SYNTHESIS OF MODEL COMPOUNDS
RELATED TO THE TETRANORTRITERPENES

BY

M. IQBAL TAHIRKHELI

A THESIS SUBMITTED TO THE DEPARTMENT OF CHEMISTRY
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF SCIENCE

LAKEHEAD UNIVERSITY

THUNDER BAY, ONTARIO, CANADA

APRIL 1971

Abstract

In this thesis some preliminary studies have been described, which were aimed at the synthesis of compounds in which a 3-substituted furan is attached to a δ-lactone ring so as to yield structures of the type observed in the naturally occurring tetranortriterpenoids (e.g. see structures [8] till [13] on pp. 2 and 3).

In an introductory literature survey various types of naturally occurring 3-substituted furan compounds have been described, and an outline has been given of some of the possible approaches to the synthesis of compounds containing a part structure [12] (p.3).

Since 3-halofurans are essential starting materials for such a synthesis, the effectiveness of some preparations of 3-iodofuran and 3-bromofuran as reported in the literature has been studied. The reactions of 3-furyl-lithium and 3-thienyl-lithium with aldehydes and esters led to the isolation of coupling products, which were studied in some detail.

Thus, oxidation of the alcohols obtained in this way gave information on the relative stabilities of this type of compounds under oxidising conditions. A mass spectrometric study of these model compounds led to the observation of some interesting fragmentation patterns which are discussed in detail.

Finally, various reactions are discussed which were directed towards the preparation of derivatives of α-tetralone, which could be used in similar coupling reactions, in order to arrive at the desired 3-furyl-lactone structure. These modifications of the α-tetralone molecule were largely unsuccessful. Therefore, the discussion is concluded with an examination of the reasons for these difficulties, and some suggestions are made with respect to future studies in this area.

ACKNOWLEDGEMENTS

The author records his deep gratitude to Dr. W.H. Baarschers, who directed this research. He is indebted to Dr. A.N. Hughes for valuable suggestions and for reading the manuscript, and to Dr. T. Griffith for assistance in spectrometric analyses.

The author is most grateful to the National Research Council of Canada and Lakehead University for their generous financial support.

TABLE OF CONTENTS

CHAPTER 1 INTRODUCTION

Most of the naturally occurring furans are substituted in the 3-position and are terpenoid in nature. The simplest of these is 3-furoic acid [1], isolated from the roots of *Evonymus atropurpureus*[1] and *Phaseolus multiformis*.[2] Perillene [2] and perilla ketone [3], isolated from various *Perilla* species,[3,4] are examples of monoterpenes.

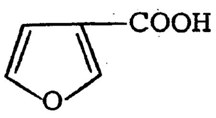
Examples of sesquiterpenes are dendrolasin [4], isolated from ants (Lasius)[5] and ipomeamarone [5], isolated from sweet potatoes infected with moulds of the *Ceratostomella species*.[6]

The most important diterpenoid furans are marrubin [6] and its derivatives, isolated from *Marrubium* species[7] and columbin [7], obtained from Colombo roots.[8,9]

The largest group of 3-substituted furans found amoung the triterpenes is mainly isolated from the plants of the *Rutaceae* and *Meliaceae* families. For example, limonin [8], nomilin [9], and obacunone [10] all have been isolated as the bitter principles of Citrus species.[10]

Although some syntheses have been reported in the mono- and sesquiterpenoid 3-furans, no total synthesis has so far been reported in the triterpene series.

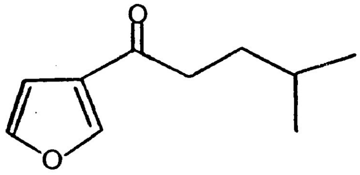
A common feature of the last group of compounds is


COOH
O

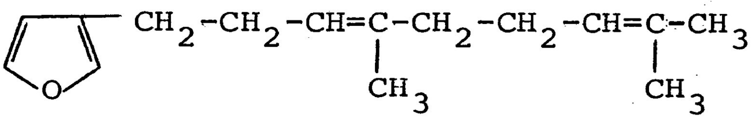
[1]


O

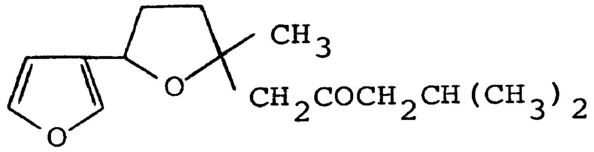
[2]


O
O

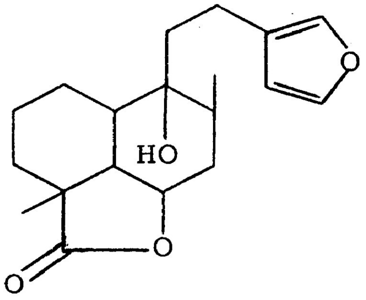
[3]


CH2-CH2-CH=C-CH2-CH2-CH=C-CH3
CH3
CH3
O

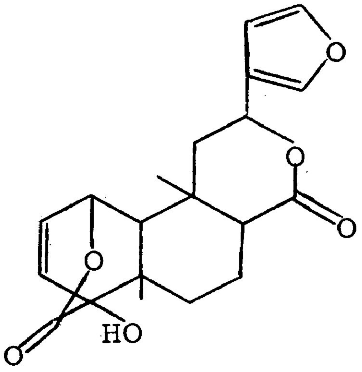
[4]


CH3
CH2COCH2CH(CH3)2
O
O

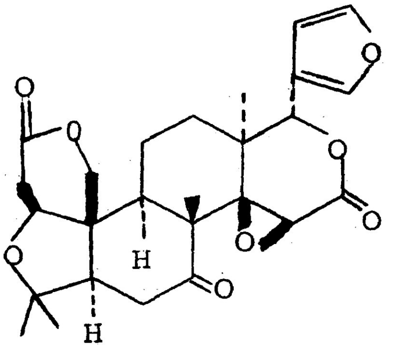
[5]


HO
O
O
O

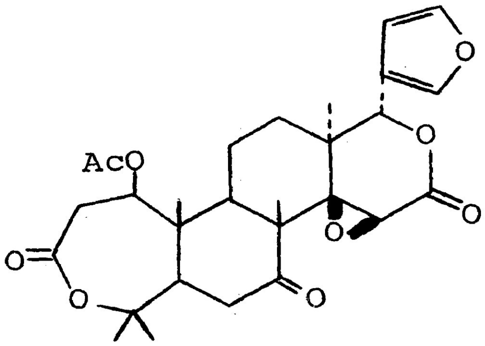
[6]


O
O
O
O
HO
O
O

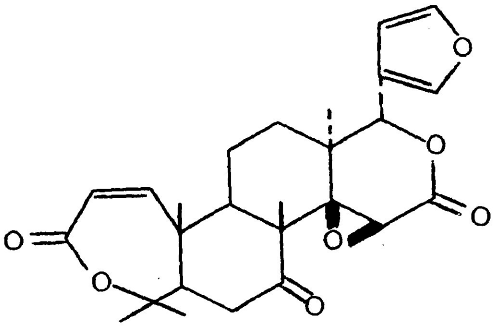
[7]



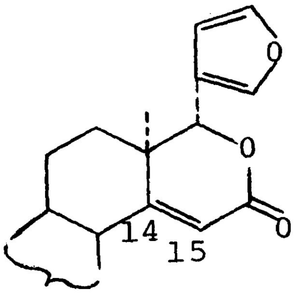
[8]



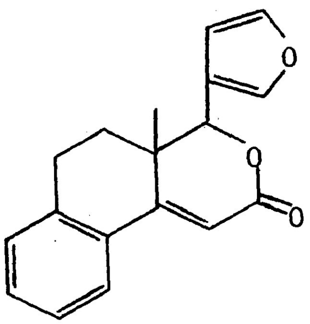
[9]



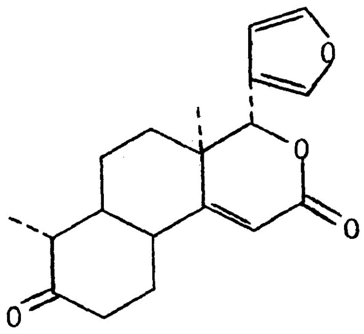
[10]



[11]



[12]



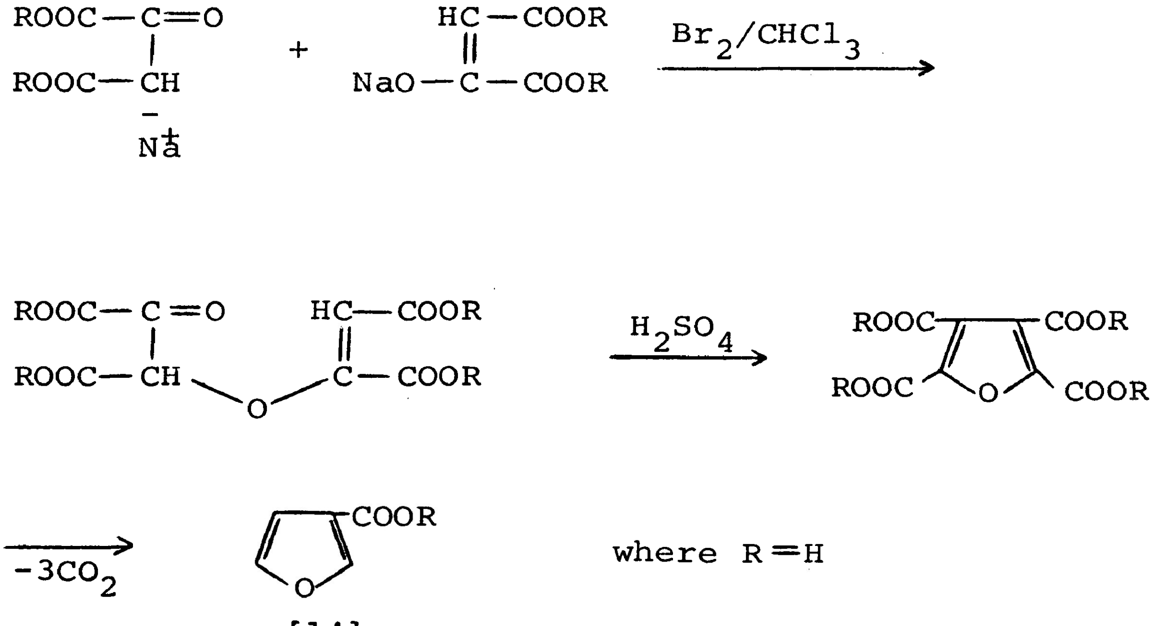
[13]

the part structure [11] with minor variations in the functionality at C_{14} and C_{15}.

The object of the present study is the investigation of suitable reactions with model compounds, which could be used initially for the synthesis of such a structure e.g. [12]. Eventually these reactions could then be used for a total synthesis for one of the simplest compounds in this series such as odoratin[11] [13].

The syntheses of most of the simpler terpenoid 3-furans involve 3-furoic acid as a starting material. The 3-furoic acid [14] itself may be synthesized as follows:-

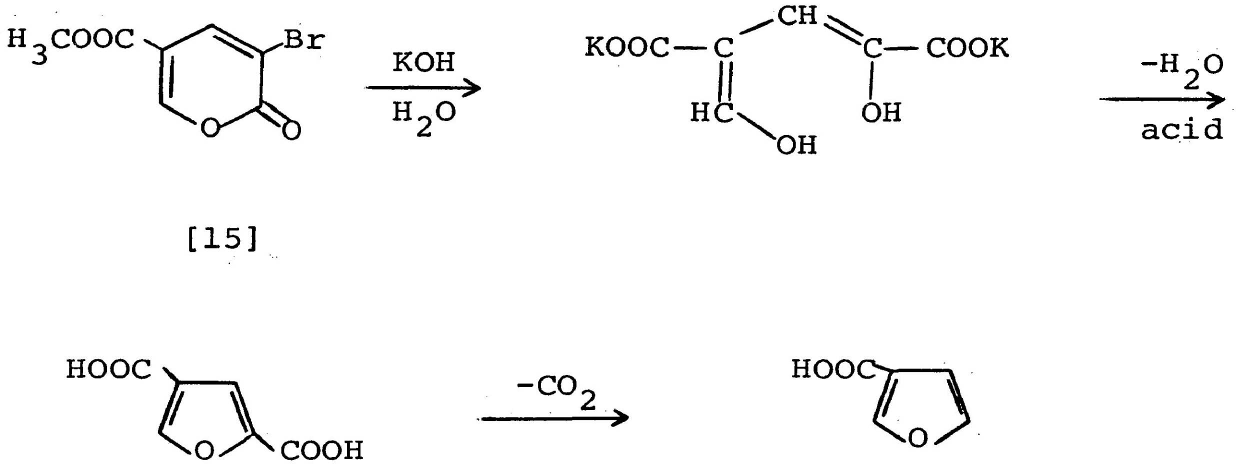
(1) By controlled decarboxylation of furan tetracarboxylic acid,[12,13] which in turn is obtained by the following reaction sequence:



[14]

where R=H

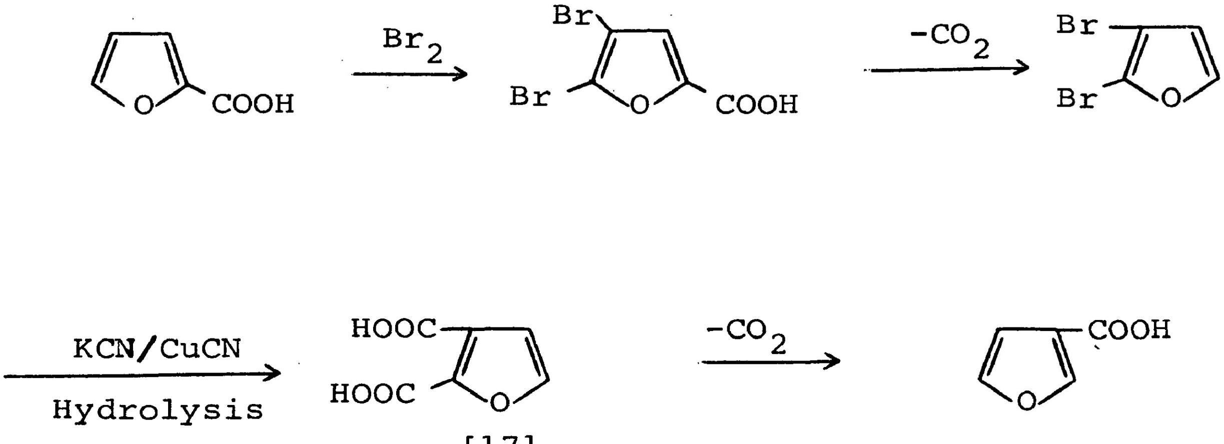
(2) By decarboxylation of furan 2,4-dicarboxylic acid [16], which is prepared from pyrone derivative[14] [15].



[15]

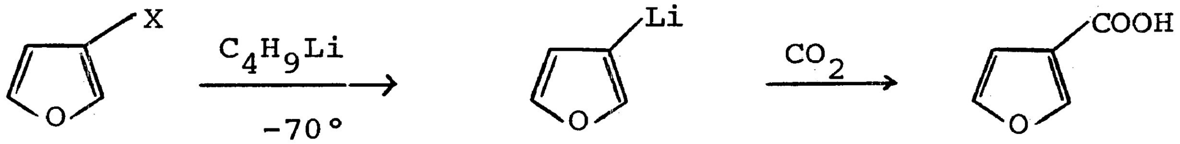
[16]

(3) By decarboxylation of furan 2,3-dicarboxylic acid[15] [17], which may be synthesized from 2-furoic acid:



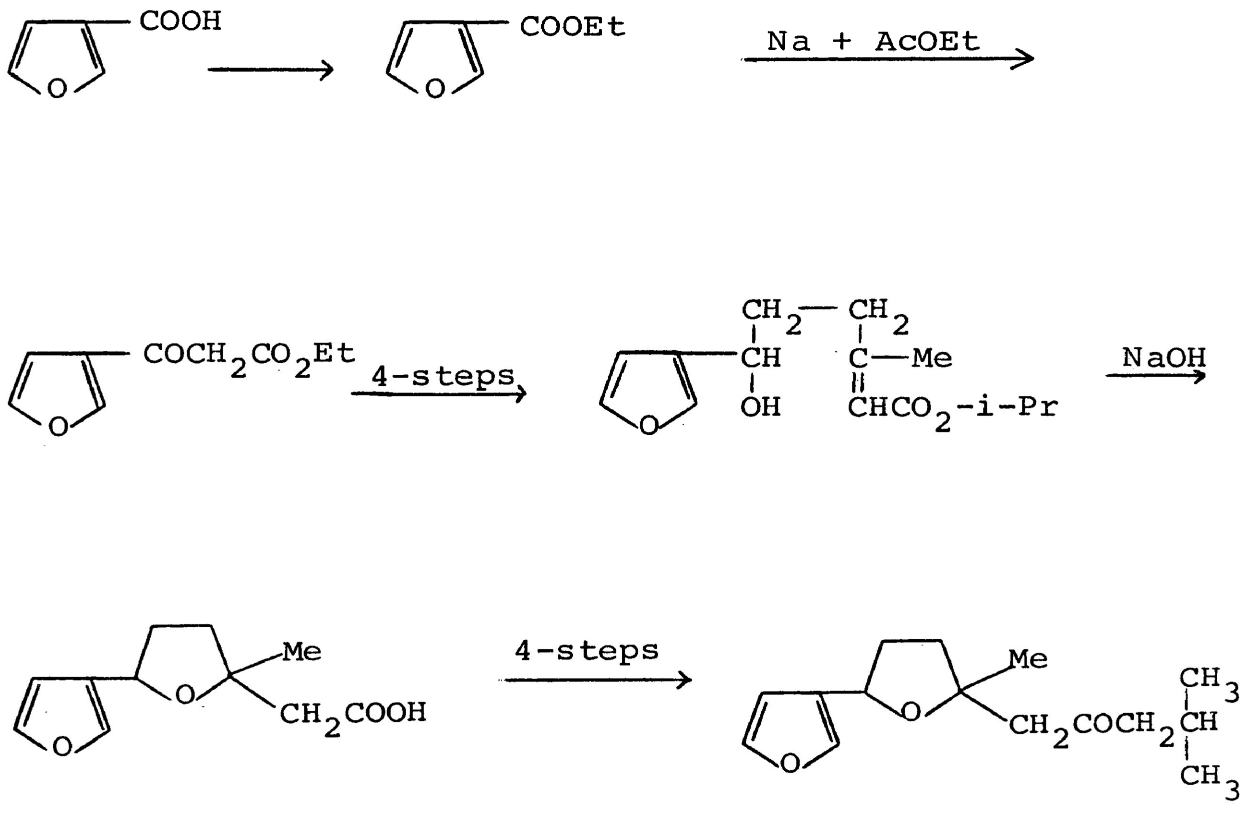
[17]

(4) From suitable 3-halofurans,[16] by reaction of the corresponding lithium derivative with solid CO_2 at -70°



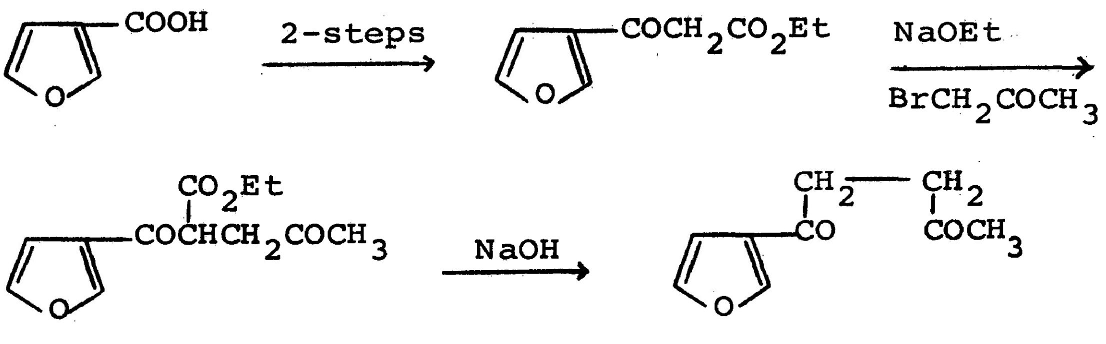
where X = Br or I

A synthesis of Ipomeamarone[17] [18] has been reported as follows:



[18]

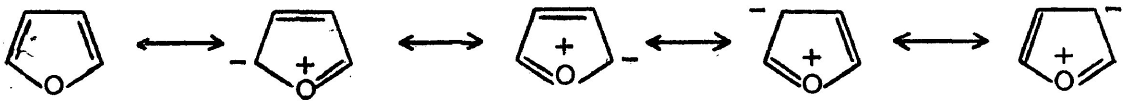
A synthesis of Ipomeanine[18] [19] is likewise reported to involve 3-furoic acid as the starting material:



[19]

3-Substituted furans in general are not easily accessable for the following reasons:

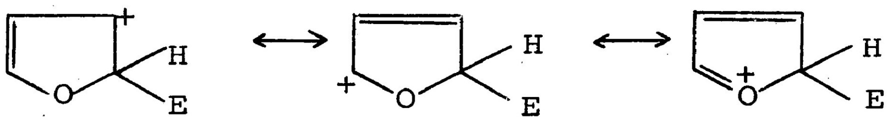
The resonance canonical forms of furan indicate that the 2-carbon atoms are more reactive towards electrophilic attack than the 3-carbon atoms.



[20] [20a] [20b] [20c] [20d]

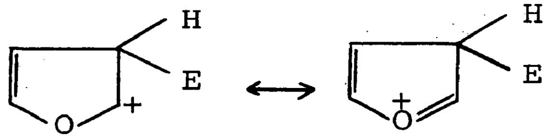
Structures [20a] and [20b] are completely conjugated and therefore make a larger contribution to the overall structure than [20c] and [20d], which are cross-conjugated. Also in [20a] and [20b] the energy required to separate the charges will be lower than in [20c] and [20d]. The transition state for electrophilic substitution at each position is stabilized by the accommodation of the positive charge by oxygen.

2-substitution



[21a] [21b] [21c]

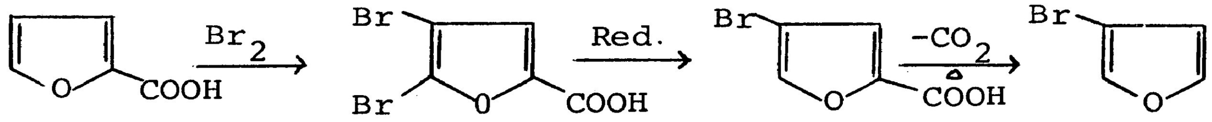
3-substitution



[21d] [21e]

2-Substitution predominates because the positive charge in the transition state is delocalized over a total of three atoms [21a-c], compared with two [21d-e] in the case of 3-substitution.

Inspite of these difficulties, some 3-substituted furans have been synthesized by multi-step processes. 3-Bromofuran[15] [24] has been prepared through reduction of 4,5-dibromo-furan-2-carboxylic acid [22] which selectively removes the 5-bromine, followed by decarboxylation of the 4-bromo-2-furan carboxylic acid [23].

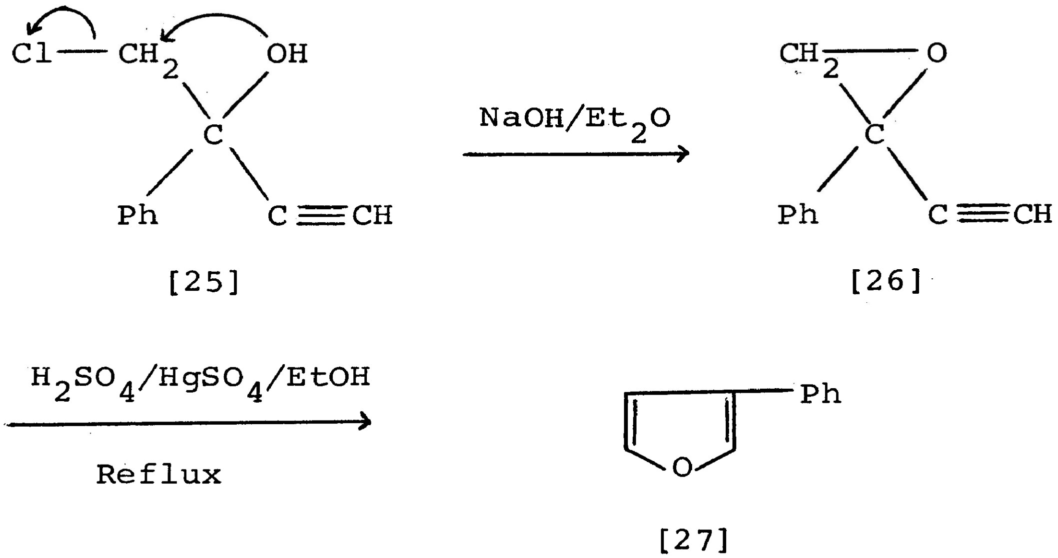


[22] [23] [24]

Some 3-substituted furan compounds such as 3-phenyl- and 3-methylfuran have been prepared. A few such compounds have been obtained by modifying the carboxyl group of furan 3-carboxylic acid.[19,20]

Wynberg[21] synthesized 3-phenylfuran from 3-hydroxytetrahydrofuran in a four step procedure. 3-Hydroxytetrahydrofuran[22] itself was prepared from 1,2,4-trihydroxybutane in the presence of p-toluene sulphonic acid as a catalyst.

Newer methods have been worked out recently. For example, 3-phenylfuran[23] [27] has been synthesized from the phenylacetylenic epoxide [26], which is obtained from the chloroacetylenic carbinol [25] in a one step procedure:

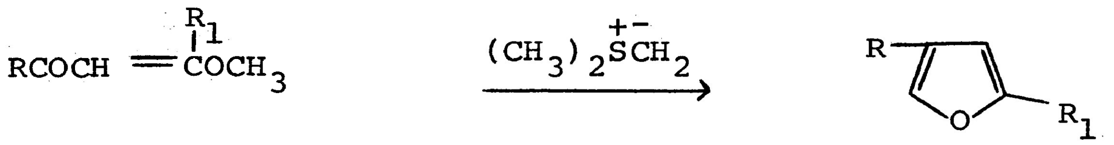


[25]

[26]

[27]

Another single step method involves the enol-ether[24] [28] according to the following reaction sequence:



[28]

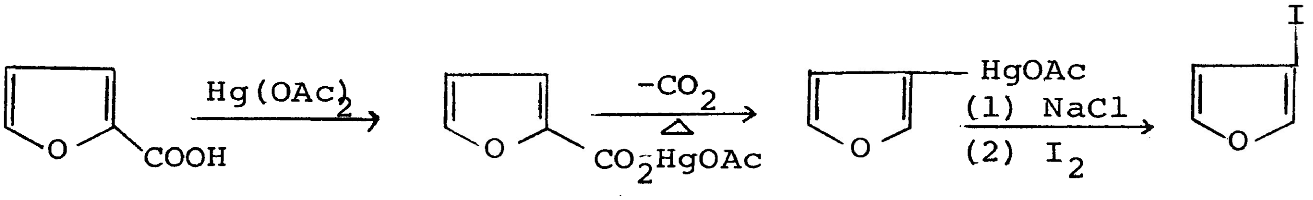
where $R=C_6H_5$; $R_1=H$

Likewise 3-methylfuran[25] [30] has been synthesized from 3,4-epoxy-3-methylbutanal diethylacetal [29] by refluxing in 0.1N sulfuric acid for 3 hr.

[29] [30]

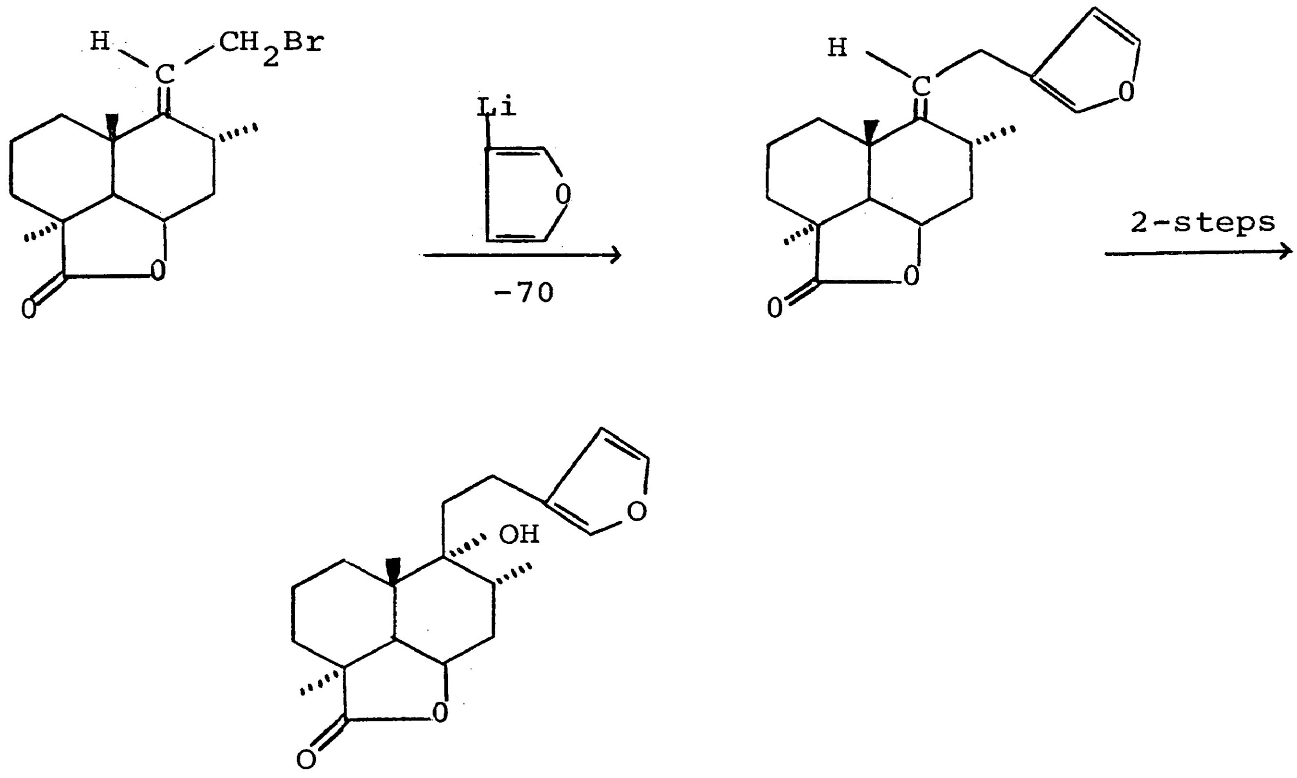
However, the alkyl and aryl groups in these molecules are not suited to the introduction of the 3-substituted furan group into a larger molecule.

A larger variety of 3-substituted furans recently became available when Gronowitz *et al.*[16] made the observation that 3-halofurans undergo lithium-halogen exchange at -70°. 3-Iodofuran [32] was made in nearly quantitative yield from the corresponding chloromercuryfuran[16] by treatment with iodine as follows:



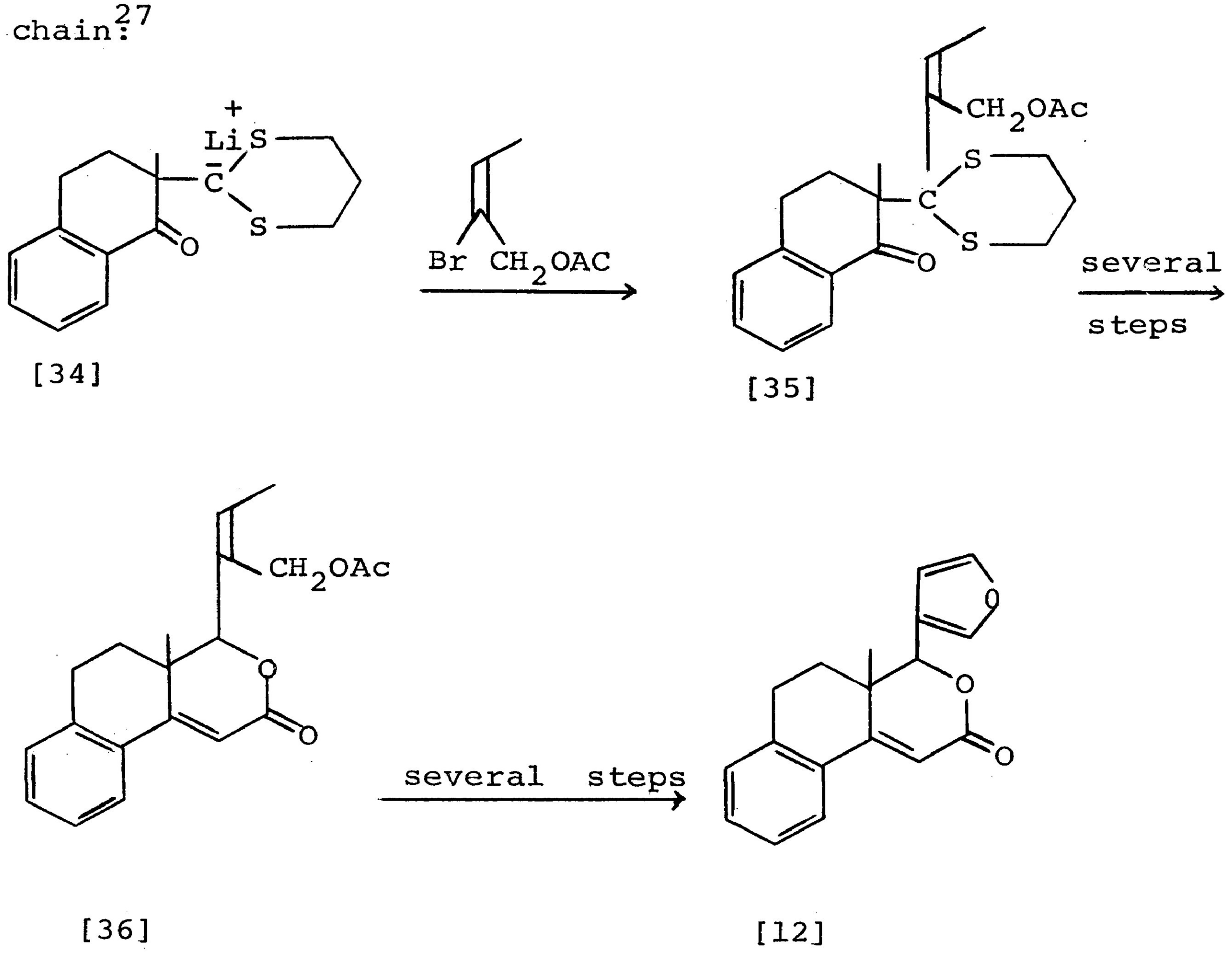
[31] [32]

As an example of this method, a partial synthesis of marrubin[26] [33] has been reported, according to the following reactions:



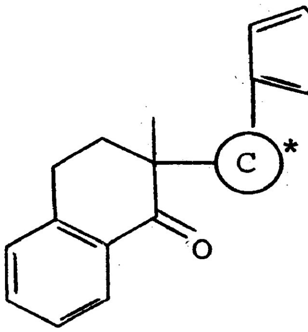
[33]

Now that the object of the present study has been placed in perspective with respect to the major aspects of 3-furan chemistry, it is necessary to discuss some of the possible approaches to a synthesis of a structure like [12] (p. 3). The logical starting point for the construction of [12] would be a suitably substituted α-tetralone. There are two general ways of introducing the furan ring into such a molecule (tetralone). Firstly, a suitable side chain, which is later cyclized to the furan may be attached to the 2-position of the α-tetralone. A method that could be useful for this purpose involves the use of the lithioderivative [34][28] which would lead to [35]. Such a compound, after introduction of the lactone ring [36], could then lead to [12] by cyclization of the side chain[27]:



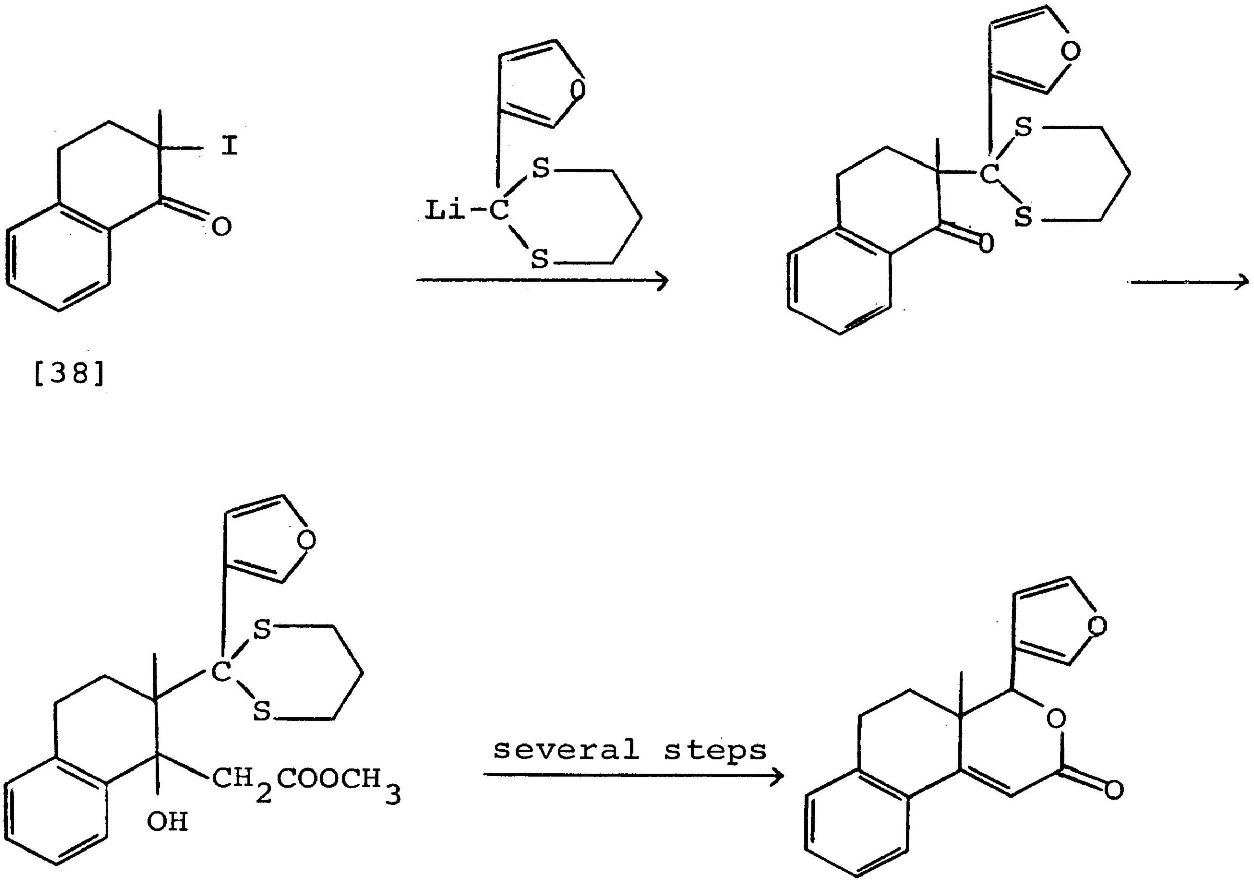
Secondly, an intact 3-substituted furan could be attached directly to the α-tetralone. In the latter case, the carbon atom ($\overset{*}{C}$) may be considered in two ways:

Referring to [37], ($\overset{*}{C}$) could initially be a part of the furan derivative used, or could be a part of the α-tetralone before introduction of the furan.



[37]

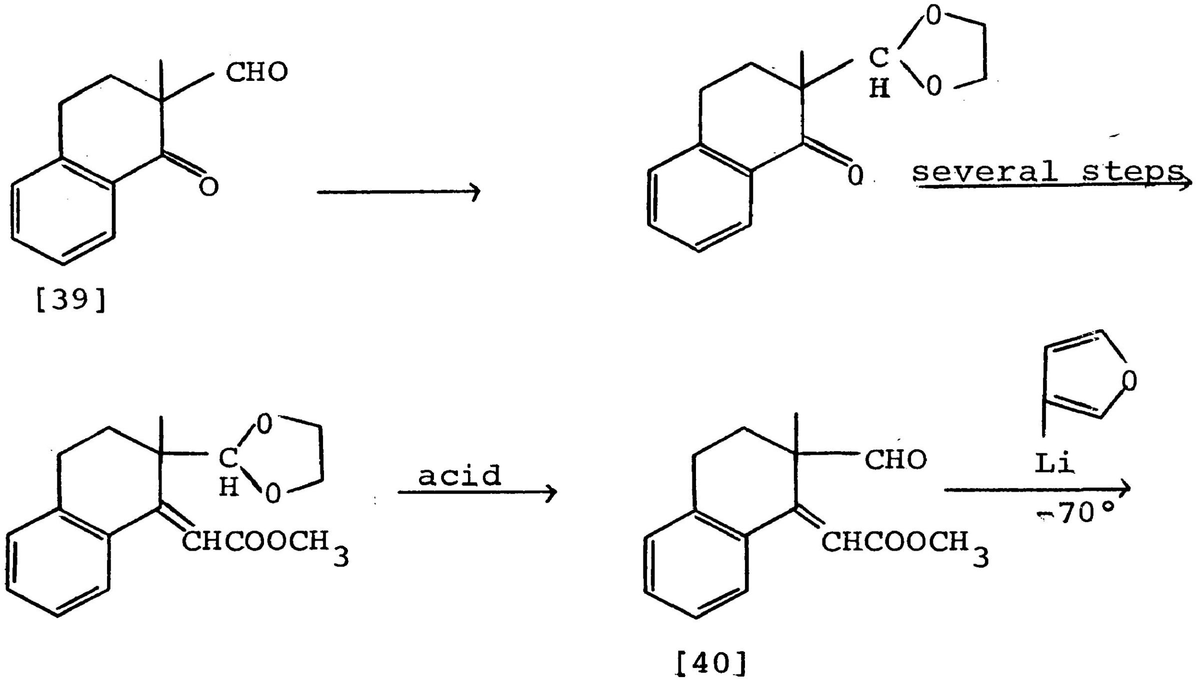
If carbon ($\overset{*}{C}$) is part of the furan system e.g., furan 3-aldehyde, one way in which it could be attached to the α-tetralone derivative [38] is *via* its dithiocarbanion:[28]

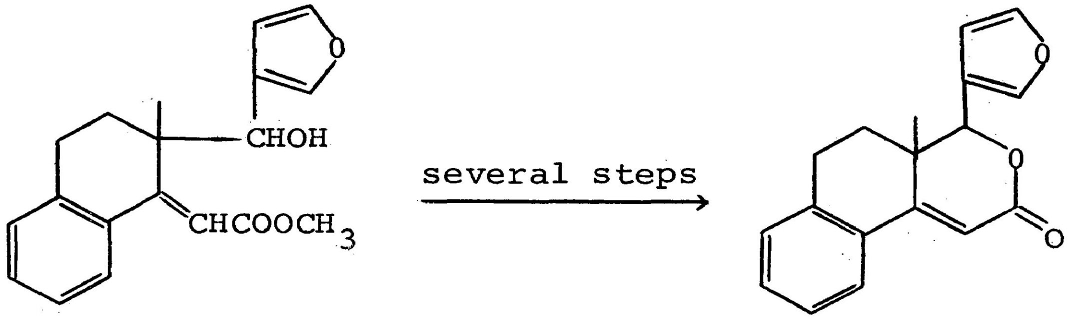


[38]

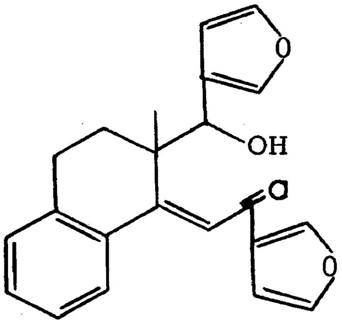
However, this type of halide [38] leads to elimination rather than to the reaction as stated.[28] Therefore this method cannot be used as such. The alternative is to start with ($\overset{*}{C}$) as part of the *a*-tetralone system and the reaction of choice is the reaction of 3-furyl lithium with that carbon atom. The carbon atom ($\overset{*}{C}$), therefore has to carry a functional group suitable for such a reaction e.g., a carbonyl group, in order to permit the subsequent formation of the lactone ring at a later stage.

In the case of the aldehyde [39], there are two reaction centres i.e., ketone and aldehyde, that may be attacked by the 3-furyl-lithium. To overcome this difficulty, it is best to protect the aldehyde with a protective group which should be inert to the reaction conditions so that a side chain which is required for lactone formation can be attached first, according to the sequence [39] → [41] → [12], below:





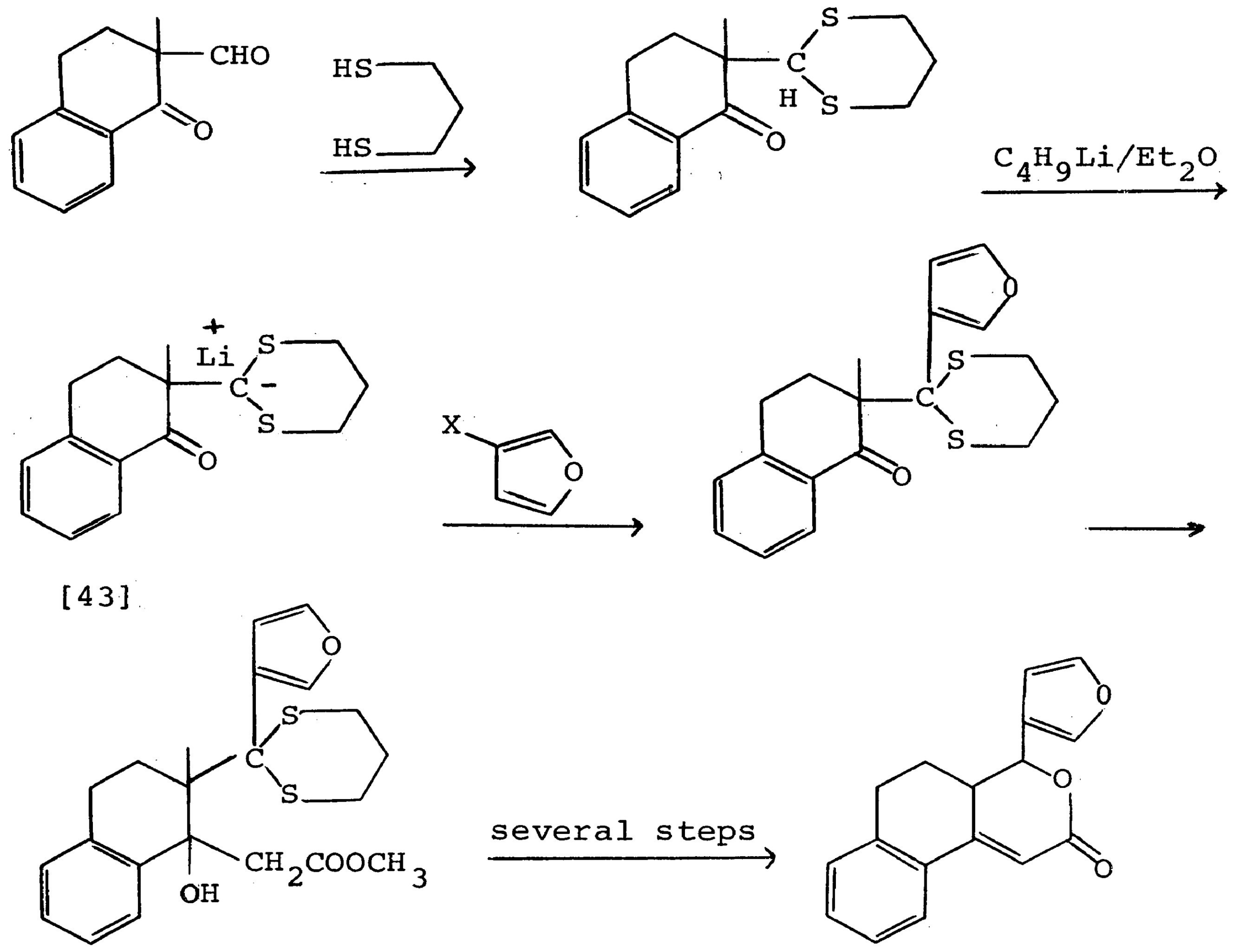
[41] [12]



[42]

The relative reactivity of the ester group and the aldehyde group is of critical importance in the conversion of [40] into [41]. Therefore, a series of experiments was done as outlined in the next chapter and it was found that the ester reacts slowly as compared to the aldehyde group (see p. 28). There is only a small chance for the formation of the side product [42], because in structure [40] the reactivity of the ester group is further reduced by its conjugation with the aromatic ring.

Another possible approach is to convert the carbonyl carbon atom into a nucleophilic centre *via* its dithiocarbanion [43] to react with a suitable 3-halofuran that could lead to the product [12].



[43]

[12]

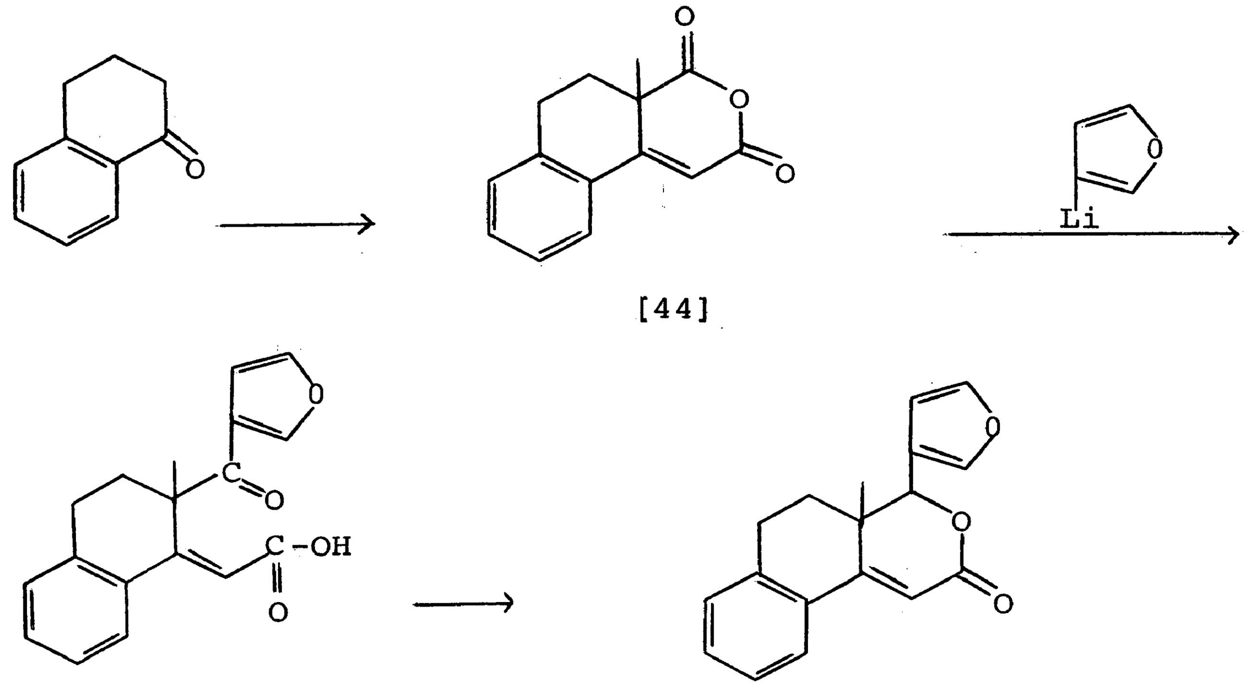
The reactivity of the dithiocarbanion [43] with aromatic halo compounds was therefore investigated[29] but the results, which will be reported elsewhere, indicated that this approach would not be successful.

Another approach is based on the observation that an anhydride like [44] should be easily attainable. The reactions of 3-furyl-lithium and similar compounds are similar to the reactions of Grignard reagents. Various reports* on the behaviour of anhydrides towards Grignard

---

*For references see description of this reaction in Chap. 2.

like reagents suggested that a sequence [44] → [45] → [12] should be considered.

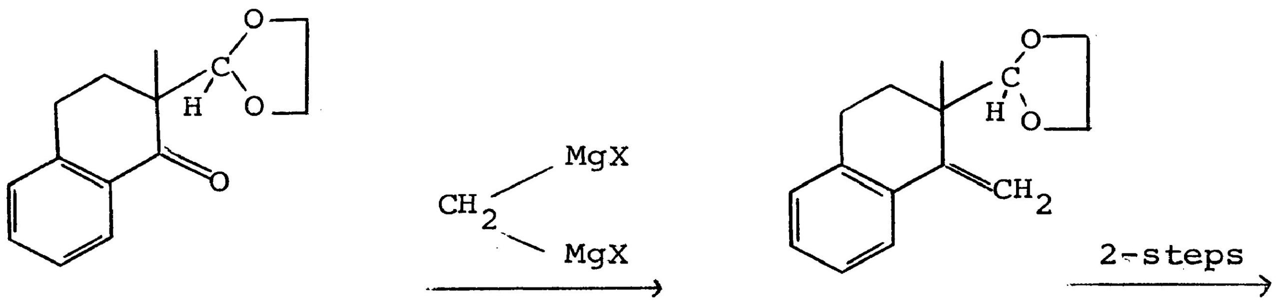


[44]

[45]

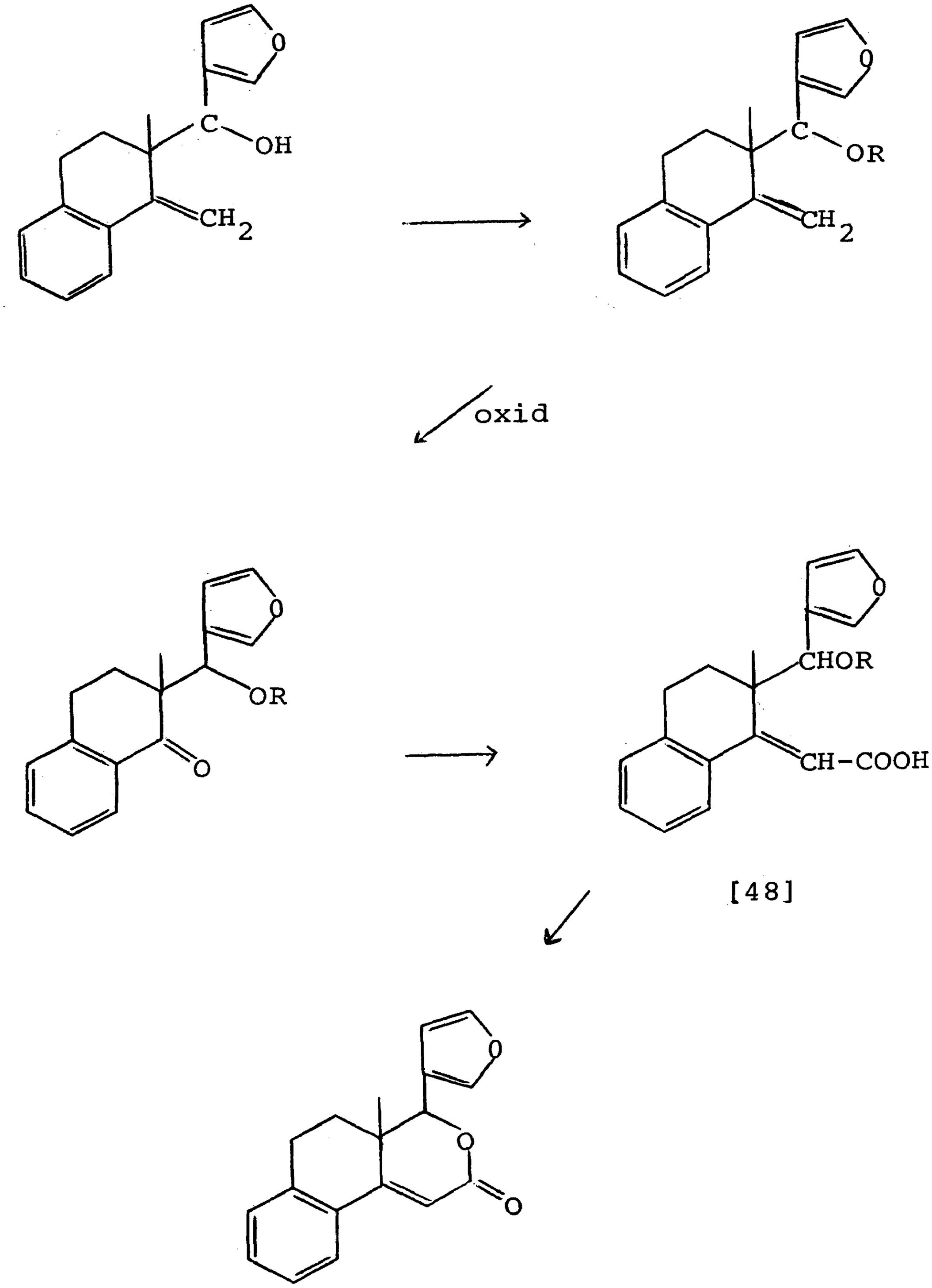
[12]

Finally, as an alternative method of protecting the ketone group of the α-tetralone system, it was found possible to convert this ketone to an exocyclic methylene group by means of a "gem di-Grignard" reagent.[30] This could be considered as the initial step in a sequence [46] → [47] → [48] → [12].



[46]

[47]



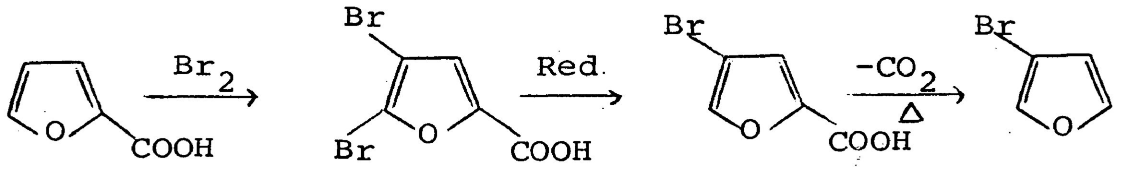
[48]

[12]

CHAPTER II , SYNTHESES OF 3-SUBSTITUTED FURANS

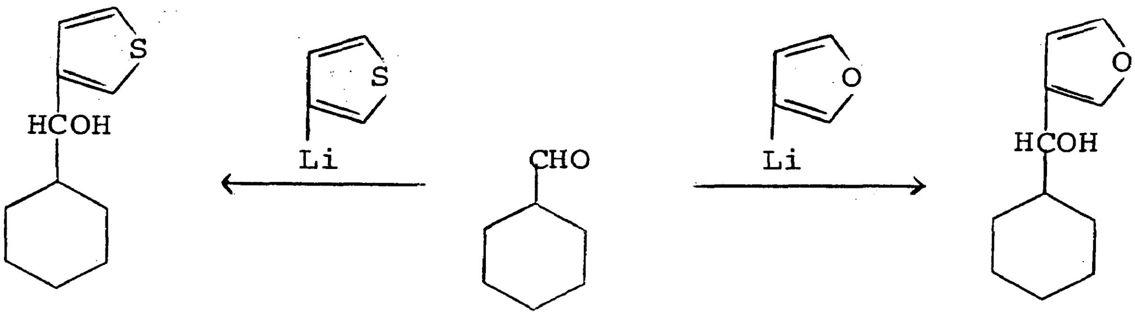
Initially the preparation of 3-iodofuran via 3-chloromercuryfuran according to Gronowitz[16] (see also p.10) appeared to be the most suitable route to the desired 3-substituted furans. The yield of 3-chloromercuryfuran has been reported by Gronowitz as approximately 15%. The use of this reaction, in our hands, although it led to the desired product, resulted in even lower yields (11%). Although the starting materials e.g., furoic acid and $Hg(OAc)_2$ are readily available, the cost involved would be considerable. Therefore, the preparation of 3-bromofuran by the procedure of Shepard *et al.*[15] was also investigated. It was found that this method proceeded smoothly up to the preparation of 3-bromo-2-furoic acid, (see sequence [49] → [50]). However, decarboxylation of this acid gave very disappointing results, and it was then decided to return to the method of Gronowitz.[16] As 3-iodofuran was required in fairly large quantities, and, as pointed out above, is expensive to prepare, an alternative solution was sought. From earlier work of Gronowitz[31] *et al.* it was noted that 3-bromothiophene, which is now commercially available, gives the same halogen metal interconversion at -70°. It was, therefore, decided to prepare a few model compounds which instead of a furan ring would contain a thiophene ring, and compare these with the corresponding furan compounds. For this purpose cyclohexanecarboxaldehyde [51] was made to react with 3-thienyl-lithium and 3-furyl-lithium for comparative studies. Both 3-thienyl-lithium and 3-furyl-lithium reacted smoothly giving nearly quantitative yields of the corresponding alcohols [52] and [53] respectively. The infrared spectra of both [52] and [53] contained strong hydroxyl bands at 3400 $cm.^{-1}$ The n.m.r. spectra contained complex multiplets at τ8.1 - 9.1 (aliphatic protons), doublets at τ5.4 - 5.6 ($\underline{H}$-C-OH, coupled with the neighbouring ring proton) and a complex multiplet at τ2.5 - 3.1 (aromatic protons) in the case of the thiophene compound [52] and three peaks at τ2.6 - 2.8 representing the α and the β-protons on the furan ring in the case of the furan compound [53].

For a full characterization of these alcohols it was decided to oxidize them to the corresponding ketones [57] and [58] from which crystalline derivatives could easily be obtained. Oxidation could be easily achieved with chromium trioxide (Jones' reagent),[32] in the case of the thiophene derivative [52] where it led to nearly quantitative yield. However, the furan alcohol [53], on treatment with this reagent, yielded a mixture of compounds from which no pure product could



[49]

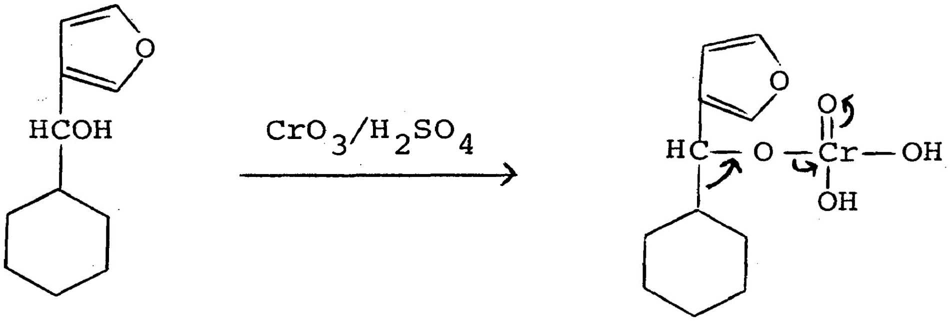
[50]



[52]

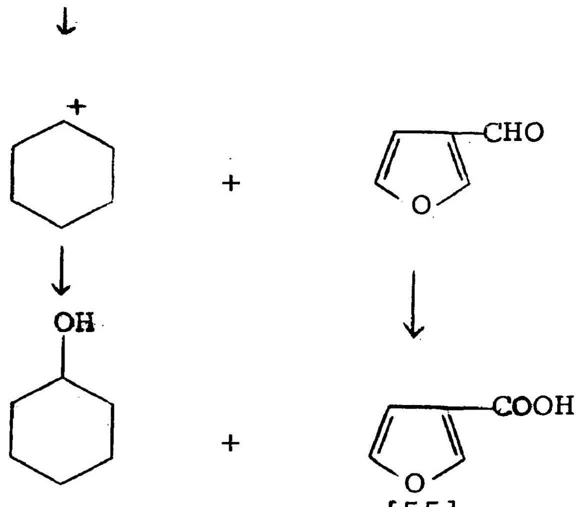
[51]

[53]

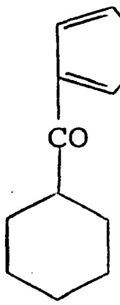


[53]

[54]



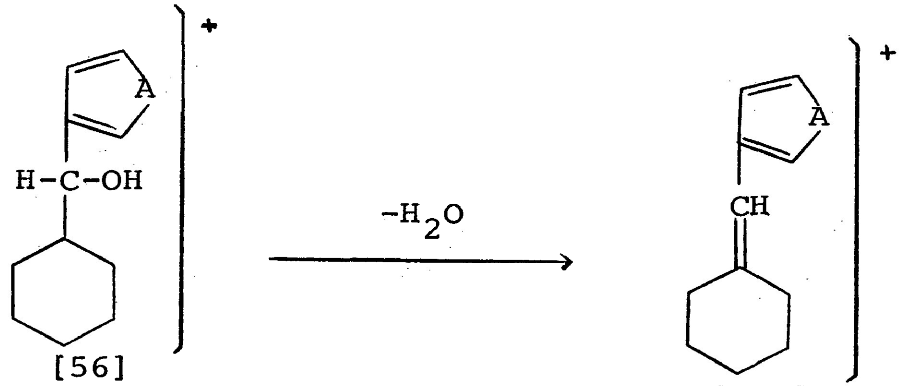
[55]



[57, A=S]
[58, A=O]

be isolated. The infrared spectrum of the crude mixture indicated the presence of carboxylic acid, which may arise from a benzylic alcohol type cleavage (ref. 32a as in sequence [53] → [54] → [55]). Manganese dioxide, which is reported to be a suitable oxidizing agent for oxidation of allylic[33] and benzylic[34] alcohols was then used successfully to oxidize the furan alcohol [53] to the corresponding ketone [58] in nearly quantitative yield. Both ketones [57] and [58] were characterized by the preparation of crystalline 2,4-dinitrophenylhydrazones[35] which gave satisfactory analytical results. The infrared spectra of the ketones no longer contained hydroxyl absorptions in the 3400 cm^{-1} region, and instead had strong carbonyl absorptions around 1680cm^{-1}.

In the n.m.r. spectra of both ketones, the signals due to the proton α to the hydroxyl group, which were observed in the spectra of the alcohols, had disappeared. The absorption patterns for the aromatic protons had changed in the spectra of the ketones as compared to those of the alcohols. In the case of the two furan compounds it could be seen easily that the resonance signal of one of the α-protons of the furan ring had shifted downfield by approximately 0.7 p.p.m., probably due to a long range shielding effect of the carbonyl group. Although the aromatic proton pattern of the thiophene compounds was not as clear, it could be



[56]

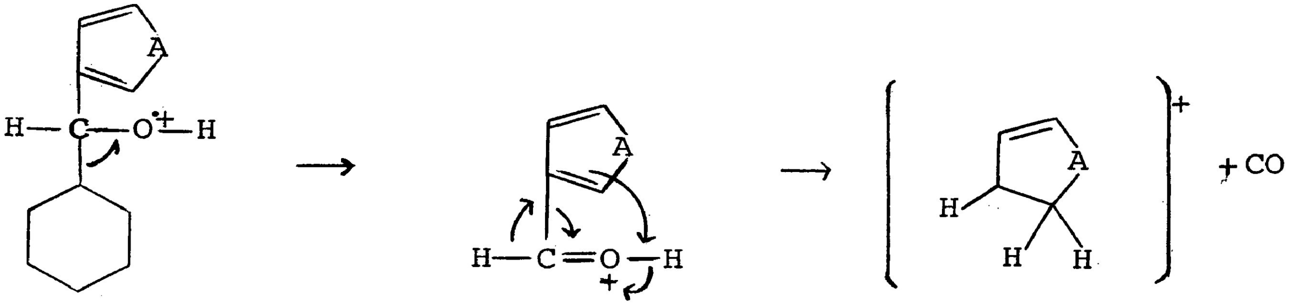
M^+= 196 (A = S)

M^+= 180 (A = O)

[56a]

m/e 178 (A = S)

m/e 162 (A = O)



[56]

[56b]

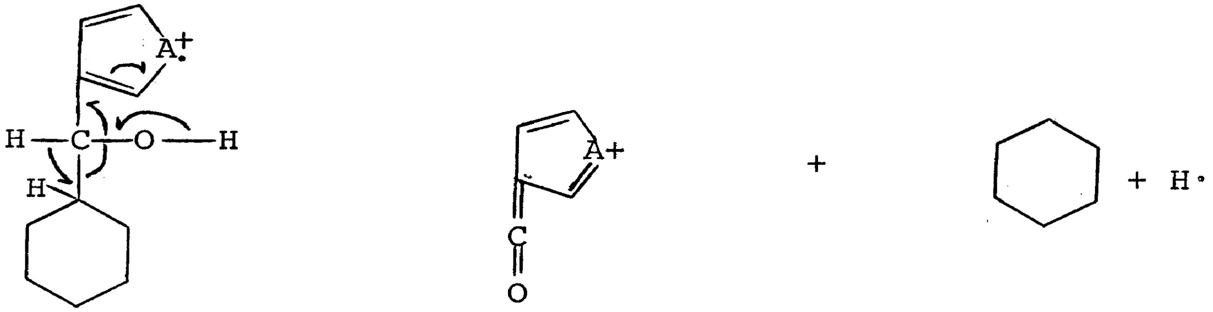
m/e 113 (A=S)

m/e 97 (A=O)

[56d]

m/e 85 (A=S)

m/e 69 (A=O)

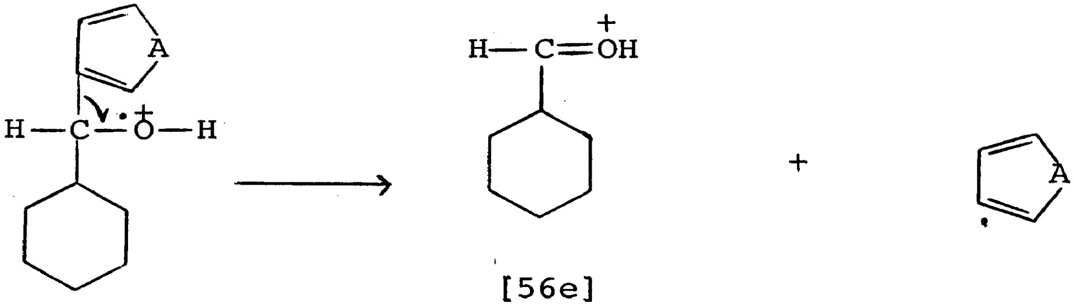


56

[56c]

m/e 111 (A=S)

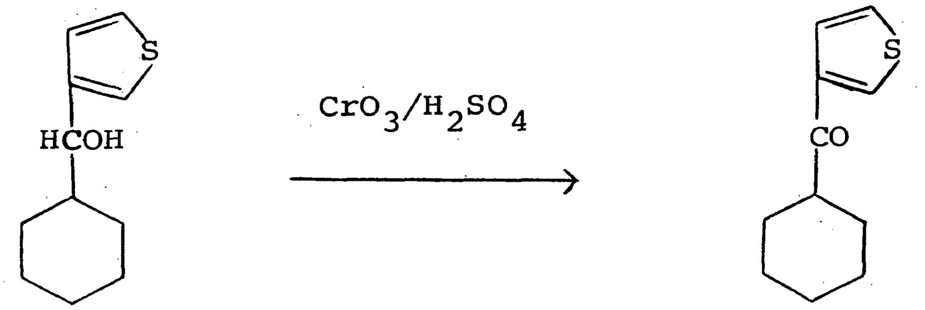
m/e 95 (A=O)



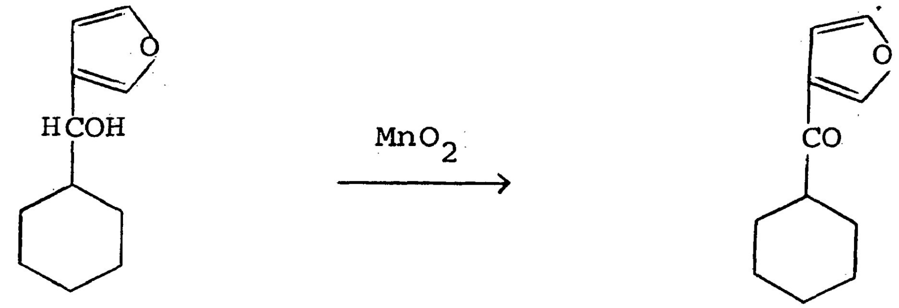
[56]

[56e]

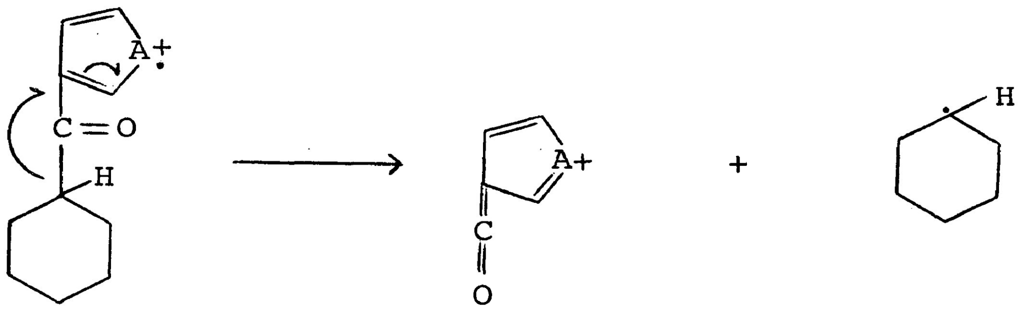
m/e 113



[52] [57]

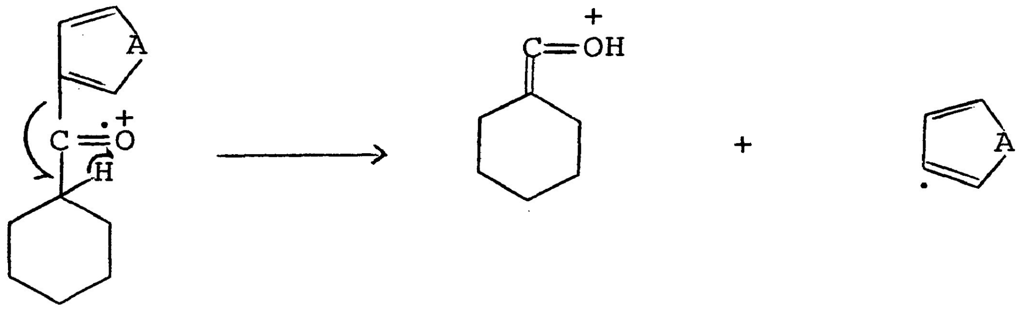


[53] [58]



[58] [58a]

m/e, 111 (A = S)
m/e, 95 (A = O)



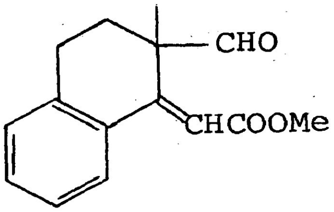
[58] [58b]

m/e, 111

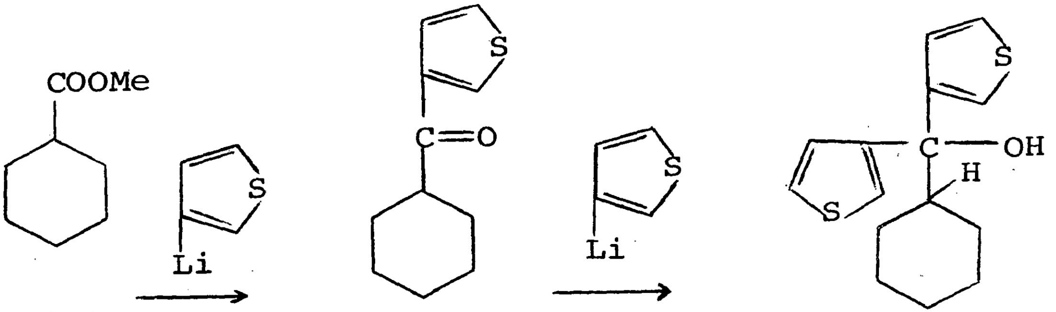
established that here also one aromatic proton signal had shifted downfield after oxidation.

The interpretation of the mass spectra, in which unfortunately no metastable peaks could be observed, is facilitated by considering both alcohol-ketone pairs simultaneously. In the case of the thienyl alcohol, an intense peak at m/e 113 is taken as the base peak and additional peaks can be identified as follows: M^+-18, corresponds to the loss of water as in [56] → [56a]. Normally the M^+-18, peak as observed in primary and secondary alcohols is stronger than the molecular ion peak itself. In the present case however, the M^+-18 peak (14%) was considerably weaker than the molecular ion peak (69%). This means that other fragmentations involving the hydroxyl group are probably more favoured. The base peak in the spectrum of the thienyl alcohol at m/e 113 can be visualized as in [56, A=S] → [56b, A=S]. A corresponding peak at m/e 97, was found in the spectrum of the furan derivative [56b, A=O]. A strong peak at m/e 111(75%) in the spectrum of the thienyl carbinol can be interpreted by the cleavage [56, A=S] → [56c, A=S]. Again a peak at m/e 95 [56c, A=O] is present in the spectrum of the corresponding furan derivative [56, A=O].

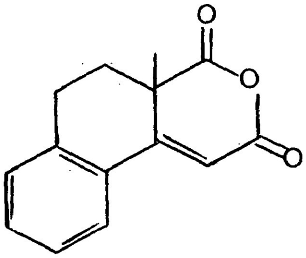
In the spectra of the two ketones, the base peaks were at m/e 111 and m/e 95 respectively. These peaks are probably due to the same fragments [56c,] which could arise from the ketones as in [58] → [58a]. As expected the peaks at m/e 113 [56b, A=S] and m/e 97 [56b, A=O] were absent in the spectra of the ketones. However, the peak at m/e 113 in the spectrum of the thiophene alcohol could also arise from the fragmentation [56] → [56e]. That such a fragmentation does indeed take place follows from the observation that the spectra of both alcohols [52] and [53] contain a strong peak at m/e 113, although the furan derivative [53] could not give rise to a fragment at m/e 113, containing the furan ring. Further information could be obtained by investigating the peak at m/e 113 in the spectrum of the thiophene alcohol [52]. If both ions [56b, A=S] and [56e] are formed, the peak at m/e 113 should be a doublet, representing both the fragments $C_7H_{13}O$ [56e] and C_5H_5SO [56b, A=S]. A high resolution spectrum of the thiophene alcohol [52] did indeed confirm this fragmentation pattern by showing the peak at m/e 113 to be a doublet consisting of m/e 113.007 [56b, A=S] and m/e 113.905 [56e] in a 15:2 intensity ratio. The intensity ratio of this doublet indicated that the formation of [56b] is strongly favoured. The loss of CO from the fragment [56b] may explain the presence of strong peaks at m/e 85 (for thiophene) and m/e 69



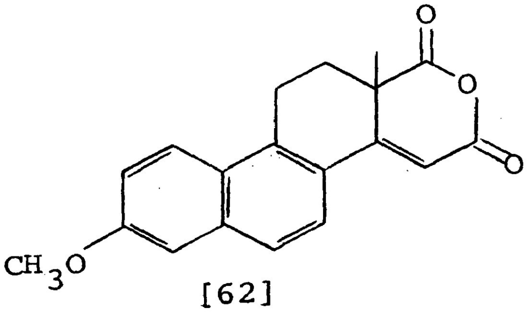
[40]



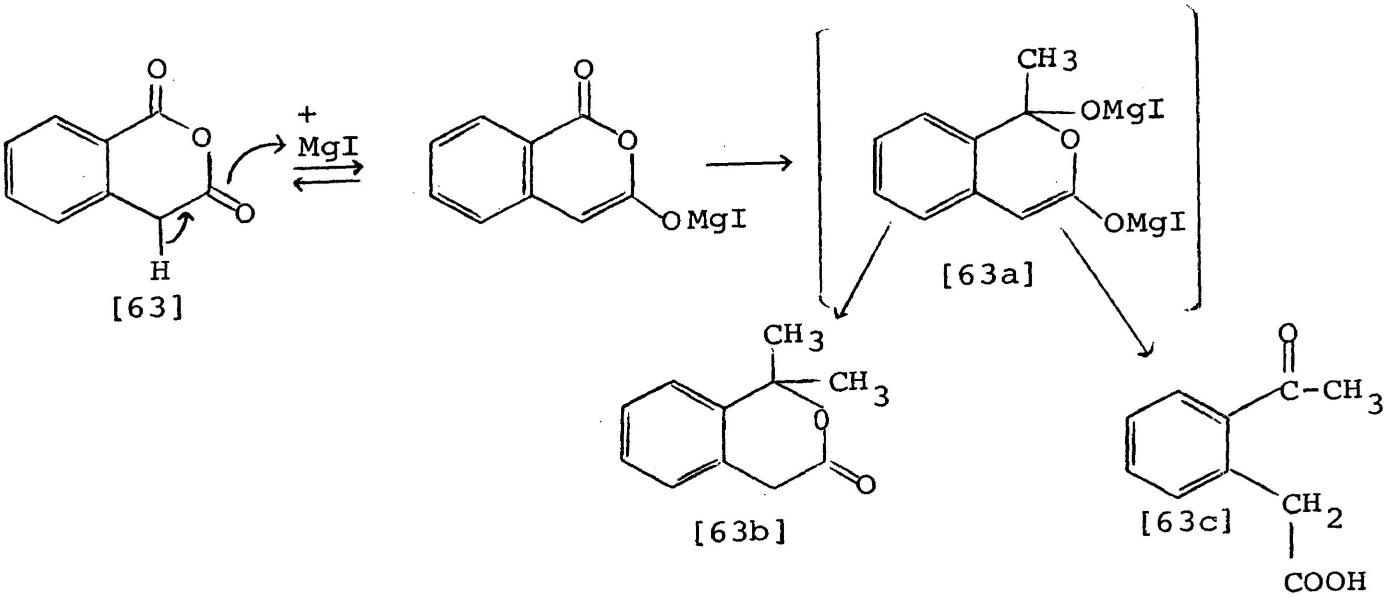
[59] [60] [61]



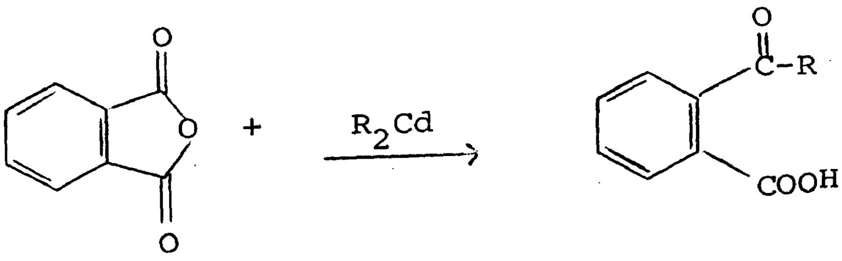
[44]



[62]



[63] [63a] [63b] [63c]



[64] [64a]

(for furan). The latter process could be rationalized in terms of a 2-electron-shift process e.g., [56b] → [56d].

As mentioned earlier (p. 15) the reactivity of the ester and aldehyde groups in a compound like [40] is of considerable importance, and in order to investigate this aspect, it was decided to attempt the conversion of the ester of cyclohexylcarboxylic acid [59] into the ketone [60]. Therefore, one mole of 3-thienyl-lithium was slowly added to one mole of the ester [59]. The crude reaction product, on thin layer chromatography, was found to consist mainly of unchanged starting material. From spectral data on this crude reaction product, it was apparent that a very small amount of material was present, for which [61] would be a likely structure. Its formation *via* [60] is straightforward and its suggested presence in the reaction mixture follows from the following observation: The infrared spectrum, although virtually indentical to that of the starting material, contained a very weak OH-band and the mass spectrum contained a peak at m/e 260, which is related to the molecular ion of [61] e.g., M^{+}(=278)-18. A strong peak at m/e 142 indicated the presence of the ester [59].

This reaction was carried out essentially under the same reaction conditions as the reaction of cyclohexane carboxyldehyde with 3-thienyl-lithium. It follows, therefore, that the ester reacts with the lithium compound much more slowly than the aldehyde and it would thus be possible to introduce the heterocyclic ring into a compound containing both an aldehyde and an ester function.

A final model reaction which was studied involved the reaction of the heterocyclic lithium compounds with dicarboxylic acid anhydrides.

First, the anhydride [62] has been reported[36] to be fairly easily obtainable. From α-tetralone, the anhydride [44] should therefore also be available. (Refer to diagrams on p. 27)

On the reaction of anhydrides with Grignard type reagents several reports are available in the literature.

Homophathalic anhydride [63], when treated with methyl magnesium iodide,[37] is apparently first hydrolyzed and subsequently reacts with one more mole of Grignard reagent to give the intermediate [63a]. The authors stated however, that this intermediate reacts rapidly with a third mole of methyl magnesium iodide to give [63b], and stressed the fact that the keto ester [63c] could not be obtained.

On the other hand, de Benneville[38] stated that the use of the alkyl cadmium compounds, prepared from the corresponding alkyl magnesium halides, react with phthalic anhydride [64] to give satisfactorily yields of the desired keto-esters [64a].

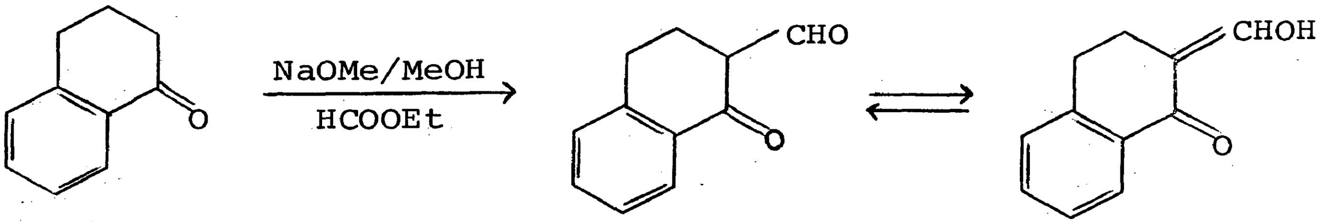
Although 3-bromothiophene is reported to undergo Grignard reactions[31] the opposite is true for the 3-halofurans.[16] Therefore, since variations in the type of organo metallic reagent lead to different results, it was decided to investigate the reaction of homophthalic anhydride with the lithium compound derived from 3-bromothiophene. The reaction was carried out in the usual way e.g., slow addition of the lithium compound to the anhydride at -70°. The product was a complex mixture, which consisted mainly of acidic material. Part of the product separated during the extraction procedure as a white solid, which was insoluble in most of the usual organic solvents. Its infrared spectrum (in Nujol) indicated a broad carboxyl band. However, the mass spectrum gave disappointing result by indicating a peak at a much higher mass number (i.e. m/e 262) than the expected m/e 246.

The rest of the mixture (50%) appeared to consist of at least four different compounds. Although the mass spectrum of this mixture showed a peak at $M^+= 246$, which could be the molecular ion of the desired product, the yield was poor and therefore further investigation was abandoned.

CHAPTER III REACTIONS WITH THE α-TETRALONE SYSTEM

As the aldehyde group proved to be the most suitable carbonyl functionality (see p. 28) for the attachment of the furan ring, it was decided to use α-tetralone [65], available commercially, as the starting material. To introduce the aldehyde group, α-tetralone was made to react with ethyl formate in the presence of alcoholic sodium methoxide according to the reaction sequence [65] → [66]. The product [66] which gave a deep violet colour with ferric chloride, had in its infrared spectrum a broad band at 2800 - 3200 cm^{-1} and the carbonyl band had shifted to lower wave number (1750 cm^{-1} from 1625 cm^{-1}) as compared to α-tetralone [65].

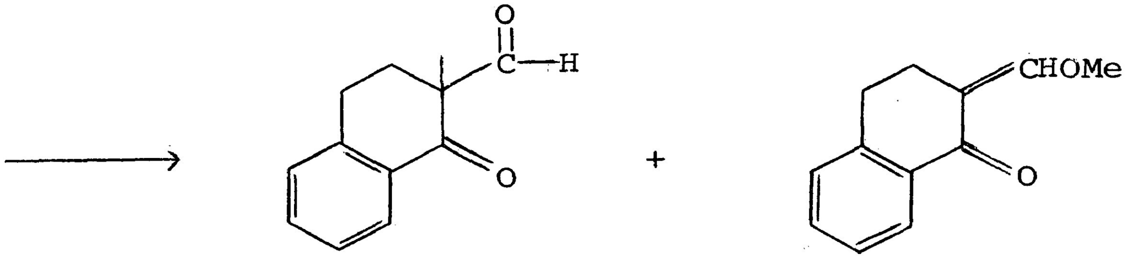
The hydroxy methylene derivative [66], was then methylated with methyl iodide in the presence of sodium carbonate to yield a mixture of methylated derivatives [67] and [68]. The infrared spectrum of the crude reaction mixture indicated the presence of the aldehyde group (1730 cm^{-1}) and the conjugated ketone group (1670 cm^{-1}). The n.m.r. spectrum indicated the presence of the aldehyde group ($\tau 0.4$), and the angular methyl group ($\tau 8.62$) of [67], and the methoxyl group ($\tau 6.13$) of [68]. From the intensity ratio of the C-Me and O-Me signals it



[65]

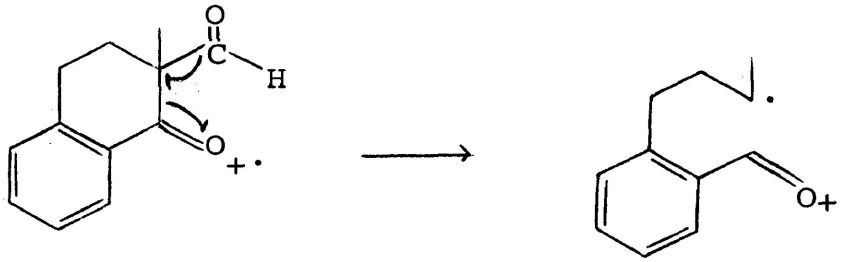
[66]

[66]



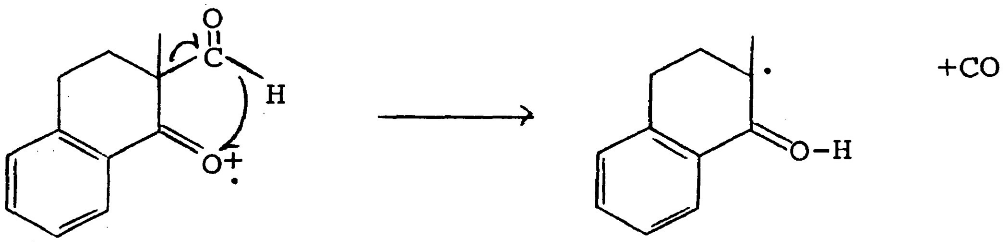
[67]

[68]



[67]

[a] m/e 159 = M^{+}-29



[67]

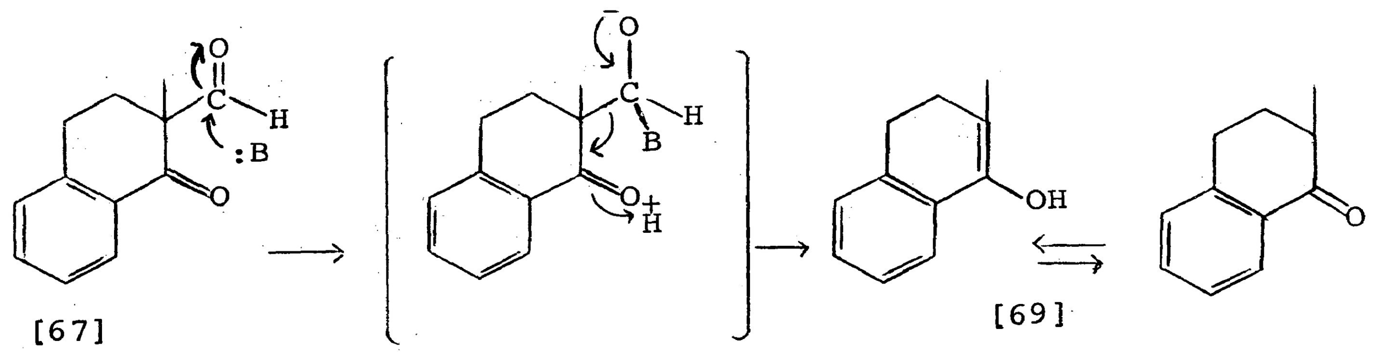
[b] m/e 160 = M^{+}-28

was concluded that the methylation reaction had yielded [67] and [68] in a 2:1 ratio. The mixture was separated by column chromatography and the pure keto-aldehyde [67] was isolated in good yield. Its n.m.r. spectrum indicated the presence of the aldehyde group (τ0.4) and the angular methyl group (τ8.63) and was compatible with its structure. In the n.m.r. spectrum of the methoxy derivative [68], the aldehyde and the angular methyl group resonances at (τ0.4 and τ8.63 respectively) were absent. Instead, a methoxyl signal at (τ6.13) was observed. The mass spectrum of the keto-aldehyde [67] gave the molecular ion peak at M^+=188 and peaks at m/e 159 i.e. loss of CHO as in [a] and m/e 160 i.e. loss of CO as in [b].

The keto-aldehyde [67] contains a β-dicarbonyl system, which under the influence of alkali will undergo cleavage to give [69]. Nevertheless it was felt that an attempt should be made to introduce the furan ring directly into this compound. Therefore, the keto-aldehyde [67] was made to react with 3-bromothiophene and butyl-lithium at -70°. However, the results indicated that cleavage indeed took place either directly as in [67] → [69], or as a second step in the reaction with 3-thienyl-lithium and the desired aldol [70] could not be isolated. The ketone [69] could be identified by its infrared spectrum, which contained a single carbonyl band at 1690 cm^{-1}. The mass spectrum contained the molecular ion at $M^{+}=160$ and peaks at m/e 132 and at m/e 91, which indicate the loss of CO and subsequent formation of the tropyllium ion as in [69] → [a] → [c].

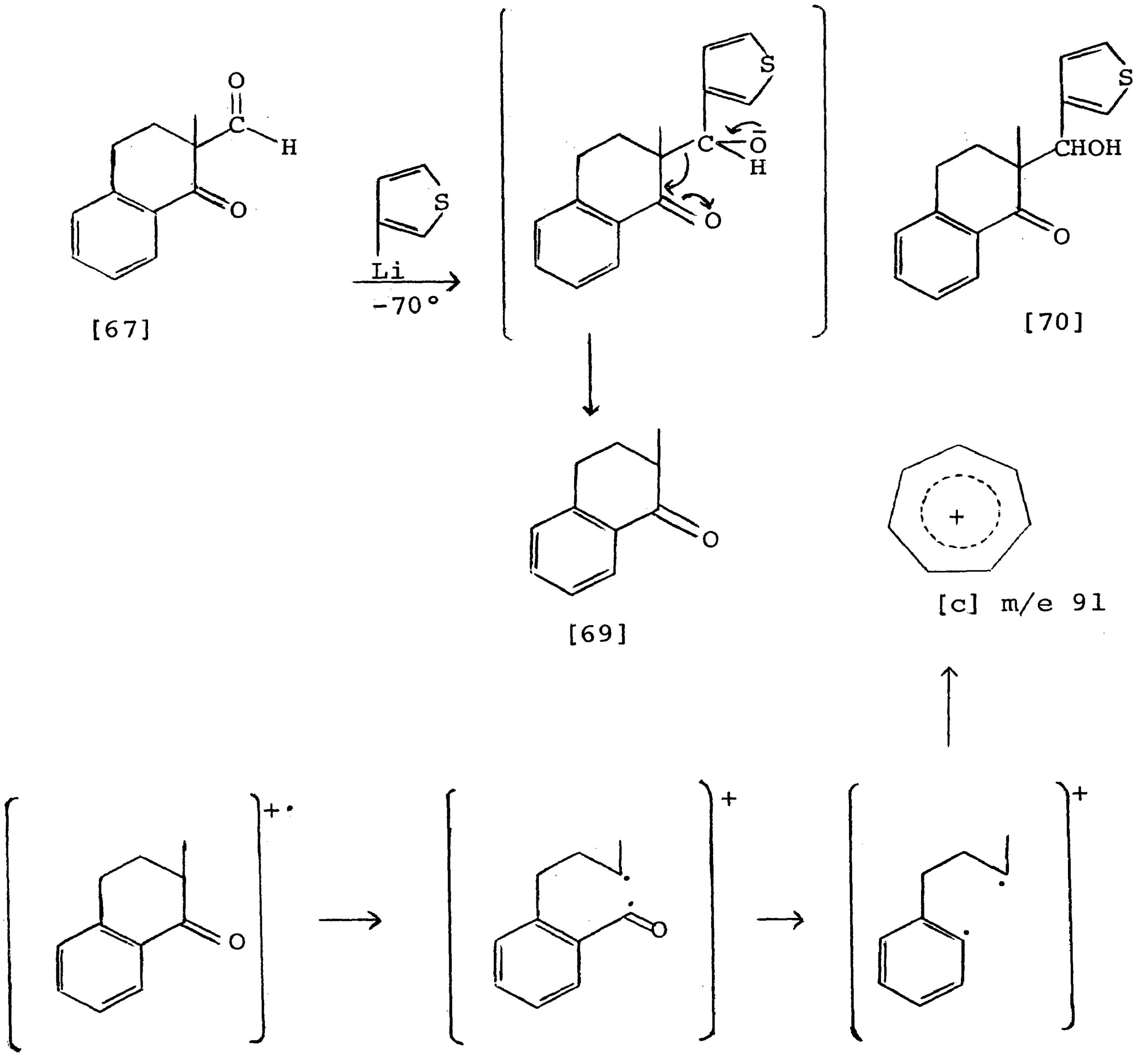
In order to prevent this type of cleavage of the keto-aldehyde under the alkaline reaction conditions required for the introduction of the heterocyclic ring, it was necessary to protect one of the carbonyl functions for further reactions with this compound. As it is not possible to introduce a ketal α- to the aromatic ring, the first attempt for such a measure was centered on the aldehyde group. Therefore, the aldehyde [67] was made to react with ethylene glycol in acidic medium to yield the acetal [71]. The infrared spectrum of [71] no longer contained the carbonyl absorption at 1750 cm^{-1}, which was previously attributed to the aldehyde group. There was also some change in the spectrum in the region 1150 - 900 cm^{-1} (due to the acetal group).

The keto-acetal [71] was then reduced in nearly quantitative yield to the corresponding hydroxy derivative [72] with lithium aluminium hydride. Various methods were used in attempts to remove the acetal group, but an effective conversion to the desire aldol [73] could not be achieved. Instead, a mixture of at least five products resulted, as indicated by thin layer chromato-



[67]

[69]



[67]

[70]

[69]

[c] m/e 91

[69], $M^+ = 160$

[a]

[b], m/e 132

graphy. The infrared spectrum of this reaction mixture contained a strong hydroxyl band, which may be attributed to the production of ethylene glycol, which was not effectively removed during work-up. Since there was no indication of the presence of the aldehyde in this mixture, it must be assumed that the aldol [73], if at all formed, is further decomposed.

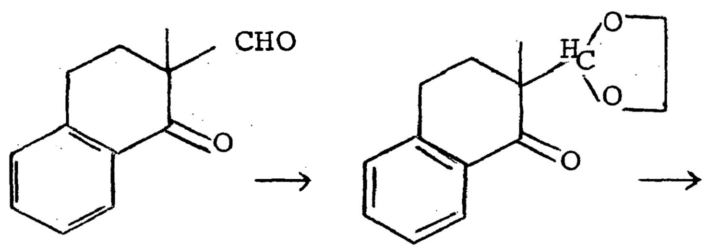
An attempt was then made to circumvent cleavage reactions of this type as follows. An alkali promoted cleavage as described above was also reported by Bachmann *et al.*[36] during attempts to saponify the diester [74] which led to [75]. These authors found that dehydration of the hydroxydiester [74], via the chloroderivative [76], gave a mixture of isomeric acids [77], which was stable to alkali.

Following a similar reasoning, it was decided to attach the ester side chain first, before removal of the acetal would be attempted. Therefore, the keto-acetal [71], was subjected to a Reformatsky reaction with methyl bromoacetate and the resulting hydroxy ester [78] was treated with thionyl chloride in pyridine to yield the corresponding chloro-compound [79].

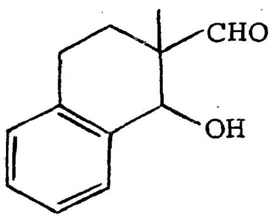
The infrared spectrum of the Reformatsky ester [78], contained a strong hydroxyl band at 3500 cm^{-1} and an ester band at 1650 $cm.^{-1}$ The n.m.r. is also consistent with structure [78], indicating the presence of the angular methyl group (τ9.02), the methyl ester group (τ6.5), a doublet of doublets of the four acetal protons (centered at τ6.05), the hydroxyl proton (τ5.0), the proton adjacent to the acetal group (τ5.32) and finally four aromatic protons (τ2.4 - 3.1) and aliphatic protons (τ6.6 - 8.3). The mass spectrum did not contain the molecular ion peak at M^+=306, instead a strong peak at m/e 288 (i.e. M^+-18) is present due to loss of water.

The infrared spectrum of the chloro-derivative [79] no longer contained a band around 3500 $cm.^{-1}$ The n.m.r. spectrum of this compound is very similar to that of [78] inso far that the one proton resonance at (τ5.0) attributed to the OH group of [78] had disappeared.

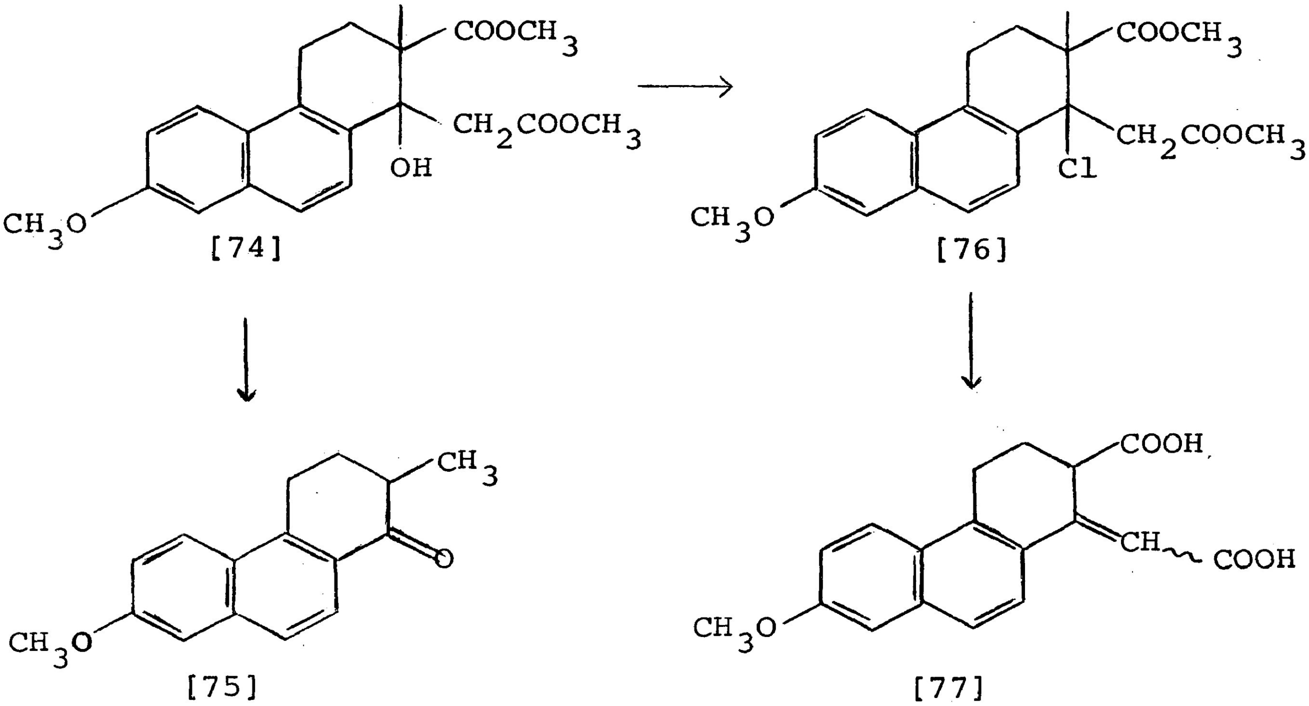
The chloro derivative [79] was treated with base in order to effect dehydrohalogenation to the corresponding α,β-unsaturated acid [80]. However, the product of this alkali treatment appeared to be a poorly defined material from which it could only be established that it was acidic in nature. Spectroscopic evidence was not consistent with the expected structure. Nevertheless, this product was treated with p-toluenesulphonic acid in acetone, to see if the resulting product would give any indication of the presence of the aldehyde group. In

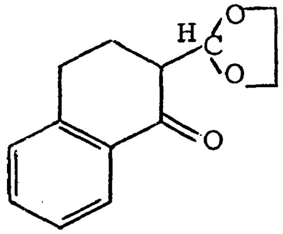


[67] [71] [72]

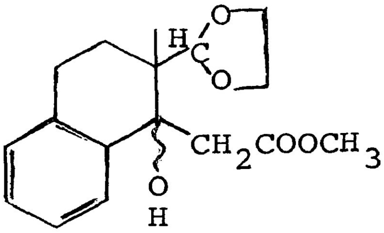


[73]

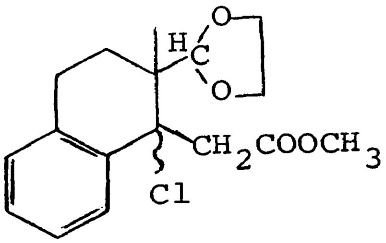




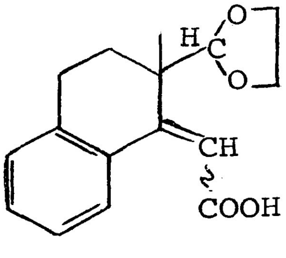
[71]



[78]



[79]



[80]

view of the results of the dehydrohalogenation reaction, it is however, not surprising that also the attempted removal of the acetal group did not yield meaningful results.

Therefore, based on the consideration discussed before (p. 29) it was decided to prepare the anhydride [87], essentially following the procedure described by Bachmann *et al.*[36]

For this purpose α-tetralone [65] was taken as a suitable starting material. It was made to react with dimethyl oxalate in the presence of alcoholic sodium methoxide to give the corresponding glyoxalate [81], which gave a dark colour with ferric chloride. The infrared spectrum clearly indicated the presence of the ester band (1750 cm^{-1}) in addition to a further carbonyl band at lower wave number (1600 cm^{-1}). (Diagrams on p. 42)

Decarbonylation was effected by heating the glyoxalate [81] in the presence of fine glass powder at approximately 180° to yield the keto-ester [82]. The yield was poor and impure products were obtained when coarse glass powder was used. However, a finely ground soda glass gave excellent yields. The product [82] gave the characteristic violet colour with ferric chloride. The infrared spectrum indicated the presence of the ketone band at 1700 cm^{-1} and the ester band at

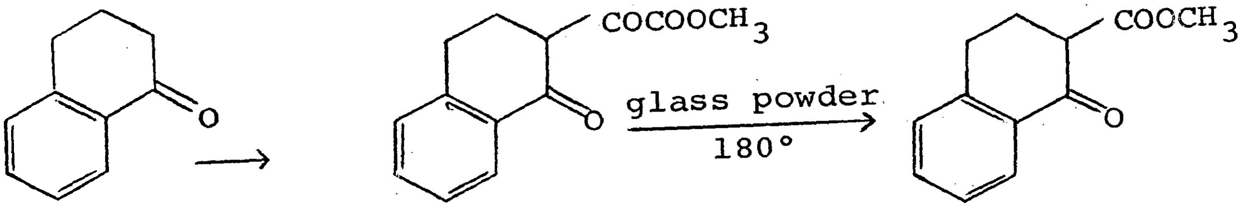
1750 $cm.^{-1}$ The n.m.r. spectrum was consistent with structure [82] and contained signals attributed to the methyl ester group (τ6.39, 3H), and the aromatic protons (τ2.5-3.0, 4H).

The keto-ester [82] was then methylated with methyl iodide in the presence of alcoholic sodium methoxide to give the methyl keto-ester [83], which no longer gave a colour with ferric chloride. The infrared spectrum of [83] indicated two carbonyl bands at 1700 cm^{-1} and 1750 cm^{-1} (ester) and differed from that of the keto-ester [82] in the region around 1400 cm^{-1} (methyl group). This compound was the first one in this sequence that was obtained in crystalline form, and could be characterised by combustion analysis. The n.m.r. spectrum confirms structure [83], showing signals due to the angular methyl group (τ8.53, 3H), the methyl ester group (τ6.39, 3H), a complex multiplet of aliphatic protons (τ7.0-8.35) and the aromatic protons (τ2.5-3.0, 4H).

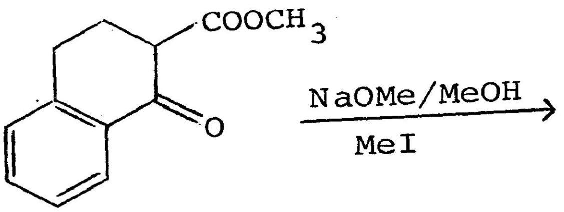
The methylated keto-ester [83] was then subjected to a Reformatsky reaction with methyl bromoacetate, and the hydroxy diester [84] was obtained in nearly quantitative yield. This compound, also obtained crystalline gave satisfactory analytical results, which together with spectral data confirmed its structure, e.g., the n.m.r. spectrum contained signals attributed to the angular methyl group (τ8.88 p.p.m., 3H), methyl ester groups (τ6.25 and τ6.45 p.p.m., 3H each), the hydroxyl proton (τ5.1 p.p.m., 1H-exchangeable with D_2O), and finally the four aromatic protons (τ2.2-3.00 p.p.m., 4H). The mass spectrum, which gave the molecular ion peak at M^+=304 and a strong peak at m/e 286 (i.e. M^+-18), completed a full characterization of this compound.

This diester [84] was then subjected to treatment with thionyl chloride in pyridine in order to produce the chloro-derivative [85], required for the final conversion into the anhydride [87]. It is clear from the spectral evidence that the chloro compound was indeed formed, but on subsequent treatment with base, the expected anhydride could not be isolated. The crude product of the chlorination reaction, which was homogeneous on thin layer chromatography, no longer had a hydroxyl band in its infrared spectrum, and also in the n.m.r. spectrum, the resonance at (τ5.1) was absent.

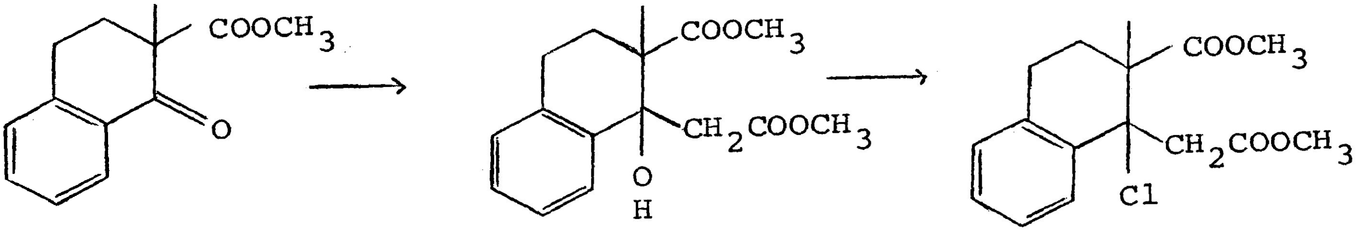
The treatment of this chloro-diester with base was repeated several times. In all cases, the product isolated was substantially less than the quantity expected. This product was found to be a mixture, with as its major component a carboxylic acid, presumably the isomer [86], which due to the stereochemistry at the double band would



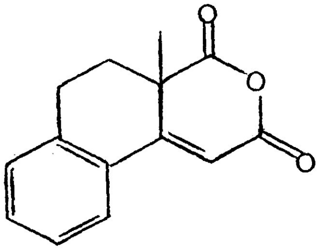
[65] [81] [82]



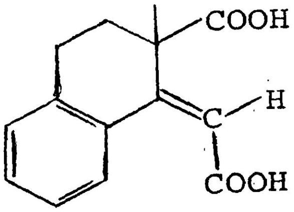
[82] [83]



[83] [84] [85]



[87]



[86]

not be capable of forming an anhydride. All attempts to isolate the desired anhydride failed. A small amount of poorly defined material was isolated by a continuous ether extraction of the aqueous layer of the reaction mixture. Investigation of this material failed to yield any evidence for the presence of an anhydride (e.g. the characteristic double carbonyl absorbtion in the 1700 - 1800 cm^{-1} area).[39]

It should perhaps be pointed out that the attempted preparation of the anhydride [87] took place while an amount of homophthalic anhydride, which was at that time not available, was on order. The attempted conversion of the hydroxy diester [84] into the anhydride [87] took place more or less concurrently with the attempted coupling of homophthalic anhydride with 3-bromothiophene described earlier (p.30). When both these reactions failed to yield the desired products, it was clear that this approach to the synthesis had to be abandoned.

CHAPTER IV CONCLUSIONS

From the experiments discussed in Chapters II and III a few general conclusions may be made.

The successful coupling of the 3-furyl-lithium and 3-thienyl-lithium with aldehydes indicates that this is most probably the best method of introducing the heterocyclic ring, and some knowledge has been acquired on the stability and the behaviour of the resulting compounds.

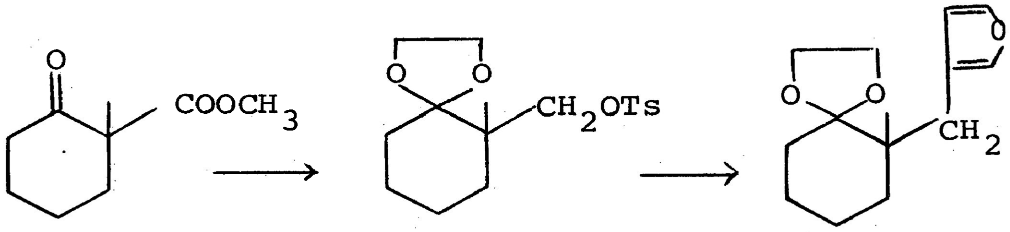
When more complex starting materials are required it has so far been found that the required combination of functional groups leads to difficulties in preparing these starting materials.

As the results discussed in the previous chapter illustrate, α-tetralone leads to compounds containing a 1,3-dicarbonyl grouping, or a potential 1,3-dicarbonyl grouping. It is suggested that the ready cleavage of such compounds under a variety of reaction conditions is a major cause of the difficulties encountered in this work. This situation is particularly difficult due to the presence of the aromatic ring, which virtually excludes the possibility of protecting the ketone function.

Therefore, with respect to future work, two approaches are suggested which should be further investigated.

The first of these involves the removal of the hydroxyl group of the Reformatsky product [78, p.38] by hydrogenolysis, either directly or via the chloro derivative [79]. This would lead to a saturated compound in which the aldehyde group and the carboxylic acid side chain are sufficiently far removed from each other so as to avoid further cleavage reactions. It should be recognized that such an approach would create another asymmetric center in the molecule, which may cause difficulties in isolating a sterochemically pure final product.

A second approach would be a starting material [87], which, after transformation into (88), may be susceptible to introduction of the furan ring. Since tosylates of aliphatic alcohols are susceptible to substitution reactions with certain organolithium compounds,[42] the reactions of such tosylates with 3-furyl-lithium and 3-thienyl-lithium should be investigated.



[87] [88] [89]

In a compound like [89] an oxygen function α to the furan ring may then be introduced by allylic bromination and replacement of the bromine with a hydroxyl group. Subsequent regeneration of the ketone and construction of the side chain would then lead to the desired β-furyl-lactone system.

CHAPTER V EXPERIMENTAL

The experimental work described in this section was carried out in the Department of Chemistry at Lakehead University, Thunder Bay, Ontario, Canada.

Physical measurements were performed as specified below unless otherwise stated.

The infrared spectra were recorded on a Perkin Elmer 137 spectrophotometer and calibrated with a standard polystyrene film.

The n.m.r. spectra were recorded on a Varian Model A-60 A spectrometer and the samples were dissolved in deuterated chloroform ($CDCl_3$) with tetramethylsilane (T.M.S.) as the internal standard at $\tau = 0.0$ p.p.m.

The mass spectra were taken on a Hitachi-Perkin Elmer RMU-7 double focussing mass spectrometer using a direct inlet system.

Neutral alumina and silicagel used in chromatography (both thin layer and column) were as supplied by Woelm.

Melting points were determined with an electrically heated metal block type apparatus and are uncorrected.

Microanalyses were carried out by W.J. Buis at the Institute for Organic Chemistry, T.N.O. Utrecht, The Netherlands.

<u>3-Chloromercuryfuran</u>. 2-Furoic acid (11.2 g., 0.1 mole) was dissolved in water (100 ml.) and slowly added to a stirred solution of mercuric acetate (15.9 g., 0.05 mole)

in water (250 ml.) The precipitated mercury salt was filtered off, dried, and pyrolyzed in a round bottomed flask fitted with a magnetic stirrer and a drying tube, in an oil bath at 135°, for 24 hr. The mixture was cooled to room temperature, glacial acid (20 ml.) was added, and stirring was continued for another 24 hr. The mixture was then poured into water (177 ml.) and sodium chloride was added until no more precipitate was formed. The precipitate was filtered off, dried (desiccator) and extracted with ether in a Soxhlet apparatus for 48 hr. After evaporation of the solvent, a solid product (4.39 g.) was obtained, which after recrystallization from ethanol gave 3-chloromercuryfuran (2.96 g., 10.7%), m.p. 183 - 184°(Lit.[15] 183 - 184°). The infra-red spectrum was identical to a published spectrum.[15]

<u>3-Iodofuran</u>. A solution of iodine (2.79 g., 0.02 mole) and potassium iodide (3.61 g., 0.02 mole) in water (15 ml.) was added dropwise to a suspension of finely powdered 3-chloromercuryfuran (3.3g., 0.01 mole) in water (45 ml.). The reaction mixture was stirred continuously during the addition. The excess of iodine was removed by adding sodium thiosulphate solution until the iodine colour just disappeared. The reaction mixture was steam distilled and the distillate extracted several times with methylene dichloride. Removal of the solvent led to the isolation of 3-iodofuran (0.973 g., 48%). The infrared spectrum of the product in chloroform resembles to a significant extent the

spectrum reported in the literature.* The n.m.r. spectrum shows the aromatic protons (τ 2.5 - 2.7, 2H) and (τ 3.5, 1H). The mass spectrum contained the molecular ion peak at M^+=194 and peaks at m/e 166, (M^+-CO), at m/e 127 due to iodine and at m/e 67 (M^+-I).

<u>3,5-Dibromofuroic Acid.</u> 2-Furoic acid (22.4 g., 0.2 mole) was treated with bromine (96.0 g., 1.2 mole) and the mixture was heated on a water bath under reflux until no more hydrogen bromide was evolved. The red viscous oil so obtained was washed with cold water and was then boiled with water in order to convert any acid bromides into the acids. The separation of the 3,5-dibromofuroic acid from the 5-bromofuroic acid, with which it was mixed was effected by precipitating its barium salt (19.5 g., 24.3%) from an ammoniacal solution by the addition of barium chloride. The barium salt, on acidification, gave 3,5-dibromofuroic acid (12.5 g.), m.p. 164 - 167° (Lit.[38], 165 - 166°).

<u>3-Bromofuroic acid</u>. Reduction of the bromine was carried out by dissolving two parts of the 3,5-dibromofuroic acid (4.0 g., 0.014 mole) in four parts of concentrated ammonia (8 ml.), diluted with fourteen parts (28 ml.) of water, and adding one part of zinc dust (2.0 g.). The

*The paper by Gronowitz[15], did not state the conditions under which this spectrum was taken.

reduction begins at once, the solution becomes hot, and in a few minutes the reaction is complete. When the ammoniacal solution no longer gives an immediate precipitate with calcium chloride, it is filtered and acidified with hydrochloric acid to give 3-bromofuroic acid (1.3 g.) as needle shaped crystals, m.p. 126 - 128° (Lit.[39] 128 - 129°).

Attempted decarboxylation of 3-bromofuroic acid. The decomposition tube used was a 9.5 inches long pyrex tube of approximately 1" diameter, which had a narrow side tube near the stoppered end, connected to a small condenser, and a receiver for the liquid distillate. The decomposition tube was closed with a stopper holding a glass tube drawn out to a narrow tip just reaching to the surface of the reaction mixture. Dry nitrogen was passed through this tube to provide an inert atmosphere and to remove the volatile products as rapidly as possible from the zone of high temperature. The decomposition tube containing 3-bromo furoic acid (2.7 g., 0.014 mole), quinoline (6 g., 0.04 mole), and copper bronze (0.6 g.), was heated in a bath of Wood's metal at a temperature of 210 - 260°. No liquid distillate could be isolated even after prolonged heating.

In another attempt, a high boiling base, diphenylamine (6.8 g., 0.04 mole, b.p. 302°) was mixed with 3-bromofuroic acid (3.0 g., 0.015 mole) and copper bronze (0.6 g.) and the mixture was heated to 300°. The desired decarboxylation product could not be obtained.

<u>Coupling reaction between 3-bromothiophene and cyclohexane carboxaldehyde</u>. A solution of 3-bromothiophene (1.63 g., 0.01 mole) in ether (10 ml. freshly distilled off calcium hydride) was placed in a three necked flask, fitted with a nitrogen inlet, a drying tube and a thin rubber stopper, suitable for injecting the reagents with a hypodermic syringe. The flask was cooled to -70° for about 10 minutes, during which time the contents were stirred continuously in a nitrogen atmosphere. Then an equimolar amount of n-butyl-lithium (7.7 ml. of an 1.3M solution in hexane) was injected into the flask, and the mixture was kept, with stirring at -70° for 10 minutes. A solution of cyclohexanecarboxaldehyde (1.12 g., 0.01 mole) in ether (10 ml.) was then injected into the reaction flask and stirring continued for another 10 minutes at -70°. The mixture was then allowed to reach room temperature, and water (20 ml.) was added. The resulting suspension was extracted several times with ether. The ether extracts were combined, washed with water, dried with anhydrous sodium sulphate and the solvent was removed. The crude product (1.4 g., 75%) contained some of the aldehyde, which could be removed by keeping the mixture at 60° under vacuum for approximately 1 hr. The infrared spectrum had a strong hydroxyl band at 3,400 cm^{-1} and no aldehyde band at 1,700 $cm.^{-1}$ The n.m.r. spectrum contained the aromatic protons of the thiophene ring (τ2.5 - 3.1, 3H), a doublet

(τ 5.4 - 5.6, $\underline{H}$-C-OH) and a complicated pattern of alicyclic proton absorptions (τ 8.1 - 9.1). The mass spectrum contained the molecular ion peak at M^+= 196.

The alcohol, as isolated from the reaction was homogeneous on thin layer chromatography (silica gel/chloroform). Since it could be converted in good yield to the corresponding ketone which was fully characterised (see below), the alcohol itself, which was an oil, was only characterized by its spectral properties as listed above.

Oxidation of cyclohexyl 3-thienyl carbinol with chromium trioxide. The above alcohol (0.1 g., 0.0005 mole) dissolved in acetone (5 ml., distilled off $KMnO_4$) was placed in a 100 ml. round bottomed flask fitted with dropping funnel, nitrogen inlet, a drying tube and a magnetic stirrer. A solution of chromium trioxide (2.67 g.) in sulphuric acid (2.3 ml., conc.) was made up to 10 ml. with water. Of this reagent a quantity was added to the alcohol until a brownish colour persisted, and the mixture was kept at 5° for a period of about 1 hr. Isopropyl alcohol (10 ml.) was then added to destroy the excess of chromium trioxide. Water (25 ml.) was added and the resulting mixture was extracted with ether. The ether extract was washed with water, dried with anhydrous sodium sulphate and the solvent removed. The oily product (0.096 g.) was homogeneous on t.l.c. (silicagel/benzene), slightly less polar than the starting alcohol. The infrared spectrum no longer contained a hydroxyl band at 3,400 $cm.^{-1}$ Instead, a strong carbonyl band at 1675 cm^{-1} was observed. The n.m.r. spectrum contained a doublet at τ5.85 (J = 12 c.p.s.), and the signal at τ8.0, observed in the spectrum of the alcohol, had disappeared. The mass spectrum contained the molecular ion peak at M^{+}= 194, as 59.0% of the base peak at m/e 111. In addition other prominent peaks were observed at m/e 139, m/e 83, m/e 55, m/e 41, and m/e 39.

The ketone (0.096 g., 0.0004 mole) in ether (1 ml.) was added to 2,4-dinitrophenylhydrazine reagent* (1.5 ml.) and the thick yellow precipitate that was formed was filtered off, and repeatedly recrystalized from ethyl alcohol, m.p. 227-228°. The mass spectrum contained the molecular ion peak at M^{+}= 374.

Found: C, 54.8; H, 4.6; N, 14.7; $C_{17}H_{18}O_4N_4S$ *requires* C, 54.5; H, 4.8; N, 14.9%.

Coupling reaction between 4-iodofuran and cyclohexane carboxaldehyde A solution of 3-iodofuran (0.388 g., 0.002 mole) in ether (7.0 ml.) was placed in a 25 ml. three necked flask, fitted with a nitrogen inlet, a drying tube and a stopper. The mixture was cooled to -70°, while stirring continued in nitrogen during the whole operation. After 10 minutes, n-butyl-lithium (1.4 ml. of a 1.3M solution in hexane) was injected into the reaction flask with a hypodermic

*Prepared by slowly adding 4.0 ml. of conc. H_2SO_4 to a suspension of 2.0 g. of dinitrophenylhydrazine in 100 ml. of methanol.

syringe through the rubber tubing of the nitrogen inlet. After another 10 minutes, a solution of cyclohexanecarboxaldehyde (0.244 g., 0.002 mole) in ether (5 ml.) was injected dropwise into the reaction flask, and the mixture was stirred for 10 minutes in nitrogen. After the mixture had come to room temperature, water (20 ml.) was added, and the aqueous mixture was extracted several times with ether. The ethereal extracts were combined, washed with water and dried with anhydrous sodium sulphate. The solvent was evaporated to yield a product (0.184 g.), which was homogeneous on t.l.c. (silicagel/chloroform). The infrared spectrum contained a strong hydroxyl band at 3400 cm^{-1}. The n.m.r. spectrum is also consistent with the structure of the alcohol and contains aromatic proton signals (τ2.5 - 2.8, 3H) a doublet (τ5.5 - 5.8, $\underline{H}$ - C-OH) and a complex pattern of cyclohexane ring proton signals (τ7.7 - 9.2). The mass spectrum had the molecular ion peak at M^+ = 180, in addition to other prominent peaks at m/e 162, m/e 152, and m/e 113.

The alcohol, as isolated from the reaction was homogeneous on thin layer chromatography (silicagel/chloroform). Since it could be converted in good yield to the corresponding ketone, which was fully characterized (see below), the oily alcohol itslef was only characterized by its spectral properties as listed above.

Oxidation of cyclohexyl 3-furyl carbinol with chromium trioxide. The above alcohol (0.182 g. 0.001 mole) dissolved in acetone (5 ml., distilled over $KMnO_4$), was placed in a 100 ml. round bottomed flask, fitted with a magnetic stirrer. A solution of chromium trioxide (2.67 g.) in sulphuric acid (prepared as above), was added dropwise until a brownish colour persisted and the reaction mixture was kept at 5° for 1 hr. Isopropyl alcohol (10 ml.) was added to destroy the excess of chromium trioxide. The reaction mixture was then worked up by the addition of water (20 ml.) and extraction with ether. The ether extracts were combined, washed with water, dried with anhydrous sodium sulphate, and the solvent removed. The product (0.07 g.), was found to be a mixture, containing some acidic components as well as some starting material as indicated by t.l.c. As also the yield was poor, no attempts were made to isolate the desired ketone.

In another attempt, the same reaction was carried out under different conditions. This time the chromium trioxide solution (10 ml.) was diluted with water (10 ml.) and added dropwise to the alcohol (0.18 g.) while the temperature was kept between 0-1° and the reaction time was reduced to 20 minutes. In this way, a mixture of at least two compounds (t.l.c.) (0.08 g.) was obtained. The crude product was dissolved in ether (10 ml.) and extracted with sodium bicarbonate (5%, aqueous solution) to remove acidic material. A carbonyl containing material (I.R.) could thus be isolated although in poor yield (0.04 g.). It was, therefore, decided to use another method of oxidation.

Oxidation of cyclohexyl 3-furyl carbinol with manganese dioxide. To the alcohol (0.236 g. 0.001 mole), dissolved in petroleum ether (6 ml; b.p. 60-80°) was added specially prepared manganese dioxide[39] (1.0 g.) and the reaction mixture was stirred at room temperature for 3 days. The reaction mixture was filtered, and the solvent removed from the filtrate to yield a product (0.127 g.), which was homogeneous on t.l.c. (silicagel/chloroform) and was less polar than the starting alcohol. The infrared spectrum contained a strong carbonyl band at 1650 cm^{-1}, and the hydroxyl band observed in the starting material at 3400 cm^{-1}, had disappeared. The n.m.r. was also consistent with the structure of the product, and contained aromatic proton signals (τ1.8 - 3.3 3H), and a complex multiplet of cyclohexane ring proton signals (τ7.8 - 9.2). The mass spectrum gave the molecular ion M^+ = 194 and other prominent peaks at m/e 111, and at m/e 83.

The ketone (0.127 g; 0.0007 moles) in ether (2 ml.) was added dropwise to a solution of 2,4-dinitrophenylhydrazine reagent (2 ml. prepared as above). A thick precipitate formed, which was filtered off and recrystallized from ethyl alcohol. The product gave one spot on t.l.c. (silicagel/chloroform) and had m.p. 174 - 175°. The mass spectrum contained the molecular ion peak $M^+ = 358$.

Found: C, 57.0; H, 5.0; N, 15.6; $C_{17}H_{18}O_5N_4$ *requires* C, 57.0; H, 5.1; N, 15.6%.

Cyclohexane carboxylic acid methyl ester. A solution of diazomethane in ether was added dropwise to cyclohexanecarboxylic acid (5.0 g; 0.03 mole) in a 50 ml. round bottomed flask until a yellow colour persisted. The reaction mixture was kept 30 minutes at room temperature and evaporated to dryness. The crude product was purified by passing it through a small column of silica gel in ether and yielded the methyl ester as an oil (4.124 g.). The infrared spectrum contains an ester band at 1700 $cm.^{-1}$ The n.m.r. spectrum contains a single sharp peak ($\tau 6.32$, OCH_3) and a complex pattern ($\tau 7.5$ - 8.9). The integration gave the intensity ratio of these two patterns as 3:11. The mass spectrum contains the molecular ion peak at $M^+ = 142$.

Coupling reaction Between 3-bromothiophene and cyclohexane carboxylic acid methyl ester. 3-Bromothiophene (0.163 g, 0.001 mole) in ether (5 ml.) was placed in a 25 ml. Erlenmeyer flask, carrying a side tube as a nitrogen inlet. A stopper with a U-tube connected this flask to another 25 ml. flask containing the ester (0.141 g., 0.001 mole) in ether (5 ml.). The flasks were cooled to -70° for about 10 minutes, during which time the contents were stirred continuously in nitrogen. Then n-butyl-lithium (0.7 ml., 1.3M) was added to the 3-bromothiophene by means of a hypodermic syringe. After about 15 minutes, a few drops of the thienyl-lithium solution were poured into the flask containing the ester solution by tilting the whole assembly. This procedure was repeated with 5 minute intervals until the addition was complete (approx. 45 minutes). After another 10 minutes at -70°, the reaction flask was allowed to reach room temperature. The reaction mixture was worked up by the addition of water (20 ml.) and several extractions with ether. The ether extracts were combined, washed with water, dried with anhydrous sodium sulphate and the solvent was removed. The crude product (0.115 g.) on t.l.c. analysis (silicagel/benzene) was found to consist mainly of the starting material (i.e., cyclohexane carboxylic acid methyl ester) and a small amount of a less polar compound. The infrared spectrum of this mixture was similar to that of the ester, except the presence of a very weak hydroxyl band. The mass spectrum contained a peak at m/e 260, which corresponds to the $M^+ - 18$ peak of the di-addition product i.e. [61] (p. 27).

The reaction was repeated several times, but the desired thienyl ketone could not be detected in any of the resulting products.

Coupling reaction of 3-bromothiophene and homophthalic anhydride. To a solution of 3-bromothiophene (1.0 g., 0.006 mole) in tetrahydrofuran (5 ml.) was added n-butyl-lithium (4.7 ml., 1.3M) at -70°, using the same assembly as described above for the reaction with cyclohexane carboxylic acid methyl ester. The thienyl-lithium formed in this way was added to homophthalic anhydride (1.0 g., 0.006 mole) in tetrahydrofuran (5 ml.) in the same dropwise manner as described above during approximately 45 minutes. After complete addition, the reaction flask was allowed to reach room temperature. The reaction mixture was then worked up by the addition of water (20 ml.) and acidification, followed by several extractions with ether. The ether extracts were combined and upon washing with water, a white solid material was formed at the interface. This material (0.343 g.) was collected by filtration. Its homogeneity could not be determined by t.l.c., since it was found to be insoluble in any of the usual organic solvents. Its infrared spectrum (in Nujol) contained a hydroxyl absorption typical of a carboxylic acid, but mass spectrometry did not give useful information as to the identity of this material. The ether soluble fraction yielded a crude product (0.455 g.), which was found to consist of a mixture of at least five components, from which no meaningful results could be obtained.

The hydroxymethylene derivative of α-tetralone. To a cold suspension of powdered sodium methoxide (3.0 g., 0.05 mole, freshly prepared) in benzene (75 ml.) were added, with stirring, α-tetralone (3.0g., 0.02 mole) and ethyl formate (3.0g., 0.04 mole). The flask was flushed with nitrogen and the mixture was allowed to stand at room temperature overnight. Then ice cold water was added and the layers were allowed to separate. The benzene layer was washed thoroughly with a cold aqueous sodium hydroxide (5%) solution. All aqueous solutions were combined, washed with ether and acidified with dilute hydrochloric acid. The resulting oily suspension was extracted several times with ether. The ether extracts were combined, washed with saturated salt solution, followed by water and then dried with anhydrous sodium sulphate. Removal of the solvent gave an oily product (3.32 g.), which gave a deep violet colour with alcoholic ferric chloride. The infrared spectrum gave a broad band at 2850 - 3125 cm^{-1} and a complex band at 1550 - 1885cm^{-1}. Some minor changes were also observed in the finger print region. This material gave one spot on t.l.c. (aluminium oxide/benzene) and was used directly for the next reaction.

Methylation of the hydroxymethylene ketone [66]. The crude hydroxymethylene ketone (2.61 g., 0.01 mole) was dissolved in acetone (40 ml., freshly distilled off molecular sieve), and placed in a 100 ml. round bottomed flask fitted with a reflux condenser. To this solution were added anhydrous sodium carbonate (2.0 g.) and methyl iodide (3.0 ml.), and the mixture was heated under reflux with stirring for 2 hrs. A further 3 ml. of methyl iodide was added and reflux continued overnight. Dry ether was added to the cold reaction mixture until no more inorganic material precipitated. The mixture was filtered and the solvent was evaporated *in vacuo* to give an oily product (2.6 g.), which on t.l.c. (silicagel/benzene) showed two spots, different from the starting material. The infrared spectrum of this mixture contained carbonyl bands at 1730 cm^{-1} and 1670 $cm.^{-1}$ The n.m.r. spectrum indicated the presence of the aldehyde group at (τ0.4 p.p.m.), a C-CH_3 group (τ8.6) and an O-CH_3 group a (τ6.15). The intensities of the O-CH_3 and C-CH_3 signals were approximately in a ratio of 1:2, indicating the approximate composition of the mixture. The mass spectrum gave the molecular ion peak at M^+=188 for both isomers.

The mixture (11.13 g.) of the keto-aldehyde and the enol ether was chromatographed on silicagel. Pure aldehyde [67], (6.8 g.) was eluted with benzene. Continued elution with chloroform gave the enol ether [68], (4.5 g.).

The keto-aldehyde was characterized as a pure compound by spectroscopic methods. The infrared spectrum contained two bands at 1700 cm^{-1} (keto-group) and 1750 cm^{-1} (aldehyde group). The n.m.r. spectrum no longer contained the O-CH_3 signal at τ6.15 present in the crude product, but had retained the signals for the aldehyde at τ0.4 p.p.m. and the C-CH_3 group at τ8.6. Its mass spectrum gave a strong molecular ion peak at $M^+ = 188$.

<u>Coupling reaction between keto-aldehyde [67] and 3-bromothiophene</u>. 3-Thienyl-lithium was generated from equimolar amounts of n-butyl-lithium (1.0 ml., 1.3M) and 3-bromothiophene (0.163 g., 0.001 mole) with dried ether (5 ml.) as a solvent at -70°. The solution was added dropwise to the keto-aldehyde (0.188 g., 0.001 mole) in ether (5 ml.) kept at -50° (the aldehyde solution solidifies at lower temperature) in nitrogen. The reaction mixture was kept at this temperature for 15 minutes, with continuous stirring. Then water (15 ml.) was added after the reaction mixture had been allowed to reach room temperature, and the resulting mixture was extracted several times with ether. The ether extracts were combined, washed with water, dried with anhydrous sodium sulphate and on removal of the solvent gave a product

(0.336 g.), which was found to be a mixture of two components as indicated by t.l.c. (silicagel/benzene, chloroform, 1:1). Attempt to separate this mixture led to isolation of a main oily fraction (0.261 g.) and a pink residue (0.003 g.)

The infrared spectrum of the main fraction contained a carbonyl band at 1690 cm^{-1}, and suggested loss of the aldehyde group. There was no OH-band at 3400 cm^{-1}. The n.m.r. spectrum indicated the presence of a secondary $C-CH_3$ group by a doublet (J = 1.3 c.p.s.) centered at $\tau 8.7$. The highest mass observable in the mass spectrum was found at m/e 160 (i.e. M^+ for $C_{11}H_{20}O$)

<u>Formation of the acetal of the keto-aldehyde [67]</u>. The keto-aldehyde (4.821 g., 0.03 mole), ethylene glycol (2.5 ml.), benzene (150 ml.) and p-toluene sulphonic acid (0.2 g.) were refluxed for 30 minutes, using a water separator. The reaction mixture, after cooling to room temperature was poured into aqueous sodium carbonate (200 ml. of a 5% aqueous solution). The benzene layer, after removal of the aqueous solution, was washed with water, dried and after removal of the solvent gave (5.478 g.) of crude product, which was homogeneous on t.l.c. (silicagel/benzene). The infrared spectrum no longer contained an aldehyde band at 1750 cm^{-1}. The n.m.r. is consistent with the structure of the acetal, e.g., it contained a 4-proton multiplet centered at

τ6.18 p.p.m. (acetal) and the C-Me signal at τ8.79 p.p.m. The mass spectrum gave the molecular ion at $M^+ = 232$.

Reduction of the acetal [71]. To a suspension of lithium aluminium hydride (0.5 g., 0.13 mole) in tetrahydrofuran (30 ml., freshly distilled off calcium hydride), was added the acetal (0.4 g., 0.0017 mole) dissolved in dry tetrahydrofuran (5 ml.). The reaction mixture was stirred at room temperature for 2 hr. The excess lithium aluminium hydride was destroyed by addition of a saturated solution of sodium sulphate, followed by some anhydrous sodium sulphate. Filtration and removal of the tetrahydrofuran gave 0.45 g. of the product. A single spot was observed on t.l.c. (silicagel/chloroform). The infrared spectrum no longer contained a carbonyl band. Instead a strong hydroxyl band was observed at 3500 $cm.^{-1}$ The n.m.r. spectrum contained signals attributed to the aromatic protons (τ2.5 - 3.0, 4H), the OH proton (τ5.1), the proton α to the hydroxyl group (τ5.25), aliphatic protons (τ7.8 - 8.11) and the angular methyl group (τ9.09). The mass spectrum contained the molecular ion peak at $M^+ = 234$ and other prominent peaks at m/e 172, m/e 162, and m/e 144.

Attempted removal of the acetal group. To the hydroxy acetal (0.05 g., 0.0002 mole) in dry acetone (5 ml., freshly distilled off molecular sieve) were added a few crystals of p-toluene sulphonic acid. The mixture was stirred for 6 hr. Excess acid was then neutralised with aqueous sodium carbonate (5%); and after the addition of more water (15 ml.), the mixture was extracted with ether. The ether extracts were washed with water and dried, and yielded a crude product (0.035 g.). T.l.c. (silicagel/chloroform) indicated the presence of at least five components. The infrared spectrum of the crude product contained a carbonyl band at 1750 cm^{-1} and a hydroxyl band at 3500 cm^{-1}. The n.m.r. spectrum contained a very weak aldehyde signal at τ0.5 p.p.m., but the major portion of the spectrum contained the same signals as that of the starting material, e.g., a signal of the proton attached to the carbon of the acetal group at τ5.28, a four proton multiplet (acetal) centered at τ4.08, a complex multiplet of aliphatic protons on the cyclo hexane ring at τ7.0-8.8 and an angular methyl group at τ9.1. Other attempts to remove the acetal group included treatment with mineral acid at room temperature and at elevated temperatures. Extensive decomposition was observed and the desired aldol [74] could not be obtained.

<u>Reformatsky reaction of the keto-acetal [71].</u> To a suspension of granulated zinc (0.8 g.) and iodine (0.023 g.) in dried benzene (8 ml.) and dried ether

(8 ml.), were added the keto-acetal (0.5 g., 0.002 mole) in ether (5 ml.) and methyl bromo-acetate (0.25 ml.). The mixture was refluxed on a water bath. The iodine colour faded and the solution became cloudy and after about 10 minutes an addition product deposited on the sides of the reaction flask. Five more additions of zinc (0.8 g., each) and iodine were made at intervals of 45 minutes. An additional 0.25 ml. of methyl bromoacetate was introduced after one and a half hour from the starting time, and reflux was continued for another 4 hr.. The addition product was dissolved by addition of glacial acetic acid (2 ml.) and methanol (8 ml.). The solution was decanted from the zinc into water (20 ml.) and the aqueous mixture was further acidified with acetic aicd. The layers were allowed to separate and the aqueous layer was extracted several times with benzene and the extracts, combined with the initial organic layers, were washed with water and with dilute ammonium hydroxide until no more colour was removed. The benzene extract was dried with anhydrous sodium sulphate and the solvent removed to give 0.59 g. of an oily product, which was found to be homogeneous on t.l.c. (silicagel/benzene). The infrared spectrum contained a strong hydroxyl band at 3500 cm^{-1} and an ester band at 1650 $cm.^{-1}$ The n.m.r. spectrum contained

signals at τ2.5 - 3.0 (4 aromatic protons), τ5.3 (i.e. the proton attached to the acetal carbon), τ5.0 (OH-proton), τ5.9 - 6.3 (4H of acetal), τ6.5 (3H of methyl-ester), τ6.5 - 8.8 (4 alicyclic protons) and at τ9.03 (3H of the angular methyl group). The mass spectrum contained a strong peak at m/e 276 (i.e. $M^+ - 18$).

Chlorination of the Reformatsky ester [74]. To a cold mixture of pyridine (0.2 ml., off molecular sieve) and dried benzene (2.0 ml.), was added thionyl chloride (0.4 ml.). The resulting solution was cooled in an ice bath and the Reformatsky ester (0.5 g., 0.0016 mole) dissolved in benzene (5.0 ml.) was added. An immediate reaction started and after a few minutes, a clear solution formed. After about 30 minutes, the mixture was refluxed in a water bath with constant stirring, for one and a half hour. After cooling to room temperature, the solution was decanted from the solid that had formed. The solid matter was extracted several times with benzene. The benzene extracts were combined, washed with water, dried and the solvent removed. The oily product (0.388 g.) was homogeneous on t.l.c. (silicagel/chloroform). The infra-red spectrum indicated complete absence of the hydroxyl band. The n.m.r. spectrum contains aromatic proton signals at (τ2.18 - 3.0, (4H), a single proton signal at τ5.3 (presumably the proton attached to the acetal carbon) the multiplet of the acetal group at τ6.1 - 6.25 (4H), a methoxyl proton signal at $\tau 6.4$ (3H), a complex multiplet of the cyclohexane ring protons at $\tau 7.1 - 8.3$ (4H), and a sharp signal of an angular methyl group at $\tau 8.82$ (3H). The mass spectrum gave a peak at m/e 288, which corresponds to $M^+ - 36$, i.e., loss of HCl from the molecular ion $M^+ = 324$, which itself could not be observed.

Attempted dehydrochlorination. To the chloro ester (0.388g.) in benzene (10 ml.) was added a solution of potassium hydroxide (0.6 g.) in methanol (10 ml.) and the mixture was refluxed for 15 minutes. Then additional 1.5 ml. of 45% potassium hydroxide was added to the cooled solution and refluxing continued for 4 hr. The reaction mixture was acidified with 5% hydrochloric acid and the solution was extracted with ether. The ether extracts, after washing and drying, yielded an oil (0.2 g.).

It could be established that this material was acidic in nature (both from the method of isolation, as well as from infrared evidence) but no single compound could be isolated and characterized.

When this poorly defined material was subsequently treated with p-toluene sulphonic acid in acetone, there was no indication of the presence of the desired unsaturated aldehydo acid in the reaction product.

Preparation of the glyoxalate of α-tetralone. Sodium methoxide was prepared from sodium (2.5 g., 0.1 mole) and methanol (50 ml.). The resulting solid cake was broken up into small pieces and dimethyl oxalate (2.36 g., 0.01 mole) was added. The reaction flask was evacuated and flushed with nitrogen. Benzene (50 ml. distilled off calcium hydride) was added and the reaction mixture swirled. Then α-tetralone (7.3 g., 0.05 mole) was added and a dark green suspension resulted, which was swirled occasionally until most of the solid material dissolved. The mixture was kept at r.t. for 4 hr., and then poured into water (50 ml.) and acidified. Some saturated sodium chloride solution was added to facilitate the separation of the two layers. The benzene layer was extracted several times with sodium hydroxide (5% aqueous solution). All aqueous extracts were combined, acidified with dilute hydrochloric acid, and extracted with ether. The ether extract was washed, dried, and after removal of the solvent gave a crystalline product (10.1 g.), which gave a dark blue colour with alcoholic ferric chloride solution. The infrared spectrum contains an ester band (1750 cm^{-1}) and another carbonyl band at lower wave number (1600 cm^{-1}). This material, which was homogeneous on t.l.c. (silicagel/benzene) was used directly in the next reaction.

Decarbonylation of the glyoxalate [81]. The first attempts to prepare the ester by heating the glyoxalate at 170° with rather coarse glass powder gave low yields and variable amounts of an impure product. Excellent yields were recorded when finely powdered soda glass was used as follows:

The glyoxalate (5.0 g., 0.02 mole) was mixed with powdered glass (2.8 g.) in a 50 ml. round bottomed flask fitted with a magnetic stirrer. The mixture was heated in an oil bath at 180° for 45 minutes. Vigorous evolution of carbon monoxide started after a few minutes, which slowed down near the end of the reaction. After cooling to room temperature, the product was separated from the glass powder with chloroform. Removal of the solvent gave the crude keto-ester as a brown semi-solid material (9.0 g.). T.l.c. (alumina/benzene) indicated the presence of very little glyoxalate by spraying with alcoholic ferric chloride solution. The crude keto ester was used directly for the methylation reaction.

Methylation of the keto ester [82]. To sodium (1.2 g., 0.05 mole), dissolved in anhydrous methanol (20 ml.), was added the keto ester (2.0 g., 0.009 mole) followed by benzene (20 ml., off calcium hydride), and the mixture was refluxed for 30 minutes. After cooling to room temperature, methyl iodide (4.0 ml.) was added to the semi-solid mass and the mixture was kept at room temperature for approximately 30 minutes, with occasional swirling. Then more methyl iodide (4.0 ml.) was added and the mixture was refluxed for another 30 minutes. Water was added (20 ml.) to the cooled suspension and the mixture was extracted several times with benzene. The benzene extracts were combined, washed with sodium hydroxide (5% aqueous solution), water, and dried with anhydrous sodium sulphate. The dried extract, after removal of the solvent, gave the crude methylation product (1.55 g.) which was homogeneous on t.l.c. (alumina/benzene) and no longer gave a colour with ferric chloride. The infra-red spectrum contained two carbonyl peaks at 1690cm^{-1} (α, β -unsaturated ketone) and at 1750 cm^{-1} (methyl ester). The n.m.r. spectrum is consistent with structure [83], p. 42 by showing the aromatic protons at τ2.5 - 3.0, the aliphatic protons on the cyclohexane ring at τ6.8 - 8.5, the angular methyl group protons at τ8.55 and the methoxyl protons at τ6.4. The material was recrystallized from heptane, m.p. 56-57°.

Found: C, 71.4; H, 6.4; $C_{13}H_{14}O_3$ *requires* C, 71.5; H, 6.5%.

Formation of hydroxy di-ester. [85]. To a mixture of dry ether (150 ml.), dry benzene (150 ml.), granulated zinc (14.4 g.), and iodine (0.4 g.) was added methyl bromoacetate (5.0 ml.) and methylated keto-ester [84] (9.0 g., 0.04 mole). When the mixture was refluxed (water bath), the iodine colour faded, the solution became turbid, and after about 10 minutes an addition product was deposited on the sides of the reaction flask. Five more additions of zinc (14.4 g.) and small amounts of iodine were made at 45 minutes intervals. After 1.5 hrs. from the starting time another addition of methyl bromoacetate (6.0 ml.) was made. The mixture was reluxed for a total of 4 hr. The addition product was dissolved by adding glacial acetic acid (2.0 ml.) and methanol (8.0 ml.) and the resulting solution was decanted from the zinc into water (500 ml.). After further acidification with acetic acid, the ether benzene layer was allowed to separate and the aqueous layer was extracted several times with benzene. The benzene extracts were combined with the first ether-benzene layer and the total organic solution was washed with dilute ammonium hydroxide until no more colour was removed. The organic extract was then washed with water, dried with anhydrous sodium sulphate, and evaporated to dryness to give the crude hydroxy di-ester (15.79 g.). Purification was effected by chromatographing this crude product on a silicagel column with benzene:chloroform (1:4). The pure hydroxy-diester was then recrystallized from n-heptane (14.5 g.) m.p. 60 - 61°. The infrared spectrum contained a hydroxyl band at 3500 $cm.^{-1}$ The n.m.r. spectrum is compatable with its structure and contained signals attributed to the aromatic protons at τ2.5 - 3.0 (4H), the OH proton at τ5.25 (exchangeable with D_2O), two methoxyl groups at τ6.3 and τ6.47 (3H, each), aliphatic protons at τ6.6 - 8.5 and an angular methyl group at τ8.8 (3H). The mass spectrum gave peaks at M^+ = 292 and M^+ - 18 (m/e 274).

Found: C, 65.7; H, 6.9; $C_{16}H_{20}O_5$ *requires* C, 65.7; H, 6.9%.

Attempted dehydration of the hydroxy di-ester [85]. The hydroxy-di-ester (1.5 g., 0.005 mole) was added to a cooled solution of thionyl chloride (1.2 ml.) and pyridine (0.6 ml., dried over molecular sieve) in dry benzene (5.0 ml.). The mixture was kept in an ice bath, and an immediate reaction started. After about 15 minutes at 0°, the reaction mixture was heated in a water bath at 25° for 30 minutes, with constant stirring. The mixture was concentrated *in vacuo*, initially at room temperature and then in a water bath at 40°. After cooling to room temperature, the insoluble pyridine hydrochloride was digested several times with benzene. The combined benzene extracts were washed with water, dried and evaporated to dryness to give the crude chloro-derivative (1.385 g.), which on t.l.c. (silicagel/chloroform) contained few impurities. The infrared spectrum no longer contained a hydroxyl band at 3500 cm^{-1}, present in the spectrum of the starting material. The n.m.r. spectrum was different from that of the starting material by the absense of the signal at $\tau 5.25$ (i.e., $-O\underline{H}$).

The crude chloro-diester was used directly, and a cooled solution of 1.385 g. (0.004 mole) in benzene (5.0 ml.), was added to a solution of potassium hydroxide (1.6 g.) in methanol (22.0 ml.). The mixture was refluxed for 15 minutes with constant stirring. After cooling, potassium hydroxide (4.5 ml. of a 45% aqueous solution) was added and the mixture was further refluxed for 45 minutes. Water (10 ml.) was added to the cooled solution and some of the methanol and benzene were removed in a current of air. The remaining aqueous mixture was again refluxed for 1 hr., and after cooling the excess of alkali was neutralized with dilute hydrochloric acid (5%), and the solution was boiled with charcoal and filtered. Acidification of the filtrate yielded a cloudy solution. Direct extraction with ether yielded a very small amount of material (0.284 g.), which was found to consist of a mixture of at least five components. (t.l.c., silicagel/chloroform) The infrared spectrum of this crude product indicated the presence of acidic material. No attempt was made to separate this mixture. A very small amount of crystalline material was obtained from the aqueous mother liquor after standing three days. This material was insoluble in most organic solvents, and no evidence for the presence of the required anhydride could be obtained.

References

1) H. Rogerson, J. Chem. Soc., *101*, 1040 (1912).

2) F.B. Power and A.H. Salway, Pharm. J., *90*, 521-522, 550-552 (1913).

3) R. Goto, J. Pharm. Soc. Japan, *57*, 77-91 (1937).

4) Y. Sebe, J. Chem. Soc. Japan, *64*, 1130-1136 (1943).

5) A. Quilico, F. Piozzi, and M. Paran, Tetrahedron, *1*, 177 (1957); A. Quilico, P. Grunanger and F. Piozzi, *ibid*, *1*, 186 (1957).

6) T. Kubota, H. Yamaguchi, K. Naya and T. Matsuura, J. Chem. Soc. Japan, *73*, 897-9 (1952), Chem. Abstr. *47*, 6394 g. (1953).

7) J. Simonsen and D.H.R. Barton, "The Terpenes" Cambridge University Press, 1961 *Vol. III*, p. 479, J. Simonsen and W.C.J. Ross, "The Terpenes", Cambridge University Press, 1957, *Vol. V*, p. 618-19.

8) D.H.R. Barton and D. Elad, J. Chem. Soc. 2085, 2090 (1956).

9) M.P. Cava dn E.J. Soboczensky, J. Am. Chem. Soc. *78*, 5317 (1956).

10) O.H. Emerson, J. Am. Chem. Soc., *70*, 545 (1948), *73*, 2621 (1951), *74*, 688 (1952).

11) W.R. Chan, D.R. Taylor and R.T. Aplin, Chem. Comm. 576 (1966).

12) T. Reichstein, A. Grussner, K. Schindler and E. Hardmeier, Helv. Chim. Acta. *16*, 276 (1933).

13) W. Broy and R. Mayer, Z. Chem. *3*, 150 (1963), C.A. *59*, 7469 (1963).

14) F. Feist, Ber. *34*, 1992 (1901); H. Gilman and R.R. Burtner, J. Am. Chem. Soc., *55*, 2903 (1933).

15) A.F. Shepard, N.R. Winslow and J.R. Johnson, J. Am. Chem. Soc., *52*, 2083 (1930).

16) S. Gronowitz and G. Sörlin, Arkiv för Kemi, *19*, 516 (1962).

17) T. Kubota and T. Matsuura, Chem. and Ind., 521 (1956).

18) A.J. Birch, R.A. Massy-Westropp, S.E. Wright, T. Kubota, T. Matsuura, and M.D. Sutherland, Chem. & Ind. 902 (1954).

19) H. Gilman and R.R. Burtner, J. Am. Chem. Soc. *55*, 2903 (1933).

20) E. Sherman and E.D. Amstutz, J. Am. Chem. Soc., *72*, 2195 (1950).

21) H. Wynberg, J. Am. Chem. Soc., *80*, 364 (1958).

22) W. Reppe, Ann., *596*, 1 (1955).

23) D. Miller, J. Chem. Soc., (C), 12 (1969).

24) T.M. Harris, C.M. Harris, J.C. Cleary, Tetrahedron Letters, 1427 (1968).

25) J.W. Cornforth, J. Chem. Soc. 1310 (1958).

26) L. Mangoni, M. Adinolfi, G. Laonigro and E. Doria, Tetrahedron Letters, 4167 (1968).

27) R. Misra and S. Dev., Tetrahedron Letters, 2685 (1968).

28) E.J. Corey and D. Seebach, Ang. Chem. (Int. Edn.), *4*, 1075 (1965).

29) T.L. Loh, personnal Communication.

30) F. Bertini, P. Grasselli, G. Zubiani and G. Cainelli, Tetrahedron, *26*, 1281 (1970).

31) S. Gronowitz, Arkiv för Kemi *7*, 267 (1954).

32) A. Bowers, T.G. Halsall, E.R.H. Jones, and A.J. Lemin, J. Chem. Soc., 2548 (1953).

32a) H.O. House, "Modern Synthetic Reactions" Benjamin, Inc., New York, 1965, p. 90.

33) H.O. House, and R.S. Ro, J. Am. Chem. Soc. *80*, 2428 (1958).

34) N.L. Wendler, H.L. Slates, N.R. Trenner and M. Tishler, J. Am. Chem. Soc., *73*, 719 (1951).

35) A.T. Vogel, "Practical Org. Chem", 3rd end. Longmans, Green and Co., London, 1966, pp. 1060.

36) W.E. Bachmann, W. Cole, and A.L. Wilds, J. Am. Chem. Soc., *62*, 824 (1940).

37) C.C. Price, F.M. Lewis and M. Meister, J. Am. Chem. Soc., *61*, 2760 (1939).

38) P.L. De Benneville, J. Org. Chem. *6*, 462 (1941).

39) K. Nakanishi, "Infrared Absorption Spectroscopy" Holden-Day Inc. San Francisco, 1962, p. 45; A.D. Cross, "Practical Infrared Spectroscopy", Butterworths, London, 1964, p. 67.

40) H.B. Hill and C.R. Sanger, Proc. Am. Acad. Arts Sci. *21*, 135 (1885).

41) M. Harfenist, A. Bavley and W.A. Lazier, J. Org. Chem., *19*, 1608 (1953).

42) W.D. Korte, L. Kinner and W.C. Kaska, Tetradron Letters 603 (1970).

NOTE ADDED IN PROOF

During the final preparation of the manuscript of this thesis, attention was again drawn to the rather unsatisfactory results obtained in carrying out the reaction sequence [78] → [80] (see p. 38). Since it was not obvious why these rather simple reactions should not be successful, and since a limited amount of the hydroxy ester [78] was still available, it was decided to repeat the last few steps of this reaction sequence.

This time it was found that the oily chloro ester [79], on treatment with base (4 hr. reflux with aqueous methanolic potassium hydroxide) gave a compound which although homogeneous on thin layer chromatography, gave an n.m.r. spectrum, typical of a mixture of closely related compounds. The material crystallized on standing, and a recrystallized sample (m.p. 108-110°) gave the correct combustion analysis for the expected α, β-unsaturated ester [80] (p. 38).

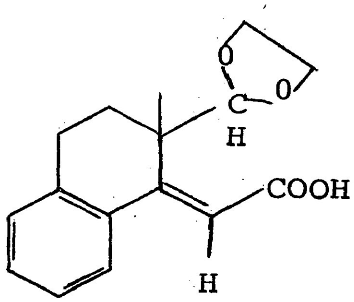
Found: C, 69.8; H, 6.8; $C_{16}H_{18}O_4$ *requires* C 70.0 H, 6.6%).

The appearance of the n.m.r. spectrum may be explained by assuming that isomerism at the double bond leads to the formation of the two unsaturated acids [80a] and [80b]. Indeed the spectrum, which contains the expected patterns compatible with structure [80] (i.e. the aromatic protons at τ2.4-3.1, alicyclic protons at τ7.0-8.4) also contains two signals for the olefinic proton at τ3.96 and at τ4.03, which have a 2:1 intensity ratio. Since in the isomer [80a] the olefinic proton is expected to be deshielded by the aromatic ring it is a reasonable assumption that the signal at lowest field (τ3.96) is due to this isomer. It is thus obvious that [80a], which has the desired geometry for later lactone formation results from the dehydration reaction in approx. 66% yield. The same 2:1 intensity ratio was observed for the C-methyl signals at τ8.82 and τ8.75 resp.

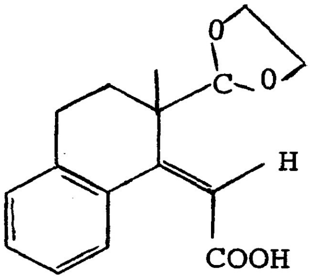
Moreover, the crystalline sample submitted for analysis gave an n.m.r. spectrum which only contains one olefinic proton signal at τ3.96, and one C-methyl signal at τ8.82. The desired isomer [80a] may thus be isolated in pure form by direct crystallization from the mixture of isomers.

Further investigation of these compounds and their conversion to the aldehyde acids [90] and [91] are presently in progress in this laboratory.

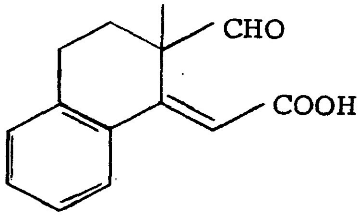
From the above discussion it follows that the suggestions for future work, as discussed in Chapter IV (p. 45), should be considered in the light of this development.



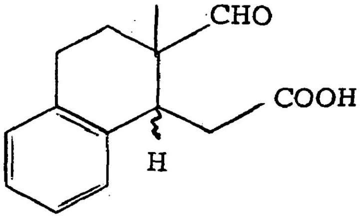
[80a]



[80b]



[90]



[91]