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AUGUSTYN - GRADKOWSKA, E.

215

NORTH LONDON POLY.

Stereocontrolled synthesis of plant growth regulators
Abscisic Acid and Xanthoxin.

The thesis submitted to the Council for National Academic
Awards in partial fulfilment of the requirements for the
degree of Doctor of Philosophy

by E. Augustyn-Gradkowska

The Polytechnic of North London

April 1985.

To my children

E. Augustyn-Gratkowska

Stereocontrolled synthesis of plant growth regulators
Abscisic Acid and Xanthoxin.

Summary

The project is concerned with the total synthesis of plant growth regulators related to abscisic acid (ABA). The biological activity of these plant growth regulators, ABA and Xanthoxin, and their derivatives is influenced by the stereochemistry of the double bond system in the side chain, the 2Z,4E-isomers being most potent. The stereocontrolled synthesis of the side chain was to be achieved by bridging the positions 1- and 4- with sulphur and for this reason 4-mercapto-3-methylbut-2-enoic acid γ -thiolactone was prepared. The synthesis of the γ -thiolactone proved difficult. The published methods of Hornfeldt and Gronowitz, and Wemple were not satisfactory for our synthesis. Thus, the former method resulted in the mixture of bromothiophenes, which could not be separated on the required scale; the method of Wemple which was reported to be successful for thioacids and aromatic α -chloro carbonyl compounds, failed to give a required product of the reaction between the bis-anion of thioacetic acid and chloroacetone; instead, 3,5-dichloro-4-hydroxy-4-methylpentan-2-one was formed by aldol condensation. Following some examples in the literature, where oxygen atom was replaced by a sulphur atom, an oxygen analogue of the

γ -thiolactone, 3-methyl-2-butenic acid γ -lactone, was prepared and reacted with phosphorous pentasulphide, but no positive results were obtained. The γ -thiolactone was successfully prepared in a new synthesis which involved preparation of 4-chloro-3-methylbut-2-enoate (E and Z isomers mixture) in a Wadsworth-Emmons reaction of triethylphosphonoacetate and chloroacetone, conversion of (E and Z) 4-chloro-3-methylbut-2-enoate to 4-acetylthio-3-methylbut-2-enoate (E and Z) and the treatment of the latter product with methanolic HCl to give the γ -thiolactone, which was isolated by distillation with 12% yield. The γ -thiolactone was then separately reacted with benzaldehyde and mesitaldehyde by the method of Gronowitz to yield crystalline compounds (3Z)(5Z)-5-benzylidene-4-methyl-3-thiolene-2-one and (3Z)(5Z)-5-mesitylidene-4-methyl-3-thiolene-2-one respectively. The new double bond formed in the condensation of the γ -thiolactone with benzaldehyde and mesitaldehyde had the required Z-configuration in both cases, the fact predicted from examination of molecular models and confirmed by means of X-ray crystallography. The successful condensation of the γ -thiolactone with aromatic aldehydes did not, unfortunately, apply to aliphatic aldehydes. Thus, β -cyclocitral, failed to condense with the

γ -thiolactone under a variety of reaction conditions, whereas, cyclohexanecarboxaldehyde reacted with the γ -thiolactone in MeOH/NaOH to give the required product with low yields, only. As an alternative route, useful derivatives of γ -thiolactone, namely 5-bromo-4-methyl-3-thiolene-2-one, trimethylsilyl (4-methylthien-2-yl) ether and diethyl-(4-methylthien-2-yl) phosphate were prepared. Since Raney nickel was reported to remove the sulphur atom from various compounds, it was used for desulphurization of 5-benzylidene-4-methyl-3-thiolene-2-one to give desulphurized and reduced product, suggesting that milder reaction conditions need to be employed in order to preclude double bond hydrogenation.

DECLARATION

Whilst registered as a candidate for this degree the author
has not been registered as a candidate for any other award.

ACKNOWLEDGEMENTS

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Appendix

1. INTRODUCTION

1. History

Plants directly or indirectly provide the food for man and animals and therefore a knowledge of their development has always been of great importance. A considerable amount of information on plant nutrition and genetics is known,¹ but there are various aspects of plant physiology which are no less important: a seed will germinate only under suitable conditions, plants always bend towards the light, a fruit when ripe falls off the tree. It is now known that these physiological processes are controlled by plant hormones, very potent chemicals produced in low concentrations within the plants.² With regard to their physiological function, the plant hormones are classified as plant growth promoting hormones (auxin, gibberellins, cytokinins) and plant growth inhibitors (Abscisic acid, Xanthoxin).

The plant hormones which were discovered first are auxins.³
⁴ These naturally occurring compounds play an important part in almost every aspect of plant growth but their most significant role is the ability to induce elongation in the plant cells. Chemically they are related to indol-3-yl-acetic acid IAA (1).⁵

The second group of plant growth hormones are gibberellins which are responsible for cell elongation and division. The first

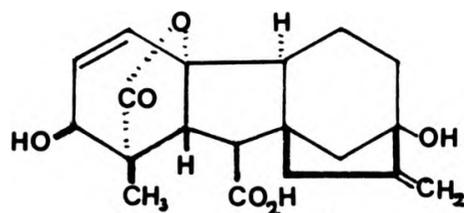
gibberellins were obtained from a fungus Gibberella fujikuroi.

6 7 8 The fungus causes a "bakanae" disease, which is characterized by the fact that affected plants were often twice as high as healthy plants. Gibberellins are structurally related to gibberellic acid (GA_3) (2).⁹

Cytokinins are compounds which are responsible for cell division. The first naturally occurring cytokinin, "Zeatin" (3) was discovered in 1964 by Letham and was identified as 6-(4-hydroxy-3-methylbut-2-enyl)-aminopurine (3).¹⁰ High levels of cytokinins have been found mainly in cells undergoing rapid division such as in germinating seeds and young fruit.



(1)

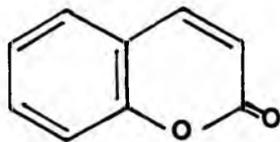


(2)



(3)

The endogenous substances which inhibit or retard physiological processes in plants are recognized as plant growth inhibitors. They represent a group of plant hormones which counteract the effects of growth promoting substances. The presence of such inhibitors in plants has been known for many years. One of the first inhibitors discovered was coumarin (4). This compound and its derivatives are widely distributed in plants.¹¹ In 1949 Hemberg showed that dormant buds of the ash tree and potato tubers contain a high level of inhibitors and that the inhibitor content diminishes towards the end of the dormancy period.¹²



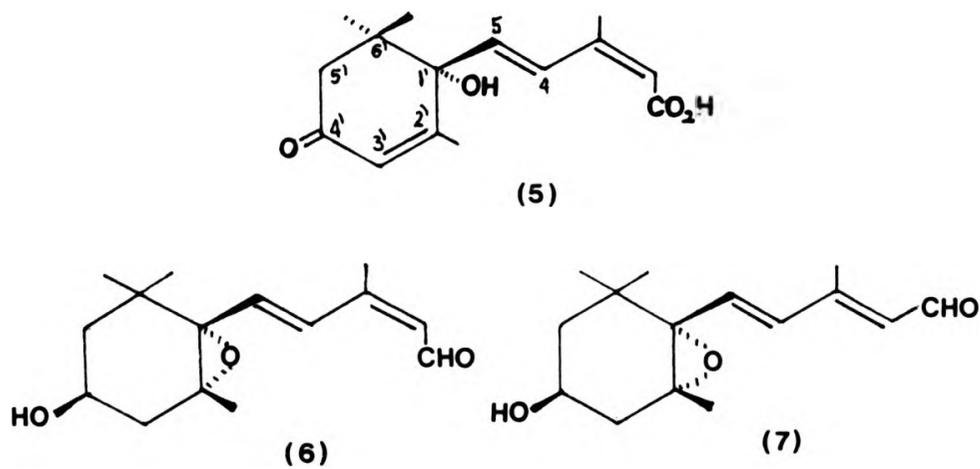
(4)

The bioassays carried out by early researchers to determine auxin levels in plants often showed that the purified and unpurified extracts exhibited different biological activity. It was concluded that some other compounds must be present which diminished the action of auxins.^{13 14} The extensive investigation of growth inhibitory compounds began in 1952, when the technique of paper chromatography was combined with growth bioassays for the analysis of plant extracts.^{14 15} The extracts of many plants analysed by means of paper chromatography showed that the growth inhibitory compounds fall within the same area. This mixture of compounds was named

"inhibitor - β ".¹⁶ Among the known components of the "inhibitor - β " complex,¹⁷ Abscisic acid (ABA) (5)¹⁸ and Xanthoxin (6) (7)²⁰ were shown to be most potent.

2. Discovery of Abscisic Acid (ABA)

Different groups of scientists working on plant hormones reported the discovery of ABA at about the same time. F. T. Addicott and K. Ohkuma (1963) isolated the active compound from young cotton fruit and named it "abscisin II".¹⁸ The compound was found to be identical to the chemical "dormin",

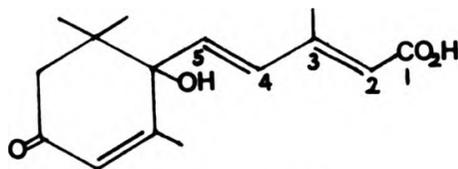


which was isolated from the leaves of birch (Eagles and Waring, 1963)²¹ and leaves of sycamore (Cornforth *et.al.*, 1965).¹⁹ At the Sixth International Conference for Plant Growth Substances held in 1967 the name "Abscisic acid" was agreed for the new biologically active inhibitor.²²

3. Occurrence and Properties of ABA

Shortly after ABA was separated from cotton fruits and sycamore leaves, researchers found its presence in the pods of lupin,²³ in the leaves of cabbage and in avocado seeds.²⁴ ABA is now known to occur widely; it is found in many species of higher plants,²⁴ in ferns and mosses;²⁵ however its concentration varies from organ to organ. Mature, senescing or dormant parts of the plant like fruits, seeds and buds have the highest content of the hormone.²⁴ ABA was recently reported to be a metabolite of the fungus Cercospora rosicola.²⁶

Soon after ABA was isolated its structure was determined by Ohkuma and Addicott (1965).²⁷ ABA(5) has one asymmetric carbon atom at C-1' and therefore exhibits optical activity. The naturally occurring enantiomer is dextrorotatory; it has the (S)-configuration at the asymmetric carbon atom. The synthetic, racemic (+)-ABA was found to be almost as potent as the naturally occurring (+)-enantiomer. Also, the (-)-enantiomer showed high biological activity in growth inhibition bioassays; however, in bioassays for stomata closure (-)-ABA was found to be much less active.²⁸ The most important aspect of the structure of ABA molecule is the geometrical stereoisomerism of the side chain. The configuration 2Z,4E is required for biological activity; the 2E,4E isomer called trans-ABA (8) is biologically inactive.²⁵



(8)

In solution light catalyzes isomerization of ABA to trans-ABA to give a 1:1 mixture of both isomers; ABA should be protected from light as much as possible to preclude this.

Natural ABA has been obtained as colourless crystals, m.p. 160° - 161° C. The infrared, ²⁷ nuclear magnetic resonance ²⁷ and mass spectra ²⁹ have been reported. ABA shows exceptionally high optical activity. This property was used to measure quantitatively amounts of ABA in plant extracts. ²⁴

4. Biosynthesis of ABA

Two biosynthetic pathways have been proposed for ABA: a) direct biosynthesis in which ABA is synthesized from isoprene units within the chloroplast and throughout the whole plant; b) indirect biosynthesis proceeds via carotenoids which are photochemically converted into ABA.

Thus, by the use of the ^{14}C labelling technique it was shown that $[2-^{14}\text{C}]$ -mevalonic acid (MVA) is incorporated into ABA

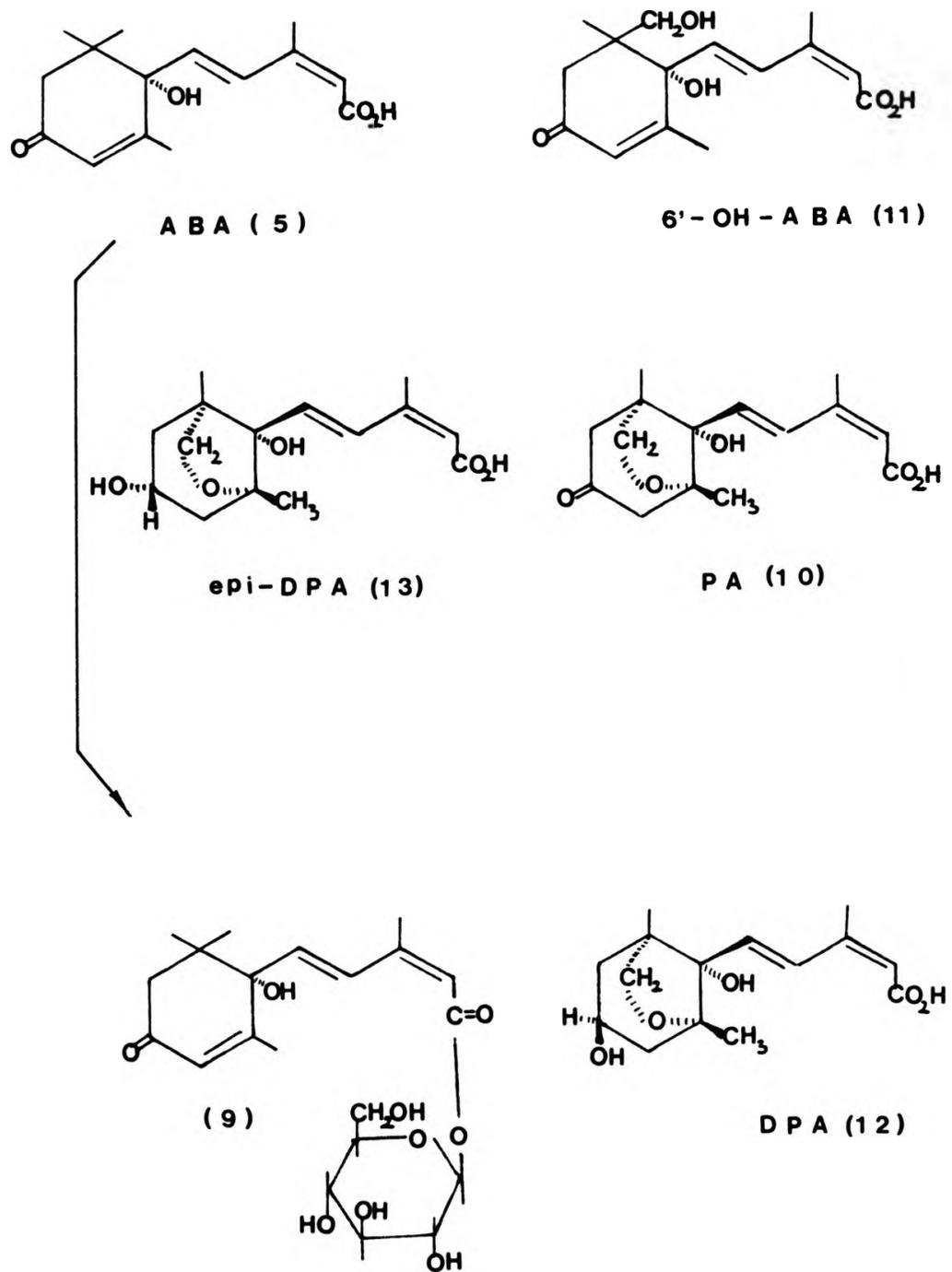
in intact plants, ³⁰ as well as in isolated chloroplasts. ³¹ With use of [4R-³H] mevalonate it was further shown that the ABA was derived from all E precursor and that 2Z double bond must have been formed at a later stage of the synthesis. ³² These results are however in favour of a direct biosynthetic route from MVA to ABA but they also indicate that the possibility of ABA being derived from carotenoids cannot be discounted.

Evidence for a synthesis of ABA from carotenoids was first presented by Taylor and Burden, who obtained Xanthoxin by illumination of a carotenoid violaxanthin. ³³ Later [2-¹⁴C] -Xanthoxin (6) was shown to undergo conversion into ABA in intact plants. ³⁴

At the present, despite the amount of work contributed to this area of research, a precise biosynthetic route to ABA is not known.

5. Metabolism of ABA

Milborrow showed that (+)- [2-¹⁴C] -ABA was metabolised by tomato shoots to a glucose ester (9) ³⁵ and phaseic acid (10). ³⁵ Metabolism of ABA to phaseic acid (10) preceded via an unstable intermediate 6'-hydroxymethyl abscisic acid (HABA) (11). Sondheimer and Walton showed that (+)- [2-¹⁴C] - ABA is metabolised by bean plants to phaseic acid (10) and



Scheme 1

dihydrophaseic acid (DPA) (12).³⁶ Further investigations on the biotransformation of ABA in plants led researchers to the discovery of a new metabolite namely epi-dihydrophaseic acid (13).³⁷ Glucose ester (9) is the only known product of metabolism of (-)-ABA.^{35 37}

The physiological role of ABA metabolites is uncertain, however, Milborrow^{35 38} as well as Wright and Hiron³⁹ suggested that the formation of glucose ester (9) represents the deactivation mechanism for an excess of ABA in the plant tissues, but, whether the process is reversible or not has not yet been established.

6. Isolation and Detection of ABA

Growth inhibitors are extracted from plant material by an organic solvent such as diethyl ether, ethyl acetate or methanol; however, the best solvent must be determined for each plant tissue. Acid-base extraction is then carried out and it is followed by chromatography; the variations used include silica gel column,³⁷ silica gel thin layer³⁹ and paper chromatography.¹⁶ The ABA content in purified plant extracts is then estimated using biological or physical methods.

The bioassay which is most frequently employed uses the ability of ABA to inhibit the plants growth;¹⁸ this

response is, however, very unspecific as many other compounds at high concentration will imitate or enhance the effect of ABA. The inhibition of seed germination test has also been used but the test takes a few days and requires large quantities of compound. ⁴⁰

The bioassay which is recognised as very sensitive and fast uses the ability of ABA to close stomata. However, other plant hormones ⁴¹ and CO₂ ⁴² have been reported to influence stomatal apertures and they may interfere with ABA in this test.

The choice of bioassay depends on several factors such as amount of compound available, cost, speed of response or specificity. However, there is no single unique method for determining biological activity of ABA; also, one needs to notice that, although exogenously applied ABA displays its activity in selected bioassays it does not necessarily mean that an endogenous hormone would influence these processes. Thus, applied (+) ABA may penetrate to the cells where it does not normally occur ^{30 31} or it may metabolise ^{35 36} and the changes observed will not represent a true response to natural ABA.

In the recent years new instrumental analytical techniques have been employed to detect ABA and other plant hormones. Spectropolarimetry, ²³ gas chromatography, ³⁷ combined

gas chromatography and mass spectrometry,^{29 43} high performance liquid chromatography⁴⁴ are the analytical methods which were found very attractive as they allow detection of very small quantities of the inhibitor without the interference of other phytohormones.

7. Biological Activity of ABA

ABA was shown to be involved in several processes of a growing plant. Thus, the first isolation of this hormone was accomplished following its abscission-accelerating activity on the cotton explants.¹⁸ The further work in this field suggested, however, that ABA was not as closely involved in the leaves abscission as it was originally thought;^{18 22} the experiments which reported the leaves abscission were carried out with the high ABA concentrations,⁴⁵ which in turn could stimulate ethylene production.⁴⁶ Therefore, there is no clear evidence of the direct influence of ABA on the leaf abscission. However, the involvement of ABA in the fruit abscission is more certain, largely as a result of work of Addicott and Davis,⁴⁷ who demonstrated the correlation between the content of ABA and the development of cotton fruits.

ABA was shown to be involved in the regulation of dormancy. Thus, large quantities of ABA were found in a number of dormant plants with a highest level of the inhibitor in buds,

19 48 tubers, 17 24 and seeds. 49 24 The content
of the inhibitor diminishes towards the end of ^{the} dormancy
period, while the levels of growth promoting hormones
sharply increase. The balance between the growth promo-
ting hormones and the inhibitors is thought to determine
the dormancy state. 25 50

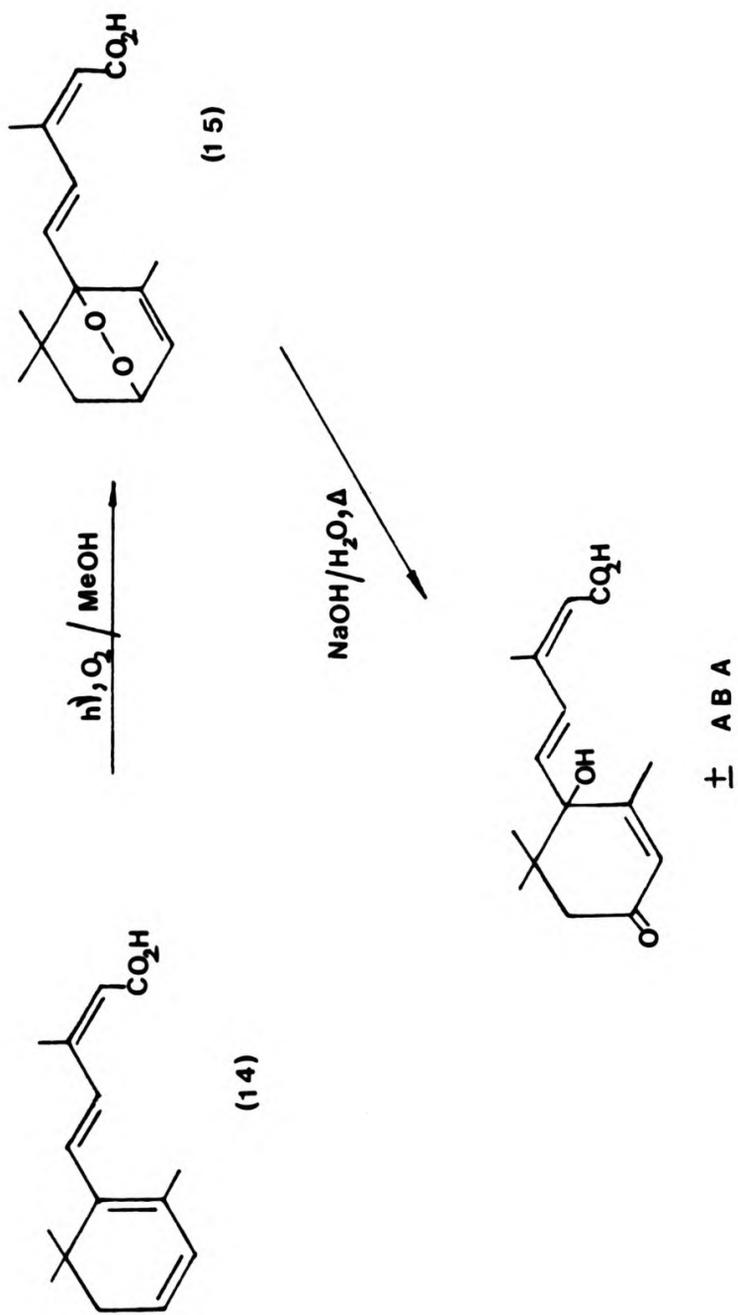
An important physiological function of ABA is its involve-
ment in the response of plants to stress conditions. Thus,
ABA was shown to affect the stomatal aperture enabling the
plants to recover from stresses such as water-logging, 39
water deficit, 36 39 or mineral deprivation. 51 The
response of stomata to ABA was shown to be reversible. 39 51

The inhibition of growth is a very pronounced response of
plants to ABA and this property has often been utilised in
the biological tests. 18 Recent experiments suggest that
ABA may also be involved in the inhibition of root growth. 52

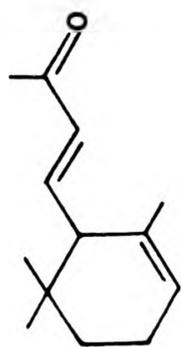
8. Synthesis of Abscisic Acid

Large quantities of ABA are required in order to carry out
investigation of its biological activity. Therefore the
elucidation of the ABA structure by Ohkuma 27 inspired the
search for synthetic routes to this hormone.

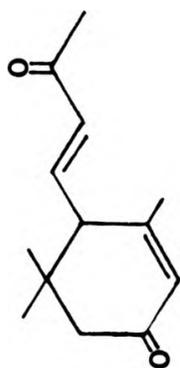
The first synthesis of ABA was achieved by J. W. Cornforth



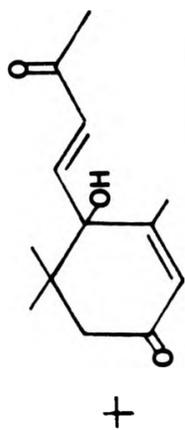
Scheme 2



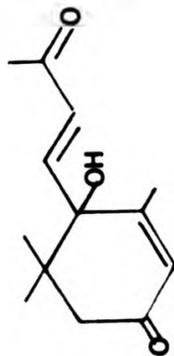
(16) α -ionone



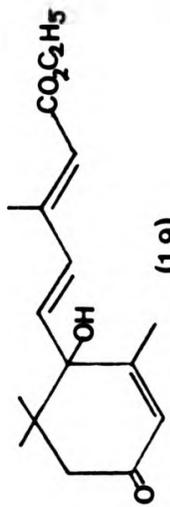
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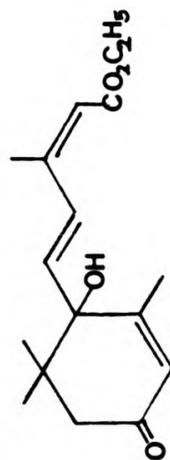
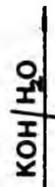
(18)



(18)



(19)



(20)



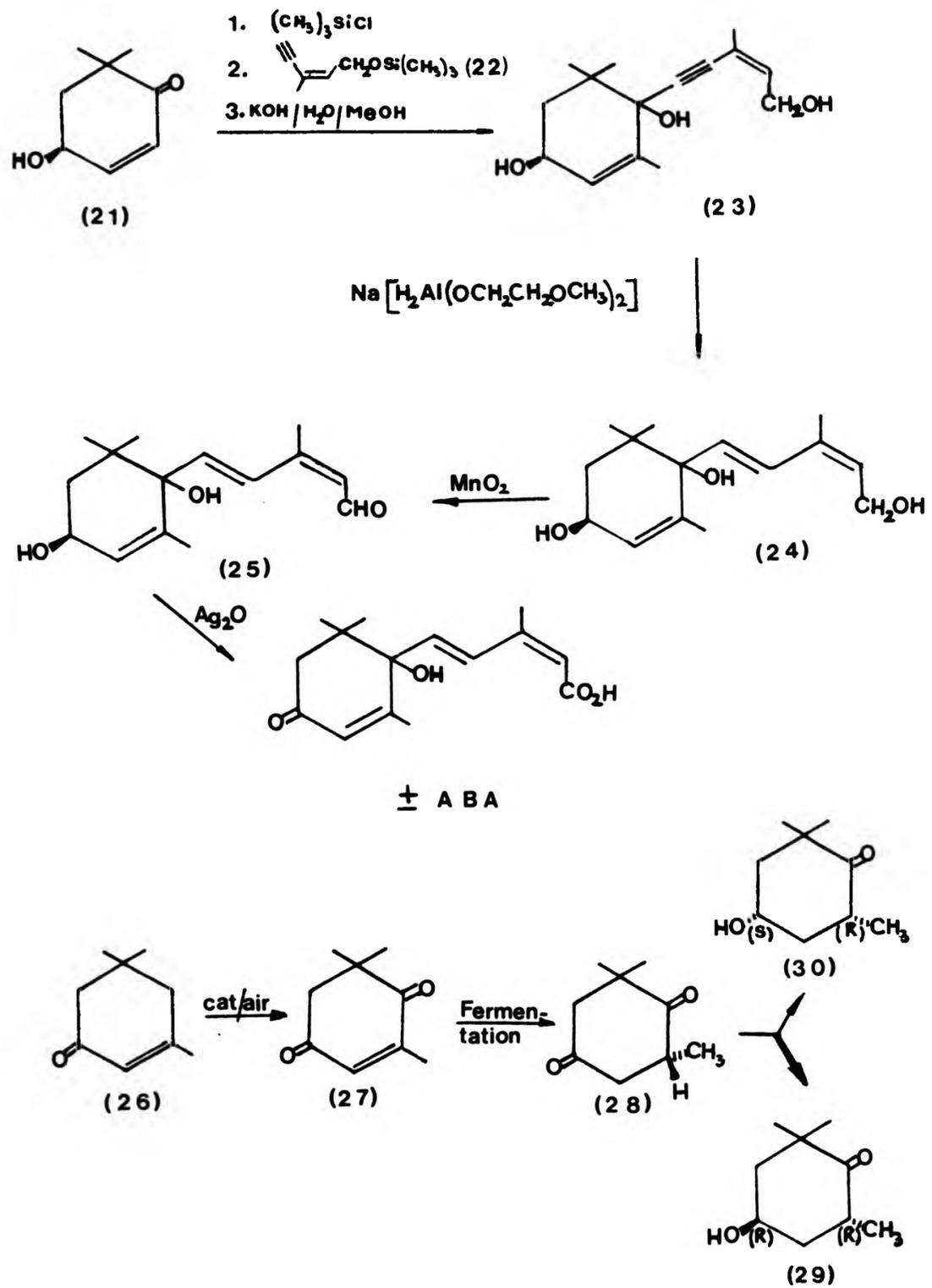
Scheme 3

in 1965.⁵³ The major step of the synthesis involved the photo-oxidation of (2Z)-3,4-dehydro- β -ionylideneacetic acid (14)⁵⁴ and subsequent re-arrangement of the corresponding endoperoxide (15) on heating with 0.07N aqueous NaOH. Racemic (+) ABA was obtained with a 7% yield (Scheme 2).

In 1966 Mousseron-Canet et al reported an improved method of re-arrangement of the endoperoxides using alumina.⁵⁵ However, Cornforth synthesis and the improved method gave low yields and were not suitable for providing the large quantities of the compound needed for biological tests.

Better yields (11%) were obtained in the synthesis designed by Roberts, 1968.⁵⁶ The preparation initially involved the reaction of α -ionone (16) with t-butyl chromate as an oxidizing agent for allylic positions and resulted in the formation of 4-oxo- α -ionone (17) and 1-hydroxy-4-oxo- α -ionone (18), a precursor of ABA. The compounds (17) and (18) were separated by chromatography on a silica gel column. 1-hydroxy-4-oxo- α -ionone (18) was then reacted with carbethoxymethylenetriphenylphosphorane to give a mixture of stereoisomeric esters (19) and (20) which were converted to the corresponding acids ABA and trans-ABA. The acids were separated by fractional crystallization from chloroform.

In 1978 F. Kienzle reported a new synthesis of ABA⁵⁷ (Scheme 4). The optically active ketone (21) was reacted with (Z)-

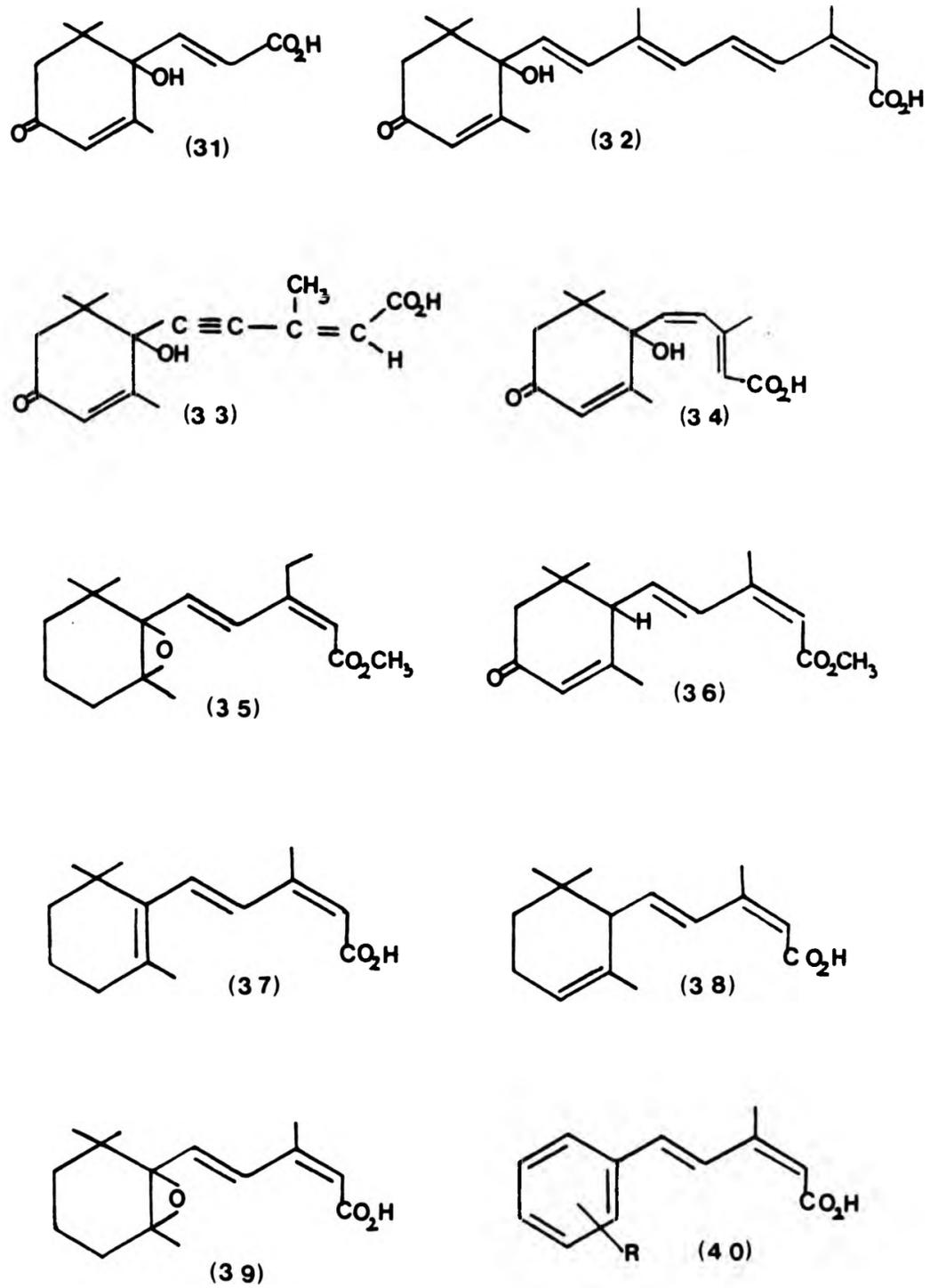


Scheme 4

trimethylsilyl(3-methyl-2-penten-4-ynyl)ether (22) to give the precursor (23) of ABA. Compound (23) was reduced with sodium bis (2-methoxyethoxy)-aluminium hydride $\text{Na} \left[\text{H}_2\text{Al} (\text{OCH}_2\text{CH}_2\text{OCH}_3)_2 \right]$ and the resulting product (24) was then oxidized with MnO_2 to the corresponding aldehyde (25) which was then reacted with Ag_2O to give the racemic (\pm)ABA (Scheme 4). The optically active ketone (21) was prepared in a separate synthesis from isophorone (26).⁵⁸ Isophorone (26) was catalytically oxidized to oxo-isophorone (27), which was then stereoselectively reduced during a fermentation process to give compound (28). The product (28) was then reduced with triisobutylaluminium (TIBA), $\text{Al} \left[(\text{CH}_3)_2\text{CHCH}_2 \right]_3$ to give predominantly the (4R,6R) isomer (29) and some (30). The former was subsequently converted to the required ketone (21).⁵⁸ Trans-ABA can be prepared by this same method using ketone (21) and the (E)-geometrical isomer of trimethylsilyl(3-methyl-2-penten-4-ynyl)ether (22). The Kienzle synthesis may be used for the preparation of some ABA analogues. Its main disadvantage, however, is the large number of stages involved.

9. The Structure-Activity Relationship

Parallel to the search for the synthesis of ABA, new routes to ABA analogues were developed. These analogues helped to determine the features of ABA molecule, which are responsible for its biological activity. One of the important aspects of



R = o-Me, m-Me, m-OMe,
p-Cl, 2,4-di-Cl

Scheme 5

the structure of ABA is the geometrical isomerism of the side chain. ²⁵ Only 2Z,4E-isomer is biologically active and any changes in the side chain, namely alteration of the length (31, 32) ⁵⁹ or stereochemistry (33, 34) ⁶⁰ of the side chain as well as the replacement of the methyl group with ethyl group (35) ⁶¹ render the compound inactive.

Other important aspects of the structure of ABA are the configuration at the asymmetric centre (C-1') and the presence of a hydroxyl group at C-1'. Since the natural (+)-ABA and its (-)-enantiomer were found to be equally potent in the growth inhibition assays but (-)-enantiomer did not affect stomatal apertures, ²⁸ therefore the different structural requirements are probably needed to control different physiological processes. Furthermore, an experiment with 1'-desoxy-ABA (36) showed that the compound is easily oxidised to ABA(5), ⁶² therefore the biological activity may be due to the fast conversion of this compound to ABA. ABA analogues with a double bond in the ring and without C-4' carbonyl group exhibit growth inhibitory activity (e.g. 37, 38). ⁶² However, these compounds can be chemically converted to ABA ^{53 56} and therefore the observable biological activity may be due to their metabolism. Also, epoxide (39), which was found very potent, can be converted to ABA(5). ⁶¹ The C-6' methyl groups do not seem to have a marked influence on the biological activity of ABA but the C-2' methyl has. ⁶³ Investigations of the biological activity of many aromatic ABA analogues (40) showed that there was no cor-

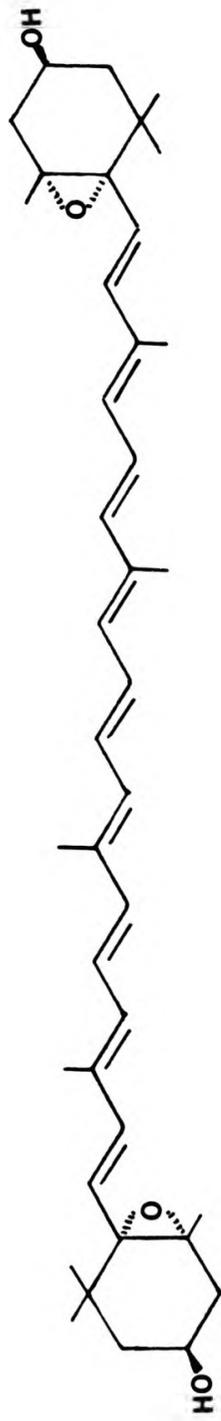
relation between the nature or number of substituents and their activity; ⁴⁰ all compounds tested (lettuce seed germination, inhibition of wheat coleoptile elongation) were found to be less active than ABA. ⁴⁰

10. Discovery of Xanthoxin

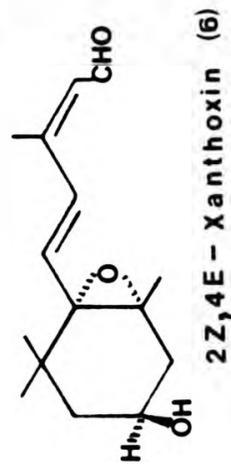
The structural similarities between ABA and some carotenoids ⁶⁴ and the observation that plants grown in light contain more inhibitor - β than those grown in the dark inspired the search for evidence that ABA could be produced from carotenoids and that light was involved in the process. ⁶⁴ In 1970 Taylor and Burden showed that in vitro illumination of violaxanthin (41) produced a growth inhibitor, ³³ which was further identified as a mixture of isomers 2Z,4E-(6) and 2E,4E-(7). The inhibitor has been named Xanthoxin. Two other products (42) and (43) were also characterized. ³³ In further work Xanthoxin was also obtained by mild oxidation of violaxanthin (41) with zinc permanganate in aqueous acetone. ³³

11. Occurrence of Xanthoxin

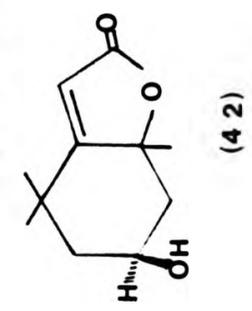
Xanthoxin occurs in nature as a mixture of stereoisomers 2Z,4E-Xanthoxin (6) and 2E,4E-Xanthoxin (7). The inhibitor was isolated from higher plants ²⁰ and also from ferns. ⁶⁵ However, the 2E-isomer (7) is found in larger amounts than



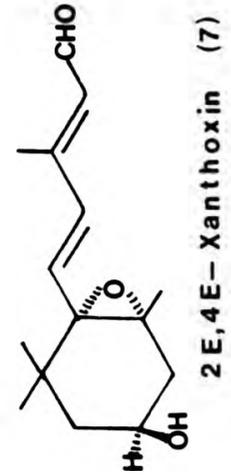
Violaxanthin (41)



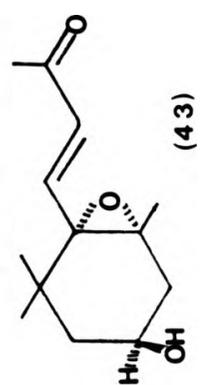
2Z,4E-Xanthoxin (6)



(42)



2E,4E-Xanthoxin (7)



(43)

Scheme 6

the 2Z-isomer (6) in most plants,⁶⁶ thus on the grounds of stereochemistry Xanthoxin can be said to derive from violaxanthin (41).

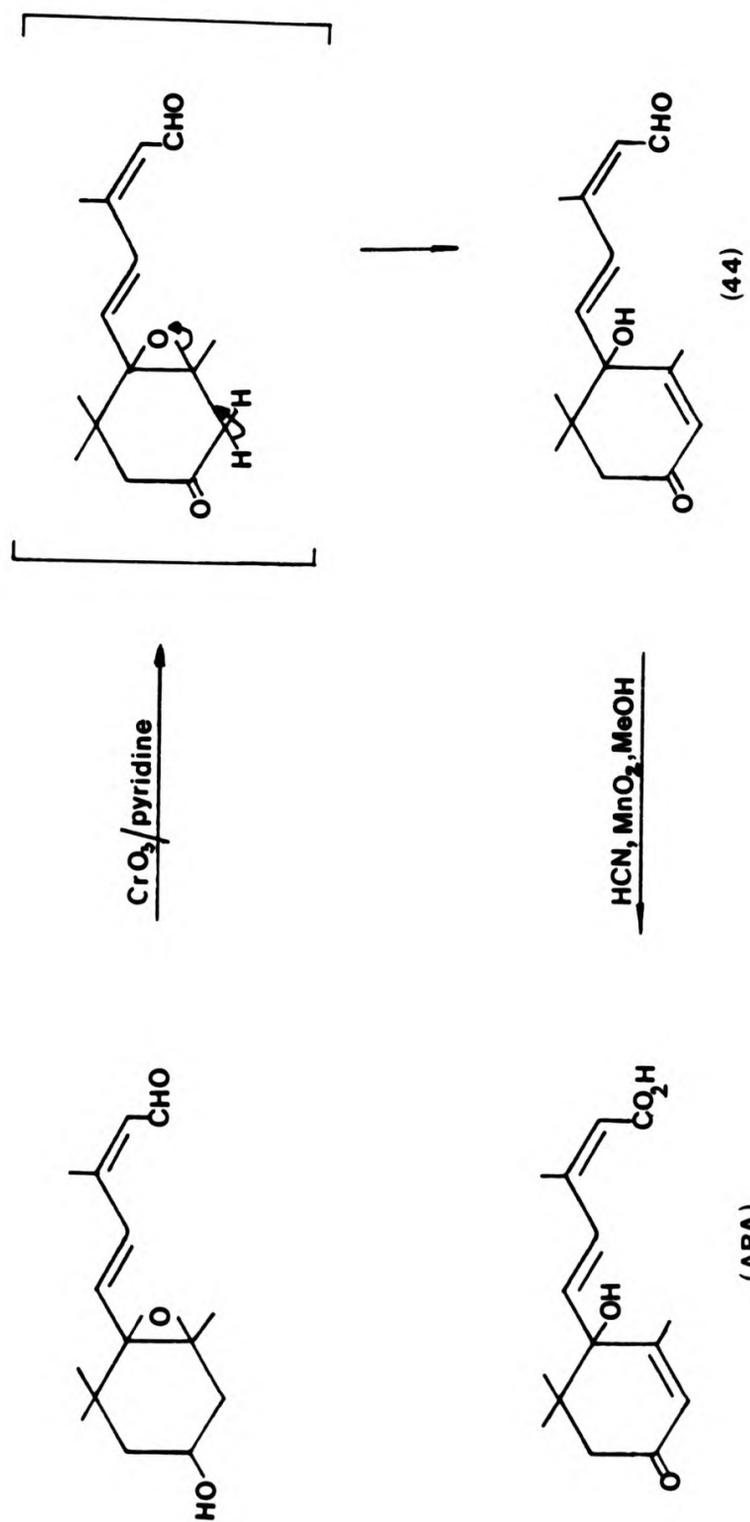
12. Properties of Xanthoxin

The biological activity of the 2Z-4E-isomer (6) is considerably greater than that of 2E,4E- and it has been shown to be comparable with that of (+)-ABA in many bioassays.³³

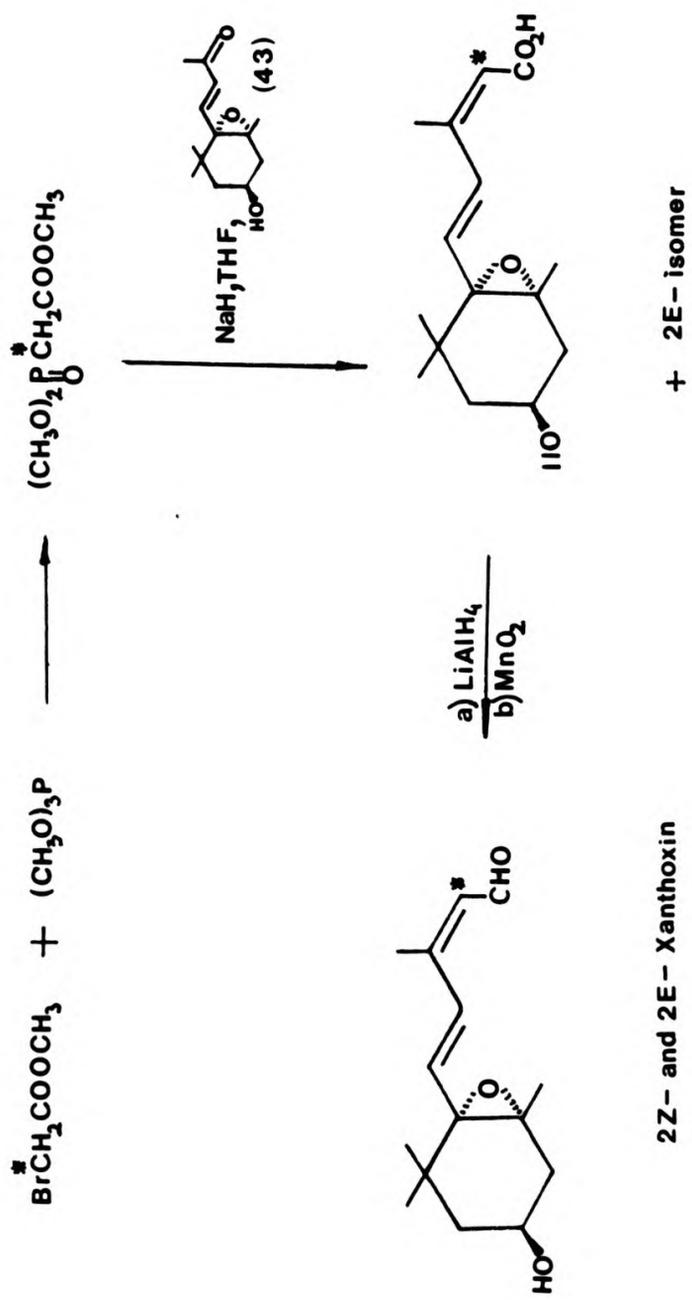
An important feature of the chemistry of Xanthoxin is the conversion of this hormone to ABA.³³ Thus Xanthoxin was oxidized to abscisic aldehyde (44) with chromium trioxide in pyridine. The resulting aldehyde (44) was further oxidized to ABA. The chemical conversion of Xanthoxin to ABA is of importance as it relates the stereochemistry of violaxanthin (41) to that of ABA and suggests that Xanthoxin could be an intermediate in the formation of ABA from carotenoids.

13. Syntheses of Xanthoxin

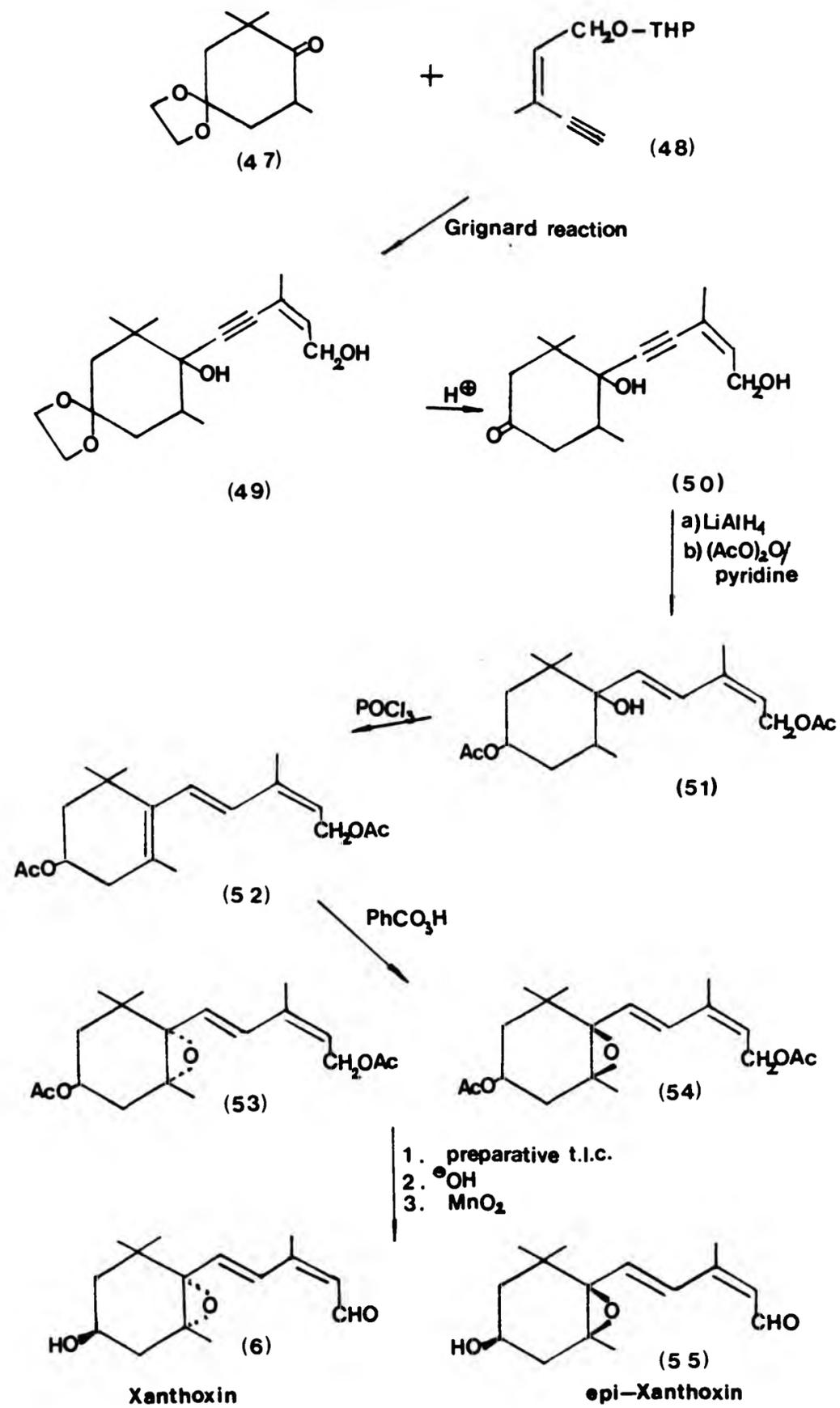
In 1972 Burden and Taylor reported a synthesis of O-methyl-xanthoxin (45) (46), the key reaction being introduction of a methoxy group into the 4' - position of β -ionone.⁶⁷



Scheme 7



Scheme 8



Scheme 9

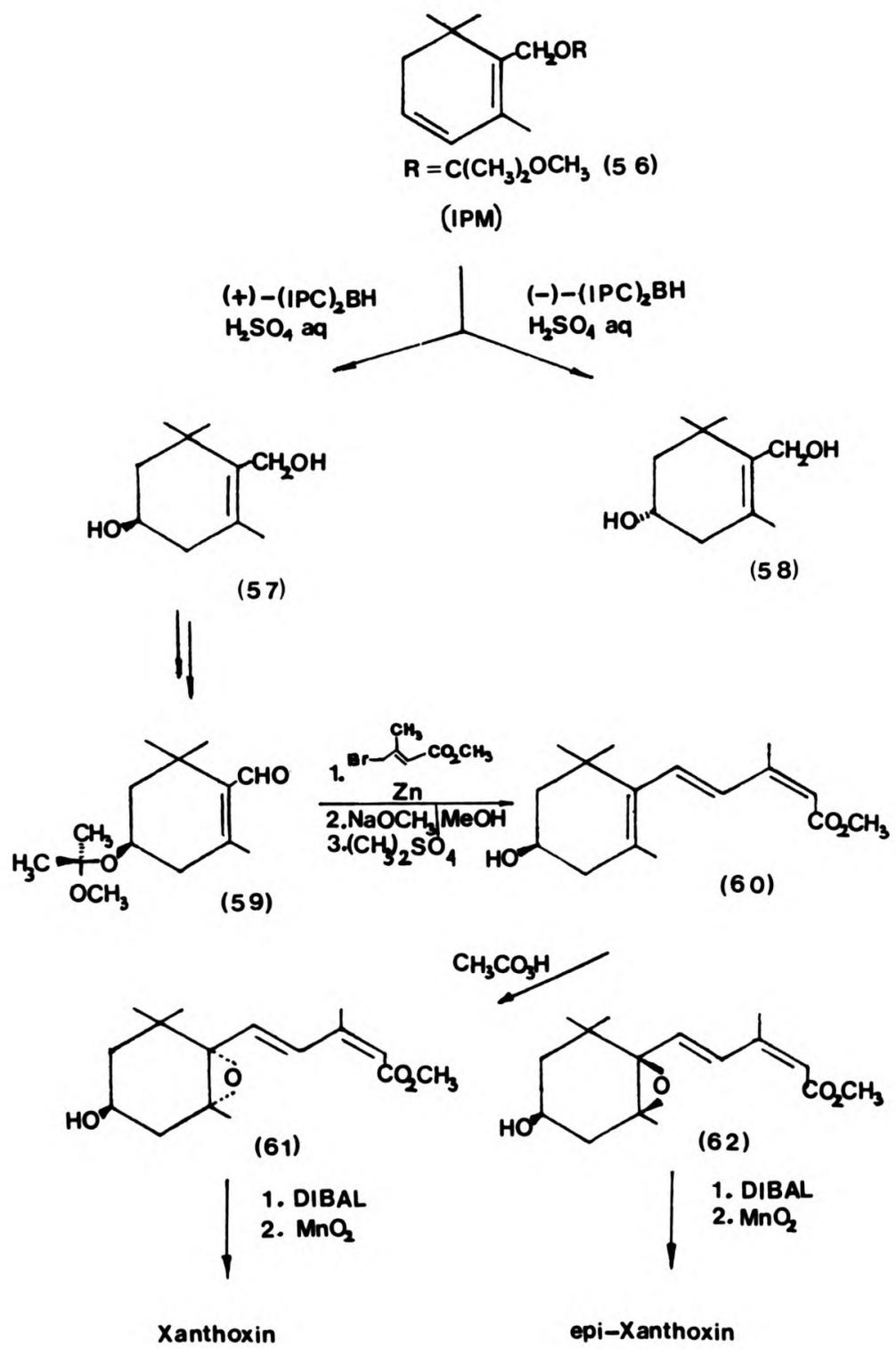
natural Xanthoxin. ³³

In 1978 F. Kienzle et al reported a synthesis of Xanthoxin, ⁵⁷ the key reaction being asymmetric hydroboration of safran α l isopropenylmethyl ether (56) with (+) and (-)-diisopinocampheylborane, (IPC)₂BH, to give the optically pure intermediates (57) and (58) respectively. Compound (57) was converted into aldehyde (59), ⁷⁰ which was further transformed into ester (60). Epoxidation of ester (60) with peracetic acid followed by column chromatography gave epoxides (61) and (62), which were subsequently converted into Xanthoxin (6) and epi-Xanthoxin (55).

14. Biosynthesis of Xanthoxin and its Relationship to Abscisic Acid

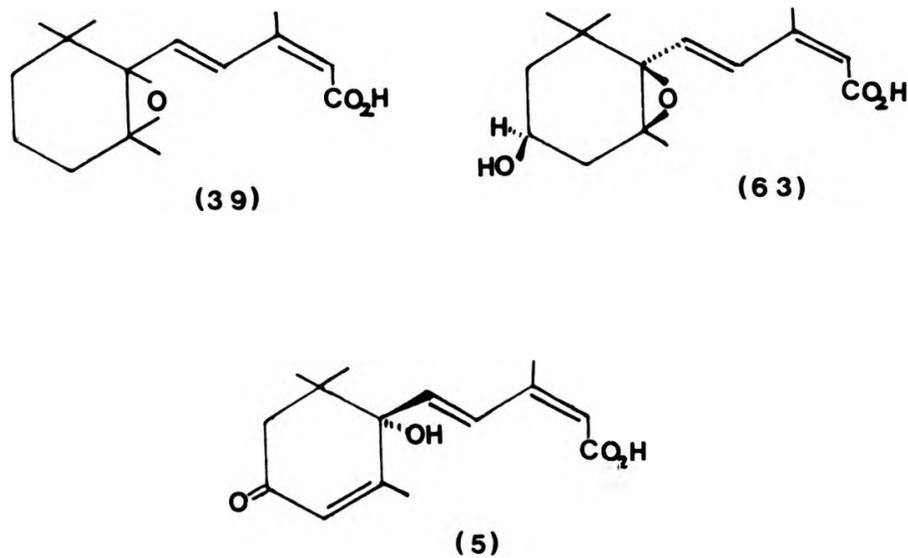
The origin of Xanthoxin is uncertain as it may be formed from violaxanthin photochemically ³³ or by the action of enzymes. ⁷¹ Xanthoxin is found in nature and is thought to be an intermediate in the biosynthesis of ABA from carotenoids. Burden ³⁴ showed that when [2-¹⁴C] 2Z-Xanthoxin was fed into tomato shoots it was converted to (+)-ABA with high yields. This experiment suggests a biosynthetic route for the formation of ABA from carotenoids and via Xanthoxin.

In 1973 Milborrow demonstrated ⁷² that avocado mesocarp fed with (+)- [2-¹⁴C] -epoxide (39) converted it into



Scheme 10

(+)ABA and (-)-1', 2'-epi-Xanthoxin acid (63). It was therefore concluded that the configuration of the 1' 2'-epoxy group controls whether or not the 4' (S)-hydroxyl group can be oxidized. Thus Xanthoxin or a related compound may be an intermediate in the direct biosynthetic route to ABA.



The in vivo relationship between carotenoids, Xanthoxin and ABA is still uncertain; the results of some experiments are in favour of the direct biosynthesis of ABA from MVA while others indicate that ABA may be derived from carotenoids.

DISCUSSION AND CONCLUSIONS

1. Introduction

The syntheses of the plant hormones ABA and Xanthoxin reported in the literature ^{53 57 68} led to the mixtures of stereoisomers from which the active isomer could only be isolated in very low yields. In our proposed stereocontrolled synthesis of plant growth regulators, an intermediate, 4-mercapto-3-methylbut-2-enoic acid γ -thiolactone (64), was to be prepared in order to control the stereochemistry at the double bond and sulphur was to be utilized as a bridging element. γ -thiolactone (64) was to be further reacted with benzaldehyde and mesitaldehyde and the new bond formed in the condensation was expected to have, and was shown to have, the required Z-configuration.

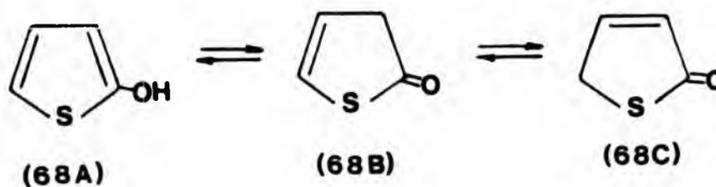
A major product of condensation of γ -thiolactone (64) and β -cyclocitral (65) was also expected to have 2Z,4Z geometry of the double bond system as shown in structure (66); formation of the 2Z,4E-isomer (67) would be unfavourable for steric reasons. Desulphurization of compound (66) followed by the introduction of oxygen into the 4'-position should yield, eventually, ABA. Introduction of the oxygen into the 4'-position might be accomplished by microbiological processes ⁷³ or by using a different aldehyde precursor.

2. Syntheses of 4-mercapto-3-methylbut-2-enoic acid

γ -thiolactone (64)

2.1 Tautomerism of Hydroxythiophenes

As has been shown above, γ -thiolactone (64) is an important element in the proposed, stereocontrolled synthesis, therefore the first part of the work was devoted to the preparation of this compound. 4-Methyl-3-thiolene-2-one (64) can be regarded as a hydroxythiophene derivative. 2-Hydroxythiophenes can theoretically exist in three tautomeric forms (68A), (68B) and (68C).^{74 75}

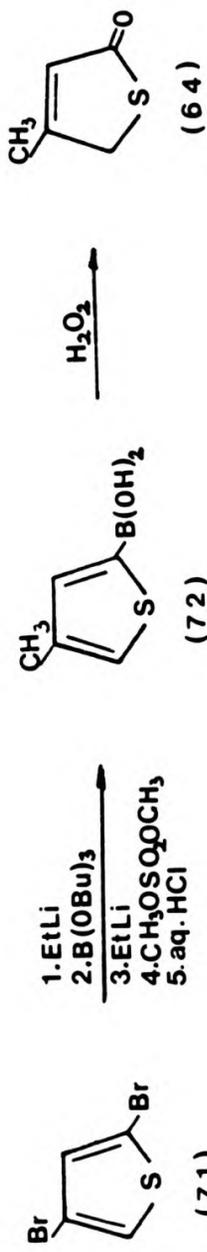
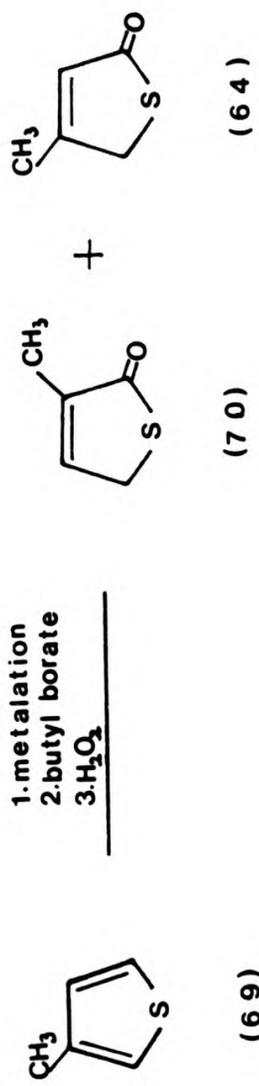


The early research on hydroxythiophenes showed that the nature and position of the substituent on the hydroxythiophene ring decides which tautomeric form will dominate.⁷⁶ Thus, with an electron attracting group in the 5-position the enol form was found to be most stable,^{76 77} while 4-methyl-3-thiolene-2-one (64) was shown to exist entirely in the conjugated keto-form.⁷⁸

2.2 Synthesis of 4-methyl-3-thiolene-2-one (64) via
metalated thiophenes

The first synthesis of 4-methyl-3-thiolene-2-one (64) initially involved metallation of 3-methyl thiophene (69) followed by treatment with butyl borate and oxidation with hydrogen peroxide.⁷⁹ The final product consisted of a mixture of 3-methyl-3-thiolene-2-one (23%) (70) and 4-methyl-3-thiolene-2-one (77%) (64).

The above method of preparation of compound (64) was later improved by A. B. Hornfeldt;⁷⁴ 2,4-dibromothiophene (71) was used as a starting material and the crude product was chromatographed on a silica column. The major step of the synthesis is a metal-halogen exchange reaction. 2,4-Dibromothiophene (71) reacts with ethyllithium specifically at the 2- and 4-positions; the resulting metalated thiophene undergoes further reactions with butyl borate and dimethyl sulphate, as represented in Scheme 12 to yield boronic acid (72), which is further oxidised to give finally the isomer free γ -thiolactone (64). We attempted to repeat this route by the synthesis of 2,4-dibromothiophene (71), as starting material. Compound (71) had previously been prepared in a three step synthesis, which proceeded via brominated thiophenes.



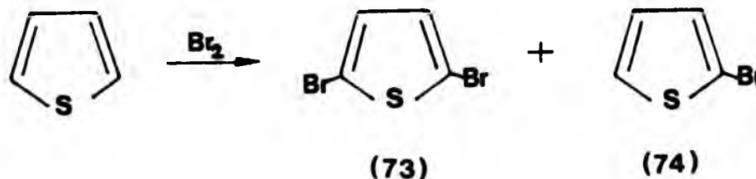
Scheme 12

3. Syntheses of Bromothiophenes

3.1 Synthesis of 2,5-dibromothiophene (73)

The bromination of thiophene was first reported by V. Mayer and involved reaction of stoichiometric amounts of bromine and thiophene ⁸⁰ without a solvent and gave a mixture of 2,5-dibromothiophene (73) and monobromothiophene (74). Compound (73) was later obtained by bromination of thiophene with N-bromoacetamide in acetone ⁸¹ and with bromine in benzene. ⁸²

2,5-Dibromothiophene was prepared in our laboratory by the method of R. Mozingo, ⁸² which involved addition of bromine to a solution of thiophene in toluene followed by heating the crude reaction mixture with ethanolic sodium hydroxide. The crude product was redistilled to give 2,5-dibromothiophene (73) (38%); monobromothiophene (74) and some low boiling compounds (32%). Compound (73) was analysed by means of i.r. and ¹H n.m.r. spectroscopic methods and its purity was checked by g.l.c.



The ^1H n.m.r. spectrum of 2,5-dibromothiophene (73) shows a single peak at $\delta 6.65$ * ⁸³; the molecule is symmetrically substituted and both protons H-3 and H-4 are magnetically equivalent.

The i.r. spectrum of 2,5-dibromothiophene (73) shows the following absorption bands: a medium intensity band at 3120 cm^{-1} is due to the C-H stretching vibrations, a band at 1520 cm^{-1} is due to the ring vibration modes ⁸⁴; the fundamental stretching frequency for C=C (at 1640 cm^{-1} in olefins) is not present in 2,5-dibromothiophene (73). This frequency would be expected to be altered, since it is enclosed in the ring and is essentially symmetrical. A band at 1310 cm^{-1} has been assigned to the vibrations of sulphur between two carbon atoms on the thiophene ring; this band appears in the spectra of many substituted thiophenes and its position was found to be little affected by substitution.

⁸⁴ A medium intensity band at 478 cm^{-1} may be due to the C-Br stretching vibrations. ⁸⁴

* Foot Note

In ^1H and ^{13}C n.m.r. spectra the chemical shifts are reported in p.p.m. on δ scale from internal standard T.M.S. ($\delta=0$).

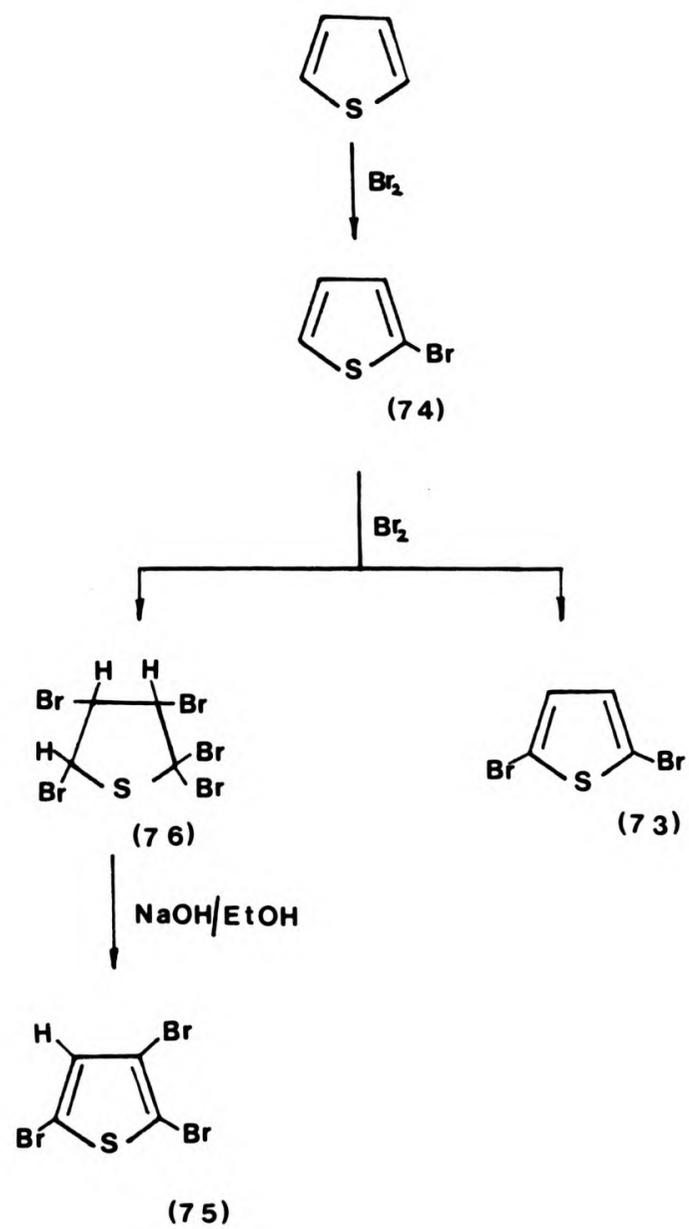
3.2 Preparation of 2,3,5,-tribromothiophene (75)

2,3,5-Tribromothiophene (75) was prepared by the method of Rossenberg,⁸⁵ which involved reaction of stoichiometric amounts of bromine and 2,5-dibromothiophene (73) followed by heating a crude reaction mixture with ethanolic sodium hydroxide. The product (75) was purified by distillation (b.p. 88°C-94°C/0.2 mm Hg). It was obtained with yields of 42.5% and 46% in two successive reactions and of purity 94.5% and 96.5% respectively (g.l.c. analysis). Tribromothiophene (75) solidified in form of long, white needles of m.p. 23°C-25°C.

The ¹H n.m.r. spectrum of 2,3,5-tribromothiophene (75) shows one peak at δ 6.72 which is due to the proton H-4.

2,3,5-Tribromothiophene (75) has also been prepared in our laboratory by the direct bromination of thiophene. The preparation involved addition of bromine to a cooled solution of thiophene in toluene followed by heating for one hour and washing with water and aq. NaOH. The crude product was re-distilled to give 41% of 2,3,5-tribromothiophene (75).

Treatment of the bromothiophenes with alcoholic KOH or NaOH^{85 86} originates from the fact that the reaction mixtures from chlorination of thiophene need to be heated



Scheme 13

with alcoholic NaOH in order to destroy stable chlorine addition products and increase the yield of chlorine substitution products. ⁸⁴ Bromine addition products (e.g. compound (76)), have never been isolated, they are thought, however, to exist as very unstable intermediates. ⁸⁴ Thus, a crude reaction mixture obtained in our preparation of 2,3,5-tribromothiophene was not heated with a base but was washed with aq. NaOH at room temperature; this procedure proved satisfactory in the preparation of product (75).

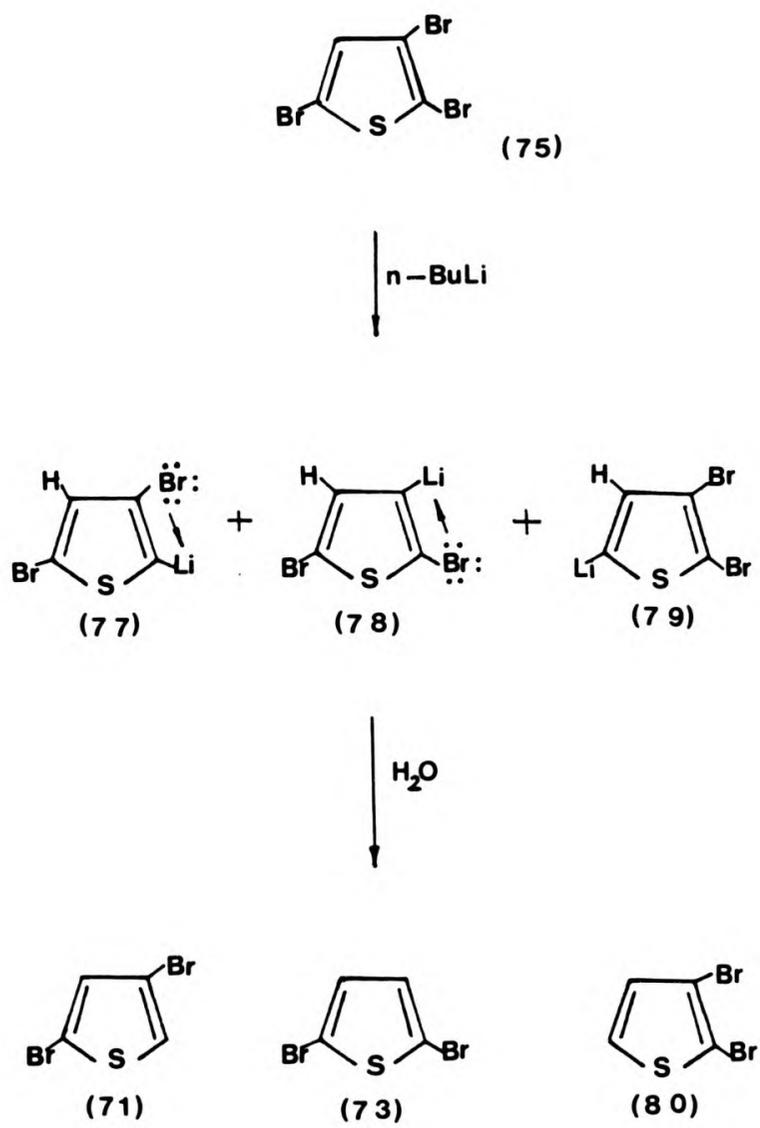
2,3,5-Tribromothiophene (75) was further used for the synthesis of 2,4-dibromothiophene (71).

3.3 Preparation of 2,4-dibromothiophene (71)

2,4-Dibromothiophene (71) was prepared by the method of Lawesson ⁸⁷ in the reaction of 2,3,5-tribromothiophene (75) with n-butyllithium in diethyl ether at low temperatures (-30°C) followed by hydrolysis of the lithiated thiophene (77).

In the reaction, one of the bromines on the thiophene ring is substituted with lithium; this type of substitution is known as the halogen-metal exchange reaction.

Among the lithiated thiophenes (77), (78) and (79) formed



Scheme 14

in the course of the reaction, compound (77) is thermodynamically most stable. ⁷⁶ The stability of the compound (77) is the result of the 2-, 5- directing properties of the sulphur ⁷⁶ and also the directing and co-ordinating properties ⁸⁸ of the bromine.

When the reaction of 2,3,5-tribromothiophene (75) with n-butyllithium was carried out over a period of 10 minutes, a mixture consisting of 2,4- (71), 2,5- (73) and 2,3- (80)-dibromothiophenes and some starting material (75) was obtained with a relative ratio of the components, calculated from the ¹H n.m.r. integrals equal to (in %): 45, 34, 9 and 12 respectively.

Better yields of the title compound (71) were obtained when the reaction time was extended to 30 minutes and the relative amounts of the products calculated from the ¹H n.m.r. integrals were as follows: 2,4-dibromothiophene (71) 74%, 2,5-dibromothiophene (73) 14%, 2,3-dibromothiophene (80) 12% and no peak corresponding to 2,3,5-tribromothiophene (75), a starting material, was found in the ¹H n.m.r. spectrum.

The products could not be separated by distillation due to their close boiling points. ⁸⁴ Attempts to analyse the mixture by means of t.l.c. technique failed as all the components of the mixture showed as a one spot, which could not

be resolved by using different solvents. Also, mixture of dibromothiophenes could not be separated by means of HPLC chloroform or hexane was used as a mobile phase; column: "Partisil 5"; U.V. 254 nm.

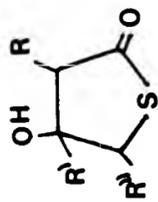
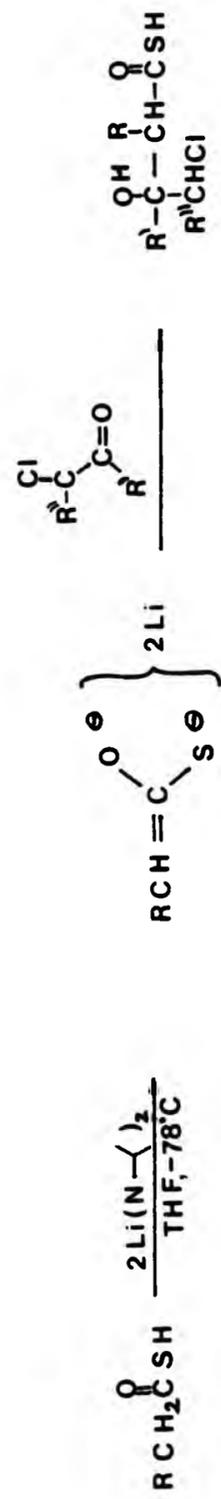
Because 2,4-dibromothiophene (73) could not be obtained free of isomers the next stage of synthesis was not undertaken, instead another synthetic route was tried.

4. Synthesis of γ -thiolactones via bismetalated thioacetic acid

4.1 Reaction of monochloroacetone with thioacetic acid initiated by LDA

Various thiolactones were prepared by Wemple and co-workers⁸⁹ in a synthesis, which involved reaction of thioacids with lithium diisopropylamide followed by condensation of the resulting bis lithium salt of thioacids with α - or β -chloro ketones, to give corresponding β -hydroxy thioacids. The latter further cyclized to thiolactones (Scheme 15).

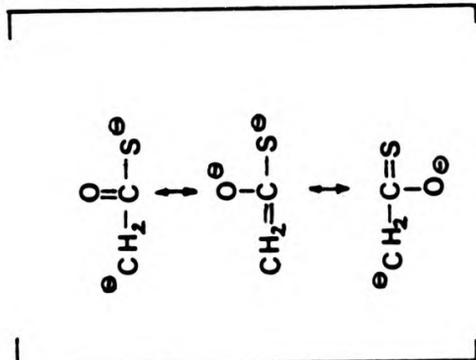
We adopted the above method of synthesis of thiolactones for preparation of 4-mercapto-3-methylbut-2-enoic acid γ -thiolactone (64) via β -hydroxy thioacid (81). Thus, thioacetic acid was first reacted with two equivalents of lithium di-



R = H, CH₃



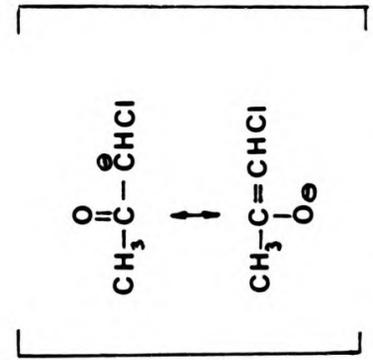
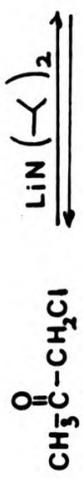
Scheme 15



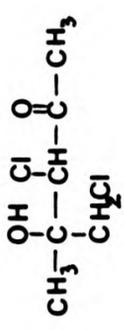
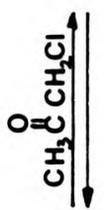
2 Li[⊕]



(81)



Li[⊕]



(82)

Scheme 16

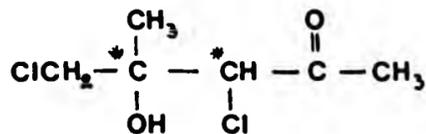
isopropylamide in THF at -78°C and the bisanion of thioacetic acid was expected to form at this stage of the synthesis. One equivalent of monochloroacetone in THF was then added to the reaction mixture and the reagents were stirred for one hour. A dark brown crude product was distilled and the distillate was further purified by chromatography on a silica column using chloroform for eluting. The product (82) was obtained with an overall yield of 5% and its structure was determined by means of i.r. and ^1H and ^{13}C n.m.r. spectroscopic methods, (spectra 1-4).

In the i.r. spectrum a band at 3400 cm^{-1} indicated the presence of an OH group; C-H str. vibrations gave rise to a band at 2995 cm^{-1} ; a C=O str. absorption band appeared at 1710 cm^{-1} and a C-Cl str. absorption was observed at 645 cm^{-1} .

The signals in ^1H n.m.r. spectrum were assigned as follows: the peaks at δ 1.42, δ 2.42 and δ 2.43 were assigned to CH_3 protons, the multiplets at δ 3.64 and δ 3.69 to CH_2 protons and the peaks at δ 4.56 and δ 4.59 to CH protons. Broad peaks at δ 3.25 and δ 3.45 which disappeared on D_2O shake were assigned to the OH groups.

The broad band decoupled ^{13}C n.m.r. spectrum showed 12 peaks, which were arranged in pairs indicating a mixture. The single frequency off-resonance decoupled ^{13}C n.m.r. spectrum showed

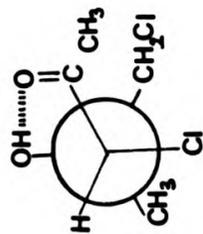
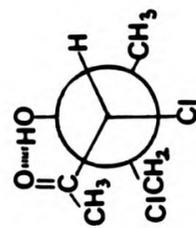
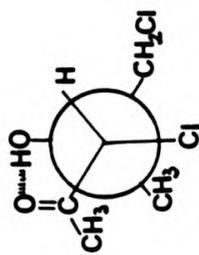
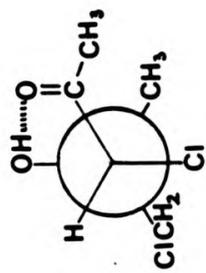
the following groups of peaks: the distinguishable quartets at δ 21.4, δ 22.8 and δ 28.8, δ 29.6, two triplets at δ 49.9 and δ 51.2, two doublets at δ 63.9 and δ 66.2 and two single peaks for the quarternary carbons at δ 73.7 and δ 74.6 and far downfield the single peaks for the carbonyl carbon were found at δ 203.7 and δ 205.0. After analysis the following structure was assigned to the reaction product:



(82)

3,5-Dichloro-4-hydroxy-4-methyl-2-pentanone (82) is a colourless liquid. The compound undergoes decomposition on standing. Its molecule has two asymmetric carbons, therefore the compound has four stereoisomers.

The Newman projections (Scheme 17) show that the protons and carbons in any pair of diastereoisomers are in magnetically different environments, therefore, they can give rise to different peaks in the n.m.r. spectra. In fact, the peaks corresponding to protons and carbons in any pair of diastereoisomers can be distinguished in the ^1H and ^{13}C n.m.r.



Newman projections

Scheme 17

spectra respectively, (spectra 1-4).

The compound (82) was formed as a result of condensation of two monochloroacetone molecules (Aldol type addition). Under the reaction conditions monochloroacetone was converted into its enolate anion which reacted further with another molecule of monochloroacetone to yield dimer (82). The formation of product (82) is not favoured mainly for steric reasons. Also, the compound (82) is likely to dehydrate easily and further polymerize. That would explain the low yields of the product (82).

The reaction of thioacetic acid with monochloroacetone was repeated in the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA); the TMEDA and n-butyllithium complex was reported to be a very good metalating agent.⁹⁰ β -Hydroxy thioacid (81) was not however formed under the adjusted reaction conditions.

β -Hydroxy thioacid (81) could not be obtained in the above synthesis, yet this preparation may suggest a method for making α , β -substituted ketones.

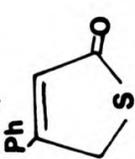
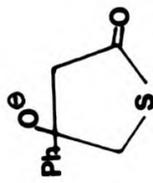
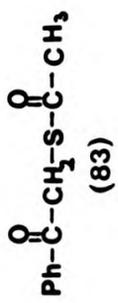
4.2 Reaction of Phenacyl Chloride with Thioacetic Acid

The reaction of phenacyl chloride with thioacetic acid ⁸⁹ was initiated by LDA and gave S-phenacyl thioacetate (83) with 15% yield and some recovered phenacyl chloride, 28%. S-Phenacyl thioacetate was then analysed by means of ¹H and ¹³C n.m.r. and i.r. spectroscopy. In the mass spectrum the fragmentation pattern represented in Scheme (18) was observed.

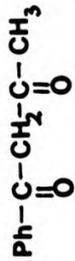
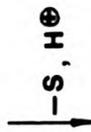
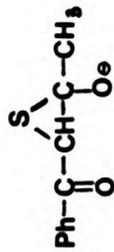
S-Phenacyl thioacetate (83) was next reacted with t-BuOK in an attempt to cyclize it to the corresponding thiolactone (84). The thiolactone (84) was not detected among the reaction products but the product (85) of desulphurization of S-phenacyl thioacetate was found. Compound (85) was then purified by means of preparative TLC technique.

The desulphurization of S-phenacyl thioacetate (83) is believed to proceed via an episulphide, which decomposes under the reaction conditions to give benzoylacetone (85).

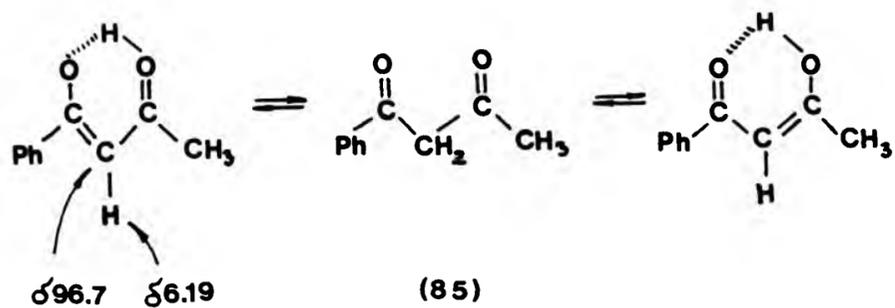
The presence of the peak at δ 6.19 in ¹H n.m.r. spectrum and the peak at δ 96.8 in ¹³C n.m.r. spectrum suggests that product (85) exists in the enol form.



(84)

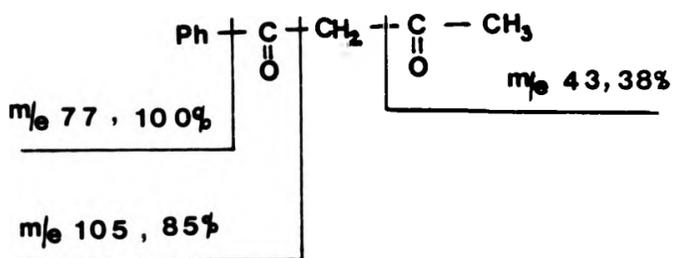


(85)



The U.V. spectrum of compound (85) recorded in MeOH showed the absorption maximum at λ_{\max} 314 nm; addition of a drop of 2M NaOH caused the λ_{\max} shift to 328 nm; acidification of the mixture with 1M HCl caused λ_{\max} shift back to 314 nm.

Mass spectrum of product (85) suggested the following fragmentation;



5. Attempted preparation of 4-mercapto-3-methylbut-2-enoic acid γ -thiolactone (64) via its oxygen analogue

5.1 Preparation of 4-hydroxy-3-methylbut-2-enoic acid γ -thiolactone (86)

As the method of Wemple⁸⁹ did not give satisfactory results when adopted for the preparation of the title compound (64), a synthetic route via its oxygen analogue was tried. Following some examples in the literature, which demonstrate that oxygen atom in a ring can be replaced with a sulphur atom using a variety of reagents, e.g. P_2S_5 ⁹¹ or p-methoxyphenylthionophosphine sulphide,⁹² we attempted to obtain γ -thiolactone (64) by reacting its oxygen analogue (86) with P_2S_5 .

Compound (86) was prepared in a 3 step synthesis.⁹³ First ethyl bromoacetate and monochloroacetone were reacted in the Reformatsky reaction to give ethyl 4-chloro-3-hydroxy-3-methylbutanoate (87) with an average yield of 35%. The product (87) was analyzed by means of 1H , ^{13}C n.m.r. and i.r. spectroscopic methods and the results were compared with those quoted in the literature.

Although the use of two α -halo carbonyl compounds might lead to two different products, the problem was overcome by reacting

a relatively reactive α -bromo ester with a α -chloro ketone which is much less reactive in the Reformatsky reaction. ⁹³

β -Hydroxy ester (87) was then treated with KOH in methanol to give a mixture of methyl-E-4-hydroxy-3-methylbut-2-enoate (88) and γ -lactone (86). The ratio of the compounds (88) and (86) present in the reaction product was calculated from ¹H n.m.r. integrals and it was found to be 2:1 respectively. Also, ¹H n.m.r. spectrum showed that under the reaction conditions transesterification took place and methyl ester (88) was obtained from ethyl ester (87).

Photo-irradiation of a mixture containing E-ester (88) and γ -lactone (86) in the ratio 66:34 gave a product which contained compounds (88) and (86) in the ratio 18:82 respectively.

The product (86) was then purified by distillation (36% yield) and analyzed by means of ¹H, ¹³C n.m.r. and i.r. spectroscopic methods. The ¹H n.m.r. and i.r. results were compared with the literature data. ⁹³ The ¹³C broad band decoupled and single frequency off resonance decoupled (s.f.o.r.d.) spectra showed following peaks: a peak at δ 14.6 corresponding to the CH₃ carbon; the methylene carbon gave rise to a peak at δ 77.4; a peak at δ 117.1

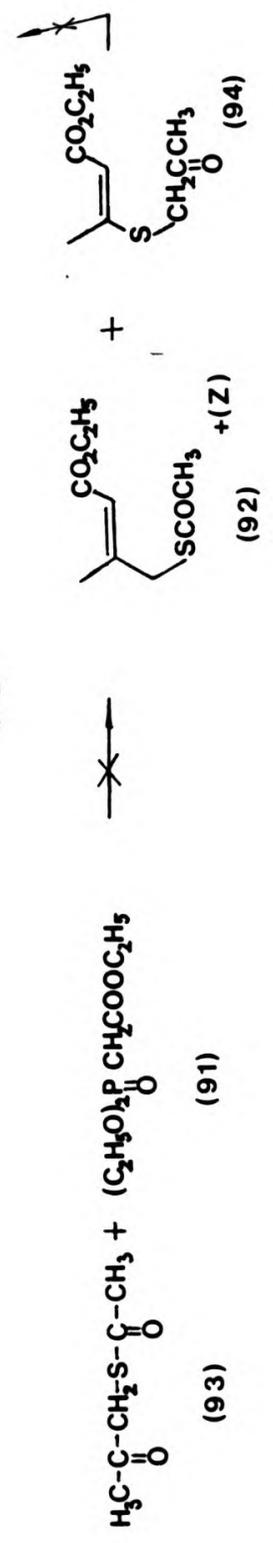
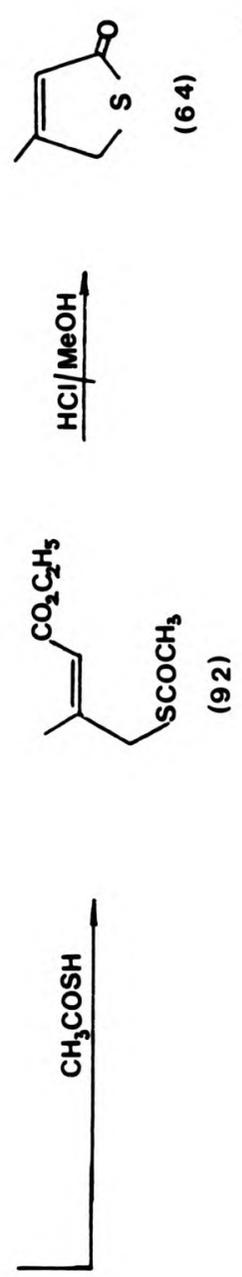
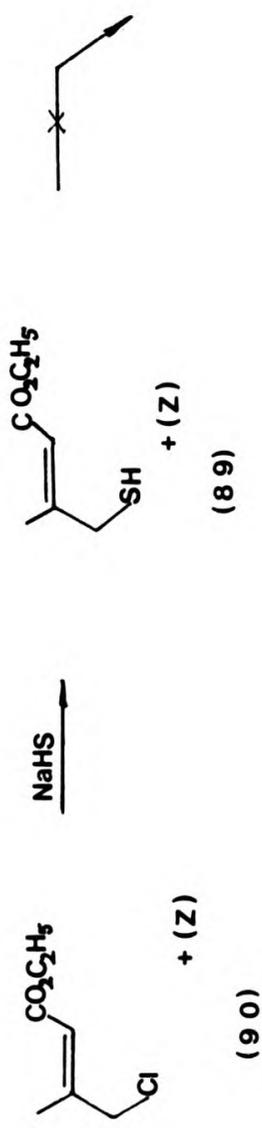
corresponding to the olefinic carbon =CH-; the quaternary carbon gave rise to a peak at δ 166.6 and downfield at δ 174.0 a peak due to the carbonyl carbon was found.

5.2 The reaction of γ -lactone (86) with P_2S_5

4-Hydroxy-3-methylbut-2-enoic acid γ -lactone (86) was then reacted with phosphorus pentasulphide. When the reaction was carried out in THF at room temperature over a period of 4 days, the 1H n.m.r. and g.l.c. analyses showed that the starting material (86) only was recovered. The reaction was repeated and the reagents were refluxed for 24 hours. The 1H n.m.r. analysis of the crude product indicated that only the starting γ -lactone (86) was present in the product. The negative results of the reaction are probably due to the low solubility of P_2S_5 in THF.

6. The novel synthesis of γ -thiolactone (64)

Due to the difficulty in obtaining the γ -thiolactone (64) by the methods described above, new synthetic routes were tried. They involved preparation of a suitable unsaturated thio- or mercapto acid which on cyclization would yield the required γ -thiolactone (64), (Scheme 21).



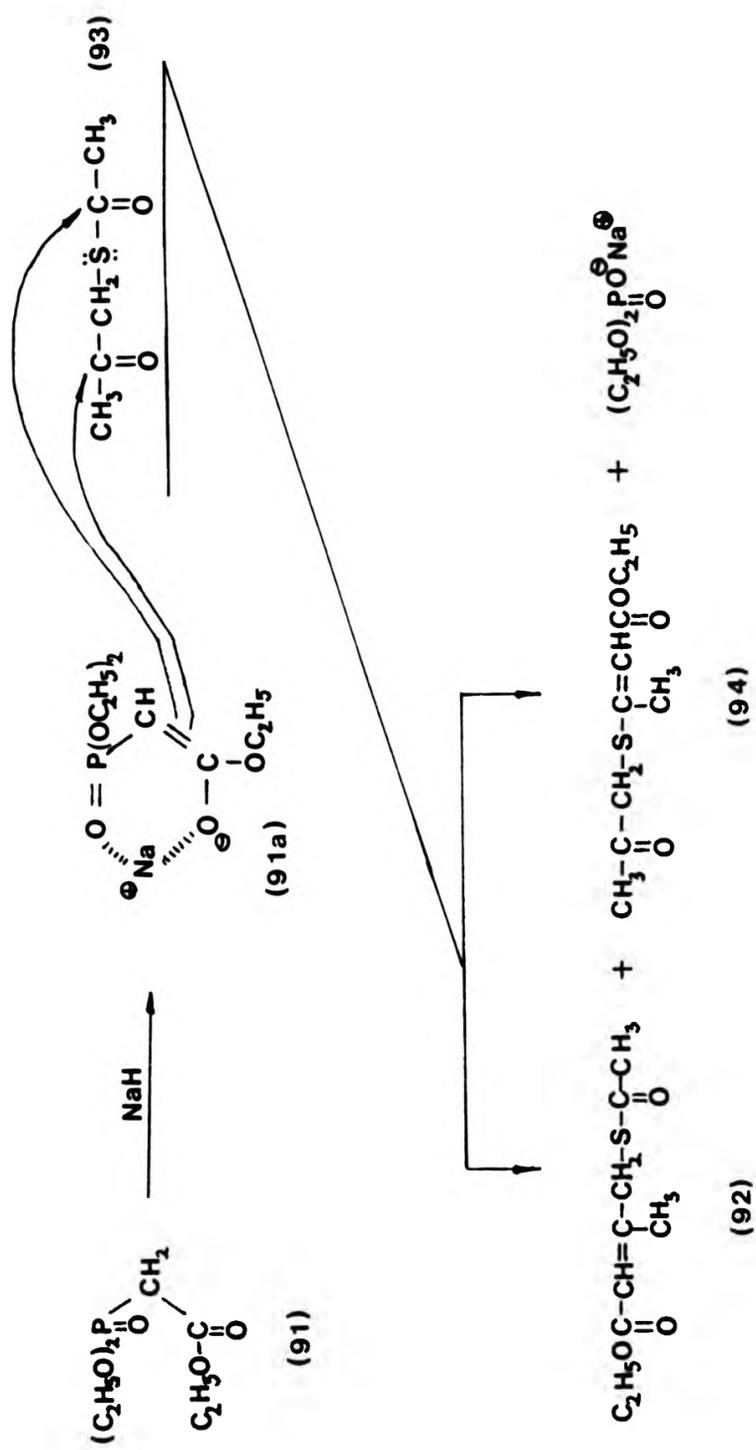
Scheme 21

6.1 Attempted preparation of γ -thiolactone (64) by
cyclization of ethyl 4-mercapto-3-methylbut-2-enoate (89)

In an attempt to obtain γ -thiolactone (64) by cyclization of Z-isomer of mercapto acid ethyl ester (89), ethyl-(E and Z)-4-chloro-3-methylbut-2-enoate (90) was reacted with NaHS. Compound (90) was prepared in our laboratory from triethylphosphonoacetate (91) and monochloroacetone by the Wadsworth Emmons' method.⁹⁴

When THF was used as a solvent, only starting materials were recovered probably due to the low solubility of NaHS in this solvent.

The reaction was then repeated in the more polar, aprotic solvent, DMSO, and the ^1H n.m.r. spectrum of the crude product showed that it contained unreacted substrate (90) and some other unidentified compounds. The expected peaks for γ -thiolactone (64) were not present in the spectrum and no further identification of the products was undertaken. Instead another method of synthesis of γ -thiolactone (64) was tried.



Scheme 22

6.2 Preparation of γ -thiolactone (64) by cyclization of ethyl 4-acetylthio-3-methylbut-2-enoate (92)

6.2.A Reaction of (2-oxopropyl)-thioacetate (93) with triethylphosphonoacetate (91)

In an attempt to prepare compound (92), (2-oxopropyl)-thioacetate (93), made in our laboratory from thioacetic acid and monochloroacetone, was reacted with triethylphosphonoacetate (91).⁹⁴ It was possible that a mixture of olefins (92) and (94) would result, (see Scheme 22).

In the compound (93) both carbonyl groups can take part in the reaction with Wadsworth-Emmons' reagent, yet it was expected that the main product would arise from nucleophilic attack of phosphonate ylid (91a) on the carbonyl carbon of the acetone moiety. Only a small amount of product was expected to form from the attack on the carbonyl carbon of the thioesterfunction.⁹⁵

The reaction conditions were altered several times; the reaction time was extended, an excess of phosphonate was used. Also the reaction was conducted at elevated temperature. ¹H n.m.r. analysis of the crude products however, showed absence of any peaks in the olefinic region of the ¹H n.m.r. spectra, suggesting that none of the expected olefins were ob-

tained; probably the phosphonate ylid was not formed under the applied reaction conditions.

6.2.B Reaction of ethyl-(E and Z)-4-chloro-3-methylbut-2-enoate (90) with thioacetic acid

Ethyl-(E and Z)-4-chloro-3-methylbut-2-enoate (90) was reacted with thioacetic acid to give ethyl-(E and Z)-4-acetylthio-3-methylbut-2-enoate (92), which was used in the further reactions without purification since the yield was better than 95%.

The structure of compound (92) was confirmed by means of ^1H and ^{13}C n.m.r. spectroscopy. From the ^1H n.m.r. integrals it was found that product (92) was a mixture of (E) and (Z) isomers in the ratio 6:4 respectively.

6.2.C Cyclization of ethyl-4-acetylthio-3-methylbut-2-enoate (92) to γ -thiolactone (64)

The following experiments were carried out in order to cyclize compound (92) to γ -thiolactone (64).

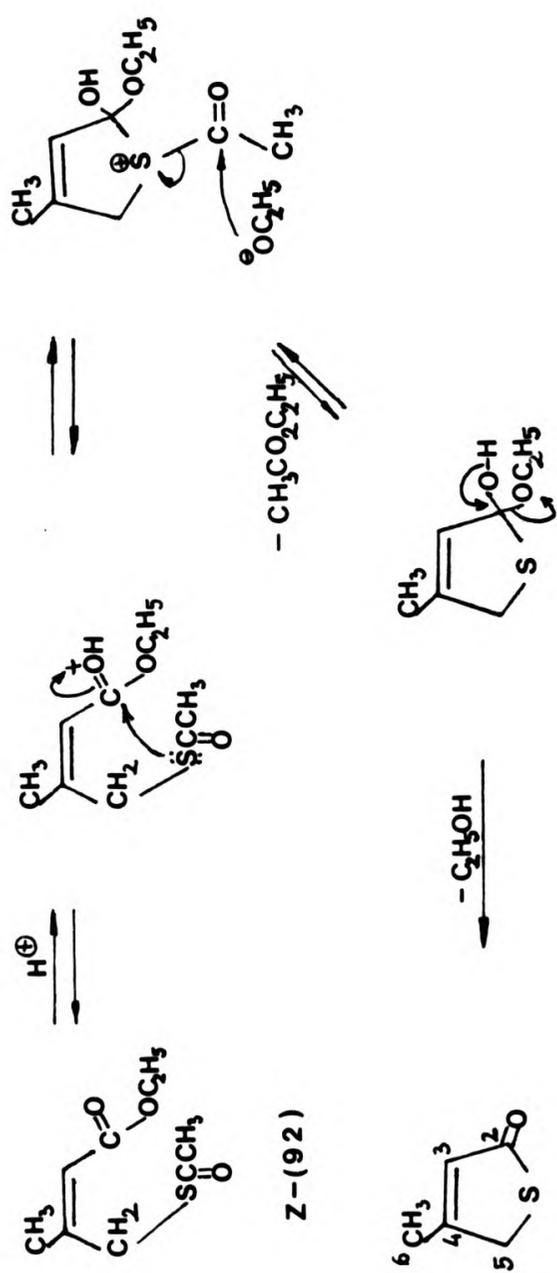
Two 10% solutions of compound (92) were prepared, one in deuterated chloroform and another in deuterated DMSO. The solutions were placed in n.m.r. tubes with a catalytic amount

of *p*-toluene sulphonic acid and the progress of the reactions was followed with ^1H n.m.r. spectroscopy. No changes were observed when the tubes were kept at room temperature. However, on raising the temperature to 60°C the peaks due to γ -thiolactone (64) appeared in the ^1H n.m.r. spectrum for the reaction carried out in CDCl_3 . The new peaks for compound (64) were found at δ 6.09 and δ 3.98. The peaks at δ 5.73, δ 4.15 and δ 2.02, which were due to the *Z*-isomer (92) had considerably diminished. From the ^1H n.m.r. integrals it was found that 68% of *Z*-isomer (92) was converted into γ -thiolactone (64) after 48 hours of heating the mixture to 60°C . The *E*-isomer (92) did not undergo any changes under the reaction conditions.

The ^1H n.m.r. spectra of the reaction carried out in DMSO showed no changes even on heating to 60°C for several days. This may suggest that the cyclization of compound (92) to γ -thiolactone (64) does not take place in highly polar solvents such as DMSO.

Ethyl-4-acetylthio-3-methylbut-2-enoate (92) was also successfully cyclized to γ -thiolactone (64) by heating it in methanol in the presence of HCl. (Scheme 23).

γ -Thiolactone (64) was purified by distillation; it was obtained 95% pure with an average yield of 12%. The low



Scheme 23

yields of the product (64) were due to the large losses of this compound in the lower boiling fraction, where it was found as an approximate 1:1 mixture with some side product, and to the fact that only the Z-isomer (92) could be cyclized to give γ -thiolactone (64). An attempt to separate product (64) from other components of the lower boiling fraction by means of high performance liquid chromatography (H.P.L.C.) was unsuccessful.

γ -Thiolactone (64) was analysed and its structure confirmed by means of ^1H , ^{13}C n.m.r. and i.r. spectroscopic methods, (spectra 5-8).

The i.r. spectrum shows a strong absorption band at 1680 cm^{-1} due to the C=O str. vibrations; a band at 1640 cm^{-1} is assigned to C=C str. vibrations and an absorption band at 840 cm^{-1} belongs to the =C-H deformational vibrations and C-H str. absorption bands are found at 2960 cm^{-1} and 3000 cm^{-1} .

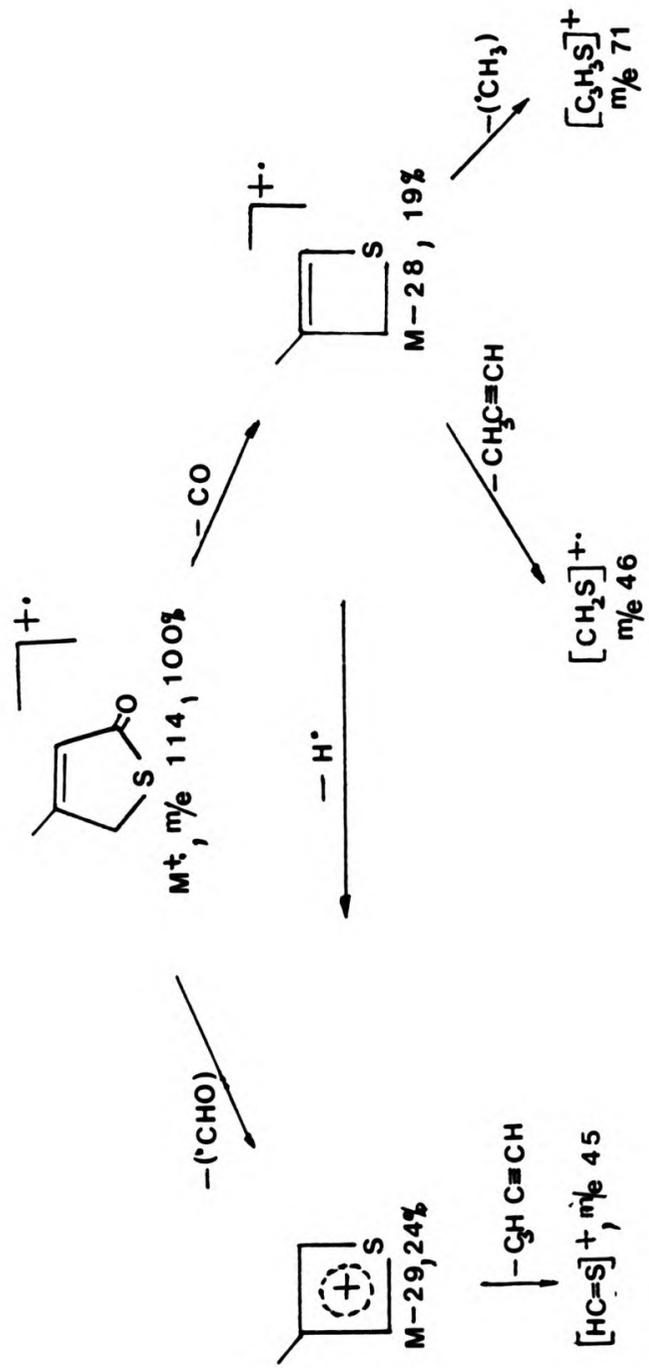
The 60 MHz and 220 MHz ^1H n.m.r. spectra were recorded for γ -thiolactone (11) and showed three peaks at δ 2.22, δ 4.01 and δ 6.15.^{78 79} The peaks were broadened due to the long range coupling between the γ -thiolactone protons. From the expanded spectrum, which showed three well resolved multiplets, the following values for coupling constants were found: $^4J(\text{CH}-\text{CH}_3) \approx ^4J(\text{CH}-\text{CH}_2) = 1.4\text{ Hz}$ and $^4J(\text{CH}_2-\text{CH}_3) = 0.7\text{ Hz}$. The ^{13}C n.m.r. broad band decoupled and s.f.o.r.d.

spectra allowed assignment of chemical shifts for γ -thiolactone (64) carbons. Thus the peaks at δ 18.9 and δ 41.0 were assigned to the methyl and methylene group carbons. A peak at δ 128.2 was assigned to the =CH carbon and it showed as a doublet in the s.f.o.r.d. spectrum. The peaks downfield from TMS at δ 168.1 and δ 199.8 belong to the quarternary and carbonyl carbons respectively and they remained as single peaks in the s.f.o.r.d. spectrum.

The fragmentation pattern observed in the mass spectrum of compound (64) (Scheme 24) follows that observed for thiolactones.⁹⁶ Thus, a molecular ion (M^+) occurs at m/e 114, it is a base peak of the spectrum; The fragmentation pattern suggests that the molecular ion undergoes fragmentation either with the loss of a CO fragment to give rise to a radical ion m/e 86 or with the loss of a CHO radical to give rise to the ion m/e 85.

7. The reactions leading to improvement of γ -thiolactone (64) yields

Because the separation of γ -thiolactone (64) from the other products of the reaction was difficult and resulted in low yields of this compound, efforts were made to improve the yield of γ -thiolactone (64) and the following experiments were carried out.



Scheme 24

A. The starting material consisting of a mixture of ethyl-(E and Z)-4-acetylthio-3-methylbut-2-enoate (92) was refluxed for 1 week in methanol in the presence of HCl. The progress of the reaction was followed with ^1H n.m.r. spectroscopy, (Table 92/1).

The ^1H n.m.r. spectra showed that isomerization of E-isomer (92) to Z-isomer (92) did not take place but Z-isomer (92) cyclized to γ -thiolactone (64) and E-isomer (92) was converted into γ -mercapto ester (95).

From the ^1H n.m.r. integral it was found that the starting reaction mixture contained 45% of Z-isomer (92) and 55% of E-isomer (92); the crude reaction product contained γ -thiolactone (84) (40%), methyl-E-4-mercapto-3-methylbut-2-enoate (95) (55%) and some other products.

Table 92/1

| Time | Relative amounts of thiolactone in reaction mixture calculated from ^1H n.m.r. integrals |
|----------|---|
| 0 | 0 |
| 1 hour | 25% |
| 3 hours | 30% |
| 6 hours | 33% |
| 24 hours | 40% |
| 7 days | 40% |

B. In the next experiment methyl-E-4-mercapto-3-methylbut-2-enoate (95), a side product in the γ -thiolactone (64) synthesis, was successfully converted to γ -thiolactone (64) in a photochemical reaction.⁹³ The reaction progress was followed with ^1H n.m.r. spectroscopy and the amounts of γ -thiolactone (64) formed in the course of the reaction were calculated from the ^1H n.m.r. integrals, (Table 92/2).

The ^1H n.m.r. spectrum showed that the reaction did not take place at room temperature, however, on heating the reaction mixture to the reflux point of methanol and irradiating (wavelength of the light: 340 nm) for 8 hours, γ -thiolactone was formed with a good yield of 54%. Further isomerization of E-isomer of γ -mercapto ester (95) could not however, be achieved as γ -thiolactone (64) began to decompose on prolonged heating under the reaction conditions.

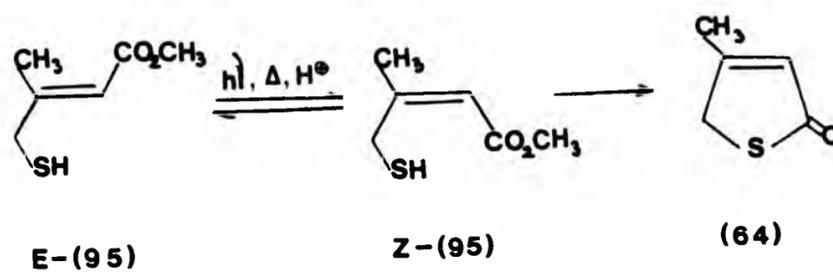


Table 92/2

| Time | Temperature | γ - thiolactone (11) content |
|----------|------------------|-------------------------------------|
| 0 | room temperature | --- |
| 3 hours | room temperature | 0 |
| 5 hours | reflux | 31 |
| 8 hours | reflux | 54 |
| 10 hours | reflux | 42 |

Re-cycling of E-mercapto ester (95) and subsequent conversion into γ -thiolactone (64) may therefore considerably improve overall yield of the latter compound.

C. Isolation of γ -thiolactone (64) by extraction.

γ -Thiolactone (64) was separated from other products of the reaction, e.g. mercapto ester (95) by extraction of ethereal solution of a mixture of reaction products with water or 5% aq. sodium hydroxide; γ -thiolactone was found in the aqueous layer and was finally obtained with 95% purity.

As the solubility of γ -thiolactone (64) in water is higher than that of other side products, e.g. compound (95), the extraction technique can provide a method for separation and purification of γ -thiolactone (64) and can give higher overall yield of this compound.

8. Isolation and identification of reaction product accompanying γ -thiolactone (64)

Methyl-E-4-mercapto-3-methylbut-2-enoate (95) can be isolated from the reaction mixture by distillation, b.p. 96°C - 99°C /0.6 mm Hg, or extraction; the structure of this compound was confirmed as follows:

The compound (95) was reacted with acetic anhydride in the presence of HClO_4 as a catalyst and the reaction product was identified by means of ^1H n.m.r. spectroscopy to be methyl-E-4-acetylthio-3-methylbut-2-enoate (92). Also, compound (95) was cyclized to γ -thiolactone (64) in the photochemical reaction.

Analysis of the ^1H n.m.r. spectrum of product (95) led to the following spectral assignments:

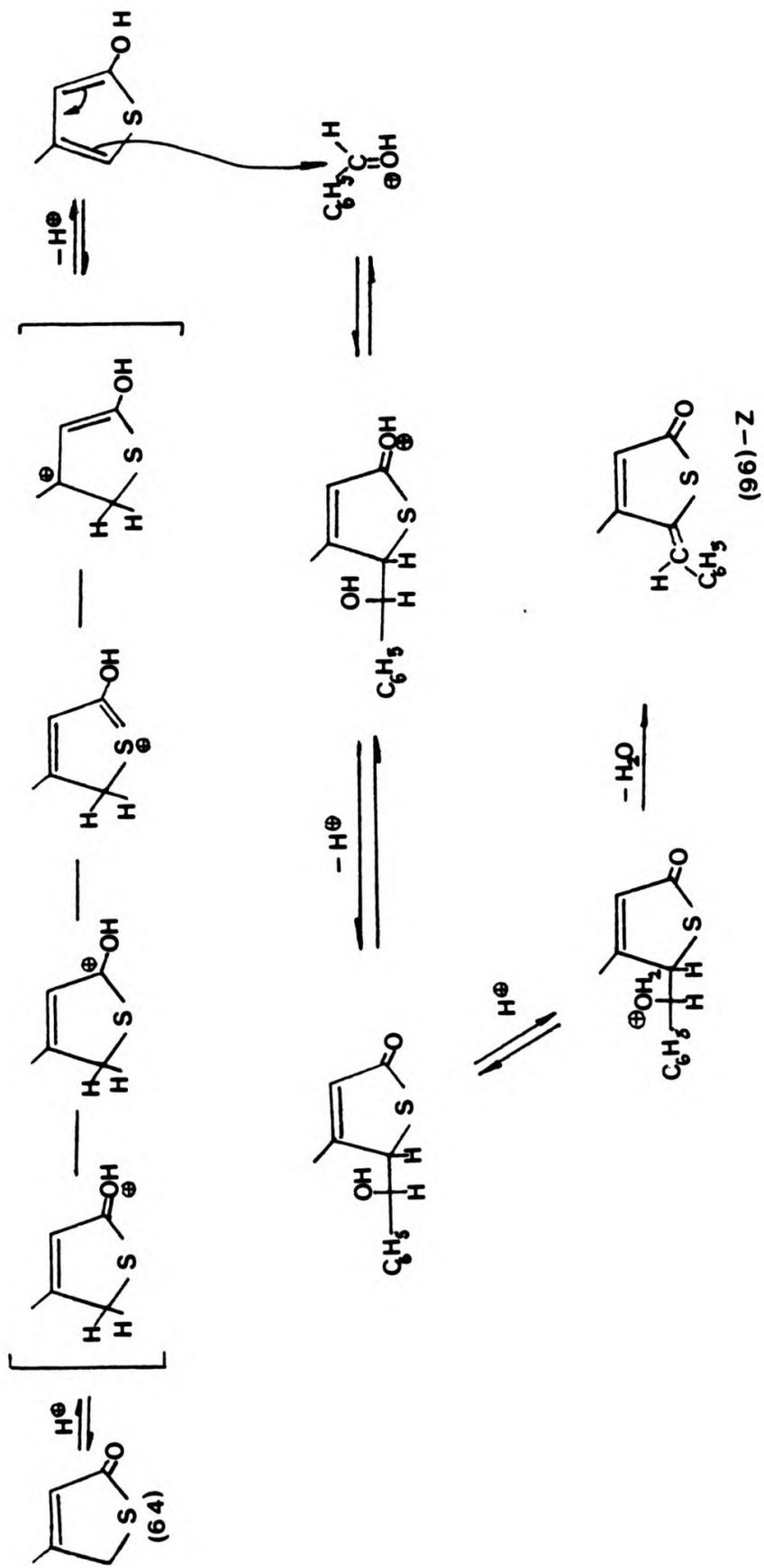
| Solvent: CDCl_3 ; internal standard T.M.S.; 80 MHz | | | | |
|---|-------------------|------------------|-------|-------------|
| proton assignment | type | δ /p.p.m. | J/Hz | Integration |
| 5 | -SH | 1.52 | (H2- | 1 |
| 6 | -CH ₃ | 2.22 | H6) = | 3 |
| 4 | -CH ₂ | 3.18 | 1.3Hz | 2 |
| 7 | -OCH ₂ | 3.70 | | 3 |
| 2 | = CH | 5.84 | | 1 |

On shaking a solution of compound (95) in CDCl_3 with D_2O , H-D exchange on S-H group took place and as the result of it a doublet at δ 3.18, due to the coupling between the methylene protons and SH proton, collapsed into a single peak and the triplet due to SH proton disappeared, (Spectra, 10, 11).

9. The reaction of γ -thiolactone (64) with benzaldehyde

4-Mercapto-3-methylbut-2-enoic acid γ -thiolactone (64) was reacted with benzaldehyde in the presence of hydrogen chloride to give 5-benzylidene-4-methyl-3-thiolen-2-one (96),⁷⁸ (Scheme 25). Under the reaction conditions product (96) crystallized out in form of yellow needles (m.p. 61.5°C - 63°C , methanol, yield 57%); analytical data for this compound were consistent with the proposed structure.

The condensation reaction of γ -thiolactone (64) with benzaldehyde was repeated and the progress of the reaction was followed with U.V. spectroscopy. A U.V. spectrum recorded for the reaction mixture after 1 hour showed a small absorption band at λ_{max} 341 nm, the intensity of which increased as reaction progressed; the U.V. spectrum of the final product (96) recorded in MeOH shows two absorption bands with the maxima at λ_{max} 341 nm and λ_{max} 238 nm ($\epsilon_1 = 3.2 \times 10^4$, $\epsilon_2 = 6.6 \times 10^2$).



Scheme 25

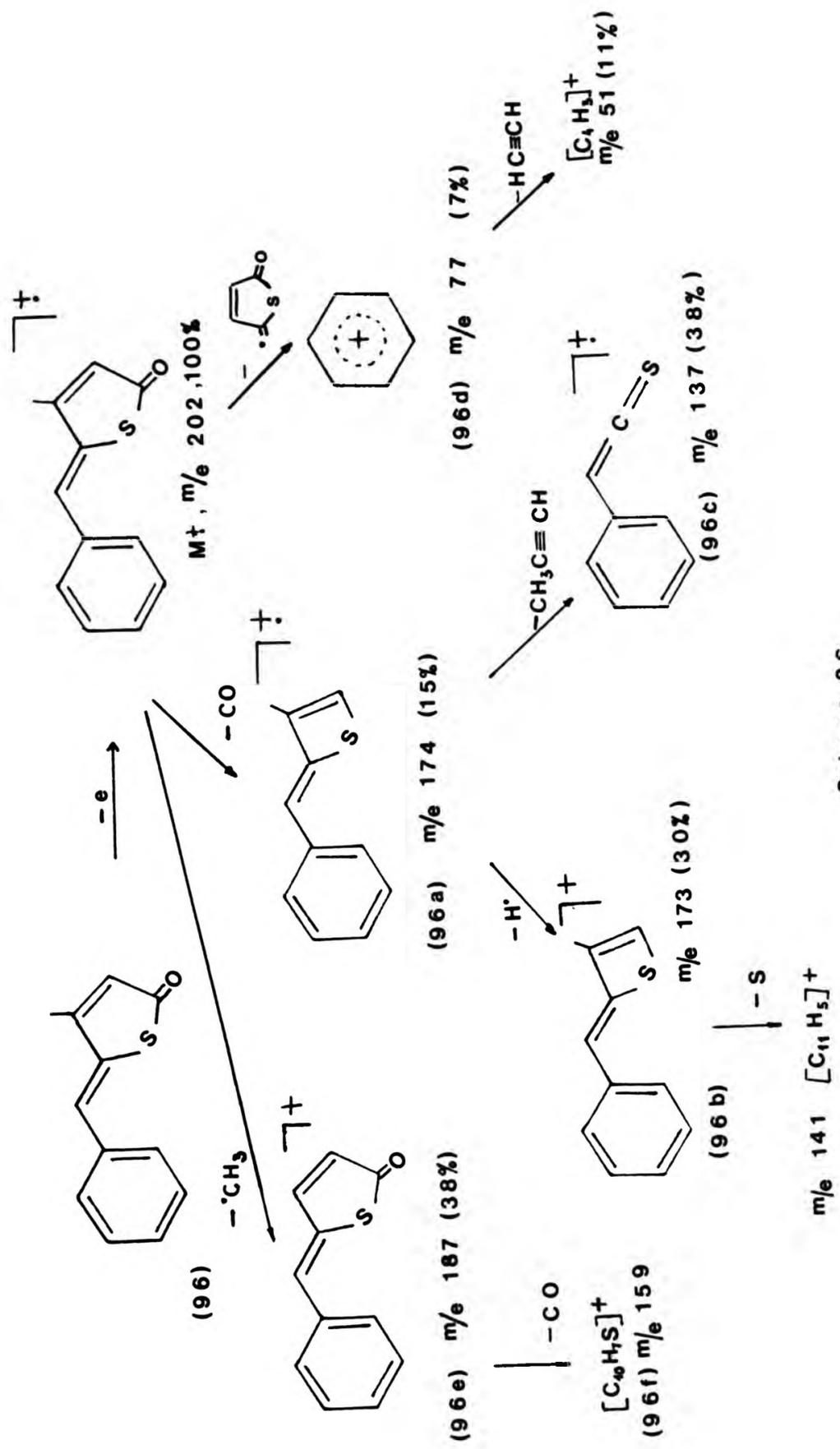
In the mass spectrum of compound (96) a molecular ion occurs at m/e 202; it is also the most abundant ion (corresponding to the base peak). The main fragmentation mode on electron impact is similar to that observed for thiolactones. ⁹⁶

Thus, the cleavage of the bonds α to the carbonyl leads to the loss of CO and the resulting ion, M-28 (96a) (Scheme 26), decomposes further either by the loss of $\text{H}_3\text{CC}=\text{CH}$ (probably to (96c) (m/e 137)) or by the loss of proton radical probably to the cation (96b) (m/e 173). The extrusion of sulphur from the latter cation (96b) corresponds to an ion at m/e 141. The loss of sulphur directly from the molecular ion, M-32, is not observed.

A weak ion at m/e 77 is probably due to the phenyl cation formed as the result of the rupture of the bond α to the benzene ring.

Another fragmentation mode occurs probably with the loss of methyl radical from molecular ion, M-15 (presumably to ion 96e) as suggested by the presence of a peak at m/e 187.

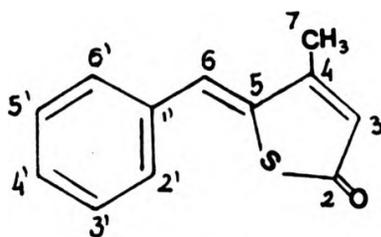
The further investigation of the structure of compound (96) was carried out by means of ^1H and ^{13}C n.m.r. spectroscopy.



Scheme 26

10. Structure determination of 5-benzylidene-4-methyl-3-thiolene-2-one (96) by means of ^1H and ^{13}C n.m.r. spectroscopy

The ^1H n.m.r. parameters are listed in table 96/H (Spectra 12, 13).



(96)

Table I 96/H

| 80MHz; Solvent: CDCl_3 ; Internal standard T.M.S. | | | | |
|--|-------------------------|------------------|--------|-------------|
| proton assignment | type | δ /p.p.m. | J/Hz | Integration |
| H(7) | CH_3 | 2.28 | H(7) | 3 |
| H3 | = C-H | 6.11 | - H(3) | 1 |
| H6 | = C-H | 7.07 | = 1.2 | 1 |
| H(2')-H(6') | $-\text{C}_6\text{H}_5$ | 7.40 | | 5 |

Irradiation of the peak at δ 2.28 caused the multiplet at δ 6.11 to collapse into a single peak. The methyl protons might be expected to couple to the alkene protons H(3) and H(6) with J [H(7) - H(3)] being larger coupling constant. Thus on the basis of the double resonance experiment the peak at δ 6.11 is assigned to H(3). The peak at δ 6.11 shows further splitting presumably due to coupling between H(3) and H(6).

Broad band proton decoupled, s.f.o.r.d. and proton-coupled ^{13}C n.m.r. spectra allowed assignment of chemical shifts for carbons in compound (96). The ^{13}C n.m.r. parameters are listed in table 96/C. (Spectra 14 - 16).

The peaks found at δ 14.9 and δ 194.3 in the ^{13}C n.m.r. spectrum were easily assigned to methyl group carbon and to carbonyl carbon respectively. The proton coupled ^{13}C n.m.r. spectrum shows the quartet of doublets at δ 14.9 for the CH_3 carbon. This multiplet arises as from coupling between C(7) - H(7) and between C(7) and -H(3). The signal from carbonyl carbon, C(2) appears at δ 194.3 as a doublet due to coupling with H(3).

The peak at δ 161.0 is assigned to C(4) as in the ^{13}C n.m.r. spectrum of 4-methyl-3-thiolen-2-one (64), a starting material, the chemical shift for this carbon is δ 168.3.

Table 96/C

| solvent CDCl ₃ , internal standard T.M.S., 20MHz | | | |
|---|-----------------|------------------|--|
| Carbon Assignment | Type | δ /p.p.m. | J_{C-H} /Hz |
| C(7) | CH ₃ | 14.9 | (C(7)-H(7)) = 128.6 (C(7)-H(3)) = 3.4 |
| C(3) | =C-H | 127.7 | (C(3)-H(3)) = 173.2 (C(3)-H(7)) = 5.1 |
| C(2'),C(6') | =C-H-ortho | 129.0 | |
| C(4') | =C-H-para | 129.4 | |
| C(6) | =C-H | 129.7 | |
| C(3'),C(5') | =C-H-meta | 130.1 | |
| C(1') | =C< | 135.0 | |
| C(5) | =C< | 136.5 | |
| C(4) | =C< | 161.0 | |
| C(2) | C=O | 194.3 | (C(2)-H(3)) = 6.7 |

Coupling constants C-H and chemical shift values for carbons in compound (96).

This same carbon gives rise to a multiplet in the proton-coupled ^{13}C n.m.r. spectrum presumably due to the coupling of this carbon with H(7) and H(3).

In the aromatic region of the spectrum, two high intensity peaks at δ 130.1 and δ 129.0 are assigned to the ortho- and meta-carbons of the benzene ring. As an olefinic substituent in monosubstituted benzene shifts the ortho-carbons upfield by 2.0 p.p.m. and meta-carbons upfield by 0.2 p.p.m. from δ 128.5 p.p.m. (shift for unsubstituted benzene),⁹⁷ the peak at δ 130.1 was assigned to meta-carbon and the peak at δ 129.0 to ortho-.

A peak at δ 127.7 is due to carbon C-3; in the spectrum of γ -thiolactone (64), a starting material, the chemical shift for this carbon is δ 128.2. In the proton-coupled ^{13}C n.m.r. spectrum this peak shows as a doublet of quartets. The peak arises as a result of coupling of carbon C(3) with H(3) and H(7).

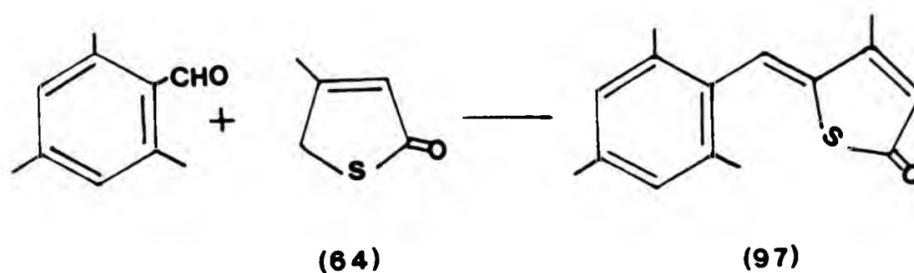
The peak at δ 129.4 was assigned to para carbon C-4'. This peak shows as a doublet in s.f.o.r.d. ^{13}C n.m.r. spectrum.

In the proton-coupled ^{13}C n.m.r. spectrum a multiplet at δ 136.5 is assigned to C(5). The peak arises as a result of coupling between C(5) and the remote hydrogens H(7) and H(6).

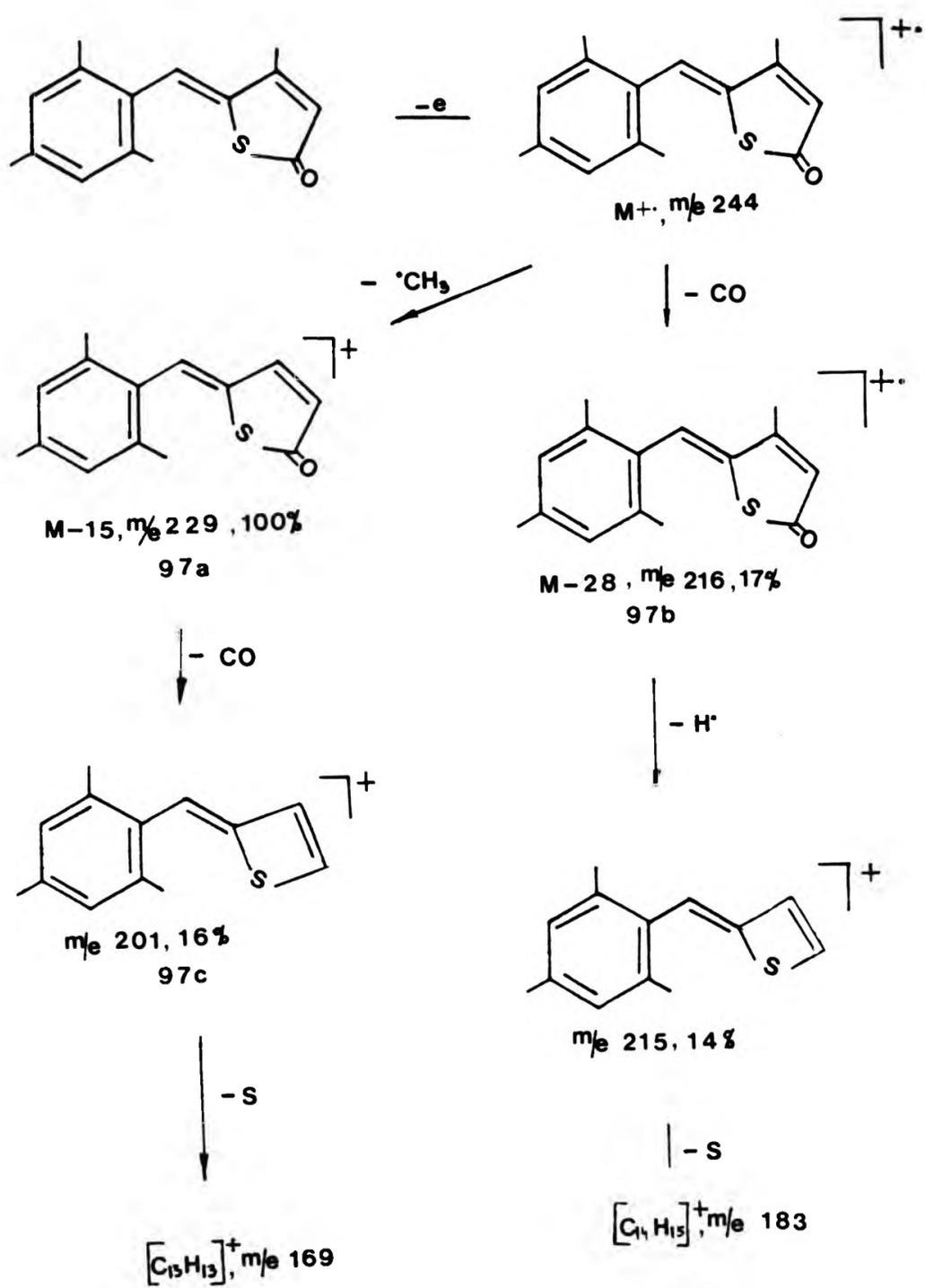
A peak at δ 135.0 is assigned to a quaternary carbon C(1^N); this peak appears as a singlet in both broad band decoupled and s.f.o.r.d. ¹³C spectra.

11. The reaction of γ -thiolactone (64) with mesitaldehyde

Since the stereochemistry of the double bond system of the compound (96) was shown (X-ray crystallography pp 85-94) to be the same as that of ABA, the reaction of the thiolactone (64) with a sterically hindered aldehyde was next investigated. Thus γ -thiolactone (64) was reacted with mesitaldehyde in the presence of hydrogen chloride to give product (97) (yield 28%, m.p. 107.2^o-109.1^oC). The reaction was carried out under the same conditions which were employed for the condensation of γ -thiolactone (64) with benzaldehyde.



In the mass spectrum product (97) exhibits a fragmentation pattern similar to that observed for its analogue (96). Thus, an abundant molecular ion (M^{+}) at m/e 244 appears to undergo fragmentation by two different pathways. One frag-



Scheme 27

mentation mode gives rise to a fragment ion at m/e 229, which is the base peak of the spectrum. The ion m/e 229 decomposes further by the loss of CO (probably to 97c, m/e 201). Alternatively the rupture of bonds α to carbonyl in the molecular ion gives fragment ion M-28 (m/e 216, probably species 97b) which appears to decompose further by loss of the proton radical followed by the loss of sulphur to give the m/e 183 ion. The latter fragmentation mode is characteristic for thiolactones. ⁹⁶ The loss of sulphur directly from the molecular ion is not observed.

12. Structure determination of 5-mesitylidene-4-methyl-3-thiolene-2-one (97) by means of ¹H and ¹³C n.m.r. spectroscopy.

The structure of the compound (97) was further investigated by means of ¹³C and ¹H n.m.r. spectroscopy, (Spectra 18-20). ¹H n.m.r. parameters are listed in table 97/H.

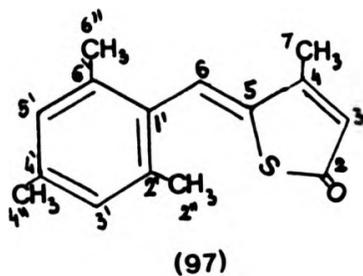


Table 97/H

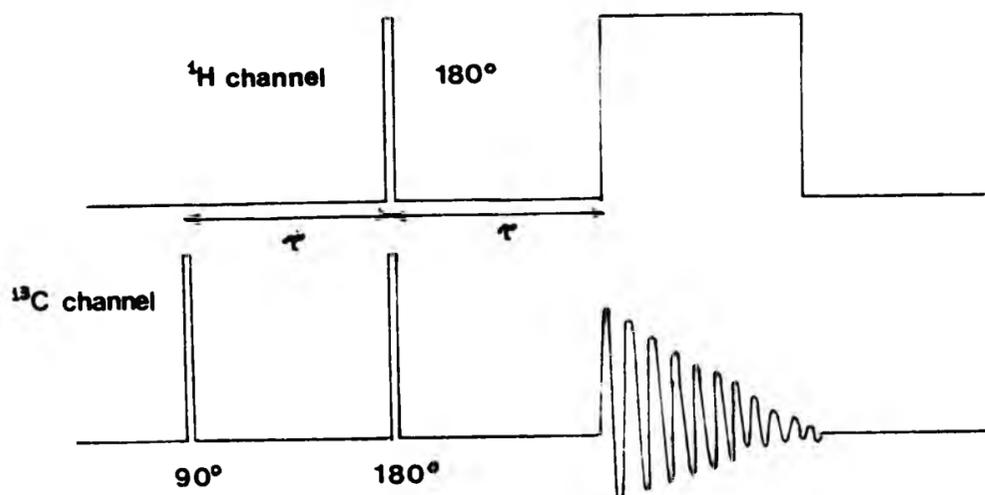
| solvent CDCl_3 ; Internal standard T.M.S., 80MHz | | | | |
|---|---------------|------------------|------------------------|-------------|
| Proton Assignment | Type | δ /p.p.m. | J/HZ | Integration |
| H(2'') H(6'') | CH_3 | 2.18 | | 6 |
| H(4'') | CH_3 | 2.28 | ${}^4J_{\text{H}(7)-}$ | 3 |
| H(7) | CH_3 | 2.38 | H(3) | 3 |
| H(3) | =CH- | 6.14 | =0.7 | 1 |
| H(5') H(3') | =CH- | 6.88 | | 2 |
| H(6) | =CH- | 7.18 | | 1 |

In a double resonance experiment a peak at δ 7.18 was irradiated but no change in the alkane region of the spectrum was observed. However, irradiation of the peak at δ 6.14 caused the doublet at δ 2.38 to collapse into a single peak. Therefore on the basis of the double resonance experiment the peak at δ 2.38 was assigned to methyl group protons H(7) and the peak at δ 6.14 to proton H(3). The peak at δ 6.14 shows further splitting probably due to coupling between H(3) and H(6).

The broad band proton decoupled and s.f.o.r.d. ${}^{13}\text{C}$ n.m.r. spectra as well as the Attached Proton Test (A.P.T.)⁹⁸ experiment allowed assignment of chemical shifts for carbons in

compound (97). The ^{13}C n.m.r. parameters are listed in the table 97/C.

The A.P.T. experiment involves a pulse sequence, which allows for the differentiation of the CH_3 and CH carbons on the one hand and the CH_2 and quaternary carbons on the other hand. The pulse sequence employed in A.P.T. is represented below.



The pulse sequence for an attached proton test in a heteronuclear system.

The time, τ , a waiting time, is closely correlated with a coupling constant. In the A.P.T. experiment carried out on the sample, τ was made equal to $\tau = \frac{1}{2} [J_{C-H}]^{-1}$ where J is the average value for the coupling in $\equiv CH$, $=CH$ and $-CH$ systems. The free induction decay (F.I.D.) for carbon nuclei is recorded and Fourier transformed after time 2τ and the spectrum obtained shows positive peaks for CH_3 and CH carbons and negative peaks for CH_2 and quaternary carbons. Thus, the carbons C-2, C-4, C-5, C-1', C-2', C-4' and C-6' give negative peaks while the carbons C-7, C-6, C-3, C-3' and C-5' give positive peaks. In the ^{13}C broad band decoupled spectrum a high intensity peak at δ 20.2 was easily assigned to the carbons of the ortho-methyl groups (C-2'' and C-6'') and a lower intensity peak at δ 21.0 to para-methyl group carbon (C-4''). A signal at δ 14.5 was assigned to carbon C-7; in the spectrum of γ -thiolactone (64) the starting material, the chemical shift for that carbon is δ 16.2.

Four olefinic carbons ($=CH$; meta-C-3', meta-C-5', C-3 and C-6) are easily found as they give positive peaks in the A.P.T. spectrum. Thus, a high intensity peak at δ 128.4 is assigned to two magnetically equivalent meta-carbons (C-3' and C-5'). The peak at δ 128.9 is assigned to carbon C-3, as in γ -thiolactone (64) spectrum carbon C-3 gives a peak at δ 129.2, therefore, the signal at δ 129.9 belongs to carbon C-6.

Table 97/C

| Solvent CDCl_3 , internal standard T.M.S., 20MHz | | |
|---|--------------------|------------------|
| Carbon Assignment | Type | δ /p.p.m. |
| C-7 | CH_3 | 14.5 |
| C-2'', C-6'' | CH_3 | 20.2 |
| C-4'' | CH_3 | 21.0 |
| C-3', C-5' | meta=C-H | 128.4 |
| C-3 | =CH- | 128.9 |
| C-6 | =CH- | 129.9 |
| C-1' | =C< | 131.9 |
| C-2', C-6' | ortho | 135.5 |
| C-5 | =C< _S - | 137.9 |
| C-4' | para | 141.9 |
| C-4 | =C< | 158.6 |
| C-2 | >C=O | 194.1 |

Chemical shift values for carbons in compound (97).

The chemical shifts for the carbonyl and quaternary carbons were then found; all these carbons give negative peaks in the A.P.T. spectrum. Thus, the carbonyl carbon (C-2) signal is found downfield at δ 194.2. A single peak at δ 158.6 is assigned to a quaternary carbon C-4, which in the spectrum of an analogue (96) shows at δ 161.0. The substituted quaternary ortho-carbons, C-2' and C-6', show an intense single peak at δ 135.5. The signal at δ 137.9 belongs to carbon C-5. In order to make further assignments for the peaks at δ 131.9 and δ 141.9 the theoretical δ values for C-1' and C-4' (para-carbon) were found. The calculated chemical shifts⁹⁷ were as follows: δ (C-1') = 134.4 and δ (C-4') = 138.4. Therefore the peak at δ 131.9 was assigned to C-1' and at δ 141.9 to C-4'.

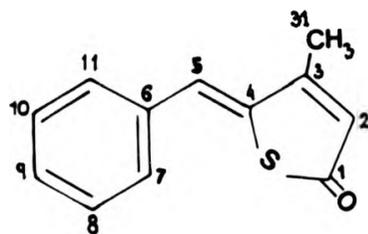
Thus, γ -thiolactone was reacted with benzaldehyde and mesitaldehyde to give ABA analogues (96) and (97) respectively and the stereochemistry of these compounds was further shown to be the same as that of ABA. For this reason compound (96) was tested for its biological activity; it caused an increase of the internodal distances when applied to growing tomato plants, but was not active in other tests.

13. X-ray Crystallography

The structures of compounds (96) and (97) were investigated by means of X-ray crystallography in order to determine the stereochemistry at the new double bond formed in the condensation of γ -thiolactone (64) with benzaldehyde and mesitaldehyde respectively. As was mentioned previously, it was important that the new double bond had the Z-configuration.

13.1 Structure determination of 5-benzylidene-4-methyl-3-thiolene-2-one (96) by means of X-ray crystallography

The compound (96) crystallised from methanol as yellow large crystals. The crystals were broken into smaller fragments and a fragment selected for the X-ray crystallography, having dimensions c.a. 0.15 x 0.12 x 0.2 mm, was mounted on a quartz fibre on a Philips PW1100 goniometerhead.



b) Determination of the structure

The data were collected on a PW1100 four circle diffractometer,

using MoK α radiation ($\lambda = 0.7069\text{\AA}$) from a graphite monochromator and a $\theta - 2\theta$ scan mode. No absorption corrections were applied.

The unit cell was found by using an automatic peak-hunt routine from 25 low angle diffraction points. Refined cell dimensions were derived from the angular measurements of 25 strong high angle reflections. Cell data and the parameters used in data collection are shown in table A.

The variance of the intensity (I) was calculated as $\{ |\sigma_c(I)|^2 + (0.04I)^2 \}^{1/2}$ where $|\sigma_c(I)|$ is variance due to counting statistics and the terms in I^2 was introduced to allow for other sources of error. ⁹⁹ I and $\sigma(I)$ were corrected for Lorentz and polarization factors with use of a program written for the PW1100 diffractometer and equivalent reflections were averaged giving a total of 848 data with $I / \sigma(I) < 3.0$.

First attempts to solve the structure by the automatic centrosymmetric direct methods using the SHELX 76 program ¹⁰⁰ and using normalised E values $E > 1.2$ by the multisolution Σ_2 sign expansion pathway failed. Examination of the E-maps produced from this run showed patterns of fused rings which were chemically not reasonable. The E values of the reflections chosen by the program for origin and multisolution determination were of the order of 3.5, which indicated a possible overconsistent solution. Subsequently a convergence

map was printed to allow hand selection of suitable origin and multiresolution reflections. These values were used with the tangent multiresolution refinement method with $E > 1.1$, again without a success. A run with $E > 1.3$ also failed to yield a recognizable solution. The structure was solved by taking the same hand selected origin and multiresolution values as used in the tangent refinement and using Σ_2 centrosymmetric method with $E > 1.1$. The E map calculated from a solution with the highest figure of merit showed the location of all non-hydrogen atoms in the molecule (the highest 14 peaks). The structure was refined first in 3 cycles using isotropic thermal parameters for 14 non-hydrogen atoms by full-matrix least squares to give $R = 0.16$. 6 cycles of anisotropic refinement for all the non-hydrogen atoms gave $R = 0.08$.

A difference map calculated at this stage gave reasonable positions for all but two of the hydrogen atoms. The methyl group was not as well defined as only one hydrogen atom was readily found. In final cycles of refinement the found hydrogen atoms were included in the calculation of structure factors at the map positions but not refined, and the second and third methyl hydrogen were calculated assuming $C-H = 1.08 \text{ \AA}$ and angle $H-C-H = 109^\circ$. The final $R = 0.073$ with $w = 1/\sigma^2 F$ and $R_w = 0.070$. The final difference map showed a maximum of 0.6 e/\AA^3 at 1.18 \AA from S atom. The scattering factors were those of Cromer and Mann¹⁰¹ and correction for the real and imaginary parts of the anomalous

dispersion were applied.

Discussion

The final atomic co-ordinates are given in Tables 1-96 and 2-96, bond lengths and angles in Tables 4-96 and 5-96, thermal parameters, table 3-96, intermolecular contact distances and important non-bonded intramolecular contacts tables 6-96 and 7-96 respectively.

The perspective view of the molecule and its planarity are shown in Figures 1 and 2 respectively. In spite of the steric interactions the molecule was found to be planar giving the maximum overlap of the π orbitals. The X-ray crystallography gave the answer to the problem of the geometrical isomerism by proving that the new double bond formed in the reaction has Z-configuration. Also interatomic distances between the ortho-H on the benzene ring and sulphur atom suggests the existence of the hydrogen bond making the molecule even more rigid. Finally, the bond angle C-1-S-C-4 has been confirmed to be near 90° . 75

Table A

| | |
|---|--|
| Formula | $C_{12}H_{10}OS$ |
| Molecular mass | 202 |
| Cell dimensions | |
| a | 10.618 |
| b \AA | 7.595 |
| c | 7.026 |
| α | 110.24 |
| β ($^{\circ}$) | 82.99 |
| γ | 104.25 |
| V \AA^3 | 514.85 |
| Z | 2 |
| Space system | triclinic |
| Space group | $\underline{p} 1$ |
| F(000) | 212 |
| μ (MoK α) | 2.30 cm^{-1} |
| $D_c \text{ g cm}^{-3}$ | $= \frac{M \times Z \times 1.66}{V} = 1.31$ |
| Data collection | |
| theta range ($^{\circ}$) | $3^{\circ} < \theta < 25^{\circ}$ |
| scan width | $/0.70 + 0.01 \tan \theta / ^{\circ}$ |
| scan mode/background mode | All possible reflections within the θ range were collected with background measuring time = $\frac{1}{2}$ scan time on each side of the reflection. |
| No. of unique data collected $\pm h \pm k \pm l$ | 848 |
| 3 standard reflections were measured every 3 hours and showed no significant decomposition. | |

TABLE 1-96 Fractional atomic coordinates and
thermal parameters (\AA^2) for $\text{C}_{12}\text{H}_{10}\text{OS}$ (96)

| Atom | x | y | z | U_{iso} or U_{eq} |
|-------|------------|------------|------------|-------------------------------------|
| S(1) | -0.0511(2) | 0.2071(2) | 0.1547(3) | 0.052(1) |
| O(1) | -0.2595(4) | -0.0811(7) | 0.0857(9) | 0.076(4) |
| C(1) | -0.2204(6) | 0.0941(10) | 0.1449(12) | 0.053(5) |
| C(2) | -0.2960(7) | 0.2399(10) | 0.2210(12) | 0.056(5) |
| C(3) | -0.2266(6) | 0.4234(9) | 0.2783(11) | 0.047(4) |
| C(4) | -0.0859(6) | 0.4394(8) | 0.2450(10) | 0.046(4) |
| C(5) | 0.0018(6) | 0.6079(9) | 0.2900(11) | 0.046(4) |
| C(6) | 0.1431(6) | 0.6530(9) | 0.2742(10) | 0.044(4) |
| C(7) | 0.2209(7) | 0.5191(11) | 0.2032(12) | 0.054(5) |
| C(8) | 0.3549(7) | 0.5738(11) | 0.1885(12) | 0.057(5) |
| C(9) | 0.4158(7) | 0.7677(12) | 0.2461(13) | 0.062(5) |
| C(10) | 0.3416(7) | 0.9024(12) | 0.3204(14) | 0.065(5) |
| C(11) | 0.2076(7) | 0.8483(10) | 0.3351(12) | 0.054(5) |
| C(31) | -0.2846(8) | 0.5979(12) | 0.3578(18) | 0.062(6) |

TABLE 2-96 Fractional atomic coordinates for the hydrogen atoms for C₁₂H₁₀OS (96)

| Atom | x | y | z |
|--------|---------|--------|--------|
| H(2) | -0.3888 | 0.2057 | 0.2551 |
| H(5) | -0.0343 | 0.7337 | 0.3511 |
| H(7) | 0.1816 | 0.3786 | 0.1670 |
| H(8) | 0.4077 | 0.4793 | 0.0976 |
| H(9) | 0.5106 | 0.8163 | 0.2181 |
| H(10) | 0.3861 | 1.0470 | 0.3551 |
| H(11) | 0.1594 | 0.9327 | 0.3796 |
| H(31a) | -0.3836 | 0.5479 | 0.4035 |
| H(31b) | -0.2470 | 0.6856 | 0.2583 |
| H(31c) | -0.2552 | 0.6733 | 0.4757 |

TABLE 3-96 Anisotropic thermal parameters (\AA^2) for $\text{C}_{12}\text{H}_{10}\text{OS}$ (96)

| Atom | U_{11} | U_{22} | U_{33} | U_{23} | U_{13} | U_{12} |
|-------|----------|----------|----------|-----------|-----------|-----------|
| S(1) | 0.050(1) | 0.039(1) | 0.068(1) | -0.003(1) | -0.011(1) | 0.011(1) |
| O(1) | 0.071(3) | 0.037(3) | 0.121(5) | 0.006(3) | -0.015(3) | -0.000(2) |
| C(1) | 0.054(4) | 0.043(4) | 0.061(5) | 0.006(4) | -0.007(4) | 0.004(4) |
| C(2) | 0.045(4) | 0.053(5) | 0.068(6) | 0.009(4) | -0.011(4) | 0.011(4) |
| C(3) | 0.047(4) | 0.043(4) | 0.052(5) | 0.000(4) | -0.016(4) | 0.011(3) |
| C(4) | 0.054(4) | 0.031(4) | 0.052(5) | 0.003(4) | -0.018(4) | 0.009(3) |
| C(5) | 0.050(4) | 0.038(4) | 0.050(5) | 0.004(4) | -0.011(4) | 0.010(4) |
| C(6) | 0.048(4) | 0.042(4) | 0.043(4) | -0.000(4) | -0.013(4) | 0.009(3) |
| C(7) | 0.053(4) | 0.048(4) | 0.060(5) | 0.004(4) | -0.021(4) | 0.004(4) |
| C(8) | 0.050(4) | 0.061(5) | 0.059(5) | 0.002(5) | -0.018(4) | 0.013(4) |
| C(9) | 0.041(4) | 0.072(6) | 0.073(6) | 0.009(5) | -0.021(4) | -0.001(4) |
| C(10) | 0.055(5) | 0.051(5) | 0.087(7) | 0.000(5) | -0.025(5) | -0.005(4) |
| C(11) | 0.056(5) | 0.042(4) | 0.066(5) | 0.000(4) | -0.018(4) | 0.006(4) |
| C(31) | 0.054(5) | 0.050(5) | 0.080(7) | -0.003(6) | -0.013(6) | 0.021(4) |

TABLE 4-96 Bond lengths (Å) for C₁₂H₁₀OS (96)

| | | | |
|--------------|-----------|-------------|-----------|
| S(1) -C(1) | 1.789(7) | S(1) -C(4) | 1.772(7) |
| O(1) -C(1) | 1.226(8) | C(1) -C(2) | 1.442(11) |
| C(2) -C(3) | 1.352(9) | C(3) -C(4) | 1.466(9) |
| C(3) -C(31) | 1.501(12) | C(4) -C(5) | 1.345(8) |
| C(5) -C(6) | 1.454(9) | C(6) -C(7) | 1.388(11) |
| C(6) -C(11) | 1.409(9) | C(7) -C(8) | 1.383(10) |
| C(8) -C(9) | 1.390(11) | C(9) -C(10) | 1.367(12) |
| C(10) -C(11) | 1.382(10) | | |

TABLE 5-96 Bond angles (°) for C₁₂H₁₀OS (96)

| | | | | | | | |
|-------|--------|-------|----------|-------|--------|-------|----------|
| C(4) | -S(1) | -C(1) | 91.8(3) | O(1) | -C(1) | -S(1) | 122.5(6) |
| C(2) | -C(1) | -S(1) | 109.2(5) | C(2) | -C(1) | -O(1) | 128.2(6) |
| C(3) | -C(2) | -C(1) | 115.5(6) | C(4) | -C(3) | -C(2) | 113.5(6) |
| C(31) | -C(3) | -C(2) | 124.7(7) | C(31) | -C(3) | -C(4) | 121.7(6) |
| C(3) | -C(4) | -S(1) | 109.8(4) | C(5) | -C(4) | -S(1) | 126.3(5) |
| C(5) | -C(4) | -C(3) | 123.8(6) | C(6) | -C(5) | -C(4) | 131.9(7) |
| C(7) | -C(6) | -C(5) | 125.4(6) | C(11) | -C(6) | -C(5) | 117.9(6) |
| C(11) | -C(6) | -C(7) | 116.7(6) | C(8) | -C(7) | -C(6) | 121.9(7) |
| C(9) | -C(8) | -C(7) | 120.2(7) | C(10) | -C(9) | -C(8) | 119.1(7) |
| C(11) | -C(10) | -C(9) | 120.9(7) | C(10) | -C(11) | -C(6) | 121.2(7) |

TABLE 6-96 Intermolecular distances (Å) for C₁₂H₁₀OS (96)

| | | | | | | |
|--------|---------|------|----|-----|-----|-----|
| S(1) | ...S(1) | 3.49 | -1 | 0.0 | 0.0 | 0.0 |
| O(1) | ...S(1) | 3.70 | -1 | 0.0 | 0.0 | 0.0 |
| C(5) | ...S(1) | 3.78 | -1 | 0.0 | 1.0 | 0.0 |
| C(6) | ...S(1) | 3.82 | -1 | 0.0 | 1.0 | 0.0 |
| H(9) | ...O(1) | 2.54 | 1 | 1.0 | 1.0 | 0.0 |
| H(31b) | ...O(1) | 2.50 | 1 | 0.0 | 1.0 | 0.0 |
| C(7) | ...O(1) | 3.34 | -1 | 0.0 | 0.0 | 0.0 |
| H(7) | ...O(1) | 2.59 | -1 | 0.0 | 0.0 | 0.0 |
| H(8) | ...O(1) | 2.96 | -1 | 0.0 | 0.0 | 0.0 |
| H(8) | ...C(8) | 3.04 | -1 | 1.0 | 1.0 | 0.0 |

TABLE 7-96 Intramolecular distances (Å) for C₁₂H₁₀OS (96)

| | | | |
|---------------|------|---------------|------|
| O(1) ...S(1) | 2.66 | C(2) ...S(1) | 2.64 |
| C(3) ...S(1) | 2.66 | C(5) ...S(1) | 2.79 |
| C(6) ...S(1) | 3.38 | C(7) ...S(1) | 3.22 |
| H(7) ...S(1) | 2.49 | C(2) ...O(1) | 2.40 |
| H(2) ...O(1) | 2.71 | C(3) ...C(1) | 2.36 |
| C(4) ...C(1) | 2.56 | H(2) ...C(1) | 2.11 |
| C(4) ...C(2) | 2.36 | C(31) ...C(2) | 2.53 |
| H(31a)...C(2) | 2.59 | C(5) ...C(3) | 2.48 |
| H(2) ...C(3) | 2.05 | H(5) ...C(3) | 2.65 |
| H(31a)...C(3) | 2.07 | H(31b)...C(3) | 2.11 |
| H(31c)...C(3) | 1.99 | C(6) ...C(4) | 2.56 |
| C(7) ...C(4) | 3.16 | C(31) ...C(4) | 2.59 |
| H(5) ...C(4) | 2.05 | H(7) ...C(4) | 2.94 |
| H(31b)...C(4) | 2.80 | H(31c)...C(4) | 2.81 |
| C(7) ...C(5) | 2.53 | C(11) ...C(5) | 2.45 |
| C(31) ...C(5) | 3.01 | H(7) ...C(5) | 2.76 |
| H(11) ...C(5) | 2.54 | H(31b)...C(5) | 2.89 |
| H(31c)...C(5) | 2.96 | C(8) ...C(6) | 2.42 |
| C(9) ...C(6) | 2.81 | C(10) ...C(6) | 2.43 |
| H(5) ...C(6) | 2.07 | H(7) ...C(6) | 2.08 |
| H(11) ...C(6) | 1.96 | C(9) ...C(7) | 2.40 |
| C(10) ...C(7) | 2.75 | C(11) ...C(7) | 2.38 |
| H(8) ...C(7) | 2.09 | C(10) ...C(8) | 2.38 |
| C(11) ...C(8) | 2.75 | H(7) ...C(8) | 2.04 |
| H(9) ...C(8) | 2.12 | C(11) ...C(9) | 2.39 |

table 7-96 continued

| | | | |
|---------------|------|----------------|------|
| H(8) ...C(9) | 2.06 | H(10) ...C(9) | 2.08 |
| H(9) ...C(10) | 2.03 | H(11) ...C(10) | 1.98 |
| H(5) ...C(11) | 2.50 | H(10) ...C(11) | 2.10 |
| H(2) ...C(31) | 2.78 | H(5) ...C(31) | 2.60 |

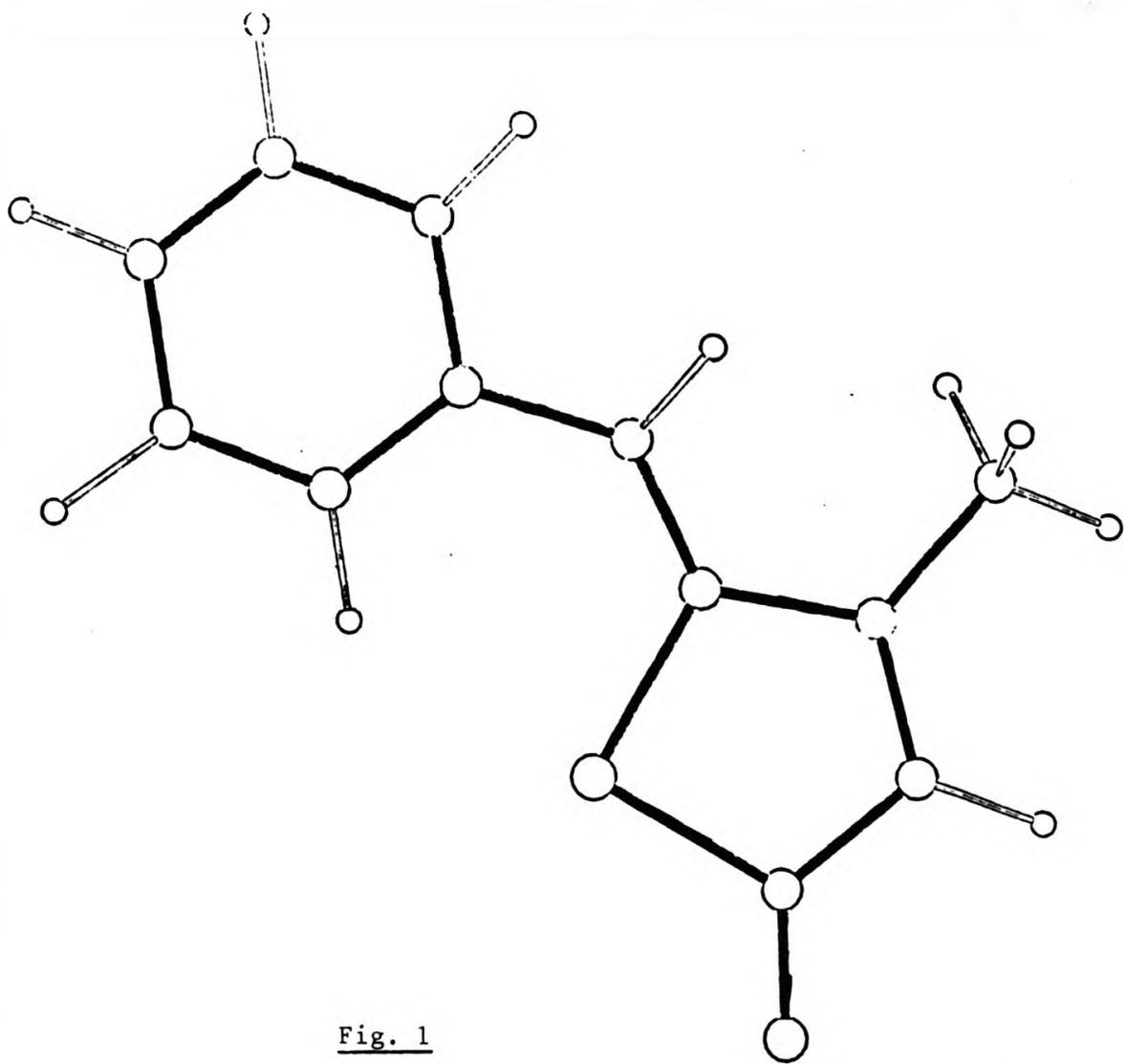


Fig. 1

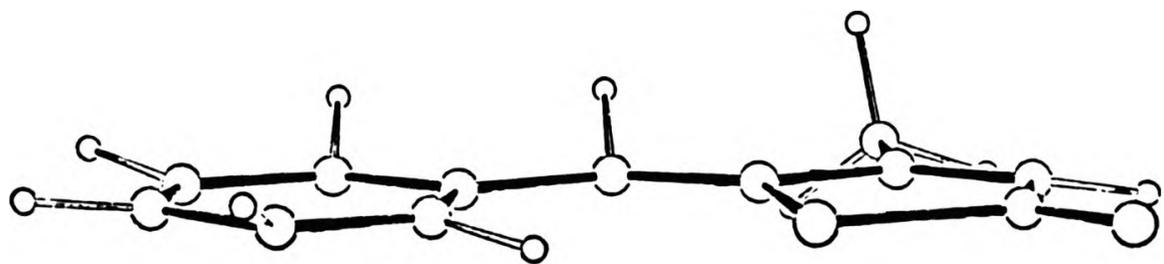


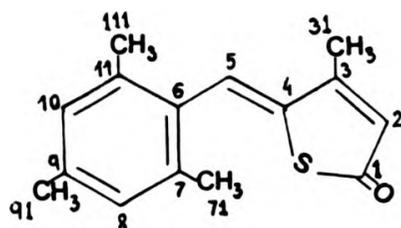
Fig. 2

Perspective view and the planarity of the molecule of
5-benzylidene-4-methyl-3-thiolene-2-one (96).

13.2 Structure determination of 5-mesitylidene-4-methyl-3-thiolene-2-one (97) by means of X-ray crystallography

a) Crystal preparation

The structure of (3Z)(5Z)-5-mesitylidene-4-methyl-3-thiolene-2-one (97) was investigated by means of X-ray crystallography. The compound (97) crystallised from methanol as pale yellow, irregular shaped crystals. The crystals were broken into smaller fragments for the preliminary measurements under a polarising microscope. A fragment of crystal selected for the X-ray study, having dimensions c.a. 0.15 x 0.12 x 0.2 mm was mounted on a quartz glass fibre on a Philips PW 1100 goniometerhead.



b) Determination of the structure

The data were collected on a PW1100 four circle diffractometer using MoK α radiation ($\lambda = 0.71069\text{\AA}$) from a graphite monochromator and a $\theta - 2\theta$ scan mode. No absorption corrections were applied. The structure was solved by use of the auto-

matic centrosymmetric direct methods using the SHELX 76 program. ¹⁰⁰ Normalised E values with $E > 1.2$ were applied to the multiresolution Σ_2 sign expansion pathway and the E map calculated from a solution with the highest figure of merit showed the location of all the non-hydrogen atoms in the molecule (the highest 17 peaks). The structure was refined first in 3 cycles using isotropic thermal parameters for 17 non-hydrogen atoms by full-matrix least squares; 6 cycles of anisotropic refinement for all the non-hydrogen atoms gave $R = 0.078$. A difference map calculated at this stage gave reasonable positions for all of the hydrogen atoms. In final cycles of refinement the found hydrogen atoms were included in the calculations of structure factors at the map positions but not refined. The final R value was 0.074 with the weighting scheme using $w = 1/\sigma^2_F$ and $R_w = 0.078$. The final difference map showed a maximum of $0.6 \text{ e}/\text{\AA}^3$ at 1.18 \AA from sulphur atom. The scattering factors were those of Cromer and Mann ¹⁰¹ and correction for the real and imaginary parts of the anomalous dispersion was applied.

c) Discussion

The final atomic co-ordinates are given in Tables 1-97 and 2-97, bond lengths and angles in tables 4-97 and 5-97, thermal parameters tables 3-97. A perspective view of the

molecule is shown in Figures 3 and 4. The molecule was found to be non-planar with a 67.5° angle between the least squares planes defined by the atoms of benzene and thiophene. The stereochemistry at the double bond between atoms C4-C5 was found to have Z-configuration.

Table A'

Formula

Molecular Mass

Cell dimensions

a 11.298
 b Å 8.132
 c 8.022

α 109.86
 β (°) 80.69
 γ 98.64

V (Å)³ 680.45
 Z 2

Space System Triclinic

Space Group P1

F(000) 260

μ (MoKα) 1.79 cm⁻¹

D_c g cm⁻³ $\frac{M \times Z \times 1.66}{V} = 1.19$

Data collection

range (θ) 3° < θ < 25°

Scan width 0.90 + 0.01 tan θ/°

scan mode/background mode All possible reflections within the θ range were collected with background measuring time = ½ scan time

Table A' (Continued)

on each side of the
reflection

No of the unique data
collected $\pm H \pm k + 1$

1599

Three standard reflections were measured every 3 hours and
showed no significant decomposition.

TABLE 1-97 Fractional atomic coordinates and
thermal parameters (\AA^2) for $\text{C}_{15}\text{H}_{16}\text{OS}$ (97)

| Atom | x | y | z | U_{iso} or U_{eq} |
|--------|-----------|------------|------------|-------------------------------------|
| S(1) | 0.7739(1) | 0.5213(2) | -0.0262(2) | 0.078(1) |
| C(1) | 0.8943(5) | 0.6770(8) | -0.0751(9) | 0.091(4) |
| O(1) | 0.9084(4) | 0.7073(7) | -0.2161(6) | 0.146(4) |
| C(2) | 0.9628(4) | 0.7516(7) | 0.0748(8) | 0.077(4) |
| C(3) | 0.9231(4) | 0.6923(6) | 0.2138(7) | 0.062(3) |
| C(31) | 0.9825(5) | 0.7480(8) | 0.3801(8) | 0.082(4) |
| C(4) | 0.8181(4) | 0.5654(6) | 0.1882(6) | 0.055(3) |
| C(5) | 0.7555(4) | 0.4898(6) | 0.3073(6) | 0.058(3) |
| C(6) | 0.6473(4) | 0.3650(5) | 0.2813(5) | 0.052(3) |
| C(7) | 0.5383(4) | 0.4131(5) | 0.2629(5) | 0.052(3) |
| C(71) | 0.5226(4) | 0.5980(6) | 0.2717(6) | 0.062(3) |
| C(8) | 0.4357(4) | 0.2893(6) | 0.2434(6) | 0.061(3) |
| C(9) | 0.4414(5) | 0.1189(6) | 0.2421(6) | 0.062(3) |
| C(91) | 0.3311(5) | -0.0110(7) | 0.2203(9) | 0.091(4) |
| C(10) | 0.5501(5) | 0.0747(6) | 0.2633(7) | 0.067(3) |
| C(11) | 0.6531(4) | 0.1923(6) | 0.2843(6) | 0.062(3) |
| C(111) | 0.7687(5) | 0.1376(7) | 0.3094(10) | 0.104(4) |

Table A' (Continued)

on each side of the
reflection

No of the unique data
collected $\pm H \pm k \pm l$

1599

Three standard reflections were measured every 3 hours and
showed no significant decomposition.

TABLE 1-97 Fractional atomic coordinates and
thermal parameters (\AA^2) for $\text{C}_{15}\text{H}_{16}\text{OS}$ (97)

| Atom | x | y | z | U_{iso} or U_{eq} |
|--------|-----------|------------|------------|-------------------------------------|
| S(1) | 0.7739(1) | 0.5213(2) | -0.0262(2) | 0.078(1) |
| C(1) | 0.8943(5) | 0.6770(8) | -0.0751(9) | 0.091(4) |
| O(1) | 0.9084(4) | 0.7073(7) | -0.2161(6) | 0.146(4) |
| C(2) | 0.9628(4) | 0.7516(7) | 0.0748(8) | 0.077(4) |
| C(3) | 0.9231(4) | 0.6923(6) | 0.2138(7) | 0.062(3) |
| C(31) | 0.9825(5) | 0.7480(8) | 0.3801(8) | 0.082(4) |
| C(4) | 0.8181(4) | 0.5654(6) | 0.1882(6) | 0.055(3) |
| C(5) | 0.7555(4) | 0.4898(6) | 0.3073(6) | 0.058(3) |
| C(6) | 0.6473(4) | 0.3650(5) | 0.2813(5) | 0.052(3) |
| C(7) | 0.5383(4) | 0.4131(5) | 0.2629(5) | 0.052(3) |
| C(71) | 0.5226(4) | 0.5980(6) | 0.2717(6) | 0.062(3) |
| C(8) | 0.4357(4) | 0.2893(6) | 0.2434(6) | 0.061(3) |
| C(9) | 0.4414(5) | 0.1189(6) | 0.2421(6) | 0.062(3) |
| C(91) | 0.3311(5) | -0.0110(7) | 0.2203(9) | 0.091(4) |
| C(10) | 0.5501(5) | 0.0747(6) | 0.2633(7) | 0.067(3) |
| C(11) | 0.6531(4) | 0.1923(6) | 0.2843(6) | 0.062(3) |
| C(111) | 0.7687(5) | 0.1376(7) | 0.3094(10) | 0.104(4) |

TABLE 2-97 Fractional atomic coordinates for the hydrogen atoms for C₁₅H₁₆OS (97)

| Atom | x | y | z |
|--------|--------|---------|--------|
| H(2) | 1.0457 | 0.8477 | 0.0707 |
| H(31a) | 1.0537 | 0.8358 | 0.3779 |
| H(31b) | 1.0045 | 0.6295 | 0.4175 |
| H(31c) | 0.9205 | 0.8064 | 0.4914 |
| H(5) | 0.7966 | 0.5420 | 0.4340 |
| H(71a) | 0.4444 | 0.6177 | 0.3014 |
| H(71b) | 0.5801 | 0.6811 | 0.3349 |
| H(71c) | 0.5442 | 0.6172 | 0.1430 |
| H(8) | 0.3566 | 0.3333 | 0.2227 |
| H(91a) | 0.2585 | 0.0376 | 0.1924 |
| H(91b) | 0.3408 | -0.0952 | 0.2772 |
| H(91c) | 0.2874 | -0.1233 | 0.1227 |
| H(10) | 0.5538 | -0.0639 | 0.2499 |
| H(11a) | 0.8406 | 0.2592 | 0.3718 |
| H(11b) | 0.7530 | 0.0004 | 0.2895 |
| H(11c) | 0.8650 | 0.1188 | 0.2674 |

TABLE 3-97 Anisotropic thermal parameters (\AA^2) for $\text{C}_{15}\text{H}_{16}\text{OS}$ (97)

| Atom | U_{11} | U_{22} | U_{33} | U_{23} | U_{13} | U_{12} |
|-------|----------|----------|----------|----------|-----------|-----------|
| S(1) | 0.069(1) | 0.108(1) | 0.056(1) | 0.042(1) | -0.009(1) | 0.004(1) |
| C(1) | 0.065(3) | 0.114(5) | 0.093(4) | 0.064(4) | 0.003(3) | 0.015(3) |
| O(1) | 0.105(3) | 0.224(6) | 0.109(4) | 0.125(4) | 0.008(3) | 0.010(3) |
| C(2) | 0.064(3) | 0.077(4) | 0.091(4) | 0.048(3) | 0.006(3) | 0.006(3) |
| C(3) | 0.061(3) | 0.060(3) | 0.067(3) | 0.027(3) | -0.000(2) | 0.006(2) |
| C(31) | 0.083(4) | 0.093(4) | 0.069(4) | 0.019(3) | -0.010(3) | -0.025(3) |
| C(4) | 0.049(2) | 0.058(3) | 0.056(3) | 0.023(2) | -0.008(2) | 0.005(2) |
| C(5) | 0.067(3) | 0.054(3) | 0.051(3) | 0.024(2) | -0.008(2) | 0.001(2) |
| C(6) | 0.060(3) | 0.049(3) | 0.046(3) | 0.024(2) | -0.001(2) | 0.009(2) |
| C(7) | 0.067(3) | 0.046(3) | 0.043(2) | 0.019(2) | -0.004(2) | 0.008(2) |
| C(71) | 0.068(3) | 0.052(3) | 0.068(3) | 0.023(2) | -0.007(2) | 0.015(2) |
| C(8) | 0.071(3) | 0.062(3) | 0.051(3) | 0.024(2) | -0.010(2) | 0.007(2) |
| C(9) | 0.079(3) | 0.056(3) | 0.051(3) | 0.018(2) | -0.000(2) | 0.000(3) |

table 3-97 continued

| | | | | | | |
|--------|----------|----------|----------|----------|-----------|-----------|
| C(91) | 0.094(4) | 0.069(4) | 0.110(5) | 0.040(3) | -0.030(4) | -0.029(3) |
| C(10) | 0.089(4) | 0.044(3) | 0.070(3) | 0.025(2) | 0.009(3) | 0.011(3) |
| C(11) | 0.072(3) | 0.056(3) | 0.059(3) | 0.028(2) | 0.005(2) | 0.015(3) |
| C(111) | 0.065(3) | 0.090(4) | 0.156(6) | 0.077(4) | 0.008(3) | 0.028(3) |

TABLE 4-97 Bond lengths (Å) for C₁₅H₁₆OS (97)

| | | | | | |
|-------|--------|-----------|-------|---------|----------|
| S(1) | -C(1) | 1.804(6) | S(1) | -C(4) | 1.772(5) |
| C(1) | -O(1) | 1.218(10) | C(1) | -C(2) | 1.442(9) |
| C(2) | -C(3) | 1.347(9) | C(3) | -C(31) | 1.491(8) |
| C(3) | -C(4) | 1.443(6) | C(4) | -C(5) | 1.356(7) |
| C(5) | -C(6) | 1.460(6) | C(6) | -C(7) | 1.391(7) |
| C(6) | -C(11) | 1.424(7) | C(7) | -C(71) | 1.516(7) |
| C(7) | -C(8) | 1.408(6) | C(8) | -C(9) | 1.393(8) |
| C(9) | -C(91) | 1.500(7) | C(9) | -C(10) | 1.382(8) |
| C(10) | -C(11) | 1.384(7) | C(11) | -C(111) | 1.506(8) |

TABLE 5-97 Bond angles (°) for C₁₅H₁₆OS (97)

| | | | | | | | |
|--------------|--------|----------|--------------|--------|----------|--------|----------|
| C(4) | -S(1) | -C(1) | 91.0(3) | O(1) | -C(1) | -S(1) | 121.6(5) |
| C(2) | -C(1) | -S(1) | 109.2(5) | C(2) | -C(1) | -O(1) | 129.1(5) |
| C(3) | -C(2) | -C(1) | 114.9(5) | C(31) | -C(3) | -C(2) | 123.8(4) |
| C(4) | -C(3) | -C(2) | 114.4(5) | C(4) | -C(3) | -C(31) | 121.7(5) |
| C(3) | -C(4) | -S(1) | 110.4(4) | C(5) | -C(4) | -S(1) | 122.1(3) |
| C(5) | -C(4) | -C(3) | 127.5(5) | C(6) | -C(5) | -C(4) | 126.9(4) |
| C(7) | -C(6) | -C(5) | 121.8(4) | C(11) | -C(6) | -C(5) | 118.6(4) |
| C(11) | -C(6) | -C(7) | 119.6(4) | C(71) | -C(7) | -C(6) | 122.8(4) |
| C(8) | -C(7) | -C(6) | 119.6(4) | C(8) | -C(7) | -C(71) | 117.6(4) |
| C(9) | -C(8) | -C(7) | 121.1(5) | C(91) | -C(9) | -C(8) | 120.2(5) |
| C(10) | -C(9) | -C(8) | 118.3(4) | C(10) | -C(9) | -C(91) | 121.5(5) |
| C(11) | -C(10) | -C(9) | 122.6(5) | C(10) | -C(11) | -C(6) | 118.8(5) |
| C(111)-C(11) | -C(6) | 120.9(4) | C(111)-C(11) | -C(10) | 120.3(5) | | |

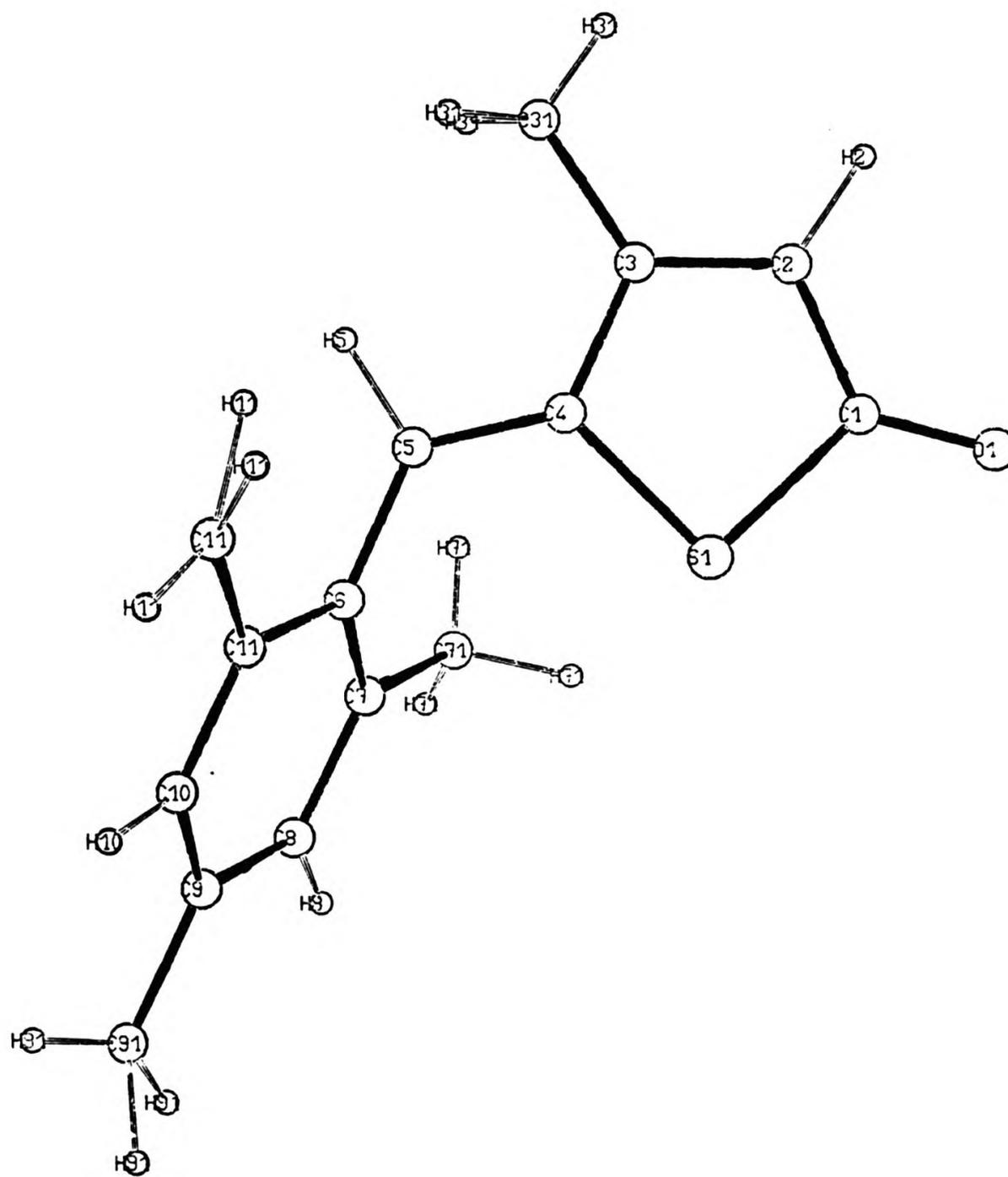


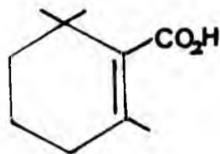
Fig. 3

Perspective view of the molecule of 5-mesitylidene-4-methyl-3-thiolene-2-one (97).

14. Reaction of γ -thiolactone (64) with β -cyclocitral (65)

Following the successful reactions of γ -thiolactone (64) with aromatic aldehydes, particularly the sterically hindered mesitaldehyde, the condensation of compound (64) with aliphatic aldehydes was investigated.

Thus, γ -thiolactone (64) was reacted with β -cyclocitral (65) and the reaction was repeated under several different conditions: the reaction was carried out in HCl/MeOH at low temperature (0° - $+5^{\circ}$ C) and at room temperature, also the reaction was performed in the presence of base in a protic solvent or using NaH in tetrahydrofuran. The oily, brown crude products were obtained in each case and were analysed by means of t.l.c. and GC-MS techniques. The analyses showed that the products consisted of the mixtures of many compounds, among which β -cyclocitral (65) and cyclohexenecarboxylic acid (98) were detected. Mass spectra of the individual components indicated that their molecular weights were different from that of the required product (66). Thus, the crude reaction products were not analysed further.



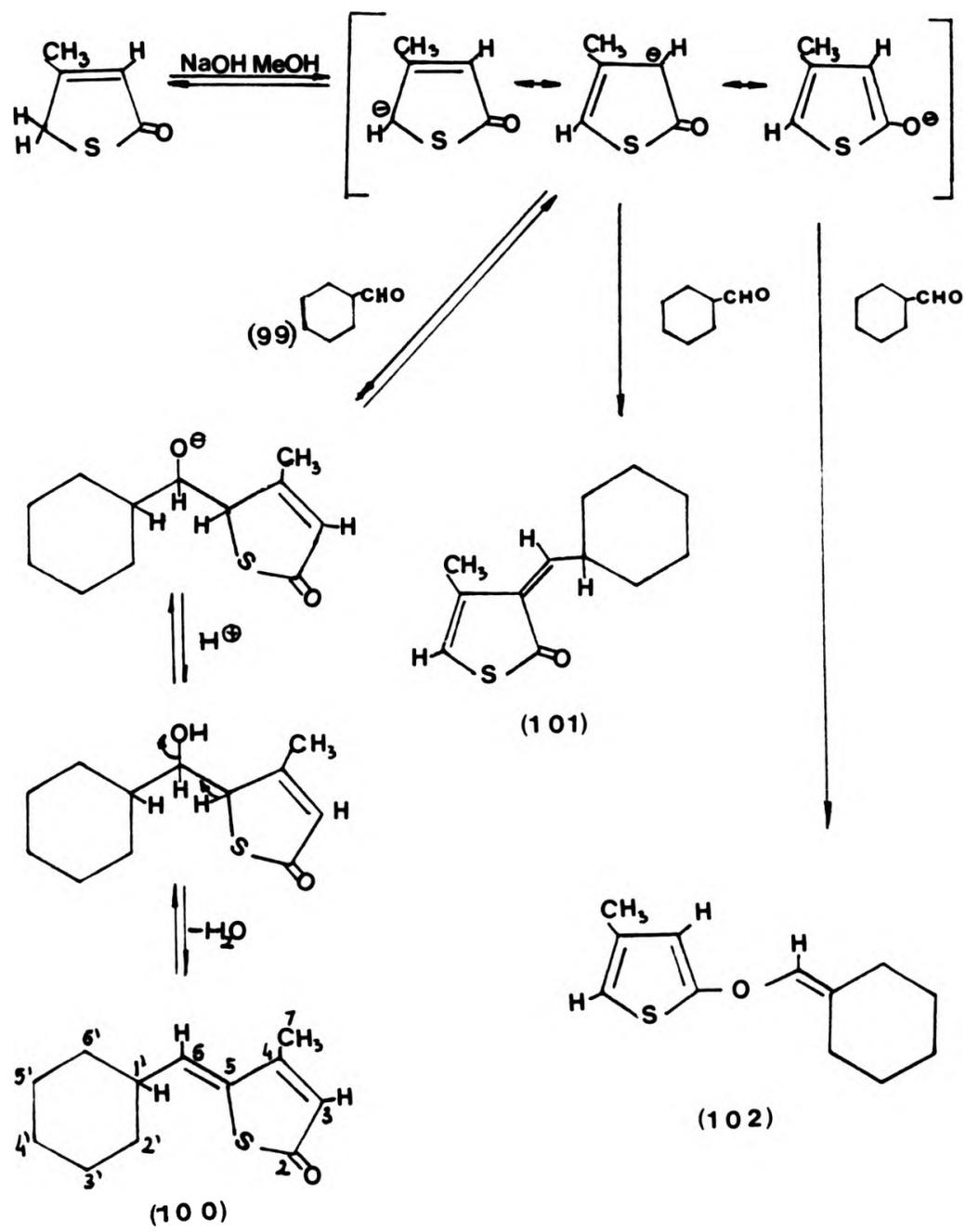
(98)

A possible explanation for the failure to condense γ -thiolactone (64) with β -cyclocitral (65) is that β -cyclocitral having acidic γ -hydrogens as well as a double bond and the carbonyl group may under the reaction conditions applied undergo isomerization or polymerization or other side reactions leading to the undesired products.

15. The reaction of γ -thiolactone (64) with cyclohexanecarboxaldehyde (99).

γ -thiolactone (64) was reacted with cyclohexanecarboxaldehyde (99) under various reaction conditions. When the reaction was carried out in the presence of hydrogen chloride, only starting materials were found in the crude reaction mixture. However, the reaction carried out in MeOH/NaOH at room temperature gave a yellow crystalline product which was chromatographed on silica column, using CH_2Cl_2 as eluant to give 0.03 g (1.8%) of a crystalline compound (t.l.c. $r_f = 0.33$, CH_2Cl_2), identified as a condensation product (100) of γ -thiolactone (64) and cyclohexanecarboxaldehyde (99). The ^1H n.m.r. analysis of the other column fractions suggested that they did not contain the required condensation product (100), therefore the detailed analysis of those fractions was not undertaken.

The mass spectrum of the reaction product (100) shows an

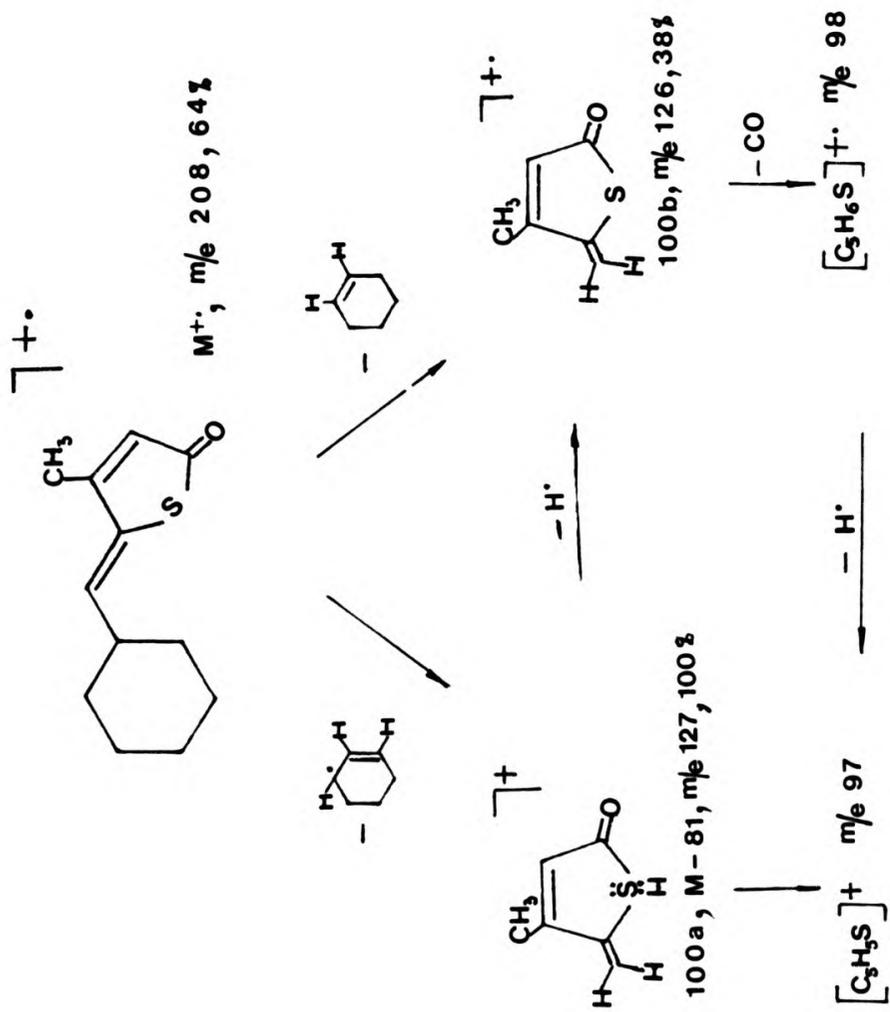


Scheme 28

abundant molecular ion at m/e 208 (64%). The base peak of the spectrum is an ion at m/e 127 (probably species 100a), corresponding to the loss of cyclohexene radical from the molecular ion; similar fragmentation is observed for alkylthiophenes and occurs with the migration of hydrogens.⁹⁶ The fragment ion at m/e 127 seems to undergo further fragmentation with loss of CH₂O to give m/e 97.

Alternatively, the molecular ion appears to undergo fragmentation by the loss of cyclohexene followed by the loss of CO to give an ion at m/e 98; a similar fragmentation mode is observed for the aromatic analogues (96) and (97).

The structure of the compound (100) was further investigated by means of ¹H and ¹³C n.m.r. spectroscopy (spectra 21-26). The ¹H n.m.r. parameters are listed in the table 100/H.



Scheme 29

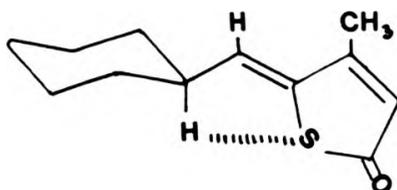
Table 100/H

| Solvent CDCl_3 ; internal standard T.M.S., 80MHz | | | | |
|---|-------------------------|---------------|-------------------|-------------|
| Proton Assignment | Type | δ /ppm | J/Hz | Integration |
| H-2', H-3' H-4' H-5' H-6' H-1' | CH ₂ ≥C-H | 1.1-2.2 | | 11 |
| H-7 | CH ₃ | 2.23 | H-3-H-7 = 1.3 | 3 |
| H-3 | =C-H | 6.11 | H-3-H-7 = 1.3 | 1 |
| H-6 | =C-H | 6.14 | H-6-H-1' = 9.3 | 1 |

Irradiation of the peak at δ 6.11 causes the doublet at δ 2.23 to collapse into a single peak; the methyl protons can be expected to couple to the alkene proton H-3. Therefore on the basis of the double resonance experiment the peak at δ 6.11 is assigned to the H-3.

Irradiation of one shoulder (δ 6.20) of the doublet at δ 6.14 causes the other shoulder (δ 6.09) to disappear.¹⁰² Thus, the peaks at δ 6.20 and δ 6.09 belong to the same doublet.

In the chair conformation the cyclohexane ring can be expected to have the large substituent in the equatorial position.



A large coupling constant $^3J_{\text{vic}}(\text{H-1}' - \text{H-6}) = 9.3\text{Hz}$. indicates that the rotational isomer, which contributes most to the J value is that with the vicinal protons H-1' and H-6 in an anti coplanar arrangement with respect to each other, that is with the dihedral angle between C-(H-1') and C-(H-6) near 180° , and with H-1' close to sulphur.

Broad band proton decoupled and ^{13}C n.m.r. s.f.o.r.d. spectra allowed assignment of the chemical shifts for all carbons in compound (100). The ^{13}C parameters are listed in table 100/C.

Table 100/C

| Solvent CDCl_3 ; internal standard T.M.S., 20MHz | | |
|---|-----------------|------------------|
| Assignment | Type | δ /p.p.m. |
| C-7 | CH_3 | 14.6 |
| C-3', C-5' | CH_2 | 25.5 |
| C-4' | CH_2 | 25.8 |
| C-2', C-6' | CH_2 | 32.1 |
| C-1' | $\geq\text{CH}$ | 42.1 |
| C-3 | = CH- | 128.9 |
| C-5 | = C< | 136.9 |
| C-6 | = CH- | 138.2 |
| C-4 | = C< | 159.4 |
| C-2 | C=O | 193.7 |

A single peak at δ 14.6, which appears as a quartet in the s.f.o.r.d. spectrum was assigned to carbon C-7. In the analogues (96) and (97) the chemical shifts for this carbon are δ 14.9 and δ 14.5 respectively.

A high intensity peak at δ 25.5 was assigned to methylene group carbons C-3' and C-5' and the lower intensity peak at δ 25.8 to carbon C-4'. The peaks show as triplets in the s.f.o.r.d. spectrum.

The methylene group carbons C-2' and C-6' are deshielded and they correspond to a peak at δ 32.1, which appears as a triplet in the s.f.o.r.d. spectrum.

The peak at δ 42.1 belongs to carbon C-1', the proton shows as a doublet in the s-f-off resonance decoupled spectrum.

The peaks at δ 193.7 and δ 159.4 are due to the carbonyl carbon C-2 and the quaternary carbon C-4 respectively. The peak at δ 136.9 shows as a singlet in both broad band decoupled and s.f.o.r.d. spectra and was assigned to C-5.

The olefinic carbons C-3 and C-6 correspond to the peaks at δ 128.9 and δ 138.2 respectively. In the ^{13}C n.m.r. spectrum of γ -thiolactone (64), a starting material, the chemical shift for C-3 is δ 128.2.

Carbon C-6, a terminal olefinic carbon, is de-shielded ¹⁰³ and it shows downfield shift at δ 138.6, comparing with the chemical shift for that carbon in the analogues (96) (δ 129.6) and (97) (δ 129.9).

The side products (101) and (102) may also form in the reaction of γ -thiolactone (64) with cyclohexanecarboxaldehyde (99). However, the analysis carried out on the isolated product suggest structure (100). Thus, in the UV spectrum of the analysed compound a bathochromic shift of λ_{max} , compared to

that recorded for the starting material indicates extended conjugation in the former. Also, the fragmentation pattern observed in the mass spectrum of the investigated compound as well as ^1H and ^{13}C n.m.r. spectroscopic analysis are in favour of structure (100).

16. Preparation of γ -thiolactone (64) derivatives

16.1 Introduction

As an alternative route to the condensation product (66) of γ -thiolactone (64) with β -cyclocitral (65) the following derivatives were prepared:

5-bromo-4-methyl-3-thiolene-2-one (103),
diethyl (4-methylthien-2-yl) phosphonate (104) and
trimethylsilyl (4-methylthien-2-yl) ether (105)

The compounds may provide suitable alternatives to (64) in the synthesis of product (66).

16.2 Preparation of 5-bromo-3-thiolene-2-one (103)

The bromination of γ -thiolactone (64) was carried out with N-bromosuccinimide in CCl_4 . Allylic bromination with N-bromosuccinimide proceeds by a free-radical mechanism, with the allylic hydrogen being abstracted by a bromine radical to give γ -thiolactone (64) radical, which on further reaction with bromine yields product (103).¹⁰⁴ (Scheme 32).

The ^1H and ^{13}C n.m.r. spectra of the major reaction product are in favour of structure (103) and suggest also that the compound (106) (the product of bromination at the methyl group) and a side reaction product (107) do not accompany C-5 brominated γ -thiolactone (64). The reaction product (103) was purified by distillation (b.p. $74^\circ\text{C}/0.3$ mm Hg), and it was obtained in 21% yield.

The structure of 4-bromo-4-mercapto-3-methylbut-2-enoic acid γ -thiolactone (103) was confirmed by means of ^1H and ^{13}C n.m.r. spectroscopy (spectra 27, 28). The ^1H n.m.r. parameters are listed in the table 103/H.

Table 103/H

| Solvent CDCl ₃ ; internal standard T.M.S., 80MHz | | | | |
|---|-----------------|---------------|------------------------|-------------|
| proton | | δ /ppm | J/Hz | Integration |
| Assignment | Type | | | |
| 3 | =CH | 6.19 | 4J (H-6 - H-3)=1.47 | 1 |
| 5 | Br-C-H | 6.12 | | 1 |
| 6 | CH ₃ | 2.32 | 4J (H-6 - H-3)=1.47 | 3 |

A doublet at δ 2.32 and a quartet at δ 6.19 arise as a result of coupling between the methyl group protons H-6 and an olefinic proton H-3, as could be established from the value of their coupling constant. Thus a peak at δ 2.32 was assigned to the methyl group and the peak at δ 6.19 to proton H-3. The peak at δ 6.19 shows further suggestion of coupling between proton H-3 and H-5. The peak at δ 6.12 was assigned to proton H-5; broadening of this peak suggested that the proton H-5 is coupled to the methyl group protons (H-6) and to proton H-3.

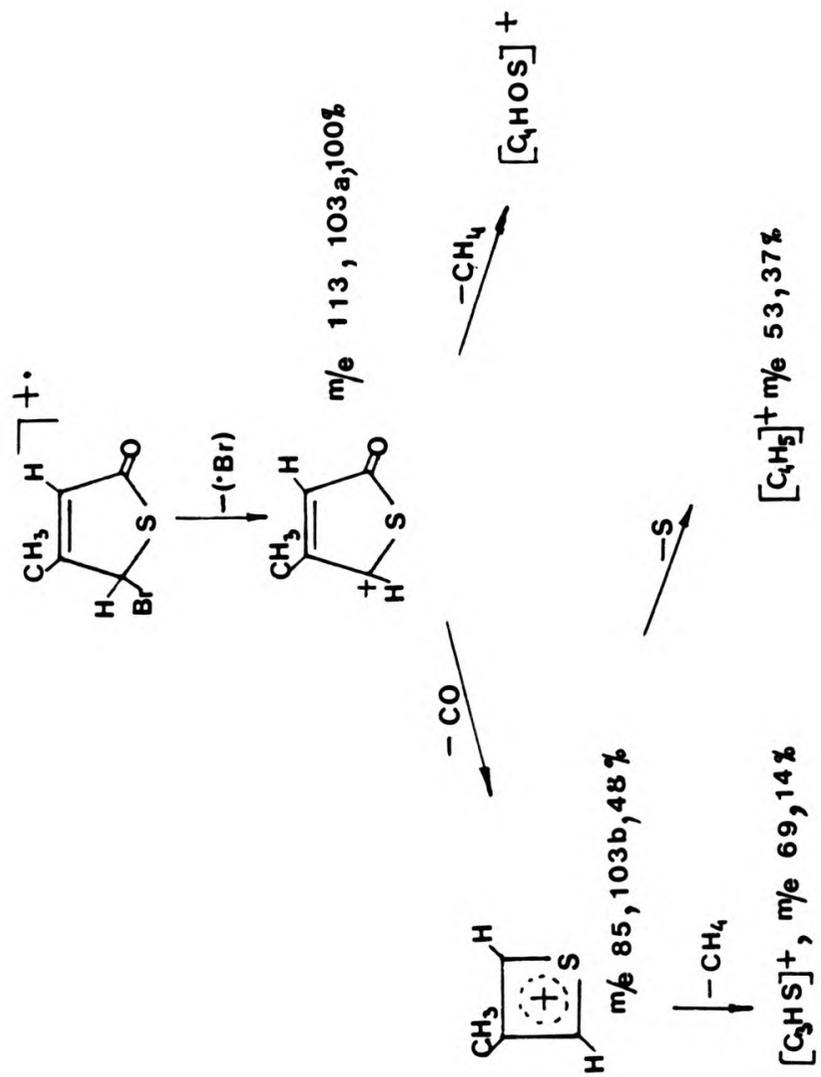
The ¹³C n.m.r. parameters for compound (103) are listed in table 103/C.

Table 103/C

| Solvent CDCl_3 ; internal standard T.M.S., 20MHz | | |
|---|----------------|------------------|
| Carbon | | δ /p.p.m. |
| Assignment | Type | |
| C-6 | CH_3 | 17.4 |
| C-5 | >C-Br | 52.2 |
| C-3 | $=\text{C-H}$ | 129.2 |
| C-4 | $=\text{C}$ | 168.2 |
| C-2 | C=O | 194.2 |

The peaks at δ 194.2 and δ 168.2 were easily assigned to a carbonyl carbon C-2 and a quarternary carbon C-4 respectively. A peak at δ 129.2 showed as a doublet in the s.f.o.r.d. ^{13}C n.m.r. spectrum and it was assigned to carbon C-3. In the ^{13}C n.m.r. spectrum of γ -thiolactone (64), a starting material, carbon C-3 shows at δ 128.2. Carbon C-5 gave rise to a peak at δ 52.2, which appeared as a doublet in the s.f.o.r.d. spectrum. A peak at δ 17.4 belongs to the methyl group C-6; it shows as a quartet in the s.f.o.r.d. ^{13}C n.m.r. spectrum.

In the mass spectrum of compound (103), the molecular ion showed as two low and equal intensity peaks at m/e 192 and at m/e 194, which confirms that the ion contains one bromine



Scheme 31

atom. The loss of bromine radical from the molecular ion gave rise to an ion at m/e 113, which is the base peak of the spectrum and it appeared to undergo further fragmentation by loss of CO to m/e 85, (48%, probably species 103b).⁹⁶ The ion at m/e 85 decomposes either by loss of sulphur to ion m/e 53 (37%) or by loss of methane to ion m/e 69 (14%). The fragmentation of compound (103) is similar to that observed for thiolactones.⁹⁶

16.3 Reaction of 5-bromo-4-methyl-3-thiolene-2-one (103) with triethylphosphite.

4-Bromo-4-mercapto-3-methylbut-2-enoic acid γ -thiolactone (103) was further reacted with triethylphosphite using a procedure of Korte.¹⁰⁵ The ^1H n.m.r. spectrum of a side product, which distilled off from the reaction vessel and was collected in a receiver, indicated that it was ethyl bromide. A light brown and oily crude reaction product was purified by distillation (b.p. 110°C - 116°C /0.3 mm Hg) to give a colourless liquid (0.36 g, 72%). The product was further analysed by ^1H , ^{13}C and ^{31}P n.m.r. spectroscopy (spectra 29-30). The ^1H n.m.r. parameters are listed in table 104/H. The structure (104) was assigned to the reaction product.

Table 104/H

| Solvent CDCl_3 ; internal standard T.M.S., 80MHz | | | |
|---|---------------|---------------|---|
| Proton | | δ /ppm | J/Hz |
| Assignment | Type | | |
| H-2' | CH_3 | 1.33 | $J(\text{H-1}'-\text{H-2}') = 7.2 \text{ Hz}$ |
| H-6 | CH_3 | 2.15 | |
| H-1' | CH_2 | 4.25 | $J(\text{H-1}'-\text{H-2}') = 7.2 \text{ Hz}$ |
| H-5 | =C-H | 6.36 | |
| H-3 | =C-H | 6.49 | |

In the ^{13}C n.m.r. spectrum the signals due to methyl and methylene carbons present in the alkoxide groups and a signal due to the methyl group carbon on the thiolactone ring were found in the aliphatic part of the spectrum, as expected.

The peaks at δ 111.7 and δ 115.7 were assigned to the olefinic carbons C-3 and C-5 respectively.¹⁰³ These peaks show as overlapping doublets in the s.f.o.r.d. spectrum. The peaks at δ 152.6 and δ 134.9 are due to the quaternary carbons C-2 and C-4 respectively.

In the ^{31}P n.m.r. spectrum compound (104) gives rise to a peak at δ (-6.50) *; this value is consistent with the

chemical shifts of similar compounds. 106

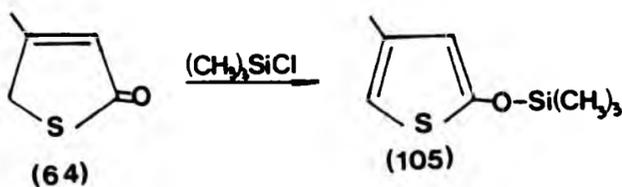
The mass spectrum of compound (104) shows a molecular ion at m/e 250 (49%). The base peak of the spectrum is a fragment ion at m/e 114, which has probably been formed as a result of a six-membered re-arrangement with hydrogen transfer. The resulting fragment ion m/e 114, appears to undergo further fragmentation similar to that observed for γ -thiolactone (64). The fragmentation pattern for product (104) suggests that alternatively the molecular ion undergoes a re-arrangement with a loss of $\text{CH}_2=\text{CH}_2$ to give fragment ion at m/e 222 (probably species 104b).

* Footnote

85% H_3PO_4 was used as an internal standard and positive δ are those downfield of H_3PO_4 signal.

16.4 Trimethylsilyl (4-methylthien-2-yl) ether (105)

The title compound (105) was prepared by the method of Brownbridge ¹⁰⁷ in the reaction of γ -thiolactone (64) and chlorotrimethylsilane. The product (105), a colourless liquid, was purified by distillation, b.p. 38^o-40^oC/0.6 mm Hg and was obtained with 32% yield; compound (105) decomposes easily on standing.



The compound (105) was next analysed by means of ¹H and ¹³C n.m.r. spectroscopy technique. The ¹H n.m.r. parameters are listed in table 105/H and the ¹³C n.m.r. parameters are in table 105/C.

In the ¹H n.m.r. spectrum two single peaks at δ 5.09 and δ 6.09 were assigned to the protons H-5 and H-3 respectively; the peaks are broadened, probably due to coupling of the protons H-2 and H-5 with methyl group protons.

Table 105/H

| Solvent CDCl ₃ , internal standard, T.M.S. 80 MHz | | | |
|--|--------------------|------|-------------|
| Proton Assignment | Type | /ppm | Integration |
| H-1' | Si-CH ₃ | 0.25 | 9 |
| H-6 | CH ₃ | 2.11 | 3 |
| H-5 | =C-H | 5.09 | 1 |
| H-3 | =C-H | 6.09 | 1 |

In the olefinic part of the broad band proton decoupled ¹³C n.m.r. spectrum two peaks at 107.9 and 111.6 are due to the carbons C-2 and C-5 respectively. The peaks appear as overlapping doublets in the s.f.o.r.d. ¹³C n.m.r. spectrum.

Table 105/C

| Solvent CDCl ₃ , internal standard, T.M.S. 20 MHz | | |
|--|-----------------|-------|
| Assignment | Type | δ/ppm |
| C-6 | CH ₃ | 16.7 |
| C-3 | =C-H | 107.9 |
| C-5 | =C-H | 111.6 |
| C-4 | >C= | 134.9 |
| C-2 | =C-O- | 159.8 |

Absence of any peaks due to the methylene protons H-5 and carbon C-5 in the ¹H and ¹³C n.m.r. spectrum confirms that the compound (105) exist as trimethylsilyl thienyl ether form.

17. Desulphurization reaction

Following some examples in the literature,^{108 109} desulphurization of 5-benzylidene-4-methyl-3-thiolene-2-one (96) with Raney nickel was attempted. Raney nickel W-2¹¹⁰ and W-5¹¹¹ were freshly prepared from nickel-aluminium alloy for the reactions.

Desulphurization with Raney nickel W-2 was not effective and compound (96), the starting material was recovered. However, sulphur atom was removed with Raney nickel W-5; the ¹H n.m.r. and i.r. spectroscopic analyses of a crude product showed that hydrogenation of the double bonds also took place, indicating that the milder reaction conditions may need to be employed to preclude this.

18. Conclusions

γ -Thiolactone (64), the key intermediate in the proposed stereocontrolled synthesis of the plant growth regulators was prepared in a three step synthesis, which was conducted under the mild reaction conditions throughout and employed readily available materials. The products prepared in the first and second stages were of high purity and were obtained with the good yields. γ -Thiolactone was formed in the third stage of the synthesis, by cyclization of 4-acetylthio-3-methylbut-2-enoic acid ethyl ester (56), with lower yields. The low

yields of this compound were due to the fact that only the Z-isomer (92) could be cyclized to give γ -thiolactone (64) and to the difficulties in separating γ -thiolactone (64) from a side product. Therefore, it is suggested that any further improvements of the γ -thiolactone (64) yield may be focussed on changing the relative amount of the isomers in the mixture, e.g. in the photochemical reaction or possibly using a different intermediate. The short synthesis leading to γ -thiolactone (64) may be considered as a model for the preparation of a wide range of 4-substituted (or 3-substituted) γ -thiolactones. The very few 4-substituted γ -thiolactones, reported so far in the literature were synthesized via 4-substituted thiophenes, which could be prepared only in long syntheses. A vital result of the stereocontrolled synthesis under investigation was the proof that the double bond formed in the condensation of γ -thiolactone (64) with the substituted and unsubstituted aromatic aldehydes had the Z-configuration, that is the configuration required by ABA and its analogues to exhibit biological activity. By the analogy, the condensation products of γ -thiolactone (64) with aliphatic aldehydes, e.g. cyclohexanecarboxaldehyde can be expected to have this same stereochemistry.

The acidic properties of the methylene group protons on γ -thiolactone ring allowed preparation of 5-arylidene and 5-bromo-derivatives with good yield.

However, γ -thiolactone (64) failed to couple with β -cyclocitral and the reaction product with cyclohexanecarboxaldehyde was obtained with low yield. Therefore in order to develop a more general method of preparation of 5-alkylidene derivatives of the γ -thiolactone and in particular to effect the condensation with β -cyclocitral another method of synthesis may be tried, e.g. preparation via enamines or employing organolithium compounds or by using different aldehydes.

In the further step of the proposed stereocontrolled synthesis, the bridging element (a sulphur atom) was removed with Raney nickel, W-5; desulphurization was, unfortunately, accompanied by hydrogenation of double bonds, suggesting that milder reaction conditions need to be employed in order to effect selective desulphurization only.

EXPERIMENTAL

1. General

Unless stated otherwise reactions were carried out under nitrogen gas, which was dried by passing it over silica gel and phosphorus pentoxide and it was then filtered through glass wool.

The silica gel adsorbent used in chromatography columns was of 70 - 230 mesh, supplied by B.D.H. Chemicals Limited.

Thin layer chromatography was conducted on commercially supplied silica-coated aluminium or glass plates of 0.25 mm thickness and with fluorescent indicator for 254 nm wavelength. Large, silica coated preparative plates were made up at the Polytechnic of North London.

2. Solvents

The solvents were of G.P.R. grade and were dried for the reactions. Thus, benzene and toluene were distilled and stored over sodium wire. THF was stored over calcium hydride and distilled for the reactions from lithium aluminium hydride in an atmosphere of nitrogen. Diethyl ether was dried over

sodium wire. Dry ethanol and methanol were prepared by refluxing with magnesium turnings. Carbon tetrachloride was dried over anhydrous calcium chloride and distilled for the reactions.

The solvents of "Analar" grade were used for U.V. and n.m.r. instrumental analysis.

3. Reagents

The reagents were mostly obtained from commercial sources.

Thioacetic acid (with CaSO_4 as a stabiliser) and chloroacetone were distilled for the reactions. Sodium hydride was used as a 50% dispersion in mineral oils.

Hydrogen chloride was either drawn from a cylinder or it was prepared from concentrated sulphuric acid and hydrochloric acids ¹¹²; the gas was dried by passing it over concentrated sulphuric acid.

n-Butyllithium was prepared by the method described by Vogel ¹¹³ in the reaction of metal lithium (shavings) (0.62 mole) with butyl bromide (0.25 mole) in sodium dried diethyl ether at -10°C and under nitrogen. Excess of lithium was separated from the product by filtration in the atmosphere of nitrogen and

butyllithium in ether was immediately used in the reaction.

4. Analytical Techniques

Carbon and hydrogen combustion analyses were carried out by the microanalytical services of the Polytechnic of North London and by ICI Laboratories, Jealott's Hill, Bracknell, Berks.

Infrared spectra in the region $600-4000\text{ cm}^{-1}$ were recorded on a Pye Unicam SP2000 double beam spectrometer. The spectra were recorded as KBr disc or liquid films as stated.

Ultraviolet spectra were recorded in the region 190-450 nm in methanol solutions, on a Pye Unicam SP1800 double beam spectrometer.

Routine ^1H n.m.r. spectra were recorded using a Perkin-Elmer R-12B 60 MHz spectrometer. Fourier Transform ^1H and ^{13}C spectra were obtained using a 80 MHz Bruker WP 80 MHz instrument at the Polytechnic of North London, a 90 MHz Jeol-90 at Jealott's Hill Laboratories (ICI) or a 220 MHz Bruker at PCMU Laboratories at Harwell. The ^1H , ^{13}C and ^{31}P n.m.r. spectra were recorded for solutions in CDCl_3 , unless otherwise stated.

Mass spectra were recorded using a Hitachi-Perkin Elmer RMS4 single focussing instrument, MS9 double focussing instrument or a Hewlett-Packard instrument equipped with facilities for combination G.C.-M.S.

Gas chromatography analyses were conducted on a Perkin-Elmer model F-11 gas chromatograph with a flame ionization detector .

H.P.L.C. analyses were carried out on a Waters Associates A.L.C. 210 instrument using Cecil Instruments variable wavelength U.V. monitor for detection.

X-ray crystallography data were obtained with a Philips PW 1100 four circle diffractometer with MoK α radiation ($\lambda = 0.71069 \text{ \AA}$) from a graphite monochromator.

Synthesis 1

2,5-Dibromothiophene (73). 82 . -

The reaction was carried out in air atmosphere.

Bromine (95g, 0.6 mole) was added dropwise to a cooled (20°C) solution of thiophene (30g, 0.3 mole) in toluene (30ml). The reagents were stirred for 1 hour at room temperature and a solution of sodium hydroxide (25g) in ethanol (70ml) was added dropwise over ½ hour. The reaction mixture was refluxed for 16 hours, cooled to room temperature and diluted with water (40ml). The brown organic layer was separated and dried with anhydrous magnesium sulphate. Toluene was removed on a rotary evaporator and a brown crude product (68g) was redistilled to give monobromothiophene (74) (17g) b.p. 46°-88°C/ 15 mm Hg and 2,5-dibromothiophene (73) (32.0g, yield 38%), which distilled as a colourless liquid at 90°C-96.5°C/15 mm Hg, (lit. 82 b.p. 200°C-210°C, yield 44%); $n_D^{20} = 1.6260$ (lit. 84 $n_D^{20} = 1.6288$); ν_{max} (liq. film) 3120, 1520, 478 (C-Br) cm^{-1} (lit. 84 ν_{max} (liq. film) 3100, 1510, 470 cm^{-1}); δ_H (60 MHz) 6.65 (2H, s) (lit. 83 δ_H (60 MHz) (cyclohexane) 6.69 (2H, s)); g.l.c.: (12' x 5 mm i.d. metal column of 15% C20M + 15% B34 on cnromosorb W, column temp. 180°C, N₂ 20 psi, chart speed 60 cm/1 h)

$t_r = 4.1$ min.

Synthesis 2

2, 3, 5-Tribromothiophene (75) ⁸⁵ . -

2,3,5-Tribromothiophene was prepared by the method of Rosenberg. ⁸⁵ It was obtained with the yield of 46% (lit. ⁸⁵ 42%), b.p. 88°C-94°C/0.2 mm Hg, m.p. 23°C-25°C (ethanol) (lit. ⁸⁵ m.p. 29°C (ethanol); δ_H (60 MHz) 6.72 (1H,s) (lit. ⁸³ δ_H (60 MHz) (cyclohexane) 6.75, 1H,s); δ_C 132.4(d), 113.6(s), 112.1(s), 110.7 (s), (lit. ¹¹⁴ δ_C (15 MHz) (CCl₄) 133.8 (d), 115.5(s), 114.0(s), 112.7 (s)); g.l.c.,: (12' x 5 mm i.d. metal column of SE30% on Chromosorb W, column temp. 150°C, N₂ 22 psi, chart speed 1 cm/min. $t_r = 3.2$ min.

Synthesis 3

The direct bromination of Thiophene. -

A solution of thiophene (30 g, 0.3 mole) in toluene (50 ml) was cooled to 0°C and bromine (96 g, 0.6 mole) was added dropwise. The reagents were stirred for 2 hours at room temperature, cooled down again to 0°C and another portion of bromine (79 g, 0.5 mole) added. The reagents were refluxed 1 hour and some water (60 ml) added. The aqueous and organic

layers were separated. The organic layer was washed with a saturated solution of sodium hydroxide (5 x 40 ml) then with water (3 x 40 ml) and dried with anhydrous MgSO_4 . Solvent was removed and the crude product (76.3 g) was re-distilled to give 2,5-dibromothiophene (27 g, yield 32%, b.p. $48^\circ\text{C}-60^\circ\text{C}/0.2$ mm Hg) and 2,3,5-tribromothiophene (44.3 g, yield 41%, b.p. $90^\circ\text{C}-96^\circ\text{C}/0.2$ mm Hg, m.p. $22^\circ\text{C}-26^\circ\text{C}$ ethanol, σ_{H} (60 MHz) 6.68 (s,2H) 2,5-dibromothiophene (73), 6.76 (s,1H), 2,3,5-tribromothiophene (75).

Synthesis 4

2,4-Dibromothiophene ⁸⁷ . -

2,3,5-Tribromothiophene (8 g, 0.02 mole) in diethyl ether (35 ml) was treated with freshly prepared n-butyllithium ¹¹³ (1.7 g, 0.02 mole) in diethyl ether (35 ml) for thirty minutes at -40°C . Cold water (50 ml) was then added and the organic and aqueous layers were separated. The aqueous layer was extracted with diethyl ether (3 x 30 ml) and the combined ether extracts were dried over anhydrous magnesium sulphate. Fractional distillation of the crude mixture (6.0 g) gave product (2.5 g, b.p. $26^\circ\text{C}-29^\circ\text{C}/1$ mm Hg), which consisted (relative amounts of compounds in the distillate were calculated from the ^1H n.m.r. integral), 2,4-dibromothiophene (71) (74%), 2,5-dibromothiophene (73) (14%), 2,3-

dibromothiophene (80) (12%).

2,4-Dibromothiophene: δ_{H} (60 MHz) 7.10 (1H,d, J_{2-4} 1.6 Hz), 6.93 (1H,d, J_{2-4} 1.6 Hz), (lit. ⁸³ δ_{H} (60 MHz) (cyclohexane) 6.97 (1H,d, J_{2-4} 1.6 Hz), 6.88 (1H,d, J_{2-4} 1.6 Hz); 2,5-dibromothiophene δ_{H} 6.65 (2H,s) (lit. ⁸³ δ_{H} (60 MHz) (cyclohexane) 6.69 (2H,s)).

Synthesis 5

3,5-Dichloro-4-hydroxy-4-methylpentan-2-one ⁸² . -

In the preparation of n-butyllithium ¹¹³ THF was used as a solvent instead of diethyl ether; other conditions of the reaction remained unchanged.

A solution of diisopropylamine (23.9 g, 0.24 mole) in THF (80 ml) was cooled to 0°C and a fresh solution of n-butyllithium in THF (200 ml) (prepared from 0.27 mole of ethyl bromide and 0.67 g atom of lithium metal) was added slowly. ⁸⁹ ¹¹³ The reagents were stirred for an additional 10 minutes. The reaction mixture was then cooled to (-78°C) (CO₂/acetone) and thioacetic acid (9 g, 0.12 mole) in THF (50 ml) was added over a period of 3 minutes. The reagents were stirred for 15 minutes and chloroacetone (10.8 g, 0.12 mole) in THF (50 ml) was added over 3 minutes. Stirring was

continued for 1 hour at -78°C . The reaction mixture was then quenched with ice cold 5% HCl (200 ml) and extracted with diethyl ether (4 x 40 ml). Drying (anhydrous magnesium sulphate) and concentration of the ether extracts gave 12.5 g of the crude product which was purified by distillation to give 2.4 g. of the product, b.p. $68^{\circ}\text{C}-94^{\circ}\text{C}/0.6$ mm Hg, which was further chromatographed on a silica column. Chloroform was used as an eluting solvent. 3,5-dichloro-4-hydroxy-4-methylpentan-2-one (82) (0.9g, 5%) was obtained.

ν_{max} (liq. film) 3400 (O-H), 2995 (C-H), 1710 (C=O), 645 (C-Cl) cm^{-1} ; δ_{H} 1.42 (2 x 3H,s), 2.42 (3H,s), 2.43 (3H,s), 3.25 (s,OH), 3.45 (s,OH), 3.64 (2H,q, AB, 11.7 Hz), 3.69 (2H,q,AB, 11.7 Hz) 4.47 (1H,s) 4.56 (1H,s); δ_{C} : 21.4 (q), 22.8 (q) 28.8 (q), 29.6 (q), 49.9 (t), 51.1 (t), 63.9 (d), 66.2 (d), 73.7 (s), 74.6 (s), 203.7 (s), 205.0 (s).

Synthesis 6

The reaction of thioacetic acid and monochloroacetone in the presence of tetramethylethylenediamine (TMEDA). -

The solution of TMEDA (27.8 g) (0.24 mole) in THF (30 ml) was added dropwise to n-butyllithium ^{89 115} (0.24 mole) in THF (200 ml) at 0°C . The reagents were stirred for $\frac{1}{2}$ hour, cooled to -78°C and thioacetic acid (9 g, 0.12 mole)

continued for 1 hour at -78°C . The reaction mixture was then quenched with ice cold 5% HCl (200 ml) and extracted with diethyl ether (4 x 40 ml). Drying (anhydrous magnesium sulphate) and concentration of the ether extracts gave 12.5 g of the crude product which was purified by distillation to give 2.4 g. of the product, b.p. $68^{\circ}\text{C}-94^{\circ}\text{C}/0.6$ mm Hg, which was further chromatographed on a silica column. Chloroform was used as an eluting solvent. 3,5-dichloro-4-hydroxy-4-methylpentan-2-one (82) (0.9g, 5%) was obtained.

ν_{max} (liq. film) 3400 (O-H), 2995 (C-H), 1710 (C=O), 645 (C-Cl) cm^{-1} ; σ_{H} 1.42 (2 x 3H,s), 2.42 (3H,s), 2.43 (3H,s), 3.25 (s,OH), 3.45 (s,OH), 3.64 (2H,q, AB, 11.7 Hz), 3.69 (2H,q,AB, 11.7 Hz) 4.47 (1H,s) 4.56 (1H,s); σ_{C} : 21.4 (q), 22.8 (q) 28.8 (q), 29.6 (q), 49.9 (t), 51.1 (t), 63.9 (d), 66.2 (d), 73.7 (s), 74.6 (s), 203.7 (s), 205.0 (s).

Synthesis 6

The reaction of thioacetic acid and monochloroacetone in the presence of tetramethylethylenediamine (TMEDA). -

The solution of TMEDA (27.8 g) (0.24 mole) in THF (30 ml) was added dropwise to n-butyllithium ^{89 115} (0.24 mole) in THF (200 ml) at 0°C . The reagents were stirred for $\frac{1}{2}$ hour, cooled to -78°C and thioacetic acid (9 g, 0.12 mole)

in THF (50 ml) was added dropwise. After stirring for 15 minutes monochloroacetone (10.8 g, 0.12 mole) in THF (50 ml) was added dropwise and stirring was continued for 1 hour. The reaction mixture was then quenched with ice cold 5% HCl (200 ml) and extracted with ether. Ether extracts were dried over anhydrous magnesium sulphate, concentrated and the crude product distilled to give 3,5-dichloro-4-hydroxy-4-methylpentan-2-one (82) (21.2%), b.p. 61°C-91°C/0.4 mm Hg. ν_{\max} (liq. film) 3500, 2995, 1720, 650 cm^{-1} ; δ_{H} (60 MHz): 1.40 (3H,s), 2.40 (3H,s), 3.65 (2H,m), 3.83 (2 x 1H,s,OH), 4.47 (1H,s), 4.55 (1H,s).

Synthesis 7

The reaction of phenacyl chloride with thioacetic acid

Thioacetic acid (9 g, 0.12 mole) in THF (50 ml) was added dropwise to a freshly prepared solution of lithium diisopropylamide ⁸⁹ (25.70 g, 0.24 mole) in THF (340 ml) at (-78°C). The reagents were stirred for 15 minutes at that temperature and phenacyl chloride (18 g, 0.12 mole) in THF (50 ml) was added. The reagents were stirred for an hour at -78°C, quenched with ice cold 5% HCl (200 ml) and extracted with ether. The ether extracts were dried over anhydrous sodium sulphate and concentrated leaving a crude product

(22 g), a light brown oil of sharp smell, which was re-distilled to give phenacyl chloride (5.1 g, recovered 28%, b.p. 82°C-86°C/0.1 mm Hg) and S-phenacyl thioacetate (83) (2.3 g, 15%, b.p. 130°C/0.1 mm Hg). The following data were recorded for S-phenacyl thioacetate (83):

ν_{max} (liq. film), 3070, 2920, 1700, (C=O), 1650 (C=C)
 cm^{-1} ; δ_{H} 2.35 (3H,s), 4.37 (2H,s), 7.43-7.82 (5H,m,Ph),
 δ_{C} 30.2 (q), 36.7 (t), 128.7 (d), 129.0 (d), 129.4 (d), 135.9(s),
193.5 (s), 194.4 (s); m/z 195 (M^{++} , 12%) 77 (100).

Synthesis 8

The reaction of phenacyl thioacetate (83) with potassium t-butoxide in t-butyl alcohol. -

Phenacyl thioacetate (83) (1.5 g, 8 mmole) in t-butyl alcohol (4 ml) was added to a freshly prepared solution of t-BuOK in t-butyl alcohol (8 ml) (prepared from 8 mmole of K and t-BuOH, 8 ml) ¹¹⁶ at room temperature. The reagents were stirred for 3 hours and 5% HCl was added, until pH 6, the organic products were extracted with diethyl ether and dried (MgSO_4). The crude product (0.9 g) was purified by means of preparative TLC to give 1-phenyl-1,3-butanedione (85) (0.15 g, (12%)) and the recovered phenacyl thioacetate (83). The T.L.C. plate (10 cm x 10 cm x 2 mm)

with a fluorescent indicator (60F-254) was used, developing solvent consisted of a mixture of n-pentane:MeOH;i-propanol = 12:2:1.

1-phenyl-1,3-butanedione (85) ν_{\max} : (KBr) 3480 (OH), 3020 (C-H), 2840 (C-H), 1620 (C=O); δ_{H} 2.21 (3H,s), 6.19 (1H,s), 7.64 (5H,s); δ_{C} 25.8 (q), 96.8 (d), 127.1 (d), 128.8 (d), 132.4 (d), 135.1(s), 183.6(s), 193.8 (s); m/z (M^+ 162, 46%), 77 (100).

Synthesis 9

Ethyl-4-chloro-3-hydroxy-3-methylbutanoate (37). -

Reformatsky reaction of ethyl bromoacetate with monochloroacetone.

The Reformatsky reaction of ethyl bromoacetate with monochloroacetone was carried out as described by W. Epstein. ⁹³

The analytical data for the product, ethyl-4-chloro-3-hydroxy-3-methylbutanoate (87), obtained with an average yield of 35%, were found as follows:

ν_{\max} (liq. film) 3480, 3000, 1740 (C=O) cm^{-1} (lit. ⁹³
 ν_{\max} (liq. film) 3540, 1730 cm^{-1}); δ_{H} (60 MHz) 1.28 (3H, t, 6.2Hz, OCH_2CH_3), 1.35 (3H, s), 2.63 (2H,s), 3.65

(2H,s, CH₂Cl), 3.78 (1H,s,OH), 4.15 (q,2H, 6.2 Hz, -OCH₂CH₃)
(lit. ⁹³ for methyl ester (87) σ_{H} 1.35 (3H,s), 2.70
(2H,s), 3.68 (2H,s,CH₂Cl), 3.76 (3H,s,OCH₃), 3.91 (1H,s,OH));
 σ_{C} 14.2 (q), 25.2 (q), 42.2 (t), 52.04 (t), 60.9 (t),
71.2 (s), 172.2 (s,C=O).

Synthesis 10

Preparation of 4-hydroxy-3-methylbut-2-enoic acid γ - lactone (86) and methyl-E-4-hydroxy-3-methylbut-2-enoate (88)

A. Preparation of 20% HCl/MeOH solution

Hydrogen chloride ¹¹² was bubbled through absolute MeOH (cooled in an ice bath) until saturation; and (1 ml) aliquot was withdrawn with a pipette, diluted with H₂O to 25 ml and the HCl concentration was estimated by titrating with 0.25 M Na₂CO₃ in the presence of methyl-red indicator. By the end of the titration the colour of the titrant had changed to yellow. The HCl/MeOH solution was diluted (4.6 times) with absolute MeOH in order to obtain the required concentration of 20% HCl in MeOH.

B. 20% w/w solution of KOH in absolute MeOH (15.3 ml) was cooled to 0°C and ethyl 4-chloro-3-hydroxy-3-methylbutanoate (87) (6 g, 0.03 mole) was added dropwise. The reagents were

stirred at this temperature for 1 hour. The reaction mixture was acidified with 20% HCl/MeOH (pH 3, universal pH indicator) and then solid NaHCO₃ was added (pH 7). The precipitates were separated and some diethyl ether (10 ml) was added to the filtrate, the precipitate was filtered off. The filtrate was dried over anhydrous magnesium sulphate, the solvent was evaporated off and the yellow, oily crude product (3.8 g) was redistilled to give a fraction (1.5 g, 42%) of b.p. 64°C-70°C/0.6 mm Hg. The integrals in the ¹H n.m.r. spectrum showed that the fraction contained 4-hydroxy-3-methylbut-2-enoic acid γ -lactone (86) (37%) and methyl-E-4-hydroxy-3-methylbut-2-enoate (88) (63%).

4-hydroxy-3-methylbut-2-enoic acid γ -lactone (86):

δ_H (60 MHz) 2.11 (3H,s), 4.68 (2H,s), 5.80 (1H,s),
(lit. ⁹³ δ_H 2.12 (3H,s), 4.73 (2H,s), 5.78 (1H,s));

methyl-E-4-hydroxy-3-methylbut-2-enoate (88): δ_H (60 MHz)
2.04 (3H, s), 3.42 (1H,s,OH), 3.65 (3H,s,OCH₃), 4.12 (2H,s),
5.92 (1H,s) (lit. ⁹³ δ_H 2.09 (3H,s), 3.69 (3H,s,OCH₃),
4.15 (2H,s), 4.94 (1H,s,OH), 6.02 (1H,s)).

Synthesis 11

Preparation of 4-hydroxy-3-methylbut-2-enoic acid γ -lactone (86) by photochemical reaction. - 93

A mixture (3.75 g) of 4-hydroxy-3-methylbut-2-enoic acid γ -lactone (86) and methyl-E-4-hydroxy-3-methylbut-2-enoate (88) and a catalytic amount (1.5 ml) of 20% HCl/MeOH (prepared as described in synthesis 10) in absolute methanol (275 ml) were placed in the U.V. reaction vessel. The reaction mixture was irradiated with U.V. light, wavelength 340 nm, for 1 hour. The solution was then poured into a round bottom flask and neutralized with solid sodium bicarbonate. The solvent was evaporated to dryness and a residue in H₂O was extracted with diethyl ether (4 x 40 ml). The ether extracts were dried over anhydrous magnesium sulphate and the solvent was removed on a rotary evaporator. The ¹H n.m.r. spectra showed that the crude product (2.8 g) contained a mixture of 4-hydroxy-3-methylbut-2-enoic acid γ -lactone (86) and methyl-E-4-hydroxy-3-methylbut-2-enoate (88) in the ratio 82:18. Distillation gave 0.8 g (36%) of pure γ -lactone (86), b.p. 52°C-59°C/0.6 mm Hg (lit. ⁹³ 58°C-62°C/0.6 mm Hg). ν_{max} 2980, 1750, 1650 cm⁻¹, (lit. ⁹³ ν_{max} (liq. film) 1750, 1640 cm⁻¹); δ_{H} (60 MHz) 2.11 (3H,s), 4.68 (2H,s), 5.80 (1H,s), (lit. ⁹³ δ_{H} 2.12 (3H,s), 4.73 (2H,s), 5.78 (1H,s)); δ_{C} 14.6 (q), 77.4 (t), 117.1 (d), 166.6 (s), 174.0 (s).

Synthesis 12

Preparation of S-(2-oxopropyl)-thioacetate (93)

To a solution of thioacetic acid (7.6 g, 0.1 mole) and potassium carbonate (13.8 g, 0.1 mole) in acetone (90 ml), a solution of chloroacetone (9.2 g, 0.1 mole) in acetone (90 ml) was added dropwise over a period of 20 minutes. The reaction mixture was cooled in an ice bath in order to keep the temperature below (+ 35°C). The reagents were stirred overnight. The precipitate was filtered off.. Acetone was removed on the rotary evaporator and some ether (80 ml) was added to the oily residue. The product in ether was washed with water (3 x 20 ml) and dried over anhydrous magnesium sulphate. Solvent was removed and the crude product (brown and oily, 11 g) was purified by distillation to yield (8.1 g 61%) S-(2-oxopropyl)-thioacetate (93), b.p. 60°C-61.5°C/0.3 mm Hg. ν_{\max} (liq. film) 2930 (C-H), 1720 (C=O), 1440 (C-H), 640 (C-S) cm^{-1} ; δ_{H} 2.24 (3H,s), 2.35 (3H,s), 3.73 (2H,s).

Synthesis 13

Preparation of triethylphosphonoacetate (91). ¹⁰⁵

A mixture of triethylphosphite (0.2 mole) and ethyl bromoacetate (0.2 mole) was slowly heated to 140°C and ethyl bromide, a side product, was collected in a Dean and Stark apparatus; the reaction was complete when no more ethyl bromide was collected. Triethylphosphonoacetate was purified by distillation, b.p. 118°C/0.7 mm Hg (lit. ¹⁰⁵ b.p. 142°-146°/9 mm Hg); yield 84%; δ_{H} (60 MHz) 1.32 (9H,m), 2.92 (2H,d, $^3\text{J}_{\text{P-H}}$ 21 Hz), 4.15 (6H,m).

Synthesis 14

Preparation of ethyl-(E and Z)-4-chloro-3-methylbut-2-enoate (90). - ⁹⁴

To a suspension of sodium hydride (0.96 g, 0.02 mole) in benzene (8 ml) triethylphosphonoacetate (7.17 g, 0.032 mole) was added dropwise and the temperature was kept within the range 30°-35°C. The reagents were then stirred for 45 minutes at room temperature. The solution became clear and monochloroacetone (1.8 g, 0.02 mole) was added dropwise at 20°C-30°C. The colour of the reaction mixture changed from yellow to brown during the addition of monochloroacetone

and a gelatinous precipitate formed. The reagents were then heated to 60°C for 5 minutes, cooled to room temperature, quenched with water (30 ml) and extracted with diethyl ether (5 x 20 ml). The ether extracts were combined and dried over anhydrous magnesium sulphate, solvent was removed on a rotary evaporator and a yellow crude product was obtained (3.58 g). Distillation gave 1.4 g (44%) of ethyl-(E and Z)-4-chloro-3-methylbut-2-enoate (90), b.p. 80°C/0.4 mm Hg. E-isomer (90): δ_{H} 1.31 (3H,t, J 8.2 Hz, -OCH₂CH₃), 2.22 (3H,s), 4.18 (2H,q, J 8.2 Hz -OCH₂CH₃), 4.65 (2H,s), 5.99 (1H,s); Z-isomer (90): δ_{H} 1.31 (3H,t, J 8.2 Hz, -OCH₂CH₃), 2.02 (3H,s), 4.02 (2H,s), 4.18 (2H,q, J 8.2 Hz, -OCH₂CH₃), 5.80 (1H,s); E-isomer (90): δ_{C} 14.4 (q), 16.6 (q), 43.1 (t), 60.2 (t,O-CH₂-), 119.6 (d), 152.6 (s), 165.9 (s,C=O); Z-isomer (90): δ_{C} 14.4 (q), 17.6 (q), 42.2 (t), 60.2 (t,O-CH₂-), 119.2 (d), 152.6 (s), 165.4 (s,C=O).

Synthesis 15

Preparation of ethyl-(E and Z)-4-acetylthio-3-methylbut-2-enoate (92). -

To a mixture of thioacetic acid (0.61 g, 0.08 mole) and potassium carbonate (1.10 g, 0.08 mole) in acetone (8 ml) ethyl-(E and Z)-4-chloro-3-methyl-2-butenate (1.30 g,

0.08 mole) in acetone (18 ml) was added dropwise at room temperature. The reaction mixture was cooled in an ice bath, to keep the temperature below 30°C. The reagents were then stirred at room temperature overnight. The precipitate was filtered off. The filtrate was concentrated and a crude product was redissolved in diethyl ether (100 ml), washed with water (2 x 15 ml) and the ether layer dried over anhydrous magnesium sulphate. Diethyl ether was then removed on a rotary evaporator and an oily, brown product (1.43 g) was purified by distillation to give ethyl-(E and Z)-4-acetylthio-3-methylbut-2-enoate (92), b.p. 92°C/0.08 mm Hg, yield 0.68 g, 41%. E-isomer (92) δ_{H} 1.22 (3H,t-OCH₂CH₃), 2.18 (3H,s-SCOCH₃), 2.02 (3H,s), 3.51 (2H,s), 4.14 (2H,q,-OCH₂CH₃), 5.90 (1H,s); Z-isomer (92) δ_{H} 1.22 (3H,t,-OCH₂CH₃), 1.92 (3H,s,-SCOCH₃), 2.02 (3H,s), 4.13 (2H,s), 4.14 (2H,q,OCH₂CH₃), 5.74 (1H,s); E-isomer (92) δ_{C} 14.29 (q), 17.79 (q), 30.12 (q), 37.93 (t,S-CH₂), 59.83 (t,-OCH₂-), 118.67 (d,=CH-), 153.25 (s), 166.22 (s,-CO-OR), 194.22 (s,-SCOCH₃); Z-isomer (92) δ_{C} 14.29 (q), 23.90 (q), 30.12 (q), 30.34 (t,S-CH₂), 59.83 (t,-OCH₂), 119.00 (d,=CH-), 154.16 (s), 166.22 (s,-CO-OR), 195.28 (s,-SCOCH₃).

0.08 mole) in acetone (18 ml) was added dropwise at room temperature. The reaction mixture was cooled in an ice bath, to keep the temperature below 30°C. The reagents were then stirred at room temperature overnight. The precipitate was filtered off. The filtrate was concentrated and a crude product was redissolved in diethyl ether (100 ml), washed with water (2 x 15 ml) and the ether layer dried over anhydrous magnesium sulphate. Diethyl ether was then removed on a rotary evaporator and an oily, brown product (1.43 g) was purified by distillation to give ethyl-(E and Z)-4-acetylthio-3-methylbut-2-enoate (92), b.p. 92°C/0.08 mm Hg, yield 0.68 g, 41%. E-isomer (92) δ_{H} 1.22 (3H,t-OCH₂CH₃), 2.18 (3H,s-SCOCH₃), 2.02 (3H,s), 3.51 (2H,s), 4.14 (2H,q,-OCH₂CH₃), 5.90 (1H,s); Z-isomer (92) δ_{H} 1.22 (3H,t,-OCH₂CH₃), 1.92 (3H,s,-SCOCH₃), 2.02 (3H,s), 4.13 (2H,s), 4.14 (2H,q,OCH₂CH₃), 5.74 (1H,s); E-isomer (92) δ_{C} 14.29 (q), 17.79 (q), 30.12 (q), 37.93 (t,S-CH₂), 59.83 (t,-OCH₂-), 118.67 (d,=CH-), 153.25 (s), 166.22 (s,-CO-OR), 194.22 (s,-SCOCH₃); Z-isomer (92) δ_{C} 14.29 (q), 23.90 (q), 30.12 (q), 30.34 (t,S-CH₂), 59.83 (t,-OCH₂), 119.00 (d,=CH-), 154.16 (s), 166.22 (s,-CO-OR), 195.28 (s,-SCOCH₃).

Synthesis 16

Preparation of 4-mercapto-3-methylbut-2-enoic acid γ -thiolactone (64). -

To a solution of HCl in absolute methanol (30 ml, prepared from 20% HCl/MeOH (5 ml) and 25 ml of absolute methanol), ethyl-(E and Z)-4-acetylthio-3-methylbut-2-enoate (4.5 g, 0.02 mole) was added dropwise at room temperature over a period of 15 minutes. The reagents were refluxed overnight. Solid sodium bicarbonate was then added to pH7. Precipitate was filtered off and methanol was removed on a rotary evaporator. The crude mixture was dissolved in diethyl ether (30 ml) and extracted with H₂O (2 x 15 ml). The organic layer was dried over anhydrous magnesium sulphate. Solvent was removed on the rotary evaporator. Distillation gave 20% of 4-mercapto-3-methylbut-2-enoic acid γ -thiolactone (64), b.p. 72°C-80°C/0.3 mm Hg (lit. ⁷⁴ b.p. 69°C-70°C/0.9 mm Hg); ν_{max} (liq. film) 3000, 2960, 1680 (C=O), 1640 (C=C) cm⁻¹, δ_{H} (220MHz) 2.22 (1H,m, J_{3,6} 1.4Hz, J_{5,6} 0.7 Hz), 4.01 (1H,m, J_{5,6} 0.7 Hz, J_{3,5} 1.4Hz, 6.15 (1H,m, J_{3,6} 1.4 Hz, J_{5,3} 1.4 Hz) (lit. ⁷⁴ δ_{H} 2.23 (1H,s, J_{5,6} 0.75 Hz, J_{3,6} 1.5 Hz), 4.02 (1H,m, J_{5,6} 0.7 Hz, J_{3,5} 1.5 Hz), 6.15 (1H,m, J_{3,6} 1.5 Hz, J_{3,5} 1.5 Hz); δ_{C} 18.9 (q), 41.0 (t), 128.2 (d,=CH-), 168.1 (s), 199.2 (s,C=O);

λ_{\max} (MeOH) 224 nm ($\epsilon:1.6 \times 10^3$), 266 nm ($\epsilon:3.8 \times 10^2$); m/z 114 (M^+ , 100%).

Synthesis 17

(2Z) (4Z)-4-mercapto-3-methyl-5-phenylpenta-2,4-dienoic acid γ -thiolactone (96). - 78

A solution of 4-mercapto-3-methylbut-2-enoic acid γ -thiolactone (64) (1.6 g, 0.014 mole) and benzaldehyde (1.48 g, 0.014 mole) in absolute methanol (14 ml) was cooled to (+ 5°C) (ice bath) and HCl-gas (dried with conc. H_2SO_4) was bubbled through. After an hour the reaction mixture was allowed to warm up to room temperature. The solvent was removed and the yellow crystalline (2Z) (4Z)-4-mercapto-3-methyl-5-phenylpenta-2,4-dienoic acid γ -thiolactone (96) was recrystallized from MeOH, m.p. 61.5°C-63°C, yield 57% ν_{\max} (KBr) 3040, 2930, 1680, 1450 cm^{-1}
 σ_H 2.28 (3H,s), 6.11 (1H,s), 7.07 (1H,s), 7.38 (5H,m);
 σ_C 14.9 (q), 127.7 (d), 129.0 (d, ortho-C), 129.4 (d), 129.7 (d, $C_6H_5-CH=$), 130.1 (d, meta-C), 135.0 (s), 136.5 (s, $=C''-S$), 161.0 (s), 194.3 (s, $C=O$); λ_{\max} (MeOH) 341 nm ($\epsilon:3.2 \times 10^4$), 238 nm ($\epsilon:6.6 \times 10^2$); m/z (M^+ 202, 100%); Found: C, 69.6; H, 5.1. $C_{12}H_{10}OS$ requires C, 71.2; H, 5.0%.

Synthesis 18

(2Z)(4Z)-4-mercapto-4-methyl-5-(2',4',6'-trimethylphenyl)
penta-2,4-dienoic acid γ -thiolactone (96). - 78

HCl gas was dried by bubbling through concentrated H_2SO_4 .
Absolute ethanol was used for the reaction.

A solution of mesitaldehyde (0.74 g, 5 mmole) and 4-methyl-4-mercapto-2-butenic acid γ -thiolactone (64) (0.55 g, 5mmole) in absolute ethanol (7.5 ml) was stirred at $0^\circ C$ and HCl was bubbled through for 1 hour. The reaction mixture was allowed to warm up to room temperature and the solvent was removed on a rotary evaporator. The product was recrystallized from methanol to give 0.34 g (28%) of (2Z)(4Z)-4-mercapto-4-methyl-5-(2',4',6'-trimethylphenyl) penta-2,4-dienoic acid γ -thiolactone (96) (yellow crystals) m.p. $107.2^\circ C - 109.1^\circ C$ ν_{max} (KBr) 3000, 2940, 1680, 1600 cm^{-1} ; δ_H 2.18 (6H,s), 2.28 (3H,s), 2.38 (3H,s), 6.14 (1H,s), 6.88 (2H,s), 7.18 (1H,s); δ_C 14.5 (q), 20.2 (q, 2 x meta CH_3), 21.0 (q, para- CH_3), 128.4 (d, meta-C), 128.9 (d), 129.9 (d), 131.9 (s), 135.5 (s, 2 x ortho-C), 137.9 (s, =C'-S), 141.9 (s), 158.6 (s), 194.1 (s, C=O); λ_{max} (MeOH) 341 nm ($\epsilon: 1.1 \times 10^3$), 267 nm ($\epsilon: 1.1 \times 10^3$), 216 nm ($\epsilon: 1.4 \times 10^3$); m/z . 244 (M^+ , 64%), 229 (100); Found C, 74.0; H, 6.5; $C_{15}H_{16}OS$ requires C 73.8, H 6.4%.

Synthesis 19

(3Z)(5Z)-5-cyclohexyl-4-mercapto-4-methylpenta-2,4-dienoic acid γ -thiolactone (100). -

Cyclohexanecarboxaldehyde was purchased from Aldrich and was used without further purification (the purity of the compound was checked by ^1H n.m.r.). 4-mercapto-3-methylbut-2-enoic acid γ -thiolactone (64) was redistilled for the reaction.

A 5% solution of sodium hydroxide (0.02 mole) in methanol (20 ml) was stirred at room temperature and (4-mercapto-3-methylbut-2-enoic acid γ -thiolactone (64) (1 g, 0.08 mole) was added dropwise. Stirring was continued for 10 minutes at room temperature and cyclohexanecarboxaldehyde (1 g, 0.08 mole) was added dropwise. The reagents were stirred for another 20 minutes at room temperature. Some solvent was removed on a rotary evaporator and the residue was dissolved in Et_2O (90 ml), washed with diluted HCl (1 x 10 ml) with aqueous sodium bicarbonate (1 x 10 ml) then with H_2O (1 x 10 ml) and dried over anhydrous MgSO_4 . The ether was removed and a brown crude product (1.02 g) was chromatographed on a silica column ("Merck" product) using CH_2Cl_2 as an eluting solvent. A white crystalline product (3Z)(5Z)-5-cyclohexyl-4-mercapto-4-methylpenta-2,4-dienoic acid γ -thiolactone (100) was obtained (0.03 g, 1.8%). mp. (CHCl_3), 80.5°C - 83°C ,

ν_{\max} (KBr) 2920, 1640, 1670 cm^{-1} ; δ_{H} 1.1-2.2 (1H,m), 2.23 (3H,s), 6.11 (1H,s), 6.14 (1H,s);
 δ_{C} 14.6 (q), 25.5 (t, 2 x CH_2), 25.8 (t), 32.1 (t, 2 x CH_3), 42.1 (d, CH), 128.9 (d, =C-H), 136.9 (s), 138.2 (d), 159.4 (s), 193.7 (s, C=O); λ_{\max} (MeOH) 281 nm (ϵ : 1.5×10^3); m/z 208 (M^+ , 64%), 127(100);
Found: C, 69.6; H, 7.8 $\text{C}_{12}\text{H}_{16}\text{OS}$ requires C, 69.2; H, 7.8%.

Synthesis 20

4-Bromo-4-mercapto-3-methylbut-2-enoic acid γ -thio-
lactone (64). - 103

4-Mercapto-3-methylbut-2-enoic acid γ -thiolactone (64) (1.14 g, 0.01 mole) and N-bromosuccinimide (1.77 g, 0.01 mole) in carbon tetrachloride (30 ml) and a catalytic amount of benzoyl peroxide were refluxed for 1.5 hours. By the end of the reaction succinimide precipitate could be seen suspended in the solvent. Heating was stopped and the reaction mixture was allowed to cool down, the precipitate was filtered off and the filtrate was concentrated to give a brown crude product (0.99 g) which was purified by distillation, b.p. $74^\circ\text{C}/0.3$ mm Hg, to give 0.39 g (21%) of 4-bromo-4-mercapto-3-methylbut-2-enoic acid γ -thiolactone (64); ν_{\max} (liq. film) 3200, 2960, 1685, 1625,

780 cm^{-1} ; δ_{H} 2.32 (3H,d, J 3.6 1.47 Hz), 6.12 (1H,s), 6.19 (1H,q, J 3.6 1.47 Hz); δ_{C} 17.4 (q), 52.2 (d, CHBr), 129.2 (d, =CH), 168.2 (s), 194.2 (s, C=O); m/z 193 (M^+ , 6.3%), 113 (100), 85, (48).

Synthesis 21

2-Diethyl (4-methylthien-2-yl) phosphonate (104). -

4-Bromo-3-methylbut-2-enoic acid γ -thiolactone (103) (0.48 g, 2 mmole) was added to triethylphosphite (0.41 g, 2 mmole) and the reagents were heated to 120°C for 15 minutes and evolving ethyl bromide (0.1 ml), a side product, was collected in a receiver. The crude product (0.69 g) was distilled to give 2-diethyl (4-methylthien-2-yl) phosphonate (104), (0.35 g, 72%) b.p. 110°C-116°C/0.3 mm Hg. ν_{max} (liq. film) 3030, 2990, 1685 (C=C), 1290 (P=O), 1040 (P-O-C); δ_{H} 1.33 (3H, q, J 7.2 Hz, $-\text{OCH}_2\text{CH}_3$), 2.15 (3H,s), 4.25 (2H, t, J 7.2 Hz, $-\text{OCH}_2\text{CH}_3$), 6.36 (1H,s), 6.49 (1H,s); δ_{C} 15.9 (q), 16.2 (q), 16.5 (q), 65.0 (t), 65.3 (t), 111.7 (d), 115.7 (d), 134.9 (s), 152.6 (s); δ_{P} -6.50; m/z 250 (M^+ , 49%), 114 (100).

Synthesis 22

Trimethylsilyl (4-methylthien-2-yl)-ether (105). -

A solution of zinc chloride (0.14 g, 0.01 mole) in triethylamine (3.03 g, 0.01 mole) was stirred for one hour at room temperature and 4-methyl-3-thiolen-2-one (64) (1.14 g, 0.01 mole) in dry acetonitrile (8 ml) was added dropwise. After 5 minutes of stirring chlorotrimethylsilane (3.2 g, 0.02 mole) was added. The reaction mixture was stirred overnight, dry diethyl ether was next added, and precipitate was filtered off. The filtrate was concentrated and the colourless, yellowish liquid **product was obtained** (1.3 g). Distillation of the crude reaction product gave trimethylsilyl (4-methylthien-2-yl) ether (105), (0.56 g, 32%), b.p. 38°-40°C/0.6 mm Hg. δ_{H} (60 MHz), 6.09 (1H,s), 5.09 (1H,s), 2.11 (3H,s), 0.25 (9H,s); δ_{C} 159.8 (s,-C-O-), 134.9 (s), 111.6 (d), 107.9 (d), 16.7 (q), -0.3 (q).

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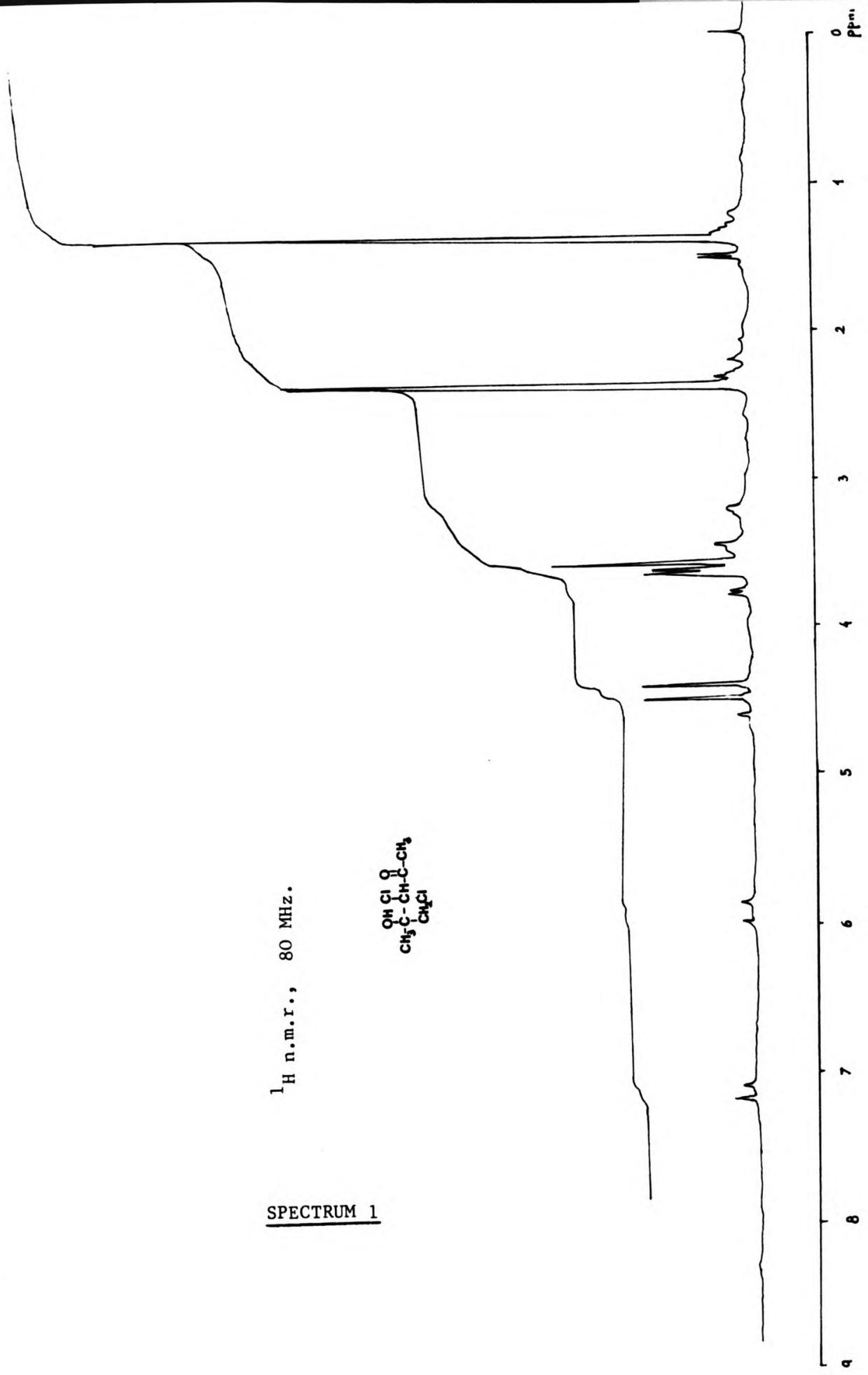
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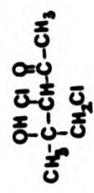
A P P E N D I X

SPECTRUM 1

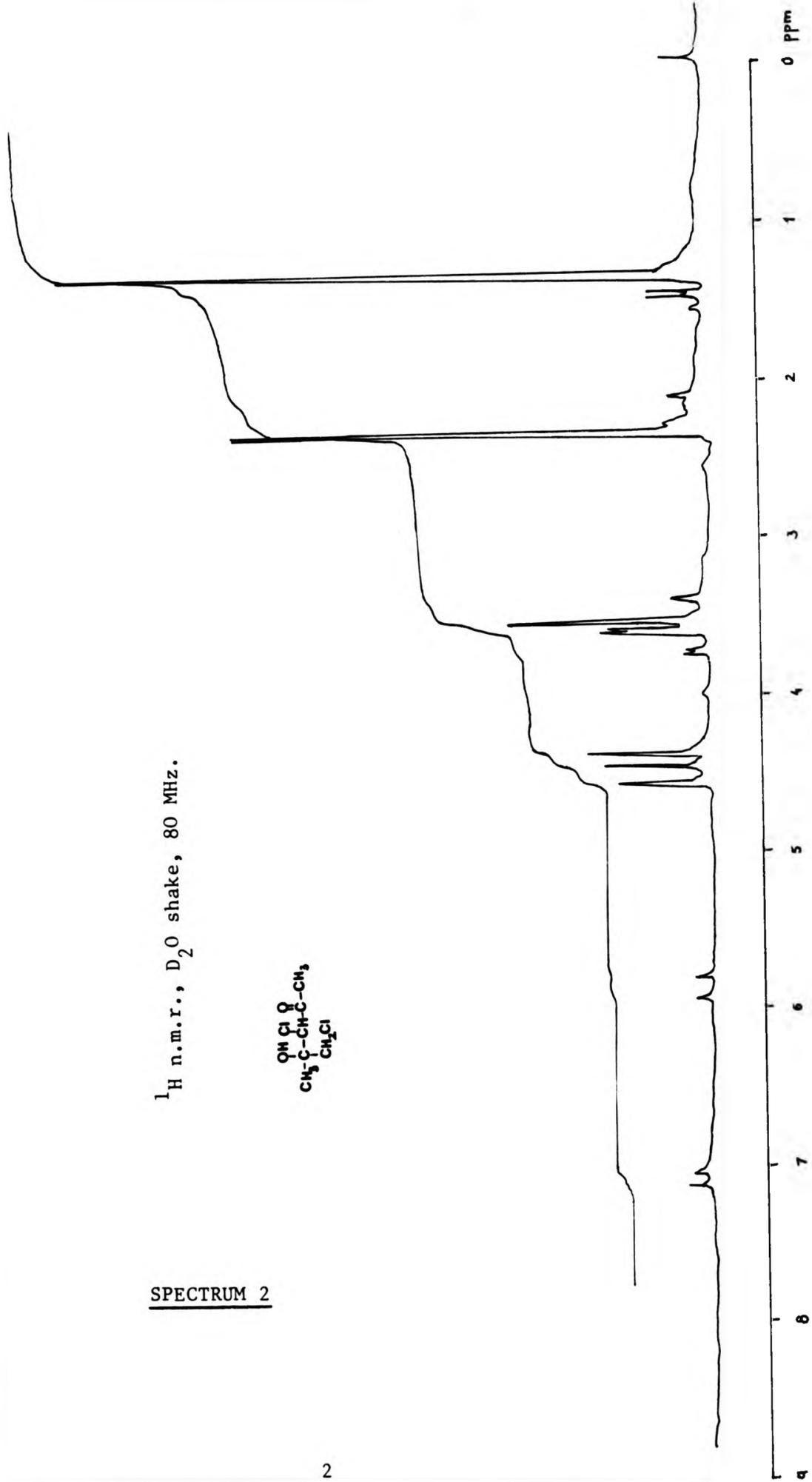
^1H n.m.r., 80 MHz.



^1H n.m.r., D_2O shake, 80 MHz.

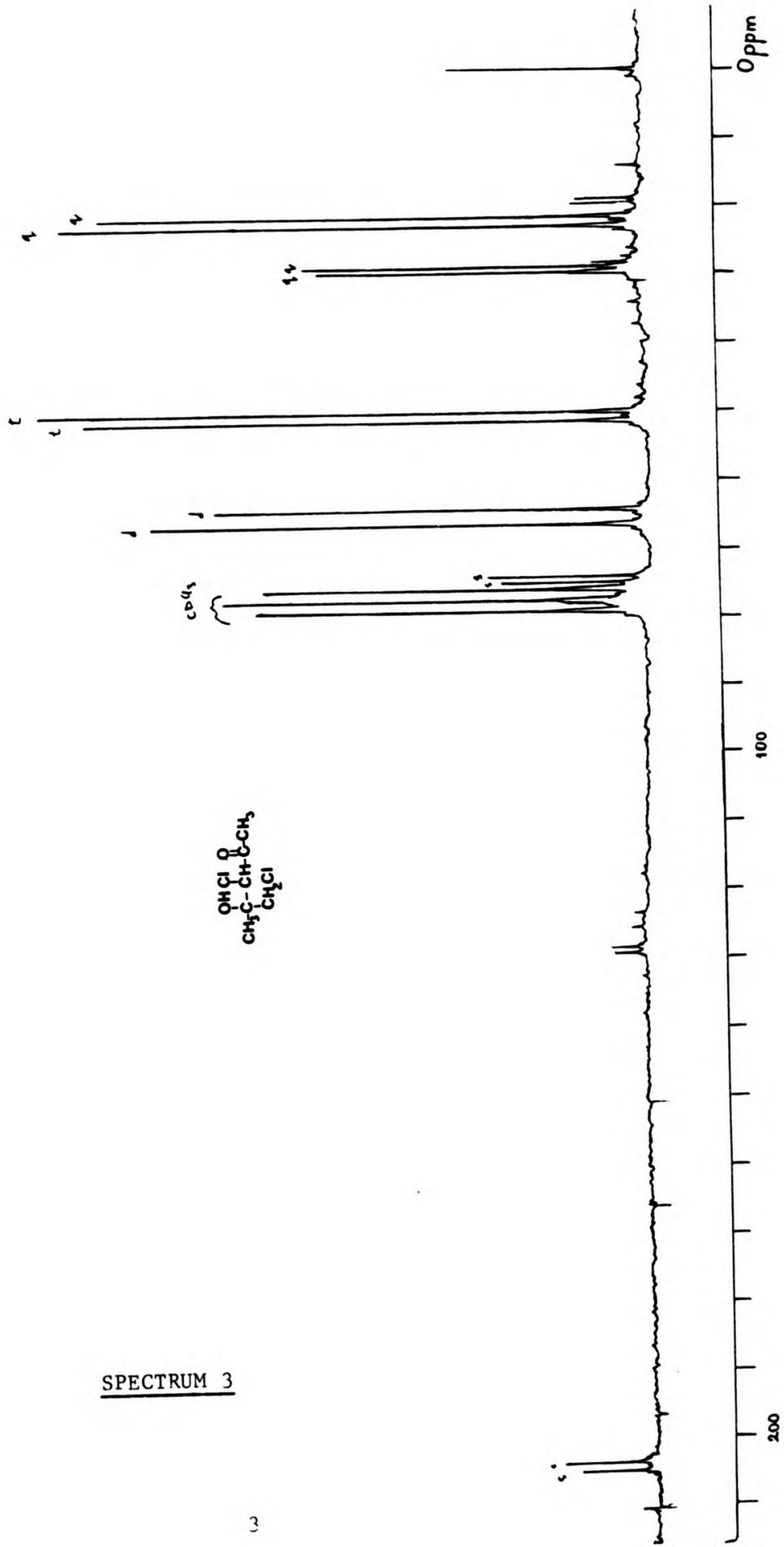


SPECTRUM 2

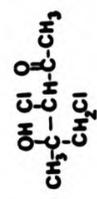


^{13}C n.m.r., broad band proton decoupled spectrum, 20 MHz.

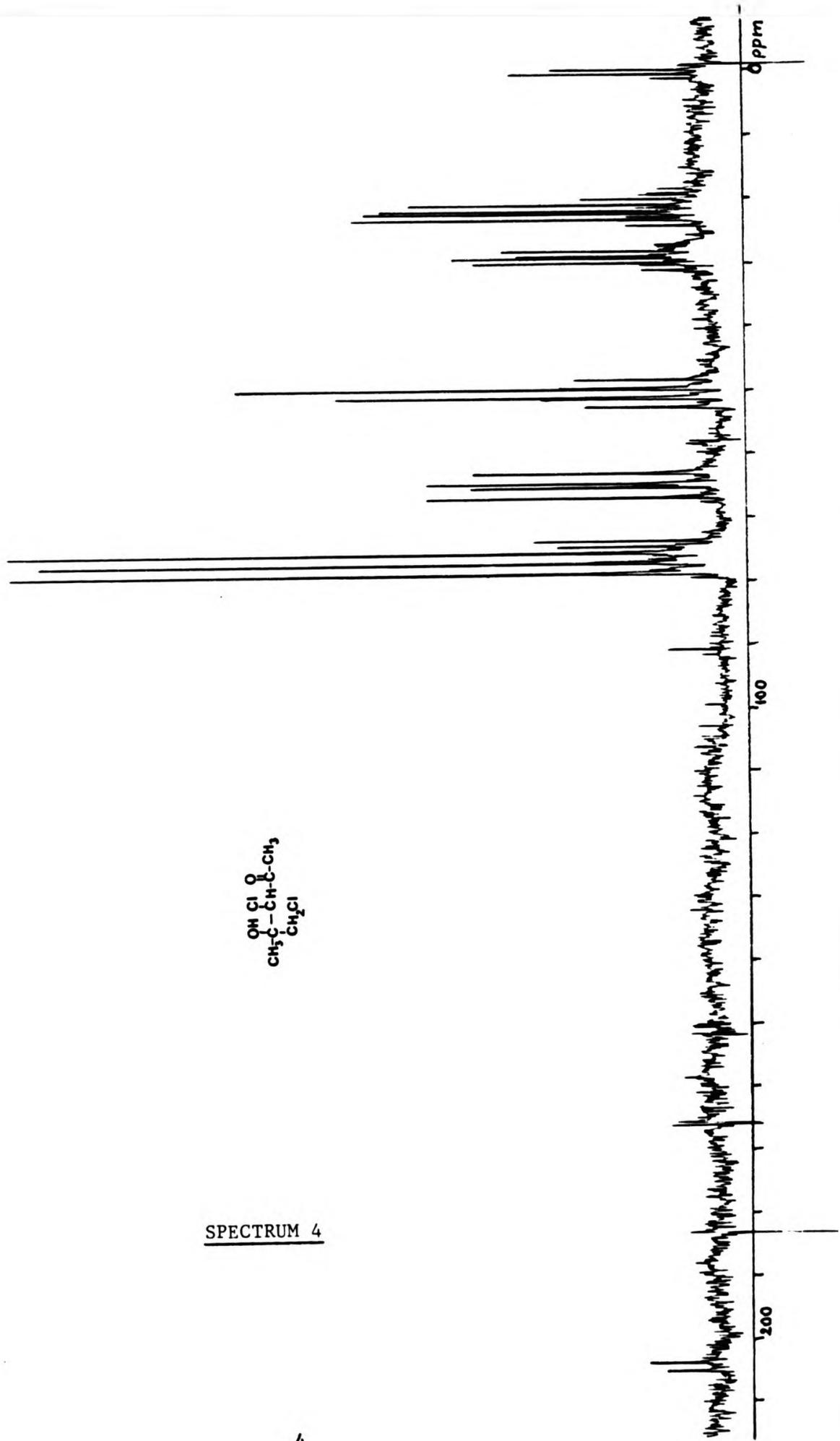
SPECTRUM 3

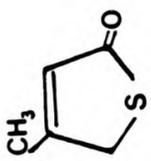


^{13}C n.m.r., s.f.o.r.d., 20 MHz.



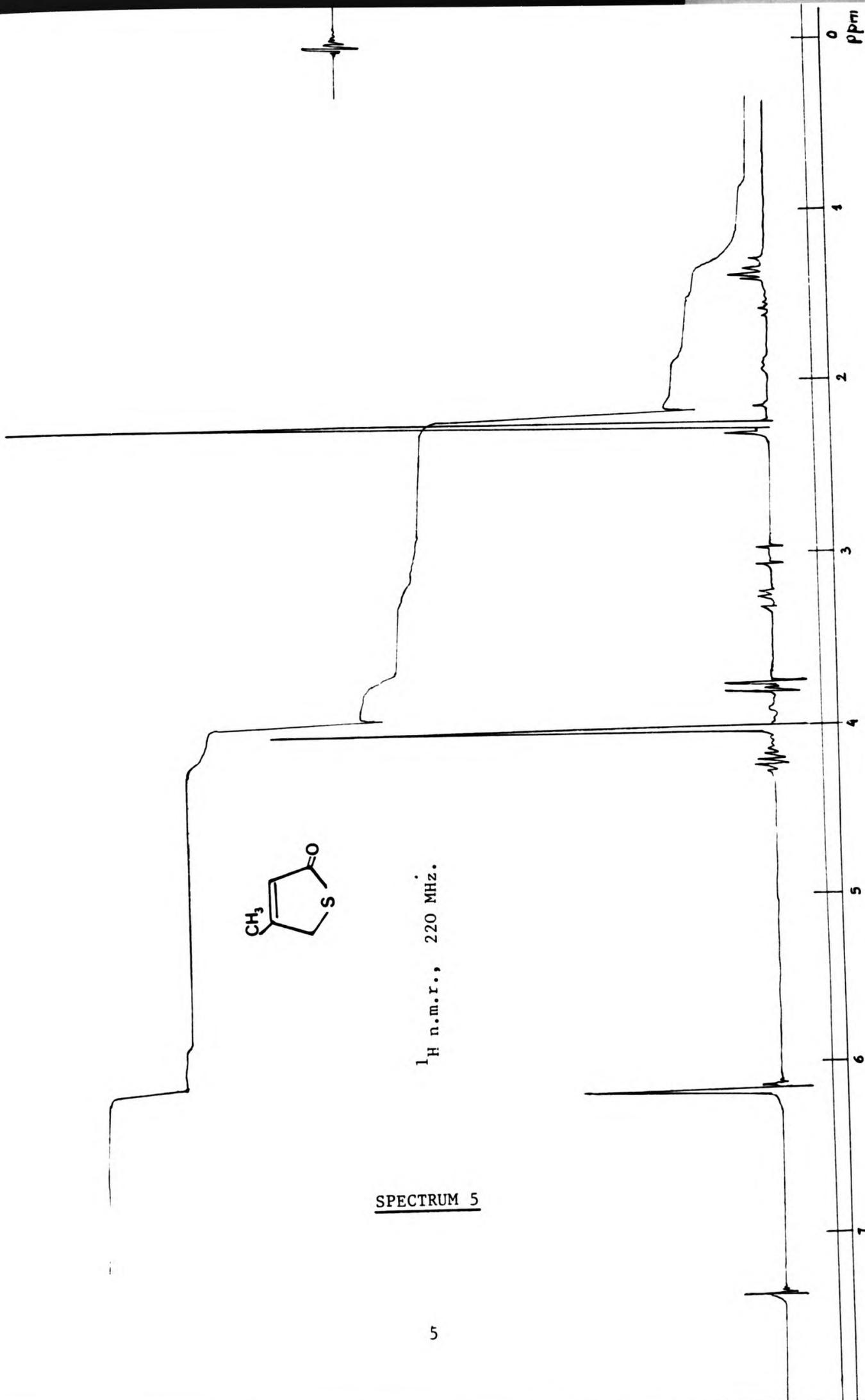
SPECTRUM 4



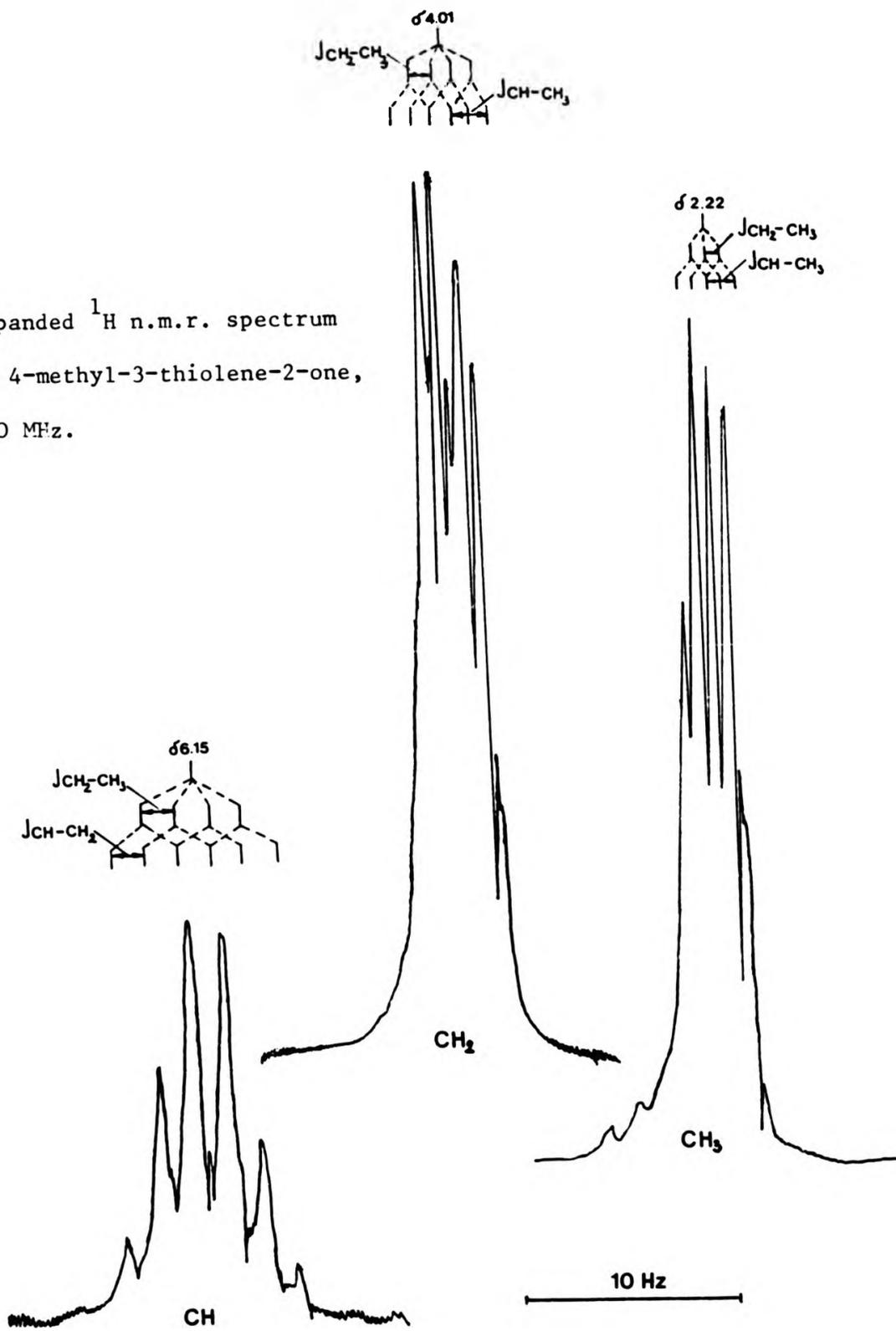


^1H n.m.r., 220 MHz.

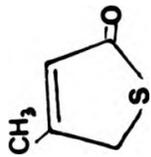
SPECTRUM 5



Expanded ^1H n.m.r. spectrum
of 4-methyl-3-thiolene-2-one,
220 MHz.

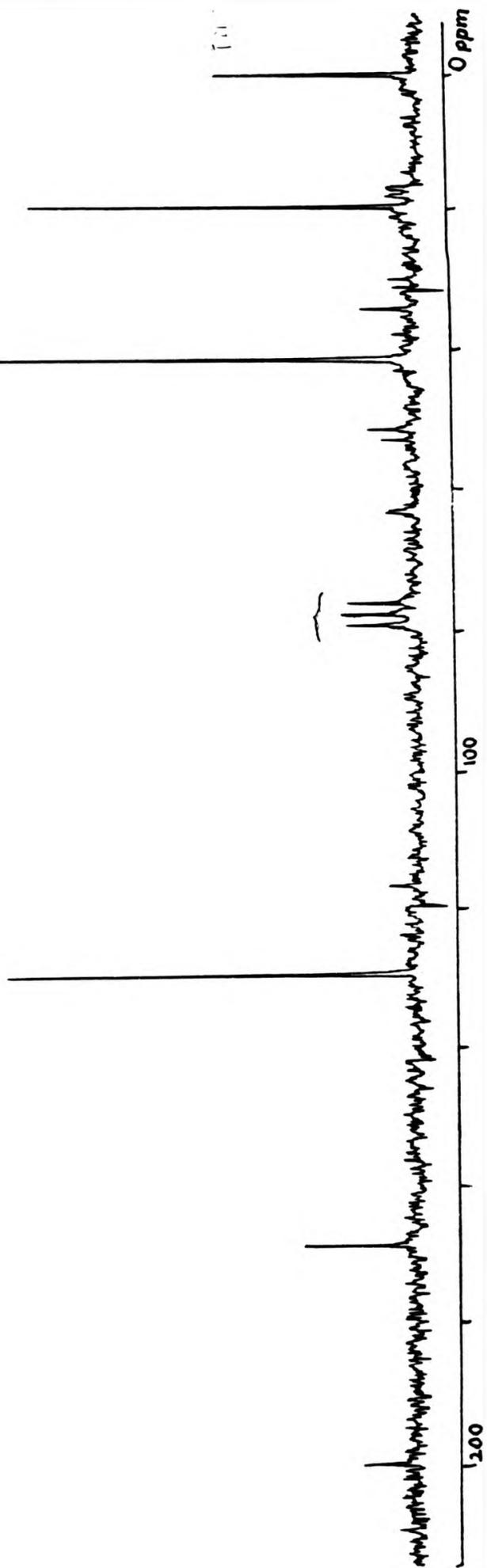


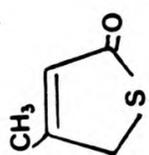
SPECTRUM 6



SPECTRUM 7

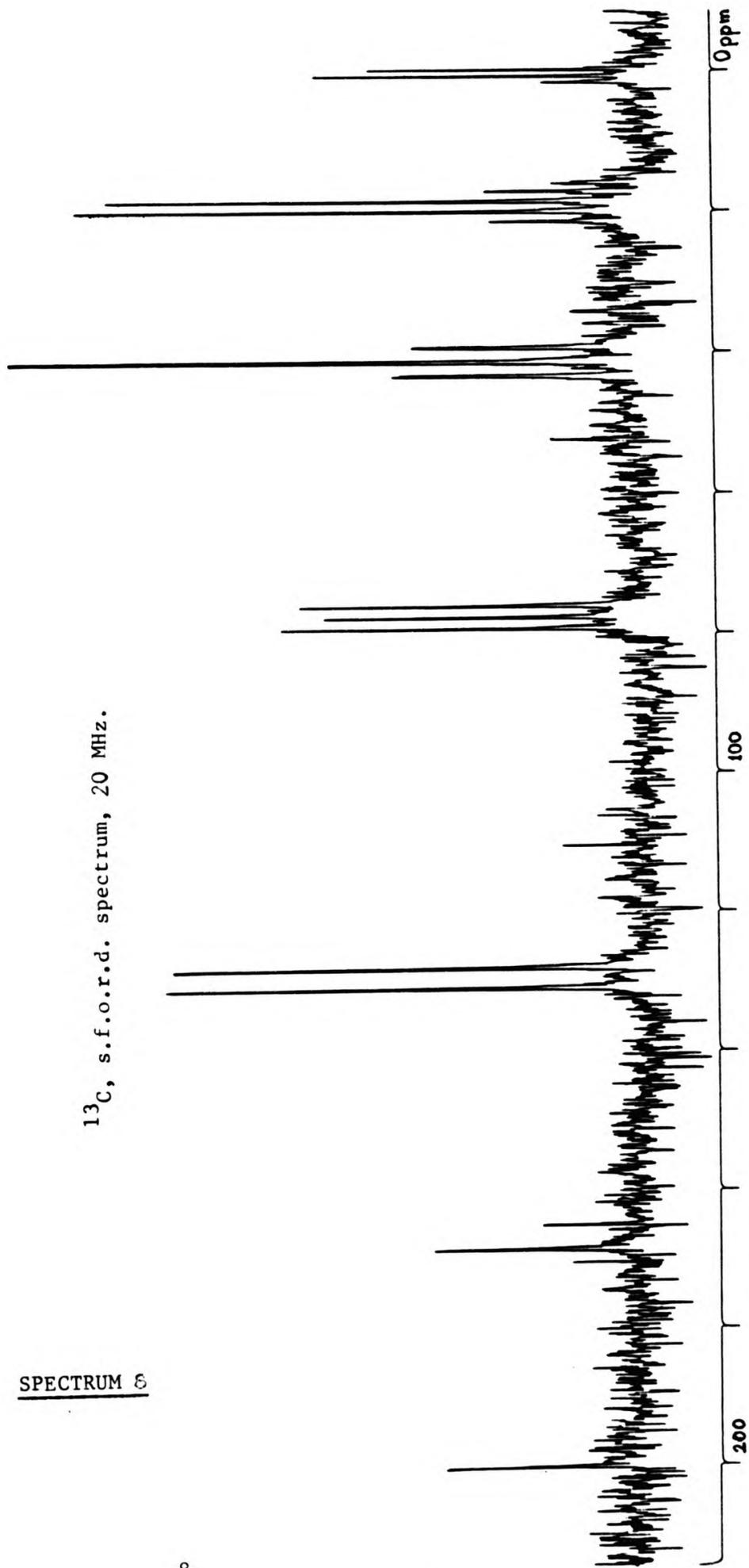
^{13}C n.m.r., broad band proton decoupled spectrum, 20 MHz.

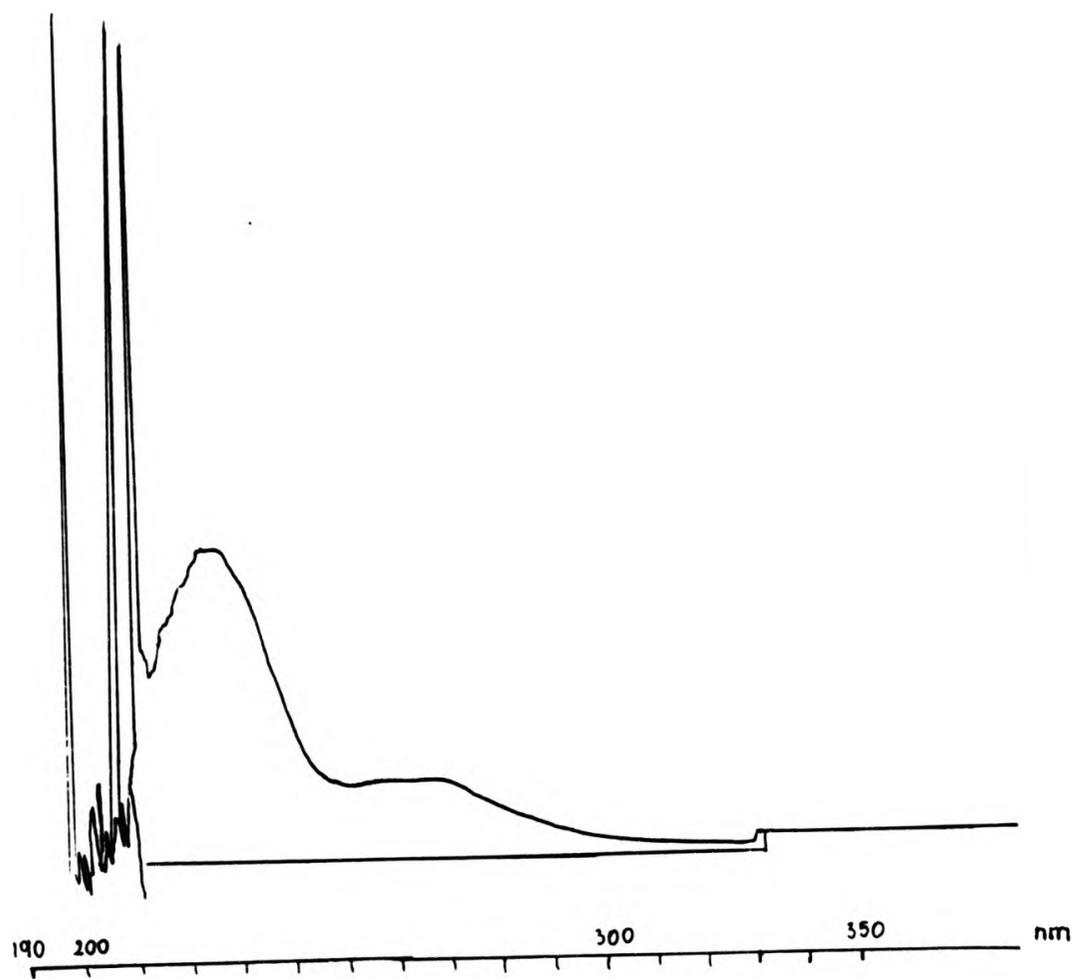




SPECTRUM 6

¹³C, s.f.o.r.d. spectrum, 20 MHz.

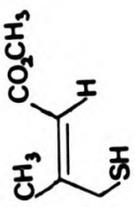




$\lambda_{\max} = 224 \text{ nm} \quad E_1: 1.6 \times 10^3$
 $\lambda_{\max} = 266 \text{ nm} \quad E_2: 3.8 \times 10^2$

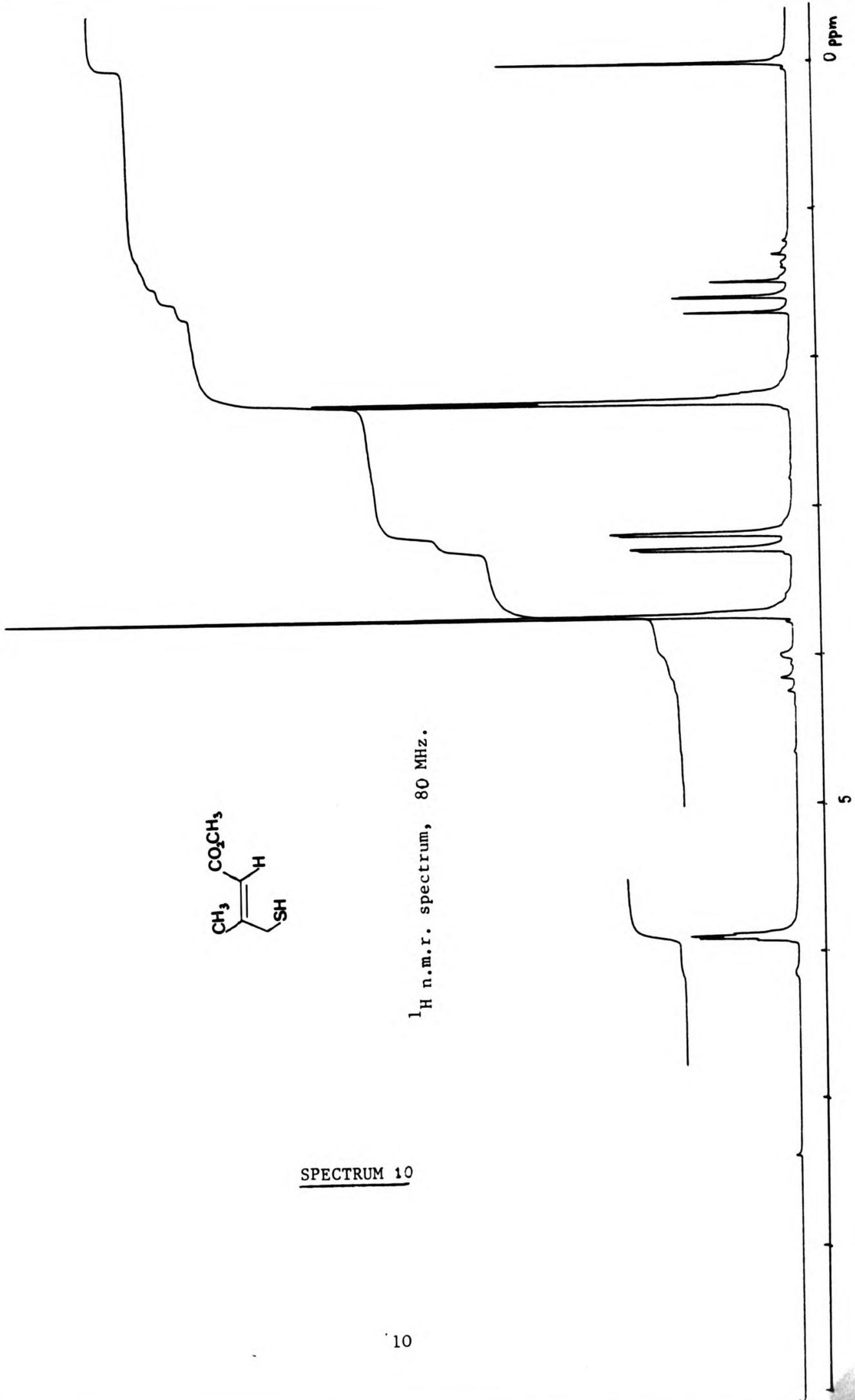
U.V. spectrum of 4-methyl-3-thiolene-2-one (64).

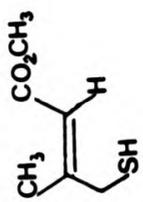
SPECTRUM 2



¹H n.m.r. spectrum, 80 MHz.

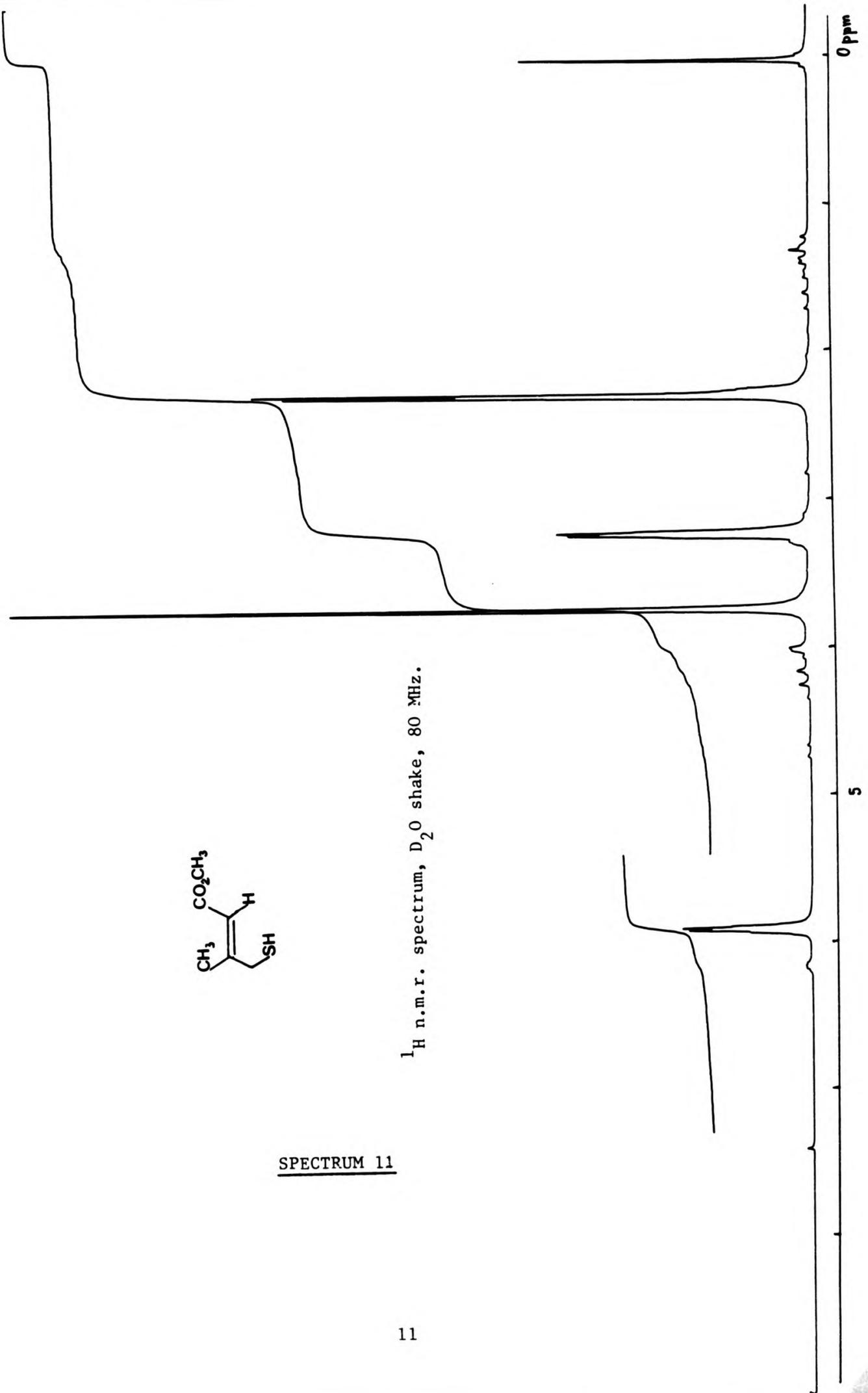
SPECTRUM 10





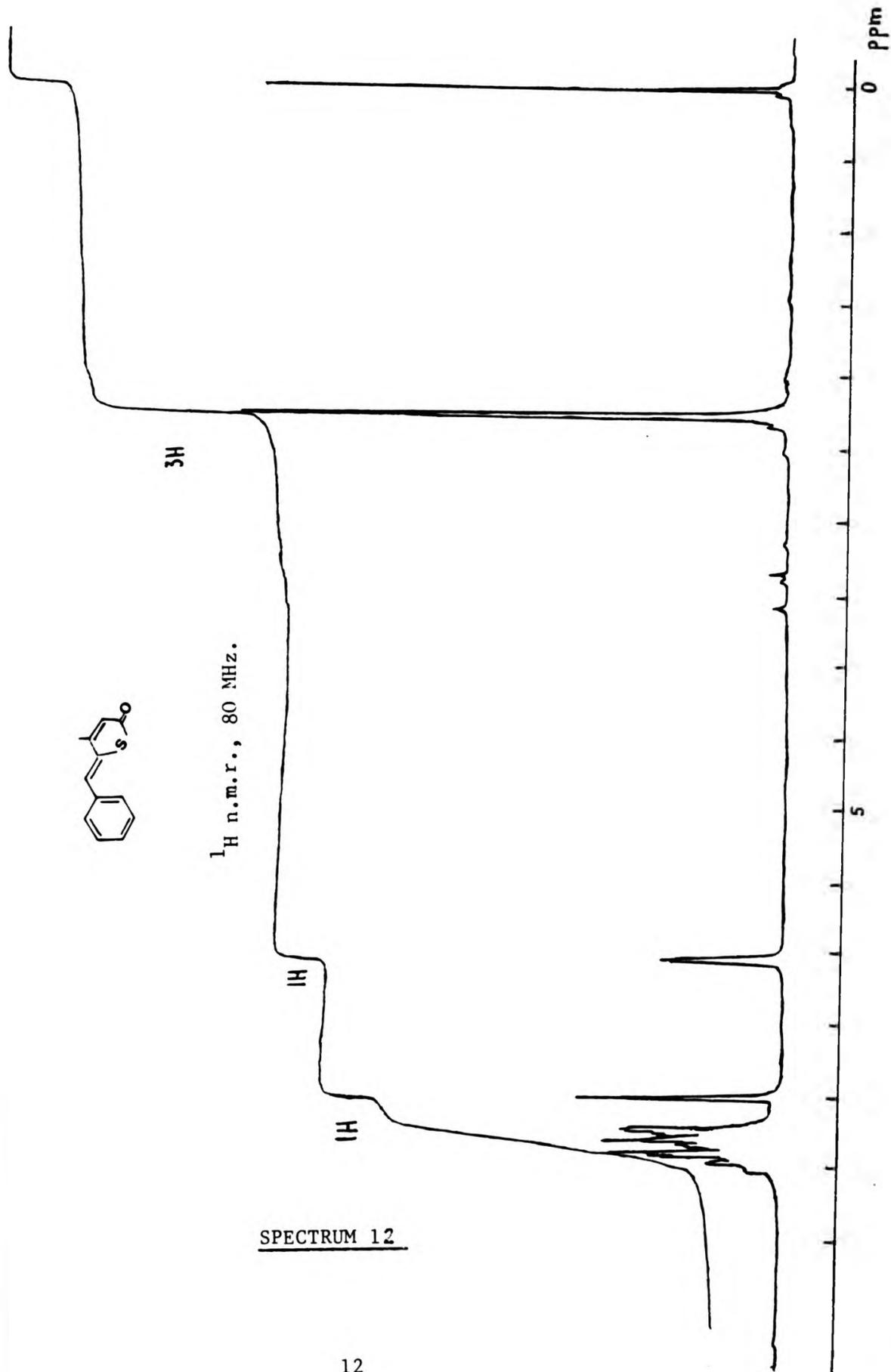
SPECTRUM 11

¹H n.m.r. spectrum, D₂O shake, 80 MHz.





^1H n.m.r., 80 MHz.

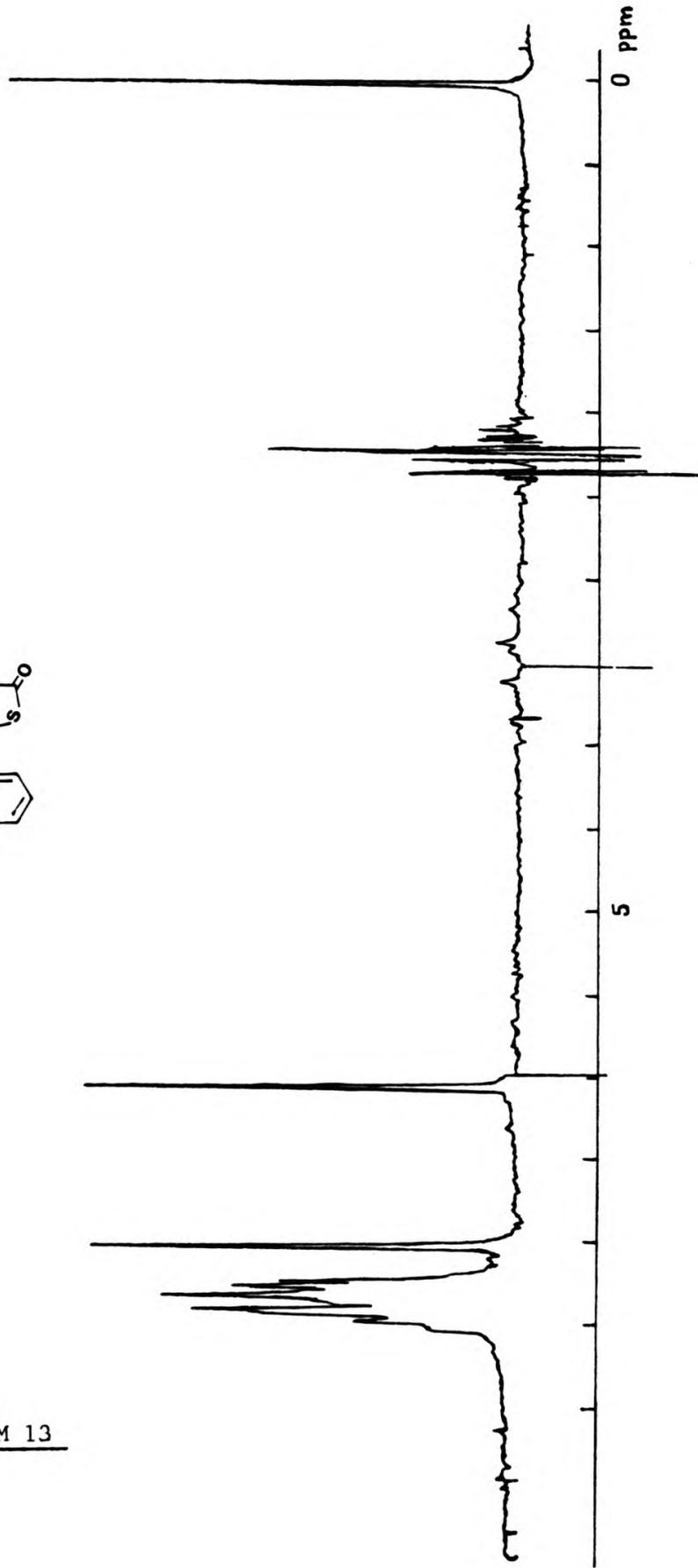


SPECTRUM 12

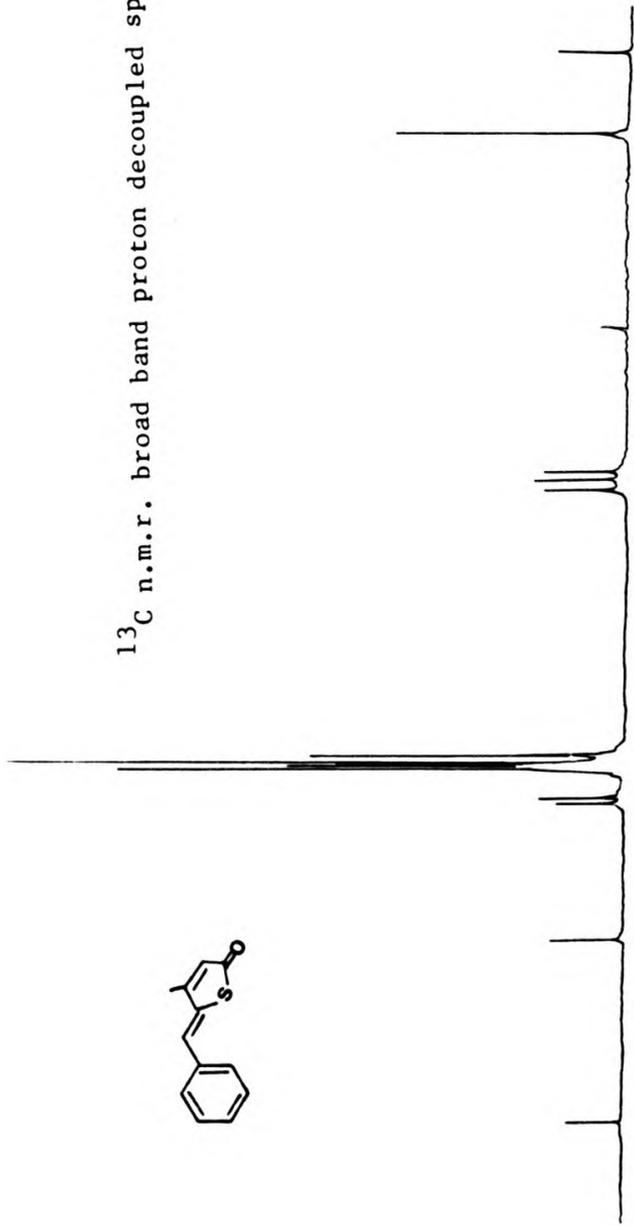
^1H n.m.r. double resonance experiment, 80 MHz.



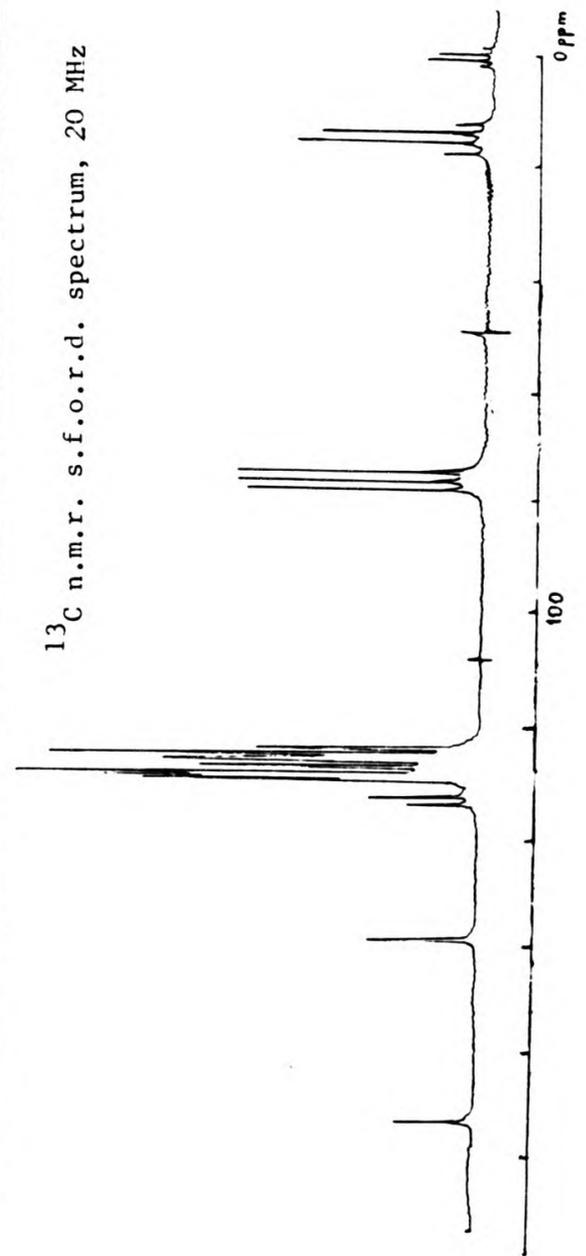
SPECTRUM 13



^{13}C n.m.r. broad band proton decoupled spectrum, 20 MHz

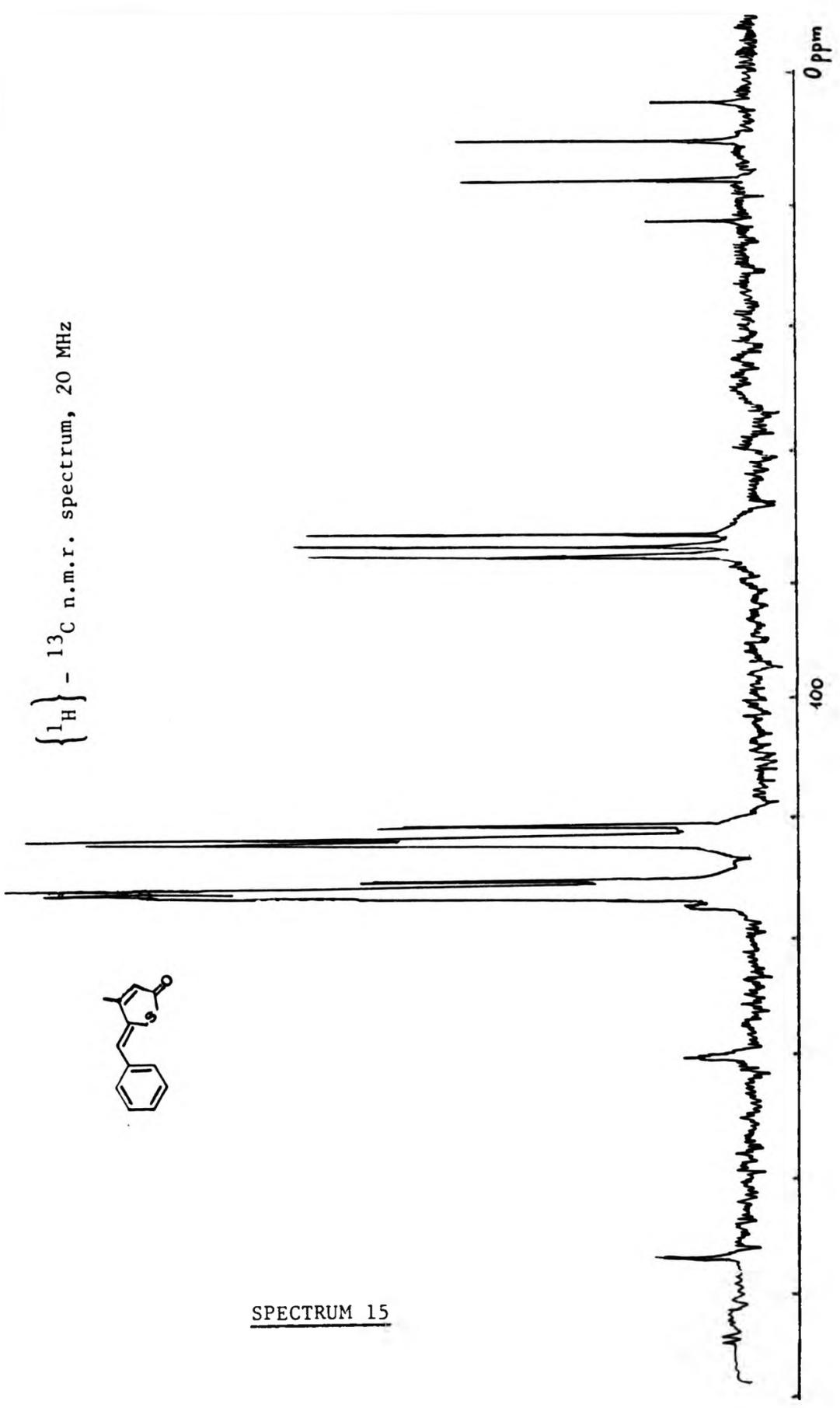


^{13}C n.m.r. s.f.o.r.d. spectrum, 20 MHz

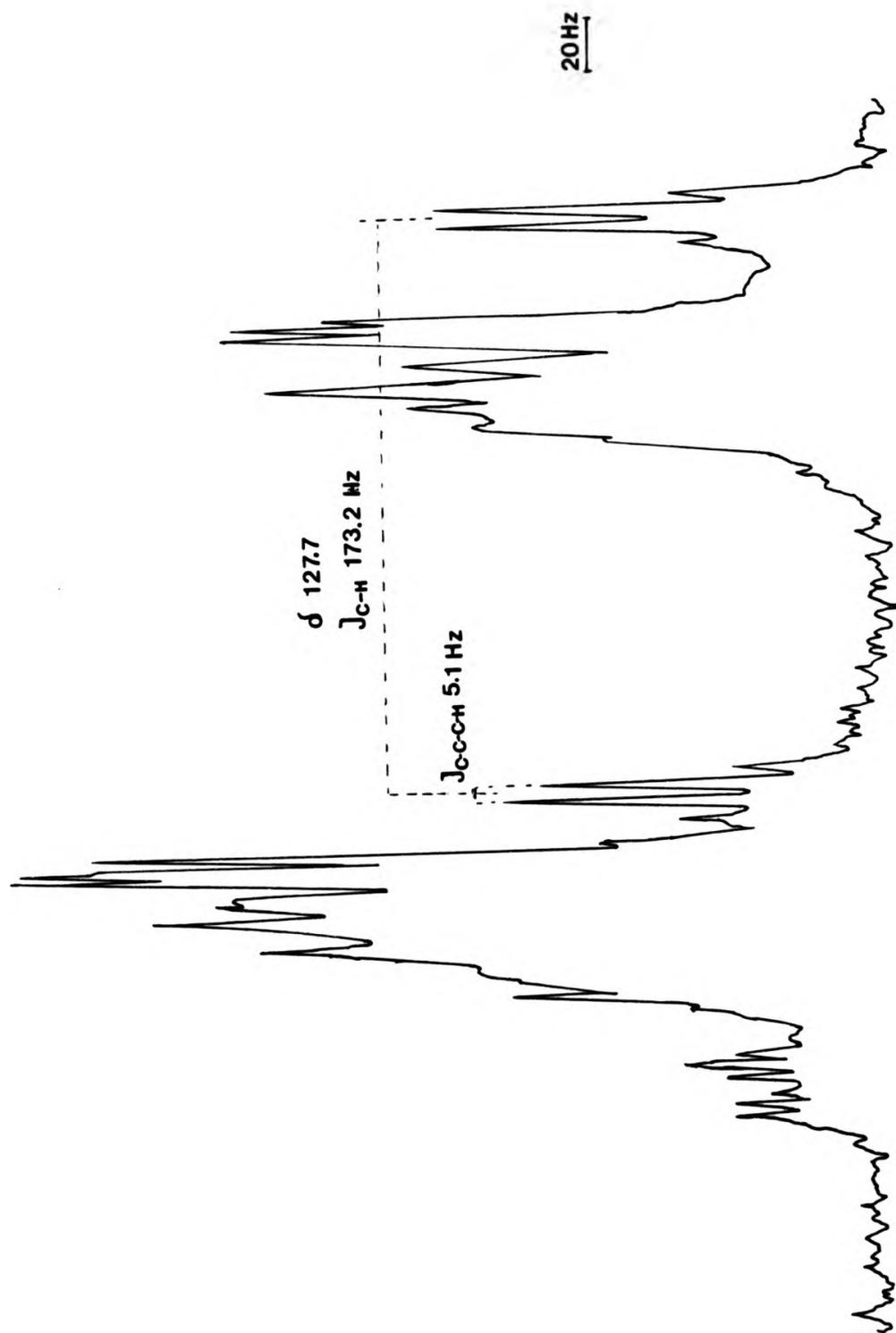


SPECTRUM 14

{¹H} - ¹³C n.m.r. spectrum, 20 MHz

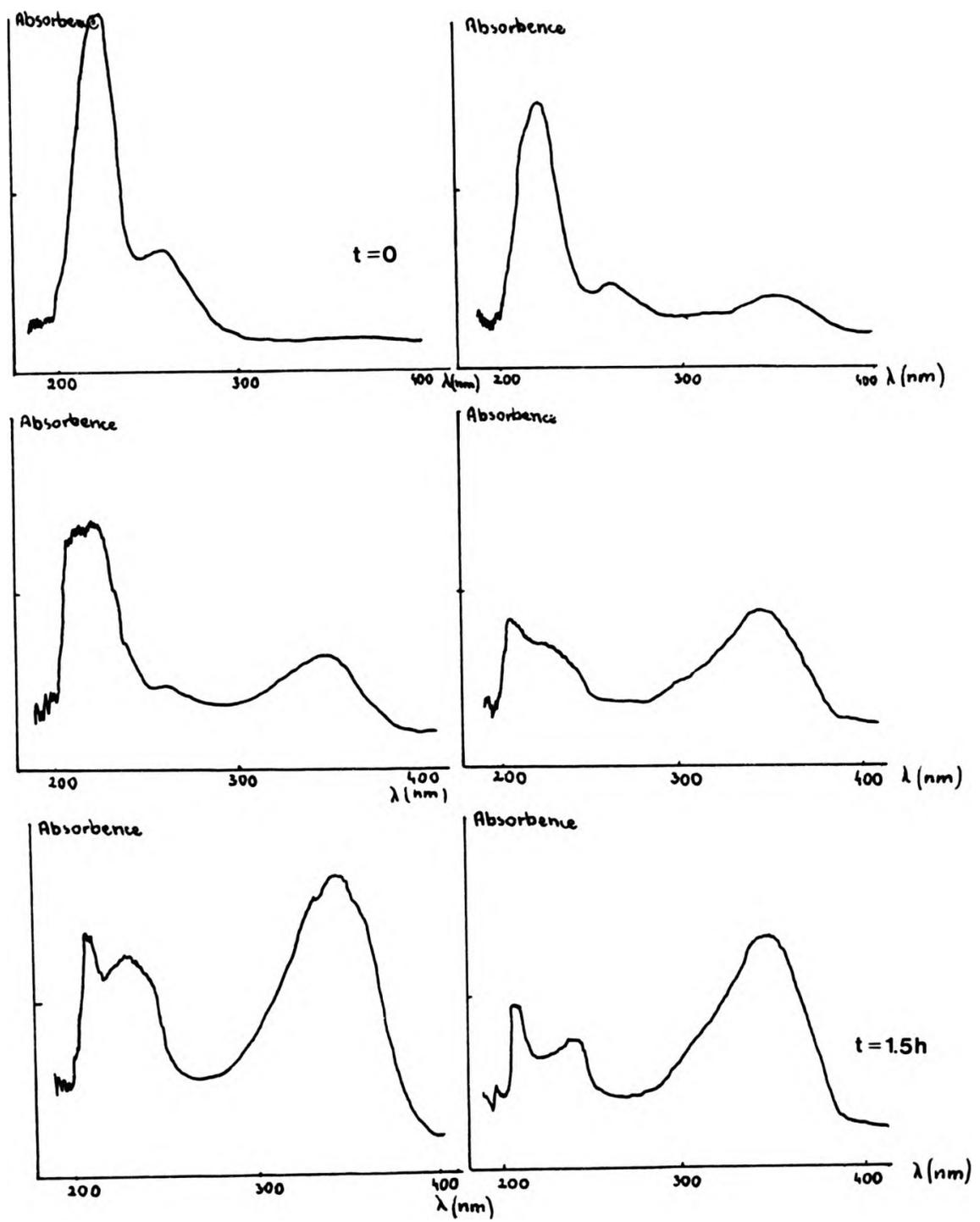


SPECTRUM 15



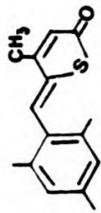
Expanded 1H coupled ^{13}C n.m.r. spectrum of 5-benzylidene-4-methyl-3-thiolen-2-one

SPECTRUM 16



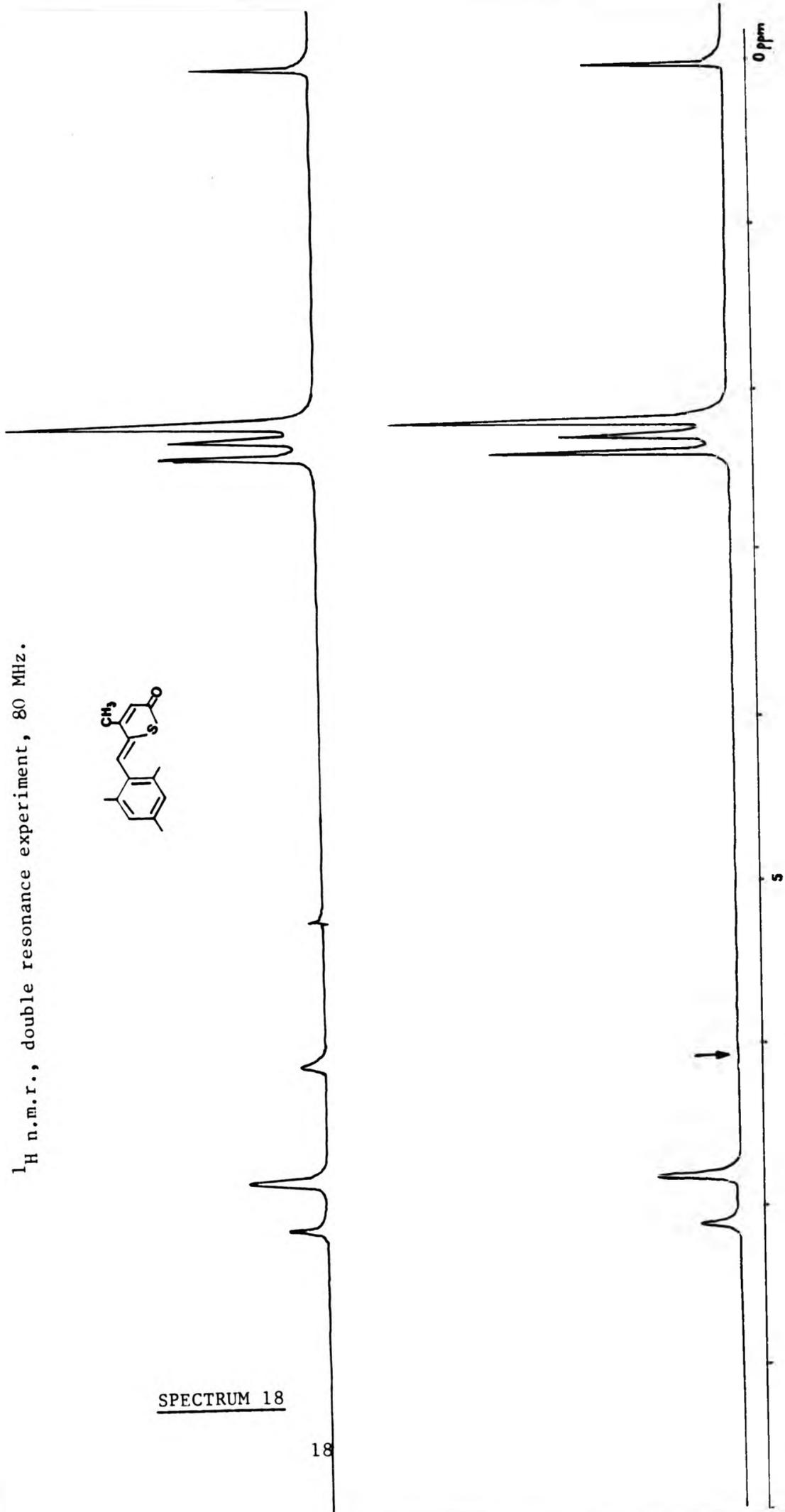
Progress of the reaction of benzaldehyde with γ -thiolactone followed with U.V. spectroscopy.

^1H n.m.r., double resonance experiment, 80 MHz.



SPECTRUM 18

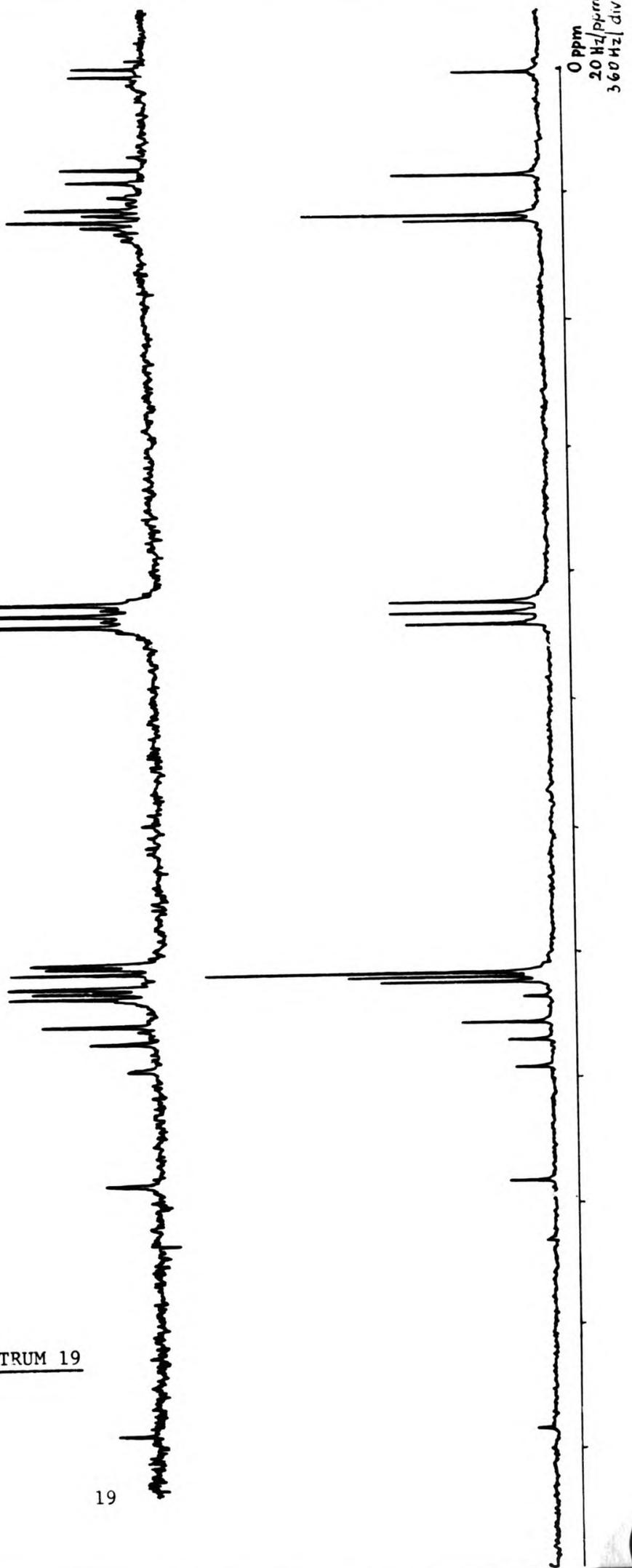
18



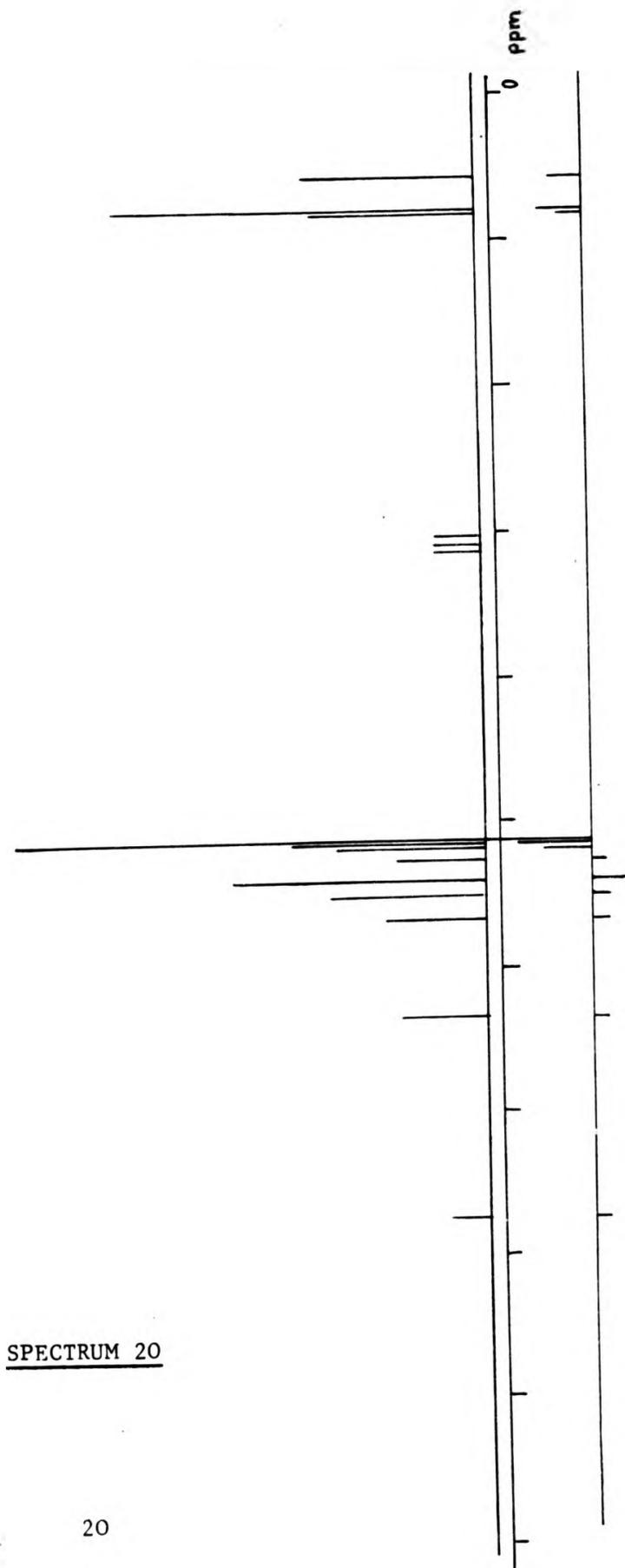
^{13}C n.m.r., broad band proton decoupled and s.f.o.r.d., 20 MHz.



SPECTRUM 19

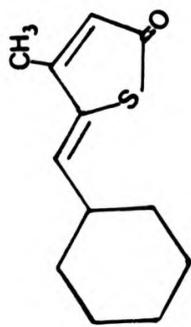


Attached Proton Test (A.T.P.), 90 MHz for ^1H

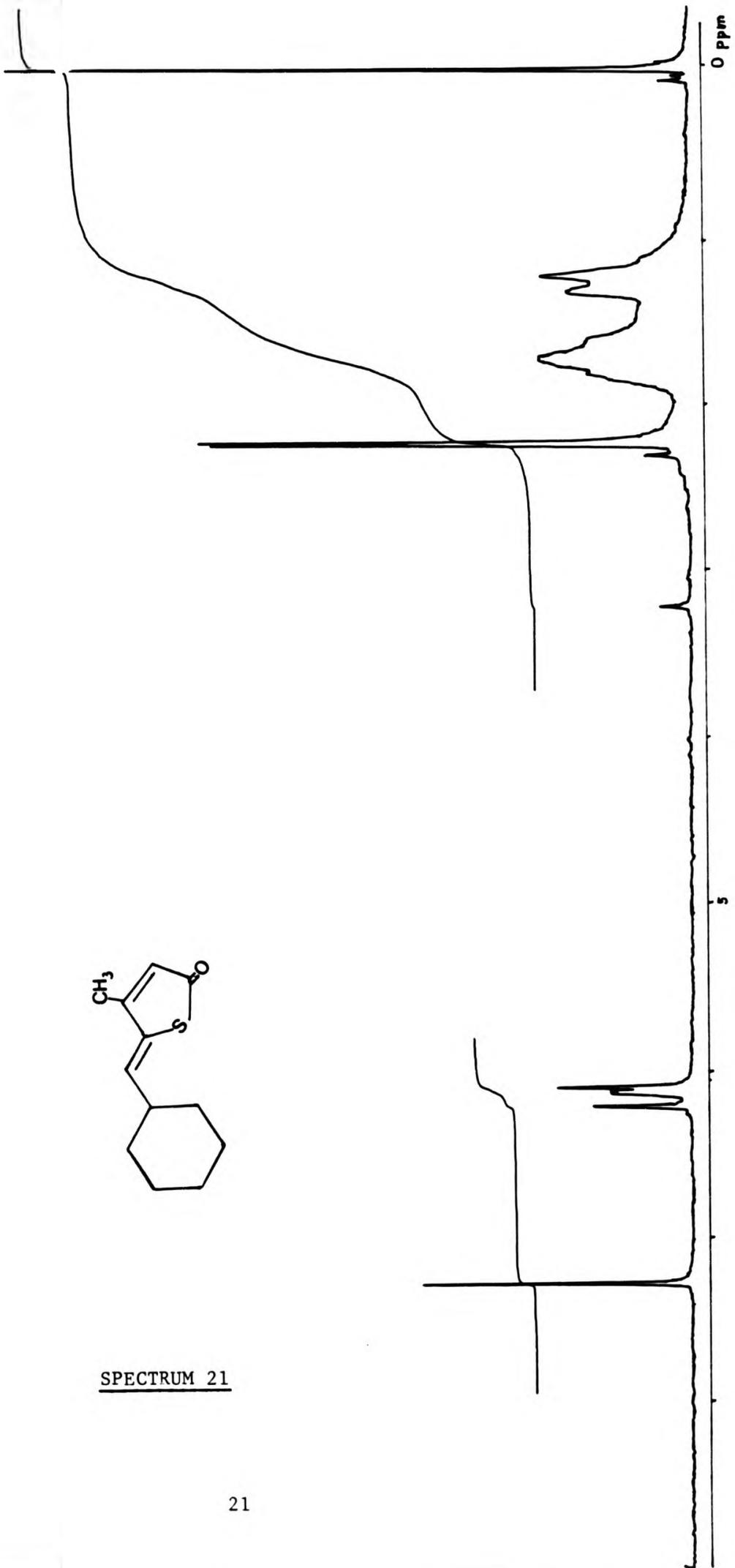


SPECTRUM 20

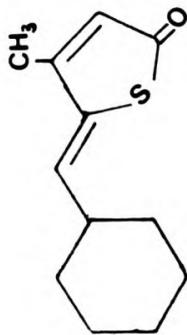
^1H n.m.r., 80 MHz.



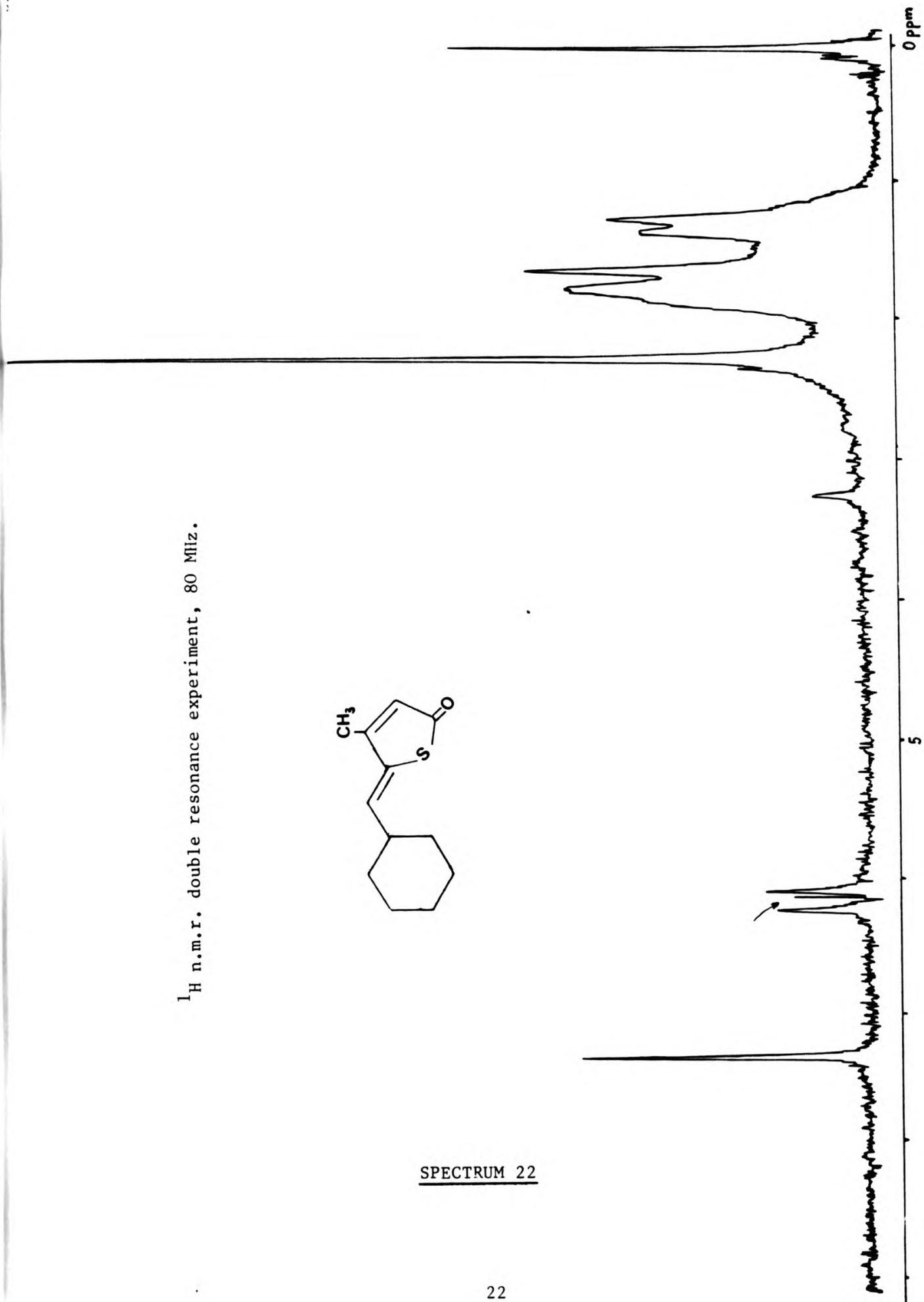
SPECTRUM 21



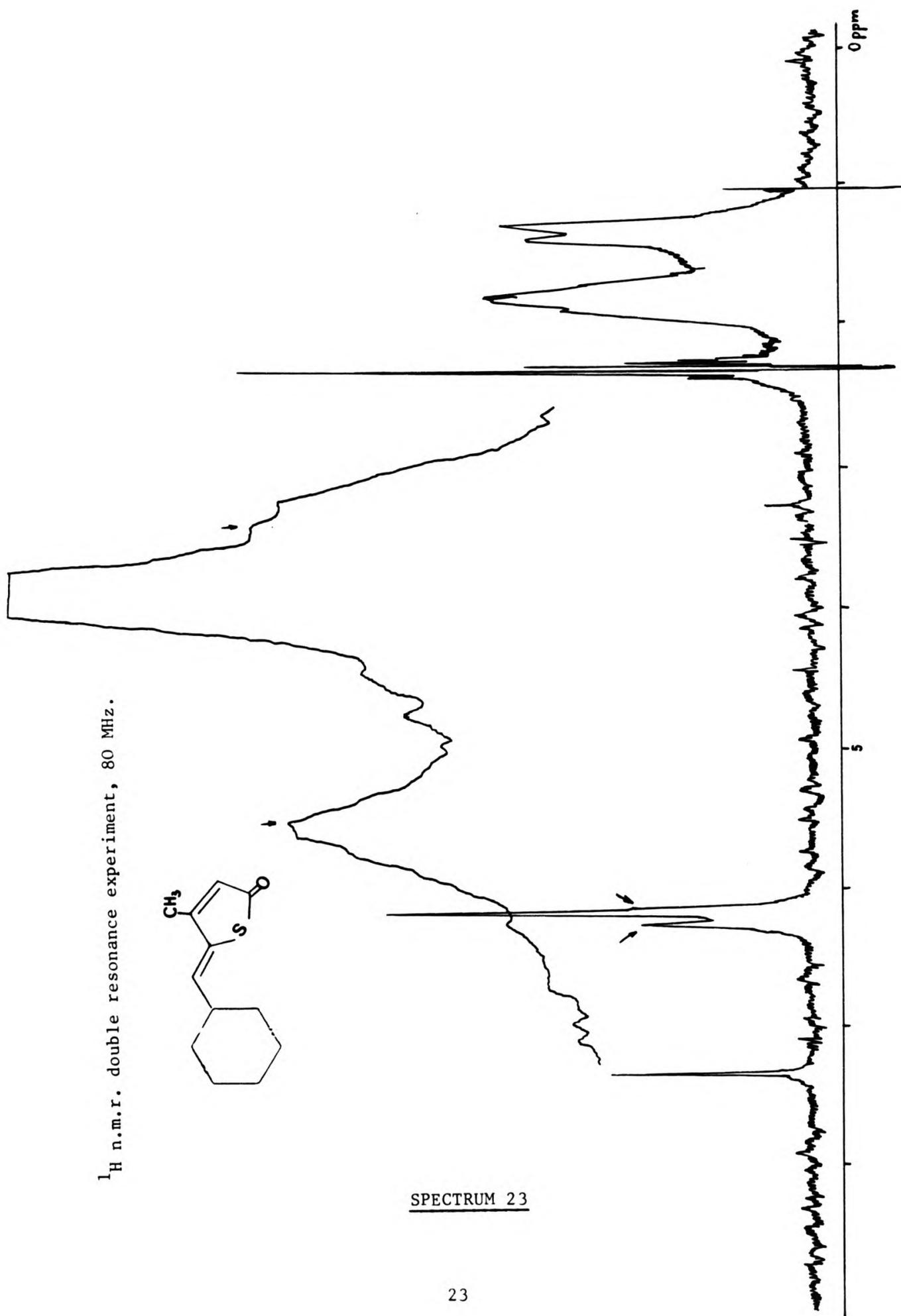
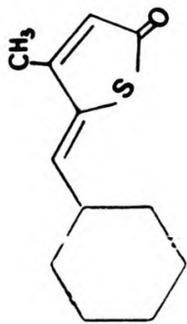
^1H n.m.r. double resonance experiment, 80 Mc.



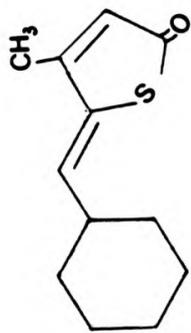
SPECTRUM 22



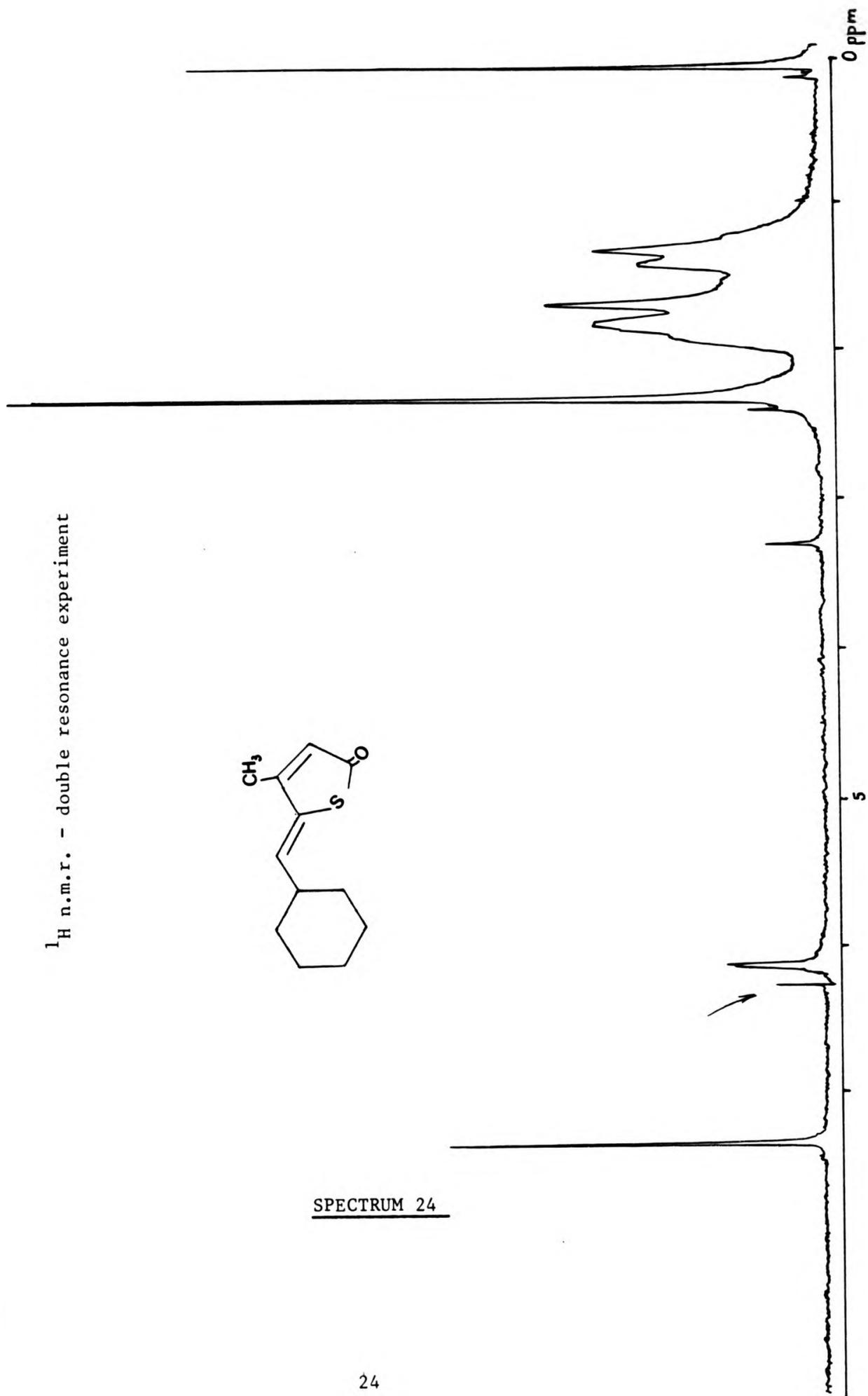
^1H n.m.r. double resonance experiment, 80 MHz.



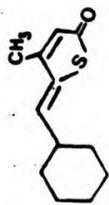
^1H n.m.r. - double resonance experiment



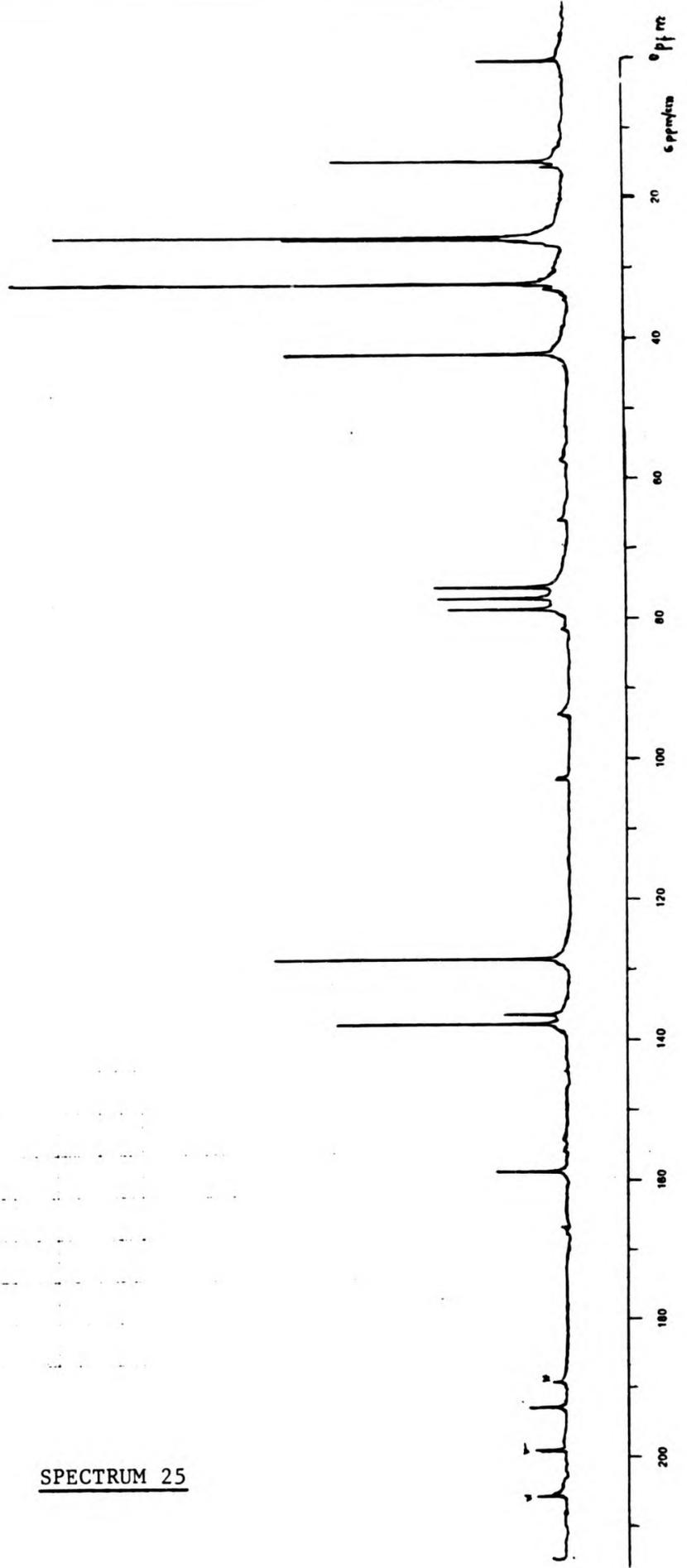
SPECTRUM 24



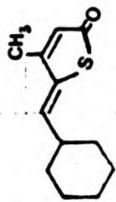
^{13}C n.m.r. broad band decoupled spectrum



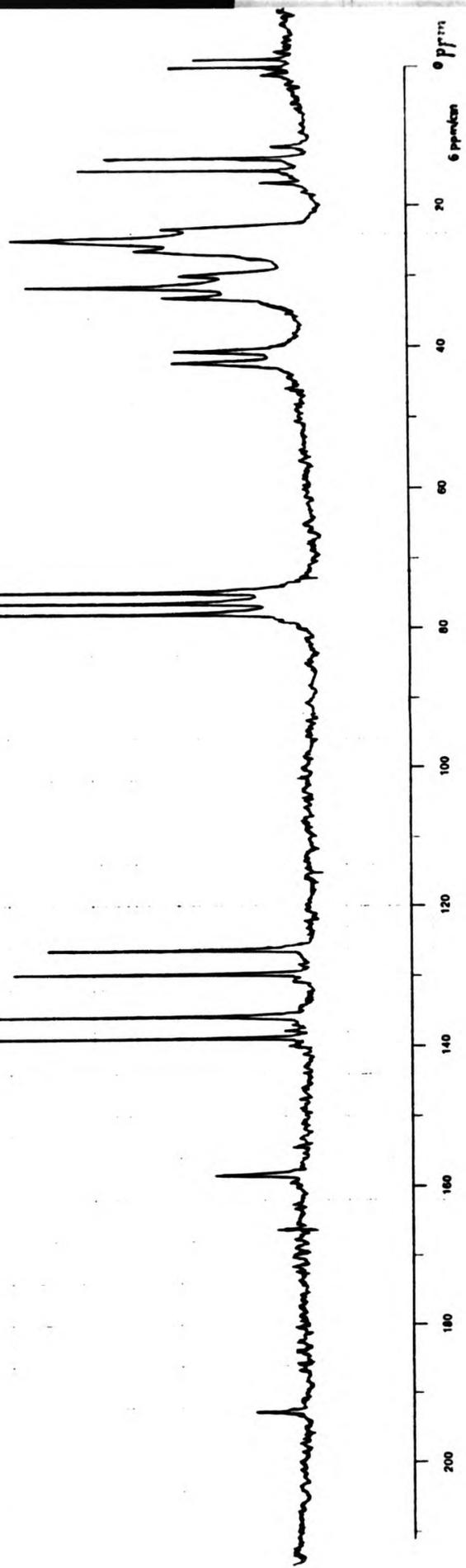
SPECTRUM 25

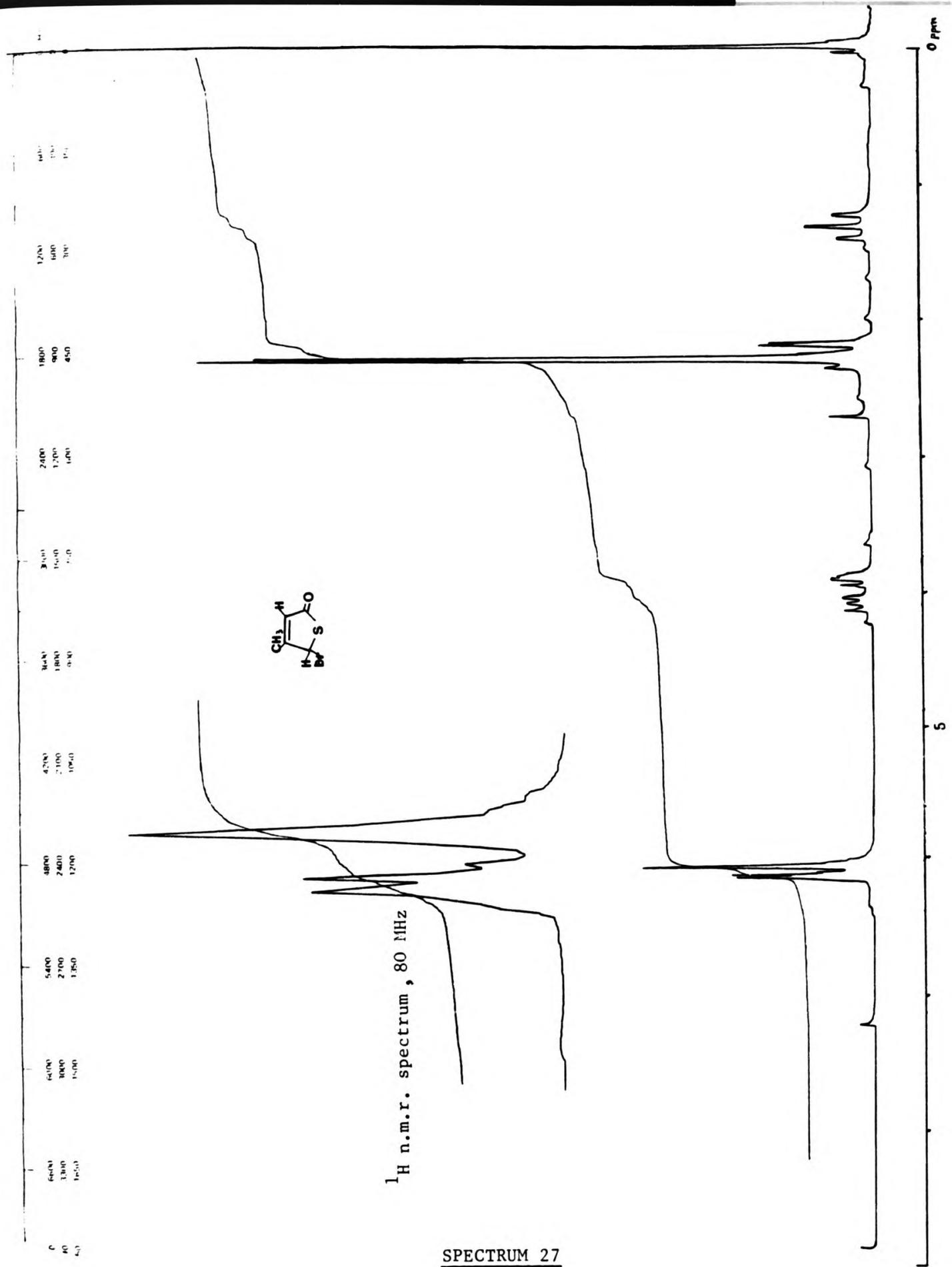


^{13}C n.m.r., s.f.o.r.d., 20 MHz.

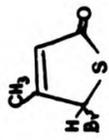


SPECTRUM 26



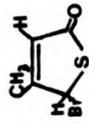
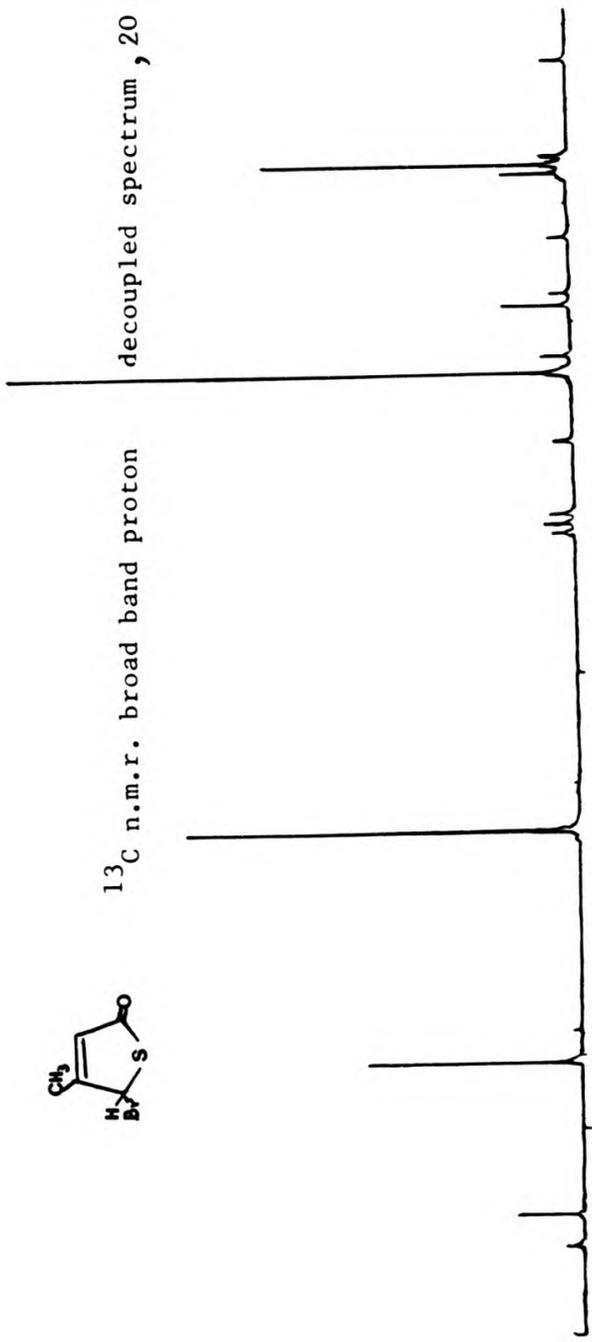


SPECTRUM 27

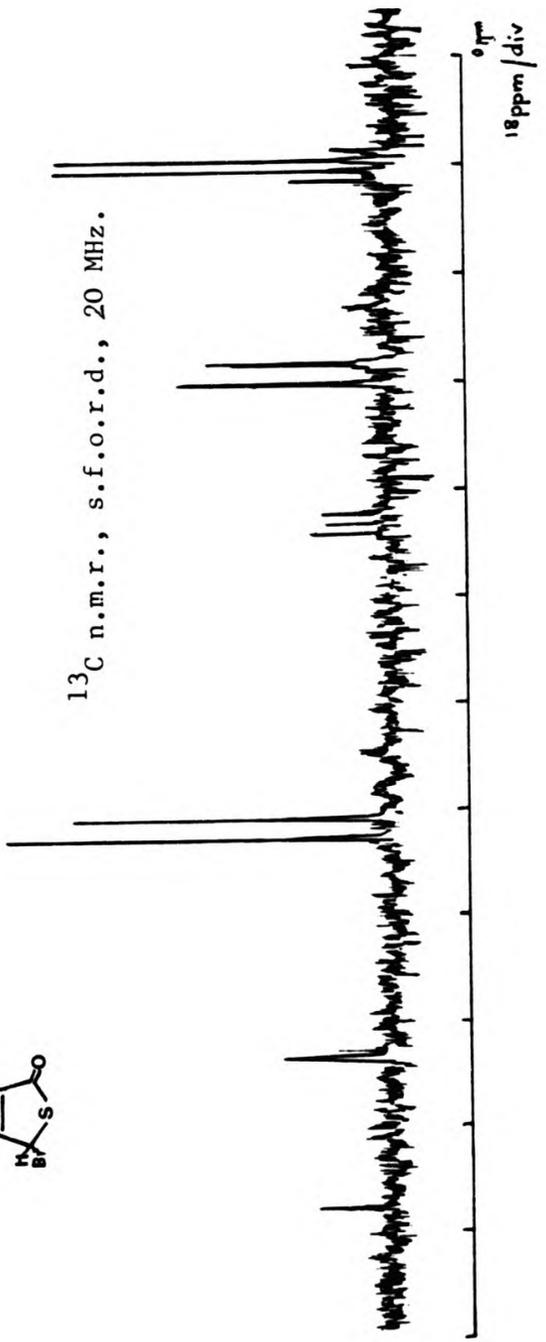


^{13}C n.m.r. broad band proton

decoupled spectrum, 20 MHz.

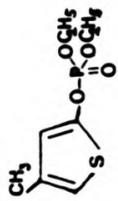


^{13}C n.m.r., s.f.o.r.d., 20 MHz.

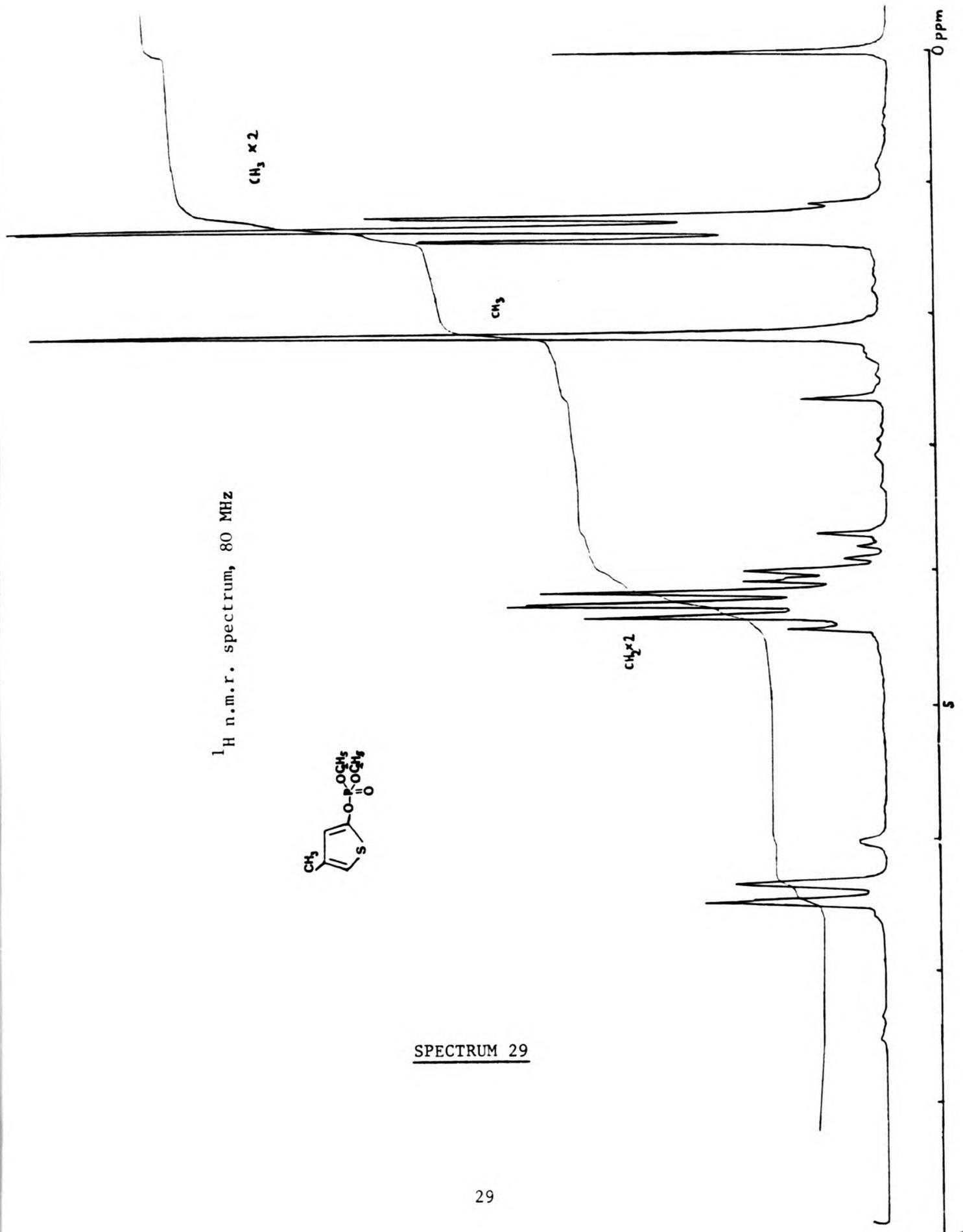


SPECTRUM 28

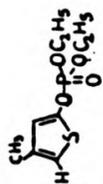
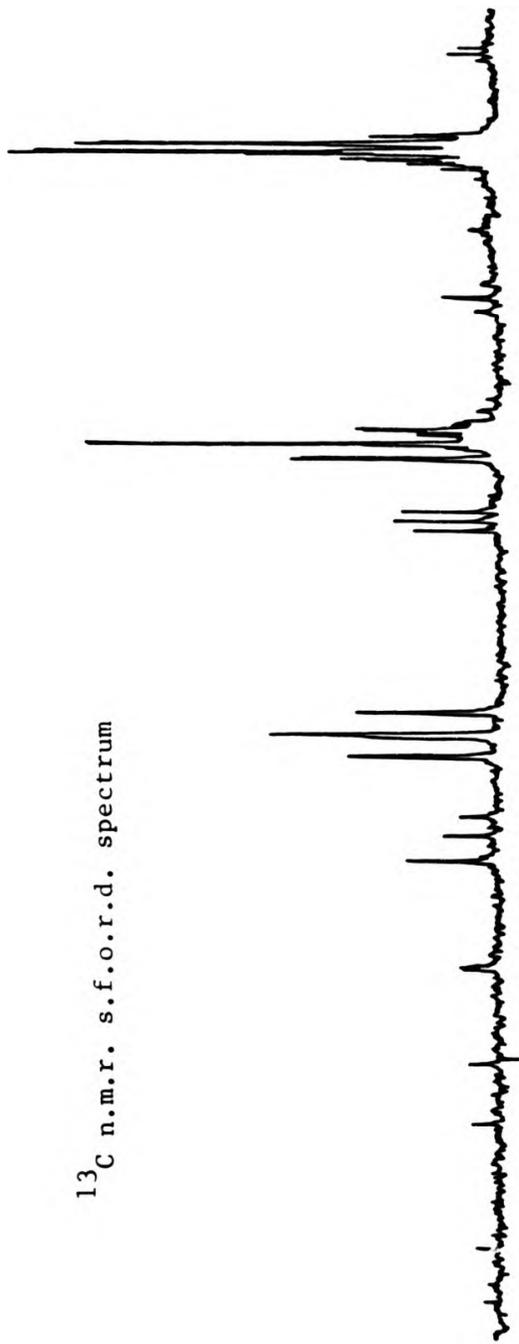
^1H n.m.r. spectrum, 80 MHz



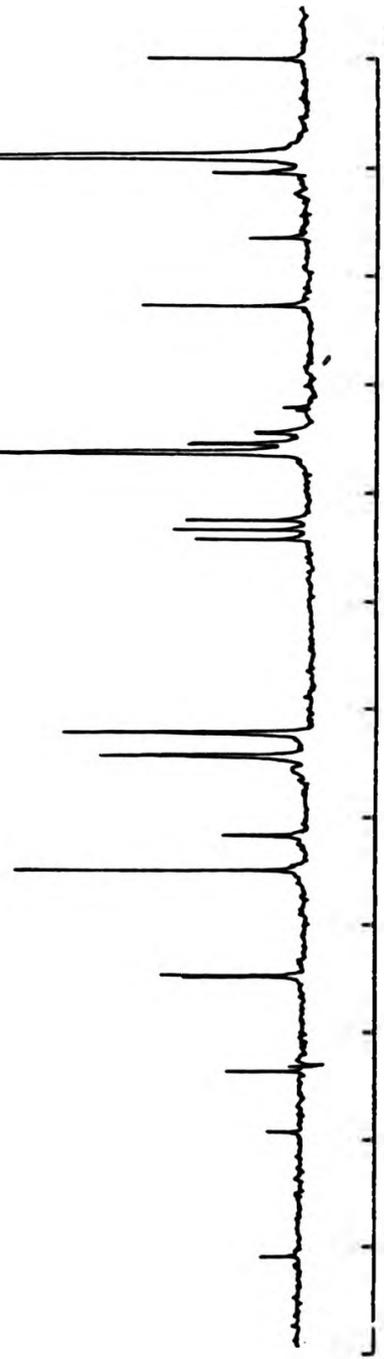
SPECTRUM 29



^{13}C n.m.r. s.f.o.r.d. spectrum

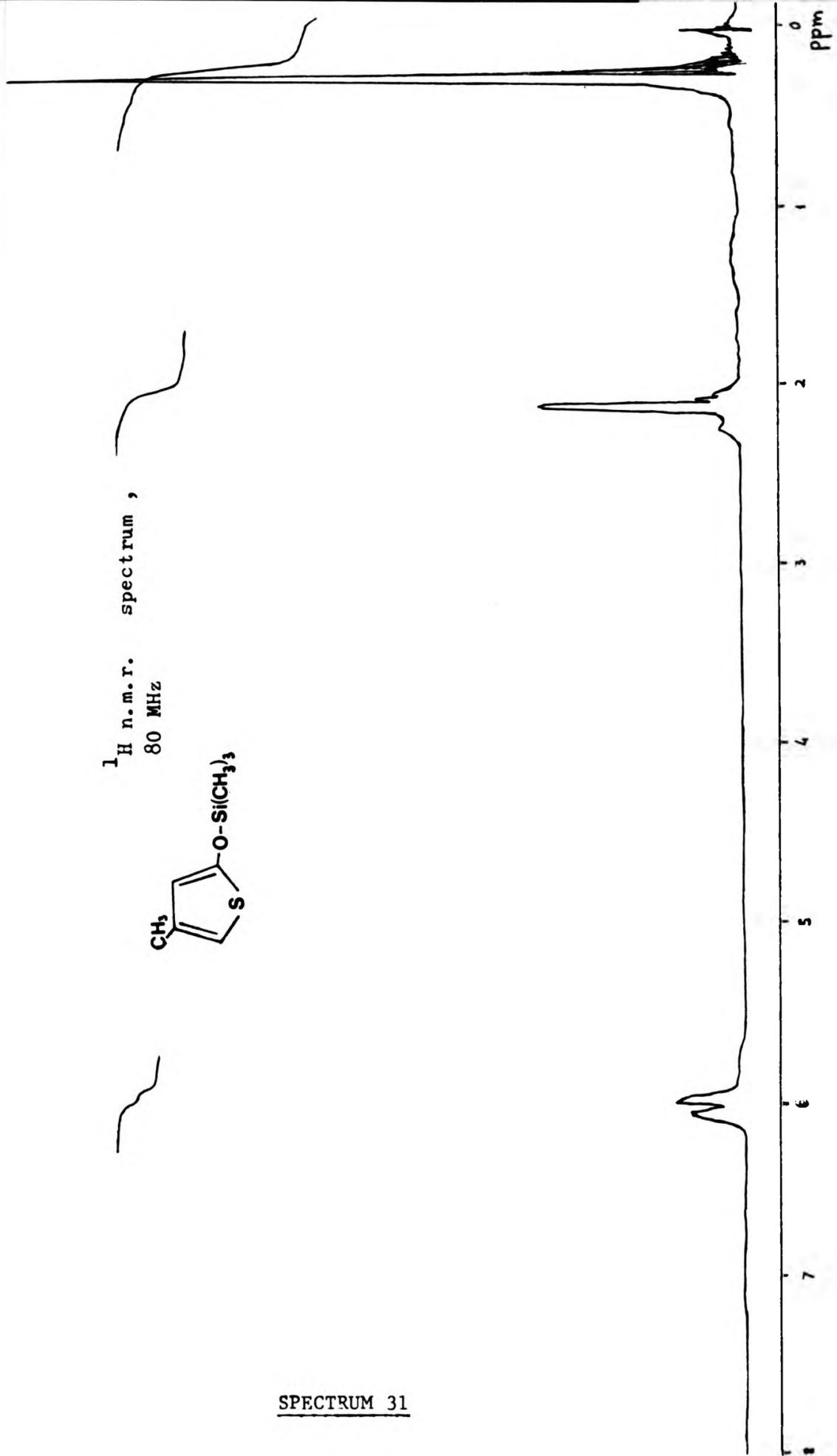
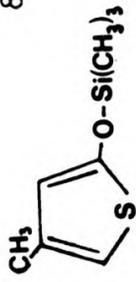


^{13}C n.m.r. broad band proton decoupled spectrum

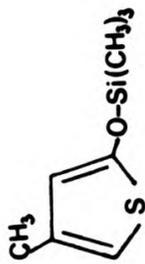


SPECTRUM 30

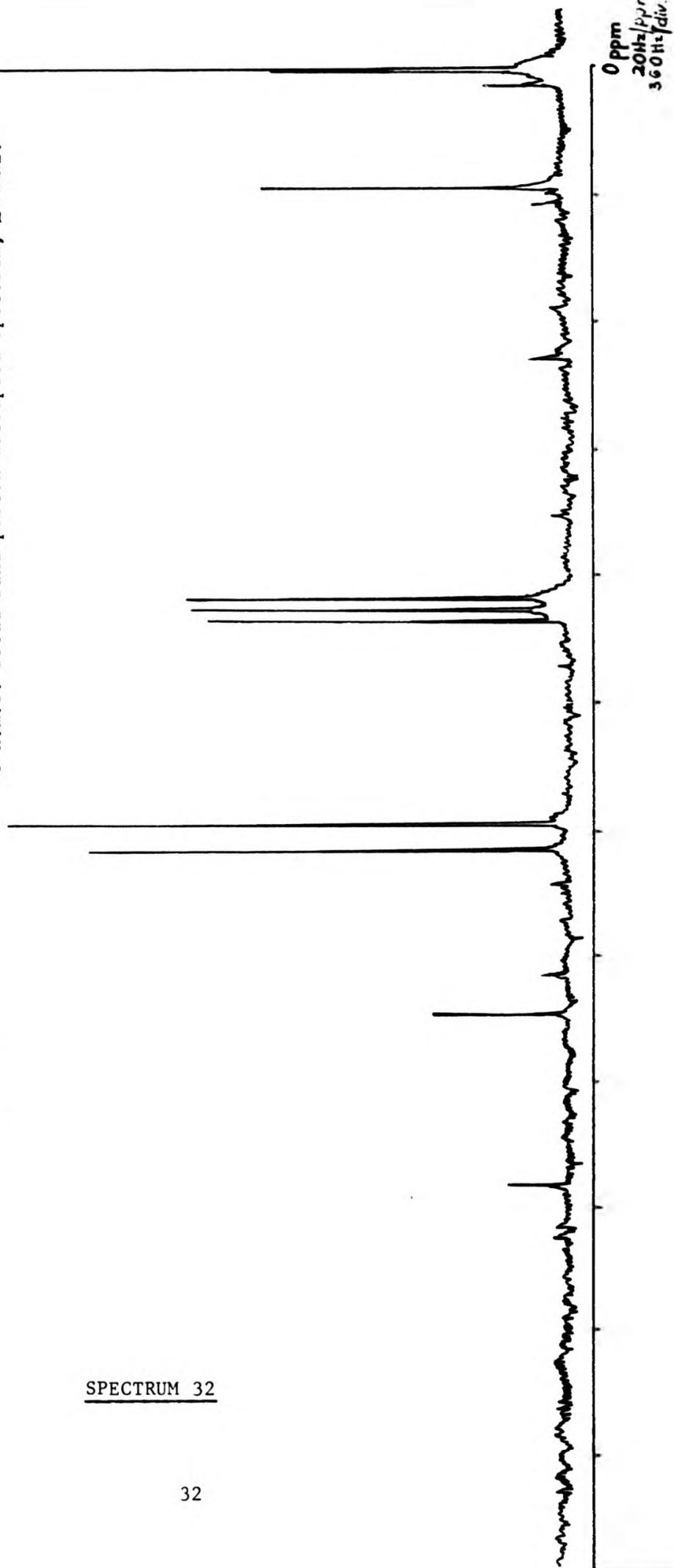
^1H n.m.r. spectrum ,
80 MHz



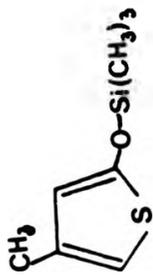
SPECTRUM 31



^{13}C n.m.r. broad band proton decoupled spectrum, 20 MHz.

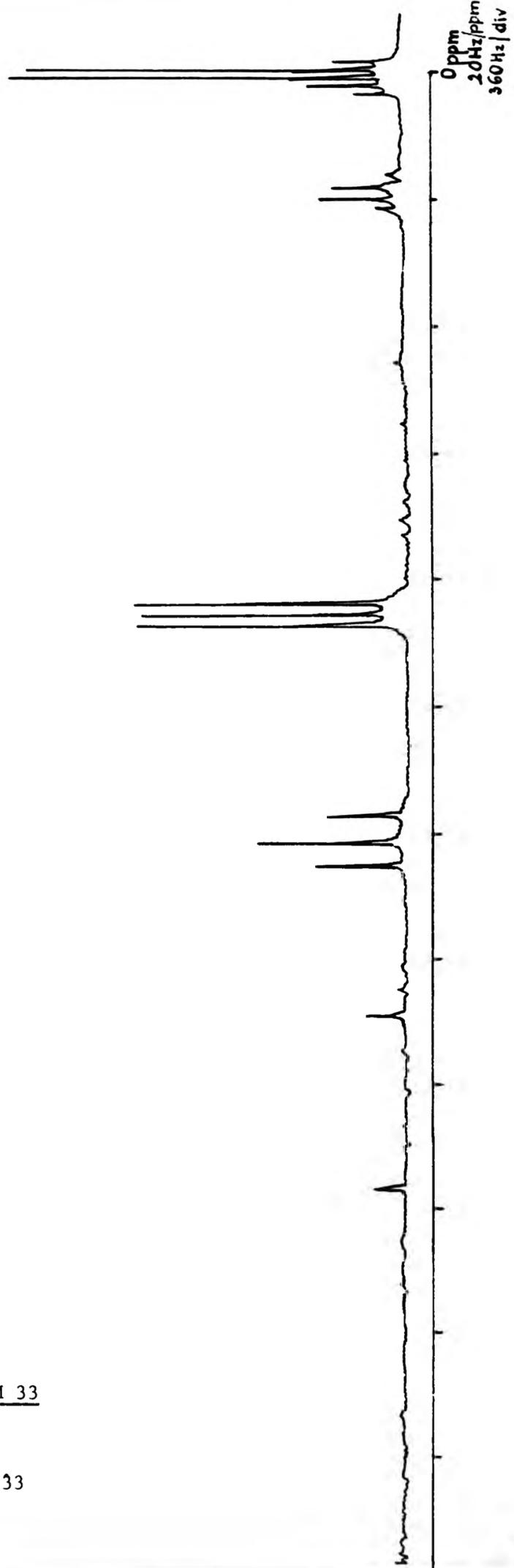


SPECTRUM 32



^{13}C n.m.r. s.f.o.r.d., 20 MHz.

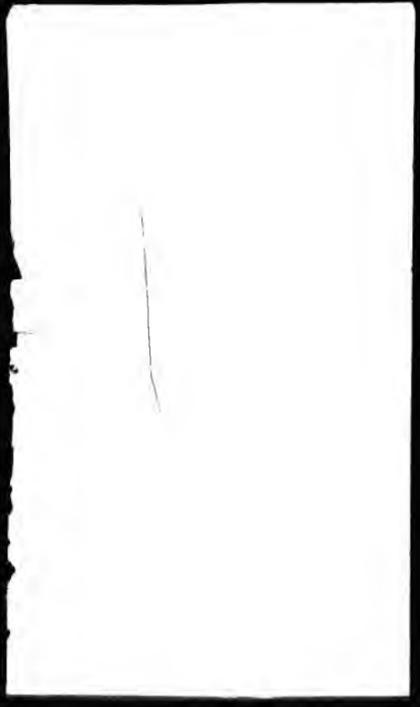
SPECTRUM 33



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END