up at this stage. Refluxing for 15 hours produced a yellow, cloudy

solution. After cooling, the reaction mixture was acidified with 100 ml. water containing 25 ml. 2N sulphuric acid. Extraction with ether and subsequent removal of the dry solvent yielded a yellow oil (2.0 g.) which, on distillation, was found to be composed of 5 fractions:

Fraction.	b.p.	press.	yield.	colour with FeCl_3	effect of $\text{NH}_3 + \text{heat}$
1.	54°	1.0 mm.	200 mgs.	red	nil
2.	54-58°	1.2 mm.	400 mgs.	pink	oil sep ^{td.}
3.	102-105°	1.0 mm.	400 mgs.	dk. red	dk. orange oil.
4.	143-144°	1.0 mm.	600 mgs.	red	orange oil.
5.	164°	1.0 mm.	100 mgs.	yellow	orange oil.

No crystalline products could be obtained from this experiment, nor from subsequent experiments, using alcoholic ammonia as catalyst.

The reaction of diethyl acetonedicarboxylate and propiolamide.

Diethyl acetonedicarboxylate (5.05 g.) was added to potassium ethoxide (2.1 g.) in minimum alcohol. After 5 minutes propiolamide¹³³ (1.72 g.) was added to the ice-cold solution. Vigorous reaction took place and the solution turned red. After dilution with 5 ml. ethanol, the solution was refluxed for 30 minutes. On cooling, dilution with 100 ml. water and acidification with dil. hydrochloric acid, the solution was extracted with ether, but no product was isolated from extraction of the mother liquors or from re-extraction of the acidified

sodium carbonate wash liquors.

The reaction of ethyl acetonedicarboxylate and phenylpropiolamide.

Phenylpropiolamide¹³⁴ (4.03 g.) was added to an ice-cold solution of (5.05 g.) diethyl acetonedicarboxylate and sodium ethoxide (1.70 g.) in ethanol (25 ml.) and the solution was then refluxed for 30 minutes on the steam-bath. Cooling, dilution with 100 ml. water and acidification with hydrochloric acid, caused turbidity in the solution but no precipitate was obtained. Extraction with ether yielded a yellow extract which, on washing with sodium carbonate solution, gave a yellow colouration in the aqueous layer. The original extract yielded only unreacted phenylpropiolamide (m.p. 109-10°) (Lit. 109-10°). The sodium carbonate washings, on acidification and re-extraction with ether, yielded 100 mg. of a yellow oil, b.p. 70° (external temperature) at 0.1 mm. This material was not the desired product.

The reaction of diethyl acetonedicarboxylate and ethyl phenylpropiolate.

Diethyl acetonedicarboxylate (10.1 g.) was added to a solution of sodium ethoxide (3.4 g.) in ethanol (50 ml.). After 5 minutes ethyl phenylpropiolate (8.7 g.) was added and the mixture was refluxed for 1 hour. After cooling, and allowing the solution to stand overnight at room temperature, the red solution was reduced in volume by distillation under reduced pressure but no crystallisation set in. Ruhemann's adducts

were insoluble in water and dilution of the solution to 200 ml. with water yielded a yellow oil after acidification with dilute hydrochloric acid. Extraction with ether gave a yellow extract which again gave coloured sodium carbonate washings. The original extract yielded a yellow oil (9 g.) which was distilled in a cup still to give a colourless oil, b.p. 120° at 0.5 mm., $n_D^{16} = 1.5303$. Ethyl β -ethoxycinnamate is a colourless liquid, b.p. $154-5^{\circ}$ at 9 mm. and $n_D^{16} = 1.5336$.

The sodium carbonate washings slowly precipitated a yellow solid. Acidification with dilute hydrochloric acid and re-extraction with ether yielded 250 mg. diethyl 2,4-dihydroxy-6-phenylbenzene-1,3-dicarboxylate (XXXIX), m.p. 157° (ethanol).

$$\nu_{\max} = 1672 \text{ cm.}^{-1} \text{ (C = O).}$$

$$\lambda_{\max} (\log_{10} \epsilon) = 304 (3.87), 260 (4.14 \text{ infl.}), 232 (4.48) \mu.$$

<u>Analysis</u>	Found:	C:65.6,	H:5.6
$C_{18}H_{18}O_6$	requires:	C:65.5,	H:5.5.

The preparation of diethyl 2-amino-6-ethoxycarbonylmethylenepyran - 3,5 dicarboxylate (XL1).

Finely ground ethyl ethoxymethylenecyanoacetate¹³⁵ (3.40 g.) was added, during 10 minutes with continuous stirring, to an ice-cold solution of potassium hydroxide (1.50 g.) in ethanol (10 ml.) containing diethyl acetonedicarboxylate (4.04 g.). The mixture was then stirred for 1 hour at room temperature and poured into water (150 ml.) containing glacial acetic acid (10 ml.) where a red

precipitate was thrown out. Filtration and subsequent drying of the precipitate yielded 1.85 g. (34%) of crude red crystals. Recrystallisation from petrol ether/ethyl acetate (3:2) gave yellow needles, m.p. 158-9°. The use of sodium ethoxide as catalyst gave the same product.

$\nu_{\max} = 3380, 3220 \text{ cm.}^{-1}$ (NH₂ stretch); 1680, 1700, 1725 cm.^{-1} (C = O)
 $\lambda_{\max} (\log_{10} \epsilon) = 393 (4.17), 322 (4.32), 312 (4.34), 255 (4.10)$
and 222 (3.88) μ .

<u>Analysis</u>	Found:	C:55.5,	H:5.5,	N:4.3.
C ₁₅ H ₁₉ NO ₇	requires:	C:55.4,	H:5.9,	N:4.3.

Treatment of the above product with ethanolic chloride.

The above product (1 g.) was added to ethanol (25 ml.) which had been saturated with hydrogen chloride. Decolourisation of the solution occurred almost immediately and a colourless solid precipitated. After refluxing the solution for 30 minutes, ether (50 ml.) was added and the colourless precipitate was filtered off (110 mg.). This precipitate was shown to be ammonium chloride. The ether/ethanol mixture was washed with a little water followed by sodium carbonate solution, which caused the organic layer to turn yellow and precipitate a yellow solid. The yellow solid was filtered off and suspended in dilute hydrochloric acid. Filtration and recrystallisation from petrol ether then gave 800 mg. (80%) of diethyl 6-ethoxycarbonylmethyl-2-pyrone-3,5-dicarboxylate (XL11),

m.p. 61-2°, as colourless needles.

$\nu_{\max} = 1715, 1745, 1748 \text{ and } 1795 \text{ cm.}^{-1} \text{ (C=O).}$

$\lambda_{\max} (\log_{10} \epsilon) = 395 (3.85), 330 (3.95 \text{ infl.}), 318 (4.07), 248 (4.01) \mu.$

sodium salt = 395 (3.85), 335 (4.11 infl.), 320 (4.11), 261 (4.38) μ

Analysis Found: C:55.2, H:5.4.

$C_{15}H_{18}O_8$ requires: C:55.2, H:5.5.

Treatment of diethyl 2-amino-6-ethoxycarbonylmethylenepyran-3,5-dicarboxylate with sodium ethoxide in ethanol.

Sodium (0.5 g.) was dissolved in ethanol (30 ml.) and the aminopyran (1.0 g.) was added to this solution. The yellow colour of the pyran was immediately discharged and a colourless precipitate began to appear. After refluxing the mixture for 1 hour, the precipitate was removed by filtration and suspended in 6% sulphuric acid for 30 minutes. Filtration and recrystallisation from ethanol gave colourless needles, m.p. 138-9° of diethyl 5-cyano-2,4-dihydroxybenzene-1,3-dicarboxylate, (XL111).

$\nu_{\max} = 2220 \text{ cm.}^{-1} \text{ (C}\equiv\text{N)} \text{ and } 1670 \text{ cm.}^{-1} \text{ (C=O).}$

$\lambda_{\max} (\log_{10} \epsilon) = 327 (4.05), 290 (4.26), 260 (4.17), 230 (4.43) \mu.$

Analysis Found: C:55.8, H:4.6, N:5.5.

$C_{13}H_{13}NO_6$ requires: C:55.9, H:4.7, N:5.0.

The preparation of diethyl 6-methyl-2-pyrone-3,5-dicarboxylate (XXXIV).

This compound was prepared by the method of Simonsen⁷⁷ and

had the following physical characteristics.

m.p. 77-9° (Lit. 79.5°).

$\nu_{\text{max}} = 1715, 1745, 1785 \text{ cm.}^{-1} \text{ (C = O).}$

$\lambda_{\text{max}} (\log_{10} \epsilon) = 320 (3.88) \text{ and } 246 (3.91) \mu.$

The preparation of triethyl 2,4-dihydroxybenzene-1,3,5-tricarboxylate⁷⁹ (XXXV11).

This compound was prepared by allowing diethyl acetone-dicarboxylate (4.04 g.) and diethyl ethoxymethylenesalonnate to react together at 0°, in presence of sodium ethoxide (0.45 g. Na.) in ethanol (30 ml.). After stirring the solution for 1 hour, at room temperature, acidification with dil. hydrochloric acid and extraction with ether gave colourless needles (1.3 g.), recrystallised from ethanol, m.p. 106-107°, (Lit.⁷⁹ m.p. 104-5°).

$\nu_{\text{max}} = 1735, 1670 \text{ cm.}^{-1} \text{ (C = O).}$

$\lambda_{\text{max}} (\log_{10} \epsilon) = 236 (3.71), 310 (3.81 \text{ infl.}), 292 (4.08), 258 (4.17), 235 (4.53) \mu.$

The N-methylation of diethyl 2-amino-6-ethoxycarbonylmethylpyran-3,5-dicarboxylate.

The pyran (1.0 g.) was dissolved in dimethylformamide (35 ml.) and sodium ethoxide (0.1 g.) was added to this solution, followed by excess of methyl iodide (1.0 g.). The solution was allowed to stand at room temperature for 40 hours before being poured into a large volume of water and extracted with ether. Removal of the ether,

after drying, gave 150 mg. yellow needles (15%), m.p. $134-5^{\circ}$, tentatively identified as diethyl-2-methylamino-6-ethoxycarbonylmethylenepyran-3,5-dicarboxylate, (XLV).

$\nu_{\max} = 3380 \text{ cm.}^{-1}$ (NH stretch), 1680, 1700, 1745 cm.^{-1} (C = O).

$\lambda_{\max} (\log_{10} \epsilon) = 395 (4.06), 323 (4.20), 258 (4.06) \text{ and } 228 (3.98) \mu.$

<u>Analysis</u>	Found:	C:55.4,	H:6.2,	N:4.1.
$\text{C}_{16}\text{H}_{21}\text{NO}_7$	requires:	C:56.6,	H:6.2,	N:3.8.

The synthesis of ethyl 2-amino-6-benzylidene-5-phenylpyran-3-carboxylate, (XLV1).

Dibenzyl ketone (8.4 g.) was dissolved in ethanol (30 ml.) containing potassium hydroxide (3 g.) and to this ice-cold solution finely ground ethyl ethoxymethylenecyanoacetate (6.8 g.) was added during 10 minutes, while the solution was vigorously stirred. Stirring was continued for 1 hour at room temperature before the mixture was poured on to 150 g. cracked ice and acidified with dil. hydrochloric acid. On acidification a white emulsion formed which deposited a red oil. The aqueous phase was decanted and trituration with a little cold ethanol caused the oil to crystallise. Recrystallisation from an ethanol/benzene mixture (50:50) gave yellow platelets, m.p. $170-2^{\circ}$.

$\nu_{\max} = 3380, 3250 \text{ cm.}^{-1}$ (NH_2 stretch), 1670 cm.^{-1} (C = O).

$\lambda_{\max} (\log_{10} \epsilon) = 395 (4.02 \text{ infl.}), 340 (4.39), 272 (4.11), 252 (4.26) \text{ and } 206 (4.36) \mu.$

<u>Analysis</u>	Found:	C:75.4,	H:5.8,	N:4.5.
$C_{21}H_{19}NO_3$	requires:	C:75.7,	H:5.7,	N:4.2.

The preparation of diethyl 1-cyano-3-(2-amino-3,5-diethoxycarbonyl-6-pyranylidene)propene - 1,3-dicarboxylate, (XIV11).

Ethyl ethoxymethylenecyanoacetate (6.8 g.) was dissolved in the minimum amount of anhydrous ethanol and cooled to 0° . To this solution was added, with stirring, diethyl acetonedicarboxylate (4.04 g.) in anhydrous ethanol (10 ml.) containing sodium ethoxide (1.0 g. Na.), keeping the temperature below 5° . Stirring was continued for 3 hours at room temperature when the red solution had begun to precipitate fine solid material. Ice (100 g.) was added and the solution was acidified with dilute acetic acid (4:1), to give a scarlet precipitate. This was removed by filtration and washed with a little water before drying and recrystallisation from petrol ether/ethyl acetate, to give red/blue needles (2.1 g.), m.p. $157-9^{\circ}$. (Mixed m.p. with the original pyran showed depression.)

$\nu_{\max} = 3400, 3300 \text{ cm.}^{-1}$ (NH_2 stretch), 2220 cm.^{-1} ($\text{C} \equiv \text{N}$), 1720, 1680, 1670 cm.^{-1} ($\text{C} = \text{O}$).

$\lambda_{\max} (\log_{10} \epsilon) = 516 (4.39), 343 (4.29), 308 (4.13) \text{ and } 253 (4.12) \mu.$

<u>Analysis</u>	Found:	C:56.4,	H:5.2,	N:6.7.
$C_{21}H_{24}N_2O_9$	requires:	C:56.4,	H:5.4,	N:6.3.

In a similar preparation but using 3.0 g. potassium hydroxide

in ethanol as catalyst, a little of the above compound was isolated along with another red crystalline compound of such higher m.p. (235-7°).

$\nu_{\text{max}} = 3400, 3300 \text{ cm.}^{-1}$ (NH_2 stretch), 2220 cm.^{-1} ($\text{C}\equiv\text{N}$), 1690, 1670 cm.^{-1} ($\text{C}=\text{O}$).

$\lambda_{\text{max}} = 490, 382, 368, 318, 303, 280$ and $254 \text{ m}\mu$.

<u>Analysis</u>	Found:	C:59.2,	H:5.6,	N:9.5.
$\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_5$	requires:	C:59.2,	H:5.3,	N:9.2.

Treatment of the above compound with ethanolic hydrogen chloride.

The above propene derivative (1.0 g.) was dissolved in 25 ml. anhydrous ethanol which had been saturated with dry hydrogen chloride and the solution was refluxed for 1 hour, cooled, re-saturated with hydrogen chloride and refluxed for a further hour. On cooling 100 ml. ether were added and the precipitate of ammonium chloride was filtered off. The ether/ethanol mixture was washed twice with 10 ml. water and finally with 20 ml. sodium carbonate solution which turned red. The sodium carbonate solution was then acidified and extracted with ether. Removal of the dry ether "in vacuo" gave 150 mg. orange solid, recrystallised from ethanol to give orange needles, m.p. 214-6°. (Compound XLV111).

$\nu_{\text{max}} = 1770, 1750, 1670 \text{ cm.}^{-1}$ ($\text{C}=\text{O}$).

<u>Analysis</u>	Found:	C:53.4,	H:4.9.
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The ether/ethanol mother liquor, when reduced to dryness, yielded

400 mg. of a yellow solid, (compound XL1X), m.p. 199-200°, (ethanol).

$\nu_{\max} = 3380, 3320 \text{ cm.}^{-1}$ (amide NH_2 stretch), 1780, 1750, 1710, 1680 cm.^{-1} (C = O).

$\lambda_{\max} = 415, 329 \text{ and } 263 \text{ m}\mu.$

Analysis Found: C:54.3, H:4.8, N:2.8.

Attempted N-methylation of the propene derivative (XLV11).

The propene derivative (XLV11) (1.0 g.) was dissolved in 200 ml. ether and excess of diazomethane in ether was added to the solution, followed by 10 drops of boron trifluoride in ether. Evolution of nitrogen was observed and the solution was allowed to stand for 60 hours. Removal of the ether and subsequent re-crystallisation of the solid material which remained from petrol/ethyl acetate gave deep red-blue needles (200 mg.), m.p. 160-2°, (mixed m.p. with compounds (XL1) and (XLV11) both showed depression). A similar experiment but using dimethyl formamide as solvent and methyl iodide yielded a small amount of the same compound.

$\nu_{\max} = 3600 \text{ cm.}^{-1}$ (-OH), 3400, 3300 cm.^{-1} (NH_2 stretch), 2220 cm.^{-1} (C \equiv N), 1720, 1680, 1670 cm.^{-1} (C = O).

$\lambda_{\max} (\log_{10} \epsilon) = 510 (4.34), 353 (4.05), 343 (4.04), 310 (4.08) \text{ and } 255 (4.04) \text{ m}\mu.$

Analysis: Found: C:54.0, H:5.8, N:6.0.

$\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}$ requires: C:54.1, H:5.6, N:6.0

This compound was also recovered from the mother liquors of a preparation of the pyran (XL1), along with a little of the pyridone (XXXV1).

The preparation of diethyl 3-cyano-8-ethoxycarbonylmethyl-6-hydroxy-4-guainolizone-1,9-dicarboxylate. (L).

To an ice-cold solution of potassium hydroxide (1.5 g.) and diethyl acetonedicarboxylate (4.04 g.) in ethanol (10 ml.) was added ethoxymethylenemalononitrile¹³⁶ (2.44 g.), keeping the temperature of the solution below 5° and stirring continuously. After stirring for 1 hour at room temperature the orange solution was poured on to 100 g. cracked ice and the solution was acidified with dilute acetic acid. The orange solid which precipitated was filtered off and recrystallised from ethanol to give 500 mg. yellow crystals (needles), m.p. 164-6°.

$\nu_{\text{max}} = 2240 \text{ cm.}^{-1} (\text{C}\equiv\text{N}), 1755, 1740 \text{ cm.}^{-1} (\text{C}=\text{O}).$

$\lambda_{\text{max}} (\log_{10} \epsilon) = 426 (4.23), 352 (3.42 \text{ infl.}), 266 (4.26) \text{ and } 230 (4.33) \mu.$

Analysis: Found: C:58.4, H:4.8, N:6.4.

$\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_8$ requires: C:58.0, H:4.3, N:6.8.

$\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_9$ " 58.6 5.3 5.95

Shaking an ethereal solution (200 mg. in 30 ml.) of this compound with an ethereal solution of lithium aluminium hydride did not produce a lithium chelate.

The synthesis of diethyl 4-amino-5-cyano-2-hydroxybenzene-1,3-dicarboxylate. (L1).

Potassium hydroxide (3 g.) was dissolved in ethanol (20 ml.) and the solution was filtered. Diethyl acetonedicarboxylate (4.04 g.) was added and the solution was then cooled on ice. Keeping the temperature of the reaction mixture below 5°, ethoxymethylene-malonitrile (2.44 g.) was added during 5 minutes while the solution was thoroughly stirred. Stirring was continued for 1 hour at room temperature, ice (100 g.) was then added and the mixture was acidified with dilute acetic acid. The pale orange precipitate which was obtained was filtered off, dried and recrystallised from ethanol, to give colourless needles, (1.3 g.) m.p. 129-30°). (Final recrystallisation from CC1₄).

$\nu_{\max} = 3420, 3350 \text{ cm}^{-1}$ (NH₂ stretch), 2230 cm^{-1} (C≡N), 1700, 1670 cm^{-1} (C=O).

$\lambda_{\max} (\log_{10} \epsilon) = 333 (3.83), 310 (3.55 \text{ infl.}), 282 (4.16), 262 (4.21), 255 (4.23), 238 (4.38 \text{ infl.})$ and $232 (4.46)_{\text{mu}}$

<u>Analysis</u>	Found:	C:56.4,	H:5.5,	N:9.7.
C ₁₃ H ₁₄ N ₂ O ₅	requires:	C:56.1,	H:5.0,	N:10.1.

The attempted use of diethyl acetonedioxalate as the dicarbonyl component in reactions with ethoxymethylene compounds.

In a typical reaction diethyl acetonedioxalate (5.12 g.), suspended in ethanol (35 ml.), was added to a solution of potassium hydroxide (1.6 g.) in ethanol (15 ml.). While this ice-cold

solution was vigorously stirred, ethyl ethoxymethylenecyanoacetate (3.40 g.) was added and the mixture was then stirred for 2 hours at room temperature. Ice (200 g.) was added and the mixture was acidified with dilute hydrochloric acid but no precipitate was obtained and extraction with ether or ethyl acetate yielded only starting material (diethyl acetonedioxalate). Repetition of this experiment with longer reaction times, with heating of the reaction mixture, with different catalysts, e.g., sodium ethoxide, with varying amounts of solvents, or with different ethoxymethylene compounds, invariably produced either starting materials or no characterisable product.

The preparation of diethyl ethoxymethyleneacetonedicarboxylate.

Diethyl acetonedicarboxylate (15 g.), triethyl orthoformate (11.25 g.) and acetic anhydride (15.05 g.) were refluxed together for 40 minutes. The mixture was then distilled at atmospheric pressure until the still-head temperature was 130°, when distillation was continued under reduced pressure with fractionation of the distillate.

Only one significant fraction was obtained, b.p. 166-9° at 0.05 mm. pressure and this appeared to consist of a solid and a liquid. Filtration removed the solid and the colourless liquid appeared to be the desired product, $n_D^{25} = 1.5050$ (3.0 g.)

Analysis Found: C:56.8, H:6.9.
 $C_{12}H_{18}O_6$ requires: C:55.9, H:7.0.

The solid was recrystallised from 40-60° petrol ether to give colourless needles, m.p. 79-80°, which appeared to be diethyl bis-(ethoxymethylene)-acetonedicarboxylate, (1.5 g.).

Analysis Found: C:57.9, H:5.8.
 $C_{15}H_{22}O_7$ requires: C:57.7, H:6.4.

The reaction of diethyl ethoxymethyleneacetonedicarboxylate and cyanoacetamide.

Cyanoacetamide (1.1 g.) suspended in ethanol (10 ml.) containing sodium ethoxide (0.3 g.Na) was added to the ethoxymethylene compound (3.0 g.) with vigorous stirring. Stirring was continued for 30 minutes and the resultant solution was then diluted with water (50 ml.), acidified with hydrochloric acid and extracted with ether. The ether extract was washed with sodium carbonate solution which became dark yellow.

After acidification (hydrochloric acid) of the sodium carbonate extract, extraction with ether yielded only an intractable oil.

Similarly, drying of the original extract and removal of the ether gave only an unworkable sludge.

Repetition of the experiment with longer reaction times produced a similar result.

The preparation of diethyl β -aminoglutaconate.¹³⁷ (LV).

Diethyl acetonedicarboxylate (30 g.) was dissolved in ether (250 ml.) and anhydrous ammonia was passed into this solution until total precipitation of the ammonium salt had occurred. (15 minutes). The suspension was then set aside for 12 hours and the colourless solution was dried and distilled. Material distilled ^{evaporated} between 114-119° at 0.5 mm. pressure was collected (19 g.) and was pure enough for synthetic purposes if used immediately.

Re-distillation of this liquid, through a 6" Vigreux column, gave a colourless product, b.p. 108° at 0.1 mm. $n_D^{25} = 1.4842$. The liquid decomposes slowly at room temperature.

$\nu_{\max} = 3400, 3300 \text{ cm.}^{-1}$ (NH_2 stretch), 1725 cm.^{-1} ($\text{C} = \text{O}$).

<u>Analysis</u>	Found:	C:54.3,	H:7.7,	N:6.5.
$\text{C}_9\text{H}_{15}\text{NO}_4$	requires:	C:53.8,	H:7.4,	N:7.0.

The synthesis of diethyl 6-ethoxycarbonylmethyl-2-pyridone-3,5-dicarboxylate. (XXXVI).

Diethyl β -aminoglutaconate (8.08 g.) was added to sodium ethoxide (1 g.Na) in ethanol (25 ml.). Keeping the temperature below 5° the solution was stirred while diethyl ethoxymethylene-malonate (8.64 g.) was added during 15 minutes. The solution was stirred at room temperature for 30 minutes and poured into water (300 ml.) containing dilute sulphuric acid (25 ml.). A yellow oil was precipitated which crystallised on attempted extraction

with ether. This precipitate was filtered off and the ether extract reduced in volume to give a little more of the same material. The solid material was combined and recrystallised

from ethanol to give colourless needles, (7.0 g.), m.p. 121-2°.

$\nu_{\text{max}} = 3300 \text{ cm.}^{-1}$ (NH stretch), 1580 cm.^{-1} (NH deformⁿ), 1750, 1705, 1660 cm.^{-1} (C = O).

$\lambda_{\text{max}} (\log \epsilon) = 328 (3.98), 300 (3.86), 263 (4.42) \text{ and } 212 (4.04) \mu.$

<u>Analysis</u>	Found:	C:55.7,	H:5.6,	N:3.8.
$\text{C}_{15}\text{H}_{19}\text{NO}_7$	requires:	C:55.4,	H:5.9,	N:4.3.

The hydrolysis of diethyl 6-ethoxycarbonylmethyl-2-pyridone-3,5-dicarboxylate.

The pyridone (1.0 g.) was dissolved in ethanol (5 ml.), added to 2N hydrochloric acid (25 ml.) and the solution was refluxed for 1 hour, cooled and extracted with ether. The dry extract yielded a colourless solid (0.1 g.) which was recrystallised from hot water containing a little ethanol, to give colourless needles, m.p. 303-4°, of 6-methyl-2-pyridone-3,5-dicarboxylic acid. (XXXV). (lit.⁹⁰ m.p. 305°).

$\nu_{\text{max}} = 3300 \text{ cm.}^{-1}$ (NH stretch), 1579 cm.^{-1} (NH deformⁿ), 1740, 1710 cm.^{-1} (C = O).

The higher carbonyl absorption (1740 cm.^{-1}) may be due to a similar effect by the C = O group of the pyridone on the 3-carboxyl group to that shown in the pyrone obtained by treatment of compound (XL1) with ethanolic hydrogen chloride.

The synthesis of the salts and complexes of tetraethyl 6-hydroxy-4-quinolizone-1,3,7,9-tetracarboxylate.

Salts. The pyridone (XXXV1) (8.1 g.) was dissolved in dimethyl formamide (75 ml) and to this solution was added dry, solid sodium ethoxide (1.6 g.) and diethyl ethoxymethylenesalonnate (5.4 g.). The solution was then heated on the steam bath for 6 hours (or refluxed for 4 hours), and poured into water (600 ml.). A bright yellow sticky solid was precipitated and the mixture was extracted with chloroform to give a strongly fluorescent extract which, on removal of the solvent, gave a yellow solid (4.2 g.), recrystallised from ethanol/chloroform to give needles, m.p. 307-8° (LV1).

$\nu_{\max} = 1750, 1715 \text{ cm.}^{-1} \text{ (C = O).}$
 $\lambda_{\max} (\log_{10} \epsilon) = 450 (4.43), 363 (4.09), 274 (4.52), 242 (4.37) \text{ and } 210 (4.44) \mu.$

<u>Analysis</u>	Found:	C:53.6,	H:5.0,	N:3.2,	Res:6.7.
$\text{C}_{21}\text{H}_{22}\text{N}_3\text{O}_{10}\text{Na}$	requires:	C:53.5,	H:4.7,	N:3.0,	Res:6.5.

A similar experiment but using 1.0 g. pyridone, 0.67 g. diethyl ethoxymethylenesalonnate and 0.2 g. lithium ethoxide gave 500 mg. of the corresponding lithium salt (L1K) recrystallised from ethanol/chloroform to give yellow needles, m.p. 318-9°.

$\nu_{\max} = 1750, 1715 \text{ cm.}^{-1} \text{ (C = O)}$
 $\lambda_{\max} (\log_{10} \epsilon) = 450 (4.41), 362 (4.07), 274 (4.03) \text{ and } 238 (4.21) \mu.$

<u>Analysis</u>	Found:	C:53.8,	H:4.7,	N:3.0,	Res: -
$\text{C}_{21}\text{H}_{22}\text{NO}_{10}\text{Li}$	requires:	C:55.3,	H:4.9,	N:3.1,	Res:0.33.

The corresponding potassium salt was obtained using the same quantities of starting material as the lithium experiment but 0.33 g. potassium ethoxide and refluxing the mixture for 8 hours. It could not be recrystallised but was boiled with acetone to purify it, m.p. 320°.

$$\nu_{\text{max}} = 1750, 1715 \text{ cm.}^{-1} \quad (\text{C} = \text{O}).$$

All three of these salts were strongly fluorescent.

Complexes.

The pyridone (XXXV1) (3.25 g.), diethyl ethoxymethylene-malonate (2.16 g.) and isoquinoline (1.19 g.) were heated together at 180-90° for 1.5 hours. Ethanol (0.7 g.) distilled from the mixture (Theoretical max. = 0.9 g.). On cooling, the mixture was poured into 50 ml. water acidified with dilute sulphuric acid where a strongly fluorescent suspension (yellow) was formed. Extraction with chloroform and removal of the solvent gave the isoquinoline complex (LX) as yellow needles, recrystallised from chloroform/acetone, m.p. 215-16° (800 mg.), exhibiting a faint bluish fluorescence in daylight but very strongly fluorescent in ultraviolet light.

$$\nu_{\text{max}} = 1740, 1690, 1660 \text{ cm.}^{-1} \quad (\text{C} = \text{O}).$$

$$\lambda_{\text{max}} (\log_{10} \epsilon) = 418 (4.45), 374 (4.36), 303 (3.56), 274 (3.83) \text{ and } 230 (4.64) \text{ } \mu.$$

<u>Analysis</u>	Found:	C:62.9,	H:4.4,	N:5.4.
$\text{C}_{30}\text{H}_{30}\text{N}_2\text{O}_{10}$	requires:	C:62.3,	H:5.2,	N:5.0.

Similarly, an identical experiment using 1.29 g. quinoline gave 750 mg. yellow needles, recrystallised from a large volume of

chloroform/ethanol, m.p. $270-2^{\circ}$.

$\nu_{\max} = 1740, 1690, 1660 \text{ cm.}^{-1} \text{ (C = O).}$

$\lambda_{\max} (\log_{10} \epsilon) \text{ (chloroform)} = 420 (4.03), 378 (3.96), 314 (3.89), 300 (4.0),$
 $276 (4.09) \text{ and } 254 (4.14) \mu.$

(A small decrease in these $\log. \epsilon$ values was noticed if the spectra were repeated at lower concentrations.)

<u>Analysis</u>	Found:	C:61.1,	H:3.9,	N:5.2.
$C_{30}H_{30}N_2O_{10}$	requires:	C:62.3,	H:5.2,	N:5.0.

Similar attempted preparations, using triethanolamine or dimethylaniline as catalysts, gave only intractable oils as products from which no crystalline material could be isolated.

Numerous attempts to release the free hydroxyquinolizones from these salts and complexes, including grinding them with 2N hydrochloric acid, treatment with zinc uranylacetate solution (sodium salt only), shaking with chloroform and hydrochloric acid in the cold, and passage of their solutions down a weak acid ion-exchange column (Amberlite 1RC 50), were without success.

The treatment of the sodium salt of tetraethyl 6-hydroxy-4-quinolizone-1,3,7,9-tetracarboxylate with ethanolic hydrogen chloride.

The sodium salt (150 g.) was dissolved in ethanol (100 ml.) which had been saturated with dry hydrogen chloride. The yellow colour and fluorescence was immediately destroyed and after the solution had been heated to boiling point it was poured into a large

volume of water and extracted with ether. Removal of the ether gave 50 mg. of a colourless solid (LV111) as needles (ethanol), m.p. 133-4°.

When an ethanolic solution of this solid was made alkaline (pH 8) the solution became deep yellow and at pH 11 a light yellow colour appeared.

$\nu_{\text{max}} = 1750, 1730, 1705, 1660 \text{ cm.}^{-1} \text{ (C=O), } 1580 \text{ cm.}^{-1} \text{ (NH deform}^n\text{)}$
 $\lambda_{\text{max}} (\log_{10} \epsilon) \text{ pH} > 7 = 370 (3.3), 310 (3.75) \text{ and } 260 (4.09) \text{ } \mu\text{.}$
 $< 7 = 335 (3.88) \text{ and } 260 (4.09) \text{ } \mu\text{.}$

<u>Analysis</u>	Found:	C:56.1,	H:6.1,	N:3.3.
$\text{C}_{23}\text{H}_{29}\text{NO}_{11}$	requires:	C:55.8,	H:5.9,	N:2.8

The same compound was obtained when the pyridone (XXXV1) (8.0 g.), diethyl ethoxymethylenemalonate (5.3 g.) and dry solid potassium ethoxide (2.1 g.) were heated together for 6 hours on the steam bath in dimethyl formamide (80 ml.). The yield was 3.5 g.

Furthermore, heating the above product (1.0 g.) in dimethyl formamide (20 ml.) with sodium ethoxide (0.14 g.) gave the sodium salt of the hydroxyquinolizone (400 mg.), m.p. 305-7°, (mixed m.p. with authentic specimen showed no depression).

Treatment of the sodium salt (LV1) with chlorinating agents.¹³⁸

The sodium salt (1 g.) was heated under reflux with phosphorus oxychloride (15 ml.) and triethylamine (3 ml.) for 1.5 hours, with the system protected from moisture. Considerable heat

was evolved initially on adding the phosphorus oxychloride to the solid. After cooling, the excess of phosphorus oxychloride and triethylamine were distilled off and the residue was poured into water where a sticky gum separated. Extraction with chloroform gave a very dark brown extract from which no crystalline material could be isolated.

The experiment was repeated without the triethylamine and after heating for 1 hour a little solid material had begun to separate. This solid was isolated by removal of the excess of reagents (as above) and pouring the residue into water. The yellow precipitate was filtered off and recrystallised from methyl alcohol to give yellow needles, m.p. 348-50° (25 mg.).

$\nu_{\text{max}} = 1750, 1715 \text{ cm.}^{-1} \text{ (C = O).}$

Analysis Found: C:50.6, H:3.2, N:4.0, Res:10
(No chlorine present).

A similar experiment using thionyl chloride (15 ml.) gave only a tar and 100 mg. starting material.

Experiments using the isoquinoline complex instead of the sodium salt and similar reaction conditions were also unsuccessful. The use of solvents, e.g., dimethyl formamide¹³⁹ or benzene, increased the amount of starting material which was recovered.

Attempts to tosylate either the sodium salt or the isoquinoline complex.

The isoquinoline complex (0.35 g.) was dissolved in dry pyridine (50 ml.) and p-toluenesulphonyl chloride (0.24 g.) was added, keeping the temperature of the mixture below 10°. After all the chloride had been dissolved the solution was heated to 60° for 0.5 hours before being gently refluxed for 0.5 hours. On cooling, the solution was carefully diluted with dilute hydrochloric acid and a bright yellow fluorescent precipitate was obtained which was filtered off and recrystallised from chloroform, m.p. 252-4° (50 mg).

$\nu_{\text{max}} = 1750, 1710, 1660 \text{ cm.}^{-1} (\text{C} = \text{O}).$

<u>Analysis</u>	Found:	C:60.9,	H:3.8,	N:4.8,	S:5.5.
$\text{C}_{28}\text{H}_{29}\text{NO}_{12}$	requires:	C:55.9,	H:4.8,	N:2.3,	S:5.3.

A similar experiment using the sodium salt as starting material yielded 20 mg. of the same product.

Attempted methylation of the 6-hydroxyl group of the sodium salt.

The sodium salt (1.0 g.) was dissolved in dimethyl formamide (15 ml.) and methyl iodide (1.0 g.) was added. After 2 weeks at room temperature the mixture was poured into water and the product isolated by extraction with chloroform. It was found to be starting material, (mixed m.p., no depression.).

A similar experiment using 1.0 g. dimethyl sulphate also

yielded starting material only.

Attempted reaction of ethyl ethoxymethylenecyanoacetate with the pyridone (XXXV1).

The pyridone (1.4 g.) ethyl ethoxymethylenecyanoacetate (0.75 g.) and isoquinoline (0.5 g.) were heated together for 2 hours at 180°. Some ethanol distilled from the melt and the resultant oil, when cool, was poured into water and acidified with dilute sulphuric acid. Extraction with chloroform and removal of the solvent gave a red fluorescent oil but no crystalline material could be isolated from it despite the use of a variety of solvents.

Similar experiments, using solid sodium ethoxide as catalyst and dimethyl formamide as solvent, also produced fluorescent oils but again no crystalline material was obtained.

Attempts to use ethyl propiolate instead of the ethoxymethylene component were also unsuccessful. Starting material was recovered.

The treatment of the pyridone (XXXV1) with thionyl chloride.

The pyridone (1.0 g.) was slowly added to ice-cold thionyl chloride (15 ml.) containing pyridine (1 ml.) and the mixture allowed to attain room temperature slowly before being refluxed for 1 hour. After the excess of thionyl chloride had been distilled off, the residue was poured into water and

extracted with chloroform. Removal of the solvent yielded an evil smelling black tar which was rejected.

Varying the reaction time either yielded unreacted starting material (short times) or similar intractable tars to that already described.

The use of other chlorinating agents, e.g., phosphorus oxychloride or phosphorus pentachloride and various inert solvents, did not prevent production of the tars.

The reaction of the pyridone (XXXV1) and diethyl acetonedicarboxylate or diethyl oxaloacetate.

The pyridone (3.25 g.), diethyl acetonedicarboxylate (2.02 g.) and isoquinoline (1.29 g.) were heated together at 180° for 2.5 hours. The mixture was cooled and poured into 200 ml. acetone and this solution into 500 ml. water acidified with dilute sulphuric acid. Extraction with chloroform and removal of the solvent yielded only unreacted pyridone, (1.2 g.).

A similar experiment but using diethyl oxaloacetate (1.9 g.) instead of diethyl acetonedicarboxylate also yielded only unreacted pyridone.

The use of sodium ethoxide as catalyst and dimethyl formamide, or ethanol, as solvent gave a similar result in both cases.

The attempted condensation of ethyl 3-cyano-6-methyl-2-pyridone-5-carboxylate (LX11) and similar compounds with diethyl ethoxymethylenemalonate.

Ethyl 3-cyano-6-methyl-2-pyridone-5-carboxylate (2.9 g.), prepared by Errera's method,⁸⁵ was dissolved in ethanol (20 ml.) and added to a solution of potassium ethoxide (0.6 g.K) in ethanol (80 ml.) After stirring for 30 minutes, diethyl ethoxymethylenemalonate (3.5 g.) was added and the mixture was stirred and refluxed for 8 hours. On pouring into water and acidification of the suspension, unreacted pyridone (2.0 g.) was the sole product.

An experiment using the same quantities of pyridone and malonate, but heating them with isoquinoline (2.0 g.) for 2 hours at 180°, also gave starting material on working up the reaction mixture.

Similar experiments using 3,5-dicyano-6-methyl-2-pyridone⁹¹ (1.7 g.) also led to recovery of the starting materials, as did a preparation attempted with 2-chloro-3,5-dicyano-6-methylpyridine.

Attempted condensation of cyanoacetamide, etc., and diethyl acetonedioxalate.

Cyanoacetamide (0.84 g.) and diethyl acetonedioxalate (2.58 g.) in ethanol (40 ml.) containing sodium ethoxide (0.23 g.Na) were refluxed together for 1 hour. The deep red solution was then cooled, poured into water (150 ml.) and acidified with dilute

sulphuric acid. Extraction with chloroform yielded only unreacted diethyl acetonedioxalate on removal of the solvent.

The experiment was repeated using potassium carbonate (1.4 g.) and piperidine (2 ml.) as catalysts, and with varying times of reaction, but only unreacted ester was recovered from these attempted preparations.

The use of ethyl malonamate¹⁴⁰ or malonamide in place of cyanoacetamide also led to recovery of starting material.

The synthesis of diethyl 2-amino-6-ethoxycarbonylmethylpyridine-3,5-dicarboxylate (LXV1).

Diethyl β -aminoglutaconate (4.04 g.) was dissolved in ethanol (25 ml.) containing sodium (0.5 g.) and the solution cooled to 0°. Keeping the temperature 5° and stirring continuously, ethyl ethoxymethylenecyanoacetate (3.4 g.) was added during 15 minutes. Stirring was continued for 45 minutes at room temperature and by then an orange solid had started to precipitate. The reaction mixture was poured into water (100 ml.) containing dilute sulphuric acid (15 ml.) where a red, oily precipitate appeared. Filtration and recrystallisation of this precipitate from petrol ether/ethyl acetate gave pale yellow fibrous needles, m.p. 88-9° (500 mg.).

$$\frac{\nu}{\text{max}} = 3400, 3200 \text{ cm.}^{-1} (\text{NH}_2 \text{ stretch}), 1740, 1700, 1680 \text{ cm.}^{-1} (\text{C} = \text{O})$$

$$\frac{\lambda}{\text{max}} = 329, 276 \text{ and } 218 \text{ m}\mu.$$

Analysis: Found: C:55.8, H:6.3, N:8.7.

$C_{15}H_{20}N_2O_6$ requires: C:55.6, H:6.1, N:8.7.

A little (50 mg.) of the red hydrate obtained in methylation attempts, etc., on compound (XLV11) was isolated from the mother liquors of this preparation.

The attempted reaction of 2-chloropyridine and diethyl glutaconate.

Diethyl glutaconate (1.85 g.), prepared by two methods,¹⁴¹ (neither of which was very satisfactory) was added to dimethyl formamide (20 ml.) containing dry sodium ethoxide (0.68 g.) and 2-chloropyridine (1.1 g.) and the solution was refluxed for 30 minutes. When cool, the red solution was poured into water and acidified (dilute sulphuric acid) but no precipitate was obtained. Extraction with chloroform yielded a small amount of red oil which appeared to be a mixture of unreacted starting materials. No crystalline product could be isolated from this oil.

Similar experiments with longer reaction times were equally unsuccessful, nor did substitution of ethanol as solvent have any effect.

The preparation of the sodium salt of 1,1,3,3-tetracyanopropene.¹⁴²

Malononitrile (6.6 g.) was added to a solution of sodium (2.3 g.) in ethanol (100 ml.). Keeping the temperature below 0°, ethoxymethylenemalononitrile (12.4 g.) was added in 15 minutes and the solid which separated was filtered off and used for the next

stage. Yield 12.0 g.

The preparation of 2-amino-6-chloro-3,5-dicyanopyridine. (LXV111).

This compound was prepared by the method of Little et alia⁹⁹ which consisted of treating the previous product, dissolved in acetone, with anhydrous hydrogen chloride. Recrystallisation from acetone gave the required compound (7.0 g.), subliming 200°.

The reaction of 2-amino-6-chloro-3,5-dicyanopyridine with diethyl glutaconate.

The pyridine derivative (1.8 g.) was added to a solution of sodium ethoxide (0.25 g.Na) in ethanol (50 ml.) and the ice-cold suspension was stirred while diethyl glutaconate (1.9 g.) was added dropwise. The mixture was then stirred for 30 minutes at room temperature, refluxed for 30 minutes, cooled and poured into water (200 ml.) and the solution was acidified with hydrochloric acid. A yellow precipitate (fluorescent in ultraviolet light) separated and was filtered off and recrystallised from ethanol to give yellow needles, m.p. 215-7°. (Lit.⁹⁹ m.p. 6-ethoxy deriv. = 223-4°.)

ν_{max} = 3400, 3300 cm^{-1} (NH_2 stretch), 2220 cm^{-1} ($\text{C}\equiv\text{N}$) 1660 cm^{-1} ($\text{C}=\text{O}$)
 λ_{max} = 392, 320 and 274 μ .

<u>Analysis</u>	Found:	C:57.1,	H:3.6,	N:16.1.
$\text{C}_{16}\text{H}_{16}\text{N}_5\text{O}_4$	requires:	C:56.0,	H:3.9,	N:17.0.

All other attempts to effect reaction between the starting materials, using longer periods of reflux, different solvents, etc., failed.

The attempted replacement of the 2-amino group in compound (LXV111) by a halogen atom.

Compound (LXV111) (700 mg.) was dissolved in tetrahydrofuran (100 ml.) and the solution was saturated with hydrogen chloride. When cool, 1.1 equivalents of isosmylnitrite were added to the colourless suspension and a pale brown colour developed in the suspension. After standing for 18 hours at room temperature the precipitate was filtered off and found to be unreacted starting material. Varying the reaction time had no effect.

Attempts to diazotise compound (LXV111) (500 mg.) in conc. hydrochloric acid (3 ml.) and tetrahydrofuran (100 ml.), by the addition of sodium nitrite (200 mg.) in water (2 ml.) to the ice-cold solution, also led to recovery of starting material.

The diazotisation of 2,6-diaminopyridine.¹⁰¹

2,6-Diaminopyridine (17.4 g.) was added cautiously to 60% hydrogen bromide (120 ml.) with continuous stirring and to this mixture bromine (48 ml.) was then slowly added. A dirty orange perbromide separated out and the mixture was cooled to 0° on an ice/salt mixture. Keeping the temperature at or below 0° and stirring continuously, a solution of sodium nitrite (55 g.) in water (80 ml.) was added dropwise. A large amount of bromine and hydrogen bromide fumes were released towards the end of the addition and, after the fumes had subsided, sodium hydroxide (120 g.)

in water (400 ml.) was added while maintaining the temperature of the mixture below 25°. This addition caused considerable frothing and more fumes were released. The light brown precipitate which was formed was filtered off and recrystallised from ethanol to give pale cream needles, m.p. 103-4° (22.0 g.). (Lit. m.p. 2,6-dibromopyridine - 118-9°).

<u>Analysis</u>	Found:	C:15.4,	H:0.6,	N:3.5,	Br:80.6.
$C_5H_3NBr_2$	requires:	C:21.1,	H:1.2,	N:5.9,	Br:67.5.
$C_5H_2NBr_3$	requires:	C:19.0,	H:0.6,	N:4.4,	Br:76.0.
C_5HNBr_4	requires:	C:15.2,	H:0.3,	N:3.8,	Br:81.0.

The reaction of the foregoing compound with phenyllithium followed by ethyl laevulinate.^{103(a).}

A solution of phenyllithium (prepared from lithium (0.3 g.), bromobenzene (3.36 g.) and ether (20 ml.)) was cooled to -55° and the foregoing product (4.8 g.) in ether (50 ml.) was added during 10 minutes with stirring at -55°. Ethyl laevulinate (3.0 g.) in ether (10 ml.) was added dropwise during 20 minutes and the red colour was slowly discharged during the addition. Stirring, at -55°, was continued for a further 20 minutes before the mixture was poured on ice and extracted with ether. Starting material (2.0 g.) was recovered but no other product could be isolated.

Similar experiments using n-butyllithium, or higher temperatures of reaction also yielded only unreacted starting

material.

Attempts to react diethyl sodioacetonedicarboxylate^{143,96} with the same starting material in tetralin/dimethyl formamide (9.1) resulted only in the formation of tars from which a little starting material was again isolated.

The condensation of cyanoacetamide and ethyl ethoxymethylenecyanoacetate.

Cyanoacetamide (1.7 g.) was added to a solution of sodium (0.5 g.) in ethanol (20 ml.). The suspension was cooled on ice and stirred while ethyl ethoxymethylenecyanoacetate (3.4 g.) was added. After further stirring for 10 minutes at room temperature, the yellow mixture was poured into water (100 ml.) containing dilute sulphuric acid (10 ml.) and the precipitate was filtered off and recrystallised from ethanol to give pale yellow needles, m.p. 286° (4.0 g.) (subliming > 220° and decomposing at m.p.) of ethyl 6-amino-3-cyano-2-pyridone-5-carboxylate, (LXX11).

$\nu_{\text{max}} = 3350, 3250 \text{ cm}^{-1}$ (NH₂ stretch), 2220 cm^{-1} (C≡N), 1700, 1680 cm^{-1} (C=O).

<u>Analysis:</u>	Found:	C:52.3,	H:4.7,	N:20.1.
$\text{C}_9\text{H}_9\text{N}_3\text{O}_3$	requires:	C:52.2,	H:4.4,	N:20.3.

Treatment of ethyl 6-amino-3-cyano-2-pyridone-5-carboxylate with ethanolic hydrogen chloride.

The compound (1.0 g.) was treated under reflux for 75

minutes with ethanol (50 ml.), which had been saturated with anhydrous hydrogen chloride, cooled and poured into water, and the colourless precipitate was filtered off and recrystallised from glacial acetic acid to give needles, m.p. 307-9°. (subliming > 295°).

<u>Analysis</u>	Found:	C:51.3,	H:4.4,	N:20.4.
$C_9H_8N_2O_4$	requires:	C:52.0,	H:3.8,	N:13.4.
$C_9H_{10}N_2O_5$	requires:	C:45.0,	H:4.2,	N:17.5.

The reaction of acetylene-bis-pyridinium bromide (LXXXVI) with acrylamide, etc.

Acetylene-bis-pyridinium bromide¹¹³ (11.1 g.) was added to methanol (150 ml.) containing acrylamide (4.26 g.). While the mixture was stirred, sodium hydroxide (2.5 g.) in ethanol (30 ml.) was added dropwise. The bromide slowly dissolved to give a deep red solution from which sodium bromide was precipitated. After 30 minutes the solution was acidified with acetic acid and poured into water. Extraction with chloroform yielded only unreacted acrylamide. Heating the alkaline solution to reflux before acidification and extraction also failed to yield a product, as did the use of potassium as catalyst.

Repetition of this experiment using ethyl acrylate, acrylonitrile or ethyl cinnamate as the unsaturated component, and ammonia in ethanol or ammonium acetate in acetic acid as catalysts, led either to the formation of untractable red oils or to recovery

of the unsaturated starting materials.

The synthesis of 6-styryl-4-phenyl-2-pyridone.

Dibenzylideneacetone¹⁴⁴ (5.75 g.), 1-(carbethoxymethyl)-pyridinium bromide¹⁴⁵ (6.15 g.), ammonium acetate (16.5 g.) and glacial acetic acid (20 ml.) were refluxed together for 2.5 hours, cooled and poured into water where a yellow solid was precipitated. After filtration, recrystallisation from ethanol gave yellow needles, m.p. 217-9^o (4.0 g.) of 6-styryl-4-phenyl-2-pyridone.

$\nu_{\text{max}} = 1655 \text{ cm.}^{-1}$ (C = O), 970 cm.^{-1} (Trans. double bond).

$\lambda_{\text{Max}} (\log_{10} \epsilon) = 365 (4.36), 278 (4.59), 235 (4.43) \text{ and } 227 (4.40) \mu.$

<u>Analysis</u>	Found:	C:83.6,	H:5.8,	N:4.9.
$\text{C}_{19}\text{H}_{15}\text{NO}$	requires:	C:83.5,	H:5.5,	N:5.1.

Repetition of this preparation with twice the quantity of the pyridinium salt led to the isolation of the same product.

Attempts to couple this pyridone with a further molecule of the pyridinium salt, using the potassium hydroxide/methanol method described in the previous experiment, led to a quantitative recovery of the pyridone.

The attempted synthesis of 6-vinyl-2-pyridone.

β -Chloropropionyl chloride¹⁴⁶ (32.25 g.) was added to a suspension of finely powdered aluminium chloride (44.5 g.) in methylene chloride (150 ml.). The solution was then decanted, via a glass wool filter, into the reaction vessel which was cooled

on a freezing mixture. Dry nitrogen was passed through the mixture at -10° , followed by dry ethylene. Passage of the ethylene was continued until absorption had ceased, keeping the reaction mixture below -5° . On pouring the reaction mixture on to ice and drying the organic layer, dichlorodiethyl ketone¹⁴⁷ (13 g.), b.p. 84° at 2.5 mm., was isolated after removal of the solvent.

Dichlorodiethyl ketone (1.55 g.) and 1-(aminocarbonylmethyl)-pyridinium chloride¹⁴⁸ (3.44 g.) were mixed together in methanol (30 ml.) and a solution of potassium hydroxide (2.4 g.) in methanol (30 ml.) added dropwise to the mixture. Pot. chloride was precipitated and a yellow colour had developed in the mixture after addition of 15 ml. of the alkaline solution. Addition of the remainder of the alkaline solution caused the reaction mixture to become deep red in colour. On filtering off the potassium chloride, pouring the filtrate into water, acidifying the solution with dilute sulphuric acid and extracting with ether, no product was isolated. Repetition of the experiment with heating of the alkaline solution, before working up, for varying periods of time led only to the isolation of intractable red oils which could not be purified by chromatography on neutralised alumina, nor could they be induced to crystallise.

The reaction of ethyl cinnamoyl acetate and 1-(aminocarbonylmethyl)-pyridinium chloride.

In a typical experiment ethyl cinnamoyl acetate¹¹⁵ (2.18 g.) and 1-(aminocarbonylmethyl)-pyridinium chloride (1.72 g.) were added to methanol (20 ml.). Sodium hydroxide 1N (10 ml.) was added dropwise to this mixture and after 1 hour at room temperature the mixture was acidified with acetic acid (10 ml.). Distillation of the mixture yielded a small amount of sticky solid which, on treatment with a little water, followed by trituration with ethanol, solidified and was shown to be unreacted ester. No other product could be isolated from this reaction, nor from reactions using ammonium acetate in acetic acid, sodium ethoxide or potassium hydroxide as catalysts, with or without heating of the reaction mixture. Attempts to induce Michael addition between ethyl cinnamoylacetate and cyanoacetamide, using sodium ethoxide or piperidine in ethanol as catalysts, were also quite unsuccessful.

Attempts to react together vinyl-pyridines and pyridinium salts.

Freshly distilled 6-methyl-2-vinylpyridine (2.4 g.) was added to sodium ethoxide (0.5 g.) in ethanol (10 ml.) and to this solution was added 1-(carbethoxymethyl)-pyridinium bromide (5.0 g.). After refluxing for 1 hour, the violet solution was cooled and the solvent and unreacted vinylpyridine were removed by distillation. Acidification with dilute hydrochloric acid and extraction with ether to remove any acidic residues was followed by basification

(sodium hydroxide) and re-extraction with ether, to give a yellow oil. The oil was purified by passage down a column of neutral alumina (solvent - ether) but although it showed the presence of an ethoxycarbonyl group (infrared), examination of the oil in a gas/liquid chromatography unit showed that it contained three components. The total yield of purified oil was 700 mg.

No product whatsoever could be isolated from similar reactions, using 2-vinylpyridine, and only minute amounts of tar from 2-vinyl or 6-methyl-2-vinylpyridine and the pyridinium salt, using other catalysts such as ammonium acetate/acetic acid, etc.

Repetition of these reactions using sodium ethoxide as catalyst and 1-(bis-ethoxycarbonyl)-methyl-pyridinium perchlorate¹⁴⁹, gave only minute amounts of sticky material (~20 mg.) which were considered too small to work up.

The preparation of 2- β -ethoxyvinylpyridine.

2-Vinylpyridine (21.0 g.) in carbon tetrachloride (40 ml.) was added slowly, with stirring, to bromine (10.6 ml.) in carbon tetrachloride (80 ml.), cooled on ice. After stirring for 5 minutes the solution was decanted from a sticky, insoluble, by-product and the carbon tetrachloride was removed "in vacuo" to give the dibromo derivative. This compound was then added dropwise to a refluxing solution of potassium hydroxide (40 g.) in ethanol (200 ml.) After 3 hours reflux the solution was cooled

and poured into water (200 ml.). Extraction with ether, and fractionation of the residual oil at 9 mm., gave 2- β -ethoxyvinylpyridine, b.p., 116-8° (20.2 g.).

The reaction of 2- β -ethoxyvinylpyridine and diethyl malonate in acid solution.

Diethyl malonate (2.0 g.) was mixed with 2- β -ethoxyvinylpyridine (1.0 g.) in glacial acetic acid (10 ml.). Concentrated hydrochloric acid (1 drop) was added and the solution was refluxed for 5 minutes before being poured into water. Extraction with chloroform yielded only a minute amount of a sticky oil which could not be crystallised. Repetition of the experiment with longer reaction times yielded similar oils.

The reaction of 2- β -ethoxyvinylpyridine and cyanoacetyl chloride.

Cyanoacetyl chloride¹⁵⁰ (1.2 g.) in acetone (10 ml.) was added to 2- β -ethoxyvinylpyridine (1.7 g.) in acetone (20 ml.) and triethylamine (3 ml.) was then added to the ice-cold solution. A white precipitate was thrown out but warming to 60° produced no further visible reaction. After refluxing the suspension for 1 hour, it was poured into water, acidified with dilute hydrochloric acid and extracted with chloroform. The extract yielded a dark sticky solid (500 mg.) which could not be purified by chromatography on alumina.

Attempted preparation of 1-(6-methyl-2-pyridyl)-2-ethoxycarbonyl-2-methylbutan-3-one, (C1).

2-Chloromethyl-6-methylpyridine hydrochloride^{2(a)} (33.0 g.) was added slowly to a stirred solution of sodium ethoxide (8.5 g. Na) in the minimum of alcohol containing ethyl -methylacetoacetate (26.6 g.) at 0°. After the addition was complete the solution was stirred for 10 minutes at room temperature, then refluxed for 10 minutes, cooled and poured into water (200 ml.). Acidification with dilute sulphuric acid and extraction with ether was followed by basification with sodium carbonate. Re-extraction of this alkaline solution with ether gave a colourless liquid from which two fractions were obtained.

Fraction 1: b.p. 134-40° at 9 mm. (8.0 g.) gave a picrate, m.p. 152-4° (ethanol).

ν_{max} (liquid) = 1730, 1710 cm.⁻¹ (C = O), 1590, 1580 cm.⁻¹ (pyridine ring).

Analysis (picrate) Found: C:43.4, H:4.5, N:14.9.

$\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_{10}$ requires: C:50.3, H:4.4, N:11.8.

Fraction 2: b.p. 154-58° at 9 mm. (10.0 g.) gave a picrate, m.p. 188-90° (ethanol).

ν_{max} (liquid) = 1740, 1715 cm.⁻¹ (C = O), 1590, 1580 cm.⁻¹ (pyridine ring).

Analysis (picrate) Found: C:45.1, H:3.6, N:15.6.

$\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_{10}$ requires: C:50.3, H:4.4, N:11.8.

The reaction of 2-chloromethyl-6-methylpyridine and diethyl malonate.

Diethyl malonate (32.2 g.) was dissolved in ethanol (200 ml.) containing sodium ethoxide (9.2 g.Na) and to this solution, at 0°, was added 2-chloromethyl-6-methylpyridine hydrochloride (35.6 g.), with stirring. Stirring was continued for 30 minutes at room temperature and the mixture was then refluxed for 1 hour, poured into water, acidified and extracted, as in the previous experiment, made basic with sodium carbonate and re-extracted with ether. This ether extract, on distillation, also gave two fractions the second of which appeared to be the desired material.

Fraction 1: b.p. 88-90° at 8 mm. (10.0 g.) was an oil which appeared to be similar to fraction 1 of the previous experiment and gave a picrate, m.p. 158-60° (ethanol).

$\nu_{\text{max}} = 1750, 1730 \text{ cm.}^{-1}$ (C = O), 1590, 1580 cm.^{-1} (pyridine ring).

Analysis Found: C:42.7, H:3.1, N:16.2.

Fraction 2: b.p. 130-2° at 0.2 mm. (24.0 g.). This was a yellow oil which yielded a picrate, m.p. 98-100° (ethanol).

$\nu_{\text{max}} = 1745 \text{ cm.}^{-1}$ (broad -(C = O), 1590, 1580 cm.^{-1} (pyridine ring).

Analysis (picrate) Found: C:49.0, H:4.7, N:11.7.

$\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_{11}$ requires: C:49.0, H:4.5, N:11.3.

(Oil). Found: C:63.8, H:7.1, N:6.5.
 $C_{14}H_{19}NO_4$ requires: C:63.4, H:7.2, N:5.3.

The preparation of 3-(6-methyl-2-pyridyl)-propionic acid hydrochloride.

The foregoing product (fraction 2, 24.0 g.) was refluxed with 50% hydrochloric acid (200 ml.) for 6 hours and the solution was then evaporated to dryness under reduced pressure. The last traces of moisture were removed by azeotropic distillation of the mixture with benzene and ethanol, to give a pale green sticky oil which solidified on the addition of a little acetone. The material could not be recrystallised but was purified by boiling with acetone several times. (15.0 g.), m.p. 71-3°.

✓
max = broad peak 2800 cm^{-1} (OH stretch), 1940 cm^{-1} (hydrochloride ?),
1730 cm^{-1} (C = O).

Analysis Found: C:49.2, H:6.4, N:6.7, Cl:16.1.
 $C_9H_{12}NO_2Cl$ requires: C:53.5, H:6.0, N:7.0, Cl:17.6.

The preparation of 3-(6-methyl-2-pyridyl)-propionyl chloride hydrochloride.

The most satisfactory preparation was the treatment of the acid hydrochloride from the previous experiment (1.0 g.) with thionyl chloride (10 ml.) in the cold and allowing the mixture to stand for 20 hours, protected from moisture, before carefully precipitating the acid chloride with anhydrous ether, (~30 ml.). A highly

deliquescent, crystalline solid (800 mg.) was obtained which was rapidly filtered and kept in a dry atmosphere. The infrared spectrum showed that some acid remained unconverted to the chloride.

$\nu_{\text{max}} = 1840 \text{ cm.}^{-1}$ (chloride C = O), 1730 cm.^{-1} (acid C = O).

Before use, the solid was dissolved in the minimum of anhydrous methylene chloride and any insoluble material was removed by filtration.

Attempts to prepare the acid chloride free of acid by heating the solution, using solvents, e.g., benzene or methylene chloride, or varying the chlorinating agent, led to the production of tars or smaller yields of the mixture. Larger scale preparations also led to smaller yields of product which contained more unreacted acid.

The treatment of 3-(6-methyl-2-pyridyl)-propionyl chloride hydrochloride with diazomethane.

The acid chloride hydrochloride (4.5 g.), dissolved in dry methylene chloride (150 ml.), was treated dropwise with an ice-cold ethereal solution of diazomethane (125 ml. containing 0.230 g. diazomethane in 10 ml. ether) while stirring the solution and keeping the temperature at or below -5° . Stirring was continued for 30 minutes at room temperature and the mixture was allowed to stand for 30 minutes at room temperature. Removal of the ether

"in vacuo" yielded a yellow oil which was purified by chromatography on deactivated alumina and the fractions were examined by infrared spectroscopy. The fraction eluted with pure ether contained the diazoketone but was contaminated with some methyl ester which could not be separated from it by further chromatography. The purified oil (1.9 g.) was used in the next stage.

$\nu_{\text{max}} = 2120 \text{ cm.}^{-1}$ ($-\text{CH}=\text{N}=\text{N}$), 1740 cm.^{-1} (ester $\text{C}=\text{O}$), 1710 cm.^{-1} (diazoketone $\text{C}=\text{O}$).

The treatment of the diazoketone obtained in the previous experiment with anhydrous hydrogen chloride.

The product from the previous experiment (1.9 g.) was dissolved in ether (10 ml.) and methylene chloride (5 ml.) and dry ethereal hydrogen chloride (2.9 ml. containing 0.124 g. hydrogen chloride/ml.) was added dropwise to the ice-cold solution. A brisk effervescence was observed and a dark brown oil was precipitated. Removal of the solvent gave a reddish brown viscous oil which was taken up in methylene chloride (25 ml.) and refluxed for 30 minutes. Removal of the solvent again gave no crystalline product. The residue was dissolved in water (100 ml.) and extracted with chloroform (3 50 ml.) but again the initial product was recovered from the aqueous phase and no product from the extract. A crystalline perchlorate could not be obtained. Finally, chromatography of the product on an ion-exchange resin (Zeo-Karb 225 - 3/4)

cross-linked), using phosphotungstic acid to detect any separation, led to elution of only one product which appeared to be the methyl ester hydrochloride from examination of its infrared spectrum.

The preparation of 2- β -bromoethyl-6-methylpyridine.

2-6¹-Methyl-2¹-pyridylethanol (30.0 g.) was refluxed with 48% hydrogen bromide (200 ml.) for 40 minutes, cooled on ice, neutralised with 6N. sodium hydroxide and extracted with a large volume of ether (800 ml.). Removal of the ether gave a pale yellow oil (34.0 g.) which polymerised slowly at room temperature. A picrate was obtained, and recrystallised from ethanol to give plates, m.p. 161-2°.

<u>Analysis</u> (picrate)	Found:	C:	H:	N:	Br:
C ₁₄ H ₁₃ N ₄ O ₆ Br	requires:	C:40.7,	H:3.2,	N:13.6,	Br:19.4.

The attempted preparation of the cadmium derivative of the foregoing product¹²² and its reaction with chloroacetyl chloride.

The method was that described by Cason.¹²² To a well stirred suspension of magnesium (8.3 g.) in dry ether (40 ml.), in an atmosphere of nitrogen, was added the bromide (34.0 g.) obtained in the previous experiment and ethyl bromide (18.5 g.) dissolved in dry ether (250 ml.). Formation of the Grignard reagent commenced almost at once and the addition was continued at a rate sufficient to keep the ether refluxing. Reflux was continued for a further

hour after the addition was complete and the solution was then cooled on ice. Anhydrous cadmium chloride (31.5 g.) was added during 10 minutes and the mixture was stirred and refluxed until a negative Gilman test¹³¹ was obtained (~ 1 hour). The ether was then distilled rapidly from the mixture until distillation became slow and stirring difficult. Dry benzene (120 ml.) was added and the distillation was repeated. Finally dry benzene (120 ml.) was added and the mixture was vigorously stirred and refluxed for 30 minutes. Chloroacetyl chloride (15.5 g.) in benzene (50 ml.) was added as quickly as possible. A vigorous reaction was observed on this addition (no external heating) and stirring and refluxing was continued for a further 30 minutes. Ice and dilute sulphuric acid were added and the aqueous phase was separated and extracted with benzene. The benzene extracts were combined with the original benzene phase and washed with sodium carbonate solution (5%), water, and a saturated solution of sodium chloride. On removal of the solvent only a sticky, black, intractable tar was obtained.

References.

- (1) Hüchel, Z. Physik., 1931, 70, 204.
Z. Electrochemie, 9337, 43, 754.
- (2) (a) Baker, Buggle, McOmie and Watkins, J., 1958, 3594.
(b) Baker in "Non-benzenoid Aromatic Hydrocarbons" - Ginsburg.
(Interscience) 1959.
- (3) Vol'phin, Russian Chem. Rev. (English translation) 1960, 3, 129.
- (4) Mislow, J.Chem.Phys., 1952, 20, 1489.
- (5) Brown, J., 1953, 3265, 3278.
- (6) Schmidt et alia, J., 1954, 3288, 3295, 3302, 3314.
- (7) Blood and Noller, J. Org. Chem. 1957, 22, 873
- (8) Boekelheide, Windgassen and Saunders, J.A.C.S., 1959, 81, 1459.
- (9) Pettit, Chem. and Ind., 1956, 1306.
- (10) Willstätter and Waser, Ber., 1911, 44, 3423.
Willstätter and Heidelberger, Ber., 1913, 46, 517.
- (11) Prelog, Frenkicl, Kobelt and Barmen, Helv. Chim. Acta., 1947, 30, 1741.
Prelog, J., 1950, 420.
- (12) Stoll and Hulstkamp, Helv.Chim. Acta., 1947, 30, 1815.
- (13) Prelog, Boarland and Polyak, Helv. Chim. Acta., 1955, 38, 434.
- (14) Prelog and Polyak, Helv. Chim. Acta., 1957, 40, 816.
- (15) Wilke, Angew. Chemie., 1957, 69, 397.
- (16) Wittig, Koenig and Clausz, Ann., 1955, 593, 127.

- (16) Wittig and Lehmann, Ber., 1957, 90, 875.
- (17) Sondheimer, Amiel and Wolovsky, J.A.C.S., 1956, 78, 4178.
J.A.C.S., 1957, 79, 4247, 6263.
Proc. Chem. Soc., 1957, 22.
- (18) Eglinton and Galbraith, Chem. and Ind., 1956, 737.
- (19) Sondheimer, Amiel and Wolovsky, J.A.C.S., 1959, 81, 4600.
- (20) Sondheimer and Wolovsky, J.A.C.S., 1959, 81, 1771.
- (21) Jones, Shaw and Whiting, J., 1954, 3212.
- (22) (a) Sondheimer and Wolovsky, Tetrahedron Letters, 1959, 3, 3.
(b) Sondheimer, Amiel and Wolovsky, J.A.C.S., 1962, 84, 230.
- (23) Sondheimer, Amiel and Gaoni, J.A.C.S., 1959, 81, 1771.
- (24) Lindlar, Helv.Chim. Acta., 1952, 35, 446.
- (25) Bohlmann, Ber., 1952, 85, 386.
- (26) Sondheimer, Amiel and Wolovsky, J.A.C.S., 1957, 79, 4247.
- (27) Sondheimer and Wolovsky, J.A.C.S., 1959, 81, 4755.
- (28) Sondheimer, Wolovsky and Gaoni, J.A.C.S., 1960, 82, 754, 755.
- (29) Sondheimer, Wolovsky and Ben-Efraim, J.A.C.S., 1961, 83, 1675.
Sondheimer, Wolovsky and Ben-Efraim, J.A.C.S., 1961, 83, 1682.
Sondheimer, Wolovsky and Ben-Efraim, J.A.C.S., 1961, 83, 1686.
- (30) Sondheimer and Gaoni, J.A.C.S., 1961, 83, 1259.
- (31) Danes, Tetrahedron Letters, 1959, 8, 4.
- (32) Coulson and Golebiewski, Tetrahedron, 1960, 11, 125.
- (33) Bregman and Rabinovitch, Acta. Cryst., 1960, 13, 1047.

and private communication quoted in Ref. 22.6.

- (34) Sondheimer and Gacni, J.A.C.S., 1960, 82, 5765.
- (35) Sondheimer and Gacni, J.A.C.S., 1960, 83, 4863.
- (36) Boekelheide and Lodge, J.A.C.S., 1951, 73, 3681.
- (37) Boekelheide and Gall, J. Org. Chem., 1954, 19, 499.
- (38) Boekelheide, Humber, Lindsay and Stokes, J.A.C.S., 1961, 83, 943.
- (39) Boekelheide, Small and Galbraith, J. Org. Chem., 1959, 24, 582.
- (40) Boekelheide, Small, Galbraith and Barnes, J.A.C.S., 1961, 83, 453.
- (41) Acheson and Taylor, J. 1960, 1691, for extensive references
to Diel's work.
- (42) Bradsher, Chem. Revs., 1946, 38, 447.
- (43) Boekelheide and Small, J.A.C.S., 1961, 83, 462.
- (44) c.f. Dewhirst and Cram, J.A.C.S., 1958, 80, 3115.
- (45) Kozac and Kalmus, Chem. Zentr., 1, 1934, 3595.
Chem. Abs., 1934, 28, 4424.
- (46) Cooper and Partridge, J., 1954, 3429.
- (47) Jacobson and Huber, Ber., 1908, 41, 660.
- (48) Redemann and Lucas, J.A.C.S., 1939, 61, 3420.
Redemann and Lucas, J.A.C.S., 1940, 62, 842.
- (49) Nozoe, Seto, Matsamura and Asano, Proc. Jap. Acad., 1956, 32, 339.
Chem. and Ind., 1955, 1257.
- (50) Westphal, Jann and Hefte, Arch. Pharm., 1961, 294, 37.
Chem. Abs., 1961, 55, 12407.
- (51) Boekelheide and Gall, J.A.C.S., 1954, 76, 1832.
- (52) Boekelheide and Ross, J.A.C.S., 1955, 77, 5691.

- (53) (a) Glover and Jones, Chem. and Ind., 1956, 1456.
(b) Glover and Jones, J., 1958, 3021.
- (54) Woodward and Witkop, J.A.C.S., 1949, 71, 379.
Woodward and McLamore, J.A.C.S., 1949, 71, 379.
- (55) Glover and Jones, J., 1959, 1686.
Collicutt and Jones, J., 1960, 4101.
- (56) Neameyanov, Chem. Abs., 1958, 52, 6349.
- (57) Bradsher and Beavers, J.A.C.S., 1955, 77, 453, and later papers.
- (58) Richards and Stevens, Chem. and Ind., 1954, 905.
Richards and Stevens, J., 1958, 3067.
- (59) Meier, Ber., 1943, 76B, 1016.
- (60) Herbet, Mors, Gottlieb and Djerassi, J.A.C.S., 1959, 81, 2427.
Buhock and Smith, J., 1960, 502.
- (61) Wischmann, Logan and Stuart, J. Org. Chem., 1961, 26, 2794.
- (62) Braude and Timmins, J., 1950, 2007.
- (63) Arnold and Zemlicka, Coll. Czech. Chem. Comm., 1959, 24, 2385.
- (64) Katada, J. Pharm. Soc., Japan, 1947, 67, 51.
Chem. Abs., 1951, 45, 9536.
- (65) (a) Boekelheide and Linn, J.A.C.S., 1954, 76, 1286.
(b) Bullett and Maynard, J.A.C.S., 1954, 76, 1370.
(c) Kobayashi and Furukawa, Pharm. Bull. (Japan) 1953, 1, 347.
(d) Traynelis and Martello, J.A.C.S., 1958, 80, 6590.
- (66) Robison, J.A.C.S., 1958, 80, 6254.
- (67) Weiss and Hauser, J.A.C.S., 1949, 71, 2026.

- (68) Stafford, W.H., Ph.D. Thesis, Edin., 1951, p. 294 (c.f.).
- (69) Doering and Weil, J.A.C.S., 1947, 69, 2461.
- (70) Jackman, Johnson and Tebby, J., 1960, 1579.
- (71) Wiley and Knabeschuh, J. Org. Chem., 1953, 18, 836.
- (72) Adams and Miyano, J.A.C.S., 1954, 76, 3168.
- (73) Diels and Pistor, Ann., 1937, 530, 87.
- (74) Adams and Reifschneider, J.A.C.S., 1959, 81, 2537.
- (75) Govindachari, Rajadurai, Subramanian and Thyagarajan,
J. 1957, 3839.
- (76) Leonard and Boyer, J.A.C.S., 1950, 72, 2980.
- (77) Simonsen, J., 1908, 1022.
- (78) Ruhemann, J., 1899, 2045.
- (79) Errera, Ber., 1899, 32, 2793.
- (80) Leaver and Bryce - unpublished work.
- (81) Bellamy, "The Infrared Spectra of Complex Molecules" -
(Methuen), 1957.
- (82) Rasmussen and Brattain, J.A.C.S., 1949, 71, 1073.
- (83) e.g., Kochetkov, Kudryashov and Gottich, Tetrahedron,
1961, 12, 63.
- (84) Mitra, J. Ind. Chem. Soc., 1938, 15, 455.
- (85) Errera, Ber., 1900, 33, 2969.
- (86) Clemo, Fox and Raper, J., 1954, 2694.
- (87) Bohlmann, Ottawa and Keller, Ann. 1954, 587, 162.
- (88) Bohlmann, Englisch, Politt, Sander and Weise, Ber. 1955, 88, 1831.

- (89) Guter and Hammond, J.A.C.S., 1956, 78, 5166.
- (90) Ochiai and Ito, Ber., 1941, 74, 1111.
- (91) Lukes and Kuthan, Coll. Czech. Chem. Comm., 1961, 76, 1845.
- (91) Bardhan, J., 1929, 2223.
- (93) Henecka, Ber., 1949, 82, 36.
- (94) Koenigs and Jaeschke, Ber., 1921, 54, 1351.
- (95) Kuhn and Richter, J.A.C.S., 1935, 57, 1927.
- (96) Walter and McElvain, J.A.C.S., 1935, 57, 1891.
- (97) Panizson, Helv. Chim. Acta., 1944, 27, 1748.
- (98) Elderfield in "Heterocyclic Compounds" Vol. 1, p.523. (Wiley.)
- (99) Little, Middleton, Engelhardt and Sausen, J.A.C.S., 1958, 80, 2832.
- (100) Weissberger - "Pyridine and its derivatives" Part 2. Ch.V1 -
(Interscience) 1961.
- (101) Craig, J.A.C.S., 1934, 56, 231.
- (102) Meyer and Graf, Ber., 1928, 61, 2202.
- (103) (a) Gilman and Spatz, J. Org. Chem., 1951, 16, 1485.
Gilman and Spatz, J.A.C.S., 1940, 62, 446.
(b) Sperber, Papa, Schwenk and Sherlock, J.A.C.S., 1951, 73, 3866.
(c) Leonard and Ryder, J. Org. Chem., 1953, 18, 598.
- (104) Proost and Wibaut, Rec. Trav. Chim., 1940, 59, 971.
- (105) Wibaut and Den Hertog, Rec. Trav. Chim., 1932, 51, 381.
Den Hertog, Rec. Trav. Chim., 1945, 64, 85.
- (106) Krollpfeifer and Schneider, Ann., 1937, 530, 38.
Pinck and Hilbert, J.A.C.S., 1946, 68, 2011.

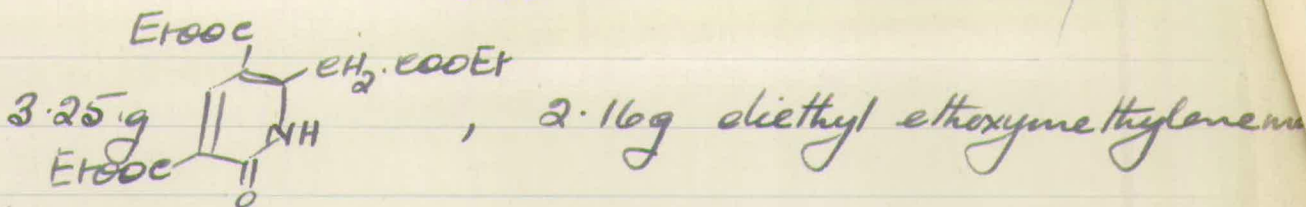
- (107) Kröhnke, Ber., 1950, 83, 253.
- (108) Weiss, J., 1942, 245.
- (109) Badger, -"Structure and Reactions of Aromatic Compounds"
(Cambridge), p. 83.
- (110) Kröhnke and Kubler, Ber., 1937, 70, 538.
- (111) Thesing and Muller, Ber., 1957, 90, 711, 720.
- (112) Kröhnke and Zecher, Ber., 1961, 94, 690.
- (113) Kröhnke and Luderitz, Ber., 1950, 83, 60.
- (114) Doering and Weil, J.A.C.S., 1947, 69, 2461.
- (115) Stanek and Holub, Chemické Listy., 1953, 47, 404.
C.A., 1955, 49, 232.
- (116) Moore and Medeiros, J.A.C.S., 1959, 81, 6026.
- (117) Westoo, Acta. Chem. Scand., 1959, 13, 604.
- (118) Huns and Bohme, Ber., 1921, 54, 726, 1921.
- (119) Kao and Robinson, J., 1955, 2865.
- (120) Organic Reactions, Vol. (X), p.179.
- (121) Organic Reactions, Vol. (V111), p.35.
- (122) Cason, Chem. Revs., 1947, 40, 15.
- (122) Cason, J.A.C.S., 1946, 68, 2078.
- (123) Grignard, Comptes. Rend., 1934, 198, 625.
- Fieser, - "Experiments in Organic Chemistry" (Heath), p.268 -
3rd. Edition.
- (124) Meier, Ber., 1943, 768, 1013.
- (125) Michael and Carlson, J.A.C.S., 1935, 57, 159. (Method C).
- (126) Organic Syntheses, 29, 44.

- (127) Organic Syntheses, 23, 83.
- (128) Chichibabin, Bull. Soc. Chim., (France), 1938, 5, 429, 436.
- (129) Katritsky and Monro, J., 1958, 152.
- (130) Stafford, Ph. D. Thesis, Edin., 1951.
Du Feu, McQuillin and Robinson, J., 1937, 53.
- (131) Gilman, - "Organic Chemistry", Vol. 1, p.496 (Wiley).
- (132) Ochiai, J. Org. Chem., 1953, 18, 534.
- (133) Strauss and Voss, Ber., 1926, 59, 1690.
Houreaux and Bongrand, Ann. de Chimie., 9, 1920, 14, 51.
- (134) Ruhemann and Merriman, J., 1905, 87, 1389.
- (135) De Bollemont, Bull. Soc. Chim., 3, 25, 20.
- (136) Passalacqua, Gazz. Chim. Ital., 1913, (11) 43, 566.
- (137) c.f. Houben-Weyl, "Methoden der Organische Chemie" 11/1, p. 173.
- (138) c.f. Nozoe, Seto, Ito and Katono, Sc. Rept^a Tohoku, Univ.,
1953, 37, 191.
Abadir, Cook, Loudon and Steel, J., 1952, 2350.
Nozoe and Kitahara, Proc. Jap. Acad., 1954, 30, 204.
- (139) c.f. Bosshard, Mory, Schmid and Zollinger, Helv. Chim. Acta.,
1959, 42, 1653.
- (140) Finner, Ber., 1895, 28, 479.
- (141) Dreifuss and Ingold, J., 1923, 2965.
Kon and Nargund, J., 1932, 2462.
Gidvani, J., 1932, 2666.
Conrad and Gutzheit, Ann., 1888³, 222, 249.
- (142) Urushibara, Bull. Chem. Jap., 1927, 2, 278.
C.A. 1928, 22, 579.

- (143) Doering and Pasternak, J.A.C.S., 1950, 72, 143.
(144) Organic Syntheses, 12, 22.
(145) Bergmann, Bendas and Resnick, J., 1953, 2564.
(146) Fieser and Seligman, J.A.C.S., 1936, 58, 2484.
(147) Jones and Taylor, J., 1961, 1345.
(148) Cook, Downer and Hornung, J., 1941, 506.
(149) Kröhnke and Kubler, Ber., 1937, 70B, 543.
(150) Schroeter and Seidler, J. pr. Chem., 2 , 1922, 105, 171.
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The ~~emulsion~~ formed into The oil precipitated slowly solidified and after filtration the mother liquors were extracted with ether, the extract dried & removed in vacuo to give a little more product. The combined solid products were recrystallised from petroleum ether / ethyl acetate to give bright yellow needles. m.p. ~~120-1~~: 120-1°.

Analysis $C_{21}H_{23}NO_{10}$ requires: 56.1% C; 5.1% H; 3.1% N
 found: 56.0% C; 5.0% H; 3.0% N

% Yield = 57%

- butyl + $SOCl_2$ in $CHCl_3$
- chloroform + $SOCl_2$ alone.
- + $SOCl_2$ + $CHCl_3$ + DMF (cat. or excess).
- + $SOCl_2$ + C_6H_6 .