«

SOME REACTIONS
0F
NN - DISUBSTITUTED THIOAMIDES

A THESIS PRESENTED TO THE
AHMADU BELLO UNIVERSITY FOR
THE DEGREE OF MASTER OF SCIENCE

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THIS THESIS IS FONDLY DEDICATED

TO MY PARENTS

A C K N O W L E D G E M E N T S

It is a pleasure to express my most sincere and immeasurable gratitude to Professor F. Stansfield, for his most inspiring guidance and superb supervision throughout the research programme.

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Finally, the bursary from the Midwest State Government is also gratefully acknowledged.

ABSTRACT
In the present work some of the synthetic applications of S-alkyl quaternary salts of NK-disub¬stituted thioamides were investigated,
NN-Disubstituted tliioamides which were prepared by the Willgerodt
Klndler procedure, 1-8 or from the amides with phosphorus pentasulphide9 were reacted With simple alkyl halides to give S-alkyl quaternary salts in good yields. The reaction of the quaternary salts With hydroxy 1amine hydrochloride produced NN-disubstituted amidoximes, while treatment of the quaternary salts with potassium cyanide gave novel S-alkyl quaternary cyanides some of which hydrolysed to cyanoamides under surprisingly mild conditions

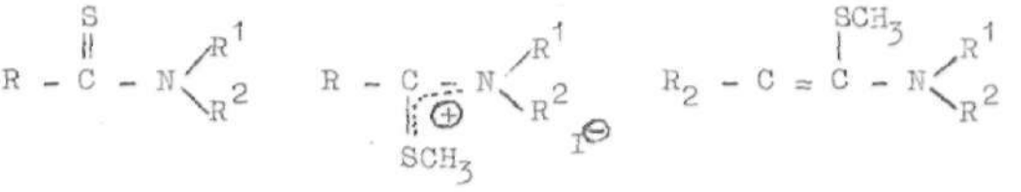
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I N T R O D U C T I O N

NN-Disubstituted thioamides(I) are readily prepared by the Willgerodt - Kindler reaction[1 - 8] or from the amides with phosphorus pentasulphide.[9] These thioamides give good yields of S-alkyl quaternary salts (II) when treated with simple alkyl halides.[8,10] The quaternary salts are of synthetic value as intermediates since they react additively with many nucleophiles, often in aqueous solution at room temperature and usually with elimination of the alkythio - or disubstituted amino - group.[8,10,11]

Alternatively, the treatment of the quaternary salts with bases may cause the elimination of hydrogen halide giving ketene SN-acetals(III)[12] which are also useful intermediates themselves.

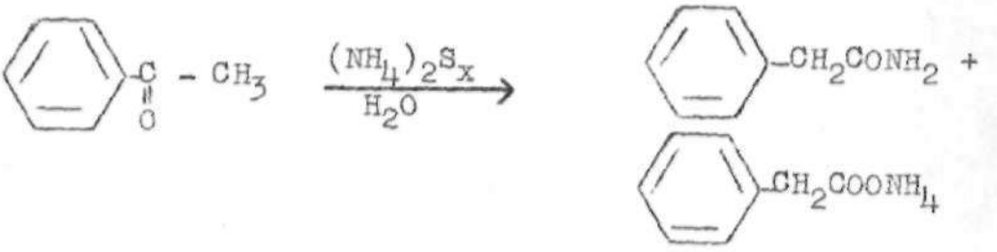


I II III

[R = alkyl or aryl; $R^1 = R^2$ = alkyl or NR^1R^2 = morpholino].

WILLGERODT REACTION:

The Willgerodt reaction[1-7] proper is the reaction of alkyl aryl ketones with aqueous ammonium phlysulphide at about 200° in a sealed tube to form aryl substituted aliphatic acid amides, together with smaller amounts of the corresponding ammonium salts of the carboxylic acids. The coversion of acetophenone into phenylacetamide and ammonium phenylacetate could serve as an illustration.



The net result of the reaction is the reduction of the carbonyl group to a methylene group and the oxidation of the terminal methyl group.

The sulphur in polysulphides acts as a thiolating agent; the presence of small amounts of hydrogen sulphide has a favourable effect on thiolation. This reaction has been applied to a number of completely aliphatic ketones. For example, pinacolone is converted

into t-butylacetamide and 2-heptanone into heptamide.

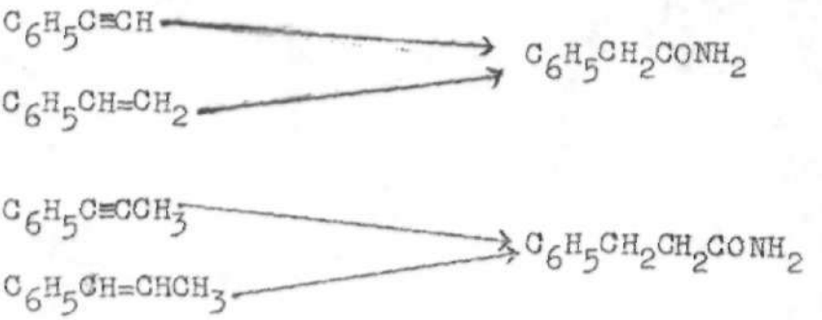
$$(CH_3)_3CCOCH_3 \longrightarrow (CH_3)_3CCH_2CONH_2$$

$$CH_3(CH_2)_4COCH_3 \longrightarrow CH_3(CH_2)_5CONH_2$$

KINDLER'S MODIFICATION:

A substantial modification of the Willgerodt reaction was devised by Kindler.[1-8] The Indler variation consists in heating the ketone with approximately equimolecular amounts of sulphur and a dry amine instead of aqueous ammonium polysulphide. A thioamide is formed as the principal product and on hydrolysis with acid or alkali affords the carboxylic acid, usually in good yield. Generally, a secondary aliphatic amine but sometimes a primary amine or even anhydrous ammonia is used. Morpholine is well suited to the Kindler version of the Willgerodt reaction; it is cheap, and its boiling point (128°) makes possible the use of open apparatus in place of an autoclave or bomb tube.

Aryl-substituted olefines and acetylenes are transformed into amides under the conditions of both the Willgerodt and Kindler procedures:



Kindler's modification of the Willgerodt reaction has since been extended to aldehydes and alcohols as starting materials.

MECHANISM OF WILLGERODT REACTION:

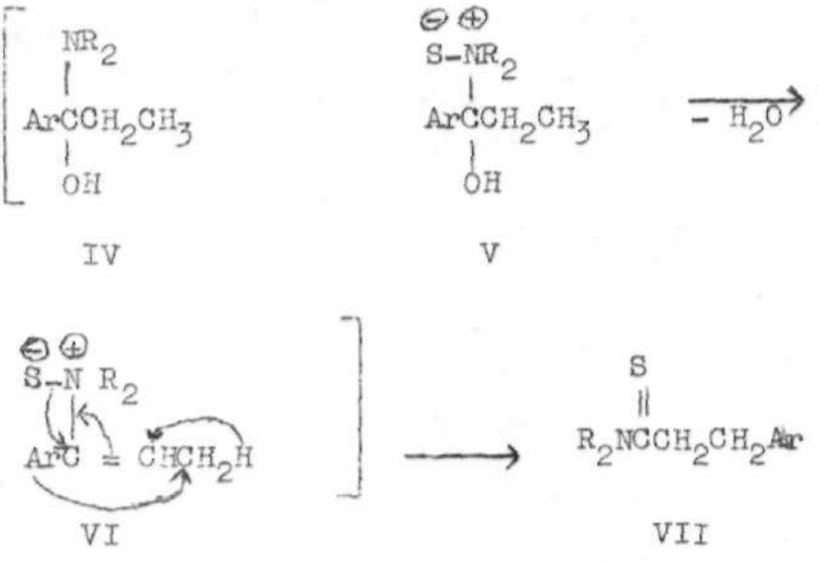
The mechanism of the Willgerodt reaction is not clear. The possibility that the ketone first undergoes reduction at the carbonyl group to form a hydrocarbon which is subsequently oxidised at the terminal methyl group was rejected when it was found that an alkyl substituent such as the ethyl group is unaffected under the conditions that bring about the reaction with ketones. Willgerodt considered it unlikely that the oxidation of the terminal methyl group of the ketone could precede the final reductive step in which the carbonyl group would be converted into a methylene unit, since there is no evidence for intermediate keto-acids and since the

latter cannot be converted into amides by the ammonium polysulphide reagent.

He concluded that the oxygen atom of the alkyl aryl ketone can, in some unknown way, wander to the end of the chain, or, in effect, exchange place with two hydrogen atoms of the methyl group to form an aldehyde isomeric with the ketone. The aldehyde would then react with sulphur and ammonia to produce the amide and hydrogen sulphide; indeed aldehydes are known to yield amides under these conditions.

Kindler suggested that the reaction may proceed by a migration of the aryl group to the carbon atom alpha to the carbonyl group in acetophenone; the original carbonyl group would thus become the thioamide function of the final product. To accommodate ketones higher than acetophenone, for example, propiophenone, he postulated migration of the phenyl group to the end of the chain, two or more atoms removed from the carbonyl group. First, he stated, there is the preliminary formation of the hydramine(IV), which adds sulphur to give an amine sulphide(V). This is dehydrated to (VI), and then the final thioamide is formed in a rearrangement which results in the simultaneous

migration of the sulphur atom, the aryl radical, and a terminal hydgrogen atom.

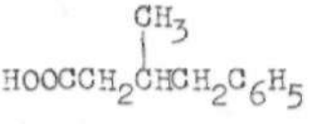


IV V VI VII

However, evidence against this mechanism is recorded in Willgerodt's observation that isovalerophenone(VIII) gives, after hydrolysis, α-methyl-γ-phenylbutyric acid (IX). According to Kindler's hypothesis the β-methyl isomer (X) should result. That IX is the product seems highly probable.

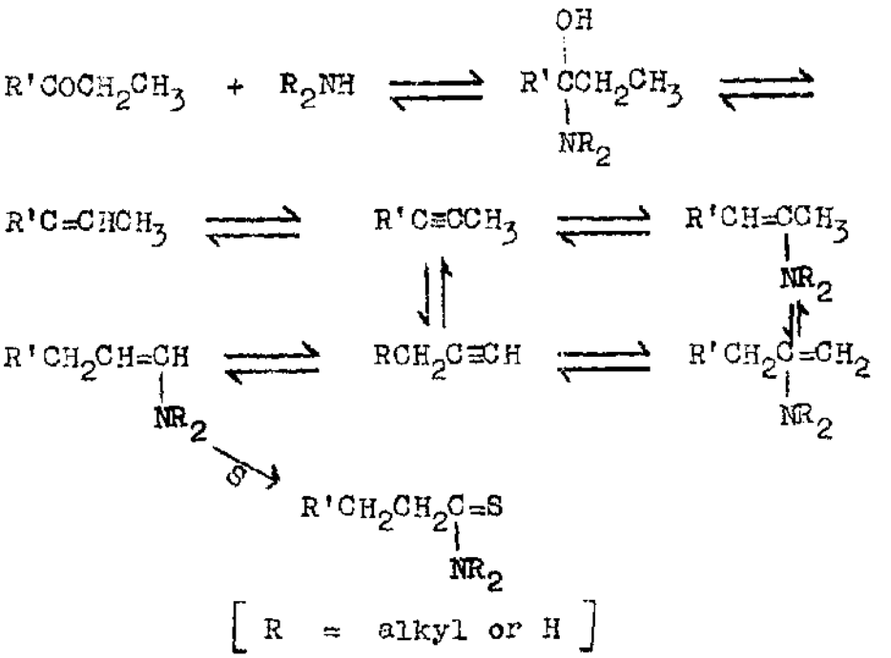


VIII IX



X

On the basis of three facts - that no change in the carbon skeleton occurs during the reaction; that all members of a family of isomeric aliphatic carbonyl compounds, differing from one another only in the position of the oxygen atom, form the same final product; and that unsaturated hydrocarbons can undergo reactions very similar to the Willgerodt and Kindler reactions of ketones - De Tar and Carmack[13] have argued that there must be one fundamental mechanism involving preliminary formation of a labile intermediate which has an unsaturated carbon - carbon bond in the side chain. They have postulated a series of reactions involving the stepwise addition, elimination, and readdition of the elements of simple molecules such as ammonia, amines, sulphur, water or hydrogen sulphide, the net result being the migration of the functional group along the chain. Irreversible oxidation by the action of sulphur, when the function reaches the terminal position, produces a thioamide. The type of process is illustrated schematically as follows:



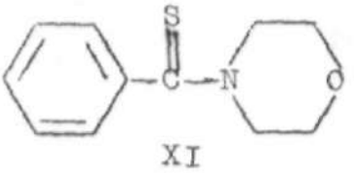
[R = alkyl or H]

That a carbonamide rather than a thioamide is isolated in the Willgerodt reaction with aqueous ammonia does not constitute an argument against the above scheme, for hot aqueous ammonia is known to convert thioamides into carbonamides. The isomerization of straight - chain acetylenic compounds (with and without aromatic substituents) to products having the acetylene function in the terminal position is known to take place in the presence of sodamide. The assumption that such unsaturated substances are intermediates in the Willgerodt reaction offers an explanation of the appearance of certain by-products.

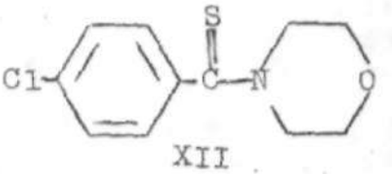
Tetrahydronaphthoic acid, isolated in small amounts from the reaction of ethyl 6-tetralyl ketone with morpholine and sulphur, may arise from an oxidative attack by sulphur on an unsaturated intermediate. The presence of traces of thiophenes in the reaction mixtures is explicable when it is considered that olefines and sulphur react at elevated temperatures to give hydrogen sulphide and thiophenes and that acetylenes also give thiophenes but with little evolution of hydrogen sulphide.

PREPARATION OF NN-DISUBSTITUTED THIOAMIDES AND QUATERNARY SALTS.

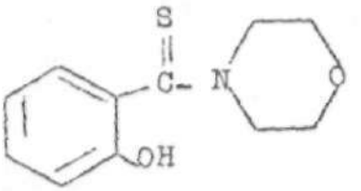
In the present investigation some NN-disubstituted thioamides were made by the Willgerodt - Kindler procedure: thiobenzomorpholide(XI), 4-chlorothiobenzomorpholide(XII), thiosalicylmorpholide(XIII), thiobenzodimethylamide(XIV) and phenylthioacetmorpholide(XV) while thioacetmorpholide(XVI) and thioformdimethylamide(XVII) were prepared by the action of phosphorus pentasulphide on the amides.



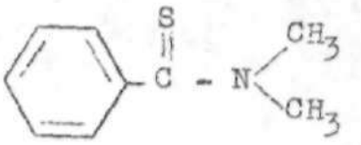
XI



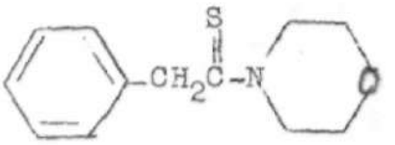
XII



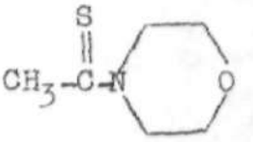
XIII



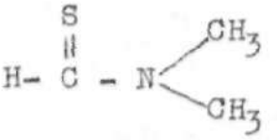
XIV



XV



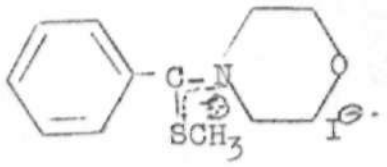
XVI



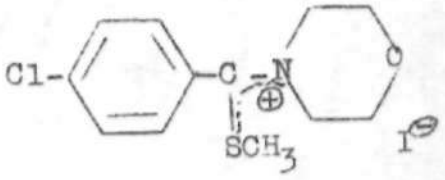
XVII

The S-alkyl quaternary salt, thiobenzomorpholide methiodide (XVIII) was obtained by heating a mixture of thiobenzomorpholide (XI) and iodomethane under reflux. The positive charge can be delocalized on nitrogen, sulphur or carbon. Similarly, the quaternary salts: (XIX), (XX), (XXI), (XXII), (XXIII) and (XIV) were made

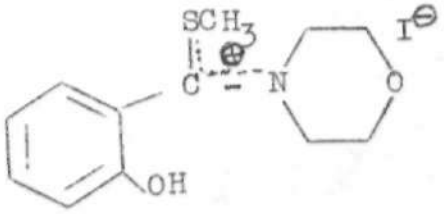
from the corresponding NN-disubstituted thicamides in good yields.



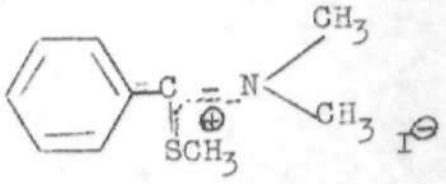
XVIII



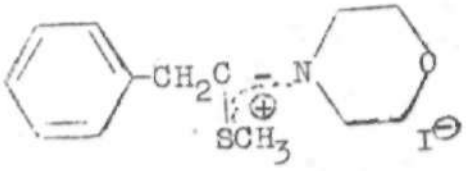
XIX



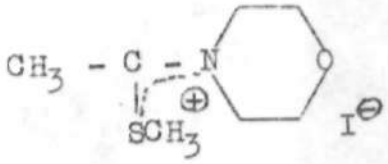
XX



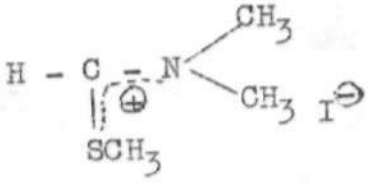
XXI



XXII



XXIII

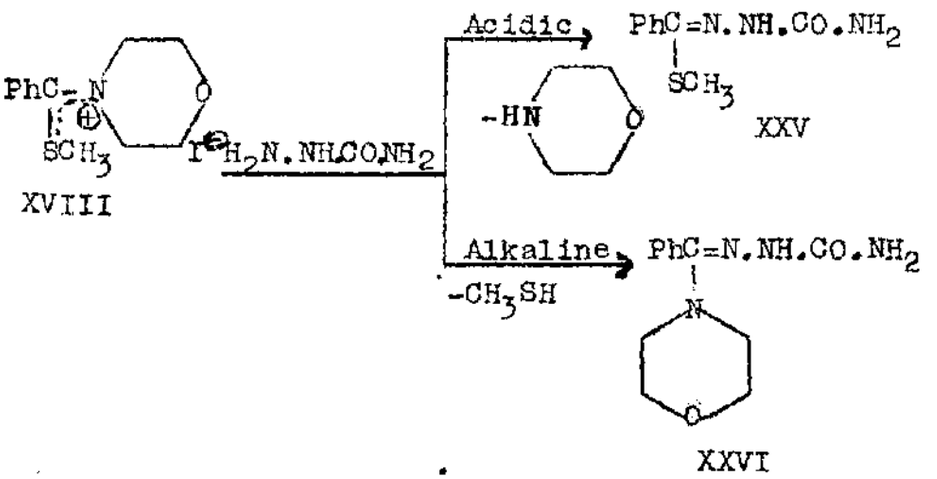


XXIV

PREVIOUS INVESTIGATIONS WITH QUATERNARY SALTS OF NN-DISUBSTITUTED THIOAMIDES.

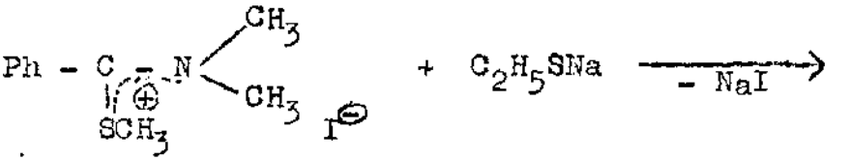
S-Alkyl quaternary salts of thioamides have been known to be quite reactive compounds.

Chabrier and Renard[14] have treated the quaternary salt(XVIII) with semicarbazide hydrochloride in aqueous ethanol and obtained 1-α-methylthiobenzylidene semicarbazide(XXV). Peak and Stansfield[8] have found that under alkaline conditions semicarbazide condensed with the quaternary salt(XVIII) with the elimination of methanethiol instead of morpholine hydriodide to give 1-α-morpholinobenzylidene semicarbazide(XXVI).

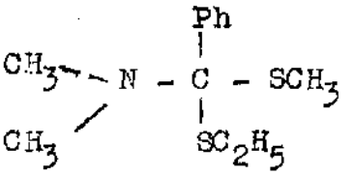


Quite recently Mukaiyama and his co-workers[10] have treated thiobenzodimethylamide methiodide(XXI)

with active methylene compounds and heavy metal salts. They caused the quaternary salt(XXI) to react with sodium ethanethiolate in dry ether at room temperature and obtained NN-dimethylbenzamide methylethylmercaptal (XXVII) in fairly good yield.

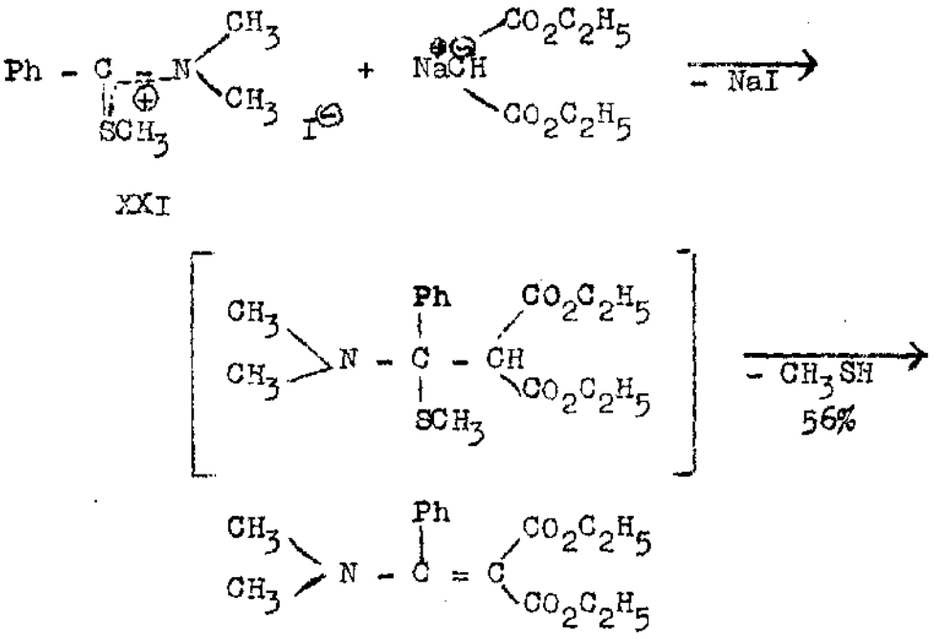


XXI



XXVII

These workers also found that diethyl α-dimethylaminobenzylidene malonate(XXVIII) was produced in 56% yield, with the evolution of methanethiol when a suspension of the quaternary salt(XXI) and the monosodium salt of ethyl malonate in dry dioxan was stirred at 80° for 2h.



XXI

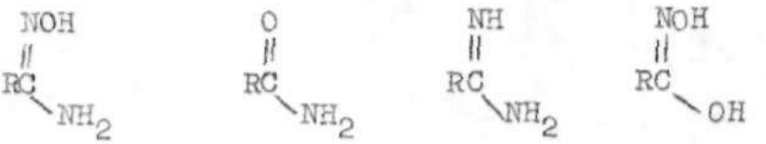
XXVIII

Similar results were obtained by treating the quaternary salt(XXI) with the monosodium salts of other active methylene compounds, such as ethyl acetoacetate, ethyl cyanoacetate, acetylacetone and nitromethane.

METHODS OF PREPARATION OF AMIDOXIMES:

The amidoxime function(XXIX)[15] can be considered either as an amide(XXX) in which the oxygen atom of the carbonyl group has been replaced by an isonitroso group, or as amidine(XXXI) whose hydrogen of the imido

group has been exchanged for a hydroxy radical; they are also related to the hydroxamic acids(XXXII).



XXIX XXX XXXI XXXII

The name "amidoxime" was first used by Tiemann[16] who carried out the structural diagnosis of this class of compounds. Not only are monoamidoximes known, but also diamidoximes(XXXIII) containing two amidoxime groups and polyamidoximes containing more than two amidoxime groups.



XXXIII

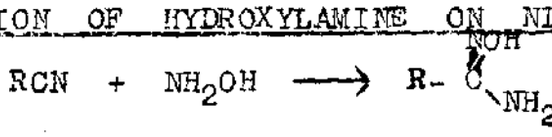
Tiemann recognised that amidoximes may be present in two tantomeric forms,



with the former being predominant.

Monoamidoximes are prepared by the following methods:

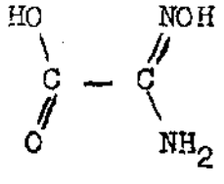
A. ACTION OF HYDROXYLAMINE ON NITRILES



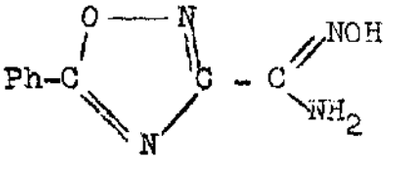
The experimental procedure[16] consists in liberating hydroxylamine from its hydrochloride using sodium carbonate, adding an equivalent amount of nitrile and enough alcohol to obtain a clear solution, and keeping the mixture at 60-80° during a few hours. This is the most used process for the preparation of amidoximes. Aromatic amidoximes generally are obtained in better yields than are aliphatic. Lower members show very high solubility in water and ethanol and this renders isolation tedious.

B. ACTION OF HYDROXYLAMINE ON AMIDES OR THIOAMIDES

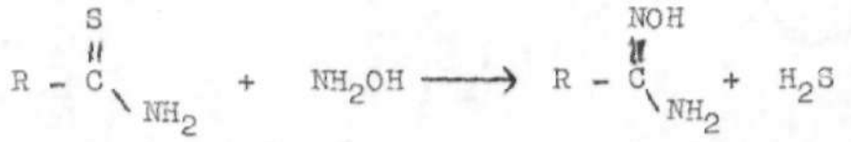
Hydroxylamine as a rule does not react with amides. This method has only been reported[17,18] for the preparation of two amidoximes:



and



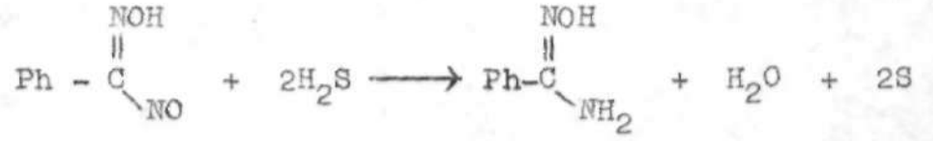
Some aromatic amidoximes have been prepared by the action of hydroxylamine on thioamides.[19-22]



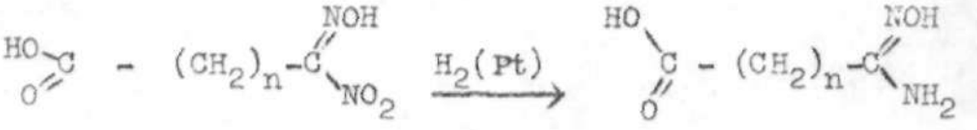
Hydroxylamine is liberated from its hydrochloride by an equivalent amount of aqueous sodium carbonate. The thioamide is then introduced and ethanol is added until the mixture is clear. The solution is refluxed for a few hours and the amidoxime isolated.

C. REDUCTION OF NITROSOLIC AND NITROLIC ACIDS

Amidoximes can be obtained by reduction of nitrosolic acids with hydrogen sulphide.[23]

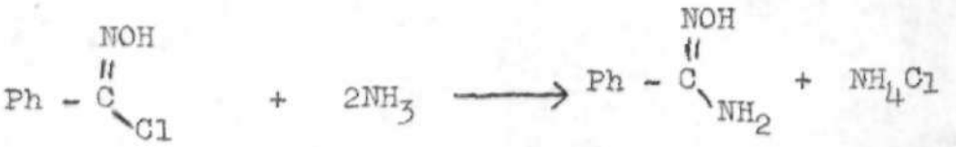


Amidoximes have also been prepared by catalytic reduction of nitrolic acids.[24]



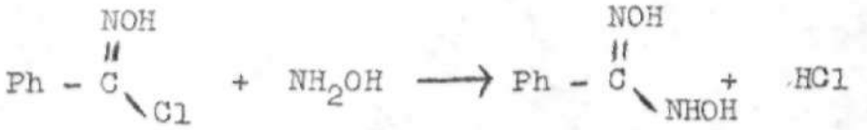
D. ACTION OF AMMONIA ON HYDROXIMIC ACID CHLORIDES [CHLOROXIMES]

Hydroximic acid chlorides are formed by direct chlorination of aldoximes. These compounds react easily with ammonia to yield amidoximes.[25,26]

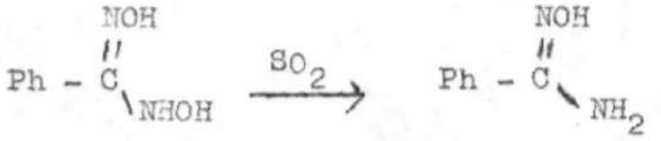


E. REDUCTION OF OXYAMIDOXIMES

Hydroximic acid chlorides also react with hydroxylamine to form oxyamidoximes. This reaction was used by Ley and Ulrich[27] to prepare benzoxyamidoxime.

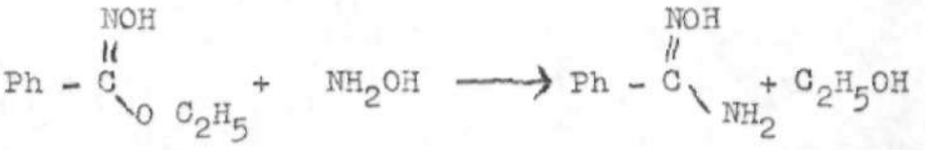


This compound is then reduced with sulphur dioxide to the corresponding amidoxime.



F. ACTION OF HYDROXYLAMINE ON IMINOETHERS

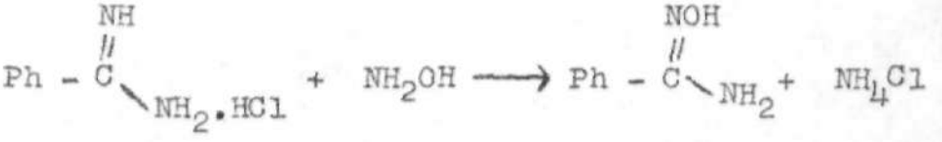
This reaction was reported by Pinner[28] and Lossen[29] who obtained benzamidoxime by treating ethyl iminobenzoate with hydroxylamine.



Since benzonitrile is the starting material for the synthesis of the iminoether, this reaction is not a practical method for the synthesis of amidoximes (compare with the more direct method A).

G. ACTION OF HYDROXYLAMINE ON AMIDINE HYDROCHLORIDES

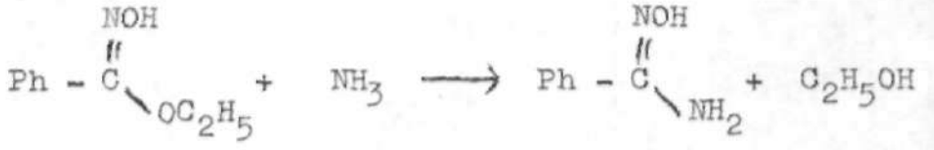
Pinner[28] prepared benzamidoxime by treating benzamidine hydrochloride with hydroxylamine.



This reaction has no practical interest since amidines generally are obtained from nitriles, thioamides, or iminoethers (compare with methods A, B and F).

H. ACTION OF AMMONIA ON OXIMINOETHERS

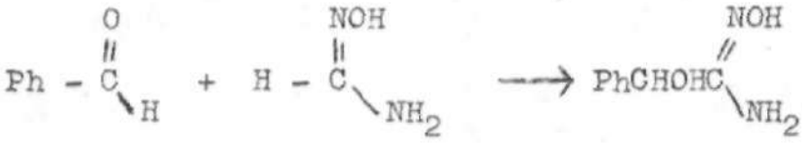
When heated in a pressure bottle for 8 h at 175°, an alcoholic solution of ammonia and ethyl benzhydroxamic acid yields benzamidoxime.[30]



This reaction has not found general application.

I. ACTION OF FORMAMIDOXIME ON AROMATIC ALDEHYDES

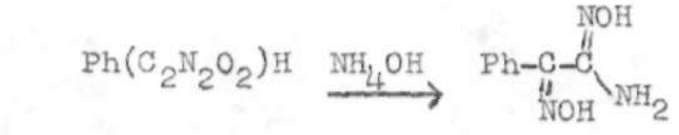
According to Conduche[31] formamidoxime reacts with aromatic aldehydes, leading to an aldol condensation.



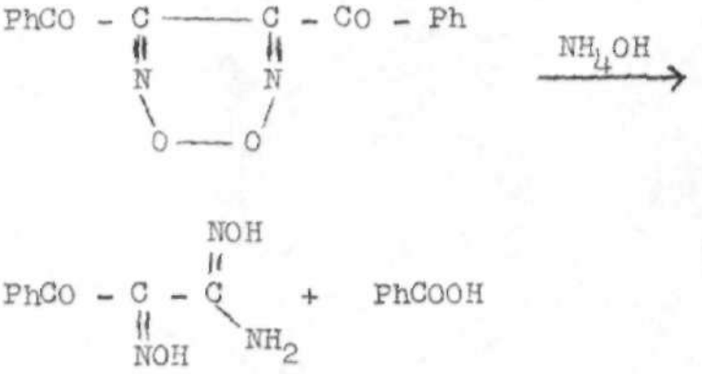
Mandelamidoxime is the only compound that has been prepared by this method.

J. ACTION OF AMMONIA ON GLYOXIME PEROXIDES

On treatment with ammonium hydroxide phenylglycoxime peroxide yields an oximinoamidoxime.[32-34]

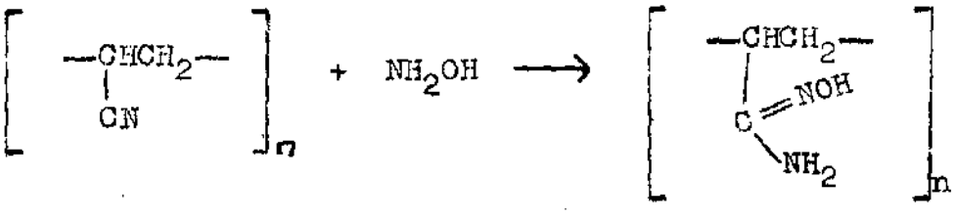


Another example is the reaction of dibenzoylglyoxime peroxide with ammonium hydroxide.[35]



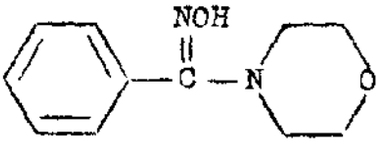
Diamidoximes can be prepared by reactions analogous to those described for the synthesis of monoamidoximes. The most usual synthesis is still the Tiemann method (dinitrile plus hydroxylamine). Highest yields are obtained if free hydroxylamine in butanol is used.[36] This procedure also facilitates the isolation of the product. With high molecular weight dinitriles an excess of hydroxylamine is needed to obtain good yields.

Polymers containing the amidoxime function have been obtained by Schouteden[37-39] by treating a polyacrylnitrile of low molecular weight with slight excess of hydroxylamine.

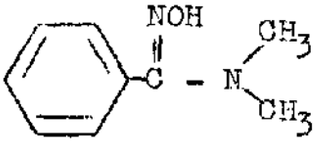


SYNTHESIS AND REACTIONS OF NN-DISUBSTITUTED AMINOXIMES

In the present investigation NN-disubstituted monoamidoximes were prepared by reacting S-alkyl quaternary salts of NN-disubstituted thioamides with hydroxylamine hydrochloride. The process involved the addition of the quaternary salt to a solution of hydroxylamine hydrochloride and excess sodium acetate in water. On gentle shaking of the resulting solution, the corresponding amidoxime precipitated immediately as a colourless crystalline compound. The two NN-disubstituted amidoximes derived from quaternary salts (see Table 1) were α-4'-morpholinobenzaldoxime(XXXIV) and α-dimethylaminobenzaldoxime(XXXV).



XXXIV

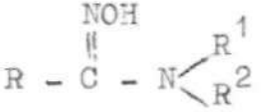


XXXV

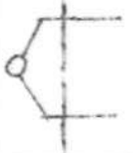
Thiosalicylmorpholide methiodide (XX) gave no amidoxime when treated with hydroxylamine hydrochloride in the presence of excess sodium acetate.

The amidoxime (XXXIV) did not appear to react with Fehling's solution even after prolonged boiling. The mixture of the amidoxime (XXXIV) and 90% formic acid which was boiled for 21 h yielded no solid product while the compound (XXXIV) also did not show any appreciable reaction on treatment with aniline.

TABLE 1:



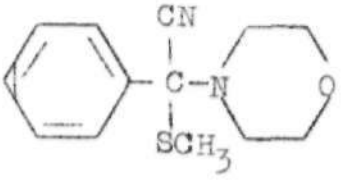
AMIDOXIMES

R	R^1	R^2	YIELD %	M.P.	MOLECULAR FORMULA	ANALYSIS *			U.V. SPEC. [ETHANOL]		I.R. SPEC. [NUJOL] cm^{-1}
						C	H	N	λ sh(nm)	ε sh	
Ph			75	121-122°	$C_{11}H_{14}N_2O_2$	64.1 (64.1)	6.9 (6.8)	13.4 (13.6)	263	2700	3280m, 2920vs, 1620m, 1600w, 1120s, 970s, 770s, 700s.
Ph	Me	Me	66	121-123°	$C_9H_{12}N_2O$	65.9 (65.9)	7.4 (7.3)	17.0 (17.1)	255	2300	3240m, 2920vs, 1620m, 1100s, 970s, 780s, 700s.

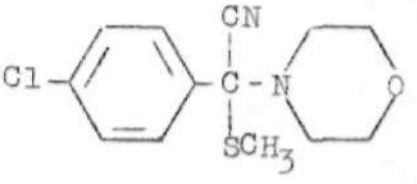
* FOUND VALUES ABOVE, REQUIRED VALUES IN BRACKETS BELOW.

SYNTHESIS AND REACTIONS OF QUATERNARY CYANIDES AND CYANOAMIDES

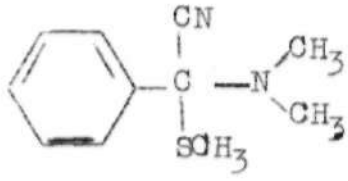
Treatment of the quaternary salts with potassium cyanide solution in water at room temperature yielded novel quaternary cyanides. Thus α-methylthio-α-4'-morpholinobenzyl cyanide(XXXVI), p-chloro-α-methylthio-α-4-morpholinobenzyl cyanide(XXXVII), α-methylthio-α-dimethylaminobenzyl cyanide(XXXVIII), 1-methylthio-1-(4'-morpholino)ethyl cyanide(XXXIX), 1-methylthio-1-(4'morpholino)-2-phenylethyl cyanide(XL) and α-methylthio-α-dimethylaminomethyl cyanide(XLI) (see Table 2) were made from the corresponding S-alkyl quaternary salts. On treatment of thiosalicylmorpholide methiodide(XX) with potassium cyanide solution a reddish solid compound was obtained which decomposed readily on exposure to air.



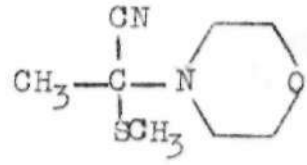
XXXVI



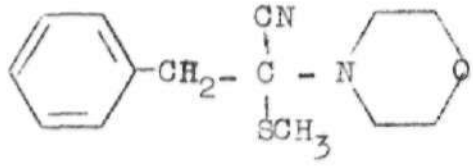
XXXVII



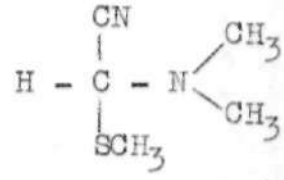
XXXVIII



XXXIX

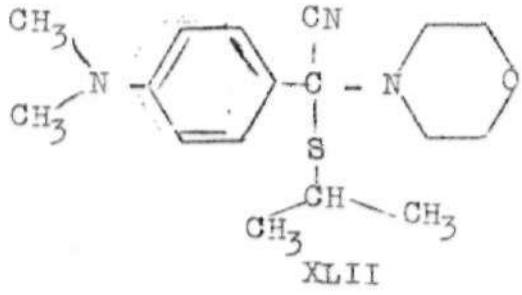


XL



XLI

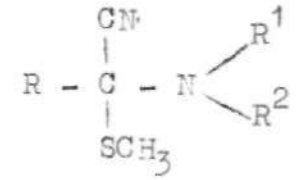
Working under similar conditions Stansfield[40] synthesised p-dimethylamino-α-4'-morpholino-α-isopropyl-thiobenzyl cyanide(XLII) by treating p-dimethylamino-4-α-isopropylthiobenzylidenemorpholinium iodide with potassium cyanide solution (see Table 2).

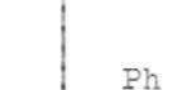
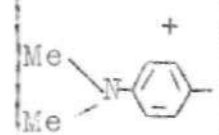


XLII

TABLE 2:

CYANIDES



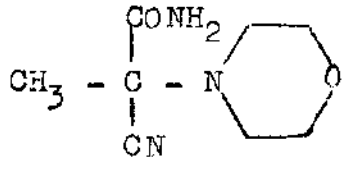
R	R^1	R^2	YIELD %	M. P.	B. P.	MOLECULAR FORMULA	ANALYSIS* C	H	N	U. V. SPEC. [ETHANOL] λ sh(nm)	ε sh	I. R. SPEC. [NUJOL] cm
Ph			99	74-75°	-	$C_{13}H_{16}N_2OS$	62.8 (62.9)	6.4 (6.5)	11.2 (11.3)	255	1000	2920vs, 2220 1600vw, 1120 1010s, 870vs 750vs, 710s,
Ph	Me	Me	99	40°	-	$C_{11}H_{14}N_2S$	64.0 (64.1)	6.8 (6.8)	13.4 (13.6)	255	2100	2920vs, 2220 1600vw, 1020 750vs, 700vs
H	Me	Me	46	-	102°"15mm	$C_5H_{10}N_2S$	46.1 (46.2)	7.9 (7.7)	21.0 (21.5)	Nil	Nil	2920vs, 2220 1680vs, 1160 1040s, 830s,
			-	68-69°	-	$C_{17}H_{25}N_3OS$	63.9 (64.0)	7.8 (7.8)	13.2 (13.2)	-	-	2920vs, 2220 1610s, 1190s 1120vs, 1000 950s, 880s, 710m.

* FOUND VALUES ABOVE, REQUIRED VALUES IN BRACKETS BELOW.

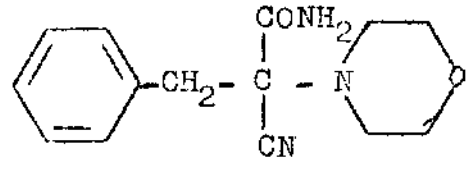
+ PREPARED BY PROF. ". STANSFIELD; METHYLTHIO-GROUP BEING REPLACED BY ISOPROPYLTHIO-GROU

The quaternary cyanide(XXXVIII) which was here obtained as a colourless crystalline compound has been claimed to have been synthesised by Mukaiyama and his co-workers[10] as a liquid substance.

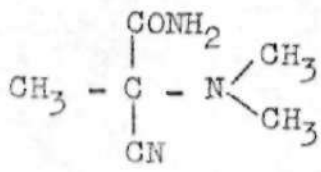
The reaction of thioacetmorpholide methiodide(XXIII) with potassium cyanide solution not only gave the quaternary cyanide(XXXIX) but also the cyanoamide, 2-cyano-2,4'-morpholinopropionamide(XLIII). In the same way the quaternary cyanide(XL) and 2-cyano-2,4'-morpholino-3-phenylpropionamide(XLIV) were obtained from the reaction of phenylthioacetmorpholide methiodide (XXII) with potassium cyanide solution. The reaction of thioacetdimethylamide methiodide with potassium cyanide solution yielded only the cyanoamide, 2-cyano-2-dimethylaminopropionamide(XLV) (see Table 3); the expected quaternary cyanide(XLVI) was not obtained.



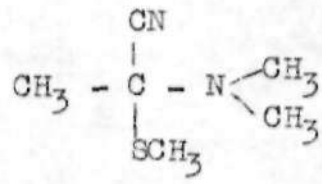
XLIII



XLIV

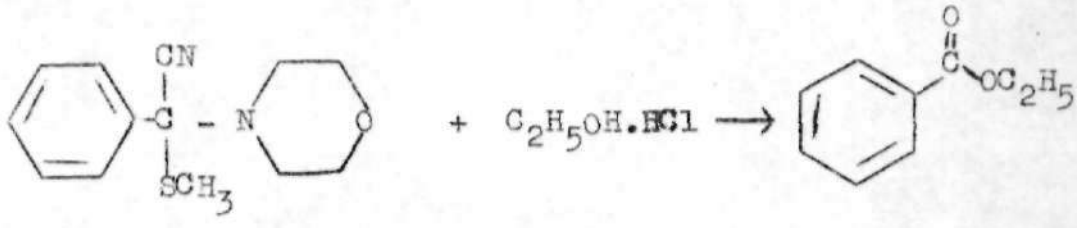


XLV



XLVI

The quaternary cyanide(XXXVI) underwent acid hydrolysis producing ethyl benzoate(XLVII).



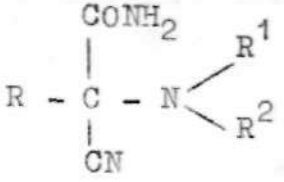
XXXVI

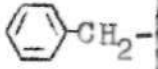
XLVII

This quaternary cyanide also showed very slight indication of base hydrolysis.

TABLE 3:

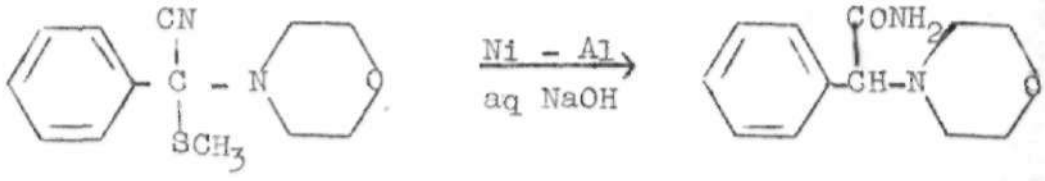
CYANOAMIDES



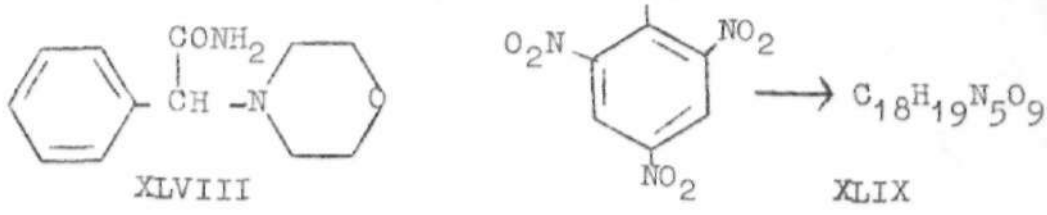
R	R^1	R^2	YIELD %	M. P.	MOLECULAR FORMULAR	ANALYSIS* C	H	N	I. R. SPEC. [NUJOL] cm^{-1}
Me			38	159-160°	$C_8H_{13}N_3O_2$	52.4 (52.5)	7.1 (7.1)	22.7 (23.0)	3400vs, 3200vs, 2920vs, 2220w, 1700s, 1600m, 1120vs, 1020s, 890s, 700s
			11	204-205°	$C_{14}H_{17}N_3O_2$	64.6 (64.9)	6.6 (6.6)	16.2 (16.3)	3400 - 3160vs, 2920vs, 2220w, 1700vs, 1600m, 1120vs, 1020m, 890m, 700m
Me	Me	Me	21	149-151°	$C_6H_{11}N_3O$	51.0 (51.1)	7.9 (7.8)	29.8 (29.8)	3380s, 3200m, 2220vw, 1680vs, 1600w, 1130m, 1100w, 980m, 845m.

* FOUND VALUES ABOVE, REQUIRED VALUES IN BRACKETS BELOW.

On treatment with nickel-aluminium alloy the quaternary cyanide(XXXVI) was degraded to α-4'-morpholinophenylacetamide(XLVIII) which gave a yellow picrate (XLIX) with saturated alcoholic picric acid solution. The elemental analytical figures for the picrate were consistent with its formula as represented by XLIX.

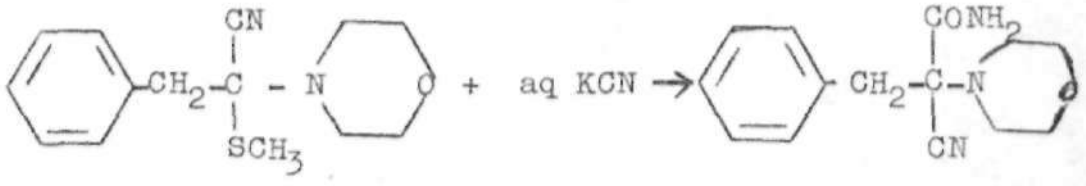


XXXVI XLVIII



XLVIII XLIX

The quaternary cyanide(XL) was caused to react with potassium cyanide solution producing the cyanoamide(XLIV) at room temperature.



XL XLIV

The attempted reaction of the cyanide(XXXVI) with benzonitrile, hydroxylamine hydrochloride, urea, O-nitrobenzaldehyde, acetonitrile, or iodomethane yielded no pure product. Boiling the quaternary cyanide(XXXVI) with toluene gave unchanged starting material, while apparently there was no reaction between the cyanide(XL) and sodium azide.

Unlike the amide(XLVIII), the cyanoamides(XLIII), (XLIV) and (XLV) formed no picrates with saturated alcoholic picric acid solution. The cyanoamide (XLIV) did not appear to give any reaction with hydroxylamine hydrochloride.

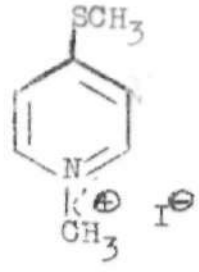
ATTEMPTED REACTIONS WITH QUATERNARY AND OTHER SALTS

All efforts to cause the quaternary salt(XVIII) to react with either potassium thiocyanate or Chloramine - T proved abortive, while the attempted

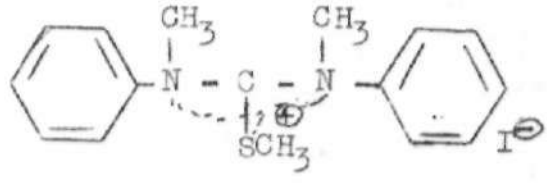
reaction of this salt with mercuric cyanide yielded a yellow compound which appeared to be a mercuric salt.

1-Methyl-4-methylthiopyridinium iodide (L), a vinylogue of previous quaternary salts, did not appear to give any reaction when treated with either hydroxylamine hydrochloride or potassium cyanide.

The isothiuronium salt, SNN'-trimethyl-NN'-diphenylthiurnium iodide (LI) could not be caused to react with potassium cyanide solution at room temperature.



L



LI

D I S C U S S I O N

THE WILLGERODT - KINDLER REACTION

The successful synthesis of thiosalicylmorpholide (XIII) in good yield from salicylaldehyde, a rather complex compound because of the presence of a hydroxyl group in its molecular constitution, is an indication that the Willgerodt - Kindler procedure is of very general scope and will indeed be applicable to a variety of compounds.

SYNTHESIS AND REACTIONS OF NN-DISUBSTITUTED AMIDOXIMES

The reaction of quaternary salts with hydroxylamine hydrochloride is of considerable utility for the preparation of NN-disubstituted amidoximes. The reaction occurs at room temperature and the amidoximes are obtained in good yields.

It is reported that some aromatic amidoximes have been made by the reaction of hydroxylamine hydrochloride on thioamides.[19-22] The liberation of hydroxylamine

from its hydrochloride is effected by aqueous sodium carbonate. The thioamide is introcuduced and ethanol is added until the mixture becomes clear. The solution is then heated under reflux for a few hours.

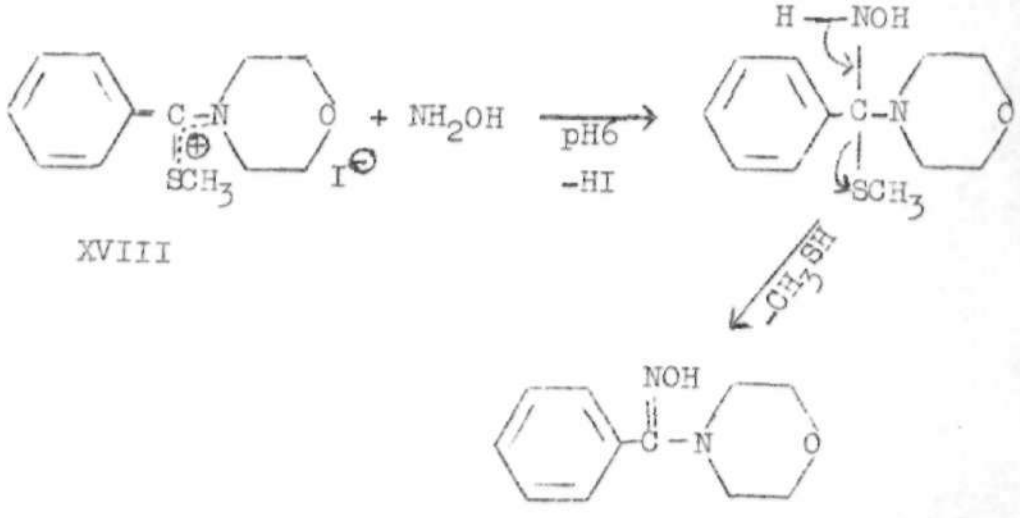
Theoretically it may seem as if the preparation of amidoximes from quaternary salts is more time - consuming than the procedure which involves the use of thioamides. This in practice is not true. The conversion of most thioamides into quaternary salts usually comes to completion in about 10 min, while the reaction of the quaternary salts with hydroxylamine hydrochloride takes place most readily at room temperature to produce the amidoximes. On the other hand, the synthesis of amidoximes from thioamides entails heating under reflux. The former method has a wider scope and its faster rate of reaction is an added advantage over the latter procedure.

No amidoxime was formed from treating thiosalicylmorpholide methiodide (XX) with hydroxylamine hydrochloride in the presence of sodium acetate; this might be due to the presence of the hydroxyl group in the quaternary salt which endows it with acidic

character, thus preventing any apparent reaction from occurring under these conditions.

The use of sodium acetate in the synthesis of amidoximes from quaternary salts was necessary to liberate hydroxylamine from its hydrochloride. The omission of sodium acetate prevented the formation of amidoximes. A mild acidic medium (pH 6) appeared to be the optimum.

The mechanism of this synthesis from quaternary salts can be illustrated with the preparation of the compound (XXXIV).



XVIII

XXXIV

Although Tiemann recognised that amidoximes may be in two tautomeric forms, the two NN-disubstituted amidoximes (XXXIV) and (XXXV) from thiobenzomorpholide methiodide (XVIII) and thiobenzodimethylamide methiodide (XXI) respectively do not exhibit tautomerism as there is no hydrogen directly attached to the nitrogen of the amino - group. The compound (XXXIV) did not undergo any change in configuration under thermal influence as the i.r. spectrum of the melt did not differ from that of the original compound.

The amidoxime (XXXIV) yielded nothing substantial with 90% formic acid even after heating the mixture under reflux for 21 h. It was thought that a Beckmann rearrangement would take place as does with some oximes under similar reaction conditions. The addition of sodium chloride to the solution formed, failed to cause the separation of any derivative.

Aniline did not appear to react with the amidoxime (XXXIV), this is not surprising as it has been reported that aniline reacts directly on only acetamidoxime and formamidoxime hydrochloride forming the corresponding N-substituted amidoxime at 80 - 90^{o} with the evolution

of ammonia.[41,42] The compound (XXXIV) has a disubstituted amino - group and this indeed explains why no reaction occurred.

The amidoximes (XXXIV) and (XXXV) gave shoulders and not peaks in the u.v. region, the former, for example, giving a shoulder at λ sh 263 nm (ε sh 2700) in ethanol (see Fig. 1).

SYNTHESIS AND REACTIONS OF QUATERNARY CYANIDES AND CYANOAMIDES

The procedure employed for the synthesis of quaternary cyanides from S-alkyl quaternary salts of NN-disubstituted thioamides is certainly a general one.

Mukaiyama and his collaborators[10] have reported the preparation of α-methylthio-α-dimethylaminobenzyl cyanide (XXXVIII) as a liquid (b. p. 93 - 94°/2mm) in 64% yield by refluxing a mixture of thiobenzodimethylamide methiodide (XXI) and potassium cyanide in dry benzene. This particular quaternary cyanide was obtained as a colourless crystalline solid (m.p.40°) at room temperature in 99% yield by merely adding thiobenzodimethylamide methiodide (XXI) to a solution of

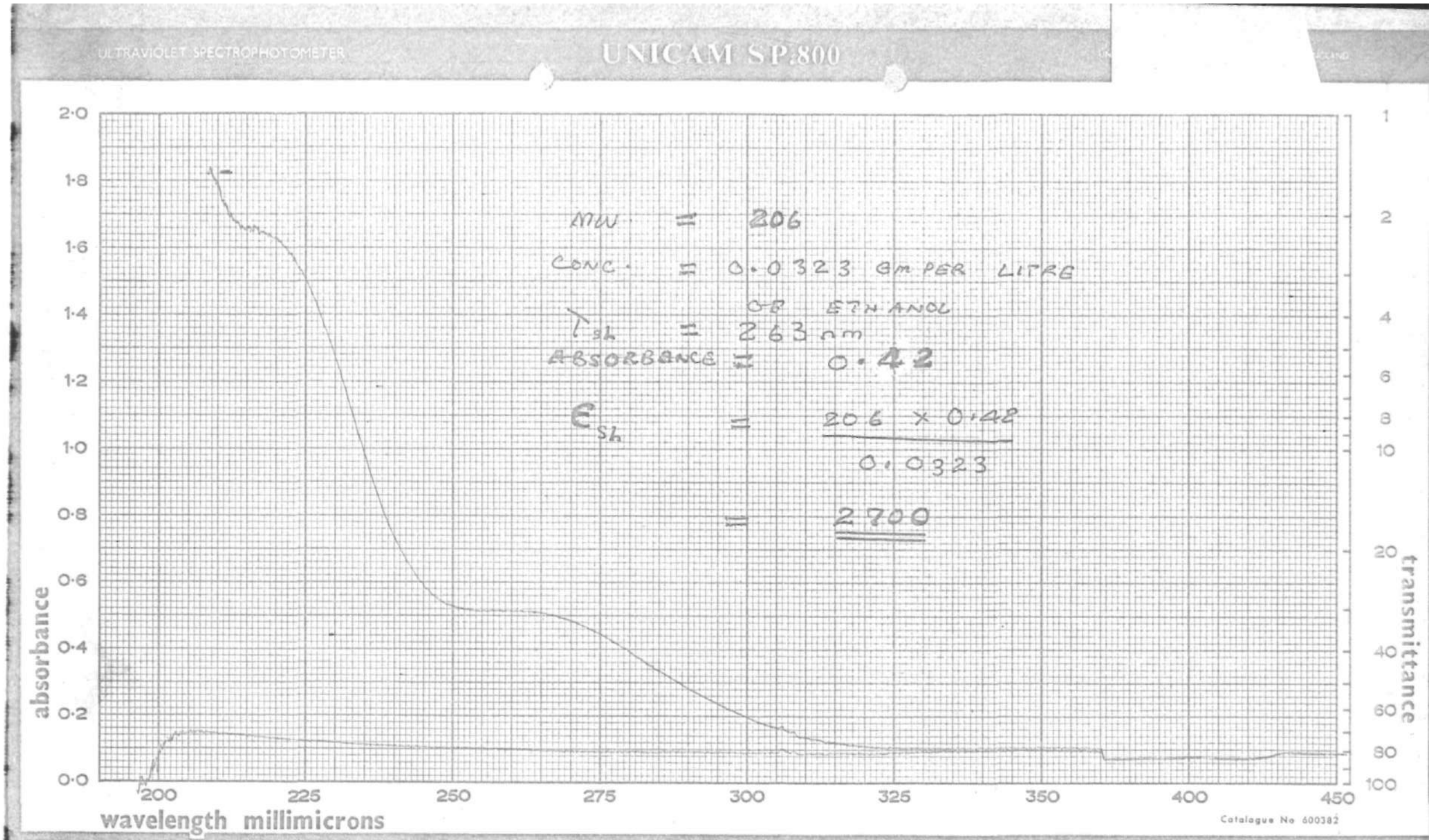
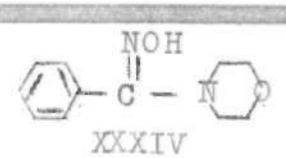

ULTRAVIOLET SPECTROPHOTOMETER
UNICAM SP.800
MW = 206
CONC. = 0·0323 GM PER LITRE
OF ETHANOL
λ sh = 263 nm
ABSORBANCE = 0·42
ε sh = 206 × 0·42 / 0·0323
= 2700
absorbance
0·0
0·2
0·4
0·6
0·8
1·0
1·2
1·4
1·6
1·8
2·0
wavelength millimicrons
200
225
250
275
300
325
350
400
450
transmittance
1
2
4
6
8
10
20
40
60
80
100
Catalogue No 600382

FIG. 1: 

XXXIV

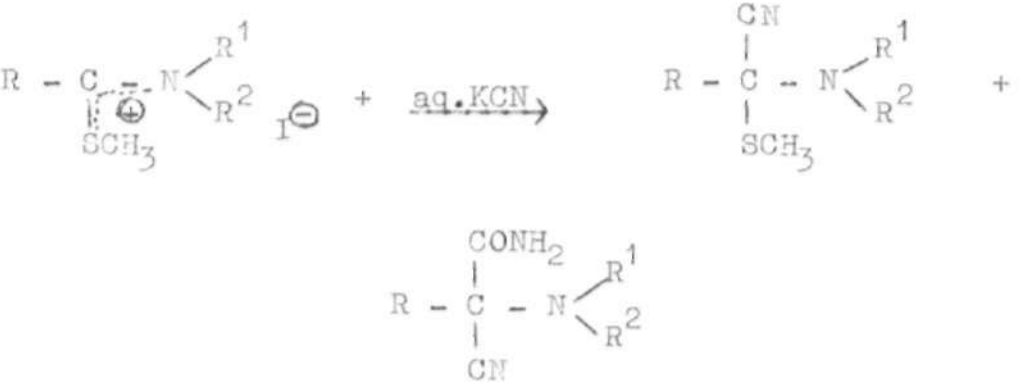
potassium cyanide in water. The relative ease with which the synthesis was carried out coupled with high yield gives this method a pride of place when compared with Mukaiyama and his co-workers' procedure.

Previous investigated reactions of S-alkyl quaternary salts of NN-disubstituted thioamides involved the elimination of either the alkythio- or the disubstituted amino - group. The synthesis of quaternary cyanides with retention of both groups is almost unique and this suggests that these compounds may have peculiar structures.

The quaternary cyanides were found to be stable compounds. The solid product obtained when thiosalicylmorpholide methiodide (XX) was treated with potassium cyanide solution decomposed readily on exposure to air. The instability could be explained on the basis of liability to oxidation conferred on the product, which appeared to possess some features of a quaternary cyanide, by the hydroxyl group present in the molecule. One striking thing common to all the solid cyanides is that they melted at low temperatures.

The liquid quaternary cyanide (XXXIX) from thioacetmorpholide methiodide (XXII) decomposed when distilled *in vacuo* at 142°/50mm. The n.m.r. spectrum of the distillate differed considerably from that of the original cyanide (XXXIX).

In the present investigation, it was observed that if the salt used had a methyl or benzyl group attached to the quaternary carbon atom, treatment with aqueous potassium cyanide at room temperature gave both the quaternary cyanide and the cyanoamide.



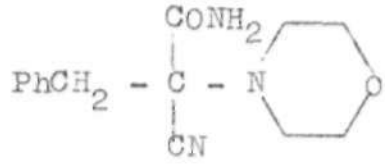
[R = Me or $PhCH_2$; $R^1 = R^2$ = alkyl or NNR^1R^2 = morpholino].

Thus, as mentioned earlier, the reaction of phenylthioacetmorpholide methiodide (XXII) with

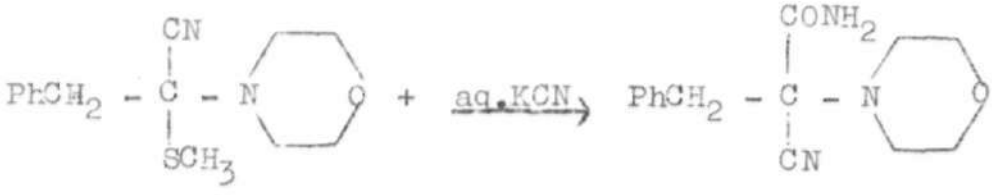
potassium cyanide solution at room temperature produced the quaternary cyanide (XL) and the cyanoamide (XLIV). Both products were probably not produced simultaneously since the treatment of the cyanide (XL) with potassium cyanide solution under similar reaction conditions yield a solid substance whose i.r. spectrum was identical with that of the cyanoamide (XLIV).



XXII XL

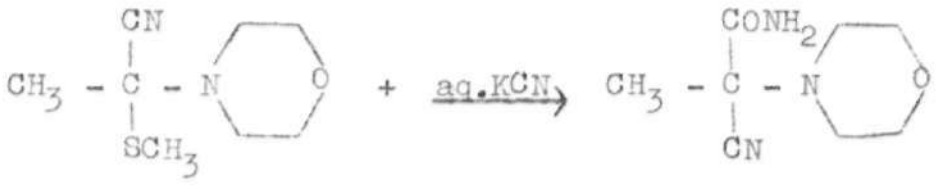


XLIV



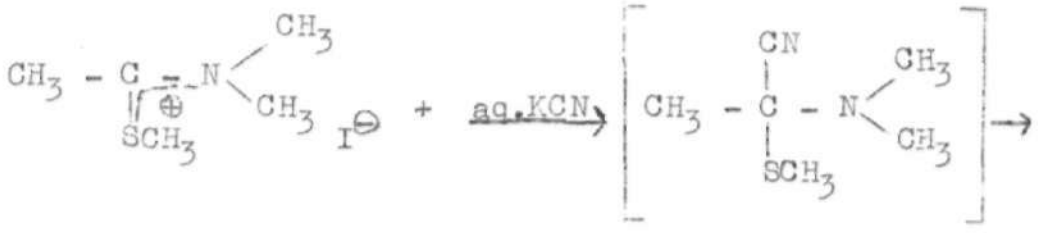
XL XLIV

Similarly the quaternary cyanide (XXXIX) from thioacetmorpholide methiodide (XXIII) was hydrolysed to the cyanoamide (XLIII).

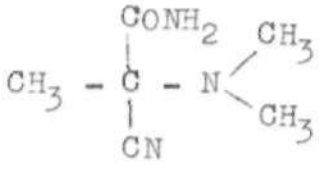


XXXIX XLIII

The reaction of thioacetdimethylamide methiodide with potassium cyanide solution yielded only the cyanoamide (XLV). This could mean that as the quaternary cyanide (XLVI) was being produced, it was all rapidly hydrolysed to the cyanoamide (XLV).



XLVI



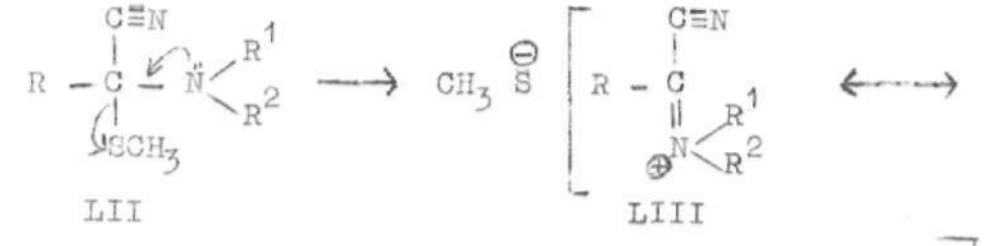
XLV

The rate of cyanohydrolysis of the cyanide (XXXIX) to the cyanoamide (XLIII) was faster than that of the cyanide (XL) to the cyanoamide (XLIV). That of the quaternary cyanide (XLVI) to the cyanoamide (XLV) was much faster than either of the two cases mentioned above; there was complete cyanohydrolysis of this compound to the cyanoamide.

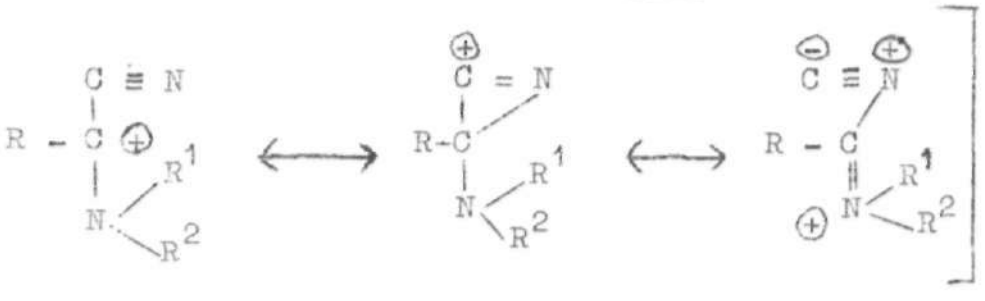
The hydrolysis of these quaternary cyanides to the cyanoamides under such mild conditions was surprising. Less steric hindrance might be among the factors responsible for this unusual hydrolysis of the quaternary cyanides. On grounds of steric hindrance compound (XLI) from thioformdimethylamide methiodide (XXIV) would be expected to undergo cyanohydrolysis most readily; this was not the case and an explanation for this could be the possibility of this compound existing predominantly in a neutral tautomeric form.

The usual hydrolysis of nitriles to amides entails more drastic conditions.[43] For example, in the hydrolysis of benzyl cyanide to an amide the solution of the nitrile in concentrated sulphuric acid is kept at 80 - 90° for 5 min, then poured into cold water.

The mechanism which accounts for the very ready cyanohydrolysis of the quaternary cyanides to cyanoamides seems very much open and in need of definitive investigation. It is not unlikely that the structure of the quaternary cyanides may facilitate the hydrolysis reaction among other factors. The quaternary cyanides (LII) could be partially ionised existing in the resonant hybrid forms (LIII), (LIV), (LV) and (LVI) shown below.



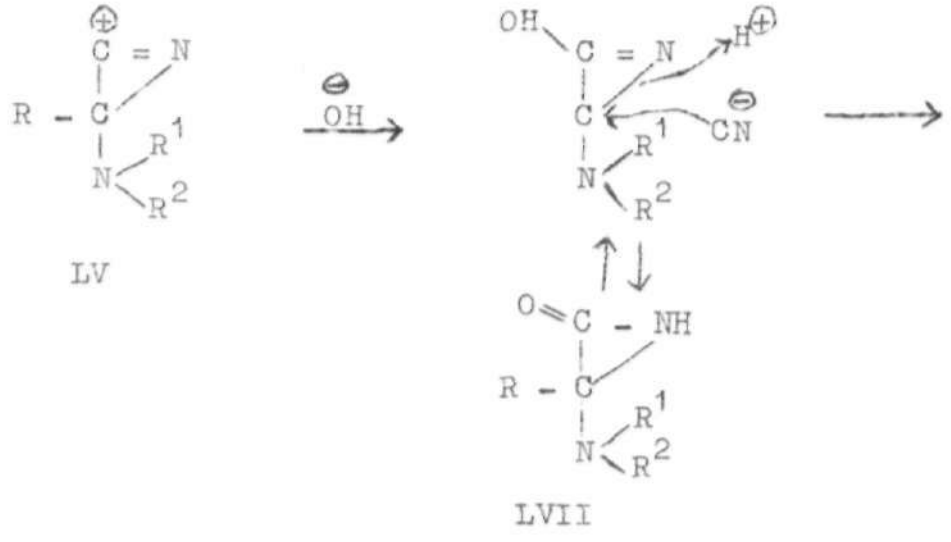
LII LIII



LIV LV LVI

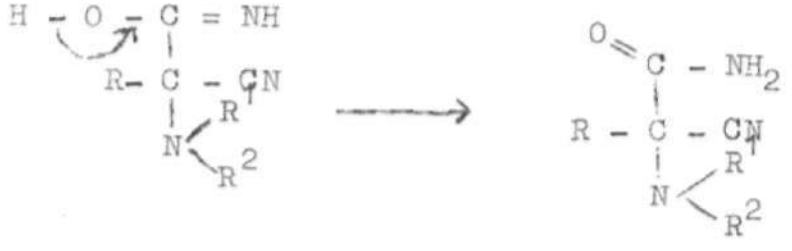
[R = H, alkyl or aryl; R' = R^2 = alkyl or NNR^1R^2 = morpholino].

The fact that the quaternary cyanides might exist in several hybrid forms explains why they are stable compounds. In the cyanides (LII; R = Me or $PhCH_2$) inductive effect enhances the chances of losing the alkylthio - group and in the resonance hybrid (LV) cyanohydrolysis to the cyanoamide can be effected with an α-lactam (LVII) being produced as an intermediate. The mechanism is postulated schematically as follows:

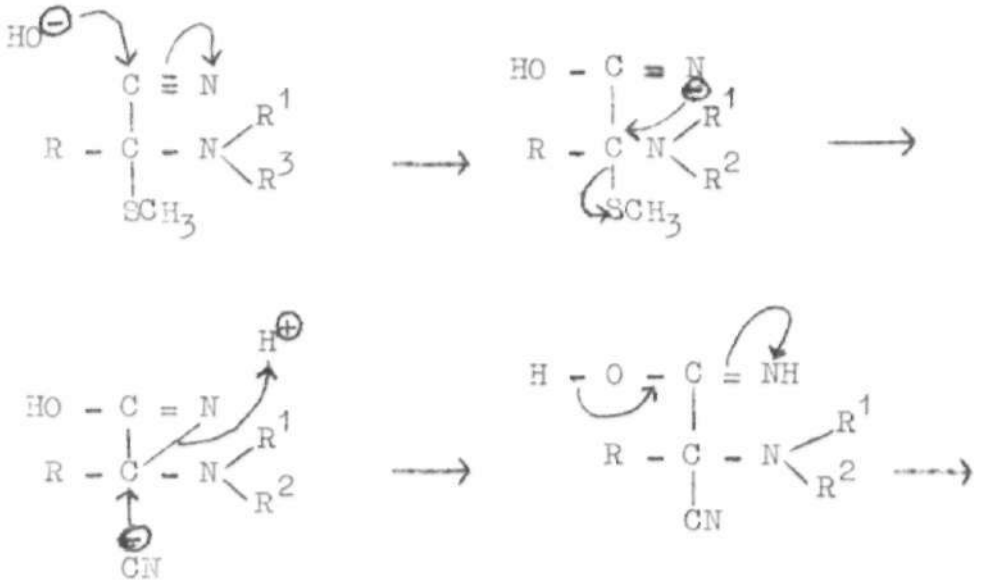


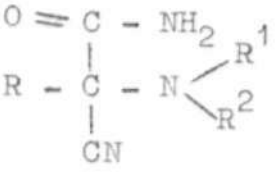
LV

LVII

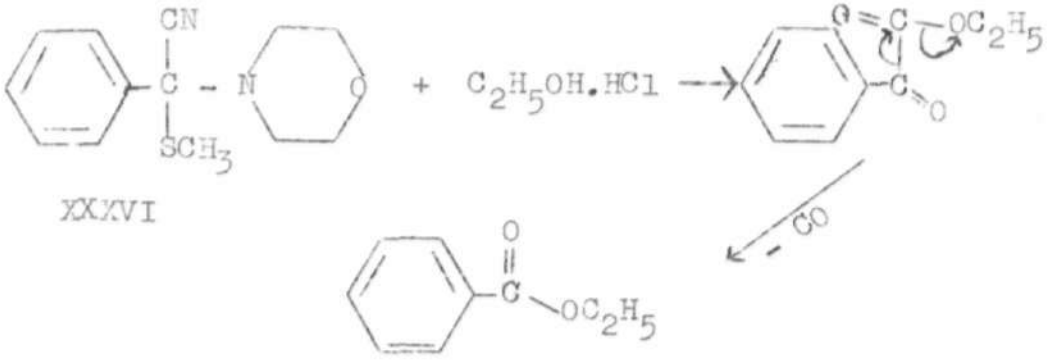


Alternatively, the mechanism of the cyanohydrolysis reaction appears explainable by steric factors and neighbouring group participation. It seems that in the process the cyanide group of the quaternary cyanide is hydrolysed to the amido-group, while the methylthio-group is lost.





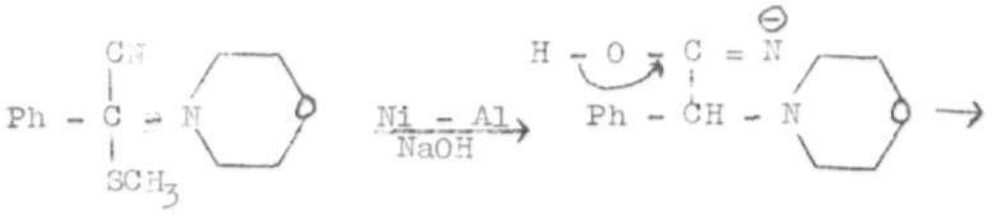
The acid hydrolysis of the quaternary cyanide (XXXVI) giving ethyl benzoate (XLVII) can only be explained on grounds of decarbonylation. The cyanide group is alcoholysed to the ethoxycarbonyl group, while both the methylthio- and the morpholino - groups are hydrolysed to the carbonyl group. With subsequent elimination of a carbon monoxide molecule from the α-keto ester formed, ethyl benzoate (XLVII) is produced.



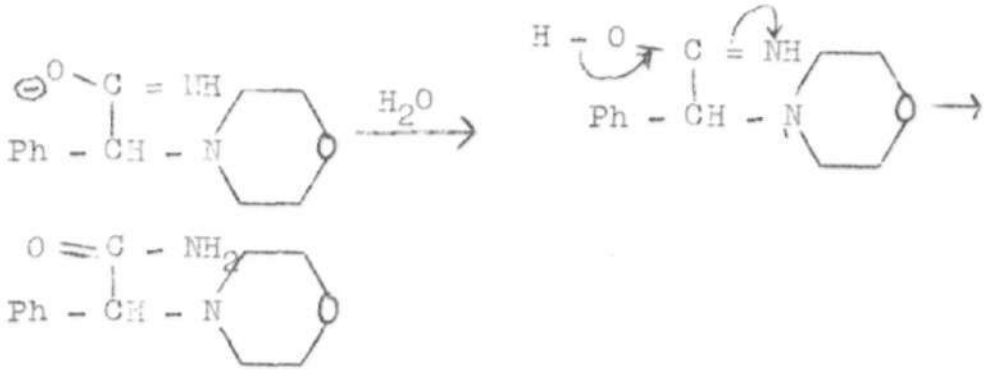
XXXVI

XLVII

With nickel - aluminium alloy in sodium hydroxide solution the quaternary cyanide (XXXVI) was degraded to the amide (XLVIII) isolated as its picrate. During the process of degradation the cyanide group is probably hydrolysed to the amido - group; the postulated mechanism for this reaction is schematically represented as shown below:

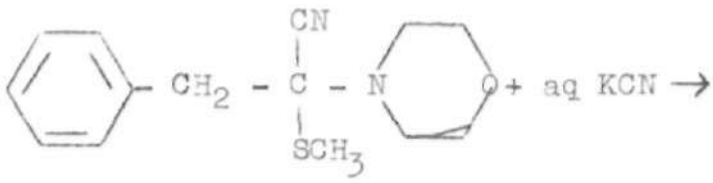


XXXVI

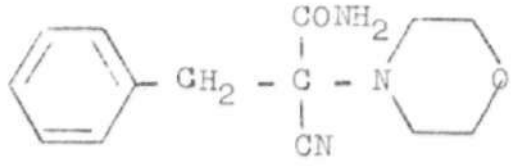


XLVIII

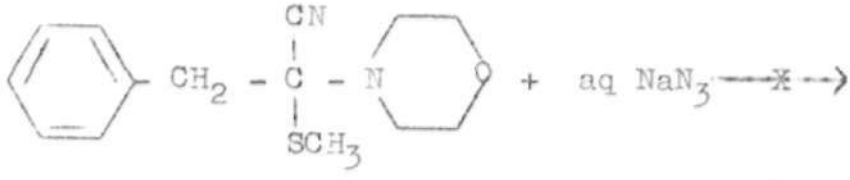
Since sodium azide solution is alkaline like potassium cyanide solution, it was thought that the former would effect the hydrolysis of the cyanide (XL) to the azidoamide (LVIII) in a manner analogous to the reaction of this quaternary cyanide with potassium cyanide solution resulting in the formation of the cyanoamide (XLIV). The expected azidoamide (LVIII) was not obtained when the compound (XL) was treated with sodium azide solution.



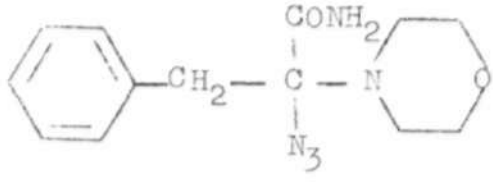
XL



XLIV



XL



LVIII

The attempted reaction of the quaternary cyanide (XXXVI) with acetonitrile yielded a compound whose i.r. spectrum was identical with that of the

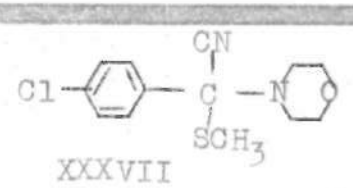
starting material; this tends to suggest that this quaternary cyanide does not exist as a 1,3-dipole since acetonitrile is known to participate in 1,3-dipolar addition reactions. It should, however, be mentioned that acetonitrile is not a good 1,3-dipolarophile and so the possibility of the cyanide (XXXVI) existing as a 1,3-dipole cannot be ruled out.

A characteric feature of the quaternary cyanides was the lack of strong i.r. absorption due to the cyanide group between 2300 and 2000 cm^{-1}. All the quaternary cyanides, for example, compound (XXXVII) from 4-chlorothiobenzomorpholide methiodide (XIX) (see Fig. 2) gave very weak absorption at 2220 cm^{-1} as Nujol mulls or liquid films.

Mukaiyama and his collaborators[10] have reported that the quaternary cyanide (XXXVIII) from thiobenzodimethylamide methiodide (XXI) which they obtained as a liquid (this compound was obtained as a solid in the course of the present investigation) gave a cyanide group absorption at 2300 cm^{-1}; they however, did not elaborate on the band intensity.


INFRARED SPECTROPHOTOMETER
UNICAM SP. 1200
UNICAM INSTRUMENTS LIMITED, CAMBRIDGE, ENGLAND
WAVELENGTH MICRONS
2·5
3
3·5
4
5
6
7
8
100
90
80
70
60
50
40
30
20
10
0
transmittance
4000
3500
3000
2500
2000
1500
1200
wavenumber
Catalogue No. 607534

FIG. 2:


Cl
CN
C
N
SCH3

XXXVII

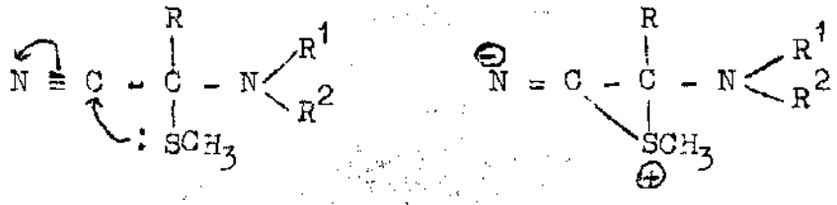
The absence of a strong absorption due to the cyanide group between 2300 and 2000 cm^{-1} was not a surprise for Kitson and Griffith[44] have found that there is a marked variation in intensity of various types of nitriles, the band varying from very strong to undetectable. Jesson and Thompson[45] have also shown that the cyanide group band intensity appears to be more susceptible than its frequency to structural influences and other factors. Bellamy,[46] however, feels that low intensities are not easy to explain in simple chemical terms, and says that the most likely explanation is probably due to interaction effects, which are too small to have much influence on the frequency but, nevertheless, produce significant changes in intensities.

The intensity due to carbon-nitrogen triple bond stretching vibration is variable; it is generally strong but is loweredby electron - withdrawing groups.[47] However, these quaternary cyanides have electron - donating groups.

The present author strongly shares the same opinion with Bellamy and suggests that an intramolecular interaction may occur in each quaternary cyanide

involving the alkylthio - and the cyanide groups; the sulphur of the alkylthio - group supplying electrons as it were to the electron - deficient carbon of the cyanide group. This situation arises as a result of the movement of electrons to the nitrogen end of the cyanide group; the nitrogen therefore bears a negative charge while the carbon of the cyanide group becomes positively charged.

Thus the quaternary cyanides (LII) may be assigned an alternative cyclic dipolar structure (LIX).



LII LIX

In the neutral form (LII) the quaternary cyanides are expected to give absorption in the i.r. region between 2300 and 2000 cm^{-1} due to carbon-nitrogen triple bond while in the cyclic dipolar form (LIX) they should give absorption that can be assigned to carbon-nitrogen double bond stretching vibration. It should be mentioned that these cyanides as represented by the cyclic

resonance hybrid (LV) may possibly give i.r. absorption due to carbon - nitrogen double bond.

In fact all the quaternary cyanides gave weak absorption at 2220 cm^{-1} due to the cyanide group and also between 1680 and 1580 cm^{-1} due to carbon-nitrogen double bond stretching vibration. The form in which each quaternary cyanide exists predominantly may be explained on the basis of the band intensity due to either carbon - nitrogen triple bond or carbon - nitrogen double bond.

Thus for the quaternary cyanide (XLI) from thioformdimethylamide methiodide (XXIV) which gave a very weak absorption at 2220 cm^{-1} and a very strong one at 1680 cm^{-1}, the equilibrium is likely to be more towards the cyclic dipolar form (LIX). In the case of the cyanide (XXXVII) from 4-chlorothiobenzomorpholide methiodide (XIX) which gave a very weak absorption at 2220 cm^{-} and also a very weak one at 1580 cm^{-1}, the equilibrium will lie between the acyclic and the cyclic dipolar forms (LII) and (LIX) respectively. From the i.r. spectra of all the quaternary cyanides it could be said that in no case does equilibrium lie

mainly to the acyclic form (LII). This suggests that the cyclic form (LIX) is likely to be predominant.

The cyanoamides (XLIII) and (XLIV) from thioacetmorpholide methiodide (XXIII) and phenylthioacetmorpholide methiodide (XXII) respectively gave weak absorption due to the cyanide group at 2220 cm^{-1}, while the cyanoamide (XLV) from thioacetdimethylamide methiodide gave a very weak absorption at the same frequency. By contrast the i.r. spectrum of cyanoacetamide showed a strong band due to the carbon - nitrogen triple bond at 2260 cm^{-1}.

The quaternary cyanides except XLI from thioformdimethylamide methiodide (XXIV) gave u.v. absorption. Those of them which absorbed in the u.v. region gave shoulders, the only exception being compound (XXXIX) from thioacetmorpholide methiodide (XXIII) which gave a peak at λ max 273nm (ϵ max 250) in ethanol (see Fig.3 and 4). The ability of the quaternary cyanides to give u.v. absorption, while acetonitrile did not, suggests that the former possess structures which favour u.v. absorption, or more importantly that they are dipolar compounds. The fact that these compounds gave u.v.

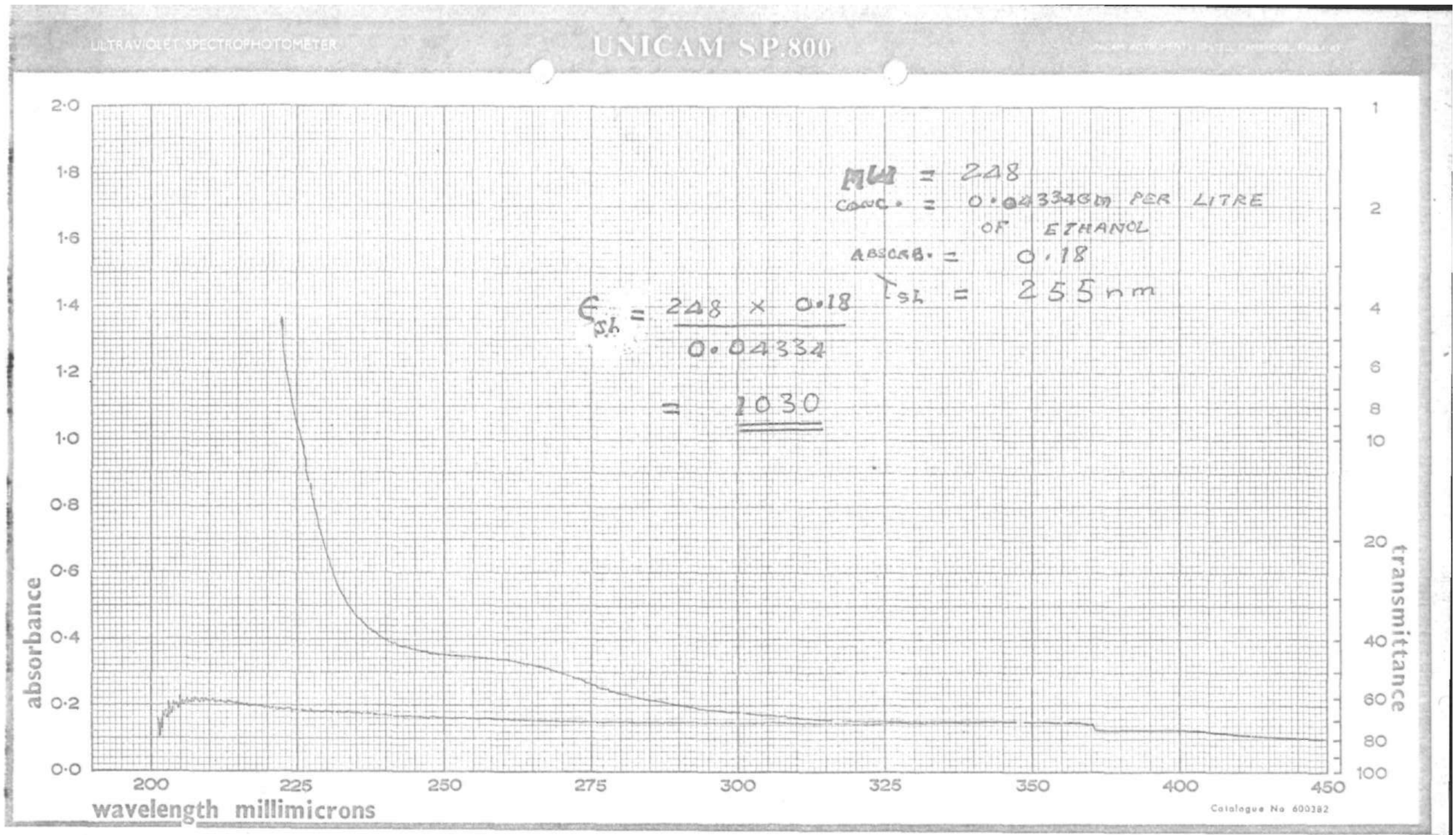
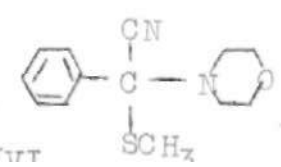
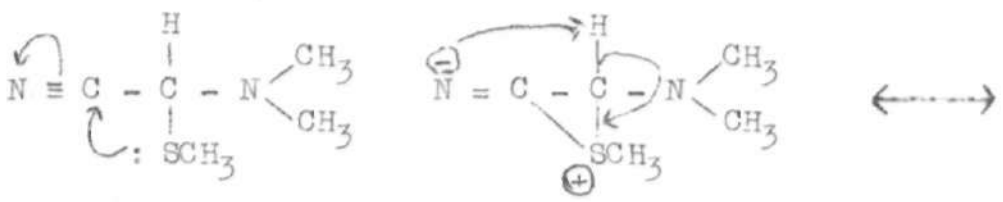

ULTRAVIOLET SPECTROPHOTOMETER
UNICAM SP.800
MW = 248
CONC. = 0.02334GM PER LITRE OF ETHANOL
ABSORB. = 0.18
λ max = 255nm
$\epsilon_{sh} = \frac{248 \times 0.18}{0.02334}$
= 1030
absorbance
0·0
0·2
0·4
0·6
0·8
1·0
1·2
1·4
1·6
1·8
2·0
200
225
250
275
300
325
350
400
450
wavelength millimicrons
transmittance
1
2
4
6
8
10
20
40
60
80
100
Catalogue No 600382

FIG. 3:

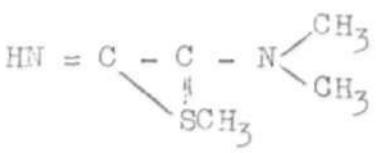


absorption helps indeed to strengthen the case for their existence as cyclic dipolar compounds (LIX).

The quaternary cyanide (XLI) from thioformdimethylamide methiodide (XXIV) did not give u.v. absorption in ethanol; only end absorption was shown. This cyanide like the others might be expected to exist in the cyclic dipolar form. In fact from its i.r. absorption it was earlier postulated that it would exist predominantly in this form. However, the hydrogen which is attached directly to the quaternary carbon atom may migrate as a proton to the negatively charged nitrogen giving rise to a tautomeric form (LX) with tetravalent sulphur and which is not dipolar. This cyclic neutral form may be predominant in this case instead of the cyclic dipolar one, and this would explain why this particular quaternary cyanide did not give u.v. absorption.



XLI



LX

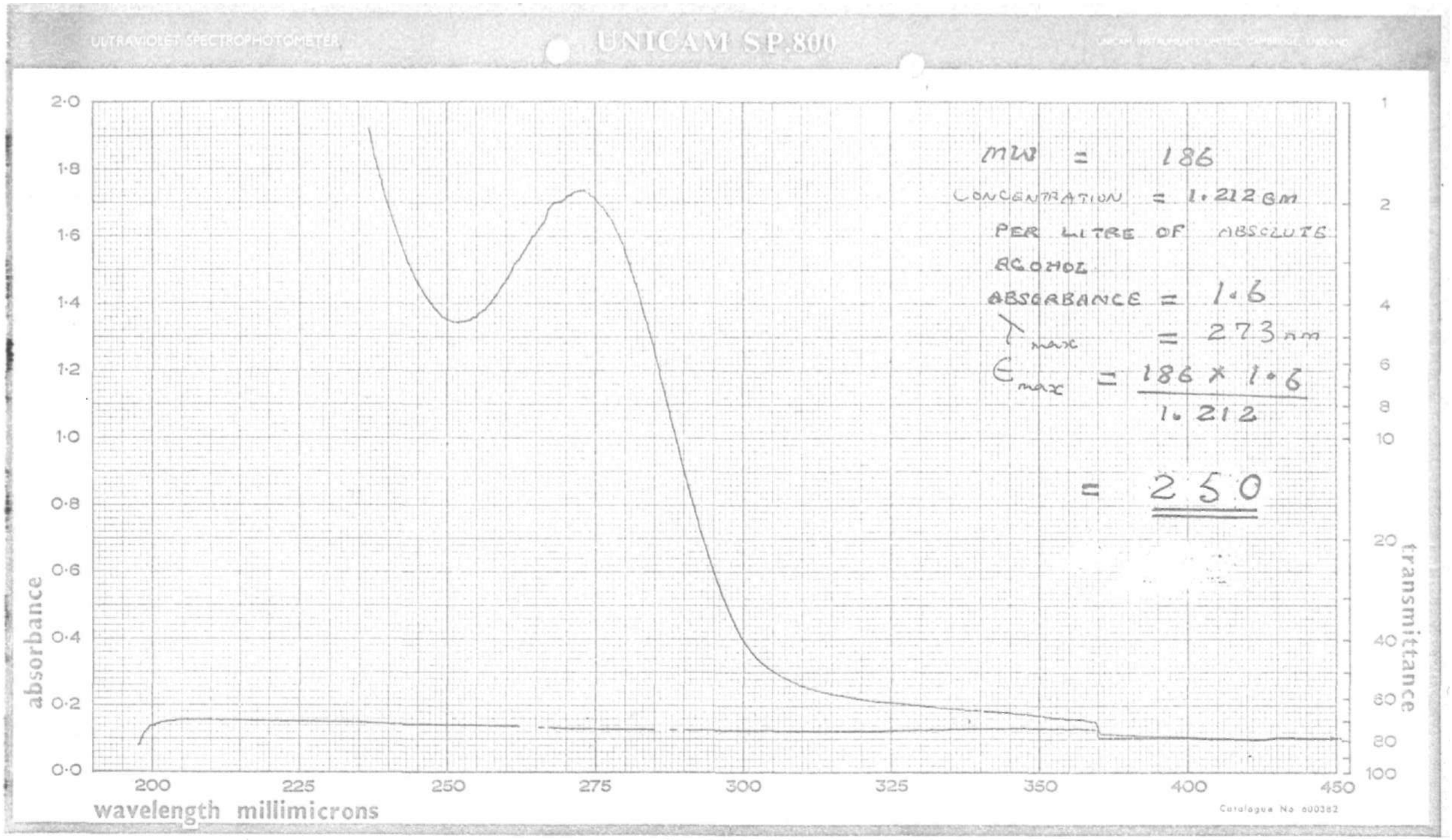
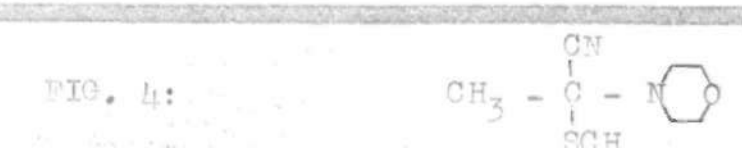

ULTRAVIOLET SPECTROPHOTOMETER
UNICAM SP.800
MW = 186
CONCENTRATION = 1.212 GM PER LITRE OF ABSOLUTE ALCOHOL
ABSORBANCE = 1.6
λ max = 273 nm
ε max = 186 × 1.6 / 1.212
= 250
absorbance
transmittance
wavelength millimicrons
Catalogue No 600362

FIG. 4:



Much as the several resonance hybrids of the quaternary cyanides discussed earlier, can account for the u.v. absorption since they are dipolar species, they, however, do not appear to give the explanation for the lack of u.v. absorption of compound (XLI) from thioformdimethylamide methiodide (XXIV).

Benzene has u.v. absorption at λ max 255 nm; the quaternary cyanides (XXXVI), (XXXVII) and (XXXVIII) from thiobenzomorpholide methiodide (XVIII), 4-chlorothiobenzomorpholide methiodide (XIX) and thiobenzodimethylamide methiodide (XXI) respectively also absorbed at λ sh 255 nm in ethanol. That the u.v. absorption by these compounds was not due to benzene was established by their molar extinction coefficients ranging from 1000 - 2100 while that due to benzene in cyclohexane is only 230. The cyanides (XXXIX) from thioacetmorpholide methiodide (XXIII), and (XL) from phenylthioacetmorpholide methiodide (XXII) gave u.v. absorption at λ max 273 nm (ε max 250) and λ sh 280nm (ε sh 1600) respectively. The u.v. absorption of each quaternary cyanide may be assigned to an n → Π* transition, this being the least energetic transition.

Like cyanoacetamide, the cyanoamides made from quaternary salts did not give any u.v. absorption. Probably no intramolecular interaction does occur in them; this means that they do not exist as dipolar compounds, which explains the lack of u.v. absorption.

The n.m.r. spectra of the quaternary cyanides provides interesting features, particularly with regard to the morpholino-substituent. For those cases in which the quaternary carbon atom has an aromatic substituent as in compounds (XXXVI), (XXXVII) and (XLII) from thiobenzomorpholide methiodide (XVIII), 4-chlorothiobenzomorpholide methiodide (XIX) and p-dimethylamino-4-α-isopropythiobenzylidenemorpholinium iodide respectively, the methylene protons next to nitrogen show a complex pattern of ten symmetrical peaks centred at δ2.6 (see Fig. 5). For alkyl-substituted quaternary cyanides (XXXIX) from thioacetmorpholide methiodide (XXIII) and (XL) from phenylthioacetmorpholide methiodide (XXII), these protons show a simpler pattern similar to the methylenes next to the oxygen atom (see Fig. 6).

Spin decoupling experiments in the former case showed that the spectra could be simplified to more

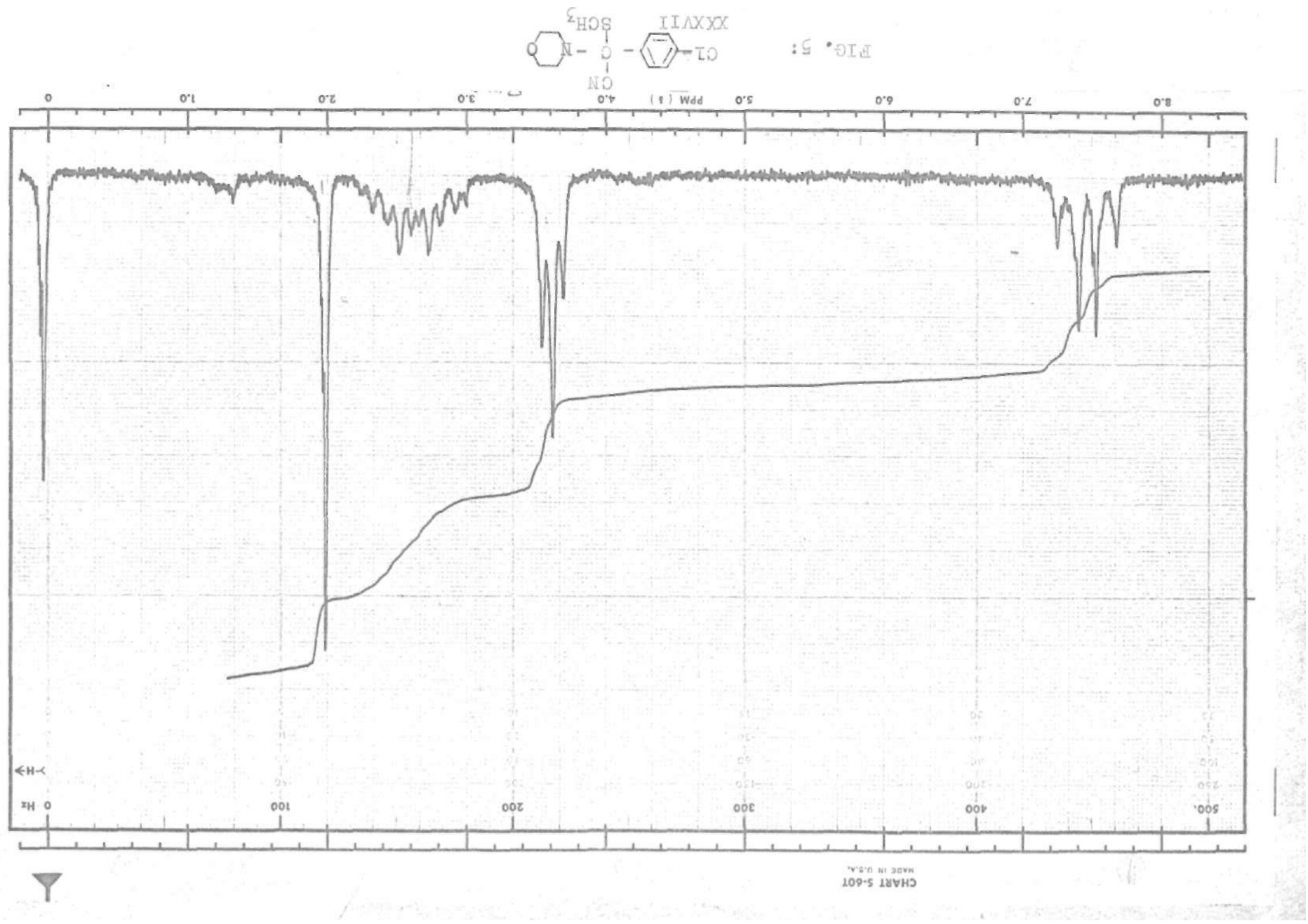
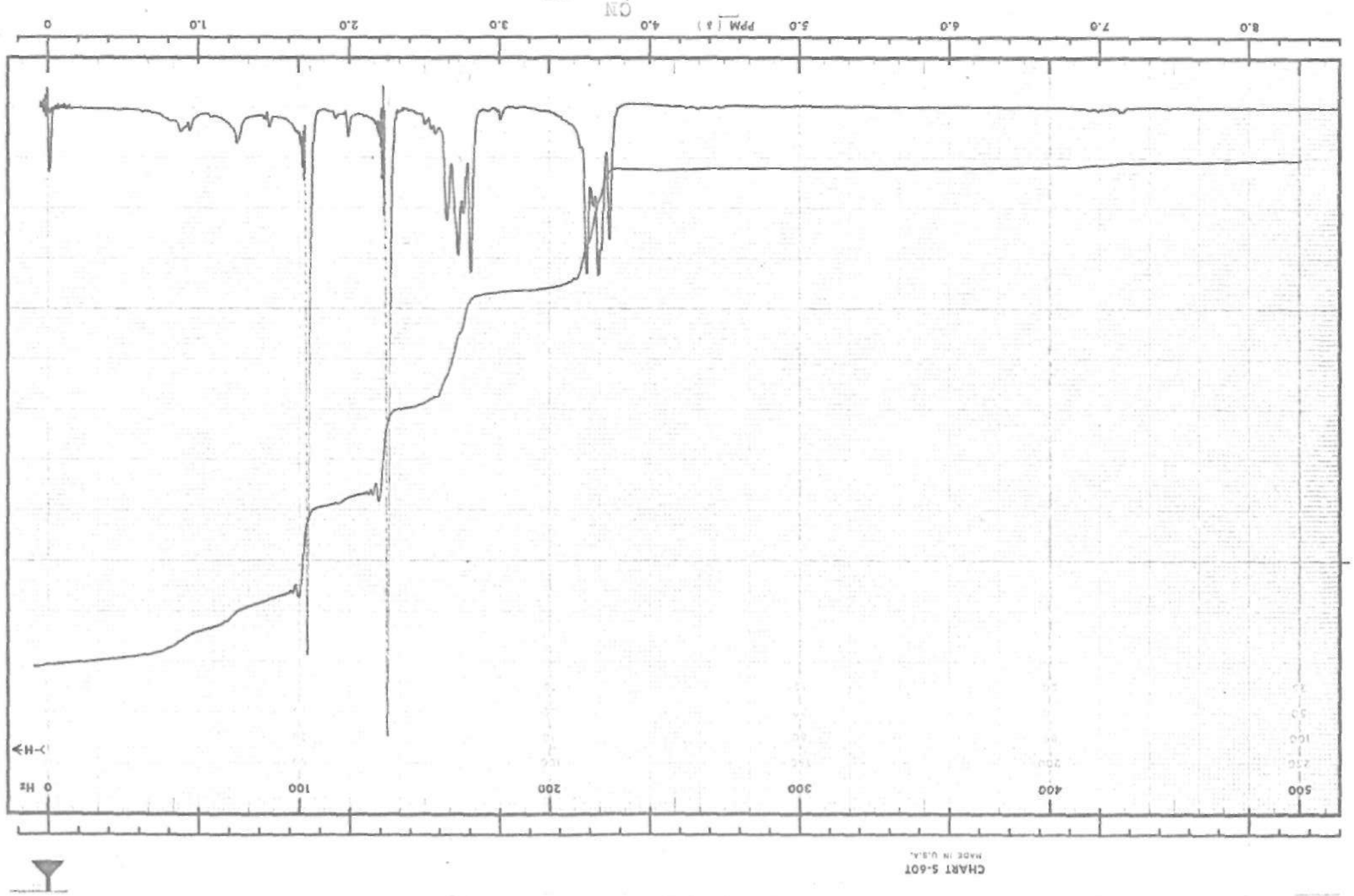

CHART 5-60T
MADE IN U.S.A.
0 Hz
100
200
300
400
500
PPM (δ)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
CN
SCH3
Cl
XXXVII

FIG. 5:

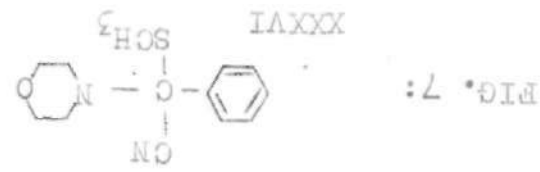
MIG. 6: $CH_3-\underset{\underset{CN}{|}}{C}-N$(ring)$-\underset{\underset{SCH_3}{|}}{C}$ XXXIX



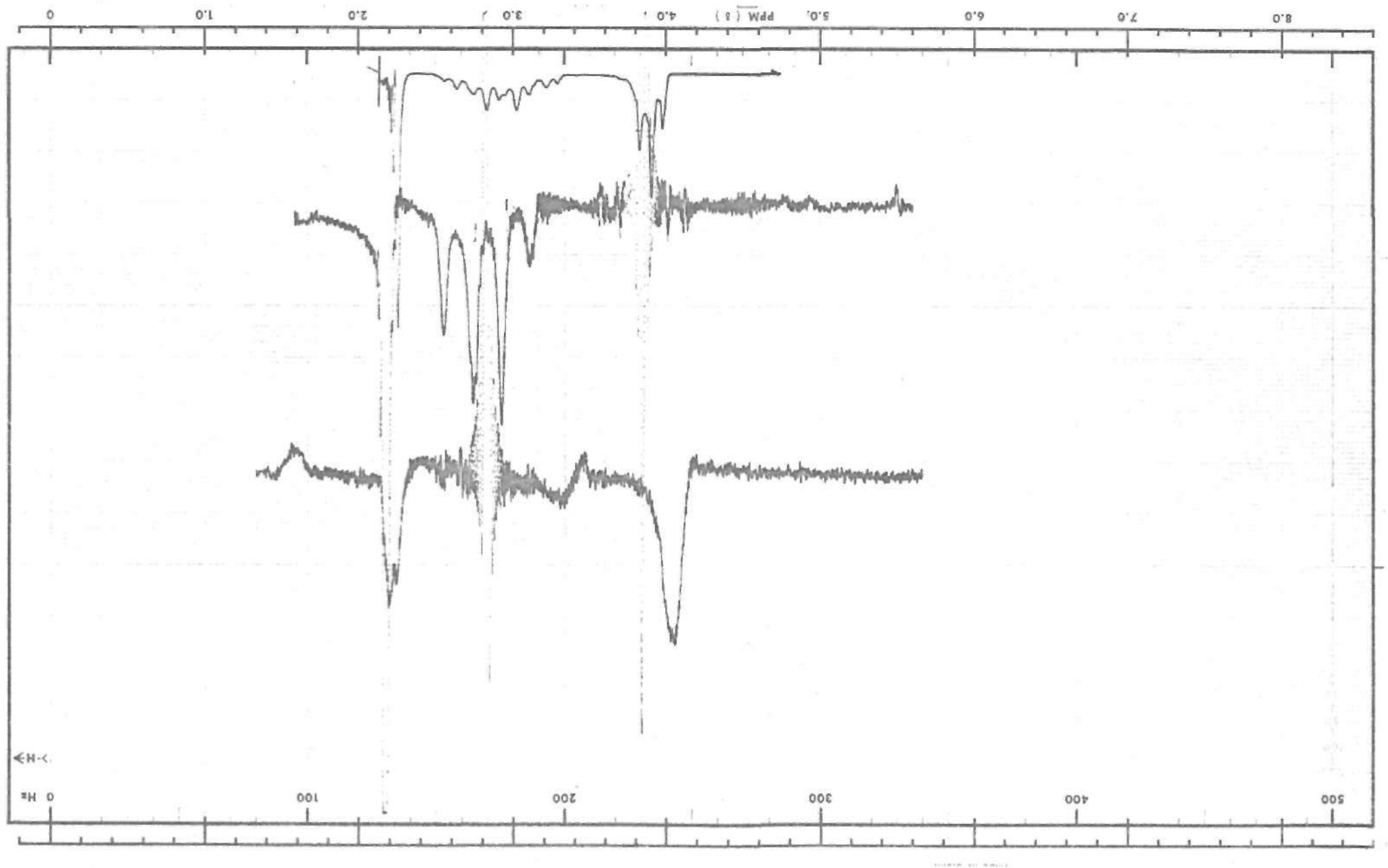
easily understandable patterns (see Fig.7). Irradiation of the δ2.6 multiplet caused the δ3.6 triplet to collapse to a singlet, suggesting that all four protons adjacent to the oxygen atom had the same chemical shift. The collapsed signal was slightly displaced from the position of the triplet. This could be explained by the Bloch - Siegert effect,[48] which depends on the separation of the resonances (the larger the separation of resonances the smaller the effect) and on the square of the power used. The effect is normally small, for example, about $0.1H_z$ for a line decoupling a coupling constant of $5H_z$, $100H_z$ away, but the Bloch-Siegert effect increases with use of increased decoupling power.

On the other hand, irradiation of the δ3.6 signal simplified the δ2.6 signal to an AB quartet (J $11H_z$). The coupling constant in this case is of the order of magnitude expected for geminal coupling, and this result suggests that the two protons of each methylene next to the nitrogen atom are non-equivalent. These results raise two major questions. First, why do the methylene groups adjacent to nitrogen behave differently from those next to oxygen in the case of aryl-substituted cyanides? Secondaly, why do alkyl substituents on the

FIG. 7:



XXXVI

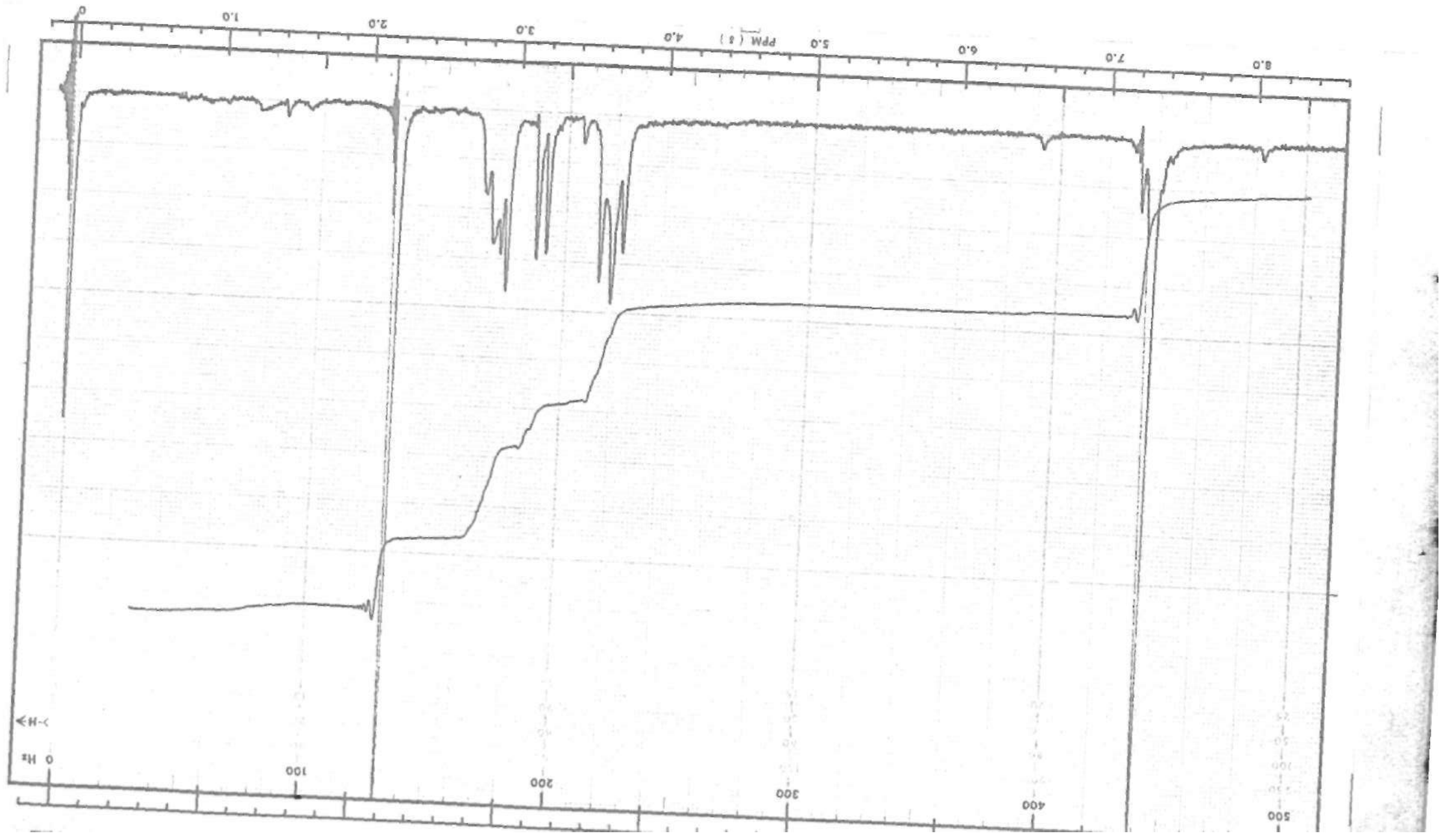


A fundamental factor which is at work in these compounds might be the ring current which, taken together with conformational rigidity would cause the Hm protons to have different chemical shift from the Hn protons. In the compund (XL) from phenylthioacetmorpholide methiodide (XXII), although a phenyl group is present, it is farther removed from these protons, and is freer to rotate than the phenyl substituent in the cyanide (XXXVI) from thiobenzomorpholide methiodide (XVIII), and this difference might be sufficient to cause the observed effect, since the influence of ring currents depends on direction and distance.

In support of this, it is interesting to note that the patterns due to the protons Hm and Hn are slightly more complicated in the compound (XL) from phenylthioacetmorpholide methiodide (XXII) than the equivalent protons in the quaternary cyanide (XXXIX) from thioacetmorpholide methiodide (XXIII) (see Fig. 6 and 10). A test of this hypothesis could be carried out by preparing the compound (XXXVI) with different substituents such as CH_3O, NO_2 and so on at the para position of the aromatic ring. These para

XL

FIG. 10:



substituents, while not causing major steric changes, should sufficiently affect the size of the ring current to effect noticeable degree of complication of methylene signals next to nitrogen.

The mass spectrum of the S-alkyl quaternary cyanide (XXXVI) from thiobenzomorpholide methiodide (XVIII) showed no parent peak; the peak at M/E 201.1083 ($M-CH_3S$) was significant (see Table 4). The case with which the alkylthio - group is lost offers the necessary explanation for the absence of a parent peak; it is this ready loss of the group that gives rise to the earlier postulated several dipolar resonance hybrids of this class of novel compounds.

TABLE 4: MASS SPECTRAL DATA FOR α-METHYLTHIO-α-4'-MORPHOLINOBENZYL CYANIDE (XXXVI)

M/M	ABUNDANCE	FRAGMENT LOST		M/E	ABUNDANCE	FRAGMENT LOST
41.0397	1.29	$C_{10}H_{11}N_2OS$		104.0501	6.54	$C_6H_{10}NOS$
42.0343	2.60	$C_{11}H_{12}NOS$		105.0723	2.82	$C_8H_3N_2O$
44.0266	2.60	$C_{11}H_{12}N_2S$		114.0371	1.51	C_8H_8NO
45.0343	2.39	$C_{11}H_{11}N_2S$		115.0427	2.60	C_8H_7NO
50.0158	2.39	$C_9H_{14}N_2OS$		116.0493	4.35	$C_5H_{10}NOS$
51.0224	3.48	$C_9H_{13}N_2OS$		117.0579	3.26	C_8H_5NO
54.0329	1.73	$C_{10}H_{12}NOS$		121.0118	3.70	$C_6H_{11}N_2O$
56.0498	5.89	$C_{10}H_{10}NOS$		130.0653	18.32	C_4H_8NOS
63.0226	1.73	$C_8H_{13}N_2OS$		133.0091	2.60	$C_2H_{15}N_2OS$
77.0376	3.70	$C_7H_{11}N_2OS$		142.0536	3.92	$C_4H_{10}OS$
79.0550	1.29	$C_7H_9N_2OS$		147.0133	1.07	$C_5H_{11}NO$
84.0458	1.29	$C_9H_{10}NS$		157.0763	1.07	C_3H_7OS
86.0604	1.29	C_9H_8NS		162.0370	6.76	C_4H_8NO
89.0380	4.79	$C_6H_{11}N_2OS$		170.0967	1.29	CH_4NOS
91.0552	6.98	$C_6H_9N_2OS$		194.0976	2.60	C_2NO
103.0432	3.26	C_9H_7NO		201.1033	100	CH_3S
103.0560	1.29	$C_8H_5N_2O$				

TABLE 4: MASS SPECTRAL DATA FOR α-METHYLTHIO-α-4'-MORPHOLINOBENZYL CYANIDE (XXXVI)

M/M	ABUNDANCE	FRAGMENT LOST		M/E	ABUNDANCE	FRAGMENT LOST
41.0397	1.29	$C_{10}H_{11}N_2OS$		104.0501	6.54	$C_6H_{10}NOS$
42.0343	2.60	$C_{11}H_{12}NOS$		105.0723	2.82	$C_8H_3N_2O$
44.0266	2.60	$C_{11}H_{12}N_2S$		114.0371	1.51	C_8H_8NO
45.0343	2.39	$C_{11}H_{11}N_2S$		115.0427	2.60	C_8H_7NO
50.0158	2.39	$C_9H_{14}N_2OS$		116.0493	4.35	$C_5H_{10}NOS$
51.0224	3.48	$C_9H_{13}N_2OS$		117.0579	3.26	C_8H_5NO
54.0329	1.73	$C_{10}H_{12}NOS$		121.0118	3.70	$C_6H_{11}N_2O$
56.0498	5.89	$C_{10}H_{10}NOS$		130.0653	18.32	C_4H_8NOS
63.0226	1.73	$C_8H_{13}N_2OS$		133.0091	2.60	$C_2H_{15}N_2OS$
77.0376	3.70	$C_7H_{11}N_2OS$		142.0536	3.92	$C_4H_{10}OS$
79.0550	1.29	$C_7H_9N_2OS$		147.0133	1.07	$C_5H_{11}NO$
84.0458	1.29	$C_9H_{10}NS$		157.0763	1.07	C_3H_7OS
86.0604	1.29	C_9H_8NS		162.0370	6.76	C_4H_8NO
89.0380	4.79	$C_6H_{11}N_2OS$		170.0967	1.29	CH_4NOS
91.0552	6.98	$C_6H_9N_2OS$		194.0976	2.60	C_2NO
103.0432	3.26	C_9H_7NO		201.1033	100	CH_3S
103.0560	1.29	$C_8H_5N_2O$				

E X P E R I M E N T A L

Elemental microanalysis and molecular weight determination by the Rast method were performed by the Scandinavian Microanalytical Laboratories, Denmark. Melting points were determined with a Gallenkamp melting point apparatus and the Kofler hot stage microscope and are uncorrected. The nuclear magnetic resonance spectra were obtained with a Varian T-60 instrument using solution containing TMS as an internal standard. Infrared measurements were made with a Unicam SP.1200 Grating Spectrophotometer. The ultraviolet spectra were obtained with a Unicam SP.800B instrument. The mass spectrum was done by I. C. I. Pharmaceutical Division, Cheshire, England, while refractive index measurements were made with Abbe '60' refractometer.

Acetone (AR) was dried with toluene-p-sulphonyl chloride and redistilled. All other chemicals were of high quality.

Thiobenzomorpholide (XI):- Morpholine (52.0g; 1.5 mol) and benzaldehyde (42.5g; 1.0 mol) were added at the same time to sulphur (19.2g; 1.5 atoms). An exothermic reaction occurred with separation of two layers. The mixture was heated under reflux for 3 h on a steam bath. During the reaction a dark brown oil resulted which sometimes solidified. The dark brown liquid was poured into boiling ethanol (95%; 800 ml). The solution was filtered from a little sulphur, and allowed to cool in a refrigerator. The beautiful yellow needles of thiobenzomorpholide were filtered off next day and dried in vacuo (72.1g; 87%); m.p.135 - 136°(lit.[8] 135 - 136°); ν max (Nujol) 2920 vs (C-H stretch), 1110 vs ($-CH_2OCH_2-$ of morpholino- group), 870s, 760vs, 700s cm^{-1}.

In the same way the following NN-disubstituted thoanides were made; the starting materials, reaction times and yields being given parenthetically in order:

4-Chlorothiobenzomorpholide (XII):- (4-Chlorobenzaldehyde; 10 h; 72%); yellow crystals, from ethanol; m.p.133-134°.

Phenylthioacetmorpholide (XV):- (Acetophenone; 17 h; 82%); light yellow crystals, from ethanol; m.p.76-77°.

Thiosalicylmorpholide (XIII):- (Salicylaldehyde; 3 h, 79%); dark yellow crystals; from ethanol and dried at 80°/17mm for 1½ h; m.p.165-167°; ν max (Nujol) 3140m (free OH), 2920vs (C-H stretch), 1600m (C=C stretch), 1110vs ($-CH_2OCH_2-$ of morpholino-group), 1030vs, 760vs cm^{-1}; δ($CDCl_3$) 7.1 (m, 5H, C_6H_4OH), 4.0(m, 8H, morpholino-group); δ($CDCl_3$ + D_2O) 4.67 (s, 1H, DOH) [Found: C, 59.0; H, 6.0; N, 6.1 $C_{11}H_{13}NO_2S$ requires C, 59.2; H, 5.8; N, 6.4%].

Thiobenzodimethylamide (XIV):- Benzaldehyde (21.2g; 0.2 mol) was added all at once to a 25 - 30% w/v solution of dimethyalmine in water (108 ml; 0.6 mol). On shaking with an electric shaker some heat was produced and the mixture became warm; and it was cooled in ice. After shaking overnight in a closed flask, the mixture was poured into a separatory funnel and the upper layer of the aminal was separated and dried (Na_2SO_4) (31.10g). Its n.m.r. spectrum (neat liquid) agreed with the aminal structure: δ7.20 (s, 5H, aromatic), 3.38 (s, 1H, methine group), 2.10 (s, 12H, four methyl groups). The aminal which remained on the sodium sulphate was recovered by washing the sodium

sulphate with dimethylformamide (10 ml). Precipitated sulphur (9.6g; 0.3. atom) and p-toluenesulphonic acid (0.4g) were added to the aminal in a 250 ml flask. No reaction occurred in the cold, but on heating on a steam bath under reflux the mixture rapidly became dark brown and a gas with ammoniacal odour (Me_2NH) was rapidly evolved. The gas evolution was complete in 5 min and some frothing occurred. After heating for 30 min under reflux on a steam bath, the mixture was cooled in ice and water (140 ml) was added, thus precipitating an oil. On ice-cooling, shaking and seeding, the oil solidified as yellow granules, which were filtered off, washed and dried (42.04g). The product was recrystallised from boiling light petroleum (80-100°; 750 ml). On cooling and seeding, the oil which first separated solidified. The yellow crystals of thiobenzodimethylamide were crushed, filtered off and dried in vacuo (24.33g; 84.4%); m.p.35-36°.

Thioacetmorpholide (XVI):- Acetmorpholide (20g; 0.155 mol) in carbon disulphide (100 ml) was added in portions to phosphorus pentasulphide (34.43g; 0.33 mol) and the mixture was gently shaken and occasionally

cooled in ice. After all the acetmorpholide in carbon disulphide had been added, the mixture was stirred magnetically for 3h and then boiled under reflux on a steam bath for 3h. The mixture was cooled in ice; warm water (300 ml) was added to decompose the phosphorus compounds and the mixture was set aside overnight. There was effervescence which persisted for a long time. The product was extracted four times with chloroform (total 600 ml) and the chloroform layer was dried (Na_2SO_4). The solvent was evaporated *in vacuo* leaving an oil which solidified on cooling. The crude thioacetmorpholide was dried *in vacuo* (22.46g; 99.9%) and recrystallised from absolute alcohol (99/100%) (charcoal) giving colourless rods (12.68g): m.p.89-90° (lit.[8] 89°); ν max (Nujol) 2920vs (C-H stretch), 1120vs ($-CH_2OCH_2-$ of morpholino-group), 1000vs, 870s, 830m, 600vs cm^{-1}.

Thioformdimethylamide (XVII):- Dry dimethylformamide (14.6g; 0.2 mol) dissolved in carbon disulphide (30 ml) was added down the reflux condenser to a suspension of phosphorus pentasulphide (44.4g; 0.2 mol) in carbon disulphide (80 ml) in a 250 ml round bottomed flask provided with double surface reflux condenser.

Much heat was produced and the solution was boiled under reflux for 2h; the solid cake of phosphorus compounds being broken with a glass rod. The mixture was cooled and water (100 ml) was added cautiously in small portions. After shaking and standing for 4h the product was filtered with suction through Celite Hyflosupercel to remove suspended solid, the material on the funnel being washed several times with chloroform. The filtrate and washings were transferred to a separatory funnel and extracted three times with chloroform (total 120 ml). The combined extracts were washed twice with water (total 100 ml), dried (Na_2SO_4) and the solvent was evaporated *in vacuo* (residue 20.08g). Distilling the oil *in vacuo* gave the thioformdimethylamide, an alsmot colourless liquid (10.4g; 58.4%); b.p.120/17mm. No other fraction was obtained.

Thiobenzomorpholide methiodide (XVIII):- Thiobenzomorpholide (XI) (20.7g; 0.1 mol) was placed in a 25 ml round bottomed flask with dry acetone (50 ml); iodomethane (42.6g; 19.5 ml; 0.3 mol) was added, and the mixture was boiled under reflux on a steam bath for 10 min. The quaternary salt soon crystallised out;

after 10 min boiling most of the acetone and iodomethane were removed by evaporation. Diethyl ether (100 ml) was added to the remaining solid, which was then filtered off. The yellow quaternary salt was washed with more ether and quickly dried in vacuo (31.0g; 89%); m.p.155-156° (decomp.) [lit.[8] 158° (decomp.)]; ν max (Nujol) 2920vs (C-H stretch), 1580m (C=C stretch), 1110vs ($-CH_2OCH_2-$ of morpholino-group), 770vs 710m cm^{-1}.

Using the same procedure the following S-alkyl quaternary salts were prepared; the starting materials, reaction times and yields being given parenthetically in order:

Thioacetmorpholide methiodide (XXIII):- (Thioacetmorpholide; 30 min; 97.6%); yellow crystals; m.p.120-122°.

4-Chlorothiobenzomorpholide methiodide (XIX):- (4-Chlorothiobenzomorpholide; 10 min; 70%); pale yellow crystals; m.p.140-141°.

Thiobenzodimethylamide methiodide (XXI):- (Thiobenzodimethylamide; 3h; 95.2%); yellow crystals; m.p.135-136° (decomp.).

Phenylthioacetmorpholide methiodide (XXII):- (Phenylthioacetmorpholide; 10 min; 74.3%); colourless leaflets which turned light yellow on drying; m.p.152-153°.

Thiosalicylmorpholide methiodide (XX):- (Thiosalicylmorpholide; 10 min; 93%; yellow crystals, from dry acetone twice and dried at 80°/30mm for 2h; m.p.150-151° (decomp.); ν max (Nujol) 3140m (free OH), 2920vs (C-H stretch), 1600 (C=C stretch), 1110vs ($-CH_2OCH_2-$ of morpholino-group), 770vs cm^{-1}.

Thioformdimethylamide methiodide (XXIV):- (Thioformdimethylamide) (XVII) (5.94g; 0.066 mol) was treated with a solution of iodomethane (28.4g; 0.2 mol) in dry acetone (20 ml). The mixture became hot and the product separated, first as an oil which suddenly solidified (bumping). The mixture was heated on a steam bath for 10 min, cooled and ether (60 ml) was added. The colourless solid was filtered off, washed quickly several times with ether and dried *in vacuo* (15.28g; 99.8%); m.p.119-120°.

Acetmorpholide:- Acetic anhydride (75.6g; 70 ml; 0.74 mol) was added to morpholine (210.0g; 2.4 mol) and the mixture was gently shaken. A highly exothermic reaction occurred and the mixture was cooled in ice overnight. Diethyl ether (500 ml) was added to the colourless morpholinium acetate formed and warmed gently on a steam bath. The salt was filtered off, washed with more ether (100 ml) and dried *in vacuo* (112.2g). Light petroleum (40-60°; 700 ml) was added to the filtrate and the oil which resulted was collected using a separatory funnel. Benzene (50 ml) was added to the oil and later the solvent was evaporated *in vacuo*. The oil was distilled *in vacuo* and acetmorpholide was obtained as a colourless oil (61.58g; 64.4%): b.p.160-162°/17mm; ν max (liquid film) 2920vs (C-H stretch), 1640s (carbonyl group), 1120vs ($-CH_2OCH_2-$ of morpholino - group), 1000vs, 850s cm^{-1}.

α-4'Morpholinobenzaldoxime (XXXIV):- A mixture of sodium acetate (80.0g; 1.025 mol) and hydroxylamine hydrochloride (2.0g; 0.0285 mol) was dissolved in water (150 ml). Thiobenzomorpholide methiodide (XVIII) (4.0g; 0.0114 mol) was added to the clear solution; the

quaternary salt dissolved while traces of sulphur were removed by decanting the solution. The solution on gentle shaking immediately produced some colourless precipitate which was cooled in ice, then filtered off and dried *in vacuo* (1.76g). The crude amidoxime (XXXIV) was recrystallised from ethanol (95%) and light petroleum (80-100°) and dried at 80/17mm for 1h; δ(CCl_4 + TMS) 8.17 (s, 1H, OH), 7.33 (s, 5H, phenyl group), 3.5 (t, 4H, two methylene groups adjacent to oxygen of morpholino-group) (J5Hz), 2.9 (t, 4H, two methylene groups adjacent to nitrogen of morpholino - group) (J5Hz).

In the same way the following NN-disubstituted monoamidoxime was made:

α-Dimethylaminobenzaldoxime (XXXV):- Colourless crystals, from ethanol (95%) and light petroleum (80-100°) and dried at 80/17mm for 1h; δ(CCl_4 + TMS) 8.33 (s, H, OH), 7.33 (s, 5H, phenyl group), 2.63 (s, 6H, two methyl groups).

Attempted reaction of thiosalicylmorpholide methiodide (XX) with hydroxylamine hydrochloride:- A mixture of sodium acetate (80.0g; 1.025 mol) and hydroxylamine

hydrochloride (2.0g; 0.0285 mol) was dissolved in water (150 ml). Thiosalicylmorpholide methiodide (XX) (4.16g; 0.0114 mol) was added to the clear solution; the quaternary salt dissolved while traces of sulphur were removed by decanting the solution. The solution was shaken gently and cooled in ice overnight, but no derivative separated. Saturated solution of picric acid was added to the solution dropwise but there was still no precipitate.

Attempted reaction of α-4'-morpholinobenzaldoxime (XXXIV) with aniline:- Aniline (1.0 ml) was added to the amidoxime (XXXIV) (0.4g; 0.0019 mol) and the mixture was refluxed under air condenser for 1h. The dark liquid formed was cooled in a refrigerator for 48h, but nothing separated. A small amount of the dark liquid was rubbed with light petroleum (80-100°), but again no derivative separated.

Attempted reaction of α-4'-morpholinobenzaldoxime (XXXIV) with Fehling's solution:- Small amount of the amidoxime (XXXIV) was added to a mixture of equal volumes of Fehling's solutions A and B; the mixture was boiled on a stean bath for about 30 min, but the

deep blue solution remained unchanged.

Attempted reaction of α-4'-morpholinobenzaldoxime (XXXIV) with formic acid:- Formic acid (90%; 10 ml) was added to the amidoxime (XXXIV) (0.12g; 0.00058 mol) and the mixture was boiled under reflux for 21h. The solution was cooled in a refrigerator for 12h, but no derivative separated. Some sodium chloride was added to the solution but again there was no precipitate.

α-Methylthio-α-4'-morpholinobenzyl cyanide (XXXVI):- Thiobenzomorpholide methiodide (XVIII) (3.0g; 0.0086 mol) was added to a solution of potassium cyanide (9.0g; 0.1385 mol) in water (75 ml). The solution quickly turned turbid and an oily mass resulted which later solidified. The mixture was left at room temperature for 3h and then cooled overnight in a refrigerator. The colourless quaternary cyanide (XXXVI) was filtered off, washed with water and dried in vacuo; then recrystallised from ethanol (95%) and light petroleum (80-100°) and dried at 56°/17mm for 45 min; δ(CCl_4 + TMS) 7.5 (m, 5H, phenyl group), 3.6 (t, 4H, two methylene groups adjacent to oxygen of morpholino-group) J3Hz), 2.6 (m, 4H, two methylene groups

adjacent to nitrogen of morpholino-group), 1.97 (s, 3H, methylthio-group); M.W.137.

The following quaternary cyanides were prepared in the same way:

p-Chloro-α-methylthio-α-4-morpholinobenzyl cyanide (XXXVII):- Yellow crystals, from absolute alcohol (99/100%) and light petroleum (80-100°) and dried in vacuo at room temperature for 3h; δ(CCl_4 + TMS) 7.5 (2d, 5H, phenyl group), 3.6 (t, 4H, two methylene groups, adjacent to oxygen of morpholino-group) (J3Hz), 2.6 (m, 4H, two methylene groups adjacent to nitrogen of morpholino-group), 1.97 (s, 3H, methylthio-group).

α-Methylthio-α-dimethylaminobenzyl cyanide (XXXVIII):- Colourless crystals, from light petroleum (80-100°) (charcoal), ethanol (95%) and again light petroleum (80-100°) and dried in vacuo overnight at room temperature; δ(CCl_4 + TMS) 7.5 (m, 5H, phenyl group), 2.37 (s, 6H, two methyl groups), 1.97 (s, 3H, methylthio-group).

p-Dimethylamino-α-4'-morpholino-α-isopropylthiobenzyl cyanide (XLII):- p-Dimethylamino-4-α-isopropylthiobenzylidenemorpholinium iodide (1.45g; 0.0035 mol) was stirred at room temperature with a solution of potassium cyanid (3.6g; 0.0554 mol) in water (20 ml) for 1½h. A pale yellow viscous oil was gradually formed.

The oil was extracted with diethyl ether (130 ml) and the extract was washed three times with water, dried (Na_2SO_4) and the solvent evaporated leaving a pale yellow oil.

Light petroleum (80-100°; 5 ml) was added and on boiling the oil dissolved. The yellow solution was treated with charcoal and with aluminium oxide and filtered twice. On cooling in a refrigerator a yellow oil separated which on rubbing and standing in a refrigerator formed yellow-white heavy crystals of the quaternary cyanide (XLII). The product was filtered off, washed twice with light petroleum (40-60°), and dried *in vacuo* at room temperature; δ(CCl_4 + TMS) 7.5 (d, 2H, aromatic, O - to Me_2N) (J8Hz), 6.6 (d, 2H, aromatic, m - to Me_2N) (J8Hz), 3.6 (t, 4H, CH_2OCH_2)

(J4Hz), 2.99 (s, 6H, Me_2N), 2.7 (m, 5H, CH_2-N-CH_2 together with >CH-), 1.3 (d, 3H, one of the CH_3-C groups) (J6Hz), 1.0 (d, 3H, the other CH_3-C group) (J6Hz).

1-Methylthio-1-dimethylaminomethyl cyanide (XLI):- Thioformdimethylamide methiodide (XXIV) (3.15g; 0.014 mol) was added to a solution of potassium cyanide (13.5g; 0.208 mol) in water (115 ml). The solution was shaken and cooled in a refrigerator for 2h. The oil formed was extracted four times with chloroform (AR; total 400 ml); the combined extracts were washed twice with water (total 200 ml) and dried (Na_2SO_4). The solvent was evaporated in vacuo (residue 3.09g); distilling the oil in vacuo gave the quaternary cyanide (XLI), an almost colourless liquid (0.82); $\delta(CCl_4$ + TMS) 4.70 (s, 1H, >C-H), 2.40 (s, 6H, two methyl groups), 2.27 (s, 3H, methylthio - group); n_D^{25} 1.4768.

Preparation of 2-cyano-2,4'-morpholino-3-phenylpropionamide (XLIV) and 1-methylthio-1-(4'-morpholino)-2-phenylethyl cyanide (XL):- Phenylthioacetmorpholide methiodide (12.48g; 0.0344 mol) was added to a solution of potassium

cyanide (36.0g; 0.5538 mol) in water (300 ml) and the mixture was stirred magnetically for 70h. The oil which resulted was cooled in ice for 5h, but it did not solidify. The oil was extracted four times with dichloromethane (total 1½ l); the combined extracts were washed twice with water (total 600 ml) and dried (Na_2SO_4). The solvent was evaporated *in vacuo*; light petroleum (80-100°; 120 ml) was added to the sticky oily substance which remained and the mixture was boiled on a steam bath to remove the stickiness. The brownish crude product which was insoluble in light petroleum (80-100°) was filtered off and dried *in vacuo* (1.01g). This was recrystallised twice from ethanol (95%) and the colourless crystals of the *cyanoamide* (XLIV) obtained were dried at 80°/17mm for 1½h.

The filtrate obtained after filtering off the crude cyanoamide, was evaporated *in vacuo* leaving an oil which solidified when placed in the deep freeze for 3 days. The light brown crude product was filtered off and dried *in vacuo* (6.23g); then recrystallised from light petroleum (80-100°) (charcoal) and the colourless *quaternary cyanide* (XL) was filtered off

and dried in vacuo at room temperature/17mm for 24h; $\delta(CCl_4)$ 7.33 (s, 5H, phenyl group), 3.7 (t, 4H, two methylene groups adjacent to oxygen of morpholino-group) (J3Hz), (2H from $-CH_2$ an AB quartet in which only three peaks were seen centred at δ3.2, the fourth peak being hidden under the complex multiplet centred at δ2.9 for 4H of the two methylene groups adjacent to nitrogen of morpholino-group) (J of the AB quartet 14Hz).

In the same way the following cyanoamide and quaternary cyanide were made after stirring magnetically the mixture of thioacetmorpholide methiodide (XXIII) and potassium cyanide solution for 19h and cooling in a refrigerator for 10h:

2-Cyano-2,4'-morpholinopropionamide (XLIII):- Colourless crystals, from benzene (charcoal) and dried at 80°/20mm for 1h; $\delta(CDCl_3$ + TMS) 7.27 (s, 1H, $CHCl_3$), 6.50 (s, 2H, NH_2), 3.8 (t, 4H, two methylene groups adjacent to oxygen of morpholino-group) (J4Hz), 2.7 (m, 4H, two methylene groups adjacent to nitrogen of morpholino-group), 1.70 (s, 3H, methylthio - group).

1-Methylthio-1-(4-morpholino)ethyl cyanide (XXXIX):- Brownish yellow oil; δ($CDCl_3$ + TMS) 3.7 (triplet with fine splittings, 4H, two methylene groups adjacent to oxygen of morpholino - group) (J3Hz), 2.7 (triplet with fine splittings, 4H, two methylene groups adjacent to nitrogen of morpholino - group) (J3Hz), 2.27 (s, 3H, methylthio - group), 1.70 (s, 3H, methyl group).

2-Cyano-2-dimethylaminopropionamide (XLV):- Thioacetdimethylamide methiodide (5.88g; 0.024 mol) was added to a solution of potassium cyanide (24.0g; 0.37 mol) in water (200 ml); the mixture was stirred magnetically for 3h, and then cooled overnight in a refrigerator. The product was extracted four times with chloroform (AR; total 500 ml); the combined extracts were washed twice with water (total 250 ml) and dried (Na_2SO_4). The solvent was evaporated *in vacuo*; the oily mass which resulted was rubbed with light petroleum (80-100°; 60 ml) and boiled on a steam bath to remove the stickiness. The brownish crude product was filtered off, washed with cold light petroleum (80-100°) and dried *in vacuo* (0.6g); then recrystallised from absolute alcohol (99/100%) and almost colourless

crystals of the cyanoamide (XLV) were obtained and dried at 80°/70mm for 1½h; δ($CDCl_3$ + TMS) 7.27 (s, 1H, $CHCl_3$), 6.50 (bs, 2H, NH_2), 2.40 (s, 6H, dimethylamino-group), 1.67 (s, 3H, methyl group).

Acid hydrolysis of α-methylthio-α-4'-morpholinobenzyl cyanide XXXVI:- The quaternary cyanide (XXXVI) (0.5g; 0.002 mol), ethanol (95%; 3 ml) and concentrated hydrochloric acid (0.3 ml) were mixed together and boiled under reflux for 2h on a steam bath. Immediately there was a strong smell of mercaptan; lead acetate paper was turned yellow by the mercaptan when placed just above the condenser (the lead acetate paper lost the yellow colour when removed from the source of mercaptan). When all the mercaptan had evolved the reflux condenser was removed and the mixture boiled to evaporate the ethanol. After cooling in ice, water (15 ml) was added to the mixture, and the oil which resulted was extracted three times with diethyl ether (total 45 ml). The combined extracts were washed with water (10 ml) and dried (Na_2SO_4). The solvent was distilled off leaving a colourless oil with a fruity smell (0.3019g; 99.9%). The i.r. spectrum of the oil was identical with that of ethyl benzoate (XLVII).

Reaction of α-methylthio-α-4'-morpholinobenzyl cyanide (XXXVI) with nickel - aluminium alloy:-

Sodium hydroxide solution (2N; 900 ml) was added to a solution of the quaternary cyanide (XXXVI) (3.0g; 0.0121 mol) in absolute alcohol (99/100%; 150 ml). Nickel aluminium alloy (50:50; 12.0g) was added in portions while the mixture was being stirred magnetically at the reaction temperature of 30 - 35° for 18h. The reaction was exothermic, effervescence and frothing being observed. The mixture was filtered through Celite Hyflosupercel; the nickel-aluminium alloy was washed with absolute alcohol (99/100°; 300 ml) and the filtrate was extracted four times with dichloromethane (total 1 l). The combined extracts were washed with water (300 ml) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* leaving some oil. The oil was cooled in ice, seeded, and light petroleum (40 - 60°) was added and the product was triturated. The brown crude product was filtered off, dried *in vacuo* (1.17g; 44%), then recrystallised twice from carbon tetrachloride (AR) and the colourless crystals of the amide (XLVIII) were filtered off and dried at 80°/18mm for 2h; m.p.156 - 157°; ν max (Nujol) 3400m (NH free), 3160m

(NH bonded), 2920vs, (C-H stretch), 1680s (carbonyl group), 1600w (NH deformation), 1120vs ($-CH_2OCH_2-$ of morpholino - group), 1010m, 880s, 710s, 640vs cm^{-1}; $\delta(CDCl_3)$ 7.53 (s, 5H, phenyl group), 7.03 (bs, 1H, a proton from amido-group), 6.70 (bs, 1H, the other proton from amido-group), 3.9 (m, 5H, a proton attached to the asymmetric carbon plus two methylene groups adjacent to oxygen of morpholino - group), 2.6 (t, 4H, two methylene groups adjacent to nitrogen of morpholino-group) (J3Hz).

Reaction of α-4'-morpholinophenylacetamide (XLVIII) with picric acid:- Absolute alcohol (99/100%; 0.8 ml) was added to the amide (XLVIII) (0.1074g; 0.0005 mol) to dissolve it with slight warming. Saturated alcoholic picric acid solution (15 ml) was added and the mixture was set aside at room temperature for 26h and stratched occasionally. The yellow picrate (XLIX) was filtered off, and dried in vacuo (0.16g; 73%). The crude picrate was recrystallised from absolute alcohol (99/100%), filtered off and dried at 80°/20mm for 1h; m.p.246 - 248°; ν max (Nujol) 2920vs, 1700m, 1620s, 1080m, 710m cm^{-1} [Found: C, 47.7; H, 4.4; N, 15.3.

$C_{18}H_{19}N_5O_9$ requires C, 48.1; H, 4.2; N, 15.6%].

Hydrolysis of 1-methylthio-1-(4'-morpholino)-2-phenyl-ethyl cyanide (XL) with potassium cyanide:- A solution of potassium cyanide (4.0g; 0.0615 mol) in water (30 ml) was added to a solution of the quaternary cyanide (XL) (1.0g; 0.0038 mol) in dioxan (AR; 1 ml). The solution soon became turbid and an oil resulted. The mixture was stirred magnetically for 9 days. The oil was extracted four times with dichloromethane (total 800 ml) and the combined extracts were washed twice with water (total 450 ml) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and some brownish solid substance crystallised out; this was cooled in ice. Light petroleum (80-100°; 100 ml) was added to the product and the mixture was heated to boiling on a steam bath. The crude product was filtered off, washed with cold light petroleum (80-100°) and dried *in vacuo* (0.3g; 30.4%); then recrystallised from absolute alcohol (99/100%) filtered off and dried *in vacuo*; m.p.204 - 205°. The i.r. spectrum of the colourless product was identical with that of the cyanoamide (XLIV).

The filtrate obtained after filtering off the solid product, was evaporated *in vacuo* and the oil which remained was cooled in the deep freeze for 5 days. The solid product was filtered off and dried *in vacuo*; its i.r. spectrum was identical with that of the quaternary cyanide (XL).

Attempted reaction of α-methylthio-α-4'-morpholino-benzyl cyanide (XXXVI) with toluene:- Toluene (25 ml) was added to the quaternary cyanide (XXXVI) (0.5g; 0.002 mol) and the mixture was heated under reflux on a steam bath for 2½h. The solvent was evaporated *in vacuo* and on cooling the liquid (0.523g) which remained crystals began to form. The mixture was rubbed with light petroleum (40 - 60°; 2 ml) and cooled in ice. The crystals were filtered off and dried *in vacuo* (0.4g). The i.r. spectrum of the product was identical with that of the starting material.

Attempted reaction of α-methylthio-α-4'-morpholino-benzyl cyanide (XXXVI) with iodomethane:- Two drops of iodomethane were added to a solution of the quaternary cyanide (XXXVI) in dry acetone, and the mixture was set aside overnight in a stoppered 5 ml conical flask.

The solution remained clear; no derivative separated.

Attempted reaction of α-methylthio-α-4'-morpholino-benzyl cyanide (XXXVI) with benzonitrile:- The quaternary cyanide (XXXVI) (1.0g; 0.004 mol) was added to benzonitrile (0.42g; 0.004 mol) and the mixture was heated under reflux on a steam bath for 12h. The mixture was cooled at room temperature for 1h and light petroleum (80 - 100°; 5 ml) was added. As colourless crystals began to form the mixture was cooled in ice. The product was filtered off and dried in vacuo; m.p.74-75°; its i.r. spectrum did not differ from that of the quaternary cyanide (XXXVI).

Attempted reaction of α-methylthio-α-4'-morpholino-benzyl cyanide (XXXVI) with hydroxylamine hydrochloride:- Water (40 ml) was added to a mixture of sodium acetate (20.0g; 0.244 mol) and hydroxylamine hydrochloride (1.0g; 0.0144 mol) and shaken. The quaternary cyanide (XXXVI) (0.5g; 0.002 mol) dissolved in terahydrofuran (3 ml) was added to the clear solution. The mixture which became turbid was stirred magnetically. Some colourless product precipitated after stirring for 30 min. The stirring was continued for 2½h and the

mixture was cooled in a refrigerator for 20 min. The product was filtered off and dried *in vacuo*; its i.r. spectrum was similar to that of the starting material.

Attempted reaction of α-methylthio-α-4'-morpholino-benzyl cyanide (XXXVI) with acetonitrile:- A mixture of the quaternary cyanide (XXXVI) (0.5g; 0.002 mol) and acetonitrile (5 ml) was heated under reflux for 3h. The solvent was distilled off and the oil which resulted was cooled in a refrigerator overnight. The oil solidified; the product was filtered off and dried *in vacuo* (0.44g); its i.r. spectrum was identical with that of the quaternary cyanide (XXXVI).

Attempted reaction of α-methylthio-α-4'-morpholino-benzyl cyanide (XXXVI) with urea:- The quaternary cyanide (XXXVI) (0.5g; 0.002 mol) was added to a solution of urea (1.0g; 0.017 mol) in ethylene glycol (30 ml) and the mixture was heated with stirring at 80 - 90°. The purple solution was cooled in a refrigerator overnight; no visible change was observed.

Attempted base hydrolysis of α-methylthio-α-4'-morpholinobenzyl cyanide (XXXVI):- The quaternary cyanide (XXXVI) (1.0g; 0.004 mol) was stirred magnetically with a solution of potassium hydroxide (2.0g; 0.036 mol) in ethanol (95%; 20 ml) for 22h at room temperature.

Half of the alcoholic solution was evaporated *in vacuo* to remove the ethanol (95%) and water (10 ml) was added. A brown oil resulted which on cooling and rubbing partly crystallised. The somewhat sticky solid was dried *in vacuo*. Its i.r. spectrum showed presence of starting material but also some "amide" might have been present (i.r. peaks at Ca ν max 3400 and 3100 cm^{-1} and carbonyl peak at Ca ν max 1700 cm^{-1}). There was also a weak C≡N peak at Ca ν max 2200 cm^{-1}.

The other half of the alcoholic solution was allowed to stand at room temperature for 4 days. A small amount of crystals (large leaflets) had formed and were filtered off and washed twice with a little ice-cold ethanol and dried; ν max 3400 - 3000vs (NH_2), 2170vs (C≡N), 1600s, 1400s, 1070m, 840s, 710vs cm^{-1}. This compound contained nitrogen but no sulphur (Lassaigne's test). It did not melt up to 260° and

was probably a potassium salt since, on heating on a spatula it melted at a high temperature, then charred and finally left a white residue. The compound was very soluble in water.

Attempted reaction of 1-methylthio-1-(4'-morpholino)-2-phenylethyl cyanide (XL) with sodium azide:-

A solution of sodium azide (2.0g; 0.031 mol) in water (10 ml) was added to a solution of the quaternary cyanide (XL) (0.52g; 0.002 mol) in dioxan (AR; 0.6 ml). An oil resulted and the mixture was stirred magnetically for 62h. The oil was extracted four times with dichloromethane (total 500 ml); the combined extracts were washed with water (350 ml) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* leaving an oil. Light petroleum (80 - 100°; 10 ml) was added to the oil; the mixture was boiled on a steam bath, then cooled in ice and rubbed simultaneously. The oil did not solidify even after cooling in the deep freeze for 4 days; ν max (liquid film) 2920vs (C-H stretch), 2220vw (C≡N), 1640m, 1600vw, 1120vs ($-CH_2OCH_2-$ of morpholino-group), 700s cm^{-1}.

Attempted reaction of 2-cyano-2,4'-morpholino-3-phenyl-propionamide (XLIV) with hydroxylamine hydrochloride:- The cyanoamide (XLIV) (0.202g; 0.00078 mol) was added to a solution of sodium acetate (5.0g; 0.061 mol) and hydroxylamine hydrochloride (0.2g; 0.0029 mol) in water (10 ml). Dioxan (AR; 10 ml) was added to the suspension and the mixture was stirred magnetically for 12h and cooled in a refrigerator overnight. The colourless solid product was filtered off and dried *in vacuo* (0.057g). The i.r. spectrum of the product was similar to that of the starting material.

Attempted reaction of thiobenzomorpholide methiodide (XVIII) with potassium thiocyanate:- Thiobenzomorpholide methiodide (XVIII) (1.0g; 0.0029 mol) was added to a solution of potassium thiocyanate (3.0g; 0.03 mol) in water (25 ml). The mixture was shaken gently and on cooling in a refrigerator overnight the solution turned turbid.

Attempted reaction of SNN'-trimethyl-NN'-diphenylthiuronium iodide (LI) with potassium cyanide:- SNN'-Trimethyl-NN'-diphenylthiuronium iodide (LI) (0.35g; 0.00088 mol) was added to a solution of potassium cyanide (3.0g; 0.046 mol) in water (25 ml) and the mixture was stirred magnetically overnight. On cooling no derivative separated.

Attempted reaction of thiosalicylmorpholide methiodide (XX) with potassium cyanide:- Thiosalicylmorpholide methiodide (XX) (4.20g; 0.0115 mol) was added to a solution of potassium cyanide (12.0g; 0.185 mol) in water (100 ml) and the mixture was gently shaken. Immediately some yellow sticky precipitate resulted. The mixture was cooled in a refrigerator overnight; after cooling for 5 min some reddish product mixed in with the yellow precipitate was observed. The product which completely turned red overnight was filtered off and dried *in vacuo* (1.88g). The red product darkened on exposure to air. The crude product was recrystallised from light petroleum (80 - 100°) (Charcoal) and again from light petroleum (80 - 100°) and dried *in vacuo* at room temperature for 2h; m.p.89 - 90° (decomp.);

ν max (Nujol) 3100vw (free OH), 2920vs (C-H stretch), 1580s, 1110vs ($-CH_2OCH_2-$ of morpholino - group), 1030s, 850s, 760s cm^{-1}.

Attempted reaction of thiobenzomorpholide methiodide (XVIII) with Chloramine - T:- Thiobenzomorpholide methiodide (XVIII) (1.0g; 0.0029 mol) was added to a solution of Chloramine-T (10.0g; 0.036 mol) in water (75 ml). Some dark precipitate (probably due to the presence of iodine) resulted. A few drops of saturated sodium thiosulphate solution were added; the brownish solution became colourless while the dark precipitate remained.

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