SYNTHESIS AND STRUCTURAL EXAMINATION

OF 4-AZAINDOLES

by

GORDON W.G. GRIFFITHS

A thesis presented for the degree of

MASTER OF PHILOSOPHY

in the

University of Aston in Birmingham

October, 1975
Department of Pharmacy
University of Aston in Birmingham
Gosta Green
Birmingham B4 7ET

SUMMARY

The literature on the methods of synthesis of azaindoles with particular reference to the 4-isomer is reviewed. Numerous methods of synthesis employ pyridine derivatives as starting materials, and methods via pyrrole are very limited.

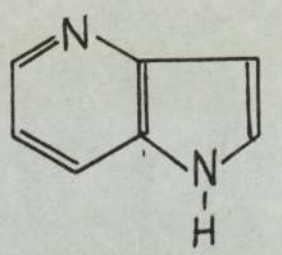
4-azaindoles are synthesised from 4-amino-2-carboethoxy-1-methyl-pyrrole. There are many difficulties in the use of amino-pyrroles as starting materials because of their tendency to oxidative decomposition, and this subject is discussed at some length. The reagents used to condense and couple with the aminopyrrole are examined and some reaction mechanisms are included.

Physical methods of structure determination of azaindoles are examined together with a discussion of the tautomerism of α-, γ- and δ-hydroxy-pyridines and quinolines. The infrared, ultraviolet and nuclear magnetic resonance spectra of the prepared 4-azaindoles are recorded and the amide/enol tautomerism of 2-carboethoxy-1-methyl-7-oxo-4-azaindole is studied.

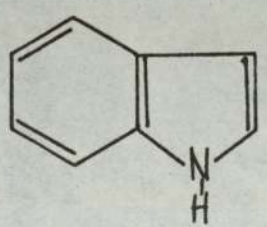
NOTE

Two forms of nomenclature are in common use to describe the fused ring system of pyrrole and pyridine.

The accepted correct nomenclature for the system under examination relates to the pyrrolo (3,2-b) pyridine root.



A second method of description draws the anology to indole giving rise to the 4-azaindole root.



In this thesis both forms are used. The latter somewhat less cumbersome nomenclature is used in the text and the former in the experimental section.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to Dr. A.Z. Britten for the interest, help and enthusiasm he has shown throughout the course of this work.

I should also like to thank Professor D.G. Wibberley for his advice and A. Broderick for useful discussion.

Invaluable assistance was given me by Dr. D.A. Couch of Warwick University with the use of N.M.R. equipment and willing technical help from Messrs. J. Charlton and P. Lowe of the Pharmacy Department, University of Aston.

CONTENTS

REVIEW OF SYNTHETIC METHODS

1.1 The 4-azaindoles are the least studied group of the four isomeric azaindoles and few members and derivatives have been prepared. In many cases the methods employed for their preparation and for the preparation of the other isomeric azaindoles tend to be limited by the necessity for harsh reaction conditions.

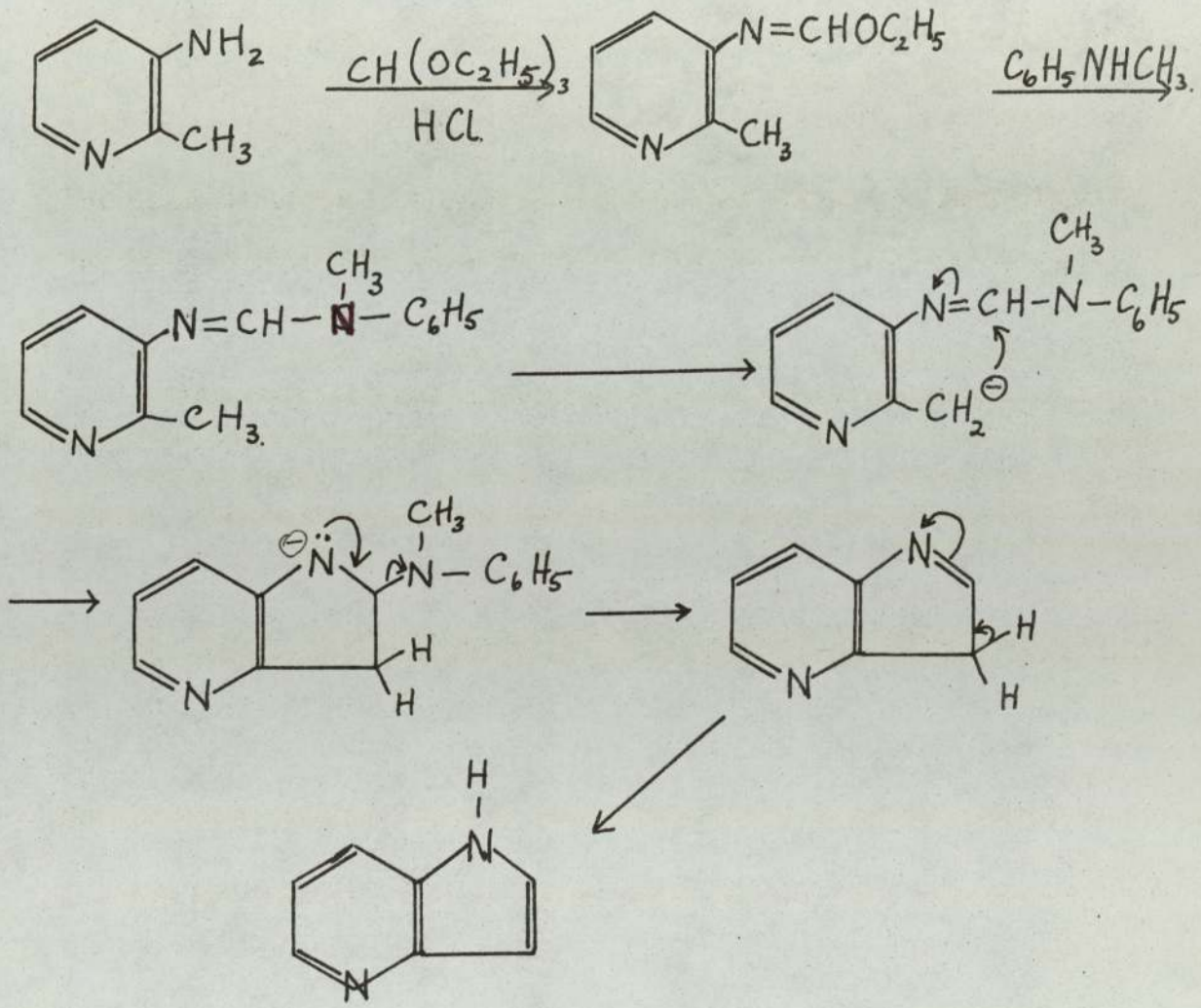
SYNTHESES

1.2 MADELUNG. The most common method of preparation of 4-azaindoles is by a Madelung type cyclisation of N-acyl-2-methyl-3-amino-pyridine at high temperature and in the presence of strong base[1-4].

Clemo and Swan found that cyclisation of 2-methyl-3-formamido-pyridine did not proceed with sodium ethoxide but was satisfactory with potassium ethoxide giving 4-azaindole[2]. 3-Diacetylamino-2-methyl-pyridine cyclised with sodium ethoxide in high yield.

Clayton and Kendall[4] prepared 5-methyl, 2,5-dimethyl and 2-phenyl-5-methyl-4-azaindole in 12, 55 and 67% yields respectively by treatment of the corresponding formyl acetyl and benzoyl derivatives of 3-amino-2,6-dimethyl-pyridine with sodium ethoxide at 310° for fifteen minutes. Variation of the base in the Madelung type cyclisation by Robison and Robison[5] resulted in significant improvement in yield and sodium anilide was used to effect by Adler and Albert in the synthesis of 4-azaindole[3] and Albert and Willett in the synthesis of 4,5-and 6-methyl-7-azaindoles[6]. The application

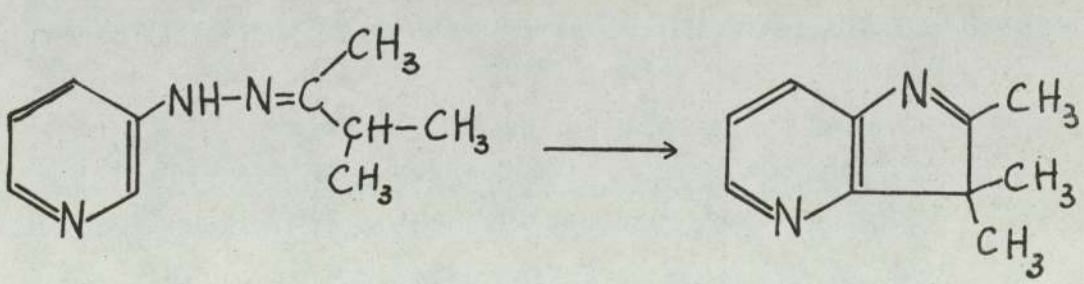
of mineral oil as a diluent in this type of synthesis was studied by Lorenz et al. and in some cases reduced loss of product by thermal decomposition[7]. 4-azaindole was obtained by the cyclisation of a formamidine derivative of 2-methyl-3-amino-pyridine but the yield was poor (6%). However the procedure gave the other isomeric azaindoles in much improved yields[7].



Although the efficiency of the method makes it commercially acceptable for the preparation of 5-and 7-azaindoles the Madelung type cyclisation is of limited usefulness for the synthesis of azaindoles substituted with sensitive groups because of the high temperatures and harsh conditions involved.

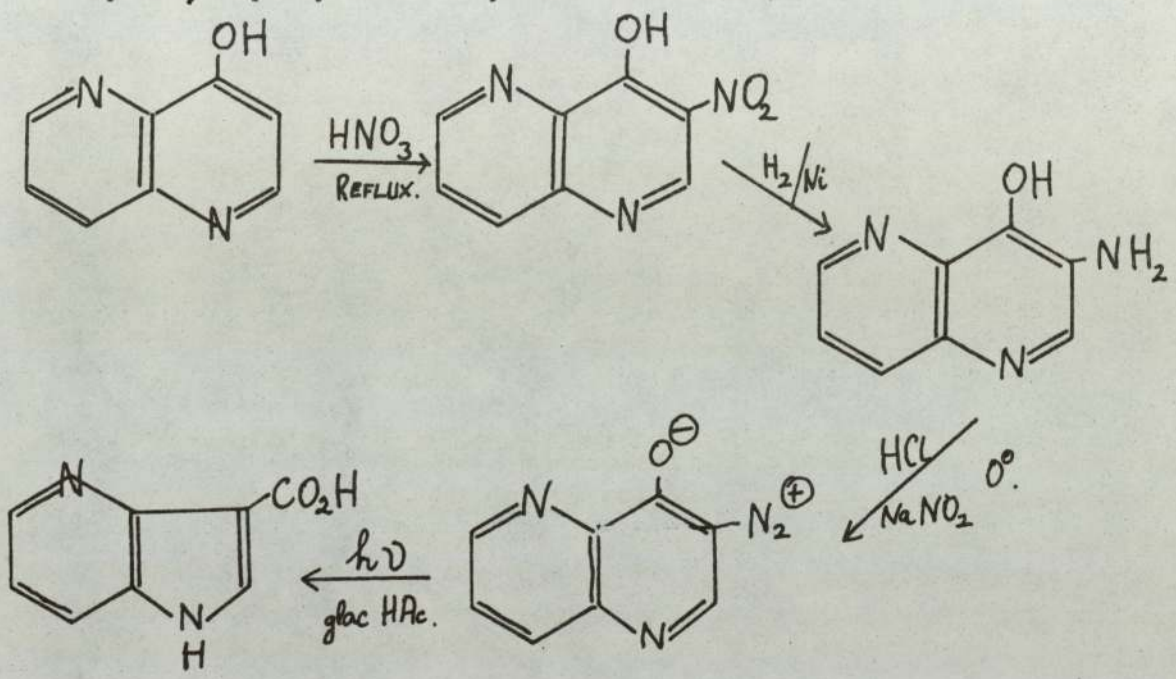
1.3 FISCHER INDOLE. The synthesis of azaindoles by this method has been tried extensively and met with varying degrees of success. Cyclisations involving an electrophilic mode of attack on a π deficient pyridine ring are invariably more difficult than with benzene. Ring closures of pyridyl or quinolyl hydrazones mainly led to carbolines or pyrrolo quinolines and the number of azaindoles prepared is very small. It has been suggested by Abramovitch and Saha that more vigorous conditions are necessary to effect closure on to the pyridine ring than on to the benzene ring[8]. Cyclisation of isopropyl methyl ketone-2-pyridyl-hydrazone required heating with zinc chloride to 250° to give 2,3,3-trimethyl-4-azaindole[9] whereas cyclisation of the corresponding phenyl-hydrazone could be effected by heating under reflux with zinc chloride in ethanol[10].

Ring closure of isopropyl methyl ketone-3-pyridyl hydrazone gives 2,3,3-trimethyl-4-azaindole[11] whereas acetone-2-chloro-5-pyridyl-hydrazone gives 5-chloro-2-methyl-4-azaindole[12].



1.4 RING CONTRACTION. It was reported by Sus and Moller that certain indoles could not be made by the Fischer Indole method[13]. Primarily these were indoles with electron withdrawing groups in

the benzene ring. However, it was found that ring contraction of the appropriate isomeric naphthyridine derivative could be used to prepare the four isomeric azaindoles. 4-azaindole-3-carboxylic acid was prepared by a lengthy synthesis from the appropriate 4-hydroxy naphthyridine in yields from 50-90%.



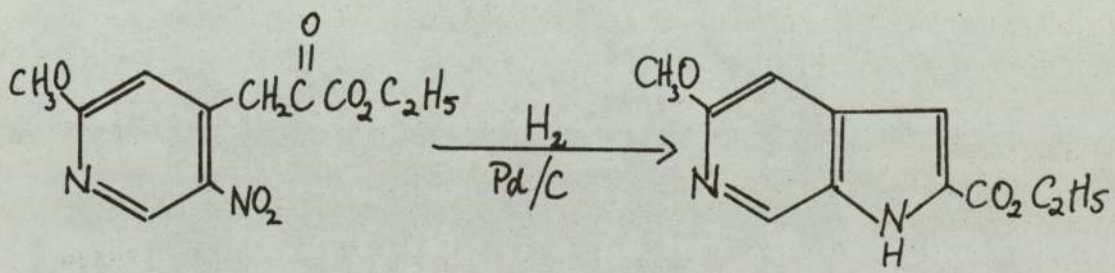
It is interesting to note that decarboxylation of the acid met with difficulty whereas the 6-aza acid could be decarboxylated by heating to the melting point.

1.5 REISSERT SYNTHESIS

The Reissert synthesis of indoles found much success using o-nitrotoluenes as starting materials but attempts of azaindole synthesis with pyridine analogues has been much more limited.

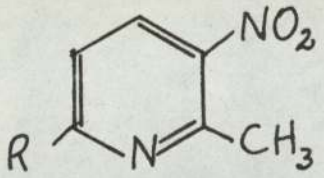
The basis of the synthesis is condensation of $\alpha\beta$-alkyl nitro-pyridines with diethyl oxalate to form the pyruvate , catalytic reduction of the nitro group to the corresponding amine and

simultaneous ring closure. The electron attracting influence of the pyridine-N-oxide increases the acidity of the methyl group and 2-and 4-picoline-N-oxides condensed with diethyl oxalate giving the corresponding pyruvates in good yield [14]. It was expected that 3-nitro-2-picoline or 3-nitro-4-picolines should give better results but the initial attempts with these compounds and with 3-nitro-2-picoline-N-oxide failed [15]. The reaction was realised by Frydman et al when 2-methoxy-5-nitro-4-picoline was treated with ethyl oxalate and potassium ethoxide to give the pyruvate at 93% yield. Hydrogenation with palladium charcoal gave the corresponding 6-azaindole [16].

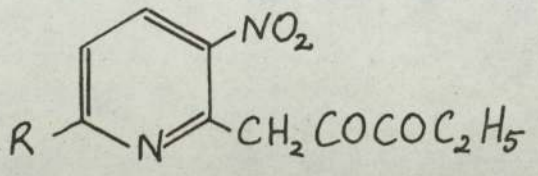


Rapoport[16] extended the reaction to a number of 4- and 6-azaindoles with and without the alkoxy groupings, although details are not reported in the literature.

Frydman et al reported the successful condensations of 3-nitro-2-picoline (1), 6-methoxy-(2) and 6-benzyloxy-3-nitro-2-picoline (3) with diethyl oxalate in the presence of potassium ethoxide to yield the corresponding ethyl-3-nitro-2-pyridine pyruvates [17] (4), (5) and (6) in contrast to earlier attempts.

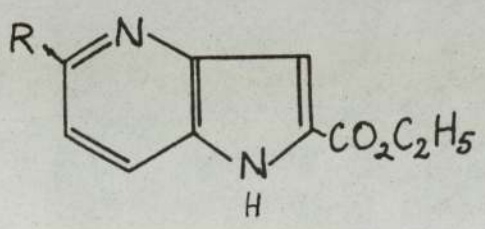


(1) R = -H
(2) R = $-OCH_3$
(3) R = $-OCH_2C_6H_5$



(4) R = $-H$
(5) R = $-OCH_3$
(6) R = $-OCH_2C_6H_5$

The pyruvate intermediates exist mainly in the enol form but on hydrogenation at atmospheric pressure gave the corresponding 2-carboethoxy-4-azaindoles in good yields.

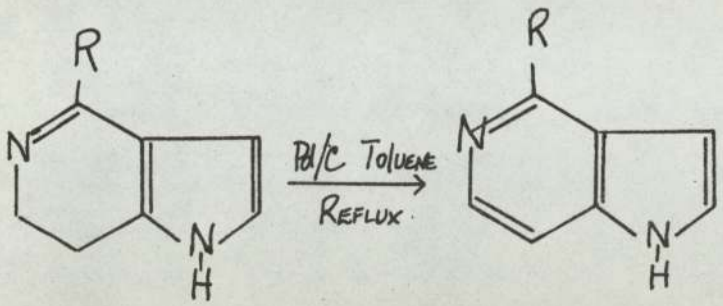


(7) R= H
(8) R = $-OCH_3$
(9) R = $-OCH_2C_6H_5$

1.6 SYNTHESES VIA THE PYRROLE RING

Attempts at azaindole syntheses starting with the pyrrole ring have met with only limited success. Hertz and Tocker[18] applied a Bischler-Napieralski type reaction to the formation of 5-azaindole derivatives. N-acetyl and N-Benzoyl derivatives of 2-(2-amino-ethyl) pyrrole were cyclised in refluxing toluene with phosphoryl chloride to give 6,7-dihydro-4-methyl-5-azaindole (1)

and 6, 7-dihydro-4-phenyl-5-aza indole (2) respectively.

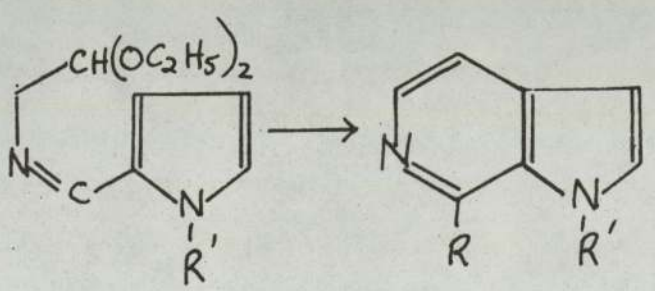


(1) $R = -CH_3$

(2) $R = -C_6H_5$

Dehydrogenation was affected by reflux in toluene with palladium charcoal.

Application of the Pomeranz-Fritsch reaction to the cyclisation of pyrrole-2-iminoacetals[3] gave 6-azaindole (4) apoharmine (5) and 1-methyl-6-azaindole (6) by heating the suitable acetal with a mixture of polyphosphoric acid and phosphoryl chloride but the yields were very low.



(4) $R = R' = -H$

(5) $R = -CH_3$
$R' = -H$

(6) $R = -H$
$R' = -CH_3$

2.1 DISCUSSION

INTRODUCTION

Review of syntheses of azaindoles shows the predominant use of pyridine derivatives as starting materials.

Although there are references to the synthesis via pyrroles success has been very limited [18,19]. The formation of any of the isomeric azaindoles depends on the preparation of simple amino or alkyl-amino-pyrroles, but it is well known that the majority of these compounds are unavailable because of oxidative decomposition.

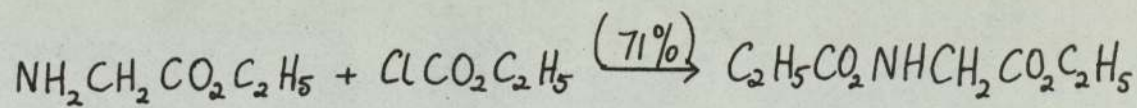
3-nitro-pyrrole and N-methyl-3-nitro-pyrrole[20] were prepared by low temperature nitration of the appropriate pyrrole with concentrated nitric acid in acetic anhydride. Reduction of the nitro compounds was attempted catalytically by atmospheric hydrogen and in view of the instability, in situ coupling with an acylating agent was attempted. This produced a violent reaction resulting in intractible tars from which no product could be obtained. No improvement was obtained when acetyl-acetone or ethyl acetoacetate were used as solvents for the hydrogenation.

The preparation of N-acetyl-3-acetamido-pyrrole was attempted by treating amino-acetaldehyde diethyl acetal in pyridine with acetic anhydride. Acetamido-acetaldehyde diethyl acetal was obtained in 63% yield after vacuum distillation. Hydrolysis and ring closure was attempted by reflux in dilute hydrochloric acid but in spite of a variety of procedures of work up no N-acetyl-3-acetamido-pyrrole

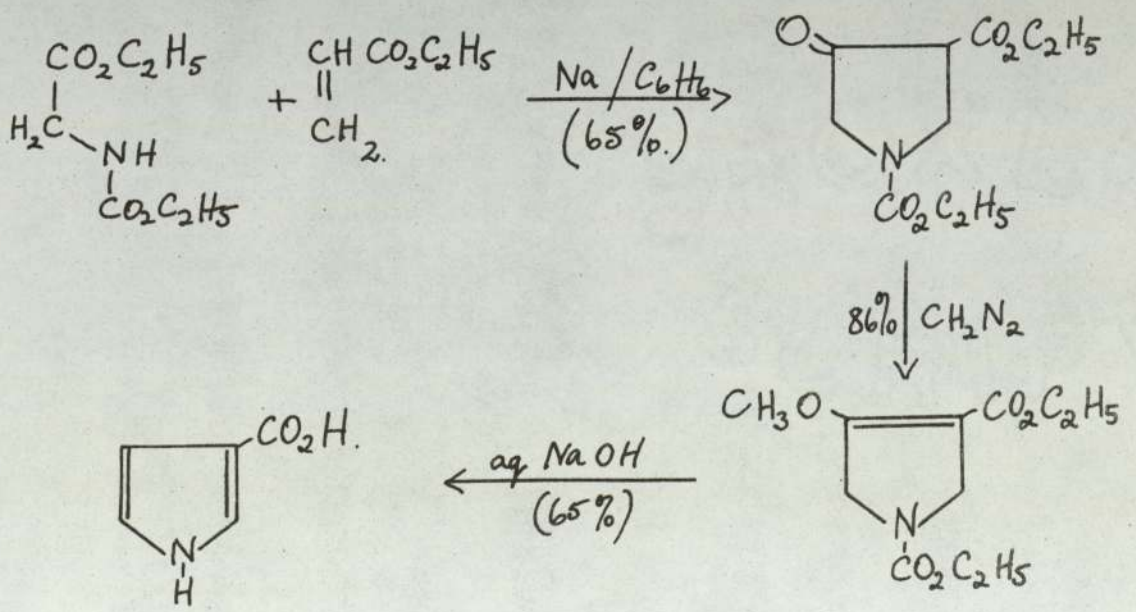
could be obtained.[21] It was considered that this compound would have been a useful precursor to 4-azaindole.

Pyrrole-3-carboxylic acid appeared to be suitable starting material for synthesis of 5-or 6-azaindoles and this was prepared by a four stage process, each stage giving acceptable yields.

Treatment of glycine ethyl ester hydrochloride in aqueous solution at 0° with ethyl chloroformate yielded N-carboethoxy-glycine ester[22].



N-carboethoxy-glycine ester in dry benzene was treated with sodium wire, followed by ethyl acrylate yielding 1,3-dicarboethoxy-4-pyrrolidone[23] which with diazomethane gave 1,3-dicarboethoxy-4-methoxy-Δ^3-pyrroline.



The pyrroline derivative on heating under reflux with aqueous sodium hydroxide gave pyrrole-3-carboxylic acid.

Reduction of the pyrrole-3-acid to the corresponding alcohol was attempted using lithium aluminium hydride in ether but was unsuccessful. A higher temperature reflux employing tetra - hydrofuran showed no improvement.

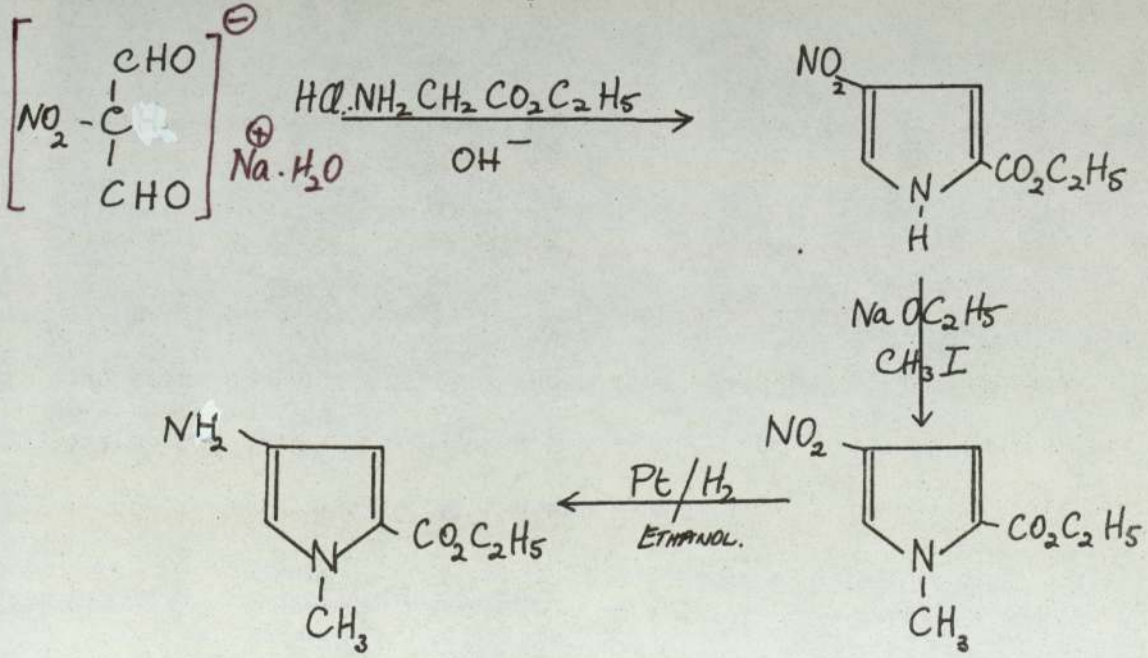
Conversion to the acid chloride was attempted with phosphorus pentachloride and with thionyl chloride but resulted in intractible tars. It appeared that the acid chloride underwent rapid decomposition, and immediate treatment with ammonia in an attempt to form the amide gave no positive results. The amide could not be prepared directly from the acid by treatment with ammonium carbonate.

Treatment of the acid with diazomethane readily formed the methyl ester but attempts to convert to the amide with concentrated ammonia and formamide and sodium methoxide were not possible. This route to a starting material was abandoned.

As the synthesis of 4-azaindoles from pyrrole starting materials was of most interest it became evident that preparation of a 3-amino-pyrrole of sufficient stability to be useful was of prime importance. The stability of the amino function is enhanced by the presence of electron withdrawing groups in the ring and it was considered that subsequent azaindole synthesis depended upon increasing the stability of the amine function by the presence of electrophilic groups in positions which would allow ring closure,

but not reduce the activity of the 2-carbon position to such an extent that the final coupling is prevented.

4-amino-2-carboethoxy-N-methyl-pyrrole proved to be a suitable starting material for the synthesis of 4-azaindoles providing it was used immediately after preparation. This starting material was prepared by treatment of mucobromic acid with sodium nitrite to yield the sodium salt of nitromalonaldehyde[24,25,26,27]. The yield for this stage is generally around 25%. Reaction with ethyl glycine ester hydrochloride under alkaline conditions gave 2-carboethoxy-4-nitro-pyrrole in favourable yield[28]. N-methylation with methyl iodide and sodium ethoxide in ethanol gave 2-carboethoxy-N-methyl-4-nitro-pyrrole[28] a compound which could be stored and reduced to the amino-pyrrole derivative when required. The nitro compound was hydrogenated at atmospheric pressure using platinum in absolute alcohol. Although the procedure is lengthy and the overall yield rather low the results are reproducible.



Preparation of a suitable 4-amino-pyrrole was sought with the object of condensation with the following types of compounds.

diketones - acetyl-acetone

ketoaldehydes - acetyl-acetaldehyde

1, 3-diesters - diethyl malonate

ketoesters - ethyl aceto-acetate, ethyl benzoyl-acetate

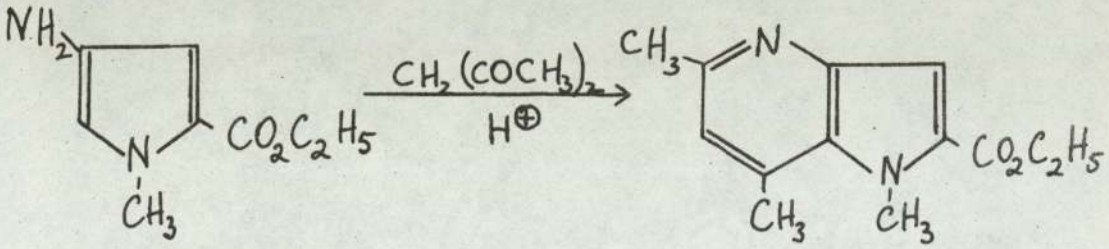
ethyl ethoxy-methylene-malonate

ethyl ethoxy-methylene-cyanoacetate

It was anticipated that these compounds would form an intermediate capable of ring closure on the 5-position in the pyrrole ring to give the resultant 4-azaindole.

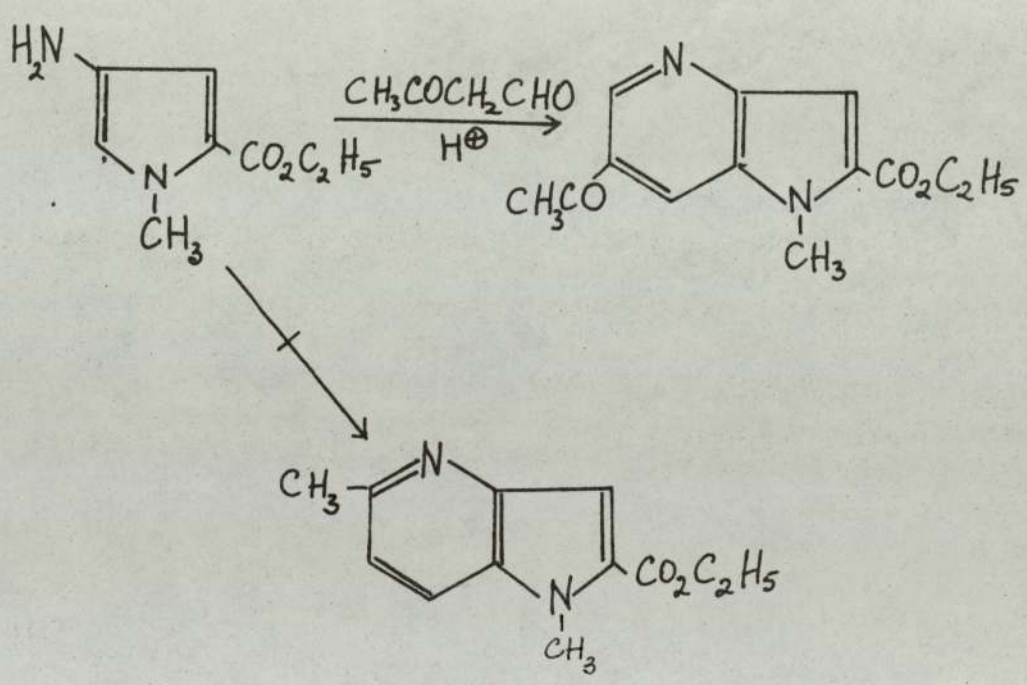
2.2 (i) ACETYLACETONE

It is known that 1,3-dicarbonyl compounds will condense with primary aromatic amines giving the anil which in the presence of acid ring closes giving a substituted quinoline [29,30]. When an ethanolic solution of 4-amino-2-carboethoxy-N-methyl-pyrrole, acetyl-acetone and concentrated hydrochloric acid was boiled under reflux 2-carboethoxy-1,5,7-trimethyl-4-azaindole was obtained by a single stage process (MP 113° - 69%).

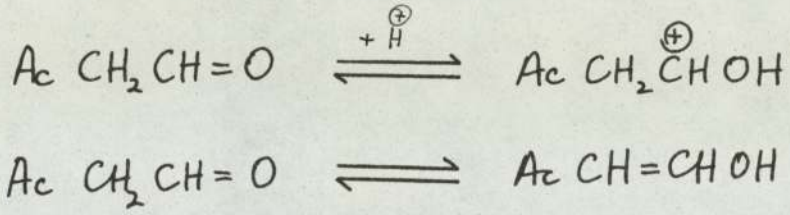


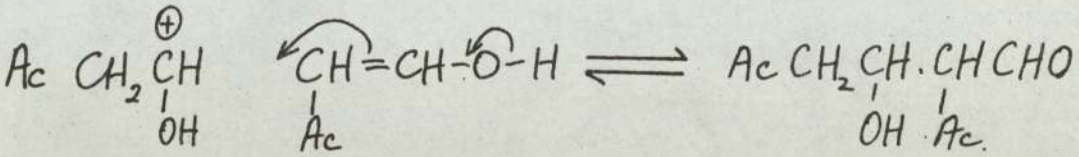
2.2 (ii) ACETYL ACETALDEHYDE

When acetyl acetaldehyde dimethyl acetal, the 4-amino-pyrrole derivative and hydrochloric acid in ethanolic solution were boiled under reflux, 6-acetyl-2-carboethoxy-1-methyl-4-azaindole (MP 180° 40%) was obtained and not the expected 2-carboethoxy-1,5-dimethyl-4-azaindole.



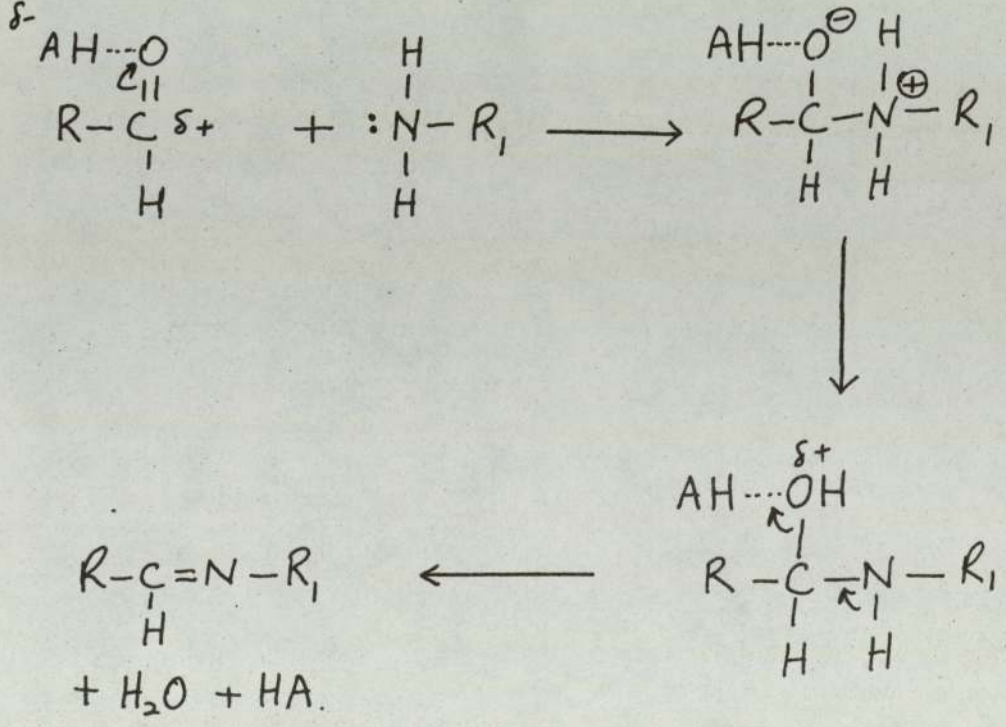
It is thought that under the acid conditions acetyl acetaldehyde undergoes an aldol type condensation. The mechanism for base catalysed aldol condensation has been clearly determined but acid catalysed condensation is less certain. It is suggested that the reaction proceeds via the conjugate acid and the enol form of the aldehyde.

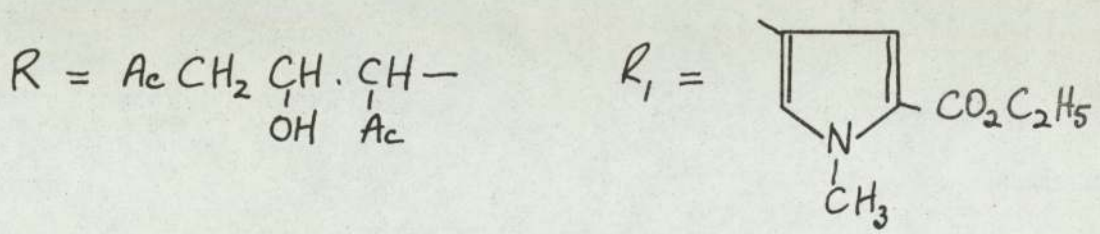




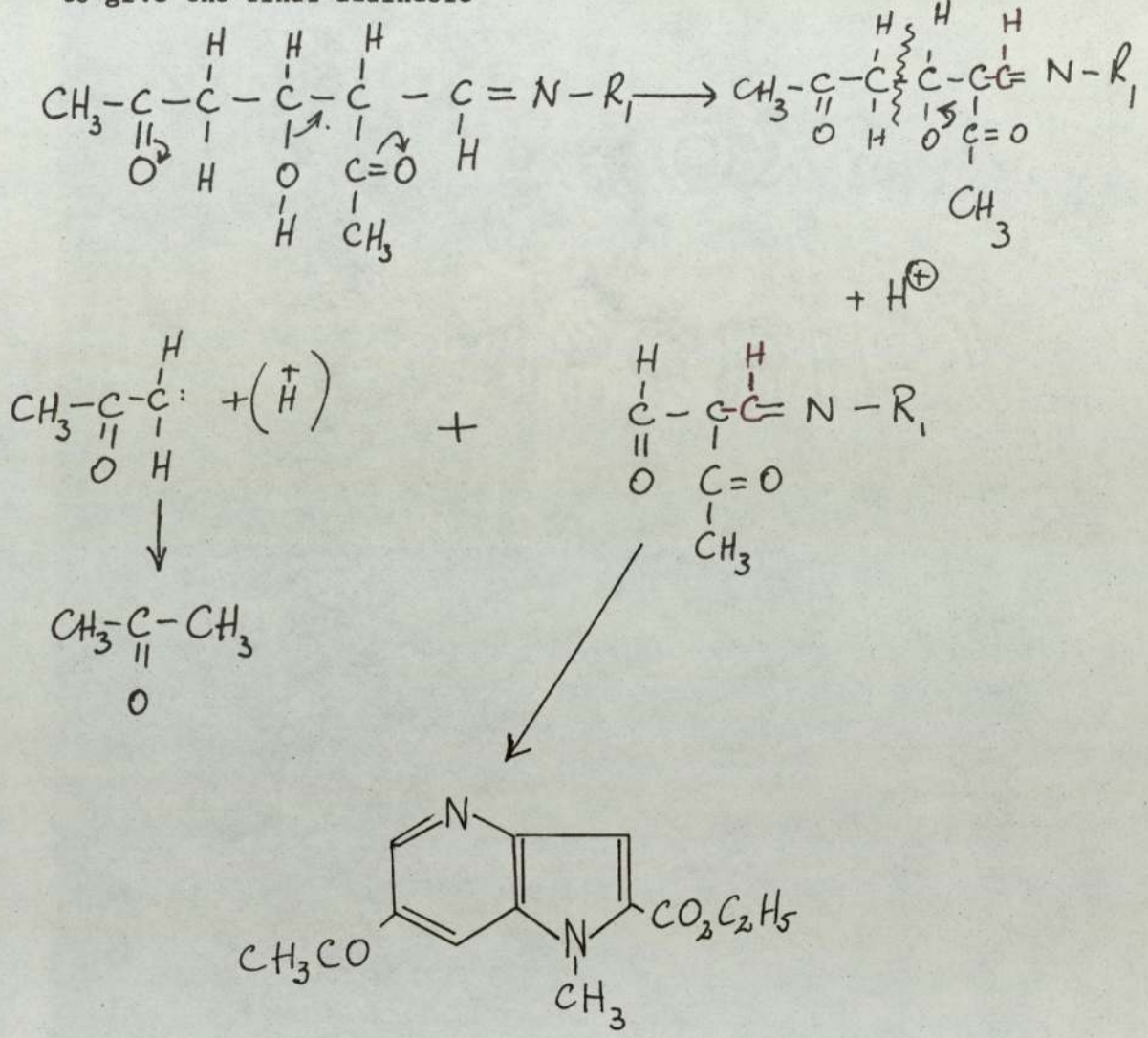
N.B. Ac = CH_3CO-

This is followed by condensation of the aldehyde function with the amine to form the Schiffs base.





Elimination of a molecule of acetone follows with ring closure to give the final azaindole



It is interesting to note that attempts at ring closure with malondialdehyde or nitro-malondialdehyde were unsuccessful and only yielded intractible tars whereas it would appear that in the reaction under consideration, after coupling with the amino function and elimination of the acetone, the product is what would have been expected if acetyl-malon-dialdehyde had been used. Analysis and mass spectra confirm the elemental composition and molecular weight. The infra red spectrum shows the presence of the acetyl carbonyl at 1660 cm^{-7}, an additional peak due to the ester carbonyl at 1700cm^{-7}.

The NMR spectrum shows the acetyl methyl as a singlet δ=2.735

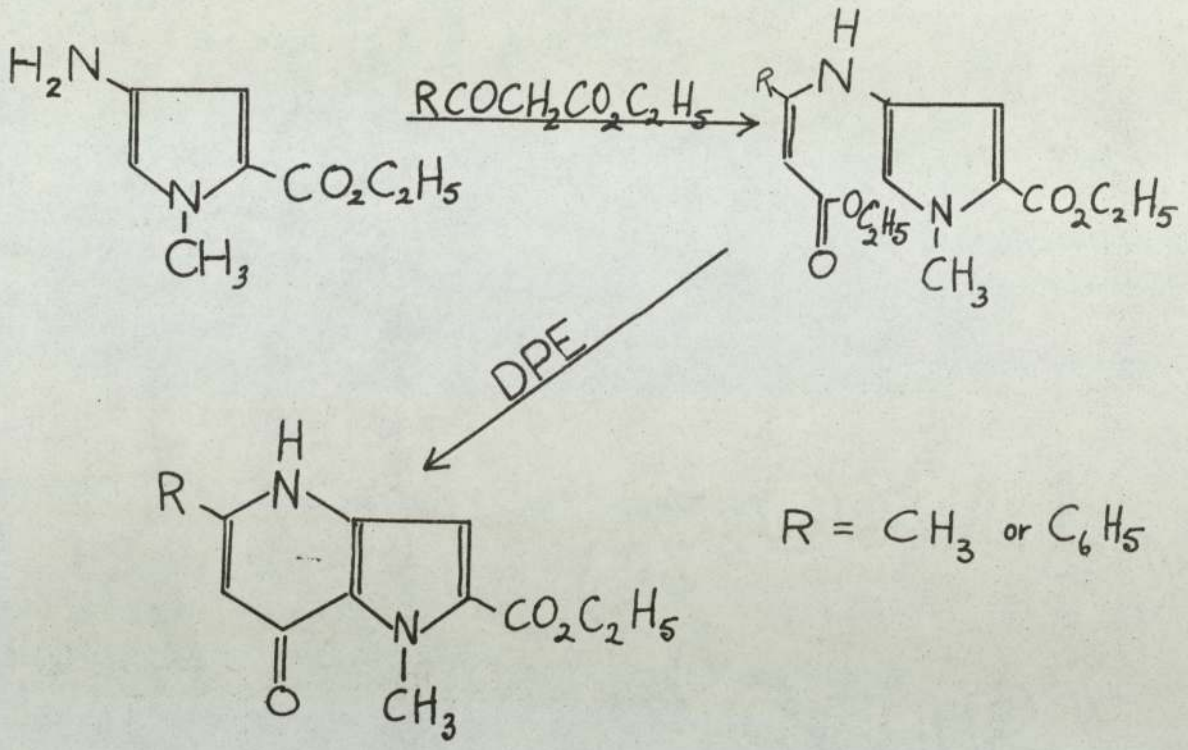
2.2 (iii) and (iv) ETHYL ACETOACETATE, ETHYL BENZOYL-ACETATE

β-keto-esters condense with aromatic amines to anils, which cyclise on heating in an inert solvent to the corresponding quinoline (Conrad-Limpach Reaction)[31,32].

Under more severe conditions at elevated temperatures keto-esters condense with primary aromatic amines to give β-keto-anilides which with strong acids yield 2-quinolones (Knorr Synthesis)[33].

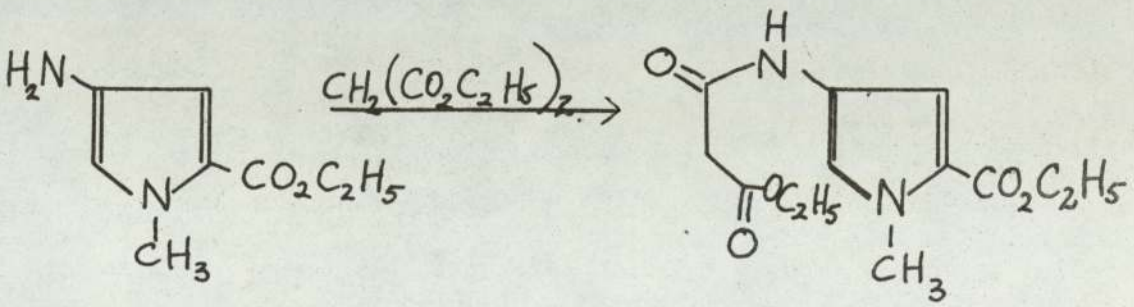
4-amino-2-carboethoxy 1-methyl-pyrrole and ethyl aceto-acetate in benzene when boiled under reflux using a Dean and Stark apparatus, condensed forming the ethyl pyrrole-amino-β-crotonate which was isolated as colourless needles MP 86°. Confirmation of the intermediate was given by the value of M^+ at 280. When the intermediate was heated in diphenyl ether cyclisation occurred readily to 2-carboethoxy-1,5-dimethyl-7-oxo-4-azaindoles.

When ethyl benzoyl-acetate was employed the condensation ring closure took place in a similar fashion. The identity of the cinnamyl intermediate was confirmed from its accurate mass.



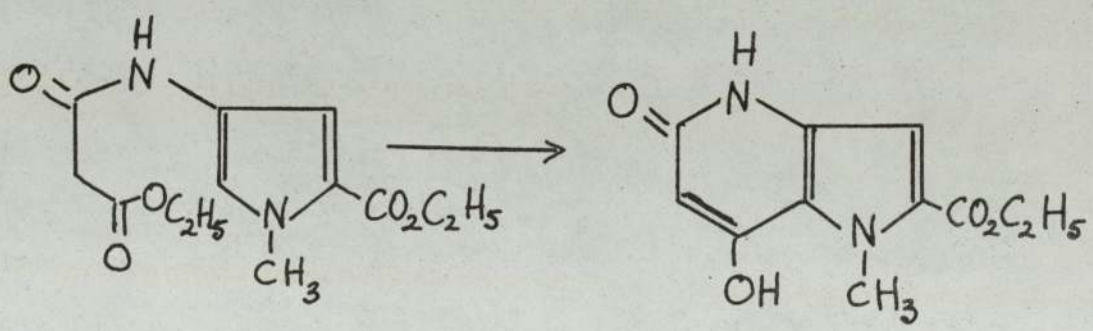
2.2 (v) DIETHYL MALONATE [34]

When 4-amino-2-carboethoxy-1-methyl-pyrrole and diethyl malonate were boiled under reflux in benzene the yield of β-keto-ester intermediate was too low to be of practical value. Diethyl malonate was used as reactant and solvent and the mixture boiled under reflux for 30 minutes. Removal of excess diethyl malonate under reduced pressure left an orange tar from which the intermediate was obtained in 34% (MP 92). A determination of the accurate mass and elemental composition confirmed the identity.



When 4-amino-2-carboethoxy-1-methyl-pyrrole and diethyl malonate were boiled under reflux for four hours it was found that slight cooling caused separation of solid. The solution was cooled and the solid removed. Distillation to reduce the volume of diethyl malonate caused further deposition of solid material proved to be the ring closed product. After recrystallisation from glacial acetic acid this was obtained as off white crystals MP. 294-6 (31%).

In the shorter reflux time producing the open chain intermediate compound, no ring closed product could be found and there was no evidence of the purple colouration indicative of oxidative decomposition of unreacted amine.

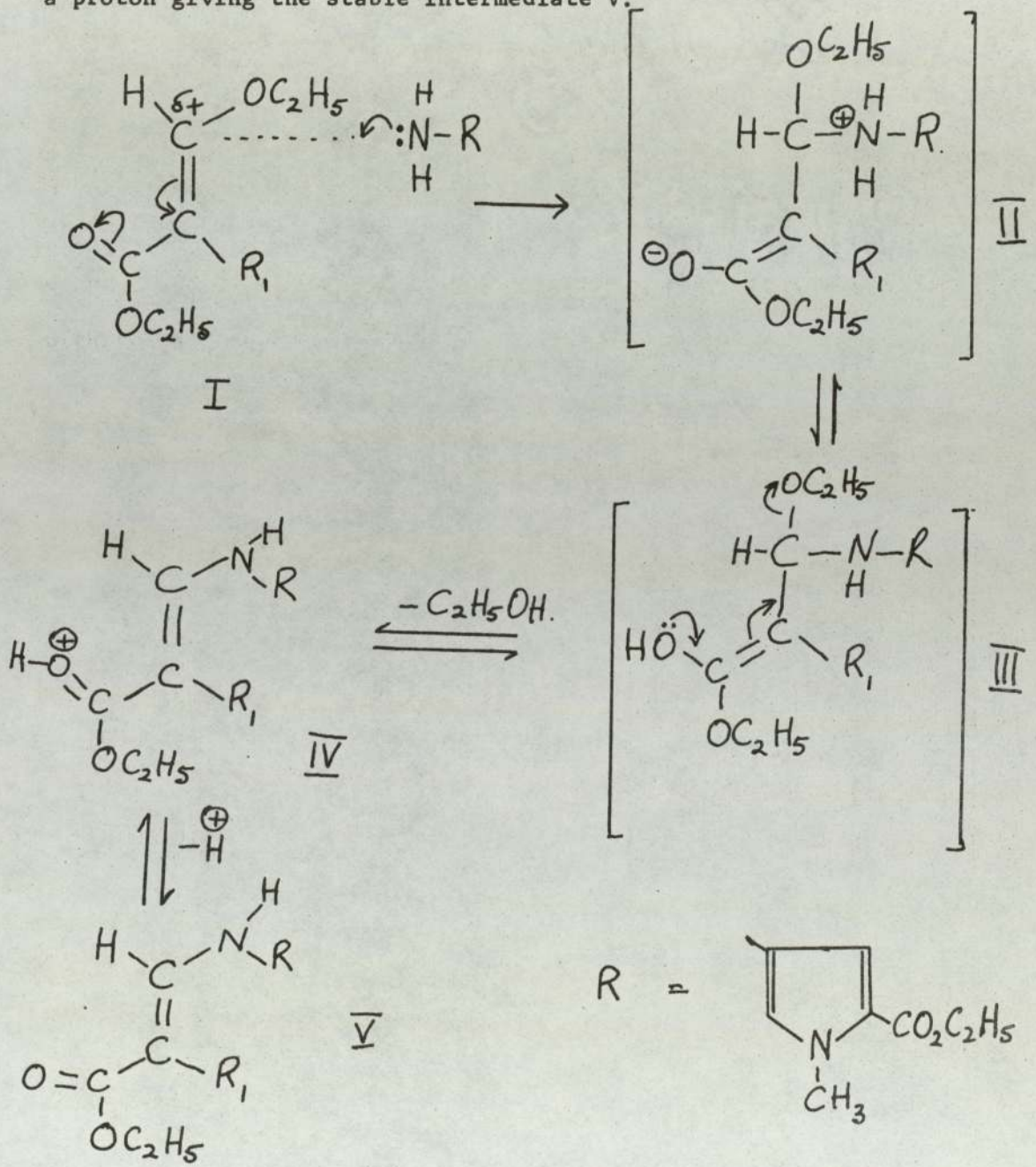


2.2 (vi) ETHYL ETHOXY METHYLENE MALONATE [35]

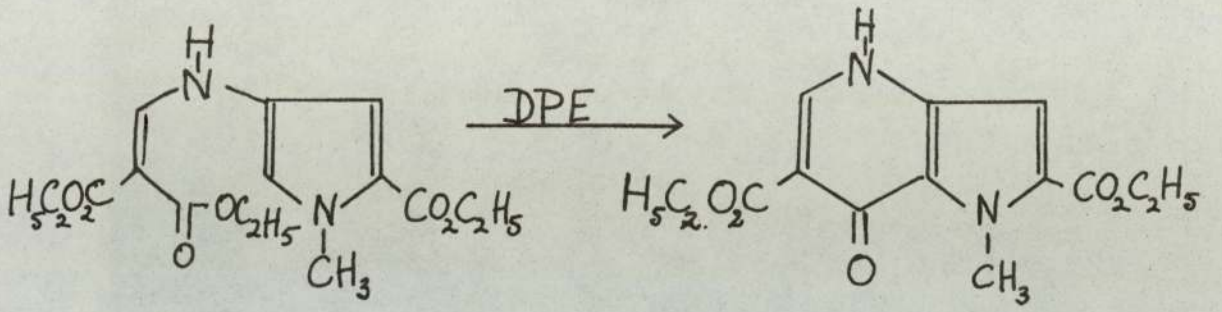
When a solution of the pyrrole amine starting material in benzene was boiled under reflux with ethyl ethoxy methylene malonate facile condensation occurred giving ethyl 2-carboethoxy-N-methyl pyrrole-4-amino methylene malonate in almost quantitative yield (MP 86° 96%).

A suggested mechanism for the condensation involves nucleophilic attack by the amino nitrogen on the electron deficient ethylenic carbon[I] giving rise to the dipolar intermediate[II] in equilibrium with the non polar form III.

This is followed by elimination of ethanol IV and finally loss of a proton giving the stable intermediate V.

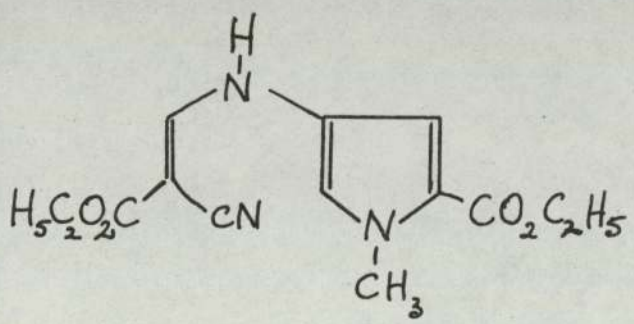


On heating the intermediate V in diphenyl ether the solution darkened rapidly. After 30 minutes the refluxing mixture was cooled and treated with petrol when a brown solid separated. The extreme insolubility of the product facilitated removal of impurities by soxhlet extraction with acetone MP 300-2 65%.



2.2 (vii) ETHYL ETHOXY METHYLENE CYANO ACETATE [36]

When ethyl ethoxy methylene cyano acetate (R_1 = CN) was used in place of ethyl ethoxy methylene malonate (R_1 = $-CO_2C_2H_5$) corresponding intermediate formed readily (MP 110 78%).



Ring closure of this intermediate could not be effected by heating in diphenyl ether as in the previous example. Acid catalysed ring closure with polyphosphoric acid was ineffective

and resulted in degradation . Attempted base catalysed ring closure with sodium ethoxide in ethanol was also unsuccessful.

When there are two carboethoxy groups on the α-carbon atom of the side chain ring closure takes place readily.

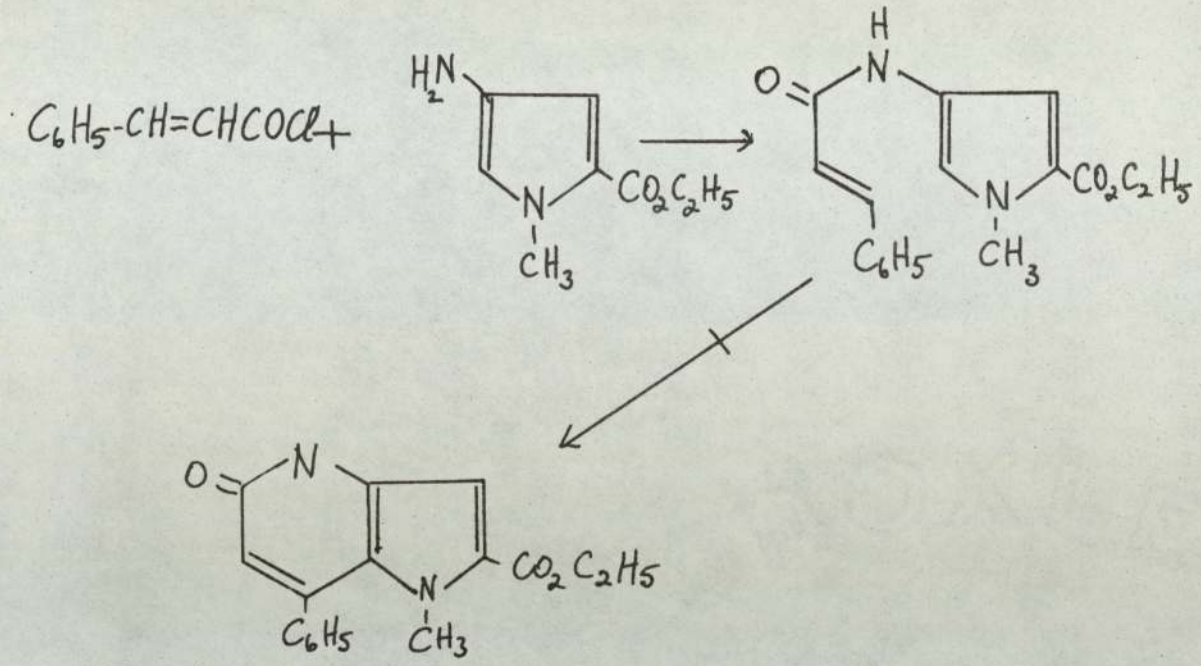
When there is a cyanide group on the α-carbon it would appear that this group, through which ring closure is unlikely, is situated next to the ring in a minimum energy orientation.

The use of a different geometric isomer of the reactant would not alter the result as from the mechanism shown in the intermediate stages (II and III) of coupling permit free rotation of the α-carbon atom.

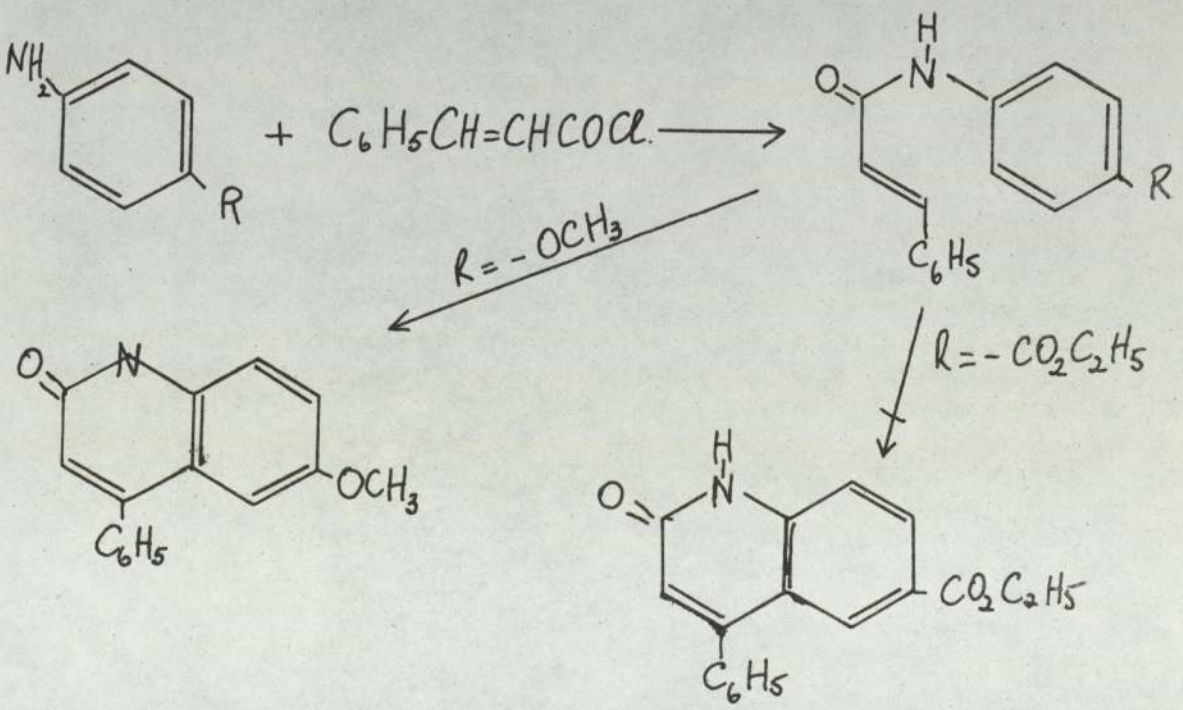
2.2 (viii) CINNAMOYL CHLORIDE [37]

Cinnamoyl chloride condenses by a Schotten-Baumann type reaction with suitable primary aromatic amines to form an N-cinnamyl intermediate. When heated in polyphosphoric acid this intermediate undergoes ring closure. There is evidence for the success of this reaction with aniline and p-methoxy-aniline.

Cinnamoyl chloride was treated with 4-amino-2-carboethoxy-pyrrole and aqueous sodium hydroxide and gave N-cinnamyl-4-amino-2-carboethoxy-pyrrole readily and in satisfactory yield. However ring closure of this intermediate could not be effected in polyphosphoric acid.



The electron withdrawing effect of the 2-carboethoxy group could deactivate the 5-carbon position of the pyrrole ring for electrophilic attack. Successful ring closures with aniline derivatives incorporated nucleophilic groups in the benzene ring. This theory was tested by condensation of cinnamoyl chloride with ethyl-p-aminobenzoate when the cinnamyl intermediate formed readily but ring closure could not be effected by any of the prescribed methods.



3. STRUCTURAL DETERMINATIONS WITH PARTICULAR REFERENCE TO TAUTOMERIC EFFECTS

3.1 INTRODUCTION

Tautomeric effects in α-and γ-hydroxy-azaindoles and in an αγ-dihydroxy-azaindole are considered in relation to the effects shown with hydroxy-pyridines and quinolines.

When a hydroxyl group is introduced into a π deficient N-hetero-aromatic nucleus the resultant substance can have properties which fall somewhere in the range which begins with pure phenols, passes through isomeric zwitterions and ends with the analogues of acid amides [38]. The state of affairs is more complex than conveyed by early literature which broadly stated that α-and γ-hydroxy derivatives are abnormal but other isomers behave as true phenols.

Methods of analysis of the tautomeric forms and the composition of the tautomeric equilibrium are now almost exclusively physical. The use of chemical methods of analysis is virtually extinct for chemical combination with one of the components of a tautomeric equilibrium results in a shift in the equilibrium and can very easily give a false impression of the tautomeric balance. This effect is emphasised if one component is particularly reactive and is rapidly reproduced by the shift in the equilibrium because of reaction. Chemical analytical techniques can be of use if the reaction is such that different products may be obtained by a change in reaction conditions and that a new equilibrium is established only very slowly [39].

Physical methods in general do not upset equilibria and the techniques employed may be classified as either 'direct or 'indirect'. The principal direct methods are Infra Red Spectra and Nuclear Magnetic Resonance. Their most valuable features include speed of obtaining results and also that results can be obtained without the need for the preparation of model compounds.

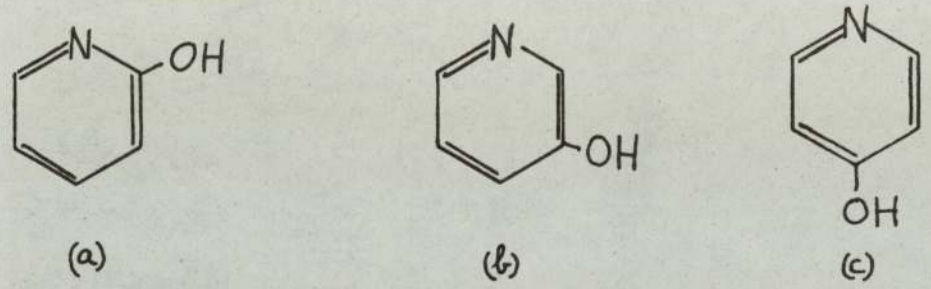
If two tautomeric forms of a compound give rise to peaks so close that they overlap giving a broad signal then the two peaks may be separated if the rate of change between the two tautomeric forms is slow compared with the frequency difference. The rate of change between the tautomeric forms may be slowed by cooling the sample tube in the probe.

The reliability of the results of Infra Red Spectra have at times been in question and there are many cases where results have been inconclusive and erroneous conclusions drawn [40].

Indirect methods are more time consuming but the results are generally more conclusive and less subject to error. Essentially the main feature of the method involves the synthesis of reference compounds in which each tautomeric structure is immobilised by replacing the free hydrogen atom by a fixed methyl group. The substance and its methyl derivatives are then examined by Ultra-violet spectroscopy. Determination of the ionisation constants of the substance in the hydrogen form and its methyl derivatives is invaluable. A characteristic feature of the methyl group is virtual transparency to ultra violet radiation and on the smallness and

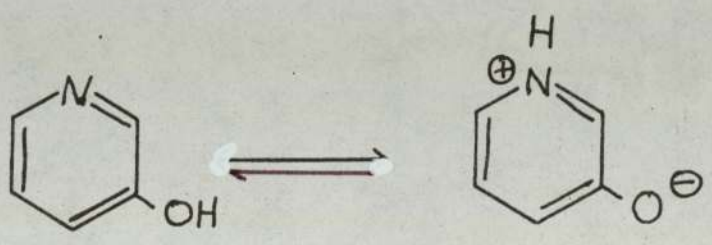
predictability of its effect on the ionisation constant. It is also possible to obtain the ratio of amide to enol forms at equilibrium by determination of the pK values for the O-methylated form and the hydroxyl form and applying them to the Eberts Equation.

3.2 HYDROXY PYRIDINES Three isomers exist

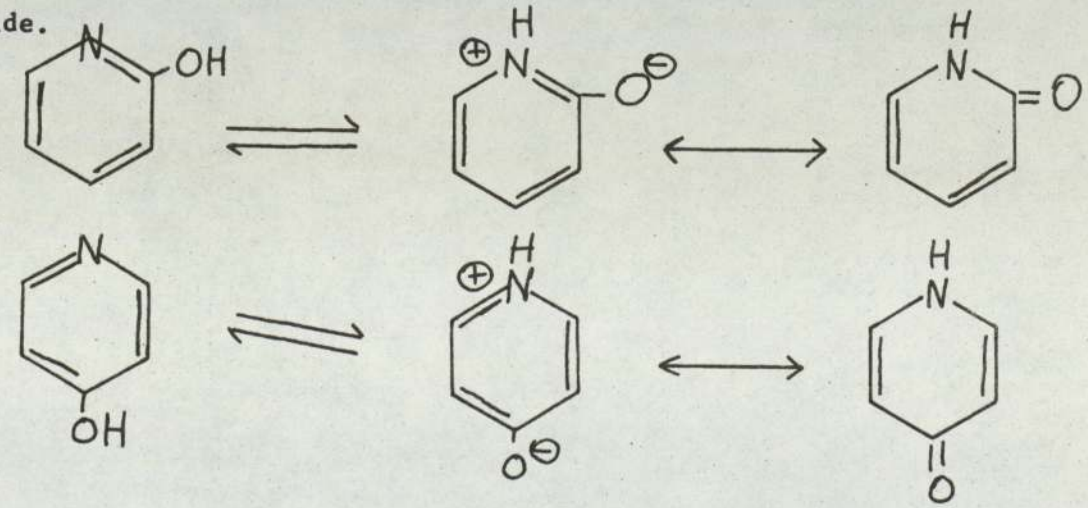


(a) (b) (c)

(a) α-or 2-hydroxy pyridine (b) β-or 3-hydroxy pyridine and (c) γ-or 4-hydroxy pyridine. 3-hydroxy pyridine can exist as the normal phenol and the zwitterion.



2-and 4-hydroxy pyridines can exist as the phenol, zwitterion and amide.



Valency considerations do not allow the 3-hydroxy~~-~~pyridine to exist as an amide.

CHEMICAL BEHAVIOUR: The three isomers react with neutral ferric chloride. 2-and 3-hydroxy~~-~~pyridine give a red colour and 4-hydroxy~~-~~pyridine a yellow colour, indications of the presence of a phenolic hydroxyl group.

All three isomers readily undergo nuclear electrophilic substitution in exactly the same fashion as phenol. They can be nitrated, sulphonated, halogenated or coupled with diazotised aniline[41,42].

Acylation of the three isomers takes place readily on the oxygen atom and in good yield[43].

When treated with alkylating agents 2-hydroxy~~-~~pyridine shows the greatest divergence from a phenol. Methylation of phenol with methyl iodide or dimethyl sulphate in alkaline solution gives the methyl ether, anisole in very good yield.

Similar treatment of 2-hydroxy~~-~~pyridine gives predominently N-methyl-2-pyridone[44]. In general exclusive N-alkylation occurs in alkaline conditions with an alkyl halide or dimethyl sulphate[45-49]. Under anhydrous conditions with methyl iodide or dimethyl sulphate doubly bound nitrogen = N - is methylated more readily than singly bound nitrogen. $\rangle$N - and quaternisation usually results. In order that facile N-methylation may take place the basic environment is necessary so that the nitrogen exists as an anion.

Treatment of the silver salt of 2-hydroxy~~-~~pyridine with methyl iodide gives a mixture of approximately equal amounts of 2-methoxy-pyridine and N-methyl-2-pyridone.

Treatment of 3-hydroxy~~-~~pyridine with methyl iodide gives the quaternary methiodide [50].

The action of diazomethane on the hydroxy~~-~~pyridines is governed by the conditions of reaction but tends to give N-methyl and O-methyl products but 2- and 3-hydroxy~~-~~pyridines methylate more on the nitrogen than on the oxygen [51].

When 2-and 4-hydroxy~~-~~pyridine is treated with phosphorus oxychloride the corresponding 2- and 4-chloro-compounds are obtained but the 3-chloro-isomer is not obtained by similar treatment of 3-hydroxy-pyridine.

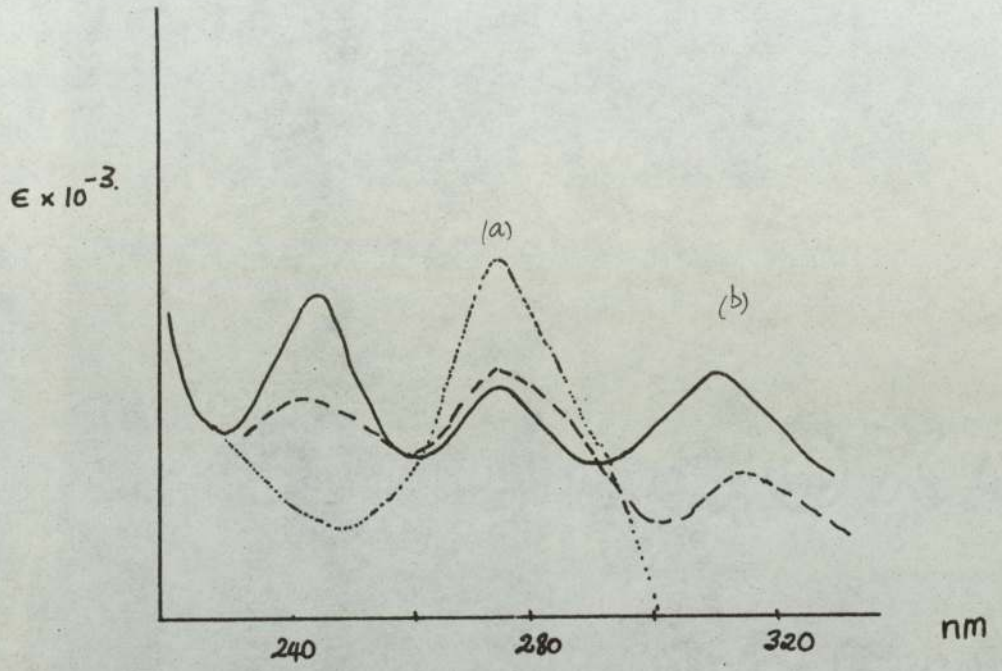
2- and 4-methoxy~~-~~pyridine are isomerised by heating to 1-methyl-2- and 4-pyridone respectively [52].

PHYSICAL DIFFERENCES

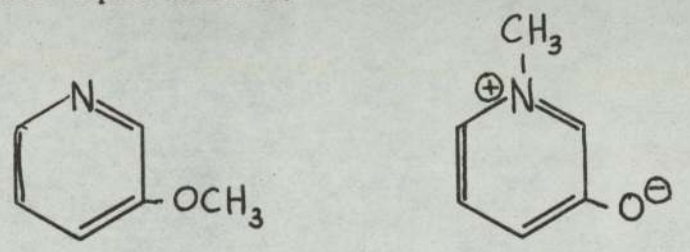
The UV spectrum of 3-hydroxy~~-~~pyridine in neutral aqueous solution shows two peaks; that at 313 nm agrees with the sole peak shown for quaternised 3-hydroxy~~-~~pyridine as the methochloride, and the other at 277 nm agrees with the peak of 3-methoxy~~-~~pyridine.

When the dielectric constant of the solution is lowered by the

addition of alcohol or dioxan the 313 nm peak disappears and the 277 nm peak rises to double the intensity [53].

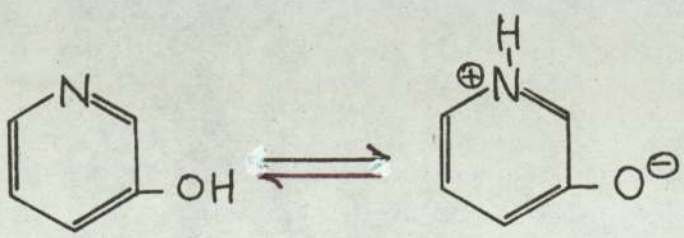


It is evident therefore that in neutral solution 3-hydroxy pyridine is a mixture of the normal phenol and the corresponding zwitterion in almost equal amounts.



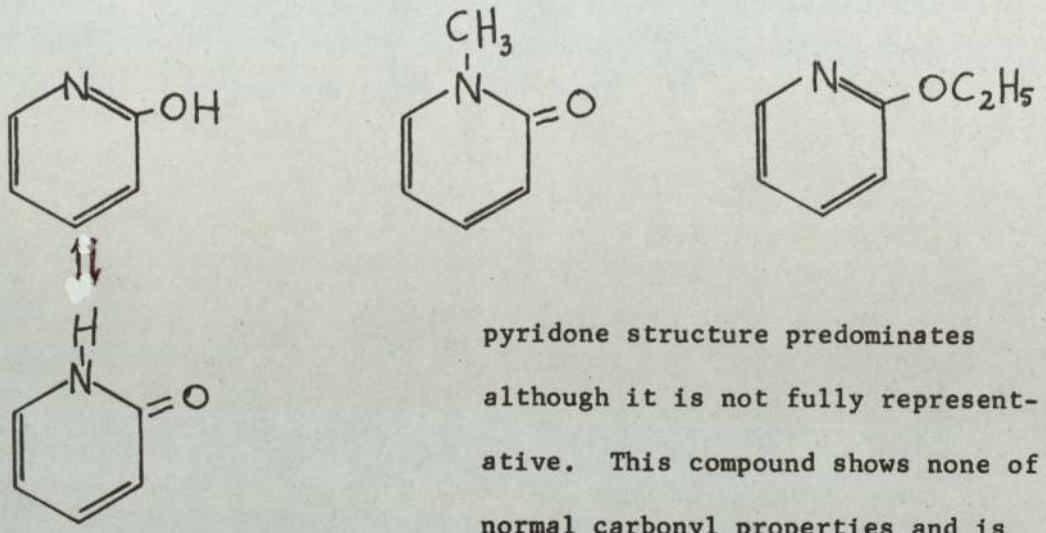
(a) ------ Intensification. ..... of OH peak with reduction of dielectric.

(b) — — — — disappearance of zwitterion peak with. with reduction of dielectric.

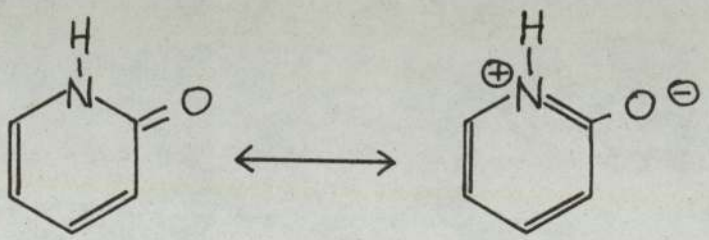


(a) (b)

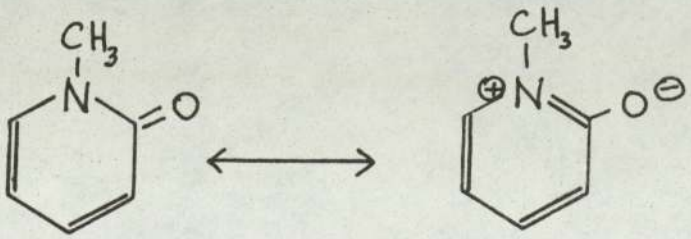
In methanol the ultraviolet spectrum of 2-hydroxy-pyridine is very similar to the spectrum of N-methyl-2-pyridone but significantly different from that of 2-ethoxy-pyridine [49]. It would appear, therefore, that the



pyridone structure predominates although it is not fully representative. This compound shows none of normal carbonyl properties and is very weakly basic. The UV spectrum shows an aromatic type of absorption which emphasises the importance of the resonance structures below.

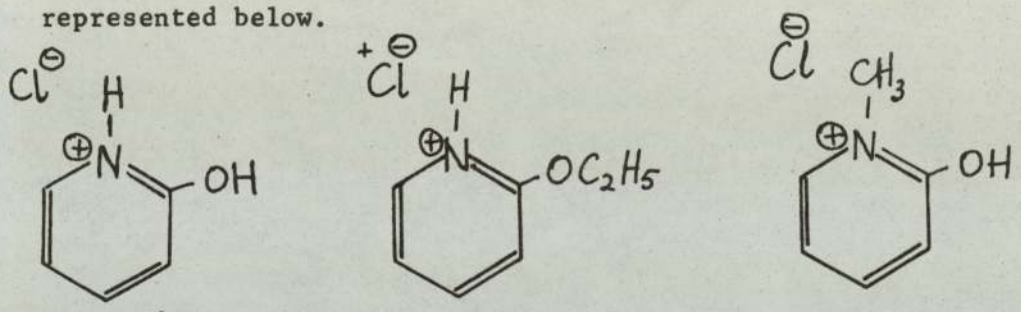


N-methyl-2-pyridone also shows the same aromatic absorption undoubtedly due to the resonance.

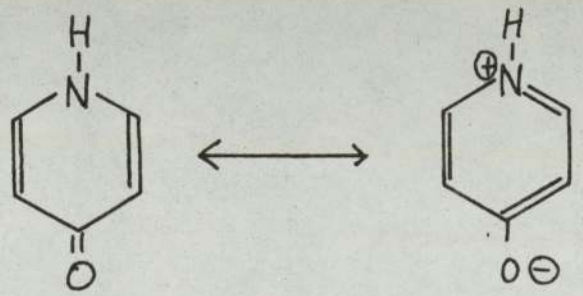


The addition of sodium methoxide has little effect on the spectrum of 2-hydroxy~~-~~pyridine.

In hydrochloric acid the spectrum conforms to the aromatic ring system and the spectra of 2-hydroxy~~-~~pyridine, 2-methoxy~~-~~pyridine, O-ethyl and N-methyl derivatives show striking similarities leaving no doubt that the conjugate acids of these three compounds are as represented below.



The ultraviolet spectrum of 4-hydroxy~~-~~pyridine is analogous to the 2-isomer indicating great preponderance of the amide structure and best represented as a resonance hybrid.



The spectra of the N- and O-alkyl derivatives correspond with the results obtained with 2-hydroxy~~-~~pyridine and the spectra of the three compounds in hydrochloric acid show the same benzenoid characteristics as above.

One difference shown by 4-hydroxy~~-~~pyridine is that in base the spectrum differs greatly from that of N-methyl-4-pyridone. Although it has a similar shape to that of 4-methoxy~~-~~pyridine it is shifted to longer wavelengths.

Determination of the basic ionisation constants for the three isomeric hydroxy~~-~~pyridines and their N- and O-methyl derivatives further substantiates the preferred tautomeric forms. Examination of the following table indicates that the basic ionisation constant approximates to that of the N-methyl derivative far more closely than to the O-methyl derivative. The small difference in value between the ionisation constant of the hydroxy~~-~~pyridine and the N-methyl derivative permits the calculation of the equilibrium of amide to enol.

Substance	pKa in water at 20°	Tautomeric Ratio amide/enol
2-hydroxy~~-~~pyridine	0.75; 11.62	340
O-CH_3	3.28	-
N-CH_3	0.32	-
3-hydroxy~~-~~pyridine	4.86; 8.72	1
O-CH_3	4.88	-
N-CH_3	4.96	-
4-hydroxy~~-~~pyridine	3.27; 11.09	2,200
O-CH_3	6.62	-
N-CH_3	3.32	-

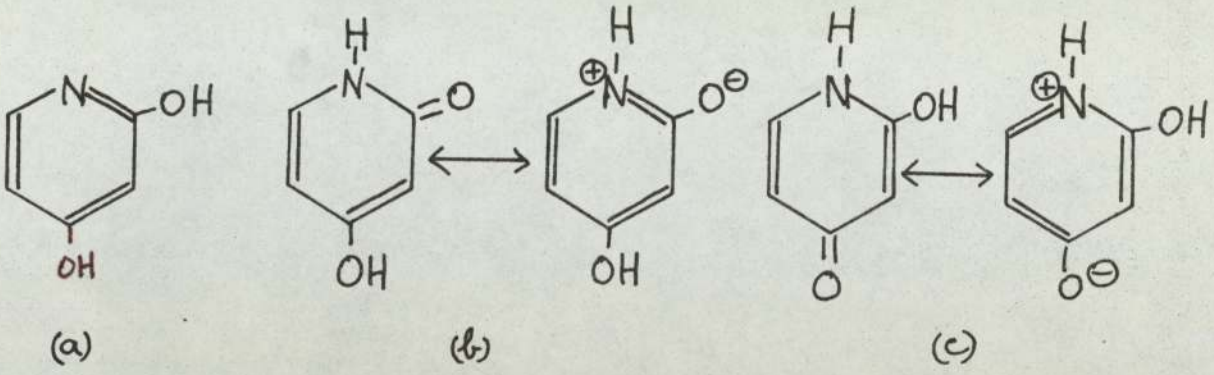
The ratio of amide/enol is approximately 6.5 times greater in the

4-isomer than in the 2-isomer. This is attributed to the more stable p-quinoidal structure than the O-quinoidal structure of the 2-pyridone.

Infrared spectra corroberate the preponderance of the amide form although these were taken as Nujol Mills and therefore correspond to the solid state[54]. The infrared spectra of 2-hydroxy-pyridine and 1-methyl-2-pyridone both show a characteristic carbonyl absorption which is absent in 2-methoxy-pyridine. Later infrared spectra supplemented by Raman spectra led to the same conclusions[55]. Solid state studies also indicated N-H---O intermolecular hydrogen bonding.

The resonance state existing between the amide and zwitterion is shown for the 2- and 4-isomers to correspond in aqueous solution to 15-20% zwitterion. Infrared studies showed that the CO band had at the most 15-20% single bond character a fact which places 15-20% as the upper limit of the zwitterion contribution[56]. In the solid state X-ray crystallographic measurements on 2-hydroxy-pyridine indicate that the zwitterionic structure contributes about 50%.

When a π deficient heteroaromatic molecule such as pyridine possesses both a 2 - and 4-hydroxy group one of them must be enolic. The true amide is preferred to the vinylogous amide, presumably because the greater change separation in the latter (in the zwitterionic contribution)permits less resonance[58].



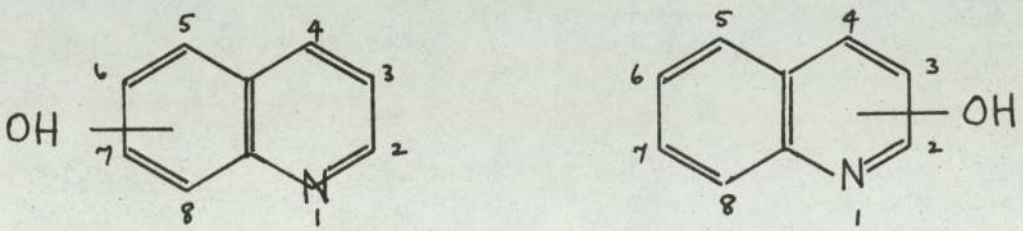
(a) (b) (c)

The three possible structures are shown and from examination of the ultraviolet spectra in aqueous alcohol it is found that structure (b) predominates.

This is established as the spectrum of 2, 4-dihydroxy~~-~~pyridine resembles that of 4-methoxy-N-methyl-2-pyridone more so than 2-methoxy-N-methyl-4-pyridone [59].

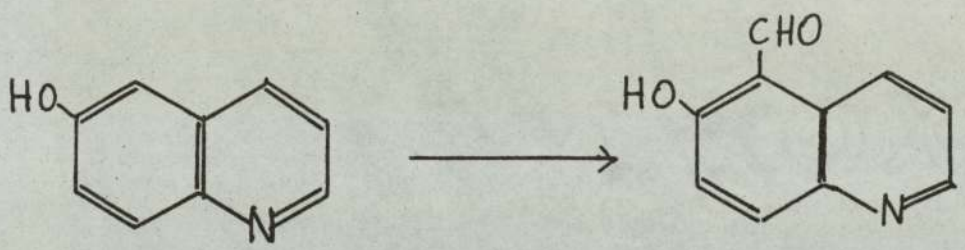
3.3 TAUTOMERISM IN THE HYDROXY~~-~~QUINOLINES

The hydroxy~~-~~quinolines may be classified conveniently into those which bear formal resemblance to (a) α-naphthol (b) β-naphthol (c) those which can be written as derivatives of 2- and 4-pyridones [59] In the context of this discussion group (c) is of most interest.



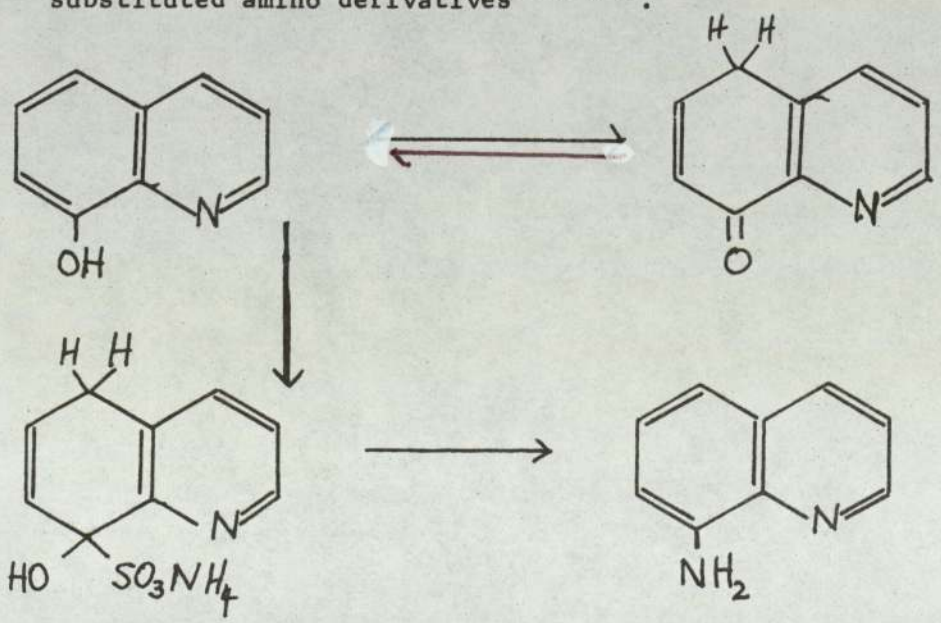
CHEMICAL BEHAVIOUR The reactions of 4, 5, 6, 7, 8-hydroxy-quinoline and 3-hydroxy-quinoline indicate that these isomers exist as true phenols. They all give characteristic colours with ferric chloride solution and some of their important reactions are given below.

6-hydroxy-quinoline undergoes the Reimer-Tiemann reaction to give 5-formyl-6-hydroxy-quinoline.



Corresponding compounds are obtained when 7-,8-hydroxy-quinolines are employed [61,62].

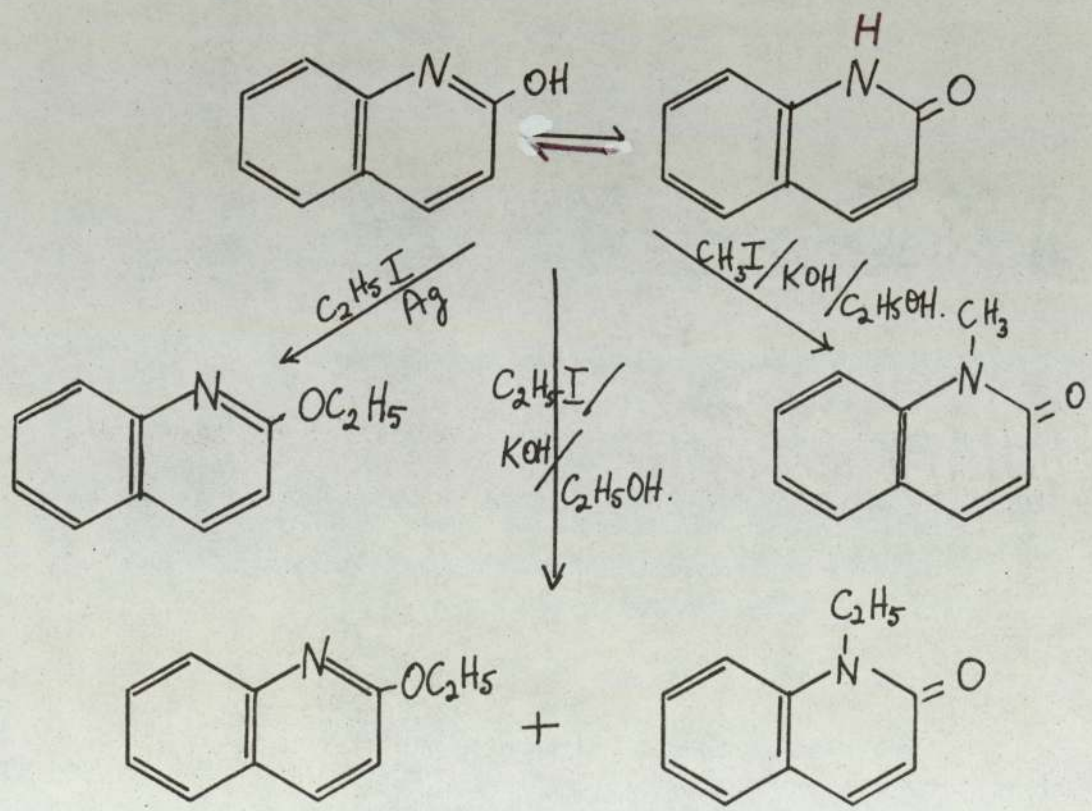
The Bucherer reaction is given by all the 'aromatic' hydroxy-quinolines in complete analogy to naphthols giving amines or substituted amino derivatives[63,64,65].



The picture with 2- and 4-hydroxy quinoline isomers is not so clear as with the 'aromatic' hydroxy quinolines. There is much chemical evidence for the presence of a phenolic hydroxyl group although the physical evidence favours preponderance of the amide form.

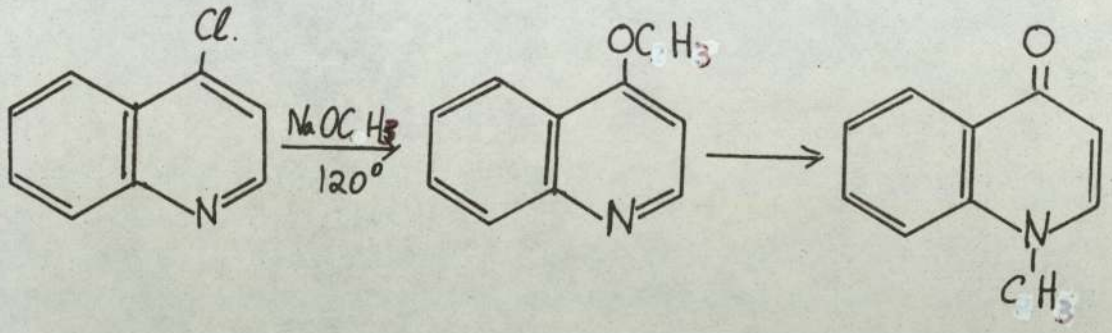
When treated with neutral ferric chloride solution 2-hydroxy-quinoline gives a brown colour and 4-hydroxy quinoline a red colour. This was initially used to suggest that the 4-isomer was in fact more phenolic than the 2-isomer, a fact substantiated by further reactions.

Alkylating agents give rise to N- and O-alkyl products the composition depending on the conditions employed. This is summarised by the following equations [66-72].

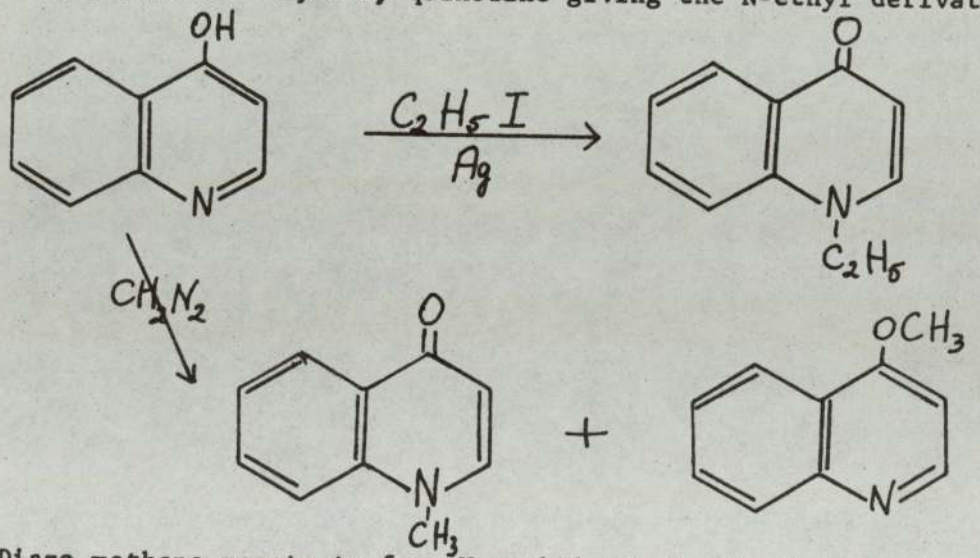


In a similar manner to 2-methoxy pyridine, 2-methoxy quinoline readily rearranges to N-methyl-2-quinolone on heating [73].

4-hydroxy-quinolines form the N-alkyl derivatives more easily than the 2-isomer. When 4-chloro-quinoline is heated with sodium methoxide, 4-methoxy-quinoline is formed but this rearranges to N-methyl-4-quinolone [74].



In contrast to 2-hydroxy-quinoline ethyl iodide reacts with the silver salt of 4-hydroxy-quinoline giving the N-ethyl derivative.

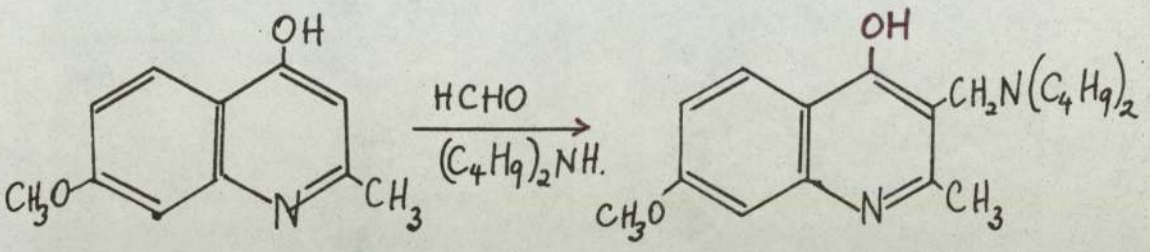


Diazo methane reacts to form N-methyl and O-methyl derivatives [75].

The Reimer-Tiemann reaction which proceeds very favourable with the aromatic hydroxy-phenols is much less successful with 4-hydroxy quinoline [76].

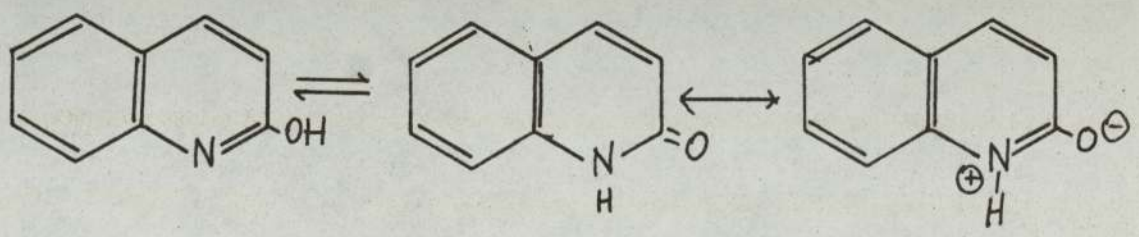
The Mannich reaction applied to 4-hydroxy-quinoline takes the usual course consistent with the presence of a phenolic hydroxyl

group[77]. This particular reaction was applied to 7-methoxy-2-methyl-4-hydroxy quinoline by the addition of formalin and dibutylamine to the solution under reflux, giving 3-dibutylamino-2-methyl-7-methoxy-4-hydroxy quinoline.

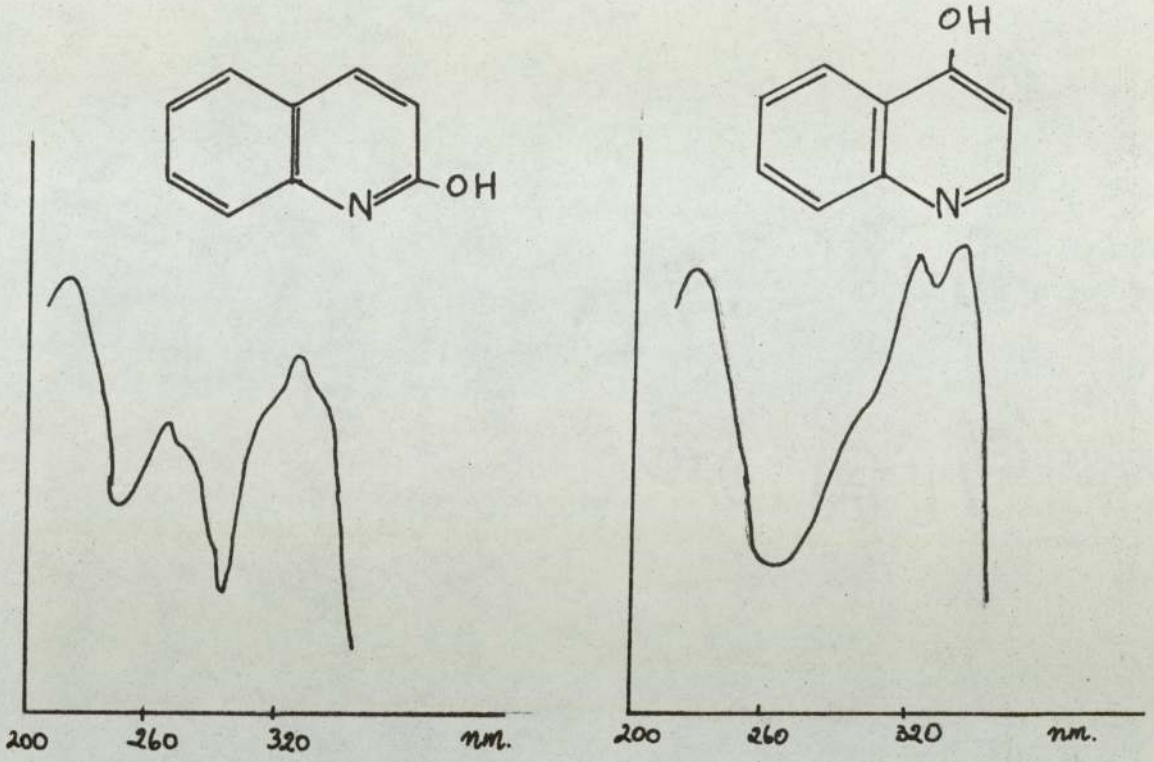


PHYSICAL METHODS

The structure of 2-hydroxy quinoline has been discussed by Huisgen[78] and the similarity of its ultraviolet spectra to that of the N-methyl derivative suggests preponderance of the cyclic amide [79,80]. The solubility in both acid and alkali indicates the importance of the zwitterionic structure.



This was substantiated when the spectra of the O-and N-methyl-derivative were examined by Ewing and Steck [81,82]. The preponderance of the amide structure in 2- and 4-hydroxy pyridine and the lack of phenolic group is indicated by the absence of any bathochromic shift in alkaline solution.



Determination of the basic ionisation constants of the 2- and 4-hydroxy-quinolines emphasise the close similarity of the N-methyl-derivatives to the parent and the difference shown by the O-methyl-derivatives.

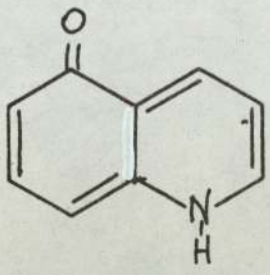
Calculation of the amide/enol ratio in 3-hydroxy-quinoline confirms the extent of phenolic properties while the ratios for 2- and 4-hydroxy-quinolines show the preponderance of amide form. It is interesting that chemical reactions suggest the 4-isomer is more phenolic than the 2-isomer and yet from the results shown the amide ratio between the 4-and 2-isomers is 8 to 1.

Substance	Basic ionisation constant	Amide/enol
2-hydroxy-quinoline	-0.31, 11.74	3000
O-CH_3	3.17	
N-CH_3	-0.71	
3-hydroxy-quinoline	4.3, 8.6	0.08
4-hydroxy-quinoline	2.27, 11.25	24,000
O-CH_3	6.65	
N-CH_3	2.46	

Study of the Infra Red Spectra of 2-hydroxy-quinoline shows that in the solid state it exists predominently as the amide form [84]. A study of a wide range of N-heterocyclic hydroxy compounds in the solid state, chloroform and carbon tetrachloride by Mason show that all compounds with a hydroxyl group α or γ to a ring nitrogen absorb in the amide C = O (1630 - 1780 cm^{-1}) and N-H (3360 - 3500 cm^{-1}) stretching vibration regions. Compounds with an O-H group which is neither α or γ to the ring nitrogen give rise in solution to a sharp band near 3600 cm^{-1} due to free OH stretching vibration or if the hydroxyl group is peri to a ring nitrogen give a broad band (3395-3470 cm^{-1}) due to an intra molecular hydrogen bonded O-H stretching vibration. The latter bands have widths in dilute solution at half extinction of 60 - 100 cm^{-1} whilst compounds with amide structures give N-H bands with half widths 15 - 30 cm^{-1} under the same conditions, allowing both types to be distinguished [85].

Hydroxy compounds with a hydroxyl group which is neither α-nor γ-

to the ring nitrogen will have an enolic structure and will not show an amide carbonyl stretching vibration even when a vinylogous amide structure is possible, e.g.



The amide carbonyl stretching vibration in α- and γ- hydroxy-quinolines is usually at a lower frequency in the solid state than in solution.

3.4 PHYSICAL METHODS OF STRUCTURE DETERMINATION OF AZAINDOLES

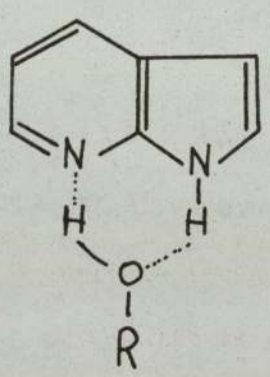
(i) INFRARED SPECTRA

Few complete spectra have been reported for azaindoles although some partial band assignments have been made. In most cases only the functional group frequencies were recorded [86]. Infrared spectra of the four parent azaindoles have been reported by Katritsky and Ambler [87] with detailed assignments of the particular absorptions [88-93].

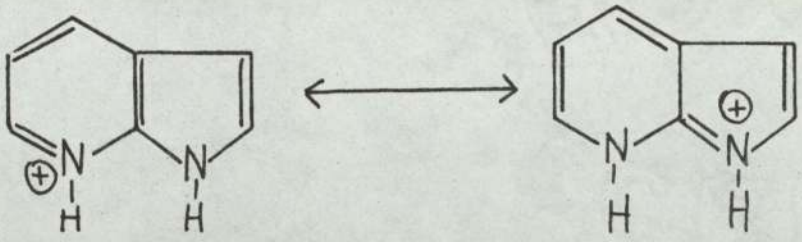
(ii) ULTRAVIOLET SPECTRA

The ultraviolet spectra of azaindoles have been more thoroughly investigated and tend to split into three bands I, II and III to $\pi \rightarrow \pi^*$ transitions and correspond also to the three principal bands of indole. These have been related to the β, p and α bands of pyridine and benzene by Mason [94].

Most of the data reported are for hydroxylic solvents which do not often show separation of the II and III bands. Adler and Albert [95] as well as Mason have discussed the spectral data of the parent azaindoles in water and as cations. The II or p band arises from a different transition to the α band and moves independently from it, showing greater sensitivity to conjugative effects and hydrogen banding [96]. When only one band at high wavelength is apparent it is assigned to band III assuming it to be a mixture of p and α bands. This was verified by examination of the spectrum of 7-azaindole where in hydroxylic solvent the p band lies under the α band because of hydrogen bonding, when examining the spectrum in heptane fine structure similar to that seen with indole in inert solvents is apparent. The same could be expected for 4-azaindole and the other isomers but their insolubility in heptane or cyclohexane prevents this. There is little difference between the spectra in dichloro-methane to that in water.

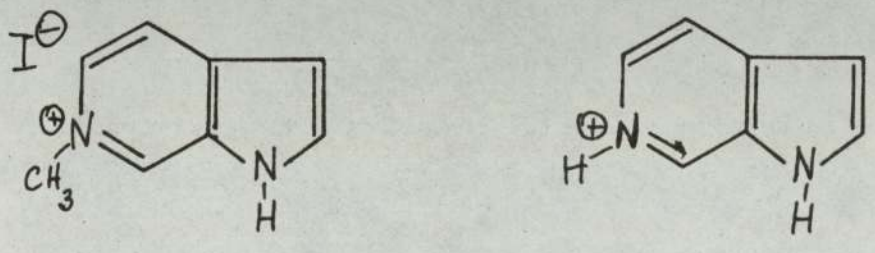


Examination of the spectra of 4- and 6-azaindoles in water shows a large red shift of band III on acidification, a feature characteristic of 3-amino-pyridine. 7-azaindole does not show as large a red shift in the cation as 2-amino-pyridine indicating that resonance stabilisation to the ortho quinonoid form is not present to any large extent.

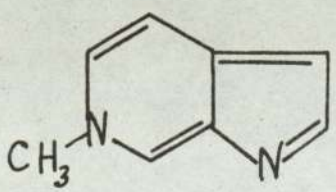


The spectra of 7-benzyl and 7-p-nitro benzyl derivatives were studied by Saxena [97]. In addition to showing the maxima were solvent dependent, giving a blue shift in hydroxylic solvents, he suggested that the long wavelength absorption is due in part to the presence of a betaine form where N(7) carries a positive charge and the unsubstituted N(1) a negative charge.

The ultraviolet spectra of apoharmine (7-methyl-6-azaindole)-methodide was studied and in ethanol resembles that of the 6-azaindole cation,



whereas in alcoholic alkali there is a red shift to 385 nm being characteristic of the para quinonoid form.



The tautomeric 6-hydroxy-4-methyl-7-azaindole shows a shift to longer wavelength, which is characteristic of 2-hydroxy-pyridine, as the neutral molecule or of 1-methyl-2-pyridone. The degree of tautomerisation is solvent dependent and Yakhontov et al.[98] have determined the ratio of tautomers from the position of the ultra-violet absorption maximum. The band at 296 nm for 6-methoxy-1,4-dimethyl-7-azaindole shifts to 327 nm for the 6-hydroxy compound in 75% ethanol where 99% of the amide form is present. If the solvent is changed to 15/85% ethanol/dioxan the amide/enol ratio falls to 0.32.

3.4 (iii) NUCLEAR MAGNETIC RESONANCE SPECTRA

The NMR spectra of azaindoles have received little attention. Frydman et al [99] reported the spectrum of 2-carboethoxy-5-methoxy-6-azaindole showing peaks for 3-H, 4-H and 7-H in $CDCl_3$ at 7.1, 7.2 and 8.78 respectively. Spectra of the parent azaindoles and the three methyl-7-azaindoles were determined by Albert and Willette[100] in $CDCl_3$ and DCl/H_2O and are listed below.

Compound	Solvent	Chemical Shift					
		2H	3H	4H	5H	6H	7H
4-azaindole	$CDCl_3$	7.56	6.78	-	8.54	7.14	7.76
	DCl/H_2O	7.91	6.62	-	8.34	7.46	8.26
5-azaindole	CD/Cl_3	7.38	6.7	9.2	-	8.34	7.39
	DCl/H_2O	7.77	6.94	8.9	-	8.21	7.78
6-azaindole	$CDCl_3$	7.49	6.6	7.63	8.3	-	8.88
	DCl/H_2O	8.09	6.84	7.98	8.18	-	8.79

continued

Compound	Solvent	Chemical Shift					
		2H	3H	4H	5H	6H	7H
7-azaindole	$CDCl_3$	7.42	6.52	8.0	7.1	8.39	-
	DCl/H_2O	7.58	6.71	8.47	7.44	8.26	-
4-methyl	$CDCl_3$	7.39	6.54	2.58	6.92	8.28	-
	DCl/H_2O	7.26	6.53	2.5	7.11	7.99	-
5-methyl	$CDCl_3$	7.38	6.39	7.79	2.44	8.24	-
	DCl/H_2O	7.53	6.56	7.97	2.42	8.12	-
6-methyl	$CDCl_3$	7.34	6.48	2.86	6.95	2.7	-
	DCl/H_2O	7.45	6.61	8.22	7.15	2.67	-

The chemical shifts for each proton is in keeping with its position relative to the pyridine nitrogen, with the order towards high field being α-, γ-, β-hydrogens. This is the same as in pyridine.

The only case of apparent 2, 6 coupling is in the DCl/D_2O spectrum of 5-azaindole where the 4-and 6-protons are split in addition to their coupling with the 7-H. The 6-H appears as a pair of doublets and the 4-H a doubly split singlet.

Unlike indole, the 2-and 3-protons couple with a large enough splitting (3-4 c/sec) that when coupling with the N-H proton occurs it gives rise to distinct pairs for each proton. One exception is noted in the $CDCl_3$ spectrum of 4-azaindole where the 2-H appears as a partially resolved, broad doublet. Greater resolution shows it split, presumably by the N-H proton. The 3-H also appears as a broad doublet. In DCl/D_2O these peaks appear as a sharp doublet and a pair of doublets respectively.

Interestingly no splitting of the 2-H and 3-H by the N-H proton was observed in the spectra of 7-azaindole. The N-H proton was found as a low broad hump at 12.1 - 12.3δ corresponding to that seen in indole at approximately 10δ.

3.5 STRUCTURAL DETERMINATIONS OF 4-AZAINDOLES

Assignation of the structures of the prepared 4-azaindoles was attempted by the physical methods indicated below. The very low solubilities of these compounds in organic solvents imposed a severe limitation on the ease of study and the methods applicable.

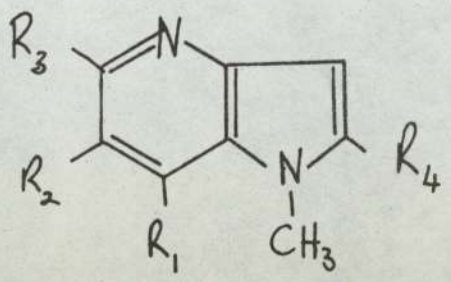
(i) Infrared Spectra

(ii) Ultraviolet Spectra

(iii) Nuclear Magnetic Resonance

(i) INFRA-RED

Spectra of the compounds were taken as mulls in Nujol; they were complex and only tentative interpretations were possible.



I	$R_1 = R_3 = CH_3$, $R_2 = H$, $R_4 = COOC_2H_5$	Ref IR 1
II	$R_1 = R_3 = OCH_3$, $R_2 = H$, $R_4 = COOC_2H_5$	IR 2
III	$R_1 = R_3 = H$, $R_2 = CH_3CO$ $R_4 = COOC_2H_5$	IR 3
IV	$R_1 = OCH_3$ $R_2 = H$ $R_3 = CH_3$ $R_4 = COOC_2H_5$	IR 4
V	$R_1 = O$, $R_2 = H$, $R_3 = CH_3$ $R_4 = COOC_2H_5$	IR 5
VI	$R_1 = O$ $R_2 = H$ $R_3 = C_6H_5$ $R_4 = COOC_2H_5$	IR 6
VII	$R_1 = O$ $R_2 = COOC_2H_5$ $R_3 = H$ $R_4 = COOC_2H_5$	IR 7
VIII	$R_1 = OH$ $R_2 = H$, $R_3 = O$, $R_4 = COOC_2H_5$	IR 8
IX	$R_1 = R_3 = CH_3$, $R_2 = H$, $R_4 = COOH$ hydrochloride	IR 9
X	$R_1 = OCH_3$ $R_2 = H$, $R_3 = CH_3$ methiodide	IR 10

In all the compounds examined the pyrrole ester carbonyl appeared as a strong band at 1700 - 1710 cm^{-1}. In compounds I, III & X a sharp band at 1585 - 1600 cm^{-1} corresponds to C = C absorption. In III the pyridine acyl carbonyl gave a strong absorption. (Ref IR 3) at 1660 cm^{-1}.

The compounds in which amide/enol tautomerism is possible should give rise to ring carbonyl and N-H bands in the amide form or an

OH band when in the enol form. It is known that ring carbonyl absorptions can occur over a wide range of energies but it is likely that in the compounds listed below which can exhibit tautomerism that these will be as follows:

V	1614 cm^{-1}	sharp
VI	1608 cm^{-1}	
VII	1607 cm^{-1}	
VIII	1620 cm^{-1}	broad

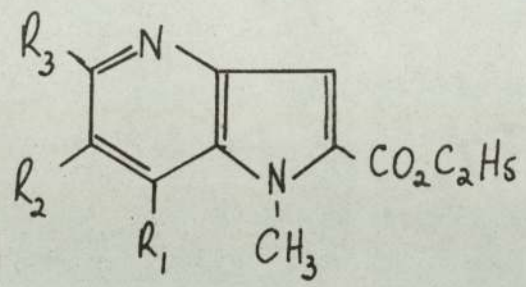
The expected accompanying N-H stretching vibration was difficult to locate and was weak, partly obscured by the C-H band from Nujol. A band appeared at 3370 cm^{-1} in compound V but this is the result of water of crystallisation and confirmation is obtained by its disappearance after a sample of the compound is heated in vacuum.

Compound VII is the only one where the absorption in the region is clear, occurring at 3100 cm^{-1}. Compound VI which is the phenyl analogue of V shows weak inconclusive absorptions at 3050 and 3230 cm^{-1}. VIII is an α,γ-dihydroxy compound which by analogy with the corresponding pyridine or quinoline compounds should exist as α-keto γ-hydroxyl is not clear because of considerable broadening around 3000 cm^{-1}.

No improvement in the appearance and identification of N-H peaks was effected when V was examined in a potassium bromide disc.

3.5 (ii) ULTRAVIOLET SPECTRA

The ultra-violet spectra of the fully aromatic 4-azaindoles showed a characteristic similarity of profile comprising two peaks at 227 - 245 nm and 297 - 317 nm.



I $R_1 = R_3 = CH_3$, $R_2 = H$, λmax 227, 308 nm Ref. UV 1

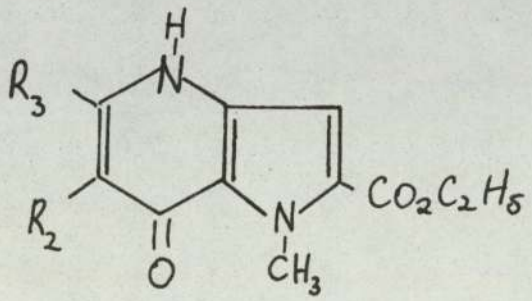
II $R_1 = R_3 = OCH_3$, $R_2 = H$, λmax 227, 310 nm UV 2

III $R_1 = R_3 = H$ $R_2 = CH_3CO$ λ max 247, 317 nm UV 3

IV $R_1 = OCH_3$, $R_2 = H$, $R_3 = CH_3$ λ max 236, 297 nm UV 4

The addition of acid or alkali has almost no effect.

Compounds capable of tautomerism between a non aromatic and an aromatic ring system show interesting behaviour in the ultraviolet region.

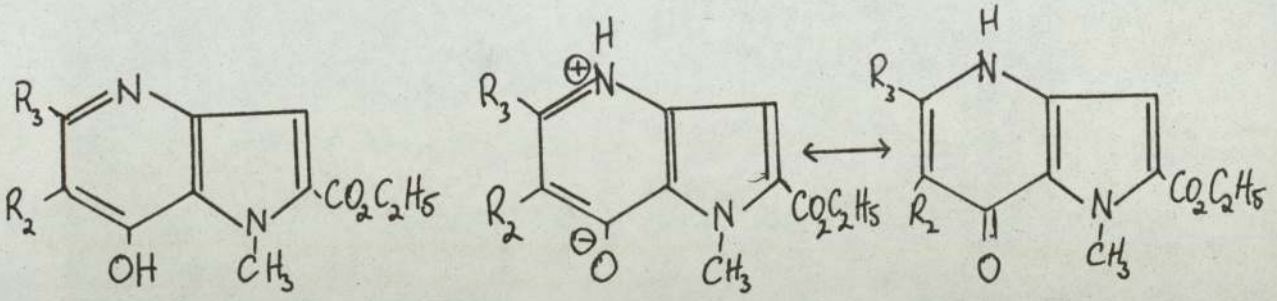


V $R_2 = H$, $R_3 = CH_3$ Ref UV 5

VI $R_2 = H$, $R_3 = C_6H_5$ Ref UV 6

VII $R_2 = COOC_2H_5$, $R_3 = H$ Ref UV 7

The 7-hydroxy-4-azaindoles in similar fashion to the 4-hydroxy-pyridines could exist as the enol, zwitterion or vinylogous amide e.g.



The ultraviolet spectrum of V in ethanol is quite different from that found for the fully aromatic azaindoles I → IV suggesting the influence of the amide structure. The importance of the contribution of the zwitterionic form is evident from the reversion to the characteristic aromatic profile (λ max 234, 295 nm) on the addition of acid.

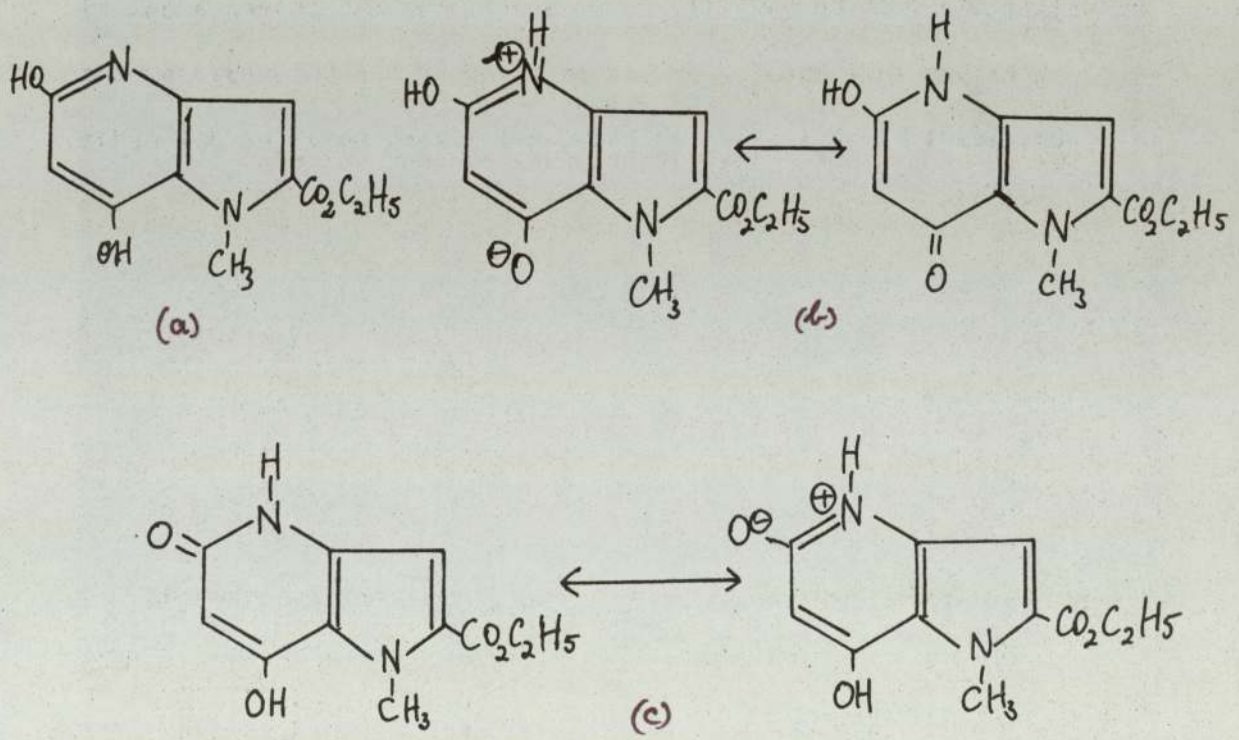
Methylation of V with diazomethane produced the O-methyl derivative IV, a compound with a fully aromatic structure. The ultraviolet spectrum is as expected (λ max 235, 297 nm) and unaffected by the addition of acid or alkali (Ref UV 4).

In spite of repeated attempts to prepare an N-methyl derivative of V this was unsuccessful and prevented observation of a spectrum existing entirely of the amide structure. It is suggested that the presence of a methyl group and the pyrrole ring peri to the nitrogen causes steric hindrance and prevents substitution.

The spectrum of VI, the phenyl analogue of V in ethanol in similar fashion to V changes to the characteristic aromatic profile on acidification (λ max 253, 320 nm) Ref UV 6.

It was expected that the spectrum of VII (Ref UV 7) would follow the pattern of V and VI but this was not clear. The neutral ethanolic solution does not show an aromatic type of absorption and unlike V and VI acidification does not produce a similar profile.

A compound with potential hydroxyl groups α- and γ- to the pyridine ring nitrogen atom was prepared and similarly to the analogous dihydroxy-pyridines and quinolines gives rise to three possible structures (a), (b), (c).



The neutral ethanolic solution of VIII (R_1 = OH, R_2 = H, R_3 = O, R_4 = COO C_2H_5) UV 8 was indicative of the non aromatic system, which on the addition of acid reverts to the aromatic type of

absorption (λ max 225, 308 nm). While this is sufficient to indicate the preference for structures (b) or (c) it does not differentiate between structures (b) and (c). This could be effected by examination of the 5- and 7-methoxy compounds (tautomerism of pyridones Ref 20). Methylation of VIII with diazomethane gave the 5, 7-dimethoxy derivative IX. In the analogous dihydroxy pyridines and quinolines it is found that the α-keto, γ-hydroxy form predominates i.e. preference for the amide rather than the vinylogous amide.

3.5 (iii) NUCLEAR MAGNETIC RESONANCE SPECTRA

The spectra of most of the compounds prepared were examined although the limited solubility in the deuterated solvents caused problems and in the case of VII no spectrum was possible.

The structures were elucidated as follows:
N-methyl in the pyrrole ring was established from the table of chemical shifts in compounds VI, VII and VIII, where this is the only methyl in the ring and appeared as a singlet at δ = 4.39, 4.39 and 4.16 ppm respectively.

In compound I, 5- and 7-methyl groups appeared as doublets on scale expansion, each being split by the 6-H proton. Differentiation between these two methyl groups was achieved by examination of the spectra of I and IV in deuterochloroform 5-methyl remains at δ = 2.58 ppm in both compounds. The pyrrole 3-H and pyridine 6-H ring protons in I were identified by the scale expansion of the

spectrum where a partly resolved quadruplet appeared. The 6-H proton is coupled to the adjacent methyl group. The 3-H appeared as a singlet at lower field (δ = 7.3 ppm) Ref NMR1(b).

It is interesting to note that when I was converted to its acid as the hydrochloride IX, protonation of the pyridine nitrogen caused a downfield shift of the pyrrole 3-H and the pyridine 6-H protons. As was expected the pyridine proton experienced the greater shift δ 6.93 $\rightarrow$ 7.455 = 0.525 ppm and the pyrrole 3-H δ 7.1 $\rightarrow$ 7.29 = 0.19 ppm. (Ref. NMR1(a) and NMR 10).

Compound III was interesting in that long range couplings across the ring were displayed between protons 3-H, 5-H and 7-H. The 6-acetyl group caused considerable deshielding resulting in progressive downfield shift of the 3-H, 7-H and 5-H.

The spectra of V is of interest corroberating the preponderance of the amide structure in that (i) the pyridine 6-H appeared at higher field in V (δ = 5.78 ppm) than in I (δ = 6.8 ppm) or IV (δ = 6.48). The fully aromatic structures of I and IV are responsible for the 6-H appearing at the lower field than in V suggesting it to be non aromatic.

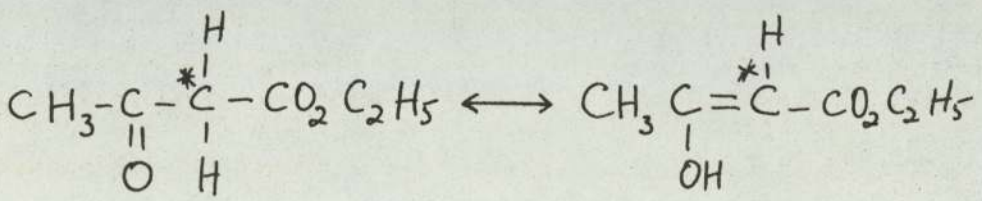
(ii) The N-H proton in V appears as a broad signal at very low field (δ = 11.5 ppm).

This evidence was corroberated in the corresponding phenyl compound in that the 6-H proton is again at higher field (δ = 6.27 ppm) than

in I or IV with a broad N-H signal at low field (δ = 11.76 ppm).

Reference to the γ-hydroxy-pyridines and quinolines indicated the preponderance of the amide structure which when determined from pK values gave a ratio of amide/enol of 2,200 and 24,000 respectively. The low solubility of the tautomeric azaindoles studied prevented the application of this technique but it was hoped this examination of the NMR spectra of V at different temperatures would provide a means of assessing the proportional population of the two species. The rate of interchange between the two species is a function of temperature. In the amide form the 6-H proton is in a non aromatic environment whereas in the zwitterion or enol form the system is aromatic. Thus it would be expected that this proton in two different environments would have two different chemical shifts. This picture was qualitatively illustrated in the examination of chemical shifts of the 6-H proton in V and VI in relation to I and IV.

If the rate of interchange between the tautomeric forms is fast a composite peak would appear but reduction of the temperature would slow the interchange and gradually two peaks could emerge. This effect is seen in ethyl acetoacetate at room temperature.



Elevation of the temperature causes the separate peaks to merge to a composite broad absorption.

The spectrum of V room temperature showed the 6-H proton at δ = 5.87 ppm 3-H at δ = 6.75 ppm a broad absorption at δ = 7.95 ppm and a broad N-H absorption at δ = 11.4 ppm. The broad absorption at δ = 7.95 caused some speculation particularly when it sharpened and moved downfield when the temperature was lowered. However, elevation of the temperature above room temperature had no effect on the absorption at δ = 6.75 ppm and the absorption δ = 7.95 ppm was found to the result of isotopic impurity in the deuterochloroform solvent. The deutero-dimethyl sulphoxide present was responsible for its appearance at lower field than expected.

3.5 (iv) CONCLUSIONS

None of the methods studied provide complete proof of the tautomeric preference in isolation but collectively suggest that in an analogous fashion to the γ-hydroxy-pyridines and quinolines the amide structure predominates, with a significant contribution by the zwitterionic form.

The evidence is summarised as follows:

1. The melting points of V, VI are high 300° compared with compound I which is of comparable molecular weight. This is indicative of the presence of strong intermolecular bonds as found in polar molecules or zwitterions.

2. In the compounds capable of tautomerism, although the spectra are complex and only partly satisfactory there is evidence for

absorptions which could be attributed to a ring carbonyl in addition to the carbonyl of the pyrrole ester function.

3. The neutral ethanolic ultraviolet spectra of V is quite different from that of the fully aromatic structure as in UV 1 or the O-methyl derivative of V Ref. UV 4.

   Acidification of V in ethanol changes the spectrum to that characteristic of the fully aromatic system.

   This is corroberated by the Ultraviolet spectra of VI the phenyl analogue of V.

   Variation in the polarity of solvent had no effect on the positions of maxima or profile of V.

4. The nuclear magnetic resonance spectra corroberated the evidence of the preference for the non aromatic amide structure showing

   (a) the presence of the N-H proton as a broad band at low field

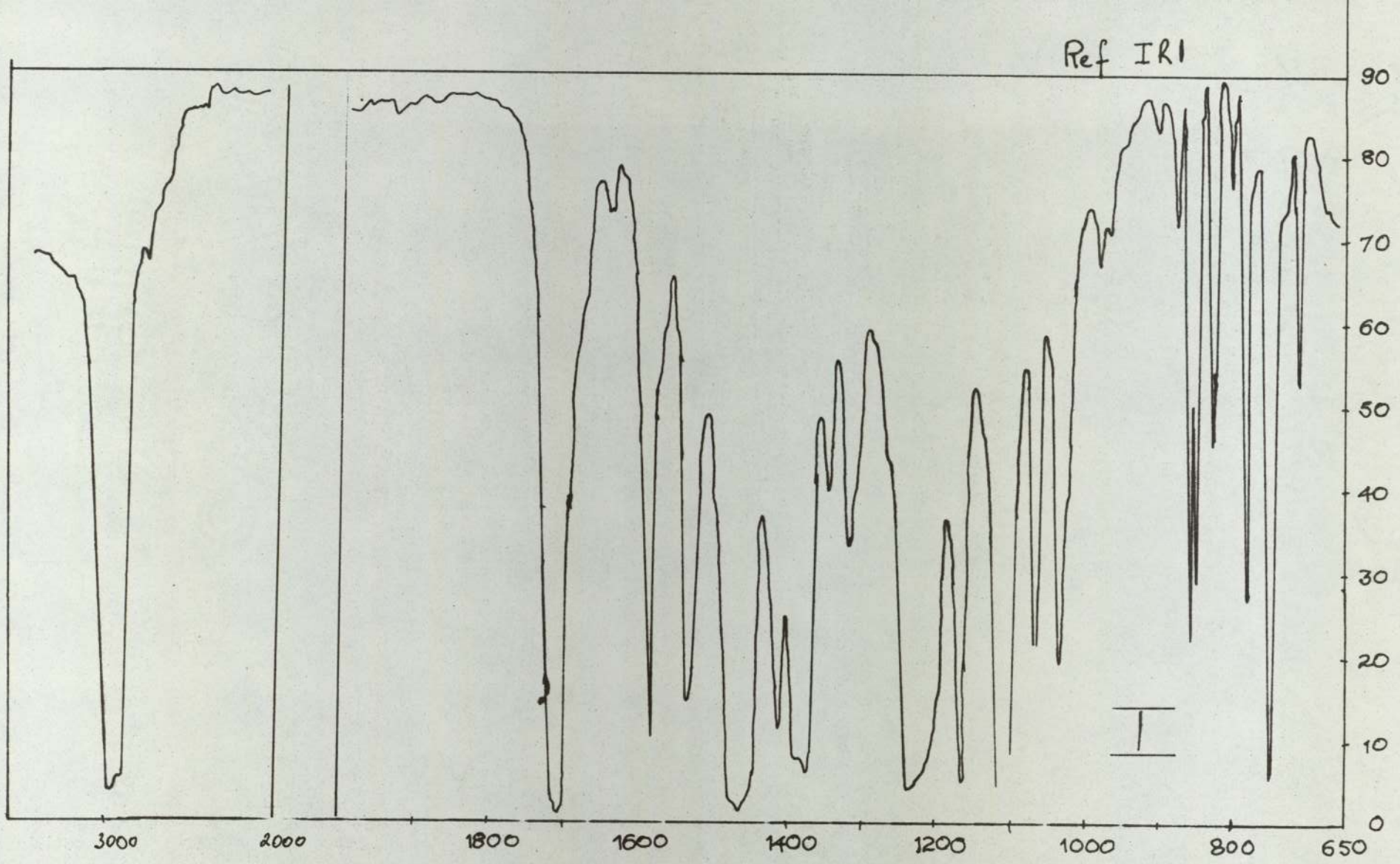
   (b) the smaller value of the chemical shift of the 6-H proton in a non aromatic environment as compared with its chemical shift in a fully aromatic system

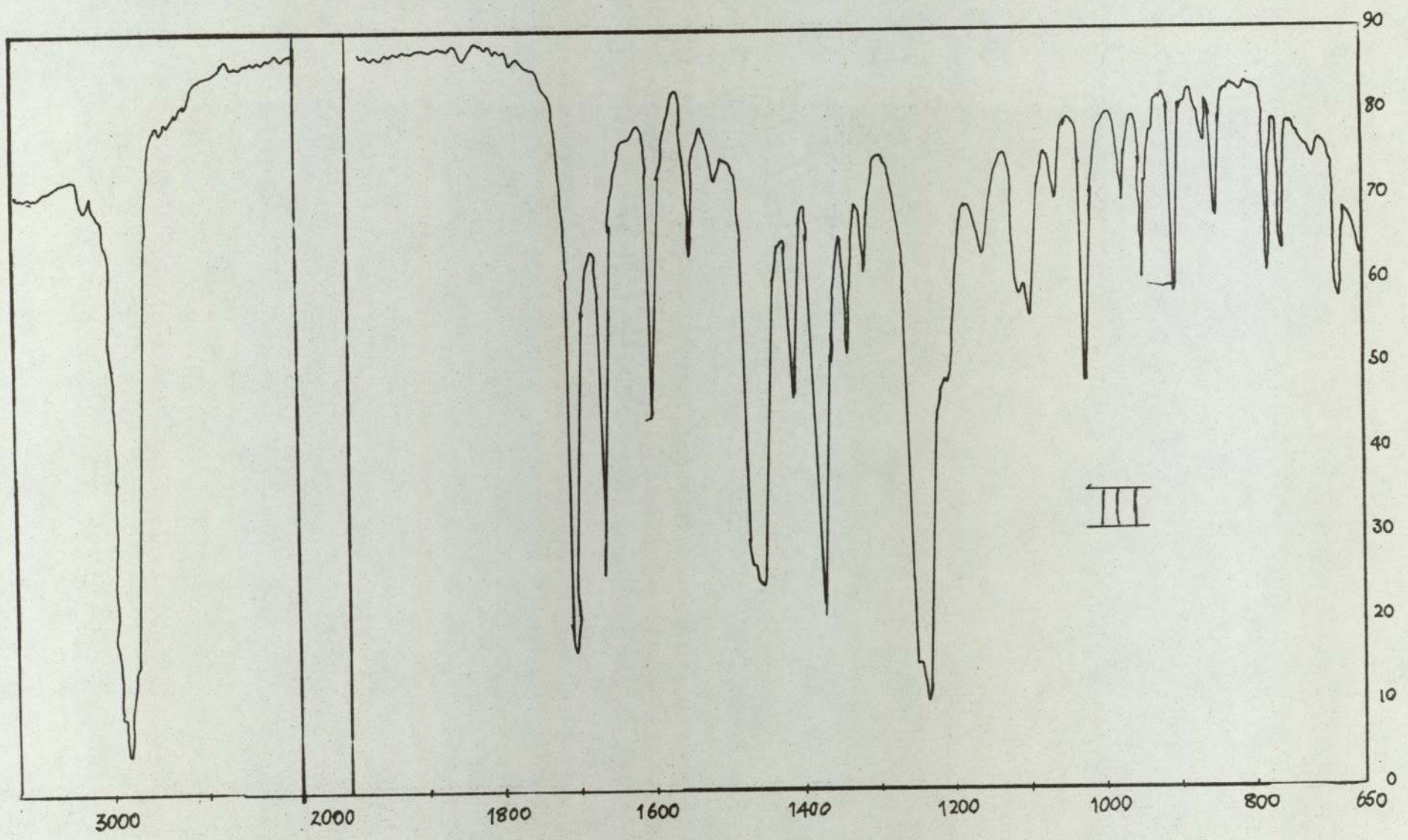
   (c) the absence of splitting of the 6-H proton by change of environment and variation of temperature. If splitting

were feasible the proportions of the two peaks would have to be comparable to be visible. The very large amide/enol values in the γ-hydroxy-pyridines and quinolines suggest that this is unlikely to be practical.

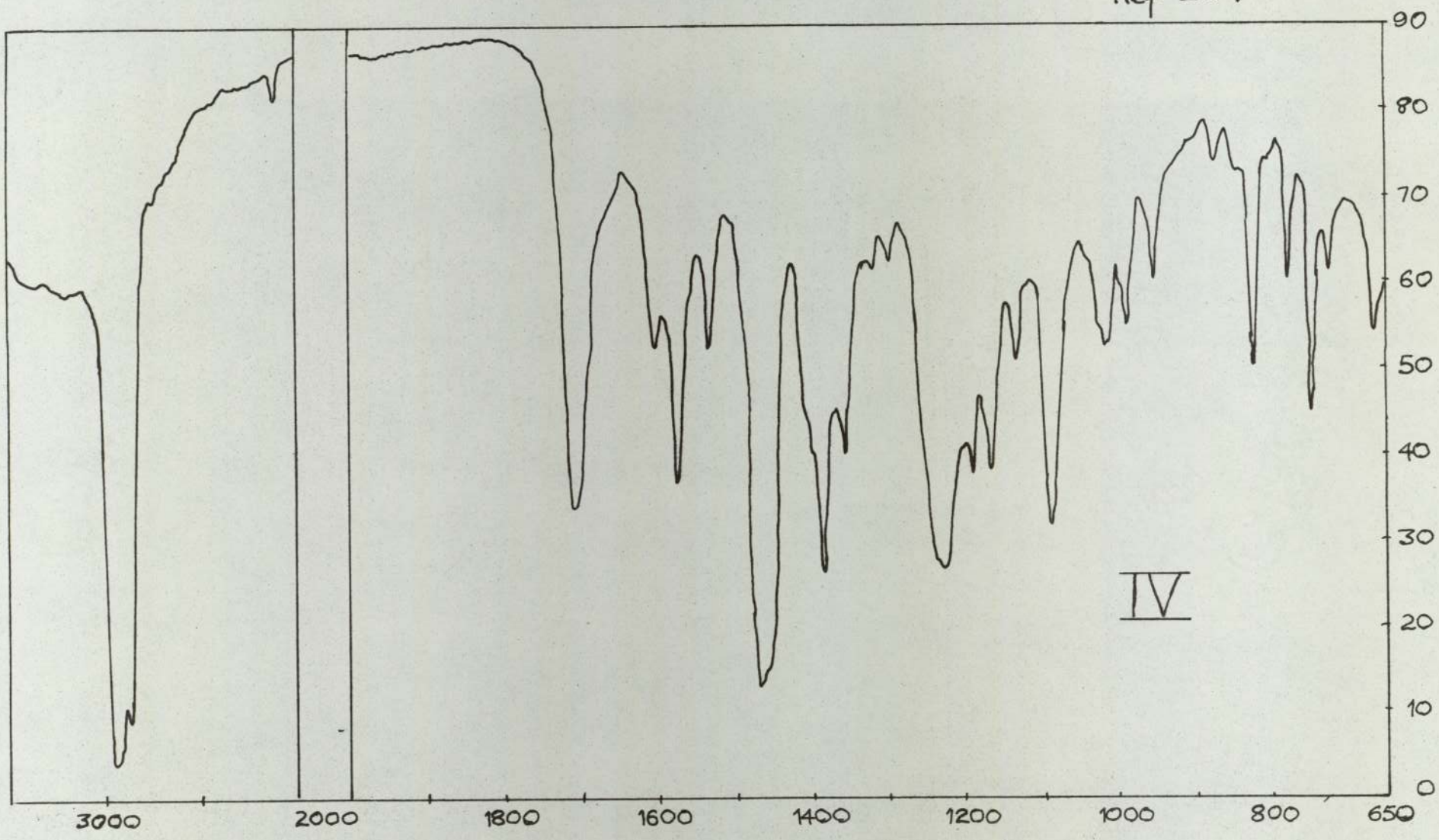
4.1 INFRARED SPECTRA

Instrument UNICAM SP 200

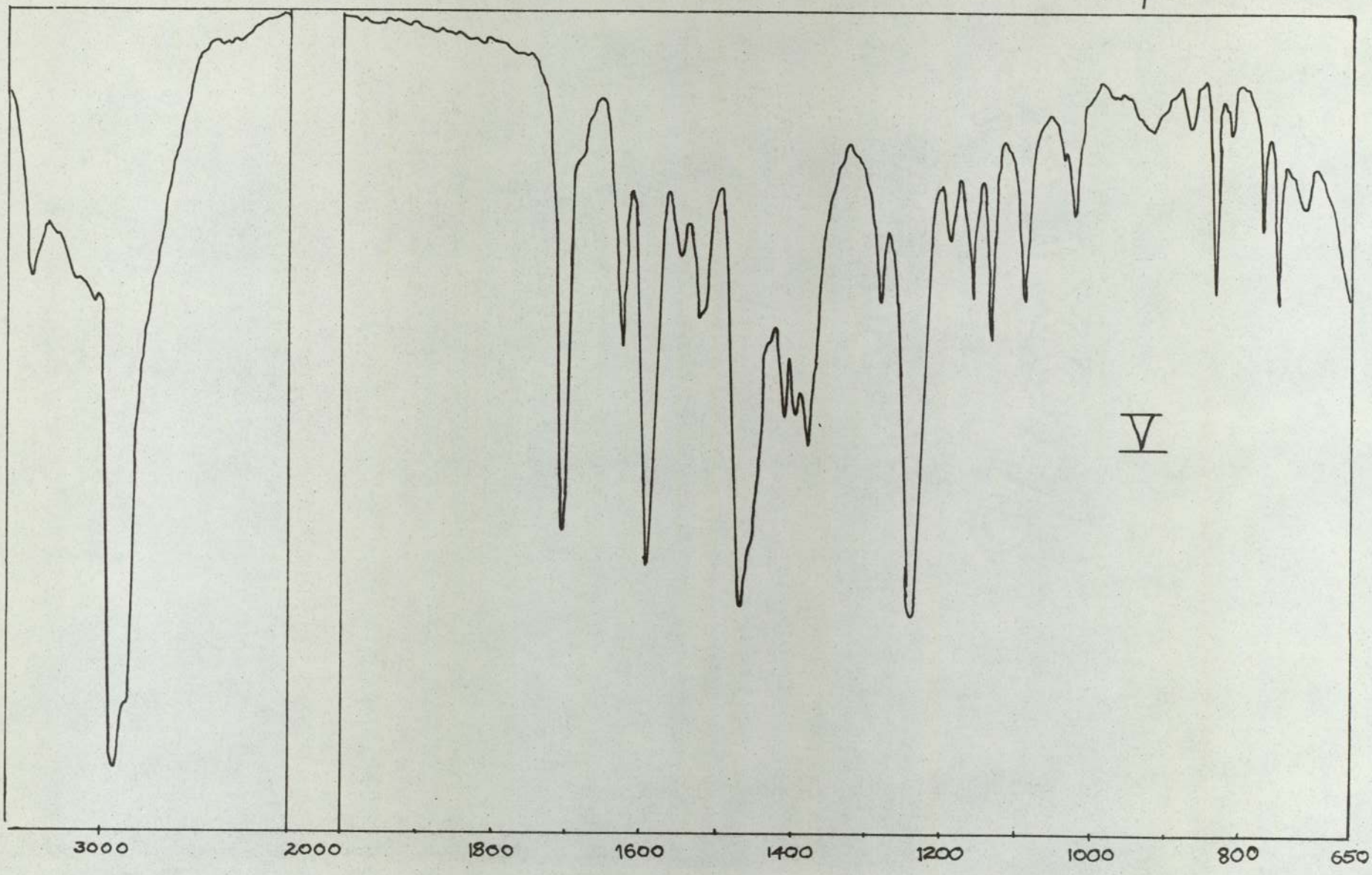

Ref IR1
90
80
70
60
50
40
30
20
10
0
3000
2000
1800
1600
1400
1200
1000
800
650


90
80
70
60
50
40
30
20
10
0
3000
2000
1800
1600
1400
1200
1000
800
650

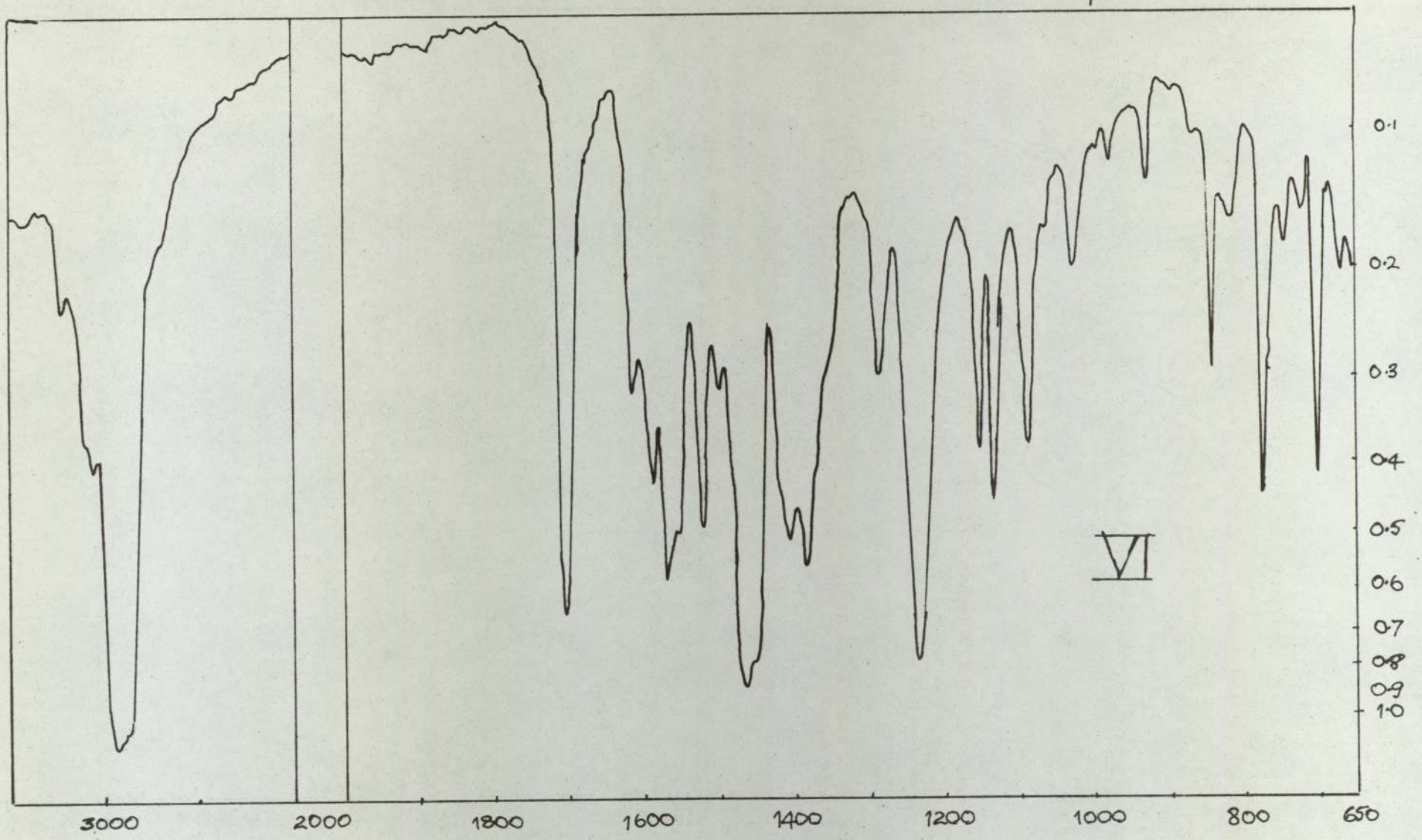
Ref IR 4


90
80
70
60
50
40
30
20
10
0
3000
2000
1800
1600
1400
1200
1000
800
650
IV

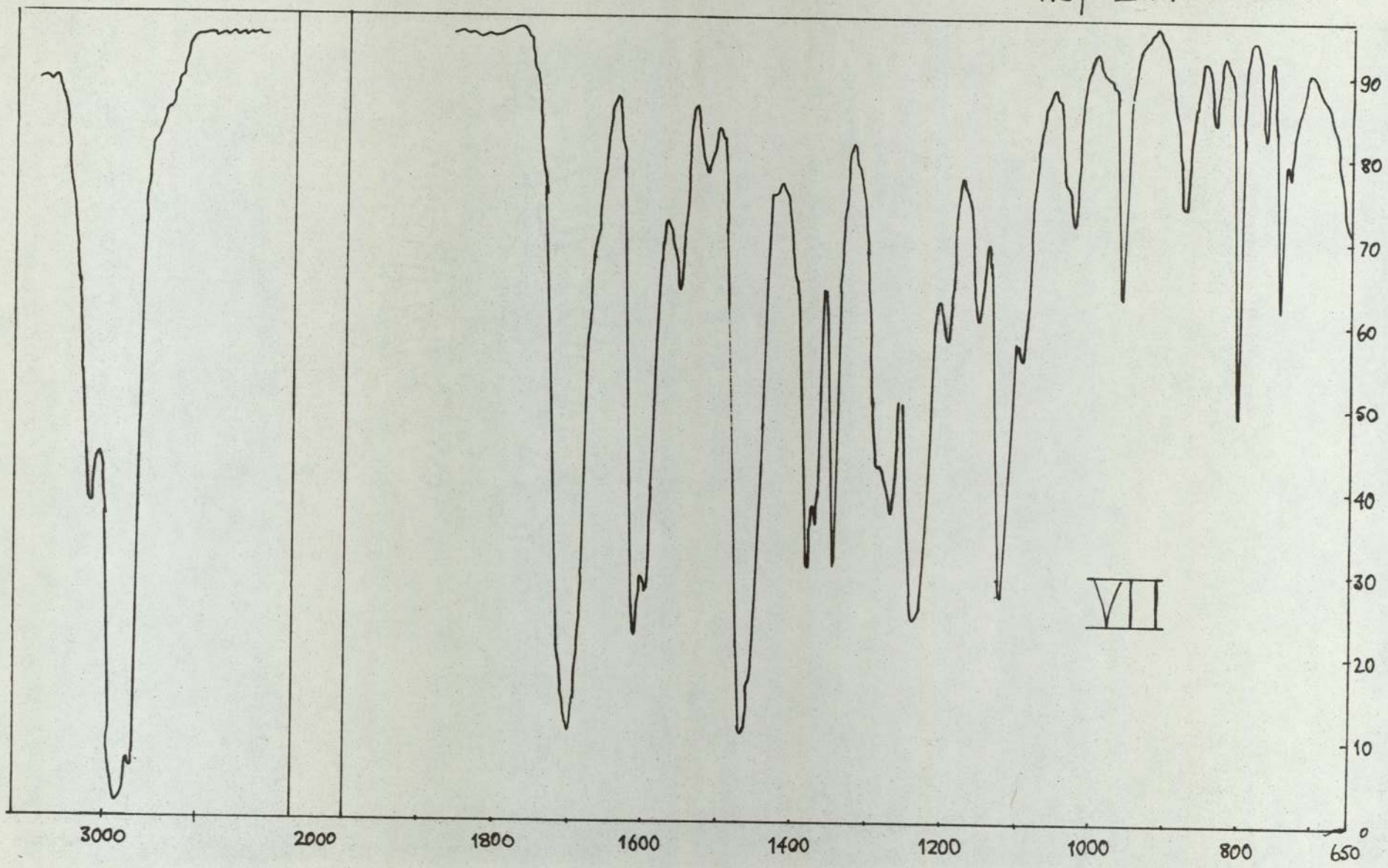
Ref IR 5



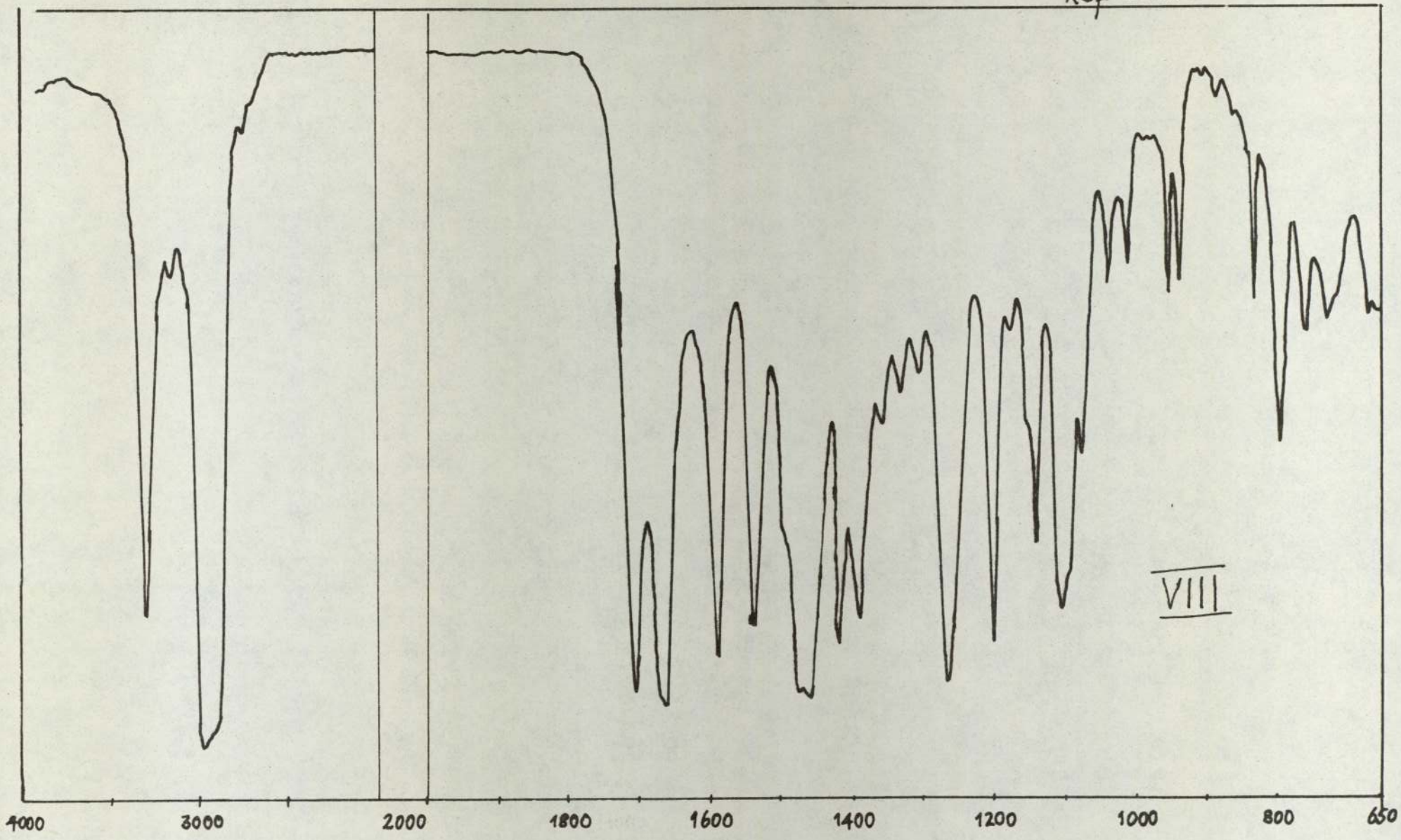
Ref IR 6


VI
0·1
0·2
0·3
0·4
0·5
0·6
0·7
0·8
0·9
1·0
3000
2000
1800
1600
1400
1200
1000
800
650

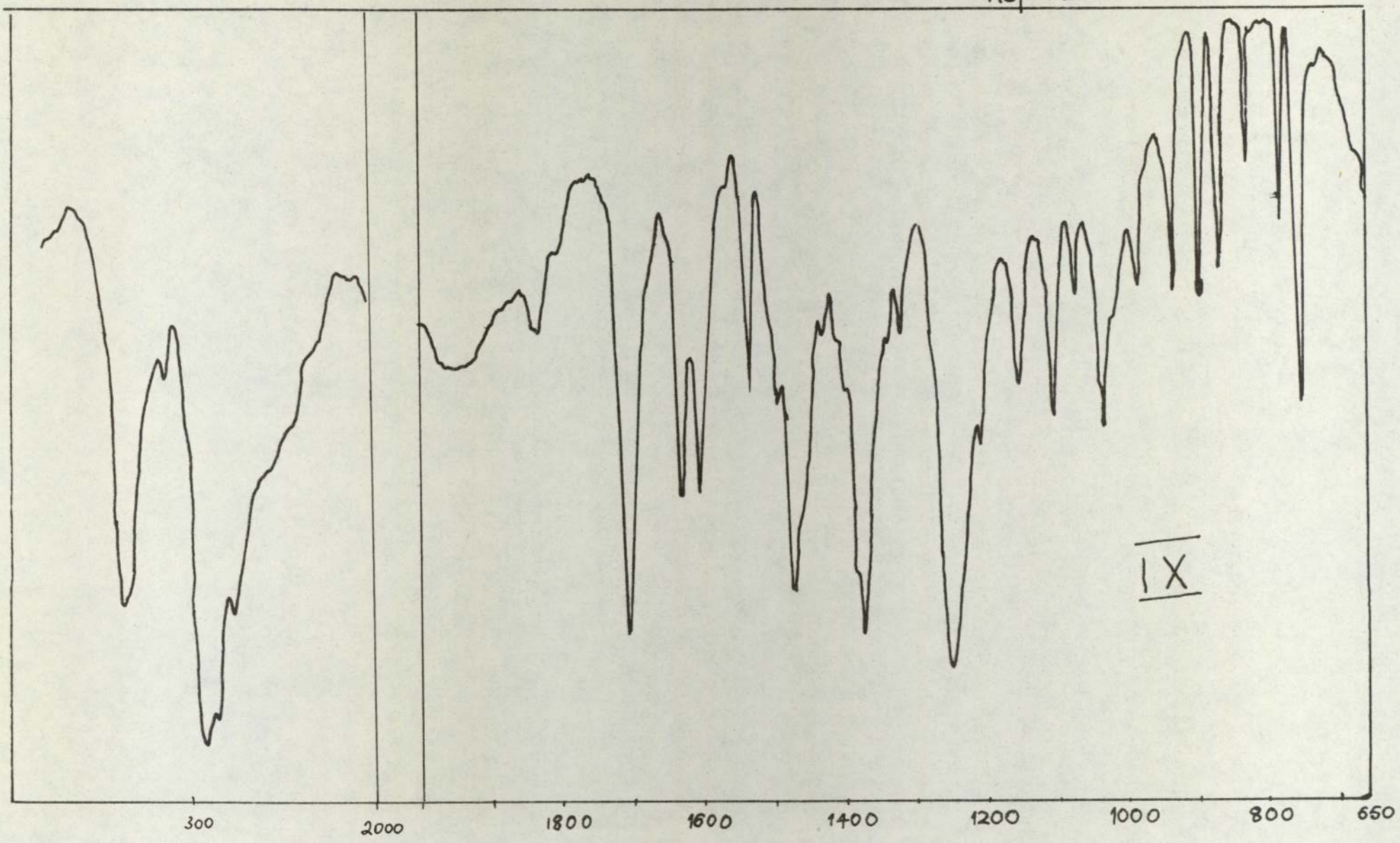
Ref IR 7


VII
3000
2000
1800
1600
1400
1200
1000
800
650
90
80
70
60
50
40
30
20
10
0

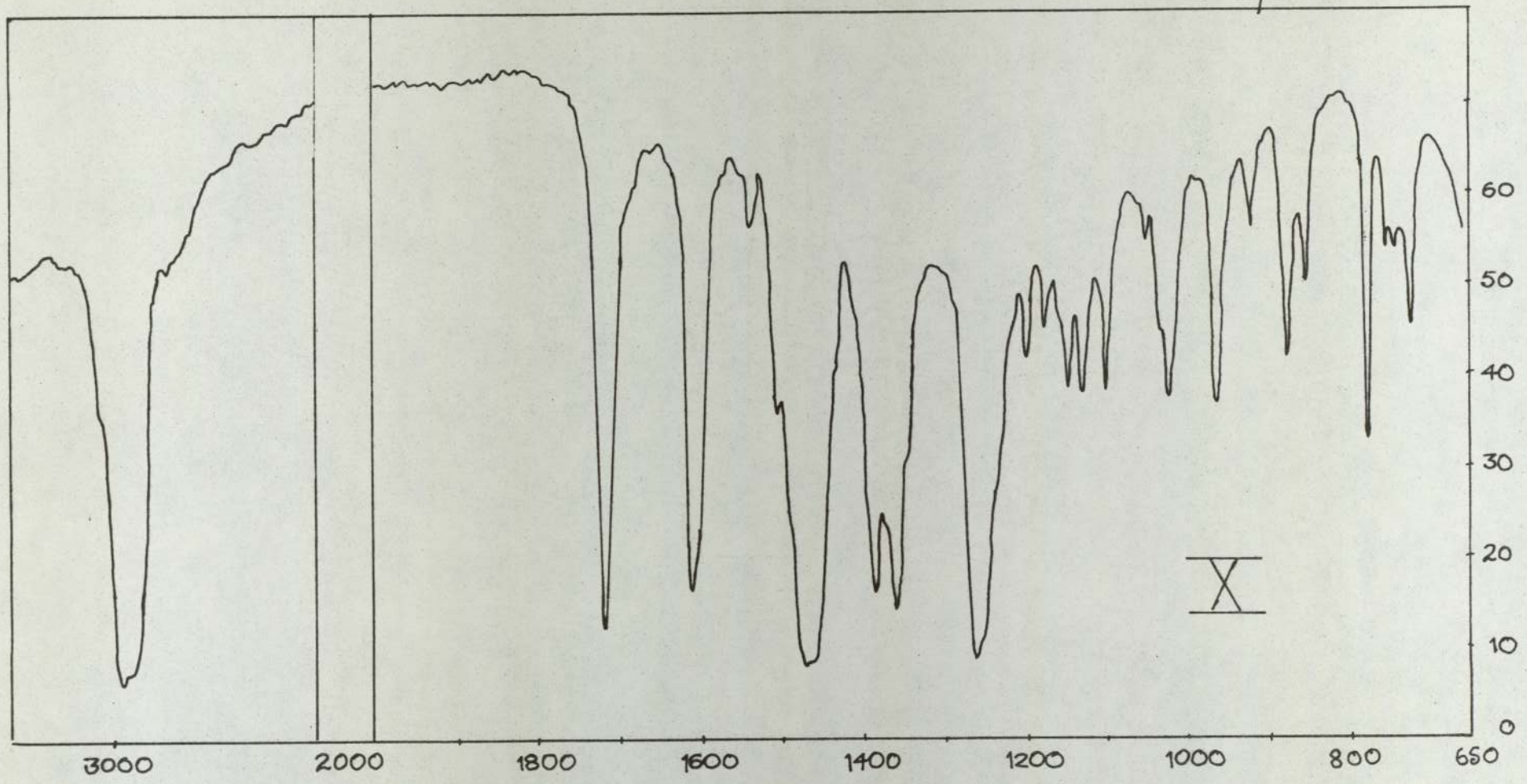
Ref IR. 8



Ref IR 9



Ref IR 10



4.2 (i) ULTRAVIOLET SPECTRA

Instrument Unicam SP 8000

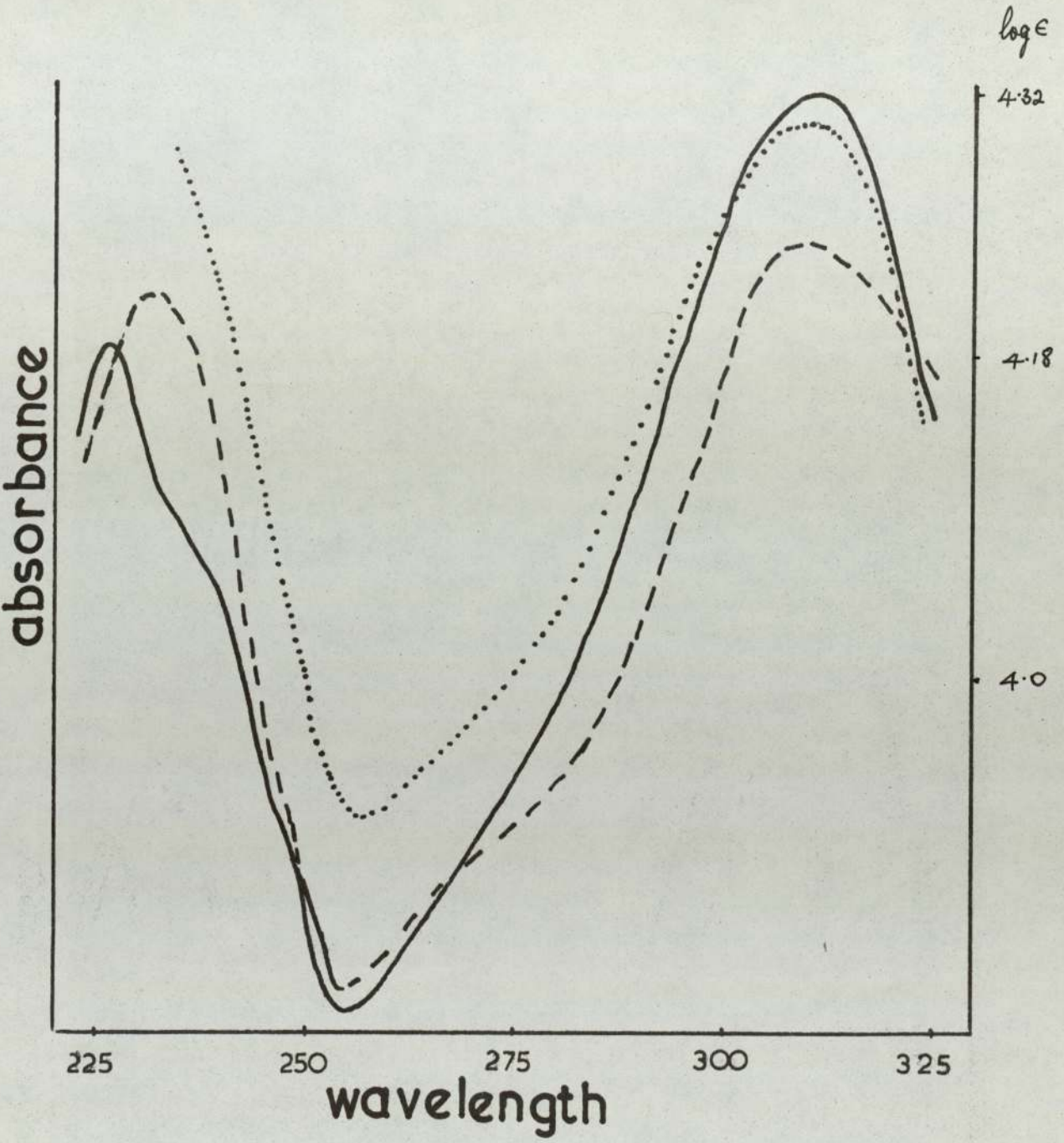
——— Neutral Solution in Ethanol

- - - Acidic Solution

..... Alkaline Solution

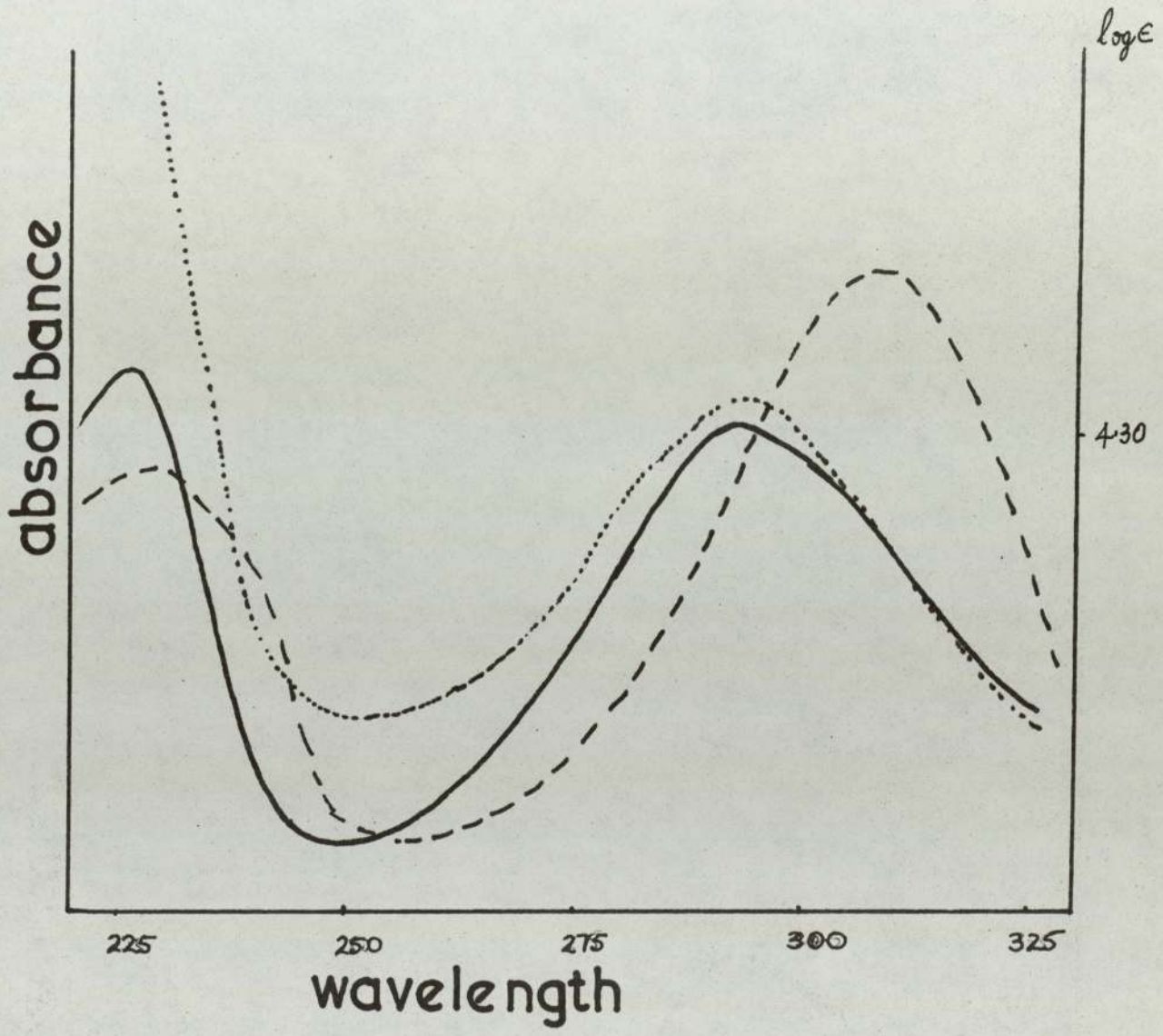
I

UV I



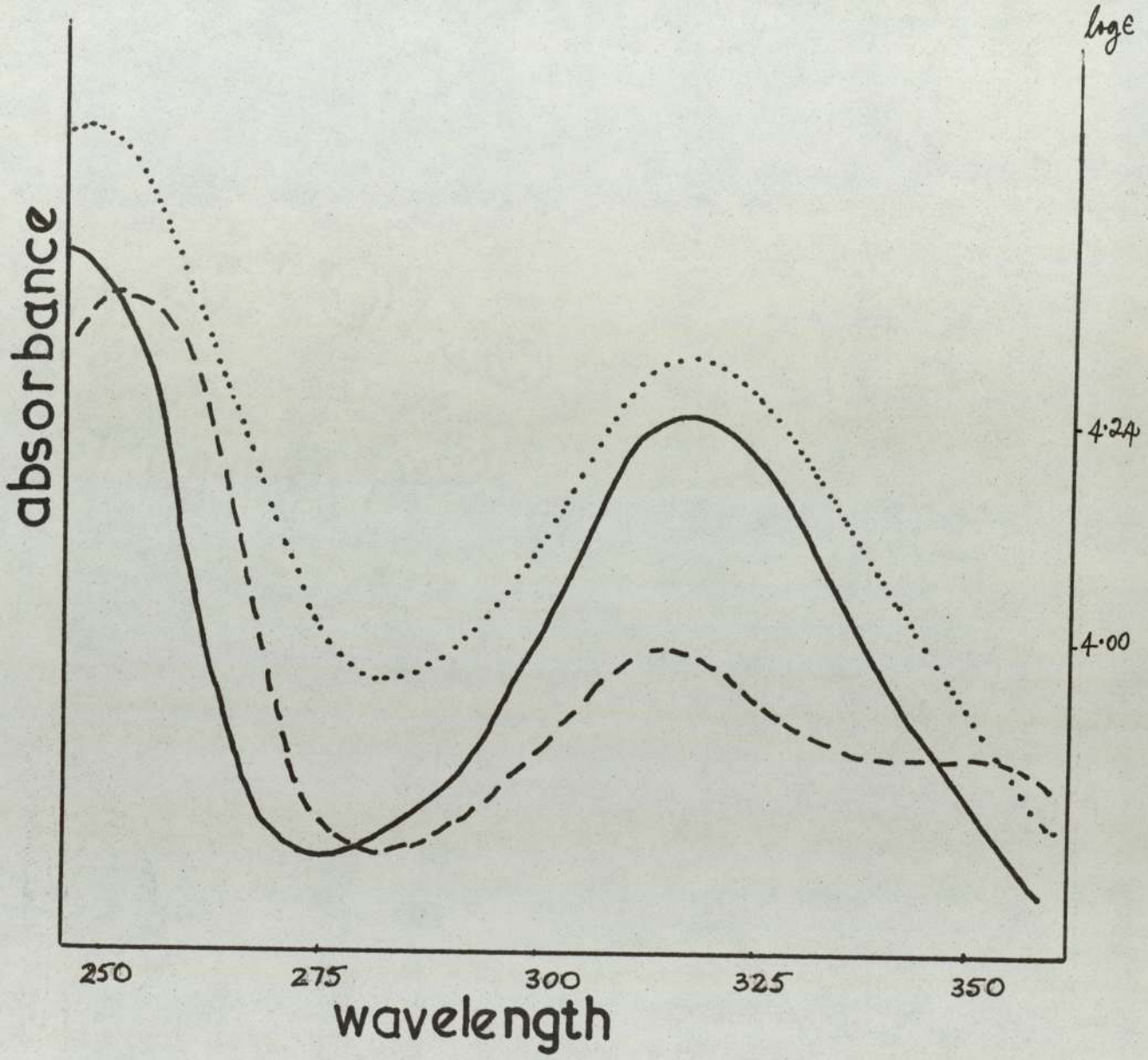
II

UV 2



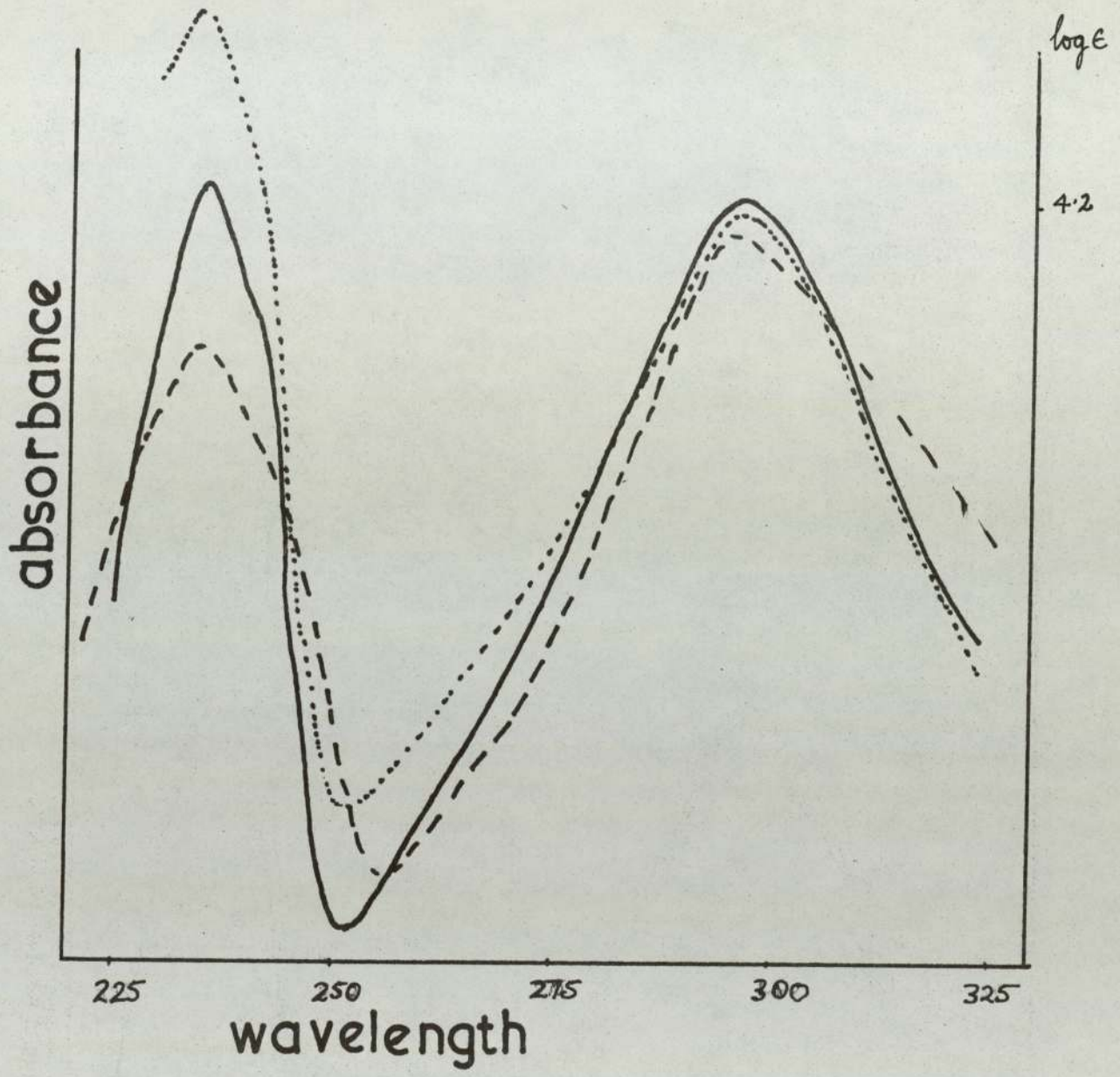
III

UV 3



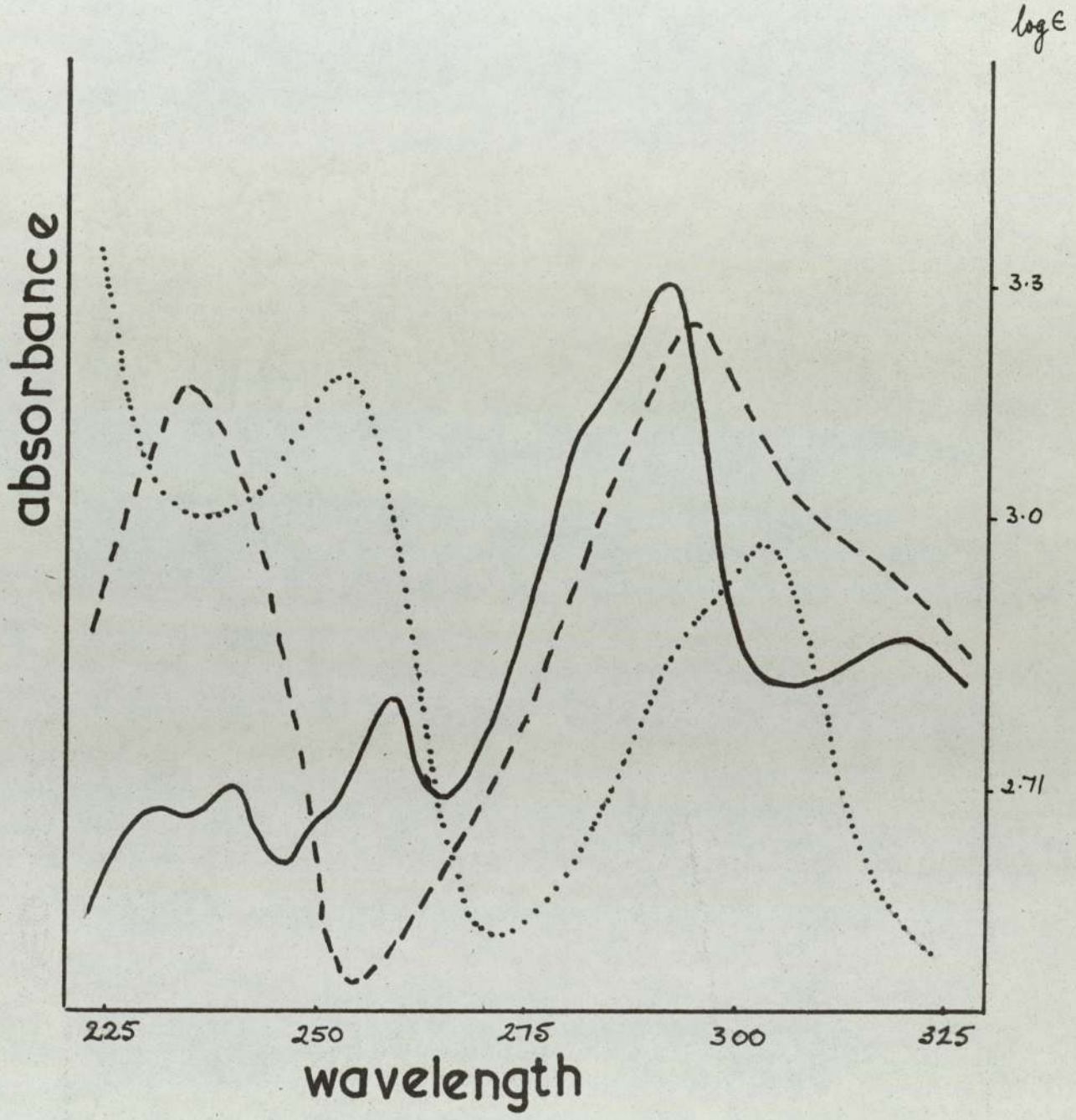
IV

UV4.



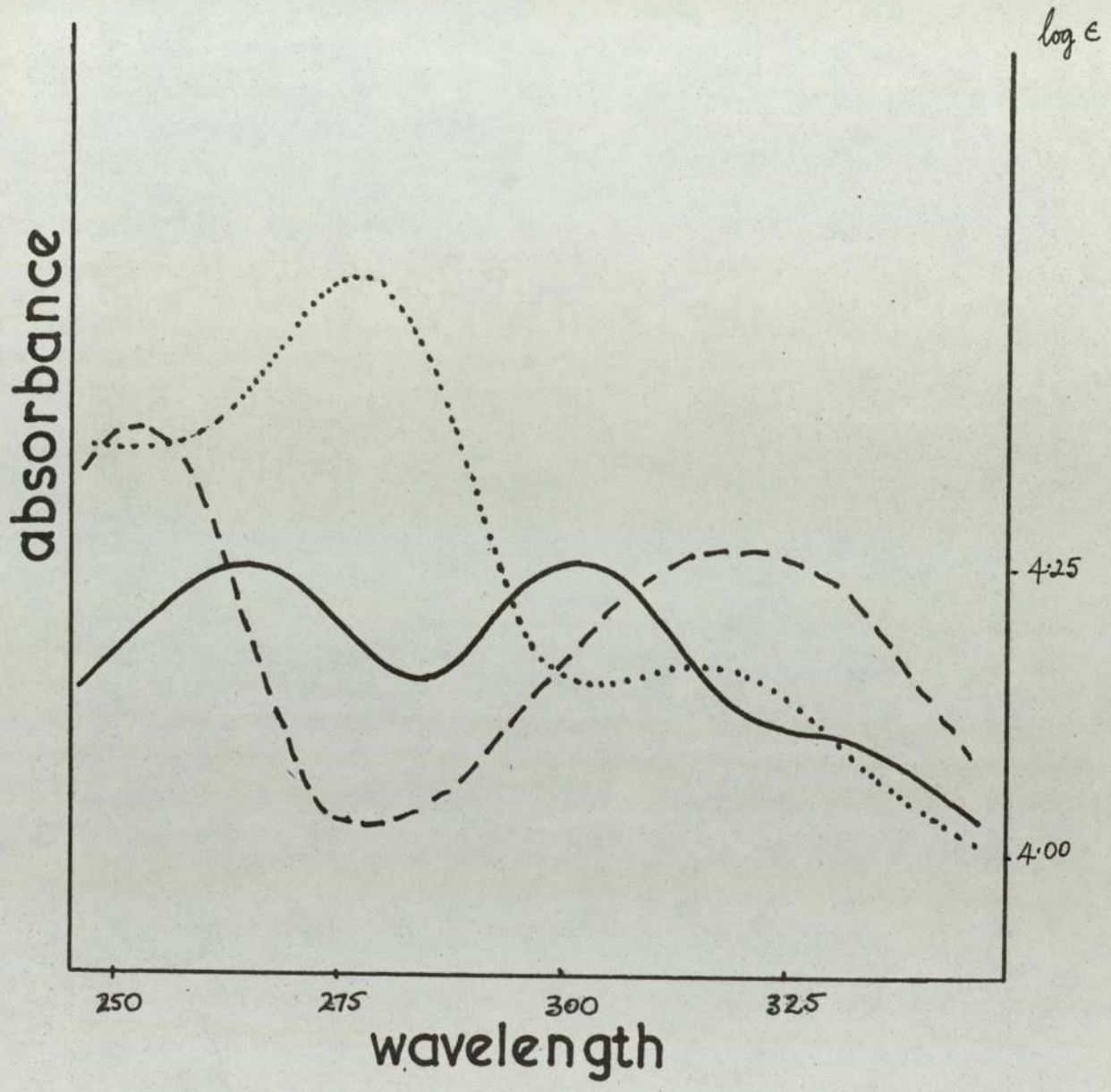
V

UV 5



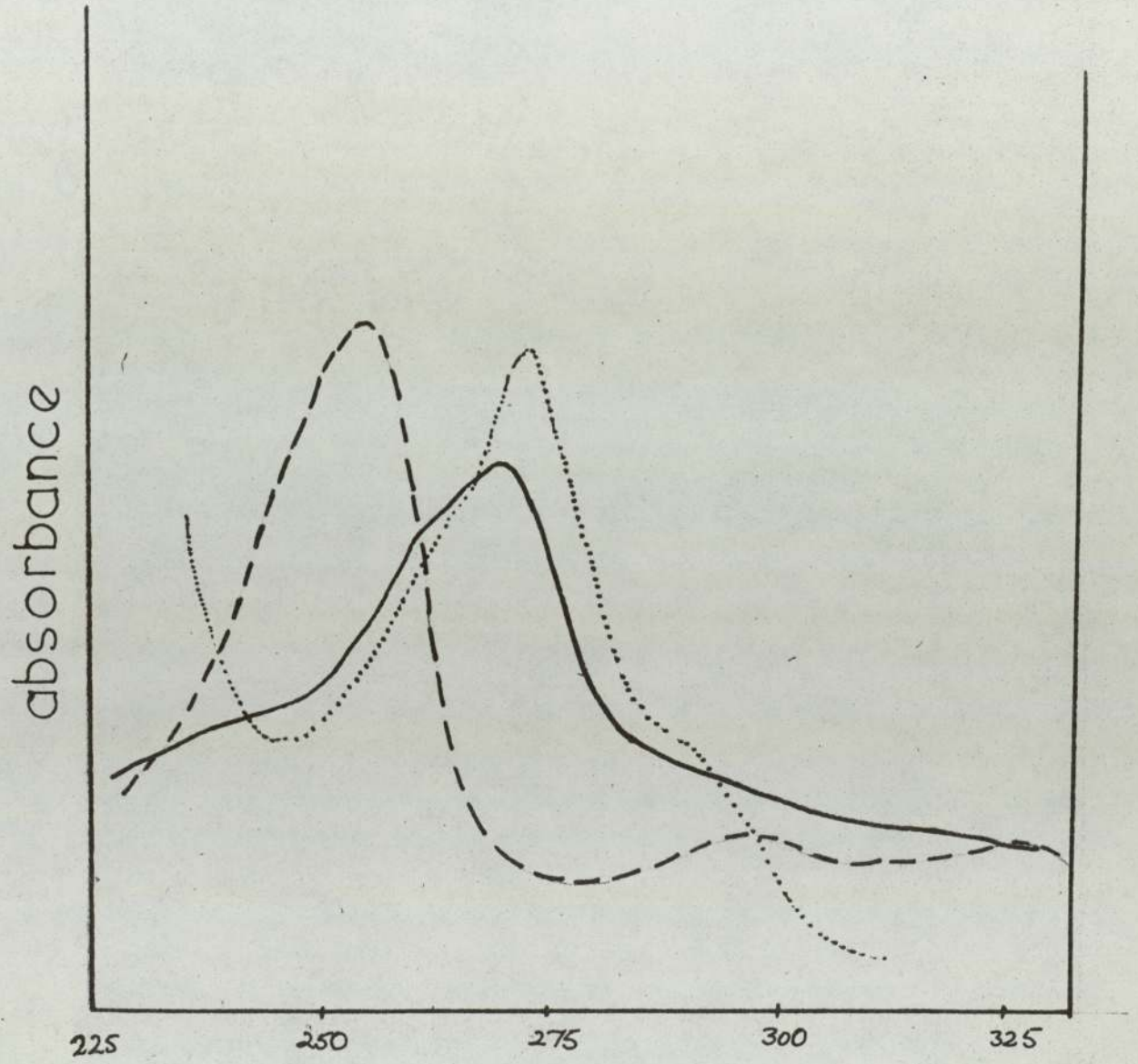
VI

UV 6



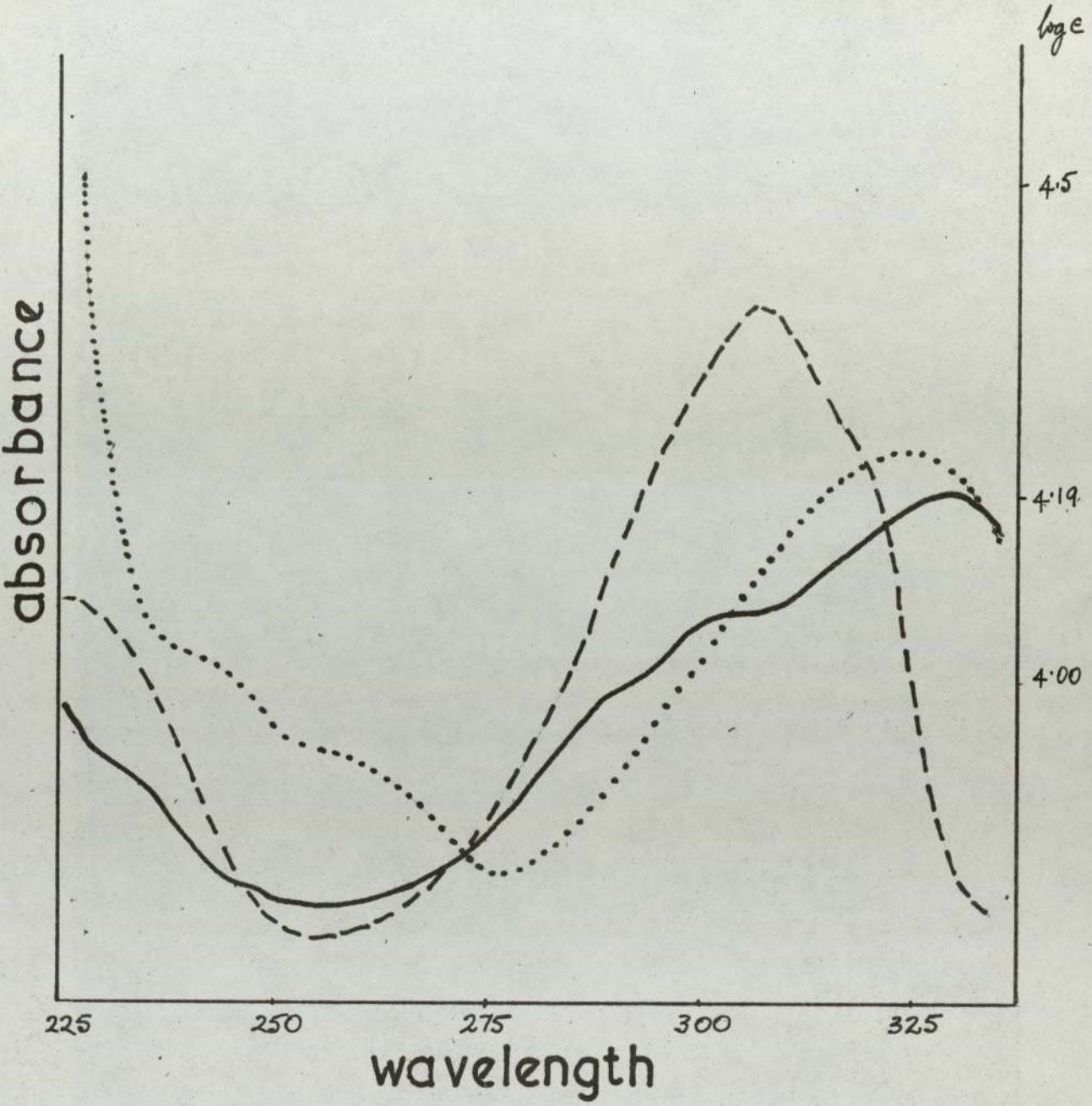
VII

UV 7



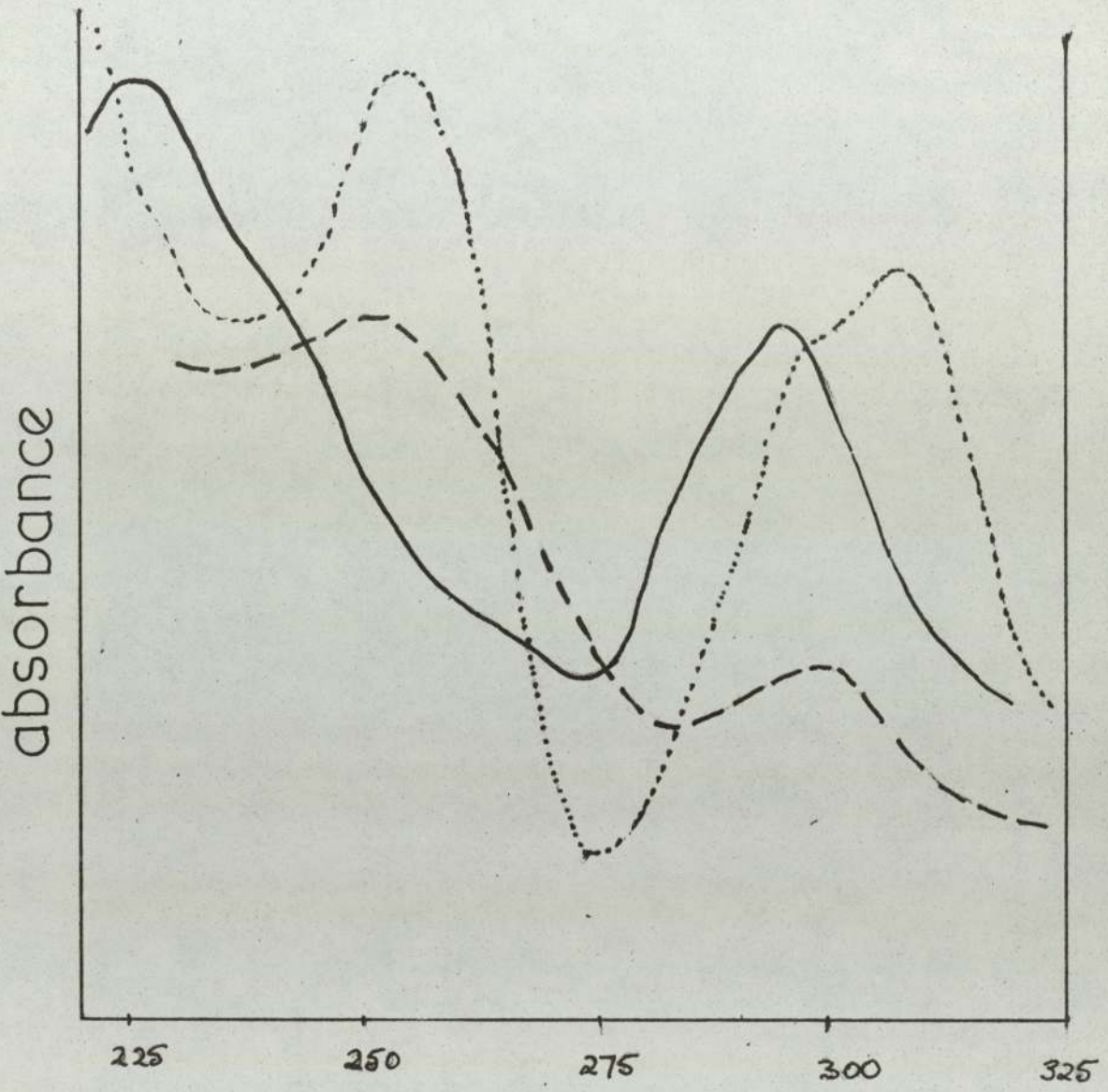
VIII

UV8



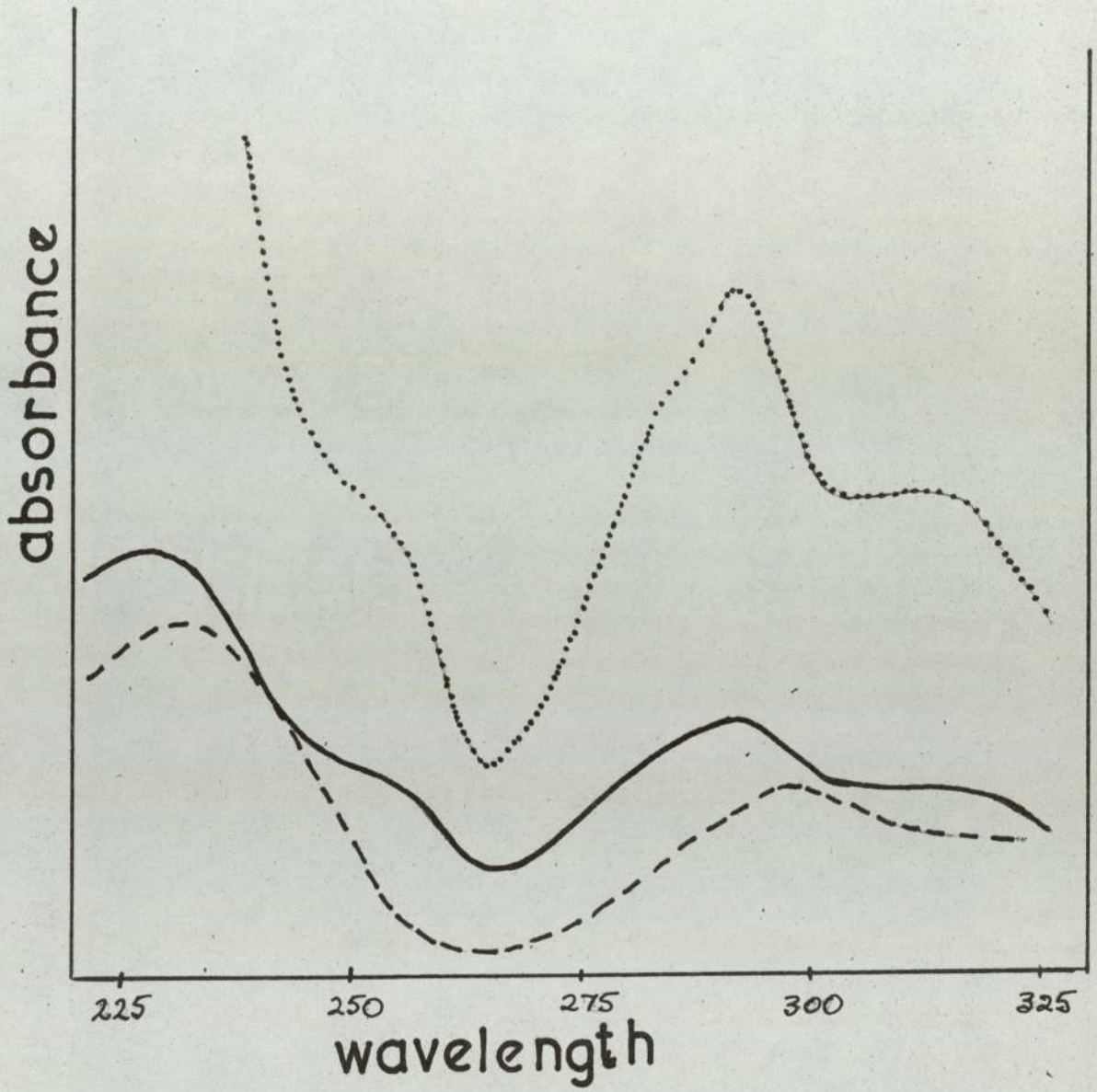
XVII

UV 9

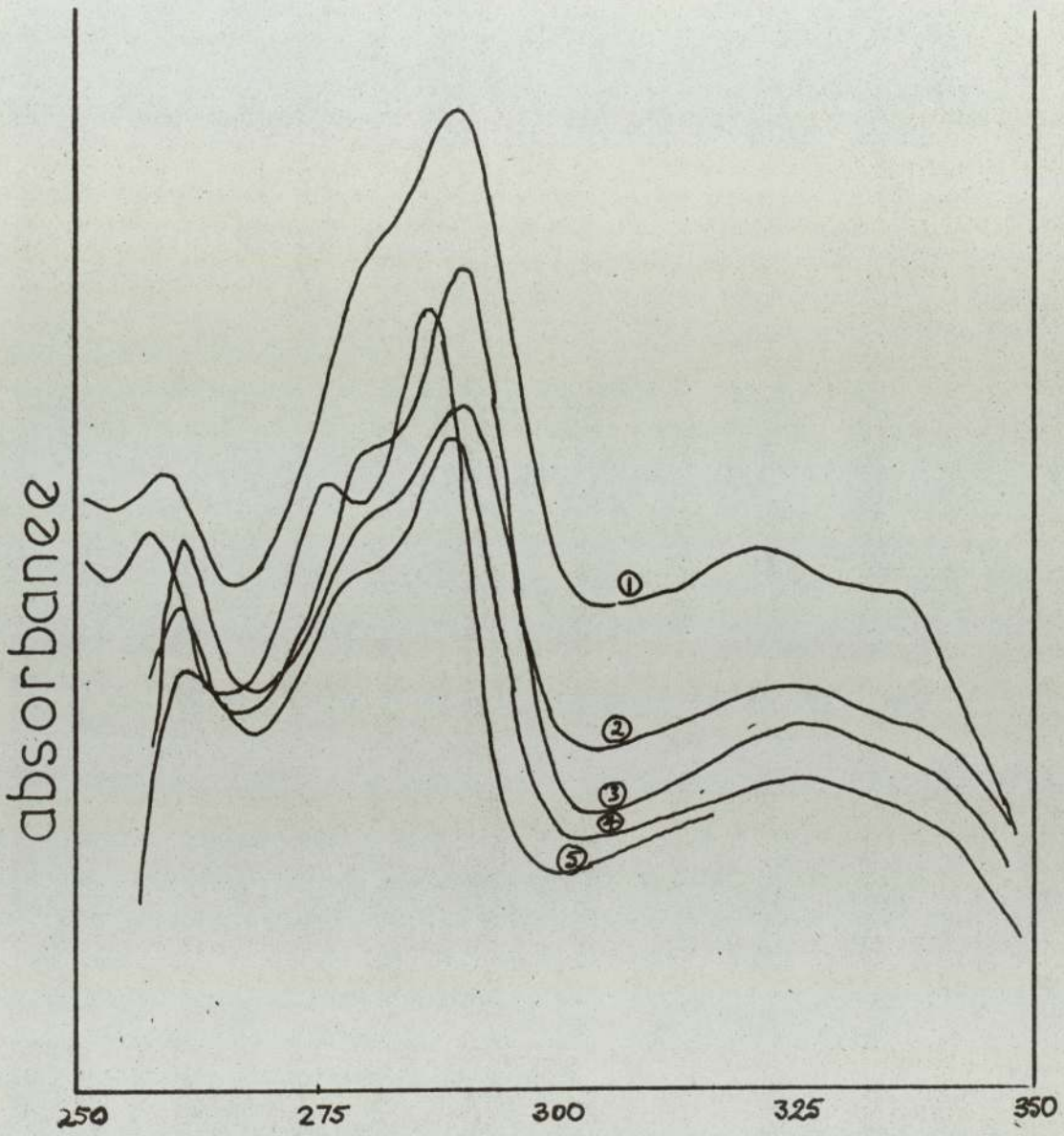


X

UV10



UV II



① CHLOROFORM.
② CHLOROFORM / CYCLOHEXANE 80/20 v/v
③ " / " 50/50 v/v
④ " / " 20/80 v/v
⑤ CYCLOHEXANE

ULTRAVIOLET ABSORPTION SPECTRA OF PYRROLO (3,2-b) PYRIDINES

COMPOUND	SOLVENT	λ max nm, (log ε)
Indole	A	219 (4.5) 270 (3.8) 278 (3.8)
4-Azaindole	H_2O	292 (3.92)
	A^+	284 (3.27)
2-Carboethoxy-1,5,7, -Me_3 I	A	227 312 (4.32)
	H^+	232 308
	OH^-	223 310
2-Carboethoxy-1,5-Me_2 7 HO ⇌ O V	A	230 240 (252) 259 (282) 292 320 (3.3)
	H^+	234 295 (320)
	OH^-	220 253 (259) 303
2-Carboethoxy-1,5,-Me_2 7-OCH_3 IV	A	236 297 (4.2)
	H^+	235 297
	OH^-	235 297
2-Carboethoxy-1,5,-Me_2 7-OCH_3 methiodide X	A	232 298 (323)
	H^+	229 (252) 293 (315)
	OH^-	(252) (285) 293 (315)
2-Carboethoxy-1-methyl 7HO ⇌ O 5-phenyl VI	A	265 303 (4.25) (330)
	H^+	253 320
	OH^-	273 315
2-Carboethoxy-5,7-HO ⇌ O 1-methyl VIII	A	(304) 330(4.19)
	H^+	(225) 308
	OH^-	(340) (260) 325

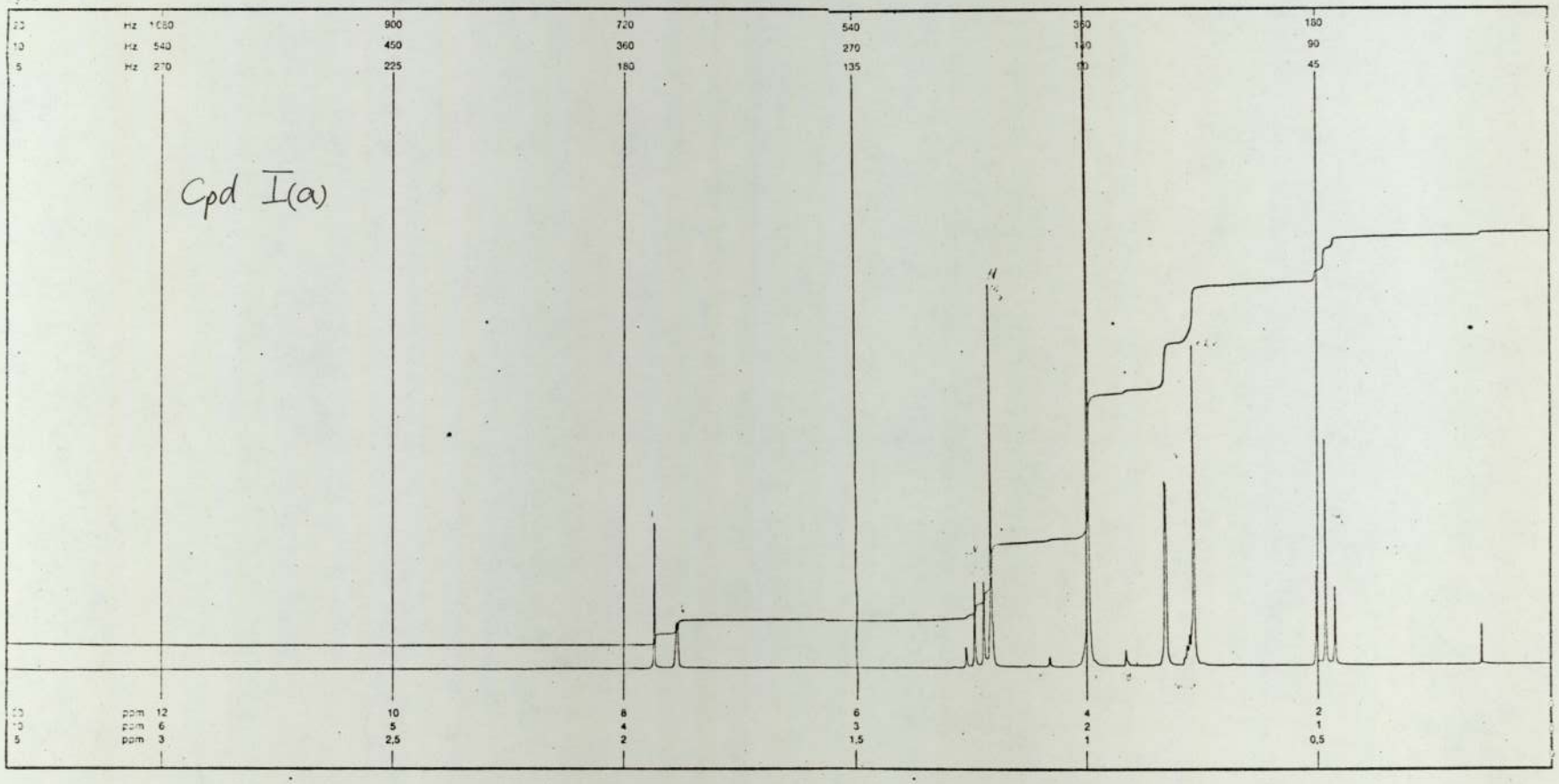
COMPOUND	SOLVENT	λ max nm, (logϵ)		
2-carboethoxy-5, 7-(O Me)$_2$ 1-Me II	A	227	294 (4.30)	
	H+	227	310	
	OH^-		294	
2, 6-dicarboethoxy-1-methyl 7-HO $\rightleftharpoons$ O VII	A	270		
	H^+	255	297*	Minor Peak
	OH^-	273	(293)	
2, 6-dicarboxy-1-methyl - 7-methoxy XVII	A	227	295	
	H^+	255	307	
	OH^-	251	297	
6-Acetyl - 2-Carboethoxy-1-methyl Pyrrole (3,2-b) pyridine III	A	247	317 (4.24)	
	H^+	247	315	
	OH^-	253	317	

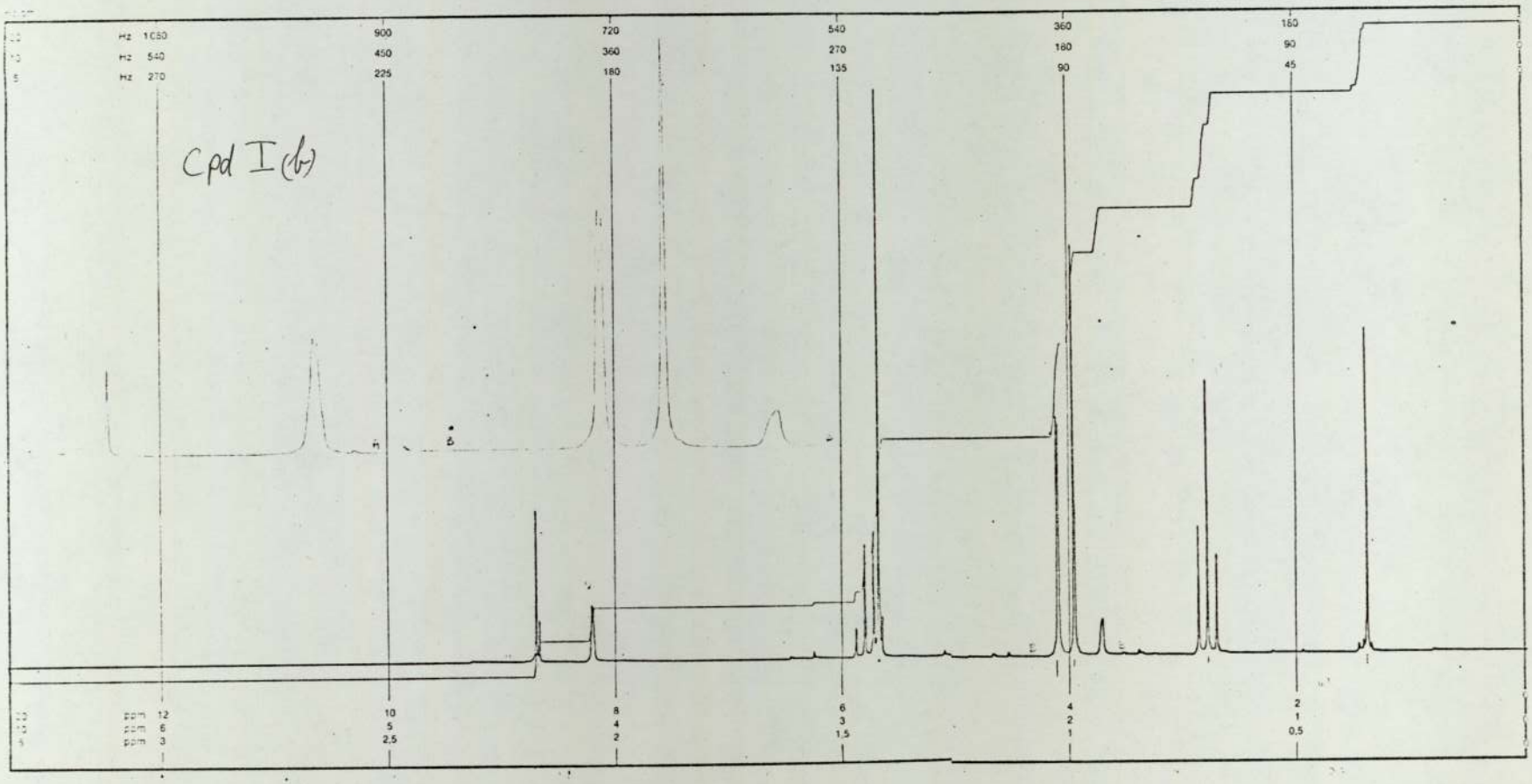
4.3 (i) N.M.R. SPECTRA

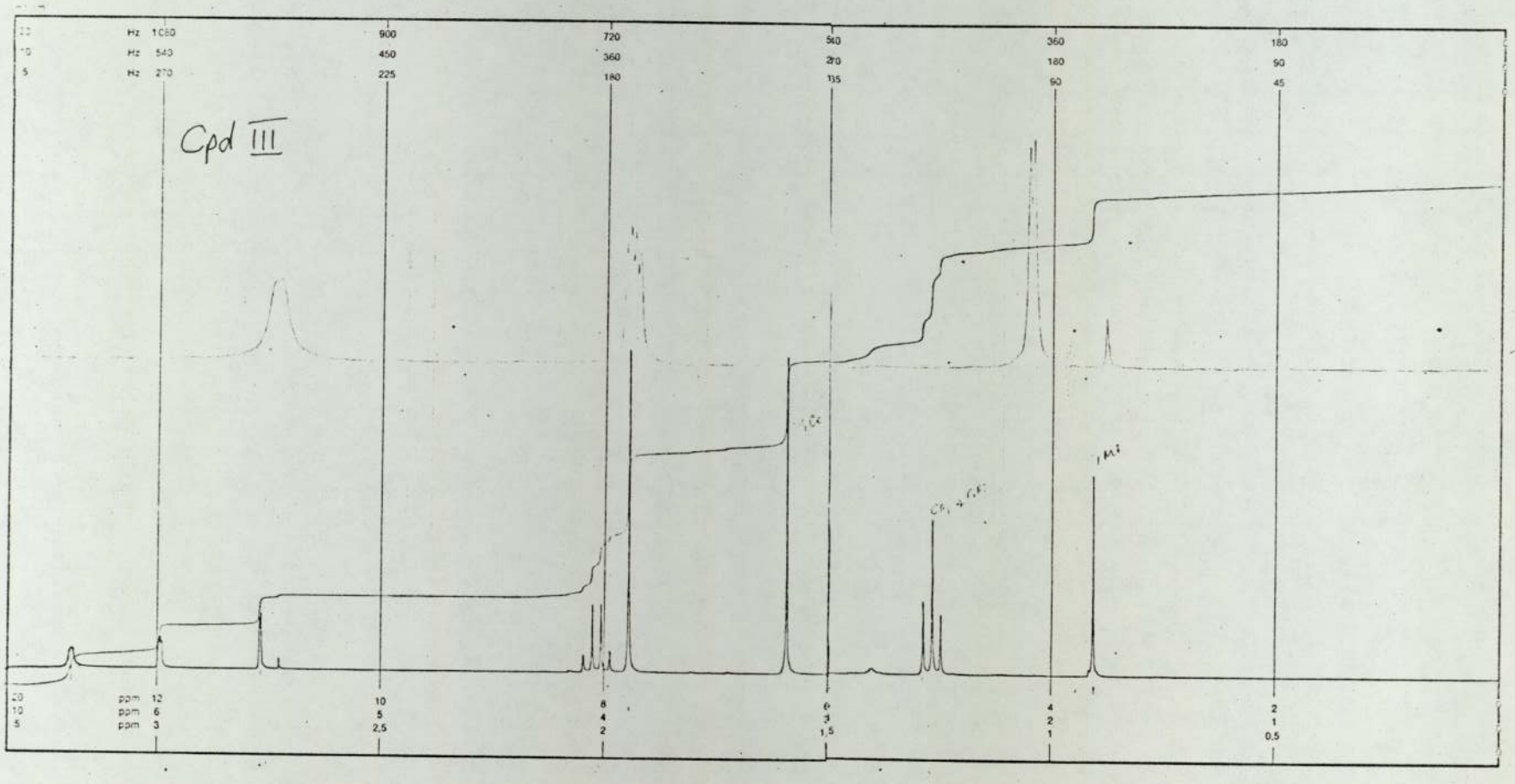
Instrument Bruker Spectrospin

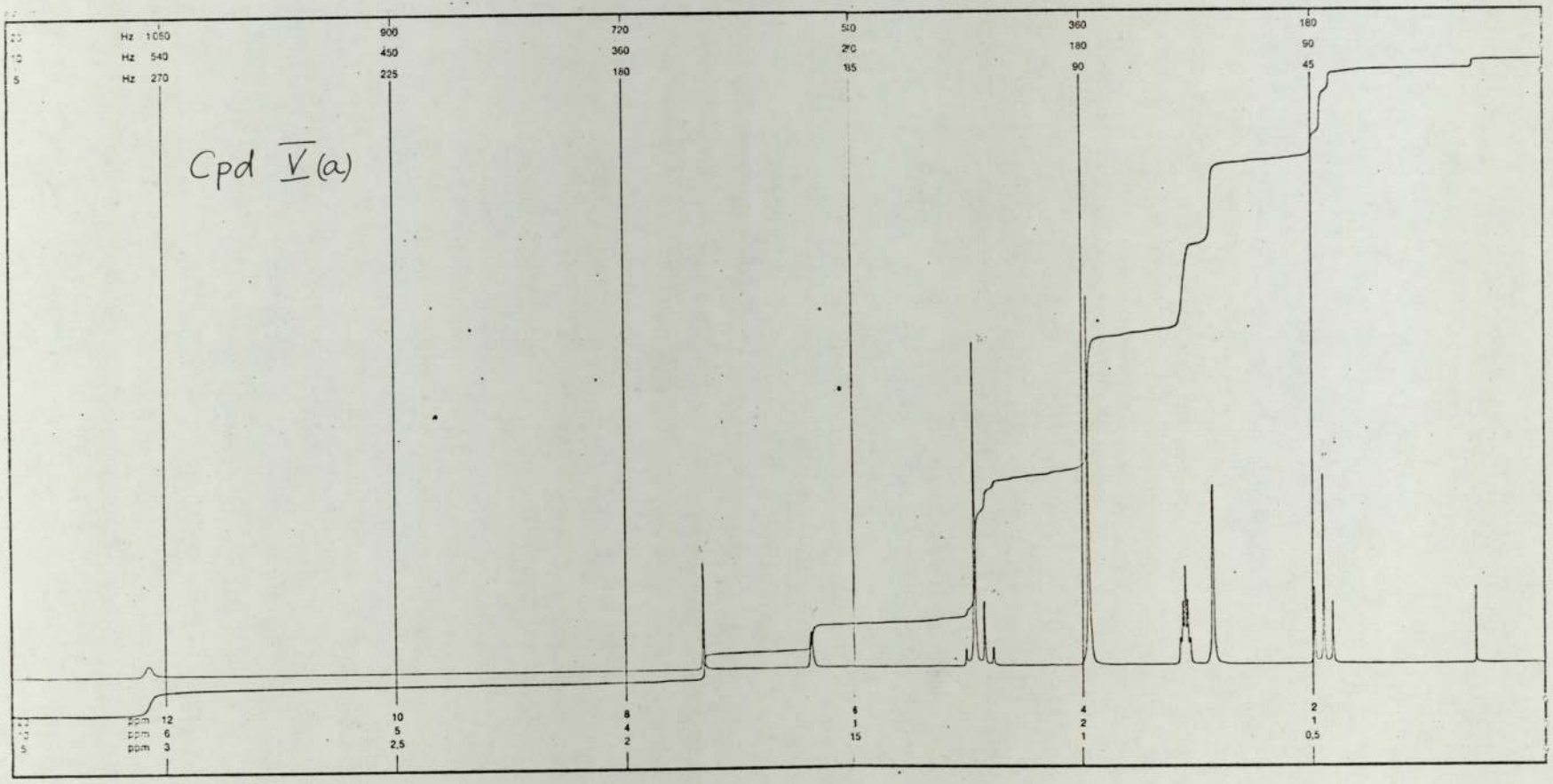
90 M Hz

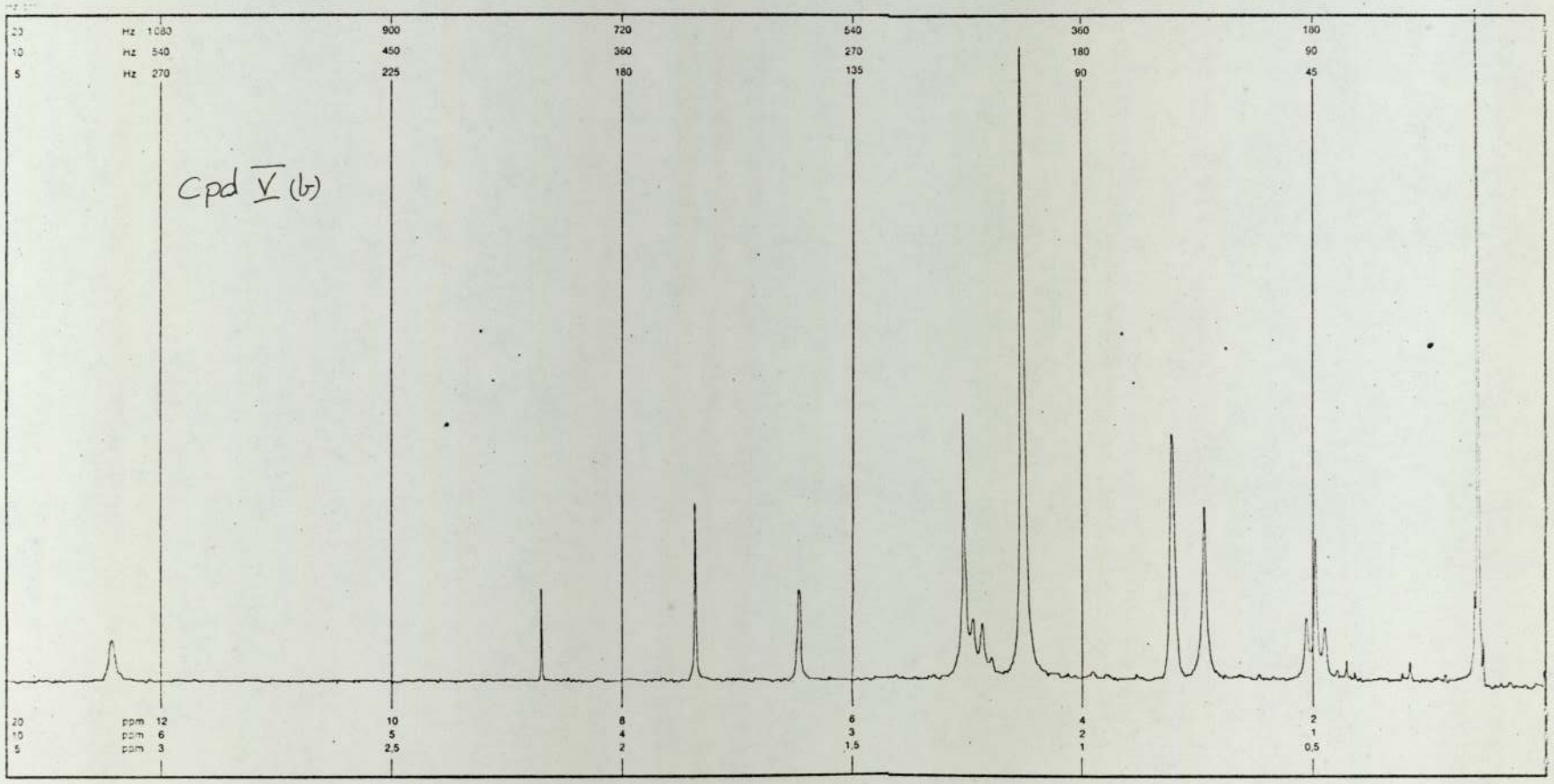
Cpd. I (a)

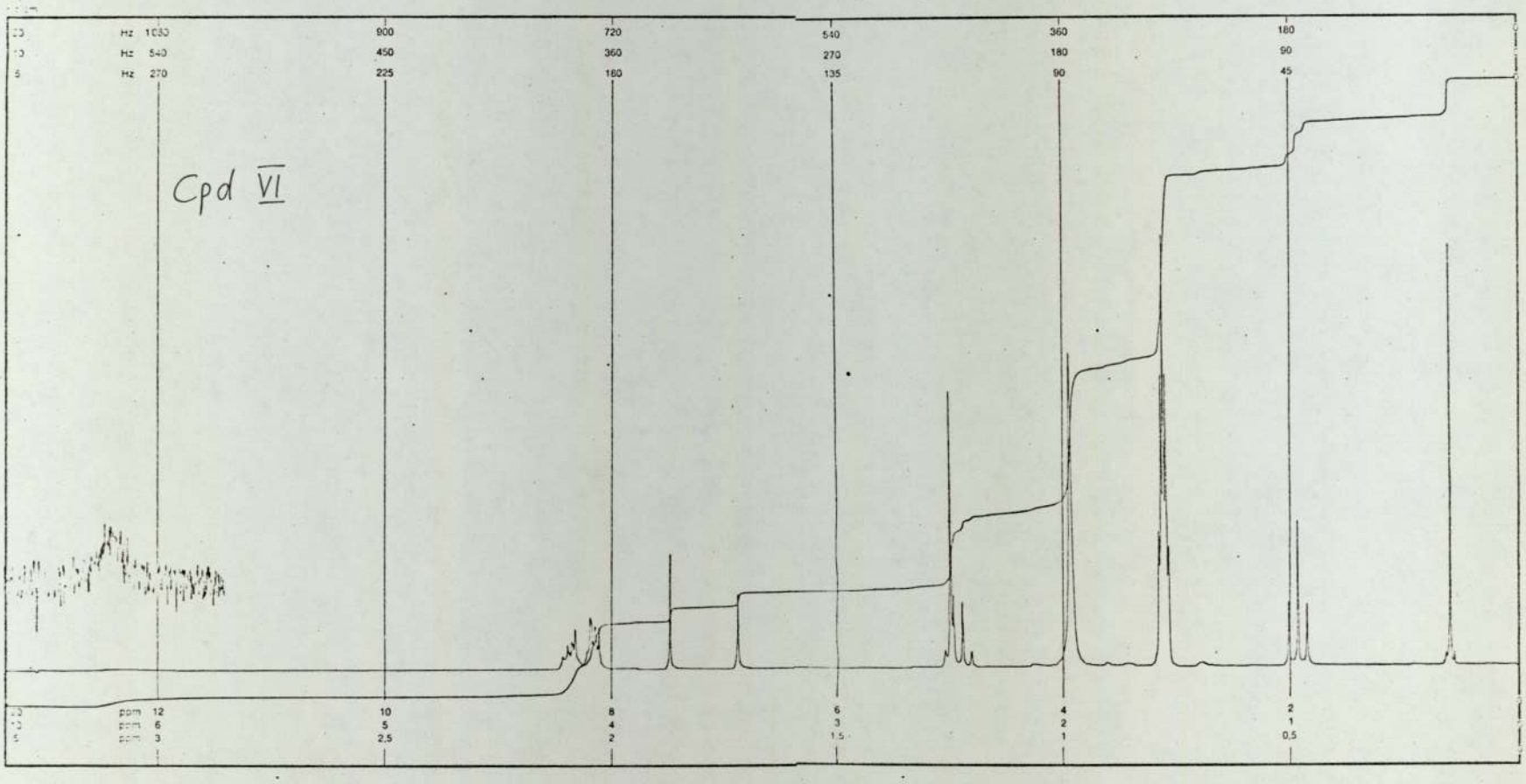

Cpd I(a)
Hz 1080
Hz 540
Hz 270
900
450
225
720
360
180
540
270
135
360
180
90
45
ppm 12
ppm 6
ppm 3
10
5
2,5
8
4
2
6
3
1,5
4
2
1
2
1
0,5

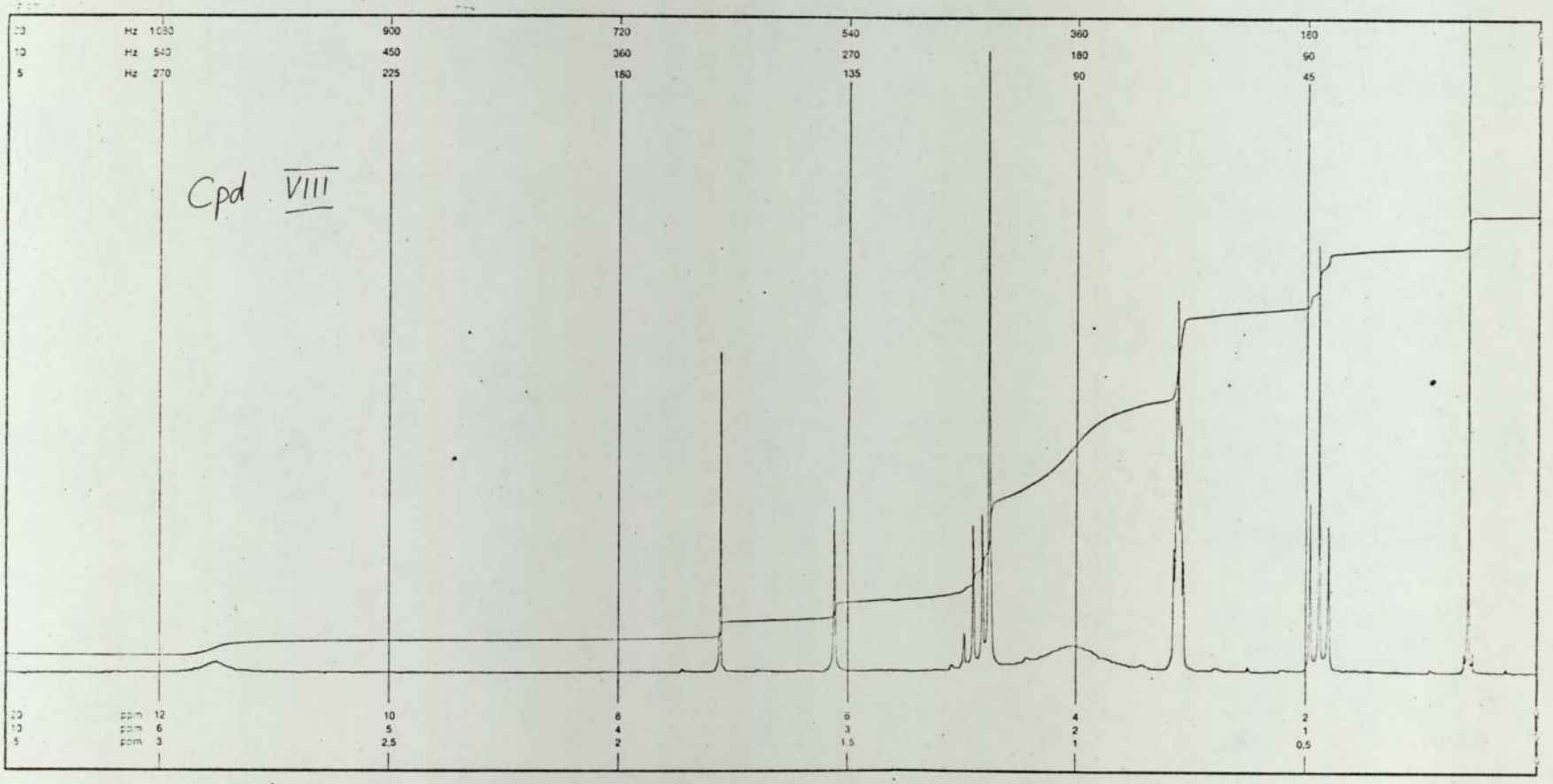

Cpd I (b)
Hz 1080
Hz 540
Hz 270
900
450
225
720
360
180
540
270
135
360
180
90
180
90
45
ppm 12
ppm 6
ppm 3
10
5
2,5
8
4
2
6
3
1,5
4
2
1
2
1
0,5

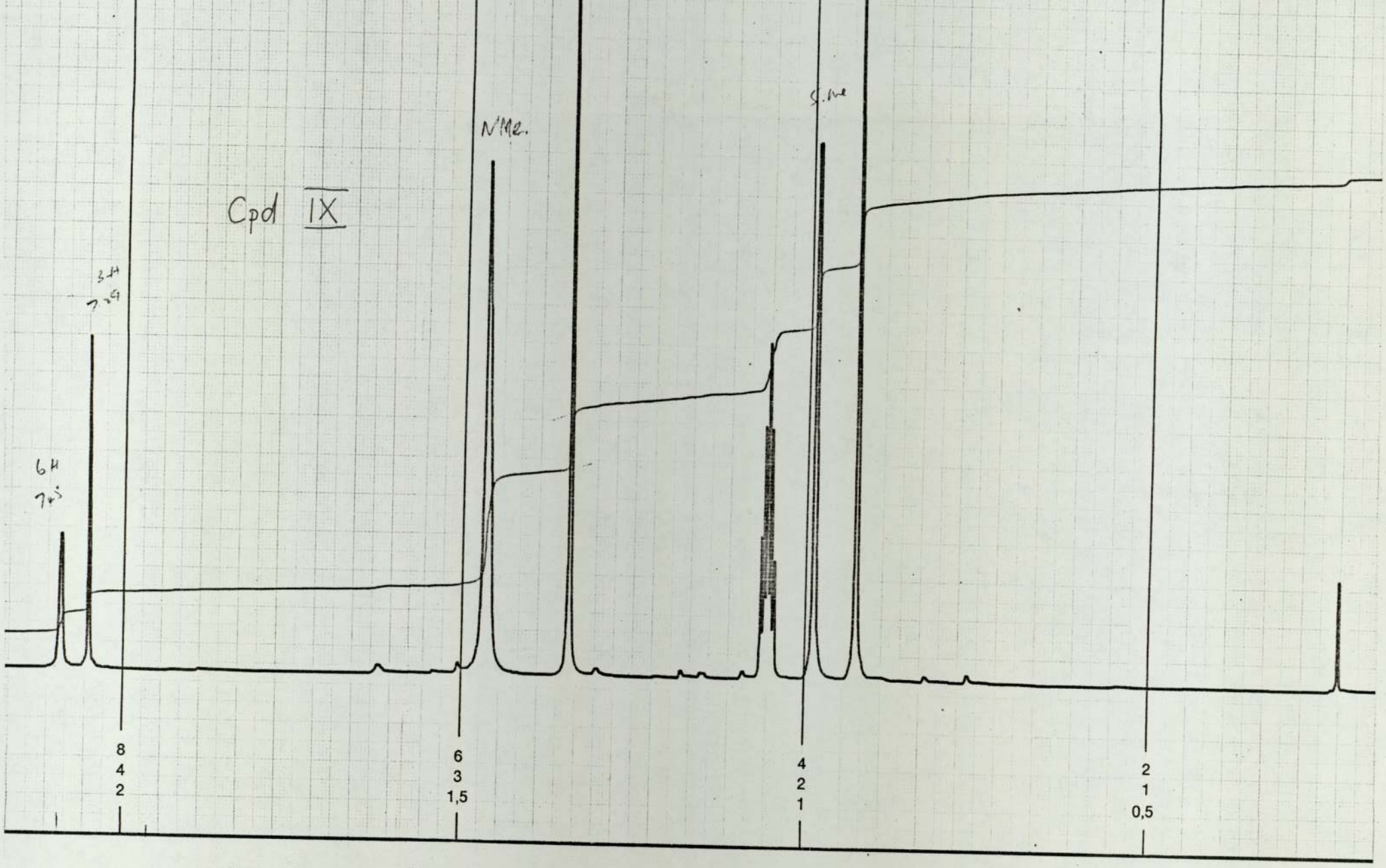

Cpd III
Hz 1080
Hz 540
Hz 270
900
450
225
720
360
180
540
270
135
360
180
90
180
90
45
ppm 12
ppm 6
ppm 3
10
5
2,5
8
4
2
6
3
1,5
4
2
1
2
1
0,5


Cpd V (a)
Hz 1080
Hz 540
Hz 270
900
450
225
720
360
180
540
270
135
360
180
90
180
90
45
ppm 12
ppm 6
ppm 3
10
5
2,5
8
4
2
6
1
1,5
4
2
1
2
1
0,5


Cpd V (b)
20 Hz 1080 900 720 540 360 180
10 Hz 540 450 360 270 180 90
5 Hz 270 225 180 135 90 45
20 ppm 12 10 8 6 4 2
10 ppm 6 5 4 3 2 1
5 ppm 3 2,5 2 1,5 1 0,5


Cpd VI
Hz 1080
Hz 540
Hz 270
900
450
225
720
360
180
540
270
135
360
180
90
180
90
45
ppm 12
ppm 6
ppm 3
10
5
2,5
8
4
2
6
3
1,5
4
2
1
2
1
0,5


Hz 1080
Hz 540
Hz 270
900
450
225
720
360
180
540
270
135
360
180
90
180
90
45
Cpd VIII
ppm 12
ppm 6
ppm 3
10
5
2.5
8
4
2
6
3
1.5
4
2
1
2
1
0.5


Cpd IX
3H
7.5
NMe.
S.Me
6H
7.5
8
4
2
6
3
1,5
4
2
1
2
1
0,5

4.3 (ii) N.M.R.

Tables of Chemical Shifts (δ ppm)

CHEMICAL SHIFTS (δ)

Cpd I									
(a) DMSO	1.26,1.34,1.42	2.47	2.71,2.72	4.23	4.23,4.29,4.37,4.44	6.93	7.1		
(b) $CDCl_3$	1.32,1.4,1.48	2.58	2.71,2.72	4.29	4.29,4.33,4.41,4.49	6.81,6.82	7.3		
	alkyl CH_3	5-CH_3	7-CH_3 split	1-CH_3	-CH_2 quadruplet	6-H	3-H		
Cpd III									
	1.36,1.44,1.51	2.73		4.15	4.32,4.4,4.48,4.55	7.44,7.48	8.32,8.33,8.34,8.35		9.12
$CDCl_3$	alkyl CH_3	CH_3 acetyl		1-CH_3	-CH_2 alkyl	3-H	7-H		5-H
Cpd V									
(a) DMSO	1.24,1.32,1.4	2.26,2.27		4.34	4.18,4.25,4.34,4.41	5.78	6.72		11.5
(b) DMSO/$CDCl_3$	1.24,1.32,1.4	2.2,2.27		4.34	4.18,4.25,4.34,4.41	5.87	6.75		11.4
	alkyl CH_3	CH_3		1-CH_3	-CH_2 alkyl	6-H	3-H		N-H
Cpd VI									
	1.25,1.33,1.41			4.39	4.2,4.28,4.36,4.49	6.27	6.87	7.5-7.8	11.76
DMSO	alkyl CH_3			1-CH_3	-CH_2 alkyl	6-H	3-H	Benzene	N-H
Cpd VIII									
	1.22,1.29,1.37			4.16	4.16,4.22,4.29,4.37	5.51	6.51	10.9	
DMSO	alkyl CH_3			1-CH_3	-CH_2 alkyl	6-H	3-H	N-H	
Cpd IV									
	1.32,1.4,1.48	2.58	3.95	4.3		6.48	7.26		
$CDCl_3$	alkyl CH_3	5-CH_3	O-CH_3	1-CH_3		6-H	3-H		
Cpd IX									
		2.8	3.04	4.46		7.29	7.45		
($CDCl_3$)		7-CH_3	5-CH_3	1-CH_3		3-H	6-H		

5. EXPERIMENTAL

2-Carboethoxy-1-methyl-4-nitro-pyrrole was prepared by a three stage process as a stock material. The nitro compound was catalytically reduced to the corresponding amino compound immediately prior to use.

1. 2-carboethoxy-1-methyl-4-nitro-pyrrole

1.1 Sodium Nitromalonaldehyde [24-27]

A solution of mucobromic acid (100g) in ethanol (100 cm^3) was added to a continuously stirred solution of sodium nitrite (100g) in 50% aqueous ethanol (160 cm^3). The addition was carried out in an efficient fume cupboard as in addition to an evolution of carbon dioxide some hydrogen cyanide is produced as a by-product.

The temperature was kept below 50^o during the addition and on standing nitromalonaldehyde sodium salt a pale orange coloured solid separated. This was filtered, washed with a little 50% aqueous ethanol followed by acetone.

NOTE: The yield is erratic in the reaction but is approximately 25% of the weight of mucobromic acid.

1.2 2-carboethoxy-4-nitro-pyrrole [28]

Sodium nitromalonaldehyde (16g) was dissolved in warm 65% aqueous

ethanol (100 cm^3). Glycine ethyl ester hydrochloride (14g) dissolved in the minimum of water was added and the resultant solution made alkaline by the dropwise addition of 40% aqueous sodium hydroxide and the solution set aside at 50°C for 45 minutes. The red crystalline mass was removed, washed with ethanol and dried (yield 75%). The product was recrystallised from ethanol as prisms. (MP 174°).

1.3 2-carboethoxy-1-methyl-4-nitro-pyrrole [28]

2-carboethoxy-4-nitro-pyrrole (40g) and methyl iodide (107g) were added to a stirred solution of sodium ethoxide (17g) in absolute ethanol (120 cm^3) in an enclosed vessel, the mixture cooled to room temperature and allowed to stand for 24 hours. The yellow crystalline mass was removed, washed with water and dried. Further product was obtained by the addition of water to the filtrate (yield 85%). Platelets were obtained by recrystallisation from ethanol (decolourising charcoal) (MP 113-114°).

2. 4-Amino-2-carboethoxy-1-methyl pyrrole [101,102]

2-carboethoxy-1-methyl-4-nitro-pyrrole (1g) dissolved in absolute ethanol (50 cm^3) with platinum oxide catalyst (0.15g) was hydrogenated at room temperature and atmospheric pressure until the calculated amount of hydrogen was absorbed. The catalyst was filtered off and the ethanol removed at room temperature, under reduced pressure, to leave a viscous colourless oil in almost quantitative yield.

NOTE: If the amine is kept, whether in the dark under nitrogen or in air, progressive darkening occurs and the liquid becomes red.

3. 2-Carboethoxy-1,5,7-trimethyl-pyrrolo (3,2-b) pyridine Cpd I

Acetyl acetone (6 cm^3) and concentrated hydrochloric acid (6 cm^3) was added to the alcoholic amine solution produced by the catalytic reduction of 2-carboethoxy-1-methyl-4-nitropyrrole (3g), and the mixture refluxed for 5 hours. After removal of the alcohol under reduced pressure the residue was dissolved in water and ether extracted (30 cm^3). The aqueous layer was made alkaline with concentrated ammonia and an off white precipitate of 2-carboethoxy-1,5,7-trimethyl-pyrrolo (3,2-b) pyridine separated (2.4g 68.6%) MP. 113° (aqueous ethanol).

Requires C 67.2, H 6.9, N 12.1 Found

C 67.12, H 6.91, N 12.08

$C_{13}H_{16}N_2O_2$ M^+ 232.121170 (232.12068)

log ϵ = 4.32 λ max 312 nm

4. Cpd XI

The methiodide separated as pale yellow needles when the above compound in acetone and excess methyl iodide was allowed to stand for one week. MP 248 dec.

λmax 310nm

5. 2-Carboxy-1,5,7-trimethyl-pyrrolo (3,2-b) pyridine Cpd IX

2-carboethoxy-1,5,7-trimethyl-pyrrolo (3,2-b) pyridine (0.2g) was refluxed for 30 minutes with aqueous sodium hydroxide (20 cm^3 5%). After cooling and acidification with concentrated hydrochloric acid a white precipitate separated (0.15g, 77%). This was recrystallised from hot water as the hydrochloride. MP 286-8°

Requires C 54.88 H 5.44, N 11.64 found C 54.76 H 5.54 N 11.28

6. Ethyl-2-carboethoxy-1-methyl-pyrrole-4-amino-β-crotonate Cpd XII

4-amino-2-carboethoxy-1-methyl-pyrrole (3g) glacial acetic acid (1 cm^3), ethyl acetoacetate (4 cm^3) and dry benzene (70 cm^3) were refluxed under Dean and Stark conditions until removal of water was complete (approximately 2 hours). The benzene was removed under reduced pressure leaving a yellow solid (72%). The product was decolourised with charcoal in ether and their recrystallised from ether/petrol MP 86°.

Requires C 60% H 7.14% N 10% found C 59.87 H 7.13 N 9.79

7. 2-Carboethoxy-1,5-dimethyl-7-oxo-pyrrolo (3,2-b) pyridine Cpd V

The above compound (3g) was refluxed in diphenyl ether (25 cm^3) when a yellow solid separated after 15 minutes. After removal of the precipitate the filtrate was treated with 60/80 petrol ether causing further precipitation. The petrol was removed from the

second filtrate and the diphenyl ether solution was refluxed for a further 15 minutes. The solution was cooled, treated with petrol when a further separation of product occurred. The bulked product was washed with petrol, boiled with ethanol and decolourising charcoal and after crystallisation from ethanol yielded a white solid monohydrate. (2.3g 77.4%) MP. 295°

Requires C 57.14 H 6.35 N 11.11 found C 57.22 H 6.26 N 11.14

λ_{max} (EtOH) 230, 240, 259, 292 log ϵ 3.3

8. 2-Carboxy-1,5-dimethyl-7-oxo-pyrrolo (3,2-b) pyridine Cpd XIII

2-Carboethoxy-1,5-dimethyl-7-oxo-pyrrolo (3,2-b) pyridine (0.1g) was refluxed in aqueous sodium hydroxide (10 cm^3 5%) for thirty minutes. After cooling the solution was acidified with concentrated hydrochloric acid. The white precipitate was filtered washed with water and crystallised from glacial acetic acid. MP 303°.

Requires C 56.25 H 4.16 N 14.58 found C 56.19 H 4.2 N 14.49

9. 2-Carboethoxy-1,5-dimethyl-7-methoxy-pyrrolo (3,2-b) pyridine Cpd IV

2-Carboethoxy-1,5-dimethyl-7-oxo-pyrrolo (3,2-b) pyridine (0.5g) (.02 mole) was added to a large excess of ethereal diazomethane. (0.1 mol/250 cm^3) at room temperature and stirred for 72 hours. The solution was evaporated to dryness under reduced pressure to leave an off white solid which was recrystallised from ether/petrol.

(MP 88° 76%)

Requires C 62.9 H 6.45 N 11.29 found C 62.63 H 6.56 N 10.98
M^+ 248.116084 (Calc 248.116261) λ max (EtOH) 235, 297 logϵ 4.2

10. Cpd X

Methyl iodide (2 cm^3) was added to a solution of the above compound in acetone (0.8g/20 cm^3) and the mixture refluxed for 15 minutes. Yellow crystals of the methiodide separated (0.7g, 74%)
MP decomp 225° λ max (EtOH) 232, 298

11. 2-Carboethoxy-1,5-dimethyl-7-oxo-pyrrolo (3,2-b) pyridine hydrochloride. Cpd XIV

A solution of 2-carboethoxy-1,5-dimethyl-7-oxo-pyrrolo (3,2-b) pyridine (0.1g) in ethanol was added to absolute ethanol (50 cm^3) saturated with dry hydrogen chloride gas. After standing for 24 hours the bulk was reduced to 15 cm^3, ether added and colourless crystals of the hydrochloride (0.07g 81%) separated MP 255-7.

Requires C 53.09 H 5.77 N 10.17 Cl 13.14 found C 53.23
H 5.55 N 10.35 Cl 13.12 λ max 241, 258, 292, 321

12. 2-Carboethoxy-1-methyl-7-oxo-5-phenyl-pyrrolo (3,2-b) pyridine
Cpd VI

4-amino-2-carboethoxy-1-methyl pyrrole (2.5g) glacial acetic acid

($1\ cm^3$), ethyl benzoyl-acetate ($3\ cm^3$) and dry benzene ($60\ cm^3$) was refluxed under Dean and Stark conditions until the removal of water was complete (2 hours). Removal of benzene under reduced pressure left an amber coloured oil. This was dissolved in ether and extracted with sodium hydroxide (5%, $20\ cm^3$). The ethereal solution was dried over magnesium sulphate and after evaporation left a low melting solid corresponding to ethyl-2-carboethoxy-1-methyl-pyrrole-4-amino - cinnamate (2.7g 53%).

(M 342.157944 calc 342.156987)

The cinnamate intermediate (2.5g) was refluxed in diphenyl ether ($30\ cm^3$) for 30 minutes. On cooling a gelatinous solid separated. Because of the nature of this solid the diphenyl ether was removed by Soxhlet extraction with petrol ether (60/80). The product dissolved in hot glacial acetic acid and separated as a white gelatinous precipitate on cooling (1.18g 55.5%) MP 292-4°.

Requires C 68.92 H 5.41 N 9.46 found C 68.64 H 5.5 N 9.42

λmax (EtOH) 265, 303 logϵ 4.25

13. 2-Carboxy-1-methyl-7-oxo-5-phenyl-pyrrolo (3,2-b) pyridine Cpd XV

2-Carboethoxy-1-methyl-7-oxo-5-phenyl-pyrrolo (3,2-b) pyridine (0.2g) was refluxed with aqueous sodium hydroxide (5%, $20\ cm^3$) for 30 minutes. The solution was cooled and made acid with concentrated hydrochloric acid when a white precipitate formed. MP 303-4°. Molecular weight by mass spectrometry in agreement.

14. Cpd XXI 2-carboethoxy-N-4-(2-carboethoxy-1-methyl pyrrolyl)-acetamide

4-amino-2-carboethoxy-1-methyl pyrrole (2.5 g) was refluxed with diethyl malonate (15 cm^3) for 30 minutes. The excess diethyl malonate was removed under reduced pressure leaving a brown tar. This was dissolved in benzene and decolourised with charcoal. The product crystallised as colourless needles by the addition of petrol ether. (1.39g 34%) MP 92°

Requires C 55.3 H 6.38 N 9.93 found C 55.08 H 6.45 N 9.82

λ max (EtOH) 238 289

15. 2-Carboethoxy-7-hydroxy-1-methyl-5-oxo-pyrrolo (3,2-b) pyridine

Cpd VIII

4-Amino-2-carboethoxy-1-methyl pyrrole (2.5g) in diethyl malonate (20 cm^3) was refluxed for 4 hours. The excess diethyl malonate was distilled off at atmospheric pressure solid started to separate. The volume was reduced to approximately 5 cm^3, cooled and ether added. The buff coloured solid was filtered and washed with ether (1.1g 32%). Recrystallisation from aqueous acetic acid gave a white solid MP 294-6

λ max (EtOH) 330 Shoulders logϵ 4.2

Requires C = 55.93 H 5.085 N 11.864 found C = 55.72, H = 5.18 N = 11.77

16. 2-Carboethoxy-5,7-dimethoxy-1-methyl-pyrrolo (3,2-b) pyridine

Cpd II

2-Carboethoxy-5-hydroxy-1-methyl-7-oxo-pyrrolo (3,2-b) pyridine (0.2g) dissolved in ethanol (20 cm^3) was added to an ethereal solution of diazomethane (2g/150 cm^3) and in an Erlenmeyer flask and the mixture stirred overnight. The ether was removed under reduced pressure leaving a pale yellow solid (0.21g 94%). Recrystallisation from ether/petrol gave a white crystalline solid MP 108°

Requires C 59.1 H 6.06 N 10.6 found C 59.76 H 6.3 N 10.09

λ max EtOH 294 logϵ 4.24

17. Ethyl-2-carboethoxy-1-methyl-pyrrole-4-amino-methylene-malonate

Cpd XVI

4-amino-2-carboethoxy-1-methyl-pyrrole (2.5g) and ethyl ethoxy-methylene-malonate (3 cm^3) were refluxed in dry benzene (50 cm^3) for 4 hours. Reduction of the volume under reduced pressure caused separation of crystals which were removed. Addition of petrol to the residual benzene solution (10 cm^3) caused a further separation of pale brown crystals (96%).

Boiling of the product in ethanol with charcoal caused some improvement of colour which was increased by recrystallisation from aqueous alcohol. Final crystallisation from benzene gave colourless crystals MP 86° M.W. confirmed by Mass Spectra.

18. 2.6-Dicarboethoxy-1-methyl-7-oxo-pyrrolo (3,2-b) pyridine

Cpd VII

The pyrrole ethoxy methylene malonate intermediate (4g) was refluxed with diphenyl ether (25 cm^3) for 30 minutes during which time the solution darkened appreciably. After cooling the addition of petrol ether resulted in the formation of a brown precipitate. Because of the insolubility of the precipitate removal of most of the coloured impurity was effected by reflux in acetone. Final crystallisation from glacial acetic acid yielded a colourless solid (2.3g, 65%) MP 300-2°

Requires C 57.43 H 5.48 N 9.59 found C 56.63 H 5.53 N 9.36

λ max (EtOH) 270

19. 2.6-Dicarboxy-7-methoxy-1-methyl-pyrrolo (3,2-b) pyridine Cpd XVII

2.6-dicarboethoxy-1-methyl-7-oxo-pyrrolo (3,2-b) pyridine (1g) was dissolved in absolute ethanol (50 cm^3) containing sodium ethoxide (1g). Methyl iodide (5 cm^3) was added mixture refluxed for 2 hours and then allowed to stand overnight. Evaporation left a white solid which was completely water soluble. The solution was ether extracted but nothing was found in the ether layer. Acidification of the aqueous layer caused separation of a white solid, (0.3g) which was recrystallised from aqueous ethanol MP 324

Requires C 52.8 H 2.5 N 11.2 found C 52.4 H 2.58 N 10.97

λ max 295 (EtOH)

20. Ethyl-2-carboethoxy-1-methyl pyrrole-4-amino-methylene-cyanoacetate Cpd XVIII

4-amino-2-carboethoxy-1-methyl pyrrole (3.5g) ethyl ethoxy methylene-cyanoacetate (3g) and benzene (70 cm^3) were refluxed on a water bath for 2 hours. The benzene was distilled off to leave a pale yellow solid (4.7g, 78%) which on recrystallisation from ethanol gave pale cream needles. MP 110°.

Found C 57.49, H 5.86% N 14.34%
Requires C 57.73 H 5.84 N 14.4

21. Attempted Ring Closures of Ethyl-2-carboethoxy-1-methyl pyrrole-4-amino-methylene-cyanoacetate

(a) The intermediate (3g) was heated in diphenyl ether (25 cm^3) for 30 minutes. The solution became dark brown. After cooling petrol ether was added and a light brown solid separated (2.7g) which was shown to be starting material.

NOTE: Further heating caused decomposition and no ring closed product was isolated.

(b) The intermediate (0.5g) was heated with polyphosphoric acid (12g) at 70° on a water bath for four hours. The solution became dark red. The mixture was poured onto ice and then made alkaline with 10% sodium hydroxide. A black tar separated from

which nothing could be isolated.

(c) The intermediate (0.5g) and sodium ethoxide (0.3g) was refluxed in absolute alcohol (25 cm^3) for four hours. Water (10 cm^3) was added to the mixture followed by concentrated hydrochloric acid dropwise until acid. The precipitate of sodium chloride was filtered off and the filtrate evaporated to dryness. The resultant solid was washed with a little water leaving a residue of 0.2g which was shown to be starting material.

22. 6-Acetyl-2-carboethoxy-1-methyl-pyrrole (3,2-b) pyridine Cpd III

4-amino-2-carboethoxy-1-methyl pyrrole (2.5g) in ethanol (50 cm^3) was treated with acetyl acetaldehyde dimethyl acetal (5 cm^3) and concentrated hydrochloric acid (2 cm^3) in 20 cm^3 of alcohol which had been allowed to stand for 10 minutes. The mixture was refluxed for 2 hours and then the solvent bulk reduced by distillation under reduced pressure. Colourless crystals separated which were re-crystallised from ethanol/ether MP 180 (1.6g, 44%).

Requires C 63.4 H 5.69 N 11.38 found C 63.16 H 5.71 N 11.65

IR C = O 1700, 1660

λ max 247, 317

23. N-Cinnamyl-4-amino-2-carboethoxy-1-methyl pyrrole Cpd XIX

4-amino-2-carboethoxy-1-methyl pyrrole (1.6g), and cinnamoyl chloride (1.4g) in benzene (40 cm^3) were refluxed for two hours.

The excess benzene was removed under reduced pressure and on cooling, off white crystals separated (1.3g 46%). The product was filtered washed with 5% sodium hydroxide,water and crystallised from ethanol. MP 134-6° M^+ 298. 131519 found 298.131734

24. Attempted ring closure of the cinnamyl intermediate

(a) The intermediate (0.6g) was refluxed with diphenyl ether (20 cm^3) for two hours. After cooling petrol ether was added when a light brown solid separated, which after washing with petrol ether was recrystallised from ether/petrol and was shown to be starting material (0.42g).

(b) The cinnamyl intermediate (0.1g) was heated with polyphosphoric acid (5g) on a water bath for one hour. Effervescence occurred during the heating. The mixture was poured onto ice and neutralised with sodium carbonate. Ether extraction and subsequent evaporation left a trace of brown oil, which from the Infra Red Spectra appeared to be starting material.

(c) The cinnamyl intermediate (0.2g) was allowed to stand with concentrated sulphuric acid (10 cm^3) for one week. Some effervescence occurred. The mixture was worked up as above giving rise to a similar brown oil shown to be starting material.

25. Ethyl-N-cinnamyl-p-amino benzoate Cpd XX

Ethyl-p-amino benzoate (15g) aqueous sodium hydroxide (100 cm^3 100%) and cinnamoyl chloride (15g) were shaken in a conical flask

for one hour and then the solid product was washed, heated on a water bath for one hour successively with sodium hydroxide, water and then crystallised from ethanol (22g, 87%) MP 174-6°.

26. Attempted cyclisation of ethyl-N-cinnamyl-p-amino-benzoate

The three methods above were attempted but in every case only starting material was recovered.

27. 4-Hydroxy-2-methyl-naphthyridine Cpd XXI

3-amino-pyridine (4g), ethyl acetoacetate (6.5 cm^3), glacial acetic acid (5 cm^3) and dry benzene (100 cm^3) were refluxed for two hours under Dean and Stark conditions when removal of water was complete. Removal of the solvent at reduced pressure left a reddish oil which was dissolved in diphenyl ether (35 cm^3) and heated under reflux for 45 minutes. After cooling petrol ether was added and a brown solid separated which was filtered and washed with petrol ether. The solid was dissolved in ethanol and decolourised with charcoal. Recrystallisation from ethanol/ether yielded an off white solid (2.9g, 83%) MP 305°
Molecular weight by mass spectra in agreement.

28. Attempted preparation of 3-acetamido-1-acetyl-pyrrole[103]

Acetic anhydride (15 cm^3) was added to amino-acetaldehyde diethyl acetal (21g) and pyridine (20 cm^3) in dry ether (150 cm^3). After 15 minutes freshly ignited potassium carbonate (25g) was added, the mixture shaken for 2 hours and then allowed to stand overnight.

Distillation gave acetamido-acetaldehyde diethyl acetal 88-90°/ 0.15mm (17.3g, 63%).

Acetamido-acetaldehyde diethyl acetal (3.3g) was heated for 15 minutes with 0.05 M hydrochloric acid (30 cm^3), cooled, saturated with sodium acetate and then boiled for two hours. After cooling the solution was extracted with ethyl acetate (3 x 30 cm^3).

Evaporation of the ethyl acetate solution left a small amount of brown residue which was dissolved in water. Addition of mercuric chloride caused precipitation. The solid was filtered, washed and then suspended in water (15 cm^3). The mercuric complex suspension was decomposed by the addition of hydrogen sulphide. After filtration to remove mercuric sulphide the filtrate was carefully neutralised and extracted with ether (3 x 15 cm^3). After drying with potassium carbonate the ether solution was evaporated but very little residue remained.

NOTE: After the heating to ring close the acetamido-acetaldehyde, extraction was attempted using methylene chloride with very little effect.

It was concluded that the method was impracticable for the preparation of a working quantity of starting material.

29. Pyrrole-3-carboxylic acid

29.1 N-Carboethoxy-glycine ethyl ester [104]

Glycine ethyl ester hydrochloride (250g) was dissolved in water (250 cm^3) 10 M sodium hydroxide (180 cm^3) was added slowly and the mixture cooled in ice. The solution was stirred continuously and ethyl chloroformate (200g) added. After standing for 15 minutes a solution of sodium carbonate (100g/ 250 cm^3) was added. The oily upper layer was separated, washed with water and then dried over sodium sulphate. Distillation under reduced pressure yielded N-carboethoxy-glycine ethyl ester (225g, 71%) BP 128/13mm

29.2 1,3-dicarboethoxy-4-pyrrolidone [105]

N-carboethoxy-glycine ethyl ester (128g) and sodium wire (14g) were reacted in dry benzene (500 cm^3). Ethyl acrylate (65g) was added slowly to the stirred mixture. The mixture became slightly blue and gelled. After standing for half an hour the mixture was refluxed for one hour. Alcohol was added to the refluxing mixture to remove the small amount of residual sodium. The excess benzene was removed under reduced pressure to leave a viscous paste. The solid was treated with iced water (500 cm^3) and stirred vigorously. Ether (100 cm^3) was added and the two phases separated. The ether phase was washed with water and the aqueous portion added to the first aqueous phase. The total aqueous phase was then added to

concentrated sulphuric acid (40 cm^3) and ice (250g) and the mixture stirred. After saturation with sodium chloride the solution was extracted with chloroform (3 x 100 cm^3). The chloroform extract was dried with sodium sulphate and after removal of the chloroform distillation at reduced pressure yielded 1,3-dicarboethoxy-pyrrolidone (115g 67%) BP 108-112°/13.

29.3 1.3-dicarboethoxy-4-methoxy -Δ^3-pyrroline [105]

A large excess of diazomethane in ether (3 fold) was added to an ethereal solution of 1,3-dicarboethoxy-4-pyrrolidone (24g) at 0°C, the addition taking about 20 minutes. The solution was allowed to stand overnight and then the ether was removed under reduced pressure. The residue was dissolved in ether and then shaken with aqueous sodium hydroxide. The ether phase was separated, dried with sodium sulphate and then distilled under reduced pressure using a short fractionating column.

1,3-dicarboethoxy-4-methoxy- Δ^3-pyrroline (21.9g 86%) was obtained at 110-140°/3mm. The product solidified to off white crystals MP 63-65°.

29.4 Pyrrole-3-carboxylic acid [105]

1,3-dicarboethoxy-Δ^3 pyrroline (40g) was refluxed with aqueous sodium hydroxide (30g/150 cm^3) for three hours. After cooling the solution was ether extracted (2 x 100 cm^3) and the aqueous phase acidified with concentrated hydrochloric acid. After saturation with sodium chloride the solution was extracted

with ethyl acetate (4 x 100 cm^3). After drying with sodium sulphate the ethyl acetate was removed under reduced pressure to leave a brown viscous oil which would not crystallise (122g 65%). A concentrated solution of the oil in ethyl acetate was placed on a six inch acid alumina column and eluted with methanol. Reduction of the volume of methanol yielded a semi-crystalline product which yielded some pyrrole-3-carboxylic acid MP 147-149 on vacuum sublimation.

30. ATTEMPTED REACTIONS ON PYRROLE-3-CARBOXYLIC ACID

1. Reduction to the corresponding alcohols

The pyrrole-3-carboxylic acid (0.3g) in ether (30 cm^3) was boiled under reflux for 3 hours using a condenser filled with a guard tube. Ethereal lithium aluminium hydride (0.1g/30cm^3) was added dropwise to the boiling solution. After cooling the excess lithium aluminium hydride was decomposed with 5% sodium hydroxide. The ether layer was separated washed with sodium hydroxide and then dried with sodium sulphate. Evaporation of this solution left very little residue (0.5g). Acidification of the aqueous layer enabled recovery of the pyrrole-3-acid

Repetition of the reduction with varied reflux times , excesses of lithium aluminium hydride and use of tetrahydrofuran as solvent made little difference.

2. Conversion to the pyrrole acid chloride

Pyrrole-3-acid (0.25g) in chloroform (30 cm^3) was warmed with phosphorus pentachloride (0.5g) under anhydrous conditions on a water bath. The solution darkened rapidly and after removal of chloroform a black tar remained.

Prolonged standing of the above mixture at room temperature caused the same effect.

The conversion was attempted using thionyl chloride in ether at room temperature but the solution darkened leaving a black residue after removal of the ether.

3. Conversion to the pyrrole amide

It was felt that conversion to the acid chloride with thionyl chloride was the more promising reaction but that the acid chloride decomposed rapidly.

The pyrrole acid (0.42g) in dry chloroform was treated with thionyl chloride (0.3 cm^3) and the mixture cooled in ice. The solution became green and after 15 minutes the cold flask was subjected to reduced pressure to attempt removal of any unreacted thionyl chloride. Addition of excess ethereal ammonia gave a cream coloured precipitate which after removal rapidly darkened and could not be recrystallised.

Direct conversion of the pyrrole-3-acid to the amide by warming the ammonium carbonate gave very little reaction and the acid was recovered almost quantitatively.

4. Preparation of 3-carbomethoxy pyrrole

Pyrrole-3-carboxylic acid (0.66g) in ether (20 cm^3) was allowed to stand at room temperature with diazomethane (0.6g/75 cm^3) for 24 hours. The ether was distilled of under reduced pressure leaving an off white residue. This was redissolved in ether, washed with sodium hydroxide and after separation and drying recrystallised from ether/petrol (0.51g 80%)
MP 84-86 (Lit 86-87)

5. Attempted conversions of 3-carbomethoxy pyrrole to the corresponding amide

(i) Methanolic 3-carbomethoxy pyrrole (0.5g/10 cm^3) was mixed with excess 0.88 aqueous ammonia and the mixture allowed to stand for five days at room temperature. Removal of solvent left a residue which proved to be starting material.

(ii) Repeat of the experiment but employing ethereal ammonia gave the same result.

(iii) A methanolic solution of ester, formamide and sodium methoxide was heated under anhydrous conditions at 90° for two days. After working up almost quantitative

recovery of starting material was obtained.

(iv) Repeat of the procedure but employing ammonium carbonate gave the same result.

31. Nitration of Pyrrole [106]

A cold solution of nitric acid (12g) in acetic anhydride (40 cm^3) was added dropwise to a stirred solution of pyrrole (10g) in acetic anhydride (80 cm^3) in an ice salt mixture. The temperature was maintained at about 0^o throughout the reaction and a black tarry mass formed. 50 cm^3 of water was added, stirred for 10 minutes and then ether extracted (2 x 100 cm^3). The ethereal layer treated with sodium bicarbonate and after drying with sodium sulphate removal of the ether under reduced pressure left a tarry oil. Tarry impurities were removed by elution on a neutral alummina column followed by boiling with charcoal. A yellow crystalline solid 2-nitro-pyrrole was obtained (7.4g, 42%) by recrystallisation from ether/petrol.

32. Nitration of N-methyl-pyrrole [107]

The nitration and extraction procedure adopted was as above. After drying the ethereal solution of the N-methyl-nitro-pyrroles the ether was removed and the residue distilled under reduced pressure using a small fractionating column. The first fraction was collected between 68-80%/0.7mm and solidified to the low melting N-methyl-2-nitro-pyrrole (MP 29-31). A second fraction

92-100°/0.7mm was collected corresponding to N-methyl-3-nitro-pyrrole which crystallised to pale yellow needles MP 61-63° (Lit 64-65°) (Yield 64%).

33. Attempted reduction and cyclisation

Because of the instability of the simple amino pyrroles reduction and ring condensation was attempted in situ.

Reduction of the 2-nitro pyrrole and N-methyl-3-nitro pyrrole could be effected with tin and hydrochloric acid or catalytically with palladium charcoal and hydrogen. However immediately amine was produced the characteristic dark red colour appeared and the presence of malondialdehyde, acetyl-acetone or even acyl chlorides did not give rise to any significant product. Addition of acyl chloride or anhydride to the catalytic hydrogenation mixture produced an explosive reaction but no identifiable product.

6. BIOLOGICAL PROPERTIES OF AZAINDOLES

As this series of compounds is the azalogue of the indoles, many of which are known to have physiological activity, and the deazalogue of the purines, considerable interest in their biological behaviour is created.

The first attempt to prepare the azalogue of a biologically active compound was made by Bernstein et al in the synthesis of 6-amino-2, 3-diphenyl-7-azaindole [108]. This was tested against Plasmodium Cophurae for antimalarial activity but showed little effect.

Protiva et al [109] prepared a series of 1-diethylaminoalkyl derivatives of 5-methyl-2-phenyl-4-azaindole as possible antihistammines but they proved to be inactive. Robison and Robison[110] prepared 7-azaindole-acetic acid, 7-azaindole-propanoic acid, 7-azatryptophan and 7-azatryptamine.

SUMMARY

The approach to synthesis of 4-azaindoles involved the coupling of a pyridine ring system to a pyrrole ring. This involved the preparation of a 3-or 4-amino-pyrrole of sufficient stability to enable use without decomposition but active enough to allow coupling with a suitable reagent followed by ring closure. Initial attempts at in situ reductions of simple nitro-pyrroles were unsuccessful. 2-carboethoxy-1-methyl-4-nitro-pyrrole proved to be a satisfactory precursor to the corresponding amino compound in that it was stable, crystallised readily and gave an amine on reduction stable enough to permit reaction before decomposition.

The nitro compound was prepared from mucobromic acid by a three stage process which is limited by the expense of the starting material and the poor conversion yield of to nitromalonaldehyde in the first stage. Large scale synthesis of mucobromic acid in the laboratory was attempted but the yields were inconsistent. The use of large quantities of bromine and the violence of the reaction made the procedure hazardous.

Successful condensations of 4-amino-2-carboethoxy-1-methyl-pyrrole were achieved with acetyl acetone, ethyl acetoacetate, ethyl benzoyl-acetate, acetyl-acetaldehyde, diethyl malonate and ethyl ethoxy-methylene-malonate,in yields which were acceptable.

Cinnamoyl chloride coupled with the amine to give a non ring closed intermediate but ring closure could not be effected. A similar result

occurred when ethyl-p-amino-benzoate was used but when this was replaced by aniline or an amino-benzene derivative not containing an electrophile facile combination and ring closure occurred.

Ethyl ethoxy-methylene-cyanoacetate reacted to give a non ring closed intermediate but the reaction would go no further. This was explained by the steric relationship of the cyano and carboethoxy groups with the pyrrole-5-carbon atom, and confirmed by the case of cyclisation when the two groups involved were both carboethoxy as in ethyl ethoxy-methylene-diethyl malonate.

Coupling with malonaldehyde or nitro-malonaldehyde could not be effected and intractible tars resulted. This was regrettable as both potential products would have been of interest.

The reaction with acetyl-acetaldehyde gave an unexpected product resulting from an aldol type condensation of the aldehyde prior to coupling. It is likely that variation of the reaction conditions would enable the formation of a product involving the reaction of a single molecule of acetyl-acetaldehyde.

The structure of the azaindoles and tautomerism of potential hydroxyl containing molecules was studied by Infrared, Ultraviolet and N.M.R. spectroscopy. N.M.R. methods clearly showed the fundamental aromatic ring protons and was most useful in establishing the preferred tautomeric forms where applicable.

Ultraviolet spectra in solvents of a range of polarities, limited by solubility, showed in contrast to analogous compounds that change of

dielectric had little effect on the tautomeric ratio. However, the preferred amide form was rapidly converted to the aromatic cation on the addition of acid, with a dramatic change in the spectrum.

N-methylation of 2-carboethoxy-1,5-dimethyl-7-oxo-4-azaindole was attempted by many methods but was unsuccessful. It was intended to examine the Ultraviolet spectrum of a compound completely in the amide form with no possible aromatic contribution. In the circumstances only the information gained from U.V. and N.M.R. methods would have been confirmatory as examination of ionisation constants would be inapplicable because of the very small solubility of these compounds.

The collective evidence of physical methods suggests that in agreement the γ-pyridones and quinolones the amide structure predominates both in the solid state and in solution.

Time did not permit examination of the molecules for their reactivity towards substitution and no extensive reactions were attempted [11].

Tests are currently in progress to establish whether the products possess any physiological activity from a class of compounds closely akin to those important in body metabolism.

BIBLIOGRAPHY

1. R.E. Willette, J.Amer.Chem.Soc. 5874 (1965)

2. C.R. Clemo & C.A. Swan J.Chem.Soc. 198 (1948)

3. T.K. Adler & A. Albert, J.Chem.Soc. 1794 (1960)

4. J.C.Clayton & J. Kenyon J.Chem.Soc. 2953 (1950)

5. M.M. Robison & B.L. Robison J.Amer.Chem.Soc., 77,6554 (1955)

6. A. Albert & R.E. Willette J.Chem.Soc. 4063 (1964)

7. R.R. Lorenz, B.F. Tullar, C.F. Koelsck & S. Archer, J.Org.Chem., 30 2531 (1965)

8. R.A. Abramovitch & J.G. Saha, Advances in Het. Chem. 6, 333 (1966)

9. G.E. Ficken & J.D. Kendall J.Chem.Soc. 3202 (1959)

10. G. Plancher Ber. 31, 1488 (1898)

11. G.E. Ficken & J.D. Kendall J.Chem.Soc. 584 (1961)

12. T. Takahashi, H. Saikachi, H. Goto, S. Shimamura, J.Pharm.Soc. Japan 64 7 (1944) CA. 45 8529 (1951)

13. O. Sus & K. Möller, Ann. Chem. 593, 91 (1955)

14. R. Adams & S. Miyano, J.Amer.Chem.Soc. 76, 3168 (1954)

15. R.E. Willette, J.Chem.Soc. 5874 (1965)

16. B. Frydman, M.E. Despuy & H. Rapoport, J.Amer.Chem.Soc. 87 3530 (1965)

17. B. Frydman, S.J. Reil, J. Boned, H. Rapoport, J.Amer.Chem.Soc. 33 3762 (1968)

18. W.Hertz & S. Tocker J.Amer.Chem.Soc. 77, 6353 (1955)

19. W. Hertz & S. Tocker J.Amer.Chem.Soc. 77, 6355 (1955)

20. W.J. Hale & W.V. Hoyt J.Amer.Chem.Soc. 37, 2550 (1915)

21. J.W. Cornforth J.Chem.Soc. 1174 (1958)

22. E. Fischer & E. Otto Ber 36 2107 (1903)

23. R. Kuhn & G. Osswald Ber 1423 (1956)

24. Hill & Torrey Am.Chem.J. 22, 95 (1899)

25. P.E. Fanta Org.Synth. Coll Vol.IV 844

26. P. Fanta Org.Synth. 46, 104 (1966)

27. Erwin Kuh & H. Stewart US patent 2, 606 93 (1952)

28. W.J. Hale & W.V. Hoyt J.Amer.Chem.Soc. 37 2538 (1915)

29. A. Combes Bull Chim.Soc. France, 49 89 (1888)

30. E. Roberts & E. E. Turner J.Chem.Soc. 1832 (1927)

31. M. Conrad & L. Limpach Ber 20 944 948 (1887)

32. Conrad-Limpach Reaction Het.Cpds. Vol.4 P.30

33. L. Knorr Ann. 236 83 (1886)

34. Rodd ID 299

35. R.G. Gould & W.A. Jacobs J.Amer.Chem.Soc., 61 2890 (1939)

36. T.L. Ulbricht, T. Okuda & C.C. Price. Org.Synth. Coll. Vol.4 566

37. N.O. Sonntag Chamber 52 272 (1953)

38. A. Albert & J.N. Phillips J.Chem.Soc. 1294 (1956)

39. F. Arndt Organic Analysis 1. 197 (1953)

40. A.R. Katritsky & A.J. Waring Chem and Ind. 695 (1962)

41. Tschichibabin and Shapiro J.Russ.Phys.Chem.Soc. 53, 253 (1921) C.A. 18 2342 (1924)

42. Dohrn and Dirksen Ger.Pat. 490,416 (1927) C.A.24 2148 (1930)

43. A. Arndt & Kalischek Ber 63, 587 (1930)

44. Rüth Ann 489, 108 (1931)

45. T.S. Gardner, F.A. Smith, E. Weiss & J. Lee J.Amer.Chem.Soc. 74, 2106 (1952)

46. J.H. Boyer, R. Borgers & L.T. Wolford J.Amer.Chem.Soc. 79, 678 (1957)

47. R. Adams & S.H. Pomerantz 76 702 (1956)

48. J.P. Wibaut & G.L. La Bastide Rec. Trav 52, 493 (1933)

49. J.P. Wibaut & G. Tilman ibid 987

50. H. Schenkel and A. Klein Helv.Chem.Acta 39, 1211 (1945)

51. N. Kornblum & G. Coffey J.Org.Chem. 31 3447 (1966)

52. H. Specker & H. Gawrosch Ber 75, 1338 (1942)

53. Metzler & Snell J.Amer.Chem.Soc. 77 2431 (1955)

54. R. Sensi & G. Gallo Ann.Chim.Rome 44, 232 (1954)

55. A. Albert & E. Spinner J.Chem.Soc. 1221 (1960)

56. S.F. Mason J.Chem.Soc. pp 4874, 5010 (1957)

57. B.R. Penfold Acta Cryst. 6, 591 (1953)

58. den Hiertog & Buurman Rec. Trav. Chim. 75, 257 (1956)

59. G.W. Ewing & E.A. Steck J.Amer.Chem.Soc. 68, 2181 (1946)

60. Bobranski J. Prakt Chem. (2) 134, 141 (1932)

61. Kochanska & Bobranski Ber 69, 1807 (1936)

62. Sen & Ray J. Indian Chem. Soc. 9, 173 (1932)

63. E.B. Hartshorn & S.L. Baird J.Amer.Chem.Soc. 68, 1562 (1946)

64. Worotshtzow & Kogan Ber 65, 142 (1932)

65. Chelintsev & Dubinin J. Gen.Chem.USSR. 10, 1395 (1940)

66. Bogart & Seil J.Amer.Chem.Soc. 29, 517 (1907)

67. Freidlander et al Ber 14, 1507 (1881)

68. " 15, 335 (1882)

69. " 14, 1421 (1882)

70. " 14, 2103 (1882)

71. " 18, 1529 (1885)

72. " 20, 2010 (1887)

73. Meyer & Beer Monatsch 34, 1173 (1913)

74. Meyer Monatsh 27, 255 (1906)

75. Meyer Monatsh 27, 987 (1906)

76. Bobranski Ber 69 1113 (1936)

77. C.C.Price & W.G.Jackson J.Amer.Chem.Soc. 68, 1282 (1946)

78. Huisgen Ann. 559 101 (1948)

79. R.A. Morton & E. Rogers J.Chem.Soc. 127, 2698 (1925)

80. Ley & Specker Ber 72 197 (1939)

81. G.Ewing & E. Steck J.Amer.Chem.Soc. 68, 2181 (1946)

82. G. Tucker & B. Irvin J.Amer.Chem.Soc. 73, 1923 (1951)

83. S.F. Mason J.Chem.Soc. 674 (1958)

84. J.A. Gibson et al J.Chem.Soc. 4340 (1955)

85. S.F. Mason J.Chem.Soc. 4874 5010 (1957)

86. M.M. Robison et al J.Amer.Chem.Soc. 79, 2573 (1957)

87. A.R. Katritsky & A.P. Ambler. Phys. Methods of Heterocyclic Chemistry 2, 161 (1963)

88. L.N. Yakhontov & M.V. Rubtsov J.Gen.Chem.(USSR) 34, 495 (1964)

89. L.N. Yakhontov et al. CA 64, 19583 (1966)

90. " Tetrahedron 22, 3233 (1966)

91. " J.Org.Chem.(USSR) 34, 1460 (1964)

92. " CA 64 17563 (1966)

93. Yakhontov & Rubtsov J.Gen.Chem. (USSR) 34, 2626 (1964)

94. S.F. Mason Phys.Methods of Heterocyclic Chem. 2, 1 (1963)

95. T.K. Adler & A. Albert J.Chem.Soc 1794 (1960)

96. S.F. Mason Phys.Methods in Het.Chem. 2,65 (1963)

97. J.P. Saxena Indian J.Chem. 5,73 (1967)

98. L.N. Yakhontov et al C.A. 66, 104506 (1967)

99. B. Frydman et al J.Amer.Chem.Soc. 87, 35306 (1965)

100. A. Albert & R.E. Willette J.Chem.Soc. 4063, (1964)

101. C. Waller, M. Weiss & J.S. Webb U.S. Patent 2,785, 181

102. " " " U.S. Patent 2,797, 228

103. J.W. Cornforth J.Chem.Soc. 1174 (1958)

104. E. Fischer & E. Otto Ber. 36, 2107 (1903)

105. R. Kuhn & G. Osswald Ber 1423 (1956)

106. K.J. Morgan & D.P. Morrey Tetrahedron 22,57 (1966)

107. Fournari Bull Soc.Chim.Fr. 488 (1963)

108. J. Bernstein, B. Stearns, E. Shaw & W.A. Hoff J.Amer.Chem.Soc. 69, 1151 (1947)

109. M. Protiva et al Chem.Psty 46, 551 (1952) CA. 48, 2710 (1954)

110. M.M.Robison & B.L. Robison J.Amer.Chem.Soc. 78, 1247 (1956)

111. L.N. Yakhontov et al Tetrahedron Letters. 24, 1909 (1969)