SYNTHETIC STUDIES ON BIOLOGICALLY ACTIVE COMPOUNDS

A thesis submitted to the
University of poona
for the degree of
Doctor of philosophy
in chemistry

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TO MY PARENTS

CERTIFICATE

Certified that the work incorporated in the thesis entitled **"Synthetic Studies on Biologically Active Compounds"** submitted by **Miss R. B. Menon** was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

January, 1990.

(T. Ravindranathan)
Research Guide

PREFACE

This thesis is an outcome of a preoccupation in our laboratory in an area of synthetic organic chemistry mainly, generating synthetic routes to biologically active and useful compounds, which are as practical and simple as possible. In this activity the identification of target structures is of utmost importance in that they should have already a proven application or the potential for a practical enduse.. We started the work on (R)-(+)-α-lipoic acid, an enzyme cofactor, with the above considerations in mind particularly its potential in anti-diabetic therapy.

The first chapter describes an effective and stereospecific route to α-lipoic acid and we believe this method is simpler and more practical than any of the half a dozen syntheses already documented. We developed this method with simplicity as the main criterion based on the simple rules of stereocenter generation and retrosynthetic analysis. The synthesis which turned out, happens to be the shortest ever recorded so far, as well and also applicable to either of the two enantiomers, natural and unnatural.

The second chapter is the result of some of the fall-out of our activity of finding a simple method for lipoic acid and analogues. This chapter describes the reactivity

of α-sulfinyl carbanion generated from cyclic asymmetric sulfoxides and also a simple methodology for carbonyl transposition based on the above reactivity.

The third chapter is a small assay in our attempt to find out a route for the crucial spiroketal intermediate for calcimycin based on similar consideration to the one we had for α-lipoic acid. In this, an idea is described and the first phase of our attempt to realise the same is recorded.

Whatever is presented in this thesis is along with relevant and timely references to previous workers and any shortcoming seen in this regard at any stage may be deemed as completely unintentional.

During the course of this work, I had an opportunity to interact with my colleagues at various levels and whose unstinting and selfless help in various ways made this work see the light of the day. Much of the stimulii in the form of suggestions, guidance and never ending inspiration came from my Research Guide **Dr. T. Ravindranathan**, an aspirer of perfection. To him, I shall always remain indebted. Valuable assistance from my seniors (Drs. S.N. Kulkarni, S.V. Hiremath, A.B. Sahasrabudhe and R.A. Joshi) enabled me solve and simplify many of the intricate aspects of the work especially at bench. To them I owe a word of gratitude. Last few years in the lab. was a period of fun and excitement and I would thank my friends Dr. M. Anilkumar,

Mr. R.B. Tejwani
and Miss Kalpana Gosavi for being an integral part of this period of my student days. Help rendered by the members of X-ray Crystallography, Spectroscopy (Mr. A.G. Samuel, Mr. K.G. Deshpande and Dr. P.R. Rajamohanan) and Microanalysis group is reflected in the following pages. This work was also made possible due to the technical help rendered by members of various Divisions including the Library. Thanks are also due to CSIR, New Delhi for financial aid in the form of a research award and to the Director, National Chemical Laboratory, Pune for his consent for this presentation as a Ph.D. thesis.

It's said "Success has many fathers". This thesis is a proof of it.

R. Menon
RANI B. MENON


I PLEDGE ALLEGIANCE TO THE ATOM, AND TO THE PERIODIC TABLE ON WHICH IT STANDS, MANY PARTICLES, INDIVISIBLE, WITH ORBITALS AND ELECTRONS FOR ALL.

CONTENTS

ABBREVIATIONS

AIBN	Azobisisobutyronitrile
DHP	Dihydropyran
DMAP	4-Dimethylaminopyridine
HMPA	Hexamethylphosphorotriamide
LAH	Lithium Aluminium Hydride
LDA	Lithium Diisopropylamide
LICA	Lithium Isopropylcyclohexylamide
PCC	Pyridinium Chlorochromate
PPTS	Pyridinium p-Toluenesulfonate
TBDMSCl	t-Butyldimethylsilyl Chloride
TBDPSCl	t-Butyldiphenylsilyl Chloride
THF	Tetrahydrofuran
THP	Tetrahydropyran
TMEDA	N,N,N',N'-Tetramethylethylenediamine
TMSCl	Trimethylsilyl Chloride

NOTES

All dry reaction were performed in flame-dried glassware under N_2. Diethyl ether and THF were distilled from sodium benzophenone ketyl. Diisopropylamine was distilled over sodium or CaH_2. TMEDA was distilled from and stored over CaH_2. HMPA was distilled from CaH_2 and stored over molecular sieves (4A). CH_2Cl_2, CH_3CN, petroleum ether and hexane were distilled from P_2O_5. nBuLi was made in petroleum ether as solvent. Work up procedure includes drying organic extracts over anhydrous Na_2SO_4, filtration and concentration in vacuo. Chromatography employed SiO_2 (60-120 mesh) unless otherwise noted. Boiling points and melting points are uncorrected. IR spectra were recorded on Perkin-Elmer model 683 spectrometer. NMR spectra were recorded on Jeol T-60, Brucker WH-90, Varian FT-80 or Brucker MSL-300 MHz spectrometer in $CDCl_3$ using TMS as internal standard and chemical shift values are expressed in δ ppm. Mass spectra were recorded on Finnigan-Mat 1020B instrument using direct inlet system at 70eV. Single crystal X-ray studies were carried out using Nonius CAD-4F-11M diffractometer. Optical rotations were recorded on Jasco Dip-181 digital polarimeter using sodium vapor lamp.

ABSTRACT

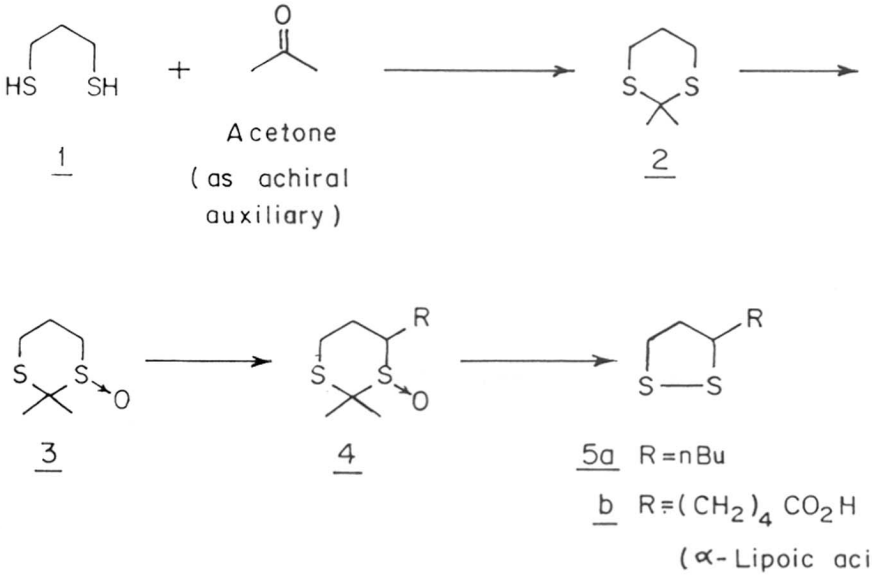
This thesis is divided into three chapters as follows:

Chapter I: Synthesis of α-Lipoic Acid

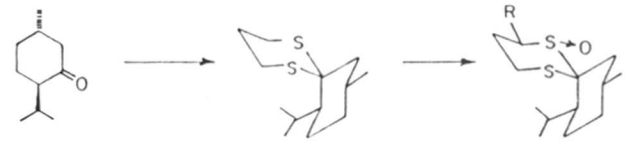
α-Lipoic acid, the coenzyme associated with α-ketoacid dehydrogenases and also a growth factor in many plants and animals, has recently been shown to bring down blood sugar in diabetic rabbits, thus increasing its biological importance. In this section, methodology employed to give both racemic and optically active α-lipoic acid by one of the simplest and shortest routes todate will be described.

The synthetic operations involved [Schemes 1 and 2] are: (a) formation of 1,3-dithiane **2** from the auxiliary ketone using 1,3-propanedithiol **1**, (b) regioselective oxidation to monosulfoxide **3**, (c) stereoselective alkylation with alkyl halide and (d) hydrolytic cyclisation to give 1,2-dithiolane **5**, **5'**.

SCHEME — 1.



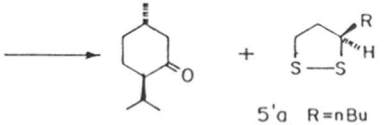
SCHEME – 2.



∝ – Menthone
(as chiral auxiliary)

3'

4'

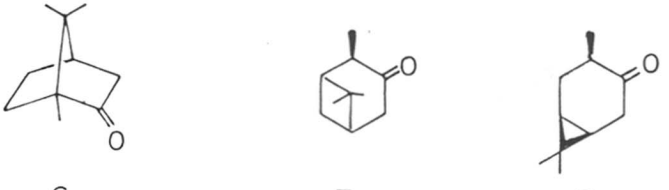


5'a R=nBu

b R=$-(CH_2)_4CO_2H$

[(R)-(+)-∝-Lipoic acid]

Thus, both (R)-(+)- and S(-)-α-lipoic acids were obtained in almost 100% optical purity, using 'd' and l-menthone, respectively, as chiral auxiliary. Thus from the above observations and model studies it was predicted that the naturally occurring (R)-(+)-α-lipoic acid could be synthesised by a careful choice of naturally occurring chiral ketones. Hence (R)-(+)-camphor **6**, (+)-isopinocamphone **7** and (-)-4-isocaranone **8** were subjected to the above set of



6 7 8

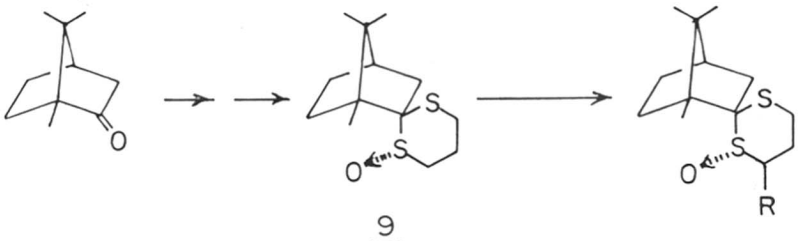
reaction sequence. However the dithiane derived from isopinocamphone and sulfoxide derived from (-)-4-isocaranone could not be obtained in practical yields and so the routes to α-lipoic acid starting from the above ketones were not pursued further. In the case of (R)-(+)-camphor, though the dithiane

and sulfoxide were obtained in good yields, the α-sulfinyl carbanion derived from the sulfoxide showed difference in reactivity towards various electrophiles.

Chapter II: Some Aspects of Chemistry of Sulfoxide

Section A: Reactivity of α-Sulfinyl Carbanions:

The sulfoxide **9** (Scheme 3) derived from (R)-(+)-camphor failed to undergo alkylations with butylbromide/iodide or bromo/iodovalerate (leading to R-(+)-α-lipoic acid) but underwent alkylation with highly reactive methyliodide to give the cis-methylated product **10**, contrary to the expected trans product.



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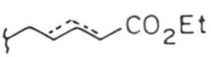
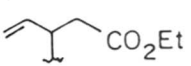
10. R = CH_3
11 R = CHO
12 R = CO_2Et
13 R = 
14 R = 

SCHEME – 3.

Though butylbromide or bromovalerate had alkylated sulfoxide derived from menthone, the failure to do so in the case of sulfoxide derived from (R)-(+)-camphor, could be attributed possibly to the faster competing side reactions obtained in the latter. Alternatively, alkylation could be achieved by introduction of an activating group such as a

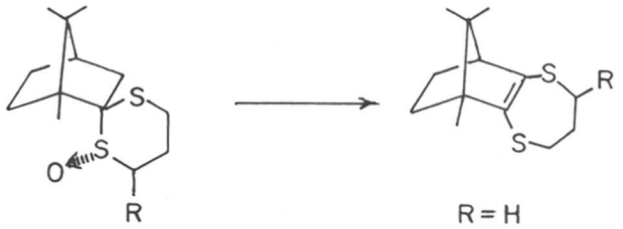
formyl or an ester function or by conjugate addition. In case of the former, operation of steric factors due to introduction of an additional functionality led to poor yields of the alkylated product. While in the latter, Michael addition with ethylacrylate and ethyl 2,4-pentadienoate proceeded smoothly. However, with ethyl 2,4-pentadienoate, the product was a 3:1 mixture of 1,6- and 1,4-adducts, contrary to the expected 1,6-adduct.

As seen in Scheme 2, l-menthone gives (S)-(-)-α-lipoic, but d-menthone can also give natural (R)-(+)-α-lipoic acid, provided the sulfoxide derived from l-menthone undergoes alkylation in a cis fashion, instead of the normally anticipated trans-alkylation. Since phosphate reagents can be made to alkylate α-sulfinyl carbanions in cis-fashion, phosphate reagents like tri-n-butylphosphate [$OP(OBu^n)_3$] and butyl tetramethylphosphorodiamidate $(Me_2N)_2OP(OBn^n)$ were used as alkylating agents. Although the sulfoxide underwent alkylation smoothly, the products obtained did not exhibit good optical purity.

Section B: Sulfoxides in 1,2-Carbonyl Transpositions:

Transposition of a carbonyl group from its original position to carbon atom 'α' to it is referred to as 1,2-carbonyl transposition. The importance of 1,2-ketone transposition in terpene and steroid field has been well recognised for some time. This section describes a simple method for site exchange with saturated ketones.

The sulfoxide **9** (Scheme 3) was found to be unstable at room temperature as a chloroform solution. It was found to undergo dehydration with rearrangement (Eqn.1) to give a dithiepin derivative, as shown by spectral and model studies (Eqn. 2).

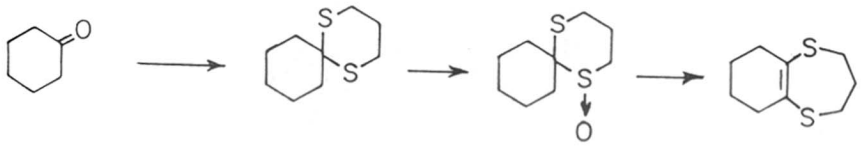


R = H
R = CH_3

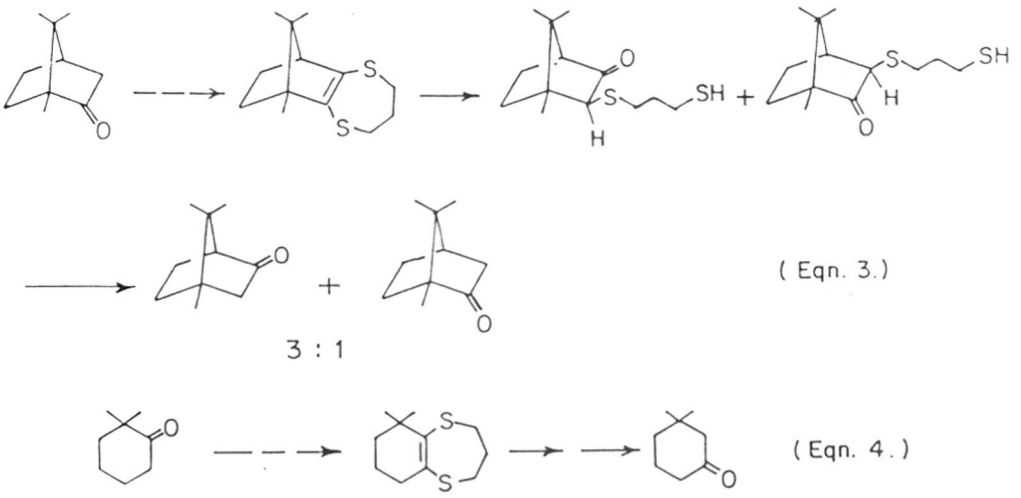
R = H
R = CH_3

(Eqn. 1.)

This dithiepin can be regioselectively hydrolysed to give a carbonyl transposition. Such carbonyl transpositions were carried out successfully on 2,2-dimethylcyclohexanone, (R)-(+)-camphor and attempts to achieve similar kind of reactions on 2-methylcyclohexanone, 4-methylcyclohex-3-enone and isophoron were not fruitful.



(Eqn.2.)

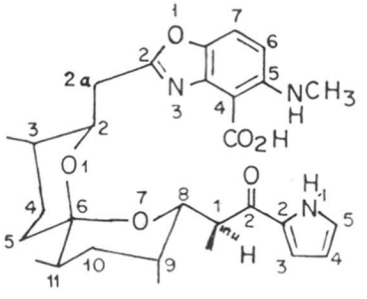


(Eqn. 3.)

(Eqn. 4.)

Chapter III: Calcimycin: Spiroketal Construction Model Studies

Calcimycin **15**, isolated in 1972 from cultures of Streptomyces charteusensis is an ionophoric antibiotic having high antimicrobial activity against gram-positive bacteria and also has potent pharmacological activities including cardiovascular and renal effects. Adding to this, its unique structural feature has prompted many total syntheses.



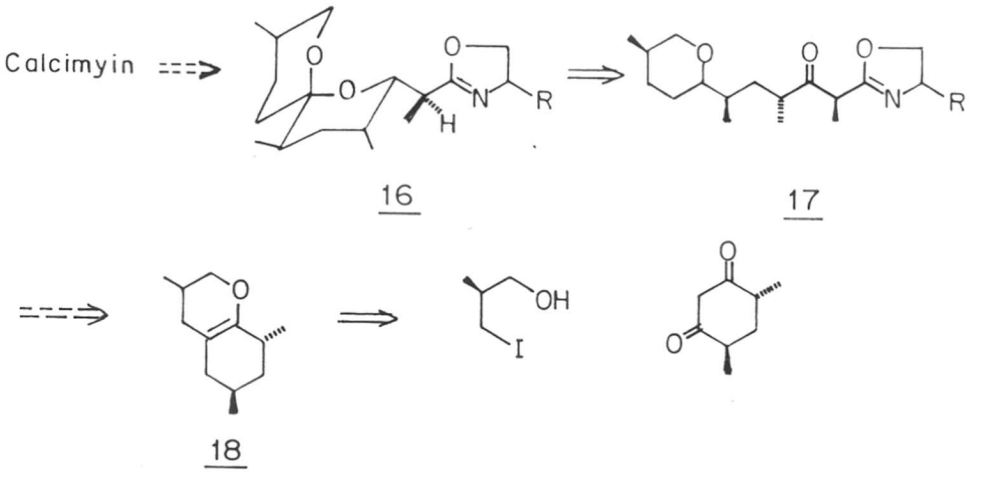
1

Synthesis:

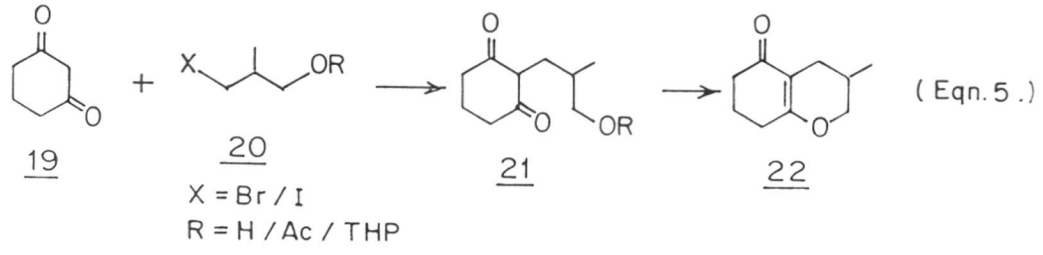
Retrosynthetic analysis as shown in Scheme-4 allows us to choose trans-2,4-dimethyl-1,3-cyclohexanedione as the starting material. Studies were carried out with model

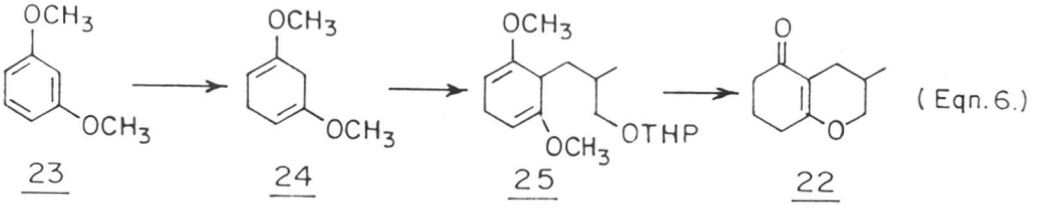
compounds cyclohexan-1,3-dione and resorcinol dimethyl ether, the easily accessible materials.

SCHEME – 4.

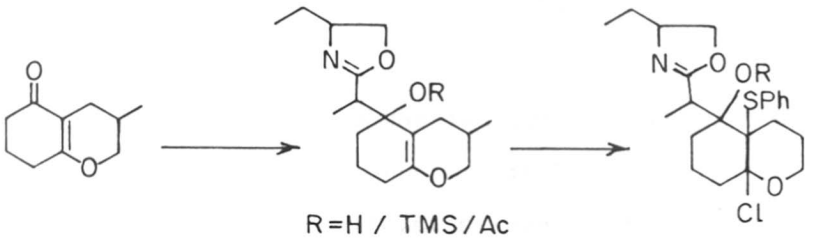


Whereas **19** failed to undergo alkylation (Eqn.5), compound 23 was successfully converted to the required bicyclic enone system **22** (Eqn. 6).

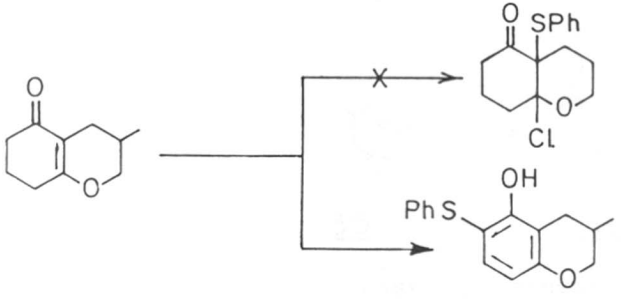




In accordance with the strategic plan, addition of 2-ethyloxazoline derivative to the carbonyl function was carried out successfully. Attempts to protect the hydroxyl group with subsequent saturation of the olefin (Eqn. 7) was encountered with problems, therefore, saturation of the olefin with phenylsulfenyl chloride, prior to carbonyl addition was attempted (Eqn. 8). However, this reaction gave only **29**. Other attempts to convert the enone **22** to **17** are currently under study.



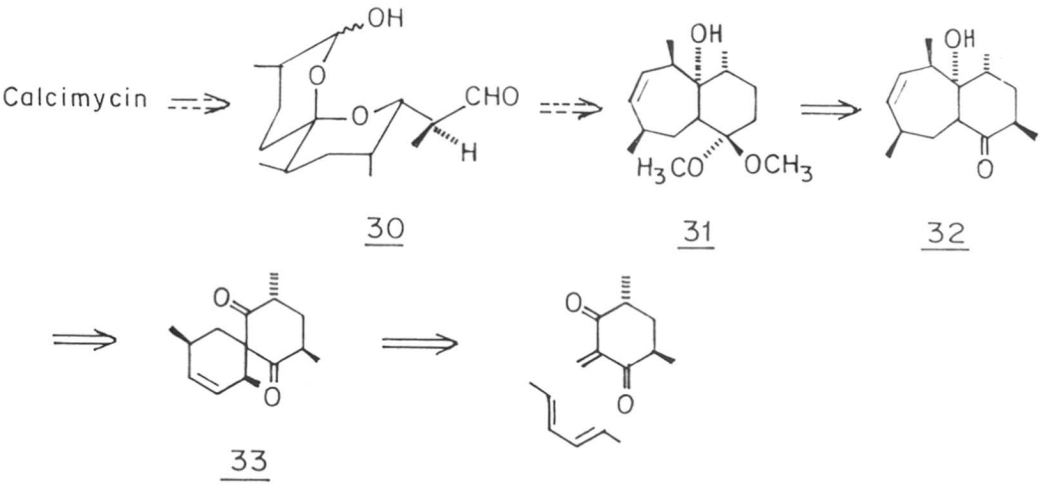
(Eqn. 7.)



(Eqn. 8.)

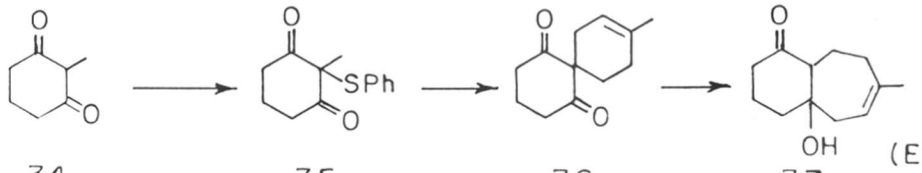
Besides the synthetic studies on calcimycin as per Scheme-4, studies were also directed towards an intermediate of calcimycin **30** (Scheme 5) by another pathway, retro-synthesis of which is shown in Scheme 5.

SCHEME – 5.



30 31 32 33

Model studies were carried out, aiming at the very first target, the spirodiketone system **33**, which was successfully obtained from 2-methylcyclohexane-1,3-dione **34** as shown in Eqn.10.



34 35 36 37 (Eqn.10)

Attempts were then focussed on converting the spiro system **36** to the fused system **37**, the key intermediate of the scheme. This conversion could be mediated by a metal via. a radical anion or by acid catalysis of a suitable derivative of **36**. The various reactions studied towards this end will be described.

CHAPTER 1

SYNTHESIS OF α-LIPOIC ACID

CHAPTER I

SYNTHESIS OF α-LIPOIC ACID

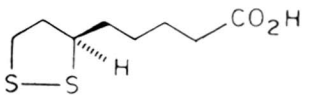
1.1 INTRODUCTION:

α-Lipoic acid (**1**), widely distributed in plants and animals, is recognised as a vital cofactor in the multi-enzyme complexes of α-keto acid dehydrogenases,[1] such as pyruvate, α-keto glutarate and branched chain α-keto acid dehydrogenases, and is also known to assume crucial roles in photosynthesis[2] as well as in the tricarboxylic acid cycle. α-Lipoic acid was first isolated from processed liver in 1950 by Reed[3] and coworkers and characterised as the cyclic disulfide 5-[3-(1,2-dithiolanyl)]-pentanoic acid. Available evidence[4] suggests that the biological activity of α-lipoic acid is confined only to the naturally occurring 'R' isomer.

Nomenclature:

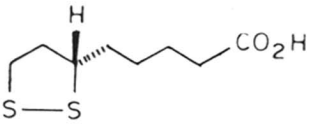
The name α-lipoic acid is derived from the fact that the compound is highly soluble in fat solvents, is acidic (pKa = 4.7) and is involved through oxidative decarboxylation of pyruvate, in the formation of acetate, a precursor of fatty acids. The crystalline compound (m.p. 47.5-48.5°C) is designated as α-lipoic acid to indicate that it is the first member to be obtained of a series of chemically related substances which possess acetate-replacing and pyruvate oxidase factor activity. Other nomenclature used

are: thioctic acid; 6,8-dithiooctanoic acid; 1,2-dithiolane-3-valeric acid and 1,2-dithiolane-3-pentanoic acid.



(R)-(+)- α-Lipoic Acid

1a



(S)-(-)- α -Lipoic Acid

1b

1.2 BIOLOGICAL IMPORTANCE:

Current interest in α-lipoic acid is derived mainly from the recognition of its importance as a factor in vital biochemical processes. α-Lipoic acid has been shown to have significant physiological and pharmacological properties.[1] It is known to have protective and curative effect in heavy metal poisoning, e.g. from As[4], Pb, Hg[5], Cu[6] and Se in animal tissues. It is found to be very effective in the treatment of liver disorders caused by Amanita phalloides.[7] α -Lipoic acid is also used for treatment of persons with chronic toxic persisting hepatitis and chronic toxic active hepatitis, resulting from occupational phosphorus exposure. This effect may be due to its activation of redox process and glycogen synthesis in the liver.[8] It is also shown to have cytoprotective effects on the gastric mucosa against ethanol aggression.[9] One of the recent and most important implications of lipoic acid is its ability to control diabetes.[10] Diabetes is a disease

that effects a significant proportion of the population and is characterised by abnormal carbohydrate, fat and protein metabolisms. The major biochemical abnormalities in diabetes are increased blood sugar (hyperglycemia), decreased glucose tolerance, urinary sugar (glucosuria), increased serum pyruvate, lactate, acetoacetate and triglycerides, reduced glycogen in the tissues, impaired fat biosynthesis in the liver and increased gluconeogenesis in the liver and kidney. These metabolic aberrations can be corrected by the administration of lipoic acid. Dithioloctanoic acid is formed from lipoic acid by reduction and substitutes for coenzyme A in several enzymatic reactions such as pyruvate dehydrogenase, citrate synthase, acetyl coenzyme A carboxylase, fatty acid synthetase, and triglyceride and phospholipid biosynthesis, but not in the oxidation of fatty acids because of the slow rates of thiolysis of α-keto acyl dithioloctanoic acid. The overall effect of these changes in the key enzymic activities is seen in the increased rates of oxidation of glucose and a reduction in fatty acid oxidation in diabetes following lipoic acid administration.

Application of lipoic acid:

Apart from the above pharmacological importance, lipoic acid also finds its use in cosmetic preparations. Skin lotions, ointments and creams containing lipoic acid prevents darkening of the skin[11] and hair preparations

containing lipoic acid is shown to control dandruff and stimulate hair growth.[12]

Besides its biochemical functions, lipoic acid also finds application in photography.[13] When lipoic acid forms an ingredient of the silver halide emulsion along with other additives and the emulsion coated on a film substrate to form a negative type photographing material, it provides an image with an extraordinary hard contrast with good dot quality upon development.

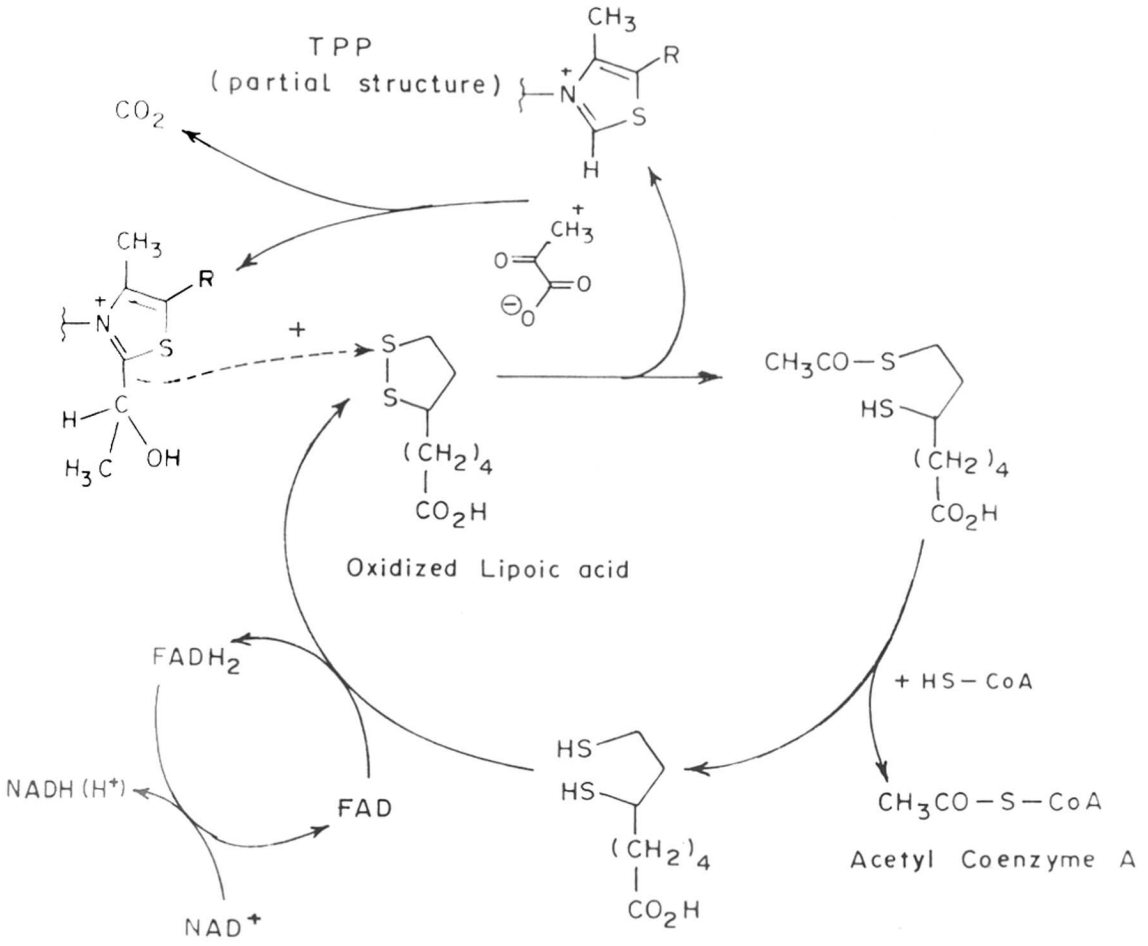
1.3 BIOSYNTHESIS OF LIPOIC ACID:

The origin of the carbon backbone was investigated by Reed, who reported that octanoic acid serves as a specific precursor of lipoic acid in Escherichia Coli,[14] Carreau et al. on the basis of in vivo studies with rats injected with essential fatty acids, suggest a hypothetical pathway leading to the release of an eight-carbon chain from linoleic acid.[15] Incorporation of labelled octanoate into lipoic acid in E.Coli was confirmed by Parry,[16] who showed also that the introduction of sulfur at C-6 and C-8 of octanoic acid takes place without loss of hydrogen from C-5 and C-7 and with inversion of the configuration of the prochiral C-6 center.[17] This author suggests, as a possible mechanism of sulfur introduction, a multistep process involving a hydroxyl derivative at C-6 of octanoate. Hydroxylation at C-8 seems to be ruled out by the observation

of Reed that 8-hydroxy [1-^{14}C] octanoate is not incorporated into lipoic acid by E. Coli.[14] It cannot be excluded, therefore, that the two sulfur atoms are added to lipoic acid at different times and by two different mechanisms. The origin of sulfur is unknown. In E. Coli the source of the sulfur moiety of biosynthesized lipoic acid appears to be inorganic sulfate ion and methionine.[18] Spoto et al. by the biosynthetic studies using ^{35}S and ^{14}C-labelled precursors have demonstrated that lipoic acid synthesis occurs predominantly in the liver and that the sulfur atom originates from an organic precursor, cysteine.[19] Since it was observed that the carbon backbone does not originate from cysteine, it indicates that sulfur atom is transferred from cysteine into lipoic acid, in a step, during the biosynthetic process. Wagh et al. have found arachidonic acid to be the immediate precursor followed by linoleic acid for the biosynthesis of lipoic acid in normal and diabetic rats.[10]

1.4 BIOCHEMICAL ROLE:

The complete oxidation of pyruvate during aerobic glycolysis takes place by the tricarboxylic acid (TCA) cycle. Before pyruvate enters this cycle, it undergoes oxidative decarboxylation. The stages in this complex process are shown in Fig. 1. Thiamine pyrophosphate (TPP) is involved in the decarboxylation stage in a similar way



NAD = Nicotinamide adenosine dinucleotide.
FAD = Flavin adenosine dinucleotide.

FIG. 1. ROLE OF LIPOIC ACID

to that in the conversion of pyruvate to CH_3CHO. However, in this case, the two-carbon fragment is not released as CH_3CHO, but passes on to the next stage, where it is oxidized and becomes bound to lipoic acid as a thioester. At the same time, part of the disulfide bond of lipoic acid is reduced to a thiol group. The acetyl group now present as a thioester is then transferred to the -SH group of co-enzyme A, by the acetyl-transfer enzyme system. Reduced lipoic acid is reoxidized by interaction with FAD, and the cycle is completed. The two-carbon fragment present as a thioester of coenzyme A (acetyl coenzyme A) then enters the TCA cycle. FAD is regenerated by interaction with NAD^+ in the electron transport system.

High biological activity of α-lipoic acid is attributed to the hydrophobic interaction and metal-ion co-ordinating ability[1b] of the molecule, which helps the free passage of the compound in various tissues. α-Lipoic acid offers metal ions two different binding sites, the carboxylate group and the disulfide linkage. The carboxylate group dominates the co-ordinating properties of this ligand towards metal ions but a disulfide metal ion interaction is still possible, and under sterically favourable conditions, may become very important, this could be true under enzymic conditions when the carbonyl group is no longer free but amide-linked to the protein. Further, due to the valeric acid side chain, the lipoyl moiety is ideally

suited to undergo hydrophobic ligand-ligand interaction in mixed ligand complexes. Such hydrophobic interactions seem to be ideal to allow migrations across cell membranes of the 14 A° long lipoyl-lysyl moiety and also to facilitate the correct fixation at the surface of the enzyme.

1.5 STEREOCHEMISTRY OF LIPOIC ACID:

α-Lipoic acid was assigned the (R)-configuration (1a) by Mislow and Meluch,[20] by comparison of the melting point-composition diagrams for mixtures of (R)-(+)-3-methyloctanedioic acid with (+)- and with (-)-3-mercapto-octanedioic acid, respectively. By synthesis these mercapto-diacids had been correlated with (-)- and (+)-α-lipoic acid, respectively. Studies of the biosynthesis of (1a) by Escherichia Coli have revealed that if α-(+)-lipoic acid has the (R)-configuration, then insertion of sulfur at C-6 of octanoic acid must occur with inversion of configuration.[17,21] This was proved by Golding et al. by the synthesis of (S)-(-)-α-lipoic acid, the optical antipode, from (S)-malic acid by a route that features a single inversion of configuration at the chiral center.[22]

1.6 SYNTHESIS OF OPTICALLY ACTIVE α-LIPOIC ACID: A REVIEW:

Since its isolation in 1950 by Reed,[3] this biologically important molecule, possessing a single chiral center, was not synthesized by an asymmetric process until 33 years later when Golding[22] reported the synthesis of the antipode

of the natural isomer and Elliot[23] followed shortly, a couple of years later, with the synthesis of the natural isomer, (R)-(+)-lipoic acid. Until then there have been a number of reports on the synthesis of racemic lipoic acid and optically pure forms of lipoic acid was obtained by resolution at some stage of the synthetic process.[24]

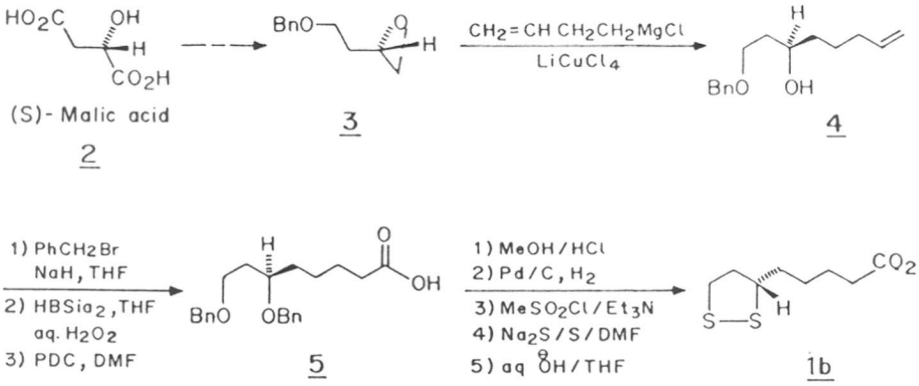
The only chiral center in this molecule could be obtained mainly by two modes: a) by the chiron approach, where the chirality present in a natural product is translated to the desired molecule and b) by induction *via.* asymmetric reactions.

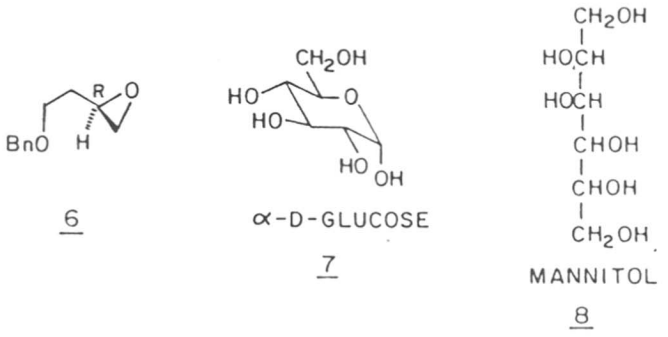
Lipoic acid has been synthesized, employing both the above modes by various groups. Synthesis by Golding[22] et al. and A.V. Rama Rao[25] et al. involves the chiron approach whereas those by Elliot[23] et al., Sutherland[26] et al. and Brookes[27] involves asymmetric synthesis.

1.6.1 Golding Synthesis:

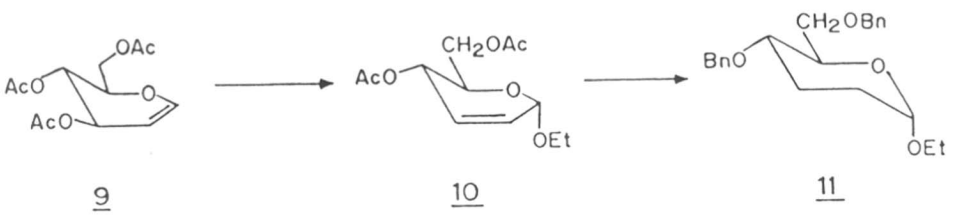
Golding et al. (1983) were the first to synthesize the optical antipode of natural α-lipoic acid and thus prove the absolute configuration of natural α-lipoic acid. The crucial step in the strategy (Scheme-1) is the opening of the epoxide 3 obtained from S-malic acid 2 with but-3-enylmagnesium chloride catalysed by lithium tetrachlorocuprate to give 6-hydroxy-8-(benzyloxy)oct-1-ene 4 which on hydroboration followed by oxidation gives 5

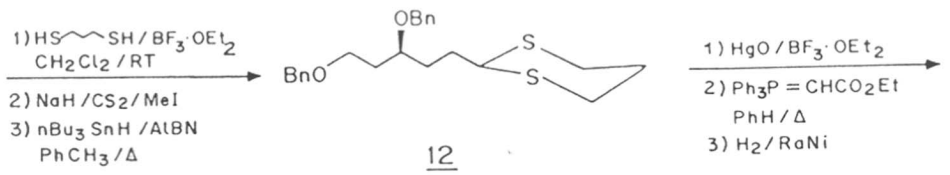
SCHEME-1

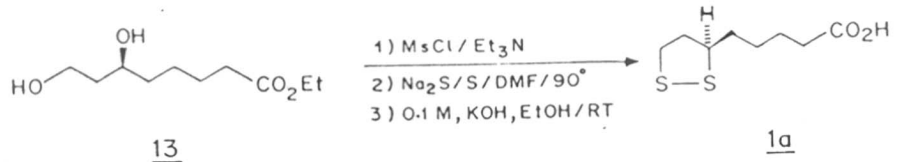




SCHEME-2







which comprises the eight-carbon skeleton of α-lipoic acid, this is then converted to lipoic acid by conventional methods in an overall yield of 25%. In this synthesis the chiral center present in (S)-malic acid forms the chiral center of lipoic acid.

Later (1988), Golding et al.[28] reported the synthesis of R-(+)-lipoic acid **1a** starting from (S)-malic acid as above but involves the inversion of configuration of intermediate **4** in three steps which eventually gives (R)-oxirane **6** leading to (R)-lipoic acid exactly as above.

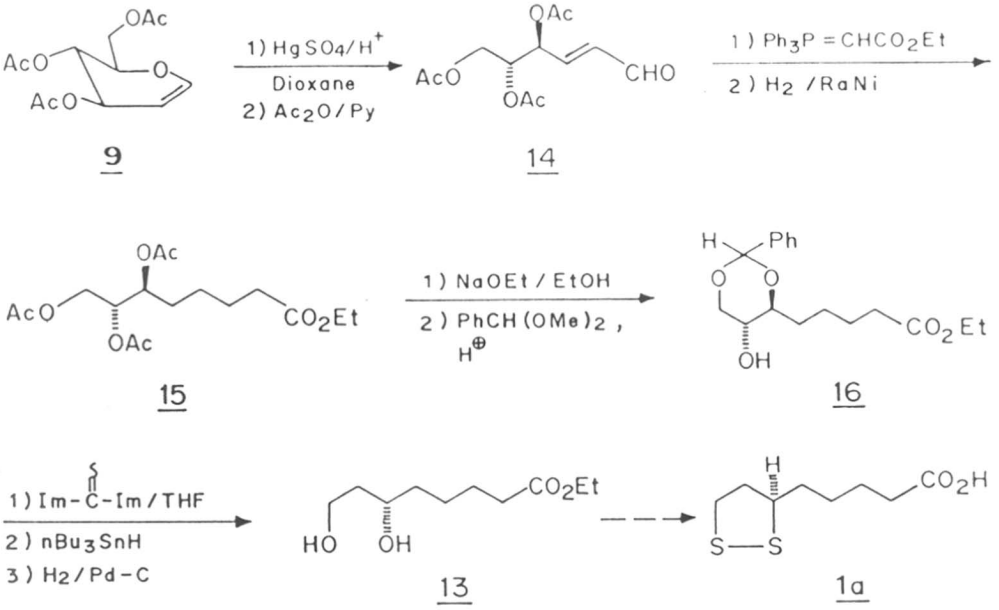
1.6.2 A.V. Rama Rao Synthesis:

Rama Rao et al. have reported synthesis of R-(+)-α-Lipoic acid by chiron approach. Starting from sugar molecules like D-glucose and D-mannitol. Lipoic acid has been synthesized by two synthetic routes starting from 3,4,6-Tri-O-acetyl-D-glucal **9**, which is derived from D-glucose. One route (Scheme - 2)[25a] involves the conversion of **9** by 4 steps to the 4,6-di-O-benzyl derivative **11** by known methods. This on treatment with propanedithiol-boron trifluoride affords the dithiane derivative which on Barton-McCombie deoxygenation affords **12**. Mercuric oxide hydrolysis of **12** gives the corresponding aldehyde which when subjected to a C_2-homologation by a Wittig reaction followed by hydrogenation in the presence of Raney nickel affords the 6,8-dihydroxyoctanoate, the carbon skeleton of lipoic acid which is then converted to α-lipoic acid **1a** as usual.

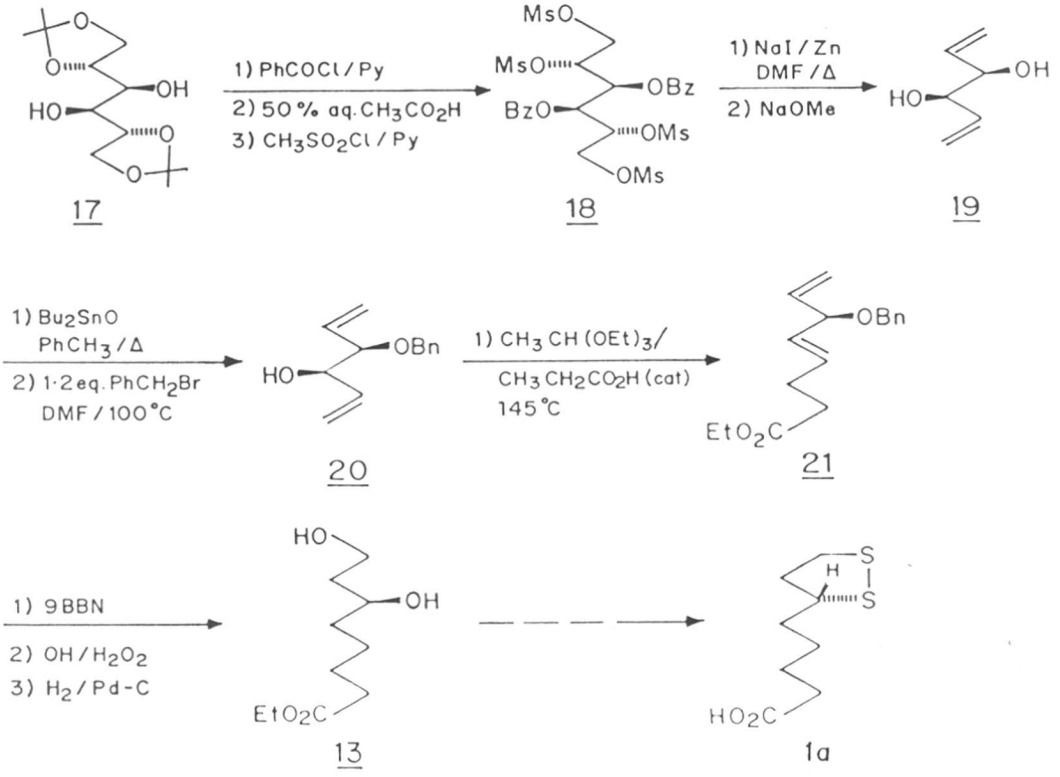
The other route (Scheme-3)[25b] also involves the 6,8-dihydroxy octanoate **13** as the precursor, but the approach to this precursor from **9** is different. 3,4,6-Tri-O-acetyl-D-glucal **9** under mercurous ion catalysed ring opening followed by acetyl protection of the alcohol gives **14**, which on two carbon homologation under Wittig conditions and subsequent hydrogenation affords ethyl-6,7,8-triacetoxy octanoate **15**. This is then deacetylated under sodium ethoxide catalysis and the 6,8-hydroxyl groups are selectively protected using α,α'-dimethoxytoluene to give the benzylidene derivative **16**. This is then transformed to the xanthate derivative followed by Barton-McCombie deoxygenation and deprotection of the 6,8-hydroxyl groups to give **13** which is elaborated to lipoic acid as in Scheme-2.

The key intermediate in the synthesis starting from D-mannitol (Scheme-4)[25c] involves the (3R,4R)-1,2-divinyl-glycol **19**. 1,2,5,6-di-O-isopropylidene-D-mannitol **17**, on benzoylation followed by hydrolysis of the isopropylidene groups and reprotection of the hydroxyl groups as the mesylate gives **18**. Further treatment of **18** with sodium iodide and zinc dust followed by debenzoylation gives the divinylglycol **19**. Monobenzylation of **19** was achieved *via* its tin derivative to give **20**. Claisen-ester rearrangement of **20** with triethylorthoacetate and subsequent hydroboration-oxidation followed by hydrogenation

SCHEME-3



SCHEME-4



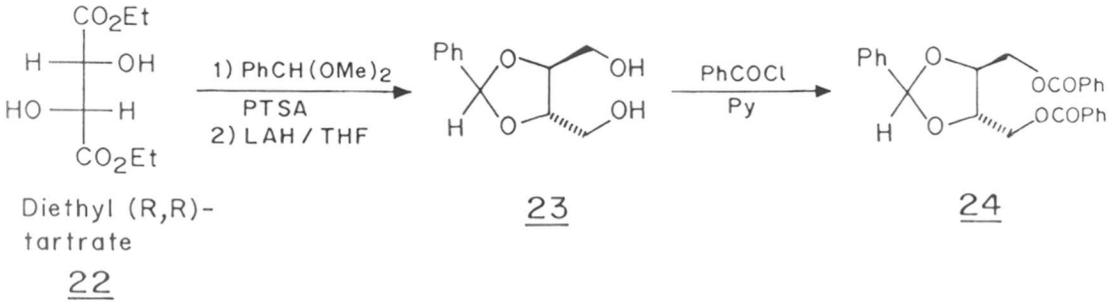
affords the intermediate **13** which is converted to α-lipoic acid by the procedure of Golding et al.

Another process by chiron approach utilises the chiral center present in natural tartaric acid (Scheme-5).[30] The chiral synthon in this strategy is 1,2R,4 -butanetriol **26**, derived from diethyl (R,R)-tartrate **22**. The dioxolane derivative **23** is obtained by treating diethyl tartrate **22** with α,α'-dimethoxytoluene in the presence of p-toluene-sulfonic acid followed by reduction of ester with lithium aluminium hydride to the diol. Protection of the diol as the benzoate **24** followed by bromination results in **25** which on reductive debromination and debenzoylation affords the triol **26**. Triol is converted to the dioxane **27** with α,α'-dimethoxytoluene and the alcohol oxidised with PCC to aldehyde. Aldehyde when subjected to Wittig olefination followed by reduction of the olefin and acid catalysed deprotection of the diol gave dihydroxyoctanoate **13**. Mesylation, disulfurization and saponification of **13**, sequentially gave R-(+)-lipoic acid.

1.6.3 Elliot Synthesis:

In this approach, the chiral center is obtained by asymmetric synthesis *via* chiral acetal templates. The most significant reaction in this synthetic strategy (Scheme-6)[23] is the $TiCl_4$-catalysed coupling of chiral acetal **31** with the ketene acetal **32** to generate the

SCHEME-5

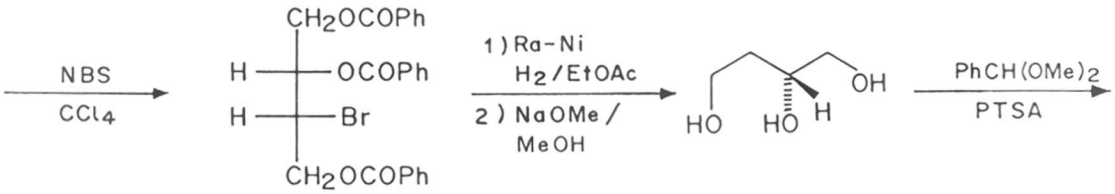


Diethyl (R,R)-tartrate

22

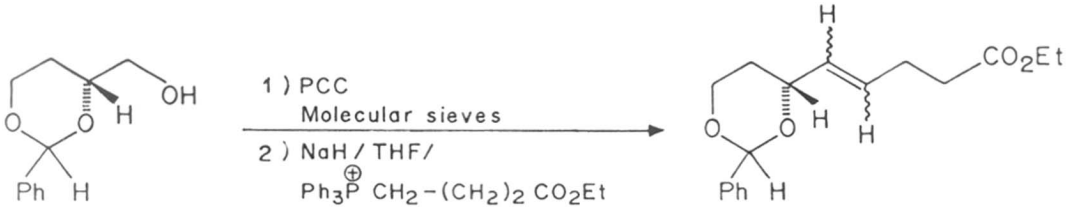
23

24



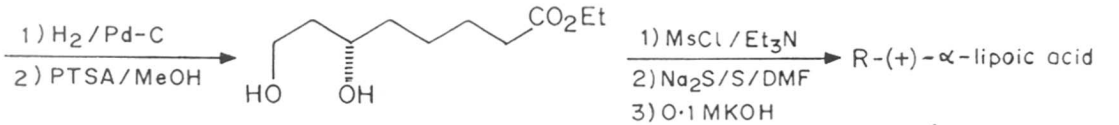
25

26



27

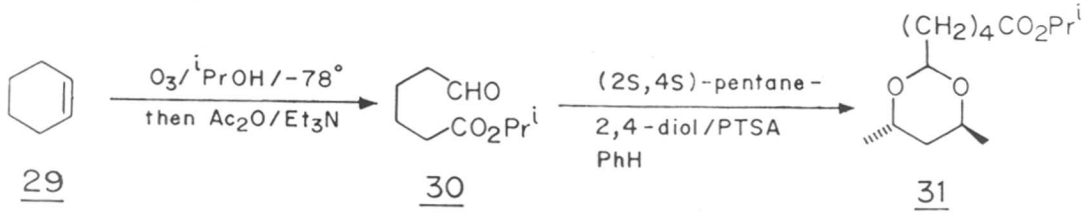
28



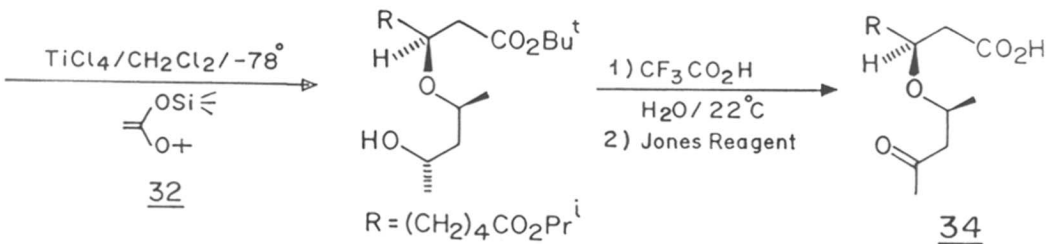
13

1a

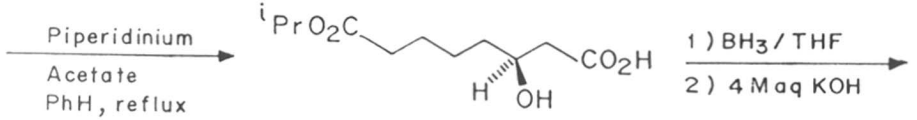
SCHEME-6



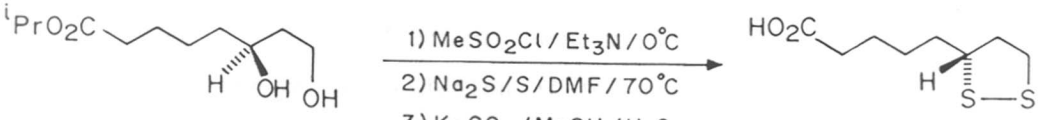
29 30 31



32 33 34



35



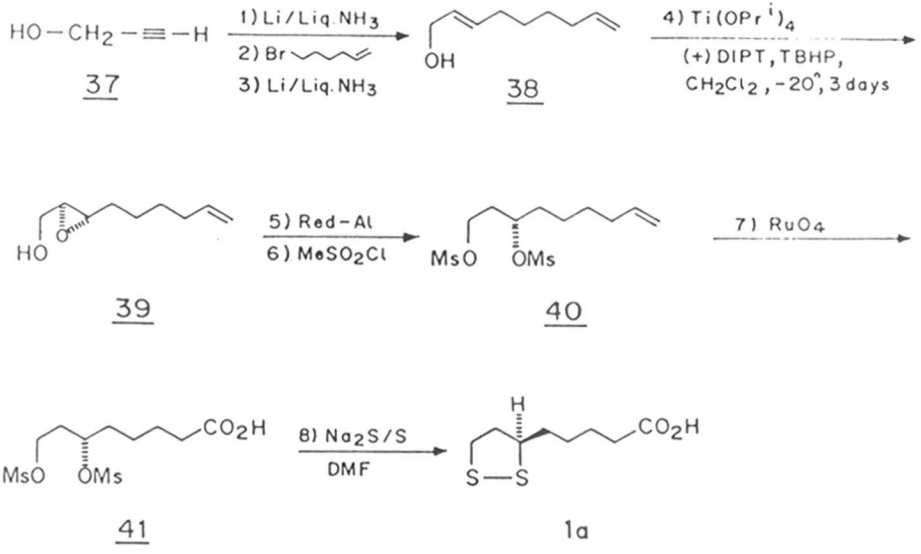
36 1a

β-alkoxycarboxylate 33 in which the new asymmetric center is formed with excellent diastereoselection. Hydrolysis of ester 33 followed by oxidation with Jones reagent gives 34. Removal of the chiral auxiliary was achieved by treating 34 with piperidinium acetate in boiling benzene to afford the β-hydroxy acid 35 which is converted to the diol 36 by hydroboration-saponification. The dihydroxy-octanoate is then converted to lipoic acid as in Golding's route. The foregoing sequence proceeded in 37% overall yield based on S,S-2,4-pentanediol.

1.6.4 Sutherland Synthesis:

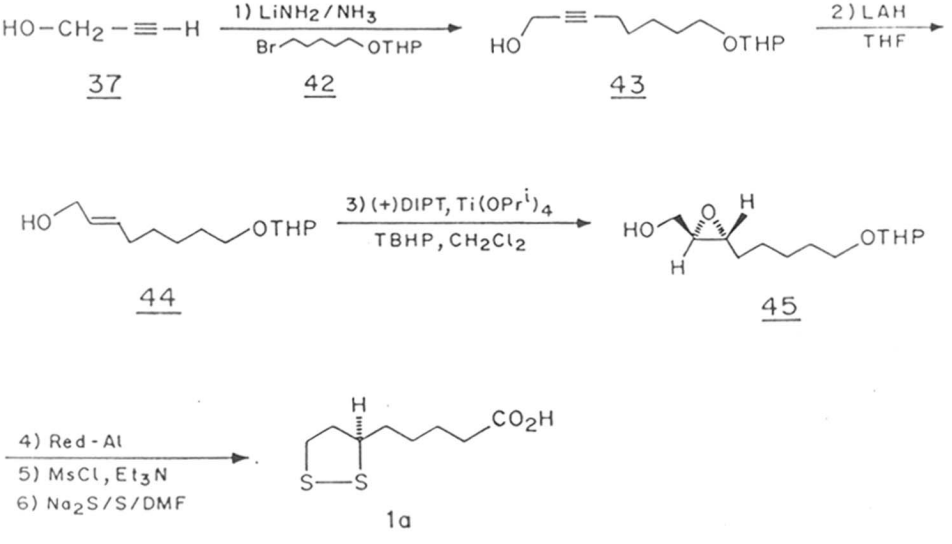
Lipoic acid has been synthesized in an enantioselective manner from achiral precursors using the Sharpless asymmetric epoxidation as the key step in the reaction sequence (Scheme-7)[26] to control the absolute configuration of the chiral center. Alkylation of the lithiodianion of propargyl alcohol 37 in liquid ammonia solution with 6-bromohex-lene followed by dissolving metal reduction of the resultant disubstituted acetylene <u>in situ</u> gave the allylic alcohol 38. Sharpless asymmetric epoxidation of 38 using L-(+)-diisopropyl tartrate as the chiral auxiliary gave the (2S,3S)-epoxyalcohol 39. Regioselective reduction of the epoxyalcohol using Red-Al followed by mesylation gave 40. Ruthenium tetraoxide oxidation of the terminal double bond using the catalytic procedure by Sharpless[29] resulted in

SCHEME-7



37 38 39 40 41 1a

SCHEME-8



37 42 43 44 45 1a

the formation of **41** which on treatment with sodium disulfide proceeded with inversion of configuration to give R-(+)-lipoic acid in an overall yield of 22%.

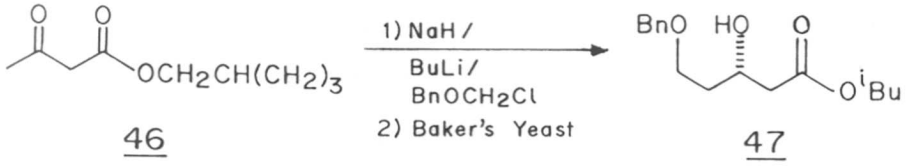
A.V. Rama Rao et al. (Scheme-8)[30] have also synthesized lipoic acid employing the same strategy with some difference. The dilithiodianion of propargyl alcohol **37** is alkylated with tetrahydropyranylated 5-bromopentanol **42** and the resulting substituted propargyl alcohol **43** is reduced with lithium aluminium hydride to give the trans allylic alcohol **44** which forms the substrate for Sharpless asymmetric epoxidation. The asymmetric epoxy alcohol **45** on regioselective reduction by Red-Al, followed by mesylation and sulfurisation gave R-(+)-lipoic acid.

1.6.5 Brooke Synthesis:

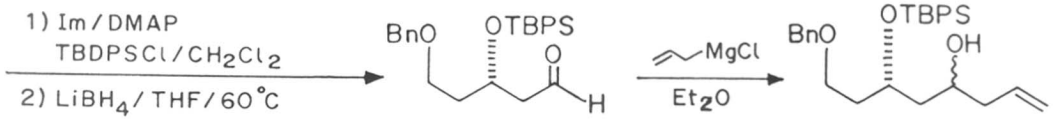
Brooke et al. (1987) reported a formal synthesis of (S)-(-)-lipoic acid, in which the chiral center is fixed by an enantioselective microbial reaction (Scheme-9).[27]

5-Benzyloxy-3-oxobutanoate ester was prepared by alkylation of the dianion of the corresponding 3-oxobutanoate **46**. Incubation of this substrate with Baker's yeast (Sacchromyces cerevisiae) at 30°C for 16 h provided (S)-5-benzyloxy-3-hydroxybutanoate **47**. This on silylation with tert-butylchlorodiphenylsilane and subsequent reduction with lithium borohydride provides the alcohol, oxidation of which with bipyridinium chlorochromate provides the

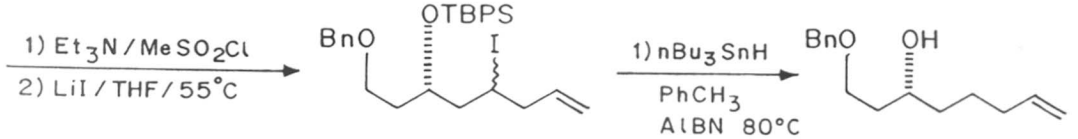
SCHEME-9



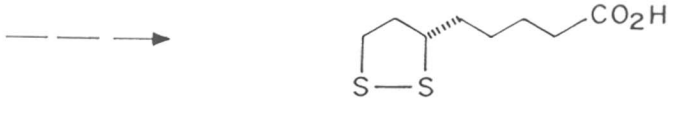
46 47



48 49



50 51



1b

aldehyde **48**, which was treated with allyl magnesium bromide resulting in formation of an epimeric mixture of alcohols **49**, which were converted to the corresponding iodides **50** by displacement of the mesylate with lithium iodide. Treatment of the iodides **50** with tri-n-butyltin hydride followed by cleavage of the silyl ether gave the chiral intermediate **51**, first synthesized by Golding and coworkers[1] from (S)-malic acid and used as a key intermediate in their total synthesis of (S)-(-)-lipoic acid (unnatural enantiomer).

PRESENT WORK

1.7 RESULTS AND DISCUSSIONS:

From the preceding section that delineates various asymmetric synthetic strategies for (R)-lipoic acid, it is evident that all the strategies without exception involve the synthesis of the chiral dihydroxyoctanoic acid derivative **13** as the immediate precursor; the chirality being introduced either *via* the chiron approach involving many steps, thus affecting the overall yield or *via* asymmetric synthesis, which though elegant, makes use of rather expensive and self-immolative chiral auxiliaries.

The synthesis of lipoic acid described in the following paragraphs was planned to develop a simple and practical synthetic route laying emphasis on the following objectives:

(a) Product of high ee and amenable to both the optical antipodes in good chemicals yields,

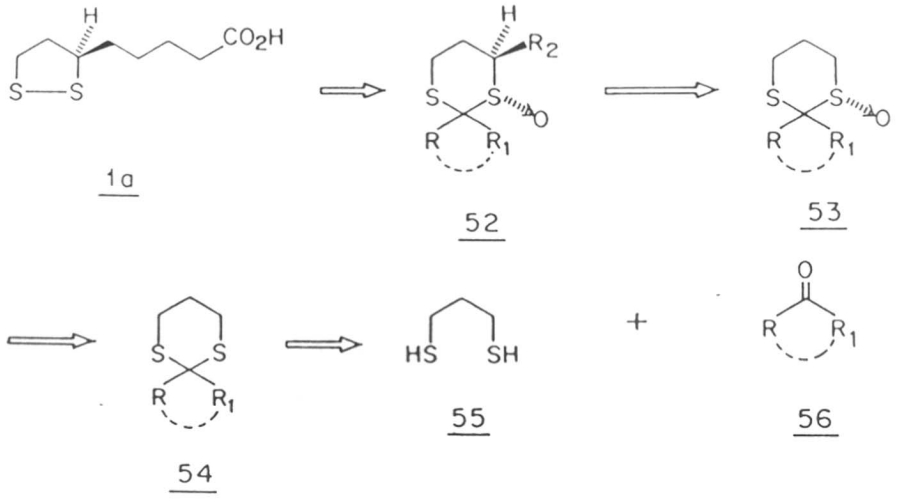
(b) Use of cheap and easily available chiral auxiliary,

(c) Recyclable chiral auxiliary, and

(d) Amenable for scale up to multigram quantities.

With this perspective, the following retrosynthetic analysis was proposed (Scheme-10).

SCHEME-10



1a

52

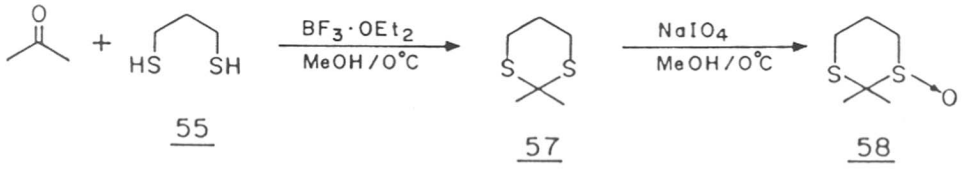
53

54

55

56

SCHEME-11



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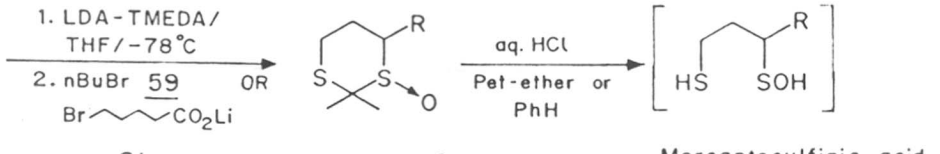
58



61

60 R = $-Bu^n$

62 R = $-(CH_2)_4CO_2H$

Mercaptosulfinic acid derivative

R = $-Bu^n$

R = $-(CH_2)_4CO_2H$

63 R = $-Bu^n$

1 R = $-(CH_2)_4CO_2H$

From the retrosynthetic analysis, it can be seen that depending upon the choice of the ketone, one can obtain dl-, d- or l-lipoic acid. A symmetrical ketone will furnish a dl-product whereas an asymmetric ketone will result in d- or l-product depending on the chirality resident in the ketone.

Initially, to start with, attempts were directed towards dl-lipoic acid. Hence the symmetrical ketone chosen was acetone (Scheme-11). 2,2-Dimethyl-1,3-dithiane **57**, was prepared as reported,[31] in 90% yields and oxidized to monosulfoxide **58** with 1 equivalent of an aqueous solution of sodium metaperiodate in methanol in 80% yield, (IR & NMR: Fig. No.1.1). The methyl groups which appeared as a singlet at 1.9 in **57**, being diastereotopic now, resonate as two singlets at 1.56 δ and 1.62 δ. IR spectrum shows the characteristic S-O stretching band at 1050 cm^{-1}. Alkylation of the sulfoxide **58** with 1 equivalent LDA-TMEDA and butyl bromide **59** in THF at -78°C gave **60** in 50-60% yield (IR & NMR: Fig. No.1.2). Treatment of **58** with 2 equivalents of LDA-TMEDA and δ-bromovaleric acid **61** resulted in **62** in 70% yields (IR & NMR: Fig. No.1.3). IR: 1720: C=O stretching of carboxyl group and 1030 cm^{-1}: S-O stretching MS: M^+ 264. Hydrolysis of 6-butyl-2,2-dimethyl-1,3-dithiane-1-oxide **60** in a two phase system of aqueous hydrochloric acid and petroleum ether forms the dithiolane system **63**

via the mercaptosulfinic acid in 84% yields (IR & NMR: Fig. No. 1.4). IR indicated absence of the S-O stretching band at 1050 cm^{-1} and presence of S-S bond absorbing at 900 cm^{-1}. Similarly, biphasic hydrolysis of **62** in aqueous hydrochloric acid and benzene affords the dithiolane system **1**, dl-α-lipoic acid in 84% yield (IR & NMR: Fig. No.1.5). Having achieved the synthesis of dl-lipoic acid, efforts were directed towards optically active lipoic acid.

In order to achieve an asymmetric synthesis, the choice of the ketone, mostly naturally occurring, is of utmost importance, since a stereospecific alkylation depends upon the regio- and stereochemistry of the sulfoxide **53**, which in turn is commanded by the stereochemistry of the ketone **56**.

Optically active sulfoxide can also be obtained by asymmetric oxidation. This was attempted on 2,2-dimethyl-1,3-dithiane employing Kagan's[+] method of asymmetric sulfoxidation using Sharpless reagents. However, the product obtained was found to racemise on keeping even at 0°C, hence this method was not pursued further. After this work, Furia's[++] report on his observation on

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+ Kagan in J. Am. Chem. Soc., **106**(26), 8188 (1984)

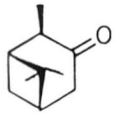
++ Furia in Tetrahedron Lett., **27**(51), 6257 (1986).

asymmetric oxidation by the same method as above, on 1,3-dithianes and 1,3-dithiolanes substantiated our findings. Enantiomeric excess was found to be poor in case of 1-3-dithianes although satisfactory in case of 1,3-dithiolanes according to Furia. Hence asymmetric oxidation is possible only by an alternative method, viz. getting the conformation of 1,3-dithiane rigid by use of chiral unsymmetrical ketones.

Fortunately nature provides such ketones and it was decided to look into the use of chiral auxiliary for the asymmetric synthesis of lipoic acid.

Examination of models of dithianes derived from naturally occurring ketones revealed that (R)-(+)-camphor **64**, (+)-isopinocamphone **65** and (-)-4-isocaranone **66** would make the best candidates for obtaining (R)-(+)-lipoic acid and l-menthone **67b**, for the optical antipode, (S)-(-)-α-lipoic acid **1b**, indicating that the unnatural d-menthone 67a should give the naturally occurring (R)-(+)-lipoic acid **1a**.

64



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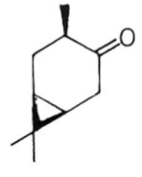

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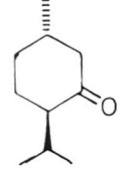
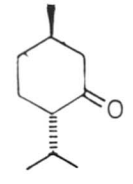


67a

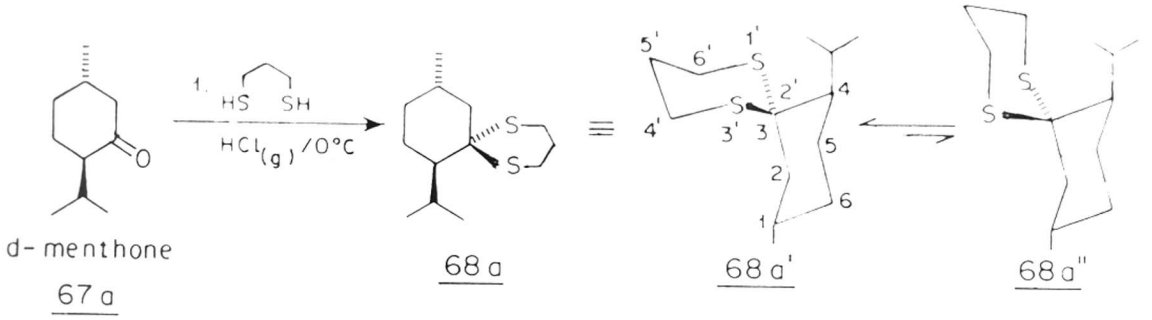


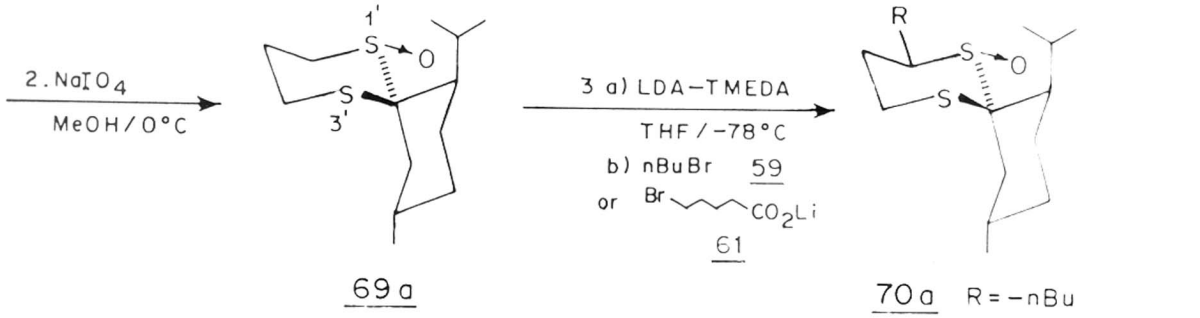
67 b

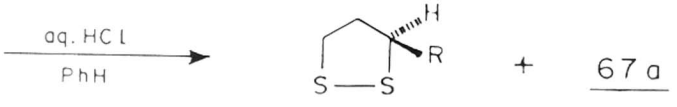
d- and l-Menthone were subjected to the same set of reaction sequence as in Scheme-11. d-Menthone[32] was spiroketalized to give dithiane **68a** (Scheme-12) with 1,3-propanedithiol mediated by an acid, as reported,[33] in 65-70% yield. Examination of the model of **68a** suggests its existence preferably in the conformation **68a'** rather than **68a"** and also its oxidation preferentially at S-1' rather than S-3' for reasons of accessibility. S-3' is rendred sterically more inaccessible by the presence of C-1 and C-5 axial protons. Furthermore, since an equatorial approach is more favoured and also from precedents[34] where equatorial sulfoxides are found to be preferred over axial ones; the sulfoxide should be an equatorial one, bearing the configuration 'S' at S-1'. Since alkylation of α-sulfinyl carbanions are known to go in a trans fashion, the above sulfoxide **69a** derived from **68a'** on alkylation should give a trans-alkylated product. This regulates the configuration at C-6' as 'R' which eventually becomes C-3 of the dithiolane system **1** with retention of configuration, on hydrolysis as mentioned earlier.

The above predictions were indeed realised when (R)-(+)-lipoic acid was obtained in high ee starting from **68**, thus proving the stereochemistry at C-6' and S-1' to be as anticipated. This was further confirmed by X-ray studies of **69b** and **71b** (Tables I and II and Figs. A&B respectively) [See Scheme-13].

SCHEME-12

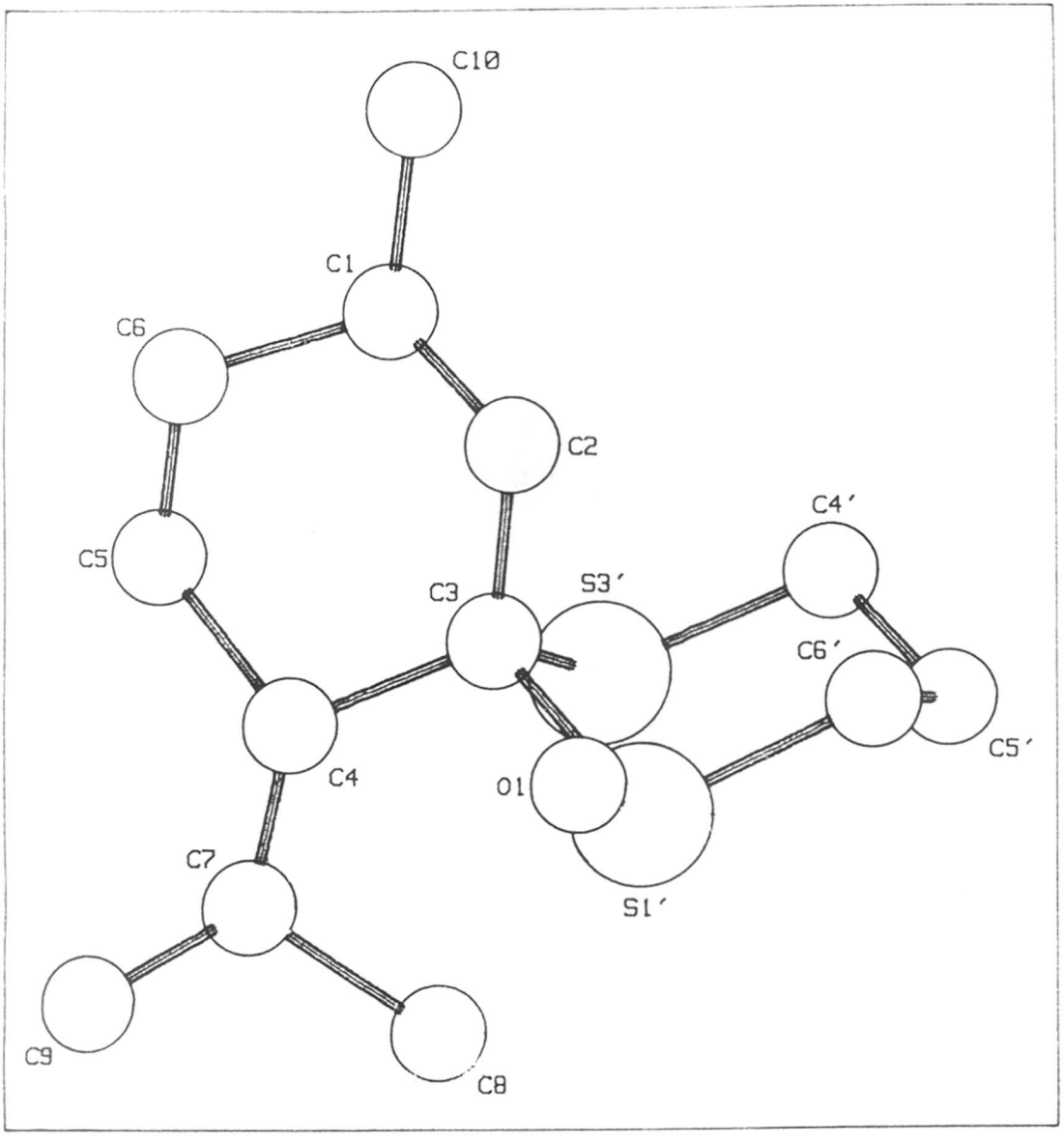






72 a R = -nBu

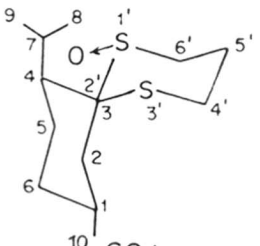
1 a R = -(CH2)4 CO2H



PLUTO diagram of Spiro [menthane-3,2'-m-dithiane]-1-oxide 69 b

FIG. A.

TABLE I



69b

Cell parameters: 8.289, 6.726, 12.799; 90.0, 96.95, 90.0 - Monoclinic ($P2_1$).

BOND LENGTHS (in Angstroms)

S1'-O	1.548	C32'-C4	1.574
S1'-C32'	1.887	C4-C5	1.651
S1'-C6'	1.835	C4-C7	1.363
S3'-C32'	1.892	C5-C6	1.411
S3'-C4'	1.810	C7-C8	1.758
C1-C2	1.470	C7-C9	1.554
C1-C6	1.569	C4'-C5'	1.496
C1-C10	1.576	C5'-C6'	1.510
C2-C32'	1.497		

BOND ANGLES (in degrees)

O-S1'-C32'	103.8	C32'-C4-C5	105.5
O-S1'-C6'	105.7	C32'-C4-C7	124.4
C32'-S1'-C6'	99.9	C5-C4-C7	117.5
C32'-S3'-C4'	100.2	C4-C5-C6	115.2
C2-C1-C6	111.8	C1-C6-C5	111.3

BOND ANGLES (in degrees) .... contd..

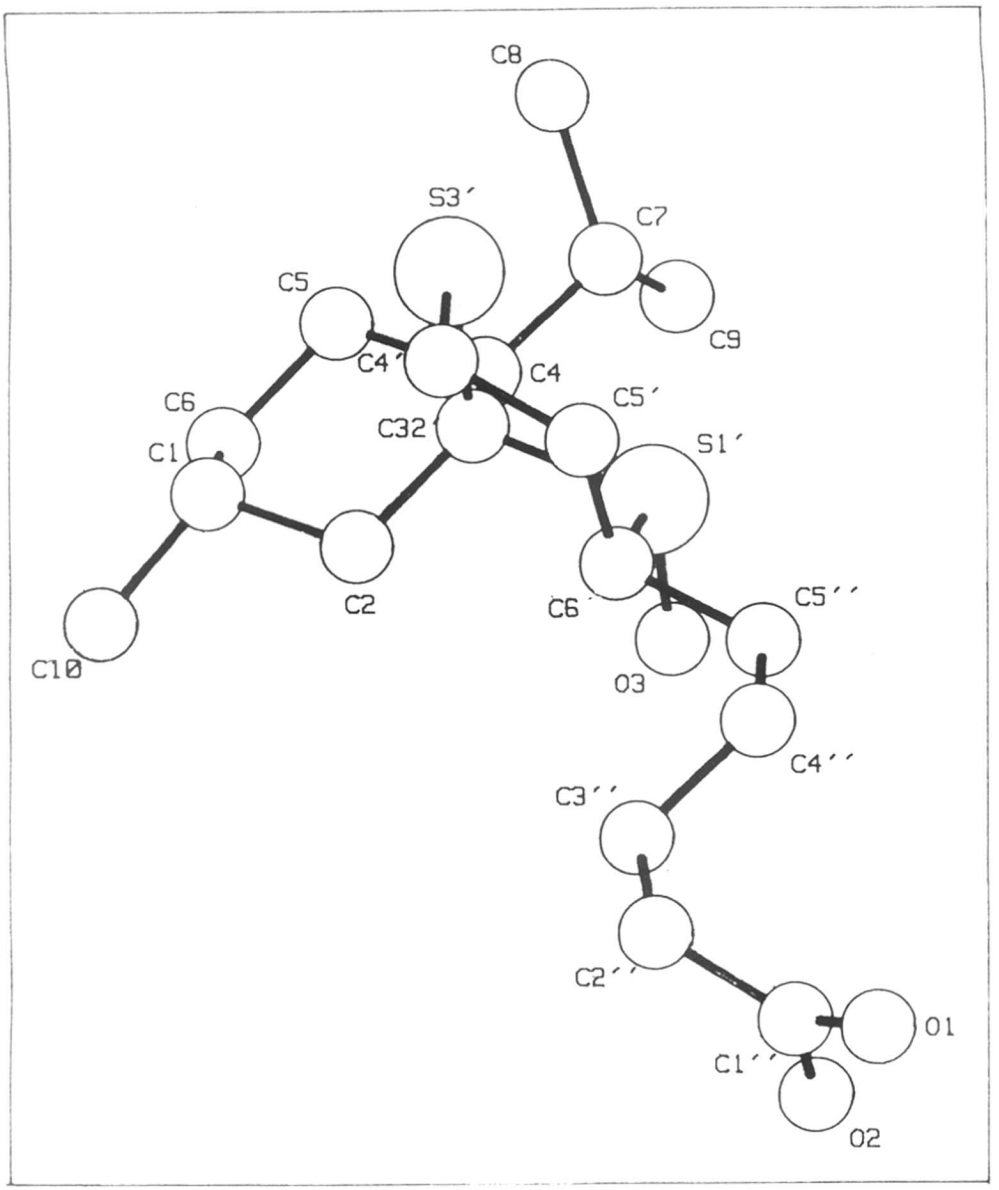
C2-C1-C10	108.7	C4-C7-C8	113.9
C6-C1-C10	111.1	C4-C7-C9	117.2
C1-C2-C32'	111.1	C8-C7-C9	123.3
S1'-C32'-S3'	99.6	S3'-C4'-C5'	110.7
S1'-C32'-C2	111.5	C4'-C5'-C6'	110.6
S1'-C32'-C4	106.6	S1'-C6'-C5'	112.9
S3'-C32'-C2	114.2		
S3'-C32'-C4	107.0		
C2-C32'-C4	116.4		

TORSION ANGLES

O-S1'-C32'-S3'	174.5	C1-C2-C32'-S3'	70.8
O-S1'-C32'-C2	53.7	C1-C2-C32'-C4	-54.7
O-S1'-C32'-C4	-74.4	S1'-C32'-C4-C5	172.2
C6'-S1'-C32'-S3'	65.6	C2-C32'-C4-C7	-47.3
C6'-S1'-C32'-C2	-55.3	S3'-C32'-C4-C5	-81.9
C6'-S1'-C32'-C4	176.7	S3'-C32'-C4-C7	58.6
O-S1'-C6'-C5'	-174.1	C2-C32'-C4-C5	47.1
C32'-S1'-C6'-C5'	-66.7	C3-C4-C7-C9	142.4
C4'-S3'-C32'-S1'	-68.5	C5-C4-C7-C8	124.2
C4'-S3'-C32'-C2	50.4	C5-C4-C7-C9	-81.3
C4'-S3'-C32'-C4	-179.3	C4-C5-C6-C1	55.3
C32'-S3'-C4'-C5'	71.3	S3'-C4'-C5'-C6'	-69.6
C6-C1-C2-C32'	56.2	C4'-C5'-C6'-S1'	67.8

TORSION ANGLES contd..

C10-C1-C2-C3	179.1	S1'-C32'-C4-C7	-47.3
C2-C1-C6-C5	-58.7	S3'-C32'-C4-C5	-81.9
C10-C1-C6-C5	179.7	S3'-C32'-C4-C7	58.6
C1-C2-C32'-S1'	-177.2	C2-C32'-C4-C5	47.1

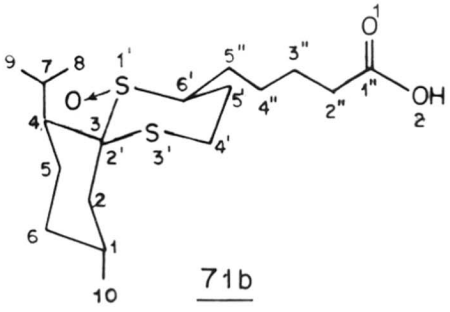


PLUTO diagram of

Spiro [menthane-3,2'-m-dithiane]-1'-oxo-6'-(5''-pentanoic acid). 71b

FIG. B.

TABLE II



71b

Cell parameters: 10.925, 12.396, 14.282; 90.0, 90.0, 90.0
Orthorhombic ($P2_12_12_1$).

BOND LENGTHS (in Angstroms):

S1'-C32'	1.854	C1-C10	1.554
S1'-C6'	1.868	C4-C5	1.537
S1'-O3	1.532	C4-C7	1.559
C32'-S3'	1.839	C5-C6	1.530
C32'-C2	1.548	C7-C8	1.582
C32'-C4	1.546	C7-C9	1.588
S3'-C4'	1.844	C1"-C2"	1.501
C4'-C5'	1.529	C1"-01	1.192
C5'-C6'	1.490	C1"-02	1.342
C6'-C5"	1.550	C2"-C3"	1.583
C1-C2	1.554	C3"-C4"	1.548
C1-C6	1.535	C4"-C5"	1.552

contd...

BOND ANGLES (in Degrees)

C32'-S1'-C6'	100.8	C6-C1-C10	111.1
C32'-S1'-03	106.0	C32'-C2-C1	110.9
C6'-S1'-03	105.1	C32'-C4-C5	110.7
S1'-C32'-S3'	103.5	C32'-C4-C7	115.6
S1'-C32'-C2	109.6	C5-C4-C7	112.2
S1'-C32'-C4	106.5	C4-C5-C6	111.3
S3'-C32'-C2	114.4	C1-C6-C5	111.2
S3'-C32'-C4	110.8	C4-C7-C8	114.9
C2-C32'-C4	111.5	C4-C7-C9	107.8
C32'-S3'-C4'	102.5	C8-C7-C9	110.1
S3'-C4'-C5'	111.7	C2"-C1"-01	124.7
C4'-C5'-C6'	114.6	C2"-C1"-02	113.4
S1'-C6'-C5'	112.0	01-C1"-02	121.9
S1'-C6'-C5"	101.9	C1"-C2"-C3"	112.4
C5'-C6'-C5"	112.8	C2"-C3"-C4"	109.3
C2-C1-C6	110.5	C3"-C4"-C5"	126.3
C2-C1-C10	107.0	C6'-C5"-C4"	112.9

TORSION ANGLES (in Degrees)

C6'-S1'-C32'-S3'	65.0	C32'-S3'-C4'-C5'	62.6
C6'-S1'-C32'-C2	-57.5	S3'-C4'-C5'-C6'	-63.7
C6'-S1'-C32'-C4	-178.2	C4'-C5'-C6'-S1'	65.1
03-S1'-C32'-S3'	174.3	C4'-C5'-C6'-C5"	179.3
03-S1'-C32'-C2	51.8	S1'-C6'-C5"-C4"	-173.2

contd..

TORSION ANGLES (contd..)

O3-S1'-C32'-C4	-68.9	C5'-C6'-C5"-C4"	66.6
C32'-S1'-C6'-C5'	-64.7	C6-C1-C2-C32'	55.5
C32'-S1'-C6'-C5"	174.6	C10-C1-C2-C32'	176.5
O3-S1'-C6'-C5'	-174.7	C2-C1-C6-C5	-57.1
O3-S1-C6'-C5"	64.5	C10-C1-C6-C5	-175.6
S1'-C32'-S3'-C4'	-65.2	C32'-C4-C5-C6	-56.2
C2-C32'-S3'-C4'	54.0	C7-C4-C5-C6	173.0
C4-C32'-S3'-C4'	-178.9	C32'-C4-C7-C8	-95.9
S1'-C32'-C2-C1	-172.5	C32'-C4-C7-C9	141.0
S3'-C32'-C2-C1	71.8	C5-C4-C7-C8	32.3
C4-C32'-C2-C1	-54.9	C5-C4-C7-C9	-90.8
S1'-C32'-C4-C5	174.4	C4-C5-C6-C1	57.7
S1'-C32'-C4-C7	-56.6	O1-C1"-C2"-C3"	133.3
S3'-C32'-C4-C5	-73.7	O2-C1"-C2"-C3"	-49.5
S3'-C32'-C4-C7	55.3	C1"-C2"-C3"-C4"	-65.6
C2-C32'-C4-C5	55.0	C2"-C3"-C4"-C5"	170.3
C2-C32'-C4-C7	-176.0	C3"-C4"-C5"-C6'	58.9

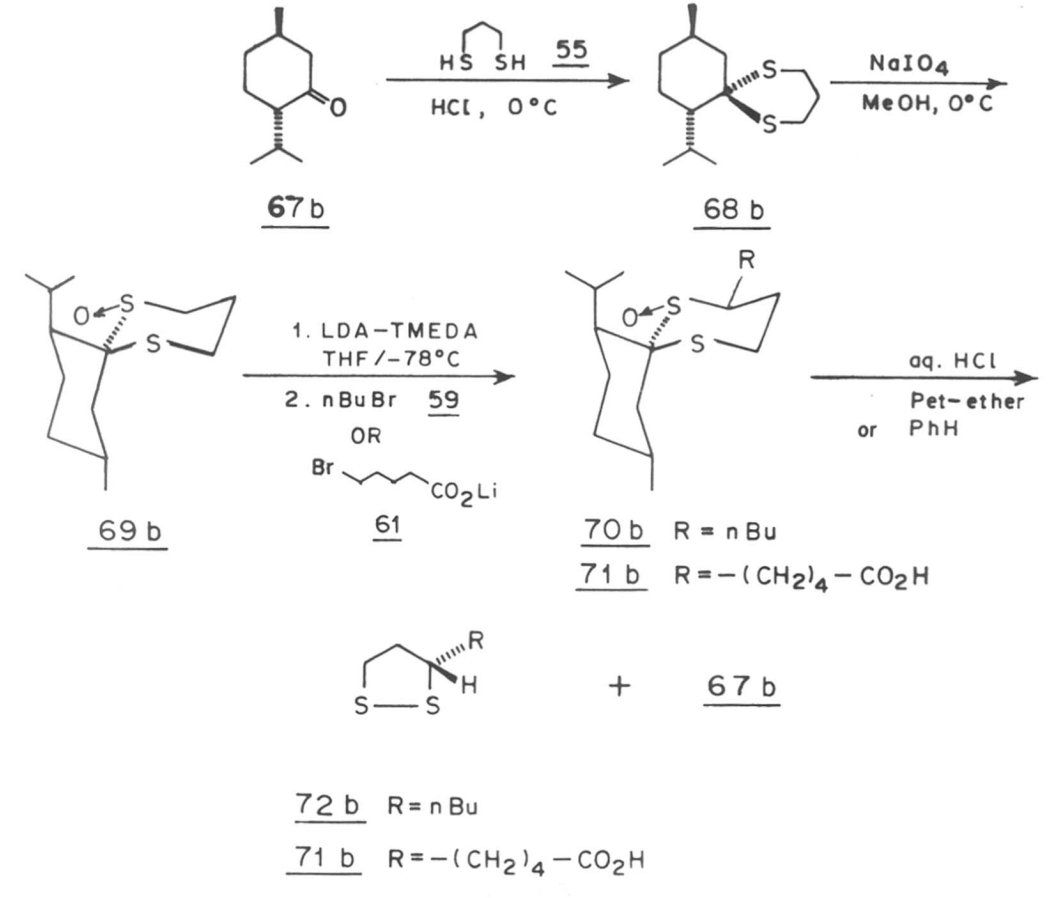
Dithiane **68a** [IR & NMR Fig.No. 1.6] on oxidation with 1.0 equiv. of sodium metaperiodate in methanol led, exclusively, to a single regio- and stereo isomer **69a** in 75-80% yield; $[\alpha]_D^{25}$: +20.8 and IR spectrum of which showed the characteristic S-O stretching band at 1040 cm^{-1} and NMR spectrum demonstrated a down-field shift of the C-6' protons to ~3 δ. Mass spectrum indicated M^+ at 260. [IR & NMR: Fig. No.1.7]. The sulfoxide **69a** when treated with 1.0 equiv. of LDA-TMEDA followed by **59** gave the butylated product **70a** (IR & NMR Fig.1.8) and and with 2.0 equiv. of LDA-TMEDA and the resulting α-sulfinyl carbanion reacted with δ-bromovaleric acid gave the sulfoxide **71a** in ~ 70% yield, with pentanoic acid incorporated, as is evident from its, IR, NMR and MS (Fig. No.1.9) and exhibited a specific rotation of +88.0° at 25°C. **71a** when subjected to hydrolytic cyclisation in a two phase system using water and benzene gave (R)-(+)-α-lipoic acid **1a** in 85% yield with $[\alpha]_D^{25}$: +102° (C, 0.45, C_6H_6) [lit.[25,26] $[\alpha]_D^{28}$: +104 (C, 0.88, C_6H_6); $[\alpha]_D^{28}$: +107 (C, 0.88, C_6H_6)]. [IR & NMR: Fig No.1.5] and d-menthone $[\alpha]_D^{25}$: +19. m.p. 44-46°C (starting d-menthone $[\alpha]_D^{25}$: +20.7°).

Similarly subjecting l-menthone **67b** ($[\alpha]_D^{25}$: -28.3°) to the same set of reaction sequence as in Schemes 11 and 12, the expected (S)-(-)-α-lipoic acid **1b**, M.p. 43-45°C, $[\alpha]_D^{25}$: -104.8° (C, 0.54, C_6H_6) (lit.[1] $[\alpha]_D^{20}$: -113° (C, 1.8, C_6H_6); $[\alpha]_D^{22}$: -117 (C, 1.8, C_6H_6) was obtained in

70-75% yield and l-menthone ($[\alpha]_D^{25}$: -28.0°) was recovered in almost quantitative yields.

The α-sulfinyl carbanion derived from **69b** (Scheme-13), the intermediate for S-(-)-lipoic acid (**1b**), when treated with butylbromide resulted in the butylated product **70b** which on hydrolytic cyclisation afforded the optically active 3-butyl-1,2-dithiolane **72b** $[\alpha]_D^{25}$: +78° (C, 0.50, PhH).

SCHEME–13

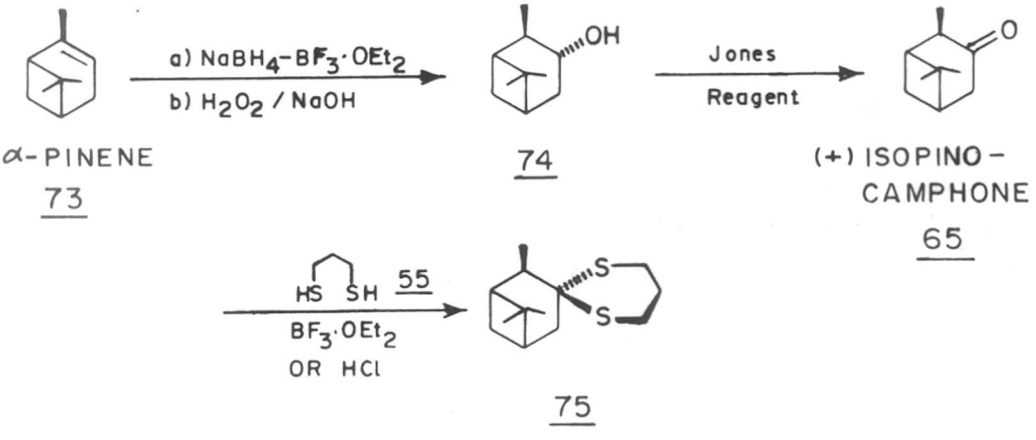


Thus it is evident that the above synthetic route can afford not only lipoic acid or its analogs but any C-3 substituted 1,2-dithiolane systems.

Having successfully accomplished the synthesis of (S)-(-)- and (R)-(+)-α-lipoic acid, with almost 100% optical induction, through the smallest number of synthetic operations, by the use of a highly efficient recyclable chiral auxiliary like menthone, attention was turned towards other naturally occurring ketones mentioned earlier.

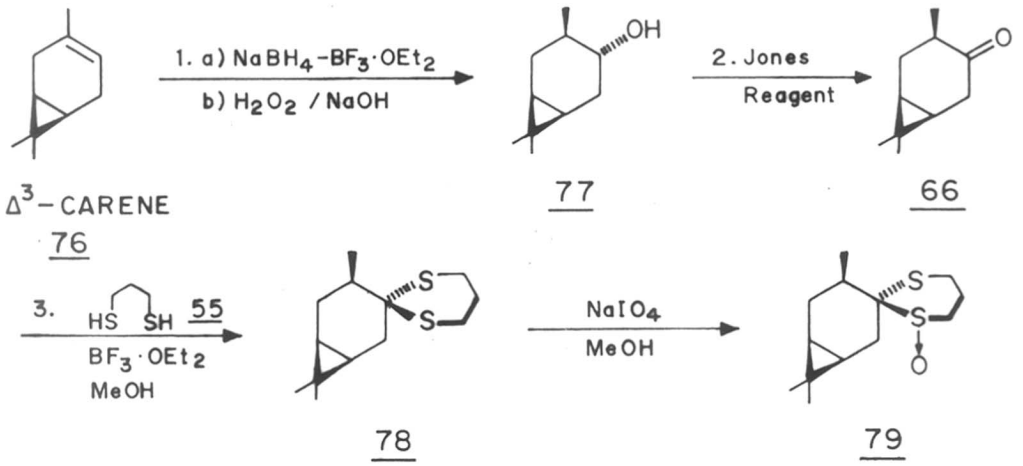
(+)-Isopinocamphone 65 was obtained from α-pinene[35] 73 in two steps as shown in Scheme-14 by: a) hydroboration-oxidation and b) oxidation by Jones reagent. Treatment of isopinocamphone 65 with 1,3-propanedithiol 55 under Lewis acid catalysis or Bronsted acid catalysis failed to yield the dithiane 75 [NMR Fig. No.1.10] in any synthetically useful yields, therefore this route was abandoned.

SCHEME-14



(-)-4-Isocaranone[36] 66 was also obtained in two steps starting from Δ^3-carene 76 (Scheme-15) by hydroboration-oxidation to give the alcohol 77 followed by oxidation with Jones reagent.

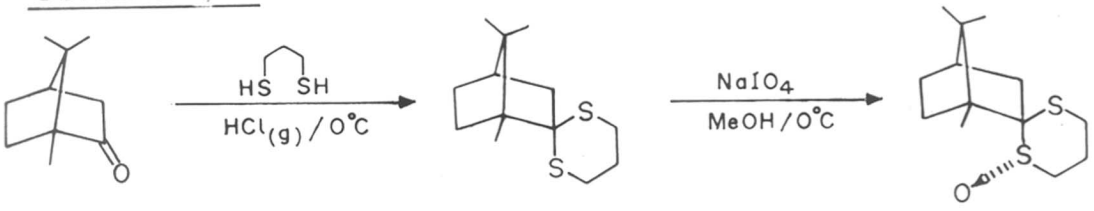
SCHEME-15



4-Isocaranone 66 was converted to the dithiane 78 [Fig. No. 1.11] in 40-50% yields by treatment with 1,3-propane-dithiol 55 in the presence of borontrifluoride etherate as catalyst. Sodium metaperiodate oxidation of the dithiane 78 gave a very poor yield of the desired sulfoxide, 79 and resulted mainly in decomposition products. Hence this route was not pursued further.

Using (R)-(+)-camphor 64 as the chiral ketone (Scheme-16), the dithiane derivative 80 [IR & NMR, Fig. No. 1.12) and its sulfoxide 81 [IR & NMR, Fig. No. 1.13] were obtained in good yields.

SCHEME – 16.



64 80 81

Attempts to alkylate sulfoxide **81** with butyl bromide **59** or δ-bromovaleric acid **61**, as carried out earlier with menthone **67a/b** were met with failure. This could be attributed to other competing reactions. It was observed that the α-sulfinyl carbanion derived from sulfoxide **81** showed difference in reactivity towards various electrophiles. The above competing reactions and the difference of α-sulfinyl carbanion reactivity were studied in some detail and are presented in the following Chapter.

1.8 EXPERIMENTAL

2,2-Dimethyl-1,3-dithiane[31] **57**

To 20 mmol acetone and 20 mmol 1,3-propanedithiol in 60 ml absolute methanol at 0°C, 2.5 ml of $BF_3.OEt_2$ was added. The resulting solution was allowed to stand for 24 h at 0°C, after which methanol was distilled out and the residue treated with 7% alkali (KOH) and extracted twice with ether. The combined extracts washed with water, dried over K_2CO_3, concentrated and the product distilled. Bp 78°C/7mm Hg. Yield 80-90% (lit.[31] 80°C/2 torr).

PMR($CDCl_3$) : 1.9, s, 6H (2 x CH_3); 2.3, m, (C_5-H_2), 3.3, t, 4H (C_4, C_6-H_2).

2,2-Dimethyl-1,3-dithiane-1-oxide[34b] **58**

A solution of 7.22 g (33.7 mmol) of $NaIO_4$ in 100 ml water was added dropwise to a solution of 5g (33.7 mmol) of 2,2-dimethyl-1,3-dithiane **57**, in 300 ml of methanol at -5°C. The resulting white slurry was stirred at -5°C for 7-8 h till the reaction was complete. The precipitated sodium iodate was removed by filtration and washed with cold methanol. Methanol was then removed in vacuo (35-40°C) and the residue extracted thrice with chloroform. The combined extracts washed with brine and worked up to yield 5.2 g of crude product which was then purified by chromatography (20 - 40% EtOAc/PhH) to give 4.5 g (84%) of the pure sulfoxide.

IR (Neat): 1025 cm^{-1} [S-O stretching]

PMR : 1.56 and 1.62, 2S, 6H (2 x CH_3); 2.2-2.4, m, 3H (C_4-H_{ax}, C5-H_2); 2.66-3.02, m, 3H (C4-H_{eq}, C6-H_2)

CMR : 16.0, q (CH_3), 25.1, q, t (CH_3, C5), 27.8, t (C4), 46.1, t (C6), 57.0, s (C2).

Asymmetric Oxidation of 2,2-Dimethyl-1,3-dithiane 57 to 58

Titanium tetraisopropoxide (1.42 g, 5.0 mmol) and diethyltartrate (2.06 g, 10 mmol) were dissolved at room temperature in 40 ml of dry CH_2Cl_2 under nitrogen. Water (0.09 g, 5 mmol) is introduced through a septum via. a microsyringe. Stirring is maintained until the yellow solution becomes homogeneous (15-20 min) and then 2,2-dimethyl-1,3-dithiane (0.740 g, 5 mmol) was added. The solution was cooled to -20° → -23°C and tert-butylhydroperoxide solution in dichloromethane (2M) was introduced. After completion of reaction (by TLC), water (10 mol equiv. i.e. 0.702 g) was added dropwise by a microsyringe to the solution at -20°C. A strong stirring was maintained for 1h at -20°C and for one additional hour at room temperature. The white gel was filtered and thoroughly washed with dichloromethane. The filtrate was then washed with brine, worked up and chromatographed ($CHCl_3$) to afford 0.591 g (72%) of the pure sulfoxide. Specific rotation recorded immediately after purification: $[\alpha]_D^{25}$: -6.69 (C, 5.2; $CHCl_3$).

6-Butyl-2,2-dimethyl-1,3-dithian-1-oxide 60

LDA was prepared by adding 1.2 ml (1.2 equiv.) of 2N nBuLi to a cooled solution (-10 → 0°C) of 0.34 ml (1.2 equiv.) diisopropylamine in 5 ml THF and stirred for 0.5h. This was then cooled to -78°C and a solution of 0.328 g (2 mmol) of 2,2-dimethyl-1,3-dithiane-1-oxide **58** in 6 ml THF was added dropwise. The reaction mixture was stirred at -78°C for 0.5 h, to complete the metalation and then a solution of 0.328 g (1.5 equiv.) of n-butylbromide in 2 ml THF was introduced dropwise and the whole mixture was stirred for 5 h at -78°C and then quenched with NH_4Cl solution at 0°C. THF was removed in vacuo and the residue extracted thrice with chloroform and worked up to afford 0.390 g of the crude product which was chromatographed (0-5% MeOH/PhH) to give 0.220 g (50%) of the butylated product **60** and 0.100 g (30%) of the starting sulfoxide 58.

IR (Neat): 1040-1050 cm^{-1} (S-O str.)

PMR: 1.1 - 2.1, m, 14H includes 2 singlets at 1.5 and 1.6 of the two methyls.

MS: M^+ 220.

2,2-Dimethyl-1,3-dithian-1-oxide-6-pentanoic acid 62

0.328 g (2 mmol) of 2,2-dimethyl-1,3-dithiane-1-oxide **58** in 6 ml THF was added dropwise to a solution of LDA-TMEDA (2.2 eq.) in 10 ml THF at -78°C. The mixture was stirred for 0.5 h at -78°C and then a solution of 0.398 g (1.1 eq.) of δ-bromovaleric acid in 2 ml THF was added dropwise and the reaction mixture was allowed to stir at -78°C for 5 h, it was then warmed up to 0°C and then quenched with aqueous HCl (1:1). THF was removed in vacuo and the aqueous layer (pH 2-3) was extracted several times with ethyl acetate, worked up and chromatographed (20% EtOAc/pet. ether) to give 0.30 g (56%) of the alkylated product

IR ($CHCl_3$) : 1030 (S-O str.), 1720 (C=O str.), 2800-3500 (-OH str.) cm^{-1}.

PMR : 1.53, S, 3H (CH_3); 1.62, S, 3H (CH_3), 1.4-1.75, m, 6H and 1.8-3.0, m, 7H.

MS: M^+ 264.

3-Butyl-1,2-dithiolane 63

To a solution of 60 mg (0.272 mmol) 6-butyl-2,2-dithiane-1-oxide **60** in 10 ml pet. ether was added 1 ml of methanolic HCl (5.3N). The reaction mixture was stirred vigorously and maintained at 40°C for 6 h, during this time the pet. ether layer was separated and replaced afresh every 1 h until the reaction was complete. The

combined pet. ether extracts were washed with water followed by brine, worked up and chromatographed (pet. ether) to afford 0.037 g (84%) of the product **63**.

IR (Neat): 910 (S-S str.) cm^{-1}.

PMR: 0.96, t, 3H (CH_3); 1.2-2.1, m, 6H (3 x CH_2), 2.43, m, 2H (C4-H_2), 3.12, m, 2H (C5-H_2); 3.56, p, 1H (C3-H)

MS : 162(M^+).

1,2-Dithiolane-3-pentanoic acid (α-Lipoic acid) 1

0.100 g (0.378 mmol) of **62** was taken in 20 ml benzene and to this was added 2 ml of aqueous HCl (1:1) and the reaction mixture was warmed to 50°C and vigorously stirred for 6-7 h until the reaction was complete. The benezene layer was separated and the aqueous layer extracted twice with benzene. The benzene extracts were combined, washed with brine, worked up and chromatographed (40% EtOAc-PhH) to afford 0.065 g (83%) of pure lipoic acid **1**.

Mp 43-45°C

IR (Neat): 910 (S-S str.), 1710 (C=O str.), 2500-3500 (O-H, str.)

PMR : 1.3-2.0; m, 8H (4 x CH_2), 2.25, t, J = 6.5H_3, 2H, (CH_2CO_2H); 3.05, m, 2H (CH_2-S), 3.48, m, 1H (CH-S).

MS, m/e: M^+ 206 (60%), 188 (3.0%), 173 (12.1%), 160 (1.3%), 155(20.8%), 141(10.4%), 137(2.1%), 127(13.4%), 123(75.4%), 113(19.5%), 105(33.4%), 99(18.2%), 95(83.2%), 85(16.7%), 81(100%), 71(14.3%), 67(29.1%), 55(51.7%), 45(29.1%), 41(30.8%).

Spiro[Menthane-3,2'-m-dithiane]/Menthone trimethylene mercaptole[33] **68a/68b**

A mixture of 1.0 g (6.49 mmol) of menthone and 0.70 g (6.49 mmol) of 1,3-propanedithiol was cooled in an ice bath and a stream of hydrogen chloride was passed through the solution till the reaction was complete (~5 h). Excess HCl was then removed in a vacuum desicator over NaOH and the mixture was dissolved in ether, washed with 5% NaOH solution, water, brine and dried over $CaCl_2$. After removal of ether the residual oil was chromatographed (30% EtOAc-pet. ether) to give the pure **68a/b** as crystalline product in 70-75% yield.

Mp 41-42°C

68a, $[\alpha]_D^{25}$ = +30.2° [C, 1.45, $CHCl_3$] (from d-menthone $[\alpha]_D^{25}$ = +20.7°)

68b, $[\alpha]_D^{25}$ = -33.8° [C, 1.5, $CHCl_3$] (from l-menthone $[\alpha]_D^{25}$ = -28.3°

PMR : 0.85-1.0, 3d, J = 5.5Hz ($3CH_3$); 1.0-2.2, m, 9H; 2.3-3.4, m, 6H ($S-(\underline{CH_2})_3-S$)

MS (m/e): M^+ 244(23.4%), 201(11.7%), 188(4.3%), 170(17.8%), 159(42.6%), 137(30.8%), 128(7.3%), 114(9.5%), 106(19.5%), 95(31.7%), 85(9.5%), 81(34.7%), 77(17.3%), 67(23.0%), 55(41.7%), 43(75.2%), 41(100%).

Spiro[Menthane-3,2'-m-dithiane]-1'-oxide **69a/69b**

To a solution of 1.0 g (4.098 mmol) of menthone trimethylene mercaptole (68a/68b) in 70 ml of MeOH was

added dropwise a solution of 0.96 g (4.482 mmol) of $NaIO_4$ in 20 ml of water at -10°C. The mixture was maintained at this temperature with stirring until the reaction was complete (7-8 h). Sodium iodate was then filtered off and methanol removed in vacuo followed by the extraction of the aqueous phase with chloroform. The chloroform extract was washed with brine, worked up and chromatographed (40% EtOAc/PhH) to afford 0.90 g (84%) of the pure white crystalline solid product **69a/b**.

Mp 135-137°C.

69a: $[\alpha]_D^{25}$ = -20.0 [C, 1.1, $CHCl_3$]

69b: $[\alpha]_D^{25}$ = +20.88 [C, 1.0, $CHCl_3$]

IR ($CHCl_3$): 1025 cm^{-1}

PMR : 0.84, d, J = 6.5Hz (CH_3); 0.86, d, J = 6.5Hz (CH_3), 0.92, d, J = 6.5Hz (CH_3), 2.4-3.4, m, 24H.

MS: M^+ 260, 244, 201, 123(100%), 95, 81.

Spiro[Menthane-3,2'-m-dithiane]-6'-butyl-1'-oxide 70b

To a solution of LDA-TMEDA (1.1 eq.) in 5 ml THF was added 1.0 mmol of sulfoxide **69b** in 5 ml THF at -78°C with stirring. After 20 min, a solution of 1.1 mmol of n-butyl bromide in 2 ml THF was added dropwise and the mixture was stirred at -78°C for 4-5 h. The reaction was then quenched with water and allowed to warm to room temperature. THF was then removed in vacuo and the residue extracted with methylene chloride 3-4 times and the combined extracts

washed with brine, worked up and chromatographed to give 60-70% of the pure product.

Mp 94-96°C

70b $[\alpha]_D^{25}$ = +120.7 [C, 1.15, $CHCl_3$]

IR ($CHCl_3$): 1020 cm^{-1}

PMR : 0.75-1.1, m, 12H (4 x CH_3); 1.2 - 2.95, m, 20H,

MS: m/e 316 (M^+)

6-Butyl-1,2-dithiolane 72b

The procedure followed was same as for **63** (3-Butyl-1,2-dithiolane)

72b: $[\alpha]_D^{25}$ = +78.0° [C, 0.55, PhH]

Spiro[Menthane-3,2'-m-dithiane]-1'-oxide-6'(5"-pentanoic acid) 71a/71b

A solution of 0.260 g (1.0 mmol) of sulfoxide **69a/69b** in 5 ml THF was added to a solution of LDA-TMEDA (2.2 eq.) in 10 ml THF at -78°C and stirred for 20-30 min. and then a solution of δ-bromovaleric acid (1.1 mmol) in 2-3 ml THF was added and the reaction mixture was stirred for 4-5 h. The reaction mixture was then quenched with water, warmed to room temperature and THF removed in vacuo. The aqueous phase was then acidified to pH 2-3 and extracted with EtOAc, 3-4 times. The combined extracts were washed with brine, worked up and chromatographed (40% EtOAc-hexane) to afford 65-75% of the pure product.

Mp : 169-171°C.

71a: $[\alpha]_D^{25}$ = -86.2° [C, 0.62, $CHCl_3$]

71b: $[\alpha]_D^{25}$ = +88.0 (C, 1.0, $CHCl_3$]

IR ($CHCl_3$) : 1000 (S-O), 1720 (C = O), 2500 - 3500 (O-H) cm^{-1}.

PMR : 0.8-1.1, 3d, 9H (3 x CH_3); 1.4-3.1, m, 22H; 5.95, bs, 1H (COOH)

MS (m/e): 360 (M^+), 343, 321, 223, 205(100%), 169, 170, 137, 95, 81.

Lipoic acid 1a/1b from 71a/71b

To a vigorously stirred solution of 0.100 g (0.277 mmol) of 71a/b in 10 ml benzene and 5 ml water, was bubbled HCl at room temperature for 1 min. The benzene layer was then separated and the aqueous phase extracted twice with benzene. The extracts were combined, washed with brine, worked up and chromatographed (10% EtOAc/hexane) to give 0.037 g (65%) of the dithiolane derivative **1** and 50-60% of the starting menthone in almost undiminished optical purity.

1a from 71a: $[\alpha]_D^{25}$ = +102.6 [C, 0.45, PhH] and recovered d-menthone; $[\alpha]_D^{25}$ = +19.0°

1b from 71b: $[\alpha]_D^{25}$ = -104.8° (C, 0.54, PhH) and recovered l-menthone, $[\alpha]_D^{25}$ = -28.0°.

Spiro[Camphane-2,2'-m-dithiane]/Camphor trimethylene mercaptole[33] 80

80 was prepared as per the procedure described for 68 and the product purified by chromatography (25% PhH/

hexane) to afford 70-80% of the pure dithiane.

$[\alpha]_D^{25}$ = -9.0° (C, 1.5, $CHCl_3$)

PMR, : 0.9, s, 3H (CH_3), 1.1, s, 3H (CH_3), 1.2, s, 3H (CH_3) 1.3-2.4, m, 7H (C3, C5, C6-H_2 and C4-H), 2.5-3.4, m, 6H (C4', C5', C6' - H_2).

MS m/e: 258(67%, M^+), 240(6.1%), 225(1%), 215(2.66%), 202(4.6%), 188(5.3%), 167(35.3%), 15.3(16.9%), 136(74.8%), 123(81.3%), 121(62.5%), 107(50.3%), 106(42%), 105(35.9%), 93(93.8%), 91(100%), 67(80.2%), 41(93.11%).

Spiro[Camphane-2,2'-m-dithiane]-1'-oxide 81

To a solution of 1.0 mmol of dithiane **80** in 15 ml of MeOH was added dropwise a solution of $NaIO_4$ (1.0 mmol) in 5 ml water at -10°C. The mixture was maintained at -10°C with stirring until the completion of reaction (7-8 h). sodium iodate was then filtered off and methanol removed in vacuo (<40°C). The residue was extracted with chloroform 3-4 times. the extracts were combined, worked up and chromatographed (60% EtOAc-hexane) to afford 70-80% of the pure sulfoxide **81**.

Mp : 107-109°C

$[\alpha]_D^{25}$ = -132.4 [C, 1.0, $CHCl_3$]

IR ($CHCl_3$) : 1030 cm^{-1}

PMR : 0.75 , s, 3H (CH_3); 0.88, s, 3H (CH_3); 0.94, s, 3H (CH_3); 1.2 - 3, m, 7H, 3 - 3.9, m, 6H.

CMR, PPM: 12.34, q (CH_3); 20.01, q (CH_3); 22.22, q (CH_3); 25.41, t (CH_2); 25.99, t (CH_2); 28.4, t (CH_2), 32.6, t (CH_2); 33.01, t (CH_2), 45.68, d (CH), 52.38, s; 52.7, t ($\underline{CH}_2$-S-O), 55.4, s; 74.9, s.

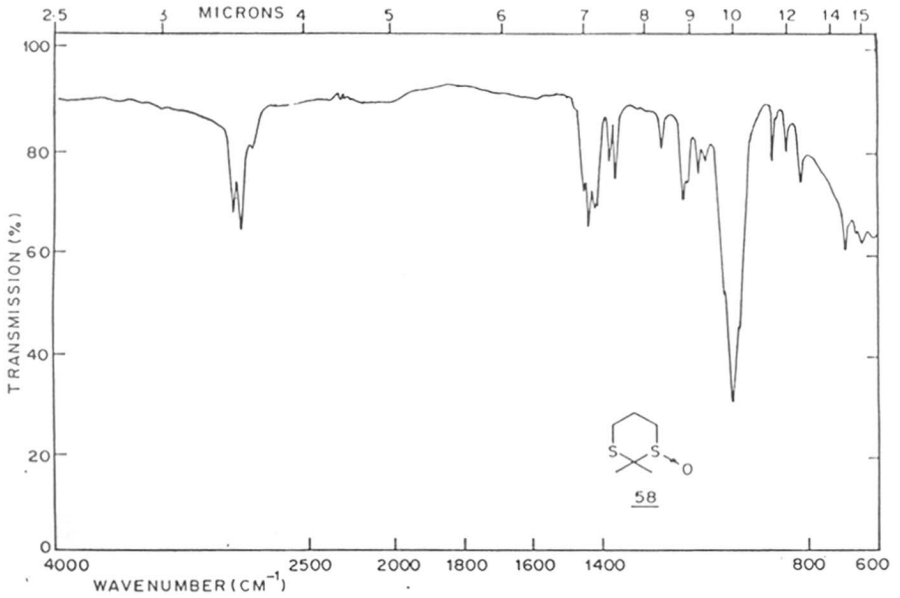
MS m/e: 258 (M^+).

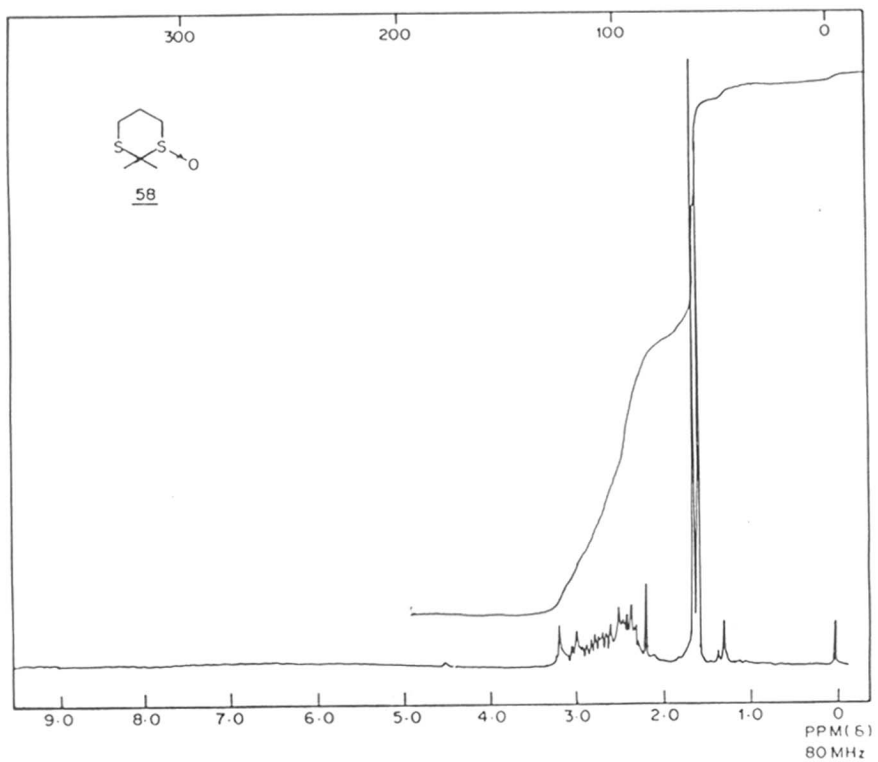
Dithiane 78 from 4-Isocaranone 66

Procedure employed was same as that for **57**.

Sulfoxide 79 from Dithiane 78

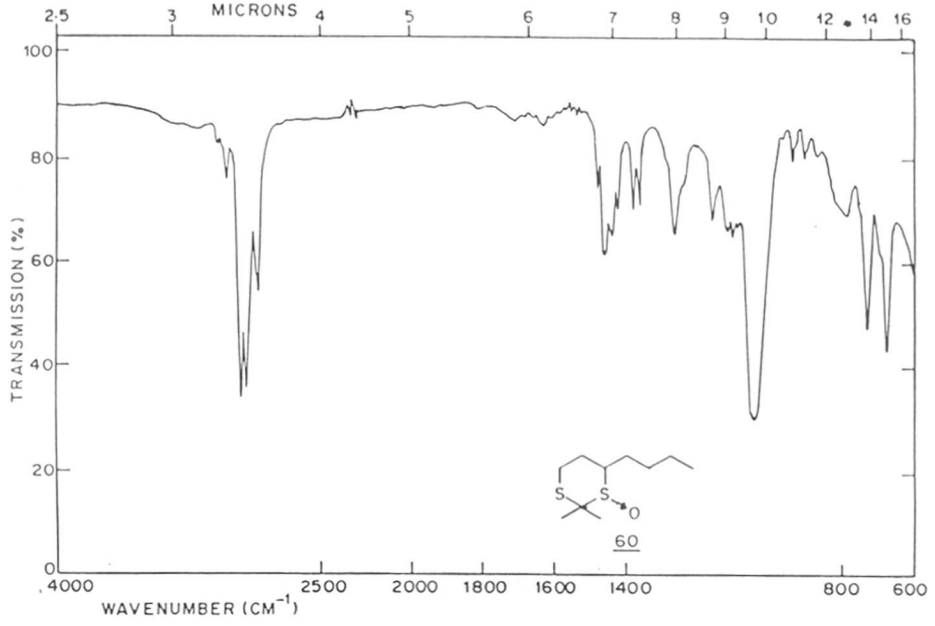
Procedure followed was same as that for **58**.

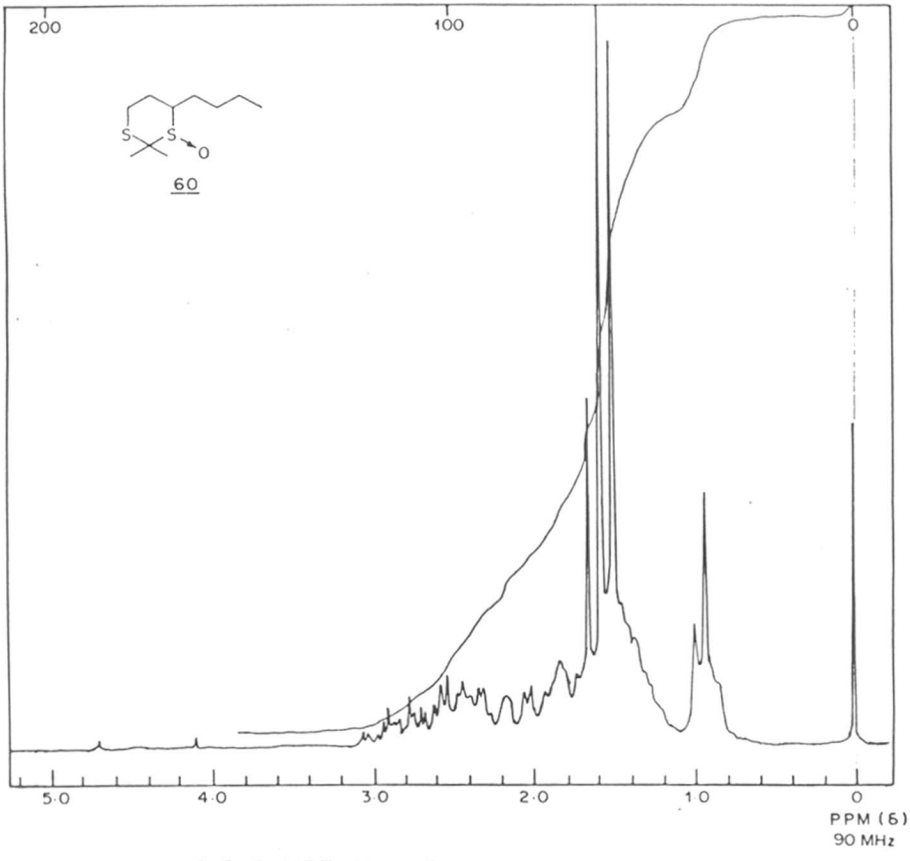




2,2-DIMETHYL-1,3-DITHIANE-1-OXIDE 58

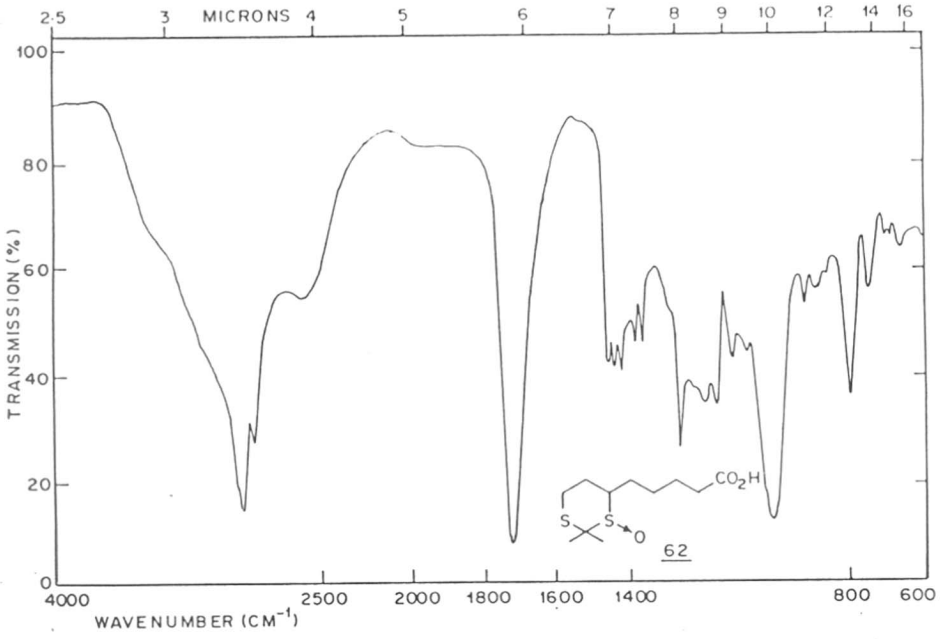
FIG. 1·1.

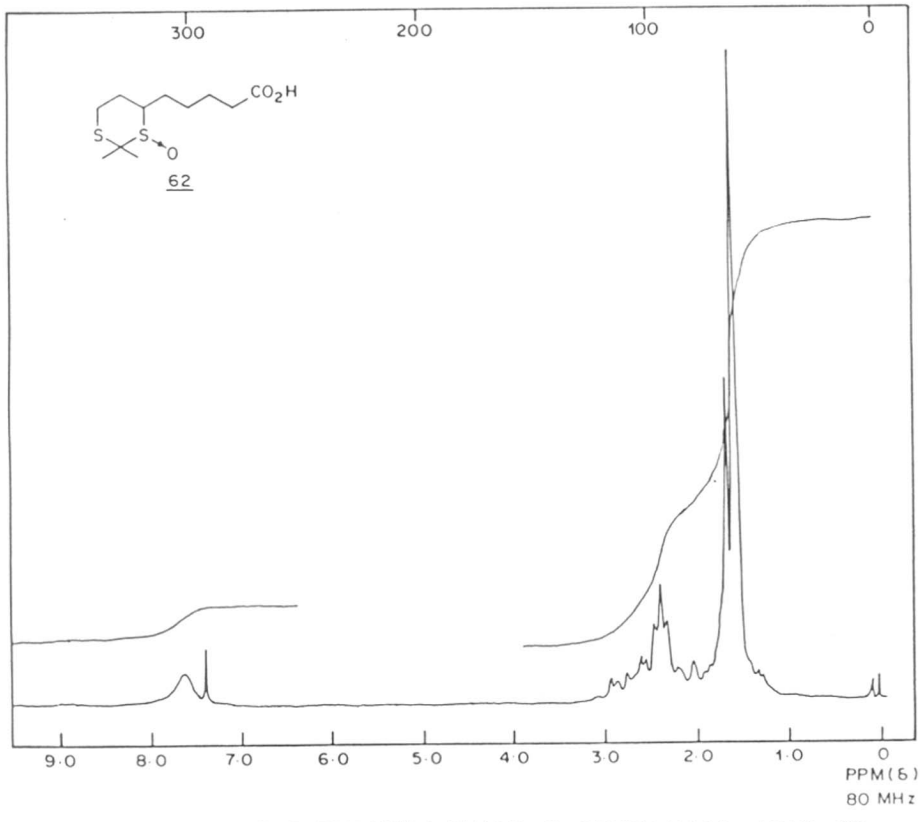




6-BUTYL-2,2-DIMETHYL-1,3-DITHIANE-1-OXIDE 60

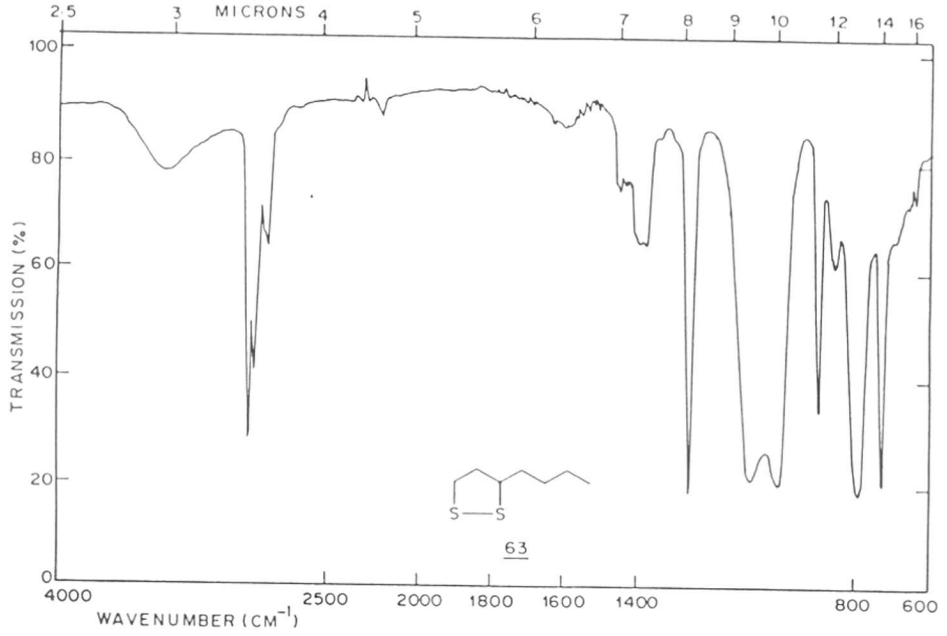
FIG. 1·2.

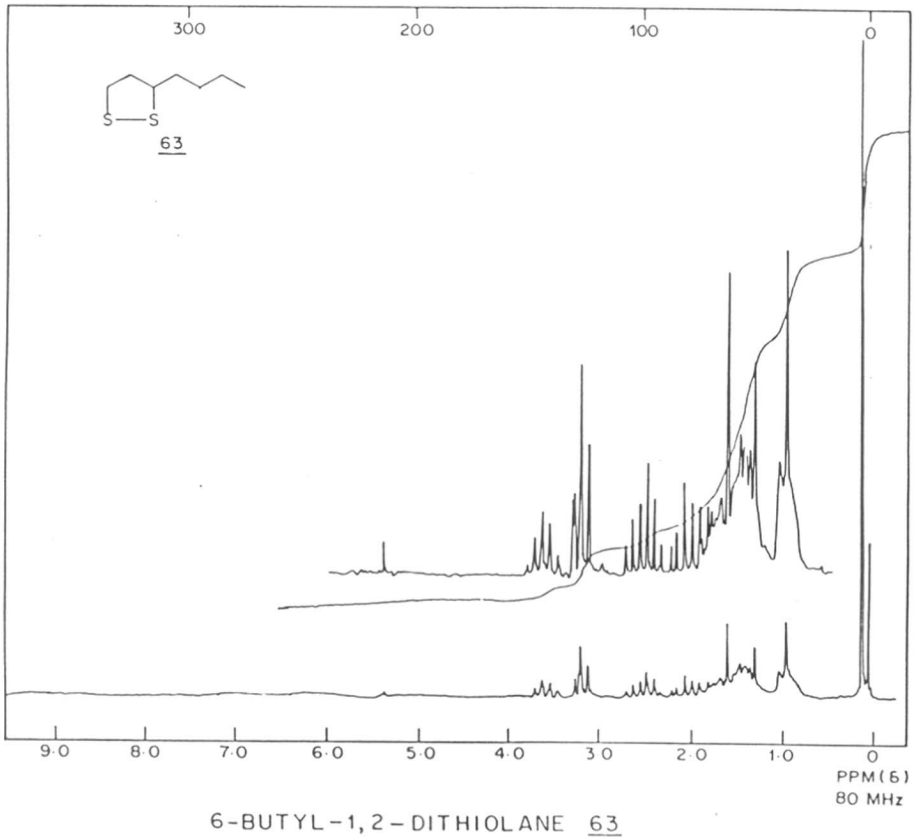




2,2-DIMETHYL-1,3-DITHIANE-1-OXIDE-6-PENTANOIC ACID 62

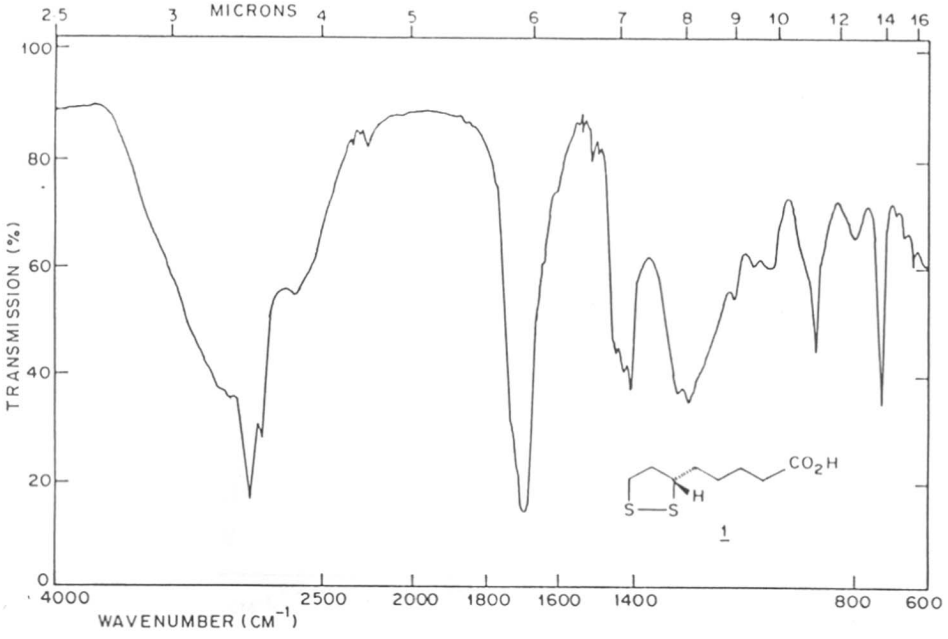
FIG. 1·3.

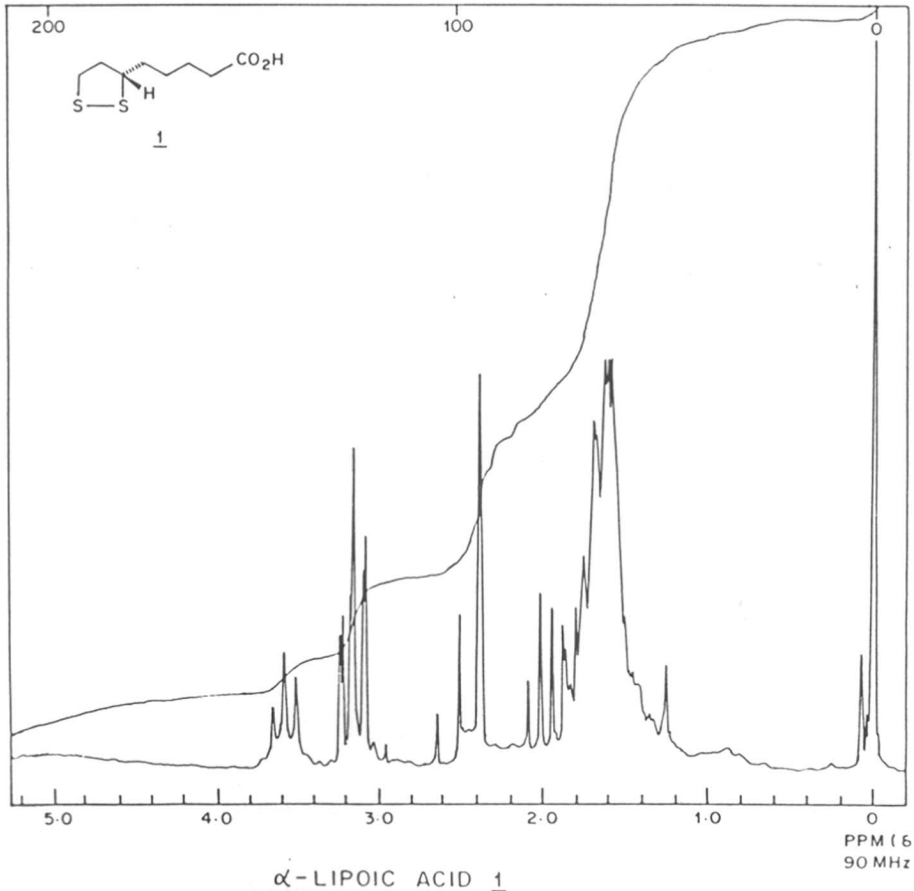




6-BUTYL-1,2-DITHIOLANE 63

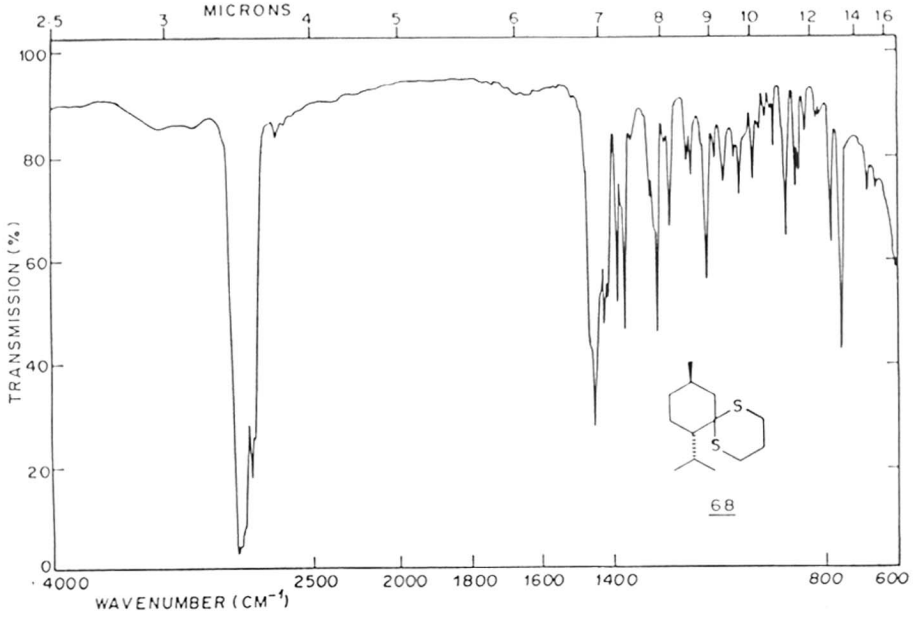
FIG. 1·4.

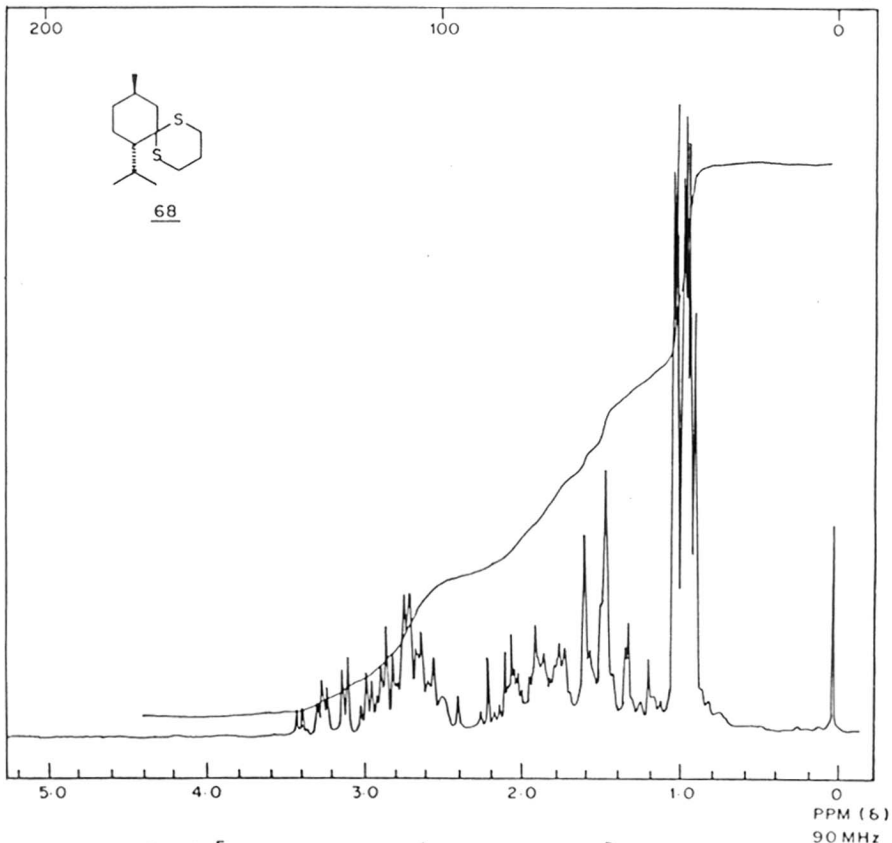




α-LIPOIC ACID 1

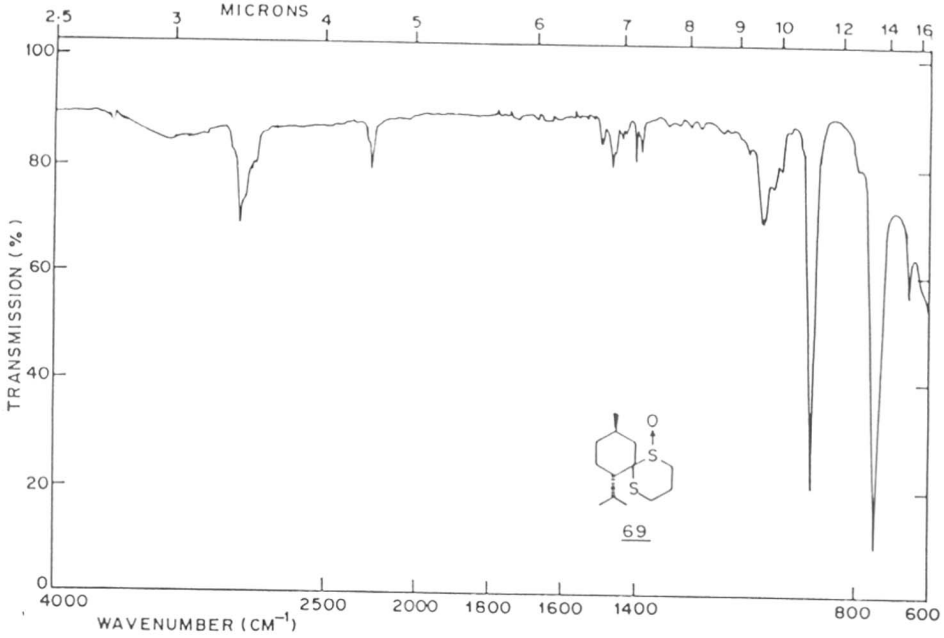
FIG. 1·5.

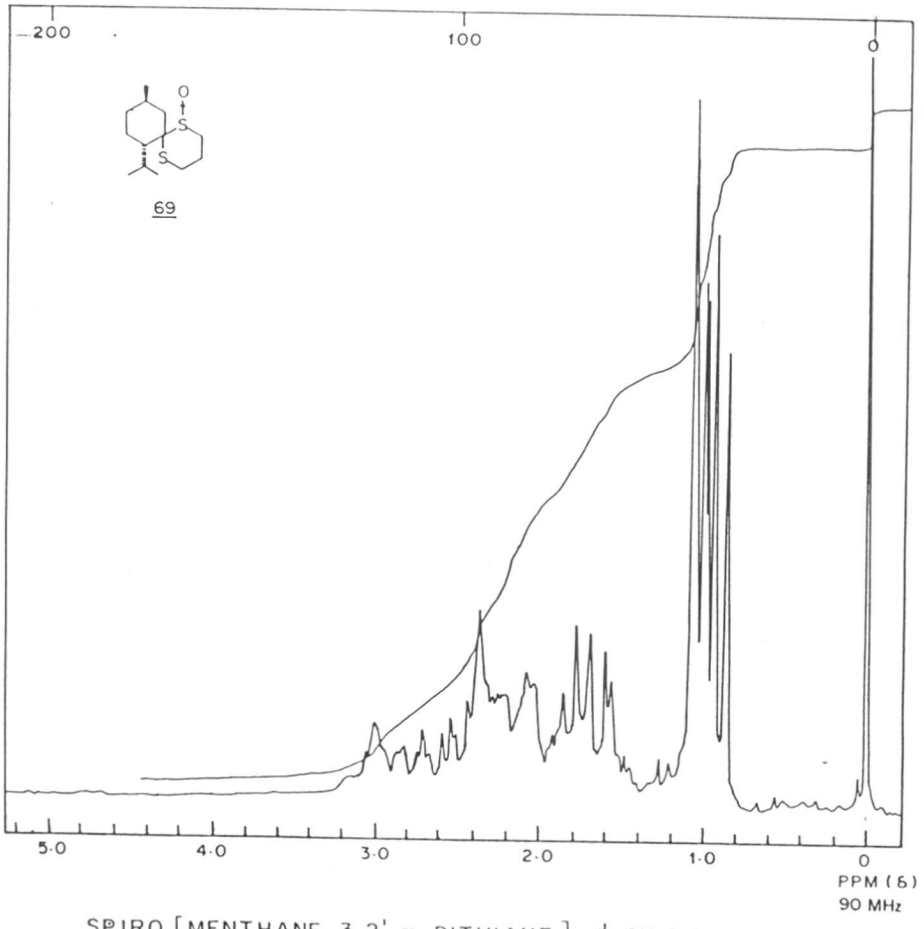




SPIRO [MENTHANE-3, 2'-m-DITHIANE] 68

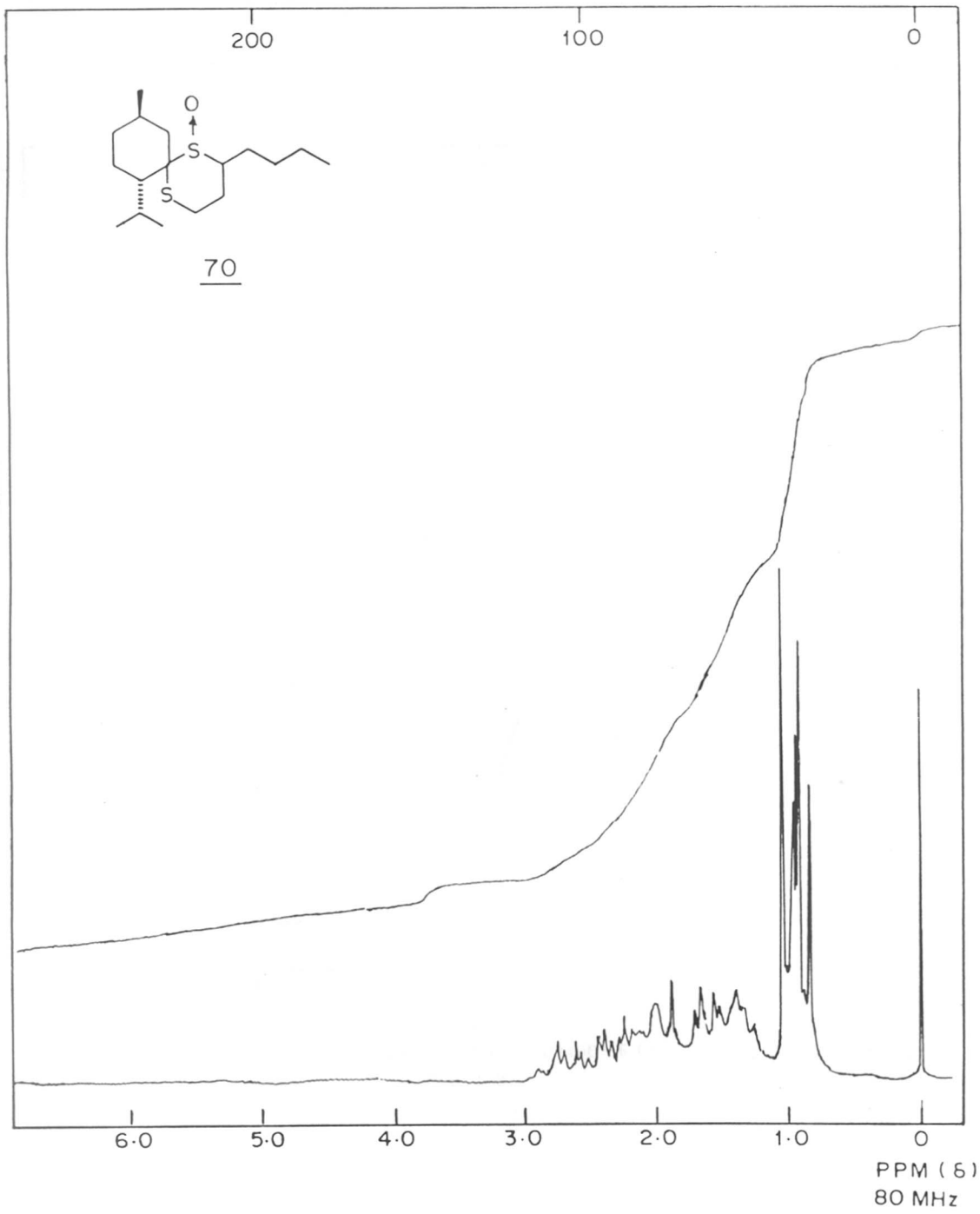
FIG 1·6.





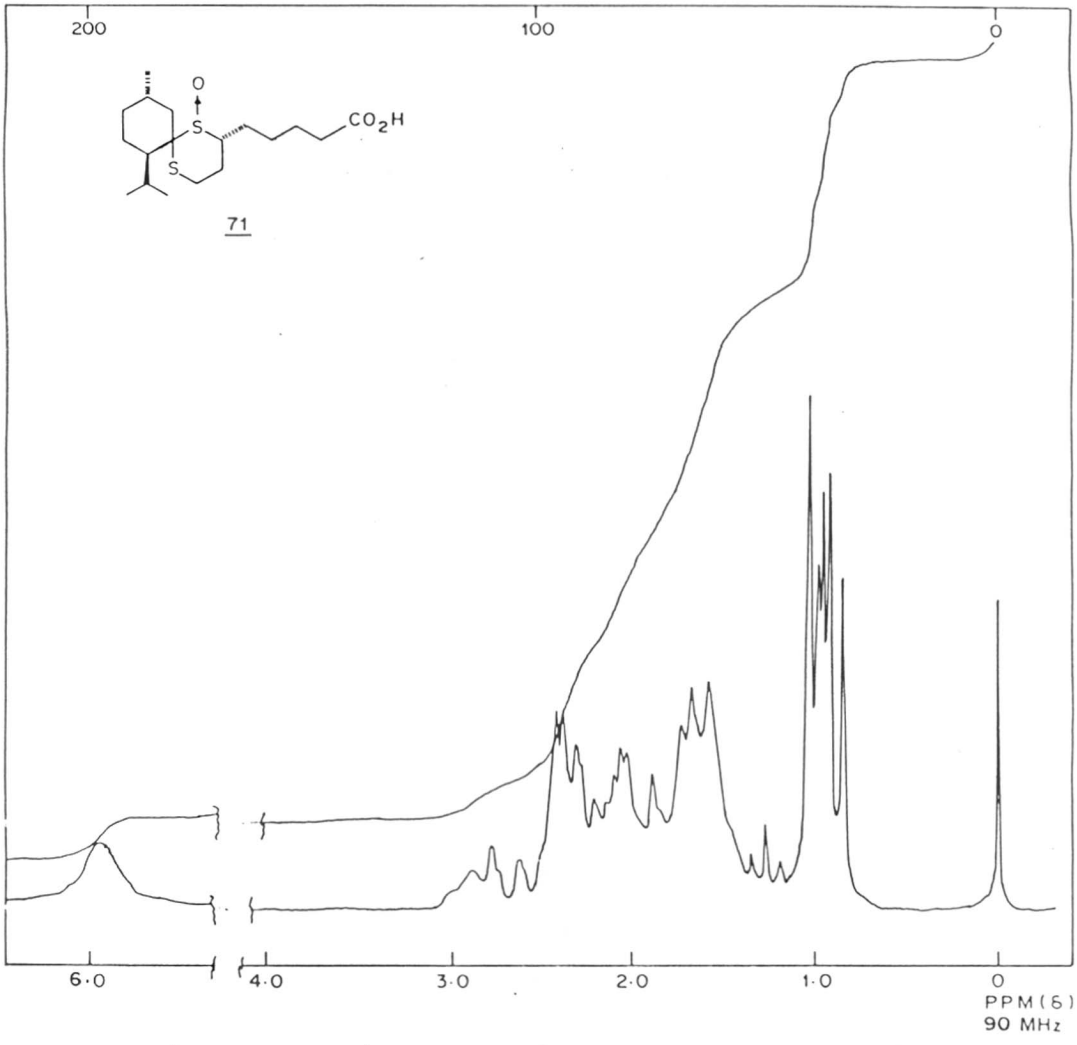
SPIRO [MENTHANE-3,2'-m-DITHIANE] -1'-OXIDE 69

FIG. 1.7.



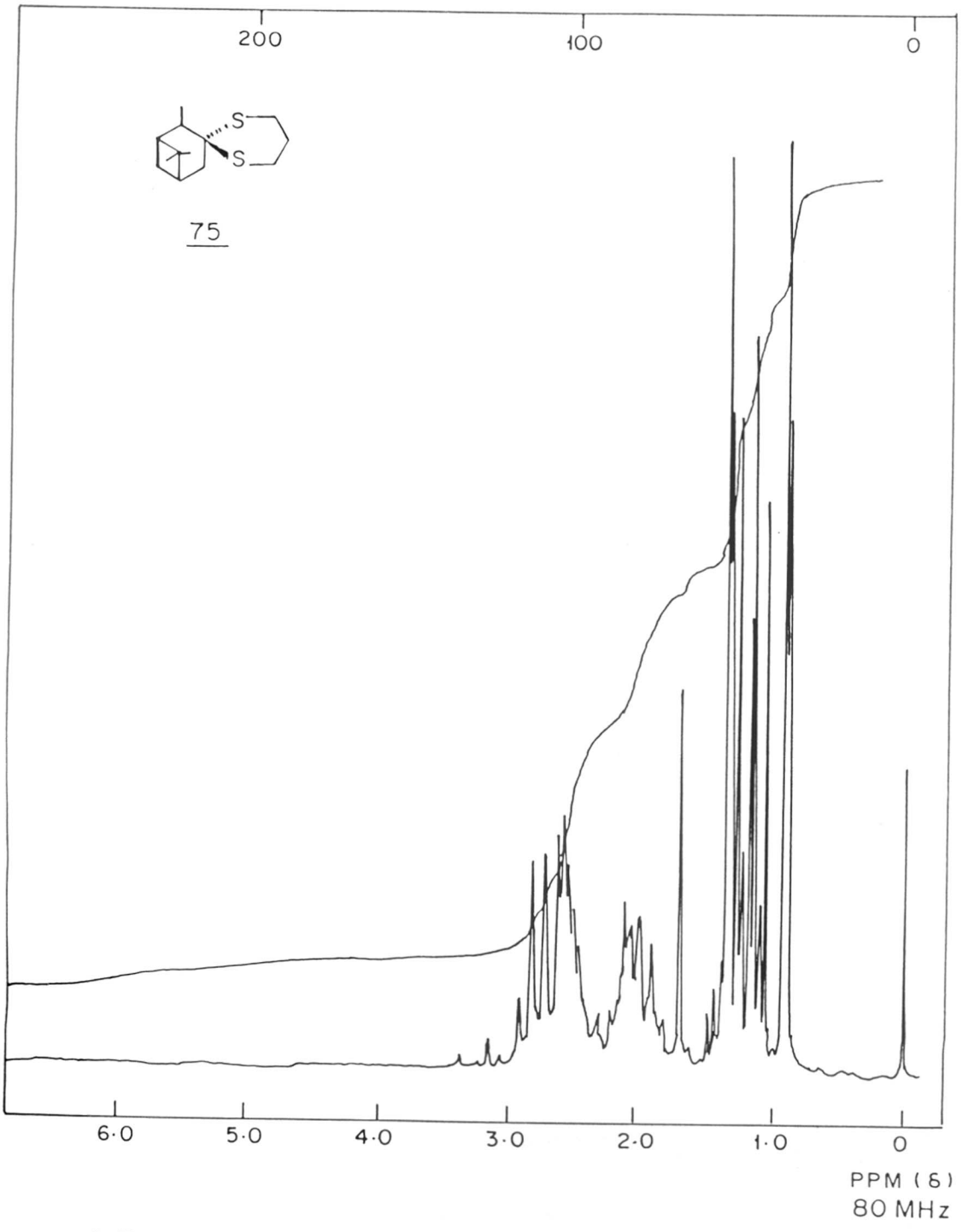
SPIRO [MENTHANE-3,2'-m-DITHIANE]-6'-BUTYL-1-OXIDE (70)

FIG. 1·8.



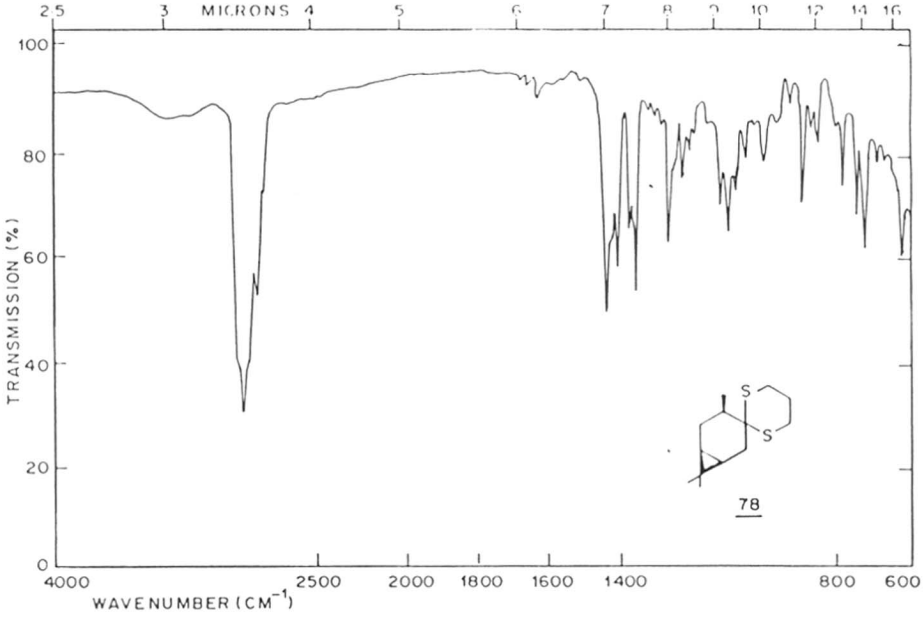
SPIRO[MENTHANE-3,2'-m-DITHIANE]-1'-OXIDE-6'(5"-PENTANOIC ACID 71

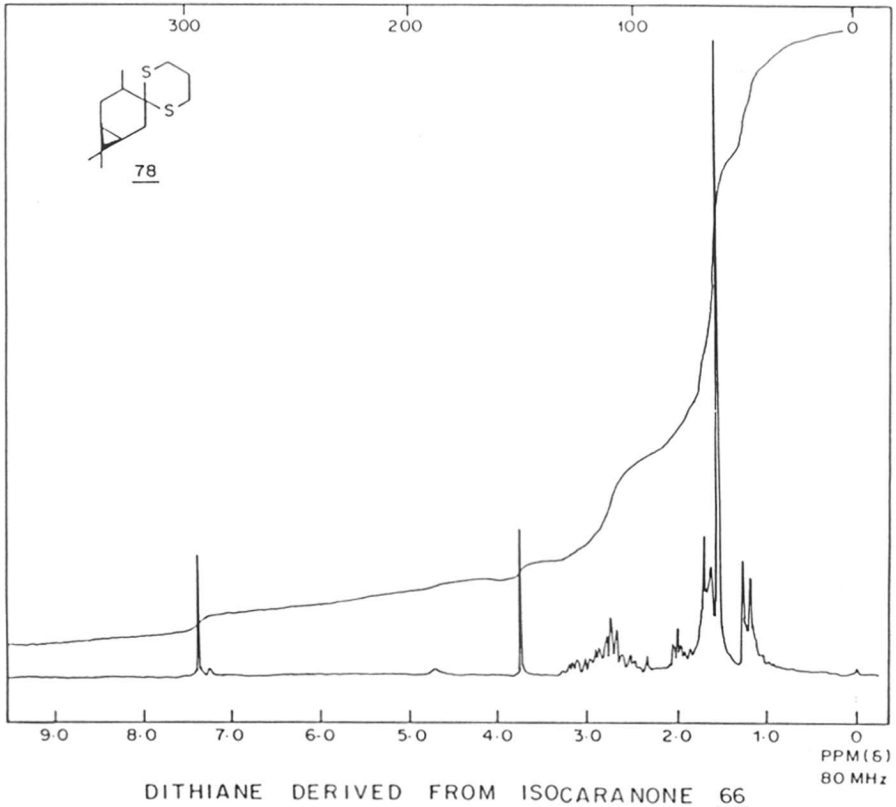
FIG. 1·9.



DITHIANE DERIVED FROM ISOPINOCAMPHONE 65

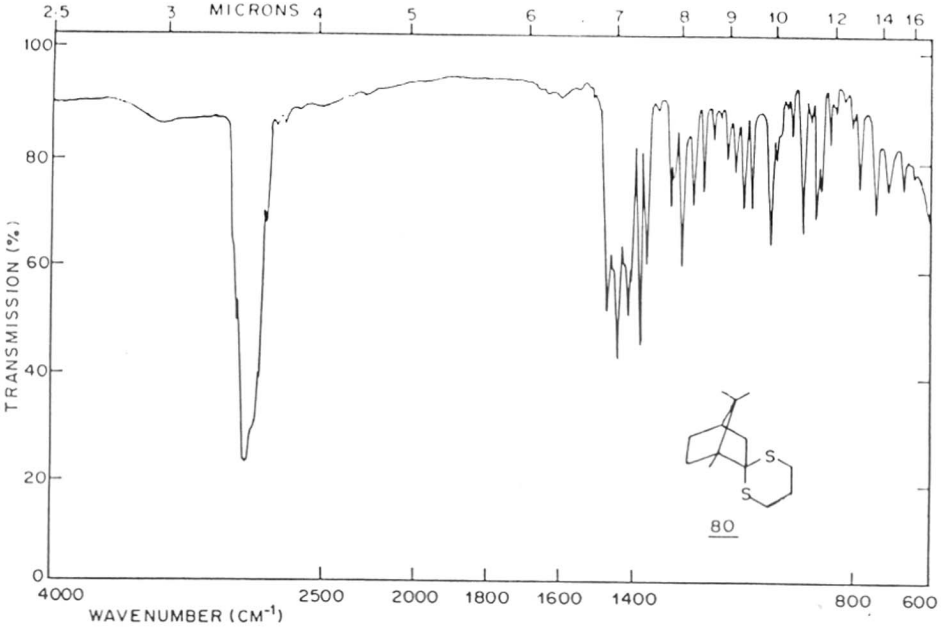
FIG. 1·10.

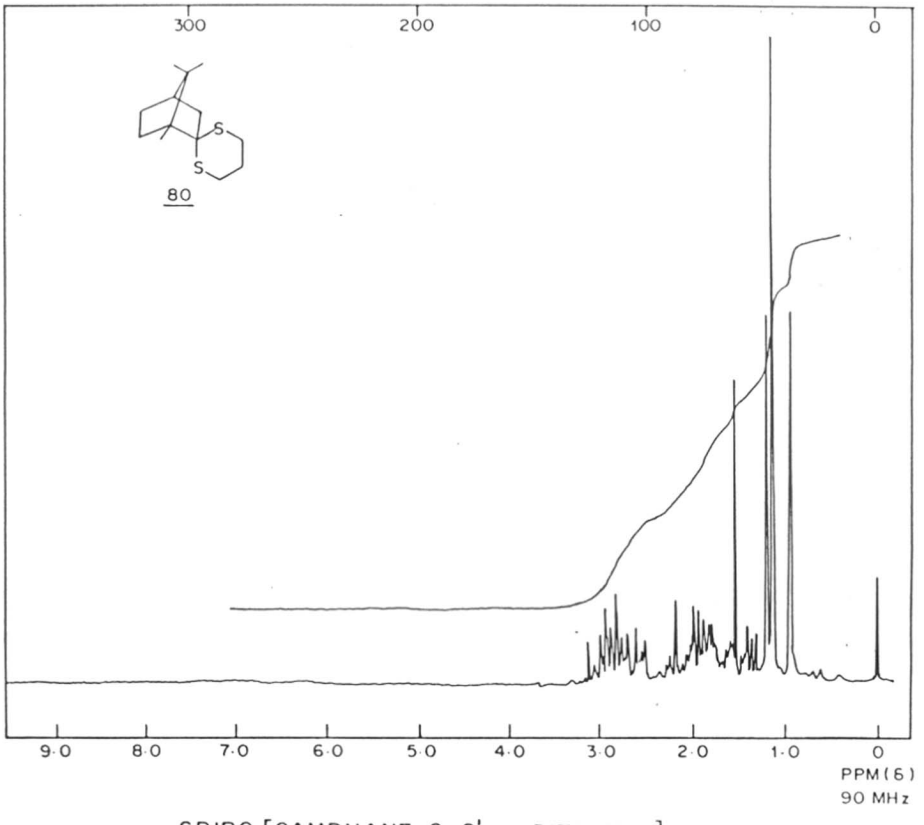




DITHIANE DERIVED FROM ISOCARANONE 66

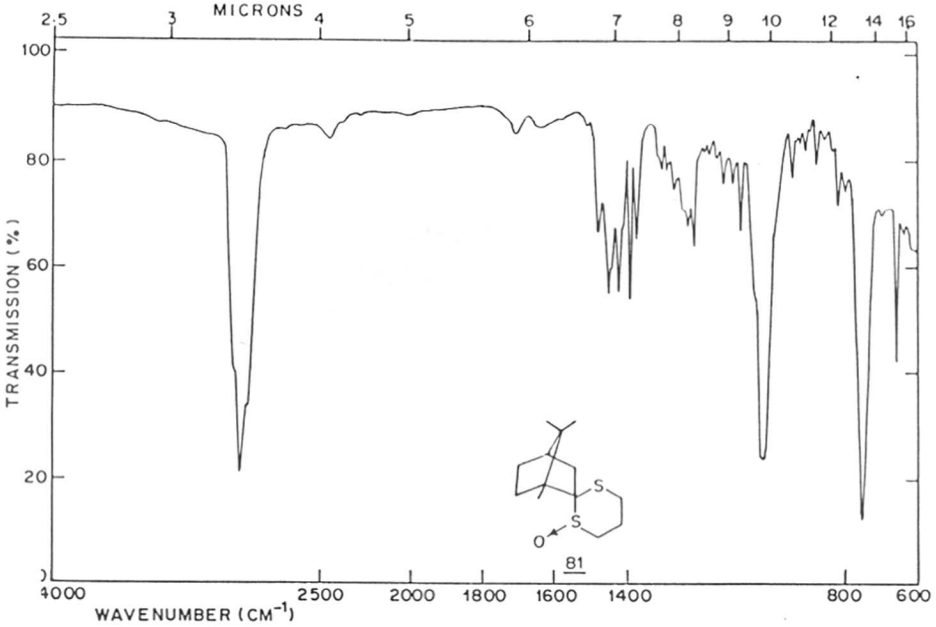
FIG. 1·11.

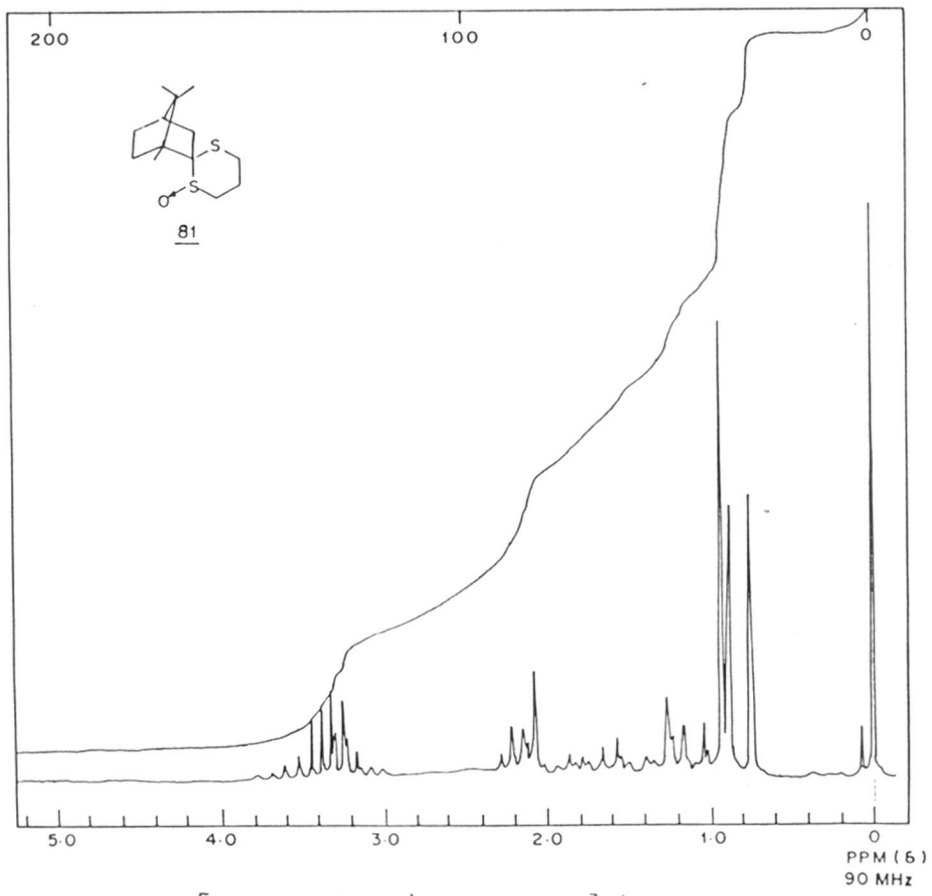




SPIRO [CAMPHANE-2, 2'-m-DITHIANE] 80

FIG. 1·12.





SPIRO [CAMPHANE-2, 2'-m-DITHIANE]-1'-OXIDE 81

FIG. 1·13.

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CHAPTER 2

SOME ASPECTS OF CHEMISTRY OF SULFOXIDES

"Twenty years it took me to discover fire—and now you tell me you can't cook."

CHAPTER 2

SOME ASPECTS OF CHEMISTRY OF SULFOXIDES

2A.0 SECTION A: Reactivity of α-Sulfinyl Carbanions

2A.1 Introduction:

The synthetic utility of sulfoxides arises from the ability of sulfur to stabilize negative charge on an adjacent carbon atom, a property which has been especially important in the development of new ways to form carbon-carbon bond.[1] A chiral sulfoxide group is characterised by the presence of three different kinds of ligands from the stereoelectronic point of view: the lone-pair of electrons, the oxygen atom, and two alkyl or aryl groups. Because they contain a chiral $R_3S(O)$ group, α-sulfinyl "carbanions" $R^1R^2C\text{-}S(O)R^3M$ have in recent years proved to be important synthetic building blocks.[2] A number of asymmetric syntheses[3] have been performed to afford a variety of sulfur-free, enantiomerically enriched compounds, taking advantage of both the easy insertion and smooth removal of an optically active sulfinyl group.

2A.2 Nature of S-O Bond:

The bonding nature of S-O bond in sulfoxides was, and to some extent is, still a matter of controversy. Double-bond character was first suggested for the S-O bond in sulfoxides by Phillips, Hunter and Sutton[3] based on the observations such as the rather small bond length (1.45 Å average) and the relatively great bond strength. Cumper

and Walker[4] recalculated the bond moments of sulfoxides and found it in the range from 2.8 to 4.3D, seemingly suggesting the S-O linkage to be better represented by a semipolar bond (a) rather than double bond (b). The rather small force constants of S-O linkage in sulfoxides, (6-8x10^5 dyne/cm)[5] which are similar to that of N-O linkage of pyridine N-oxides (6-7 x 10^5 dyne/cm), the strong hydrogen bonding property of sulfoxides,[5-7] the smaller value of calculated bond order,[8] and the relatively small bond dissociation energy of S-O linkage in sulfoxides (86 Kcal/mole average) as compared to that in sulfone (112 Kcal/mole average) were taken to suggest that the S-O linkage in sulfoxides is best described as a semipolar single bond (a).

(a) (b)

However, this does not imply that the "back-donating bonding" involving p-orbitals on oxygen and 3d orbitals of the sulfur is not important. The "back-donating bonding" has been in fact believed to be quite important not only on theoretical grounds from early period (1950)[8] and essential,[9] but also for explaining the marked stereochemical stability of optically active sulfoxides.[10] The double bond in this case (b) is not a classical 2p-3p type but a 2p-3d overlap type which does not require any coplanarity for those groups attached to the S-O bond.

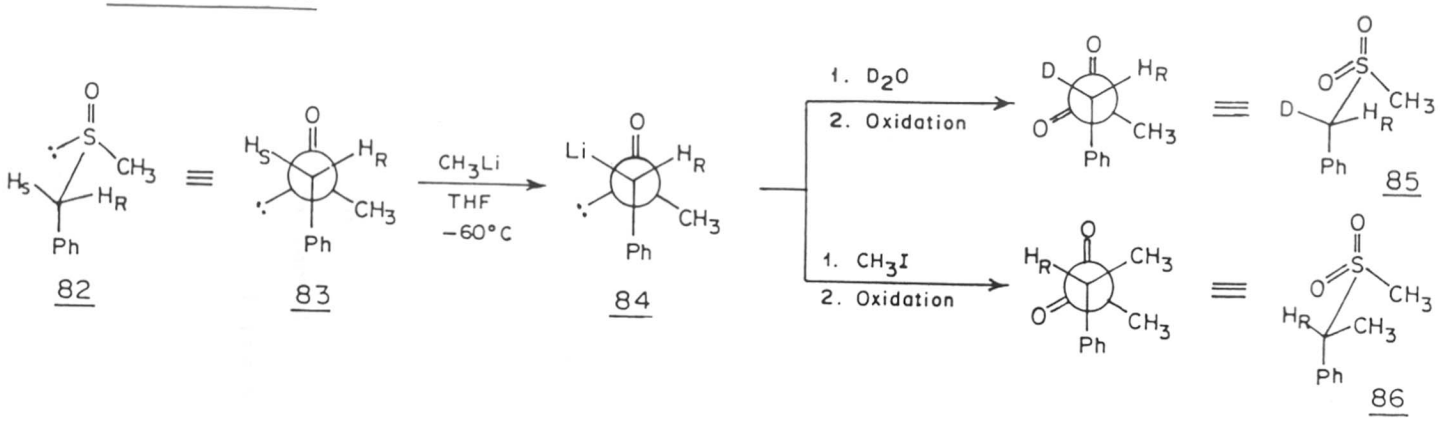
2A.3 Nature of α-Sulfinyl Carbanion:

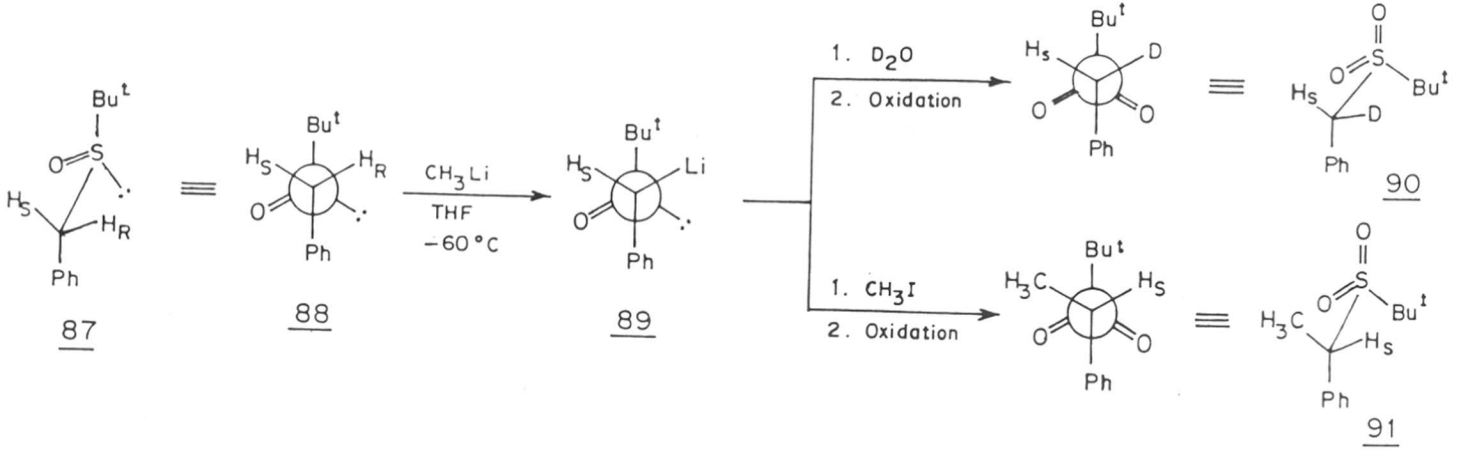
The greater kinetic acidity produced by an α-RS than an α-RO group has been assumed by most experimentalists to be associated with a greater ability of divalent sulfur to stabilize an incipient carbanion in the transition state of deprotonation reactions by a conjugative effect involving 3d orbitals.

The stabilization of α-sulfinyl carbanions was ascribed earlier to the 2p-3d π-resonance between carbon and sulfur bond[11] and later to the special charge-transfer polarisation between the negatively charged carbon and positively charged sulfur atom without involving 3d orbitals of sulfur.[12-14] This controversy has been continued more than a decade. However, upon using a new basis set for ab initio calculation on model compounds, i.e. $H_2\overset{\ominus}{C}-\overset{\oplus}{S}(O)H$, $H_2\overset{\ominus}{C}-\overset{\oplus}{S}H_2$ and $H_2\overset{\ominus}{C}-SO_2H$, Wolfe came up to the conclusion that the $\overset{\ominus}{C}-\overset{\oplus}{S}$ bond in these compounds are shortened and subtantially stabilized by the participation of 3d orbitals of sulfur atom.[15]

Wolfe et al. reported[2a,16] in 1965 that, in basic medium, the diastereotopic methylene protons of benzyl methylsulfoxide undergo hydrogen-deuterium exchange at unequal rates; the relative ratio being 16/1. Thus, reaction of (+)-(S)-benzyl methylsulfoxide **82** (Scheme-1) with methyllithium in tetrahydrofuran at -60° yields the (S,S)-α lithiobenzyl derivative **84** with a selectivity of 15:1

SCHEME – 1.

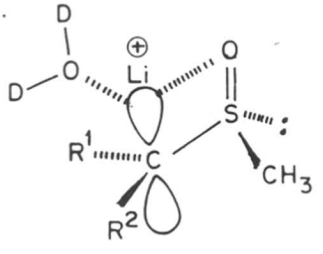

82
83
84
85
86
CH_3Li
THF
−60°C
1. D_2O
2. Oxidation
1. CH_3I
2. Oxidation


87
88
89
90
91
CH_3Li
THF
−60°C
1. D_2O
2. Oxidation
1. CH_3I
2. Oxidation

whereas the same reaction of (+)-(R)-benzyl 2-butylsulfoxide **87** having the same chirality as **82**, leads almost exclusively to the isomeric (R,R)-α-lithio derivative **89**. In the conformation **88**, H_R which is antiperiplanar to the S-O bond is more acidic and hence more favoured and this preference has been explained from ab initio calculations[17,18] which indicate the carbanion trans to oxygen more stable than the one trans to sulfur lone pair of electrons as a result of the gauche effect,[19] i.e. gauche interactions between adjacent electron pairs and/or polar bonds.[14]

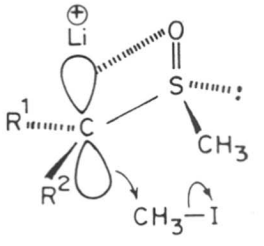
Quenching the lithium derivative **84** and **89** with deuterium oxide, leads to deuterium incorporation with retention of configuration (diastereomeric ratio, 15:1 and 99:1, respectively), while by quenching the lithium species with methyl iodide, the methyl group was incorporated with the same stereoselectivity as deuterium but with inversion of configuration. The results can be rationalised on the basis of solvent effect, the ion pairing phenomena and the base used. The stereoselectivity of deuterolysis is related to the chelation ability of the proton donor, assuming an electrophilic assistance (Fig. I). As the carbanion α to a

FIG.-I.



(CHELATING)

Retention of configuration

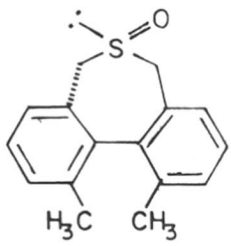


(NON-CHELATING)

Inversion of configuration

sulfoxide and to a phenyl group has certainly some degree of sp^2 character, an sp^2 carbanion engaged in an ion pair tends to react with retention with a chelating reagent and with inversion with a non-chelating agent. On the other hand, an sp^3 carbanion would react with retention with all reagents. However, cyclic sulfoxides may react differently.

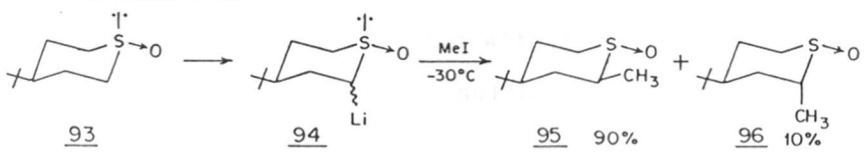
In conformationally rigid sulfoxide[20] **92**, the rates of base-catalyzed H-D exchange of the diastereotopic hydrogen atoms α to the sulfoxide group differed by factor of 10^3.



92

Bory and Marquet[21] on their work on 4-t-butylthiane oxides (Scheme-2) showed that methylation of the α-lithio carbanions with methyliodide occurs always trans to the S-O bond with a high stereoselectivity, even in highly crowded compounds.

SCHEME-2.



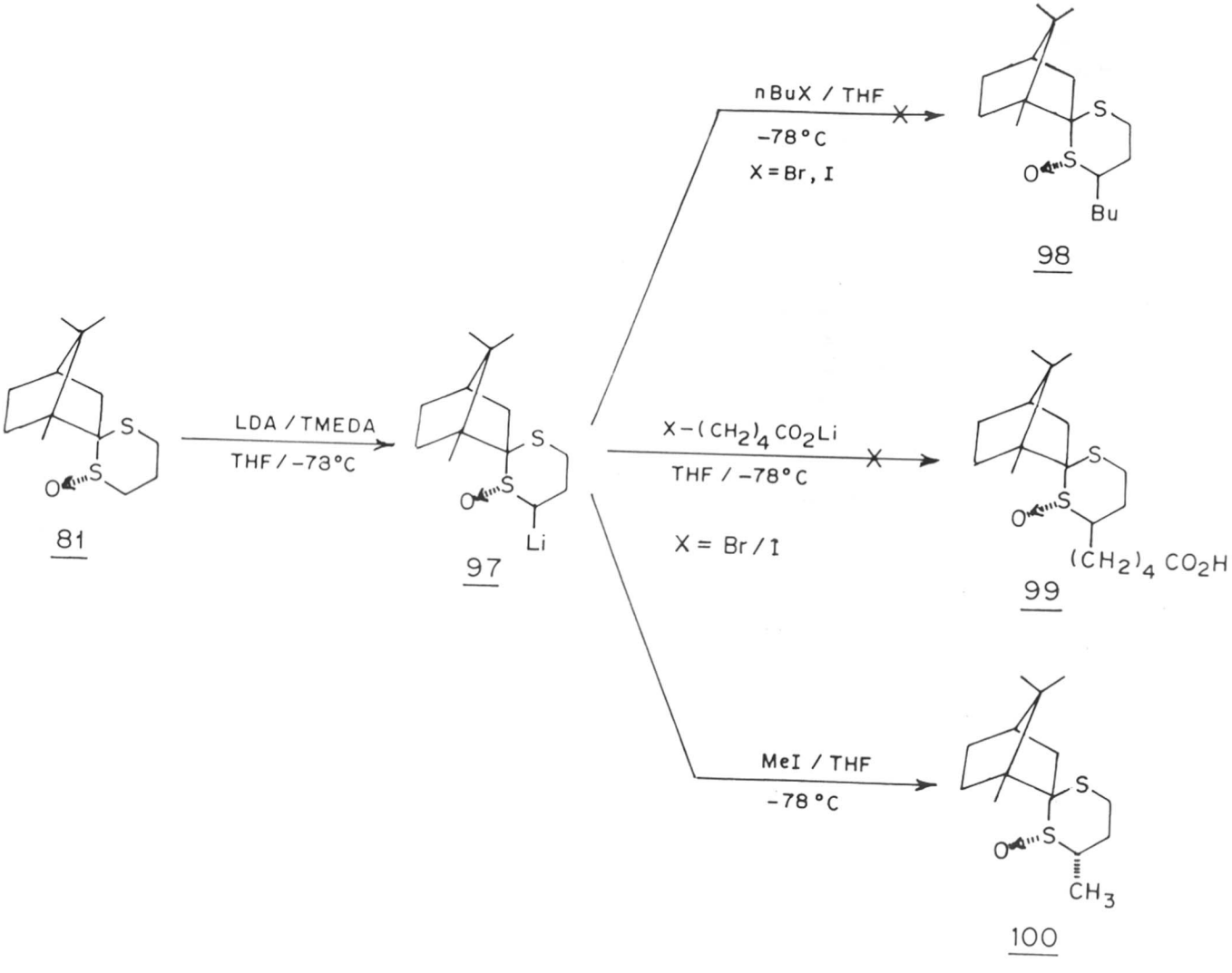
93 94 95 90% 96 10%

2A.4 RESULTS AND DISCUSSIONS

Reactivity of α-lithiocarbanion of sulfoxide **81** (Scheme-16, Chapter-I), derived from R-(+)-camphor was studied. The structure and absolute stereochemistry of this sulfoxide was confirmed through the aegis of single-crystal X-ray analysis, which revealed the conformation of the S-O bond to be equatorial, thus possessing the configuration (S).

It was observed that unlike the sulfoxides **69a** and **69b** (Schemes 12 and 13 respectively), derived from menthone, the camphor analogue **81** was thermolabile especially in the presence of a solvent. Sulfoxide **81** failed to give alkylated products with butyl bromide/iodide or bromo/iodovalerate, under the same conditions as mentioned previously for menthone (Scheme-12, Chapter I). This could be ascribed to faster competing side reactions occurring under the conditions employed. However, when the α-lithiocarbanion **97** (Scheme-3) was exposed to a strong electrophile like iodomethane, methylation took place smoothly to give the methylated product **100** [IR & NMR Fig. No.2.0]. A single-crystal X-ray analysis of the methylated product **100**[22] (Table-I, Fig.II) indicated an equatorial orientation for the methyl group, bearing the configuration (S) at C6' and the S-O bond with an axial orientation with the stereochemistry at sulfur maintained as (S).

SCHEME – 3



81 97 98 99 100

Table I

Cell Parameters: $P2_12_12_1$ = 10.903, 11.004, 12.058 - Orthorhombic

BOND LENGTHS (in Angstroms)

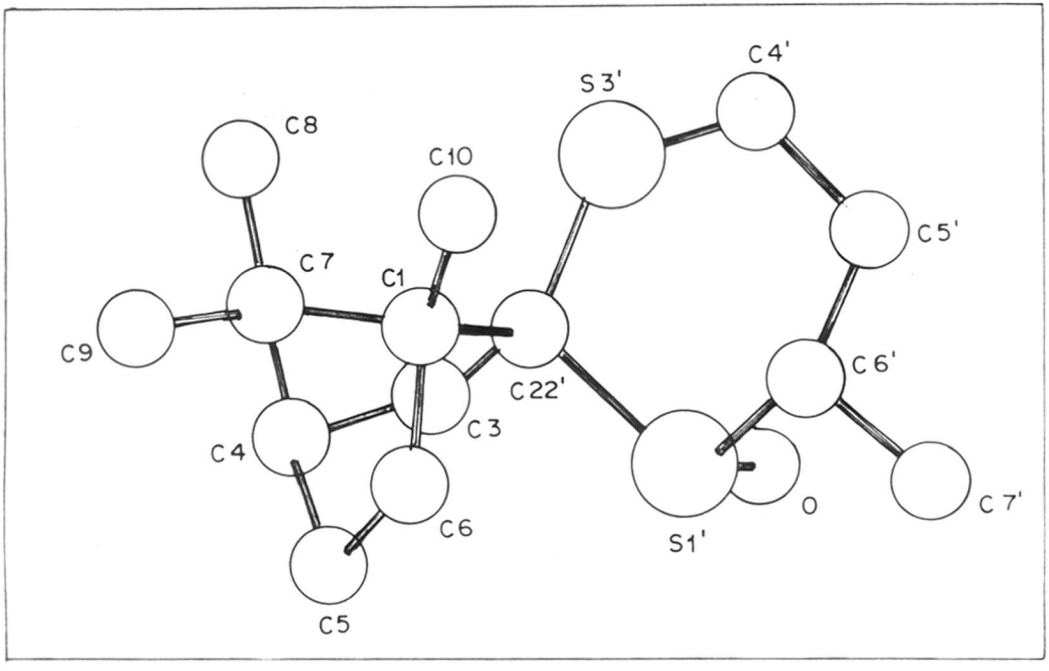
C1 - C2	1.584	C5 - C6	1.537
C1 - C6	1.549	C7 -C8	1.540
C1 - C7	1.569	C7 -C9	1.539
C1 - C10	1.539	C4'-C5'	1.504
C22'-C3	1.561	C4'-S3'	1.814
C22'-S1'	1.879	C5'-C6'	1.562
C22'-S3'	1.822	C6'-C7'	1.521
C3 - C4	1.514	C6'-S1'	1.813
C4 - C5	1.560	O - S1'	1.499
C4 - C7	1.546		

BOND ANGLES (in degrees)

C22'-C1-C6	106.3	C1-C6-C5	103.2
C22'-C1-C7	102.9	C1-C7-C4	93.2
C22'-C1-C10	116.7	C1-C7-C8	115.8
C6-C1-C7	100.2	C1-C7-C9	114.0
C6-C1-C10	114.0	C4-C7-C8	114.0
C7-C1-C10	114.8	C4-C7-C9	112.5
C1-C22'-C3	102.3	C8-C7-C9	107.1
C1-C22'-S1'	114.4	C22'-S3'-C4'	101.9
C1-C22'-S3'	119.0	C5'-C4'-S3'	114.6
C3 - C22'-S1'	103.9	C4'-C5'-C6'	112.8
C3-C22'-S3'	108.0	C5'-C6'-C7'	111.5
S1'-C22'-S3'	107.9	C5'-C6'-S1'	110.7
C3-C4-C5	108.0	C7'-C6'-S1'	106.4
C3-C4-C7	102.8	C22'-S1'-C6'	101.7
C5-C4-C7	101.9	C22'S1'-O	106.8
C4-C5-C6	103.7	C6'-S1'-O	106.0

TORSION ANGLES (in degrees)

C6-C1-C22'-C3	-76.0	S3'-C22'-S1'-C6'	-59.0
C7-C1-C22'-C3	28.8	C1-C22'-S1'-O	-173.5
C10-C1-C22'-C3	155.5	C3-C22'-S1'-O	-62.8
C6-C1-C22'-S1'	35.5	S3'-C22'-S1'-O	51.6
C7-C1-C22'-S1'	140.4	C1-C22'-S3'-C4'	-78.2
C10-C1-C22'-S1'	-92.9	C3-C22'-S3'-C4'	165.9
C6-C1-C22'-S3'	165.0	S1'-C22'-S3'-C4'	54.2
C7-C1-C22'-S3'	-90.0	C22'-C3-C4-C5	65.9
C10-C1-C22'-S3'	36.6	C22'-C3-C4-C7	-41.3
C22'-C1-C6-C5	66.8	C3-C4-C5-C6	-75.8
C7-C1-C6-C5	-39.9	C3-C4-C7-C1	57.1
C22'-C1-C7-C4	-51.5	C5-C4-C7-C1	-54.7
C6-C1-C7-C4	57.9	C3-C4-C7-C8	-62.8
C10-C1-C7-C4	-179.4	C5-C4-C7-C8	-174.7
C22'-C1-C7-C8	67.0	C3-C4-C7-C9	174.8
C6-C1-C7-C8	176.5	C5-C4-C7-C9	62.9
C10-C1-C7-C8	-60.9	C4-C5-C6-C1	5.19
C22'-C1-C7-C9	-168.0	S3'-C4'-C5'-C6'	63.5
C6-C1-C7-C9	-58.5	C5'-C4'-S3'-C22'	-55.4
C10-C1-C7-C9	+64.0	C4'-C5'-C6'-C7'	172.0
C1-C22'-C3-C4	7.0	C4'-C5'-C6'-S1'	-69.7
S1'-C22'-C3-C4	-112.3	C7'-C6'-S1'-C22'	-173.4
C1-C22'-S1'-C6'	75.6	C5'-C6'-S1'-O	-46.1
C3-C22'-S1'-C6'	-173.7	C7'-C6'-S1'-O	75.1
C10-C1-C6-C5	163.1	C7-C4-C5-C6	32.0
S3'-C22'-C3-C4	133.3	C5'-C6'-S1'-C22'	65.3



PLUTO diagram of

Spiro [camphane-2, 2'-m-dithiane]-6'-methyl-1'-oxide 100 b

FIG. II.

This indicates that the conformation of the dithiane ring is not the same as in the starting sulfoxide, this difference is reflected in certain torsion angles of **81** and **100** as shown in Table-II.

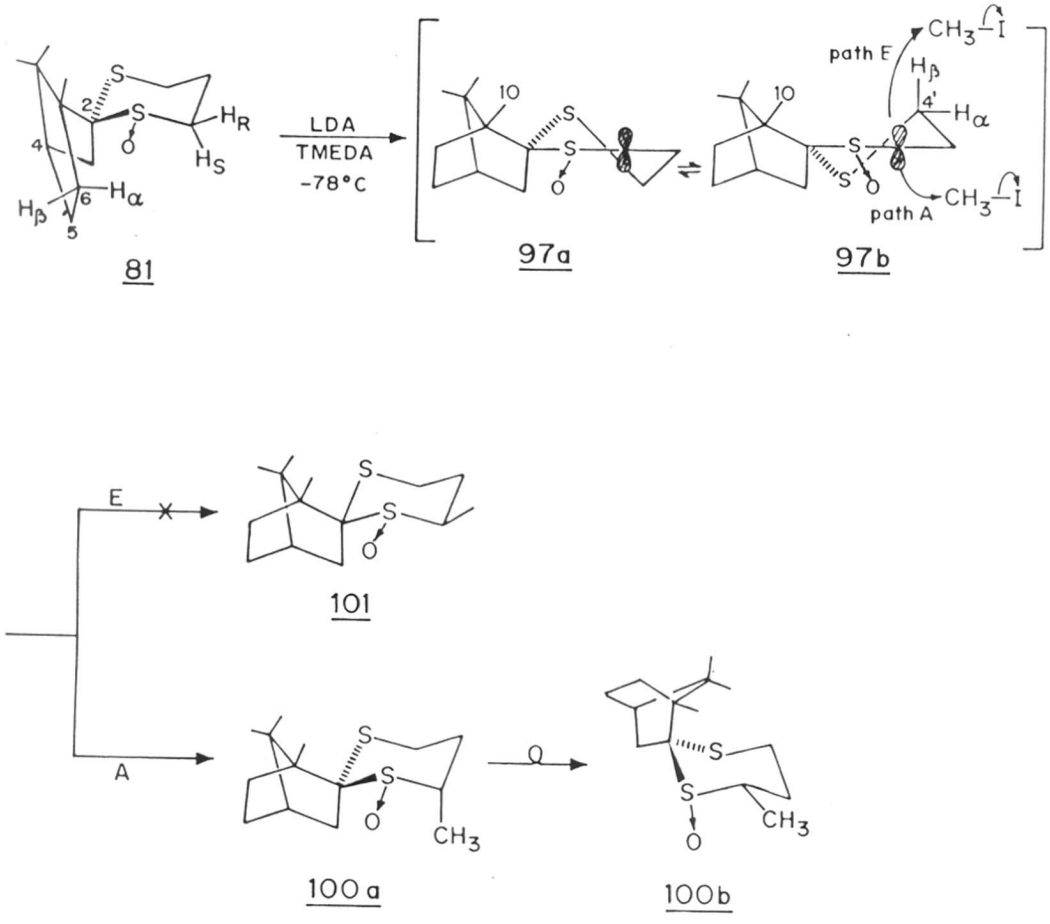
Table-II : Comparison of torsion angles of 81 and 100 (in degrees)

	81	100
C1-C22'-S1'-O	-73.0	-173.0
S2'-C22'-S1'-O	166.0	51.6
C5'-C6'-S1'-O	-172.7	-46.1

Alkylation (here methylation) of the α-carbanion **97** (Scheme-3) would normally be expected to result in an equatorial product, by abstraction of the equatorial hydrogen H_R in **81** (Scheme-4), resulting in the thermodynamically more stable lithiocarbanion to give the trans alkylated product **101**. Instead, here methylation results in a cis product and X-ray analysis shows the conformation as **100b** (see torsion angle comparison in Table-II).

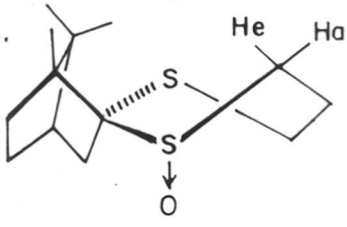
According to Wolfe et al, in acyclic systems, the hydrogen antiperiplanar to the S-O bond, being more acidic is preferentially deprotonated to result in a thermodynamically more stable pyramidal carbanion. The resultant carbanion deuterates with retention of configuration and alkylates with inversion of configuration (Section 2A.3). Such a stereochemical preference may not be valid in a

SCHEME-4

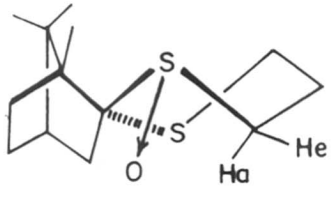


rigid cyclic sulfoxide as **81**. Thus results of alkylation expected may be different from simple acyclic sulfoxides. The formation of a cis-product observed could be rationalized in the following manner: though X-ray analysis of **100** (solid state) reveals the conformation as **100b**, the conformation in solution may be different. From its molecular model studies, it can be observed that the oxygen atom in **81** is close in proximity to the C6-α-H (Scheme-4) when the dithiane ring is considered a perfect chair, but this interaction is minimised when the dithiane ring assumes a skew form **81a** (Fig. III). The alternate skew form **81b** is

FIG. III.



81a



81b

not preferred as the interactions persists in this conformation. Thus, if alkylation is to take place via the conformation **81a**, then for steric reasons, the depronating agent and the electrophile would interact from the side of Ha, resulting in an axial product **100a**, which would rearrange to the conformationally more stable **100b** as shown by X-ray.

Cis-alkylation can also be explained by assuming a planar carbanion (Scheme-4). The carbanion in conformation **97a** or **97b** can react with methyliodide either by path E or path A leading to equatorial or axial product respectively.

Path E is encountered by steric effects due to the presence of C10-methyl group and C4'-β-H on the same face whereas path A has relatively less steric encumbrance, therefore reaction takes place via path A to result in a product with the methyl group axial and cis to the S-O bond, signifying that in this system the steric factors have an overriding effect over the electronic factors. Since the number of syn-axial interactions are more in the conformation **100a**, a preferred conformation **100b**, with minimized interactions is attained, where the methyl function is equatorial and the S-O bond is axial, as is exhibited by X-ray studies.

Thus methylation takes place in the usually unfavoured fashion (syn-methylation) i.e. the same side of the S-O bond in a sterically demanding environment. This explains probably the non-reactivity of the carbanion towards other alkylating agents bulkier than methyl which are sterically more demanding.

As reactions of carbanion **97** with an electrophilic sp^3 center were not achieved, reactions with reagents which could be elaborated to lipoic acid and possessing an electrophilic sp^2 center were studied. The reagents chosen were ethyl formate, ethyl chloroformate, ethyl acrylate and ethyl 2,4-pentadienoate. The carbanion **97** did react with all the aforesaid reagents. This reactivity could be

attributed to the planar reactive center leading to a difference in the steric requirements as compared to a reactive sp^3 center. This also could be due to an electrophilic assistance by an initial interaction of the carbanion counter cation (Li^+) (which probably is also coordinated to the sulfinyl oxygen) with the polar groups of the reagents like the carbonyl function (Fig. IV). This would then result in a directed reaction from the same face as the S-O bond i.e. the Hs or the Si face, giving a cis product, as is observed in case of methylation.

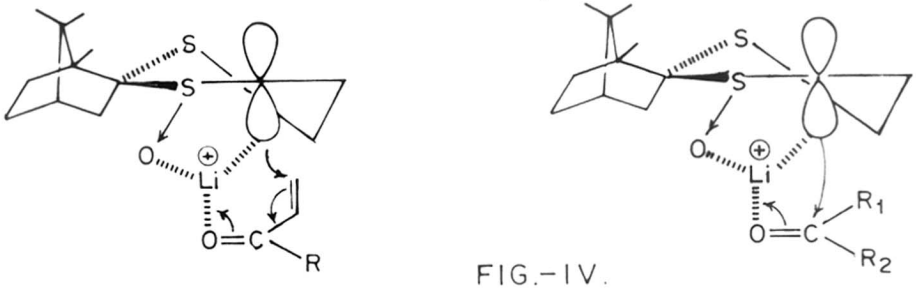
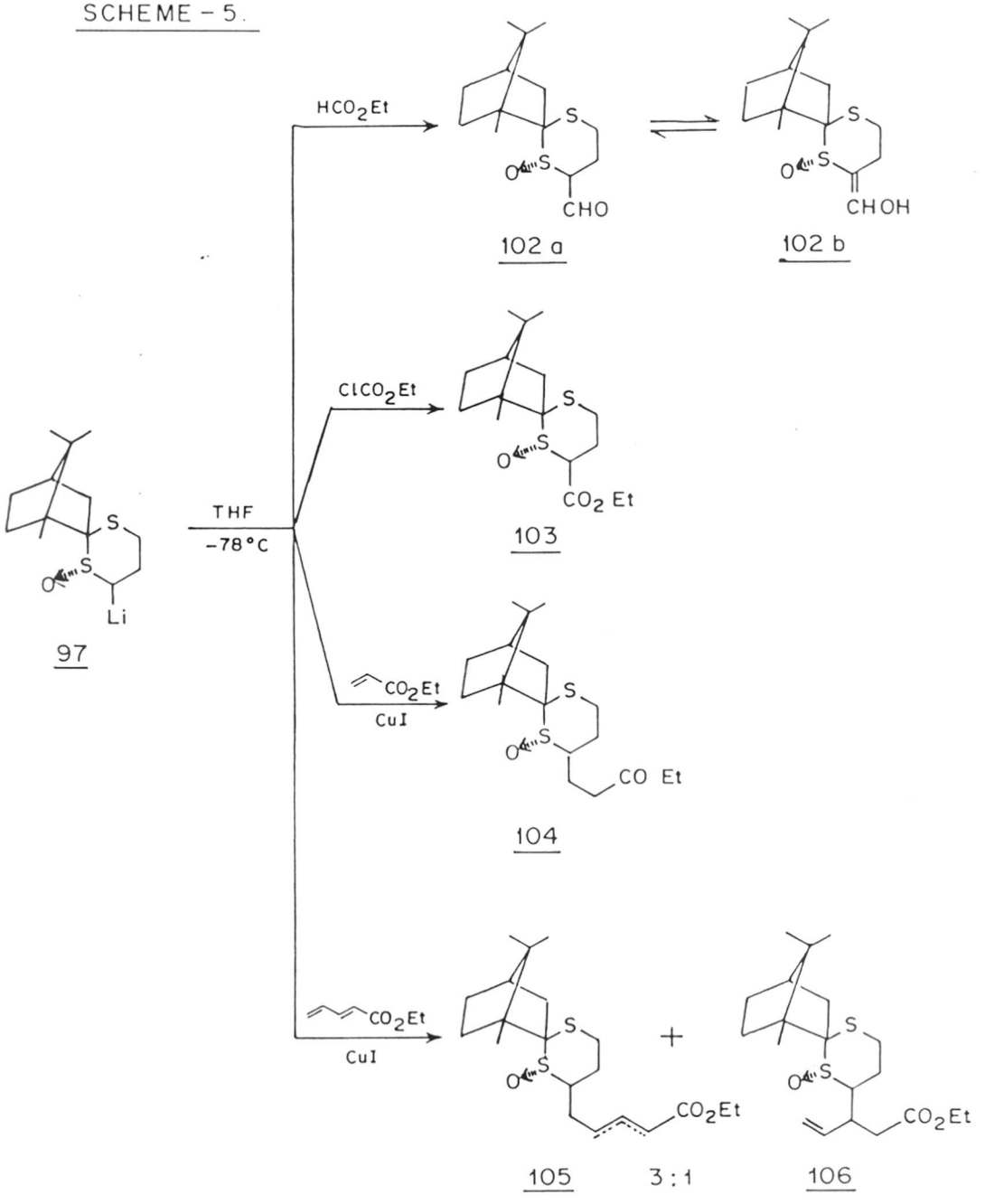


FIG.-IV.

Carbanion **97**, when treated with ethyl formate resulted in α-formyl sulfoxide **102** (Scheme-5) in ca 50% yield [IR & NMR Fig. No.2.1]. Similarly treating the carbanion **97** with ethyl chloroformate under the same conditions, afforded the carbethoxylated product **103**, ca 50% yield [IR & NMR Fig.No.2.2]. Attempts to alkylate **102** with δ-bromovaleric acid resulted in very poor yields of the alkylated product (see Experimental Section), as anticipated, since in this system **102**, though the α-sulfinyl proton is rendered more acidic, and the carbanion generated would be better stabilized, by the sulfoxide

SCHEME – 5.



97

102 a

102 b

103

104

105 3 : 1 106

and the formyl functions, the steric factor too has increased as compared to the starting sulfoxide **81**.

Michael addition reactions were studied with the α-lithiosulfoxide **97**. Ethyl acrylate was chosen as a model reagent, hence treatment of **97** with ethyl acrylate in the presence of cuprous iodide afforded the 1,4-adduct **104** (Scheme-5) in about 40% yield [IR & NMR Fig. No.2.3]. This adduct on hydrolysis would result in bisnorlipoic acid, an analogue of lipoic acid. The lithio sulfoxide **97** was then subjected to reaction with ethyl 2,4-pentadienoate as the Michael substrate to result in a 1,6-adduct which on hydrolysis would give didehydrolipoic acid. However, the reaction proceeded to give 40-45% yield of 1,6- and 1,4-addition products **105** (Fig.No.2.4) and **106** (Fig.No.2.5) respectively in a ratio of 3:1 of the isolated products. Since the selectivity and yields of the reaction were poor to give any substantial amount of the desired product **105** the reaction was not pursued further.

The preceeding Chapter manifests the utility of sulfoxide **69b** derived from the naturally abundant product l-menthone, in the synthesis of (S)-(-)-α-lipoic acid. It would be worthwhile if (R)-(+)-α-lipoic acid could be obtained from the same l-menthone as the starting material.

In the synthetic sequence, the chirality present in α-lipoic acid is generated at the alkylation stage, where

alkylation takes place trans to the S_R-O bond to result in a C_S product. If alkylation is made to proceed in a cis fashion, the result would be a C_R product, thus leading to (R)-(+)-α-lipoic acid.

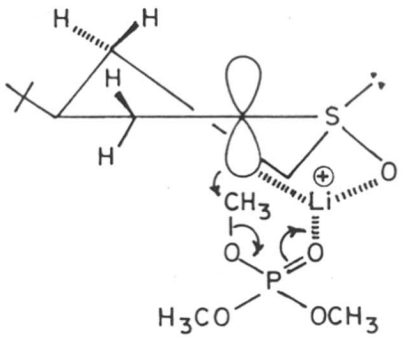
Marquet et al.[23] observed that for 4-t-butyl-α-lithiothiacyclohexane oxide in THF at 20°C, the ratio of methylated products is almost reversed from 10:90 (cis:trans) with CH_3I to 93:7 with trimethylphosphate [$O=P(OCH_3)_3$] (Scheme-6). This difference in the selectivity is ascribed

SCHEME-6.

CH_3I	90	10
$O=P(OCH_3)_3$	7	93

to counter cation (Li^+) assisted reactivity of the reagent. The cation complexes with the O=P bond and hence methylation takes place from the same side as the S-O bond as shown in Fig. V. It was decided to utilize this observation in the synthesis of α-lipoic acid. A phosphate reagent with valeric acid residue should result in cis alkylation, leading to C_R alkylated product, to afford natural α-lipoic acid.

FIG.–V.

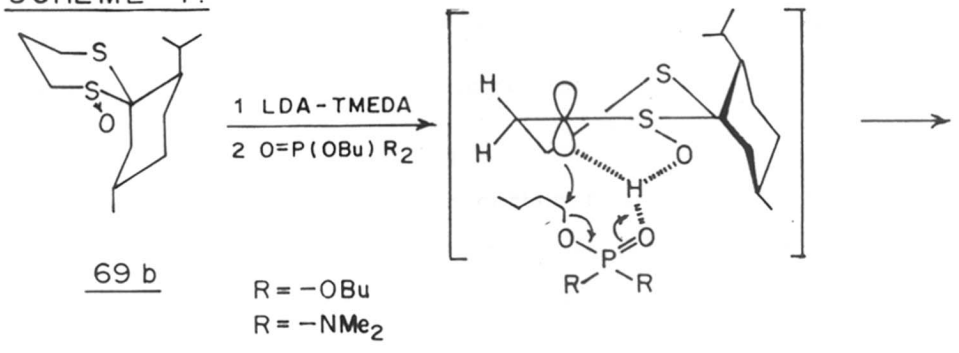


Model experiments were performed with tri-butylphosphate $O=P(OBu^n)_3$ and butyl tetramethylphosphorodiamidate $[Me_2N)_2OP(OBu^n)]$ as alkylating agents, which were prepared as reported.[24] In case of trialkylphosphate as an alkylating agent, since only one alkyl group is consumed in the reaction and the remaining two are wasted, the latter alkyl tetramethylphosphorodiamidate is the reagent of choice since it contains a single alkoxy group for alkylation, thus making it more economical.

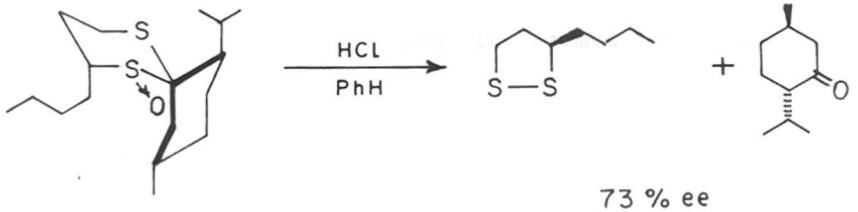
Reactions were carried out on the sulfoxide **69b** . (Scheme-7). The sulfoxide was lithiated using LDA-TMEDA in the THF at -78°C and reacted with the aforementioned phosphorus reagents, to provide the butylated product **107**. This was then subjected to hydrolytic cyclisation to furnish 3-butyl-1,2-dithiolane, the optical rotation obtained $[\alpha]_D^{25}$: -57.0° using tributyl-phosphate was compared with 3-butyl-1,2-dithiolane ($[\alpha]_D^{25}$: +78°) obtained from the same sulfoxide **69b**, using n-butylbromide as the alkylating agent. Assuming exclusive trans alkylation with

n-butyl bromide, $[\alpha]_D^{25}$: +78.0° would represent optically pure (S) dithiolane. Hence the dithiolane obtained by phosphorus reagent showing $[\alpha]_D^{25}$: -57.0° has 73% ee. When butyl tetramethylphosphorodiamidate was used as the alkylating agent, specific rotation observed was only +14.0°

SCHEME-7.



69 b



107

73 % ee

representing an optical purity of 18%. The poor optical purity obtained using phosphorus reagents could be attributed to salt effect (salts present in reagent n-butyllithium) where the reagent is activated by external lithium salt, resulting in a loss of the directing effect of the chelated lithium cation. Since these reactions did not result in satisfactory optical purity of the product, extension to the formation of R-(+)-α-lipoic acid fromL-menthone was not attempted.

2B.0 SECTION B: Sulfoxides in 1,2-Carbonyl Transpositions

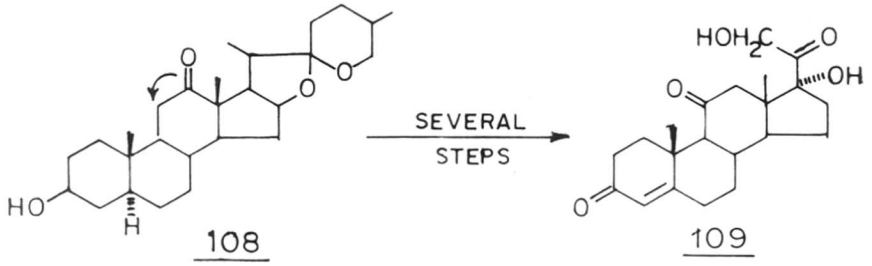
2B.1 Introduction:

The carbonyl group in its various forms as aldehydes, ketones, carboxylic acids and derivatives is the most versatile functional unit in organic synthesis, owing to its capability to undergo a wide variety of bond forming reactions both at the carbonyl carbon atom and sites influenced by its polarity.

The transposition of a carbonyl function from its original position to carbon atoms α, β or γ to it is referred to as carbonyl transposition or carbonyl metathesis[25] (metathesis, from the Greek word metatithenai meaning to transpose). The exchange of a carbonyl function with an adjacent methylene is termed as 1,2-carbonyl transposition.

Carbonyl transposition is the method of choice when: (i) a readily accessible material can be converted to a compound which is otherwise difficult to obtain, as is demonstrated in the work of Cornforth[26] and Djerassi[27] in the conversion of hecogenin, a 12-keto steroid **108** (Scheme-8)

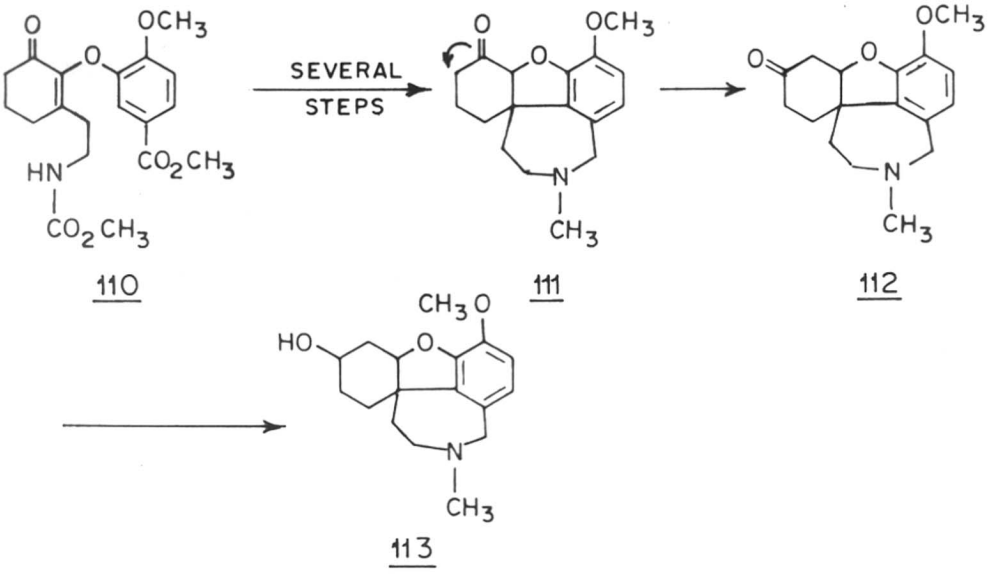
SCHEME – 8.



108 109

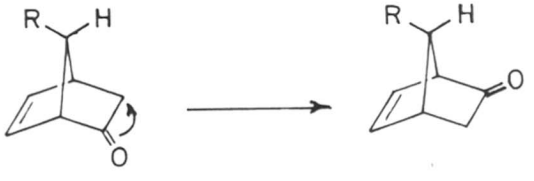
which is obtained as a by-product in the manufacture of sisal fibre, to cortisone **109** (Scheme-8); or (ii) is required as a part of the strategy involved in the synthesis of complex organic molecules, as is illustrated in the following example, in the synthesis of dl-lycoramine[28] **113** (Scheme-9), and (iii) could be used in racemisation or epimerisation of bicyclic ketones, (Scheme-10).

SCHEME-9.



110 111 112 113

SCHEME-10.



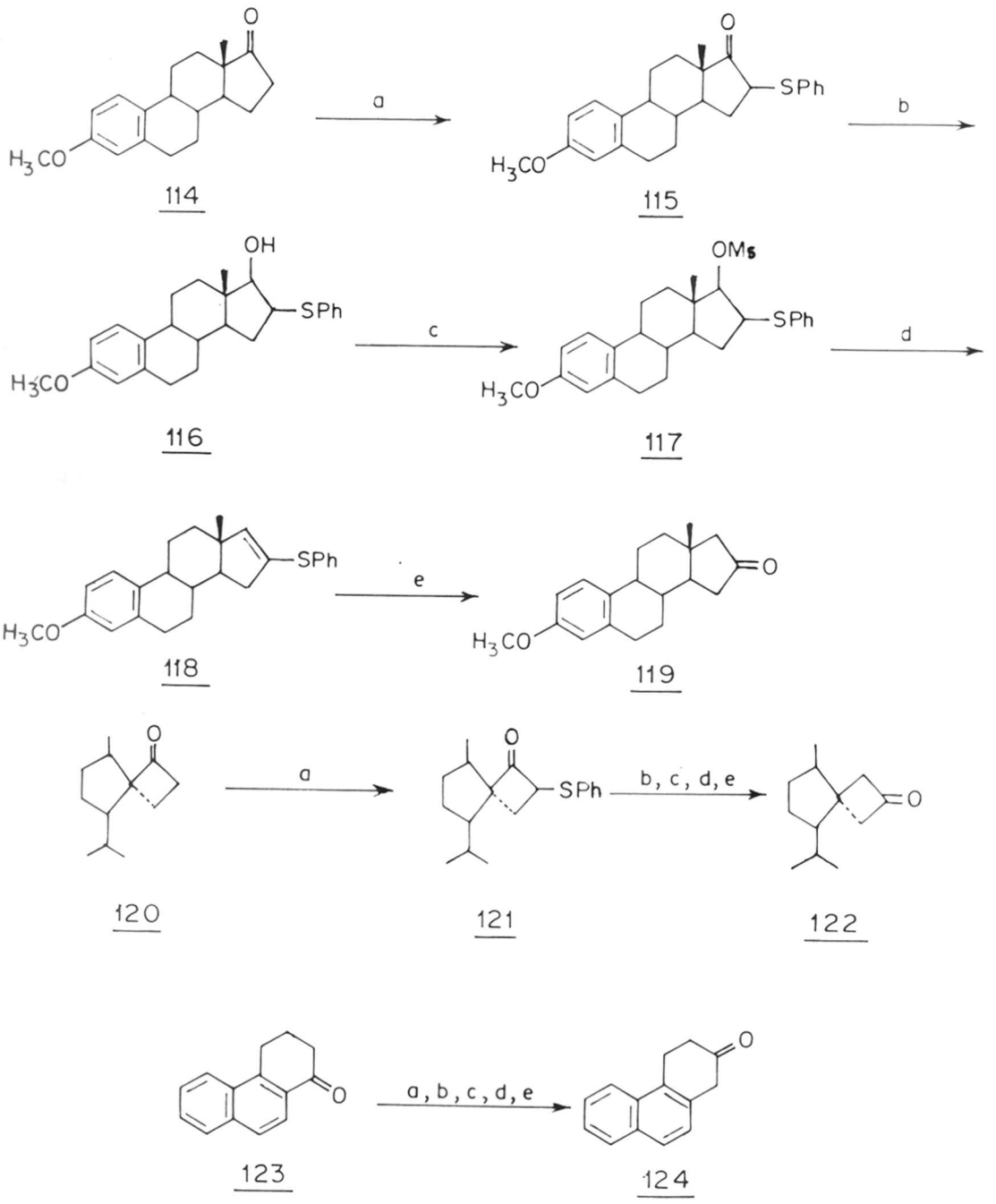
The importance of 1,2-ketone transposition in the field of steroids and terpenes are well documented.[29] There are numerous reports on 1,2-carbonyl transposition based on hydroboration, organosulfur reagent, organosilicon reagents, and many others.[2] In this section only 1,2-carbonyl transposition based on sulfur reagents will be considered.

2B.2 1,2-Carbonyl Transposition Employing Sulfur Reagents: A Review

The ability of sulfur to stabilize both negative and positive charges on an adjacent carbon has been thoroughly exploited in recent years for the development of many new synthetic methodologies, and 1,2-carbonyl transposition is one of them. Most of the methods involve α-sulfenylation of the carbonyl compound, which is then converted to an enol thioether, subsequent hydrolysis of which affords the transposed ketone, as illustrated in the following Schemes.

One of the most general procedures for carbonyl transposition has been provided by Trost and coworkers[30] (Scheme-11). The 1,2-carbonyl transposition was accomplished by monosulfenylation of the ketone, reduction of the β-ketosulfide, formation of mesylate **117** and its elimination with base to give the enol thioether **118**, hydrolysis of which yields the transposed ketone **119**. This method can also transpose the carbonyl group of an ester to a methyl ketone as shown in Scheme-12.

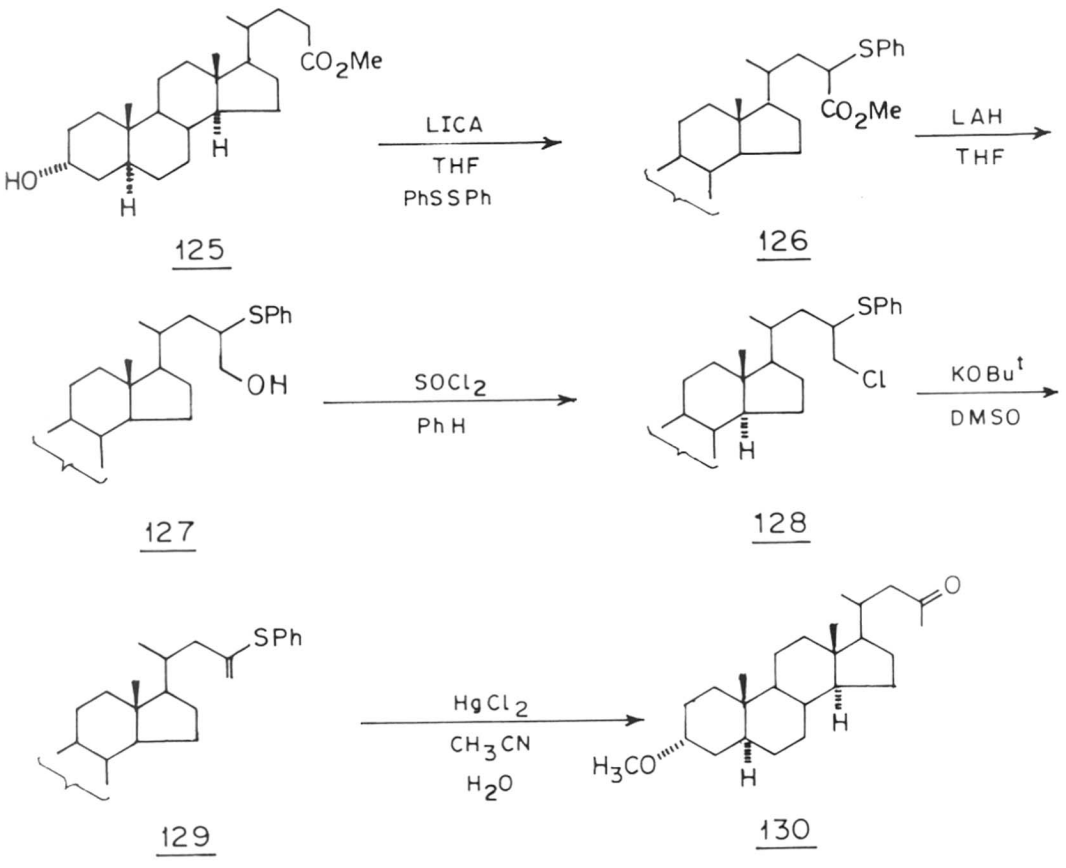
SCHEME – 11.



a) $LiN(i\text{-}C_3H_7)(C\text{-}C_6H_{11})$ – HMPA – THF – PhSSPh; b) $LiAlH_4$ – THF

c) $CH_3SO_2Cl - C_5H_5N$; d) KOC_4H_9-t – DMSO; e) $HgCl_2$, $CH_3CN - H_2O$

SCHEME — 12.



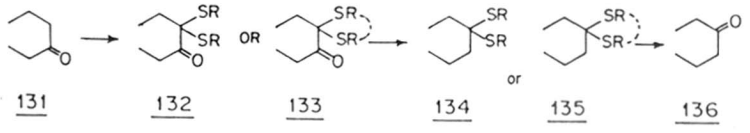
125 126

127 128

129 130

Introduction of two sulfur substituents α to a ketone group in a molecular framework constitutes a net oxidation of a methylene group, this property has been explored for the transposition of a carbonyl group as depicted in Scheme-13.

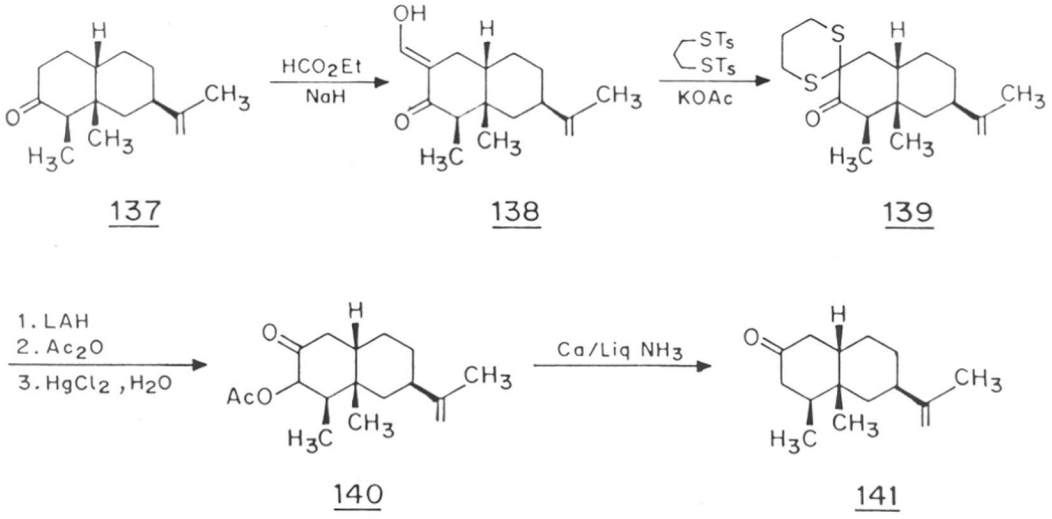
SCHEME – 13.



Marshall and Roebke[31] were the first to utilize this process to effect 1,2-carbonyl transposition (Scheme-14). Ketone **137** was converted through an intermediate hydroxymethylene ketone **138** to the thioketone **139**. Reduction of **139** with lithium aluminium hydride gave the alcohol which on acetylation followed by hydrolysis afforded the acetoxy ketone **140**. Reduction of **140** with calcium and liquid ammonia afforded the desired transposed ketone **141** in an overall yield of **50%**. Similar procedure has been utilized in a number of natural product synthesis.[27,32]

A facile, one-pot transformation of a ketone tosylhydrazone to the thioenol ether of the transposed ketone was developed by Nakai and Mimuria[33] (Scheme-15). This method is based on the regioselective sulfenylation of a dianion obtained by the addition of an organolithium reagent to the tosylhydrazone followed by Shapiro-Shechter reaction[34] of the regenerated dianion to furnish a thioenol

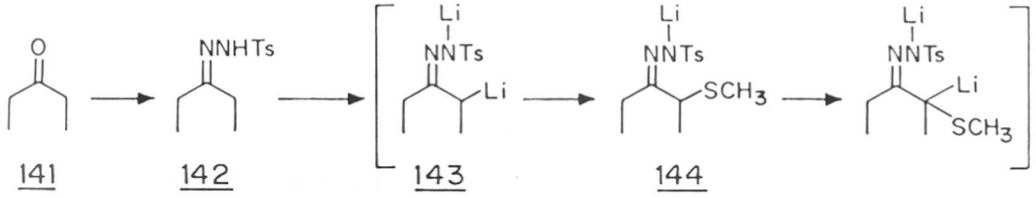
SCHEME-14



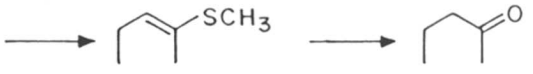
137 138 139

140 141

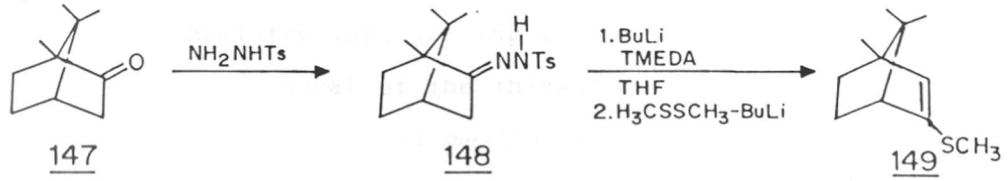
SCHEME-15



141 142 143 144



145 146



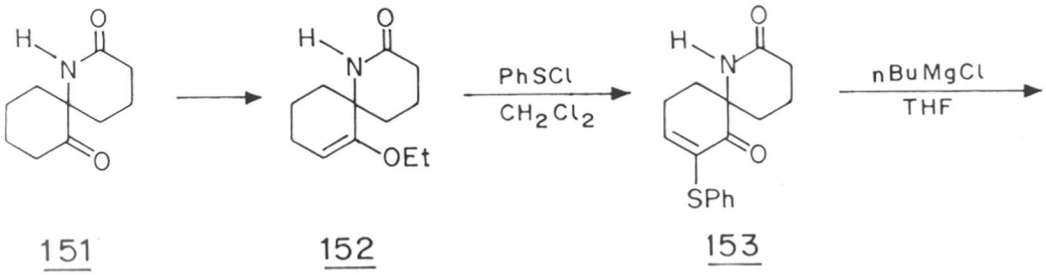
147 148 149 150

ether, hydrolysis of which results in the transposed ketone. The versatility of this procedure was demonstrated by conversion of menthone to carvomenthone and d-camphor **147** to 1-epicamphor **150**.

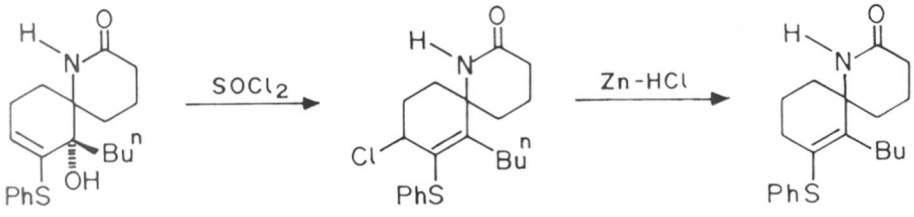
Another example of 1,2-carbonyl transposition is that provided by Kishi in the stereocontrolled synthesis of (±) perhydrohistrionicotoxin[35] in which the spiro ketolactam **151** (Scheme-16) is converted to transposed spiro ketolactam **157**. The key step was conversion of the enol ether **152** with phenylsulfenyl chloride to give the thiophenyl-enone **153** which on treatment with butyl-magnesium chloride gave the carbinol **154**. Chlorination and subsequent reduction affords the thioenol ether **156**. Acid hydrolysis then furnishes mixture of two epimeric transposed ketones **157** in an overall yield of 20%.

Bulman-Page et al.[36] found that sulfuryl chloride reacts with 1,3-oxathiolanes and 1,3-dithiolanes to yield intermediates which can be converted on hydrolytic work up to α-ketothioacetals, suggesting the synthetic potential of this chemistry for carrying out carbonyl transposition by reductive removal of the thioacetal group. Reaction of 1,3-dithiolane **158** (Scheme-17) with sulfuryl chloride gave **159**. Work up with triethylamine and wet silica gel afforded the α-ketodithiolane **160** in 86% yield. However, the same reaction sequence with 4-t-butyl dithiolane gave

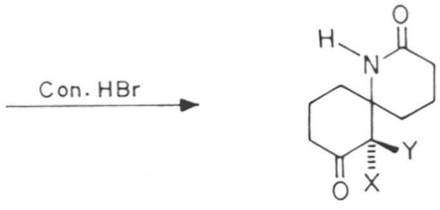
SCHEME-16



151 152 153



154 155 156

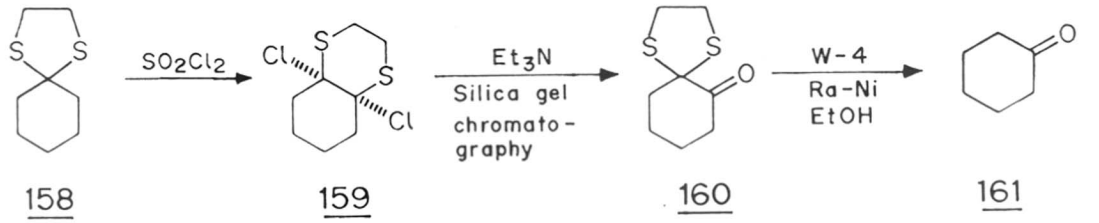


157

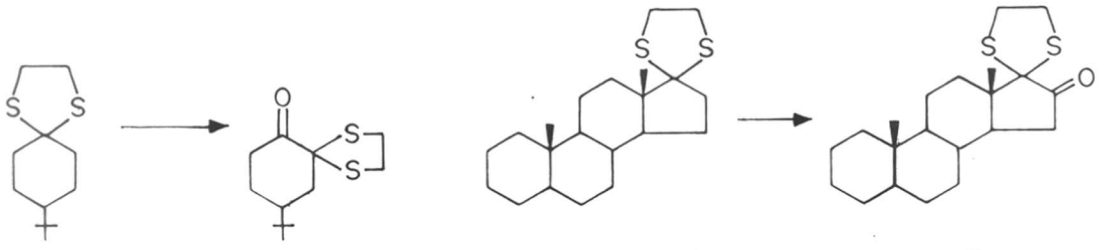
a : X = H, Y = nC_4H_9

b : X = n-C_4H_9, Y = H

SCHEME – 17.



158 159 160 161

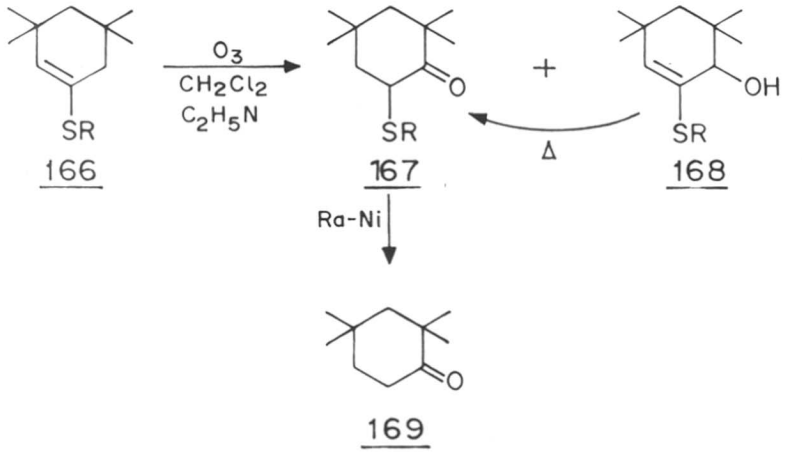


162 163 164 165

mainly **163** and in the case of androstane dithiolane **164** very little of the desired product **165** was obtained, indicating the limited scope of this reaction sequence.

A recently described procedure by Paquer et al[2] for 1,2-carbonyl transposition involves the oxidation of thioenol ether **166** (Scheme-18) with ozone to give the transposed β-ketosulfide **167** and alcohol **168** in the ratio

SCHEME–18.



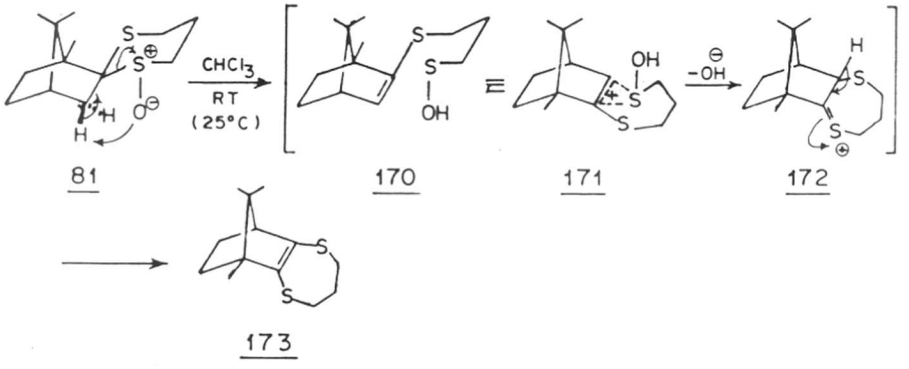
1:12, however, thermolysis of **168** gave exclusively the β-ketosulfide **167** which can be converted to the transposed ketone with Raney nickel to give **169**. This method would then be the reverse of all the previous schemes described so far, which usually involves α-sulfenylation of the carbonyl compound followed by conversion to its enol thioether and subsequent hydrolysis whereas here a thioenol ether to start with is oxidized to an α-sulfenyl carbonyl compound and then desulfurized to afford the ketone.

Thus, many methods have been developed for 1,2-carbonyl transposition since early this century, however the need for milder and efficient method still inspires organic chemists to develop new methods, as most of the methods have limited applications due to low overall yields and/or the presence of reagent sensitive functional groups.

2B.3 PRESENT WORK AND DISCUSSIONS

During the course of work on synthesis of α-lipoic acid, starting from d-camphor **64**, it was observed that its sulfoxide derivative **81** was thermally unstable, particularly as a solution in chloroform. TLC analysis indicated a less polar component, IR spectrum of which indicated the absence of the S-O bond (the S-O stretching frequency at 1040 cm^{-1} was absent) and its ^{13}C NMR revealed the presence of two quaternary olefinic carbons. Mass spectrum of this compound exhibited M^+ ion at 240 m/e, indicating loss of a water molecule. Thus, the structure of the compound was deduced to be **173** formed mechanistically as shown in Scheme-19,

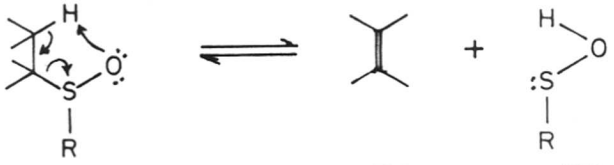
SCHEME – 19.



where the initial step is apparently the thermal ring opening reaction to sulfenic acid intermediate **170** via an assumed β-cis-elimination, which is very facile in this case where the geometry of the molecule renders the S-O bond and C3-α-H in close proximity.

The elimination of sulfenic acid on thermolysis of sulfoxides is generally regarded as a concerted process and since unshared pairs of electrons on the hetero-atom must be involved in the synchronism of bond making and breaking, it is possibly considered a pseudopericyclic[38] process, as represented in the following equilibrium, (Scheme-20).

SCHEME - 20.

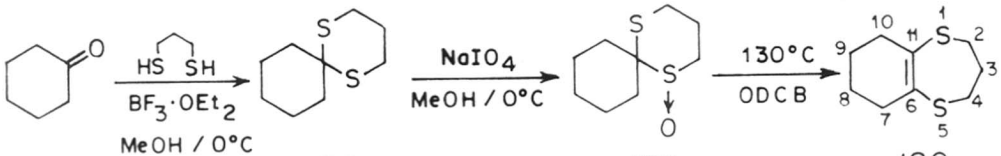


174 175 176

The sulfenic acid thus formed undergoes a ring closure reaction by an electrophilic addition of the sulfenic acid function and the newly generated olefinic function to form a dithiepin derivative **173** [IR & NMR Fig. No. 2.6].

Formation of a dithiepin derivative from a spiro dithiane oxide was also confirmed by subjecting cyclohexanone as a model to the same set of reaction sequence as shown in Scheme-21. Thermolysis of the sulfoxide **179** [IR & NMR Fig. No.2.7] at

SCHEME - 21.

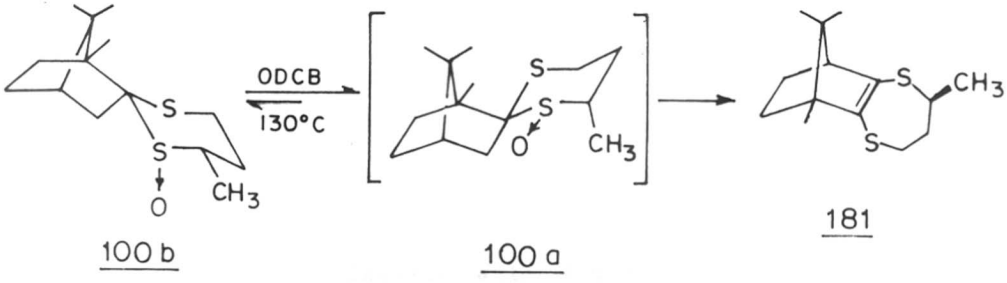


178 179 180

130°C in ortho dichlorobenzene (ODCB) afforded the dithiepin derivative **180**, which was characterised by its ^{1}H and ^{13}C NMR [Fig No. 2.8] and MS.

The methylated analogue of **81** i.e. sulfoxide **100b**, was found to be very stable at 25°C, neat or as a solution in chloroform. However, thermolysis at 130°C in ODCB did furnish the dithiepin derivative **181** (Scheme-22) which

SCHEME - 22.

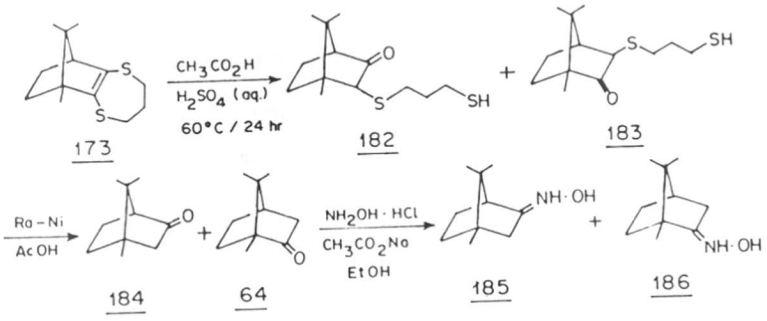


100 b 100 a 181

was characterised by its ^{1}H and ^{13}C NMR [Fig. No. 2.9]. This experiment not only confirms the dithiepin formation but also indicates the difference in geometry of the two sulfoxides **81** and **100** (see Scheme-4). In sulfoxide **81**, where the conformation makes the S-O bond equatorial, the proximity of the β-hydrogen (C3-α-H) facilitates an easy elimination reaction and hence reacts at 25°C whereas in sulfoxide **100b**, the conformation of the molecule bears the S - O bond axial, with no β-hydrogen in the vicinity of the S-O bond for such an elimination reaction, therefore it needs to be heated up to 130°C to undergo elimination reaction probably via its conformer **100a**.

The dithiepin **173** thus obtained was subjected to acid hydrolysis using acetic acid and catalytic amount of sulfuric acid in water to yield a mixture of two regio-isomeric keto-sulfides **182** & **183** [IR & NMR Fig.No.2.10] (Scheme-23). This was then

SCHEME – 23.



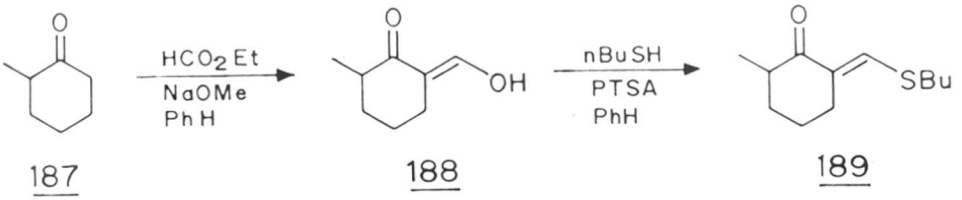
subjected to desulfurization with Raney nickel to afford the two ketones, camphor **64** and epicamphor **184** in a ratio of 1:3 (by GC). This mixture was then derivatized to its oximes and separated. The oxime derivatives of the two ketones exhibited specific rotations as: d-camphor-oxime **186**; $[\alpha]_D^{25}$ = -53.73° (C, 1.0; PhH), oxime prepared from d-camphor; $[\alpha]_D^{25}$ = -53.75 (C, 1.5; PhH) [lit.[39] $[\alpha]_D^{25}$ = -56.0] and l-epicamphor oxime **185** [NMR Fig.No.2.11]; $[\alpha]_D^{25}$ = +93.3° [lit.[39] $[\alpha]_D^{25}$ = +100.5° (C, 6.2; PhH). Thus, starting from d-camphor, converting it to its dithiane oxide derivative **81** and subjecting it to the set of reaction mentioned in Schemes-19 and 23, one gets a 1,2-carbonyl transposition to l-epicamphor in ca 20% overall yields. The key reagent in the above

sequence is 1,3-propanedithiol which initially acts as a thioketalisation agent and finally is removed reductively using Raney nickel to result in a transposed ketone.

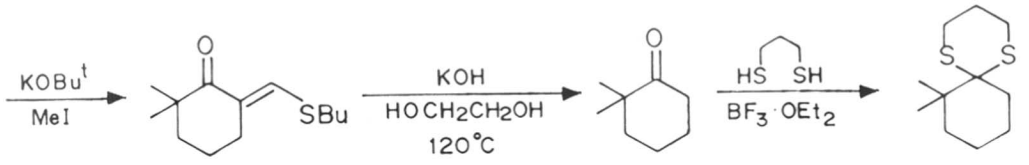
Having achieved 1,2-carbonyl transposition in case of d-camphor, the same set of reaction sequence was subjected on 2,2-dimethylcyclohexanone **191** [IR & NMR Fig. No. 2.12]. 2,2-Dimethylcyclohexanone was synthesized from 2-methyl-cyclohexanone by reported[40] methods as shown in Scheme-24. Dithiane **192** [NMR: Fig No.2.13] was obtained by borontri-fluoride etherate catalyzed reaction of the ketone **191** and 1,3-propanedithiol in methanol. Oxidation of the dithiane **192** with 1.0 equiv. of $NaIO_4$ furnished the sulfoxide **193** [NMR: Fig. No. 2.14] which on thermolysis at 140°C in ODCB provided the dithiepin derivative **194** [NMR: Fig. No. 2.15]. Acid hydrolysis afforded a mixture of β-ketosulfides **195** and **196** [IR & NMR: Fig. No. 2.16] which on desulfuriza-tion with Raney nickel provided the carbonyl transposed ketone **197** [IR & NMR: Fig. No. 2.17] and the starting ketone **191** in a ratio of 9:1, respectively.

The above set of reactions were also employed on 2-methylcyclohexanone **187** and enones 4-methyl-cyclohex-3-enone **201** and isophoron **206** (Scheme-25). Enone **206** was chosen in order to study an enone transposition. Though the carbonyl compounds **187** and **201** afforded the respective

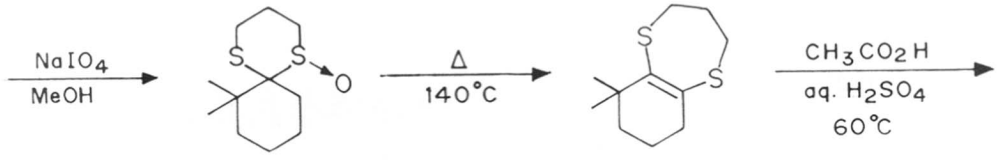
SCHEME-24



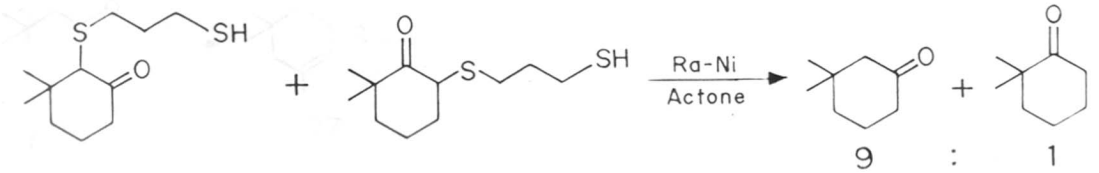
187 188 189



190 191 192



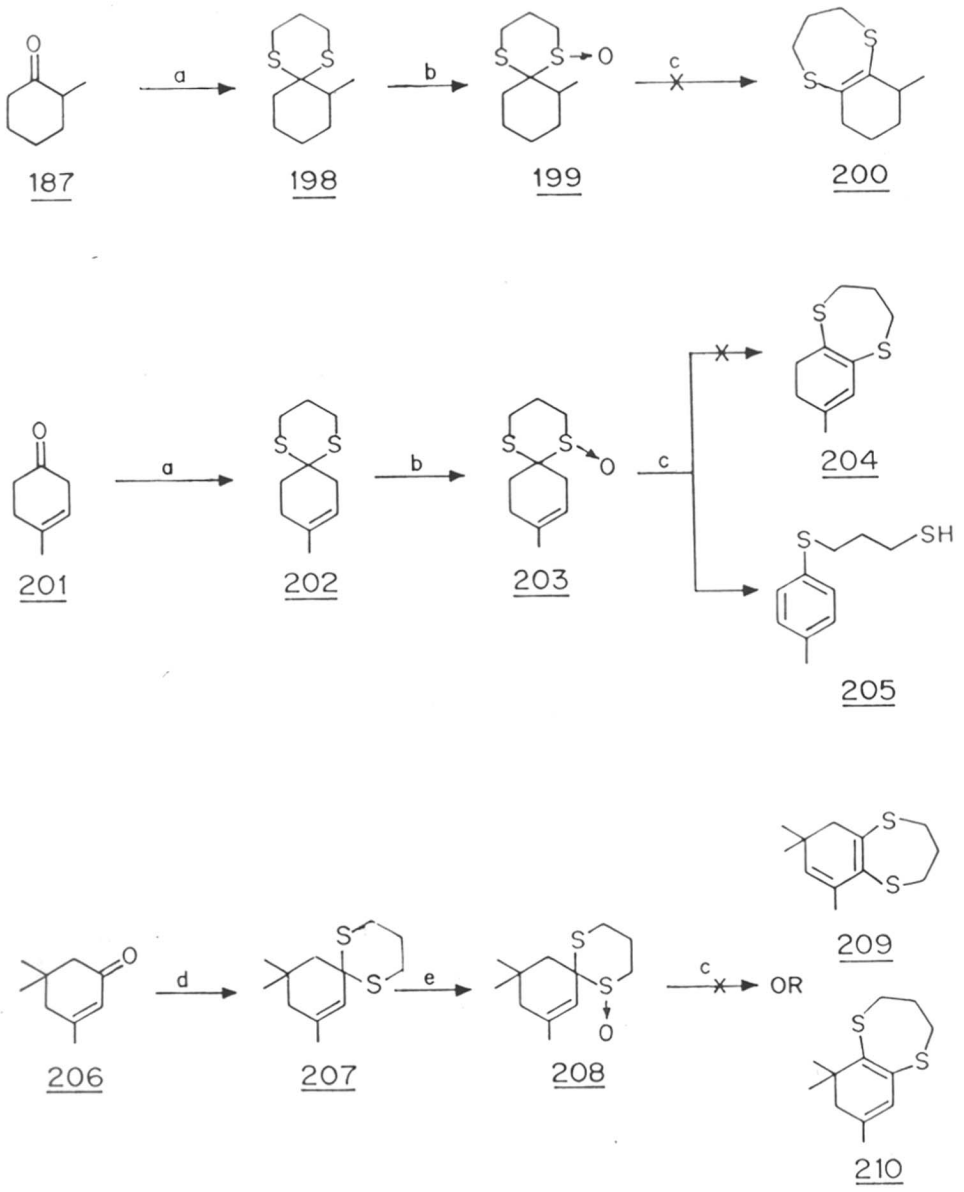
193 194



195 196 9 : 1

197 191

SCHEME-25



Reagents :

a) $HSCH_2CH_2CH_2SH$, $BF_3 \cdot OEt_2$, MeOH, 0°C ; b) $NaIO_4$, MeOH, 0°C

c) Xylene or ODCB , 130°C ; d) $HSCH_2CH_2CH_2SH$, $BF_3 \cdot OEt_2$, CH_2Cl_2, MS-4A°, 0°C ; e) MCPBA, CH_2Cl_2, Satd. $NaHCO_3$, 0°C

dithianes **198** [NMR Fig. 2.18] and **202** [NMR Fig. No. 2.20] and sulfoxides **199** [IR and NMR Fig. No. 2.19] and **203** [NMR Fig. No. 2.21], they failed to yield the desired products **200** and **204** respectively. In case of **203**, thermolysis resulted in some amount of aromatised product **205** [NMR Fig. No. 2.22]. Similarly, the sulfoxide **208** [NMR Fig.2.24] derived from isophoron **206** did not result in the dithiepin derivatives **209** or **210** under various conditions, hence further studies towards these were not pursued.

2B.4 EXPERIMENTAL

Alkylation and Acylation of Sulfoxide 81: A General Procedure

To a solution of LDA-TMEDA (1.1 mmol) in THF (5 ml) at -90°C was added a solution of sulfoxide **81** (0.258 g, 1.0 mmol) in THF (5 ml) dropwise and stirring continued for 20 min. The alkylating agent or the acylating agent (1.2 mmol in 2 ml THF) was then added dropwise. After 2-3h, the solution was quenched with water (5 ml). The THF layer was separated, the aqueous layer was extracted with ether or ethyl acetate. The combined extracts were washed with brine, worked up and the crude product was purified by column chromatography employing ethyl acetate/petroleum ether as eluent.

[Spiro(camphane-2,2'-m-dithiane)-6'-methyl-1'-oxide] **100**: solid, m.p: 123°C $[\alpha]_D^{25}$: -164.4 (C, 1.30, $CHCl_3$).

IR ($CHCl_3$): 1040 cm^{-1}

PMR : 0.9, s, 3H (CH_3); 1.17, s, 3H (CH_3); 1.2, s, 3H (CH_3); 1.3, d, J = ~7.5Hz, 3H (CH_3); 1.3-1.4, m, 1H; 1.5-1.65, m, 2H; 1.7-2.1, m, 5H; 2.25, d, J = ~13Hz, 1H; 2.63, m, 1H; 2.77-2.94, m, 2H.

CMR: 14.04, q (CH_3); 16.95, q (CH_3); 20.24, q (CH_3), 20.33, t (CH_2), 21.15, q (CH_3); 26.0, t (CH_2); 26.2, t (CH_2); 31.51, t (CH_2), 38.27, t (CH_2); 44.77, d (CH); 48.6, d (CH); 51.77, s; 55.14, s; 72.23, s.

MS (m/e): 272(70.4%, M^+), 255(6.9), 239(2.3), 202(10), 181(6.5), 168(40.8), 153(21.7), 137(96.3), 136(100),

135(41.7), 121(44.3), 105(32.1), 97(7.8), 93(23.6), 85(8.6), 77(10), 68(10), 55(19), 41(14).

[Spiro(camphane-2,2'-m-dithiane)6'-formyl-1'-oxide], 102: Viscous liquid.

IR (Neat): 1010-1060, 1380, 1400, 1750 and 3100-3700 cm^{-1}.

PMR : 0.9, s, 3H (CH_3); 1.05, s, 3H (CH_3); 1.25, s, 3H (CH_3); 1.9-2.9, m, 8H; 3.2-4.2, m, 3H; 4.85, bs, 1H (OH); 8.1, s, 1H (C<u>H</u>OH); 9.9, s, 1H (CHO).

MS (m/e): 286(58.2%, M^+), 268(30), 253(10), 235(61.1), 225(26.6), 207(36.6), 195(29.4), 179(30.8), 168(81.2), 167(100), 163(35.7), 153(63.5), 139(52.6), 135(56.2), 125(58), 121(54.4), 105(76.7), 93(99), 91(95.5), 85(41), 77(48), 55(16), 45(7.1).

[Spiro (camphane-2,2'-m-dithane)-6'-carbethoxy-1'-oxide] 103. Viscous liquid; $[\alpha]_D^{25}$: -137 (C, 1.1; $CHCl_3$).

IR (Neat): 1050, 1380, 1400, 1745 cm^{-1}

PMR : 0.9, s, 3H (CH_3); 1.05, s (CH_3); 1.1, t (CH_3); 1.3-2.8, m, 11H; 3.8-4.1, m, q, 6H ($COC\underline{H}_2CH_3$) and (C<u>H</u>-CO_2Et).

Spiro (camphane-2,2'-m-dithiane)-6'-formyl-1'-oxo-6'-(5"-pentanoic acid).

To a solution of 3.0 mmol of LDA-TMEDA was added 1.0 mmol of the sulfoxide **81** at -78°C and stirred for 0.5 h. Then a solution of ethyl formate (1.1 mmol in 2 ml THF) was added dropwise and stirred for 0.5 h. A solution of δ-bromovaleric acid (1.2 mmol in 2 ml THF) was then added to

the reaction mixture and stirring continued for 1 h. The reaction was then quenched with saturated NH_4Cl and THF removed in vacuo. The residue was acidified and extracted with ethylacetate. The combined extracts were washed with brine, worked up and chromatographed (40% EtOAc/PhH) to provide 10% yield of the product.

IR (Neat): 1050, 1370, 1390, 1720, 2700, 3000-3600 cm^{-1}.

PMR: 0.7-1.35, m, 15H; 1.4-1.9, m, 3H, 2-2.6, m, 3H, 2.6-3.3, m, 3H; 3.3-4.45, m, 4H; 8.15, s, 1H; 9.8, s, 1H.

MS (m/e): 387 (M^+ +1, 0.4%), 358(0.4), 282(6), 268(67.8), 253(37), 235(70), 207(100), 197(71), 179(80), 105(7), 101(10%).

Michael Addition Reactions of Sulfoxide 81: A General Procedure

A solution of sulfoxide **81** (0.258 g, 1.0 mmol) in THF (5 ml) was added to a solution of LDA (1.1 mmol) in THF (5 ml) at -90°C and stirred for 20 min. Cuprous iodide (1.0 mmol) was then added to the solution and stirred for 15 min, followed by the addition of the Michael substrate (1.2 mmol) in THF (2 ml). The solution was then quenched with saturated NH_4Cl (2 ml) after 3-5 h. THF is then removed in vacuo and the aqueous layer extracted with dichloromethane 3-4 times. The combined extracts were washed with brine, worked up and the crude product was purified by column chromatography employing ethylacetate/petroleum ether as eluent. Yield: 60-70%.

Ethyl spiro (camphane-2,2'-m-dithiane)-1'-oxo-6'-(3"-propanoate **104**. Viscous liquid.

IR ($CHCl_3$): 1045, 1370, 1390, 1735 cm^{-1}.

PMR : 0.83, s, 3H (CH_3); 1.0-1.2, m, 9H (3 x CH_3); 1.37-3.0, m, 15H; 3.9-4.3, m, 3H.

Ethyl spiro (camphane-2,2'-m-dithiane)-1'-oxo-6'-(5"-pent-2"/3"-enoate) **105**.

PMR: 0.8, t, 3H ($OCH_2\underline{CH}_3$); 1.15, s, 3H (CH_3); 1.18, s, 3H (CH_3); 1.22, s, 3H (CH_3); 1.42-3.17, m, 16H; 4.13, q, 2H ($O\underline{CH}_2CH_3$); 5.05-5.31, m, 1H (=$CH\underline{CO}_2Et$); 5.8, m, 1H (-$\underline{CH}$=$CHCO_2Et$).

Ethyl spiro (camphane-2,2'-m-dithiane)-1'-oxo-6'-(3"-pent-4"-enoate) **106**. Viscous liquid.

IR (Neat): 1040, 1360, 1380, 1640, 1720 cm^{-1}.

PMR : 0.75-1.07, m, 16H; 1.16-1.34, bt, 4H; 1.54-1.8, bs, 2H; 2.51, d, J=7.5Hz, 2H ($C\underline{H}_2CO_2Et$), 3.12, m, 2H ($S-CH_2$); 3.82-4.31, m, 3H ($OC\underline{H}_2CH_3$, $SO-C\underline{H}$); 4.9-5.17, m, 2H ($\underline{H}_2C$ = CH-); 5.75-6.17, m, 1H ($H_2C=C\underline{H}$-).

Preparation of Dithianes: A General Procedure

A mixture of 10 mmol of the ketone and 10 mmol of 1,3-propanedithiol in 10 ml of methanol was cooled to 0°C and 2 mmol of $BF_3.OEt_2$ was added and allowed to stand at 0°C for 24 h. Methanol was then removed in vacuo and the residue taken in ether and treated with 5% alkali, washed

with water, brine and worked up to afford the crude product which was purified by chromatography to afford 60-70% of the dithiane derivative.

1,5-Dithiaspiro[5,5]undecane-7,7-dimethyl **192**

PMR: 1.15, s, 6H (2 x CH_3); 1.51, bs, 3H; 1.68-2.0, m, 2H; 2.25, bs, 3H; 2.40-3.15, m, 6H (S-$(CH_2)_3$-S)

1,5-Dithiaspiro[5,5]undecane-7-methyl **198**

PMR: 1.5, d, J = 6.5Hz, 3H (CH_3), 1.3-2.15, m, 10H, 2.35-3.25, m, 5H.

1,5-Dithiaspiro[5,5]undecane-8-ene-9-methyl **202**

PMR: 0.8, d, 3H (CH_3); 1.77-2.15, m, 6H; 2.3-2.5, bs, 6H; 2.65-3.1, m, 4H (2 x CH_2-S); 5.2, bs, 1H.

1,5-Dithiaspiro[5,5]undecane-7-ene-8,10,10-trimethyl **207**

IR (Neat): 1370, 1380, 1390, 1660 cm^{-1}.

PMR: 1.0, s, 6H (2 x CH_3), 1.15-2.06, m, 7H, 5.8, bd, 1H (=CH).

Preparation of Sulfoxides: A General Procedure

A solution of 10 mmol of the dithiane derivative in methanol was chilled (5°C) and to this was then added a solution of 10 mmol of sodium metaperiodate in water. After the completion of the reaction (7-9h), methanol is removed in vacuo and the residue taken in ether, washed with brine and worked up to afford the sulfoxide which was purified by chromatography, yield 60-80%.

1,5-Dithiaspiro[5,5]undecane-1-oxide **179**

Solid: m.p. 71-73°C

IR (Nujol): 1035, 1055 cm^{-1}

PMR: 1.67-2.45, m, 10H; 2.56-3.0, m, 4H; 3.06-3.45, m, 2H.

1,5-Dithiaspiro[5,5]undecane-7,7-dimethyl-1-oxide **193**

Solid: m.p. 52-54°C

IR (Nujol): 1020, 1370, 1390 cm^{-1}.

PMR: 1.15, s, 3H (CH_3); 1.37, s, 3H (CH_3); 1.47-2.0, m, 6H; 2.06-2.16, m, 1H; 2.16-2.37, m, 4H; 2.38-3.26, m, 3H.

1,5-Dithiaspiro[5,5]undecane-7-methyl-1-oxide **199**

IR (Neat): 1020-1040 cm^{-1}.

PMR: 0.9, d, J = 6.5Hz, 3H (CH_3), 1.0-2.6, m, 15H.

1,5-Dithiaspiro[5,5]undecane-8-ene-9-methyl-1-oxide **203**

IR : 1040, 1615 cm^{-1}.

PMR: 1.7, bs, 3H (CH_3); 2.0-2.6, m, 4H; 2.7-3.2, m, ($S-CH_2$,CH_2SO), 5.35, bs, 1H.

1,5-Dithiaspiro[5,5]undecane-7-ene-1-oxo-8,10,10-trimethyl **208**

IR ($CHCl_3$): 1050, 1370, 1390, 1640 cm^{-1}.

PMR: 1.0, s, 3H (CH_3), 1.03, s, 3H (CH_3); 1.77-1.95, m, 4H; 1.97-2.13, m, 3H; 2.17-3.42, m, 1H, 2.44-2.73, m, 2H, 2.8-3.2, m, 3H; 5.6, m, 1H.

Thermolysis of Sulfoxides: A General Procedure

The sulfoxides were taken in appropriate solvent and heated until complete conversion of the reaction. O-Dichlorobenzene (ODCB) or xylene was used as the solvent when

thermolysed at 130-140°C. Chloroform was used for reactions at room temperature and above. After completion of the reaction the solvent (chloroform or xylene) was removed in vacuo and passed through a column. With ODCB as solvent, the reaction mixture was directly chromatographed, yield 60-80%.

Thermolysis of spiro[camphane-2,2'-m-dithiane]-1'-oxide **81** to **173**

Solvent: $CHCl_3$/25°C

Liquid: $[\alpha]_D^{25}$: -2.95 (c, 1.0, $CHCl_3$)

IR (Neat): 1370, 1390, 1550 cm^{-1}

PMR : 0.73, s, 3H (CH_3): 0.86, s, 3H (CH_3): 0.88, s, 3H (CH_3); 1.11-1.37, m, 2H; 1.51-1.6, m, 2H; 1.7-1.88, m, 1H; 2.04-2.28, m, 2H; 2.97-3.68, m, 4H.

CMR : 11.5, q (CH_3): 19.02, q (CH_3); 19.07, q (CH_3); 26.09, t (CH_2); 32.06, t (CH_2); 32.10, t (CH_2), 32.49, t (CH_2), 33.07, t (CH_2); 54.57, s; 58.27, s; 58.7, d (CH); 132.96, s; 135.50, s.

MS: 240 (M^+ 57%), 225(68), 212(83), 197(28), 179(22), 165(26), 138(67), 105(82), 91(100), 85(14), 77(22%).

Thermolysis of spiro[camphane-2,2'-m-dithiane-6'-methyl-1'-oxide **100** to **181**

Solvent: ODCB/130°C

Liquid: $[\alpha]_D^{25}$: -37 [c, 1.5, $CHCl_3$]

PMR : 0.7, s, 3H (CH_3): 0.8, s, 3H (CH_3): 0.9, s, 3H (CH_3); 1.15-1.25, m, 5H; 1.5-1.62, m, 1H; 1.7-1.92, m, 2H; 2.1-2.27, m, 2H; 2.65-2.77, m, 1H (S-CH$<$); 3.8-3.97, m, 2H (S-CH_2-)

CMR : 11.67, q (CH_3); 19.08, q (CH_3); 19.10, q (CH_3); 21.28, q (CH_3); 25.27, t (CH_2); 30.80, t (CH_2); 33.76, t (CH_2); 41.42, t (CH_2); 43.32, d (CH); 53.71, s; 57.93, s: 58.95; d (CH); 130.83, s; 137.74, s.

Thermolysis of 1,5-dithiaspiro[5,5]undecane-1-oxide **179** to **180**

Solvent: ODCB/140°C

Product: Liquid; 2,3-tetramethylene-5,6-dihydro-1,4-dithiepin (See Scheme-21 for numbering)

PMR: 1.59, m, 4H (8,9-CH_2); 1.89-2.23, m, 6H (3,7,10-CH_2); 3.23, t, J = 6.4Hz, 4H (2,4-CH_2)

CMR: 22.92, t (8,9-CH_2), 30.42, t (3-CH_2); 31.33, t (7,10-CH_2); 34.07, t (2,4-CH_2), 127.65, s (6,11-C).

Thermolysis of 1,5-dithiaspiro[5,5]undecane-7,7-dimethyl-1-oxide **193** to **194**

Solvent: ODCB/130°C

PMR: 1.13, s, 6H (2 x CH_3); 1.48-1.61, m, 3H; 1.95-2.37, m, 5H; 2.88, m, 4H (2 x CH_2-S)

Thermolysis of 1,5-dithiaspiro[5,5]-undecane-8-ene-9-methyl **203** to **205**

Solvent: ODCB or Xylene 130°

Product: 3-Mercaptopropyl-p-methylphenylsulfide **205**

PMR: 1.5, s, 1H (SH); 1.95, m, 2H; 2.3, s, 3H (CH_3); 2.6-3.05, m, 4H (2 x CH_2-S); 7.02, d, J=8Hz, 2H (2 x ortho-H); 7.24, d, J=8Hz, 2H (2 x meta-H).

Hydrolysis of 5,6-Dihydro-1,4-dithiepin Derivatives: A General Procedure

To 1.0 mmol of the dithiepin derivative in acetic acid (2 ml) was added 0.2 ml of conc. H_2SO_4 and 0.5 ml of water. The mixture was maintained at 60°C with vigorous stirring till the completion of reaction (24 hours). Acetic acid was then removed in vacuo and the residue was taken in ether, neutralised with sodium bicarbonate. The ether layer was then washed with water, brine, worked up and chromatographed (40% EtOAc/n-hexane) to afford the α-ketosulfide derivative in 30-40% yield.

2(ϒ-Mercaptopropyl)thio epicamphor and 3(ϒ-mercaptopropyl) camphor **182** and **183**

IR (Neat): 1380, 1400, 1735, 2720 (SH) cm^{-1}.

PMR : 0.88-1.15, 3s & m, 10H (3 x CH_3, SH), 1.2-2.3, m, 8H: 2.7-3.04, m, 4H (2 x CH_2S), 3.4, d, J = 5Hz, 1H (CO-CH-S)

3,3-Dimethyl-2 (ϒ-mercaptopropyl)thio cyclohexanone **195** and **196**.

IR (Neat): 1695, 1705, 2630 cm^{-1}

PMR : 1.0, s, 3H (CH_3); 1.08, s, 3H (CH_3); 1.24, s, 1H (SH), 1.73-2.31, m, 7H; 2.4-3.24, m, 6H.

Desulfurisation-Derivatisation of 182 and 183

Raney nickel was prepared according to the method of Mozingo[41] and deactivated by refluxing in ethyl acetate and in acetone for 15 min each, before use. A mixture of

182 and **183** (0.210 g) in acetone (2 ml) was added to deactivatated Raney nickel (2 g) in acetone (30 ml) and stirred at room temperature for 2 h. The mixture was then filtered and concentrated in vacuo and the residue was taken in ethanol (5 ml). To this was added hydroxylamine hydrochloride (0.100 g) and sodium acetate (0.100 g) and heated on a water bath for 1.5 h. Ethanol was then removed in vacuo. To the residue was added water (5 ml) and extracted thrice with ether. The combined extracts were washed with brine, worked up and chromatographed employing a column of neutral alumina and 20% EtOAc/n-hexane as eluent to provide 0.109 g of l-epicamphoroxime **185**.

M.p: 92-98°C, $[\alpha]_D^{25}$: +93.3° (C, 0.6, PhH) [lit.[39]: +100.5 (C, 6.2; PhH).

PMR: 0.84, s, 3H (CH_3); 0.90, s, 3H (CH_3), 0.96, s, 3H (CH_3); 1.12-2.46, m, 6H; 3.0, d, 1H; 7.43, bs, 1H (OH) and 0.036 g of camphoroxime **186**.

M.p: 109-110°C, $[\alpha]_D^{25}$: -53.73° (C, 1.0, PhH) [lit.[39] -56.0°, PhH]

PMR: 0.77, s, 3H (CH_3); 0.90, s, 3H (CH_3); 1.12-2.09, m, 5H; 2.29-2.74, m, 2H; 8.41, bs, 1H (OH).

Camphoroxime **186** prepared from (R)-(+)-camphor employing the same method as above exhibited a specific rotation $[\alpha]_D^{25}$: 53.75°C (C, 1.5, PhH).

Desulfurisation of 195, 196

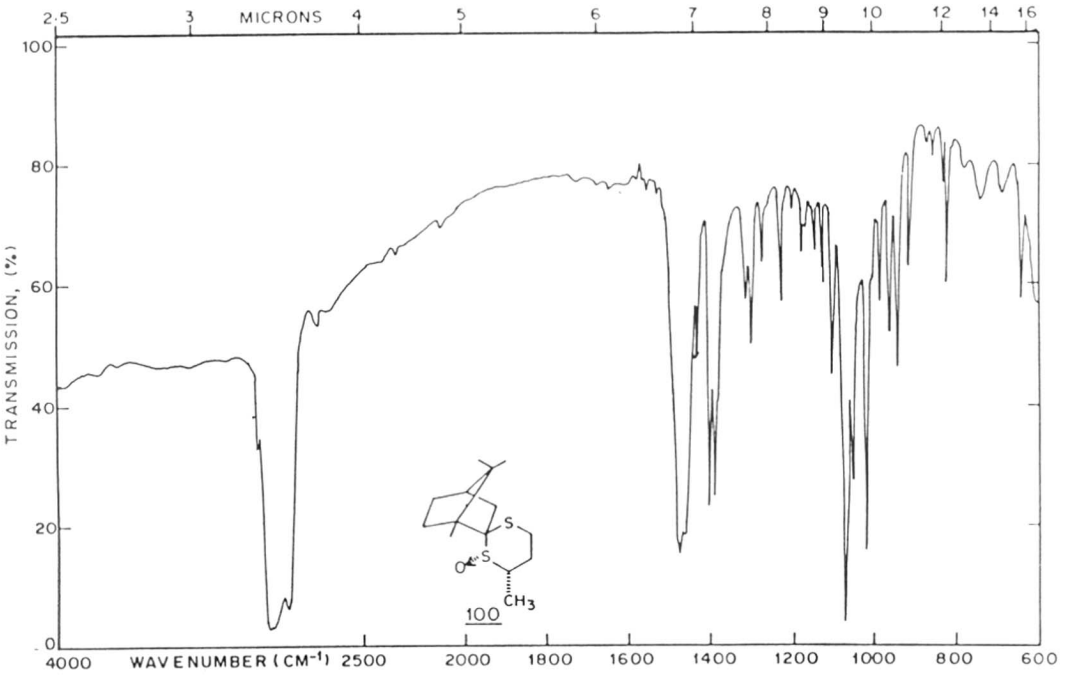
To deactivated Raney nickel (1.5 g) in 20 ml acetone was added a solution of ketosulfide **195** (and **196**) (0.178g) in acetone and stirred at room temperature for 2 h. The mixture was then filtered and concentrated in vacuo, GC analysis on a Carbowax column indicated 7.4% of starting ketone and 64.7% of transposed ketone. Chromatography (20% EtOAc/n-hexane) yielded 0.032 g (36%) of 3,3-dimethylcyclohexanone **197**.

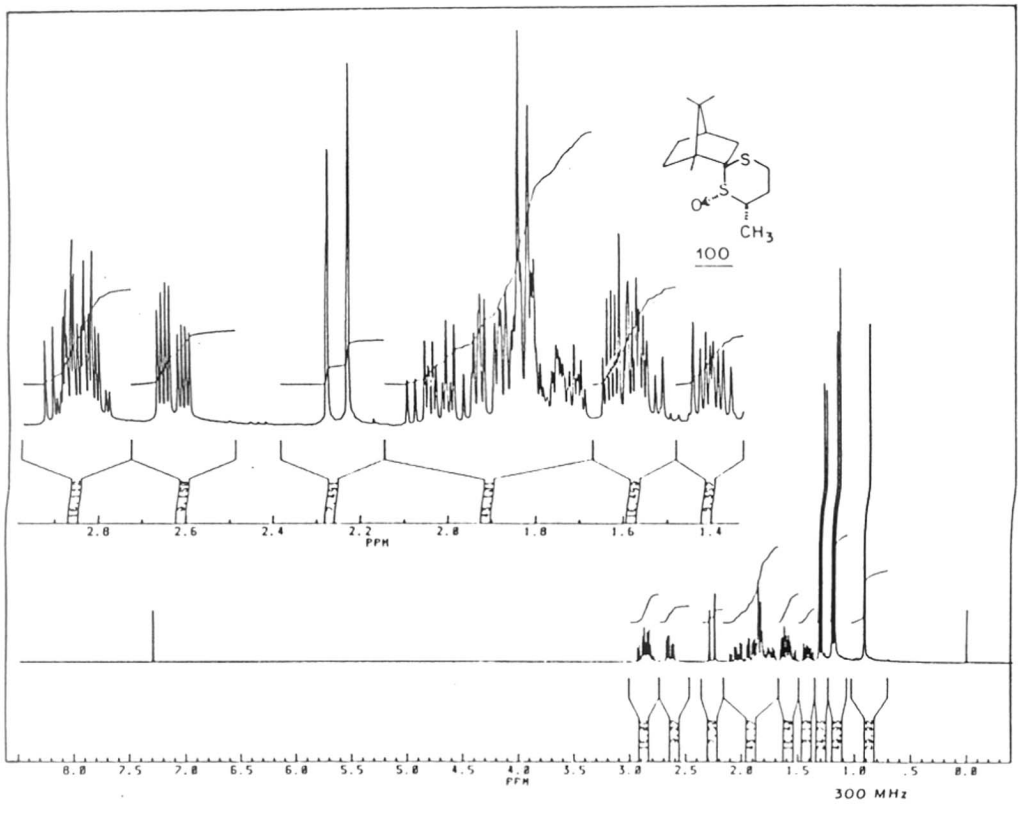
IR (Neat): 1370, 1390, 1710 cm^{-1}.

PMR: 0.97, s, 6H (2 x CH_3); 1.48-1.7, m, 2H (C4-H_2); 1.74-2.04, m, 2H (C5-H_2); 2.13-2.45, m, 4H (C2, C6-H_2) and 0.008 g (9%) of the starting ketone, 2,2-dimethylcyclohexanone **191**.

IR: 1370, 1390, 1710 cm^{-1}.

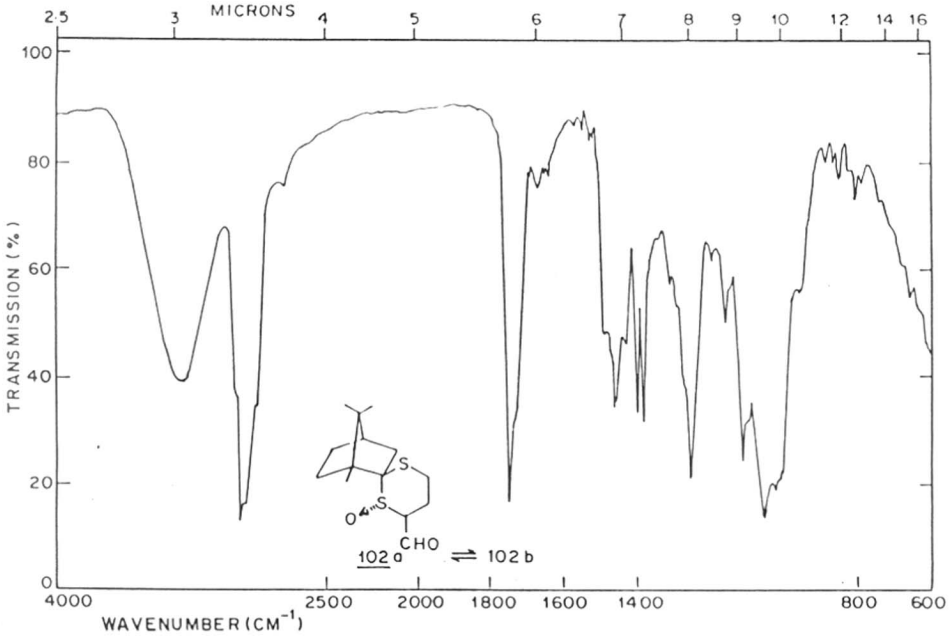
PMR: 1.08, s, 6H (2 x CH_3); 1.58-1.93, m, 6H (C3, C4, C5-H_2); 2,42, bt, 2H (C6-H_2).

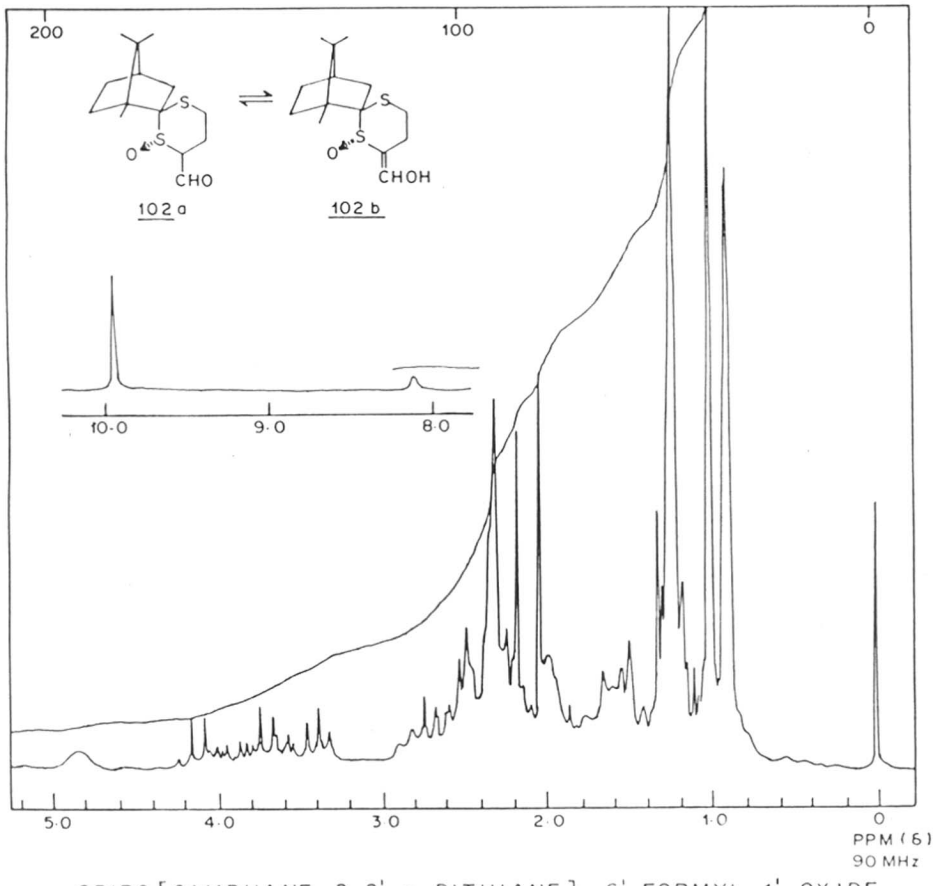




SPIRO [CAMPHANE-2,2'-m-DITHIANE] 6' METHYL-1-OXIDE

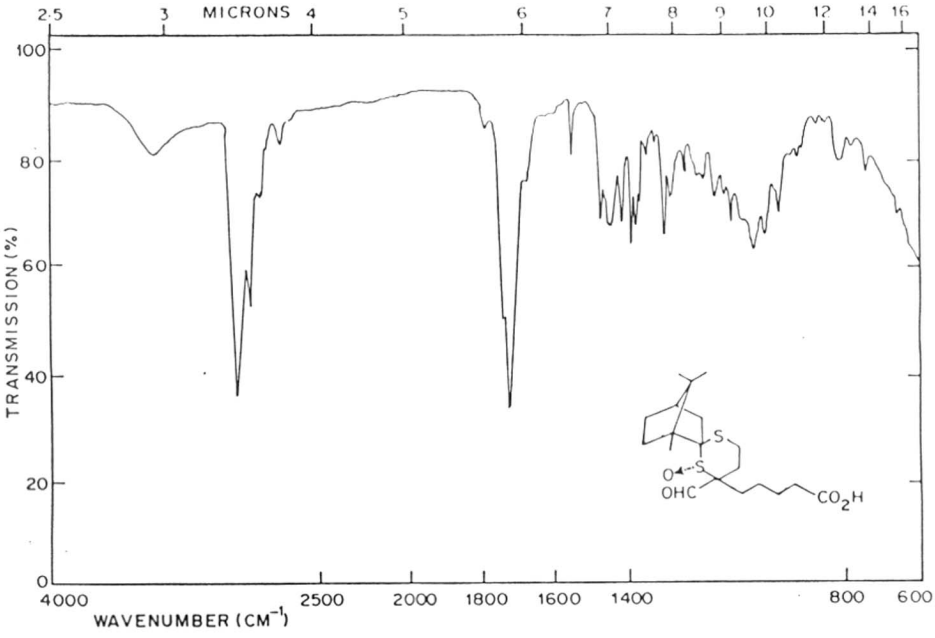
FIG. 2·0

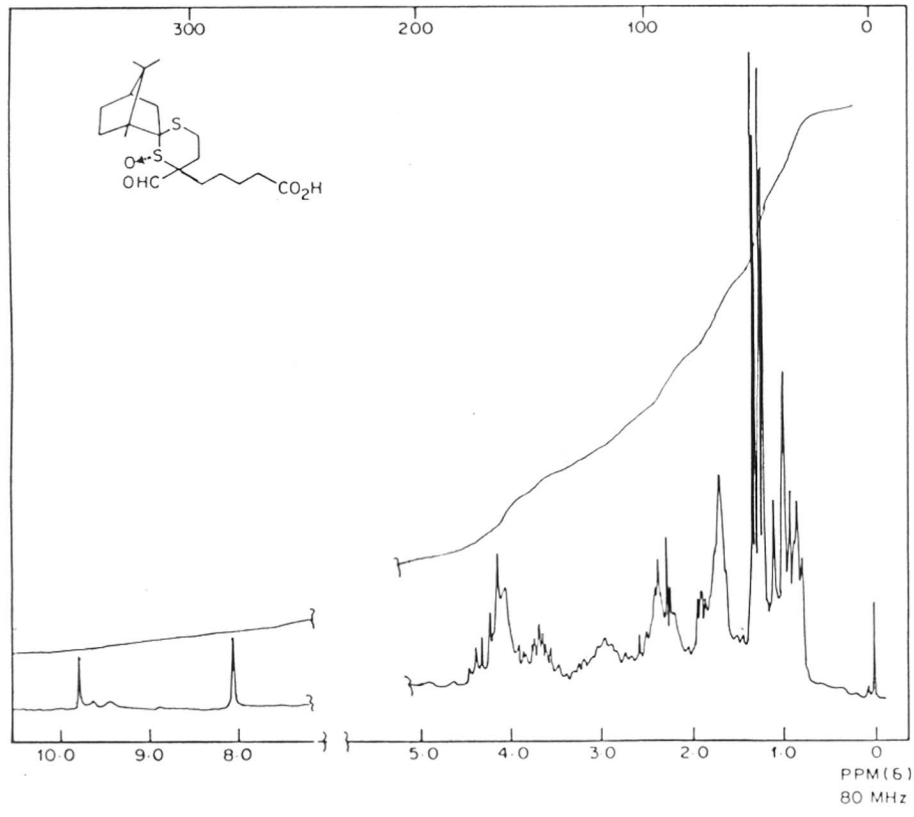




SPIRO [CAMPHANE-2,2'-m-DITHIANE] -6'-FORMYL-1'-OXIDE

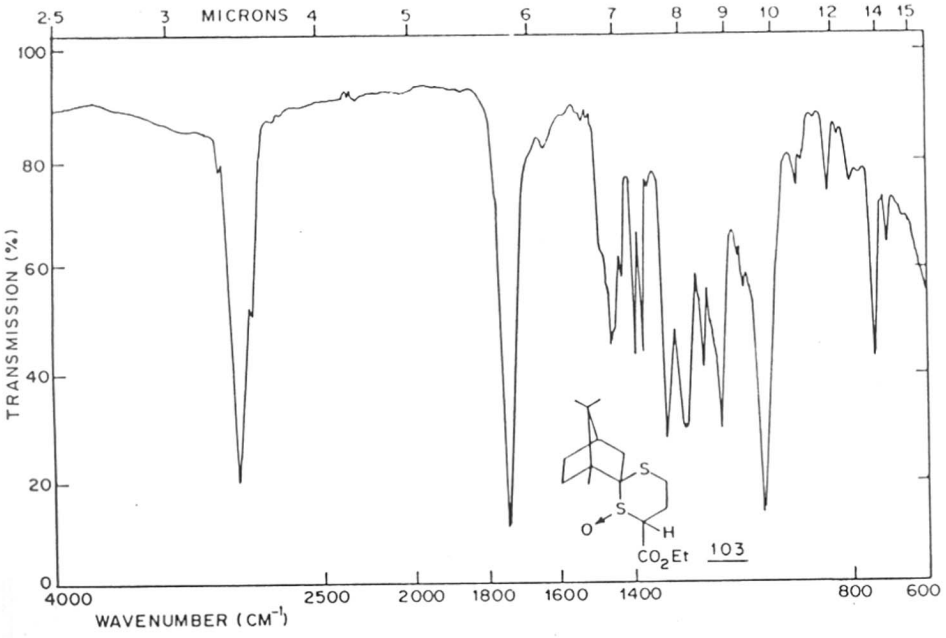
FIG. 2·1.

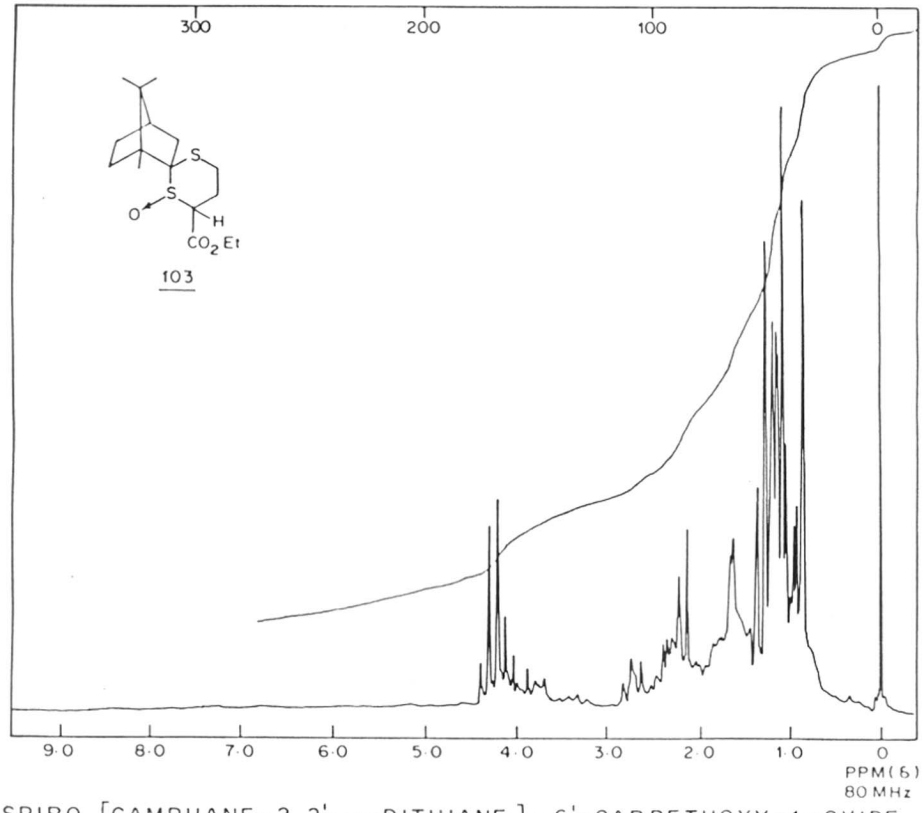




SPIRO(CAMPHANE-2-2'-m-DITHIANE)-6-FORMYL-1-OXO-6'-(5"-PENTANOIC ACID)

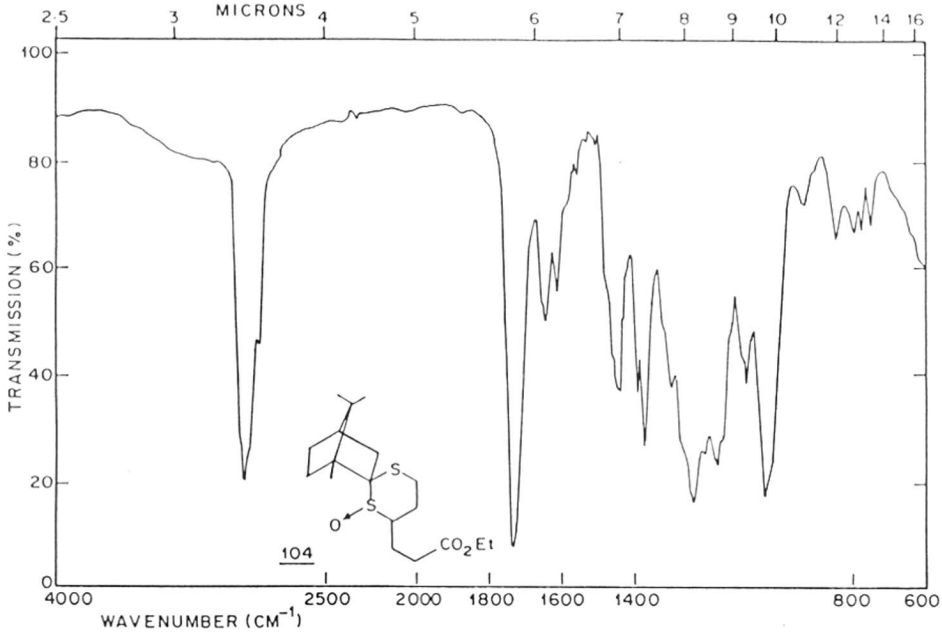
FIG. 2·1A

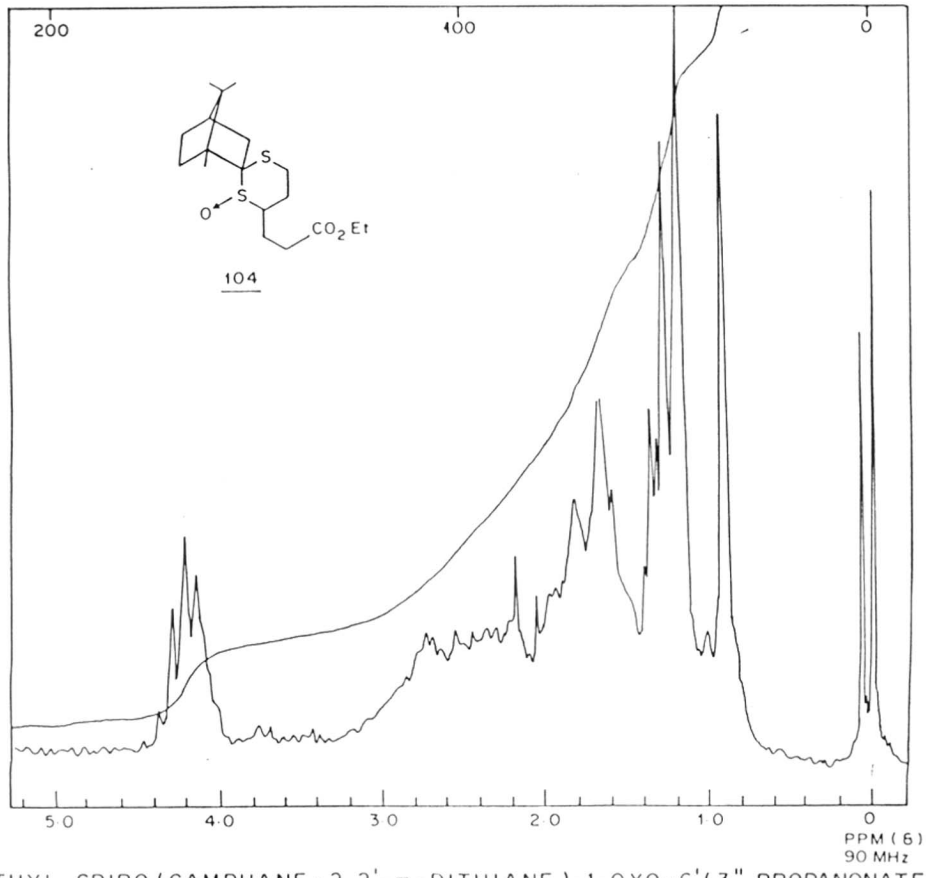




SPIRO [CAMPHANE-2,2'-m-DITHIANE]-6'-CARBETHOXY-1-OXIDE

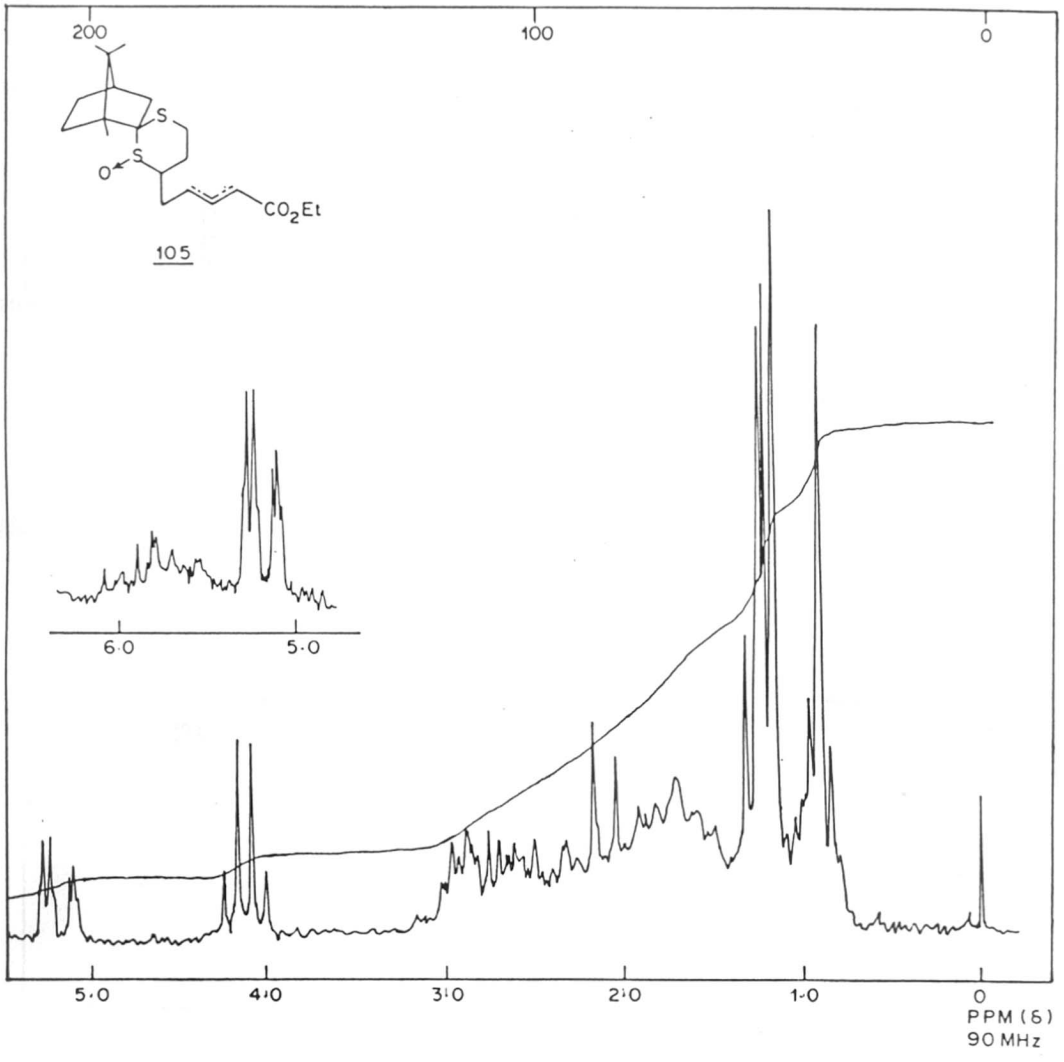
FIG. 2·2.





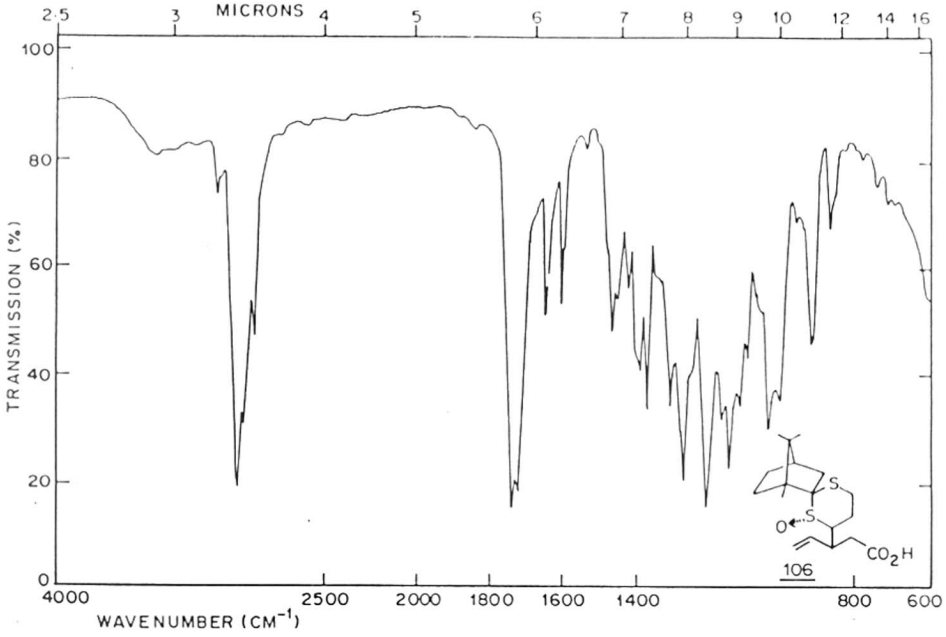
ETHYL SPIRO(CAMPHANE-2,2'-m-DITHIANE)-1-OXO-6'(3"-PROPANONATE)

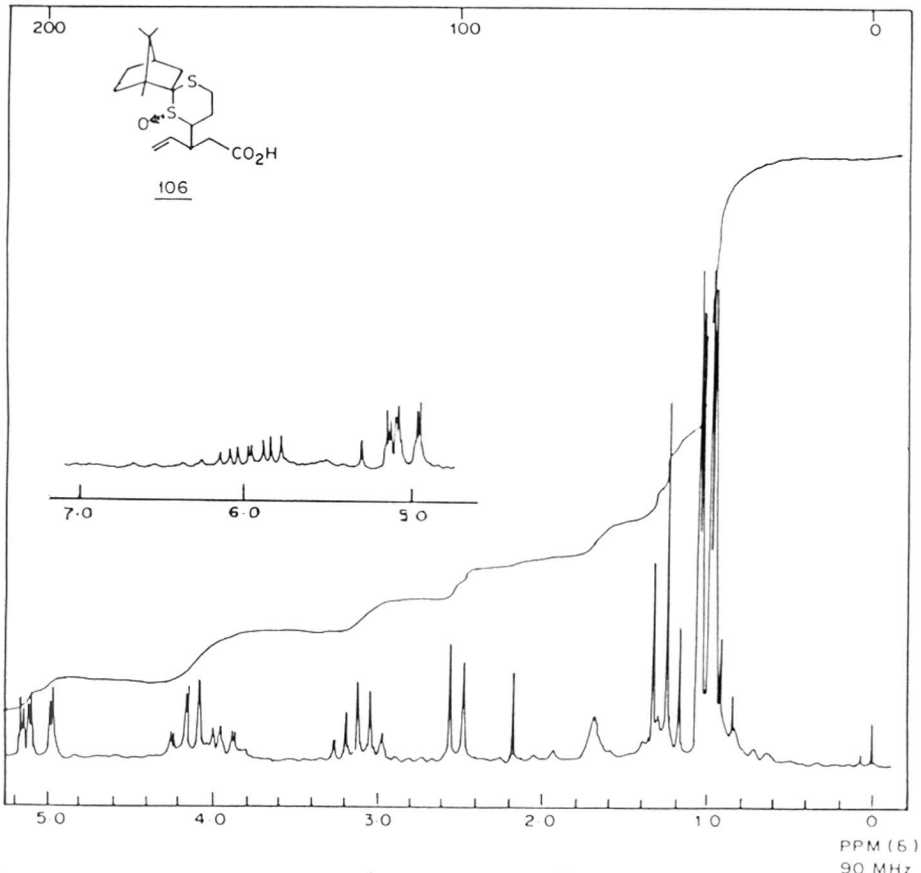
FIG. 2.3.



ETHYL SPIRO (CAMPHANE-2,2'-m-DITHIANE)-1'-OXO-6'(5"-PENT-2"/3"-ENOATE)

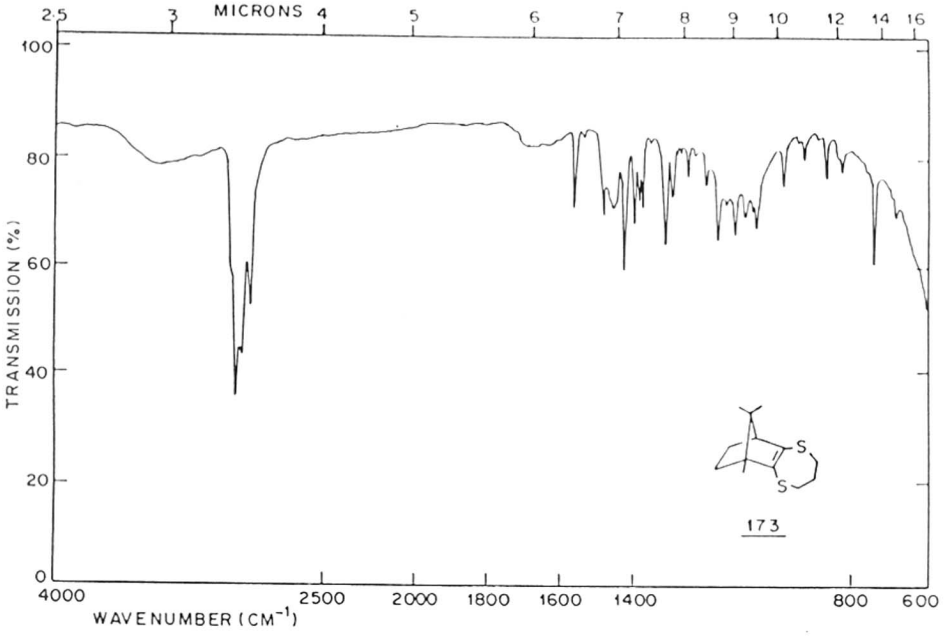
FIG. 2·4.





ETHYL SPIRO-(CAMPHANE-2-2'-m-DITHINE)-1'-OXO-6'-(3"-PENT-4"-ENOATE)

FIG. 2·5.


MICRONS
2.5
3
4
5
6
7
8
9
10
12
14
16
100
80
60
40
20
0
TRANSMISSION (%)
4000
2500
2000
1800
1600
1400
800
600
WAVENUMBER (CM⁻¹)
S
S
173

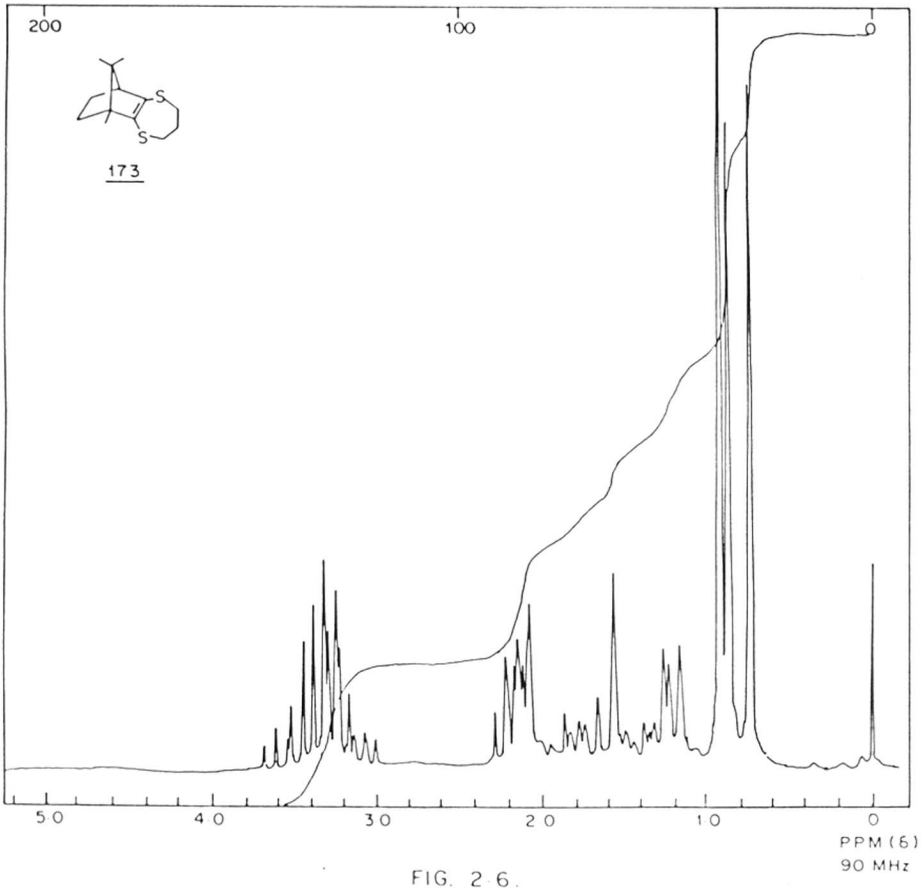
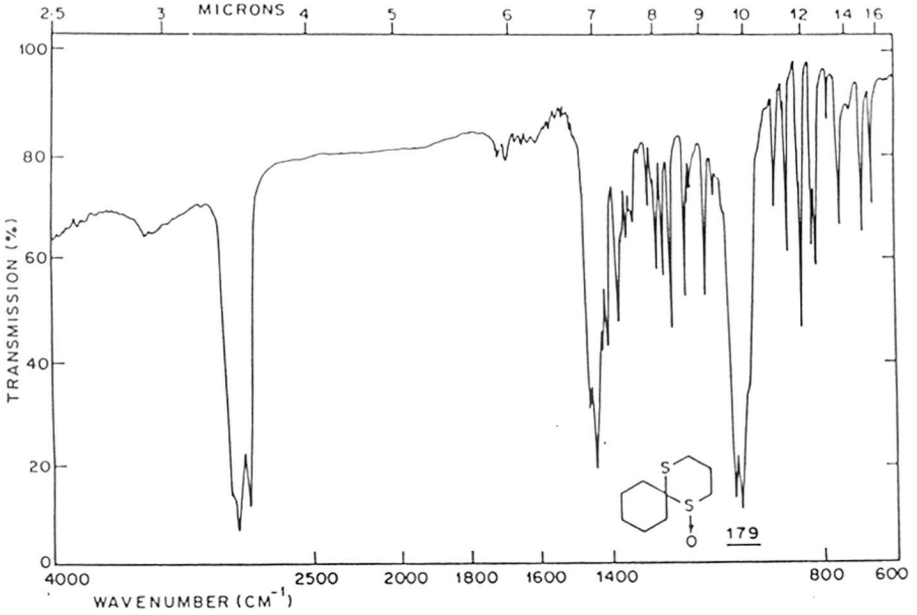
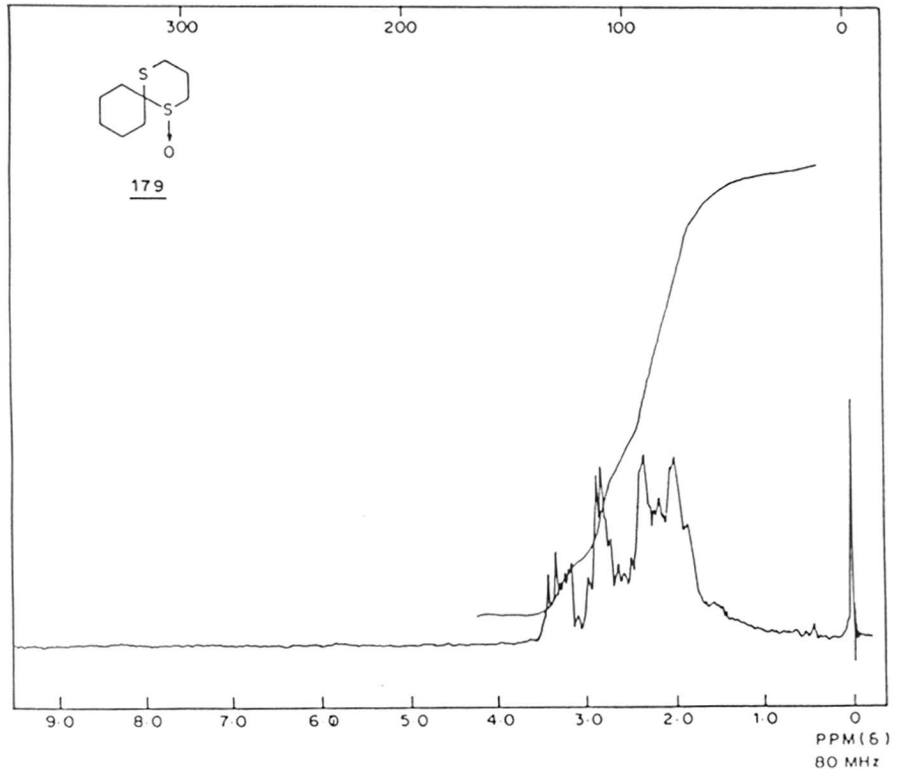

200
100
0
S
S
173
50
40
30
20
10
0
PPM (δ)
90 MHz

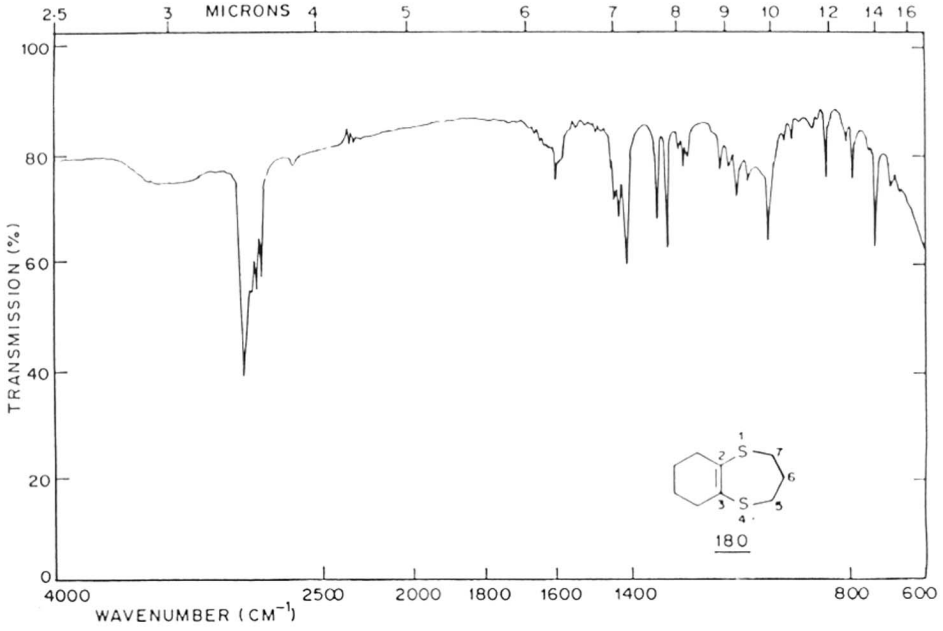
FIG. 2·6.

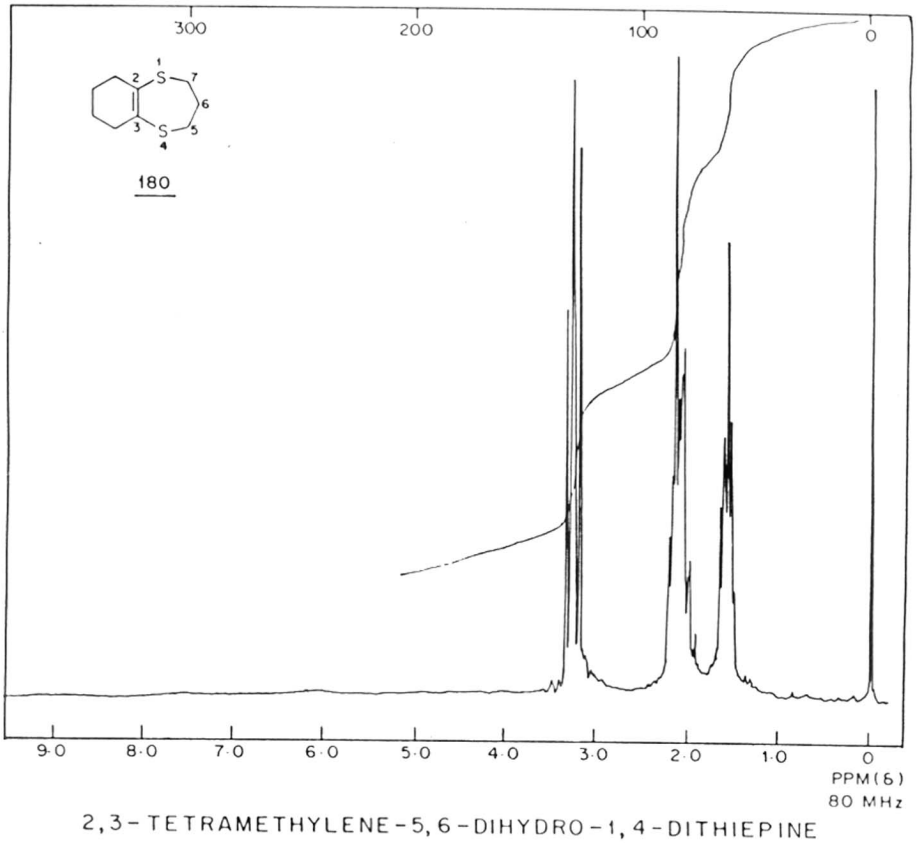




1,5-DITHIASPIRO [5,5] UNDECANE-1-OXIDE

FIG. 2·7.





2,3-TETRAMETHYLENE-5,6-DIHYDRO-1,4-DITHIEPINE

FIG. 2·8.

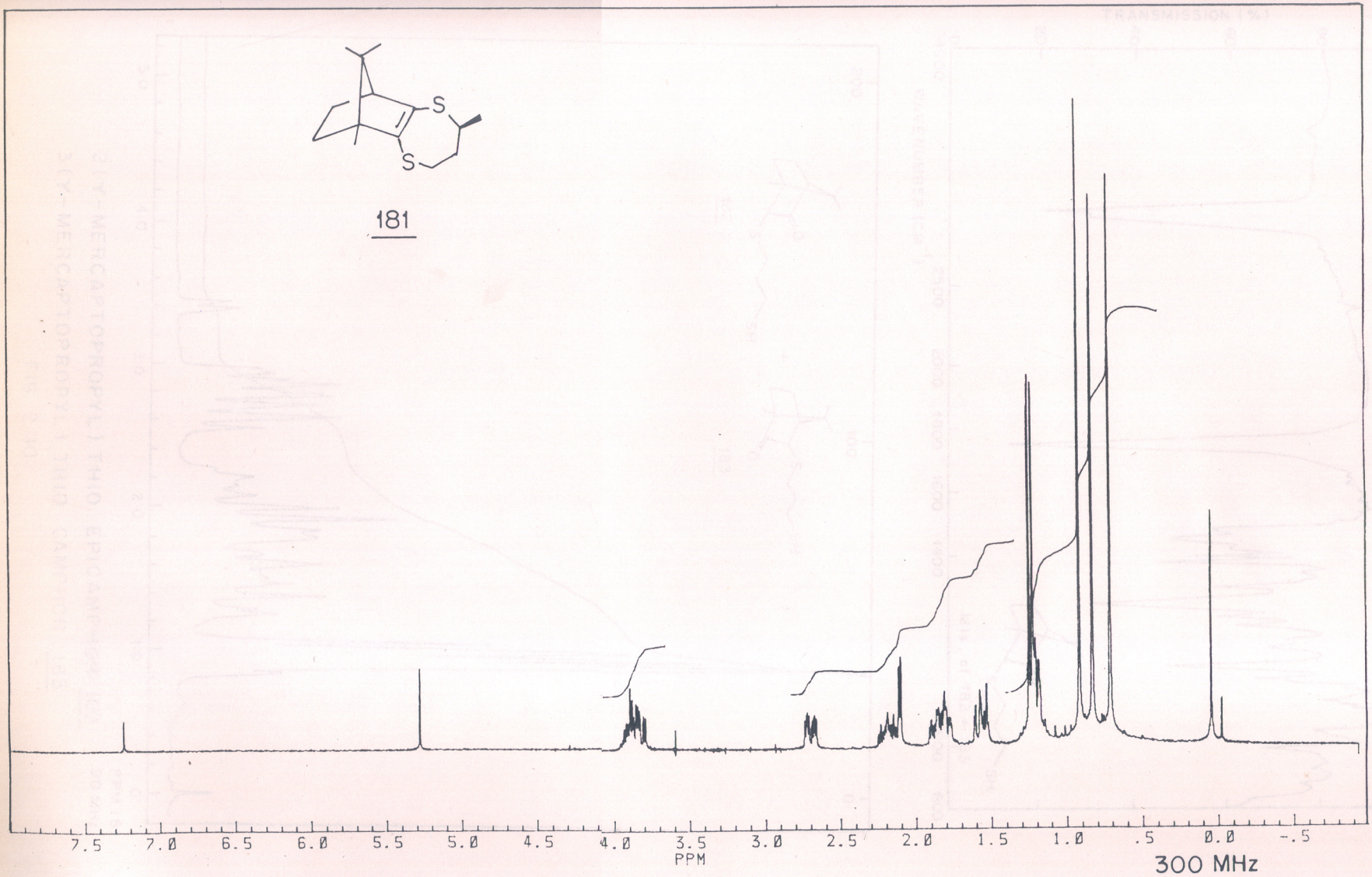
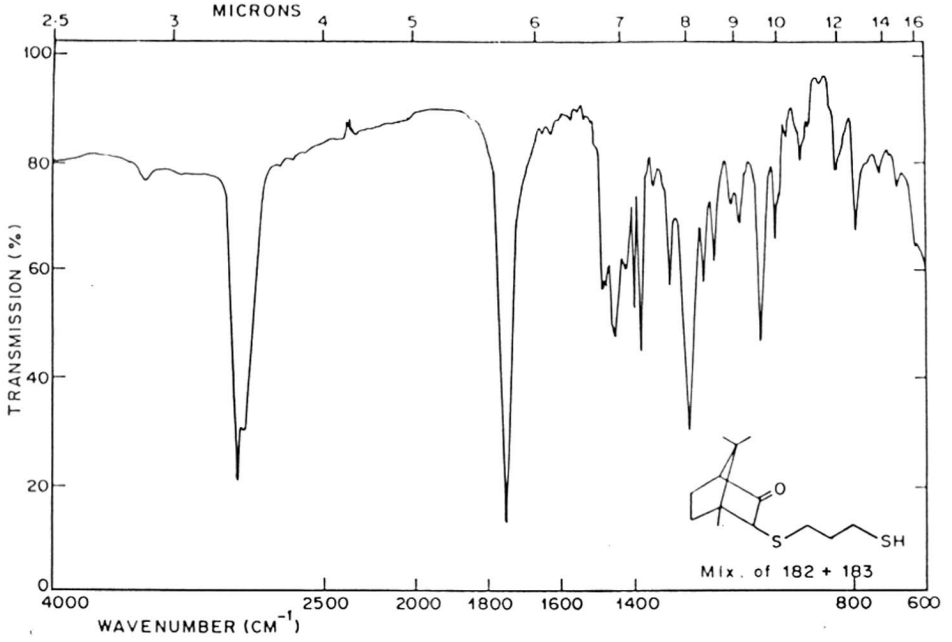
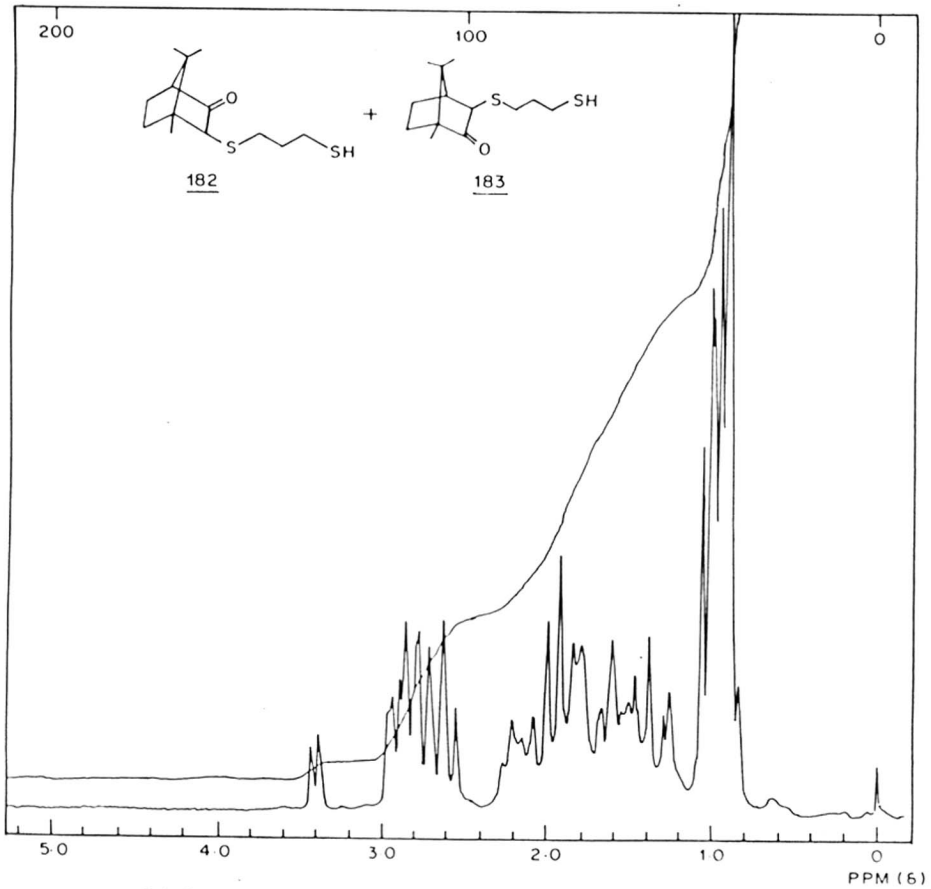


FIG. 2·9.

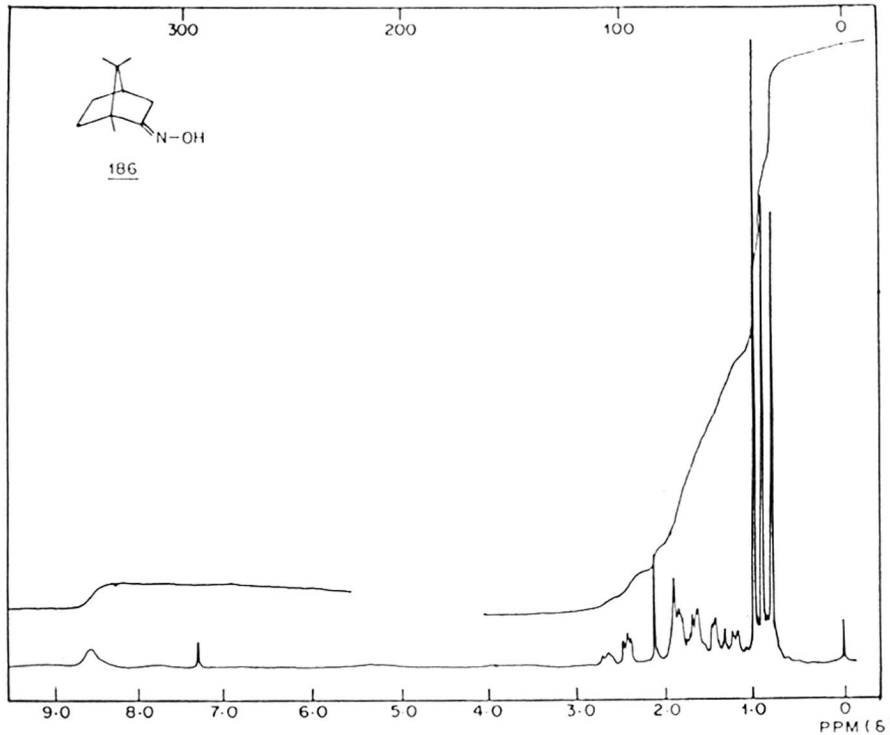




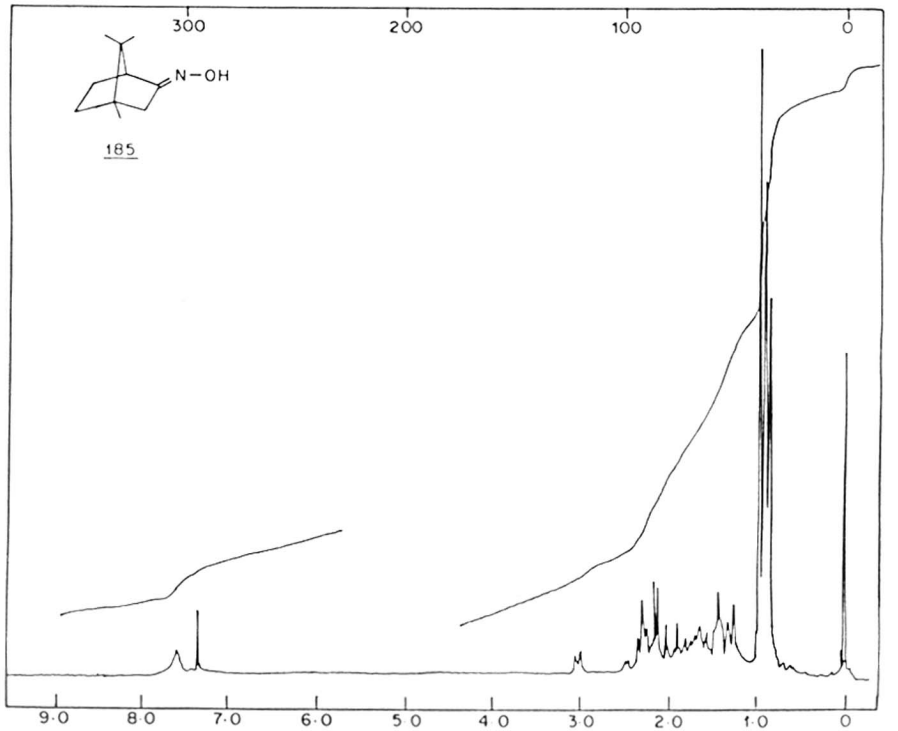
2(γ-MERCAPTOPROPYL) THIO EPICAMPHOR 182

3(γ-MERCAPTOPROPYL) THIO CAMPHOR 183

FIG 2·10.

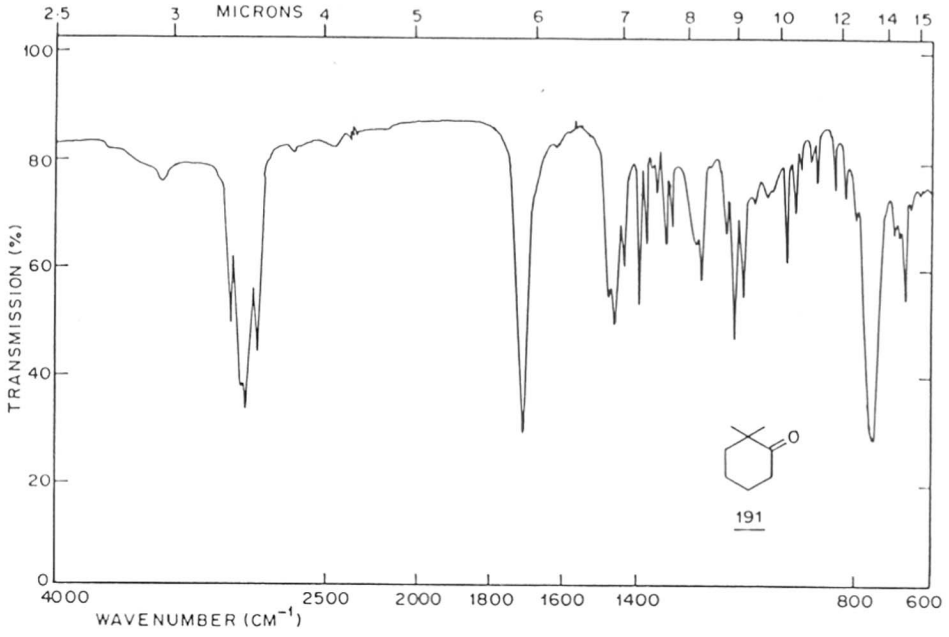


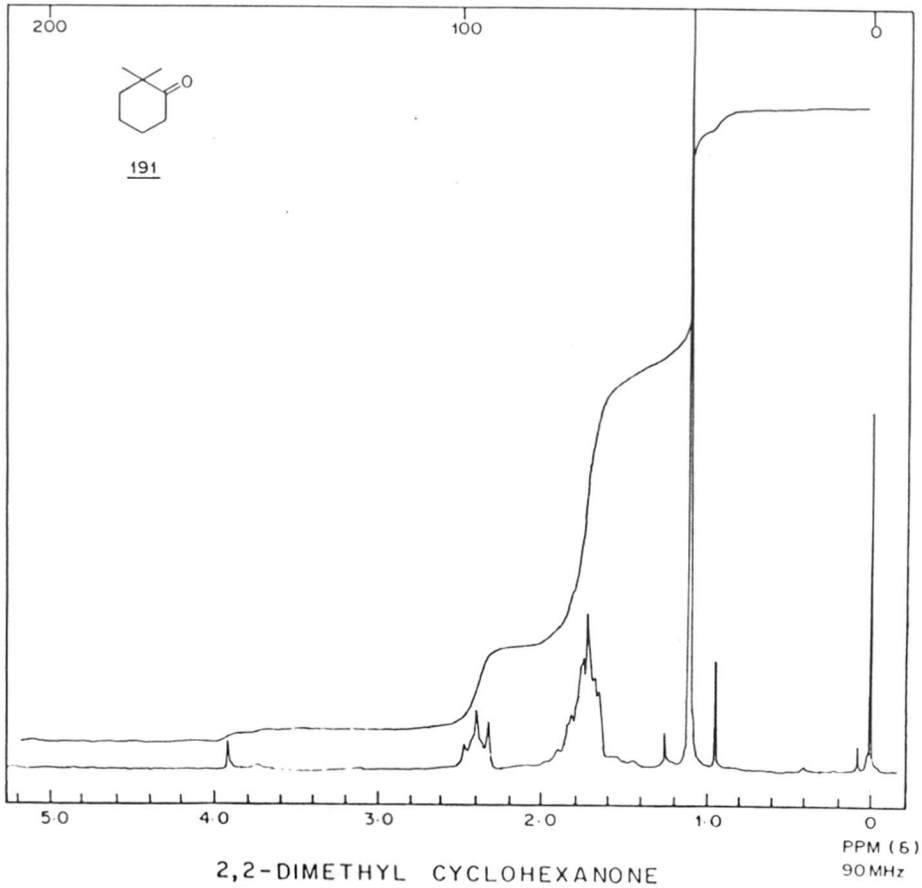
CAMPHOROXIME



EPICAMPHOR OXIME

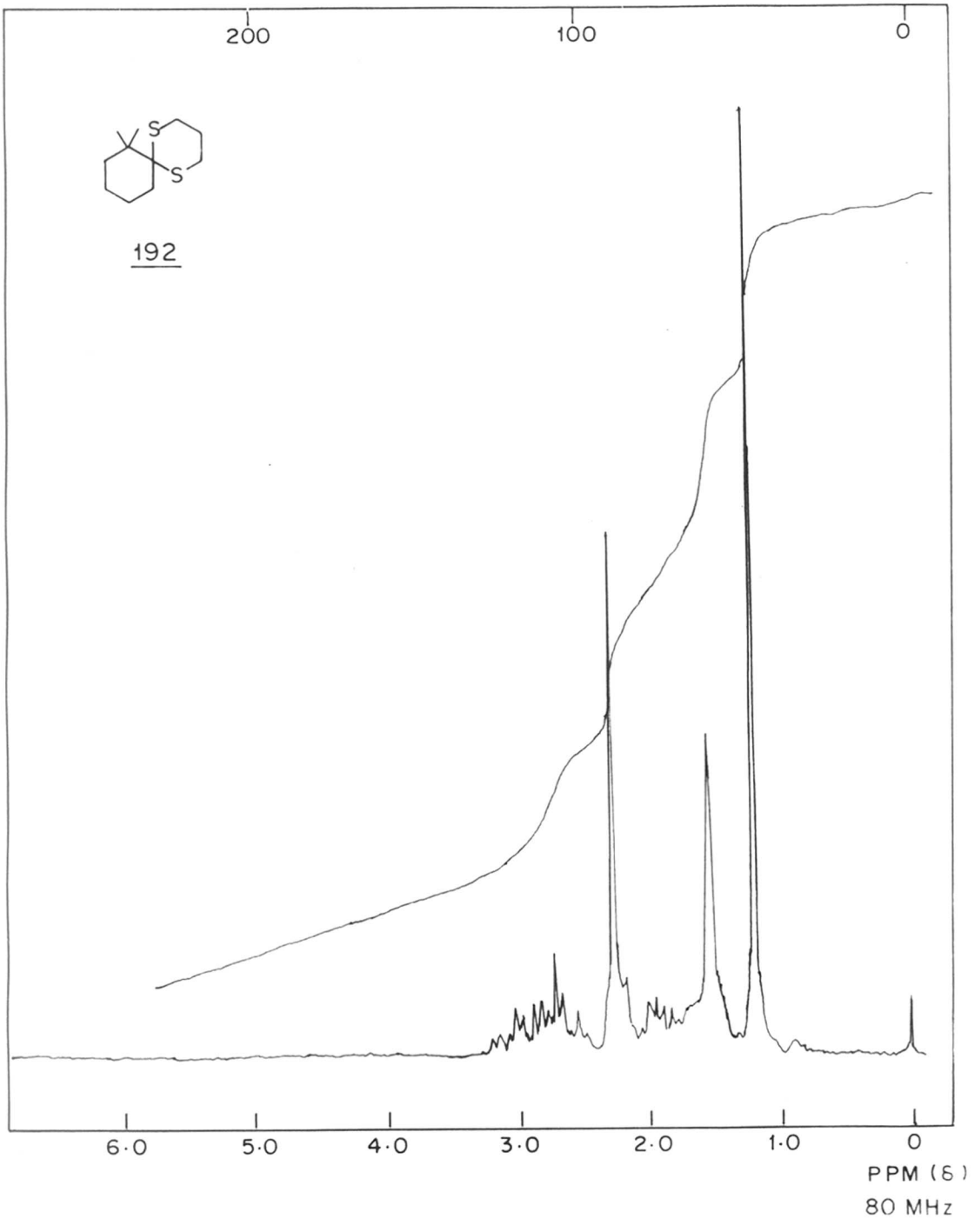
FIG. 2·11.





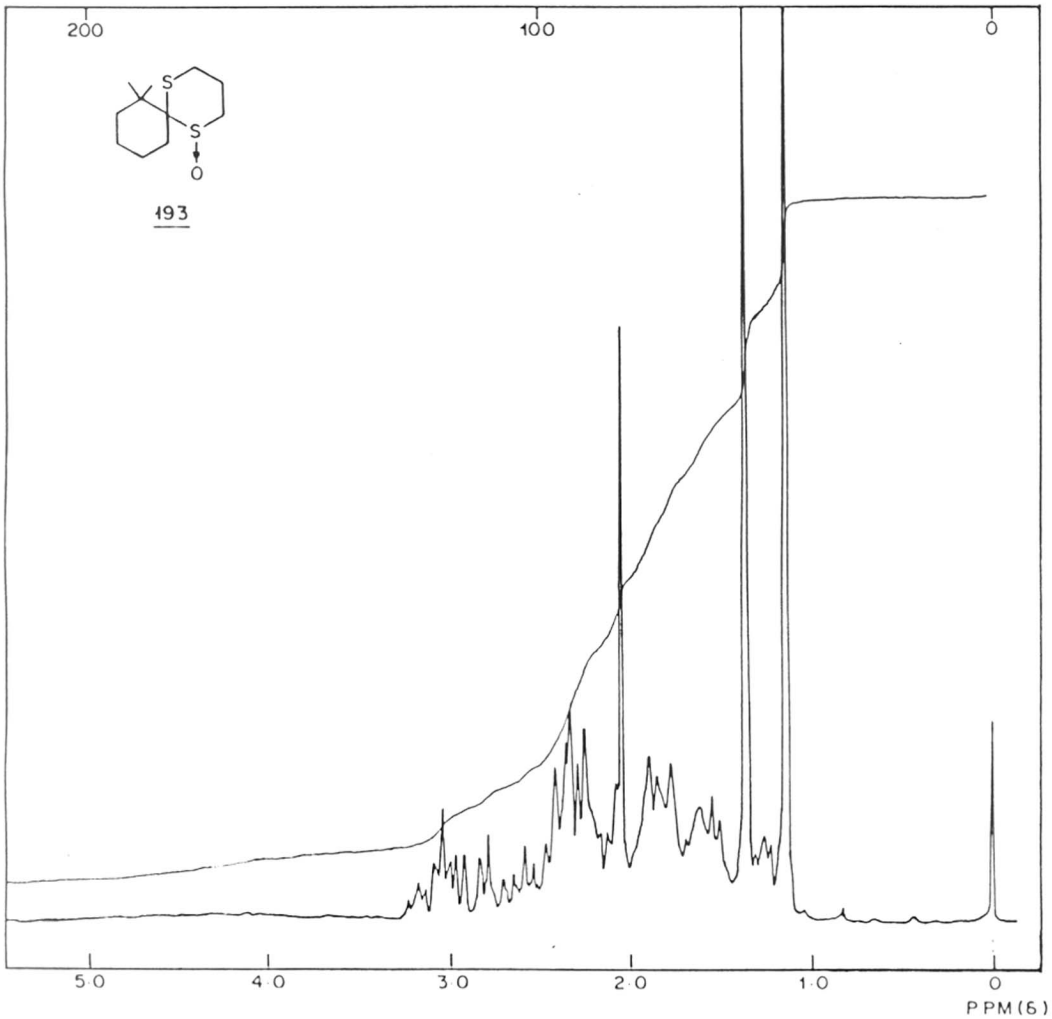
2,2-DIMETHYL CYCLOHEXANONE

FIG. 2·12.



1,5-DITHIASPIRO [5,5] UNDECANE-7, 7-DIMETHYL

FIG. 2·13.



1,5-DITHIASPIRO-[5,5]UNDECANE-7,7-DIMETHYL-1-OXIDE

FIG. 2·14.

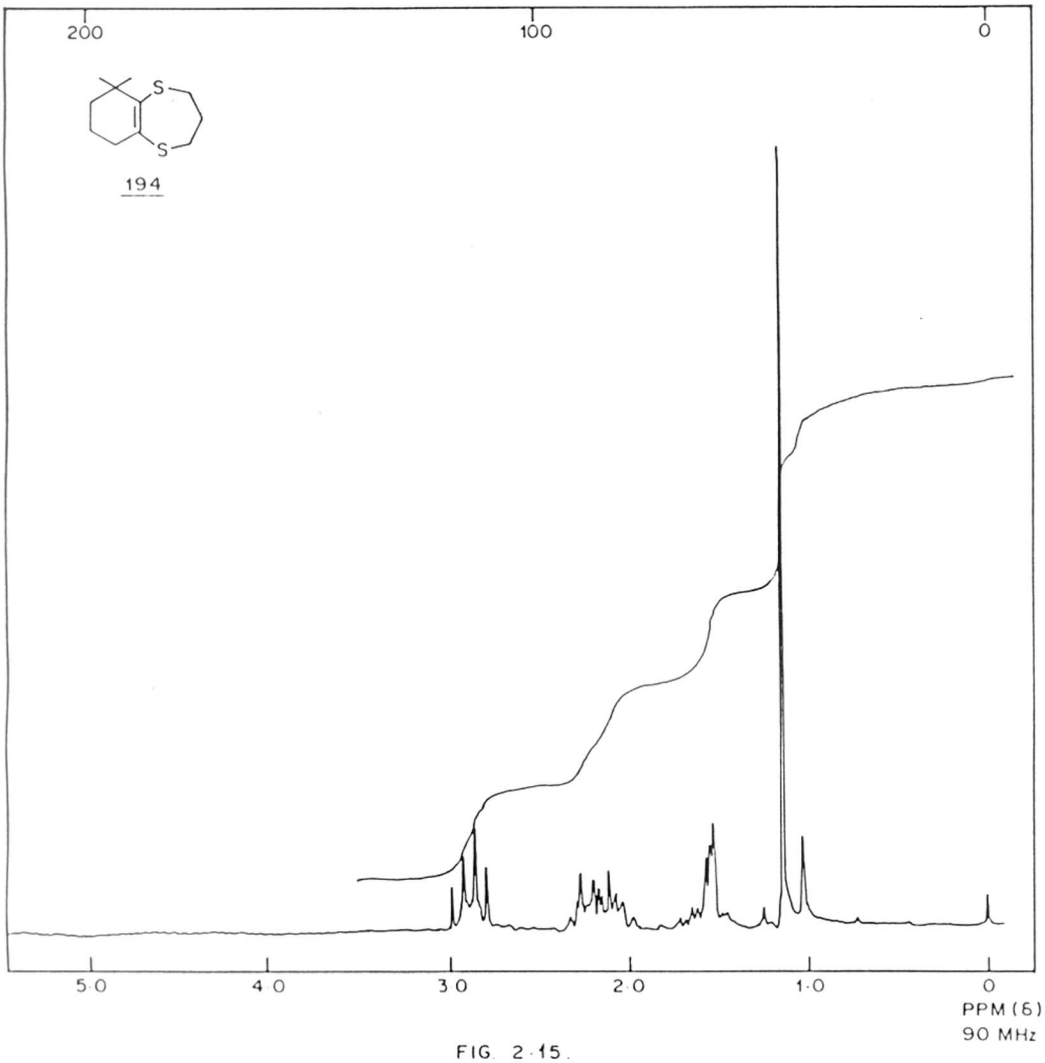
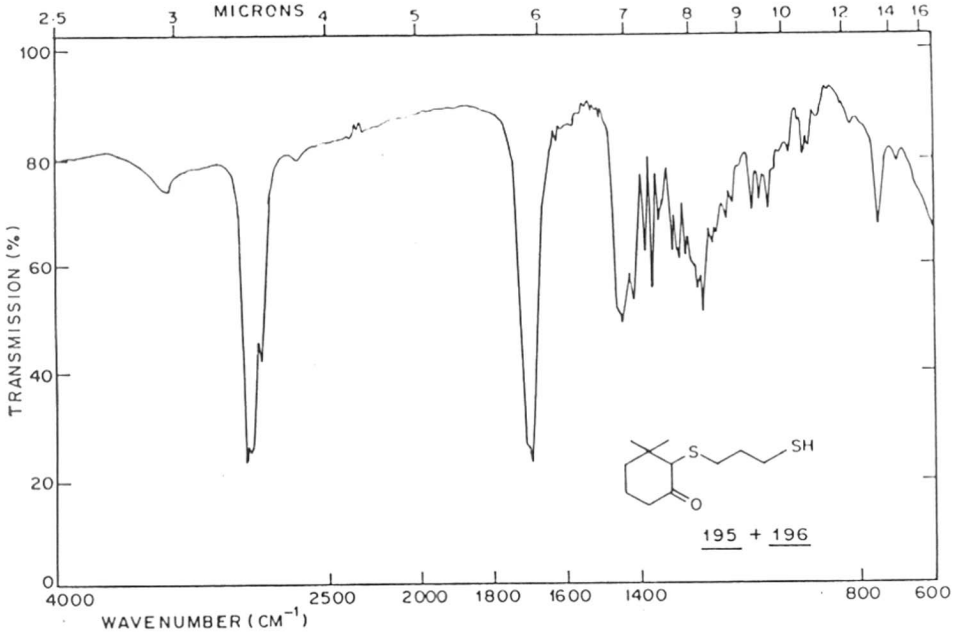
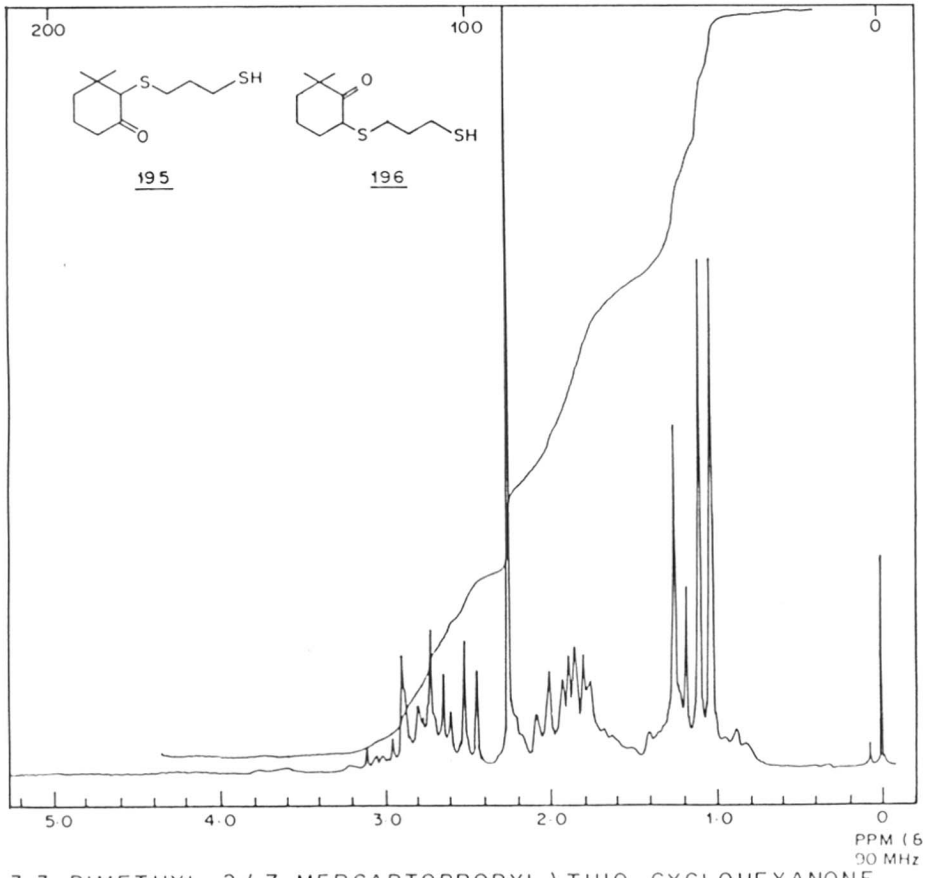


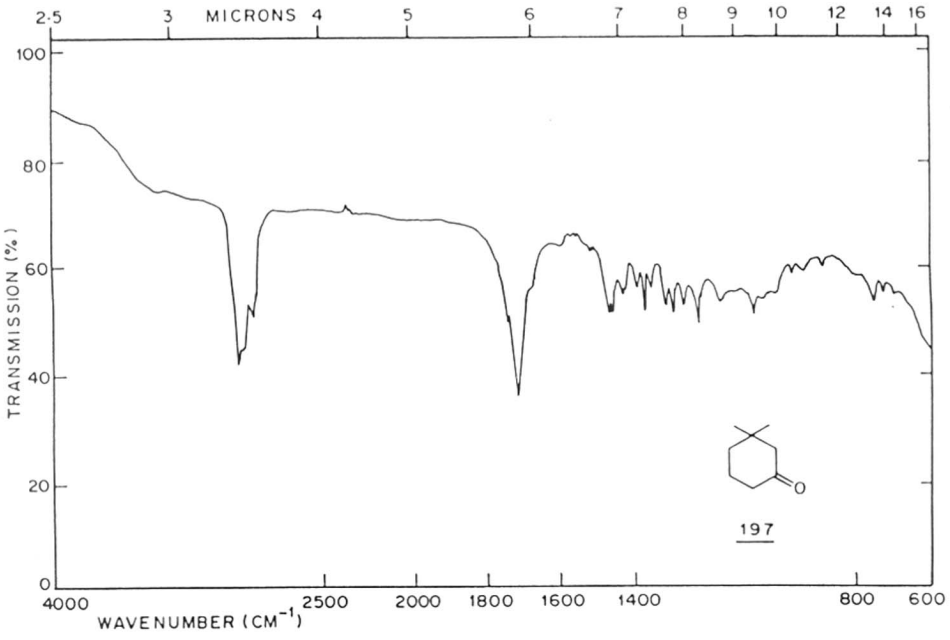
FIG. 2·15.

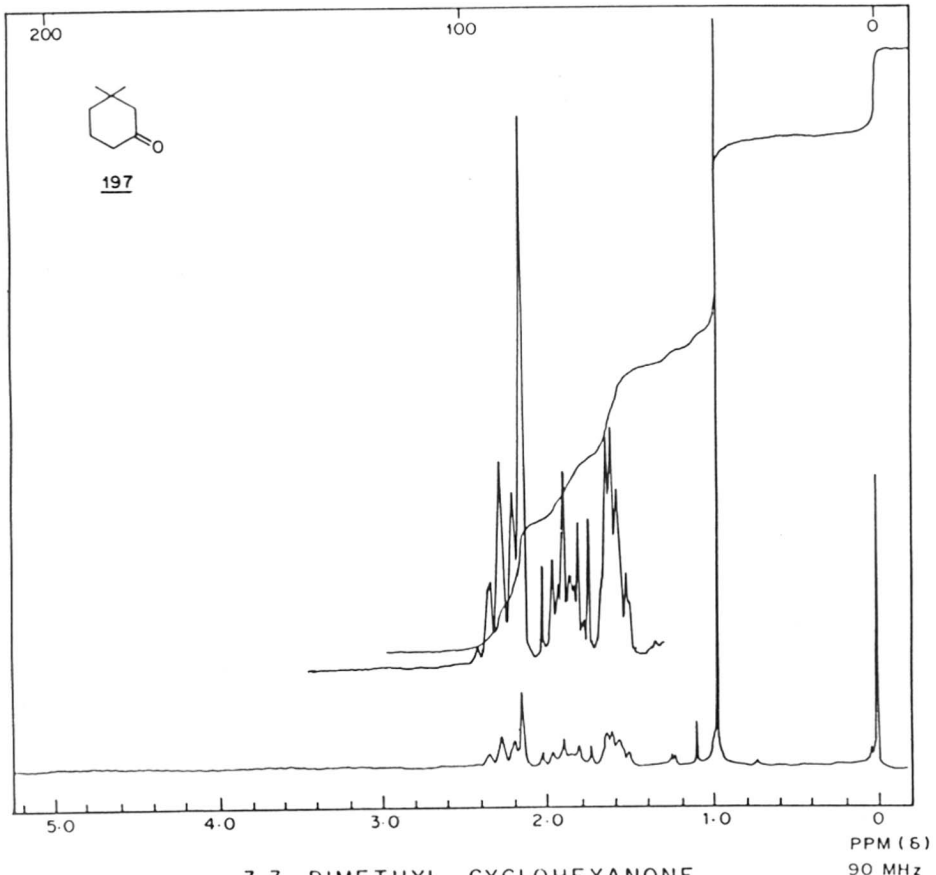




3,3-DIMETHYL-2 (7-MERCAPTOPROPYL) THIO CYCLOHEXANONE

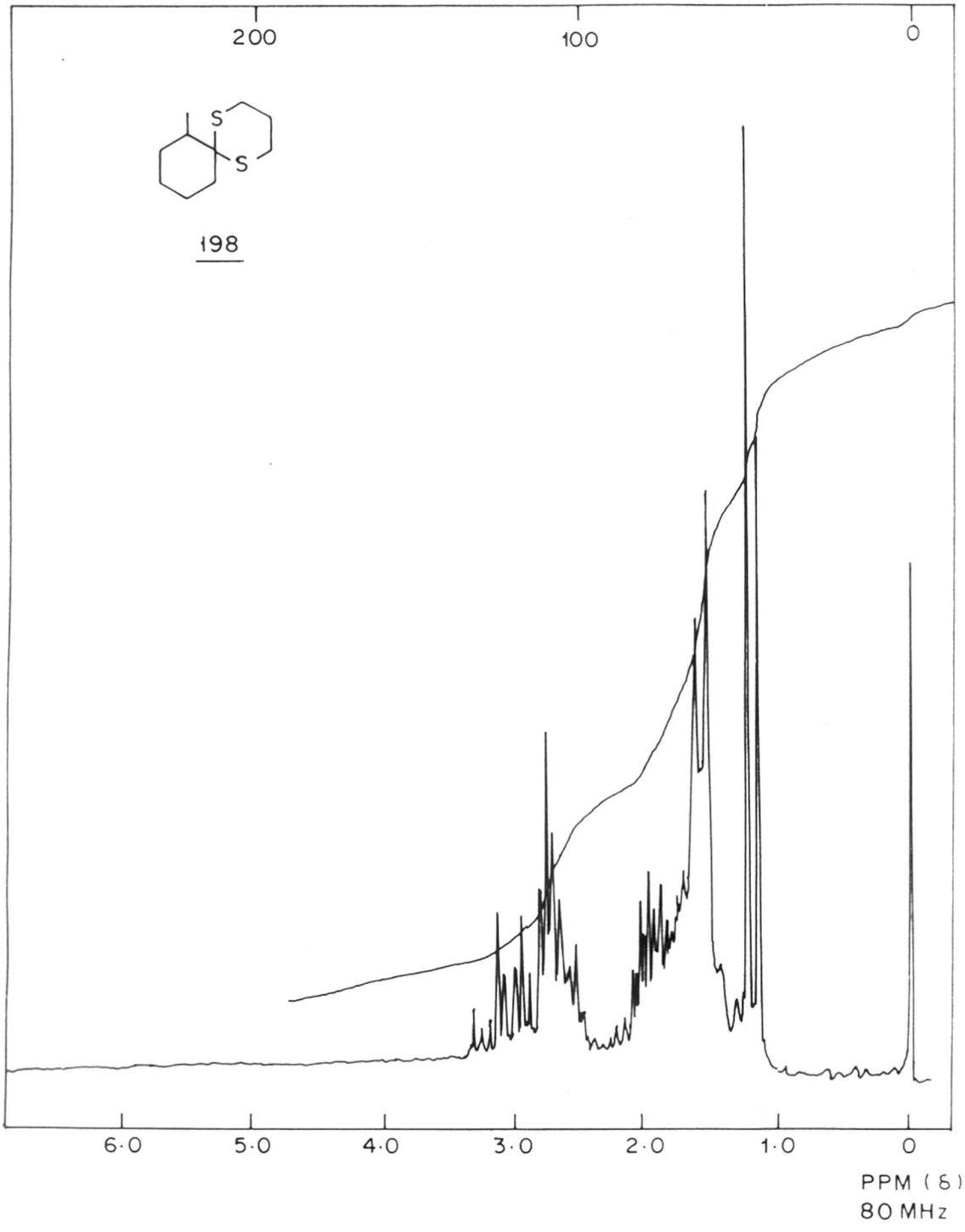
FIG. 2·16.





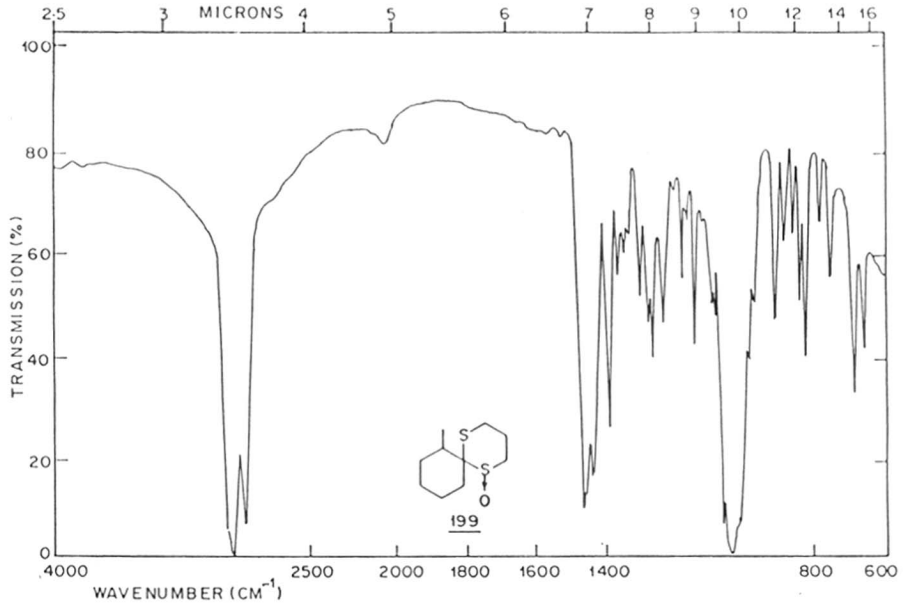
3,3-DIMETHYL CYCLOHEXANONE

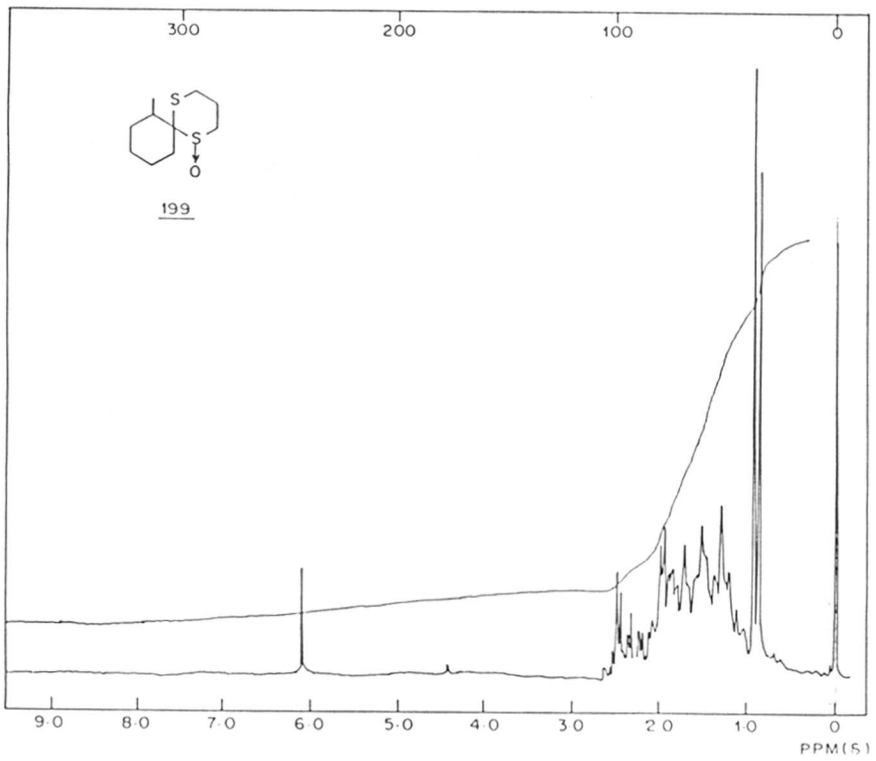
FIG. 2-17.



1,5-DITHIASPIRO-[5,5]-UNDECANE-7-METHYL

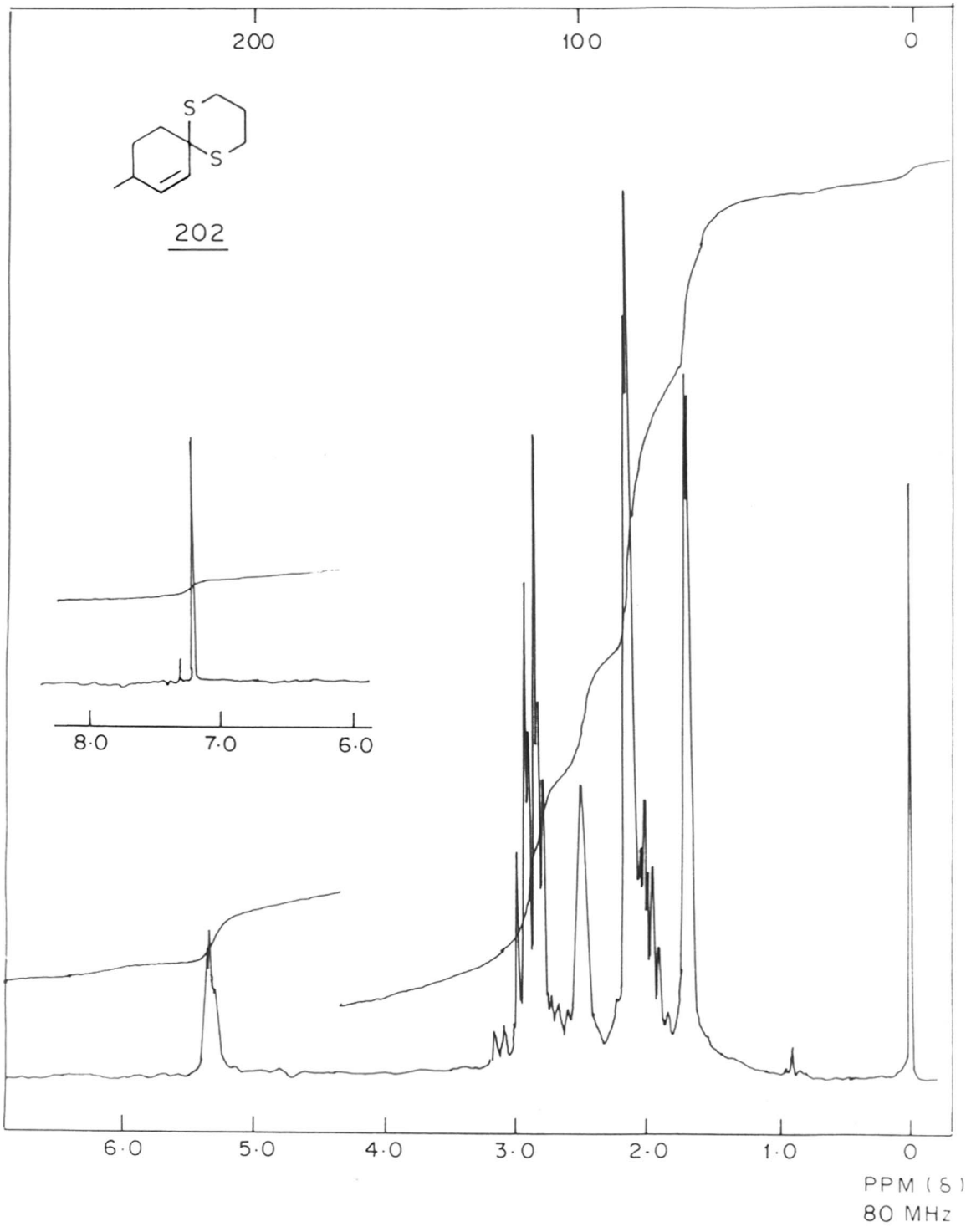
FIG. 2·18.





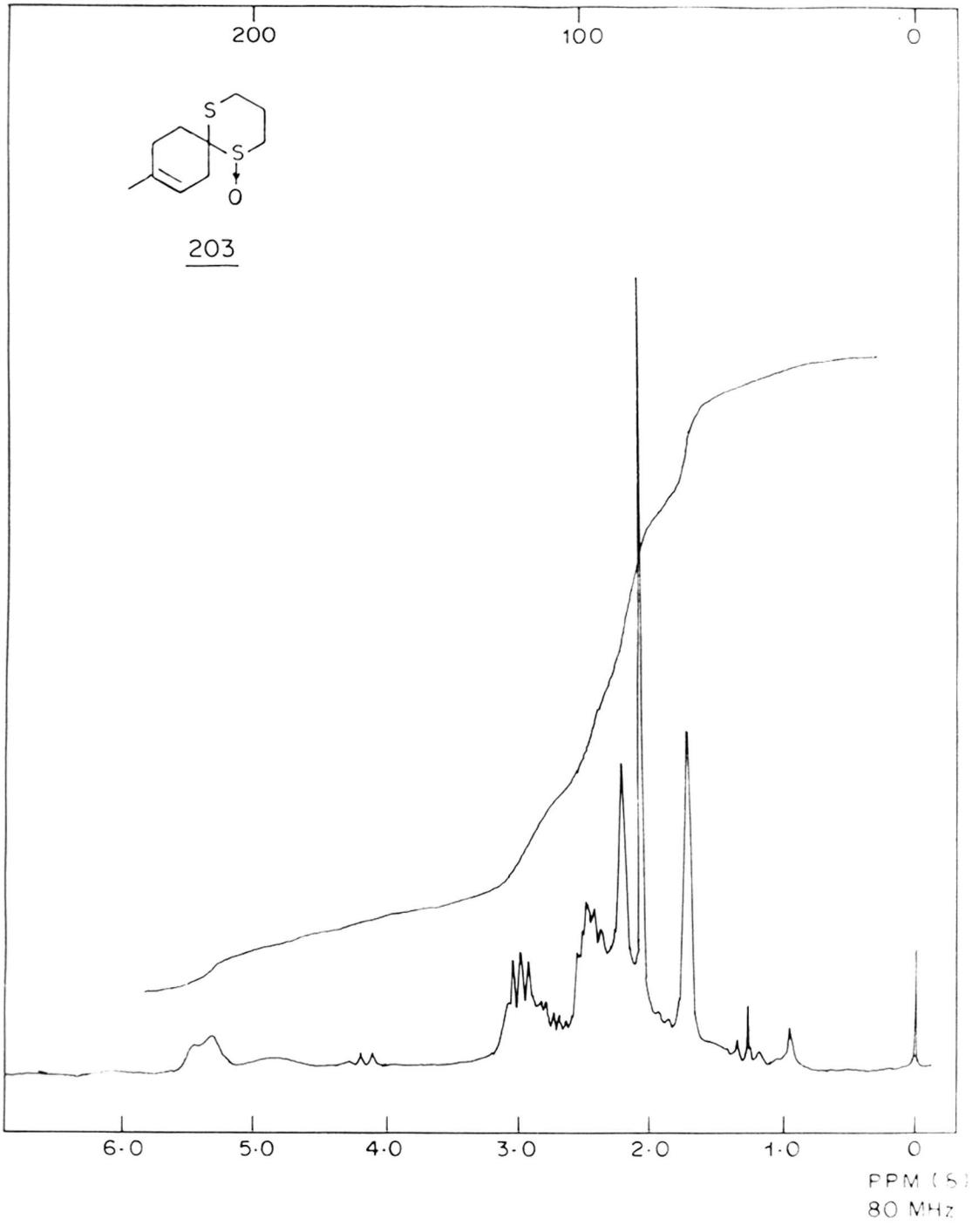
1,5-DITHIASPIRO [5,5] UNDECANE-7-METHYL-1-OXIDE

FIG. 2·19.



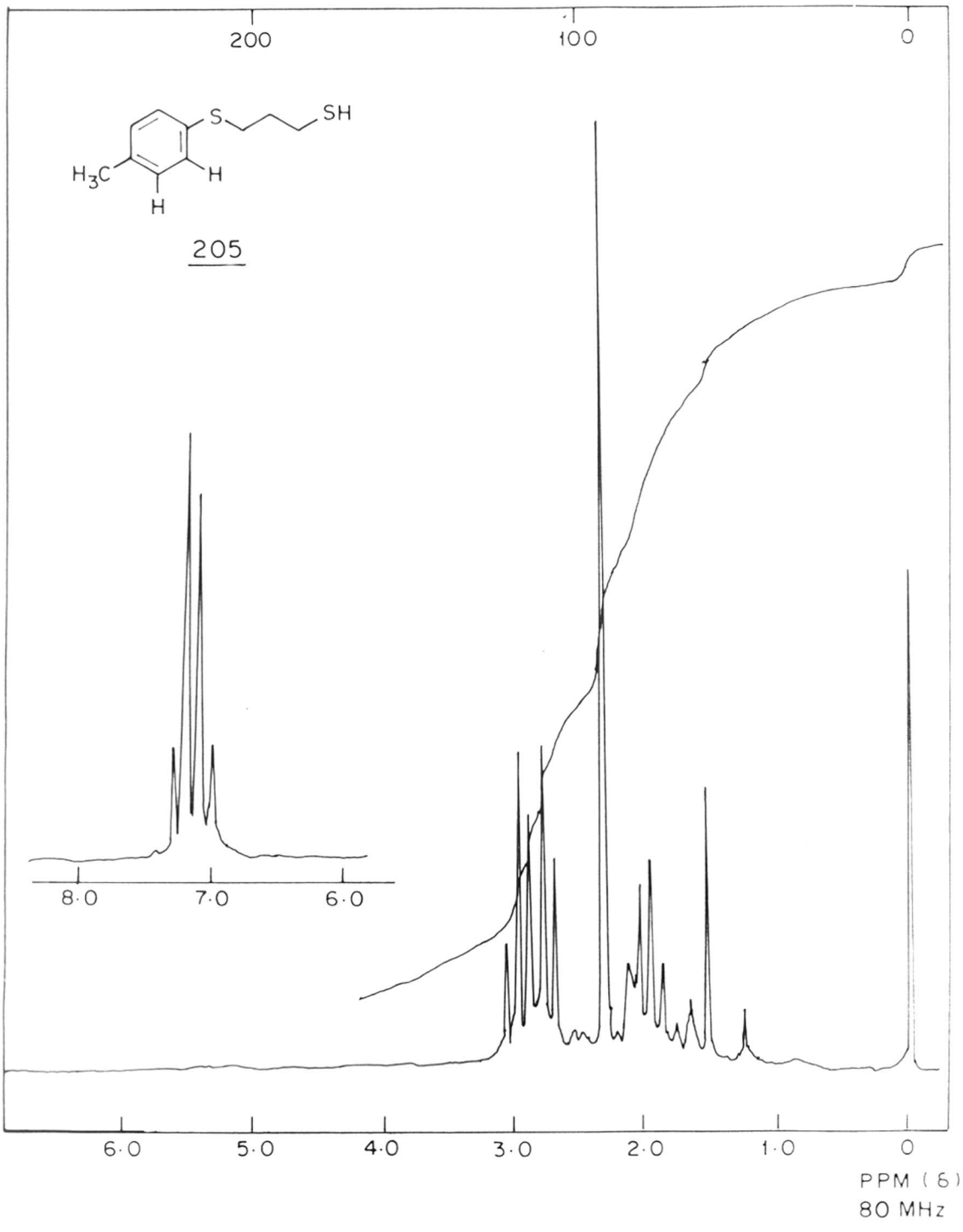
1,5-DITHIASPIRO-[5,5]-UNDECANE-8-ENE-9-METHYL

FIG. 2-20.



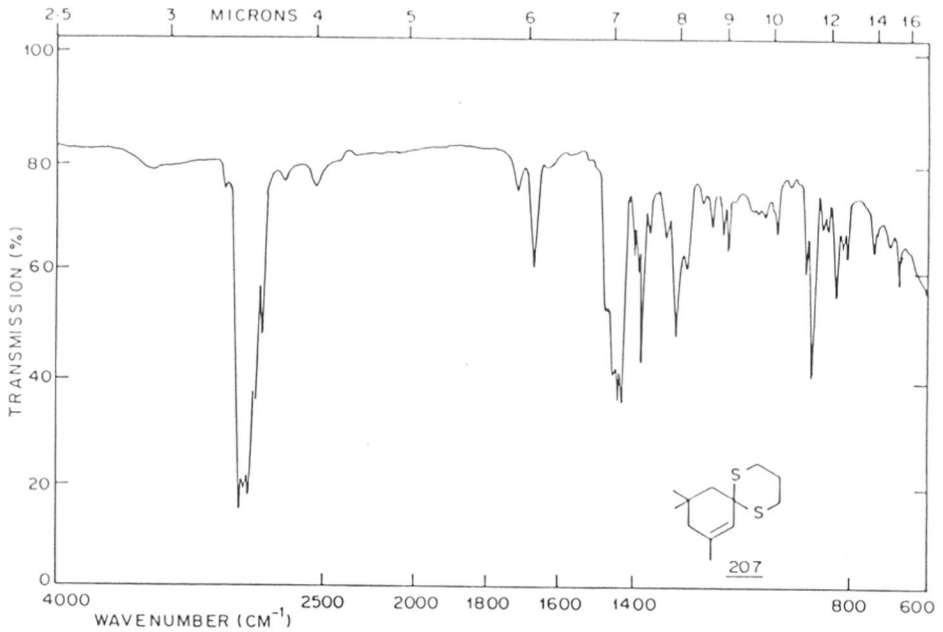
1,5-DITHIASPIRO-[5,5]-UNDECANE-8-ENE-9-METHYL-1-OXIDE

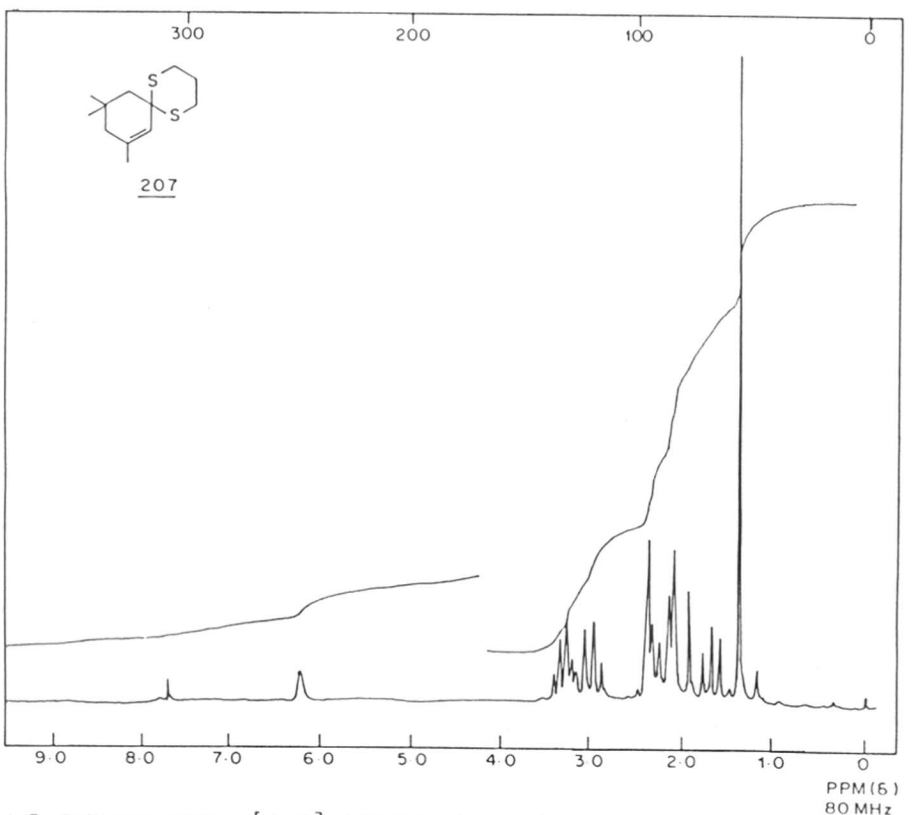
FIG. 2·21.



3-MERCAPTOPROPYL-p-METHYLPHENYLSULFIDE

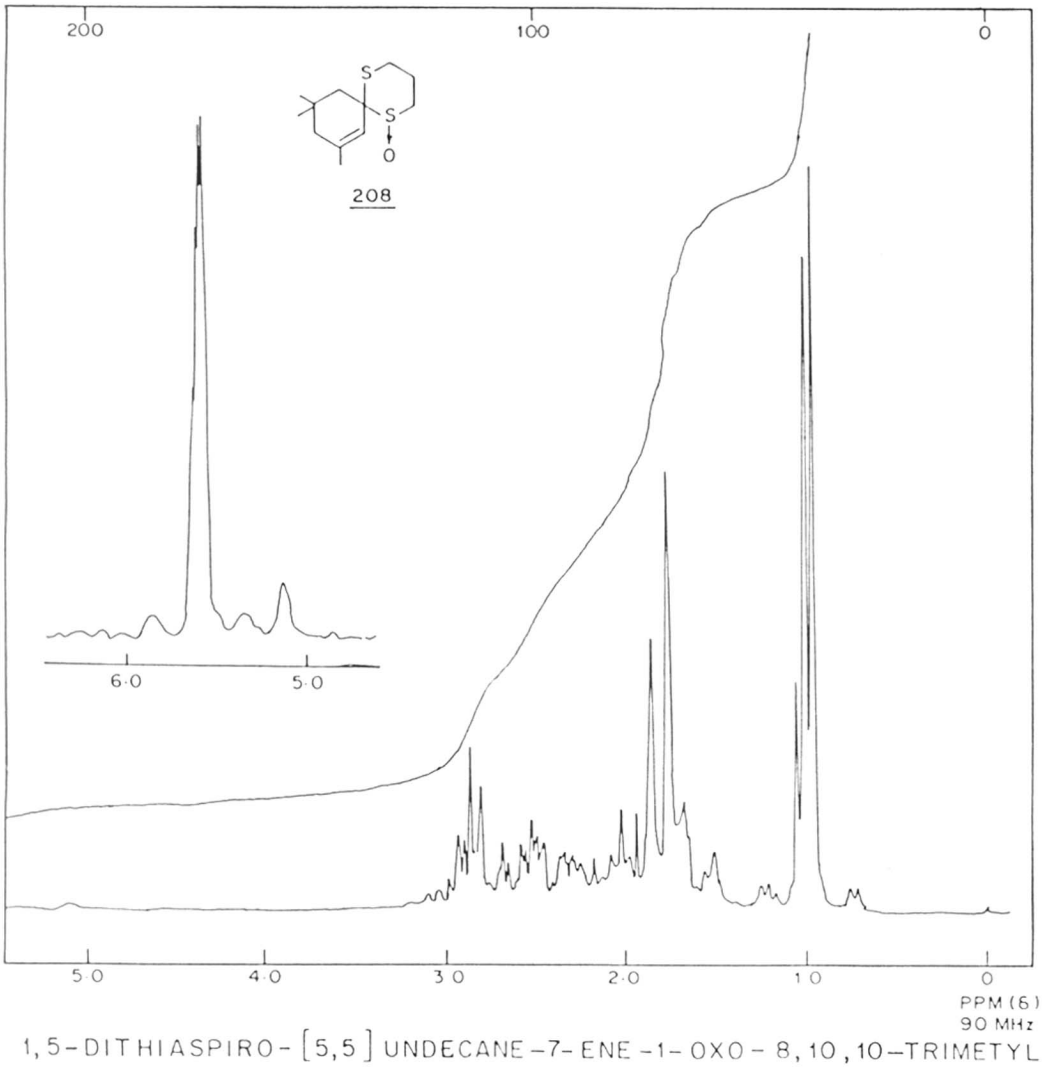
FIG. 2·22





1,5-DITHIASPIRO-[5,5]-UNDECANE-7-ENE-8,10,10-TRIMETHYL

FIG. 2·23.



1,5-DITHIASPIRO-[5,5]UNDECANE-7-ENE-1-OXO-8,10,10-TRIMETYL

FIG. 2·24.

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A pseudopericyclic reaction is a concerted transformation whose primary changes in bonding compass a cyclic array of atoms at one (or more) of which nonbonding and bonding atomic orbitals interchange roles. In a crucial sense, the role interchange means a "disconnection" in the cyclic array of overlapping orbitals because the atomic orbitals switching functions are mutually orthogonal. Hence pseudopericyclic reactions cannot be orbital symmetry forbidden.

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CHAPTER 3

CALCIMYCIN: SPIROKETAL CONSTRUCTION - MODEL STUDIES

"It is no excuse, saying reactants are not in a mood to react."

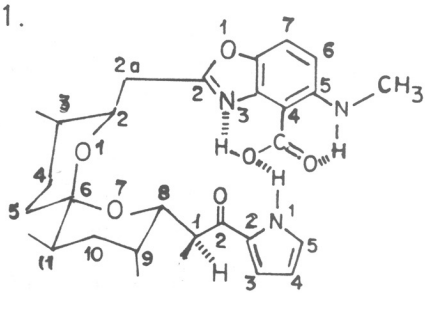
CHAPTER 3

CALCIMYCIN: SPIROKETAL CONSTRUCTION - MODEL STUDIES

3.0 Introduction:

Calcimycin (A23187) 1 belongs to the class of polyether antibiotics.[1] This rapidly growing class of compounds, produced mainly by Streptomyces organisms characteristically form lipophilic metal ion complexes which are effective in ion transport across lipid barriers.[2] To date, the ionophore antibiotic A 23187 (Calcimycin),[3] isolated in 1972 from Streptomyces charteusis[4] NRRL 3883 appears to be unique in its divalent cation transport selectivity.[5] Extensive literature is now rapidly accumulating on the application of the ionophore as an effective probe for the involvement of metal ions in the control of numerous physiological processes.[6]

FIG. 1.



1

3.1 Nomenclature and Classification:

Calcimycin/A23187 whose chemical notation[7] is 4-benzoxazole carboxylic acid, 5-(methylamino)-2-[[3,9,11-trimethyl-8-[1-methyl-2-oxo-2-(1H-pyrrol-2-yl)ethyl]-1,7-dioxaspiro[5,5]-undec-2-yl]methyl]-[6S, 2S, 3R, 8R, 9R, 11R] is included in the class of polyether antibiotics, though it lacks the multiplicity of cyclic ethers, because of its very similar ionophoric properties to the nonnitrogenous members of the class. A23187 belongs to the fifth class of carboxylic acid ionophores which consists of the pyrrole ethers.

3.2 Structure:

The crystal structures have been determined for the free acid[3] of A23187 (m.p. 181-182°C) and for two solvated calcium salts, a dihydrate[8] and a diethanolate.[9] A stereoscopic view of the free acid as in Fig.1, shows the familiar circular shape with the polar atoms mainly directed toward the interior and the exterior consisting of hydrocarbon groups. The circular formation is stabilized by three apparent hydrogen bonds: N(1)-H---O(4C); N(5A)-H---O(4B) and O(4C)-H---N(3). The latter hydrogen bond would require an antiplanar configuration for the carboxyl group which would be quite unusual.[10] However, the dimensions O(4C)--N(3) of 2.65(1) Å and C(4A)-O---N(3) of 92.9(5)° are consistent with such a hydrogen bond.

In many cases (of polyether antibiotics) there is very little change in conformation between the free acid and salt forms of the antibiotics. Antibiotic A23187 is an outstanding exception to this generalization.

The structures of the two solvated calcium salts; dihydrate and diethanolate, have many similarities but several interesting differences.[11] In both complexes the calcium ion is co-ordinated to A-23187 anions and the structures of the two complexes possess pseudo twofold rotational symmetry. In each case the Ca^{2+} ion is co-ordinated to O(4C), O(2A) and N(3), (Fig. 1), in both anions.

When a polyether antibiotic assumes the characteristic cyclic conformation, the molecule concentrates all the oxygen functions at the center of the structure where they are available for complexation of a suitable cation, while the many branched alkyl groups are simultaneously being spread over the outer surface, rendering the complex lipid soluble. This elegant molecular design gives these antibiotics the ability to conduct cations across membranes down the concentration gradient by a mechanism known as passive diffusion.[12]

3.3 Biological Action:

The divalent pyrrole ether A23187 shows a well-documented ability to transport Ca^{2+} in biological system and although

it forms complexes with alkali metal cations,[5b,6] it does not appear to transport K^+ directly[13] or to carry Na^+, at least in the presence of physiological concentrations of divalent cations,[14] across erythrocyte membranes.

One of the first calcium dependent processes to be studied with A23187 was contraction of smooth, skeletal or cardiac muscle.[15] By investigating the effect of A23187 on various in vitro preparations, it became apparent that this ionophore did indeed enhance cardiac contractility in a calcium dependent manner,[16] since contraction of cardiac muscle is initiated during action potentials by an increased flux of Ca^{2+} into the myocardial cell.

As part of a study on calcimycin in regulation of arachidonic acid oxygenation, it was shown that the ionophore stimulated the release of prostaglandins from renal medullary minces.[17] A23187 increased the release of PGE_2, $PGF_{2\alpha}$ and PGD_2 and their effect was calcium dependent.

In one of the few experiments studied on ion fluxes in renal tubules, in which A23187 was given intravenously to whole animals, an infusion rate of 0.38 μmol/kg body weight per hour to rats produced a significant fall in serum Ca^{2+} in normal and parathyroidectomized rats without changes in blood pressure of glomerular filtration rate.[18] In normal rats, infusion of A23187 decreased the fractional excretion of phosphate, but this was not seen in parathyroidectomized

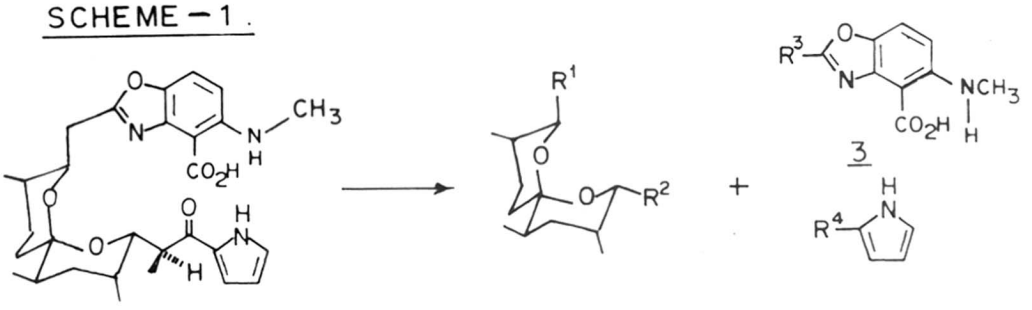
animals and therefore concluded that increased cytoplasmic calcium in the tubule cells acted to inhibit parathormones effects on renal adenylate cyclase and thus prevented hormone-induced phosphaturia.

3.4 Synthesis of A23187 (Calcimycin): A Review:

The ionophore antibiotics encompass a class of biologically important molecules whose members are structurally quite diverse and often stereochemically complex.[19] The important biological activity and unusual structural features of this group including a 1,7-dioxaspiro[5,5] undecane ring system on which seven stereogenic centers are arrayed along with α-keto pyrrole and benzoxazole residues, have drawn much attention from synthetic chemists. The first total synthesis of antibiotic A23187 (Calcimycin) was achieved by Evans[20] et al (1979). Grieco[21] et al (1980) synthesized the key intermediate of the Evans synthesis from a bicyclo precursor. Nakahara[22] et al. (1984, 1986) have synthesized A23187 from D-glucose. Boeckman[23] et al. (1987) devised a synthesis which involves cyclic vinyl ether anion in the key reaction. Kishi[24] et al. (1987) synthesis involves the stereospecific cyclization of the β-hydroxy ketone into the spiroketal under basic conditions as the key step. The latest synthesis by F.E. Ziegler[25] utilises 3-Me-γ-butyrolactone as chiral template for the synthesis.

A23187 can be fragmented into three units as shown below (Scheme-1): the C-9 spiroketal (2) system and the two heterocyclic systems.

SCHEME – 1.



1 2 3 4

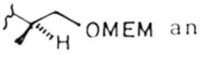
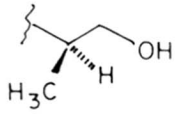
The C-9 spiroketal fragment contains the seven asymmetric centers of the molecule. Depending on the chemistry employed by different authors for the generation of this spiroketal fragment; R^1 and R^2 (Scheme-1) differ. In Evan's and Kishi's approaches, spiroketal is a C-9 unit where R^1 and R^2 are 'H' and the additional carbon atoms 2, 2a and 1, 2 (calcimycin numbering Fig.1) come along with the heterocycle components viz. benzoxazole and pyrrole derivatives, respectively. The C-1 stereocenter is created when the pyrrole derivative is attached by an aldol reaction. In Grieco's method R^1 is H and R^2 =  and the spiroketal precursor is C-11. The intermediate in the work of Nakahara, Boeckman and Ziegler, the spiroketal fragment is C-13 where R^1 = $-CH_2CH_2OTBDS$ and R^2=  (see Table-I)

TABLE-I

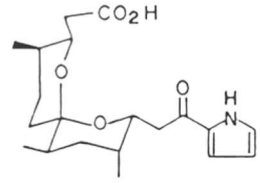
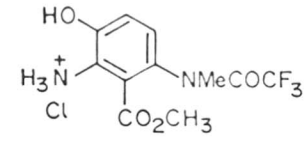
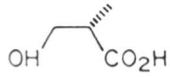
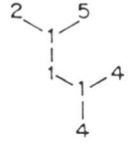
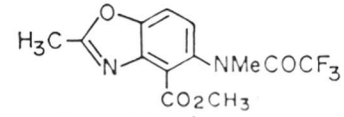
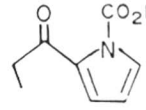
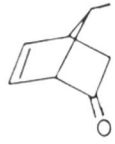
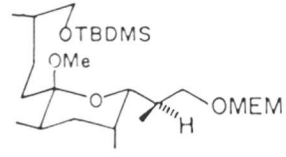
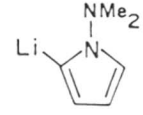
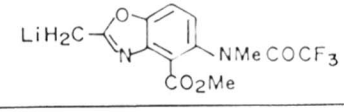
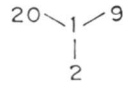
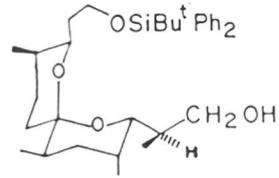
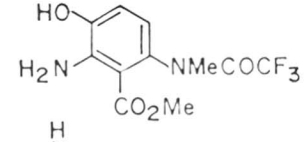
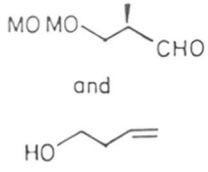
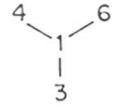
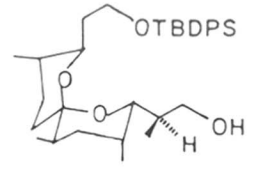
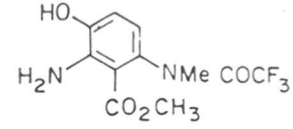
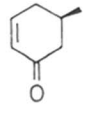
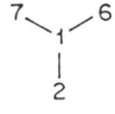
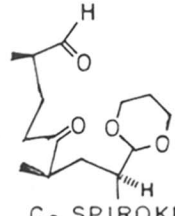
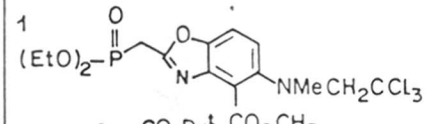
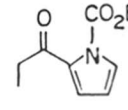
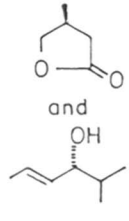
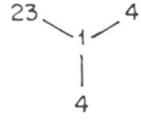
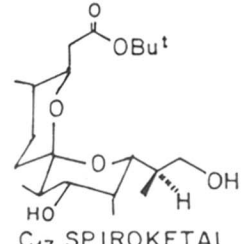
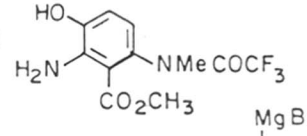
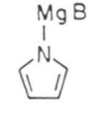
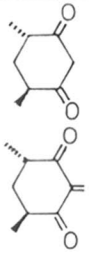
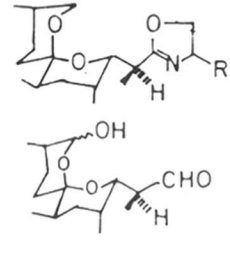
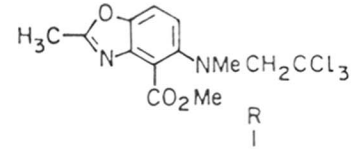
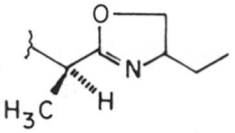
No.	METHOD	FROM	METHOD OF SYNTHESIS & NO. OF STEPS INVOLVED	SPIROKETAL OR PRECURSOR	HETEROCYCLIC COMPONENTS / PRECURSOR, WITH SEQUENCE OF ATTACHMENT
1	PRODHUME (1983)	CALCIMYCIN	SEMISYNTHETIC	 C_{13} SPIROKETAL	2 
2	EVANS (1979)	 COMMON PRECURSOR	CONVERGENT 18 STEPS 	 C_9 SPIROKETAL PRECURSOR	1.  2. 
3	GRIECO (1982)		LINEAR 24 STEPS	 C_{11} SPIROKETAL PRECURSOR	1.  2. 
4	NAKAHARA (1986)	D-GLUCOSE	CONVERGENT 32 STEPS 	 C_{13} SPIROKETAL	2.  1. 

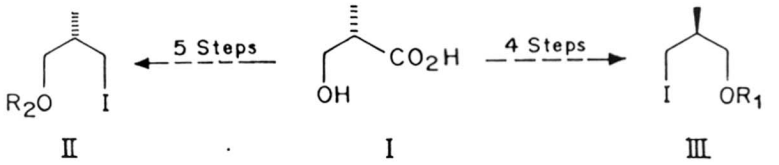
TABLE – I. (contd.)

5	BOECKMAN (1987)		CONVERGENT 14 STEPS 	 C_{13} SPIROKETAL	2  1 
6	KISHI (1987)		CONVERGENT 16 STEPS 	 C_9 SPIROKETAL	1  2 
7	ZIEGLER (1989)		CONVERGENT 32 STEPS 	 C_{13} SPIROKETAL	1  2 
8	NCL (PROPOSED)		LINEAR 7 STEPS LINEAR 10 STEPS	 C_{11} SPIROKETAL	2  1 

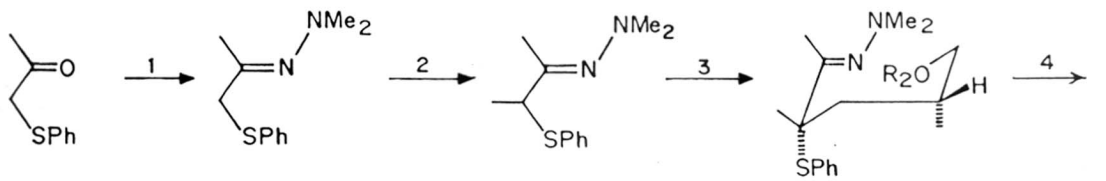
In the envisaged plan for the spiroketal precursor for calcimycin in this chapter, a C-11 unit is proposed where R^1 = H and R^2 =  . The heterocyclic residues are clipped up to the spiroketal fragment by addition reaction or by Wittig reaction as in the Kishi synthesis or it is built up on the molecule as in the Boeckman synthesis. Table-I constitutes a synthetic profile of all the syntheses reported so far. The different methodologies employed for the spiroketal intermediate is shown graphically in Schemes 2-7.

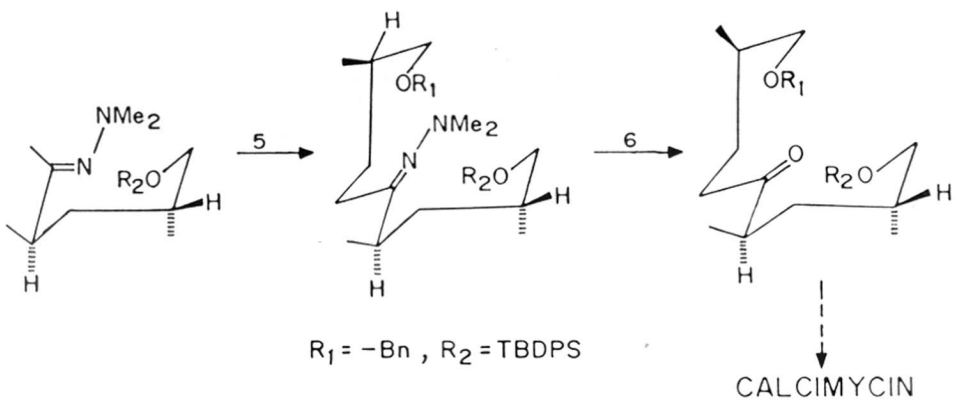
EVANS SYNTESIS (1979)

SCHEME – 2.



II I III



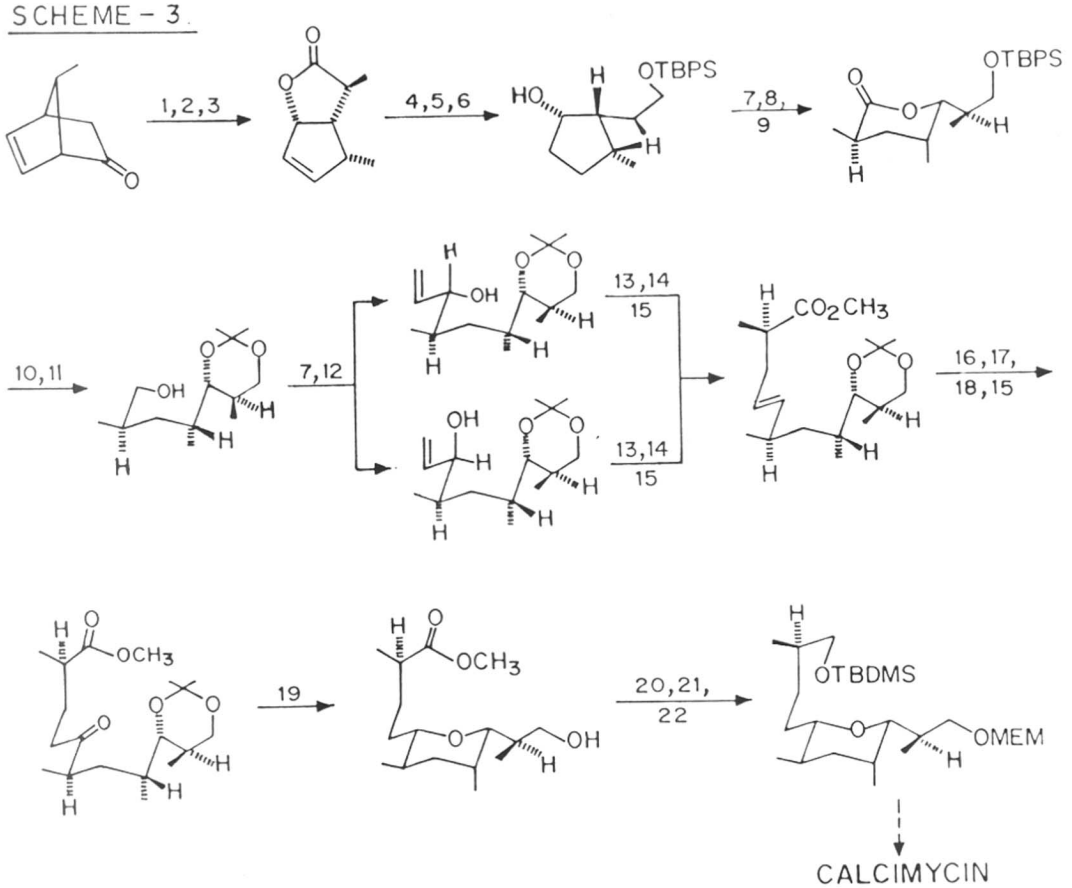


1) Me_2N-NH_2 / 50°C ; 2) KH, MeI / THF ; 3) KH, $KOBu^t$ (0·03 eq) / THF / Δ II ;

4) Li / NH_3 ; 5) LDA / THF / 0° / III ; 6) $CuCl_2$ / THF / H_2O

GRIECO SYNTESIS (1982)

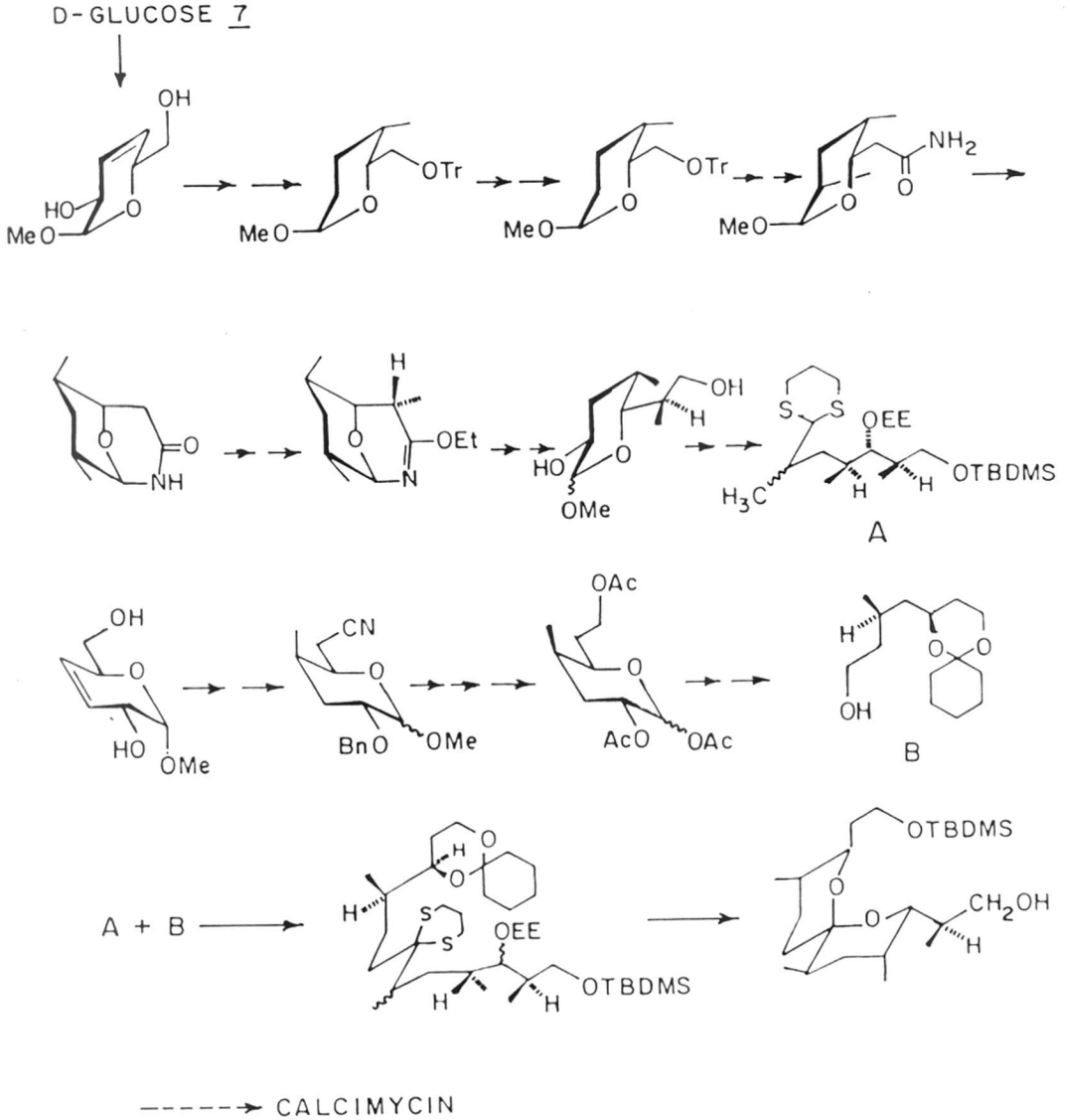
SCHEME - 3



1. H_2O_2/OH/MeOH; 2. $BF_3.OEt_2$/PhH; 3. LDA/THF/HMPA/MeI; 4. LAH/Et_2O; 5. H_2/Pt, EtOAc; 6. TBDSCl/CH_2Cl_2/DMAP/Et_3N; 7. CrO_3.2Py/CH_2Cl_2/ 0°, 20 min. 8. MCPBA/$NaHCO_3$/CH_2Cl_2, 0-5°. 9. LDA/THF/HMPA, -78°/ MeI. 10. LAH/Et_2O. 11. Acetone/$CuSO_4$, TsOH; 12. CH_2=CH-MgBr/ THF, -78°. 13. C_2H_5COCl/Py. 14. LDA/THF/HMPA, -78°; TBSCl/HMPA, 1.5h. nBu_4NF. 15. CH_2N_2. 16. OsO_4/Py/$NaHSO_3$,CSA,PhH; 17. Me_2SO/ $(COCl)_2$/CH_2Cl_2, Et_3N, -65° - RT. 18. Al(Hg)/THF/H_2O/EtOH/$NaHSO_3$/0°. 19. PTSA/MeOH, 0°. 20. MEMCl/CH_2Cl_2/iPr_2NEt. 21. LAH/Et_2O. 22. TBDSCl/CH_2Cl_2.

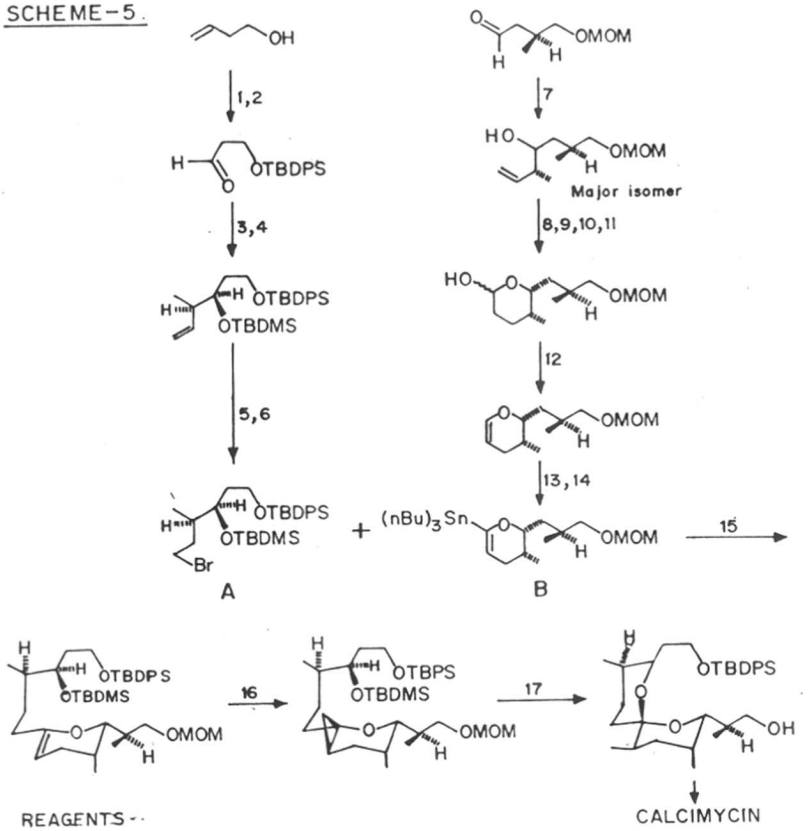
NAKAHARA SYNTHESIS (1986)

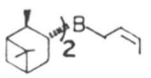
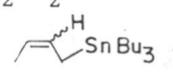
SCHEME-4.



BOECKMAN SYNTHESIS(1987)

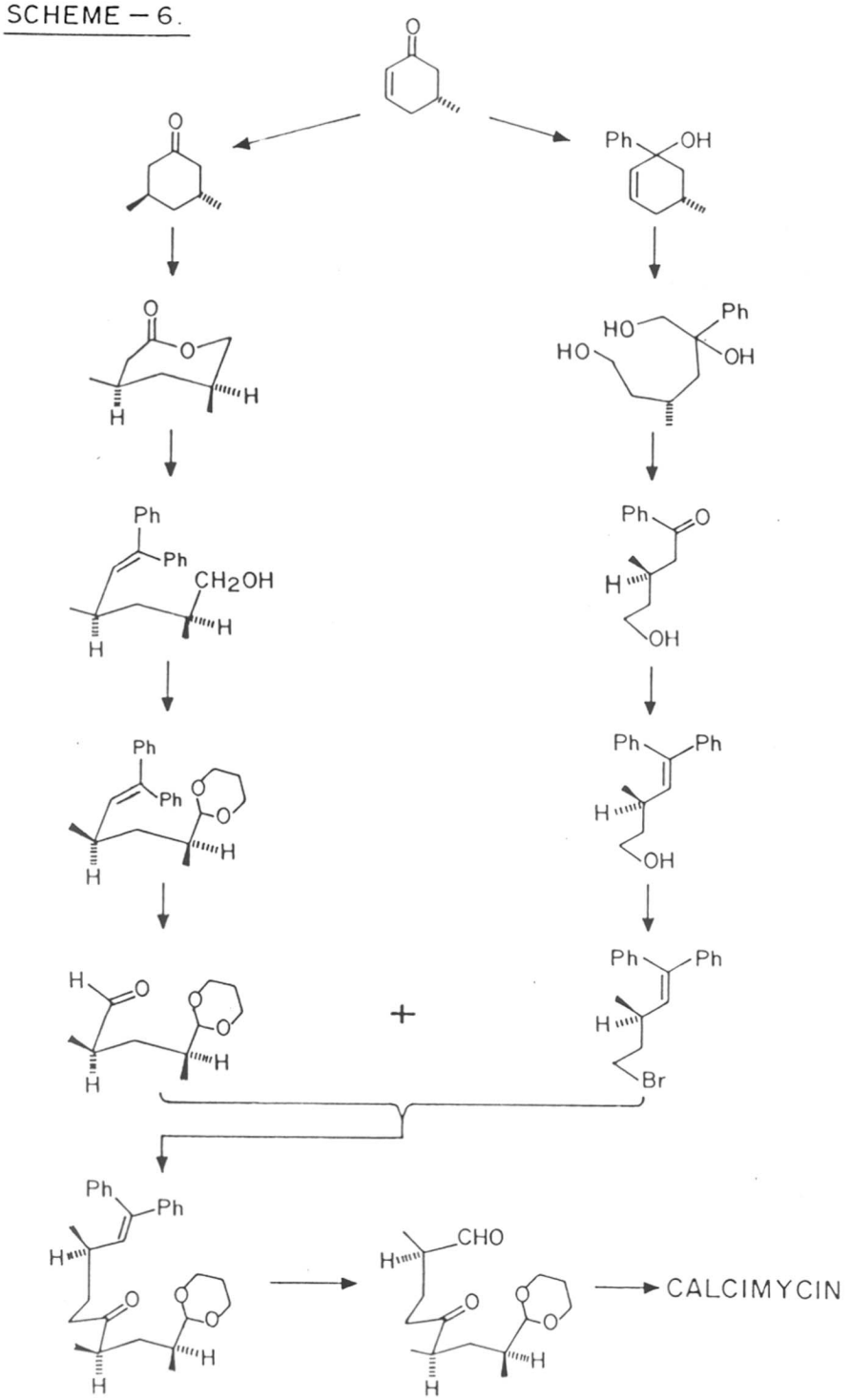
SCHEME-5.



1. TBDPS/1m/DMF/RT/6hr; 2. O_3/CH_2Cl_2-MeOH/-78°,DMS/-78°/RT/ 6 hr; 3.  THF,78°/5hr, H_2O_2/NaOH: 4. TBDMSOTf/Et_3N/ CH_2Cl_2/RT/1hr; 5. BH_3/THF,H_2O_2/NaOH; 6. $Ph_3P/CBr_4/Et_2O$,RT/6hr; 7.  /MgBr.Et_2O/CH_2Cl_2, -23°/3hr; 8. BH_3-THF/RT/ 12hr; 9. MeOH(1 eq.)/0°-RT/2hr; 10. $LiCH(SPh)OCH_3$/THF, -40°--10°/2hr; 11. $HgCl_2$/-10°-RT/3hr, H_2O_2/pH7,RT/3hr; 12. MsCl/ THF/Et_3N/14hr; 13. $KoBu^t$ (3 eq.),nBuLi(3 eq.)/THF, -78°; 14. nBu_3SnCl (3.2 eq.) -78°-RT/45 min; 15. nBuLi/THF, -78-0°/ 20 min, A (1.5 eq.)/THF-HMPA/0°-RT/16hr; 16. Et_2Zn/CH_2I_2/ Et_2O, RT/5hr; 17. PTSA-H_2O/PhH, 55°/5hr.

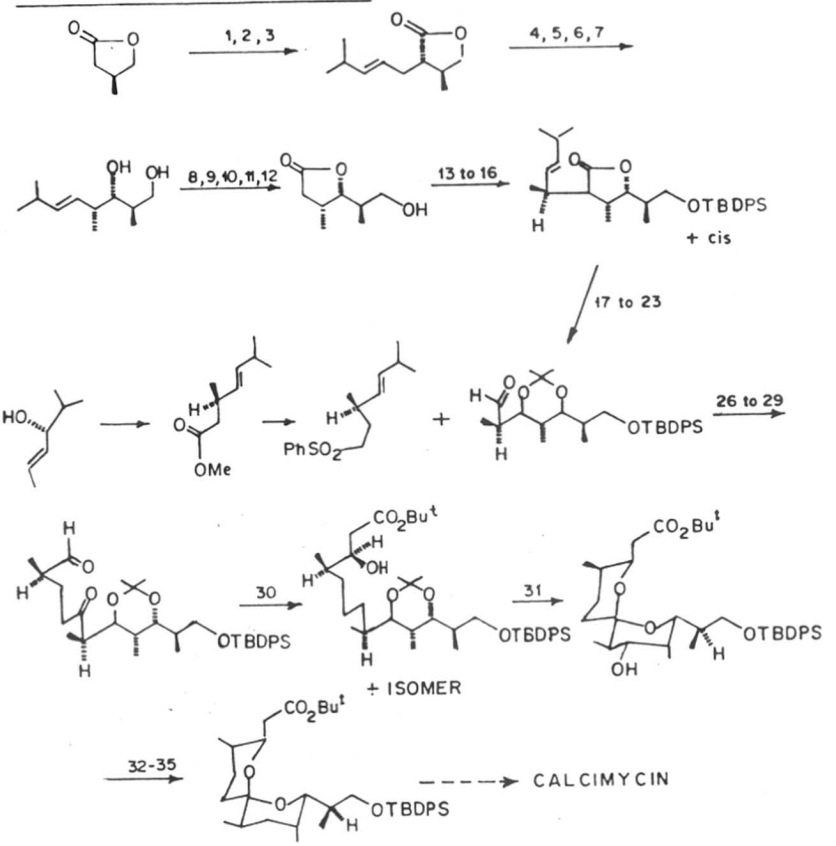
KISHI SYNTHESIS (1988)

SCHEME – 6.

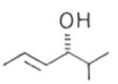


SCHEME – 7.

ZIEGLER SYNTHESIS (1989)



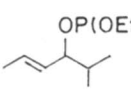
REAGENTS:

1. $Et_3O^+BF^-_4/EtONa/EtOH$; 2.  , Me_3CCO_2H/Δ

3. Bu^tOK/Bu^tOH; 4. MeLi; 5. H_2O_2, H^+; 6. Ac_2O; 7. LAH;

8. $Me_2C(OMe)_2/H^+$ 9. O_3, LAH; 10. TsCl/Py; 11. NaCN/DMSo;

12. HCl/MeOH; 13. TBDPSCl, 1m/DMF; 14. LDA, $NCCO_2Me$/THF;

15. NaH,  $/Ph_3P)_4Pd$, Ph_3P/THF; 16. LiCl/DMSO/H_2O;

17. MeLi, 18. H_2O_2/H^+; 19. Ac_2O/DMAP; 20. DIBAL; 21. $Me_2C(OMe)_2$, H^+; 22. O_3/LAH; 23. $(COCl)_2$, DMSO; 24. Claisen; 25. $-CO_2Me \rightarrow -CH_2SO_2Ph$;

26. nBuLi; 27. $COCL_2$, DMSO; 28. Na-Hg; 29. O_3/DMS; 30. $LiCH_2-CO_2Bu^t$;

31. PTSA/6hr/25°; 32. TBDPSCl, 1m/DMF; 33. PhOCSCl/DMAP/CH_3CN; 34. nBu_4NF;

35. RuO_2/KIO_4.

PRESENT WORK

3.5 Introduction:

Two synthetic routes for the synthesis of the C-9 spiroketal **9** and **44** (Schemes 8 and 9, respectively) were envisaged starting from a common precursor, trans-2,4-dimethylcyclohexanedione **16** (Scheme-8). In Scheme-8, alkylation followed by cyclisation can fix three stereocenters in **14**. Asymmetric addition reaction on this system can further fix another stereocenter. In Scheme-9*, trans-2,4-dimethylcyclohexanone derivative **54** forms the dienophile for a Diels-Alder reaction with trans-2,4-hexadiene **53** which can generate a system with the required 4 asymmetric centers of the spiroketal, thereby building 4 stereocenters by a small number of operations.

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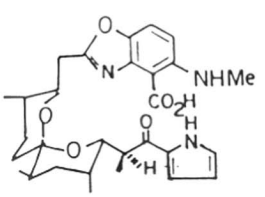
* See page 184

3.6 RESULTS AND DISCUSSION

The retro-synthetic analysis (Scheme-8), pronounce trans-4,6-dimethyl-1,3-cyclohexanedione (**16**) as the starting material. However, studies were carried out with the model compound 1,3-cyclohexanedione/dihydroresorcinol **17** (Eqn. 2), easily accessible from resorcinol,[26] for the construction of the intermediate corresponding to **14** (Scheme-8). The most obvious route to obtain this subtarget **14**, would be to alkylate 1,3-cyclohexanedione with 3-halo-2-methylpropan-1-ol[27] derivative, prepared as shown in Eqn. 1, and then cyclize to the bicyclic system, as in Eqn. 2. However, all attempts to alkylate **17** (Eqn. 2) with any of the alkylating agents **20** under various conditions using different bases like pyridine, piperidine, Et_3N, NaH, KOH, KOMe, $KOBu^t$, NaOH/PTC, K_2CO_3/PTC etc. with appropriate solvents resulted in either o-alkylation or highly unacceptable yields of C-alkylation.

Another route to **21a** would be via. allylation of **17**, followed by hydroboration-oxidation. Allylation with methallyl chloride proceeded to give the product **23** [IR & PMR: Fig.No. 3.0] (Eqn. 3) in 50% yield. During the conversion of **21a** to **22**, **22** can undergo dehydration under the conditions employed. In order to prevent this, it was decided to sulfenylate **23** prior to hydroboration. Treatment of **23** with sodium hydride and phenylsulfenylchloride did not yield the desired product **24**, but resulted in **27**

SCHEME – 8. (RETROSYNTHESIS)



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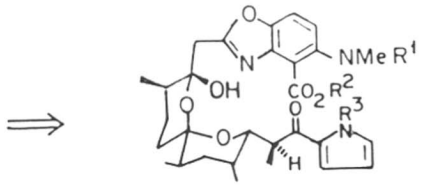

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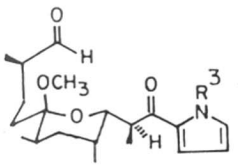

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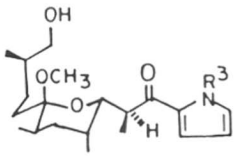

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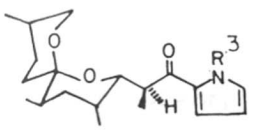

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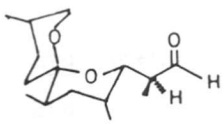

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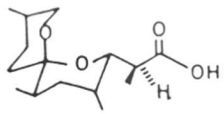

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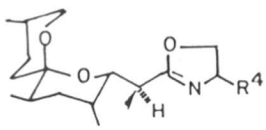

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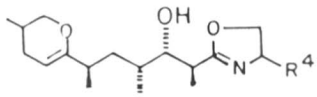

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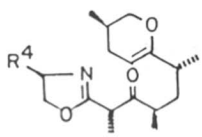

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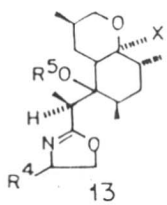

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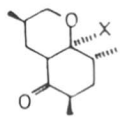
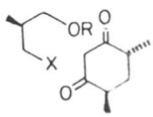


X = OR / SR

14



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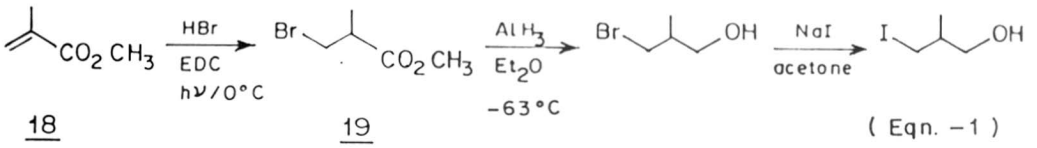
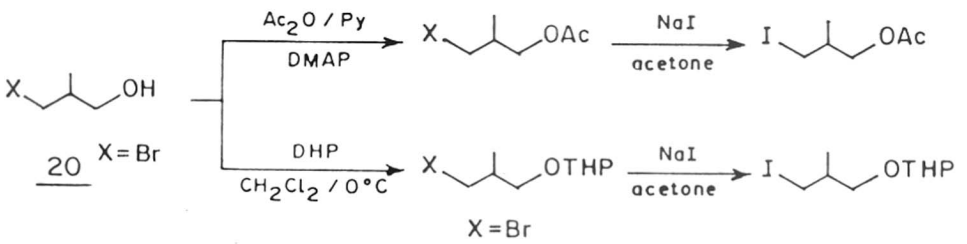
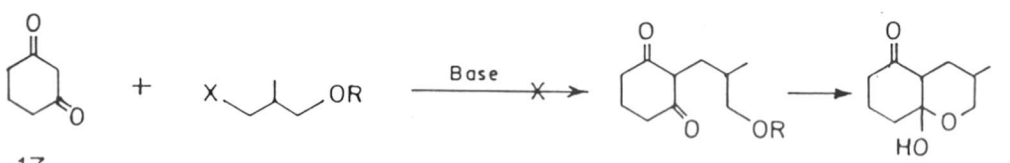


18 19 (Eqn. – 1)



20 X=Br



17 22

20 a. X=Br, R=H 21 a. R=H

20 b. X=Br, R=Ac 21 b. R=Ac

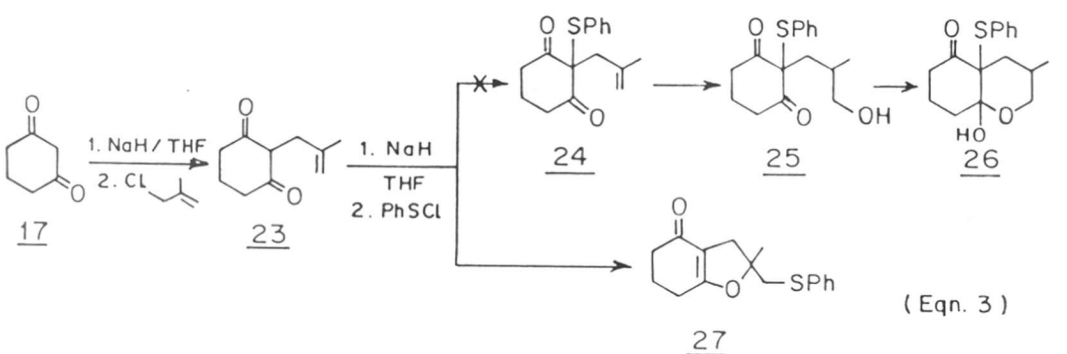
20 c. X=Br, R=THP 21c. R=THP

20 d. X=I, R=H

20 e. X=I, R=Ac

20 f. X=I R=THP

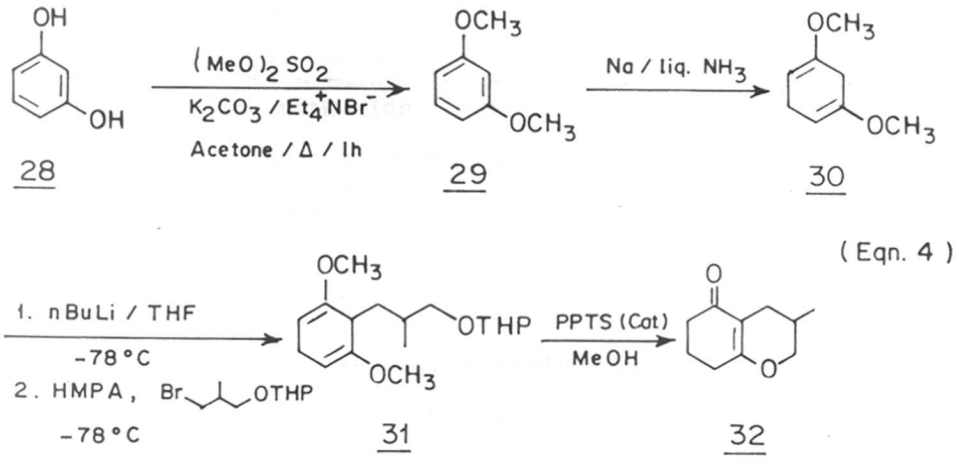
(Eqn. 2)



17 23 24 25 26 27

(Eqn. 3)

as the major product in 30% yield, structure of which was confirmed by spectral methods [IR & NMR, Fig. No. 3.1]. Since this scheme was not satisfactory, an alternative one was sought to have **21** in better yields. This was partially realised in the following method (Eqn. 4).

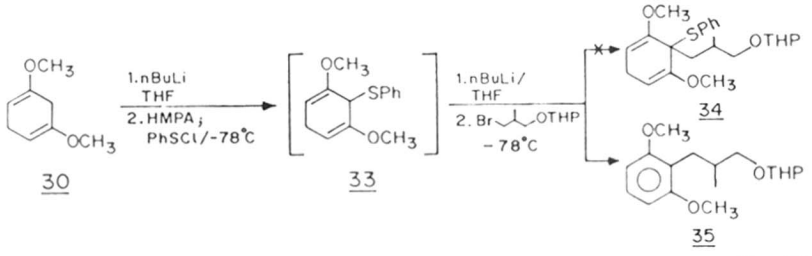


(Eqn. 4)

Resorcinol **28** was converted quantitatively to its dimethyl ether **29** using dimethylsulfate in the presence of potassium carbonate and a phase transfer catalyst. This was then subjected to Birch reduction with sodium in liquid ammonia to afford 1,5-dimethoxy-1,4-cyclohexadiene[28] **30** in 80-85% yield, which was further subjected to alkylation using n-butyllithium and tetrahydropyranyl derivative of 3-bromo-2-methylpropanol as the alkylating agent to furnish the alkylated product **31** [NMR Fig. No.3.2] in 55-60% yield. Treatment of **31** with catalytic amount of pyridinium p-toluenesulfonate in methanol at room temperature

yielded the bicyclic enone system **32**, structure of which was confirmed by IR, PMR, CMR and MS [IR, PMR Fig. No.3.3].

According to the strategy designed, the bicyclic system **32**, should bear a function like -OR, -SR or a halo atom β to the carbonyl function, which indicatively demands addition of HOR, HSR or HX across the unsaturation. Addition of $HOCH_3$ via acid catalysed methanolysis or Michael addition with methoxide ion or via. solvomercuration-demercuration was met with failure, probably due to the steric factors accompanying a tetra-substituted olefinic system in **32** or easy elimination due to presence of a highly acidic α-methine proton. The latter problem could be solved if the α-methine proton be substituted by a function which could be easily removed at a later stage. For this purpose, the thiophenyl group was chosen as the right candidate. Accordingly, on sulfenylation of **30** (Eqn-5), the product **33** was found to be highly prone to aromatisation.

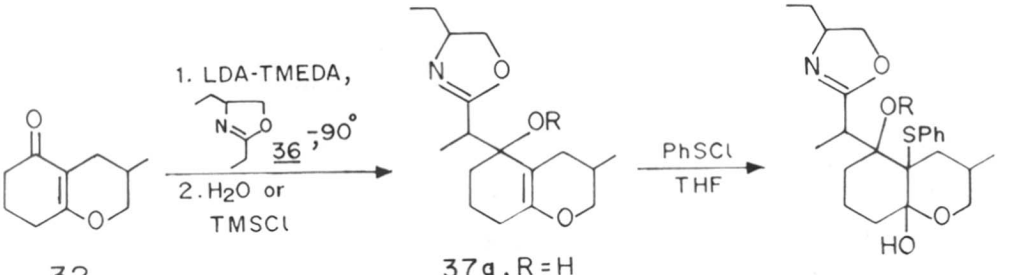


30 33 34 35

(Eqn.5)

A one-pot reaction of sulfenylation followed by alkylation was also of no avail, since the alkylation too was accompanied by aromatization **35**, probably due to the easy elimination of the thiophenol moiety. Hence this route to the sub-target **14** was not pursued further.

Attention was then drawn to the intermediate **13** (Scheme-8), which could be obtained by addition of 2-ethyloxazoline derivative to the carbonyl function of the enone system **32** followed by subsequent saturation of the olefin. Phenylsulfenyl chloride was chosen as the addend since this will not only result in the desired group β to the carbonyl function but will also result in substitution α to the carbonyl function and thus prevent undesired elimination reaction. 2,4-Diethyloxazoline was prepared from (dl)-2-aminobutanol and propanoic acid as reported.[29] The lithium salt of 2,4-diethyloxazoline obtained by treatment with LDA-TMEDA, when treated with the enone 32 at -90°C undergoes 1,2-addition smoothly to give the adduct **37** [IR, PMR Fig. No.3.4] (Eqn. 6), confirmed by spectral analysis.



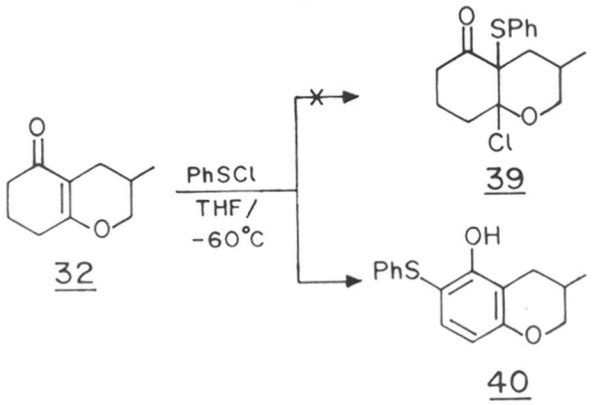
32

37a, R = H
37b, R = TMS
37c, R = Ac

38

(Eqn. 6.)

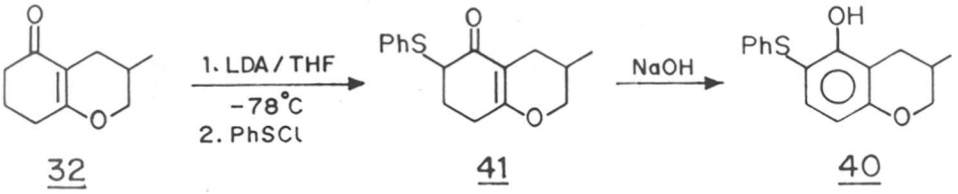
Quenching the reaction mixture with trimethylsilyl chloride gives the silyl derivative **37b**, which was found to be highly acid labile, leading to desylation. Alternatively, quenching the reaction mixture with acetyl chloride and catalytic amount of 4-dimethylaminopyridine resulted in poor yields of **37c** [IR & PMR: Fig. No.3.5]. Attempts to saturate the olefin in **37b** with phenylsulfenyl chloride did not result in **38**, instead the reaction reverted to give back the enone **32** and the oxazoline **36**. To circumvent this, addition of phenylsulfenyl chloride to olefin prior to carbonyl addition was tried (Eqn. 7). But, reaction of



(Eqn. 7.)

phenylsulfenyl chloride with the enone **32** in THF at -60°C did not yield the desired product **39**, instead resulted in **40**, the only product [IR & NMR fig. No.3.6] which was characterized by spectroscopic and chemical methods. α-Sulfenylation of enone **32** (Eqn. 8) using LDA and phenylsulphenyl chloride followed by aromatisation resulted in a product identical to **40** in all respects thus proving the

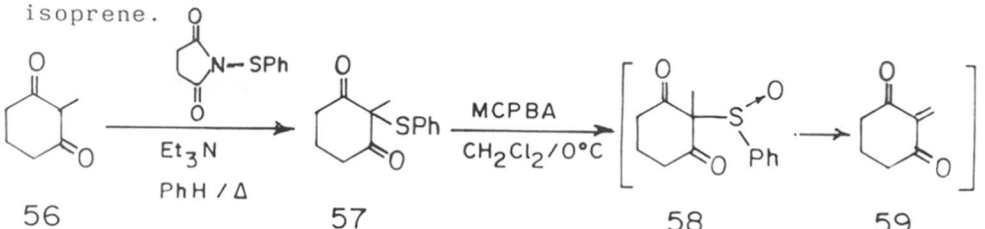
structure of **40**, bearing the thiophenyl group ortho to the hydroxy function.



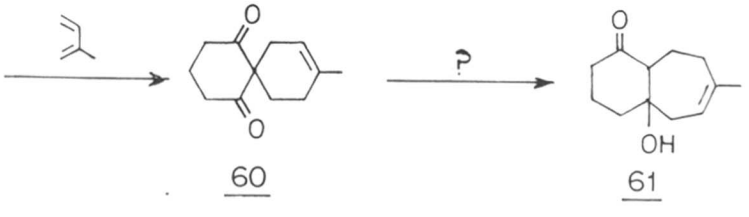
32 **41** **40**

(Eqn.8.)

At this stage of the studies based on Scheme-8, we shifted our attention to the alternate Scheme-9, starting with 2-methylene-1,3-cyclohexanedione **59**. The important intermediates in this are: **51** and **52** in which 4 stereo-centers of 6 chiral centers in 2 are fixed. These studies were also carried out on model compounds. The very first target in this scheme is the spirodiketone system **52**, for which the precursors of Diels-Alder reactions are 2,4,6-trimethylcyclohexan-1,3-dione **55** and trans, trans-2,4-hexadiene[31] **53**. Analogous precursors chosen for the model studies were 2-methylcyclohexan-1,3-dione[30] **56** (Eqn.9) readily obtained by reduction and methylation of resorcinol **28**, and isoprene.



56 **57** **58** **59**

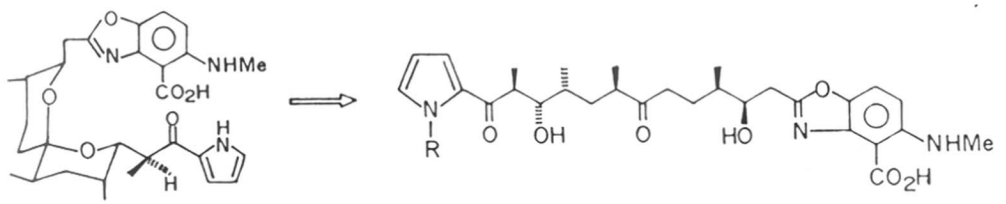


60 **61**

(Eqn. 9)

SCHEME-9

RETROSYNTHESIS :



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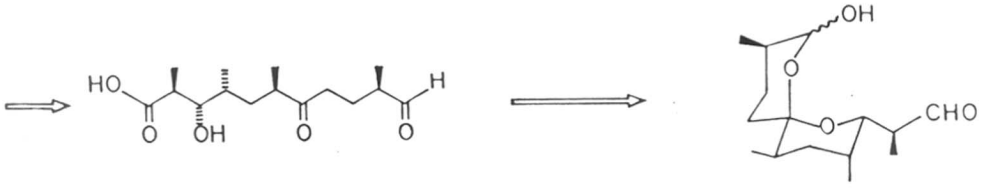
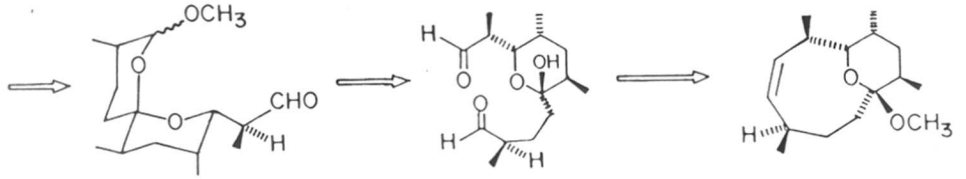
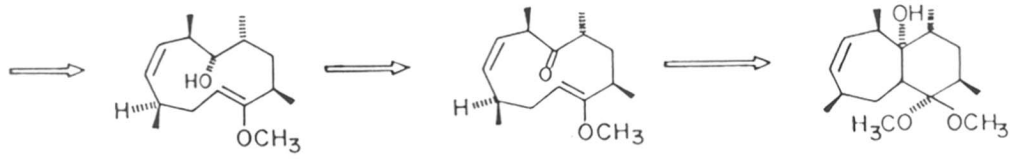


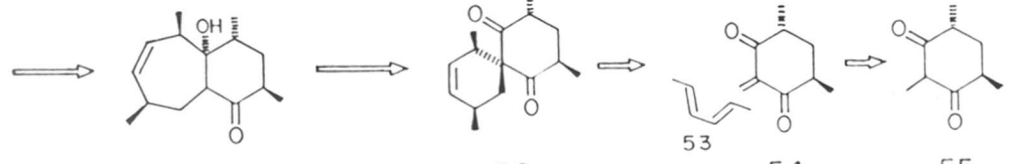
43 44



45 46 47



48 49 50

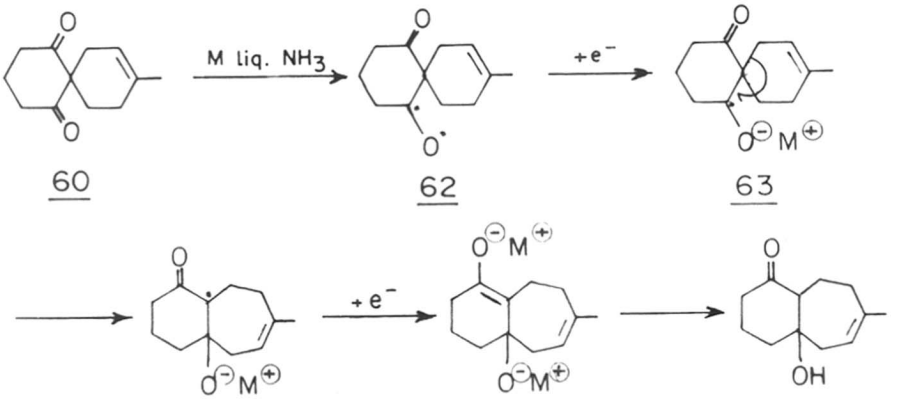


51 52 54 55

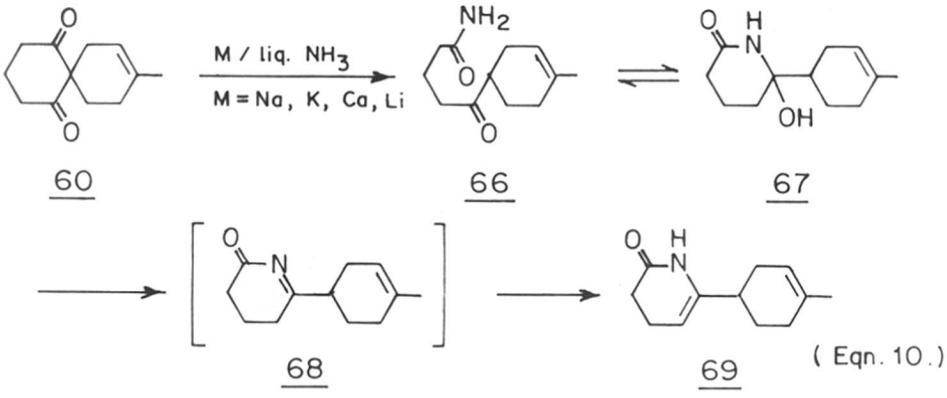
N-thiophenylsuccinimide,[32] which is easily made by reacting N-bromosuccinimide and diphenyldisulfide in the presence of light, when reacted with 2-methylcyclohexan-1,3-dione **56** in the presence of triethylamine provided the phenylsulfenylated cyclohexan-1,3-dione derivative **57**. The sulfide **57** on oxidation with metachloroperbenzoic acid at 0°C gave the sulfoxide **58** which undergoes a β-elimination reaction to form 2-methylenecyclohexan-1,3-dione **59** which was trapped by isoprene to give the Diels-Alder adduct **60** [IR & PMR, Fig. No.3.7], in an overall yield of 45% (starting from 2-methylcyclohexan-1,3-dione), thus setting the stage for the crucial reaction of the scheme where the spiro[5,5]undecane derivative **60** is to be converted to a fused [5,4]undecane system **61**.

One of the methods to achieve this would be by reductive ring expansion using a metal solution reaction in ammonia, ether etc. by a probable mechanism shown below (Scheme-10).

SCHEME – 10.



Hence the reactions were studied with Li, Na, K or Ca in liq. ammonia. In all the cases, the reaction resulted in the opening up of the dione system, to afford an amide 66 (Eqn. 10) which easily gets converted to the lactam derivative 69

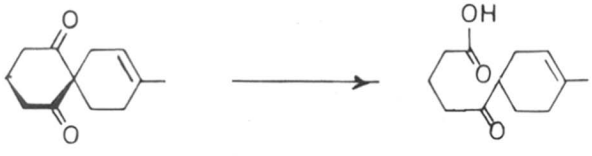


60 66 67

68 69 (Eqn. 10.)

[IR & NMR, Figs. 3.8 & 3.9 respectively). Similar kind of reaction with zinc amalgam or zinc-copper couple[33] under sonication did not result in any reaction.

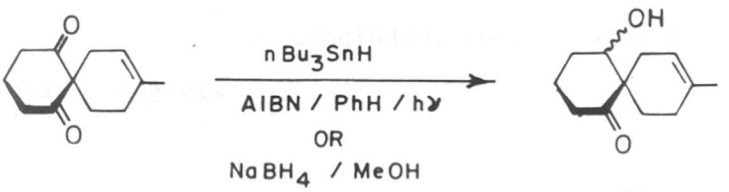
Sodium or potassium in ether or THF, under various conditions, did not yield any clean products and mainly resulted in decomposition with time to yield the ketoacid 70 (Eqn. 11).



70 Eqn. 11.

Employing Corey's[34] method for the generation of radical anion, utilizing zinc and trimethylsilylchloride in the presence of a base, e.g. lutidine also did not afford the desired reaction.

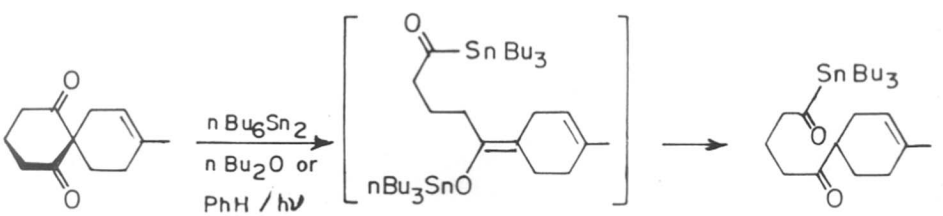
Reaction of the diketone **60** with tributyltinhydride in the presence of AIBN and light afforded a reduced product, the ketoalcohol **71** (Eq. 12). The formation of ketoalcohol



71

Eqn. 12.

was also confirmed by reduction of the diketone **60** with 1.0 equiv. $NaBH_4$ in methanol which afforded the same product **71** [IR & NMR, Fig. No.3.10]. In order to avoid reduction of the carbonyl function to alcohol, reaction was performed with hexabutyltin[35] in dibutylether or benzene as solvent, in the presence of light. The reaction afforded a product which was characterised to be a tributyltin keto ester **73** (Eqn. 13), probably formed via the tin



72 73

(Eqn.13.)

enolate intermediate **72**. However, use of tin reagents did not afford the desired product.

Reaction of **60** utilizing sodium naphthalenide as a radical generator resulted in unidentifiable products with incorporation of naphthalene moiety.

With the above mentioned studies the first phase of work on the utilization of the enone **32** and spiroketone **60** for the generation of a C-9 spiroketal intermediate for calcimycin is concluded. Further studies are currently under progress.

It was a brilliant experiment. Unfortunately, I forgot to note down what I did.

3.7 EXPERIMENTAL

Methyl-3-bromo-2-methylpropionate 19

23 g of methyl methacrylate **18** was taken in a flask having arrangements for passing gas. 70 ml of 1,2-dichloroethane was added to it as a solvent. The flask was cooled to 0°C. Sunlamp was arranged in such a way that light from the lamp can enter the reaction flask. Dry HBr gas (generated from 40% aq. HBr and conc. H_2SO_4) was passed into the reaction mixture till it absorbed the required amount (19 g, followed by increase in the wieght of the reaction contents, the time required was 3-4 h) of HBr gas. One gram of excess gas was passed in. The excess gas was then removed by bubbling air through the mixture. The remaining mixture was then distilled, first solvent was removed and the residue was distilled to obtain (84%) of a constant boiling fraction at 157°C/760 mm.

3-Bromo-2-methylpropanol[27] **20**

A solution of 3.97 g (0.1 mol) of LAH in 100 ml ether (dry) was placed in a three-necked flask and cooled to 0°C. Through a dropping funnel, a solution of 13.3 g (0.1 mol) of aluminium chloride in 150 ml of ether was added rapidly to the hydride solution. After 15 min. a solution of 18.1g (0.1 mol) of methyl-3-bromo-2-methylpropionate **20** in 150 ml of ether was added to 0.1 mol of LAH-$AlCl_3$ reagent which was cooled to -60°C. One hour after the last addition

of ether, a solution containing 20 ml of methanol and 20 ml of ether was added dropwise to destroy the excess hydride. After allowing the mixture to warm to room temperature, 100 ml of water and 100 ml of 6N H_2SO_4 were added. The clear solution was transferred to a separatory funnel and after removing the ether layer, the aq. layer was extracted 4 times. The extracts were combined, dried and distilled to afford 12.8 g (83%) of the alcohol boiling at 86-88°C/15 mm Hg.

1,3-Cyclohexanedione/Dihydroresorcinol 17

Prepared as in Reference 26.

2-Methylcyclohexan-1,3-dione 56

Prepared as in Reference 30.

2-Methallycyclohexan-1,3-dione 23

To a solution of 0.39 g of potassium in 3 ml of dry methanol was added 1.12 g (10 mmol) of 1,3-cyclohexanedione in 5 ml methanol and stirred for 0.5 h. Methallyl chloride 1.3 g (15 mmol) in 2 ml methanol was then added to the mixture followed by potassium iodide (1.66 g). The mixture was stirred for 1 h and then methanol was removed in vacuo. The residue was acidified with dil. HCl and extracted with ethylacetate. The extract was washed with brine, worked up and chromatographed (20% EtOAc/pet.ether) to afford 0.716 g (63%) of 23.

M.p.: 120°C

IR (Nujol): 1570, 1650, 1720, 2100-2700 cm^{-1}.

PMR: 1.7, m, 3H (CH_3), 1.85-2.1, m, 2H; 2.27-2.55, m, 5H; 3.1, dd, 2H; 4.85, m, 2H.

MS (m/e): 166 (M^+, 76.5%), 151(100), 148(16.9), 138(15.2), 133(13), 123(18), 110(15.6), 95(31.7%).

Sulfenylation of 2-Methallylcyclohexan-1,3-dione 23 to 27

0.08 g (0.48 mmol) of **23** in 4 ml THF was added to a suspension of 0.0127 g (0.52 mmol) of sodium hydride in 2 ml THF. After stirring for 0.5 h, 0.08 g (0.55 mmol) of phenylsulfenylchloride in 1 ml THF was added and stirring continued for 0.5 h. THF was then removed in vacuo, the residue taken in water and extracted with ethyl acetate thrice. The combined extract was washed with brine, worked up and chromatographed to afford 0.040 g (30%) of **27** as the major product.

IR (Neat): 1630, 1720 cm^{-1}.

PMR : 1.48, s, 3H (CH_3); 1.91-2.11, m, 2H; 2.11-2.44, m, 4H, 2.57, d, J=14Hz, 1H; 2.92, d, J=14Hz, 1H; 3.11, d, J=14Hz, 1H; 3.3, d, J=14Hz, 1H; 7.13-7.46, m, 5H.

MS (m/e): 274 (M^+ 26.5%); 165(50.4), 151(100), 137(4.7), 124(35), 109(4%).

1,5-Dimethoxy-1,4-cyclohexadiene 30

Prepared as in Reference 28

Alkylation of 1,5-Dimethoxy-1,4-cyclohexadiene 30 to 31

To a solution of nBuLi (1.2 equiv.) in cold (-78°C) THF (30 ml) was added 5.0 g of 1,5-dimethoxy-1,4-cyclohexadiene **30** and the resultant solution was stirred at -78°C for 1 h. HMPA (1.1 equiv.) was added and stirring continued for an additional 15 min. Addition of the tetrahydropyranyl derivative of 3-bromo-2-methylpropanol **20c** (1.2 equiv.) resulted in an immediate change in colour of the reaction. The reaction mixture was allowed to warm to room temperature, diluted with 10 ml of water. THF was separated and the aqueous layer extracted thrice with ether. The combined extracts were washed with brine, worked up and chromatographed (4% EtOAc/n-Hexane) to afford 55-60% of **31**.

PMR: 0.9, d, J = 6.4Hz, 3H (CH_3); 1.3-2.0, m, 11H; 2.65-2.97, m, 2H; 3.0-3.3, m, 2H; 3.3-3.6, S and m, 7H ($2xCH_3$); 3.65-4, m, 1H; 4.6, m, 2H.

Hydrolysis of 31 to 32

To a solution of 0.800 g (2.7 mmol) of **15** in methanol, in an inert atmosphere was added 0.030 g (0.11 mmol) of pyridinium p-toluenesulfonate and stirred at room temperature for 3-4 h until the reaction was complete. Methanol was then removed in vacuo and the residue was taken in ethyl acetate and washed with bicarbonate solution, then brine and worked up to afford the crude product which was chromatographed (20% EtOAc/n-hexane) to furnish 0.393 g (87%)

of a crystalline product **32**.

M.p.: 47-50°C

IR ($CHCl_3$): 1620, 1640 cm^{-1}

PMR: 1.04, d, J=6.4Hz, 3H (CH_3); 1.72-2.06, m, 4H; 2.16-2.56, m, 5H; 3.3, dd, J = 9.6Hz, 1H; 4.06, m, 1H.

CMR: 16.7, q (CH_3); 20.8, t (CH_2); 25.8, d (CH); 36.65, t,(CH_2); 72.46, t,(CH_2); 111.0,s; 170.98, s; 198.02, s (CO).

MS (M/e): 166 (M^+, 80%), 151(100), 138(67.8), 123(9.3), 110(9), 95(22%).

Addition of 2,4-Diethyloxazoline to 32 to form 37a, 37b or 37c

To a cooled solution (-90°C) of LDA (1.2 equiv.) in THF (2 ml) was added 0.1686 g (1.1 mmol) of 2,4-diethyl-oxazoline and stirred for 0.5 h. Then a solution of **32** (0.20 g in 2 ml THF) was introduced into the reaction mixture. After 2 h since the addition of **32** the mixture was quenched with H_2O, warmed up to room temperature, THF separated and the aqueous layer extracted with ether. The combined ether extracts were washed with brine, worked up and chromatographed (20% EtOAc/pet. ether) to afford 60% of the alcohol **37a**. Quenching the reaction mixture with TMSCl followed by work up and chromatography affords the silylated product **37b** and quenching the reaction with acetyl chloride and DMAP results in the product **37c**.

37a: IR (Neat): 1610, 1650, 3400-3600 cm^{-1}.

PMR: 0.8-1.1, m, 9H (3 x CH_3); 1.4-1.7, m, 3H; 1.72-2.08, m, 5H; 2.2-2.46, m, 4H; 2.64-3.00, m, 1H; 3.1-4.4, m, 5H.

37c: NMR Fig. No.3.5.

Phenylsulfenyl chloride addition on 32 to form 40

To a cooled (-60°C) solution of 1.0 mmol of **32** in 2 ml THF was added a solution of phenylsulfenyl chloride (2.0 mmol in 1 ml THF) and stirred for 0.5 h. The mixture was then warmed to room temperature. THF was removed in vacuo and the residue chroamtographed (5% EtOAc/n-hexane) to afford 60-70% of **40**.

M.p.: 86-88°C

IR (Nujol): 1580, 1600, 3380 (phenolic OH)

PMR : 1.1, d, J = 8Hz, 3H (CH_3); 2.1, m, 1H (C3-H); 2.25, dd, J = 11Hz and 16.6Hz, 1H; 2.9, m, 1H (C3-H); 3.65, m, 1H (C2-H); 4.15, m, 1H (C2-H); 6.45, d, J = 8.3Hz, 1H (C7-H), 6.65, s, 1H (OH); 7.05-7.3, m, 6H (C8-H and Ph-S).

CMR, PPM: 17.04, q (CH_3), 26.31, d (C3-H); 28.0, t, (CH_2); 71.6, t (C2-H_2); 105.5, s; 109.5, s; 109.8, d (=CH); 125.6, d (=CH); 126.2, d (2 x =CH); 129.0, d (2 x =CH); 134.6, d (=CH); 137.0, s; 155.9, s; 157.7, s.

2-Methyl-2-phenylthiocyclohexan-1,3-dione 57

To a mixture of 10 mmol of 2-methyl-1,3-cyclohexane-dione **56** and 11 mmol of triethylamine in 25 ml benzene is added 11 mmol of N-thiophenylsuccinimide and the mixture is refluxed for 7-8 h. The mixture is then cooled to room temperature, washed with 0.1M H_2SO_4, water, brine and worked up to afford the crude product which was purified by chromatography (40% n-hexane/$CHCl_3$) to provide 60-70% of **57**. **M.p.** 90-93°C [Lit.[36] m.p. 94-95°C].

Spiro[5,5]undeca-8-ene-1,5-dione-9-methyl 60

To a cooled (0°C) solution of 1.2 g (5.1 mmol) of 57 in dry dichloromethane (30 ml) was added m-chloroperoxybenzoic acid (1.09 g, 6.3 mmol) in small portions in 15 min. The mixture was allowed to stir for 1.5 h at 0°C and then m-chlorobenzoic acid was filtered off when cold. To the filtrate was added isoprene (0.7 g, 10 mmol), and the mixture was stirred at room temperature for 4-5 h. The mixture was then washed with water, brine, worked up and chromatographed (20% EtOAc/pet. ether) to provide 0.64 g (65%) of **60**.

M.p.: 93°C

UV (λ_{max}): 217, 1,327 and 290, 0.1766

IR (Nujol): 1680-1740 cm^{-1}

PMR: 1.6, m, 3H (CH_3); 1.8-2.2, m, 6H; 2.2-2.45, m, 2H; 2.4-3.0, m, 4H, 5.3, bs, 1H.

CMR: 18.32, t (CH_2); 22.94, q (CH_3); 27.23, t (2 x CH_2); 29.83, t (CH_2); 36.9, t (2 x CH_2); 65.89, s, 118.4, d, (=CH); 131.6, s.

MS (m/e): 192 (M^+, 14%), 174(30), 164(28), 149(87), 136(100), 121(54), 107(15), 91(24), 77(28%).

Metal ammonia reduction of 60 to 69

To a solution of 2.0 mmol of metal (Na, Li or Ca) in ammonia was added a solution of **60** (0.192 g, 1 mmol in 1 ml THF) dropwise at -60°C. The mixture was stirred at

-60°C till the completion of reaction (1 h). Ammonia was then allowed to evaporate and to the residue was added ammonium chloride solution. It was then extracted thrice with ether. The combined extract was washed with brine, worked up and chromatographed (20% EtOAc/pet. ether) to provide 40-50% of **69**.

M.p.: 92-98°C

IR (Nujol): 1620, 1650, 1690, 3160 cm^{-1}

PMR : 1.5, m, 1H (C7-H); 1.65; s, 3H (CH_3); 1.8-2.2, m, 4H; 2.2-2.3, m, 3H; 2.4-2.5, m, 3H, 4.8, m, 1H (C5-H); 5.35, bs, 1H (C9-H), 7.05, bs, 1H (NH).

CMR: 19.93, t (CH_2); 23.26, d (CH), 26.95, t (CH_2), 29.75, t (CH_2), 30.44, t (CH_2); 36.9, q (CH_3); 98.42, d (C5-H); 119.5, d (C9-H), 133.91, s (C-10), 140.92, s (C-6), 171.85, s (CONH), and 10% of **66**. **M.p.**: 120-122°C.

IR (Nujol): 1620, 1660, 1700, 3190, 3340 cm^{-1}.

PMR: 1.6, bs, 3H (CH_3); 1.75-2.4, m, 11H; 2.55, m, 2H; 5.3, bs, 1H; 5.6, bs, 2H.

MS (m/e): 209 (M^+ 2.6%), 192(32.6), 174(100), 164(13), 156(10), 149(50), 136(33.9), 123(47.8), 118(30), 105(39), 95(47), 86(40).

Reaction of n-tributyltinhydride OR sodium borohydride on 60 to form 71

(a) Employing tri-n-butyltinhydride: To a solution of 1.0 mmol of **60** in benzene was added 1.0 mmol of nBu_3SuH and AIBN as catalyst and refluxed for 1 h. Benzene was then

removed in vacuo and the residue chromatographed (25% EtOAc/n-hexane) to afford 80% of the alcohol **71**.

(b) Employing sodium borohydride: To a solution of 1.0 mmol of **48** in methanol was added 0.3 mmol of $NaBH_4$ at room temperature with stirring. After 40 min, methanol was removed in vacuo, the residue was taken in ether, washed with brine, worked up and chromatographed (25% EtOAc/n-hexane) to afford 80-85% of the alcohol **71**.

IR (Neat): 1690, 3200-3600 cm^{-1}

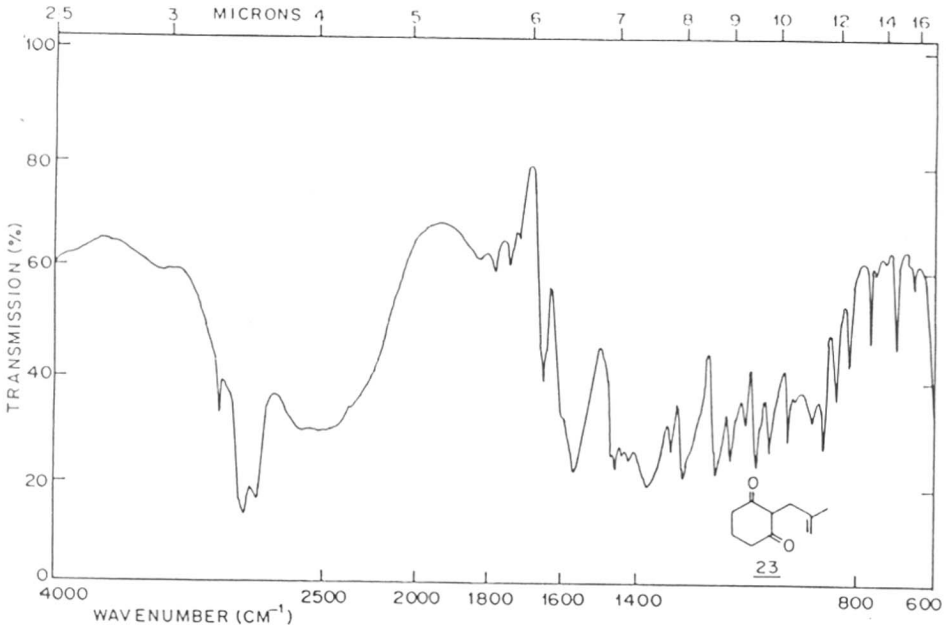
PMR : 1.6, d, 3H (CH_3); 1.71-2.2, m, 10H; 2.24-2.47, m, 2H; 3.88, m, 1H; 5.26, bs, 1H.

Reaction of hexabutylditin and 60 to form 73

In a flame dried 2-necked flask was introduced 1.0 mmol of **60** in 2 ml of di n-butyl ether and 2.0 mmol of hexabutylditin. The mixture was allowed to stir in the presence of light till the disappearance of the starting (by TLC). Dibutyl ether was then removed in vacuo and the residue chromatographed (0-20% EtOAc/n-hexane) to afford 30% of **73** and mainly keto-acid **70**. Both **73** and **70** were characterised by spectral analysis.

73: IR ($CHCl_3$): 1080 (Sn-C), 1570 (SnC=O), 1715 (C=O) cm^{-1}

PMR: 0.84, t, J=7Hz, 9H ($3xCH_3$); 1.06 - 1.55, m, 18H; 1.6, bs, 3H (CH_3), 1.65-2.4, m, 13H, 5.3, bs, 1H.


2.5
3
MICRONS
4
5
6
7
8
9
10
12
14
16
100
80
60
40
20
0
TRANSMISSION (%)
4000
2500
2000
1800
1600
1400
800
600
WAVENUMBER (CM⁻¹)
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O
23

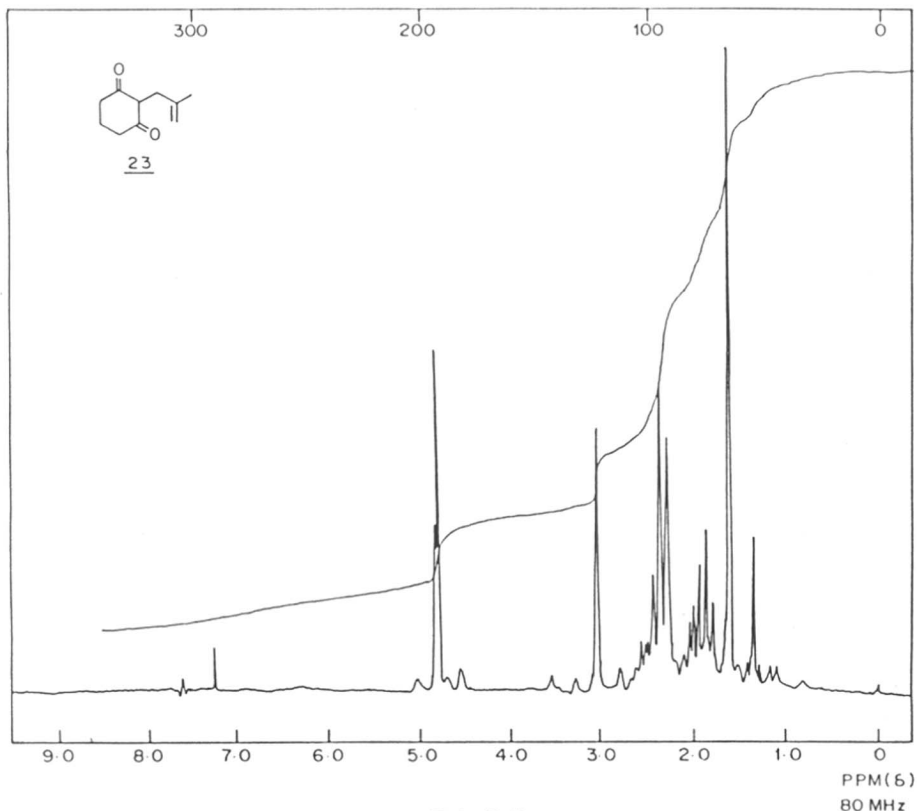
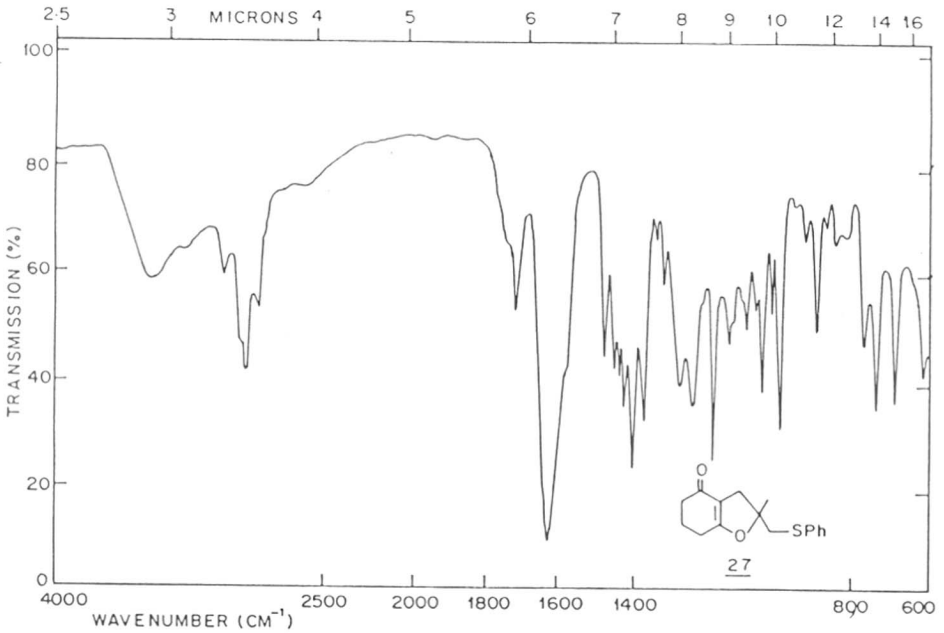

300
200
100
0
O
O
23
9·0
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM(δ)
80 MHz

FIG. 3·0.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8
9
10
12
14
16
100
80
60
40
20
0
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2000
1800
1600
1400
800
600
WAVENUMBER (CM⁻¹)
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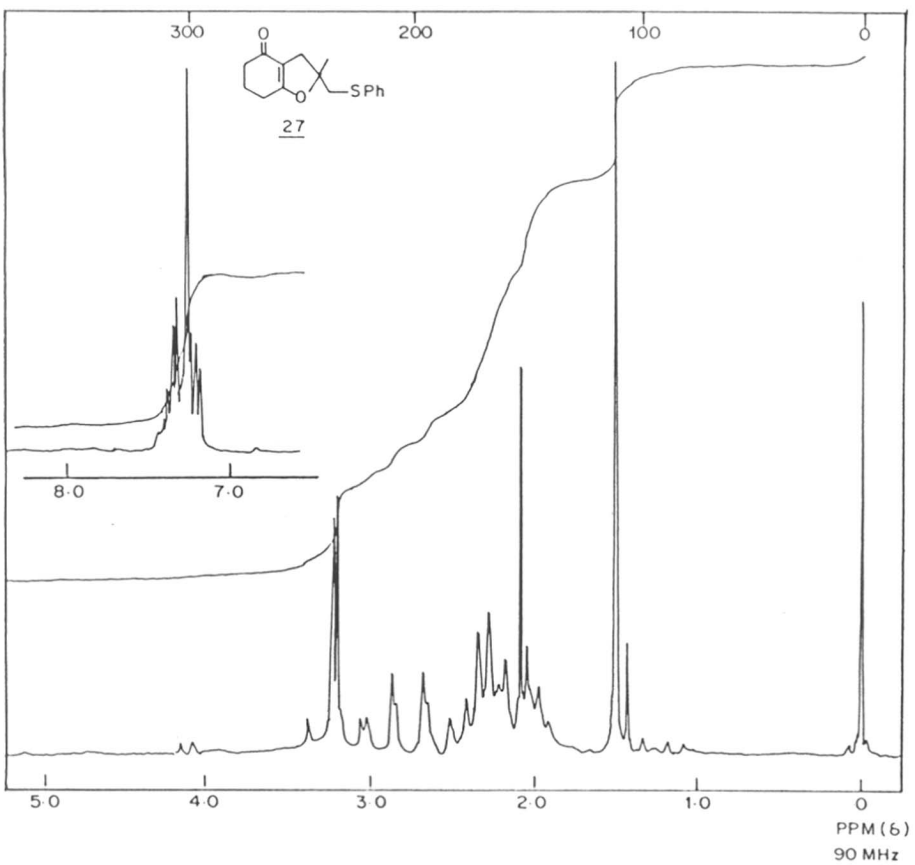
SPh
O
27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200
100
0
O
SPh
O
27
8·0
7·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)
90 MHz

FIG. 3·1.

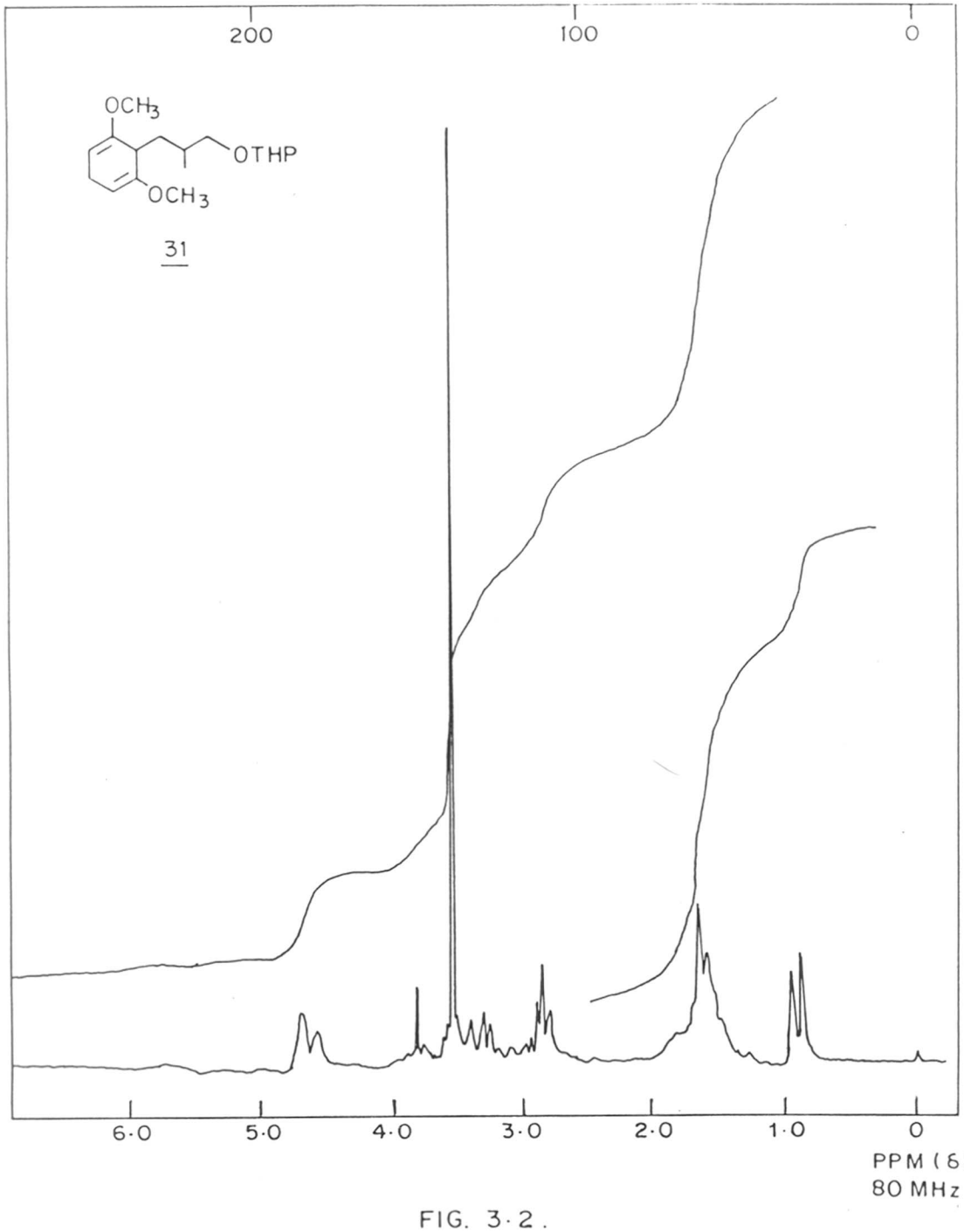
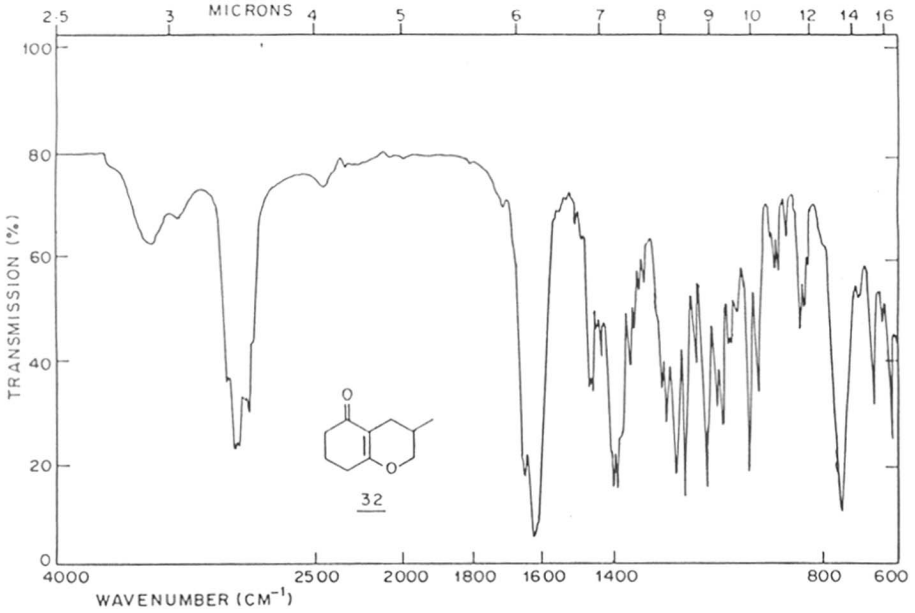


FIG. 3·2.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7
8
9
10
12
14
16
100
80
60
40
20
0
TRANSMISSION (%)
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2500
2000
1800
1600
1400
800
600
WAVENUMBER (CM⁻¹)
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O
32

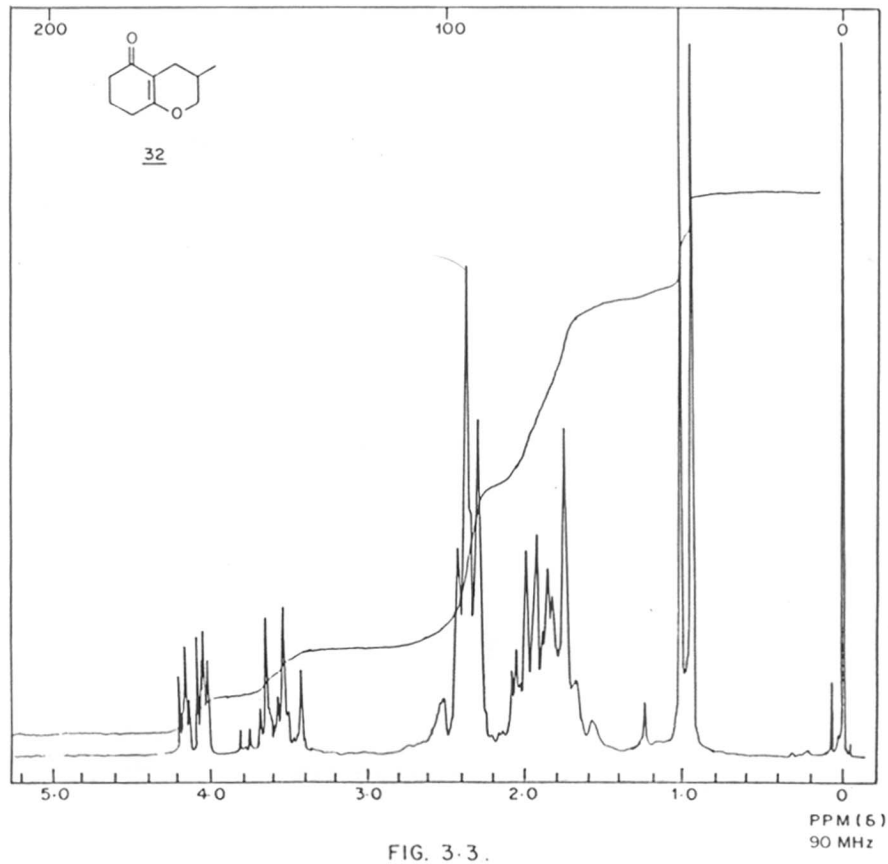
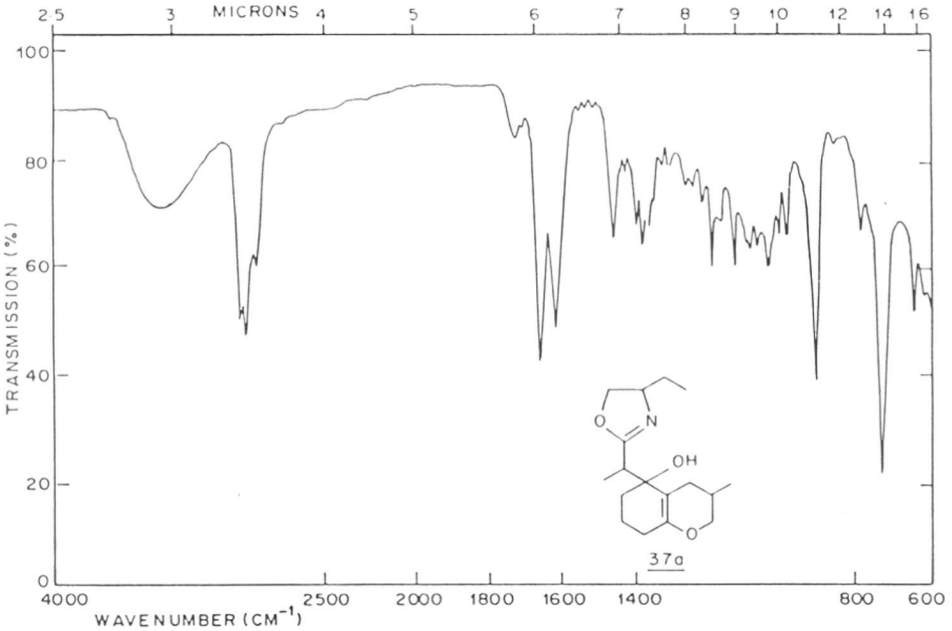

200
100
0
O
O
32
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)
90 MHz

FIG. 3·3.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MICRONS
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6
7
8
9
10
12
14
16
100
80
60
40
20
0
TRANSMISSION (%)
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2500
2000
1800
1600
1400
800
600
WAVENUMBER (CM⁻¹)
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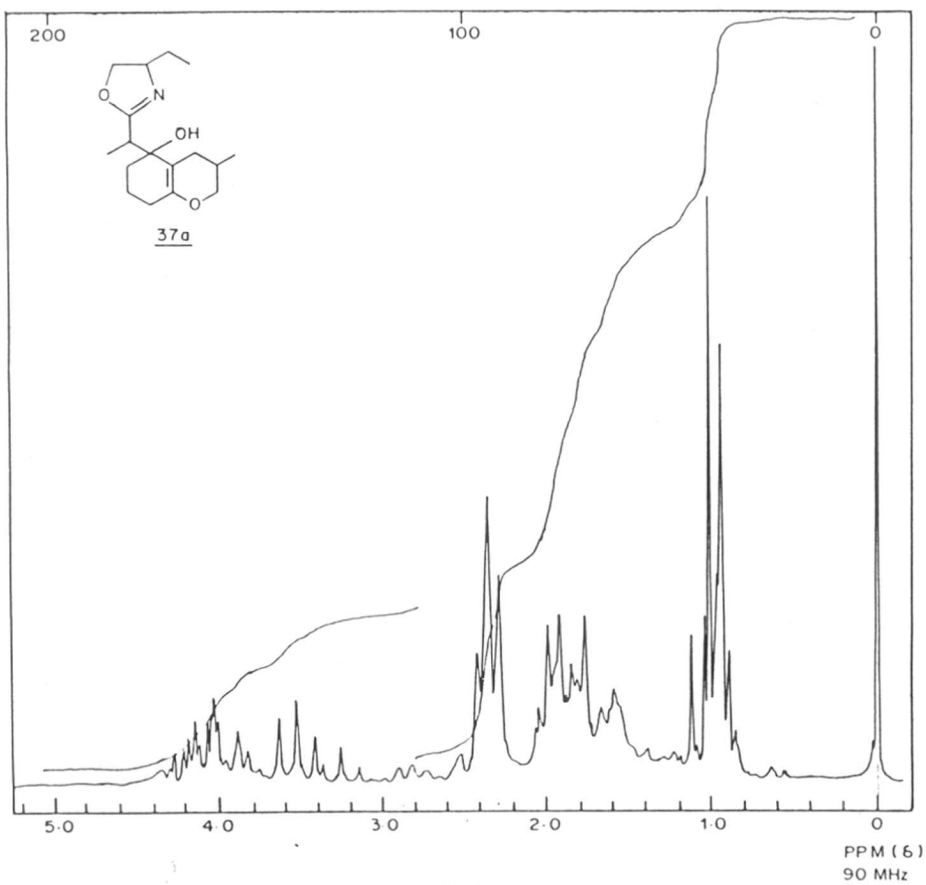
N
OH
O
37a


200
100
0
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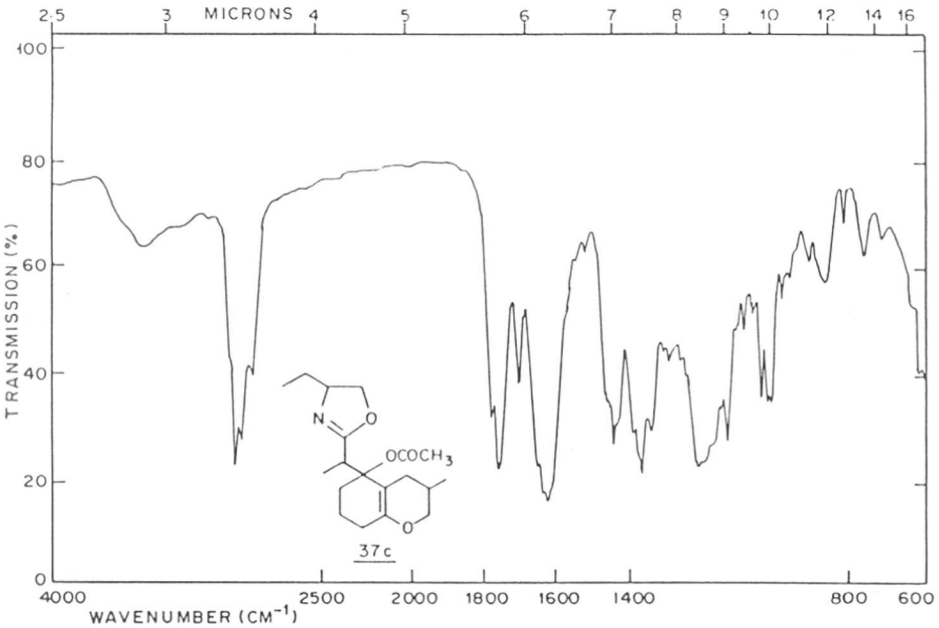
N
OH
O
37a
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)
90 MHz

FIG. 3·4.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3
MICRONS
4
5
6
7
8
9
10
12
14
16
100
80
60
40
20
0
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2000
1800
1600
1400
800
600
WAVENUMBER (CM-1)

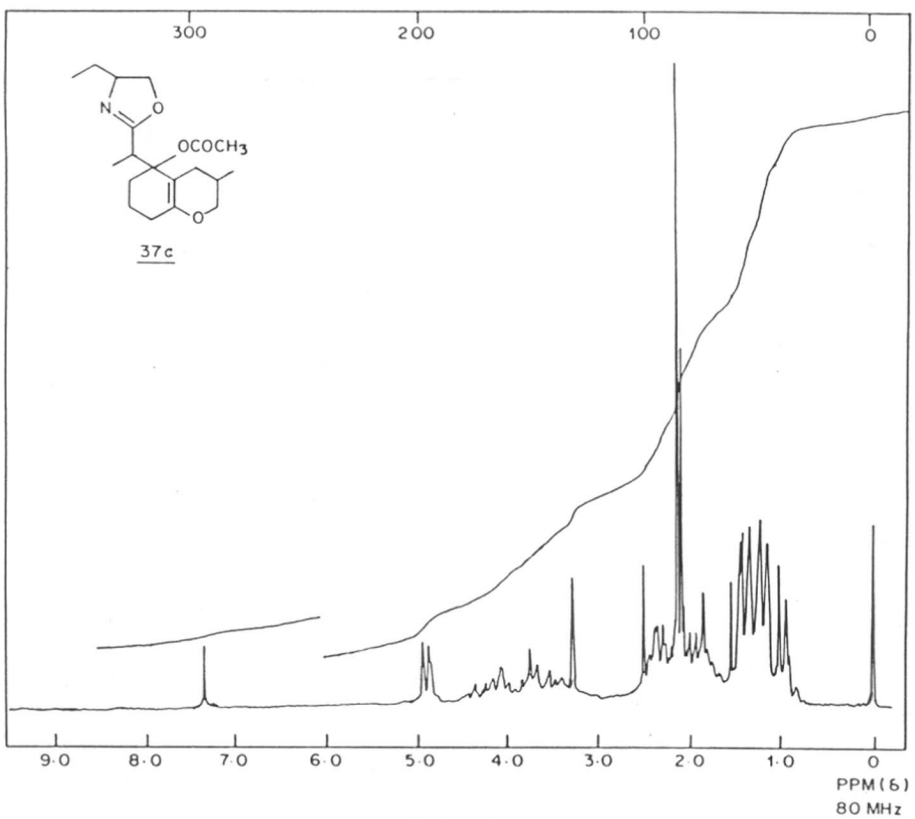
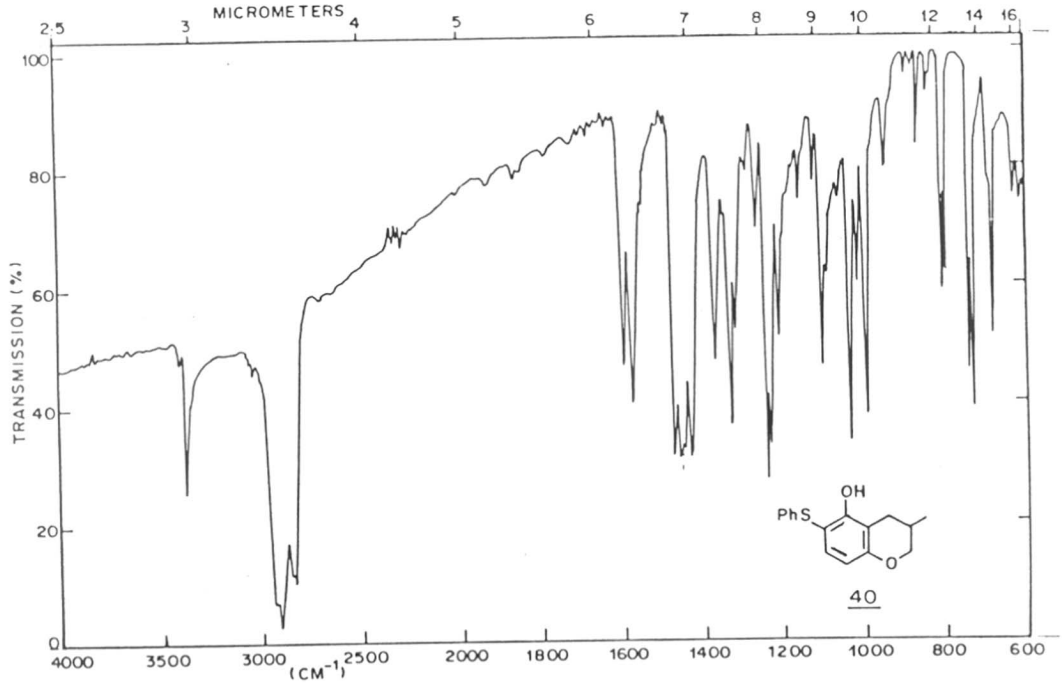

300
200
100
0
OCOCH3
37c
9·0
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)
80 MHz

FIG. 3·5.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7
8
9
10
12
14
16
100
80
60
40
20
0
TRANSMISSION (%)
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3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
(CM⁻¹)
OH
PhS
O
40

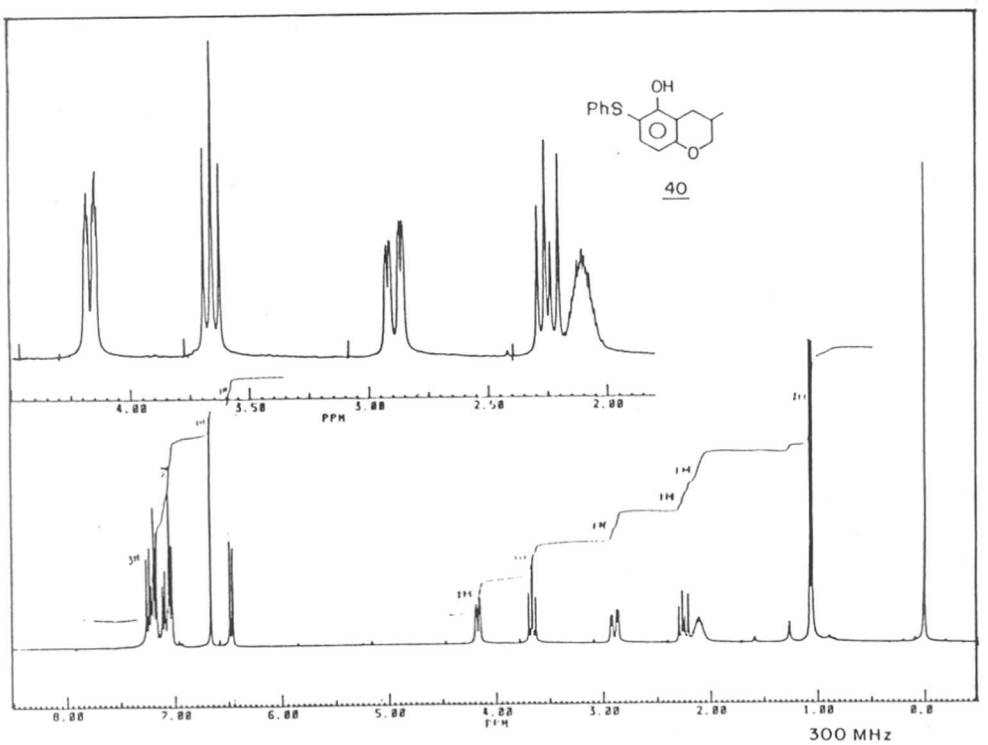
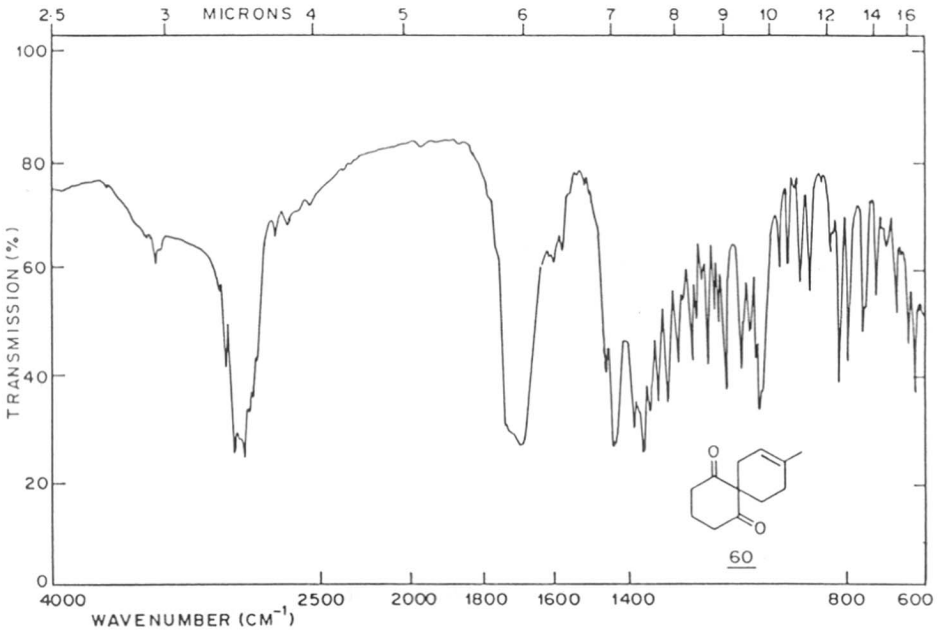

OH
PhS
O
40
4.00
3.50
3.00
2.50
2.00
PPM
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM
300 MHz

FIG. 3·6.


2·5
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MICRONS
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6
7
8
9
10
12
14
16
100
80
60
40
20
0
TRANSMISSION (%)
4000
2500
2000
1800
1600
1400
800
600
WAVENUMBER (CM⁻¹)
O
O
60

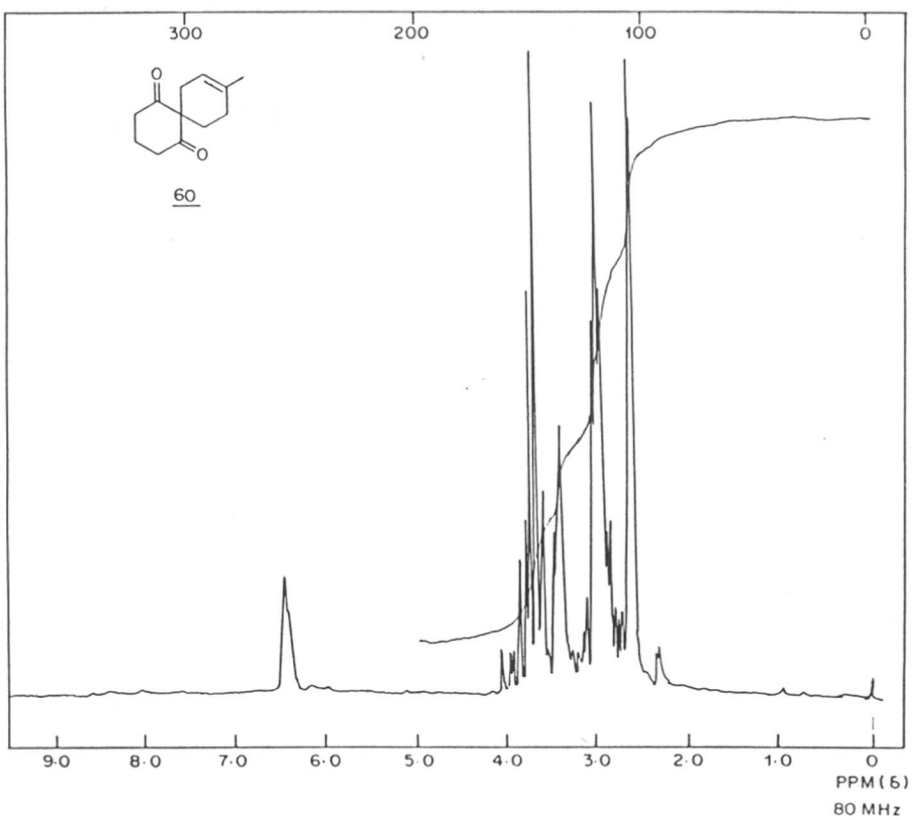
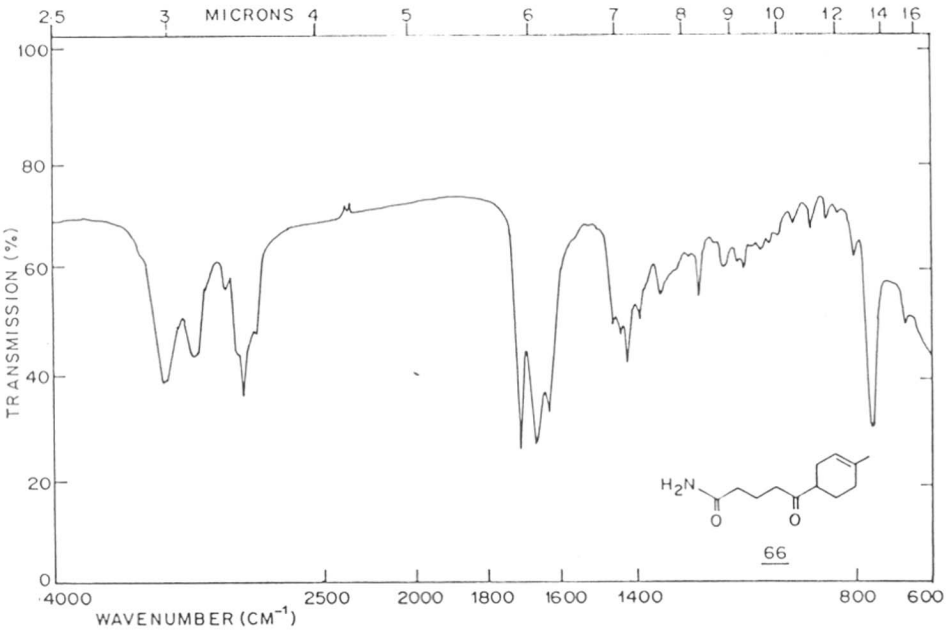

300
200
100
0
O
O
60
9·0
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)
80 MHz

FIG. 3·7.


2.5
3
MICRONS
4
5
6
7
8
9
10
12
14
16
100
80
60
40
20
0
TRANSMISSION (%)
4000
2500
2000
1800
1600
1400
800
600
WAVENUMBER (CM⁻¹)
H2N
O
O
66

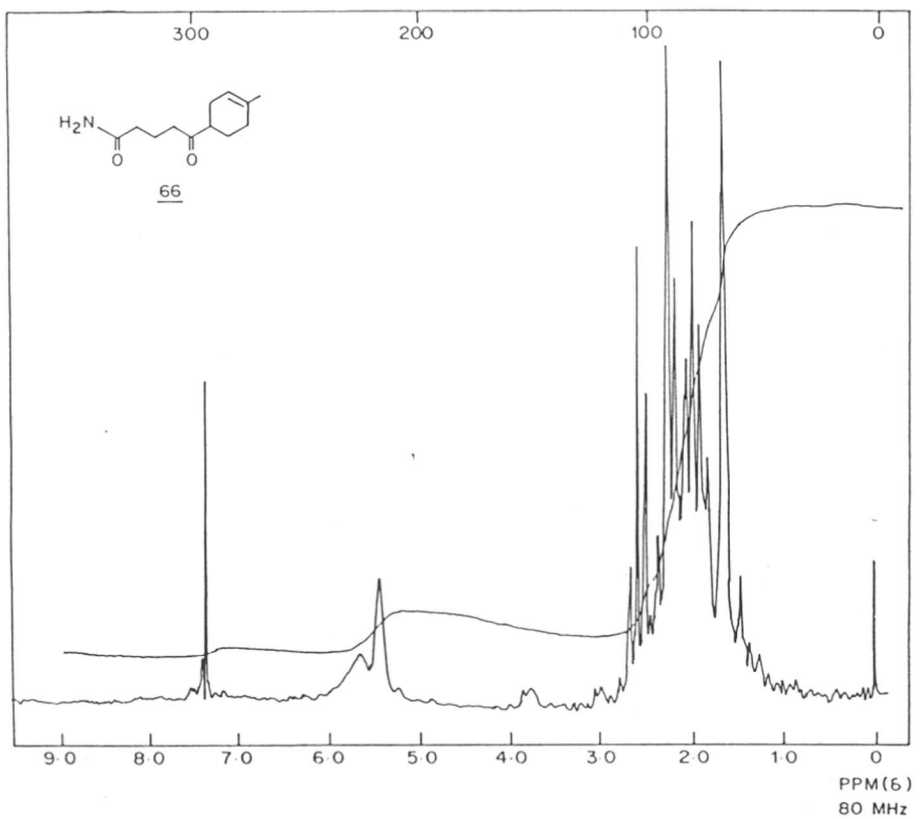
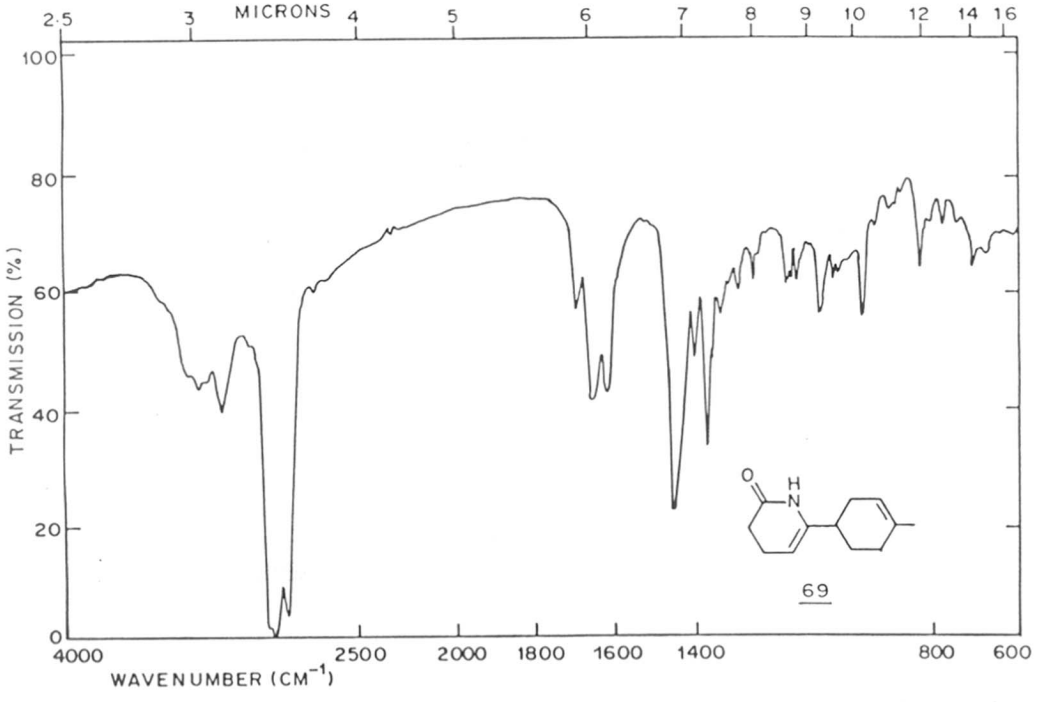

300
200
100
0
H2N
O
O
66
9·0
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM(δ)
80 MHz

FIG. 3·8.


MICRONS
2.5
3
4
5
6
7
8
9
10
12
14
16
100
80
60
40
20
0
TRANSMISSION (%)
4000
2500
2000
1800
1600
1400
800
600
WAVENUMBER (CM⁻¹)
69

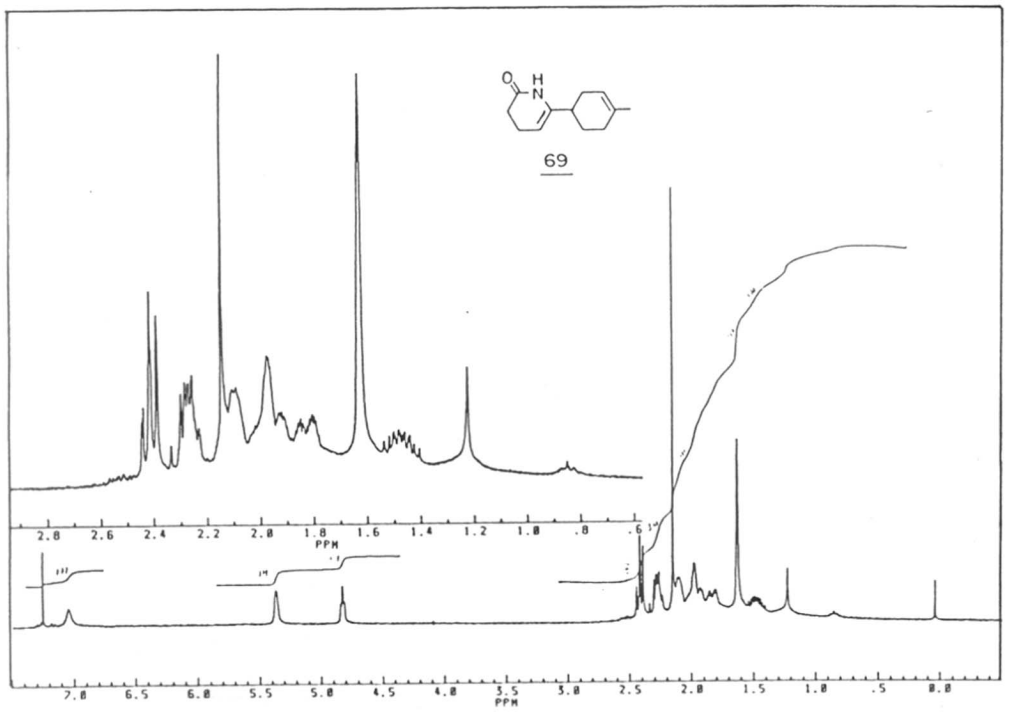
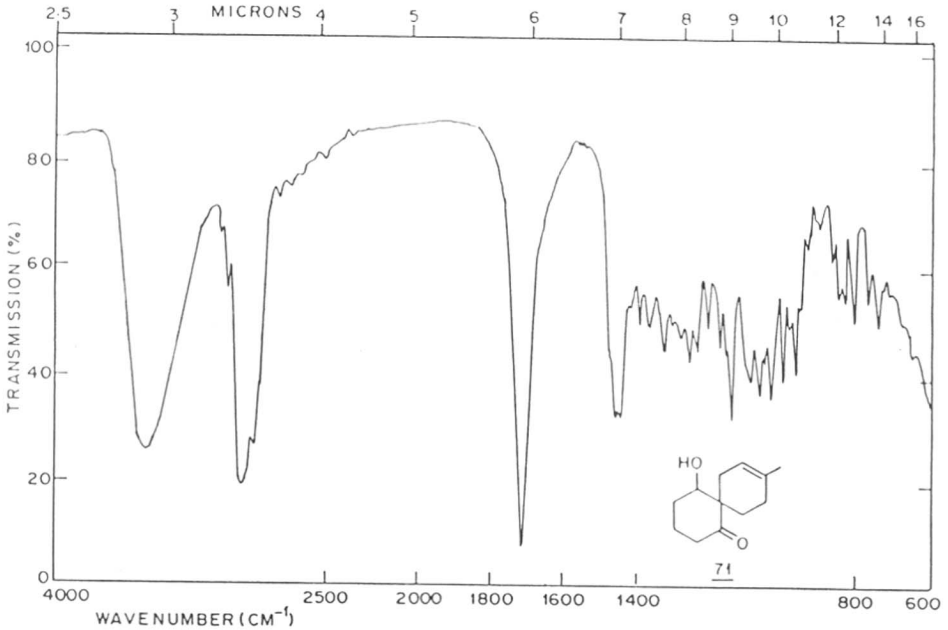

69
PPM
PPM

FIG 3·9


2.5
3
MICRONS
4
5
6
7
8
9
10
12
14
16
100
80
60
40
20
0
TRANSMISSION (%)
HO
O
71
4000
2500
2000
1800
1600
1400
800
600
WAVENUMBER (CM⁻¹)

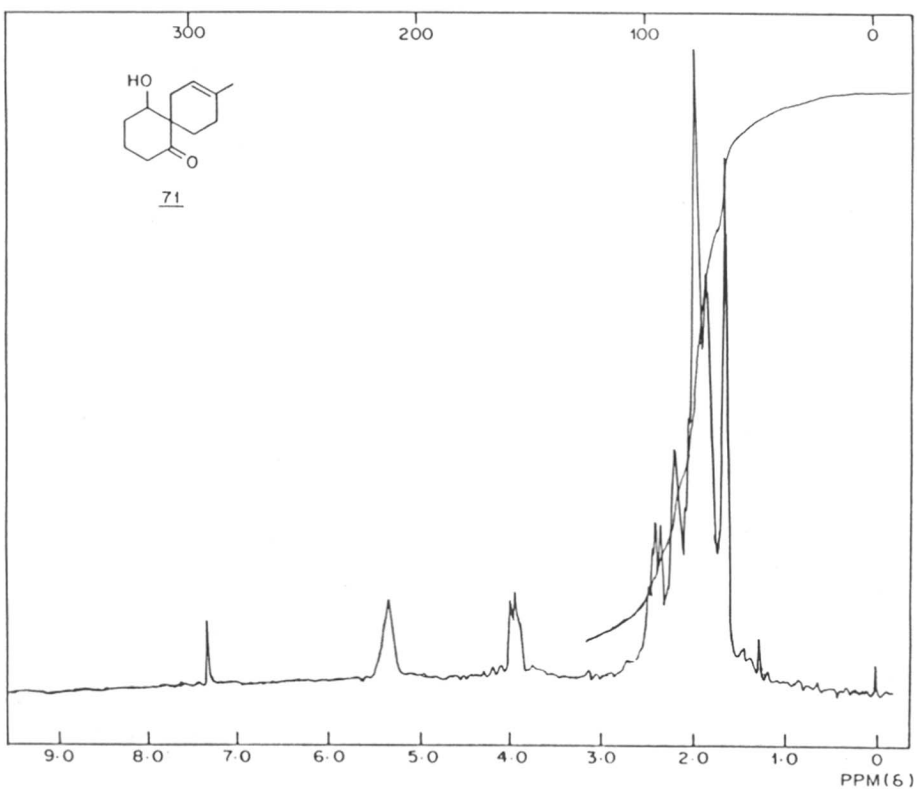

300
200
100
0
HO
O
71
9·0
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM(δ)
80 MHz

FIG. 3·10.

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STEREOSPECIFIC SYNTHESIS OF α-LIPOIC ACID

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Summary: Short and highly stereospecific synthesis of (S)-(-)- and (R)-(+)-α-lipoic acid using menthone as a recyclable chiral auxiliary is presented.

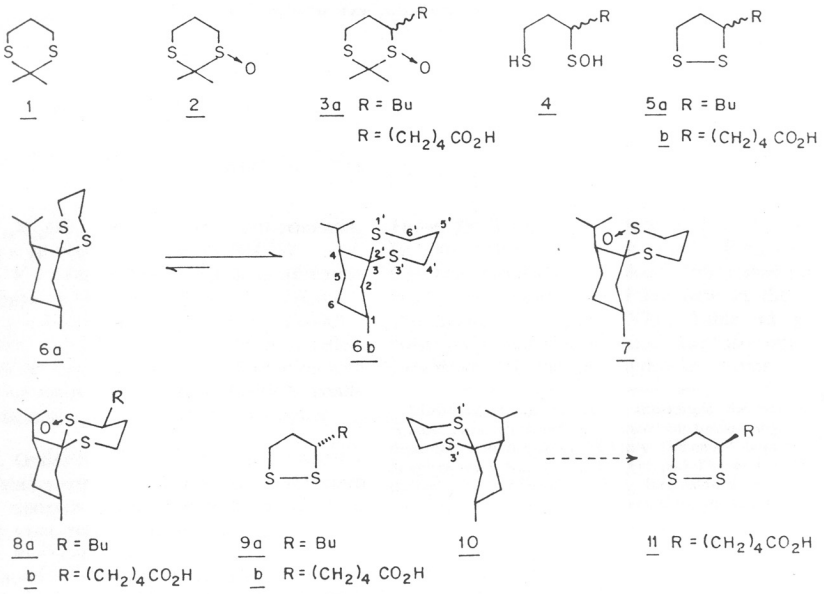
A short stereospecific synthetic strategy has been developed for 1,2-dithiolanes. This strategy has been mainly applied for the synthesis of dl-, (S)-(-)- and (R)-(+)-α-lipoic acids, (R)-(+)-α-lipoic acid being the naturally occurring one, finds its importance as a vital cofactor in enzyme complexes that catalyze decarboxylation of α-ketoacids[1] and also has been shown to reduce blood sugar in diabetic rabbits[2]. Lately a number of strategies have been put forth for the synthesis of optically active α-lipoic acid[3]. This paper presents the shortest synthetic route to this molecule with almost 100% optical induction.

The strategy involves formation of 1,3-dithiane from 1,3-propanedithiol and a ketone which could subsequently lead to racemic or optically active 1,2-dithiolanes, depending on the choice of the ketone. Formation of dithiane from a chiral ketone like l-menthone, which serves as a chiral template, controls the regiochemistry of the oxidation of the dithiane. Examination of its model revealed that oxidation should preferentially take place at S-1' **6b** rather than S-3', since the molecule in its most stable conformation **6b**, is more accessible to oxidation at S-1' rather than S-3', where approach of the reagent is inhibited due to the presence of C-2, C-1 and C-6 on the same side. Oxidation at S-1' takes place to give the more favoured equatorial sulfoxide.[4] This was practically found to be true. The sulfoxide **7** thus formed was subjected to stereoselective alkylation via the sulfinyl carbanion[5] to give a trans-alkylated product **8** which thus regulates the absolute configuration at C-3 of dithiolane **9**.

Dithiane **1**[6] on treatment with 1 equiv. $NaIO_4$ in MeOH at -5°C afforded sulfoxide in 80% yield. Alkylation of **2** with 1 equiv. LDA-TMEDA/BuBr or 2 equiv. LDA/TMEDA/$Br(CH_2)_4CO_2H$ in THF results in **3a** or **3b** respectively, in 65-75% yield. **3a** and **3b**, when subjected to hydrolysis in a two phase system of aqueous HCl and petroleum ether or benzene respectively, formed the ketone and the corresponding 3-mercaptosulfinic acid **4** which cyclises immediately under acid catalysis to form 1,2-dithiolanes **5a** and **5b** respectively, in 70-75% yield which is recovered from the organic phase.[7,+]

Applying the same method but starting with dithiane **6** derived from menthone afforded sulfoxide **7** of a single regioisomer, as anticipated, in 80% yield. Stereoselective alkylation of **7** followed by hydrolytic cyclization as above, afforded 1,2-dithiolane **9** with retention of configuration at C-3, as at C-6' in **8** and the starting ketone was recovered with its optical purity maintained. Thus starting with l-menthone ($[\alpha]_D^{25}$: -28.3), the expected (S)-(-)-α-lipoic acid **9b**; m.p. 43-45°C $[\alpha]_D^{25}$ -104.8° (C, 0.54, C_6H_6) [lit.[3a] $[\alpha]_D^{20}$ -113° (C, 1.8, C_6H_6); $[\alpha]_D^{22}$ -117° (C, 1.8, C_6H_6)] was obtained in 70% yield and l-menthone ($[\alpha]_D^{25}$ -28.0°) was recovered in almost quantitative yields. Similarly dithiane **10** derived from d-menthone ($[\alpha]_D^{25}$: +20.7°) yielded (R)-(+)-α-lipoic acid **11** the natural antipode,

*NCL Communication No. 4232



M.p. 43-45°C $[\alpha]_D^{25}$ +102.8° (C,0.45 C_6H_6) [lit.[3a] $[\alpha]_D^{28}$ +104° (C,0.88, C_6H_6); $[\alpha]_D^{28}$ +107° (C, 0.88, C_6H_6)] and d-menthone ($[\alpha]_D^{25}$ +19) was recovered.

This methodology can provide lipoic acid or its analogues, with the required absolute configuration, by a highly efficient use of a recyclable chiral auxiliary and through the shortest number of synthetic operations so far reported.

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+ We discovered, after completionof this work, that the same synthesis had been used by D. Arigoni at the E.T.H. of Zurich; we thank a referee for this information and D. Arigoni for correspondence.

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Structure of Bornane-2-spiro-2′-(6′-methyl)-1′,3′-dithiane 1′-Sulfoxide*

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(*Received* 5 *August* 1988; *accepted* 5 *December* 1988)

Abstract. $C_{14}H_{24}OS_2$, $M_r = 272{\cdot}5$, orthorhombic, $P2_12_12_1$, $a = 10{\cdot}903$ (1), $b = 11{\cdot}004$ (1), $c = 12{\cdot}058$ (2) Å, $V = 1446{\cdot}7$ (3) Å^3, $Z = 4$, D_m(flotation in KBr solution) = 1·26, $D_x = 1{\cdot}25$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 3{\cdot}825$ mm^{-1}, $T = 293$ K, $F(000) = 592$, $R = 0{\cdot}049$, $S = 1{\cdot}51$ for 1157 observed reflections. The dithiane ring has a 'chair' conformation with the methyl group equatorial and the sulfoxide is axially substituted indicating a novel *cis* alkylation product.

Experimental. Optically active α-lipoic acid (Menon, Kumar & Ravindranathan, 1987) has been synthesized starting with optically active menthone as a chiral template. The same reaction sequence was attempted starting with *R*(+)-camphor as the starting ketone; however the monosulfoxide derivative failed to undergo alkylation with δ-bromovaleric acid as with menthone, which would lead to α-lipoic acid. The sulfoxide derivative, however, reacted with iodomethane under the alkylation conditions to give the methylated derivative. The stereochemistry of this methylated derivative was studied by X-ray crystallography. Crystal approx. 0·25 × 0·35 × 0·50 mm used, Nonius CAD-4F-11M diffractometer, Ni-filtered Cu radiation, $\omega/2\theta$ scan mode, scan speed 1° min^{-1}, $\theta < 60°$, h 0 to 12, k 0 to 12, l 0 to 13, 1326 unique reflections collected, 1157 judged significant ($|F_o| > 3\sigma|F_o|$), lattice parameters from 22 reflections ($27 < 2\theta < 57°$). Three standard reflections ($\bar{4}60$, $\bar{5}5\bar{2}$, 228) every 3600 s, 4% variation in intensity. No correction for absorption. Structure solved by direct methods using *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). Full-matrix least-squares refinement (on F) using anisotropic thermal parameters (isotropic thermal parameters for H held fixed at the value of the non-hydrogen atoms to which they are attached, H positions calculated by stereochemistry and confirmed by difference Fourier synthesis); convergence at $R = 0{\cdot}049$, $wR = 0{\cdot}043$, $S = 1{\cdot}51$, $\sum w(|F_o| - |F_c|)^2$ minimized, $w = (3{\cdot}5 + 1{\cdot}0|F_o| + 0{\cdot}025|F_o|^2)^{-1}$, $(\Delta/\sigma)_{max} = 0{\cdot}1$, final $\Delta\rho$ excursions $< |0{\cdot}3|$ e Å^{-3}. No corrections for secondary extinction. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974). Corrections for anomalous scattering used. Program *LALS* (Gantzel, Sparks & Trueblood, 1961) used for refinement. Fig. 1 gives a *PLUTO* view of the molecule (Motherwell & Clegg, 1978). Table 1‡ gives the positional parameters and equivalent isotropic thermal parameters of the non-hydrogen atoms with their

‡ Lists of structure factors, anisotropic thermal parameters, H-atom parameters and some important torsion angles have been deposited with the British Library Document Supply Centre as Supplementary No. SUP 51669 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

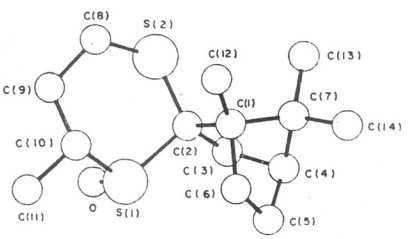

Fig. 1. *PLUTO* diagram (Motherwell & Clegg, 1978) of the molecule showing the crystallographic numbering scheme.

Table 1. *Atomic coordinates* (× 10^4) *and equivalent isotropic thermal parameters for non-hydrogen atoms with e.s.d.'s in parentheses*

$B_{eq} = \frac{4}{3}(B_{11}a^2 + B_{22}b^2 + B_{33}c^2)$.

	x	y	z	B_{eq}(Å^2)
C(1)	−956 (7)	−241 (7)	4595 (6)	3·29 (10)
C(2)	344 (7)	361 (7)	4800 (6)	3·02 (9)
C(3)	1155 (8)	−267 (8)	3900 (7)	3·87 (10)
C(4)	241 (8)	−988 (8)	3222 (7)	3·89 (10)
C(5)	−623 (9)	−71 (10)	2619 (7)	4·67 (13)
C(6)	−1487 (7)	370 (8)	3543 (7)	4·23 (11)
C(7)	−617 (8)	−1525 (7)	4117 (7)	3·59 (11)
C(8)	334 (11)	1209 (9)	7074 (7)	5·72 (14)
C(9)	346 (11)	2511 (9)	6695 (8)	5·33 (13)
C(10)	−375 (8)	2709 (8)	5591 (8)	3·78 (10)
C(11)	−498 (10)	4053 (8)	5317 (9)	5·43 (12)
C(12)	−1846 (8)	263 (8)	5585 (8)	4·84 (12)
C(13)	26 (10)	−2398 (9)	4929 (9)	5·16 (12)
C(14)	−1712 (9)	−2217 (8)	3617 (9)	5·01 (13)
O	1745 (5)	2390 (6)	4554 (6)	4·86 (8)
S(1)	429 (2)	2020 (2)	4435 (2)	3·17 (3)
S(2)	1089 (2)	155 (2)	6140 (2)	4·29 (3)

* NCL Communication No. 4511.

† To whom all correspondence should be addressed.

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e.s.d.'s while Table 2 gives the bond lengths and angles for the non-hydrogen atoms.

Table 2. *Bond distances* (Å) *and bond angles* (°) *with e.s.d.'s in parentheses*

C(1)–C(2)	1·584 (11)	C(5)–C(6)	1·537 (12)
C(1)–C(6)	1·549 (11)	C(7)–C(13)	1·540 (13)
C(1)–C(7)	1·569 (11)	C(7)–C(14)	1·539 (13)
C(1)–C(12)	1·539 (12)	C(8)–C(9)	1·504 (14)
C(2)–C(3)	1·561 (11)	C(8)–S(2)	1·814 (10)
C(2)–S(1)	1·879 (8)	C(9)–C(10)	1·562 (14)
C(2)–S(2)	1·822 (8)	C(10)–C(11)	1·521 (13)
C(3)–C(4)	1·514 (12)	C(10)–S(1)	1·813 (10)
C(4)–C(5)	1·560 (13)	O–S(1)	1·499 (6)
C(4)–C(7)	1·546 (12)		
C(2)–C(1)–C(6)	106·3 (6)	C(4)–C(5)–C(6)	103·7 (7)
C(2)–C(1)–C(7)	102·9 (6)	C(1)–C(6)–C(5)	103·2 (7)
C(2)–C(1)–C(12)	116·7 (6)	C(1)–C(7)–C(4)	93·2 (6)
C(6)–C(1)–C(7)	100·2 (6)	C(1)–C(7)–C(13)	115·8 (7)
C(6)–C(1)–C(12)	114·0 (7)	C(1)–C(7)–C(14)	114·0 (7)
C(7)–C(1)–C(12)	114·8 (7)	C(4)–C(7)–C(13)	114·0 (7)
C(1)–C(2)–C(3)	102·3 (6)	C(4)–C(7)–C(14)	112·6 (7)
C(1)–C(2)–S(1)	114·4 (5)	C(13)–C(7)–C(14)	107·1 (7)
C(1)–C(2)–S(2)	119·0 (5)	C(2)–S(2)–C(8)	105·6 (4)
C(3)–C(2)–S(1)	103·9 (5)	C(9)–C(8)–S(2)	114·6 (7)
C(3)–C(2)–S(2)	108·0 (5)	C(8)–C(9)–C(10)	112·8 (8)
S(1)–C(2)–S(2)	107·9 (4)	C(9)–C(10)–C(11)	111·5 (8)
C(2)–C(3)–C(4)	103·6 (7)	C(9)–C(10)–S(1)	110·7 (6)
C(3)–C(4)–C(5)	108·0 (7)	C(11)–C(10)–S(1)	106·4 (6)
C(3)–C(4)–C(7)	102·8 (7)	C(2)–S(1)–C(10)	101·7 (4)
C(5)–C(4)–C(7)	101·9 (7)	C(2)–S(1)–O	106·8 (4)
		C(10)–S(1)–O	106·0 (4)

Related literature. The S(1)→O bond distance is 1·499 (6) Å. Both the sulfoxide and the methyl groups are *cis*. The methyl group is equatorial while the sulfoxide is axial. The norbornane ring has a *synchro* twist (*S*++) (Acharya, Tavale & Guru Row, 1984). The molecules in the crystal are held together by van der Waals interactions.

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