STUDIES IN THE CHEMISTRY OF THIOAMIDE DERIVATIVES

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BY

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April, 1976

THIS THESIS IS FONDLY DEDICATED

TO

OLISEYENUM ENUDEME OKECHA

AND

OTUNUYA ANIMAM OKECHA

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

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A B S T R A C T

Reactions of quaternary salts of NN-disubstituted thioamides have been studied. Treatment of the amidinium salt (14) with some nucleophiles gave novel compounds, a strange rearrangement reaction being observed with potassium thiocyanate.

The action of reducing agents on α-dialkylamino-α-methylthiocyanides was investigated. The methylthio-group of cyanide (25a) was, surprisingly reduced to hydrogen by primary aliphatic mono- and di-amines; with morpholine an intriguing rearrangement occurred.

The mechanism of "cyanohydrolysis" of compound (25g) to (26c) which we previously reported was currently established by ^{13}C n.m.r. spectroscopy; and desulphurisation of some α-methylthiocyanides with methyl iodide was achieved.

Some novel compounds were isolated from reaction of the dithiocarbamidium salt (42) with nucleophiles.

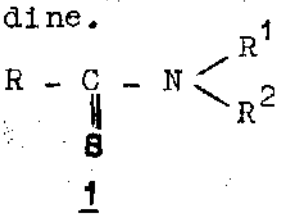
CHAPTER ONE

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

PREPARATION OF NN-DISUBSTITUTED THIOAMIDES AND S-ALKYL QUATERNARY SLATS

NN-Disubstituted thioamides(1) are readily synthesised by the Willgerodt-Kindler reaction[1-8] or from the amides with phosphorus pentasulphide.[9] The former reaction[1-8] entails the heating of a ketone, an aldehyde, or sometimes an alcohol with approximately equimolar amounts of sulphur and a dry amine. Generally, a secondary aliphatic amine, but sometimes a primary amine or even anhydrous ammonia is used.

In this investigation, NN-disubstituted thioamides(1) have also been made by a method which is essentially a modification of the Willgerodt-Kindler procedure: boiling a mixture of an aldehyde, a secondary amine salt and sulphur in the presence of anhydrous sodium acetate in dry pyridine.

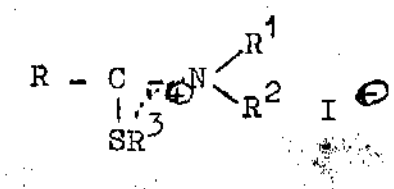


1

	R	R^1, R^2, or NR^1R^2
a	C_6H_5-	morpholino
b	p-Cl.C_6H_4-	morpholino
c	C_6H_5-	$R^1 = R^2 = Me$

d	CH_3-	morpholino
e	$C_6H_5CH_2$-	morpholino
f	o-HO.C_6H_4-	morpholino
g	CH_3-	$R^1 = R^2 = Me$
h	H-	$R^1 = R^2 = Me$
i	p-$(CH_3)_2N.C_6H_4$-	morpholino
j	p-$CH_3O.C_6H_4$-	morpholino
k	$(CH_3)_2CH$-	morpholino
l	$(CH_3)_2CH$-	$R^1 = R^2 = Me$

The corresponding S-alkyl quaternary salts(2) were obtained in high yields by treating NN-disubstituted thioamides(1) with simple alkyl halides.[8,10a,11] These organic salts are known to be reactive compounds.



2

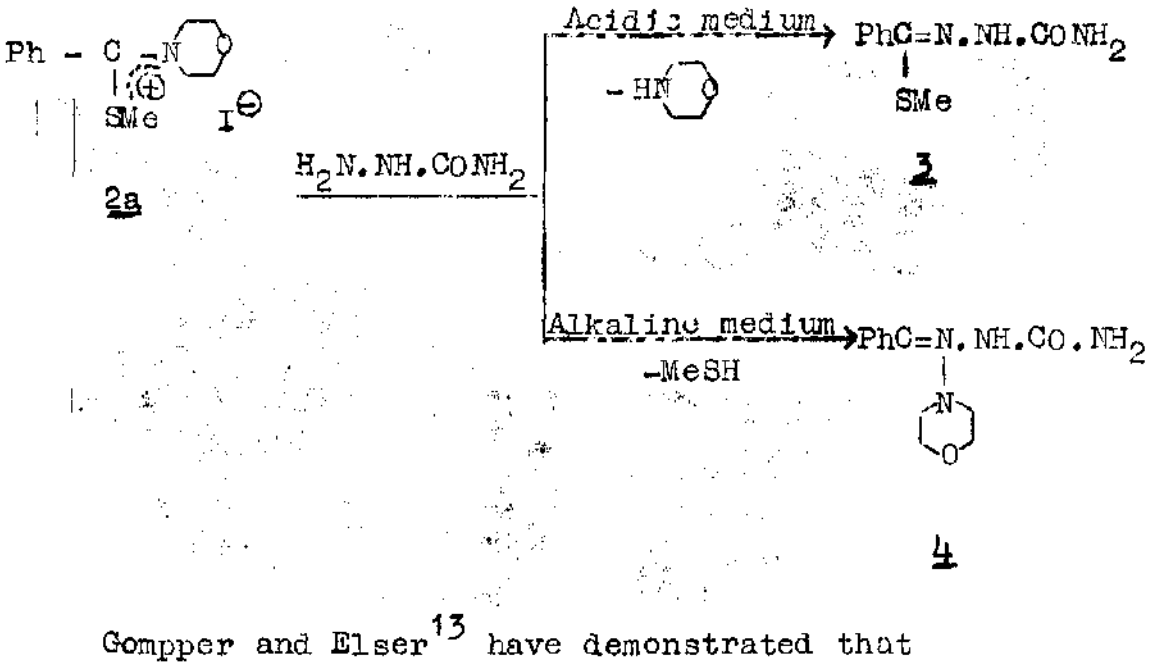
	R	R^1, R^2, or NR^1R^2	R^3
a	C_6H_5-	morpholino	Me
b	p-Cl.C_6H_4-	morpholino	Me
c	C_6H_5-	$R^1 = R^2 = Me$	Me
d	CH_3-	morpholino	Me

e	$C_6H_5CH_2$-	morpholino	Me
f	o-HO.C_6H_4-	morpholino	Me
g	CH_3-	$R^1 = R^2 = Me$	Me
h	H-	$R^1 = R^2 = Me$	Me
i	p-$(CH_3)_2N.C_6H_4$-	morpholino	Me
j	p-$CH_3O.C_6H_4$-	morpholino	Me
k	$(CH_3)_2CH$-	morpholino	Me
l	$(CH_3)_2CH$-	$R^1 = R^2 = Me$	Me
m	p-$(CH_3)_2N.C_6H_4$-	morpholino	Me_2CH

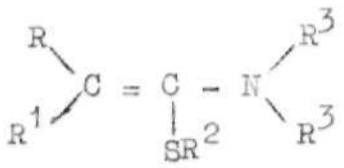
The quaternary compounds react additively with many nucleophiles often in aqueous solution at room temperature. Such reactions usually result in the elimination of the alkylthio- group in an alkaline medium or may lead to the elimination of the disubstituted amino- group in acidic medium. The reaction of thiobenzomorpholide methiodide(2a) with semicarbazide is typical and illustrative.

On reacting the quaternary salt (2a) with semicarbazide hydrochloride in aqueous ethanol, Chabrier and Renard[12] obtained 1-α-methythiobenzylidenesemicarbazide (3), the morpholino- group being lost. On the other hand, Peak and Stansfield[8] showed that under alkaline

conditions elimination of methanethiol occurred instead of morpholine to give 1-α-morpholinobenzylidene-semicarbazide(4).



Gompper and Elser[13] have demonstrated that treatment with bases of S-alkyl quaternary salts(2) which have hydrogen in the alpha position to the quaternary carbon atom may cause the elimination of hydrogen halide resulting in the formation of ketene SN-acetals(5); these serve as useful intermediates and compounds (5; R^1 = H) give rise to ynamines(6).[14]



5



6

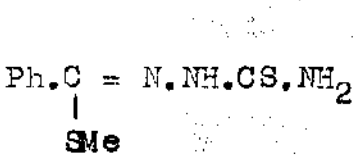
[R = alkyl or aryl; R^1 = alkyl, aryl or H; R^2 = alkyl; R^3 = alkyl or NR^3R^3 = morpholino].

REVIEW OF THE SYNTHETIC APPLICATIONS OF THE QUATERNARY SALTS OF NN-DISUBSTITUTED THIOAMIDES

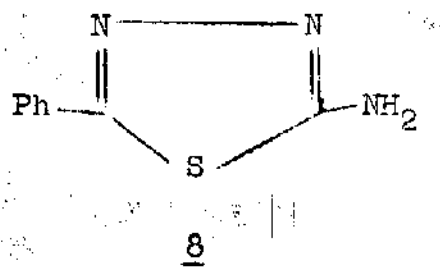
It was not until very recently that the chemistry of S-alkyl quaternary salts(2) was extensively investigated though study began about twenty five years ago. The reactions of the methiodide(2a) with semicarbazide by Chabrier and Renard[12] (1950) and Peak and Stansfield[8] (1952) have been mentioned.

The latter authors also showed that this salt condensed with thiosemicarbazide under acid or neutral conditions with, presumably, the intermediate formation of compound(7) which, however, was too unstable for isolation since it cyclised to 2-amino-5-phenyl-1,3,4-thiadiazole(8) with the loss of methanethiol.

The spontaneous cyclisation was in contrast to the behaviour of the oxygen analogue (3) which did not cyclise.

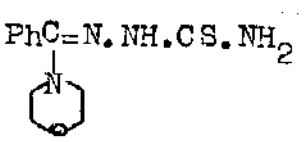


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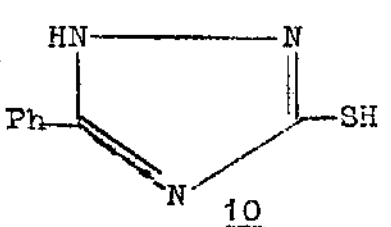


8

These authors further found[8] that under basic conditions, for example in aqueous potassium hydrogen carbonate or in pyridine, preferably in the presence of a strong base such as diethylamine or triethylamine, the condensation of methiodide(2a) with thiosemicarbazide took a different course and 1-α-morpholinobenzylidenethiosemicarbazide(9) was obtained, methanethiol being eliminated instead of morpholine. This compound was soluble in dilute acids but was rapidly cyclised to 2-amino-5-phenyl-1,3-4-thiadiazole(8). It was much more stable to alkali but was cyclised by long boiling with alcoholic potassium hydroxide to 3-mercapto-5-phenyl-1,2,4-triazole(10).

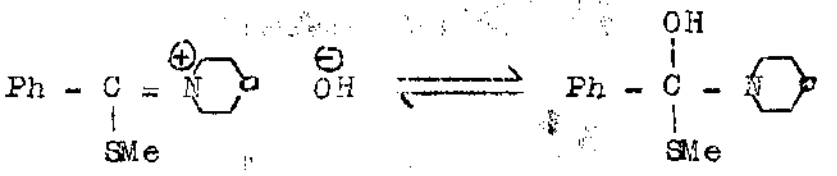


9



10

Chabrier and Renard[12] observed that a solution of the salt (2a) in aqueous ammonia soon deposited an oil which later solidified and finally redissolved, the end products being benzamidine and morpholine hydriodide. Peak and Stansfield[8] examined this solid and found that its properties were consistent with its formulation as a pseudo-base (11) corresponding to the hypothetical quaternary hydroxide(12). The substance was almost neutral but was reconverted by hydrogen iodide into the original salt(2a).



12 11

When boiled with aqueous ethanol it gave a mixture of benzomorpholide and thiobenzomorpholide(1a) which could be formed by loss of either methanethiol or methanol from the pseudo-base(11).

Peak and Stansfield[8] also found that dithiocarboxylic esters could be formed by treating the methiodides(2) with hydrogen sulphide. The salt(2a) reacted readily with hydrogen sulphide in pyridine or ethanol to give

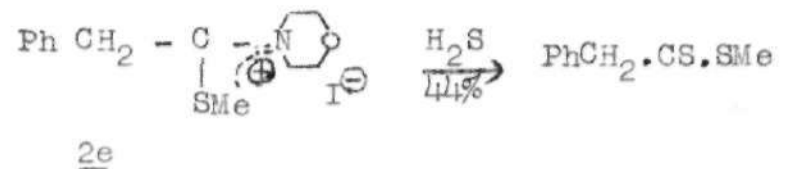
methyl dithiobenzoate in good yield. The methiodides (2d) and (2e) similarly gave methyl dithioacetate and methyl phenyldithioacetate respectively.



2a

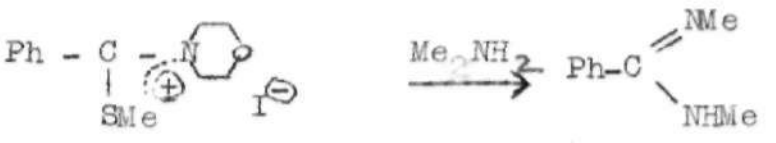


2d

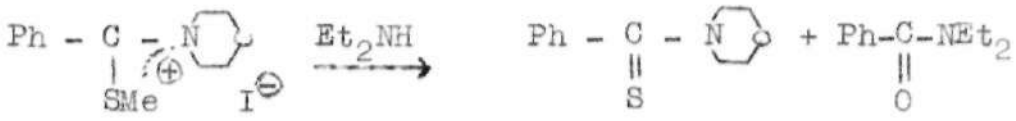


2e

Chabrier and Renard[12] have shown that in ethanol the methiodide(2a) reacted with methylamine giving NN'-dimethylbenzamidine, while diethylamine afforded mainly thiobenzomorpholide(1a) with some benzodiethylamide.

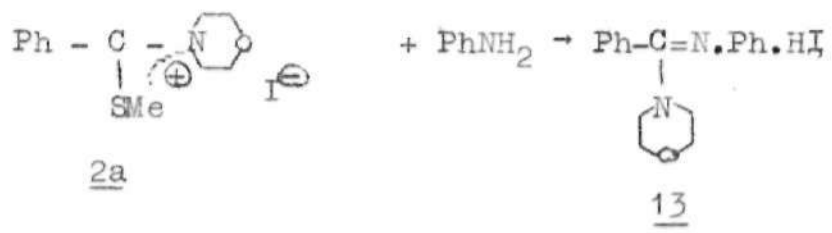


2a

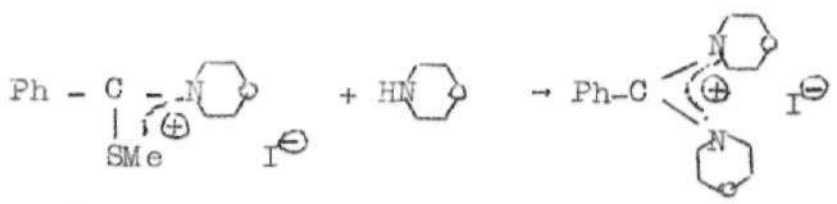


2a 1a

Peak and Stansfield,[8] however, have demonstrated that under anhydrous conditions the reaction with primary and secondary amines proceeded differently. Thus the salt(2a) reacted with aniline giving N-phenylbenzimidylmorpholinium iodide(13). With morpholine the quaternary amidinium compound(14) was formed.



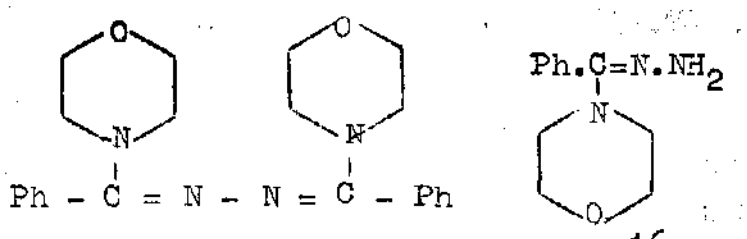
2a 13



2a 14

Much later, Stansfield[11] treated the quaternary salt(2a) with hydrazine hydrate at room temperature and

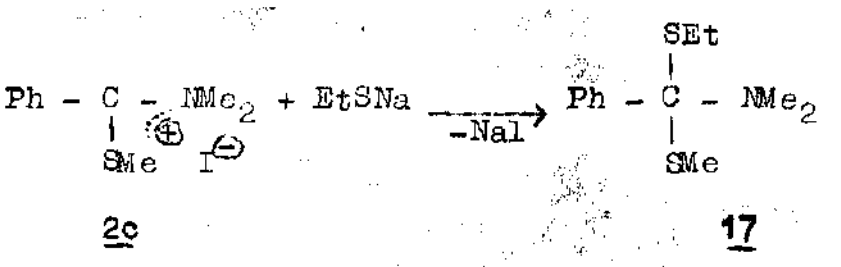
obtained an orange - coloured oil which quickly solidified to yield a mixture of bis(α-4'-morpholinobenzylidene) hydrazine (15), the amidrazone (16) and a small amount of thiobenzomorpholide(1a).



15

16

In 1965 Mukaiyama and his co-workers[15] reacted thiobenzodimethylamide methiodide(2c) with active methylene compounds and with heavy metal salts. They also treated it with sodium ethanethiolate in dry ether at room temperature and obtained NN-dimethylbenzamide ethylmethylmercaptal(17) in fairly good yield.

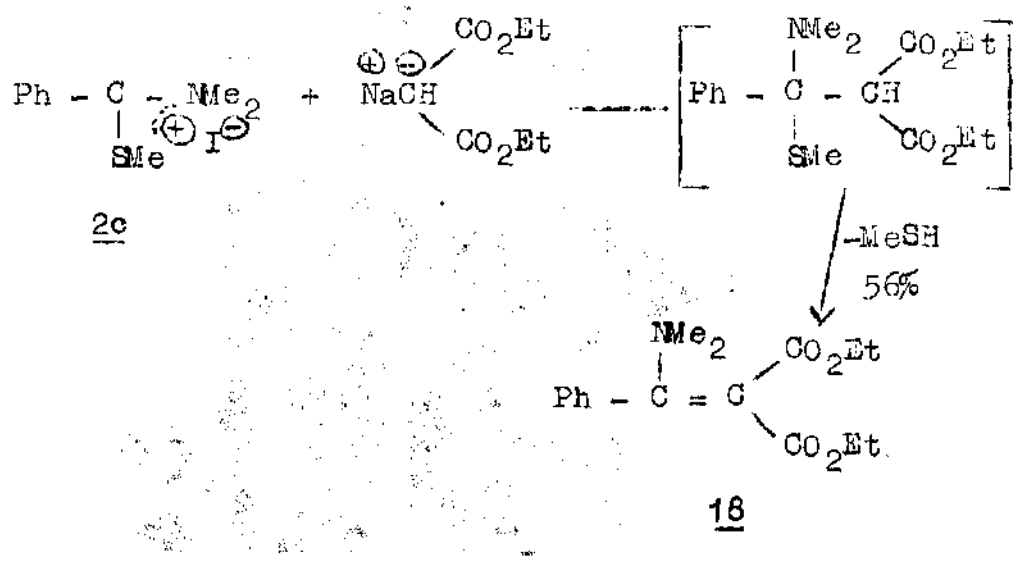


2c

17

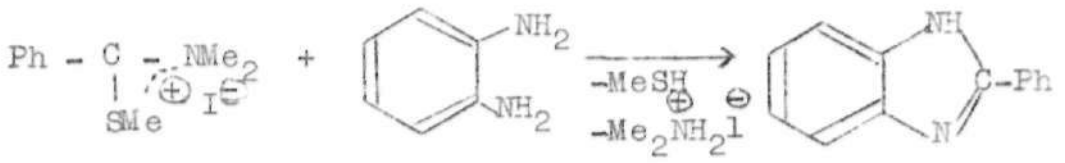
This group found that diethyl α-dimethylaminobenzylidenemalonate(18) was produced in 56% yield with the evolution of methanethiol when a suspension of the

quaternary salt(2c) and the monosodium salt of diethyl malonate in dry dioxane was stirred at 80° for 2h.

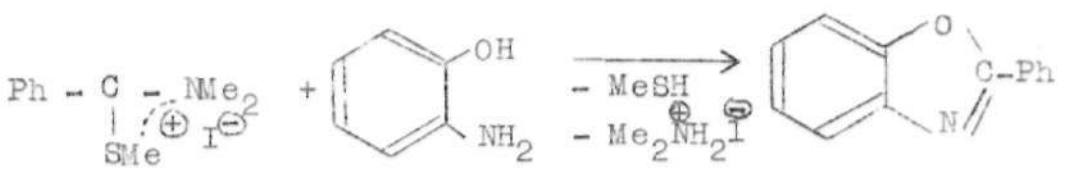


Similar results were obtained by treating methiodide(2c) with the monosodium salts of other active methylene compounds, such as ethyl acetoacetate, ethyl cyanoacetate, acetylacetone and nitromethane.

When o-phenylenediamine was reacted with the salt(2c) at room temperature in ethanol, 2-phenylbenzimidazole(19) was isolated in high yield. In a similar way, 2-phenylbenzoxazole(20) was prepared in good yield by reaction between o-aminophenol and the methiodide(2c).

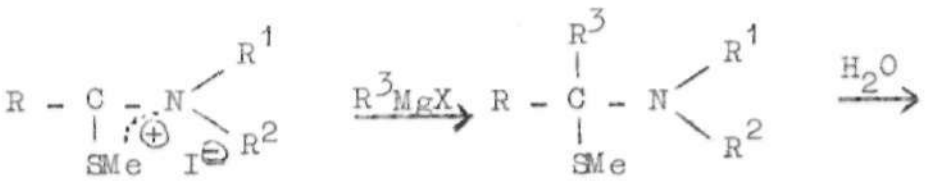


2c 19



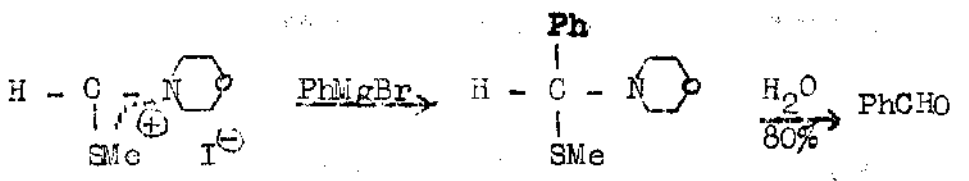
2c 20

Yamaguchi and his co-workers[16] reported that the treatment of the salts(2) with Grignard reagents gave carbonyl compounds after hydrolysis.



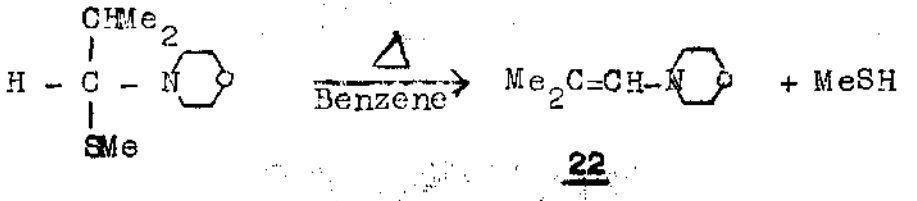
$R_2CO.R^3$

For example, when thioformomorpholide methiodide was reacted with phenylmagnesium bromide, benzaldehyde was obtained in 80% yield.



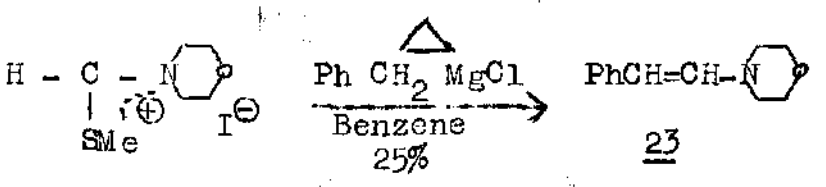
Similarly, reaction of thiobenzomorpholide methiodide(2a) with phenylmagnesium bromide gave benzophenone in 97% yield; other aldehydes and ketones were also obtained (55 - 57% yields).

Some of the compounds (21) were isolated as oils, for example compound (21; R = H; NR^1R^2 = morpholino; R^3 = Me_2CH), which on heating in benzene gave the enamine (22).



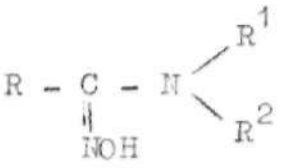
22

Boiling thicformomorpholide methiodide with benzylmagnesium chloride in benzene produced compound (23) in poor yield.



We have recently treated the S-alkyl quaternary salts(2) with other nucleophiles.[10b] Thus NN-disubstituted amidoximes(24) were obtained from the action of

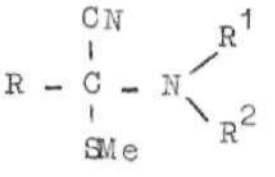
hydroxyammonium chloride on compounds (2a) and (2c) in presence of excess sodium acetate in aqueous solution at room temperature, methanethiol being evolved.



24

	R	R^1, R^2, or NR^1R^2
a	C_6H_5-	morpholino
b	C_6H_5-	$R^1 = R^2 = Me$

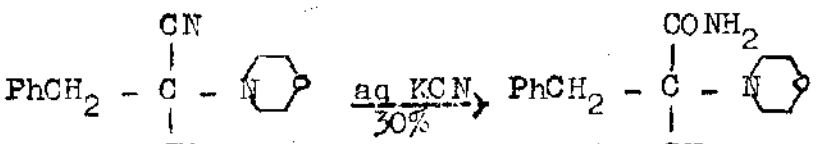
On reacting most of the salts(2) with aqueous potassium cyanide at room temperature, we obtained S-alkyl quaternary cyanides(25),[10c] compounds which showed unusal retention of both the alkylthio- and disubstituted amino- groups. In the present investigation, however, three new quaternary cyanides (25; g, h, and i) were prepared using the general procedure described above.



25

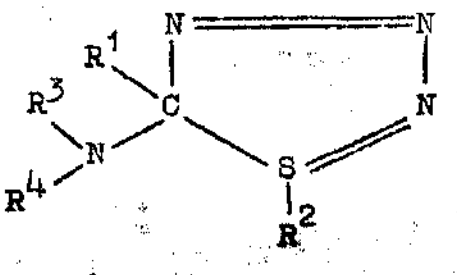
	R	R^1, R^2, or NR^1R^2
a	CH_3-	morpholino
b	$C_6H_5CH_2$-	morpholino
c	CH_3-	$R^1 = R^2 = Me$

The quaternary cyanides(25; R = alkyl) have been shown[10e] to be the precursors of the cyanoamides(26), e.g. treatment of the cyanide (25e) with aqueous potassium cyanide at room temperature gave the corresponding cyanoamide(26b).



25e 26b

Recently the synthesis of 1,5-dihydro-1,2,3,4-thia (S^{IV}) triazoles(27) in high yields from the quaternary salts of NN-disubstituted thioamides and sodium azide was reported by Mathew and Stanfield.[17]



27

[R^1 = aryl or alkyl; R^2 = alkyl; R^3 = R^4 = alkyl or NR^3R^4 = morpholino].

CHAPTER TWO

RESULTS AND DISCUSSION

THE WILLGERODT-KINDLER REACTION

We have previously reported[10f] the synthesis of thiosalicylmorpholide (1f) in good yield from salicylaldehyde, an indication that the Willgerodt-Kindler procedure is of general scope.

In the present investigation, thioisobutyromorpholide (1k) was made in 78% yield by reacting isobutyraldehyde, sulphur and morpholine under the Willgerodt-Kindler conditions, despite steric hindrance. The success of the synthesis of this thioamide further establishes the wide applicability of this synthetic procedure.

Thioisobutyrodimethylamide (1l) was obtained in 71% yield when a mixture of isobutyraldehyde, sulphur, dimethylammonium chloride, and anhydrous sodium acetate was boiled in dry pyridine, a modification of the Willgerodt-Kindler procedure.

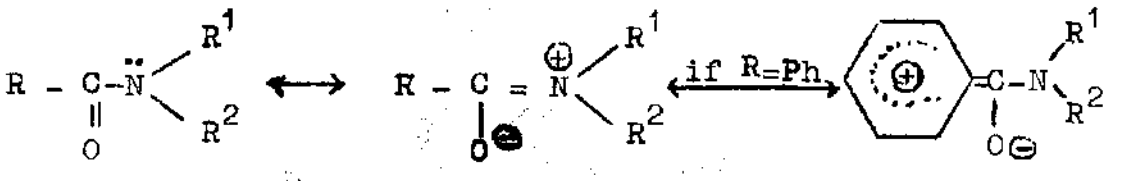
NMR SPECTRA OF NN-DISUBSTITUTED THIOAMIDES

The n.m.r. spectra of NN-disubstituted thioamides (1) show interesting features, particularly in connection with the N-substituents.

The two methyl substituents of the dimethylamino-group in thiobenzo- (1c) and thioisobutyro-dimethylamide (11) are non-equivalent; the former show multiplets at δ3.0 and 3.6 (Fig. 1) whilst the latter give singlets at 3.40 and 3.50 (Fig. 2).

It is well-known that n.m.r. spectra of NN-disubstituted amides and thioamides exhibit separate signals for the groups cis- and trans- to the oxygen or sulphur atom.

Rotation about the carbon-nitrogen bond of an amide (28)[19] is hindered by participation in the ground state of the limiting structures (29), though in the case of a substituted benzamide, a resonance contribution (30) reduces the C=N character and therefore the rotation threshold.



28 29 30

Thioamides show greater resistance to free rotation than amides. The non-equivalence of the two methyl groups of thiodimethylamides (1c) and (11) is therefore understandable.

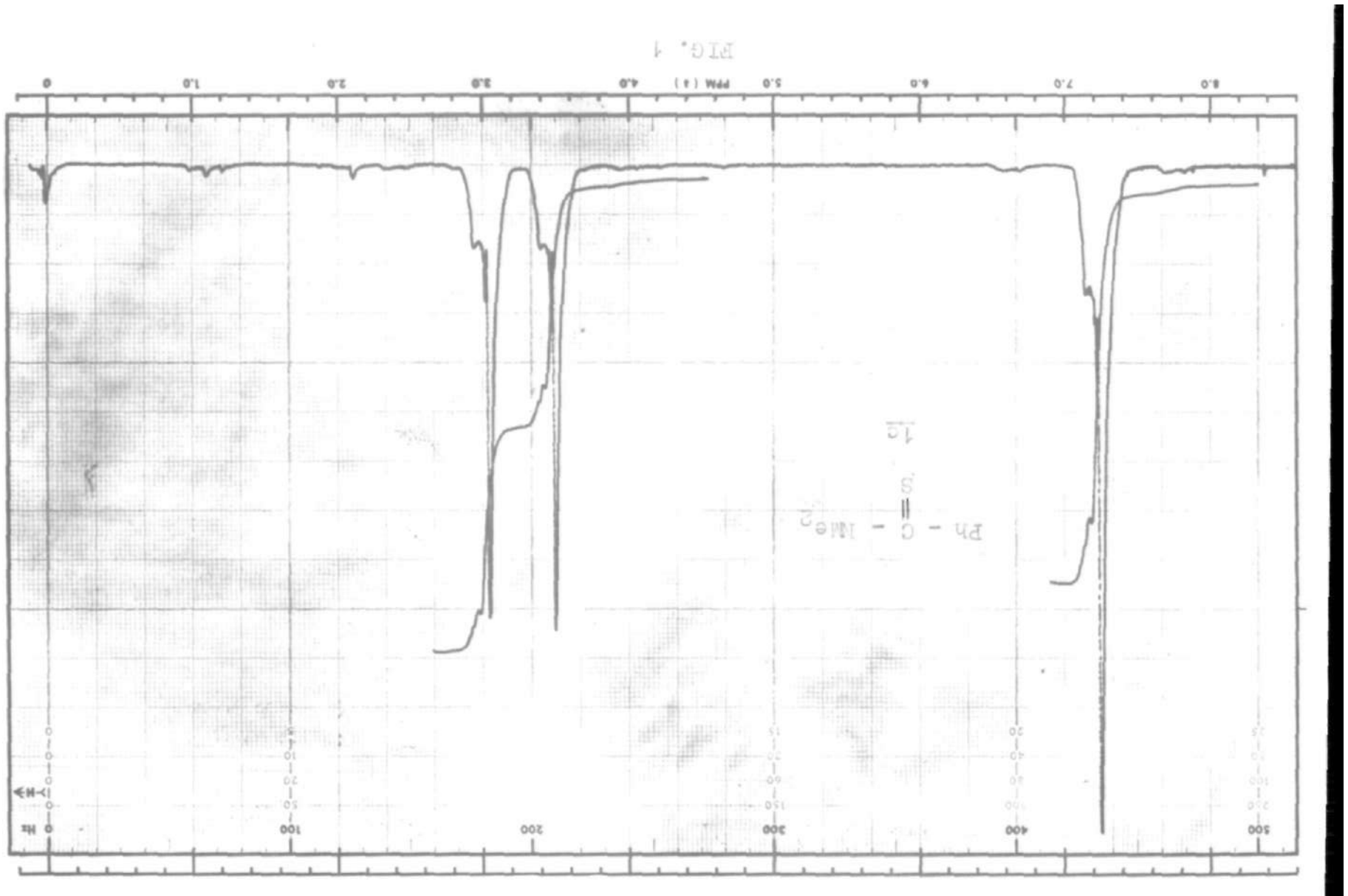

8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0
500
400
300
200
100
0 Hz
INTEGRAL
Ph - C - NMe_2
S
^{13}C

FIG. 1

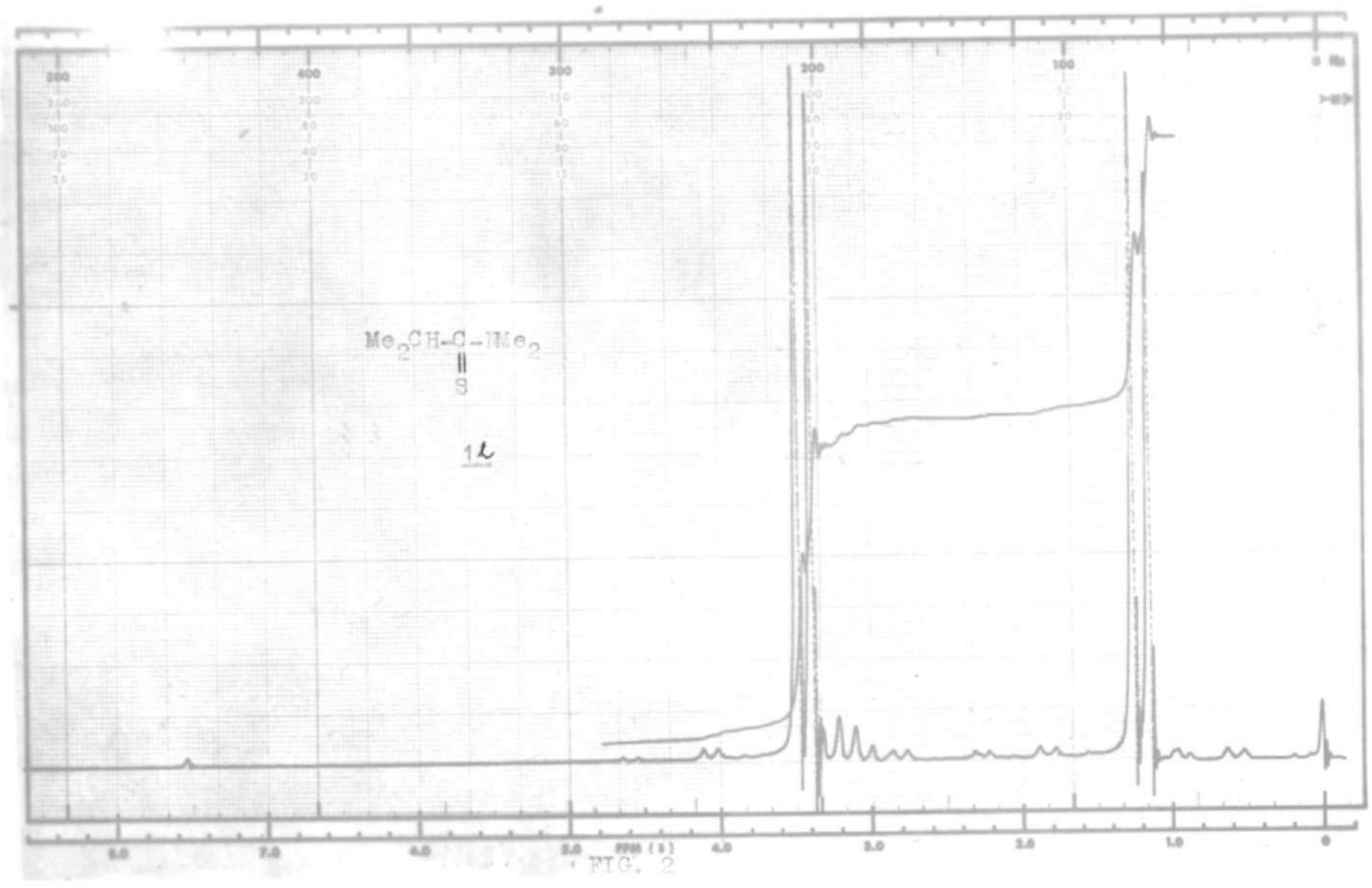


FIG. 2

Frucht et al[20] have shown that in general for NN-disubstituted amides in aromatic solvents the signals associated with the N-substituents trans- to the carbonyl oxygen are upfield. No generalisation was made regarding the signal positions in non-aromatic solvents. Although the n.m.r. spectra of thioamides (1c) and (11) were run in deuteriochloroform, it is, nevertheless, conceivable to assign the downfield signal to the N-methyl group cis- to the thiocarbonyl sulphur mainly on grounds of inductive effect.

The signals due to the morpholino- group of thiobenzo- (1a) and thioisobutyro- morpholide (1k) are interesting. The morpholino- group of thioamide (1a) is represented by two triplets at δ4.4 and 3.8 (each 2H) and a singlet at 3.60 (4H) (Fig. 3). The fact that the four methylene groups are non-equivalent is not surprising since the real structure of thiobenzo-morpholide is not (1a) but a hybrid which includes contributions from the other canonical forms (31) and (32). Restricted rotation about the carbon-nitrogen bond explains the non-equivalence of the four methylene groups.

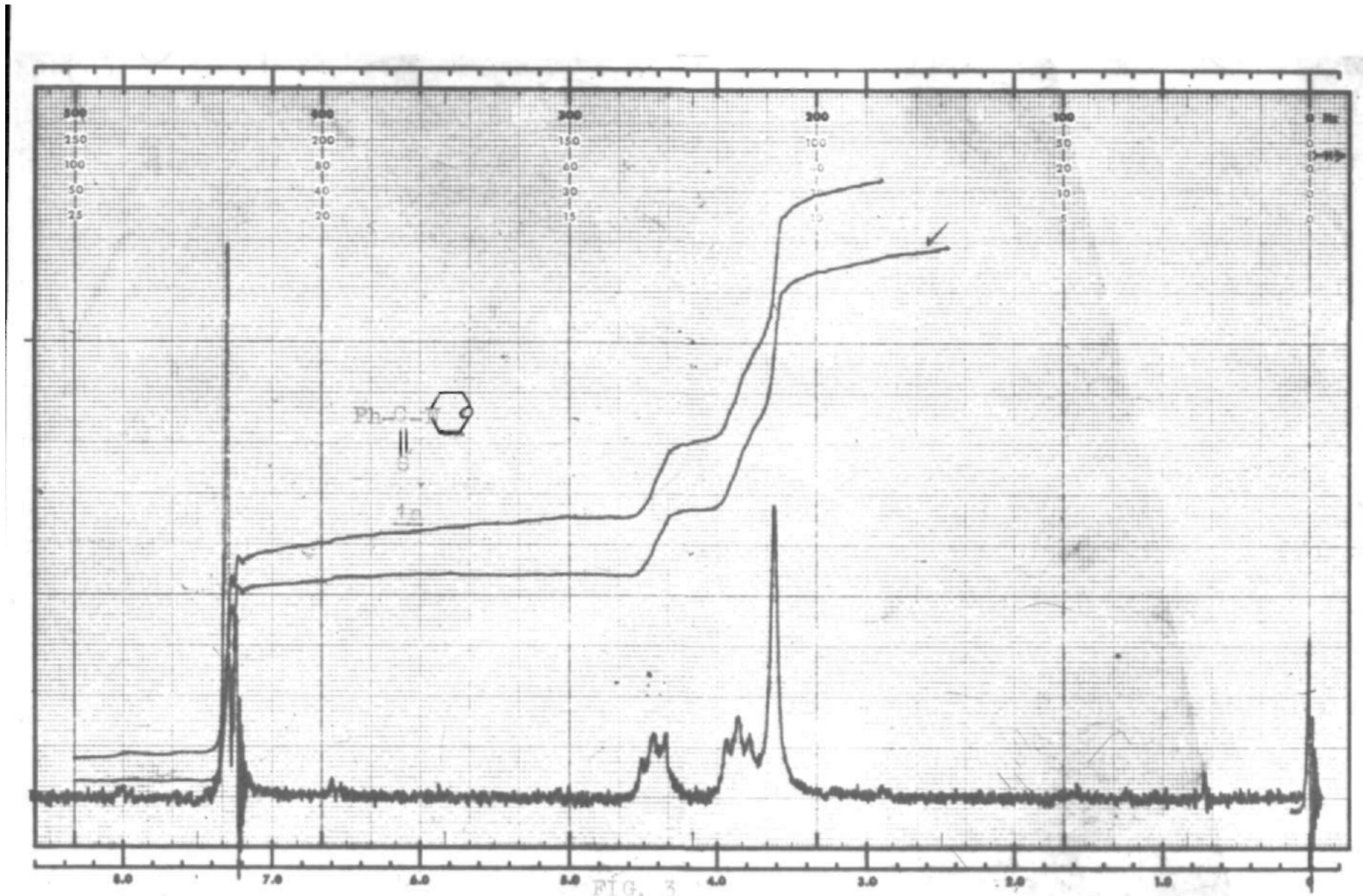
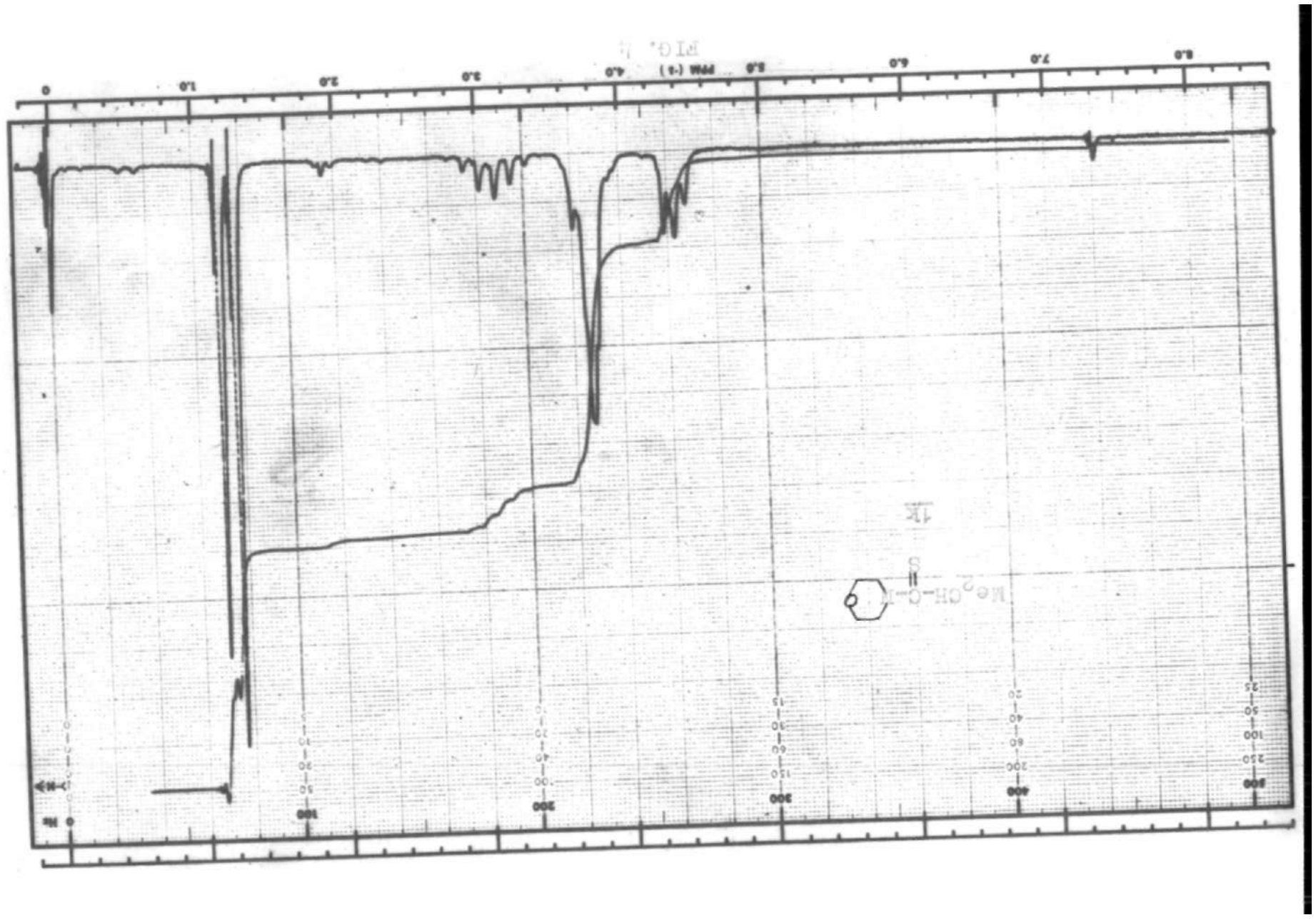


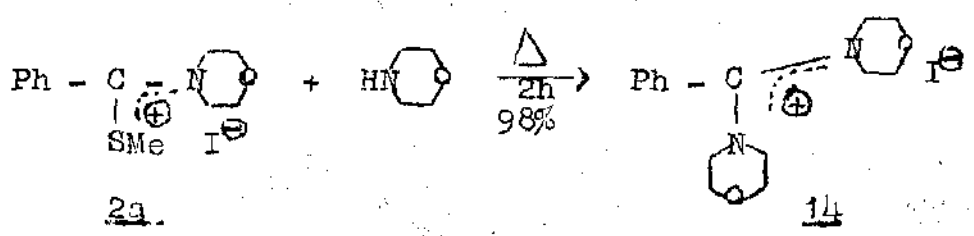
FIG. 3


FIG. 1
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0
1K
S
Me2CH-C-N

the N-methylene cis- to the thiocarbonyl sulphur, the multiplet at 3.8 is probably due to a triplet and singlet which have merged.

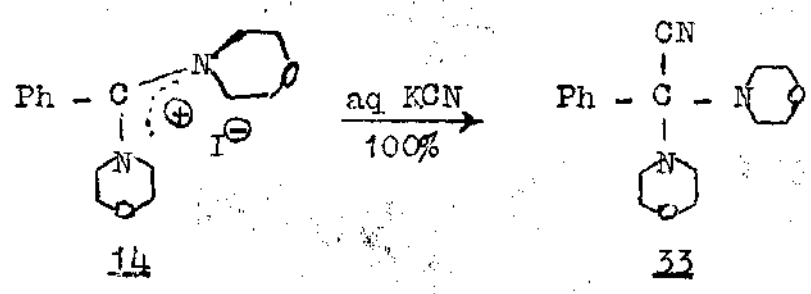
PREPARATION AND REACTIONS OF AMIDINIUM SALTS

In this study the amidinium salt (14)[8] was prepared in high yield by heating a mixture of thiobenzomorpholide methiodide (2a) and morpholine.



2a. 14

Reaction of salt (14) with aqueous potassium cyanide at room temperature gave quantitatively aa-dimorpholinobenzyl cyanide (33).



14 33

This expected product was characterised by it s spectral properties and elemental analysis. Its fairly high melting point (160°) and slight solubility in ether suggest that it has appreciable ionic character.

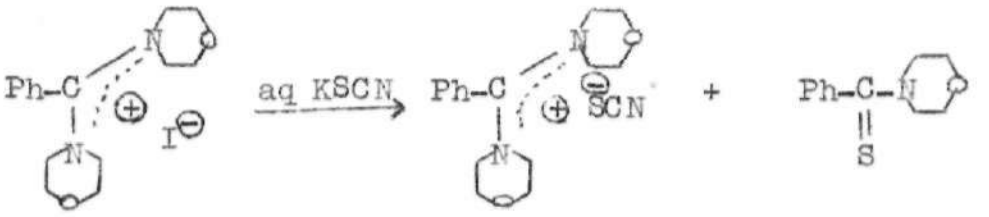
A characteristic feature of compound (33) was the absence of cyanide group absorption between 2300 and 2000 cm^{-1} (Fig. 5). This was not a surprise considering the reports about the i.r. absorption of this group. Kitson and Griffith[21] have found that there is a marked variation in absorption intensity of various types of nitriles, varying from very strong to undetectable. Jesson and Thompson[22] have also shown that the cyanide band intensity appears to be more susceptible than its frequency to structural influences and other factors. Bellamy,[23] however, states that low intensities are not easy to explain in simple chemical terms, and are probably due to interaction effects, which are too small to have much influence on the frequency but, produce significant changes in intensities.

The intensity due to C≡N stretching is variable; it is generally strong but is lowered by electron - withdrawing groups.[24] However, compound (33) has electron-donating groups.

We share the opinion of Jesson and Thompson[22] and suggest that the absence of i.r. cyanide absorption by compound (33) may be due largely to structural influences.

The n.m.r. spectrum of cyanide (33) was simple (Fig. 6) considering the extensive steric hindrance in its molecular constitution. The spectrum showed a singlet at δ7.43 (5H, C_6H_5), a triplet at 3.7 (8H, two CH_2-O-CH_2)(J $3H_z$) and a multiplet at 2.6 (8H, two CH_2-N-CH_2).

On stirring a mixture of the amidinium salt (14) and aqueous potassium thiocyanate at room temperature for 12h, the amidinium thiocyanate (34) was produced in good yield together with a smaller amount of thiobenzomorpholide (1a).



14 — 34, 65% — 1a, 46%

The thiocyanate (34) was characterised by elemental analysis, by its spectral properties, and by its picrate. Its insolubility in ether and its high melting

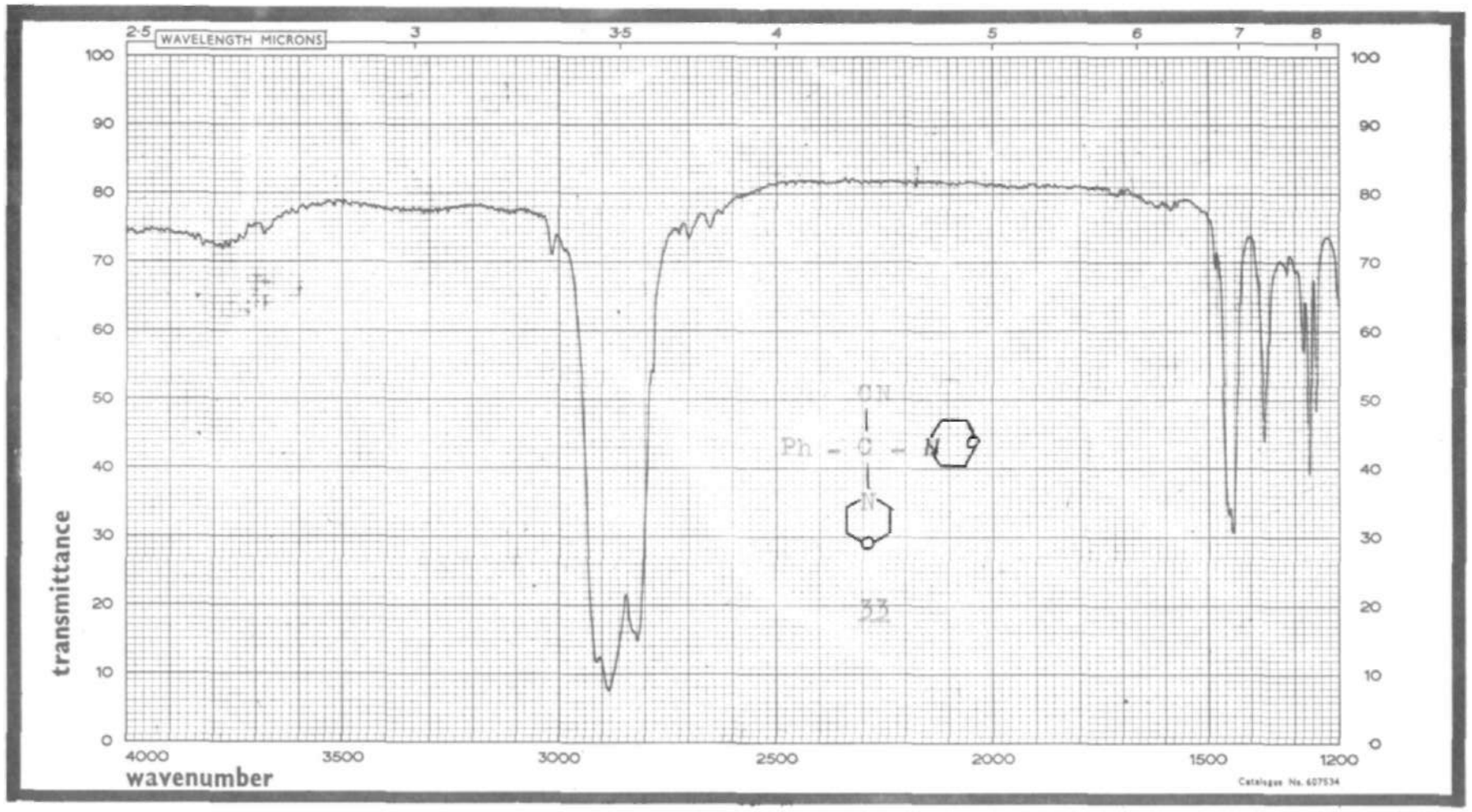
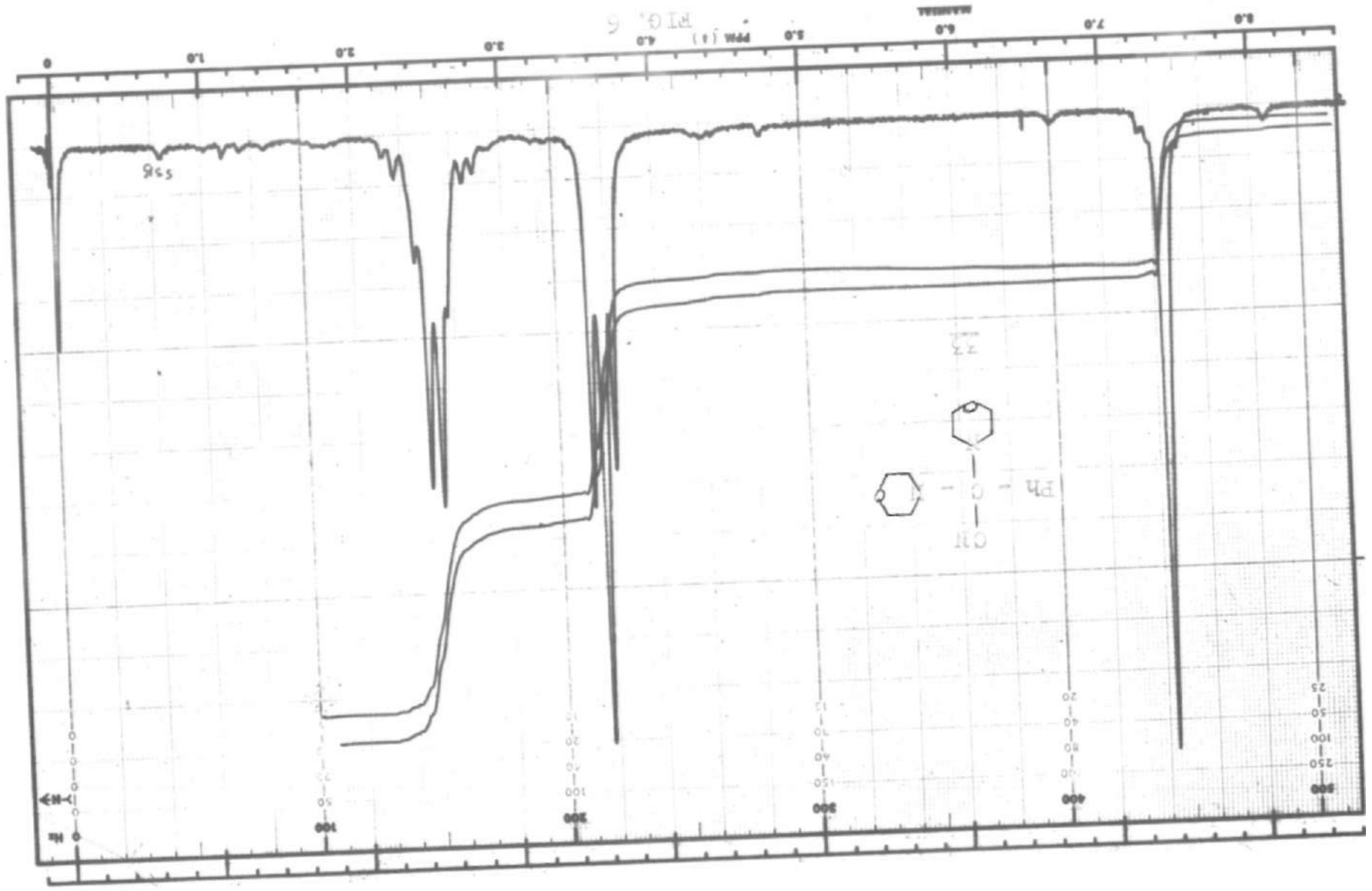
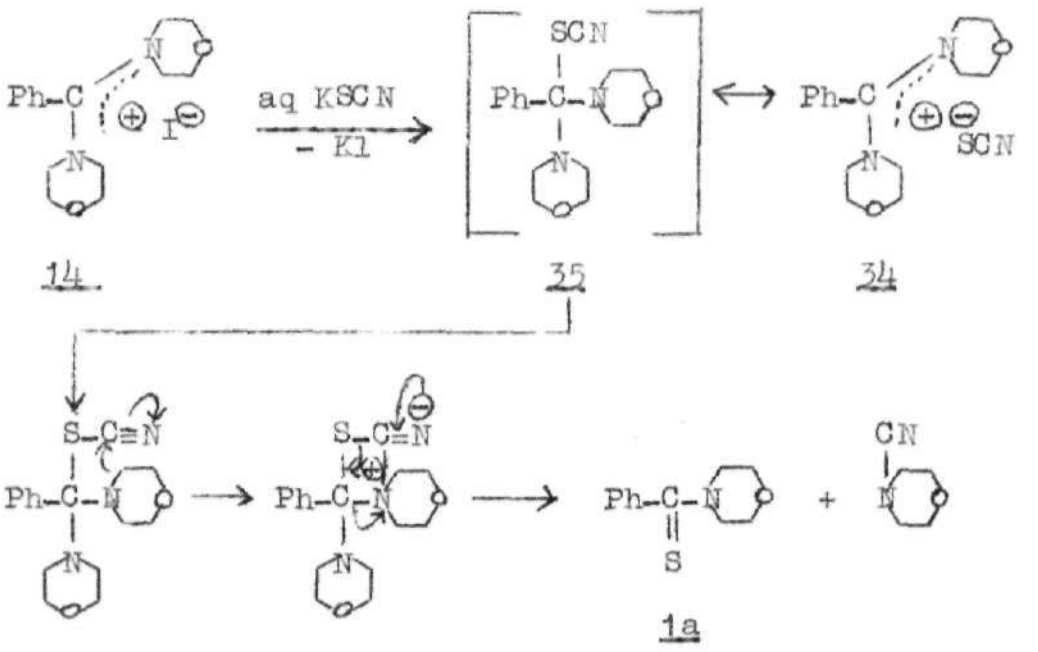

WAVELENGTH MICRONS
2·5
3
3·5
4
5
6
7
8
100
90
80
70
60
50
40
30
20
10
0
transmittance
4000
3500
3000
2500
2000
1500
1200
wavenumber
Ph - C - N
O
N
33
Catalogue No. 607534

FIG. 5


FIG. 6
PPM (δ)
INTEGRAL
5.26
Ph - C - Cl
CH

point (254-255°) suggest that it exists predominantly in ionic form. It showed very strong thiocyanate absorption at 2040 cm^{-1} (Fig. 7).

The surprising formation of thioamide (1a) appears explicable by steric factors and neighbouring group participation. The covalent intermediate (35) perhaps undergoes mesomerism for steric reasons to give the thiocyanate (34) and also affords thioamide (1a) by neighbouring group participation.



Experiments were carried out to establish the mechanism of the formation of thiobenzomorpholide (1a).

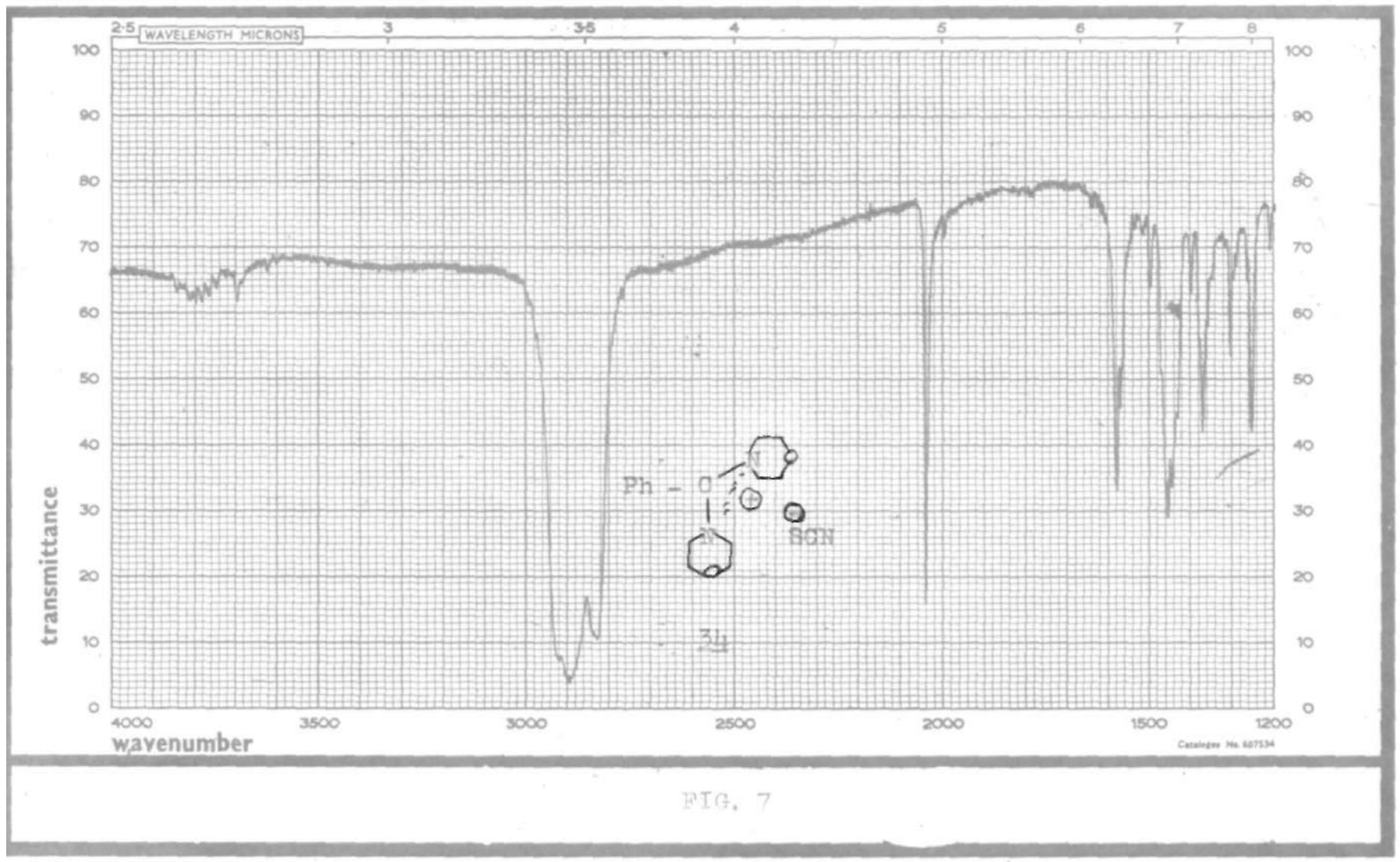
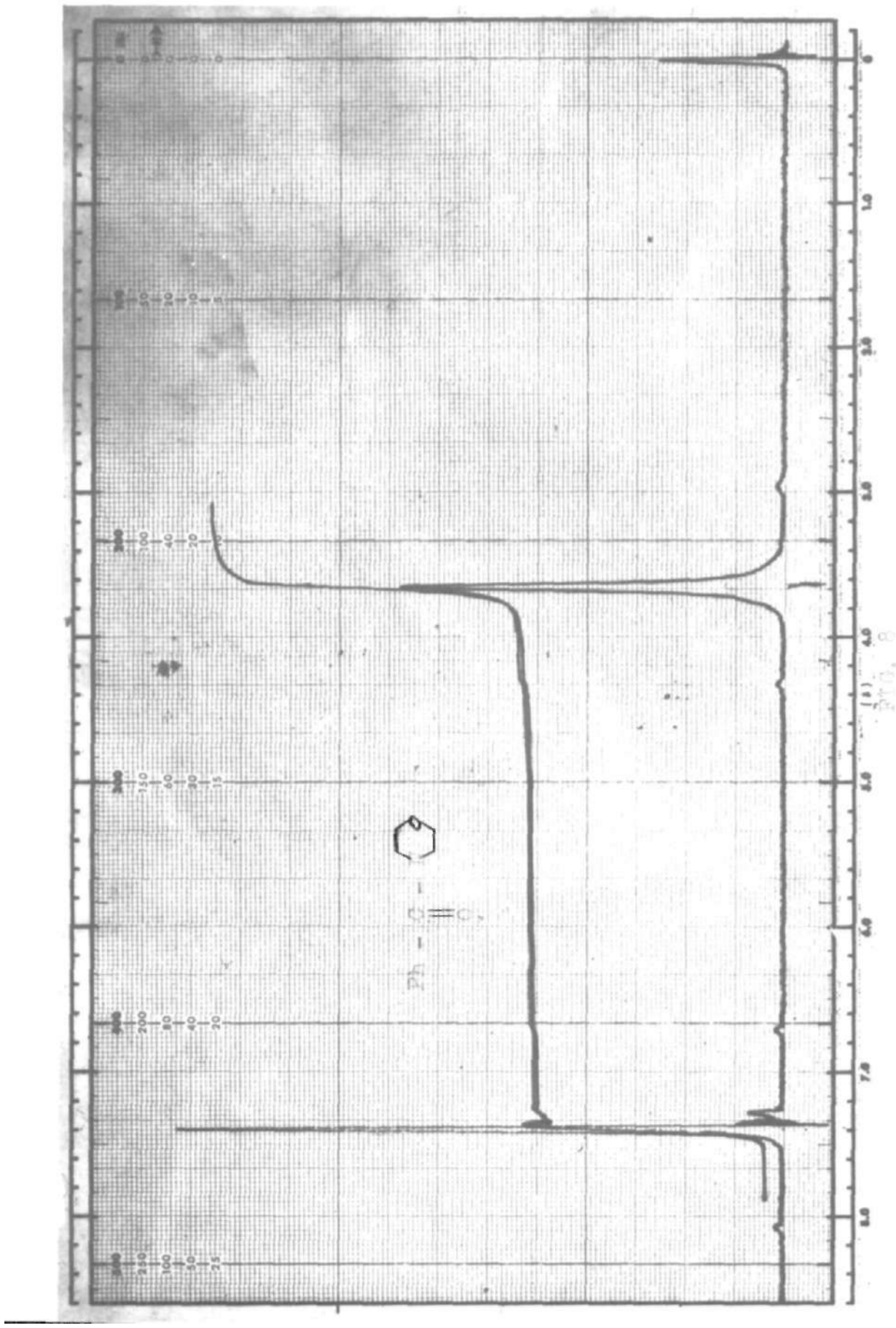

2·5
WAVELENGTH MICRONS
3
3·5
4
5
6
7
8
100
90
80
70
60
50
40
30
20
10
0
transmittance
Ph – O
BGN
34
4000
3500
3000
2500
2000
1500
1200
wavenumber
Catalogue No. 667534

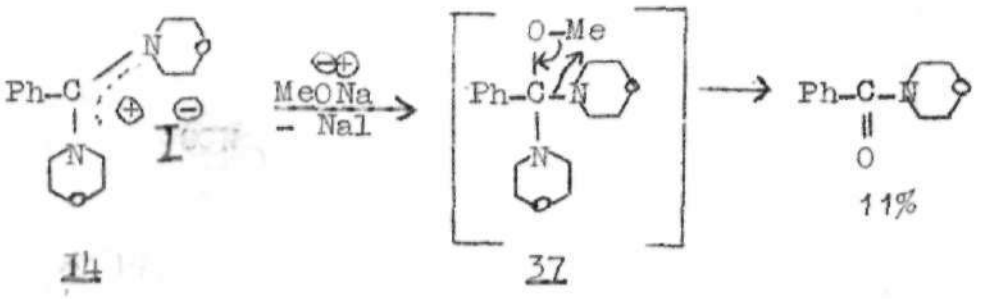
FIG. 7



Reaction of the amidinium thiocyanate (34) and aqueous potassium thiocyanate was repeated in the presence of potassium iodide to create the original reaction conditions but the attempt led to the recovery of the thiocyanate (34). Boiling a mixture of the amidinium salt (34) and potassium thiocyanate in acetonitrile also led to recovery of starting material.

From the above results it appears that the amidinium thiocyanate (34) is not the precursor of thiobenzomorpholide (1a), which probably arises from some other intermediate.

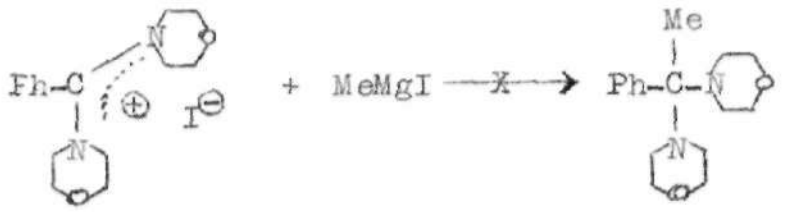
When amidinium iodide (14) was treated with sodium methoxide benzomorpholide was obtained in poor yield. A simple mechanism for this reaction would entail formation of the intermediate (37) which may lose N-methylmorpholine to give the amide.



14 37

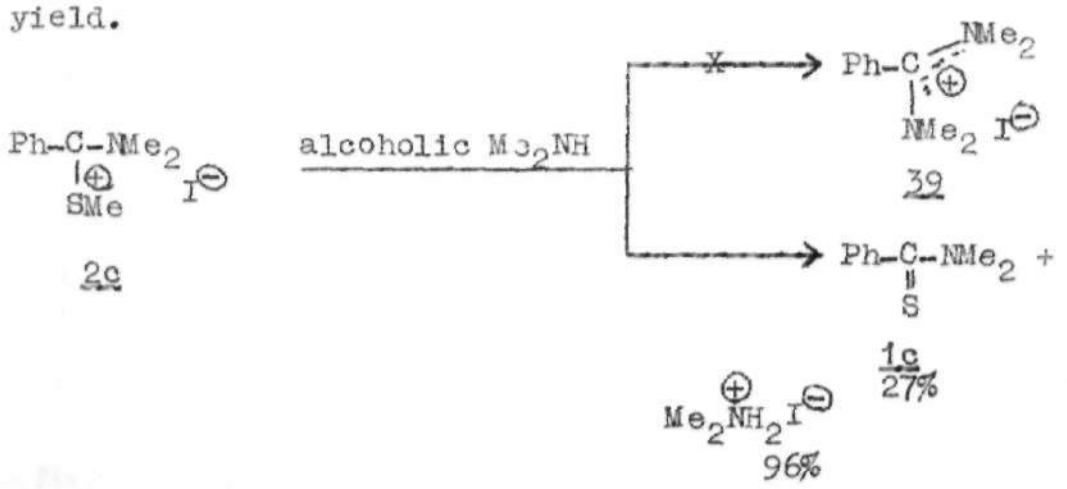
The amidinium salt (14) was recovered unchanged from reaction with methylmagnesium iodide. It was

hoped to isolate compound (38) which would probably after hydrolysis give a carbonyl compound. Carbonyl compounds are usually formed by treating quaternary salts (2) with Grignard reagents, followed by hydrolysis.[16]



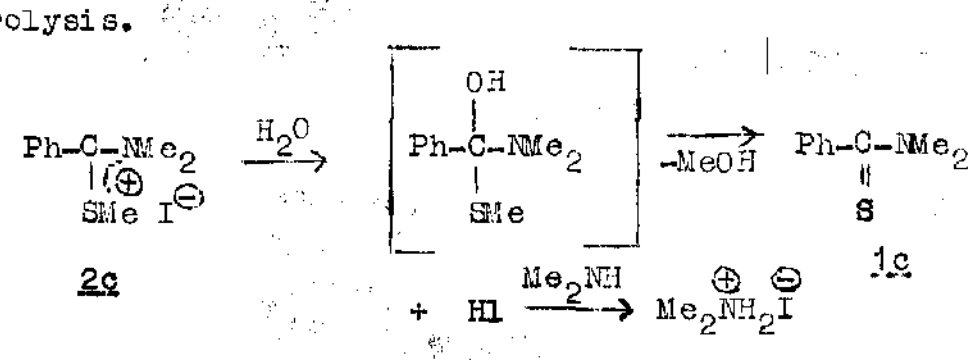
14 38

Attempts made to prepare the amidinium salt (39) by the reaction of thiobenzodimethylamide methiodide (2c) with dimethylamine proved abortive. Treating the methiodide (2c) with aqueous dimethylamine gave thiobenzodimethylamide (1c) in poor yield, whereas the treatment of salt (2c) with alcoholic dimethylamine solution produced not only the thioamide (1c) in poor yield, but also dimethylammonium iodide in excellent yield.

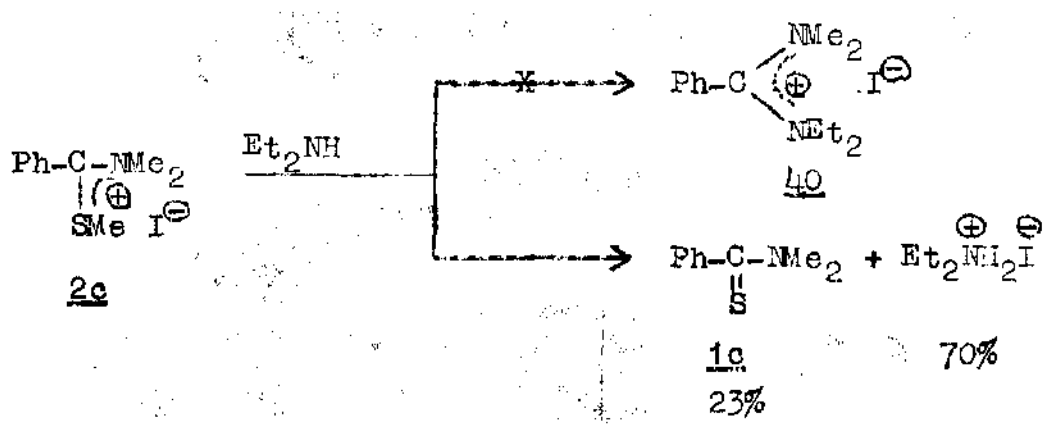


2c 39 1c 27%

Dimethylammonium iodide was probably formed also with aqueous dimethylamine, but could not be isolated because it is extremely water-soluble. Formation of thiobenzodimethylamide (1c) could be explained by hydrolysis.



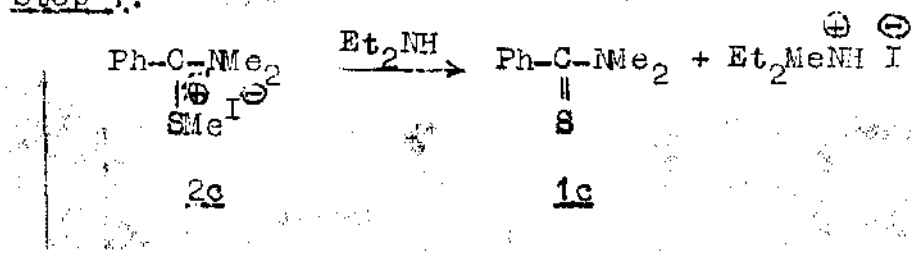
Similarly, the methiodide (2c) with diethylamine failed to give the expected amidinium salt (40), but gave the thioamide (1c) and diethylammonium iodide.



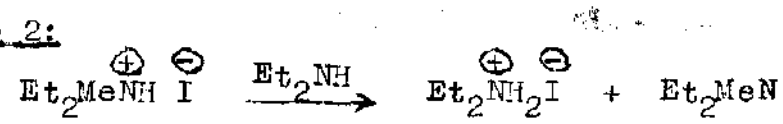
The course of this reaction can be explained by a two-step mechanism, the first step shows the formation

of the thioamide (1c) and ethylmethylammonium iodide which reacts with excess of the amine in the second step to give diethylammonium iodide and diethylmethylamine.

Step 1:



Step 2:



PREPARATION AND REACTIONS OF NN'S'-TETRAMETHYLDITHIOCARBAMIDIUM IODIDE

The thioester, methyl NN-dimethyldithiocarbamate (41) was made as reported by Ainley *et al.*[25] by treating a mixture of aqueous solutions of dimethylamine and sodium hydroxide with carbon disulphide, followed by the addition of dimethylsulphate. It was also prepared by reacting sodium dimethyldithiocarbamate with methyl iodide.

Quarternisation of the thioester (41) with methyl iodide to the salt (42) was carried out by the method of Hartke et al.[26]



41 42

Treatment of the salt (42) with aqueous potassium cyanide at room temperature gave dimethylaminobis(methylthio)-methyl cyanide (43) in high yield. The product was characterised by its spectral properties and elemental analysis.



42 43

Compound (43) gave weak cyanide absorption at 2220 cm^{-1} (Fig. 9) and aborbed at λ_{sh} 275 nm in ethanol (ε_{sh} 93) (Fig. 10). From the very low intensity it would seem that the latter is a forbidden transition and could be attributed to $n \rightarrow \Pi^*$ transition. The n.m.r. spectrum (neat) of compound (43) is extremely simple,

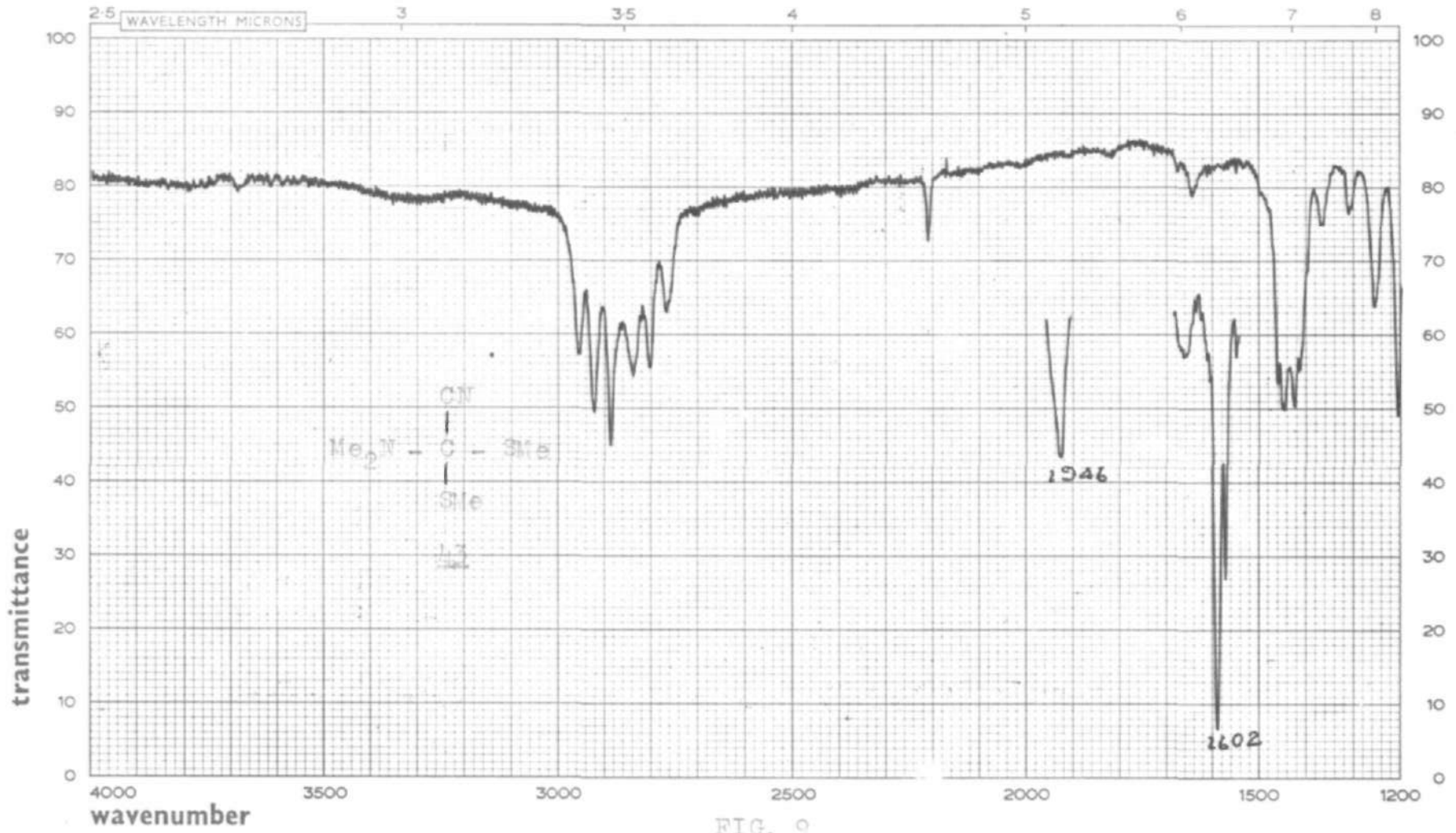

2·5
WAVELENGTH MICRONS
3
3·5
4
5
6
7
8
100
90
80
70
60
50
40
30
20
10
0
transmittance
4000
3500
3000
2500
2000
1500
1200
wavenumber
1946
1602

FIG. 9

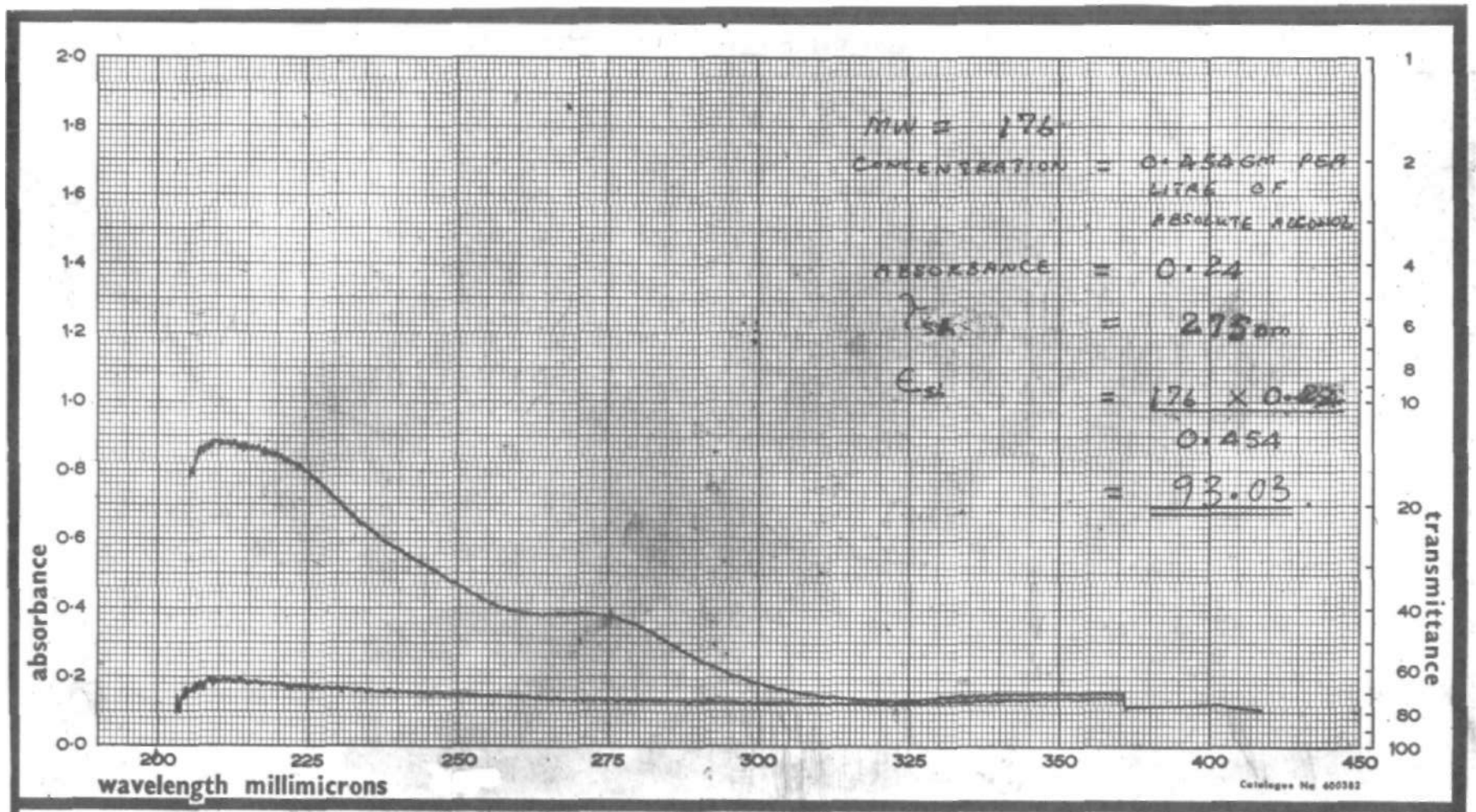
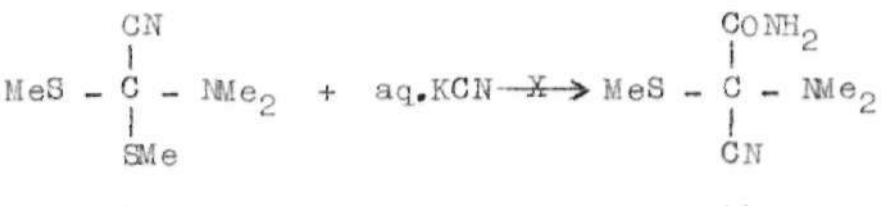


FIG. 10

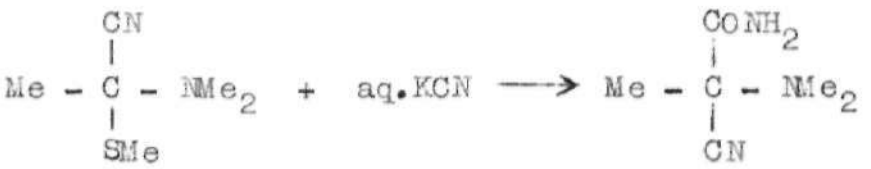
$Me_2N - \overset{CN}{\underset{SMe}{\overset{|}{\underset{|}{C}}}} - SMe$

showing two singlets at δ2.60 ($CH_3.N.CH_3$) and at 2.33 (two CH_3S) (Fig. 11).

The cyanide (43) was expected to result from the reaction, but it was also expected that it would undergo "cyanohydrolysis" to give the cyanoamide (44). We have already shown[10e] that with quaternary cyanides (25; R = alkyl) in some cases "cyanohydrolysis" does occur, e.g. compound (25g) gives the cyanoamide (26c) under the same conditions.



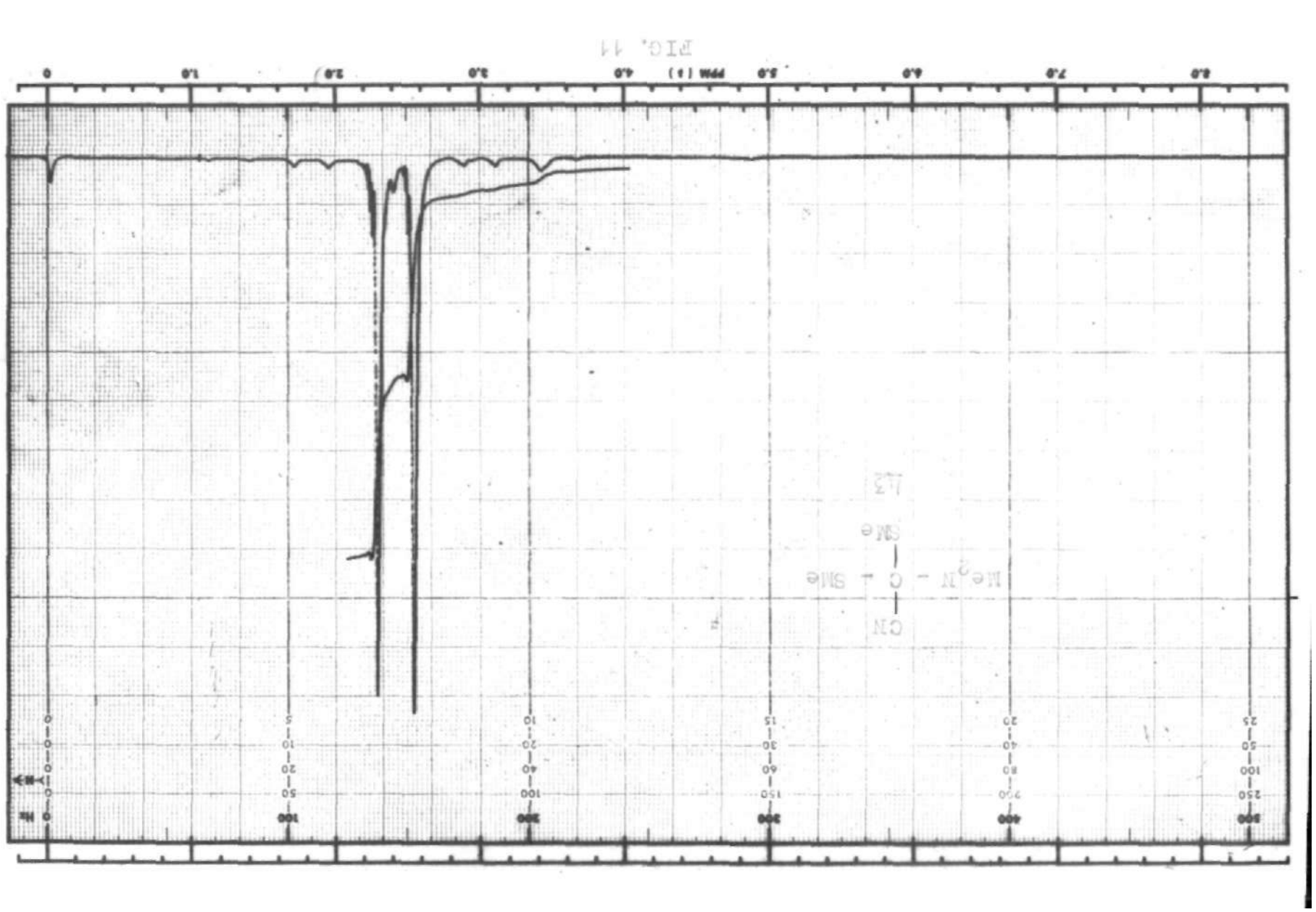
43 44



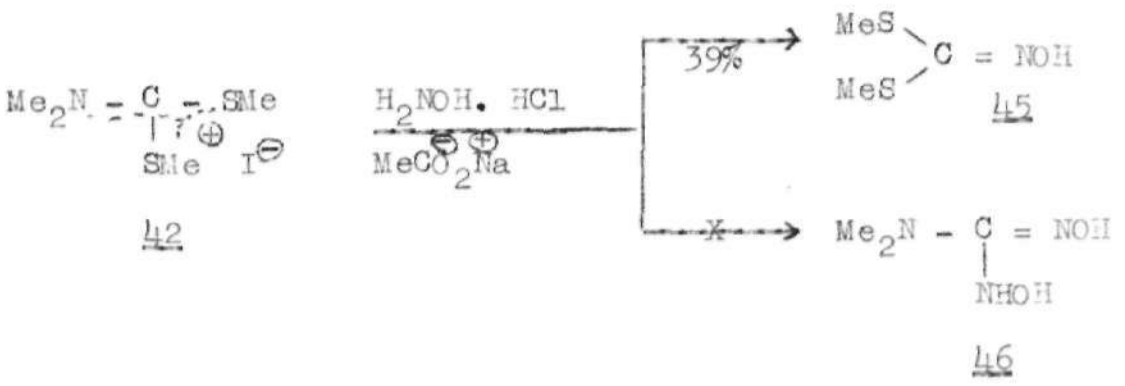
25g 26c

The inability of the cyanide (43) to undergo "cyanohydrolysis" could be due to steric hindrance.

Reaction of the salt (42) with aqueous hydroxyammonium chloride in presence of excess sodium acetate at room temperature gave bis(methylthio)formaldoxime (45)

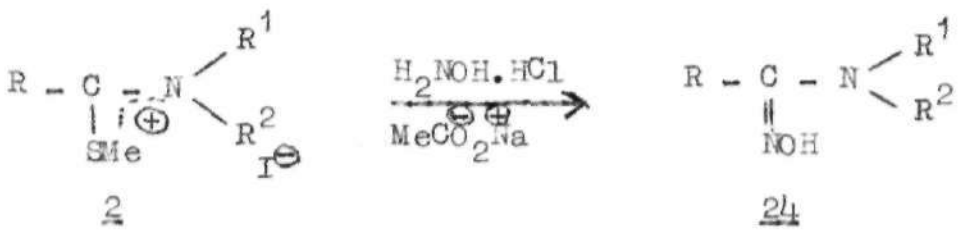

8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

in rather poor yield, instead of the expected product (46).



42 45 46

This reaction was surprising because under basic conditions we expected the elimination of the methylthio-groups as we earlier observed[10b] on treatment of the quaternary salts (2) with hydroxyammonium chloride under similar conditions which led to the isolation of amidoximes (24).

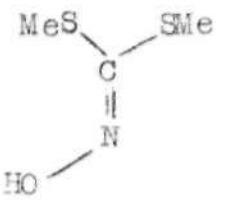


2 24

The formaldoxime (45) showed broad absorption of medium intensity at 3250 (bonded O-H) and also absorption of medium intensity at 1600 cm^{-1} (C = N). Its n.m.r. spectrum showed a singlet at δ9.40 (OH) and also the

non-equivalence of the two methylthio- groups, although the signals almost coincided (singlets at 2.50 and 2.45) (Fig. 12).

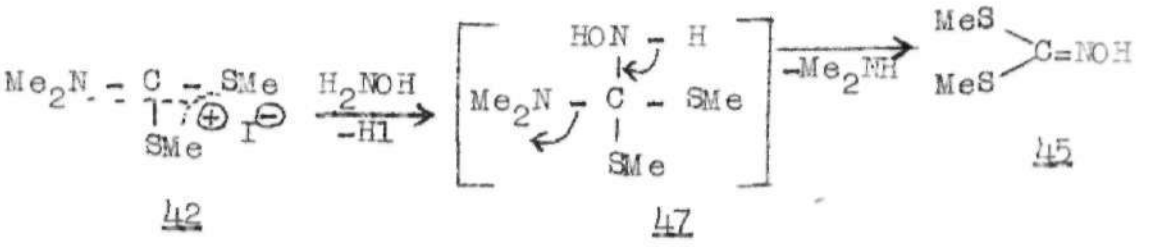
The carbon-nitrogen bond has partial double bond character hence the hydroxyl group remains fixed cis- to one methylthio- group and trans- to the other.



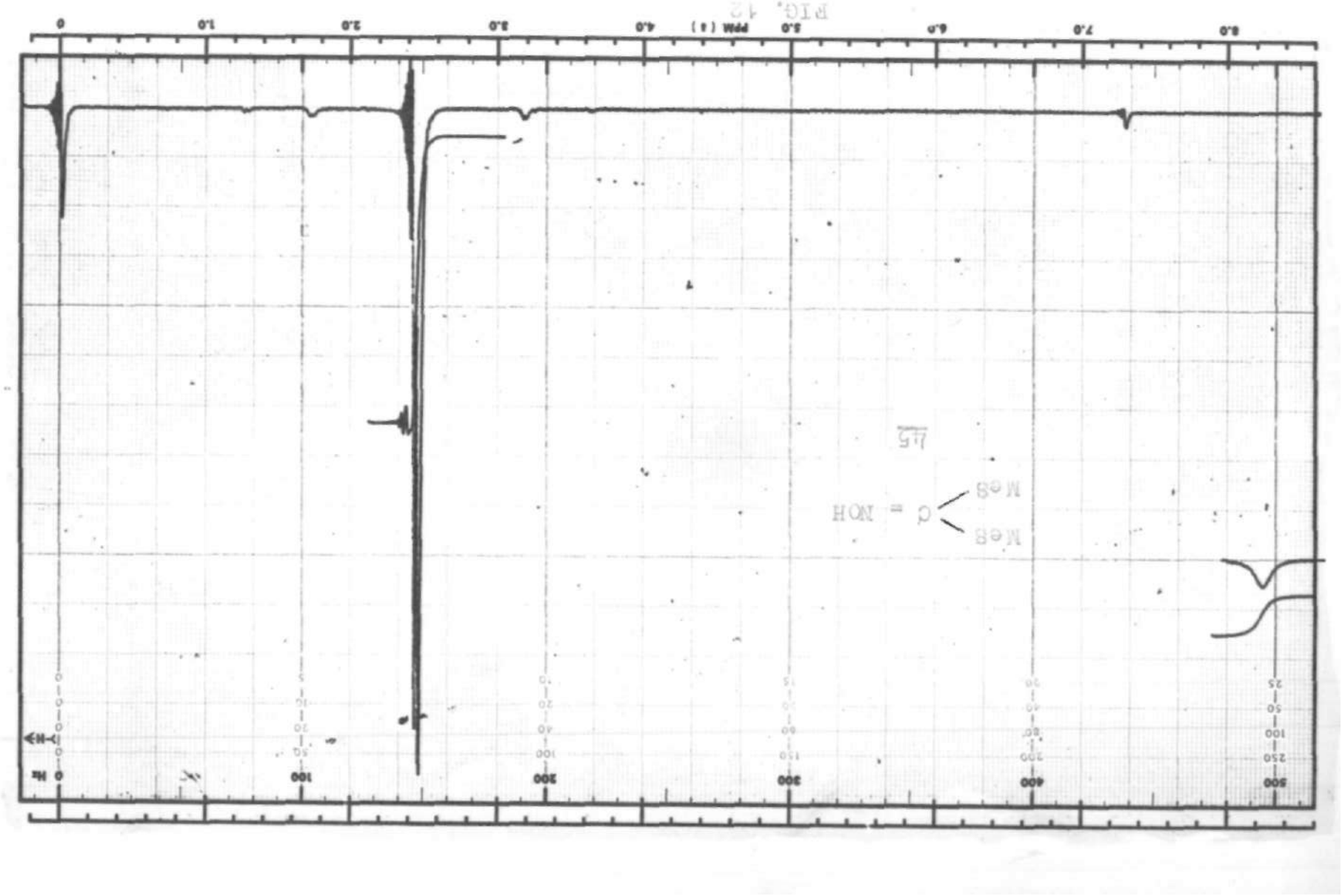
45

The downfield signal could probably be assigned to the methylthio- group cis- to the hydroxyl group on grounds of inductive effect, but this is not conclusive and the nuclear Overhauser effect would probably give a more definitive solution.

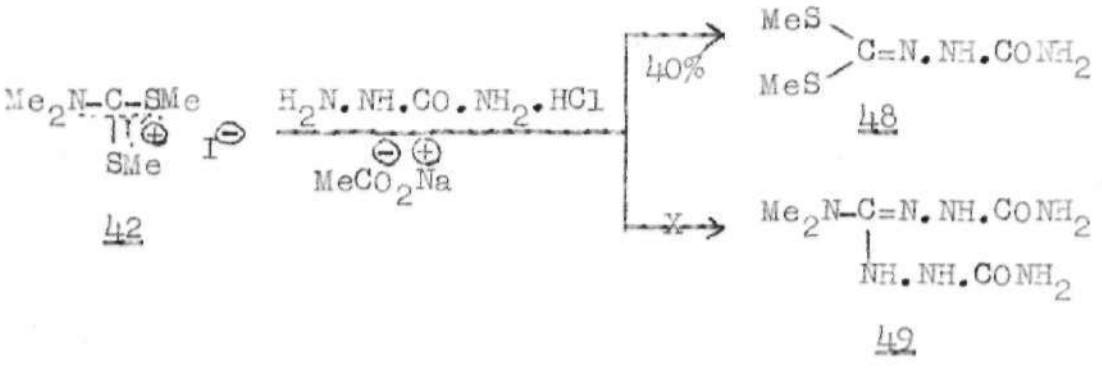
The mechanism of formation of formaldoxime (45) is probably simple, involving loss of dimethylamine from the intermediate (47).



42 47 45


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
PPM (δ)
0 Hz
100
200
300
400
500

Similarly, treatment of salt (42) with an aqueous solution of semicarbazide hydrochloride in presence of excess sodium acetate at room temperature afforded bis(methylthio)formaldehyde semicarbazone (48) in modest yield and not compound (49) which one would explect to result from the basic medium.



The semicarbazone (48) showed strong absorptions at 3475 (free NH), 3175 (NH bonded), 1700 (CO) and at 1600 cm^{-1} (C=N)(Fig. 13). The n.m.r. spectrum of semicarbazone (48) showed absorption at δ8.40 (1H, br s, NH), 5.90 (2H, br s, NH_2), 2.50 and 2.40 (each 3H, s, SCH_3) (Fig. 14).

The non-equivalence of the methylthio- groups and the assignment of signals to them could be explained as for the formaldoxime (45) above, and the mechanism of the reaction is probably similar.

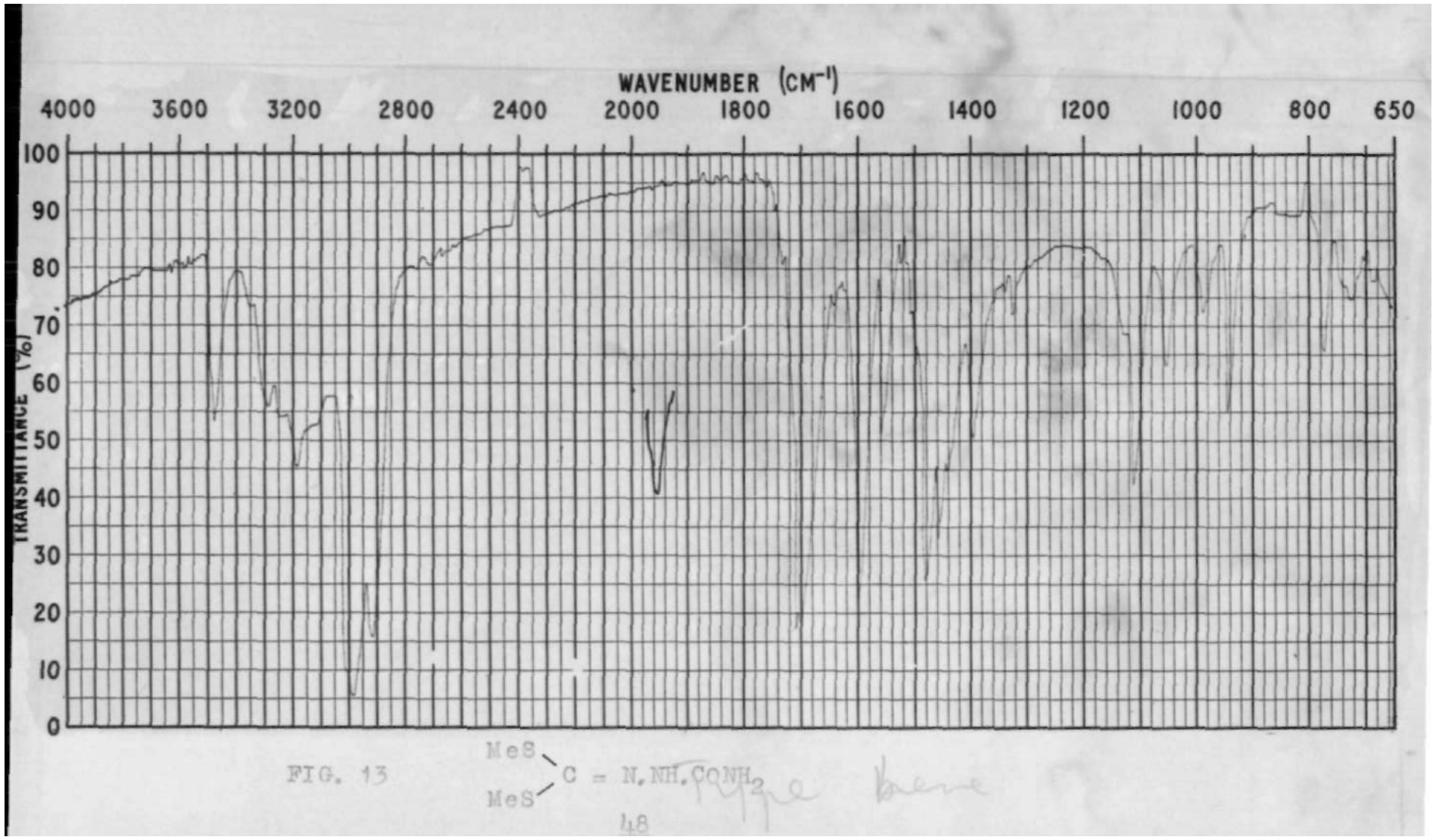
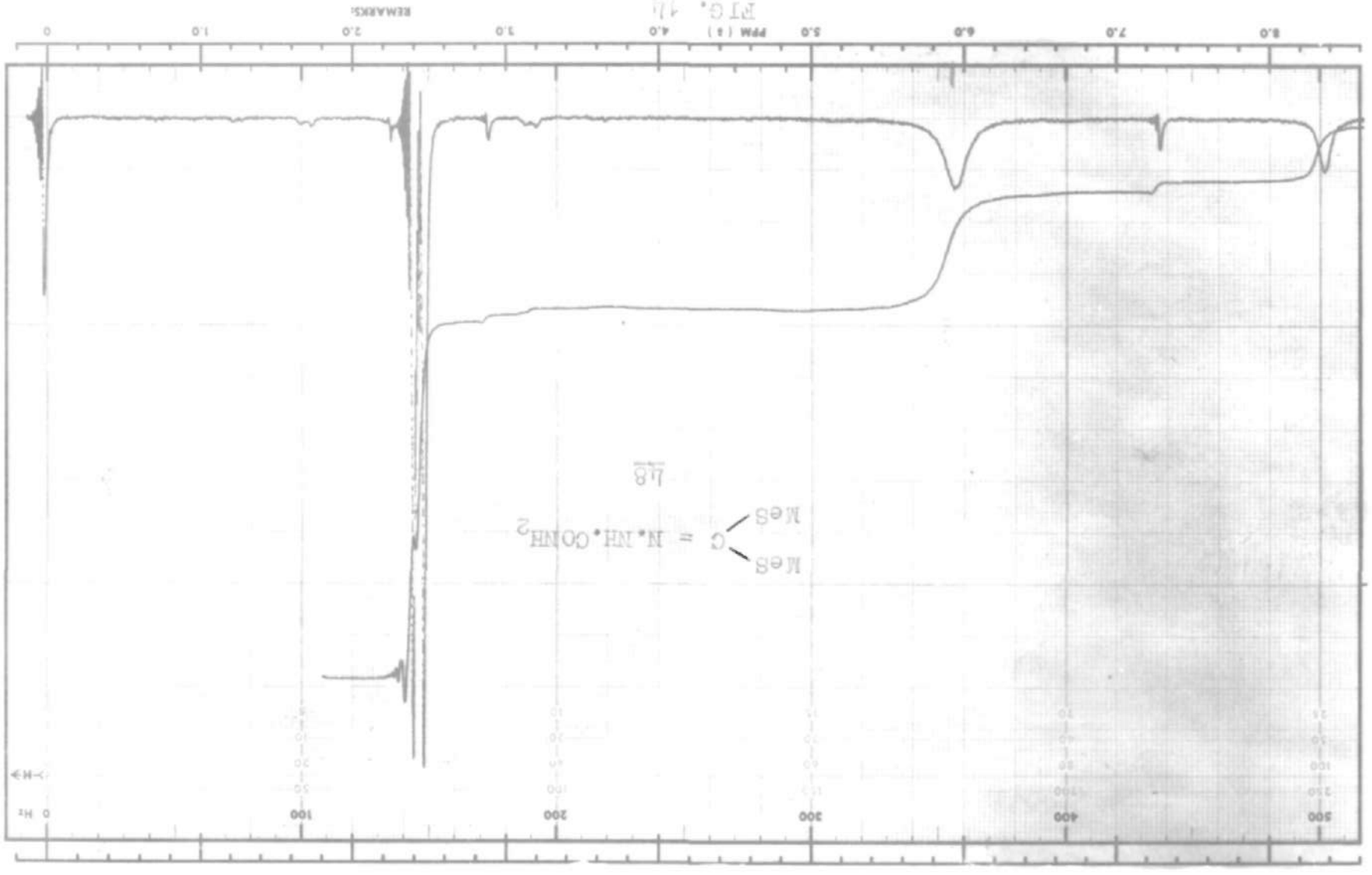


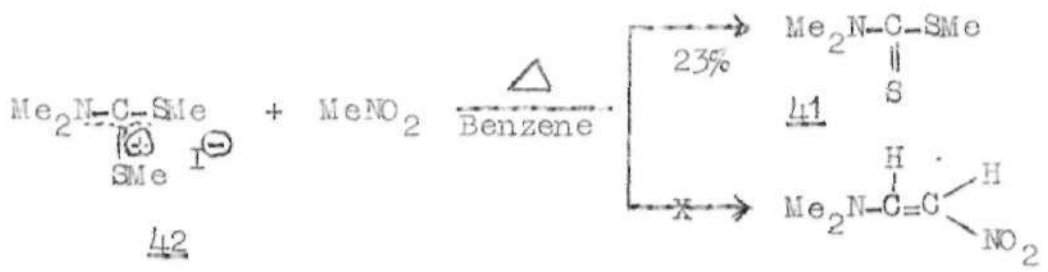
FIG. 13

MeS
MeS
C = N.NH.CONH$_2$

FIG. 4A


REMARKS:
PPM (δ)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
0 Hz
100
200
300
400
500
Me S
C = N.NH.CONH2
Me S
4.8

Boiling a mixture of salt (42) and nitromethane under reflux in benzene effected the demethylation of the salt to the thioester (41) in poor yield. The expected product (50) was not obtained.



42 41 50

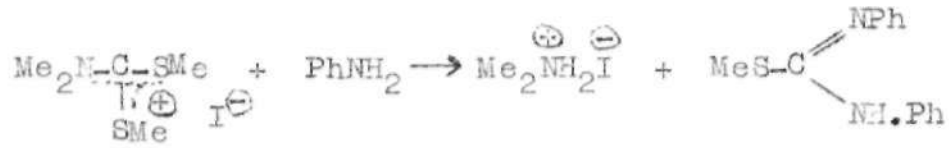
A similar demethylation of salt (42) occurred in poor yield when it was boiled alone in benzene. The demethylation at 80° of salt (42) precludes its use for reactions at elevated temperatures.

Stansfield[11] observed demethylation of methiodide (2a), m.p. 158° (dec.) giving thiobenzomorpholide (1a) at slightly below its melting point.



2a 1a

Reaction of salt (42) and excess aniline gave dimethylammonium iodide and S-methyl-NN'-diphenylisothiourea were isoltated in high and low yields respectively.

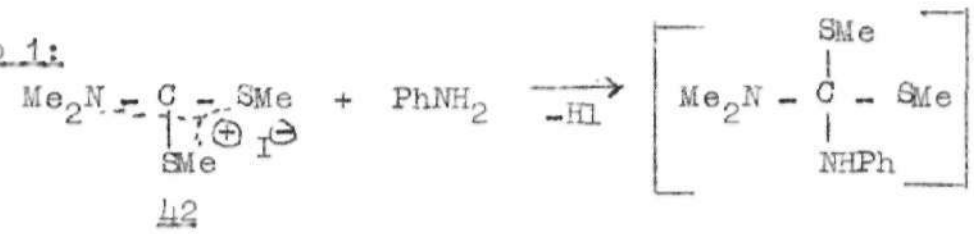


42

Both products were characterised by their spectral properties. The n.m.r. spectrum of the thiourea showed absorption at δ7.2(10H, m, $2C_6H_5$), 5.60 (1H, br s, NH) and 2.30 (3H, s, SCH_3) (Fig. 15).

A mechanism involving tetrahedral intermediate appears feasible to explain this reaction.

Step 1:



42

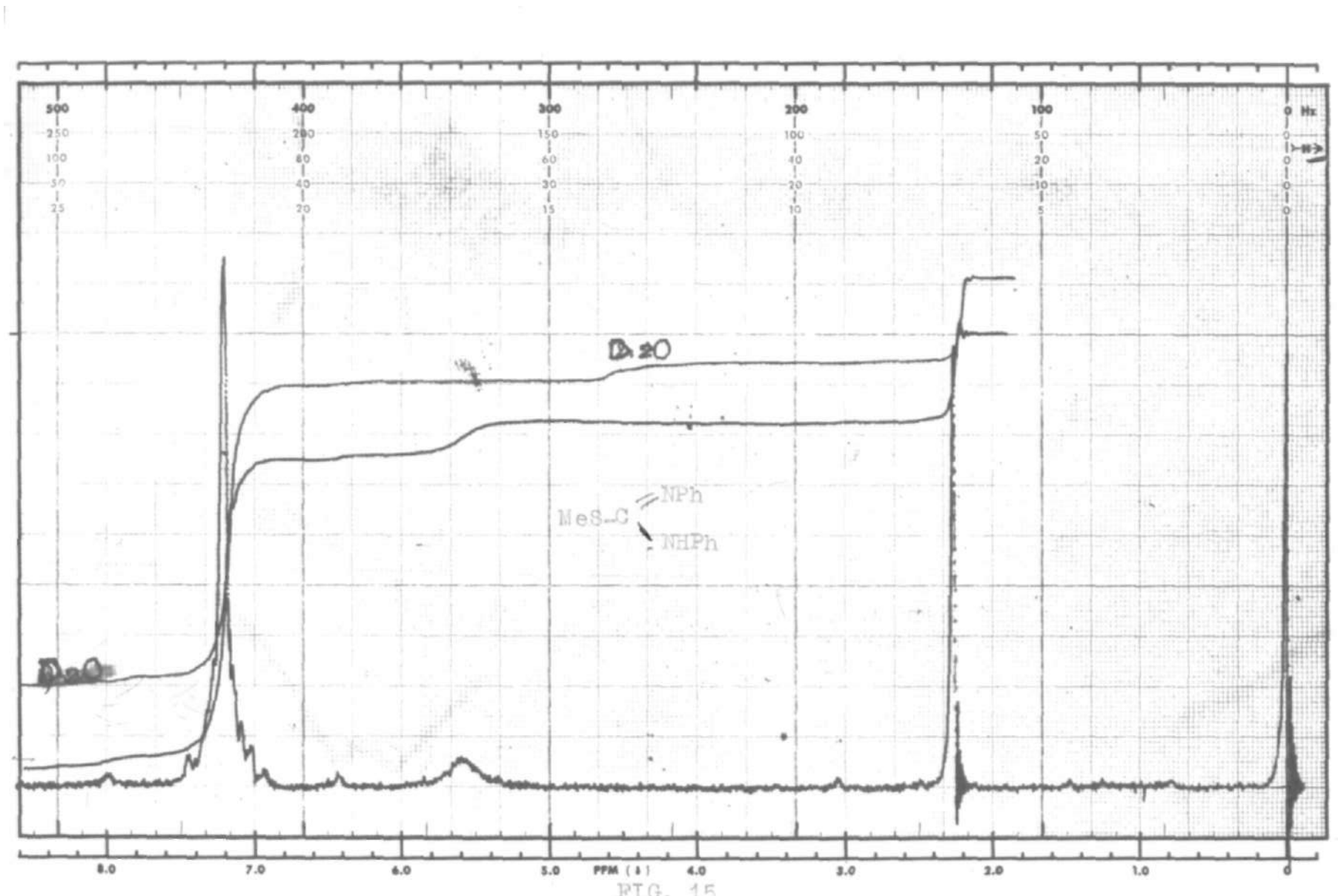
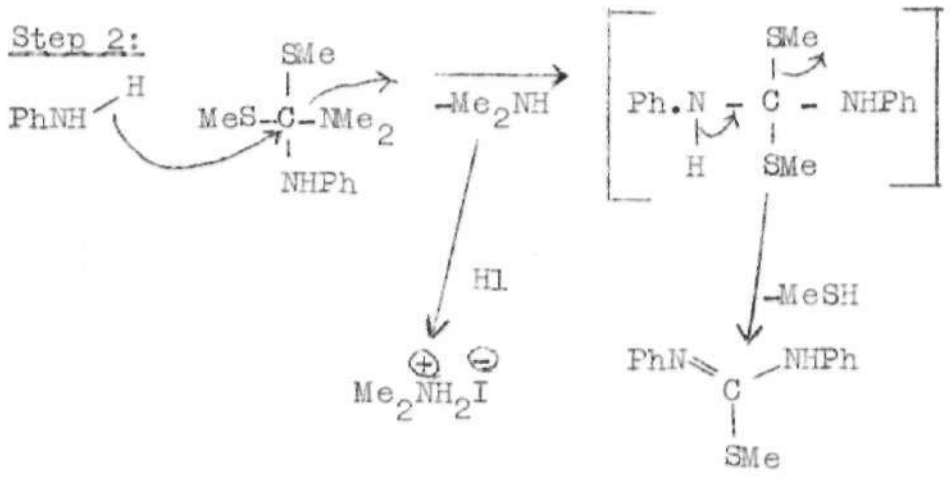
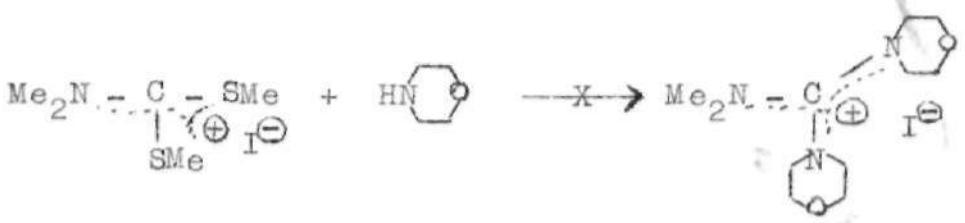

500
400
300
200
100
0 Hz
D. 20
MeS-C
NPh
NHPh
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

FIG. 15



Treatment of methiodide (42) with morpholine gave an extremely hygroscopic colourless compound, m.p. 296-297° (dec.) containing nitrogen and iodine, but whose elemental analysis did not fit the expected guanidinium salt (51).



42

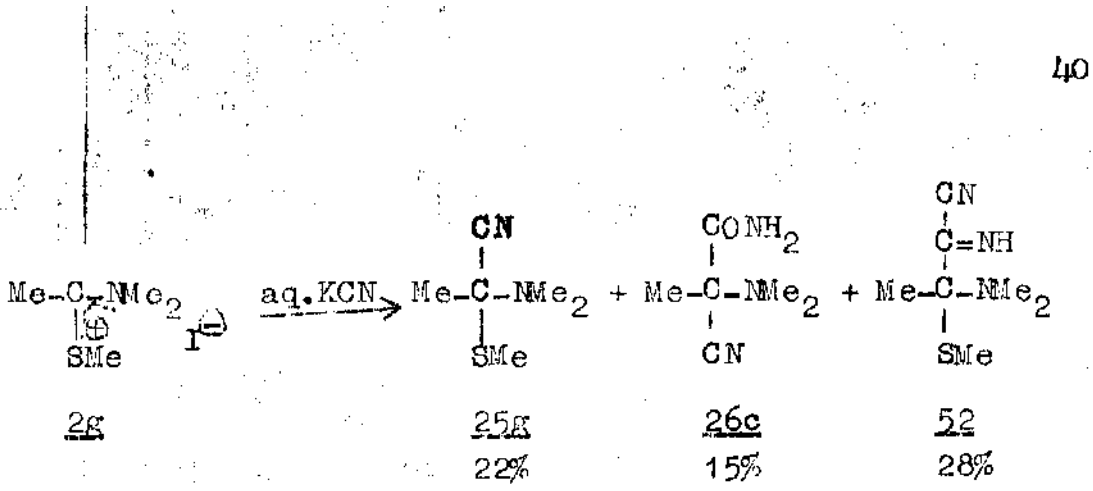
51

PREPARATION OF S-ALKYL QUATERNARY CYANIDES AND CYANOAMIDES

In the present investigation the quaternary cyanides (25) were synthesised by treating each of the salts (2) with aqueous potassium cyanide solution as reported by us.[10c] Thus compounds (25g, h, and i) were characterised in the present study, after isolation by the general procedure.

The cyanoamides (26) were also made as we previously described[10d] by reacting salts (2; R = alkyl) with excess aqueous potassium cyanide solution at room temperature. In the present investigation aqueous sodium cyanide solution was found to give similar products.

We reported[10d] that salt (2g) with excess aqueous potassium cyanide gave only the cyanoamide (26c) rapidly at room temperature in 21% yield; the isolation of its precursor (25g) was not achieved. However, on currently repeating this experiment both the quaternary cyanide (25g) and the cyanoamide (26c) were obtained in poor yields. One most interesting achievement was the further isolation of the iminonitrile (52) though in poor yield. This compound was characterised by its spectral properties and elemental analysis.

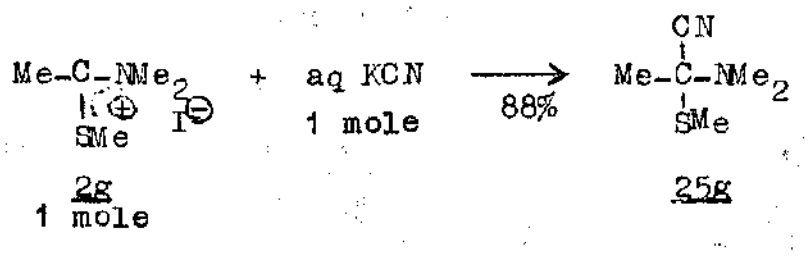


2g	25g	26c	52
	22%	15%	28%

The cyanides (25g, h and i) each showed very weak cyanide absorption at 2220 cm^{-1} (Figs. 16, 17, and 18), characteristic of the cyanides we previously made.[10c] The iminonitrile (52) showed ν_{max}(Nujol) 3240w (NH), 2220vw (C≡N), and 1600 cm^{-1} (C=N) (Fig. 19); δ9.50 (1H, br s, NH), 2.30 (6H, s, $CH_3.N.CH_3$) and 2.20 (3H, s, $S.CH_3$), the latter two being incompletely resolved and at 1.60 (3H, s, $C.CH_3$) (Fig. 20).

It absorbed at λ_{max} 235nm in ethanol (ε_{max} 4500) (Fig. 21). This intense absorption could be due to Π→Π* transition.

When the methiodide (2g) was treated with aqueous potassium cyanide solution in equimolar amounts at room temperature only the cyanide (25g) was obtained in high yield.



2g			25g
1 mole	1 mole	88%	

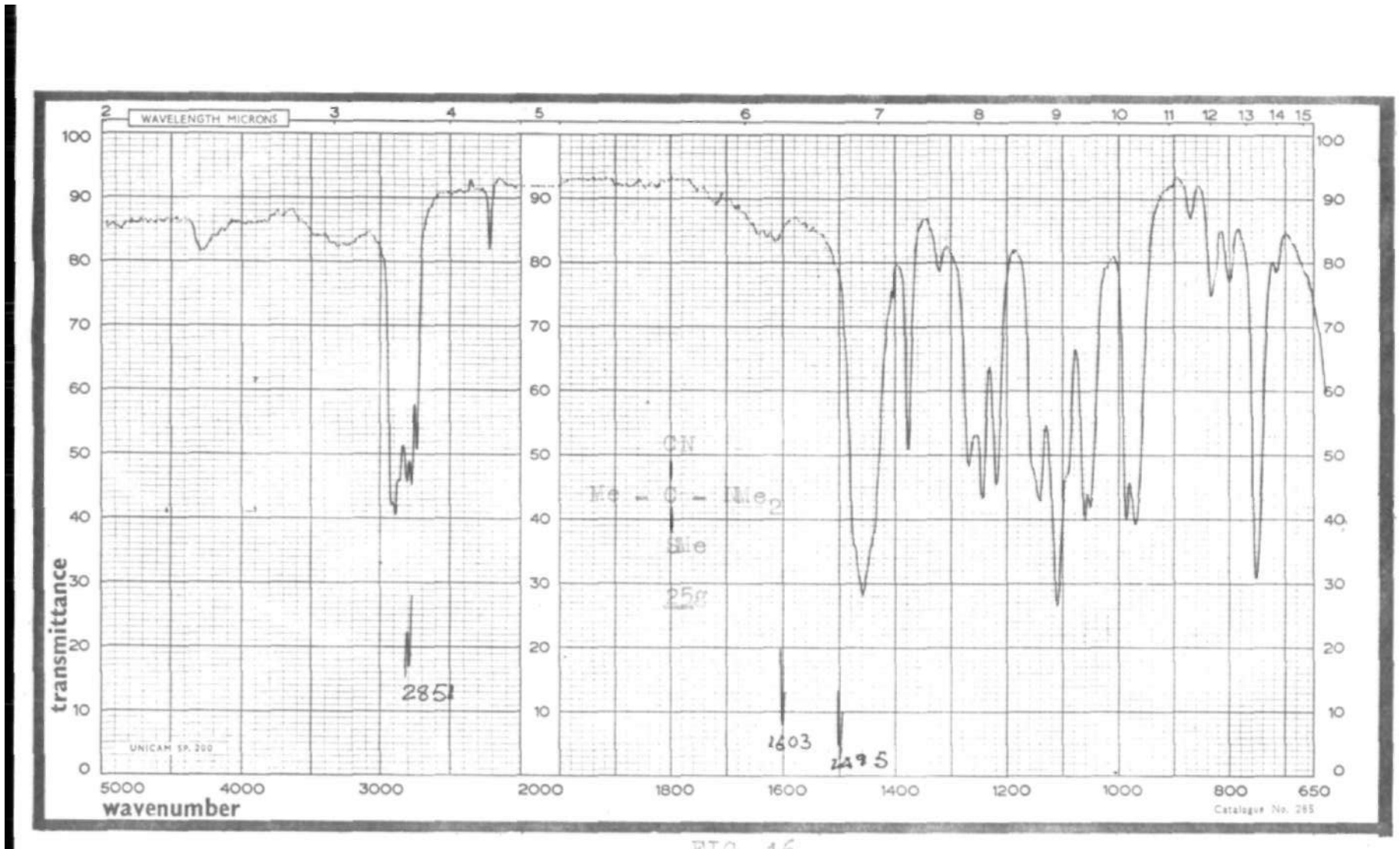

WAVELENGTH MICRONS
2
3
4
5
6
7
8
9
10
11
12
13
14
15
100
90
80
70
60
50
40
30
20
10
0
transmittance
CN
Me – C – Me2
Me
2252
2851
1603
1495
UNICAM SP. 200
5000
4000
3000
2000
1800
1600
1400
1200
1000
800
650
wavenumber
Catalogue No. 285

FIG. 16

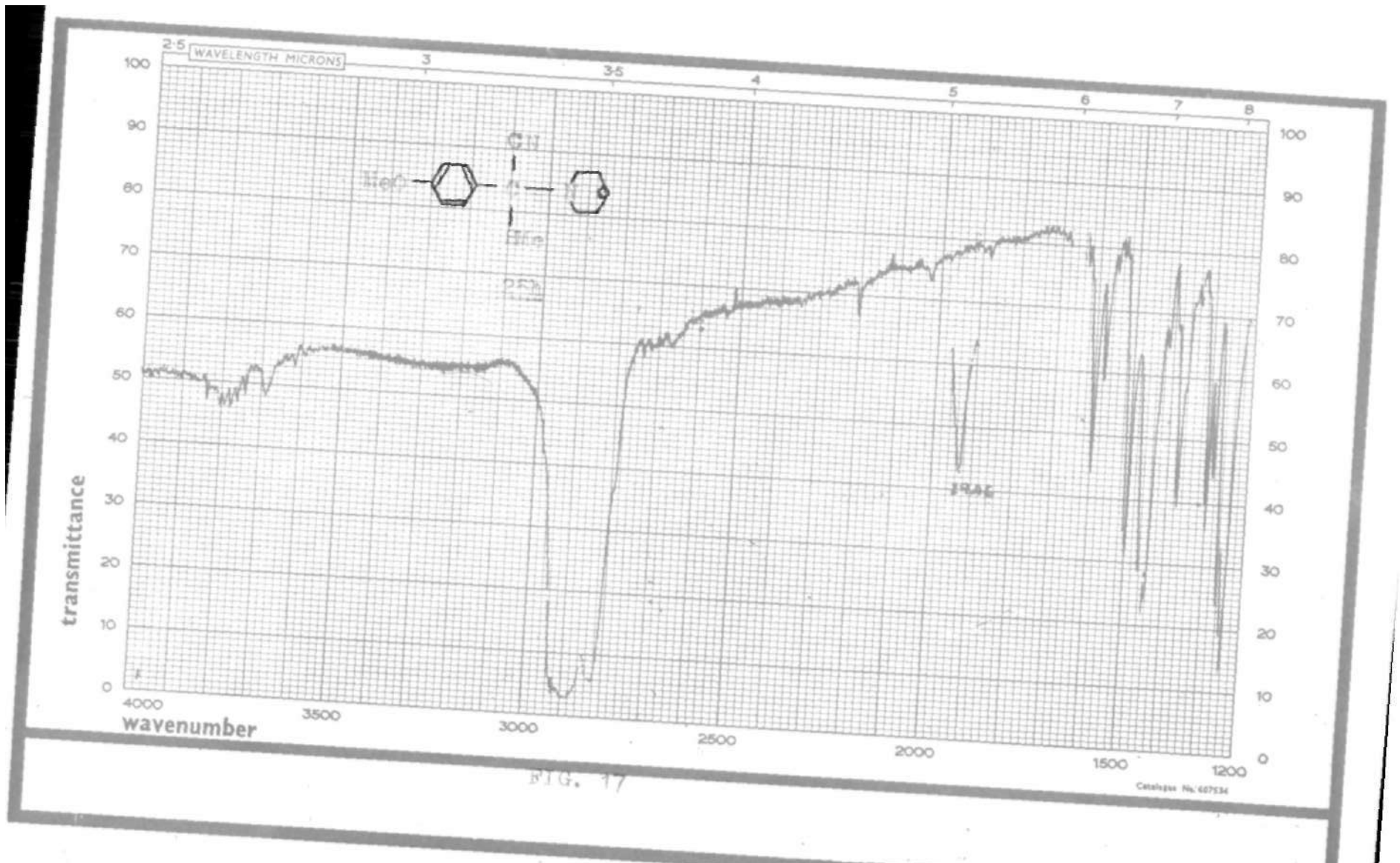

WAVELENGTH MICRONS
2·5
3
3·5
4
5
6
7
8
100
90
80
70
60
50
40
30
20
10
0
transmittance
4000
3500
3000
2500
2000
1500
1200
wavenumber

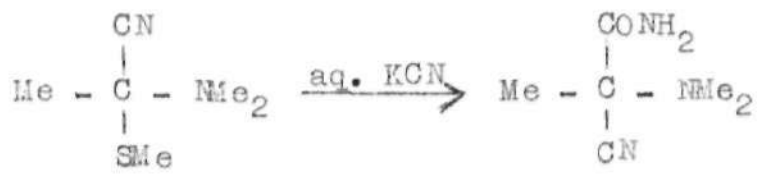
FIG. 17

That the cyanides (25; R = alkyl) are the precursors of the cyanoamides (26) has been reported by us; this was illustrated by reaction of the cyanide (25e) with aqueous potassium cyanide at room temperature which gave the expected cyanoamide (26b).[10e]



25e 26b

The observation was further established during the present study since similar treatment of cyanide (25g) gave cyanoamide (26c) in good yield.



25g 26c

However, it is interesting to note that the cyanide (25i; also R = alkyl) did not give the corresponding cyanoamide (53) under similar conditions; only the starting material was recovered.

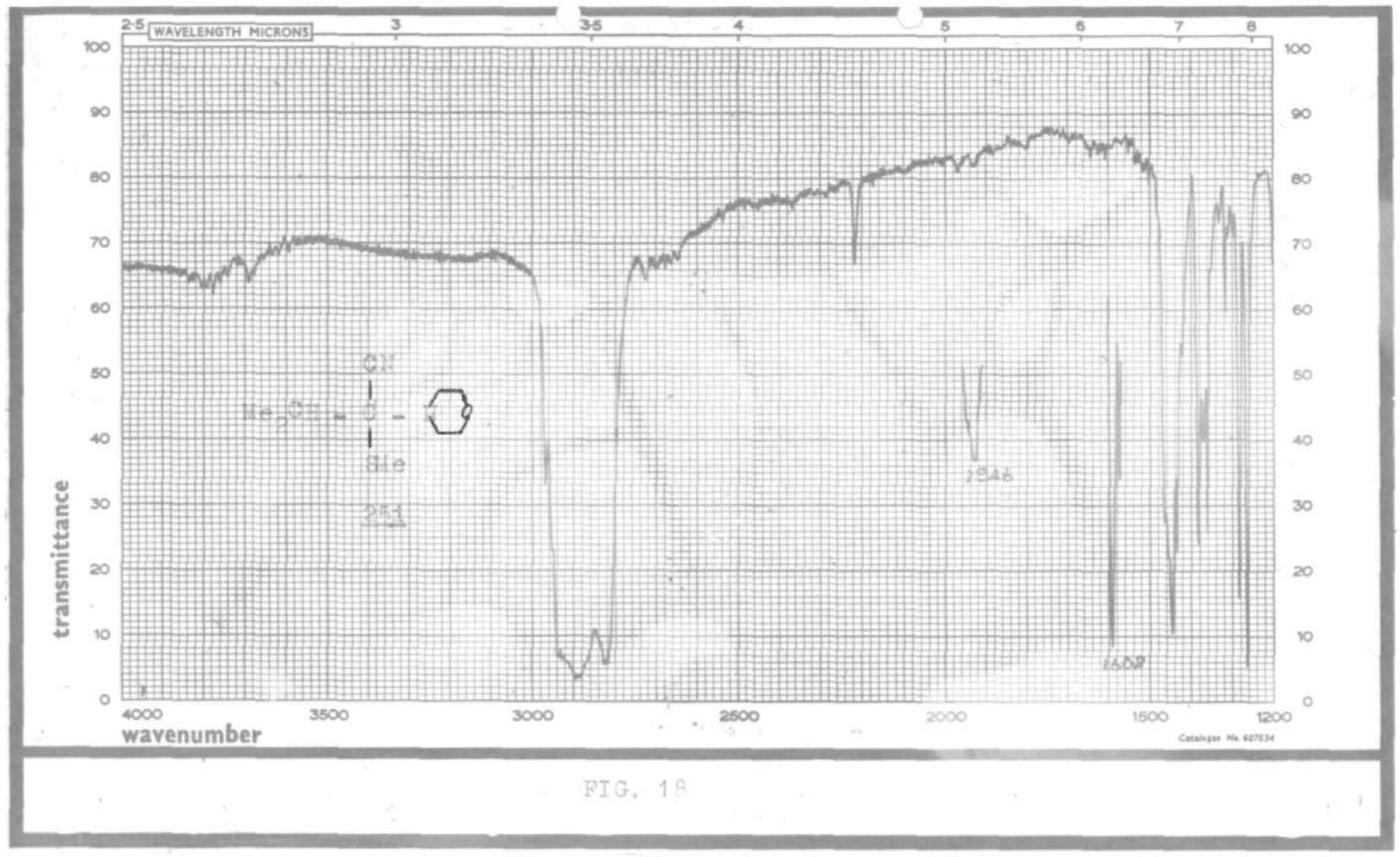

2·5
WAVELENGTH MICRONS
3
3·5
4
5
6
7
8
100
90
80
70
60
50
40
30
20
10
0
transmittance
4000
3500
3000
2500
2000
1500
1200
wavenumber
1548
1609
Catalogue No. 407534

FIG. 18

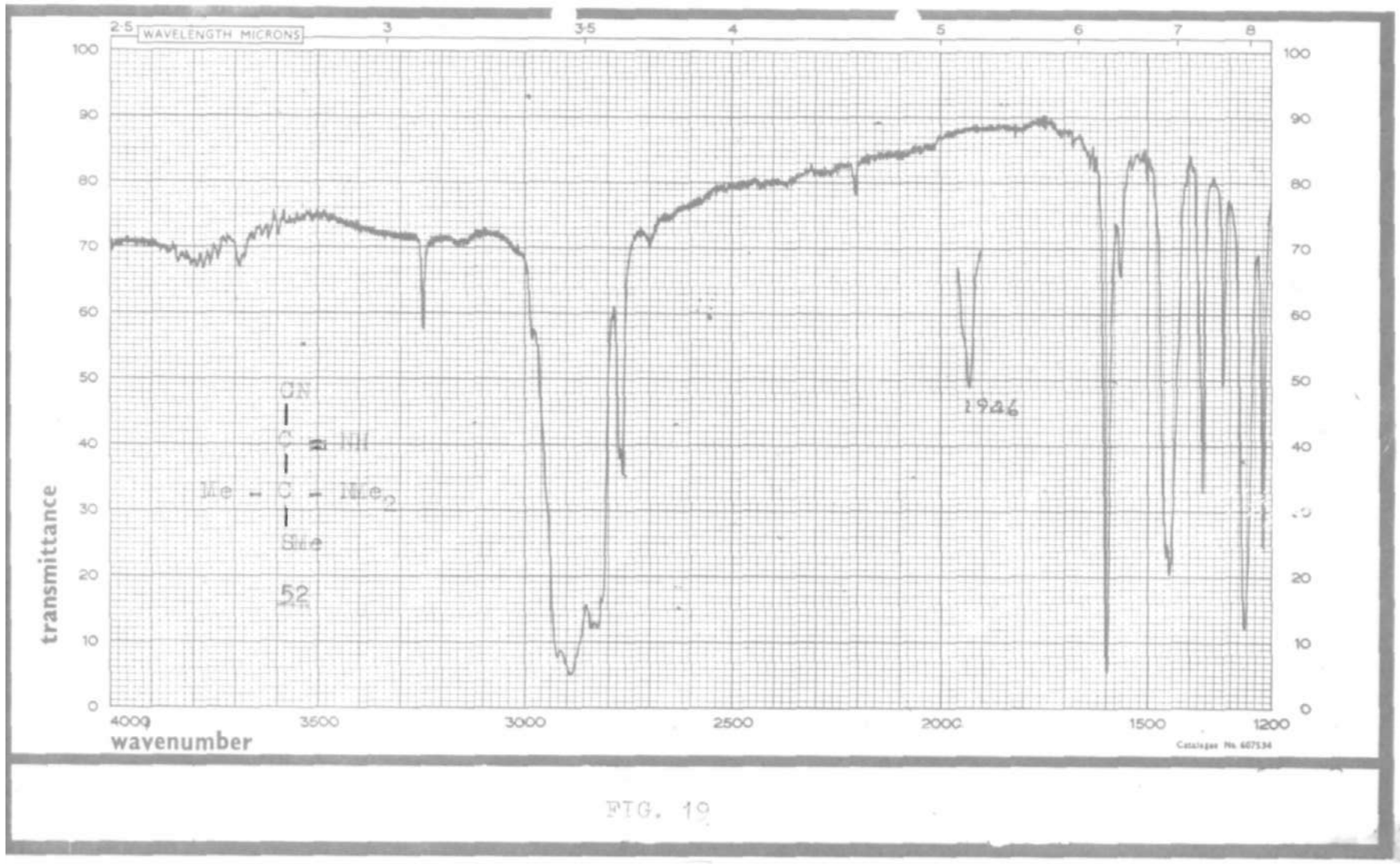
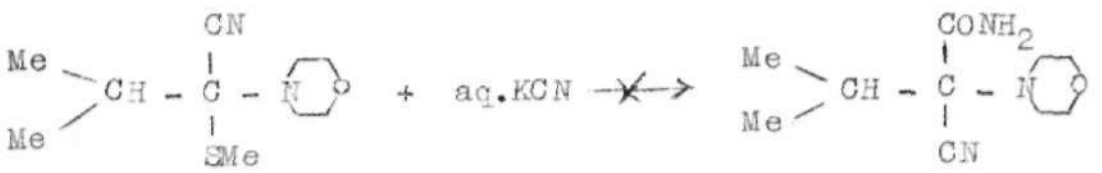

2·5
WAVELENGTH MICRONS
3
3·5
4
5
6
7
8
100
90
80
70
60
50
40
30
20
10
0
transmittance
1944
CN
C
Me – C – Me2
Me
52
4000
3500
3000
2500
2000
1500
1200
wavenumber

FIG. 19



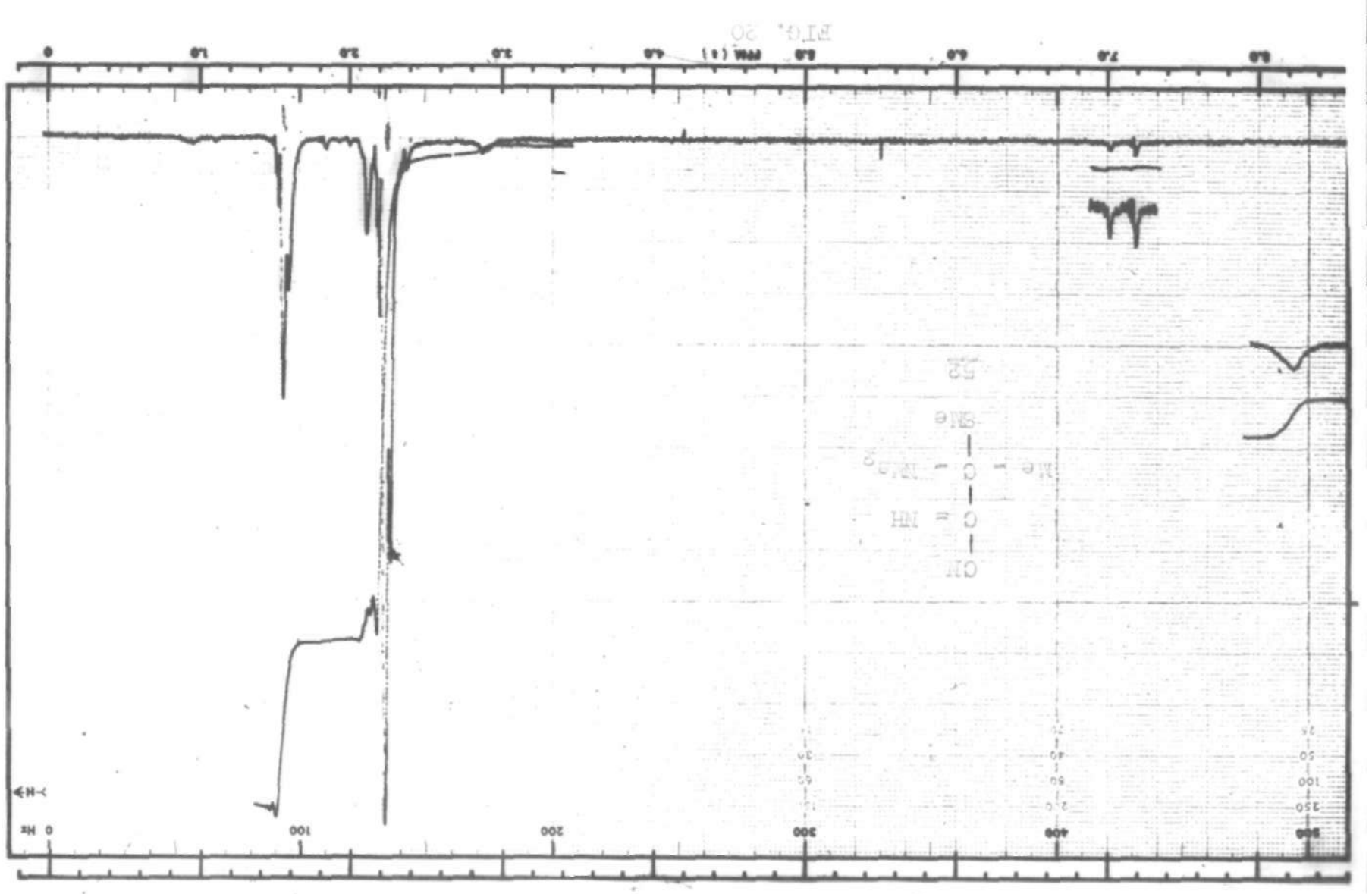
25i 53

This observation further establishes the fact that steric hindrance is unfavourable to "cyanohydrolysis".

THE MECHANISM OF "CYANOHYDROLYSIS"

The hydrolysis of quaternary cyanides to the cyanoamides at room temperature is most unusual; hydrolysis of nitriles to amides entails more drastic conditions.[27] For example, in the hydrolysis of benzyl cyanide to an amide the solution of the nitrile in concentrated sulphuric acid is kept at 80-90° for 5 min, then poured into cold water.

The formation of cyanoamides from quaternary salts suggests that two cyanide groups are incorporated simultaneously or at different times in some intermediate, from which one of the cyanide groups becomes hydrolysed to the amido- group. However, it appears clear that both cyanide groups do not replace the leaving groups simultaneously, since a quaternary cyanide can give a cyanoamide under similar conditions - a fact which we



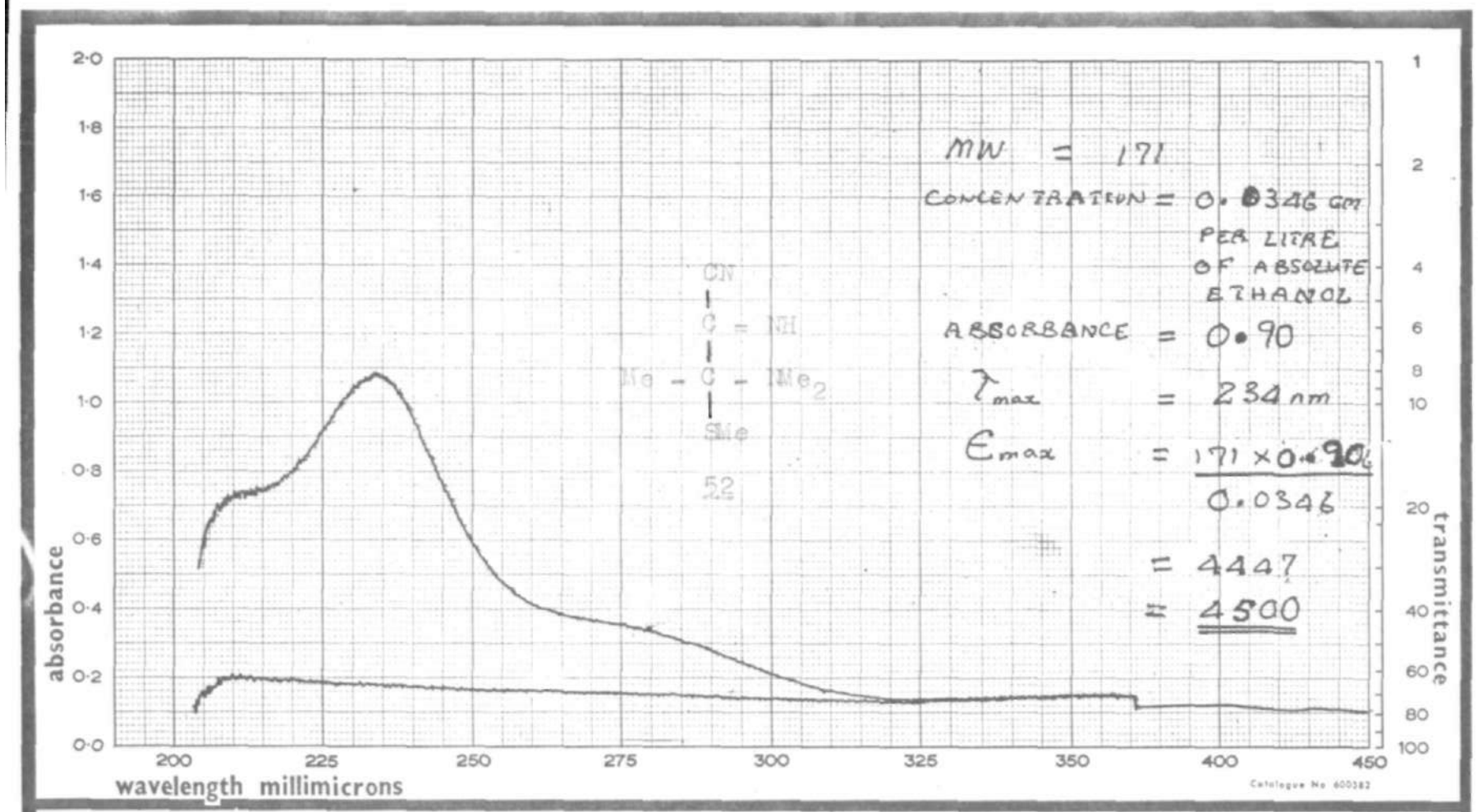
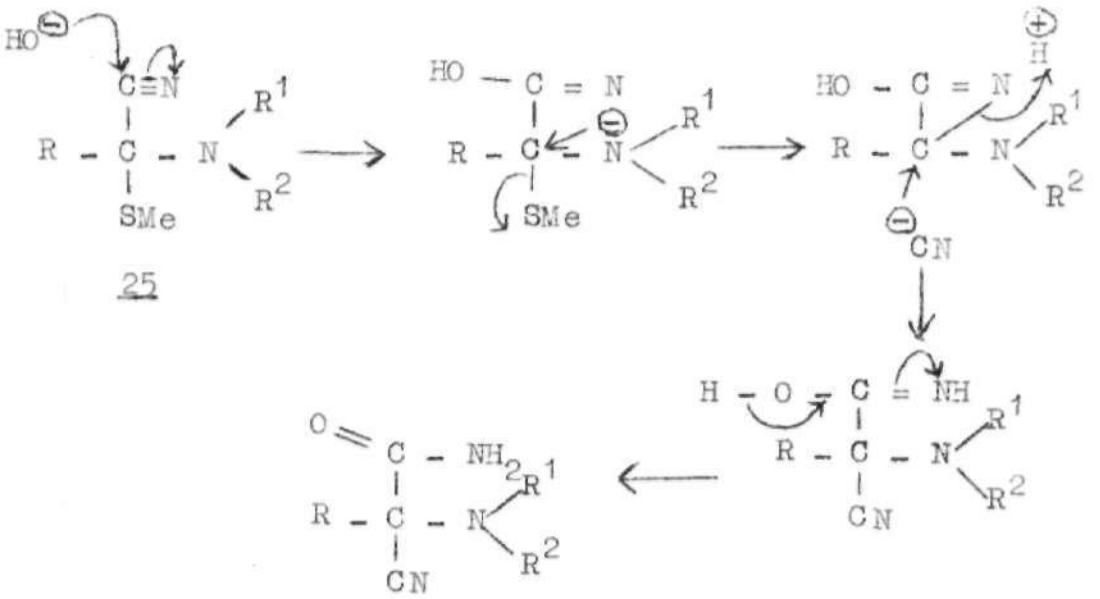

MW = 171
CONCENTRATION = 0.0346 GM PER LITRE OF ABSOLUTE ETHANOL
ABSORBANCE = 0.90
λmax = 234 nm
εmax = 171 × 0.90 / 0.0346
= 4447
= 4500
CN
C = NH
Me - C - NMe2
SMe
52
absorbance
transmittance
wavelength millimicrons
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
1
2
4
6
8
10
20
40
60
80
100
200
225
250
275
300
325
350
400
450
Catalogue No 600382

FIG. 21

have fully established.

We have previously postulated[10g] a mechanism of "cyanohydrolysis" which involves neighbouring group participation.

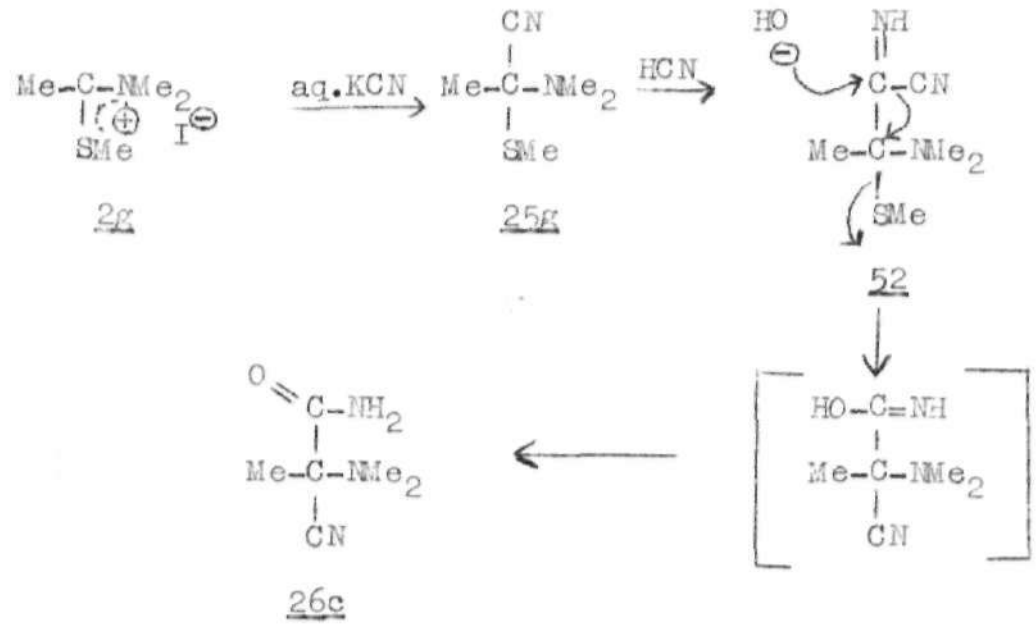


25



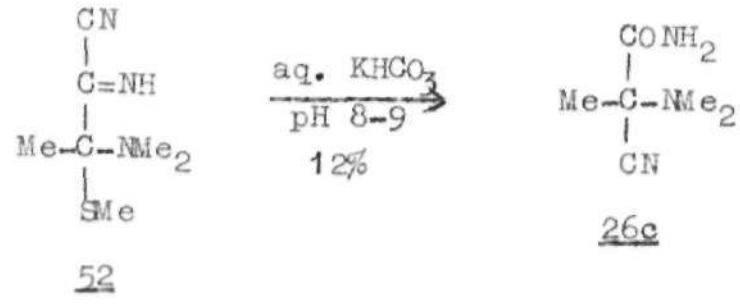
26

The isolation of the iminonitrile (56) together with the cyanide (25g) and the cyanoamide (26c) from treatment of salt (2g) with aqueous potassium cyanide suggested the formulation of a different mechanism of cyanohydrolysis which shows the iminonitrile (52) as an intermediate.



2g 25g 52 26c

If the iminonitrile (52) were in fact an intermediate as postulated, it should on hydrolysis in basic medium give the cyanoamide (26c); this it did when stirred in aqueous potassium hydrogen carbonate at room temperature.



52 26c

The success of this reaction tended to establish the above mechanism to some extent. With the iminonitrile (52) as an intermediate it would therefore appear that it is the cyanide group of the quaternary cyanide which is hydrolysed to the amido- group. To confirm this, experiments were carried out with isotopically enriched $K^{13}CN$.

Treatment of cyanide (25g) with aqueous potassium cyanide gave cyanoamide (26c); the peaks in the ^{13}C n.m.r. spectrum of the cyanoamide, containing only natural abundance of ^{13}C, were identified (Fig. 22) by comparison with known chemical shifts for carbon.[20a,b,c,d]

The unlabelled cyanide (25g) was similarly treated with aqueous $K^{13}CN$; the ^{13}C n.m.r. spectrum of the cyanoamide produced showed that both cyano- and carbonyl- groups were labelled to approximately the same extent (Fig. 23). The chemical shifts were the same as in the spectrum of the unlabelled cyanoamide (26c).

Treatment of the iminonitrile (52) with aqueous potassium cyanide gave the cyanoamide (26c) in very poor yield.

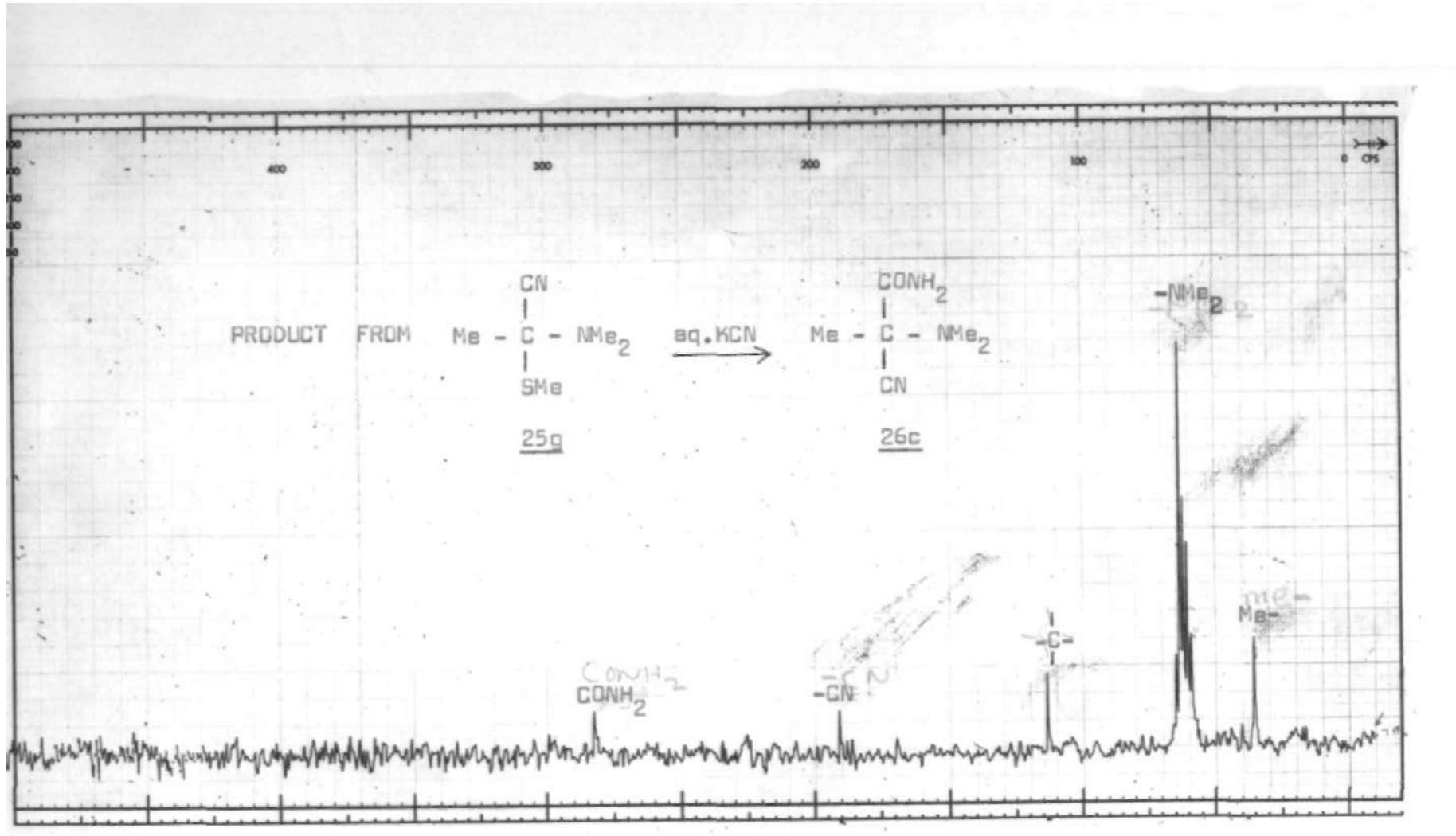

400
300
200
100
0 CPS
PRODUCT FROM
Me - C - NMe2
SMe
aq.KCN
Me - C - NMe2
CN
CONH2
-NMe2
25g
26c
CONH2
-CN
-C-
Me-

FIG. 22

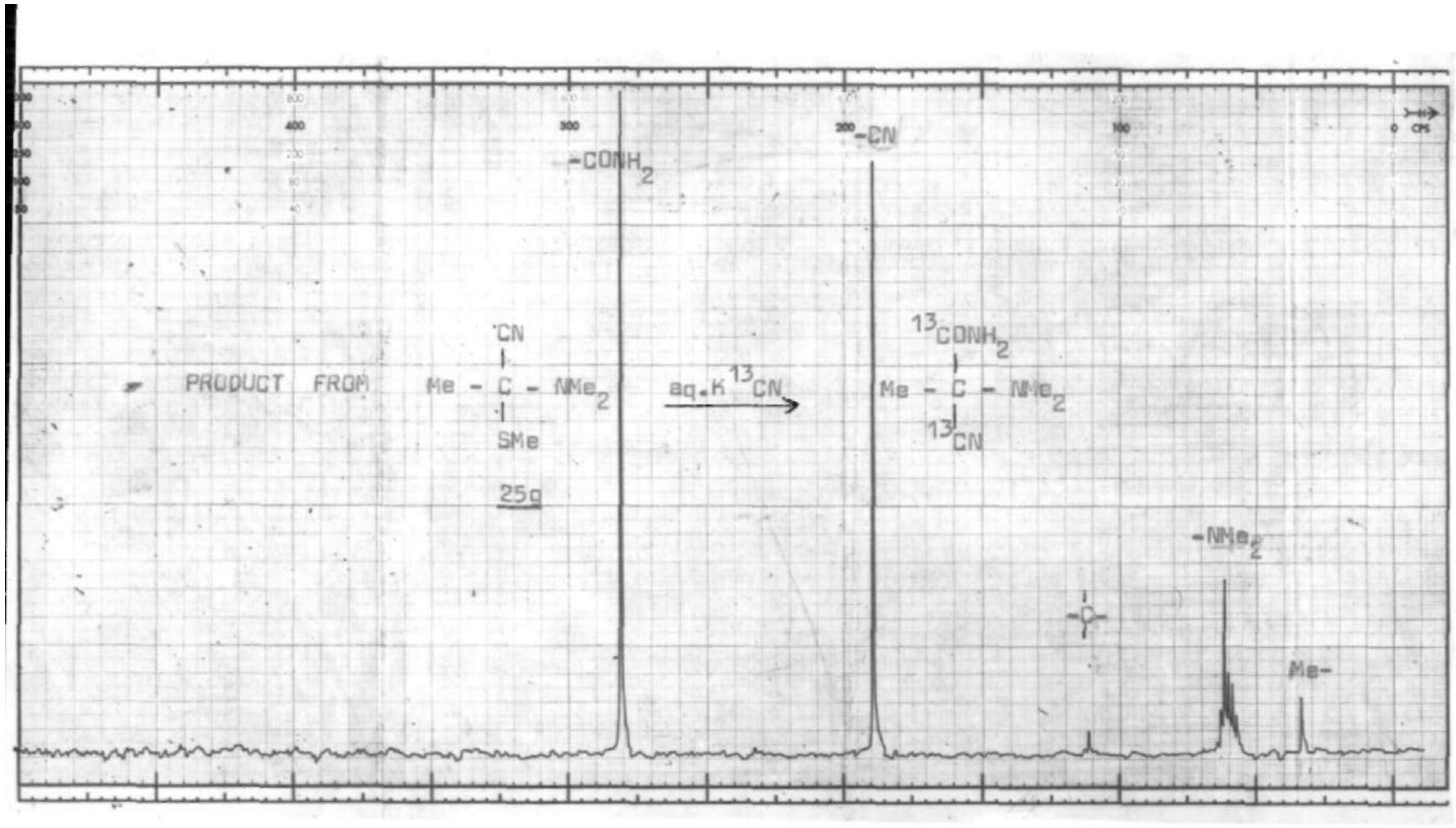
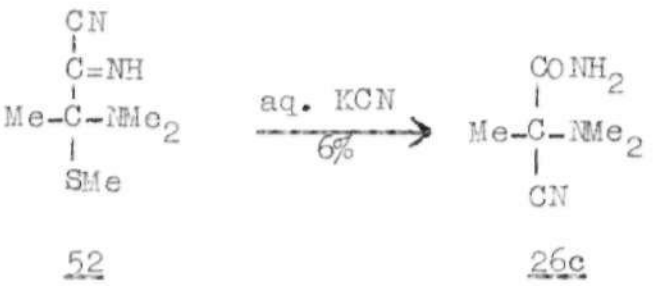

PRODUCT FROM
Me - C - NMe2
CN
SMe
25g
aq.K 13CN
-CONH2
-CN
13CONH2
Me - C - NMe2
13CN
-NMe2
-O-
Me-
CPS

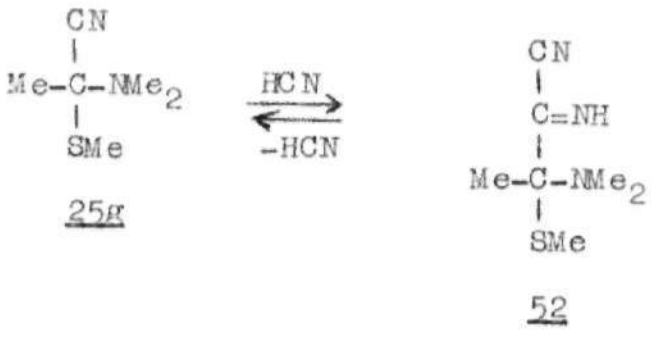
FIG.23



52 26c

Similar treatment of the iminonitrile (52) with enriched $K^{13}CN$ afforded the cyanoamide, whose ^{13}C n.m.r. spectrum showed ^{13}C labelling at both cyano- and amido- groups to the same extent (Fig. 24).

It is thus impossible to say which of the cyanide groups is hydrolysed. The above mechanism in which the iminonitrile (52) is an intermediate is therefore not feasible. The iminonitrile (52) could simply be a bye-product which reverts to the cyanide (25g) by loss of one hydrogen cyanide molecule.



25g 52

Equal labelling of cyano- and amido- groups suggests the intermediacy of a symmetrical compound, probably the malononitrile (54). We treated salt (2g)

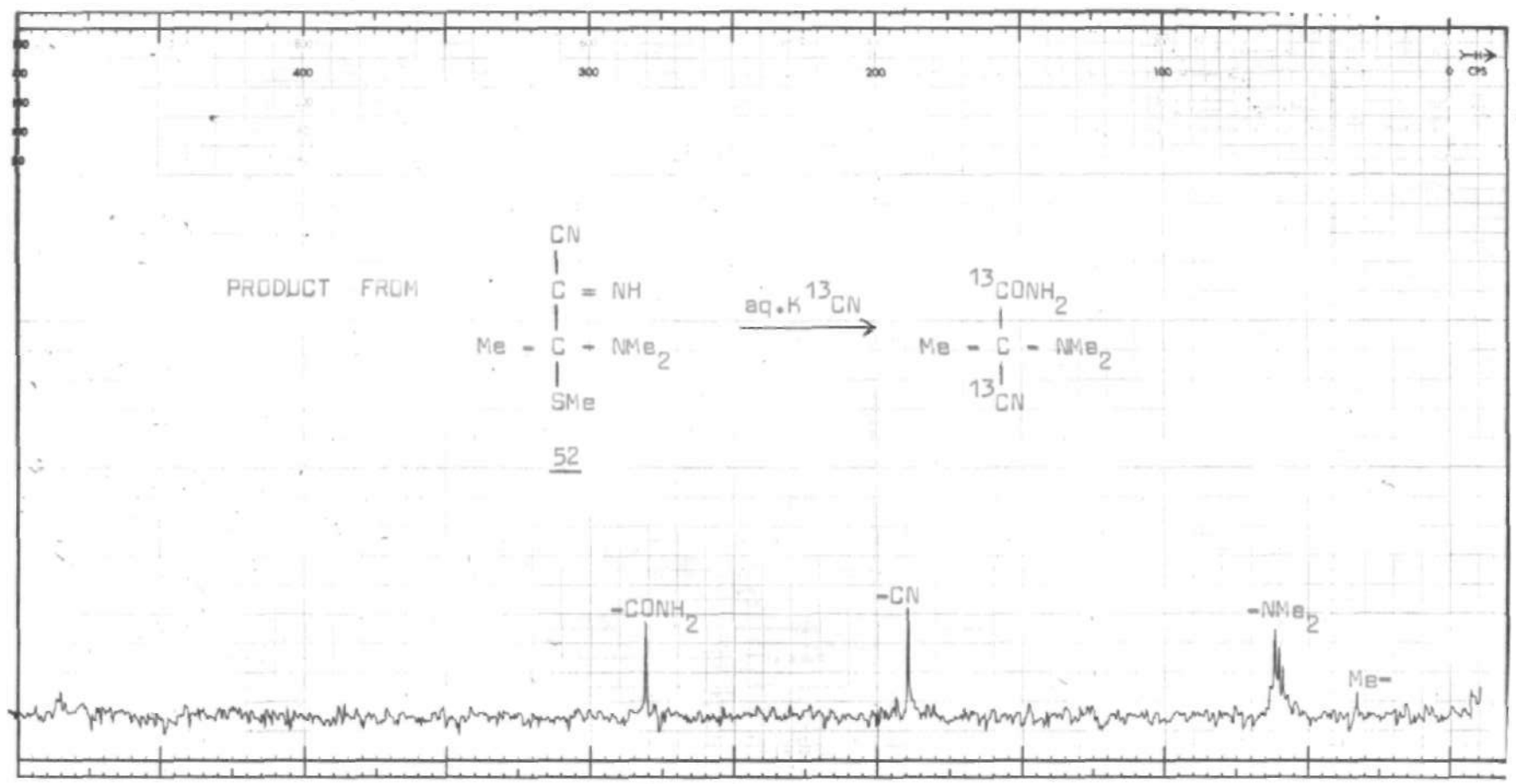
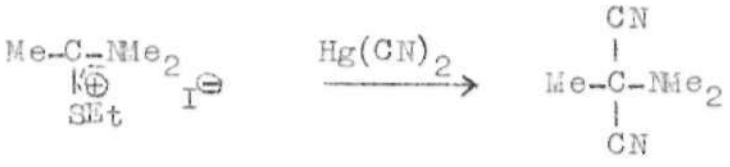

400
300
200
100
0 CPS
PRODUCT FROM
CN
C = NH
Me - C - NMe2
SMe
aq.K 13CN
13CONH2
Me - C - NMe2
13CN
52
-CONH2
-CN
-NMe2
Me-

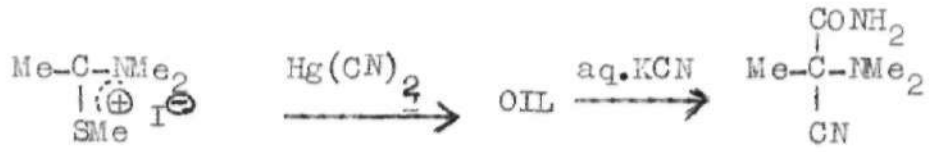
FIG. 24

with mercuric cyanide to obtain this intermédiate using the procedure of Yamaguchi *et al.*[29] who synthesised it similarly from thioacetdimethylamide ethiodide.



54

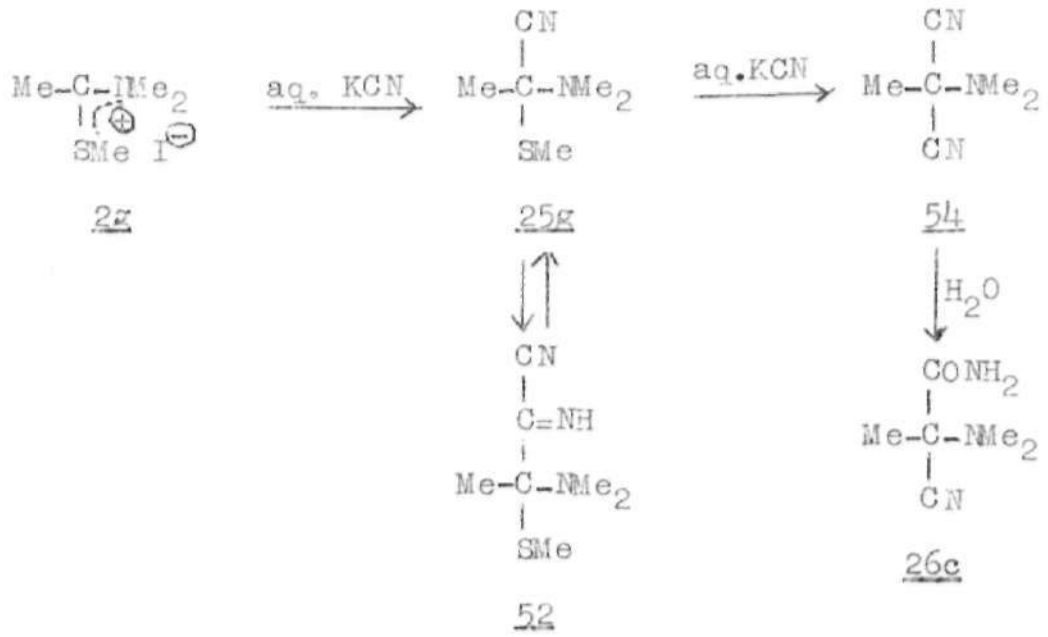
The oil we obtained had b.p. 76-77°/20mm Hg as reported[29] for the malononitrile (54), but our product was not homogeneous to t.l.c., gave a complex n.m.r. spectrum, and resisted attempts to purify it. Perhaps significantly, no spectral properties were reported for this compound. Our oil, with aqueous potassium cyanide, gave cyanoamide (26c), however.



29 26c

From all evidence it therefore seems most probable that malononitrile (54) is an intermediate in "cyanohydrolysis", though the selective hydrolysis of

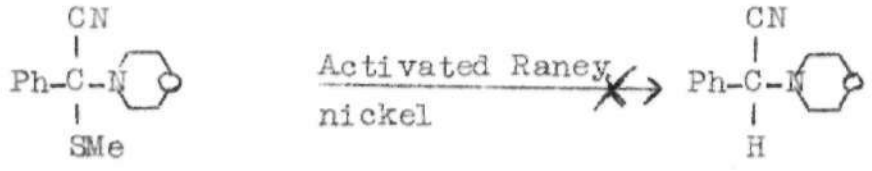
only one of its cyano- groups is unexplained.



2g 25g 54 26c 52

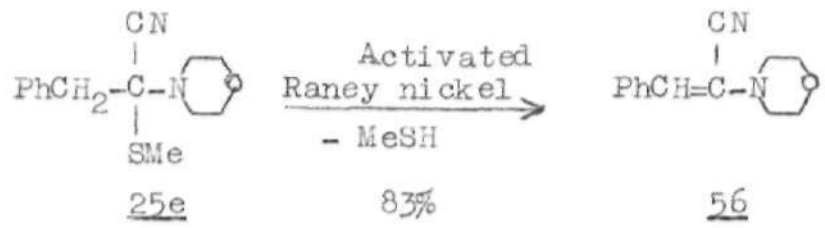
REACTIONS OF QUATERNARY CYANIDES WITH RANEY NICKEL AND SODIUM BOROHYDRIDE

When a mixture of cyanide (25a) and commercial activated pelletized Raney nickel was boiled under reflux in benzene, the starting material was obtained and not the expected reduction product (55).



25a 55

Similar treatment of cyanide (25c) gave a dark brown oil which was too small to be characterised, whilst cyanide (25e) gave the elimination product (56), characterised by its special properties and elemental analysis.



25e 83% 56

On boiling under reflux a benzene solution of cyanide (25e) alone, compound (56) was isolated in very poor yield.

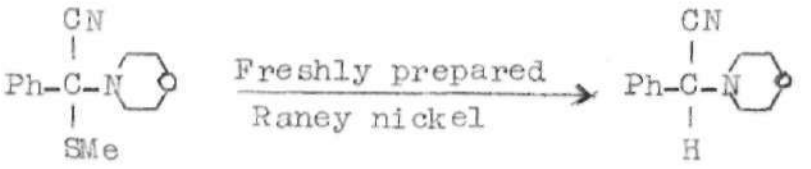


25e 3% 56

Thus the commercial Raney nickel did not appear to reduce the quaternary cyanides as expected; although the elimination product (56) was obtained by thermal decomposition of cyanide (25e) in 3% yield, the excellent yield of compound (56) obtained with activated Raney nickel suggests that this reagent probably assisted desulphurisation. Further attempts were made to effect

the desulphurisation of cyanides (25) using freshly prepared Raney nickel.[30]

Boiling under reflux a benzene solution of cyanide (25a) and freshly prepared nickel gave the expected product (55) in low yield. Compound (55) was characterised by its spectral properties and elemental analysis. Its i.r. spectrum showed weak cyanide absorption (Fig. 25).

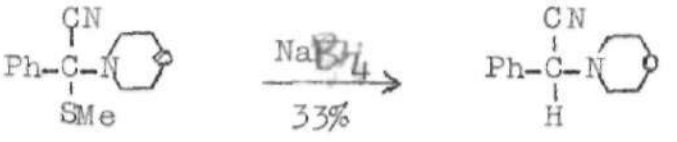


25a 23% 55

Similar treatment with cyanides (25c and e) gave respectively an oil and a solid, m.p. 46-48°, both in small amounts too small to characterise.

Freshly prepared Raney nickel thus appears to be a better desulphurising agent than the commercial form.

Treatment of cyanide (25a) with sodium borohydride in isopropanol led to isolation of compound (55) in low yield.



25a 55

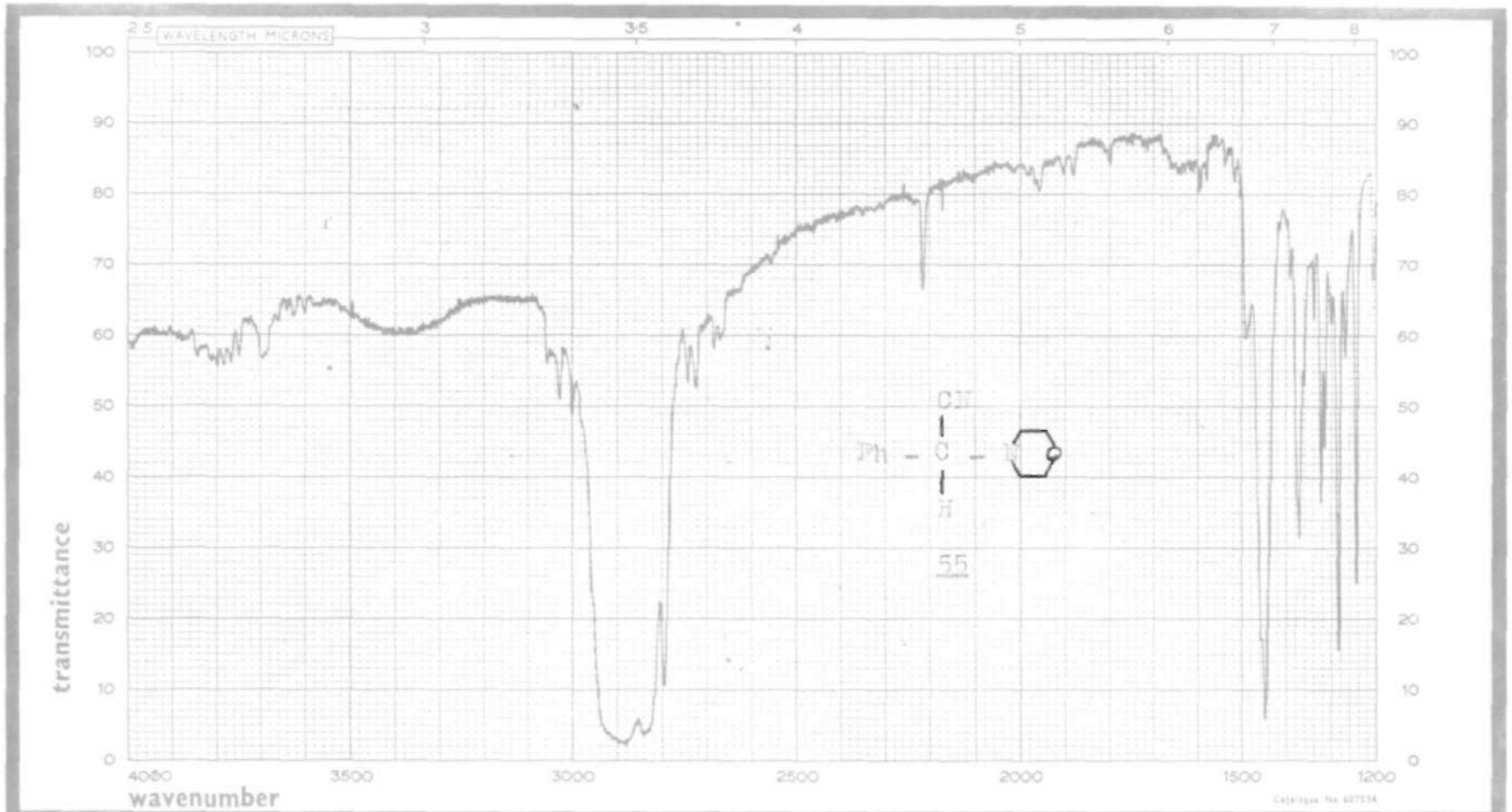
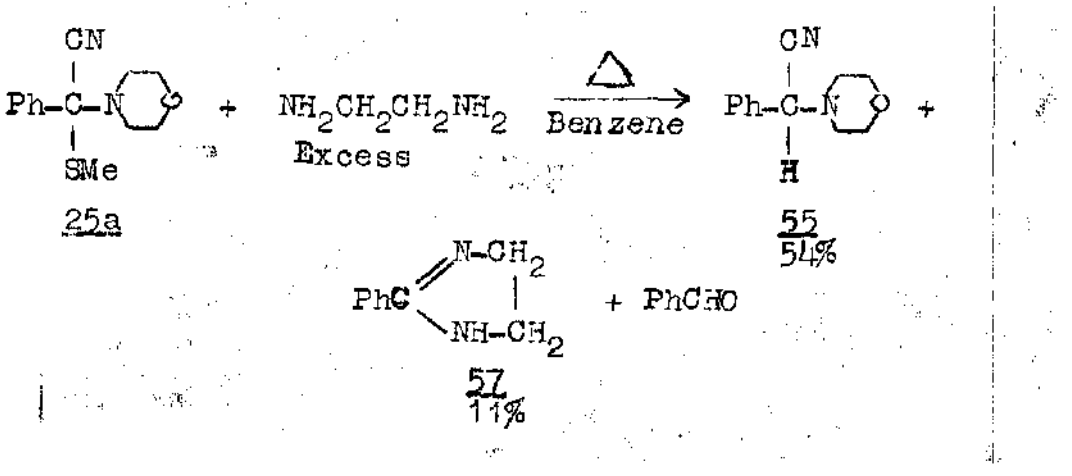

WAVELENGTH MICRONS
2.5
3
3.5
4
5
6
7
8
100
90
80
70
60
50
40
30
20
10
0
transmittance
4000
3500
3000
2500
2000
1500
1200
wavenumber
Ph – C – N
H
55

FIG. 25

This reduction was a much cleaner and faster reaction than with freshly prepared Raney nickel and the yield was higher.

REACTIONS OF QUATERNARY CYANIDES WITH AMINES

In the present investigation, a novel reduction was effected with aliphatic primary amines as reducing agents. When a mixture of cyanide (25a) and excess ethylene-diamine was boiled under reflux in benzene, the reduction product (55) and 2-phenyl-Δ^2-imidazoline (57) were obtained in fair and very low yields respctively. The imidazoline (57) was characterised by its spectral properties, its elemental anaylsis and that of its picrate. Benzaldehyde was isolated by steam distillation of the crude product and was characterised by its dinitrophenylhydrazone whose i.r. spectrum was identical with that of an authentic sample.



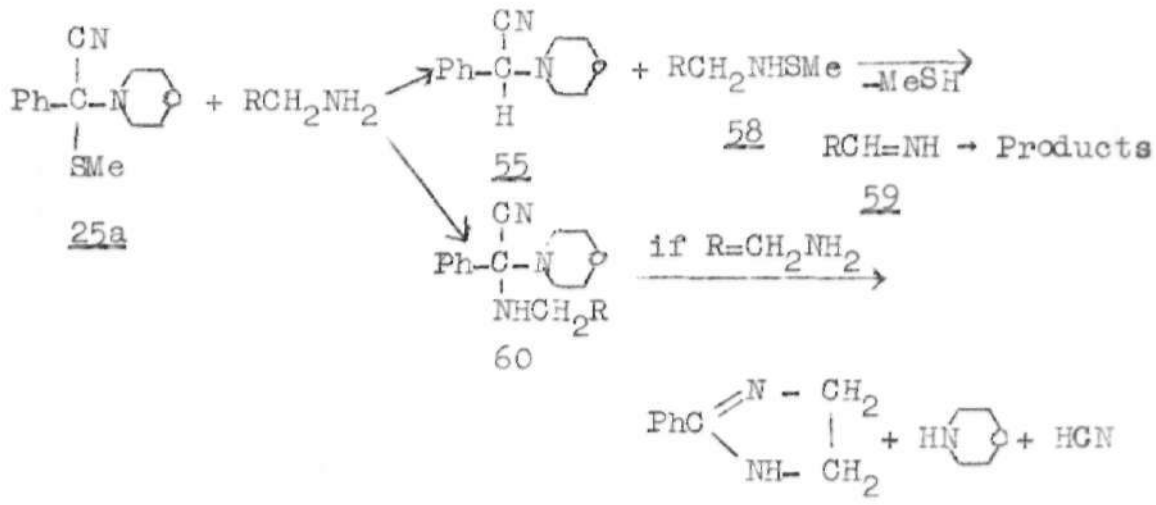
There was no appreciable reaction when cyanide (25a) was boiled with an equimolar amount of ethylenediamine in benzene.

Ethylenediamine has never been reported as a reducing agent; this diamine, is however, employed as a complexing agent in the preparation of aryl cyanides.[31] After the reaction of an aryl halide with cuprous cyanide to form a nitrile, added ethylenediamine complexes with cuprous and cupric ions and facilitates isolation of the nitrile. The other application of ethylenediamine is in connection with propargylic rearrangement.[32] Strong bases such as sodium amide and n-butyllithium do not rearrange 3-hexyne within 72h at room temperature. However, the combination of such bases and ethylenediamine rearranges 3-hexyne rapidly.

Reaction of cyanide (25a) with excess of two other aliphatic amines: 1,2-diamino- and 1,3-diamino-propane gave compound (55) in 41% and 63% yields respectively; similar treatment of cyanide (25a) with n-butylamine also afforded the reduction product (55) in 28% yield.

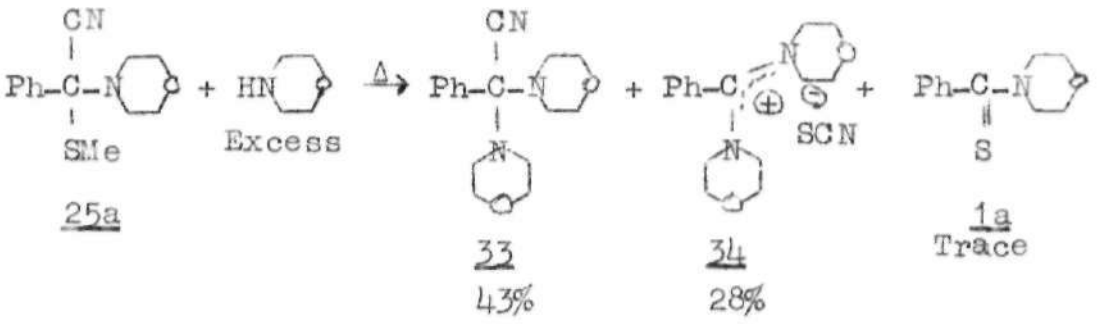
A variety of bivalent sulphur compounds act as sulphenylating reagents towards amines, giving sulphenamides; most routes to these compounds are of this type.[33] The cyanide (25a) may act in this way

with formation of the reduction product (55) and simultaneous production of a sulphenamide (58). By loss of methanethiol the sulphenamide (58) may then give the imine (59) which would decompose to other products. The intermediate (60) may also be formed as a side product from which the observed imidazoline (57) might arise in the case of ethylenediamine.



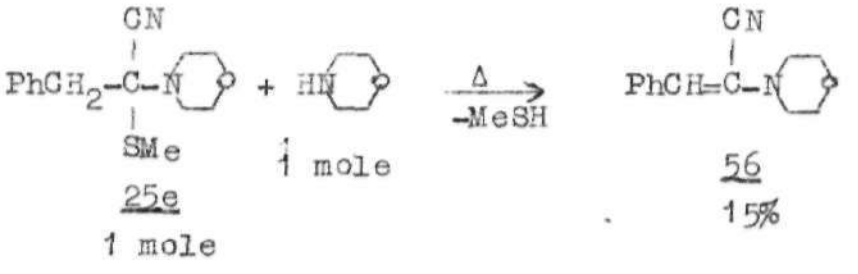
The source of benzaldehyde formed on steam distillation of the crude product is unknown; it may be formed by hydrolysis of the reduction product (55). Although its formation does not give any clue to the mechanism of the reduction reaction, nevertheless, it confirms the presence of the benzylidene group (PhCH<) in compound (55).

The reaction of cyanide (25a) with morpholine was curious and intriguing. When mixed with excess morpholine and the solution boiled under reflux, the expected covalent compound (33) was obtained in modest yield; in addition the amidinium salt (34) was isolated in poor yield together with traces of thiobenzomorpholide (1a).

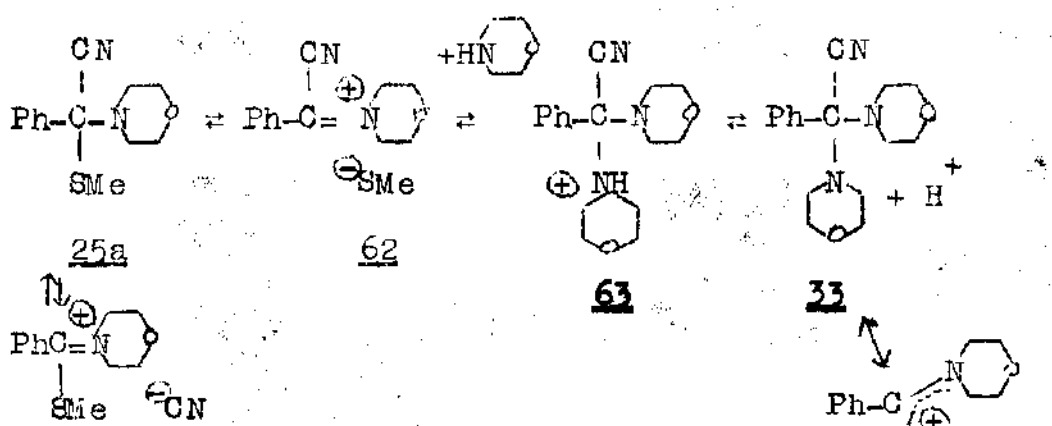


Repeating the experiment with equimolar amounts of reactants led to the isolation of the amidinium thiocyanate (34) in 10% yield and recovery of some starting material.

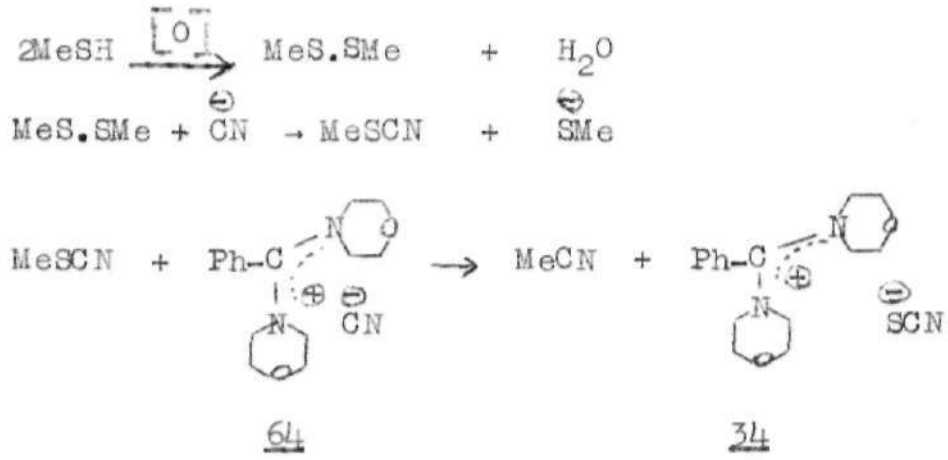
Heating the cyanide (25e) with an equimolar amount of morpholine gave the alkene (56) in very poor yield.



The covalent cyanide (25a) could exist in equilibrium with the ionic forms (61) and (62). The latter may react with morpholine to give the intermediate (63) and hence the isolated compound (33) which may possess some ionic character (64).

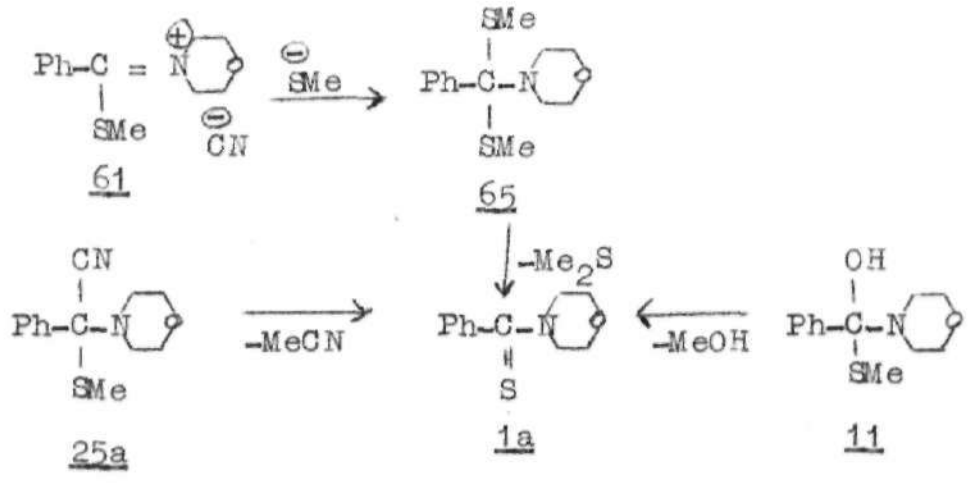


Oxidation by air of the methanethiol produced to dimethyl disulphide would be favoured by the medium of high pH. Perhaps the cyanide ion present would then effect nucleophilic fission of the disulphide bond to give methyl thiocyanate, which could react with compound (64) affording the amidinium thiocyanate (34) by nucleophilic displacement.



64 34

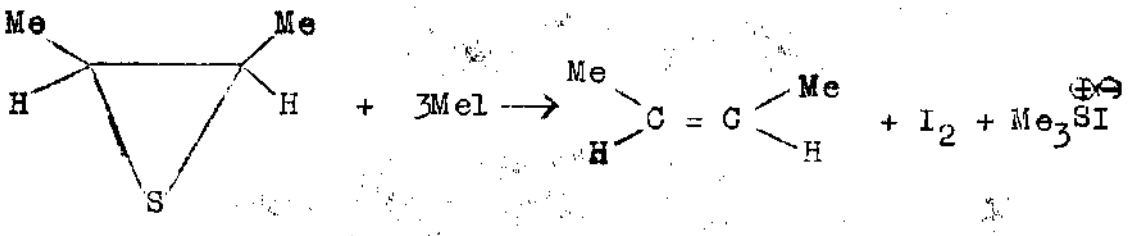
Thiobenzomorpholide (1a) may arise by elimination of dimethyl sulphide from the intermediate (65) which might be formed by a nucleophilic displacement reaction between compound (61) and methanethiolate ion. The thioamide (1a) could also arise directly from the quaternary cyanide (25a) by loss of methyl cyanide. Another possible source of the thioamide (1a) is the pseudo-base (11) which may be formed by nucleophilic displacement reaction of compound (61) with hydroxide ion.



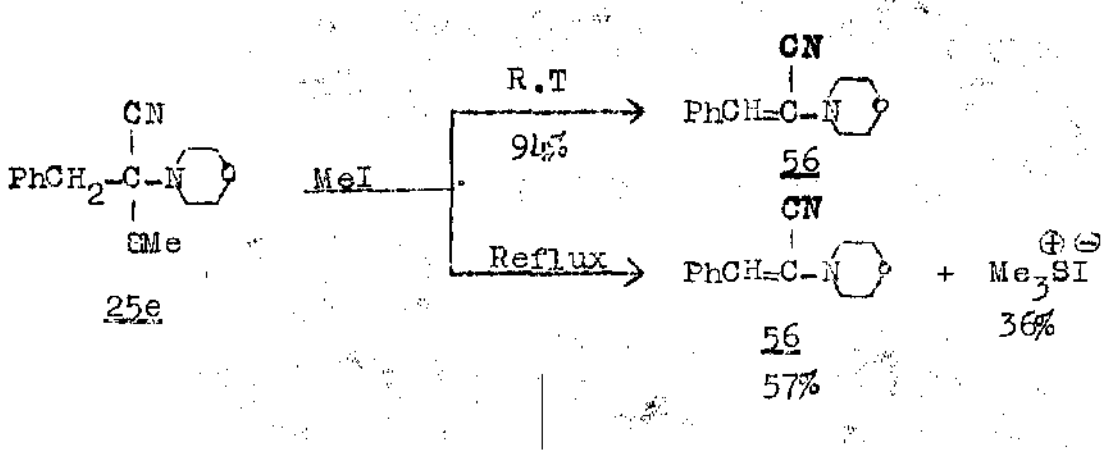
61 65 25a 1a 11

REACTIONS OF QUATERNARY CYANIDES WITH METHYL IODIDE

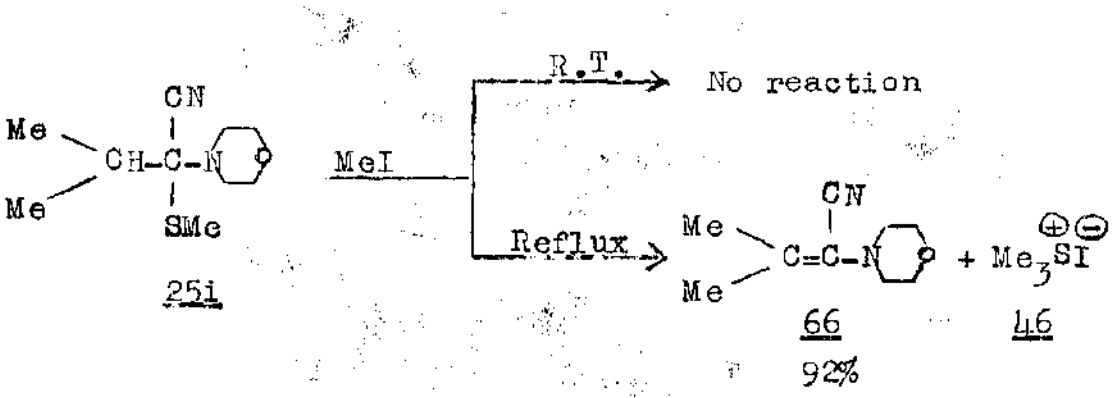
The stereoselective desulphurisation of thiiranes with methyl iodide has been reported by Helmkamp and Pettitt,[34] who for example, obtained cis-2-butene, iodine and trimethylsulphonium iodide in approximately equivalent amounts from treatment of cis-2,3-dimethylthiirane with methyl iodide in refluxing acetone.



This suggested the similar treatment of the quaternary cyanides. When a mixture of the cyanide (25e) and excess methyl iodide was stirred at room temperature the unsaturated compound (56) was obtained in excellent yield; likewise boiling the reactants in acetone under reflux gave compound (56) also in good yield and trimethylsulphonium iodide in poor yield.

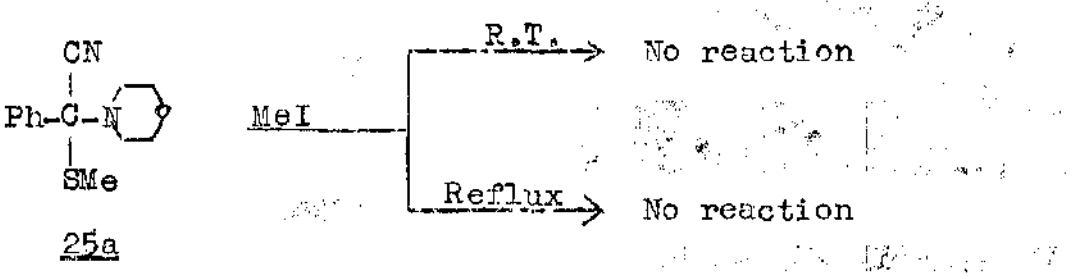


Similar treatment of the more sterically hindered cyanide (25i) with excess methyl iodide at room temperature gave no reaction even after long stirring. However, when the cyanide and excess methyl iodide was boiled in acetone under reflux trimethylsulphonium iodide was obtained, and also a colourless oil, b.p. 62°/15mm Hg, whose spectral properties suggest the alkene (66).

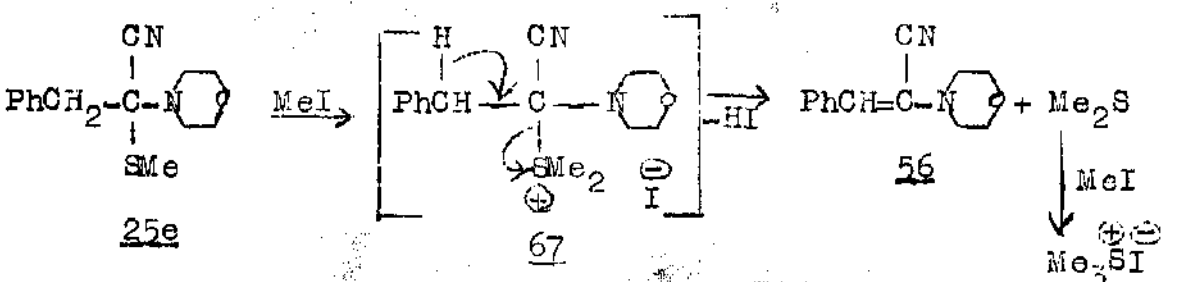


Stirring of a mixture of cyanide (25a) and excess methyl iodide at room temperature resulted in recovery

of the starting material as also did the boiling under reflux of the substances in acetone.

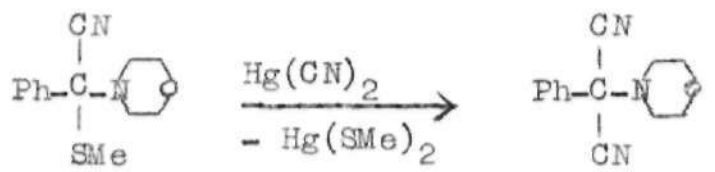


The desulphurisation of cyanide (25e) probably involves initial formation of the sulphonium compound (67), which is the precursor of compound (56). Reaction of dimethyl sulphide formed with methyl iodide would then give trimethylsulphonium iodide. The formation of trialkylsulphonium halides from treatment of thioethers with alkyl halides is well known.[35]



REACTION OF QUATERNARY CYANIDES WITH MERCURIC CYANIDE

Mercuric cyanide has been used as a desulphurising agent by Yamaguchi et al.[29,36] In order to extend further this reaction, mercuric cyanide was added to a solution of cyanide (25a) in acetonitrile and the mixture stirred at room temperature. The reaction gave the expected malononitrile (68) in excellent yield; the product was characterised by its spectral properties and elemental analysis.



25a 99% 68

The i.r. spectrum of the malononitrile (68) surprisingly showed complete absence of cyanide absorption despite the presence of two cyano- groups in the molecule (Fig. 26).

This desulphurisation could be explained by the bonding interaction of mercuric ion toward sulphur atom.[36] The interaction of mercuric ion is explicable by the hard and soft acids and bases principle;[37] by this concept mercuric ion, being a soft acid, would

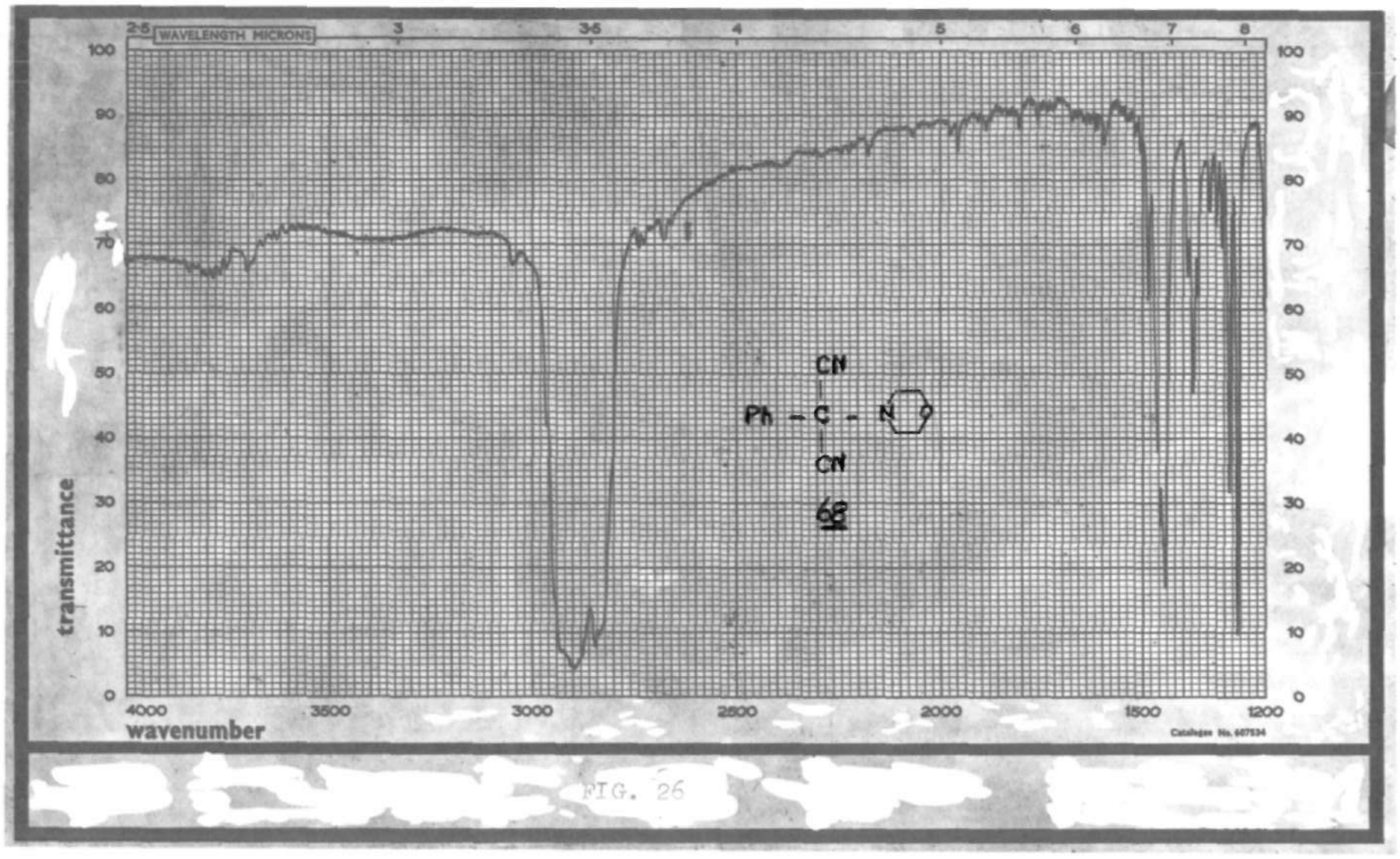
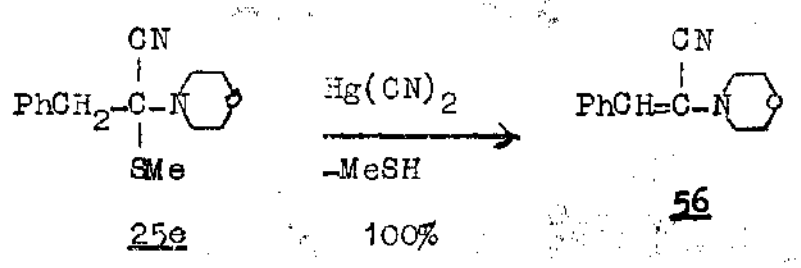

2·5
WAVELENGTH MICRONS
3
3·5
4
5
6
7
8
100
90
80
70
60
50
40
30
20
10
0
transmittance
CN
Ph – C – N
CN
68
4000
3500
3000
2500
2000
1500
1200
wavenumber

FIG. 26

form a strong bond with methylthio- group, which is a soft base.

On the other hand, a dialkylamino- group has been reported[36] to be an excellent electron donor and is most effective for the elimination of an alkylthio- group as an alkylthiolate anion. Thus the electron-donating function of the morpholino- group would enhance the elimination of the methylthio- group as a methylthiolate anion.

Treatment of the benzyl substituted cyanide (25e) with mercuric cyanide afforded the elimination product (56) in quantitative yield, whilst the cyanide (25c) gave a colourless solid which was too small to be characterised.



25e 100% 56

ATTEMPTED RESOLUTION OF A QUATERNARY CYANIDE

The presence of a chiral centre in the cyanides (25) prompted several efforts in this investigation to obtain cyanide (25a) in an optically active form, either by

resolution or by asymmetric synthesis.

When this cyanide was chromatographed in chloroform on a column of D-lactose it was found that various fractions of efluent showed no optical activity.

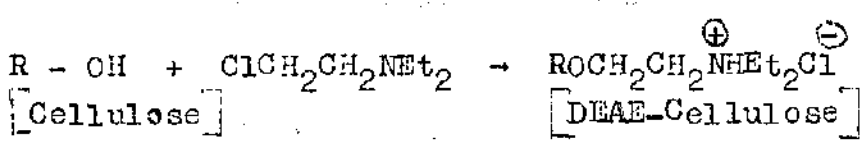
Many methods have been used for resolution of compounds which do not possess a functional group capable of salt formation with an optically active acid or base.[38] One of such methods is chromatography over optically active adsorbents.[39,40,41,42,43] In principle the enantiomers should move down the column at different rates and should be separable. This has been successfully accomplished with paper and column chromatography. For example, DL-mandelic acid has been almost completely resolved by column chromatography on starch,[44,45] and DL-cysteine has been resolved by paper chromatography.[46] Separations involving gas chromatography with a column packed with an optically active adsorbent has only recently been accomplished.[47]

Considering the various reported successes in resolution of compounds by chromatography, we were therefore surprised at our failure to resolve cyanide (25a) over D-lactose.

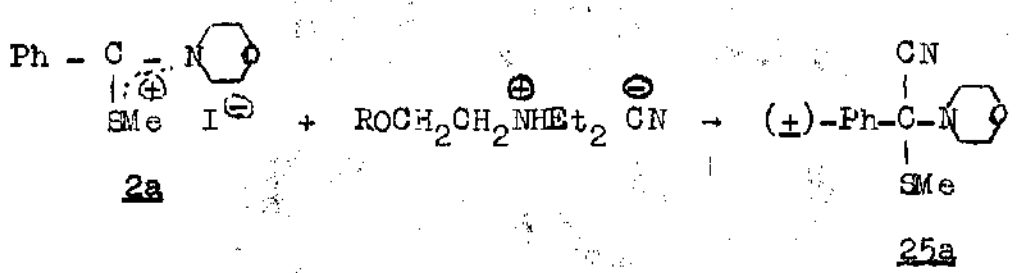
Crystallisation from an optically active solvent has also been used for resolution of compounds.[48] We employed this technique by recrystallising cyanide (25a) from D-limonene, but the substance obtained was also optically inactive.

Optically active substances have been obtained by asymmetric synthesis.[49] Such synthesis usually involves the use of active substrate or active reagent. Active catalyst or solvent has been used; also reactions in presence of circularly polarized light[50] have effected asymmetric synthesis.

In the present investigation unsuccessful attempts were made to produce an optically active form of cyanide (25a) by asymmetric synthesis; treatment of thiobenzomorpholide methiodide (2a) with aqueous potassium cyanide in the presence of D-glucose at room temperature gave an optically inactive compound, as did also the treatment of a solution of the methiodide (2a) in chloroform with potassium cyanide in the presence of diethylaminoethyl (DEAE) cellulose. The latter is prpared by treating a high-purity wood cellulose with 2-chloroethyldiethylamine hydrochloride.[51]

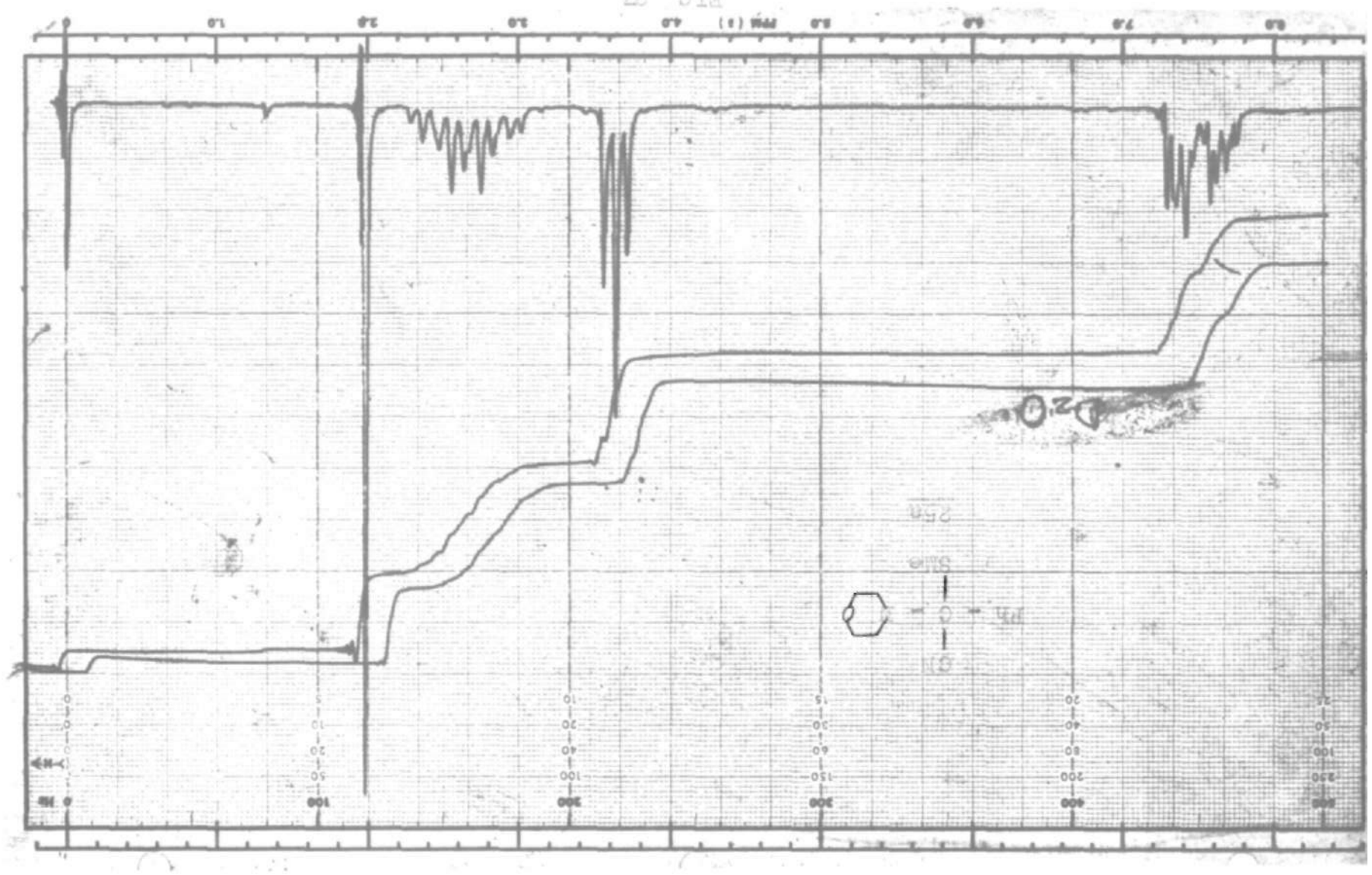


In the present study, also, a mixture of the methiodide (2a) and the cyanide form of DEAE-Cellulose in chloroform, was stirred at room temperature, but the reaction gave an inactive product.



N.M.R. SPECTRA OF QUATERNARY CYANIDES

We have shown[10h] that the n.m.r. spectra of the quaternary cyanides (25) provide interesting features, particularly with regard to the morpholino- substituent. For those cases in which the quaternary carbon atom has an aromatic substituent as in compounds (25a,b, and h) the methylene protons next to nitrogen show a complex pattern of ten symmetrical peaks centred at δ2.6 (Figs. 27, 28, and 29). For alkyl-substituted cyanides (25d, e, and i) these protons show a simpler pattern



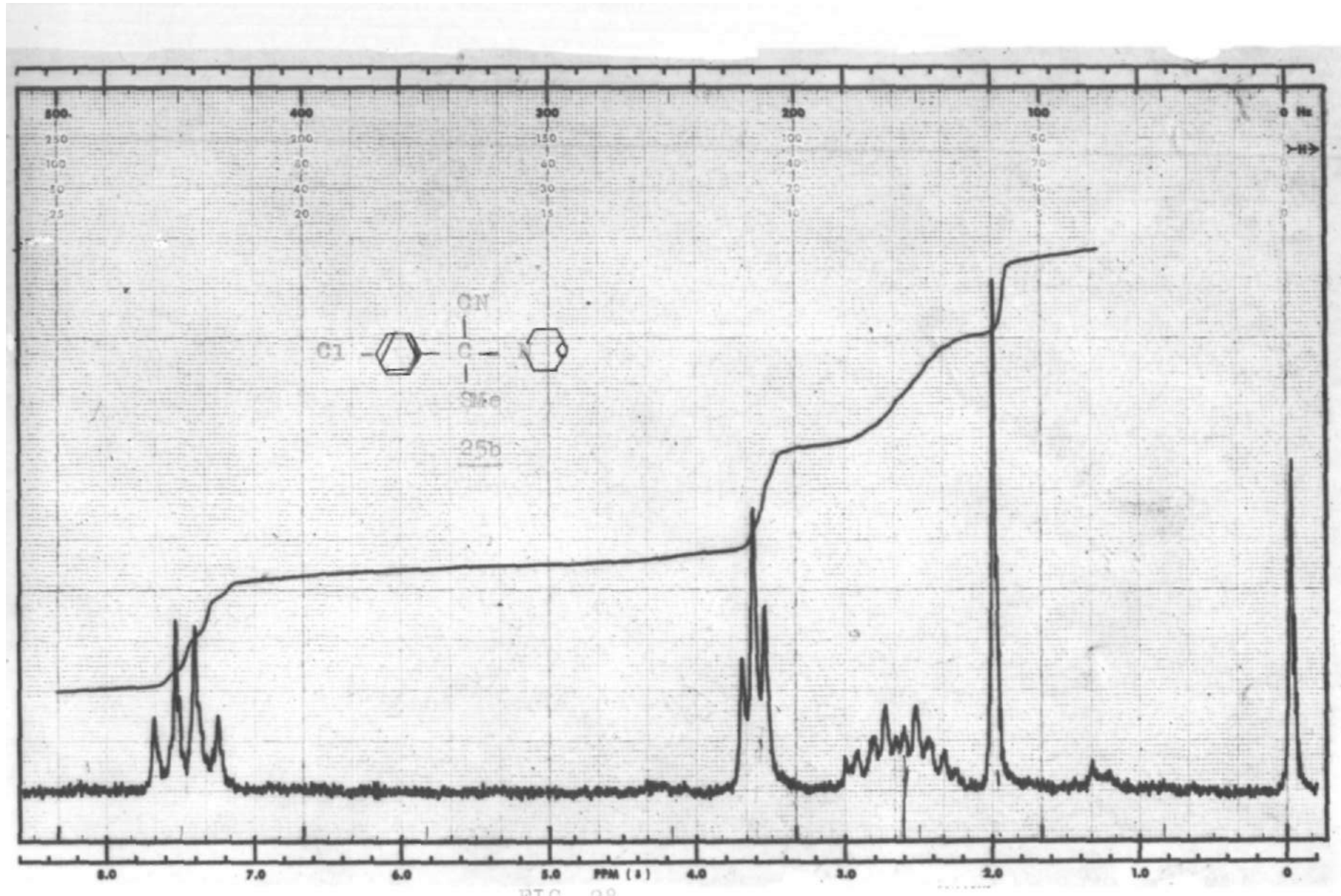
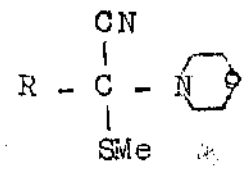


FIG. 2P

similar or nearly so to the methylene protons next to the oxygen atom (Figs. 30, 31, and 32).



25

a. R = C_6H_5-

b. R = p.ClC_6H_4-

d. R = CH_3-

e. R = $C_6H_5CH_2$-

h. R = p.$CH_3O.C_6H_4$-

i. R = $(CH_3)_2CH$-

Spin decoupling experiments in the former case (25a) showed that the spectra could be simplified to more easily understandable patterns (Fig..33). Irradiation of the δ2.6 multiplet caused the 3.6δ triplet to collapse to a singlet, suggesting that all four protons adjacent to the oxygen atom have the same chemical shift. On the other hand, irradiation of the δ3.6 signal simplified the 2.6 signet to an AB quartet (J 11Hz). The coupling constant in this case is of the order of magnitude

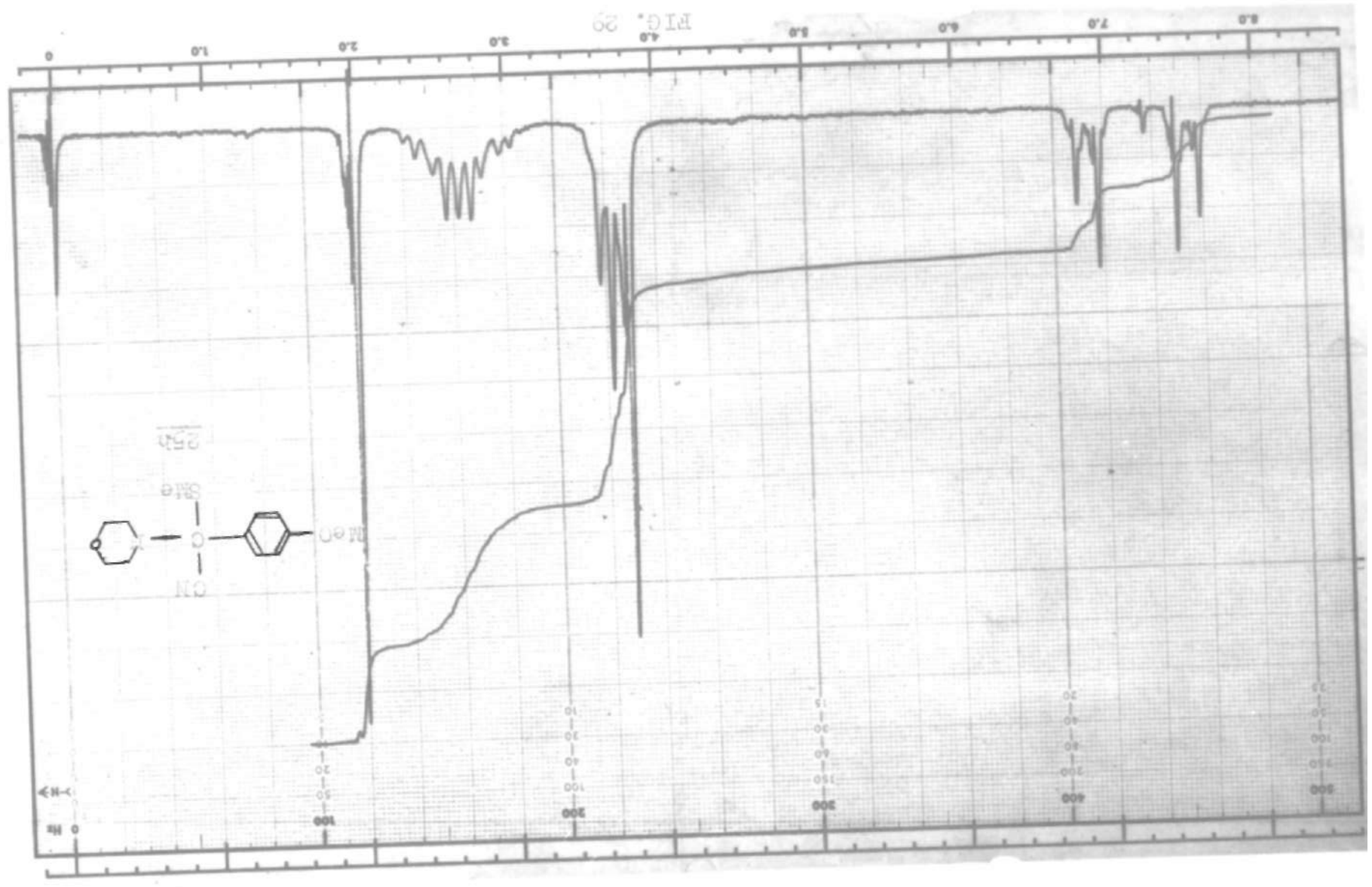


FIG. 29

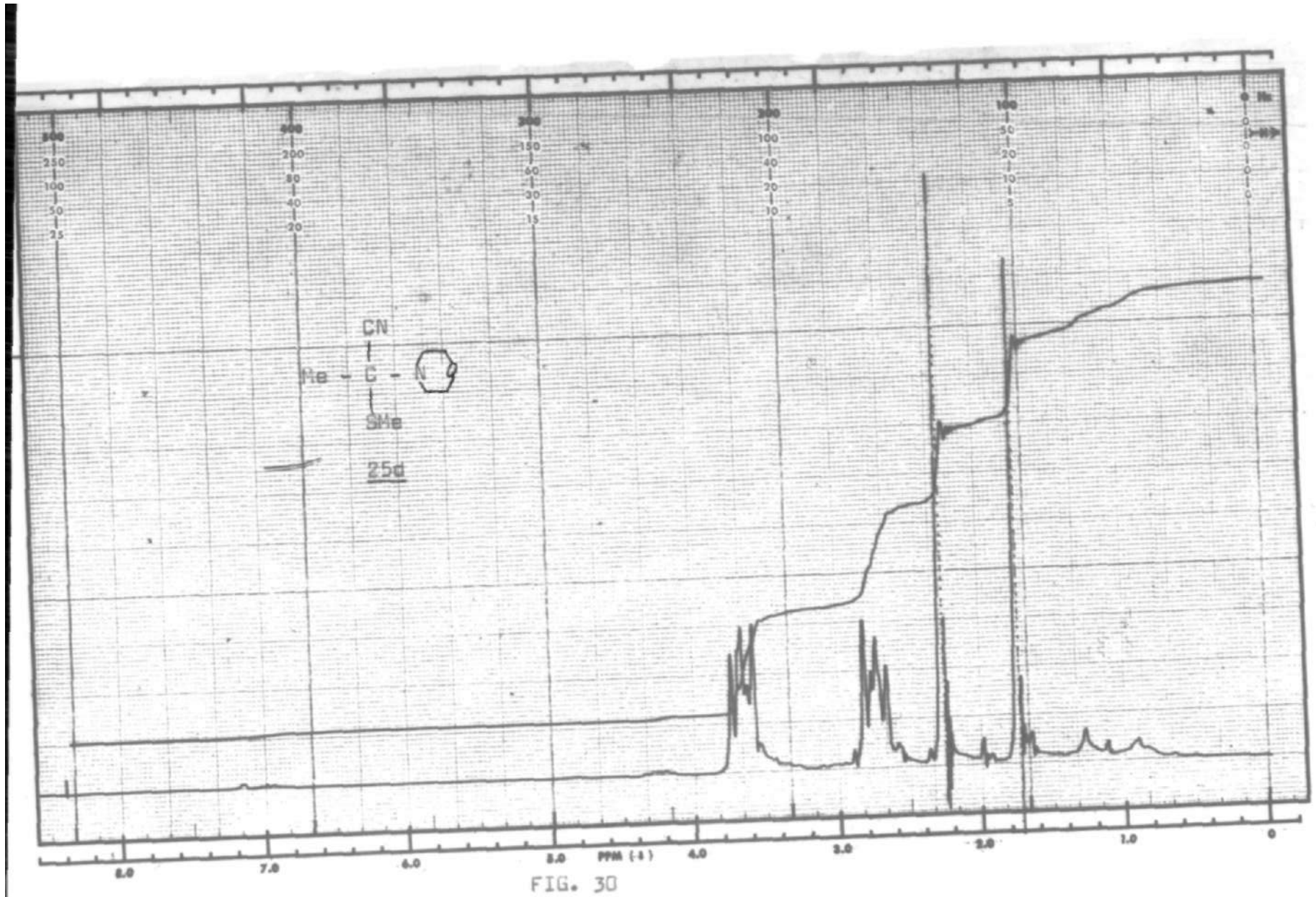


FIG. 30

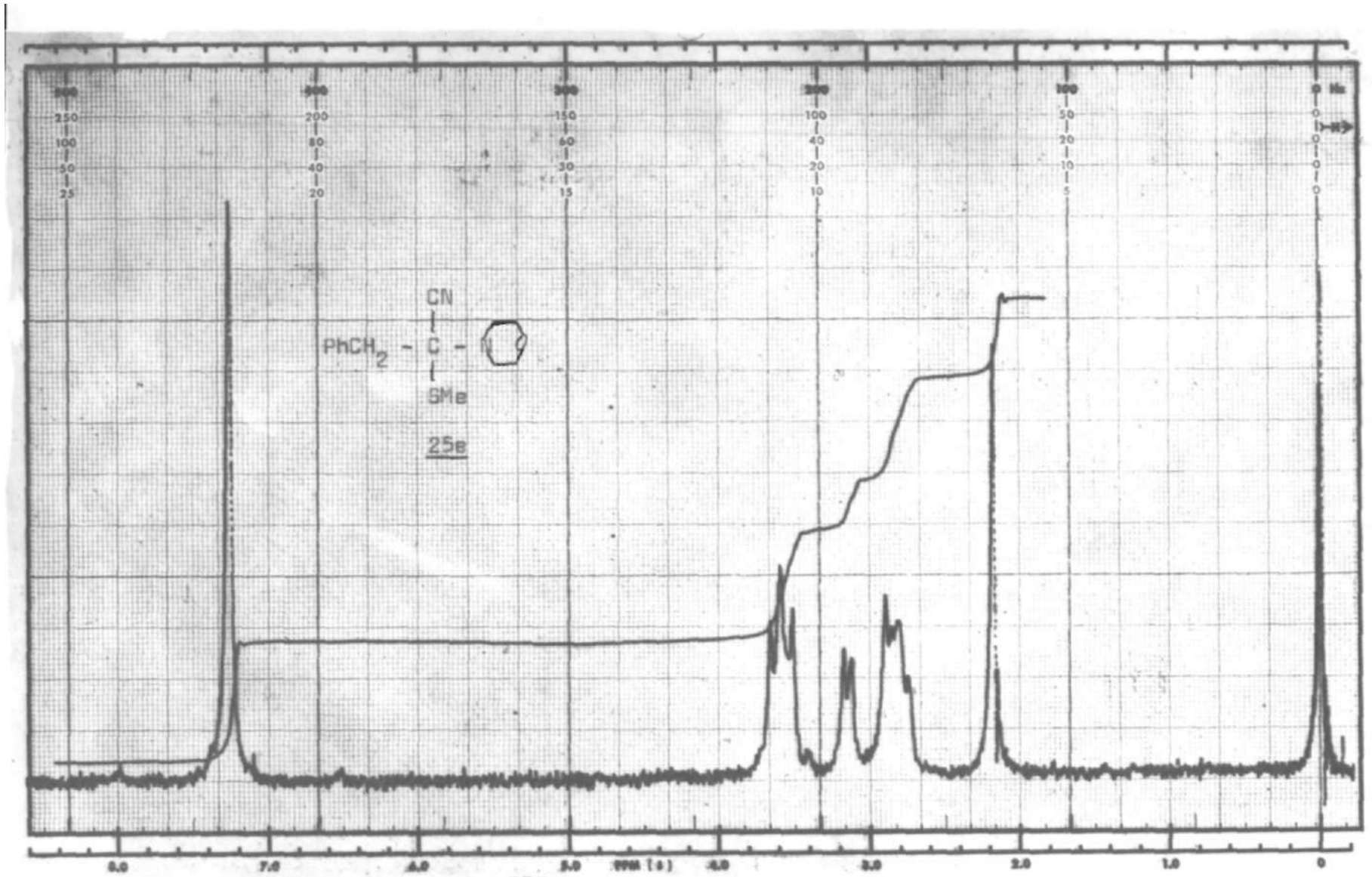


FIG. 31

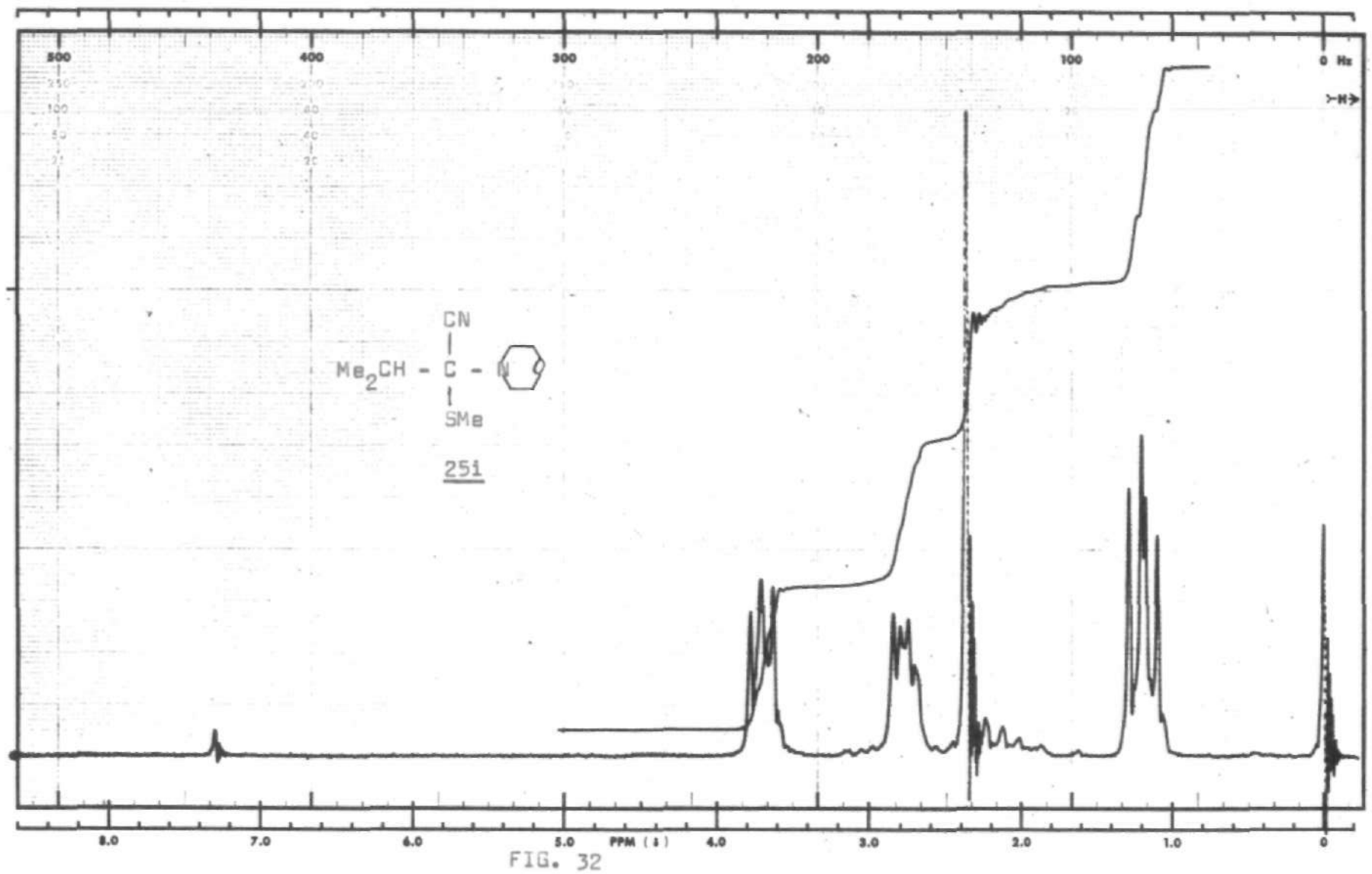
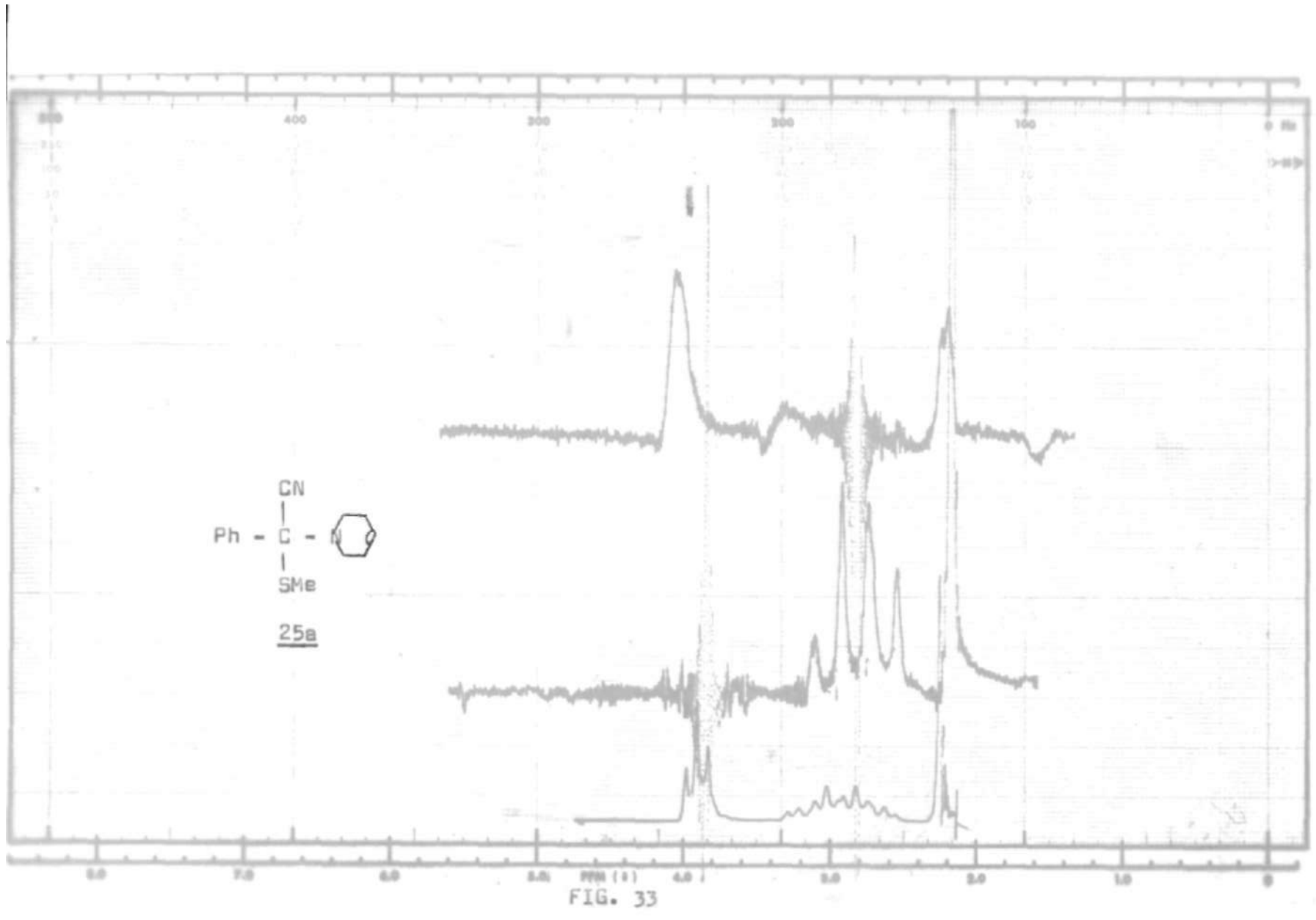

500
400
300
200
100
0 Hz
CN
Me2CH - C - N
SMe
251
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

FIG. 32



25a

FIG. 33

expected for geminal coupling, and this suggests that the two protons of each methylene next to the nitrogen atom are non-equivalent.

We previously explained[10h] the difference in behaviour of methylenes next to nitrogen from those adjacent to oxygen in terms of conformational rigidity imposed by the bulky substituents on the nitrogen end of the morpholino- group. Since no such restriction exists at the oxygen end, this means that the only conformational changes which the morpholino-six-membered ring can undergo would be the chair-boat ring inversion. The chair-boat conversion would be sufficient to equalise the chemical shifts of protons Hr and Hs but not of Hm and Hn (Fig. 34).

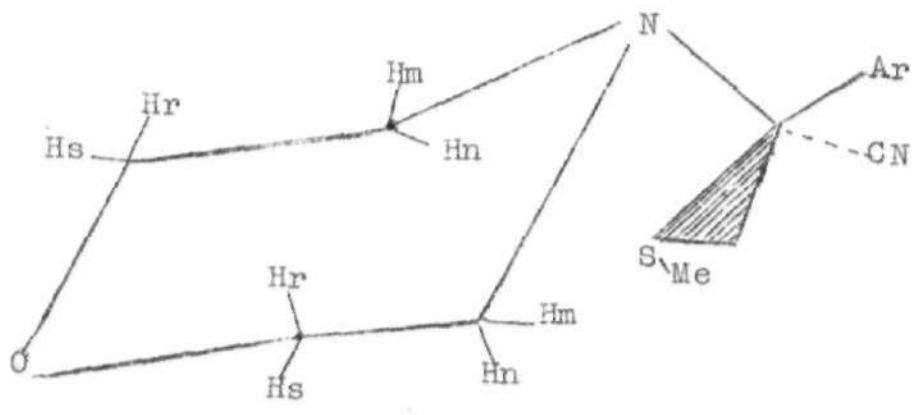


Fig.34: Chair conformation of morpholino-group in aryl substituted quaternary cyanides.

We also postulated that a field due to aromatic ring current operates at the N-methylene protons of the aryl substituted compounds, and this taken together with conformational rigidity would give rise to the observed spectral pattern.

In cyanide (25e) from phenylthioacetmorpholide methiodide (2e), although a phenyl group is present, it is further removed from the methylene protons next to nitrogen, and is more free to rotate than the phenyl substituent in cyanide (25a) (Figs. 27 and 31). This difference might be sufficient to cause the observed effect, since the influence of ring currents depends on direction and distance. In support of this, it is interesting to note that the methylene proton patterns in cyanide (25e) are more complex than those of the corresponding protons in cyanide (25d) (Figs. 30 and 31).

We suggested that a test of this hypothesis could be carried out by susbstituting electron-withdrawing or - donating groups at the para-position in cyanide (25a), since such substituents would affect the size of the ring current and hence the complexity of the signals for methylene protons next to nitrogen. However, no change was observed in the spectral pattern of the

p-chlorophenyl homologue (25b) (Fig. 28). Similarly the spectral pattern of the p-methoxy compound (25h), made in the present investigation, did not vary from that of cyanide (25a) (Figs. 27 and 29).

The n.m.r. spectrum of compound (55) or the malononitrile (68) shows that the signal due to the methylenes next to oxygen has the same pattern as that of the methylenes adjacent to nitrogen, each set being represented by a triplet (Figs. 35 and 36).



55

68

Spin decoupling shows that the methylene groups next to oxygen in compound (55) are equivalent, while those adjacent to nitrogen are also equivalent.

We strongly suggest that the bulk of the methylthio- group in the cyanides which have an aromatic substituent contributes largely to the observed spectral pattern of the methylene groups next to nitrogen. The hydrogen atom and the cyano- group in compounds (55) and (68) respectively do not present such a steric problem, hence the simpler spectral patterns observed with both compounds.

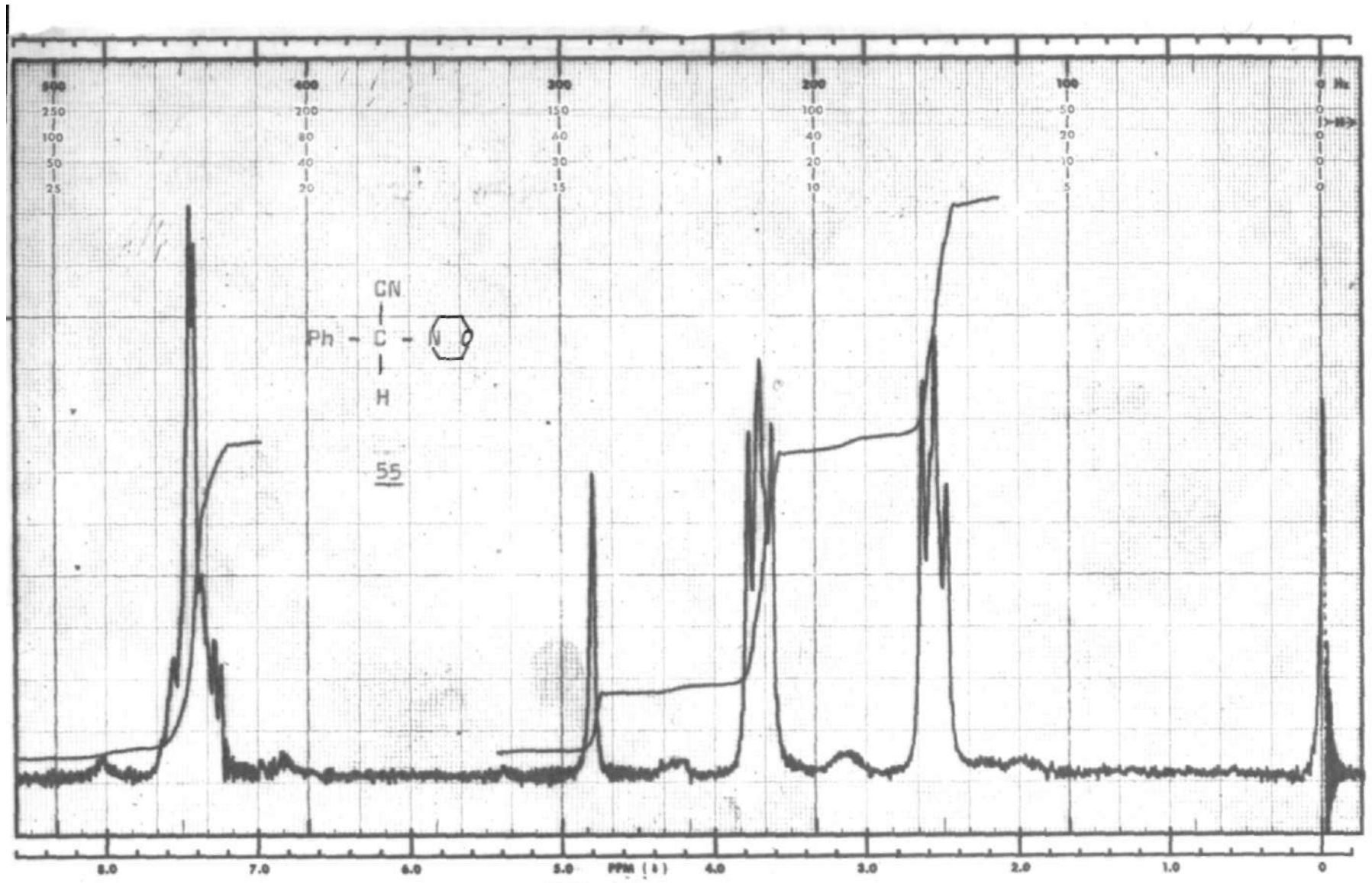


FIG. 35

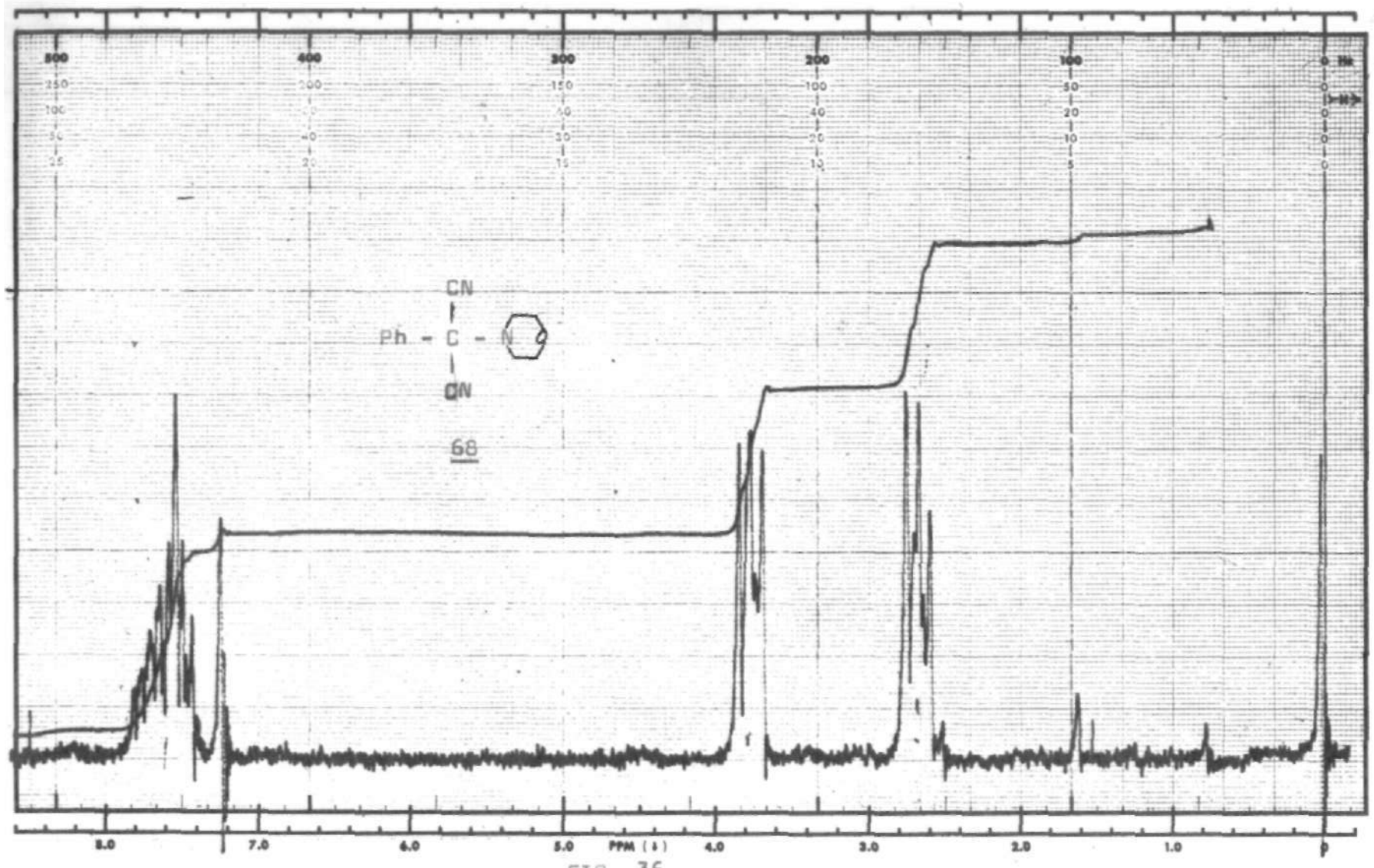


FIG. 36

From the present investigation it thus appears that conformational rigidity imposed by the bulky substituents on the nitrogen end of the morpholino- group is mainly responsible for the difference in behaviour of methylenes next to nitrogen from those adjacent to oxygen. There might also be some contribution towards the observed spectral pattern by ring current effect as we suggested in our previous study.[10h]

The N-methylenes appear to affect the aromatic signal pattern; models of aryl substituted cyanides provide ample evidence. The spectrum of cyanide (25a) or its p-chloro- (25b) or p-methoxy (25h) phenyl homologue shows a complex signal for the aromatic group, whereas that of the benzyl substituted cyanide (25e) shows a singlet for that group (Figs. 27, 28, 29 and 31). The simple aromatic signal in the latter case could be explained by the fact that the phenyl group and the N-methylene protons are farther apart.

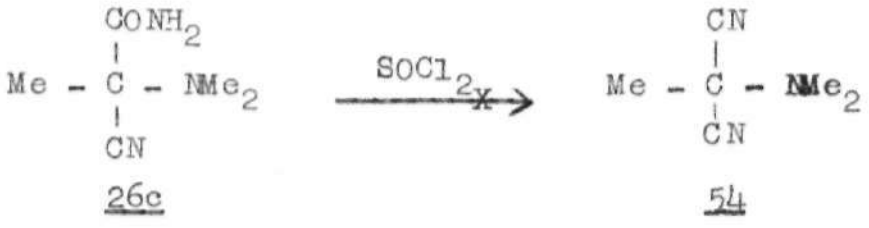
The spectrum of cyanide (25e) also shows that the methylene protons of the benzyl group are non-equivalent, being represented by an AB quartet, in which only three peaks are seen centred at δ3.2, the fourth peak hidden

under the complex multiplet centred at 2.9 for the N-methylenes (Fig. 31). The two methylene protons of the benzyl group are diastereotopic,[52] hence their non-equivalence.

The methyl groups of the isopropyl group in cyanide (25i) are also diastereotopic[52] and non-equivalent, being represented as expected by two doublets (Fig. 32).

MISCELLANEOUS REACTIONS

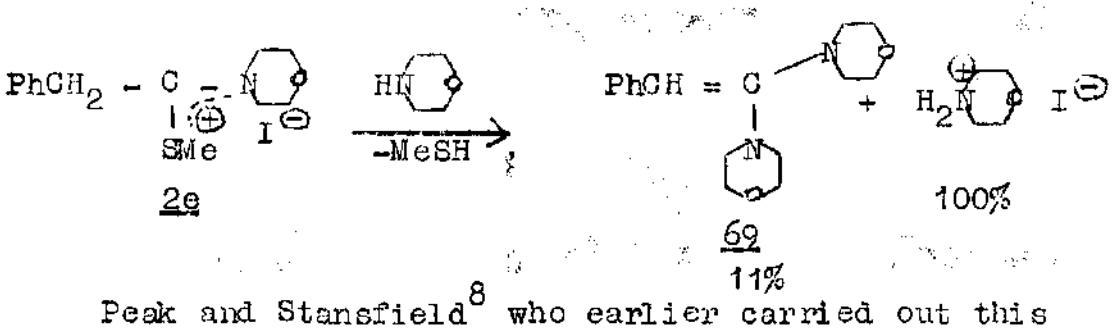
(a) In the present investigation an attempt was made to dehydrate the cyanoamide (26c) with the expectation of obtaining the malononitrile (54) using Krynitsky and Cahart's procedure,[53] employing thionyl chloride as dehydrating agent. The only solid product isolated in trace amount gave weak i.r. absorption at 2200 cm^{-1} and an n.m.r. singlet at δ3.70.



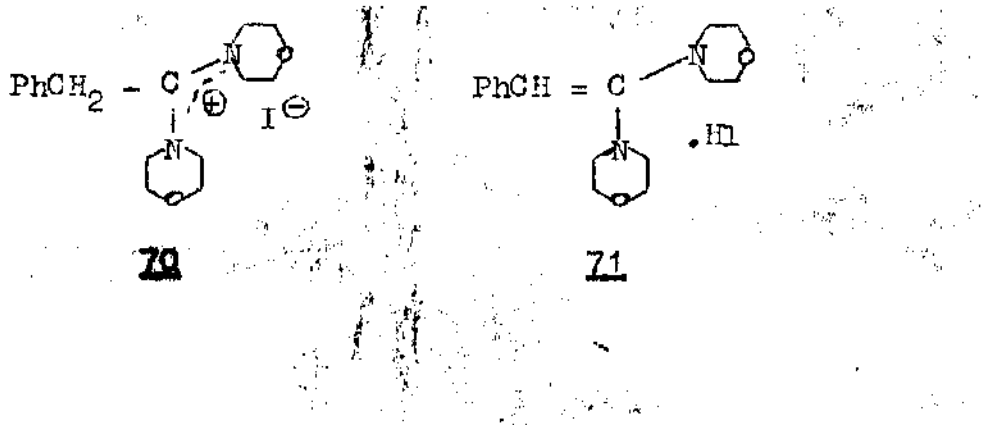
26c 54

Attempted dehydration of the cyanoamide (26c) with NN'-dicyclohexylcarbodiimide[54] gave only recovered starting material.

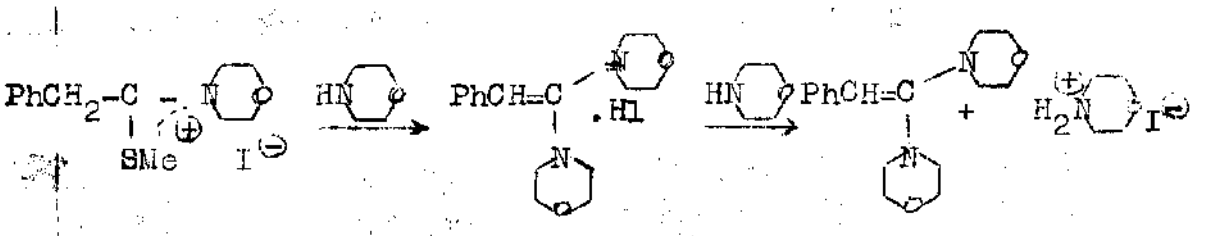
(b) Addition of excess morpholine to phenylthioacetmorpholide methiodide (2e) resulted in a spontaneous reaction; on heating the mixture for 8h, methanethiol was profusely evolved while the alkene (69) and morpholinium iodide were isolated in poor and quantitative yields respectively, and were characterised by their spectral properties and elemental analyses.



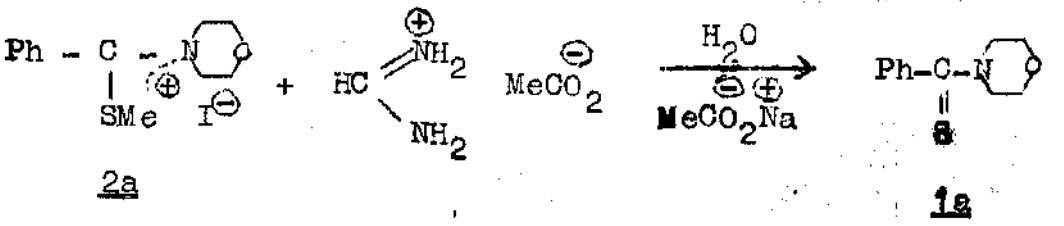
Peak and Stansfield[8] who earlier carried out this reaction obtained the quaternary amidinium iodide (70) or the isomeric hydriodide (71), but not in analytically pure state. However, they did not mention the molar proportions of the reactants in their procedure.



The hydriodide (71) formed probably reacts in our case with excess morpholine to give the isolated products.

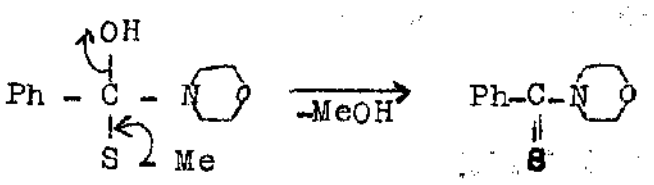


(c) Thiobenzomorpholide (1a) was obtained in low yield when a mixture of the methiodide (2a) and formamidine acetate in water was stirred at room temperature for 8h in the presence of excess sodium acetate.



2a 1a

The pseudo-base (11) probably formed in the medium would give the thioamide (1a) attended by loss of methanol.



11 1a

CHAPTER THREE

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

GENERAL. - Elemental microanalysis was done by Scandinavian Microanalytical Laboratories, Denmark. Melting points (uncorrected) were determined with a Gallenkamp melting point apparatus and a Kofler hot stage microscope.

The p.m.r. spectra were measured with a Varian T-60 instrument whilst ^{13}C n.m.r. spectra were obtained on a Varian XL-100FT spectrometer. All p,m.r. and n.m.r. chemical shifts are relative to tetramethylsilane as internal standard.

I.r. measurements were made with a Unicam SP1200 and Perkin-Elmer 700 instruments.

The u.v. spectra were determined on Unicam SP800B spectrometer. Mass spectra were recorded with MS 9 and MS 12 instruments.

Thiobenzomorpholide (1a).[55] - Morpholine (52.0g; 1.5 mol) and benzaldehyde (42.5g; 1.0 mol) were added at the same time to sulphur (19.2g; 1.5 atoms). An exothermic reaction occurred with separation of two layers. The mixture was heated under reflux for 3h on a steam bath. During the reaction a dark brown oil resulted which sometimes solidified.

The dark brown product was dissolved in boiling ethanol (800 ml). The solution was filtered from a little sulphur, and allowed to cool in a refrigerator. The golden-yellow needles of thiobenzomorpholide were filtered off and dried (73.7g; 90%). The compound was recrystallised from light petroleum (b.p.80-100°); m.p.135-136° (lit.[55] 137-138°).

In the same way the following NN-disubstituted thioamides were made; starting materials, reaction times and yields being given parenthetically in order: p-Chlorothiobenzomorpholide (1b). - (p-Chlorobenzaldehyde, 10h; 76%); yellow crystals from ethanol, m.p. 141-142° (Found: C, 54.7; H, 5.0; N, 6.0. $C_{11}H_{12}ClNOS$ requires C, 54.7; H, 5.0; N, 5.8%).

Phenylthioacetmorpholide (1e).[56] - (Acetophenone; 17h; 83%); light yellow crystals from ethanol, m.p.75-77° (lit.[56] 76-77°).

Thiosalicylmorpholide (1f)[10i]. - Salicylaldehyde; 3h; 80%); deep yellow crystals from ethanol, m.p.166-167° (lit.[10i] 165-167°).

p-Dimethylaminothiobenzomorpholide (1i).[57a] - (p-Dimethylaminobenzaldehyde; 3h; 95%); bright yellow crystals from ethanol, m.p. 139° (lit.[57a] 137-138°).

p-Methoxythiobenzomorpholide (1j).[8] - (Anisaldehyde; 3h; 99%); golden yellow needles from ethanol, m.p.108-109° (lit.[8] 109-110°).

Thioacetmorpholide (1d).[58] - Acetmorpholide (20.0g; 0.16 mol) dissolved in carbon disulphide (100 ml) was added in portions to phosphorus pentasulphide (34.4g; 0.33 mol) and the mixture was gently shaken and occasionally cooled in ice. After all the acetmorpholide solution had been added, the mixture was stirred magnetically for 3h and then boiled under reflux for 3h on a steam bath.

The mixture was cooled in ice; warm water (300 ml) was added to decompose the phosphorus compounds and the mixture was set aside overnight.

The product was extracted four times with chloroform (total 600 ml) and the extract was dried. The solvent was evaporated leaving an oil which solidified on cooling. The product was dried (22.5g; 95%). Recrystallisation from ethanol (charcoal) gave colourless rods of

thioacetmorpholide, m.p.89-90° (lit.[58] 89-90°).

The following NN-disubstituted thioamides were prepared in the same way from acid amides; starting materials, reaction times and yields are given in parenthesis in order:

Thioacetdimethylamide (1g). - (NN-Dimethylacetamide; 1.5h; 92%); colourless crystals from light petroleum (b.p. 80-100°) (charcoal), m.p.74° (Found: C, 46.8; H, 8.9; N, 13.6. C_4H_9NS requires C, 46.6; H, 8.7; N, 13.6).

Thioformdimethylamide (1h).[59] - (Dimethylformamide; 2h; 82%); almost colourless liquid, b.p.120°/17mm Hg (lit.[59] 97°/12mm Hg).

Thiobenzodimethylamide (1c).[60] - Benzaldehyde (21.2g; 0.2 mol) was added all at once to a 25-30% w/v solution of dimethylamine in water (108 ml; 0.6 mol). On shaking mechanically some heat was produced and the mixture became warm and was cooled in ice.

Shaking was continued overnight in a closed flask, the mixture was poured into a separatory funnel and the upper layer of the aminal was separated and dried (Na_2SO_4) (31.1g). Its n.m.r. spectrum (neat liquid)

agreed with the aminal structure: δ7.20 (5H, s, aromatic), 3.38 (1H,s, methine group), 2.10 (12H,s, four methyl groups). The aminal which remained on the sodium sulphate was recovered by washing it with dimethylformamide (10 ml) and decanting it into the main product. Sulphur (9.6g; 0.3 atom) and toluene-p-sulphonic acid (0.4g) were then added.

No reaction occurred in the cold, but on heating on a steam bath under reflux the mixture rapidly became dark brown and dimiethylamine was rapidly evolved. Gas evolution with frothing was complete in 5 min. After heating for 30 min. the mixture was cooled in ice and water (140 ml) was added, thus precipitating an oil.

On ice-cooling, shaking and seeding the oil solidified as yellow granules, which were filtered off, washed and dried (42.0g). The product was recrystallised from light petroleum (80-100°). On cooling and seeding the oil which first separated solidified. The yellow crystals were crushed, filtered off and dried (25.3g; 88%); m.p.65-66° (lit.[60] 67°).

Thioisobutyrodimethylamide (11). - Isobutyraldehyde (14.4g; 0.2 mol), dimethylammonium chloride (32.6g;

0.4 mol), anhydrous sodium acetate (32.8g; 0.4 mol) and sulphur (12.8g; 0.4 atom) in dry pyridine (800 ml) were boiled under reflux (air condenser) for 3h. The dark brown mixture was cooled and poured into dilute hydrochloric acid (2N; 400 ml), concentrated hydrochloric acid (80 ml) was added and the product allowed to stand overnight in a refrigerator. The oil was extracted four times with dichloromethane (total 1l) and the extract washed with dilute hydrochloric acid (2N; 500 ml) then with saturated sodium hydrogen carbonate solution (1l).

The solution was dried, and the solvent evaporated leaving a dark oil, which was distilled giving thioisobutyrodimethylamide as a yellow oil (18.5g; 71%), b.p.64-66°/10mm Hg (Found: C,55.0; H, 9.9; N, 10.4. $C_6H_{13}NS$ requires C, 55.0; H, 9.9; N, 10.7%); ν_{max} (liquid film) 2920vs, 1500vs, 1275vs, 1158s, 1010vs cm^{-1}; $\delta(CDCl_3)$ 3.50 (3H, $N-CH_3$), 3.40 (3H, s, the other $N-CH_3$), 3.0 (1H, m, methine group), 1.2 (6H, d, Me_2C).

Thioisobutyromorpholide 1k). - Morpholine (52.3g; 0.6 mol) and isobutyraldehyde (28.8g; 0.4 mol) were added at once to sulphur (19.2g; 0.6 atom). There was an immediate exothermic reaction; the mixture was boiled under reflux for 16h in a heating mantle. The dark oil

was poured into water (300 ml) and extracted three times with dichloromethane (total 500 ml).

The combined extracts were washed with water (250 ml) and dried. After evaporating the solvent, dilute hydrochloric acid (2N; 200 ml) was added to the black viscous oil, which on shaking and trituration began to crystallise. The mixture was cooled in ice with shaking for 3h and the product was filtered off and washed repeatedly with cold dilute hydrochloric acid (2N; total 100 ml), then with water.

The product was shaken for 45 min with saturated sodium sulphide solution to remove sulphur; the brown crystalline product was filtered off, washed thoroughly with water and dried (54.0g; 78%). It was recrystallised twice from light petroleum (b.p.60-80°) (charcoal) giving large colourless leaflets of thioisobutyromorpholide, m.p. 41-42° (Found: C, 55.6; H, 8.8; N, 7.9. $C_8H_{15}NOS$ requires C, 55.5; H, 8.7; N, 8.1%); ν_{max} (Nujol) 2900vs, 1460vs, 1380s (doublet, sym-bending for CH_3, characteristic of isopropyl group), 1260s, 1220vs, 1120vs (C-O stretch, CH_2-O-CH_2), 1005vs, 870s cm^{-1}; $\delta(CDCl_3)$ 4.4 (2H, t, N-methylene cis- to the thiocarbonyl sulphur) (J 3Hz), 3.8 (6H, m, the other

three methylene groups), 3.2 (1H, m, methine group), 1.2 (6H, d, Me_2C).

Methyl NN-dimethyldithiocarbamate (41) Method (a)[25].-

A mixture of aqueous dimethylamine solution (25/30% w/v; 176 ml), aqueous sodium hydroxide (31%; 96 ml) and water 100 ml) was treated with carbon disulphide (61 ml). An exothermic reaction occurred and an oil precipitated. The mixture was left at room temperature for 1h. Dimethyl sulphate (195 ml) was added; an exothermic reaction began immediately and was controlled by keeping the temperature at 30-40°. The mixture was then stirred magnetically for 2h.

The ester was extracted four times with diethyl ether (1l) and the combined extracts were dried, and the solvent was evaporated; the yellow solid product was filtered off and dried (89.0g; 89%). Recrystallisation from methanol gave colourless prisms of the ester, m.p.45-46° (lit.[25] 45-46°).

Method (b).- Sodium dimethyldithiocarbamate dihydrate (17.9g; 0.1 mol) suspended in methanol (30 ml) was stirred magnetically and colled in ice whilst methyl iodide (14.2g; 0.1 mol) was added dropwise over 10 min. Stirring was continued at room temperature for 3h more, and the mixture was allowed to stand overnight at room temperature.

The yellow oil was poured into water (150 ml) and extracted three times with diisopropyl ether (total 300 ml); the combined extracts were washed with water (60 ml) and dried. The solvent was evaporated and the remaining oil solidified on cooling in ice. The almost colourless product was filtered off and dried (10.6g; 79%). Recrystallisation from methanol gave colourless prisms, m.p.45-46° (lit.[25] 45-46°).

Thiobenzomorpholide methiodide (2a).[8] - The thioamide (1a) (20.7g; 0.1 mol), dry acetone (50 ml) and methyl iodide (42.6g; 0.3 mol) were boiled under reflux for 10 min, moisture being excluded. The quaternary salt soon crystallised out; most of the acetone and methyl iodide were then removed by evaporation.

Diethyl ether (100 ml) was added and the yellow crystalline solid was washed with ether and quickly dried (31.0g; 89%); light yellow plates from ethanol-ether, m.p.155-156° (decomp.) [lit.[8] 158° (decomp.)].

In this way, other S-alkyl quaternary salts were prepared. The products so obtained were used directly for further reactions, but purification could often be accomplished by dissolving them in absolute ethanol at

room temperature and precipitating them in crystalline form by slow addition of ether with stirring and seeding if necessary.

The quaternary salts are water-soluble, but are slowly decomposed even by atmospheric moisture, and melt with decomposition (usually with liberation of methyl iodide and regeneration of the thioamides).

The following quaternary salts were made from thioamides; reaction times and yields being given parenthetically:

Phenylthioacetmorpholide methiodide (2e).[8] - (10 min; 78%); colourless leaflets which turned light yellow on drying, m.p.152-153° (decomp.) [lit.[8] 158°(decomp.)].

p-Chlorothiobenzomorpholide methiodide (2b). - (10 min; 72%); pale yellow crystals, m.p.140-141° (decomp.)

Thiosalicylmorpholide methiodide (2f). - (10 min; 95%); yellow crystals, m.p.150-151° (decomp.)

p-Methoxythiobenzomorpholide methiodide (2j). - (10 min; 82%); yellow hairs, m.p.141° (decomp.) [lit.[8] 142° (decomp.)]

p-Dimethylaminothiobenzomorpholide methiodide (2i).— (10 min; 99%); yellow crystals, m.p.169-171° (decomp.) (Found: C, 42.8; H, 5.5; N, 7.1. $C_{14}H_{21}IN_2OS$ requires C, 42.9; H, 5.4; N, 7.1%).

Thioacetmorpholide methiodide (2d). - (30 min; 98%): yellow crystals, m.p.120-122° (decomp.).

Thioacetdimethylamide methiodide (2g). - (10 min; 100%); very hygroscopic yellow-brown crystals.

Thioformdimethylamide methiodide (2h). - (10 min; 99%); colourless crystals, m.p.119-120° (decomp.).

Thiobenzodimethylamide methiodide (2c).[15] - (3h; 96%); yellow crystals from acetone, m.p.135-136° (decomp.) (lit.[15] 148-149°).

Thioisobutyromorpholide methiodide (2k). - (30 min; 68%); yellow crystals, m.p.210-212° (decomp.).

Thioisobutyrodimethylamide methiodide (2l). - (1h; 99%); yellow crystals, m.p.118-119° (decomp.).

p-Dimethylaminothiobenzomorpholide isopropiodide (2m).[57b] (25h; 96%); yellow crystals, m.p.164-165° (decomp.) (lit.[57b] 166°).

NNSS'-Tetramethyldithiocarbamidium iodide (42).[26] - The thioester (41) (13.5g; 0.1 mol) was dissolved in methyl iodide (42.6g; 0.3 mol) and the mxiture was allowed to stand at room temperature for 24 h. The precipitated bright yellow crystals were filtered off, washed with hot acetone and dried (25.3g; 91%), m.p.95-96° (lit.[26] 95-96°).

4-α-Morpholinobenzylidenemorpholinium iodide (14).[8] - Thiobenzomorpholide methiodide (22.0g; 0.06 mol) and morpholine (15 mol) were heated on a steam bath, moisture being excluded. A vigororous reaction with evolution of methanethiol occurred almost at once and heating was continued for 2h. The mixture was cooled and the solid formed triturated with diethyl ether and dried (24.0g; 98%). The crude product was recrystallised from ethanol giving pale yellow needles of the amidinium iodide, m.p. 290° (decomp.) [lit.[8] 291° (decomp.)].

Reaction of the amidinium iodide (14) with sodium methoxide. - Sodium metal (10.0g; 0.44 atom) was reacted in portions with methanol (120 ml). The amidinium salt (6.0g; 0.016 mol) was added to the solution and the mixture was boiled under reflux on a steam bath for 1h.

Water (70 ml) was added to the mixture; this was extracted four times with dichloromethane (total 250 ml). The combined extracts were washed with water (250 ml) and dried. The solvent was evaporated; the oil which remained was rubbed with ethanol (2 ml) while cooling in ice, and the colourless solid formed was filtered off and dried (0.33g; 11%).

The product was recrystallised from light petroleum (b.p.80-100°). Its m.p.(74°) and i.r. spectrum were identical with those of an authentic sample of benzomorpholide.

Reaction of the amidinium iodide (14) with potassium cyanide.- The amidinium salt (10.0g; 0.026 mol) was added to a solution of potassium cyanide (36.0g; 0.55 mol) in water (300 ml), and the mixture was stirred magnetically at room temperature for 15h. The colourless solid formed was filtered off, washed with water and dried (7.38g; 100%). Recrystallisation from ethanol gave colourless crystals of α,α-dimorpholinobenzyl cyanide m.p.160° (Found: C, 66.9; H, 7.3; N, 14.5. $C_{16}H_{21}N_3O_2$ requires C, 66.9; H, 7.3; N, 14.6%); ν_{max} (Nujol) 2920vs, 1115vs (C-O stretch, CH_2-O-CH_2), 1020vs, 875vs, 770s, 710vs cm^{-1}; δ($CDCl_3$) 7.43 (5H, s, aromatic), 3.7 (8H, t, four -OCH_2-) (J 3Hz), 2.6 (8H, m, four -NCH_2-).

Attempted reaction of the amidinium iodide (14) with methylmagnesium iodide. - The amidinium salt (5.0g; 0.013 mol) and methylmagnesium iodide from magnesium turnings (0.48g; 0.02 atom) in methyl iodide (5.0g; 0.035 mol) and dry ether (25 ml) were mixed in dry ether (100 ml) and boiled under reflux for 1h, after which the mixture was stirred magnetically for 3h.

Water (50 ml) was added and the mixture was extracted three times with dichloromethane (total 300 ml). The combined extracts were washed with water (150 ml) and dried.

The solvent was evaporated; the remaining viscous liquid solidified on scratching and the solid was dried (0.15g). It was recrystallised from ethanol; its m.p. and spectral properties were identical with those of the starting material.

Reaction of the amidinium iodide (14) with potassium thiocyanate. - The iodide (17.5g; 0.045 mol) was added to a solution of potassium thiocyanate (120.0g; 1.24 mol) in water (250 ml) and the mixture stirred magnetically at room temperature for 22h. The light yellow solid formed was filtered off and dried.

The product was boiled with dichloromethane (60 ml) and the colourless solid was filtered off, washed with dichloromethane and dried (9.3g; 65%). Recrystallisation from ethanol gave beautiful colourless needles of 4-α-morpholinobenzylidenemorpholinium thiocyanate, m.p.254-255° (Found: C, 60.1; H, 6.6; N, 13.0. $C_{16}H_{21}N_3O_2S$ requires C, 60.2; H, 6.6; N, 13.1%); ν_{max} (Nujol) 2040vs (SCN), 1600vs, 1480s, 1320m, 1280vs, 1130vs(C-O stretch, CH_2-O-CH_2), 1050m, 890s, 840m, 780m cm^{-1}.

The thiocyanate with aqueous saturated sodium picrate solution afforded the amidinium picrate which formed yellow cubic crystals from ethanol, m.p.154° (lit.[8] 153°) (Found: C, 51.5; H, 4.7; N, 14.6. Calc. for $C_{21}H_{23}N_3O_7$: C, 51.5; H, 4.7; N, 14.3%).

The dichloromethane filtrate from the thiocyanate was evaporated and the yellow solid which remained was dried (4.25g; 46%). Recrystallisation from light petroleum (b.p.80-100°) gave beautiful needles of thiobenzomorpholide, m.p.136-137° (lit.[55] 137-138°) (Found: C, 63.6; H, 6.3; N, 6.6. Calc. for $C_{11}H_{13}NOS$: C, 63.8; H, 6.3; N, 6.8%).

Reaction of the amidinium thiocyanate (34) with potassium thiocyanate. - The thiocyanate (2.0g; 0.0063 mol) was added to a solution of potassium thiocyanate (25.0g; 0.26 mol) in water (50 ml). The mixture was heated under reflux on a steam bath for 10h. After cooling, it was extracted with dichloromethane. Evaporation of the solvent and recrystallisation of the solid product from light petroleum gave benzomorpholide (0.24g; 20%); its m.p.(74°) and i.r. spectrum were identical with those of an authentic sample.

Boiling a mixture of the amidinium thiocyanate and potassium thiocyanate under reflux in acetonitrile gave the starting material.

Reaction of the carbamidium iodide (42) with potassium cyanide. - The iodide (8.0g; 0.029 mol) was added to a solution of potassium cyanide (20.0g; 0.31 mol) in water (150 ml). The solution turned turbid and an oil resulted, methanethiol being evolved. The mixture was shaken for 2 min and cooled in a refrigerator for 1h.

The oil was extracted four times with dichloromethane (total 500 ml); the combined extracted were washed once with water (150 ml) and dried. The solvent was evaporated giving dimethylaminobis(methylthio)methyl cyanide (43) (5.0g; 98%); b.p.58-60°/0.8mm Hg (Found: C, 41.0; H, 7.1;

N, 16.1. $C_6H_{12}N_2S_2$ requires C, 40.9; H, 6.8; N, 15.9%); η_D^{23} 1.5246; spectral data have been given in the results section.

Reaction of the carbamidium iodide (42) with aniline. - Aniline (4.09g; 0.044 mol) was added to the iodide (4.00g; 0.014 mol); there was an immediate exothermic reaction. Benzene (30 mol) was added and the mixture boiled under reflux for 3h. It was cooled and the solid formed was filtered off and dried (1.85g; 74%). The compound was recrystallised from ethanol; its m.p. and spectral properties were identical with those of dimethylammonium iodide.

The solvent of the mother liquor was evaporated, the oil which remained was rubbed with ethanol and cooled in a refrigerator overnight. The colourless solid formed was filtered off and dried (0.68g; 20%). Recrystallisation from ethanol gave needles of S-methyl-NN-diphenylisothiourea, characterised by its spectral properties; m.p.108° (lit.[61] 109°); ν_{max} (Nujol) 3250s (NH), 1570s, 1480s, 1370m, 780 cm^{-1}; for p.m.r. data see results section.

Reaction of the carbamidium iodide (42) with hydroxyammonium chloride. - The iodide (13.0g; 0.047 mol) was added to a solution of anhydrous sodium acetate (70.0g; 0.85 mol) and hydroxyammonium chloride (6.0g; 0.086 mol) in water (150 ml). The mixture became turbid while some oil precipitated. It was shaken for 3 min and cooled in a refrigerator for 3h.

The colourless solid was filtered off and dried (2.5g; 39%). Recrystallisation from light petroleum (b.p.80-100°) gave colourless bis(methylthio)formaldoxime (45); m.p. 74° (Found: C, 26.3; H, 5.1; N, 10.2. $C_3H_7NOS_2$ requires C, 26.3; H, 5.1; N, 10.2%); spectral data in the results section.

Reaction of the carbamdium iodide (42) with semicarbazide hydrochloride. - The iodide (12.0g; 0.043 mol) was added to a solution of semicarbazide hydrochloride (9.0g; 0.08 mol) and sodium acetate trihydrate (60.0g; 0.44 mol) in water (190 ml). The mixture was shaken for 5 min and cooled for 1h in a refrigerator.

The colourless product was filtered off and dried (3.1g; 40%). Recrystallisation from ethanol gave bis(methylthio)formaldehyde semicarbazone (48); m.p.125° (Found: C, 27.0; H, 5.0; N, 23.8; S, 35.6. $C_4H_9N_3OS_2$

requires C, 26.8; H, 5.0; N, 23.5; S, 35.8%); spectral data have been given in the results section.

Reaction of the carbamidium iodide (42) with morpholine. - Morpholine (5 ml) was added to the iodide (3.0g; 0.01 mol); an exothermic reaction started immediately. The mixture was heated under reflux for 10 min, methanethiol being given off. The colourless solid formed was cooled, triturated with ether (50 ml), filtered off, and dried (3.6g). It was recrystallised from ethanol; m.p.296-297° (decomp.). The compound was extremely hygroscopic; it contained nitrogen and iodine, but could not be further characterised.

Reaction of the carbamidium iodide (42) with nitromethane.- A mixture of the iodide (2.0g; 0.007 mol) and nitromethane (2 ml) was boiled under reflux in benzene (10 ml) for 2h. The solvent was evaporated leaving an oil. On ice-cooling the oil solidified giving a sticky substance which was rubbed with ethanol; the free-flowing solid was filtered off and dried (0.22g; 23%). Recrystallisation from methanol gave the thioester (41), m.p. 45-46° (lit.[25] 45-46°), identical in spectral properties with an authentic sample.

Boiling of the salt (42) alone in benzene also gave the thioester (41) in 28% yield.

α-Methylthio-α-4'-morpholinobenzyl cyanide (25a)[10c]. - The quaternary salt (2a) (3.0g; 0.0086 mol) was added to a solution of potassium cyanide (9.0g; 0.14 mol) in water (75 ml). The mixture was cooled overnight in a refrigerator; the solid formed was filtered off and dried (2.1g; 99%). Recrystallisation from ethanol gave colourless heavy crystals whose m.p. and i.r. spectrum were identical with those previously reported[10c] for cyanide (25a).

The following quaternary cyanides were prepared similarly from the corresponding thioamide methiodides, crude yields being given in parenthesis:

p-Chloro-α-methylthio-α-4-morpholinobenzyl cyanide (25b)[10c].— Yellow crystals from ethanol, m.p.55-56° (lit.[10c] 55-56°) (99%).

α-Dimethylamino-α-methylthiobenzyl cyanide (25c)[10c].— Colourless crystals from ethanol, m.p. 40° (lit.[10c] 40°) (99%).

2-Methyl-1-methylthio-1-morpholinopropyl cyanide (25i).— Colourless crystals from ethanol, m.p.55° (98%) (Found: C, 56.1; H, 8.5; N, 12.9. $C_{10}H_{18}N_2OS$ requires C, 56.1; H, 8.4; N, 13.1%); ν_{max} (Nujol) 2220w(C≡N), 1460vs, 1380s (doublet, sym-bending for CH_3, characteristic of isopropyl group), 1320w, 1280s, 1260vs, 1120vs, (C–O stretch, CH_2–O–CH_2), 1100s, 1070m, 1020vs, 910s, 880vs, 800vs cm^{-1}; δ($CDCl_3$) 3.7(4H, t, CH_2–O–CH_2) (J 3Hz), 2.8(4H, m, CH_2–N–CH_2), 2.40(3H, s, SMe), 2.2(1H, m, CH–), 1.3(3H, d, CMe) (J 4Hz), 1.1(3H, d, CMe) (J 4Hz).

p-Methoxy-α-methylthio-α-4'-morpholinobenzyl cyanide (25h).— p-Methoxythiobenzomorpholide methiodide (14.0g; 0.037 mol) was added to a solution of potassium cyanide (40.0g; 0.62 mol) in water (200 ml) and the mixture stirred for 20 min. The oil formed was extracted four times with dichloromethane (total 500 ml); the combined extracts were washed with water (200 ml) and dried.

The solvent was evaporated leaving an oil, which was triturated with light petroleum (b.p.40–60°), then cooled overnight in a refrigerator. The solid formed was filtered off and dried (5.1g; 50%). Recrystallisation from light petroleum (b.p.60–80°) (charcoal) gave

colourless crystals of the quaternary cyanide, m.p.40-41° (Found: C, 60.4; H, 6.6; N, 10.1. $C_{14}H_{18}N_2O_2S$ requires C, 60.4; H, 6.5; N, 10.1%) ν_{max} (Nujol) 2220vw (C≡N), 1600s (C=C, aromatic), 1500s, 1460s, 1380s, 1250vs, 1175s, 1120vs (C-O stretch, CH_2-O-CH_2), 1100m, 1030s, 1000s, 875s cm^{-1}; δ($CDCl_3$) 7.6 (2H, d, aromatic) (J 10Hz), 6.8 (2H, d, aromatic) (J 10Hz), 3.80 (3H, s, OMe), 3.7 (4H, t, CH_2-O-CH_2) (J 3Hz), 2.7 (4H, m, CH_2-N-CH_2), 2.00 (3H, s, SMe).

In the same way the following quaternary cyanide was made from the corresponding methiodide:

1-Dimethylamino-1-methylthiomethyl cyanide (25f)[10c].— Almost colourless liquid, b.p. 102°/15mm Hg (lit.[10c] 102°/15mm Hg) (50%).

Preparation of cyanoamide (26b)[10d] and quaternary cyanide (25e)[10c].— Phenylthiocetmorpholide methiodide (12.5g; 0.034 mol) was added to a solution of potassium cyanide (36.0g; 0.55 mol) in water (300 ml) and the mixture stirred at room temperature for 70h. The oil which resulted was extracted four times with dichloromethane (total 1.5 l); the combined extracts were washed twice with water (total 600 ml) and dried.

The solvent was evaporated; light petroleum (b.p.80-100°; 120 ml) was added to the sticky substance which remained and the mixture boiled. The brownish crude product insoluble in light petroleum, was filtered off and dried (1.1g; 12%). Recrystallisation from ethanol gave a colourless solid whose m.p. and i.r. spectrum were identical with those of the cyanoamide (25b).[10d]

The solvent of the filtrate was evaporated leaving an oil which solidified when cooled in the deep freeze for 3 days. This was filtered off and dried (6.3g; 70%). Recrystallisation from light petroleum (b.p.80-100°) (charcoal) gave the cyanide (25e).[10c] having spectral properties identical with those of an authentic sample.

Similar treatment of thioacetmorpholide methiodide with excess aqueous potassium cyanide gave the cyanoamide (26a)[10d] and the quaternary cyanide (25d)[10c] in 38% and 37% yields respectively; the i.r. spectrum of each compound was identical with that of an authentic sample.

Preparation of cyanoamide (26c),[10d] iminonitrile (52) and quaternary cyanide (25g).— Thioacetdimethylamide methiodide (36.0g; 0.15 mol) was added to a solution of sodium cyanide (80.0g; 1.23 mol) in water (480 ml) and the mixture stirred at room temperature for 30 min and extracted four times with dichloromethane (total 500 ml). The combined extracts were washed with water (150 ml) and dried.

The solvent was evaporated leaving an almost colourless oily semi-solid residue. Light petroleum (b.p.60-80°; 100 ml) was added and the mixture heated on a steam bath. The colourless solid was filtered off from the hot solution, washed twice with hot light petroleum and dried (3.0g; 15%). Recrystallisation from ethanol gave colourless crystals of cyanoamide (26c);[10d] its m.p. and i.r. spectrum were identical with those of an authentic sample.

On cooling the light petroleum filtrate a slightly brown oil precipitated, which crystallised when placed in the deep freeze. The solid was filtered off, washed with cold light petroleum (b.p.40-60°) and dried (7.1g; 28%). Recrystallistation from light petroleum (b.p.60-80°) (charcoal) gave almost colourless cubic crystals of

3-dimethylamino-2-imino-3-methylthiobutyronitrile, m.p.54-55° (Found: C, 49.1; H, 7.8; N, 24.4. $C_7H_{13}N_3S$ requires C, 49.1; H, 7.6; N, 24.6%); i.r., p.m.r. and u.v. spectral data have been given in results section; $(M-CN)^+$ highest m/e (1.2% base peak), $(M-HCN-SMe)^+$ base peak.

The light petroleum filtrate from the iminonitrile was evaporated to remove the solvent, the residual almost colourless product was distilled giving colourless 2-methylthio-2-dimethylaminopropionitrile (4.6g; 22%), b.p.58-60°/2mm Hg (Found: C, 49.5; H, 8.4; N, 19.4. $C_6H_{12}N_2S$ requires C, 50.0; H, 8.3; N, 19.5%); ν_{max} (liquid film) 2250w (C≡N), 1460vs, 1380w, 1270m, 1110s, 980m, 750s cm^{-1}; $\delta(CDCl_3)$ 2.44 (6H, s, NMe_2), 2.30 (3H, s, SMe), 1.77 (3H, s, CMe); n_D^{22} 1.4816.

Reaction of thioacetdimethylamide methiodide with potassium cyanide in equimolar amounts gave only the quaternary cyanide (25g) in 88% yield.

Reaction of iminonitrile (52) with potassium hydrogen carbonate.— The iminonitrile (1.0g; 0.0059 mol) was added to a solution of potassium hydrogen carbonate (10.0g; 0.1 mol) in water (50 ml) and the suspension stirred for 18h. The mixture was extracted three times with

dichloromethane (total 200 ml), the combined extracts were washed with water (100 ml) and dried.

The solvent was evaporated, light petroleum (b.p.40-60°) was added to the remaining oil and some solid separated. The mixture was warmed, cooled, and the dark solid was filtered off and dried (0.1g; 12%). Recrystallisation from ethanol gave the cyanoamide (26c),[10d] its i.r. spectrum being identical with that of an authentic sample.

Reaction of iminonitrile (52) with potassium cyanide.— The iminonitrile (0.5g; 0.003 mol) was dissolved by warming in 1,2-dimethoxyethane (0.3 ml) and a solution of potassium cyanide (0.5g; 0.008 mol) in water (1 ml) was added. Two layers were formed; the mixture was shaken mechanically for 48h. Water (5 ml) was added to the pale brown mixture, which was then extracted with dichloromethane (20 ml); the extract was washed with water (5 ml) and dried.

The solvent was evaporated, and the residual oil triturated with boiling light petroleum (b.p.60-80°; 5 ml). The solid formed was filtered off and dried (25.5mg; 6%); its m.p. and i.r. spectrum were identical

with those of the cyanoamide (26c).[10d]

Treatment of the iminonitrile with $K^{13}CN$ (37% labelled) also gave the cyanoamide which showed equal ^{13}C labelling for the CN and $CONH_2$ groups.

Reaction of quaternary cyanides with potassium cyanide.— The cyanide (25g; from thiocetdimethylamide methiodide) (0.5g; 0.0035 mol), potassium cyanide (0.5g; 0.008 mol) and water (1 ml) were shaken mechanically at room rempe-rature for 72h. Water (5 ml) was added and the product extracted with dichloromethane (20 ml); the extract washed with water (5 ml) and dried.

The solvent was evaporated leaving some sticky crystalline solid, which was stirred with boiling light petroleum (b.p.60-80°; 5 ml), filtered off and dried (good yield); its i.r. spectrum was identical with that of the cyanoamide (26c);[10d] $(M-CN)^+$ highest m/e (1.2% base peak), $CH_3C(CN)NMe_2^+$ base peak.

Reaction of the quaternary cyanide with $K^{13}CN$ (37% labelled) also gave the cyanoamide which showed equal ^{13}C labelling for CN and $CONH_2$ groups and only natural abundance for the other C atoms; the positions of absorption in ppm relative to T.M.S. were: 174.6 (>CO),

120.0 (-C≡N), 74.1 ($-\overset{|}{\underset{|}{C}}-$), 43.6 ($CH_3$-N-$CH_3$), 27.8 (C-$CH_3$).

Treatment of the quaternary cyanide (25i; from thioisobutyromorpholide methiodide) with aqueous potassium cyanide gave the starting material.

Reaction of quaternary cyanides with Raney nickel.[30] The cyanide (25a; from thiobenzomorpholide methiodide) (3.5g; 0.014 mol) was added to a mixture of freshly prepared Raney nickel[30] (two teaspoonfuls) and benzene (60 ml), and boiled under reflux for 40h; methanethiol being given off. The solution was filtered and the Raney nickel washed several times with benzene.

The solvent was evaporated and the remaining oil showed signs of crystallisation. This was cooled in a refrigerator, and the solid formed filtered off and dried (0.64g; 23%). Recrystallisation from light petroleum (b.p.80-100°) gave colourless crystals of α-4'-morpholinobenzyl cyanide, m.p.65° (Found: C, 71.4; H, 7.0; N, 13.8. $C_{12}H_{14}N_2O$ requires C, 71.3; H, 6.9; N, 13.9%); ν_{max} (Nujol) 2220m (C≡N), 1120vs (C-O stretch, CH_2-O-CH_2), 1075s, 1010vs, 920s, 870vs, 800s cm^{-1}; δ($CDCl_3$) 7.5 (5H, m, aromatic), 3.7 (4H, t, CH_2.O.CH_2) (J 3Hz), 2.6 (4H, t, CH_2.N.CH_2) (J 3Hz).

In the same way treatment of cyanide (25e; from phenylthioacetmorpholide methiodide) with freshly prepared Raney nickel gave a solid (m.p.46-48°), too small to characterise.

Similar reaction of cyanide (25c; from thiobenzodimethylamide methiodide) gave an oil, also too small to characterise.

Treatment of cyanide (25a) with commercial activated pelletized Raney nickel yielded the starting material; with cyanide (25c) an oil was obtained, too small to characterise, whilst cyanide(25e) gave 1-cyano-1-morpholino-2-phenylethylene (56) (83%), from ethanol, m.p. 100-101° (lit.[29] 100-100.5°) (Found: C, 72.7; H, 6.6; N, 13.0. Calc. for $C_{13}H_{14}N_2O$: C, 72.9; H, 6.5; N, 13.1%); ν_{max} (Nujol) 2220m (C≡N), 1610s (C=C stretch), 1115vs (C-O stretch, CH_2-O-CH_2).

Boiling a solution of cyanide (25e) in benzene under reflux also afforded the elimination product (56) (3%).

Reaction of cyanide (25a; from thiobenzomorpholide methiodide) with sodium borohydride.— Sodium borohydride (3.03g; 0.08 mol) was added in portions with ice-cooling to a solution of the cyanide (4.96g; 0.02 mol) in

isopropanol (230 ml) while stirring magnetically. Stirring was continued for 15h at room temperature. The solvent was evaporated and water (80 ml) was added to the remaining colourless solid to dissolve excess sodium borohydride.

The oil produced was extracted three times with ether (total 250 ml); the combined extracts were washed with water (100 ml) and dried. The solvent was evaporated leaving an oil, which solidified on cooling in a refrigerator for 30 min. The product was filtered off and dried (0.82g; 33%). Recrystallisation from ethanol gave α-4'-morpholinobenzyl cyanide, whose i.r. spectrum was identical with that of an authentic sample.

Reaction of cyanide (25a) with primary aliphatic amines.— Ethylenediamine (27.0g; 0.45 mol) was added to a solution of the cyanide (10.0g; 0.04 mol) in benzene (60 ml) and the mixture boiled under reflux for 6h. The solvent was evaporated leaving an oil (with two layers). Water (30 ml) was added and the mixture scratched with ice-cooling. The solid formed was filtered off and dried (4.42g; 54%). Recrystallisation from ethanol gave α-4'-morpholinobenzyl cyanide, its i.r. spectrum being

identical with that of an authentic sample.

The water in the aqueous filtrate was evaporated and the remaining oil cooled in a refrigerator overnight. The solid formed was filtered off and dried (0.67g; 11%). Recrystallisation from water gave light yellow crystals of 2-phenyl-Δ^2-imidazoline, m.p.100° (lit.[15] 100-101°) (Found: C, 73.8; H, 6.9; N, 19.2. Calc. for $C_9H_{10}N_2$: C, 74.0; H, 6.9; N, 19.2%); ν_{max} (Nujol) 3200m (NH); 1600m (C=N), 1500m, 1460os, 1370s, 980 cm^{-1}; $\delta(CDCl_3)$ 7.6 (5H, m, aromatic), 4.67 (1H, s, -NH-), 3.80 (4H, s, two CH_2 groups).

The imidazoline formed a picrate with aqueous sodium picrate; it was recrystallised from ethanol, m.p. 239-241° (decomp.) (Found: C, 48.0; H, 3.6; N, 18.7. $C_{15}H_{13}N_5O_7$ requires C, 48.0; H, 3.5; N, 18.7%).

On repeating the experiment, benzaldehyde was obtained by steam distillation of the crude product; it was characterised as its dinitrophenylhydrazone, whose i.r. spectrum was identical with that of an authentic sample.

Treatment of the quaternary cyanide with ethylenediamine in equimolar amounts gave the starting material.

Reaction of the cyanide with excess 1,2-diamino- and 1,3-diamino-propane gave α-4'-morpholinobenzyl cyanide in 41% and 63% yields respectively; similar treatment with n-butylamine also afforded this product in 28% yield.

Reaction of cyanide (25a) with morpholine.— Morpholine (6.09g; 0.07 mol) was added to the cyanide (4.96g; 0.02 mol) and the mixture boiled under reflux (air condenser). Within 5 min the solid completely dissolved giving a golden yellow homogeneous solution; heating was continued for 3.5h.

After ca 20 min some yellow solid began to crystallise. The mixture was cooled in ice, triturated with diisopropyl ether (130 ml), and the colourless solid filtered off and dried (1.8g; 28%). Recrystallisation from ethanol gave 4-α-morpholinobenzyldenemorpholinium thiocyanate, whose i.r. spectrum was identical with that of an authentic sample.

The filtrate was washed five times with water (total 300 ml) and the ether solution dried. The solvent was evaporated leaving some slightly sticky yellow solid, which was rubbed with ethanol, and the free-flowing solid filtered and dried (2.49g; 43%). Recrystallisation from ethanol gave α,α-dimorpholinobenzyl cyanide, its spectral

properties being identical with those of an authentic sample.

Thiobenzomorpholide was isolated in trace amount also from the reaction.

Repeating the experiment with equimolar amounts of reactants led to the isolation of the amidinium thiocyanate (10%) and recovery of some starting material.

Similar treatment of cyanide (25e; from phenylthioacetmorpholide methiodide) with morpholine in equimolar amounts gave 1-cyano-1-morpholino-2-phenylethylene (15%), its i.r. spectrum being identical with that of an authentic specimen.

Reaction of cyanide (25a) with mercuric cyanide.— Mercuric cyanide (5.06g; 0.02 mol) was added in portions to a magnetically stirred solution of the quaternary cyanide (4.96g; 0.02 mol) in acetonitrile (60 ml). Stirring was continued for 7h, the yellow solid formed (mercuric methylthiolate) was filtered off and dried (3.03g). The solvent of the filtrate was evaporated leaving an almost colourless solid which was dried (4.5g; 99%). Recrystallisation from ethanol gave 2,4'-morpholino-2-phenylmalononitrile, m.p.109-110° (Found: C, 68.6; H, 5.7; N, 18.6. $C_{13}H_{13}N_3O$ requires C, 68.7; H, 5.7; N,

18.5%); ν_{max} (Nujol) 1115vs (C-O stretch, CH_2-O-CH_2), 1090m, 990vs, 970s, 925s, 875vs, 750vs cm^{-1}; $\delta(CDCl_3)$ 7.6 (5H, m, aromatic), 3.8 (4H, t, CH_2.O.CH_2) (J 3Hz), 2.7 (4H, t, CH_2.N.CH_2) (J 3Hz).

Similar treatment of cyanide (25e; from phenylthioacetmorpholide methiodide) with mercuric cyanide gave 1-cyano-1-morpholino-2-phenylethylene (100%), its i.r. spectrum being identical with that of an authentic sample, whilst cyanide (25c; from thiobenzodimethylamide methiodide) gave a colourless solid too small to characterise.

Reaction of quaternary cyanides with methyl iodide.— Methyl iodide (14.2g; 0.10 mol) was added to a solution of the cyanide (25e; from phenylthioacetmorpholide methiodide) (5.24g; 0.02 mol) in dry acetone (20 ml) and the mixture boiled under reflux for 2h. The excess methyl iodide and acetone were evaporated leaving an almost colourless solid; ether (150 ml) was added and the solid triturated, filtered off, and dried (1.45g; 36%). Recrystallisation from ethanol gave colourless trimethylsulphonium iodide, its m.p. and i.r. spectrum being identical with those of an authentic sample.

The solvent of the filtrate was evaporated, the solid obtained was rubbed with ethanol, and the colourless compound filtered off and dried (2.42g; 57%). Recrystallisation from light petroleum (b.p.80-100°) gave 1-cyano-1-morpholino-2-phenylethylene, whose i.r. spectrum was identical with that of an authentic sample.

Treatment of the cyanide with excess methyl iodide at room temperature gave the above alkene (94%).

Boiling a mixture of the cyanide (25i; from thioisobutyromorpholide methiodide) and excess methyl iodide under reflux gave, trimethylsulphonium iodide (46%) and an oil b.p.62°/15mm Hg, whose spectral properties suggest 1-cyano-1-morpholino-2-methylpropene (92%). There was no reaction at room temperature.

Similar treatment of cyanide (25a; (from thiobenzomorpholide methiodide) gave no reaction under both conditions.

Attempted dehydration of cyanoamide (26c; from thiobenzodimethylamide methiodide) with thionyl chloride.— A mixture of the cyanoamide (3.5g; 0.03 mol) and thionyl chloride (15 ml) was boiled under reflux in benzene (150 ml) for 22h. The mixture was cooled in ice, then

crushed ice (100g) and water (100 ml) were added to decompose excess thionyl chloride. Cold potassium hydroxide solution (50%) was added with stirring until the mixture was alkaline.

The two layers formed were separated, and the aqueous layer extracted twice with benzene (total 500 ml); the combined extracts were washed with sodium carbonate solution (1%; 250 ml), then twice with water (total 300 ml) and dried.

The solvent was evaporated and the remaining solid was dried (0.05g) but was too small to characterise; ν_{max} (Nujol) 2220w cm^{-1}; $\delta(CDCl_3)$ 3.7.

Attempted dehydration of the cyanoamide with NN'-dicyclohexylcarbodiimide gave the starting material.

Reaction of thiobenzodimethylamide methiodide (2c) with dimethylamine.— Dimethylamine solution in ethanol (33%, w/w; 300 ml; 1.61 mol) was added to the methiodide (15.0g; 0.049 mol) and the mixture boiled was evaporated, the remaining oily mass was cooled in ice, triturated with ether (500 ml) and the brownish solid formed filtered off and dried (8.1g; 96%). Recrystallisation from ethanol gave colourless dimethylammonium iodide, its m.p. and i.r. spectrum being identical with those of an authentic sample.

The filtrate was washed with water and the ether solution dried and evaporated. The remaining oil was cooled and scratched. The solid formed was filtered off, dried (2.2g; 27%) and recrystallised from ethanol; its spectra properties were identical with those of an authentic specimen of thiobenzodimethylamide.

Boiling the methiodide with aqueous dimethylamine solution under reflux gave the thioamide (32%).

Reaction of the methiodide with diethylamine afforded dimethylammonium iodide (70%); its i.r. spectrum being identical with that of an authentic sample (Found: C, 24.0; H, 6.0; N, 6.9 Calc. for $C_4H_{12}IN$: C, 23.9; H, 6.0; N, 7.0%), and also thiobenzodimethylamide (23%).

Reaction of phenylthioacetmorpholide methiodide (2e) with morpholine.- Morpholine (16 ml) was added to the methiodide (20.0g; 0.06 mol); there was an immediate exothermic reaction. The mixture was heated on a steam bath for 8h, moisture being excluded. It was cooled, the solid formed triturated with ether (120 ml), filtered off and dried (11.83g; 100%). Recrystallisation from ethanol gave colourless morpholinium iodide, its m.p. and i.r. spectrum being identical with those of an authentic sample (Found: C, 22.4; H, 4.7; N, 6.5. Calc. for

$C_4H_{10}INO$: C, 22.3; H, 4.7; N, 6.5%).

The ethereal filtrate was evaporated; the remaining oil was cooled in a refrigerator for 1h and rubbed with ethanol. The colourless solid formed was filtered off and dried (1.52g; 11%). Recrystallisation from ethanol gave colourless 1,1-dimorpholino-2-phenylethylene, m.p.135-136° (Found: C, 69.9; H, 8.1; N, 10.1. $C_{16}H_{22}N_2O_2$ requires C, 70.1; H, 8.0; N, 10.2%); ν_{max} (Nujol) 1590s (C=C), 1580s, 1125s, 1110vs (C-O stretch, CH_2-O-CH_2), 1030s, 985s, 890s cm^{-1}; $\delta(CDCl_3)$ 7.3 (5H, m, aromatic), 4.80 (1H, s, -CH=C), 3.7 (8H, m, two CH_2.O.CH_2 groups), 3.1 (8H, m, two CH_2.N.CH_2 groups).

Reaction of thiobenzomorpholide methiodide (2a) with formamidine acetate.— The methiodide (6.98g; 0.02 mol) was added to a solution of formamidine acetate (3.12g; 0.03 mol) and sodium acetate trihydrate (100.0g; 0.74 mol) in water (220 ml) and the mixture stirred magnetically at room temperature for 8h. It was extracted three times with dichloromethane (total 300 ml), the combined extracts were washed twice with water (total 200 ml) and dried.

The solvent was evaporated and the remaining oil triturated with light petroleum (b.p.40-60°; ca 3 ml) with ice-cooling. The solid formed was filtered off and

dried (1.46g; 35%). Recrystallisation from ethanol gave thiobenzomorpholide, its i.r. spectrum being identical with that of an authentic sample.

Reaction of thioacetdimethylamide methiodide (2g) with mercuric cyanide.— Mercuric cyanide (20.2g; 0.08 mol) was added to a solution of the methiodide (19.6g; 0.08 mol) in acetonitrile (150 ml) and the mixture stirred mechanically for 2.5h. The yellow mercuric methylthiolate was filtered off and dried (27.9g).

The filtrate was evaporated leaving some brown oil (9.6g); the crude product was distilled, b.p.76-77°/20mm Hg. ν_{max} (liquid film) 2760s (N-methyl C-H stretch), 2220m (C≡N), 1580vs, 1480m, 1440s, 1380m, 1350s, 1190m, 1020s cm^{-1}. Lassaigne test showed presence of nitrogen and absence of sulphur and hologen. However, it showed several spots on a t.L.c. plate.

Reaction of the oil with aqueous potassium cyanide at room temperature gave the cyanoamide (26c).

Attempted resolution of cyanide (25a).— The cyanide (25a) (0.5g; 0.002 mol) dissolved in a few ml of chloroform was chromatographed in chloroform on a column of D-lactose (BDH, approx 27 cm x 2 cm). Ten samples each

of 25 ml of effluent were taken and each sample examined in a quartz u.v. cell.

Virtually all the product appeared in the third fraction. This fraction, however, and other fractions showed no optical rotation.

Recrystallisation of the cyanide from D-limonene gave an inactive compound.

Attempted asymmetric synthesis of cyanide (25a).— Anhydrous D-glucose (27.0g; 0.15 mol) and potassium cyanide (9.75g; 0.15 mol) were dissolved in water (75 ml); the clear solution was added to thiobenzomorpholide methiodide (3.0g; 0.009 mol) thus precipitating an oil.

The mixture was swirled and left overnight in a refrigerator; the oil was seeded with a few crystals of the racemic quaternary cyanide (25a). The product was filtered off and dried. Its optical rotation in chloroform was negligible.

Treatment of a solution of thiobenzomorpholide methiodide in chloroform with potassium cyanide in the presence of DEAE-cellulose gave an optically inactive compound, as did also the treatment of the methiodide with DEAE-cellulose in the cyanide form at room temperature.

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