SOME ASPECTS
OF THE
ORGANIC CHEMISTRY OF SULPHUR

A THESIS PRESENTED TO THE
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BY

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DEDICATED TO MY PARENTS.

".....SYNTHESIS FOR ITS OWN SAKE WILL CONTINUE. THERE IS EXCITEMENT, ADVENTURE, AND CHALLENGE AND THERE CAN BE GREAT ART IN ORGANIC SYNTHESIS."

WOODWARD, R.B.

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

It is a great pleasure to have another opportunity to express my profound gratitude to Professor F. Stansfield, my supervisor, for the interest, love and kindness shown thoroughout the course of this work. I believe God will faithfully reward you.

I would also like to express my gratitude to Professor A. R. Mathieson for the keen interest shown in the progress of this work. I am grateful to Dr. H. T. Bozimo and Mr. S. A. Okecha for discussions.

I like to express sincere thanks to Mr. O. K. Abubakar for running all the n.m.r. spectra and Mr. J. O. Aina for typing the thesis.

Finally, I thank all the Laboratory, Stores and Technical staff for their assistance.

March, 1976. J. O. Amupitan.

ABSTRACT

In this report, the Wmgerodt-Kindler reaction has been reviewed, and a. variant of the reaction has "been developed.

In this, good yields of thioamides have been obtained "by reaction of aldehydes or ketones with salts of volatile amines and anhydrous sodium acetate in dimethylformamide at moderate temperatures, thus avoiding the conventional use of pressure vessels and high temperatures.

The thioamides with alkyl halides give S-alkylquaternary salts, which have been reacted with various nucleophilic reagents: hydrazine hydrate, sodium borohydride and diazomethane: giving interesting products.

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T A B L E S.

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

Thioamides (I) are most useful intermediates which can be prepared by a variety of methods[1]. The most useful of these are:-

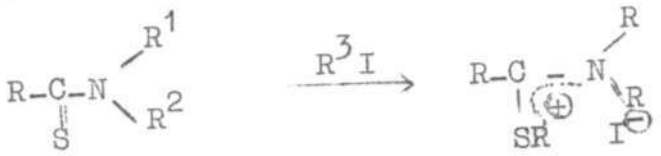
(a) reaction of amides with phosphorus pentasulphide[2],

(b) the Willgerodt-Kindler reaction[3-8] and

(c) extension of (b) which involves the use of salts of volatile amines.

This is described later.

When thioamides are reacted with simple alkyl halides, they give almost quantitative yields of S-alkylquaternary salts (II) which are of high synthetic value. They are often beautifully crystalline compounds.

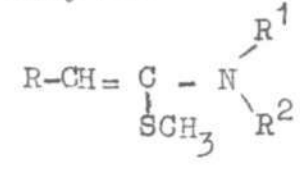


I II

(R = alkyl or aryl; $R^1 = R^2$ = alkyl or NNR^1R^2 = morpholino; R^3 usually Me or ethyl).

The salts are stable and can be stored for a long period under dry conditions. The positive charge is stabilised by delocalisation on to the carbon, sulphur and nitrogen atoms.

They however, react rapidly with nucleophiles, or if hydrogen is present on the α-carbon atom, with bases to give ketene SN-acetals[5] which are themselves useful intermediates (III). They are



(III)

thus valuable intermediates of great synthetic utility.

THE WILLGERODT REACTION:

This reaction will be briefly discussed as there are standard books[5-7] and papers[9-20] where detailed information can be obtained.

The Willgerodt reaction, consists of the reaction of alkyl aryl ketones with aqueous ammonium polysulphide at an elevated temperature (200°, usually in an autoclave). Carboxylic acids and their amides containing the same number of carbon atoms as the starting ketones are obtained.

$$Ar - CO-(CH_2)_n-CH_3 + (NH_4)_2Sx\ H_2O \longrightarrow$$

$$Ar - (CH_2)_{n+1}- COOH + Ar(CH_2)_{n+1}CONH_2.$$

A small amount of the corresponding ammonium salt of the carboxylic acid is obtained.

Example: $C_6H_5COCH_3 \xrightarrow[H_2O]{(NH_4)_2Sx} C_6H_4CH_2.CONH_2 + C_6H_5CH_2COONH_4$

The reaction proceeds, in effect, as though the methyl group were oxidised to a carboxylic acid group, and the carbonyl group converted into a methylene group or that the carbonyl group migrates to a terminal position.

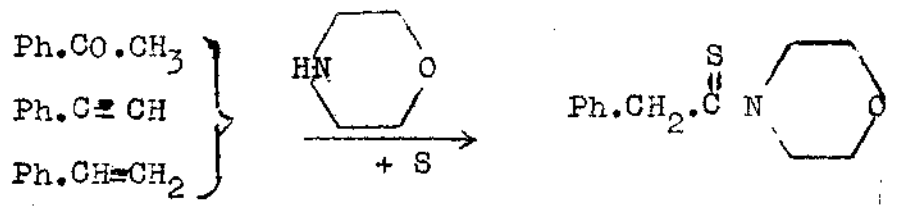
THE KINDLER MODIFICATION:

Kindler's modification involves the replacement of the aqueous ammonium polysulphide in the reaction above by equimolar amounts of sulphur and a dry amine. Instead of an amide, a thioamide is formed which can be hydrolysed to the acid with alkali. Secondary and primary aliphatic amines and ammonia have been used.

In addition to ketones many other types of compounds also gave thioamides under the same condition. They included aldehydes, the reduction products of ketones, thiols, disulphides, imines, olefins, acetylenes, α,β- unsaturated acid which gave thioamides of the next lower homologues and even alcohols.

For example, acetophenone, phenylacetylene and styrene all gave phenylthioacetmorpholide in about the same

yield upon heating to 150°C with morpholine and sulphur.



The use of high boiling amines such as morpholine, in this procedure has made it possible to carry out the reaction in open vessels rather than autoclaves or sealed tubes[11].

The theoretical molecular proportions of reactants in Kindler's procedure are 1 mole of amine and 1 gm. atom of sulphur for each mole of ketone. The proportions which have been used vary from almost the theoretical to ratios of 1.5/1.5/1 for amine, sulphur and ketone[4]. Amines most frequently used are dimethylamine and morpholine. Others are methylamine, piperidine, anhydrous ammonia, and benzylamine.

When a high boiling amine, for example, morpholine, is used, no special closed apparatus is required since the reaction mixture can be heated in conventional glass equipment under a reflux condenser.

EXTENSION OF THE WILLGERODT-KINDLER REACTION:

Major disadvantages of this reaction are that when a volatile amine is used for example, dimethylamine, methylamine or ammonia, a sealed glass tube or autoclave is usually needed and in the case of ammonia, ammonium polysulphide, $(NH_4)_2Sx$, an unpleasant reagent is used. Thus earlier experiments were carried out at about 200° whilst in later developments temperature ranges in the order of 140°-160° have been applied.

In the case of the high-boiling secondary amines, e.g. morpholine, the reaction mixture was simply refluxed as mentioned earlier.

In this report, we shall show that thioamides can be prepared in reasonably high yields using volatile amine salts in conventional glass equipment and comparatively short reaction time, with lower temperature and at atmospheric pressure.

This method was used to prepare all the thioamides reported in this work. Such amine salt as dimethyl-ammonium chloride was mixed with sulphur and anhydrous sodium acetate in dimethylformamide (DMF) or pyridine as solvent.

DMF was found to be a better solvent for this reaction since it is cheaper than pyridine, less toxic, gives

better yields, and can be used at lower temperatures.

Ammonium chloride may be used but yields are poor; probably due to escape of ammonia from the reaction medium as it is generated *in situ*. Thus this method cannot be adequate for preparation of primary thioamides. Preparation by oxidation of benzylamines with sulphur is probably the most convenient method[13] for preparing primary thiobenzamides.

It was found that by heating equimolecular portions of benzylamine and sulphur a 91% yield of thiobenzamide was obtained.

Some of our reactions were carried out on the steam bath. Reaction time varied from three to four hours.

Having established optimum conditions for one aldehyde, we then extended the reaction to ketones and to aliphatic aldehydes. For example, *iso*-butyraldehyde was reacted successfully with dimethylammonium chloride and sodium acetate in boiling pyridine or in DMF on the steam bath.

Our method has no doubt amounted to a synthetic break-through having made preparation of thioamides easy and cheap.

MECHANISM OF THE WILLGERODT REACTION:

In thinking about the mechanism of this reaction the following three salient observations must be borne in mind:

(i) that no change in the carbon skeleton occurs during the reactions,

(ii) that all members of a family of isomeric aliphatic carbonyl compounds, differing from one another only in the position of theoxygen atom, form the same final product[16] and

(iii) that unsaturated hydrocarbons can undergo similar reactions[15-19].

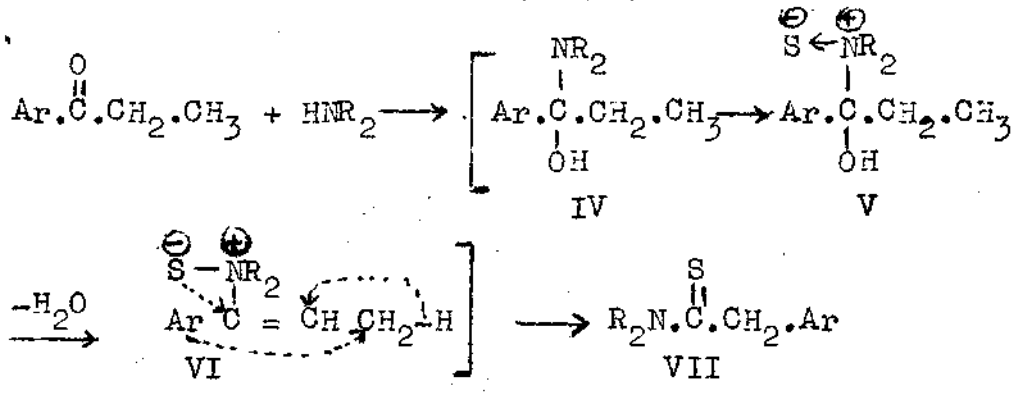
The mechanism of the reaction is not clear and the following is a review of possible mechanisms that have been postulated by various workers.

Willgerodt's earlier views that oxidation of the terminal methyl group, for example in acetophenone, preceded reduction of the keto group was rejected as no keto acids were isolated nor could the latter be converted into amides by the ammonium polysulphide reagent. Neither would the reduction of the carbonyl prior to oxidation be feasible since the hydrocarbon then obtained would not react under these conditions.

Willgerodt finally postulated the isomerisation of the alkyl aryl ketone into an aldehyde, involving some method by which the oxygen atom wandered to the end of the chain, in effect exchanging place with two hydrogen atoms of the terminal methyl group to form an aldehyde. The latter could then react with sulphur and ammonia to yield the corresponding amide; indeed aldehydes are known to yield amides under these conditions.

Kindler, however, suggested a mechanism whereby a phenyl group migrates during the course of the reaction with sulphur, but there is no evidence of any isomerisation of the ketone during the oxidation.

He postulated that the reaction goes <u>via</u> the formation of a hydramine (IV) which then adds on sulphur to give an amine sulphide (V). The latter is dehydrated to (VI), which forms the thioamide (VII) by rearrangement.



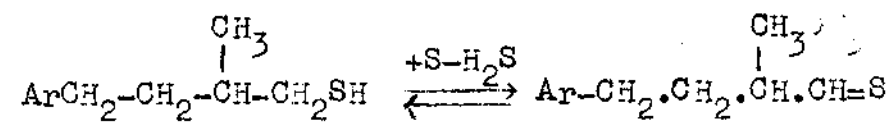
This mechanism breaks down with higher ketones.

King and McMillan[14] had observed that ketones in which the carbonyl group is adjacent to an aromatic ring, and which contain a quaternary carbon atom, give hydrocarbons exclusively and no carboxylic acids.

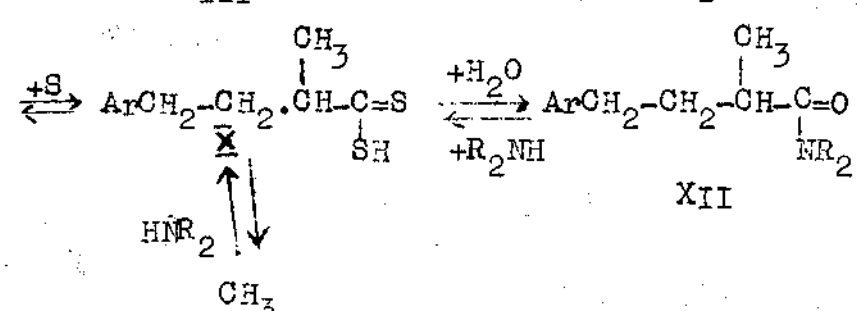
De Tar and Carmack[16] suggested that a reactive group - probably the amino group - migrates along the hydrocarbon chain during the course of the reaction, via addition to acetylenic compounds produced as intermediates. The same authors pointed out that lower yields were obtained from the Willgerodt-Kindler reaction undergone by phenylacetaldehyde and β-phenyl propionaldehyde than by acetophenone and propiophenone respectively. It is concluded from this fact that it is not merely a case of the carbonyl group's migration along the carbon chain.

McMillan[14,20] assumes that the reaction starts with the addition of hydrogen sulphide to the keto group, followed by dehydration to the thioketone, the latter's reduction to a mercaptan, elimination of hydrogen sulphide to give an olefin, renewed hydrogen sulphide addition which can proceed in two directions to give isomeric mercaptans, again elimination of hydrogen sulphide to give two isomeric olefins and so on. The thiol group thus migrates along the whole aliphatic chain.

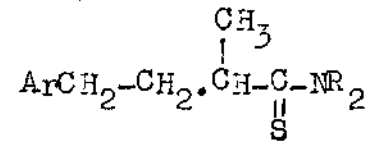
The primary mercaptan finally obtained (VIII) is dehydrogenated to the thioaldehyde(IX) and the latter irreversibly converted into the dithiocarboxylic acid (X). This last step may also involve stabilisation to the thioacid amide (XI) or acid amide (XII).



VIII IX



XII



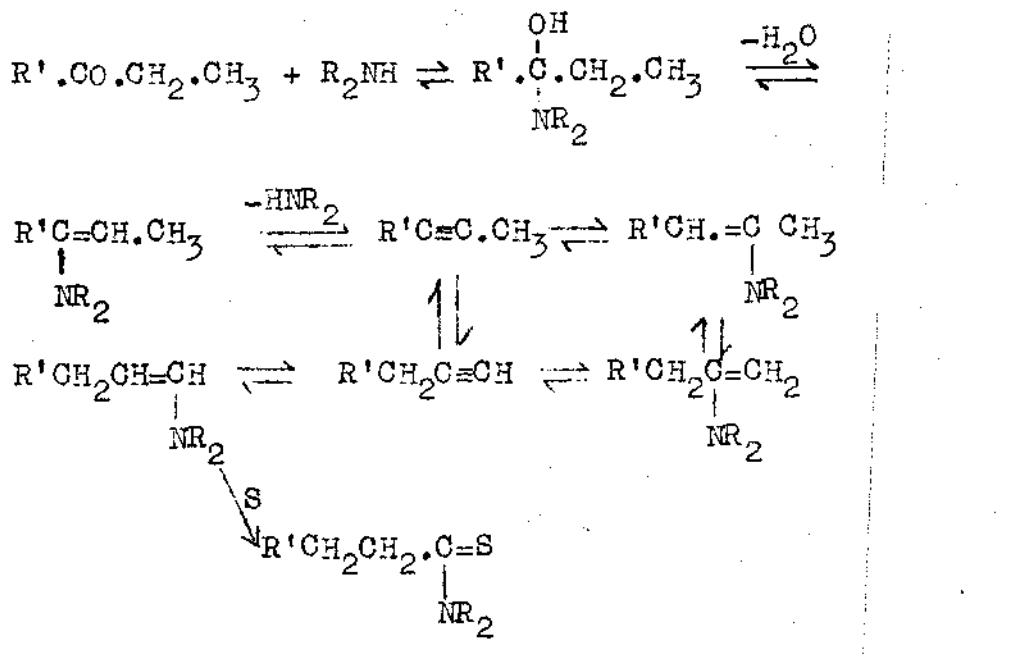
XI

No mention was made in this mechanism of the reversible conversion of secondary mercaptans into thioketones which is possible at every step. Also the possibility that disulphides are likely to be formed in the reaction of sulphur and olefins. They represent labile compounds which readily undergo further reaction without being true intermediates. There are, however, supporting evidences.

For example the reduction of a keto group by hydrogen sulphide to give a methylene group has been proved in various ways. Benzophenone can be reduced to diphenylmethane by hydrogen sulphide in the presence of morpholine; this reaction proceeds via the thiol compound as evidenced by isolation of disulphides. The ready reducability of the keto group is also shown by the notable yields of hydrocarbon (observed by Willgerodt in his original work) resulting from the reaction between aralkyl ketones and colourless ammonium polysulphide which contains hydrogen sulphide from the very beginning. Ammonium polysulphide reduces cyclohexanone to cyclohexanethiol[21]. The straight forward conversion of terminal thiols - present as intermediates - into dithiocarboxylic acids has been confirmed experimentally by McMillan[22].

Carmack and De Tar[16,23] have also postulated a sequence involving the stepwise addition, elimination and re-addition of simple molecules such as ammonia, amines, sulphur, water or hydrogen sulphide, resulting in the migration of the functional group along the chain. Irreversible oxidation by the action of sulphur on the function at the terminal position produces a thioamide. The mechanism assumes the observation that olefins and

acetylenes give thioamides with sulphur and amines.



R = alkyl or H.

Inspite of empirical observations, mechanistic routes commencing with the reduction of the carbonyl group are thought not to completely represent the Willgerodt-Kindler reaction. Facts show that a methylene group adjacent to a carbonyl group reacts with exceptional readiness, even at room temperature, with sulphur to form a thiol group (cf the Asinger reaction).

The newer view is that the primary attack takes place at the particularly reactive methylene group. This is followed by oxidations of the mercaptan formed, partly to

the labile disulphide, but especially to the thioketone accompanied by the formation of hydrogen sulphide. The latter is then able to reduce the carbonyl group to a methylene group. The renewed attack by sulphur can then take place at an activated methylene group once again. The oxidation - reduction cycle proceeds by a sequence of equilibrium reactions up to the end of the chain, when a dithiocarboxylic acid is irreversibly formed.

The mechanism proceeding most readily would be that *via* olefins, accompanied by the formation of mercaptan intermediates.

Naylor and Anderson[24] support the mechanism through olefin and disulphide intermediates.

RESULTS AND DISCUSSION

PREPARATION OF NN-DISUBSTITUTED THIOAMIDES:

As previously mentioned, thioamides are often prepared by two major methods:-

(a) by reaction of amides with phosphorus pentasulphide and

(b) by the Willgerodt reaction.

Method (a) is easily carried out, but phosphorus pentasulphide is expensive and, in the case of primary thioamides, the product may be partly converted to a nitrile by the phosphorus pentoxide formed.

$$RCSNH_2 \xrightarrow{P_2O_5} RCN + H_2S.$$

To minimize the effect of this reaction it is important to isolate the thioamide as soon as it is formed.

In the present investigation, a variant of Willgerodt reaction was used to prepare several thioamide derivatives using the amine salts instead of the amines themselves. The following thioamides were prepared in good yields (Table 1).

R*. CS. NMe_2

XIII R = C_6H_5-

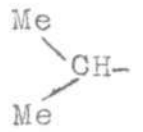
XIV R = $C_6H_5CH_2$-

XV R = $Br.C_6H_4$-

XVI R = $Cl.C_6H_4$-

XVII R = $MeO.C_6H_4$-

XVIII R = $O_2N.C_6H_4$-

XIX R = 

The following thiobenzomorpholide derivatives were made by the Willgerodt-Kindler reaction.

R*. CS. 

XX R = C_6H_5-

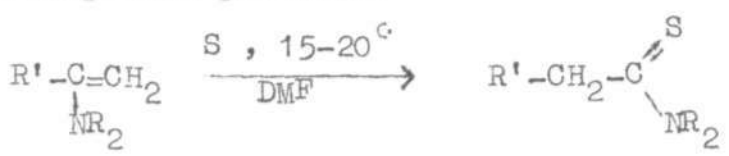
XXI R = $C_6H_5CH_2$-

XXII R = $Cl.C_6H_4$-

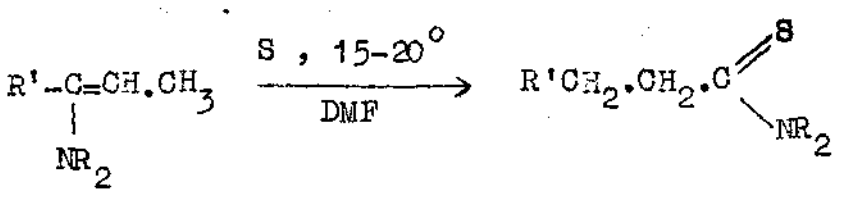
XXIII R = $MeO.C_6H_4$-

XXIV R = $Me_2N.C_6H_4$-

Another variant of the Willgerodt reaction which allows synthesis of thioamides at room temperature has been described[25]. This involves the reaction of elemental sulphur with alkenylamines in DMF at room temperature and atmospheric pressure.



(* substitutions are <u>para</u>)



This useful variant can start directly from ketones, which are treated in the conventional manner with a secondary amine and sulphur, a catalyst, e.g. toluene-*p*-sulphonic acid, being added to accelerate the formation of the alkenylamine. Good yields were also obtained.

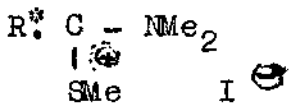
The ability to use conventional glass equipment in these reactions would reduce the cost of production of any thioamide or its hydrolytic or reduction derivative that can be made by the present method, using the amine salts instead of the amines.

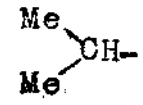
Work-up of products is simple. The mixture, directly from the oil bath is poured on to cold water. Sodium salts, D.M.F., and unreacted amine salts are all soluble in water. The only major impurity left is excess sulphur which is eliminated on recrystallisation of the product from alcohol or aqueous alcohol.

Petroleum ether was useful for purifying most of the thioamide derivatives obtained. The yields were high (54-92%) Table 1.

PREPARATION OF S-ALKYL QUATERNARY SALTS:

Thioamides react with alkyl halides, usually iodomethane or iodoethane giving S-alkyl quaternary ammonium salts, the synthetic value of which has undergone continuous exploitation for years. Salts of all thioamides (XIII-XXIV) were prepared.



XXV R = C_6H_5-
XXVI R = $C_6H_5CH_2$-
XXVII R = Br.C_6H_4-
XXVIII R = Cl.C_6H_4-
XXIX R = MeO.C_6H_4-
XXX R = $Me_2N.C_6H_4$
XXXI R = $O_2N.C_6H_4$-
XXXII R = 

The following thiobenzomorpholide methiodide derivatives were also prepared.



XXXIII R = C_6H_5-
XXXIV R = Cl.C_6H_4-
XXXV R = $Me_2N.C_6H_4$-
XXXVI R = MeO.C_6H_4
XXXVII R = $C_6H_5CH_2$-

(* substitutions are para)
(Table 2)

REACTIONS OF QUATERNARY SALTS OF N,N-DISUBSTITUTED THIOAMIDES:

The synthetic utility of the quaternary salts of NN-disubstituted thioamides have been mentioned in brief.

With water or hydrogen sulphide, for example they give good yields of thiol- or dithio- esters, respectively. This is probably the best way of preparing the latter, and it is not even necessary to isolate the thioamidinium salt[8]. With ammonia or with amines they give amidines or amidinium salts, and they react additively with semicarbazide or thiosemicarbazide, with subsequent elimination of either a thiol or a secondary amine depending on the conditions.

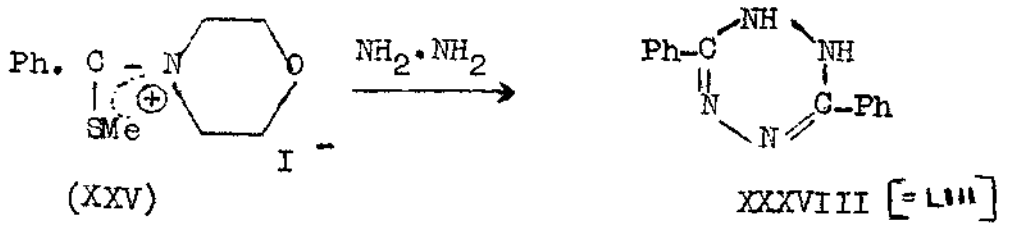
This possibility of obtaining different products by elimination of different groups from the asymmetric carbon first formed, increases the versatility of the syntheses. Below is a table of some reactions of these salts done by various workers. In some cases different products are obtained under acidic and under basic conditions due to preferential elimination of the alkylthio- or dialkylamino- groups.

(TABLE 3)

The reaction of thiobenzomorpholide methiodide (XXXIII) with the Grignard reagent, RMgBr, is worthy of note because it provides a useful method of making ketones. By using thioformdimethylamide methiodide derivatives, aldehydes are obtained[28].

The reaction of potassium cyanide with thiobenzdimethylamide methiodide (XXV) has been repeated in aqueous solution at room temperature and a purer product was obtained[27] than when the same reaction was done in boiling benzene.

The reaction of thiobenzdimethylamide methiodide (XXV) with hydrazine has also been investigated. Chabrier and Renard[30] reported that thiobenzomorpholide methiodide (XXXIII) reacted with excess hydrazine to give the 3,6-diphenyl-1,2-dihydro-1,2, 4,5-tetrazine.



(XXV) XXXVIII [= LIII]

No experimental conditions for this reaction were given.

Table 3: SOME REACTIONS OF QUATERNARY N,N-DISUBSTITUTED THIOAMIDE SALTS.

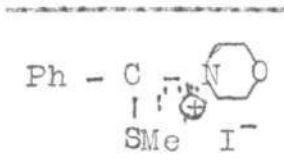
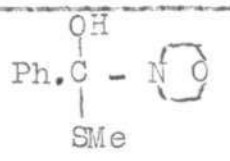
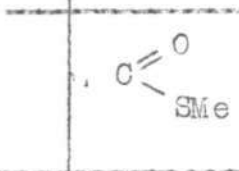
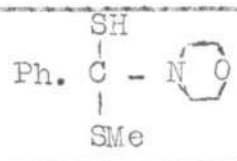
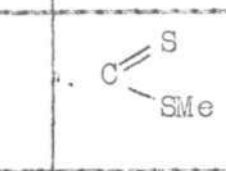
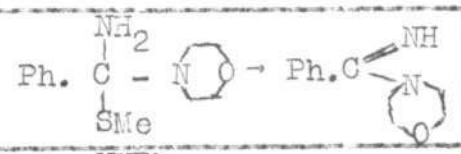
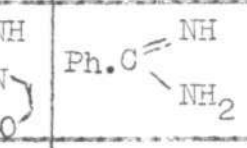
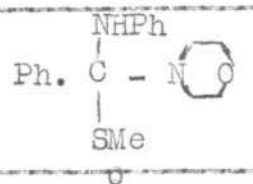
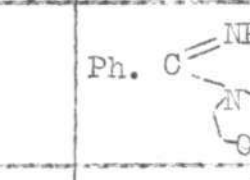
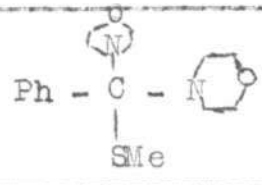
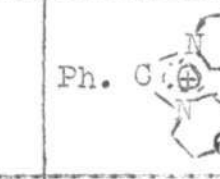
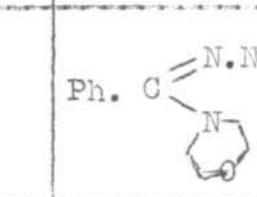
SUBSTRATE	REAGENT	INTERMEDIATE	PRODUCT	
	H_2O			
	H_2S			8
	NH_3			8
	$PhNH_2$			
				8
* $H_2N.CO.NH.NH_2$ (alkaline)				8

Table 3 contd.

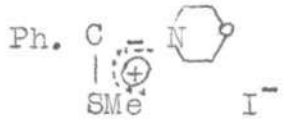
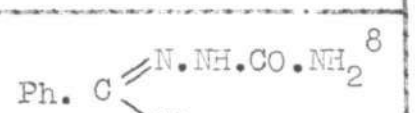
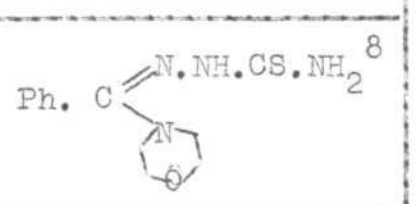
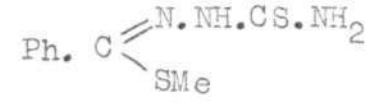
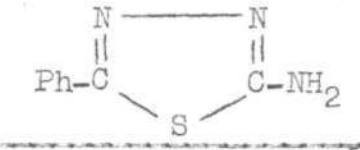
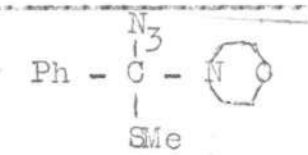
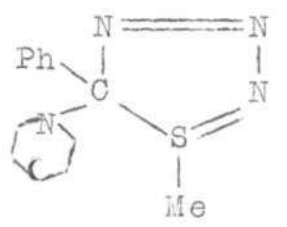
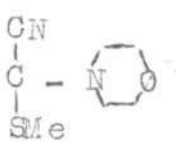
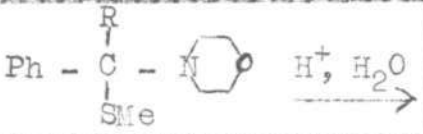
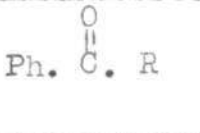
SUBSTRATE	REAGENT	INTERMEDIATE	PRODUCT
	* $H_2N.CO.NH.NH_2$ (neutral or acid)		 8
	* $H_2N.CS.NH.NH_2$ (alkaline)		 8
	* $H_2N.CS.NH.NH_2$ neutral or acid		 8
	$^+NaN_3$		 26
	^+NaCN		 27
	RMgBr		 28

Table 3 contd.

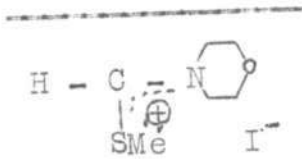
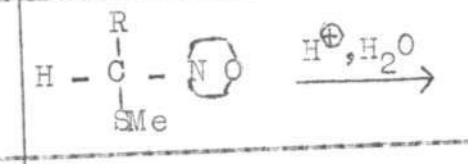
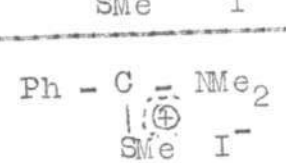
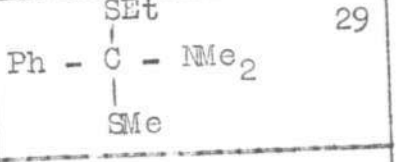
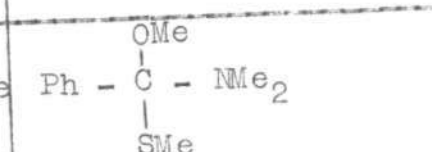
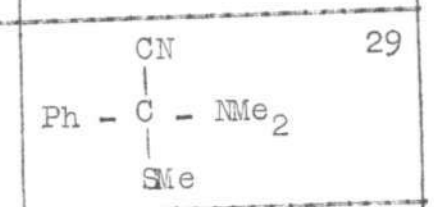
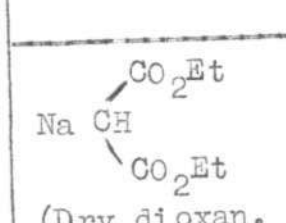
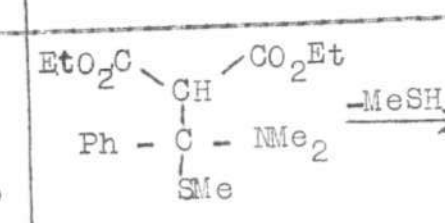
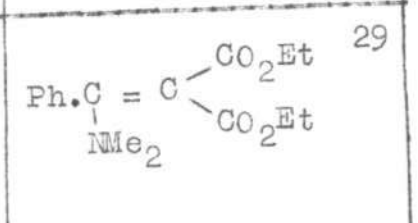
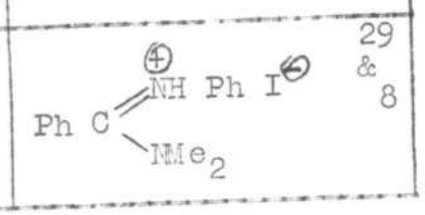
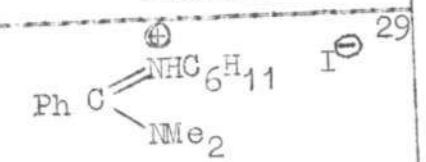
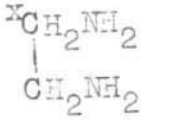
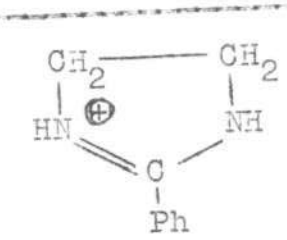
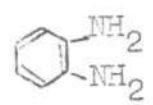
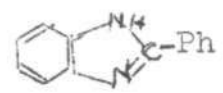
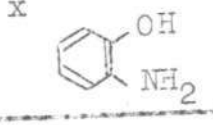
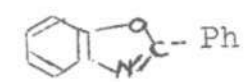
SUBSTRATE	REAGENT	INTERMEDIATE	PRODUCT
	RMgBr		RCHO 28
	EtSNa in dry Et_2O		 29
	dry NaOMe in boiling Benzene Reac^{n} slow r.t		$Ph.CO.NMe_2 + Me_2S$ 29
KCN Boiling Benzene			 29
 (Dry dioxan, 80° 2hr.)			 29
$Ph.NH_2$			 29 & 8

Table 3 contd.

SUBSTRATE	REAGENT	INTERMEDIATE	PRODUCT
Ph – C(=⊕SMe) – NMe_2 I^-	(Cyclohexylamine)		 29
			 29
x 			 29
x 			 29
NH_2OH			Ph – C(=N.OH)–NMe_2 27

* Note that SMe is eliminated under alkaline conditions but is eliminated in neutral or acid solution.

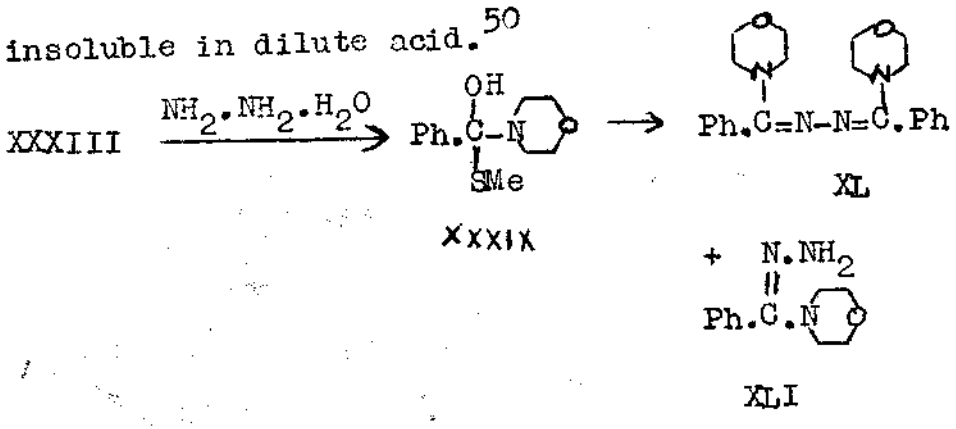
\+ Nothing eliminated.

x Note the elimination of both $-NMe_2$, and -SMe in these reactions.

However, in this report, it will be mentioned later how the same compound has been much more easily obtained by reaction of thiobenzdimethylamide with hydrazine hydrate at room - and elevated - temperatures.

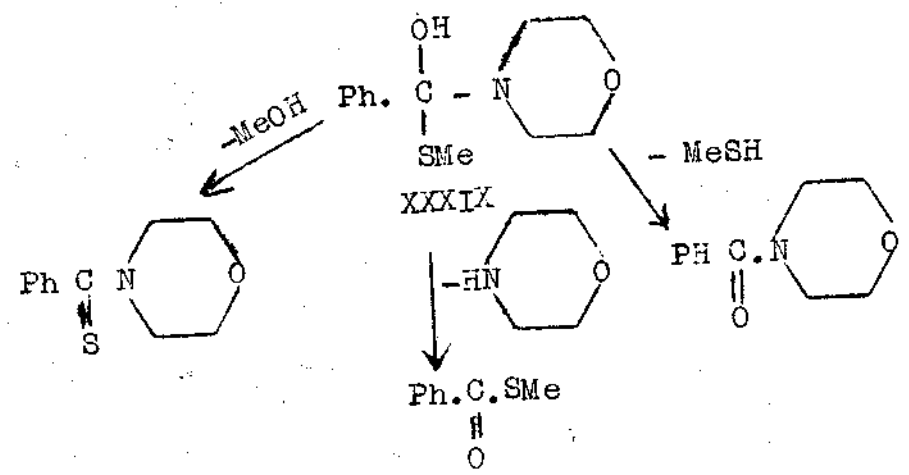
$$Ph\,CS\,NMe_2 \xrightarrow{NH_2.NH_2.H_2O} \text{XXXVIII}$$

We found that at room temperature, Chabrier and Renard's salt (XXXIII) with hydrazine hydrate gave an organge coloured oil which quickly solidified to yield a mixture of the amidrazine, bis(α-4'-morpholinobenzylidene) hydrazine (XL), the corresponding amidrazone (XLI), and a small amount of thiobenzomorpholide which can easily be removed since unlike the other two products, it is insoluble in dilute acid.[50]

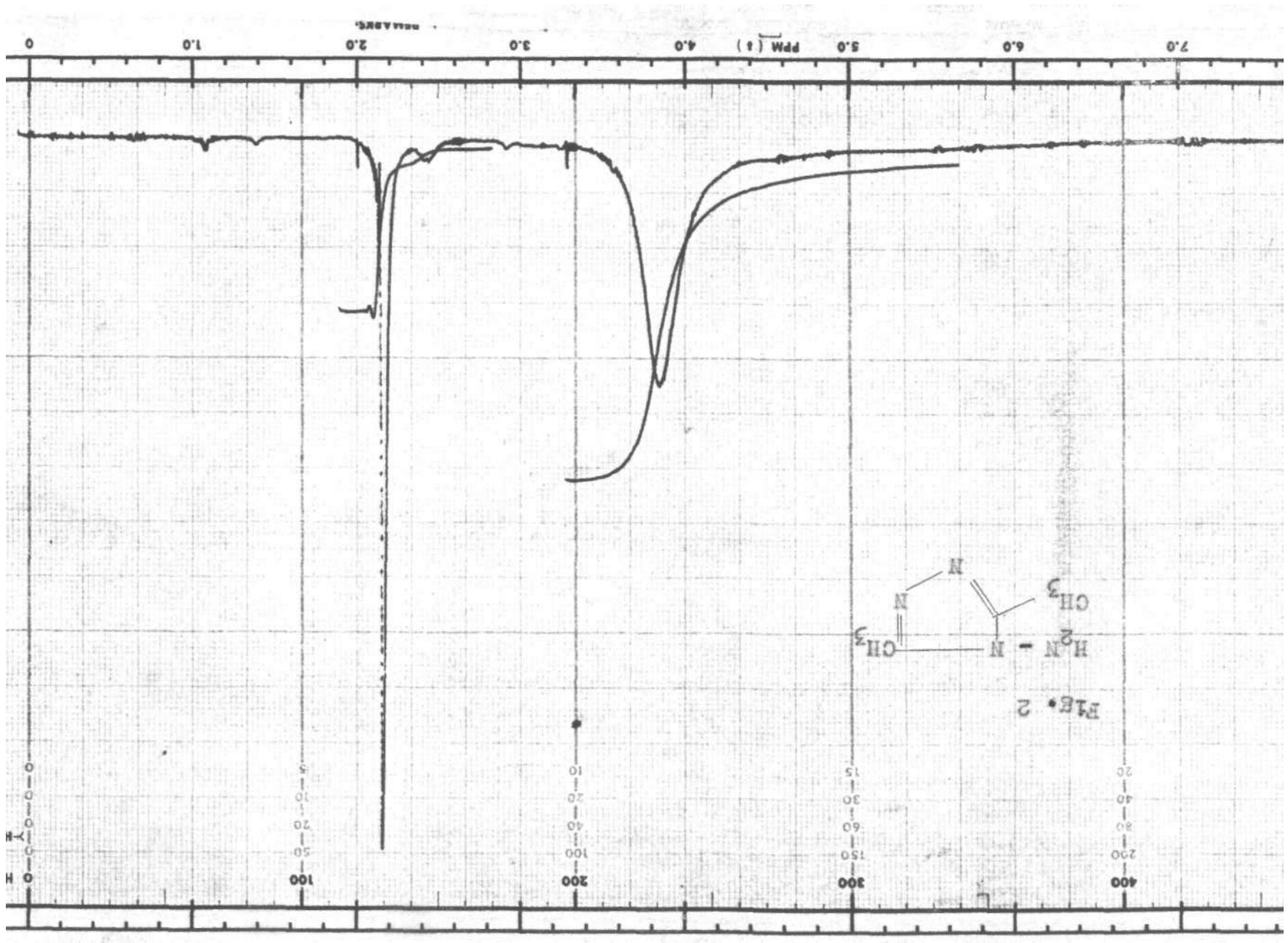


No dihydrotetrazine was formed. The reaction is analogous to that of salt (XXXIII) with aqueous ammonia which yields, initially, an oil, solidifying to the pseudobase (XXXIX) which has been shown to give both benzo- and thiobenzo-morpholide on decomposition, as well as reacting with ammonia to give benzamidine.[8]

The pseudobase (XXXIX)is the precursor of benzomorpholide and of thiobenzomorpholide. It can decompose by loss of a molecule of methanol or of methanethiol resulting in the formation of thiobenzomorpholide, or of benzomorpholide respectively, Loss of morpholine gives a thiol ester (cf products obtained from the reaction of diazomethane with an S-alkyl quaternary salt as described later).



Compounds analogous to N,N'-bis(α-4'-morpholinobenzylidene) hydrazine (XL) were obtained by Pinner as intermediates in the reaction of imidates with hydrazine, and referred to as dihydrazidines[30], but might better be called 'amidrazines' since they are related to amidrazones (XLI)

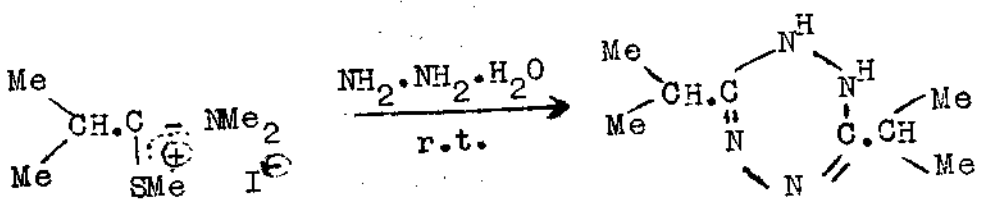


Фиг. 2

The amidrazine (XLII, Fig. 1) dihydrotetrazine (XLIII) and the tetrazine (XLIV) were all characterised by analysis and by their spectra.

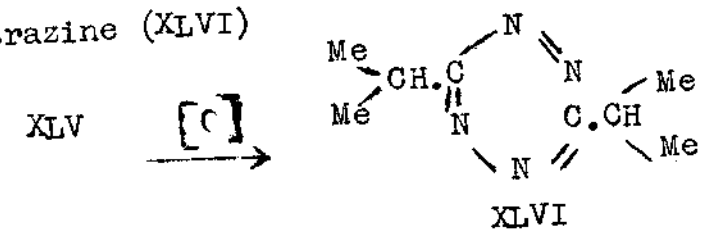
Another method by which both dihydrotetrazines and tetrazines can be made in better yields will be described later.

It was interesting to note that in these reactions of the quaternary salts with hydrazine hydrate, no amidrazine derivatives were isolated when the phenyl groups were substituted at the p-position by electron donating groups e.g. $-NMe_2$ or -OMe, nor with NN-dimethylthioisobutyramide methiodide. No amidrazones were isolated, instead only the dihydrotetrazines were formed.



XXXII XLV

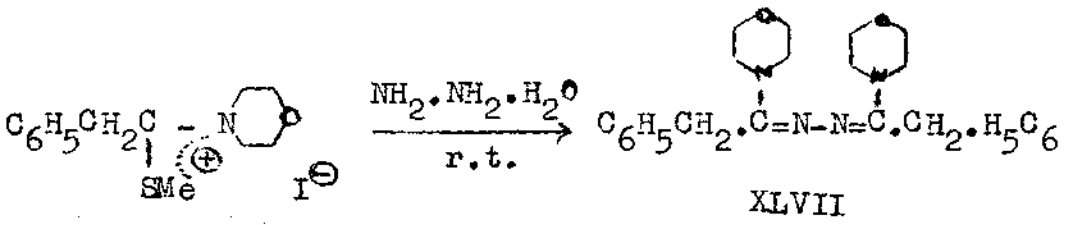
The dihydrotetrazine (XLV) is easily air-oxidised to the tetrazine (XLVI)



XLVI

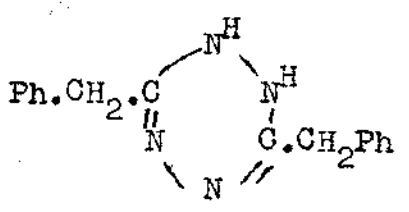
Phenylthioacetdimethylamide methiodide (XXVI) was also reacted with excess hydrazine hydrate at room temperature. A colourless compound, the surface of which turned red was produced. On work up and recrystallisation from toluene, colourless needles were obtained. Here again, the colourless dihydrotetrazine and the red tetrazine were formed.

However, when phenylthioacetmorpholide methiodide (XXXVII) was similarly reacted, the amidrazine (XLVII) was the major product whereas a very small quantity of the dihydrotetrazine was formed.



XLVII

+



XLVIII

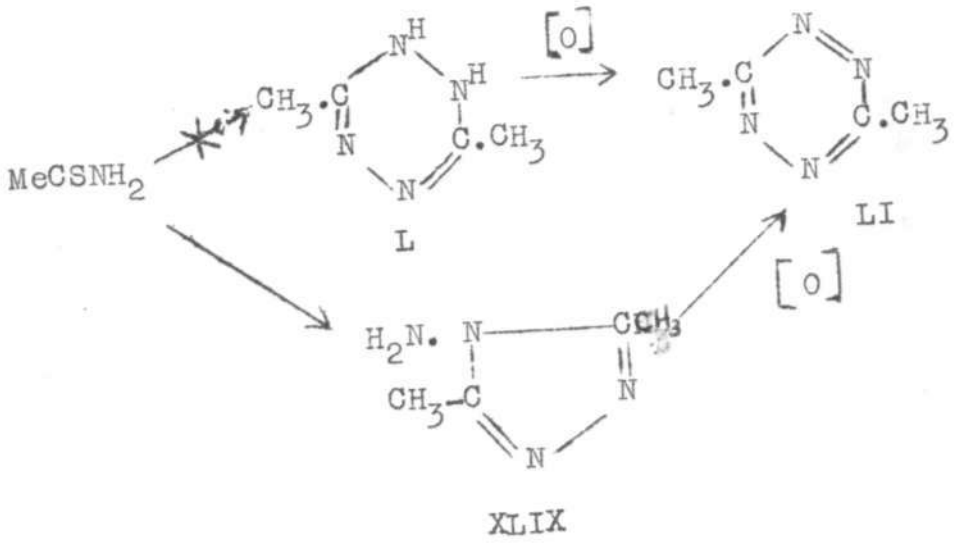
In the reaction of p-chlorothiobenzomorpholide methiodide, the dihydrotetrazine and the amidrazine were also formed. No amidrazone was isolated.

It thus appears that the substituents of the quaternary salts have a profound influence on the nature of the products.

REACTIONS OF THIOAMIDES WITH HYDRAZINE HYDRATE AT ROOM TEMPERATURE:

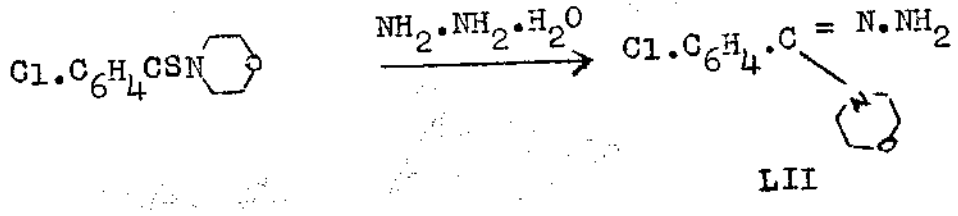
The reactions of some thioamides with excess hydrazine hydrate at room temperature were investigated.

Thioacetamide[50] under these conditions gave a clear yellow solution which was allowed to stand overnight. Large colourless crystals separated. These were found to be the aminodimethyltriazole (XLIX) which is isomeric with dimethyldihydrotetrazine (L).



The dimethyldihydrotetrazine (L) and its oxidation product (LI) have previously been made[31] from acetonitrile and anhydrous hydrazine, whilst the triazole was made from acetonitrile and hydrazine hydrate at 180°. Both n.m.r. and i.r. methods (Fig.2) confirm the structure of the triazole.

p-Dimethylaminothiobenzdimethylamide reacted vigorously with hydrazine hydrate at room temperature to give the corresponding dihydrotetrazine. p-chlorothiobenzomorpholide, however, gave not the dihydrotetrazine but the amidrazone (LII) Figs. 3 & 4)..



LII

Similarly, thiobenzomorpholide with hydrazine hydrate yields N(α-4'-morpholinobenzylidene) hydrazine. (Table 5).

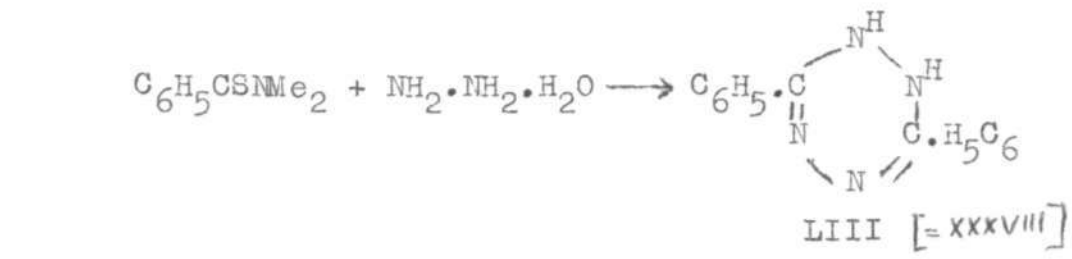
This provides a more convenient method of synthesis of amidrazones in good yields, whereas, as previously mentioned, the quaternary salts give either the amidrazine or dihydrotetrazine sometimes together with amidrazone.

REACTIONS OF THIOAMIDES WITH HYDRAZINE HYDRATE AT 100°

The thioamides were also reacted with excess hydrazine hydrate in an oil bath at 100° resulting in the formation of dihydrotetrazines as the major or only product of the reaction. This proved a convenient method of making these compounds.

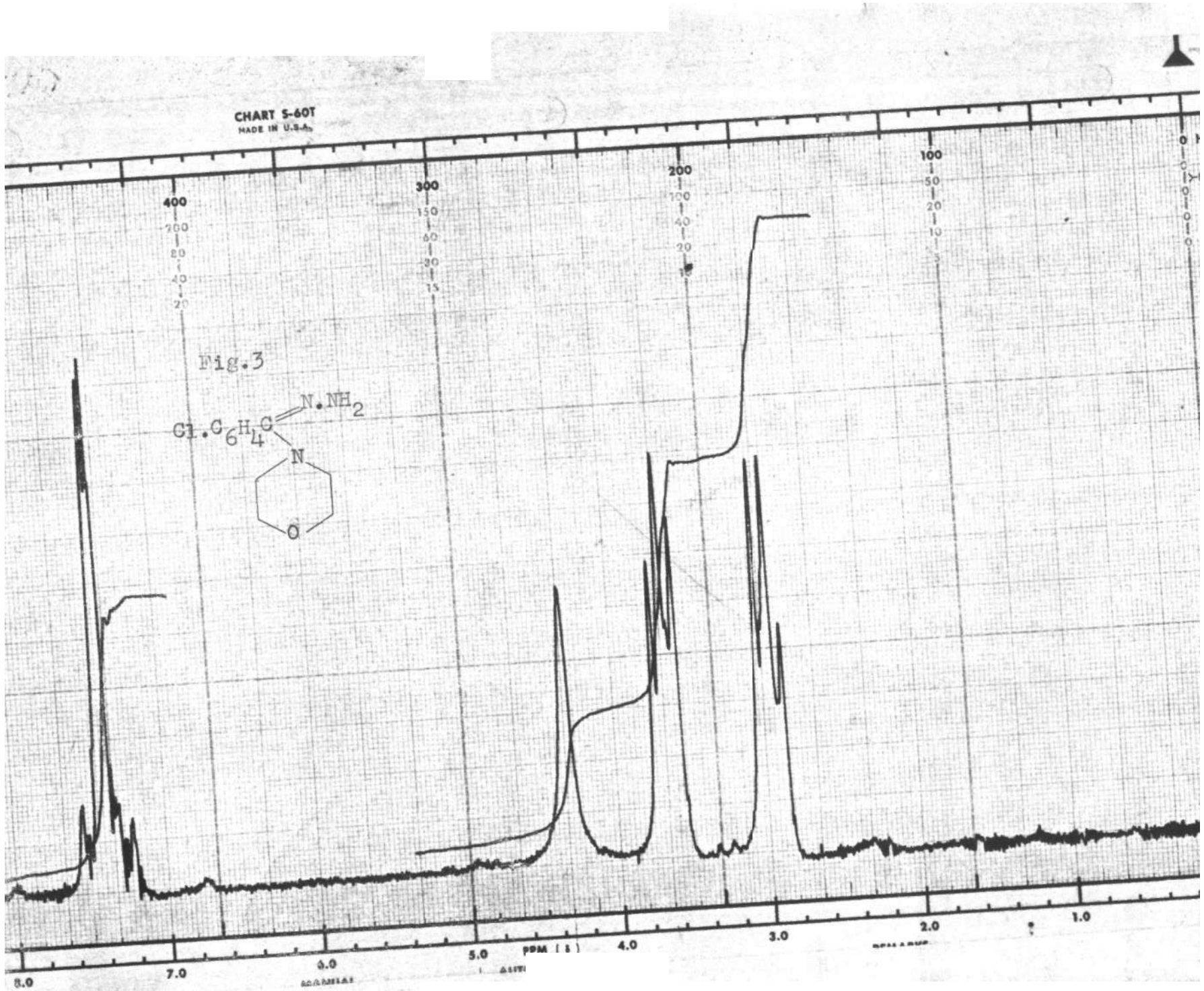
Diphenyldihydrotetrazine has been obtained[32] as the main product from the reaction of one mole of ethyl benzimidate hydrochloride with 1.5 mole hydrazine sulphate in the calculated amount of 33% potassium hydroxide with addition of ethanol. It was also prepared by boiling an alcoholic solution of thiobenzamide with aqueous hydrazine solution[32].

The reaction has currently been further investigated. The same products were isolated from primary and secondary thioamides.



LIII [= XXXVIII]

As mentioned earlier, dihydrotetrazines, for example, 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine (LIII) are


CHART 5-60T
MADE IN U.S.A.
400
300
200
100
0
Fig.3
Cl.C6H4C
N.NH2
N
O
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0

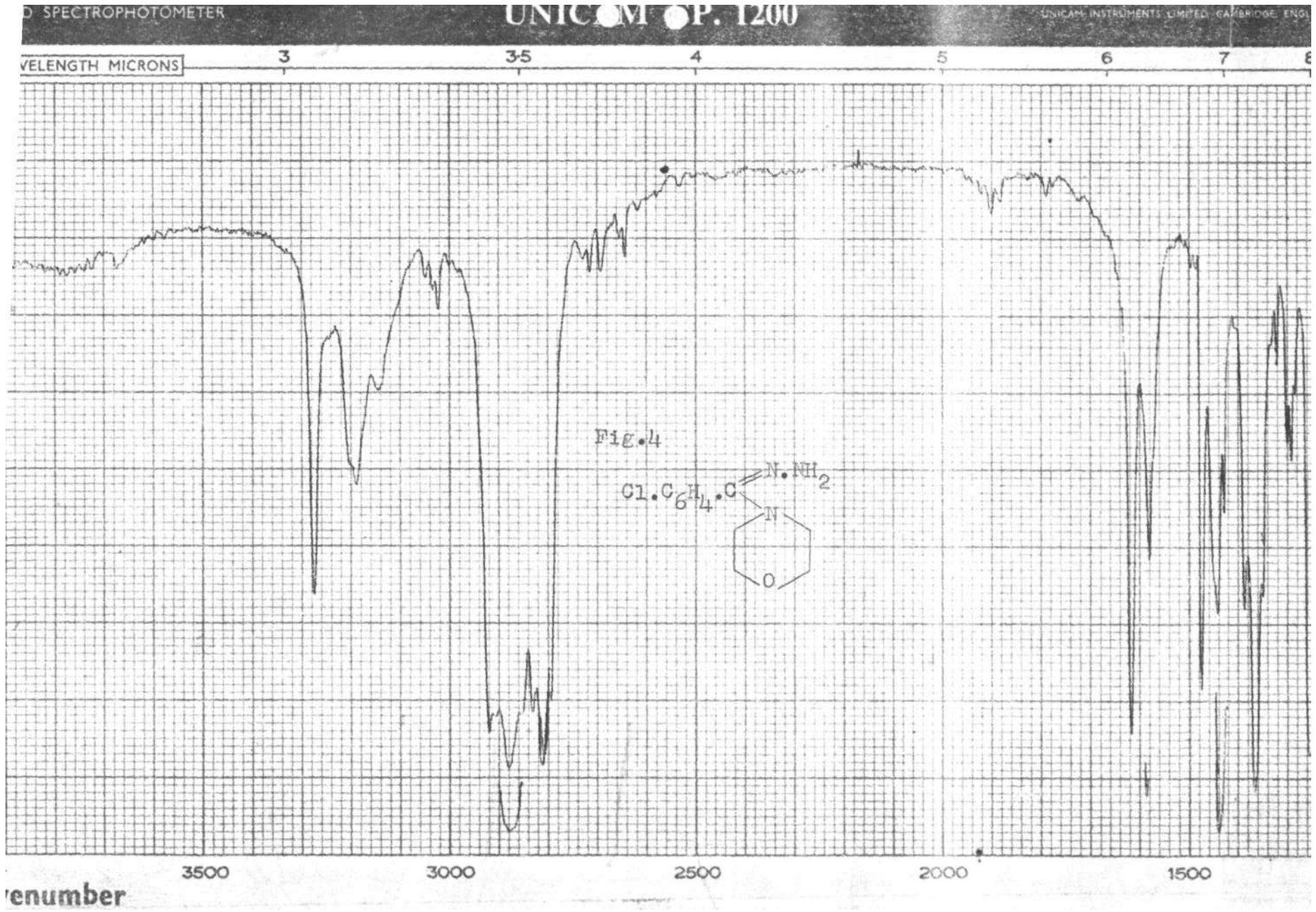

SPECTROPHOTOMETER
UNICAM SP. 1200
UNICAM INSTRUMENTS LIMITED CAMBRIDGE ENG
VELENGTH MICRONS
3
3·5
4
5
6
7
Fig.4
Cl.C6H4.C
N.NH2
N
O
3500
3000
2500
2000
1500
enumber

Fig. 2

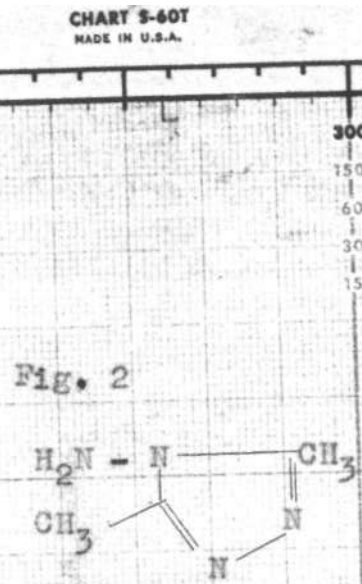
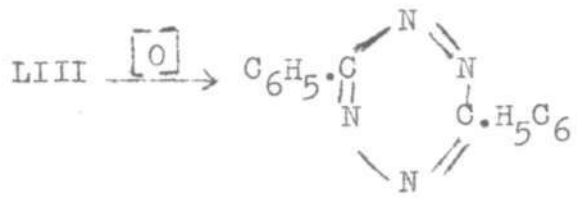


CHART 5-60T
MADE IN U.S.A.
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0

easily oxidised when exposed to air to give the tetrazine.



LIV

The tetrazines are deep red in colour whereas the dihydrotetrazines vary from colourless to yellow compounds.

We found it more convenient to oxidise the dihydrotetrazines by hydrogen peroxide: glacial acetic acid (2:1) mixtures, using 30% w/v 100v hydrogen peroxide.

Various dihydrotetrazines and their oxidation products were prepared and characterised by usual physical methods. (Tables 6 & 7).

As previously mentioned, thioamides are easily hydrolysed by acids and bases to the carboxylic acids or the amides, and nitriles can be prepared by elimination of hydrogen sulphide.

Thioamides undergo most of the reactions undergone by their oxygen analogues. The major differences between sulphur and oxygen compounds can usually be attributed to one of the following:-

(i) one more electron layer (shell) in sulphur, gives a smaller effective nuclear charge (smaller inductive effects) and greater electron mobility,

(ii) sulphur compounds have higher molecular weight and in some cases this is responsible for differences in physical properties,

(iii) whereas oxygen is unable to expand its valence shell there are indications that sulphur may do so; therefore, oxygen and sulphur analogues may react by different mechanisms.

The condensation with hydroxylamine giving an amidoxime has also been investigated[27].

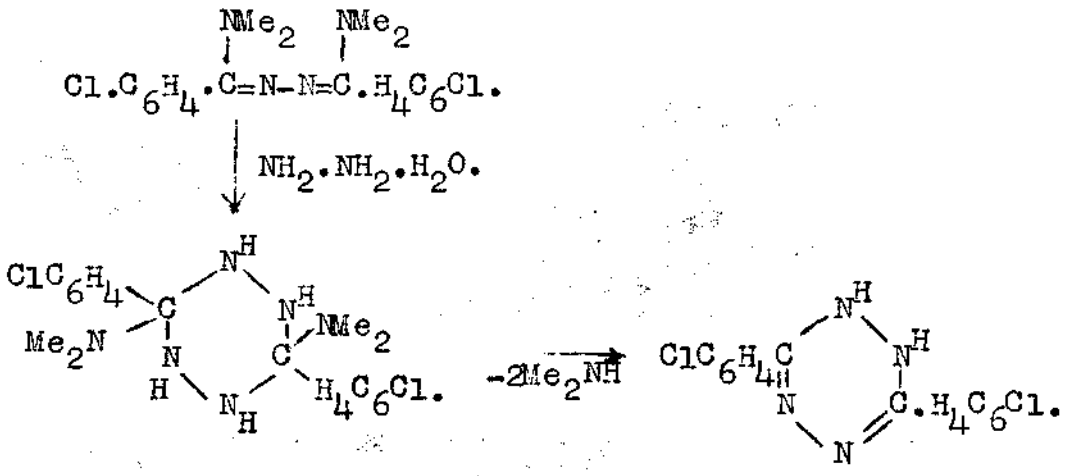
$$C_6H_5CSNH_2 + NH_2OH \longrightarrow C_6H_5\overset{\overset{NOH}{\|}}{C}.NH_2 + H_2S$$

The mechanism for the formation of the tetrazines will be illustrated by the reactions of p-chlorothiobenzdimethylamide at room temperature and at elevated temperatures.

Formation of the corresponding amidrazone involves condensation of the thioamide with a molecule of hydrazine. In the formation of the amidrazine another molecule of the thioamide condenses with the amidrazone formed. Finally a molecule of hydrazine attacks the amidrazine molecule

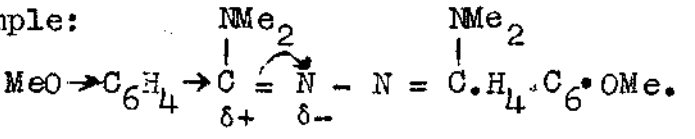
at the amino substituted carbon atoms forming the dihydrotetrazine.

In this reaction, hydrazine probably adds across the carbon-nitrogen double bond, forming a tetrahedral carbon intermediate, which then splits out dimethylamine.



The participation of the electron-donating substituents in the p-position of the aromatic rings has been mentioned. Considering the carbon-nitrogen double bond alone, since the nitrogen atom is more electronegative than carbon, the latter has a finite positive charge as a result of inductive effect. The effect of these electron-donating substituents is to strengthen the dipole moment which aids the nucleophilic attack of hydrazine at this carbon atom.

For example:



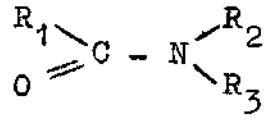
This might explain why only dihydrotetrazines and not the corresponding amidrazines and amidrazones were obtained. Electron-withdrawing groups e.g. the nitro- group would be expected to oppose the dipole hence making the reaction much less vigorous.

The halogens are known to be electron-withdrawing inductively, but electron-donating mesomerically. Hence they occupy an intermediate position between two extremes.

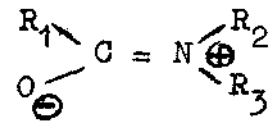
The relative rates of reaction, and even the extent might best be investigated through kinetic studies. It is not difficult however, to observe the very exothermic reactions of the thioamides with electron-donating substituents with hydrazine hydrate.

RESTRICTED ROTATION IN AMIDES[33] AND THIOAMIDES:

It is a well-known phenomenon that the n.m.r. spectra of tertiary amides exhibit separate signals for groups syn- or anti- to the carbonyl oxygen.



(I)

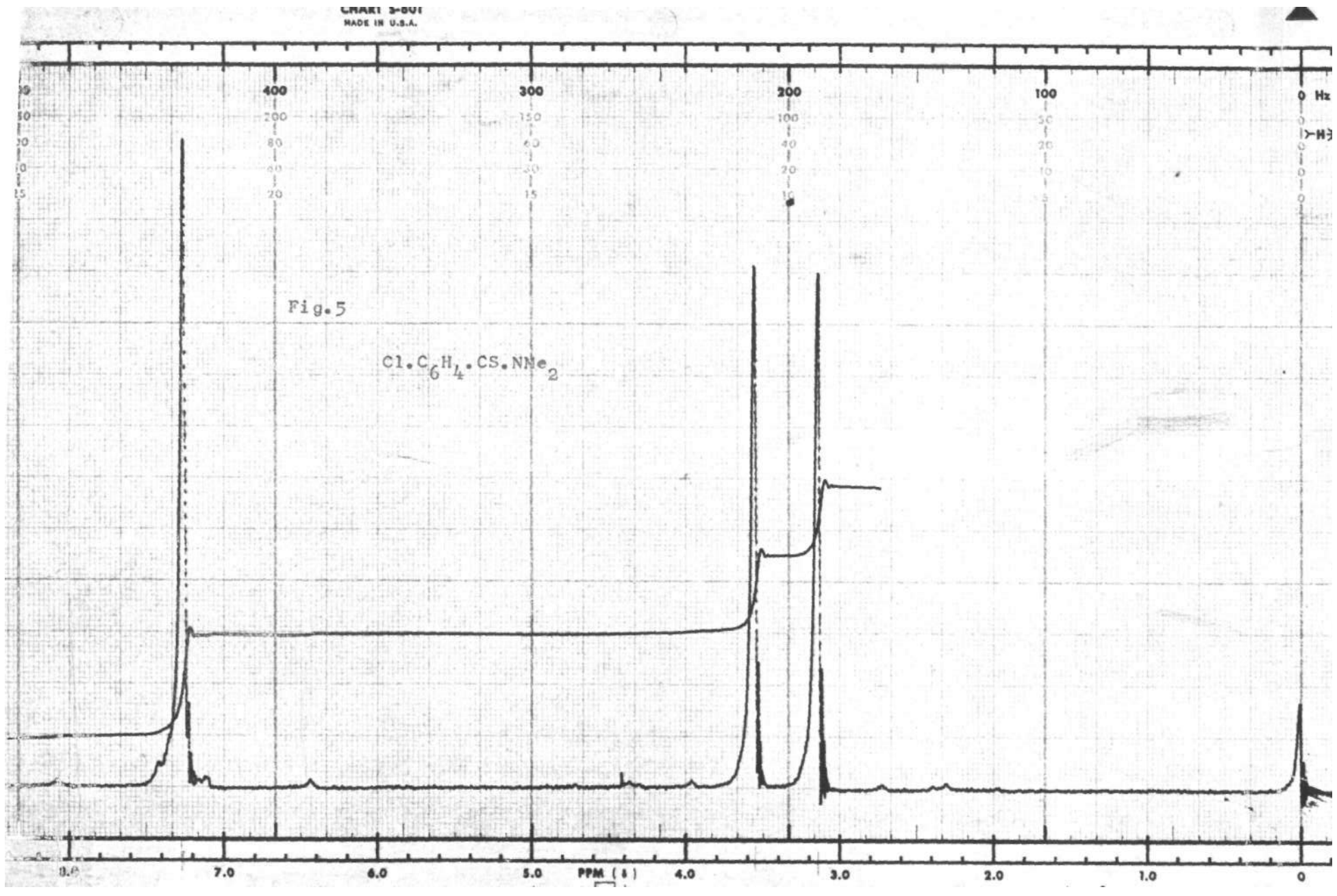


(II)

Structure (I) above is the conventional way of representing the amides but Pauling postulated that form (II)

Fig.5

$Cl.C_6H_4.CS.NMe_2$



with a nitrogen-carbon double bond makes a significant contribution to their electronic structure. The doublet absorption of the two methyl groups must be due to their non-equivalence.

The chemical shifts originate in difference in electronic environment of the nuclei, and such differences will occur if the double bonded form (II) makes a significant contribution to the structure of the amides. In this event, the skeleton of the molecule is co-planar, one of the methyl groups (R_2) is <u>trans</u> (anti) and the other (R_3) is <u>cis</u> (syn) to the oxygen atom.

The double bond provides a potential barrier to re-orientations about the -C-N- bond, and the hindrance to such internal rotation must be high so that the re-orientation rate is too slow, at room temperature, to average out the small resonance shift between the two methyl groups.

At high temperature the rate of re-orientation increases and the doublet coalesces to give a single line. Thus it is clear that the oxygen of the amide group contributes a significant amount of double bond character to the C-N amide bond.

We observed thioamides to show greater resistance to free rotation than amides. This may be due to steric

hindrance to rotation as a result of greater atomic radius of sulphur compared to oxygen. Since oxygen is more electronegative than sulphur, one might not expect the carbon-nitrogen double bond to be so great.

However, since the sulphur atom is capable of expanding its valence shell, the double bond character between carbon and sulphur in the thiocarbonyl moiety might be small, thus enhancing the double bond character of the carbon-nitrogen bond.

We observed a particular case in which a single peak was given by the two methyl groups on the nitrogen atom of the amide, whereas two peaks were observed for the sulphur analogue (Figs. 5 & 10).

ATTEMPTED PHOTOLYSIS AND THERMOLYSIS OF THE TETRAZINES:

Photolysis[34,35]

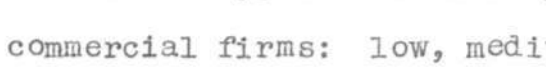
Photo-elimination proceeding by bond homolysis, with the concomitant elimination of a neutral molecule is well known. Reactive intermediates are formed in most cases. For example, molecular nitrogen is readily lost from organic azides on photolysis to give nitrenes which undergo subsequent intra- and inter- molecular reactions.

Molecular nitrogen is also eliminated in both thermal and photochemical reactions to form carbenes which can

undergo insertion and addition reactions. Methylene is also obtained by thermolysis or photolysis of diazomethane, and photolysis of ketene and diazirine

$$CH_2N_2 \xrightarrow[\text{or } \Delta]{h\nu} :CH_2 + N_2.$$

$$CH_2{=}C{=}O \xrightarrow{h\nu} :CH_2 + CO.$$



Most organic photochemical reactions have been investigated in the wavelength region from 200-380nm; although many photooxidation reactions are brought about by visible light. Mercury lamps are used to cover this range.

There are three types of such lamps which are obtainable from commercial firms: low, medium and high pressure lamps.

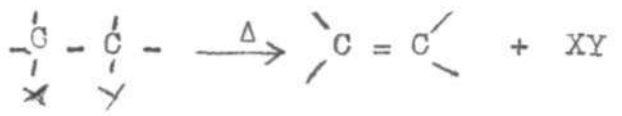
An attempt was made to degrade the tetrazines by the photochemical method using a medium pressure mercury lamp (internal or immersion) and by an external lamp (250-watt tungsten electric bulb). The latter allows the source of light to be placed outside the reaction vessel to bring about the photochemical reaction. The photolysis was attempted in an atmosphere of nitrogen and when no evidence of degradation was observed, a few crystals of

benzophenone were added as a sensitizer, but no decomposition was observed to take place.

Pyrolysis[36]:

During melting point determination of one of the tetrazine derivatives (XLIV) it was observed to decompose with formation of gas bubbles and the red colour of the compound disappeared. This appeared to be due to thermolysis.

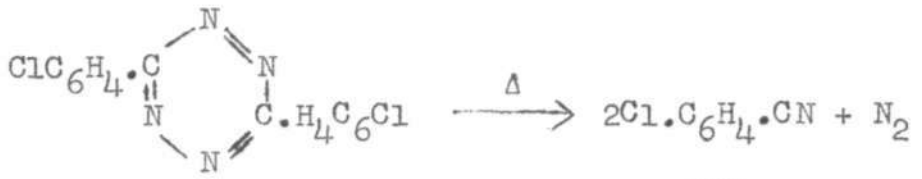
A number of organic molecules fragment when heated with the formation of an olefin or some reactive intermediate (cf. photolysis). Some of such eliminations have been investigated and have been found to be of some synthetic utility; for example, the reactions are often the method of choice for the introduction of unsaturation under mild conditions.

e.g. 

It has been observed that the products formed in pyrolytic eliminations often differ appreciably in composition from those formed in other types of eliminations, for example, photolysis. It has also been found that pyrolytic eliminations take place by a unique steric course. The groups involved must then be cis-coplanar for maximum

overlap of breaking and forming bond orbitals. Simple products are formed unlike under other eliminating conditions.

On heating the 3,6-bis(p-chlorophenyl)-1,2,4,5-tetrazine (XLIV) and its p-bromophenyl analogue, a colourless sublimate was obtained from each compound, and later characterised as the p-chloro-, and p-bromo- benzonitriles[37]. Other phenyltetrazine derivatives with electron-donating substituents were found to be stable to heat under the conditions employed. To investigate further the participation of ring substituents on degradation of these compounds, the p-nitrophenyl tetrazine analogue was prepared but could not be degraded under the same conditions.

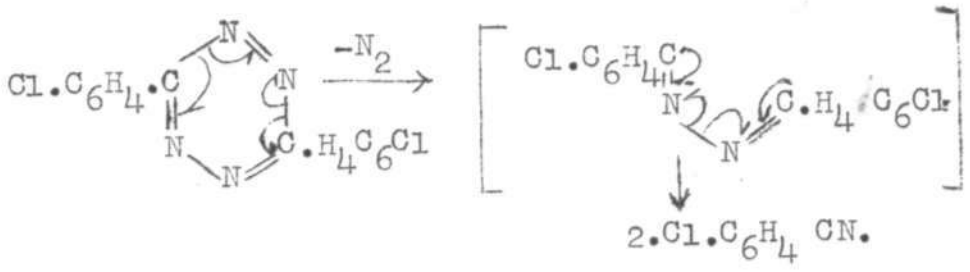


XLIV LV

Hence only a molecule of nitrogen was lost. The p-chloro- and p-bromobenznitriles have been characterised by comparison of their physical constants with literature[37] values (Table 8).

We thought that the degradation of 3,6-bis(p-chlorophenyl)-1,2,4,5-tetrazine and its p-bromo- analogue

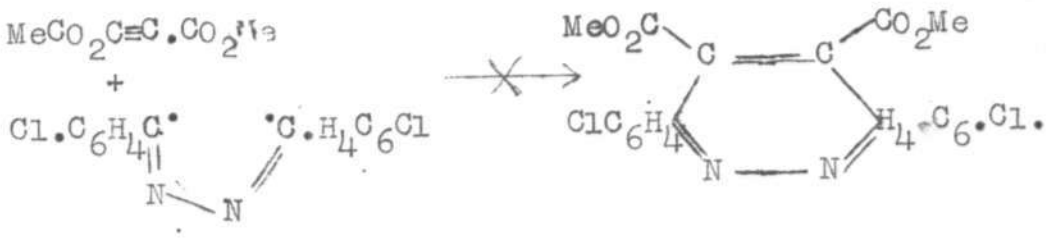
involved formation of a diradical intermediate after the loss of a molecule of nitrogen per molecule of the tetrazine.



The diradical would then be formed as a result of homolytic fission of two carbon-nitrogen single bonds as shown.

p-Chlorobenzonitrile would then be formed also as a result of homolytic fission of nitrogen-nitrogen single bonds.

An attempt was made to trap this diradical, if formed, by degrading the molecule in presence of dimethyl acetylenedicarboxylate which is often used as a trapping agent. The product expected would have been the following addition compound.



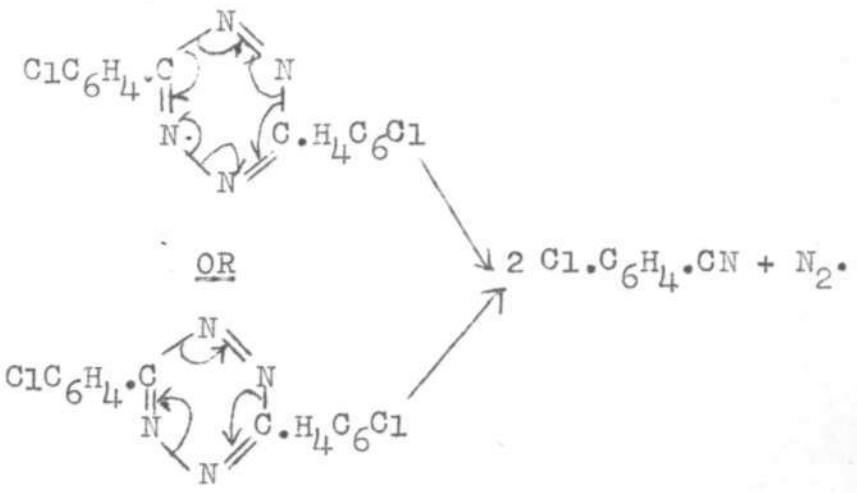
This attempt was not successful. This may not mean that the reaction is impossible, but under our reaction conditions, one could not heat the mixture of the dimethyl acetylenedicarboxylate and the tetrazine to the temperature degradation was observed to take place. If the reaction is done in a sealed tube, it might be possible to isolate the expected addition product. This may, however, not be a good method since explosion might occur as a result of liberation of nitrogen gas during the reaction.

An argument supporting the view that the diradical may not have existed as an intermediate is that if it was formed, it may have been possible that a carbon-carbon bond could be formed from the diradical involving formation of a four membered ring as follows:-



No such product was isolated or detectable upon work-up and even if formed would be unstable as a result of ring strain, and for electronic reasons.

A one-step or concerted mechanism is then proposed for the degradation involving a homolytic or heterolytic fission of two carbon-nitrogen bond as follows:-



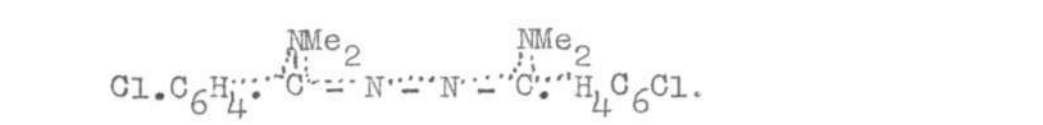
OXIDATIVE CLEAVAGE OF THE AMIDRAZINES:

Oxidative cleavage of aromatic azines with periodic acid is known[38]. On treatment of aromatic and heterocyclic azines with periodic acid at room temperature, brisk evolution of nitrogen was observed in all cases investigated indicating the lability of the hydrazino moiety (>C=N-N=C<) of the azines towards this reagent. Parent aldehydes or ketones were obtained in high yields. Aromatic azines have also been cleaved using peroxyacetic acid.

Photolysis of azines in the presence of oxygen is known to give nitriles[39] and olefin is obtained from pyrolysis of benzalazine.

Since our amidrazines could be considered derivatives of benzalazine, we tried reacting the amidrazine with periodic acid. However, no decomposition occured.

The stability to oxidative cleavage is rationalized in terms of the conjugative effect of the system. The lone-pair electrons on the nitrogen atoms of the dimethylamino substituents can be considered to be involved in conjugation with the hydrazino moeity. Thus the whole carbon-nitrogen chain is embedded in a cloud of electrons. The conjugation is further strengthened by



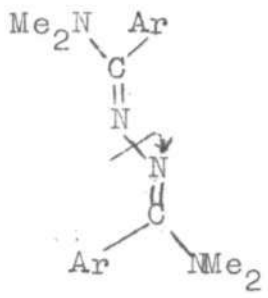
the aromatic ring system.

Transition-metal Complexes:

The amidrazines would be expected to form transition-metal complexes in which the Π-electrons of the carbon-nitrogen double-bond and the non-bonded electrons on the nitrogen would participate.

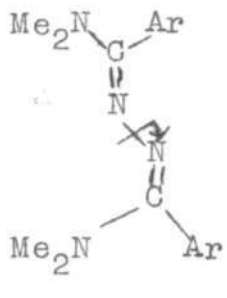
Of great importance is the relative orientation of the orbitals of the non-bonding electrons with respect to those of the empty or acceptor orbitals of the metal atom.

The following are the geometrical isomers of the amidrazines. Whichever of the structures predominates might be due to steric effects of the large substituent groups.



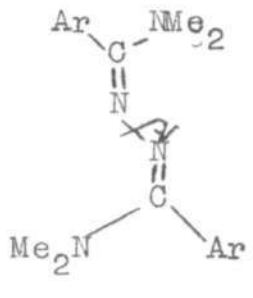
(a)

anti-anti



(b)

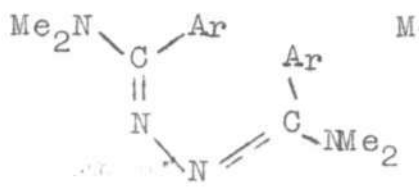
syn-anti



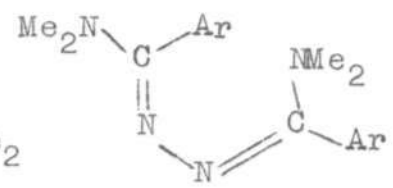
(c)

syn-syn.

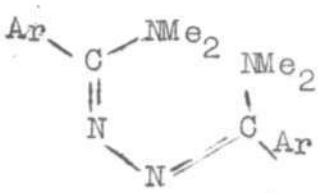
The structure (c) is the mirror image of (a). The cisoid structures are obtained by rotating the nitrogen-nitrogen single bond along the axis shown. The structures (d), (e), and (f) are then obtained by rotation of (a), (b) and (c) respectively.



(d)



(e)



(f)

As mentioned earlier, the relative amounts of any of the isomers may depend largely on the steric effects

of the bulky substituents. However, since rotation is relatively easy and possible along the nitrogen-nitrogen single bonds, the molecules are expected to assume a configuration in space with minimum interaction of the substituents.

They are geometric not structural isomers. When the system is compared to simpler systems in unsaturated hydrocarbons, (a) may be described as trans/trans, (b) trans/cis, whilst (c) cis/cis. However, on comparison with oxime systems, (a) may be described as anti/anti, (b) syn/anti, whilst (c) is syn/syn.

As mentioned earlier, if the carbon-nitrogen double bond and the lone pair on nitrogen atoms contribute to the formation of a metal complex, a structure comparable to the ones given below may be expected.

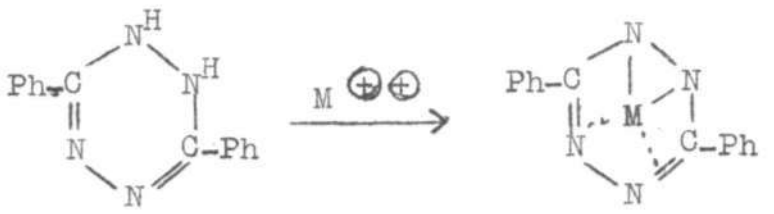


(i) (ii)

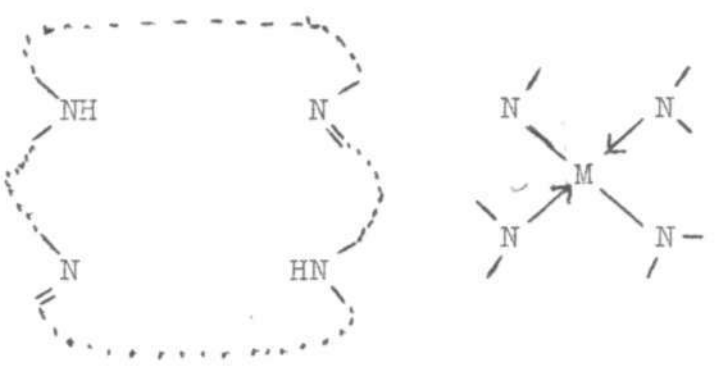
Structure (i) may be expected if the complex formation involves only the carbon-nitrogen double-bond. If however, the aryl groups participate the structure (ii) might be possible, and may be a method of stabilizing the

cisoid structure (d). Not much work has yet been done in this respect but it is hoped that a complex can be obtained.

The diaryldihydrotetrazines were also thought to be capable of behaving as ligands comparable to porphyrins e.g. chlorophyll or heamoglobin.



Compare



A Porphyrin system.

A few salts have been tried, no co-ordination compounds have been obtained, though in one case, using a mercury salt, the dihydrotetrazine was oxidised to the tetrazine almost immediately. The reactions may be feasible under vacuum conditions or under nitrogen. The work is still in progress.

REACTIONS OF S-ALKYL QUATERNARY SALTS WITH SODIUM BOROHYDRIDE:

Sodium borohydride has been widely used in organic synthesis as a reducing agent. It is often used as its aqueous or alcoholic solution which has been observed to effect remarkably efficient and specific reduction of aldehydes, ketones and acid chlorides[40].

In the present work, an aqueous solution of sodium borohydride was cooled in an ice-bath and, while stirring magnetically, the quaternary salt was added a little at a time. A strong smell of methanethiol was evident. A solid was formed and was filtered off, washed and dried. It was characterised by physical methods and by elemental analysis.

For example, when thiobenzdimethylamide methiodide was reacted with sodium borohydride, NN-dimethylbenzylamine borane was obtained.



XXX LVI

A series of similar reactions was carried out using different quaternary salts and excess of the sodium borohydride(Table

All derivatives prepared were nicely crystalline and appear quite stable.

N,N-Dimethylbenzylamine borane (LVI) has been prepared[41] by reacting diborane with N,N-dimethylbenzylamine in dry tetrahydrofuran.

Our method is preferable since diborane is a poisonous, spontaneously inflammable gas, and difficult to handle.

p-Dimethylaminothiobenzomorpholide methiodide, (XXXV) was also reacted with sodium borohydride to find whether hydroboration would occur on the more sterically hindered nitrogen of the morpholino group. It also seemed that it might be possible to hydroborate the dimethylamino group on the aromatic ring. From the elemental analysis of the resulting product, it was evident that there was no hydroboration of the dimethylamino group. This is not surprising since the lone pair electrons on the dimethylamino nitrogen are involved in resonance with the aromatic ring, and if hydroboration had also taken place on the morpholino nitrogen atom, then two partial positive charges would have been created on same molecule, which is unlikely.

In the reaction of p-dimethylamino thiobenzdimethylamide methiodide (XXX) with sodium borohydride, again

only the aliphatic dimethylamino group was hydroborated.

In each of the experiments carried out, some oil was formed.

In the reaction of p-chlorothiobenz dimethylamide methiodide, the oil was extracted in ether and was later characterised as p-chlorobenzylamine. Thus the other similar oils may well have been the corresponding amine derivatives.

REACTIONS OF ALKYLAMINE BORANES:

Dimethylamine borane[42] has been used to reduce a number of Schiff bases with various functional groups such as chloro, nitro, methoxy, ethoxycarbonyl, sulphonamido and carboxy groups, to their respective secondary amines. The reduction was done in glacial acetic acid. The yields of the secondary amines were quite high and ranged from 80-97%.

It was interesting however, to note that none of the other functional groups were affected under the reaction condition.

$$Ar - CH = N - Ar' + (CH_3)_2NH \rightarrow BH_3$$

$$\downarrow \quad \text{Glacial Acetic Acid.}$$

$$Ar.CH_2.NH.Ar'.$$

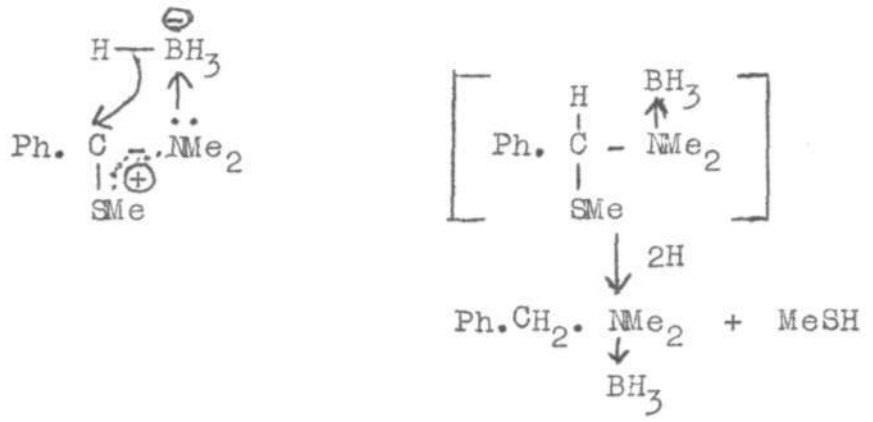
The ease and speed with which this reduction takes place is considered comparable if not better than reductions using sodium borohydride or lithium aluminium hydride. The reaction takes place in a matter of minutes at about room temperature. The fact that glacial acetic acid can be used is interesting and important in that reductions may now be performed in an acid medium. This cannot be done with any of the hydrides e.g. lithium aluminium hydride or sodium borohydride.
Since in the conditions used in the experiments, the nitro, carboxy, sulphonamino- etc groups were not affected, dimethylamino borane must then be similar to sodium borohydride.

The various alkylamine boranes prepared in this report (Table 9) may not be expected to give similar reduction reactions as a result of steric hindrance.

The alkylamine boranes with concentrated hydrochloric acid were found to generate bubbles of diborane and, neutralisation with dilute sodium hydroxide an oil, supposedly the amine, was obtained.

They all ignite when in contact with a hot surface. The lower alkylamine boranes have been observed to ignite in air as diborane itself.

The reduction mechanism may involve either a co-ordination of the borohydride ion with the nitrogen of the S-alkyl quaternary salt followed by an intra-molecular hydrogen transfer from boron to carbon (i.e. the carbonium ion of the quaternary salt) after which the proposed intermediate is further reduced by removal of methanethiol supposedly by the hydrogen generated in the aqueous medium, or a direct intermolecular hydride transfer from the borohydride to the carbon atom of the quaternary salt.



The latter intermolecular hydride transfer mechanism might suggest possible formation of borane which could then either co-ordinate to the nitrogen atom or dimerise to give diborane. There is, however, no evidence for or against the formation of diborane. It was however observed that even using excess sodium borohydride some free amine was produced. This may suggest possible formation of

diborane and a competition between hydroboration and dimerisation may explain the formation of the free amines. It may also mean that the amines would not react with diborane under these reaction conditions to give alkylamine boranes.

This may not be surprising since the conditions for reductions with diborane do not exactly parallel those for sodium borohydride. The latter is a nucleophile and reacts by addition of hydride ion to the more positive end of a polarised multiple bond. Diborane, however, is a Lewis acid and only attacks electron rich centres.

The spectra of these alkylamine borane compounds are worthy of note. The n.m.r. spectra obtained with the Varian T-60 Instrument (Fig. 6) show no protons attached to boron, and the presence of a BH_3 group could only be confirmed from the i.r. spectra (Fig. 7) and by elemental analysis (Table 9). Boranes have characteristic absorption between 2290-2530 cm^{-1} ascribed to the B-H vibrations.

Boron itself (^{11}B) with spin $^3/_2$ should be detectable on higher resolution instruments. The special problems which arise to a greater or lesser degree in applying high resolution techniques to measurements of this nucleus and others (e.g. ^{13}C, ^{14}N, ^{17}O, ^{29}Si, ^{31}P and ^{33}S and the halogens) are due to:-

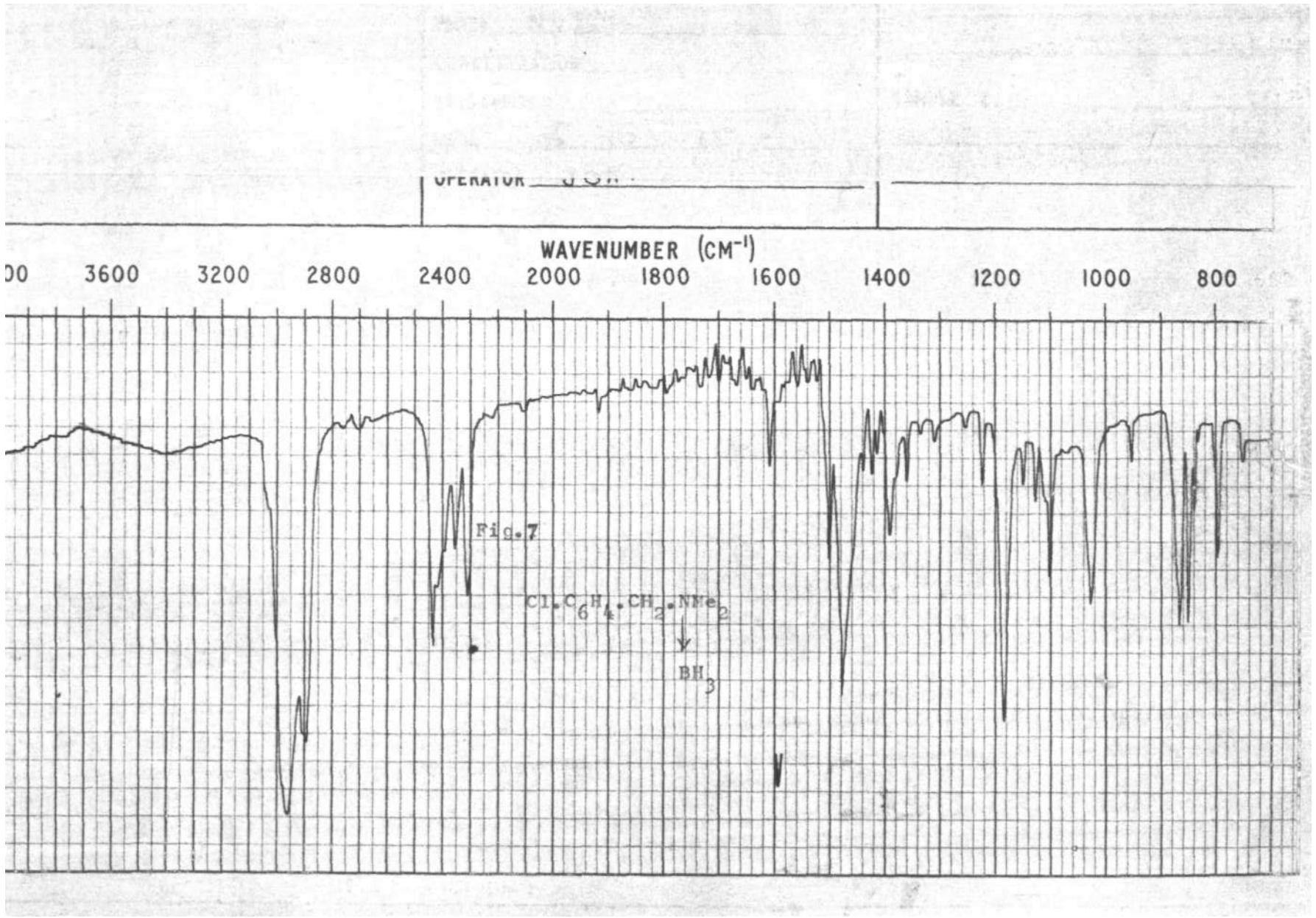


Fig.7

$Cl.C_6H_4.CH_2.NMe_2$

$\downarrow$

BH_3

(i) low signal strengths, which may be further reduced by

(ii) low isotopic abundance of the particular magnetic nucleus,

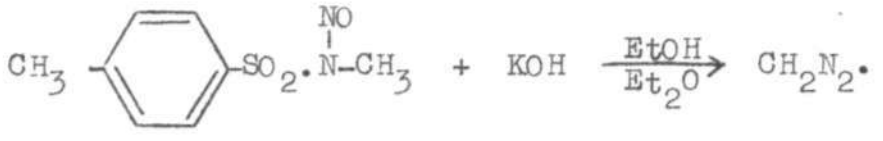
(iii) a nuclear electric quadrupole moment which may cause excessive signal broadening and

(iv) an unfavourably long spin-lattice relaxation time.

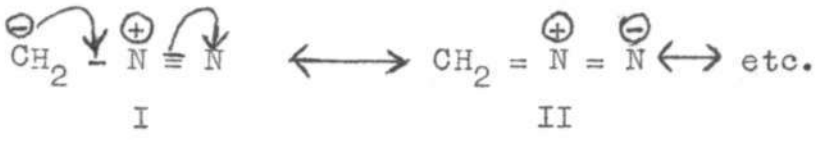
From the foregoing, the absorption may well have been so broad that protons attached to boron could not be detected at this level of resolution. The coupling between proton and boron (^{11}B). J_{B-H} (direct), is found to vary between 80-90 Hertz.

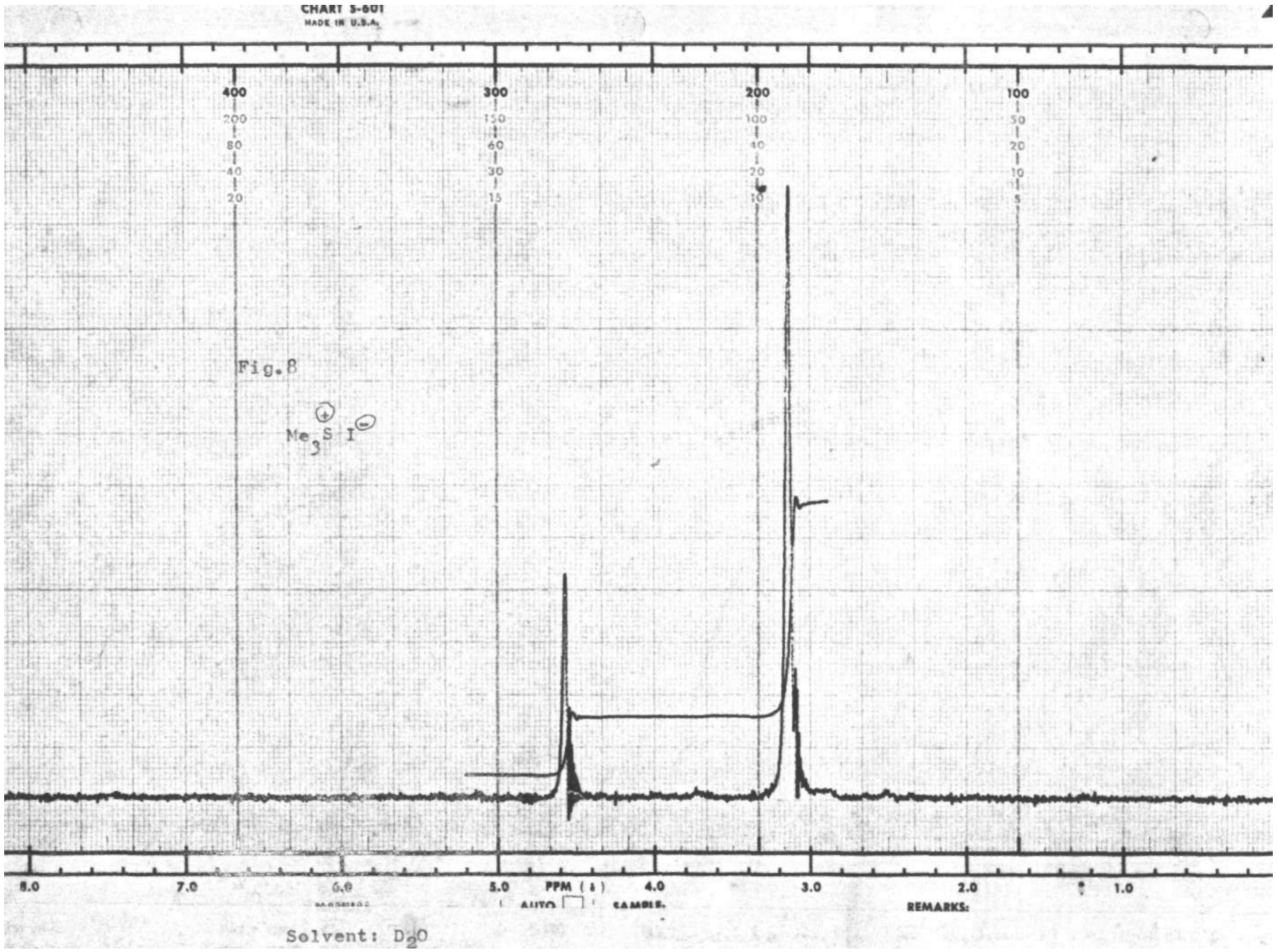
ATTEMPTED REACTION OF DIAZOMETHANE WITH AN N-ALKYLQUATERNARY SALT:

Diazomethane for this reaction was generated from N-methyl-N-nitroso-p-toluene-sulphonamide (Diazald).

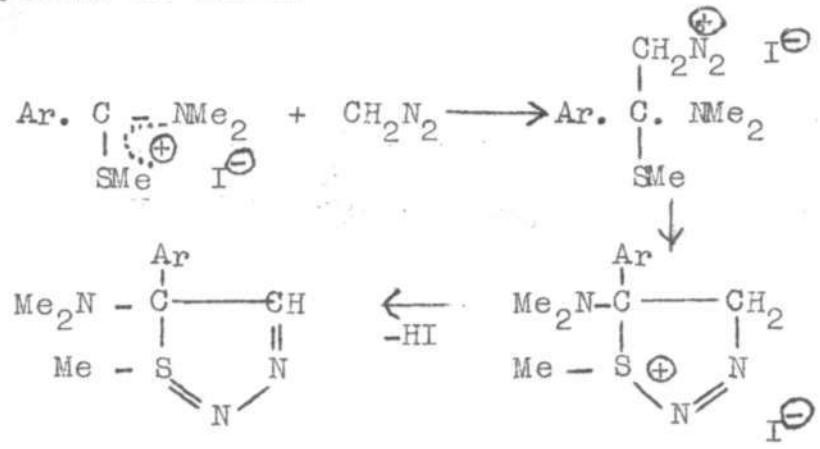


From the different contributing structures, the carbanion (I) is expected to attack the positive centre of the quaternary salt,




CHART 5-601
MADE IN U.S.A.
400
200
80
40
20
300
150
60
30
15
200
100
40
20
10
100
50
20
10
5
Fig.8
Me3S I
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
REMARKS:
Solvent: D2O

giving first of all a tetrahedral intermediate which might cyclize as shown.



Ar = p - $Cl.C_6H_4$-

There was no evidence that the expected product was formed; instead three compounds were isolated from the crude product by column chromatography.

The first was a colourless water-soluble solid, which was characterised as trimethyl sulphonium iodide, both from its n.m.r. spectrum and comparison with an authentic sample (Fig. 8).

Another product obtained from the first fraction from the column, was a low melting solid, an oil at room temperature which showed from its n.m.r. (Fig. 9) and i.r. spectra that it was probably a mixture of the S-methyl and a little S-ethyl thiol ester formed by hydrolysis of the quaternary salt.

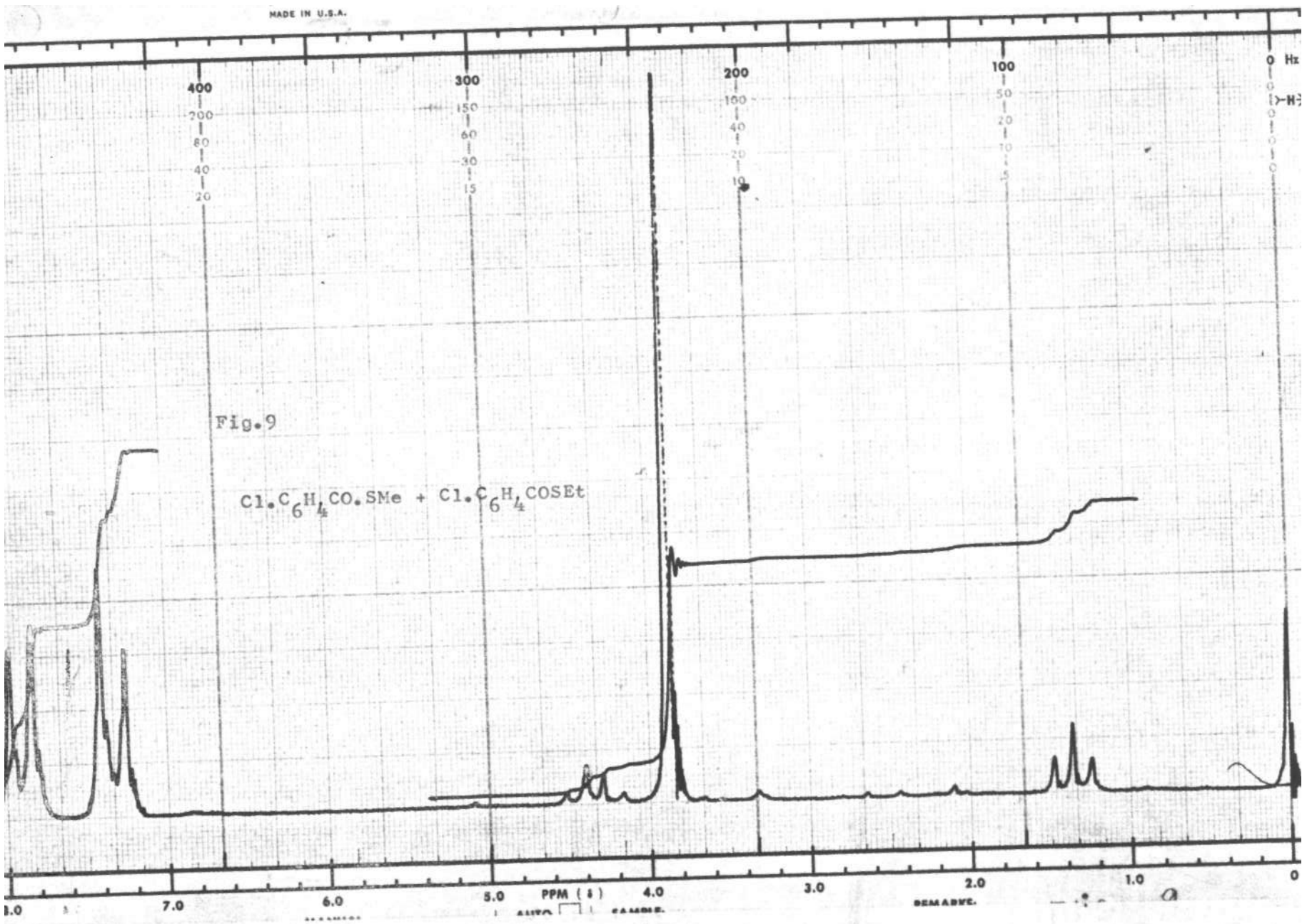
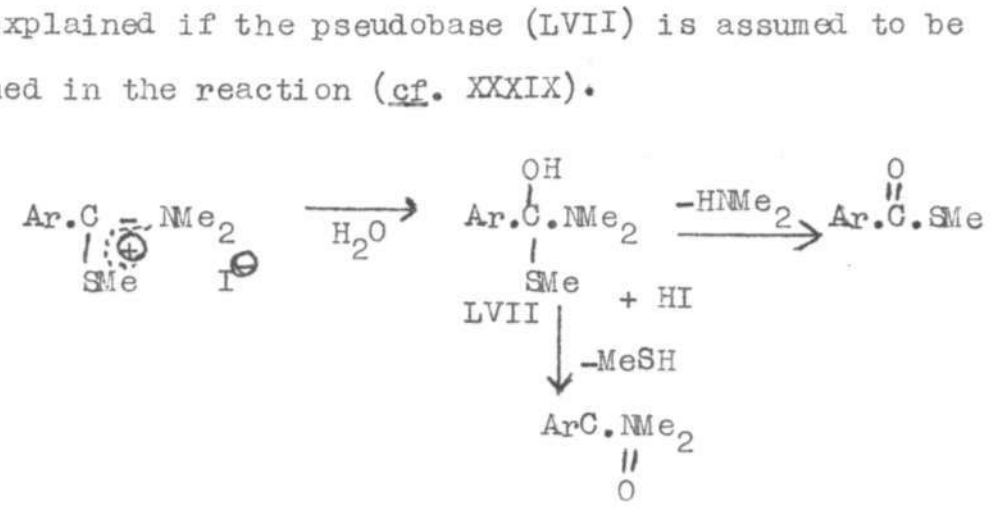


Fig.9

$Cl.C_6H_4CO.SMe + Cl.C_6H_4COSEt$

The third product was characterised by n.m.r. and i.r. spectra and comparison with an authentic sample as p-chloro-benzodimethylamide (Fig. 10). From the foregoing, it appears that only the hydrolysis products of the quaternary salt were obtained, with the diazomethane reacting with some of the by-products with evolution of nitrogen that was also evident from the reaction.

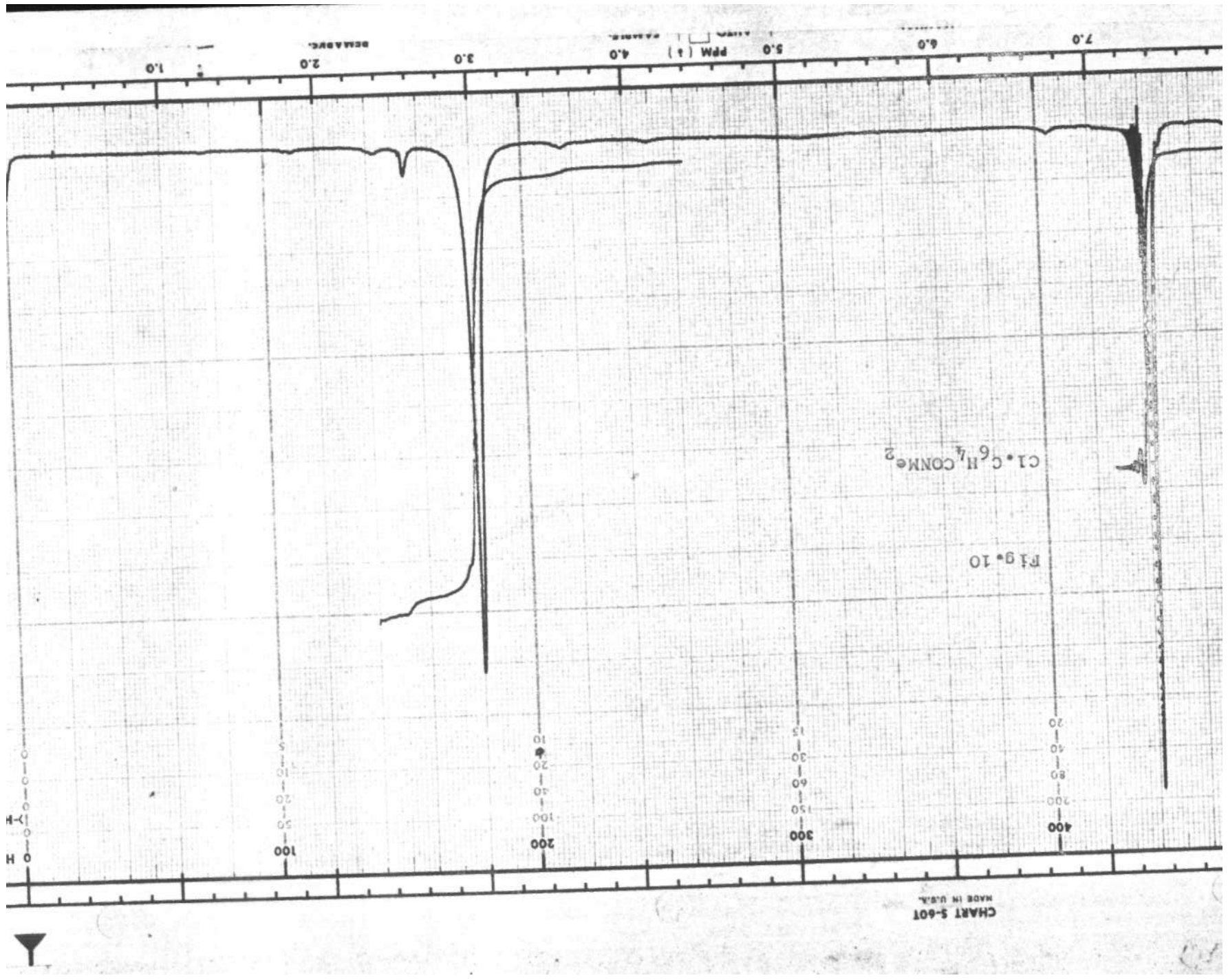
The formation of the thiol ester, and the amide might be explained if the pseudobase (LVII) is assumed to be formed in the reaction (cf. XXXIX).



The generation of nitrogen during the reaction could be explained by reaction of hydrogen iodide, dimethylamine or methanethiol with diazomethane.

Iodomethane and dimethylsulphide both generated *in situ* might react to give the trimethylsulphonium iodide.

$$Me_2S + MeI \longrightarrow Me_3S^{\oplus}\ I^{\ominus}.$$

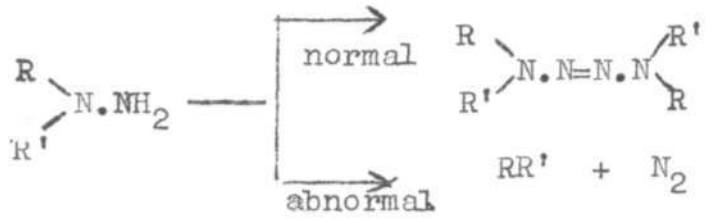

c1.c6H4CONMe2
Fig. 10
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM (δ)
100
200
300
400
CHART S-60T
MADE IN U.S.A.

There is no doubt that the ethereal diazomethane solution contained some moisture, since water was present in the mixture from which it was generated and since methanol is hygroscopic.

It might be possible to isolate the expected cyclic addition product of the diazomethane to the quaternary salt, if the reaction could be carried out in anhydrous conditions. Cooling of the reaction mixture in an ice-bath no doubt reduced the volatility of otherwise volatile by products, namely dimethylsulphide and iodomethane.

OXIDATION OF 1,1-DISUBSTITUTED HYDRAZINES:

The oxidation of 1,1-disubstituted hydrazines[43,44] with yellow mercuric oxide and lead tetra-acetate has been carried out on a number of compounds.



The abnormal oxidation of hydrazones to coupled and olefinic products and nitrogen has been studied. A diazo-like intermediate (g) (an aminonitrene) has been postulated to

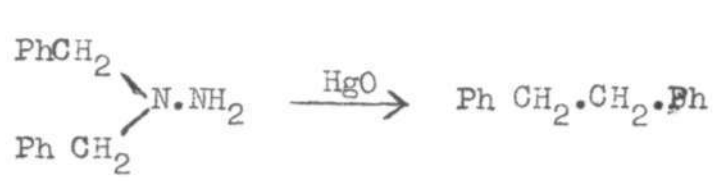
explain the formation of the observed products.



(9)

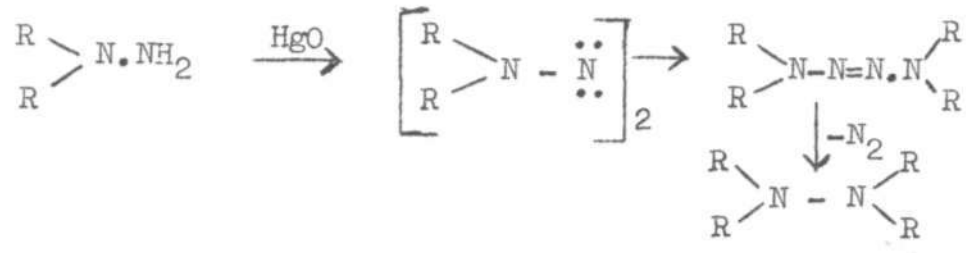
The collapse of the intermediate nitrene may proceed via radical or ionic paths with considerable contribution from the former.

For example, in the oxidation of 1,1-dibenzylhydrazine by mercuric oxide, dibenzyl was obtained[45].

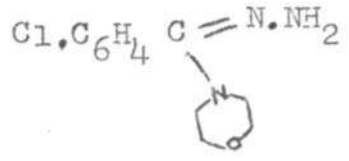


It was concluded that the mechanism did not involve either the tetrazene or the azo compound, $PhCH_2N{=}N.CH_2Ph$ but that the reaction is intramolecular since no crossed products were obtained with unsymmetrical hydrazines. Loss of nitrogen from the nitrene might be concerted with the formation of the coupling product.

As mentioned above the normal oxidation product is the tetrazene which forms a tetra-alkylhydrazine derivative by loss of nitrogen.

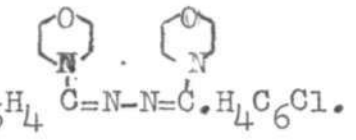


With the possibility of this reaction in mind an attempt was made to oxidise the amidrazones, i.e. compounds obtained from the reaction of hydrazine hydrate with some thiobenzomorpholide derivatives at room temperature e.g.



T.l.c. of the crude oil product showed it contained several components but it was evident that there was a major fraction with a relatively high R_f value when petroleum ether (b.p.60-80°) and ethyl acetate (7:3) solvent mixture was used. The components were then separated by column chromatography on silica gel.

Two major fractions were obtained, the first being a low melting solid, whereas the second was high melting colourless solid. The melting point, mixed melting point, n.m.r. and i.r. spectra showed the latter to be the amidrazine, a type of compound obtainable from the reaction of S- alkylquaternary salts with hydrazine hydrate e.g.

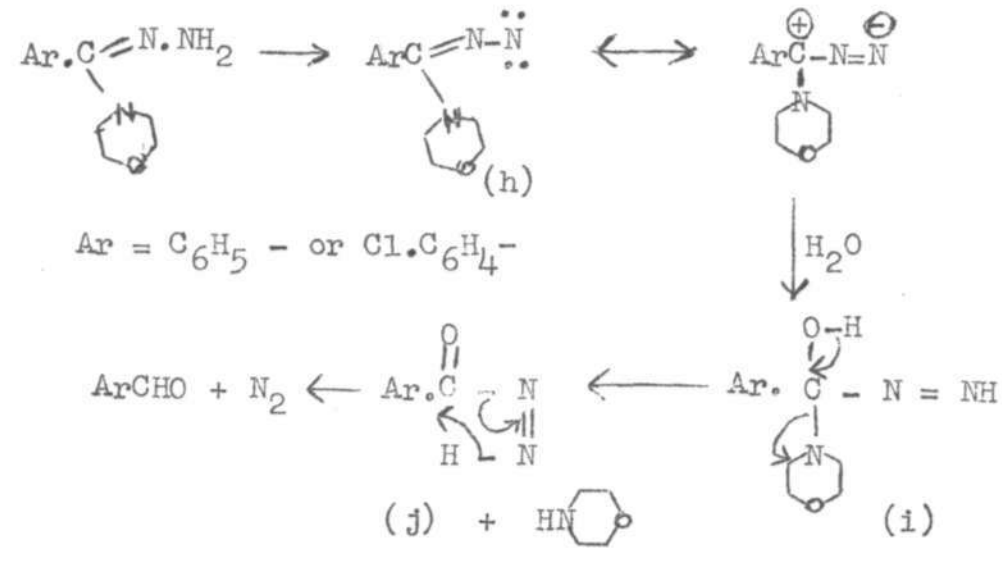


The first compound isolated from the column was characterised as 4-chlorobenzaldehyde, the n.m.r. and i.r.

spectra and melting point being in agreement.

The following mechanism might explain the formation of the aldehyde:

The amidrazone (LII) may be converted to a nitrene (h) whose ionic form may contribute to the formation of the aldehyde. This adds on a molecule of water, which is one of the products of the oxidation reaction, to form a tetrahedral intermediate (i) which loses morpholine to give the aroyldiimide intermediate (j). By a 1,3-hydride shift, the latter loses nitrogen and forms the aldehyde.



1,3-Hydride shifts are postulated in several reaction mechanisms for example, the Wolff-Kishner reduction. The aroyldiimide (j) has also been postulated to be an

intermediate in the lead tetracetate oxidation of aroyl-hydrazines to the corresponding carboxylic acid[46].

Diimides are known to be produced from mercuric oxide oxidation of hydrazines and are known to reduce olefins, alkynes, and azo compounds.

The production of the aldehyde may be avoided if the reaction is done in the presence of a drying agent e.g. anhydrous sodium sulphate, which would remove the water immediately it formed, however, the yield of the aldehyde may be enchanced if an aqueous medium was used, for example, aqueous methanol.

In fact, in the mercuric oxide oxidation of hydrazones, it has been established[43] that the oxidation was catalysed not only by alkali, but initially also by traces of water. Our reaction was observed to be more rapid in benzene or petroleum ether than ether. Silver oxide reagent was also found to be distinctly inferior to yellow mercuric oxide.

The amidrazine might be formed from the corresponding tetrazene obtained as a 'normal' product of oxidation of the amidrazone (cf. hydrazones). The tetrazene would be formed by the coupling of the nitrene intermediate. Hence the nitrene structure is thought to contribute to the

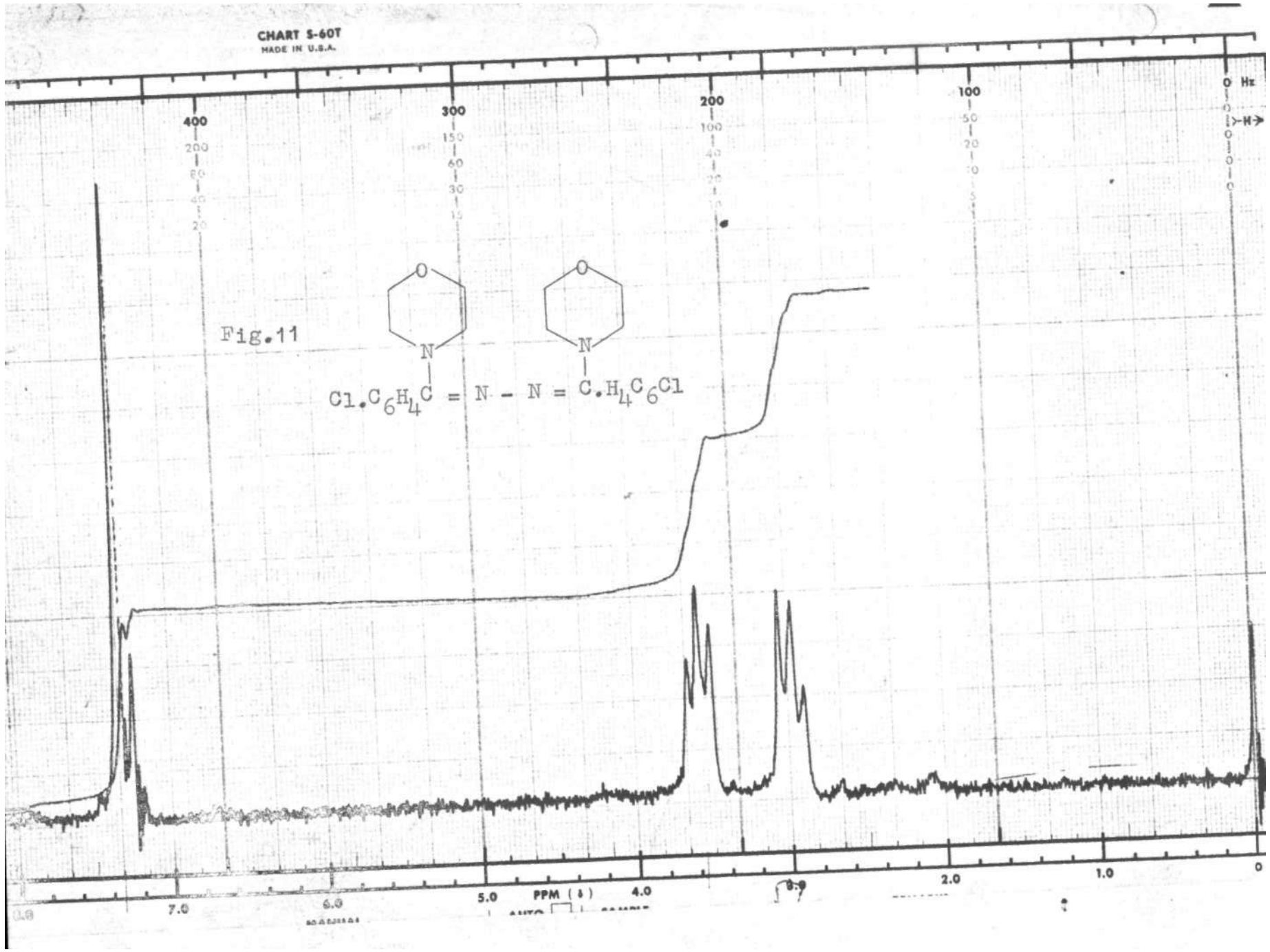
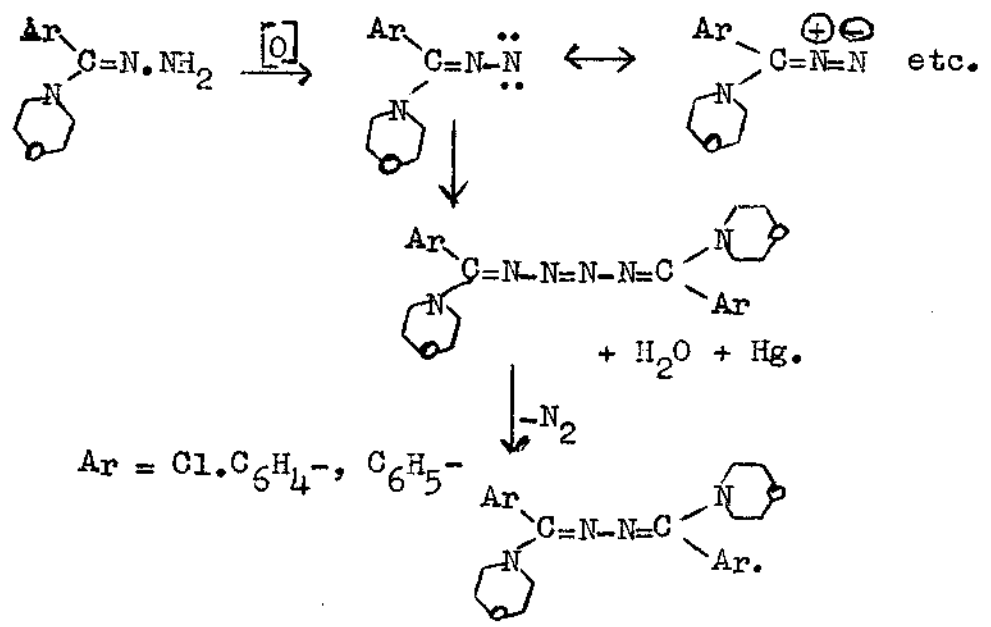


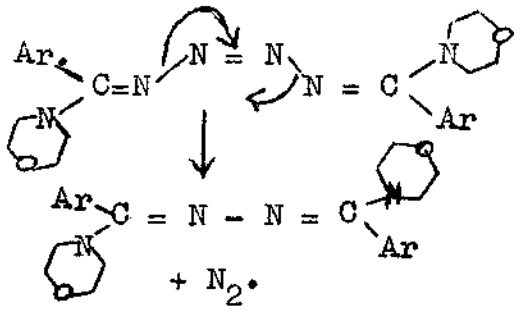
Fig.11

$Cl.C_6H_4C = N - N = C.H_4C_6Cl$

formation of the tetrazene. The amidrazine (Fig. 11) would then be formed by loss of a mole of nitrogen per mole of tetrazene.

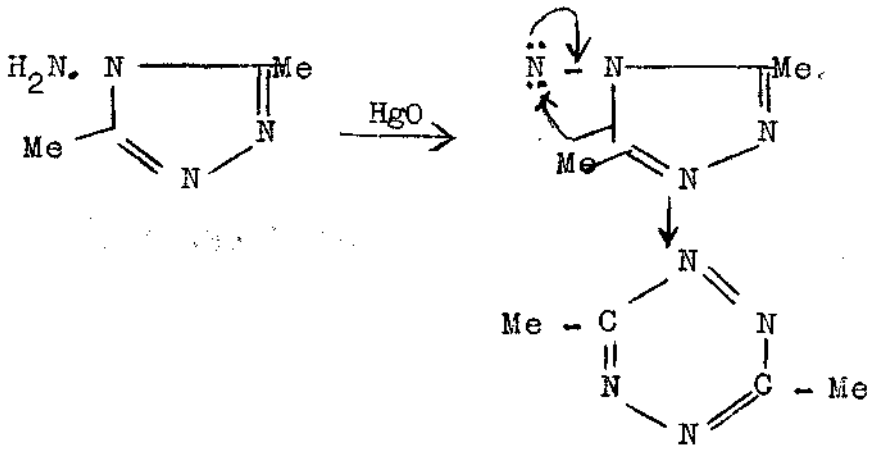


Loss of nitrogen and formation of the amidrazine might be a concerted process as follows:-



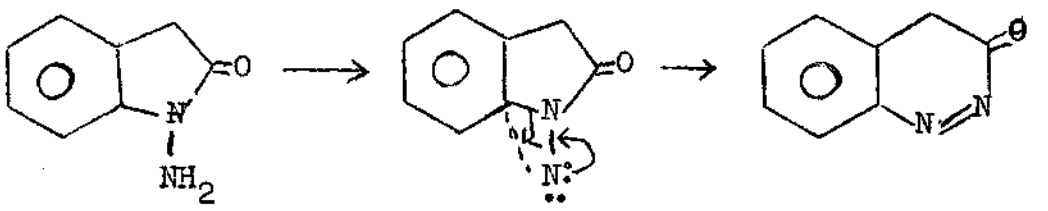
An attempt was also made to oxidise 4-Amino-3,5-dimethyl-1,2,4-triazole (XLIX) with mercuric oxide. This is the compound obtained by the reaction of thioacetamide with hydrazine hydrate at room temperature. The compound is comparable to 1,1-disubstituted hydrazines. On oxidation in petroleum ether, a bright red solution was obtained. Upon work up, bright red crystalline needles of 3,6-dimethyl 1,2,4,5-tetrazine (LI) were obtained.

The mechanism may involve initial formation of nitrene and consequent insertion into the triazole (XLIX) to give the tetrazine (LI).



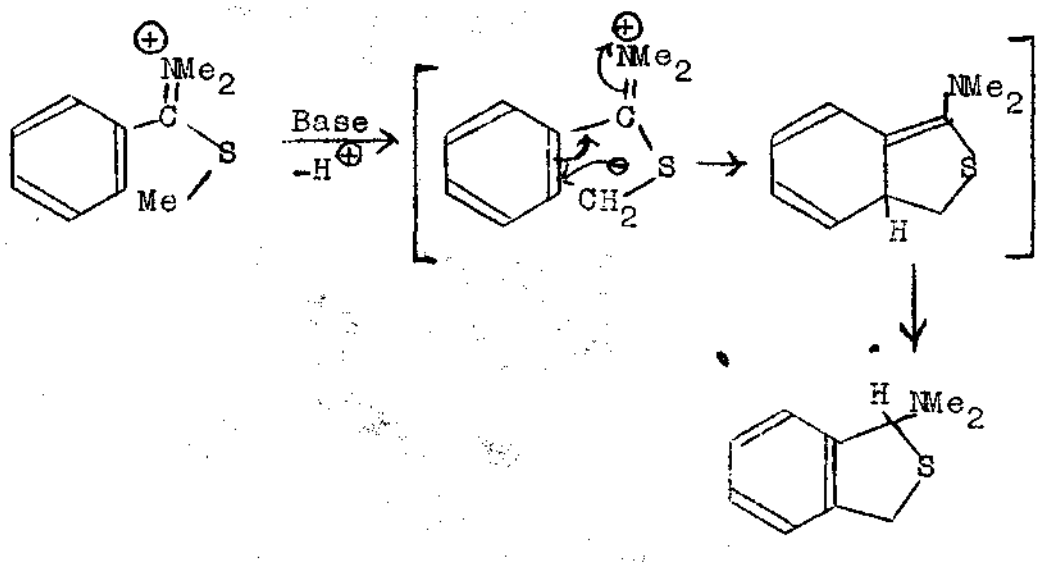
LI

A comparable oxidation reaction, followed by insertion of an intermediate nitrene is as follows[45]:-



REACTION OF S-ALKYLQUATERNARY SALTS WITH TERTIARY AMINES:

It might be expected that quaternary thioamide salts would give ylides which could then undergo the Sommelet-Hauser rearrangement as follows:-



Bases like triethylamine, morpholine and pyridine were tried, but without success.

In the reaction of p-Chlorothiobenzdimethylamide methiodide in chloroform with triethylamine, two main products were obtained, the corresponding thioamide, and

a colourless solid which separated from the medium and was later characterised as tetraethylammonium iodide (Fig.12).

In the n.m.r. spectrum, the usual absorption for an ethyl group was present, but each of the methyl triplet peaks was further split into a triplet, giving a triplet of triplets.

From the methyl resonances of a number of ammonium salts it is apparent that an observable coupling constant is restricted to the protons on the β-carbon[48]. The electric field at the nitrogen atom in these compounds is considered symmetrical and this is believed to lead to an increase in the quadrupole relaxation time of ^{14}N and hence to the observation of a sharp line with ^{14}N spin couplings[49].

The ethanol present in chloroform as a stabilizer is thought to react in some way in the formation of tetraethylammonium iodide. The latter was not obtained when the ethanol was removed.

The reaction may perhaps be compared to the Williamson synthesis of ethers.in which sodium alkoxide is treated with an alkyl halide.

In our reaction, ethanol may behave like an alkoxide in presence of the fairly strong base, triethylamine.

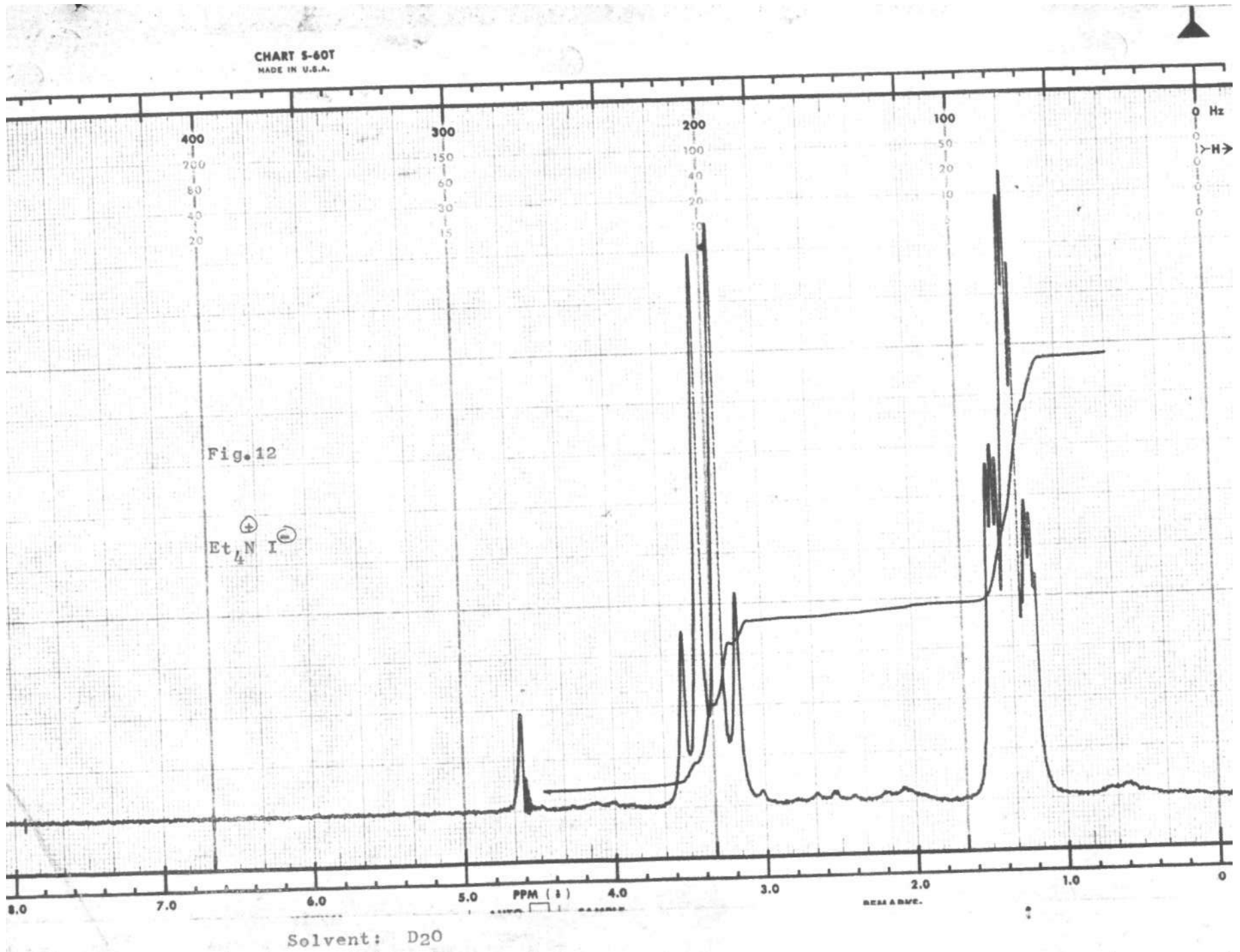
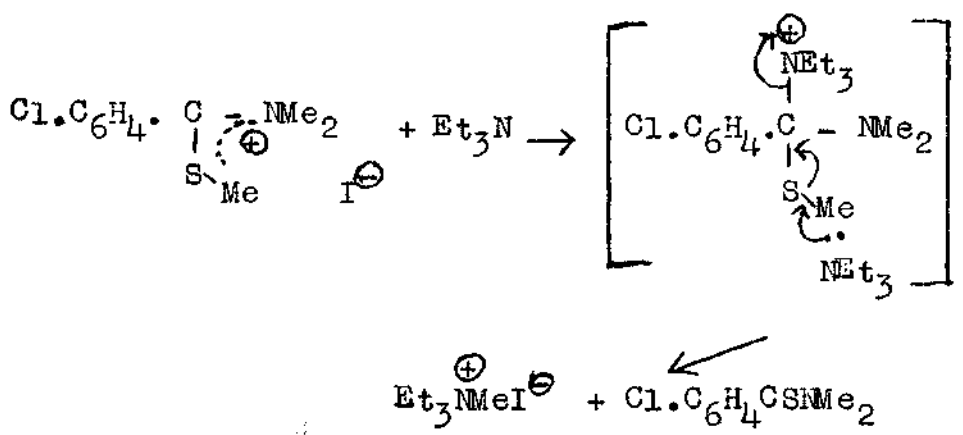


Fig.12

$Et_4\overset{\oplus}{N}\ \overset{\ominus}{I}$

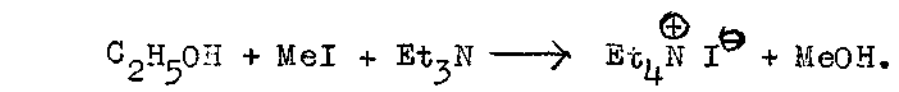
Solvent: D_2O

It reacts with methyliodide which could be generated in one of two ways: either by heat or by abstraction from the quaternary salt by triethylamine as follows:-



Triethymethylammonium iodide was also isolated from the medium. The latter is soluble in chloroform whereas tetraethylammonium iodide is not.

The reaction may then be represented as follows:-



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

NMR spectra were run with a Varian T-60 spectrometer using tetramethylsilane as internal standard and deuteriochloroform as solvent except where otherwise stated. Unicam SP.1200 and Perkin-Elmer 700 instruments were used for the i.r. spectra which were run either neat or as Nujol mulls. The u.v. spectra were done with a Unicam SP.800B spectrometer using clinical absolute ethanol except where otherwise stated.

All melting points (uncorrected) were taken with the Kofler hot stage microscope.

Elemental microanalyses were carried out by Scandinavian Microanalytical Laboratories. Solvents used were purified by standard methods. Petroleum ether had b.p. 60-80^{o} unless otherwise specified.

A. THIOAMIDES:

(a) 4-Methoxythiobenzdimethylamide (XVII). Anisaldehyde (13.6g; 0.1m), dimethylammonium chloride (12.2g, 0.15m), anhydrous sodium acetate (12.3g, 0.15m), sulphur (4.8g, 0.15 atom), and DMF (40 ml) were placed in a flask provided with a reflux air condenser and drying tube and supported in a paraffin-bath on a magnetic-stirrer hotplate.

The mixture was stirred whilst the paraffin temperature was raised to 100° over ½h. and kept at this for 3h. The dark brown mixture was poured into water (300 ml) and cooled in ice with shaking. The yellow oil solidified and after keeping the mixture in the refrigerator for 4h the product was filtered off, washed and dried. It was then crystallised from boiling petroleum ether (b.p. 80-100°, 800 ml) (charcoal) forming large yellow prisms (17.7g, 91%, m.p. 69-70°).

The spectral data of this compound and the following analogous preparations will be found in Table 1, and also their melting points and percentage yields. The reaction times are in brackets.

(b) Thiobenzdimethylamide (XIII , 5h.) yellow plates.

(c) Phenythioacetdimethylamide (XIV, 3h.) colourless cubes.

(d) 4-Dimethylaminothiobenzdimethylamide (2h) yellow plates.

(e) 4-Chlorothiobenzdimethylamide (XVI, 3h.) yellow needles, (Found: C,54.2; H,5.1; N,7.0, $C_9H_{10}ClNS$ requires C,54.1; H,5.0; N,7.0%).

(f) 4-Bromothiobenzdimethylamide (XV, 4h.) Yellow needles (Found: C,44.5; H,4.3; N,5.6, $C_9H_{10}BrNS$ requires C,44.3; H,4.1; N,5.7%).

(g) 4-Nitrothiobenzdimethylamide (XVIII, 3h.) Orange crystals.

(h) Thioisobutyrodimethylamide (XIX, 3h.) Yellow liquid.

(i) 4-Chlorothiobenzomorpholide (XXII) Morpholine, (26.1g, 0.3 m). 4-Chlorobenzaldehyde (28.1, 0.2m.). sulphur (9.6g, 0.3g atom). DMF 30 ml. Reflux time 3h.

The reaction mixture was poured unto cold ethanol (200 ml). The oil formed crystallised immediately and the solid was filtered off, washed, dried and purified from petroleum ether (b.p.80-100°) as yellow needles.

In the same way there were prepared the following derivatives.

(j) Thiobenzomorpholide (XX, 3h.) yellow plates.

(k) Phenylthioacetmorpholide (XXI, 3h.) colourless needles.

(l) 4-Methoxythiobenzomorpholide (XXIII, 3h.) yellow plates.

B. QUATERNARY SALTS OF THIOAMIDES:

(a) α-Methylthiobenzylidenedimethylammonium iodide (XXV) Thiobenzdimethylamide (23.6g; 0.14m.), and iodomethane (42.6g, 0.3m.) were dissolved in acetone (100 ml). The reaction was exothermic and was completed by boiling under reflux for 20 min. when the methiodide separated out. The mixture was cooled in ice, some ether added, since a little more is then precipitated, and filtered. The salt was hygroscopic and was transferred to a vacuum desiccator as quickly as possible. The yield was almost quantitative.

(b) 4-α-Methylthiobenzylidenemorpholinium iodide (XXXIII) and other derivatives similarly prepared are found in Table 2. In all the cases, the reactions were complete in less than ½h.

C. BORANES:

(a) NN-Dimethylbenzylamine borane (LVI) Sodium borohydride (11.25g, 0.3m) was dissolved in water (25 ml) and cooled in ice. Thiobenzdimethylamide methiodide (6.14g, 0.02m.) was added in small portions over 10min., whilst stirring magnetically. Frothing occurred and there was a strong smell of methanethiol.

After stirring for 1h. the mixture was allowed to stand for 2h. and the solid produced was filtered off, washed and dried (2.70g). The substance formed colourless plates from petroleum ether. The following derivatives were prepared and the physical data will be found in Table 9.

(b) NN-Dimethyl-2-phenylethylamine borane, colourless needles.

(c) NN-Dimethyl-4-Methoxybenzylamine borane: colourless needles from petroleum ether.

(d) N-4-Dimethylaminobenzylmorpholine ~~4'-Morpholino-4-dimethylaminobenzylamine~~ borane, colourless needles from toluene or ethanol (charcoal).

(e) NN-Dimethyl-4-Chlorobenzylamine borane, colourless needles from petroleum ether.

In each of these reactions, an oily by-product is usually obtained, e.g. with 4-chlorothiobenzdimethylamide methiodide and sodium borohydride, a yellow oil was produced which was extracted with diethyl ether, the solution was dried and evaporated in vacuum and the product distilled. A colourless distillate was obtained which was characterised as the free amine, NN-dimethyl-4-chlorobenzylamine b.p .90-2°, lit.[47] 90-90.5°).

D. DIHYDROTETRAZINES AND TETRAZINES:

(a) 3,6-Diphenyl-1,2-dihydro-1,2,4,5-tetrazine (XXXVIII)

Thiobenzdimethylamide (XIII, 12.0g, 0.7m) finely ground and hydrazine hydrate (15 ml) was boiled under reflux for 1h. Gas (dimethylamine?) was evolved and the dark liquid crystallised on cooling. The product was triturated with water (40 ml.), cooled in the refrigerator, filtered off, washed and dried (7.6g), crystallised from glacial acetic acid as yellow needles. The compound was characterised as 3,6-diphenyl-1,2-dihydrotetrazine[30], which on oxidation with bromine water or hydrogen peroxide: glacial acetic acid (1:1) gave 3,6-diphenyl-1,2,4,5-tetrazine[30]. The following dihydrotetrazines and tetrazines (Tables 6 and 7 respectively) were prepared by the same method and purified from toluene (charcoal).

(b) 3,6-Bis(4'-dimethylaminophenyl)-1,2-dihydro-1,2,4,5-tetrazine as orange needles.

(c) 3,6-Bis(4'-dimethylaminophenyl)-1,2,4,5-tetrazine: Brick-red crystals.

(d) 3,6-Dibenzyl-1,2-dihydro-1,2,4,5-tetrazine. Colourless needles.

(e) 3,6-Dibenzyl-1,2,4,5-tetrazine. Bright red crystals.

(f) 3,6-Bis(4'-Methoxyphenyl)-1,2-dihydro-1,2,4,5-tetrazine Yellow crystals.

(g) 3,6-Bis(4'-Methoxyphenyl)-1,2,4,5-tetrazine. Bright red crystals.

(h) 3,6-Bis(4'-Chlorophenyl)-1,2-dihydro-1,2,4,5-tetrazine Yellow needles from glacial acetic acid (charcoal).

(i) 3,6-Bis(4'-Chlorophenyl)-1,2,4,5-tetrazine. Bright red crystals.

E. BENZONITRILES:

3,6-Bis(4'-Chlorophenyl)-1,2,4,5-tetrazine was heated in a cold finger apparatus using a bunsen flame. A colourless sublimate was obtained which was crystallised from ethanol and was found to be 4-Chlorobenzonitrile[37]. (Table 8). The 4-Bromobenzonitrile was prepared by the same method. None of the other tetrazines derivatives could be similarly degraded.

F. REACTIONS OF THIOAMIDES WITH HYDRAZINE HYDRATE AT ROOM TEMPERATURE:

(a) 4-Amino-3,5-dimethyl-1,2,4-triazole (XLIX) Thioacetamide (3.5g, 0.05m) was added[50] in portions over 5min. with occasional cooling (exothermic reaction) to 99-100% hydrazine hydrate (7 ml). The clear yellow solution was

allowed to stand overnight when some large colourless crystals were observed to separate out. It was further cooled in the refrigerator for several hours and the crystals filtered off on a sintered glass funnel and dried (2.25g, 43%). A sample was crystallised twice from boiling dioxan (m.p. 204-5° lit.[31] 199°). Found; C,42.7; H,7.1; N,49.6. Calc. for $C_4H_8N_4$ C,42.9; H,7.1; N,50.0%). The i.r. spec. (Nujol) shows two strong and broad peaks at 3100, 3190 ($-NH_2$); 1638 (-C=N-) 1255s, 1090s, 760s, 660s, cm^{-1}. The n.m.r. spectrum agrees with the structure. Fig. 2.

(b) N(α-4'-Morpholinobenzylidene)hydrazine XLI) Thiobenzomorpholide (10g, 0.05m) and hydrazine hydrate (20 ml) were reacted at room temperature. A colourless solid (8.6g) was obtained, which was crystallised from ethanol.

(c) Similarly, N(α-4'-morpholino-4-chlorobenzylidene) hydrazine (LII) was prepared from 4-Chlorothiobenzomorpholide as colourless cubes from toluene.

In (b) and (c) above dihydrotetrazines were also formed but in small amounts. (Table 5). Thiobenzdimethylamide and derivatives with electron-donating groups in the p-position gave only the dihydrotetrazines.

G. REACTION OF S-ALKYL QUATERNARY SALTS WITH HYDRAZINE HYDRATE AT ROOM TEMPERATURE:

Crude thiobenzomorpholide methiodide (10g) was added[50] in portions over 5min. to hydrazine hydrate (30 ml), which had previously been cooled in ice. No appreciable amount of heat was produced. An orange coloured oil was first formed which rapidly solidified. The lump was broken up and the solid triturated for 20 min. with ice-cooling. The yellowish-white solid was filtered off, washed repeatedly with water and dried (4.4g).

It was shaken with dilute hydrochloric acid (2N, 75 ml) and a small amount of insoluble solid was filtered off, washed with water and dried (0.22g). The acidic filtrate was basified by addition of excess sodium hydroxide with ice-cooling and the almost colourless solid was filtered off, washed with water and dried (1.9g). The product formed colourless crystals from ethanol and was characterised as N(α-4'-morpholinobenzylidene) hydrazine (XLI), whereas the acid insoluble was found to be thiobenzomorpholide.

It was noted that the aqueous alkaline extract on standing in the refrigerator overnight deposited a large amount of slightly pink crystalline material. This crystalline substance (0.6g) was shown by its i.r. spectrum

to be identical to NN'bis(α-4'-morpholinobenzylidene) hydrazine (XL). Similar products were isolated from reaction of 4-chlorothiobenzomorpholide methiodide (XXXIV) phenylthioacetmorpholide methiodide (XXXVII) and 4-chlorothiobenzdimethylamide methiodide (XXVIII). Dihydrotetrazines were also formed in small amounts in each case. Other thiobenzdimethylamide methiodide derivatives gave only the dihydrotetrazines.

H. REACTION OF DIAZOMETHANE WITH 4-CHLOROTHIOBENZDIMETHYLAMIDE METHIODIDE:

A methanolic solution (15 ml) of 4-chlorothiobenzdimethylamide methiodide (XXVIII, 9.5g) was added in small amounts over 15 min. to a solution of diazomethane (ca 3g) in diethyl ether. Some solid was observed to separate immediately. No gas evolution was observed until after 10 min.

The mixture was stirred magnetically with ice cooling for 4h. and some colourless solid was then filtered off (0.4g). The filtrate was evaporated in air and finally under vacuum leaving an oil with some dispersed solid material. Chloroform (30 ml) was added and the oil was soluble leaving the solid which was filetered off and was found identical with the one above

and later characterised as trimethylsulphoniun iodide (Fig. 8).

The chloroform solution was washed with water (3 x 20 ml), dried (anhydrous sodium sulphate) and evaporated in vacuum. An oil was obtained which did not crystallise until the components were separated by column chromatography on silica gel using chloroform/ethylacetate (7:3).

Two fractions were obtained and characterised as (a) the S-methyl with a trace of S-ethyl thiol ester of 4-chlorobenzoic acid (Fig. 9) and (b) the corresponding amide (Fig. 10).

J. REACTION OF AMIDRAZONES WITH YELLOW MERCURIC OXIDE:

The amidrazone, N(α-4'-morpholino-4-chlorobenzylidene) hydrazine (LII) (3,6g, 0.015m) and yellow mercuric oxide (4.32g, 0.02m) in petroleum ether (100 ml) were stirred magnetically for 12h. at room temp. in the dark.

A greenish-yellow solution was obtained which was decanted from the mercury formed. Water was also formed and was removed by anhydrous sodium sulphate. The solvent was then evaporated in vacuum, leaving an oil which failed to crystallise.

By column chromatography on silica gel using petroleum ether: ethylacetate (7:3), two products were isolated;- the amidrazine, NN'-bis(α-4'-morpholino-4-chlorobenzyl-idene) hydrazine and 4-chlorobenzaldehyde were isolated.

K. OXIDATION OF 4-AMINO-3,5-DIMETHYL-1,2,4-TRIAZOLE WITH YELLOW MERCURIC OXIDE:

4-Aminodimethyltriazole (3.0g, 0.02m), yellow mercuric oxide (4.4g, 0.02m) and petroleum ether (100 ml) were stirred magnetically in the dark at room temp. for 12h. A red solution resulted, which was evaporated at room temp., since the resulting solid sublimed in vacuum. Bright red needles of 3,6-dimethyl-1,2,4,5-tetrazine (LI) were obtained (0.5g, m.p. 73° lit.[31] 74°). Water was also formed which was removed by anhydrous sodium sulphate.

L. REACTION OF TRIETHYLAMINE WITH S-ALKYL-QUATERNARY SALTS:

4-Chlorothiobenzdimethylamide methiodide (8.7g, 0.025m) was dissolved in chloroform (40 ml) and triethyl-amine (15g) was added dropwise with ice-cooling. The mixture was then boiled under reflux for 3h. at 100°. During the reaction a colourless solid separated out and was filtered off and dried (1.8g) and crystallised from

ethanol, m.p. 281-2°. It was soluble in water. This was characterised as tetraethylammonium iodide (Fig. 12).

The chloroform filtrate was washed twice with water (total 50 ml) dried, and evaporated. An oil was obtained which solidified on cooling and was found to be 4-chlorothiobenzdimethylamide. Methyltriethylammonium iodide was also formed and was isolated in a separate experiment by fractional precipitation using diethyl ether. The latter is soluble in chloroform. The tetraethylammonium iodide was not formed when ethanol was removed from the chloroform by shaking with sulphuric acid.

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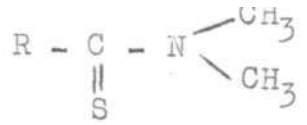
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Table 1: THIOAMIDES



R (p-subtd.)		YIELD (%)	M.P.[a] (°C)	U.V. SPECTRA (EtOH) λ_{max} (nm)	U.V. SPECTRA (EtOH) ε (x 10^6)	I.R. SPEC. (NUJOL) cm^{-1}	NMR (δ-values)
$MeO.C_6H_4$-	51	91	68-9 (68.5)	273	1.39	1600s, 1522s, 1300s 1250s, 1178s, 1165m 992m, 840s, 782m	3.20(3H,s, NMe) 3.58(3H,s, NMe) 3.80(3H,s, MeO.) 7.04(4H,q, aromatic)
C_6H_5-	52	82	67-68 (67 corr)	278 238	0.98 0.98	1660s, 1600s, 1520s 1300m, 1280m, 1110vs 972m, 858s, 750s,720vs	3.06(3H,s, NMe), 3.46(3H,s,NMe) 7.26(5H,s, aromatic)
$C_6H_5CH_2$-	53	87	78-80 (80-1)	273	1.33	1320vw, 1280vw 1118s, 722w	3.13(3H,s, NMe), 3.43(3H,s,NMe) 4.26(2H,s, $-CH_2-$) 7.26(4H,s, aromatic)
$Me_2N.C_6H_4$-	54	54	106-7 (105-6 corr)	283	1.13	1600s, 1380m, 1368m 1300m, 1180m, 1065m 975m, 945s, 825s	2.88(6H,s, $-NMe_2$ aromatic) 3.24(3H,s, -NMe) 3.46(3H,s, -NMe) 6.95(4H,q, aromatic)
Cl.C_6H_4-		92	79-80	248 277	1.28 0.94	1580vs, 1530s, 1300s, 1280vs, 1145s, 1120w, 1082s, 834vs, 732vs	3.12(3H,s, NMe) 3.48(3H,s, NMe) 7.26(4H,s, aromatic)
Br.C_6H_4-		76	120-1	251.5 277	1.40 1.01	1640s, 1300s, 1125m 1000m, 820vs	3.12(3H,s, -NMe) 3.48(3H,s, -NMe) 7.28(4H,q, aromatic)
$O_2N.C_6H_4$-	55	83	145-5	260 310	1.66 0.56	1600w, 1540m, 1510s 1300s, 1140m, 860s	3.18(3H,s, NMe) 3.60(3H,s, NMe) 7.83(4H,q, aromatic)
Me Me>CH-		87	b.p. 58-70/0.7mm			3000s, 2975s, 1740m 1665s, 1520m, 1400s, 1020m	1.20(6H,d, C-Me_2) 3.40(6H,d, -NMe_2)

a Lit. values in brackets.

Table 1 contd. THIOAMIDES 

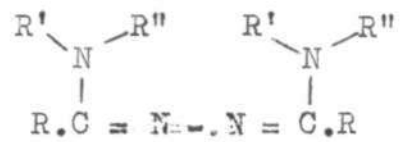
R (p-subtd.)	YIELD (%)	M.P[a] (°C)	U.V. SPECTRA (EtOH) λ_{max} (nm)	U.V. SPECTRA (EtOH) ε (x 10^6)	I.R. SPECTRA (NUJOL) cm^{-1}	NMR, (δ-values)
$Cl.C_6H_4$-	66	79	247 285	1.5 1.21	2920vs, 1383m, 1300s 1120s, 805s	3.60-4.40(8H,m, morpholino) 7.30(4H,s, aromatic)
$C_6H_5CH_2$- [56]	62	79.5 (79-79.5)	281	0.064	3050vs, 1560s, 1180s 1020m,	3.60(8H,sextet, morpholino) 4.32(2H,s, $-CH_2-$) 7.32(5H,s, aromatic)
$MeO.C_6H_4$- [8]	72	110-1 (109-110)			2920vs, 1610w, 1295s 1275s, 1130s, 1018s, 805s	3.75-4.35(11H,m,MeO- & morpholino) 7.05(4H,q, aromatic)
C_6H_5- [20]	76	136-7 (137.5-138.5)	287 338	0.051 0.049	3020vs, 1540s, 1360w, 1290s, 1180s, 820w	3.55-4.40(8H,m, morpholino) 7.30(5H,s, aromatic)
$Me_2N.C_6H_4$-	70	148-9	251 288 378	0.004 0.008 0.002	2920vs, 1600s, 1520w,1280s 1220m, 1120s, 1040m 820w	3.00(6H,s, $-NMe_2$) 3.65-4.05(8H,m, morpholino) 7.00(4H,q, aromatic)

a. Lit. values in brackets.

Table 2: QUATERNARY SALTS OF THIOAMIDES R. C(SMe) – N(R')(R") $I^{\ominus}$

R (P-subtd.)	R'	R"	YIELD (%)	M.P (°C)	NMR (δ-values)
C_6H_5-	Me	Me	93	138d	2.35(3H,s,.SMe) 3.90(3H,s,NMe) 3.61(3H,s,NMe) 7.70(5H,m, aromatic)
MeO.C_6H_4-	Me	Me	98	144d	2.36(3H,s, -SMe); 3.62(3H,s, -OMe) 3.90(6H,NMe_2); 7.43(eH,q, aromatic)
Cl.C_6H_4-	Me	Me	90	142d	2.38(3H,s, -SMe). 3.90(3H,s,NMe) 3.60(3H,s, NMe) 7.80(4H,q, aromatic)
Br.C_6H_4-	Me	Me	92	-	2.30(3H,s, SMe) 3.90(3H,s, NMe) 3.58(3H,s, NMe) 7.75(4H,q, aromatic)
$C_6H_5CH_2$-	Me	Me	80	144d	2.90(3H,s, SMe) 4.68(2H,s, $-CH_2$) 3.81(6H,s, $-NMe_2$) 7.35(5H,s, aromatic)
$Me_2N.C_6H_4$-	Me	Me	91	108d	2.40(3H,s, SMe) 3.65(3H,s, NMe) 7.20(4H,q, aromatic) 3.10(6H,s, NMe_2) 3.85(3H,s, NMe)
Me(Me)CH-	Me	Me	65	-	1.50(6H,d, $C(Me)_2$) 3.82(6H,d, $-NMe_2$) 3.10(3H,s, SMe)
Cl.C_6H_4-			72	148d	2.40(3H,s, SMe) 4.40(4H,m, $-CH_2-O-CH_2-$) 3.95(4H,s, $-CH_2-N-CH_2-$) 7.80(4H,q, aromatic)
$PhCH_2$-			78	150d	1.85(3H,s, SMe); 4.38(2H,s, $-CH_2-$), 7.35(5H,s, aromatic); 3.62(8H,m, morpholino)
C_6H_5			89	152d	2.40(3H,s, SMe) 4.41(4H,d, $-CH_2-O-CH_2-$) 4.00(4H,s,$-CH_2-N-CH_2-$) 7.80(5H,m, aromatic)
$Me_2N.C_6H_4$-			90	153d	2.50(3H,s, SMe) 4.00(4H,m, $-CH_2-N-CH_2$) 7.25(4H,q, aromatic) 3.15(6H,s,$-NMe_2$) 4.50(4H,d, $-CH_2-O-CH_2$

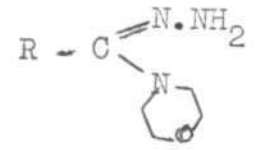
Table 4: AMIDRAZINES



R (p-subtd)	R'	R"	YIELD (%)	M.P (°C)	ANALYSIS* %C	%H	%N	U.V. SPECTRA(EtOH) λ_{max} (nm)	ε(x 10^6)	I.R. SPECTRA (NUJOL) cm^{-1}	N.M.R. SPECTRA (δ-values)
$C_6H_5CH_2$-			82	167-9	71.0 (71.0)	7.5 (7.4)	13.7 (13.8)	284	1.75	2880vs, 1450s, 1262s, 1300w, 1250s, 1262s, 1140m, 1120(broad)	3.40(16H, sextet, morpholino) 4.20(2H,s, $-CH_2-$) 7.20(5H,s, aromatic)
Cl.C_6H_4-	Me	Me	25	250-1	59.6 (59.5)	(5.5) (5.5)	15.3 (15.4)	227 325	4.06 0.73	2950vs, 1595vs, 1100s, 1095s, 1020w, 928s, 842s, 962s, 942m, 735s, 710w	2.58(12H,s, $-NMe_2$) 7.26(4H,s, aromatic)
C_6H_5-			89		69.8 (69.8)	6.9 (6.9)	14.8 (14.8)			2920vs, 1595vs, 1250s, 1110s, 965s.	2.98(8H,t, $-NH_2-N-CH_2-$) 3.64(8H,t, $-CH_2-O-CH_2-$) 7.36(10H,s, aromatic)
Cl.C_6H_4-			92	248-9	59.1 (59.1)	5.3 (5.4)	12.4 (12.5)	230 320	1.76 1.35	2920vs, 1598s, 1278s, 1160m, 1118s, 1100m, 905s, 840w.	3.00(8H,t, $-CH_2-O-CH_2-$) 3.65(8H,t, $-CH_2-N-CH_2-$) 7.32(4H,s, aromatic)

* FOUND VALUES ABOVE, REQUIRED VALUES IN BRACKETS.

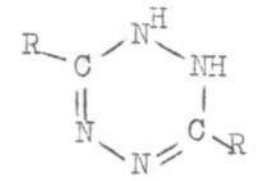
Table 5: AMIDRAZONES



R (p-subtd.)	YIELD (%)	M.P. (°C)	ANALYSIS* %C	%H	%N	U.V. SPECTRA (EtOH) λ_{max} (nm)	ε (x 10^6)	I.R. SPECTRA (NUJOL) cm^{-1}	N.M.R. SPECTRA (δ-values)
C_6H_5-	91	108-110	64.2 (64.4)	7.3 (7.3)	21.0 (20.5)	221 275	1.31 4.33	3220s, 3350w, 1640s, 1280s, 1130s, 1030w, 918w 928w, 780s	2.98(4H,t, $-CH_2-N-CH_2-$) 3.62(4H,t,$-CH_2-O-CH_2$) 4.32(2H,s, $-NH_2$) 7.40(5H,s, aromatic)
Cl.C_6H_4-	77	159-160	55.2 (55.1)	5.8 (5.8)	17.3 (17.5)	225 275	1.36 0.39	3350m, 3250w,1638s 1600w, 1275s,1120s 1100s, 1012s, 815s	3.00(4H,t,$-CH_2-N-CH_2-$) 3.66(4H,t,$-CH_2-O-CH_2-$) 4.52(2H,s, $-NH_2$) 7.40(4H,q, aromatic)

* FOUND VALUES ABOVE, REQUIRED VALUES IN BRACKETS.

Table 6: DIHYDROTETRAZINES

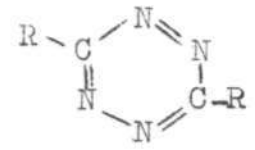


R (p-subtd.)	YIELD (%)	M.P.[a] (°C)	ANALYSIS* %C	%H	%N	U.V. SPECTRA (EtOH) λ_{max} (nm)	ε (x 10^6)	I.R. SPECTRA (NUJOL) cm^{-1}	N.M.R. SPECTRA (δ-values)
C_6H_5- [32]	89	161 (160)				245	1.33	3230vs, 1640s, 1400s 1320s,1108s,1065,1025s 920m, 770vs, 700s	7.50(10H,m, aromatic) 7.95(2H,d,-NH-NH-)
$C_6H_5CH_2$-	94	164-5	72.6 (72.7)	6.0 (6.1)	21.3 (21.2)	228	6.77	3245, 3220m, 3100s, 1420m,1500s,1150s,1160s 965s, 735s, 700s	4.03(4H,s,-CH_2-) 4.65(2H,s,-NH-NH-) 7.18(5H,s, aromatic)
$Me_2N.C_6H_4$-	85	263-4	73.4 (73.5)	7.6 (7.5)	18.9 (19.0)	381.5 325 241 495	3.48 0.85 1.21 0.13	3245m, 1600s, 1520s, 1068w, 945s, 820vs	2.98(12H,s,-$N(CH_3)_2$) 7.20(8H,q, aromatic)
$Cl.C_6H_4$-	92	206-7	55.2 (55.1)	3.3 (3.3)	18.0 (18.3)	255 298	2.44 0.74	3250s, 1600s, 1340s 1100vs, 1015s, 840s 725m	7.50(8H,q, aromatic 8.0(2H,m, - NH-NH-)
Me, Me>CH-	20	169-171	57.0 (57.1)	9.4 (9.5)	33.3 (33.3)			3250s,1320s,1228w,1115m 1020m, 760m	1.15(12H,d,-$(CH_3)_2$-) 2.48(1H,m, CH-) 6.15(2H,s, -NH-NH-)

* FOUND VALUES ABOVE, REQUIRED VALUES IN BRACKETS.

a. Lit. values in brackets

Table 7: TETRAZINES



R (p-subtd.)	YIELD (%)	M.P.[a] (°C)	ANALYSIS* %C	%H	%N	U.V. SPECTRA (EtOH)+ λ_{max} (nm)	ϵ (x 10^6)	I.R. SPECTRA (NUJOL) cm^{-1}
C_6H_5- [32]	94	191-2 (191-2)				296	0.43	
$C_6H_5CH_2$-	96	70-2	73.4 (73.3)	5.5 (5.3)	21.3 (21.4)	536	0.5	2920vs, 1595w, 1160w 660vs, 648m
$Cl.C_6H_4$-	98	260d	55.6 (55.4)	2.7 (2.6)	18.2 (18.5)	311+	3.5	1490vs, 1175s, 1110vs, 1092vs, 1010vs, 920s 850s, 715s
$OMeC_6H_4$-	97	235-6	65.3 (65.3)	4.8 (4.8)	- -	334+	4.57	1603s, 1480vs, 1390vs, 1300s 1245vs, 1180vs, 1050s, 1020s, 918s, 840vs.
$Br.C_6H_4$-	93	295d	-	-	-	315+	3.99	1598m, 1075s, 1005m, 820m.

* FOUND VALUES ABOVE, REQUIRED VALUES IN BRACKETS

\+ CHLOROFORM AS SOLVENT

a Lit. values in brackets

Table 8: NITRILES $X.C_6H_4.CN$

X	M.P.° °C	ANALYSIS* %C	%H	%N	U.V. SPECTRA (EtOH) λ_{max} (nm)	ϵ (x 10^6)	I.R. SPECTRA (NUJOL) cm^{-1}	N.M.R. SPECTRA (δ-values)
3] Cl	94-5 (92-3)	60.9 (61.1)	3.0 (2.9)	9.9 (10.1)	235	1.26	2250s, 1580s, 1090s 1018m, 830s, 780w	7.50(4H,q, aromatic)
3] Br	110-111 (110-111)	46.1 (46.1)	2.4 (2.2)	- -	240	1.59	2250s, 1575s, 1080m 812s.	7.58(4H,q, aromatic)

* FOUND VALUES ABOVE, REQUIRED VALUES IN BRACKETS.

a. Lit. values in brackets.

Table 9:

BORANES $R-(CH_2)_n-N(BH_3)(R')(R'')$

R (P-subtd.)	n	R'	R''	YIELD (%)	M.P (°C)	ANALYSIS* %C	%H	%N	U.V. SPECTRA (EtOH) λ_{max} (nm)	ε (x 10^6)	I.R. SPECTRA (NUJOL) cm^{-1}	N.M.R. SPECTRA (δ-values)
C_6H_5- [41]	1	Me	Me	89	93-5	72.5 (72.6)	10.7 (10.8)	9.3 (9.4)	262 257 267	1.09 1.05 1.00	2925vs, 2400vs, 2325m, 2290s 1170vs, 1005s, 800m, 750s, 700s	2.50(6H,s,-NMe_2) 3.95(2H,s,-CH_2-) 7.40(5H,s, aromatic)
C_6H_5-	2	Me	Me	89	60	73.7 (73.7)	11.1 (11.1)	8.6 (8.6)	258 252 263 267	1.18 0.09 1.03 0.82	2920vs, 2400vs, 2330w, 2300m, 1190vs, 880m, 700s	2.65(6H,s, -NMe_2) 3.0(4H,s, -CH_2-) 7.25(4H,s,aromatic)
$Cl.C_6H_4$-	1	Me	Me	60	89-90	58.9 (58.9)	8.1 (8.2)	7.6 (7.5)	250 256 263	1.05 0.99 0.87	2950vs, 2448s, 2350w, 2300m, 1180vs, 1025m, 865m, 845m, 800w	2.46(6H,s,-NMe_2) 3.87(2H,s, -CH_2-) 7.38(4H,s,aromatic)
$Me_2N.C_6H_4$-	1	Me	Me	47	147-8	68.6 (68.8)	11.0 (10.9)	14.8 (14.6)	264	22.5	3050vs, 2520s, 2450w, 2410m, 1680s, 1595s, 1510m, 1218s, 880w	2.40(6H,s, -NMe_2, aliphatic) 2.98(6H,s, -NMe_2, aromatic) 3.86(2H,s, -CH_2-) 6.90(4H,q,aromatic)
$Me_2N.C_6H_5$-	1			91	132-3	66.5 (66.7)	9.7 (9.8)	12.0 (12.0	264 300	11.1 1.32	2925vs, 2400s, 2300w, 1610s, 1520s, 1190w, 1160w, 1110s, 800s	3.55(8H,m,morpholino) 3.35(2H,s, -CH_2-) 3.82(6H,s, NMe_2) 7.15(4H,q,aromatic)
OMe.C_6H_4-	1	Me	Me	96	79-80	67.0 (67.1)	10.0 (10.1)	7.9 (7.8)	228 273 279	13.2 5.25 4.96	3050vs, 2525s, 2450w, 2420m, 1678m, 1580s, 1520s, 1320s, 1240,1100s,880m	2.90(6H,s, NMe_2) 3.65(5H,m,-OMe & -CH_2-) 6.85(4H,q,aromatic)

* FOUND VALUES IN ABOVE, REQUIRED VALUE IN BRACKETS.