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DENDROBINE: A DIELS-ALDER APPROACH

DIENES FROM 2,5-DIHYDROTHIOPHENES

BY

H. BRUCE GOODBRAND

A DISSERTATION

Submitted to the Faculty of Graduate Studies through the
Department of Chemistry in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Philosophy at the
University of Windsor

Windsor, Ontario
1973

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To Dorothy, David and Susan

ABSTRACT

A synthesis of the stereochemically complex sesquiterpene alkaloid dendrobine was attempted in which a Diels-Alder reaction was incorporated as the central feature. The synthesis of three highly functionalized conjugated dienes was undertaken for use in this reaction. The two initial diene syntheses were abandoned because of difficulties encountered with some of their precursors. The third diene, 4-isopropyl-2-pyrone, was successfully synthesized but because of its exceptional stability, proved unsuitable for the proposed synthesis.

The generation of conjugated dienes by thermolysis of 2,5-dihydrothiophene - 1,1 - dioxides was investigated and a new preparative route to the parent 2,5-dihydrothiophene ring system was established. The selective oxidation of these compounds to their corresponding sulfones was shown to be a facile reaction. Pyrolysis of the sulfones at moderate temperatures gave dienes and greatly improved yields over conventional synthetic methods were obtained in certain instances. A preliminary investigation of the feasibility of employing this new method in a dendrobine synthesis is described.

ACKNOWLEDGMENT

I shall always be indebted to my research advisor, Dr. John M. McIntosh, who consistently gave of his time and experience, and whose enthusiastic guidance influenced all aspects of this undertaking. To Mrs. Dorothy Goodbrand I am sincerely grateful for both typing and assisting in the editorial processes involved in the preparation of this dissertation. The generous support of both the National Research Council of Canada and the University of Windsor, who provided scholarships during the period that this work was undertaken, is also gratefully acknowledged.

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DENDROBINE: A DIELS-ALDER APPROACH

CHAPTER I

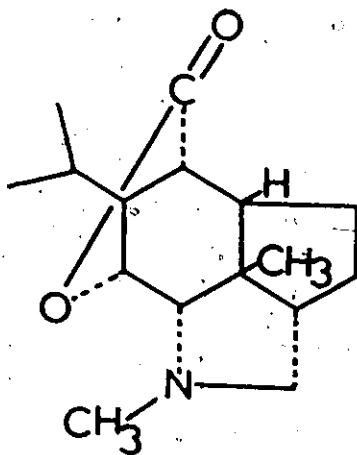
A GENERAL INTRODUCTION

The chemical analysis of folk remedies has long been an area holding great interest for natural products chemists and many valuable chemotherapeutic agents have come to light as the result of such investigations. In 1932, Suzuki and coworkers¹ began an examination of the constitution of an herbal preparation which had been in use in the Orient for centuries. Known as "Chin-Shih-Hu" in China² and as "Kinsokikoku" in Japan³, this preparation was regularly used as a tonic and was reported to be particularly useful in strengthening the digestive system after high fever.⁴ Suzuki's investigations revealed the presence of a number of alkaloids which he surmised were the biologically active ingredients. Originally there was some doubt as to the origin of these alkaloids because of the complex nature of the commercial product. However, it has now been firmly established that these compounds are elaborated by only one genus, the Dendrobium orchids, particularly D. nobile Lindley.³ This species is endemic to central and western China and is in common cultivation in Hong Kong both for medicinal purposes and as a highly prized ornamental plant.⁵ A total of seven alkaloids have been isolated from D. nobile, but by far the most abundant is dendrobine.²

The pharmacology of dendrobine was the object of some early clinical studies.^{6,7} The drug possesses slight analgesic and antipyretic activity. Moderate hyperglycemia, diminished cardiac

activity and suppressed respiration all result from moderate dosage levels while high levels severely impair the central nervous system and death results.

After the original isolation of dendrobine, the elucidation of its molecular formula as $C_{16}H_{25}NO_2$, and the demonstration that its functionality included an N-methyl group, no double bonds and the presence of a γ -lactone¹, over thirty years were required for a complete structure proof. Independently, three groups led by Hirata⁸, Inubushi⁹, and Okamoto¹⁰, by employing modern spectroscopic aids in conjunction with degradation studies, succeeded in determining the relative configuration of dendrobine as 1.

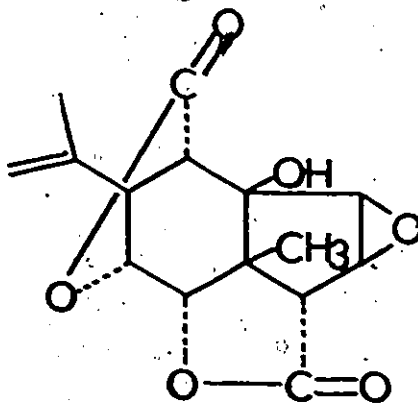


1

Figure 1 - Relative Configuration of Dendrobine

Since dendrobine contains fifteen skeletal carbon atoms, it seemed reasonable to think of this compound as a sesquiterpene. However, no unrearranged combination of three isoprene units can yield dendrobine. This places it in a realm of sesquiterpenes of abnormal structure known as the picrotoxanes.^{2,4} This name derives from the first known

atypical sesquiterpene, picrotoxinin 2.



2

Figure 2 - Picrotoxinin

The picrotoxanes contain both a terpenoid series, exemplified by coriamyrtin, tutin and mellitoxin, and an alkaloid series, and it is this latter group to which dendrobine belongs.

The question of the in vivo assembly of such an unusual carbon framework has stimulated considerable interest. Early experimental work by Okamoto¹¹, employing radioactively labelled mevalonic acid lactone, indicated that dendrobine did indeed have a mevalonoid origin. Subsequently, three possible routes to the picrotoxane skeleton were advanced in the literature.^{12,13,14} Recently, however, Edwards¹⁵, by employing 4- ¹⁴C- mevalonolactone 3 and carrying out the appropriate degradation procedures, was able to demonstrate that the incorporation of the radio-label was consistent with a biosynthetic pathway involving trans - cis farnesol 4, germacrane 5 and cadalane 6 skeletons.

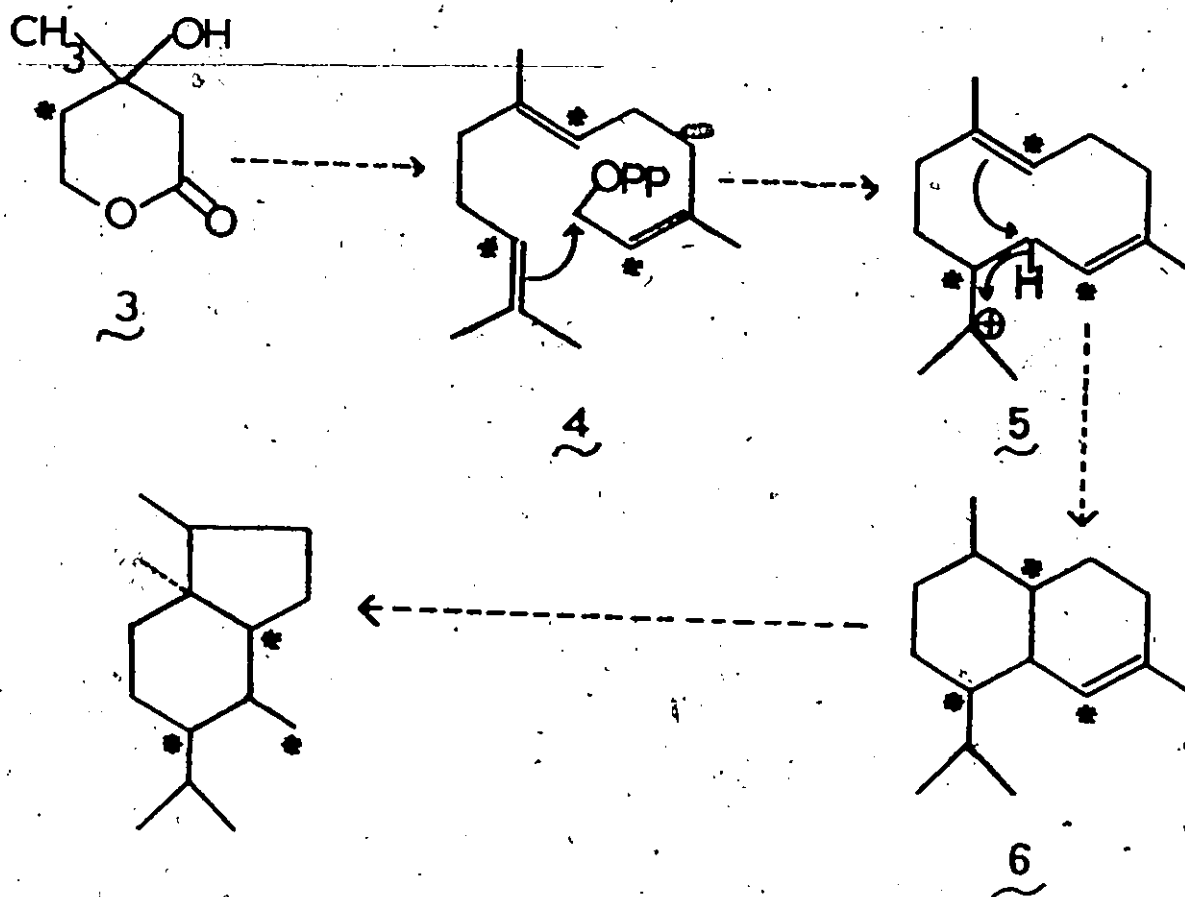


Figure 3 - Intermediates in the Biosynthesis of Dendrobine

Our interest in dendrobine as a synthetic objective arose from our familiarity with the investigations carried out by Edwards. An examination of dendrobine shows that it possesses seven asymmetric centres, with all six centres of the carbocyclic "A" ring being asymmetric. In addition, because all ring junctions are cis-fused, the molecule is forced into assuming the tightly locked cage arrangement characteristic of the picrotoxanes. These structural details taken together present an interesting and formidable challenge to the synthetic chemist.

After work was begun on this project, it quickly became evident that other groups were also interested in synthesizing dendrobine.

A report of the synthesis of the basic tricyclic dendrobine skeleton 8 soon appeared.¹⁶ A Diels-Alder reaction involving carvotanacetone 7 and butadiene followed by a ring contraction reaction was the central feature in this synthesis.

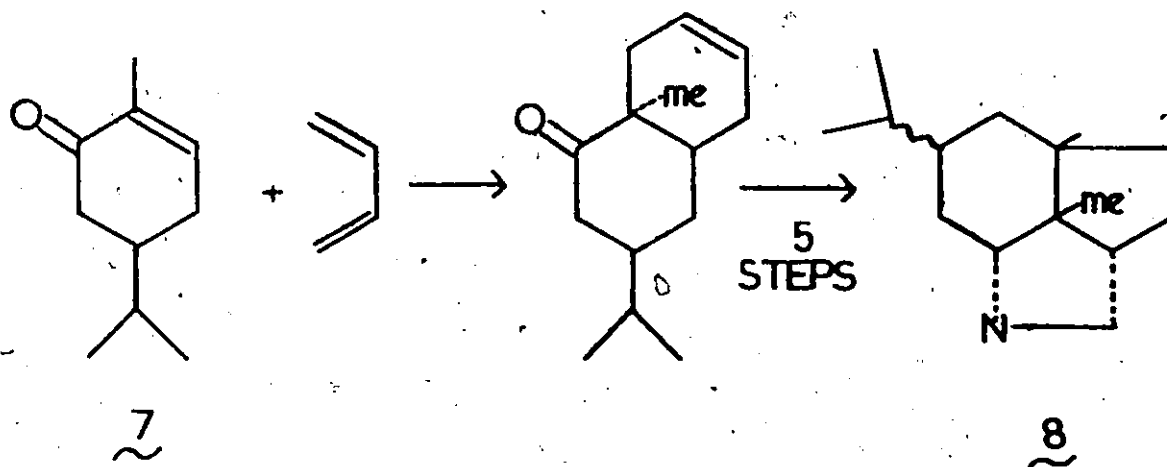


Figure 4 - Synthesis of the Unfunctionalized Dendrobine Skeleton

Soon, another Japanese group led by Yamada published a total synthesis of dl-dendrobine.^{17,18,19} Using as starting material, 3,4-dihydro-7-methoxy-5-methyl-1(2H)-naphthalenone, the synthesis of racemic dendrobine was completed in 21 steps. The crucial step in this elegant synthesis utilized a stereocontrolled synthesis for the cis-hydrindane skeleton developed by W.S. Johnson²⁰ and D.H.R. Barton.²¹ A 76% yield of the tricyclic intermediate 10 was isolated after an internal Michael-aldol reaction sequence was performed on the α - β -unsaturated ketone 9. (Figure 5).

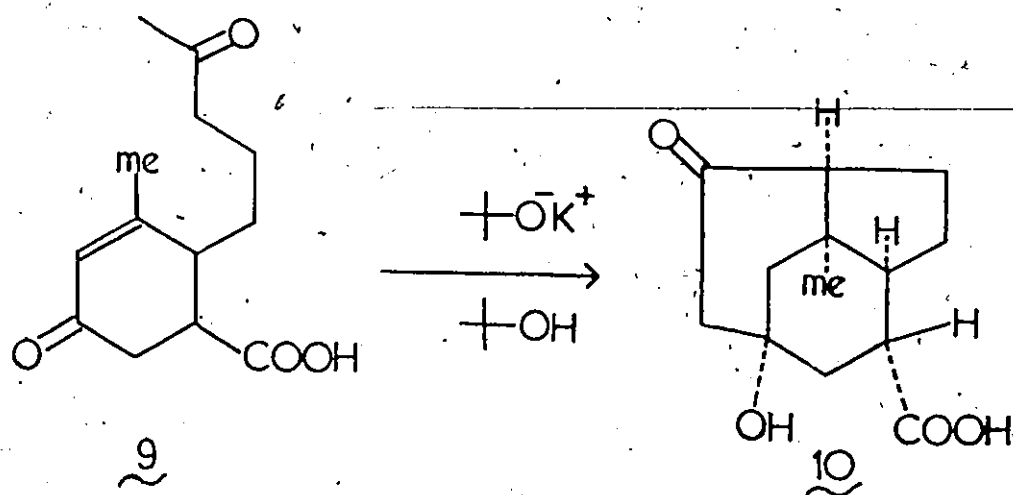


Figure 5 - The Central Reaction of Yamada's Dendrobine Synthesis

The main thrust of our own synthetic attempt was directed at the highly functionalized "A" ring, since it is this ring which bears the majority of asymmetric sites. A Diels-Alder reaction was envisaged as the central reaction in the proposed synthesis because of its well known stereoselectivity.²² The stereochemistry of Diels-Alder adducts is generally highly predictable because of stereochemical constraints embodied in the so-called Alder-Stein rules. The cis-principle dictates that the geometric arrangement of substituents in both the diene and dienophile components be preserved in the 1:1 Diels-Alder adduct. In addition, the Alder endo rule, sometimes termed the principle of maximum accumulation of unsaturation, often allows one to predict the relationship of the diene substituents to those carried by the dienophile. Finally, with unsymmetrically substituted dienes and dienophiles, there exist two possible modes of addition. Generally, however, it is observed that one mode of addition predominates. Although the Diels-Alder reaction is thought not to involve diradical intermediates, the predominate mode of addition can often be determined

by a consideration of the relative stabilities of this type of intermediate.²³

We believed that the Diels-Alder reaction was admirably suited for approaching the complex stereochemistry of dendrobine. The initial reaction could immediately establish stereochemistry at three points in the "A" ring and the further introduction of asymmetry would be controlled by these centres.

RESULTS AND DISCUSSION

Specifically, we hoped to employ 4-methyl-2-pentenoic acid 11 or a suitable derivative thereof as the dienophile, since the trans relationship of the isopropyl and carboxylate groups ensures a similar arrangement in the Diels-Alder adduct. This is precisely the required arrangement for dendrobine (Figure 6).

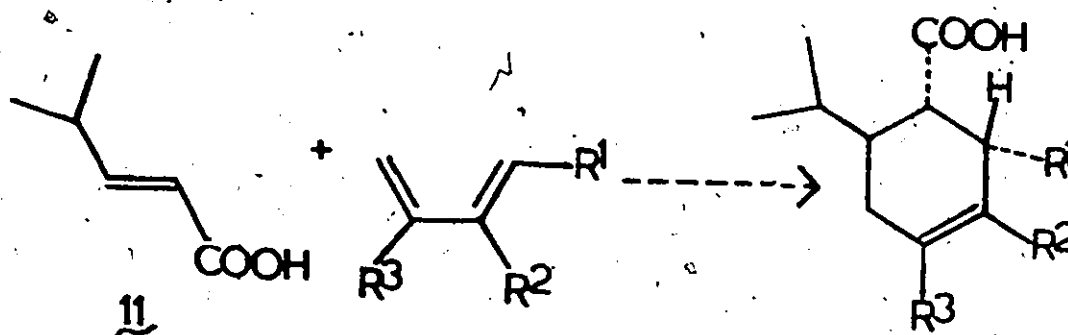


Figure 6 - Proposed Entry to "A" Ring of Dendrobine

This dienophile component presented no synthetic problems and was formed in one step from isobutyraldehyde and malonic acid by the Doebner modification of the Knoevenagel reaction.²⁴

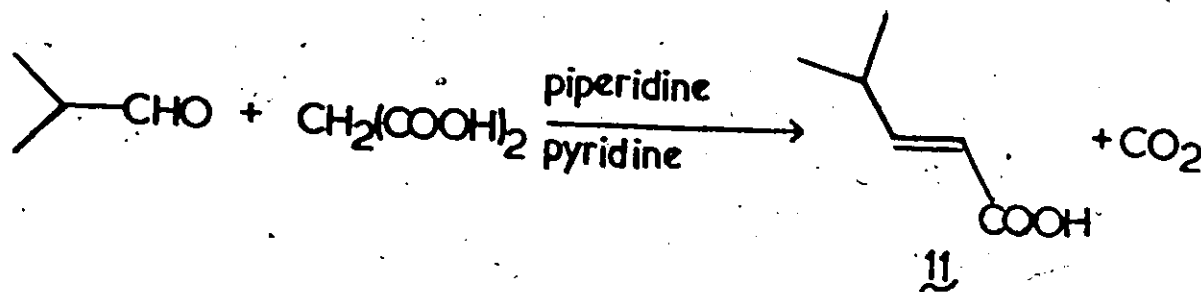


Figure 7 - Synthesis of 4-Methyl-2-Pentenoic Acid

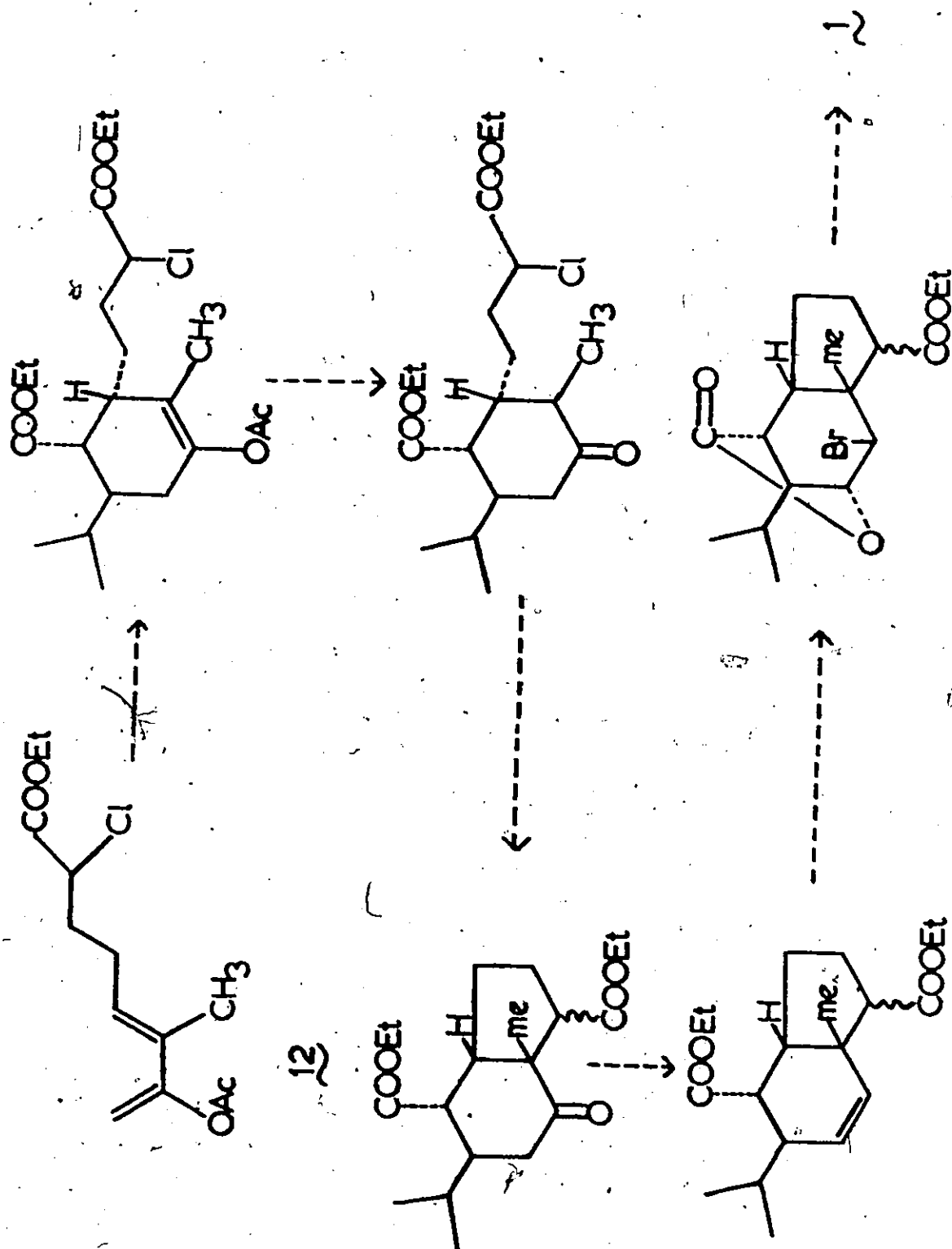
The general principle which was followed in the design of the diene components was to provide the dienes with reactive groups which could be used to effect further ring closures while affording the opportunity to establish the proper stereochemistry of the "A" ring.

The first diene whose synthesis was attempted was the acyclic diene 12 and its proposed elaboration into dendrobine is illustrated in Scheme I. This diene carries a reactive side chain as well as a methyl group destined for the angular position. The halolactonization reaction of this proposed synthesis demonstrates how the stereochemistry established by the initial Diels-Alder reaction would be used to control other points of asymmetry in the same ring. The projected synthesis of 12 is shown in Scheme II.

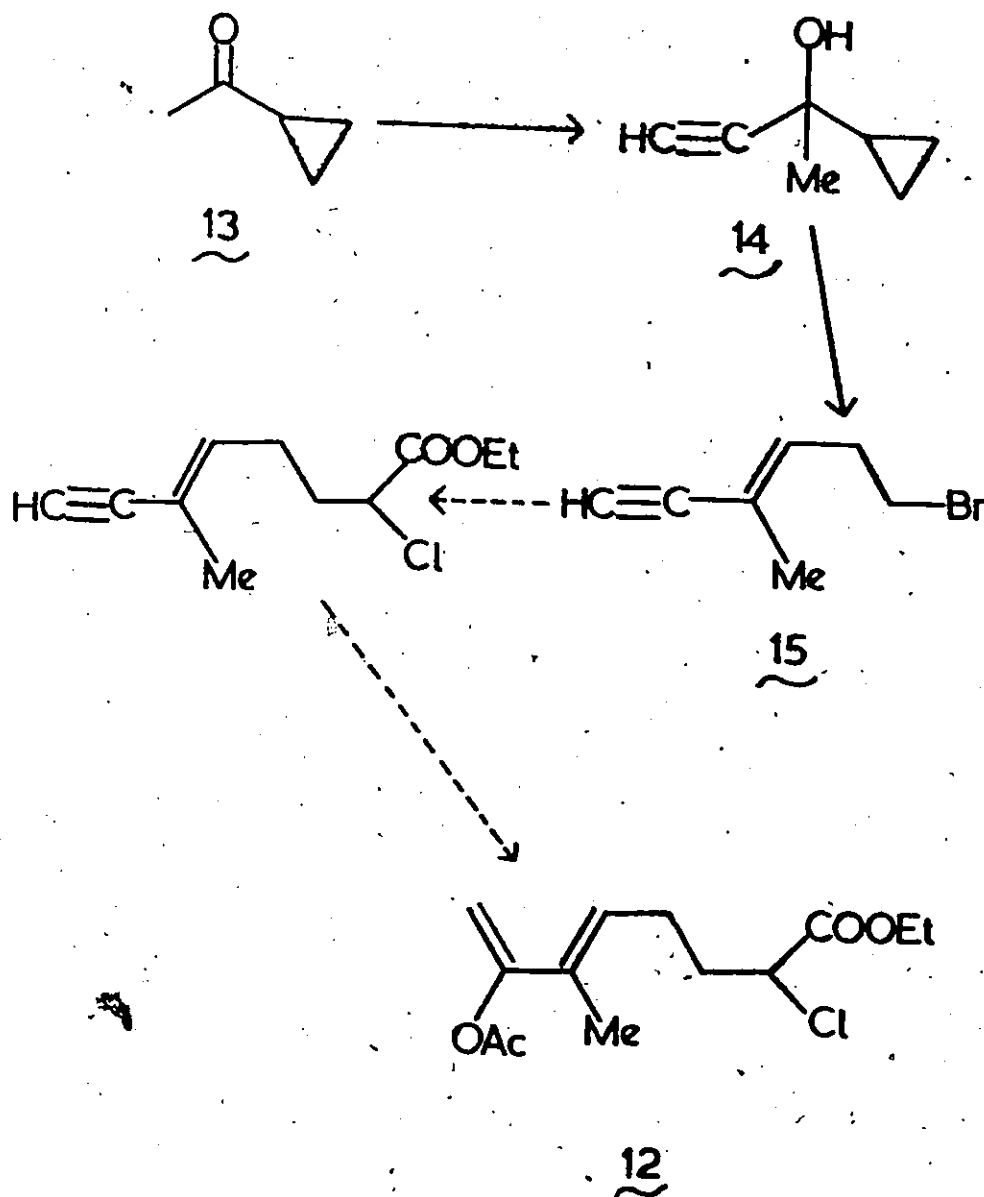
For this synthesis, a modification of the Julia olefin synthesis was adopted.²⁵ The addition of sodium acetylide to cyclopropyl methyl ketone 13 afforded the acetylenic alcohol 14 in good yield. Concomitant ring opening and dehydration of the alcohol by 48% HBr generated the enyne 15 in quantitative yield. However, all attempts to displace bromide by the anion of ethyl chloroacetate failed. Under all reaction conditions and in a variety of solvents, gas chromatographic examination of the reaction mixtures failed to reveal the desired product. Since the displacement of bromide by cyanide ion proved to be a facile reaction as reported²⁵, we have no satisfactory explanation for the failure of this reaction.

Our attention was subsequently directed to the synthesis of a similar diene 16 contained in an indan skeleton. The projected

SCHEME I



SCHEME II

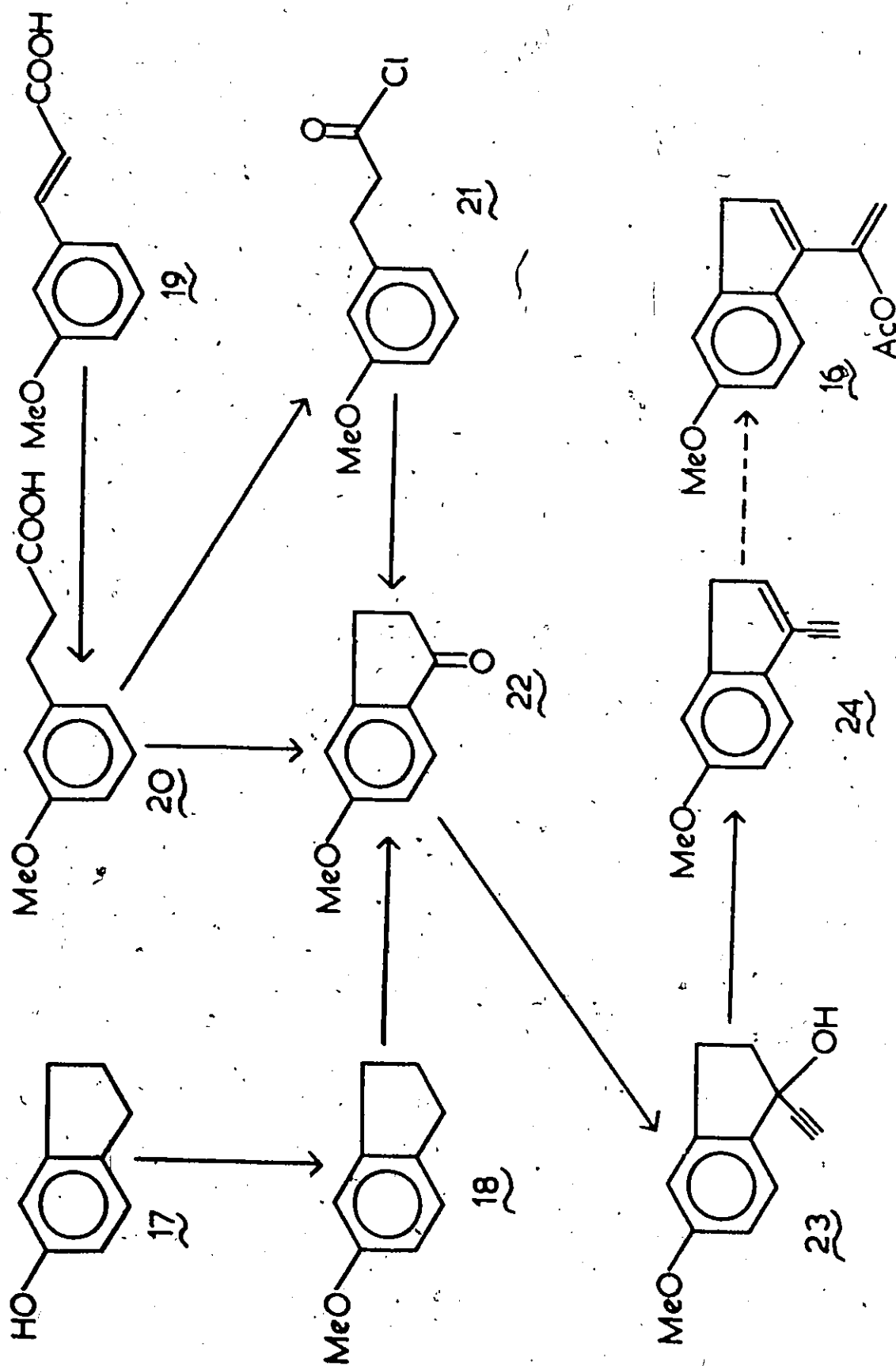


use of this compound in a synthesis of dendrobine is illustrated in Scheme III. The aromatic nucleus would serve as a platform on whose substituents the majority of synthetic operations would be performed. Final functionalization could then be achieved by a disruption of the aromaticity of this ring through Birch reduction. We hoped to solve the problem of angular methyl group insertion by applying the method of House²⁶ on the Diels-Alder adduct. Alkylation of non-symmetric ketones generally leads to a variety of products and di- and tri-substitution are the rule rather than the exception. House, however, has shown that enol acetates can be employed for the monoalkylation of ketones. By reaction of the enol acetate with two equivalents of methyl lithium, the lithium enolate can be generated in a regiospecific manner and alkylation with methyl iodide affords the desired monoalkylated product. The thermodynamically favoured cis-bicyclo[4.3.0]nonane ring system would be expected to result from this operation.

The proposed synthesis of the diene is depicted in Scheme IV. The synthesis of the indanone 22 was accomplished in a number of ways. The initial synthesis employed m-methoxycinnamic acid 19 as a starting material. After hydrogen reduction, the hydrocinnamic acid 20 could be cyclized either by dehydration²⁷ or by an internal Friedel-Craft acylation reaction.²⁸ Average yields of approximately 60% were obtained in each instance. As evidenced by their nuclear magnetic resonance (nmr) spectra, each reaction produced a mixture of isomers (5- and 7- methoxy-indanones) but the desired isomer could be obtained relatively pure by repeated recrystallization.

A more economical procedure and one which yields an isomerically pure product has been described by Panetta and Bunce.²⁹ Starting with

SCHEME IV



5-indanol 17, the required ketone was realized in 75% yield after methylation and oxidation.

Difficulties arose at this point. The standard methods for the preparation of acetylenic alcohols require the use of acetylenic organometallic reagents. Lithium acetylide generated in liquid ammonia and ethynyl magnesium bromide in both tetrahydrofuran and dioxane were employed in an attempt to generate the acetylenic alcohol. The results of these reactions were very discouraging, as only small yields of the required alcohol could be recovered.

We resorted to a stabilized form of lithium acetylide, the ethylene diamine complex, which had been reported to be useful in certain instances.³⁰ Again, only small yields of the acetylenic alcohol could be recovered. Consistently, the products of all the above reactions proved to be dark oils containing starting ketone, acetylenic alcohol and enyne resulting from dehydration of the alcohol. Vacuum distillation failed to effect a separation of these components and very crude separations of the alcohol darkened quickly, even under an inert atmosphere at low temperature protected from light.

Perhaps the main reason for the failure of this reaction is that the carbonyl group of this indanone is extremely resistant to nucleophilic attack because of the resonance effect of the methoxy group. This severe damping of carbonyl character does not affect reductions by strong reducing agents such as lithium aluminum hydride (78% yield of corresponding alcohol.²⁹) However, reactions involving acetylenic organometallics generally cannot be run at temperatures exceeding 40° because of the well-known propensity of this type of compound to

disproportionate. Consequently, reactions involving these reagents are typically run at room temperature with relatively long reaction times. In our case, reaction times of from four days to a week using a three-fold excess of reagent were employed and under these conditions yields were extremely poor. Crude preparations of the alcohol 23 were dehydrated to the enyne 24, but the resulting dark oil was exceptionally unstable. Although the enyne could be isolated as a low melting white solid by preparative scale thin-layer chromatography, decomposition readily occurred within 24 hours, even when elaborate precautions were taken. The tendency of similar systems to polymerize has been noted in the literature.³¹ Since the low yields and instability of these intermediates were clearly unacceptable, this approach was abandoned and less conventional dienes were considered for the Diels-Alder approach to dendrobine.

CHAPTER II

An attractive alternate approach to solving the difficult stereochemical problems associated with dendrobine involved the utilization of an α -pyrone 25 as a Diels-Alder diene.

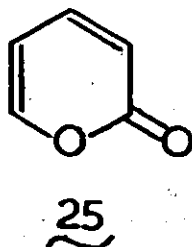


Figure 8 - α -Pyrone

The α -pyrones are extremely interesting compounds. In nature they are found both in plant and animal species. In particular, they form part of the cardioactive glycosides found in the red squill plant (*Urginea maritima*) as well as in various toad venoms.^{32,33} The physiological activity of these glycosides resides chiefly in the aglycone residue where the 17 β -sidechain of the steroid nucleus takes the form of a 5-substituted α -pyrone.

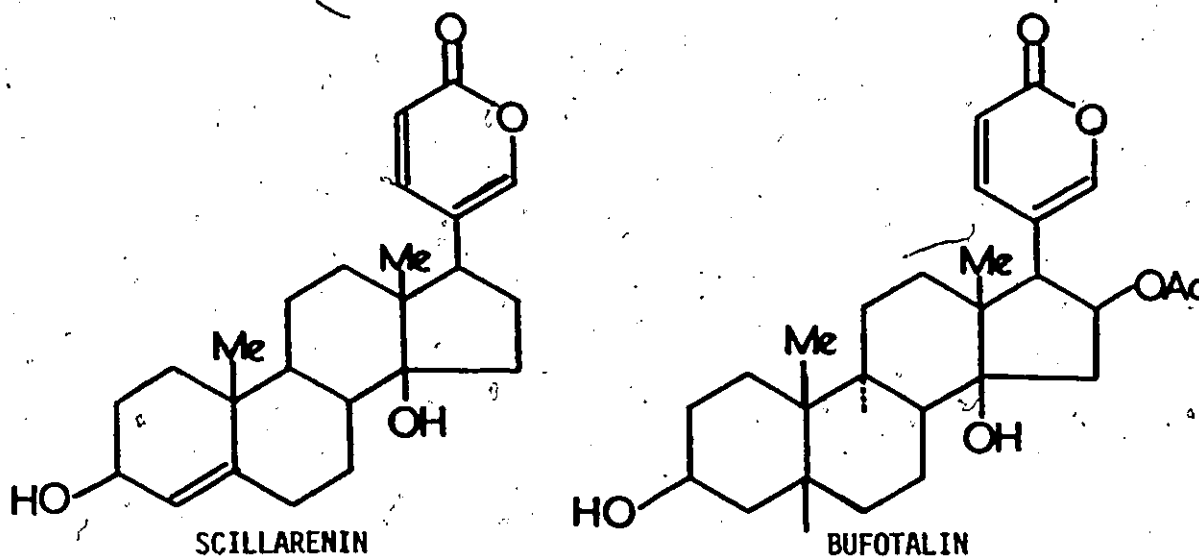


Figure 9 - Cardioactive Glycosides Containing the α -Pyrone Chromophore

The glycosides of plant origin (scilladenolides) are widely used as rodenticides while the toad venoms (bufadienolides) have long been employed by certain South American tribes as lethal blowdart poisons. These poisonous principles are roughly equivalent in toxicity to curare and strychnine. Some bufadienolides have been shown to possess a potent inhibitory action against cells derived from human cancers.³⁴

As a result, there has been considerable interest in developing synthetic methods for the attachment of the α -pyrone chromophore to steroid nuclei and several naturally occurring bufadienolides have recently been synthesized.^{35,36} The chemistry of α -pyrone itself has been the object of renewed interest³⁷, particularly its reactions with nucleophiles^{38,39}, its photochemistry^{40,41}, and its behaviour as a Diels-Alder diene.^{42,43}

Von Pechmann first prepared the parent compound, α -pyrone 25, by pyrolyzing the mercury salt of coumalic acid.⁴⁴

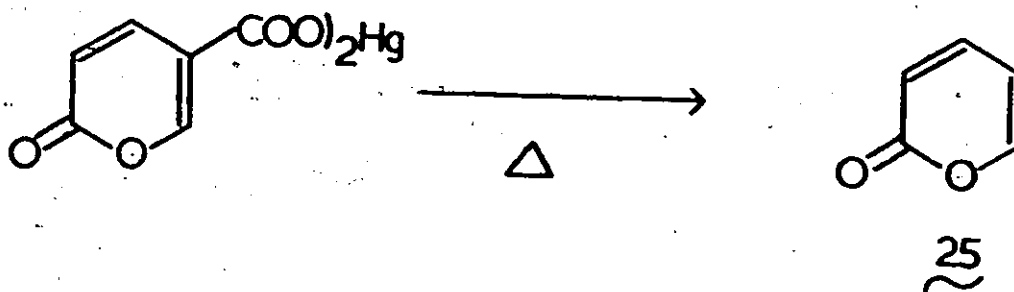


Figure 10 - Von Pechmann's Preparation of α -Pyrone

This compound exhibited excellent properties as a Diels-Alder diene with the classical dienophiles.⁴² Since α -pyrone can be viewed as possessing both an electron withdrawing group as well as an

electron donating substituent, in theory, it should exhibit useful reactivity with a wide range of dienophiles.

Zimmerman ably demonstrated the synthetic utility of α -pyrone in his novel synthesis of the theoretically interesting molecule barreleñe 26,⁴⁵ (Scheme V). Seyferth has used the α -pyrone nucleus as an entry to highly strained stannane systems 27 inaccessible by conventional methods.⁴³ (Scheme V). In light of results such as these, it is somewhat surprising that α -pyrones have not found greater use as synthons.

The 1:1 Diels-Alder adducts of α -pyrones contain a bridging lactone structure which is thermally unstable and at relatively low temperatures, undergoes a retrograde Diels-Alder reaction eliminating carbon dioxide and forming a new diene. It was hoped that if mild reaction conditions were employed, one could largely avoid the loss of CO_2 and maintain the lactone intact. Because bridged systems such as these possess a favoured direction of approach, one could establish stereochemistry by hydrogen reduction of the remaining double bond.

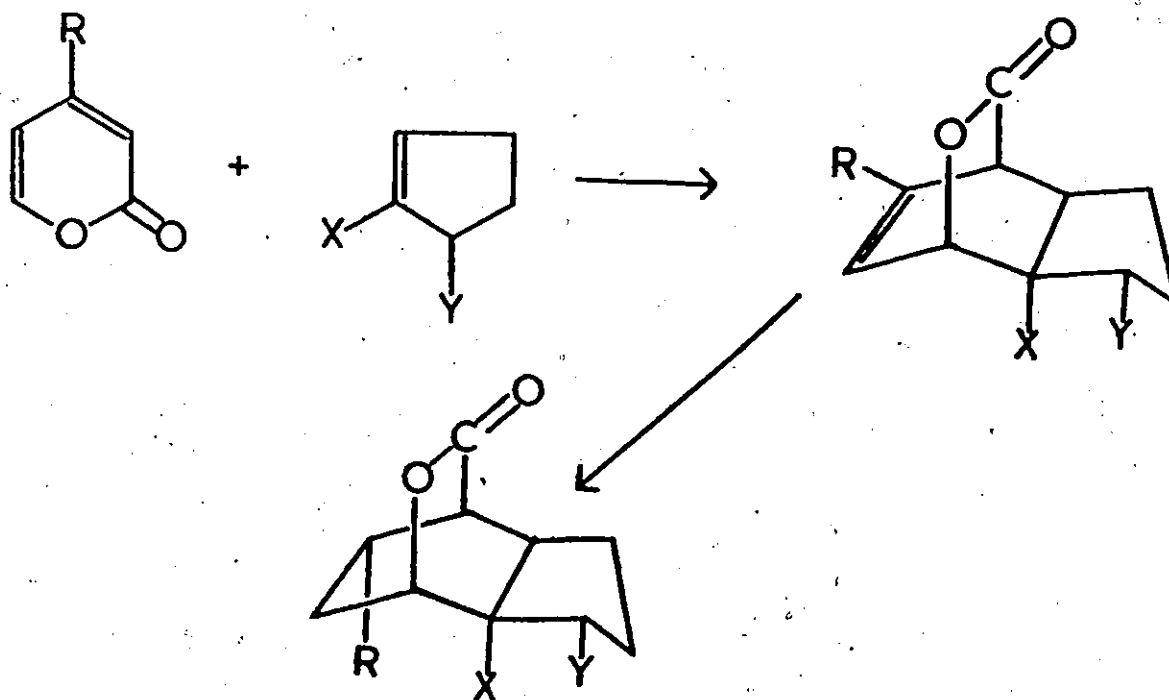
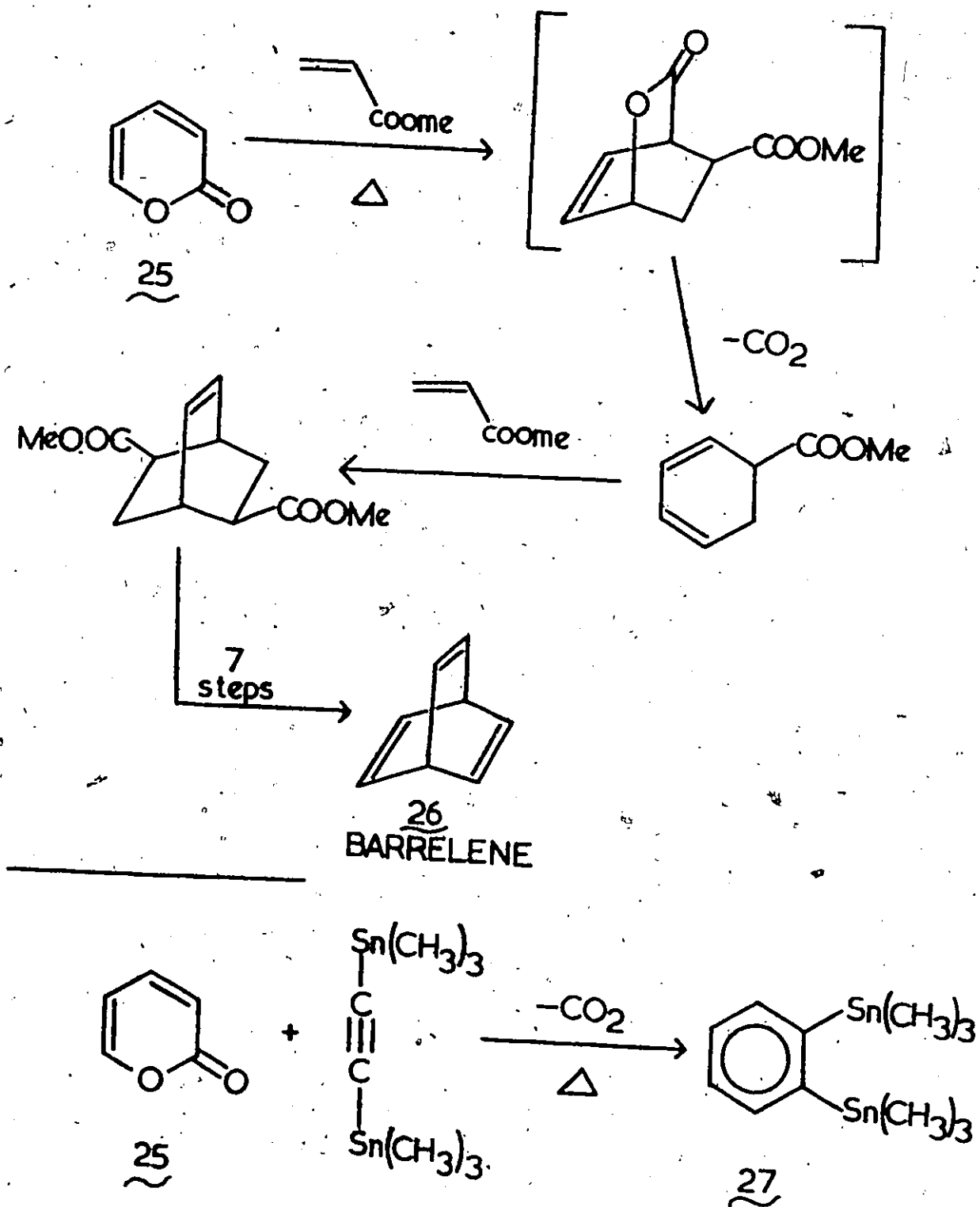
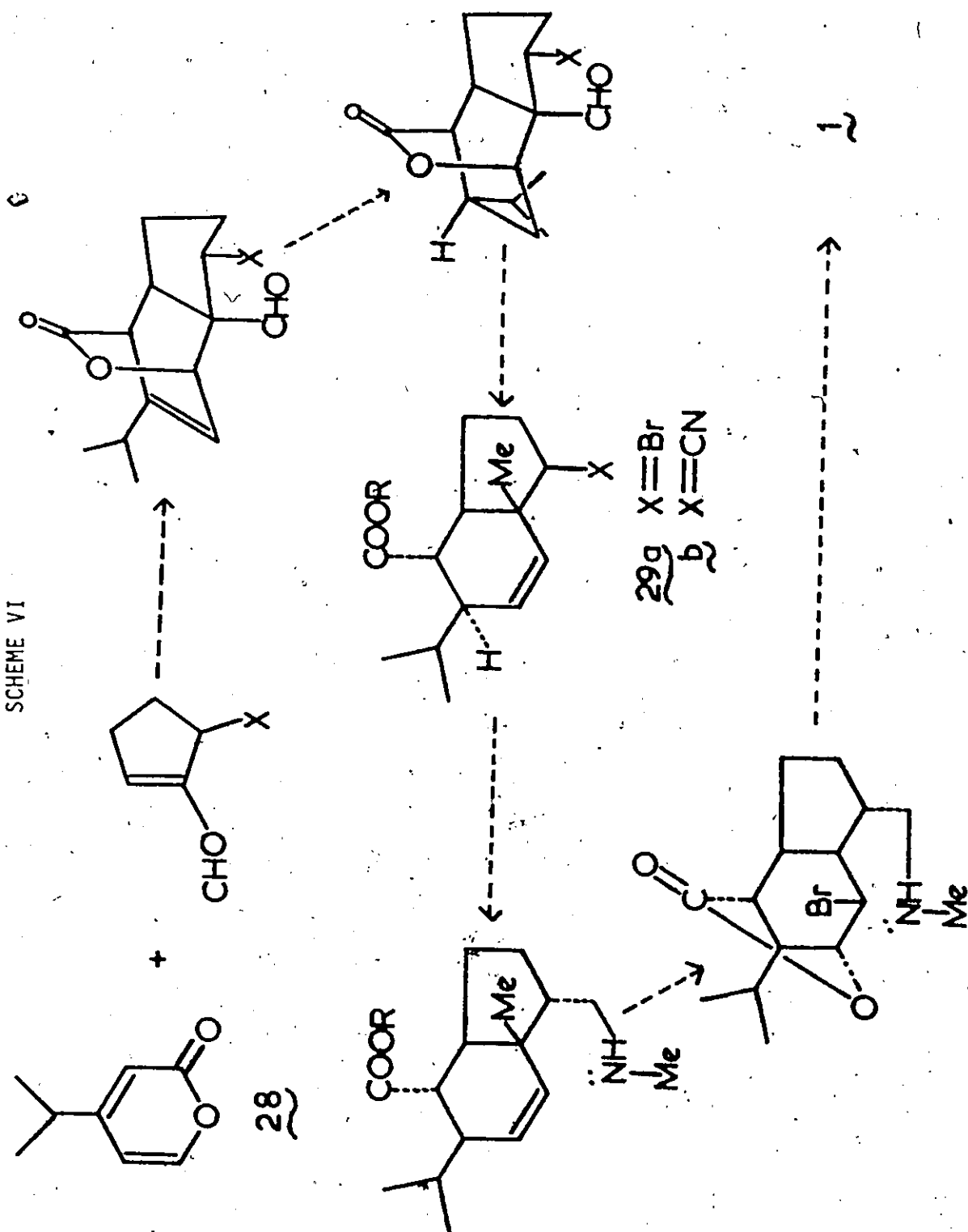


Figure 11 - Hydrogen Reduction of the α -Pyrone Diels-Alder Monoadduct

SCHEME V



SCHEME VI



In the majority of reported instances, the Diels-Alder diadduct was isolated. This arises by a second addition of dienophile to the diene formed by thermal elimination of CO_2 from the monoadduct. However, a Russian group led by Shusherina has shown the feasibility of stopping the reaction after the addition of one mole of dienophile.⁴⁶ By employing N-phenylmaleimide as the dienophile and utilizing various α -pyrones, they were able to obtain the monoadducts in boiling benzene or toluene as solvent. Raising the reaction temperature to 140° , however, caused elimination of CO_2 and formation of the diadduct.

Clearly the pyrone required for the Diels-Alder reaction was 4-isopropyl-2-pyrone 28 and its projected use in the synthesis of dendrobine is depicted in Scheme VI. Unfortunately, a survey of the literature revealed that with the exception of methyl and deuterium substitution³⁷ there were no known examples of α -pyrones substituted solely in the 4 position. The synthesis of α -pyrone derivatives has been reviewed^{47,48,49}. Of three generalized approaches to α -pyrones, only cyclization reactions can be employed to generate monoalkylated pyrones. Basically there are two systems which can be satisfactorily cyclized, the glutaraldehydic acids (figure 12) and the glutaconic acids (figure 13).

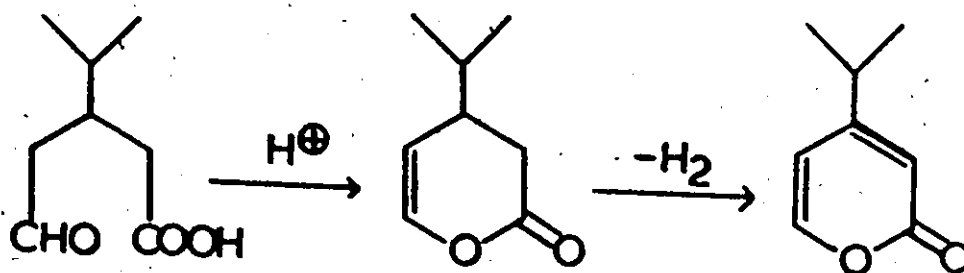


Figure 12 - Cyclization of a Glutaraldehydic Acid

The enol form of a glutaraldehydic acid can be lactonized under acid catalysis forming an enol lactone, and there exist a number of methods for introducing the final degree of unsaturation.^{35,36}

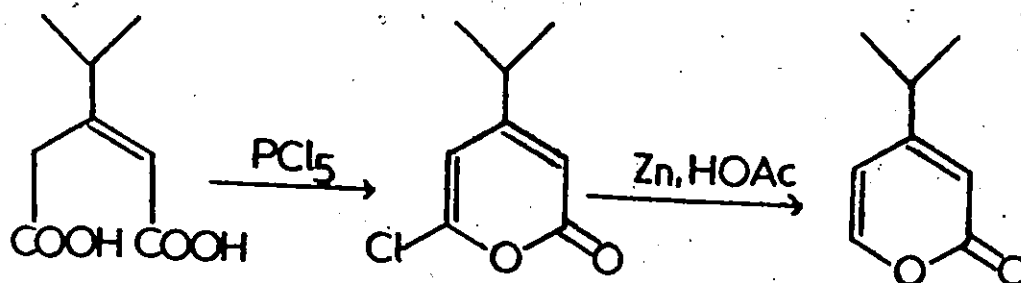


Figure 13 - Cyclization of a Glutaconic Acid

Glutaconic acids yield 6-chloro-2-pyrones directly on heating with phosphorus pentachloride. The halogen may then be removed by zinc-acetic acid reduction to yield the α -pyrone.³⁷

Subsequent to the completion of this project an abstract of a doctoral dissertation appeared which described an attempt to employ 4-isopropyl-2-pyrone in a Diels-Alder synthesis of dendrobine.⁵⁰ The design of this synthetic approach remarkably paralleled our own and an attempt will be made to compare and contrast this work with our own.

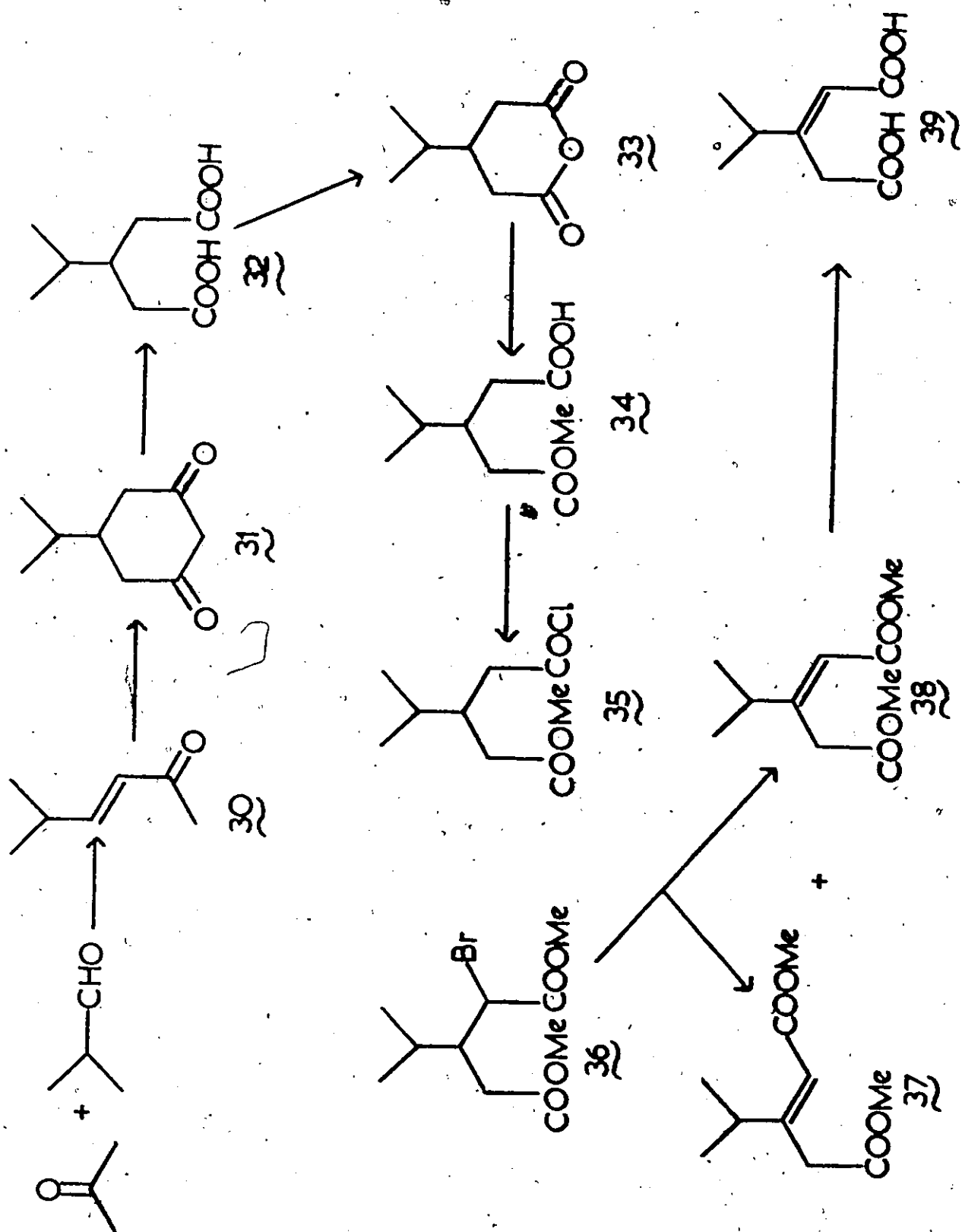
RESULTS AND DISCUSSION

The synthesis of 3-isopropyl glutaconic acid 39 was attempted first. This diacid had already been the object of two unsuccessful syntheses.^{51,52} Our projected synthetic method is illustrated in Scheme VII.

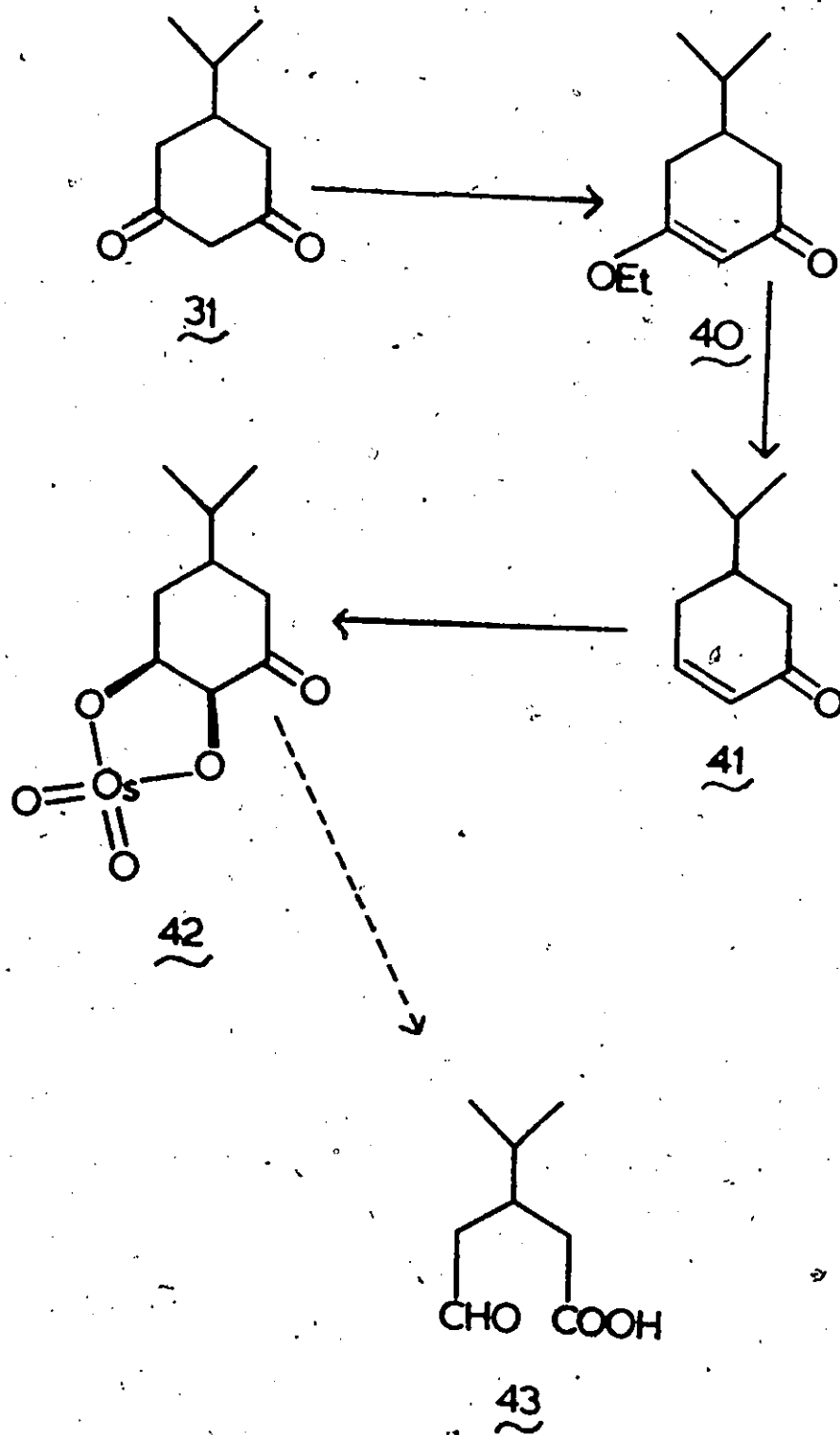
The known 5-isopropyl -1,3- cyclohexanedione 31⁵³ was oxidatively opened to the glutaric acid 32 whose half-ester 34 was prepared via the anhydride 33. This half-ester was converted to the monoacid chloride 35 with SOCl_2 and brominated in the presence of excess SOCl_2 as solvent.⁵⁴ The product of this reaction was immediately quenched with excess methanol to yield the dimethyl bromoglutarate 36. Subsequent distillation gave an approximately equimolar mixture of cis and trans- dimethyl glutaconates 37 and 38. Because it proved extremely difficult to effect a separation of the synthetically useful isomer, 38, this synthesis was abandoned in favour of the glutaraldehydic acid 43 (Scheme VIII).

The same cyclohexanedione 31 could be converted to the vinylogous ester 40 which was reduced with lithium aluminum hydride to the cyclohexenone 41. We had hoped to selectively oxidize this system to the glutaraldehydic acid 43. Woodward, in his synthesis of reserpine⁵⁵, employed osmium tetroxide to oxidize an α,β - unsaturated ketone to a vic-diol. This compound was further oxidized to an aldehydic acid by periodic acid. In view of the expense of osmium tetroxide, a modification of this procedure was adopted, in which the osmium tetroxide is used catalytically in conjunction with barium chlorate.⁵⁶ In this instance, the intermediate osmate ester is oxidized by chlorate ion, regenerating osmium tetroxide and yielding the vic-diol. When this procedure was applied to compound 41, the osmate ester did form, as witnessed by its black colour, but it proved extremely

SCHEME VII



SCHEME VIII

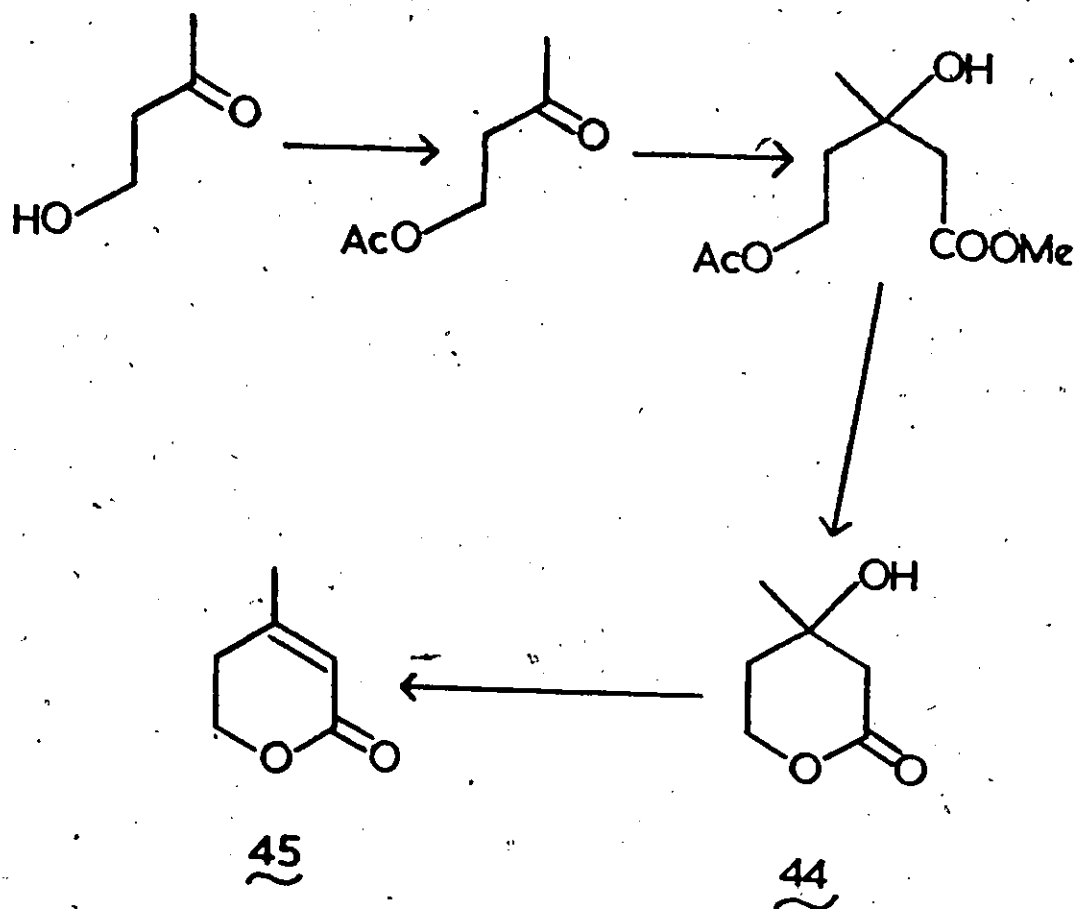


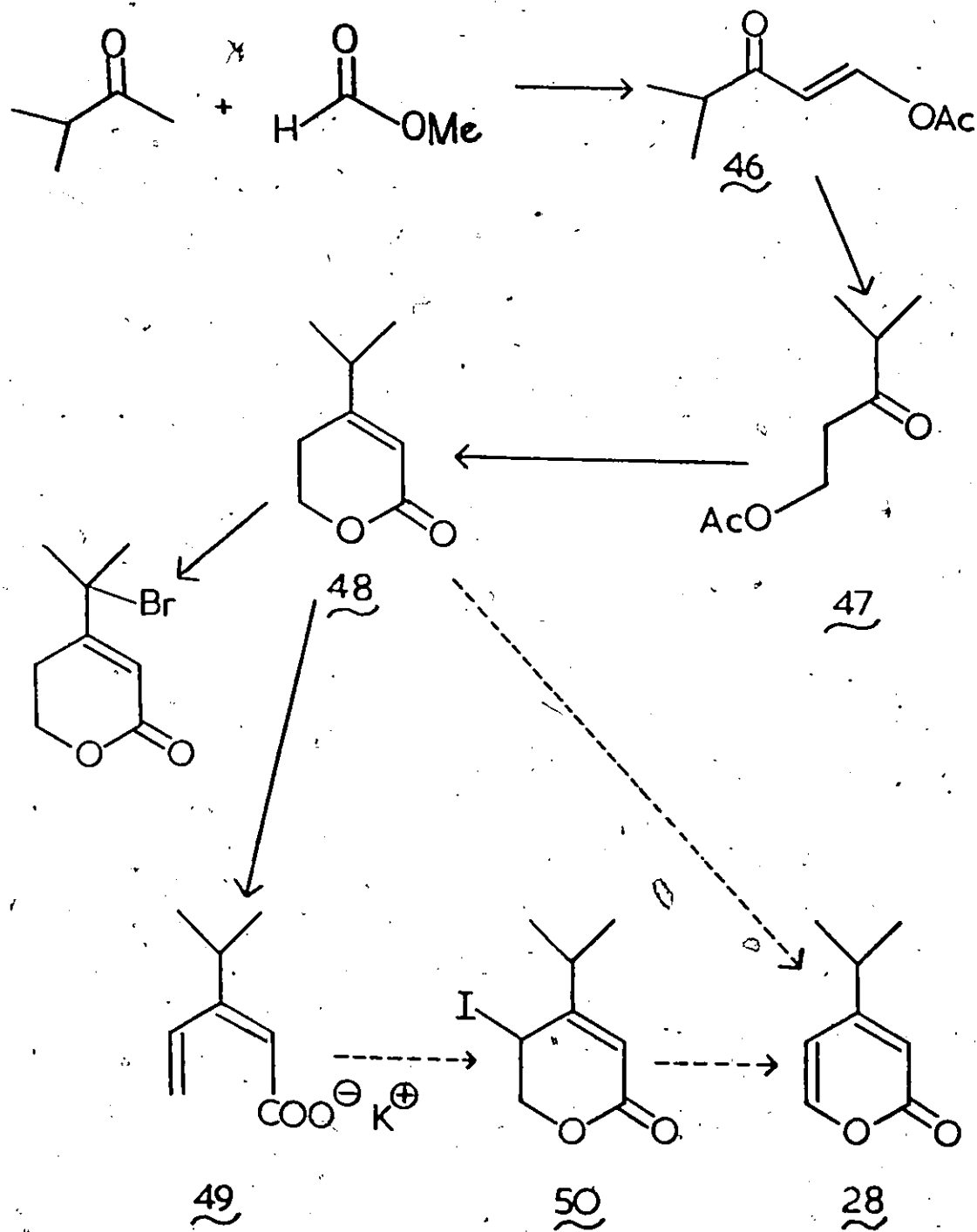
resistant to oxidation under all conditions.

Cornforth's well-known synthesis of mevalonolactone 44⁵⁷ (Scheme IX) was considered as an alternate approach to the required pyrone. If the unsaturated δ -lactone could be suitably functionalized at the 4-position, this would provide an opportunity for introducing the second double bond of the pyrone.

The enolate ion from the Claisen condensation of methyl isopropyl ketone and methyl formate was quenched with acetyl chloride to yield the keto enolacetate 46, (Scheme X). Hydrogen reduction of the carbon-carbon double bond afforded the keto ester 47 in quantitative yield. A Reformatsky reaction employing ethyl bromoacetate proved to be very sluggish and the reaction could only be initiated at very high temperature. After normal work-up, the product was not the expected β -hydroxy ester but rather the δ -lactone 48. This reaction had produced in one step the same type of transformation that Cornforth had carried out in three steps and a comparable overall yield was obtained. All attempts to functionalize this compound failed, however. Allylic bromination by N-bromosuccinimide functionalized the tertiary position of the isopropyl group as expected.⁵⁸ Treatment of the lactone with selenium dioxide in both refluxing tert-butyl alcohol and acetic acid, procedures known to effect dehydrogenation,^{59,60} yielded only starting material. Attempted dehydrogenation using palladium on charcoal, in p-cymene as solvent,⁶¹ unexpectedly led to reduction of the double bond of the lactone. The use of sulfur for dehydrogenation, a method used with some success in bufadienolide syntheses,^{35,36} was also investigated. Hydrogen sulfide was evolved when the lactone was dropped onto molten sulfur, an indication

SCHEME IX





that dehydrogenation had occurred, but the product was an intractable tar. The well documented base induced ring opening of lactones such as 48 was confirmed and the potassium salt of the dienolic acid 49 could be isolated in good yield.⁶² All attempts to recycle this compound by halolactonization to a functionalized δ -lactone 50 were unsuccessful, however.

The approach which eventually did lead to the synthesis of the desired pyrone is outlined in Scheme XI. Subjecting the known keto acetal 51⁶³ to both Reformatsky and Wittig reaction conditions did not provide the required product. In contrast to the results of Wade⁵⁰ who reported only the isolation of starting materials from these reactions, a fact which he attributes to steric hindrance by the isopropyl group, these reactions in our hands gave high yields of the keto enol ether 52. Clearly the Reformatsky and Wittig reagents are acting as strong bases in these reactions, and this result is paralleled by the formation of 52 from 51 by simple distillation from a catalytic amount of sodium methoxide.⁶⁴

The Minnesota workers did synthesize the β -hydroxy ester 53 by applying the relatively new procedure of Rathke.⁶⁵ In this procedure, the keto acetal 51 was added to lithio ethyl acetate generated quantitatively at -70° by lithium bis(trimethylsilyl) amide. The resulting β -hydroxy ester was hydrolyzed, dehydrated, and cyclized to the α -pyrone 28 in an overall yield of 37%. These same workers found that this reaction sequence could be applied equally well to the keto enol ether 52. The β -hydroxy ester 54 also yielded the pyrone when the usual dehydration procedures were employed.

We found that the pyrone 28 could be formed by a Reformatsky reaction

on the keto enol acetate 46. The distilled product of this reaction, isolated in 36% yield, was identical in all respects to Wade's pyrone. Since the reaction was carried out at high temperature with no attempt to moderate the reaction, any postulated mechanism for this unusual cyclization reaction is highly speculative. A possible mechanism is suggested in figure 14.

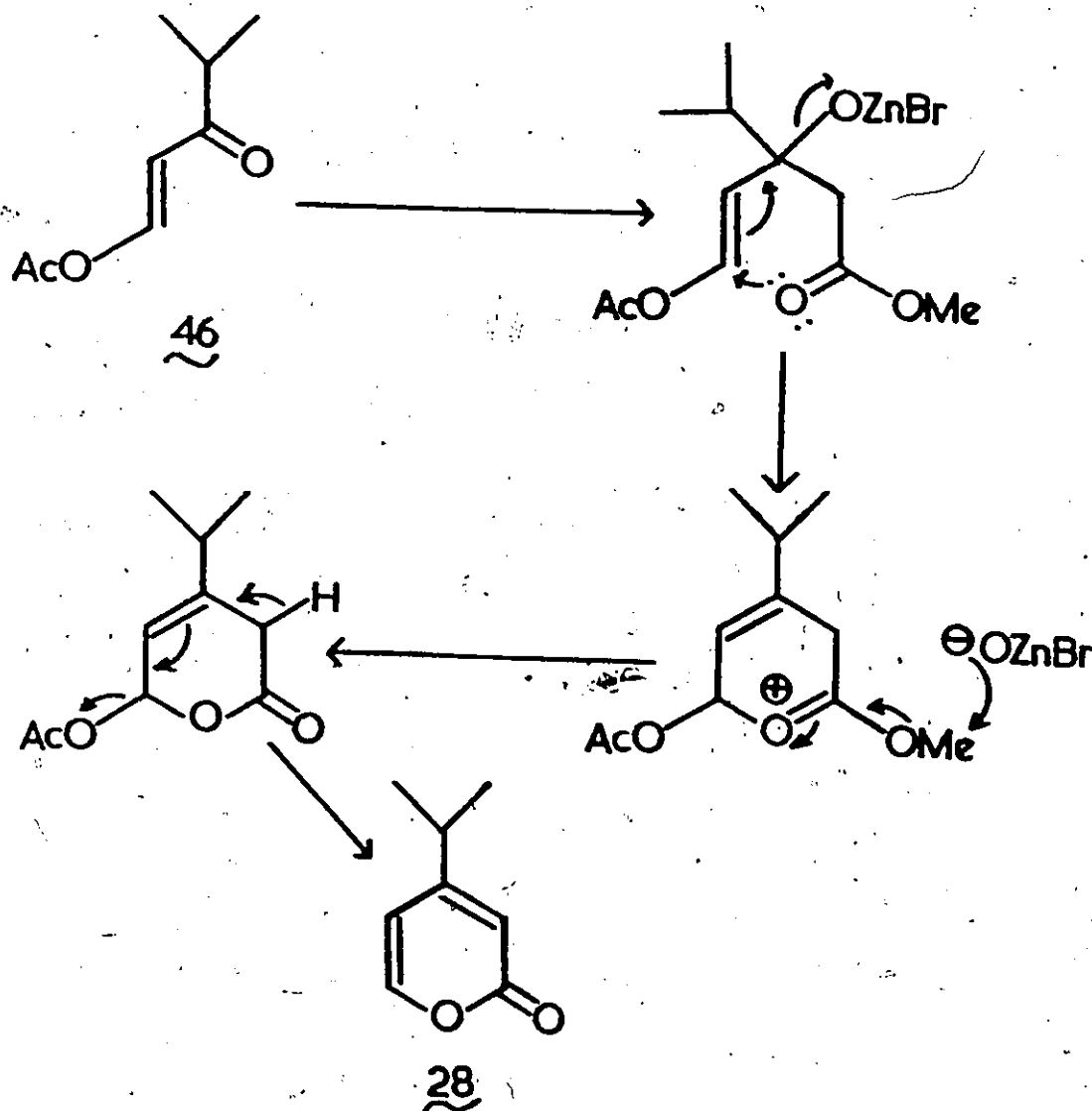
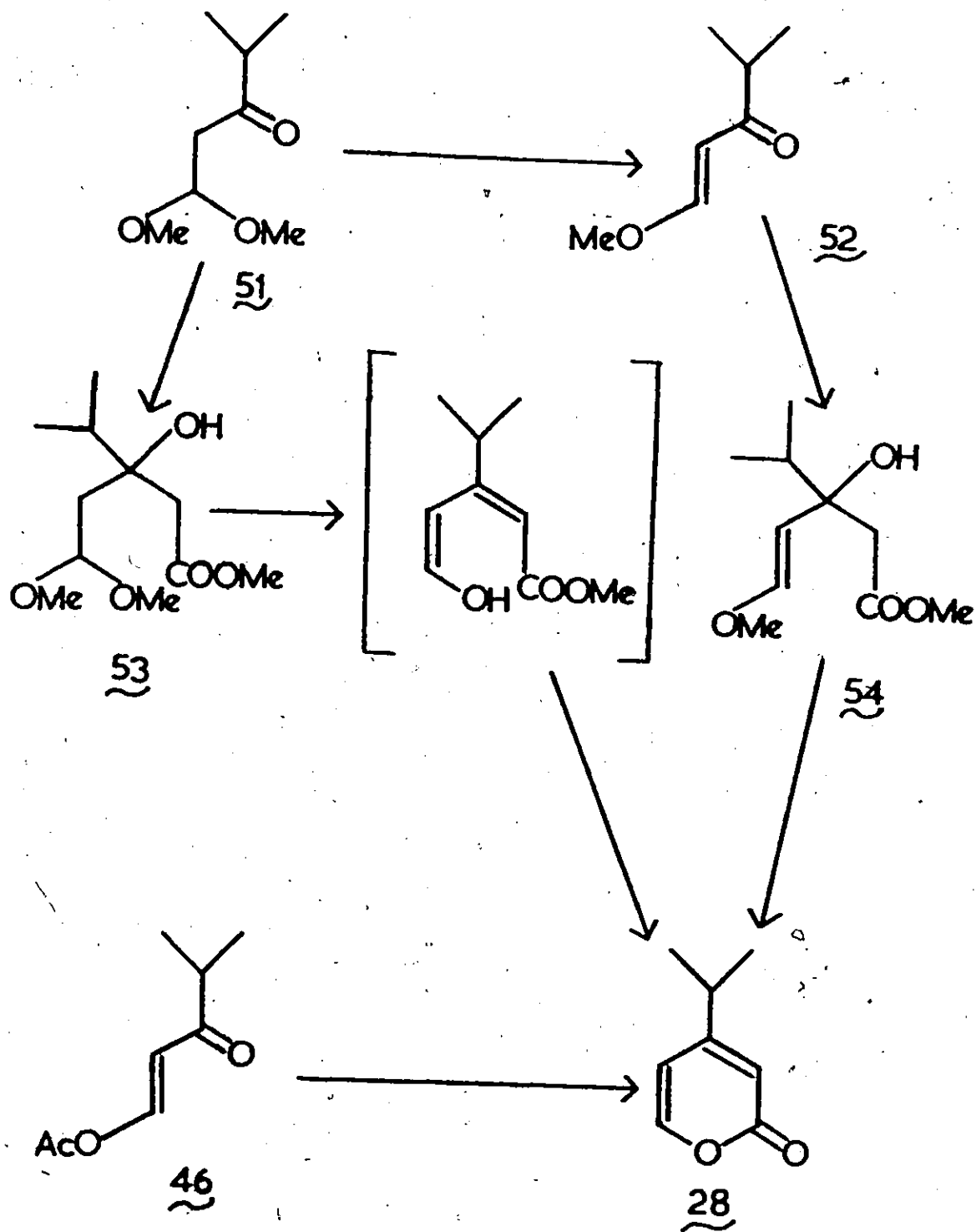


Figure 14 - Possible Mechanism for the Formation of α -Pyrone 28

SCHEME XI



With the required pyrone in hand, we proceeded to investigate its properties as a Diels-Alder diene. Unfortunately it proved to be a very poor one. Both dimethyl acetylenedicarboxylate and maleic anhydride, two excellent dienophiles, failed to react with this pyrone when stirred together at room temperature for a week. Raising the temperature to that of refluxing benzene also failed to effect a reaction.

The attempts by Wade to utilize 28 in similar reactions also met with failure. He found that under various conditions of time, temperature, solvent and Lewis acid catalysis, the dienophiles 55, 56 and 57 did not react. A Diels-Alder adduct was obtained with maleic anhydride but only after extended refluxing of the two components in toluene. In this case, the product was shown to be the diadduct 58 which, of course, was unsuitable for the proposed synthesis of dendrobine. Because of the exceptional stability of this pyrone, high temperatures were required to force it to react and under these conditions only the diadduct could be isolated. Manipulation of the reaction conditions either led to no reaction or formation of the synthetically useless diadduct.

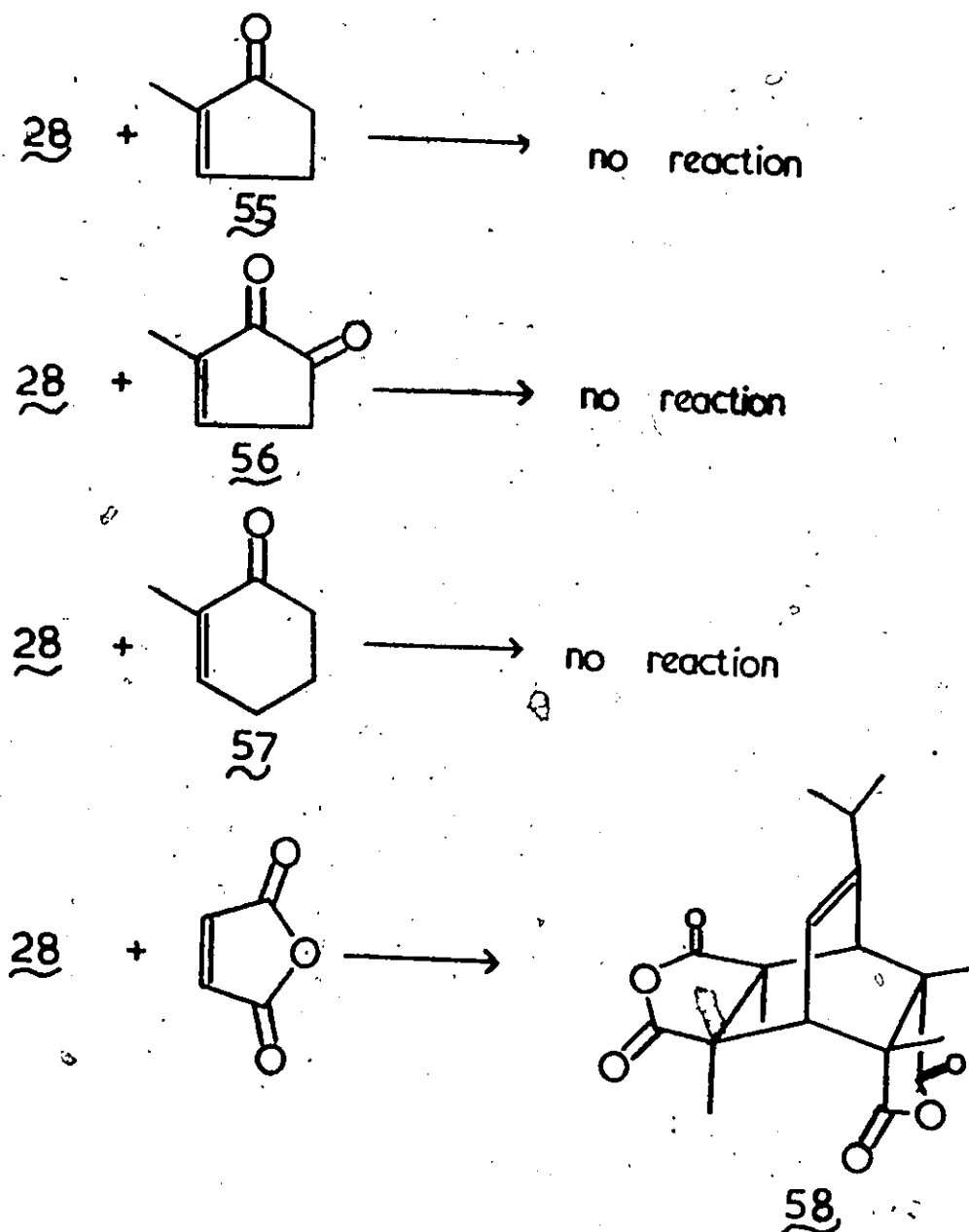


Figure 15 - Diels-Alder Reactions of α -Pyrone (28)

CHAPTER III

The advantages offered by the Diels-Alder reaction for approaching stereochemically complex structures has already been mentioned. Our own experience verified the fact that perhaps the reason this approach has not been put to greater use is the difficulties that arise in synthesizing highly functionalized conjugated dienes for this reaction. Synthetic methods for the dienophile components, most often unsaturated carbonyl compounds, are well established, but regiospecific and stereospecific syntheses of the dienes are generally much more difficult.

One procedure for the production of dienes which has received comparatively little attention has been the thermal decomposition of 2,5 - dihydrothiophene - 1,1 - dioxides 56.

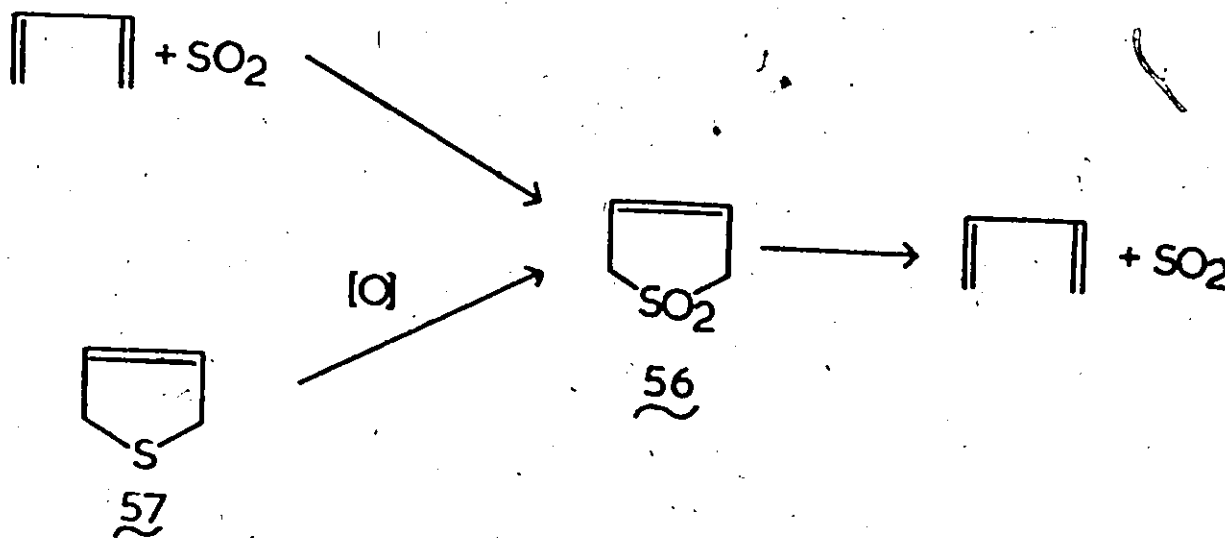


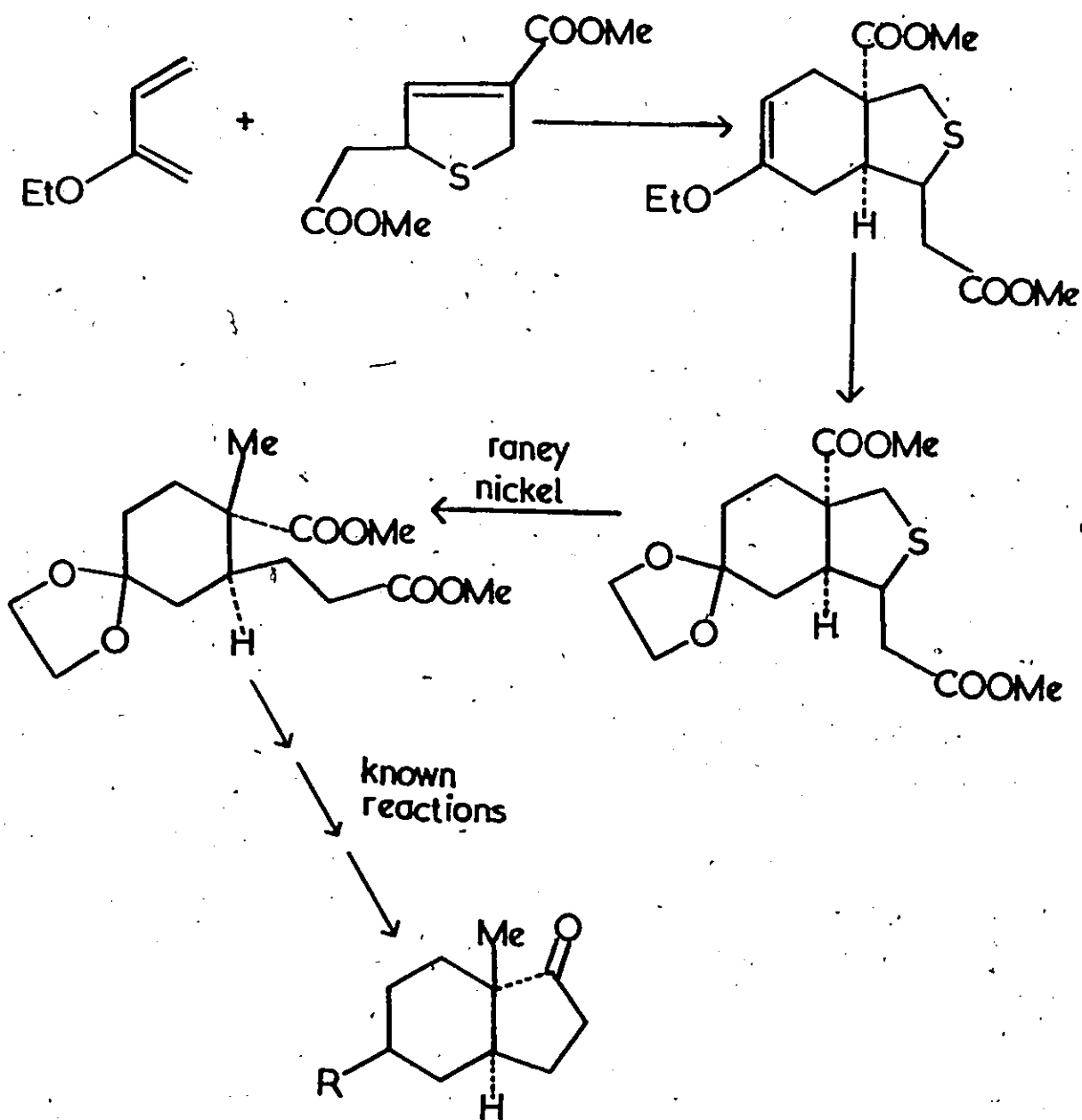
Figure 16 - Thermal Decomposition of 2,5 - Dihydrothiophene - 1,1 - Dioxides

This method has been used as the terminal step in the purification of diene mixtures and, in fact, constitutes an important industrial procedure for production of high purity diene monomers.⁶⁶ This thermal decomposition is known to proceed in a regiospecific and stereospecific

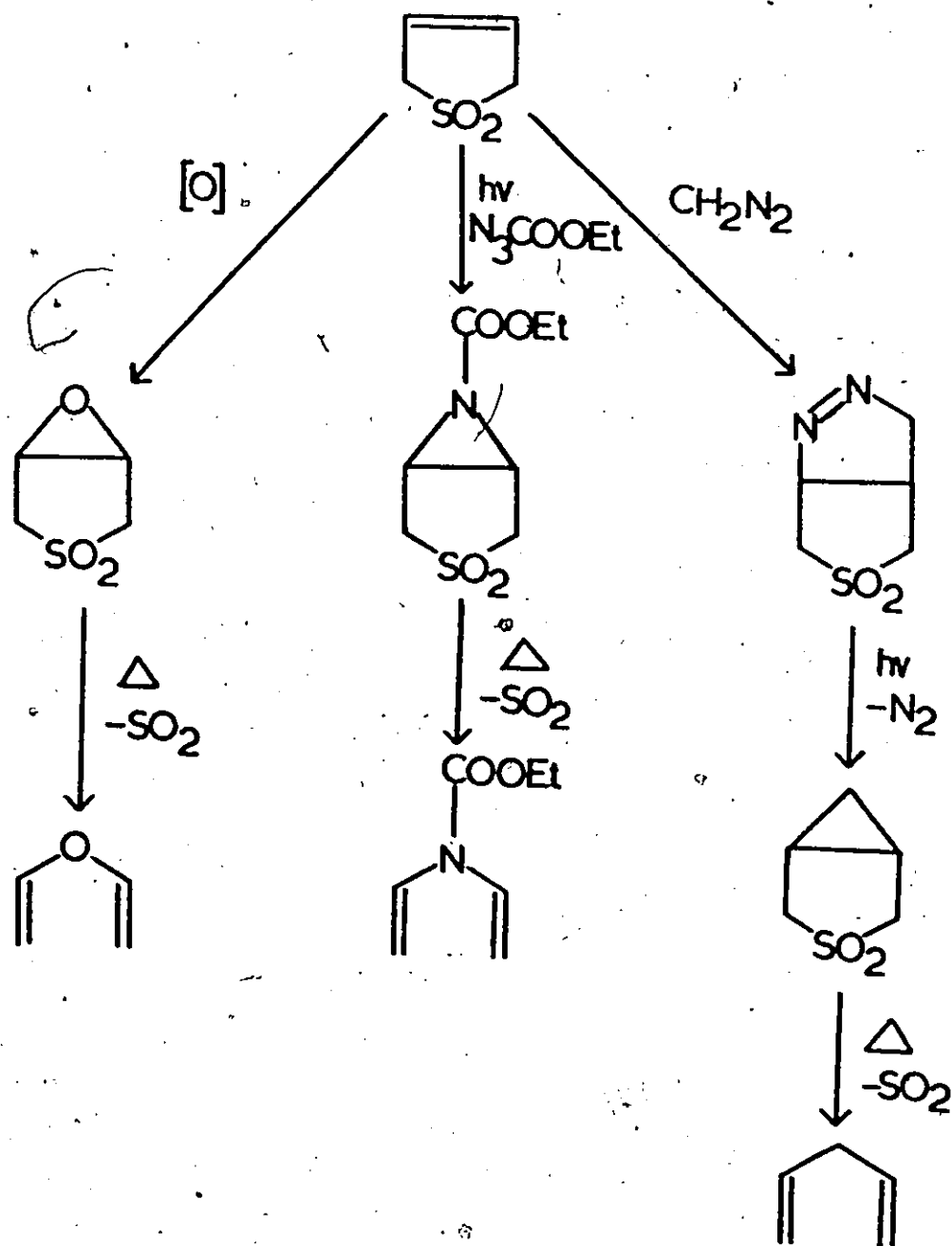
disrotatory manner at relatively low temperatures.^{67,68,69} The primary method for forming sulfones of type 56 involves the so-called cheletropic reaction of sulfur dioxide and a diene under moderate pressure and temperature.⁶⁶ This procedure is clearly not a synthetic method for dienes as the diene is required as a starting material. An alternate approach is the oxidation of a suitably substituted 2,5 - dihydrothiophene 57. Thus, if a generalized procedure could be found for the formation of this type of compound, it would constitute a valuable method for the production of dienes.

This ring system has been shown to have synthetic utility in other areas. An elegant example of the use of a dihydrothiophene derivative is the stereospecific approach to trans - fused bicyclic systems developed by Stork and Stotter⁷⁰ depicted in Scheme XII. In addition, the sulfones are becoming more important in organic synthesis. Alteration of the 2,5 - dihydrothiophene sulfone skeleton before thermolysis allows the production of divinyl ethers, amines and methanes^{71,72} (Scheme XIII). The scope of all these reactions, however, has remained rather limited because of the relative inaccessibility of 2,5 - dihydrothiophenes and their corresponding sulfones. A route to these compounds not dependent on dienes as a starting material would significantly increase their utility.

A number of methods have been described in the literature for the synthesis of 2,5 - dihydrothiophenes, but all suffer from major difficulties and none can be described as a general synthesis. Two of these, addition of sulfenyl chloride to a conjugated diene⁷³ followed by elimination of the elements of chlorine, and cyclization of a mercaptomuconate⁷⁴ are clearly unsuited to our needs because of



SCHEME XIII



the requirement for the diene as a starting material. The most obvious method, the reduction of a suitably substituted thiophene, suffers from low yields because of the necessary separation of the isomeric 2,3- and 2,5 - dihydrothiophenes. In addition, geminally substituted compounds cannot be prepared by this method. Finally, a Japanese group⁷⁵ has prepared a limited number of 3,4 - disubstituted 2,5 - dihydrothiophenes in low yield by the Michael reaction sequence outlined in figure 17.

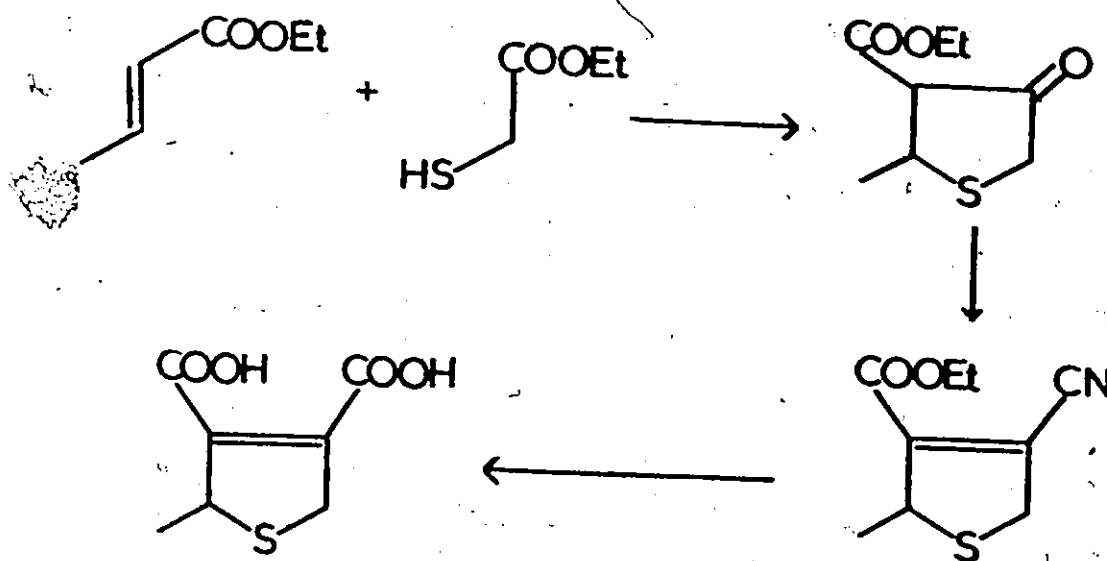


Figure 17 - Synthesis of 3,4 - Disubstituted 2,5 - Dihydrothiophenes

Again, this procedure suffers from low yields and the attainable substitution pattern is severely limited.

The use of vinylphosphonium salts as part of a generalized route to dihydrothiophenes was investigated. Although salts of this type have been known for over a century⁷⁶, their chemistry remained largely

unexplored until two publications stimulated renewed interest. In 1953, Wittig described the reaction which has elevated organophosphorus compounds to such an important position in organic chemistry.⁷⁷ Subsequently, Doering and Schreiber demonstrated that vinylsulfonium salts underwent anionic additions yielding ylids stabilized by $p\pi - d\pi$ orbital overlap between sulfur and carbon.⁷⁸ Since this type of stabilization was known to exist in the phosphorus analogs, the phosphoranes, Keough and Grayson initiated a study of the electrophilic reactivity of vinylphosphonium salts towards compounds containing a replaceable hydrogen.⁷⁹ They showed that these salts were excellent Michael-type acceptors and that compounds containing -CH, -NH, -PH, -OH, and -SH bonds could undergo addition. The term "phosphonioethylation" was coined by these authors to describe this type of conjugate addition.

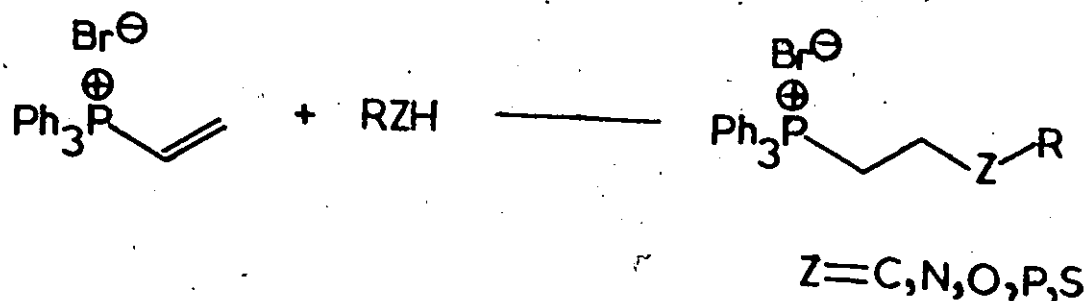


Figure 18 - Phosphonioethylation Reactions

At about the same time, Schweizer began a series of studies of the chemistry of vinylphosphonium salts and their substituted analogs. In the course of his approximately forty papers on this subject, he

has delineated a large number of useful synthetic procedures employing, in particular, vinyltriphenylphosphonium bromide. These reactions can be broadly categorized into two distinct groups.

(a) CHAIN-LENGTHENING PROCESSES

Negatively charged nucleophiles add to the vinyl salt forming a phosphorane which reacts with carbonyl compounds in the standard Wittig fashion and leads to chain-extended products and triphenylphosphine oxide.^{80,81} Compounds containing heteroatoms may also be used in this process.^{81,82} (Scheme XIV)

β -diketones have been C-alkylated to yield inner phosphonium salts.⁸³

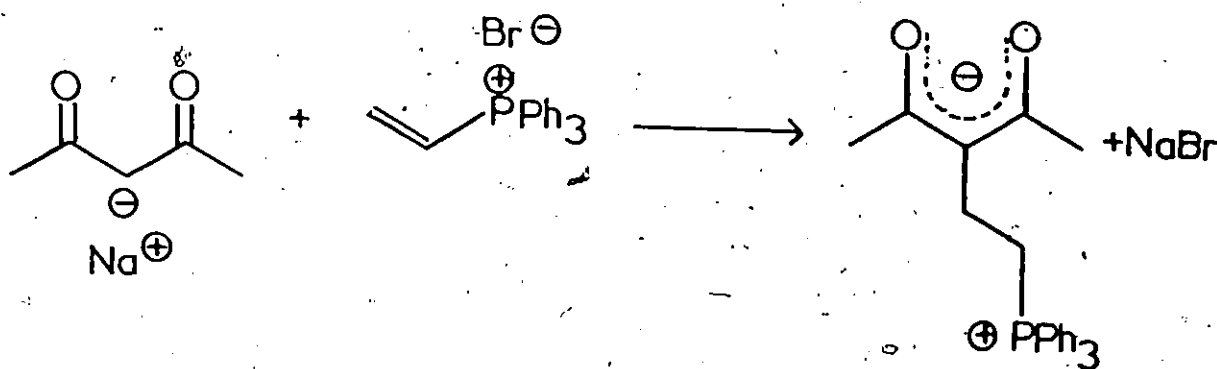


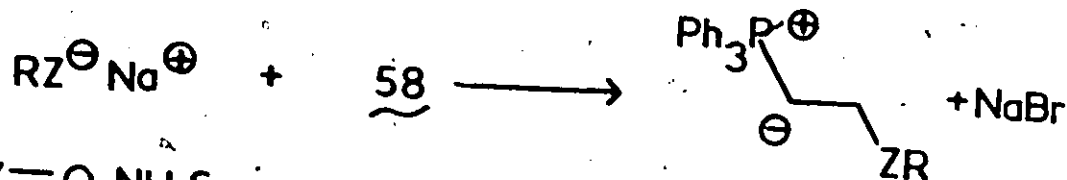
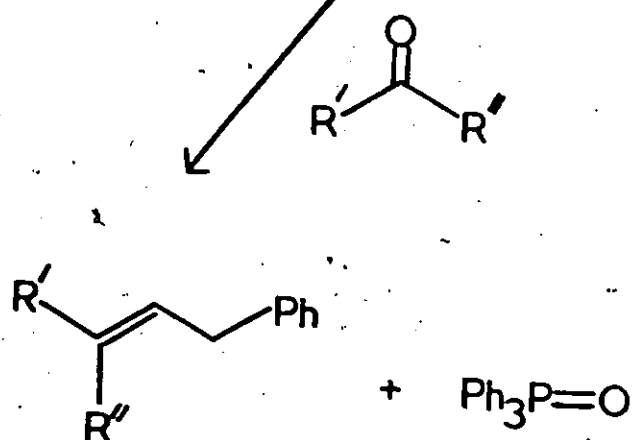
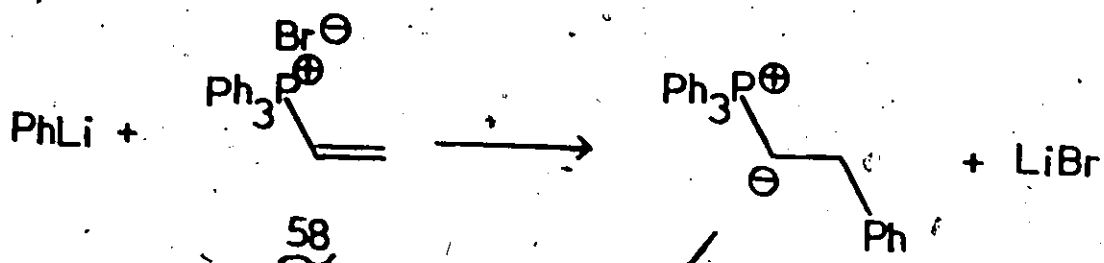
Figure 19 - C-Alkylation of β -Diketones

(b) RING SYNTHESSES

If a carbonyl group is incorporated into the Michael donor, a Michael-Wittig reaction sequence takes place and a variety of useful carbocyclic and heterocyclic products can be obtained.⁸⁴⁻⁸⁸ (Scheme XV).

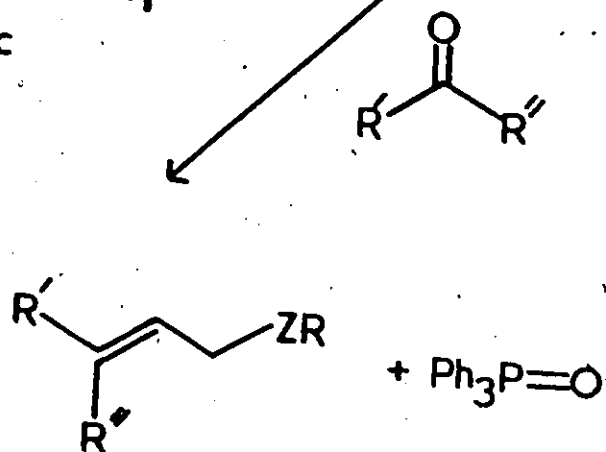
β -functionalized carbonyl compounds also have been cyclized to the corresponding 2(H)-1-benzopyrans (3-chromenes) and 1,2-dihydroquinolines.^{89,90}

SCHEME XIV

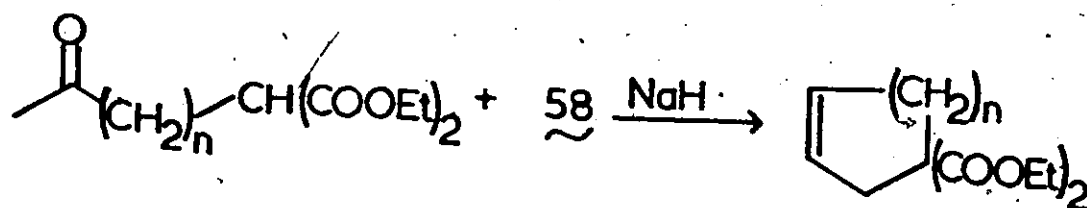
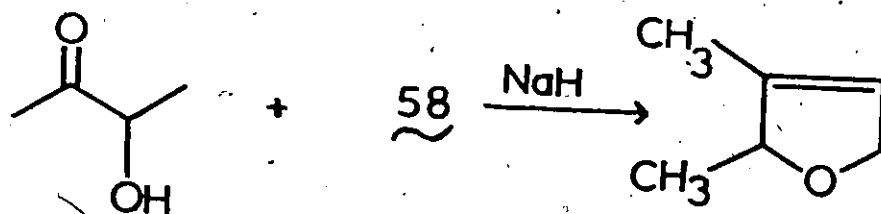
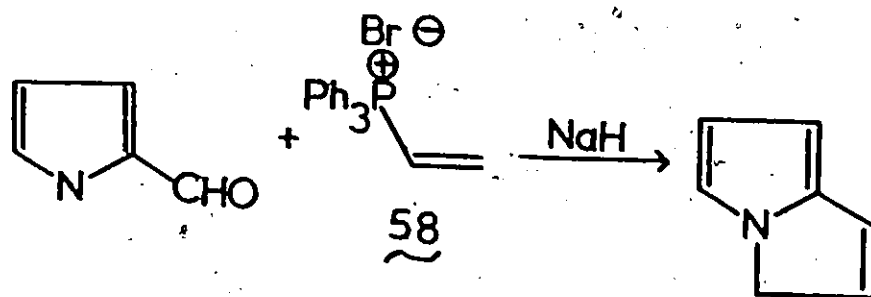
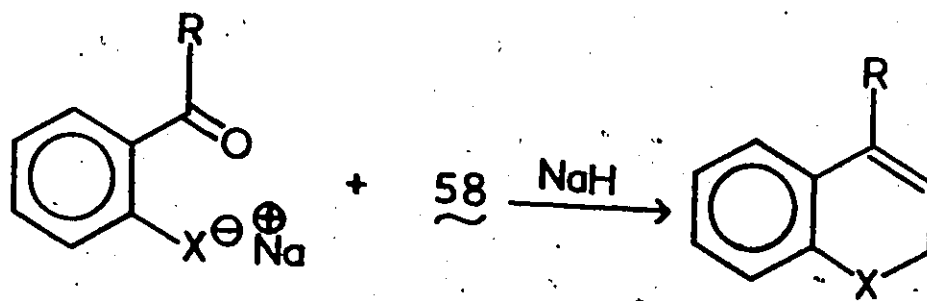


$\text{Z}=\text{O}, \text{NH}, \text{S}$

$\text{R}=\text{Aliphatic, Aromatic, Heterocyclic}$



SCHEME XV


 $n = 1, 2$


The behaviour of vinylphosphonium salts with 1,3 - dipolarophiles has been investigated and shown to be a general reaction.⁹¹

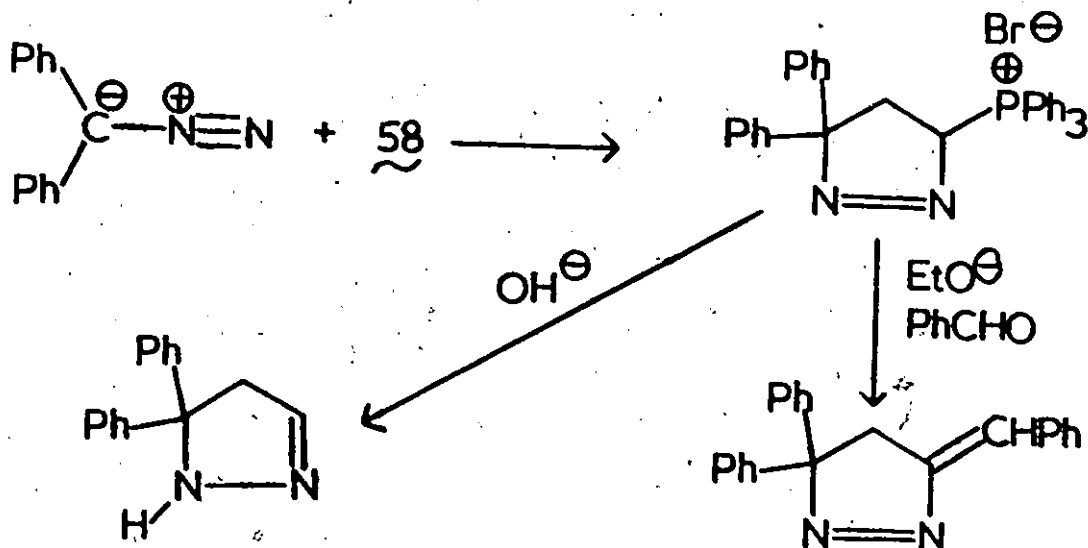


Figure 20 - Reaction of a Dipolarophile with Vinyl Salt 58

The vinyl salts have been investigated as potential labelling agents for proteins.⁹² Under physiological conditions, thiol groups add easily to this salt and the resulting adduct precipitates from solution.

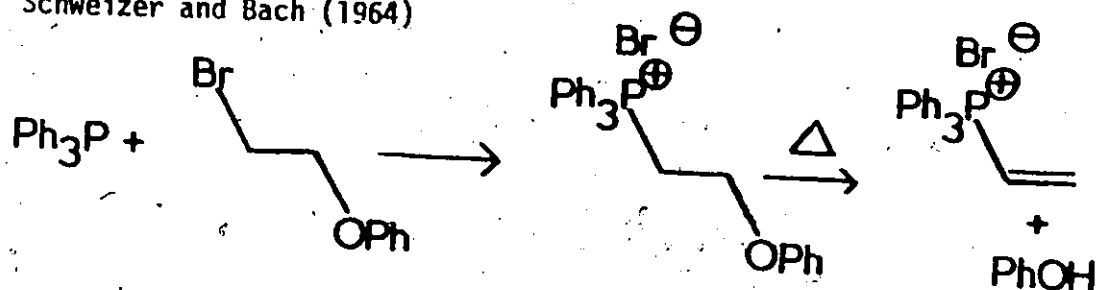
These clear demonstrations of the facile addition of various anions to 58 coupled with Schweizer's work on 2,5 - dihydrofurans and pyrroles indicated to us that the formation of 2,5 - dihydrothiophenes should also be readily achieved. Subsequent oxidation of these compounds would provide the intermediates required for the proposed diene synthesis.

The required vinyl triphenylphosphonium bromide 58 is available by a number of different synthetic routes (Scheme XVI), the most often quoted being that of Schweizer.⁹³ Triphenylphosphine is reacted with *p*-bromophenetole to form a phosphonium salt. At moderate temperatures, this salt eliminates phenol to yield the vinyl salt 58. A slightly modified procedure was recently reported in which *p*-bromoethanol was employed.⁹² Finally, 58 may be prepared from ethane - 1,2 - bis (triphenylphosphonium) dibromide by base-induced elimination of triphenylphosphine.⁹⁴ Each of these methods was employed to prepare the vinyl salt, but because each was tedious and time-consuming, it was found more economical to employ the commercially available product.

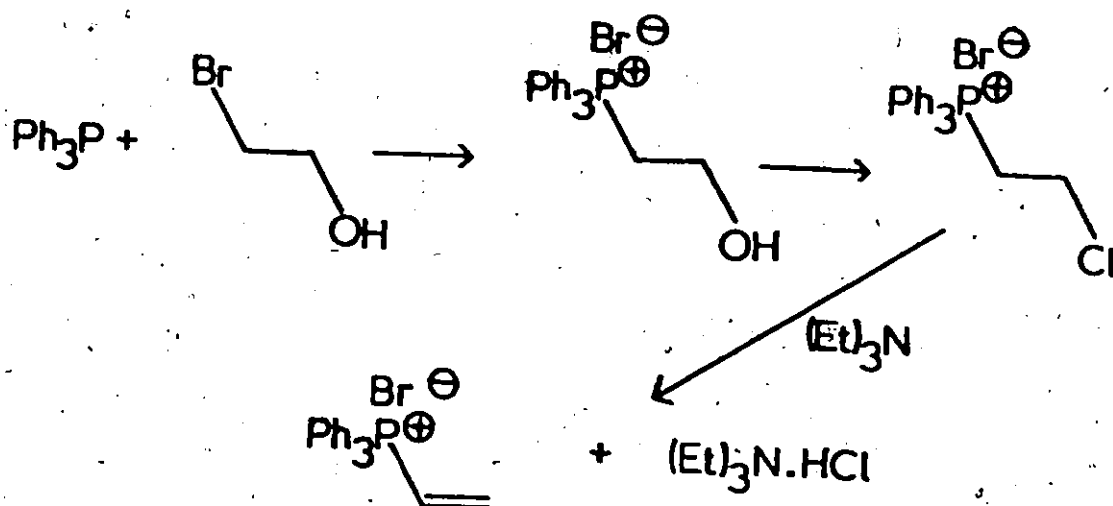
In order to attain generality for the synthesis, a reliable preparation of α -mercaptoketones and their α -haloketone precursors was required. The regiospecific halogenation of carbonyl compounds has been reviewed⁹⁵ and a recently reported procedure involving *N*-halosuccinimide halogenation of enol borinates seems to offer a highly regiospecific synthesis for this type of compound.⁹⁶ In this work, ketones were selected in which the site of halogenation was unambiguous. The α -haloketones are well known as being excellent substrates for displacement reactions and the replacement of halide by the sulfhydryl group proved to be a facile reaction. In certain instances, the α -mercaptoketones were isolated as highly insoluble dimeric dihydroxy - 1,4 - dithianes.^{97,98} These dimers are known⁹⁷ to be sensitive to traces of acid and readily dehydrate to transannular ethers (figure 21).

SCHEME XVI

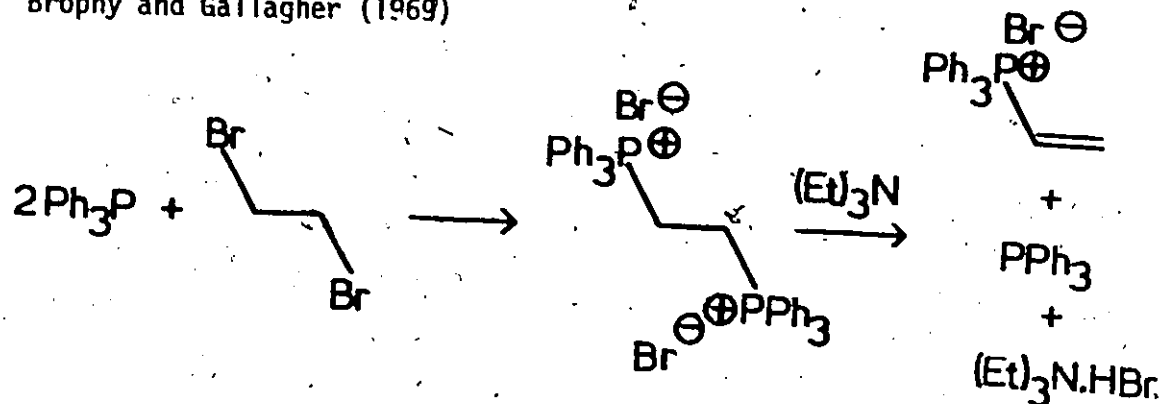
Schweizer and Bach (1964)



Swan and Wright (1971)



Brophy and Gallagher (1969)



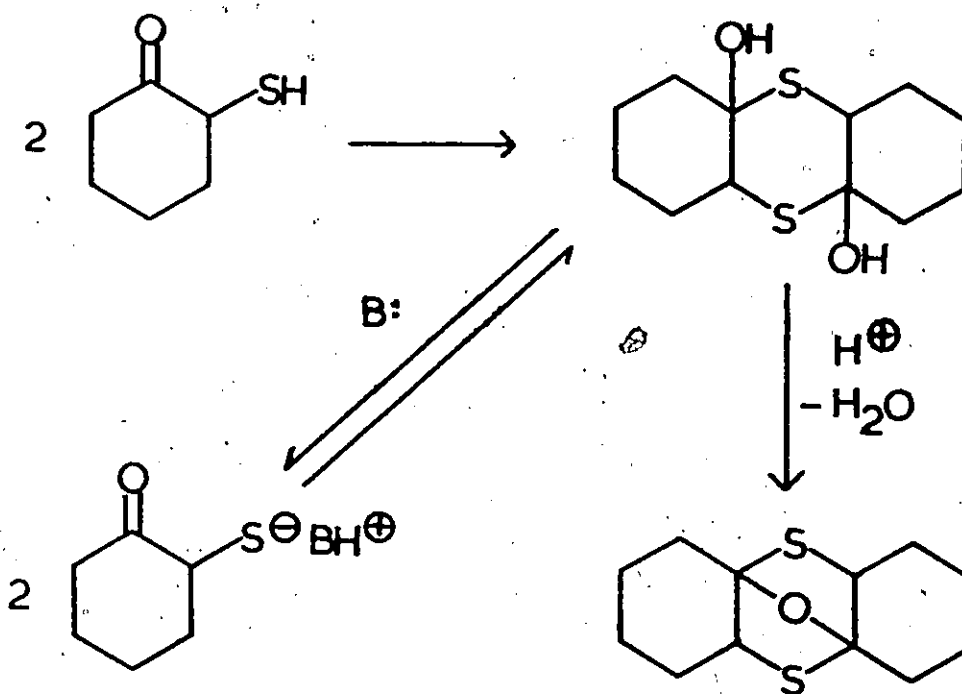


Figure 21 - Acid-Base Reactions of the Dimeric α -Mercaptoketones

In basic solution, however, an equilibrium is established between monomer and dimer and the material becomes readily soluble.⁹⁹

Our initial attempts to synthesize a dihydrothiophene followed Schweizer's methodology closely.

Sodium hydride in tetrahydrofuran was used to generate the mercaptide anion. A dimethyl formamide (DMF) solution of the vinyl salt was then added. DMF was employed as the co-solvent in an effort to improve the solubilities of the reactants. However, the mixture of dihydrothiophene, DMF and triphenylphosphine oxide which was obtained on aqueous work-up proved extremely difficult to separate. Repeated triturations with pentane, followed by filtration and elution through an alumina column were required to effect the separation. As a result of these manipulations, only modest yields of dihydrothiophene could be recovered, and while

the reaction showed the merit of the proposed scheme, the isolation procedure required was tedious and wasteful of product.

In an attempt to simplify the work-up procedure and optimize yields, tert-butanol was investigated as a reaction solvent. The lower alcohols cannot be used as solvents since they undergo conjugate addition to the vinyl salt forming inactive β -alkoxy-phosphonium salts. Again, however, difficulties were encountered in the work-up. Eventually most of these procedural difficulties were overcome by employing pyridine as the reaction solvent. It possesses the ability to dissolve both of the reactants creating a homogeneous reaction mixture as well as to serve as the required base. The ease with which it could be removed from the products by simple acid extraction was also an important consideration. Some dihydrothiophenes were formed in this manner, but the addition of a stoichiometric amount of the stronger base triethylamine was routinely employed to speed the reaction and to insure complete reaction. Simple column chromatography through acidic alumina eliminated all phosphorus-containing compounds as well as coloured impurities. Typically, gas chromatographic examination of the column eluates revealed product purities of 95% or greater. A number of 2,5 - dihydrothiophenes have been prepared using this standardized procedure¹⁰⁰, and they are summarized in Table I.

Physical properties of these compounds are outlined in Tables II and III.

TABLE I

Products and Yields of 2,5-Dihydrothiophenes

α -Mercaptoketone	Ref.	Salt	Product	Compound number	Time (hr.)	Yield (%)
	101	<u>58</u>		<u>59</u>	24	60
	102	<u>58</u>		<u>60</u>	30	95
	103	<u>58</u>		<u>61</u>	18	74
	102	<u>58</u>		<u>62</u>	18	76
	104	<u>58</u>		<u>63</u>	168	65

TABLE II

Indices of Refraction and NMR Parameters

<u>Compound Number</u>	n_D^{25}	<u>NMR Spectral Data^a</u>
59	1.5192	5.40 (s,1), 3.57 (s,4), 1.81 (s,3).
60	1.4912	5.32 (m,1), 3.60 (t,2,J=2), 1.72 (d,3,J=1.5), 1.51 (s,2).
61	1.5476	5.35 (m,1), 3.70 (m,3), 2.80-1.01 (m,8).
62	1.5408	5.35 (br.s,1), 4.26 (m,1), 4.00 (m,2), 2.5-1.2 (m,6).
63	1.5186	7.12 (s,5), 5.50 (m,1), 4.85 (m,1), 3.71 (m,2), 1.51 (m,3).

a) Tabulation follows the order chemical shift (δ), multiplicity, number of protons, coupling constant. All spectra run in CDCl_3 with TMS as internal standard.

TABLE III
ANALYTICAL DATA

<u>Compound Number</u>	<u>Calculated</u>			<u>Found</u>		
	<u>C</u>	<u>H</u>	<u>S</u>	<u>C</u>	<u>H</u>	<u>S</u>
<u>60</u>	65.60	9.44	24.97	65.67	9.55	24.21
<u>61</u>	68.55	8.63	22.83	68.68	8.74	22.82
<u>62</u>	66.65	7.99	25.36	66.69	8.01	25.11
<u>63</u>	74.98	6.86	18.16	75.14	6.94	18.09

Difficulties were encountered in synthesizing the mercaptans of certain aromatic ketones. The mercaptans from desyl chloride and phenacyl bromide proved to be highly susceptible to oxidation and high yields of disulfides, starting ketone and elemental sulfur were recovered from these preparations. These mercaptans had been prepared previously^{105,106}, but elaborate precautions such as distillation under a reducing atmosphere of hydrogen sulfide had to be taken to prevent these undesirable side reactions. The preparation of these compounds was discontinued at this point, since we were more concerned with pursuing the chemistry of the dihydrothiophene sulfones.

The reported selective oxidation of 2,5-dihydrothiophenes was confirmed.¹⁰⁷ The synthetic utility of this ring type is illustrated by the oxidation-cycloelimination - cycloaddition sequence depicted in figure 22.

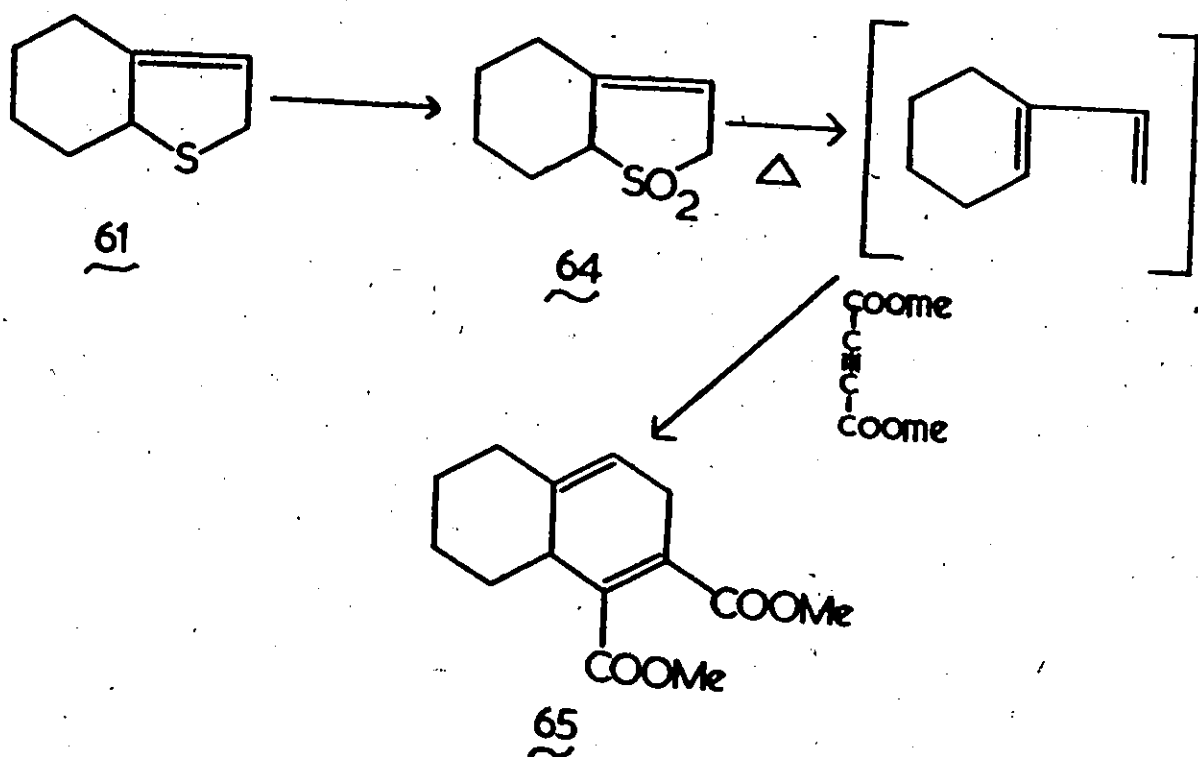


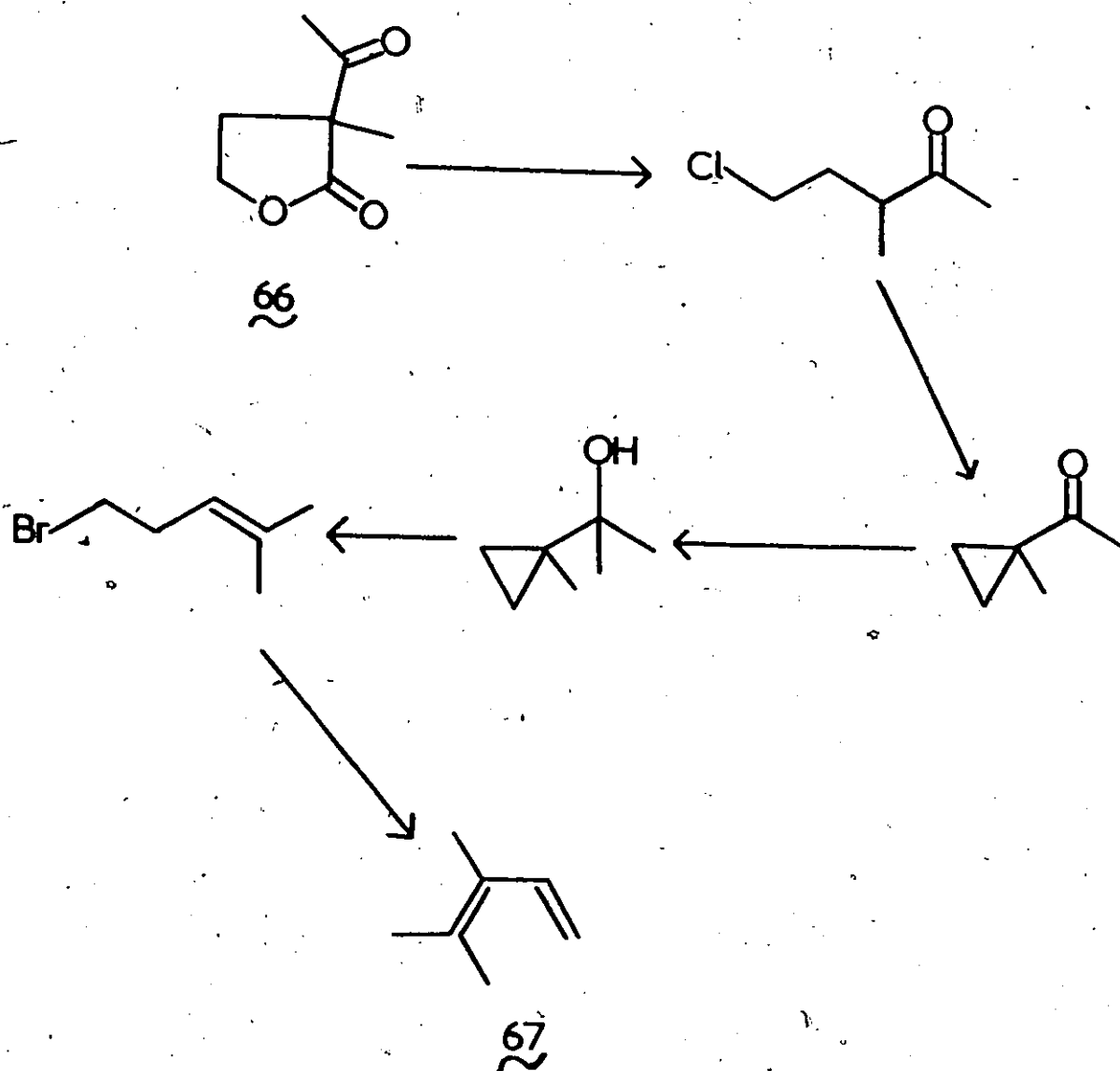
Figure 22 - Oxidation-Cycloelimination - Cycloaddition Reaction Sequence

Oxidation of 61 with two equivalents of *m*-chloroperbenzoic acid afforded the sulfone 64 in quantitative yield. Thermolysis of this compound in refluxing xylene (140°) in the presence of dimethyl acetylenedicarboxylate afforded the known¹⁰⁸ dimethyl 3,5,6,7,8,8a - hexahydronaphthalene - 1,2 - dicarboxylate 65 in an overall yield of 78% from 61. Although this reaction sequence showed the utility of this method, it must be mentioned that the diene, 1-vinylcyclohexene, obtained in this sequence can be readily prepared in quantity by alternate methods. As a demonstration of the value of this method for diene synthesis, we sought to prepare a diene which was not so readily available by conventional methods.

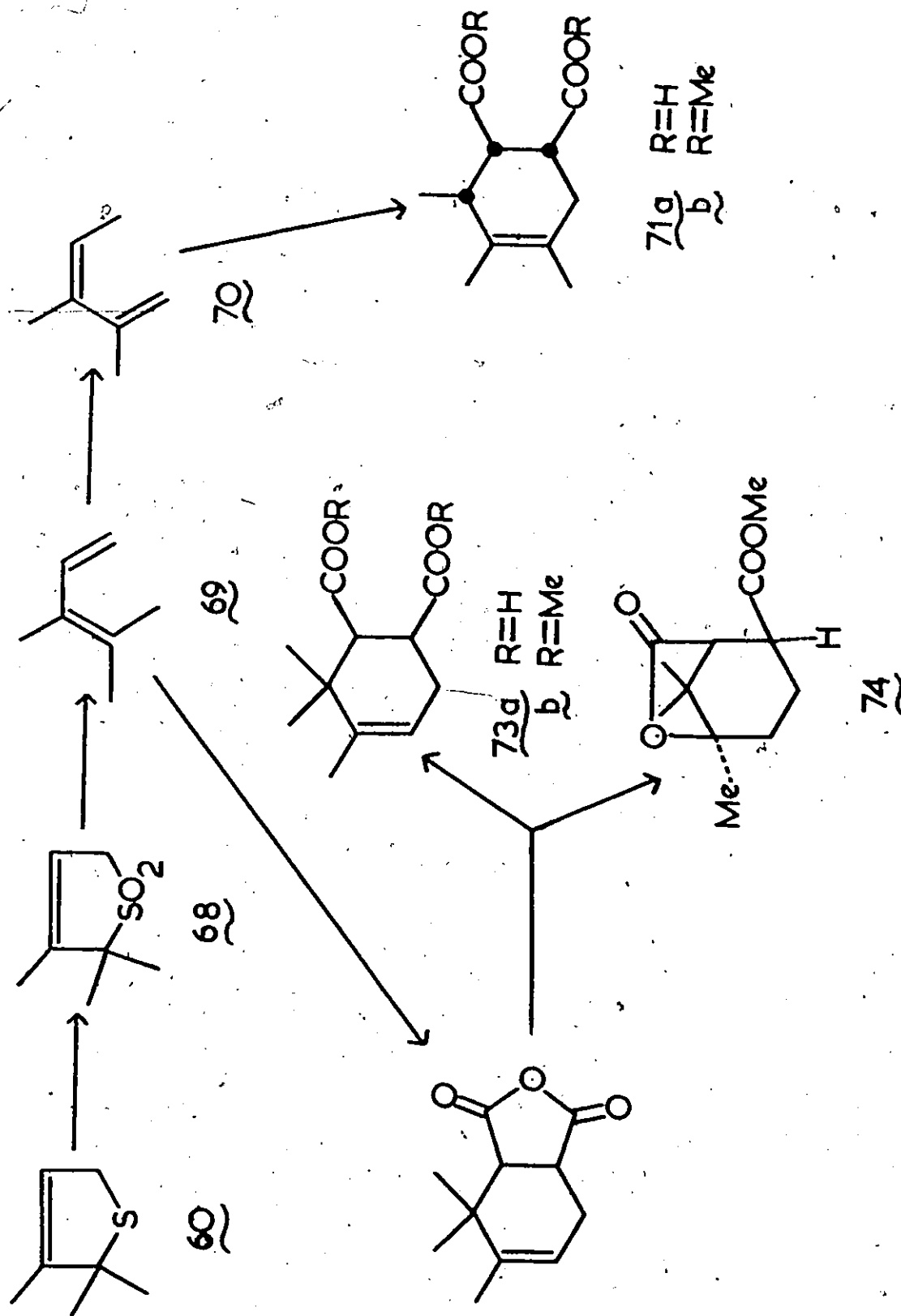
In 1963, Goldman¹⁰⁹ prepared the diene 67 by the sequence outlined in Scheme XVII in an overall yield of 8% from the starting material 66. We investigated the synthesis of this diene utilizing the dihydrothiophene 60 (Scheme XVIII). Oxidation with *m*-chloroperbenzoic acid afforded the sulfone 68 in quantitative yield. In refluxing xylene solution in the presence of maleic anhydride, a rapid evolution of sulfur dioxide occurred, but the product isolated in 58% yield after hydrolysis was the diacid 71 derived from the rearranged diene 70.¹¹⁰ This type of sigmatropic rearrangement, sometimes called an internal ene synthesis, has been well documented.^{110,111}

Reducing the reaction temperature to 110° reduced the rate of reaction drastically but after a prolonged reaction time, a quantitative recovery of three products was achieved. Hydrolysis and esterification of these materials led to the isolation of the rearranged adduct 71 (19%), unrearranged diester 73b^{108,109} and the known

SCHEME XVII



SCHEME XVIII



lactone ester 74¹⁰⁹ derived from the diacid 73a. The unambiguous synthesis of diene 69 thus proceeds in 74% overall yield in three steps from the easily prepared compound 60.

In an effort to extend the usefulness of this new procedure, methods for the further functionalization of the 2,5 - dihydrothiophene sulfones were investigated. Our continuing interest in dienes for a Diels-Alder route to dendrobine led us to investigate synthetic methods for generating sulfones, which on thermolysis, would yield adducts containing enol acetates or enol ethers. Thus the required sulfones would bear alkoxy or acyloxy groups in the 3-position (figure 23).

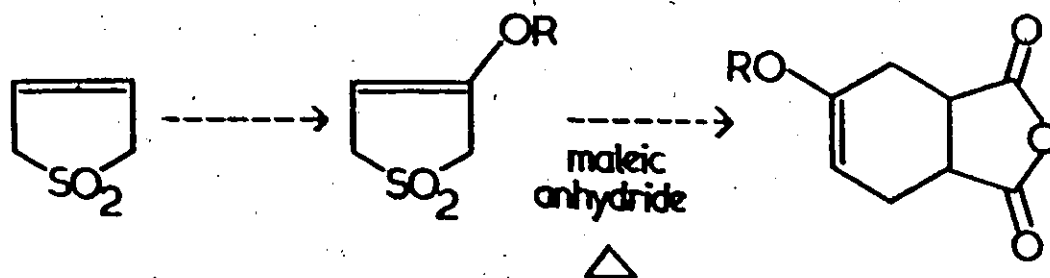


Figure 23 - Oxygen-Functionalized Dihydrothiophene Sulfones

One possible approach to sulfones functionalized in this way is illustrated in figure 24.

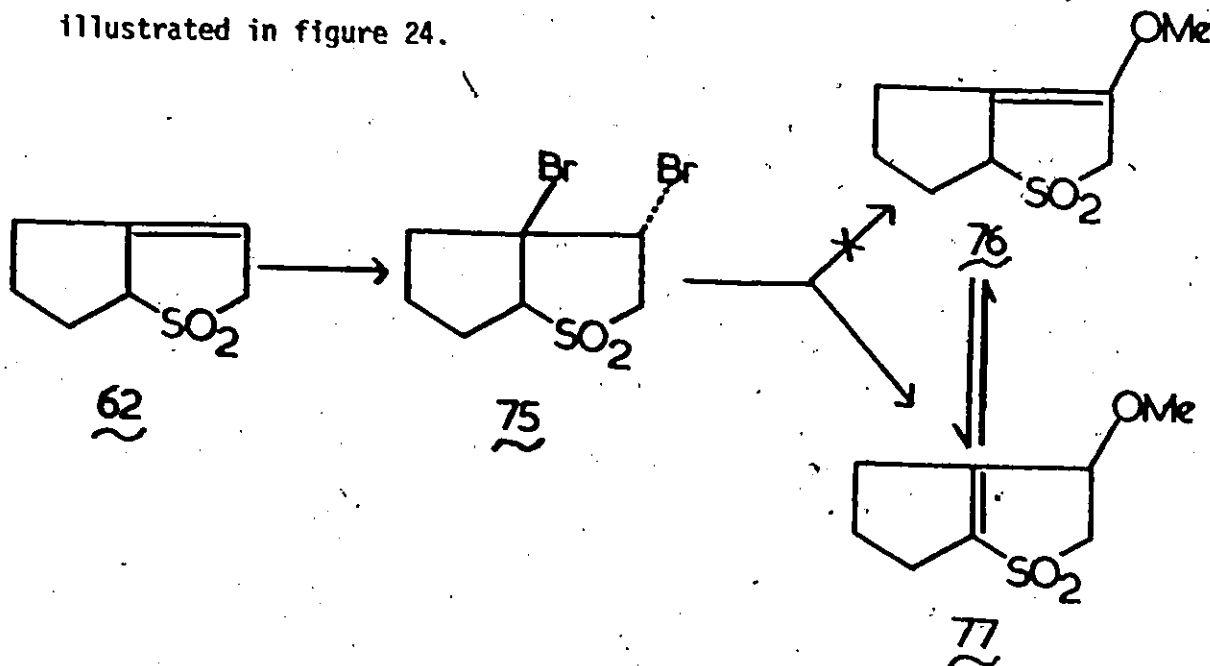


Figure 24 - Formation of 3-Methoxydihydrothiophenes

Bromine, as expected,¹¹² added smoothly to sulfone 62 forming the dibromosulfone 75. An attempt to effect both substitution and dehydrohalogenation by reacting this compound with two equivalents of sodium methoxide in methanol led to only one (77) of the two possible isomeric methoxy-sulfones (76 and 77). Since the double bond of isomer 77 is in conjugation with the sulfone group, this result was not surprising.¹¹³ However, one report suggested that in a similar system, under base catalysis, the double bond became mobile, and depending on the solvent employed, either of these isomers could be isolated.¹¹⁴ All attempts to carry out a prototropic rearrangement of 77 to 76 appeared to produce an equilibrium mixture in which 77 predominated. Isomer 77 is, of course, not synthetically useful, since it does not undergo thermolytic elimination of sulfur dioxide.

An alternate approach to the formation of the desired sulfones involves the reaction of α -mercaptoketones with substituted vinylphosphonium salts. We had already demonstrated that a number of β -alkyl and β -aryl substituted vinyl salts gave excellent yields of dihydrothiophenes.¹¹⁵ To carry out our objective, the required vinyl salts would have to bear oxygenated functional groups at the α -position. The preparation of one such salt, α -ethoxyvinylphosphonium bromide 79, is shown in figure 25.

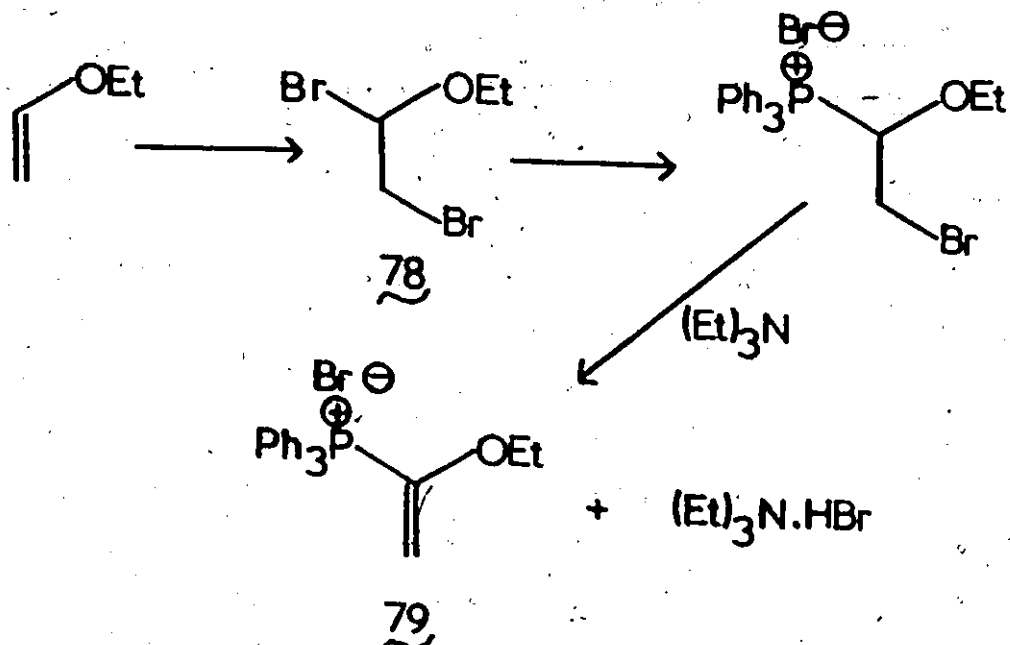


Figure 25 - Preparation of α -Ethoxyvinyltriphenylphosphonium Bromide

Salt 79 was employed in several reactions utilizing the usual method for producing 2,5-dihydrothiophenes. An almost quantitative yield of triphenylphosphine was recovered from each reaction. Schweizer also observed in some instances anomalous results when α -substituted vinyl salts were employed in his heterocyclic ring syntheses.¹¹⁶ A possible rationalization for this result is shown in figure 26.

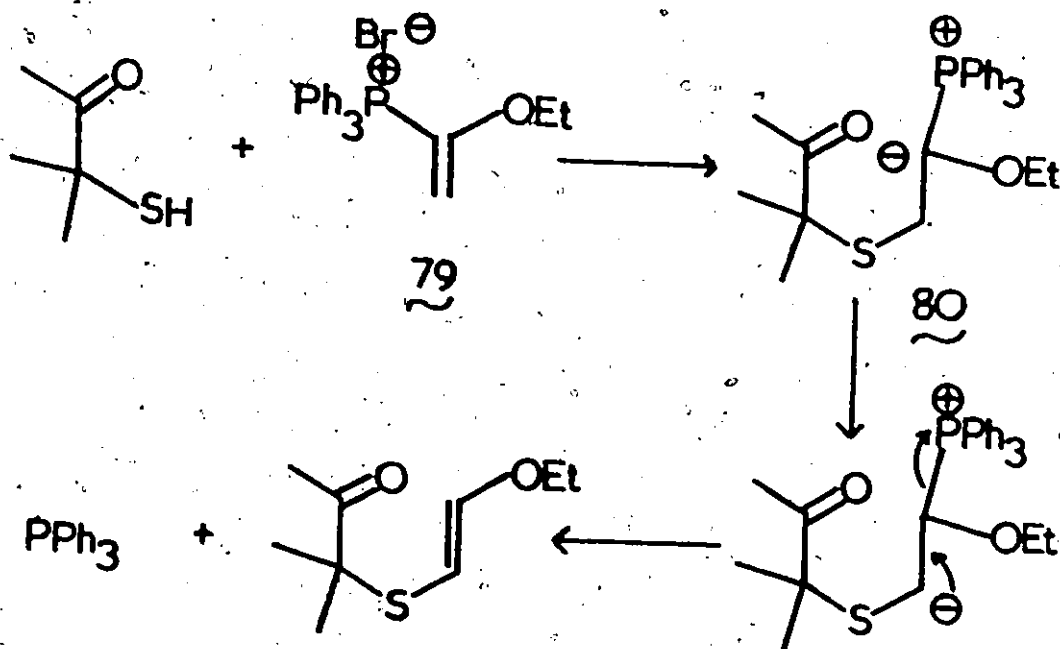


Figure 26 -A Phosphorane Rearrangement Leading to Elimination of Triphenylphosphine

Because a completely normal phosphonoethylation reaction could be carried out with benzenethiol to form 2-thiophenoxy-1-ethoxy-ethyltriphenylphosphonium bromide 83, we believe that salt 79 remains a fairly active Michael acceptor. The intermediate phosphorane 80 is in this case destabilized by the adjacent ether oxygen and a rearrangement to 81 seems feasible. This compound could then undergo a facile elimination of triphenylphosphine to form the vinyl sulfide 82. No evidence for the formation of 82 was obtained, however, as the only product which could be recovered from column chromatography was triphenylphosphine.

An analogous synthesis of α -acetoxyvinyltriphenylphosphonium bromide was attempted. Fusion of 1,2-dibromoethyl acetate with triphenylphosphine produced what appeared to be a high-melting bis-phosphonium salt. On reaction with triethylamine this compound gave vinyltriphenylphosphonium bromide and triphenylphosphine oxide in approximately equal amounts. The spectral properties and combustion analysis of the bis-phosphonium salt were of no help in elucidating its structure. This problem is currently under investigation.

Since the conclusion of this project, other members of this research group have shown the complete generality of this new method for the synthesis of 2,5-dihydrothiophenes. The reaction has been extended to include α -mercaptoaldehydes¹¹⁷, as well as many substituted vinylphosphonium salts.¹¹⁸ In addition, promising results have been obtained with a vinylphosphonate modification of this reaction.¹¹⁹

EXPERIMENTAL SECTIONGENERAL COMMENTS

Reagent grade chemicals were used without further purification unless so specified. Infrared (ir) spectra were recorded on Beckman IR12 and IR20A instruments in 10% solution. Nuclear magnetic resonance (nmr) spectra were obtained on a JEOLCO C60HL spectrometer and are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. The splitting pattern of each resonance is codified as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and b = broad. Electron impact mass spectra were recorded at 70eV on a Varian MAT CH5 - DF spectrometer. Ultraviolet (uv) spectra were recorded on a Beckman DB spectrophotometer. Glc analyses were performed on Hewlett-Packard 720 and 5750 instruments with peak areas determined by disc integration. A Fisher-Johns melting point apparatus was employed to determine melting points and indices of refraction were measured with a Carl Zeiss refractometer. Combustion analyses were performed by A. B. Gygli Microanalysis Laboratory, Toronto, Ontario and Galbraith Laboratories, Knoxville, Tennessee.

4 - Methyl - 2 - Pentenoic Acid (11) was prepared by the method of Goldberg and Linstead²⁴ in 76% yield: bp 103 - 105° (10 mm), n_D^{25} 1.4494 (reported bp 104 (10 mm)); ir (CHCl₃) 3500 - 2500, 1700, 1655 cm⁻¹; nmr (CCl₄) δ 1.10 (d, 6), 2.42 (m, 1), 5.70 (dd, 1), 7.00 (m, 1).

3 - Methyl - 7 - bromohept - 3 - en - 1 - yne (14) was prepared according to the method of Julia and Descoins²⁵ in 41% yield: ir (CCl₄) 3310, 1625 cm⁻¹; nmr (CCl₄) δ 1.5 (s, 1), 1.85 (s, 3), 2.5 - 3.5 (m, 4), 5.65 (t, 1).

5 - Methoxy - 1 - indanone (22) was prepared by the method of Birch et al.²⁷ in 63% yield as well as by the method of Johnson and Glenn²⁸ in 62% yield. Both preparations gave light tan crystals whose wide melting range, 65 - 108°, indicated an isomeric mixture. Repeated crystallization from aqueous methanol eventually gave an isomerically pure product melting at 108°. The method of Panetta and Bunce²⁹ afforded 22 in an overall yield of 75%. This isomerically pure product melted at 108.5 - 109.5° (reported 108 - 109°):
ir (CHCl₃) 1700, 1600 cm⁻¹; nmr (CDCl₃) δ 2.70 (m, 2), 3.10 (m, 2), 3.87 (s, 3), 7.30 (m, 3).

5 - Methoxy - 1 - ethynyl - 1 - indanone (23) - In a 1 l. three-necked flask equipped with mechanical stirrer, 250 ml. dropping funnel and reflux condenser with attached mercury bubbler, was added 8.50 g (0.35 moles) magnesium turnings and 200 ml. of LAH dried THF. Ethyl bromide (43.6 g, 0.40 moles) dissolved in a small amount of THF was added over a period of 2 hr. and after a further period of 3 hr. this solution was transferred under nitrogen to a 500 ml. dropping funnel. In a 2 l. three-necked flask thoroughly flushed with nitrogen and fitted with a mechanical stirrer, reflux condenser with drying tube and gas inlet, was added 100 ml. of dry THF. The solvent was saturated with dry acetylene for fifteen minutes. Ethyl magnesium bromide was added in 5 ml. portions allowing time after each addition for the evolution of ethane. Approximately 3 hr. were required for this addition, after which the solution was homogeneous. 5 - Methoxy - 1 - indanone, 16.2 g (0.1 mole) in THF solution was then added over a period of 1 hour. The reaction mixture was stirred for four days, then carefully neutralized with saturated ammonium chloride solution. The organic layer was washed several times with brine and

dried over anhydrous sodium sulfate. Solvent was removed in vacuo and the resulting material vacuum distilled to yield 7.3 g of a rapidly discoloured clear oil containing 22, 23 and 24. Without further purification, this material was dehydrated by azeotropic distillation of water from benzene containing a few crystals of p - toluenesulfonic acid. The solution was decolorized with Norit, dried over sodium sulfate and solvent removed in vacuo.

The resulting dark oil was subjected to preparative scale thin-layer chromatography on silica gel using benzene as eluant. From a fast-running fluorescent band ($R_f = 0.7$) a small amount of a low melting white solid was isolated: ir (CHCl_3) 3310, 1610, 1590, 1480 cm^{-1} ; nmr (CDCl_3) δ 3.13 (s, 1), 3.35 (bs, 2), 3.75 (s, 3), 6.66 (m, 1), 7.16 (m, 3).

5 - Isopropyl - 1,3 - cyclohexanedione (31) was prepared according to the method of Frank and Hall⁵³ and was isolated as the monohydrate in 80% yield: mp 55° (reported mp 62°); ir (KBr) 1730, 1710 cm^{-1} .

5 - Isopropyl - 2 - Cyclohexenone (41) was prepared from 31 by esterification and reduction according to Frank and Hall⁵³ in an overall yield of 46%: bp 108 - 120 (18 mm), (reported bp 104 - 108° (13 mm)); ir (CHCl_3) 1675 cm^{-1} ; nmr (CDCl_3) δ 0.90 (d, 6), 1.65 (m, 1), 2.25 (m, 4), 5.98 (m, 1), 6.96 (m, 1).

3 - Isopropyl - Glutaric Acid (32) - A solution of 218 g (5.45 moles) of sodium hydroxide in 300 ml of water was cooled by the addition of 1250 g of ice. A stream of chlorine was passed rapidly through this solution until 161 g (2.27 moles) had been absorbed. A solution consisting of 72 g (0.5 moles) of 31 dissolved in 525 ml. of water

containing 65 g (1.16 moles) of potassium hydroxide was run slowly into the sodium hypochlorite solution. After addition was complete the reaction was stirred for 8 hr. after which 50 g of sodium sulfite was added to decompose excess sodium hypochlorite. The solution was acidified to Congo red with hydrochloric acid and water added to redissolve the precipitated salts. The mixture was extracted with three 200 ml portions of ether and the extracts dried over sodium sulfate. Solvent was removed in vacuo to yield 80 g (92%) of light yellow crystals: nmr (CDCl_3) δ 0.85 (d, 6), 1.78 (m, 1), 2.34 (m, 5), 10.01 (s, 2).

3 - Isopropyl Glutaric Anhydride (33) - To an excess of acetic anhydride was added 56.5 g (0.32 moles) of the diacid 32. The solution was refluxed for 5 hrs. and allowed to stand overnight. After removal of the solvent by distillation at atmospheric pressure, the residue was vacuum distilled to yield 41.4 g (75%) of a light yellow oil which became semi-solid at room temperature: bp 130° (0.75 mm); i r (CHCl_3) $1815, 1765 \text{ cm}^{-1}$; nmr (CDCl_3) δ 0.92 (d, 6), 1.78 (m, 1), 2.60 (m, 5).

Methyl 3 - Isopropyl Hydrogen Glutarate (34) - The anhydride 33, 41.4 g (0.265 moles), dissolved in 100 ml of methanol was added slowly to a methanol solution containing 1 equivalent of sodium methoxide. The solution was stirred overnight then refluxed for 1 hr. The mixture was poured onto an acid slush and extracted with three 100 ml portions of chloroform. The organic extract was dried over anhydrous sodium sulfate and the solvent removed to yield 48.0 g (96% of essentially pure 34 as shown by glc. examination: bp 120° (0.25 mm);

ir (CHCl_3) $1730, 1710 \text{ cm}^{-1}$; nmr (CDCl_3) δ 0.90 (d, 6), 1.82 (m, 1), 2.43 (bs, 4), 11.00 (s, 1).

Cis and Trans -Dimethyl 3 - Isopropylglutaconates (37) and (38) - In

an excess of thionyl chloride, 10 g (0.053 moles) of the half-ester 34 was refluxed until all gas evolution ceased. The reaction was cooled to 0° and 8.9 g (0.55 moles, 1.05 molar excess) of bromine was added. After 1 hr the mixture was refluxed for 3 hrs. and let stand overnight. A large excess of methanol was added and the solution refluxed for 3 hrs. Solvent was removed in vacuo, and the residue was taken up in ether, washed with dilute sodium bicarbonate and dried over sodium sulfate. Removal of solvent gave 1.5 g of a light yellow oil which was vacuum distilled. Extensive decomposition occurred and glc. examination of the distillate revealed one large peak which proved to be an approximately equimolar mixture of 37 and 38: ir(CHCl_3) 1750 cm^{-1} ; nmr (CDCl_3) δ 0.95 (d, 6H), 1.08 (d, 6H), 2.10 (m, 6H), 4.5 (m, 1), 4.94 (m, 1).

3 - Ethoxy - 5 - isopropyl - 2 - cyclohexenone (40) was prepared according to the procedure of Frank and Hall⁵³ and isolated in 72% yield: bp 95° (1.2 mm), λ_{max} (95% EtOH) 250 nm (reported bp 124° (1.2 mm), λ_{max} (95% EtOH) 249.5 nm); ir (CHCl_3) $1650, 1610 \text{ cm}^{-1}$; nmr (CDCl_3) δ 0.88 (d, 6), 1.32 (t, 3), 2.10 (m, 6), 3.84 (d, 2), 5.25 (s, 1).

1 - Acetoxy - 4 - methyl - 1 - penten - 3 - one (46). - To 70.32 g (3.05 moles) of sodium hydride in a 1 l. three-necked round bottom flask fitted with a thermometer, dropping funnel and mechanical stirrer was added 175.8 g (2.93 moles) of methyl formate. A catalytic amount

of absolute ethanol was added and 126.1 g (1.47 moles) of methyl isopropyl ketone in 100 ml of dry ether was added over a period of one hour. After stirring for six hours, the reaction mixture was cooled to -10° and 230 g (2.93 moles) of acetyl chloride was slowly added. After an additional six hours, ether and water was added and the organic layer was washed with 75 ml of saturated sodium bicarbonate solution and 50 ml of brine. After drying over sodium sulfate and removal of solvent, vacuum distillation gave 111 g (48%) of a colourless liquid: bp 55° (0.35 mm); ir (CHCl_3) 1775, 1695, 1630 cm^{-1} ; nmr (CDCl_3) δ 1.10 (d, 6), 2.23 (s, 3), 2.80 (m, 1), 6.06 (d, 1), 8.28 (d, 1).

2 - Methyl - 5 - Acetoxy - 3 - pentanone-(47) - Compound 46,

19.1 g (0.123 moles), was hydrogenated in ethyl acetate at atmospheric pressure over 5% palladium on carbon. The progress of the hydrogenation was followed by glc (8 ft. X 0.375 in. 20% SE-30 on Chromosorb W column. 125°) and a quantitative recovery of product was obtained: bp 57° (0.35 mm); ir (CHCl_3) 1740, 1710 cm^{-1} ; nmr (CDCl_3) δ 1.10 (d, 6), 2.01 (s, 3), 2.61 (m, 1), 2.78 (t, 2), 4.33 (t, 2).

3 - Isopropyl - 5 - Hydroxy - 2 - Pentenoic Acid Lactone 48

To a mixture of 9.66 g (0.064 moles) of methyl bromoacetate and 8.24 g (0.13 g-atoms) of activated zinc in 30 ml of benzene was added 10 g (0.064 moles) of compound 47 and a crystal of iodine. The reaction flask was heated with a flame and after approximately ten minutes of intermittent heating, the reaction began and proceeded with reflux. After the exothermic reaction had ceased, the mixture was heated at reflux overnight and 4 ml. of acetic acid in 30 ml of water was added.

The reaction was extracted with four 25 ml portions of ether, and this extract was washed with dilute sodium bicarbonate solution and dried over anhydrous sodium sulfate. Vacuum distillation afforded 2.6 g of a clear oil: bp 87-95° (0.35 mm); ir (CCl₄) 1725, 1640 cm⁻¹; nmr (CCl₄) δ 1.16 (d, 6), 2.35 (m, 1), 2.40 (bt, 2), 4.30 (t, 2) 5.65 (m, 1).

Potassium 3-Isopropyl - 2,4 - Pentadienoate (49) - An ethereal solution of lactone 48, 1 g (0.007 moles), was added to 0.81 g (0.007 moles) of potassium tert-butoxide in 3 ml tert-butanol. The reaction was heated gently for 4 hours, cooled, and the solvent removed to yield 1.1 g (91%) of the acid salt: nmr (D₂O) δ 1.1 (d, 6), 2.75 (m, 1), 5.4 (m, 3), 6.98 (m, 1).

4 - Isopropyl - 2 - pyrone (28) - A reaction mixture consisting of 19.6 g (0.128 moles) of methyl bromoacetate and 16.7 g (0.25 g-atoms) of activated zinc in 30 ml. of benzene containing a small amount of iodine and 46 was heated with a flame until the reaction began. The mixture was kept refluxing by the slow addition of 20 g (0.128 moles) of 46. After stirring four hours 8 ml of acetic acid in 50 ml of water was added. The product was extracted with ethyl acetate, washed with dilute sodium bicarbonate solution and dried over anhydrous sodium sulfate. After removal of solvent, the product was vacuum distilled to yield 6.5 g (36%) of a yellow liquid: bp 80 (0.35 mm), uv (95% EtOH) λ max 288 nm (ϵ = 4300) (reported⁵⁰ bp 56-59 (0.05 mm), uv (95% EtOH) λ max 285 nm (ϵ = 4500)); ir (CHCl₃) 1720 cm⁻¹; nmr (CDCl₃) δ 1.18 (d, 6), 2.60 (m, 1), 5.97 (m, 1), 6.00 (dd, 1), 7.20 (dd, 1).

Preparation of α -mercaptoketones. All α -mercaptoketones were prepared according to the reference given in Table I.

Preparation of 2,5 - dihydrothiophenes. All the dihydrothiophenes listed in Table I were prepared by the following procedure.

Vinyltriphenylphosphonium bromide (0.01 moles) was dissolved in 50 ml of dry pyridine in a 100 ml flask equipped with magnetic stirring, reflux condenser and nitrogen inlet. Triethylamine was added (0.015 moles) and the mixture was stirred at room temperature for 30 minutes. The appropriate α -mercaptoketone (0.01 moles) was heated at reflux for the period of time indicated in Table I. The cooled solution was poured into 600 ml of water and extracted twice with 100 ml of ether and twice with 100 ml of pentane. The combined organic layers were washed with two 100 ml portions of 10% hydrochloric acid and dried. The solution was reduced in volume to approximately 10 ml and chromatographed on alumina using pentane as the eluant. This removed all phosphorus-containing and colored impurities. Solvent was removed in vacuo to yield the dihydrothiophene which glc analysis showed to be greater than 95% pure. Analytical samples were collected by glc. Indices of refraction and nmr parameters are shown in Table II. The results of combustion analysis are shown in Table III. Except for the lack of carbonyl absorption the ir spectra were uninformative.

2,4,5,6,7,7a - Hexahydrobenzo[b] thiophene - 1,1 - dioxide (64) - To a cold solution of 1.4 g (0.010 moles) of dihydrothiophene 61 was added 3.96 g (0.022 moles) of m-chloroperbenzoic acid in two equal portions. The solution was stirred at 0° for 3 hr. and at room

temperature for 1 hr. The precipitate of *m*-chlorobenzoic acid was removed by filtration and the filtrate was washed with two 75 ml portions of saturated sodium carbonate solution, and dried. Evaporation of solvent afforded 1.67 g (98%) of a colourless liquid: ν (CHCl₃) 1310, 1130 cm⁻¹; nmr (CDCl₃) δ 1.1 - 2.7 (m, 8), 3.3 - 3.8 (m, 3), 5.57 (m, 1).

Dimethyl 3,5,6,7,8,8a - hexahydronaphthalene -1, 2 - dicarboxylate (65)¹⁰⁸

Sulfone 64, 1 g (0.0058 moles), was dissolved in 5 ml of xylene and 0.28 g (0.0058 moles) of dimethyl acetylenedicarboxylate and a small amount of hydroquinone were added. The solution was heated at reflux for 6 hr. and the xylene was removed by distillation at atmospheric pressure. Glc analysis of the residue revealed only one peak which was collected and shown to be 65. The yield was calculated to be 78%: ν (CHCl₃) 1730, 1660 cm⁻¹; nmr (CDCl₃) δ 1.10 - 2.32 (m, 8), 2.197 (m, 3), 3.75 (s, 3), 3.80 (s, 3), 5.35 (m, 1).

2,2,3 - Trimethyl - 2,5 - dihydrothiophene - 1, 1 - dioxide (68)

To a cold solution of 2 g (0.016 moles) of 60 in methylene chloride was added 6.18 g (0.032 moles) of *m*-chloroperbenzoic acid in two equal portions. The exothermic reaction was moderated by an ice-bath. The solution was stirred at 0° for 3 hours and at room temperature for one hour. The precipitate was removed by filtration and the filtrate was washed with two 75 ml portions of saturated sodium carbonate solution, dried and evaporated. The residue solidified to give 2.5 g (100%) of a white solid: mp 64 - 65°; ν (CHCl₃) 1310, 1140, 1110 cm⁻¹; nmr (CDCl₃) δ 1.44 (s, 6), 1.81 (m, 3), 3.71 (m, 2), 5.70 (m, 1).

Anal. Calculated for $C_7H_{12}O_2S$: C, 52.46; H, 7.51; S, 20.00.

Found: C, 52.62; H, 7.72; S, 19.86.

3,4,5 - Trimethyl - 4 - cyclohexene - 1,2 - dicarboxylic acid (71a)¹¹⁰

Sulfone 68, 0.5 g (0.0031 moles) and 6.31 g (0.0031 moles) of maleic anhydride were dissolved in 5 ml of xylene and a small amount of hydroquinone was added. The solution was refluxed for 6 hours, cooled and evaporated to afford 0.5 g of a solid which was immediately hydrolyzed in boiling water for 1.5 hours. Evaporation and recrystallization of the residue from water gave 0.45 (58%) of the diacid:

mp 173-174° (reported¹¹⁰ 173-174°); ir (KBr) 3500 - 2500, 1705 cm^{-1} .

Reaction of (68) with maleic anhydride in toluene.

The reaction was run as before except that toluene was employed as the solvent. The evolution of sulfur dioxide was much slower and the reaction was monitored by nmr. After 165 hours of reflux, the reaction was essentially complete. The reaction was worked up as before and a mixture of acids was obtained from which 65 mg of 71 precipitated and was isolated by filtration. Esterification of the evaporated mother liquors with diazomethane gave a mixture of three esters which were separated by glc (8 ft. X 0.375 in SE-30 on Chromosorb w). These proved to be diester 71b, dimethyl 3,3,4 - trimethyl - 4 - cyclohexene - 1,2 - dicarboxylate 73b and 2 - carbomethoxy - 5 - hydroxy - 5,6,6 - trimethylcyclohexanecarboxylic acid lactone 74.

2 - Thiabicyclo [3.3.0] oct-4-ene - 2,2 - dioxide (75)

To a cold solution of 2.3 g (0.018 moles) of dihydrothiophene 62 was added 7.2 g (0.045 moles) of m-chloroperbenzoic acid in two equal

portions. The solution was stirred 1 hour at 0° and at room temperature for 1.5 hours. The solution was filtered and washed with two 25 ml portions of saturated sodium carbonate solution, dried and evaporated. The residue crystallized immediately to afford 2.5 g (87%) of a slightly yellow solid: mp 73-74°; ir (CHCl₃) 1325, 1140 cm⁻¹; nmr (CDCl₃) δ 1.7-2.6 (m, 6), 3.8 - 4.2 (m, 3), 5.75 (m, 1).

2 - Thia - 4,5 - dibromobicyclo [3.3.0] octane -2,2 - dioxide (75)

To 1.5 g (0.0094 moles) of 62 dissolved in 30 ml of carbon tetrachloride at 0° was added 1.5 g (0.0094 moles) of bromide dropwise over 0.5 hour. The reaction was stirred 1 hour at 0° and an additional hour at room temperature. The solution was evaporated and recrystallized from absolute ethanol to yield 2.5 g (83%) of white crystals: mp 116 - 118°; ir (CHCl₃) 1335, 1125 cm⁻¹; nmr (CDCl₃) δ 1.5 - 2.7 (m, 6), 3.44 (m, 2), 3.80 (t, 1), 4.88 (m, 1).

4,5-Dihydro - 4 - methoxycyclopentano[b] thiophene - 1,1 - dioxide (77)

To an excess of sodium methoxide in methanol was added 0.5 g (0.0015 moles) of the dibromosulfone 75. After stirring for 2 hours at room temperature, the solvent was removed and the residue taken up in ethyl acetate. The extract was washed with water, then brine, and dried over sodium sulfate. Evaporation of the solvent left a white solid: nmr (CDCl₃) δ 2.00 - 2.90 (m, 6), 3.42 (s, 3), 3.75 (m, 2), 4.60 (m, 1).

1,2 - Dibromo - 1 - ethoxyethane (78) was prepared according to the method of Batkibekova *et al.*¹²⁰ in 68% yield: bp 88° (35 mm) (reported bp 68-71° (10 mm)).

1 - Ethoxyvinyltriphenylphosphonium bromide (79)- A benzene solution of 22.00 g (0.1 moles) of the dibromide 78 and 26.2 g (0.1 moles) of triphenylphosphine was stirred at room temperature for 5 hours. The precipitate of 2 - bromo - 1 ethoxyethylphosphonium bromide was filtered off and immediately dissolved in methylene chloride. To this solution was slowly added 10.1 g (0.1 mole) of triethylamine. The exothermic reaction was moderated by cooling and the reaction was stirred for 3 hours. The precipitate of triethylamine hydrobromide was filtered off and solvent was removed from the filtrate. The resulting oil was heated in ethyl acetate for 0.5 hours to induce crystallization. A total of 17.0 g (41%) was isolated: mp 173 - 175°; nmr (CDCl₃) δ 1.39 (t, 3), 4.26 (q, 2), 4.80 - 6.20 (m, 2), 7.0 - 7.9 (m, 15).

2 - Thiophenoxy - 1 - ethoxyethyltriphenylphosphonium bromide (83)

To an excess of thiophenol containing a catalytic amount of triethylamine was added 2.0 g (0.0048 moles) of 79. The reaction mixture was refluxed overnight and a large excess of ethyl acetate was added to induce precipitation. Filtration and recrystallization from methylene chloride - ethyl acetate gave 0.85 g (33%) of a white crystalline solid: mp 177 - 180°; nmr (CDCl₃) δ 1.43 (t, 3), 3.12 (q, 2), 4.60 (q, 3), 7.60 (m, 20).

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VITA AUCTORIS

Born:

April 9, 1947; Toronto, Ontario.
Son of Mrs. Dorothy E. Goodbrand and the late Mr.
H. Benson Goodbrand.

Education:

Williamson Road Public School, Toronto, Ontario, 1951-1952.

Hugh Beaton Public School, Windsor, Ontario, 1952-1960.

Walkerville Collegiate Institute, Windsor, Ontario, 1960-1965.

University of Windsor, Windsor, Ontario, 1965-1969.
Degree: B. Sc. (Honours Biology and Chemistry), 1969.

University of Windsor, Windsor, Ontario, 1969-1973.
Graduate Studies leading to Ph. D. degree.

Awards:

University of Windsor Graduate Scholarship, 1973.

National Research Council of Canada Postgraduate Scholarship,
1969-1973.

Society of Chemical Industry Award of Merit, 1969.

University of Windsor Entrance and Renewal Scholarships,
1965-1969.

Ontario Scholar, 1965.

Publications:

Dihydrothiophenes I, A New Synthesis, J. M. McIntosh
and H. B. Goodbrand, Tetrahedron Lett., 3157 (1973).

Dihydrothiophenes II, The Preparation and Properties
of Some Alkylated 2,5-Dihydrothiophenes, J.M. McIntosh,
H.B. Goodbrand and G. M. Masse, J. Org. Chem. (in press).

Professional Affiliations:

The Chemical Institute of Canada.