SYNTHETIC AND ANALYTICAL STUDIES OF S-ALKYL QUATERNARY SALTS.

BY

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FACULTY OF SCIENCE,
AHMADU BELLO UNIVERSITY,
ZARIA.

JUNE 1984.

DECLARATION

I hereby declare that this thesis has been written by me and that it is a record of my own research work. It has not been presented in any previous application for a higher degree. All quotations are indicated and the sources of information are specifically acknowledged by means of references.

ALWAN KAHTAN

Date: 18th JUNE 1984

DEDICATION

Dedicated to my late brother,

ABBAS ALWAN HASHIM.

ACKNOWLEDGEMENTS

My sincere gratitude to my supervisor, Dr. S.A. Okecha for his guidance throughout the duration of the project. I am also grateful to Dr. P.F. Olurinola of Faculty of Pharmaceutical sciences for supervising all aspects of the microbiological screening. My thanks also go to all the members of my family, especially my uncle, Abdulkarim Hassan and my late brother, Abbas Alwan Hashim for their financial help.

The kind efforts of my class mates, workers of the chemical store and the departments' technologists, especially Mr. Chris Uwadiale, A. Atodo and S.O.D. Amadu are acknowledged.

ABSTRACT

p-Bromo-a,4'-morpholinobenzamidoxime (Br - MBA) has been found to have some activity against Staphylococcus aureus. No appreciable activity, against psuedomonas aeruginosa and Escherichia coli was observed.

The reaction of s-alkyl quaternary salts(4) with monosodium salts of some active methylene compounds at low temperatures led, in some cases, to the isolation of the condensation products.

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CHAPTER ONE

1.0 AIM

The purpose of carrying out this study was to:

(a) synthesize structurally modified (halogenated) amidoximes, in order to subject them to Pharmacological and Microbiological screening, and

(b) react some S-alkyl quaternary salts with active methylene compounds and use analytical and spectroscopic tools to establish the structures of any products isolated.

1.1 INTRODUCTION

The parent compounds for synthesising both the halogenated amidoximes for screening and the S-alkyl quaternary salts used for reactions with active methylene compounds are NN-disubstituted thioamides (1). These thioamides are made in several ways as follows:

1.1.1 WILLGERODT-KINDLER REACTION.

Thioamides can be prepared by the Willgerodt-Kindler reaction,[1-5] which entails the reaction of an aldehyde or a ketone with equimolar amounts of sulphur and a secondary amine. Yield varies between 58 - 92%.

$$R^1 - CHO + S + HNR_2^2 \longrightarrow R^1 - \underset{\underset{S}{\|}}{C} - NR_2^2$$

Aldehyde Sulphur Secondary amine

(1)

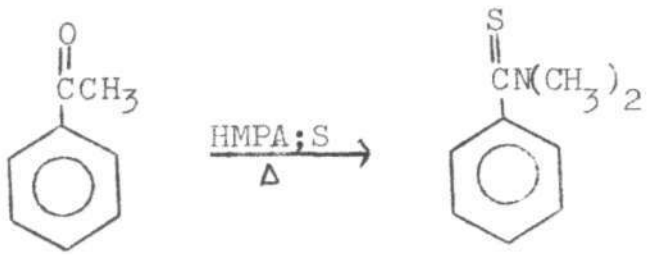
Acetylenes and olefins have also been found to undergo the Willgerodt-Kindler reaction, giving thioamides.[6-8] The use of high boiling amines, like morpholine, which is cheap and has a boiling point of 128°C, makes possible the use of open apparatus instead of an autoclave.[4]

1.1.2 BY REACTING HEXAMETHYLPHOSPHOROTRIAMIDE (HMPA) WITH METHYLPICOLINES AND BENZYLIC COMPOUNDS.

Methylpicolines and benzylic compounds when heated in HMPA in the presence of sulphur give the corresponding aromatic NN-dimethylthioamides.[9] Yields of between 45 - 81% are obtained.

$$ArCH_2X \xrightarrow[\Delta]{HMPA;S} Ar\overset{\overset{S}{\|}}{C}NMe_2$$

Degradation of ketones occur when alkyl aryl ketones are heated in HMPA with an excess of sulphur, resulting in the isolation of aromatic N,N-dimethylthioamides as the main products.



1.1.3 REACTION OF AMIDES WITH PHOSPHORUS PENTASULPHIDE.

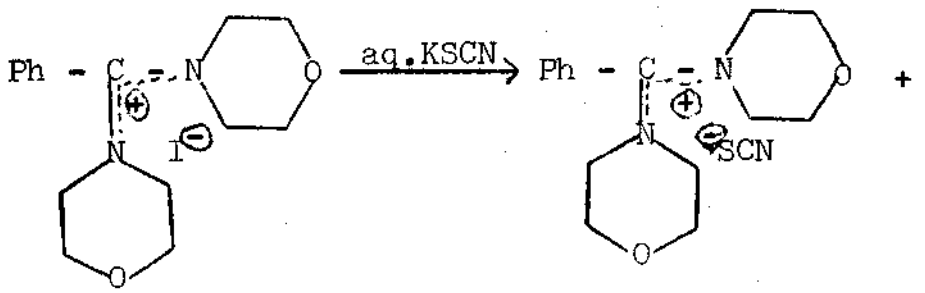
Phosphorus pentasulphide has found wide use in the preparation of thioamides from amides.[10-11]

$$5R^1CONH_2^2 + P_2S_5 \longrightarrow 5R^1\underset{\underset{S}{\|}}{C} - NR_2^2 + P_2O_5$$

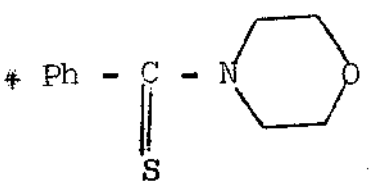
Gomper and Elser's procedure consists of adding the amide to a suspension of phosphorus pentasulphide in carbon disulphide with stirring until the mixture becomes viscous.[10] Further addition of amide is carried out under reflux without stirring. Addition of water decomposes the phosphorous compounds making it possible and easier to extract the pure thioamide.

1.1.4 REACTION OF AN AMIDINIUM SALT WITH AQUEOUS POTASSIUM THIOCYANATE.

The reaction of the amidinium salt (2) with aqueous potassium thiocyanate gives compound (3) together with the thioamide.[12]

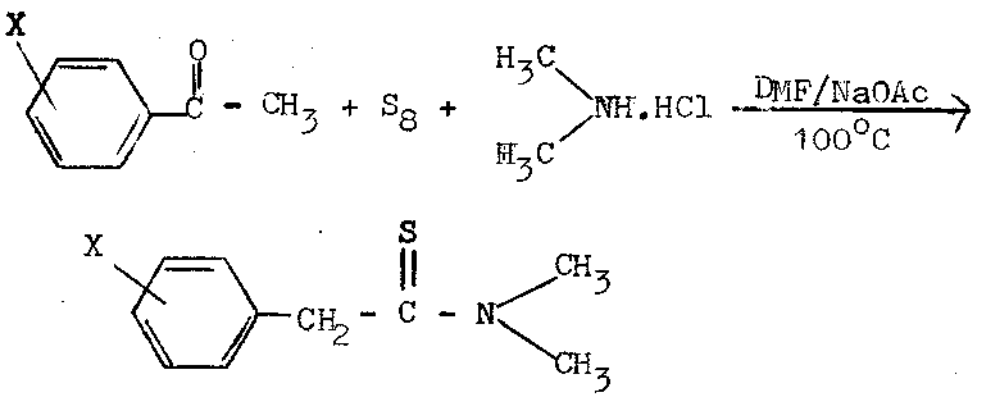


(2) (3)



1.1.5 MODIFIED WILLGERODT-KINDLER REACTION.

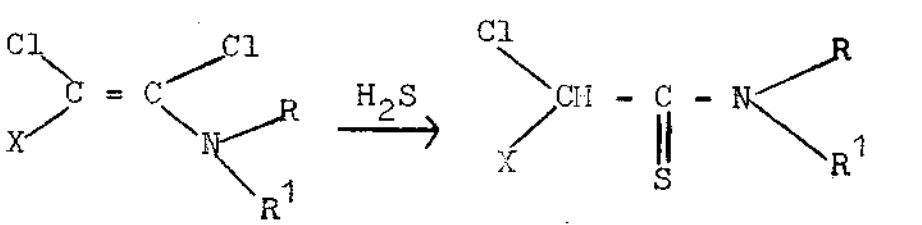
A modified form of the Willgerodt-Kindler reaction that makes use of the hydrochloride salt of a volatile amine, dimethylamine, has been reported.[13] Aldehydes or ketones when reacted with dimethylammonium chloride, sulphur and anhydrous sodium acetate in dimethylformamide at 100°C give the corresponding thioamides. The anhydrous sodium acetate generates dimethylamine in situ from dimethylammonium chloride. This method eliminates the use of an autoclave if volatile dimethylamine were to be used.



A similar reaction has been carried out by Okecha[14] which involves refluxing the aldehyde or ketone, sulphur, demethylammonium chloride and anhydrous sodium acetate in dry pyridine at 80°C to give the corresponding thioamide.

1.1.6 ACTION OF HYDROGEN SULPHIDE ON CHLOROACETAMIDES.

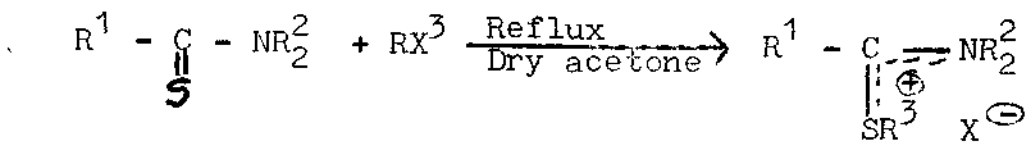
Chloroacetamides react with hydrogen sulphide at low temperatures to give the corresponding thioamides.[15]



(X = Cl or H)

1.1.7 REACTIONS OF S-ALKYL QUATERNARY SALTS.

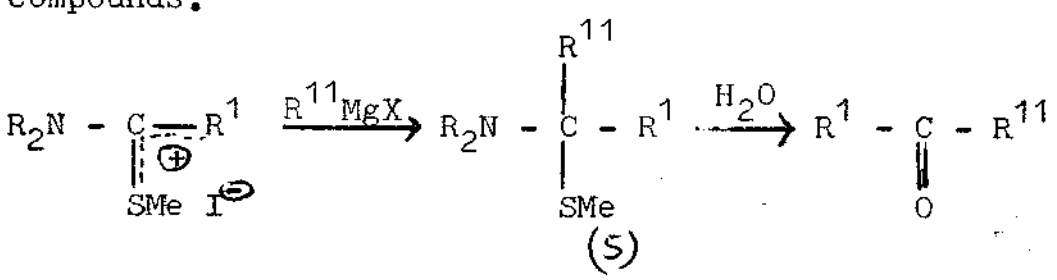
S-alkyl quaternary salts (4) are readily obtained when N,N-disubstituted thioamides are refluxed with alkyl halides in dry acetone.



(4)

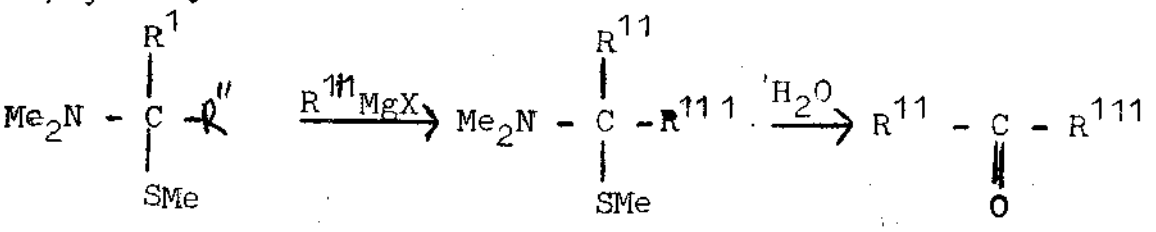
These quaternary salts are valuable synthetic intermediates for further reactions.[16] They react additively with many nucleophiles, often in aqueous solution at room temperature and usually with the elimination of alkylthio or disubstituted amino group.[17]

Yamaguchi and his co-workers reported that quaternary salts (4) react with grignard reagents yielding N,S-acetals (5) which when poured in ice-cold water give the corresponding carbonyl compounds.[18]



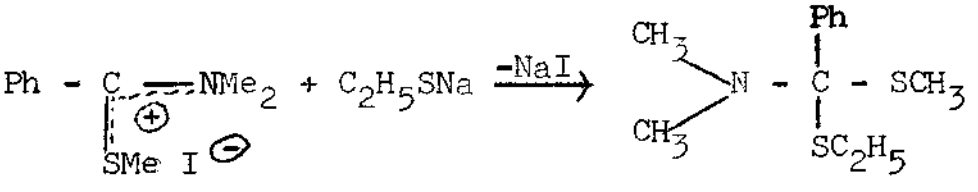
(5)

Futher reaction of the N,S-acetal (5; R^1 = SMe) with more grignard reagent followed by pouring in ice-cold water gives an unsymmetrical ketone (6) in 61% yield.



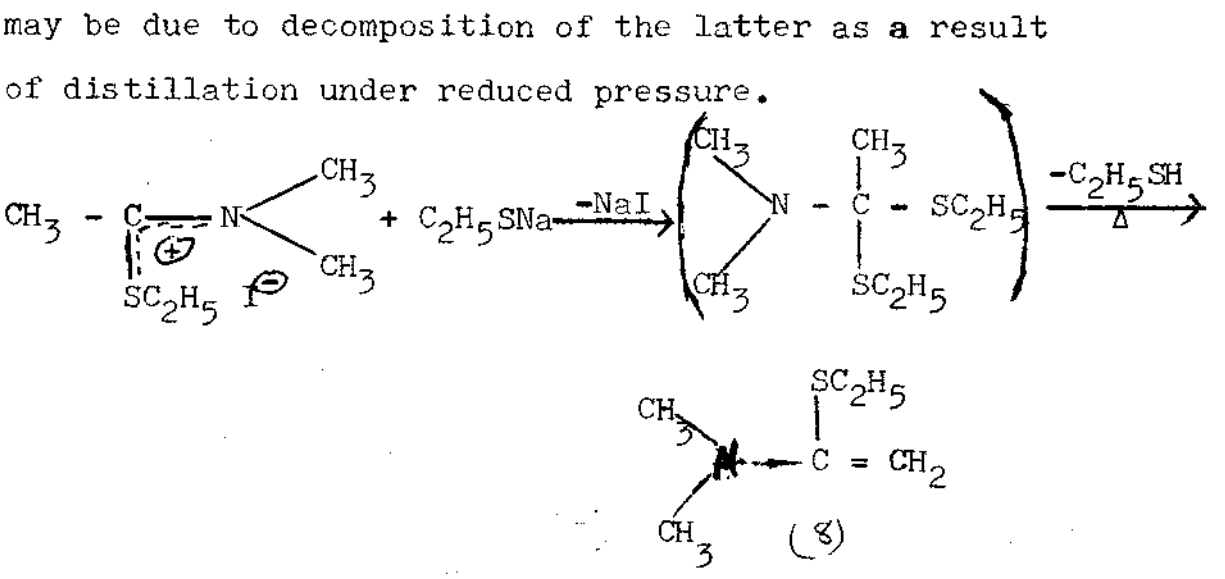
(6)

Reaction of S-alkyl quaternary salt (4; R^1 = Ph, NR^2_2 = NMe_2, R^3 = Me) with sodium ethylmercaptide, sodium methoxide and primary amines has been investigated.[19] The salt easily reacts with sodium ethylmercaptide in dry ether at room temperature giving N,N-dimethylbenzamide methylethylmercaptole (7) in fairly good yield.



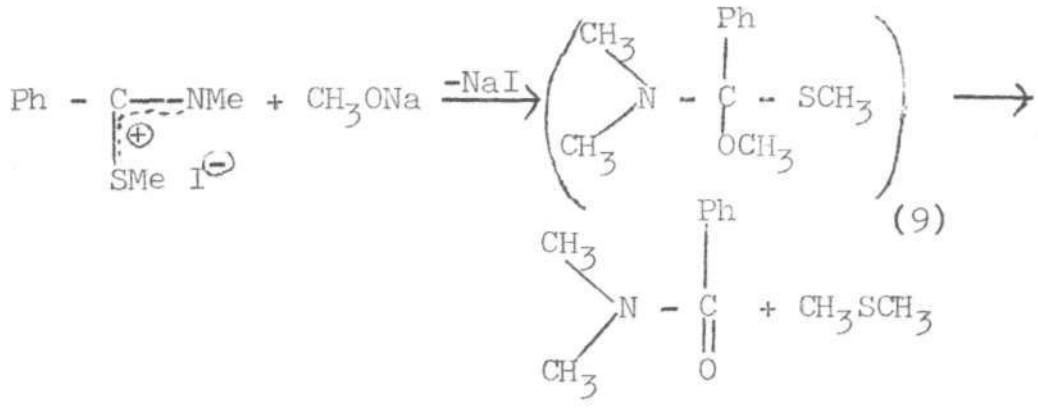
(7)

With sodium ethylmercaptide, the salt (4) gives a ketene-N,S-acetal (8) in fairly good yield, instead of N,N-dimethylacetamide diethylmercaptole.[20] This may be due to decomposition of the latter as a result of distillation under reduced pressure.



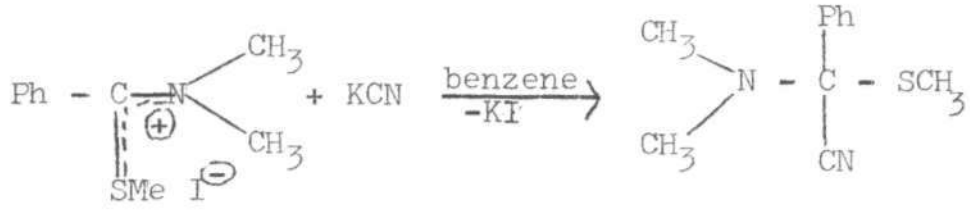
The reaction of the quaternary salt (4; R^1 = Ph, NR^2_2 = NMe_2, R^3 = Me) with sodium methoxide can hardly occur at

room temperature, but when refluxed in dry benzene for 1h it gives N,N-dimethylbenzamide along with dimethyl sulphide, instead of the expected product, N,N-dimethyl-benzamide monothioketal (9).[19]



(9)

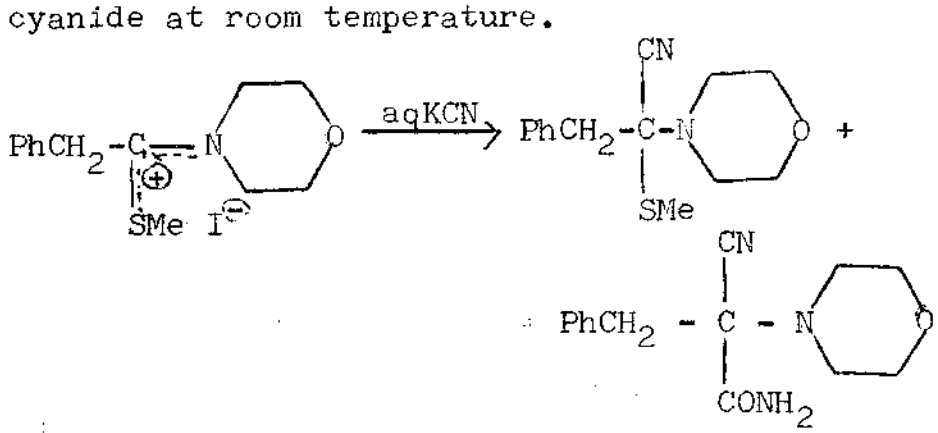
When this salt (4; R^1 = Ph, NR^2_2 = NMe_2, R^3 = Me) is refluxed with potassium cyanide in dry benzene for 1h, it gives α-dimethylamino-α-methylthiobenzyl cyanide (10) as a liquid with elimination of potassium iodide.



(10)

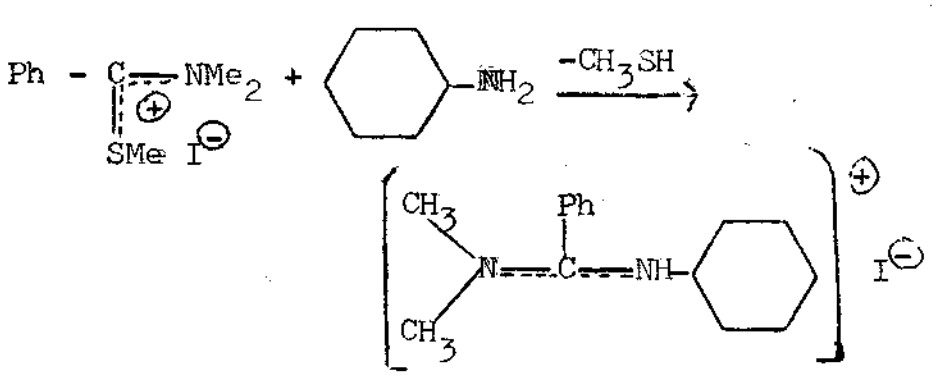
Stansfield and Okecha[16] have reported the preparation of (10) in solid form from the reaction of the quaternary salt (4) with potassium cyanide in aqueous solution at room temperature. Their method is a general one and a series of quaternary cyanides have been prepared. A mixture of quaternary cyanide and α-cyanoamide (11) are

obtained when the quaternary salt (4; R^1 = $PhCH_2$, NR^2_2 = morpholino, R^3 = Me) reacts with aqueous potassium cyanide at room temperature.



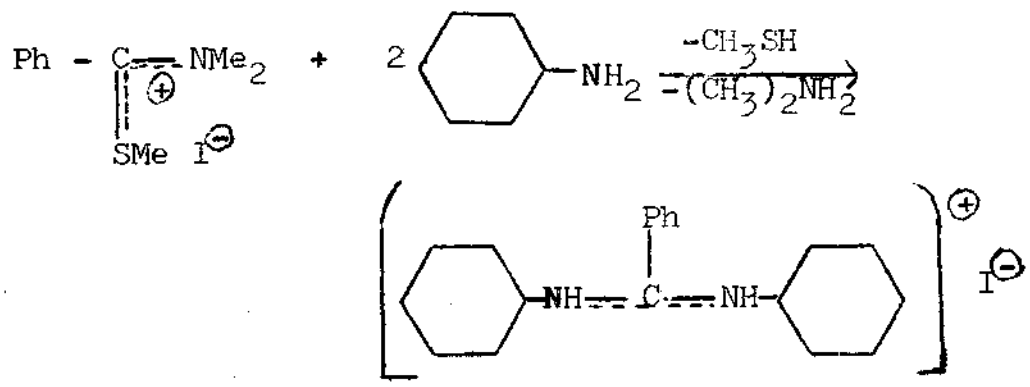
(11)

Reaction of the quaternary salt (4; R^1= Ph, NR^2_2 = NMe_2, R^3 = Me) with cyclohexamine, a primary amine, in ethanol at room temperature gives N,N-dimethyl-N^1-cyclohexylbenzamidine hydroiodide in high yield together with the evolution of methyl mercaptan.[19]

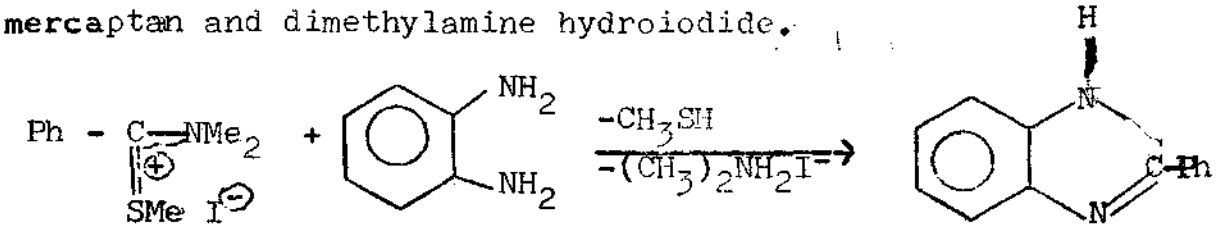


However, when a mole of the salt (4; R^1 = Ph, NR^2_2 = NMe_2, R^3 = Me) is refluxed for 2h with two moles of cyclohexamine, N,N^1-dicyclohexylbenzamidine hydroiodide is

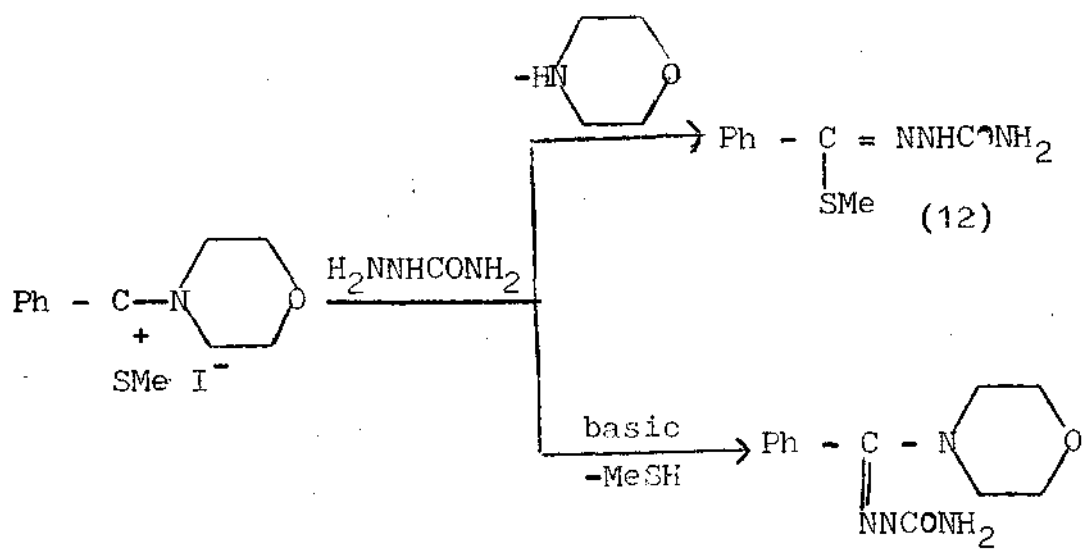
given in 49% yield together with methyl mercaptan and dimethylamine.



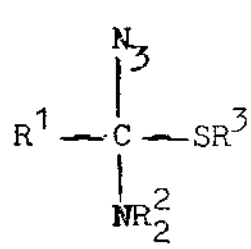
It has also been found that diamines, such as O-phenylenediamine easily condense with quaternary salts (4; R^1 = Ph, NR^2_2 = NMe_2, R^3 = Me) to yield heterocyclic compounds like 2-phenylbenzimidazole in good yield, together with elimination of methyl mercaptan and dimethylamine hydroiodide.



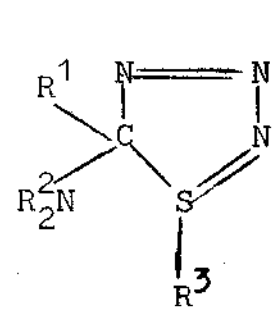
With semicarbazide hydrochloride in aqueous ethanol, quaternary salt (4; R^1 = Ph, NR^2_2 = morpholino, R^3 = Me) condensed to give (12) with the elimination of morpholino group.[21] Under alkaline conditions however, compound (13) is obtained with the elimination of the methylthio-group.[17]



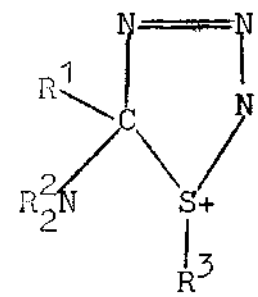
Quaternary salts (4; R^1 = Ph, NR^2_2 = morpholino, R^3 = Me) react with sodium azide in aqueous solution at room temperature to give an azide (14) which the authors proposed to have been the 1,5-dihydro-1,2,3,4-thia(S^{IV})triazole structure (15 - 17) or the three membered ring structure (18).[22] Recent X-ray analysis has shown the structure to be represented by (19).



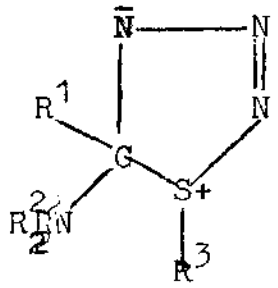
(14)



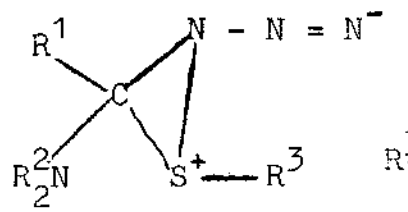
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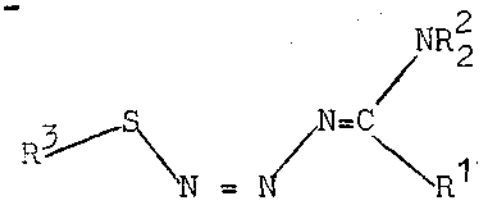
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(17)

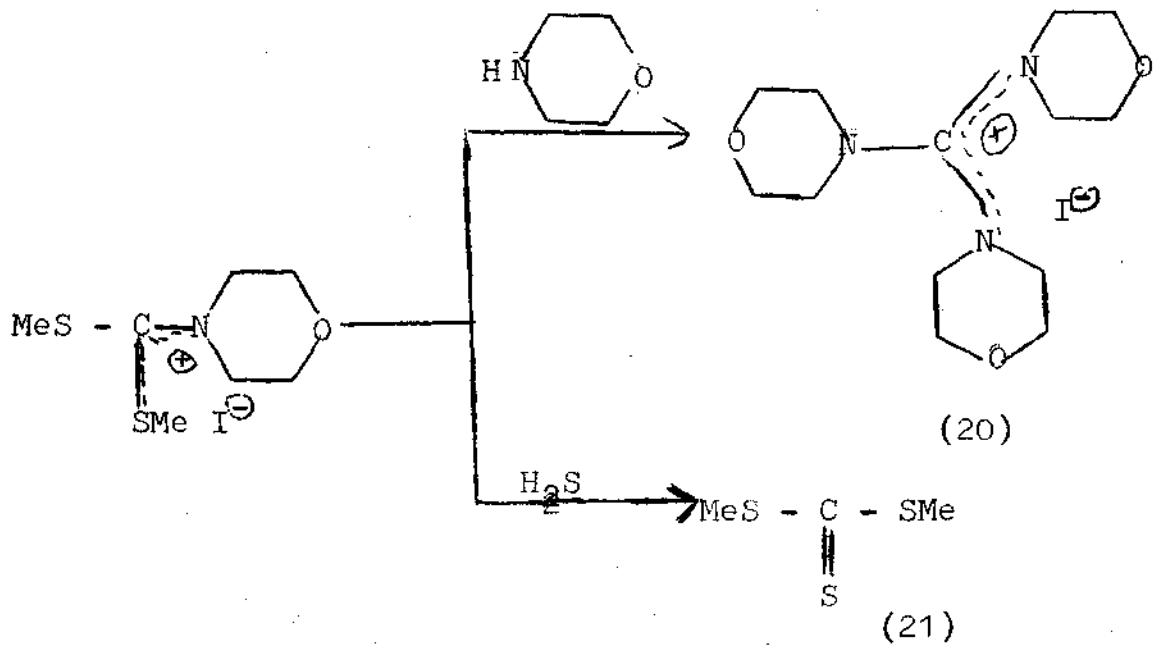


(18)



(19)

Stansfield and Coomassie[23] have shown that the quaternary salt (4; R^1 = SMe, NR^2_2 = morpholino, R^3 = Me) on heating with morpholine yields the guanidinium iodide (20) while with hydrogen sulphide in methanol, dimethyl trithiocarbonate (21) is obtained.

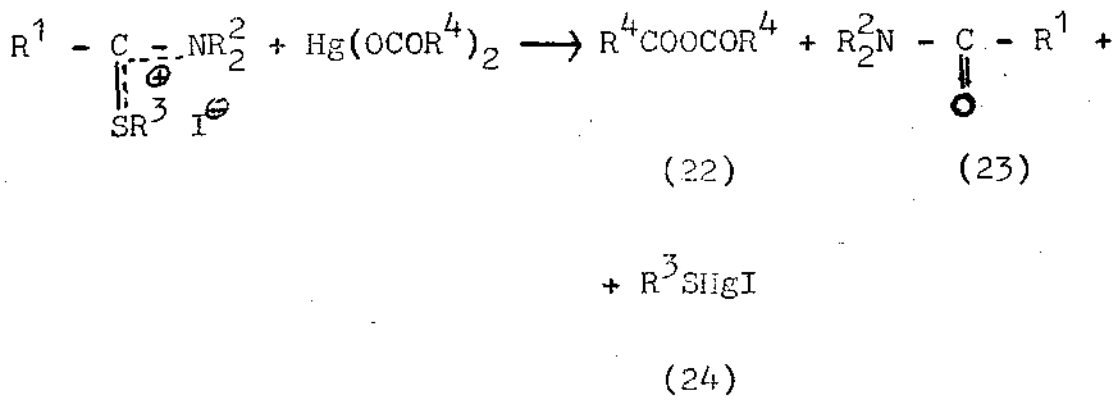


(20)

(21)

Quaternary salts (4) have been found to react with mercuric carboxylates in acetonitrile at room temperature to give the corresponding acid anhydrides

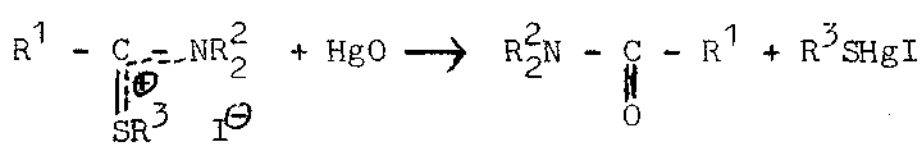
(22) and amides (23) in good yields together with alkylmercaptomercuric iodide (24).[24]



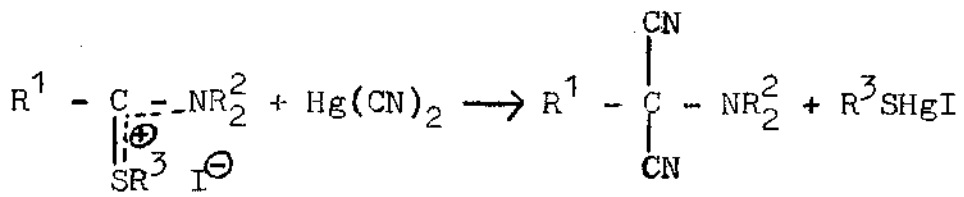
(22) (23)

(24)

When a suspension of mercuric oxide in acetonitrile is treated with quaternary salts (4) the corresponding N,N-disubstituted amides together with ethylmercapto-mercuric iodide are obtained.

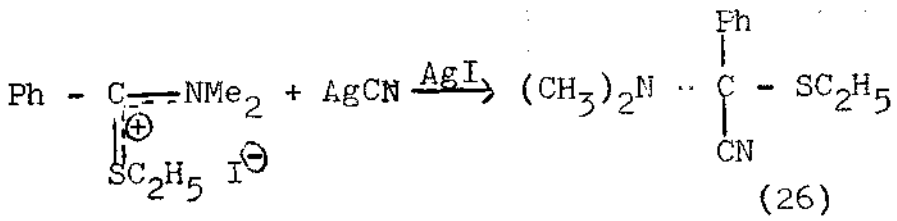


With mercuric cyanide, quaternary salts have been found to give the corresponding malononitriles (25).



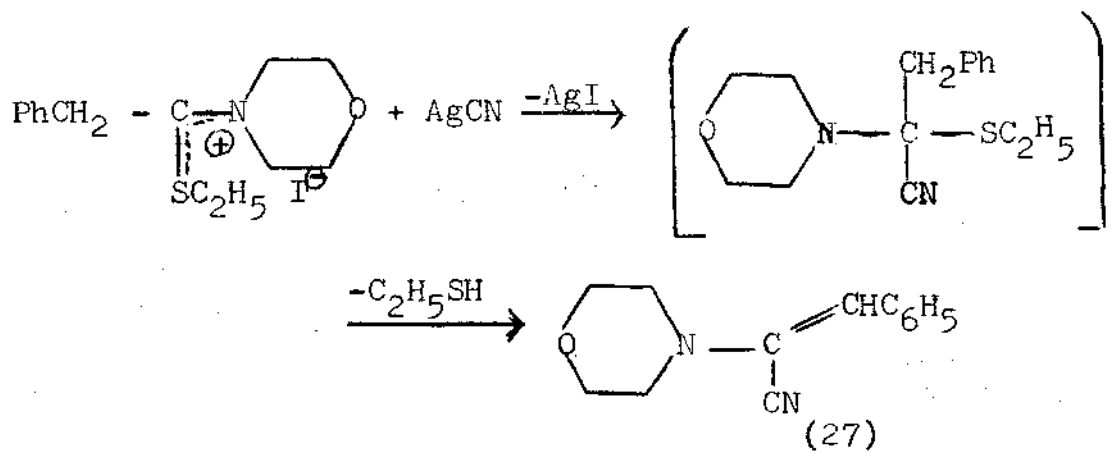
(25)

Silver cyanide reacts with quaternary salt (4; R^1 = Ph, NR^2_2 = NMe_2, R^3 = C_2H_5) at room temperature in acetonitrile giving α-dimethylamino-α-ethylthio-phenylacetonitrile (26) in 61% yield, along with silver iodide.



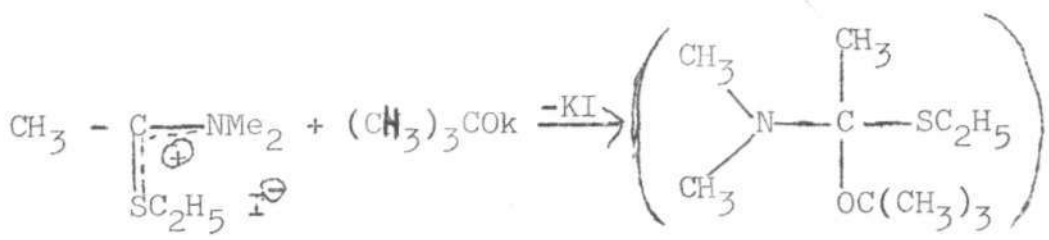
(26)

However, treatment of the quaternary salt (4; R^1 = $PhCH_2$, NR^2_2 = morpholino, R^3 = C_2H_5) with silver cyanide under the same conditions gives α-morpholino-ß-Phenylacrylonitrile (27) in 87% yield with evolution of ethyl mercaptan.



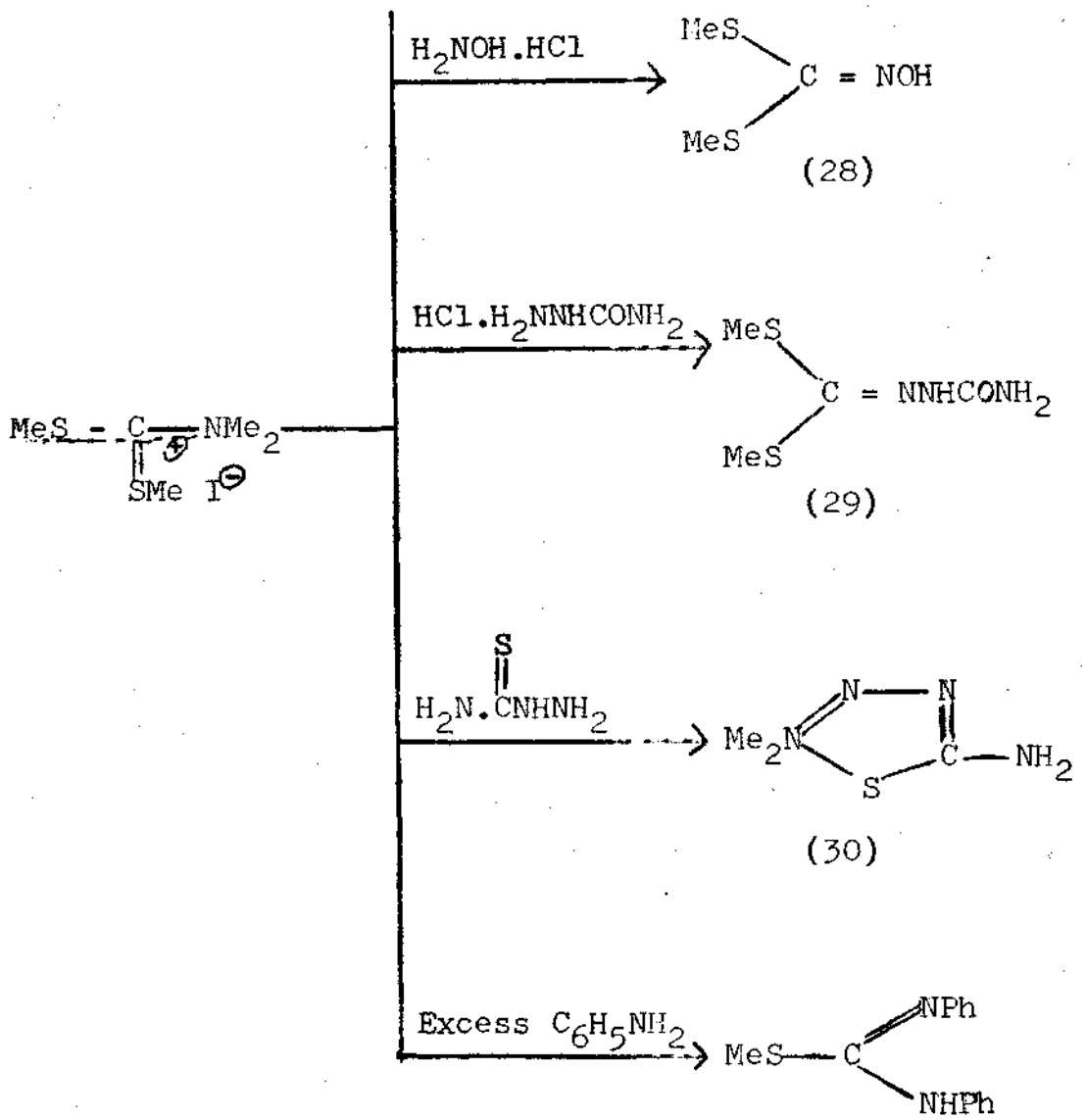
(27)

Quaternary salts (4; R^1 = CH_3, NR^2_2 = NMe_2, R^3 = C_2H_5) have been found to react in ether at room temperature with some alcoholates like potassium t-butoxide, to give ketene-N,S-acetal (8) in 67% yield.[20] It was however found that other alcoholates, like sodium isopropoxide, sodium n-propoxide and sodium benzyloxide react with these salts to give undesirable by-products as N,N-dimethylacetamide and N,N-dimethylacetamide dialkylacetal along with the ketene-N,s-acetal.



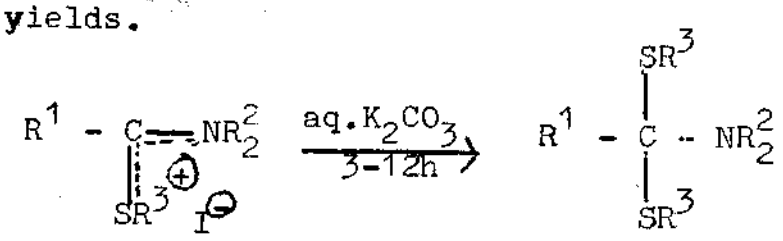
(8)

The reaction of a quaternary salt (4; R^1 = SMe, NR^2_2 = NMe_2, R^3 = Me) at room temperature and in excess of sodium acetate with aqueous hydroxylammonium chloride to give bis(methylthio) formaldoximé (28) has been reported.[25] With semicarbazide hydrochloride the semicarbazone (29) is obtained while with thiosemicarbazide in triethylaminepyridine it gives the thiadiazole (30). When reacted with excess aniline at room temperature, the isothiourea (31) isolated.



(31)

Okecha[26] has recently reported the reaction of S-alkyl quaternary salts (4) with aqueous potassium carbonate to give amide thioketals (32) in excellent yields.

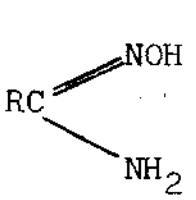


(32)

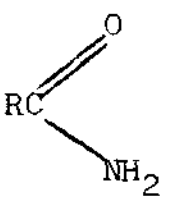
When however, the quaternary salt (4; R^1 = BrC_6H_4, NR^2_2 = morpholino, R^3 = Me) was treated with aqueous potassium carbonate, the starting material was recovered. This anomaly may be due to stearic and electronic factors.

1.2 SYNTHESIS OF AMIDOXIMES.

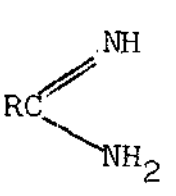
A review of the chemistry of amidoximes has been written by Eloy and Lanaers.[27] The amidoxime function (33) can be considered either as an amide (34) in which the oxygen atom of the carbonyl group has been replaced by an isonitro group, or as an amidine (35) whose hydrogen atom of the **imino** group has been exchanged for a hydroxyl radical.



(33)



(34)

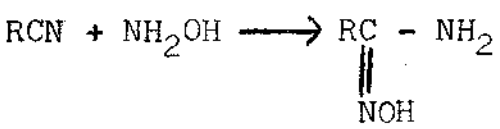


(35)

Among the methods of synthesizing amidoximes they cited include:

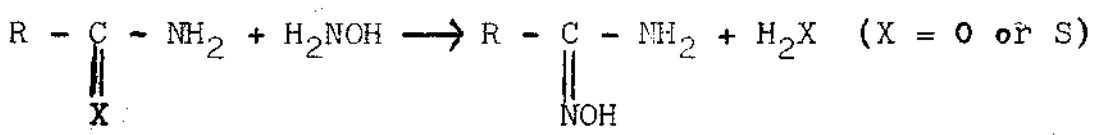
1.2.1 ACTION OF HYDROXYLAMINE ON NITRILES

This consists of liberating the hydroxylamine from its hydrochloride using sodium carbonate, sodium or potassium hydroxide or sodium ethoxide and then adding the nitrile and enough alcohol.

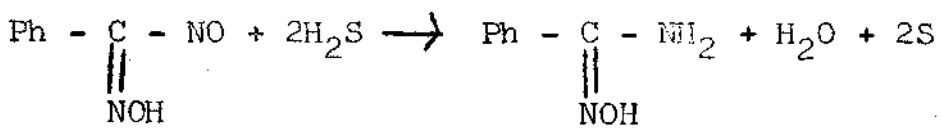


1.2.2 ACTION OF HYDROXYLAMINE ON AMIDES AND THIOAMIDES.

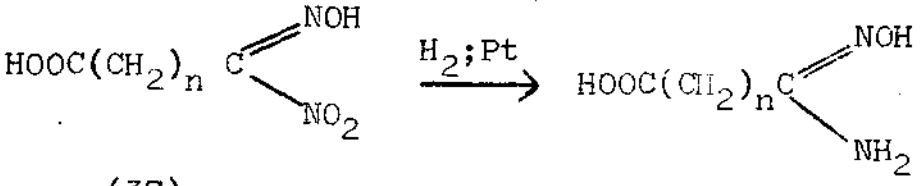
This is not a general method and only some few amidoximes have been prepared.



1.2.3 BY REDUCTION OF NITROSILIC (36) AND NITROLIC (37) ACIDS.



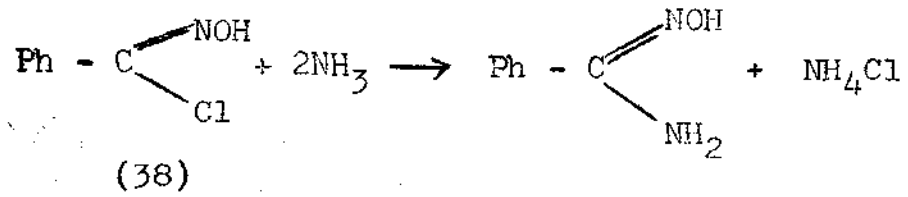
(36)



(37)

1.2.4 REACTION OF HYDROXIMIC ACID CHLORIDES (38) WITH AMMONIA.

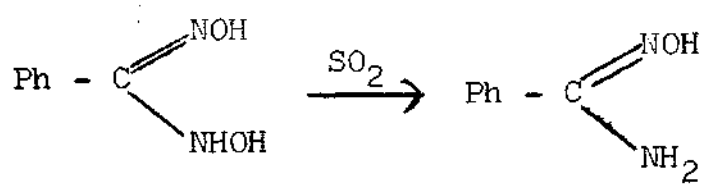
This reaction occurs readily and amidoximes, like benzamidoxime, has been prepared.



(38)

1.2.5 **REDUCTION OF OXYAMIDOXIMES (39) WITH SULPHUR DIOXIDE.**

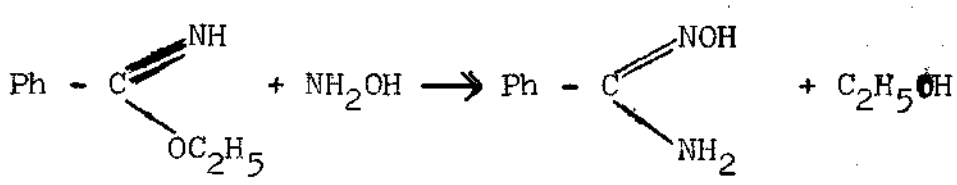
This reaction yields the corresponding amidoximes.



(39)

1.2.6 ACTION OF HYDROXYLAMINE ON IMINOETHERS.

Treatment of ethyl iminobenzoate (40) with hydroxylamine gives benzamidoxime.

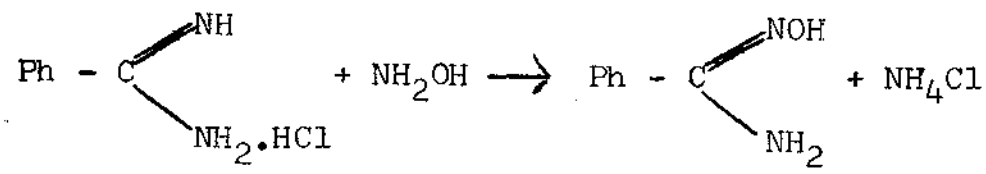


(40)

That benzonitrile is used for the synthesis of the aminoether renders this method not a practical one for the synthesis of amidoximes, as compared to method (1.2.1).

1.2.7 ACTION OF HYDROXYLAMINE ON AMIDINE HYDROCHLORIDES.

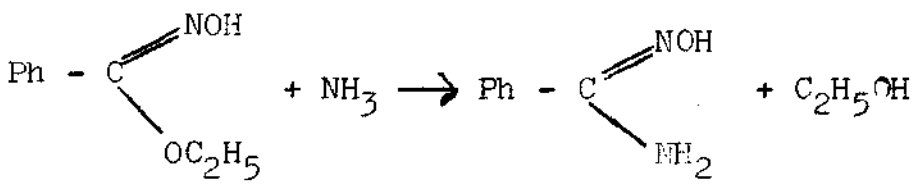
Treatment of benzamidine hydrochloride (41) with hydroxylamine gives benzamidoxime.



(41)

1.2.8 REACTION OF OXIMINOETHERS WITH AMMONIA

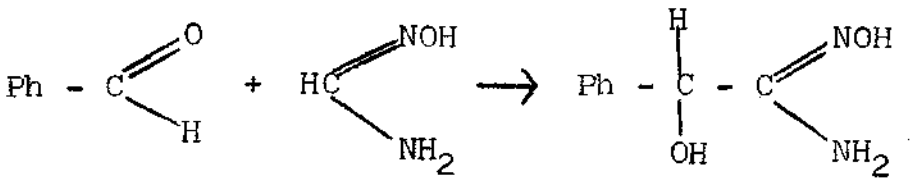
Benzamidoxime is obtained when ethyl benzhydroxamic acid (42) reacts with alcoholic solution of ammonia at 175°C for 8h.



(42)

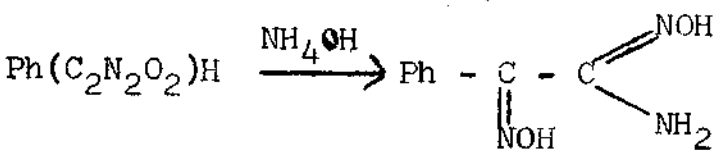
1.2.9 ACTION OF FORMAMIDOXIME ON AROMATIC ALDEHYDES.

This method is not a general one and has only been used in preparing maldelamidoxime.



1.2.10 ACTION OF AMMONIA ON GLYOXIMIC PEROXIDES.

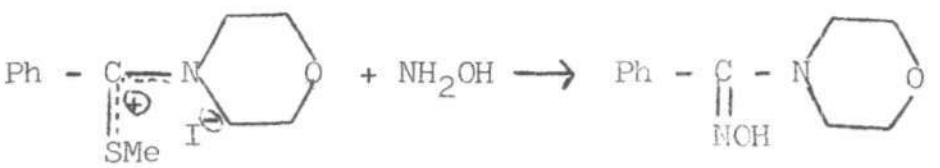
Phenylglyoxime peroxide when heated with ammonia yields an oxime containing amidoxime (43).



(43)

1.2.11 REACTION OF QUATERNARY SALTS WITH HYDROXYLAMINE

Hydroxylammonium chloride in presence of excess sodium acetate at room temperature reacts with the quaternary salt (4; R^1 = Ph, NR^2_2 = morpholino, R^3 = Me) to give α-4^1-morpholinobenzamidoxime (MBA).[25]



Some amidoximes have been reported to be pharmacologically and therapeutically active. Walker and his co-workers reported some activity of **p**-sulphamidobenzamidoxime on experimental thypus infections in mice.[28] Goldberg and Kelly reported 2-methoxy-9-aminoacridine-6-aminodoxime as products having pharmacological properties and are useful in therapeutics.[29] The study of trypanocide activity of several diamidoximes have been carried out.[30] In vitro activity against mycobacterium tuberculosis has also been shown by some halogenated phenols carrying an amidoxime group.[31]

Mukhtar, in the preliminary pharmacological screening of α-4^1-morpholinobenzamidoxime (MBA) found the compound to cause positive ionotrophy (i.e, increase force of myocardial contraction) and negative chronotrophy

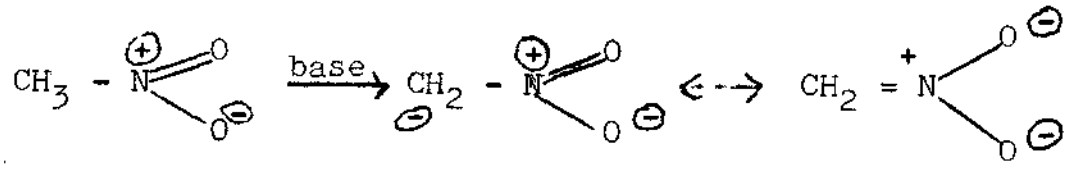
(i.e, decrease rate of myocardial contraction) on isolated rabbit heart.[32] MBA was also found to have a stimulant effect (causes contraction) on both chick eosophagus and isolated guinea pig iluem, though no effect was observed with isolated rat iluem. Different concentration of MBA relaxed the uterus of rat and also produced a blockade of nerve-induced stimulation which was concentration dependant. It also antagonizes the effect of exogeneous acetylcholine on skeletal muscle, although it had no effect on the magnitude of muscle contraction when stimulated directly.

Though having no effect on its own, MBA was found to antagonize the effect of standard drugs in the aortic strip of the rat. It also relaxes rat colon and when used with acetylcholine, a concentration dependant antagonism was observed. The electroshock threshold in young chicks was increased time and dose dependantly when MBA was administered. Two hour pretreatment time using 10mg/kg gave the best protection against shock. Lower doses of MBA (10mg/kg intraperitoneally) excited the chicks while higher doses (greater than 80mg/kg) sedated them. The compound has no effect on Cat's blood pressure.

1.3 ACTIVE METHYLENE COMPOUNDS AND SOME OF THEIR REACTIONS.

Certain unsaturated functions, like cyano, carbonyl, nitro or phenol, when present as substituent at a saturated carbon atom render any hydrogen atoms bonded to that carbon relatively acidic. These compounds are called active methylene compounds and the acidity of the C-H bonds in them is attributed to a combination of the inductive electron withdrawing ability of the unsaturated substituents and the ability of these substituents to delocalize the negative charge of the conjugate base.

$$CH_3 - C \equiv N \xrightarrow{base} \ominus CH_2 - C \equiv N \longleftrightarrow CH_2 = C = N^-$$

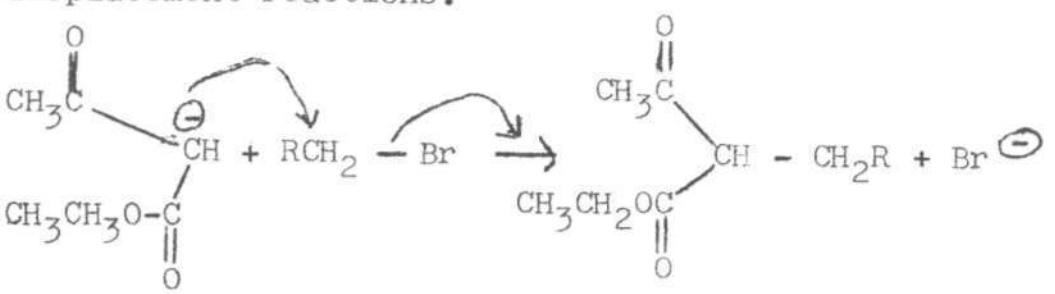


The order of effectiveness of these unsaturated functions is as follows: $-NO_2$ > $-CO-R$ > $-SO_2R$ > $-CO-OR$ and $-C \equiv N$ > $-SO-R$ > $-NO_2$. The acidity of an active methylene compound is further enhanced by the presence of two unsaturated substituents or an electron withdrawing bromo or chloro substituent. Alkyl substituents decrease the acidity due to the weak inductive effect of the alkyl group.

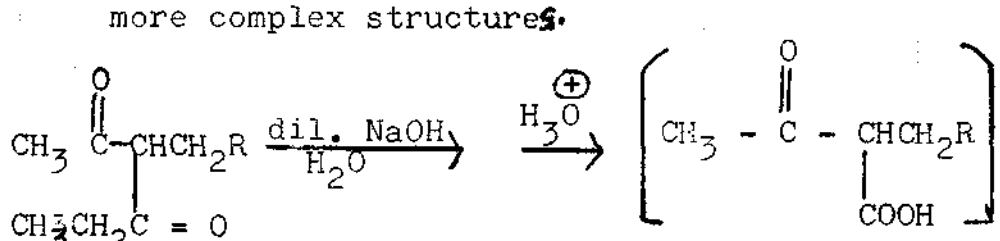
Examples of active methylene compounds include acetylacetone, ethyl acetoacetate, diethyl malonate, nitromethane, cyanoacetamide and cyanomethane. Formation and subsequent reaction of anions derived from active methylene compounds involve procedures that are very important and are synthetically useful class of organic reactions. The reactions in which the anion has been derived by the removal of a proton from the carbon atom alpha to a carbonyl group constitutes perhaps the most important of this class. These anions are called enolate anions and are highly nucleophilic species. Active methylene compounds can be converted in large part to their enolate anions by treatment with an anhydrous alcohol solution of a metal alkoxide.[34]

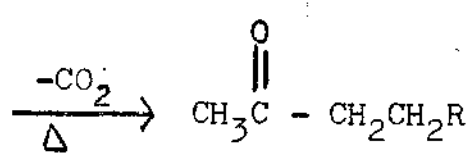


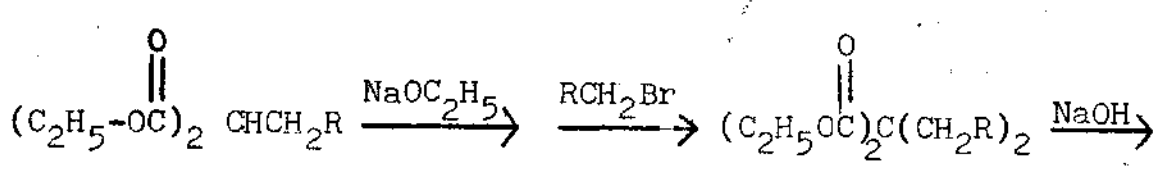
The enolate anions are capable of displacing halide ion from primary alkyl halide. With the carbon atoms of the enolate as the nucleophilic atoms, a carbon-carbon bond is formed as a result of the displacement reactions.[35]

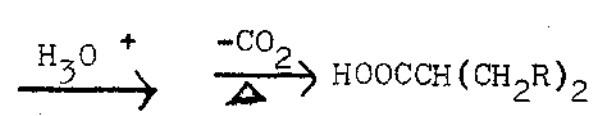


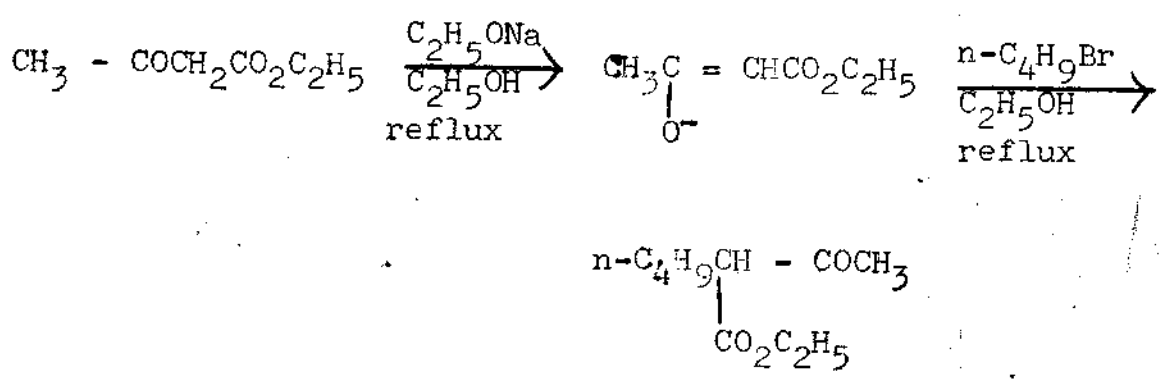
These enolate reactions of β-dicarbonyl compounds are important in that the products can be transformed into ketones or acids which have two or three more carbon atoms than the original alkyl halide. The initial products can once again be alkylated to produce disubstituted ketones or acids with more complex structures.





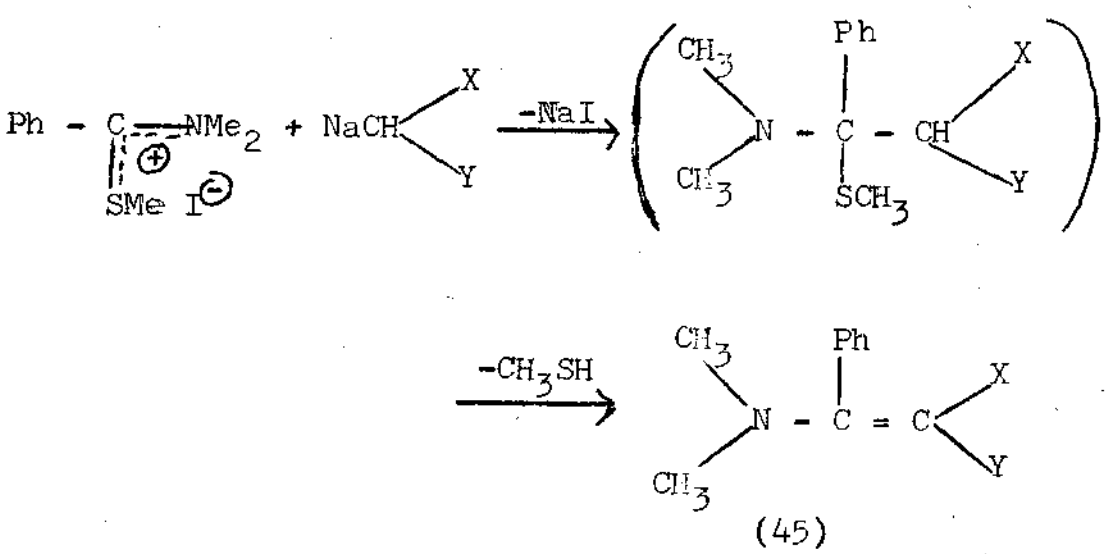






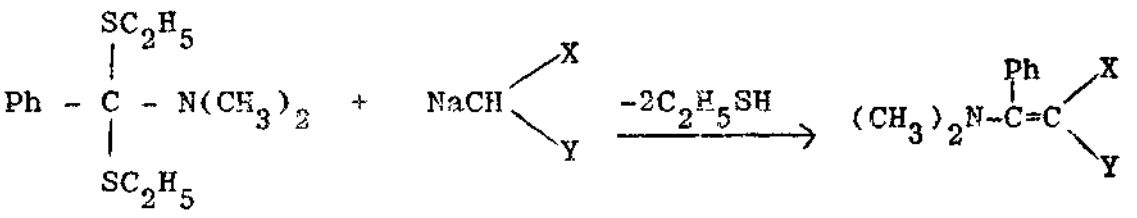
There is a qualitative relationship between the rate of proton removal and dissociation constant for the active methylene compounds, for proton removal is usually more rapid for more acidic compounds. Proton removal rates, however, do not necessarily provide a quantitatively accurate measure of relative acidities for these compounds. The presence of alkyl substituents, particularly branch chain alkyl substituents at the alpha carbon atom retard the rate of proton removal from the active methylene compounds. This may be due to increased stearic hindrance to approach of the base for proton abstraction.[33]

Mukaiyama and his co-workers, on treating an S-alkyl quaternary salt (4; R^1 = Ph, NR^2_2 = NMe_2, R^3 = Me) with mono sodium salts of active methylene compounds in dry dioxane at 80°C for 2h. obtained the condensation products (45).[19]



(45)

An amide mercaptole (46) has been found to give similar products.



(46)

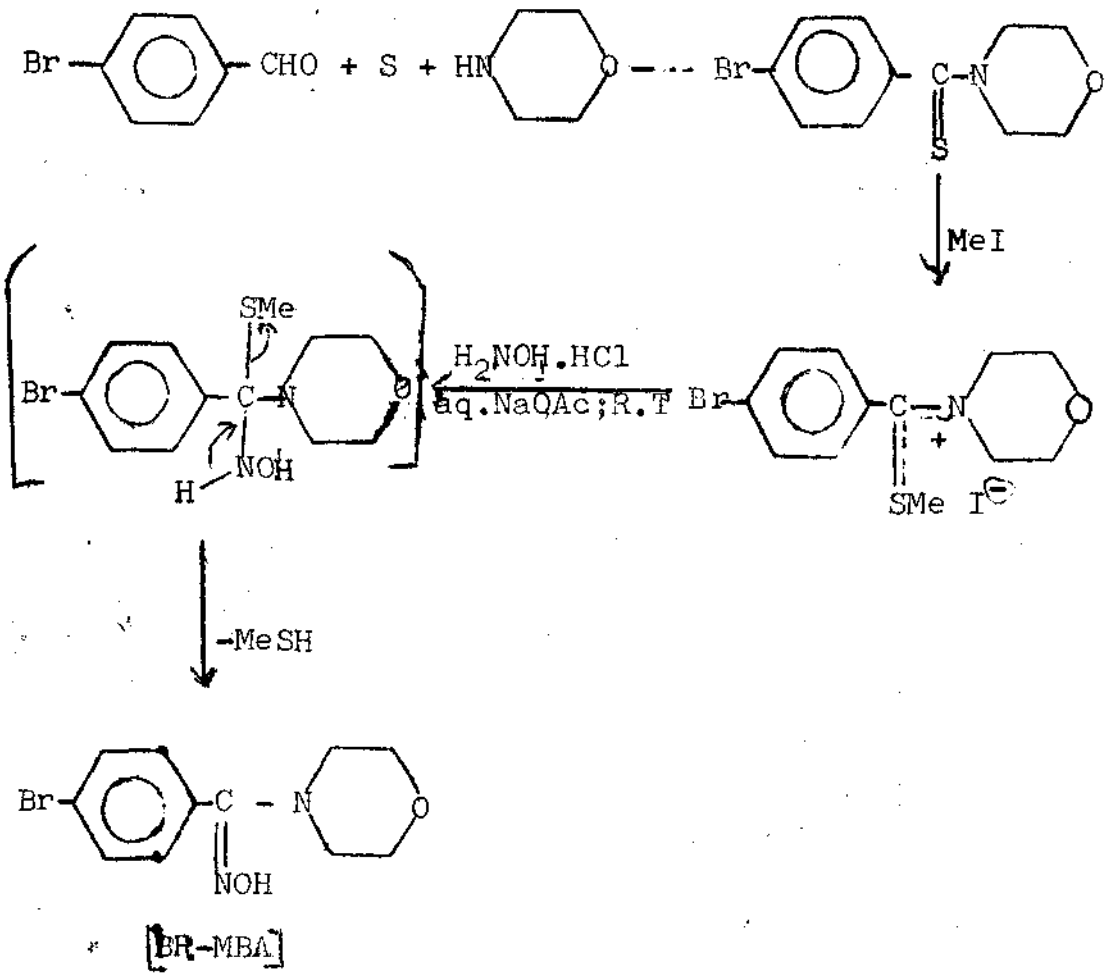
In the present investigations, structurally modified amidoximes (p-Bromo-α, 4'-morpholinobenzamidoxime and its chloro analogue) were synthesized for microbiological screening. Three S-alkyl quaternary salts, thiobenzomopholide methiodide thiobenzopiperidide methiodide and p-bromothiobenzomorpholide methiodide were reacted with active methylene compounds such as nitromethane, cyanoacetamide, ethyl acetoacetate and acetylacetone.

CHAPTER TWO

RESULTS AND DISCUSSIONS

2.1.1 SYNTHESIS OF p-BROMO-α, 4[1]-MORPHOLINOBENZAMIDOXIME (Br - MBA).

The parent thioamide was synthesised by refluxing p-bromobenzaldehyde with sulphur and morpholine for nine hours. The thioamide was then quaternised by refluxing it with methyl iodide in acetone for ten minutes. This quaternary salt was then reacted with a solution of sodium acetate and hydroxylammonium chloride for two hours. The purpose of the sodium acetate was to liberate the hydroxylammonium from its salt so that it reacts with the quaternary salt. The mechanistic scheme which explains this reaction is shown below.



p-Chloro-α, 4^1-morpholinobenzamidoxime [Cl-MBA], the chloro analogue, was synthesised using p-chloro-benzaldehyde as starting material in place of p-bromobenzaldehyde.

Attempt was made to subject both the Br-MBA and Cl-MBA to pharmacological screening using rats and possibly guinea pigs as the test animals. This, unfortunately had to be scrapped due to lack of funds to finance the purchase of the animals. Instead, Br-MBA was subjected to microbiological screening. The test organisms used were Escherichia coli, Staphylococcus aureus and Psuedomonas aeruginosa. 1 mg/ml and 10 mg/ml of the Br - MBA in absolute alcohol were tested on these organisms. Absolute alcohol, which also has some effect on micro-organisms (being bacteriostatic) was used as control.

From tables I and II which show the area of the zone of inhibition, it is clear that absolute alcohol has no visible effect on any of the three test organisms using both the gutter and the paper strip method. Using the gutter method, it was found that 1 mg/ml of Br-MBA in absolute alcohol had not much effect on E. coli and P. aeruginosa. 10 mg/ml of the same compound also had no appreciable effect on

E. coli. However, 1 mg/ml of Br-MBA showed some pronounced activity against S. aureus whilst 10 mg/ml of the Br-MBA showed a much more pronounced activity against both S. aureus and P. aeruginosa.

The paper strip method confirmed what was obtained with the gutter method when absolute alcohol was also used. Using this method, an almost identical result with that of the gutter method was obtained showing that 1 mg/ml of Br - MBA had no visible effect on both E. coli and P. aeruginosa. A slight activity was recorded on S. aureus when 1 mg/ml was tested. Using 10 mg/ml on both E. coli and P. aeruginosa, some activity was observed. 10 mg/ml of the compound, however, showed a greater activity against S. aureus, thus confirming the previous observations using the gutter method.

A difference is noticeable in the readings between the gutter method and the paper strip method. This can be attributed to the differences between the two methods. In the gutter method, 0.5ml of the test solution was placed in the gutter formed while in the paper strip method, the paper was just soaked and placed on the nutrient agar plate.

Despite the fact that the same concentrations were used, it was still clear that the amount of test solution in contact with the micro-organisms was more using the gutter method. This might be a reason why the zone of inhibition was larger in the gutter than the paper strip method. Another reason might be due to the higher concentration of bacteria in the paper strip method; in the gutter method the bacteria were just streaked in lines perpendicular to the gutter whilst 1 ml was used in the paper strip method. Despite the discrepancy, it is clear that 10 mg/ml of Br - MBA in absolute alcohol is active against S. aureus.

TABLE I

GUTTER METHOD

Chemical	Zone of inhibition in mm		
	E. coil	S. aureus	P. aeruginosa
Absolute alcohol	0,0,0	0,0,0	0,0,0
1mg/ml of Br-MBA in alcohol	0,1	17,5,22,2	3,1
10mg/ml of Br-MBA in alcohol	0,1	55,25	35,10

TABLE II

PAPER STRIP METHOD

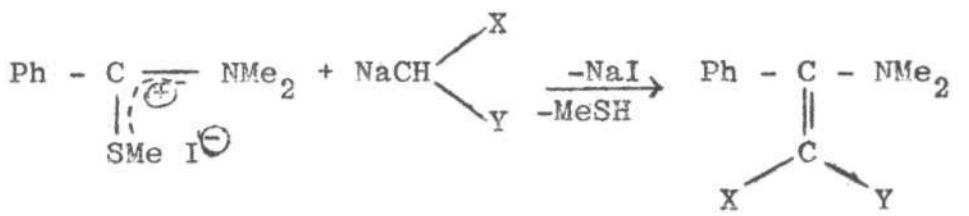
Chemical	Zone of inhibition in mm		
	E. Coli	S. aureus	P. aeruginosa
Absolute alcohol	0,0,0	0,0,0	0,0,0
1 mg/ml of Br-MBA in alcohol	0,0,0	4,0,0	0,0,0
10 mg/ml of Br-MBA in alcohol	1,2,0	20,22	1,1,1,2

2.2 REACTIONS OF S-ALKYL QUATERNARY SALTS WITH ACTIVE METHYLENE COMPOUNDS.

Some unsaturated functions like nitro, carbonyl, cyano or phenyl, to mention a few, when present as substituents at a saturated carbon atom render any hydrogen atoms bonded to that carbon atom relatively acidic. These compounds, examples of which include cyanoacetamide, nitromethane, acetylacetone and ethyl acetoacetate, are called active methylene compounds.

No extensive work has been carried out relating to quaternary salts and active methylene compounds. However, one quaternary salt (4; R^1 = Ph, NR^2_2 = NMe_2, R^3 = Me) was recently treated with monosodium salt of

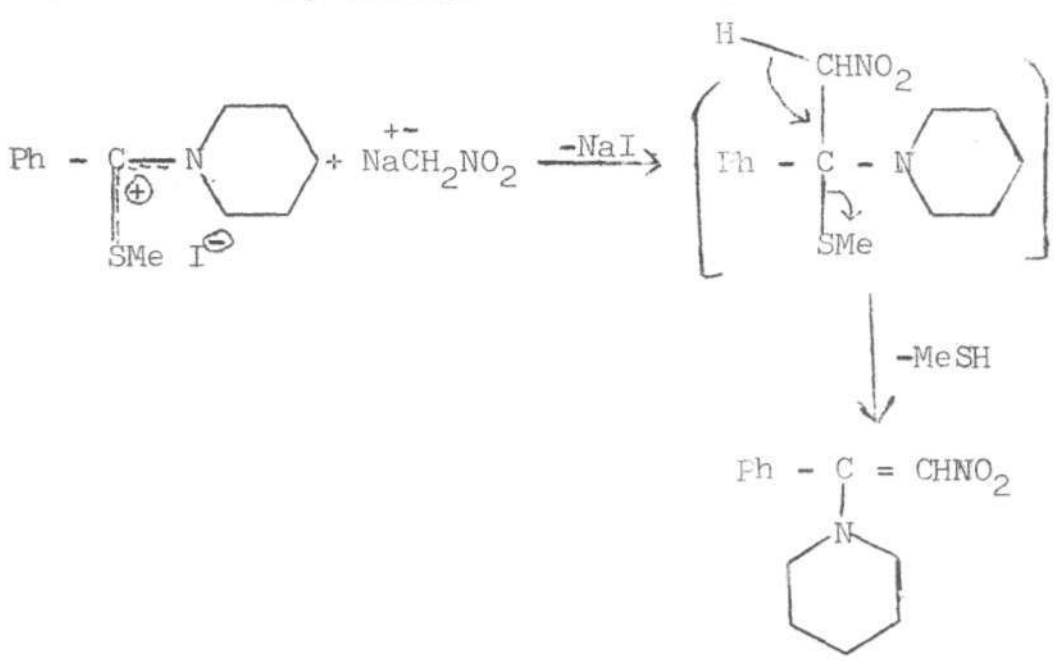
some active methylene compounds. This was done by refluxing the quaternary salt with the monosodium salts for 2h. at 89°C in dioxane to give the condensation products.[19]



In this investigation, different quaternary salts were treated with the active methylene compounds in order to extend the scope of the scanty work earlier reported by Mukaiyama and his co-workers.[19] In our study the reactions were carried our under less drastic conditions to prevent de-alkylation, which has been observed with S-alkyl quaternary salts. The monosodium salts were prepared by refluxing the active methylene compounds with sodium in dry benzene until all the sodium disappeared (usually takes 30 min. to 6h).

When the quaternary salt (4; R^1 = Ph, NR^2_2 = piperidino, R^3 = Me) was treated with the monosodium salt of nitromethane, a yellow solid was obtained which was recrystallized twice from carbon tetrachloride; its melting point was 110 - 111°C; sodium fusion test showed presence of nitrogen but absence of sulphur and halogens.

The infra red spectrum of the pure product showed two strong bands at 1540 and 1330cm^{-1} (nitro group). The n.m.r. spectrum provided very useful clues concerning the structure of the compound: $\delta CDCl_3$ 7.4(m, 5H, Ph), 6.80 (S, 1H, O_2N-C-H), 3.2(m, 4H, $CH_2.N.CH_2$), 1.48 (s, 6H, the other three CH_2 groups of piperidino group). The spectral properties of the product suggest that it is probably compound (47) (see Fig. 1A and 1B). The mechanism of the reaction is schematically shown below.

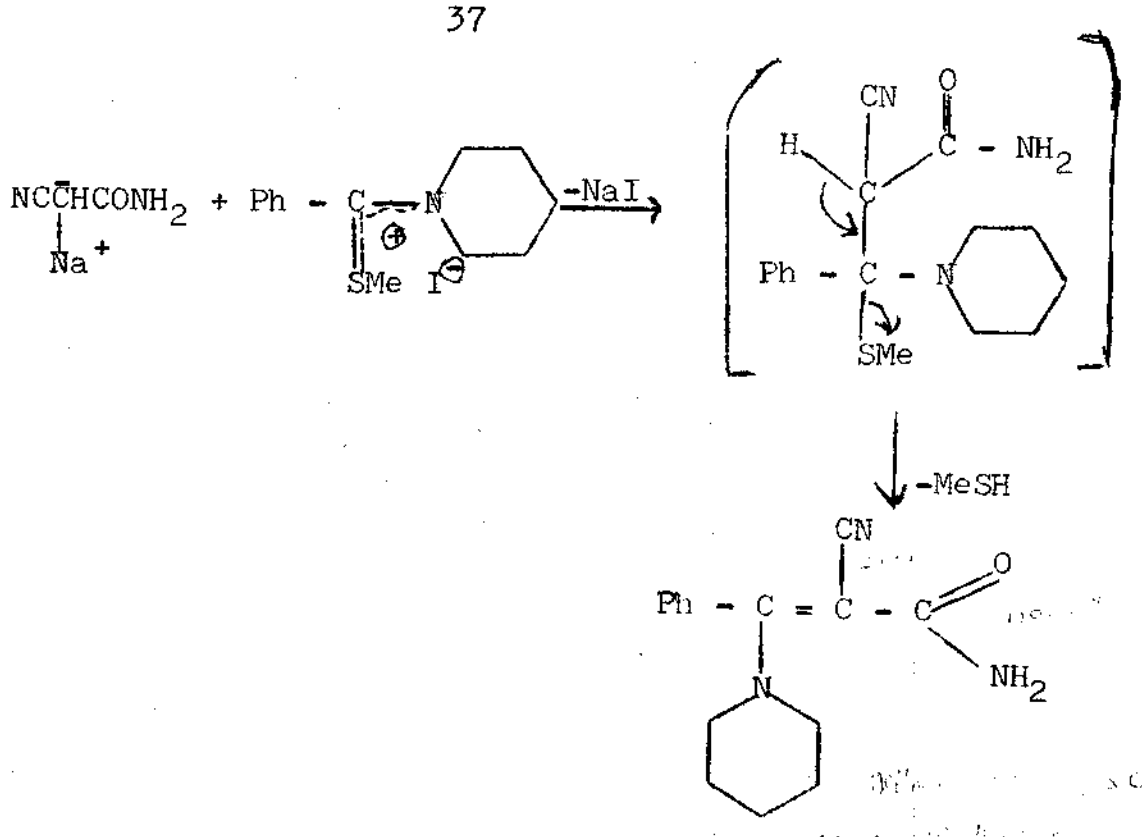


(47)

The reaction of the same quaternary salt (4; R^1 = Ph, NR^2_2 = piperidino group, R^3 = Me) with the monosodium salt of cyanoacetamide gave a yellow solid which was recrystallized twice from methanol; its melting point was 201 - 203°C; Lassaigne's test showed presence of nitrogen but absence of sulphur and halogens.

The i.r. spectrum (see Fig. 2B) of the pure product showed three absorption bands at 3410, 3340 and 3300cm^{-1} ($-NH_2$ group), 2175 cm^{-1} (-C = N group) and a strong band at 1630 cm^{-1} (carbonyl group). The n.m.r. spectrum (see Fig. 2A) also provided some important information on the structure of the product: $\delta CDCl_3$ 7.5(m, 5H, Ph), 5.7(m, 2H, $-\underset{\underset{O}{\|}}{C}-NH_2$; the signal was broad and almost unobservable[37]), 3.4(m, 4H, $CH_2.N.CH_2$), 1.75(s, 6H, the three other CH_2 groups of piperidino group). The product was conclusively established as the cyanoenamide (48) on the basis of its spectral properties and elemental analysis.

$$NCCH_2CONH_2 + Na \xrightarrow[\text{dry benzene}]{\text{reflux}} NCCH(Na^+)CONH_2$$



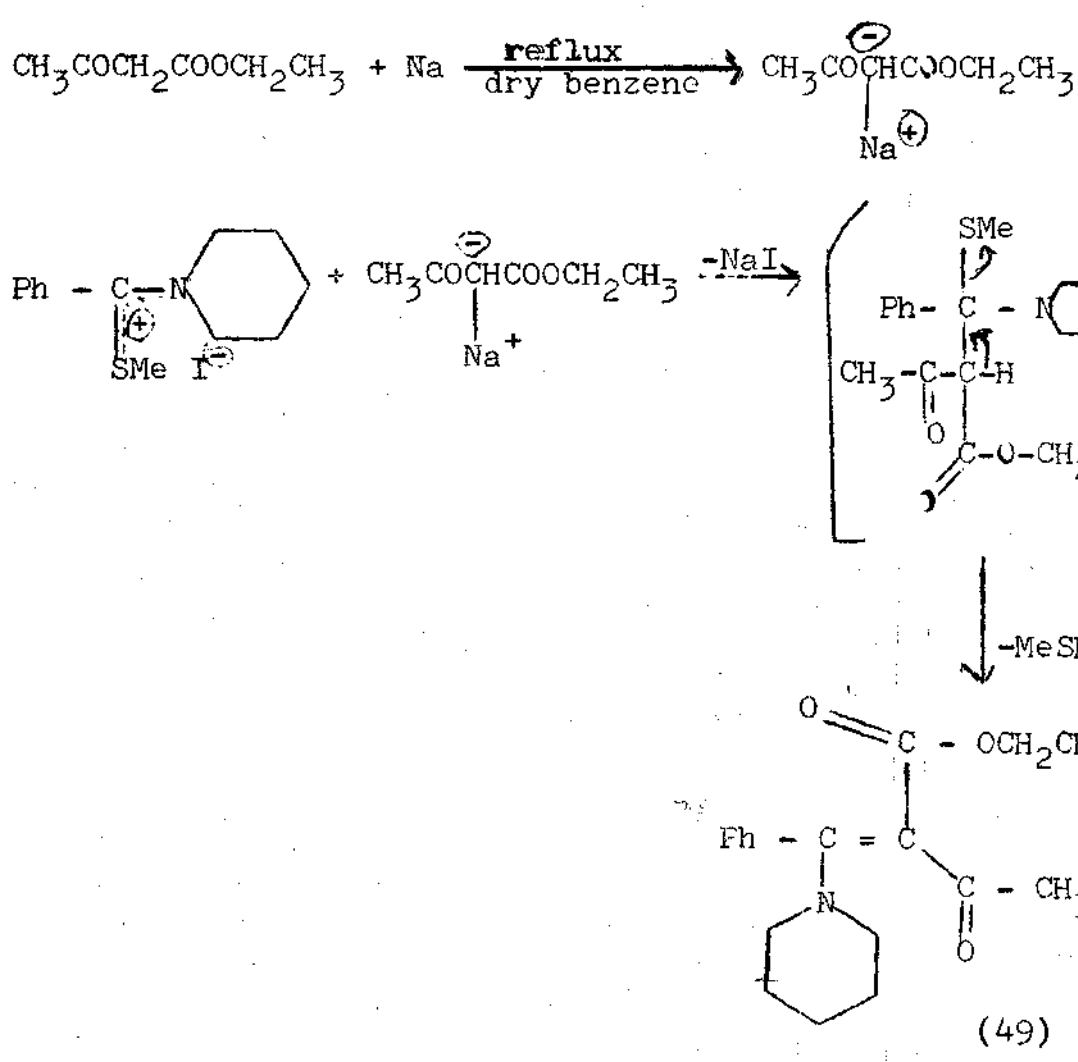
(48)

Treatment of the monosodium salt of ethyl acetoacetate with quaternary salt (4; R^1 = Ph, NR_2^2 = Piperidino group, R^3 = Me) gave a yellow solid which was recrystallized twice from petroleum spirit (b.p 100 - 120°C). The product melted at 101 - 102°C; sodium fusion test showed presence of nitrogen but absence of sulphur and halogens.

(see Fig. 3B)

The i.r. spectrum of the compound showed absorption bands at 1672 (C = O), and 1620cm^{-1} (C = C).

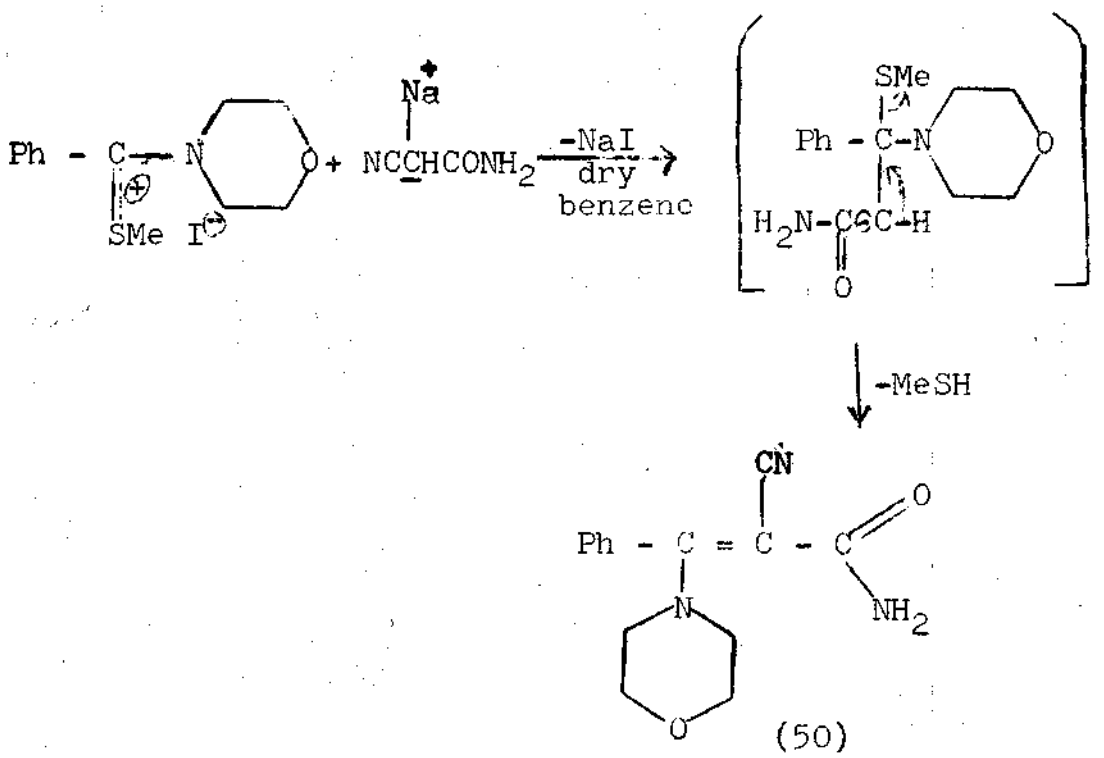
The n.m.r. spectrum (see Fig. 3A) of the product also gave some important clues: δCDCl 7.34 (s, 5H, Ph), 3.6 (m, 2H, $-OCH_2-$), 3.2 (m, 4H, $CH_2.N.CH_2$), 2.20(s, 3H, $-\overset{O}{\overset{\|}{C}}-CH_3$), 1.8(m, 6H, three CH_2 groups of piperidino group), 1.7(t, 3H, CH_3 of the ethyl group). The spectral data obtained for this product were in agreement with the proposed structure (49). However, elemental analysis or mass spectral data of the compound would conclusively establish its structure. The mechanism of the reaction may probably fit what we have schematically shown below:



(49)

When the quaternary salt (4; R^1 = Ph, NR^2_2 = morpholino, R^3 = Me) was treated with monosodium salt of cyanoacetamide, a white solid was obtained which was recrystallized twice from water. The common organic solvents were found unsuitable for its recrystallization either because of its gross solubility or insolubility in them. It melted at 121 - 122°C and Lassaigne's test showed presence of nitrogen but absence of sulphur and halogens.

(see Fig. 4B)
The i.r. spectrum of the product showed absorption bands at 3470, 3200 (N - H), 2200 (-C ≡ N), 1685 (carbonyl group), 1640 (-C=C-) and 1100cm^{-1} (C-O-C of morpholino group). The n.m.r. spectrum (see Fig.4A) also provided some valuable information. $\delta CDCl_3$ 7.50(s, 5H, Ph), 5.8(m, 2H, - C(=O) - NH_2), 3.7(m, 4H, CH_2.O.CH_2), 3.4(m, 4H, CH_2.N.CH_2). Spectroscopic properties of the product were used to deduce the structure (50) as being the probable one for the compound isolated.



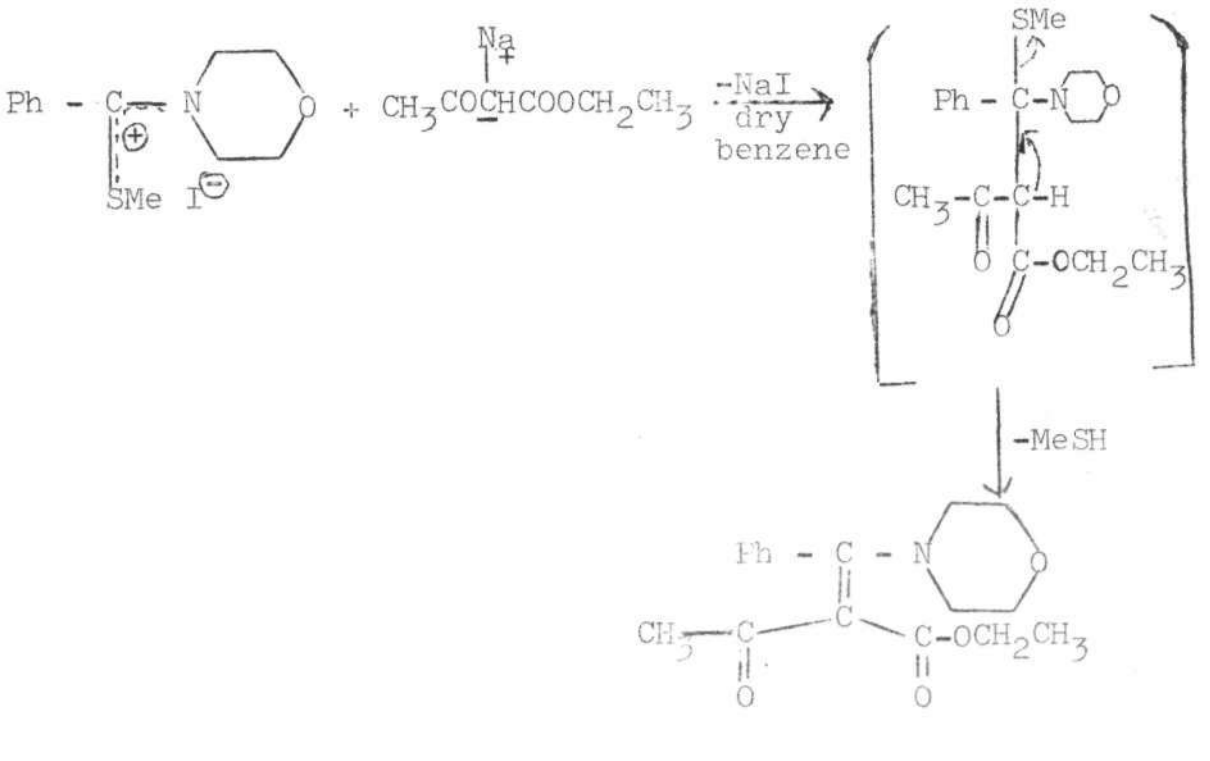
(50)

The reaction of the monosodium salt of ethyl acetoacetate with the quaternary salt (4; R^1 = Ph, NR_2^2 = morpholino, R^3 = Me) gave a yellow solid which was recrystallized twice from petroleum spirit (b.p 100 - 120°C); its melting point was 100 - 102°C; Lossaigne's test showed presence of nitrogen but absence of sulphur and halogens.

(see Fig. 5B)

The i.r spectrum showed strong absorption bands at 1670 (carbonyl group), 1612 (C = C), 1020_w (C - N bond) and 1100 cm^{-1} (C - O - C of morpholino group). Important clues were obtained from the n.m.r. spectrum (see Fig. 5A);

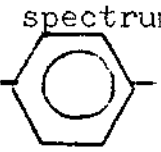
$\delta CDCl_3$ 7.50 (s, 5H, Ph), 3.8(m, 6H, $CH_2.O.CH_2$ and $C(=O)-OCH_2$), 3.2(t, 4H, $CH_2.N.CH_2$), 2.25(s, 3H, $-C(=O)-CH_3$) and 0.6(t, 3H, CH_3 of the ethyl group). The solid product obtained was not enough for elemental analysis. However, from the n.m.r. and i.r. spectral data obtained, the proposed structure (51) was assigned to it.

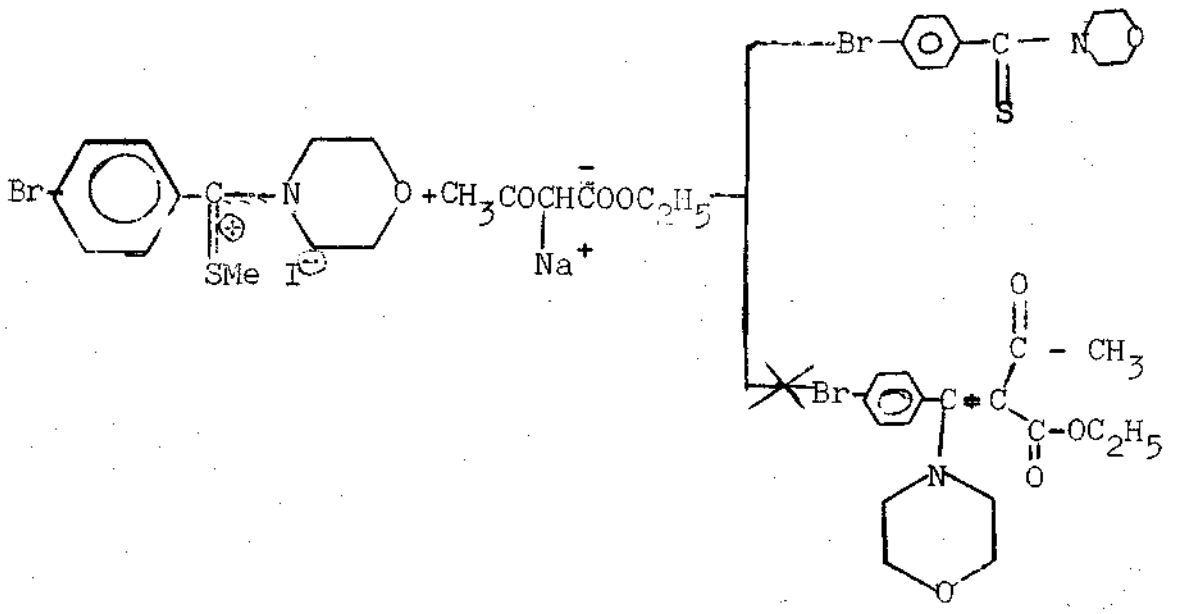


(51)

On repeating the experiment to obtain more of the product for elemental analysis, a yellow liquid, b.p 113° - $114^{\circ}C$/0.5mmHg was obtained; its i.r. spectrum showed absorption bands at 1750 (carbonyl group), 1630(C=C) and 1100 cm^{-1}(C-O-C of morpholino group).

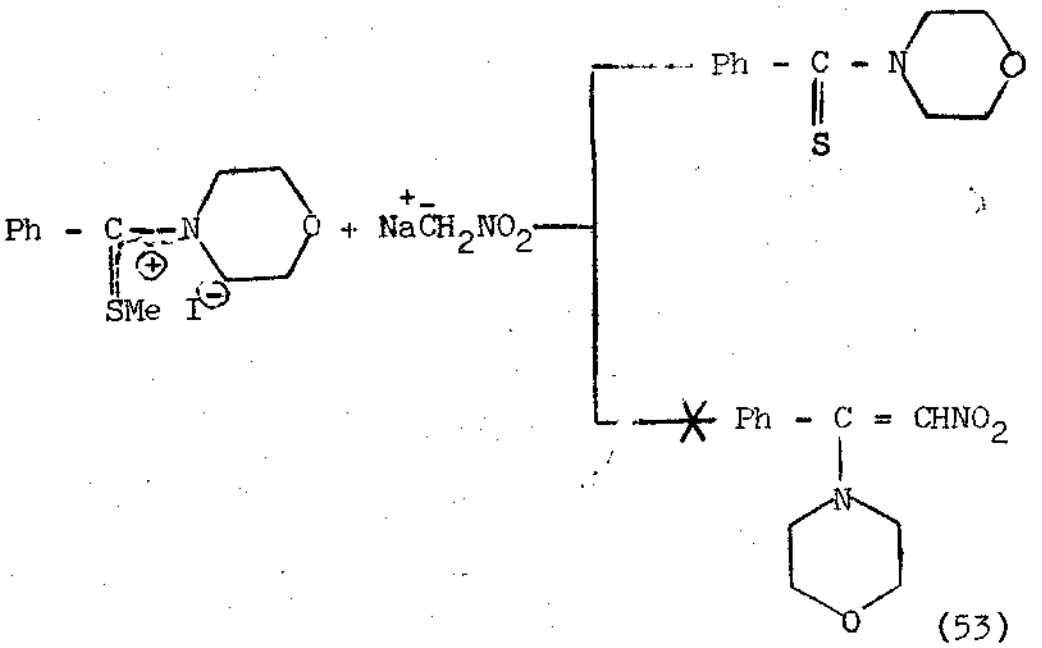
(see Fig.6A)
The n.m.r. spectrum of the liquid product is very complicated and different from the expected condensation products (51). It is hereby suggested that this reaction should be investigated futher.

When the quaternary salt (4; R^1 = Br-, NR^2_2 = morpholino, R^3 = Me) was treated with the monosodium salt of ethyl acetoacetate a yellow solid was obtained, which after purification, was found to have identical i.r. spectrum with p-bromothiobenzomorpholide (1, R^1 = Br-, NR'_2 = morpholino), instead of the condensation product (52)



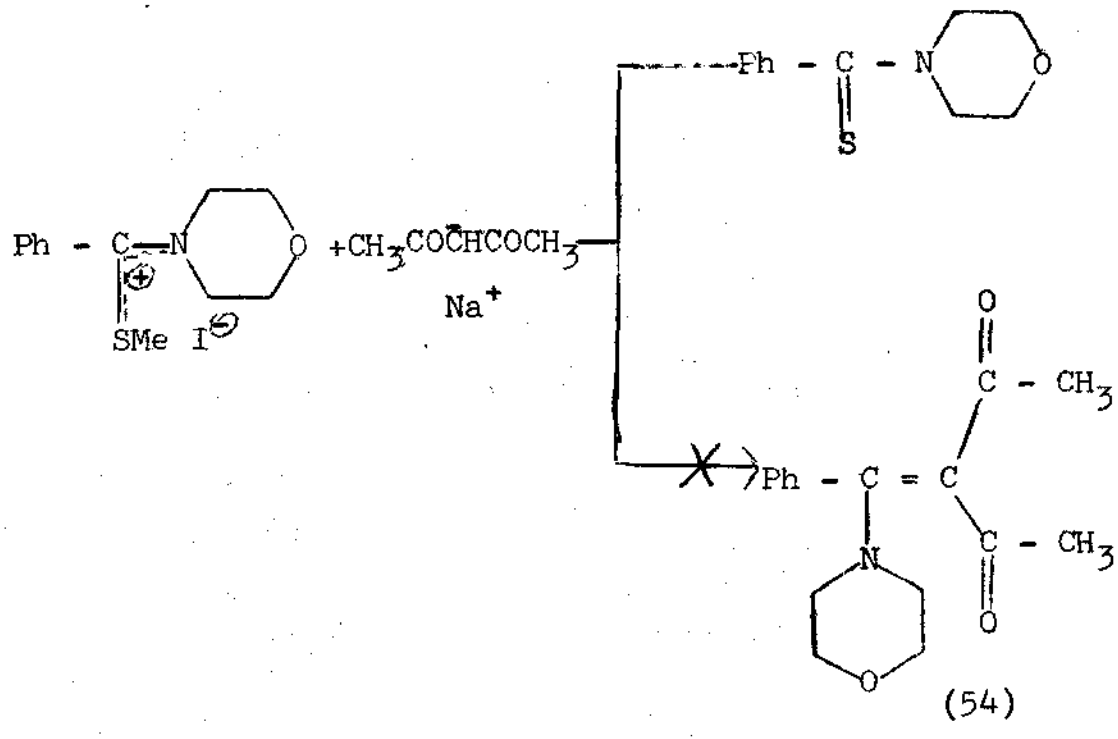
(52)

Treatment of the salt (4; R^1 = Ph, NR^2_2 = morpholino, R^3 = Me) with the monosodium salt of nitromethane resulted in the formation of the thioamide (1; R^1 = Ph, NR^2_2 = morpholino) instead of compound (53).



(53)

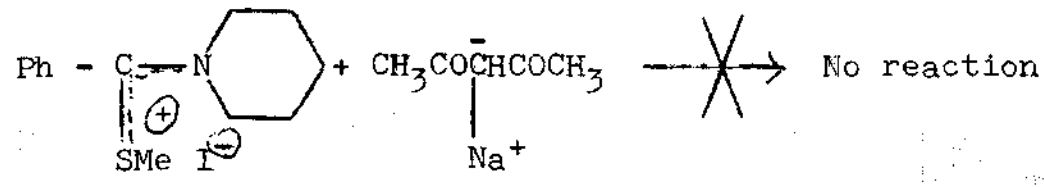
Reaction of the same salt (4; R^1 = Ph, NR^2_2 = morpholino, R^3 = Me) with the monosodium salt of acetylacetone also led to the isolation of a compound whose melting point and i.r. spectrum were the same as those of an authentic sample of thioamide (1; R^1 = Ph, NR^2_2 = morpholino), instead of the expected condensation product (54).



(54)

In the above three experiments involving quaternary salts and monosodium salts of active methylene compounds, a thioamide was obtained in each case. This shows surprisingly, that demethylation has occurred under the reaction conditions which involved ice-cooling.

Treatment of a salt (4; R^1 = Ph, NR^2_2 = piperidino, R^3 = Me) with the monosodium salt of acetyl acetone however, gave no reaction.



2.2 CONCLUSION

In the present investigation it has been demonstrated that p-bromo- ,4'-morpholinobenzamidoxime (Br - MBA) has some reasonable degree of activity against Staphylococcus aureus at 1mg/ml and 10mg/ml. However, the same concentrations of the compound failed to show any appreciable inhibition against Escherichia coli and Psuedomonas aeruginosa. Further work to determine the optimum concentration using a much wider variety of bacteria is hereby suggested. Additionally, the compound should be structurally modified to a water soluble analogue which will render the microbial screening more feasible.

The investigations of the reactions of S-alkyl quaternary salts with the monosodium salts of active methylene compounds have been shown to give condensation products with olefinic bonds, formed between the quaternary carbons of the quaternary salts and the nucleophilic carbons of the monosodium salts. The compounds would experience reasonable overcrowding, particularly with an aryl and an NN-disubstituted amino groups being attached to one of the olefinic carbons, and so their synthesis is note-worthy. The molecular constitution of each of the new compounds

isolated suggests that it could be of interest for further synthetic investigations, using it as a substrate. Mukaiyama and his co-workers carried out the reactions of one quaternary salt (4; R^1 = Ph, NR^2_2 = NMe_2 , R^3 = Me) with some active methylene compounds by heating the reaction mixtures under reflux at 80°C. However, in our present study the reactions were carried out at much lower temperatures (ice-cooling); there is also enough evidence that the reactions can conveniently take place even at room temperature. This, of course, suggests that our reaction procedure entails less drastic conditions than that of Mukaiyama and his co-workers and therefore should be preferred.

In some cases, the reactions did not give the expected condensation products, but instead lead to the isolation of NN-disubstituted thioamides. This can only be explained on the grounds of demethylation, which is indeed surprising at such low temperatures. However, in one case there was no reaction at all as the quaternary salt was recovered almost quantitatively.

The reactions of quaternary salts with active methylene compounds are interesting, and further work on them is recommended with some modifications of the reaction conditions for the purpose of improving the yields of products and to see if the unreactive salts could eventually give some reactions.

CHAPTER THREE

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

I.r spectrum was recorded using a PERKIN ELMER 700 instrument while n.m.r. was recorded using Varian T-60 instrument. Melting points were determined using Reichert melting point apparatus while elemental analysis was done by the Scandinavian micro-analytical laboratories.

3.1 Preparation of 4-bromothiobenzomorpholide:

p-Bromobenzaldehyde (55.5g), sulphur (14.4g) and morpholine (39.15g) were mixed in a flask (an exothermic reaction occurred) and heated under reflux on a steam bath for nine hours. Ethanol (600ml) was added and the boiling continued until all the compound dissolved in the solvent; the dissolved compound was decanted from traces of insoluble material (probably sulphur), cooled and the yellow crystals formed were filtered and dried (50.44g; 58.79%). The m.p. and i.r. spectrum of the product were identical with that of an authentic sample of 4-bromothiobenzomorpholide.

3.2 Preparation of 4-bromothiobenzomorpholide methiodide

Methyl iodide (56.8g) was added to the prepared thioamide (30.0g) in dry acetone (25ml) and the mixture refluxed for ten minutes. The yellow solid formed was cooled in ice, triturated with diethyl ether (250ml), filtered off and washed with more diethyl ether (100ml). The product was dried (32.65g; 73%) and its m.p and i.r. spectrum found to be identical with an authentic sample of 4-bromothio-benzomorpholide methiodide.

3.3 Preparation of p-bromo-$\alpha,4^1$-morpholinobenzamidoxide (Br - MBA).

Sodium acetate trihydrate (350g) and hydroxylammonium chloride (8.0g) were dissolved in distilled water (600ml) and the prepared quaternary salt (18,0g) was added and the mixture mechanically stirred for two hours. The pink product was filtered off, dried and recrystallized twice from 95% ethanol (6.83g; 57%). Its m.p and i.r. spectrum were identical with that of an authentic sample of Br - MBA.

3.4 Preparation of 4-chlorothiobenzomorpholide:

p-Chlorobenzaldehyde (24.56g), sulphur (8.4g) and morpholine (22.82g) were mixed in a flask (an exothermic reaction occurred) and heated under

reflux on a steam bath for ten hours. The brownish-yellow crystalline mass was heated in 95% ethanol (350ml) until it dissolved, leaving behind a small amount of insoluble material (probably sulphur) which was filtered off. The solution was cooled and the crystals formed were filtered off and dried (30.43g; 73.27%). The m.p and i.r spectrum of the product were identical with that of an authentic sample of 4-chlorothiobenzomorpholide.

3.5 Preparation of 4-chlorothiobenzomorpholide methiodide:

4-Chlorothiobenzomorpholide (30.5g) was dissolved in dry acetone (150ml) and methyl iodide (56.8g) added and refluxed for ten minutes on steam bath. The yellow product formed was cooled in ice, washed with diethyl ether (500ml), filtered and dried (38.90g; 80.32%). The products melting point and i.r. spectrum were identical with that of an authentic sample of 4-chlorothiobenzomorpholide methiodide.

3.6 Preparation of p-chloro-α,4^1-morpholinobenzamidoxime (Cl - MBA):

A mixture of sodium acetate trihydrate (350g) and hydroxylamonium chloride (8.0g) was dissolved in water (600ml) and the quaternary salt (16.48g) added;

the mixture was mechanically stirred for three hours, the product filtered off and recrystallized twice from 95% ethanol (charcoal) and dried (4.7g; 49.6%). The m.p. and i.r spectrum of the product were identical with that of an authentic sample of Cl - MBA.

3.7 Preparation of agar medium and screening of p-bromo-α,4'-morpholinobenzamidoxime (Br-MBA):

The solid agar (28g) was suspended in distilled water (1 l) and brought to the boil until it dissolved completely. 20ml of the solution each was poured into a clean McCartney bottle and the contents sterilized by autoclaving at 121°C for fifteen minutes. The liquid agar from each bottle was then poured into clean sterile petri-dish enclosed in a sterile screen and allowed to solidify.

In the gutter method, a sterile ampoule file was used to remove a strip of agar (5 - 7 x 0.2 -0.3cm) from a nutrient agar plate and 0.5ml of the material to be tested was placed in the gutter formed. Sterile swabs were used to streak the tests micro-organisms in lines perpendicular to the gutter, beginning from the base of the plate and ending just near the gutter. The whole set-up was left for two hours at room temperature to allow for diffusion of the test solution and then incubated at 37°C for twenty four hours.

The degree of inhibition (in mm) was recorded. The test solutions used were 10mg/ml and 1 mg/ml of Br-MBA in absolute alcohol and absolute alcohol itself, the solvent vehicle which was used as control. The test micro-organisms used were Escherichia coli, Staphylococcus aureus and Psuedomonas aeruginosa. The whole experiment was repeated thrice.

In the paper strip method, 1 ml of the test micro-organisms was poured on the solid agar and allowed to diffuse. A filter paper strip was soaked in the test solution, shaken to remove excess fluid and placed at one end of the nutrient agar plate. This was left for two hours to allow for diffusion of the anti-microbial agent. The set up was incubated at 37°C for twenty four hours and the degree of inhibition of each organism recorded. The same concentration of test solutions and solvent vehicle together with the same test micro-organisms as in the gutter method were used. Each test was repeated thrice.

3.8 Reaction of thiobenzopiperidide methiodide with the monosodium salt of nitromethane:

To clean metallic sodium (0.23g; 0.01 mol) in benzene (20 ml) was added nitromethane (0.61ml; 0.01mol) and refluxed until all the sodium disappeared.

To this mixture was added the quaternary salt (3.47g; 0.01mol) with stirring and ice-cooling for two hours. The benzene was evaporated, water (40 ml) cautiously added and the product extracted four times with dichloromethane (100ml) and dried (anhydrous sodium sulphate). The solvent was evaporated and the brownish liquid obtained scratched with ice-cooling.

Ethanol was used to titutrate the yellow solid obtained; this product was then filtered, dried (0.58g) and recrystallized twice from carbon tetrachloride (m.p. 110 - 111°C). Lassaigne's test showed presence of nitrogen but absence of sulphur and halogens; ν_{max} (nujol) 1540_s, 1330 cm^{-1} (nitro group); $\delta CDCl_3$ 7.4(m, 5H, Ph), 6.80 (m, 1H, $O_2N - C - H$), 3.2(m, 4H, $CH_2.N.CH_2$), 1.48(s, 6H, the other three CH_2 groups of piperidino group).

3.9 Reaction of thiobenzopiperidide methiodide with the monosodium salt of cyanoacetamide:

Cyanoacetamide (0.84g; 0.01 mol.) was added to clean metallic sodium (0.23g; 0.01 mol) in benzene (20ml) and refluxed until all the sodium disappeared. To this mixture was added the quaternary salt (3.47; 0.01mol) and stirred with ice-cooling for two hours. The benzene was extracted, water (40ml) cautiously added and the product extracted four times with dichloromethane (100ml).

The extract was dried (anhydrous sodium sulphate), the solvent removed and the brownish liquid obtained cooled with scratching. The crystals formed were triturated with methanol, filtered and dried (0.82g; 32.16%).

Recrystalization from methanol gave 2-cyano-3, phenyl-3-piperidinopropenamide, m.p 201 - 203°C (found: C,70.5; H,6.8; N,16.5. $C_{15}H_{17}N_3O$ requires C,70.6; H,6.7; N, 16.5%); ν_{max} (nujol) 3410, 3340, 3300 ($-NH_2$ group), 2175 ($-C \equiv N$ group), 1630_s (carbonyl group); $\delta CDCl_3$ 7.5(m, 5H, Ph), 5.7 (m, 2H, $-\overset{\overset{O}{\|}}{C}-NH_2$) 3.4(m, 4H $CH_2.N.CH_2$), 1.75(s, 6H, the three other CH_2 groups of piperidino group).

3.10 Reaction of thiobenzopiperidide methiodide with the monosodium salt of ethyl acetoacetate:

Ethyl acetoacetate (1.4 ml; 0.01 mol) was added to clean metallic sodium (0.23g; 0.01mol) in benzene (20 ml) and stirred at room temperature until all the sodium disappeared. To this mixture was added the quaternary salt (3.47g, 0.01mol) with stirring and ice-cooling for two hours. The benzene was evaporated, water (40ml) cautiously added and the product extracted four times with dichloromethene (100ml) and dried

(anhydrous sodium sulphate). The solvent was evaporated and the brownish liquid obtained cooled with scretching after two drops of petroleum spirit (b.p. 100 - 120°C) had been added.

The yellow solid obtained was divided into two, one half was squeezed between filter paper to remove the stickiness while the remaining half has titurated with petroleum spirit (b.p. 100 - 120°C) and filtered. The combined product (1.87g) was recrystallied twice from petroleum spirit (b.p. 100 - 120°C) and dried (m.p. 101 - 102°C). Lassaigne's test showed presence of nitrogen but absence of sulpur and nitrogen; ν_{max} (nujol) 1672_s (C = O), and 1620 cm^{-1} (C = C), $\delta CDCl_3$ 7.34(s, 5H, Ph), 3.6(m, 2H - OCH_2-) 3.2 (m, 4H, $CH_2.N.CH_2$), 2,2)(s, 3H, $\underset{O}{C}$ - CH_3), 1.8(m, 6H, three CH_2 groups of piperidino group), 1.7(t, 3H, CH_3 group of the ethyl group).

3.11 Reaction of thiobenzomorpholide methiodide with the monosodium salt of cyanoacetamide.

To clean metallic sodium (0.23g; 0.01 mol) in benzene (20ml) was added cyanoacetamide 0.84g; 0.01 mol) and the mixture refluxed until all the sodium disappeared.

The quaternary salt (3.49g; 0.01 mol) was added to this mixture, stirred with ice cooling for two hours and the benzene evaporated. Water (40ml) was cautiously added. The product was extracted four times with dichloromethane (100 ml) and dried (anhydrous sodium sulphate). The extract was concentrated, ice-cooled with scratching and the solid obtained triturated with petroleum spirit (b.p 100 - 120°C), filtered and dried (0.842g). The product was recrystallized from water and dried (m.p. 121 - 122°C). sodium fusion test showed presence of nitrogen but absence of sulphur and halogens; ν_{max} (nujol) 3470, 3200 (N - H), 2200 (-C ≡ N), 1685 (carbonyl group), 1640 (C = C), 1100cm^{-1} (C-O-C- of morpholino group); $\delta CDCl_3$ 7.50(s, 5H, Ph), 5.8 (m, 2H, $-\overset{\overset{O}{\|}}{C}-NH_2$), 3.7(m, 4H, $CH_2.O.CH_2$), 3.4 (m, 4H, $CH_2.N.CH_2$).

3.12 Reaction of thiobenzomorpholide methiodide with monosodium salt of ethyl acetoacetate:

Ethyl acetoacetate (0.70ml; 0.005 mol) was added to clean metallic sodium (0.12g ; 0.005 mol) in benzene (20 ml) and refluxed until all the sodium disappeared. To this mixture was added the quaternary salt (1.75g; 0.005mol) and stirred with ice-cooling for two hours.

The benzen was evaporated, water (40 ml) cautiously added and the product extracted four times with dichloromethane (100ml). The extract was dried (anhydrous sodium sulphate), concentrated and cooled with scratching. The yellow solid formed was triturated with petroleum spirit (b.p. 100 - 120°C), filtered, dried (0.68g) and recrystallized twice from petroleum spirit (b.p. 100 - 120°C). The product melted at 100 - 102°C. Lassaigne's test showed presence of nitrogen but absence of sulphur and halogens ν_{max} (nujol) 1670_s (carbonyl group), 1612_m (C = C), 1020_w (C - N), 1100 cm^{-1} (C-O-C of morpholino group); $\delta CDCl_3$ 7.50(s; 5H, Ph), 3.8(m, 6H, $CH_2.O.CH_2$ and $-\overset{O}{\overset{\|}{C}}-OCH_2$), 3.2(t, 4H, $CH_2.N.CH_2$), 2.25(s, 3H, $-\overset{O}{\overset{\|}{C}}-CH_3$) and 0.6(t, 3H, CH_3 of the ethyl group).

On repeating this experiment, a liquid was obtained which was distilled at 113 - 114°C/0.5mmHg. Sodium fusion test showed presence of both sulphur and nitrogen, but absence of halogens; ν_{max} (nujol) 1750_s (carbonyl group), 1630 (C = C), 1100cm^{-1} (C-O-C of morpholino group).

3.13 Reaction of p-bromothiobenzomorpholide methiodide with the monosodium salt of ethyl acetoacetate:

To clean metallic sodium (0.23g; 0.01mol) in dry benzene (20ml) was added ethyl acetoacetate (1.4g; 0.0.01 mol) and refluxed until all the sodium disappeared. To this was added the quaternary salt (4.28g; 0.01mol) and the mixture stirred with ice-cooling for two hours. The benzene was the evaporated, water (40ml) added and the product extracted four times with dichloromethane (100ml). The extract was dried (anhydrous sodium sulphate), concentrated, triturated with petroleum spirit (b.p 100 - 120°C), filtered and dried (0.5g). Recrystallization from ethanol gave a yellow solid whose i.r. spectrum was identical with that of an authentic sample of p-bromothiobenzomorpholide.

3.14 Reaction of thiobenzomorpholide methiodide with the monosodium salt of nitromethane:

Nitromethane (0.61ml; 0.01mol) was added to clean sodium metal (0.23g; 0.01mol) in benzene (20ml) and refluxed until all the sodium disappeared. To this mixture was added the quaternary salt (3.49g; 0.01mol) and stirred with ice-cooling for two hours. The benzene was evaporated, water (40ml) added and the product extracted four times with dichloromethane (100ml). The extract was dried (anhydrous sodium sulphate), concentrated, cooled and the solid triturated with ethanol. The product was filtered and dried (1.5g); recrystallization from ethanol gave a yellow solid whose melting point (136 - 138°C, lit. 137 - 138°C) and i.r. spectrum were identical with that of an authentic sample of thiobenzomorpholide.

3.15 Reaction of thiobenzomorpholide methiodide with monosodium salt of acetylacetone:

To clean metallic sodium (0.23g; 0.01mol) in benzene (20ml) was added acetylacetone (1.1ml; 0.01mol) and the mixture refluxed until all the sodium disappeared.

To this was added the quaternary salt (3.49g; 0.01mol) with ice-cooling and the mixture stirred for two hours. The benzene was evaporated, water (40ml) added and the product extracted four times with dichloromethane (100ml). The extract was dried (anhydrous sodium sulphate) and triturated with ethanol to give a yellow solid. Recrystalization from ethanol gave a compound whose melting point (135 - 137°C. lit. 137 - 138°C) and I.r. spectrum were identical with that of an authentic sample of thiobenzomorpholide.

3.16 Reaction of thiobenzomorpholide methiodide with the monosodium salt of acetylacetone:

Acetylacetone (1.1 ml; 0.01mol) was added to clean metallic sodium (0.23g; 0.01mol) in benzene (20ml) and refluxed until all the sodium disappeared. To this was added the quaternary salt (3.47g; 0.01mol) and the mixture ice-cooled with stirring for two hours. The benzene was then evaporated, water (40ml) added and the product extracted four times with dichloromethane (100ml). The extract was dried (anhydrous sodium sulphate), concentrated and cooled with scratching. The yellow solid formed was triturated with acetone, filtered and dried (2.16g). Recrystallization from acetone gave a compound whose melting point and i.r. spectrum were identical with that of the starting material.

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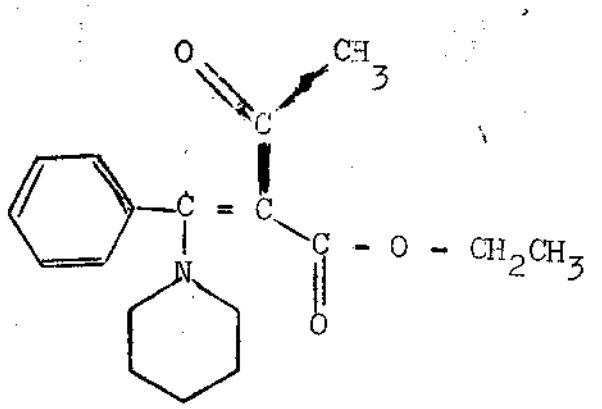
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APPENDIX

The product which was obtained from the reaction of quaternary salt (4; R^1 = Ph, NR^2_2 = piperidino, R^3 = Me) with ethyl acetoacetate that was sent abroad for elemental analysis can now emphatically said to be 1-phenyl-1-piperidino-2-acetyl ethylpropenoate (49) shown below:



Elemental analysis result:

Found C,71.8; H,7.8; N,4.5. $C_{18}H_{23}NO_3$ requires C, 71.8; H,7.6; N,4.7%.

Fig. 1A

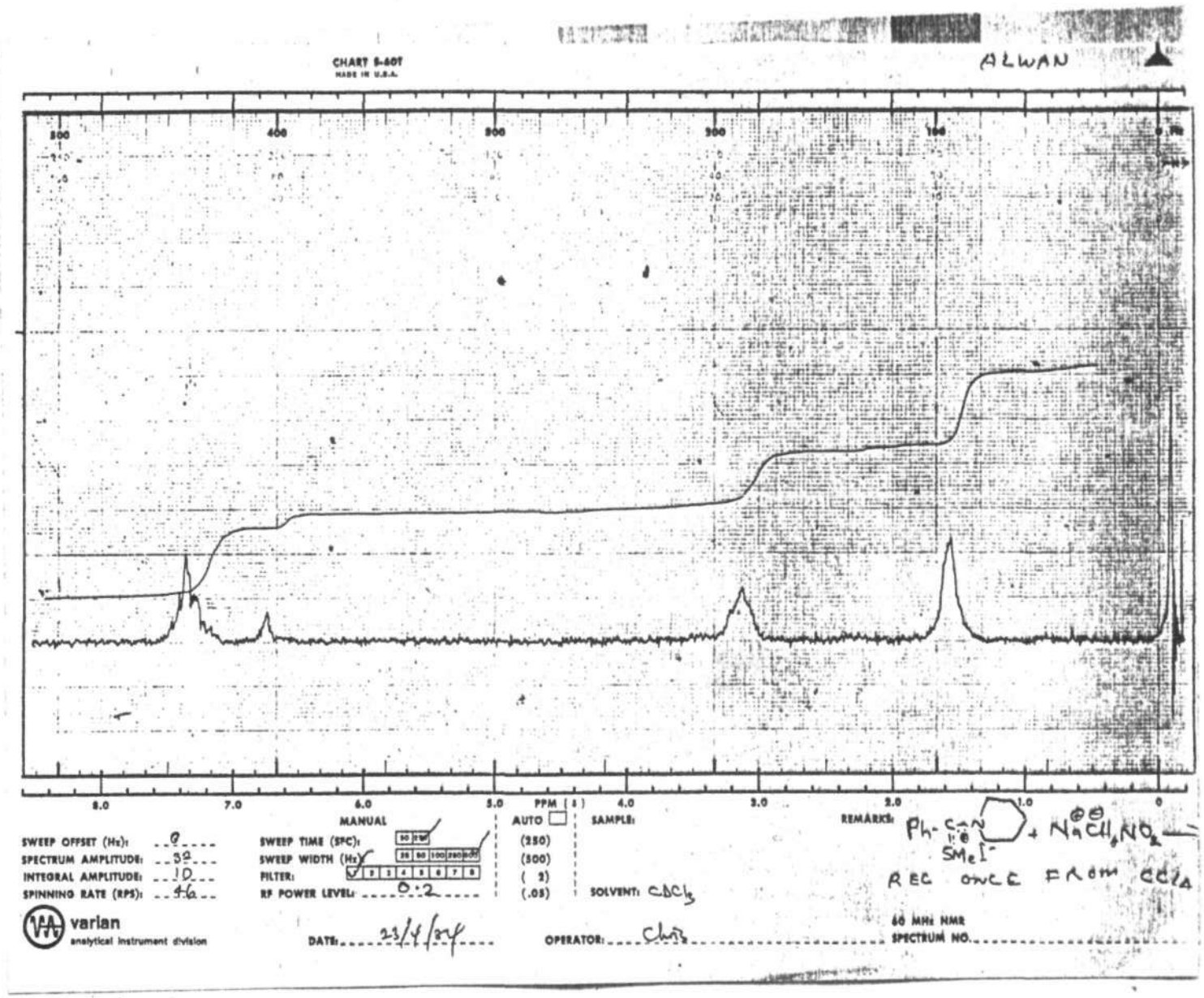

CHART S-60T
MADE IN U.S.A.
ALWAN
500
400
300
200
100
0 PPM
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
MANUAL
AUTO
SWEEP OFFSET (Hz): 0
SPECTRUM AMPLITUDE: 32
INTEGRAL AMPLITUDE: 10
SPINNING RATE (RPS): 46
SWEEP TIME (SPC):
SWEEP WIDTH (Hz):
FILTER:
RF POWER LEVEL: 0.2
(250)
(500)
(2)
(.05)
SAMPLE:
SOLVENT: CDCl3
REMARKS:
Ph-C≡N
SMe I⊖
+ Na⊕ ⊖CH2NO2
REC ONCE FROM CCl4
varian
analytical instrument division
DATE: 23/4/74
OPERATOR: Chris
60 MHz NMR
SPECTRUM NO.

Fig. 1B

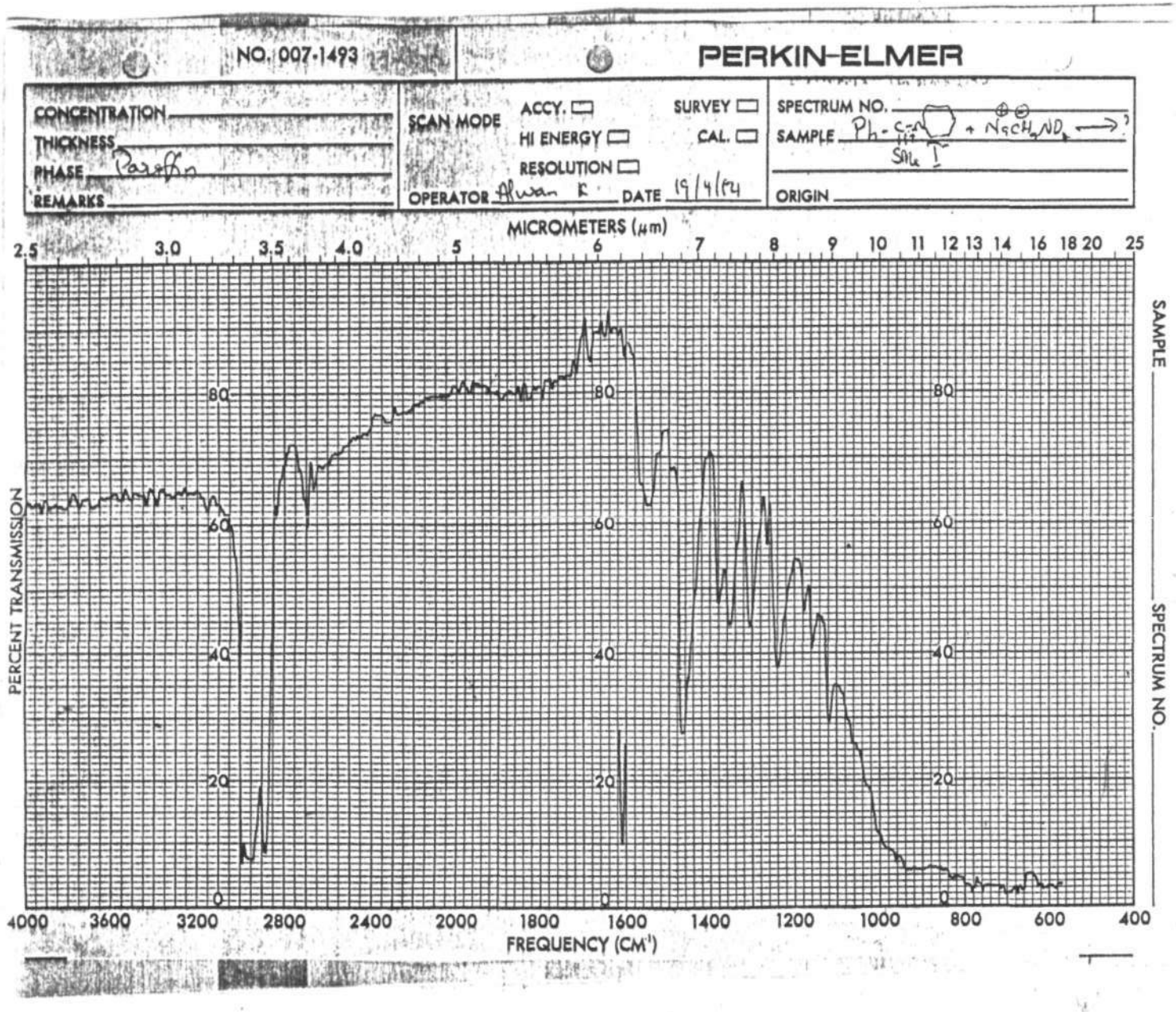

NO. 007-1493
PERKIN-ELMER
CONCENTRATION
THICKNESS
PHASE Paraffin
REMARKS
SCAN MODE
ACCY.
HI ENERGY
RESOLUTION
SURVEY
CAL.
OPERATOR Alwan K
DATE 19/4/84
SPECTRUM NO.
SAMPLE
ORIGIN
MICROMETERS (μm)
2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 16 18 20 25
PERCENT TRANSMISSION
100 80 60 40 20 0
SAMPLE
SPECTRUM NO.
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
FREQUENCY (CM⁻¹)

Fig. 2A

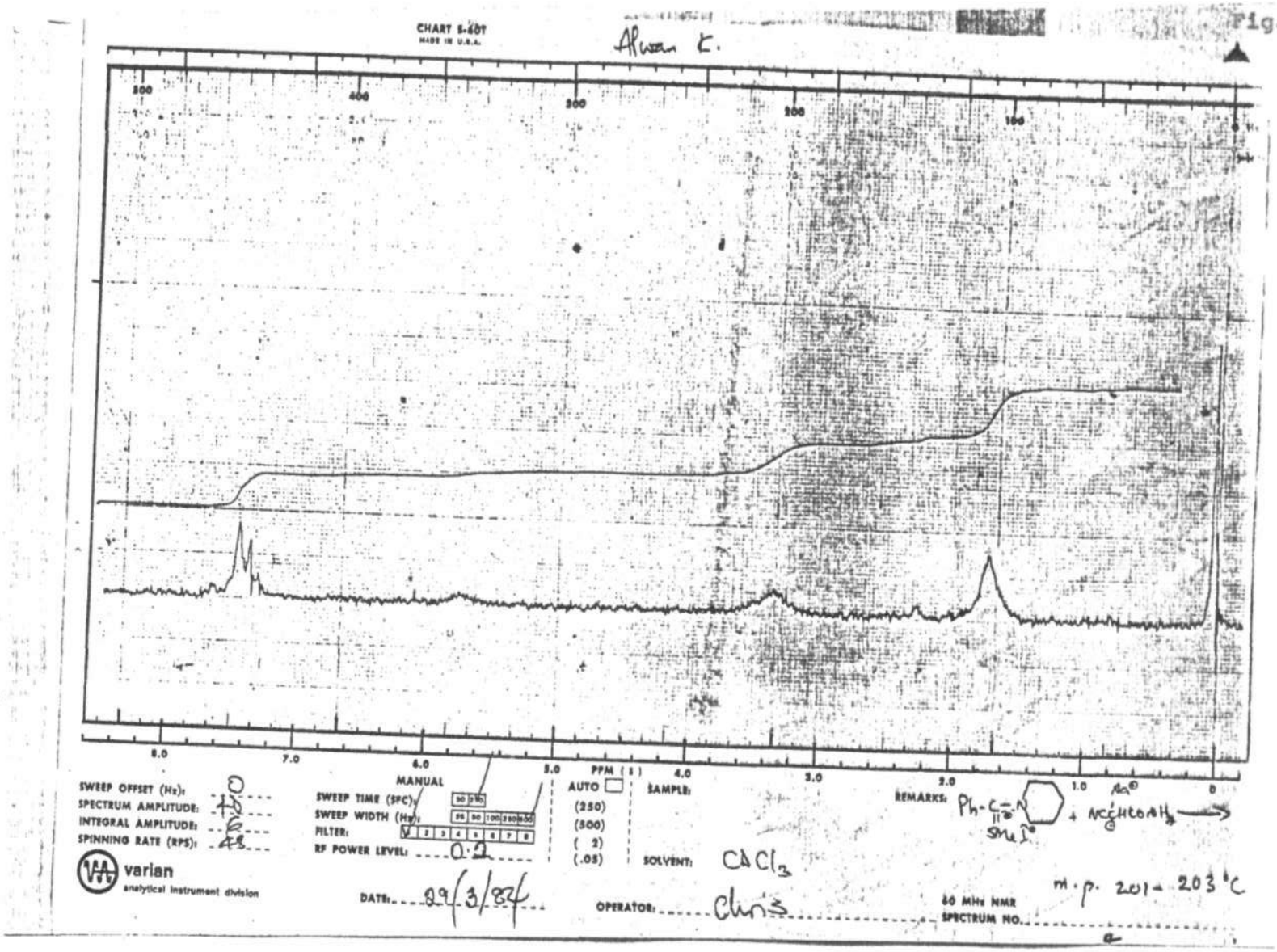

CHART E-60T
MADE IN U.S.A.
Akram K.
500
400
300
200
100
0
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
SWEEP OFFSET (Hz): 0
SPECTRUM AMPLITUDE: 10
INTEGRAL AMPLITUDE: 6
SPINNING RATE (RPS): 48
varian
analytical instrument division
MANUAL
SWEEP TIME (SEC):
SWEEP WIDTH (Hz):
FILTER:
RF POWER LEVEL: 0.2
AUTO
(250)
(500)
(2)
(.05)
SAMPLE:
SOLVENT: CDCl3
REMARKS:
DATE: 29/3/84
OPERATOR: Chris
60 MHz NMR
SPECTRUM NO.
m.p. 201 - 203 °C

Fig. 2B

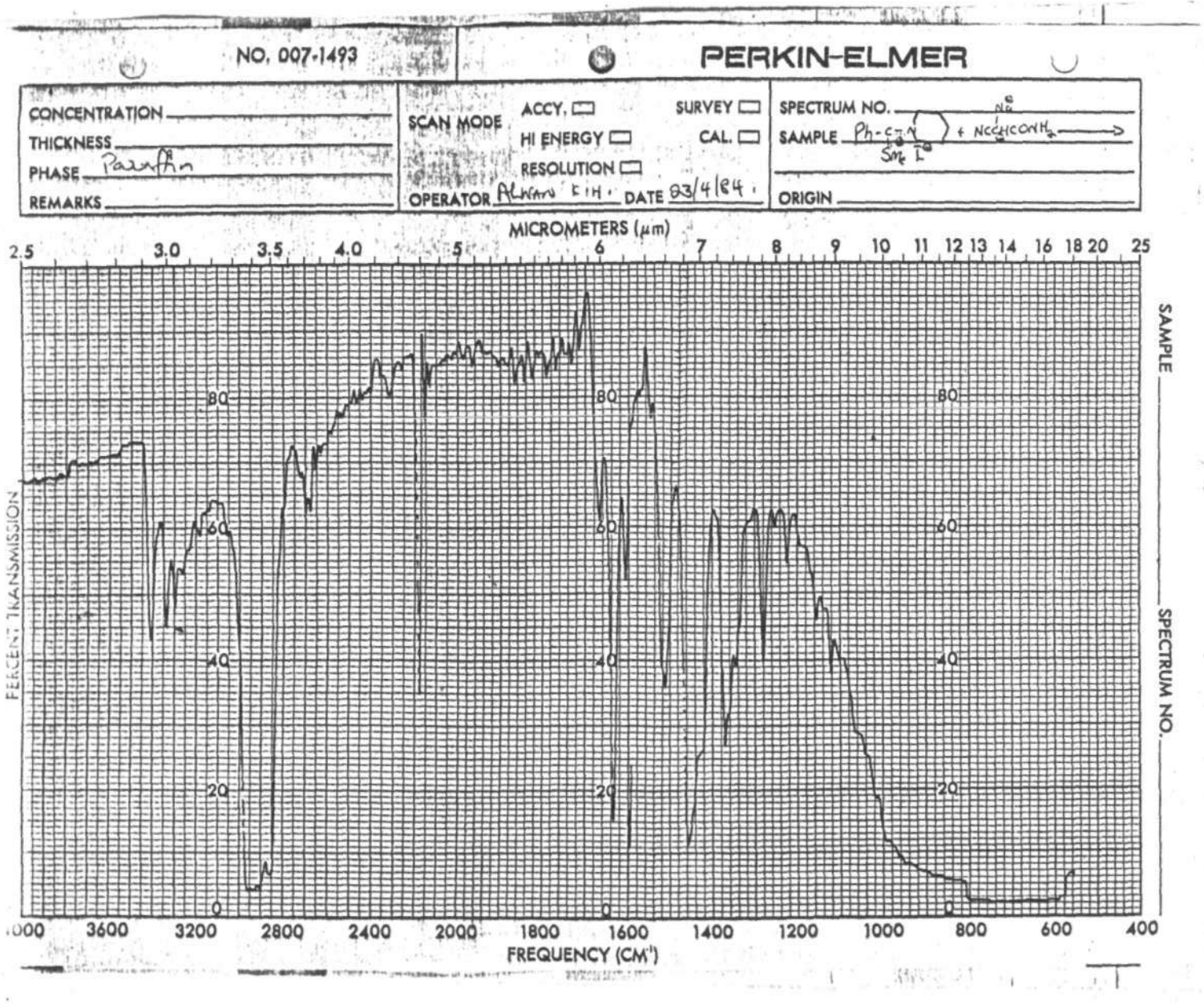

NO. 007-1493
PERKIN-ELMER
CONCENTRATION
THICKNESS
PHASE Paraffin
REMARKS
SCAN MODE
ACCY.
HI ENERGY
RESOLUTION
SURVEY
CAL.
OPERATOR Alvaro C.H. DATE 03/4/84
SPECTRUM NO.
SAMPLE
ORIGIN
MICROMETERS (μm)
2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 16 18 20 25
PERCENT TRANSMISSION
80 60 40 20 0
SAMPLE
SPECTRUM NO.
3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
FREQUENCY (CM⁻¹)

Fig. 3A

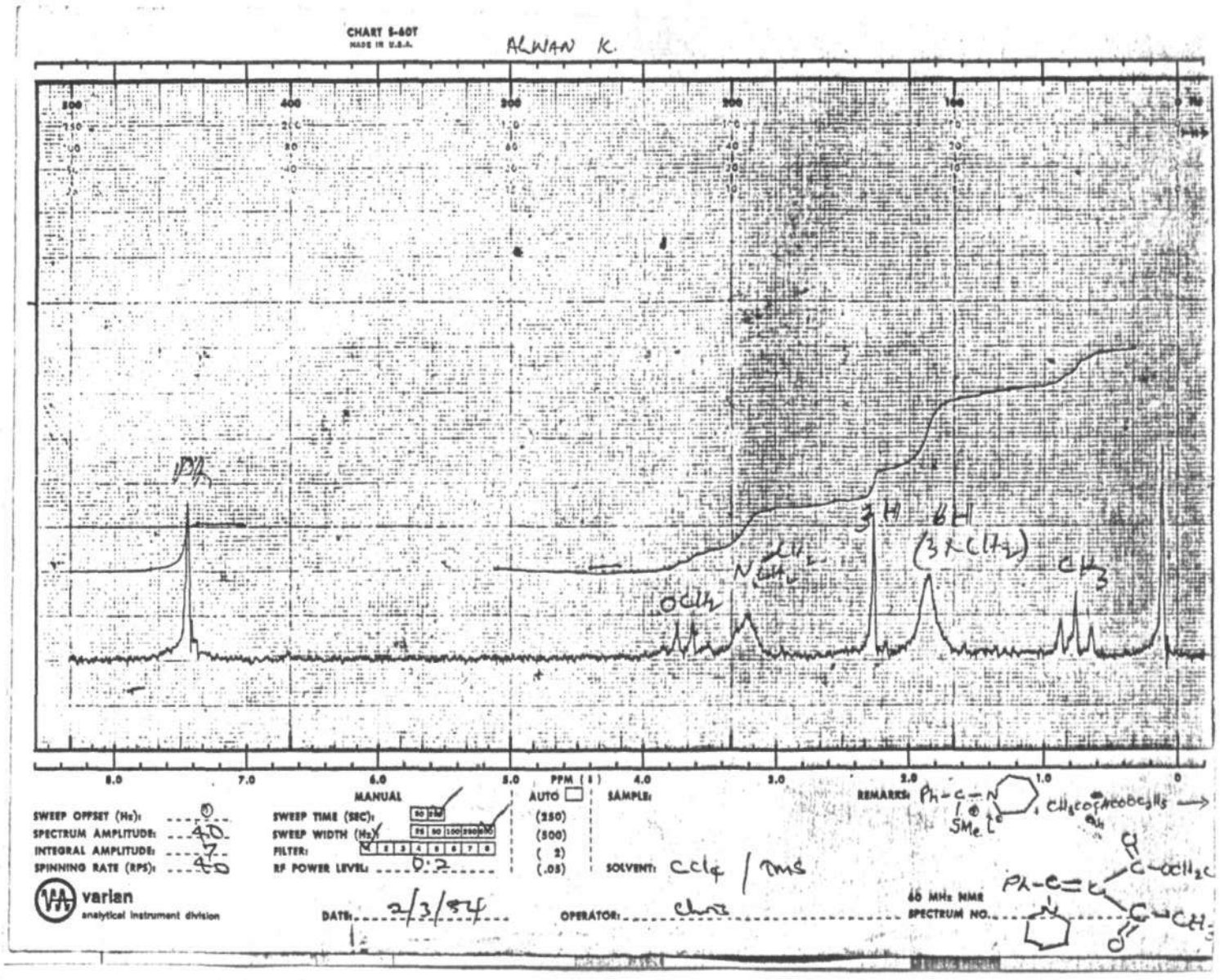

CHART 5-60T
MADE IN U.S.A.
ALWAN K.
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0
MANUAL
AUTO
SWEEP OFFSET (Hz): 0
SPECTRUM AMPLITUDE: 40
INTEGRAL AMPLITUDE: 7
SPINNING RATE (RPS): 40
SWEEP TIME (SEC): (250)
SWEEP WIDTH (Hz): (500)
FILTER: (2)
RF POWER LEVEL: 0.2 (.05)
SAMPLE:
SOLVENT: CCl4 / TMS
REMARKS:
varian
analytical instrument division
DATE: 2/3/54
OPERATOR: chm
60 MHz NMR
SPECTRUM NO.

Fig. 3B

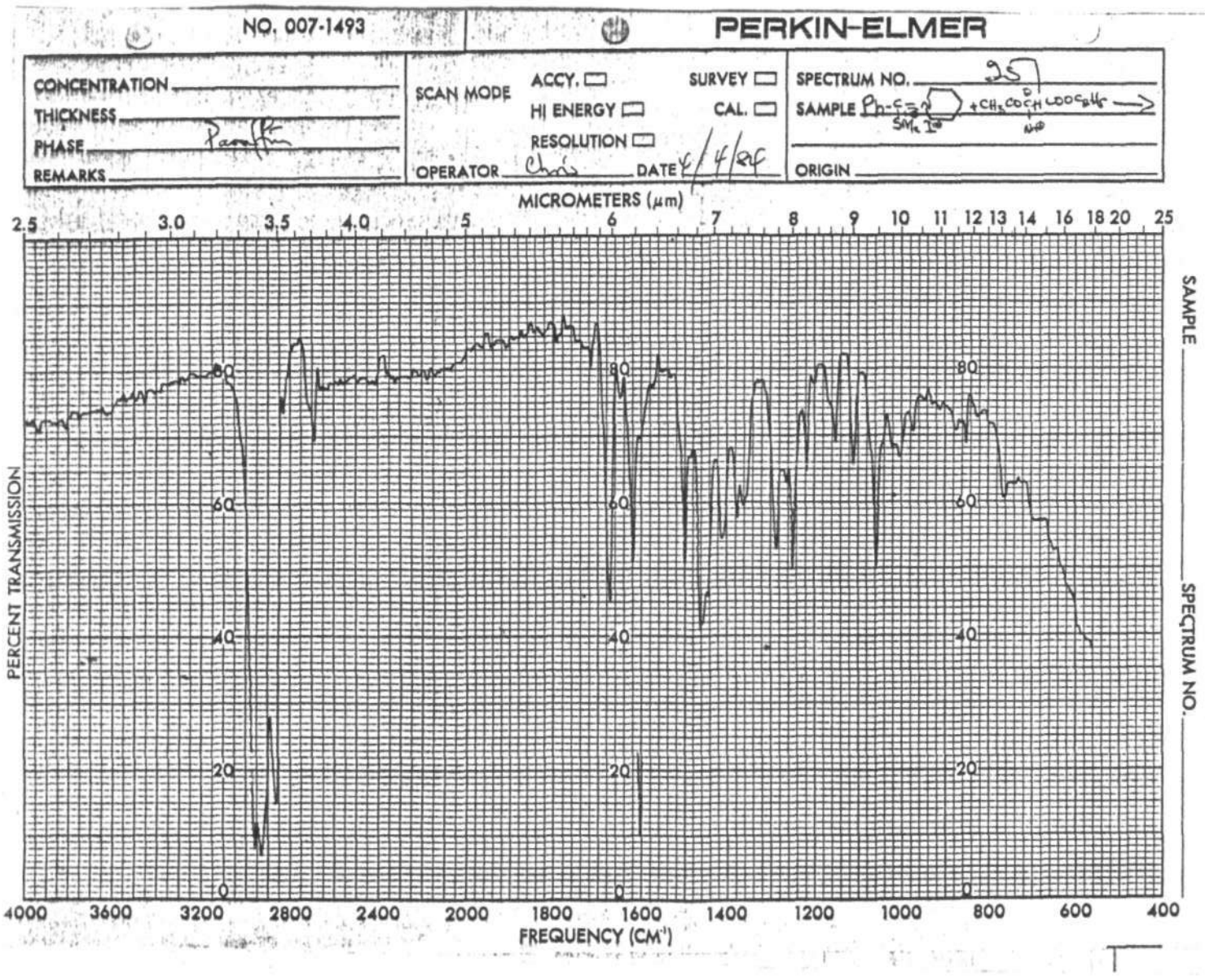

NO. 007-1493
PERKIN-ELMER
CONCENTRATION
THICKNESS
PHASE Paraffin
REMARKS
SCAN MODE
ACCY.
HI ENERGY
RESOLUTION
SURVEY
CAL.
OPERATOR Chris
DATE 4/4/84
SPECTRUM NO. 25
SAMPLE
ORIGIN
MICROMETERS (μm)
2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 16 18 20 25
PERCENT TRANSMISSION
100 80 60 40 20 0
SAMPLE
SPECTRUM NO.
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
FREQUENCY (CM⁻¹)

Fig. 4A

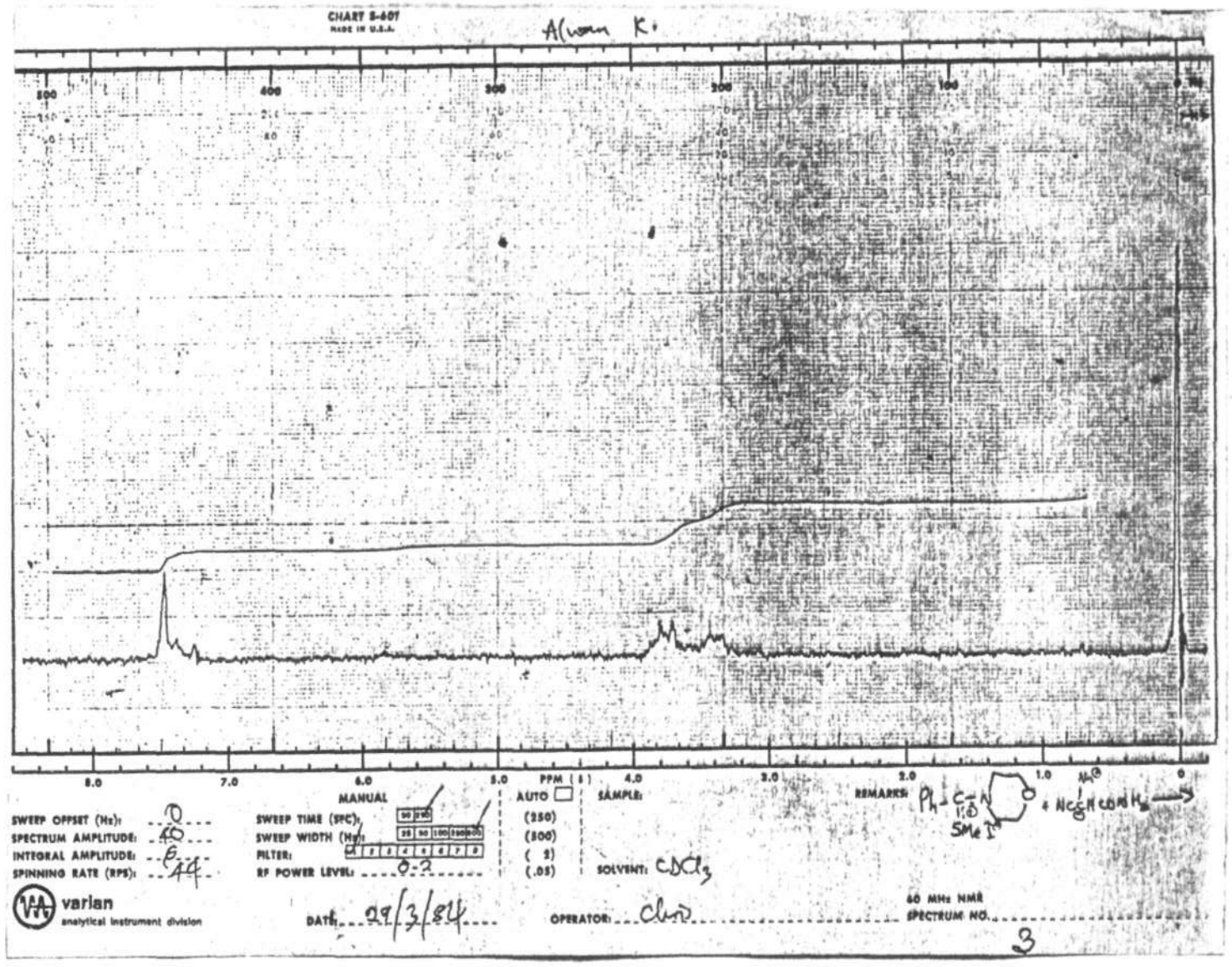

CHART S-60T
MADE IN U.S.A.
Alwan K.
500
400
300
200
100
0
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0
MANUAL
AUTO
SAMPLE:
SWEEP OFFSET (Hz): 0
SPECTRUM AMPLITUDE: 40
INTEGRAL AMPLITUDE: 6.44
SPINNING RATE (RPS): 44
SWEEP TIME (SEC): (250)
SWEEP WIDTH (Hz): (500)
FILTER: (2)
RF POWER LEVEL: 0.2 (.05)
SOLVENT: CDCl3
REMARKS:
SMe I⊖
varian
analytical instrument division
DATE: 29/3/84
OPERATOR: Chm
60 MHz NMR
SPECTRUM NO. 3

Fig. 4B

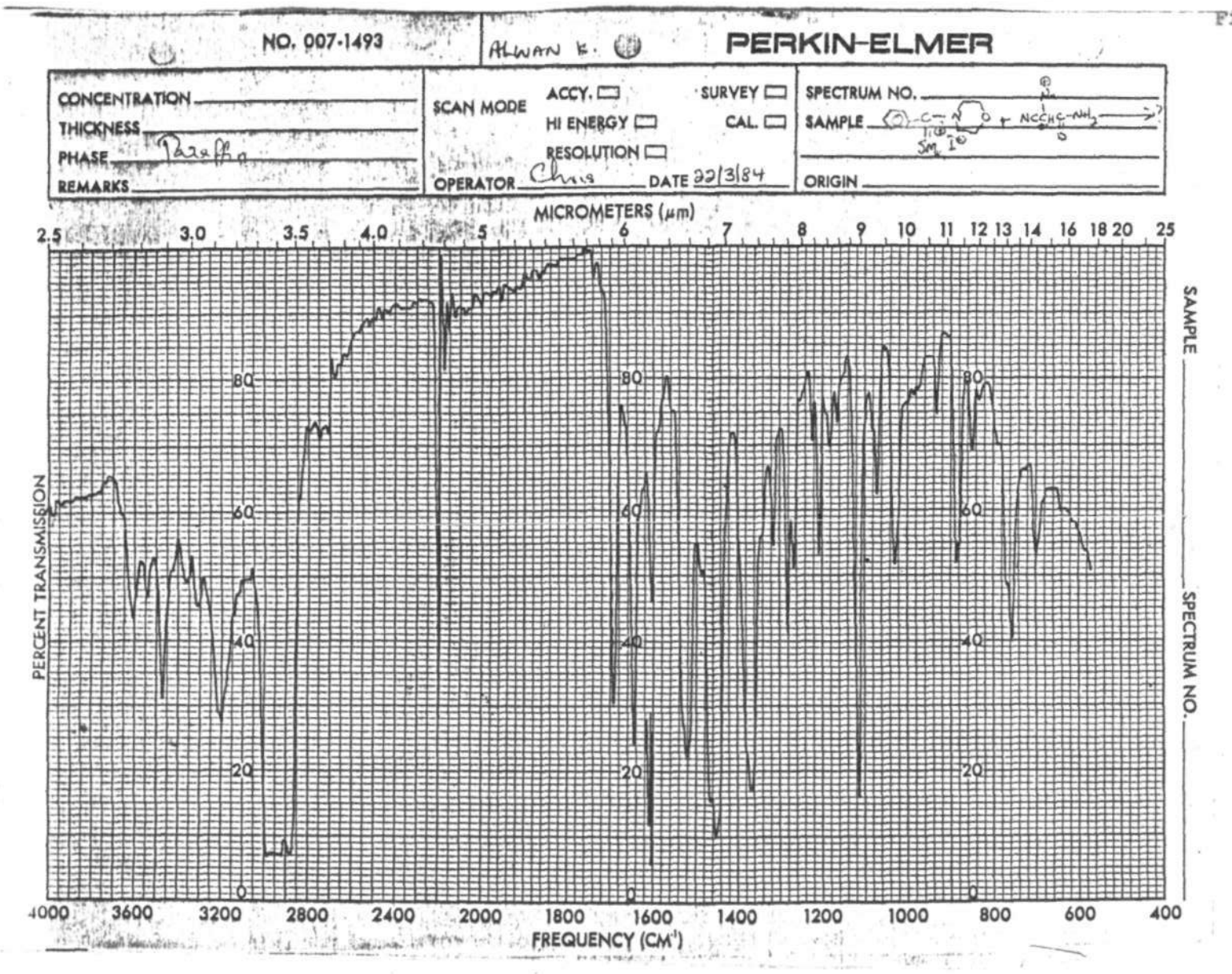

NO. 007-1493
ALWAN K.
PERKIN-ELMER
CONCENTRATION
THICKNESS
PHASE Nujol
REMARKS
SCAN MODE
ACCY.
SURVEY
HI ENERGY
CAL.
RESOLUTION
OPERATOR Chris
DATE 2/3/84
SPECTRUM NO.
SAMPLE
ORIGIN
MICROMETERS (μm)
2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 16 18 20 25
PERCENT TRANSMISSION
100 80 60 40 20 0
SAMPLE
SPECTRUM NO.
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
FREQUENCY (CM⁻¹)

Fig. 5A

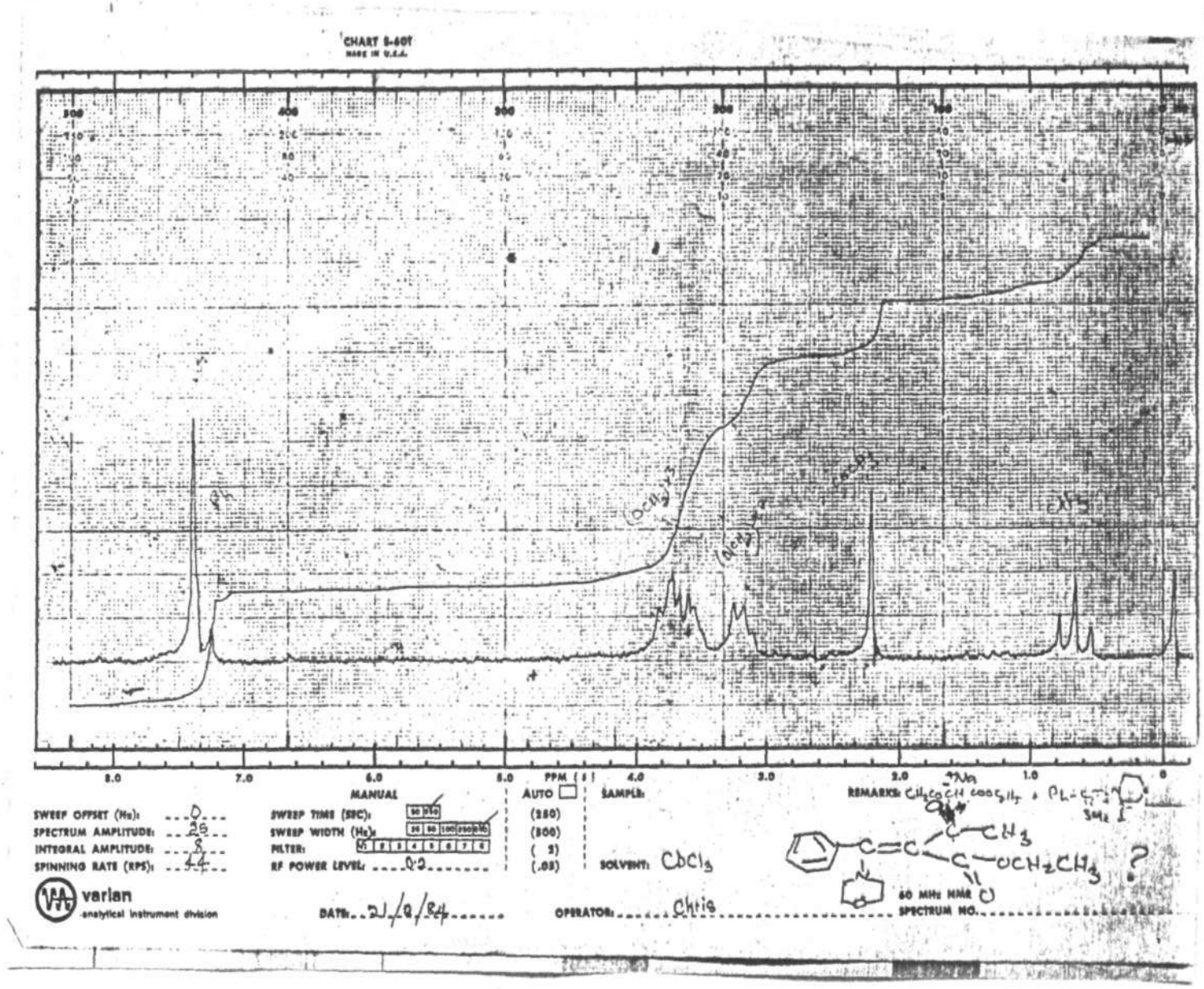

CHART S-60T
MADE IN U.S.A.
8.0
7.0
6.0
5.0 PPM (δ)
4.0
3.0
2.0
1.0
0
MANUAL
AUTO
SWEEP OFFSET (Hz): 0
SPECTRUM AMPLITUDE: 25
INTEGRAL AMPLITUDE: 8
SPINNING RATE (RPS): 44
SWEEP TIME (SEC):
SWEEP WIDTH (Hz):
FILTER:
RF POWER LEVEL: 0.3
(250)
(500)
(2)
(.03)
SAMPLE:
SOLVENT: CDCl3
REMARKS:
varian
analytical instrument division
DATE: 21/9/84
OPERATOR: Chris
60 MHz NMR
SPECTRUM NO.

Fig. 5B

NO. 007-1493

ALWAN K

PERKIN-ELMER

CONCENTRATION

THICKNESS

PHASE Paraffin

REMARKS

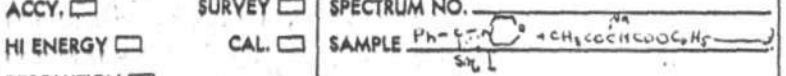
SCAN MODE ACCY. ☐ SURVEY ☐

HI ENERGY ☐ CAL. ☐

RESOLUTION ☐

OPERATOR Chris DATE 21-2-84

SPECTRUM NO.

SAMPLE 

ORIGIN

MICROMETERS (μm)

2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 16 18 20 25

PERCENT TRANSMISSION

100 80 60 40 20 0

4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400

FREQUENCY (CM^{-1})

SAMPLE

SPECTRUM NO.

Fig. 6A

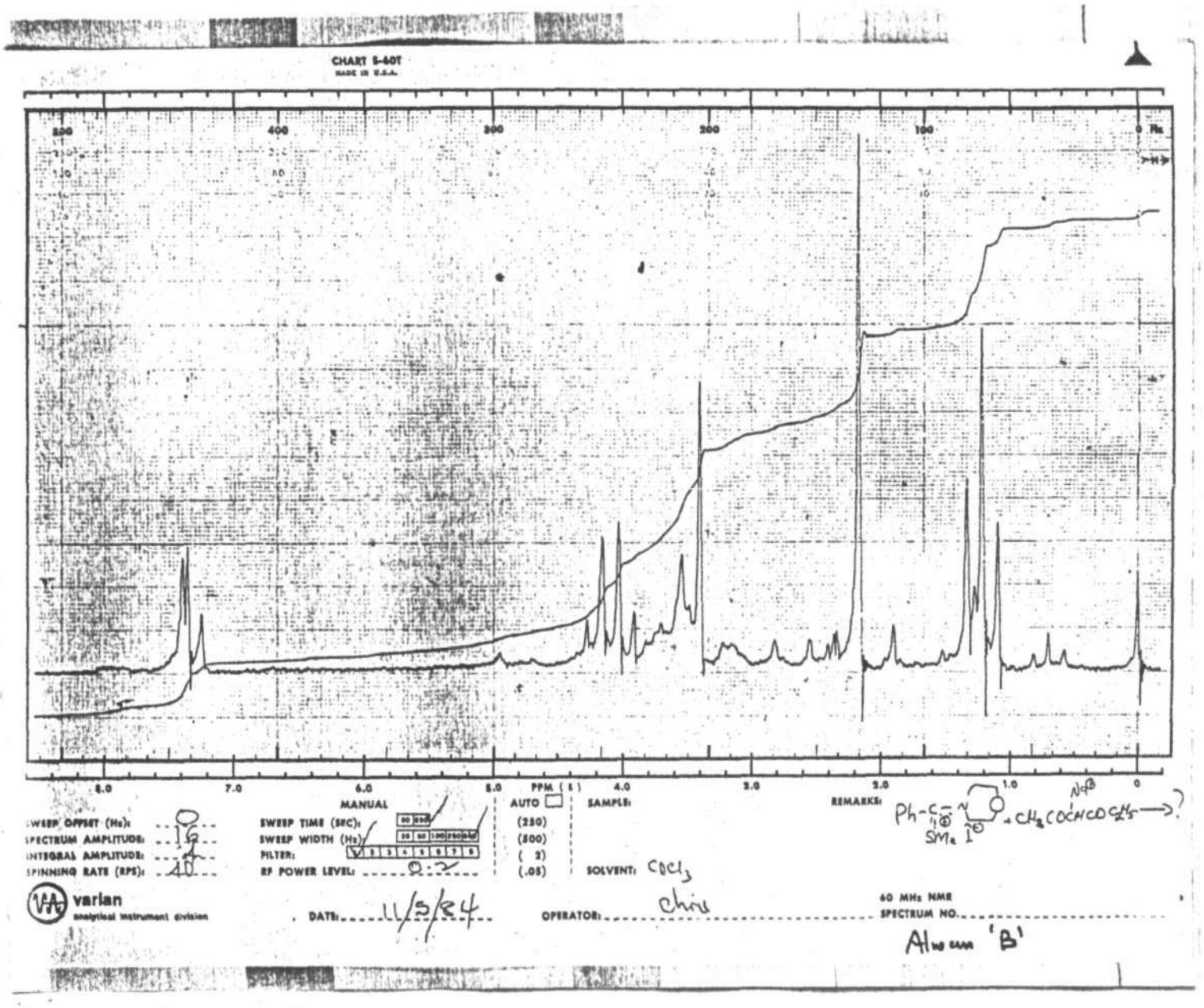

CHART S-60T
MADE IN U.S.A.
500
400
300
200
100
0 Hz
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0
MANUAL
AUTO
SWEEP OFFSET (Hz):
SPECTRUM AMPLITUDE:
INTEGRAL AMPLITUDE:
SPINNING RATE (RPS):
SWEEP TIME (SEC):
SWEEP WIDTH (Hz):
FILTER:
RF POWER LEVEL:
(250)
(500)
(2)
(.05)
SAMPLE:
SOLVENT: CDCl3
REMARKS:
varian
analytical instrument division
DATE: 11/3/64
OPERATOR: Chris
60 MHz NMR
SPECTRUM NO.
Also run 'B'

Fig. 6B

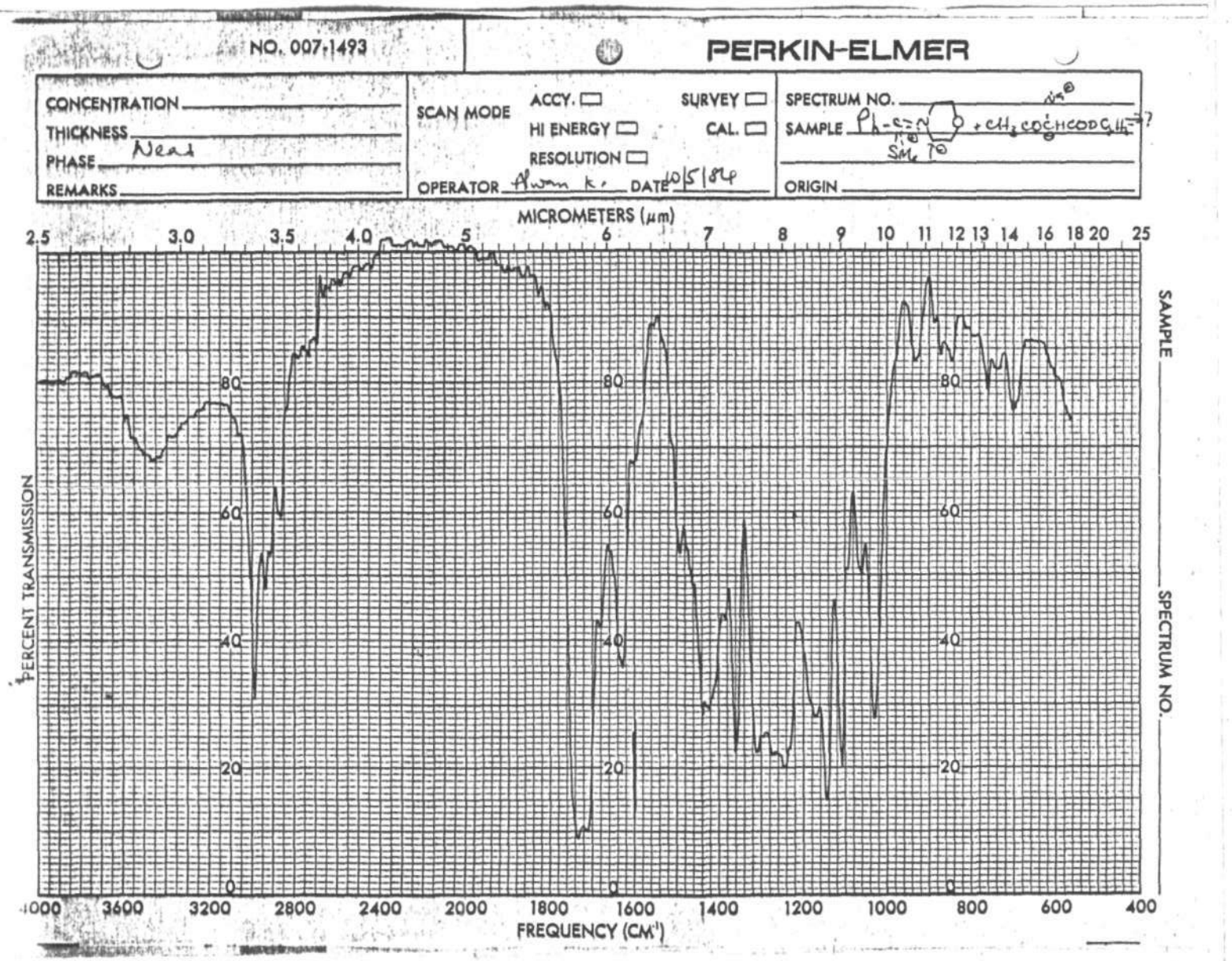

NO. 007-1493
PERKIN-ELMER
CONCENTRATION
THICKNESS
PHASE Neat
REMARKS
SCAN MODE
ACCY.
SURVEY
HI ENERGY
CAL.
RESOLUTION
OPERATOR Awm K. DATE 10/5/84
SPECTRUM NO.
SAMPLE
ORIGIN
MICROMETERS (μm)
2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 16 18 20 25
PERCENT TRANSMISSION
80 60 40 20 0
SAMPLE
SPECTRUM NO.
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
FREQUENCY (CM⁻¹)

Fig. 7A

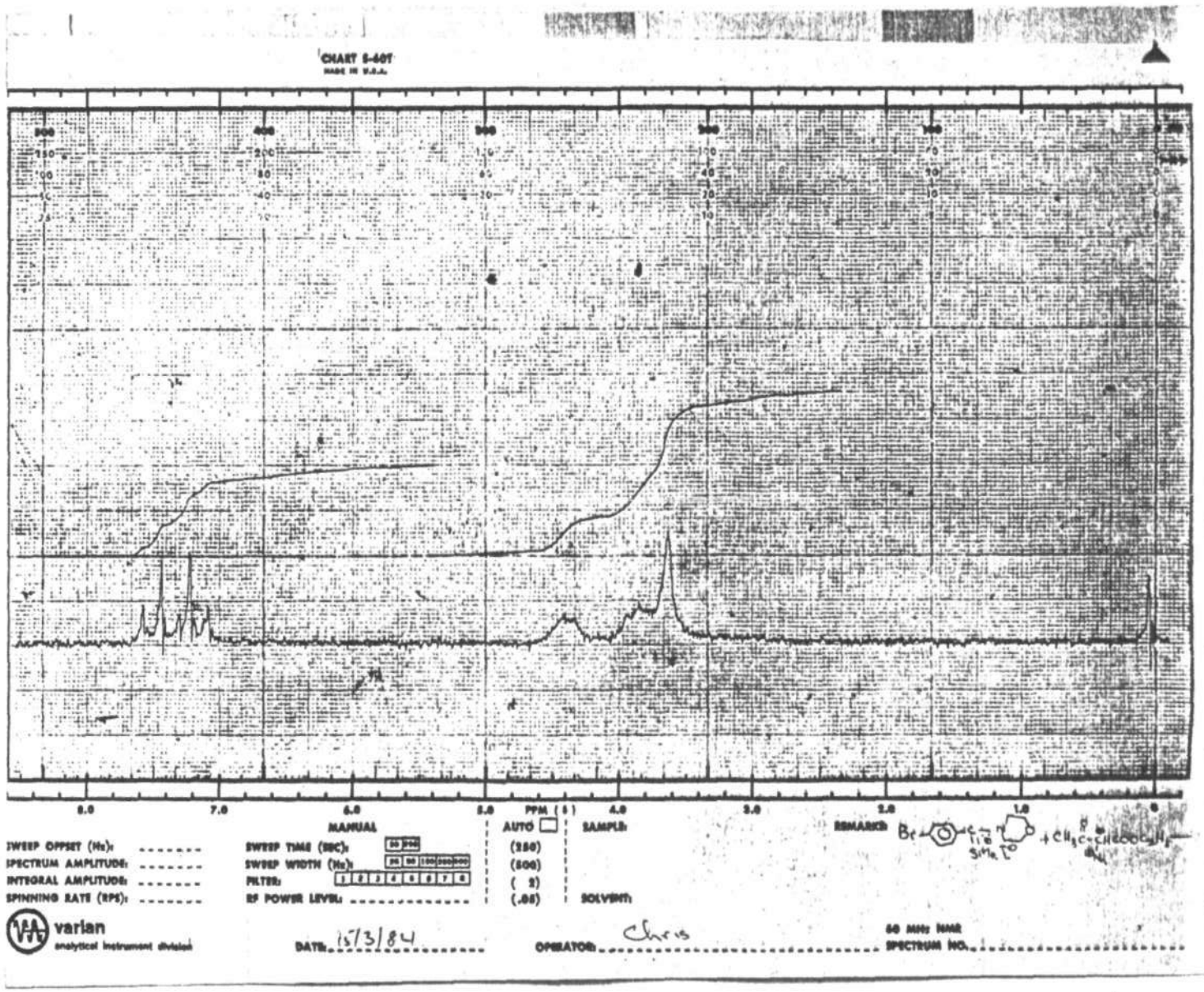

CHART S-60T
MADE IN U.S.A.
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0
MANUAL
AUTO
SAMPLE:
REMARKS:
SWEEP OFFSET (Hz):
SPECTRUM AMPLITUDE:
INTEGRAL AMPLITUDE:
SPINNING RATE (RPS):
SWEEP TIME (SEC):
SWEEP WIDTH (Hz):
FILTER:
RF POWER LEVEL:
(250)
(500)
(2)
(.05)
SOLVENT:
varian
analytical instrument division
DATE 15/3/84
OPERATOR Chris
60 MHz NMR
SPECTRUM NO.

Fig. 7B

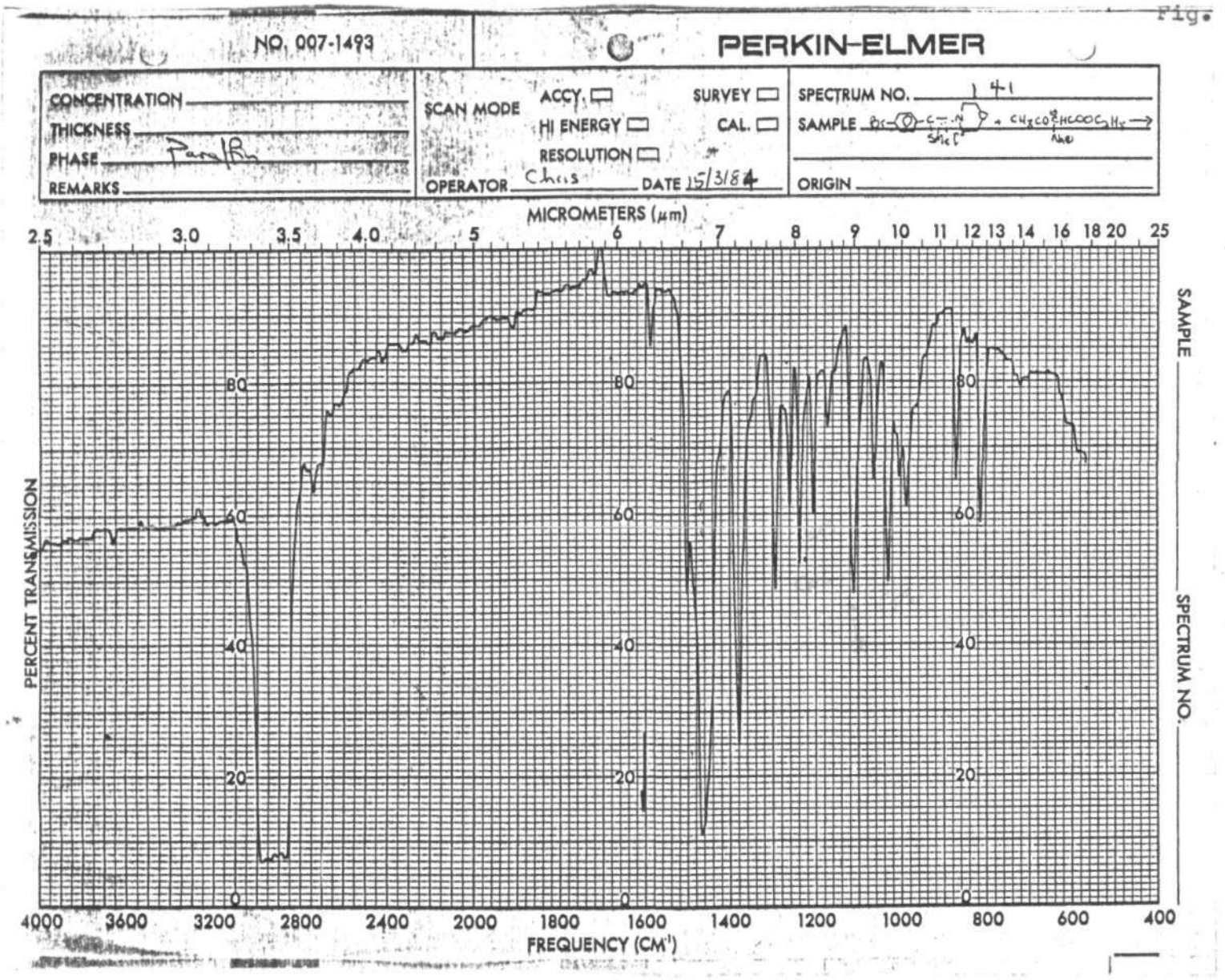
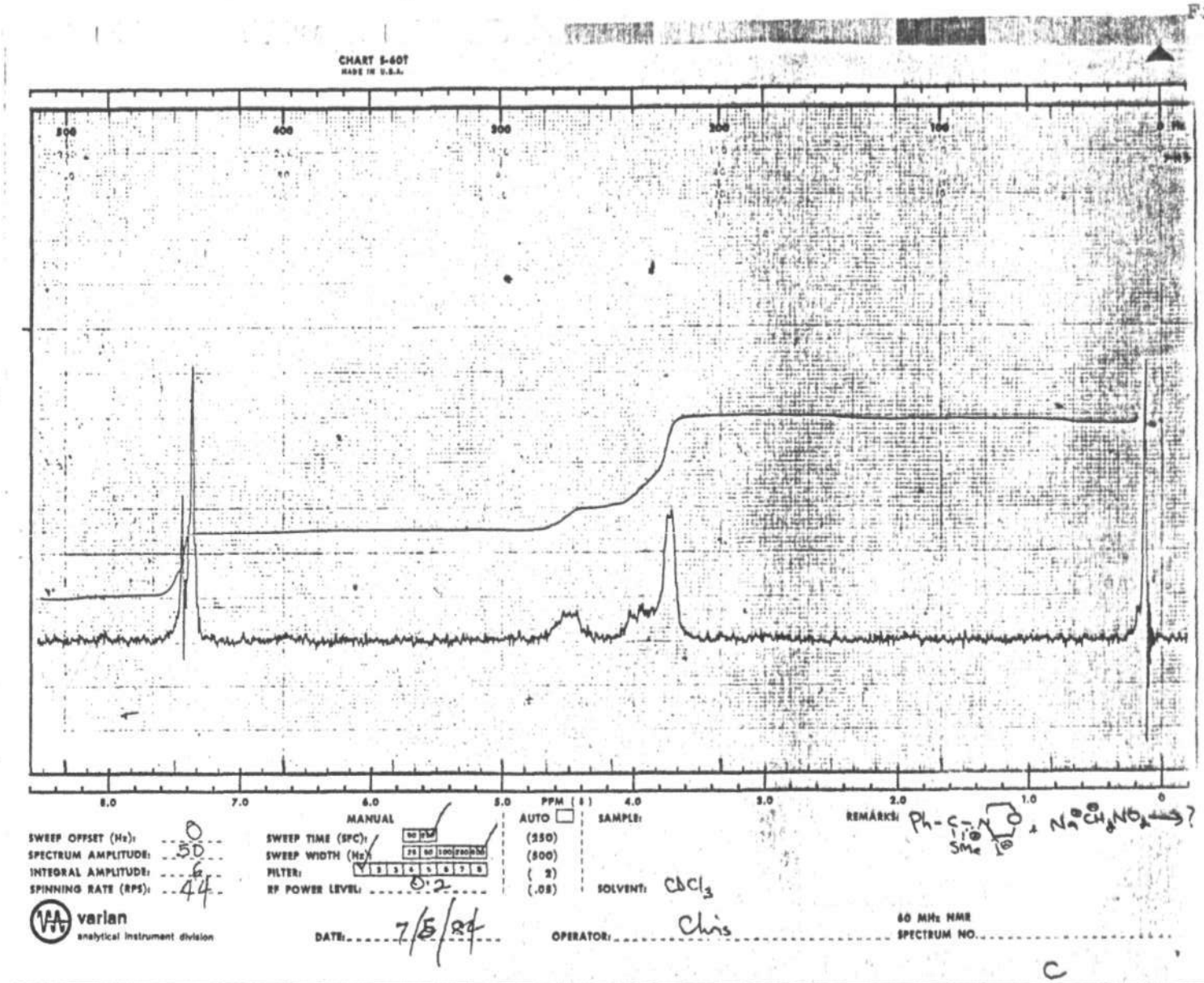

NO. 007-1493
PERKIN-ELMER
CONCENTRATION
THICKNESS
PHASE Pan/Br
REMARKS
SCAN MODE
ACCY.
HI ENERGY
RESOLUTION
SURVEY
CAL.
OPERATOR Chris
DATE 15/3/84
SPECTRUM NO. 141
SAMPLE
ORIGIN
MICROMETERS (μm)
2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 16 18 20 25
PERCENT TRANSMISSION
100 80 60 40 20 0
SAMPLE
SPECTRUM NO.
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
FREQUENCY (CM⁻¹)

Fig. 8A


CHART S-60T
MADE IN U.S.A.
300
400
500
200
100
0 PPM
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0
MANUAL
AUTO
SWEEP OFFSET (Hz): 0
SPECTRUM AMPLITUDE: 50
INTEGRAL AMPLITUDE: 6
SPINNING RATE (RPS): 44
SWEEP TIME (SEC):
SWEEP WIDTH (Hz):
FILTER:
RF POWER LEVEL: 0.2
(250)
(500)
(2)
(.08)
SAMPLE:
SOLVENT: $CDCl_3$
REMARKS:
varian
analytical instrument division
DATE: 7/5/84
OPERATOR: Chris
60 MHz NMR
SPECTRUM NO.
C

NO. 007-1493

PERKIN-ELMER

CONCENTRATION _____
THICKNESS _____
PHASE Solid in Liquid Paraffin
REMARKS _____

SCAN MODE ACCY. ☐ SURVEY ☐
HI ENERGY ☐ CAL. ☐
RESOLUTION ☐
OPERATOR Chris DATE 6/6/84

SPECTRUM NO. 330 A
SAMPLE Ph-C(=N-O)-CH2-CO2Et + NaCH2NO2 → (5 MeI)
ORIGIN _____

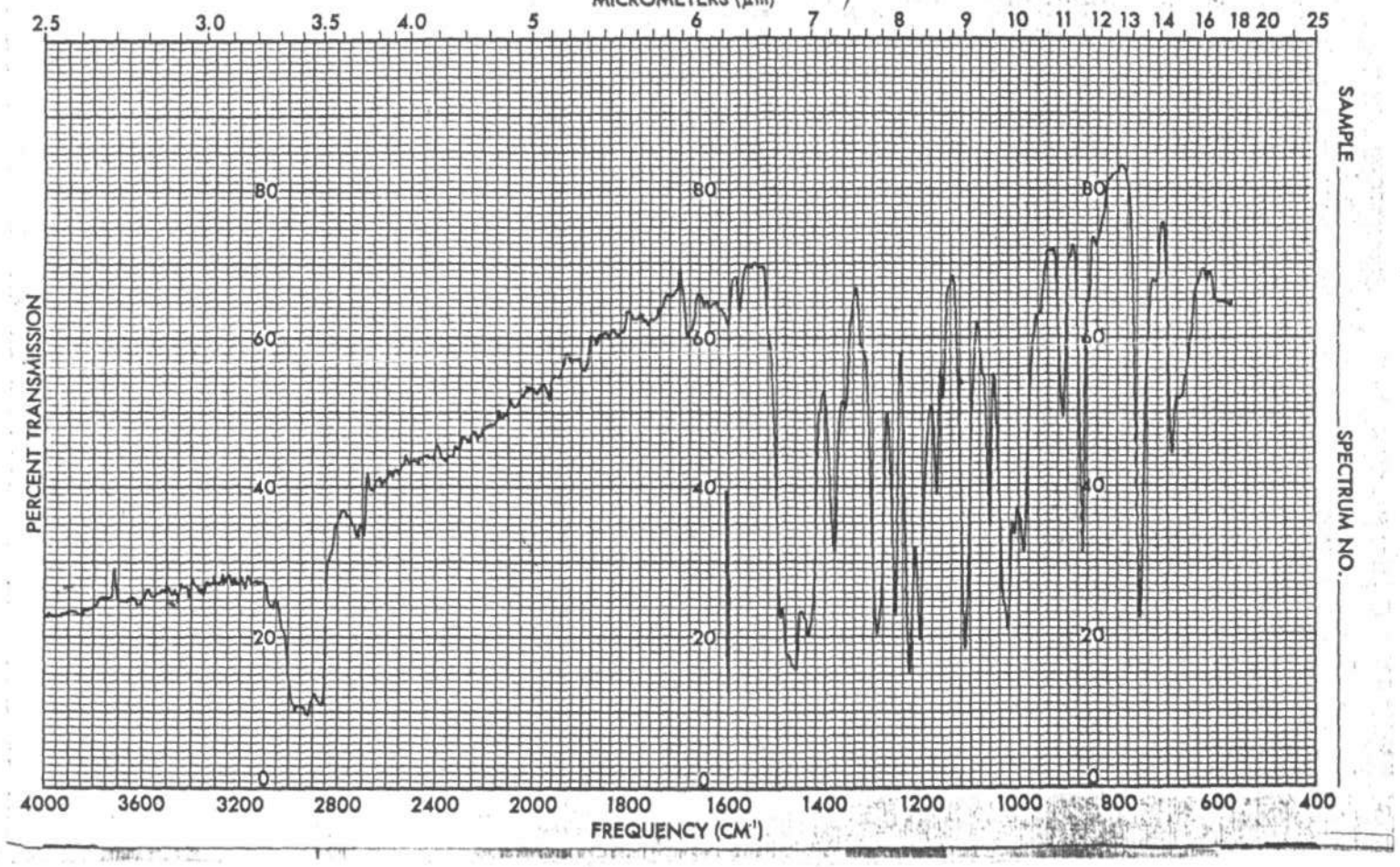


Fig. 9A

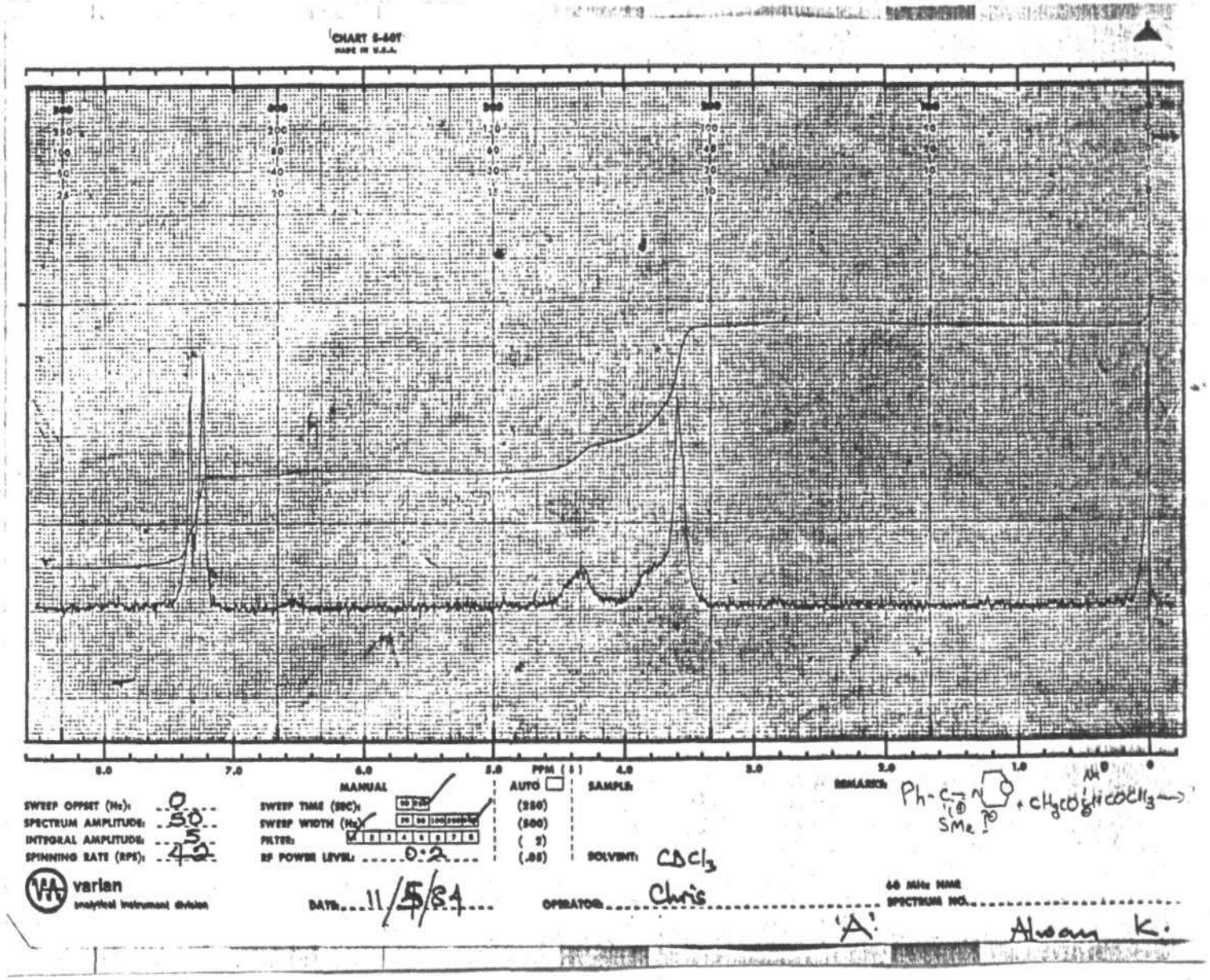

CHART S-60T
MADE IN U.S.A.
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0
MANUAL
AUTO
SAMPLE:
REMARKS:
SWEEP OFFSET (Hz): 0
SPECTRUM AMPLITUDE: 50
INTEGRAL AMPLITUDE: 5
SPINNING RATE (RPS): 45
SWEEP TIME (SEC):
SWEEP WIDTH (Hz):
FILTER:
RF POWER LEVEL: 0.2
(250)
(500)
(2)
(.05)
SOLVENT: CDCl3
varian
analytical instrument division
DATE: 11/5/81
OPERATOR: Chris
60 MHz NMR
SPECTRUM NO.
'A'
Akram K.

Fig. 9B

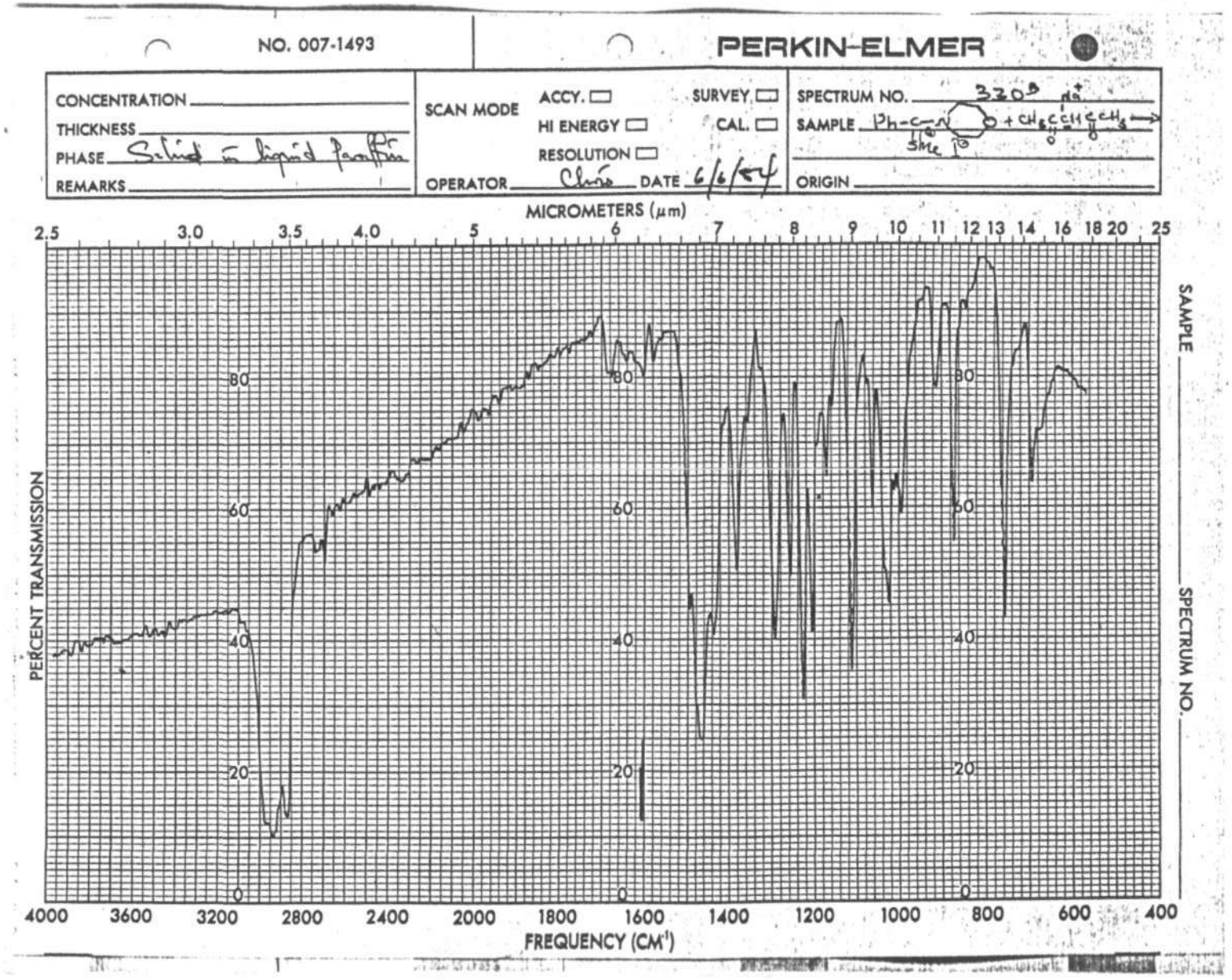

NO. 007-1493
PERKIN-ELMER
CONCENTRATION
THICKNESS
PHASE Solid in liquid paraffin
REMARKS
SCAN MODE
ACCY.
HI ENERGY
RESOLUTION
SURVEY
CAL.
OPERATOR Chris DATE 6/6/74
SPECTRUM NO. 3305
SAMPLE
ORIGIN
MICROMETERS (μm)
2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 16 18 20 25
PERCENT TRANSMISSION
100 80 60 40 20 0
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
FREQUENCY (CM⁻¹)
SAMPLE
SPECTRUM NO.

Fig. 10A

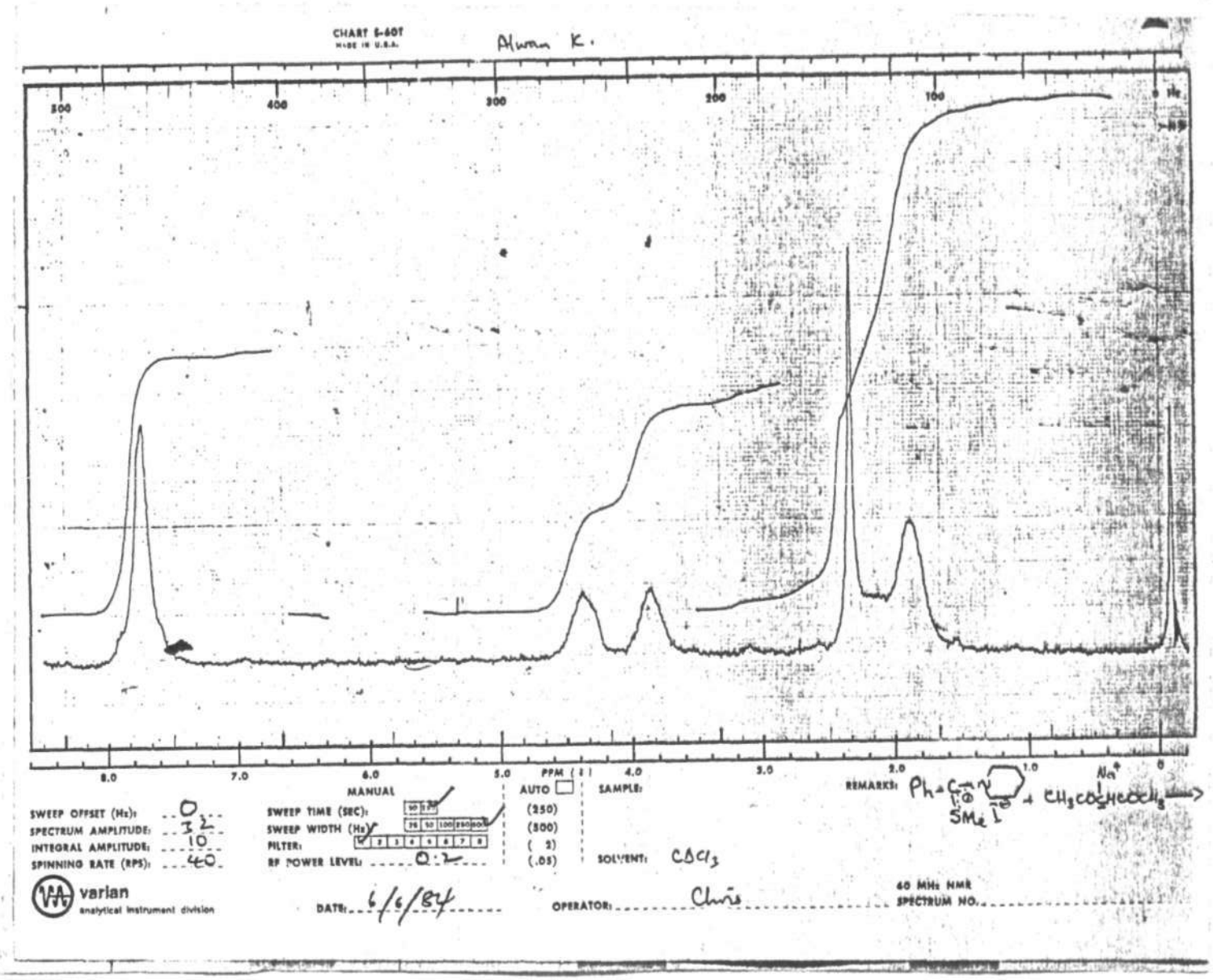
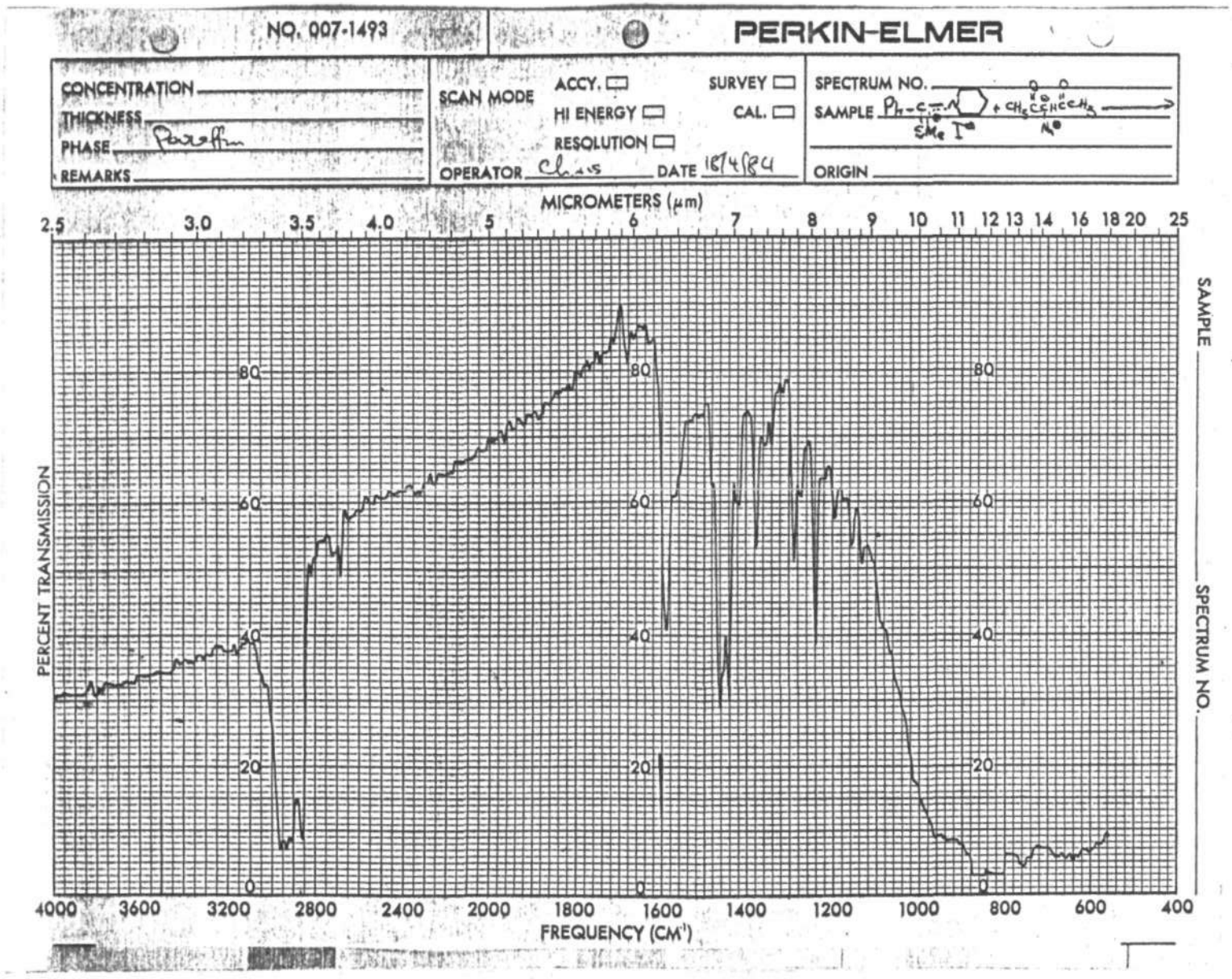

CHART S-60T
MADE IN U.S.A.
Alwin K.
500
400
300
200
100
0 Hz
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0
MANUAL
AUTO
SWEEP OFFSET (Hz): 0
SPECTRUM AMPLITUDE: 32
INTEGRAL AMPLITUDE: 10
SPINNING RATE (RPS): 40
SWEEP TIME (SEC):
SWEEP WIDTH (Hz)
FILTER:
RF POWER LEVEL: 0.2
(250)
(500)
(2)
(.05)
SAMPLE:
SOLVENT: CDCl3
REMARKS:
varian
analytical instrument division
DATE: 6/6/84
OPERATOR: Chris
40 MHz NMR
SPECTRUM NO.

Fig. 10B


NO. 007-1493
PERKIN-ELMER
CONCENTRATION
THICKNESS
PHASE Paraffin
REMARKS
SCAN MODE
ACCY.
HI ENERGY
RESOLUTION
SURVEY
CAL.
OPERATOR Chris
DATE 10/4/84
SPECTRUM NO.
SAMPLE
ORIGIN
MICROMETERS (μm)
2.5 3.0 3.5 4.0 5 6 7 8 9 10 11 12 13 14 16 18 20 25
PERCENT TRANSMISSION
SAMPLE
SPECTRUM NO.
100 80 60 40 20 0
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
FREQUENCY (CM⁻¹)