

A Thesis
entitled

SYNTHESIS AND CHARACTERIZATION
OF
SOME THIOPYRAN COMPOUNDS

Presented by
Mrs. Kishwar Jahan

in partial fulfilment of the requirements of
for the degree of
MASTER OF PHILOSOPHY



DEPARTMENT OF CHEMISTRY
BANGLADESH UNIVERSITY OF ENGINEERING & TECHNOLOGY
DHAKA




April, 1988.

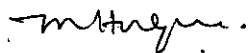
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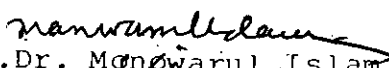
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The thesis entitled, "SYNTHESIS AND CHARACTERIZATION OF SOME THIOPYRAN COMPOUNDS", submitted by Mrs. Kishwar Jahan, has been unanimously approved for the degree of MASTER OF PHILOSOPHY.

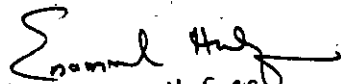
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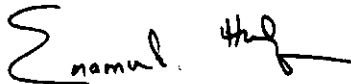

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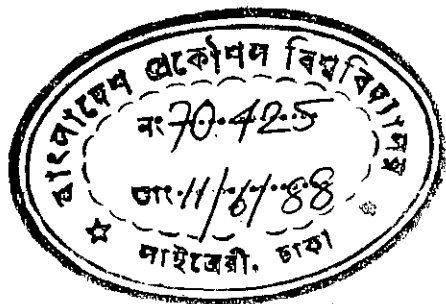
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CHAPTER ONE



INTRODUCTION

Since this research is concerned with the preparation and characterisation of compounds containing thiopyran groups, it was thought interesting to carry out a literature survey on the synthesis and reactions of thiopyrans and their derivatives.

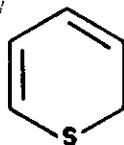
The following pages describe what has been possible to collect on this field from the literature available in this country.

Later on, after the literature survey, the aim and the historical background of the project have been described.

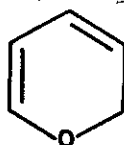
AN UP-TO-DATE REVIEW ON THIOPYRAN AND SOME OF
THEIR IMPORTANT DERIVATIVES

1.1 INTRODUCTION:

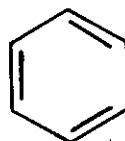
Thiopyrans are six-numbered heterocyclic compounds containing sulphur as the hetero atom. They contain methylene groups like pyrans do and lack the conjugated cyclic double bond system which benzene or pyridine has. They are thus unsaturated sulphur-heterocyclic compounds containing only two conjugated double bonds. They are not aromatic in character.



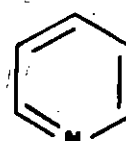
2H-Thiopyran
or
 α - Thiopyran



Pyran



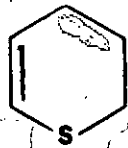
Benzene



Pyridine

1.2 CLASSIFICATION:

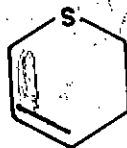
Thiopyrans are classified according as which one or how many of the two double bonds are hydrogenated.



3,4-Dihydro-2H-thiopyran

or

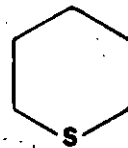
Δ^2 -Dihydrothiopyran



5,6-Dihydro-2H-thiopyran

or

Δ^3 -Dihydrothiopyran



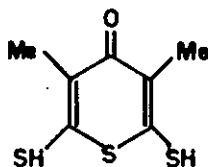
Tetrahydro-
thiopyran

The sign delta, Δ , signifies the presence of a double bond and the superfix signifies the position of the double bond. Other derivatives of thiopyran form other classes of compounds which are described below.

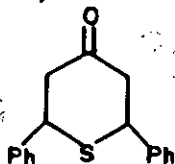
Thiopyrones:

Thiopyrones are six-membered sulphur heterocyclic keto compounds, derived from parent thiopyran compounds by the replacement of a methylene group with a carbonyl group.

As for example:



2,6-Dimercapto-3,5-dimethyl-4-thiopyrone



2,6-Diphenyltetrahydro-4-thiopyrone

Thiopyrilium salts:

Thiopyrilium salts contain "thiopyrylium ions" which are six-membered positively charged sulphur heterocyclic compounds where two electrons are removed from either 2H- or 4H-thiopyran rings with the simultaneous participation of the unshared pair of electrons of the sulphur. They are considered as "aromatic" or "pseudo-aromatic", since they follow the Hückel $(4n + 2) \uparrow$ electrons rule. As for example,



Thiopyrilium ions.

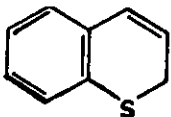
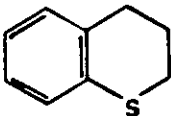
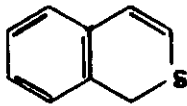
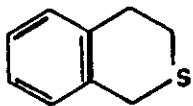
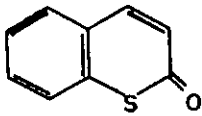
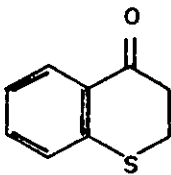
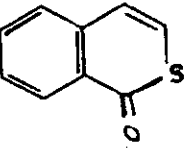
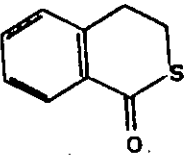
There are some other types of thiopyran compounds which originate from fusing a thiopyran ring with benzene or other ring systems.

The fusions occur at two positions:

- a) 5,6 fusion gives normal thiopyran and above categories of compounds; and
- b) 3,4 fusion gives the "isothiopyran compounds".

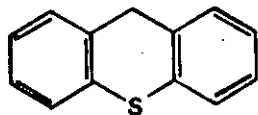
Table 1 gives some examples.

Table 1. Different Types of Thiopyran Compounds
Derived From Fusing Benzene Rings

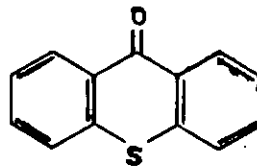
	Fusion of one benzene ring at 5,6 position		Fusion of benzene ring at 3,4 position	
	Of thiopyran	Of dihydrothiopyran	Before hydrogenate	After hydrogenated
Formula				
Name	2H-Thiachromene	Thia chroman or 1-- Thiatetra- lin	iso-Thia- chromene	iso-Thia- chroman
Formula				
Name	α -Thia- chromone	Thia- chromanone	iso-Thia- counarin	iso-Thia- chromanone

When two or more benzene rings are attached with the main structure of thiopyran type of compound, then they may have angular or linear structures.

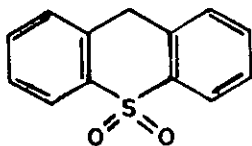
i) Linearly fused ring systems containing thiopyran structure:



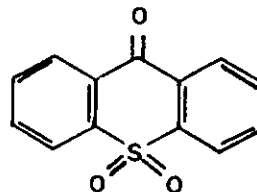
Thioxanthene



Thioxanthone

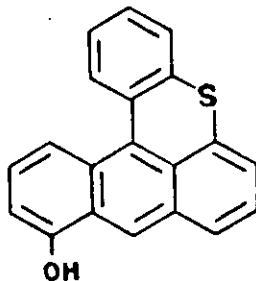


Dibenzothiopyran S-dioxide



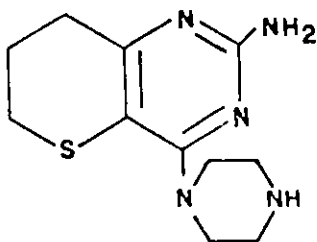
Dibenzothiopyrone S-dioxide

ii) Angular type of structure:



9-Hydroxycerothiene

There are many other thiopyran derivatives which are not under the above category. As for example:



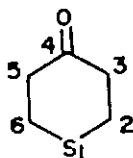
2-amino-7, 8-dihydro-4- piperidinyl- 6H- thiopyran
(3,2 - d)pyrimidine

1.3 NOMENCLATURE AND NUMBERING

There are no uniform systems of nomenclature for thiopyrans. This non-uniformity has often caused confusion. Whereas until recently, especially in the German literature, compounds in which the ring oxygen was replaced by sulphur were designated by "thia", on the other hand the thiocarbonyl group was characterised by the prefix "thio". Now-a-days all compounds derived by replacement of oxygen by sulphur take the prefix "thio", irrespective of whether the ring or the carbonyl oxygen atom has been substituted. There are a number of conventions, concerning the numbering of the atoms and substituents in simple heterocyclic rings. The IUPAC system is described below:

- (1) In a simple heterocyclic system, the hetero atom is counted as number 1 atom.
- (2) Then substituents are given the lowest possible numbers and then are arranged in alphabetical order.

As for example:

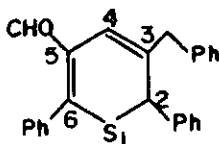


Tetrahydro-4-thiopyrones.

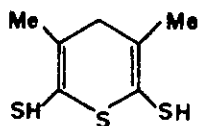
In compounds with maximum unsaturation, if the double bonds can be arranged in more than one way, their positions

are defined by indicating the sulphur or carbon atom which are not multiply bonded and consequently carry on "extra" hydrogen atom by 1H-, 2H- etc.²

For example:

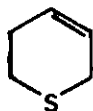


3-Benzyl-2,6-diphenyl-2H-thiopyran-5-carboxaldehyde



2,6-Dimercapto-3,5-dimethyl-4H-thiopyran.

Now in partially saturated compounds, the positions of the hydrogen atoms can be indicated by 1,2-dihydro etc. (together with the 1H-type notation if necessary).² Alternately the positions of the double bonds can be specified by the Greek letter Δ . For example:



5,6-Dihydro-2H-thiopyran
or
 Δ^3 -Dihydrothiopyran

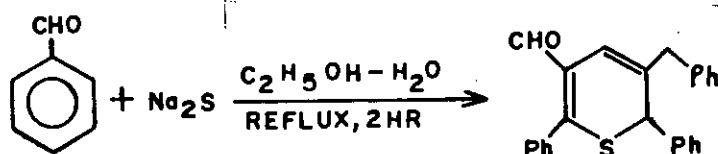
Nomenclature and numbering become more complicated for condensed or fused ring systems and is outside the scope of the present review.

1.4 PREPARATION OF THIOPYRAN TYPE OF COMPOUNDS:

The parent compound, 2H-thiopyran is not known. However, their derivatives are known.

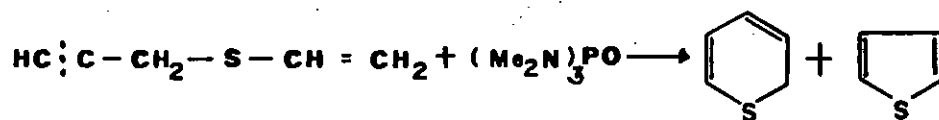
3-Benzyl-2,6-diphenyl-2H-thiopyran-5-carboxaldehyde:

The compound (I) was prepared by Latif and co-workers by refluxing benzaldehyde with sodium sulphide in aqueous ethanol.^{3,4,5}



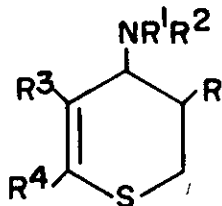
2H-Thiopyran and derivatives:

2H-thiopyran and a number of derivatives were obtained in fair to good yields by heating compounds containing the system C:CCSC:C in (Me₂N)₃PO. Mixture of 2H-thiopyrans and thiophenes are formed when heating is performed in this solvent or in dimethyl sulphoxide in the presence of amines.



Thiopyrans, having an alkyl group on ring C-atom 4, are partly converted into the exo compounds, 4-alkylidene-2,3-dihydro-4H-thiopyrans.⁶

Thiopyrans of the type, II, were prepared by 1,4-cycloaddition of $\text{CH}_2\text{:CHR}$ with $\text{R}^4\text{CSCR}^3\text{:CHNR}^2\text{R}^1$. Subsequently elimination gave, the derivatives of 2H-thiopyran III, which were quaternized⁷ with $\text{Ph}_3\text{C}^+\text{ClO}_4^-$.

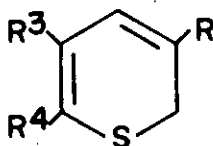


II. $\text{NR}^1\text{R}^2 = \text{NMe}_2, \text{NEt}_2, \text{piperidino},$

1-pyrrolidinyl, morpholino, $\text{NHC}_6\text{H}_4\text{Me-4}$

$\text{R}^3 = \text{H}, \text{Ph}; \text{R} = \text{CONH}_2, \text{CN}, \text{CH}_3\text{CO}$

$\text{R}^4 = \text{C}_6\text{H}_4\text{OMe-4}, \text{C}_6\text{H}_4\text{Br-4}, \text{C}_6\text{H}_4\text{Cl-4}, 2\text{-thienyl}, \text{SMe}$



III

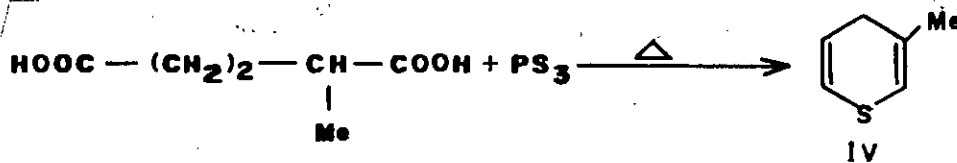
III. $\text{R} = \text{CONH}_2, \text{COOMe}, \text{CN}, \text{CHO}$

$\text{R}^3 = \text{H}, \text{Ph}$

$\text{R}^4 = \text{C}_6\text{H}_4\text{OMe-4}, \text{C}_6\text{H}_4\text{Br-4}, \text{SMe}.$

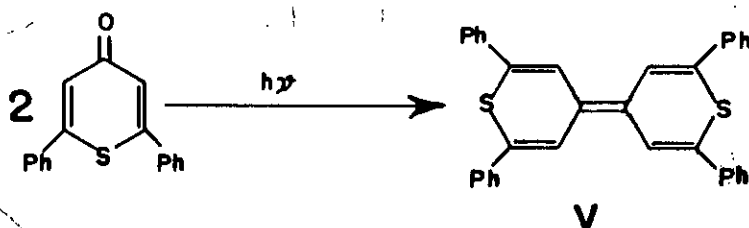
3-Methyl-4H-thiopyran:

The compound, IV, has been prepared by heating α -methylglutaric acid with phosphorus trisulphide.⁸

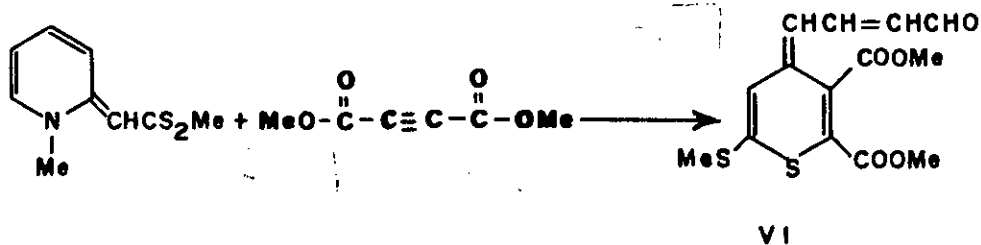


Derivatives of 4H-thiopyran:

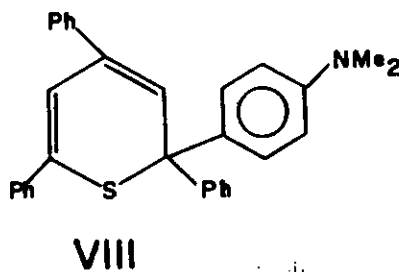
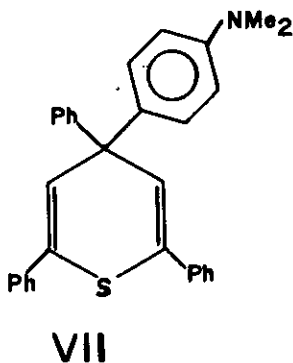
Photolysis of 2,6-diphenyl-4-thiopyrone gave 2,2',6,6'-tetraphenyl-4,4'-bithio pyranylidene (V) ⁹.



The reaction of N-methyl-2-(methylthiocarbonylmethylene)-1,2-dihydropyridine with dimethyl acetylenedicarboxylate gave 15% thiopyran compound (VI) ¹⁰



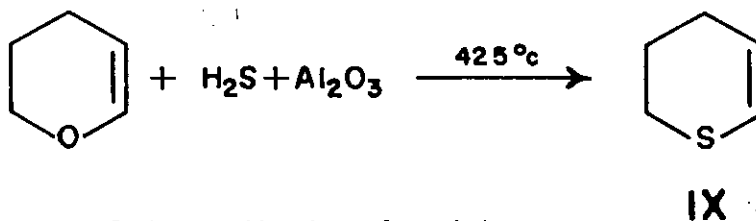
On the other hand 1-(4-dimethylaminophenyl)-2,4,6-triphenylthiopyran is more stable than its analogue without the 4-dimethylamino group. It is decomposed by heat, light or acid and gave a mixture of 4-(4-dimethylaminophenyl)-2,4,6-triphenyl-4H-thiopyran (VII) and 2-(4-dimethylaminophenyl)-2,4,6-triphenyl-2H-thiopyran (VIII).



Both VII and VIII are also given directly by the reaction of 2,4,6-triphenylthiopyrylium ion with 4-dimethylamino-phenylmagnesium bromide.¹¹

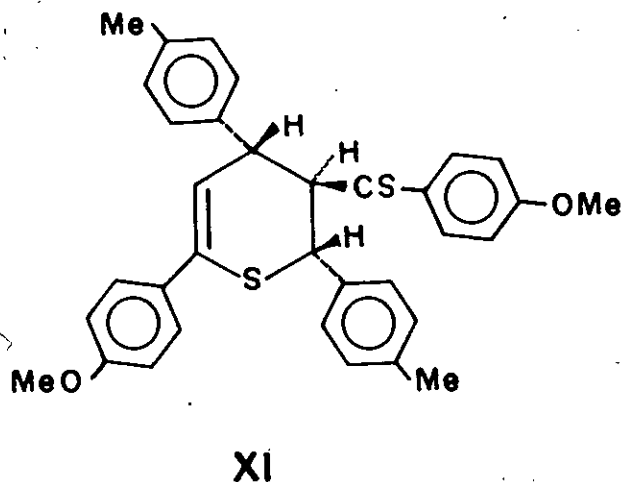
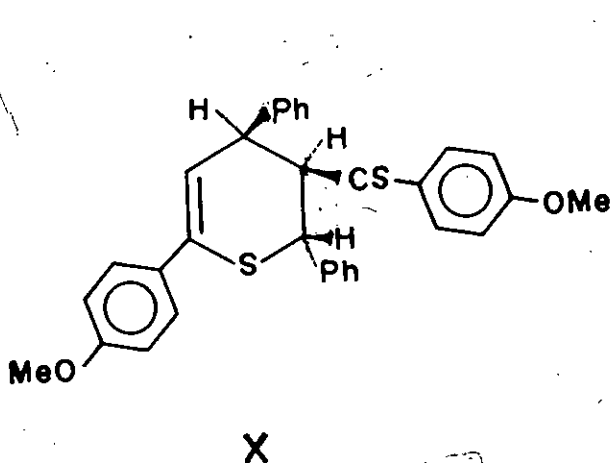
3,4-dihydro-2H-thiopyran

When Δ^2 -dihydropyran is heated with hydrogen sulphide and alumina at 425°C, it yields 2H-dihydrothiopyrans (IX).¹²



Derivatives of 3,4-Dihydro-2H-Thiopyran

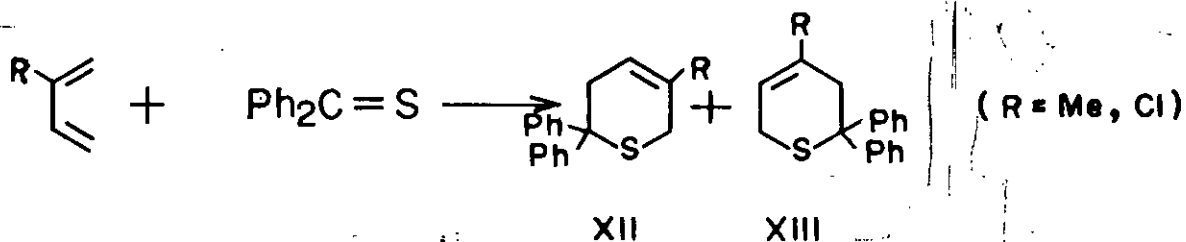
A derivative of 2H-dihydrothiopyran was prepared by treating 4-MeOC₆H₄CSCH:CHNET₂ with phenylmagnesium bromide. On heating, X was isomerised irreversibly to its epimer at the 4-position. Similarly, when 4-methylphenylmagnesium bromide was used as the Grignard reagent, XI, was obtained directly.¹³



5,6-Dihydro-2H-Thiopyran derivatives:

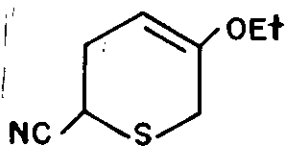
It is prepared by Diels-Alder Reaction. As for example, thiocarbonyl compounds react with dienes. The reactivity of these compounds is far greater than that of the corresponding oxygen analogues. Although most reactions proceed thermally, they appear to be catalysed by light. No detailed study on the mechanism has been made. However, the fact that unsymmetrically substituted dienes afford nearly equimolar amounts of two possible adduct isomers, suggests a one-step radical like mechanism.¹⁴

Typical examples are:



Methylation of 2-acyl-1,3-dithiolanes with MeOSO_2F affords sulphonium salts which undergo cycloreversion to α -oxo dithio-esters RCOCS_2Me (R = Me, Ph).

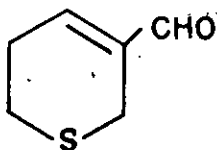
In the presence of dienes, good yields of 2-acyl-2-(methylthio)-3,6-dihydrothiopyrans are formed. Treatment of the adducts with thiophiles affords 2-acyl-3,6-dihydro-2H-thiopyrans. Diels-Alder trapping of a reactive thioaldehyde (NCCHS) by 2-ethoxybutadiene gave 15% (XIV)¹⁵.



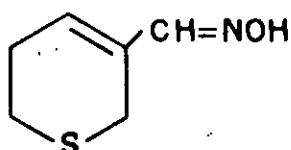
XIV

[dienes = 2,3-dimethyl-1-methyl⁻,
or, 1,3-dimethylbutadiene]

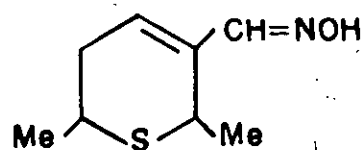
Cyclization of acrolein with hydrogen sulphide in dichloromethane containing copper-turnings and triethylamine at -10° gave 86% of aldehyde (XV) which was oximated with hydroxylamine to give 53% of oxime (XVI). Similarly prepared was also XVII from the aldehyde.¹⁶



XV



XVI



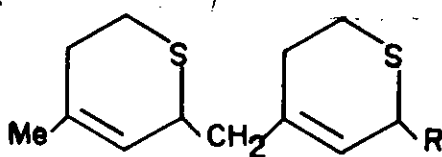
XVII

Derivative of 5,6-dihydro-2H-thiopyran:

The derivatives (XVIII) were prepared from the carbanion of (XVIII).¹⁷

(XVIII) R = CH_2CHMeOH , $\text{CH}_2\text{CMe:CHCH}_2\text{OH}$.

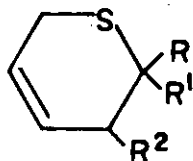
(XVIII) Carbanion of (XVIII) R=H.



XVIII

Thiopyranoside derivatives (XIX) and (XX) i.e., novel carbohydrate derivatives with sulphur in the ring can be prepared by "Diels-Alder reaction" of $\text{SC}(\text{CN})\text{SMe}$ with $\text{CH}_2:\text{CHCH}:\text{CHR}$ (R=H, trans OMe).

The structure of (XIX) and (XX) were determined by NMR of their oxidation and reduction products. The conformation of (XX) was $^{\circ}\text{H}_2$ in chloroform.⁽¹⁸⁾

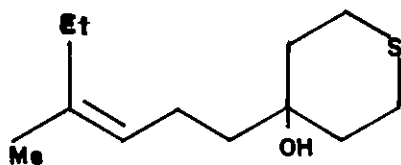


XIX & XX

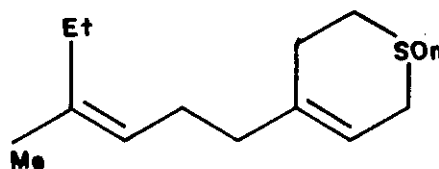
(XIX) R = CN, R¹ = SMe, R² = H.

(XX) R = SMe, R¹ = CN, R² = OMe

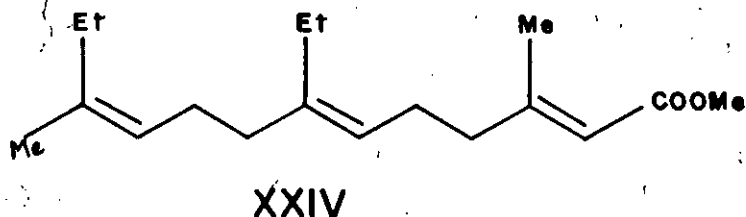
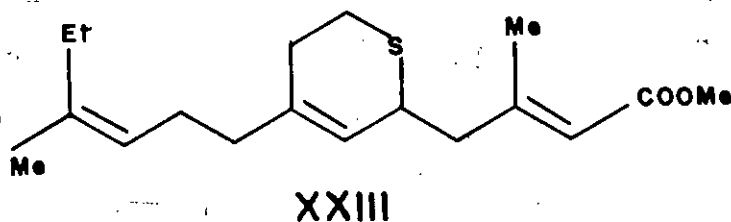
Another important derivative was prepared; first (Z)-EtCMe:CH(CH₂)Br was prepared from the tosylate and lithium bromide, this was then treated with lithium and subsequently with thiacyclohexane to give (XXI). The compound (XXI), was dehydrated with POCl₃ in pyridine to give (XXII) (n=0), which was converted with hydrogen peroxide into the S-oxide (n=1). When this reacted with (E)-BrCH₂CH₂CMe:CHCOOMe in the presence of butyllithium at -40°C, it gave the S-oxide of (XXIII). The S-oxide was reduced with tin(II)chloride in DMF and methyl cyanide to give (XXIII), which on treatment with Raney nickel in ethanol and acetone yielded (XXIV).⁽¹⁹⁾



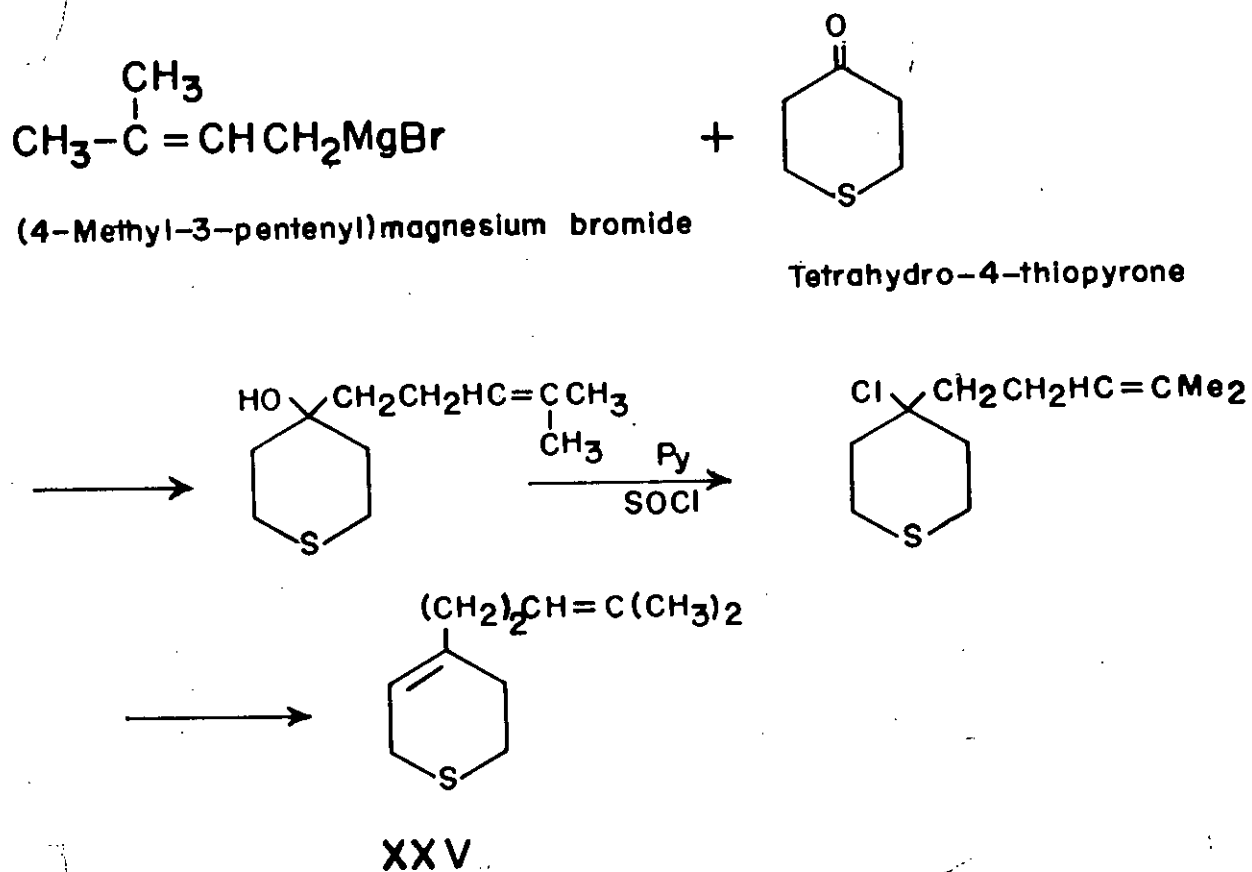
XXI



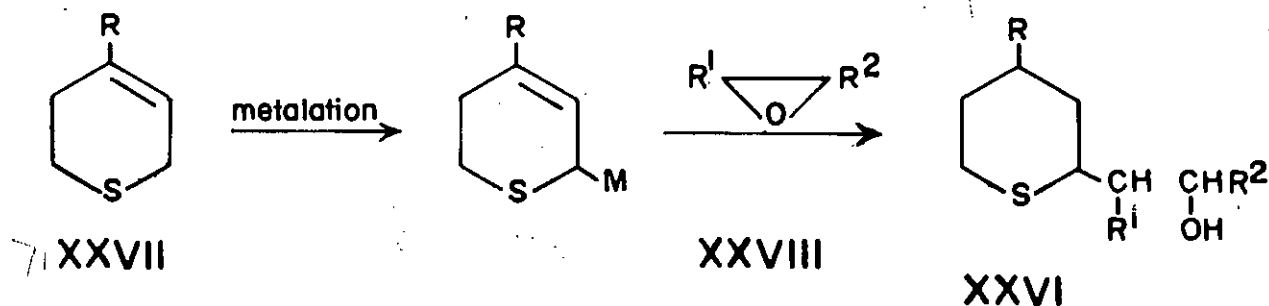
XXII



4-(4-Methyl-3-pentenyl)-5,6-dihydro-2H-thiopyran (XXV) was prepared²⁰ by the following sequence of reactions:

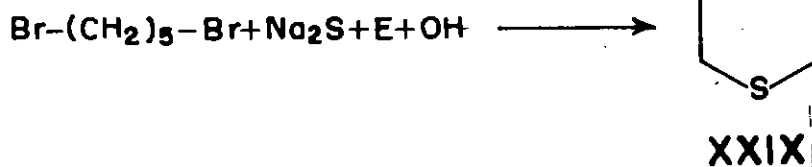


Also prepared was the 5,6-Dihydro-2H-thiopyran alcohol derivatives (XXVI) by the same author in 1975 by metalation of (XXVII) followed by the reaction with oxiranes (XXVIII).²¹

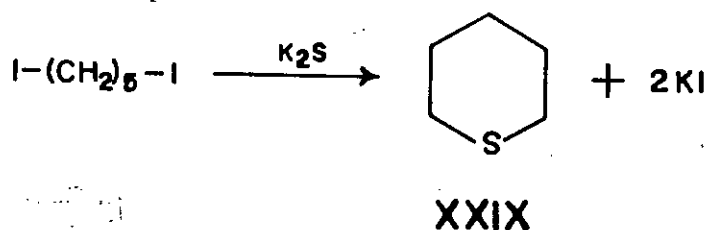


Tetrahydrothiopyrans:

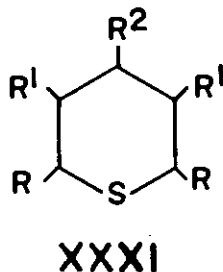
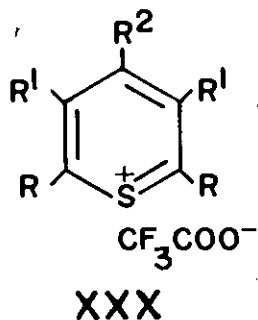
It is prepared from pentamethylene dibromide and sodium sulphide in ethanol (XXIX).²²



It can also be prepared from 1,5-diiodopentane and potassium sulphide.²³



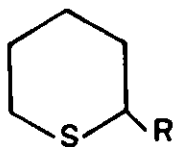
Several thiocyclohexane derivatives were also prepared by the reaction of 1,5-diketone such as $\text{RCOCHR}^1\text{CHR}^2\text{CHR}^1\text{COR}$ with $\text{H}_2\text{S}-\text{CF}_3\text{COOH}$.²⁴



R = Ph, *α*-thienyl
 R¹ = H, Me
 R² = H, Me, Ph,
 C₆H₄OMe-4

Derivatives of tetrahydrothiopyrans:

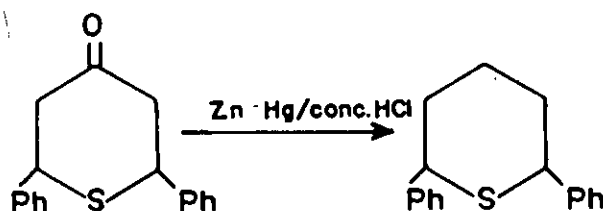
Many 2-substituted derivatives of tetrahydrothiopyrans (XXXII) were prepared by treatment of dihydropyran with RH.²⁵



R = MeO, BuO, PrS, BuS, EtMe₂CS,
 PhS, PhCH₂S, (MeO)₂P(S)S,
 (EtO)₂P(S)S

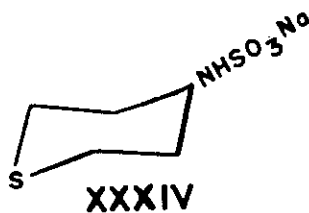
2,6-Diphenyltetrahydrothiopyran:

It is obtained by the "Clemensen reduction" of cis- and trans-2,6-diphenyltetrahydro-4-thiopyrone to the corresponding 2,6-diphenyltetrahydrothiopyrans.²⁶



XXXIII

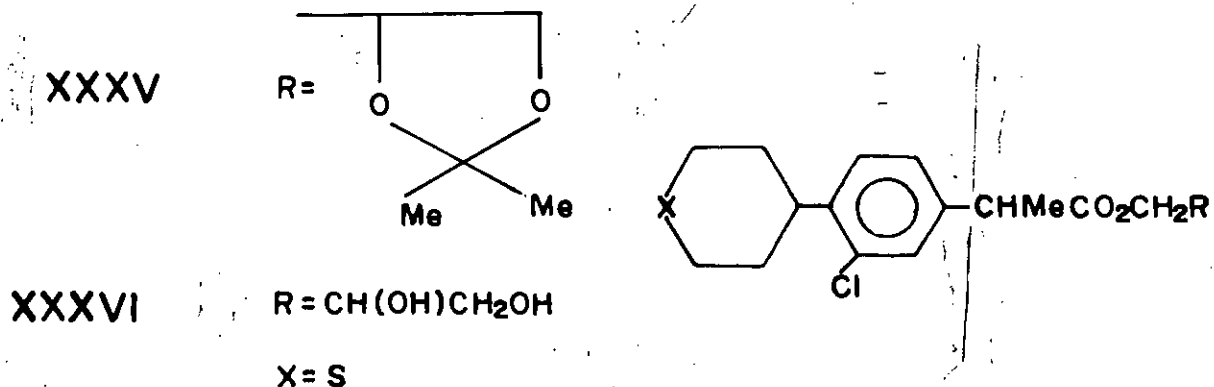
Sodium-4-thiacyclohexyl sulphamate (XXXIV) were prepared in 31% yield by oximation of ketones and reduction of the product (Na-EtOH), treatment with ClSO_3H and finally converting into the salt.²⁷



XXXIV

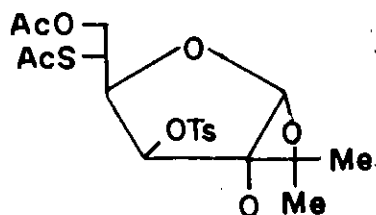
Phenylacetic acid ester derivatives of tetrahydrothiopyran (XXXV) & (XXXVI) were prepared by heating the corresponding pyranylphenylpropionic acids with SOCl_2 , cooling to 5° and stirring with 2,2-dimethyl-1,3-dioxolane-4-methanol in pyridine.

The dioxolanylmethyl propionates (XXXV) formed treated with boric acid to give (XXXVI)²⁸.

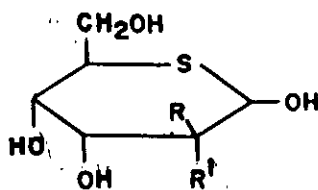


5-Thio-D-allose and 5-thio-D-altrose:

Deacylation of the diacetate (XXXVII) (Ts = 4-MeC₆H₄SO₂) followed by isopropylidene, desulfoxylation, C-3 epimerization by oxidation/reduction and acid hydrolysis gave 5-thio-D-allose (XXXVIII, a). The XXXVII with methanol/hydrochloric acid gave the glycoside (XXXIX) which on sequential isopropylidene, epoxidation, epoxide ring opening with sodium hydroxide (4:1 altro:gluco), and hydrolysis gave 5-thio-D-altrose (XXXVIII, b),²⁹

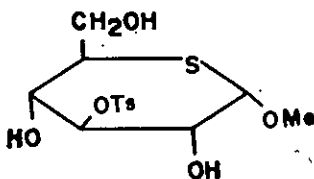


XXXVII



XXXVIII

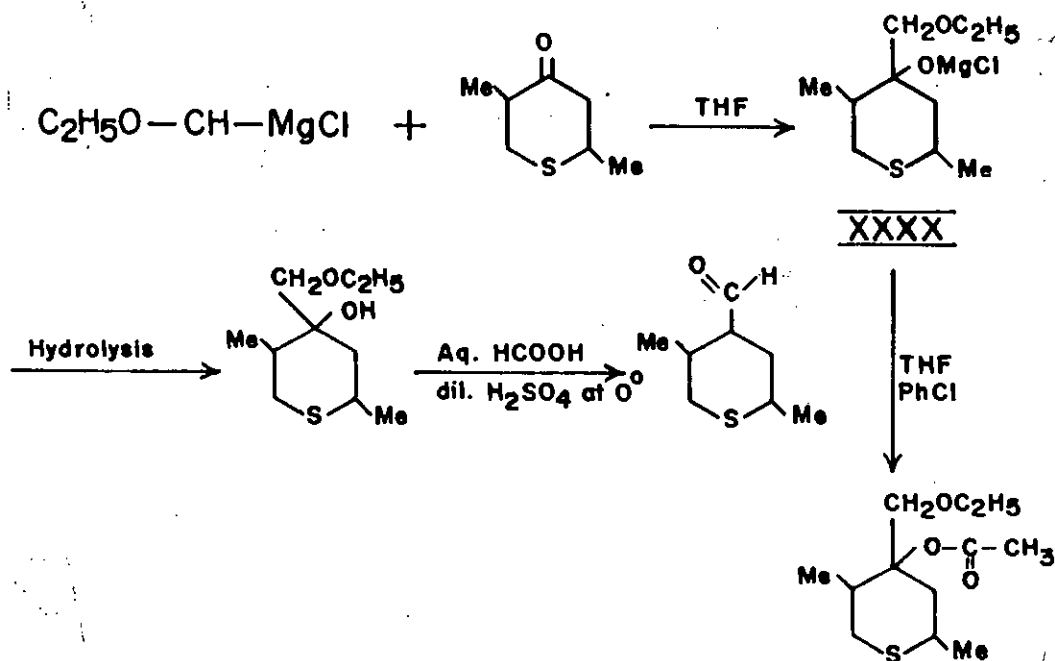
- a) R = H, R' = OH
b) R = OH, R' = H



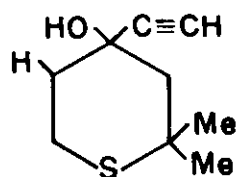
XXXIX

Substituted 4-(ethoxymethyl) tetrahydrothiopyran-4-ols:

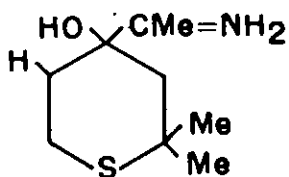
Ethoxymethylmagnesium chloride is added to 2,2-and 2,5-dimethyl-, 2-propyl-, 2-methyl-, 2-ethyl-, and 2,3,6-trimethyltetrahydro-4-thiopyrone in THF; hydrolysis of the intermediate adduct(XXXX) afforded the substituted (4-ethoxymethyl) tetrahydrothiopyran-4-ols in 42-65% yield, which gave the tetrahydrothiopyran-4-carboxaldehydes in 50-84% yield with refluxing aqueous formic acid, followed by dil. sulphuric acid at 0°C. Treatment of (XXXX) in THF with chlorobenzene produced the corresponding 4-acetoxy-4-(ethoxymethyl)-2,5-tetrahydrothiopyrans in $\geq 44-57\%$ yield.³⁰



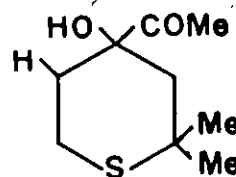
Heating (XXXXI) with $N_2H_4 \cdot H_2O$ 8-10 hours at $140-150^\circ C$ Gave 80-85% (XXXXII), also prepared by independent synthesis via ketones (XXXXIII), which with $N_2H_4 \cdot H_2SO_4$ gave (XXXXII). Hydrogenation of XXXXII on Ni-V alloy gave saturated heterocyclic alcohols. Dehydration of XXXXI gave XXXXIV, which with $N_2H_4 \cdot H_2O$ gave XXXXV. The kinetics of halogenation of XXXXV over Raney nickel and other Ni-Catalysts were studied.³¹



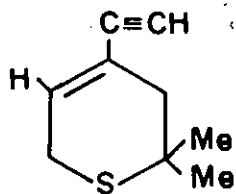
XXXXI



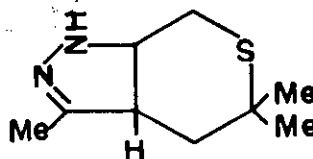
XXXXII



XXXXIII



XXXXIV

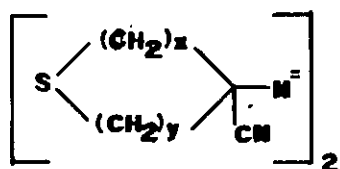


XXXXV

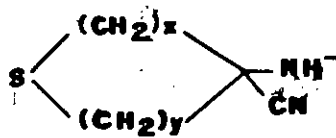
Azo bis (1-cyanothiocyclohexane) compounds:

The compound (XXXXVI) were prepared by oxidising the corresponding hydrazine (XXXXVII) ($x, y=0-4$; $x+y = 4$) e.g. 4.23 g(XXXXVII) ($x = y = 2$) in 400 ml ethanol saturated with hydrochloric acid was treated with ice-cooling to give 3.2 g

(77%) XXXXVI ($x=y=2$). Similarly prepared was XXXXVI ($x=1, y=3$).³²



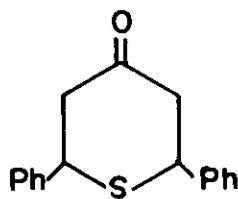
XXXXVI



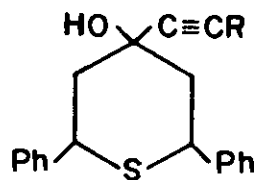
XXXXVII

2,6-Diphenyl-4-ethynyl(phenylethynyl) tetrahydrothio-
pyran-4-ol.

Treatment of (XXXXVIII) with $RC:CH$ ($R=H, Ph$) gave 77.3% (XXXXIX) ($R=H$) and 69.25% (XXXXIX) ($R=Ph$). (XXXXIX) were hydrogenated to the saturated alcohols over Ni-Mo.³³



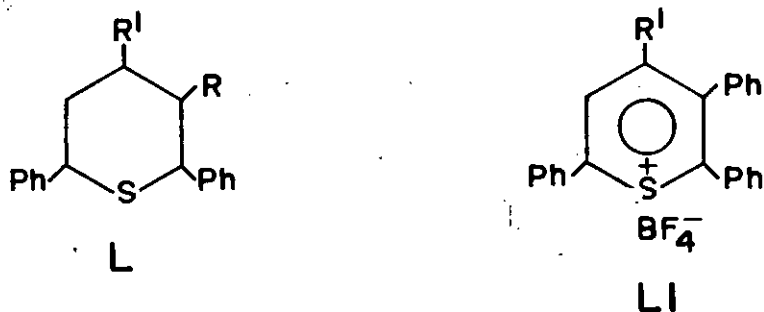
XXXXVIII



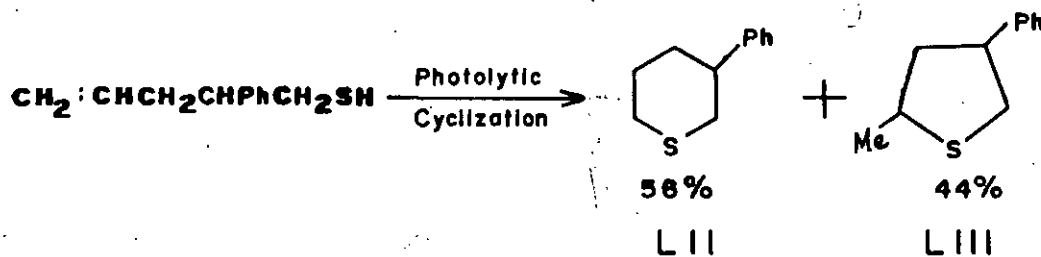
XXXXIX

Cyclization of $(BzCH_2)_2CH_2$ with BF_3-Et_2O and hydrogen sulphide at 20° in ether for 100 hours or in acetic acid

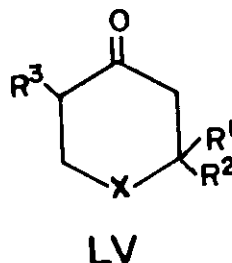
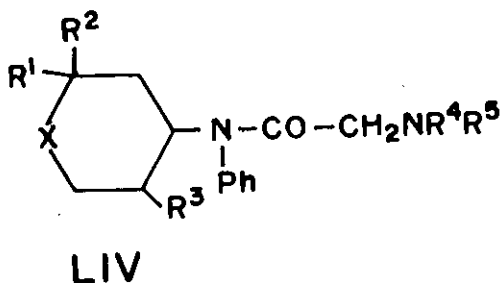
for 20 hours gave 25-30% (L) and 60% (LI).³⁴



3-phenyltetrahydrothiopyran (LII) in 56% yield with minor amount of tetrahydrothiophene derivative (LIII) in 44% yield, were prepared by photolytic cyclization of $\text{CH}_2=\text{CHCH}_2\text{CHPhCH}_2\text{SH}$.³⁵

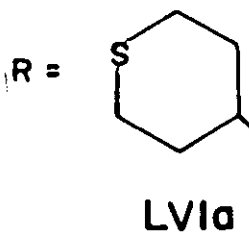
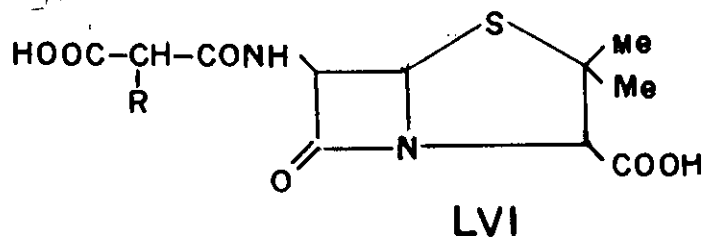


The compounds (LIV) were prepared in 4 steps by condensation of aniline with (LV), reduction of formed schiffs base, N-acylation by chloroacetyl chloride and amination by the appropriate $\text{R}^4\text{R}^5\text{NH}$.³⁶



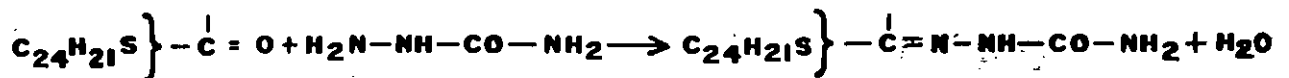
LIV, $R^1 = \text{Me}$; $R^2, R^3 = \text{Me, H}$; $\text{NR}^4\text{R}^5 = \text{NMe}_2, \text{NEt}_2, \text{pyrrolidino, piperidino, morpholino}$; $x = \text{S, O, NMe}$.

Another derivative of tetrahydrothiopyran and their sodium or calcium salts were prepared by the reaction of 6-aminopenicillanic acid (LVI) or its benzyl ester with HOOC-CH(R)COX ($x = \text{OH, Cl, OCH}_2\text{Ph}$) or their chlorides and optionally hydrogenation. Thus, the following compound (LVIa) was prepared.³⁷



1.5 PHYSICAL AND CHEMICAL PROPERTIES2H- and 4H-Thiopyrans:3-Benzyl-2,6-diphenyl-2H-thiopyran-5-carboxaldehyde:

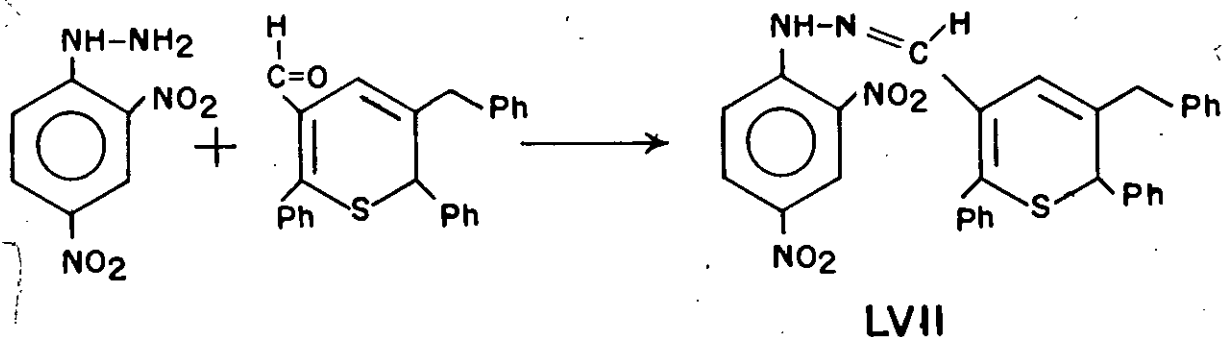
It is a bright yellow needle shaped crystals. It forms white needle shaped semicarbazone ppt. (m.p. 215°) with semicarbazide.³⁸



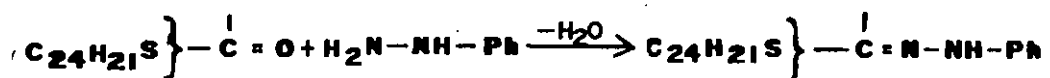
prepared original
compound

semicarbozone

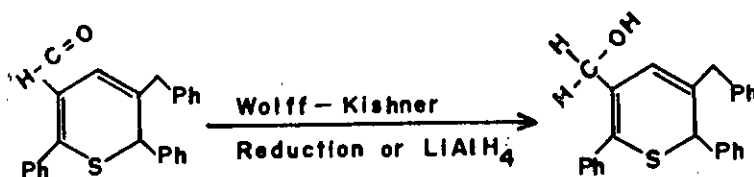
It forms red 2,4-dinitrophenylhydrozone derivatives LVII with 2,4-DNP.³⁸



It forms orange yellow ppt. of phenylhydrazone derivative (m.p. 120°C) with phenylhydrazine.³⁸



The keto group of the above substance was reduced by "Wolff-Kishner" reduction and lithium aluminium hydride. From the IR spectrum of original compound and reduced product, it is very clear that no keto stretching peak is present in the IR spectrum of reduced compound.³⁹

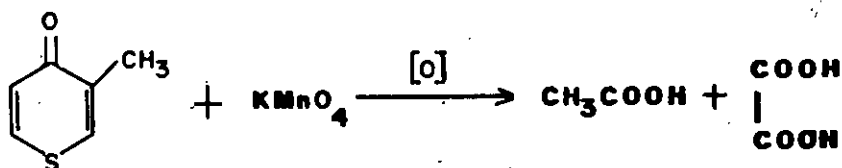


3-Methyl-4H-thiopyran

It is a volatile oil, having a smell similar to that of xylene.

It resembles thiophene, giving a colour with isatin, H_2SO_4 and phenanthraquinone; and with acetyl chloride and aluminium chloride forming an acetyl compound.

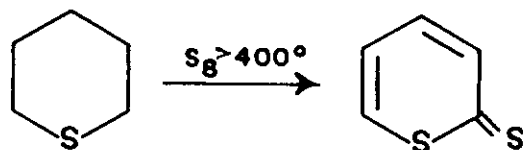
It is oxidised by potassium permanganate to acetic and oxalic acid.⁸



3,4-Dihydro-2H-thiopyran:

It is a liquid. With methyl iodide it yields mainly trimethyl-sulphonium iodide.⁴⁰

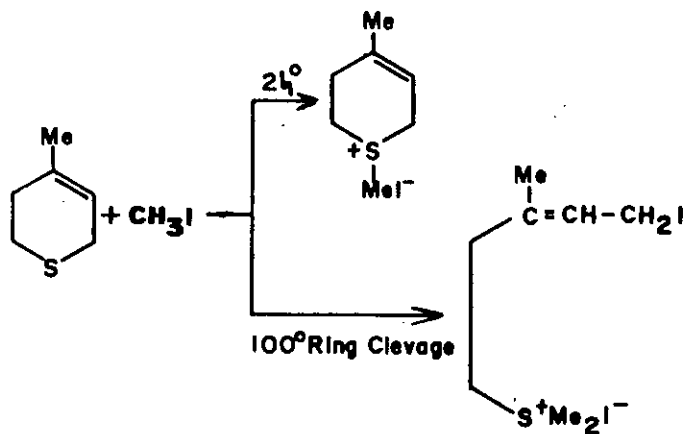
When treated with sulphur at greater than 400°C , by dehydrogenation forms thiopyran-2-thione. This is the first preparative method for 2H-dithiopyrones which formed as the end-products in thermal sulphurisation reaction.⁴¹



LVIII

5,6-Dihydro-2H-thiopyran:

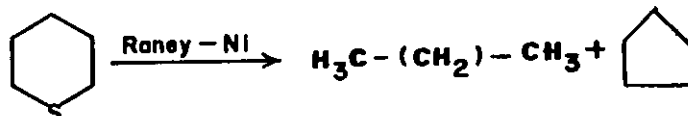
It is a liquid. 4-Methyl-5,6-Dihydro-2H-thiopyran with methyl iodide at 24° gives the methylsulphonium iodide (m.p. 142.5°) but at 100° ring cleavage occurs giving dimethyl-5-iodo-3-methylpent-3-enylsulphonium iodide LIX, which is a red brown needle.⁴²



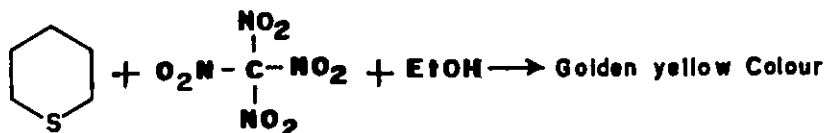
LIX

Tetrahydrothiopyran:

It is a liquid. With Raney nickel it undergoes hydrogenolysis yielding n-pentane (91.8%) and cyclopentane (7.8%).⁴³



It gives a golden yellow colour with tetranitromethane in ethanol.⁴⁴



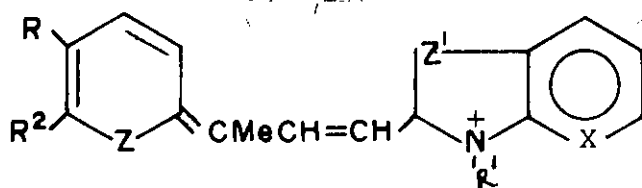
It yields the methylsulphonium iodide, subliming at 192°, a sulfoxide, yellow liquid and the sulphone.⁴⁵

1.6 APPLICATION OF THIOPYRAN COMPOUNDS:

Thiopyran compounds and their derivatives have wide applications. In practical field some of the thiopyran compounds and their derivatives are used in medicine, whereas others may be cited to demonstrate outstanding biological and industrial importance. Some of these uses are described below.

Use in sensitizers:

Derivatives of 2H-thiopyran e.g, LX, have been employed as sensitizers.⁴⁶



LX

X = Cl, Br, S.
R = R' = Me or ph

RR' = benzo;

R¹ = H, Et or Me;
Z = S, O;

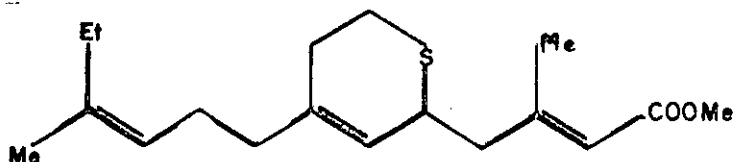
Z' = CMe₂, CH₂CMe₂S,

CH₂CMe₂NH or S

2,4,6-Triphenylthiopyrylium perchlorate derivatives are also known to possess powerful sensitizing properties.⁴⁷

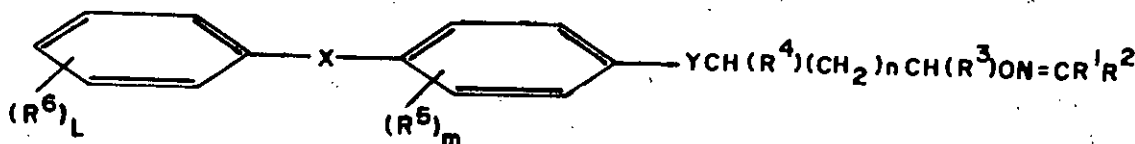
Use in insecticides & herbicides:

The following type of compounds are active against *Dysdercus intermedius* larvae.¹⁹



XXIII

A compound containing oxime ethers LXI used as insecticides.⁴⁸



LXI

R^1 & R^2 = H, alkyl, alkoxyalkyl, alkenyl, etc.;

R^3 & R^4 = H or Me;

R^5 = Me or halo

R^6 = alkyl, methoxy, halo, etc.;

x = S

y = S

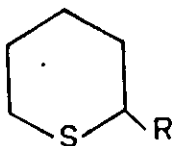
l = 0-5 integer

m = 0-4 "

n = 0-2 "

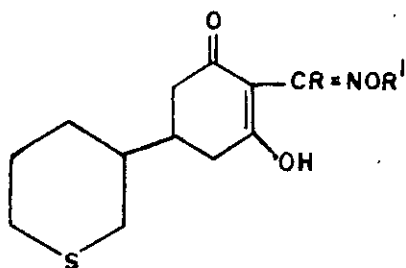
Azobis(1-cyanothiocylohexane) type of compounds can be used as herbicides, insecticides and polymer initiators. 32

2-substituted tetrahydrothiopyran compounds of the following type are useful in the control of mosquitoes.²⁵



XXXII

Another kind of compounds, eg., 5-(tetrahydro-2H-thiopyran-3-yl)-2-cyclohexene-1-one, is effective as pre-emergence herbicides against certain grasses.⁴⁹



LXII

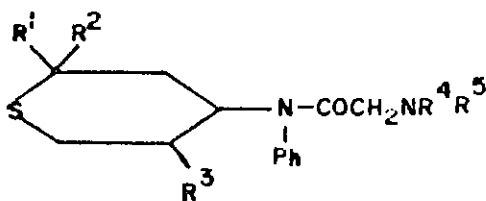
R = alkyl

R¹ = chloroalkynyl

Use in Medicine & as Antibacterial Agents:

It is reported that the following compounds have antibacterial properties:

N-(5,6-Dihydro-2H-thiopyran-4-yl) tetracycline⁵⁰
and N-(Tetrahydrothiopyran-4-yl) tetracycline.⁵¹ Some tetrahydrothiopyran derivatives of phenylacetic acid ester have analgesic and anti-inflammatory activities.²⁸ (Carboxymethyl) penicillins of the type and/or their Na/Ca salts are useful as bactericides, feed additives and drugs for the treatment of matities.²⁹ The following compounds are reported to have analgesic and local anesthetic properties.³⁶



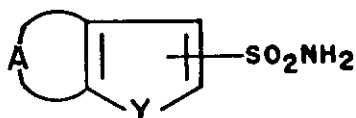
LIV

R¹ = Me, R^{2,3} = Me, HNR^{4,5} = NMe₂, NEt₂,

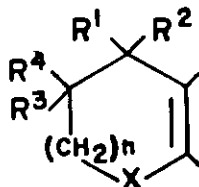
Pyrrolidino, Morpholino,

Piperidino,

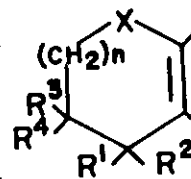
The following compounds LXIII, LXIV & LXV are cited⁵² to be effective glaucoma inhibitors.



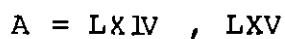
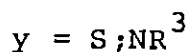
LXIII



LXIV



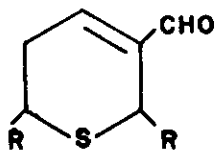
LXV



where $R^{1-4} = H, OH, amino$ etc.

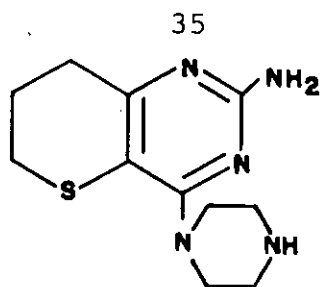


5,6-Dihydro-2H-thiopyran-3-carboxaldehyde (LXVI) are⁵³ useful as intermediates for pharmaceutical & plant protective agents.



LXVI

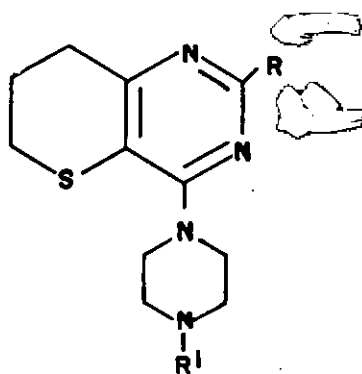
In a recent report it has been revealed that the compound LXVII has hypoglycemic activity.⁵⁴



LXVII

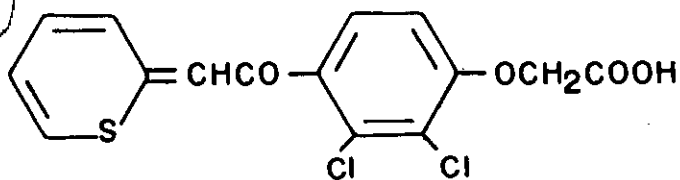
2-amino-7,8-dihydro-4-piperazinyl-6H-thiopyran(3,2-d)pyrimidine⁵⁵

Other compounds with similar structure moiety have been described as having antidiabetic activities.⁵⁵



LXVIII

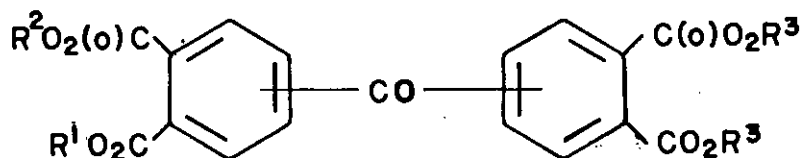
The following compound is an interesting example of a thiopyran derivatives having low diuretic activities.⁵⁶



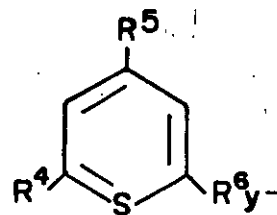
LXIX

In synthesis:

The compound LXX and LXXI are useful for the photo-sensitive lithographic printing plate.⁵⁷



LXX



LXXI

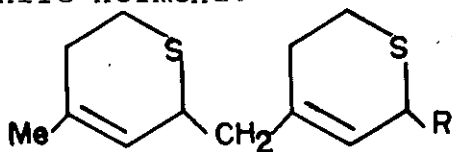
$R^1, R^2 = C_{4-8}$ tert-alkyl, C_{9-12} ter - uralkyl

$R^1, R^3 = H, C_{4-8}$ ter-alkoxy, C_{9-12} tert-aralkyloxy

$R^4, R^5, R^6 = H, \text{Halogen, alkyl, haloalkyl, ethylenyl, styryl, alkoxy, ph, naphthyl, alkylphenyl, alkoxyphenyl, hydroxyphenyl, halophenyl, nitro phenyl, aminophenyl, NO}_2, \text{OH,}$

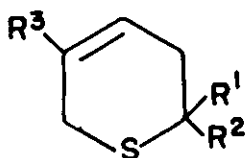
$y^- = \text{anion}$

A derivative of 5,6-Dihydro-2H-thiopyran in the following form can be used as in the synthesis of recemic cecropia juvenile hormone.¹⁷



XVIII

Certain fire-resistant polymers are prepared from the following monomers.⁵⁸

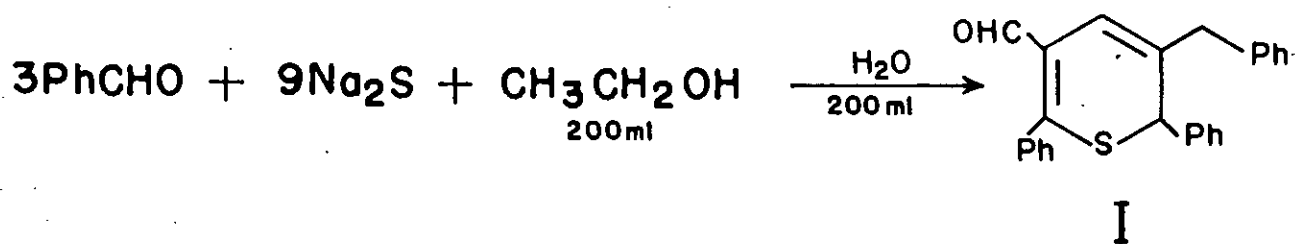


LXXII

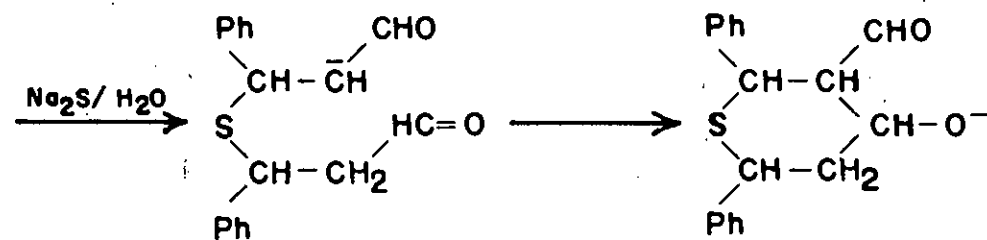
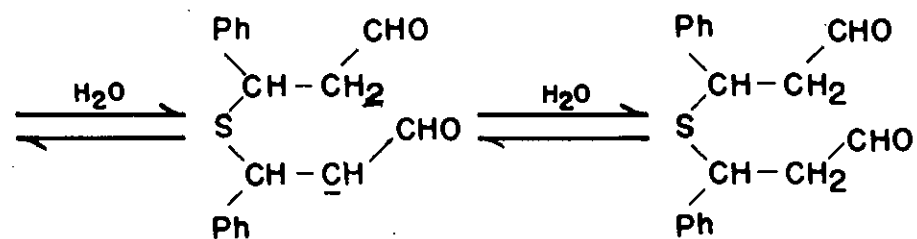
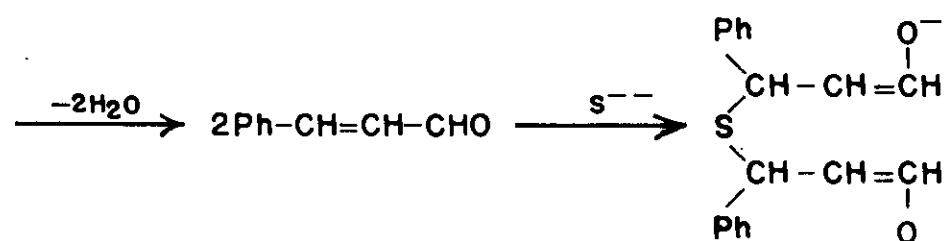
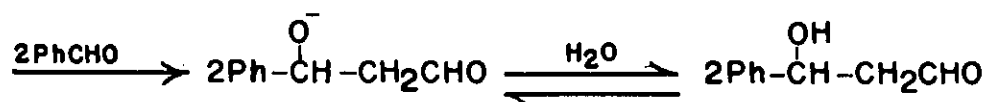
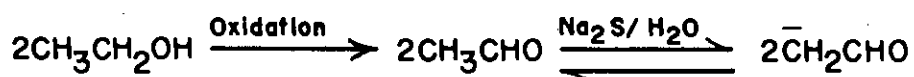
Tetrahydrothiopyran compound can be used as catalyst for the manufacture of stereospecific butadiene rubber.⁵⁹

1.7 AIM OF THE PRESENT RESEARCH:

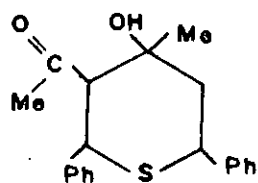
Latif et al.^{3,4} discovered that when benzaldehyde reacts with sodium sulphide in aqueous ethanol, it gives 3-benzyl-2,6-diphenyl-2H-thiopyran-5-carboxaldehyde(I) in 40% yield.



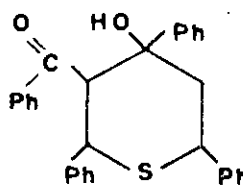
The structure of this compound was proposed by Cremer and Subbaratnam from spectroscopic studies and later was confirmed by x-ray crystallography independently by Haque and Caughlan⁵ as well as by Chowdhury.⁶⁰ Cremer and Subbaratnam explained the formation of I by proposing a mechanism which when expanded may look like the following:



Cremer and Subbaratnam did not give any experimental evidence supporting their mechanism. Rahman and Co-workers⁶¹ showed that the above mechanism is acceptable because they were able to prepare compound I starting with either acetaldehyde or cinnamaldehyde and benzaldehyde in the presence of aqueous sodium sulphide. Ethanol was not necessary any more. They also detected the presence of cinnamaldehyde in the Latif reaction medium & isolated a compound from the reaction medium which they thought has the structure LXXIII. In further support of this mechanism Rahman and Das⁶² isolated compound LXXV when they reacted acetone with benzaldehyde in the presence of aqueous sodium sulphide. They also prepared the corresponding phenyl analogue of LXXV formulated as LXXVI, when they reacted acetophenone rather than acetone with benzaldehyde and aqueous sodium sulphide.



LXXV



LXXVI

The compounds LXXV and LXXVI which are similar in structure to LXXII, also prepared by reacting respectively, benzalacetone and benzalacetophenone with benzaldehyde in the presence of aqueous sodium sulphide.

The Latif reaction is interesting on two accounts. Firstly, it is a simple one-pot synthesis of a complicated polyfunctional thiopyran derivative in very high yield (40%). Secondly, many compounds containing the thiopyran moiety are biologically active. These compounds have innumerable applications in medicine and industry. It was thus considered interesting to study the scope of the Latif reaction and decided to examine whether or not nuclear substituted benzaldehyde also give compounds of the type I.

During this research it was found that 4-methylbenzaldehyde and 4-methoxybenzaldehyde react similar to benzaldehyde in the Latif reaction, but 4-nitro, 4-chloro, and 4-bromo benzaldehyde tend to behave differently.

CHAPTER TWO

2.1 GENERAL TECHNIQUES AND EQUIPMENTS

The general techniques and equipments that have been employed during this research are briefly described below:

1) Spectroscopic analysis:

a) Infra-Red(IR) spectroscopy:

The IR spectra were recorded either as "nujol mulls" or "thin liquid film" between sodium chloride plates in PYE-UNICAM SP1025 INFRA-RED SPECTROPHOTOMETER at the "Instrument and IR Laboratory" of the Department of Chemistry, Dhaka University.

b) ^1H Proton Nuclear Magnetic Resonance(^1H NMR) Spectroscopy:

The ^1H NMR spectra were recorded by using the VARIAN XL-400 NMR machine in the "Department of Organic Chemistry, Chalmers University of Technology", Göteborg, Sweden. The ^1H NMR spectra were also recorded by JEOL JNM-PMX60 60MHz spectrometer in CDCl_3 in the "Department of Organic Chemistry" Dhaka University.

In every cases, TMS was taken as "Internal standard" during the recording of spectra.

c) ^{13}C Nuclear Magnetic Resonance(^{13}C NMR) Spectroscopy:

The ^{13}C NMR spectra were recorded by using a VARIAN XL-400 machine in the Department of Organic Chemistry, Chalmers

University of Technology" Göteborg, Sweden.

d) The Pulse Sequence ^1H NMR and ^{13}C NMR spectra were recorded in the Department of Chemistry and Molecular Biology, Swedish University of Agricultural Sciences, Uppsala.

e) Mass Spectroscopy:

The mass spectra were recorded in the "Spectroscopic Laboratories" of the "Department of Organic Chemistry, Chalmers University of Technology", Göteborg, Sweden.

2) Concentration of solution using vacuum rotary evaporation:

The rotary evaporating flask containing the solution of samples was heated in a water-bath. Vacuum was created in the system by a Gallenhamp filter water pump. Evacuation with simultaneous heating caused rapid evaporation of the solvent and a solution could be concentrated with a short time without heating it to a high temperature. In this system, the solvent was collected in a receiving flask. By this apparatus the various fractions which are collected during column chromatographic separation of a mixture, can be separated by the same procedure.

3) Drying of products:

The products after separation and purification, if solid, were dried under vacuum in a dessicator containing blue silica gel.

Liquid products were dried or purified by fractional distillation.

4) Determination of melting points:

In general, a sharp melting point (within 0.5°) is one of the most characteristic properties of a pure organic compound.

The m.p and mixed m.p were determined by Gallenkamp melting point apparatus.

5) Determination of boiling points:⁶³

The boiling points of liquid products were determined by the conventional methods.

6) Separation of reaction mixtures:

The reaction mixtures were separated by the following methods.

a) Solvent extraction:⁶⁴

The process of extraction with solvent was employed either for the isolation of dissolved substances from solutions, or from solid mixtures or for the removal of undesired soluble impurities from mixtures. The solvents generally used were diethyl ether, benzene, chloroform and petroleum ether. The

selection of solvent was dependent upon the solubility of the substance to be extracted in that solvent and upon the ease with which the solvent could be removed from the solute. Diethyl ether, owing to its powerful solvent properties and its low boiling point (35°C), was the most used one during this work.

b) Fractional recrystallisation:⁶⁵

Solid organic compounds when isolated from organic reactions are seldom pure; they were usually contaminated with small amounts of other compounds (impurities) which were produced along with the desired product. The purification of impure crystalline compounds is usually effected by crystallization from a suitable solvent or mixture of solvents.

Solid substances were purified by recrystallization. The solvents generally used for recrystallization were benzene, petroleum ether ($60-80^{\circ}\text{C}$).

c) Fractional distillation under normal or reduced pressure:^{66, 67}

Distillation of organic reagents and products was carried out in a distillation apparatus shown in Fig. Fractional distillation of small amounts of samples was carried out in a 2-vigreux column fitted with specially designed distilling head (Fig.1,P.51)An efficient rotary oil pump, Hitachi Ltd, and a manometer were connected with the systems during the fractional distillations under reduced pressures.

Semi-micro and micro distillation of small amounts of reagents or samples were carried out with equipments shown in Fig. 2 and 3 page 52.

7) Chromatographic analysis:

a) Gas Liquid Chromatography: (GLC)

GLC was used for identification of number of products present in the reaction mixtures. It was done in the Chemistry Department of Dhaka University using a PYE-UNICAM GCD CHROMATOGRAPH with a 1 meter 5% OV-1 column.

b) Column Chromatography:

To separate the different fractions of the reaction products a 100 cm long, 3 cm in diameter glass column was used. The column was prepared by the slurry method, silica gel 60 G.E. Merck 230-400 mesh ASTM, being the stationary phase. Petroleum ether (60-80°C) and benzene were used as solvents for making the column. The adsorbent was supported on a plug of glass wool placed at the bottom of the column. Exclusion of air bubble was effected by making the column as quickly as possible. The surface of the column was covered with glass-wool also. The mixture of products in as concentrated a solution as possible was applied at the top of the column. The mixture was allowed to be adsorbed on the surface of the column and eluted with the solvent. The fractions coming out

of the column were collected in small portions (20 ml) in conical flask, concentrated and were followed either by thin layer chromatography or by gas-liquid chromatography (GLC) to check the progress of separations.

The column was gradually eluted with solvents of increasing polarity.

c) Thin layer chromatography (TLC):⁶⁸

The separation and identification of reaction mixture were carried out by tlc Silica gel 60G (E. merch) HF₂₅₄₊₃₆₆ for thin layer chromatography was used for making the static phase. A slurry was made with silica gel and chloroform (1:2) in a previously cleaned and dried reagent bottle. All the air bubbles were removed from the slurry by stirring with glass rod. Then a pair of cleaned and dried slides (7.6X2.6 cm) were dipped into the slurry and removed immediately. An uniform silica gel layer was formed on the plate, the thickness of the layer was about 0.2 mm. The plates were dried in the air.

Sometimes commercially available UV-active silica gel plates (made of aluminium) were directly used for the tlc study.

To spot a plate, firstly a mark was made about 1 cm above the bottom of the plate and the sample solution was spotted by means of a fine, narrow capillary glass tube. A

suitable solvent or a mixture of solvents were used as the mobile phase in the chromatographic tank of suitable size and fitted with a lid. The spotted tlc plate was then dipped into the solvent (a small amount) so that the spotted marks of the samples remained above the solvent phase. The plates were removed when the solvent front had reached the top boundary of the plate, allowed to dry & then the chromatograms were developed in an iodine chamber or visualized in UV light.

d) Preparative T.L.C.:

Similarly, thin-layers were produced by spreading film of an aqueous slurry of the adsorbent over the entire surfaces of the plates (20X20 cm, 20X5 cm). Merck silica gel 60G HF₂₅₄₊₃₆₆ for thin-layer chromatography which contains 10 to 75% calcined CaSO₄, was mixed with about twice the weight of water and a slurry was made. The spreading machine was used to obtain uniform layers of slurry on the glass plates. The thickness of the silica gel layers was 0.5-1.0 mm. The plates were dried first in the air & finally activated by heating at 110°C for 30 minutes.

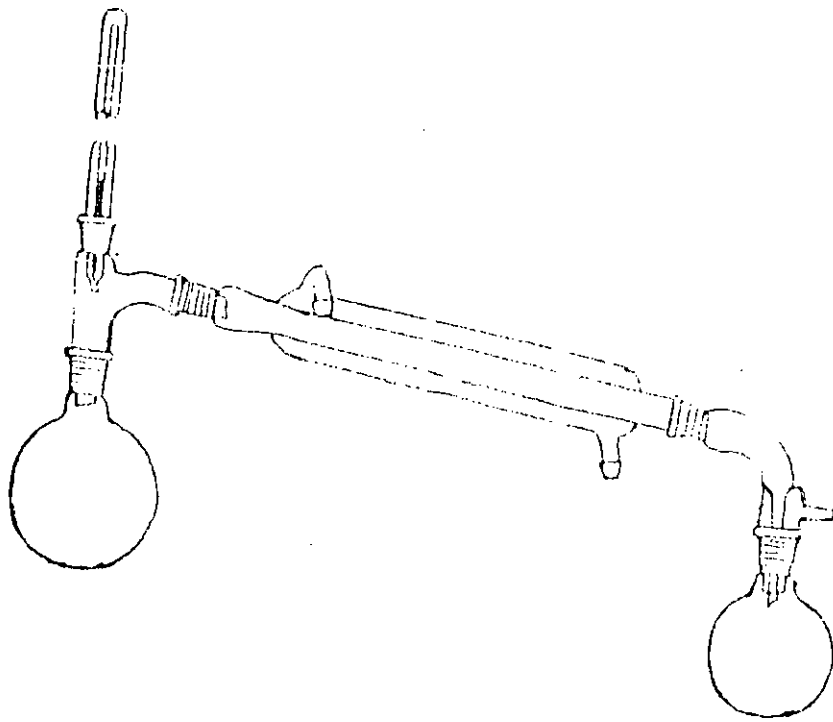


Fig. 1: Arrangement of Fractional Distillation.

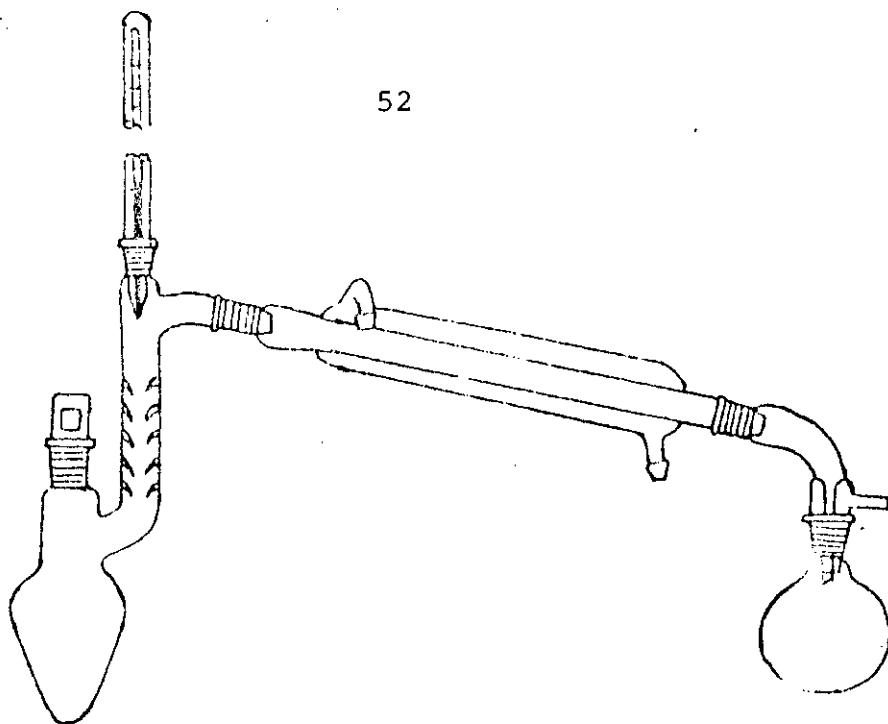


Fig. 2: Arrangement of Semi-micro Distillation.

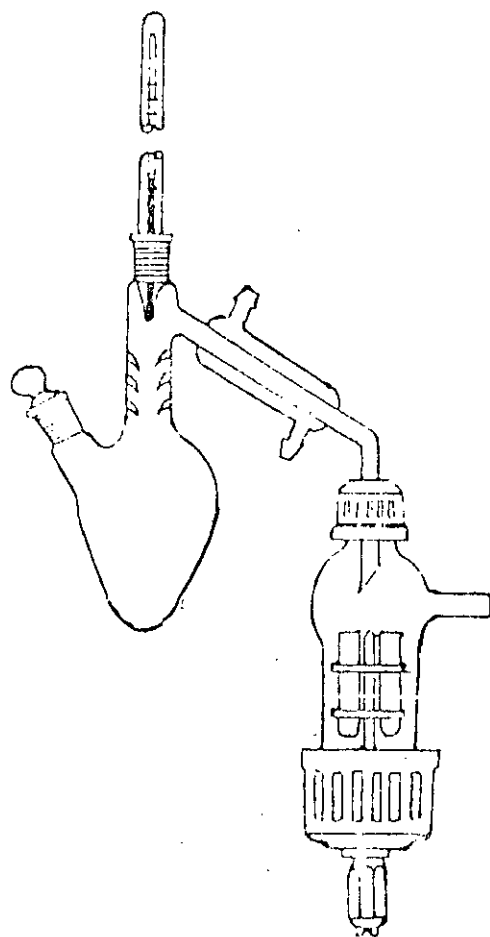


Fig. 3: Arrangement of micro Distillation.

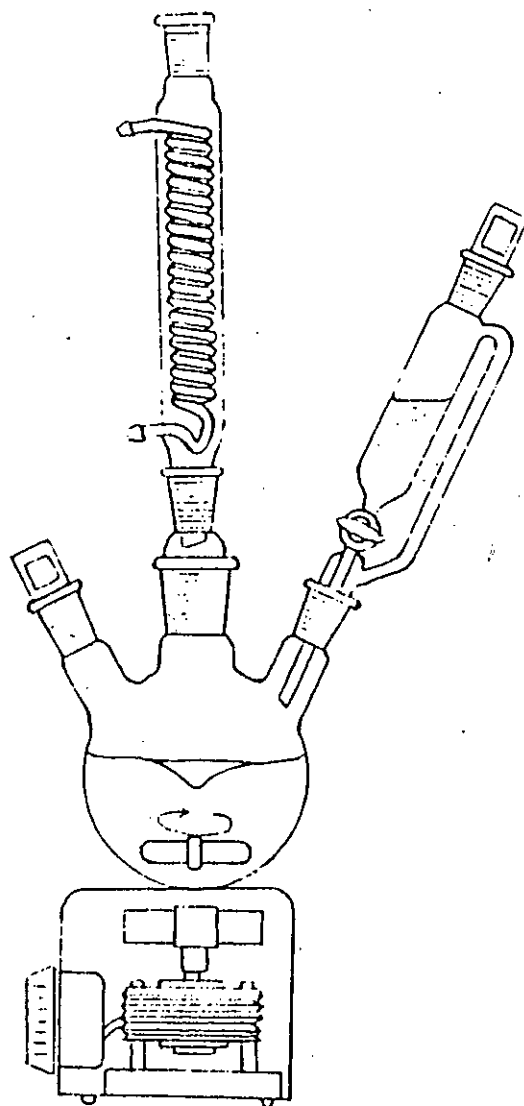


Fig. 4. Arrangement of apparatus for reactions

2.2 PURIFICATION AND DRYING OF REAGENTS AND SOLVENTS:

2.2.1 REAGENTS:

- a) Benzaldehyde: Commercial grade benzaldehyde was neutralized with solid potassium carbonate and then filtered. The filtrate was distilled and a colourless liquid distilling at 178-180°C was collected as pure benzaldehyde.
- b) Para-Methoxy Benzaldehyde: It was purified by distilling under reduced pressure. The clear liquid collecting at 80°C and at pressure 2 mm was para-methoxy benzaldehyde.
- c) Para-Methyl Benzaldehyde: It was purified by distilling under reduced pressure. The clear liquid collecting at 50°C and at pressure 2 mm was para-methyl benzaldehyde.

2.2.2 SOLVENTS:

- a) Diethyl ether: Diethyl ether was dried over sodium wire and decanted prior to use.
- b) Petroleum ether (60-80°C): It was dried over sodium wire and distilled prior to use.
- c) Benzene: Benzene was dried over and distilled from sodium wire before use.
- d) Ethanol: Commercial ethanol was always purified by distillation before use.

REACTION NUMBER 1The Reaction of Benzaldehyde with Sodium Sulphide
and Ethanol in Water.^{3,4}

Benzaldehyde (10.6 gm, 0.10 Mole) and absolute alcohol (200 cm³) were placed in a three-necked distilling flask (1 litre), fitted with a reflux condenser, a pressure equalizing dropping funnel and an efficient magnetic stirrer. Filtered sodium sulphide solution (72 gm, 0.3 Mole) was then added drop by drop from the dropping funnel. The mixture was refluxed on an oil-bath for two hours with continued stirring. The temperature of the oil bath was maintained between 110-105°C. The addition of sodium sulphide solution took 45 minutes. The reaction mixture was then cooled and kept standing overnight at room temperature. Copious precipitate appeared. This was filtered, washed with alcohol-water mixture (5%) and dried. Recrystallisation from acetone gave pure 3-benzyl-2,6-diphenyl-2H-thiopyran-5-carboxaldehyde, m.p. 153°C (reported³⁸ 153°C). The yield was 29%.

The IR spectrum (nujol mull Fig. 5 Page 56) of the compound showed the characteristic absorption band for carbonyl stretching at 1644 cm⁻¹.

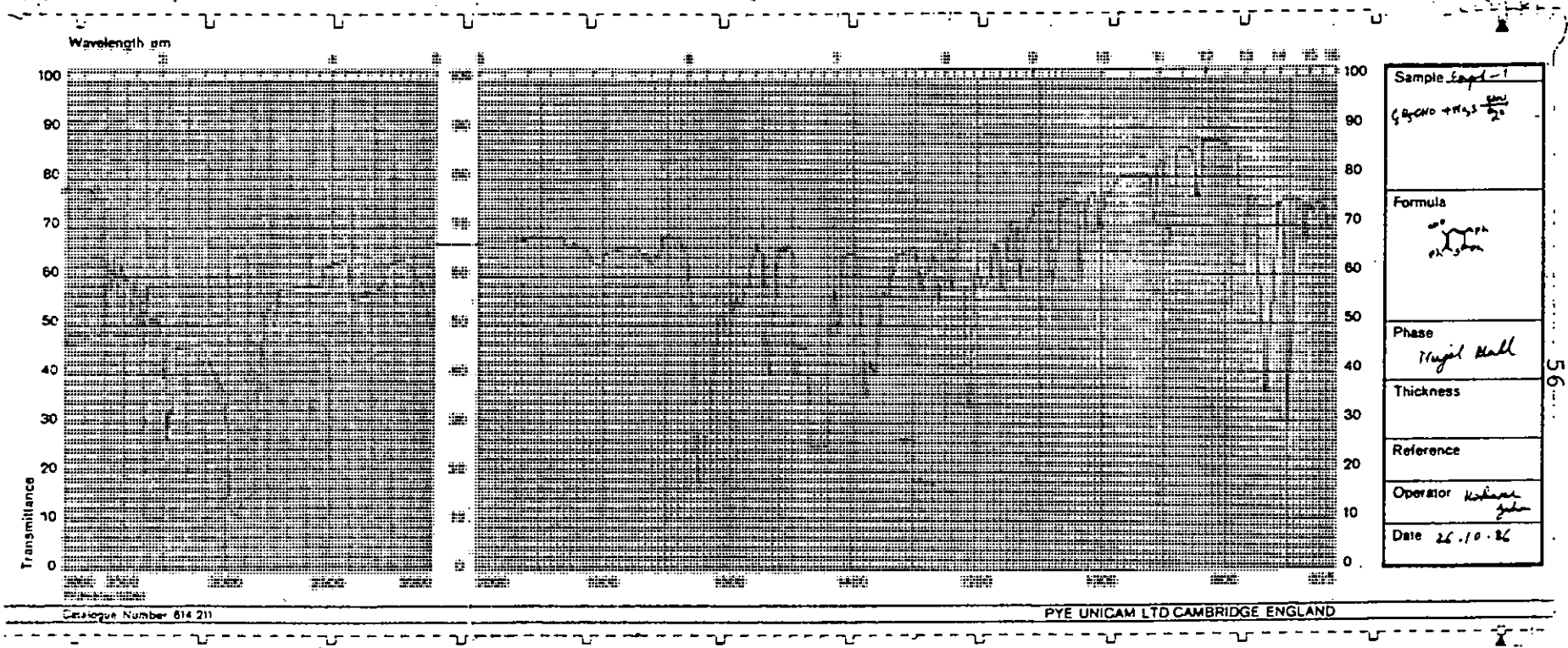
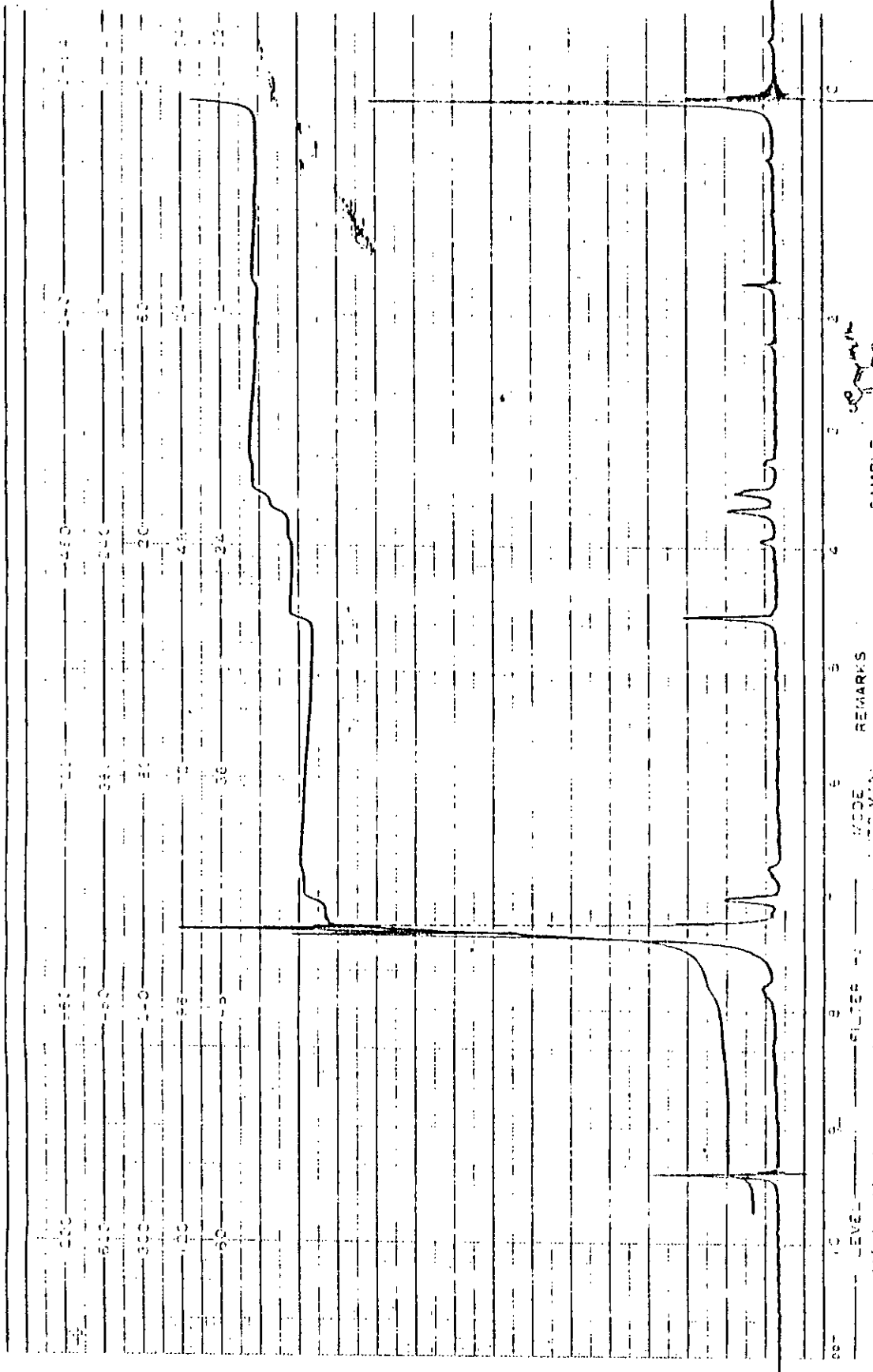


Fig 5:- The IR spectrum of the compound 3-benzyl-2,6-diphenyl-2H- thiopyran-5-carboxaldehyde



LEVEL 10 FILTER 1 MODE FM
 SWEEP WIDTH Hz 100 OFFSE 0
 SWEEP TIME SEC 10 AMPLITUDE 50
 CONC. 0.1M DATE 2014.85
 REFERENCE TMS OPERATOR MTQ
 SOLVENT CDCl3 SPECTRUM NO
 SAMPLE 10001

Fig-6:- The ¹H NMR spectra of 3-benzyl-2, 6-diphenyl-2H-thiopyran - 5-carboxaldehyde.

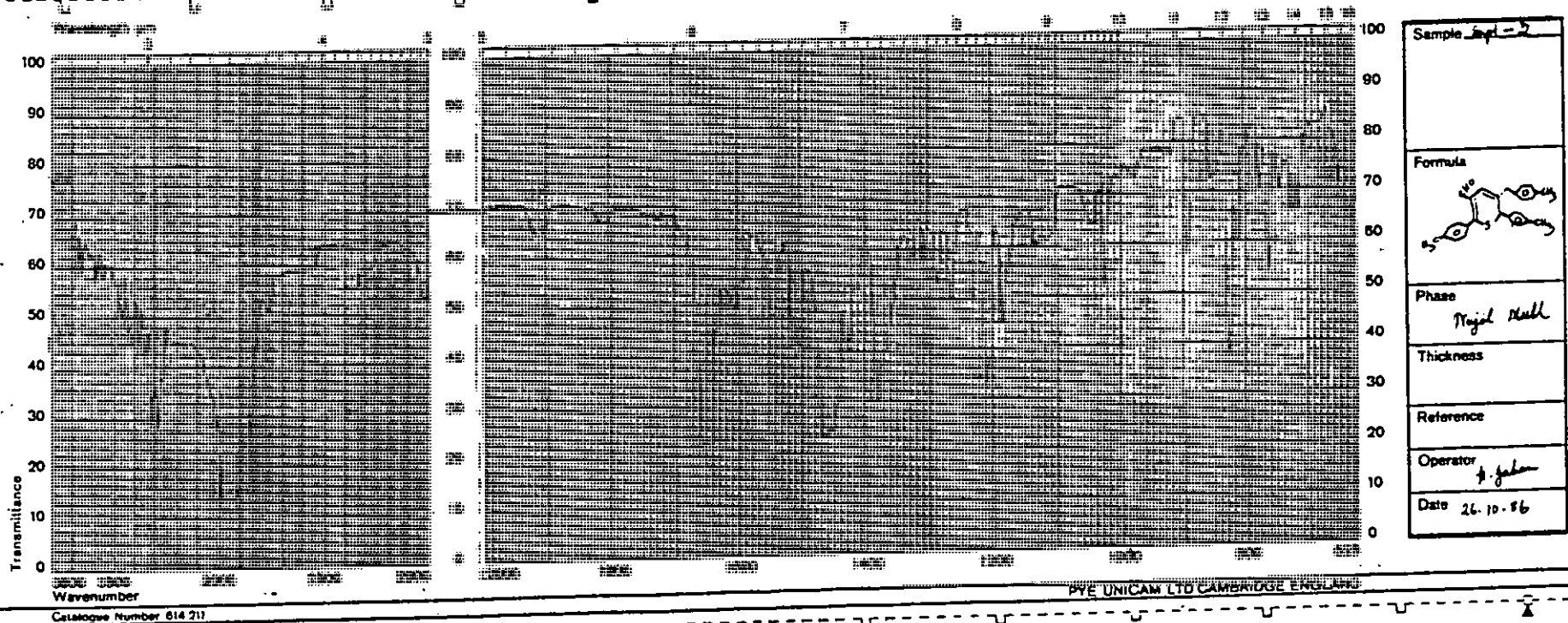
The NMR spectrum (in CDCl_3 , TMS as internal standard)
(Fig. 6 page 57) gave the following signals.

δ (ppm) = 9.27 (s, 1H, CHO)
= 7.17 (m, 15H, aromatic proton)
= 6.88 (s, 1H, olefinic proton)
= 4.5 (s, 1H, S-CH-Ph)
= 3.6 (q, 2H, AB pattern, $J_{AB} = 15$ Hz
benzylic protons adjacent to an asymmetric centre).

REACTION NUMBER 2The Reaction of 4-Methylbenzaldehyde with Sodium Sulphide and Ethanol in Water.

4-Methylbenzaldehyde (8.40 gm, 0.07 Mole) and absolute alcohol (140 cm³) were placed in a three-necked distilling flask (1 litre), fitted with a reflux condenser, a pressure equalizing dropping funnel and an efficient magnetic stirrer. A filtered sodium sulphide solution (50.4 gm, (0.21 Mole) of Na₂S, 9H₂O dissolved in 140 cm³ of water) was then added gradually from the dropping funnel over a period of 15 minutes. The mixture was refluxed on an oil bath for four hours with continued stirring. The oil-bath temperature was maintained between 90-100°C. The temperature of the reaction mixture was 78°C.

After the reflux period was over, it was cooled and kept standing overnight. No solid precipitate appeared. The mixture was then diluted with water and extracted with ether. The ether layer was dried over anhydrous sodium sulphate, filtered and then solvent removed by means of a rotary evaporator. This treatment gave a viscous liquid and some solid which was kept in a refrigerator for two days for complete precipitation. The precipitate was separated by filtration and dried under vacuum to give a product which on recrystilization from petroleum spirit (b.p, 60-80°)-benzene(80:20 mixture) gave 2,6-bis(4-methylphenyl)-3-(4-methylbenzyl)-2H-thiopyran-5-carboxaldehyde, m.p. 140-141°C, yield 29%.



09

Fig-7. The IR spectrum of 2,6-bis(4-methylphenyl)-3-(4-methylbenzyl)-2H-thiopyran-5-carboxaldehyde.

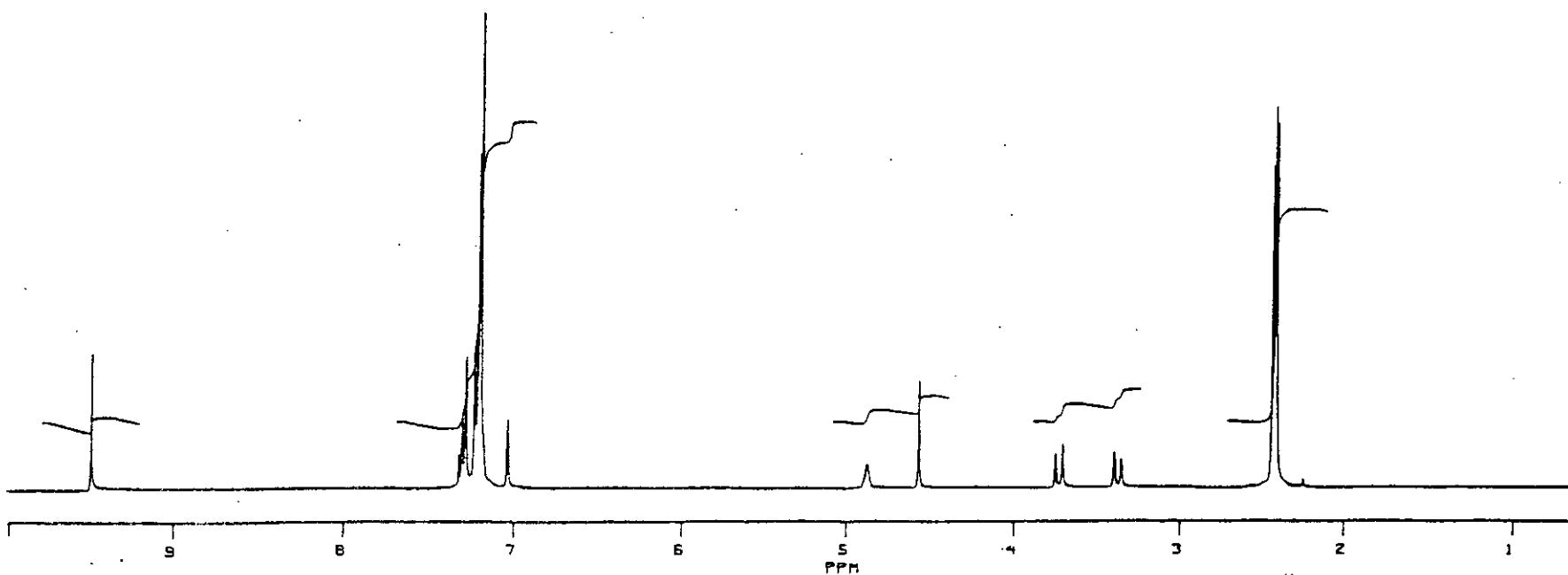


Fig-8. ^1H NMR spectrum of 2,6-bis(4-methylphenyl)-3-(4-methylbenzyl)-2H-thiopyran-5-carboxaldehyde.



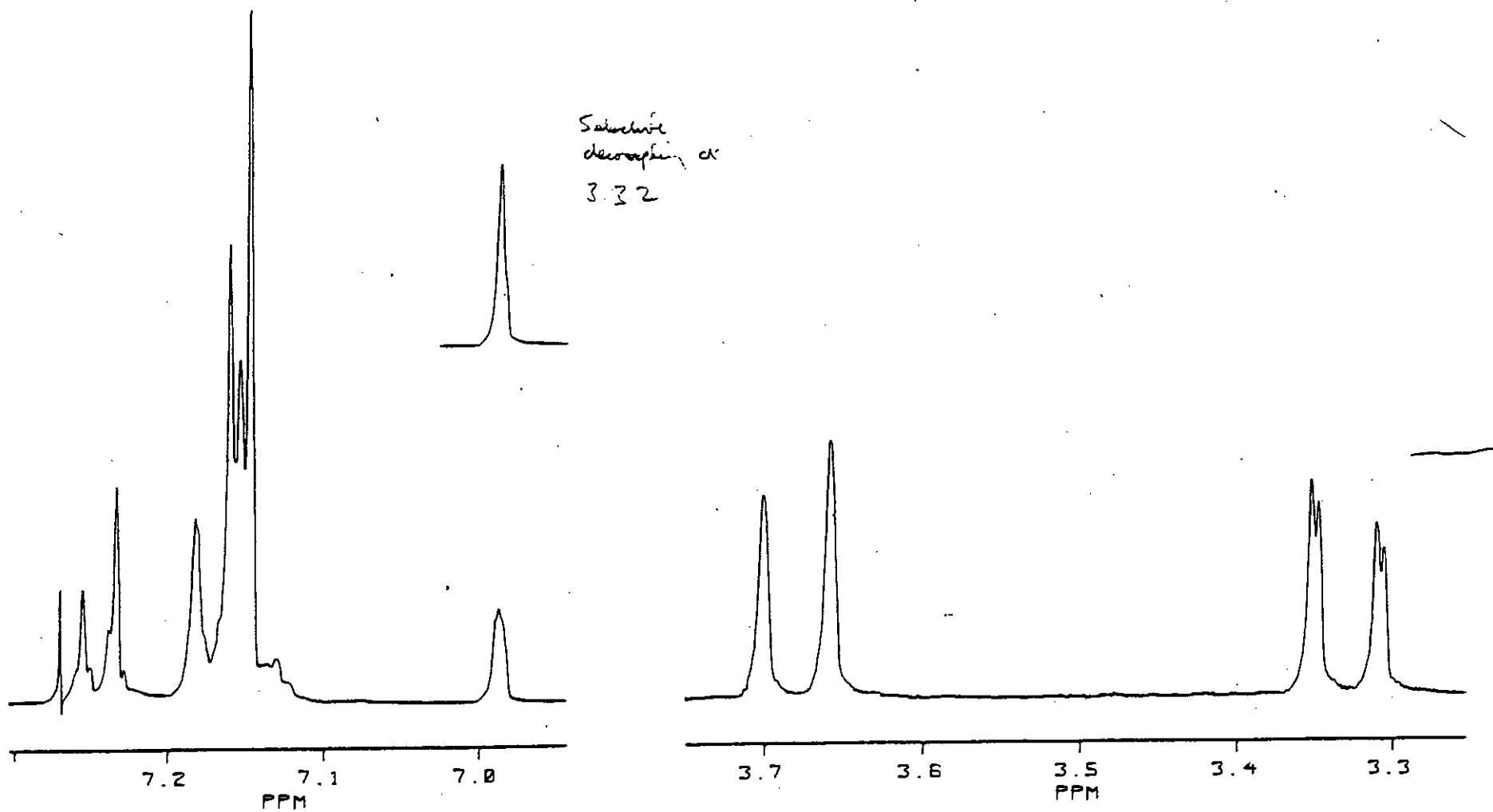


Fig-9. ¹H NMR of 2,6-bis (4-methylphenyl)-3-(4-methylbenzyl)-2H-thiopyran-5-carboxaldehyde
 Expansion of the spectrum between the region $\delta=3.7-3.3\text{ppm}$ and $\delta=7.3-7.0\text{ppm}$;

70425

3.PP

AGAIN. 001

MIN. INTENSITY = 1.799 P MAXY = 20.00000
 INTENS. LEVEL = 1.799 NOISE = .02990
 F1 = 3601.44 HZ = 10.0003 PPM F2 = .14 HZ = .0004 PPM

PP CONSTANT = 1.00000
 SENS. LEVEL = .11959
 .14 HZ = .0004 PPM

F	CURSOR	FREQUENCY	PPM	INTENSITY
1	1270	3400.455	9.4422	14.142
2	4654	2618.187	7.2700	5.626
3	4677	2612.778	7.2550	5.649
4	4685	2610.906	7.2498	1.923
5	4705	2606.481	7.2375	3.758
6	4713	2604.592	7.2323	10.367
7	4721	2602.732	7.2271	1.807
8	4793	2596.018	7.1807	8.824
9	4828	2578.015	7.1585	21.617
10	4838	2575.622	7.1518	16.093
11	4849	2573.167	7.1450	32.403
12	4865	2569.317	7.1343	1.980
13	4874	2567.246	7.1286	2.282
14	5097	2515.758	6.9856	4.517
15	8953	1624.271	4.5102	8.267
16	10216	1332.187	3.6991	1.406
17	10282	1316.912	3.6567	3.046
18	10758	1207.056	3.3517	2.543
19	10765	1205.354	3.3470	2.284
20	10824	1191.779	3.3093	2.041
21	12268	957.924	2.6822	21.977
22	12290	952.888	2.6683	26.956
23	12309	948.479	2.6560	26.864
24	13463	561.515	1.6147	3.074

3.2 2.7 2.LP

AGAIN. 001

WD QM QP A0 DP = 2L TD = 32K
 A0 = 4.3253760 SI = 32K SF = 360.1339798
 D1 = 5780.000 D2 = 5178.900 SW = 3787.879

HZ/

3.D0 2.7 2.2 2.3 3.EP 3.CX = 50.000 13
 3.EP F1(HZ) = 3601.441 25> 2630 F2(HZ) = .136 2500
 HZ/CM = 10.00 PPM/CM = .0278 OFFSET = -1.000
 MARK SEPARATION 1.00P .1P MARK CM = -.300
 F1(HZ) = 2629.965 1350 F2(HZ) = 2500.034 1170
 HZ/CM = 13.85 PPM/CM = .0384 3.CX = 13.000 18

Fig-10. Computer print of the ¹H NMR spectrum of (4-methylphenyl)-3-(4-methylbenzyl)-2H-thio-
 pyran-5-carboxaldehyde.

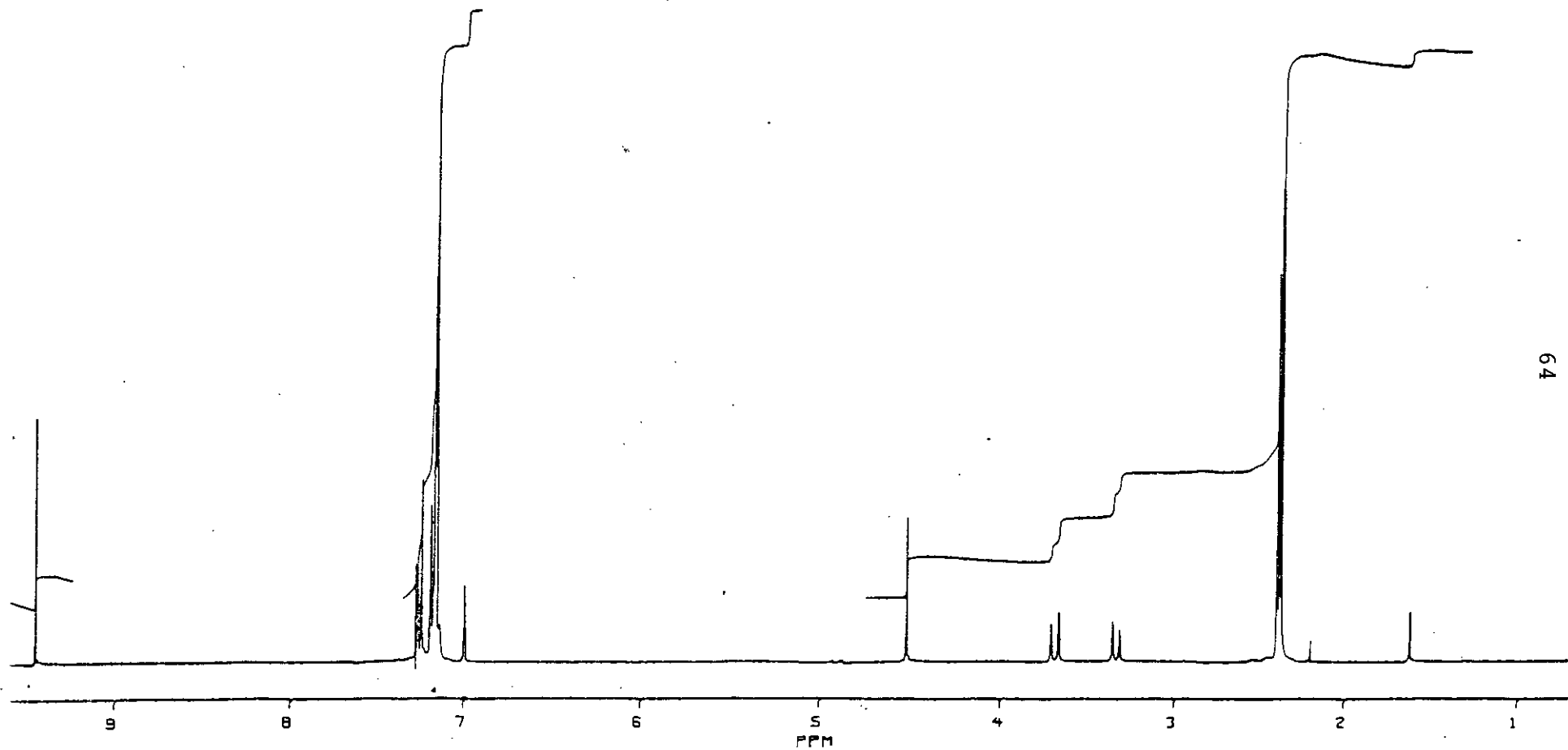
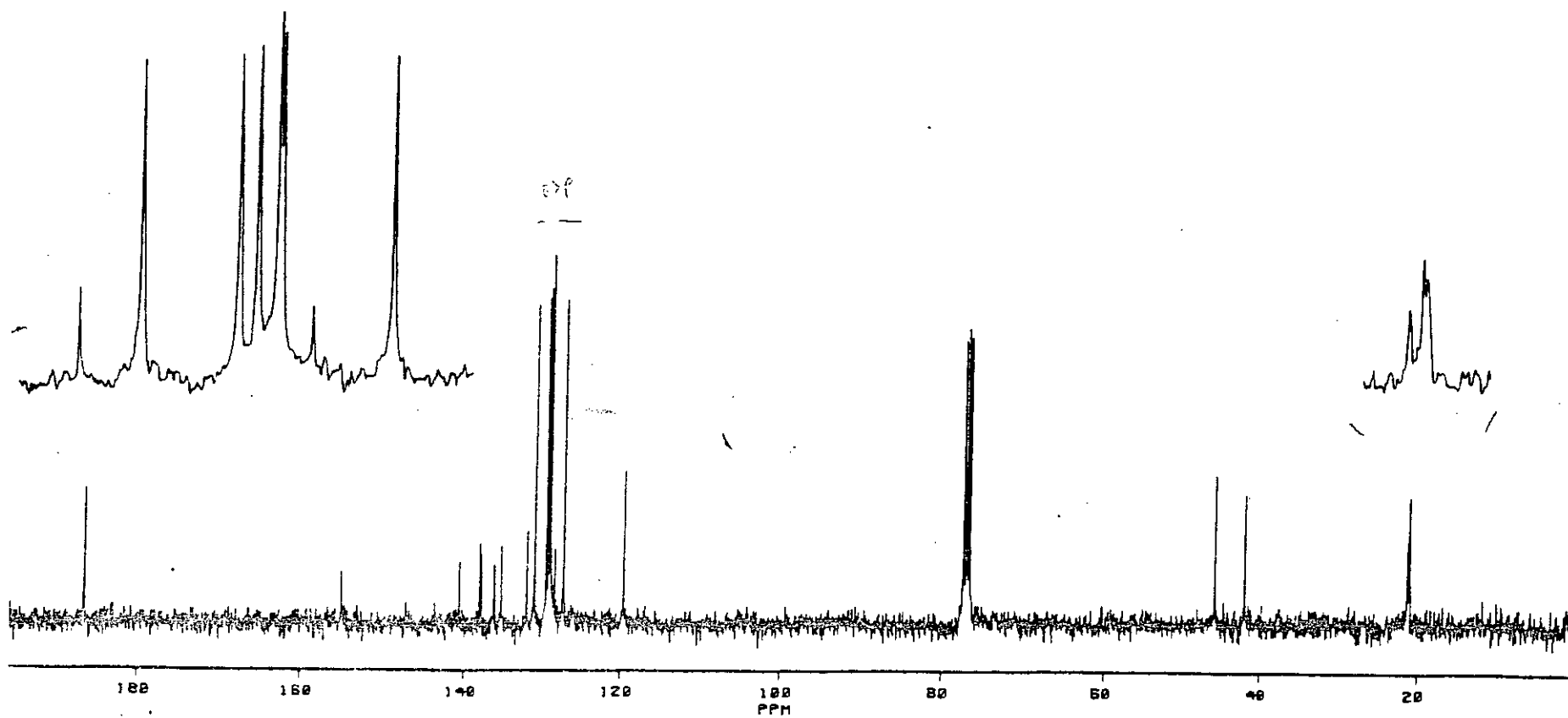


Fig-11: ^1H NMR of 2,6- bis (4-methylphenyl) -3-(4-methylbenzyl) -2H-thiopyran-5-carboxaldehyde in the presence of D_2O .



65

Fig-12. ^{13}C spectrum of 2,6-bis (4-methylphenyl)-3-(4-methylbenzyl)-2H-thiopyran-5-carbaldehyde.

```

1.3      3.TR = 1      1.LB = 2.000 2
1.EF    1.EP    1.7    1.3    3.7    3.TR = 1
1.TR(RT) 1.EF    1.EP    1.7    1.3    3.TR = 1
1.LB = 2.000      1.EP    1.EP    1.57
1.07    1.7      1.EP      F1[PPM] = 140.525 200
F2[PPM] = 119.462 0      HZ/CM = 362.22 PPM/CM = 4.0000
1.FP
    
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```

ASR13C.001
MIN. INTENSITY = -.281 P      MAXY = 20.00000      PP CONSTANT = 1.00000
INTENS. LEVEL = -.281      NOISE = .20845      SENS. LEVEL = .82382
F1 = 18111.71 HZ = 200.0062 PPM      F2 = .91 HZ = .0101 PPM
    
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L	CURSOR	FREQUENCY	PPM	INTENSITY
1	4116	16912.124	186.7593	4.230
2	6184	14043.100	155.0769	1.631
3	7116	12750.758	140.8057	2.027
4	7290	12509.190	138.1380	2.569
5	7306	12486.649	137.8891	2.210
6	7413	12338.805	136.2565	1.950
7	7472	12256.473	135.3473	2.451
8	7685	11960.986	132.0843	2.872
9	7749	11872.213	131.1039	9.935
10	7847	11736.002	129.5998	10.315
11	7866	11710.234	129.3152	10.581
12	7886	11682.517	129.0091	11.537
13	7890	11677.225	128.9507	11.293
14	7921	11633.563	128.4686	2.397
15	8000	11523.872	127.2572	10.197
16	8436	10836.036	119.6615	4.783
17	11257	7005.392	77.3600	9.251
18	11281	6973.423	77.0070	9.592
19	11303	6941.616	76.6557	9.299
20	13312	4155.728	45.8214	4.785
21	13562	3908.920	42.0616	4.188
22	14918	1927.449	21.2847	2.707
23	14931	1909.110	21.0822	4.163
24	15534	1073.213	11.8514	.872
25	15651	910.862	10.0586	.837
26	16281	36.972	.4083	.853

```

1.7      1.EP    1.7      1.PE JOB ACTIVE      1.AGA31F.001?
1.2      2.RE SAUD.011 AGA>> KAA195FT.011      2.SW = 83333.333 HZ 1.0817E3 PPM
00000
AQ= .164      2.PM = 24.0 40      2.FD = .1000000 0T
2.7      2.FD = 0.0      2.TD = 32K 511M
AQ= .003      2.GS      2.7      2.PE KAA195FT.011
2.W?      2.W?      2.SY= 70.7700000 67.67      2.7
2.EP      2.EP      F1[HZ]=13851.467      F2[HZ]=-19682.039
HZ/CM= 259.18      PPM/CM= 2.8982
2.1      1.EP      F1[PPM]= 200.006
F2[PPM] = .010      HZ/CM= 362.22      PPM/CM= 3.9999
OFFSET = -1.500      MARK SEPARATION 20.00P 20
MARK CM = -.300      1.3      3.2      2.PE KAA195FT.011
2.25      2.SW = 83333.333 2.LB = 3.000      2.AQ = .1966080
TD = 32K      2.LB = 3.000 10      2.EF
    
```

Fig-13. Computer print of the ¹³C spectrum of Fig-12 .

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02-12/88 23:20:00 + 2:21
SAMPLE:

DATA: BINU #141

BASE M/E: 185
RIC: 122368.

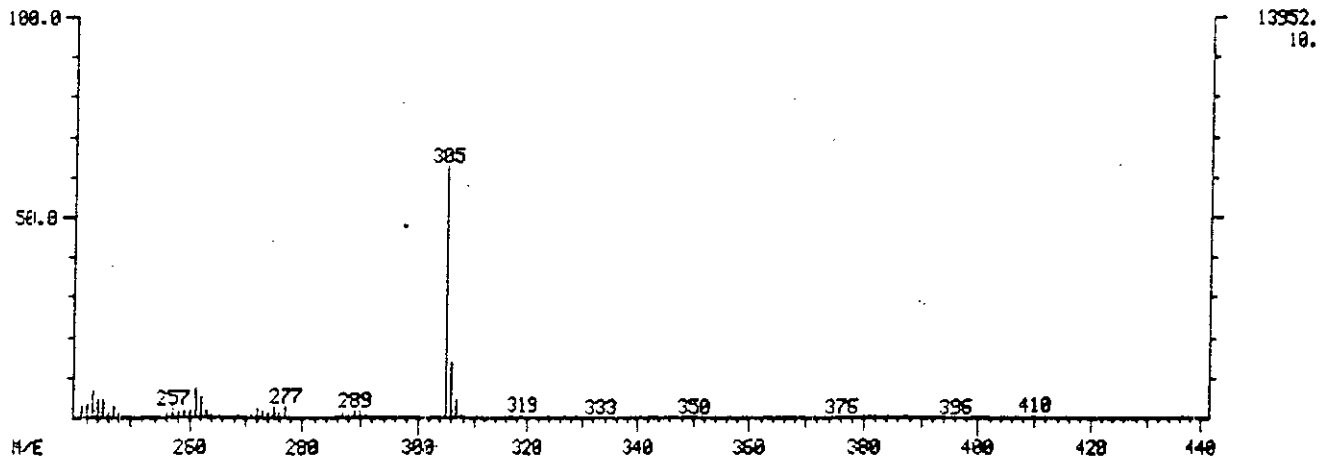
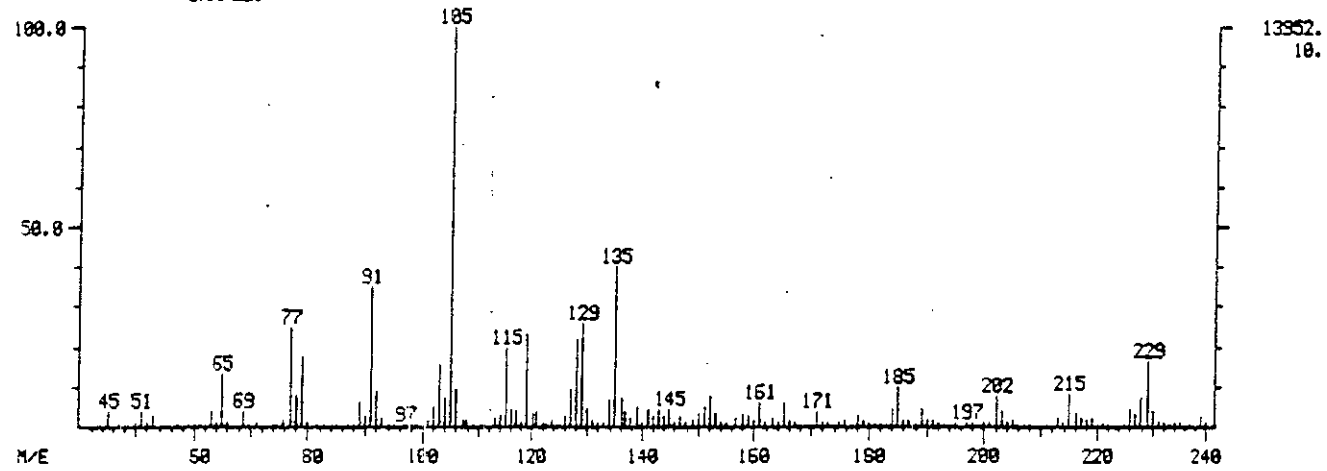


Fig-14. The Mass spectrum of 2,6-bis(4-methylphenyl)-3(4-methylbenzyl)-2H-thiopyran-5-carboxaldehyde

MASS SPECTRUM
02/12/88 23:28:00 + 2:21
SAMPLE:

DATA: BINU #141

BASE M/E: 105
RIC: 122368.

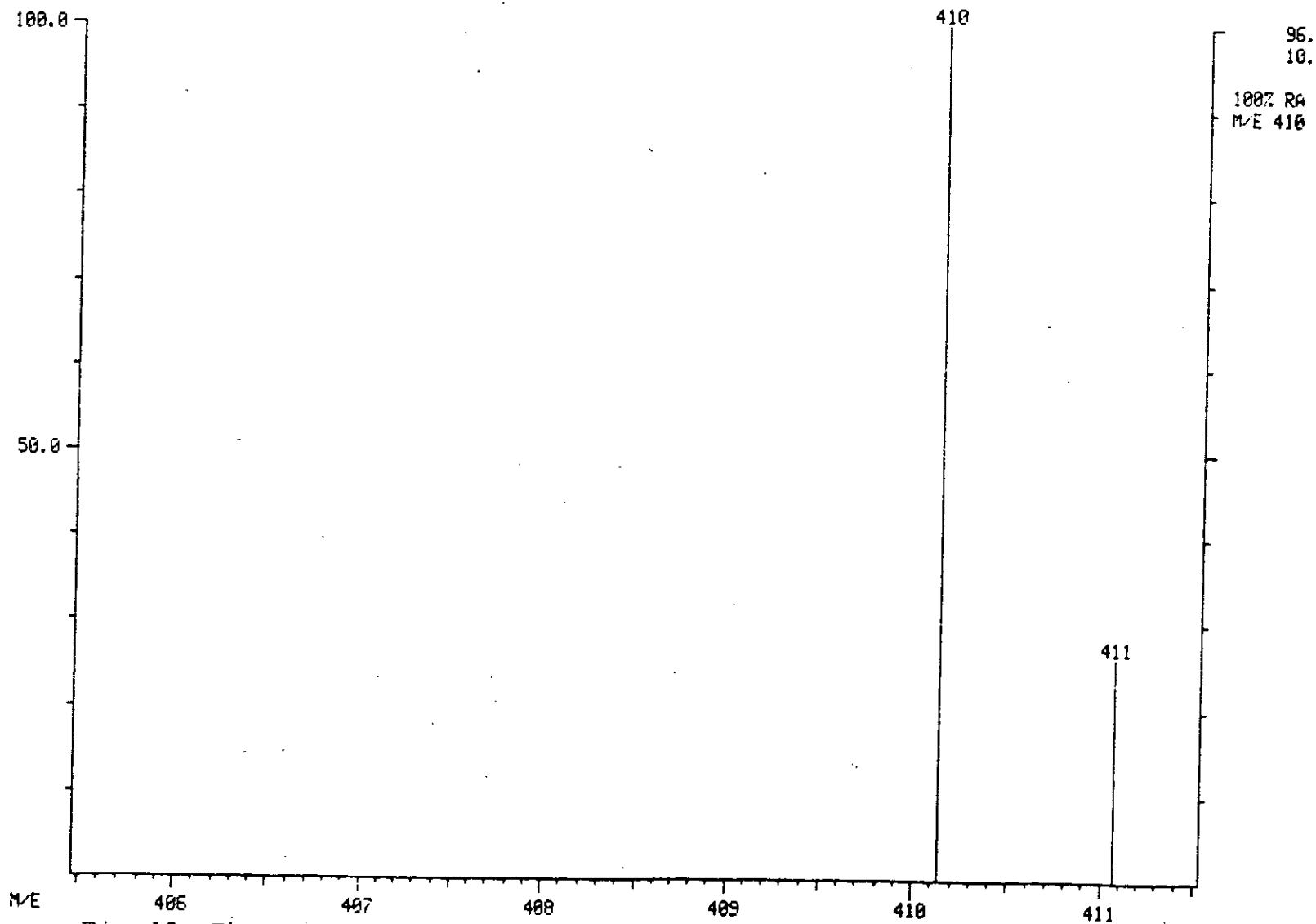


Fig-15. The Mass spectrum of the compound of Fig.-14 expansion between m/e 405.5-411.5

IR Spectrum

The IR spectrum (as nujol mull) of the compound has the following important absorption bands ν_{\max} at cm^{-1} : 2760w(H-CO), 1650vs(CO), 1605w, 1590w(aromatic skeletal), 1540m, 1510n, sh, 1324w, 1310w, 1287w, 1263m, 1230w, 1210s, 1186m, 1118m, sh, 1045m, 1026m, 890s, 861m, sh, 827s, sh, 778w, 762m, 745w, 727w and 715w.

^1H NMR Spectrum

The ^1H NMR spectrum of the compound was taken in CDCl_3 with TMS as the internal standard. The spectrum shows the following signals at δ (ppm): 9.442(s, 1H, CHO); 7.270-7.145 (m, 12H, ArH), 6.986(s, 1H, olefin), 4.510(s, 1H, benzylic), 3.678 (d, 1H, benzylic adjacent to an asymmetric centre) 3.355(d, 1H, benzylic, adjacent to an asymmetric centre. $J_{AB}=15.3 \text{ Hz}$, 2.382 (s, 3H, CH_3) 2.368 (s, 3H, CH_3), 2.356 (s, 3H, CH_3), (fig.8, Page 61).

Shaking the CDCl_3 solution of this compound with D_2O does not change the nature of the spectrum (fig.11, Page 64).

^{13}C NMR Spectrum

The ^{13}C NMR spectrum of the compound was taken in CDCl_3 with TMS as internal standard. The spectrum has the following signals at δ (ppm): 186.759(CO), 155, 077, 140.806, 138, 137.889, 136.257, 135.347, 132.084, 131.104, 129.600, 129.315, 129.001, 128.951, 128.469, 127.257, 119.661(aromatic and olefinic carbons),

45.891, 42.061 (aliphatic carbon), 21.2847, 21.100 and 21.062 (methyl carbon) (fig. 12 page 65).

Mass Spectrum

The mass spectrum of the compound has the following important peaks at $m/e=410(M)^+$, $319(M-Tol)^+$, $305(M-CH_2Tol)^+$, $229(M-C_6H_4CH_3, -C_6H_4CH_2)^+$, $215(M-C_6H_4CH_3, -C_6H_4CH_2, -CH_2)^+$, $185(M-C_6H_4CH_3, -C_6H_4CH_2, -CH_2, -CHOH)^+$, $135(Tol-CS)^+$, $105(TolCH_2)^+$, $91(C_7H_7)^+$, $77(C_6H_5)^+$, $65(C_5H_5)^+$, $51(C_4H_3)^+$.

Treatment of the mother layer

The mother layer contained a number of compounds one of which was isolated by preparative tlc as 4-methylbenzyl alcohol, m.p. 58-59°C, (reported m.p. 60°C), yield 10%.

The reaction mixture also contained some 4-methylbenzoic acid and elemental sulphur but these were not quantified.

REACTION NUMBER 3The Reaction of 4-Methoxybenzaldehyde with SodiumSulphide and Ethanol in Water.

4-Methoxybenzaldehyde (4.08 gm, 0.03 Mole) and freshly distilled absolute alcohol (60 cm³) were placed in a 1 litre three-necked flask, fitted with a reflux condenser, a pressure-equalizing dropping funnel and an efficient magnetic stirrer. Aqueous sodium sulphide solution (21.6 gm, 0.09 Mole of Na₂S, 9H₂O in 60 cm³ of water) was then added slowly from the dropping funnel over a period of 10 minutes. The mixture was refluxed on an oil bath for four hours with continued stirring and the temperature of the oil-bath was maintained between 90-100°C. The temperature of the reaction medium was 78°C. The reaction mixture was then cooled and kept standing overnight. No precipitate appeared. The mixture was diluted with water and extracted with ether. The ether layer was dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure when a brown viscous liquid 3.18 gm, was obtained. Separation of the mixture on a silical gel column with pet. ether (b.p. 60-80°C)-benzene (80:20 v/v) as eluent gave pure 2,6-bis(4-methoxyphenyl)-3-(4-methoxybenzyl)-2H-thiopyran-5-carboxaldehyde, m.p. 171-173°C(uncorrected); yield, 1%.

Because of the particularly low yield of the compound there was only enough sample for NMR studies.

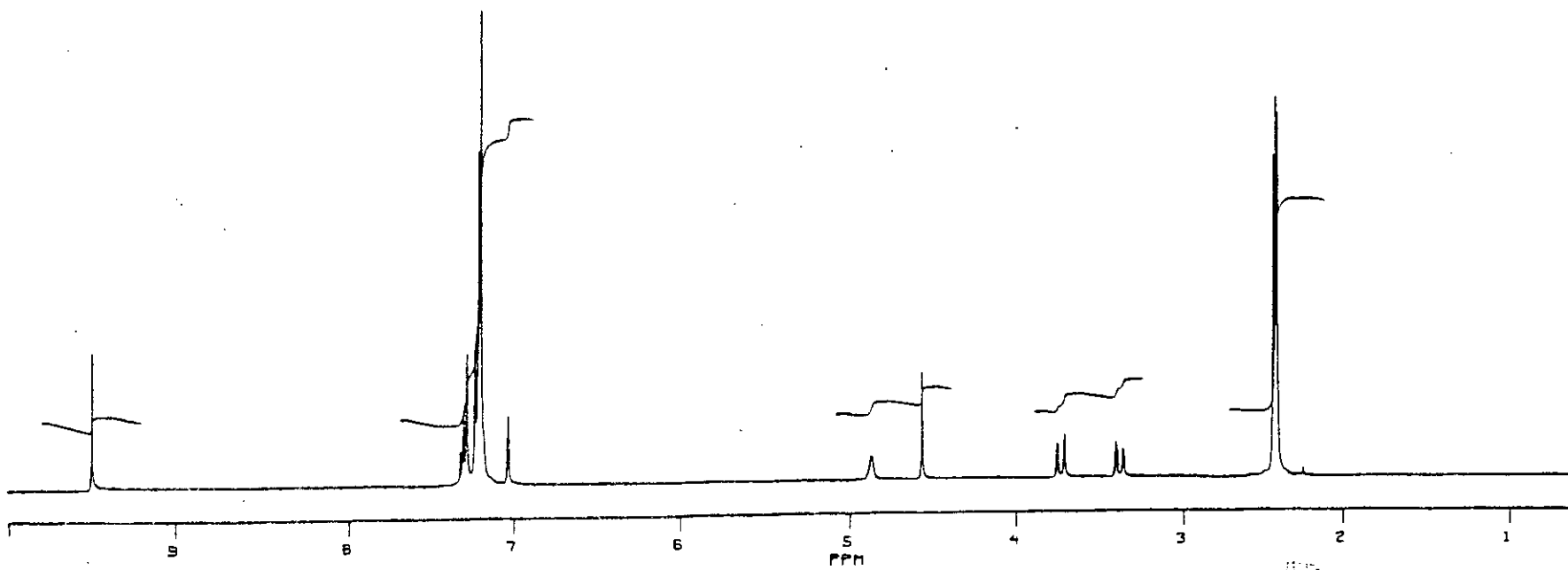


Fig-16. The ^1H NMR spectrum of 2,6-bis(4-methoxyphenyl)-3-(4-methoxybenzyl)-2H-thiopyran-5-carboxaldehyde.

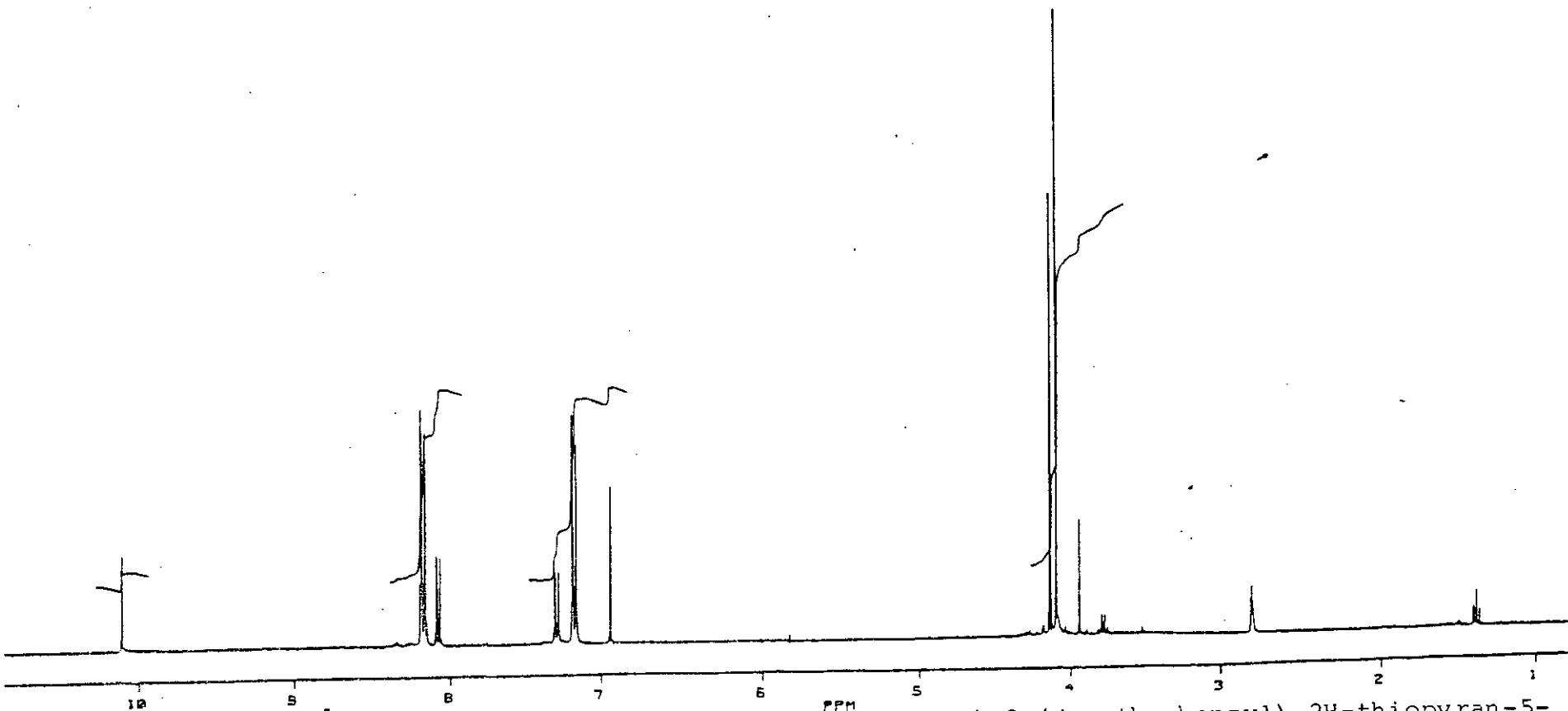


Fig-16a: The ^1H NMR spectrum of 2,6-bis(4-methoxyphenyl)-3-(4-methoxybenzyl)-2H-thiopyran-5-carboxaldehyde in the presence of D_2O .

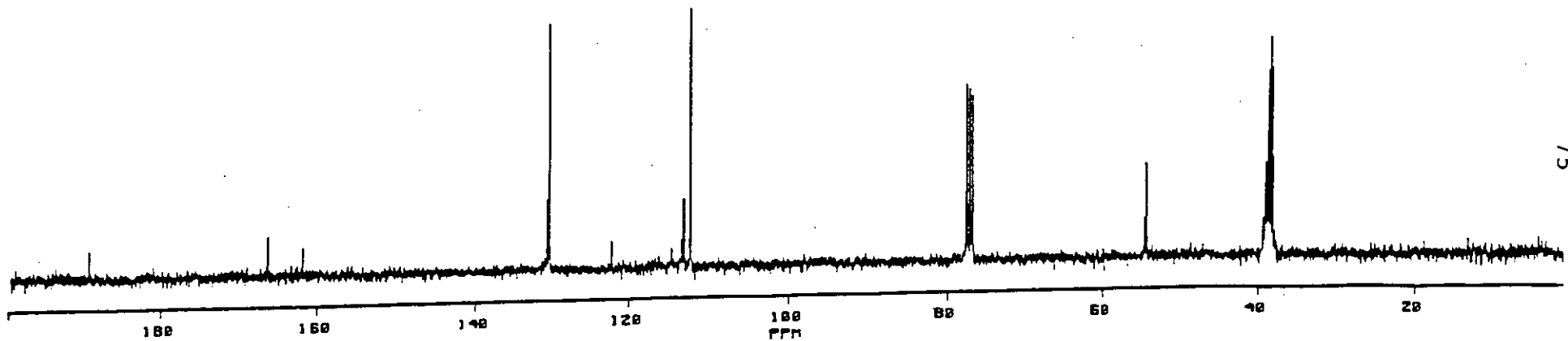
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 PULP. 11.00 = 2.10 PULP. = 20.00000
 P1 = 3.1108 HZ = 11.0000 PPM P2 = 1.07 Hz = 1.0002 PPM

L	CURSDP	FREQUENCY	PPM	INTENSITY
1	1668	2927.242	10.0997	3.069
2	4646	2948.800	8.1881	1.088
3	4142	2949.107	8.1862	2.145
4	1653	2947.113	8.1834	1.111
5	4665	2944.100	8.1759	1.791
6	4674	2942.109	8.1700	2.093
7	4634	2937.953	8.1568	2.799
8	4701	2935.945	8.1524	5.699
9	4704	2935.424	8.1509	7.342
10	4715	2932.087	8.1433	1.818
11	4813	2919.165	8.0808	2.996
12	4822	2909.093	8.0750	1.827
13	4842	2903.366	8.0619	1.110
14	4849	2901.742	8.0574	2.142
15	4951	2901.311	8.0562	2.875
16	6038	2626.802	7.2940	2.405
17	6047	2624.841	7.2865	1.649
18	6076	2618.111	7.2698	2.361
19	6248	2587.651	7.1853	1.127
20	6249	2584.944	7.1777	7.587
21	6289	2582.619	7.1719	1.318
22	6249	2578.037	7.1586	2.607
23	6258	2575.986	7.1529	6.464
24	6270	2573.193	7.1451	1.738
25	6300	2496.813	6.9333	2.373
26	6303	2496.274	6.9315	5.039
27	11247	1487.257	4.1397	8.042
28	11249	1486.723	4.1383	14.713
29	11249	1471.214	4.0352	35.532
30	11246	1469.085	4.0293	1.977
31	11277	1415.651	3.9203	3.788
32	11503	1363.427	3.7859	1.735
33	11503	1356.463	3.7666	1.717
34	11501	1010.092	2.8048	1.133
35	11039	1008.275	2.7997	1.580
36	13048	1006.328	2.7943	1.087
37	15266	493.467	1.3702	1.753
38	15268	492.891	1.3686	1.245

3.11

AGAIN.001
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 AQ = 4.3253760 SI = 32K SF = 360.1335292
 DI = 5780.000 D2 = 0.0 SM = 3787.879
 HZ/FT = .231 FM = 4800 TE = 297
 FD = 0.0 FW = 20.0 HE = 88
 DS = 0 DW = 132 DE = 66.0
 DP CURRENT = 12 SV = 0.0 EP = 1.1
 EG = 100
 HC = 1 LB = -1.750 GR = 0.0
 TM1 = 0 TM2 = 0 RPH = 0
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 CY = 0.0 MAXX = 35 MAXY = 20.000
 SE = 3651.094 IS = 1 AZEM = 0.00
 GATE = 0 ABSC = 5
 PASC = 0 NOBC = 0 ISLN = 128
 MI = .648P PC = 1.000 AI = 0
 PDI = 0.0 PDI = 0.0 GS GAMMA =
 PDI = 0.0 PDI = 0 SREP =
 3 3.2 2.02 = 0. 2.1M 772.879 H. 100 CM

Fig-17, Computer print of the ^1H NMR spectrum of the compound of Fig-16.



75

Fig-18. ^{13}C spectrum of 2,6-bis(4-methoxyphenyl)-3-(4-methoxybenzyl)-2H-thiopyran-5-carboxaldehyde.

MARK CM = 300 NI = 3.387 P 1.PP
 SM.011
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 F1 = 18111.75 HZ = 200.0054 PPM F2 = .96 HZ = .0106 PPM

L	CURSOR	FREQUENCY	PPM	INTENSITY
1	3553	17120.521	189.0593	3.901
2	5054	15037.803	166.0602	5.131
3	5344	14634.893	161.6109	3.957
4	7387	11802.067	130.3285	9.428
5	7404	11777.743	130.0598	31.296
6	7933	11044.606	121.9639	3.813
7	8504	10252.534	113.2172	3.773
8	8520	10230.413	112.9729	9.098
9	8575	10153.439	112.1229	32.729
10	10844	7006.164	77.3680	22.456
11	10868	6973.221	77.0042	22.333
12	10891	6940.500	76.6438	21.427
13	12358	4905.420	54.1698	5.525
14	12374	4883.778	53.9309	11.986
15	13328	3560.016	39.3127	5.128
16	13343	3539.225	39.0831	12.226
17	13359	3517.990	38.8486	24.176
18	13374	3496.919	38.6160	28.006
19	13389	3475.873	38.3835	24.022
20	13404	3455.046	38.1536	12.768

1.7 1.LP
 SM.011

BB ON OP AO DP = 8H TD = 32K
 AQ = .7208960 SI = 32K SF = 90.5563326
 BI = 37017.510 DI = 7500.000 SW = 22727.273
 HZ/PT = 1.387 FM = 28500 TE = 297
 RD = 2.0000000 FM = 15.0 NS = 1384
 DS = 0 DM = 22 DE = 11.0
 DP DIFFERENTIAL = 12 SY = 67.4000000 PR = H 1
 RG = 400
 NC = 3 LP = 2.000 GB = 0.0
 TH1 = 0 TH2 = 0 APKN = 0
 F1(PPM) = 200.005 F2(PPM) = .011
 HZ/CM = 362.22 PPM/CM = 3.9999 CX = 50.000
 CY = 0.0 MAXX = 25 MAXY = 20.000
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 AZFE = 0 ABSG = 5 ABSL = 3
 FADE = 0 HUBC = 0 ISEN = 128
 MI = 3.387P PC = 1.000 AI = 0
 PCO = 0.0 FLI = 0.0 QS GAMMA = 0.0
 ALPHA = 0.0 HZP = 0 SEEP = B
 1. DEL SM. + DELETE (Y OR N): Y 1. DEL DL. + FILE NOT FOUND

Fig-19. Computer print of ¹³C spectrum of compound of Fig- 18 .

^1H NMR Spectrum

The ^1H NMR spectrum was taken in CDCl_3 solution with TMS as internal standard. The spectrum shows the following signals at δ (ppm): 10.100 (s, 1H, CHO), 8.188-8.062(m, 12H, ArH), 6.933(s, 1H, olefinic), 4.128(s, 3H, MeO), 4.085(s, 6H, MeO), 3.931(s, 1H, S-CH-Ar), 2.799(AB pattern, adjacent to an asymmetric centre, 2H, benzylic).

^{13}C NMR Spectrum

189.059 (CHO), 166.060, 161.611, 130.328, 130.060, 121.964, 114.400, 113.217, 112.973, 112.123(aromatic and olefinic), 54.170, 53.931(aliphatic & benzylic), 39.313, 39.083, 38.849 (methoxy).

Beside this, some 4-methoxybenzyl alcohol, 4-methoxybenzoic acid were obtained in approximately, equimolar ratio (1.0 & 11%). Some elemental sulphur was isolated but it was not quantized.

REACTION NUMBER 4The Reaction of 4-Chlorobenzaldehyde with Sodium Sulphide and Ethanol in Water.

4-chlorobenzaldehyde (4.215 gm, 0.03 Mole) and absolute alcohol (60 cm³) were placed in a three-necked distilling flask (1 litre), fitted with a reflux condenser, a pressure-equalizing dropping funnel and an efficient magnetic stirrer. A filtered sodium sulphide solution (21.6 gm, 0.09 Mole of Na₂S, 9H₂O dissolved in 60 cm³ fo water) was then added gradually from the dropping funnel over a period of 15 minutes. The mixture was refluxed on an oil bath for two hours with continued stirring and the oil-bath temperature was maintained between 90-100°C. The temperature of the reaction mixture was 78°C. The reaction mixture was then cooled & kept standing overnight. No solid precipitate appeared. The mixture was then diluted with water and extracted with ether. The ether layer was dried over anhydrous sodium sulphate, filtered and then solvent removed by means of a rotatory evaporater.

This gave a brown viscous liquid, 2.8049 gm. This was extracted with boiling pet. ether (b.p. 60-80°C). From the ether extract there was obtained 0.79 gm of light yellow coloured needle shaped crystals, m.p. 75°C, (reported ⁶⁹m.p. of 4-chlorobenzyl alcohol, 75°C).

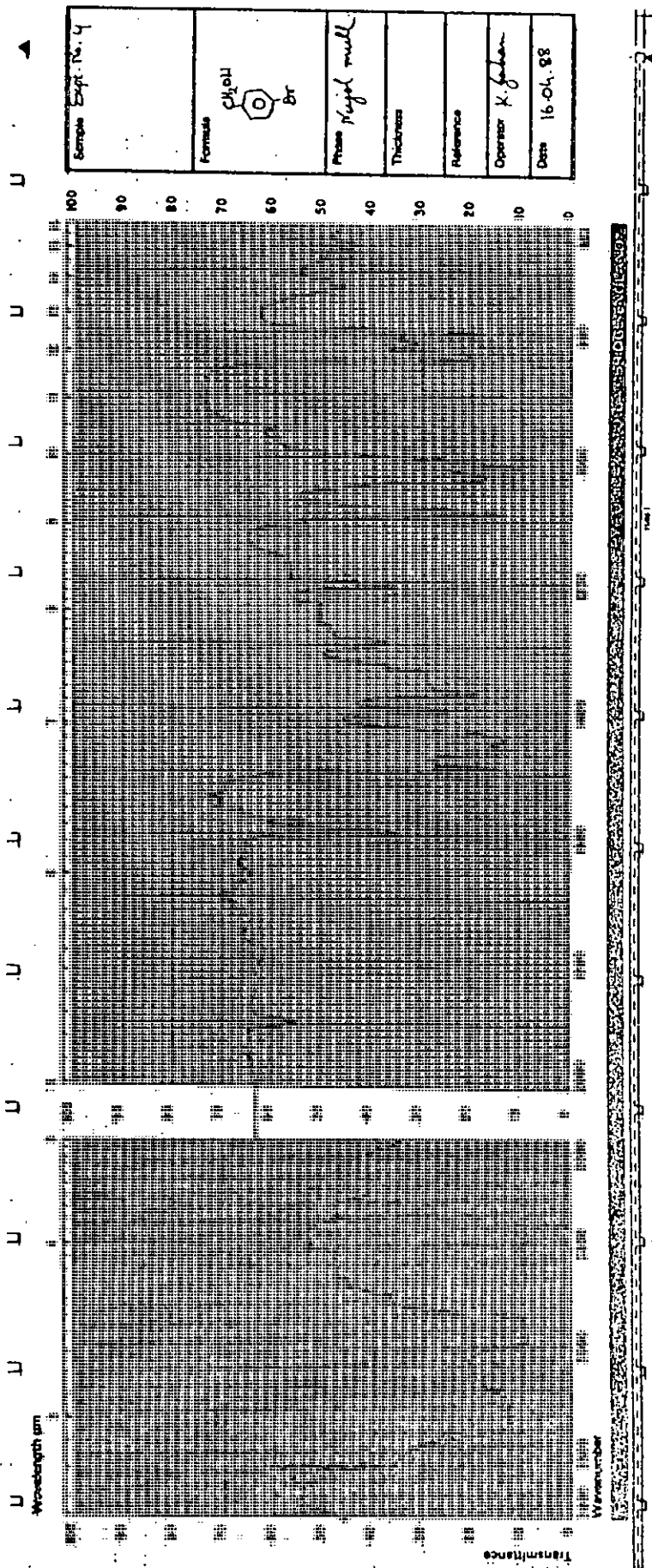


Fig-20. IR spectrum of 4-chlorobenzyl alcohol.

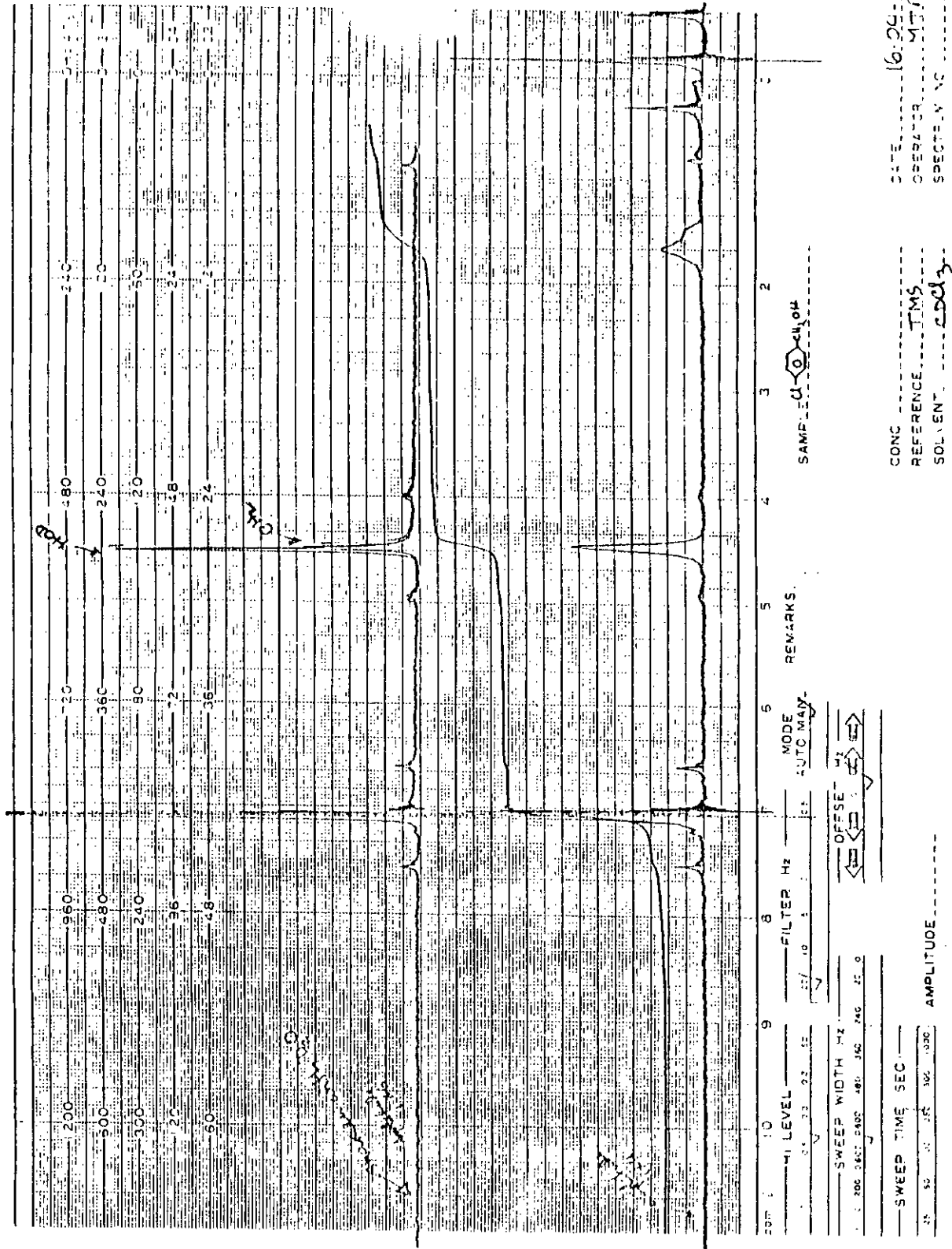


Fig- 21. ¹H NMR spectrum of 4-chlorobenzyl alcohol .

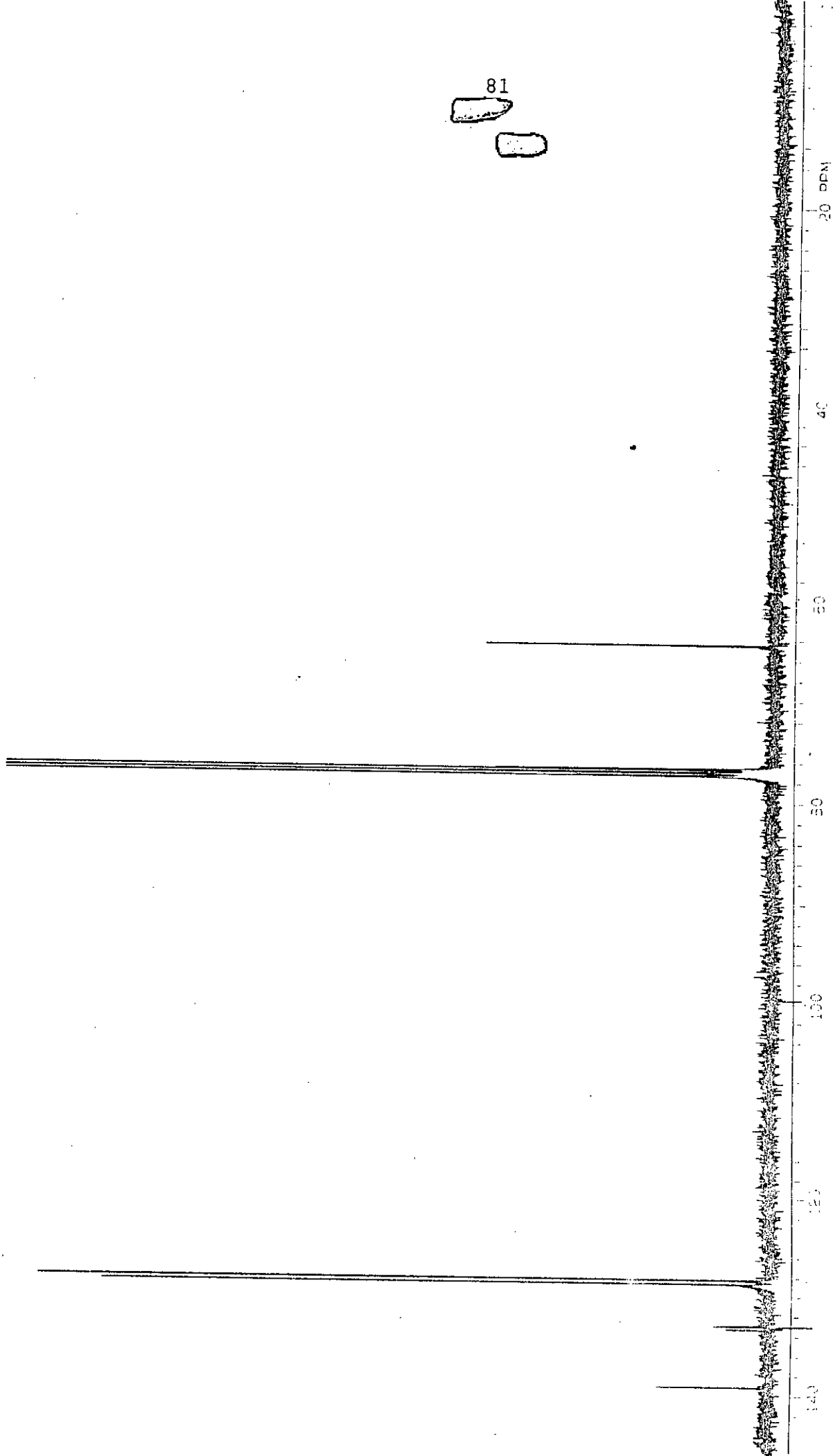


Fig-22. ^{13}C spectrum of 4-chlorobenzyl alcohol.

IR Spectrum

The IR spectrum (fig. 20 page 79) was taken as nujol mull and it has the following major peaks at ν_{\max} (cm^{-1}): 3400 br (OH), 1596 m, 1588 w (aromatic skeletal), 1480 s, 1403 s, 1296 m, 1210 s, 1088 s, 1030 s, 1016 s, 837 s, sh & 800 s.

 ^1H NMR Spectrum

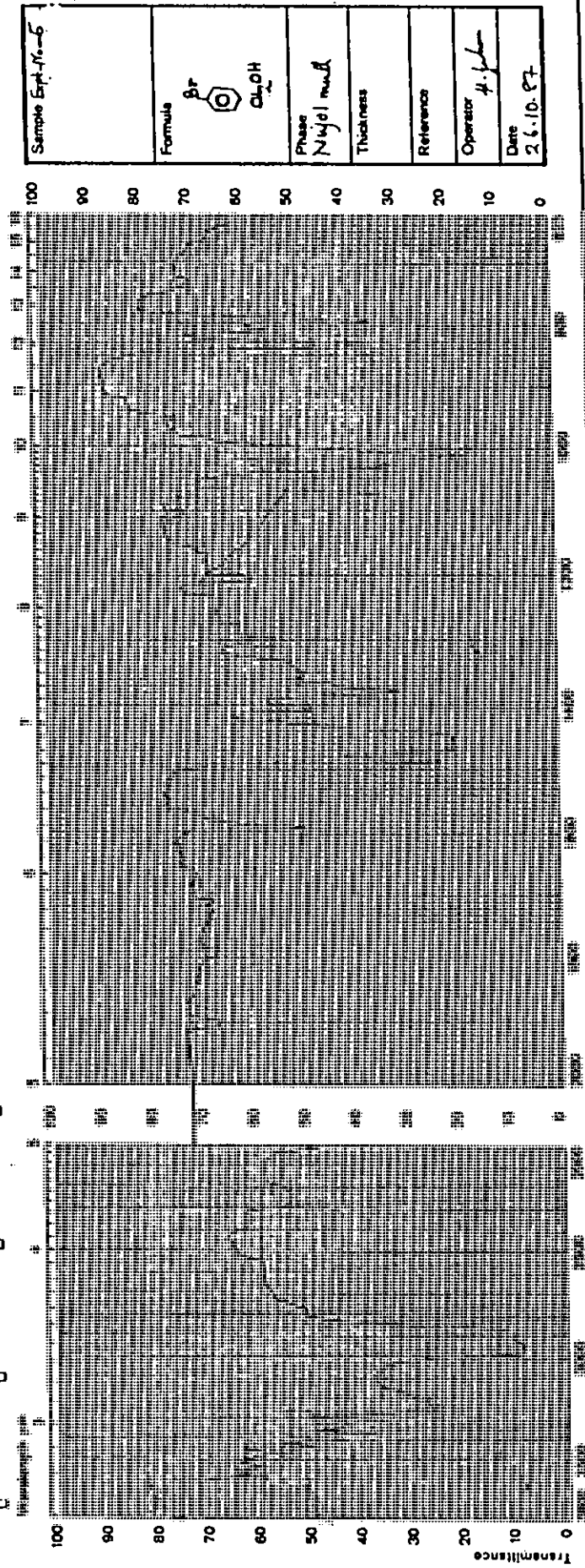
The ^1H NMR spectrum (fig. 21 page 80) of the compound was taken in CDCl_3 with TMS as internal standard and it has the following signals at δ (ppm) = 7.23(s, 4H, aromatic proton), 4.60(s, 2H, benzylic proton) and 1.83 (s, 1H, OH).

 ^{13}C NMR Spectrum

The ^{13}C NMR spectrum (fig. 22 page 81) was taken on a 400 MHz machine in CDCl_3 and TMS as internal standard. The spectrum has following signals at δ (ppm) = 139.5, 133.5, 133.0, 129.0, 128.5 (aromatic carbon) and 64.5 (benzylic carbon).

REACTION NUMBER 5The Reaction of 4-Bromobenzaldehyde with Sodium Sulphide
and Ethanol in Water.

4-Bromobenzaldehyde (5.547 gm, 0.03 Mole) and absolute alcohol (60 cm³) were placed in a three-necked distilling flask (1 litre), fitted with a reflux condenser, a pressure-equalizing dropping funnel and an efficient magnetic stirrer. A filtered sodium sulphide solution (21.6 gm, 0.09 Mole of Na₂S, 9H₂O dissolved in 60 cm³ of water) was then added gradually from the dropping funnel over a period of 15 minutes. The mixture was refluxed on an oil bath for two hours with continued stirring and the oil-bath temperature was maintained between 90-100°C. The temperature of the reaction mixture was 78°C. The reaction mixture was then cooled and kept standing overnight. No solid precipitate appeared. The mixture was then diluted with water and extracted with ether. The ether layer was dried over anhydrous sodium sulphate, filtered and then solvent removed by means of a rotatory evaporater. This gave a brown viscous liquid, 1.280 gm. This was extracted with boiling pet. ether (b.p. 60-80°C). From the ether extract there was obtained 0.48 gm needle shaped crystals, m.p. 76°C (reported⁶⁹ m.p. for 4-bromo-benzyl alcohol is 76°C). The yield was 8%.



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Fig-23. IR spectrum of 4-Bromobenzyl alcohol.

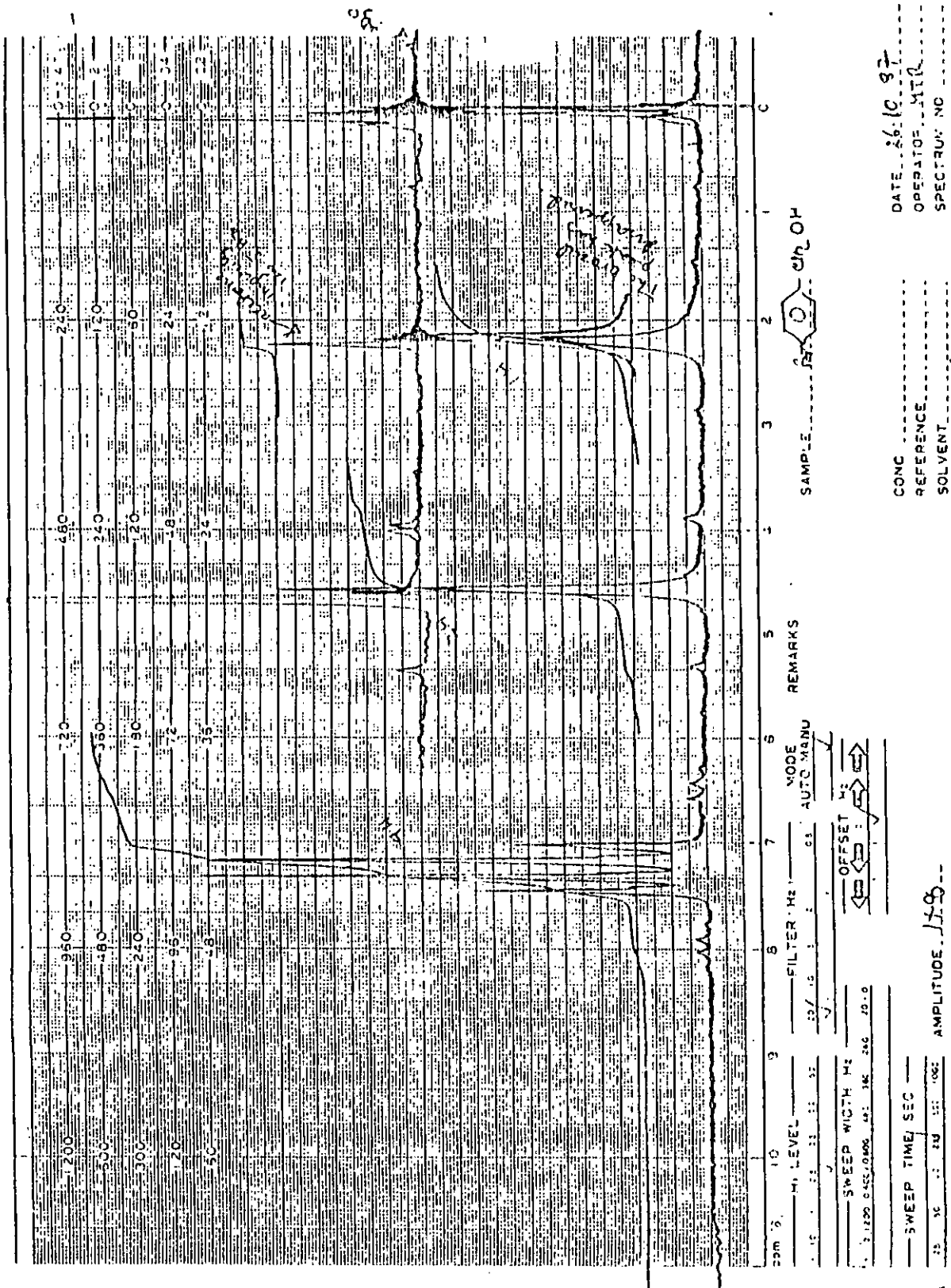


Fig-24. ¹H NMR spectrum of 4-Bromobenzyl alcohol.

IR Spectrum

The IR spectrum (as nujol mull) of the compound has the following absorption band ν_{\max} at cm^{-1} ; 3250(-OH), 1592 m (aromatic skeletal) 1487 s, 1407 w, 1298 w,sh, 1208 m, 1073 s, 1030 vs, 1014 vs, 831 s, 810 m, 795 s, 727 w.

 ^1H NMR Spectrum

The ^1H NMR spectrum was taken in CDCl_3 solution with TMS as internal standard. The spectrum has the following signals at δ (ppm): 7.50-7.00(m, 4H, ArH), 4.5(s, 2H, benzylproton) and 2.13(s, 1H, OH, exchangeable with D_2O).

REACTION NUMBER 6The Reaction of 4-Nitrobenzaldehyde with Sodium Sulphide and Ethanol in Water.

4-Nitrobenzaldehyde (1.51 gm, 0.01 Mole) and 60 cm³ of absolute alcohol were placed in a three-necked distilling flask (500 cm³) fitted with a reflux condenser, a pressure-equalizing dropping funnel and an efficient magnetic stirrer. A filtered sodium sulphide solution (7.2 gm, 0.03 Mole) was then added slowly from the dropping funnel over a period of 15 minutes to the ice cooled nitrobenzaldehyde solution. The reaction mixture was stirred at 0°C for 20 hrs and then at room temperature for 10 hrs. No precipitate appeared.

The mixture was then diluted with water and extracted with ether. The separated ether layer was dried over anhydrous sodium sulphate. Removal of the solvent gave a bright yellow solid which did not melt even at 300°C. The weight of the crude product was 1.02 gm.

Investigation with the yellow solidTLC Study

A TLC study with three different sets of solvent system indicated that this solid was a single product.

Solubility

The product is insoluble in petroleum ether (b.p. 60-80°C), carbon tetrachloride, Benzene, Ether, Ethyl acetate, Acetone, Ethanol, Acetic Acid.

IR Spectrum

The IR spectrum (as nujol mull) of the compound has the following important absorption bands ν_{\max} at cm^{-1} : 3400 br, 1680 s, 1625 m, 1585 m, 1555 s, 1510 w, 1305 m, 1285 w, 1197 m, 1116 s, 1110 m, 980 m, 900 s, 858 s, 837 s

Since this yellow compound could not be dissolved in any organic solvent, an NMR spectrum could not be taken. In the absence of further data, no conclusion can be drawn as to the identity of this compound.

When the same reaction was carried out at a higher temperature (i.e. 100°C), a similar yellow singularly insoluble compound was obtained. The IR spectra of these two compounds (fig. 25 page 89) & (fig. 26 page 90) were superimposable.

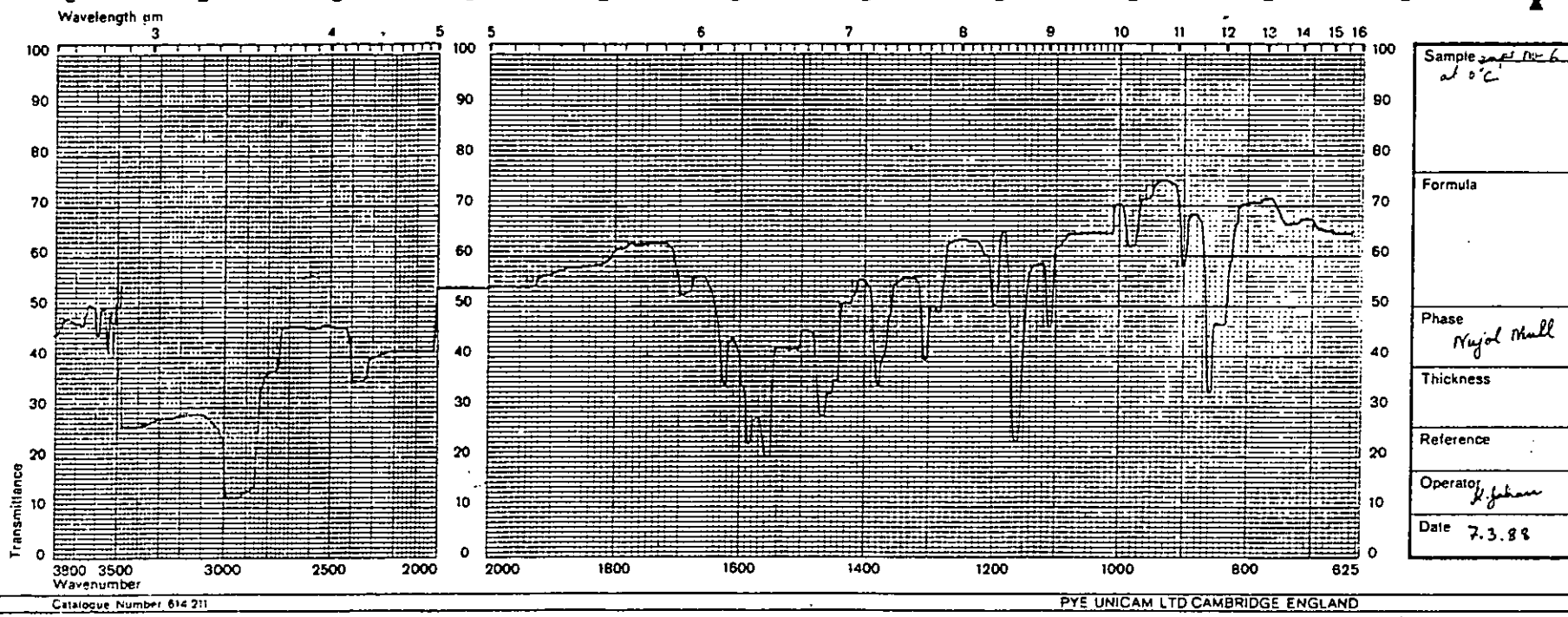
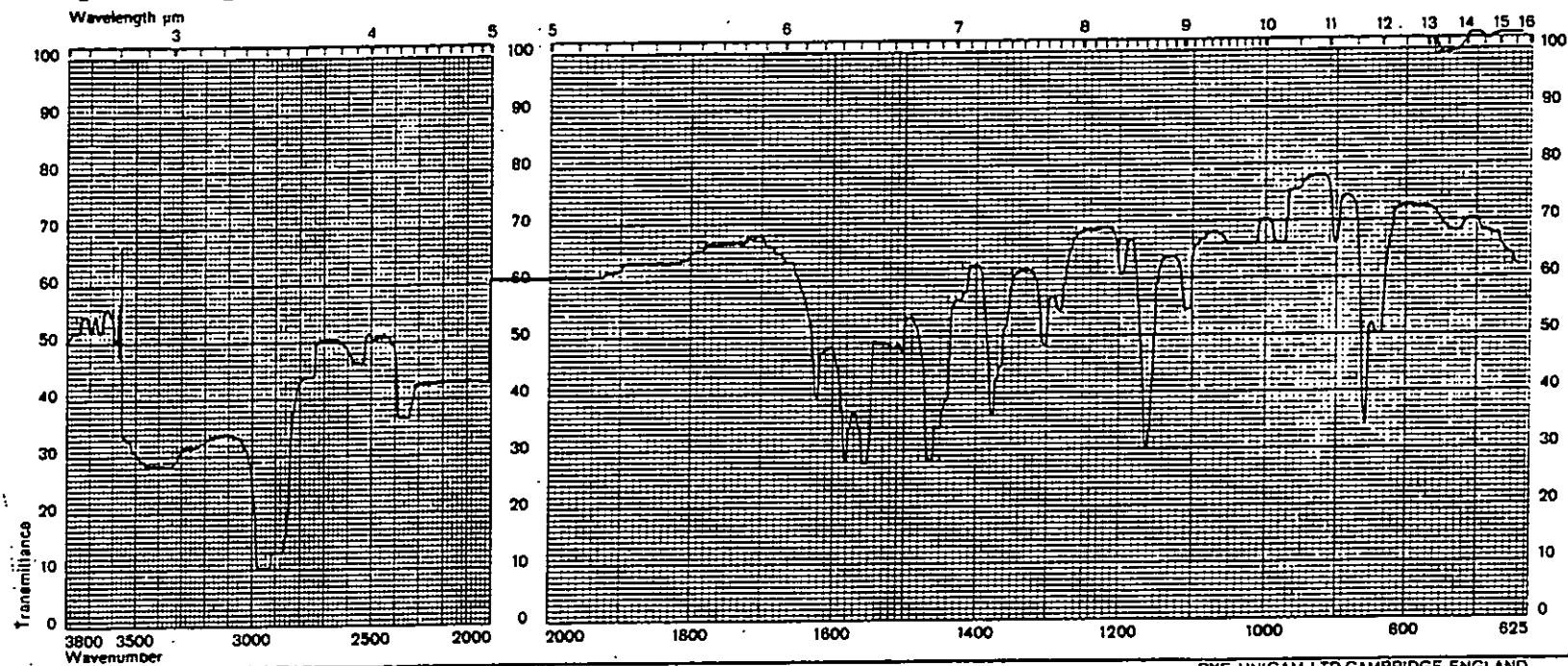


Fig-25. IR spectrum of the Expt. No. 6 at 0°C



Sample	4
	at 100°C
Formula	
Phase	Moist Mull
Thickness	
Reference	
Operator	W. Johnson
Date	5.3.88

06

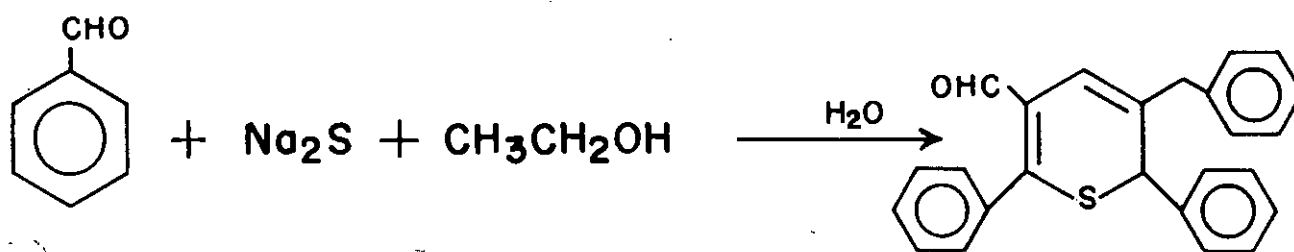
Fig-26. IR spectrum of the eExpt. No. 6 at 100°C.

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CHAPTER THREE

3.1 RESULTS AND DISCUSSION

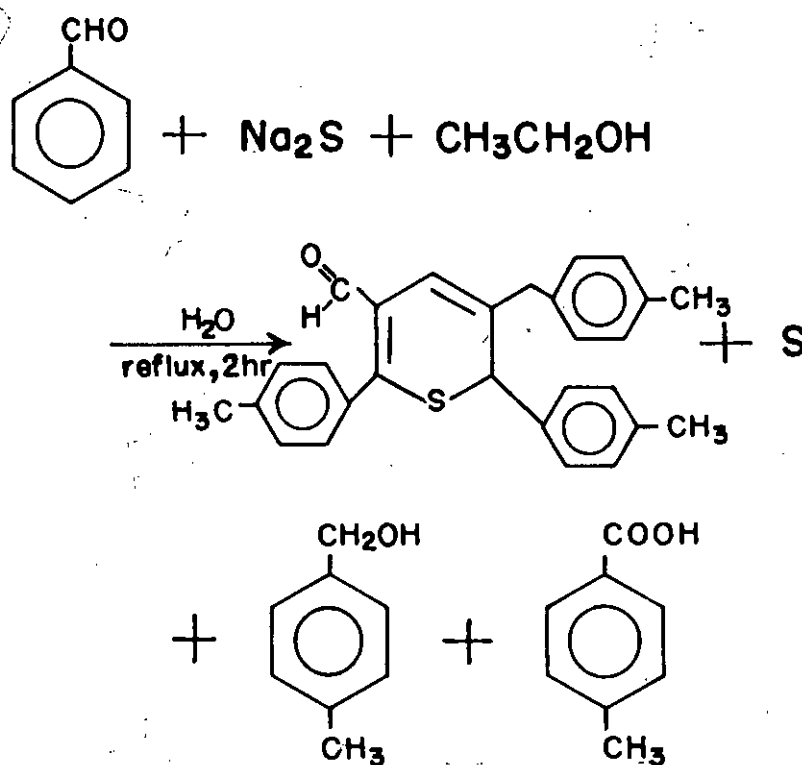
As has been mentioned in the section under "The Aim of This Project", the Latif reaction provides with a simple one-step synthesis of a polyfunctional sulphur-heterocycle. The heterocycle is thiopyran derivative and it is formed in 40% yield by reacting benzaldehyde with sodium sulphide in aqueous ethanol.



The purpose of this research was three-fold; Firstly, to examine how general the Latif reaction is for the synthesis of thiopyran derivatives by employing substituted benzaldehydes in the above synthesis; secondly to establish effects of nuclear substitution, if any, on the yields of thio-pyrans and finally, to further test the validity of the Cremer-Subbratanam mechanism. With this end in view five substituted benzaldehyde compounds, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde & 4-nitrobenzaldehyde were separately employed in the Latif reaction. The results are described below:

The Reaction of 4-methylbenzaldehyde with sodium sulphide and Ethanol in Water

When one equivalent of 4-methylbenzaldehyde is refluxed with three equivalents of sodium sulphide in ethanol-water (1:1 v/v) for 2 hours, 3-(4-methylbenzyl)-2,6-bis(4-methylphenyl)-2H-thiopyran-5-carboxaldehyde (LXXVII) was obtained in 29% yield. Also obtained from this reaction were 4-methylbenzyl alcohol (10%), 4-methylbenzoic acid and some elemental sulphur.

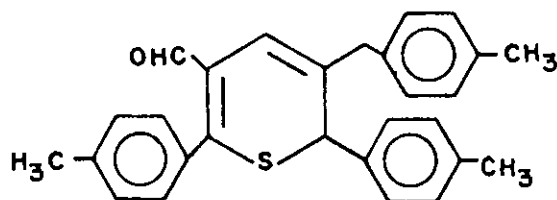


The structure of LXXVII was established from its spectroscopic data. The IR spectrum (fig. 7 page 60) of this compound shows that this compound contains a -CHO group conjugated with either a phenyl group or an olefinic group (ν_{max} 2760 cm^{-1} , OC-H str. and ν_{max} 1650 cm^{-1} , conjugated C=O str.)

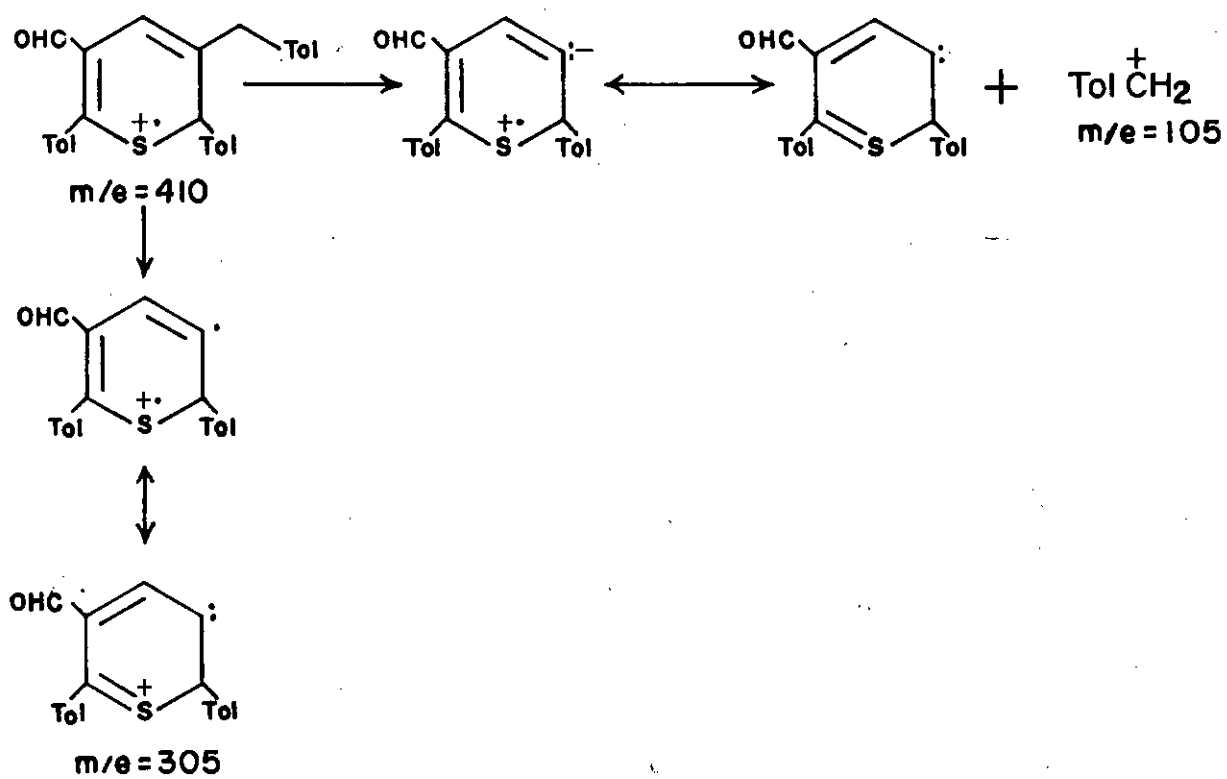
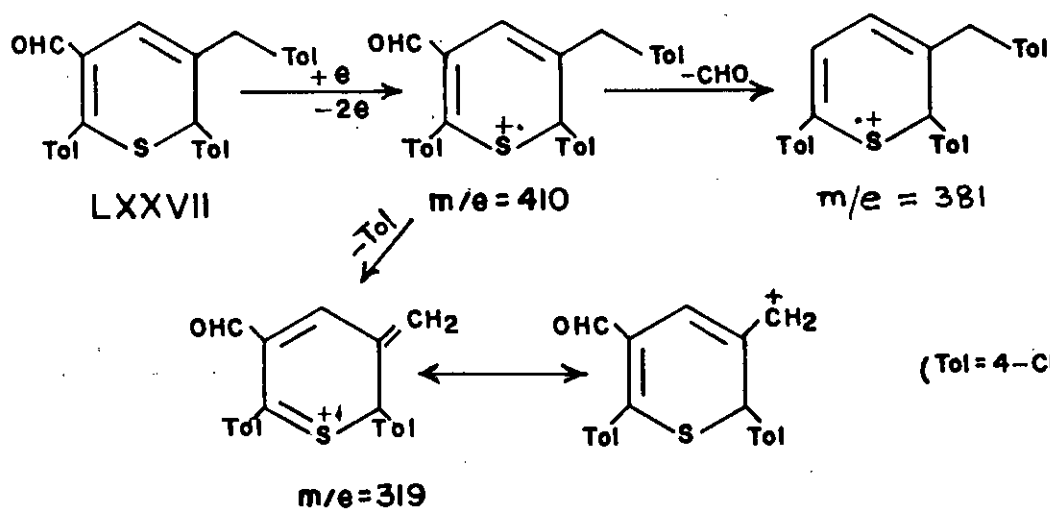
olefinic linkage and/or aromatic nuclei (ν_{\max} cm^{-1} ; 1605, 1590, 1540, 1510, 890, 861, 827, 778). The ^1H NMR spectrum (fig. 8 page 61) indicates that compound, LXXVII, has a CHO group ($\delta = 9.442$ ppm), 12 aromatic protons ($\delta = 7.270$ - 7.145 ppm), one olefinic proton ($\delta = 6.986$ ppm), one benzylic proton adjacent to an electronegative atom, ($\delta = 4.510$ ppm; S-CH-Ar), two benzylic protons adjacent to an asymmetric centre, AB pattern, ($\delta = 3.678$ d & 3.355 d, $J_{\text{AB}} = 15.3$ H_z), three methyl groups each connected to electronegative groups or phenyl rings ($\delta = 2.382$, 2.368 and 2.356 ppm). Thus, if it is assumed that the methyl groups are attached to benzene rings and the rings are connected to the main molecule then each benzene ring will contain four nuclear hydrogen atoms. Since there are twelve aromatic hydrogens and there are three methyl groups and compound LXXVII was obtained from 4-methylbenzaldehyde, it may be concluded that compound LXXVII contains three 4- CH_3 - C_6H_4 -moieties. From ^1H NMR it is also reasonable to assume that one of these aryl groups is present as S-CH- C_6H_4 - CH_3 -4 moiety in the main molecule. The molecule also contains a conjugated aldehydic group & one olefinic proton. From these pieces of information and from the structure of the original Latif compound it may be concluded that the reaction between 4-methylbenzaldehyde, sodium sulphide & ethanol gave 3-(4-methylbenzyl)-2,6-bis(4-methylphenyl)-2H-thiopyran-5-carboxaldehyde whose structure is shown by LXXVII.

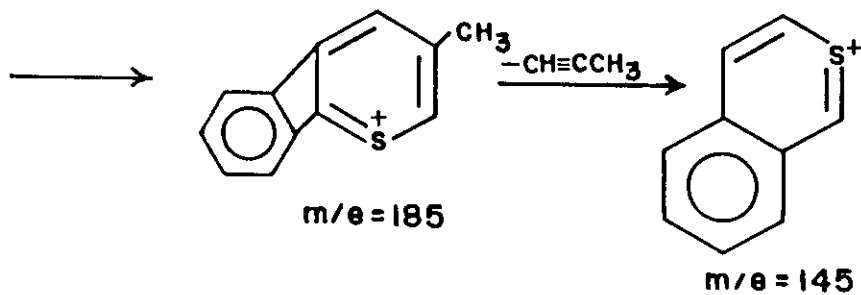
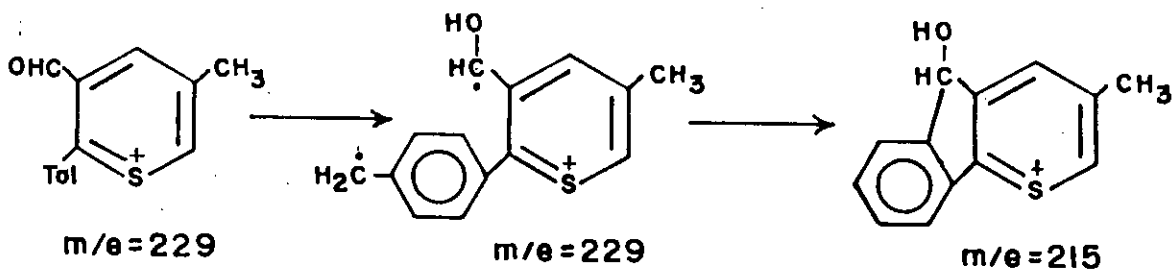
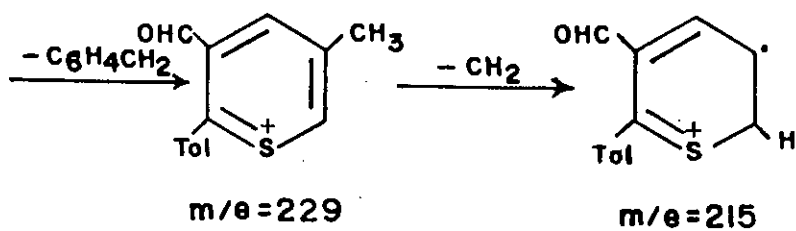
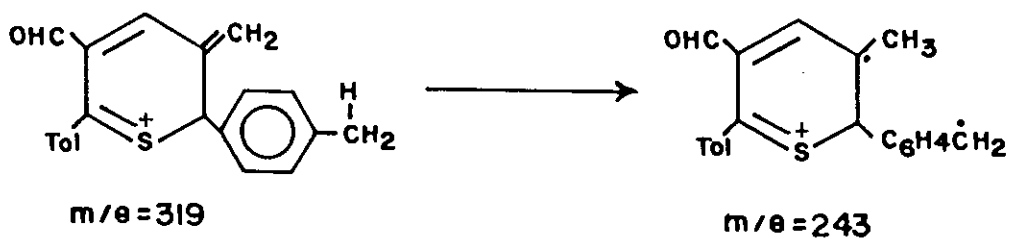
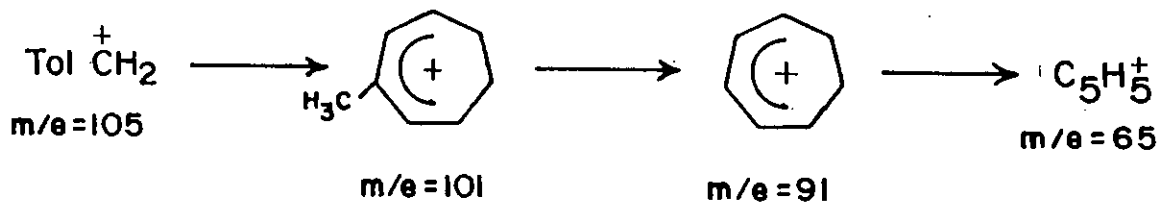
The ^{13}C NMR spectrum (fig. 12 Page 65) of this compound also indicates strongly that it has the structure as formulated by LXXVII. Thus the ^{13}C NMR spectrum shows that it contains a carbonyl carbon ($\delta = 186.76$ ppm), a total of sixteen types of aromatic and olefinic carbons ($\delta = 155.08-119.66$ ppm), two types of benzylic carbons ($\delta = 45.89$ and 42.06 ppm) and three different methyl carbons (21.28 , 21.10 and 21.06 ppm).

The above structure for this compound is further supported by its mass spectrum (fig. 14 page 67). On the basis that this compound has structure, LXXVII, the mass spectrum may be explained as follows:

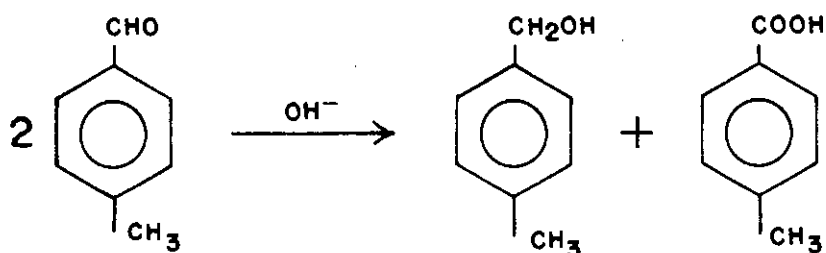


LXXVII



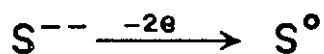


The other two important products of this reaction are 4-methylbenzoic acid and 4-methylbenzyl alcohol. These have presumably been formed by the Cannizzaro type of reaction of 4-methylbenzaldehyde under the strongly alkaline conditions of the reaction. Thus



Similar Cannizzaro products have been reported to have formed when benzaldehyde is employed in the above reaction.

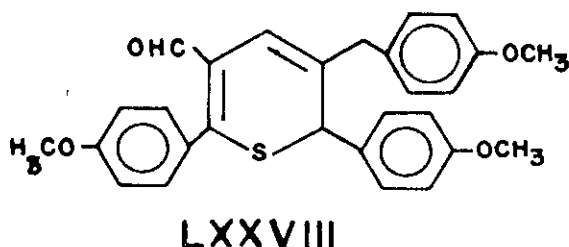
Elemental sulphur is always formed in this type of reactions and it is almost certainly formed by the oxidation of the sulphide ion.



The Reaction of 4-methoxybenzaldehyde with Sodium Sulphide and Ethanol in Water

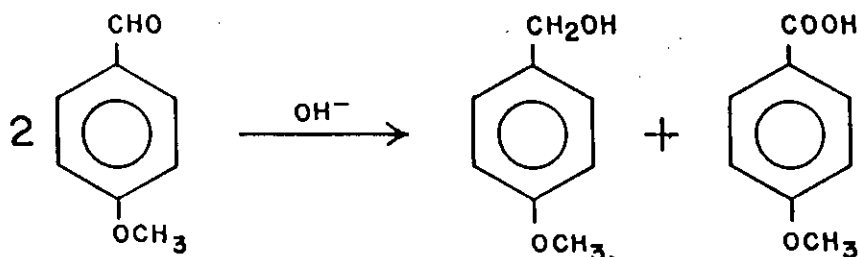
When 4-methoxybenzaldehyde (0.03 mole) is refluxed with three equivalents of sodium sulphide in aqueous alcohol (120 cm³, 1:1 v/v) for four hours, it gives 3-(4-methoxybenzyl)-2,6-bis(4-methoxyphenyl)-2H-thiopyran-5-carboxaldehyde LXXVIII in 1% yield. From the reaction mixture also isolated were 4-methoxybenzyl alcohol and 4-methoxybenzoic acid and some elemental sulphur. The structure of 3-(4-methoxybenzyl)-2,6-bis(4-methoxyphenyl)-2H-thiopyran-5-carboxaldehyde is shown to be LXXVIII from its ¹H and ¹³C NMR spectra. Thus ¹H NMR spectrum shows that this compound contains an aldehydic group (δ=10.10 ppm) twelve aromatic protons (δ =8.19-8.06 ppm) one olefinic proton (δ =6.93 ppm), three methoxy groups (δ =4.13 & 4.09 ppm), one benzylic proton adjacent to an electronegative atom (δ =3.93 ppm, S-CH-Ar) and two other benzylic protons adjacent to an asymmetric centre (AB pattern). From the fact that this molecule contains three methoxy groups, twelve aromatic protons and because this compound is obtained by the reaction of 4-methoxybenzaldehyde, LXXV it is likely that compound contains three 4-CH₃-C₆H₄ groupings.

The ¹H NMR spectrum of the compounds and its method of formation thus strongly suggest that it has the structure as shown in LXXVIII

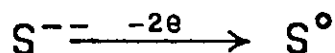


The above structure for this compound is confirmed by its ^{13}C NMR spectrum (fig. 18 page 75). Thus the spectrum shows that the compound contains a carbonyl group ($\delta = 189.06$ ppm). The spectrum shows signals which show that the molecule contains aromatic and olefinic carbons ($\delta = 166.06 - 112.12$ ppm), three methoxy carbons ($\delta = 39.31, 39.08$ & 38.85 ppm) and two benzylic carbons ($\delta = 54.17$ and 53.93 ppm). These resonances can be well explained on the basis of structure LXXVIII for the compound.

Among other products obtained from this reaction were 4-methoxybenzyl alcohol, 4-methoxybenzoic acid and some elemental sulphur. As before the formation of 4-methoxybenzoic acid and 4-methoxybenzyl alcohol are probably formed by the following Cannizzaro type of reaction under the strongly alkaline conditions.



As described previously elemental sulphur must have formed by the following oxidation reaction:



The Reaction of 4-chlorobenzaldehyde with Sodium Sulphide and Ethanol in Water

The reaction of one equivalent of 4-chlorobenzaldehyde with three equivalents of sodium sulphide in ethanol-water (1:1 v/v) at 80°C for 2 hours gave, subsequent to usual work-up 4-chlorobenzyl alcohol (13%) and an intractable mass. No compound corresponding to LXXVII or LXXVIII was obtained. 4-chlorobenzyl alcohol was almost invariably formed by Cannizzaro type of reaction. This reaction should in principle give some 4-chlorobenzoic acid but in the alkaline aqueous reaction medium if it remained, it would stay as

the sodium salt. The aqueous layer was not thought interesting for further investigation as the Latif product would be expected not to be present there.

An alternative explanation for the formation of 4-chlorobenzyl alcohol may be the reduction of 4-chlorobenzaldehyde by sodium sulphide. Since the benzyl alcohol and the corresponding benzoic acid are obtained in almost equimolar ratios as described in the earlier experiments, it is likely that the former compound in this reaction is formed by Cannizzaro reaction.

The Reaction of 4-Bromobenzaldehyde with Sodium Sulphide and Ethanol in Water

The reaction of one equivalent of 4-bromobenzaldehyde with three equivalents of sodium sulphide in aqueous ethanol at 80°C for two hours gave, subsequent to conventional work up, 4-bromobenzyl alcohol, 8%. The alkaline aqueous solution was not worked up but it almost certainly contained 4-bromobenzoic acid. Anyway, no compound corresponding to LXXVII or LXXVIII was detected to have formed.

As before, the formation of 4-bromobenzyl alcohol may be explained on the basis of Cannizzaro reaction, although alternative explanation is possible.

The Reaction of 4-nitrobenzaldehyde with Sodium Sulphide and Ethanol in Water

When 4-nitrobenzaldehyde was reacted with three equivalents of sodium sulphide in aqueous ethanol at 0°C for 20 hours and then at room temperature for 10 hours and worked up in the customary way, a bright yellow solid was obtained. This solid was insoluble in common organic solvents and did not melt even at 300°C. The IR spectrum of the solid indicated the presence of OH & CHO groups and aromatic skeleton. For want of a suitable solvent, an NMR spectrum could not be taken. The compound has been sent abroad for elemental analysis and the recording of the mass spectrum. In the absence of further evidence, no conclusion can be drawn on the structure of this compound. No compound corresponding to compound LXXVII or LXXVIII could be isolated from this reaction.

A similar (superimposable IR) unidentified yellow solid was also obtained when the above reaction was carried out at 100°C for 2 hours.

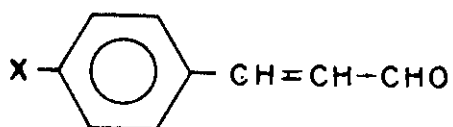
For the insolubility and high melting point of this solid obtained in both experiments, it appears that this solid is probably a polymer.

3.2 CONCLUSION

The reaction of 4-methyl and 4-methoxybenzaldehyde with sodium sulphide in aqueous ethanol gives compounds having structures (LXXVII & LXXVIII) corresponding to that (I) of the Latif product bringing further support for the mechanism proposed for the reaction and also widening the scope of this reaction. With very reactive benzaldehydes i.e., those containing electron withdrawing groups, such as, chloro-bromo and nitro group in the 4 position, side reactions become more important giving unidentified polymeric mass. No compounds similar to the Latif product could be obtained in any detectable yield.

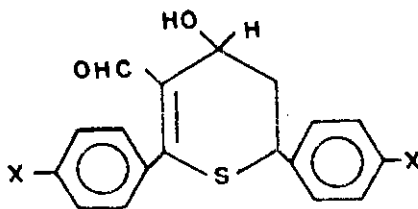
3.3 DIRECTION FOR THE FUTURE RESEARCH

Electronegative substituents at 4 position of benzaldehyde molecules make these compounds very reactive towards nucleophiles. Thus before such benzaldehydes react to produce Latif type of compounds, they react differently, producing compounds other than the Latif compounds. It thus appears interesting to perform some reaction of preformed substituted Cinnamaldehydes e.g.



Where $X = \text{Cl}, \text{Br}, \text{NO}_2$ etc.

with aqueous-ethanolic sodium sulphide and examine if compounds of the following type are obtained.



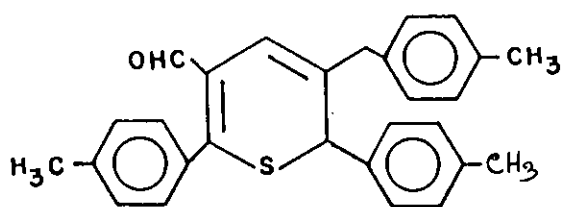
These compounds would be expected to be formed if the Cremer-Subbratanam mechanism is operative.

Furthermore reaction of the above type of compounds with benzaldehyde in alkaline reaction conditions should in principle produce Latif type of compounds. If this method proves successful, then this will open up a new route for the synthesis of Latif compounds with two different arene moieties in the molecule.

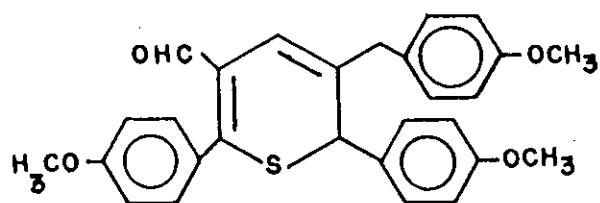
3.4 SUMMARY

During this research an up-to-date literature survey was carried out on thiopyrans and their derivatives.

In order to examine the generality of the Latif reaction, a number of substituted benzaldehyde was reacted with sodium sulphide in aqueous ethanol solution. The reaction of 4-methylbenzaldehyde with aqueous-ethanolic sodium sulphide gives 3-(4-methylbenzyl)-2,6-bis(4-methylphenyl)-2H-thiopyran-5-carboxaldehyde LXXVII, in 29% yield. A similar reaction with 4-methoxybenzaldehyde gives the corresponding thiopyran derivative, LXXVIII, in 1% yield.



LXXVII



LXXVIII

Corresponding reactions with either 4-chlorobenzaldehyde, 4-bromobenzaldehyde or 4-nitrobenzaldehyde do not give compounds of the type LXXVII or LXXVIII. In these reactions intractible polymeric mass is obtained. The failure to obtain products like LXXVII or LXXVIII indicates that when electron withdrawing substituents are present in the benzaldehyde molecules, the latter become very reactive towards nucleophiles and side reactions predominate. The formation of LXXVII and LXXVIII from respectively, 4-methylbenzaldehyde and 4-methoxybenzaldehyde, provides further support for the Creamer-Subbratnam mechanism for the Latif reaction.

CHAPTER FOUR

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