STUDIES IN ISOTHIAZOLE CHEMISTRY

I. ISOTHIAZOLO[5,4-b]PYRIDINES

II. APPROACHES TO ISOTHIAZOLYNES

BY

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TO

MY SISTER AND BROTHER-IN-LAW

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ABSTRACT

The first part of this thesis describes investigations on the synthesis and chemistry of isothiazolo[5,4-b]pyridines.

The syntheses of a number of alkyl isothiazolo[5,4-b]pyridines from 5-amino-3-methylisothiazole under conditions of the Skraup reaction are described and their nuclear magnetic resonance spectra are discussed.

The reactions of 3-methyl- and 3,6-dimethylisothiazolo[5,4-b]pyridine have been studied. In particular they did not undergo nitration under the conditions employed and whereas the 3-methyl compound did not condense with benzaldehyde, 3,6-dimethylisothiazolo[5,4-b]pyridine gave mono-styryl products with benzaldehyde and*p*-nitrobenzaldehyde. Potassium permanganate oxidation gave isothiazolo[5,4-b]pyrid-3(2H)-one 1,1-dioxides rather than the expected isothiazolo[5,4-b]pyridine carboxylic acids and chromic acid oxidation resulted in cleavage of the isothiazole ring to give 2,3-disubstituted pyridines.

Ethyl 4-hydroxy-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate was readily obtained by thermal cyclisation of the malonate from 5-amino-3-methylisothiazole and ethoxymethylenemalonic ester. The hydroxy ester was converted to a number of substituted isothiazolo[5,4-b]pyridines. In addition it has been established that methylation at nitrogen rather than oxygen occurs with both the 4-hydroxy ester and the 4-hydroxy compound which has been shown to exist preferentially in the carbonyl form, namely 3-methylisothiazolo[5,4-b]pyrid-4-one.

The reaction of 5-amino-3-methylisothiazole with ethylacetoacetate and with acetylacetone under the conditions of the Conrad Limpach reaction and the Combes reaction respectively, did not give isothiazolo[5,4-b]-pyridines. The latter gave a product which has been tentatively formulated as 5-acetyl-3,4-dimethylisothiazole.

The second part of this work describes the synthesis of 5-amino-3-chloroisothiazole-4-carboxylic acid, 4-amino-3-methylisothiazole--5-carboxylic acid and 4-aminoisothiazole-3-carboxylic acid and experiments aimed at investigating the possible intermediacy of isothiazolynes. Attempts to generate and trap isothiazolynes by their aprotic diazotisation with isoamyl nitrite in the presence of 2,3,4,5-tetraphenylcyclopentadienone gave only small quantities of isothiazoles in addition to a variety of oxidation products derived from the arynophile.

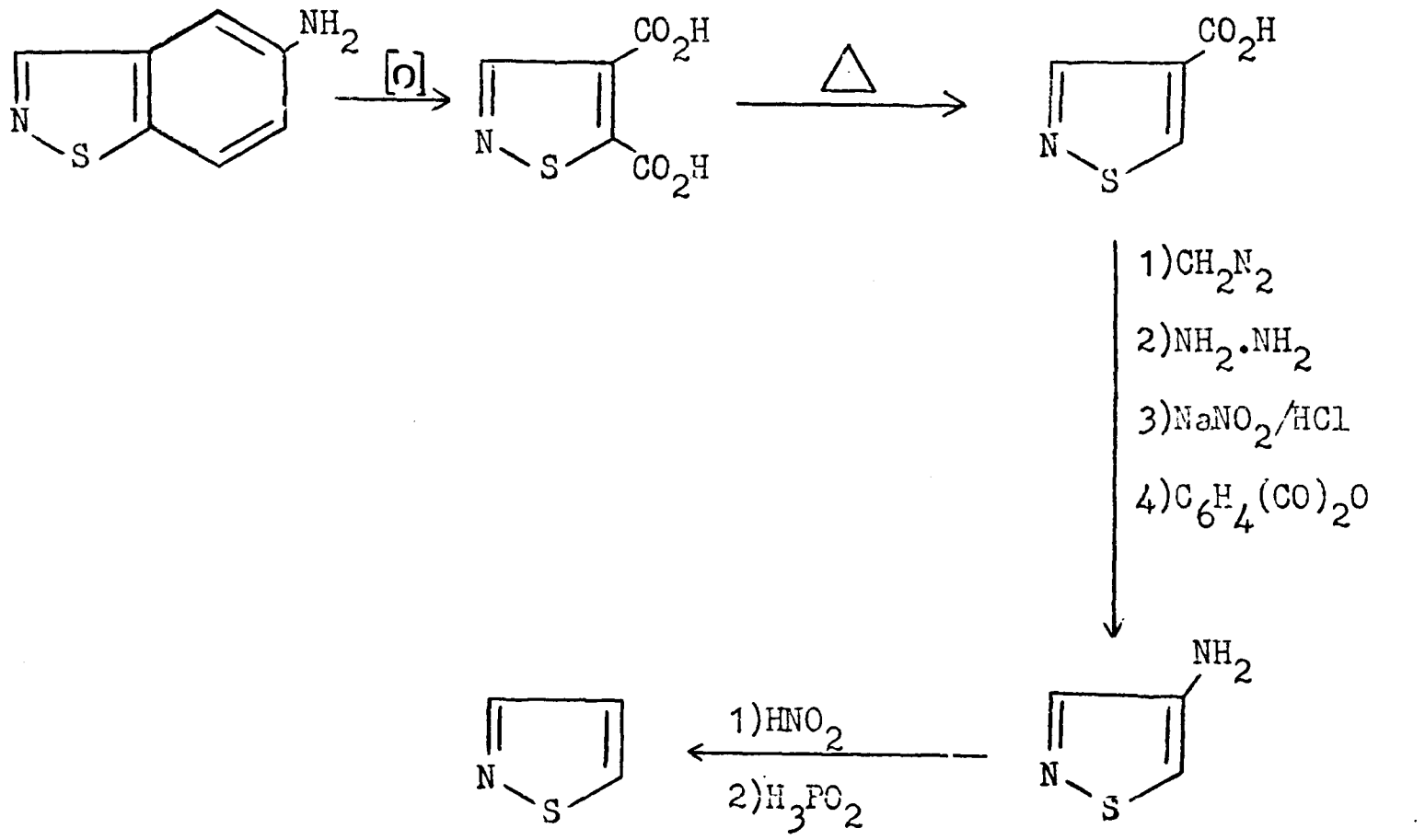
4-Amino3-methylisothiazole-5-carboxylic acid gave isothiazolyl-substituted products when furan and anthracene were used as trapping agents, and it was found that the reaction of isothiazcle-4-diazonium carboxylate hydrochloride and propylene oxide in the presence of furan gave 4-cyano-1,2,3-thiadiazole.

In none of the reactions investigated was there any evidence for the formation of isothiazolyne intermediates.

INTRODUCTION

Isothiazole

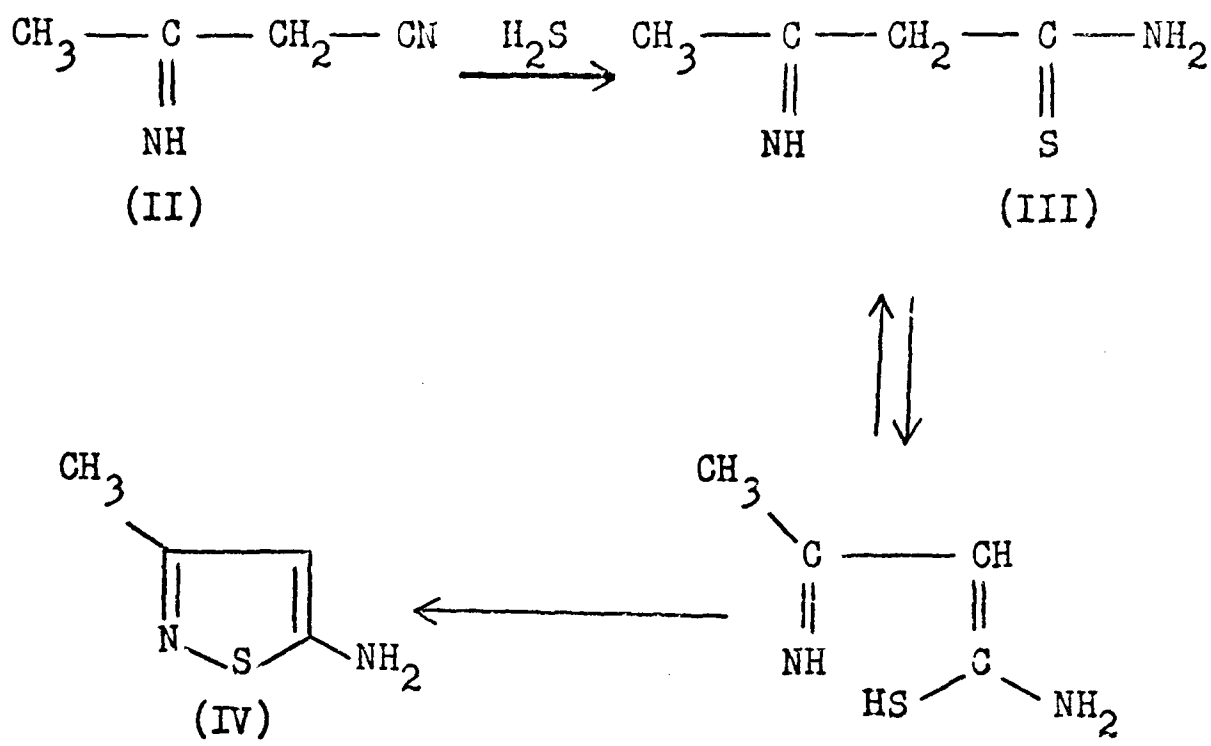
Isothiazole (I) is the sulphur analogue of isoxazole. Bicyclic systems involving the isothiazole (1,2-thiazole) structure have long been known but it was not until 1956 that Adams and Slack[1] reported the synthesis of the simple five-membered heterocyclic from a substituted benzisothiazole by the following route:



(I)

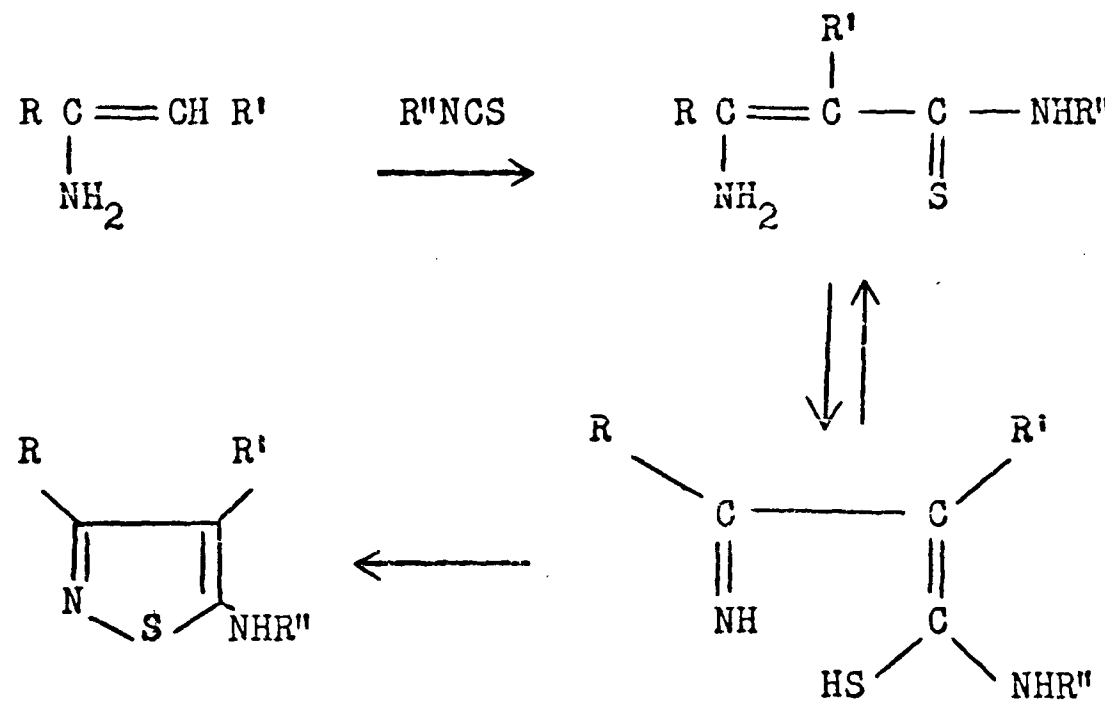
Interest in this heterocyclic compound has greatly increased since publication of the first syntnesis and has occasioned the appearance of four reviews of this subject, in 1963, 1965, 1970 and 1972.[2,3,4,5]

Adams and Slack's[6] second isothiazole synthesis involved the preparation of β-iminothiobutyramide (III) from the nitrile II and cyclisation with chloramine or better, hydrogen peroxide or salts of peracids, e.g. ammonium persulphate, to give 5-amino-3-methylisothiazole (IV).

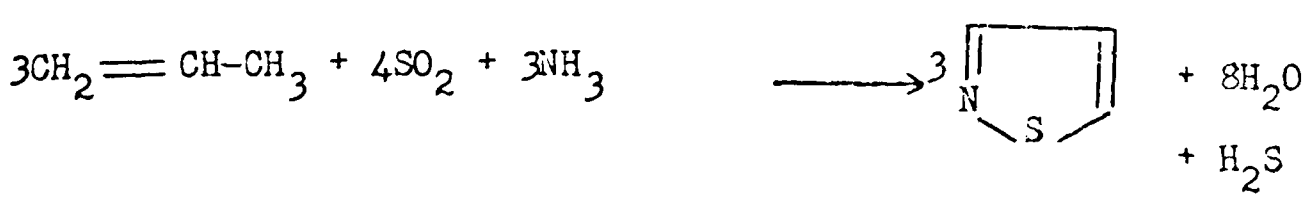


[7,8,9,10]

This synthesis has been extended by Goerdeler and his co-workers to give a variety of substituted 5-amino-isothiazoles, the thioamides required for the oxidative cyclisation being prepared by reaction of isothiocyanates with enamines.

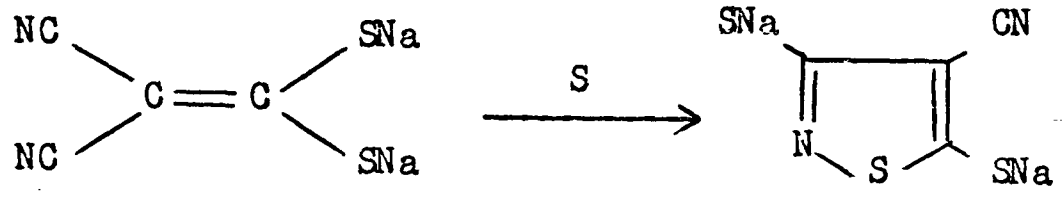


Hübenett, Flock and Hofmann [11] have shown that propylene reacts with sulphur dioxide and ammonia in the presence of a catalyst such as activated alumina to give a high yield of isothiazole.

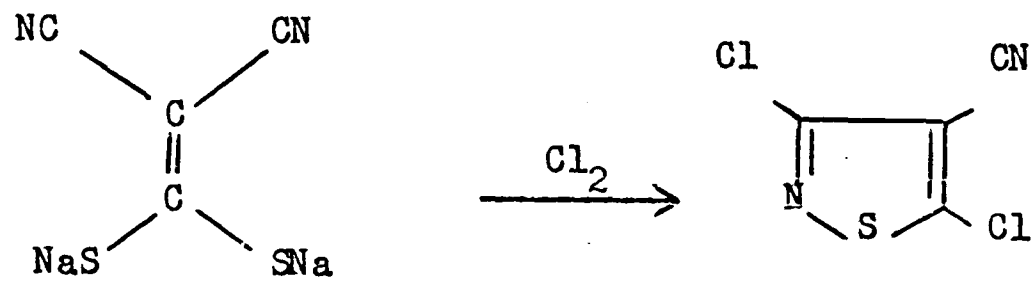


This reaction is applicable to certain substituted propenes, thus isobutylene gives 4-methylisothiazole, and α-methylstyrene gives 4-phenylisothiazole. Olefin isomerisation may, however, occur and 1- or 2-butene gives a mixture of 3- and 5-methylisothiazole. Yields of 25 - 65% have been achieved with the simpler compounds and the reaction temperatures (200°) emphasize the inherent stability of isothiazoles.

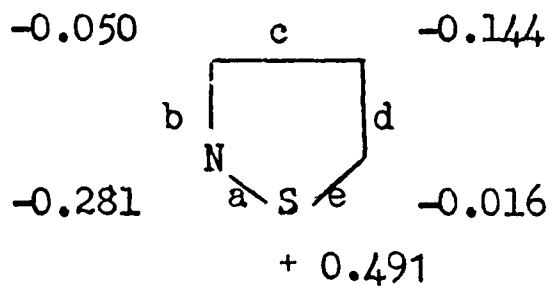
In 1963, Soederbaeck [12] cyclised sodium dicyanoethylenedithiolate, readily obtained from malononitrile, carbon disulphide and sodium hydroxide, by treatment with sulphur in ethanol.



A similar isothiazole synthesis was reported independently by Hatchard, [13] who obtained 4-cyano-3,5-dichloroisothiazole by carrying out the cyclisation with chlorine.

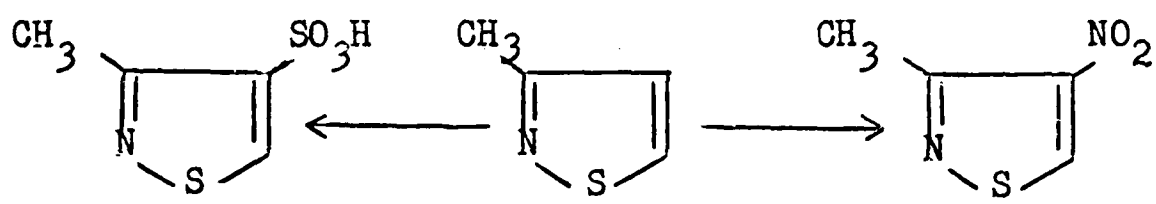


In their initial work Adams and Slack [6] commented on the electronic similarity between -S- and -CH=CH-, particularly in aromatic systems, and compared the electron densities and mobile bond orders of the parent molecule, which were obtained by simplified molecular orbital calculations, with those of thiazole and pyridine. Their results emphasised the inherent stability of the unsubstituted molecule and its similarity to both pyridine and thiazole. This has, since then, been amply confirmed by a consideration of its chemical behaviour and by n.m.r. spectroscopy.



Bond	Bond Order
a	0.502
b	0.705
c	0.634
d	0.707
e	0.594

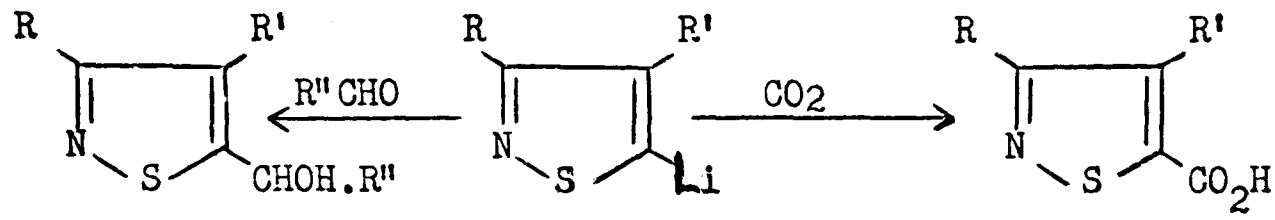
The substitution reactions of isothiazole are in broad agreement with the electron distribution pattern. Thus electrophilic substitution occurs predominantly in the 4-position, if this is free, and metallation occurs in the 5-position. The weakly basic isothiazole would be expected to be almost completely protonated in strong acid media, but nevertheless readily undergoes nitration with a mixture of fuming nitric acid and sulphuric acid in good yield.[2] Adams and Slack[6] also reported the nitration of 3-methylisothiazole in 90% yield using potassium nitrate and fuming sulphuric acid. Sulphonation of 3-methylisothiazole with oleum or sulphur trioxide has been reported by Pain and Parnell[14] to occur readily to give 3-methylisothiazole-4-sulphonic acid.



Isothiazole and 3- and 5-alkylisothiazoles have been brominated under various conditions[15,16] but yields of 4-bromoisothiazoles have not been very good possibly because of the formation of perbromocompounds. High yields of 4-brominated products have, however, been reported from isothiazoles with electron releasing substituents in the 3- or 5-position.

A study of hydrogen-deuterium exchange rates by n.m.r. spectroscopy showed that the 5-proton exchanged very rapidly under basic conditions

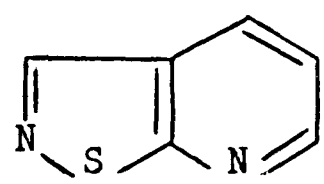
indicating the formation of a relatively stable anion. 5-Lithio-isothiazoles may be readily prepared by treatment of isothiazoles with butyl lithium allowing introduction of a wide variety of substituents into the 5-position.[17]



Data has also been obtained by n.m.r. techniques concerning the relative rates of hydrogen-deuterium exchange in 3-methyl-, 4-methyl-, 5-methyl- and 3,5-dimethylisothiazoles: the relative rates of exchange of both the ring protons and the methyl protons decrease for the respective positions in the order 5->3->4-. The ease of removal of a proton from the 5-methyl group has been discussed by White and Anderson.[18]

Fused Bicyclic Isothiazoles

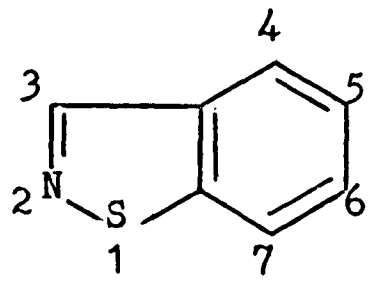
The aim of the work described in the first part of this thesis was to investigate methods for the formation of the bicyclic isothiazole system, isothiazolo[5,4-b]pyridine (V) and to carry out a preliminary examination of its reactions.



(V)

Two series of fused bicyclic compounds incorporating both an isothiazole and a benzene ring have been known for sometime. These ring systems are now generally known as 1,2-benzisothiazole (VI) and 2,1-benz-

isothiazole (VII).



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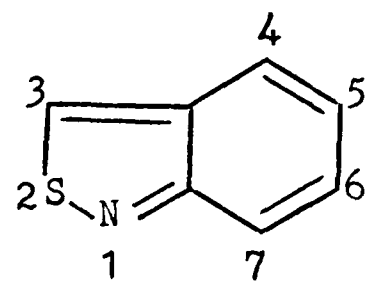
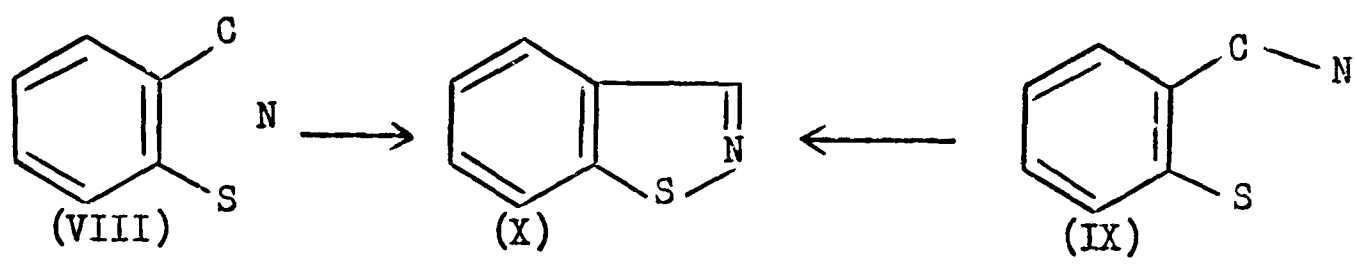


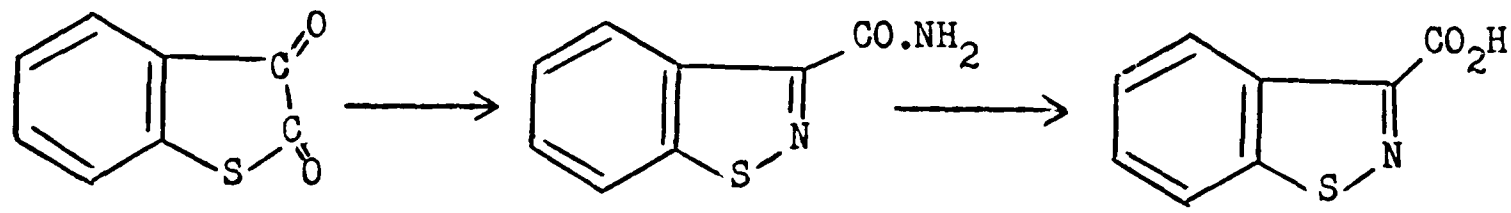
(VII)

Both series of compounds have been known for more than fifty years. Almost all the syntheses for the more well known 1,2-benzisothiazole system require as a precursor, an aromatic sulphur-containing compound with a functionalized carbon atom ortho to the sulphur. The general pattern is thus either from VIII or IX to 1,2-benzisothiazole (X).



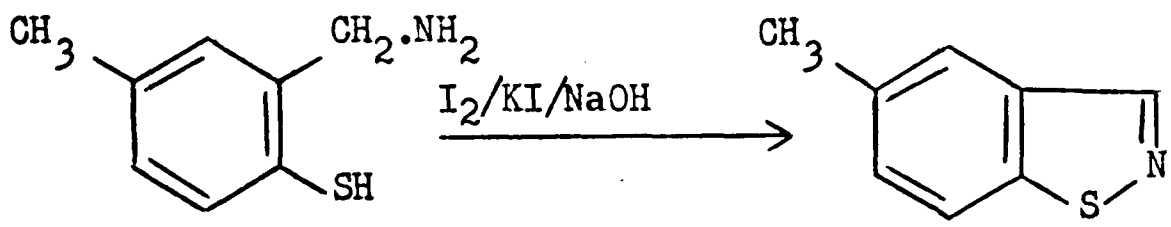
(VIII) (X) (IX)

The parent compound X was first prepared in 1923 by Stollé and co-workers.[19,20] They found that treatment of the thianaphthenequinone (XI) with aqueous ammonia and hydrogen peroxide afforded 1,2-benzisothiazole-3-carboxamide (XII). The amide was hydrolysed to the acid XIII and this gave the parent system on decarboxylation.



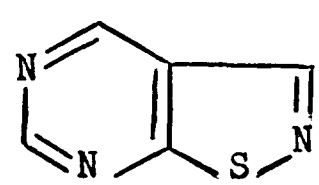
(XI) (XII) (XIII)

In 1959, Goerdeler and Kandler[21] reported that the oxidation of the aminothiol XIV with iodine or bromine afforded 5-methyl-1,2-benzisothiazole in excellent yield. Boudet and Bourgoin-Legay[22] showed, in the following year, that alkaline ferricyanide was an equally effective oxidising agent.

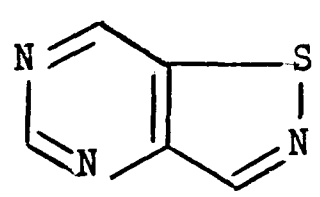


(XIV)

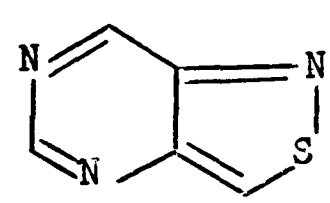
In 1964, Goerdeler and Horn[8] reported the synthesis of isothiazolo-[5,4-d]pyrimidine (XV) and in the following year Holland, Slack, Warren and Buttimore[23] reported the synthesis of isothiazolo[4,5-d]pyrimidines (XVI) and isothiazolo[4,3-d]pyrimidines (XVII).



(XV)

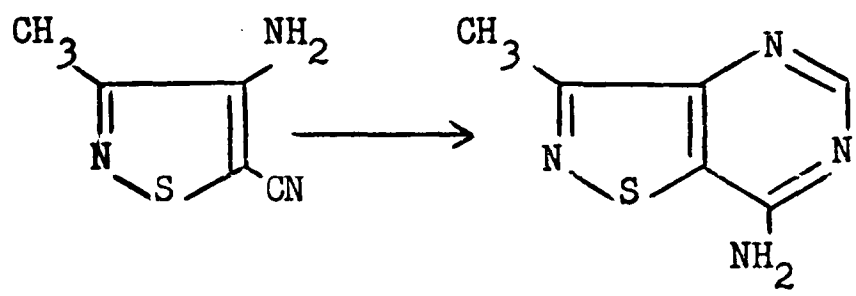


(XVI)



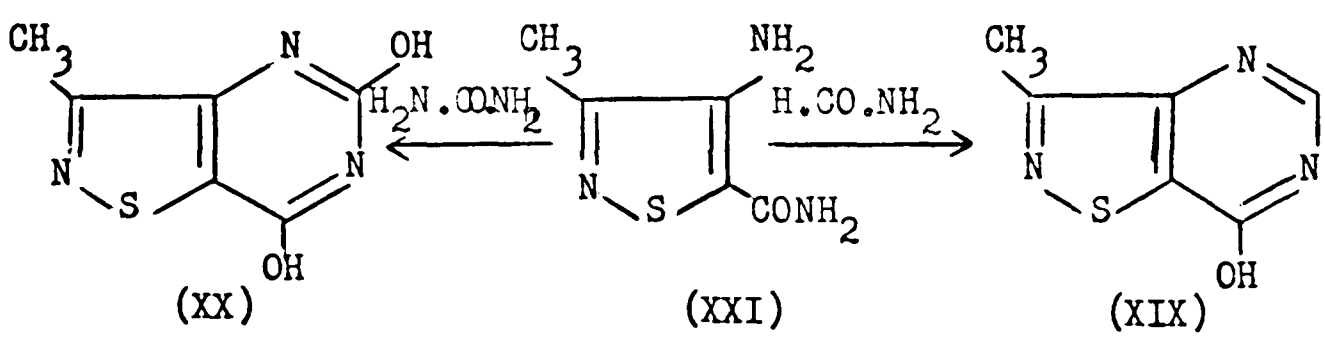
(XVII)

Holland and co-workers obtained 7-amino-3-methylisothiazolo[4,5-d]-pyrimidine (XVIII) in poor yield on reaction of 4-amino-5-cyano-3-methylisothiazole with formamide.



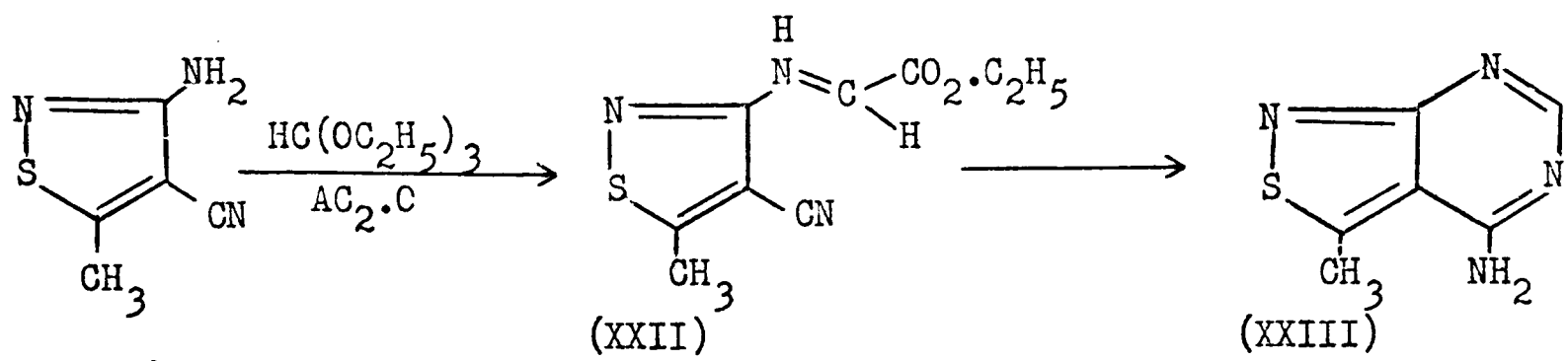
(XVIII)

The corresponding 7-hydroxy- and 5,7-dihydroxy-compounds, XIX and XX, were readily prepared from the amino-amide XXI by reaction with formamide and urea, respectively.

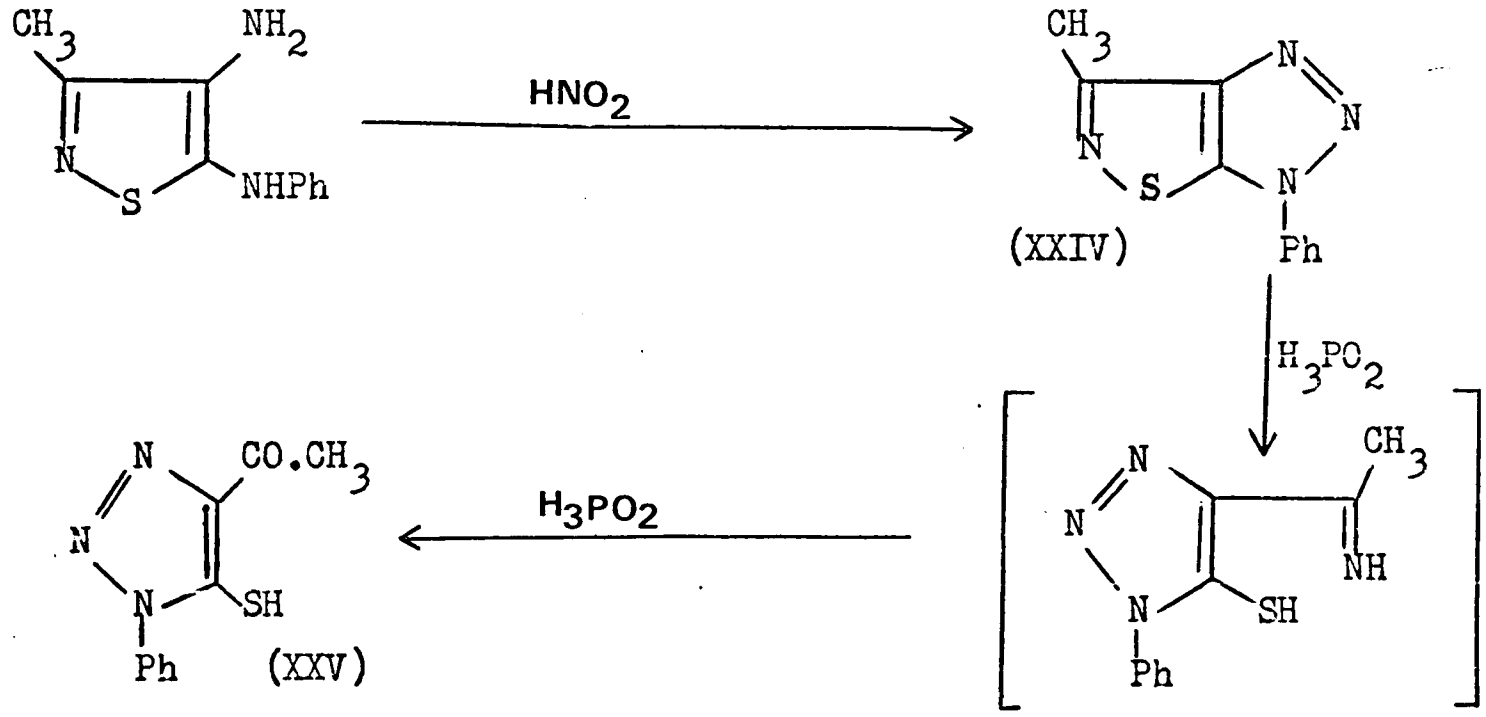


(XX) (XXI) (XIX)

In 1967, Hartke and Peshkar[24] reported the synthesis of 6-amino-7-methylisothiazolo[3,4-d]pyrimidine (XXIII). Reaction of 3-amino-4-cyano-5-methylisothiazole with an equimolar mixture of ethyl orthoformate and acetic anhydride gave the nitrile XXII in 90% yield, which with an excess of alcoholic ammonia at room temperature gave XXIII in 85% yield.

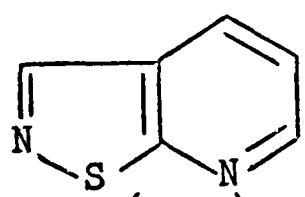


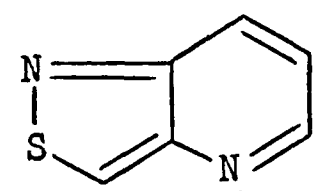
The isothiazolo[5,4-b]triazole XXIV has been obtained from the reaction of the 4,5-diaminoisothiazole with nitrous acid. It was reported to suffer reductive cleavage to the triazole XXV on treatment with hypophosphorous acid.[25]



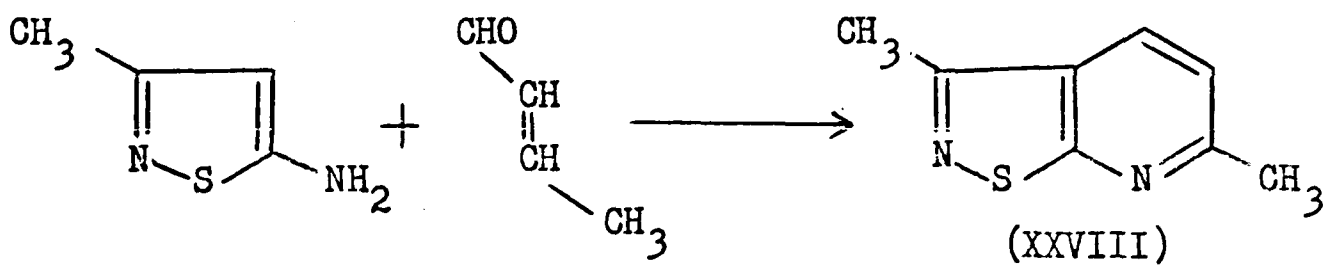
A number of isomeric isothiazolopyridines may be formally derived by construction of a pyridine ring on the isothiazole nucleus. Thus two groups of such compounds may be considered, the first being derived by construction of a pyridine ring to include the 4,5 carbon-carbon bond of isothiazole, e.g. isothiazolo[5,4-b]pyridine (XXVI) and the second to

include the 3,4 carbon-carbon bond of isothiazole, e.g. isothiazolo-[4,3-b]pyridine (XXVII). Depending on the relative position of the nitrogen four bicyclic systems may be constructed in each group.

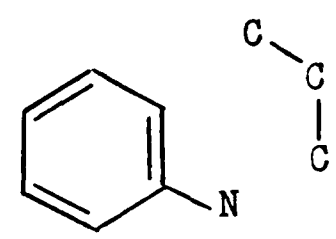

(XXVI)

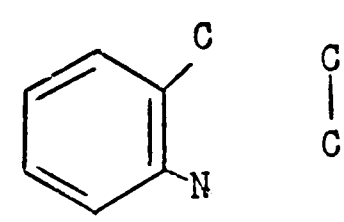

(XXVII)

At the commencement of this work only one example of an isothiazolo-pyridine, viz. 3,6-dimethylisothiazolo[5,4-b]pyridine (XXVIII) had been reported.[26] This compound, described only in a review[5] of isothiazole chemistry, had been obtained by the reaction of 5-amino-3-methylisothiazole with crotonaldehyde in the presence of a mixture of nitrobenzenesulphonic acid in concentrated sulphuric acid (sulphomix). The object of the first part of the work described in this thesis was to investigate the synthesis of isothiazolo[5,4-b]pyridines from the readily available 5-amino-3-methylisothiazole.


(XXVIII)

Methods for construction of pyridine rings on other aromatic nuclei may be conveniently classified into two types. Type A methods employ aromatic amines as starting materials. Type B methods employ ortho substituted amines.

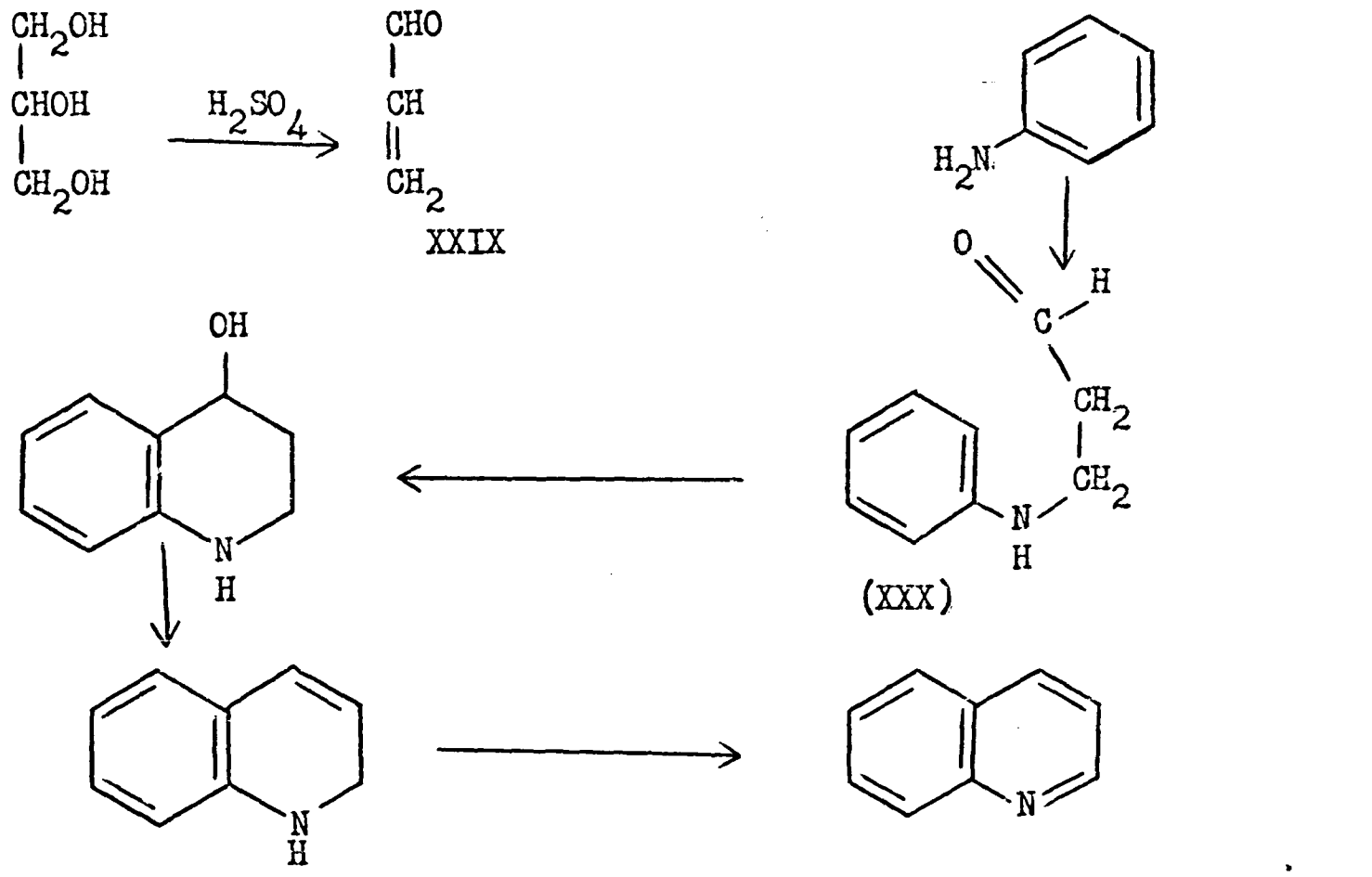

Type A


Type B

Ring formation reactions of type A are most common and involve the interaction of an aromatic amine, containing at least one free ortho

position with some reactant or reactants that provide the carbon atoms required to complete the pyridine ring in a manner such that the pyridine ring is built up on the free ortho position.

The Skraup reaction is one of the most important synthetic routes to quinolines. In this reaction an aromatic amine with at least one vacant position ortho to the amino group is heated with an α,β-unsaturated carbonyl compound or precursor, an oxidising agent such as nitrobenzene, and sulphuric acid. The overall course of the reaction, as at present understood, may be illustrated by considering the formation of quinoline itself in the reaction of aniline with glycerol under these conditions.

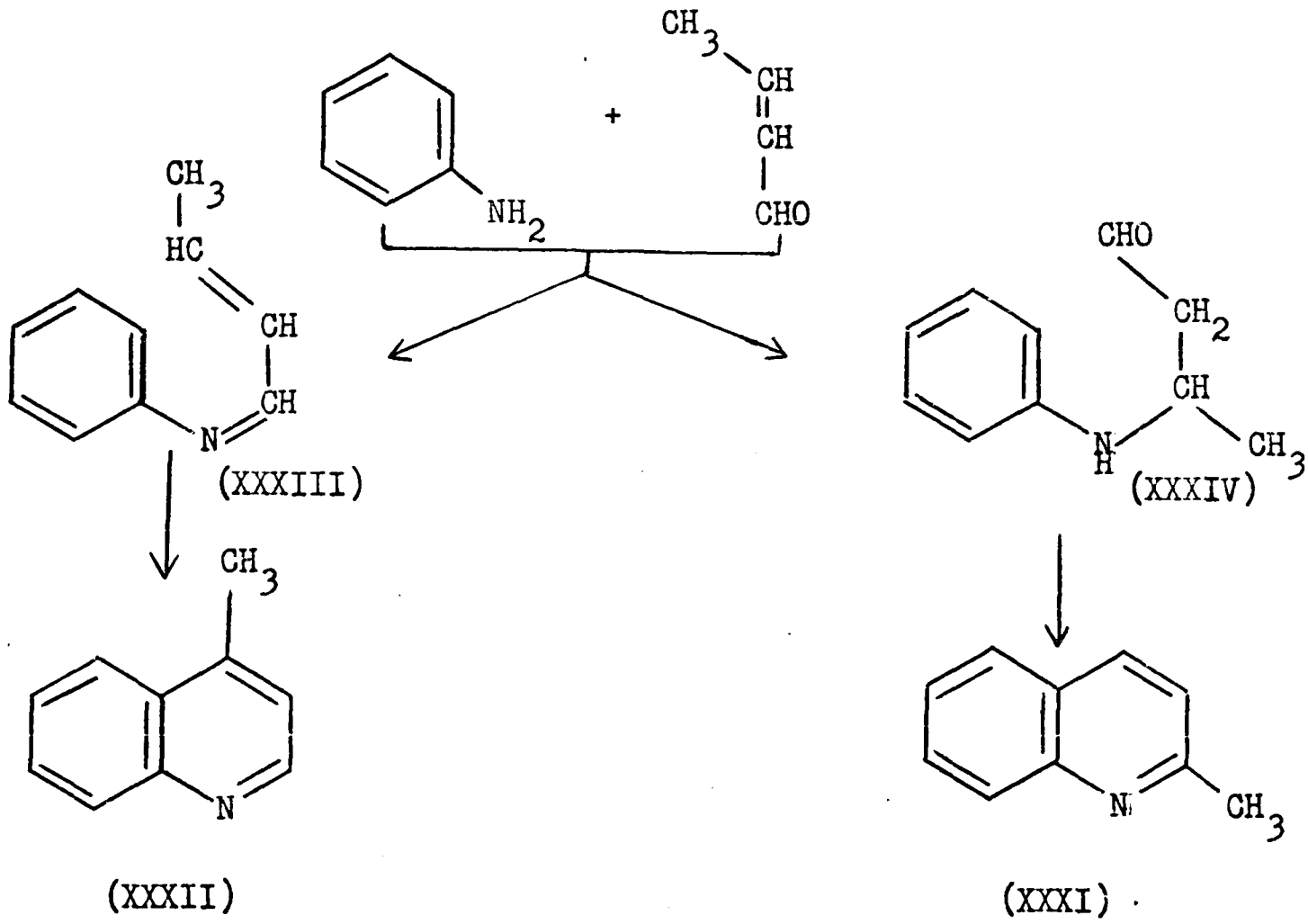


Four successive steps are believed to occur. Dehydration of glycerol to acrolein (XXIX) is followed by Michael addition of the amine to the unsaturated aldehyde. Cyclisation of β-arylaminoaldehyde (XXX) and dehydration under the influence of the acid gives the 1,2-dihydroquinoline which is subsequently oxidised to quinoline.

A useful oxidising agent to remove the two hydrogens from the intermediate dihydroquinoline is the nitro compound corresponding to the amine used in the synthesis. As the requisite nitro-compound is not

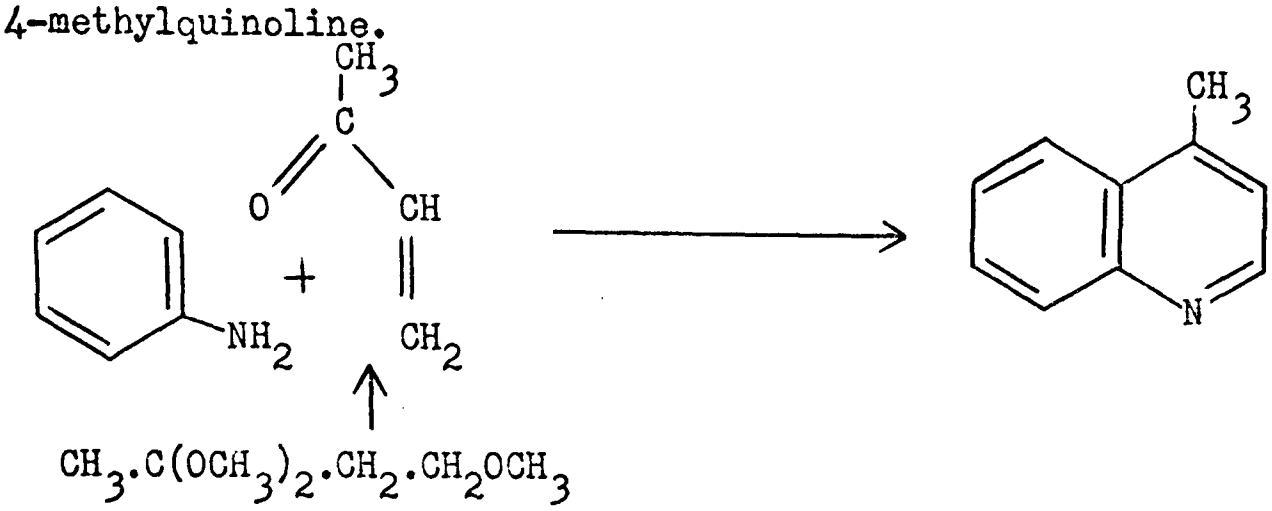
always accessible, a variety of other oxidants has been used. These include m-nitrobenzene sulphonic acid or its salts, arsenic pentoxide, ferric chloride and stannic chloride.

The original mechanism put forward by Skraup, which involved formation of a Schiff's base as an intermediate, was shown, in 1907 by Simon[27] to be untenable. It was found that reaction of crotonaldehyde with aniline under the conditions of the Skraup reaction gave quinaldine (XXXI) and not lepidine (XXXII), which would be expected if a Schiff base intermediate such as XXXIII was involved. The formation of quinaldine indicated the intermediacy of XXXIV, formed by Michael addition of the amine to the α,β-unsaturated carbonyl compound.



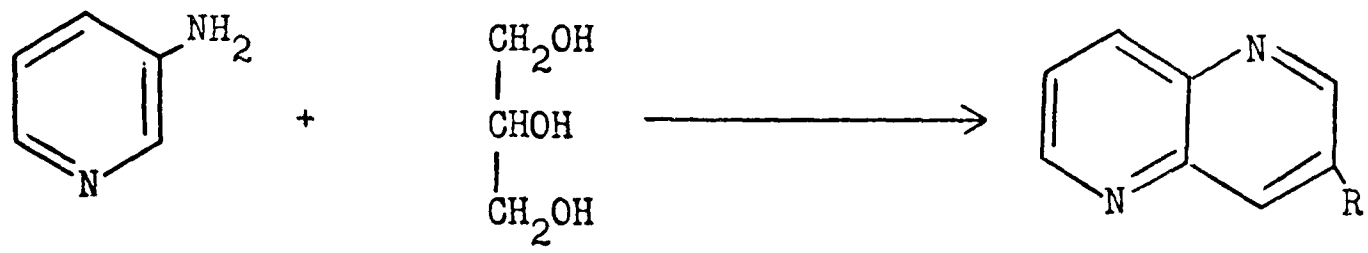
The Skraup reaction is of almost universal applicability. In general it may be used with glycerol to yield an almost unlimited variety of quinolines substituted in the benzene ring. Only substituents in the aromatic amine which are sensitive to hot strong acid undergo drastic alteration or elimination during the reaction.

4-Alkylquinolines have been prepared by the use of α,β-unsaturated ketones. Thus condensation of the amine, e.g. aniline, with methyl vinyl ketone, or preferably with 1,3,3-trimethoxybutane from which methyl vinyl ketone may be easily generated in situ, gives 4-methylquinoline.



Similarly ethyl vinyl ketone or α-chlorodiethyl ketone, from which the ketone is formed during reaction, gives 4-ethylquinoline on reaction with aniline.[28]

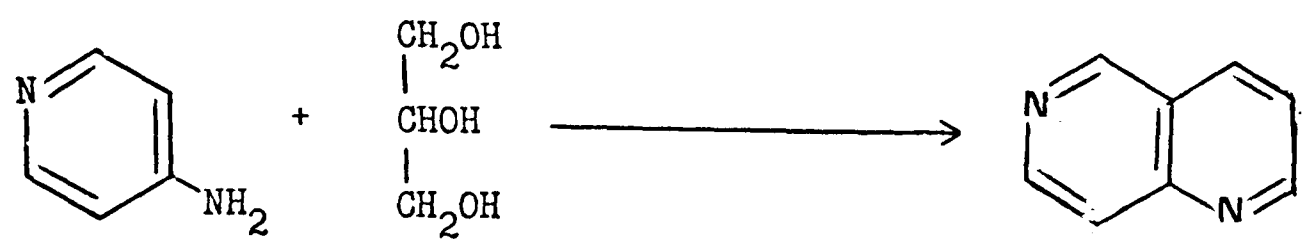
The Skraup reaction has also been successfully applied to hetero-cyclic primary amines. It has recently been reported to be successful with the aminopyridines though previous workers had reported the failure of this reaction with 4-amino and 2-aminopyridine and it was suggested that this was due to the low basicity of these amines.[29,30] In 1950, Hauser and Reynolds [31] synthesized 1,5-naphthyridine (XXXV, R=H) from 3-aminopyridine. The same reaction was later investigated in detail by Rapoport and Batcho [32] who obtained the naphthyridine in 31% yield. Small amounts of the 3-methyl and 3-ethyl isomers (XXXV, R=CH_3,C_2H_5) were also obtained and it was suggested that these arose by way of intermediates formed by the aldol condensation of the intermediate arylamino aldehyde with formaldehyde and acetaldehyde respectively, both of which may be formed by a retro-aldol reaction of the intermediate dehydration product of glycerol, β-hydroxypropionaldehyde.



(XXXV)

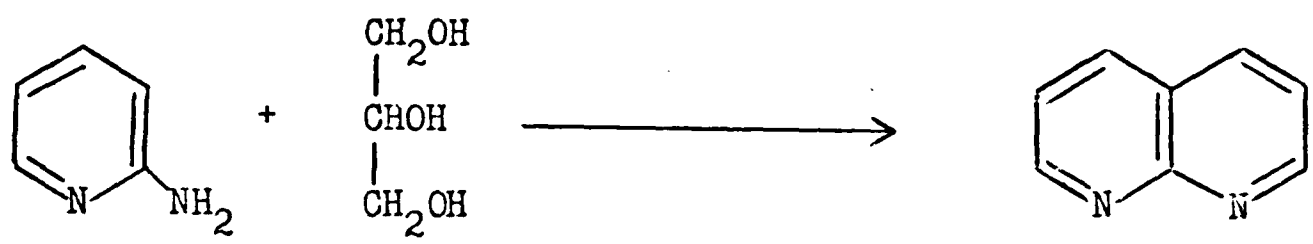
2-Methyl- and 4-methyl-1,5-naphthyridine were also prepared from the appropriate α,β -unsaturated carbonyl compound.

In 1966 Paudler and Kress [33,34] synthesised 4-methyl- and 2-methyl-1,6-naphthyridine from 4-aminopyridine in 1% and 0.5% yield respectively. The parent 1,6-naphthyridine was obtained in 40% yield.[35]



(XXXVI)

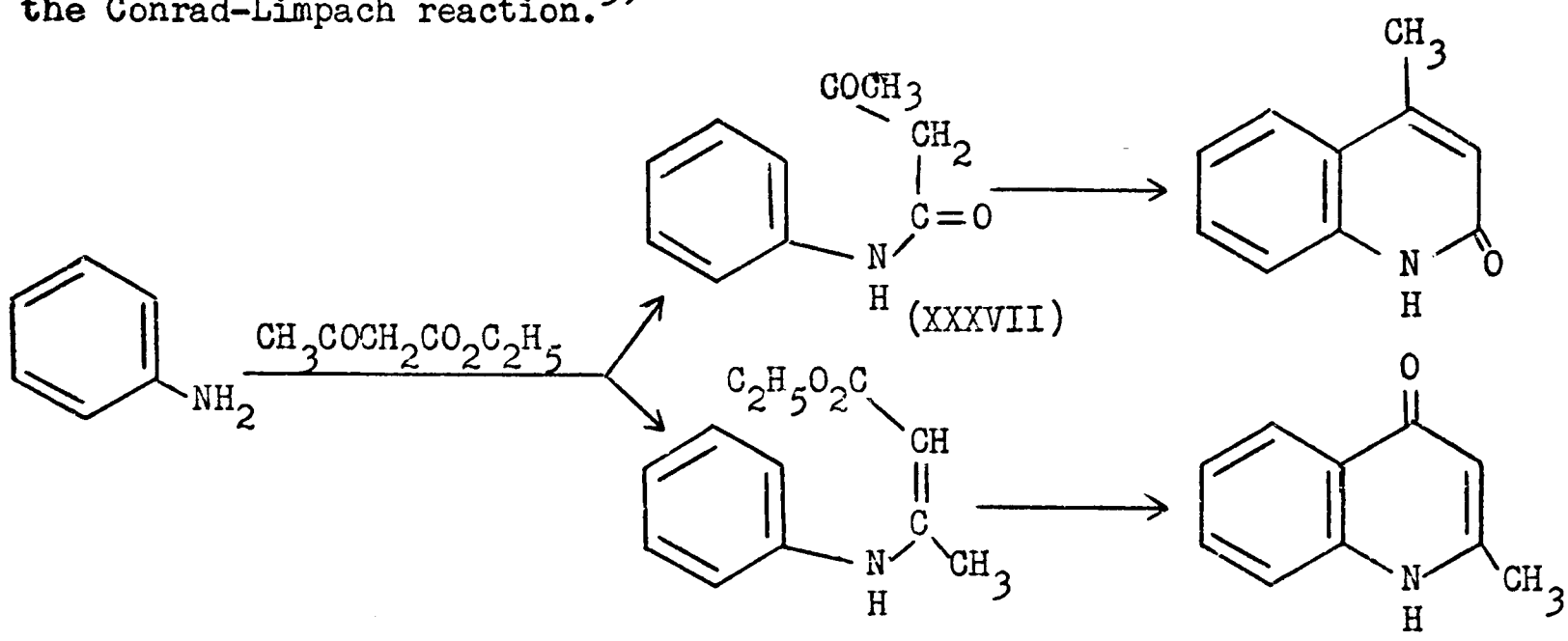
In the following year, 1,8-naphthyridine (XXXVI) was prepared in 30% yield from 2-aminopyridine and glycerol. The synthesis of 2-methyl-, 3-methyl-, 4-methyl- and 2,4-dimethyl-1,8-naphthyridine was also reported by Paudler and Kress. [35,36] It was concluded that 1,8-naphthyridine, which is not steam volatile, had been missed by earlier workers during the traditional steam-distillation work-up procedure usually employed in Skraup reactions.



(XXXVI)

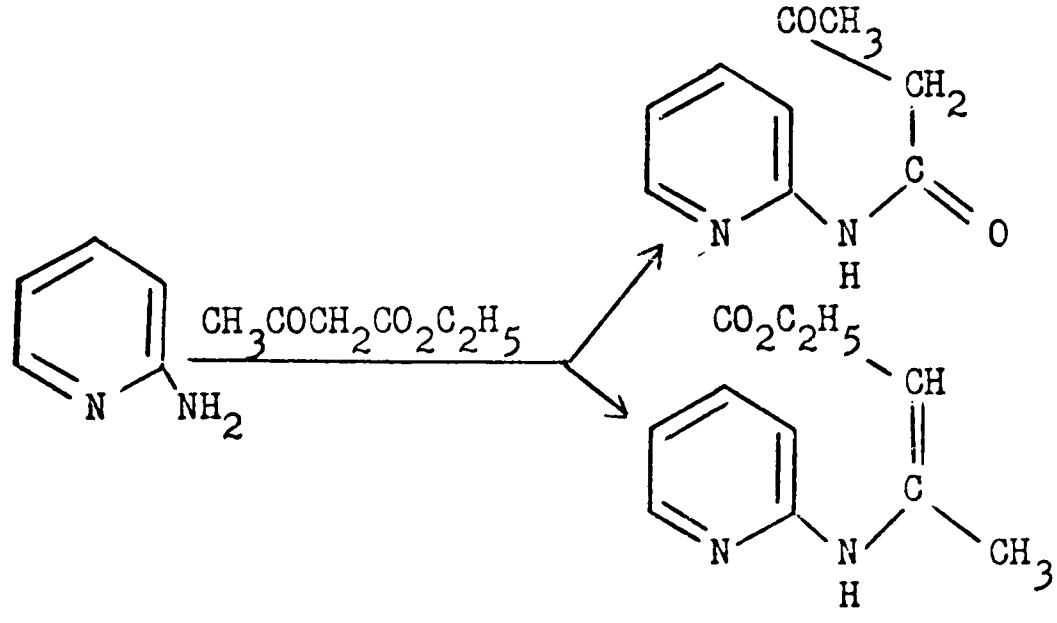
Steinkopf and Lutzkendorf [37] have reported the application of the Skraup reaction to 2-aminothiophene. Thieno[2,3-b]pyridine was obtained in only 5% yield.

The reaction of an aromatic amine with ethylacetoacetate can proceed in two ways to give either an anilide or an enamine depending on the conditions of the reaction. Thus with aniline, the anilide XXXVII is usually formed by heating the reactants under reflux whereas the enamine XXXVIII is formed when the reactants are heated in ethanol in the presence of a trace of acid. Cyclisation of the anilide with concentrated sulphuric acid gives 4-methyl-2-quinolone. Cyclisation of the enamine in mineral oil or refluxing diphenyl ether gives 2-methyl-4-quinolone. The former reaction is usually called the Knorr reaction [38] and the latter the Conrad-Limpach reaction.[39]

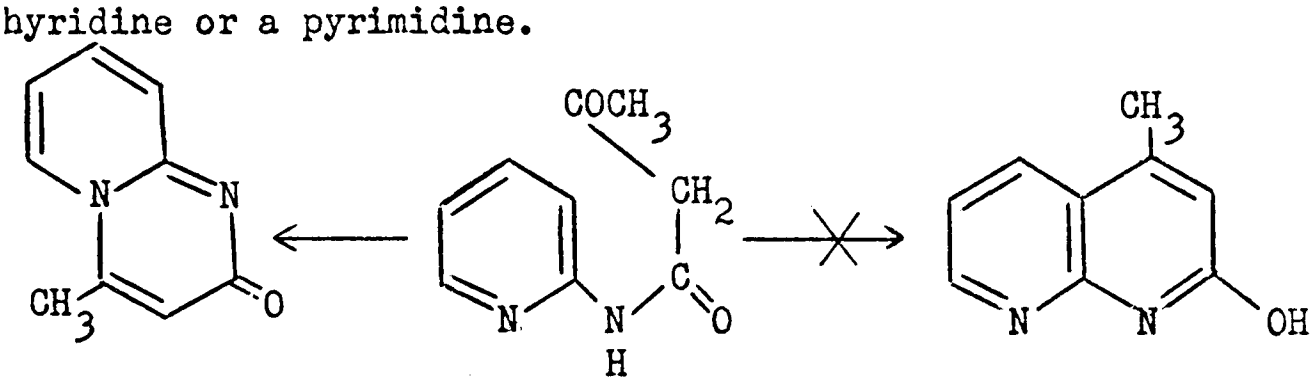


(XXXVIII)

The Knorr and Conrad-Limpach methods have not been successfully extended to the preparation of hydroxy-naphthyridines. The reaction of 2-aminopyridine with ethylacetoacetate gives either the amide XXXIX or the enamine XL depending on the conditions.



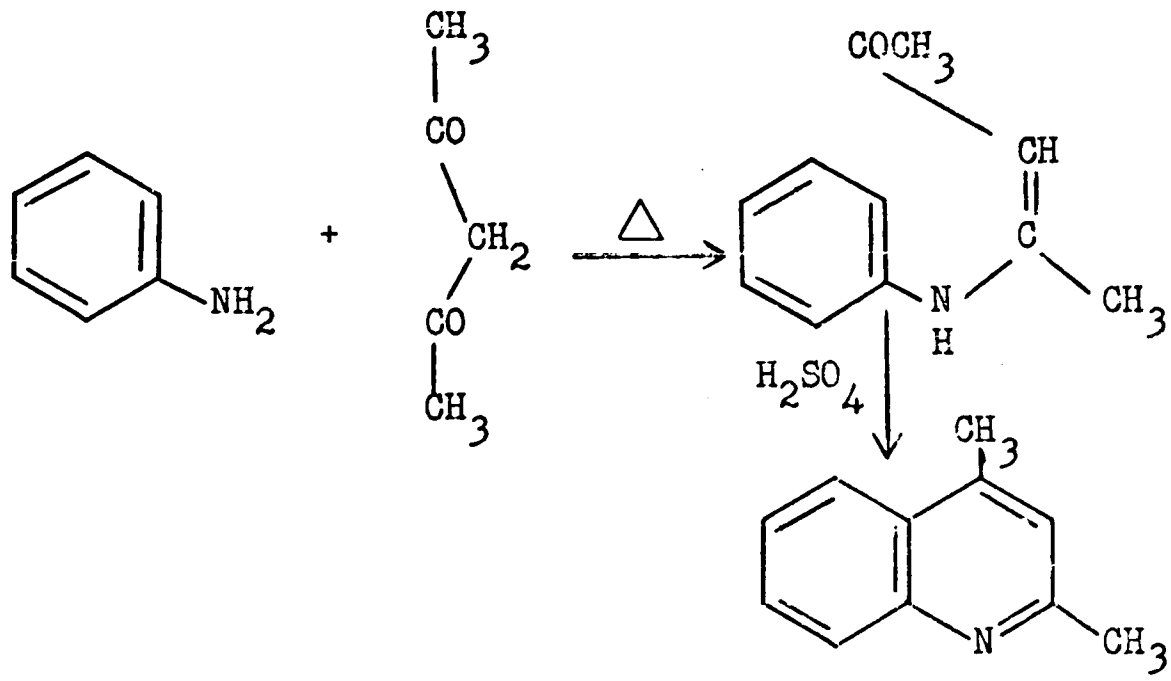
Cyclisation of the amide can lead to either a 2-hydroxy-1,8-naphthyridine or a pyrimidine.



Similarly cyclisation of the enamine can lead to either a 4-hydroxy-1,8-naphthyridine or a pyrimidine. Both the amide and the enamine have, in fact, been reported to form the pyrimidine only. [40,41]

Hauser and Reynolds [31] have isolated the intermediate amide and enamine derived from 3-aminopyridine and ethyl acetoacetate but have found that these could not be cyclised to the corresponding hydroxy-naphthyridines. 4-Aminopyridine was reported not to undergo the Knorr and the Conrad-Limpach reactions.[31]

In the Combes reaction, aromatic amines are condensed with 1,3-diketones and the resulting intermediates are then ring-closed to 2,4-disubstituted quinolines by treatment with hot concentrated sulphuric acid.

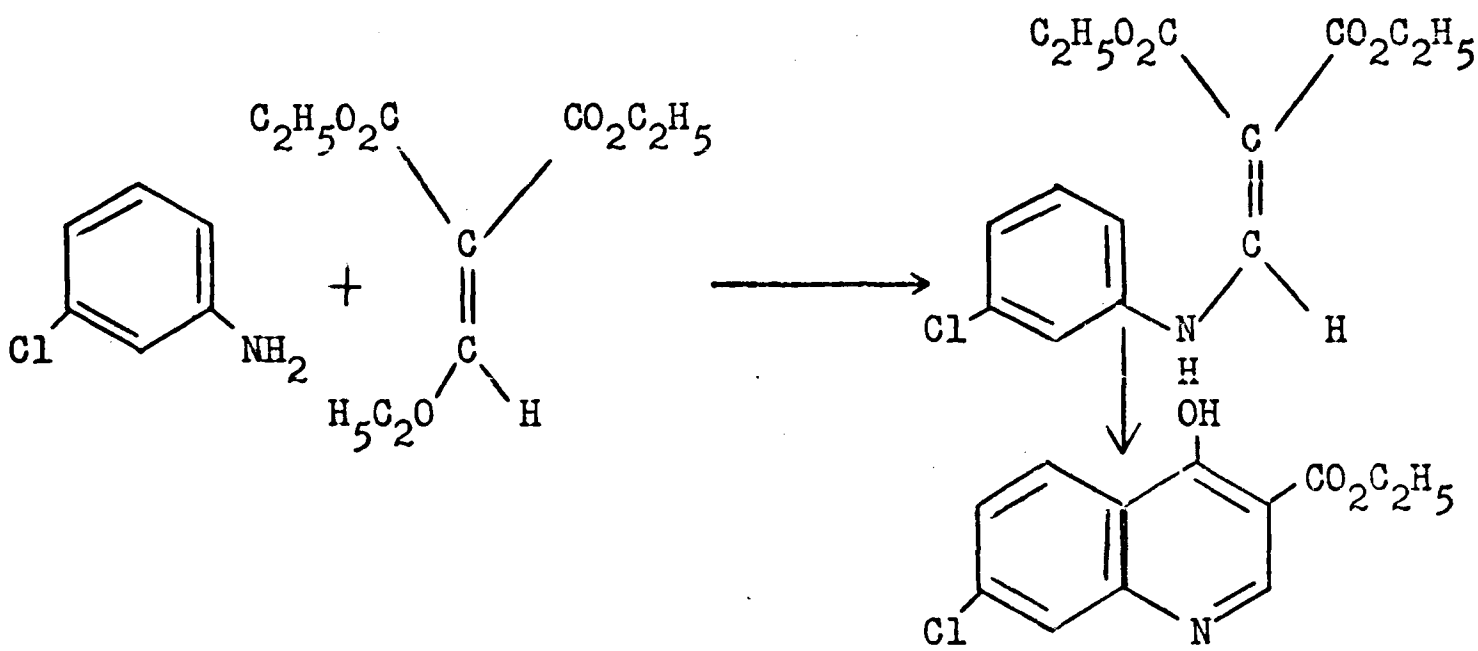


The Combes reaction has been extensively studied by Roberts and Turner, [42] particularly from the point of view of orientation in the ring-closure step. It was concluded that, when a strongly ortho, para-

orienting group is present in a position meta to the nitrogen, ring closure proceeds readily. On the other hand, when a strongly ortho, para-orienting group is present para to the nitrogen (e.g. p-anisidine), ring closure is prevented.

The Combes reaction with aminopyridines has been reported not to be very successful. 2,6-Diaminopyridine has been found to give the expected intermediate with acetylacetone and on cyclisation 2,4-dimethyl-7-amino-1,8--naphthyridine was obtained in 60-70% yield.[43,44] The enamine from 2-amino--6-methylpyridine was prepared by Hauser and Weiss but cyclisation could not be effected.[41] The Combes reaction also failed with 3-aminopyridine[31] and 3-aminopyridine-1-oxide.[45]

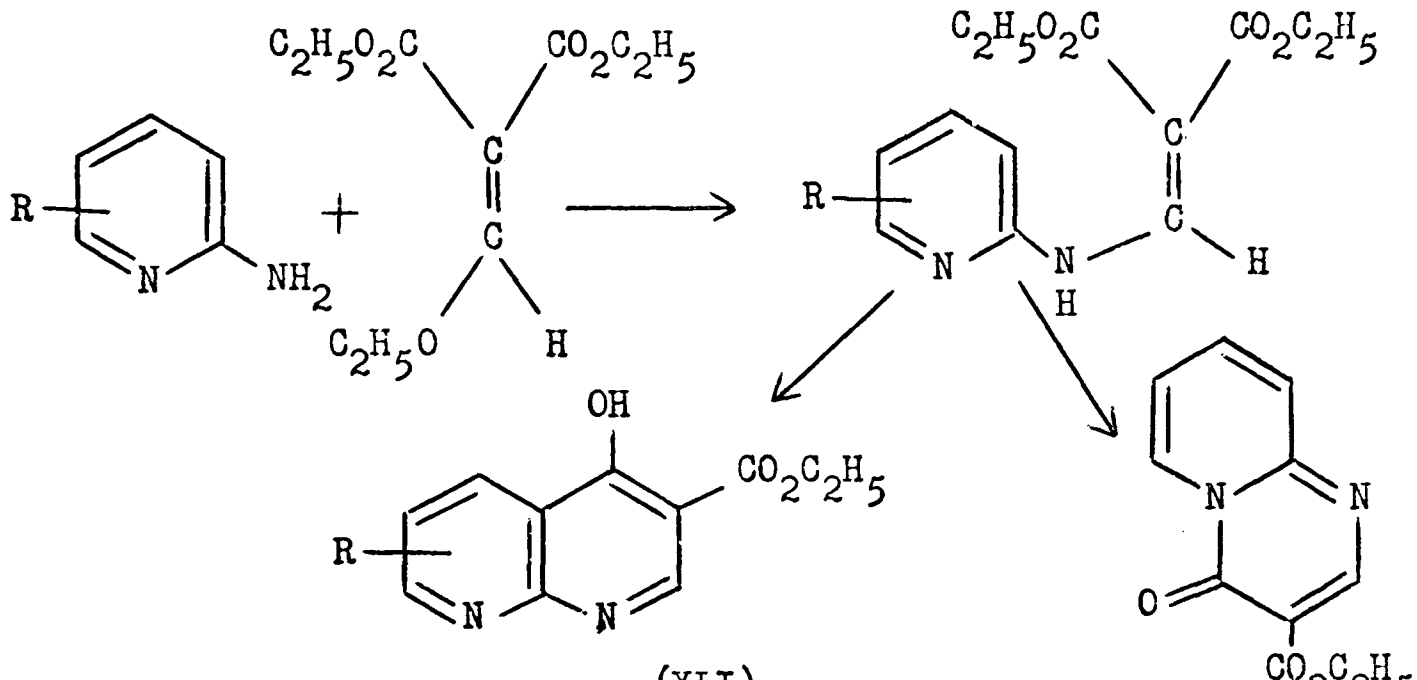
The most generally useful method for the preparation of 4-hydroxyquinolines carrying a carboxyl group in the 3-position is that due originally to Gould and Jacobs.[46] In this reaction the aromatic amine is condensed with diethyl ethoxymethylenemalonate and the resulting acrylate is cyclised by heating in mineral oil or Dowtherm.



This reaction has been reported to be clean-cut and to proceed in good yield. In 1946, the reaction was developed by Price and Roberts[47] and it has been found that almost any aromatic amine can take part in the reaction and 4-hydroxyquinolines containing a variety of substituents in the benzene ring have been prepared.

The reactions of aminopyridines with ethoxymethylenemalonic ester have been extensively investigated.

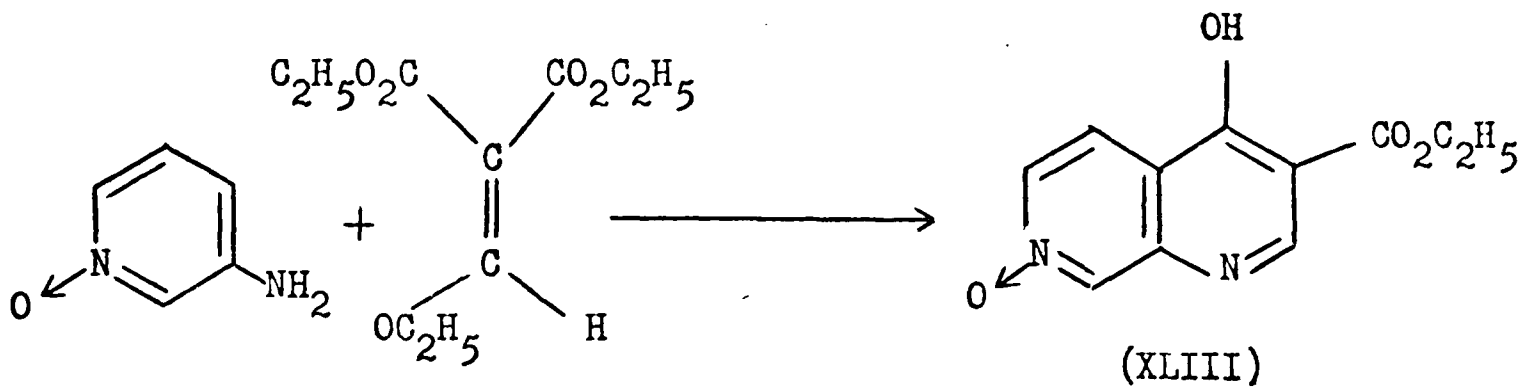
The crotonate from 2-aminopyridine and ethoxymethylenemalonic ester could possibly cyclise to give either ethyl 4-hydroxy-1,8-naphthyridine-3-carboxylate (XLI) or the pyrimidine XLII as shown, but it has been found that only cyclisation to the hydroxy-ester occurred when R is a 6-amino, 6-methyl, or 6-ethoxy group. [48,49]



(XLI)

(XLII)

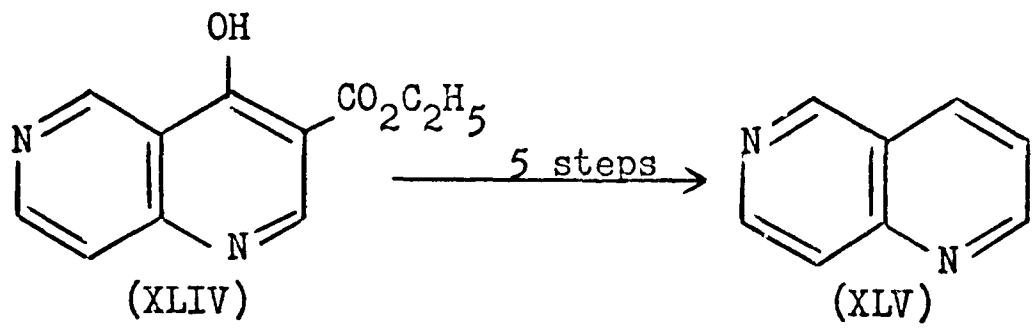
The reaction of 3-aminopyridine with ethoxymethylenemalonic ester gave ethyl 4-hydroxy-1,5-naphthyridine-3-carboxylate. [47,49] However, the yield was satisfactory only when the reaction was carried out in refluxing Dowtherm in very dilute solution. With 3-aminopyridine-1-oxide the reaction proceeded via cyclisation at position 4 of the pyridine to give a 1,7-naphthyridine XLIII. [45]



(XLIII)

The reaction of 4-aminopyridine with ethoxymethylenemalonic ester gave the hydroxy-ester XLIV after cyclisation. Hydrolysis of the ester followed by decarboxylation and then removal of the hydroxyl group afforded the

1,6-naphthyridine (XLV) in 68% yield.[31]



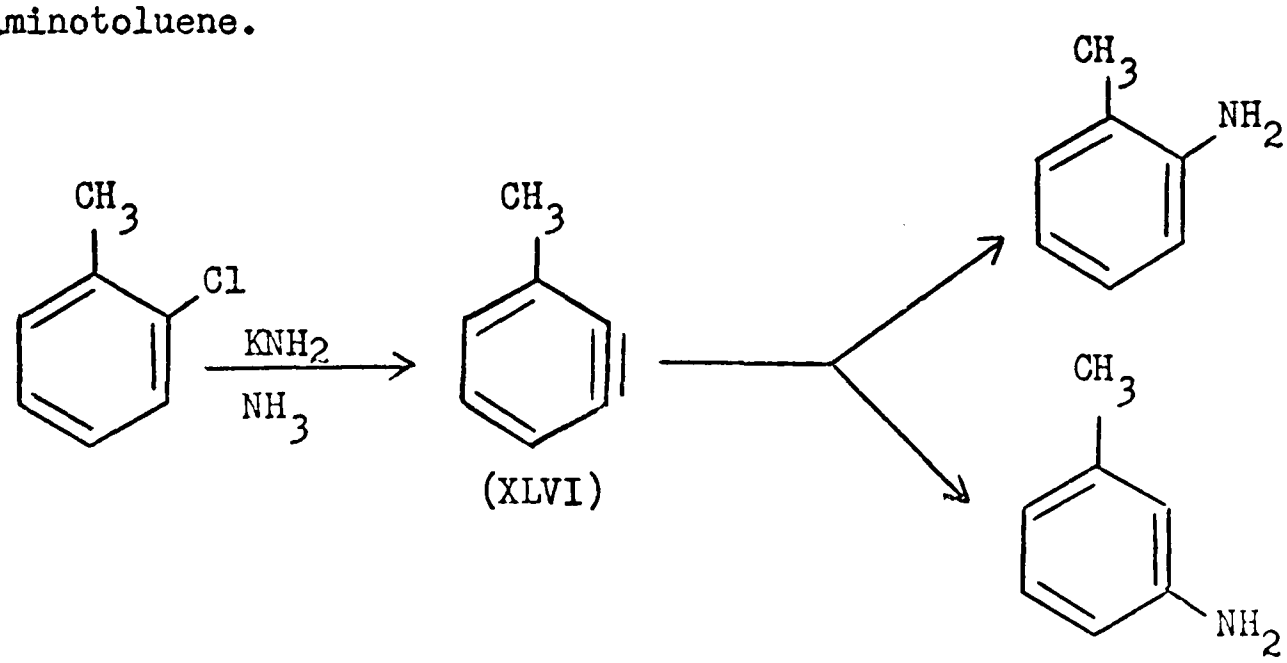
(XLIV) (XLV)

Arynes and Hetarynes

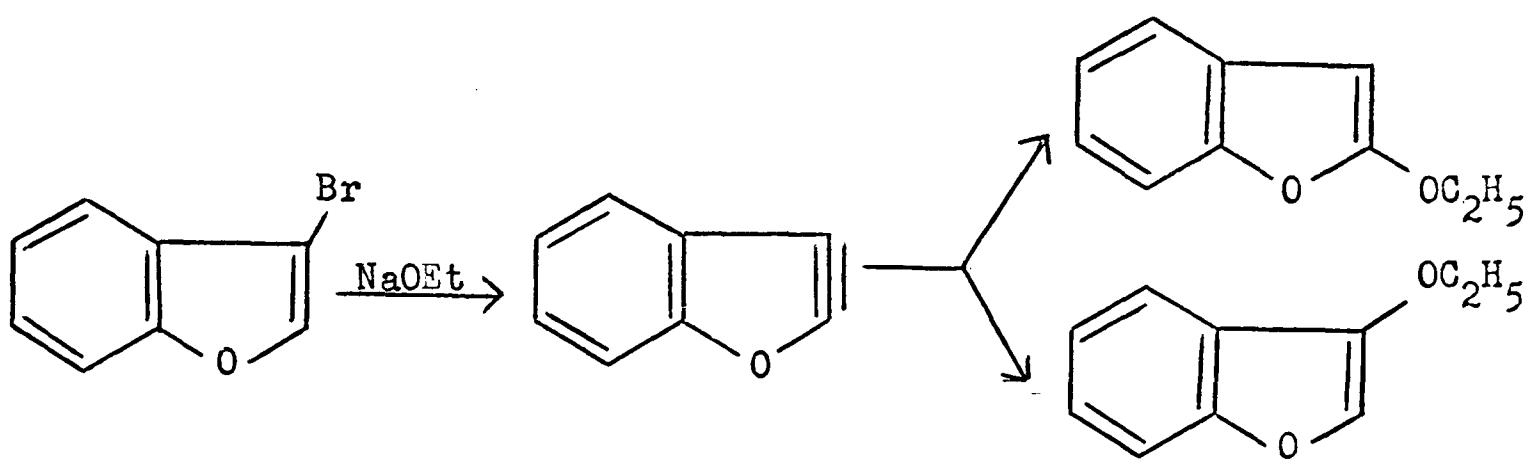
Prior to 1960 little work had been done on reactions of heterocyclic compounds involving hetarynes, i.e. intermediates with a "triple bond" in the nucleus containing the hetero atom. Since then interest in hetarynes has grown and investigations in this area are developing rapidly using information available from carbocyclic aryne chemistry. A brief account of aryne chemistry is presented first as this has naturally formed a basis for the development of hetaryne chemistry.

Arynes

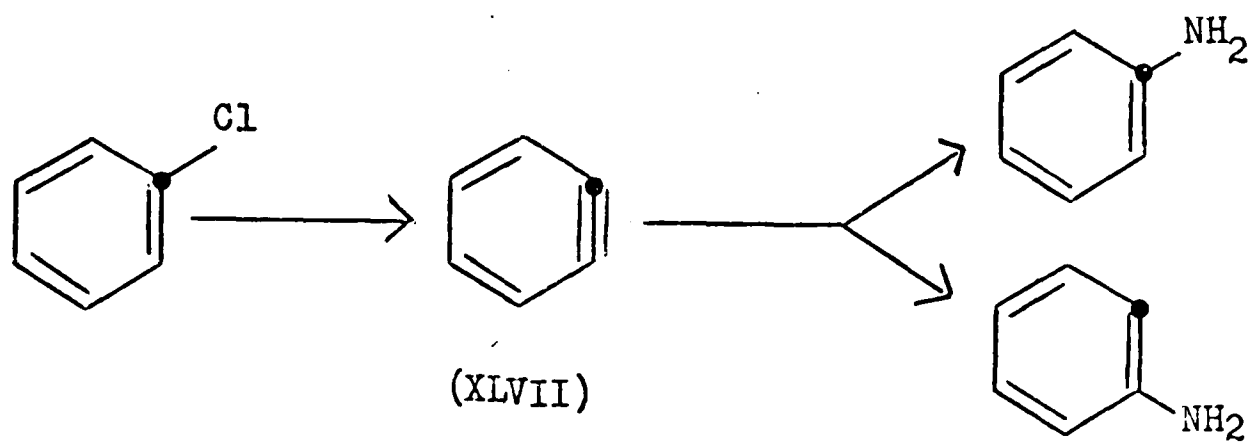
Arynes are intermediates in certain reactions of aromatic compounds, especially in some nucleophilic substitution reactions. They are generated by abstraction of atoms or groups from adjacent positions in the nucleus and react as strong electrophiles and as dienophiles in fast addition reactions. An example of a reaction occurring via an aryne is the amination of o-chlorctoluene with potassium amide in liquid ammonia. 3-Methylbenzyne (XLVI) is first formed by elimination of hydrogen chloride and subsequent addition of ammonia to the "triple bond" yields o-aminotoluene and m-aminotoluene.



Rearrangements during reactions of aromatic halocompounds with strong nucleophiles have been observed for a long time, and it was to explain these phenomena that the aryne hypothesis was first introduced. The first aromatic system containing a'triple bond' was proposed by Stoermer and Kahlert, in 1902,[50] to account for the formation of 2-ethoxybenzofuran in addition to the expected 3-ethoxybenzofuran on reaction of 3-bromobenzofuran with sodium ethoxide.



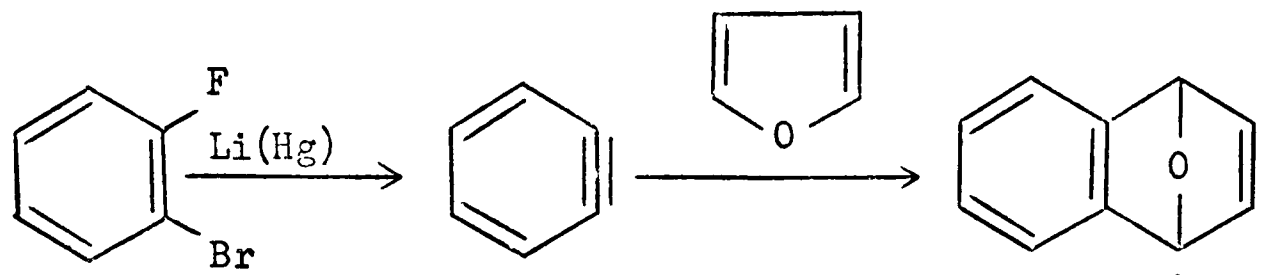
Important introductory work was done by Wittig and in 1953-54 a solid base for the development of aryne chemistry was laid by Roberts and Huisgen and their groups.[51,52,53,54] By applying labelling techniques Roberts and his collaborators[52] obtained results which indicated that benzyne (XLVII) occurs as an intermediate in the amination of chlorobenzene with potassium amide in liquid ammonia. Thus from chlorobenzene-1-^{14}C approximately equal amounts of aniline-1-^{14}C and aniline-2-^{14}C were formed, supporting the involvement of a symmetrical intermediate.



(XLVII)

Reactions were then discovered wherein benzyne was "captured" by reagents which cannot generate it from the starting material; e.g. the reaction of o-bromofluorobenzene with lithium amalgam in the presence of furan yielded dihydronaphthalene-1,4-endoxide (XLVIII) by Diels Alder

cycloaddition of the intermediate to the 2,5-positions of the heterocycle.[55]



(XLVIII)

Following this work interest and investigations in aryne chemistry expanded rapidly, the reactions of these intermediates were studied and a number of methods of generating them were developed. Some of the more important of these are as follows:

(1) Action of alkali amides and alkyl- and aryl-lithiums on monohalogeno aromatic compounds.

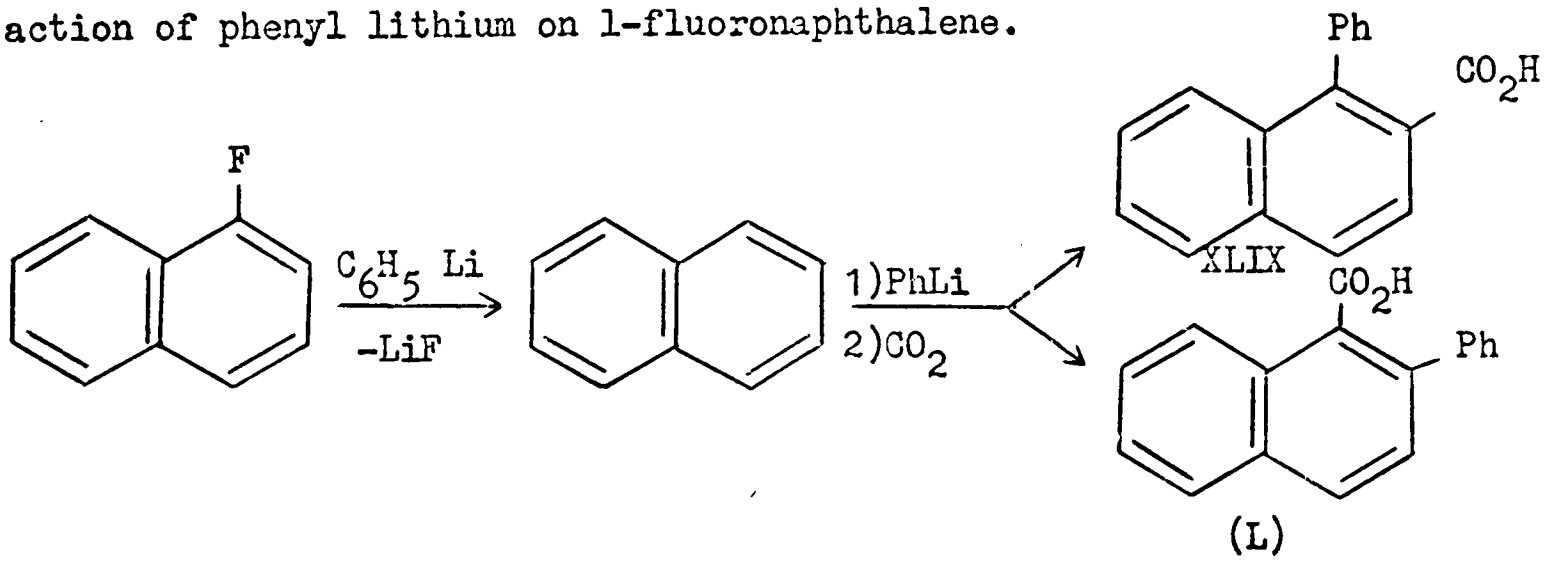
(2) Heating of aryl halides or aryl sulphonates with alkali hydroxides.

(3) Treatment of dihalogeno aromatics with lithium amalgam, magnesium or zinc.

(4) Heating of ortho-arenediazonium carbcxylates or 1,2,3-arenothiadiazole-1,1-dioxides.

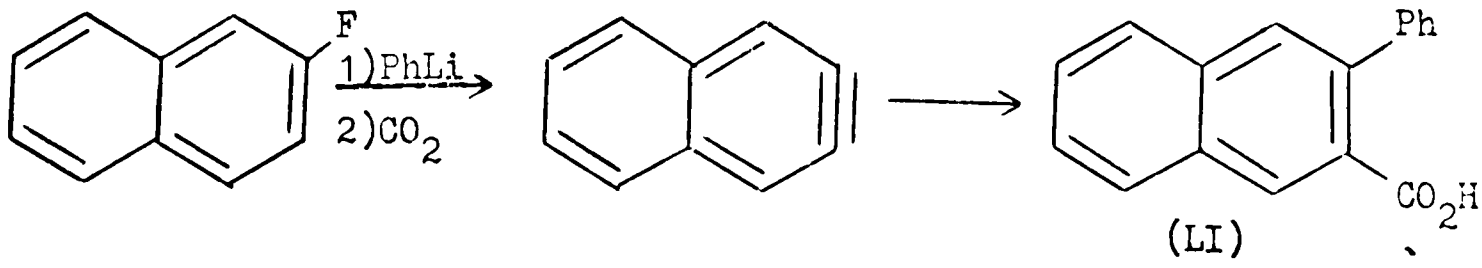
(5) Heating of ortho-iodoarenemercuric iodides.

An example of an aryne reaction proceeding by the first method is the action of phenyl lithium on 1-fluoronaphthalene.



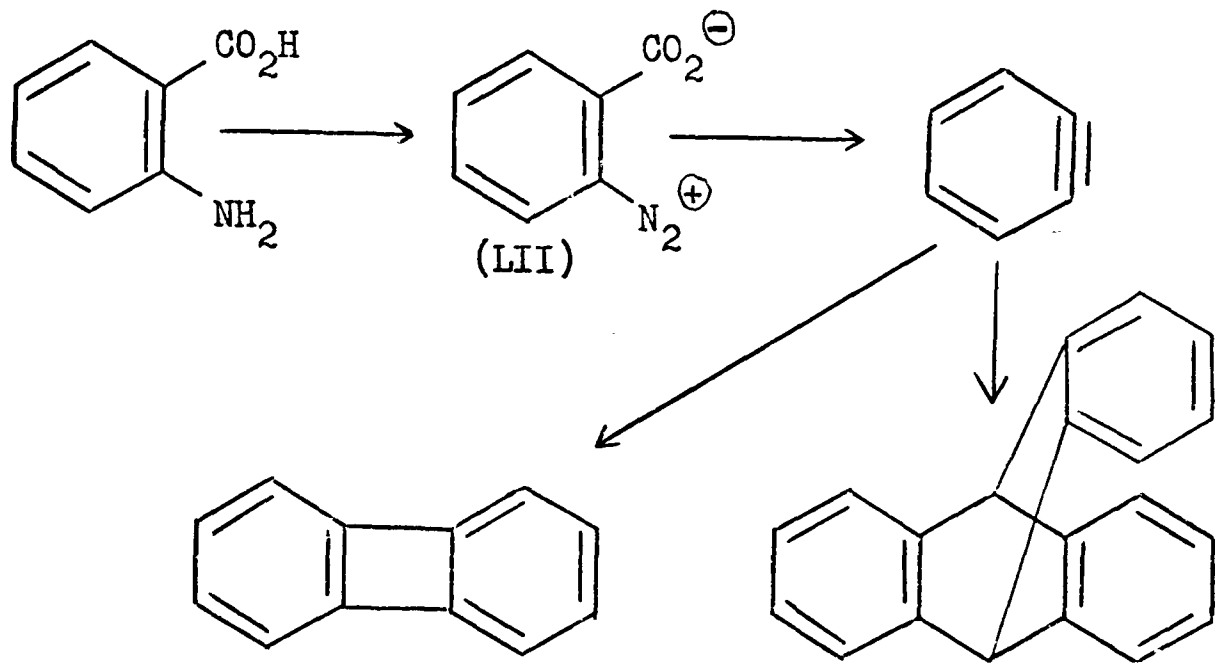
(L)

2-Fluoronaphthalene gave (in addition to XLIX and L) a third isomeric acid LI formed via the 2,3-naphthalyne.[51]



(LI)

One of the most useful methods for generating arynes is that originally due to Stiles and Miller.[55] The zwitterionic diazonium salt, benzenediazonium-2-carboxylate (LII), readily obtained from anthranilic acid by aprotic diazotisation, was found to give benzyne on heating. Thus on warming the compound in furan, naphthalene-1,4-endoxide was obtained in 55% yield, and triptycene (LIII) was obtained with anthracene in benzene solution. Berry, Spokes and Stiles[56] have demonstrated by flash photolysis the formation of gaseous benzyne, from solid o-benzenediazonium carboxylate, as a precursor of biphenylene (LIV).



(LII)

(LIV)

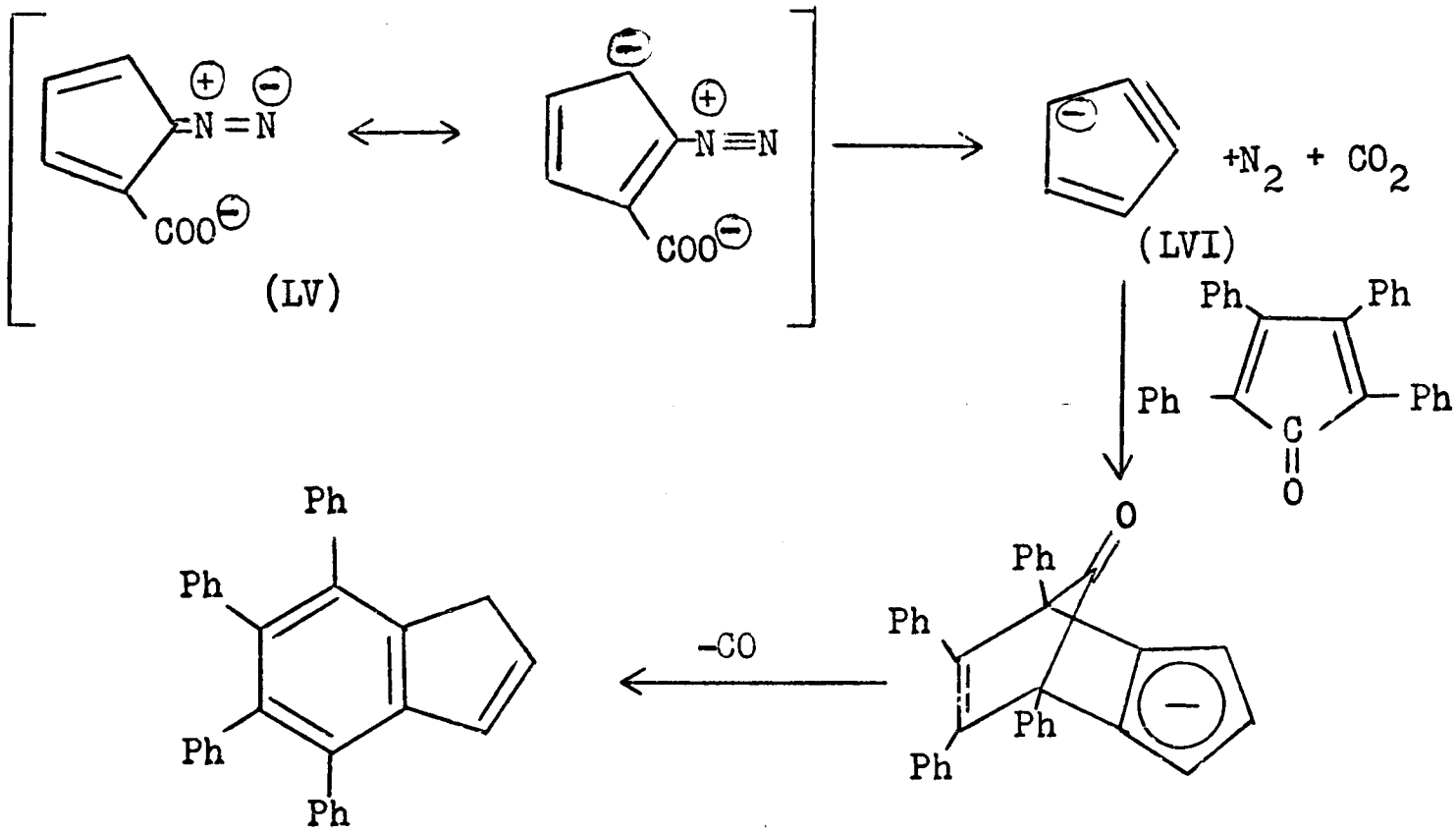
(LIII)

Benzyne has frequently been generated <u>in situ</u> from anthranilic acid by reaction with isoamyl nitrite in aprotic solvents.

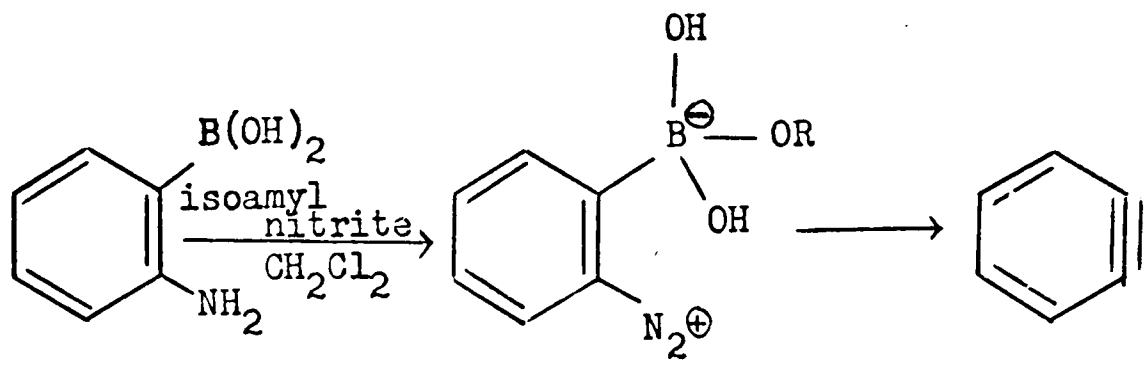
The use of propylene oxide for generating arynes from the solid diazonium carboxylate hydrochlorides has been described by Roberts and collaborators[57] and later by Ziegler.[58] This method has the advantage over the Stiles procedure in that it avoids isolating and thus handling of the hazardous, explosive diazonium carboxylate salt. Decomposition of benzenediazonium-2-carboxylate hydrochloride with propylene oxide in the presence of anthracene gave triptycene. Ziegler prepared 1,4-epoxy-1,4-dihydronaphthalene from the same benzyne precursor and furan. The propylene oxide, in these experiments, reacts rapidly and irreversibly with the hydrogen chloride to give LII and propylene chlorohydrin which can be

readily removed from the reaction products by distillation.

The thermal decomposition of diazocyclopentadiene-2-carboxylate anion (LV) under a variety of conditions gave carbon dioxide, nitrogen and dehydrocyclopentadienyl anion (LVI). The intermediacy of LVI was established by trapping with 2,3,4,5-tetraphenylcyclopentadienone (tetracyclone).[59]

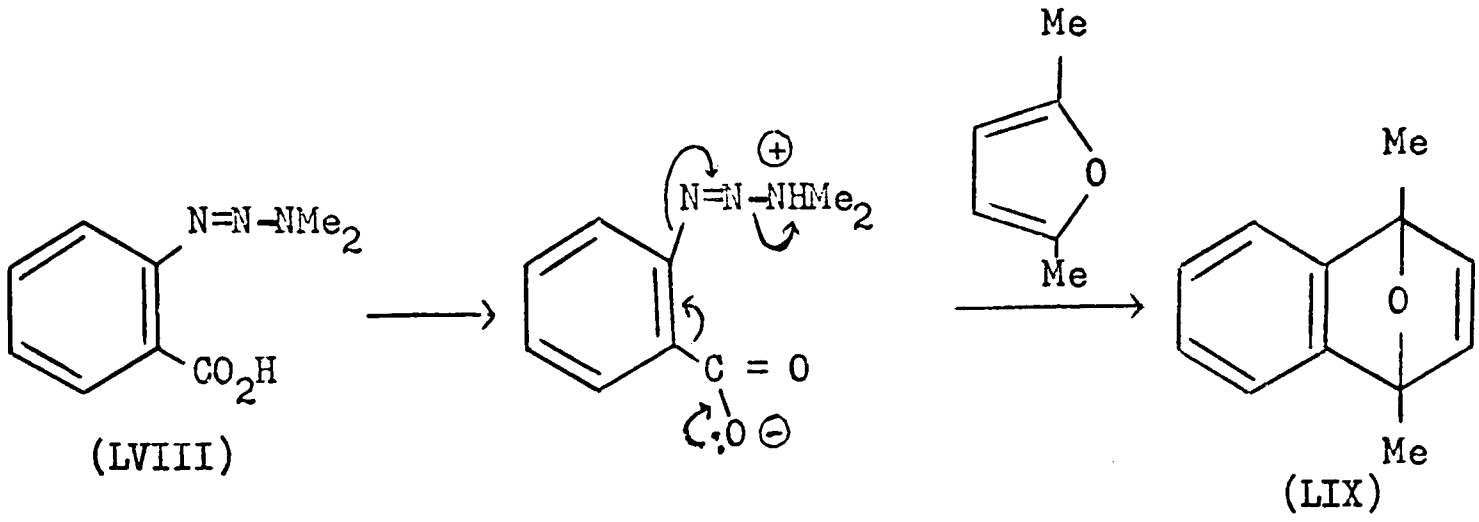


During recent years a large number of new methods of generating benzyne have been investigated. In 1966, Verbit and co-workers[60] reported the generation of benzyne from o-aminophenylboronic acid (LVII); the adduct, triptycene, was isolated in 45-60% yield.

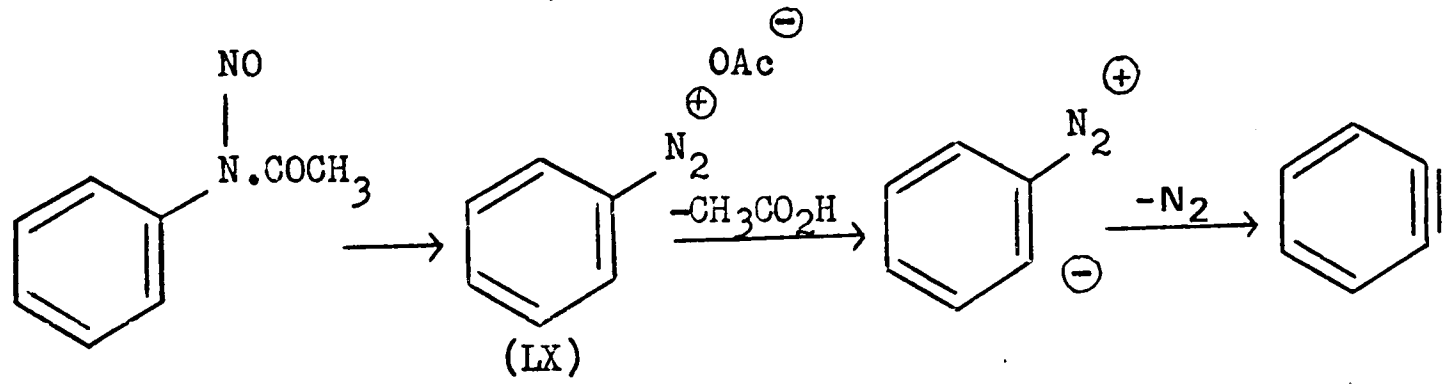


In 1970, Nakayama, Simamura and Yoshida[61] generated benzyne by heating 1-(2-carboxyphenyl)-3,3-dimethyltriazene (LVIII) in chloroform,

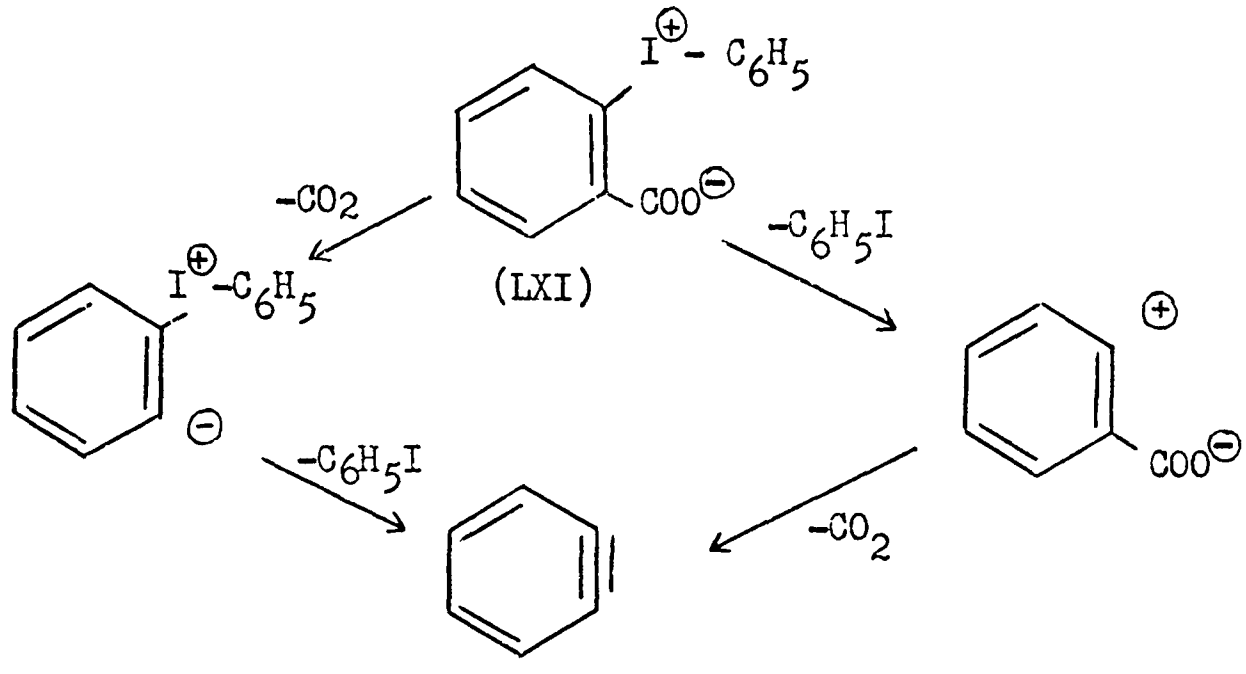
the intermediacy of benzyne being shown by trapping with 2,3,4,5-tetraphenylcyclopentadienone. With 2,5-dimethylfuran in refluxing acetonitrile the aryne precursor gave 1,4-expoxy-1,4-dimethyl-1,4-dihydronaphthalene (LIX) in 77% yield.



A simple, one-step, conversion of aniline into benzyne has been reported by Cadogan, Mitchell and Sharp.[62] Reaction of aniline with acetic anhydride, pentyl nitrite and tetracyclone in benzene gave tetraphenylnaphthalene in 32% yield. Benzyne is generated from the initially formed N-nitroscacetanilide, via the diazonium acetate LX.

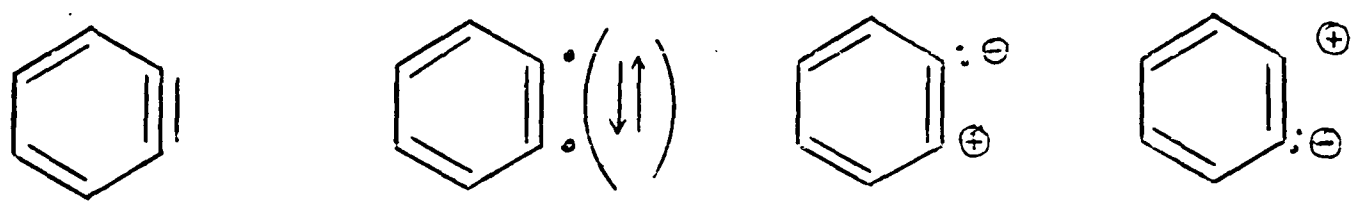


The thermal decomposition of diphenyliodonium-2-carboxylate (LXI) reported by LeGoff in 1962[63] and by Beringer and Huang in 1963[64] to give benzyne has, up to now, not found application in the field of hetaryne chemistry. It is not known whether carbon dioxide or iodobenzene is first lost from LXI or whether a concerted mechanism is involved.



When betaine LXI was heated at 162° in diglyme containing 1,3-diphenylisobenzofuran, 9,10-diphenylanthracene was formed in 21% yield. The effects of trapping agents were also investigated in this reaction and it was reported that 2,5-di-p-anisyl-3,4-diphenylcyclopentadienone was a very effective 'trap' as 1,4-di-p-anisyl-2,3-diphenylnaphthalene was isolated in 79%. It was concluded that addition reactions of benzyne are favoured by increased electron density in the diene.

Although neither benzyne nor any other aryne has been isolated, it appears from the foregoing that one is justified in considering these intermediates to be short lived species which may be described as a mesomeric structure to which the following canonical forms contribute.



Hetarynes

It has been stated that the generation and reactions of hetarynes can be expected to differ from carbocyclic arynes in several respects.

(1) There are usually isomers of an unsubstituted hetaryne.

(2) Since unsubstituted hetarynes are usually not symmetric their participation in a reaction can manifest itself in the occurrence of a rearrangement.

(3) The properties of a hetaryne in which the 'triple bond' is adjacent to the hetero atom may differ considerably from those of its isomers.

(4) The ratio of the amounts of isomeric addition products will depend on the orienting effect of the hetero atom in the nucleus.

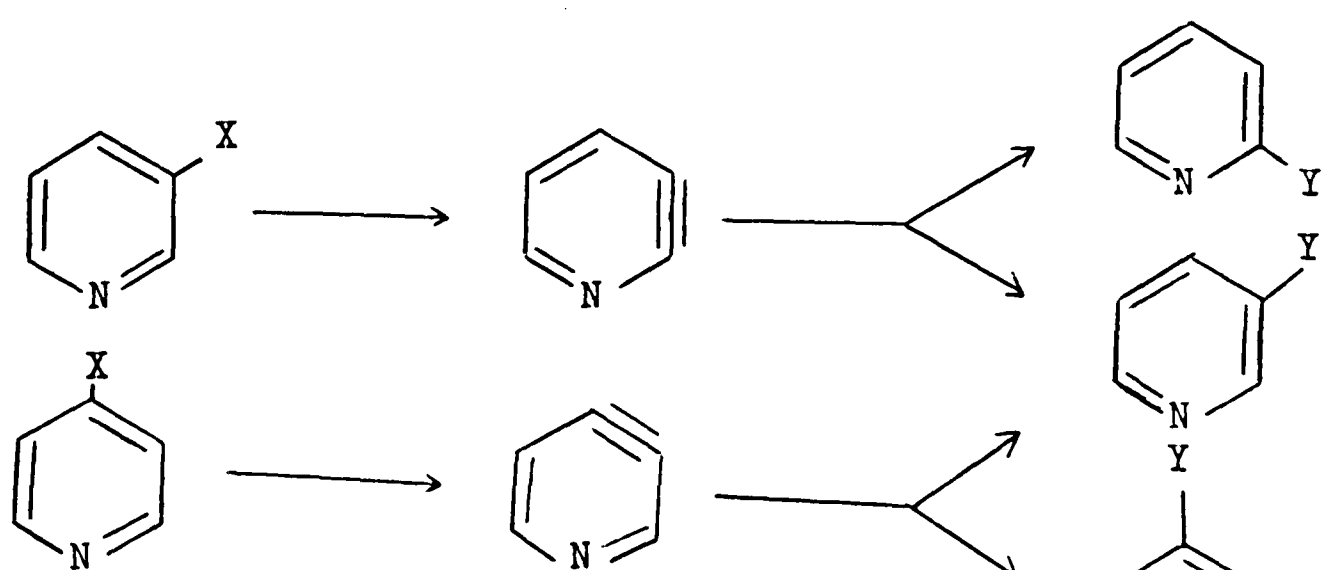
(5) The action of nucleophiles on a monosubstituted heterocyclic compound may generate isomeric hetarynes.

(6) Heterocyclic compounds may show a higher tendency than carbocycles to react with nucleophiles by the addition-elimination mechanism than via arynes.

Pyridyne intermediates have been investigated more extensively than any other hetarynes. Whereas only one dehydrobenzene is possible, two pyridynes viz. 2,3-and 3,4-pyridyne may be obtained.

The first amination of a halogeno pyridine involving a rearrangement was carried out by Levine and Leake in 1955[65] in an attempt to prepare 3-phenacylpyridine by reacting 3-bromopyridine with sodium amide in liquid ammonia in the presence of sodio-acetophenone; 10% of 4-aminopyridine and 13.5% of 4-phenacylpyridine was isolated.

In 1961 Pieterse and den Hertog [66] carried out a more extensive investigation of the amination of 3- and 4-halogenopyridines with potassium amide in liquid ammonia at -33°. Mixtures of 3- and 4-aminopyridine in the ratio of 1:2 were isolated in all cases with 3-chloro, 3-bromo and 3-iodo-pyridines and the corresponding 4-substituted pyridines.



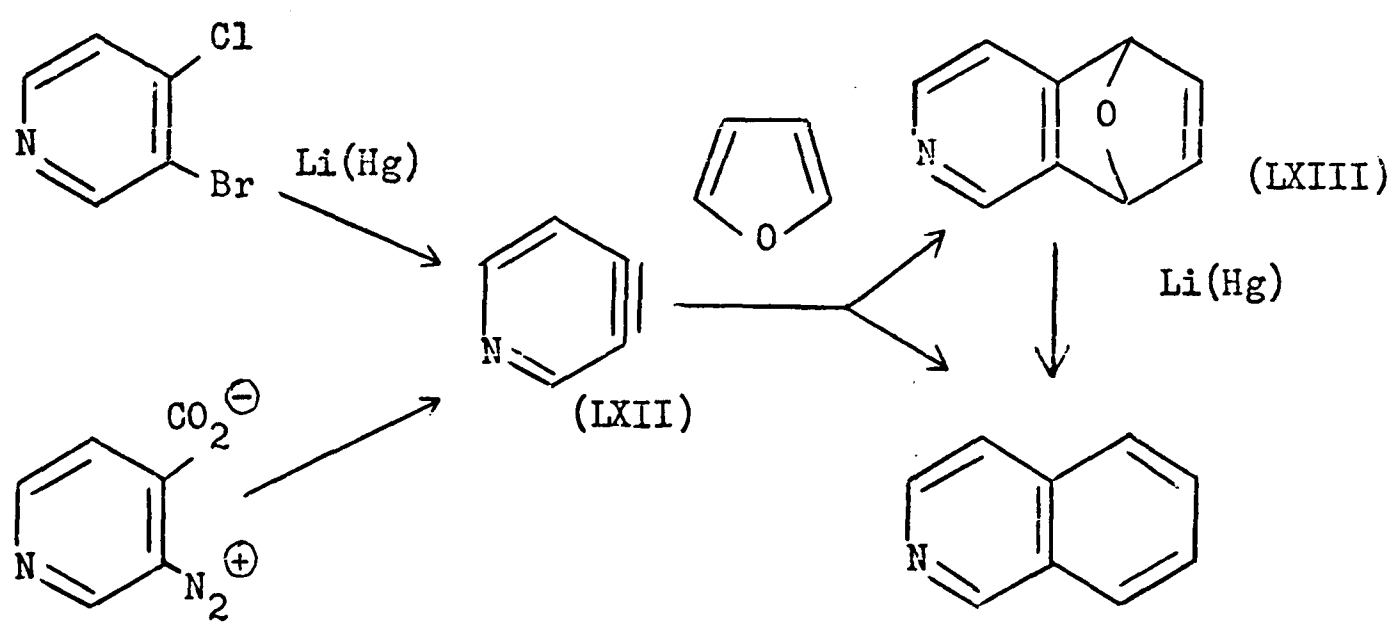
X = Cl, Br or I

Y = NH_2

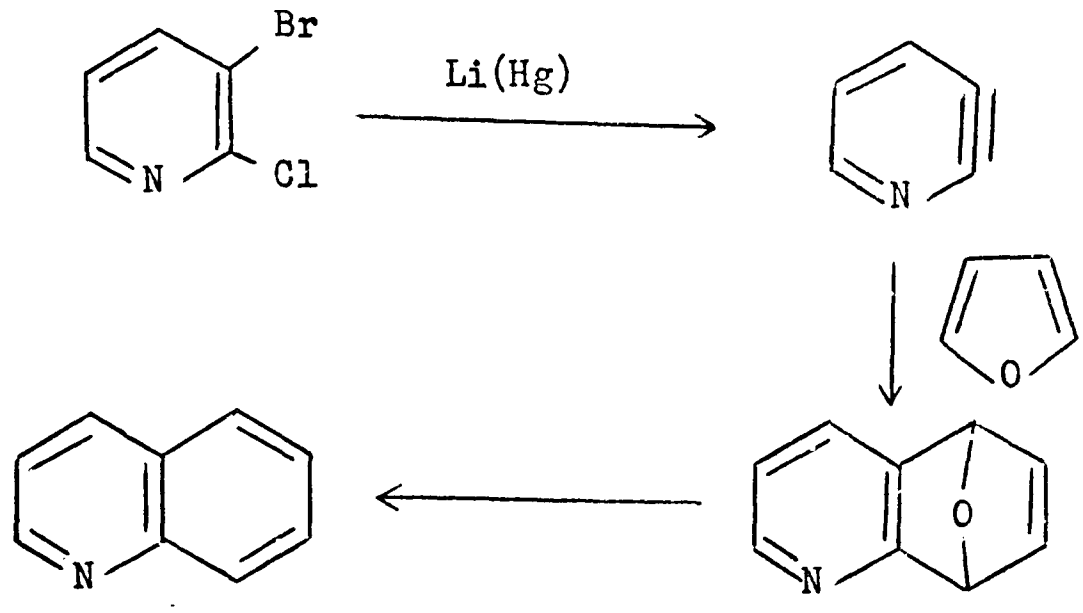
The independence of the composition of the reaction products from the nature and position of the halogeno substituent clearly demonstrated the intermediacy of 3,4-pyridyne and not a mixture of 2,3- and 3,4-pyridyne.

The reactions of various halogeno pyridines with lithium piperidide and piperidine have been studied by Kauffman and Boettcher [67,68] and the results of these experiments support the 3,4-pyridyne intermediate. Increasing the amounts of lithium piperidide and piperidine to five to ten equivalents, respectively, did not change the composition of the reaction products.

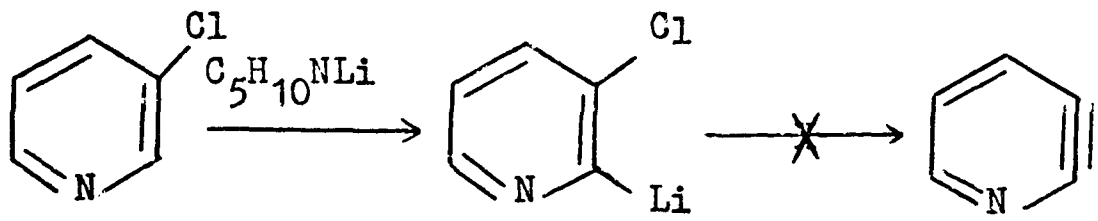
3,4-Pyridyne (LXII) is formed and reacts as a dienophile in a number of reactions analogous to those described by Wittig and Pohmer[53] and by Stiles and Miller[55] in benzyne chemistry. Shaking 3-bromo-4-chloropyridine with lithium amalgam and furan gave a mixture from which isoquinoline was isolated in 14% yield; the initially formed endoxide is deoxygenated by the amalgam. By heating 3-pyridinediazonium-4-carboxylate in furan, the endoxide LXIII could be isolated in greater than 60% yield.[67,69]



2,3-Pyridyne has been shown to exist by trapping with furan.[70] Thus it has been considered as an intermediate in the reaction of 3-bromo-2-chloropyridine with lithium amalgan in order to explain the small amount of quinoline (2% formed).

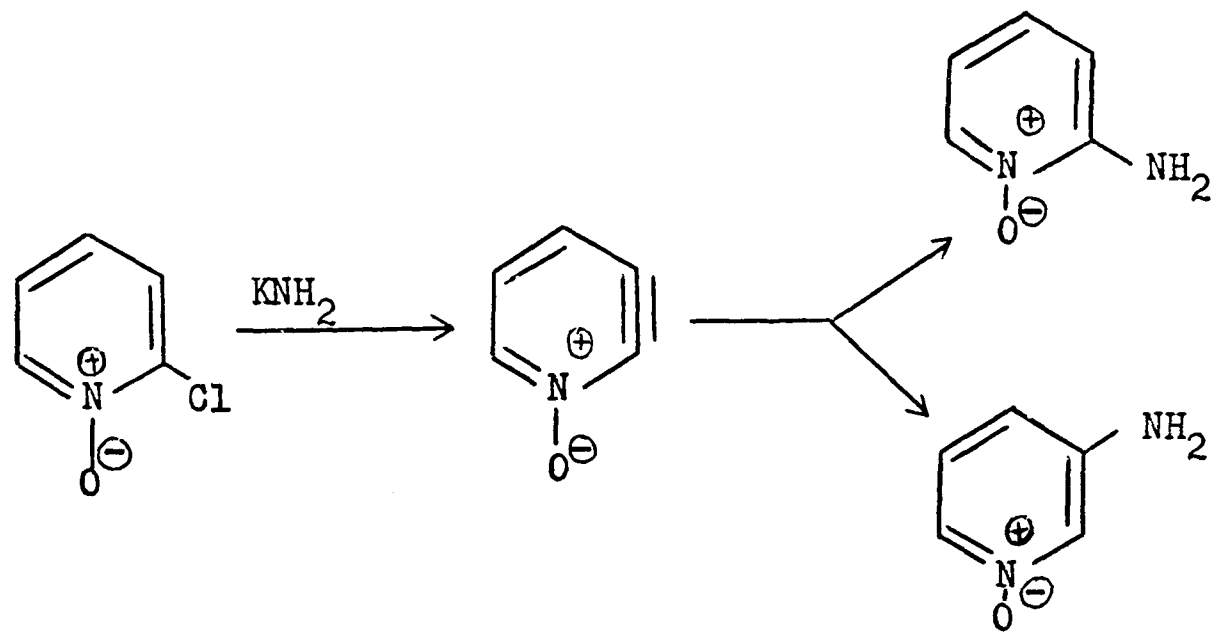


An explanation for the absence of 2,3-pyridyne in the reaction of 3-chloropyridine with lithium piperidide has been given by Kauffmann and Boettcher.[68] It is supposed that metallation to give 3-chloro-2-lithiopyridine (LXIV) does take place, but that the negative charge at C-2, resulting from polarisation of the lithium-carbon bond, is weakened by the inductive effect of the ring nitrogen atom and, therefore does not weaken the neighbouring chlorine-carbon bond. Thus lithium chloride is not eliminated and the formation of 2,3-pyridyne does not occur.

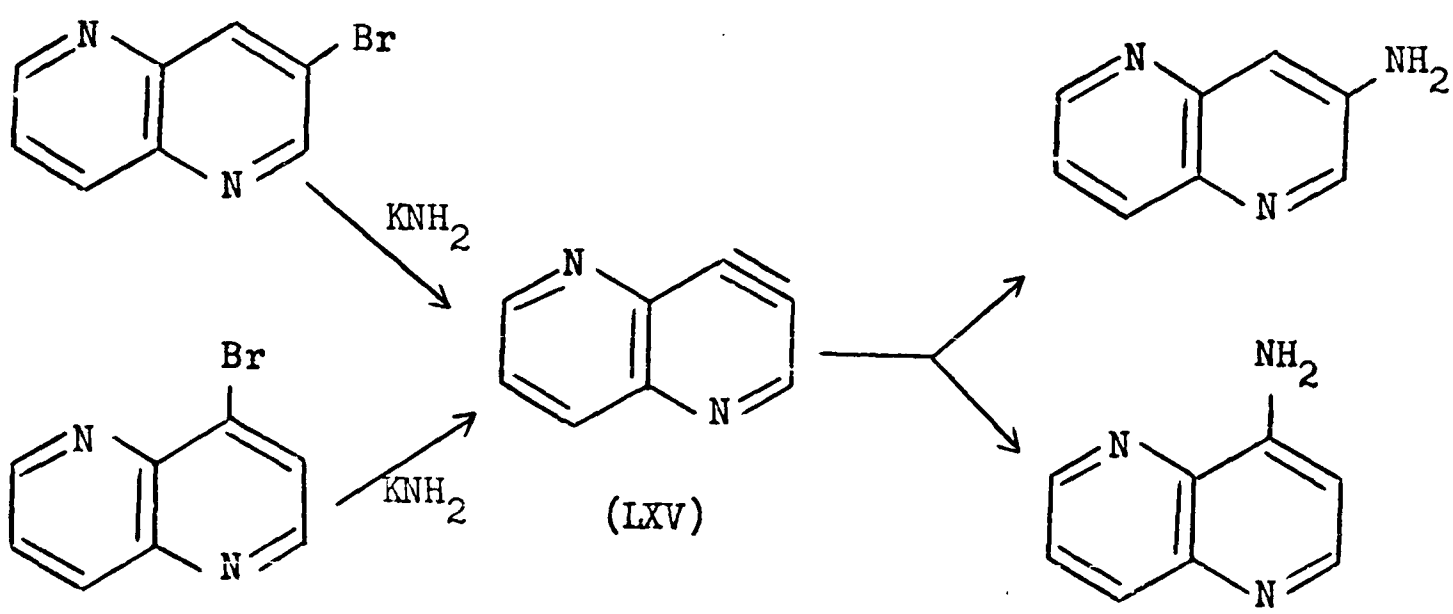


(LXIV)

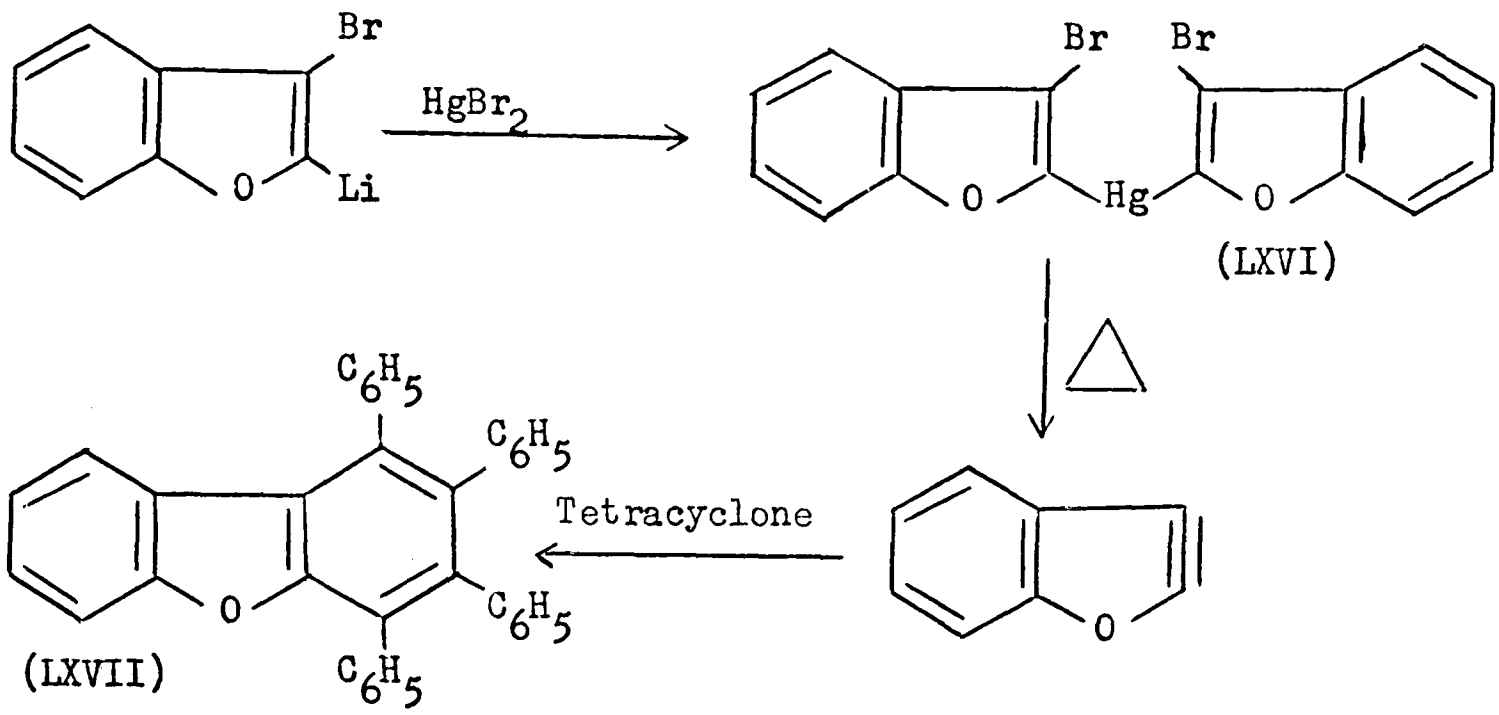
The amination of 2-chloropyridine-N-oxide with potassium amide in liquid ammonia gave a mixture of 2- and 3-aminopyridine-N-oxide in 5-10% total yield.[70] This rearrangement has been explained by an aryne mechanism involving 2,3-pyridyne-N-oxide, a result which has been confirmed by Kato, Niitsuma and Kusaka.[71]



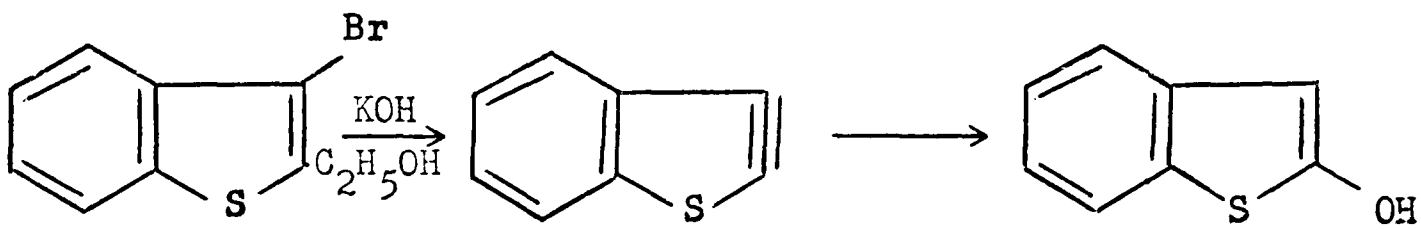
There has been evidence for the formation of 1,5-naphthyrid-3,4-yne (LXV), but none for 1,5-naphthyrid-2,3-yne from the results of the amination of 3- and 4-bromo-1,5-naphthyridine with potassium amide in liquid ammonia. Mixtures of 3- and 4-amino-1,5-naphthyridine were produced but 2-amino-1,5-naphthyridine was not found.[72]



Apparently only one hetaryne containing oxygen as a heteroatom, 2,3-dehydrobenzofuran, has been described so far. Quite recently this legendary aryne was again generated by Wittig and Boos[73] and proved to have dienophilic properties, thus confirming the original work of Stoermer and Kahlert. The dehydrobenzofuran was obtained by heating the mercury compound LXVI, formed by treatment of 3-bromo-2-lithiobenzofuran with mercuric bromide. The aryne was trapped with 2,3,4,5-tetraphenylcyclopentadienone and the adduct LXVII was isolated in 70% yield.

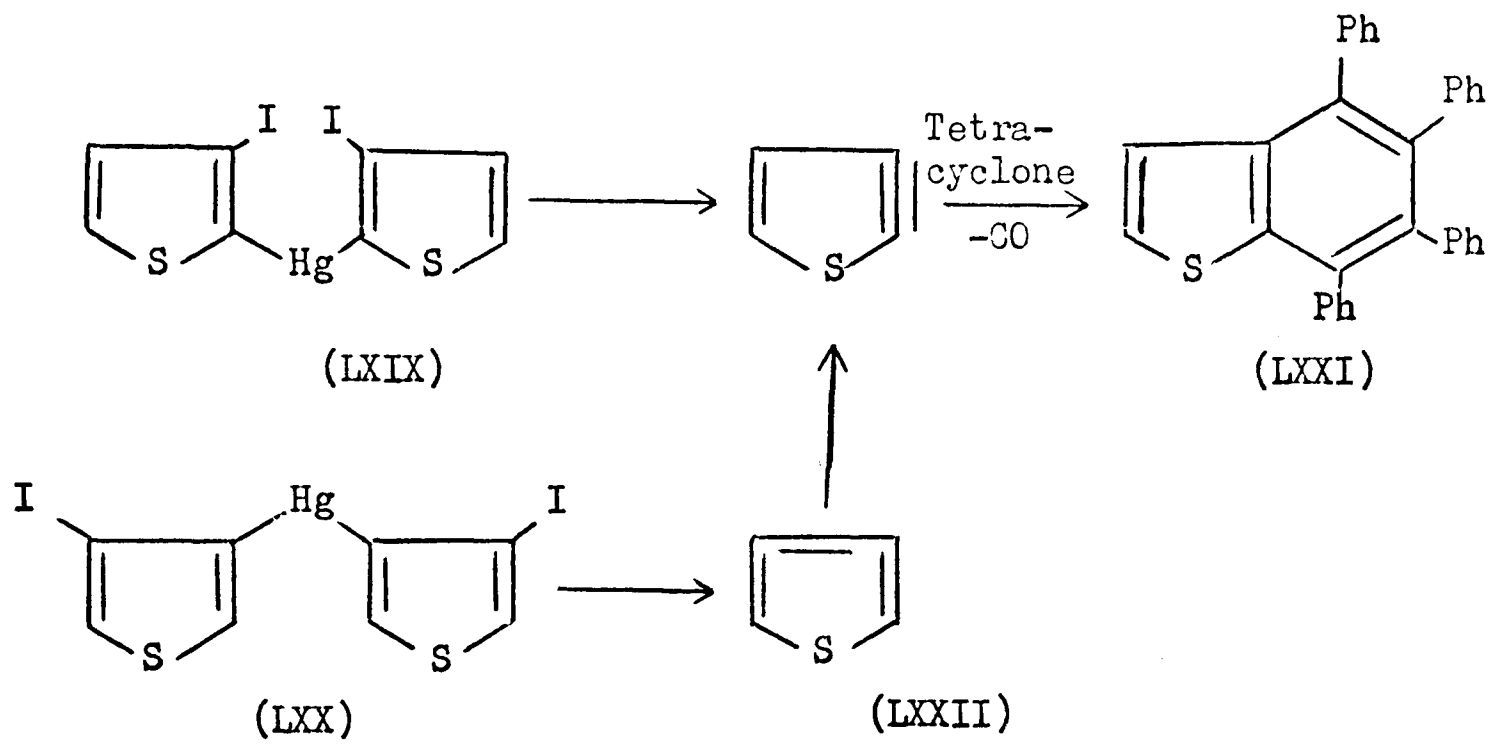


The first thiaaryne, 2,3-benzothiophyne, may have been generated by Komppa and Weckmann in 1933.[74] On heating 3-bromobenzothiophene (LXVIII) with a solution of potassium hydroxide in ethanol at 200°, a reaction mixture was obtained consisting of starting material, benzothiophene and 2-hydroxybenzothiophene. This reaction is analogous to the reaction of 3-bromobenzofuran with sodium ethoxide. If both are examples of aryne chemistry they illustrate the addition of a nucleophile to the 2-position of a 2,3-hetaryne.

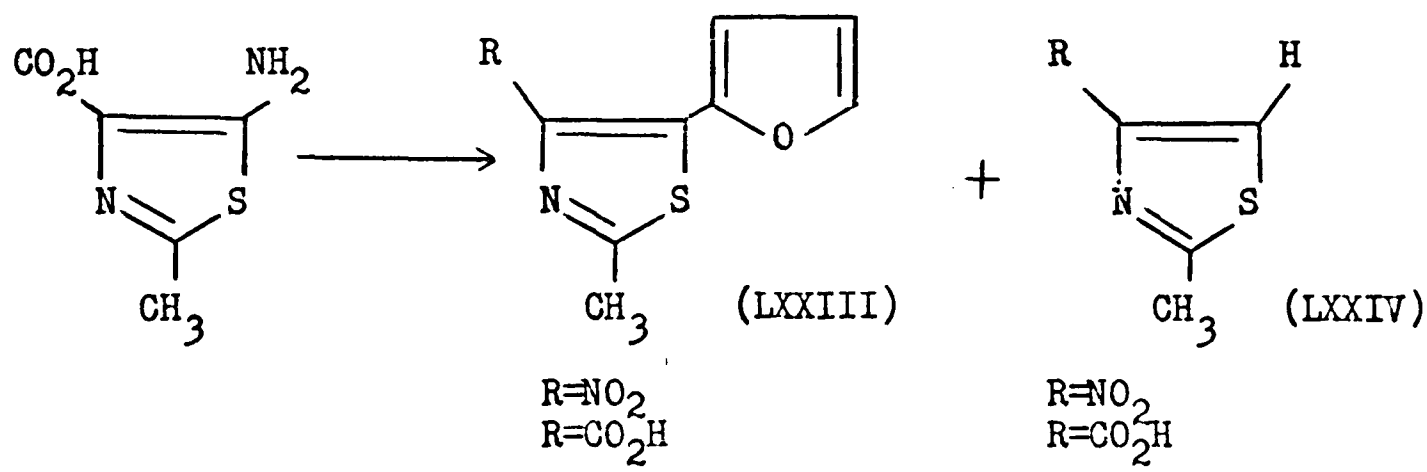


(LXVIII)

The 2,3-hetaryne derived from thiophene was obtained by Wittig and Wahl [75] by heating bis-(3-iodothienyl-2)-mercury (LXIX) and trapped with tetracyclone, the adduct being isolated in 9% yield. Bis-(3-iodothienyl-4)-mercury (LXX) when heated with tetraphenylcyclopentadienone, was reported to give the same tetraphenylbenzothiophene (LXXI) as its isomer. The 3,4-dehydrothiophene (XXII) had apparently rearranged to the 2,3-isomer prior to cyclo-addition.



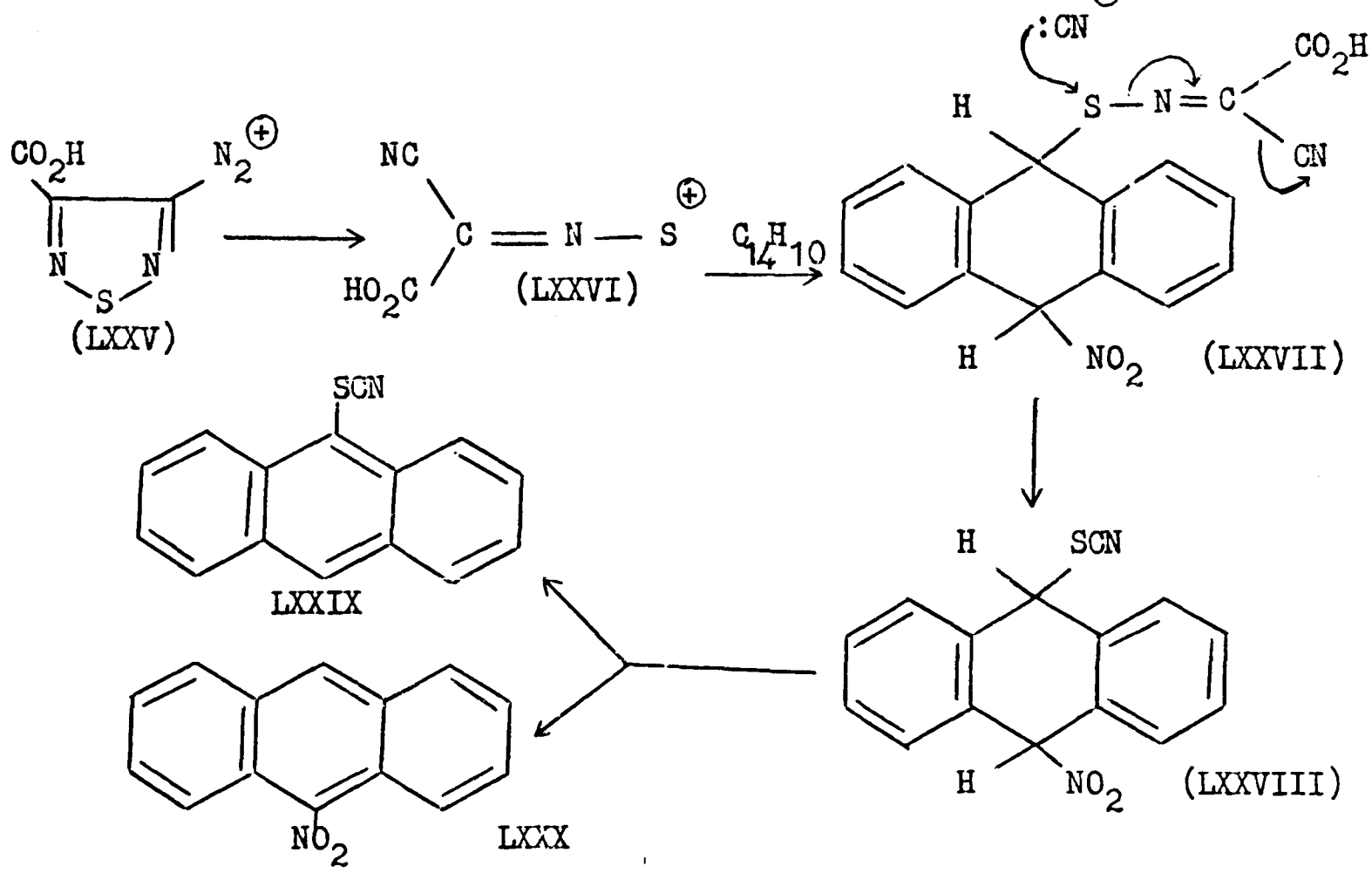
The possibility of generating five membered hetarynes containing nitrogen and sulphur has only recently been investigated. In 1971, Tamura, Miyamoto and Ikeda [76] investigated the reaction of 5-amino-2-methylthiazole-4-carboxylic acid with isoamyl nitrite in the presence of furan and also tetraphenylcyclopentadienone. With furan, 5-(2'-furyl)-2-methyl-4-nitrothiazole (LXXIII: R=NO_2,0.53%) and 2-methyl-4-nitrothiazole (LXXIV, R=NO_2,0.33%) were isolated in addition to 5-(2'-furyl)-2-methylthiazole-4-carboxylic acid (LXXIII, R=CO_2H, 10.7%) and 2-methylthiazole-4-carboxylic acid (LXXIV, R=CO_2H,2.7%)



In the presence of tetracyclone, (LXXIV, R=CO_2H, 9%) was isolated and a trace of two unidentified compounds of molecular weight 390 and 400. In these two experiments the reaction mixture was carefully screened for the desired Diels-Alder adduct of dehydrothiazole with furan or tetra-

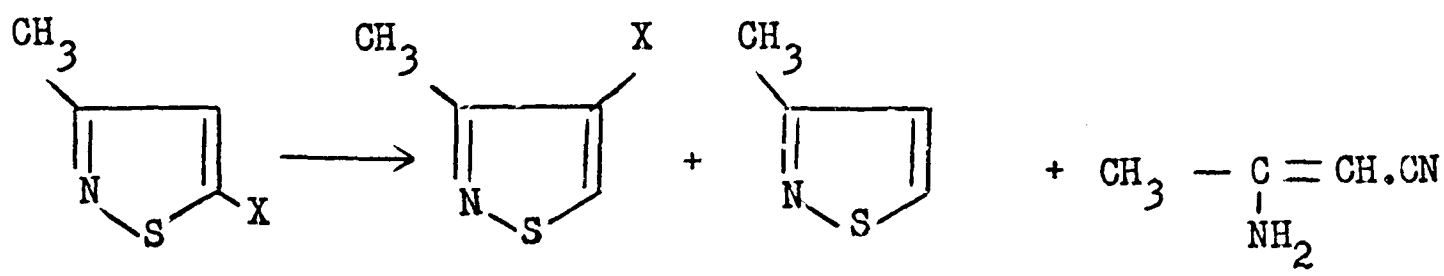
cyclone, but none was detected.

Bird and Wong, in 1971, [77] attempted to generate 1,2,5-thiadiazolyne by the aprotic diazotisation of 3-amino-1,2,5-thiadiazole-4-carboxylic acid in the presence of anthracene. None of the anticipated thiazolyne adduct was obtained; instead 9-nitroanthracene and a small amount of 9-thiocyanoanthracene were isolated. It was suggested that these arose by collapse of the diazonium cation LXXV to the electrophilic sulphur cation LXXVI. Subsequent attack of LXXVI on the anthracene followed by addition of nitrite ion gave LXXVII. Displacement of the organic residue attached to sulphur by cyanide ion then gave the intermediate LXXVIII. Finally, base treatment during the work up effected rearomatisation with formation of LXXIX and LXXX. The preponderance of 9-nitroanthracene was attributed to the greater acidity of the proton geminal to the nitro group in LXXVIII.



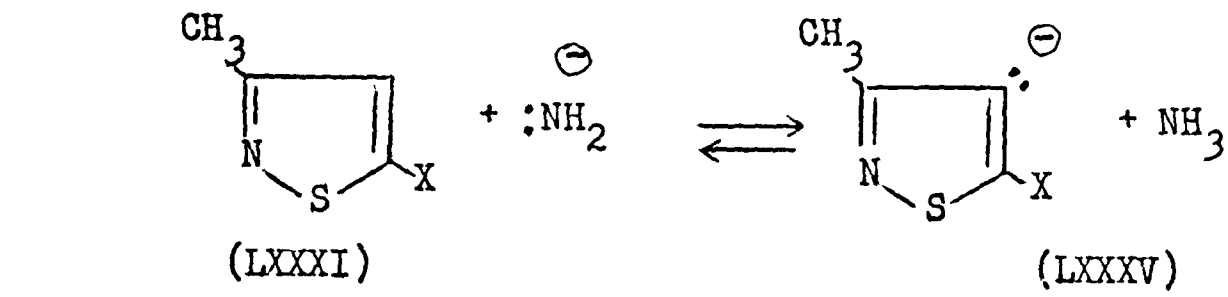
The amination of halogenoisothiazoles with potassium amide in liquid ammonia has recently been studied by de Bie and Van der Plas.[78] They found that under the conditions of the reactions, halogen migration occurs and that amination, if any, only takes place to a small extent.

Thus 5-bromo-3-methylisothiazole (LXXXI, X=Br) when treated with a four-fold molar quantity of potassium amide in liquid ammonia at -33° for 5 minutes gave 4-bromo-3-methylisothiazole (LXXXII, X=Br) and a small amount of 3-methylisothiazole (LXXXIII).

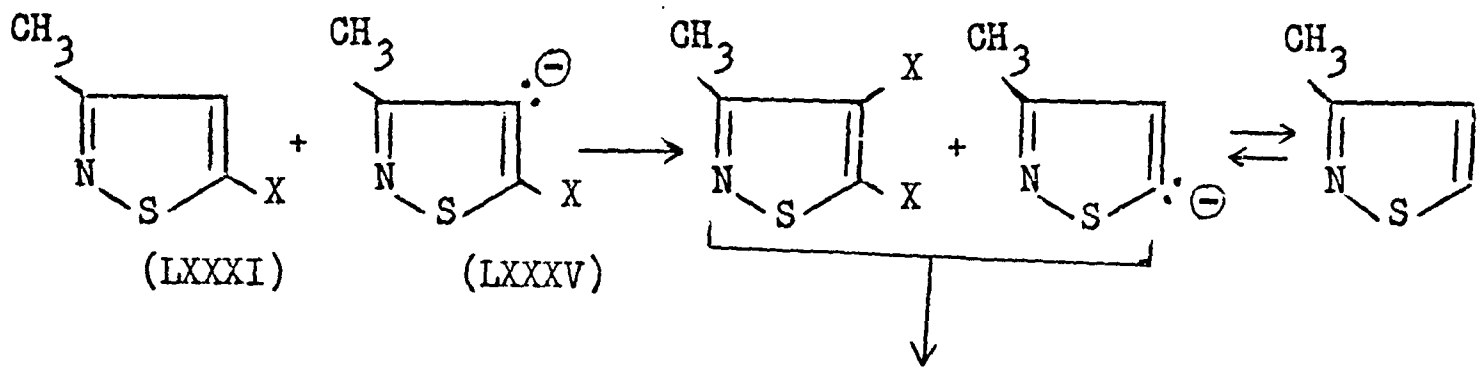


(LXXXI) (LXXXII) (LXXXIII) (LXXXIV)

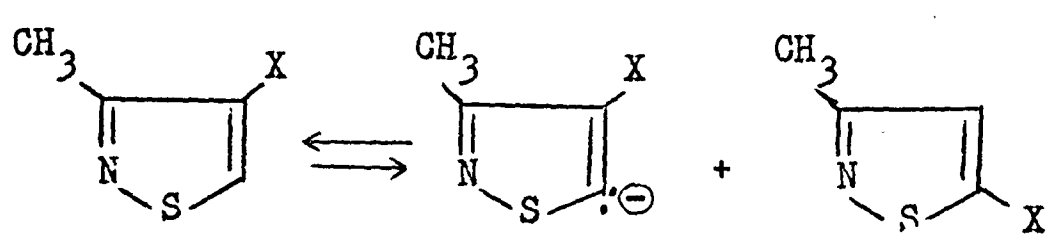
The same 5-bromo-3-methylisothiazole gave a greater yield of LXXXII when the reaction was carried out for 15 minutes. No indication was obtained for the formation of 4- and 5-amino-3-methylisothiazole even when the reaction time was enhanced to 2 hours. Similar results were obtained with the 5-chloro compound (LXXXI, X=Cl); the rate of the isomerisation was lower than that of the 5-bromo compound. However, the 5-iodo compound gave different results, deiodination to 3-methylisothiazole being the main process while the rearranged product was present only in very small amount. A reasonable amount of β-aminocrotonitrile (LXXXIV) was obtained and its formation was believed to occur by fission of 5-amino-3-methyl-isothiazole. The following mechanism was proposed for the halogen migration.



(LXXXI) (LXXXV)



(LXXXI) (LXXXV)



In general, thermal decomposition of o-arenediazonium carboxylates formed by aprotic diazotisation of o-amino acids has proved a valuable and convenient method of forming arynes. This would also appear to be a potentially useful method of generating isothiazolynes and the second part of this work describes the synthesis of a number of isothiazole amino acids and experiments designed to investigate the formation of isothiazolyne.

DISCUSSION

The first part of this section describes investigations on the synthesis and reactions of isothiazolo[5,4-b]pyridines; the second part is concerned with the synthesis of amino acids of isothiazole and attempts to generate isothiazolynes by their aprotic diazotisation.

I. Isothiazolo[5,4-b]pyridines

Skraup synthesis of alkylisothiazolo[5,4-b]pyridines

At the commencement of this work the only isothiazolo[5,4-b]pyridine described was 3,6-dimethylisothiazolo[5,4-b]pyridine, obtained by the Skraup reaction of 5-amino-3-methylisothiazole with crotonaldehyde.[26] This reaction had, since then, not been studied in detail and the chemistry and reactions of this compound had not been investigated to any extent. The success of this synthesis and, in addition, the availability of 5-amino-3-methylisothiazole suggested that this route to isothiazolo[5,4-b]pyridines would be worth exploring.

As described previously the Skraup reaction involves heating a primary aromatic amine with an α,β-unsaturated aldehyde or ketone or a suitable precursor in concentrated sulphuric acid in the presence of an oxidising agent.

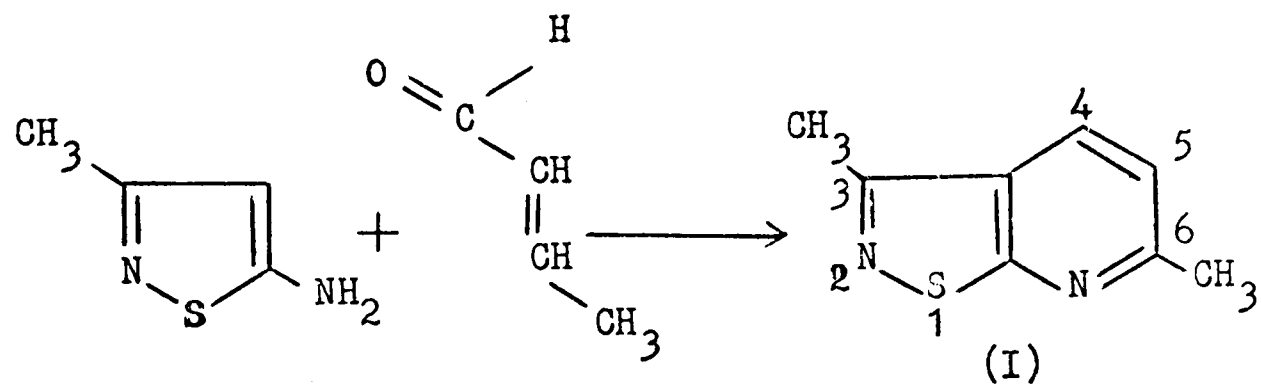
The reaction is often vigorous and a number of compounds, such as ferrous sulphate, acetic or boric acid have occasionally been added to moderate the vigour.[79] In practice the reaction usually involves slow addition of the carbonyl compound to a rapidly stirred mixture of the amine and oxidising agent at a rate and temperature such that the reaction does not become too violent. Most often the work up of the reaction has involved basification of the cold reaction mixture, followed by isolation of the product by steam distillation and extraction of the distillate.

A large number of oxidising agents have been employed, including arsenic acid, stannous chloride, oxygen and ferric chloride.[80] Utermohlen

has reported that attainment of good yields depends on the use of a suitable oxidising agent, and he found that m-nitrobenzenesulphonic acid was especially useful in this respect. The acid is prepared in solution by heating a mixture of nitrobenzene and fuming sulphuric acid. The mixture is diluted with water and used as such; it is often referred to simply as 'sulphomix' and this description is used here. Sodium m-nitrobenzenesulphonate in concentrated sulphuric acid containing a little water has often been used as an alternative to sulphomix, with good results. Good yields of naphthyridines from aminopyridines have been obtained when these oxidising systems have been employed.

The original synthesis of 3,6-dimethylisothiazolo[5,4-b]pyridine involved the addition of crotonaldehyde to a solution of the amine in sulphomix. In view of this and with regard to the above it was decided to investigate the synthesis of isothiazolo[5,4-b]pyridines using largely m-nitrobenzenesulphonic acid as the oxidising agent. Variation of the unsaturated carbonyl compound of the reaction was expected to allow the synthesis of a variety of alkyl substituted isothiazolo[5,4-b]pyridines.

3,6-Dimethylisothiazolo[5,4-b]pyridine (I) was prepared by addition of crotonaldehyde to a solution of 5-amino-3-methylisothiazole in sulphomix at 85-90°, the rate of addition was such the temperature did not rise above 90°. After heating for 45 min. at 95-100° the mixture was cooled, basified and the isothiazolo[5,4-b]pyridine isolated by steam distillation. The compound was obtained as colourless needles, m.p. 92-93°, in 18.5% yield. When the reaction was carried out at 80-90°, the compound was obtained in 10% yield; no product was obtained when the reaction was effected at 110-120°.



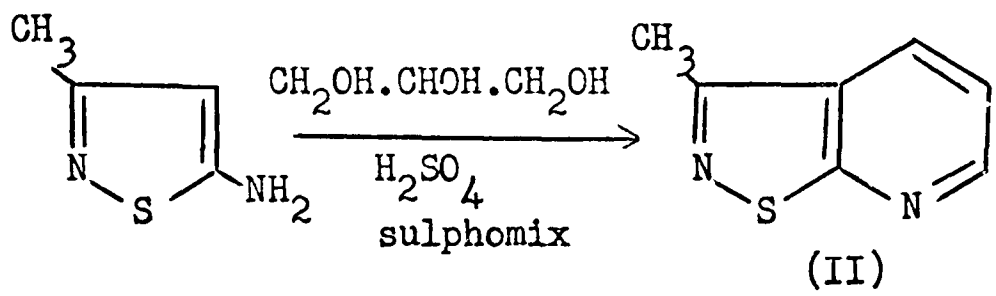
(I)

In a subsequent preparation of 3,6-dimethylisothiazolo[5,4-b]-pyridine, sodium m-nitrobenzenesulphonate was used as the oxidising agent, under almost similar conditions as the previous synthesis. The yield (19%) was virtually unchanged but less darkening of the reaction mixture was apparent. It is possible that a study of the effect of temperature and time on the reaction may lead to an improvement in the yield.

The compound readily formed a picrate, and analysis indicated that it was a 1:1 complex. The ultraviolet spectrum (U.V.I) showed absorption bands at 234 (ε 26,600) and 300 nm (5,160). The n.m.r. spectrum (N.M.R.1) is consistent with its formulation. The two ring protons appeared as a typical AB system with H-4 as a doublet centered at δ 8.1 p.p.m. and H-5 as a doublet centered at δ 7.25 p.p.m (J_{45} 8.5 Hz). The 3-methyl and 6-methyl protons were observed as singlets at δ 2.69 and δ 2.71 p.p.m.; the very similar shift positions did not allow individual assignments of the signals. Further discussion and comparison of the U.V. and n.m.r. spectrum of this and other isothiazolo[5,4-b]pyridines is presented later (p.50, 52).

3-Methylisothiazolo[5,4-b]pyridine (II) was prepared by heating a mixture of glycerol, sulphomix and 5-amino-3-methyl isothiazole at 110-115° for 3.5h. The compound, isolated by steam distillation of the basic solution followed by ether extraction of the distillate, was obtained as colourless plates, m.p. 84-85°, from light petroleum in 26% yield. When sodium m-nitrobenzenesulphonate was used as the oxidising agent and the reaction carried out at 120-125° for 3.5 h., 3-methylisothiazolo[5,4-b]-pyridine was obtained in 13.5% yield. With arsenic acid and acrolein

in 85% phosphoric acid at 100°, 5-amino-3-methylisothiazole gave II in 5% yield only.



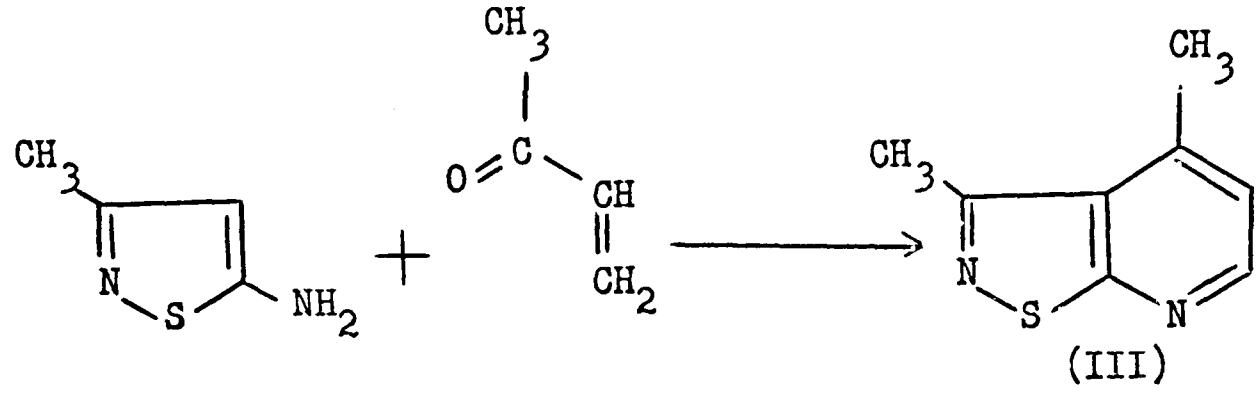
(II)

The ultraviolet spectrum showed absorption bands at 232 (ε 26,000) and 302 nm (ε 5,390). The n.m.r. spectrum (N.M.R.2) in deuterochloroform showed the methyl group as a three proton singlet at δ 2.68 p.p.m. From low to high field the three groups of lower field signals represent the H-6, H-4 and H-5 protons respectively and depict an AMX system with three coupling constants. The low field doublet of doublets centered at δ 8.70 p.p.m. was assigned to H-6, it being adjacent to nitrogen, and the doublet of doublets centered at δ 8.17 and δ 7.32 p.p.m. were assigned to H-4 and H-5 respectively by comparison with the n.m.r. spectra of the other isothiazolo[5,4-b]pyridines.

The compound readily formed a picrate, and analysis indicated that it was a 1:1 complex.

The reaction of an aromatic amine with methyl vinyl ketone under the usual Skraup conditions gives a product carrying a methyl group in the 4-position relative to the nitrogen. 1,3,3-Trimethoxybutane and methyl β-chloro ethyl ketone[81] have also been recommended as suitable precursors to methyl vinyl ketone in this reaction. Addition of methyl vinyl ketone to a stirred mixture of 5-amino-3-methylisothiazole and the sodium m-nitrobenzenesulphonate in sulphuric acid at 75-80°, followed by heating for 35 min at 80-85° and work up in the usual way gave 3,4-dimethylisothiazolo[5,4-b]pyridine (III) as needles, m.p. 139-140°, from acetone in 2.6% yield only. When the reaction was repeated under the

same conditions except that sulphomix was used instead of the sodium m-nitrobenzenesulphonate only a very slight improvement in the yield (3.4%) was obtained.



(III)

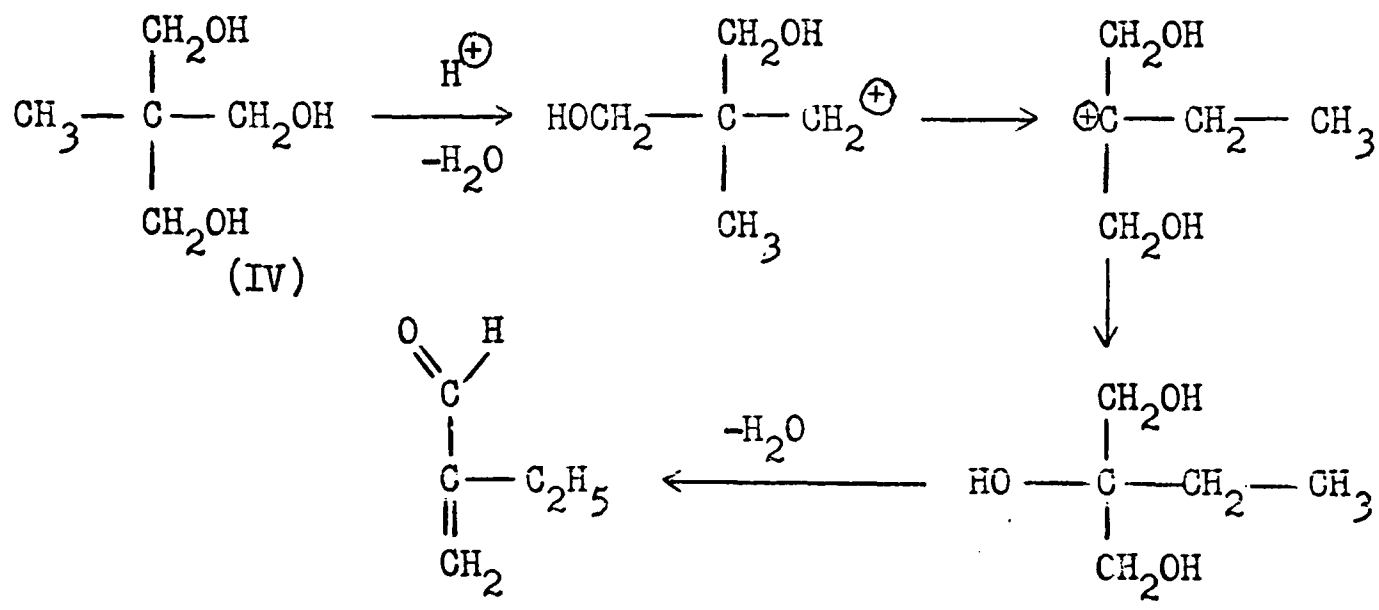
Campbell and Schaffer[82] have described the synthesis in relatively good yield, of 4-methylquinoline from methyl vinyl ketone, aniline hydrochloride, zinc chloride (as dehydrating agent) and hydrated ferric chloride in absolute ethanol. 5-Amino-3-methylisothiazole hydrochloride, prepared by passing dry hydrogen chloride through a solution of the amine in ether, was thus heated with hydrated ferric chloride and anhydrous zinc chloride in ethanol to 70-75°. Methyl vinyl ketone was added slowly to the stirred mixture which was then heated under reflux for 2 h. After evaporation of the ethanol, the mixture was made basic and the 3,4-dimethylisothiazolo[5,4-b]pyridine obtained in the usual way. The yield, however, was only 1%. The mixture did not become very dark during the course of the reaction, and it is possible that extending the reaction time would result in improved yields of the isothiazolo[5,4-b]pyridine.

The picrate was prepared in dilute hydrochloric acid with aqueous picric acid because of the poor solubility of the base in ethanol; analysis indicated that it was a 1:1 complex.

The ultraviolet spectrum of 3,4-dimethylisothiazolo[5,4-b]pyridine showed bands at 230 (ε 27,000) and 302nm (ε 6,200) as in the other alkylisothiazolo[5,4-b]pyridines. The n.m.r. spectrum (N.M.R.3) in deuterochloroform was consistent with the proposed formulation. H-6 was observed as a doublet centered at δ 8.51 p.p.m., due to coupling with

H-5 (J_{65} 5Hz). H-5 was observed as a doublet of ~~doublets~~ quartets centered at δ 7.05 p.p.m., due to coupling with H-6 (J_{56} 5Hz) and also with the methyl group in the 4-position (J_{CH_3-4}, H_5 0.8Hz). The 3-methyl and 4-methyl protons appeared as a singlet and a doublet (J 0.8 Hz) at δ 2.88 and δ 2.78 p.p.m. respectively.

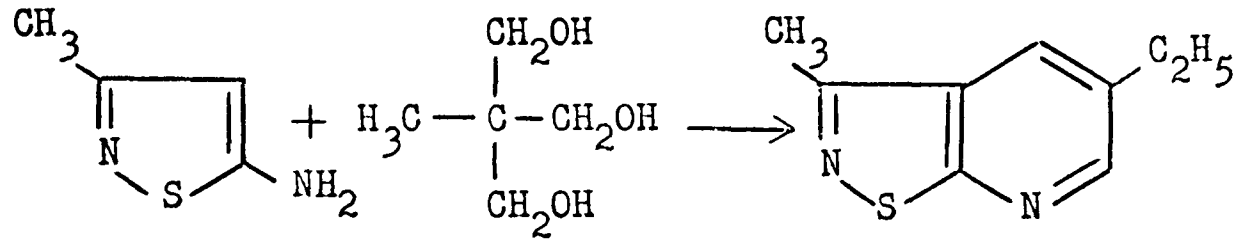
The synthesis of 5-ethyl-3-methylisothiazolo[5,4-b]pyridine required α-ethylacrolein as the α,β-unsaturated carbonyl component in the Skraup reaction. Rapoport and Batcho[32] found that 2-hydroxymethyl-2-methylpropane-1,3-diol (IV) was a useful precursor for α-ethylacrolein and with this compound and 3-aminopyridine, under Skraup conditions, they obtained a 12.5% yield of 3-ethyl-1,5-naphthyridine. The formation of α-ethylacrolein is believed to occur as follows:



Reaction of 5-amino-3-methylisothiazole with the triol in the presence of sulphomix at 110-115° and work up in the usual manner gave only a small amount of an oil.

T.l.c. showed a mixture of compounds, one of which was a major component. Attempts to crystallise the material were to no avail but a picrate was readily obtained with ethanolic picric acid; it was readily purified by recrystallisation and was shown by elemental analysis and

n.m.r. spectroscopy (N.M.R.4) to be the picrate of 5-ethyl-3-methylisothiazolo[5,4-b]pyridine.



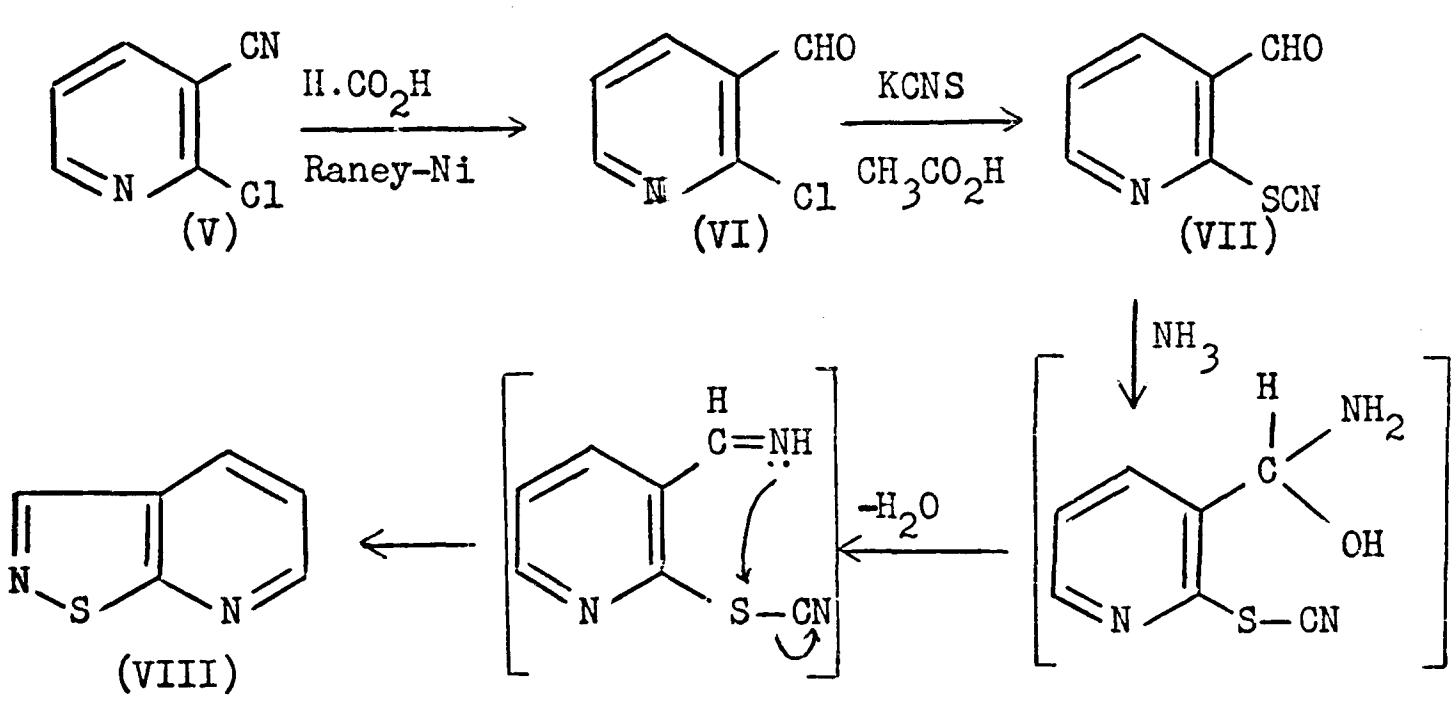
The methyl and methylene protons of the ethyl group were observed as a three proton triplet and a two proton quartet at δ 1.33 and δ 2.88 p.p.m. respectively, and the H-6 and H-4 protons appeared as doublets at δ 8.79 and δ 8.43 p.p.m. (J_{46} 2Hz) respectively. Fine splitting of the H-4 doublet was noted, as expected on the basis of some double bond localisation at the 4,5-positions as observed previously, but the spectrum was not sufficiently well defined to give a useful coupling constant. The aromatic protons of the picric acid were observed at δ 8.66 p.p.m. and the hydroxy proton at δ 5.8 p.p.m.

A small amount of the free base was obtained by treatment of the picrate with aqueous sodium hydroxide; it was homogeneous by t.l.c. but could not be recrystallised. The n.m.r. spectrum was poorly resolved but supports its formulation as 5-ethyl-3-methylisothiazolo[5,4-b]pyridine; the details are included later (Table I p.50) for comparison purposes.

The preparation was attempted using a different procedure. A mixture of ferrous sulphate, arsenic pentoxide, 5-amino-3-methylisothiazole, boric acid and 2-hydroxymethyl-2-methylpropane-1,3-diol in concentrated sulphuric acid was heated to 150° when a violent reaction ensued and the reaction mixture became completely black. None of the expected product was obtained.

Near the end of the experimental work described in this thesis, a synthesis of the parent system, isothiazolo[5,4-b]pyridine was reported

by A. Taurins and V. Tan Khouw.[83] The starting material for this synthesis was 2-chloronicotinonitrile (V) which was reduced with formic acid-Raney nickel to give 2-chloronicotinaldehyde (VI). With potassium thiocyanate in glacial acetic acid under nitrogen, 2-chloronicotinaldehyde gave 2-thiacyanonicotinaldehyde (VII) which gave isothiazolo[5,4-b]-pyridine (VIII) on treatment with a large excess of liquid ammonia at -50° for 4h. Three other isomeric isothiazolopyridines were prepared via O-disubstituted pyridines.

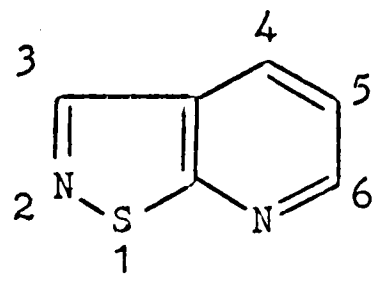


A study of the n.m.r. and u.v. spectra was reported in detail and the results are included in the following discussion on the spectra of the alkylisothiazolo[5,4-b]pyridines for completeness.

Nuclear Magnetic Resonance Spectra

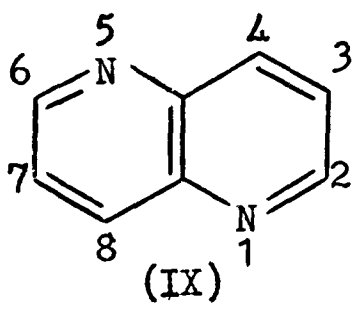
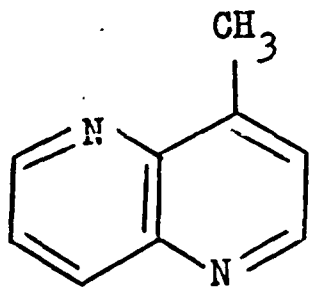
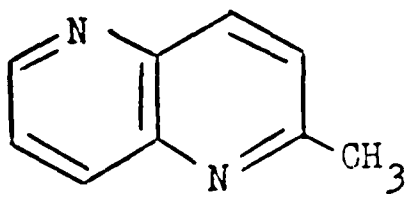
The n.m.r. data of the various alkylisothiazolo[5,4-b]pyridine are collected in Table I.

Table I

Compound	N.M.R. No.	Chemical Shifts (δ) p.p.m.								Coupling Constants (Hz)			
		CH_3-3	CH_3-4	$-CH_2.CH_3$	CH_3-6	H-3	H-4	H-5	H-6	$J_{CH_3\text{-}4,H\text{-}5}$	J_{45}	J_{46}	J_{56}
 Isothiazolo[5,4-b]pyridine	-	-	-	-	-	8.91	8.30	7.35	8.76	-	8.0	1.5	4.8
3,6-Dimethyl	1	2.69 or 2.71	-	-	2.69 or 2.71	-	8.1	7.25	-	-	8.5	-	-
3-Methyl	2	2.68	-	-	-	-	8.1	7.32	8.70	-	8.3	1.8	4.8
3,4-Dimethyl	3	2.88	2.78	-	-	-	-	7.05	8.51	0.8	-	-	5.0
3-Methyl-5-ethyl Solvent: $CDCl_3$	4	2.76	-	1.39 $-CH_2.\underline{CH_3}$ 2.94 $-\underline{CH_2}.CH_3$	-	-	8.24	-	8.76	-	-	-	-

It is interesting to note the similarity of the chemical shifts and coupling constants of the 6-,5- and 4-protons of the pyridine ring of the isothiazolo[5,4-b]pyridines with those of the corresponding protons at positions 2-, 3- and 4- of the 1,5-naphthyridine (IX).[84] Further, as in 4-methyl-1,5-naphthyridine, the corresponding hydrogen at the 5-position of 3,4-dimethylisothiazolo[5,4-b]pyridine is also coupled with the methyl protons (J 0.8 Hz) indicating a relatively high degree of double bond character in the 4,5-position in the isothiazolo[5,4-b]pyridine.

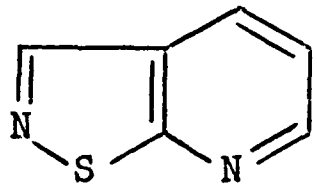
The methyl group at position 6 in 3,6-dimethylisothiazolo[5,4-b]-pyridine has a virtually identical chemical shift to the methyl group in 2-methyl-1,5-naphthyridine and both occur as sharp singlets. The coupling constant of the corresponding protons is also of the same order of magnitude.

	Chemical Shifts δ(p.p.m)		Coupling Constants (Hz)	
 (IX)	H-4	8.40	J_{23}	4.1
	H-3	7.58	J_{24}	1.8
	H-2	8.97	J_{34}	8.0
	CH_3-4	2.86	$J_{CH_3\text{-}4,H_3}$	0.9
	H-3	7.56	J_{23}	4.4
	H-2	8.97		
	H-4	8.23		
	H-3	7.48	J_{34}	8.8
	CH_3-2	2.70		

Ultraviolet Spectra

The ultraviolet spectrum of each of the alkylisothiazolo[5,4-b]-pyridines (Table II) consists of two absorption bands. That of the parent isothiazolo[5,4-b]pyridine is included for comparison purposes. It should be noted that the ε values reported for that compound are approximately half those obtained with the alkyl-compounds. A feature of the spectra is the small bathochromic shift in the low wavelength absorption band of the methyl compounds compared with the parent compound.

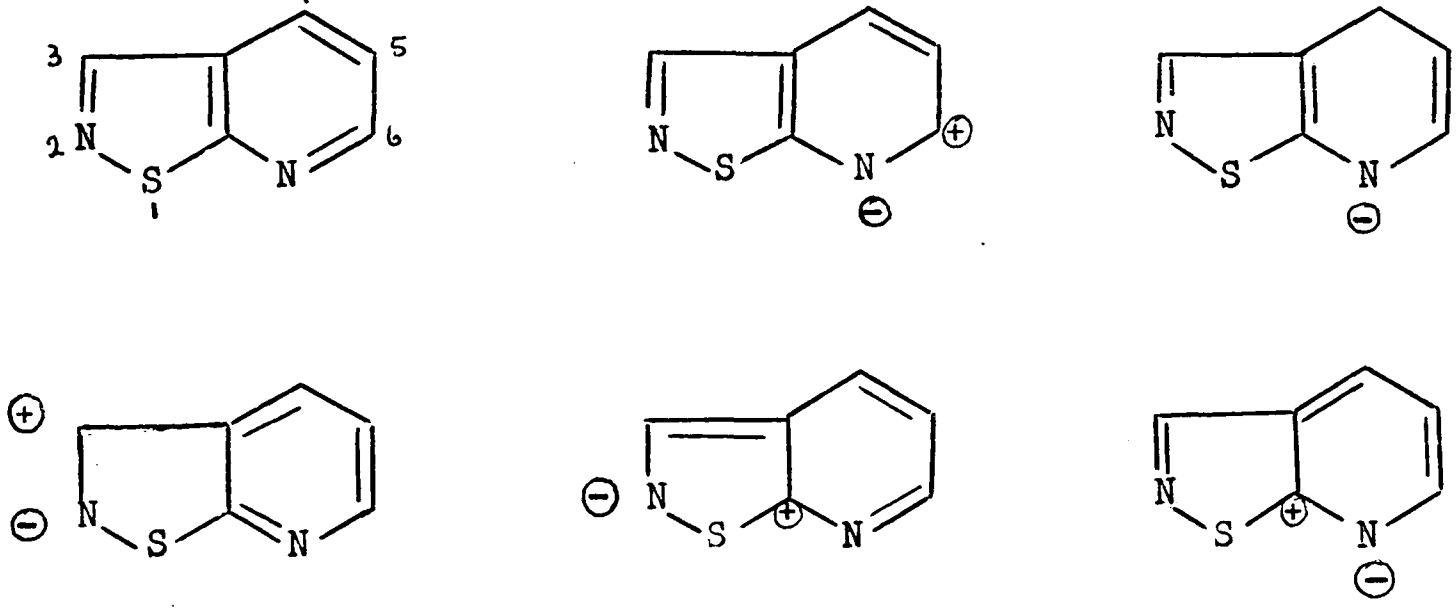
Table II

	λ_{max}(nm)	ε	λ_{max}(nm)	ε
	228	15,490	298	2884
			307sh	2512
3,4-Dimethyl-	230	27,000	302	6200
3-Methyl-	232	26,000	302	5390
3,6-Dimethyl-	234	26,600	300	5160

Investigation of the reactions of 3-methyl- and 3,6-dimethyl-isothiazolo[5,4-b]pyridine

The following describes attempted electrophilic and nucleophilic substitution reactions on 3-methyl- and 3,6-dimethylisothiazolo[5,4-b]-pyridine; viz., bromination, nitration and amination. Studies on the aldol type reactivity of the methyl compounds were carried out and oxidations with potassium permanganate and chromic acid were investigated.

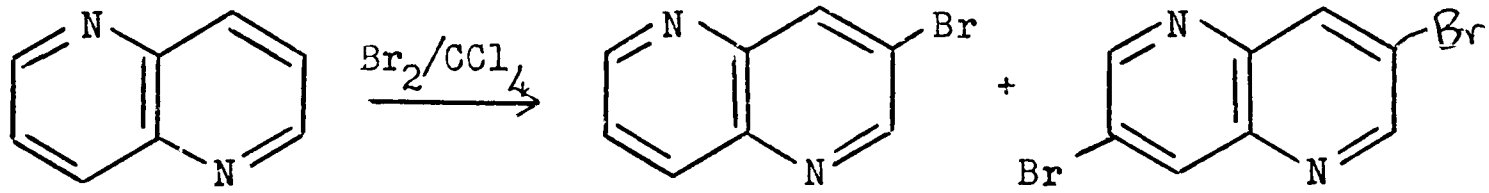
The chemistry of isothiazolo[5,4-b]pyridines and the alkyl substituted compounds would be expected to be similar in certain respects to that of pyridine and the naphthyridines. Thus a number of dipolar structures would be expected to contribute to the overall structure of the molecule, and some of these are shown below.



In particular the 6- and 4- positions would be expected to be electron deficient and susceptible to attack by nucleophiles. Electrophilic attack would be expected to occur at position 5. Attack may initially occur at the nitrogen atom to give a charged species; however, although the absolute values of the π electron densities are different for a charged ion, the relative distribution of electron density

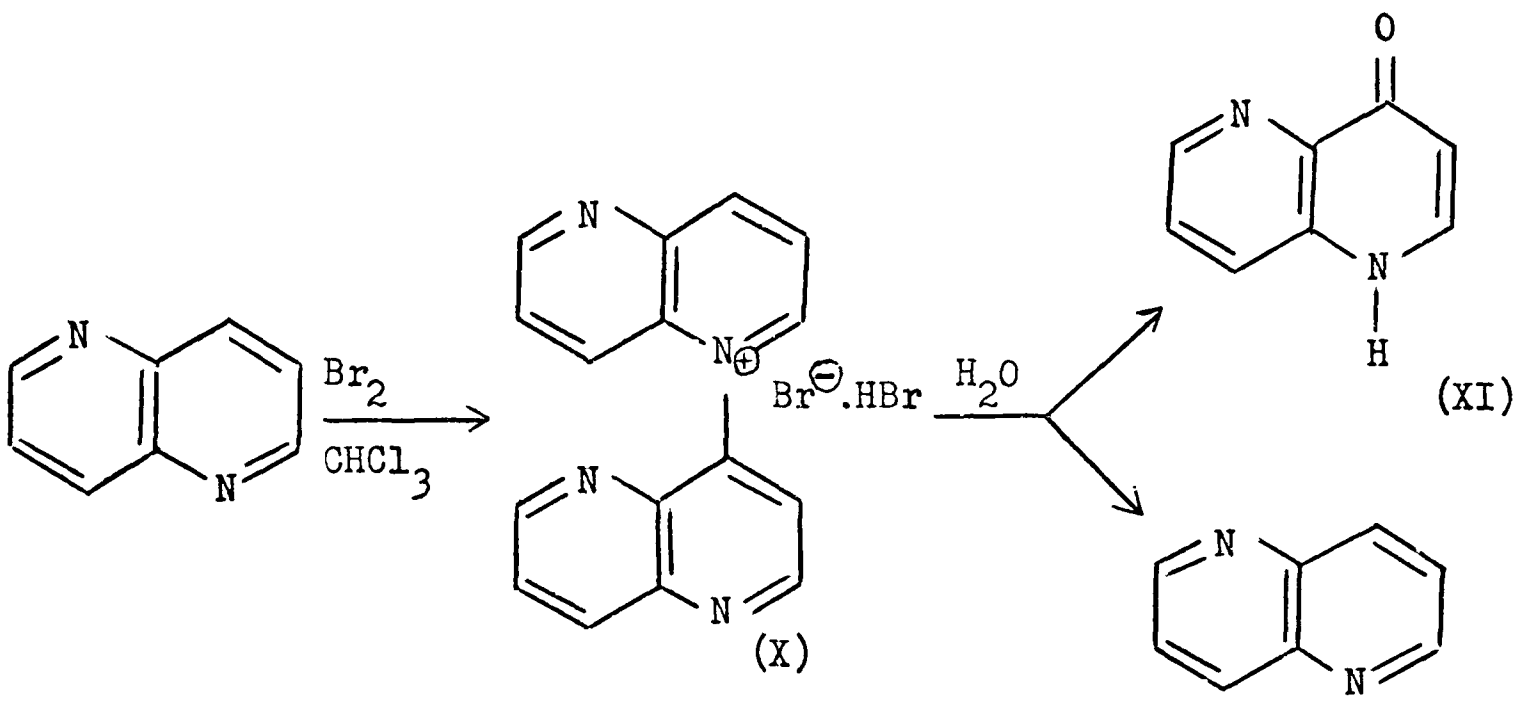
at the ring carbon atoms should remain almost unchanged. Therefore, no matter if electrophilic attack at carbon occurs upon the charged species or the free base, substitution should occur at the 5-position.

In 1962 a novel method for the introduction of bromine into electron deficient nitrogen heterocyclic compounds was described by Eisch.[85] This method involves the formation of a bromine-heterocyclic compound complex by addition of bromine to the compound in boiling carbon tetrachloride. Addition of pyridine to the boiling solution decomposes the complex and affords a halogenated derivative of the heterocyclic compound. This method has been used by Paudler and Kress[86] to brominate all the naphthyridines, both monobromo- and dibromo compounds were obtained. Thus 1,5-naphthyridine gave 3-bromo and 3,7-dibromo-1,5-naphthyridine in 27 and 10% yield respectively.



The bromination of 3-methylisothiazolo[5,4-b]pyridine was attempted under these conditions. There was, however, no indication of any compound other than starting material by t.l.c. and upon work up only 3-methylisothiazolo[5,4-b]pyridine was obtained.

The attempted bromination of 1,5-naphthyridine with bromine in cold chloroform was reported by Hart [87] to give the naphthyridyl-naphthyridium salt (X) which precipitated from the chloroform solution. When heated with water, this gave 1,5-naphthyridin-4-one (XI) and 1,5-naphthyridine.



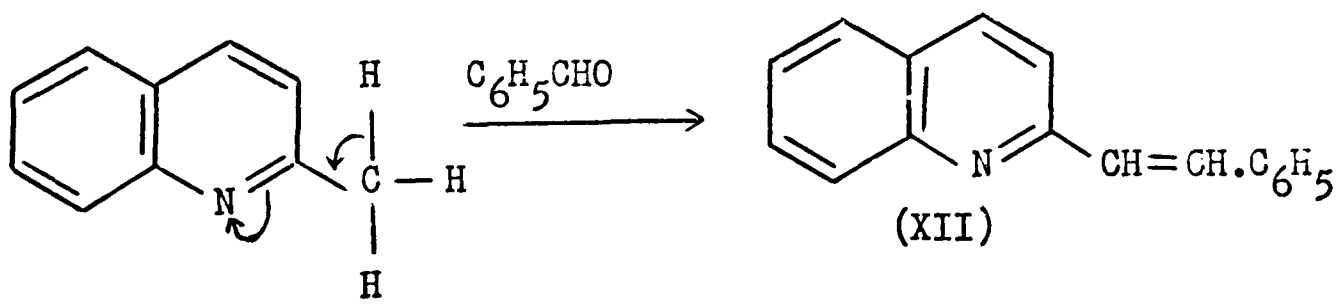
The reaction of 3-methylisothiazolo[5,4-b]pyridine with bromine in chloroform under these conditions was therefore investigated to see whether bromination or a similar type of oxidation occurred. No solid separated from the reaction and a mixture of two compounds was obtained by dilution of the solution with light petroleum. One of these was soluble in acetone and proved to be starting material (50% recovery). The other acetone insoluble material was soluble in water, and gave a positive test for bromide ion with silver nitrate. Elemental analysis indicated that the compound was 3-methylisothiazolo[5,4-b]pyridine hydrobromide which was obtained in 16.5% yield. No other compound was isolated.

The nitration of 1,5-naphthyridine using a range of concentrated and fuming acids was unsuccessfully attempted by Hart.[87] Nitration of the isothiazolo[5,4-b]pyridine system would also be expected to be unfavourable and an attempted nitration of 3-methylisothiazolo[5,4-b]-pyridine using fuming sulphuric acid-potassium nitrate at steam bath temperature for 7 h. gave only 72% recovery of starting material. 3,6-Dimethylisothiazolo[5,4-b]pyridine, when reacted with fuming sulphuric acid and concentrated nitric acid at 75-80° for 1.5 h., gave no product whatsoever; concentrated sulphuric acid and potassium nitrate at steam bath

temperature for 1 h. gave 93% recovery of starting material. In this respect, the reactivity of 3-methyl and 3,6-dimethylisothiazolo[5,4-b]-pyridine can be said to resemble that of 1,5-naphthyridine.

Paudler and Kress[86] were unable to repeat the amination of 1,5-naphthyridine with sodium in liquid ammonia in the presence of ammonium nitrate as described by Hart.[87] By using potassium nitrate and a trace of ferric chloride in a sealed tube they successfully obtained 2-amino-1,5-naphthyridine, and other naphthyridines were similarly aminated. An attempt was made to aminate 3-methylisothiazolo[5,4-b]pyridine under these conditions but only starting material (55% recovery) was isolated.

Methyl groups in the 2- and 4-positions of pyridine and quinoline are strongly activated by the electron attracting properties of the nitrogen atom. The protons are acidic and are readily removed by strong bases and the resulting carbanions can undergo various condensation reactions. A number of acid catalysed condensations also occur; thus 2-methylquinoline readily condenses with benzaldehyde in the presence of zinc chloride or acetic anhydride to give 2-styrylquinoline (XII), and mild oxidation of this compound is a good route to quinoline-2-carboxylic acid.

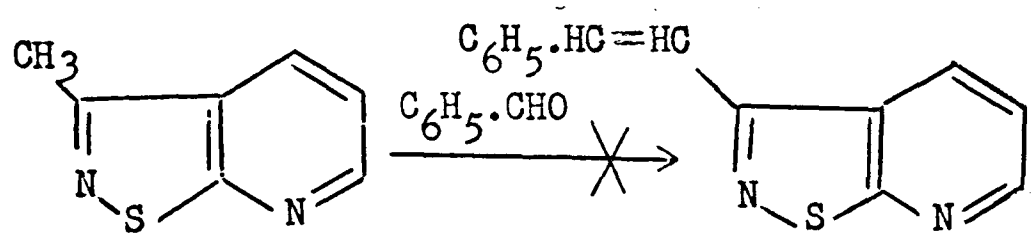


(XII)

It would be expected that the methyl group in the 4- and 6-positions of isothiazolo[5,4-b]pyridine would be similarly activated and undergo condensation with e.g. benzaldehyde. A methyl group in the 3-position may also be expected to behave similarly, but it is interesting to note that such reactivity was not shown by the methyl group in 3-methylisothiazole.[88]

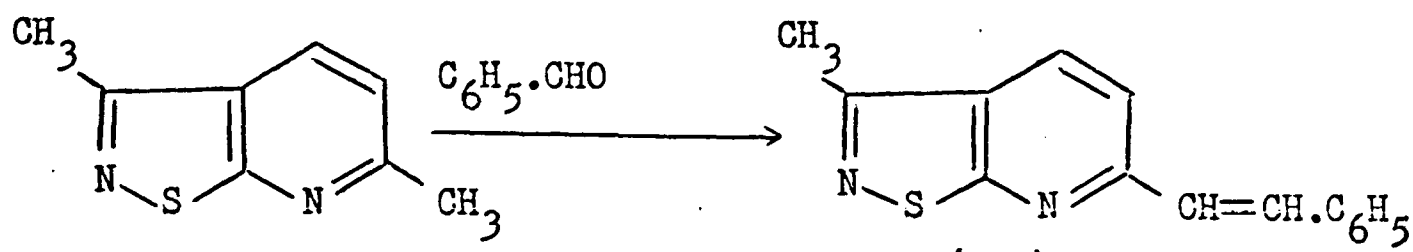
Treatment of 3-methylisothiazolo[5,4-b]pyridine with benzaldehyde in boiling acetic acid and acetic anhydride for two days gave an 87%

recovery of starting material instead of the expected 3-styryl compound (XIII). T.l.c. monitoring of the reaction did not show the formation of any new product. The failure of this methyl group to react is perhaps not too surprising with regard to the above comments.



(XIII)

Condensation of 3,6-dimethylisothiazolo[5,4-b]pyridine with benzaldehyde in the presence of zinc chloride was effected on heating the reactants to 130-135° for 4 h. T.l.c. monitoring showed the appearance of a new spot and a small amount of this compound was isolated by dry column chromatography; crystallisation from acetone gave the product as pale yellow plates, m.p. 139-140°. Elemental analysis and the n.m.r. spectrum (N.M.R.5) were consistent with formulation of the compound as 6-styryl-3--methylisothiazolo[5,4-b]pyridine (XIV).



(XIV)

A three proton singlet at 2.68 p.p.m. was assigned to the 3-methyl group, a doublet centered at δ 8.47 p.p.m. to H-4 and an eight proton multiplet at δ 7.38-7.98 p.p.m. to the olefinic, benzenoid and H-5 protons. The compound was formulated as 3-methyl-6-styrylisothiazolo[5,4-b]-pyridine rather than the 3-styryl derivative on the basis of the unreactivity of the 3-methyl compound with benzaldehyde in the previous experiment.

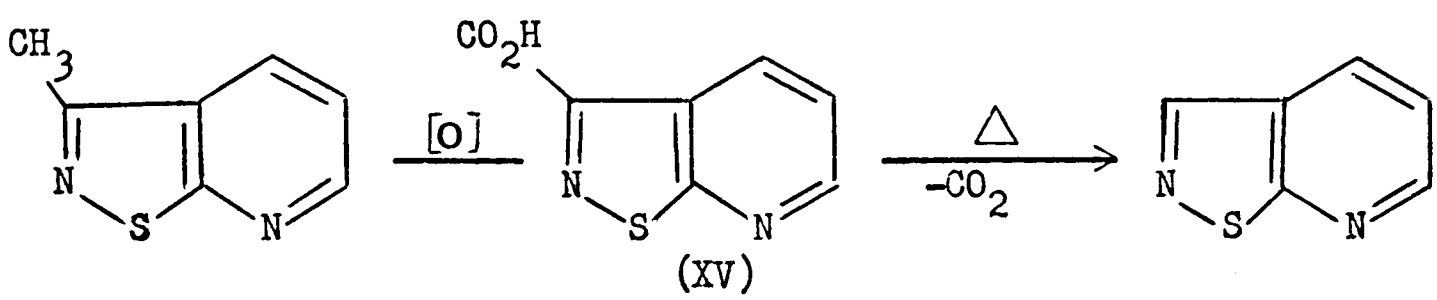
The reaction of 3,6-dimethylisothiazolo[5,4-b]pyridine with benzaldehyde in the presence of acetic acid-acetic anhydride was also investigated. After refluxing for two days a small amount of 3-methyl-6--styrylisothiazolo[5,4-b]pyridine was detected by t.l.c. but no attempt was made to isolate the compound.

p-Nitrobenzaldehyde is known to be more reactive than benzaldehyde in these condensations due to the electron withdrawing effect of the nitro group on the carbonyl carbon. Heating this compound with 3,6-dimethylisothiazolo[5,4-b]pyridine in acetic acid-acetic anhydride at reflux for 15 h. gave a mixture which showed four components on t.l.c., two of which corresponded to starting materials. One of the compounds was isolated by triturating with acetone; it crystallised from glacial acetic acid as yellow needles, m.p. 214-216°. Elemental analysis gave a molecular formula $C_{15}H_{11}N_3OS$, indicating condensation of one of the methyl groups with p-nitrobenzaldehyde. The compound was assigned the structure, 6-(p-nitrostyryl)-3-methylisothiazolo[5,4-b]pyridine on the basis of previous conclusions. The second product was isolated as a gum by dry column chromatography but the small amount of material precluded further investigation.

From the above brief study it can be concluded, at this stage, that the 6-methyl group of 3,6-dimethylisothiazolo[5,4-b]pyridine does resemble the methyl groups of 2-methylpyridine, 2-methylquinoline and 2-methyl-1,5-naphthyridine but is much less reactive. A more detailed investigation would be worthwhile.

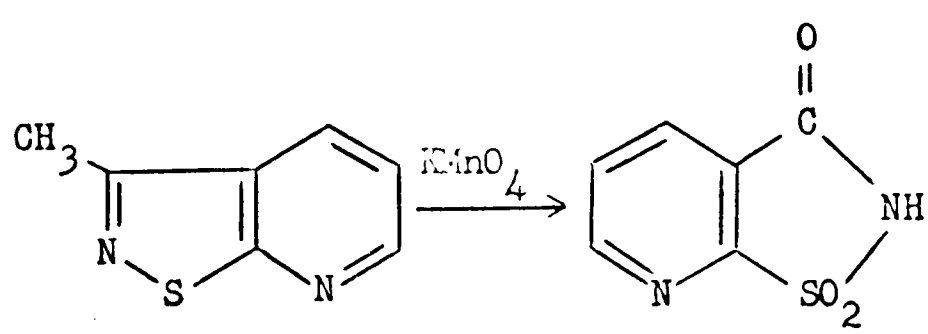
Oxidation of 3-methyl- and 3,6-dimethyl-isothiazolo[5,4-b]pyridine

A promising route to the parent isothiazolo[5,4-b]pyridine system appeared to be via the carboxylic acid XV, which would be expected to loose carbon dioxide readily on heating. In addition the acid would be a suitable substrate for conversion to other substituted isothiazolo[5,4-b]-pyridines. A similar sequence of reactions was envisaged for the dimethyl compound.



(XV)

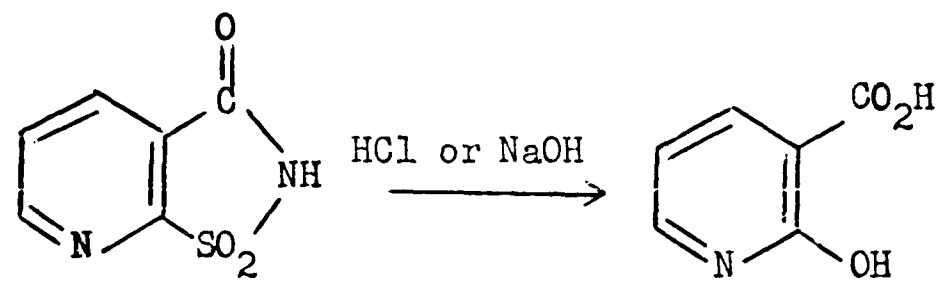
Oxidation of 3-methylisothiazolo[5,4-b]pyridine was carried out with potassium permanganate by a procedure similar to that described by Rapoport and Batcho[32] for the oxidation of alkyl 1,5-naphthyridines. Potassium permanganate was added portion wise to a stirred aqueous solution of 3-methylisothiazolo[5,4-b]pyridine at 70°. After another 30 min. at that temperature, manganese dioxide was separated and the neutral and basic materials were removed from the filtrate by methylene chloride extraction. Ether extraction of the acidified solution gave a solid which crystallised from aqueous ethanol as white needles, m.p. 207-210°. The molecular formula $C_6H_4N_2O_3S$, from elemental analysis, showed loss of one carbon atom indicating the product was not the expected acid XV. The infrared spectrum (I.R.1) showed N-H absorption at 3180 cm^{-1} and a carbonyl band at 1745 cm^{-1}. The compound was formulated as isothiazolo[5,4-b]pyridin-3(2H)-one 1,1-dioxide (XVI) on the basis of its molecular formula and spectroscopic evidence.



(XVI)

The n.m.r. spectrum (N.M.R.6) was indicative of a 2,3-disubstituted pyridine; H-6, H-4 and H-5 were each observed as one proton doublet of doublets centered at δ 8.81, 8.2 and 7.76 p.p.m. respectively and the coupling constants (J_{45} 8 Hz, J_{46} 2Hz, and J_{56} 5Hz) were in line with those observed in pyridine systems. The signal at δ 8.55 p.p.m. was assigned to the N-H proton.

Further support for the structure XVI came from its reaction with dilute hydrochloric acid which gave a white crystalline compound m.p. 253-255°; it was shown to be an acid by its solubility in sodium bicarbonate solution and absorption bands at 3000 cm^{-1} and 1730 cm^{-1} in the infrared spectrum. Elemental analysis indicated a molecular formula $C_6H_5NO_3$ and the compound was formulated as 2-hydroxypyridine-3-carboxylic acid (XVII). This was supported by its n.m.r. spectrum (N.M.R.7) which showed H-6, H-5 and H-4 each as a single proton doublet of doublets centered at δ 8.47, 6.66 and 8.01 p.p.m; a two proton broad peak at δ 14.1 p.p.m. was assigned to the carboxyl and hydroxyl protons. A mixed melting point with an authentic sample[89] of 2-hydroxypyridine-3-carboxylic acid was undepressed and the infrared spectra were identical.

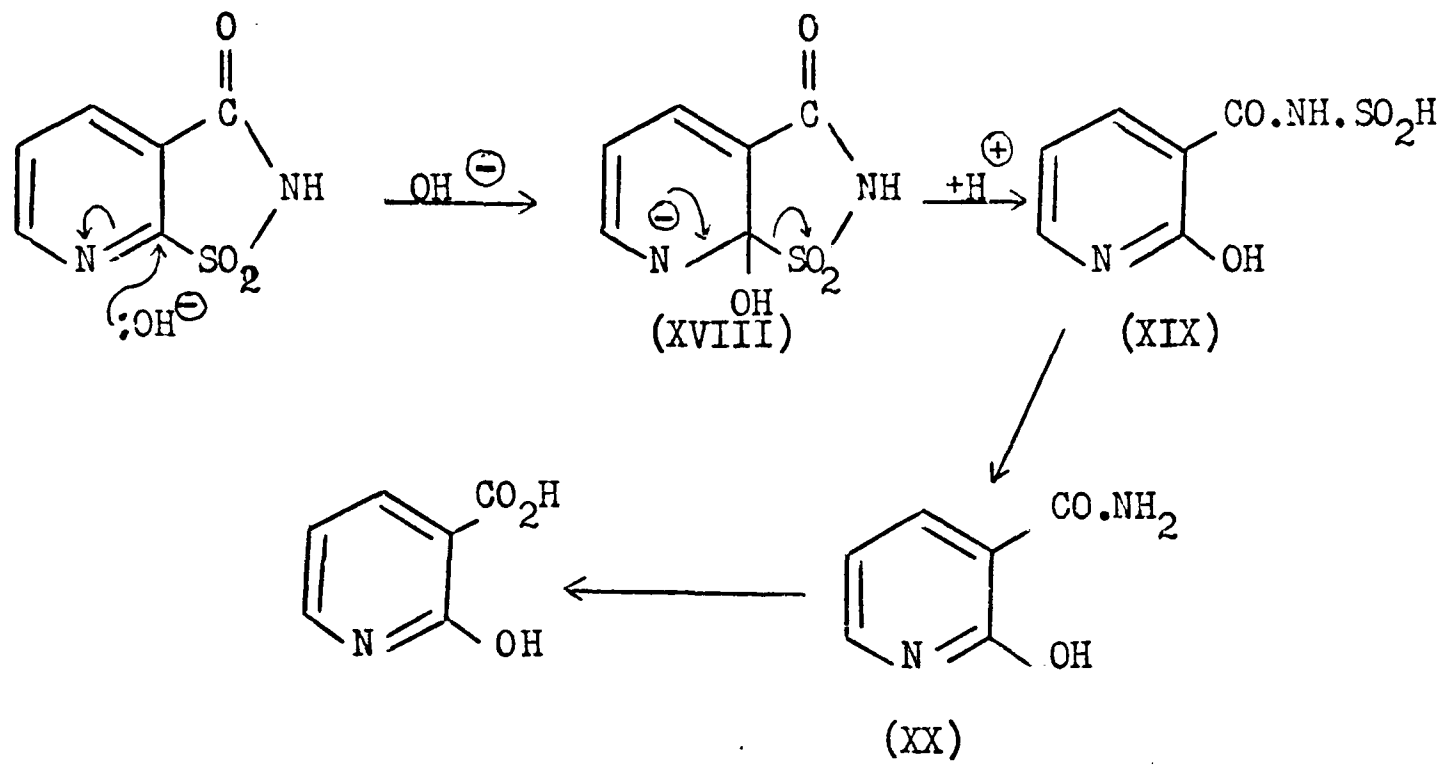


(XVII)

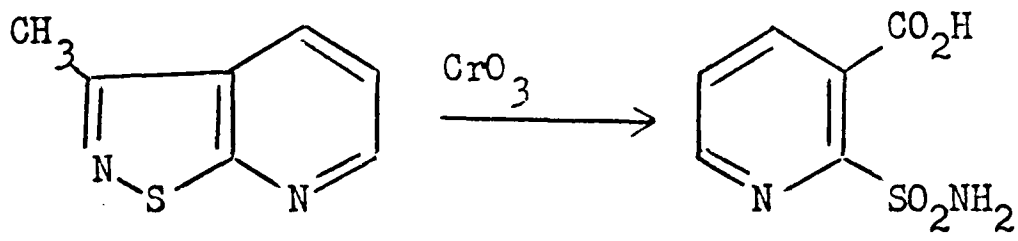
2-Hydroxypyridine-3-carboxylic acid was also obtained, in good yield, from the reaction of isothiazolo[5,4-b]pyridin-3(2H)-one 1,1-dioxide with aqueous sodium hydroxide.

A possible mechanism for the reaction is indicated below and involves attack of OH^- at the electron deficient bridge-head carbon between the ring nitrogen and the 1,1-dioxide grouping. Rearrangement of the

intermediate XVIII and protonation to give the acid XIX followed by loss of sulphur dioxide would give 2-hydroxypyridine-3-carboxamide(XX). Hydrolysis of the amide would then give the hydroxy-acid.

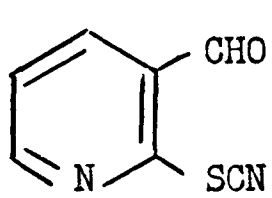


The methyl group in 3-methylisothiazole, and other 3-methyl substituted isothiazoles, has been successfully oxidised to the corresponding acid with chromic acid. This prompted the investigation of the oxidation of 3-methylisothiazolo[5,4-b]pyridine with chromic acid. Oxidation in concentrated sulphuric acid at 40° gave a compound, m.p. 156-158°, which effervesced on heating to approximately 20° above its melting point; a dark brown gum remained after the effervescence. Elemental analysis gave a molecular formula $C_6H_6N_2O_3S$ indicating loss of one carbon. The infrared spectrum (I.R.2) showed N-H bands at 3345 and 3245 cm^{-1}. A carbonyl group at 1710 cm^{-1}, and broad bands at 2600 and 2500 cm^{-1} indicated the presence of a carboxylic acid, as confirmed by evolution of carbon dioxide with aqueous sodium bicarbonate. Bands at 1360 and 1180 cm^{-1} were assigned to an $-SO_2N<$ group. On this evidence the compound was formulated as 2-sulphoamidopyridine-3-carboxylic acid (XXI).



(XXI)

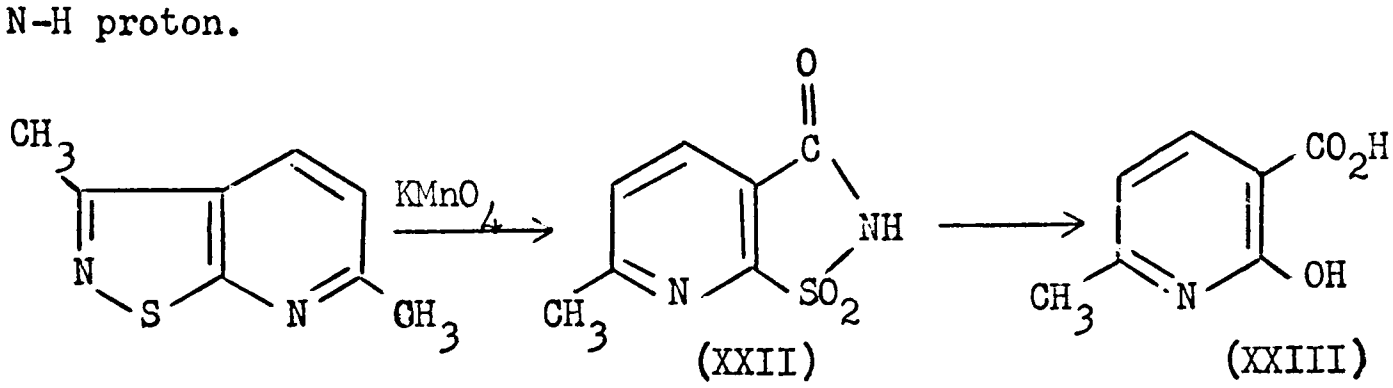
The n.m.r. spectrum (N.M.R.8) was indicative of a 2,3-disubstituted pyridine and supported this structure. H-6, H-5 and H-4 were each observed as one proton doublet of doublets centered at δ 8.81, 7.75 and 8.17 p.p.m. respectively. The magnitudes of the coupling constants and chemical shift positions were in line with those observed in other disubstituted pyridines.

	Coupling constants (Hz)			Chemical shifts (δ) p.p.m.		
	J_{45}	J_{46}	J_{56}	H_4	H_5	H_6
	8	1.9	5	8.17	7.76	8.81
	8	2.0	5	8.52	7.76	8.63

Carbon-sulphur bonds of sulphonamides undergo reductive cleavage with zinc and acid.[90] Thus reductive cleavage of XXI would be expected to give nicotinic acid and a small amount of this compound was obtained with zinc dust in acetic acid-hydrochloric acid, confirming structure XXI.

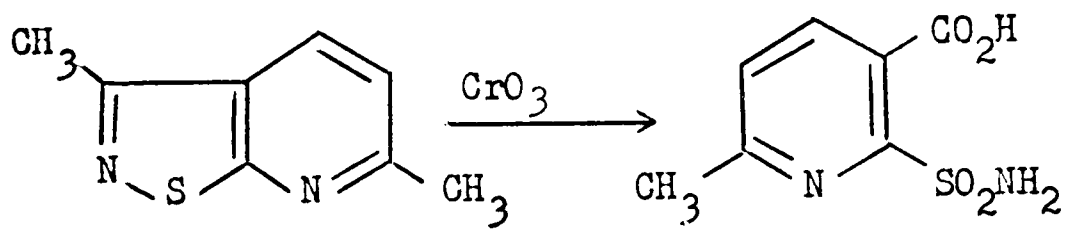
Potassium permanganate oxidation of 3,6-dimethylisothiazolo[5,4-b]-pyridine was carried out as described with the monomethyl compound. The compound isolated from the acidic solution was obtained as colourless needles, m.p. 190-192°. Elemental analysis was consistent with a molecular formula $C_7H_6N_2O_3S$, except that the carbon content was slightly lower than calculated. The compound was formulated as 6-methylisothiazolo[5,4-b]-pyridin-3(2H)-one 1,1-dioxide (XXII) on the basis of its infrared and n.m.r. spectra.

The infrared spectrum (I.R.3) showed a sharp band at 3260 and 1760 cm^{-1} indicating imino and carbonyl groups and bands at 1240 and 1170 cm^{-1} were assigned to the $-SO_2N\langle$ group. In the n.m.r. spectrum (N.M.R.9), a three proton sharp singlet at δ 2.78 p.p.m. was assigned to the 6-methyl group, doublets at δ 8.31 and 7.8 p.p.m. to H-4 and H-5 (J 8Hz) respectively and a one proton singlet at δ 9.36 p.p.m. to the N-H proton.



On the basis of the formation of 2-hydroxynicotinic acid by acid treatment of the monomethyl oxidation product it would be expected that a similar treatment of compound XXII would give 2-hydroxy-6-methyl-pyridine-3-carboxylic acid (XXIII). This was achieved in good yield; elemental analysis, its infrared and n.m.r. spectra (N.M.R.10) fully supported this structure.

Chromic acid oxidation of 3,6-dimethylisothiazolo[5,4-b]pyridine under essentially the same conditions as described for 3-methylisothiazolo-[5,4-b]pyridine gave a compound, the infrared spectrum (I.R.4) of which was virtually identical to that of the compound formulated as 2-sulphoamidopyridine-3-carboxylic acid except for a sharp band at 3505 cm^{-1}. The compound melted at 128-130° and effervesced on heating to ca. 170°. A satisfactory elemental analysis could not be obtained but was in reasonable agreement with the compound being a monohydrate of 6-methyl--2-sulphoamidopyridine-3-carboxylic acid viz., $C_7H_8N_2O_4S.H_2O$, and this would account for the band at 3505 cm^{-1} in the infrared spectrum.



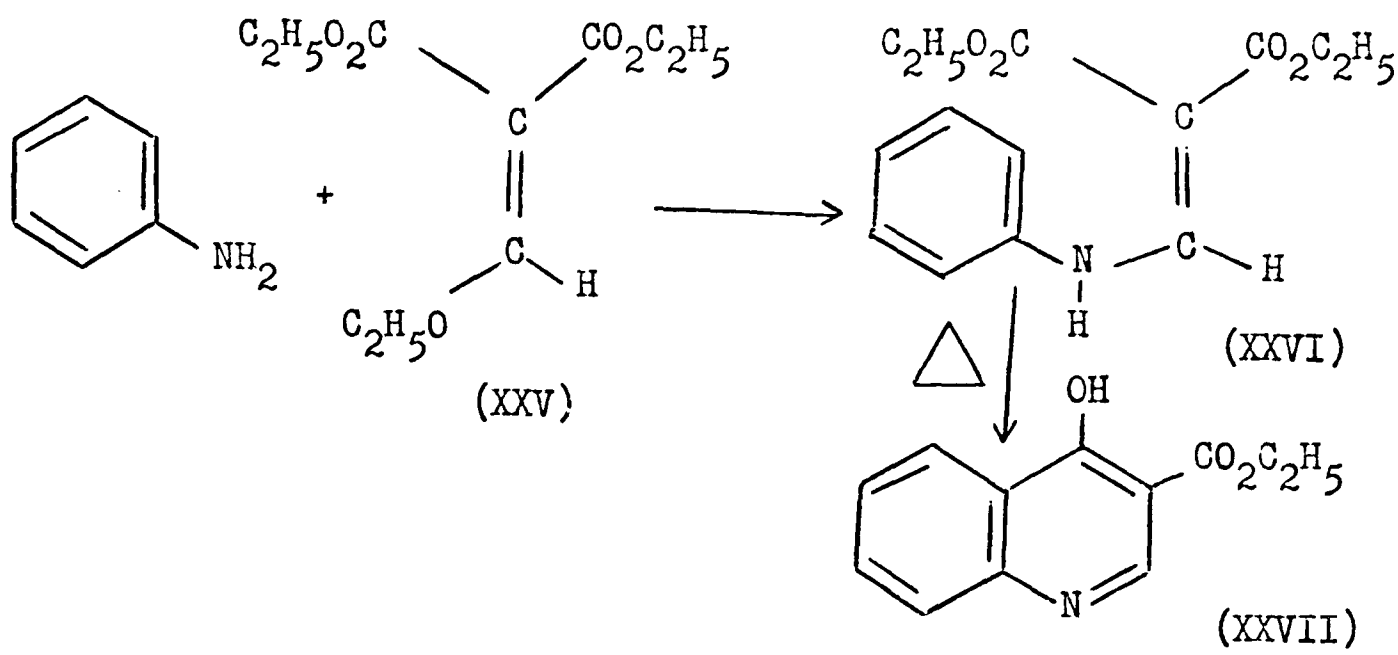
(XXIV)

The n.m.r. spectrum (N.M.R.11) supported the structure XXIV; a sharp three proton singlet at δ 2.6 p.p.m. was consistent with the 6-methyl group, a pair of doublets at δ 8.03 and 7.5 p.p.m. (J 8Hz) with H-4 and H-5, and a broad three proton signal at δ 7.38 p.p.m. with the carboxyl and sulphonamide protons.

It was hoped that molecular weight determination of the compound would support the proposed structure. Accurate mass determination of the parent ion indicated a molecular formula $C_7H_6N_2O_3S$, i.e. structure XXIV less one molecule of water. This is interpreted as loss of water in the spectrometer from XXIV to give 6-methylisothiazolo[5,4-b]pyrid-3(2H)--one 1,1-dioxide (XXII).

Synthesis and reactions of Isothiazolo[5,4-b]pyridines derived from 5-amino-3-methylisothiazole and ethoxymethylenemalonic ester.

The condensation of aniline with ethoxymethylenemalonic ester (XXV) to give anilinomethylenemalonic ester (XXVI) was reported as early as 1897 by Claisen[91] who carried out the reaction by heating the compounds for a short time on a steam bath. This reaction has been reported by Gould and Jacobs,[46] and later by Price and Roberts,[47] to proceed even at room temperature.



Gould and Jacobs found that cyclisation of the ester XXVI to the quinoline hydroxyester XXVII occurred readily on heating the malonate with from two to ten times its weight of "mineral oil" at 240-250° for 15 -20 minutes. These conditions are the same as those used for cyclisation of the intermediate esters in the Conrad Limpach reaction.

It was later found that both diphenyl ether and Dowtherm - a mixture of diphenyl and diphenyl ether - are far superior as a cyclisation medium.[47]

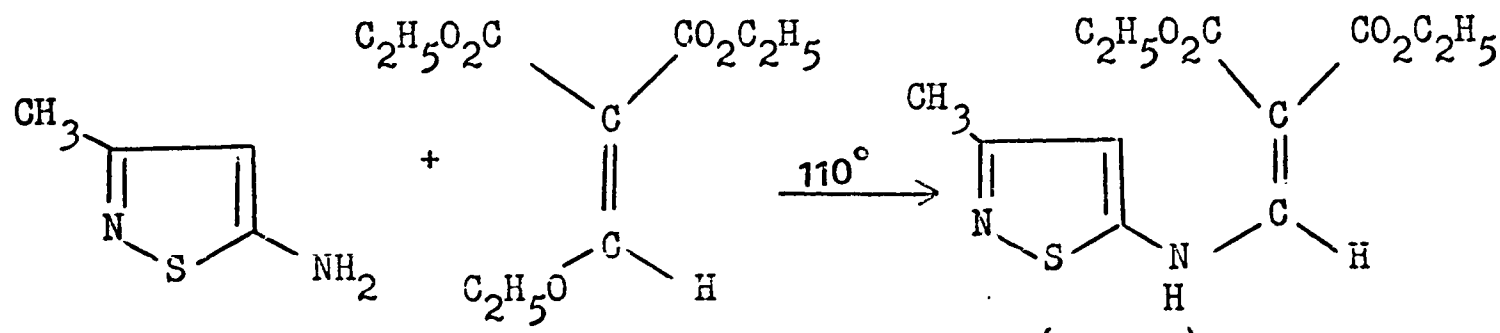
These solvents boil at a temperature which appear to be optimum for the cyclisation, are much less viscous and more easily removed from the product by filtration and generally results in the formation of a much cleaner product. The volume of solvent required for cyclisation of the various malonate esters was found to vary considerably. In some cases cyclisation could be effected without solvent, in others dilution with up to forty volumes of Dowtherm was required.

Price and Roberts found that the reaction of an amine with ethoxymethylenemalonic ester was very satisfactory on a small scale, but when large amounts were prepared the isolation of the malonate could be circumvented by mixing the reactants in diphenyl ether at room temperature and then heating this solution directly to the cyclising temperature of 250°.

The successful synthesis of naphthyridines from aminopyridines and ethoxymethylenemalonic ester prompted the investigation of this method as a route to isothiazolo[5,4-b]pyridines.

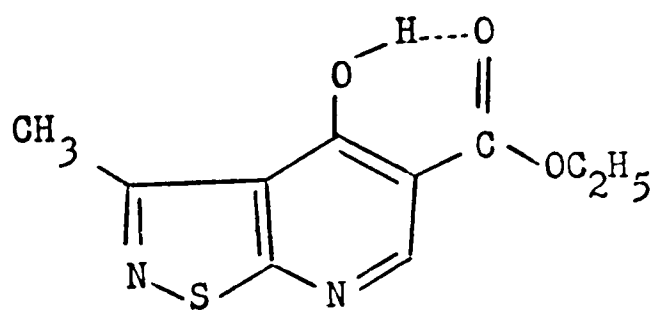
Equimolar quantities of 5-amino-3-methylisothiazole and ethoxymethylenemalonic ester were heated to 110° and samples were removed at regular intervals and investigated by g.l.c. and by t.l.c. T.l.c. showed the appearance of a single product and g.l.c. showed the disappearance of the reactants with time but no peak corresponding to the malonate derivative was observed probably because the product was not sufficiently volatile at the column temperature.

Dissolving the reaction mixture in benzene and dilution with a large volume of light petroleum followed by recrystallisation of the resulting solid from the same solvent gave diethyl 2-(3-methylisothiazol-5--ylaminomethylene)malonate (XXVIII) as pale yellow cubes, m.p. 78-79° in 66% yield.

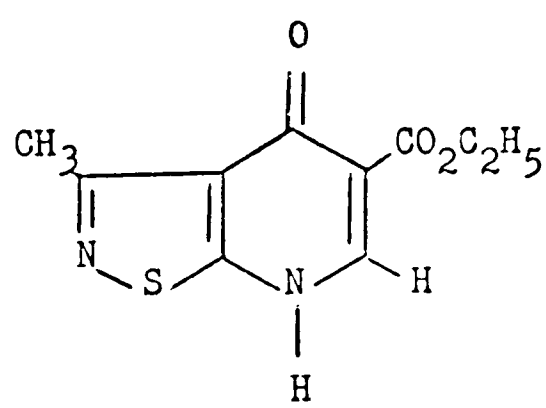


(XXVIII)

Cyclisation of the ester was readily effected in refluxing diphenyl ether to give ethyl 4-hydroxy-3-methylisothiazolo[5,4-b]pyridine-5--carboxylate (XXIX). It was isolated by dilution of the reaction mixture with light petroleum.



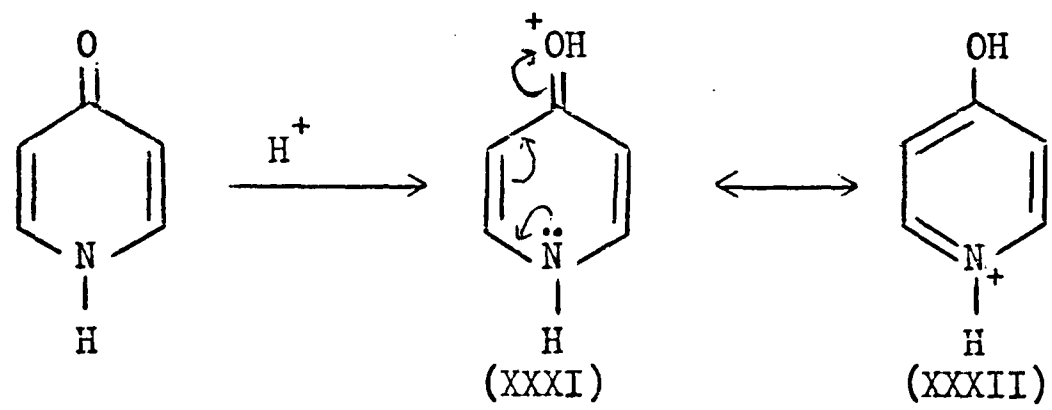
(XXIX)



(XXX)

It is known that 2-hydroxy and 4-hydroxy quinoline exist largely in the keto form. The possibility that the cyclised compound existed in the keto form XXX was considered but rejected on the basis of its infrared spectrum (I.R.6) which showed a broad -OH band at 3450 cm^{-1}, and its ultraviolet spectrum (U.V.2) which was very similar to that of methyl 4--methoxy-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate (U.V.8) described later. Hydrogen bonding, as shown, would be expected to stabilise the hydroxy form.

The n.m.r. spectrum (N.M.R.13) in trifluoroacetic acid showed the ethyl group as a three proton triplet and a two proton quartet at δ 1.58 and 4.78 p.p.m. (J 7Hz) respectively, the 3-methyl proton as a singlet at δ 3.11 p.p.m. and H-6 as a sharp one proton singlet at δ 9.1 p.p.m. The n.m.r. spectrum was not expected to be helpful in ascertaining the structure of the ester as in trifluoroacetic acid protonation on oxygen would occur, as in the case of 4-pyridone which has been shown to protonate on oxygen[92] and can thus be represented by the canonical forms XXXI and XXXII, i.e. a N-protonated 4-hydroxypyridine.

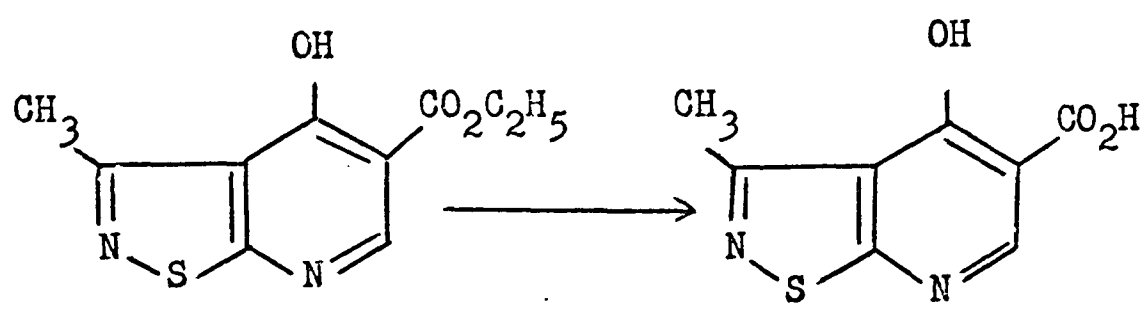


(XXXI) (XXXII)

The hydroxy-ester did not give a colour reaction with ferric chloride solution. This is not surprising since it is known that colour formation is suppressed by electron withdrawing substituents ortho to the hydroxy group. This effect is to be expected, since colour depends on the complex formation between the nucleophilic oxygen and ferric ion; any diminution of electron density inhibits the test.

The hydroxy-ester XXIX was readily hydrolysed with acid and with base to the corresponding hydroxy-acid XXXIII. Hydrolysis with hydrochloric

acid gave the hydroxy-acid contaminated with a small amount of the hydroxy-ester as shown by its n.m.r. spectrum. Suspended solid remained present during the reaction and it was not possible to assess the extent of the hydrolysis but no doubt a longer reflux period would give the pure acid. Basic hydrolysis with hot aqueous sodium hydroxide was more convenient and gave the hydroxy-acid in 80% yield. It melted with decarboxylation at 271-274° and the solid which immediately formed at this stage then melted at 295-300°, with decomposition. Elemental analysis, infrared and n.m.r. (N.M.R.14) were in agreement with the structure XXXIII.



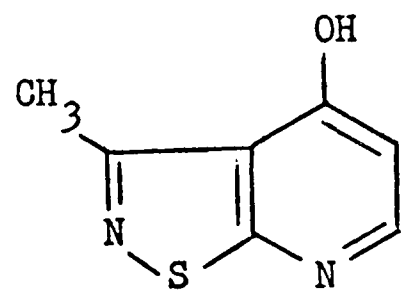
(XXIX) (XXXIII)

4-Hydroxy-3-methylisothiazolo[5,4-b]pyridine-5-carboxylic acid was readily decarboxylated on heating. This was carried out initially in a thermogravimetric apparatus. A considerable amount of charring was observed but this technique had the advantage over the other methods described below in that the reaction could be carefully controlled. However, the small amount of material, approximately 100 mg, that could be handled at a time made it inconvenient.

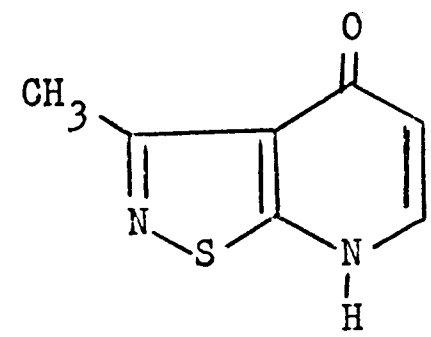
Heating the hydroxy-acid as a thin layer in a wide glass container in a Woods metal bath proved to be more convenient and 2-3g quantities could be easily handled in this way and yields of up to 65% of the product were obtained. Decarboxylation with copper-quinoline was also effective but the acid was obtained in poor yield.

Elemental analysis indicated the molecular formula $C_7H_6N_2OS$, confirming the loss of carbon dioxide. The product would be expected to be capable of tautomerism and be represented by either the hydroxy structure

XXXIV or the carbonyl structure XXXV.

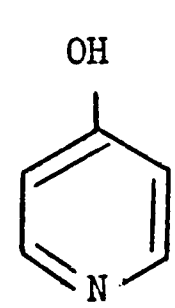


(XXXIV)

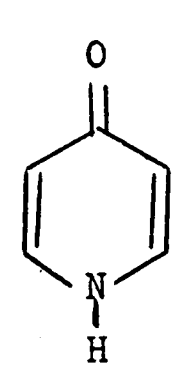


(XXXV)

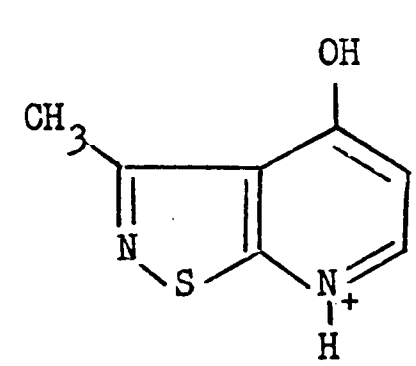
This situation is similar to that of 4-hydroxypyridine (XXXVI) which has been shown to exist preferentially in the carbonyl form (XXXVII) by means of n.m.r.,[92] i.r.[93] and u.v.[94] spectroscopy and the compound should properly be referred to, therefore, as pyrid-4-one. The 2-substituted pyridine is also in the carbonyl form. On the basis of similar studies the 4- and 2-hydroxyquinolines have also been shown to exist preferentially in the carbonyl forms and are best referred to as quinol-4-one and quinol-2-one.



(XXXVI)



(XXXVII)

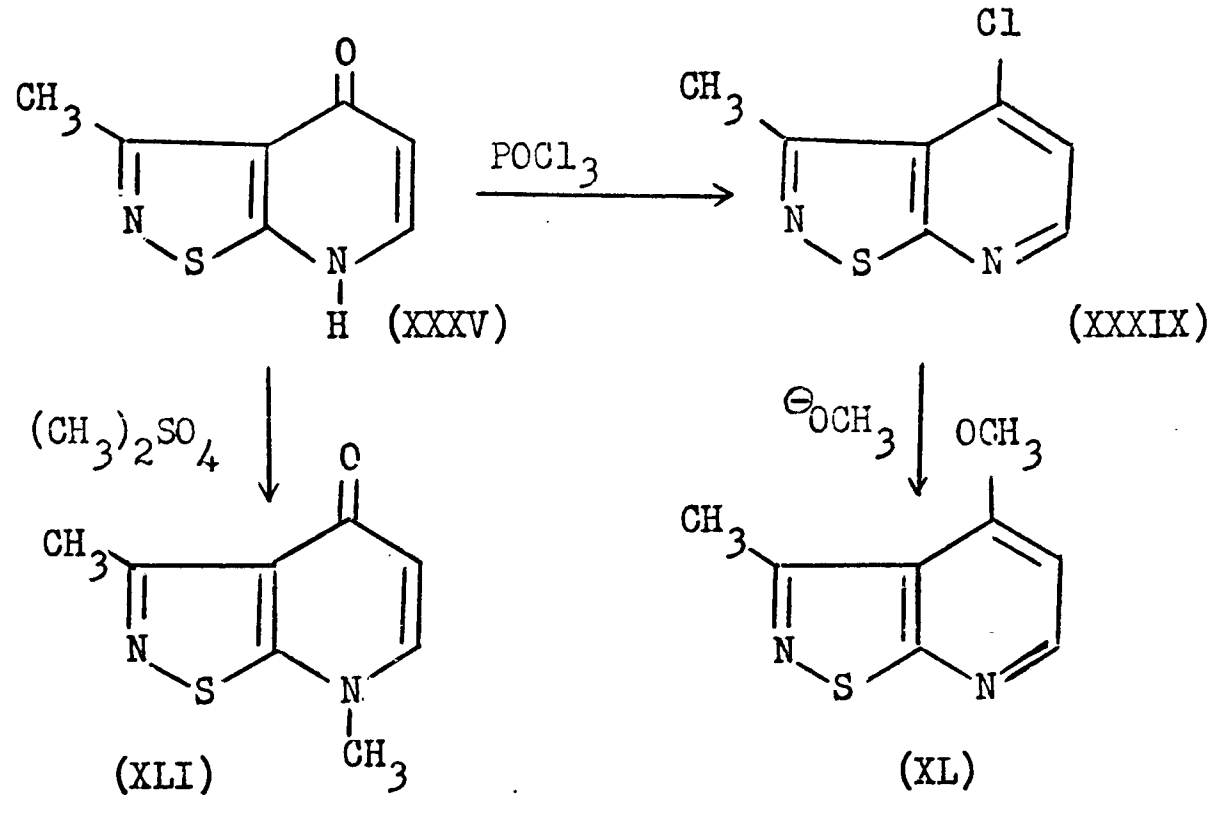


(XXXVIII)

The only suitable solvent for the n.m.r. study of the compound was trifluoroacetic acid and in this solvent the compound would be expected to be protonated on the oxygen[92] so that the spectrum (N.M.R.15) would be of structure XXXVIII and would therefore be of no help in ascertaining which structure would be predominant.

The compound gave no colouration with aqueous or alcoholic ferric chloride. There was no hydroxyl absorption in the infrared spectrum (I.R.8) and bands at 3180 cm^{-1} (N-H) and at 1640 cm^{-1} (C=O) indicated that the compound was in fact 3-methylisothiazolo[5,4-b]pyrid-4-one (XXXV). This was confirmed by comparison of its ultraviolet spectrum with that of both the N-methyl-3-methylisothiazolo[5,4-b]pyrid-4-one (XLI) and 4-methoxy--3-methylisothiazolo[5,4-b]pyridine (XL) described below. The

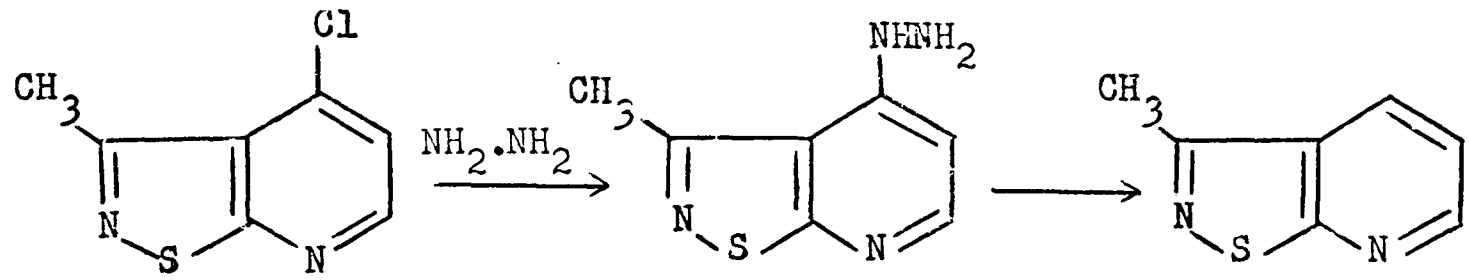
ultraviolet spectrum of the decarboxylation product (U.V.3) was quite different to that of XL (U.V.5) and virtually identical with that of the N-methyl compound XLI (U.V.6).



As expected from analogous reactions in the quinoline and naphthyridine series,[47,95,96] reaction of 3-methylisothiazolo[5,4-b]-pyrid-4-one (XXXV) with phosphoryl chloride readily gave 4-chloroisothiazolo-[5,4-b]pyridine (XXXIX) in 49% yield as colourless needles, m.p. 125-126°. The chlorine was readily displaced by sodium methoxide in methanol giving, unambiguously, 4-methoxy-3-methylisothiazolo[5,4-b]-pyridine (XL) as white needles, m.p. 145-146°, in good yield. Methylation of XXXV with dimethyl sulphate in aqueous sodium hydroxide gave a different methylated compound, m.p. 215-217°, which must consequently be the product of N-methylation, viz. N-methyl-3-methylisothiazolo[5,4-b]pyrid-4-one. (XLI). The infrared, ultraviolet (U.V.5 and U.V.6) and n.m.r. spectra (N.M.R. 17 and N.M.R. 18) of XL and XLI are quite different, as expected. In particular the n.m.r. spectra showed the 3-methyl protons as singlets at δ 2.81 and 2.83 p.p.m. respectively, H-6 and H-5 as doublets at δ 8.6 and 6.75 p.p.m. for XL and 7.35 and 6.25 p.p.m. for XLI. The O-methyl protons appeared as a singlet at δ 4.05 p.p.m. and the N-methyl protons

as a singlet at δ 3.73 p.p.m., in line with that expected on the basis of the greater electronegativity of oxygen. The larger coupling constant between the 5 and 6 protons in the N-methyl (J 8Hz) as compared to the O-methyl compound (J 5.5 Hz) is also expected on the basis of the larger double bond character between carbons 5 and 6 in the N-methyl compound.

Reaction of 4-chloro-3-methylisothiazolo[5,4-b]pyridine with hydrazine hydrate in ethanol gave a solid product, which could not be purified by crystallisation and was not analysed. Its spectral properties were, however, consistent with it being the 4-hydrazino-3-methylisothiazolo[5,4-b]pyridine compound (XLII). Treatment of this crude material with cupric sulphate in acetic acid gave a 40% yield of 3-methylisothiazolo[5,4-b]pyridine (II), identical (mixed m.p., i.r. and t.l.c.) with the compound obtained by the reaction of 5-amino-3-methylisothiazole and glycerol under Skraup conditions.



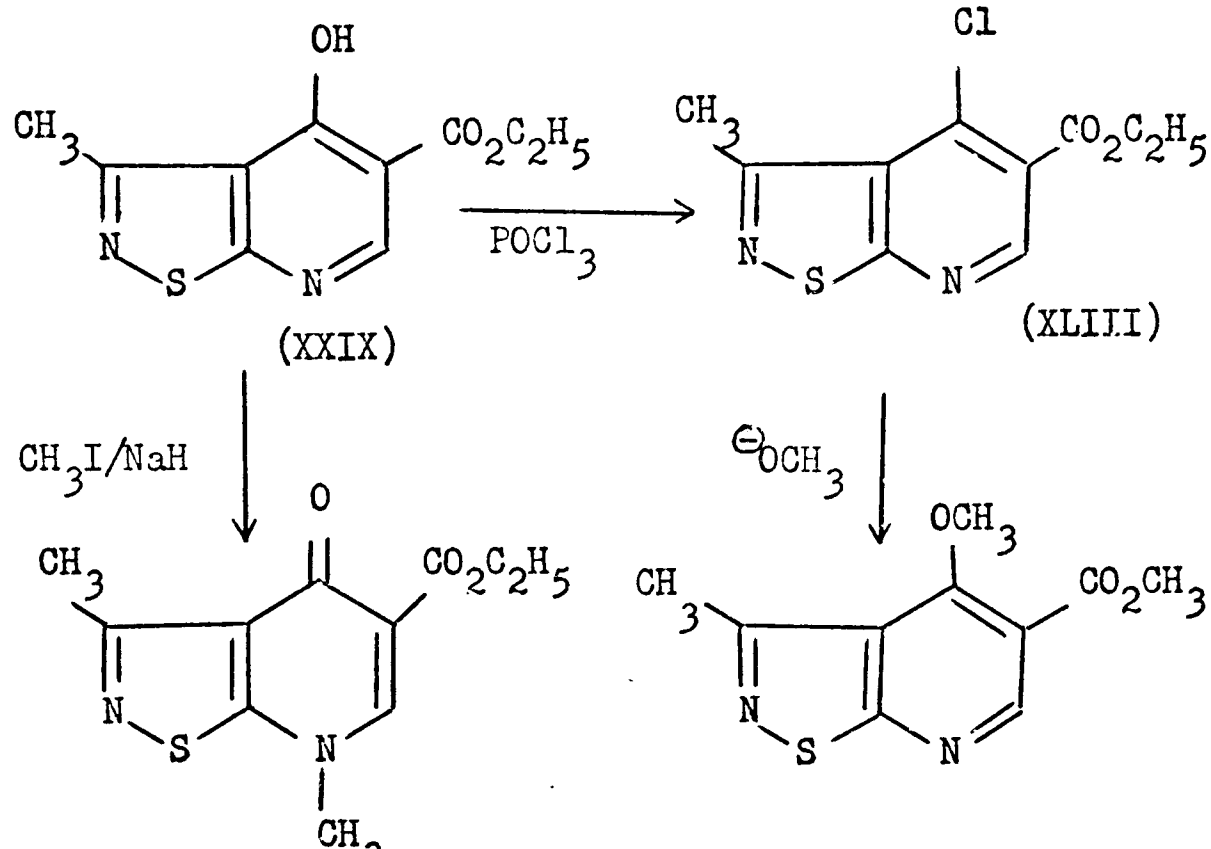
(XL) (XLII) (II)

Reaction of ethyl 4-hydroxy-3-methylisothiazolo[5,4-b]pyridine-5--carboxylate (XXIX) with phosphorous oxychloride afforded ethyl 4-chloro--3-methylisothiazolo[5,4-b]pyridine-5-carboxylate (XLIII) in 53% yield.

Treatment of the chloro-ester with sodium methoxide in methanol gave a product (75%), the n.m.r spectrum (N.M.R 21) of which indicated absence of an ethyl group. Instead three proton singlets at δ 2.87, 4.03 and 4.17 p.p.m. indicated that in addition to nucleophilic displacement of the chlorine, transesterification had occurred to give methyl 4-methoxy-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate (XLIV). The signal at δ 2.87 p.p.m. was assigned to the 3-methyl protons, that at δ 4.03 p.p.m. to the O-methyl protons, on the basis of the position of the methoxy

protons in 4-methoxy-3-methylisothiazolo[5,4-b]pyridine (δ 4.05 p.p.m.) and the signal at δ 4.17 p.p.m. to the ester methyl protons.

H-6 was observed as a one proton singlet at δ 9.03 p.p.m.



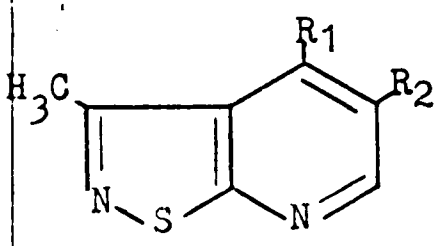
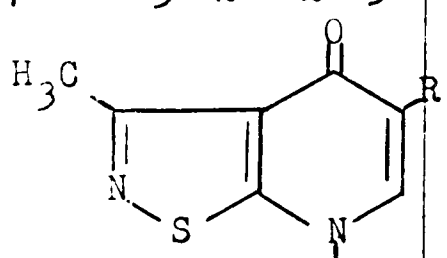
Treatment of the hydroxy-ester (XXIX) with methyl iodide and sodium hydride in dimethylformamide gave a compound which analysed correctly for a methylated derivative, $C_{11}H_{12}N_2O_3S$, and which could, therefore, be either the O-methyl or N-methyl product. Spectroscopic evidence indicated that the product was in fact ethyl N-methyl-3-methylisothiazolo[5,4-b]pyrid--4-one-5-carboxylate (XLV). The n.m.r. spectrum (N.M.R 22) showed a three proton singlet at δ 3.83 p.p.m., which is at higher field than the O-methyl signal (δ 4.03) in ester XLIV and approximately the same as that of the N-methyl signal (δ 3.73) in N-methyl-3-methylisothiazolo[5,4-b]-pyrid-4-one (XLI). In addition, the infrared spectrum showed a band at 1640 cm^{-1}, assigned to the ring carbonyl, as well as an ester carbonyl band at 1700 cm^{-1}. The ultraviolet spectrum (U.V. 9) was similar to that of N-methyl-3-methylisothiazolo[5,4-b]pyrid-4-one (U.V. 6) and quite

different to that (U.V. 8) of the methoxy ester XLIV.

Attempts at acetylation of ethyl 4-hydroxy-3-methylisothiazolo-[5,4-b]pyridine-5-carboxylate did not prove successful. Acetic anhydride and sodium acetate and also acetyl chloride and sodium hydride in dimethylformamide gave only starting material.

The n.m.r spectra of the compounds described above are collected, for comparison purposes, in Table III.

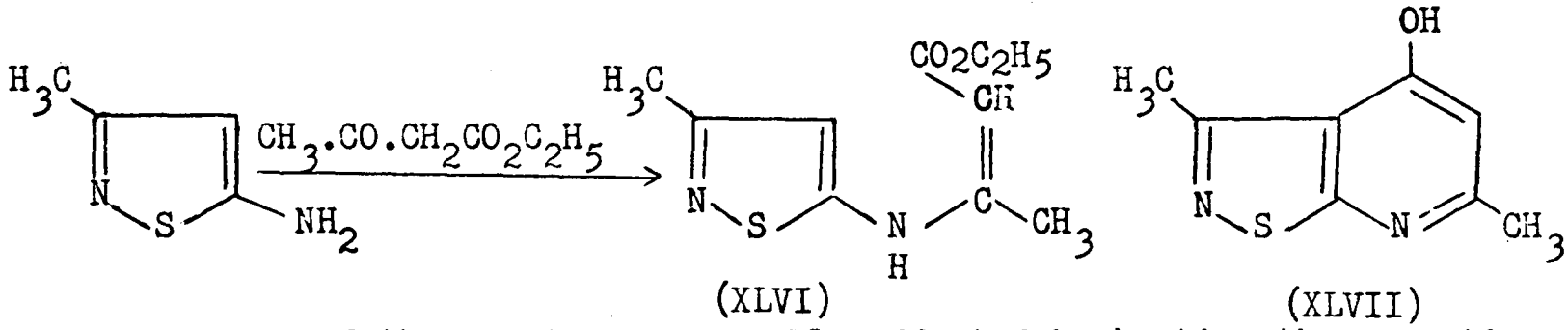
TABLE III

Compound	N.M.R No.	SOLVENT	Chemical shifts (δ) p.p.m.								Coupling Constants (Hz) J_{56}
			CH_3-3	$\underline{CH_3}.CH_2$-	$CH_3.\underline{CH_2}$-	$-OCH_3$	$-NCH_3$	$-CO_2CH_3$	H_5	H_6	
											
$R_1 = OH, R_2 = CO_2C_2H_5$	13	TFA	3.11	1.58	4.78	-	-	-	-	9.15	-
$R_1 = OH, R_2 = CO_2H$	14	TFA	2.75	-	-	-	-	-	-	9.1	-
$R_1 = Cl, R_2 = H$	16	$CDCl_3$	2.96	-	-	-	-	-	7.38	8.56	5.0
$R_1 = OCH_3, R_2 = H$	17	$CDCl_3$	2.81	-	-	4.05	-	-	6.75	8.6	5.5
$R_1 = Cl, R_2 = CO_2C_2H_5$	19	$DMSOd_6$	2.91	1.4	4.48	-	-	-	-	9.08	-
$R_1 = OCH_3, R_2 = CO_2CH_3$	20	$CDCl_3$	2.87	-	-	4.03	-	4.17	-	9.03	-
											
$R = H, R_1 = H$	15	TFA	3.1	-	-	-	-	-	7.48	8.74	7.0
$R = H, R_1 = CH_3$	18	$CDCl_3$	2.83	-	-	-	3.73	-	6.25	7.35	8.0
$R = CO_2C_2H_5, R_1 = CH_3$	21	$DMSOd_6$	2.66	1.33	4.26	-	3.83	-	-	8.50	-

Investigation of the reaction of 5-amino-3-methylisothiazole with ethyl acetoacetate

The reaction of aromatic amines with ethylacetoacetate followed by cyclisation of the resultant enamine in diphenyl ether has proved to be a good method for the synthesis of 2-methyl-4-hydroxyquinolines. This reaction sequence, known as Conrad-Limpach reaction, has not been successful with 3- and 4-aminopyridines. 2-Aminopyridine has been shown to undergo condensation with ethyl acetoacetate but the enamine so formed gave a pyrimidine rather than a naphthyridine on cyclisation.

The reaction of 5-amino-3-methylisothiazole with ethylacetoacetate was investigated as a possible synthesis of 4-hydroxy-3,6-dimethylisothiazolo [5,4-b] pyridine (XLVII) via the enamine XLVI.

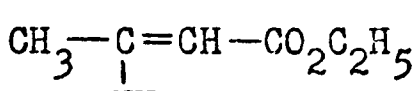


(XLVI) (XLVII)

Formation of the enamine is normally effected by heating the aromatic amine in ethanol with ethylacetoacetate in the presence of Drierite and a catalytic amount of glacial acetic acid or hydrochloric acid.[97] The reaction of 5-amino-3-methylisothiazole with ethylacetoacetate under these conditions gave a gum which was shown by g.l.c to consist of at least five components, two of which were identified as starting materials. The major component was observed as a broad peak at R_t 30.4 min (ca. 50%). Attempted distillation of the crude mixture gave only about 8% of a mixture consisting of ethylacetoacetate and a low boiling component (R_t 1.2 min). Preparative g.l.c. gave this component as an oil which was shown by high resolution mass spectrometry to have the molecular formula $C_6H_{11}NO_2$. The infrared spectrum (I.R.13) showed the presence of an amino group (3440 and

3340 cm^{-1}) and an ester carbonyl group (1660 cm^{-1}) The n.m.r. spectrum (N.M.R. 23) showed a three proton triplet at δ 1.25 p.p.m. and a two proton quartet at δ 4.2 p.p.m. indicating the presence of an ethyl group. A three proton singlet at δ 1.9 p.p.m. was assigned to a methyl group and a sharp one proton singlet at δ 4.52 p.p.m. to a methine proton.

From this data it was concluded that the compound was ethyl 3-aminocrotonate (XLVIII) and this was supported by the recorded infrared date [98] for this compound.



(XLVIII)

The residue after distillation, consisting of the other two components and some starting material, was heated with diphenyl ether in the hope that one of these compounds was the enamine XLVI and that cyclisation would occur. However, dilution with light petroleum gave only an intractable gum.

Another method which has been successful for preparing the enamine from an aromatic amine and ethylacetoacetate involves keeping the mixture containing a few drops of concentrated hydrochloric acid under vacuum over concentrated sulphuric for about seven days.[97] The reaction of 5-amino-3--methylisothiazole with ethylacetoacetate under these conditions gave a red oil which was shown by g.l.c. to contain the same number of components with identical retention times as the mixture obtained above. The two major components at R_t 11.6 and 30.4 min were obtained by preparative g.l.c. The compound at R_t 11.6 min was obtained as a brown amorphous solid; its n.m.r. spectrum was not very informative and the compound was not further investigated. The compound at R_t 30.4 min was obtained as yellow needles, m.p. 90-92°. The molecular formula, $C_{10}H_{14}N_2O_2S$, obtained by high resolution mass spectrometry suggested that it was the expected product XLVI. This was confirmed by its infrared spectrum (I.R.14) which showed an N-H band at 3405 cm^{-1} and an ester carbonyl band at 1680 cm^{-1} and its n.m.r.

spectrum (N.M.R 24) which showed an ethyl group as a three proton triplet at δ 1.31 p.p.m. and a two proton quartet at δ 4.3 p.p.m. The 3-methyl protons appeared as a sharp singlet at δ 2.63 p.p.m.; a three proton singlet at δ 1.97 was assigned to the methyl group adjacent to the nitrogen and the olefinic hydrogen to a singlet at δ 5.16 p.p.m. A one proton signal at δ 6.65 p.p.m, which disappeared on shaking with deuterium oxide, was assigned to the N-H proton.

Despite the formation of the enamine in these reactions, it was considered advisable to abandon this possible route to isothiazolo[5,4-b]-pyridine as the separation of the desired intermediate was very tedious. A more detailed study of the thermal cyclisation of the crude condensation mixture, would help to assess the feasibility of this method of synthesis.

Investigation of the reaction of 5-amino-3-methylisothiazole with acetylacetone

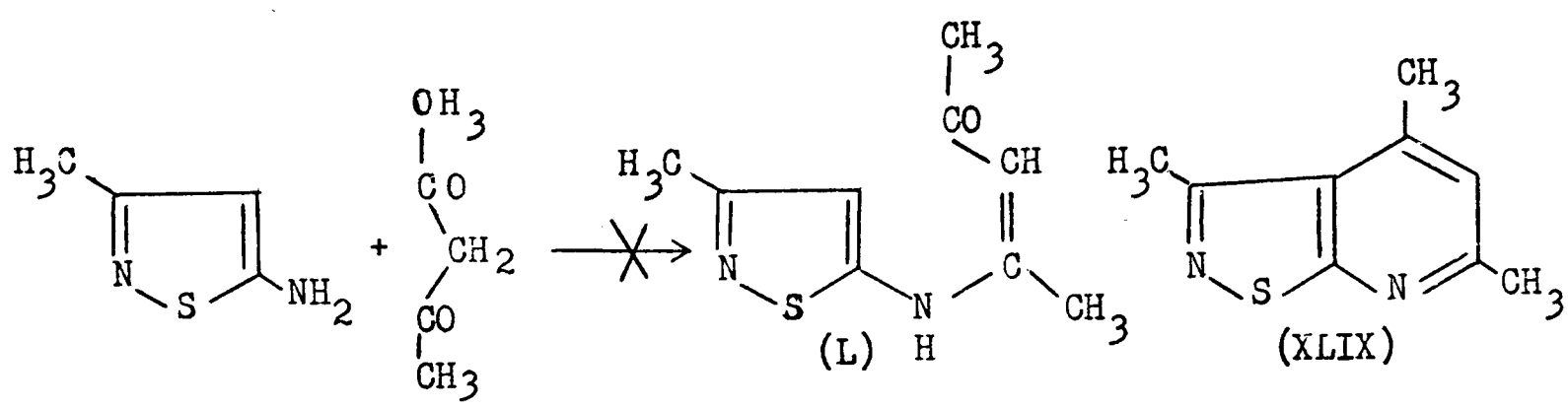
In the Combes synthesis of quinolines, an aromatic amine is condensed with a 1,3-diketone, and the resulting enamine is then cyclised with concentrated sulphuric acid to a 2,4-disubstituted quinoline.[99]

The ease of condensation of an aromatic amine with acetylacetone has been reported by Roberts and Turner to be affected by the basicity of the amine used. They found that no nitroaniline, simple or complex, could be caused to condense with acetylacetone.[42] Similar failures with the aminopyridines have been attributed to the low basicities of the amines. The original Combes reaction involved heating the aromatic amine with acetylacetone under reflux, or in some cases, on a steam bath until water separated out. With aniline and acetylacetone the reaction is complete in a few minutes. The intermediate has, in a few cases, been isolated by distillation and after cyclisation with concentrated sulphuric acid, the quinoline is obtained from the basic solution.

In a modified preparation of the enamine, the amine and acetylacetone were refluxed in xylene until the theoretical amount of water was collected in a Dean Stark attachment.[100]

In another method, the reactants were heated in the presence of Drierite.[101]

The reaction of 5-amino-3-methylisothiazole with acetylacetone was investigated as a possible route to 4,6-dimethyl-3-methylisothiazolo[5,4-b]-pyridine (XLIX) via the expected enamine L.

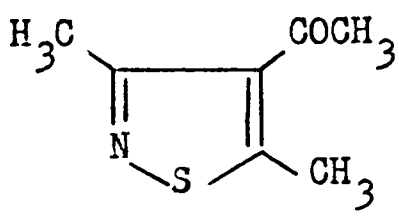


Heating 5-amino-3-methylisothiazole with acetylacetone in the presence of Drierite gave a mixture, which was shown by g.l.c. to contain at least four components at R_t 1.2, 2.5, 10.2 and 27.2 min; the major component (ca. 50%) was observed at R_t 27.2 min. Effective separation could not be achieved by t.l.c. and it was thought desirable to proceed directly to the next stage. The mixture, a viscous oil, was treated with concentrated sulphuric acid and, after standing, made alkaline. Work up gave a liquid which distilled at 66-68° at 0.6 mm Hg. The crude and distilled product was homogenous by t.l.c. and showed only one peak on g.l.c., R_t 3.8 min. The molecular weight, obtained by high resolution mass spectrometry, indicated the molecular formula C_7H_9NOS. The infrared spectrum showed a carbonyl band at 1675 cm^{-1} and the compound readily formed an oxime. The n.m.r. spectrum (N.M.R. 25) showed three three proton singlets at δ 2.4, 2.60 and 2.63 p.p.m, indicating the presence of three methyl groups. The u.v. spectrum showed two bands at 274 and 212 nm.

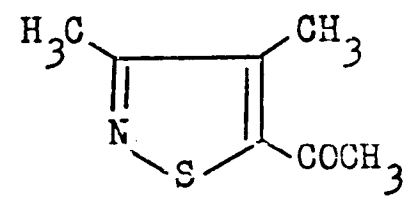
This data suggested that the product was an acetyl-dimethylisothiazole.

It was initially suspected that the compound was 4-acetyl-3,5--dimethylisothiazole, (LI) as its n.m.r spectrum was very similar to that reported by Rajappa, Akekar and Iyer for LI, with one higher field methyl signal and two closely spaced lower field methyl signals.[102] Direct comparison with the spectra of LI, kindly supplied by Dr. Rajappa, showed that this was not the case. The published n.m.r. data on LI was not in agreement with the spectrum which, in fact, showed two closely spaced singlets at high field and one at lower field, as shown in parentheses below. In addition the i.r. spectra were different and LI absorbed at shorter wavelength in the U.V. spectrum. 3-Acetylisothiazole[104] has λ max 262 nm also, whereas 5-acetyl-3-methylisothiazole has λ max 284 nm[105] The product was tentatively formulated as 5-acetyl-3,4-dimethylisothiazole (LII) although the possibility that the compound is a trisubstituted thiazole cannot be ruled out.

	(δ p.p.m.)	λ max.	ν max.
Product	2.4	274	1675
	2.60	214	
	2.63		
	2.45 (2.45)		
	2.63 (2.5)	262	1680
	2.73 (2.65)		



(LI)

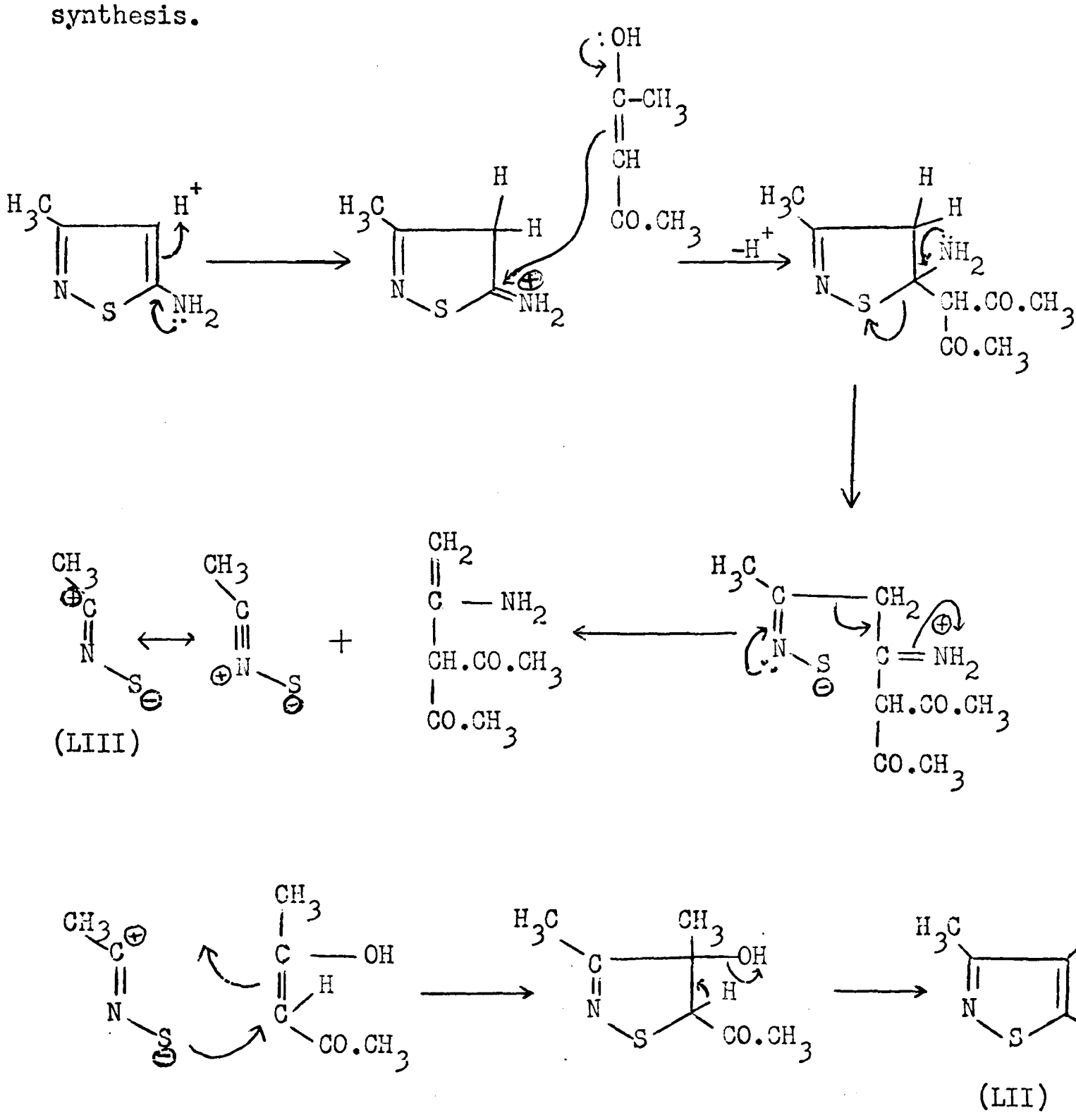


(LII)

The nature of the product indicates that a major rearrangement involving ring cleavage followed by ring formation occurred during this reaction and further studies would be necessary to rationalise this interesting result.

A speculative explanation for the formation of this unusual product, assuming it is 5-acetyl-3,5-dimethylisothiazole, could involve the dipolar intermediate LIII. This could conceivably be formed by attack of acetylacetone on the imino form of 5-amino-3-methylisothiazole followed by ring cleavage as shown. Addition of the intermediate acetonitrile

sulphide LIII to acetylacetone as shown could lead to LII. It is interesting to note that an intermediate benzonitrile sulphide, $C_6H_5C{\equiv}N{\rightarrow}S$ has been postulated by Franz and Black[103] in an isothiazole synthesis.

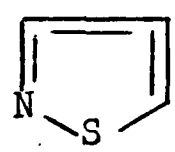


II. APPROACHES TO ISOTHIAZOLYNES

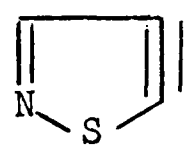
As described earlier, one of the most useful methods available for the generation of arynes is by aprotic diazotisation of the appropriate amino acid. The aryne so formed may be reacted with various substrates or trapped with suitable arynophiles.

Before a systematic investigation of isothiazolyne intermediates could be undertaken it was necessary to synthesise a number of suitable isothiazole amino acids.

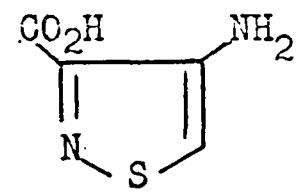
Two isomeric isothiazolynes are possible, viz. 3,4-isothiazolyne (I) and 4,5-isothiazolyne (II). The aprotic diazotisation of the isomeric amino acids III and IV would be expected to give 3,4-isothiazolyne and the isomeric amino acids V and VI would be expected to give 4,5-isothiazolyne if this approach to isothiazolyne formation is feasible. In addition, Wittig and Wahl generated 3,4-thiophyne and found that it rearranged to 2,3-thiophyne, so the possibility of rearrangement of 3,4-isothiazolyne to 4,5-isothiazolyne should also be considered.



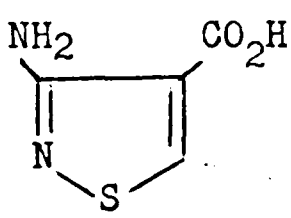
(I)



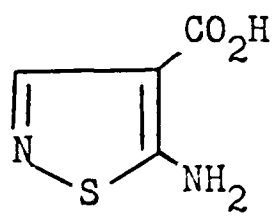
(II)



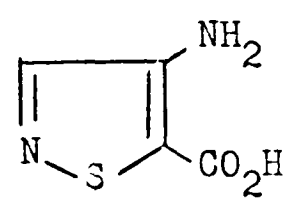
(III)



(IV)



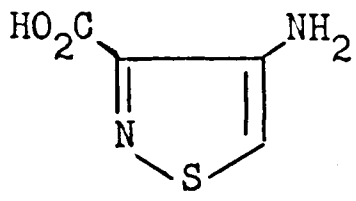
(V)



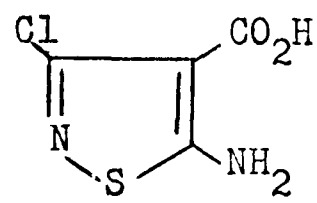
(VI)

Three isothiazole amino acids were prepared viz. 4-aminoisothiazole--3-carboxylic acid (III), 3-chloro-5-aminoisothiazole-4-carboxylic acid (VII) and 4-amino-3-methylisothiazole-5-carboxylic acid (VIII). The synthesis of

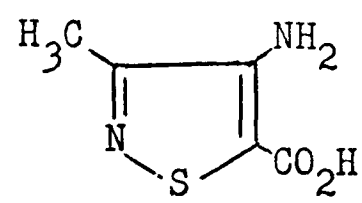
the amino acid VIII had been reported previously.



(III)



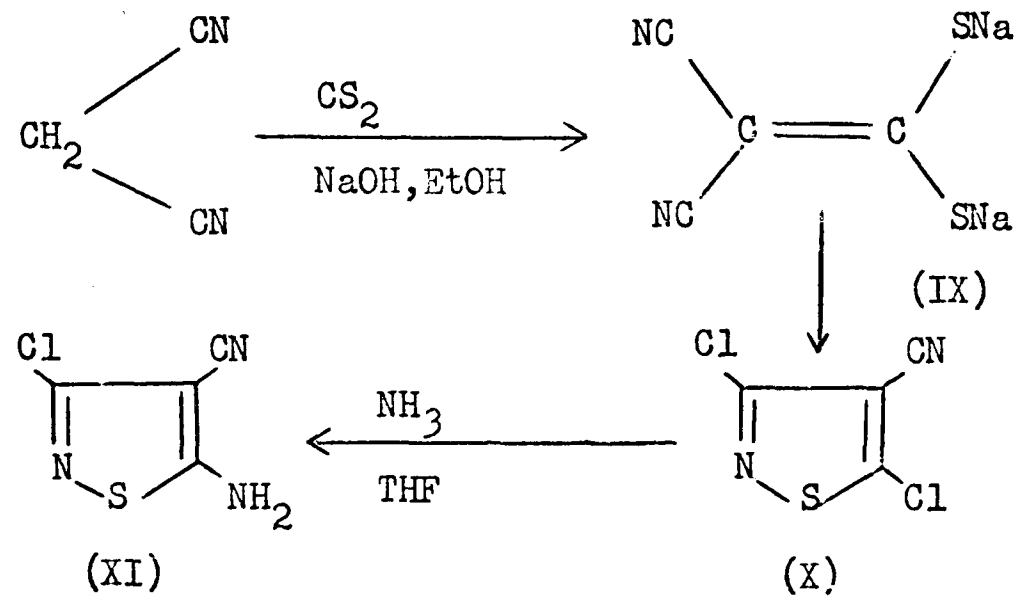
(VII)



(VIII)

Synthesis of 5-amino-3-chloroisothiazole-4-carboxylic acid

The synthesis of 5-amino-3-chloro-4-cyanoisothiazole from malononitrile was described by Hatchard [13] and it was felt that this would provide a convenient route to 5-amino-3-chloroisothiazole-4-carboxylic acid, aprotic diazotisation of which could possibly give a 3-substituted 4,5-isothiazolyne.

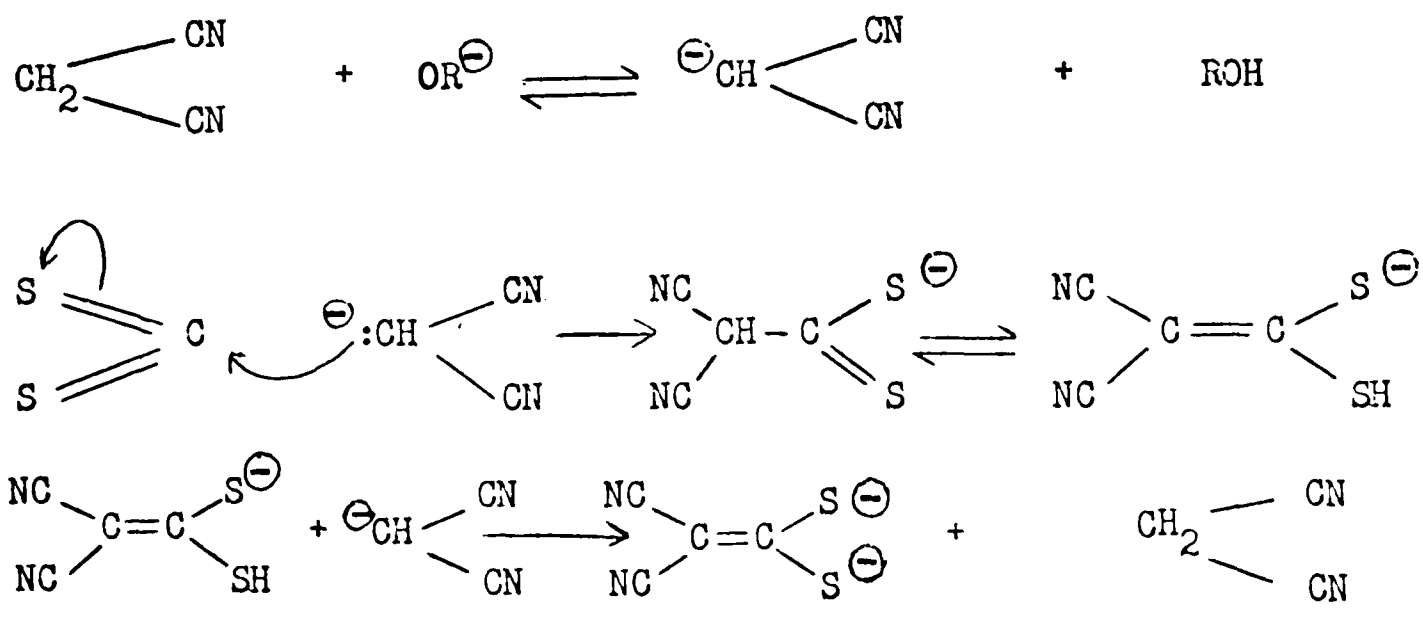


(IX)

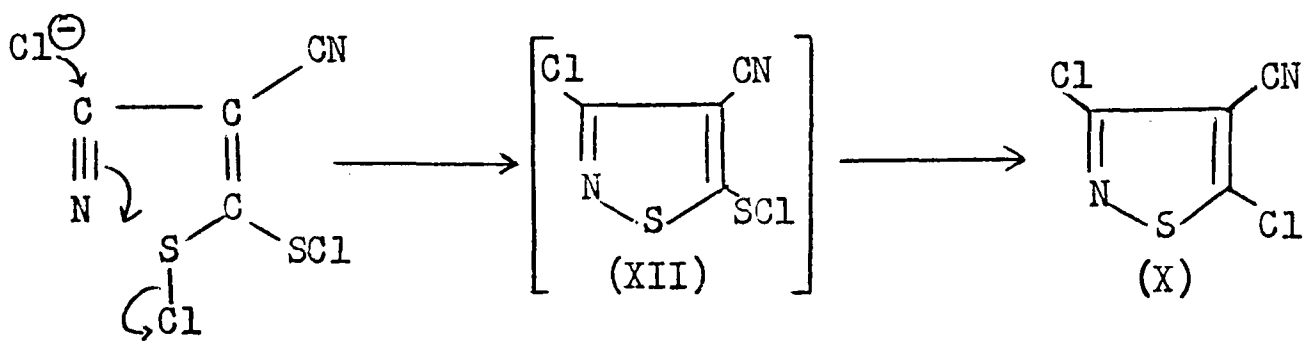
(XI)

(X)

Reaction of malononitrile with carbon disulphide in ethanolic sodium hydroxide gave the very hygroscopic di(sodiomercapto)methylenemalononitrile (IX) in 78-80% yield. G ompper and Topfl [106] proposed the following mechanism for the formation of this salt.



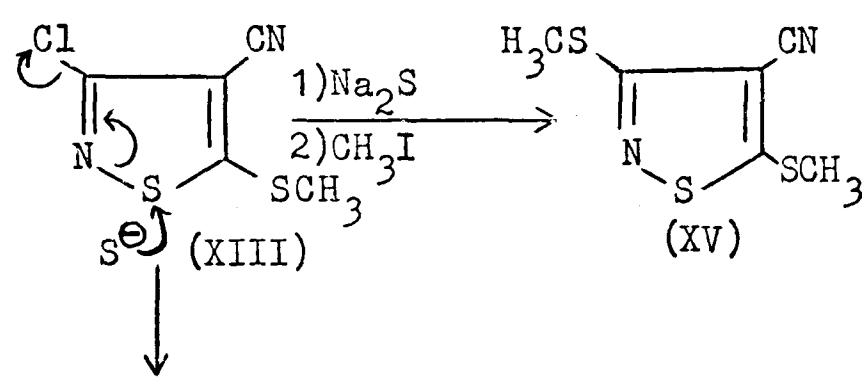
Passing chlorine through a suspension of the salt in dry carbon tetrachloride gave the dichloronitrile X in a maximum yield of 35%. Hatchard reported a yield of 57% of the dichloronitrile and commented that it was necessary that the salt be in a very anhydrous state, however despite thorough drying of the salt the yield quoted could not be attained. Hatchard also proposed a mechanism for this interesting conversion involving initial conversion of the bismercaptide to the bissulphenyl halide followed by cyclisation as shown to XII. In the presence of excess chlorine XII is then converted to X.

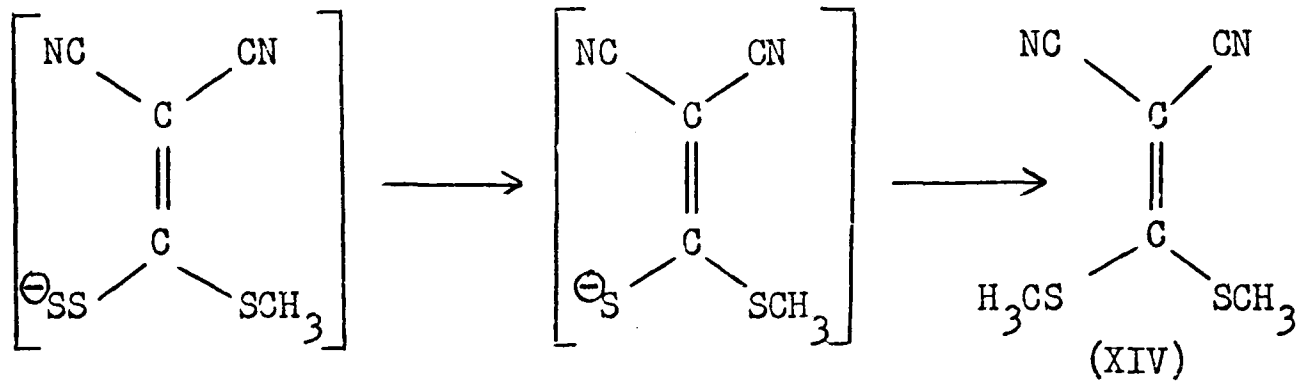


4-Cyano-3,5-dichloroisothiazole (X) was converted to 5-amino-3--chloro-4-cyanoisothiazole (XI) by refluxing with ammonia in purified tetrahydrofuran as described by Hatchard. A maximum yield of 30% was obtained under these conditions though a yield of 92% was reported. It was subsequently found that the yield could be almost doubled by carrying out the reaction at room temperature. It was later reported that the 5-amino--3-chloro-4-cyanoisothiazole formed in this reaction reacts further with the starting material to give a bis-isothiazolylamine as by-product.[107]

It was expected that hydrolysis of the nitrile or the amide to 5-amino-3-chloroisothiazole-4-carboxylic acid would occur readily, however none of the standard methods gave the amino acid. Reaction of 5-amino-3--chloroisothiazole-4-carboxamide with aqueous sodium hydroxide gave a white crystalline compound which did not melt and did not contain sulphur or chlorine. Elemental analysis indicated a molecular formula $C_4H_5N_3O_2$. The n.m.r. spectrum in deuterodimethylsulphoxide showed only one broad signal

at δ 7.6 p.p.m. Bands at 3400, 3300, 3230 cm^{-1} and also at 1630 and 1560 cm^{-1} in the i.r. spectrum suggested the presence of an amide group and a band at 2200 cm^{-1} indicated the presence of a nitrile group. Breakdown of the isothiazole nucleus had thus occurred and this is in line with observations reported by several authors. Thus Hatchard found that the nitrile XIII gave the dicyanoethylene XIV on treatment with sodium sulphide followed by methyl iodide, in addition to the expected dithioether XV, and explained the ring cleavage by attack of the sulphide anion as shown.





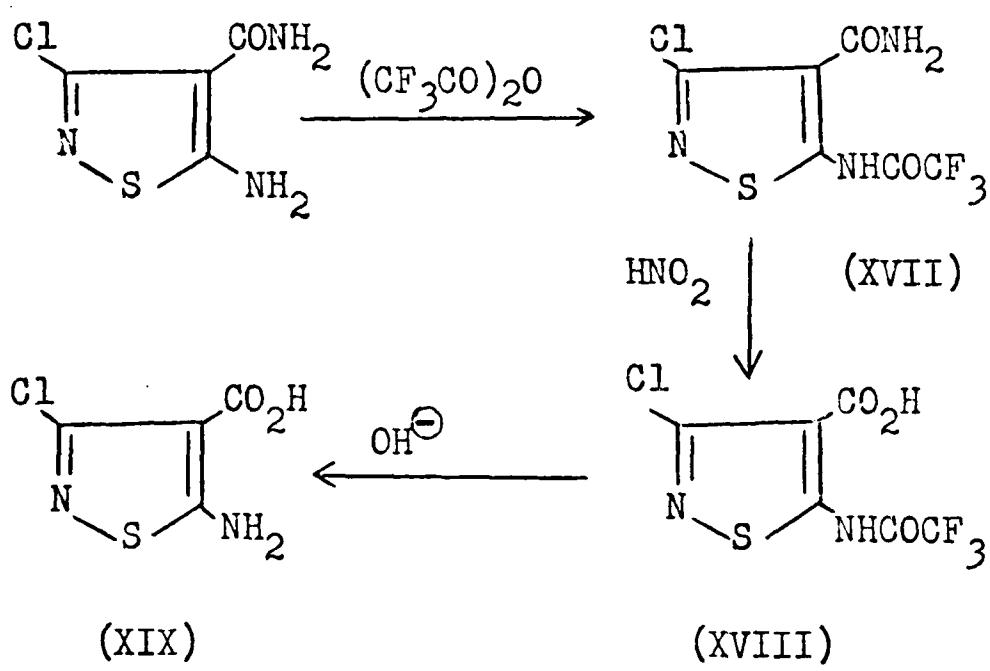
Crenshaw and co-workers[108] hydrolysed 5-methyl-3-phenyl-4-isothiazole carbonitrile to the corresponding acid by treatment with potassium hydroxide in ethylene glycol. Under the same conditions, 5-amino-3-chloro-4--cyanoisothiazole gave ammonium chloride as the only isolable product indicating that destruction of the isothiazole ring had again occurred.

Attempted acid hydrolysis by boiling with concentrated hydrochloric acid afforded only a small amount of the dehydrated product, 5-amino-3--chloro-4-cyanoisothiazole. Treatment with 90% sulphuric acid at 80-85° for 6 h gave only starting material.

Berger and Olivier[109] have reported on the hydrolytic properties of 100% phosphoric acid; with this reagent they successfully hydrolysed a

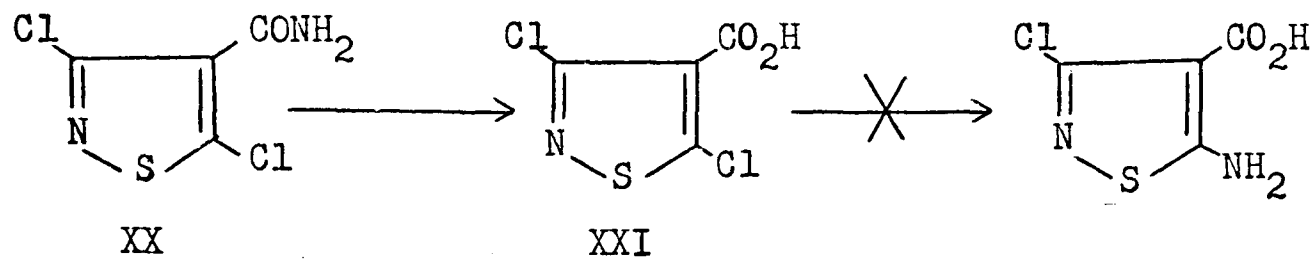
number of aromatic nitriles and amides, which are normally resistant to the usual hydrolytic agents. However, with 5-amino-3-chloroisothiazole-4--carboxamide, at 145-150° for 30 min, 100% phosphoric acid gave mostly polymeric material. At 85-90°, for one hour, mostly starting material was recovered and at 125-130° a substantial amount of starting material was recovered, but none of the amino acid was isolated.

Nitrous acid has been successfully employed to hydrolyse amides and the failure of acid or base hydrolysis to give the amino acid prompted application of this method. The amino group in 5-amino-3-chloroisothiazole--4-carboxamide (XVI) was first protected by conversion to the trifluoroacetyl derivative XVII by treatment with trifluoroacetic anhydride at room temperature. Treatment of this with nitrous acid gave 3-chloro-5-N--trifluoroacetyl aminoisothiazole-4-carboxylic acid (XVIII) in rather poor yield (20%). Mild base hydrolysis of XVIII readily gave 5-amino-3--chloroisothiazole-4-carboxylic acid (XIX) in 64% yield. Its infrared spectrum showed bands at 3460 and 3310 cm^{-1} due to the $-NH_2$ group and the carboxylic acid bands were observed at 3000-2300 and 1695 cm^{-1}.



The overall yield of this reaction sequence was fairly low due mainly to the nitrous acid hydrolysis step.

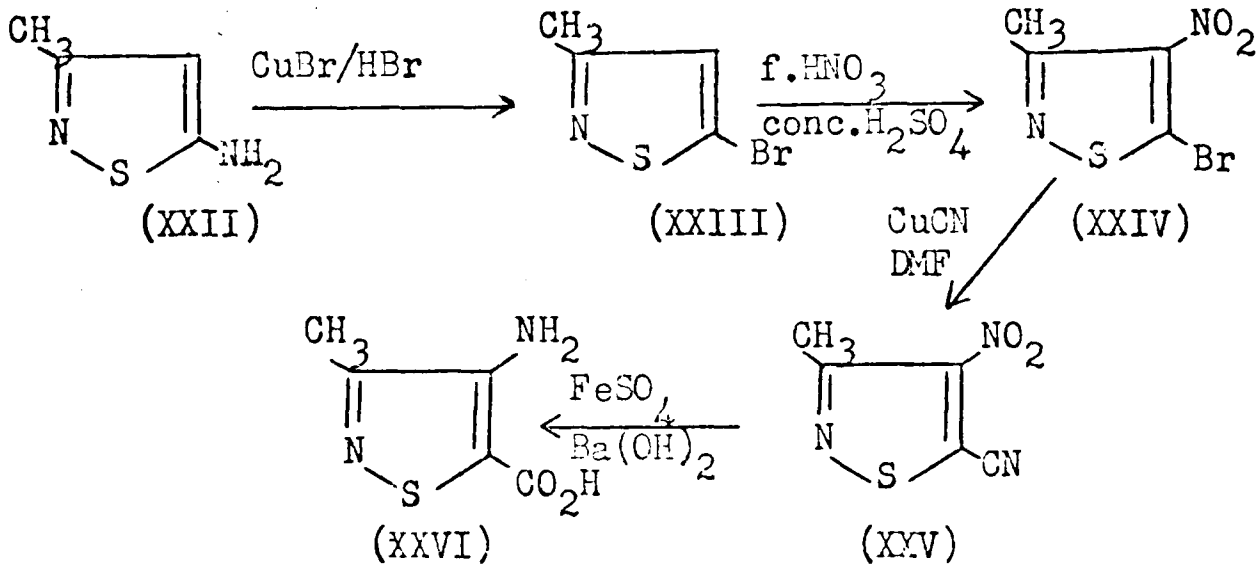
As an alternative route to the amino acid an attempt was made to displace the 5-chlorine in 3,5-dichloroisothiazole-4-carboxylic acid (XXI) with ammonia. The acid XXI[13] was obtained by nitrous acid hydrolysis of the 4-carboxamide XX which itself was readily obtained by reaction of 3,5-dichloroisothiazole-4-carbonitrile with concentrated sulphuric acid. Refluxing the acid XXI with dry ammonia in tetrahydrofuran led to precipitation of the ammonium salt, and only starting material was obtained on work up.



3,5-Dichloroisothiazole-4-carboxamide has also been reported not to undergo any reaction with ammonia.[110]

Synthesis of 4-amino-3-methylisothiazole-5-carboxylic acid

This amino acid was prepared by the method described by Holland and co-workers,[23] starting from 5-bromo-3-methyl-4-nitroisothiazole (XXIV) which had been reported earlier by Adams and Slack.[6]



Diazotisation of 5-amino-3-methylisothiazole (XXII) and reaction of

the diazonium salt with cuprous bromide in hydrobromic acid gave 5-bromo-3-methylisothiazole (XXIII) in 30% yield. Nitration of the bromo compound with fuming nitric acid in concentrated sulphuric acid afforded 5-bromo-3-methyl-4-nitroisothiazole (XXIV) (43% yield) which with cuprous cyanide and dimethylformamide in boiling light petroleum gave 5-cyano-3--methyl-4-nitroisothiazole (XXV) in 66% yield. This compound could only be recrystallised from light petroleum (b.p. 100-120°) and not light petroleum (b.p. 60-80°) as reported.

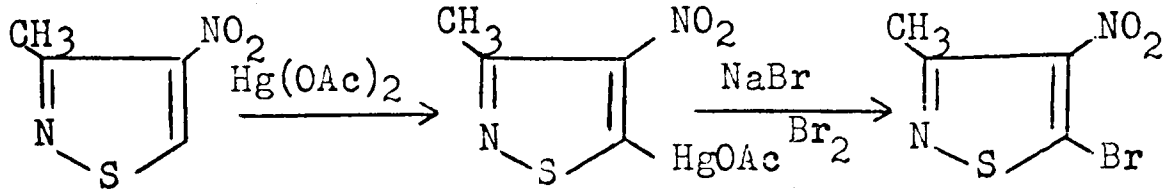
Reductive hydrolysis of XXV with ferrous sulphate-barium hydroxide gave only a moderate yield (20 %) of 4-amino-3-methylisothiazole-5--carboxylic acid (XXVI). The infrared spectrum showed bands at 3440 and 3340 cm^{-1} indicating that unlike 4-aminoisothiazole-3-carboxylic acid, described later, the compound is not in the zwitterionic form; this was supported by the absence of absorption at 2100 cm^{-1}.

This method did not prove satisfactory for preparing the amino acid in reasonable quantities. The low solubility of barium hydroxide in water necessitates a large volume of water and the reaction could only be conveniently carried out on 3-4 g of the nitro-nitrile at a time to give approximately 1 g of the amino acid.

The availability of 3-methylisothiazole and the success of the preparation of 5-bromo-4-nitroisothiazole from 4-nitroisothiazole via the 5-mercuriacetate [111] prompted a similar investigation with 3-methyl-4--nitroisothiazole (XXVII). Reaction of this compound with mercuric acetate in boiling glacial acetic acid and ethanol gave the mercuriacetate XXVIII as yellow needles, m.p. 199-200°, in 76% yield. A sample recrystallised from glacial acetic acid did not show any change in melting point but elemental analysis on this material did not agree with the expected molecular formula $C_6H_6HgN_2O_4S$; it is possible that a non-stoichiometric complex was formed.

Reaction of the mercuriacetate XXVIII with bromine and sodium bromide

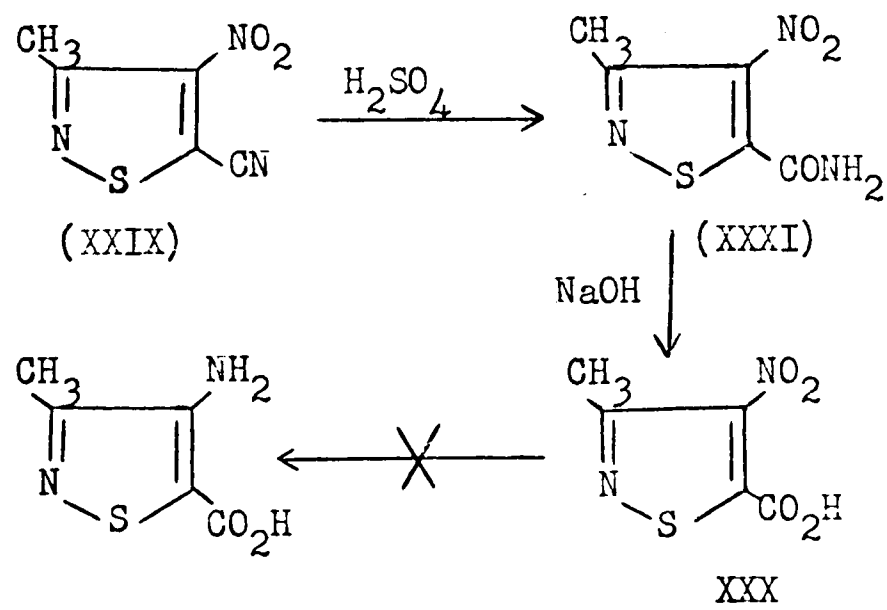
at room temperature afforded 5-bromo-3-methyl-4-nitroisothiazole in 60% yield; this proved to be a more convenient route to this compound than the one described previously.



(XXVII) (XXVIII) (XXIV)

The poor yield in the reductive hydrolysis to the amino acid led to a consideration of the possibility of converting 3-methyl-4-nitroisothiazole--5-carboxylic acid to the amino acid by reduction. The nitro-nitrile XXIX was reported to undergo hydrolysis to the nitro-acid XXX with dilute sulphuric acid at 85° [23] but when the reaction was carried out under these conditions it was found that hydrolysis was accompanied by decarboxylation and a 57% yield of 3-methyl-4-nitroisothiazole was obtained. The nitro-acid XXX was, however, prepared in 47% yield when the reaction was carried out at 80±1°.

As an alternative to this hydrolysis the formation of the acid via the known amide XXXI was investigated, but basic hydrolysis of the amide gave the nitro acid in only 9% yield.



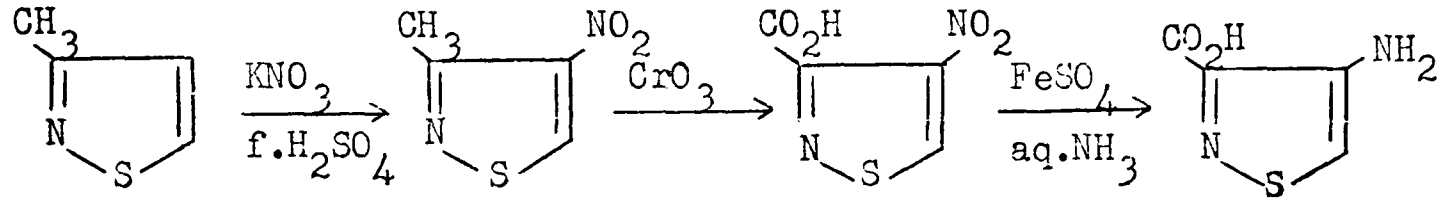
(XXIX) (XXXI) XXX

An attempted reduction of 3-methyl-4-nitroisothiazole-5-carboxylic acid with palladium charcoal and sodium borohydride[113] gave none of the expected amino acid and because of the relatively poor yield of the nitro

acid this potential route to the amino acid was not further investigated.

Synthesis of 4-Aminoisothiazole-3-carboxylic acid

The availability of 3-methylisothiazole (XXXII) and its known ready conversion to 4-nitroisothiazole-3-carboxylic acid (XXXIII) prompted the synthesis of 4-aminoisothiazole-3-carboxylic acid by the following route:

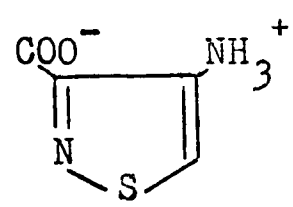


(XXXII) (XXVII) (XXXIII) (XXXIV)

Reaction of 3-methylisothiazole with potassium nitrate in fuming sulphuric acid, as described by Adams and Slack,[6] gave 3-methyl-4--nitroisothiazole (XXVII) in 78% yield. Oxidation of this with chromic acid was reported by Holland and co-workers [23] to give a 43% yield of the crude nitro acid XXXIII. Yields of up to 40% of crude product were obtained following the literature procedure, but the pure compound was obtained in only 25% yield. This reaction, which involved addition of solid chromium trioxide to a stirred solution of the nitro compound in sulphuric acid, proved very sensitive to temperature and rate of addition of chromium trioxide and in one instance the reaction was sufficiently violent to eject the contents of the reaction vessel.

The successful reduction of 4-nitroisothiazole appears to depend on the use of a mild reducing agent; [6,23] its reduction to 4-aminoisothiazole with stannous chloride has been reported to proceed in low yield and this has been attributed to extensive disruption of the isothiazole ring.[112] In view of the success of ferrous sulphate-ammonia as a reducing agent for the preparation of 4-amino-3-methylisothiazole from the corresponding nitro compound as reported by Adams and Slack,[6] it was decided to apply this method to the preparation of 4-aminoisothiazole-3-carboxylic acid.

A hot solution of the 4-nitroisothiazole-3-carboxylic acid and ammonia in ethanol was added to a hot solution of ferrous sulphate. After heating at 75-80° for 30 min, the inorganic materials were separated and the amino acid obtained by ether extraction of the acidified solution. 4-Amino-isothiazole-3-carboxylic acid was obtained in 50% yield as pale yellow needles, m.p. 189-190°. The i.r and n.m.r spectra suggested that this compound was in the zwitterionic form XXXV.



(XXXV)

The infrared spectrum (I.R.16) showed a broad band at 1585 cm^{-1} due to the carboxylate group and a band at 2600 cm^{-1} was assigned to the NH_3^+ group.

A weak band at 2100 cm^{-1} is also characteristic of amino acids in the zwitterionic form. The n.m.r spectrum (N.M.R.26) showed a broad three proton signal at δ 6.63 p.p.m., which was assigned to NH_3^+, and a one proton singlet at δ 7.68 p.p.m. to H-5.

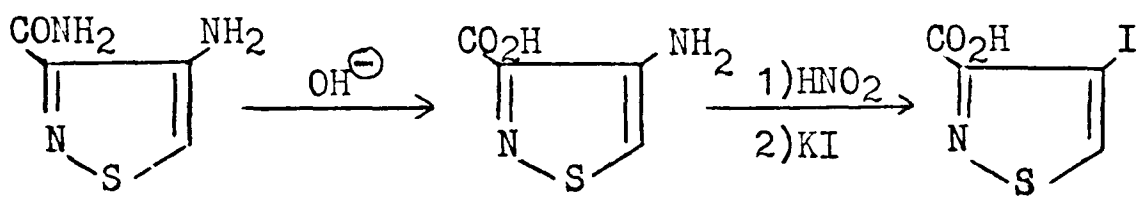
An attempt to obtain a better yield of the amino acid by ferrous sulphate-barium hydroxide reduction gave only a low yield (14%) of 4-aminoisothiazole-3-carboxylic acid. Reaction of 4-nitroisothiazole-3--carboxylic acid with palladium charcoal and sodium borohydride in aqueous methanol gave only a very small amount of material which was shown by t.l.c. to be a mixture of the amino acid and the nitro acid.

Purification by recrystallisation was not successful and this method of reduction was not investigated further.

Hydrolysis of a sample [114] of 4-aminoisothiazole-3-carboxamide (XXXVI) with aqueous sodium hydroxide also gave 4-aminoisothiazole-3-carboxylic acid, in 50% yield, identical in every respect with the compound obtained

by reduction of the nitro acid.

The amino group in 4-aminoisothiazole-3-carboxylic acid was shown to behave normally towards diazotisation. Thus reaction with sodium nitrite in sulphuric acid followed by treatment of the diazonium salt with potassium iodide afforded a 40% yield of 4-iodoisothiazole-3-carboxylic acid (XXXVII) as white needles, m.p. 184-185°.

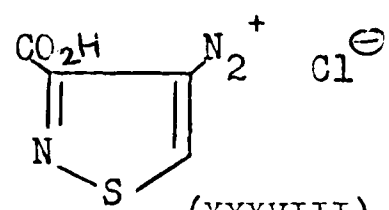


(XXXVI) (XXXIV) (XXXVII)

The convenient method of generating benzyne from benzene diazonium carboxylate hydrochloride and propylene oxide,[57,58] prompted the preparation of 4-isothiazolediazonium-3-carboxylate hydrochloride with a view to similarly generating isothiazolyne. Treatment of 4-aminoisothiazole-3-carboxylic acid in dioxan-methanol with hydrogen chloride and isoamyl nitrite, followed by dilution with dry ether gave 4-isothiazolediazonium-3-carboxylate hydrochloride (XXXVIII) as a white solid, m.p. 163-165° in 63% yield.

The compound decomposed at its melting point; it appeared to be quite stable at room temperature but was nevertheless kept at 0° under nitrogen and used when required.

The i.r. spectrum showed a carbonyl band at 1705 cm^{-1} and a band at 2258 cm^{-1} was assigned to the diazonium group.

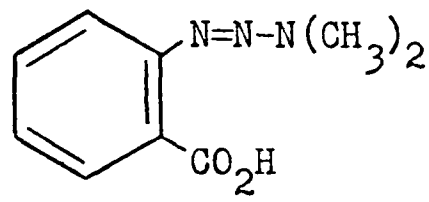


(XXXVIII)

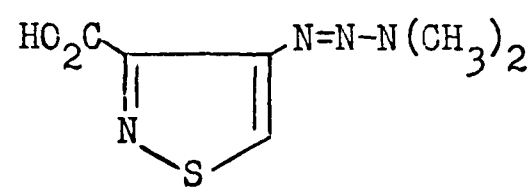
The decomposition products of the salt were investigated by mass spectrometry. A sample was heated at its m.p. and the vapours leaked into

the instrument; ions of m/e values corresponding to carbon dioxide, nitrogen and hydrogen chloride were observed.

As described earlier, the thermal decomposition of 1-(2-carboxyphenyl)-3,3-dimethyltriazene (XXXIX) has been reported to be a convenient way of generating benzyne.[61] A similar route to isothiazolyne was envisaged and an attempt was made to prepare 1-(3-carboxy-4--isothiazolyl)-3,3-dimethyltriazene (XL) from 4-aminoisothiazole-3--carboxylic acid (XXXIV). However, diazotisation of this amino acid followed by addition of dimethylamine and chloroform extraction did not give any of the expected material; under the same conditions, anthranilic acid gave a good yield of the triazene XXXIX.[115]



(XXXIX)

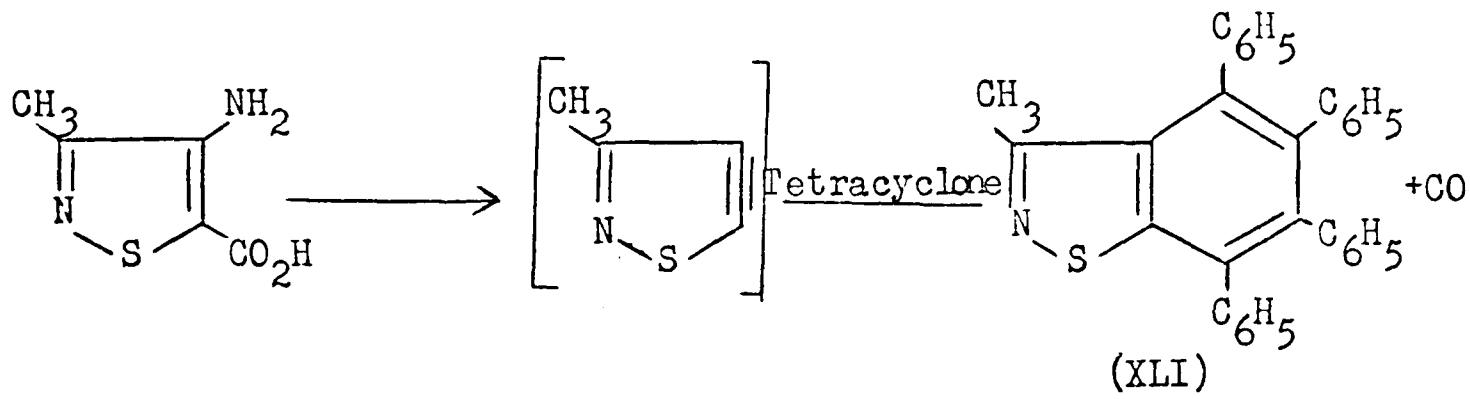


(XL)

Attempted generation of isothiazolynes.

Evidence for the formation of arynes is conveniently obtained by trapping these intermediates with arynophiles. Tetracyclone has been used extensively as an arynophile and disappearance of its purple colour has been regarded as indicative of completion of the reaction.

An isothiazole amino acid e.g. 4-amino-3-methylisothiazole--5-carboxylic acid upon aprotic diazotisation in the presence of tetracyclone would be expected to give adduct XLI if an isothiazolyne intermediate is formed.

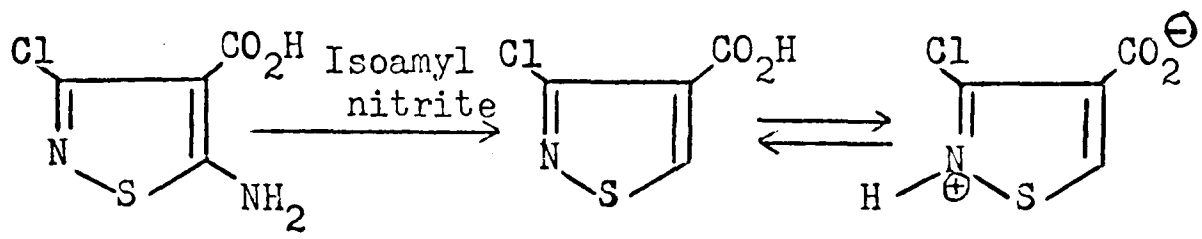


(XLI)

The procedure used in the reactions investigated was essentially the same as that due to Fieser and Haddadin[116] and also Friedman and Logullo[117] in which solutions of the amino acid and isoamyl nitrite are added simultaneously over a period of time to a refluxing solution of the arynophile. In general tetracyclone was used as the trapping agent and in all the experiments carried out the purple colour eventually disappeared; furan and anthracene were used in a few experiments.

Reaction of 5-amino-3-chloroisothiazole-4-carboxylic acid with isoamylnitrite in the presence of tetracyclone.

The reaction of 5-amino-3-chloroisothiazole-4-carboxylic acid with isoamyl nitrite in the presence of tetracyclone gave a mixture of products which was separated into neutral and acidic fractions. The acidic fraction gave a small amount of a compound, m.p. 241-242°. Elemental analysis indicated a molecular formula $C_4H_2NO_2SCl$ and the compound was formulated as 3-chloroisothiazole-5-carboxylic acid (XLII) on the basis of its infrared spectrum which showed typical carboxyl bands at 2900-2520 and 1720 cm^{-1}. The n.m.r. spectrum (N.M.R.26) in deuterodimethylsulphoxide showed two one proton signals; the signal at δ 9.7 p.p.m. was assigned to H-5. The signal at δ 5.58 p.p.m. was at very much higher field than that expected for a carboxyl proton and together with its broad nature suggested that it was attached to nitrogen, i.e. that the compound exists as the zwitterion in the polar n.m.r. solvent.



(XLII)

The neutral fraction gave three compounds which were separated by dry column chromatography on silica gel. Elemental analysis and high resolution mass spectrometry of the first component indicated the molecular formula $C_{28}H_{20}O_2$. The n.m.r. spectrum showed only aromatic protons and the compound was identified as 2-benzoyl-3,4,5-triphenylfuran by comparison (mixed m.p. and i.r. spectrum) with an authentic sample obtained by a two step reaction from tetracyclone.[118]

An uncharacterised compound of the same melting point (167°) and same molecular weight has been reported by Tamura, Miyamoto and Ikeda[76] in their investigation of the reaction of 5-amino-2-methylthiazole-5-carboxylic acid with amyl nitrite in the presence of tetracyclone. No spectral data was reported but it would appear from the foregoing observations that the compound is 2-benzoyl-3,4,5-triphenylfuran (XLIII).

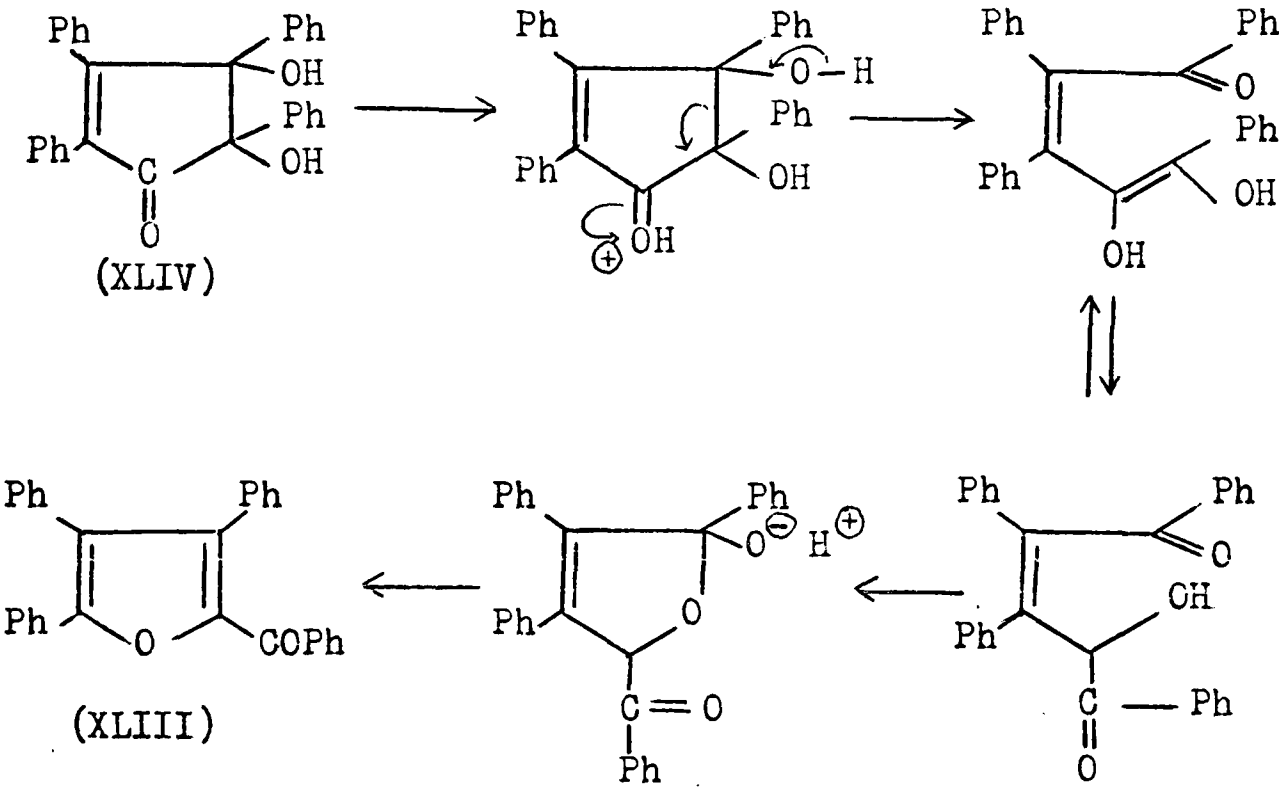
A second component, m.p. 189-191°, from the neutral fraction had a molecular formula $C_{29}H_{22}O_3$ by elemental analysis and by mass spectrometry and was characterised as 2,3-dihydroxy-2,3,4,5-tetraphenylcyclopent-4-enone (XLIV) by comparison of its infrared spectrum, mixed m.p. and t.l.c. with an authentic sample prepared by nitric acid oxidation of tetracyclone as described by Dilthey and co-workers.[118]

The third compound isolated was found by elemental analysis to have the molecular formula $(C_{12}H_8O)_n$. The infrared spectrum showed a hydroxyl band at 3400 cm^{-1} and a carbonyl band at 1710 cm^{-1}. The n.m.r. spectrum showed only signals in the aromatic region and as the compound was believed

to be another tetracyclone oxidation product it was not further investigated.

No basic material was obtained from the reaction and no other product was isolated.

2-Benzoyl-3,4,5-triphenylfuran was prepared from XLIV by boiling with alcoholic potassium hydroxide as described by Dilthey and co-workers. Yates and Stout[119] reported that this conversion was catalysed by both acid and base and proposed the following mechanism for this transformation. Presumably the furan arises from the dihydroxy-compound XLIV in a similar way in the above reaction.



Reaction of 4-amino-3-methylisothiazole-5-carboxylic acid with isoamyl nitrite in the presence of (a) tetracyclone, (b) furan and (c) anthracene.

4-Amino-3-methylisothiazole-5-carboxylic acid was considered to be the most likely of the three amino acids investigated to give an isothiazolyne. The amino group in the 4-position of isothiazoles behaves like a normal aromatic amine and diazotises readily and the carboxyl group in the 5-position is known to be lost readily under appropriate conditions.

(a) With tetracyclone

Reaction of 4-amino-3-methylisothiazole-5-carboxylic acid with isoamyl nitrite in the presence of tetracyclone gave a mixture of at least five components which were separated with difficulty, by dry column chromatography and by preparative t.l.c. The only isothiazole isolated proved to be 3-methyl-4-nitroisothiazole. The compound was obtained in poor yield and was identified by comparison with an authentic sample. The formation of this compound parallels the observation by Tamura and co-workers[76] of the formation of 2-methyl-4-nitrothiazole in the reaction of 5-amino-2-methylthiazole-4-carboxylic acid with amyl nitrite in the presence of furan.

Three of the four compounds isolated from the neutral fraction were identical in every respect with the compounds isolated in the previous trapping experiments viz. 2-benzoyl-3,4,5-triphenylfuran, 2,3-dihydroxy-2,3,4,5-tetraphenylcyclopent-4-enone and the compound of molecular formula $(C_{12}H_8O)_n$.

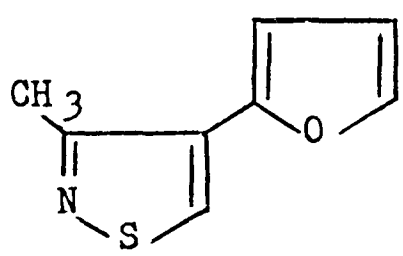
Elemental analysis on the fourth compound gave a molecular formula $(C_6H_6O)_n$. The infrared spectrum showed a hydroxyl band at 3420 cm^{-1} and a carbonyl band at 1750 cm^{-1}. A complete characterisation of this compound was not attempted as it is believed to be another tetracyclone oxidation product.

(b) With furan

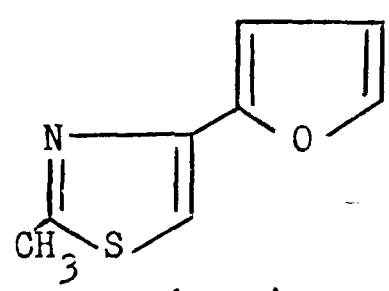
The reaction of 4-amino-3-methylisothiazole-5-carboxylic acid with isoamyl nitrite in the presence of furan gave only one isolable product. A substantial amount of oily product obtained from the acidic fraction could not be crystallised and was not further investigated. The neutral component was obtained by preparative t.l.c; it showed one peak on g.l.c. at R_t 3.8 min and was homogeneous by t.l.c. The molecular formula obtained by high resolution mass spectrometry was C_8H_7NOS and suggested that addition of one furan molecule to the isothiazole system had occurred.

The n.m.r. spectrum (N.M.R.28) showed a three proton singlet at δ 2.66, a two proton multiplet at δ 6.55, a one proton multiplet at δ 7.5 and a one proton singlet at δ 8.73 p.p.m. which was assigned to H-5 of the isothiazole ring. On this data the compound was formulated at 4-(2'-furyl)-3-methylisothiazole (XLV).

A similar type of product, XLVI, was reported formed in the reaction of 5-amino-2-methylthiazole-4-carboxylic acid with amyl nitrite in the presence of furan.[76]



(XLV)



(XLVI)

(c) With anthracene

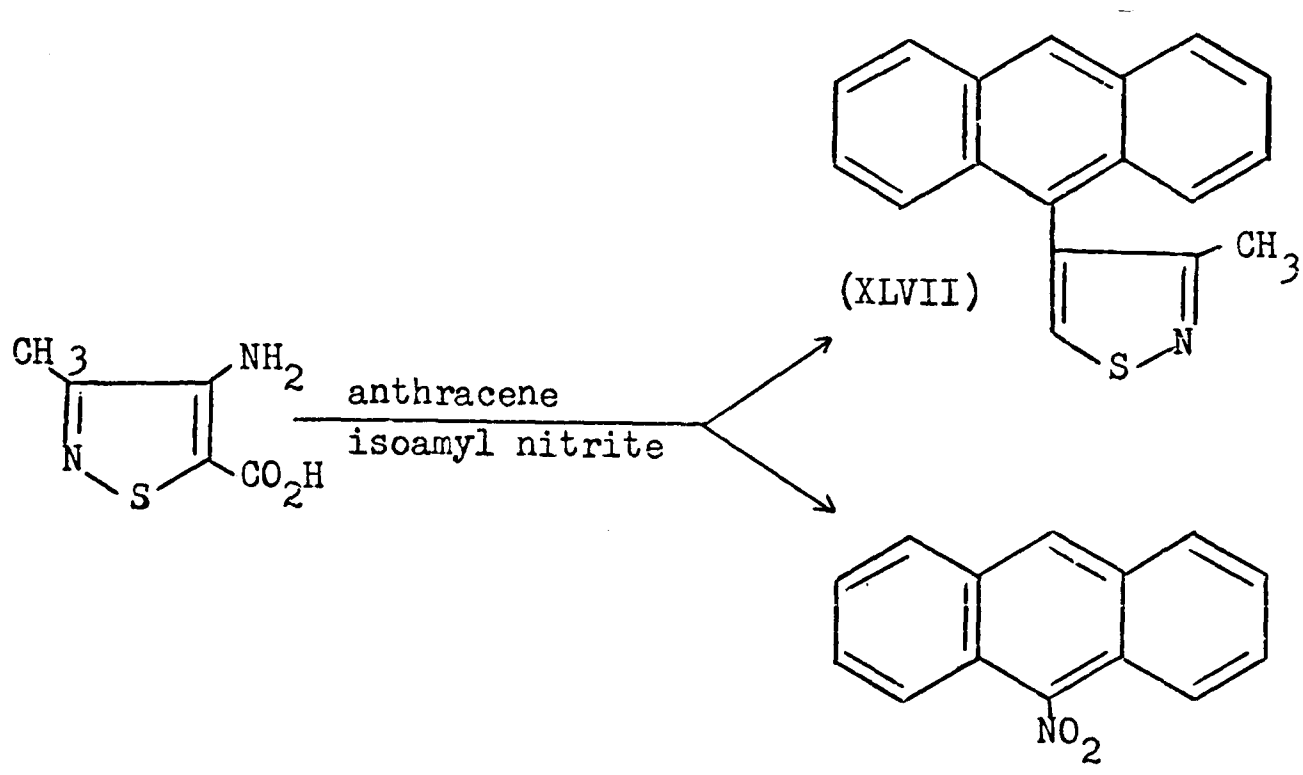
The reaction of 4-amino-3-methylisothiazole-5-carboxylic acid with isoamyl nitrite in the presence of anthracene was subsequently investigated as this arynophile has been quite successful in trapping experiments with benzyne intermediates. In addition there would be little or no possibility of oxidation of the arynophile occurring as with tetracyclone.

The acidic fraction consisted of a small amount of brown gum and no basic material was obtained.

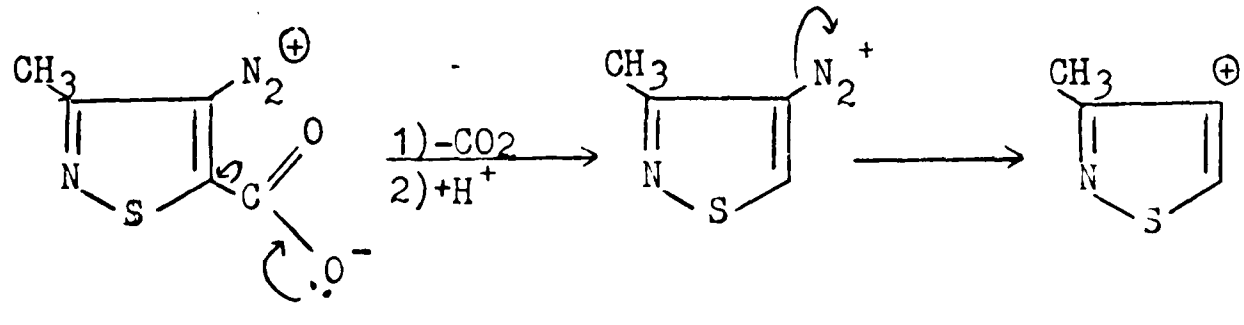
Chromatography of the neutral material gave a small amount of a yellow crystalline solid, m.p. 145-146° and a very small amount of a pale yellow compound, m.p. 225-227°. High resolution mass spectrometry of the lower melting compound indicated a molecular formula $C_{14}H_9NO_2$. The n.m.r. spectrum (N.M.R.29) showed a one proton singlet at δ 8.44 p.p.m. and two four proton multiplets between δ 7.27-8.06 p.p.m. which indicated a monosubstituted anthracene. The compound was characterised as 9-nitro anthracene on the basis of its melting point and the infrared spectrum which showed a nitro band at 1570 cm^{-1}. A similar nitration of anthracene

has been reported by Bird and Wong[77] in investigations on the attempted generation of thiadiazolyne from 3-amino-1,2,5-thiadiazole-4-carboxylic acid by its aprotic diazotisation in the presence of anthracene.

The molecular formula of the higher melting compound, obtained by high resolution mass spectrometry, was $C_{18}H_{13}NS$ and indicated an isothiazolyl substituted anthracene; the compound was formulated as 9-(3-methyl-4-isothiazolyl) anthracene (XLVII), rather than the isothiazolyne-anthracene adduct, on the basis of the similarity of its ultraviolet spectrum (U.V.12) to that of 9-nitroanthracene (U.V.11). The small amount of material did not allow further study.



The formation of the above compound and also the isothiazolyl-furan XLV suggested that decarboxylation of the diazonium carboxylate occurred followed by protonation and subsequent loss of nitrogen from the diazonium compound to give an electrophilic species which then attacks the anthracene and the furan in the usual way.



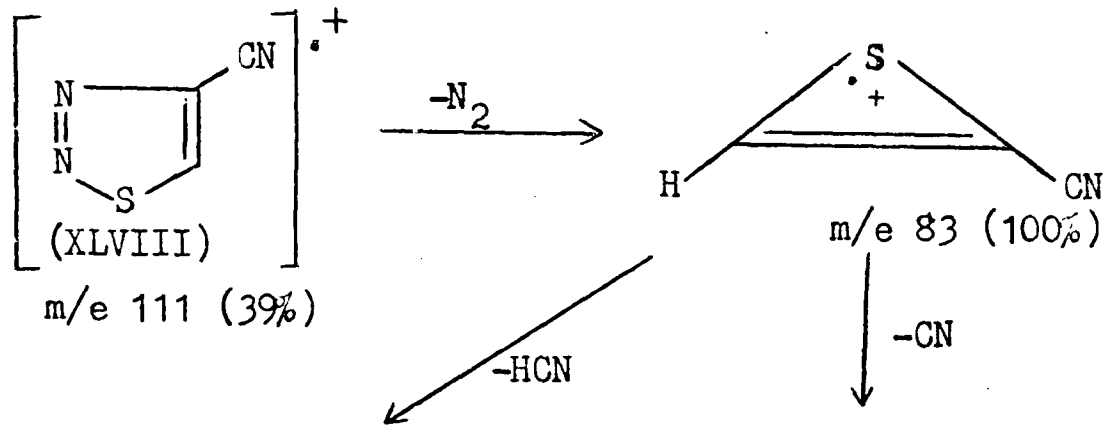
Reaction of 4-aminoisothiazole-3-carboxylic acid with isoamyl nitrite in the presence of tetracyclone.

4-Aminoisothiazole-3-carboxylic acid and isoamyl nitrite in the presence of tetracyclone gave a complex mixture of products as indicated by t.l.c. The acidic fraction gave a compound, m.p. 133-135°; its n.m.r. spectrum showed a one proton singlet at δ 9.01 and two one proton doublets centered at δ 7.89 and 9.15 p.p.m. The compound was characterised as isothiazole-3-carboxylic acid by comparison (mixed m.p. and i.r.) with an authentic sample.[114]

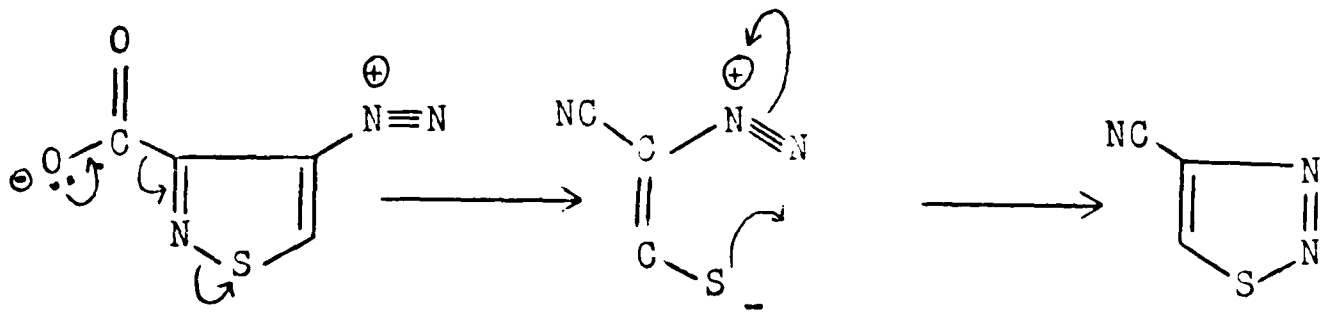
Four compounds isolated by dry column chromatography of the neutral fraction were identical in every respect with those obtained in the previous trapping experiments. Two were characterised as 2-benzoyl-3,4,5-triphenylfuran and 2,3-dihydroxy-2,3,4,5-tetraphenylcyclopent-4-enone and the others had molecular formulae $(C_{12}H_8O)_n$ and $(C_6H_6O)_n$.

In an alternative approach to 3,4-isothiazolyne,4-isothiazolediazonium-3-carboxylate hydrochloride was heated under reflux with propylene oxide in the presence of furan. A small amount of oil was obtained from the acidic fraction, it could not be crystallised and was not further investigated. A very small amount of a compound, m.p. 60-61°, was isolated from the neutral fraction by preparative t.l.c. and purified by recrystallisation from light petroleum. The molecular formula obtained by high resolution mass spectrometry was C_3HN_3S. The infrared spectrum showed the presence of nitrile group at 2240 cm^{-1}; the n.m.r. spectrum (N.M.R.30) showed only a singlet at δ 9.2 p.p.m. The compound was formulated as 4-cyano-1,2,3-thiadiazole (XLVIII) on the basis of the foregoing data and its mass spectrum; in addition to the molecular ion at m/e 111, major fragments were noted at m/e 83, 57 and 56 which were consistent with the scheme shown below. Loss of nitrogen to give the base peak at m/e 83 is consistent with the known fragmentation of 1,2,3-

thiadiazoles.[120] Fragmentation corresponded with that quoted for 4-cyano-1,2,3-thiadiazole reported by Millard and Pain [121] except that the peak intensities were different and this is no doubt due to the different source temperatures used; these authors determined the spectrum at 200° source temperature, whereas the intensities quoted here were determined at 100°. The structure was confirmed by comparison (mixed m.p. and i.r.) with an authentic sample.[122]



A similar rearrangement of an isothiazole to a thiadiazole has been reported by Lee and Volpp [123] who found that diazotisation of 4-amino-3-methylisothiazole in the presence of thiourea gave 4-acetyl-1,2,3-thiadiazole. It was suggested, in their proposed mechanism, that the sulphur of the thiadiazole came from the thiourea. A possible mechanism for the above rearrangement is shown below, involving loss of carbon dioxide with simultaneous ring cleavage followed by ring closure.



The studies with tetracyclone as trapping agent were complicated by the formation of its oxidation products. In one experiment tetracyclone was heated with isoamyl nitrite and a trace of trichloroacetic acid in 1,2-dimethoxyethane, the colour of the ketone disappeared with time and a substantial amount of 2,3-dihydroxy-2,3,4,5-tetraphenylcyclopent-4-enone was isolated. The reactions with anthracene and furan proved more informative. Nevertheless it would appear from the results of these experiments that isothiazolynes are not formed as intermediate capable of being trapped under the conditions described in these investigations.

General Techniques

Infrared (i.r.) spectra were determined in potassium bromide discs, unless otherwise specified, using a Perkin Elmer 257 or a Perkin Elmer 337 spectrophotometer. Ultraviolet (U.V.) spectra were recorded in absolute ethanol on a Unicam S.P. 800 spectrophotometer.

Nuclear magnetic resonance (n.m.r.) spectra were obtained for the appropriate compounds in the solvents indicated on Varian A60 (60MHz) and HA-100D (100 MHz) spectrometers as indicated, with tetramethyl silane as internal standard. The 100 MHz spectra and also mass spectra, determined on an AEI MS902 Spectrometer, were obtained through the Physico-Chemical Measurements Unit at Harwell and Aldermaston. Microanalyses were carried out by the Microanalytical Division of May and Baker Ltd. Dagenham.

Thin layer chromatography (t.l.c.) was carried out on Silica gel HF_{254} (0.25 mm) with the solvents as indicated; the components were detected with iodine or U.V. light. Melting points were determined on a Kofler block (Reichert).

1,2-Dimethoxyethane was distilled and kept over molecular sieve 'type 4A'. Isoamyl nitrite was distilled before use.

Light petroleum refers to the fraction b.p. 60-80° unless otherwise stated.

5-Amino-3-methylisothiazole was purified by passing a solution of the crude amine in ether through a thick pad of alumina (Spence, type H) and eluting with ether. Dry hydrogen chloride was passed through the ethereal solution and the precipitated hydrochloride collected. Treatment of the salt with aqueous sodium hydroxide and continuous ether extraction followed by evaporation of the dried extract gave the amine (pure by g.l.c. and t.l.c.) in about 80% yield.

3-Methylisothiazole and 5-amino-3-methylisothiazole were kindly supplied by May and Baker Ltd.

I ISOTHIAZOLO[5,4-b]PYRIDINES

Skraup synthesis of Alkylisothiazolo[5,4-b]pyridines

Preparation of "sulphomix"[80]

Nitrobenzene (49.25 g) was added to stirred fuming sulphuric acid (20%, 220 g) at 25-30°. The mixture was heated to 60-70° until a sample was completely soluble in water (about 10 h).

3,6-Dimethylisothiazolo[5,4-b]pyridine

Method (a) Water (45 ml) was added to a chilled, vigorously stirred mixture of sulphomix (117 g) and 5-amino-3-methylisothiazole (9.12 g, 0.08 mol) at such a rate that the temperature did not rise above 35°. The stirred mixture was then heated to 75-80° and redistilled crotonaldehyde (7.0 g, 0.10 mol) was added dropwise over 30 min, whilst the temperature was kept below 90°. The mixture was heated for 45 min at 95-100°, cooled to room temperature and poured onto ice (200 g). The pH was adjusted to 11-12 with 50% aqueous sodium hydroxide; the mixture became very hot and was cooled to 35-40°. A strong smell of ammonia was detected during the basification. Steam distillation of the resultant dark mixture followed by saturation of the distillate (1.6 L) with sodium chloride and continuous ether extraction of the aqueous solution for 48 h gave a gummy solid (2.68 g) after evaporation of the dried (K_2CO_3) extract. Recrystallisation from light petroleum (charcoal) gave 3,6-dimethylisothiazolo[5,4-b]pyridine (2.45 g, 18.5%) as colourless needles, m.p. 92-93°. (Found: C, 58.4; H, 4.76; N, 17.0; S, 19.6. $C_8H_8N_2S$ requires: C,58.5; H, 4.91; N, 1706; S, 19.52%). λ max. (U.V.1) 234 (ε 26,600), 300 nm (5,160). ν max. 990, 870, 835, 820, 780, 750, 725 cm^{-1}. δ ($CDCl_3$, N.M.R 1) 2.69 (3H, s, CH_3-3 or CH_3-6), 2.71 (3H, s, CH_3-6 or CH_3-3), 7.23 (1H, d, J 8.5 Hz, H-5), 8.1 (1H, d, J 8.5 Hz, H-4) p.p.m.

When the reaction was carried out as above except that the mixture

was heated at 80-90° for the last 45 min, the yield was 10%; at 110-120° no product was obtained.

Method (b) To a vigorously stirred mixture of 5-amino-3--methylisothiazole (4.0 g, 0.035 mol), sodium m-nitrobenzenesulphonate (17.5 g, 0.078 mol) and water (22.5 ml) was added concentrated sulphuric acid (41 g), with cooling to 35-40°, over a period of 25 min. The mixture was heated to 75-80° and crotonaldehyde (2.45 g, 0.035 mol) was added dropwise over a period of 30 min whilst the temperature was kept at 80-85°. The mixture was then heated for a further 30 min at 95-100°. The cooled, black viscous product was poured on to ice-water (100 g) and basified to pH 11-13 with 50% sodium hydroxide solution with cooling to 30-35°; strong evolution of ammonia was detected. The resulting solution was steam distilled and the distillate (1.5 L) saturated with sodium chloride and continuously extracted with ether for 36 h. Evaporation of the dried ($Mg\ SO_4$) extract gave needles (1.10 g, 19%), m.p. 84-89°. Recrystallisation from light petroleum (charcoal) gave pale yellow needles (1.0g, 17.5%) ,m.p. 92-93° of 3,6-dimethylisothiazolo[5,4-b]pyridine; identical (mixed m.p, t.l.c) with the material prepared by the above method.

3,6-Dimethylisothiazolo[5,4-b]pyridine picrate

To a solution of 3,6-dimethylisothiazolo[5,4-b]pyridine (100 mg) in absolute alcohol (2 ml) was added a saturated solution (5 ml) of picric acid in ethanol. The yellow precipitate (210 mg), m.p. 150-152° was recrystallised from ethanol to give the picrate (160 mg), m.p. 152-153°, as yellow plates. (Found: C, 42.6; H,2.77; N,18.0; S, 8.2. $C_{14}H_{11}N_5O_7S$ requires C, 42.75; H, 2.82; N, 17.81; S, 8.15%).

3-Methylisothiazolo[5,4-b]pyridine

Method (a) Glycerol (31.5 g, 0.34 mol) was added dropwise, with cooling, to stirred sulphomix (117 g). 5-Amino-3-methylisothiazole

(9.12 g, 0.08 mol) was then added followed by water (45 ml), dropwise and with cooling. The mixture was stirred at room temperature for 30 min and then heated at 110-115° for 3.5 h. The black viscous mixture was cooled to room temperature and poured onto ice (200 g). The pH of the solution was adjusted to 12-13, with cooling to 35-40°, with 50% aqueous sodium hydroxide, when a strong smell of ammonia was detected. Steam distillation of the basic solution followed by continuous ether extraction of the distillate (1.6 L) for 38 h gave, after evaporation of the dried (K_2CO_3) extract, off-white plates (3.3 g, 27.5%), m.p. 78-82°. Recrystallisation from light petroleum gave 3-methylisothiazolo[5,4-b]pyridine (3.1 g, 26%) as colourless plates, m.p. 84-85°. (Found: C, 55.6; H, 4.0; N, 18.7; S, 21.6. $C_6H_7N_2S$ requires C, 55.97; H, 4.027: N, 18.65; S, 21.35%). λ max. 232 (ε26,000), 302 nm (5,390). ν max. 995, 800, 770, 750, 705 cm^{-1}. δ ($CDCl_3$, N.M.R 2) 2.68 (3H, s, H-3) 7.32 (1H, dd, J_{54} 8.3 Hz, J_{56} 4.8 Hz, H-5), 8.17 (1H, dd, J_{45} 8.3 Hz, J_{46} 1.8 Hz, H-4), 8.70 (1H,dd, J_{65} 4.8 Hz, J_{64} 1.8 Hz, H-6) p.p.m.

Method (b) To a vigorously stirred mixture of 5-amino-3--methylisothiazole (9.12 g, 0.08 mol), sodium m-nitrobenzenesulphonate (35 g, 0.155 mol), water (45 ml), and glycerol (31.5 g, 0.34 mol) was added concentrated sulphuric acid (82 g) at such a rate that the temperature did not rise above 40°; cooling in a freezing mixture was required. The resulting reddish brown mixture was heated at 120-125° for 3.5 h and then cooled to room temperature and poured onto ice (200 g). The solution was basified to pH 12-13 with 50% aqueous sodium hydroxide, with cooling to 20-30°; strong evolution of ammonia was detected. The resultant dark brown suspension was steam distilled until a portion gave no precipitate with aqueous picric acid on standing. The distillate (2 L) was saturated with sodium chloride and continuously extracted with ether for 36 h. The dried (K_2CO_3) ethereal extract upon evaporation gave a pale yellow solid

(1.86 g, 15.5%), m.p. 74-80°. Recrystallisation from light petroleum (charcoal) gave 3-methylisothiazolo[5,4-b]pyridine (1.62 g, 13.5 %) as colourless plates, m.p. 84-85°; identical (t.l.c and mixed m.p.) with the compound obtained above.

Method (c) A stirred mixture of 5-amino-3-methylisothiazole (456 g, 0.04 mol) and arsenic acid (11.36 g, 0.08 mol) in 85% phosphoric acid (80 ml) was heated to 100° and acrolein (3.4 g, 0.06 mol) added dropwise over 25 min. such that the temperature was kept at 100±2°. After the last addition, heating was continued for another 30 min at 100°. The cooled black mixture was poured into water (200 ml) and basified to pH 10-11 with 50% aqueous sodium hydroxide. Steam distillation followed by continuous ether extraction of the distillate (1L) gave a pale yellow solid (0.39 g) m.p. 72-81°. Recrystallisation from light petroleum gave 3-methylisothiazolo[5,4-b]pyridine (0.3 g, 5%) as colourless plates, m.p. 84-85°, identical (t.l.c and mixed m.p.) with the compound prepared above.

3-Methylisothiazolo[5,4-b]pyridine picrate

3-Methylisothiazolo[5,4-b]pyridine (100 mg) was dissolved in absolute alcohol (2 ml) and a saturated solution (5ml) of picric acid in ethanol added. The yellow precipitate was collected (162 mg), m.p. 168-171°. Recrystallisation from ethanol give the picrate (112 mg) as yellow plates, m.p. 170-172°. (Found: C, 41.0; H, 2.4; N, 18.2; S, 8.5. $C_{13}H_9N_5O_7S$ requires: C, 41.14; H, 2.39; N, 18.46; S, 8.45%).

3,4-Dimethylisothiazolo[5,4-b]pyridine

Method (a) To a vigorously stirred mixture of sodium m-nitrobenzene-sulphonate (17.5 g, 0.078 mol) in water (22.5 ml) was added concentrated sulphuric acid (41 ml) with cooling to 25-30°. 5-Amino-3-methylisothiazole (4.56 g, 0.04 mol) was added to the mixture which was then stirred at room

temperature for 30 min. It was then heated to 75° and methyl vinyl ketone (2.8 g, 0.04 mol) added over 20 min, the temperature being kept between 75-80°. The stirred mixture was heated for a further 35 min at 80-85° and allowed to stand overnight at room temperature. The cold mixture was poured onto ice (200 g) and basified with 50% aqueous sodium hydroxide. Steam distillation followed by continuous ether extraction of the distillate (IL) for 36 h gave, after evaporation of the dried ($MgSO_4$) extract, a yellow gummy solid (842 mg). T.l.c. of the crude product showed some starting material. The crude product was dissolved in dilute hydrochloric acid (3 ml, 2.5 N) and treated with excess aqueous sodium nitrite at 10-15° after which the mixture was heated on a water bath (70°) for 20 min. The solution was basified to pH 10-11 with dilute sodium hydroxide solution and continuously extracted with ether for 36 h. Evaporation of the dried ($MgSO_4$) extract gave a yellow gummy solid (324 mg). On standing in a small amount of acetone 3,4-dimethylisothiazolo[5,4-b]-pyridine separated, in two crops, as colourless needles (211 mg, 2.6%), m.p. 139-140°. (Found: C, 58.5; H, 5.0; N, 17.0. $C_8H_8N_2S$ requires: C, 58.5; H, 4.91; N, 17.06%). λmax. 230 (ε 27,000), and 302 nm (ε 6,200). ν max. 1000, 910, 845, 805, 780 cm^{-1}. δ ($CDCl_3$, N.M.R 3) 2.78 (3H, d, J_{45} 0.8 Hz, CH_3-4) 2.88 (3H, s, CH_3-3), 7.05 (1H, dd, J 0.8 Hz, J_{56} 5 Hz, H-5), 8.51 (1H, d, J_{65} 5 Hz, H-6) p.p.m.

Method (b) Water (22.5 ml) was added to chilled vigorously stirred sulphomix (58.5 g) at such a rate that the temperature did not rise above 35°. 5-Amino-3-methylisothiazole (4.6 g, 0.04 mol) was added and the mixture heated to 75-80°. Methyl vinyl ketone (2.8 g, 0.04 mol) was added over 15 min, the temperature being kept between 75-80°. The stirred mixture was heated for a further 30 min at 80-85°, cooledto room temperature and then poured into ice-water (150 g). The mixture was basified with 50% aqueous sodium hydroxide and steam distilled. The distillate (1.6 L)

was saturated with sodium chloride and continuously extracted with ether for 36 h. Evaporation of the dried ($MgSO_4$) extract gave a yellow gummy solid (360 mg); t.l.c showed mainly one component. Crystallisation from acetone gave 3,4-dimethylisothiazolo[5,4-b]pyridine (222 mg, 3.4 %) as pale yellow needles m.p. 139-140°, identical (mixed m.p. and t.l.c) with the compound prepared above.

Method (C) A stirred mixture of 3-methyl-5-aminoisothiazole hydrochloride (5.7 g, 0.05 mol), hydrated ferric chloride (21.6 g, 0.08 mol) and anhydrous zinc chloride (0.8 g) in 95 % ethanol (40 ml) was heated on a steam bath to 70-75°. Methyl vinyl ketone (3.0 g, 0.046 mol) was added over 45 min, the stirred mixture heated under reflux for 2 h then kept overnight at room temperature. The alcohol was evaporated under reduced pressure and the residue basified to pH 10-11 with 50% aqueous sodium hydroxide. Steam distillation followed by continuous ether extraction of the distillate (IL) for 24 h gave, upon evaporation of the dried ($MgSO_4$) extract, a pale yellow gummy solid (150 mg). Recrystallisation from acetone-light petroleum (b.p. 40-60°) gave an off-white solid (84 mg, 1.05%) m.p. 128-135°. Recrystallisation from acetone gave white needles (50 mg, 0.6 %), m.p. 138-139°. A second crop (12 mg), m.p. 136-138° was obtained. The compound was identical (mixed m.p. and t.l.c) with 3,4-dimethylisothiazolo[5,4-b]pyridine prepared as above.

3,4-Dimethylisothiazolo[5,4-b]pyridine picrate

To a solution of 3,4-dimethylisothiazolo[5,4-b]pyridine (50 mg) in dilute hydrochloric acid (2.5 N, 5 ml) was added a saturated solution of picric acid (4.0 ml) in water at room temperature. The yellow precipitate (61 mg), m.p. 130-146 (decomposition) was recrystallised from ethanol to give the picrate (42 mg) as yellow plates, m.p. 173-176° (decomposition). (Found: C, 42.6; H, 2.82; N, 17.6; S, 8.2. $C_{14}H_{11}N_5O_7S$ requires: C, 42.75; H, 2.82; N, 17.81; S, 8.15%).

5-Ethyl-3-methylisothiazolo[5,4-b]pyridine (as its picrate)

Sulphomix (58.5 g) was diluted with water (22.5 ml) with stirring and cooling to 25-30°. 5-Amino-3-methylisothiazole (4.56 g, 0.04 mol) was added and the stirred mixture heated to 90-95°, 2-(Hydroxymethyl)-2--methylpropane-1,3-diol (14.4 g, 0.12 mol) was added over 30 min and the mixture heated to 110-115° for 3 h. The cold solution was poured onto ice (200 g) and basified with 50% sodium hydroxide solution to pH 11-12. Steam distillation, followed by continuous ether extraction of the distillate (IL) for 24 h gave, after evaporation of the dried ($MgSO_4$) extract, a yellow oil (325 mg). The crude product showed one major spot on t.l.c; attempts at crystallisation were unsuccessful.

The oil was dissolved in absolute alcohol and a saturated solution of picric acid in ethanol was added. The yellow precipitate (286 mg) was recrystallised from ethanol to give yellow plates (218 mg), m.p. 128-130° of 5-ethyl-3-methylisothiazolo[5,4-b]pyridine picrate. (Found: C, 44.0; H, 3.0; N, 17.0; S, 8.1. $C_{15}H_{13}N_5O_7S$ requires: C, 44.22; H, 3.2; N, 17.19; S, 7.9%). δ (DMSO d_6, N.M.R 4) 1.33 (3H, t, J 7 Hz, $-CH_2\ \underline{CH_3}$), 2.75 (3H, s, H-3), 2.88 (2H, q, J 7 Hz, $-\underline{CH_2}\ CH_3$), 5.8 (1H, broad s, -OH), 8.43 (1H, d, $J_{4,6}$ 2 Hz, H-4), 8.79 (1H, d, $J_{6,4}$ 2 Hz, H-6), 8.66 (2H, s, aromatic H's) p.p.m.

A sample of the picrate was dissolved in sodium hydroxide solution (2 ml, 2.5N) and extracted with chloroform; the concentrated extract showed only one spot, corresponding to the free base, on t.l.c. Evaporation and trituration with acetone gave a small amount of the solid base, m.p. 124-130°; details of the rather poor n.m.r. spectrum are recorded in Table I in the Discussion.

Attempted preparation of 5-ethyl-3-methylisothiazolo[5,4-b]pyridine

A mixture of ferrous sulphate ($FeSO_4.7H_2O$, 0.6 g), arsenic pentoxide (7 g, 0.03 mol), 5-amino-3-methylisothiazole (5.7 g, 0.05 mol), boric acid

(3.1 g, 0.05 mol), 2-(hydroxymethyl)-2-methylpropane-1,3-diol (18 g, 0.15 mol) and concentrated sulphuric acid (28 ml) was heated to 150° with vigorous stirring. Between 145-150° the reaction mixture went completely black and at 150° a vigorous reaction occurred. The heating was stopped and resumed when the reaction had subsided and the temperature maintained at 128-130° for 3h. The dark gummy product was poured onto ice (200 g) and basified to pH 10-11 with 50% sodium hydroxide solution. The aqueous solution was steam distilled and portions of the distillate tested with picric acid in water gave no picrate. Continuous ether extraction of the aqueous solution (1.8 L) for 32 h gave upon evaporation of the dried (K_2CO_3) extract a brown oil (0.2 g), t.l.c of which showed a mixture of at least five components. Picric acid in ethanol was added and the solution allowed to stand for 4 weeks, however no crystalline material was obtained.

Investigation of the reactions of 3-methyl-and 3,6-dimethylisothiazolo[5,4-b]pyridine.

Attempted bromination of 3-methylisothiazolo[5,4-b]pyridine

(a) With bromine in carbon tetrachloride

Bromine (1.08 g, 6 m mol) in carbon tetrachloride (5 ml) was added to a vigorously stirred solution of 3-methylisothiazolo[5,4-b]pyridine (0.57 g, 5 mmol) in carbon tetrachloride (5 ml) and the mixture was refluxed for 1 h. Pyridine (0.40 g, 5 mmol) in carbon tetrachloride (5 ml) was added over 45 min to the refluxing solution and the mixture heated for an additional 6 h. The mixture was allowed to stand overnight at room temperature and then filtered from a small amount of brown solid. Evaporation of the organic solvent gave a yellow gummy solid (522 mg) the R_f of which was the same as that of starting material. Recrystallisation from light petroleum gave 3-methylisothiazolo[5,4-b]pyridine (500 mg), m.p. 83-85°, mixed m.p. 83-85°. A small amount of a yellow gummy solid (14 mg), insoluble in light petroleum, but soluble in ethanol, was isolated during recrystallisation; sodium fusion showed the absence of bromine.

(b) With bromine in chloroform

A stirred solution of 3-methylisothiazolo[5,4-b]pyridine (0.46 g, 3.1 mmol) in chloroform (3 ml) was treated dropwise with a solution of bromine (0.1 ml) in chloroform (3 ml). The red solution was stirred at room temperature for 2 h then diluted with light petroleum and allowed to stand for 3 h when a yellow solid (0.21 g) separated. Part of the material melted at 76-84° leaving needles which sublimed at 160-163°. On further standing, another 132 mg of product was obtained. The crude product was treated with acetone and filtered from a white solid (144 mg) which sublimed at 163-165°. Purification by sublimation at 100-105°/0.2 mmHg gave 3-methylisothiazolo[5,4-b]pyridine hydrobromide (112 mg, 16.5%) as white needles subliming at 163-165°. (Found: C, 36.1; H, 2.67; N, 11.9; S, 14.0; Br, 34.9. $C_7H_7N_2SBr$ requires C, 36.38; H, 3.05; N, 12.12; S, 13.87; Br, 34.57%).

Evaporation of the acetone liquors gave a solid (300 mg) m.p. 76-84°, t.l.c. of which showed the presence of starting material only. Recrystallisation from light petroleum gave 3-methylisothiazolo[5,4-b]-pyridine (217 mg) as needles, m.p. 83-85°, mixed m.p. 83-84°.

Attempted nitration of 3-methylisothiazolo[5,4-b]pyridine

3-Methylisothiazolo[5,4-b]pyridine (0.5 g, 3.3 mmol) was dissolved in fuming sulphuric acid (3 ml, 20%) with cooling to 30-35°. Potassium nitrate (0.33 g) was added in small portions and the mixture set aside for 48 h at room temperature. The mixture was then heated on a steam bath for 7 h, cooled, and poured onto ice (15 g). The yellow solution was basified to pH 8-9 with sodium carbonate and the pale yellow solid which separated was washed with water and dried. The material (100 mg), m.p. 81-85°, was found to be starting material by t.l.c.

The aqueous solution was continuously extracted with chloroform for 24 h. Evaporation of the dried (K_2CO_3) extract gave a gummy solid (325 mg), t.l.c of which showed it to be mainly starting material. Recrystallisation of the combined solids from light petroleum gave 3-methylisothiazolo-[5,4-b]pyridine (361 mg) as needles, m.p. 83-85°, undepressed on admixture with starting material.

Attempted nitration of 3,6-dimethylisothiazolo[5,4-b]pyridine

(a) 3,6-Dimethylisothiazolo[5,4-b]pyridine (0.5 g) was dissolved in concentrated nitric acid (5.0 ml) and fuming sulphuric acid (20%, 5 ml) was added portionwise with swirling and cooling to 20-25°. The mixture was kept at room temperature for 30 min then heated at 75-80° for 1.5 h, cooled and poured onto ice (20 g) giving a dark green solution which gradually became yellow. Basification with saturated aqueous sodium carbonate and extraction with ether (3x30 ml) followed by evaporation of the dried ($MgSO_4$) extract gave no residue.

The aqueous solution was evaporated to dryness and the yellow residue extracted with boiling ethanol (20 ml); evaporation of the extract gave no material. The yellow residue was dissolved in water, acidified to pH 2-3 and continuously extracted with ether for 18 h. Evaporation gave a yellow gum (25 mg) which could not be crystallised.

(b) 3,6-Dimethylisothiazolo[5,4-b]pyridine (300 mg) was dissolved in concentrated sulphuric acid (2 ml) and treated portionwise with potassium nitrate (0.204 g). The mixture was heated on a steam bath for 1 h and the cooled solution poured onto ice (10 g); no solid separated. The acid solution was treated with solid potassium carbonate to pH 9-10, water was added to dissolve the inorganic salts and the solution continuously extracted with chloroform for 28 h. Evaporation of the dried ($MgSO_4$) extract gave a white solid (282 mg), m.p. 89-91°. Recrystallisation from light petroleum gave 3,6-dimethylisothiazolo-[5, 4-b]pyridine (264 mg) as needles, m.p. 91-92°, mixed m.p. with starting material 91-92°.

Attempted amination of 3-methylisothiazolo[5,4-b]pyridine

A dry Carius tube was charged with liquid ammonia (15 ml), followed by a crystal of ferric chloride and freshly cut potassium metal (0.525 g, 0.026 g aton). After theevolution of hydrogen had ceased, 3-methylisothiazolo[5,4-b]pyridine (630 mg, 0.0042 mol) and potassium nitrate (0.57 g) were added simultaneously. The tube was sealed and allowed to stand at room temperature, with occasional shaking, for 8 days. The cooled tube was opened and a 1:1 mixture of benzene/ethanol (20 ml) was added dropwise. After the ammonia had evaporated (about 2 h), water (20 ml) was added and the organic layer separated and evaporated leaving a dark brown gummy solid (300 mg). Recrystallisation from light petroleum (charcoal gave 3-methylisothiazolo[5,4-b]pyridine (261 mg), m.p. 83-85°, further characterised by t.l.c.

Continuous chloroform extraction of the aqueous solution (pH 10-11) gave a brown gum (108 mg). T.l.c showed largely (ca. 90%) starting material.

Attempted condensation of 3-methylisothiazolo[5,4-b]pyridine with benzaldehyde

A mixture of glacial acetic acid (0.25 ml), acetic anhydride (0.5 ml), benzaldehyde (0.5 ml) and 3-methylisothiazolo[5,4-b]pyridine (0.5 g, 3.6 mmol) was heated under reflux for two days. T.l.c. of a sample showed the presence of starting materials only.

Addition of 2.5 N-hydrochloric acid (50 ml) and extraction with methylene chloride gave a yellow oil (521 mg), consisting mainly of benzaldehyde. Basification of the aqueous solution followed by continuous chloroform extraction gave a pale yellow solid (452 mg), m.p. 80-83°. Recrystallisation from light petroleum gave 3-methylisothiazolo[5,4-b]-pyridine (436 mg), m.p. 84-85°, identified by mixed m.p. and t.l.c.

Condensation of 3,6-dimethylisothiazolo[5,4-b]pyridine with benzaldehyde

3,6-Dimethylisothiazolo[5,4-b]pyridine (0.55 g, 3.35 m mol) was mixed with benzaldehyde (0.71 g, 4.4 mmol) in the presence of fused zinc chloride (50 mg) and allowed to stand at room temperature for two days.

T.l.c. of a sample showed starting materials only. The mixture was then heated at 130-135°; a sample taken after 2 h showed an additional spot. After a further 2 h at 130-135° the reaction mixture was cooled, acetone (15 ml) was added and the zinc chloride removed by filtration. Evaporation of the filtrate gave a gum which was separated by dry column chromatography on silica gel (60 g) using chloroform as developing solvent. The column was divided into three parts:

(i) Elution of the lower fraction with methanol gave benzaldehyde.

(ii) Elution of the top fraction with methanol gave recovered starting

material (462 mg), identified by t.l.c, m.p. and mixed m.p.

(iii) The middle fraction gave a pale yellow gummy solid (82 mg). Crystallisation from acetone gave 3-methyl-6-styrylisothiazolo-[5,4-b]pyridine (38 mg) as pale yellow plates, m.p. 139-140°. (Found: C, 71.2; H, 4.64; N, 10.9; S, 12.7. $C_{15}N_{12}N_2S$ requires C, 71.4; H, 4.7; N, 11.1; S, 12.7%). δ [$(CD_3)_2SO$, 100 MHz, N.M.R. 5] 2.68 (3H, s, CH_3-3), 7.38 - 8.52 (9H, m, 2 vinyl and 7 aromatic protons) p.p.m.

Condensation of 3,6-dimethylisothiazolo[5,4-b]pyridine with p-nitrobenzaldehyde.

3,6-Dimethylisothiazolo[5,4-b]pyridine (429 mg, 2.6 mmol) and p-nitrobenzaldehyde (1.0 g, 6.6 m mol) in acetic acid (0.6 ml) and acetic anhydride (0.6 ml) was heated at 140° (oil bath) for 15 h. T.l.c. of a sample showed four spots, two of which corresponded to starting materials. On cooling a yellow gummy solid separated. Trituration with acetone gave a yellow solid (206 mg), m.p. 182-196°; recrystallisation from glacial acetic acid gave 6-(p-nitrostyryl)-3-methylisothiazolo[5,4-b]pyridine (182 mg), m.p. 214-216°. (Found: C, 61.1; H, 3.40; N, 14.2; S, 10.9. $C_{15}H_{11}N_3O_2S$ requires C, 60.59; H, 3.73; N, 14.13; S, 10.78%).

The acetone solution was evaporated to dryness and the residual oil dissolved in sodium hydroxide solution (2.5N, 20 ml). Ether extraction (3x25 ml) gave a yellow gummy solid (1.1 g). T.l.c. showed the presence of three spots, two of which corresponded to starting materials. Dry column chromatography on silica gel (60 g) and eluting with chloroform gave p-nitrobenzaldehyde (726 mg), 3,6-dimethylisothiazolo[5,4-b]pyridine (206 mg) and a gummy solid (36 mg). A poor n.m.r. spectrum of the product was not informative and because of lack of material it was not investigated further.

Oxidation of 3-methyl- and 3,6-dimethylisothiazolo[5,4-b]pyridine

Potassium permanganate oxidation of 3-methylisothiazolo[5,4-b]pyridine

To a stirred solution of 3-methylisothiazolo[5,4-b]pyridine (855 mg, 5.7 mmol) in water (20 ml) heated to 70° was added potassium permanganate (3.6g, 2.95 mmol) in six equal portions over 1 h. The suspension was heated for an additional 30 min and filtered. The manganese dioxide residue was digested with hot water (3 x 10 ml) and the liquors added to the filtrate and the solution (pH 8-9) was extracted with methylene chloride (3x15 ml). Evaporation of the dried (K_2CO_3) extract gave a pale yellow solid (106 mg), m.p. 79-82°, identical (t.l.c.) with starting material.

The aqueous solution was acidified to pH 1-2 with concentrated hydrochloric acid and continuously extracted with ether for 26 h. Evaporation of the organic solvent under reduced pressure gave a gummy solid (421 mg). Recrystallisation from aqueous ethanol gave isothiazolo[5,4-b]pyridin-3(2H)-one 1,1-dioxide (198 mg), as white plates, m.p. 207-210°. (Found: C,38.8; H, 2.22; N, 14.8; S, 17.5. $C_6H_4N_2O_3S$ requires C, 39.12; H, 2.2; N, 15.21; S, 17.41 %). $\nu_{max.}$ (I.R 1) 3180, 3100, 2700, 1745 (C=O), 1470, 1410, 1350 cm^{-1}. δ [$(CD_3)_2SO$, N.M.R. δ] 7.76 (1 H,dd, J_{54} 8 Hz, J_{56} 5 Hz, H-5), 8.2 (1H, dd, J_{45} 8 Hz, J_{46} 2Hz, H-4), 8.55 (1H, s, N-H), 8.81 (1H, dd, J_{65} 5 Hz, J_{64} 2Hz, H-6) p.p.m.

Reaction of isothiazolo[5,4-b]pyridin-3(2H)-one 1,1-dioxide with acid and with base.

(a) With acid. The dioxide (500 mg) in hydrochloric acid (2.5N, 5 ml) was heated under reflux for 3.5 h. The solid went into solution after ca. 30 min. The solution was allowed to cool and the white solid which separated was collected and washed with ice cold water to give white needles (430 mg), m.p. 248-252°. Recrystallisation from water gave 2-hydroxy-pyridine-3-carboxylic acid (360 mg) as white needles, m.p. 253-255°,

identical (mixed m.p. and i.r.) with an authentic sample.[114] (Found: C, 51.5; H, 3.4; N, 10.1. $C_6H_5NO_3$ requires C, 51.8; H, 3.62; N, 10.07%) ν max. 3080 (C-H), 3000 (broad, -OH), 1730 (c=o) cm^{-1}. δ [$(CD_3)_2SO$, N.M.R] 6.66 (1H, dd, J_{56} 7.5 Hz, J_{54} 7 Hz, H-5), 8.01 (1H, dd, J_{45} 7 Hz, J_{46} 2.5 Hz, H-4), 8.47 (1H, dd, J_{64} 2.5 Hz, J_{65} 7.5 Hz, H-6) 14.1 (2H, broad, $-CO_2H$, -OH)p.p.m.

(b) With base. A solution of the dioxide (300 mg) in aqueous sodium hydroxide (2.5N, 10 ml) was heated under reflux for 3 h. The cold solution was acidified to pH 1-2 and the white solid which separated was collected (264 mg), m.p.251-253°. Recrystallisation from water gave 2-hydroxypyridine--3-carboxylic acid (214 mg) as white needles, m.p. 254-255°, identical (m.p., mixed m.p. and i.r.) with an authentic sample. The product gave carbon dioxide with sodium bicarbonate solution.

Chromic acid oxidation of 3-methylisothiazolo[5,4-b]pyridine

Powdered chromium trioxide (1.56 g) was added portionwise over 4h to a stirred solution of 3-methylisothiazolo[5,4-b]pyridine (1.0 g, 0.0066 mol) in concentrated sulphuric acid (12 ml) kept at 40°. After a further 28 h at 40° the mixture was poured onto ice (20 g) and continuously extracted with ether for 36 h. Evaporation of the dried ($MgSO_4$) extract gave a gummy solid (425 mg) which was dissolved in saturated sodium bicarbonate solution (5 ml) and extracted with ether. The aqueous solution was acidified to pH 1-2 with concentrated hydrochloric acid and cooled when a cream coloured solid (105 mg), m.p. 152-155° separated. Recrystallisation from aqueous ethanol gave 2-sulphoamidopyridine-3-carboxylic acid (72 mg) as off-white needles, m.p. 156-158°. The material decomposed (presumably loss of carbondioxide) on heating to ca. 176°. (Found. C, 35.8; H, 2.95; N, 13.8; S, 15.9. $C_6H_6N_2O_4S$ requires C, 35.64; H, 2.99; N, 13.86; S, 15.86%). ν max. (I.R.2) 3345, 3245 (NH_2), 2900-2500 (bonded OH), 1710 (C = O) 1590 (-NH def.), 1360, 1180 ($-SO_2N<$) cm^{-1}. δ [$(CD_3)_2SO$, N.M.R.8) 7.45 (3H, broad S, $-SO_2NH_2$,

$-CO_2H$), 7.76 (1H, dd, J_{56} 5 Hz, J_{54} 8 Hz, H-5), 8.17 (1H, dd, J_{45} 8 Hz, J_{46} 1.9 Hz, H-4), 8.81 (1H, dd, J_{64} 1.9 Hz, J_{65} 5 Hz, H-6) p.p.m.

Reaction of 2-sulphoamidopyridine-3-carboxylic acid with zinc dust and acid

A mixture of 2-sulphoamidopyridine-3-carboxylic acid (200 mg) in glacial acetic acid (4 ml), concentrated hydrochloric acid (1.0 ml) and zinc dust (50 mg) was heated on a steam bath for 30 min and thereafter at 110° (oil bath) for another 30 min. The reddish brown solution was diluted with water (10 ml) and continuously extracted with ether for 36 h. Evaporation of the dried ($MgSO_4$) extract gave a gummy solid (59 mg). Recrystallisation from aqueous ethanol (charcoal) gave a pink crystalline solid (36 mg) m.p. 223-228°. Further recrystallisation from water gave nicotinic acid as white needles (14 mg) m.p. 230-232°, mixed m.p. 230-232° with an authentic sample (Lit.,[124] m.p. 232°). The infrared spectrum was identical in every respect with that of nicotinic acid.

Potassium permanganate oxidation of 3,6-dimethylisothiazolo[5,4-b]pyridine

To a stirred mixture of 3,6-dimethylisothiazolo[5,4-b]pyridine (935 mg, 5.7 mmol) in water (15 ml) at 75-80° was added potassium permanganate (7.2g, 5.9 mmol) in six equal portions over 1 h. The suspension was heated for an additional 35 min and the manganese dioxide was separated by filtration, digested with hot water (3x10 ml) and the liquors added to the filtrate. The solution (pH9) was extracted with chloroform (3x20 ml) and the dried ($MgSO_4$) extract evaporated to give needles (116 mg) m.p. 82-89°. Recrystallisation from light petroleum gave 3,6-dimethylisothiazolo[5,4-b]-pyridine (92 mg), m.p. 91-92°, undepressed with starting material.

The aqueous solution was acidified to pH 1-2 with concentrated hydrochloric acid and continuously extracted with ether for 30 h. Evaporation of the dried ($MgSO_4$) extract gave a brown gummy solid (312 mg). Recrystallisation from water (charcoal) gave 6-methylisothiazolo[5,4-b]pyridin-3-

(2H)-one 1,1-dioxide (126 mg), as colourless needles, mp. 190-192°. (Found: C, 41.6; H, 2.98; N, 13.7; S, 15.9. $C_7H_6N_2O_3S$ requires C, 42.4; H, 3.05; N, 14.10; S, 16.18%). ν max. (I.R.3) 3260 (N-H), 3100-2200 (broad), 1760 (C=O), 1240, 1170 cm^{-1}. δ [$(CD_3)_2SO$, N.M.R.9) 2.78 (3H,s, CH_3-6), 7.8 (1H, d, J_{54} 8 Hz, H-5), 8.31 (1H, d, J_{45} 8 Hz, H-4), 9.36 (1H, s, -NH) p.p.m.

Reaction of 6-methylisothiazolo[5,4-b]pyridin-3(2H)-one 1,1-dioxide with acid

The dioxide (300 mg) in 2.5 N-hydrochloric acid (5 ml) was heated under reflux for 3h. On cooling a pale yellow solid (55 mg) separated; it did not melt up to 360°. The aqueous solution was continuously extracted with ether for 24 h. Evaporation of the dried ($MgSO_4$) extract gave a gummy solid (82 mg). Recrystallisation from water (charcoal) gave white plates (61 mg), m.p. 227-229°, identified as 2-hydroxy-6-methyl-pyridine-3-carboxylic acid (lit.,[125] m.p. 223°). (Found. C,54.2; H, 4.48; N, 8.9. $C_7H_7NO_3$ requires C, 54.9; H, 4.6; N, 9.15%). ν max. 3300-2200 (bonded OH), 1720 (C=O). δ [$(CD_3)_2$ SO, N.M.R.10] 2.4 (3H, s, CH_3-6), 6.57 (1H, d, J_{54} 8 Hz, H-5), 8.32 (1H, d, J_{45} 8 Hz, H-4), 13.3 (2H, broad s, $-CO_2H$, -OH) p.p.m.

Chromic acid oxidation of 3,6-dimethylisothiazolo[5,4-b]pyridine

Powdered chromium trioxide (3.2 g) was added portionwise over 3h to a stirred solution of 3,6-dimethylisothiazolo[5,4-b]pyridine (1.0 g, 0.0061 mol) in concentrated sulphuric acid (22.0 ml) kept at 40°. After a further 18 h at 40° the mixture was poured into ice/water (50 g). Continuous ether extraction for 24 h followed by evaporation of the dried ($MgSO_4$) extract gave a gummy solid (460 mg) which was dissolved in saturated potassium carbonate solution (5 ml) and extracted with ether (3x10 ml). The aqueous solution was acidified to pH 1-2 with concentrated hydrochloric acid and on cooling, a white solid (280 mg) m.p. 123-128°

was obtained. Recrystallisation from aqueous ethanol gave 6-methyl -2-sulphoamidopyridine-3-carboxylic acid (117 mg) as white needles, m.p. 128-130°. The material decomposed on heating to ca. 170° (Found: C,35.9; H, 4.33; N, 11.96; S, 13.69. $C_7H_8N_2O_4S.H_2O$ requires C,37.2; H, 4.01; N, 11.9; S, 14.3%). ν_{max} (I.R.4) 3505 (OH), 3360, 3260 (NH_2), 1710 (C=O), 1590 (-NH def.), 1340, 1180 ($-SO_2N<$) cm^{-1}. δ[$(CD_3)_2SO$, N.M.R.1]2.6 (3H, s, CH_3-6), 7.38 (3H, s, $-CO_2H$, $-SO_2NH_2$), 7.5 (1H, d, J 8 Hz, H-5), 8.03 (1H, d, J 8 Hz, H-4) p.p.m.

The acidic chromium solution was treated with sodium carbonate until alkaline and the thick green suspension extracted with ether (4x40 ml). Evaporation of the combined dried ($MgSO_4$) extracts gave a pale yellow solid (132 mg), m.p. 86-90°, identical (t.l.c) with starting material. Recrystallisation from light petroleum gave 3,6-dimethylisothiazolo[5,4-b]-pyridine (94 mg), m.p. 91-93° undepressed on admixture with an authentic sample.

Diethyl 2-(3-methylisothiazol-5-ylaminomethylene)malonate

A mixture of 5-amino-3-methylisothiazole (11.4 g, 0.1 mol) and diethyl ethoxymethylenemalonate (21.6 g, 0.1 mol) was heated, with stirring, on an oil bath maintained at 108-110°. Samples were removed at 30 min, 1 h.,2 h and 3 h intervals and investigated by g.l.c. on a silicone oil column at 168°. The 3 h sample showed only trace amounts of the reactants. The course of the reaction was also followed by t.l.c. on silica gel with chloroform as developing solvent; the crotonate was observed at R_f 0.25 and only very small amounts of the reactants could be detected after 3 h.

The mixture was kept overnight at room temperature when it partially solidified. The yellowish red mixture was dissolved in the minimum of cold benzene (50 ml) and light petroleum (400 ml) was added. A yellow solid (20 g), m.p. 67-77° separated on standing. Recrystallisation from light petroleum (charcoal), after decantation from a small amount of insoluble

resinous material, gave diethyl 2-(3-methylisothiazol-5-ylaminomethylene)-malonate as yellow cubes (16 g, 57%) m.p. 74-77°. An analytical sample obtained by two further recrystallisations from light petroleum had m.p. 78-79°. (Found: C, 50.6; H, 5.77; N, 9.7; S, 11.4. $C_{12}H_{16}N_2O_4S$ requires: C, 50.68; H, 5.67; N, 9.85; S, 11.28%).) max (I.R.5) 3210 (N-H), 3080, 2990, 2490, 2905 (C-H,) 1685 (C=O)cm^{-1}. δ ($CDCl_3$, N.M.R.12) 1.34 (3H, t, J 7 Hz, $-CH_2.\underline{CH_3}$), 1.38 (3H, t, J 7 Hz, $-CH_2.CH_3$), 2.41 (3H, s, CH_3-3), 4.30 (2H, q, J 7 Hz, $-\underline{CH_2}.CH_3$), 4.35 (2H, q, J 7 Hz, $-\underline{CH_2}.CH_3$), 6.66 (1H, s, H-4), 8.1 (1H, d, J 13 Hz, =C<u>H</u>-), 11.22 (1H, d, J 13 Hz, N-H) p.p.m.

Ethyl 4-hydroxy-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate

The above malonate (8.0 g, 0.028 mol) was added rapidly to refluxing diphenyl ether (100 ml) contained in a flask fitted with a sealed stirrer and an air condenser. The mixture was stirred vigorously for 20 min and then rapidly cooled to 40-45° when a brown solid separated. The reaction mixture was diluted with light petroleum (b.p. 100-120°, 400 ml) and the precipitated solid collected by filtration and washed with the same solvent. The vacuum dried product (6.2 g, 92%) sublimed without melting between 260-264°.

Purification by sublimation at 200°/0.5 mmHg gave the hydroxy-ester as a pale yellow amorphous solid (6.0 g, 90%) which sublimes at 264-266°. The compound may be recrystallised from dimethylformamide. (Found: C, 50.5; H, 4.41; N, 11.6; S, 13.6. $C_{10}H_{10}N_2O_3S$ requires C, 50.4; H, 4.23; N, 11.76; S, 13.46%)./227 and 310 nm. $\lambda_{max.}$ (U.V.2)) max. (I.R.6) 3400 (broad, -OH), 2980, 1690 (C O), 1605 cm^{-1}. δ (TFA, N.M.R.13) 1.58 (3H, t, J 7 Hz, $-CH_2.\underline{CH_3}$), 3.11 (3H, s, CH_3-3), 4.78 (2H, q, J 7 Hz, $-\underline{CH_2}.CH_3$) 9.15 (1H, s, H-6) p.p.m The compound did not give a colour with ferric chloride solution.

4-Hydroxy -3-methylisothiazolo[5,4-b]pyridine-5-carboxylic acid

(a) Basic hydrolysis

Ethyl 4-hydroxy-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate

(4.0 g, 0.017 mol) in aqueous sodium hydroxide (60 ml, 2.5N) was heated under reflux, with stirring, for 5h. The hydroxy-ester slowly dissolved during 20 min to give a clear solution which was then cooled to 5-10° and acidified with concentrated hydrochloric acid. The precipitate was collected, washed with water and dried under vacuum at 80° to give an amorphous solid (3.5 g) m.p. 269-274° (decomposition). The material solidified immediately after decomposition and then melted at 291-300° (decomposition). Recrystallisation from dimethylformamide (charcoal) gave the hydroxy-acid (2.82 g, 80%) as a white amorphous solid, m.p. 271-274° (decomposition), followed by m.p. 295-300° (decomposition) after solidification (Found: C, 45.2; H, 2.81; N, 13.30; S, 15.10. $C_8H_6N_2O_3S$ requires: C, 45.7; H, 2.88; N, 13.33; S, 15.25%). $\nu_{max.}$ (I.R.7) 3350 (broad, -OH), 2940 (broad, carboxyl -OH), 1680 (C=O), 1600 cm^{-1}. δ (TFA, N.M.R.14) 2.75 (3 H, s, $-CH_3$), 9.1 (1H, s, H-6) p.p.m.

(b) Acid hydrolysis

The hydroxy-ester (1.0 g) in hydrochloric acid (5N, 20 ml) was heated under reflux, with stirring, for 3 h. Suspended solid remained present throughout the reaction. The mixture was cooled and the pale yellow solid collected, washed with water and dried, (520 mg) m.p. 270-275° (decomposition), with partial sublimation. Decomposition was followed by formation of plates m.p. 290-295° (decomposition). Recrystallisation from dimethylformamide (charcoal) gave the hydroxy-acid (412 mg) m.p. 270-274° (decomposition) contaminated with about 5% of the hydroxy-ester as shown by its n.m.r. spectrum.

Decarboxylation of 4-hydroxy-3-methylisothiazolo[5,4-b]pyridine-5-carboxylic acid

Thermal decarboxylation.

(a) The hydroxy-acid was decarboxylated in a thermogravimetric apparatus in three 105 mg portions. Decarboxylation took place between

270-280° as shown by the loss in weight indicated by the recorder. The combined crude product (182 mg) was heated under reflux with ethanol (10 ml) and the insoluble black material filtered off and the liquors treated with charcoal. The ethanolic solution was concentrated to about 2 ml and allowed to cool. The white solid (94 mg, 38%) m.p. 294-298° (decomposition) was collected and recrystallised from ethanol to give 3-methylisothiazolo[5,4-b]pyrid-4-one (62 mg, 25%) as white needles, m.p. 304-306° (decomposition). (Found: C, 50.9; H, 3.59; N, 16.9; S, 19.2. $C_7H_6N_2OS$ requires C, 50.59; H, 3.64; N, 16.86; S, 19.29%). λ max. (U.V.3) 225 (ε 14,500), 268 (5,300), 294(8,100), 305 nm (7,200). ν max. (I.R.8) 3180 (N-H), 1640 (C O) cm^{-1}. δ (TFA, N.M.R.15) 3.1 (3H, s, CH_3-3), 7.48 (1H, d, J 7 Hz, H-5), 8.74 (1H, d, J 7 Hz, H-6) p.p.m.

The compound did not give a colour with aqueous or ethanolic ferric chloride.

(b) The hydroxy-acid (400 mg) was heated in an open hard glass vessel on a Woods metal bath maintained at 275-280° for 40 min. The product was boiled with ethanol (15 ml) and the insoluble material removed by filtration. Concentration and cooling of the filtrate, after treatment with charcoal, gave a white solid (241 mg) m.p. 294-301° (decomposition). Recrystallisation from ethanol gave 3-methylisothiazolo-[5,4-b]pyrid-4-one (202 mg, 65%) as white needles m.p. 304-306° (decomposition), identical (i.r. and t.l.c) with the product obtained above.

Copper/Quinoline

The hydroxy-acid (300 mg) and copper powder (0.1g) in quinoline (5 ml) was heated under reflux, with stirring, for 20 min. The hot solution was filtered and allowed to cool. The filtrate was diluted with acetone and the precipitated solid washed with a large volume of acetone to give a pale yellow crystalline solid (179 mg), m.p. 282-293° (decomposition). Recrystallisation from aqueous ethanol (charcoal) gave cream coloured needles (102 mg), m.p. 294-297° (decomposition). Further recrystallisation

of the material (50 mg) from ethanol gave 3-methylisothiazolo[5,4-b]-pyrid-4-one as colourless needles (36 mg), m.p. 298-302° (decomposition).

4-Chloro-3-methylisothiazolo[5,4-b]pyridine

3-Methylisothiazolo[5,4-b]pyrid-4-one (300 mg, 1.8 mmol) and phosphoryl chloride (6 ml) was heated on a steam bath for 2 h. The excess phosphoryl chloride was evaporated under reduced pressure and water (15 ml) was added to the residual gummy product. The resulting solid was collected and washed with water to give needles (190 mg, 57%). m.p. 122-125°. Recrystallisation from light petroleum gave 4-chloro-3-methylisothiazolo-[5,4-b]pyridine (162 mg, 49%) as white needles, m.p. 125-126°. (Found: C, 45.5; H, 2.52; N, 15.2; S, 17.4; Cl, 19.4. $C_7H_5N_2SCl$ requires: C, 45.53; H, 2.73; N, 15.18; S, 17.37; Cl, 19.20%). λ max (U.V.4) 232 (ε 27,500) and 312 nm (5,390). δ ($CDCl_3$, N.M.R.16) 2.96 (3H, s, CH_3-3), 7.38 (1H, d, J 5 Hz, H-5), 8.56 (1H, d, J 5 Hz, H-6) p.p.m.

4-Methoxy-3-methylisothiazolo[5,4-b]pyridine

4-Chloro-3-methylisothiazolo[5,4-b]pyridine (0.56 g, 3 mmol) was added to a solution of sodium methoxide from (92 mg, 0.004 g atom sodium) in dry methanol (10 ml). The mixture was heated under reflux for 3h then the alcohol was evaporated under reduced pressure to give a pale yellow solid (510 mg) which was dissolved in chloroform (15 ml) and washed with water (2x10 ml). The combined washings were back extracted with chloroform (15 ml) and the extracts dried (K_2CO_3). Evaporation of the chloroform gave a white solid (305 mg, 56%), m.p. 138-142°. Recrystallisation from benzene-light petroleum gave 4-methoxy-3-methylisothiazolo[5,4-b]pyridine (220 mg, 40%) as white needles, m.p. 145-146°. (Found: C,53.6; H, 4.41; N, 15.7; S, 17.8. $C_8H_7N_2OS$ requires C, 53.3; H, 4.47; N, 15.55; S, 17.80%). λ max. (U.V.5) 223 (ε 25,900), 298 (6,390) and 308 nm (6,390). ν max. 3080, 2980, 2820 (C-H) 1570 cm^{-1}. δ ($CDCl_3$, N.M.R.17) 2.81 (3H, s, CH_3-3), 4.05 (3H, s, $-OCH_3$), 6.75

(1H, d, J 5.5 Hz, H-5), 8.6 (1H, d, J 5.5 Hz, H-6) p.p.m.

N-methyl-3-methylisothiazolo[5,4-b]pyrid-4-one

Dimethyl sulphate (1.0 ml) was added to a solution of 3-methylisothiazolo[5,4-b]pyrid-4-one (400 mg, 2.5 mmol) in aqueous sodium hydroxide (5ml, 2.5N). The solution was stirred at room temperature for 30 min and then heated under reflux for 30 min. A further quantity of dimethyl sulphate (1.0 ml) was added and heating continued for a further 30 min. The yellow solution was cooled to room temperature and poured onto ice (20 g). The pH of the solution was adjusted to 8-9 with solid potassium carbonate and the inorganic salts which separated removed by filtration.

Continuous extraction of the filtrate with chloroform for 18 h and evaporation of the dried (K_2CO_3) extract gave a gummy solid (210 mg) which crystallised from chloroform-light petroleum to give N-methyl-3-methylisothiazolo[5,4-b]pyrid-4-one (182 mg, 41%) as white needles, m.p. 215-217°. (Found: C, 52.9; H, 4.49: N, 15.4; S, 18.1. $C_8H_8N_2OS$ requires C, 53.3; H, 4.47; N, 15.55; S, 17.80%). λ max (U.V.6) 225 (ε19,400), 271 (7560), 298 (9,360) and 309 nm (7,760). ν max. (I.R.9) 3060, 2980, 2920, (C-H), 1640 (C=O, ring) cm^{-1}. δ ($CDCl_3$, N.M.R.18) 2.83 (3H, s, CH_3-3), 3.73 (3H, s, N-CH_3), 6.25 (1H, d, J 8 Hz, H-5), 7.35 (1H, d, J 8 Hz, H-6) p.p.m.

Conversion of 4-chloro-3-methylisothiazolo[5, 4-b]pyridine to 3-methylisothiazolo[5,4-b]pyridine

Hydrazine hydrate (3.3 ml, 60% solution) was added to 4-chloro--3-methylisothiazolo[5,4-b]pyridine (0.55 g, 0.003 mol) in ethanol (10 ml) and the stirred mixture heated under reflux for 1 h. Evaporation to dryness under reduced pressure left a gum which partially solidified on standing. Trituration with water gave a pale yellow solid (300 mg) m.p. 225-232°,

identified as 4-hydrazino-3-methylisothiazolo[5,4-b]pyridine on the basis of its spectroscopic properties. It could not be recrystallised and was used without further purification.) max (Nujol) 3320, 3280, 3200 (N-H), 1580 (N-H) cm^{-1}. δ (TFA), 3.16 (3H, s, CH_3-3), 7.29 (1H, d, J 7 Hz, H-5), 8.62 (1H, d, J 7 Hz, H-6) p.p.m.

An aqueous solution of copper sulphate (10%, 5 ml) was added dropwise to a suspension of 4-hydrazino-3-methylisothiazolo[5,4-b]pyridine (250 mg) in water (5 ml) and glacial acetic acid (2 ml) and the blue mixture heated on a steam bath for 1 h. The resulting yellow suspension was made basic (to pH 11-12) with aqueous sodium hydroxide and the brown mixture continuously extracted with methylene chloride for 24 h. Evaporation of the dried (K_2CO_3) extract gave a pale yellow solid (100 mg, 48%) m.p. 80-84°. Recrystallisation from light petroleum gave 3-methylisothiazolo-[5,4-b]pyridine (82 mg, 40%) as colourless plates, m.p. 84-85°, identical (m.p, mixed m.p. and t.l.c.) with an authentic sample prepared by the Skraup reaction.

Ethyl 4-chloro-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate

Ethyl 4-hydroxy-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate (952 mg, 0.004 mol) and phosphoryl chloride (10 ml) was heated on a steam bath for 2.5 h; a clear solution was obtained after about 1 h. The excess phosphoryl chloride was evaporated under reduced pressure leaving a yellow gum. Water (20 ml) was added and the solid which formed on trituration was collected and washed with water to give cream coloured needles (685 mg, 69%), m.p. 76-79°. Recrystallisation from ethanol gave ethyl 4-chloro-3-methylisothiazolo [5,4-b]pyridine-5-carboxylate (525 mg, 53%) as colourless needles, m.p. 79-81°. (Found: C, 46.8; H, 3.54; N, 10.9; Cl, 14.0. $C_{10}H_9N_2O_2SCl$ requires C, 46.78; H, 3.53; N, 10.92; Cl, 13.81%) λ max (U.V.7) 212 (ε 14,900), 246 (22,600) and 307 nm (5,330). max. (I.R.10) 2980 (C-H), 1735 (C=O, ester) cm^{-1}. δ [$(CD_3)_2SO$, N.M.R.19]

1.4 (3H, t, J 7 Hz, $-CH_2.\underline{CH_3}$), 2.91 (3H, s, CH_3-3), 4.48 (2H, q, J 7 Hz, $-\underline{CH_2}.CH_3$), 9.08 (1H, s, H-6) p.p.m.

Methyl 4-methoxy-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate

Ethyl 4-chloro-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate (0.405 g, 1.6 mmol) was added to a solution of sodium methoxide from (46 mg, .002g atom of sodium) in dry methanol (10 ml). The mixture was heated under reflux for 4 h and the solvent was evaporated under reduced pressure. The residual white solid was dissolved in chloroform (15 ml) and washed with water (2x10 ml). The aqueous solution was back extracted with chloroform (10 ml) and the chloroform extracts dried (K_2CO_3) and evaporated to give a white solid (365 mg, 91%), m.p. 86-91°. The product was homogenous by t.l.c. Recrystallisation from light petroleum gave methyl 4-methoxy-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate (300 mg, 75%) as white needles, m.p. 94-95°. (Found: C, 50.7; H, 4.70; N, 11.4; S, 13.1. $C_{10}H_{10}N_2O_3S$ requires: C, 50.41; H, 4.23; N, 11.76; S, 13.46%). $\lambda_{max.}$ (U.V.8) 236 (ε29,500), 300 (4,265) and 310 nm (4,265). $\nu_{max.}$ (I.R.11) 2960, 1720 (C=O), 1575 cm^{-1}. δ ($CDCl_3$, N.M.R.20) 2.87 (3H, s, CH_3-3), 4.03 (3H, s, $-OCH_3$), 4.17 (3H, s, $-CO_2CH_3$), 9.03 (1H, s, H-6) p.p.m.

Ethyl N-methyl-3-methylisothiazolo[5,4-b]pyrid-4-one-5-carboxylate

Ethyl 4-hydroxy-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate (0.47 g, 2.0 mmol) in dry dimethylformamide (10 ml) was treated with sodium hydride (0.11 g, 2.3 mmol, 50% suspension in mineral oil) and after evolution of hydrogen had ceased, methyl iodide (0.30 g, 2.1 mmol) was added. The mixture was heated on a steam bath for 1.5 h and the clear yellowish brown solution poured into water (30 ml). The solution was cooled for 48 h and the pink coloured needles (273 mg, 54%), m.p. 126-128°, which separated, were collected. Recrystallisation from water (charcoal) gave ethyl N-methyl-3-methylisothiazolo[5,4-b]pyrid-4-one-5-carboxylate (252 mg

50%), m.p. 129-130°, as colourless needles. (Found: C, 52.10; H, 4.7; N, 11.3; S, 12.7. $C_{11}H_{12}N_2O_3S$ requires C, 52.37; H, 4.69; N, 11.2; S, 12.71%) λmax. (U.V.9) 221 (ε17,280), 234 (16,920), 272 (5,940) and 310 nm (10,800) νmax. (Nujol, I.R. 12) 3080, 1700 (C=O, ester) 1640 (C=O, ring), 810 cm^{-1} δ [$(CD_3)_2SO$, N.M.R.21] 1.3 (3H, t, J 7 Hz, $-CH_2.\underline{CH_3}$), 2.66 (3H, s, CH_3-3), 3.83 (3H, s, N-CH_3), 4.26 (2H, q, J 7 Hz, $-\underline{CH_2}.CH_3$), 8.50 (1H, s, H-6) p.p.m.

Attempted acetylation of ethyl 4-hydroxy-3-methylisothiazolo[5,4-b]-pyridine-5-carboxylate.

(a) With acetic anhydride and sodium acetate

A solution of the hydroxy-ester (0.5 g, 2.1 mmol) in acetic anhydride (10 ml) containing sodium acetate (0.2 g) was heated under reflux, with stirring, for 1.5 h during which time the solution became dark brown. The reaction mixture was poured onto ice (40 g) and the brown oil which separated solidified on cooling and scratching. The solid (410 mg) sublimin at 260-268° was recrystallised from dimethylformamide (charcoal) to give the hydroxy-ester (362 mg) as an amorphous solid subliming at 264-268°. The infrared spectrum was identical with that of an authentic sample.

(b) With acetyl chloride and sodium hydride

The hydroxy-ester (500 mg) was suspended in dry dimethyl formamide (10 ml) and treated with sodium hydride (0.14 g, 2.8 mmol, 50% suspension in mineral oil), and stirred with gentle warming on a steam bath for 20 min. Acetyl chloride (0.25 ml) was added over 3 min and the mixture heated on the steam bath for 1 h. After cooling it was poured onto ice (50 g) and the precipitate was collected and washed with water to give the hydroxy-ester (424 mg) as an amorphous solid, subliming at 260-264°. The n.m.r. spectrum of this crude product in trifluoroacetic acid showed the presence of ethyl 4-hydroxy-3-methylisothiazolo[5,4-b]pyridine-5--carboxylate only.

Investigation of the reaction between 5-amino-3-methylisothiazole and ethyl acetcacetate.

Method (a). A mixture of 5-amino-3-methylisothiazole (4.3 g, 0.038 mol), ethyl acetoacetate (4.9 g, 0.038 mol), Drierite (self indicating 10 g) and four drops of glacial acetic acid in absolute alcohol was stirred and heated under reflux for 8 h. The Drierite was removed by filtration and the solvent evaporated under reduced pressure to give a dark viscous oil. T.l.c. showed a mixture of at least four components. G.l.c. on silicone oil at 160° showed a mixture of three components with retention times 1.2, 11.6 and 30.4 min; 5-amino-3-methylisothiazole and ethyl-acetoacetate were also present in small amount.

An attempt at distillation under reduced pressure gave a mixture of ethyl acetoacetate and the component with retention time 1.2 min (1.4 g) b.p. 60-74° at 1.5 mmHg. Preparative g.l.c. on silicone oil (10%, 10ft column at 170°) gave the compound as a colourless oil which solidified at 0°. (Found: M^+, 129.0789. $C_6H_{11}NO_2$ requires: M, 129.0790). $\nu_{max.}$ (liquid film, I.R. 13) 3440, 3340 (NH_2), 2980, 2920, 2900 (C - H), 1660 (C=O) cm^{-1}. δ [($CDCl_3$), 100 MHz, N.M.R.22] 1.25 (3H, t, J 7 Hz, $-CH_2.\underline{CH_3}$), 1.9 (3H, s, $CH_3 - \underset{\overset{|}{NH_2}}{C} = CH$) 4.2 (2H, J 7 Hz, $-\underline{CH_2}.CH_3$), 4.52 (1H, s, $-\underline{CH} - \underset{\overset{|}{NH_2}}{C} - CH_3$

The spectral evidence suggested that the compound was β-aminocrotonic ester. It was not further investigated.

The residue in the pot after distillation still showed the two major components (g.l.c). The gum was refluxed with diphenyl ether for 15 min and the cold mixture diluted with light petroleum (b.p. 100-120°). An intractable gum was obtained which was not investigated further.

Method (b). A mixture of 5-amino-3-methylisothiazole (5.7 g, 0.05 mol ethyl acetoacetate (6.5 g, 0.05 mol) and three drops of concentrated hydrochloric acid was kept in an evacuated desiccator over concentrated sulphuric acid for seven days. The red viscous oil was dissolved in

chloroform and filtered from a small amount of red solid. T.l.c. of the filtrate showed at least four spots. G.l.c. on silicone oil at 170° showed a mixture of at least five components, two of which were identified as ethyl acetoacetate and 5-amino-3-methylisothiazole. The retention times and shapes of the peaks were identical to the components of the mixture obtained in the previous experiment.

Preparative g.l.c. on silicone oil (10%, 10 ft column) at 170° gave the two major components. The product at retention time 30.4 min was isolated as a yellow crystalline solid, m.p. 90-92° and identified as ethyl 3-(3-methylisothiazol-5-ylamino)crotonate. (Found: M^+, 226.0775. $C_{10}H_{14}N_2O_2S$ requires M, 226.0776). ν max. (I.R.14) 3405 (N-H), 1680 (C=O, ester), 1620 (N-H) cm^{-1}. δ ($CDCl_3$, N.M.R.23) 1.31 (3H, t, J 7 Hz, $-CH_2.\underline{CH_3}$), 1.97 (3H, s, CH_3-3), 2.63 (3H, s, $= \underset{\underset{NH}{|}}{C} - \underline{CH_3}$), 4.3 (2H, q, J 7 Hz, $-\underline{CH_2}.CH_3$), 5.16 (1H, s, $= C\underline{H}.CO_2C_2H_5$), 6.65 (1H, broad, N-H) p.p.m. The signal at δ 6.65 p.p.m. disappeared on shaking with deuterium oxide.

The product at retention time 11.6 min was a yellow gummy solid, its n.m.r. spectrum not informative and it was not investigated further.

Investigation of the reaction between 5-amino-3-methylisothiazole and acetylacetone.

A mixture of 5-amino-3-methylisothiazole (4.56 g, 0.04 mol), acetyl acetone (4.0 g, 0.04 mol) and Drierite (6 g) was heated on a steam bath for 4 h. The thick dark oily mixture was diluted with chloroform and filtered. T.l.c. (ether) of the filtrate on silica gel showed at least three spots, one corresponding to unreacted amine. C.l.c. of the mixture on silicone oil at 160° showed a mixture of four components with retention times 1.2, 2.5, 10.2 and 27.2 min, the major component being the broad peak at retention time 27.2 min.

The chloroform solution was evaporated and the residue was treated

slowly with concentrated sulphuric acid (40 ml) with cooling in a freezing mixture. The resultant mixture was poured into ice/water (150 g) and basifi to pH 11-12 with 50% sodium hydroxide solution. Ether extraction (3x150 ml) gave a brown oil (800 mg) after evaporation of the dried ($MgSO_4$) extract. The oil showed one major peak on g.l.c., retention time 3.8 min, and only one spot on t.l.c.

The dark brown aqueous solution was steam distilled, the distillate (1000 ml) saturated with sodium chloride and continuously extracted with ether for 34 h. Evaporation of the dried ($MgSO_4$) extract gave a yellow oil (1.0 g) with the same retention time and same R_f as the product isolated by ether extraction.

Molecular distillation of the combined crude product at 2.0 mm Hg and 85-90° (oil bath temperature) gave a colourless liquid (1.7 g). Distillation under reduced pressure gave a colourless liquid (1.3 g), b.p. 66-68° at 0.6 mmHg, the structure of which is tentatively assigned as 5-acetyl-3,4-dimethylisothiazole on the basis of elemental and spectroscopic analysis. (Found: C, 54.1; H, 6.06; N, 9.50; S, 19.5; M^+ 155.0406. C_7H_9NOS requires C, 54.18; H, 5.85; N, 9.02; S, 20.65%; M 155.0404). λ max. (U.V.10) 212 (ε 5,373) and 274 nm (ε 12,400). ν max. (liquid film I.R.15) 2910 (C-H), 1675 (C=O)cm^{-1}. δ (CCl_4, N.M.R.24) 2.4 (3H,s, $-CH_3$), 2.62 (3H, s, $-CH_3$), 2.64 (3H, s, $-CH_3$) p.p.m.

The oxime from hydroxylamine hydrochloride (0.4 g), hydrated sodium acetate (0.8 g) and the above ketone (0.2 g) in water (4.0 ml), crystallised from aqueous ethanol as white needles (84 mg), m.p. 128-129°. (Found: C, 49.30; H, 6.1; N, 16.5; S, 18.9. $C_7H_{10}N_2OS$ requires C, 49.35; H, 5.92; N, 16.46; S, 18.83%).

The compound in dioxan and aqueous sodium hydroxide did not give iodoform with excess iodine in potassium iodide even though the iodine colour discharged initially. A brown coloured solution was obtained, the colour of which was not discharged with excess sodium hydroxide.

II. APPROACHES TO ISOTHIAZOLYNES

Synthesis of 5-amino-3-chloroisothiazole-4-carboxylic acid

Di-(sodiomercapto)methylenemalononitrile[13]

Malononitrile (33 g, 0.5 mol) was added over 15 min to a stirred suspension of sodium hydroxide (40 g, 1 mol) in absolute alcohol (450 ml) while the temperature of the mixture was maintained at 10-15°. Carbon disulphide (38 g, 0.5 mol) was added dropwise, with cooling to below 20°, over a period of 30 min, and the resulting heavy, yellow slurry stirred an additional hour at room temperature. Filtration, washing with alcohol and drying under vacuum for 24 h and at 80° over phosphorous pentoxide for 24 h gave the salt as a pale tan powder (68 g, 78%).

3,5-Dichloroisothiazole-4-carbonitrile[13]

Dry chlorine gas was passed into a stirred slurry of anhydrous di-(sodiomercapto)methylenemalononitrile (50.0 g, 0.30 mol) in dry carbon tetrachloride (400 ml) at 45-50° for 2 h. Heat evolution caused the mixture to reflux for the first hour, but during the second hour it cooled to 35-40°. The colour of the reaction mixture changed from tan to yellow and finally to reddish brown. The warm mixture was filtered from insoluble material, the residue washed with dry carbon tetrachloride (100 ml) and the combined filtrate and washing was evaporated to remove carbon tetrachloride and sulphur chlorides. The residue was steam distilled and from the distillate (800 ml), a white solid (15.0 g), m.p. 53-61° was obtained. Recrystallisation from light petroleum gave 3,5-dichloroisothiazole-4-carbonitrile (14.0 g, 34.5%), m.p. 62-64° (lit.,[13] m.p. 64-65°).

5-Amino-3-chloroisothiazole-4-carbonitrile[13]

Dry ammonia gas was passed into a stirred solution of 3,5-dichloroisothiazole-4-carbonitrile (10 g, 0.056 mol) in purified tetrahydrofuran (500 ml) for 7 h. The mixture was kept overnight at room temperature. The ammonium chloride (3.6 g) which separated was removed by filtration and the filtrate concentrated to about 50 ml. Dilution with benzene (150 ml) gave a tan solid (6.9 g), m.p. 208-212°. Recrystallisation from methanol gave 5-amino-3-chloroisothiazole-4--carbonitrile (5.6 g, 62%) as tan needles, m.p. 210-212° (lit.,[13] m.p. 210-212°).

5-Amino-3-chloroisothiazole-4-carboxamide

This was obtained in 71% yield, by treatment of above nitrile with concentrated sulphuric acid as described by Hatchard, as colourless needles, m.p. 198-199°. (lit.,[13] m.p. 198-199°).

Attempted hydrolysis of 5-amino-3-chloroisothiazole-4-carboxamide

(a) With aqueous sodium hydroxide. The amide (230 mg) was dissolved in hot aqueous sodium hydroxide (2.5N, 3.0 ml) and the mixture heated for 30 min on a steam bath; no ammonia was detected during the heating. The cold solution was acidified to pH 2-3 with 2.5N-hydrochloric acid. At pH 6-7 a cloudiness appeared and at pH 2-3 precipitation of a white solid (200 mg), not melting below 300°, was complete. Evolution of hydrogen sulphide was detected during acidification. Recrystallisation of the product from water gave off-white needles (64 mg) which did not melt below 320° but changed colour to yellow, orange and finally brown. (Found: C, 38.3; H, 4.0; N, 33.0; $C_4H_5N_3O_2$ requires C, 37.8; H, 3.965; N, 33.06%). ν max. 3405, 3320 ($-NH_2$), 2196 ($C\equiv N$), 1660-1640, 1550-1490 ($C=O$, amide) cm^{-1}. The n.m.r. spectrum in $(CD_3)_2SO$ showed only one broad signal at δ 7.58 p.p.m.

(b) With 90% sulphuric acid. 5-Amino-3-chloroisothiazole-4-carboxamide (500 mg) was dissolved in concentrated sulphuric acid (3 ml) and water (0.2 ml) and the mixture heated on a steam bath for 6 h. The clear yellow solution was poured onto ice (10 g) and the cream coloured solid which separated was collected and washed with water (450 mg), m.p. 196-198°. Recrystallisation from methanol gave starting material (400 mg), as needles, m.p. 197-199°; mixed m.p. with an authentic sample, 196-198°, further characterised by i.r. and t.l.c.

(c) With concentrated hydrochloric acid. The amide (1.0 g) was dissolved in concentrated hydrochloric acid (25 ml) and heated under reflux for 15 h. The mixture was cooled in an ice-salt mixture for 30 min and filtered from a small amount of insoluble material. The filtrate, on dilution with water, gave a yellow solid (400 mg) m.p. 205-211°. Recrystallisation from water gave colourless needles (240 mg) m.p. 210-213°, identified as 5-amino-3-chloroisothiazole-4-carbonitrile by i.r., t.l.c. and mixed m.p., 209-212°. Continuous ether extraction of the aqueous solution at pH 2-3 gave none of the expected amino acid.

(d) With 100% phosphoric acid.

(1) At 140-150° The amide (500 mg) was heated with 100% phosphoric acid (2.0 ml) at 140-150° for 1 h during which time the mixture became dark brown. The cold mixture was poured onto ice when a brown solid (300 mg) separated; it did not melt below 300° and its i.r. spectrum showed none of the characteristics of an amino acid. The aqueous solution was adjusted to pH 2-3 with potassium carbonate and continuously extracted with ether for 24 h. Evaporation of the dried ($MgSO_4$) extract gave no residue. Adjustment of the pH to 6-7 and continuous ether extraction for 24 h similarly gave no residue.

(2) At 120-130° The amide (500 mg) in 100% phosphoric acid (2.0 ml) was heated at 120-130° for 45 min. The cold mixture was poured onto ice (20 g)

and the cream coloured solid (285 mg), m.p. 184-190° which separated was recrystallised from aqueous ethanol to give colourless needles (232 mg) of unchanged amide, m.p. 196-198°, mixed m.p. 197-198°, confirmed by i.r. and t.l.c. Continuous ether extraction of the filtrate, after adjusting to pH 1-2 with potassium carbonate, gave no residue.

(3) At 85-90° Heating the amide (500 mg) with 100% phosphoric acid (2.0 ml) at 85-90° for 6 h gave unchanged amide (450 mg) m.p. 184-192°; recrystallisation from aqueous ethanol gave colourless needles (360 mg), m.p. 197-199°.

Attempted hydrolysis of 5-amino-3-chloroisothiazole-4-carbonitrile

The nitrile (1.0 g) was added to a mixture of ethylene glycol (8.9 ml), water (1.8 ml) and potassium hydroxide (0.9 g) and heated under reflux for 24 h after which the cold brown mixture was poured onto ice (20 g). The solution was acidified to pH 2-3 with 2.5N-hydrochloric acid and filtered from a small amount of brown solid. Continuous ether extraction of the acid solution for 24 h followed by evaporation of the dried ($MgSO_4$) extract gave no residue.

During the reaction a white solid (300 mg) subliming at 116-128° separated in the condenser; it was identified as ammonium chloride.

3,5-Dichloroisothiazole-4-carboxylic acid[13]

Hydrolysis of 3,5-dichloroisothiazole-4-carbonitrile with concentrated sulphuric acid, as described in the literature gave the corresponding amide in 70% yield. Nitrous acid hydrolysis of the amide gave the acid (40%) as white plates, m.p. 154-156°. (lit.,[13] m.p. 155-156°).

Attempted preparation of 5-amino-3-chloroisothiazole-4-carboxylic acid from 3,5-dichloroisothiazole-4-carboxylic acid.

(a) With aqueous ammonia. A solution of 3,5-dichloroisothiazole-4-carboxyli

acid (500 mg) in ethanol (5 ml) and aqueous ammonia (d, 0.88, 30 ml) was heated under reflux; after 30 min another 20 ml of aqueous ammonia was added and heating continued for a further 1.5 h. The mixture was kept overnight at room temperature. The solvent was evaporated under reduced pressure and water (2.0 ml) added to the residue followed by 2.5N-hydrochlori acid (1.0 ml). After 30 min at room temperature the mixture was evaporated to dryness leaving a white solid (500 mg) m.p. 144-152°. Two recrystallisations from water gave 3,5-dichloroisothiazole-4-carboxylic acid (314 mg), m.p. 155-156° undepressed on admixture with an authentic sample.

Ether extraction of the aqueous liquor, acidified to pH 2-3, gave a further quantity (60 mg) of unchanged acid, m.p. 150-155°.

(b) With ammonia. Dry ammonia was passed through a boiling solution of 3,5-dichloroisothiazole-4-carboxylic acid (2.0 g) in dry tetrahydrofuran (150 ml). After 10 min a thick white precipitate, presumably the ammonium salt, separated. Sufficient aqueous ethanol (1:1) was added to dissolve the precipitate and ammonia gas passed through the refluxing mixture for 5 h. The reaction mixture was allowed tc stand overnight at room temperature and the solvent was removed under reduced pressure. Water (10 ml) was added to the residue and the solution acidified with concentrated hydrochloric acid when a white solid (1.8 g) separated, m.p. 153-155°. Recrystallisation from benzene gave 3,5-dichloroisothiazole-4-carboxylic acid (1.6 g) as white needles, m.p. 154-156° undepressed on admixture with an authentic sample.

3-Chloro-5-N-trifluoroacetylaminoisothiazole-4-carboxamide

3-Chloro-5-aminoisothiazole-4-carboxamide (1.1 g) in trifluoroacetic anhydride (6.0 ml) was kept at room temperature for 1.5 h. Water (50 ml) was added to the almost clear solution and the white solid which separated

was collected and washed well with water, (1.1 g), m.p. 148-150°. Recrystallisation from aqueous ethanol gave 3-chloro-5-N-trifluoroacetylaminoisothiazole-4-carboxamide (1.01 g, 70%) as colourless plates, m.p. 150-152° (Found: C, 26.6; H, 1.1; N, 15.2; S, 11.8. $C_6H_3N_3O_2SF_3Cl$ requires: C, 26.34; H, 1.105; N, 15.36; S, 11.71%). $\nu_{max.}$ 3450, 3320 (N-H), 3260, 3240-3000, 1730 (C=O)cm^{-1}.

3-Chloro-5-N-trifluoroacetylaminoisothiazole-4-carboxylic acid

A solution of sodium nitrite (0.21 g, 0.003 mol) in water(0.7 ml) was added over 10 min to a stirred cold solution (5-10°) of 3-chloro-5--N-trifluoroacetylaminoisothiazole-4-carboxamide (0.55g, 0.002 mol) in concentrated sulphuric acid (2.7 ml) and water (0.7 ml). Addition was made at such a rate that the temperature was maintained at 10-15°. It was further stirred at room temperature for 30 min and then at 50-60° for 20 min. The cold mixture was poured onto ice-water (20 g) and the resulting yellow solid (230 mg), m.p. 143-146°, was recrystallised from benzene (charcoal), after removal of a small quantity of insoluble material, to give 3-chloro-5-N-trifluoroacetylaminoisothiazole-4--carboxylic acid (109 mg, 20%) as white needles m.p. 148-149° (Found: C, 26.5; H, 0.90; N, 10.2; S, 12.0. $C_6H_2N_2O_3SF_3Cl$ requires: C, 26.24; H, 0.73; N, 10.2; S, 11.69%) $\nu_{max.}$ 3480, 3260, 3200-2300, 1730 (C=O)cm^{-1}.

5-Amino-3-chloroisothiazole-4-carboxylic acid

3-Chloro-5-N-trifluoroacetylaminoisothiazole-4-carboxylic acid (80 mg) was treated with saturated potassium carbonate solution (2.0 ml) and warmed at 45-50° for 10 min. The cold solution was allowed to stand at room temperature for 30 min and then acidified with concentrated hydrochloric acid, with cooling to 0°. The flocculent white solid which separated (50 mg) did not melt below 300°. Recrystallisation from water gave 5-amino-3-chloroisothiazole-4-carboxylic acid (33 mg, 64%), as

white needles which did not melt up to 335°. (Found: C, 27.0; H, 1.8; N, 15.5; S, 18.1. $C_4H_3N_2O_2Cl$ requires C, 26.9; H, 1.69; N, 15.68; S, 17.94%). $\nu_{max.}$ (I.R.17) 3460, 3310 (NH_2), 3000-2300 (bonded-OH), 1695 (C=O), 1610 (N-H) cm^{-1}.

The amino acid was similarly obtained (51% yield) by treatment of the trifluoroacetylamino compound with cold 2.5N-sodium hydroxide followed by acidification.

Synthesis of 4-amino-3-methylisothiazole-5-carboxylic acid

3-Methyl-4-nitroisothiazole-5-mercuriacetate

3-Methyl-4-nitroisothiazole (5.2 g, 0.036 mol) and mercuric acetate (14.0 g, 0.022 mol) in aqueous ethanol (24 ml, 50%) and glacial acetic acid (2 ml) was heated under reflux, with stirring, for 5 h. A solid began to separate after one hour. The yellow mixture was cooled to room temperature, diluted with water (100 ml) and allowed to stand at room temperature for 2 h. The yellow solid was collected, washed with water and dried (11.4 g, 76% calculated as the mercuriacetate) m.p. 199-201°. A sample recrystallised from glacial acetic acid gave the mercuriacetate as white needles, m.p. 199-200°. A satisfactory analysis could not be obtained. (Found: C, 16.5; H, 1.4; Hg, 32.8; N, 2.3; S, 6.66. $C_6H_6HgN_2O_4S$ requires: C, 17.89; H, 1.50; Hg, 49.8; N, 6.95; S, 7.96%).

5-Bromo-3-methyl-4-nitroisothiazole

(a) From 5-amino-3-methylisothiazole. 5-Bromo-3-methylisothiazole, b.p. 71-73° at 13-14 mmHg, was obtained in 30% yield from the above amine by diazotisation and treatment with cuprous bromide as described by Adams and Slack.[6]

Nitration of the bromo-compound with fuming nitric acid in concentrated sulphuric acid, as described by the same authors gave 5-bromo-4-nitro-3-methylisothiazole as colourless needles, m.p. 75-77° (lit.,[6] m.p. 77-78°) in 43% yield.

(b) From 3-methyl-4-nitroisothiazole-5-mercuriacetate . 3-Methyl-4--nitroisothiazole-5-mercuriacetate (7.2 g) was suspended in water (60 ml); sodium bromide (4.12 g, 0.036 mol) and bromine (3.2 g, 0.04 mol) were added and the mixture stirred at room temperature for 20 h. The pale yellow solid which separated during the course of the reaction was collected, washed with water and dried, (2.9 g), m.p. 70-75°. It was dissolved in ether and filtered from a small amount of insoluble material. Evaporation of the dried ($MgSO_4$) solution gave a crystalline solid (2.8 g), m.p. 71-75°; recrystallisation from ethanol gave 5-bromo-3-methyl-4-nitroisothiazole (2.25 g, 60%) as colourless needles, m.p. 75-77°. A mixed m.p. with the bromo-compound prepared as described above was 75-77°.

3-Methyl-4-nitroisothiazole-5-carbonitrile[23]

Dimethylformamide (2.0 g) was added to a stirred refluxing suspension of 5-bromo-3-methyl-4-nitroisothiazole (3.0 g, 0.013 mol) and cuprous cyanide (2.6 g, 0.029 mol) in light petroleum (b.p. 100-120°, 65 ml) and the mixture heated for 3.5 h. The hot solution was decanted from the residue which was extracted with boiling light petroleum (b.p. 100-120°, 2x25 ml). The combined petroleum extracts were concentrated to approximately 40 ml, cooled to 0° and the crude product collected (2.0 g), m.p. 102-105°. Recrystallisation from light petroleum (b.p. 100-120°) gave 3-methyl-4-nitroisothiazole-5-carbonitrile (1.5 g, 66%), as glistening plates, m.p. 104-106° (lit.,[23] m.p. 103-104°).

4-Amino-3-methylisothiazole-5-carboxylic acid[23]

Ferrous sulphate ($FeSO_4 . 7 H_2O$, 51.6 g, 0.19 mol) in water (550 ml) was added to a well stirred suspension of barium hydroxide [$Ba(OH)_2 . 8 H_2O$, 315.4g, 1.0 mol] in water (1.65 L) at 70°. 3-Methyl-4-nitroisothiazole--5-carbonitrile (3.4 g, 0.02 mol) was added in four portions at 5 min intervals to the stirred mixture which was maintained at 90°, and then heated for a further 1.25 h at this temperature. The brown inorganic materials were removed by filtration, the filtrate cooled to 0° and acidifie

to pH 1-2 with concentrated hydrochloric acid. The aqueous solution was continuously extracted with ether for 36 h and evaporation of the dried ($MgSO_4$) extract under reduced pressure gave a yellow solid (1.2 g), m.p. 182-191°. Recrystallisation from water (charcoal) gave the amino acid (1.0 g) as pale yellow needles, m.p. 192-198°. Further recrystallisation gave the pure amino acid (622 mg, 20%), as colourless needles, m.p. 203-204° (lit.,[23] m.p. 203°)

3-Methyl-4-nitroisothiazole-5-carboxamide[23]

Hydrolysis of 3-methyl-4-nitroisothiazole-5-carbonitrile with sulphuric acid as described by Holland and co-workers gave the carboxamide (39%) as cream coloured needles, m.p. 164-165° (lit.,[23] m.p. 166°).

3-Methyl-4-nitroisothiazole-5-carboxylic acid[23]

(a) 3-Methyl-4-nitroisothiazole-5-carbonitrile (1.1 g, 0.06 mol) was added to a mixture of concentrated sulphuric acid (3.0 ml) and water (0.71 ml) and the solution heated to 79-80° for 6 h. The cold solution was poured onto ice (10 g) and the separated solid dissolved in sodium hydroxide solution (2N, 5 ml). Filtration from insoluble material and acidification of the filtrate to pH1 gave the nitro acid (0.35 g), m.p. 118-120° (decomposition). The filtrate was extracted with ether (2x50 ml) and the combined, dried ($MgSO_4$) ethereal extract upon evaporation under reduced pressure gave a further amount of the nitro acid (0.25 g) m.p. 118-120° (decomposition). Recrystallisation from toluene gave 3-methyl-4--nitroisothiazole-5-carboxylic acid (0.51 g, 46%), as white needles, m.p. 119-120° (decomposition) (lit.,[23] m.p. 120°).

When the hydrolysis was carried out at 83-85° only 3-methyl--4-nitroisothiazole (57%) was obtained.

(b) 3-Methyl-4-nitroisothiazole-5-carboxamide (0.935 g, 0.05 mol) in sodium hydroxide solution (2.5N, 15 ml) was heated on a steam bath for 45 min. The cold solution was acidified to pH 1-2 with dilute hydrochloric acid and continuously extracted with ether for 48 h. Evaporation of the

dried ($MgSO_4$) extract gave an amorphous solid (140 mg) which was dissolved in saturated sodium bicarbonate solution. Addition of acid gave a white precipitate (106 mg), m.p. 114-118°. Recrystallisation from toluene gave 3-methyl-4-nitroisothiazole-5-carboxylic acid (82 mg, 9%) as white needles, m.p. 118-120° (decomposition).

Attempted reduction of 3-methyl-4-nitroisothiazole-5-carboxylic acid with palladium charcoal-sodium borohydride.

Sodium borohydride (0.26 g, 0.06 mol) in water (5 ml) was added to a suspension of palladised charcoal (10%, 16 mg) in water (5 ml). A slow stream of nitrogen was bubbled through the mixture and a solution of 3-methyl-4-nitroisothiazole-5-carboxylic acid (0.56 g, 0.003 mol) in methanol (10 ml) was added dropwise during 10 min. The mixture was allowed to stand at room temperature for a further 10 min and then made acid (pH 2-3) with dilute hydrochloric acid. Continuous ether extraction of the aqueous solution for 24 h followed by evaporation of the dried ($MgSO_4$) extract gave a brown water soluble gum (162 mg) from which no amino acid could be obtained.

Synthesis of 4-aminoisothiazole-3-carboxylic acid

3-Methyl-4-nitroisothiazole[6]

This was prepared by the nitration of 3-methylisothiazole with potassium nitrate in 20% fuming sulphuric acid at 100° as described by Adams and Slack. The compound, a pale yellow oil, b.p. 92° at 8 mmHg, was obtained in 78% yield.

4-Nitroisothiazole-3-carboxylic acid[23]

3-Methyl-4-nitroisothiazole (43.2 g, 0.3 mol) was added dropwise to concentrated sulphuric acid (270 ml), with stirring, below 30°. The reaction mixture was warmed to 40-45° and powdered chromium trioxide (90.0 g, 0.90 mol) added portionwise during 6 h to the stirred solution, the temperature being kept between 40-45°. (this was essential in order to moderate the vigour of the reaction). Stirring was continued overnight

at 40-45° and the thick green mixture was poured onto ice (800 g). The resulting solution was extracted with ether (4x250 ml) and then continuously extracted for 24 h. The combined ether extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a pale yellow semi-solid (21.2 g). The solid was dissolved in saturated potassium carbonate solution and extracted with ether (2x250 ml). The extracts were combined, dried ($MgSO_4$) and evaporated to give 3-methyl--4-nitroisothiazole as a pale yellow oil (4.1 g) identified by i.r. and t.l.

The aqueous alkaline solution was acidified with 6N-hydrochloric acid and extracted with ether (4x200 ml). The combined, dried ($MgSO_4$) extracts upon evaporation gave the nitro-acid (12.1 g), m.p. 140-143°. Recrystallisation from benzene gave 4-nitroisothiazole-3-carboxylic acid (10.2 g, 21%) as colourless needles, m.p. 144-146° (lit.,[23] m.p. 146°).

4-Aminoisothiazole-3-carboxylic acid

(a) Ferrous sulphate/ammonia reduction. 4-Nitroisothiazole-3-carboxylic acid (2.2 g, 0.0127 mol) in a hot mixture of absolute ethanol (75 ml) and aqueous ammonia (d, 0.88, 35 ml) was added in small portions over 15 min to a vigorously stirred hot (90°) solution of ferrous sulphate, ($FeSO_4 . 7 H_2O$, 30.5 g, 0.11 mol) in water (100 ml). Throughout the addition the temperature was maintained at 85-90°. Thirty minutes after the last addition, the black inorganic materials were removed by filtration, the filtrate concentrated to about 100 ml, cooled to 0° and acidified to pH 1 with concentrated hydrochloric acid. Continuous ether extraction of the acqueous solution for 36 h and evaporation of the dried ($MgSO_4$) extract under reduced pressure gave a pale yellow crystalline solid (1.0 g), m.p. 188-190°. Recrystallisation from water (charcoal) gave 4-aminoisothiazole--3-carboxylic acid as pale yellow needles (0.80 g, 44%) m.p. 190-191°. (Found: C, 33.0; H, 2.7; N, 19.5; S, 21.7. $C_4H_4N_2O_2S$ requires C, 33.3; H, 2.93; N, 19.43; S, 22.24%). $\nu_{max.}$ (I.R.16) 3080 (C-H), 3000-2360

(NH_3^+), 2080 (band characteristic of amino acids), 1650-1550 (CO_2^-)cm^{-1}. δ [$(CD_3)_2SO$, N.M.R.25] 6.55 (3H, broad, NH_3^+) 7.7 (1H, s, H-5) p.p.m.

(b) Ferrous sulphate/barium hydroxide reduction. Barium hydroxide, ($Ba(OH)_2.\ 8H_2O$, 29.3 g, 0.09 mol) in water (200 ml) was heated on a steam bath to 80°, with vigorous stirring. A cold solution of ferrous sulphate ($FeSO_4.\ 7\ H_2O$, 25.8 g, 0.09 mol) in water (100 ml) was added, followed by a hot solution of 4-nitroisothiazole-3-carboxylic acid (1.75 g, 0.01 mol) in ethanol (10 ml) over a period of 15 min. The stirred mixture was heated at 85-90° for 1.5 h after which inorganic solids were removed. The filtrate was cooled to 0°, acidified to pH 1 with 2.5N-hydrochloric acid and continuously extracted with ether for 72 h. Evaporation of the dried ($MgSO_4$) extract gave a pale yellow crystalline solid (300 mg), m.p. 184-187°. Recrystallisation from aqueous ethanol gave pale yellow needles of 4-aminoisothiazole-3-carboxylic acid (200 mg, 14%), m.p. 186-187°. Furth recrystallisation from water raised the m.p. to 189-191°; mixed m.p. 189-191°.

(c) Hydrolysis of 4-aminoisothiazole-3-carboxamide 4-Aminoisothiazole--3-carboxamide[114] (150 mg) in aqueous sodium hydroxide (2.5N, 40 ml) was heated on a steam bath for 30 min; ammonia was freely evolved. The cold solution was acidified to pH 4 with 2.5N-hydrochloric acid when a white solid separated (20 mg), m.p. 185-186°. The filtrate was continuously extracted with ether for 24 h and the dried ($MgSO_4$) ethereal extract evaporated under reduced pressure to give a pale yellow crystalline solid (100 mg) m.p. 185-187°. Recrystallisation of the combined solids from water gave the amino acid as pale yellow needles (56 mg, 50%), m.p. 187-188° Further recrystallisation raised the m.p. to 189-191°; the i.r. spectrum was identical with that of the amino acid obtained by reduction of the nitro acid.

Attempted reduction of 4-nitroisothiazole-3-carboxylic acid with palladium charcoal-sodium borohydride.

Sodium borohydride (0.26 g, 0.06 mol) in water (5 ml) was added to a suspension of palladised charcoal (10%, 16 mg) in water (5 ml). A slow stream of nitrogen was bubbled through the mixture and a solution of 4-nitroisothiazole-3-carboxylic acid (0.52 g, 0.003 mol) in methanol (10 ml) was added dropwise during 10 min. The mixture was allowed to stand at room temperature for 10 min and then acidified to pH 2-3. Continuous ether extraction of the aqueous solution for 24 h followed by evaporation of the dried ($MgSO_4$) extract gave a gummy solid (106 mg) which was shown by t.l.c. to consist of a mixture of the nitro-acid and the amino acid (ca 1:1); a system of butanol, acetic acid and water (8:1:1) was used as developing solvent. Attempted crystallisation from aqueous ethanol gave a solid (66 mg) m.p. 148-162°. Further purification could not be achieved and the infrared spectrum indicated that it was impure amino acid.

4-Iodoisothiazole-3-carboxylic acid

4-Aminoisothiazole-3-carboxylic acid (0.44 g, 3 mmol) was dissolved in a mixture of concentrated sulphuric acid (0.75 ml) and water (3 ml) by warming and then cooled to 0-5° when a solid, presumably the salt, separated. A solution of sodium nitrite (0.22 g, 3.2 mmol) in water (1.5 ml) was added dropwise to the stirred mixture keeping the temperature below 5°. After stirring for 5 min a solution of potassium iodide (0.51 g, 3.07 mmol) in water (2 ml) was added dropwise; a brown solid separated. The mixture was kept at room temperature for 5 min and then warmed to 40-45°; frothing occurred whilst nitrogen was evolved and a solid separated. After 10 min the mixture was heated for 10 min on a steam bath, then cooled in ice water. Excess iodine was removed by the addition of a little solid sodium bisulphite. The solid was collected, washed with water, and recrystallised from water (charcoal) to give the iodo-acid (300 mg, 40%) as colourless needles, m.p. 184-185°. (Found: C, 19.2; H, 0.87; N, 5.32

S, 12.50; I, 49.80. $C_4H_2NO_2SI$ requires C, 18.82; H, 0.78; N, 5.52; S, 12.57; I, 49.73%). ν max 3080 (C-H), 2900-2550 (bonded OH), 1720 (C=O), 800 cm^{-1}.

4-Isothiazolediazonium-3-carboxylate hydrochloride

4-Aminoisothiazole-3-carboxylic acid (600 mg, 4.2 mmol) was dissolved in a mixture of dry methanol (100 ml) and dioxan (50 ml) saturated with dry hydrogen chloride at 25-30°. The stirred solution was treated dropwise at 10-12° with isoamyl nitrite (1.0 ml, 7.4 mmol) and then kept at 0° in the dark for 1 h. After dilution with dry ether (500 ml), the mixture was kept 1 h in the dark at 0° and the white solid diazoniumcarboxylate hydrochloride collected on a plastic funnel and washed with dry ether, (500 mg, 63%) m.p. 163-165° (decomposition). (Found: C, 25.1; H, 1.10; N, 22.0; S, 16.6. $C_4H_2N_3O_2SCl$ requires: C, 25.07; H, 1.052; N, 21.93; S, 16.6%). ν max. 3105 (C-H), 2900-2520 (bonded OH), 2258 ($-\overset{+}{N}\equiv N$), 1708 (C=O) cm^{-1}.

The salt was stored at 0°, under nitrogen, in the dark.

Attempted preparation of 1-(3-carboxy-4-isothiazolyl)-3,3-dimethyltriazene

4-Aminoisothiazole-3-carboxylic acid (0.44 g, 0.003 mol) was dissolved in a mixture of concentrated sulphuric acid (0.75 ml) and water (3.0 ml). The stirred mixture was cooled to 0-5° and a solution of sodium nitrite (0.22 g) in water (1.5 ml) added slowly, keeping the temperature below 5°.

The cold diazonium solution was then added over 5 min to a stirred solution of dimethylamine (0.8 g) in sodium carbonate (2.0 g, 0.019 mol) in water (7.0 ml). The resulting yellow mixture was stirred for 30 min at 10-15° and then acidified with 0.1N-hydrochloric acid to pH 4-5. Continuous chloroform extraction for 28 h gave no product.

Attempted generation of isothiazolynes

Investigation of the reaction between 5-amino-3-chloroisothiazole-4--carboxylic acid and isoamylnitrite in the presence of 2,3,4,5--tetraphenylcyclopentadienone(tetracyclone)

5-Amino-3-chloroisothiazole-4-carboxylic acid (300 mg, 1.7 mmol) in 1,2-dimethoxyethane (10 ml) and isoamylnitrite (1.0 ml, 7.5 mmol) in 1,2-dimethoxyethane were added in portions, from separate funnels, to a stirred refluxing solution of tetracyclone (400 mg, 1.05 mmol) in 1,2-dimethoxyethane under nitrogen. It was necessary to warm the amino acid solution to 35-40° to prevent solid separating. Addition was made over 20 min and the mixture heated for a further 10 min when the purple colour changed suddenly to light yellow. Evaporation of the clear solution under reduced pressure gave an orange coloured semi-solid (700 mg); t.l.c. (methylene chloride) showed at least three spots.

The semi solid was dissolved in chloroform (15 ml) and extracted firstly with saturated potassium carbonate solution (7 ml) and then with 6N-hydrochloric acid (10 ml). Each aqueous extract was back extracted with chloroform (8 ml) which was added to the chloroform solution.

Basification of the acid extract followed by continuous ether extraction gave no residue.

Acidification of the alkaline solution with dilute hydrochloric acid followed by ether extraction (3x15 ml) and evaporation of the dried extracts gave a yellow gummy solid (98 mg). Trituration with benzene gave a yellow solid (65 mg), m.p. 212-234°. Recrystallisation from water (charcoal) gave 3-chloroisothiazole-4-carboxylic acid (44 mg) as colourless needles, m.p. 241-242°. (Found: C, 29.2; H, 1.19; N, 8.5; Cl, 21.50. $C_4H_2NO_2SCl$ requires C, 29.37; H, 1.22; N, 8.6; Cl, 21.68%). ν max. 3110 (C-H), 2900-2520 (broad, bonded -OH), 1720 (C=O) cm^{-1} δ [$(CD_3)_2SO$, N.M.R.26] 5.58 (1H, s, $=\overset{\oplus}{N}H$), 9.7 (1H, s, H-5) p.p.m.

Evaporation of the dried ($MgSO_4$) chloroform solution gave a yellowish-brown semi-solid (580 mg), t.l.c. of which showed the same three spots as above. The material was subjected to dry column chromatography on silica gel (45 g, 13" x 1") with methylene chloride as developing solvent; the column was divided into thirteen fractions each of which was eluted, examined by t.l.c., and the appropriate fractions combined.

Fractions 1-6 gave a yellow semi solid (76 mg).

Recrystallisation from acetone-light petroleum (b.p. 40-60°) gave 2-benzoyl-3,4,5-triphenylfuran (47 mg), m.p. 166-167°, identical (mixed m.p., t.l.c. and i.r.) with an authentic sample.

Fractions 7-8 gave a yellow gummy solid (73 mg) which showed a major compound and a trace of two other compounds on t.l.c. Further dry column chromatography gave the major compound as a yellow solid (85 mg); recrystallisation from ethyl acetate-light petroleum gave yellow needles (49 mg), m.p. 166-168°. (Found: C, 85.4; H, 5.07. $(C_{12}H_8O)_n$ requires C, 85.69; H, 4.8%). $\nu_{max.}$ 3400 (-OH), 3040, 3010 (C-H), 1710 (C=O) cm^{-1}. δ [$(CD_3)_2CO$] 6.92-7.3 (aromatic H's).

Fractions 9-13 gave a solid (191 mg); recrystallisation from benzene-light petroleum gave 2,3-dihydroxytetraphenylcyclopentenone as colourless needles (162 mg), m.p. 189-191°, identical (mixed m.p., t.l.c. and i.r.) with an authentic sample.

2,3,4,5-Tetraphenyl-2,3-dihydroxycyclopentenone[118]

Oxidation of 2,3,4,5-tetraphenylcyclopentadienone with nitric acid in dioxan as described in the literature gave the dihydroxycyclopentenone as colourless needles m.p. 189-191° (lit.,[118] m.p. 190-191°).

2-Benzoyl-3,4,5-triphenylfuran[118]

Treatment of the foregoing dihydroxycyclopentenone in pyridine with alcoholic potassium hydroxide as described by Dilthey and co-workers gave 2-benzoyl-3,4,5-triphenylfuran as buff coloured needles, m.p. 165-167° (lit.,[118] m.p. 166-167°).

Investigation of the reaction between tetracyclone and isoamyl nitrite in the presence of trichloroacetic acid.

A stirred mixture of tetracyclone (0.35 g), isoamylnitrite (1.0 ml) and trichloroacetic acid (5 mg) in 1,2-dimethoxyethane (10 ml) was heated under reflux; the purple colour of the tetracyclone faded gradually and after 25-30 min, solvents were removed from the clear yellow solution leaving a gummy solid (0.36 g). Treatment with benzene-light petroleum gave a solid (280 mg), m.p. 160-179°. Recrystallisation from benzene (charcoal) gave 2,3-dihydroxy-2,3,4,5-tetraphenylcyclopent-4-enone (220 mg, 60%) as white needles, m.p. 189-191°, identical (mixed m.p., i.r. and t.l.c.) with an authentic sample.

Investigation of the reaction between 4-amino-3-methylisothiazole-5-carboxylic acid and isoamylnitrite in the presence of tetracyclone.

4-Amino-3-methylisothiazole-5-carboxylic acid (500 mg, 3.15 mmol) in 1,2-dimethoxyethane (7.0 ml) and isoamyl nitrite (1.0 ml, 7.5 mmol) in 1,2-dimethoxyethane (6 ml) were added in portions from separate funnels, to a stirred refluxing solution of tetracyclone (900 mg, 2.3 mmol) in 1,2-dimethoxyethane under nitrogen. Addition was made over a period of 45 min and heating continued for another 45 min during which time the purple colour of the solution gradually changed to pink. Evaporation under reduced pressure gave a yellowish-red oil (1.41 g); t.l.c. (methylene chloride) showed a mixture of at least five components.

The residue was dissolved in chloroform (10 ml) and extracted first with saturated potassium carbonate solution (5 ml) and then with 6N-hydrochloric acid. Each aqueous extract was back extracted with

chloroform (5 ml) which was added to the chloroform solution.

Basification of the acid extract followed by ether extraction (3 x 10 ml) and evaporation of the dried ($MgSO_4$) extracts gave no residue.

Acidification of the alkaline solution with dilute hydrochloric acid followed by ether extraction (3x10 ml) and evaporation of the dried ($MgSO_4$) extracts gave a brown oil (42 mg) which could not be obtained crystalline and was not further investigated.

Evaporation of the dried ($MgSO_4$) chloroform solution left a yellowish red oil (1.22 g) which was chromatographed on a column of dry alumina (activity II - III, 200 g, 36" x 1") using methylene chloride as developing solvent. The column was divided into thirtysix portions and these were combined appropriately after t.l.c. examination.

Fractions 1-7 (82 mg) gave a mixture of three components. Preparative t.l.c. on silica gel (PF_{254}, 1.3 mm, 20x20 cm) with methylene chloride gave

(a) tetracyclone (15 mg)

(b) 2-benzoyl-3,4,5-triphenylfuran (16 mg) m.p. 164-166° from acetone-light petroleum (b.p. 40-60°); identical (mixed m.p., t.l.c. and i.r.) with an authentic sample.

(c) 3-methyl-4-nitroisothiazole (34 mg) as a yellow oil; identified by comparison (g.l.c., t.l.c. and n.m.r.) with an authentic sample.

Fractions 10-20 gave a gum (226 mg); preparative t.l.c. on silica gel (PF_{254}, 1.5 mm, 20x20 cm) with methylene chloride as developing solvent gave three products:

(d) a solid (26 mg) m.p. 166-168°, identical with the compound $(C_{12}H_8O)_n$ obtained in the previous trapping experiment (p.148)

(e) a white solid (68 mg). Recrystallisation from benzene-light petroleum gave the compound (31 mg) as plates, m.p. 161-164°, after softening from 155°. (Found: C, 76.8, H, 5.99; $(C_6H_6O)_n$ requires C, 76.57; H, 6.43%).)) max. 3420 (-OH), 3050, 2900 (C-H), 1750 (C=O) cm^{-1}.

(f) 2,3-dihydroxytetraphenylcyclopentenone (86 mg), m.p. 189-191° from benzene-light petroleum, identical (mixed m.p., t.l.c. and i.r.) with an authentic sample.

Fractions 26-36 gave a further amount (97 mg) of 2,3-dihydroxytetraphenylcyclopentenone.

Investigation of the reaction between 4-amino-3-methylisothiazole--5-carboxylic acid and isoamyl nitrite in the presence of furan.

4-Amino-3-methylisothiazole-5-carboxylic acid (0.632 g, 0.004 mol) in dry 1,2-dimethoxyethane (10 ml) and isoamyl nitrite (1.5 ml, 0.0112 mol) in 1,2-dimethoxyethane (10 ml) were added, in portions from separate funnels to a stirred refluxing solution of furan (15 ml) and 1,2-dimethoxyethane (15 ml). Addition was made over 35 min and the mixture heated for another 1 h thereafter. Evaporation of the clear solution under reduced pressure gave a brown oily residue (608 mg); t.l.c. (benzene) showed one major spot.

The residue was dissolved in chloroform (10 ml) and extracted first with saturated sodium bicarbonate solution (6 ml) and then with 6N-hydrochloric acid (6 ml). Each aqueous extract was back extracted with chloroform (10 ml) which was added to the chloroform solution.

Basification of the acid extract followed by continuous ether extraction gave no residue.

Acidification of the alkaline solution with dilute hydrochloric acid followed by continuous ether extraction for 24 h and evaporation of the dried ($MgSO_4$) extract gave a brown oily residue (121 mg) which could not be crystallised and was not further investigated.

Evaporation of the dried ($MgSO_4$) chloroform solution gave a reddish brown oil (138 mg); t.l.c. showed only one major component. Molecular distillation of the neutral fraction at 73-76° (oil bath) at 1 mmHg gave a pale yellow oil (82 mg) which slowly turned red on standing. The product showed one peak on g.l.c. (t, 3.8 min, 5% carbowax, 164°) and was homogeneous by t.l.c. The product was identified as 4-(2'-furyl)-3-methylisothiazole, (Found: M^+, 165.025. C_8H_7NOS requires, M, 165.0249). δ($CDCl_3$, N.M.R.27) 2.66 (3H, s, CH_3-3), 6.55 (2H,m), 7.5 (1H, m), 8.73 (1H, s, H-5) p.p.m.

Investigation of the reaction between 4-amino-3-methylisothiazole--5-carboxylic acid and anthracene with isoamyl nitrite.

4-Amino-3-methylisothiazole-5-carboxylic acid (1.2 g, 0.0075 mol) in 1,2-dimethoxyethane (15 ml) and isoamyl nitrite (2 ml, .0224 mol) in 1,2-dimethoxyethane (13 ml) were added, in portions from separate funnels, to a stirred refluxing suspension of anthracene (1.78 g, 0.01 mol) in 1,2-dimethoxyethane. Addition was made over 20 min and the red solution heated for another 20 min. Solvents were removed under reduced pressure to give a reddish brown gum (2.68 g).

The residue was dissolved in chloroform (25 ml) and extracted first with saturated sodium bicarbonate solution (10 ml) and then with 6N-hydrochloric acid (10 ml). Each aqueous extract was back extracted with chloroform (10 ml) which was combined with the chloroform solution.

Basification of the acid extract followed by continuous ether extraction gave no residue.

Acidification of the alkaline solution with dilute hydrochloric acid followed by continuous ether extraction gave a brown gum (102 mg) which resisted crystallisation and was not further investigated.

Evaporation of the dried ($MgSO_4$) chloroform solution gave a reddish brown gum (2.08 g). T.l.c. (benzene) showed a major spot corresponding

to anthracene and a trace of two other compounds. The mixture was subjected to chromatography on neutral alumina (60 g, 2.5x15 cm) and eluted as follows:

Fraction (1) Light petroleum (10x25 ml) gave anthracene (1.62 g)

Fraction (2) Light petroleum 90%-ether 10% (8x25 ml) gave 100 mg of a yellow solid consisting mostly of anthracene.

Fraction (3) Light petroleum 80%-ether 20% (4x25 ml) gave 64 mg of a gum consisting of a yellow spot and a trace of another compound.

Fraction (4) Light petroleum-ether (50:50, 4x25 ml) gave 20 mg of gummy solid as in (3)

Fraction (5) Ether (100 ml) gave no residue.

Fraction (6) Methanol (200 ml) gave a brown residue which was not investigated further.

Fractions (3) and (4) were combined and further subjected to dry column chromatography on silica gel (55 g, 10x1") and eluted with carbon tetrachloride. The major compound was obtained as a yellow gum (48 mg) which was recrystallised from light petroleum to give yellow needles (40 mg) m.p. 145-146°, identified as 9-nitroanthracene (lit., m.p. 146°) (Found: M^+, 223.0634. $C_{14}H_9NO_2$ requires M, 223,0633). λ max. (U.V.11) 252 nm (ε 78,000). δ ($CDCl_3$, N.M.R.28) 7.27-8.06 (8H, m), 8.44 (1H, s) p.p.m.

The minor component was obtained as pale yellow needles (8 mg), from acetone, m.p. 225-227°. The compound was identified as 9-(3-methyl-4-isothiazolyl) anthracene on the basis of its ultraviolet spectrum which was very similar to that of 9-nitroanthracene. (Found M^+, 275.0774. $C_{18}H_{13}NS$ requires M, 275.0769). λ max. (U.V.12) 254 nm.

Investigation of the reaction between 4-aminoisothiazole-3-carboxylic acid and isoamyl nitrite in the presence of tetracyclone.

A suspension of 4-aminoisothiazole-3-carboxylic acid (1.44 g, 0.01 mol) in 1,2-dimethoxyethane (20 ml) and isoamyl nitrite (2.5 ml, 0.0188 mol) in 1,2-dimethoxyethane (8.5 ml) were added in portions to a stirred refluxing solution of tetracyclone (3.84 g, 0.01 mol) in 1,2-dimethoxyethane (25 ml) under nitrogen. Addition was made over 50 min; rapid evolution of gas was observed after each addition. Heating was continued for a further 15 min during which time the purple colour of the solution changed to yellow. Evaporation under reduced pressure gave a reddish brown gummy residue (5.11 g); t.l.c. (methylene chloride) showed at least five spots, two of which corresponded to 2-benzoyl-3,4,5-triphenylfuran and 2,3-dihydroxytetraphenylcyclopentenone.

The residue was dissolved in chloroform (20 ml) and extracted first with saturated potassium carbonate solution (10 ml) and then with 6N-hydrochloric acid (10 ml). Each aqueous extract was back extracted with chloroform (10 ml) which was added to the chloroform solution.

Basification of the acid extract followed by ether extraction (3 x 15 ml) gave no residue.

Acidification of the alkaline solution with dilute hydrochloric acid followed by ether extraction (3x20 ml) and evaporation of the dried ($MgSO_4$) extracts gave a yellow gummy solid (260 mg). Trituration with benzene gave a yellow solid (162 mg), m.p. 129-131°. Recrystallisation from ethyl acetate (charcoal)-light petroleum gave isothiazole-3-carboxylic acid (108 mg as yellow plates, m.p. 133-135° identical (mixed m.p. and i.r.) with an authentic sample. δ [$(CD_3)_2SO$] 7.89 (1H, d, J 5 Hz, H-4), 9.01 (1H, s, $-CO_2H$), 9.15 (1H, d, J 5 Hz, H-5) p.p.m.

Evaporation of the dried ($MgSO_4$) chloroform solution gave a yellowish-red gum (4.61 g); t.l.c. (methylene chloride) showed at least five spots.

The material was subjected to dry column chromatography on neutral alumina (activity III, 140 g, 10x2") with methylene chloride as developing solvent; the column was divided into ten fractions each of which was eluted with methyl alcohol, examined by t.l.c. and the appropriate fractions combined.

Fractions 1-4 gave a reddish brown oil (2.86 g). Methanol was added and the solution cooled at 0° for 48 h. The yellow solid (1.2 g) m.p. 161-164° was recrystallised from acetone-light petroleum (b.p. 40-60°) gave 2-benzoyl-3,4,5-triphenylfuran (1.0 g), m.p. 166-167°, identical (mixed m.p. i.r. and t.l.c.) with an authentic sample.

Fractions 6-8 gave a yellow gummy solid (862 mg) which was dissolved in hot benzene. Addition of light petroleum and allowing to stand overnight at room temperature gave white needles (610 mg), m.p. 176-182°. Recrystallisation from benzene (charcoal)-light petroleum gave 2,3-dihydroxytetraphenylcyclopentenone. (508 mg), m.p. 189-191° identical with an authentic sample.

Further dry column chromatography and preparative t.l.c. of the liquors from fractions 1-4 (1.4 g) gave 2-benzoyl-3,4,5-triphenylfuran (32 mg) and the compounds of molecular formulae $(C_{12}H_8O)_n$, m.p. 166-168° (142 mg) and $(C_6H_6)_nO$, m.p. 163-165°, described previously, as the only isolable products.

Investigation of the reaction between 4-isothiazolediazonium--3-carboxylate hydrochloride and furan in the presence of propylene oxide.

A mixture of 4-isothiazolediazonium-3-carboxylate hydrochloride (500 mg 0.0026 mol), furan (23 g, 0.3 mol), and propylene oxide (2.0 ml) in 1,2-dichloroethane (20 ml) was heated under reflux, with stirring for 30 h when a light brown solution was obtained. A small amount of insoluble material was separated by filtration and the organic solvents evaporated under reduced pressure leaving a brown oily residue (384 mg); t.l.c. (chloroform) showed one major spot. The residue was dissolved in chloroform (15 ml) and extracted first with saturated sodium bicarbonate solution (5 ml) and then with 2.5N-hydrochloric acid (5.0 ml).

Basification of the acid extract followed by ether extraction (3x15 ml) gave no residue.

Acidification of the alkaline solution with dilute hydrochloric acid followed by ether extraction (3x15 ml) and evaporation of the dried ($MgSO_4$) extracts gave a brown oily residue (64 mg) which could not be crystallised and was not further investigated.

Evaporation of the dried ($MgSO_4$) chloroform solution gave a brown viscous oil; t.l.c. (methylene chloride) showed only one component. Preparative t.l.c. of the material (269 mg) with methylene chloride as developing solvent gave the major spot as a brown oil (26 mg) which was recrystallised from light petroleum (charcoal). The product (17 mg) was obtained as colourless needles m.p. 60-61° and identified as 4-cyano-1,2,3-thiadiazole by comparison (mixed m.p. and i.r.) with an authentic sample.[122] The molecular formula obtained by mass spectrometry was C_3HN_3S. (Found: M^+, 110.9897. C_3HN_3S requires M, 110.9891). ν max. ($CHCl_3$) 3110 (C-H), 2240 (C≡N), 970, 880 cm^{-1}. δ ($CDCl_3$, 100 MHz, N.M.R.29) 9.2 (1H, s, H-5) p.p.m. m/e 111 (39%), 83 (100%), 57 (6%).

The residue (115 mg) after further elution of the plate could not be crystallised and was not further investigated.

SPECTRA

Ultraviolet Spectra

U.V. 1. 3,6-Dimethylisothiazolo[5,4-b]pyridine

2. Ethyl 4-hydroxy-3-methylisothiazolo[5,4-b]pyridine--5-carboxylate

3. 3-Methylisothiazolo[5,4-b]pyrid-4-one

4. 4-Chloro-3-methylisothiazole[5,4-b]pyridine

5. 4-Methoxy-3-methylisothiazolo[5,4-b]pyridine

6. N-Methyl-3-methylisothiazolo[5,4-b]pyrid-4-one

7. Ethyl 4-chloro-3-methylisothiazolo[5,4-b]pyridine-5-carboxylate

8. Methyl 4-methoxy-3-methylisothiazolo[5,4-b]pyridine--5-carboxylate

9. Ethyl N-methyl-3-methylisothiazolo[5,4-b]pyrid--4-one-5-carboxylate

10. 5-Acetyl-3,4-dimethylisothiazole

11. 9-Nitroanthracene

12. 9-(3-methyl-4-isothiazolyl) anthracene

Infrared Spectra

I.R. 1. Isothiazolo[5,4-b]pyrid-3(2H)one 1,1-dioxide

2. 2-Sulphoamidopyridine-3-carboxylic acid

3. 6-Methylisothiazolo[5,4-b]pyrid-3-(2H)one1,1-dioxide

4. 6-Methyl-2-sulphoamidopyridine-3-carboxylic acid

5. Diethyl 2-(3-methylisothiazol-5-ylaminomethylene)malonate

6. Ethyl 4-hydroxy-3-methylisothiazolo[5,4-b]pyridine--5-carboxylate

7. 4-Hydroxy-3-methylisothiazolo[5,4-b]pyridine-5-carboxylic acid.

8. 3-Methylisothiazolo[5,4-b]pyrid-4-one

9. N-Methyl-3-methylisothiazolo[5,4-b]pyrid-4-one

10. Ethyl 4-chloro-3-methylisothiazolo[5,4-b]pyridine--5-carboxylate

11. Methyl 4-methoxy-3-methylisothiazolo[5,4-b]pyridine--5-carboxylate

12. Ethyl N-methyl-3-methylisothiazolo[5,4-b]pyrid-4-one--5-carboxylate

13. Ethyl 3-aminocrotonate

14. Ethyl 3-(3-methylisothiazol-5ylamino)crotonate

15. 4-Acetyl-3,4-dimethylisothiazole

16. 4-Aminoisothiazole-3-carboxylic acid

17. 5-Amino-3-chloroisothiazole-4-carboxylic acid

Nuclear Magnetic Resonance Spectra

N.M.R.1. 3,6-Dimethylisothiazolo[5,4-b]pyridine

2. 3-Methylisothiazolo[5,4-b]pyridine

3. 3,4-Dimethylisothiazolo[5,4-b]pyridine

4. 5-Ethyl-3-methylisothiazolo[5,4-b]pyridine picrate

5. 3-Methyl-6-styrylisothiazolo[5,4-b]pyridine

6. Isothiazolo[5,4-b]pyrid-3(2H)-one 1,1-dioxide.

7. 2-Hydroxypyridine-3-carboxylic acid

8. 2-Sulphoamidopyridine-3-carboxylic acid

9. 6-Methylisothiazolo[5,4-b]pyrid-3(2H)-one 1,1-dioxide

10. 2-Hydroxy-6-methylpyridine-3-carboxylic acid

11. 6-Methyl-2-sulphoamidopyridine-3-carboxylic acid

12. Diethyl 2-(3-methylisothiazol-5-ylaminomethylene)malonate

13. Ethyl 4-hydroxy-3-methylisothiazolo[5,4-b]pyridine--5-carboxylate

14. 4-Hydroxy-3-methylisothiazolo[5,4-b]pyridine-5-carboxylic acid

15. 3-Methylisothiazolo[5,4-b]pyrid-4-one

16. 4-Chloro-3-methylisothiazolo[5,4-b]pyridine

17. 4-Methoxy-3-methylisothiazolo[5,4-b]pyridine

18. N-Methyl-3-methylisothiazolo[5,4-b]pyrid-4-one

19. Ethyl 4-chloro-3-methylisothiazolo[5,4-b]pyridine-5--carboxylate

20. Methyl 4-methoxy-3-methylisothiazolo[5,4-b]pyridine--5-carboxylate

21. Ethyl N-Methyl-3-methylisothiazolo[5,4-b]pyrid-4-one-5-carboxylate

22. Ethyl 3-aminocrotonate

23. Ethyl 3-(3-methylisothiazol-5ylamino)crotonate

24. 5-Acetyl-3,4-dimethylisothiazole

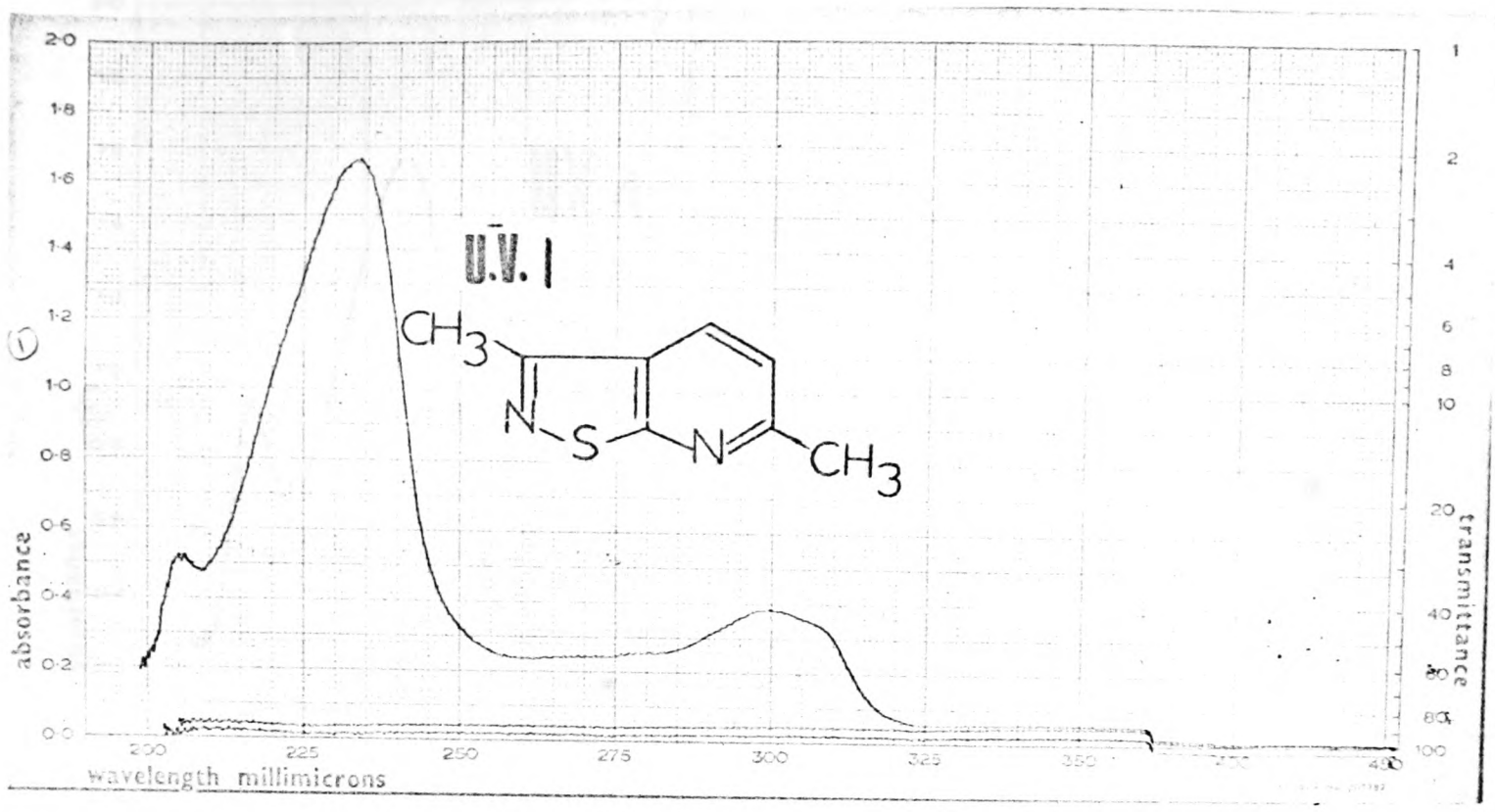
25. 4-Aminoisothiazole-3-carboxylic acid

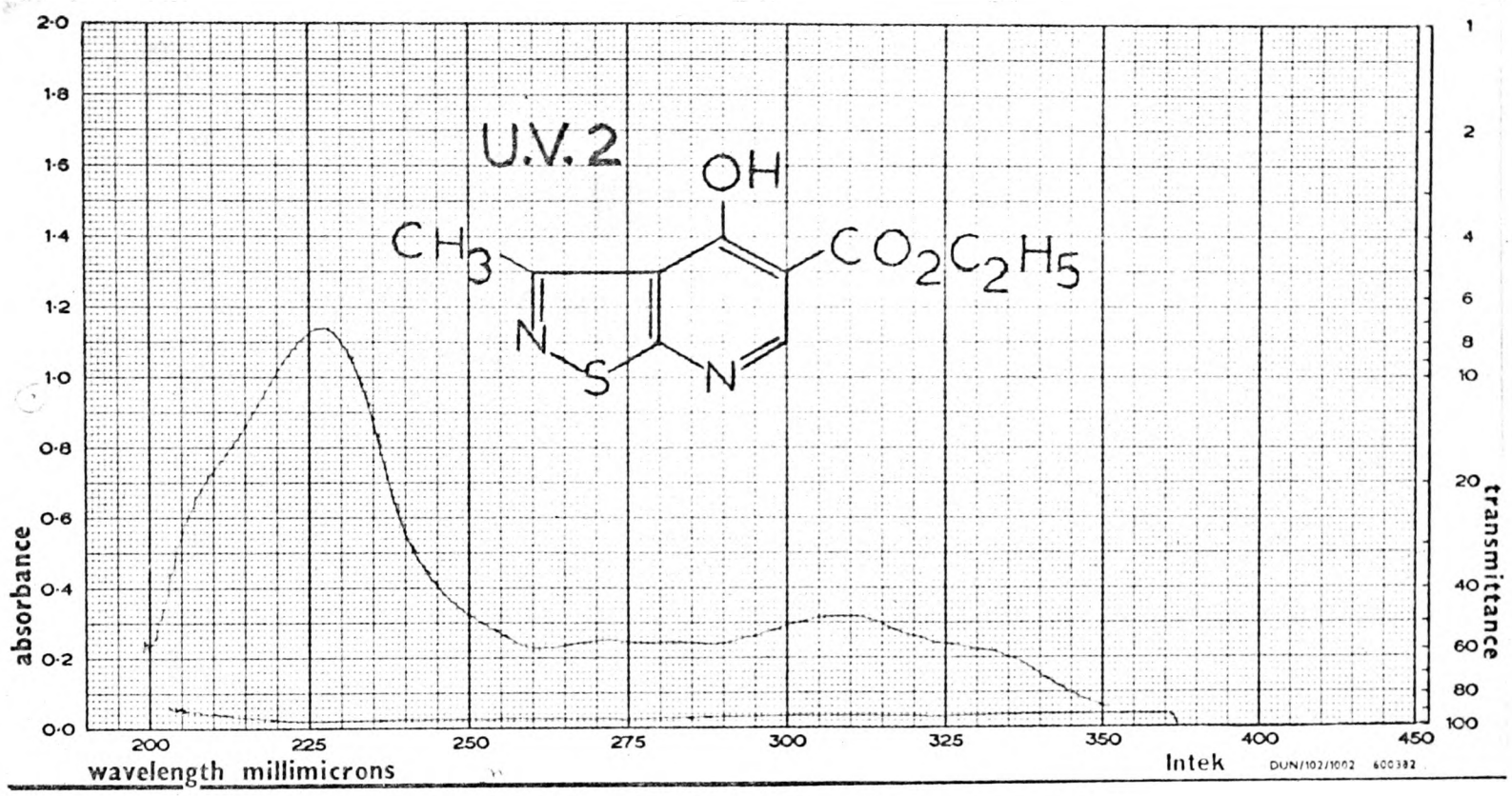
26. 3-Chloroisothiazole-4-carboxylic acid

27. 4-(2'-furyl)-3-methylisothiazole

28. 9-Nitroanthracene

29. 4-Cyano-1,2,3-thiadiazole


U.V. 1
CH3
N
S
N
CH3
absorbance
transmittance
wavelength millimicrons
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
200
225
250
275
300
325
350
1
2
4
6
8
10
20
40
60
80
100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OH
CH3
CO2C2H5
N
S
N
absorbance
transmittance
wavelength millimicrons
Intek
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
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6
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80
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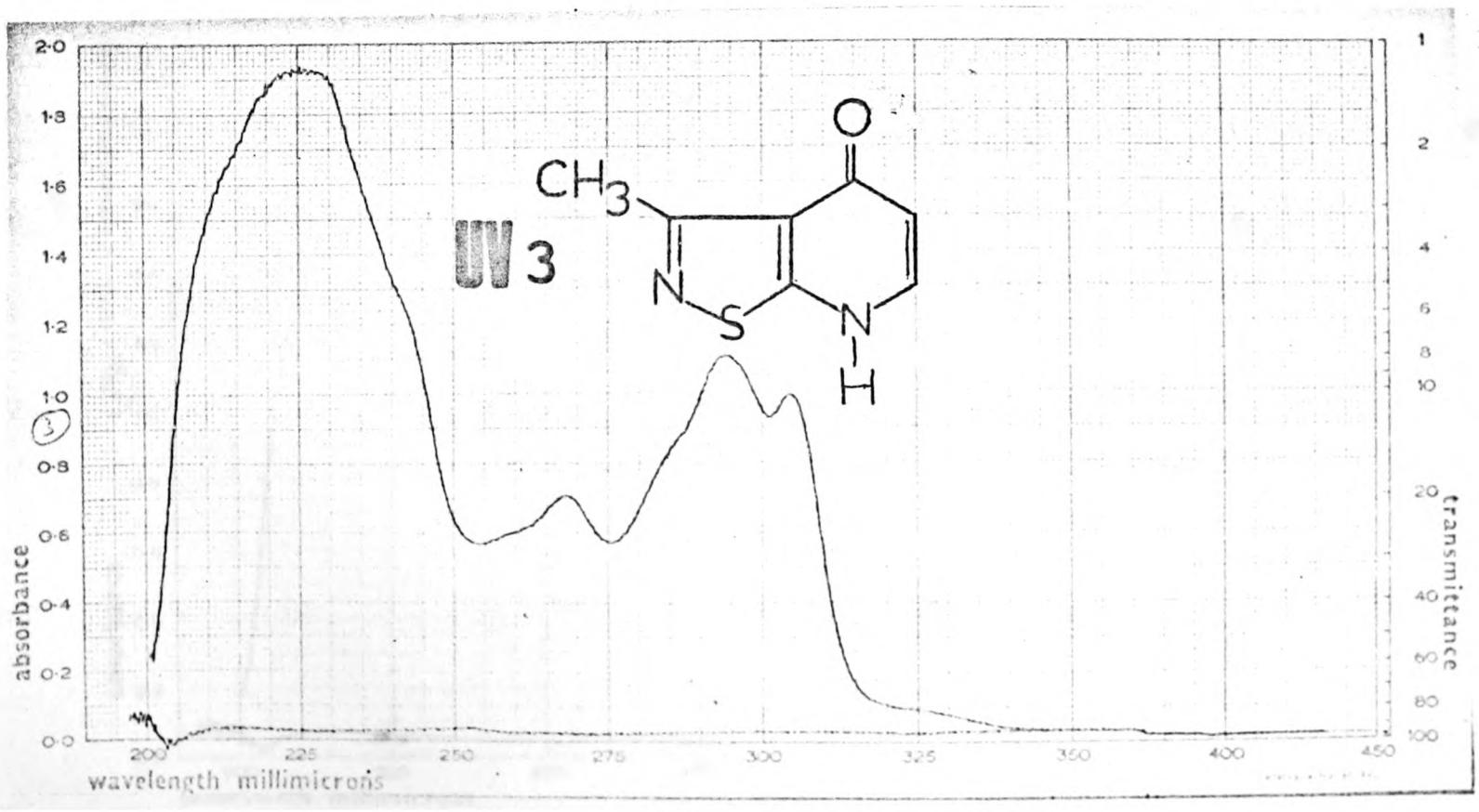
UV 3
O
CH3
N
S
N
H
absorbance
transmittance
wavelength millimicrons
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
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80
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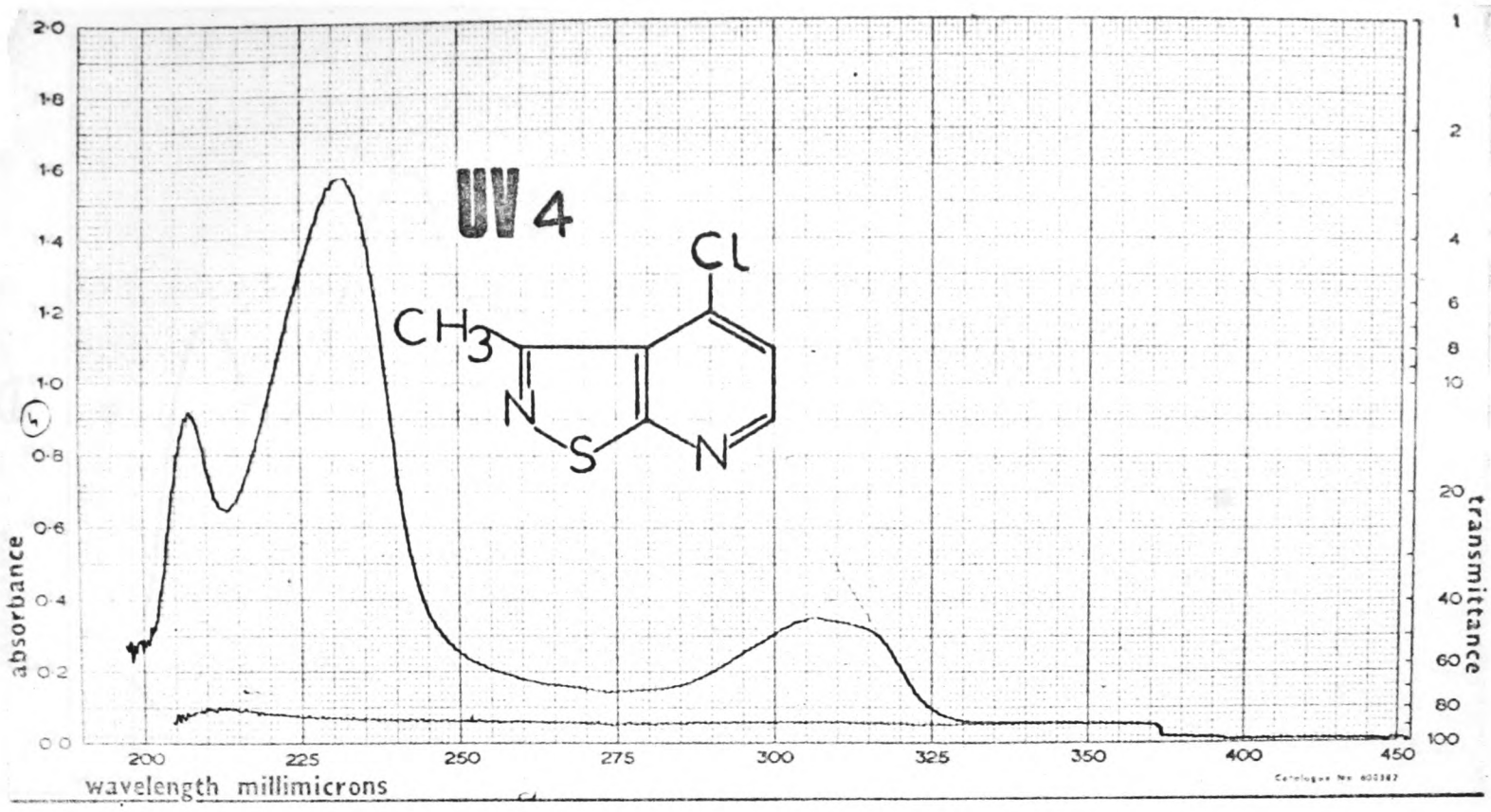
UV 4
Cl
CH3
N
S
N
absorbance
transmittance
wavelength millimicrons
200
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250
275
300
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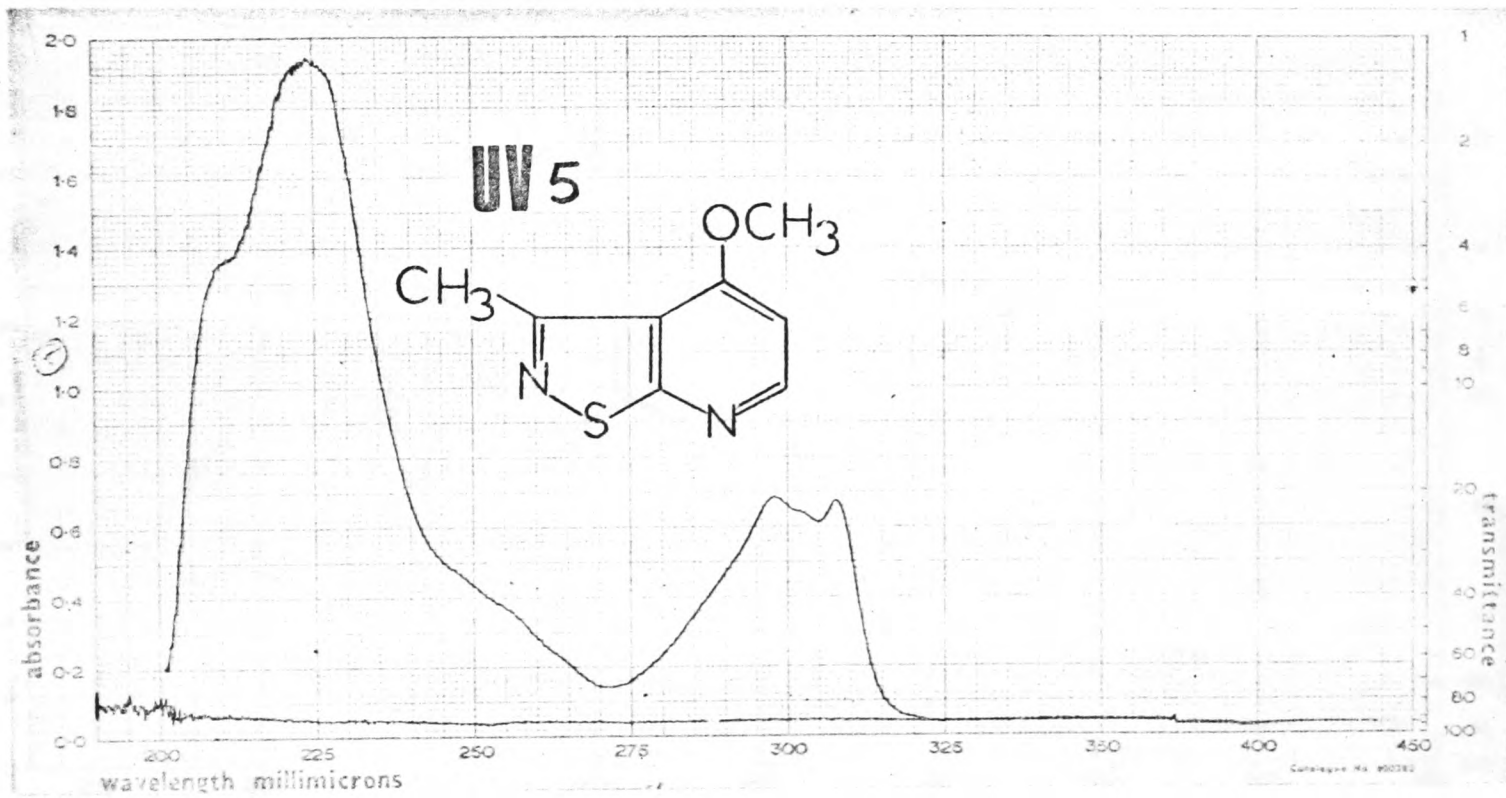
350
400
450


UV 5
OCH3
CH3
N
S
N
absorbance
transmittance
wavelength millimicrons
200
225
250
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400
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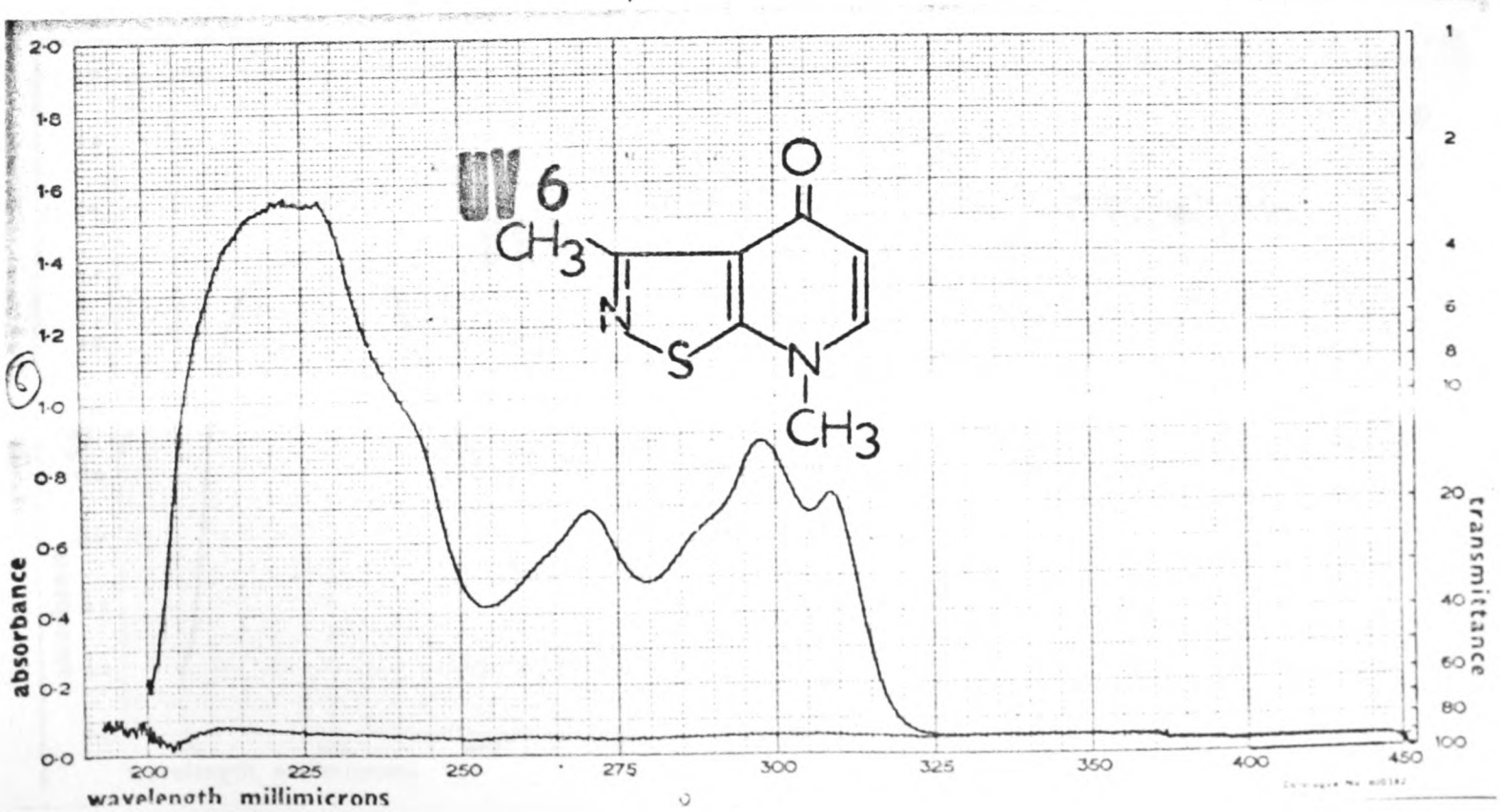
UV 6
CH3
O
N
S
N
CH3
absorbance
transmittance
wavelength millimicrons
200
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250
275
300
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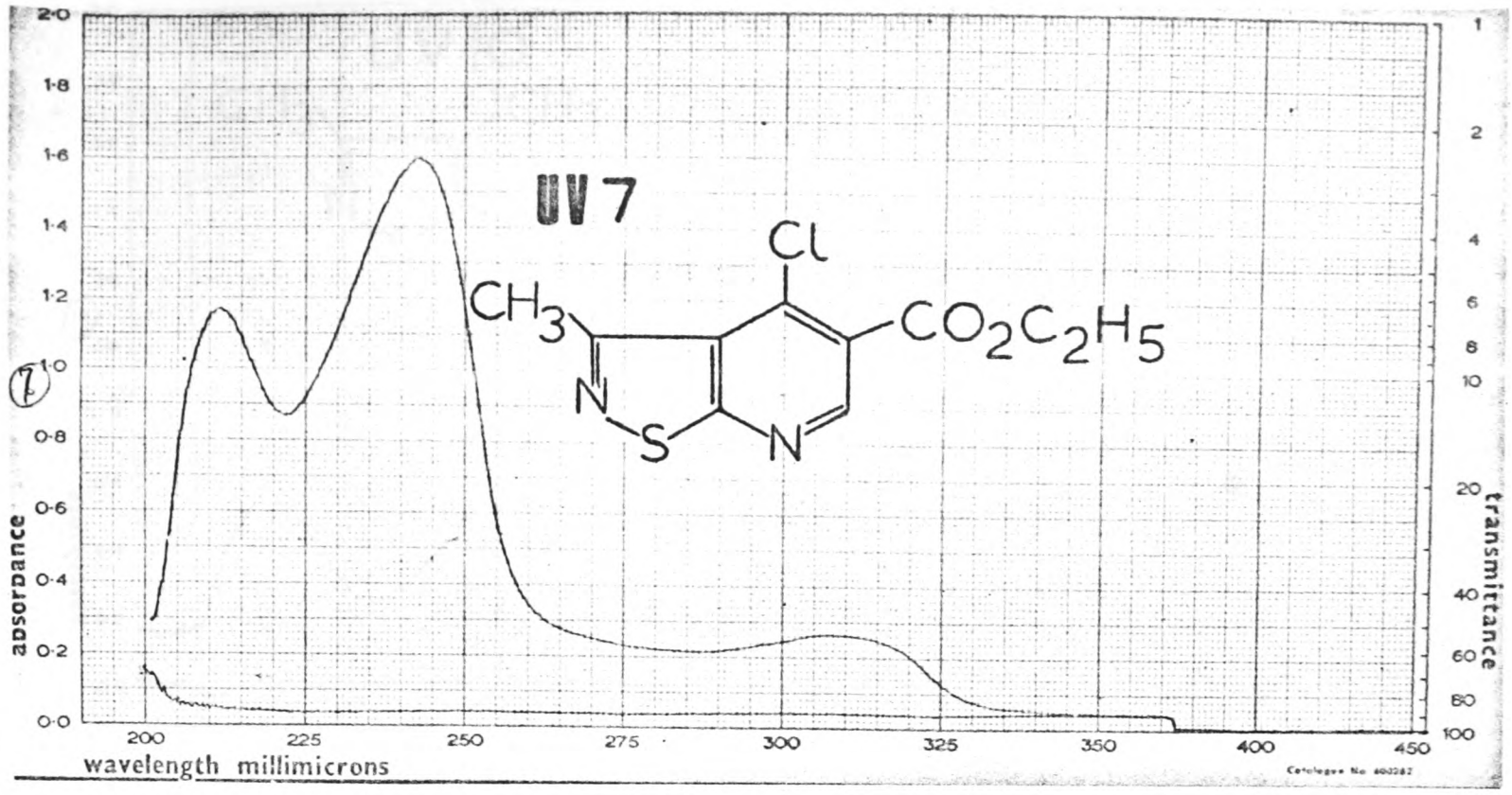
400
450


UV 7
Cl
CH3
CO2C2H5
N
S
N
absorbance
transmittance
wavelength millimicrons
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
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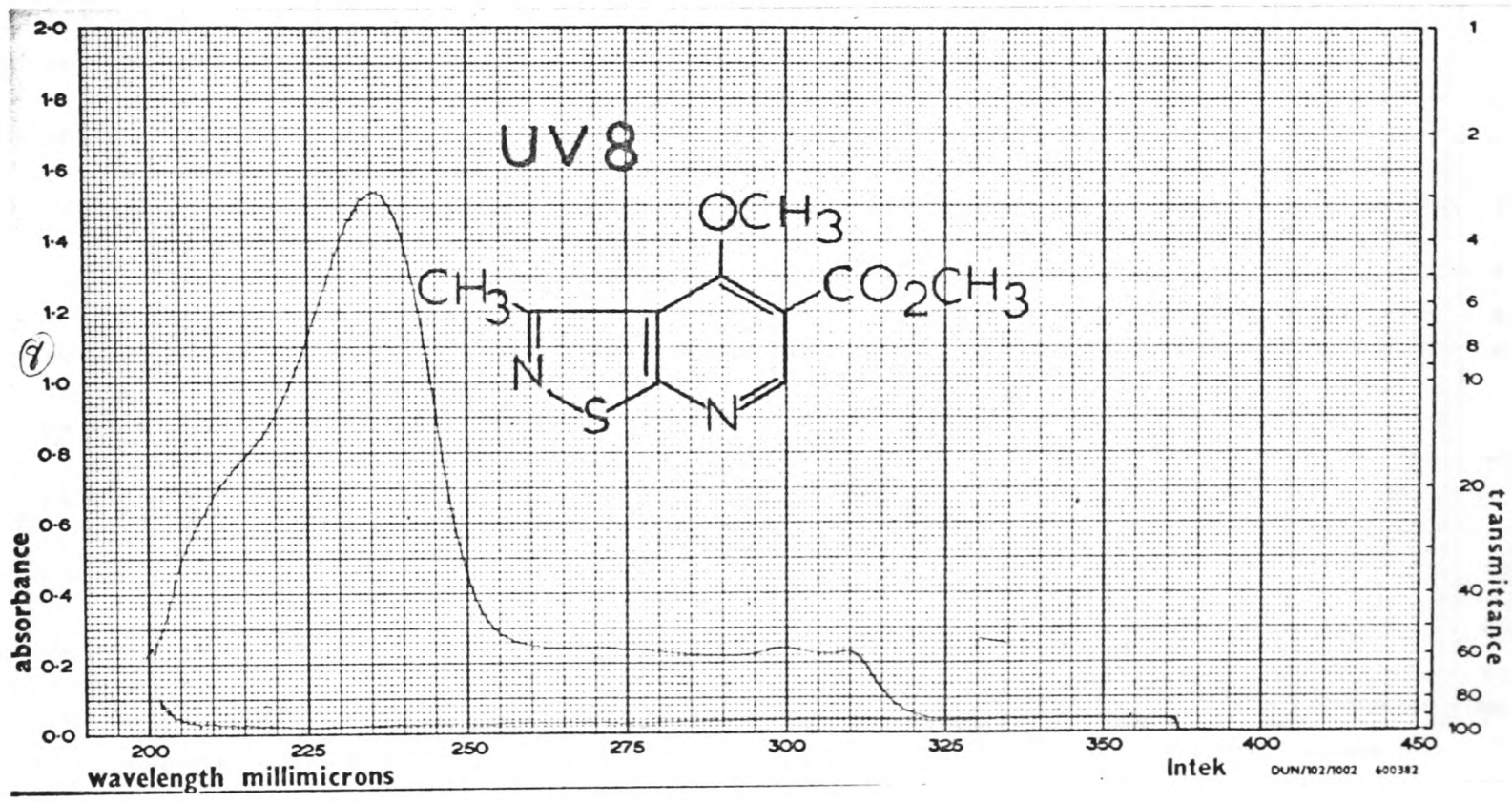
UV 8
OCH3
CH3
CO2CH3
N
S
N
absorbance
transmittance
wavelength millimicrons
Intek
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
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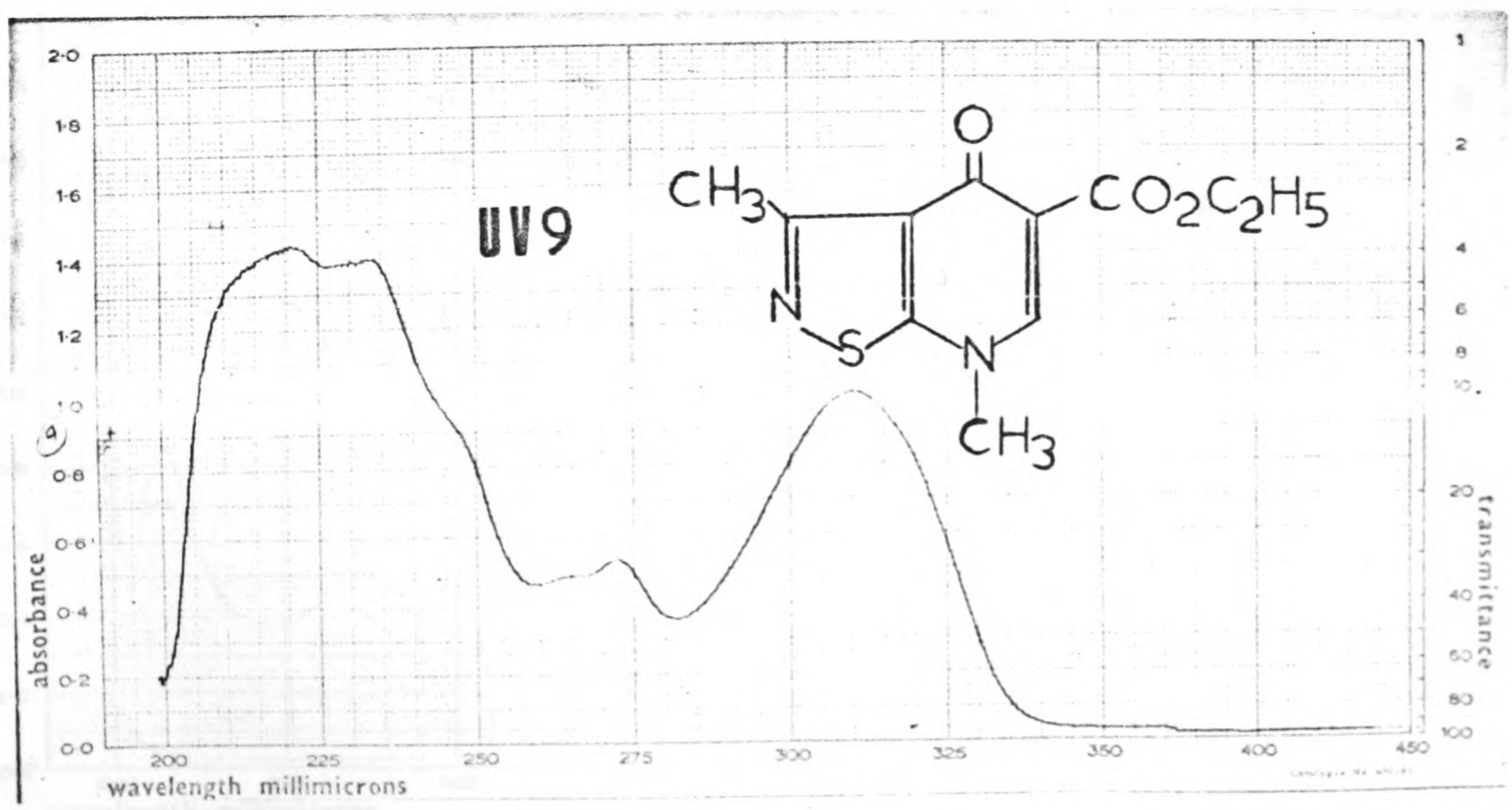
UV 9
O
CH3
CO2C2H5
N
S
N
CH3
absorbance
transmittance
wavelength millimicrons
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
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225
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350
400
450
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6
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40
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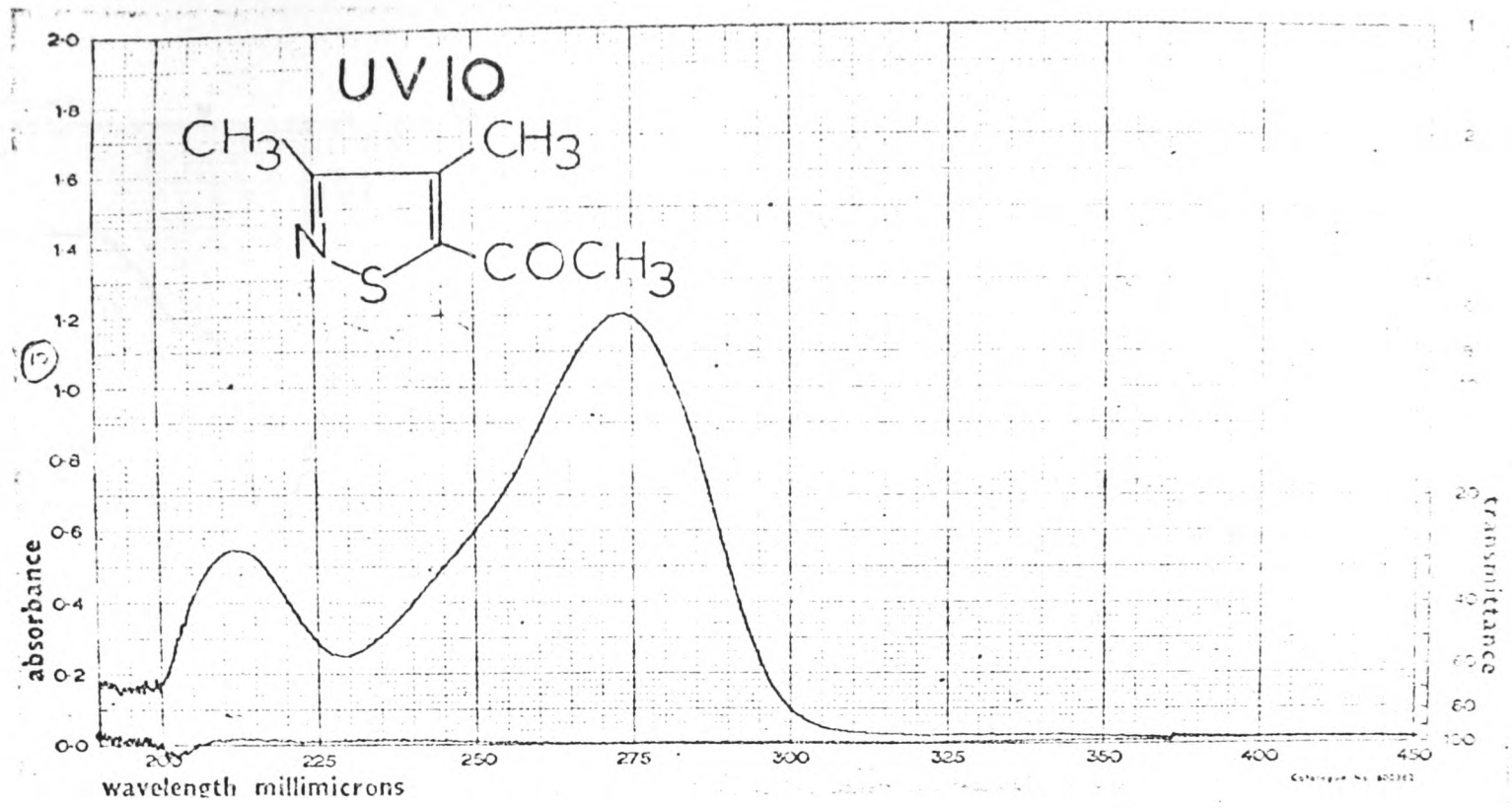
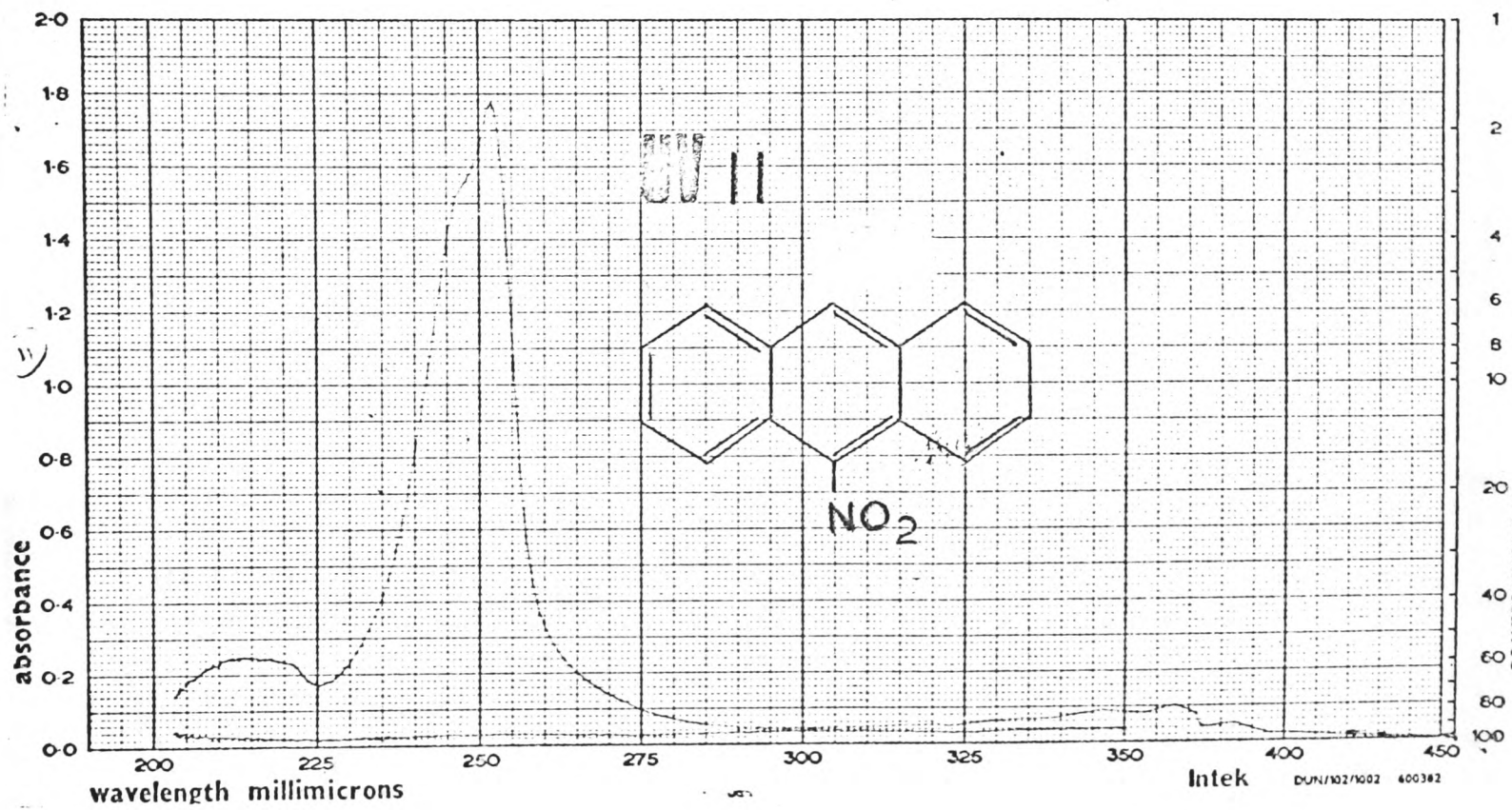
80
100


UV 10
CH3
CH3
N
S
COCH3
absorbance
transmittance
wavelength millimicrons
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
200
225
250
275
300
325
350
400
450


UV 11
NO2
absorbance
transmittance
wavelength millimicrons
Intek
2·0
1·8
1·6
1·4
1·2
1·0
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0·6
0·4
0·2
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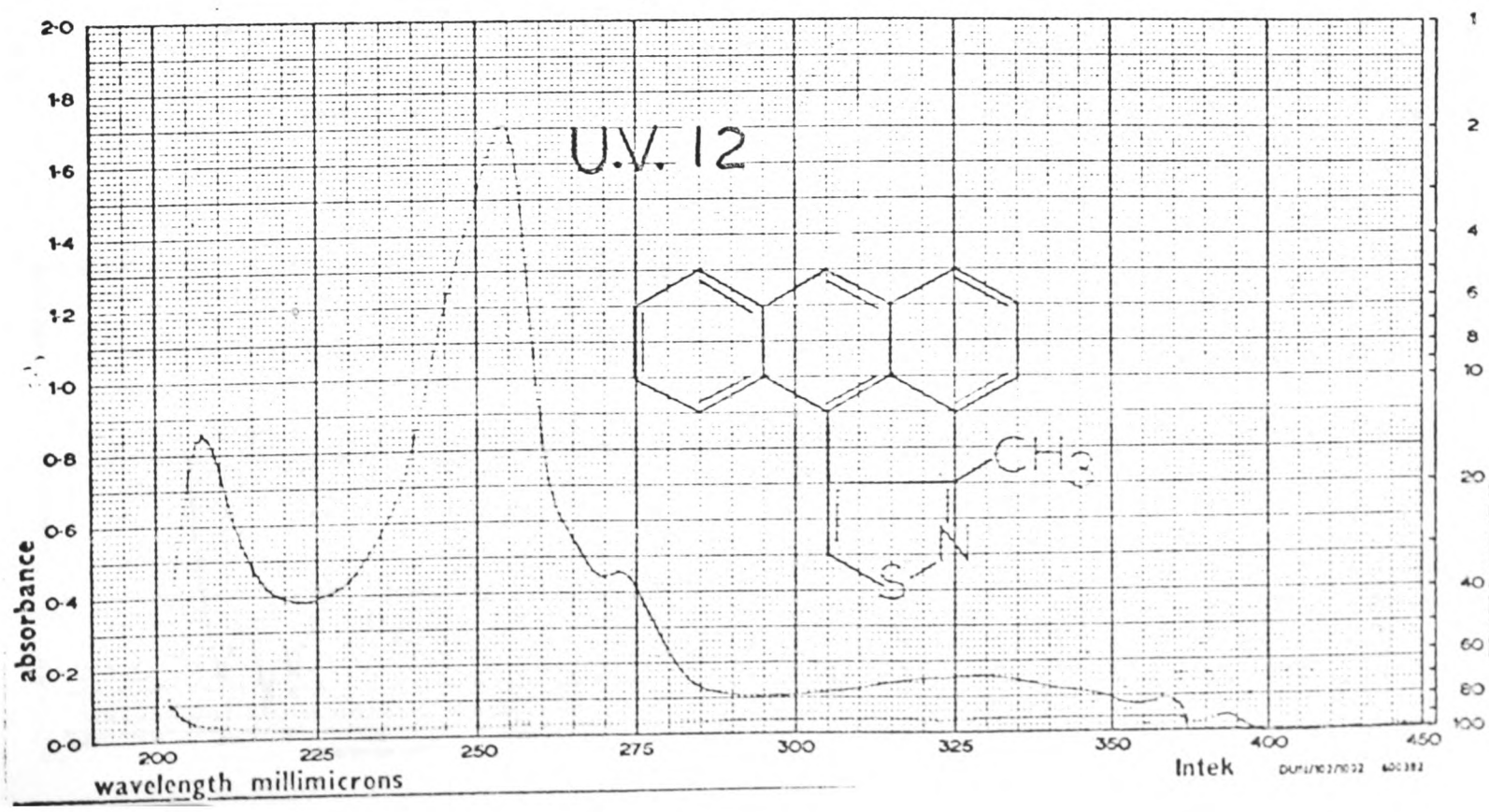
U.V. 12
CH3
N
S
absorbance
transmittance
wavelength millimicrons
Intek
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
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400
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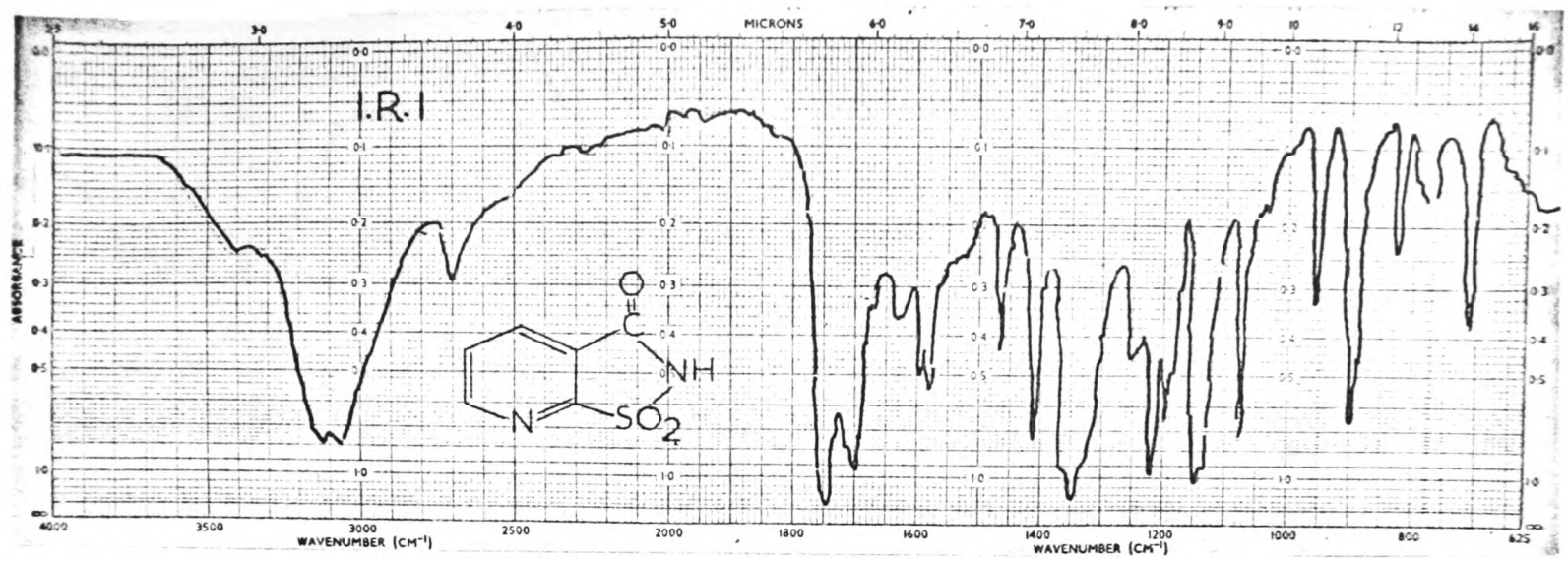
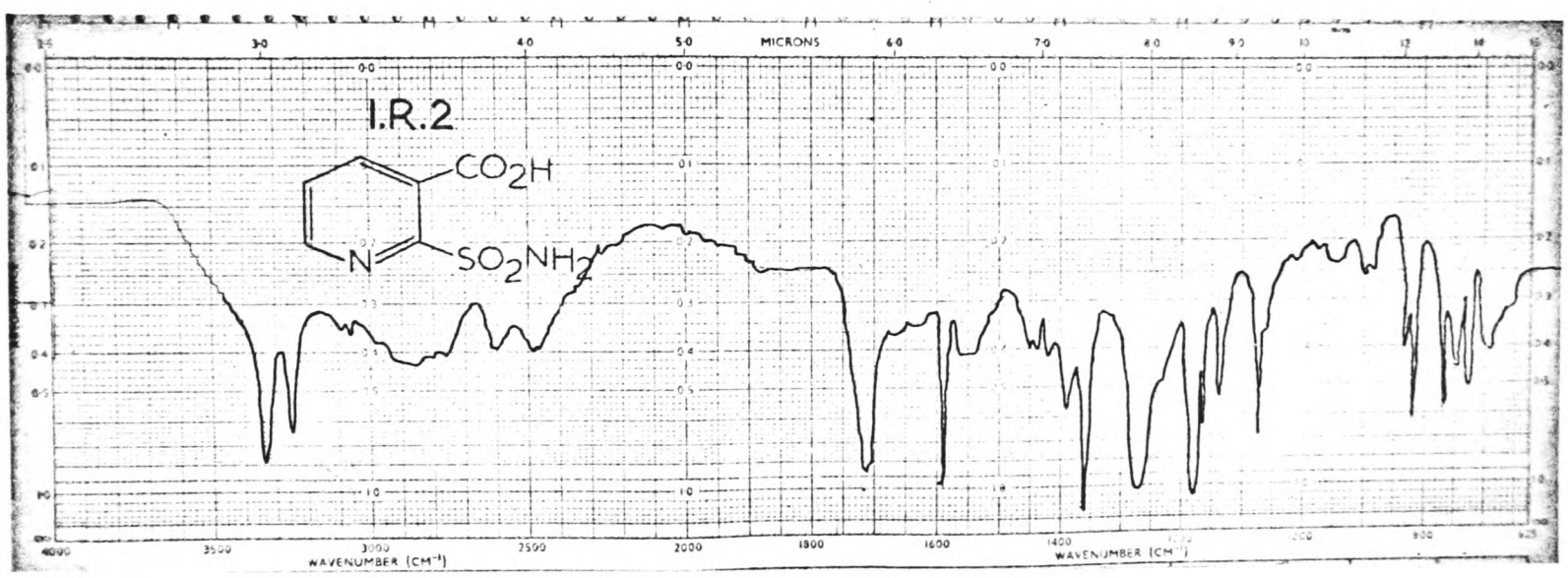
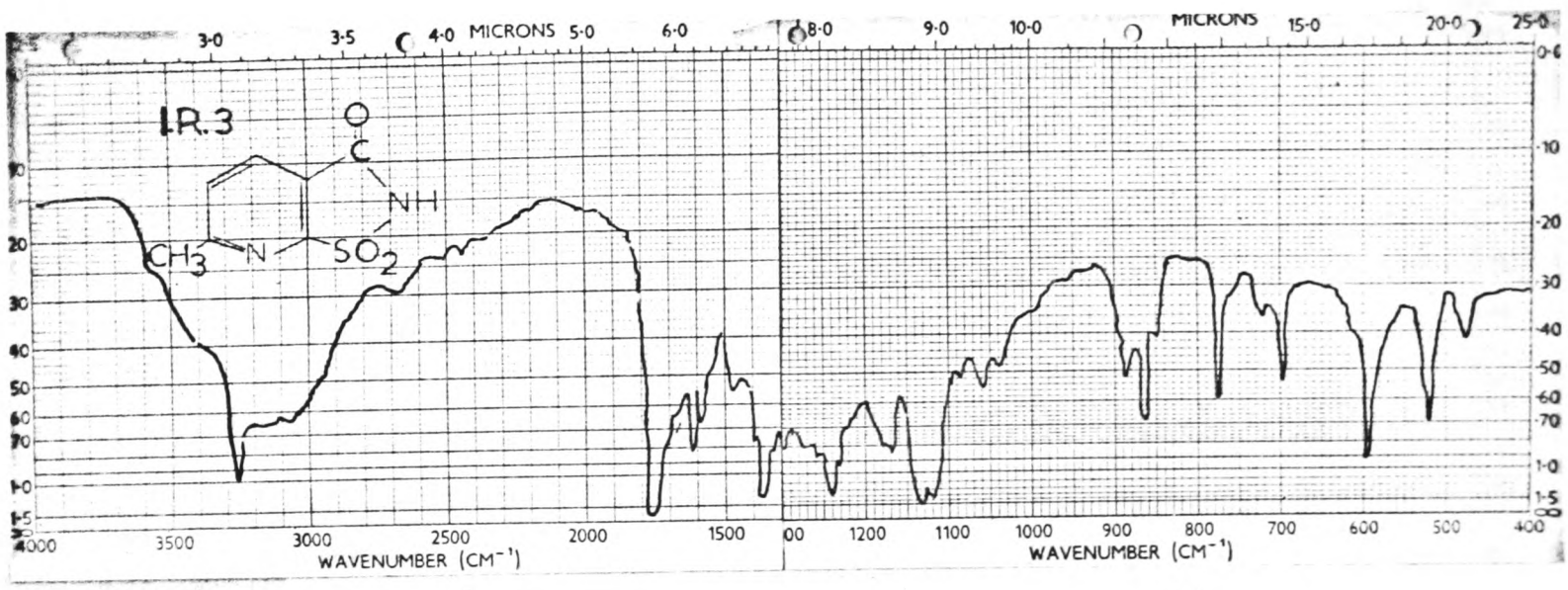
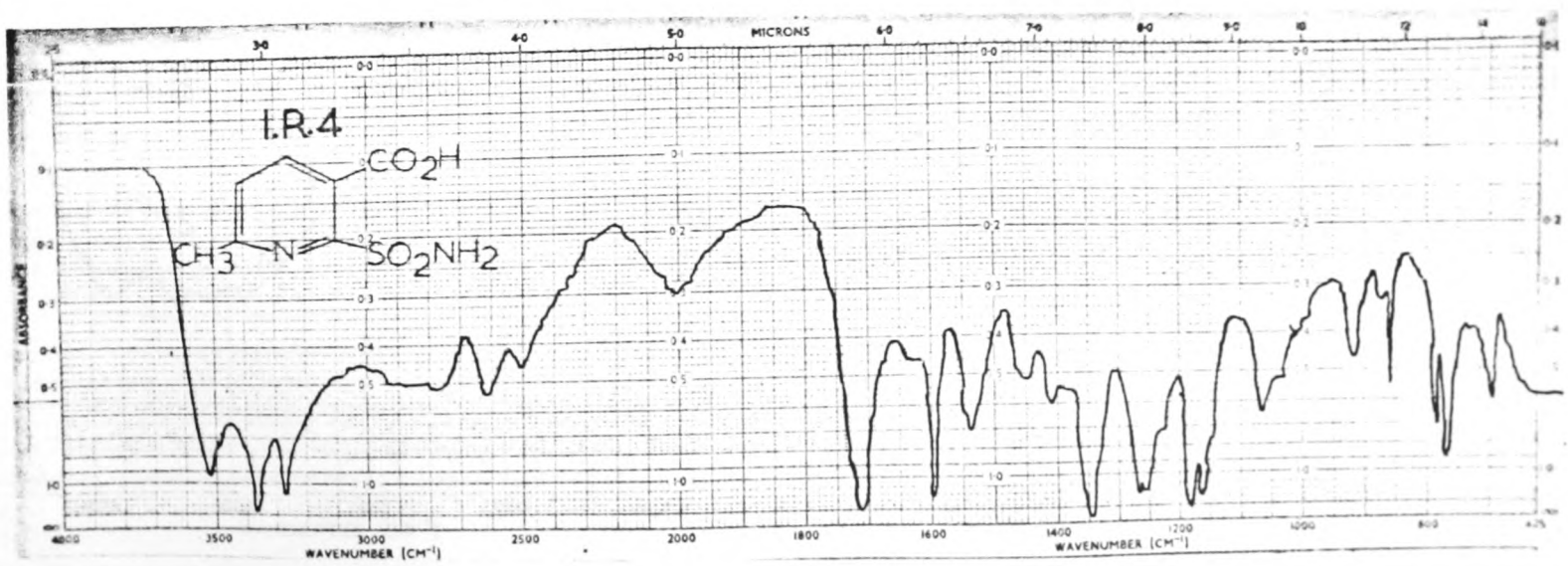
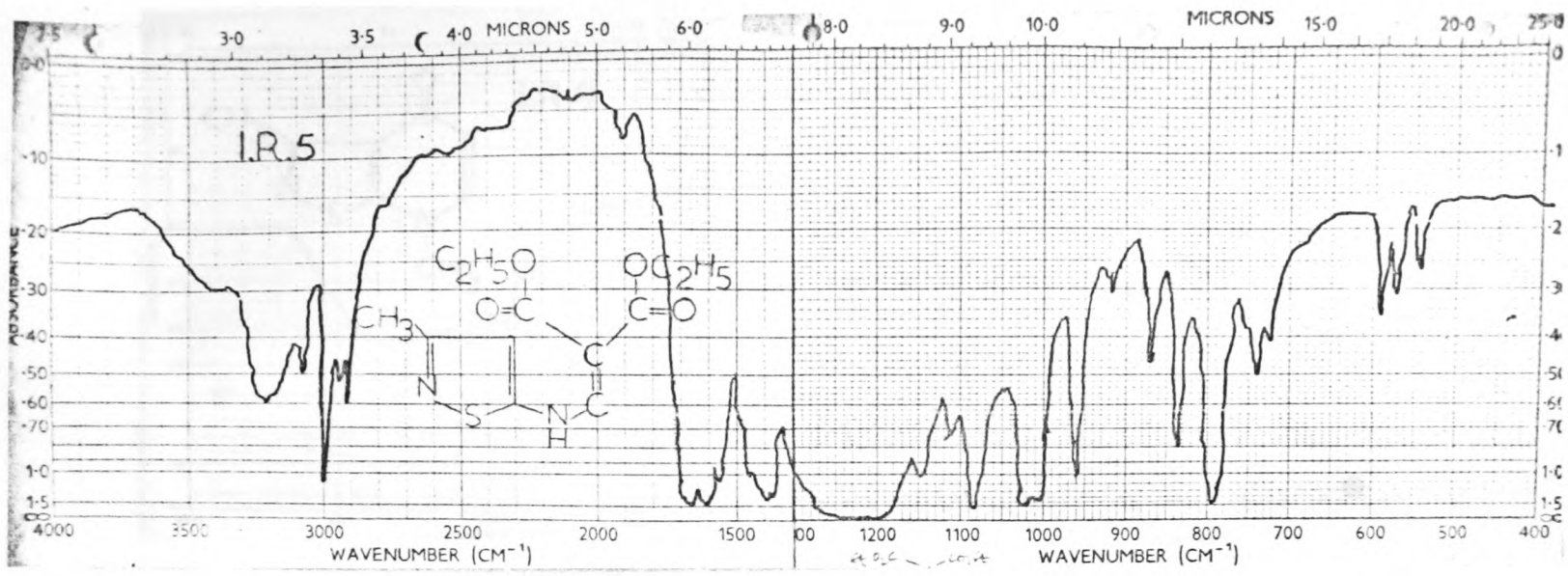
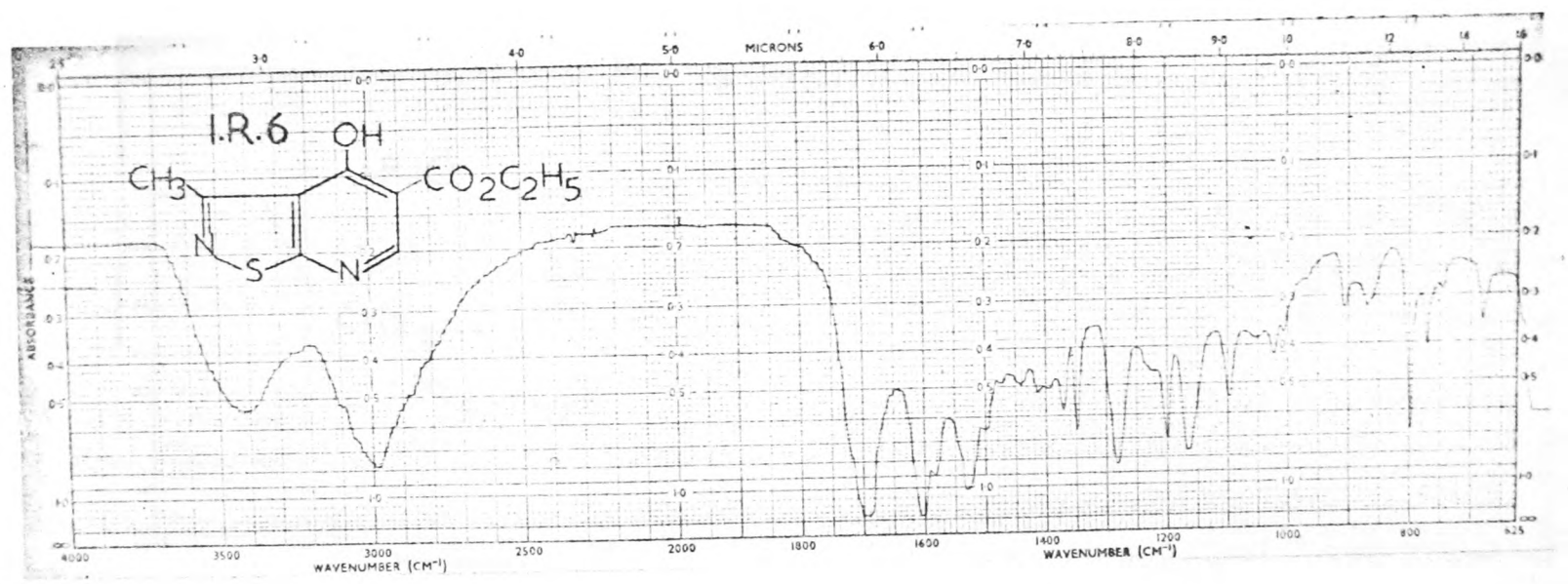

I.R.1
MICRONS
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)

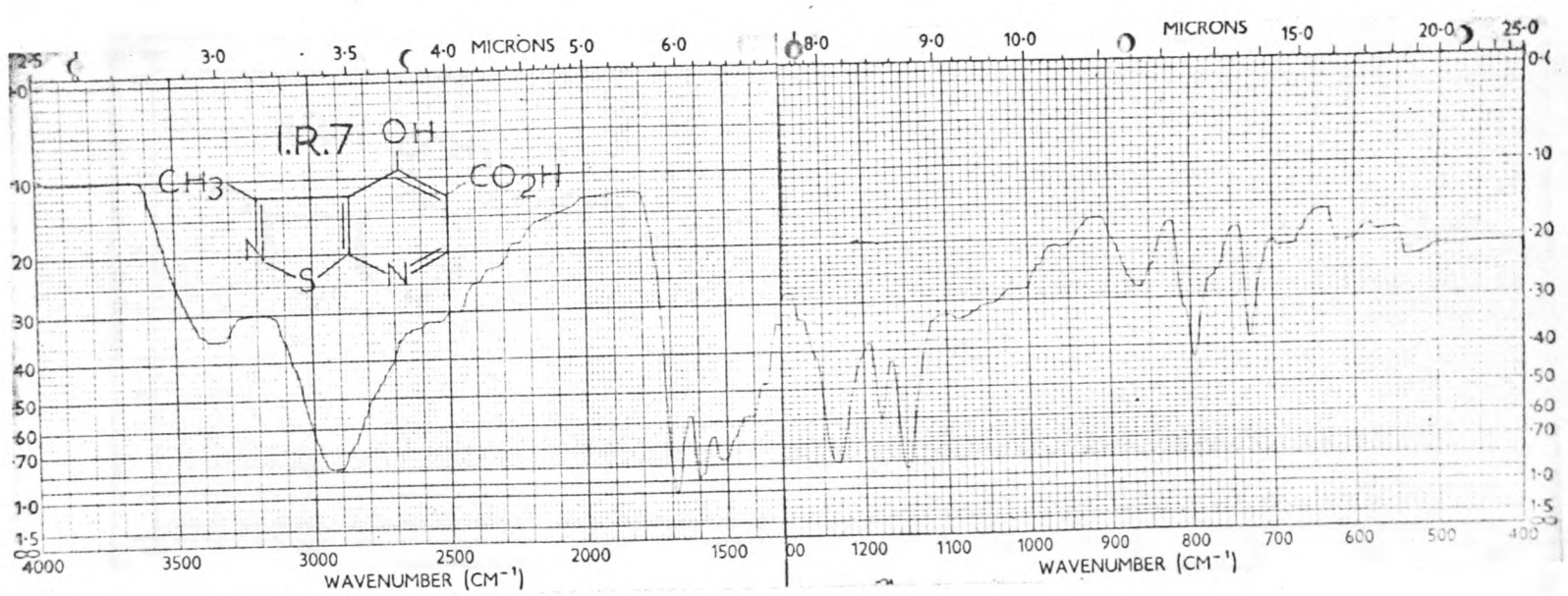

I.R.2
MICRONS
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)

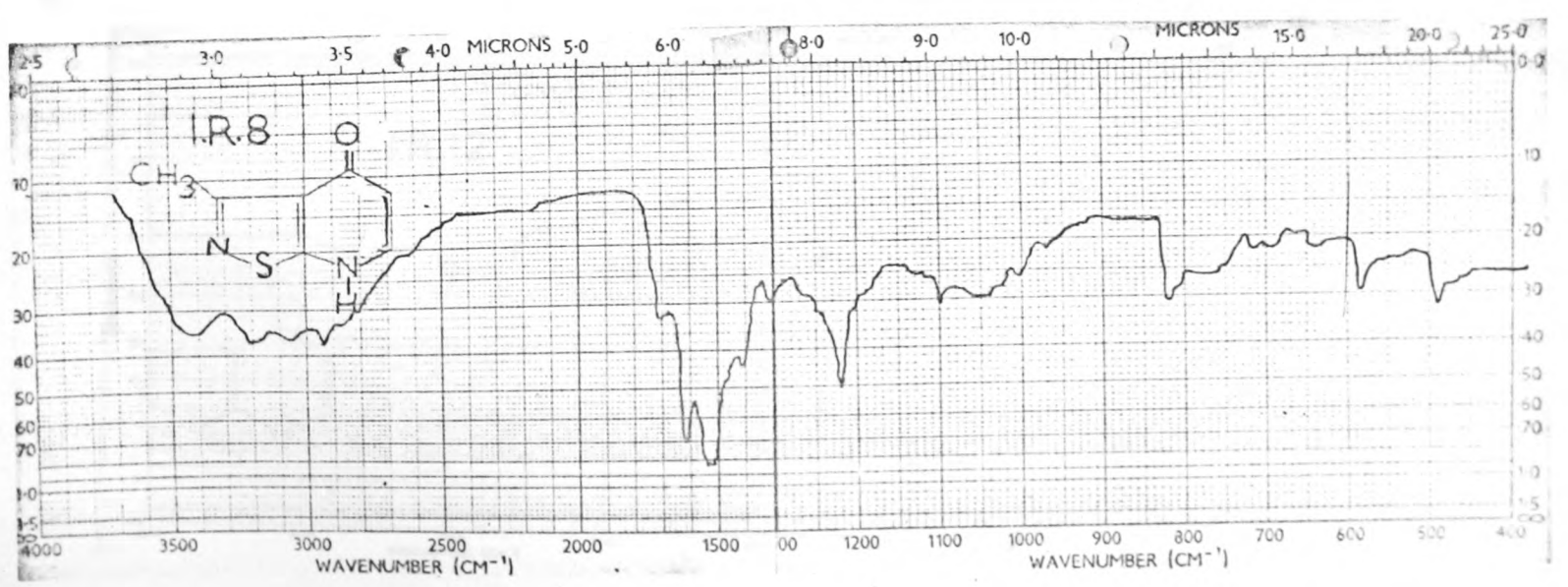

I.R.3
MICRONS
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)

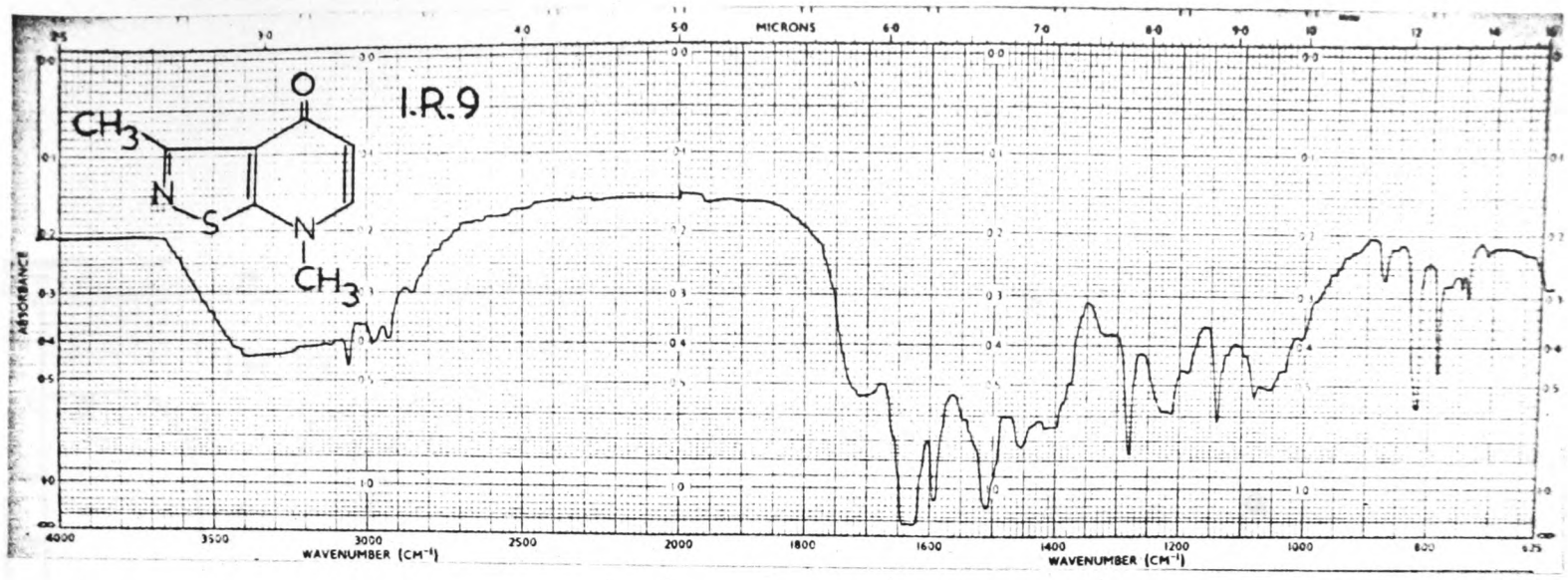

I.R.4
MICRONS
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)

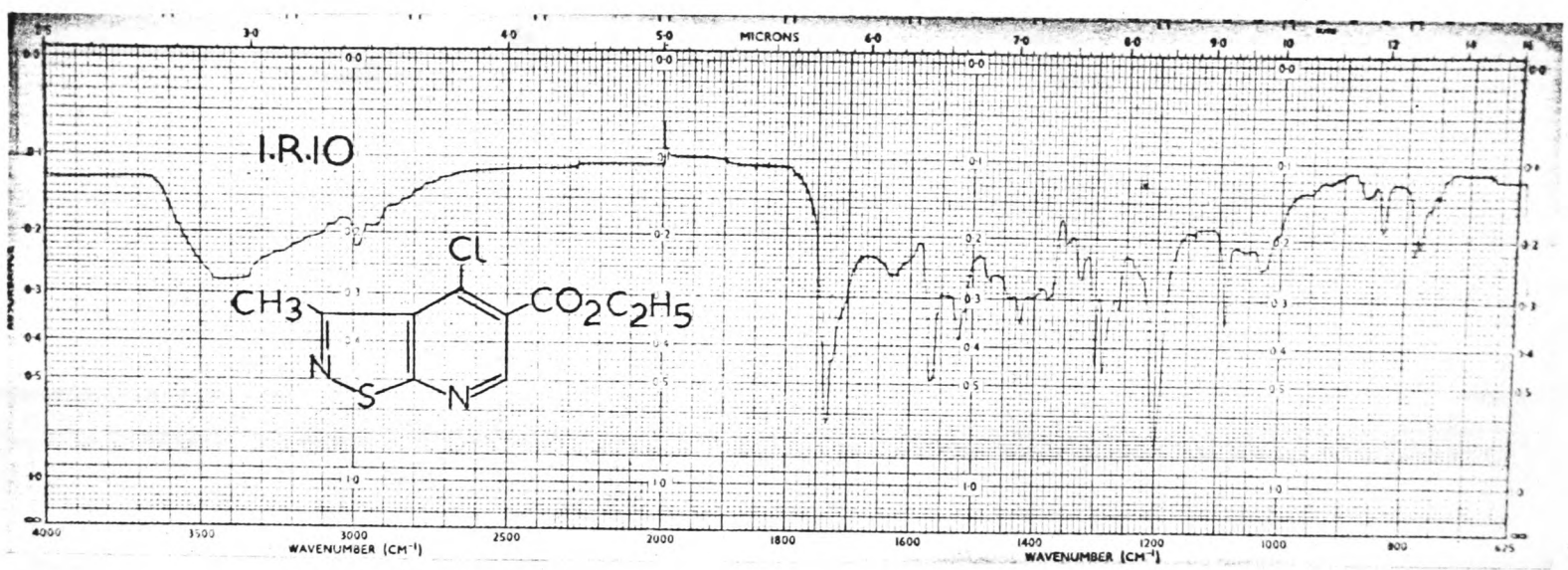

I.R.5
MICRONS
WAVENUMBER (CM⁻¹)
ABSORBANCE

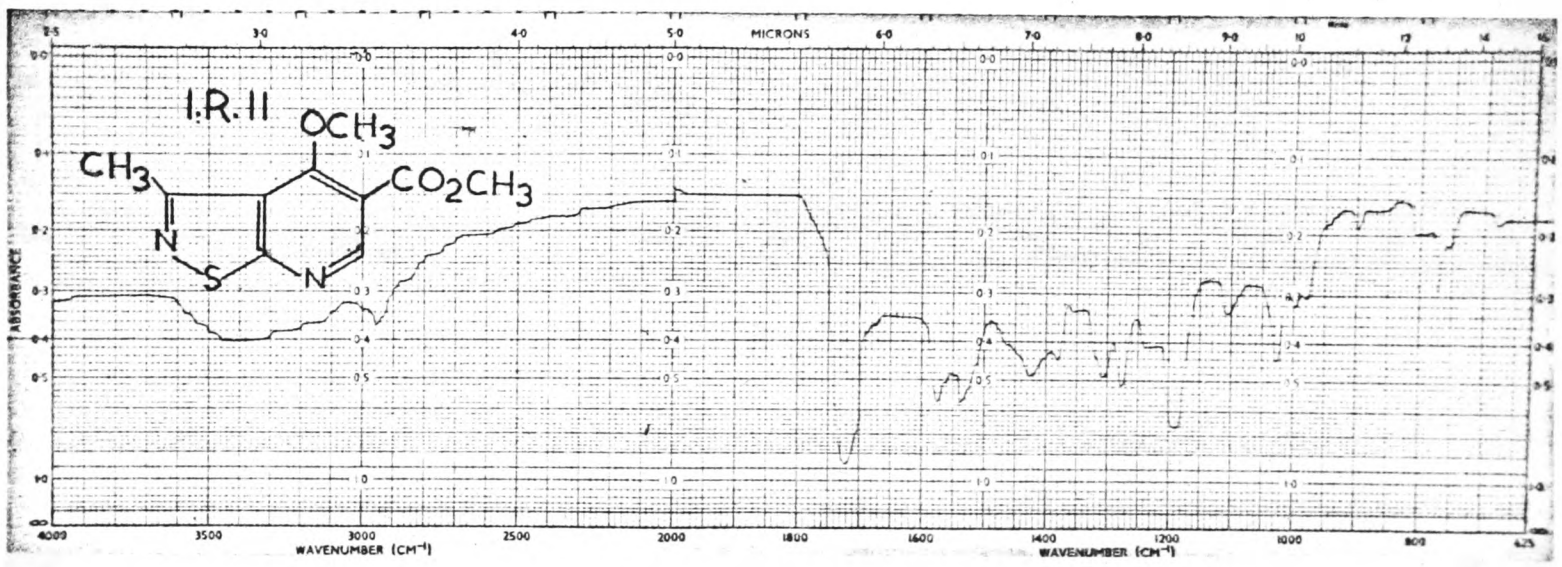

I.R.6
OH
CH3
CO2C2H5
MICRONS
WAVENUMBER (CM⁻¹)
ABSORBANCE

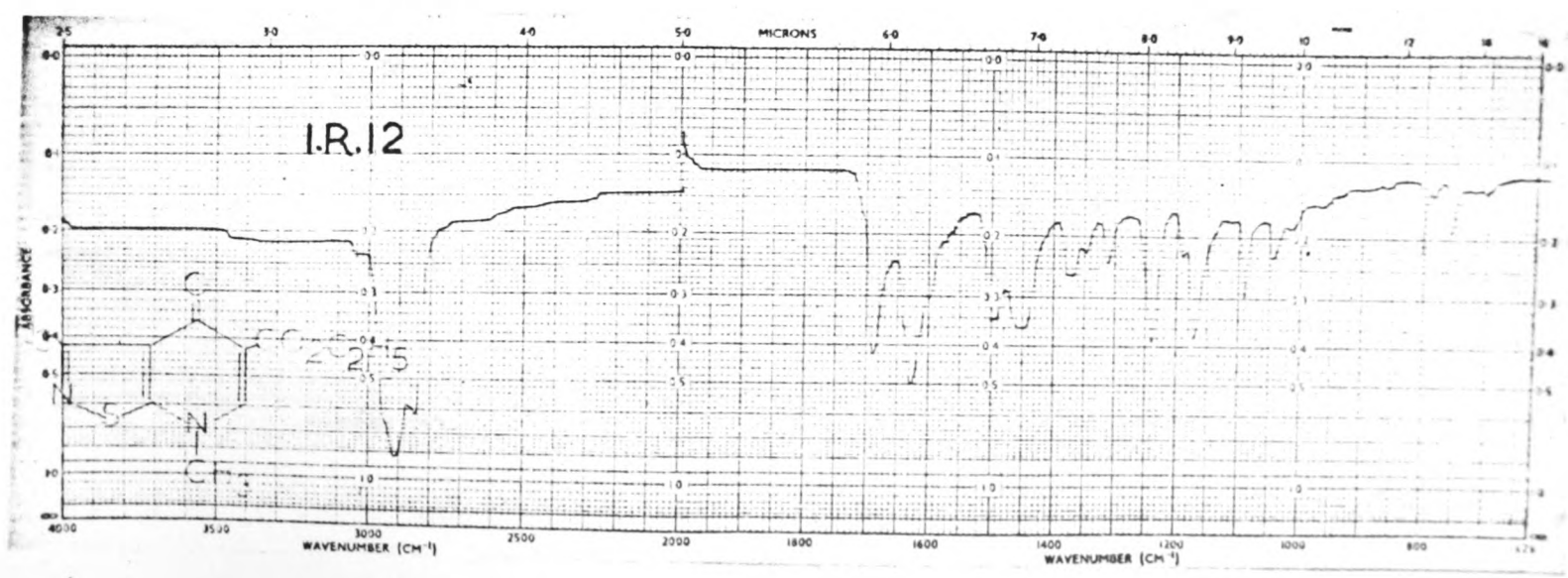

I.R.7
OH
CH3
CO2H
MICRONS
WAVENUMBER (CM⁻¹)

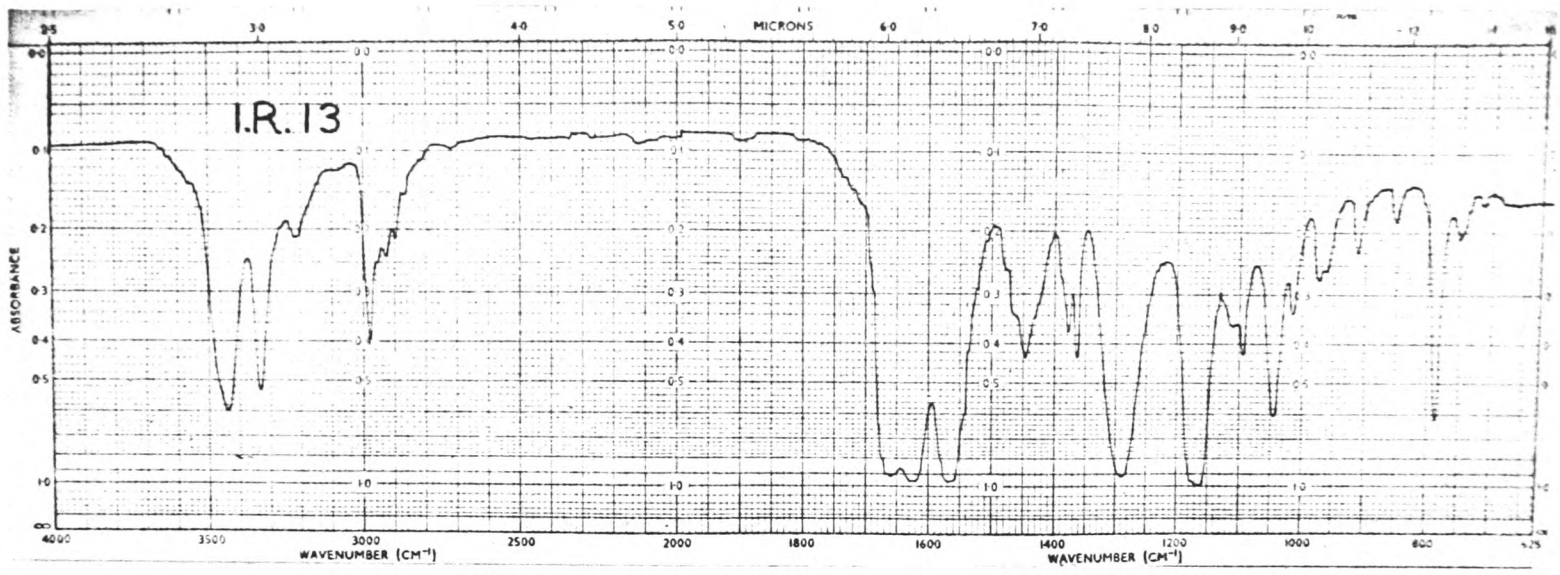

I.R.8
O
CH3
MICRONS
WAVENUMBER (CM⁻¹)

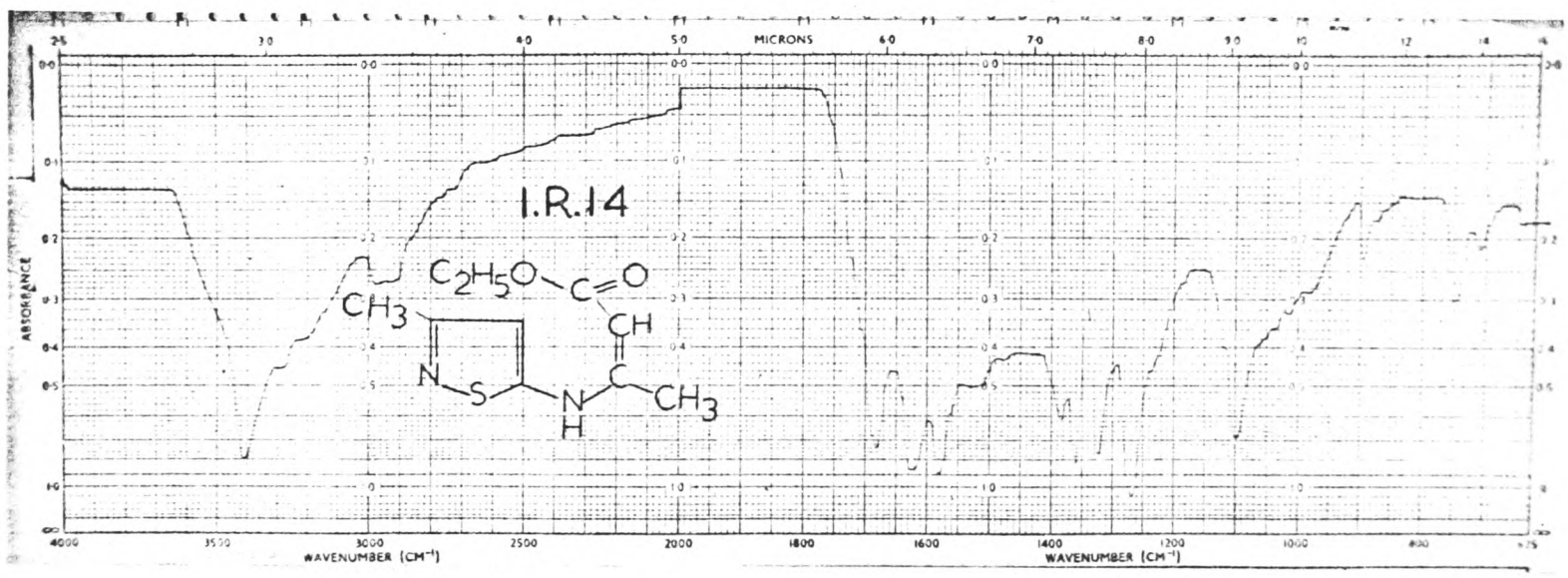

I.R.9
MICRONS
WAVENUMBER (CM⁻¹)
ABSORBANCE

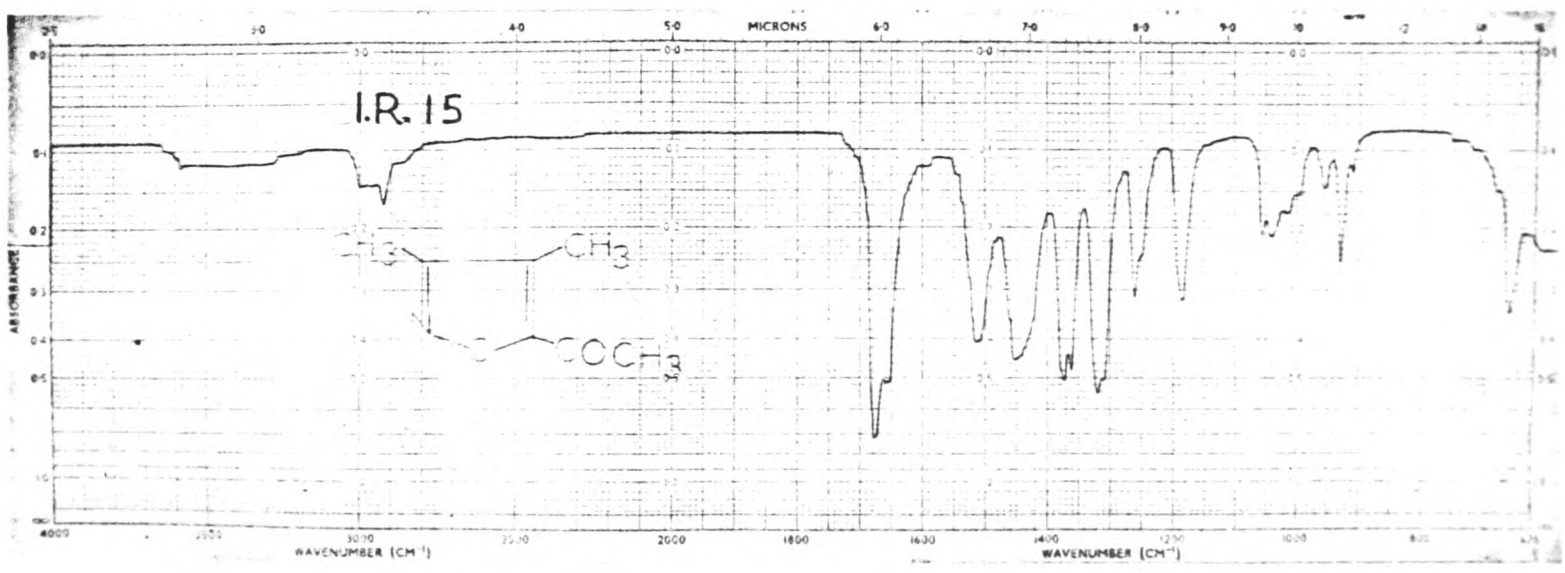

I.R.10
MICRONS
WAVENUMBER (CM⁻¹)

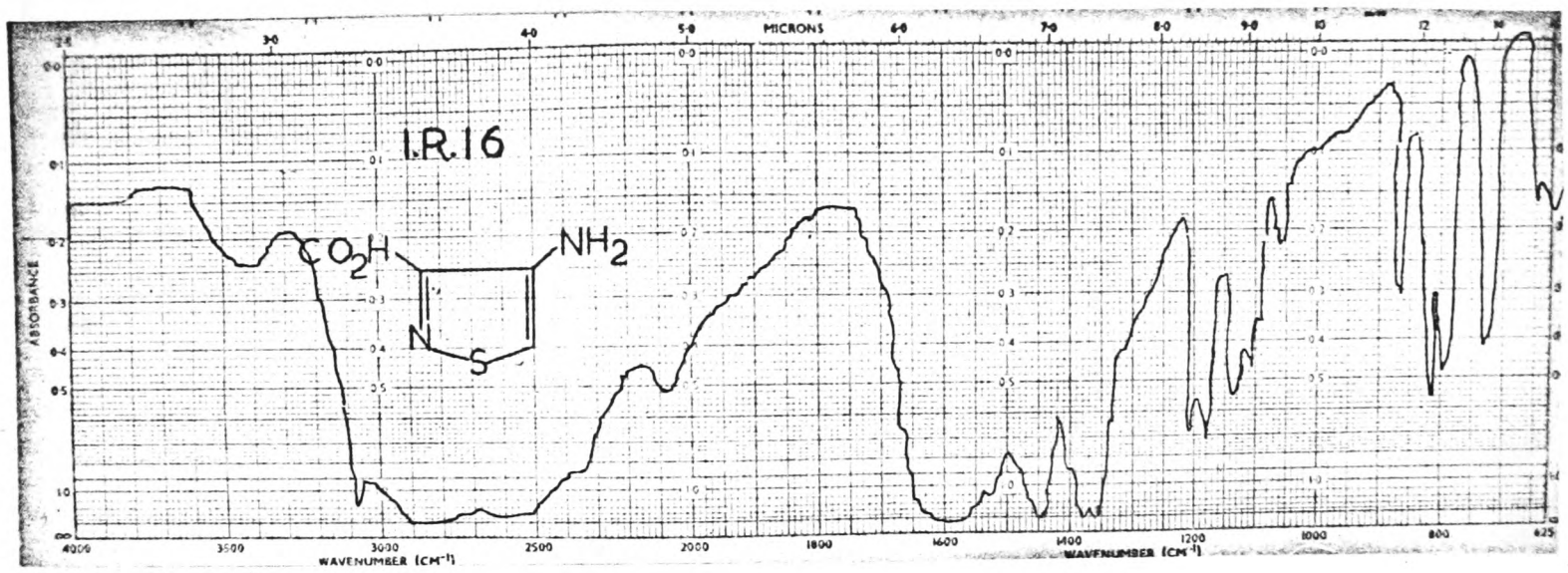

I.R.11
MICRONS
WAVENUMBER (CM⁻¹)
ABSORBANCE

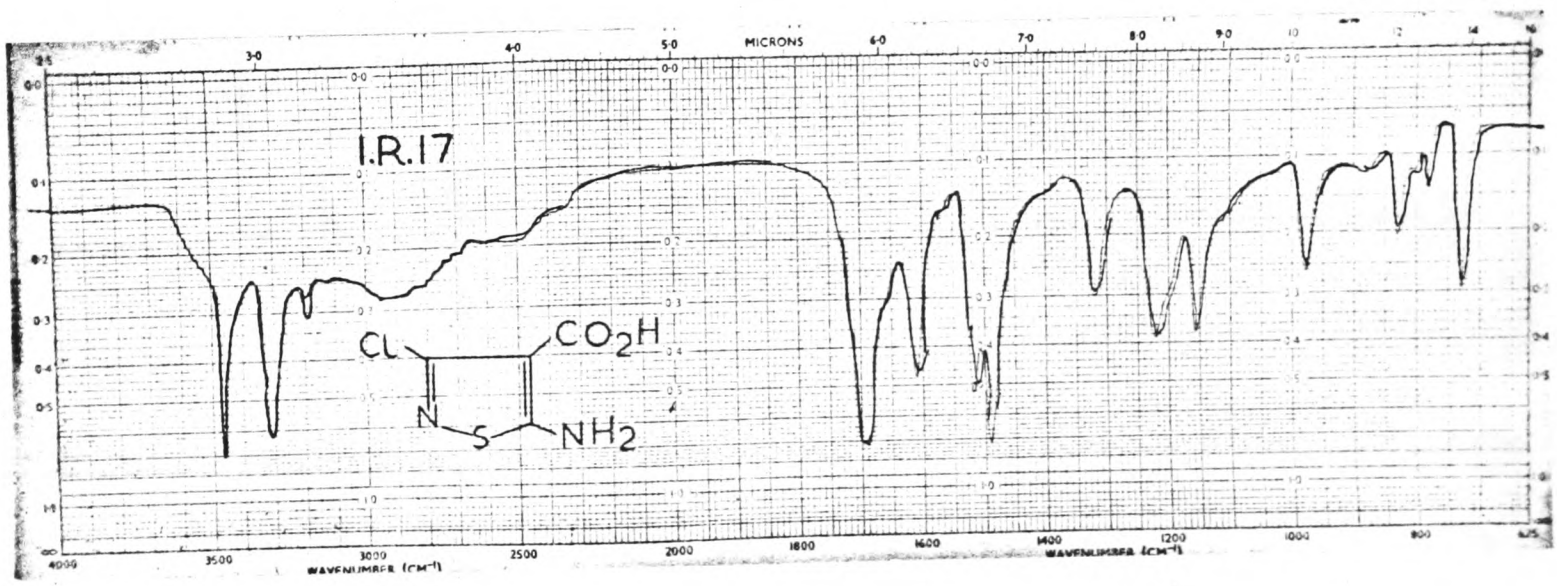

I.R.12
MICRONS
WAVENUMBER (CM⁻¹)
ABSORBANCE

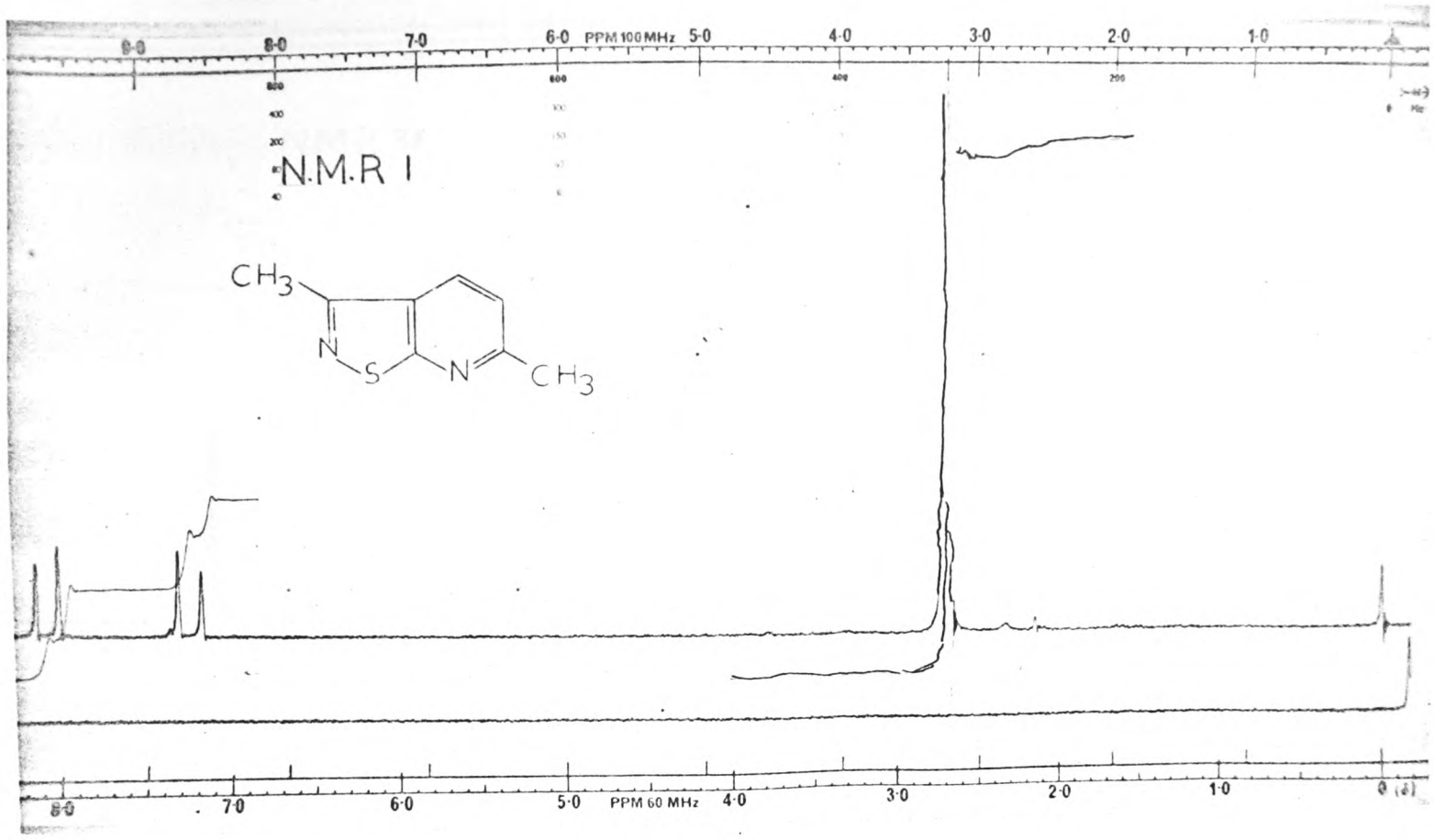

I.R.13
MICRONS
ABSORBANCE
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)

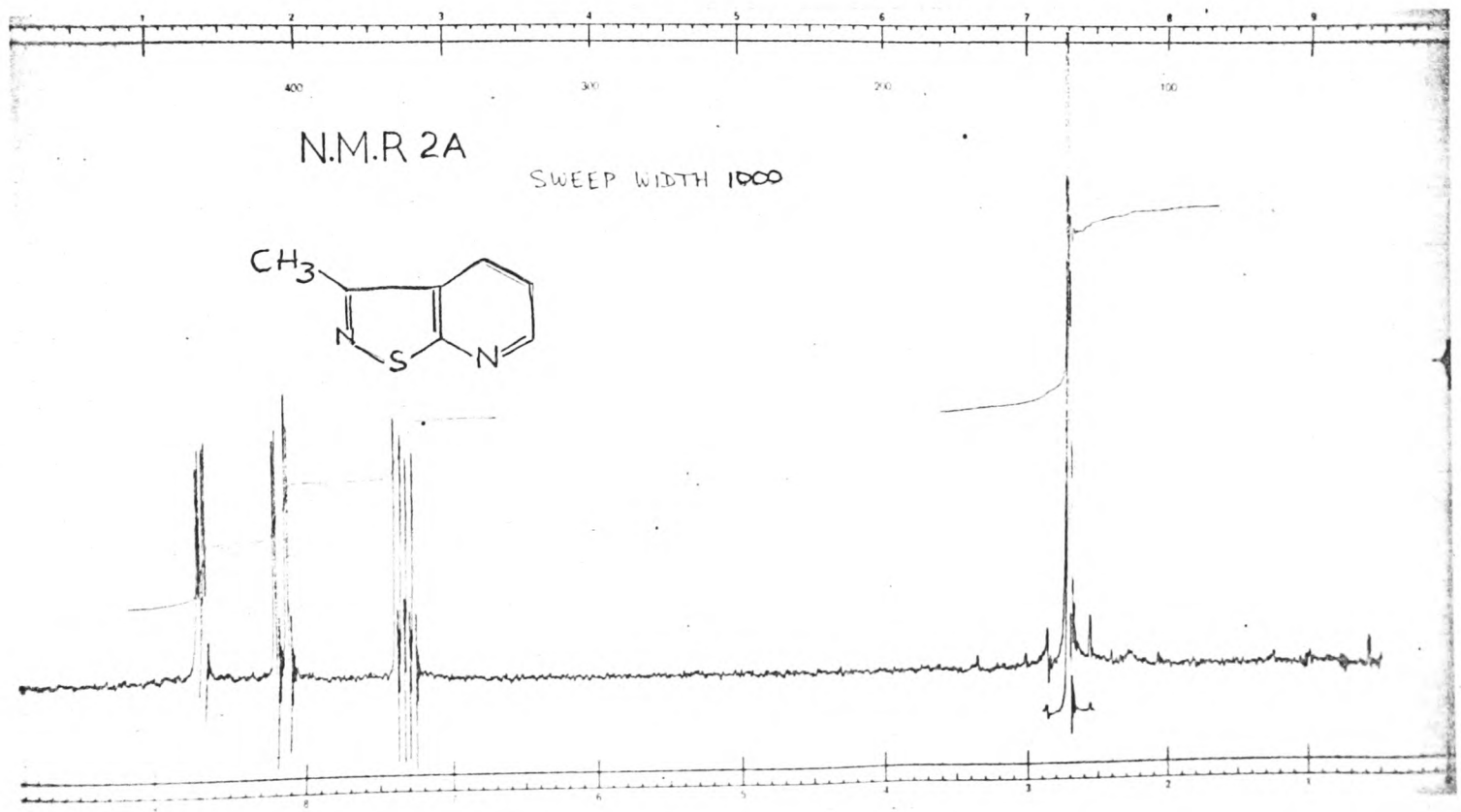

I.R.14
MICRONS
ABSORBANCE
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)

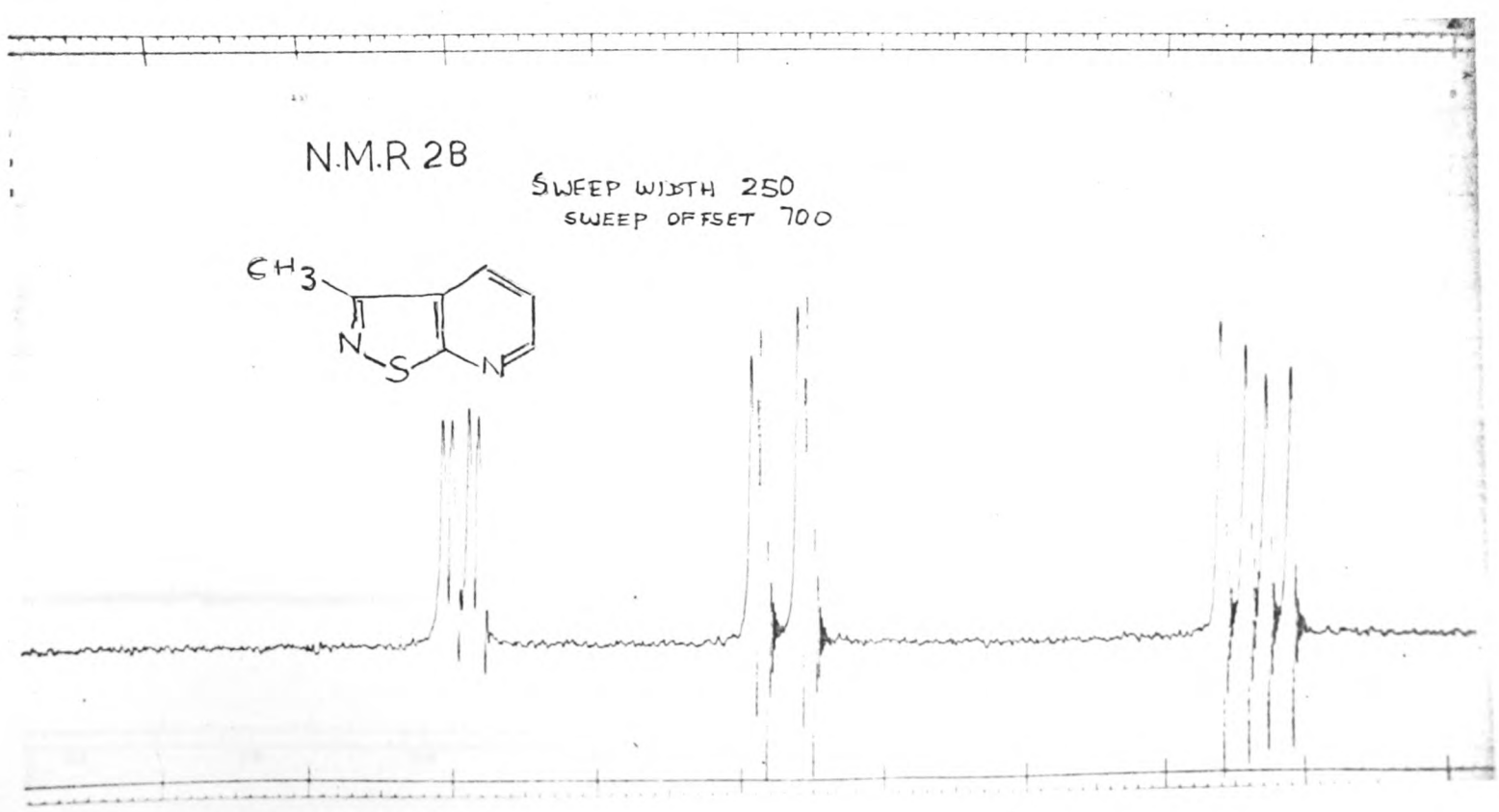

I.R.15
MICRONS
ABSORBANCE
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)


I.R.16
CO_2H
NH_2
N
S
MICRONS
ABSORBANCE
WAVENUMBER (CM⁻¹)


I.R.17
Cl
CO_2H
N
S
NH_2
MICRONS
WAVENUMBER (CM⁻¹)

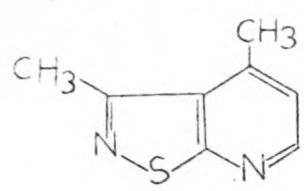

N.M.R 1
PPM 100 MHz
PPM 60 MHz
CH3
N
S
N
CH3


N.M.R 2A
SWEEP WIDTH 1000
CH3
N
S
N


N.M.R 2B
SWEEP WIDTH 250
SWEEP OFFSET 700
CH3
N
S
N

N.M.R 3A

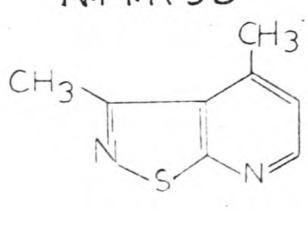
SWEEP WIDTH 1000



N.M.R 3B

SWEEP WIDTH 100

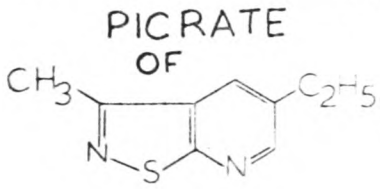
SWEEP OFFSET 270
650

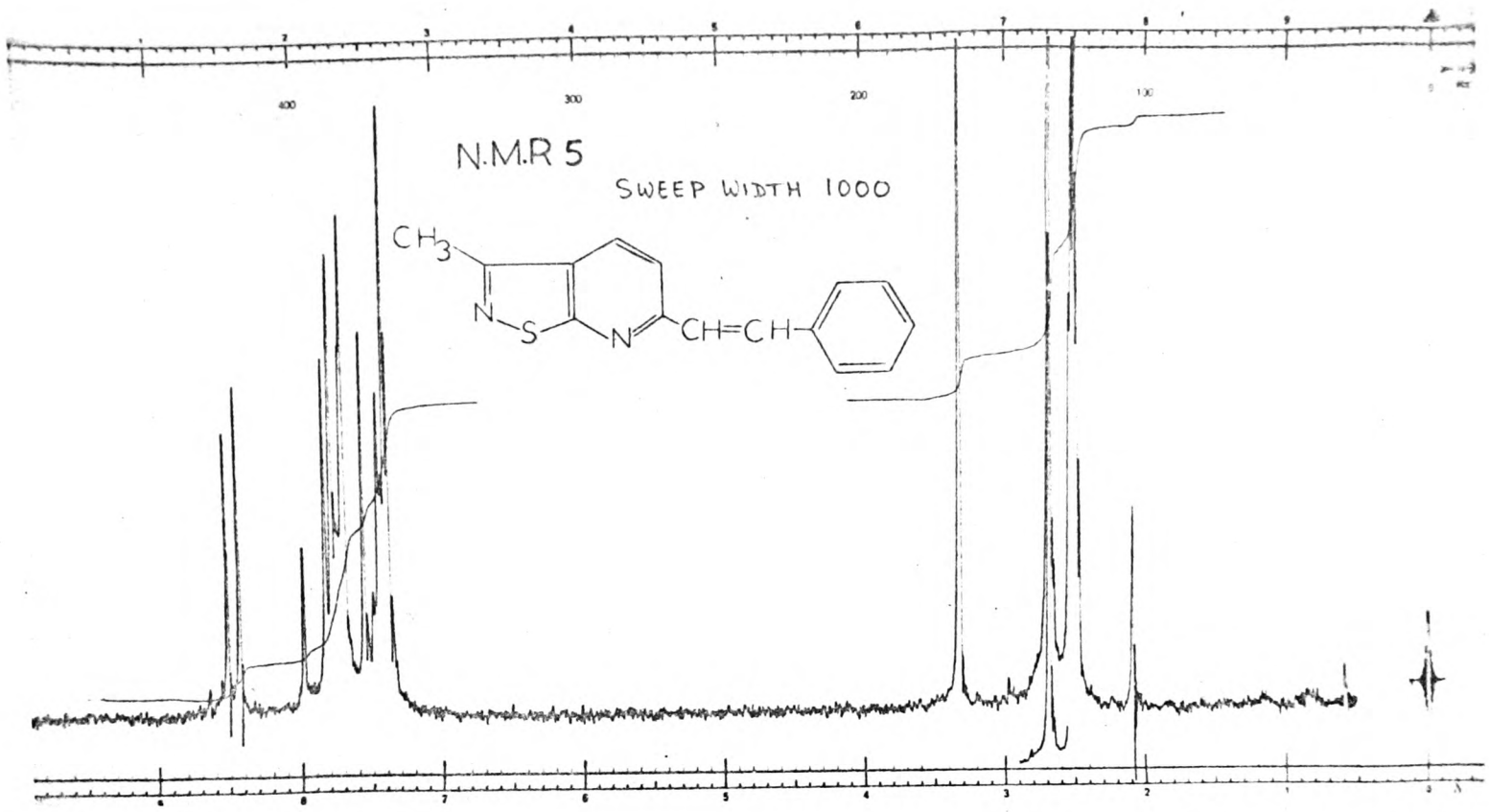


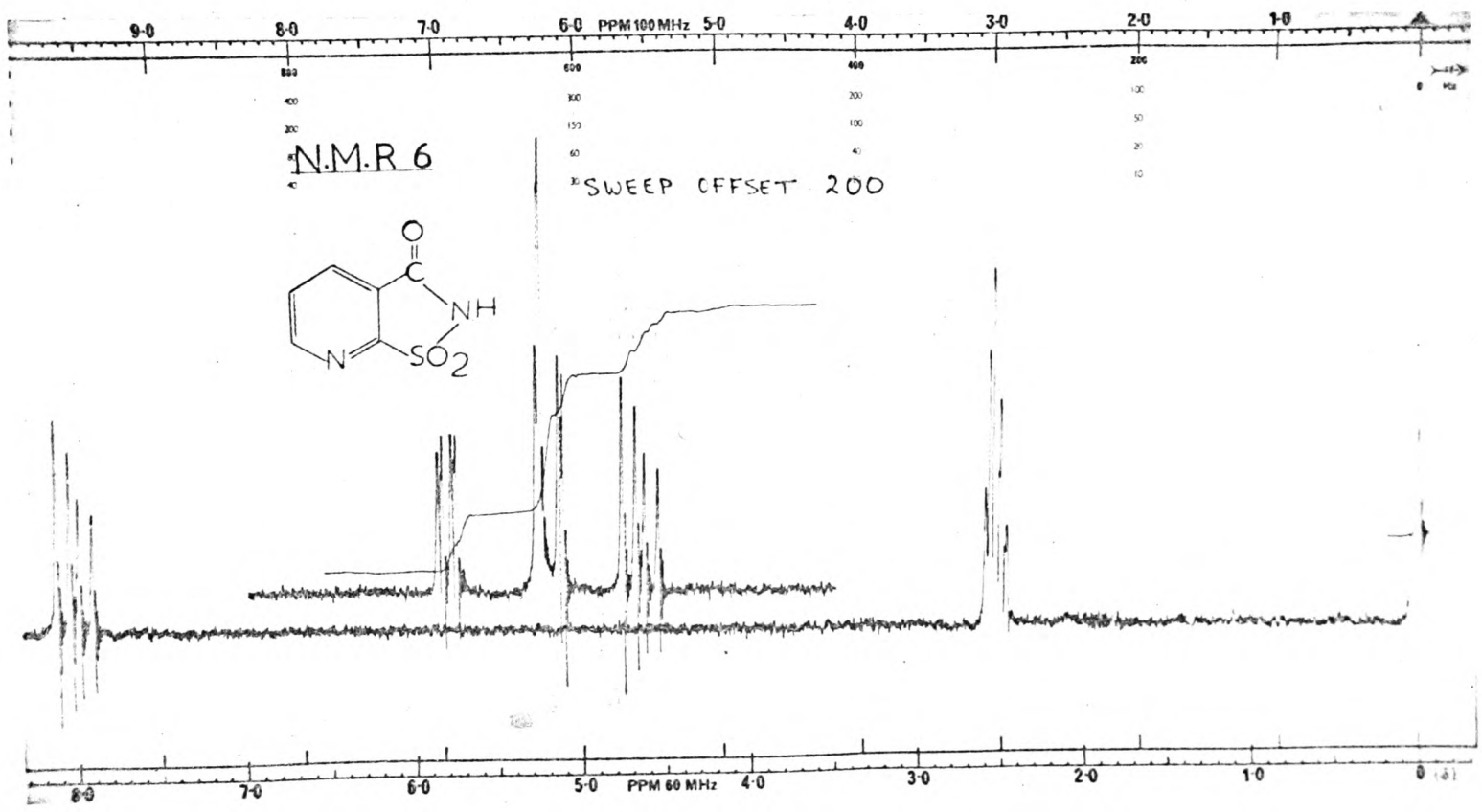
N.M.R 4

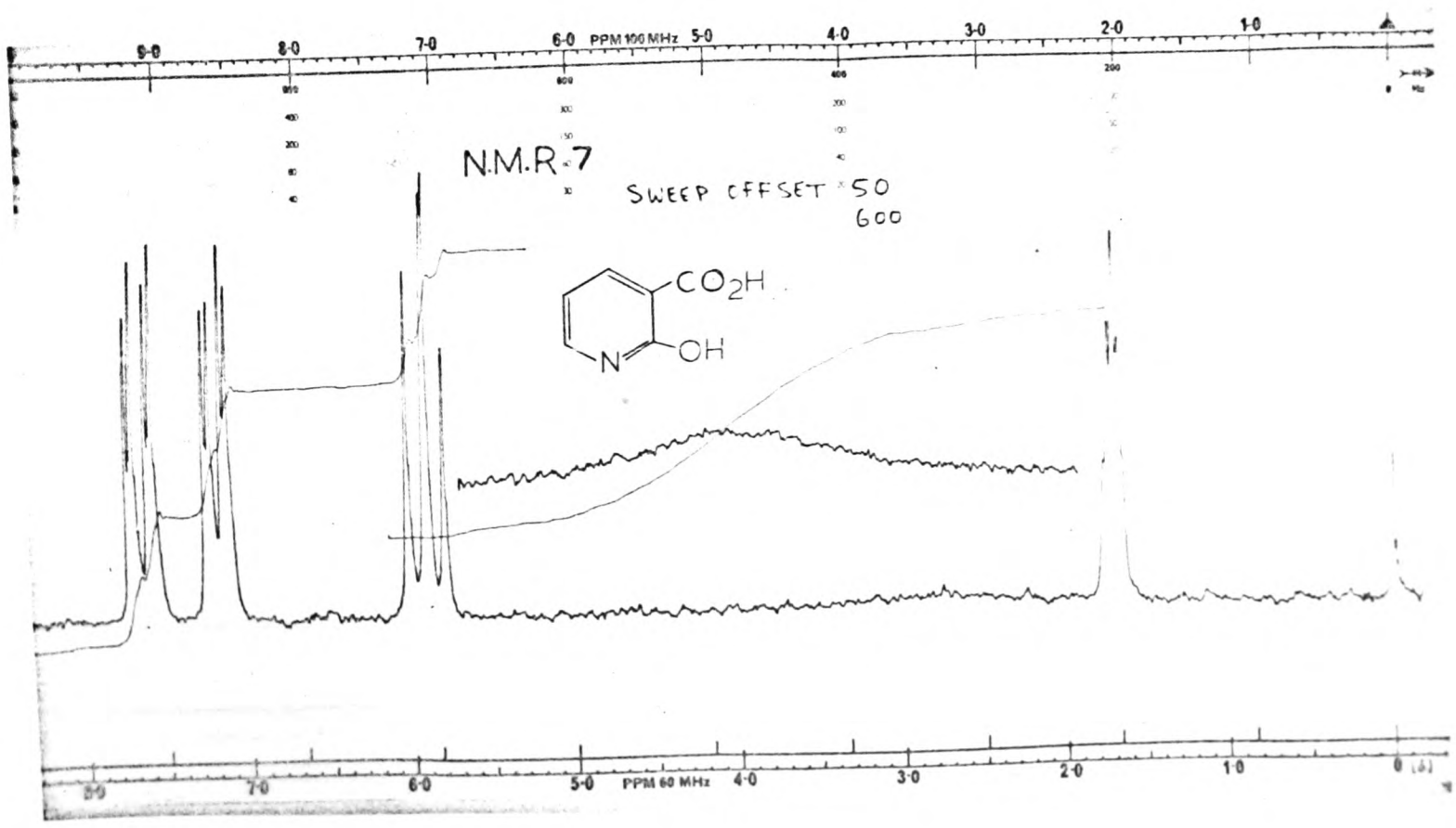
SWEEP OFFSET 500

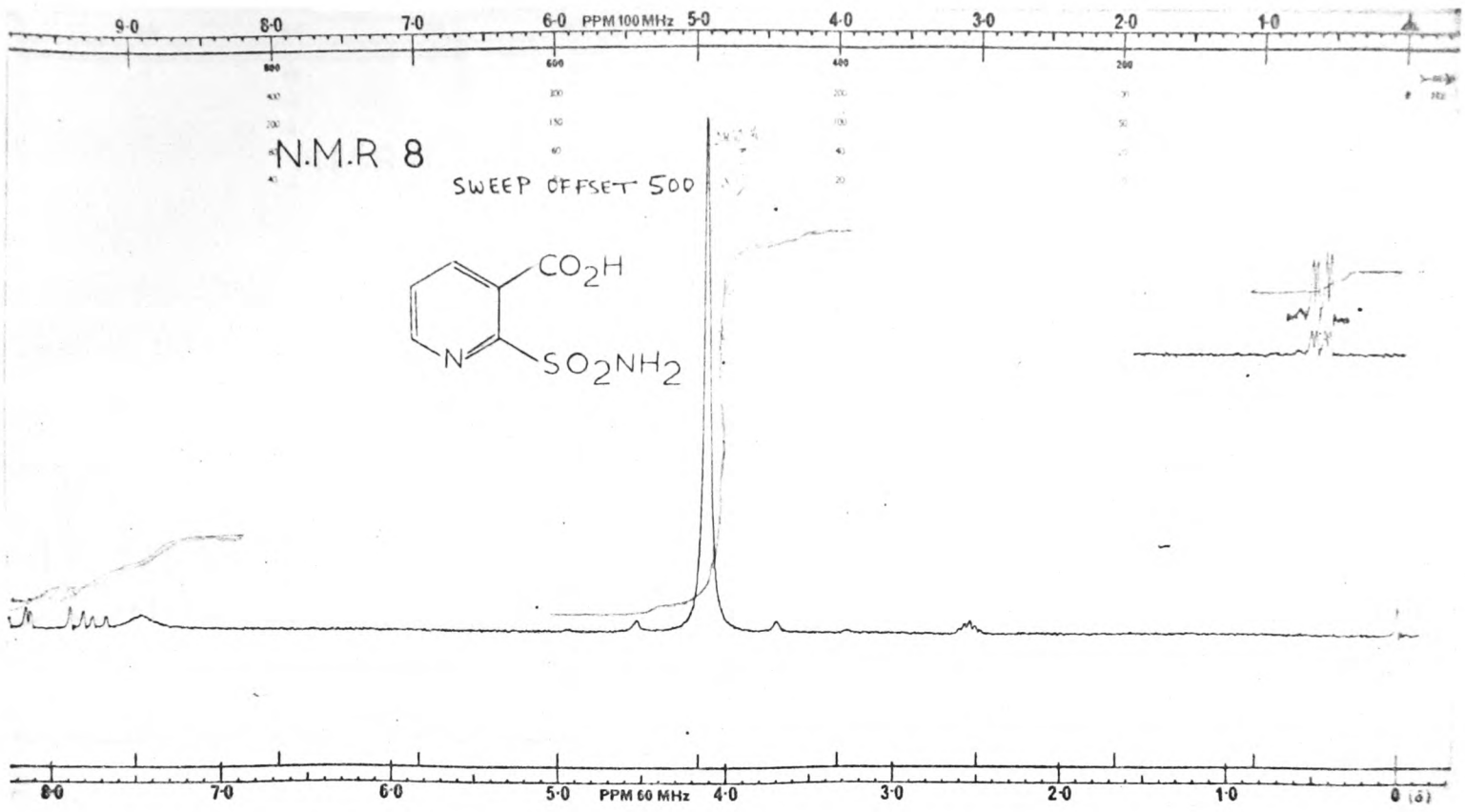
PICRATE
OF

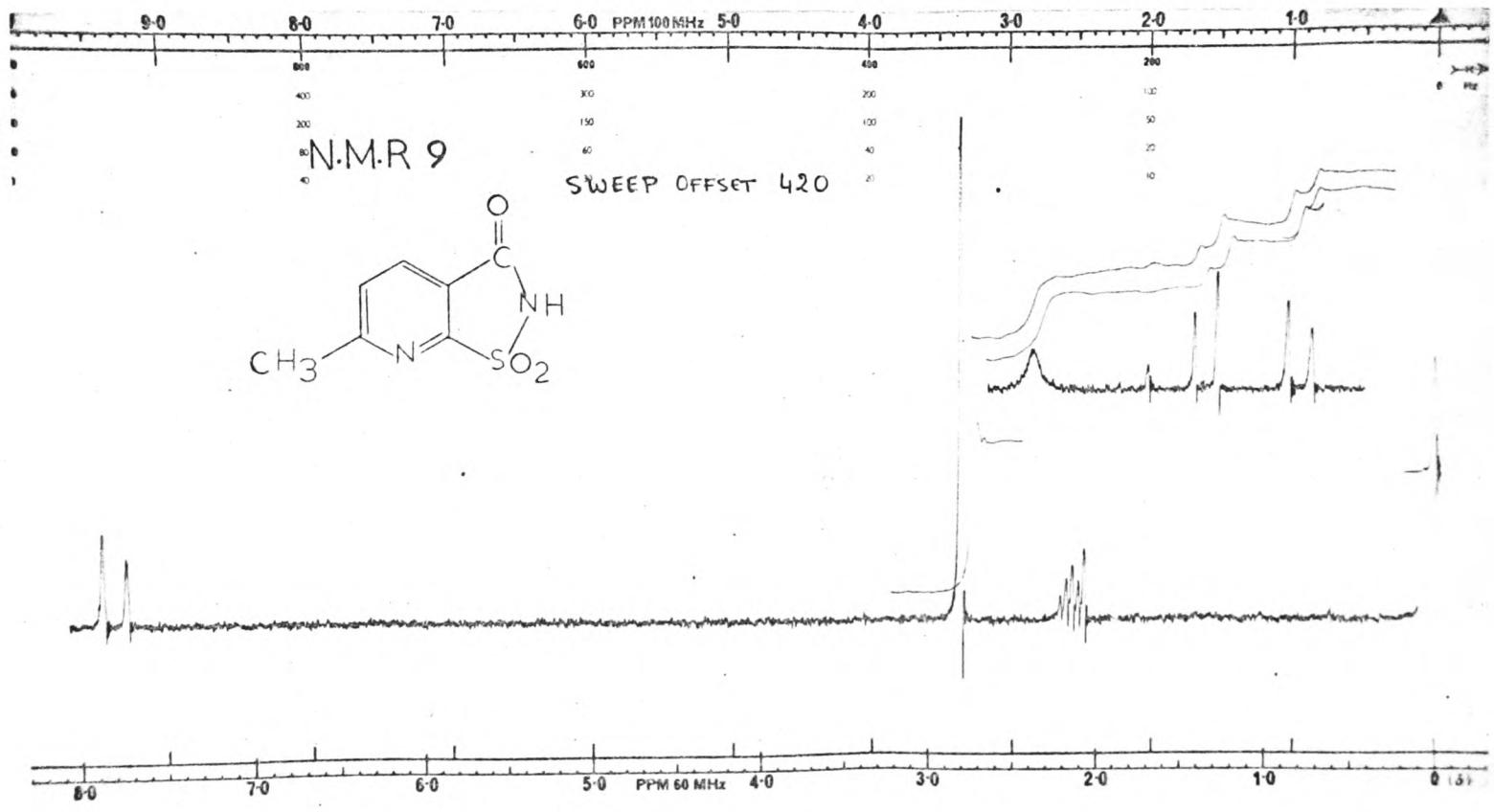


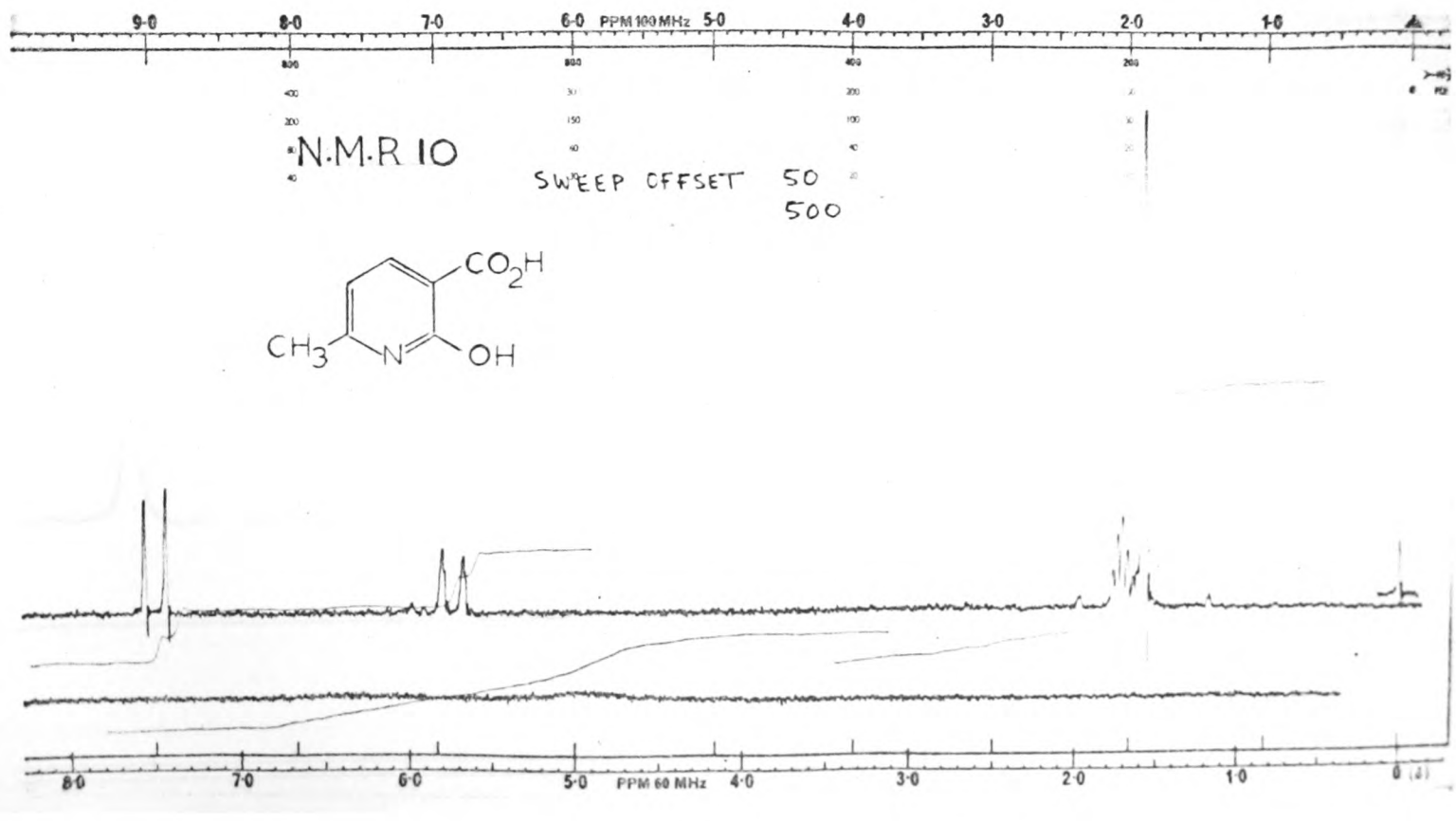

N.M.R 5
SWEEP WIDTH 1000
CH3
N
S
N
CH=CH


N.M.R 6
SWEEP OFFSET 200
C
NH
N
SO2
PPM 100 MHz
PPM 60 MHz

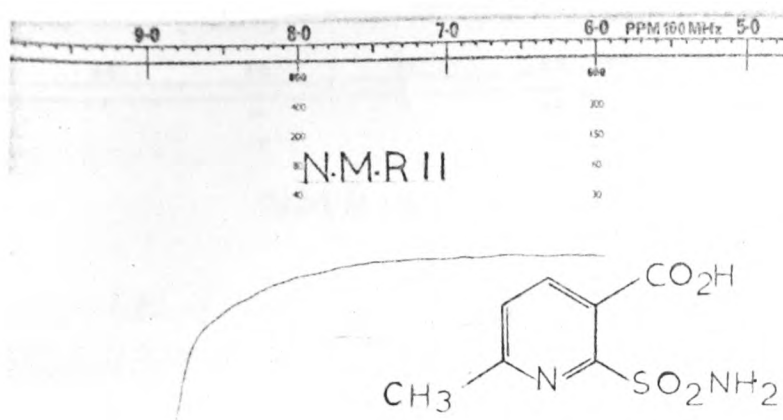

N.M.R 7
SWEEP OFFSET 50
600
CO2H
OH
N
PPM 100 MHz
PPM 60 MHz


9·0 8·0 7·0 6·0 PPM 100 MHz 5·0 4·0 3·0 2·0 1·0
N.M.R 8
SWEEP OFFSET 500
CO2H
N
SO2NH2
8·0 7·0 6·0 5·0 PPM 60 MHz 4·0 3·0 2·0 1·0 0 (δ)


9·0 8·0 7·0 6·0 PPM 100 MHz 5·0 4·0 3·0 2·0 1·0
N.M.R 9
SWEEP OFFSET 420
O
C
NH
CH3
N
SO2
8·0 7·0 6·0 5·0 PPM 60 MHz 4·0 3·0 2·0 1·0 0 (δ)

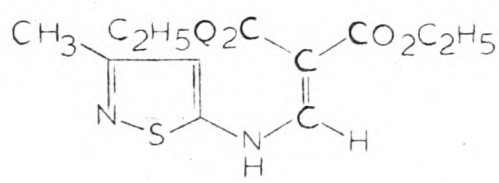

9·0 8·0 7·0 6·0 PPM 100 MHz 5·0 4·0 3·0 2·0 1·0
N.M.R 10
SWEEP OFFSET 50
500
CO2H
CH3
N
OH
8·0 7·0 6·0 5·0 PPM 60 MHz 4·0 3·0 2·0 1·0 0 (δ)

N.M.R 11



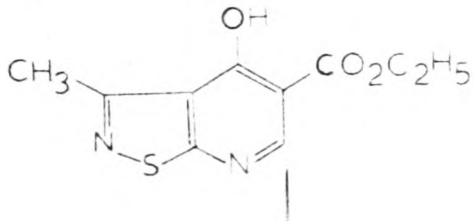
N.M.R 12

SWEEP OFFSET 450



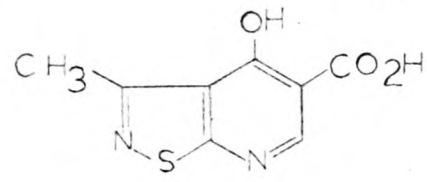
N.M.R 13

SWEEP OFFSET 250



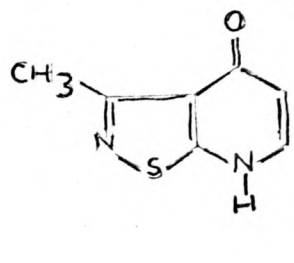
N.M.R 14

SWEEP OFFSET 500



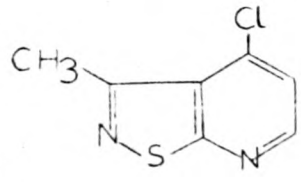
N.M.R 15

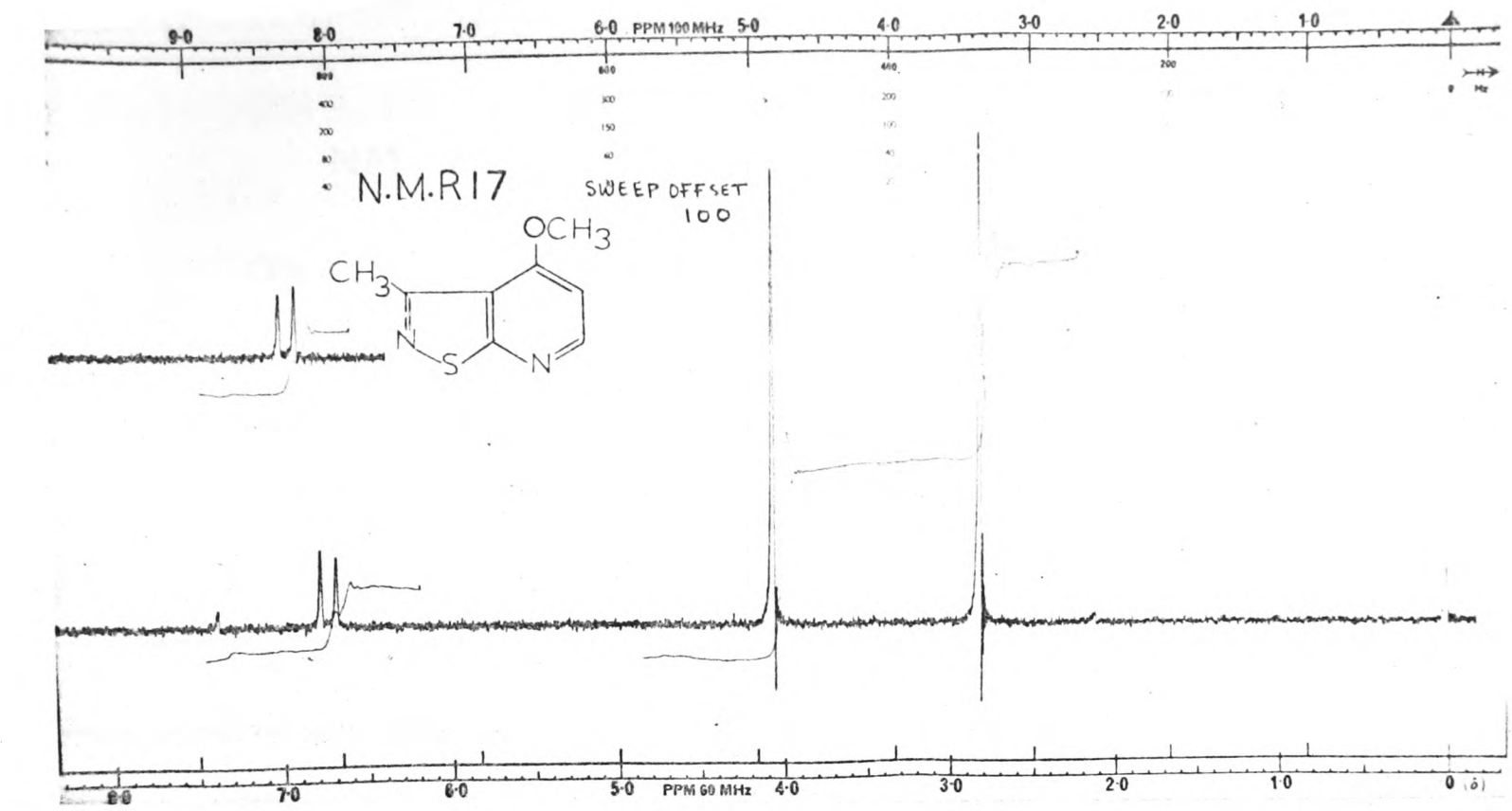
SWEEP OFFSET 500

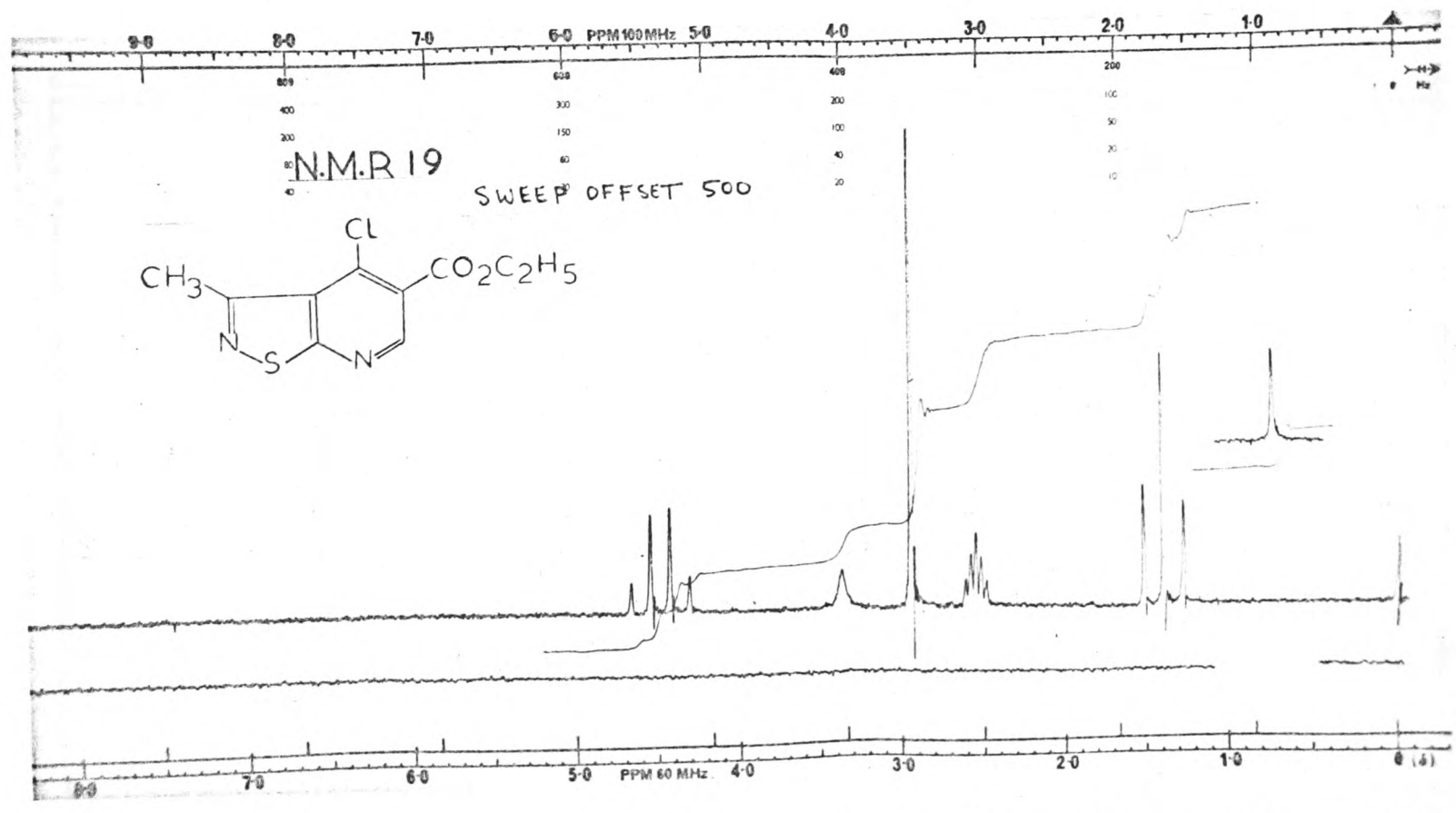


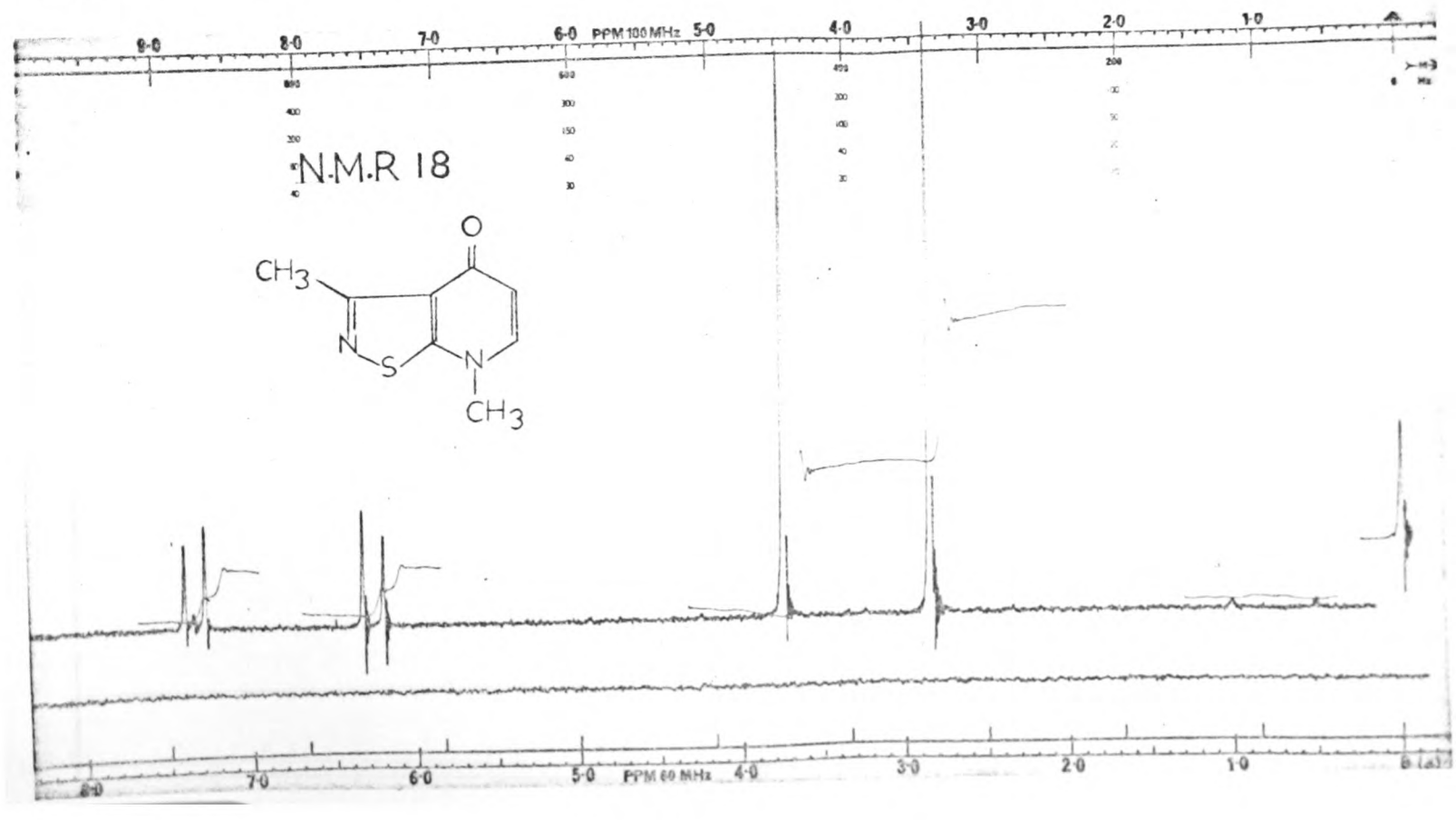
N.M.R 16

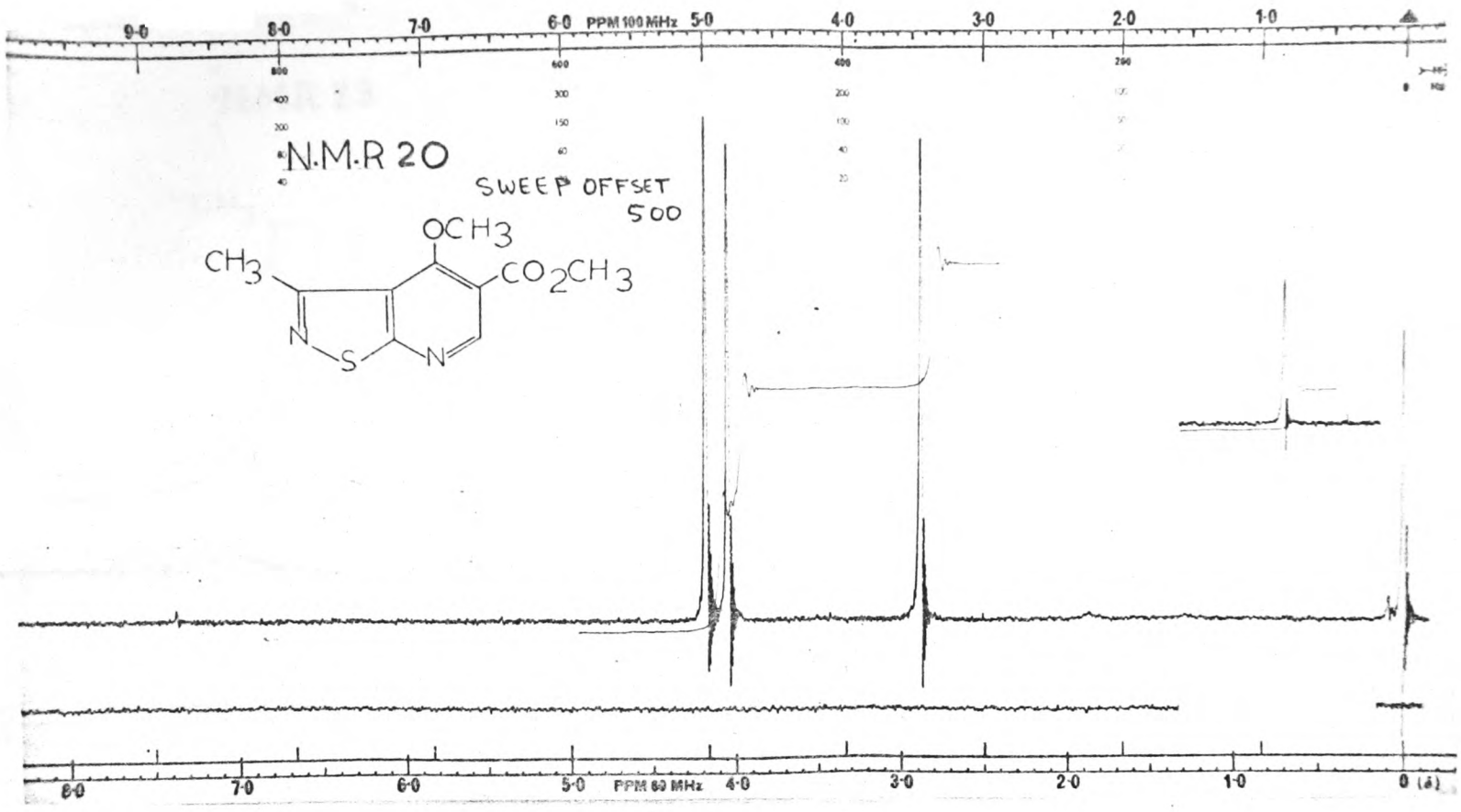
SWEEP OFFSET 500

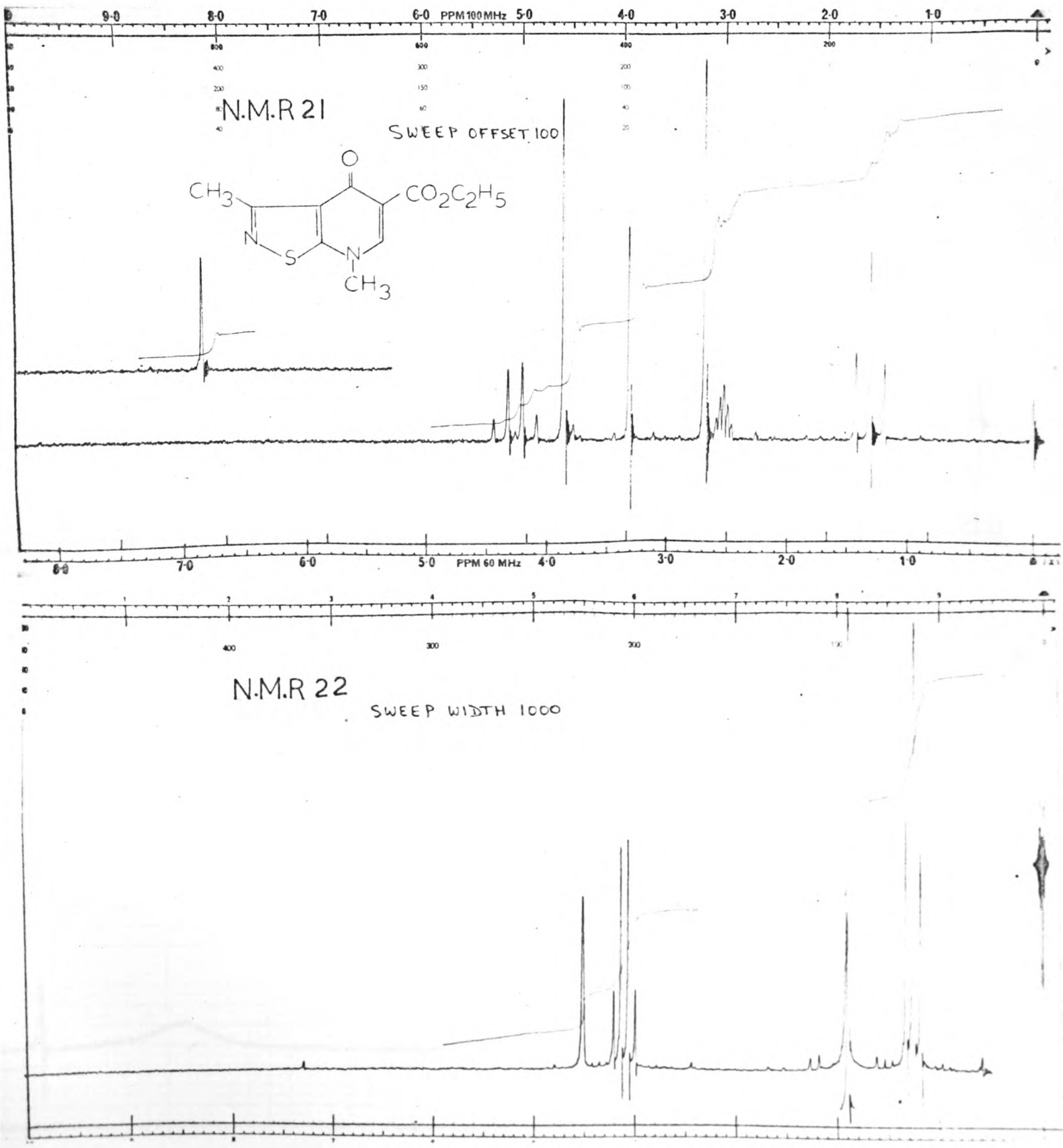



N.M.R 17
SWEEP OFFSET 100
OCH3
CH3
N
S
N
9·0 8·0 7·0 6·0 PPM 100 MHz 5·0 4·0 3·0 2·0 1·0
9·0 7·0 6·0 5·0 PPM 60 MHz 4·0 3·0 2·0 1·0 0 (δ)


N.M.R 19
SWEEP OFFSET 500
CL
CH3
CO2C2H5
N
S
N
9·0 8·0 7·0 6·0 PPM 100 MHz 5·0 4·0 3·0 2·0 1·0
9·0 7·0 6·0 5·0 PPM 60 MHz 4·0 3·0 2·0 1·0 0 (δ)

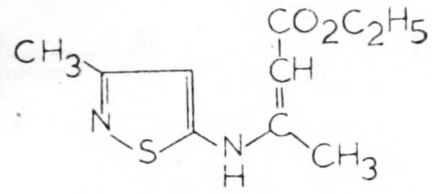

N.M.R 18
O
CH3
N
S
N
CH3
9·0 8·0 7·0 6·0 PPM 100 MHz 5·0 4·0 3·0 2·0 1·0
9·0 7·0 6·0 5·0 PPM 60 MHz 4·0 3·0 2·0 1·0 0 (δ)


N.M.R 20
SWEEP OFFSET 500
OCH3
CH3
CO2CH3
N
S
N
9·0 8·0 7·0 6·0 PPM 100 MHz 5·0 4·0 3·0 2·0 1·0
8·0 7·0 6·0 5·0 PPM 60 MHz 4·0 3·0 2·0 1·0 0 (δ)

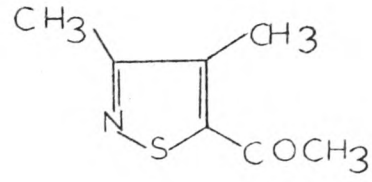

N.M.R 21
SWEEP OFFSET 100
O
CH3
CO2C2H5
N
S
N
CH3
9·0 8·0 7·0 6·0 PPM 100 MHz 5·0 4·0 3·0 2·0 1·0
8·0 7·0 6·0 5·0 PPM 60 MHz 4·0 3·0 2·0 1·0

N.M.R 22
SWEEP WIDTH 1000

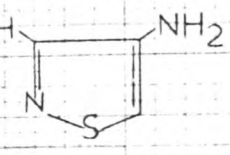
N.M.R 23

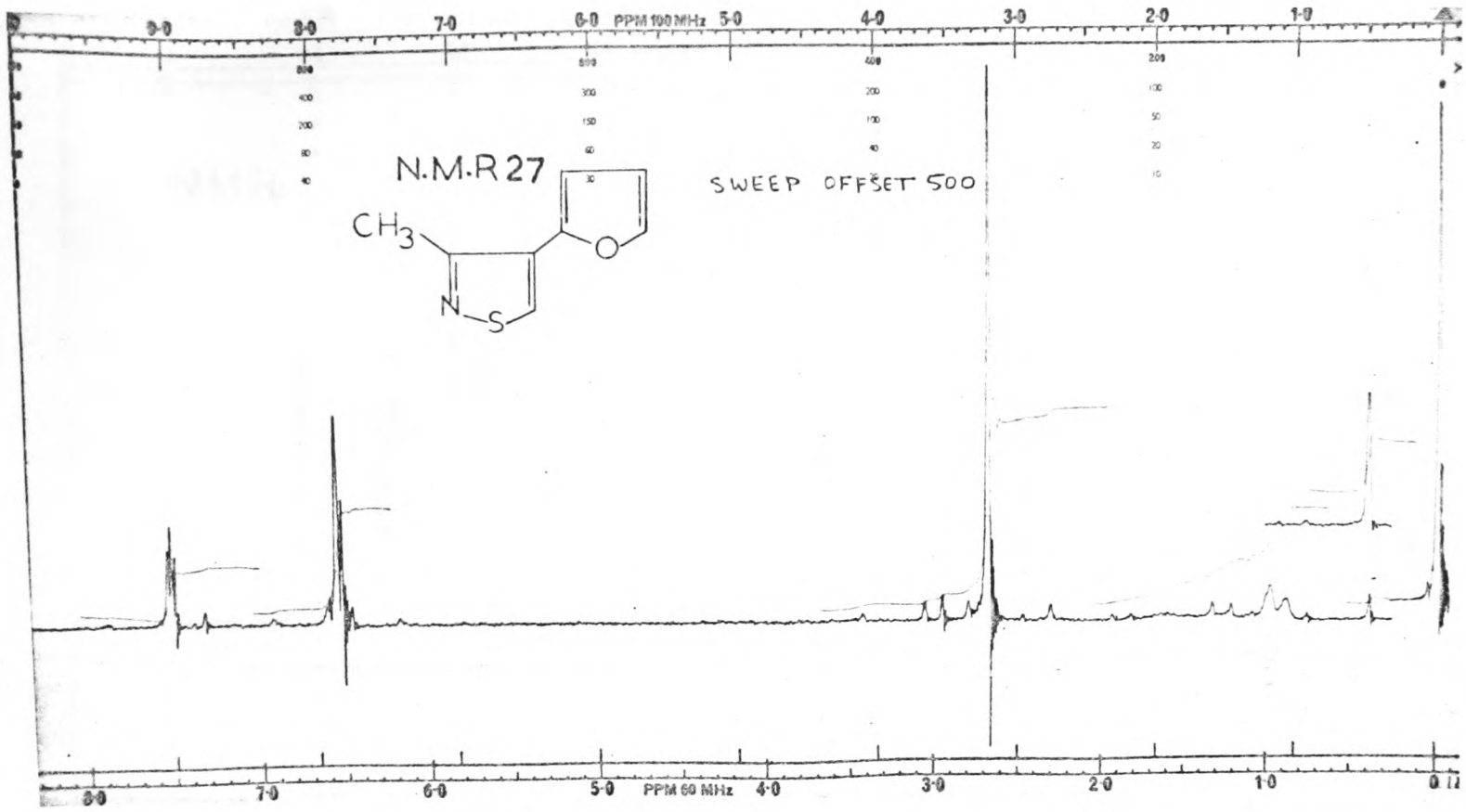


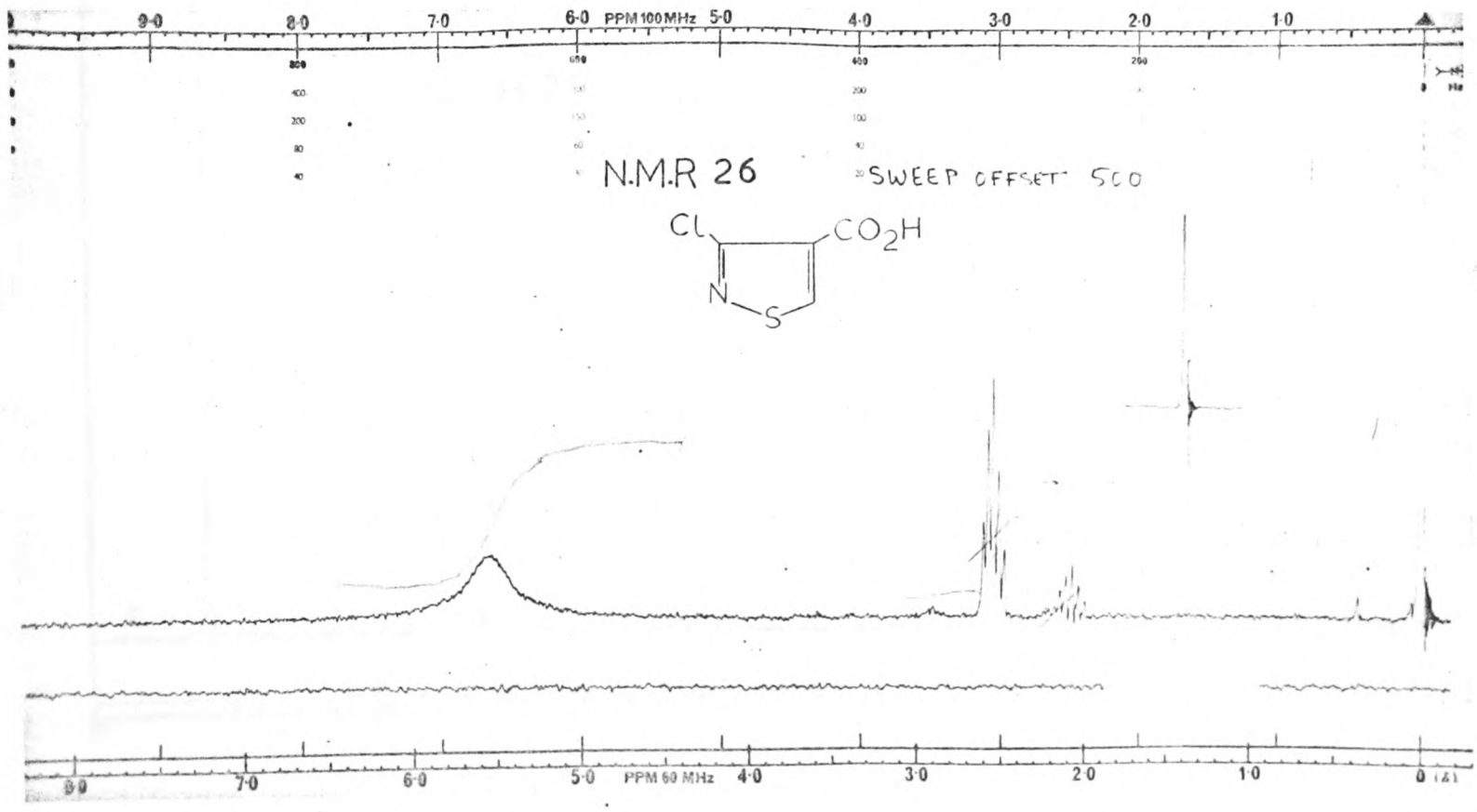
N.M.R 24

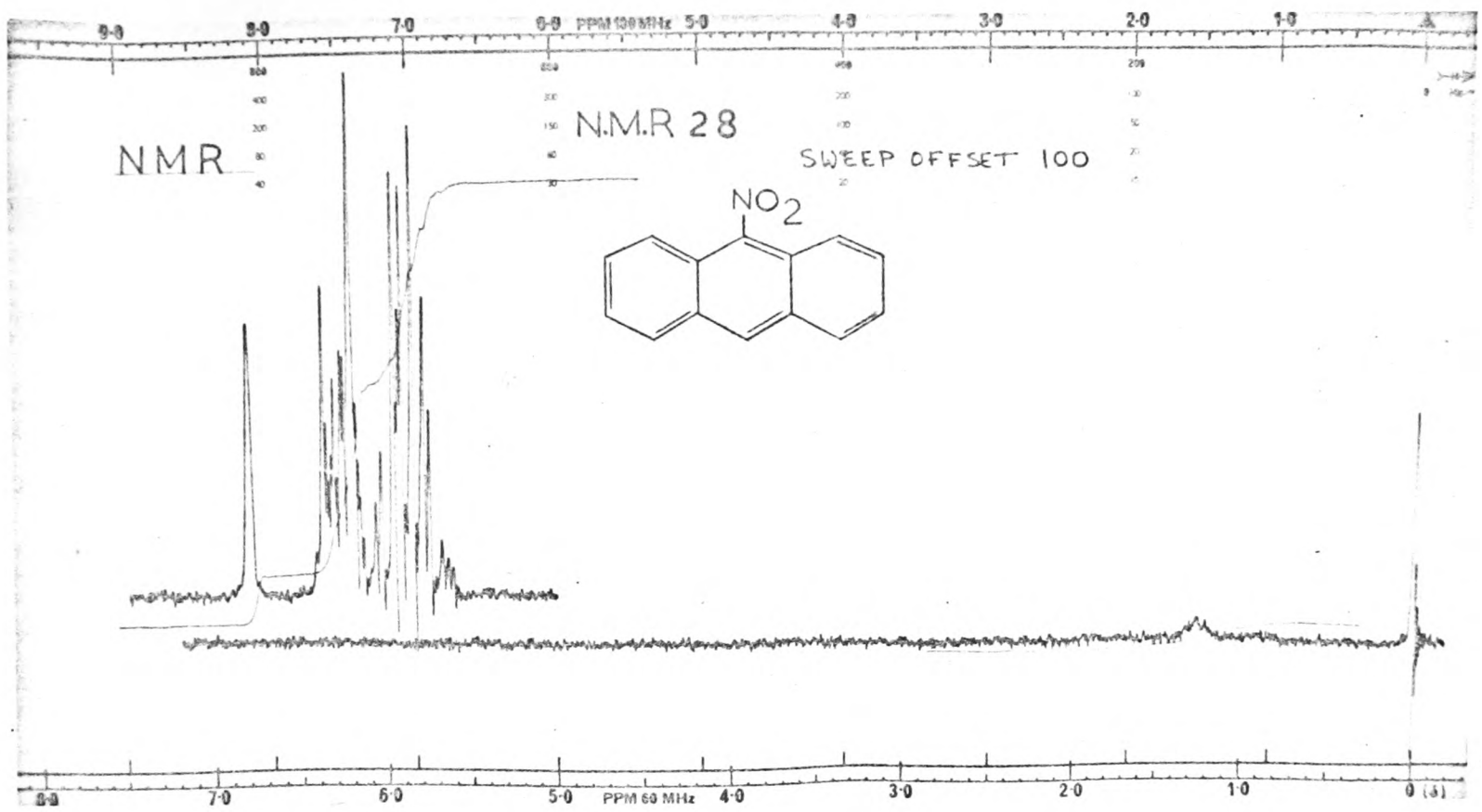


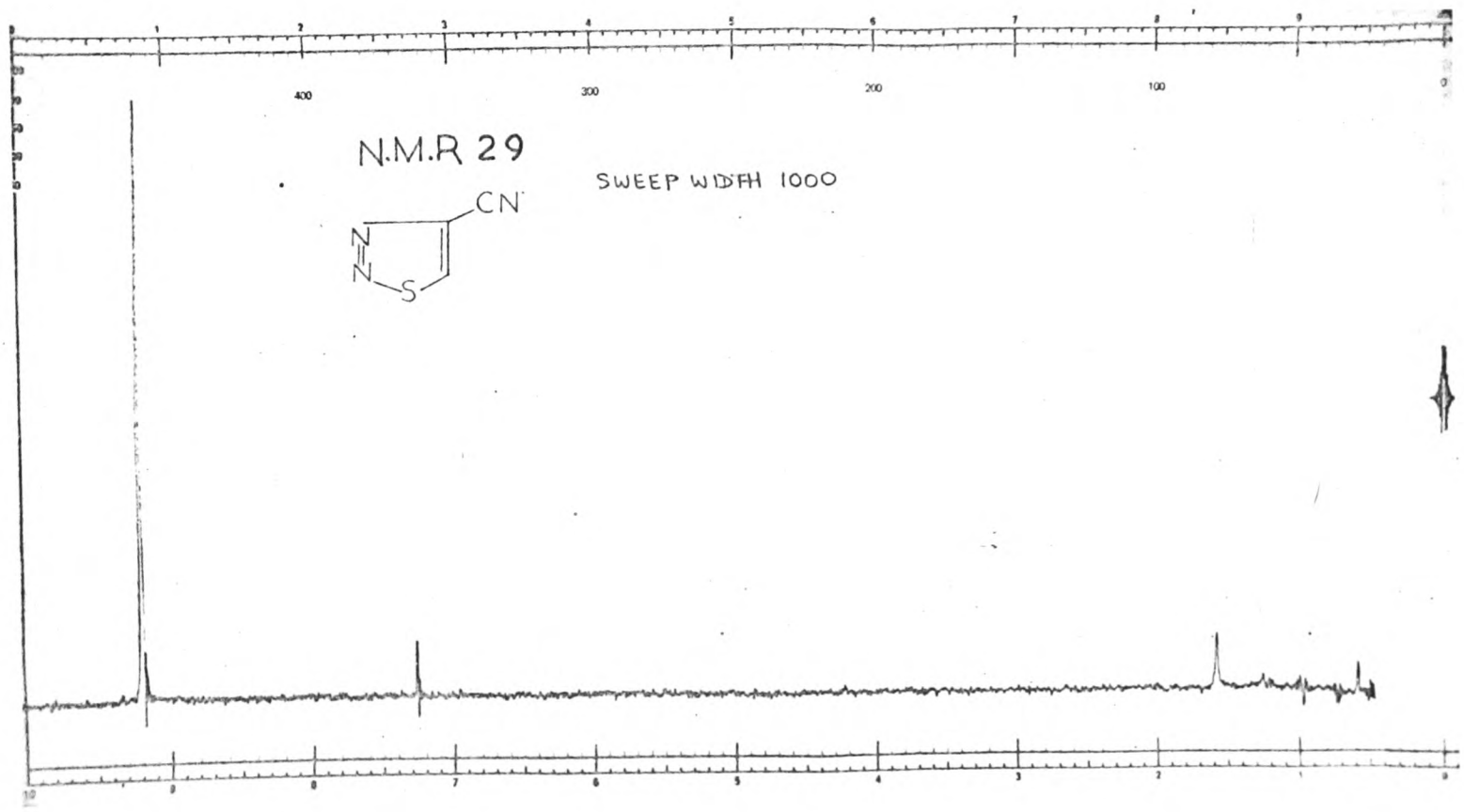
N.M.R 25




N.M.R 27
SWEEP OFFSET 500
PPM 100 MHz
PPM 60 MHz


N.M.R 26
SWEEP OFFSET 500
PPM 100 MHz
PPM 60 MHz


NMR
N.M.R 28
SWEEP OFFSET 100
NO2
PPM 60 MHz


N.M.R 29
SWEEP WIDTH 1000
CN
N
S

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