SYNTHESIS OF 3-SUBSTITUTED FURANS AND THIOPHENES

BY

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ABSTRACT

Some preliminary studies have been made directed to the synthesis of 3-substituted furans and thiophenes, with the object of finding an entry to the synthesis of naturally occuring 3-substituted furans.

One approach involved the study of the reactions of 1,3-dithiane carbanions with aromatic substrates, which led to a novel synthesis of 2-pyridyl aryl ketones.

A second series of reactions yielded a synthetic method for the preparation of 3-thienyl aryl sulfones, a class of compounds that has not been reported in the literature to date.

These two results, although not directly applicable to the problem under investigation, are of importance in their own right, as novel synthetic methods. The recent literature of these two topics has been reviewed in some detail.

By using the nucleophilic addition of 3-thienyllithium to the aldehyde group, a 3-thienyl lactone system, related to the 3-furyl lactone moiety of the tetranortriterpenes, has been synthesized. The solvent shifts caused by benzene in the nuclear magnetic resonance spectra of the resulting compounds have been used to study the stereochemistry.

The discussion is concluded with an evaluation of the various results and with some suggestions for the further development of this synthetic study.

ACKNOWLEDGEMENTS

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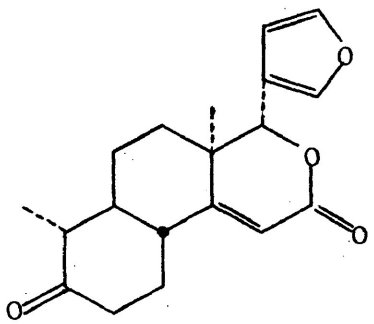
INTRODUCTION

The Tetranortriterpenes

The limonoids are a group of highly oxygenated triterpenes, isolated from the three plant families, i.e. the Rutaceae, Meliaceae, and the Simaroubaceae. In these compounds the normal triterpene side chain has been transformed into a 3-substituted furan, with the loss of 4 carbon atoms. The chemistry and natural occurence of these compounds has recently been reviewed.[1a] The simplest compound in this group is odoratin [1], which is to be considered a member of this family of compounds on the ground of its suggested biosynthesis. In fact this compound has been reported[1b] as an undecanortriterpene.

A total synthesis has so far not been reported for any of the tetranortriterpenes, although partial syntheses have been studied by Halsall *et al.*[2] Halsall converted the naturally occurring turraenthin [2] into tetranortirucallane triterpenoids[2] [4], containing a 3-furyl side chain, by treating turraenthin [2] with sodium metaperiodate to give [3]. Treatment of this compound with *p*-toluene sulfonic acid gave the 3-substituted furan [4].

With the total synthesis of a compound like odoratin [1] in mind, the first point that attracts attention is the 3-furyl lactone system, depicted in part structure [5]. This



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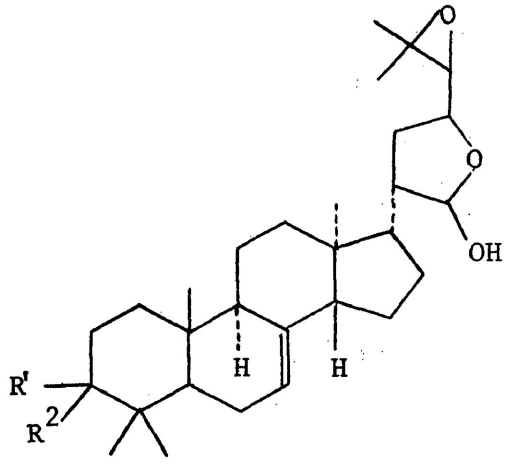

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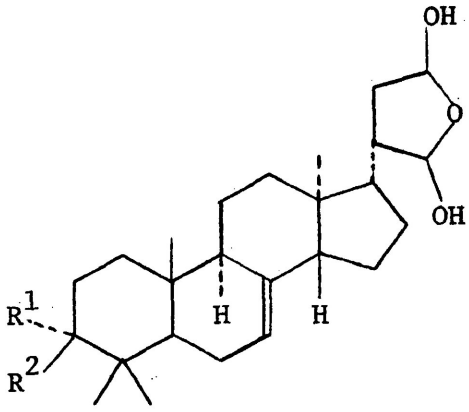

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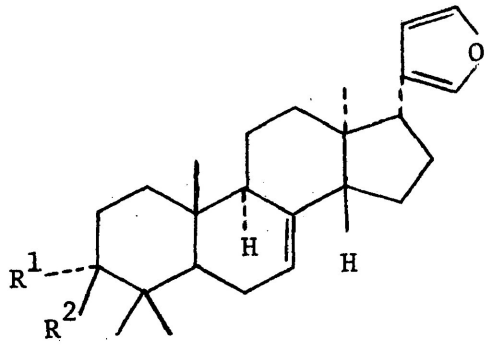

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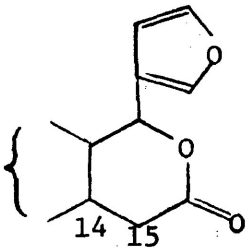

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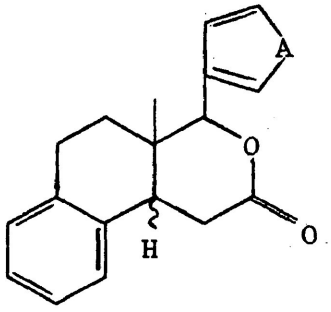

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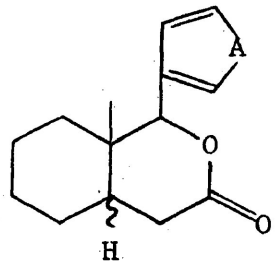


[7]

system, with a number of variations in the functionality at C_{14}-C_{15} (e.g. a double bond, an epoxide, a C_{14} hydroxyl or ether group) is a general feature of a large majority of compounds of the Meliacin family. Since most reactions involving the furan compounds require 3-iodofuran as a reagent, many experiments were first carried out with commercially available 3-bromothiophene, which led to the 3-thienyl analogs of the desired furan compounds. Thus it may be stated that the primary object of the present study is the synthesis of the compounds like [6] and [7], where A=S or A=O.

The Reactions of 1,3-Dithiane Carbanions with Aromatic Substrates

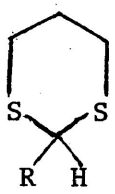
Preliminary studies[3] indicated that the best method to introduce the furan ring into a suitable intermediate is the reaction of 3-furyllithium with a properly situated aldehyde group. While these preliminary studies[3] were in progress, another approach was studied, in which it was attempted to utilize the sulfur stabilized 1,3-dithiane carbanions [9] which can be formed from aldehydes.

Corey *et al.* has reported[4] a useful synthetic method based on a temporary modification of the aldehyde carbonyl group. The treatment of dithianes [8] with alkyllithium leads to the formation of the stable carbanions [9]. In this way the original carbonyl carbon may be converted into a nucleophilic species, which then undergoes the usual displacement and addition reactions.

1,3-Dithiane carbanions of type [9] which can be generated from dithianes [8] by the action of n-butyllithium, undergo alkylation in excellent yields with a wide variety of alkyl halides.[4] A practical application of such an alkylation is illustrated by Reece *et al.*[5], who made use of this reaction to synthesize[5] 2-methyl-6-methylene-7-octen-4-ol [10] and 2-methyl-6-methylene-2,7-octadiene-4-ol [11] which they were unable to prepare by means of a Grignard reagent or a corresponding organolithium compound. These carbanions also react readily with epoxides as demonstrated in the work of Jones and Grayshan[6] who successfully made use of this reaction to prepare stereospecifically substituted steroids,[6] such as both epimers of 2-methyl-3-oxo- [12] and 3-methyl-2-oxo-5α-cholestane [13]. Reactions of carbanions [9] with CO_2, ethyl chloroformate and ketones have also been reported.[4,8] 1,3-Dithiane carbanions undergo oxidative dimerizations with oxidizing agents,[4] such as 1,2-dibromomethane, Cu(II), or iodine to afford a route to 1,2-dicarbonyl compounds by removal of the dithio-ketal groups from the coupling product [14].

The conversion of the substituted dithianes back to carbonyl compounds can be accomplished by several procedures[7] such as treatment with mercuric chloride and cadmium carbonate or with silver nitrate and N-chlorosuccinimide.

To date no reports have appeared in the literature on the reactions of these 1,3-dithiane carbanions with aromatic substrates, with the exception of the paper by Seebach and Leik.[9]



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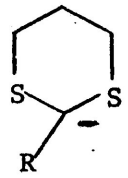

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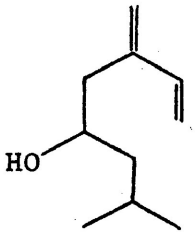

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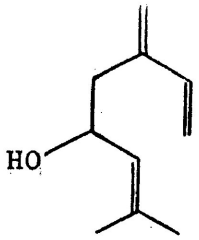

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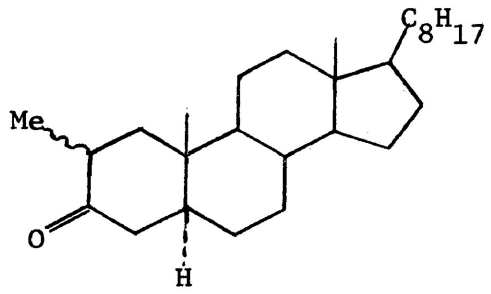

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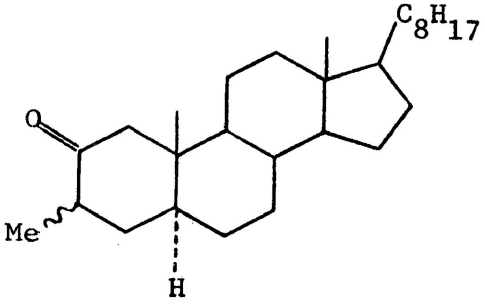

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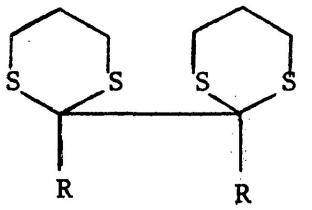


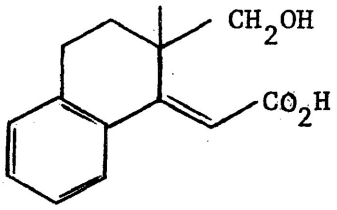
[14]

These authors described the 1,4 addition of 1,3-dithiane carbanions to substituted ω-nitrostyrenes. It was felt that carbanions of this type might be used in nucleophilic substitution reactions with aromatic substrates, and could possibly lead to a method of introducing a heterocyclic ring into a suitable intermediate containing a 1,3-dithiane group. Experiments designed for this purpose were carried out as part of this thesis and are described later.

Synthetic Intermediates

Tahirkhelis work[3] initially indicated that the use of the aldehyde group might not be suitable in view of the difficulties encountered in preparing the intermediates containing such an aldehyde. Tahirkheli therefore suggested that a useful approach might be conversion of a compound [15] into [19] (where A=S or A=O), via the tosylate [16], followed by allylic bromination of the coupling product [17] with NBS, and hydrolysis of the allylic bromide. This suggestion was based on the report of Korte *et al.*[10] which describes the reactions of certain charge delocalized organolithium reagents with *p*-toluenesulfonate esters.

However, the intended allylic bromination could be expected to lead to difficulties due to the presence of the benzene ring, since this reaction would lead to the introduction of two bromine atoms as in [17] → [18]. As the presence of the aromatic ring initially also caused difficulties in Tahirkheli's work,[3] the use of a fully saturated system, involving the sequence [20] →



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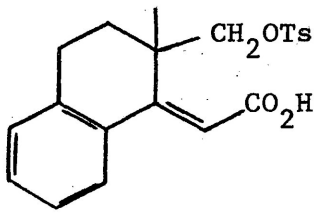

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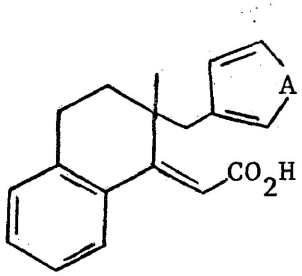

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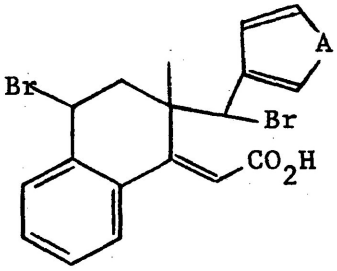

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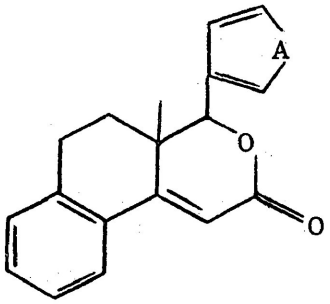

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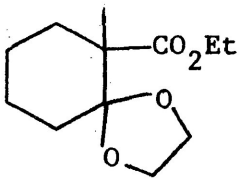

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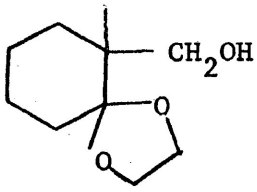

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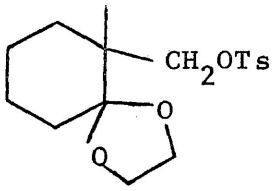

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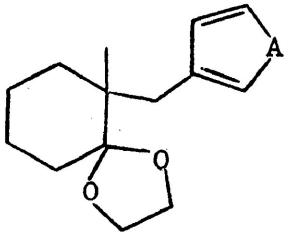

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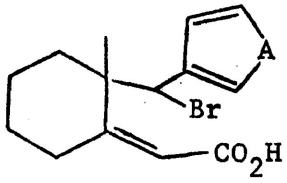

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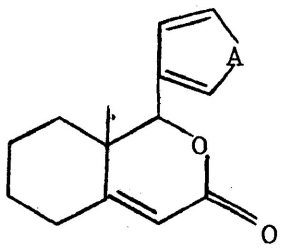


[25]

[25] was considered. The substitution of an allylic bromide by a hydroxyl group as in [24] → [25] is not expected to cause a problem, as such a reaction may easily be performed with aqueous hydroxide.[11] The construction of a synthon like [21] involves the reduction of ester groups (or similar functionalities) situated β to a ketal. The difficulty encountered with this reaction was found to be similar to those experienced[12] during the reduction of 1,3-dicarbonyl systems. In such systems, elimination or cleavage reactions frequently take place.

Difficulties of this kind might well lead to a major investigation in order to produce a synthon like [21]. Therefore it was decided first to investigate the use of tosylates in general for a conversion like [22] → [23].

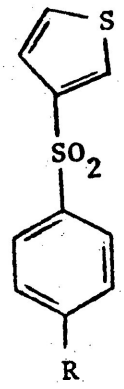
The Synthesis of Sulfones

Korte *et al.* have found that certain charge delocalized organolithium reagents, e.g. benzyl-lithium and allyllithium displace the bromide and chloride leaving groups from secondary carbon with a high degree of stereospecificity, indicating a typical Sn2 type displacement.[13] Further studies[10] indicate that allyllithium also displaces both *p*-toluene sulfonate and iodide with inversion of configuration. Since very little is known about the behaviour of 3-furyllithium and 3-thienyllithium under such conditions, it was decided to investigate this aspect of furan and thiophene chemistry in more detail.

It was found during the present studies that 3-thienyl-lithium reacts with tosylate and benzenesulfonate esters in a quite different fashion. Instead of leading to substitution at carbon, this lithium compound is apparently a strong enough base to effect substitution at sulfur. Consequently the products of these reactions were found to be 3-thienyl-aryl sulfones [26, R=H and CH_3].

In general, substitution at the carbon atom of sulfonate esters, with fision of the C-O bond takes place more readily than substitution at sulfur, as is evident from the use of tosylate as a good leaving group in elimination and substitution reactions. A common type of C-O cleavage is found in the report of Goering *et al.*[14] who reduced the tosylate [27] with lithium alumium hydride to [28]. A limited number of examples of sulfur-oxygen cleavage of sulfonate esters in steroidal[15] and carbohydrate[16] systems by base have been known for some time, especially in carbohydrate chemistry. Such a reaction occurs if Sn2 displacement at carbon is unfavourable because of steric or electronic factors. The glucoside mesylate [29] undergoes sulfur oxygen cleavage in DMSO containing sodium methoxide.[16] Chang *et al.* reported[15] that 3β-cholestanol mesylate [30] and 3α-cholestanol mesylate [31] were converted to the corresponding alcohols [32] and [33] by t-butoxide in DMSO.

A number of general methods for the formation of sulfones are known. Diaryl or alkyl aryl sulfones are most commonly made by Friedel-Crafts aromatic sulfonations,[17] in which arene or



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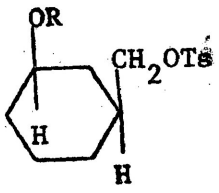

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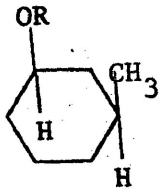

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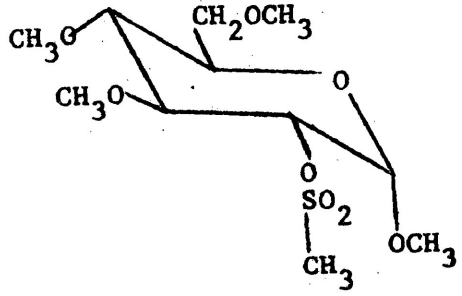

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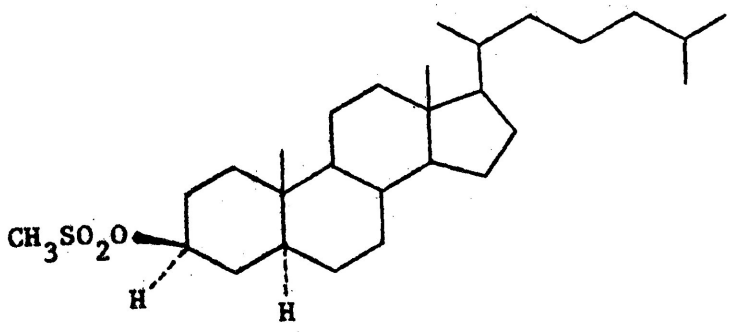

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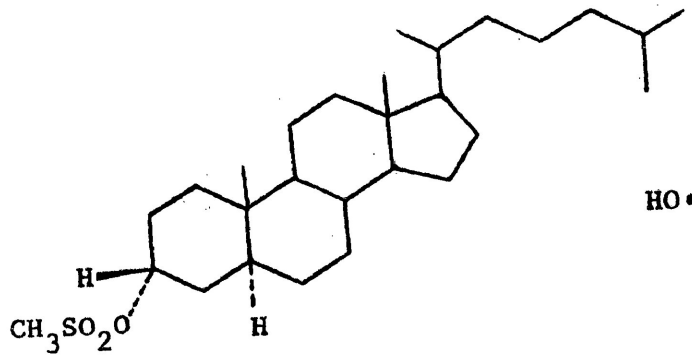

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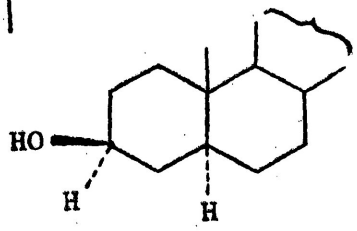

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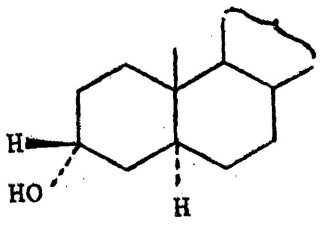


[33]

alkanesulfonyl chlorides react with aromatic substrates in the presence of aluminium trichloride:

$$ArH + RSO_2Cl \xrightarrow{AlCl_3} ArSO_2R$$

Dialkyl sulfones have been prepared by oxidation of dialkyl sulfide with hydrogen peroxide.[18] Dialkyl sulfones may be also prepared by reaction of a suitable sodium alkyl sulfinate with an alkyl halide:[19]

$$RSO_2Na + R'X \longrightarrow RSO_2R'$$

A new method for the preparation of diaryl or alkyl aryl sulfones has recently been described by Bhattacharya *et al.*[20] in which a reactive carbon-metal bond also plays a rôle. These authors[20] found a possible route to sulfones which involves the cleavage of aryl-MMe_3 bonds where M=Si or Sn. Thus, treatment of aryl-MMe_3 with alkyl- or aryl-sulfonyl chloride in the presence of aluminium chloride leads to sulfone formation in good yield:

$$ArMMe_3 + RSO_2Cl \xrightarrow{AlCl_3} ArSO_2R + Me_3MCl$$

Most of the above methods for the preparation of sulfones involve electrophilic substitution in the aromatic part of the final molecule. Since such a process is distinctly unfavourable in the 3-position of thiophene and furan rings, it would appear that these methods can not be applied to the construction of sulfones of type [26].

Indeed a careful search of the literature of the chemistry of sulfones, carried out as part of the present study, indicated

that these sulfones have not previously been reported.

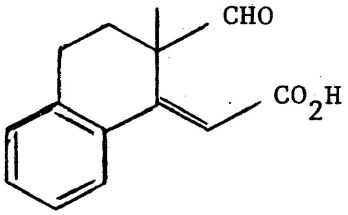
Synthesis of the Thienyl Lactone System and its Stereochemical Implications

While the above mentioned approaches to the synthesis of [6] were investigated, it became clear from the final stages of Tahirkheli's work[3] that the synthon [34] could indeed be obtained in good yield. Further studies with the unsaturated aldehydo acid [34] led to the decision to temporarily continue the investigation with the dihydro derivative of [34], i.e. the saturated aldehydo acid [35]. In this way, it was found possible to synthesize the thienyl-lactone [6, A=S, p. 2].

However, since the C_{14}-C_{15} double bond was no longer present, a third asymmetric centre was introduced, leading to a greater number of possible isomers in the product. As at least one component of the resulting mixture could be isolated by fractional crystallization, attempts have been made to establish the stereochemistry of this compound.

The solvent shifts observed in n.m.r. spectra of organic solutes have been utilized in the determination of structure and stereochemistry in a large number of cases. Since this method seemed suitable to apply to the present problem, the use of these solvent shifts is briefly discussed here.

Thus, n.m.r. measurements on a number of ketones in benzene solution led to the suggestion of a solvent-solute collision complex, for which the geometry [36] has been proposed.[21] The π-electrons of the benzene (solvent) molecule interact with



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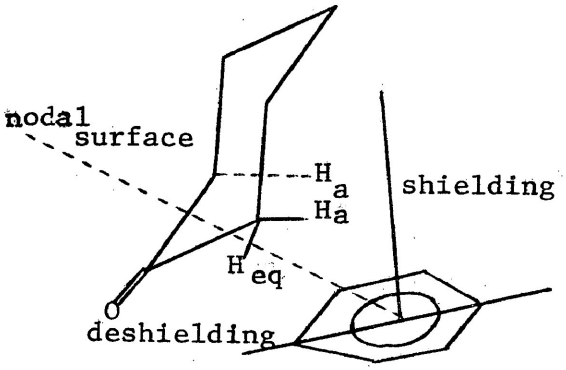
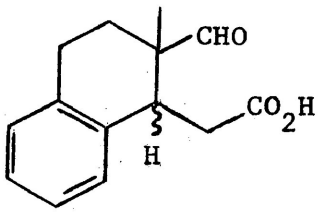


[36]



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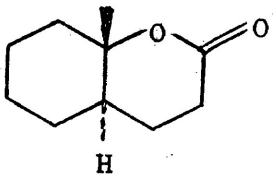
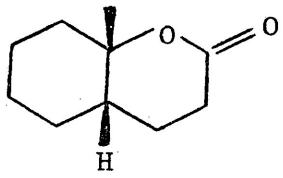


[37]



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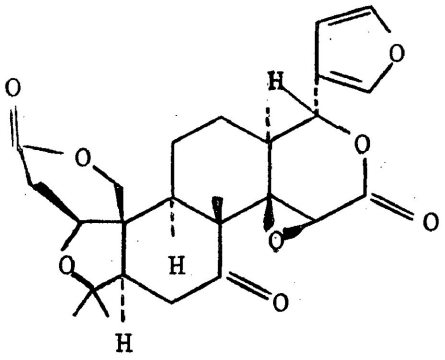
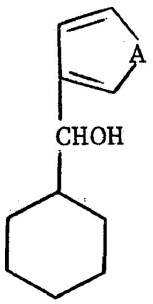


[39]



[40] A = O, S.

the partial positive charge of the carbonyl carbon atom, while at the same time the benzene ring will be in such a position that the partly negative charge of the carbonyl oxygen atom is furthest removed from the benzene π-electrons. It was found that axial protons and methyl groups are shielded due to the magnetic anisotropy of the benzene ring. Therefore, the signals due to such groups appear at high field as compared to the respective resonance signals obtained with a deutero-chloroform solution. Equatorial methyl groups or protons are little influenced or are slightly deshielded. Similar results have been obtained for lactones,[22] such as [37] and [38]. Williams *et al.* also reported[23] on the n.m.r. solvent shifts by benzene in ortho- and meta-substituted methoxybenzenes, pyridines, quinolines, pyrroles, and indoles. The shifts are so characteristic in sign and magnitude as to be useful in structure elucidation. Structure work on some tetranortriterpenes of the limonin [39] type, revealed an interesting exception. It was expected that the signal due to the axial C_{17} proton which has a characteristic[24 a,b] position at τ4.4, would shift to high field, owing to the influence of the lactone carbonyl group. Instead, a large deshielding was observed for this proton in several compounds of this type, when the spectra were recorded for pyridine solutions.[24 c] Instead of a carbonyl-solvent complex, another type of association, possibly involving the heterocyclic aromatic ring, may thus play a rôle in these cases.

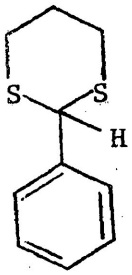
The availability of the model compounds [40] made it possible to study the solvent shifts for these compounds in somewhat more detail, and the results obtained are discussed later as applied to the present problem.

RESULTS AND DISCUSSION

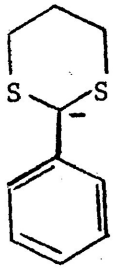
The Reactions of 1,3-Dithiane Carbanions with Aromatic Substrates

As the 1,3-dithiane carbanions described before are strong nucleophilic species, their reactions with aromatic substrates only concern those compounds that are suitably activated toward nucleophilic attack. Therefore some halobenzenes activated by one or more nitrogroups were chosen for preliminary experiments. The starting material used was prepared from the dithiane derivative [41] of benzaldehyde, which in turn was formed by addition of 1,3-propanedithiol to benzaldehyde. The 1,3-dithiane carbanion [42], which is stabilized by the d-orbitals of two sulfur atoms can readily be generated by treatment of the dithiane with n-butyllithium at -30°.[4]

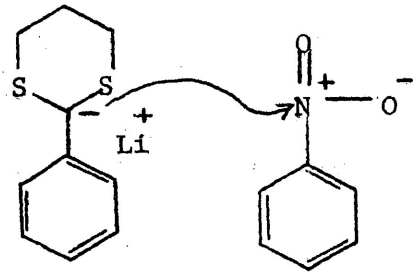
When the 1,3-dithiane carbanion [42] was treated with 2,4-dinitrobromobenzene, no nucleophilic substitution took place. Instead, a crystalline product was formed, which had the composition $C_{20}H_{22}S_4$, and which in its n.m.r. spectrum displayed signals attributed to aromatic protons at τ2.32-2.88, to protons adjacent to sulfur at τ7.20-7.48 and to protons β to sulfur at τ8.1-8.3. The empirical formula, the n.m.r. spectrum and also the molecular weight as indicated by mass spectrometry (M^+, $m/e = 390$) suggested that the structure [44] should be assigned to this product. Desulfurization of this compound with hydrazine[25] resulted in the formation of an oil, which was

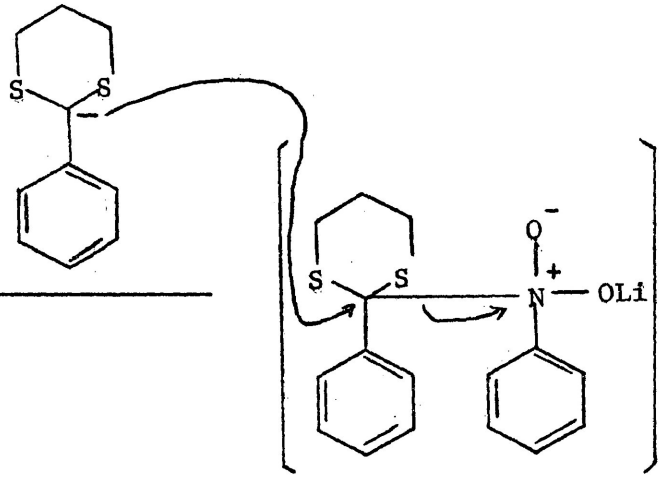


[41]

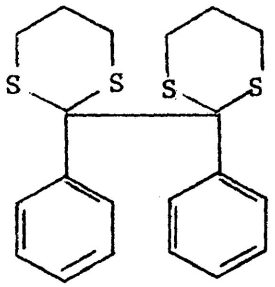


[42]





[43]



[44]

homogeneous on t.l.c., and which was identical in all respects to commercial bibenzyl.

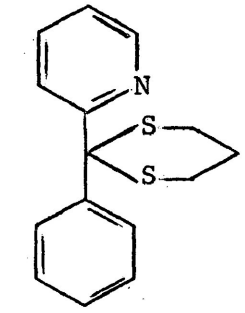
The same dimerization product [44] was also formed when the carbanion [42] was treated with 2,4-dinitrobenzene or with nitrobenzene. Such an oxidative coupling reaction has also been reported[4] to take place with other oxidizing agents such as 1,2-dibromomethane, Cu (II), or iodine.

Apparently the various nitrobenzenes are strong enough oxidizing agents to promote this kind of reaction. It is of interest to note here that substituted ω-nitrostyrenes, which undergo a 1,4 addition with 1,3-dithiane carbanions[9], do not give rise to such an oxidative dimerization reaction. The mechanism of such a dimerization has been mentioned[26] as being of a free radical nature, although that proposal was not substantiated by experimental evidence. It is equally possible that oxidation by nitro compounds, as in the present case, takes place through an ionic mechanism. An intermediate like [43] may be visualized which, after subsequent reaction with a second carbanion would lead to [44]. However, other mechanisms are possible and the correctness of the present suggestion was not investigated experimentally.

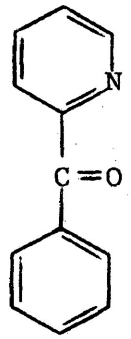
Instead, attention was then directed to other suitable aromatic substrates. The halopyridines are activated toward nucleophilic aromatic substitution in a way similar to the nitrobenzenes. At the same time these compounds do not possess the undersirable oxidizing properties inherent to the nitro group.

The 1,3-dithiane carbanion [42] reacted with 2-bromopyridine to form the disubstituted 1,3-dithiane [45] in 47% yield. The product [45] was indentified initially by spectroscopic methods. The n.m.r. spectrum contains signals due to the four pyridine protons at τ1.44-1.52 and τ2.0-2.18, the five benzene protons at τ2.58-2.85 and the six protons of the dithiane ring at τ7.45-7.68 and τ8.2-8.45. Of the last two groups, the four proton signal at lower field is assigned to the protons adjacent to the sulfur atoms. The mass spectrum indicated the molecular weight as $M^+ = 273$. A final indentification could be made when the 1,3-dithiane group was converted into a ketone by means of an oxidative hydrolysis with N-chlorosuccinimide and silver nitrate in combination with aqueous acetonitrile.[8] The resulting 2-pyridyl ketone [46] was indentical in all respects with a specimen obtained by permangnate oxidation[27] of commercial 2-benzylpyridine [47].

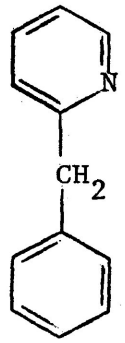
Since nucleophilic substitution of the halogen atom in 2-halopyridines usually takes place via an addition elimination mechanism[28] it is reasonable to assume that the formation of [45] involves an intermediate carbanion[48], which leads to [45] with the loss of bromide ion. Such a mechanism may be understood from a consideration of a structure like [49] in which the 2-position possesses positive character caused by the electron attracting properties of the nitrogen atom,[29a] both as a direct resonance effect and also as a strong inductive effect. On the other hand, the 3-position of the 3-halopyridines



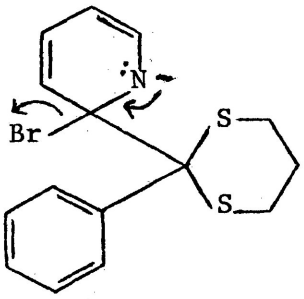
[45]



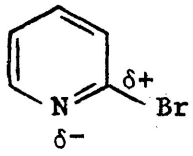
[46]



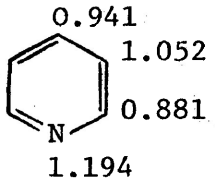
[47]



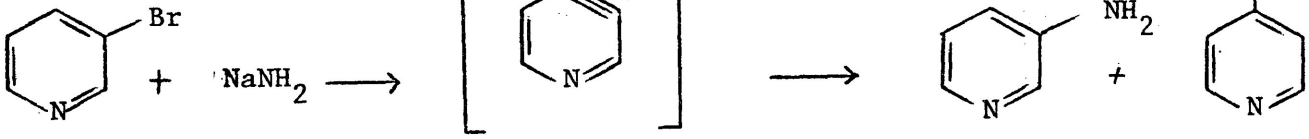
[48]



[49]



[51]



[50] [52] [53]

[50] can not acquire a positive charge by resonance. Also the π-electron densities [29b] of the pyridine ring as in structure [51] indicate the stronger positive character of the 2-position with respect to the 3-position.

It is therefore that 3-halopyridines usually react with nucleophil es through a benzyne type intermediate as in [50] → [53].[29c] Since such an intermediate offers two possible positions susceptible to attack, rearrangement frequently takes place, resulting in the formation of a mixture of position isomers. For less obvious reasons, 4-halo-pyridines also react with nucleophil es in this fashion.[28] Such a benzyne formation requires that the attacking anion is not only a strong nucleophile, but also a strong enough base to cause initial elimination of hydrogen bromide in order to produce the required benzyne intermediate. Although the 1,3-dithiane carbanion [42, P.17] is a strong nucleophilic reagent, it is doubtful that is is a strong enough base to lead to the formation of the pyridyne intermediate. Such a suggestion is not inconsistent with the fact that, when carbanion [42] was treated with 3-bromo- and 4-bromopyridine respectively, the starting material, i.e. [41], was recovered unchanged in both cases. Also, iodobenzene and 3-bromothiophene did not react on treatment with the 1,3-dithiane carbanion [42].

Thus, the coupling of 1,3-dithiane carbanions with aromatic substrates is apparently limited to 2-halopyridines. However, this reaction may well be useful for the construction of the

2-pyridyl phenyl ketone moiety in cases where other acid sensitive groups preclude the use of the normal Friedel-Crafts acylation reaction.[30]

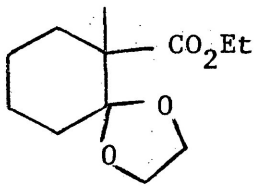
Attempted Synthesis of a 3-Thienyl Substituted Lactone Starting with Cyclohexanone.

The major obstacles experienced by Tahirkheli in the synthesis of the desired lactone-3-furyl system (e.g. [19], P. 7) were cleavage reactions to which the aromatic ring of α-tetralone contributed, as well as initial failure to produce the desired aldehyde function in a precursor like [54]. For these reasons, the possibilities of starting with a saturated system were investigated.

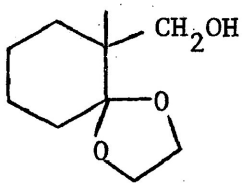
Since the unusual reaction of the lithio heterocycles with tosylates, as reported in the following section, was not known at the time, Tahirkheli suggested a sequence [20] → [25] as a possible approach to the desired system. Although a study of this series of reactions was superseded by other developments, the results are recorded here.

The ketal [20] of the β-keto ester [55] was prepared without difficulty according to the procedure of Snyder *et al.*[31] It was the succeeding step, i.e. the reduction of the ketal ester [20] to the primary alcohol [21] which proved to be the major obstacle in a possible synthesis of the lactone [25].

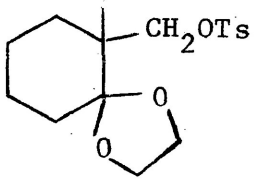
A direct reduction of the ester group with lithium aluminum hydride was unsuccessful. Thin layer chromatography



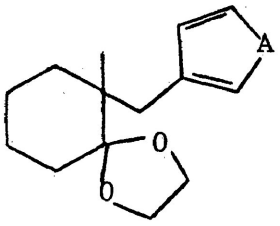
[20]



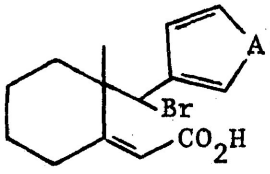
[21]



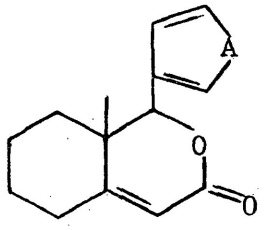
[22]



[23]

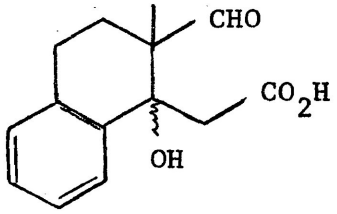


[24]



[25]

A = S or A = O



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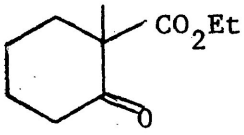
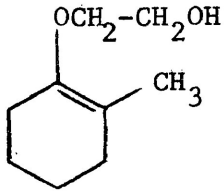


[55]



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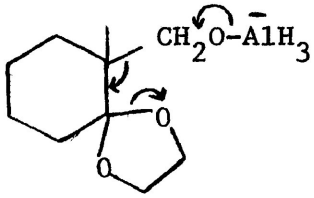

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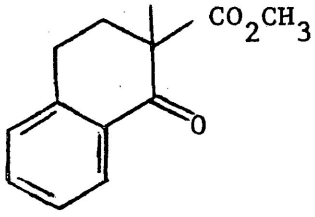
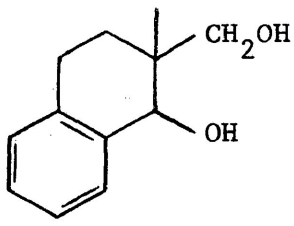


[58]



[59]

of the reduction mixture indicated a large number of components. A major compound, which constituted approximately 60% of the reaction mixture was isolated by column chromatography. Although the infrared spectrum of this compound indicated the formation of a hydroxyl function and the loss of the ester group, it was clear from other spectroscopic evidence that this product was not the desired hydroxyl ketal [21]. Thus, the largest fragment that could be observed in the mass spectrum was indicated by a peak at *m/e* 156, and the molecular ion of the expected product [21] at *m/e* 186 was absent. Also, the characteristic signals due to the ketal function were absent from the n.m.r. spectrum.

It is therefore suggested that the product is the enol ether [56] which may have been formed by cleavage of the alkoxyl ion [57], which is an intermediate in the lithium aluminum hydride reduction.

A precedent for such a cleavage is found in the results of lithium aluminum hydride reduction of 1,3-dicarbonyl compounds, which are also reported to undergo cleavage under those conditions.[12] In the case of 1,3-dicarbonyl compounds, this problem could be circumvented by the use of sodium borohydride in a hydroxylic solvent, which allows immediate protonation of the intermediate alkoxide. Since Tahirkheli[3] stated that the diol [59] was formed when the keto ester [58] was treated with excess of sodium borohydride, a similar attempt was made to reduce the ester group of [20] by sodium borohydride. However, a large excess

of sodium borohydride as well as prolonged reaction times[32] failed to effect a reduction.

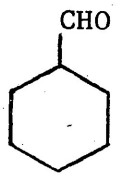
Also, treatment of the ester [20] with sodium in ethanol (Bouveault-Blanc reduction)[33] yielded only unchanged starting material.

The failure to effect a reduction of the ester function of [20] suggests that an entirely different approach might be required in order to synthesize the synthon [21]. Since it was at this time by no means certain that a tosylate like [22] could be converted into the 3-furyl substituted compound [23], it was decided that a study of the reactions of tosylates with 3-furyllithium was of higher priority.

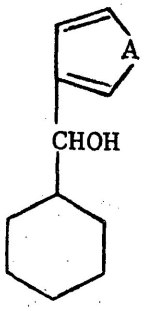
The Reactions of 3-Furyllithium and 3-Thienyllithium

Tahirkheli's work[3] indicated that 3-furyl-lithium and 3-thienyllithium react with cyclohexanecarboxaldehyde [60] to form the alcohol [40] in good yield, which could be oxidized to the corresponding ketones without difficulty. Tahirkheli also stated[3] that these lithium compounds react only very slowly with esters of carboxylic acids.

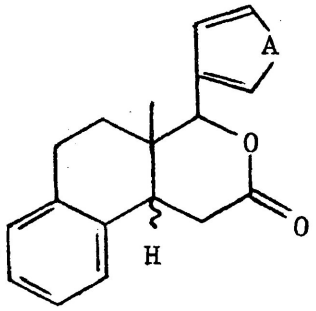
As it appeared that these reactions promised to be of extreme importance in the synthesis of compounds like [6] and [7], it was felt that more information on the reactions of 3-furyllithium and 3-thienyllithium was needed. Since the desired route to a molecule like [6] probably involves an aldehydo-ester [61], the relative reactivity of aldehydes and esters towards the two lithium compounds under discussion is critical.



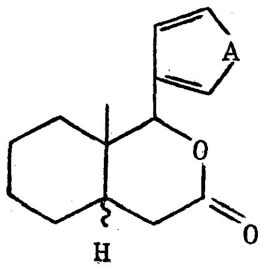
[60]



[40]

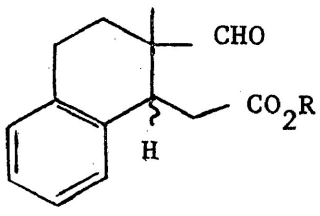


[6]

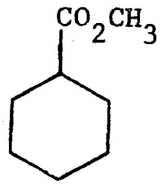


[7]

A = O or S



[61]

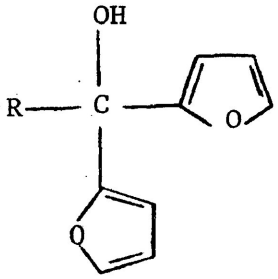


[62]

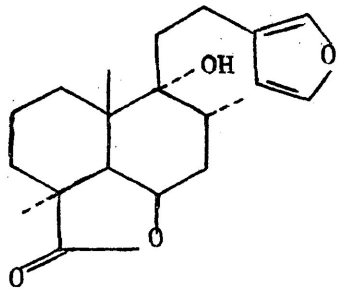
In order to estimate these relative reactivities, competitive experiments were carried out with both 3-thienyllithium and 3-furyllithium.

To one molar equivalent of 3-thienyllithium was added a mixture of one equivalent of cyclohexanecarboxaldehyde [60] and one equivalent of methyl cyclohexanecarboxylate [62]. The 1:1 molar ratio of the substrate mixture was confirmed by n.m.r. (i.e. the 1:3 intensity ratio of the aldehyde signal of [60] at τ0.37 and the methyl ester signal of [62] at τ6.33). The reaction mixture was worked up in the usual way[3] until the product was obtained as a fairly concentrated solution in ether. An n.m.r. spectrum of this solution contained the signals of the carbinol proton of the coupling product [40, A=S] at τ5.54 (J=6cps) and of the methyl ester group in a 1:3 intensity ratio. That the alcohol [40] and the ester [62] were the only products was established by thin layer chromatographic comparision with authentic specimens. From the above results it can thus be concluded that 3-thienyllithium reacts specifically with an aldehyde group in the presence of a structurally analogous ester.

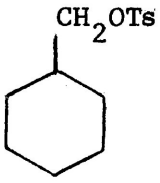
Although 3-thienyllithium and 3-furyllithium behave similarly in many reactions, there are certain differences due to the difference in aromatic character of the two heterocyclic rings. One specific example of such different behaviour will be discussed below. Moreover, since 2-furyllithium has been reported[34] to react with esters to give tertiary alcohols [63], it was necessary



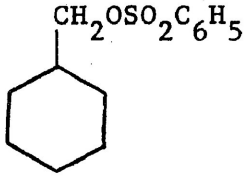
[63]



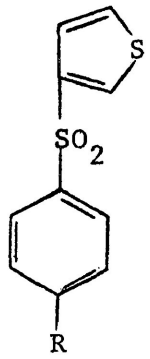
[64]



[65]



[66]



[26]

to carry out a similar competitive experiment with 3-furyllithium. The results of such an experiment did however indicate that in this reaction 3-furyllithium behaves in the same fashion as 3-thienyllithium, i.e. by adding specifically to the aldehyde group, and leaving the carboxylic ester unchanged.

A second point of interest was the reactions of 3-furyllithium and 3-thienyllithium in nucleophilic substitution reactions at a saturated carbon atom. One such substitution, i.e. the reaction of 3-furyllithium with an allyl bromide, has been described[35] as part of a synthesis of marrubin [64].

For reasons explained before, it was of interest to study the reaction of the two lithium compounds under discussion, with sulfonic acid esters.

The sulfonate esters used were those of cyclohexylmethanol, so that a successful substitution reaction would yield products analogous to previously prepared model compounds [40], P. 26.

3-Thienyllithium reacted with the tosylate [65] and the benzene sulfonate [66] to give 3-thienyl aryl sulfones [26, R=CH_3 and R=H respectively] in 60-50% yield.

The sulfones [26] were characterized by analytical determination of their empirical formulae and also by spectroscopic results as follows:

The n.m.r. spectrum of 3-thienyl *p*-tolyl sulfone [26, R=CH_3] contains signals which could be attributed to an aromatic methyl group at τ7.61 and two groups of aromatic protons at τ2.63-2.76 (3H) and τ1.9-2.2 (4H). The total intensity of the aromatic

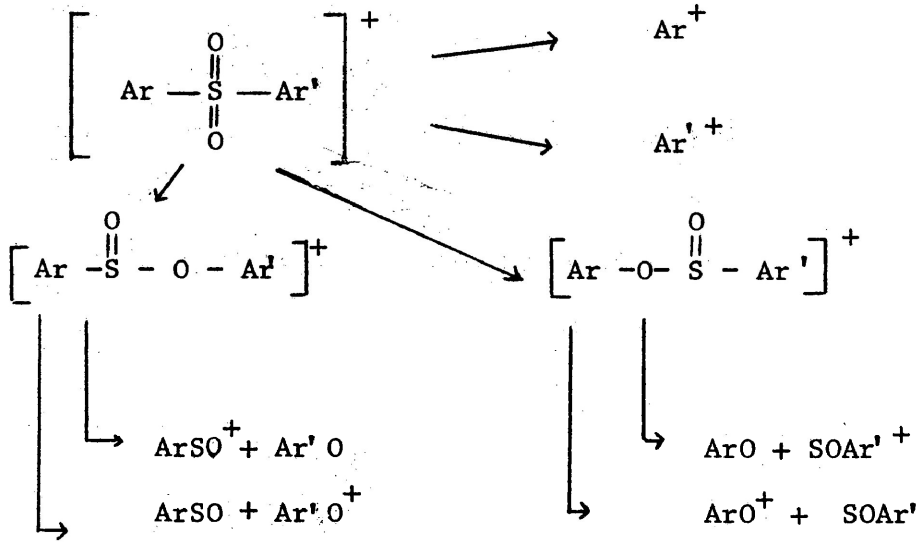
proton signals had a ratio 7:3 with respect to the methyl group signal. The n.m.r. spectrum of 3-thienyl phenyl sulfone [26, R=H] only contains aromatic proton signals at τ1.85-2.05 and τ2.4-2.67, but the two groups of signals could not be readily assigned. Although lack of a reference signal did not allow an assignment of relative intensity to those signals, this spectrum was also in agreement with the expected structure [26, R=H] of this compound.

The sulfone group itself is transparent in the ultraviolet region of the spectrum, and it was initially stated that no conjugation effects were observed in the U.V. spectra of aromatic sulfones.[36] Another paper[37] however states that conjugation of the sulfone group with π—electrons of aromatic rings and double bonds does indeed occur. In view of these findings it may be stated that the U.V. spectra of the sulfones [26], although not very characteristic, are in agreement with their expected structures. Thus, 3-thienyl-*p*-tolyl sulfone [26, R=CH_3] had λ_{max} 248 mμ (ε = 15,200), and λ_{max} 228 mμ (ε = 9870), and 3-thienyl phenyl sulfone [26, R=H] had λ_{max} 244 mμ (ε = 13,200) an λ_{max} 222 mμ (ε = 9720).

More characteristic data was obtained from the infrared and mass spectra of the sulfones [26]. Both compounds in their infrared spectra, had strong bands characteristic[38] of the sulfone group at ν_{max} 1350-1320 and at ν_{max} 1135 - 1109 $cm.^{-1}$

Also the mass spectra of these two compounds were found to be similar to the spectra of the diaryl sulfones. The mass

spectra of diaryl sulfones[39] usually show a strong peak representing the molecular ion. Further fragmentation is then visualized as involving an initial rearrangement of the molecular ion to an arylarenesulfinate ester, followed by the rupture of the S-OAr bond, as indicated in scheme 1 below. Consequently the major fragments in the spectrum of a diaryl sulfone are the ions $ArSO^+$, $Ar'SO^+$, ArO^+ and $Ar'O^+$. Other fragments observed are Ar^+ and Ar'^+.



Scheme 1

In the above scheme 1 (and also in scheme 2 on P.35), all fragments are written as cations, although it is recognized that some are in actual fact cation-radicals.

In a similar fashion the thienyl sulfones [26] would be expected to lead to analogous fragments as indicated in scheme 2. Although the actual spectra of the thienyl sulfones as reproduced in Fig. 1, and 2, do not contain all the fragments that were expected according to scheme 2, the spectra may nevertheless be considered as characteristic for the compounds under discussion.

Thus, the spectrum of 3-thienyl *p*-tolyl sulfone [26, R = CH_3] (Fig. 1) in addition to the molecular ion at *m/e* 238 (100%), displays strong peaks corresponding to the ions [c, R = CH_3], $C_7H_7OS^+$, at *m/e* 139 (61%), [d, R = CH_3], $C_7H_7O^+$, at *m/e* 107 (45%) and [e], $C_4H_3OS_2^+$ at *m/e* 131 (97%). The ion [f], which is the thienyl analogue of [d], was not observed. Also, of the ions [a] and [b], only [a] gave rise to a peak at *m/e* 91 [48%). The presence of the ion [b] is doubtful, since at *m/e* 83 only a very weak peak can be observed (approximately 5%).

The spectrum (Fig.2) of the 3-thienyl phenyl sulfone [26, R = H] is very similar and contains in addition to the molecular ion peak at *m/e* 224 (80%) peaks representing the ions [c, R=H] at *m/e* 125 (50%), [e] at *m/e* 131 (100%) and [f] at *m/e* 99 (21%). The ion peak [a, R=H] is present at *m/e* 77 (54%) and the absence of appreciable ion current at *m/e* 83 indicates that ions [b] and, somewhat surprisingly, ion [d] are not formed.

Unfortunately, metastable peaks were extremely difficult to recognize in these two spectra, even when recorded at an ionizing current of 30 MeV. Only in the spectrum of 3-thienyl phenyl

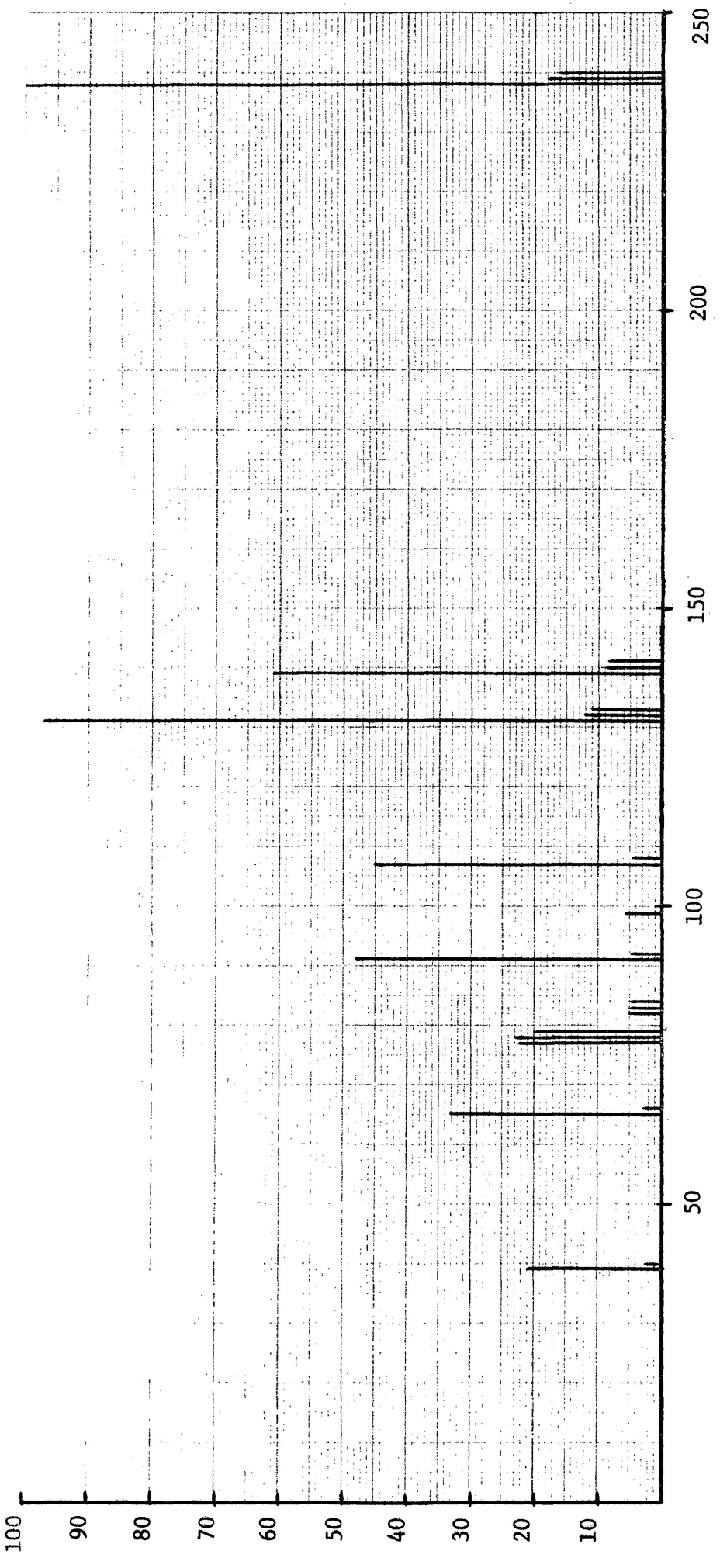


FIG. 1 MASS SPECTRUM OF 3-THIENYL P-TOLYL SULFONE

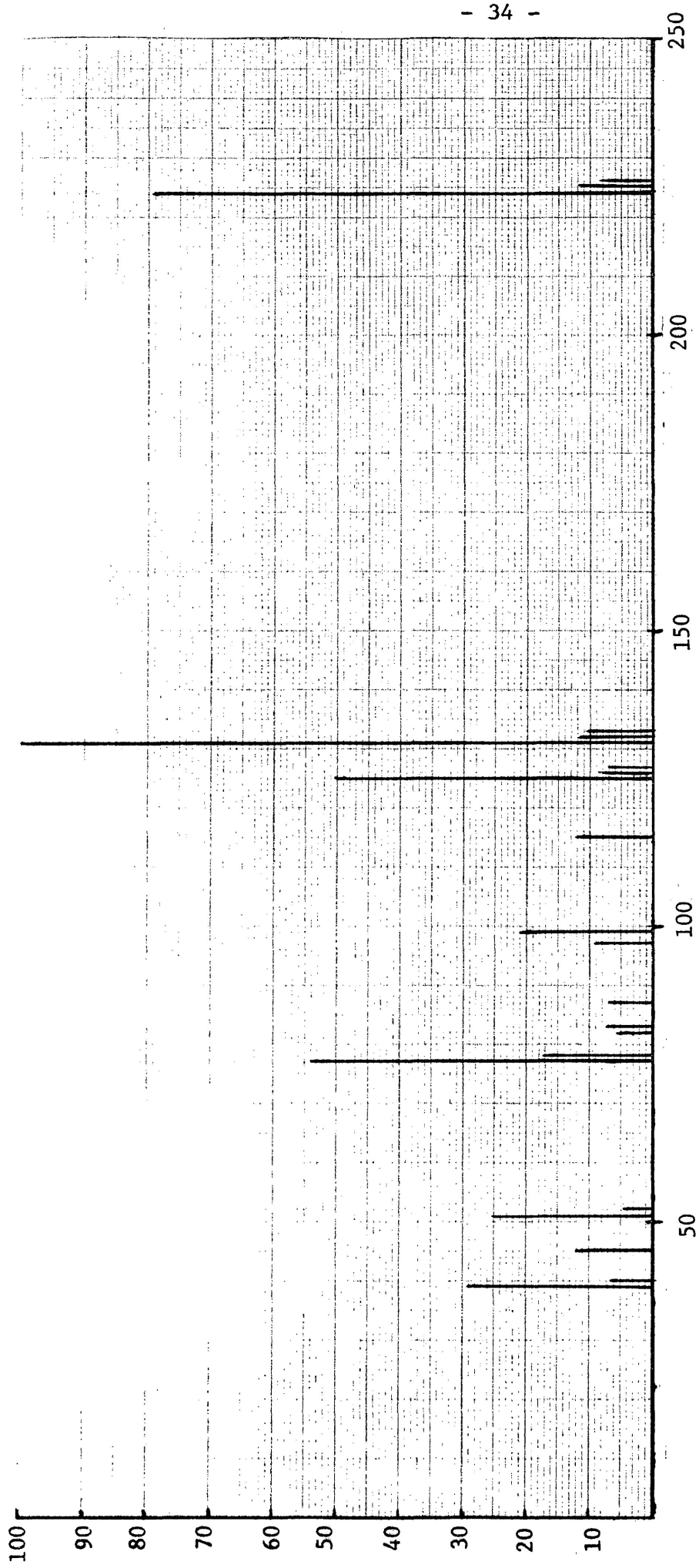
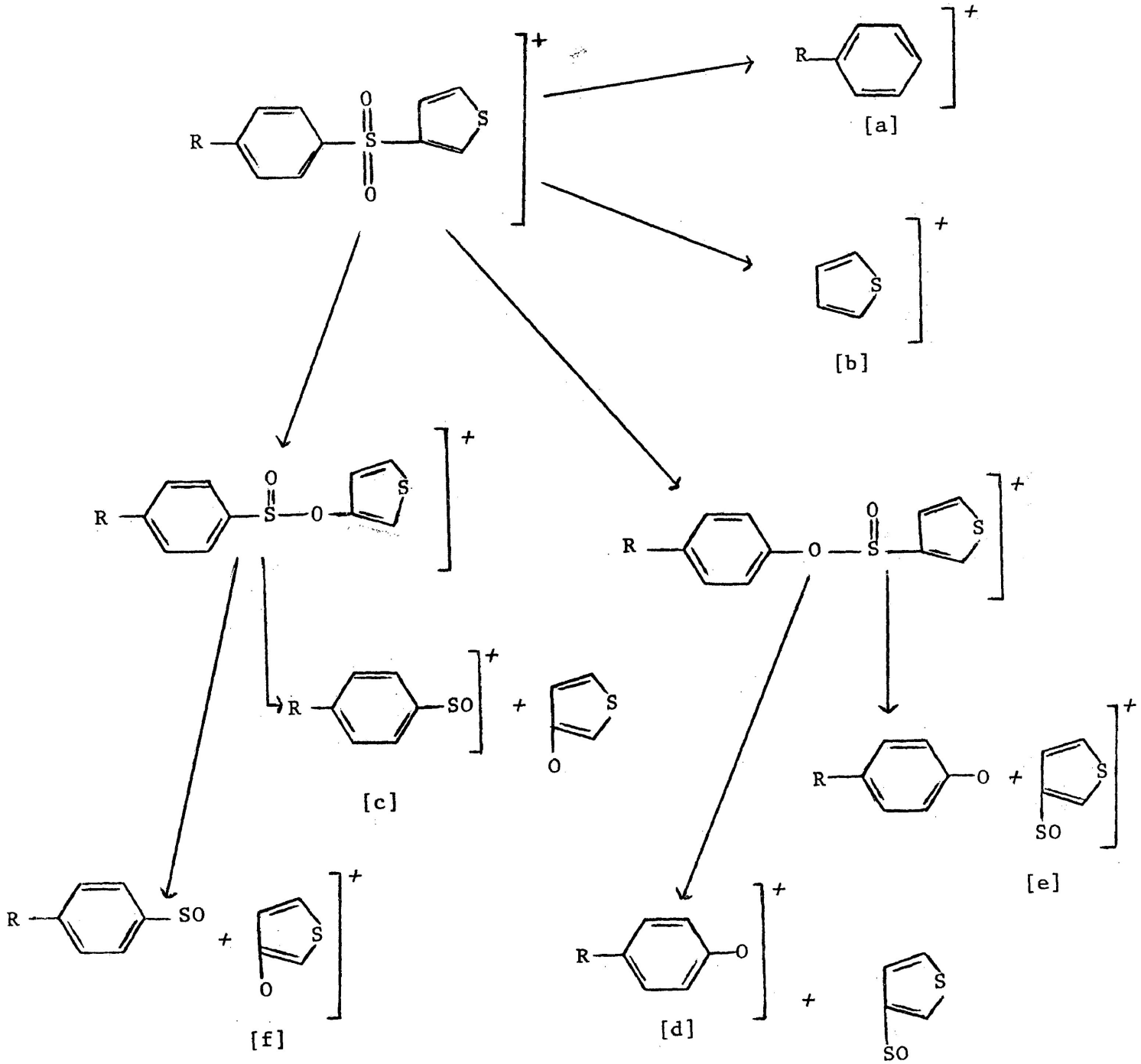


FIG. 2 MASS SPECTRUM OF 3-THIENYL PHENYL SULFONE

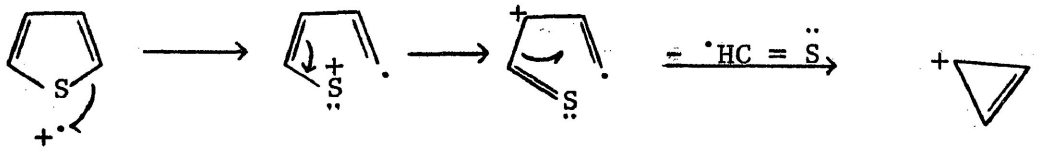


Scheme 2

sulfone [26, R=H] the formation of the ions [c, R=H] and [e] from the molecular ion could be confirmed by the observation of metastable peaks at *m/e* 69.6 (calc. 69.8) and at *m/e* 76.4 (calc. 76.6) respectively.

In comparing the two spectra with each other, it is evident that the fragmentation depends to some extend on the substituents present on the phenyl part of the sulfone, which probably governs the stability of the molecular ion relative to the ion [e], as well as the absence or presence of the ions [d].

With respect to the diaryl sulfones, the thienyl sulfones are only substantially different with respect to the ion [b]. However, the absence of a peak at *m/e* 83 may well be explained by assuming that such a fragment is rapidly decomposed to form the ion [g], according to the sequence[40] [b] → [g]. A moderately strong peak at *m/e* 39 is present in both spectra.



[b] [g] *m/e* 39

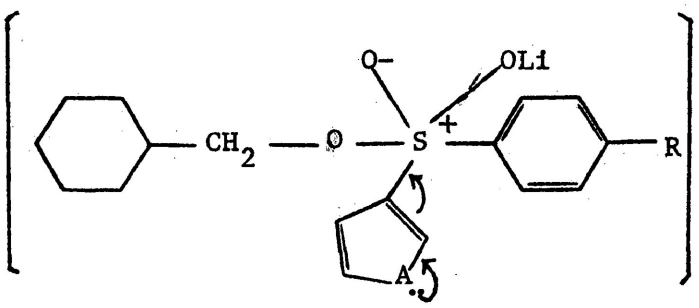
Whereas the spectral evidence presented above establishes the identity of these two sulfones, a few remarks with respect to their formation are required here.

3-Furyllithium did not react with the tosylate [65] or with the benzene sulfonate ester [66] to give sulfur oxygen

cleavage and in fact the tosylate [65] and sulfonate ester [66] were recovered unchanged from the reaction mixtures.

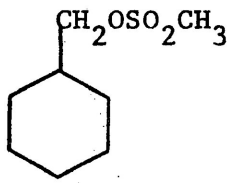
The different behaviour of 3-furyllithium with respect to sulfonic acid esters of this kind may be considered in the light of two factors.

Firstly, the absence of S-O cleavage which would lead to sulfone formation, may be the result of a low stability of a transition state like [67], in the case where A=O. On the other hand, a structure like [67] would be expected to be stabilized by sulfur in the case where A=S. In other words, the stability of [67] depends on the aromatic character of the heterocyclic ring.

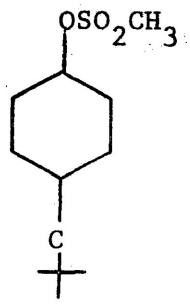


[67] A =O,S.

R =H, CH_3



[68]



[69]

Secondly, in a transition state like [67] a successful sulfone formation must also be influenced by the properties of the alkoxide as a leaving group. The question therefore arises

whether the use of a phenoxy group as the leaving group (i.e. the use of phenyl aryl sulfonates) would

a) make the formation of 3-furyl sulfones possible, and

b) improve the yield of the 3-thienyl sulfones.

As these factors only affect S-O cleavage resulting in sulfone formation, it is at present difficult to explain why no regular C-O cleavage took place resulting in substitution at carbon during the reaction with furyllithium.

Treatment of the methyl sulfonate of cyclohexyl methanol [68] with 3-thienyllithium led to the recovery of unchanged starting material. It is probable that in this case one of the acidic methyl protons is initially abstracted by the lithium compound, resulting in a proton exchange. Since a similar reaction has been observed before, e.g. in the reactions of the methyl ester of methyl sulfonic acid[41] ($CH_3SO_2OCH_3$) and of the methyl sulfonate[42] [69] with n-butyl-lithium, it was not considered necessary to investigate the present case in more detail.

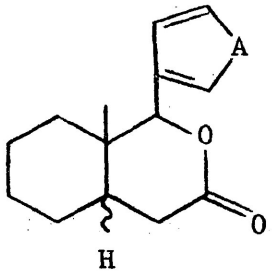
The reactions described in this section are obviously not applicable to the synthesis of 3-substituted furans and thiophenes like [19] (P. 40). However, this novel method for the preparation of heteroaromatic sulfones, at least those related to thiophene, is of considerable importance for synthetic purposes.

Further comments on a few points raised in the above discussion will be given in the conclusion of this thesis.

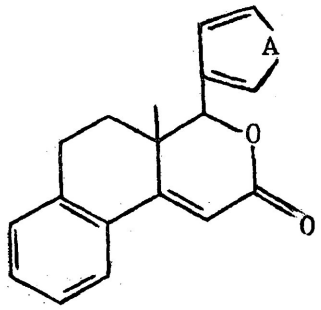
Synthesis of the 3-Thienyl Lactone System and its Stereochemical Implications

The successful preparation of the aldehydo acid [34] by Tahirkheli[3] took place at approximately the time when previously described studies indicated that the synthesis of a saturated system like [7] would meet with several major difficulties. It was therefore obvious that the original approach to the synthesis of the tetralone derivative [19] offered a much better chance of success.

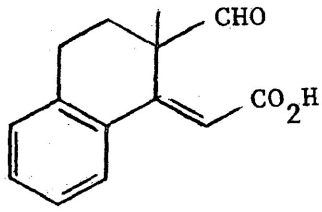
As pointed out by Takirkheli, the treatment of the keto aldehyde [70] with either 3-thienyllithium or with 3-furyllithium lead to the cleavage of the aldehyde group to give the ketone [71]. It was expected that a similar cleavage reaction would take place if the unsaturated aldehydo ester [72] is brought into contact with strong base (e.g. [72] → [73]). The free carboxylic acid [34] was expected to be stable under alkaline conditions, since the negatively charged carboxylate anion should oppose a cleavage reaction of this kind. An extra mole of the lithium compound would be required in order to neutralize the carboxylic acid in such a reaction. When the aldehydo acid [34] was treated with two molar equivalents of 3-thienyllithium, the acidic portion of the product was found to consist of a large number of components (t.l.c.). A mass spectrum of the crude mixture gave no indication that the desired lactone [19, A=S] had been formed. No attempts were made to identify any components of this mixture. Instead, it was decided to sacrifice the double



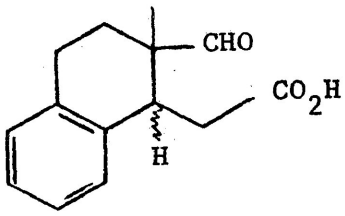
[7]



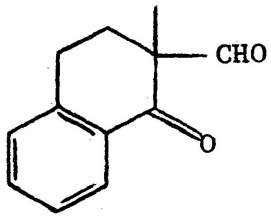
[19]



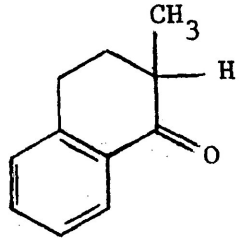
[34]



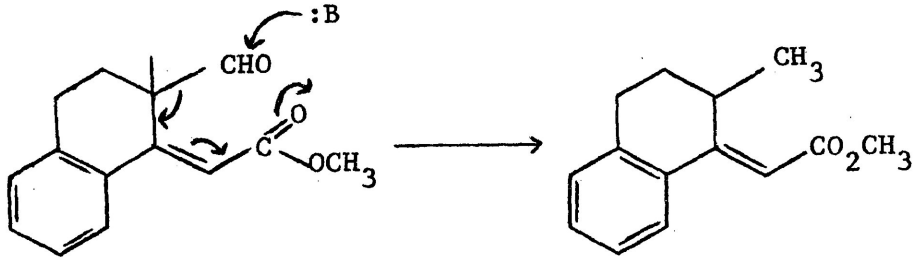
[35]



[70]



[71]

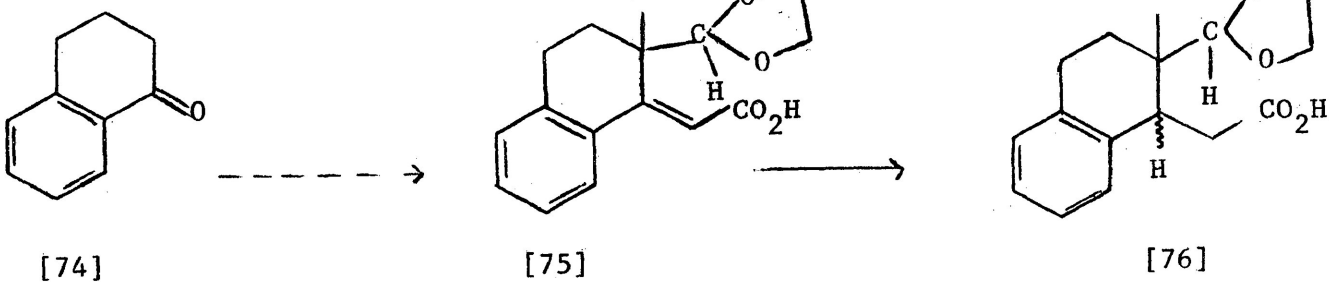


[72] [73]

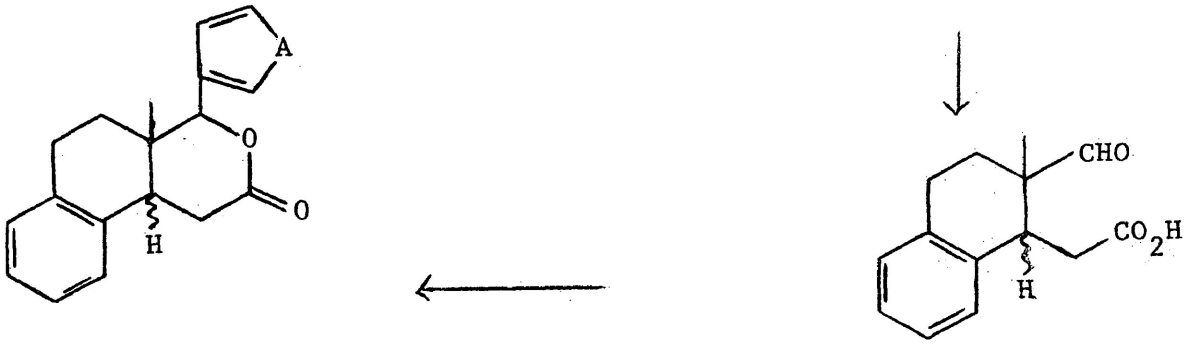
bond, hopefully only temporarily, i.e. to attempt the coupling reaction with the saturated aldehydo acid [35].

Therefore the unsaturated acetal acid [75] which was prepared from α-tetralone [74] according to the procedure of Tahirkheli[3], was reduced with sodium amalgam to give [76] in quantitative yield. Evidence for complete reduction was found in the shift of the infrared absorption to 1730 cm^{-1} from 1710 cm^{-1} previously observed for the α,β-unsaturated acid [75]. Also, the n.m.r. spectrum of [76] no longer contains the olefinic proton which in the spectrum of [75] gives rise to a signal at τ3.93. Although the methyl group of the saturated compound [76] gives a single signal at τ9.07, a double signal representing the proton next to the acetal group at τ5.26 and τ5.32 (1H) is evidence that a mixture of isomers was formed in the reduction reaction. However, these observations were not accurate enough to allow a firm conclusion concerning the composition of this mixture of isomers, and further comments on this aspect will be presented later.

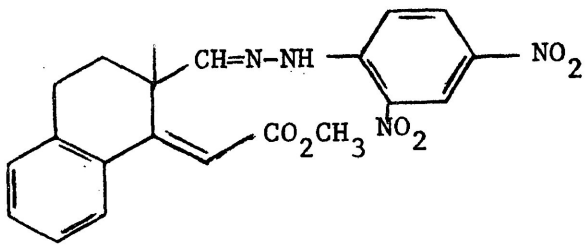
Removal of the acetal group then gave the mixture of aldehydo acids [35], which was characterized via its crystalline 2,4-dinitrophenylhydrazone. It may be mentioned here that for both the aldehydo acids [34] and [35], the treatment with a methanolic solution of 2,4-dinitrophenylhydrazine and conc. sulfuric acid, led to the formation of the hydrazone derivative of the aldehyde group, as well as to esterfication of the carboxyl group. The derivatives actually formed where thus



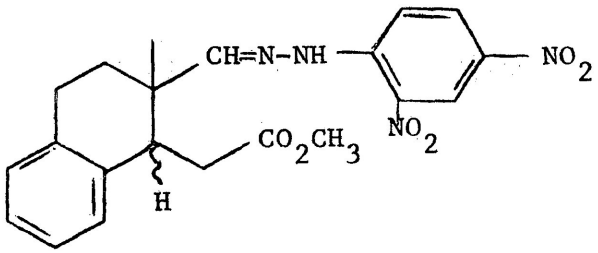
[74] [75] [76]



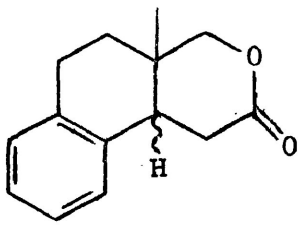
[6] [35]



[77]



[78]



[79] a, trans-isomer

b, cis-isomer

[77] and [78], which was clear from the mass spectra as well as from the analyses of these compounds.

The saturated aldehydo acid [35] was then made to react with two moles of 3-thienyllithium. The acidic portion of the reaction mixture contained two major components, which could be separated from minor impurities by filtration through a small amount of silicagel. The semicrystalline mixture of these two major components was found to be a mixture of two isomers with the structure [6, A=S], and this conclusion is based on the following evidence.

The infrared spectrum of the mixture indicates the presence of a δ-lactone by a carbonyl band at 1750 cm^{-1} and the absence of the typical acidic hydroxyl group of the starting material.

The mass spectrum, fig. 3, contains the molecular ion peak at *m/e* 298 (12%). The loss of the thiophene ring (Scheme 3) as the neutral thienyl aldehyde, to form the ion [a] at *m/e* 186 (8%) corresponds to a similar fragmentation observed for the meliacins[43] where an M^+-96 peak is usually observed. In the present case there is also a moderately strong peak at *m/e* 187 (16%). This fragment may arise by a hydrogen transfer during the formation of [a], thus leading to the closely related ion [b] at *m/e* 187. Further loss of the side chain then leads to the formation of ion [c] at *m/e* 144 which is the base peak of the spectrum. Loss of the methyl group to give [d] at *m/e* 129 (38%) which further decomposed to [e] at *m/e* 91 (24%) completes the main features of this spectrum, as indicated in Scheme 3. When the initial ionization takes place at the sulfur atom, the formation of the ion [f] leads to a peak at *m/e* 111 which in the present case is of relatively low intensity (10%).

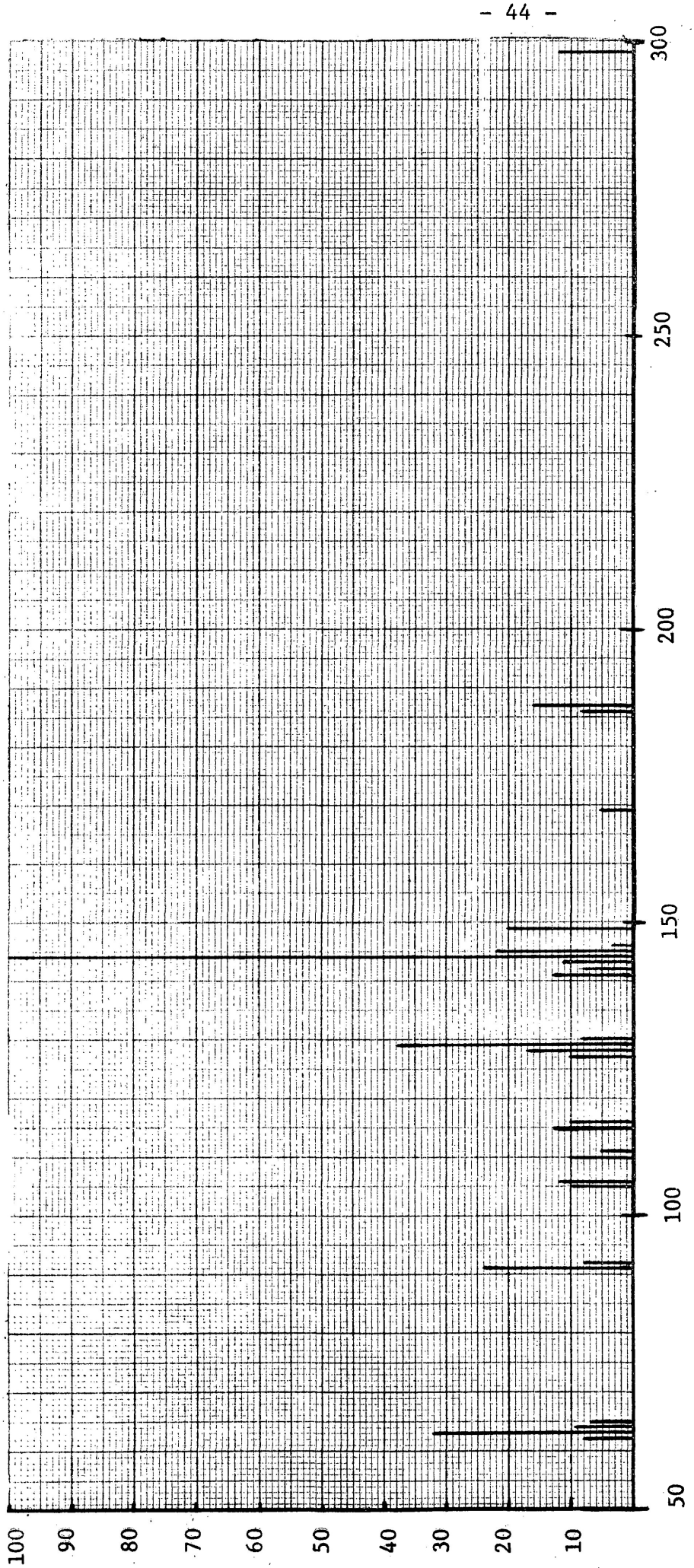
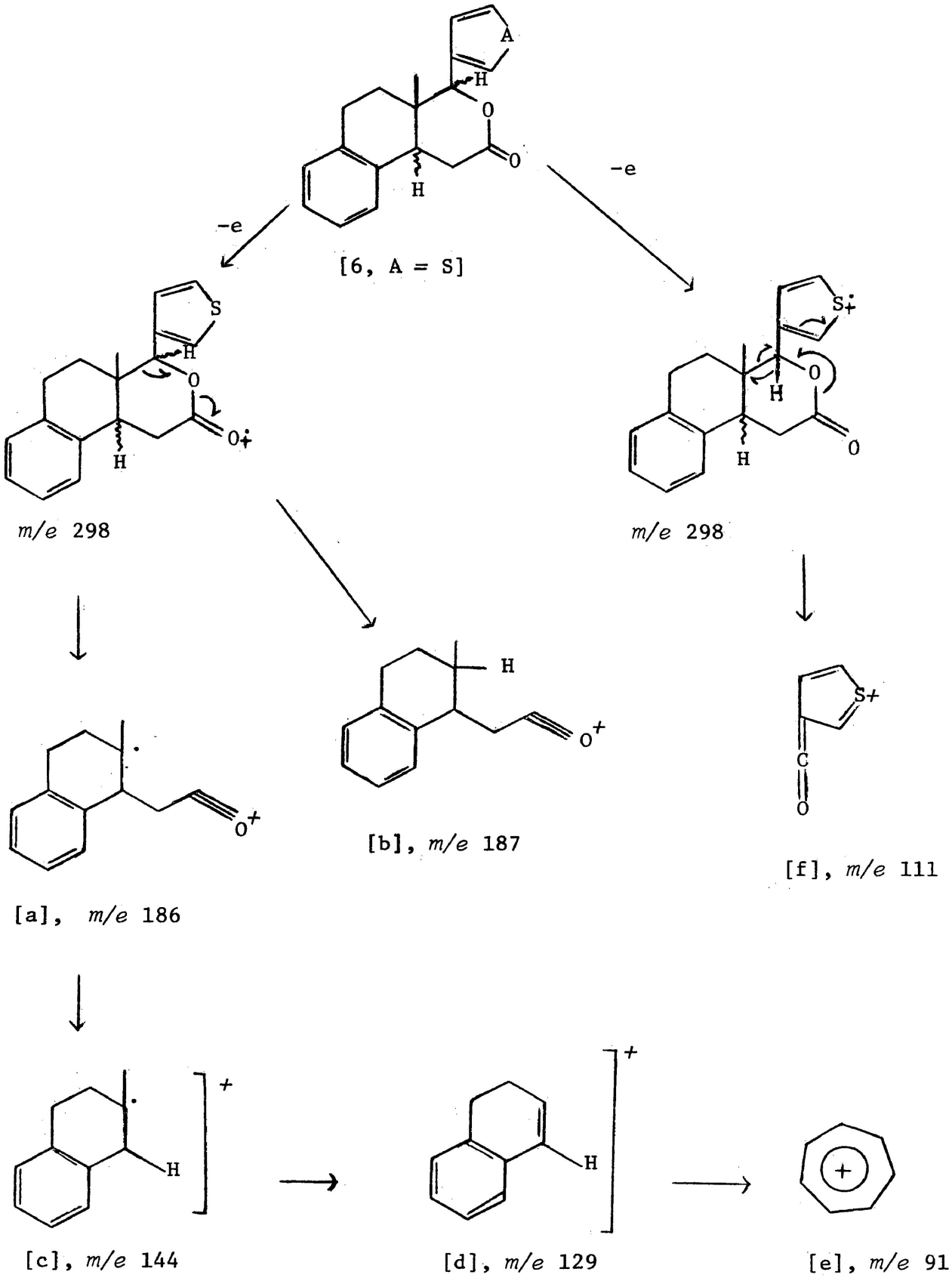


FIG. 3 MASS SPECTRUM OF 3-THIENYL LACTONE [6, A=S]


A
H
O
O
H
-e
-e
[6, A = S]
S
H
O
O+
H
m/e 298
S+
O
H
O
m/e 298
H
O+
[b], m/e 187
S+
C
O
[f], m/e 111
O+
[a], m/e 186
H
+
[c], m/e 144
H
+
[d], m/e 129
+
[e], m/e 91

Scheme 3

The n.m.r. spectrum clearly indicates that the product is a mixture of two isomers by the presence of two methyl signals at τ9.23 and τ9.09. The methine proton, which is adjacent to both the ether oxygen and the thiophene ring, and which therefore absorbs at a characteristically low field[24b], is also represented by two signals at τ4.71 and τ4.62. It is evident from the spectrum (fig. 4) that these two isomers are formed in an approximately 2:3 ratio. Additional weak signals at τ4.47 and τ4.56 as well as a shoulder on the lower field methyl signal indicate that probably other stereoisomers were formed in small quantities. This is not susprising since the 3-thienyl lactone [6, A=S] contains 3 asymmetric carbon atoms and theoretically eight stereoisomers are possible.

Careful chromatography on a silicagel column, eluting with chloroform/benzene (1:1), led to the separation of this mixture into two components. The more polar isomer, obtained pure by recrystallization from benzene, had an n.m.r. spectrum as reproduced in fig. 5, gave satisfactory analytical results, and had m.p. 197-199°. The other isomer, although crystalline, was not obtained in sufficient quantity to permit purification for analytical purposes.

In order to study the stereochemistry of these two isomers it was decided first to investigate the stereochemistry of the sodium amalgam reduction of the double bond. Therefore, the mixture of saturated aldehydo acids [35], resulting from that reduction was converted into the lactones [79a] and [79b] by

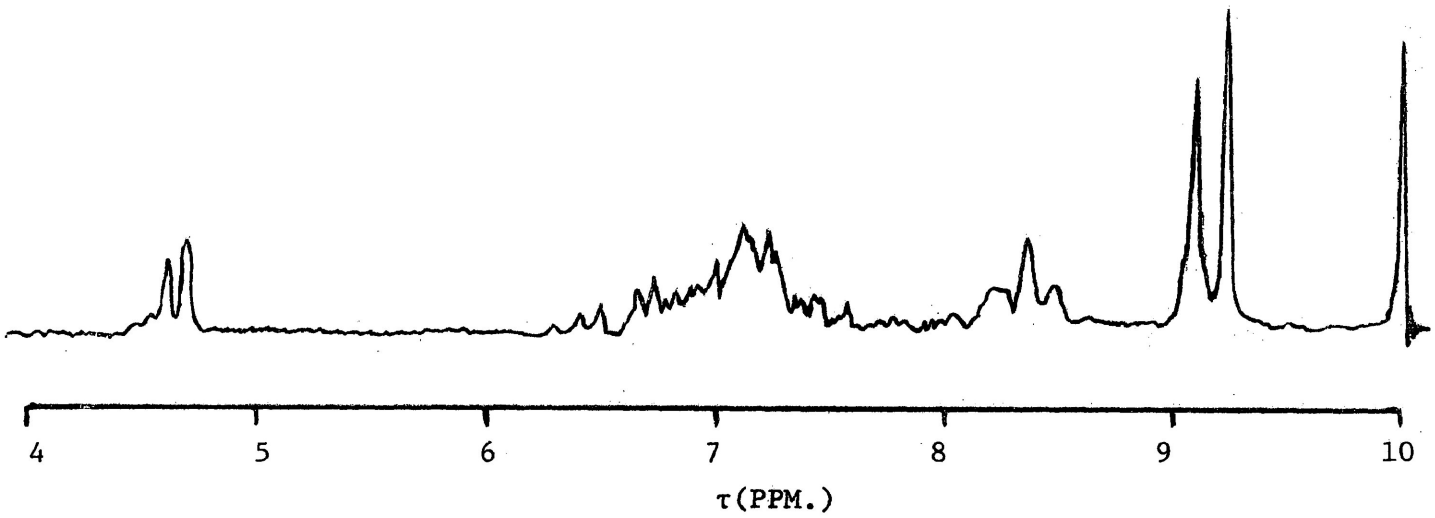


FIG. 4 N.m.r. Spectrum of the mixture of isomeric 3-thienyl lactones [6, A=S] in deuterochloroform.

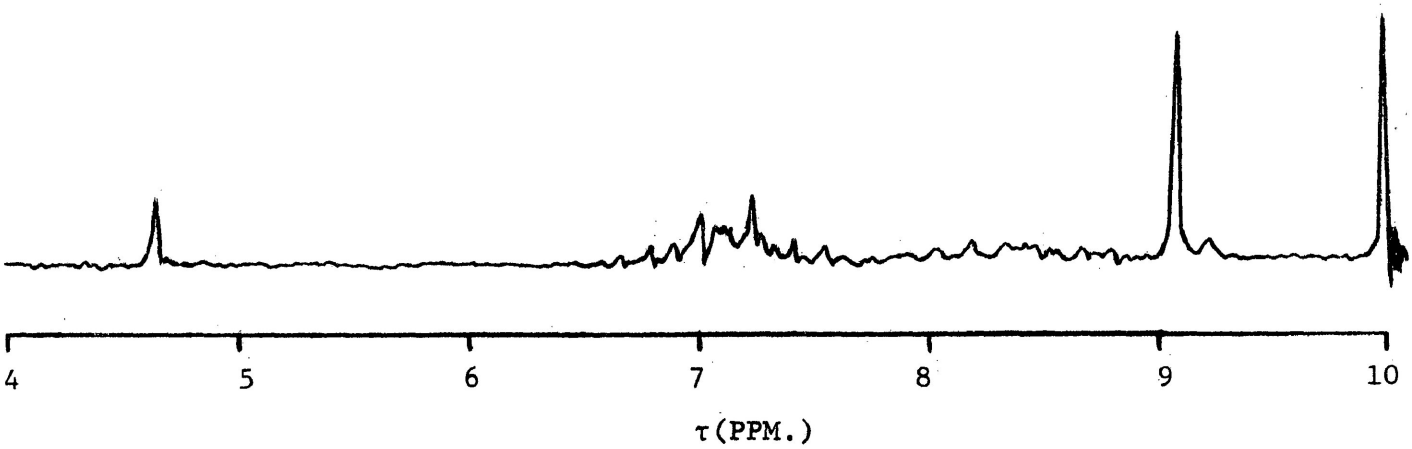


FIG. 5 N.m.r. Spectrum of one pure isomer of 3-thienyl lactone [6, A=S] in deuterochloroform.

treatment of [35] with sodium borohydride. Acidification of the reduction mixture led directly to the mixture of lactones [79]. Although the lactone mixture could not easily be separated into its components, its identity and composition could be deduced from spectral data. Thus, the infrared spectrum indicates the presence of the δ-lactone by a band at 1755 cm^{-1}, and the molecular ion is found in the mass spectrum at *m/e* 215.

The n.m.r. spectrum in deuteriochloroform (Fig. 6) clearly indicates the presence of the stereoisomers [79a] and [79b] by the two signals due to the angular methyl group at τ8.91 and τ9.02. A study of molecular models indicated that the trans isomer might well be the thermodynamically more stable one, and should therefore be the most abundant component of the mixture. Supporting evidence for such a suggestion was obtained from the n.m.r. spectrum (Fig.7) of a benzene solution of the lactone mixture [79]. From the discussion of the solvent shifts observed for benzene solutions of such carbonyl compounds (see Introduction, P. 12), it follows that the solvent solute complexes from both lactones may be visualized as in [80] and [81]. From these diagrams, as well as from molecular models, it may be seen that in the cis isomer [80] the angular methyl group is equatorial with respect to the lactone ring, and is therefore slightly further removed from the solvent benzene molecule as the methyl group of the trans isomer [81], which is axial with respect to the lactone ring. Indeed the solvent shift δ(i.e. $\tau C_6H_6 - \tau CHCl_3$) is larger (0.48 ppm) for the high intensity signal than the value

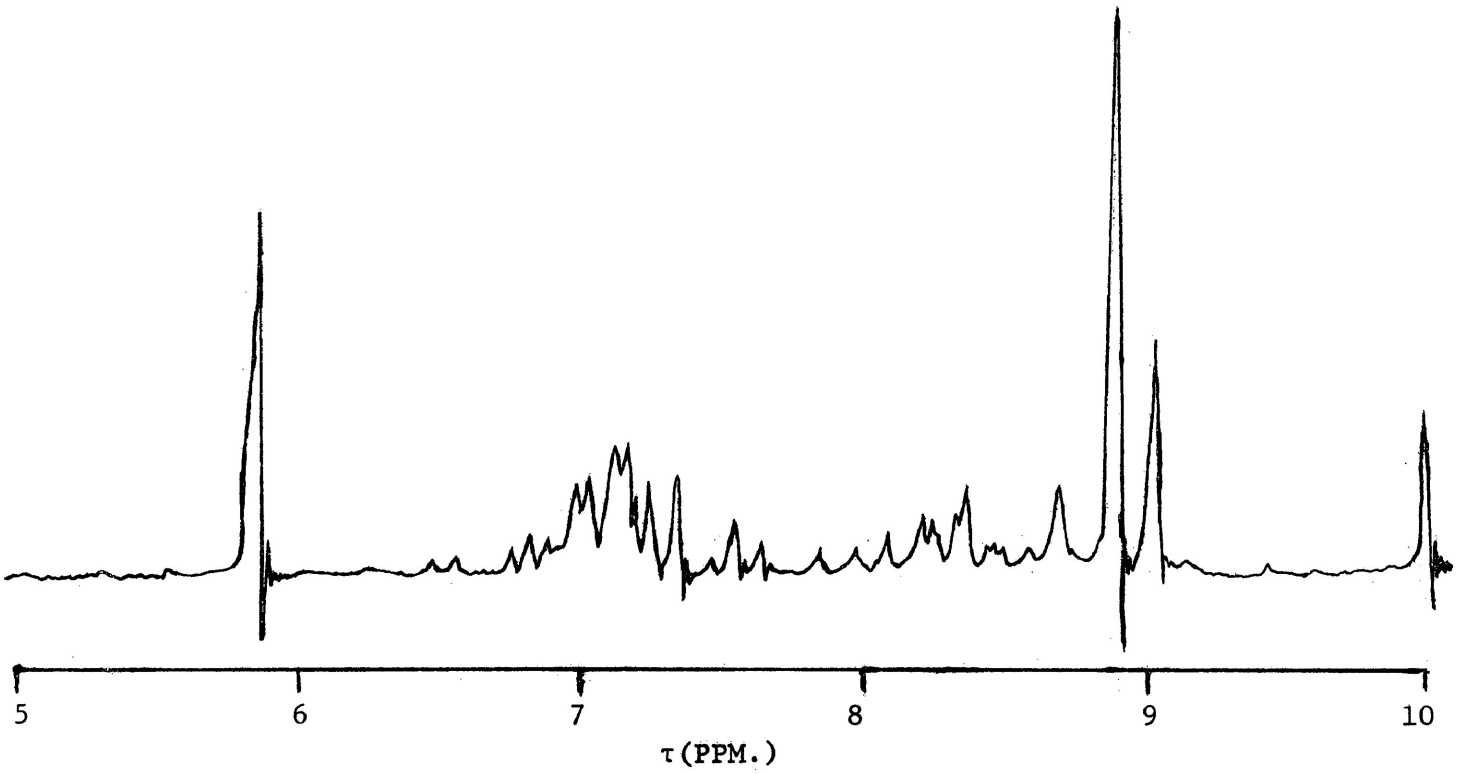


FIG. 6 N.m.r. Spectrum of Lactones [79] in deuterochloroform

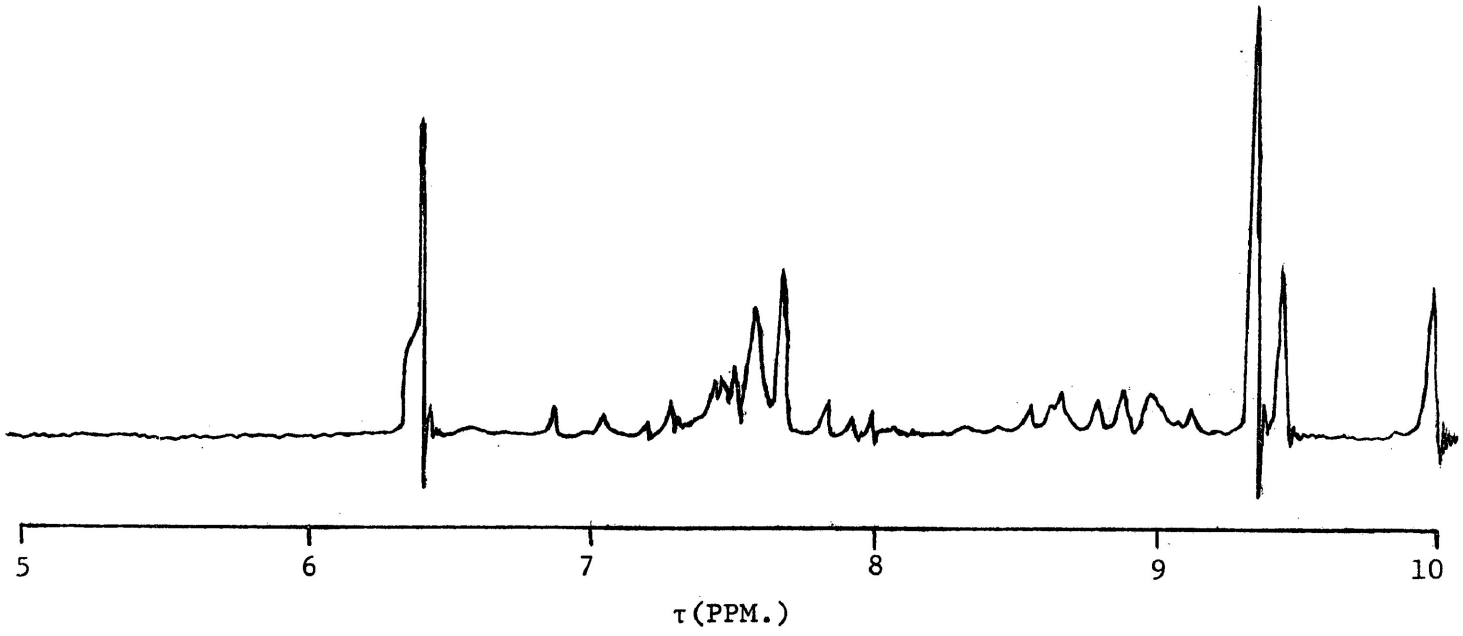
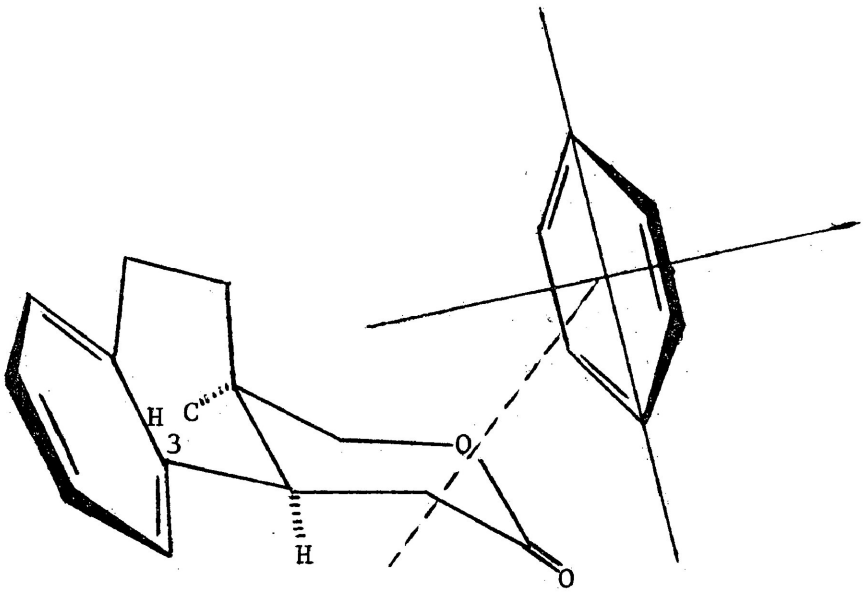
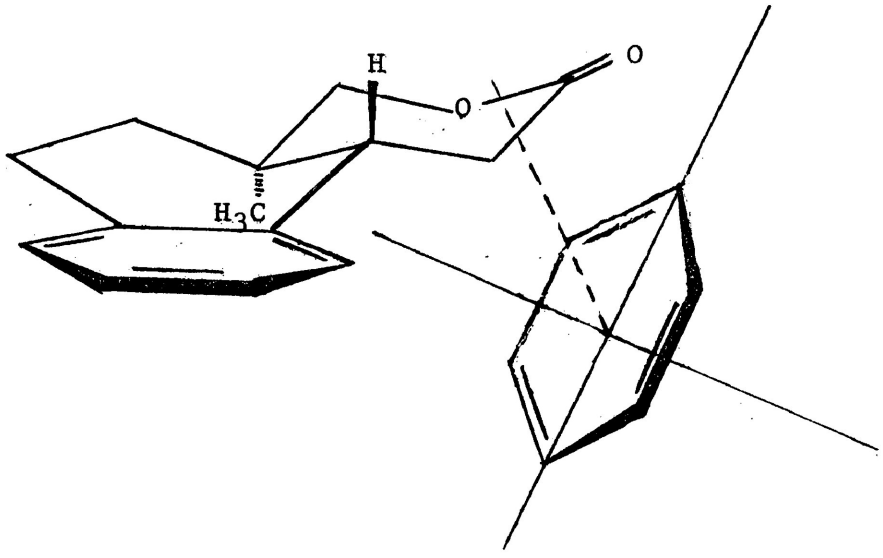


FIG. 7 N.m.r. Spectrum of Lactones [79] in benzene.



[80]



[81]

(0.44 ppm) observed for the low intensity methyl signal. It is thus reasonable to assume that in the sodium amalgam reduction, the formation of the trans isomer is favoured and that in the product, the trans/cis ratio is approximately 2:1. Such an interpretation of the solvent effect caused by benzene on the spectra of this lactone mixture is in agreement with the observation made by Dimaio *et al.*[22] during a study of the lactones [37] and [38], (P. 13).

Returning now to a consideration of the two isomeric 3-thienyl lactones [6, A=S], a few remarks may be made concerning the stereochemistry of these compounds.

The relative stereochemistry of the 3-thienyl side chain and the angular methyl group depends on the side of attack of the 3-thienyllithium on the aldehyde group of the aldehydo acid [35]. Since the prefered side of attack in turn depends on the stereochemistry of that aldehydo acid, it is at present not possible to come to any firm conclusions. The stereochemistry of the aldehydo acid [35] not only determines the side of attack of the 3-thienyllithium but may well influence the reactivity as such. It must first be determined if the two isomers [6] resulted from the coupling of only one isomer of [35] with 3-thienyllithium, or if both isomers [35] underwent a coupling reaction with 3-thienyllithium. Some suggestions as to how to resolve this question will be presented in the next section.

One final remark should be made with respect to the solvent effects observed in the n.m.r. spectra of benzene and pyridine solutions of these compounds. In the introduction (P. 14) it

was suggested that this shift to lower field, caused by pyridine, of certain signals in the spectra of some meliacins was an anomalous result. A further study of several available model compounds has now shown that in all cases pyridine causes such downfield shifts, but in benzene solutions the normal shift to higher field is observed for all characteristic signals. It follows then, that in the case of the lactones [6], benzene solvent shifts may be used to study the stereochemistry, and that observations made for the lactones [79] may be used as reference material. Such a study however, as explained in the next section, must await further chemical work on this mixture of isomers.

CONCLUSIONS

Exploratory experiments, although not successful in the sense that the results were directly applicable to the synthesis of the lactone [6], have yielded some interesting observations. Positive results have been obtained which are directly applicable to synthetic organic chemistry in a wider sense.

Thus, the reaction of 1,3-dithiane carbanions with some aromatic substrates led to a new method for the preparation of 2-pyridyl phenyl ketones.

Furthermore, the reaction of 3-thienyllithium with sulfonate esters led to the formation of the sulfones [26, R=CH_3, H]. This suggests that a new method for the synthesis of heterocyclic sulfones may be developed based on this reaction. Before such a new method can be considered of general applicability however, several questions will have to be answered. Firstly , the effect of the leaving group on this substitution reaction must be studied. To this end, the sulfonate esters of other alcohols should be made to react with 3-thienyllithium and the use of a good leaving group, as in phenyl sulfonates, may improve the yield of thienyl sulfones, and may also make it possible to produce furyl sulfones in the same way. Secondly, electron donating substituents on the aromatic ring of the sulfonic acid portion of the substrate molecule may effect the transition state to a considerable extent.

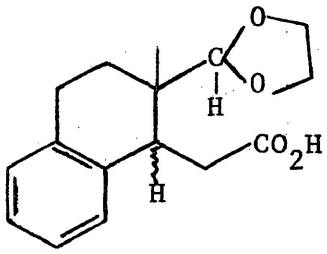
It is suggested that investigation of these two aspects may well be considered as the substance of an independent study,

which does not fall within the scope of this thesis.

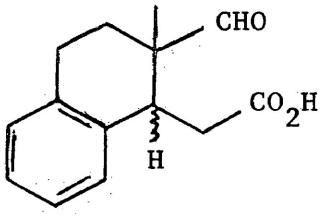
The successful synthesis of the 3-thienyl lactones [6, A=S, P. 45] means that an entry has been found to the synthesis of this structural portion of the tetranortriterpene molecule. Several problems will have to be solved, however, before such a synthesis can be completed, of which the stereochemical aspect is obviously of primary importance. It is suggested that the best approach will probably be a separation of the stereoisomers of the acetal acid [76], either directly or via a suitable derivative. Once this has been achieved, the reaction of each isomer of the aldehydo acid [35] with 3-thienyllithium (or with 3-furyllithium) will establish any difference in reactivity that might exist between these isomers, and will probably give the answer to stereochemical questions pertaining to the mixture of lactones [6].

In order to obtain the right stereochemistry of the desired product, e.g. [83], it may be necessary to produce the hydroxyl ester [82], which after oxidation and stereospecific reduction could lead to the desired product.

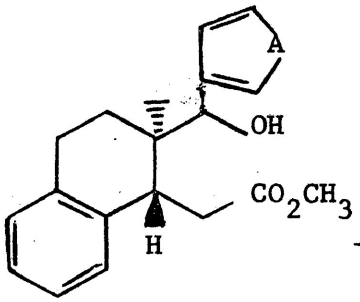
Finally, when these stereochemical questions have been settled, a method must be found reintroduce the double bond, i.e. the conversion of [83] into [84].



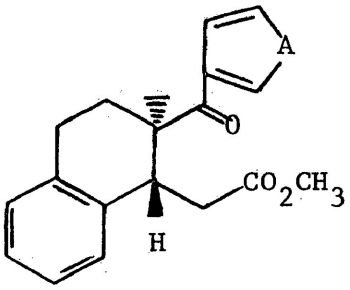
[76]



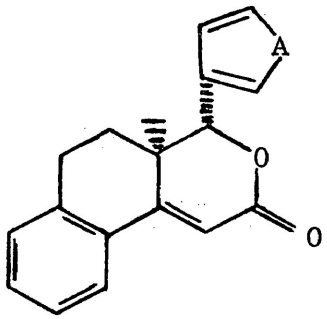
[35]



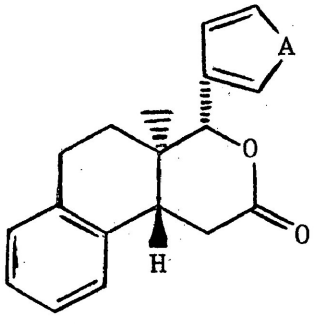
[82]



1) reduction
2) hydrolysis
3) H^+



[84]



[83]

EXPERIMENTAL

Introduction

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 for solutions in chloroform, and were 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 deuteriochloroform form ($CDCl_3$) with tetramethylsilane (T.M.S.) as the internal standard at τ=10.0 P.P.M.

The ultraviolet spectra, for ethanol solutions, were recorded on a Cary 14 recording spectrophotometer.

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 with a Perkin-Elmer 240 elemental analyzer, and also by W.J. Buis at the Institute for Organic Chemistry, T.N.O., Utrecht, The Netherlands.

Preparation of 1,3-Dithiane [41]

To a mixture of equimolar amounts of benzaldehyde (2.0g) and 1,3-propanedithiol (3 ml.) in dry benzene (200 ml.) in a flask fitted with a reflux condenser and a magnetic stirrer, were added several drops of conc. hydrochloric acid, and the reaction mixture was kept at 0° for 15 minutes. The mixture was then heated on a steam bath for 15 minutes, cooled to room temperature, and poured into water (100 ml.). The aqueous suspension was extracted with chloroform, the extracts washed several times with water, and dried with sodium sulfate. Removal of the solvent yielded 2.6g.(70%) of 1,3-dithiane [41], as a semicrystalline solid, which was homogeneous on t.l.c. (silicagel, benzene). Its n.m.r. spectrum contains signals of aromatic protons at τ2.5-2.8 (5H), the benzylic proton at τ4.85 (1H) and the protons of the dithiane ring at τ6.93-7.16 (4H) and τ7.85-8.33 (2H). The mass spectrum contains the molecular ion peak at *m/e* 196.

Generation of the Carbanion [42]

The conditions of the carbanion generating reaction as indicated by Corey[4] were confirmed by the following experiment. A solution of 1,3-dithiane [41] (1.0g., 0.0051 mole) in tetrahydrofuran (50 ml.) was treated with n-butyllithium (0.0051 mole) at -20° to -30° and the mixture stirred in nitrogen for 1.5 hr. Deuterium oxide was added and the deuterated dithiane was isolated by extraction with chloroform. The n.m.r. spectrum of the product,

which on t.l.c. was identical to the starting material, shows complete absence of the benzylic proton, previously observed at τ4.85.

Reaction of the 1,3-Dithiane Carbanion [42] with 2,4-Dinitrobromobenzene

To a solution of the 1,3-dithiane carbanion [42] in tetrahydrofuran, generated from 1,3-dithiane [41] (1.0 g.) as above, was added 2,4-dinitrobromobenzene (1.20 g.) in tetrahydrofuran. The mixture was kept at -10° to +5° for 35 min. Addition of water (10 ml.) and extraction with chloroform yielded 1.0 g. of the crystalline dimer [44], which after recrystallization (benzene) had m.p. 204°.

The product in its n.m.r. spectrum displays signals attributed to aromatic protons at τ2.32-2.88 (10H), to protons adjacent to sulfur at τ7.20-7.48 (8H) and to protons β to sulfur at τ8.1-8.3 (4H). Mass spectrometry indicates the molecular ion peak at *m/e* 390.

Anal. Calcd. for $C_{20}H_{22}S_4$: C, 61.5; H, 5.7; S, 32.8. Found: C, 61.8; H, 5.6; S, 32.7.

The product (0.1 g.) in ethylene glycol (2 ml.) and water (0.2 ml.) was refluxed with hydrazine hydrate (0.2 g.) and potassium hydroxide (0.5 g.) for 3 hours. The mixture was extracted with benzene, and the extract evapourated to dryness to give a product (0.03 g.) which on t.l.c. (silicagel/benzene) was homogeneous and identical to commercial bibenzyl. Also the infrared

and mass spectra of the product were identical to those of bibenzyl.

Reaction of 1,3-Dithiane Carbanion [42] with 2,4-Dinitrobenzene and with Nitrobenzene

The 1,3-dithiane carbanion [42] was generated as above from 1,3-dithiane [41] (1.0 g.) and 2,4-dinitrobenzene (1.20 g.) in tetrahydrofuran was added. The mixture was kept at -10° to $+5^{\circ}$ for 35 minutes. Addition of water and chloroform extraction led to the isolation of a crystalline product (1.0 g.) which was identical in all respects to the dimer [44] described above.

When this reaction was repeated with nitrobenzene instead of 2,4-dinitrobenzene, a similar yield of dimer [44] was obtained.

Reaction of 1,3-Dithiane Carbanion [42] with 2-Bromopyridine

To a solution of the 1,3-dithiane carbanion [42] in tetrahydrofuran, generated as above from 1,3-dithiane [41] (3.0 g.), was added 2-bromopyridine (2.42 g.) in tetrahydrofuran. The mixture was kept at 0° for 1 hr., poured into water (50 ml.), and the resulting suspension extracted with chloroform. The extracts were washed with water and dried with sodium sulfate. Removal of the solvent yielded a crude product (3.97 g.). Chromatography on silicagel led to the isolation of the pure substituted dithiane [44] (2.47 g., 47%), eluted with chloroform/benzene (2:8), which was homogeneous on t.l.c. (silicagel/chloroform). The n.m.r.

spectrum of this product contains signals due to the pyridine protons at τ1.44-1.52 and τ2.0-2.18 (4H), the benzene protons at τ2.58-2.85 (5H) and the protons of the dithiane ring at τ7.45-7.68 (4H) and τ8.2-8.45 (2H). The mass spectrum contains the molecular ion at *m/e* 273.

The coupling product [44] (0.25 g.) in acetonitrile (15 ml.) and water (10 ml.) was stirred with silver nitrate (1.04 g.) and N-chlorosuccinimide (0.62 g.) at 0^{o} in nitrogen for 40 minutes. Dimethyl sulfoxide (6 ml.) was then added and the mixture was allowed to reach room temperature, kept for 1.5 hr., and water was added. The mixture was extracted with chloroform and the extracts washed with water and dried with sodium sulfate. Removal of the solvent yielded 2-pyridyl phenyl ketone [46] (0.16 g., 60%), as a homogeneous oil. The infrared spectrum has a strong band at 1680 cm^{-1} indicative of an α,β-unsaturated ketone. The n.m.r. spectrum contains signals at τ1.30-1.38 (1H), τ1.80-2.24 (4H) and τ2.34-2.68 (4H). The mass spectrum indicates M^{+}=183. The 2-pyridyl phenyl ketone obtained in this way was identical (t.l.c. and the above mentioned spectral properties) to a specimen obtained as follows:

2-Benzyl pyridine [47] (1.0 g.) was refluxed with potassium permanganate (1.3 g.) in water (100 ml.) for 2 hr. The cooled mixture was extracted with benzene and the extracts dried with sodium sulfate. Removal of the solvent gave 2-pyridyl phenyl ketone (0.85 g., 80%).

Attempted Reactions of 1,3-Dithiane Carbanion [42] with Bromobenzene and with 3-Bromothiophene

To the carbanion [42], generated as above from 1,3-dithiane [41] (0.5 g.) was added 3-bromothiophene (0.4g.) in tetrahydrofuran and the mixture kept at 0° for 1 hr., and poured into water. The resulting suspension was extracted with chloroform, and the combined extracts dried with sodium sulfate. Removal of solvent yielded unchanged 1,3-dithiane [41] (0.5 g.).

The same result was obtained when the carbanion [42] was treated in a similar way with 3-bromothiophene.

Attempted Reaction of 1,3-Dithiane Carbanion [42] with 3-Bromopyridine and with 4-Bromopyridine

The 1,3-dithiane carbanion [42] was generated as above from 1,3-dithiane [41] (0.5 g.). 3-Bromopyridine (0. 41 g.) in tetrahydrofuran was added, the mixture kept at 0° for 1 hr., and poured into water. Chloroform extraction led to the isolation of unchanged 1,3-dithiane [41] (0. 5 g.).

When this reaction was repeated with 4-bromopyridine (0.41 g.) unchanged 1,3-dithiane [41] (0.5 g.) was likewise isolated.

Preparation of the Keto Ester [55]

Ethyl 2-ketohexahydrobenzoate (12 g.) was prepared from cyclohexanone (19.6 g.) according to the procedure of Snyder *et al.*[31] The identity of the homogeneous product was confirmed

by its spectral properties. The n.m.r. spectrum contains the triplet (τ8.68) and quartet (τ5.73) of the five ethyl ester protons (J=7 cps), a group of signals at τ7.6-8.46 (8H) due to the cyclohexane ring protons and an acidic proton at τ -3.3. The mass spectrum contains the molecular ion at *m/e* 170.

Ethyl 2-ketohexahydrobenzoate (1.70 g.) in dry benzene (20 ml.) was treated with a solution of sodium (0.38 g.) in anhydrous ethanol (10 ml.). The solution was refluxed for 30 min., cooled, and methyl iodide (2 ml.) was added. The mixture was kept at room temperature for 45 min., and more methyl iodide (2 ml.) was added. The resulting solution, after standing at room temp. for another 1/2 hr., was then refluxed for 45 min., cooled, and neutralized with dil. hydrochloric acid. Extraction with benzene and removal of the solvent gave the methylated keto ester [55] (1.45 g., 80%). The n.m.r. spectrum contains signals due to the angular methyl protons at τ8.72 (3H), the ethyl group protons at τ5.78 (2H, quartet, J=7 c.p.s.) and τ8.74 (3H, triplet.), and the cyclohexyl protons at τ7.37-8.44 (8H).

Preparation of the Ketal [20]

To the keto ester [55] (1.45 g.) in benzene (50 ml.) and ethylene glycol (10 ml) was added a small amount of *p*-toluene sulfonic acid, and the mixture was refluxed (water separator)

for 16 hr. When no more water was produced, the mixture was cooled and extracted with benzene. Removal of the solvent from the dried extracts yielded the ketal ester [20] (1.50 g.). The n.m.r. of the product contains signals due to the ketal protons at τ6.03 (4H), the angular methyl group at τ8.75 (3H), the ethyl ester group at τ5.83 (2H, quartet, J=7 c.p.s.) and τ8.73 (3H, triplet) and finally the cyclohexyl protons at τ8.0-8.6 (8H). The mass spectrum indicates the molecular ion at *m/e* 184.

Attempted Reduction of the Ketal Ester [20] with Lithium Aluminum Hydride

The ketal ester (0.8 g.) in tetrahydrofuran (20 ml.) was refluxed with lithium aluminum hydride (0.4 g.) for 3 hr. in nitrogen. Slow addition of water to the cooled reaction mixture was followed by extraction with ether. Removal of the solvent from the dried extracts gave a crude product (0.56 g.). Thin layer chromatography of this product indicated a number of minor components and one major component, which constituted approx. 60% of the reaction mixture. This major component was eluted pure from a silicagel column with chloroform/benzene (1:3). The largest fragment that could be observed in the mass spectrum was indicated by a peak at *m/e* 156, and the molecular ion of the expected product [21] at *m/e* 186 was absent. The n.m.r. spectrum no longer contains the characteristic 4 proton signal of the ketal group at τ6.03.

Further Attempts to Reduce the Ester Group of [20]

In a 250 ml. round bottomed flask were placed sodium (0.33 g.) and dry toluene (10 ml.). The flask was heated in an oil bath until the sodium had melted. The sodium was finely divided, by allowing the mixture to cool to 60° with stirring. The ketal ester [20] (0.5 g.) in absolute alcohol (6 ml.) was added through a dropping funnel. After the reaction had subsided, the flask was heated on a steam bath until the sodium had dissolved completely. Addition of water and extraction of the mixture with benzene led to the recovery of unchanged starting material (0.5 g.).

The ketal ester [20] (0.5 g.) was then refluxed in methanol (15 ml.), with sodium borohydride (0.3 g., 10 fold excess) for 2 hr. Water was added and the mixture was acidified with dil. hydrochloric acid and extracted with benzene, to yield unchanged starting material as the only product.

Competitive Reaction of Cyclohexanealdehyde [60] and Methyl Cyclohexanecarboxylate [62] with 3-Thienyllithium

n-Butyllithium (0.0075 mole.) was added to a solution of 3-bromothiophene (1.30 g.) in dry ether (20 ml.) at -70°, in nitrogen. After 15 min., a mixture of cyclohexanealdehyde (0.56 g., 0.005 mole) and methyl cyclohexanecarboxylate (0.71g., 0.005 mole) in dry ether was added and the reaction mixture kept between -70° and -60° for 1/2 hour. 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 extracts were combined, washed with water, dried with sodium sulfate and the solvent was partly removed *in vacuo* at room temperature. Deuteriochloroform was added and the n.m.r. spectrum was recorded. The signals of the carbinol proton of the coupling product [40, A=S] at τ 5.54 (J=6 c.p.s.) and the methyl ester group of [62] at τ6.33 were observed in a 1:3 intensity ratio. Thin layer chromatography (silicagel/ chloroform) indicated that the mixture contained only the ester [62] and the carbinol [40, A=S].

Competitive Reaction of Cyclohexanealdehyde [60] and Methyl Cyclohexanecarboxylate [62] with 3-Furyllithium

n-Butyllithium (0.00375 mole) was added to a solution of 3-iodofuran (0.73 g., 0.00375 mole), prepared from 3-chloromercuryfuran according to Gronowitz[44], in dry ether (20 ml.) at -70° in nitrogen. After 15 min., a mixture of cyclohexanealdehyde (0.28 g., 0.0025 mole) and methyl cyclohexanecarboxylate (0.355 g., 0.0025 mole) in dry ether (20 ml.) was added and the reaction mixture kept between -70° and -60° for 1/2 hr. The mixture was allowed to come to room temp., and water (20 ml.) was added. The resulting suspension was extracted several times with ether. The extracts were combined, dried with sodium sulfate and the solvent was partly removed *in vacuo* at room temperature. The n.m.r. spectrum of this mixture, recorded after addition of deuteriochloroform, contains the signals of the carbinol

proton of the coupling product [40, A=O] at τ5.65 (J=6 c.p.s.) and of the methyl ester group of [62] at τ6.33 in a 1:4 intensity ratio. A weak signal at τ0.47 indicates the presence of some unchanged aldehyde. On thin layer chromatography, the mixture was found to contain only the ester [62], the coupling product [40, A=O) and a small amount of cyclohexane-aldehyde.

Preparation of the Tosylate [65]

To a solution of cyclohexyl methanol (4.4 g.) in benzene (10 ml.) and pyridine (10 ml.) was added *p*-tolulenesulfonyl chloride (7.3 g.) and the mixture was stirred overnight at room temperature. The pyridine-hydrochloride was filtered off, and washed with benzene. This extract was added to the filtrate, and the resulting solution was washed with water and dried with sodium sulfate. Removal of the solvent gave the tosylate [65] (8.52 g., 83%) as a chromatographically homogeneous, semicrystalline product. The n.m.r. spectrum contains two doublets (J_{AB}=8 c.p.s.) centered at τ_A 2.2 and τ_B 2.63 (4 aromatic protons), a doublet (J=6 c.p.s.) centered at τ6.17 (methylene group, 2H), and a signal at τ7.60 (3H, aromatic methyl group) and the cyclohexyl protons at τ8.25-9.08 (11H). The mass spectrum indicates the molecular ion at *m/e* 268.

Preparation of the Benzene Sulfonate [66] and the Methyl Sulfonate [68]

Cyclohexyl methanol (3.0 g.) on treatment with benzene sulfonyl chloride (4.63 g.) gave the benzene sulfonate ester [66] in good yield (5.7 g.) Also, treatment of cylcohexyl methanol (3.0 g.) with methane sulfonyl chloride (3.0 g.) gave the methyl sulfonate ester [68] (3.8 g.). The reaction conditions and work-up procedures for these preparations were the same as described above for the tosylate [65]. The relevant spectra were in agreement with the expected structures of these esters.

Preparation of 3-Thienyl-*p*-toluene Sulfone [26, R=CH_3]

n-Butyllithium (0.015 mole) was added to a solution of 3-bromothiophene (2.44 g., 0.015 mole) in dry ether (20 ml.) at -70° in nitrogen. After 15 min., the tosylate [65] (2.65g., 0.01 mole) in dry ether was added and the reaction mixture was allowed to reach room temperature and kept for 5 hr. Water (10 ml.) was added, and the resulting suspension was extracted with benzene. Removal of the solvent gave 2.12 g. of a crude semicrystalline product, which after chromatography on an alumina column [chloroform/benzene (1:1)] gave 3-thienyl *p*-toluene sulfone [26, R=CH_3] (1.4 g., 60%).

The pure product, recrystallized from benzene/heptane had m.p. 138-140°. Its n.m.r. spectrum contains signals attributed to an aromatic methyl group at τ7.61 and to two

groups of aromatic protons at τ2.63-2.76 (3H) and τ1.9-2.2 (4H). The total intensity of the aromatic protons signals had a ratio 7:3 with respect to the methyl group signal. The ultraviolet spectrum has λ_{max} 248 mμ (ε=15,200) and λ_{max} 228 mμ (ε=9870). The infrared spectrum has strong bands at ν_{max} 1330 cm^{-1} and at ν_{max} 1135 cm^{-1}. Finally the mass spectrum (Fig. 1, P. 33) contains the molecular ion peak at *m/e* 238 (100%) and major fragments at *m/e* 139 (61%), *m/e* 131 (97%), *m/e* 107 (45%), *m/e* 91 (48%), *m/e* 78 (23%), *m/e* 65 (33%) and *m/e* 39 (21%).

Anal. Calcd. for $C_{11}H_{10}S_2O_2$: C, 55.4; H, 4.3. Found: C, 55.5; H, 4.2.

Preparation of 3-Thienyl Phenyl Sulfone [26, R=H]

n-Butyllithium (0.015 mole) was added to a solution of 3-bromothiophene (2.44 g., 0.015 mole) in dry ether (20 ml.) at -70° in nitrogen. After 15 min., the benzene sulfonate [66] (2.54 g., 0.01 mole) in dry ether was added and the reaction mixture was allowed to reach room temperature and kept for 5 hr. Water (10 ml.) was added, and the suspension was extracted with benzene. Removal of the solvent gave 2.09 g. of crude product, which was chromatographed on an alumina column. 3-Thienyl phenyl sulfone [26, R=H] (1.10 g., 50%) was eluted with benzene, and after recrystallization from benzene/heptane had m.p. 113-115°. The n.m.r. spectrum contains aromatic proton signals at τ1.85-2.05 and at τ2.4-2.67. The

ultraviolet spectrum has λ_{max} 244 mμ (ε=13,200) and λ_{max} 224 mμ (ε=9700). The infrared spectrum contains bands at ν_{max} 1345 and 1134 cm^{-1}. Finally the mass spectrum (Fig. 2, p. 34) contains the molecular ion peak at *m/e* 224 (79%), and other major peaks at *m/e* 131 (100%), *m/e* 125 (50%), *m/e* 99 (21%), *m/e* 77 (54%) and *m/e* 39 (29%).

Anal. Calcd. for $C_{10}H_8S_2O_2$: C, 53.6; H, 3.6. Found: C, 53.6; H, 3.7.

Preparation of the α,β-Unsaturated Aldehydo Acid [34]

The acetal acid [75] (0.50 g.), which was prepared from α-tetralone according to the procedure[3] of Tahirkheli, was refluxed with water (10 ml.) dioxane (10 ml.) and dilute hydrochloric acid (1 ml.) for 1 hr. The mixture was extracted with chloroform. Removal of solvent from the dried (sodium sulfate) extract gave the α,β-unsaturated aldehydo acid [34] (0.34 g., 80%). The n.m.r. spectrum contains signals for the aromatic protons at τ2.40-2.58 (1H) and at τ2.7-2.93 (3H), the angular methyl group at τ8.70 (3H), one olefinic proton at τ4.15, the aliphatic protons at τ7.08-8.50 (4H), the acid proton at τ0.05 (1H), and the aldehyde proton at τ0.56 (1H). The mass spectrum indicates the molecular ion peak at *m/e* 230.

Although the aldehydo acid [34] crystallized on standing, it could not easily be purified by recrystallization. Therefore, a crystalline derivative was prepared for a final characteriza-

tion. Treatment with 2,4-dinitrophenylhydrazine in methanol and conc. sulfuric acid led to the 2,4-dinitrophenylhydrazine ester [77], which had m.p. 158-159° and M^+=424.

Anal. Calcd. for $C_{21}H_{20}N_4O_6$: C, 59.4; H, 4.8. Found: C, 59.2; H, 4.8.

Attempted Coupling of 3-Thienyllithium with the α,β-Unsaturated Aldehydo Acid [34]

n-Butyllithium (0.0046 mole) was added to a solution of 3-bromothiophene (0.75 g., 0.0046 mole) in dry ether (20 ml.) at -70°, in nitrogen. After 15 min., the aldehydo acid [34] (0.51 g., 0.0023 mole) in dry ether was added and the temperature was allowed to reach 10°. The mixture was acidified and extracted with benzene. Removal of solvent from the dried extract gave a product (0.37 g.) which on t.l.c. was found to contain several components. No major component could be separated, and spectral examination of the crude mixture did not give any indication of the presence of the desired product.

Preparation of the Saturated Acetal Acid [76]

A warm solution of the unsaturated acetal acid [75] in 45% of potassium hydroxide (0.6 ml.) and water (10 ml.) was stirred with 2% of sodium amalgam (14 g.) for 25 min. The aqueous mixture was acidified with dil. hydrochloric acid, extracted with chloroform and the extract was dried with

sodium sulfate. Removal of the solvent yielded the saturated acetal acid [76] (0.51 g., 100%). The infrared spectrum contains a strong band at 1730 cm^{-1} (carboxylic acid). The n.m.r. spectrum indicates the presence of aromatic protons at τ2.82 (4H), the proton adjacent to the acetal at τ5.32 and at τ5.26 (1H, two isomers), acetal protons at τ6.06-6.13 (4H), methyl protons at τ9.07 (3H), an acid proton at τ-1.2 (1H) and finally the aliphatic protons at τ6.77-7.6 and τ8.06-8.37 (7H). The mass spectrum contains the molecular ion peak at *m/e* 276.

Preparation of the Saturated Aldehydo Acid [35]

The acetal acid [76] (0.50 g.) was dissolved in dioxane (10 ml.), and to the solution was added water (10 ml.) and dil. hydrochloric acid (1 ml.). The mixture was refluxed for 1 hr., cooled to room temp., and extracted with chloroform. The chloroform extract yielded the saturated aldehydo acid [35] (0.34 g., 80%) which in its n.m.r. spectrum has signals due to aromatic protons at τ2.8 (4H), aliphatic protons at τ6.3-8.35 (7H) and methyl protons at τ8.90-8.93 (3H). The infrared spectrum has a broad peak at 2500-3600 cm^{-1} (carboxylic acid OH) and two carbonyl group absorptions at 1730 and 1760 $cm.^{-1}$ The mass spectrum contains the molecular ion peak at *m/e* 232. Treatment with 2,4-dinitrophenylhydrazine in methanol and conc. sulfuric acid led to the 2,4-dinitrophenylhydrazone ester [78], which had m.p. 141-143°, and M^{+}=426.

Anal. Calcd. for $C_{21}H_{22}N_4O_6$: C, 59.2; H, 5.2. Found: C, 58.8; H, 5.2.

Preparation of 3-Thienyl Lactone [6, A=S]

n-Butyllithium (2.0 g., 0.031 mole) was added to a solution of 3-bromothiophene (5.42 g.) in dry ether (30 ml.) at -70° in nitrogen. After 15 minutes, the saturated aldehydo acid [35] (1.42 g.) in ether was added, and the temperature was allowed to rise slowly to +10°. Water was added and the mixture was extracted with chloroform to remove all non-acidic material. The aqueous layer was then acidified with dil. hydrochloric acid. A chloroform extract of this acidified aqueous layer was concentrated to a small volume and filtered through a small amount of silicagel, to give the lactone [6, A=S] (0.77 g., 42%). The product gave a mass spectrum (fig. 3, P. 44), which indicates the presence of the molecular ion peak at *m/e* 298 (12%), and other major peaks at *m/e* 187 (16%), *m/e* 186 (8%), *m/e* 144 (100%), *m/e* 129 (38%), *m/e* 91 (24%), and *m/e* 111 (10%).

The infrared spectrum no longer contains hydroxyl absorbtions, instead a single carbonyl band at ν_{max} 1750 cm^{-1} is observed. The n.m.r. spectrum (fig. 4, P. 47) indicates the presence of two isomers by showing two methyl group signals at τ9.09 and τ9.23 and two signals for the methine proton at τ4.71 and τ4.62. Groups of signals at τ2.75-2.88 and at τ6.7-8.50 were attributed to aromatic protons (7H) and alicyclic

protons (7H) respectively.

This mixture of isomers was eluted with chloroform/benzene (1:1) from a silicagel column, and was separated into two crystalline products. The more polar isomer (approx. 0.3 g.) obtained pure by recrystallization from benzene had m.p. 197-199°.

Anal. Calc. for $C_{18}H_{18}SO_2$: C, 72.5; H, 6.1. Found: C, 72.6; H, 6.1.

Preparation of the Lactones [79]

A solution of the aldehydo acid [35] (0.33 g.), potassium hydroxide (0.18 g.) and sodium borohydride (0.20g) in methanol (10 ml.) was stirred at 0° for 4 hr. The mixture was acidified with dil hydrochloric acid and extracted with chloroform. Removal of solvent gave the lactone mixture [79] (0.34 g. 100%), which gave one spot on t.l.c. (silicagel/chloroform). The infrared spectrum contains the lactone band at 1755 cm^{-1}. The n.m.r. spectrum (Fig. 6. P. 49) contains the signals of the angular methyl group at τ8.91 and τ9.02. The protons adjacent to the lactone ether oxygen at τ5.88 (2H), the aromatic protons at τ2.81 (4H) and other alicyclic protons at τ6.75-8.69 (7H). The mass spectrum contains the molecular ion peak at *m/e* 215.

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