2-FORMYL-4-NITROBENZENESULPHENYL CHLORIDE

A thesis submitted to the University of Glasgow

for the degree of Ph.D.

by

Samuel Marshall

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Acknowledgments

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S. M.

Preface

In recent times, increasing interest has been shown in the chemistry of sulphenyl halides, from both a pure chemical and a biological standpoint. The diversity of their reactions is such that for several years the natural desire to find ever more uses for the compounds was dominant and certain areas which appeared amenable to further study were neglected. It was the purpose of this work to investigate one such area. Such is the latent potential of even this small corner that the study has been far from exhaustive, and in some respects shows how wide the application of the sulphenyl halides, given the opportunity, could be to chemistry.

The reactions of the reagent* have been interpreted throughout in terms of ionic mechanisms and on the assumption - as yet unproved - that the initial reaction of a ketone with the reagent occurs at the sulphur atom. One example only of an uncyclised product from such reactions has been isolated**, and it provides no evidence as to the site of initial reaction.

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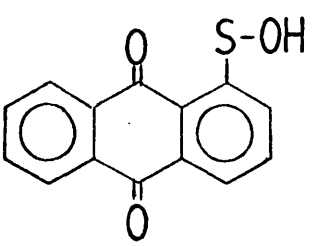
CHAPTER I

Introduction

1. A Brief Summary of the Chemistry of the Sulphenyl Halides

The sulphenyl halides are compounds which can be represented by the formula RSX, where X = halogen and R may be an alkyl, acyl, aryl, or even inorganic residue. They may be regarded as the halogen derivatives of the sulphenic acids RSOH. This relationship is formally the same as that between carboxylic acid halides and their acids, but in fact in many ways the relation is reversed, for the sulphenyl halides are better known and much easier to prepare than the acids. So much so, that despite the many halides which have been characterised only one sulphenic acid, anthaquinone-2-sulphenic acid (1) has been isolated.[1]



(1)

Typical acid chloride reactions are reversed,

$$RCOCl + H_2O \longrightarrow RCOOH + HCl$$

and $$RCOCl + 2HNMe_2 \longrightarrow RCONMe_2 + HNMe_2.HCl$$

while in the sulphenyl case

$$RSOH + HCl \longrightarrow RSCl + H_2O$$

and $$RSNMe_2 + 2HCl \longrightarrow RSCl + HNMe_2.HCl.$$

Aryl sulphenyl halides are usually easiest to prepare because of the

stability induced in the sulphenyl residue by the aromatic ring. From now on, we shall be concerned with aromatic sulphenyl halides only. The sulphenyl chlorides are more readily obtained than the bromides and iodides, in that order, and are of the greatest synthetic utility.

Aromatic sulphenyl halides were first encountered by Zincke, in Germany, who demonstrated[2] that sulphenyl chlorides and bromides could be synthesised by three essentially similar methods, involving the action of chlorine or bromine on aryl disulphides, thiophenols or aryl benzyl sulphides.

$$ArSSAr + X_2 \longrightarrow 2ArSX$$

$$ArSH + X_2 \longrightarrow ArSX + HX$$

$$ArSCH_2Ph + 2X_2 \longrightarrow ArSX + PhCHX_2 + HX.$$

In certain cases, Zincke showed that these methods could be used alternatively to synthesise the same sulphenyl chloride. The halogenations were carried out at relatively low temperatures, under anhydrous conditions. Solvents such as carbon tetrachloride, chloroform, ethylene chloride and sometimes benzene, pentane or other hydrocarbons were employed.

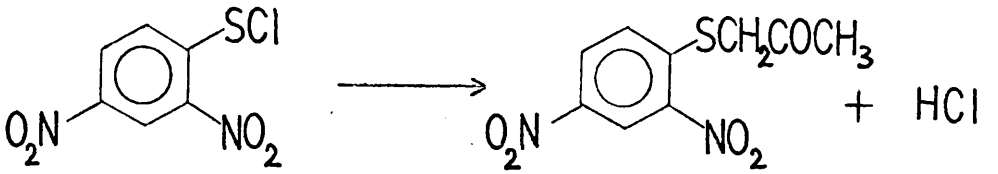
The existence of sulphenyl chlorides was anticipated by Otto as early as 1868 when he reported the preparation of benzene-sulphenyl chloride (PhSCl) from phenyl disulphide.[3] However, it was shown later by Zincke that, under the conditions employed by Otto, scission of the disulphide linkage had not occurred, and that nuclear substitution had

taken place. Otto's product was, in fact, 4-bromo-phenyl disulphide. This was the first illustration of one of the drawbacks involved in the preparation of sulphenyl halides - substitution of the aromatic ring. This limitation is serious when the aromatic nucleus contains electron donating substituents such as -OH or $-NH_2$, when halogenation of the ring may take precedence over halogenolysis. However, electron withdrawing groups - NO_2 or C = O - protect the ring from substitution, and, as a result, the anthaquinone, nitro and dinitro benzene sulphenyl halides are the most easily prepared: they are, as it happens, also the most stable.

The sulphenyl halides are very reactive towards a great variety of substances including ketones, amines, olefins, acetylenes, alcohols etc. In fact, almost any substance capable of acting as a nucleophile appears to attack the sulphur atom. The massive scope of reactions they, the sulphenyl halides, can undergo has been indicated by Kharasch [4] in a review of the uses of one example, 2,4-dinitro benzene sulphenyl chloride. This substance was particularly suitable for such a study since it is stable and provides, in most cases, crystalline, sharp-melting derivatives. Tables of these derivatives together with general preparative methods have been published by Langford and Lawson.[5]

Sulphenyl halides normally react with ketones of the form RCH_2COR' to give keto-sulphides of the form $ArSCH(R)COR'$. An illustration of this is shown - the reaction of 2,4-dinitro benzene sulphenyl chloride

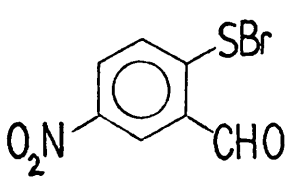
with acetone which yields the keto-sulphide (2) and hydrogen chloride.



(2)

A survey of the literature revealed that relatively little use had been made of the fact that this type of reaction, in releasing hydrogen chloride, provides a built-in acid catalyst for further condensation. Apart from the early work of Fries, this subject appeared to be completely open.

Fries prepared the sulphenyl bromide (3) by scission of the corresponding disulphide (4) with bromine.[6] He found that (3), when warmed with ammonia, yielded a product which he identified as the benziosothiazole (5).[7]



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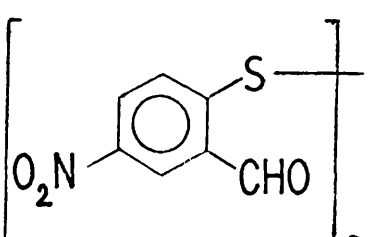

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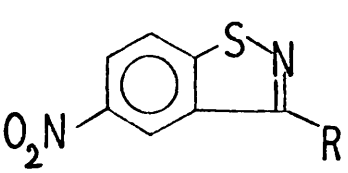
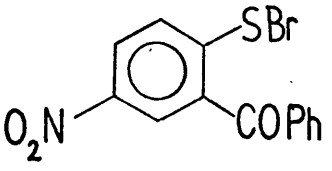


(5) R = H
(7) R = Ph

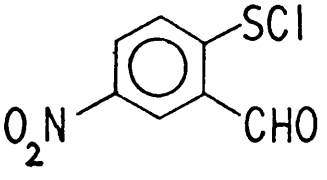
He also prepared[8] the phenone benzene sulphenyl bromide (6) which reacted similarly with ammonia giving the benzisothiazole (7). However,



(6)

(6), when warmed with acetone, effected halogenation and bromoacetone and disulphide were obtained. It appears that the sulphenyl bromides are inclined to give rise to halogenated products of this sort, while the chlorides are not so liable to produce such complications.

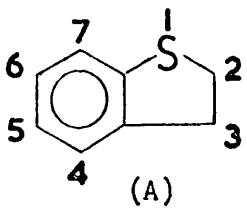
The sulphenyl chloride (8), the chlorine analogue of (3), was therefore selected here as a promising bidentate electrophile. We determined to effect its synthesis and to examine its reactions with ketones, with a view to discovering what influence the ortho-formyl group would have on the products from such reactions.



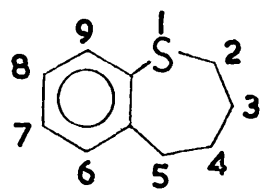
(8)

2. Nomenclature

In this thesis, compounds possessing the ring system (A) are named as benzo[b]thiophene derivatives, according to the numbering system shown. Often in the text, however, the trivial name thianaphthene is used alternatively.



(A)



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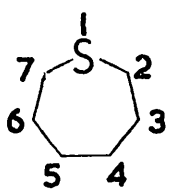
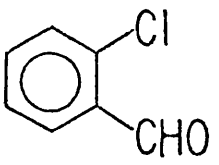


(C)

For compounds having the ring system (B) the systematic method of nomenclature, i.e. as a hydrogenated benzothiepin, was considered to be rather unwieldy. For this reason, such compounds have been named as derivatives of the thiepane ring (C), by which (B) becomes a benzo[b]thiepane and is numbered accordingly. Certain compounds will be encountered later which have an (n)-methylene bridge (where n = 2 or 3) between positions 2 and 4, and are named as 2,4 di- or 2,4tri- methylene derivatives respectively, of the benzothiepane.

CHAPTER II

The Reagent and its reactions with some ketones.



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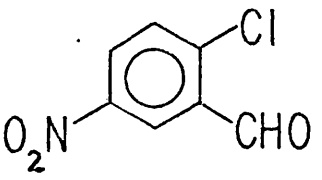

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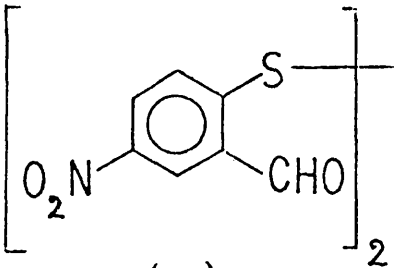

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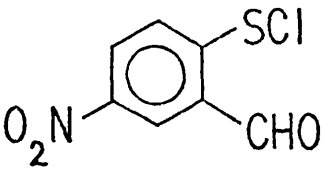

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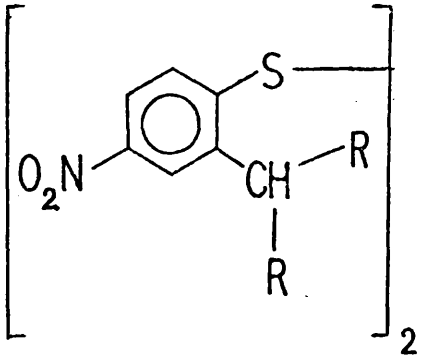
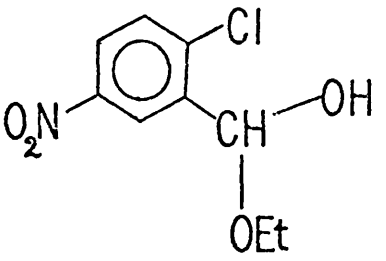


(11), R=OEt
(12), R=OMe



(14)

1. The Reagent

2-Formyl - 4-nitrobenzene sulphenyl chloride (the reagent) was prepared by the route (9) → (10) → (4) → (8). Chloroaldehyde (9) was converted to (10) by treatment with a mixture of nitric and sulphuric acids according to Erdmann.[9] Disulphide (4) was obtained from the reaction of (10) with sodium disulphide in aqueous ethanol, as described originally by Fries and Brothuhn.[6] It was purified by recrystallisation from dimethylformamide, a procedure which was found to be more effective than previous methods.

Chlorinolysis of (4) in dry ethylene dichloride provided the sulphenyl chloride (8) in good yield, as sturdy, bright-yellow needles. It was identified by analysis and by its easy conversion in aqueous ammonia to the known benzisothiazole (5).

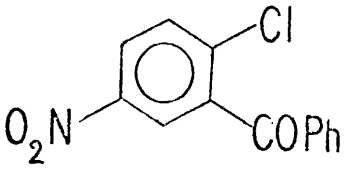
The sulphenyl chloride proved to be stable to air, but on warming or on long exposure to light it reverted to the parent disulphide. Again, on fast heating, the reagent melted, largely between 130 and 160°C, but thereafter crystals were seen to form, whose melting point was that of the disulphide. However, when the temperature was raised slowly, no true fusion was observed, but a steady decomposition above 120°.

Attempts to form a sulphenic ester from (8) by treatment with boiling ethanol and methanol led only to the disulphide acetals (11) and (12) respectively.

Oxidation of the reagent by nitric acid afforded the corresponding sulphonyl chloride (13), a compound which was more conveniently prepared by treating the disulphide (4) with chlorine in aqueous acetic acid,

thereby combining chlorinolysis and oxidation. (Samples from both sources were identical).

In preparation of (10), attempted recrystallisation of the product from ethanol yielded fine colourless needles of a compound whose infrared spectrum contained no carbonyl absorption. Its melting point was close to that of (10), to which it could be readily transformed by heating or by addition of dilute mineral acid to its solution in ethanolic sodium hydroxide. These observations, coupled with the spectral evidence suggested the hemiacetal structure (14) for the compound, a conclusion which was in agreement with the subsequent elemental analysis.



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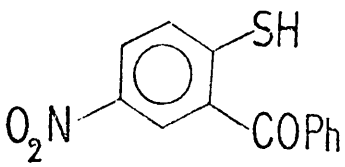

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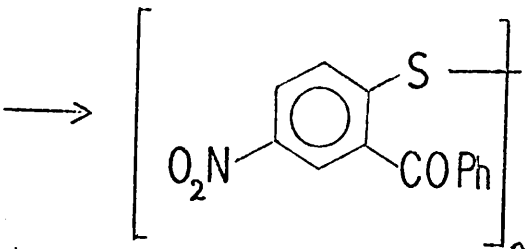

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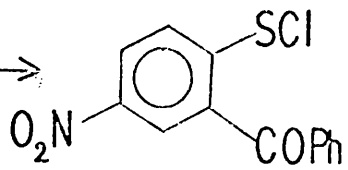

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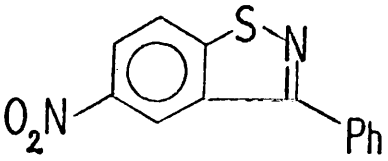


(7)

2. Some spectral properties of the reagent and related compounds

A feature of the infrared spectrum (nujol mull) of the reagent was the position and shape of the carbonyl absorption. The peak occurred at 1640cm^{-1} and was rather broad and stunted. Even allowing for the depression of a normal aryl carbonyl by the nitro group, this value was considerably lower than might have been expected.

Oxidation of the sulphenyl residue to sulphonyl raised the aldehyde frequency by approximately 50 wave numbers to 1690 cm^{-1}. Furthermore, the disulphide (4) also showed carbonyl absorption at 1690cm^{-1}. For the purposes of comparison, the sulphenyl bromide (3) was prepared and this too showed a depressed carbonyl which appeared ca. 1650 cm^{-1}.

The closely analagous sulphenyl chloride (15) was prepared by the reaction sequence (16) $\longrightarrow$ (17) $\longrightarrow$ (18) $\longrightarrow$ (15). The chloride was identified by analysis and by its conversion to the expected benzisothiazole (7).

The infrared spectrum (nujol mull) of (15) displayed no appreciable absorption above 1600 cm^{-1}. Thus, the lowering of the frequency of the carbonyl, if present, relative to the corresponding disulphide (18) (1650 - 1660 cm^{-1}) was again considerable. Once more, conversion of the sulphenyl chloride to a sulphonyl caused the carbonyl frequency to be raised, in this instance to ca. 1670 cm^{-1}.

Better resolved spectra were obtained for sulphenyl chlorides (8)

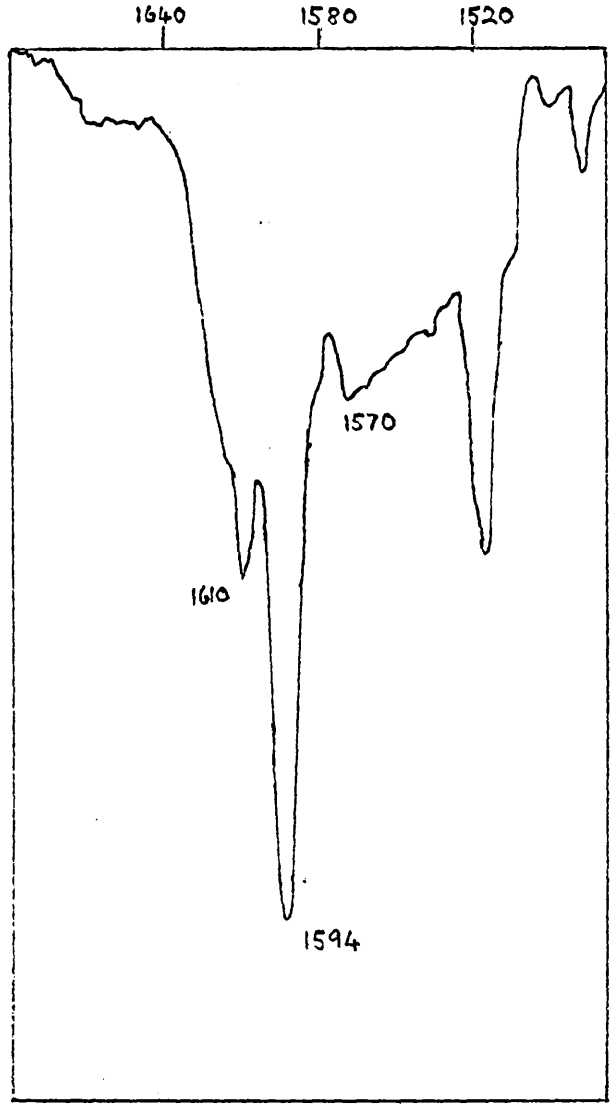


Fig 1

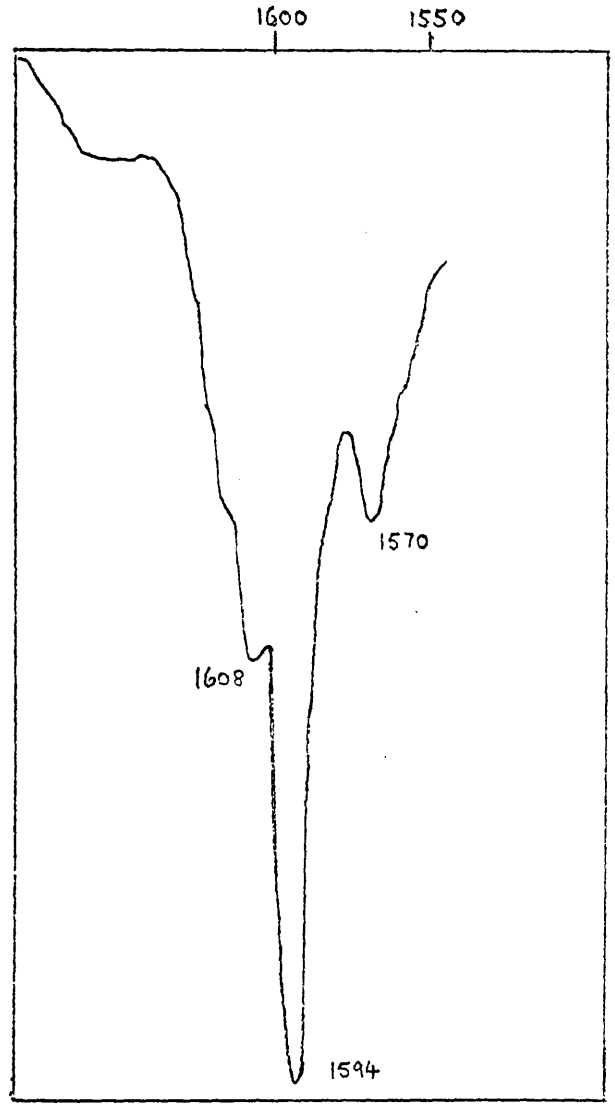


Fig 2

and (15) in both solid state (KBr disc) and in CCl_4 solution in each case. As expected the solid state spectra were similar to those run as a nujol mull. In carbon tetrachloride, the aldehyde carbonyl of (8) was observed at 1660 cm^{-1}. For (15), the 1600 cm^{-1} region (CCl_4) is reproduced (Fig 1). The same region ($CHCl_3$ solution) is shown in Fig. 2. It can be seen that no significant shift has occurred for any of the observable peaks and so the carbonyl, if it exists, must be masked by these absorptions.

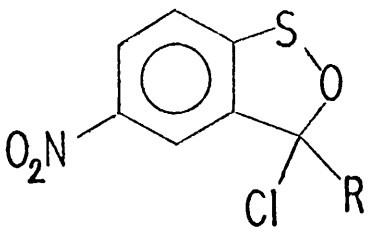
It seemed, therefore, that in the cases of these chlorides, there were two possible explanations for the observed spectra, one or both of which might be viable.

1. The sulphenyl chlorides could exist in an isomeric form which did not incorporate a carbonyl group. The spectra might be interpreted in such terms if the formyl sulphenyl chloride (8) existed partly, and the phenone sulphenyl chloride (15) wholly in such a form.

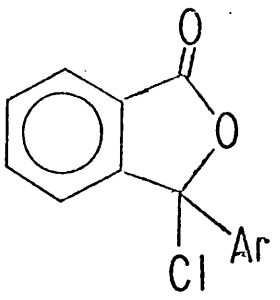
2. A potent effect (unspecified) was in operation causing depression of the carbonyl absorptions.

Let us consider these possibilities in turn.

It is known[10] that aromatic carboxylic acid chlorides having a carbonyl in the ortho position can exist in a pseudo form whereby the chlorine atom is transferred from one carbon atom to the other and a five membered ring is formed (see (19)). If we could extrapolate this idea to the sulphenic acid chlorides then (8) and (15) might be capable of existing in the forms (20) and (21) respectively. Such a situation is



(20), R=H
(21), R=Ph



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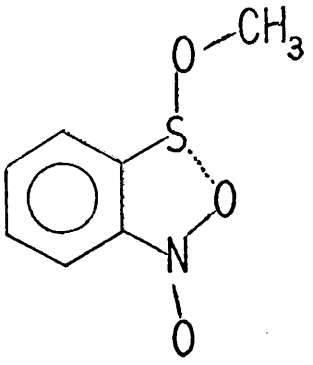


(22)

not unimaginable, for a recent X-ray crystallographic study[11] of the o-nitrobenzene sulphenate ester (22) has shown that an oxygen of the nitro group is sufficiehtly close to the sulphur atom to allow some kind of interaction, short of complete bonding, to take place.

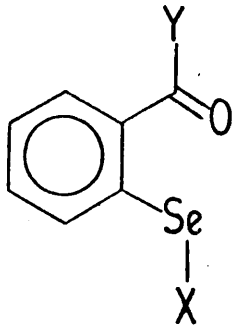
It was expected that for structure (20), where R = H, the signal due to this latter proton would be observable in the n.m.r. spectrum. However, no evidence for such a signal was found, but a sharp singlet at -0.2 τ could readily be assigned to an aldehydic proton. From this evidence, it appears that (8) exists wholly in the normal form and that the low intensity of the carbonyl band must be due to some other property of the molecule. For the sulphenyl chloride (15) no such simple n.m.r. structure proof is possible (R = Ph).

Thus, it is plain that the second possibility, some potent depressive effect, is in operation for (8), and probably also in the case of (15).

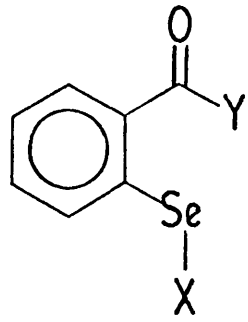
Renson and Piette,[12] during the course of some synthetic studies,[13] have shown that the infrared frequency of an aromatic carbonyl group undergoes significant and systematic lowering when the group is fixed in a position ortho to certain sulphenyl or selenyl residues. A dramatic example of the effect occurs for acetophenone substituted in the 2-position by a selenyl chloride grouping, when the carbonyl absorbs at 1590 cm^{-1} (CCl_4) compared with 1690 cm^{-1} in the unsubstituted compound.

To explain this and similar results they suggested that a molecule

of the type under consideration could exist in two rotational forms (A) and (B), called cis and trans forms, respectively.



(A) cis

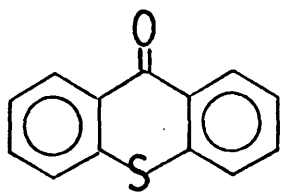


(B) trans

The lowering process would occur by attraction of the negative oxygen of the carbonyl towards the selenium (or sulphur), made positive by the electron withdrawing effect of the group X. For a large depression then, X should be strongly electronegative and the molecule should be in the cis form.

That the effect was not due to the presence of the selenium (or sulphur) atom alone was emphasised by the fact that for $X = CH_3$ only a very small effect was obtained.

The lowering of a carbonyl frequency by sulphur has also been observed[14] with the thioxanthone (23),



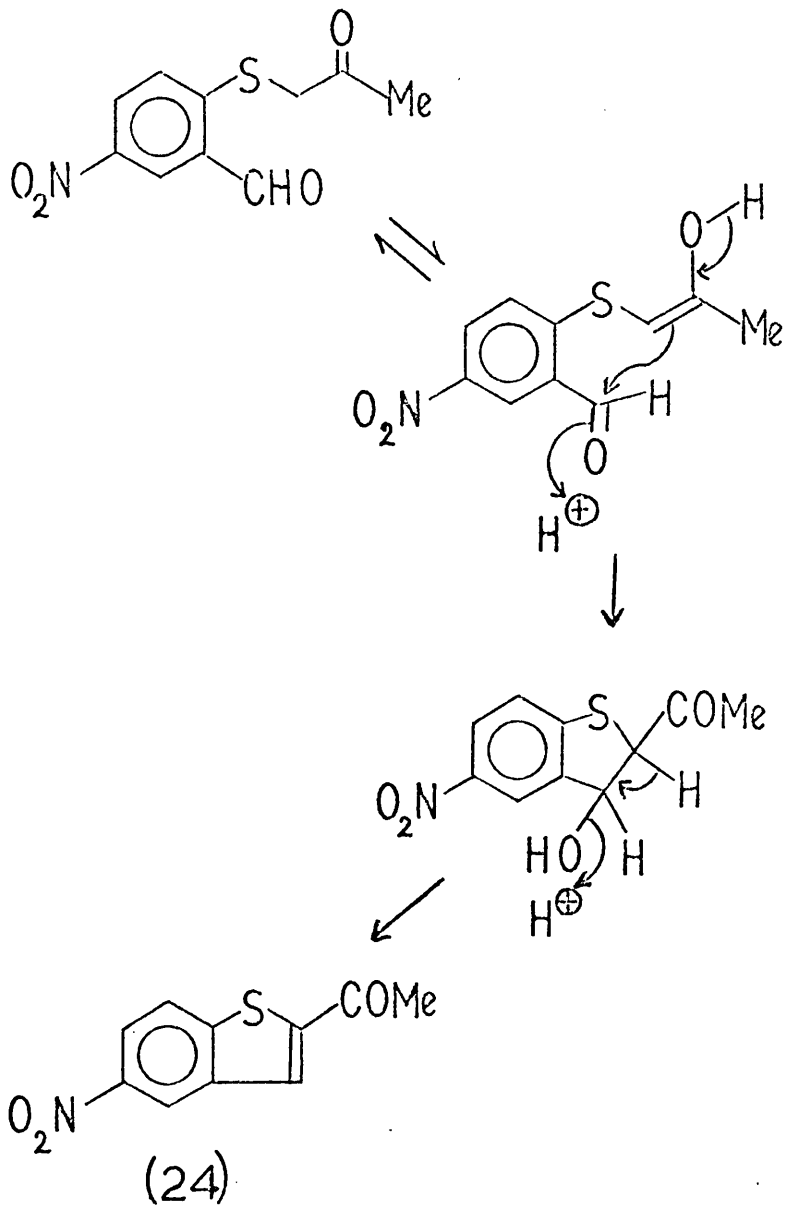
(23)

for which the carbonyl bond (CH_2Cl_2) appears at 1642 cm^{-1}. Oxidation of the sulphur atom to the sulphoxide or the sulphone destroyed the effect ($\nu_{C=O}$ (CH_2Cl_2) = 1672 in each case). The explanation offered for the depression was that the positive character of the carbonyl carbon was reduced by the influence, through the ring, of the non-bonded electrons on sulphur. For the sulphoxide and sulphone these electrons were not available - hence the disappearance of the effect. However, these results were obtained for a carbonyl in a relatively rigid ring system and are of doubtful application in our case.

It would appear, then, that we have observed effects comparable with those of Renson and Piette. Their explanation suggests not only how the lowering might occur but also why a smaller depression was observed for the sulphenyl bromide (Cl > Br in electronegativity). It does not seem to explain, in electronegativity terms at any rate, why the sulphonyl chloride, wherein the sulphur atom would surely be more positive than in a sulphide, fails to cause a depression. However, such an objection is barely admissible in the absence of knowledge of the steric factors involved, and of model compounds.

Instrumentation

The solution and solid state (KBr disc) spectra for this section were recorded on a Perkin Elmer 225 Grating Spectrophotometer.



(24)

3. Reactions with ketones

a. Reactions at ambient temperature

As was explained in the introduction, the purpose in preparing the reagent was to study its reactions with ketones, and to see what effect the formyl group in the ortho position would have on the products from such reactions. In order to achieve a sense of order in the study it seemed reasonable to begin with the simplest possible ketone, acetone.

When the reagent was warmed or stirred at room temperature, for a short time, with an excess of acetone, a solid product could be obtained simply by evaporating to dryness. The residue showed a sharp absorption in the infrared at 1665 cm^{-1} and a single peak at 277 mu in the ultraviolet. From this information, coupled with n.m.r. and analysis evidence, the product was deduced to be the acetyl thianaphthene (24). On the assumption that keto-sulphide formation was the initial step in the reaction, the most likely mechanism involved subsequent condensation between the methylene and formyl groups, in aldol fashion followed by dehydration of the aldol intermediate.

Attempts to isolate this intermediate under mild reaction conditions were uniformly unsuccessful, the material isolated from various runs being either the benzothiophene or unreacted sulphenyl chloride. Therefore the loss of water from the aldol, once formed, must have been rapid.

Barltrop and Morgan have examined the reactions of o-nitrobenzene

sulphenyl chloride with unsymmetrical ketones.[15] In each case, two ketonic α - positions were available and so two isomeric keto sulphides were possible. They devised a neat method of identifying their products through Beckmann rearrangement of the oximes followed by hydrolysis of the resultant amides.

By this means they demonstrated that o-nitro-benzenesulphenyl chloride had reacted preferentially with the methylene carbon atom.

We planned to examine the reaction of ethyl methyl ketone with our reagent, but thought it advisable, first of all, to consider the symmetrical diethyl ketone.

When the finely powdered reagent was stirred in an excess of diethyl ketone, at ambient temperature, it dissolved slowly, leaving a small amount of pale-yellow solid in suspension. This proved to be disulphide, arising probably from traces of moisture in the ketone. Removal, under reduced pressure, of excess ketone from the filtered solution, left a yellow oil which crystallised on trituration with carbon tetrachloride. Recrystallisation from the same solvent provided beautiful colourless needles of a product which gave only one spot on a thin-layer plate. The material showed a broad peak ca. 340 mu in the ultraviolet and both hydroxyl and carbonyl absorption in the infrared region. From this spectrum and elemental analysis the product was formulated as either (25) or (26). The issue was resolved by the n.m.r. spectrum. A methyl singlet found at 8.35 τ was enough to discount (26), since the latter would contain no unsplit methyl groups. A doublet,

integrating for one proton, at 6.97 τ , disappeared on treatment with D_2O, confirming the presence of a hydroxyl group. This signal showed also that the hydroxyl proton was coupled, presumably with an α-hydrogen atom. Another doublet, centred at 4.35 τ was attributed to this hydrogen under the hydroxyl group, since on the same D_2O treatment it collapsed to a sharp singlet. The rest of the spectrum was also compatible with structure (25).

There was no evidence for the presence of (26) or any other aldol in the reaction mixture. Nevertheless, aldol (25) had been formed in acid surroundings and it was reasoned that had the cyclisation occurred under basic influence then formation of (26) might have been more encouraged. It was therefore decided to observe the effect of base on (25), in the hope that in its presence the aldehyde group would be regenerated and recyclisation would perhaps give a seven-membered ring. Such experiments were in vain, however, for aldol (25) proved to be remarkably stable in basic environments. When the U.V. spectrum of (25) was run, addition of aqueous sodium hydroxide to the ethanolic sample produced little effect on the spectrum. Further, the aldol was capable of standing for long periods in solutions of piperidine and diethylamine, respectively, in acetic acid without significant change.

The conditions of the previous experiment were then applied to ethyl methyl ketone. The aldol product, which could be crystallised from aqueous methanol, was characterised as before, conclusive structure proof again being provided by the n.m.r. spectrum. Methyl singlets were

observed at 8.34 τ and 7.65 τ . This discounted any seven-membered ring structure and indicated (27) as the structural formula. The lower-field methyl was attributed to the methyl of the acetyl group and the other to that on position 2 of the five-membered heterocyclic ring. Doublets, each integrating for 1 proton, appeared at 7.15 τ and 4.40 τ and on D_2O exchange the first of these disappeared and the other became a singlet. They were therefore assigned to the hydroxyl hydrogen, and to the hydrogen under hydroxyl respectively.

These n.m.r. spectra were clear and sharp, possibly due to the fact that the samples, being crystalline solids could readily be obtained in a high degree of purity. Every signal could be assigned and the splittings of hydroxyl and α-hydrogen were near-classic examples.

An infrared study of (25) and (27) revealed that a small proportion of the hydroxyl absorption was attributable to bonded hydroxyl. Since this part of the absorption did not disappear on dilution of the solution it appeared that the bonding was of the internal variety.

It should therefore denote the presence in the samples (25) and (27) of a small proportion of the epimeric aldol in which the cis arrangement of hydroxyl and acyl functions permits of internal hydrogen bonding. When treated by gas chromatography sample (25) did indeed show two close-set peaks one of which was much smaller than the other. However,neither in this case nor in any of those to be described in the sequel was a practicable separation of epimers achieved. Accordingly, the crystalline compounds here described are treated as essentially

homogeneous and as having the form with the trans orientation of hydroxyl and acyl groups.

The two preceding experiments are specific examples of what seems to be a fairly general type of reaction between the reagent and liquid ketones. The reactivity of the sulphenyl group is such that it will often enter into reaction without the assistance of heat or added catalyst.

A similar technique, which consisted of stirring the reagent in an excess of ketone was used successfully with such compounds as acetyl acetone, ethylacetoacetate and cyclohexanone, yielding the aldol products, (28), (29) and (30) respectively, which were characterised by the usual methods. The spectral evidence for the existence of (30) is very strong, but unfortunately a satisfactory analysis has not yet been obtained.

For ketones which required considerable time to react, an indication of the extent of reaction was often given by the amount of discolouration, due to HCl, of the silica gel used as a protector with all these reactions.

From our experience with ethyl methyl ketone it appeared that, concerning reaction with the sulphenyl chloride, an active methylene group would react before a methyl. Since, in the prevailing acidic environment, the preferred direction of enolisation in the ketone is probably an important factor, it seemed not unreasonable

to suppose that a methine group would show a similar preference. Further, in such a case, after initial keto-sulphide formation, no further condensation would be possible at the original methine position and any subsequent reaction would be forced to occur at another centre.

In anticipation of this, we subjected isopropyl-methyl ketone to the previous treatment. The sulphenyl chloride soon dissolved. After some time a solid separated out and was recrystallised from acetic acid as colourless platelets. The infrared spectrum of this compound showed carbonyl and hydroxyl bonds as did former aldols but its U.V. spectrum was very different. Its bands at 263 and 315 mu were in contrast with the broad absorption around 340 mu shown by all previous aldol products.

It appeared, therefore, that our expectations had been fulfilled, and the product was confirmed by the n.m.r. spectrum, which showed methyl singlets at 8.76τ and 8.51τ respectively, and a peak ca. 8.35τ which disappeared on treatment with D_2O, to be the seven-membered ring aldol (31).

Thus we have been able to demonstrate that the synthesis of a seven membered hetrocyclic ring may readily be accomplished in this specific instance. It is true that the experiment was designed such that, after initial keto-sulphide formation, no other simple cyclisation path was available to the molecule. However, this does not detract from the significance of the result for it shows that the formation of the five-membered ring compounds obtained earlier (from ethyl methyl and diethyl ketones), occurred very probably through a preference of

one ketonic α-position to react, at the keto-sulphide stage, and not because of an inability of the competing centre to do so.

b. Reactions in acetic acid as solvent

As a vehicle for studying the reactions of our reagent with ketones, the procedure described in the previous section had obvious limitations. It excluded the use of solid ketones and, by demanding a relatively large excess of liquid ketone, as suspension medium, was rather wasteful. These undesirable features would be eliminated if the reactants could be brought together in a suitable solvent.

The choice of solvent was fairly straightforward. It was known that sulphenyl chlorides are reluctant to react in non polar media. We verified this in our own case by bringing together the reagent and diethyl ketone in benzene, and heating under reflux for about $1\frac{1}{2}$ hours. The reagent was recovered unchanged from the cooled reaction mixture and no trace of HCl was detected.

Acetic acid was chosen for the following reasons. It was polar and the reagent could be subjected to boiling actic over limited periods without significant damage. Also, Langford and Lawson had used it successfully as a solvent for reactions of 2,4-dinitrobenzenesulphenyl chloride.[5]

It was known that certain sulphenyl chloride reactions, such as addition to double bonds, can be accomplished in acetic acid, at room temperature. The same does not appear to be generally true of the reaction with ketones for when the reagent was stirred with a small excess of acetone, ethyl methyl ketone or diethyl ketone, respectively, in acetic acid, it could be recovered almost quantitatively by filtration

and no evidence of any reaction was found. With dibenzyl ketone under similar conditions, however, the reagent dissolved in the medium, HCl gas was evolved, and a solid was isolated which had the spectral properties one might expect for the aldol (32). However, we were unable to obtain a good analysis for this compound. In any case, the benzene rings have considerable activating influence on the methylene groups.

We decided to examine the reactions of ketones with the reagent in acetic acid under reflux conditions.

The reagent together with a small excess of acetophenone was heated under reflux in acetic acid. The solid soon dissolved and little by little the reaction became brown in colour. Needles began to crystallise out of the refluxing solution, and, after half an hour, heating was stopped, producing considerable further crystallisation. The product had a peak in the infrared at 1635 cm^{-1} and a single absorption in the U.V. at 286 mu. From these data, and analysis results, the compound was identified as (33), the benzoyl analogue of (24). The mechanism invoked for the formation of (24) appeared to be equally applicable in this instance.

At this point it seemed worth while to reconsider the reactions of diethyl and ethyl methyl ketones under these conditions.

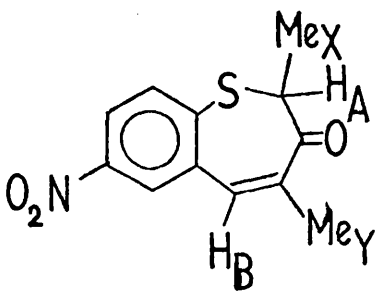
From a reflux of diethyl ketone with the reagent in acetic acid, an oil was produced by dilution of the cooled reaction mixture with water. After a short time it solidified and was chromatographed in

benzene on silica gel. Two compounds (pure by T.L.C.) were recovered from the column. The less polar of these crystallised from ethanol as colourless needles. Its infrared spectrum showed the presence of a nitro group but lacked any hydroxyl or carbonyl absorption. The n.m.r. spectrum showed the familiar aromatic pattern together with a 3 proton doublet centred at 7.36 τ and a collapsed quartet integrating for one proton at 2.84 τ . From this information, analysis evidence and the molecular wt. of 193, determined by mass spectrometry, the structure (34) was postulated for the compound. This was supported by the thianaphthene-type U.V. spectrum (maxima at 306, 266, 253 mu.)

The second and minor product from the column possessed carbonyl absorption at 1660 cm^{-1} in the infrared and a single U.V. maximum at 294 mu. The elemental analysis was consistent with the formula $C_{12}H_{11}NO_3S$. From this evidence (35) was deduced to be the structure and this idea was subsequently confirmed by the n.m.r. spectrum.

Thus we have again succeeded in forming a seven-membered ring, this time in the face of competition, at the cyclisation step, from the more reactive tertiary carbon.

(35)



The n.m.r. spectrum shows, apart from the usual aromatic splittings:

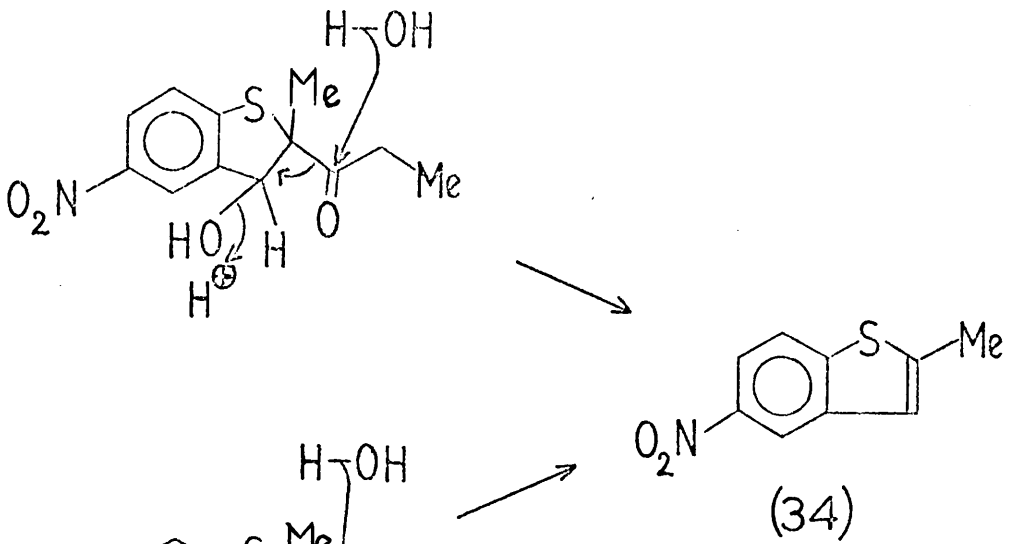
Doublet (3H, centre 8.53τ, J 7 cycles) - Me_X

Doublet (3H, centre 7.79τ, J 2 cycles) - Me_Y

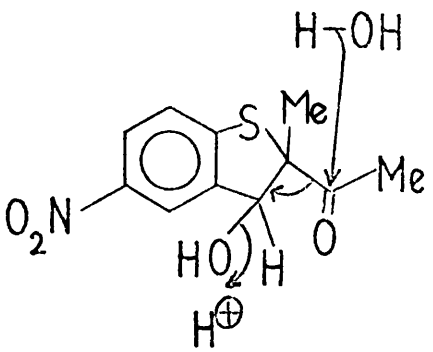
Quartet (1H, centre 6.52τ, J 7 cycles) - H_A

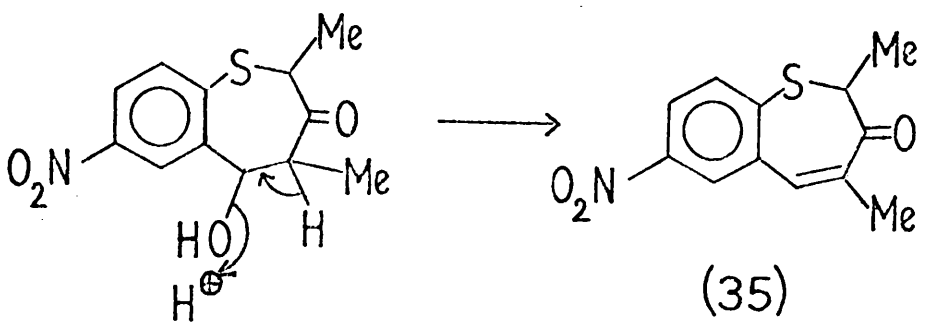
Quartet (1H, centre 2.71τ, J 2 cycles) - H_B

The general form of the spectrum, the multiplicities, the chemical shift values and the coupling constants are all in agreement with structure. (35).


H–OH
Me
S
O_2N
Me
HO
H
O
$H^{\oplus}$
S
Me
O_2N

(34)


H–OH
Me
S
Me
O_2N
HO
H
O
$H^{\oplus}$


Me
S
O
O_2N
Me
HO
H
$H^{\oplus}$
S
Me
O
O_2N
Me

(35)

The conditions of the previous reactions were employed with ethyl methyl ketone. When a column of the product was run (in benzene on silica) one compound only was recovered, which proved to be the methyl thianaphthene. (34). Infrared and U.V. spectra of the product were superimposable on those of an authentic sample and mp. and mixed mp. were identical.

Mechanistically, then, it was necessary to postulate routes which would explain the formation of the same thianaphthene from diethyl ketone as from ethyl methyl ketone. The most plausible mechanisms involved the generation of the aldols (25) and (27), as before, followed by acid-catalysed elimination of propionic or acetic acid as shown opposite. The mechanism required the participation of water but this would be self-generating and so only a catalytic amount would be necessary. Support for aldol intermediacy was obtained when to a solution of (25) in acetic acid, was added a drop of concentrated sulphuric acid, and the resultant mixture warmed for a few minutes. A high yield of (34) which crystallised out of the cooled reaction medium, was recovered.

The production of the thiepanone (35) from diethyl ketone is explicable as the dehydration of an intermediate aldol (26).

It is worth remembering that no trace was found of this aldol during the earlier experiments, and so formation of a seven-membered ring appears to be encouraged in hot acetic acid. Our failure to obtain a corresponding thiepanone from ethyl methyl ketone could be the result of a reluctance of the active methyl group to react, relative to a methylene,

in the cyclisation step.

In these reactions with diethyl and ethyl methyl ketones the yields of products were poor, especially in the case of the thiepanone. The experiment with diethyl ketone was repeated, but this time after the solution had cooled, one drop was removed and its U.V. spectrum in ethanol was recorded. Bands arising from (34), (35) and also from aldol (25) could be recognised. It appeared therefore that a large proportion of the reaction product had remained at the aldol stage.

To a sample of the diethyl ketone reaction was added a few drops of concentrated sulphuric acid. The whole was warmed for 20 minutes, and thereafter the U.V. was run again. It was then apparent that the peak due to the aldol had disappeared almost completely, and correspondingly, the thianaphthene absorption was considerably augmented. As far as could be seen, little change seemed to have been effected in the thiepanone peak. By way of confirming that the thiepanone was, in fact, undisturbed by acid, a pure sample was treated as above. Its spectrum proved to be indeed unaltered.

Thus, the yield of (34) could be considerably increased by treatment of the reaction solution with mineral acid. On the other hand, the change in thiepanone yield seemed to be negligible.

Similar products have been obtained by heating the reagent in diethyl ketone alone. Prolonged heating was required, however, since after an hour, the U.V. spectrum of the reaction solution was still that of aldol (25).

However, when ethyl methyl ketone was heated under reflux with the reagent for 1 hour, addition of ethanol to the concentrated reaction mixture caused a small amount of solid to be precipitated. The spectral properties of this material were very reminiscent of the acetyl benzothiophene (24), and indeed analysis confirmed that the compound was 2-propionyl, 5-nitro benzothiophene (36).

The ethanolic mother liquors were concentrated in vacuo and the oily residue on trituration with carbon tetrachloride yielded yellowish

crystalline material spectroscopically identical to (27). No trace of any other aldol, or of the methyl thianaphthene, (34) was observed.

The isolation of (36) in very small yield showed that the site of initial reaction of the reagent with ethyl methyl ketone was not entirely specific, although very nearly so. This result is compatible with the findings of Barltrop and Morgan,* who, on converting the keto-sulphide product from the reaction of ethyl methyl ketone with o-nitrobenzenesulphenyl chloride to the oxime noticed the presence of a small proportion of that isomer arising from the initial substitution of the sulphenyl chloride by the α-methyl carbon.

* see page 15.

Other reactions conducted in refluxing acetic acid were those with dibenzoylmethane and benzoylacetone. These each provided a product already obtained by other means. The dibenzoylmethane reaction yielded material identical in all respects to the benzoyl thianaphthene (33) presumably by the suggested acid-elimination mechanism.

It might have been expected that benzoylacetone would furnish the same product. This was not the case. The product was, in fact, the acetyl thianaphthene (24). Its formation can be explained by considering the probable stereochemistry of the intermediate aldol (37). Because of the bulk of the benzoyl grouping, it would prefer to take up the position trans to the hydroxyl as shown, so placing itself in the best position for elimination.

At this point we decided to substantiate the elimination mechanism by isolating an acid from one such reaction. Circumstantial evidence for the existence of such an acid had been obtained when the sulphenyl chloride was reacted with dibenzyl ketone under refluxing acetic conditions. The sole product isolated was 2-phenyl-5-nitro benzo thiophene (38), but the unpleasant smell of phenylacetic acid was detected.

After a brief flirtation with the idea of trying to produce benzoic acid, it was realised that it would be much more satisfying to obtain an acid which remained linked to the thianaphthene system. For example, reaction of the reagent with cyclohexanone under refluxing

acetic conditions should yield the intermediate spiro-aldol (30) which on elimination of acid would yield the compound (39) without loss of carbon.

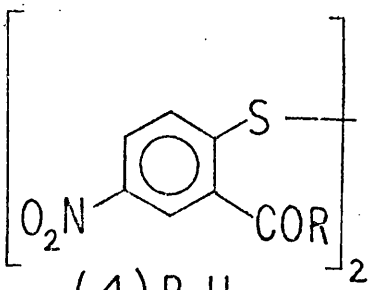
In pursuit of this objective, cyclohexanone, together with the reagent in acetic acid, was heated under reflux for 2 days. Cooling of the brown reaction solution produced no solid but an addition of water a dark oil separated out, from which a crystalline solid was isolated. These crystals had a U.V. spectrum similar to that of the methyl thianaphthene (34) and showed a broad carbonyl peak in the infrared at 1690 cm^{-1}. The structure of this material as the acid was proved by analysis and by the n.m.r. spectrum wherein a diffuse signal between 1.5 τ and 2.75 τ disappeared completely on addition of D_2O to the sample.

From similar reactions with cyclopentanone, cycloheptanone and cyclooctanone, the homologous acids (40), (41), and (42) respectively, were generated. With these reactions heating time was cut to $1\frac{1}{2}$ hours and the yields were not particularly good (20% or less).

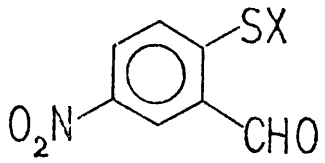
The fact that these acids can be obtained at all, of course, lends a great deal of credibility to our mechanism. However, these products are extremely interesting compounds in their own right, and they are almost certainly most inaccessible by other routes. The reaction appears to be general and there seems no reason why substitution on the acid chain should not be permissible. Further, it would be intriguing

to observe the result of Friedel-Crafts conditions on the related acid chlorides, for further cyclisation, were it to occur, could not fail to produce an unusual ring system, and different acid chain lengths might well give rise to varied substitution patterns. Unfortunately the time required for such a study would have been rather more than we could afford.

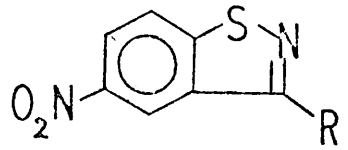
As might have been anticipated from previous experience, it was found that if a few drops of concentrated sulphuric acid were added to the reaction, following the $1\frac{1}{2}$ hours reflux, and the flask was warmed for 20 minutes, a spectacular increase in the yields of the acids could be effected. In certain cases the product even crystallised out of the medium. By this variation yields of over 70% were recorded.



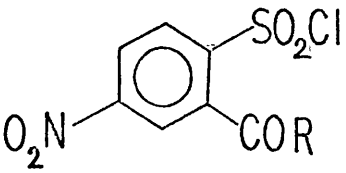
(4), R=H
(18), R=Ph



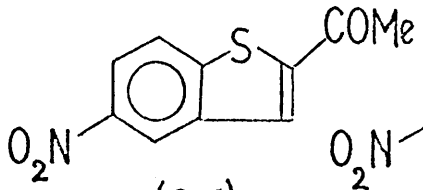
(8), X=Cl
(3), X=Br



(5), R=H
(7), R=Ph



(13), R=H



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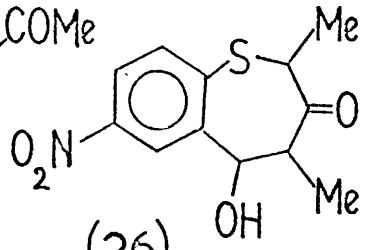

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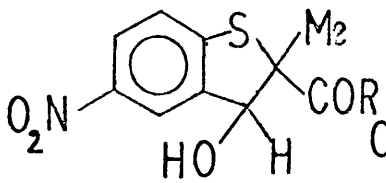
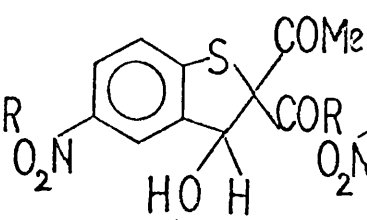


(25), R=Et
(27), R=Me



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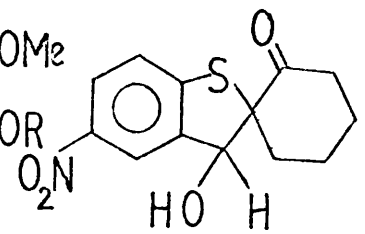

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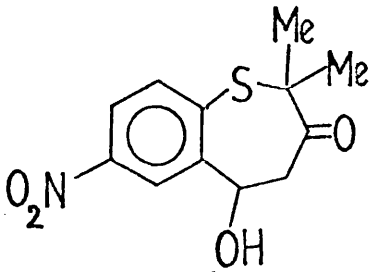

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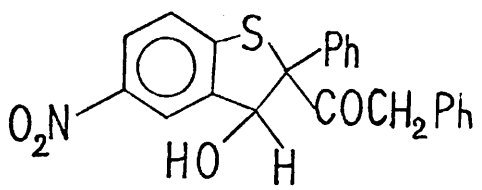

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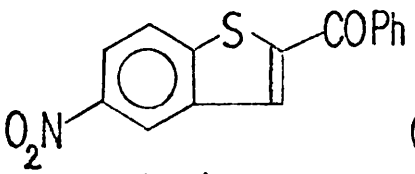

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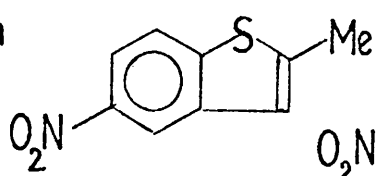

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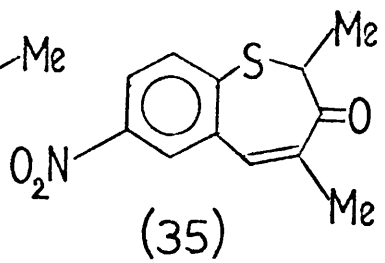

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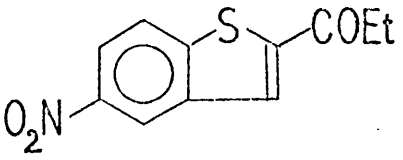
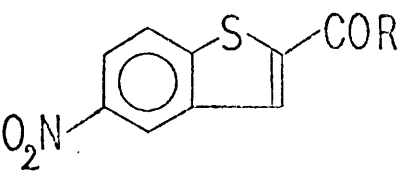
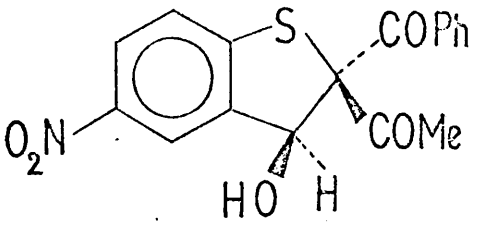


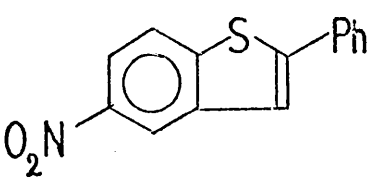
(36)



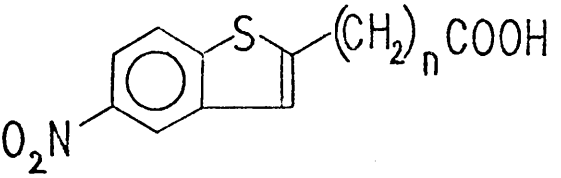
(24), R = Me
(33), R = Ph



(37)



(38)



(39), n = 4
(40), n = 3
(41), n = 5
(42), n = 6

CHAPTER III

2,4 - Trimethylene benzo [b] thiepanes and related compounds

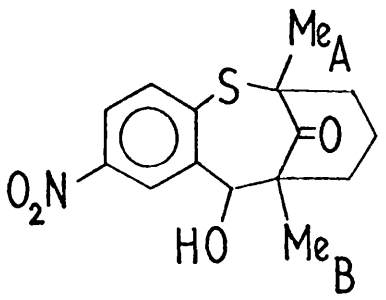
1. 2,4 Trimethylene benzo /b/ thiepan-5-ols and related compounds

Following the formation of the aldols discussed in the previous chapter, by stirring the reagent with ketones, the potential of this type of reaction to produce hitherto unknown ring systems was recognised. Our reasoning was based particularly on the reaction with methyl isopropyl ketone which yielded a substituted benzo /b/ thiepane. This result had shown that a seven-membered heterocyclic ring could readily be obtained by this method. If, then, such a reaction could be extended to selected cyclic ketones it would be possible to form compounds having a sulphur-containing bicyclo system fused to the aromatic ring.

As with the open-chain examples we decided to consider first a symmetrical ketone. 2,6 - Dimethylcyclohexanone was chosen, and it was obtained from 2-methylcyclohexanone by the method of Parker et al.[1]

From a stirring reaction of the reagent with 2,6 - dimethylcyclohexanone, solid material was readily isolated, which showed two spots on T.L.C. One of these, the less polar, was far larger than the other. The major product, which could be obtained pure by crystallisation of the whole from benzene, showed both hydroxyl and carbonyl absorption in the infrared, at 3550 and 1690 cm^{-1} respectively. This information alone strongly suggested that an aldol had been formed, and the elemental analysis was compatible with a formula obtained by eliminating HCl between the ketone and the reagent. The gross structure of such a compound, ignoring rearrangements, would be (1). The n.m.r. showed the presence

of singlets (each 3H) at 9.00τ and 8.60τ . Since the only methyl groups in the system were those on the cyclohexanone ring, it was concluded that both methine hydrogens of the ketone had undergone replacement. On addition of D_2O to the sample, a signal at 7.55τ disappeared and a diffuse one proton signal at 3.80τ became a sharp singlet. The former observation revealed the existence of a hydroxyl group, while the latter type of behaviour was typical of a hydrogen under hydroxyl. The methyl singlet at 9.0τ was attributed to the methyl next to the hydroxyl-bearing carbon (Me_B), and the other at 8.6τ to that β to the sulphur atom. (Me_A)



(1)

These values may be compared with those of the methyl groups of diethyl ketone which appear at 8.96τ (CCl_4). Methyl (B) was not significantly shifted from this value, the effect of a γ oxygen atom being almost negligible. However, the presence of an electronegative entity such as sulphur in the α or β position produces a marked shift downfield. Such a displacement is observed for methyl (A).

It was at first suspected that the lesser spot observed on T.L.C. was attributable to an epimer of (1). However, when a small quantity

of this material was isolated from a preparative T.L.C. plate, it was found to be similar but not identical to (1) in terms of its infrared spectrum. It was shown later to be identical in infrared spectrum, mp. and mixed mp., to the product obtained from a stirred reaction of the reagent with 2-methylcyclohexanone, and arose, presumably, from a trace of the latter ketone in the 2,6 - dimethylcyclohexanone. Thus, from T.L.C. evidence, it appeared that (1) was represented by a single epimeric form.

The aforementioned product from 2-methylcyclohexanone was an aldol with spectral properties similar to those of (1). Its n.m.r. spectrum showed a singlet methyl at 8,58 τ . Comparison with the spectrum of (1) showed that this methyl was of the (A) type. Hence initial reaction must have occurred at the methine carbon atom, and the aldol was formulated as (2).

Since the difference in chemical shift between methyls (A) and (B) of (1) was considerable, it seemed logical enough to use the fact as a method of determining the products from condensation of the reagent with methylcyclanones.

Thus, by formation of these aldols, our expectations had been borne out, and a new ring system had been formed with considerable facility. Furthermore, the products were again stable crystalline solids, and the orientation of condensation of 2-methylcyclohexanone with the reagent was further evidence of the preference of a tertiary centre, compared with a secondary, to react with the sulphenyl residue.

A further experiment of the above type using 2-carbethoxy, 6-methylcyclohexanone gave rise to two products. The first of these was an aldol but the other showed no hydroxyl band in the infrared, and was considerably less polar (from T.L.C.)

The aldol displayed an unsplit methyl signal at 8.95τ in the n.m.r. suggesting that it had an environment similar to that of methyl (B) of (1). From this and from the other spectral and analytical data this aldol was shown to be (3).

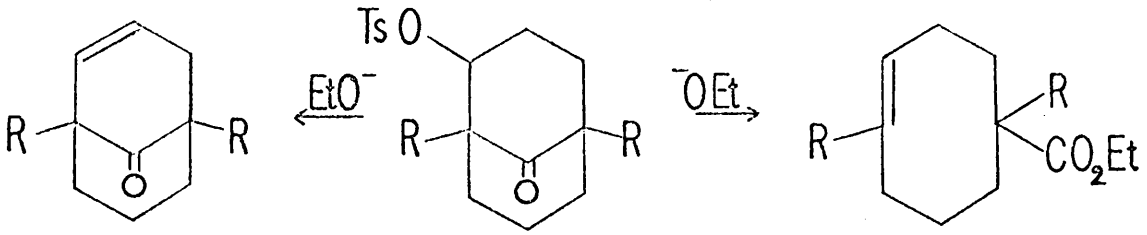
The other product, which showed a one proton singlet at -0.48τ was identified as an aldehyde obtained by simple addition of the reagent to position 2 of the keto-ester. The fact that such a compound was isolated at all led us to suspect that it might be different in some way from the aldehyde which would have been an intermediate in aldol formation.

We argued that the non-cyclisation might be explained if the stereochemistry of (4) was such that cyclisation was not encouraged. That such suspicions were unfounded was shown by the ready cyclisation of (4), in the presence of mineral acid, to aldol (3).

This aldol itself could be exposed to simulated reaction conditions, without change, and so it appears that the aldol formation is not easily reversible under the reaction conditions.

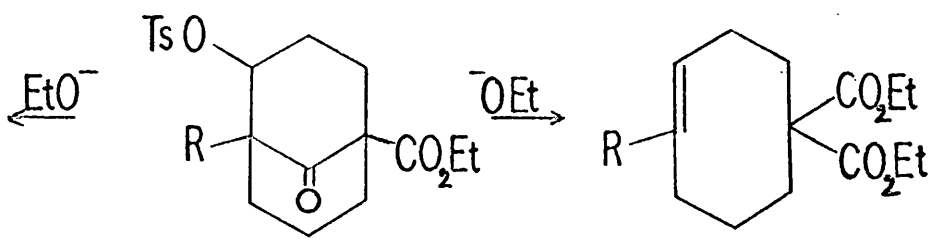
From the limited information at our disposal we can say that where a choice has existed, the sulphenyl chloride has preferred to react with ketonic α-positions in the following order:

doubly activated > methine > methylene > methyl.



(7) (5) (6)

(8)axial



(8) (9)

R = Me

It often happens that the satisfaction of having built a sand castle is almost immediately succeeded by a desire to knock it down. In our own case, this seeming reversal of purpose manifested itself in a desire to find how we might modify our newly-formed ring system.

An obvious beginning was to attempt to split the carbonyl bridge, so forming a medium-sized heterocyclic ring. Allowing correct stereo-chemistry, such a cleavage might be accomplished by treating a suitable derivative of the alcohol with base. Reactions of this type have been studied in Glasgow for tosylate derivatives of alcohols of the 3,3,1 bicycle-nonane system.

The epimeric tosylates (5) have been found[2] to react in distinct ways and at different rates when treated with ethoxide. The more reactive tosylate gave the cyclo-octene derivative (6), while the less reactive epimer afforded (7).

No assignments were made as to the stereo-chemistry of the respective tosylates, but later[3] it was found that an epimeric mixture of the tosylates (8), on ethoxide treatment, yielded the cyclo-octene gem-diester (9), together with returned tosylate, which proved to consist exclusively of the axial epimer.

It seems, therefore, that for the realisation of a bridge scission reaction of this sort, the stereochemistry of the tosylate relative to the bridge is critical, an optimum occurring when the two bonds involved are trans-antiparallel.

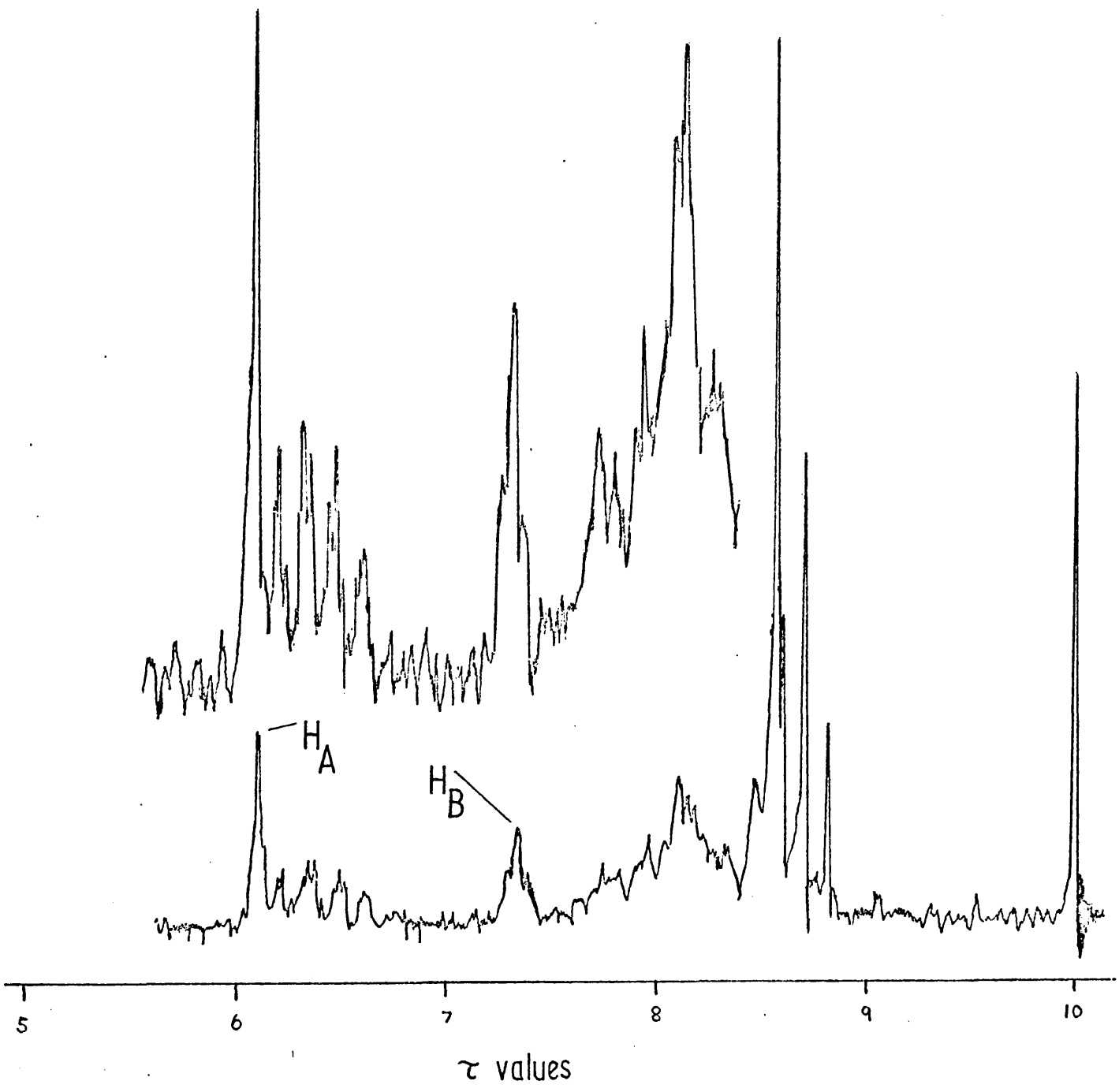
In our case, of course, a reaction similar to that leading to (7) would not be possible, since the position α to the alcohol is blocked by the aromatic ring.

Thus, if the reaction were to run true to form, we should obtain from such a reaction, either the medium ring ester, or returned starting material.

Tosylates (10), and (11), were prepared by reaction of the respective alcohols with p-toluenesulphonyl chloride, in dry pyridine, in the usual manner. The esters were obtained as colourless crystals and were characterised by elemental analysis and spectral data.

When tosylate (10) was heated briefly under reflux with ethanolic sodium ethoxide only the starting tosylate was identified in the work up. Since the opening of a bicyclic system in this way has, in the past, proved to be a most facile process, such a result suggested that the stereochemistry of our system was such that bridge scission was disfavoured. Tosylate (11) which was treated similarly with a catalytic amount of sodium ethoxide was also unreactive. This was not unexpected since it seemed reasonable to assume that the lack of a single methyl group would not greatly affect the ring conformations.

However, when this same tosylate was treated with more concentrated ethoxide for a prolonged period, dilution of the cooled reaction mixture with water, followed by extraction of the aqueous phase gave a yellow oil, less polar (by T.L.C.) than the starting tosylate, and crystallising readily from ethanol as fine, colourless needles.

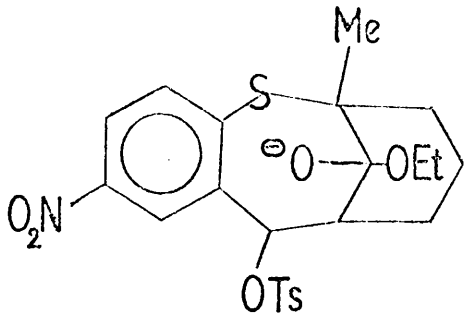

H_A
H_B
5
6
7
8
9
10
τ values

The infrared spectrum of this product was distinguished by a total lack of carbonyl absorption, and the doublet close to 1100 cm^{-1}, characteristic of tosylates, was absent. In the ultraviolet, bands were observed at 328 and 235 mu. Analysis indicated an empirical formula $C_{16}H_{19}NO_4S$ and that this was, in fact, the molecular formula, was confirmed by the mass spectrum which showed a parent ion at 321 mass units.

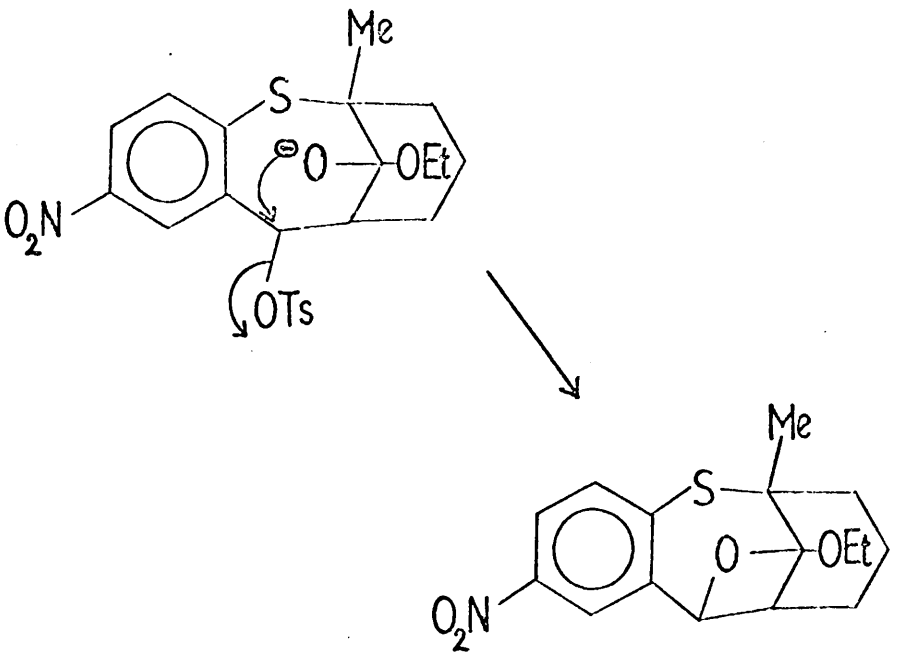
Thus, it appeared that tosylate had been eliminated and that an oxygen and two carbon atoms, the latter with their respective hydrogens, had been added to the remainder of the molecule. It seemed highly likely that these had come from the solvent and would be in the form of an ethoxy grouping. In fact, straight replacement of tosylate by ethoxyl would be compatible with the molecular formula of the product, but would not, of course, fit with the other data.

The problem of identifying the product, therefore, resolved itself into the postulation of a structure in agreement with the above data, and with the n.m.r. spectrum which is shown opposite.

The methyl singlet at 8.58τ is not far removed from its position in the starting tosylate (8.6τ). Thus, assuming that the bridge is still intact, then the effect of the substituent or substituents on the bridge must be similar to that of the carbonyl. The triplet centred at 8.7τ together with the split quartet at 6.3τ is reminiscent of an ethoxy group. This ethoxyl, as suggested earlier, could arise from entry of ethoxide into the molecule and the splitting of the usual methylene quartet into two similar, slightly-spaced groups of peaks is a phenomenon



(12)

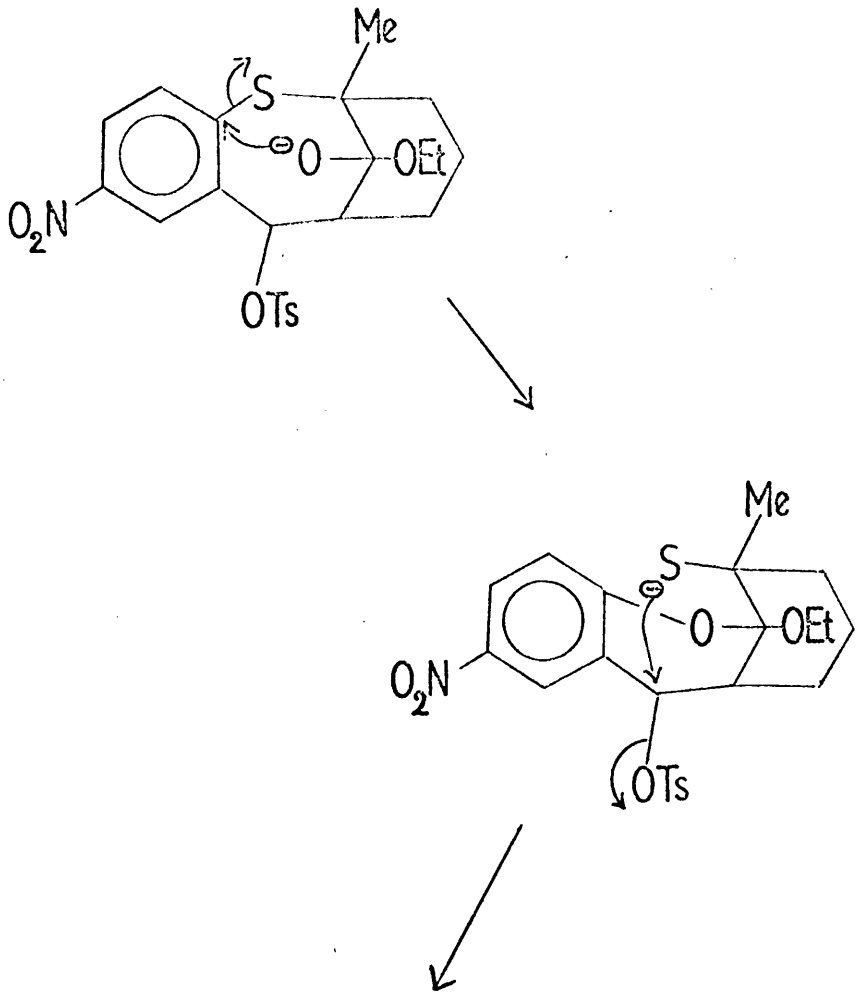


(13)

associated with an ethoxyl attached to asymmetric carbon. The effect arises from the non-equivalence of the methylene hydrogen atoms, in this situation.

It seemed reasonable, in the light of the information available, that the initial step in the reaction had been an attack of ethoxide on the bridge carbonyl, generating the hemi-acetal anion (12). This would also have been the first step in a normal bridge-scission reaction.

Direct attack of this anionic oxygen on the tosylate would produce the compound (13) whose structure incorporates an oxetane ring. This proposal was rather difficult to accept since the structure appeared to be very strained. Nevertheless, a brief excursion into the literature revealed that, for open chain analogues, i.e. mono-tosylates of 1,3 diols, oxetane formation, by treatment with base, was well known.[4] Further, the structure appeared to be compatible with the infrared and analysis data. A major stumbling block was encountered, however, when n.m.r. assignments were attempted. It was necessary to attribute the singlet at 6.1 τ and the triplet centre 7.32 τ to H_A and H_B respectively, of structure (13). It can be seen from the multiplicity of these signals that the coupling constant between H_A and H_B would require to be very small or zero. For this to be the case, the Karplus equation demands that such hydrogen atoms should be orthogonal. An inspection of molecular models showed that fulfilment of such a condition would produce near-intolerable stress on the already highly strained oxetane ring. On this account especially, we decided to look for a more suitable structure.



(14)

Having come so close to a molecule satisfying all requirements we became reasonably confident that ethoxide attack on the carbonyl group had indeed been the initial step in the reaction. Since the tosylate group had been eliminated, seemingly, in the basic environment, by a nucleophilic process, the problem was to find another nucleophile or potential nucleophile.

Given the correct ring conformation the anionic oxygen of the hemiacetal might not be far removed from that carbon of the benzene ring which is linked to sulphur. Attack at this carbon might generate mercaptide ion which could then expel tosylate. This process is represented on the facing page.

The unsymmetrical ketal (14) which results can be seen, from models, to be relatively free from strain, and fulfils the analytical and infrared obligations. For n.m.r. purposes most of the molecule is unchanged relative to the oxetane. (13). However, the dispositions of the H_A and H_B bonds, seen along the C_A C_B linkage are very nearly at right angles to one another. Therefore, from the Karplus curve the coupling constant between these hydrogens must of needs be very small. It must be admitted that the Karplus curve cannot be rigorously applied in this instance since it concerns itself with purely carbocyclic systems. However, it has been shown[5] that an electronegative substituent, such as oxygen or sulphur, on one of the linking carbon atoms of such a system has a depressive effect on the coupling constant, causing it to be closer to zero.

The remainder of the n.m.r. spectrum can also readily be accommodated by structure (14). The methyl group on the bridgehead is now bonded to a carbon atom which is α to two oxygen atoms and they could well have an effect on the chemical shift similar to that of the carbonyl. The ethoxyl is indeed attached to an asymmetric carbon atom and this would explain the observed splitting of the methylene quartet.

Since (14) was a ketal it appeared likely that it would be hydrolysed readily by dilute mineral acid. If the structure were correct, then the product of such a hydrolysis would probably be (15) which has a thia-bicyclo-octane system bonded to a p-nitrophenol residue.

A few milligrams of the suspected ketal were recovered unchanged from a brief contact with boiling 6N hydrochloric acid. However, when this material was heated with the ethanolic acid, under reflux conditions, on work up a dark oil was produced which showed both carbonyl and hydroxyl absorption in the infrared. The shortage and nature of the material allowed only a qualitative U.V. spectrum to be run. Nevertheless, peaks were observed at 233 and 315 mu. On the addition of base to the sample the peak at 315 mu became more intense and was shifted to 411 mu. This behaviour may be related to that of p-nitrophenol which absorbs at 225 and 312 mu. The latter peak, under the influence of base, shifts to 402 mu with considerably increased intensity.

It can be seen that these absorption maxima and shifts are of a similar order of magnitude, and together with the infrared evidence suggest that the hydrolysis product is indeed the compound (15).

It is clear that the presence of heterocyclic sulphur, at least when para to a nitro group, greatly complicates the reactions of these systems in base, and for a full understanding of such reactions an extended study would be required.

2. The Crystal Structure of 2,4-Dimethyl-7-nitro-3-oxo-2,4-trimethylene-benzo [b] thiepan-5-yl-p-bromobenzenesulphonate

Introduction

Following the synthesis of the alcohol (1), described in the previous section, it was considered that it would be desirable to know its detailed structure. A successful X-ray diffraction study of (1) or of a suitable derivative would serve a two-fold purpose. First, a solution of the structure by the X-ray method would provide irrefutable evidence that (1) had indeed been formed. Further, knowledge of the stereochemistry of this novel ring system would be of general interest and would provide a valuable insight into the reactions of the system.

Crystal Data

2,4 dimethyl-7-nitro-3-oxo-2,4-trimethylene benzo [b] thiepan-5-yl-p-bromobenzene sulphonate (M = 526) was prepared from the alcohol (1) by a standard method and was allowed to crystallise slowly from a methanol solution, yielding colourless needles of the brosylate.

A single crystal (cross section 0.12 x 0.06 mm) was mounted so as to rotate about the needle axis. By the use of aluminium wire as calibration, accurate cell dimensions were obtained from c - axis, oscillation, hk0 Weissenberg, and h0l precession photographs. The following information, concerning the unit cell, was obtained.

Monoclinic, a = 11.37 ($\pm$ .02)A^{o}, b = 18.93 ($\pm$ .03) A^{o}

C = 10.84 ($\pm$ .02) A^{o} β = 109.58^{o}

D_x (calculated density for Z = 4) = 1.59

Space Group (from systematic absences) $P2_1/C$ ($C^5 2h$)

V (Unit cell volume) = 2198.2A^{o3} .

Data Collection

Data were collected using a Hilger and Watts Y290 computer-controlled four circle diffractometer. The crystal was remounted together with its glass-fibre, on a goniometer suitable for use with the diffractometer, and set up as recommended.[6] Automatic data collection was then initiated using the strong reflections 5,0,0 and 0,10,0, as standards. The data were obtained as reciprocal lattice nets normal to the h - axis with l varying more rapidly than k.

The layers of h = 0 to 3 and a little of the fourth layer were collected without mishap. Unfortunately, at this juncture a malfunction of the instrument threatened to cause considerable delay, and so it was decided to process the then existing data which amounted to about a third of the total number of reflections.

Data Processing and Refinement

From a 3-dimensional Patterson vector map, which was computed as sections along y, the bromine atom was located, and a structure factor calculation based on this single bromine position yielded an R-factor of 64.7%.

An electron density distribution based on the signs of these structure factors indicated the positions of the two sulphur atoms. A second Fourier synthesis using the phases derived from the bromine and two sulphur atoms revealed a further 13 atoms and after a third round of calculation there were 26 recognisable atomic positions, which gave an

R-factor of 35.5% in a subsequent structure factor calculation.

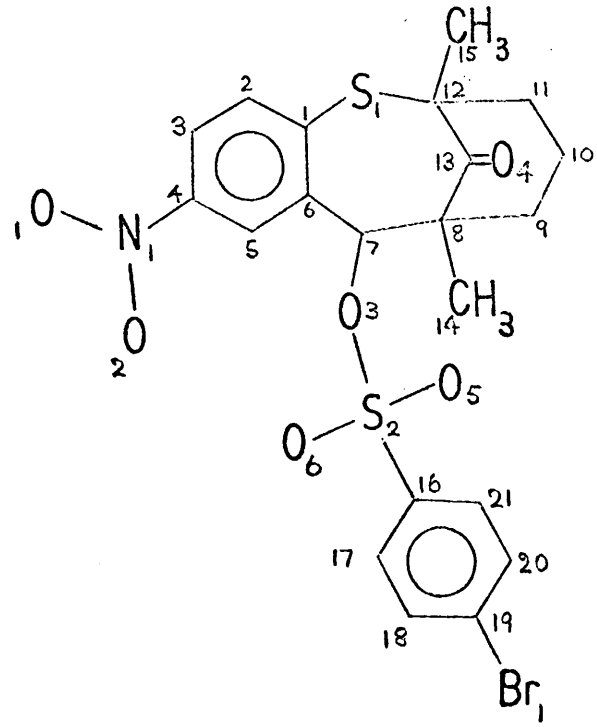
The Fourier sections, which were obtained in a coded, approximately scaled form, were contoured directly and drawn out on stacked glass sheets. The gross structure proved to be recognisable and was almost complete, apart from an uncertainty about the positions of some atoms owing to the lack of resolution in the x direction, which was in turn attributable to the shortage of data.

The near solution of the structure at this stage, being somewhat unexpected, was, therefore, all the more gratifying, and was an indication of the quality of the partial data obtained from the diffractometer. It was, nevertheless, appreciated that a structure derived with limited data would never refine satisfactorily, and so the refinement process was delayed until further data became available.

Generation of new life in the diffractometer permitted the collection of complete data to the end of 6,k,l, and, by design, the very strong planes of the 7 to 10,k,l, layers.

A structure factor calculation with all 31 atoms and utilising all available data then gave R = 40.2%, a figure which, on two Fourier refinement cycles, was reduced to 28.1 Two cycles of the least squares calculation using the program developed by Cruikshank and Smith further lowered R to 21.9%.

This present value is sufficient for our immediate purposes, since it leaves no doubt as to the authenticity of the structure. Further crystallographic work is being carried out on this structure by Drs. G. Ferguson and J. G. Sime of this department.


CH3
15
S1
12
11
2
1
3
13
O4
10
4
6
O1
N1
5
7
8
9
O3
CH3
14
O2
S2
O5
O6
16
21
17
20
19
18
Br1

Computing

The programs used in the various calculations were devised largely by members of the Glasgow crystallography group, including D. W. J. Cruikshank, J. G. F. Smith, J. G. Sime, D. McGregor, K. Muir and J. C. Speakman.

Nomenclature

For the purpose of simplicity in the assignment of atoms during the structure elucidation each of the carbon, oxygen and sulphur atoms were numbered - C_1, C_2 .....O_1, O_2 etc. The numbering system used, which was entirely arbitrary, is shown opposite.

Results and Discussion

Bond distances and angles in the molecule and various projection diagrams are shown on the following pages.

It is apparent that the thiepane ring exists as a boat, while the cyclohexane adopts a chair conformation, facts which are enlightening, if not particularly surprising and from which the observed exo position of the brosylate group, with respect to the thiabicyclodecane system, might readily have been predicted.

Errors in bond lengths are of the order of $\pm$ 0.04Å for bonds involving C, N or O; for sulphur bonds, the errors are $\pm$ 0.03Å.

In terms of the standard deviations the bond lengths and angles do not appear to show any marked inconsistencies with expected values.

ATOMIC POSITIONS

Br(1)	0.89890;	0.70328;	0.30534
S(1)	0.70162;	0.37041;	1.01006
S(2)	0.70980;	0.60996;	0.76965
O(1)	0.11355;	0.49127;	0.76642
O(2)	0.20535;	0.54668;	0.64672
O(3)	0.63841;	0.53865;	0.71691
O(4)	0.58108;	0.31141;	0.67245
O(5)	0.62012;	0.65972;	0.77602
O(6)	0.81567;	0.59[illegible];	0.88367
N(1)	0.20735;	0.50548;	0.73288
C(1)	0.55950;	0.40875;	0.92571
C(2)	0.44813;	0.38684;	0.96206
C(3)	0.33176;	0.42149;	0.89601
C(4)	0.32854;	0.47098;	0.79371
C(5)	0.42926;	0.48984;	0.75705
C(6)	0.54246;	0.45683;	0.82185
C(7)	0.66438;	0.47305;	0.79459
C(8)	0.70170;	0.41574;	0.70852
C(9)	0.84565;	0.41841;	0.73405
C(10)	0.92056;	0.39903;	0.87270
C(11)	0.74103;	0.31641;	0.88849
C(12)	0.74103;	0.31641;	0.88849
C(13)	0.66893;	0.34185;	0.75851
C(14)	0.62583;	0.42647;	0.56450

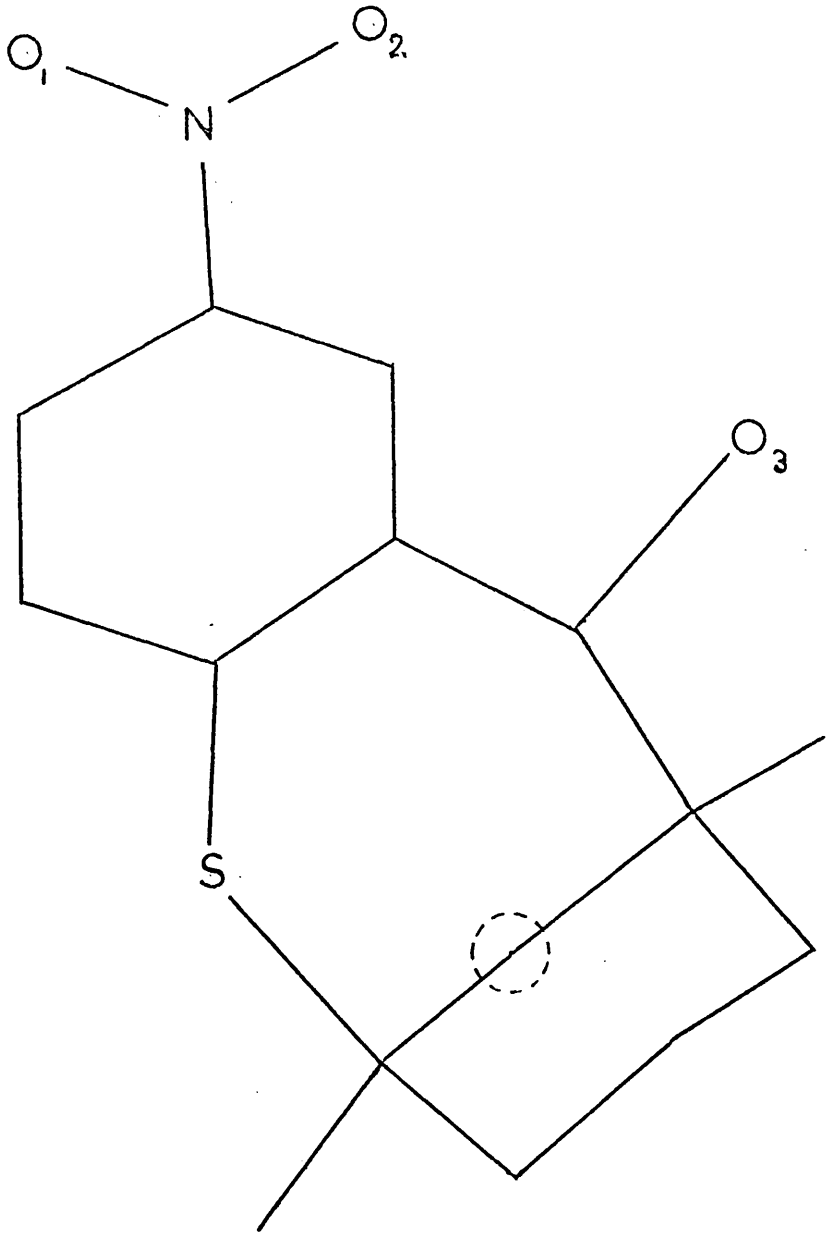
C(15)	0.71513;	0.23602;	0.89911
C(16)	0.76465;	0.63384;	0.64093
C(17)	0.88211;	0.61718;	0.64483
C(18)	0.92916;	0.63650;	0.54259
C(19)	0.83573;	0.67170;	0.44385
C(20)	0.72328;	0.69221;	0.43754
C(21)	0.68314;	0.67074;	0.53405

BOND LENGTHS

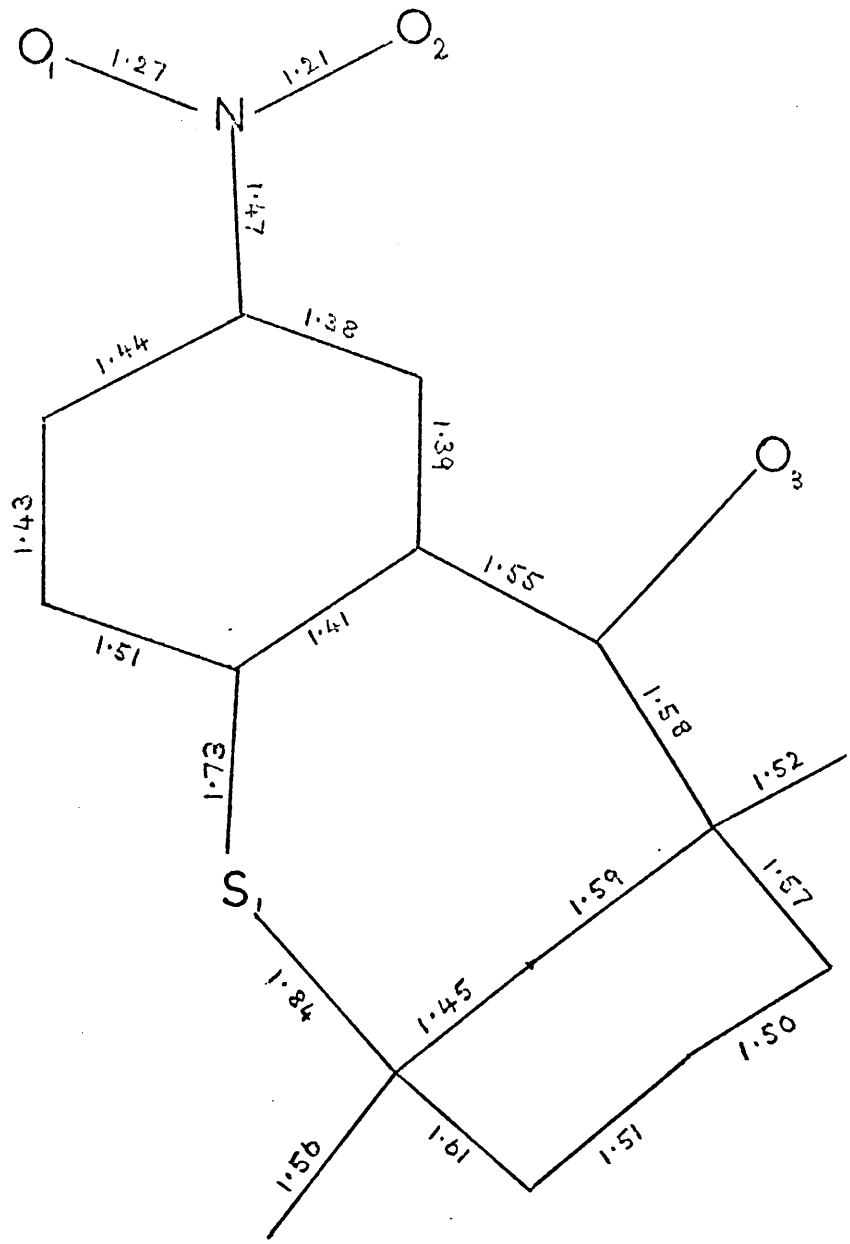
$N_1 - O_1$	1.27	$C_{11} - C_{12}$	1.61
$N_1 - O_2$	1.21	$C_{12} - C_{15}$	1.56
$N_1 - C_4$	1.47	$C_{12} - C_{13}$	1.45
$C_1 - C_2$	1.51	$C_{13} - C_8$	1.59
$C_2 - C_3$	1.43	$C_{13} - O_4$	1.25
$C_3 - C_4$	1.44	$C_7 - O_3$	1.47
$C_4 - C_5$	1.38	$O_3 - S_2$	1.58
$C_5 - C_6$	1.39	$S_2 - O_5$	1.41
$C_6 - C_1$	1.41	$S_2 - O_6$	1.43
$C_1 - S_1$	1.73	$S_2 - C_{16}$	1.77
$S_1 - C_{12}$	1.84	$C_{16} - C_{17}$	1.36
$C_6 - C_7$	1.55	$C_{17} - C_{18}$	1.43
$C_7 - C_8$	1.58	$C_{18} - C_{19}$	1.40
$C_8 - C_9$	1.57	$C_{19} - C_{20}$	1.32
$C_8 - C_{14}$	1.52	$C_{20} - C_{21}$	1.34
$C_9 - C_{10}$	1.50	$C_{21} - C_{16}$	1.40
$C_{10} - C_{11}$	1.51	$C_{19} - Br_1$	1.97

BOND ANGLES

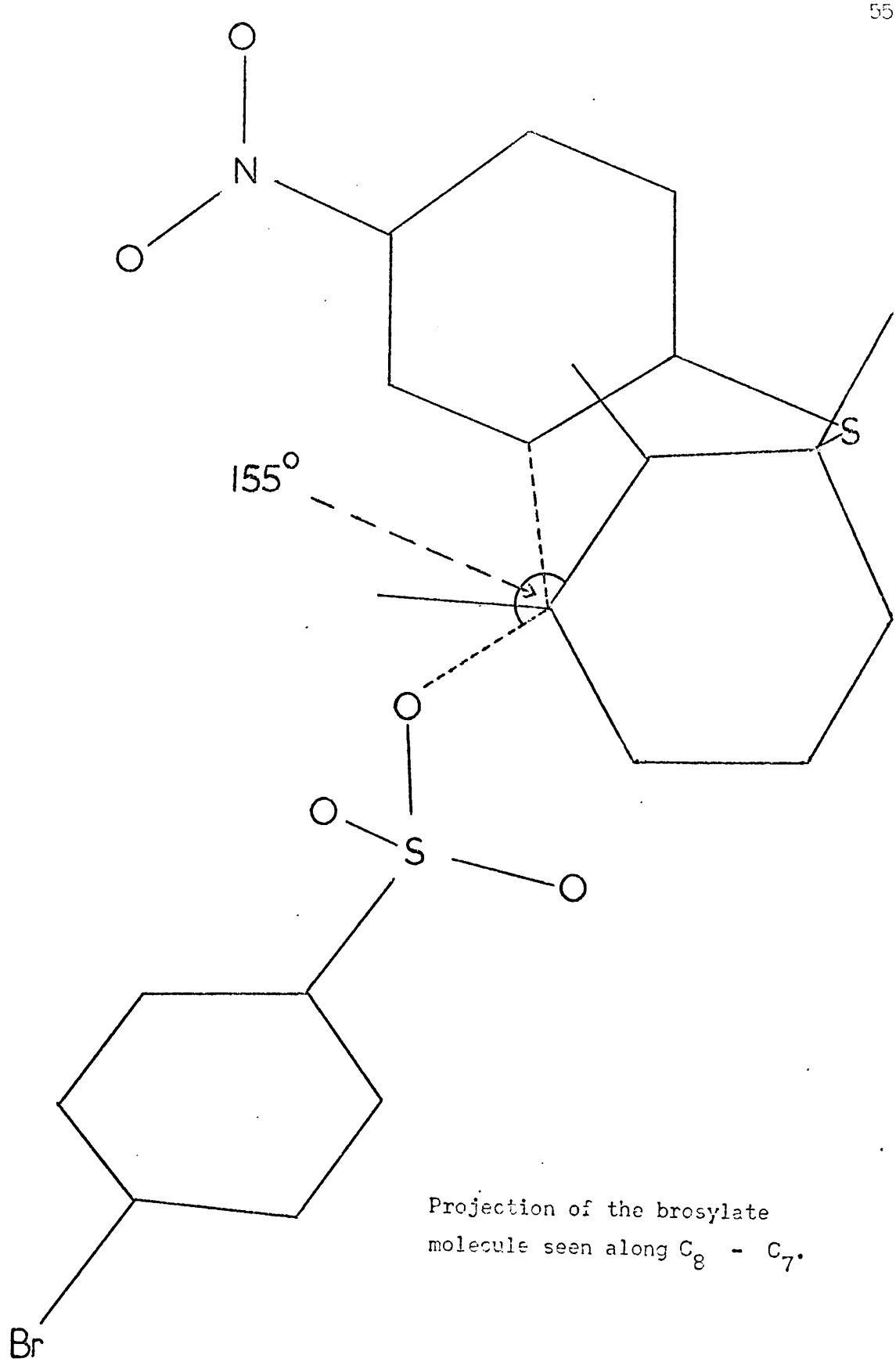
$O_1 - N_1 - O_2$	124	$C_9 - C_{10} - C_{11}$	112
$O_1 - N_1 - C_4$	122	$C_{10} - C_{11} - C_{12}$	114
$O_2 - N_1 - C_4$	114	$C_{11} - C_{12} - S_1$	109
$N_1 - C_4 - C_3$	114	$C_{11} - C_{12} - C_{13}$	108
$N_1 - C_4 - C_5$	120	$C_{11} - C_{12} - C_{15}$	109
$C_1 - C_2 - C_3$	117	$S_1 - C_{12} - C_{13}$	108
$C_2 - C_3 - C_4$	117	$S_1 - C_{12} - C_{15}$	113
$C_3 - C_4 - C_5$	126	$C_{13} - C_{12} - C_{15}$	110
$C_4 - C_5 - C_6$	117	$O_4 - C_{13} - C_8$	112
$C_5 - C_6 - C_1$	123	$O_4 - C_{13} - C_{12}$	128
$C_6 - C_1 - C_2$	119	$O_5 - S_2 - O_6$	120
$C_7 - C_6 - C_1$	113	$O_5 - S_2 - O_3$	107
$C_7 - C_6 - C_5$	123	$O_5 - S_2 - C_{16}$	109
$S_1 - C_1 - C_2$	118	$O_6 - S_2 - O_3$	109
$S_1 - C_1 - C_6$	123	$O_6 - S_2 - C_{16}$	108
$C_6 - C_7 - C_8$	115	$O_3 - S_2 - C_{16}$	102
$O_3 - C_7 - C_6$	105	$C_{17} - C_{16} - C_{21}$	121
$O_3 - C_7 - C_8$	106	$C_{17} - C_{16} - S_2$	122
$C_1 - S_1 - C_{12}$	105	$C_{21} - C_{16} - S_2$	118
$C_7 - C_8 - C_9$	116	$C_{16} - C_{17} - C_{18}$	123
$C_7 - C_8 - C_{13}$	105	$C_{19} - C_{18} - C_{17}$	109
$C_7 - C_8 - C_{14}$	110	$C_{20} - C_{19} - C_{18}$	131
$C_9 - C_8 - C_{13}$	109	$C_{20} - C_{19} - Br_1$	118
$C_9 - C_8 - C_{14}$	112	$C_{18} - C_{19} - Br_1$	110
$C_{13} - C_8 - C_{14}$	111	$C_{19} - C_{20} - C_{21}$	117
$C_8 - C_9 - C_{10}$	112	$C_{20} - C_{21} - C_{16}$	119



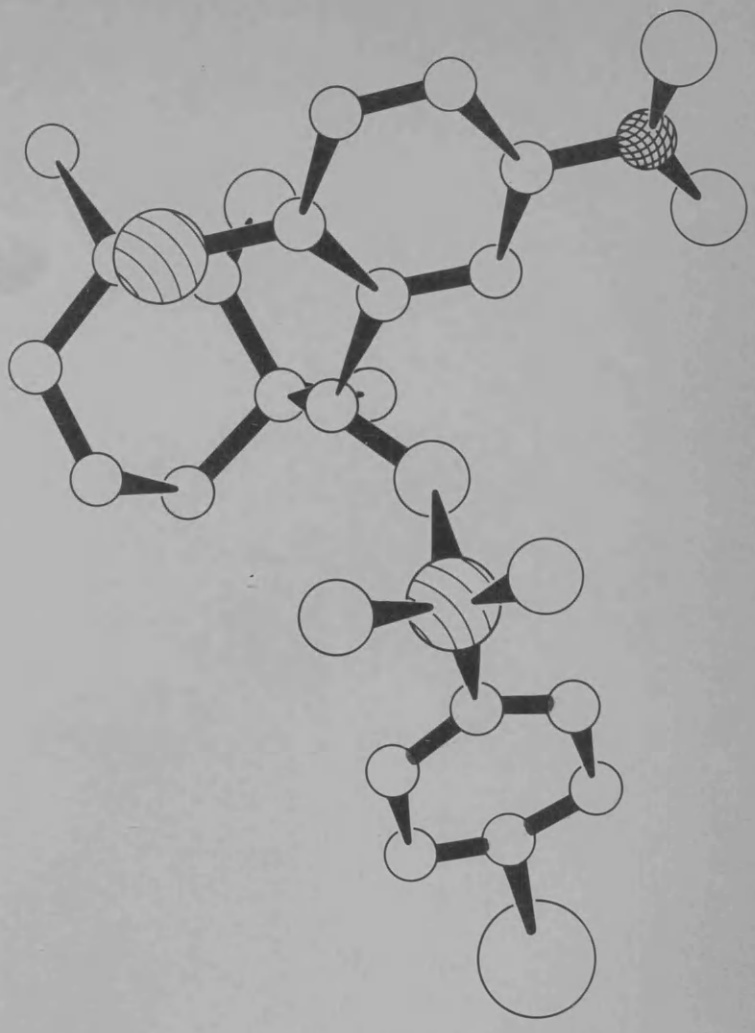
Projection diagram of the 2,4-trimethylene benzo [b] thiepane ring system seen along the carbonyl group (C_{13} - O_4).



Bond lengths for trimethylene benzo [b] thiepane ring system.



Projection of the brosylate molecule seen along C_8 - C_7.



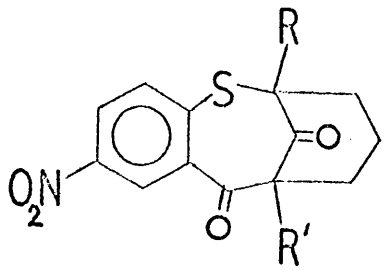
Projection diagram of the molecule (seen in relief).

From an inspection of the projection diagram on page 55 it appears that the angle between the $C_8 - C_{13}$ and the $C_7 - O_3$ bonds, seen along the $C_7 - C_8$ linkage, is approximately 155°. That is, it is 25° removed from collinearity, the apparent ideal for a bridge scission reaction, with tosylate elimination, to occur.

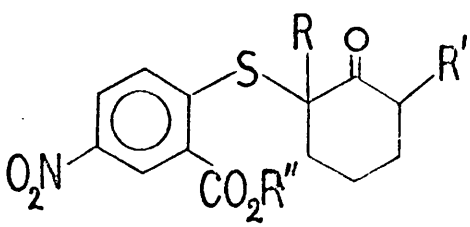
If we assume that the molecule exists in solution in the same form as in the crystal, an extrapolation which can admittedly be hazardous, then our results would indicate that this deviation (25°) is too much for the bridge cleavage to proceed easily.

If we make the less dangerous assumption that nor-methyl tosylate (11) exists in the same conformation as (10) then we may more readily interpret, in terms of models, the reaction leading to ketal (14).

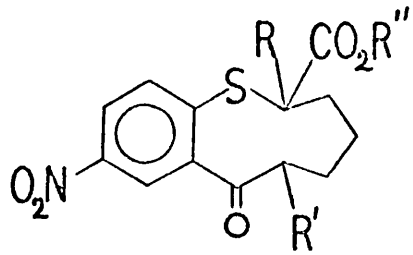
If ethoxide were to attack from the cyclohexane side of the bridge carbonyl in (11) then the oxy-anion produced would indeed be within striking distance of the aromatic ring, as postulated earlier. The resultant mercaptide ion can also be seen to be sufficiently close to the tosylate-bearing carbon to make the suggested tosylate displacement credible.



R = Me, R′ = Me. (16)
R = Me, R′ = H. (17)



(a)



(b)

(X), R = Me, R′ = Me, R″ = Me.
(Y), R = Me, R′ = H, R″ = Me.
(Z), R = Me, R′ = H, R″ = Et.

2,4 Trimethylene benzo [b] thiepan-diones and their cleavage with base

Our failure to obtain simple splitting of the 2,4 trimethylene benzo [b] thiepane ring system by the use of tosylates prompted another approach to the problem.

It was reasoned that oxidation of keto-alcohols (1) and (2) to β-diketones would furnish a system which would undergo facile cleavage with alkali.

The diketones (16) and (17) were obtained in good yield by Jones oxidation of the appropriate alcohols, and were characterised by the usual analytical and spectroscopic methods.

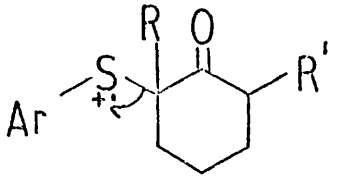
It was apparent that from an alkaline cleavage of these diketones there would be two possible products in each case, depending upon the preferred site of nucleophilic attack. It is known that several factors can influence the products obtained from such reactions. These include hindrance to the approach of base by neighbouring groups, the relative electrophilicity of carbon atoms of the respective carbonyls, and the direction of enolisation of the β-diketone. This last factor was insignificant in our case since (16) cannot enolise, and (17) is virtually non enolisable. Thus, any product, or products, obtained from cleavage of these diketones was likely to be controlled by the other factors.

Diketone (16), on treatment with sodium methoxide in refluxing methanol, yielded a single product (X), of molecular formula $C_{16}H_{19}NO_5S$. It was clear from this, and from spectral evidence, that cleavage had

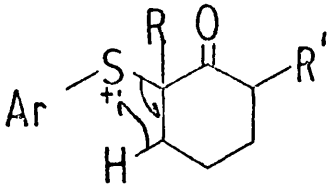
occurred, the methyl ester being easily recognised in the n.m.r. spectrum. However, in the absence of suitable standard compounds it was exceptionally difficult, from the evidence available, i.e. analysis, infrared and U.V. spectra, n.m.r. spectrum, to determine which cleavage product had been obtained, the cyclohexanone derivative (Xa) or the medium-ring keto-ester (Xb). This was largely because the effect of a sulphur atom on the neighbouring group frequencies was not well understood, and the extent of deconjugation of the aryl-carbonyl function in (Xb), on account of ring strain, was a matter for conjecture.

The methyl signals in the n.m.r. of X were shifted from 8.49 τ and 8.99 τ to 8.61 τ and 9.05 τ respectively, when the solvent was changed from $CDCl_3$ to benzene. These shifts can be seen to be of the same order of magnitude and hence tend to support the cyclohexanone-type structure (Xa) since with the alternative compound (Xb) a considerably greater difference in the size of shift between the two methyls might have been expected. (Plane rule).[7] This was, however, little more than weak circumstantial evidence, because of the lack of information about the conformation (Xb) would adopt.

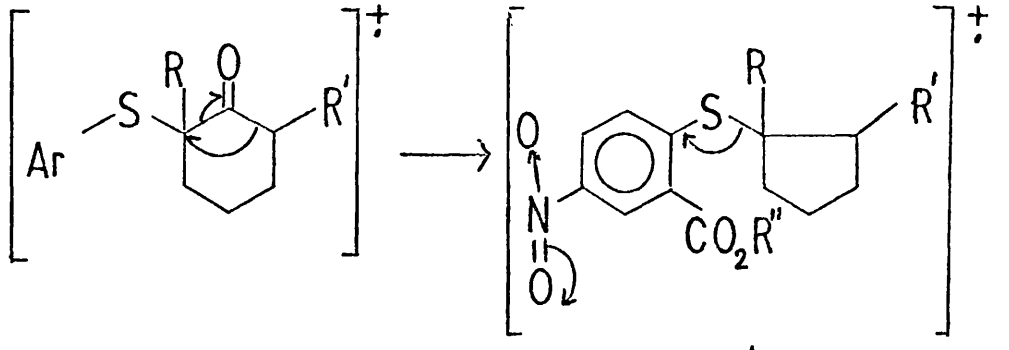
A similar difficulty of product identification was encountered when diketone (17) was split by methoxide or ethoxide, in each case yielding a unique product (Y) or (Z) respectively, each of whose spectral properties were comparable with those of the other and with the properties of (X). (For an n.m.r. comparison see table (2)). It appeared therefore that a similar type of cleavage had occurred in all three reactions.

(A) 

(18) X, Y, m/e 212 (14·5, 8 %)
(19) Z, m/e 226 (10 %)

(B) 

(20) X, Y, m/e 213 (30, 18 %)
(21) Z, m/e 227 (24 %)

(C) 

X, R = Me, R' = Me, R'' = Me
Y, R = Me, R' = H, R'' = Me
Z, R = Me, R' = H, R'' = Et

(22) X, m/e 97 (100 %)
(23) Y, Z, m/e 83
(100, 100 %)

Strong evidence as to the direction of cleavage was provided by a mass spectral study of these compounds.

A study of the fragmentation of the thioethers (X), (Y) and (Z) in the mass spectrometer revealed that a considerable degree of parallelism exists in their cracking patterns. The fragmentations can readily be interpreted in terms of the cyclohexanone structures (Xa), (Ya) and (Za) respectively, and mechanisms have been proposed for the three principal fragmentation pathways.

The first of these processes leads to the abundant ion at $^{m}/_{e}$ 212(18) observed for (X) and (Y), which can be readily explained by scission of the aliphatic carbon - sulphur linkage, and a similar process applied to (Z) leads to the significant ion at $m/_{e}$ 226(19)(See mechanism (A)).

An interesting variation of this process may occur to give the ions at $m/_{e}$ 213 (20) for (X) and (Y) and $m/_{e}$ 227 (21) for (Z). It involves transfer of a hydrogen atom from the cyclohexanone ring to sulphur forming a mercaptan ion. Such processes are well known[8] and recent labelling studies[9] on aliphatic thioethers have shown that hydrogen-transfer occurs mainly, though not exclusively, from the β-position, utilising a four-membered transition state, as shown in (B).

Finally, the ions occurring at $m/_{e}$ 97 for (X), and $m/_{e}$83 for both (Y) and (Z) provide the most abundant of the spectra, (the abundancies of all ions in each of the respective fragmentations are expressed as percentages of the appropriate base peak). The difference of 14 mass units between the aforementioned $m/_{e}$ 97 and $m/_{e}$ 83 peaks

suggested that the fragmentation leading to these ions involved cracking of the cyclohexanone ring ((X) has an additional methyl substituent compared with (Y) and (Z)). The peaks can be explained in terms of an extrusion of carbon monoxide from the cyclohexanone ring followed by aliphatic C - S cleavage with the charge remaining with the resultant cyclopentane (22,23). Such a process would be encouraged by the electron withdrawing effect of the nitro group. The loss of carbon monoxide (28 mass units) was corroborated by the presence of metastable peaks at ca. 269 and ca. 283 mass units respectively in the spectra of (Y) and (Z).

The fragmentations observed in the mass spectra cannot readily be accommodated by the cyclononyl keto-esters (Xb), (Yb) and (Zb). Hence, this study provides strong, if not incontrovertible evidence that the structures obtained from the base cleavage reactions are in fact (Xa), (Ya) and (Za).

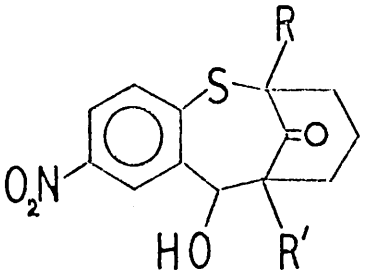
If this is the case, then our results are in agreement with the findings of Bradley and Robinson[10], who postulated that where a choice exists, β -diketone cleavage occurs so as to yield the stronger acid (with aqueous base) or the ester of the stronger acid (with alkoxide). It is probable that the nitro-aromatic acids derived from (Xa), (Ya) and (Za) would be considerably stronger than those obtained from the corresponding medium-ring esters (Xb), (Yb) and (Zb).

Thus it appears that the carbonyl bridge is also reluctant to cleave under these conditions.

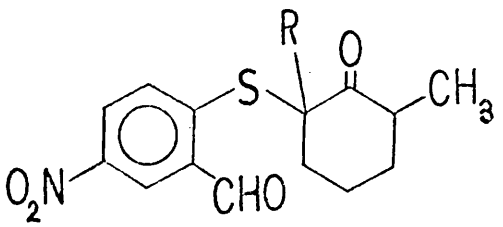
One further bridge cleavage attempt was made. It was suspected

that replacement of the cyclohexanone ring of the diketones by a cyclopentanone ring would increase bridge strain, and would, in addition, cause less hindrance to the approach of a nucleophile to the bridge carbonyl. These factors, it was reasoned, might be enough to allow scission.

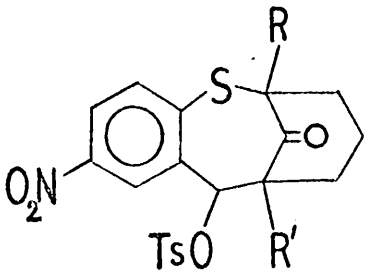
Oxidation of alcohol (24), obtained from a reaction of the reagent with 2-methylcyclopentanone, yielded diketone (25), which was then treated with methoxide as before. A single product was obtained whose mass spectrum was comparable with those of the previous products, and so it seems that even in this instance scission of the diketone system gives the aromatic ester (26).



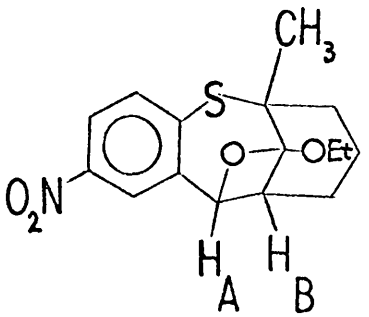
(1), R=Me, R′=Me
(2), R=Me, R′=H
(3), R=CO_2Et, R′=Me



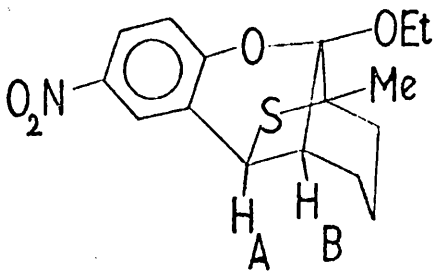
(4), R=CO_2Et



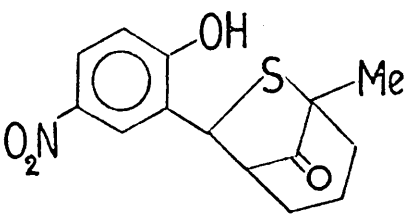
(10), R=Me, R′=Me
(11), R=Me, R′=H



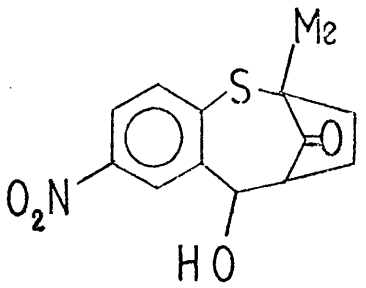
(13)



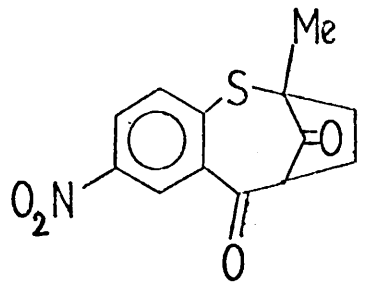
(14)



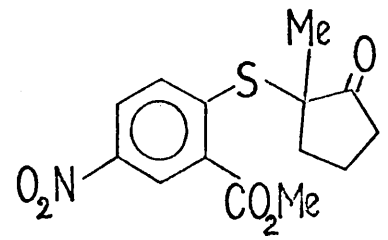
(15)



(24)



(25)



(26)

Experimental Section

Experimental Section

Melting points (m.p.) were taken on a Kofler microscope hot-stage. Infrared spectra were run as Nujol mulls on a Unicam S.P. 200 infrared spectrophotometer except where indicated in the text. Ultraviolet spectra were measured in 95% ethanol. Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Perkin Elmer R.10 60 Mc/s spectrometer using tetramethyl silane as internal standard. Mass spectra were run on an A.E.I. M.S. 12 instrument.

N.m.r. spectra were recorded in $CDCl_3$ solution and a table of pertinent data is given after the experimental section for chapters II and III.

Experimental - ChapterII

Section 1

2-Formyl-4-nitrobenzenesulphenyl chloride

Dry chlorine was passed into a suspension of 2,2 diformyl, 4,4 dinitrophenyl disulphide (30.1 g) in dry ethylene chloride with continuous stirring, at ambient temperature, for 1½ hours. The reaction mixture was then warmed until all the solid product had dissolved and the hot solution filtered. On cooling the resultant orange solution, sturdy yellow needles of the product were obtained (27.9 g) m.p. (on fast heating, 140 - 160°C with resolidification to the starting disulphide which melts at 262°C).

On slow heating only the melting point of the disulphide was observed after a steady decomposition above 120°. (Found: C,38.5; H, 1.7; N, 6.6. $C_7H_4NO_3ClS$ requires: C, 38.35; H, 1.8; N, 6.5%)

ν_{max} 1640, 1520, 1345

Warming the sulphenyl chloride with ammonia yielded yellow crystals of benzisothiazole (5) m.p. 151°

(lit. 151°C) [7]

Acetals (12) and (11)

Treatment of the reagent (0.25 g) with boiling methanol (20 ml) for 15 minutes, followed by cooling produced colourless needles of the acetal m.p. 168 - 169 (from methanol). (Found: C, 47.2; H, 4.0; $C_{18}H_{20}N_2O_8S_2$ requires C, 47.4; H, 4.4%)

A similar reaction with ethanol produced the corresponding ethyl

acetal which was identical in m.p., mixed m.p. and i.r. spectrum with an authentic sample.

2-Formyl-4-nitrobenzenesulphonyl chloride (13)

Sulphenyl chloride (1 g) was added portionwise conc to nitric acid (2 ml) contained in a small conical flask. The vigorous reaction which ensued was allowed to subside before each subsequent portion was added. After complete addition a yellowish solid could be seen. The excess HNO_3 was pipetted off as far as possible and water (5 ml) was added. The solid was filtered off (0.8 g), washed with water, dried, and recrystallised from carbon tetrachloride affording the sulphonyl chloride as colourless plates m.p. 93 94°. (Found: C,33.9; H, 1.9; N, 5.9. $C_7H_4ClNO_5S$ requires; C, 33.7; H, 1.6; N, 5.6 %).

ν_{max} 1695, 1540, 1375, 1360, 1175.

Alternative preparation of (13)

Chlorine was passed into a stirred suspension of 2,2 diformyl-4,4 dinitrophenyl disulphide in 10% aqueous acetic acid (5 ml) for 2 hours. Gradually, during the reaction, the yellow appearance of the disulphide disappeared and a cleaner suspension developed. The whitish solid was filtered off and the clear filtrate cautiously diluted with water with swirling until no further lightening in colour could be seen on further addition of water. The solid formed was collected and recrystallised from carbon tetrachloride affording material (0.6 g) identical in all respects to the authentic sample of the sulphonyl chloride.

Hemiacetal (14)

In preparations of 2-chloro-5-nitrobenzaldehyde, recrystallisation of the crude product (whose aqueous suspension was neutral to indicator paper) from ethanol, afforded fine needles of a compound which showed no carbonyl absorption in the infrared. This material melted, on fast heating, between 71 and 75°C (cf. aldehyde 80°C), and on resolidification, regenerated the aldehyde. A solution of the compound in ethanol containing aqueous NaOH when treated with dilute hydrochloric acid (6N) precipitated a colourless solid which proved to be the aldehyde. A sample of the no-carbonyl compound was submitted for analysis. (Found: C, 46.6; H, 4.2; N, 5.9. $C_9H_{10}ClNO_4$ requires: C, 46.65; H, 4.3; N, 6.05 %) The compound was thus formulated as the hemiacetal (14).

2-Benzoyl-4-nitrobenzenesulphenyl chloride (15)*

2,2 - dibenzoyl-4,4 - dinitrophenyl disulphide (18) was prepared by the method of Fries.

Dry chlorine was passed into a solution of the disulphide (4.05 g) in dry ethylene dichloride (40 ml) until a heavy yellow ppt. was obtained. The solid was recovered by filtration augmented by further crops, and recrystallised to give fine yellow needles of the product m.p. 128 - 130° (from benzene/petrol). (Found: C, 53.3; H, 2.8; N, 4.55. $C_{13}H_8ClNO_3S$ requires: C, 53.15; H, 2.7; N, 4.8 %).

The product was sensitive to light and slowly decomposed to give 2,2 -dibenzoyl-4,4 -dinitrophenyl disulphide.

A solution of (15) (0.11 g) in benzene (0.5 ml) and ammonia (0.88, 0.5 ml) was refluxed for 10 minutes. From the benzene layer a product was recovered, which crystallised as fine colourless needles m.p. 124° (lit. 124°) (Found: C, 61.1; H, 3.3; N, 10.9. Calcd. for $C_{13}H_8N_2O_2S$: C, 60.9; H, 3.15; N, 10.9 %)

2-benzoyl-4-nitro benzenesulphonyl chloride

To nitric acid (0.5 ml) was added, slowly, 2-benzoyl-4-nitro benzenesulphenyl chloride. After the vigorous reaction a colourless solid separated out. The acid medium was diluted with water (5 ml) and the solid product was filtered off (0.025 g). Recrystallisation from carbon tetrachloride gave the sulphonyl chloride m.p. 149 - 150° as colourless plates. (Found: C, 47.7; H, 2.5; N, 4.3.

* H. Keogh, B.Sc. thesis, Glasgow 1967.

$C_{13}H_{18}ClNO_5S$ requires: C, 47.9; H, 2.5; N, 4.3 %).

ν max 1670, 1535, 1350

λ max 253 mu (ε 22,000)

Alternative preparation of above

Chlorine was passed into a stirred suspension of 2,2-dibenzoyl, 4,4 dinitrophenyl disulphide (0.5 g) in 10% aqueous acetic acid for 2 hours. The colourless solid formed was filtered off and proved to be product. Further product was obtained by dilution of the filtrate with water until addition produced no lightening. The combined samples of product (0.41 g) were recrystallised from carbon tetrachloride and were identical in all respects to an authentic sample of the sulphonyl chloride.

Section 3

2-Acetyl-5-nitrobenzo /b/ thiophene

Halide (0.5 g) was stirred in acetone (5 ml) for 2 hours. The colourless ppt formed was collected by filtration (440 mg), and recrystallised to give the thianaphthene m.p. 183° (from ethanol).(lit.172°) (Found: C, 54.25; H, 3.5; N, 6.5; $C_{10}H_7NO_3S$ requires: C, 54.3; H, 3.2; N, 6.3 %).

ν max 1665, 1510, 1345

λ max 277 (ε 25,000)

In another experiment, the sulphenyl chloride was stirred with acetone at ice temperature for 20 minutes. The solid remaining in the bottom of the flask on collection proved to be sulphenyl chloride. The whole was then returned to the reaction flask and stirred at room temperature for 10 minutes. The solid then apparent was filtered off. This material showed no-OH in the infrared and the spectrum was that of the acetyl thianaphthene. In no experiment was an aldehyde or the aldol isolated.

2-Methyl-2-propionyl-3-hydroxy-5-nitro-2,3-dihydrobenzothiophene (25)

The finely powdered reagent (5 g) was stirred in diethyl ketone (25 ml) at ice temperature for 3 hours. After a further 10 hours at ambient temperature, the bulk of the diethyl ketone was removed in vacuo The residual oil was crystallised from carbon tetrachloride affording the

product (4 g) m.p. 96 - 97°C. (Found: C, 54.1; H, 4.7; N, 5.1. $C_{12}H_{13}NO_4S$ requires: C, 53.9; H, 4.9; N, 5.2 %).

ν Max 1713, 1530, 1345.

λ max 342 (ε12,500)

Treatment of aldol (25) with nitrogen base in acetic acid.

To a small conical flask were added acetic acid (40 drops) and piperidine (5 drops) . When the white vapour had dispersed aldol (30 mg) was added to the flask. It dissolved almost immediately, on shaking, to give a clear, pale-yellow solution. The flask was stoppered and shaken at intervals for a short time. After 1 hour, an aliquot was removed and diluted with water producing colourless needles of the starting aldol. The U.V. spectrum of the acetic solution was checked several times over a fortnight but no significant change was observed.

A similar result was obtained when the aldol was treated with diethylamine in acetic acid in the same way.

2-Methyl-2-acetyl-3-hydroxy-5-nitro-2,3-dihydrobenzothiophene (27)

The sulphenyl chloride (0.5 g) was stirred in ethyl methyl ketone (5 ml) at ice temperature for 2 hours and then for 1 hour at ambient temperature. After standing a further 2 hours the solution was filtered (to remove small amount of disulphide) and concentrated in vacuo giving a yellow oil. The oil was recrystallised (carbon tetrachloride) to give the alcohol (0.39 g) m.p. 95°C. A sample was crystallised for analysis from methanol/water. (Found: C, 52.4; H, 4.4;

N, 5.6. $C_{11}H_{11}NO_4S$ requires C, 52.2; H, 4.4; N, 5.5 %)

ν max 3500, 1685, 1520, 1345

λ max 341, (ε 12,000)

2,2-Diacetyl-3-hydroxy-5-nitro-2,3-dihydro benzothiophene (28)

The reagent (220 mg) was stirred at room temperature with acetyl acetone (1 ml) for 40 minutes. Ice water (10 ml) was added and the yellow oil formed was induced to solidify with water and dried to give the crude product (270 mgs). Recrystallisation from benzene/petrol afforded the aldol m.p. 134°. (Found: C, 51.3; H, 3.9; N, 4.8. $C_{12}H_{11}NO_5S$ requires: C, 51.25; H, 3.9; N, 5.0 %)

ν max 3510, 1705, 1520, 1345

2-Acetyl-2-carbethoxy-3-hydroxy -5-nitro dihydrobenzothiophene (29)

The finely powdered reagent (1 g) was stirred in ethyl aceto-acetate (2 ml) at ambient temperature for 2 days, and then the reaction mixture was allowed to stand for 1 week. No solid was observed. When the protecting drying tube was removed, however, after a short time a crystalline precipitate was seen to have formed. This material was filtered off (0.7 g) and recrystallised to give colourless needles of the aldol m.p. 111° (from benzene/petrol). (Found: C, 50.1; H, 4.2; N, 4.3. $C_{13}H_{13}NO_6S$ requires: C, 50.2; H, 4.2; N, 4.5 %)

ν max 3550, 1745, 1700, 1520, 1350.

λ max 338 mu (ε 12,000)

Spiro-aldol (30)

The sulphenyl chloride (2 g) was stirred in cyclohexanone (3 ml) for 12 hours at ambient temperature. The whole was dissolved in benzene and the benzene solution extracted successively with water, bicarbonate, and again with water, dried and concentrated in vacuo to give a brown oil. The oil could not be persuaded to produce any solid and was extracted with boiling petrol, (3 x 50 ml). These extracts were combined and on cooling and standing over-night, crystalline material was formed. It was crystallised from benzene/petrol to give material m.p. 95°. (Found: C, 57.7; H, 4.6; N, 5.0. $C_{13}H_{13}NO_4S$ requires: C, 55.9; H, 4.7; N, 5.0 %).

ν max 3500, 1695, 1510, 1340.

λ max 342 mu.

2,2-Dimethyl-3-oxo-5-hydroxy-7-nitro-benzo [b] thiepane (31)

The sulphenyl chloride (4.9 g) and methyl isopropyl ketone (15 ml) were stirred together at room temperature. After about ½ hour, almost all the halide was seen to have dissolved. Stirring was stopped after 14 hours and the solid material which had been formed in the reaction was filtered off. (3.9 g). The solid material was found to be light in colour and crystalline, and was recrystallised to give the alcohol m.p. 160° (from acetic acid). (Found: C, 53.7; H, 4.7; N, 5.3. $C_{12}H_{13}NO_4S$ requires: C, 53.9; H, 4.9; N, 5.2 %).

ν max 3500, 1690, 1520, 1550

λ max 263, 315 mu

Treatment of the reagent with ketones at ambient temperature (in acetic acid)

The reagent (0.5 g) was stirred with small excesses of acetone, ethyl methyl ketone, diethyl ketone and dibenzyl ketone, respectively in acetic acid (2 ml) for 12 hours.

For the first three ketones no reaction was observed and the starting material was readily recovered.

With dibenzyl ketone the silica gel of the protecting tube was discoloured suggesting the evolution of HCl. After a further 36 hours, the yellow solution was cautiously diluted with water producing a yellow oil. The oil was washed successively with water, ethanol, petrol and allowed to stand for 2 days. Some crystallisation was seen to have occurred. Addition of carbon tetrachloride (2 ml) allowed better separation of the crystals which were collected by filtration (80 mg) m.p. 165° (from CCl_4).

ν_{max} 3550, 1690, 1520, 1340

2-Benzoyl-5-nitrothianaphthene (33)

The sulphenyl chloride (0.1 g) together with acetophenone (0.1 g) in glacial acetic acid was heated under reflux. It dissolved almost immediately and soon light-coloured crystals were seen to form in the reaction medium. After 1 hour, the reaction mixture was allowed to cool producing further crystallisation. The solid (90 mg) was collected by filtration and recrystallised to give colourless needles of the thianaphthene product m.p. 218° (from acetic acid). (Found: C, 63.4;

H, 3.0; N, 5.1. $C_{15}H_9NO_3S$ requires: C, 63.6; H, 3.2; N, 4.95 %).

ν max 1635, 1520, 1350

λ max 286 mu (ε 11,700)

2-Methyl-5-nitro-benzo[b]thiophene (34) and 2,4-dimethyl-7-nitro-4,5 dehydrobenzo[b]thiepan-3-one (35)

Reagent (5 g) was heated with diethyl ketone (10 ml) in refluxing acetic acid (100 ml). After $1\frac{1}{2}$ hours, the solution was allowed to cool and water (ca 1 vol.) was added. On short standing the oil which separated out became solid, and was chromatographed in benzene on silica gel. The early fractions produced colourless needles of a compound which showed no carbonyl absorption in the infrared. It was recrystallised affording the benzothiophene (1.2 g) m.p. 110° (from ethanol). (Found: C, 55.75; H, 3.6; N, 7.2. $C_9H_7NO_2S$ requires: C, 56.0; H, 3.65; N, 7.25 %)

ν max 1340, 1520 cm^{-1}

λ max 306; 266; 253; (ε 5700; 15900; 17000)

Following (34) from the column was a compound (showing carbonyl absorption) which was also recrystallised from ethanol yielding the thiepanone (0.25 g) m.p. 147 - 149° (Found: C, 57.5; H, 4.2; N, 5.8. $C_{12}H_{11}NO_3S$ requires: C, 57.8; H, 4.45; N, 5.6 %).

ν max 1660, 1510, 1345

λ max 294 (ε 19000)

λ max 245
NaOH

A similar experiment using ethyl methyl ketone in place of diethyl ketone on work up yielded an oil which solidified as before. When this solid was chromotographed as above, only one product was obtained from the column. This material was identical with respect to infrared spectrum, U.V. spectrum, m.p. and mixed m.p. with methyl benzothiophene (34).

Reagent and diethyl ketone alone

The reagent (0.5 g) was heated in diethyl ketone (10 ml) under reflux for 1½ hours. The excess ketone was removed in vacuo. The remaining oil was reluctant to solidify but had a U.V. spectrum superimposable on that of aldol (25). Trituration with carbon tetrachloride gave a solid (0.17 g) whose infrared spectrum was identical to that of (25). No change in U.V. was observed in the material obtained when the mother liquors were allowed to evaporate to dryness.

2-Propionyl-5-nitrothianaphthene (36)

Sulphenyl chloride (0.5 g) was mixed with ethyl methyl ketone and the mixture heated under reflux. After 1 hour, the excess ketone was removed in vacuo and ethanol (5 ml) added to the residual oil. A solid separated out and was recovered by suction filtration (30 mg). The spectral properties of the solid were reminiscent of the acetyl thienaphthene. A sample of the solid was purified to give the propionyl thianaphthene m.p. 215° (from ethanol) . (Found: C, 56.5; H, 3.9;

N, 6.2. $C_{11}H_9NO_3S$ requires: C, 56.2; H, 3.9; N, 6.0 %).

ν max 1660, 1525, 1340

λ max 277 mu (ε 20,000)

Ethanol was removed from the mother liquors of the above filtration and the residue was triturated with CCl_4 giving yellowish crystalline material (0.49 g) whose infrared and U.V. spectra were superimposable on those of the aldol obtained from the sulphenyl chloride and methyl ethyl ketone. No trace of any other aldol or of the methyl thianaphthene was found.

Reaction with benzoyl acetone

Reagent (0.1 g) together with benzoyl acetone (0.1 g) were heated in refluxing acetic acid (4 ml) for 1½ hours. Cooling and dilution with water produced a solid product (0.065 g) m.p. 172 - 175° The product was recrystallised from ethanol and proved to be identical in infrared, m.p. and mixed m.p. with the acetyl benzothiophene (24).

Reaction with dibenzoyl methane

Halide (0.1 g) and dibenzoyl methane (0.13 g) were heated in refluxing acetic acid (2 ml) for 1½ Hours. Colourless needles of a product separated out and on cooling these were filtered off (0.12 g) m.p. 216 - 218°. The infrared spectrum was superimposable with that of the benzoyl thianaphthene (33) and m.p. and mixed m.p. (216 - 218) were identical.

2-Phenyl-5-nitro-benzo[b]thiophene(38)

Sulphenyl chloride (0.5 g) together with dibenzyl ketone (1 g) in glacial acetic acid (25 ml) was heated under reflux. A clear brown solution was obtained and after 2 hours the bulk of the acetic acid was distilled off leaving a solution (5 ml) which on cooling produced a crystalline solid m.p. 188° (from acetic acid). (Found: C, 65.55; H, 3.6; N, 5.5; $C_{14}H_8NO_2S$ requires: C, 65.9; H, 3.55; N, 5.5 %).

2-Pentanoic acid-5-nitro benzo[b]thiophene(39)

Reagent (1 g) and cyclohexanone (1 ml) were heated under reflux in glacial acetic acid (25 ml) for 2 days. The acetic solution was allowed to cool and diluted with water until addition gave no further lightening. The brown solid produced was recovered, dissolved in ether and the ether solution extracted with bicarbonate. The bicarbonate layer was separated off, acidified (6NHCl) and extracted with chloroform. The chloroform extract was washed with water, dried and concentrated to a brown solid which was then recrystallised to give the acid (0.34 g) m.p. 119 - 121° (from ethanol). (Found: C, 56.2; H, 4.7; N, 5.0. $C_{13}H_{13}NO_4S$ requires: C, 55.9; H, 4.7; N, 5.0 %).

ν max 1690, 1505, 1340

λ max 254; 266; 306 mu (ε 25,000; 22,000; 7,700)

Cyclopentanone, cycloheptanone and cyclooctanone were submitted to similar reaction conditions and worked up in the same way. The results obtained (for weights of reagent of 1 g) are shown below:

Ketone	Heating Time	Yield of acid
cyclopentanone (1 ml)	1½ hrs.	0.26 g
cycloheptanone "	"	0.24 g
cyclooctanone "	"	0.125 g

The technique was modified as described in the text and details for these reactions are shown below.

2-Butanoic acid-5-nitro-benzo[b] thiophene (40)

Reagent (0.5 g) was heated with cyclopentanone (1 ml) in glacial acetic acid (5 ml) for 5 minutes. The solution was then allowed to stand at ambient temperature and after 16 hours brown crystalline needles had formed. These were filtered off (75 mg). To the mother liquors was added conc. sulphuric acid (3 drops) and the whole warmed on the steam bath (with swirling) for 10 minutes. The cooled solution was diluted with water (1 volume) until addition produced no further lightening in colour. The solid formed was collected (0.45 g) and recrystallised to give the acid m.p.138-140°C (from benzene).

ν_{max} 1700, 1510, 1345

A good analysis was not obtained for this compound. (Found: C, 54.7; H, 4.7; N, 5.5. $C_{12}H_{11}NO_4S$ requires: C, 54.3; H, 4.2: N, 5.3 %)

The early product was not positively identified. The analysis figures were C, 58.75; H, 4.1; N, 5.9 %, and are nearly compatible with a compound obtained by elimination of two molecules of water between two molecules of cyclopentanone and disulphide (4).

2-Hexanoic acid-5-nitro benzo[b]thiophene (41)

Reagent (0.25 g) together with cycloheptanone (0.5 ml) was heated in refluxing glacial acetic acid for 1½ hours. To the cooled solution was added sulphuric acid (3 drops) and the whole was allowed to stand on a steam bath for 20 minutes. Thereafter, the solution was diluted with water (1 volume) and the resultant oil induced to solidify by scratching. The solid was recrystallised to give the acid (0.2 g) m.p. 105°C (from aqueous acetic). (Found: C, 57.2; H, 5.2; N, 4.5. $C_{14}H_{15}NO_4S$ requires: C, 57.3; H, 5.2; N, 4.8 %)

ν max ca. 1705, 1505, 1345

2-Heptanoic acid-5-nitro benzo [b] thiophene (42)

Sulphenyl chloride (0.5 g) was heated under reflux conditions with cyclooctanone (1 ml) in glacial acetic acid (5 ml) for 1½ hours Cooling produced precipitation. Conc. sulphuric acid (5 drops) was added to the solution and the whole allowed to sit on a steam bath for

20 minutes. On cooling, the colourless crystals obtained were recovered by filtration (0.44 g). Further crops gave a total yield of the acid (0.6 g) m.p. 113 - 118° (from ethanol). (Found: C, 58.7; H, 5.6; N, 4.4. $C_{15}H_{17}NO_4S$ requires: C, 58.6; H, 5.6; N, 4.6 %).

ν max 1700, 1510, 1340

N. M. R. TABLE I

sulphenyl chloride (8)	s(1H) - 0.2 τ
sulphonyl chloride (13)	s(1H) - 0.21 τ
acetyl benzothiophene (24)	s(3H) 7.27 τ
aldol (25)	t (3H) centre 8.89 τ, J = 6 - 7 c/s; s(3H) 8.35 τ; quartet (2H) centre 7.26 τ J = 6 - 7 c/s; d, centre 6.97 τ, J = 6 c/s (disappears with D_2O); d (1H) centre 4.35 τ, J = 6 c/s (singlet with D_2O)
aldol (27)	s(3H) 8.34 τ; s(3H) 7.65 τ; diffuse d(1H) (disappears with D_2O); diffuse d(1H) centre 4.40 τ (singlet with D_2O).
aldol (29)	t(3H) centre 8.7 τ; J = 7 c/s; s (3H) 7.65 τ; broad signal ca. 6.87 τ (disappears with D_2O); quartet (2H) centre 5.66 τ, J = 7 c/s; diffuse d (1H) centre 4.22 τ (singlet with D_2O)
spiro - aldol (30)	broad s (1H) 6.35 τ (sharpens with D_2O); signal 7.3 τ (disappears with D_2O)
aldol (31)	s (3H) 8.76 τ; s(3H) 8.52 τ; signal (1H) 8.75 τ (disappears with D_2O); diffuse multiplet ca. 4.7 τ (clears with D_2O).
Methyl benzothiophene (34)	d (3H) centre 7.36 τ, J = 1 - 2 c/s; broad s (1H) 2.84 τ .

thiepanone (35)	d(3H) centre 8.53 τ, J = 7 c/s; d (3H) centre 7.79 τ, J = 2 c/s; quartet (ca. 1H) centre 6.52 τ, J = 7 c/s; broad s (ca. 1H) centre 2.71 τ, J = 2 c/s.
benzothiophene acid (39)	methylene signals (8H) 6.9 - 8.4 τ; broad singlet (1H) 2.84 τ; broad signal ca. 2.3 τ (disappears with D_2O)
benzothiophene acid (40)	methylene signals (6H) 6.8 - 8.1 τ; broad s, 2.87 τ; broad signal ca. 2.5 τ (disappears with D_2O)

Experimental - Chapter III

Section 1

2,4-Dimethyl-7-nitro-3-oxo-2,4 trimethylene benzo/b/thiepan-5-ol

The reagent (2 g) was stirred in 2,6-dimethyl-cyclohexanone (3 ml) at ambient temperature. The reaction mixture became brown and sludgy and after 24 hours the solid material was filtered off. This was washed with petroleum ether and recrystallised from benzene to give colourless crystals (1.45 g) which showed hydroxyl and carbonyl absorptions in the infrared. The material showed two spots on T.L.C. of which the less polar was by far the larger. Further crystallisation produced pure material m.p. 177 - 178° (from benzene) (Found: C, 58.7; H, 5.6; N, 4.5. $C_{15}H_{17}NO_4S$ requires: C, 58.6; H, 5.6; N, 4.6 %).

ν max 3550, 1690, 1520, 1350.

λ max 261 (ε6,700), 324 (ε5300).

2-Methyl-7-nitro-3-oxo-2,4-trimethylene benzo/b/thiepan-5-ol

The reagent (5 g) was stirred, at ambient temperature, in 2-methyl cyclohexanone (10 ml) for 3 hours. The greyish solid formed was recovered by filtration (3.2 g) and washed thoroughly with carbon tetrachloride. It was shown, furthermore, by T.L.C. that the mother liquors still contained a good deal of the product. The solid showed spectral characteristics similar to those of the alcohol from 2,6-dimethyl cyclohexanone. A sample was crystallised for analysis yielding the product m.p. 179 - 180° (from aqueous acetic acid). (Found: C, 57.1;

H, 5.0; N, 4.6. $C_{14}H_{15}NO_4S$ requires: C, 57.3; H, 5.2; N, 4.8 %).

ν max 3500, 1685, 1525, 1350.

λ max 261 (ε7,400), 322 (ε5,970).

2-Carbethoxy-4-methyl-7-nitro-3-oxo-2,4 trimethylene benzo[b]thiepan-5-ol (3)

and

2-carbethoxy-2-(2-formyl-4-nitrophenyl sulphide)-6-methyl cyclohexanone (4)

The reagent (1 g) was stirred at ambient temperature in 2-carbethoxy-6-methyl cyclohexanone. The reaction became sludgy in appearance and after 2 days stirring was stopped. Benzene (5 ml) was added to help separate the solid, which was recovered by filtration (0.5 g). This material showed only one spot when run on T.L.C. and was recrystallised to give aldol (3) m.p.211°.(from ethanol). (Found: C, 55.7; H, 5.05; N, 3.8, $C_{17}H_{19}NO_6S$ requires: C, 55.9; H, 5.2; N, 3.8 %).

ν max 3550, 1700, 1530, 1350.

λ max 261; 316 (ε10,800; 7,700)

The mother liquors of the filtration were evaporated to small volume and light petroleum (b.p. 40/60) was added slowly. A light-coloured precipitate was seen to form, and addition was stopped when no further precipitation was observed. This material (0.3 g) also showed one spot on T.L.C., much less polar than that of alcohol.(3) It was recrystallised affording the aldehyde (4) m.p. 126° (from ethanol).

(Found: C, 55.7; H, 4.9; N, 4.1. Calcd. for $C_{17}H_{19}NO_6S$: C, 55.9; H, 5.2; N, 3.8 %).

ν_{max} 1725, 1690, 1530, 1345

λ_{max} 327. (ε9,300)

A suspension of ester (3) (0.5g) in 2-carbethoxy-6-methyl cyclohexanone (1 ml) in a small conical flask was treated with a vigorous stream of dry HCl gas for about half a minute. The flask was then stoppered and the suspension stirred at ambient temperature for 1 week. Thereafter, pet. ether (bp 40/60) was added slowly and the colourless solid obtained was filtered off (0.43 g). This material proved to be identical to the starting material with respect to infrared spectrum, m.p. and mixed m.p.

Aldehyde (4) (17 mg) was mixed in a small conical flask with 2-carbethoxy, 6-methyl cyclohexanone (0.25 ml) and dry HCl gas passed as before for half a minute. After 5 minutes, most of the solid had dissolved to give a pale yellow solution, but after a further half hour, considerably more solid was in evidence. After 16 hours, pet. ether (2 ml) was added and the colourless crystalline solid (12 mg) filtered off. This material was identical to alcohol-ester (3) in infrared spectrum, m.p. and mixed m.p.

Tosylate (10)

To the alcohol (1.75 g) in a minimum of dry pyridine was added a small excess of tosyl chloride (1.4 g) in a similar solution. The reaction mix was allowed to stand overnight in a stoppered flask, and thereafter poured into ice-water. The oil which separated immediately was extracted in chloroform, the chloroform layer-washed thoroughly with water, dried (anhyd. magnesium sulphate), and the solvent removed under reduced pressure. This left a light-yellow oil which on treatment with methanol gave a white crystalline solid (1.05 g) which proved to be tosylate. Two further crops, (totalling 0.65 g) consisted largely of starting material and were resubmitted to tosylation conditions. The tosylate was recrystallised for analysis yielding colourless plates m.p. 148° (from methanol). (Found: C, 57.3; H, 4.8; N, 3.1. Calcd. for $C_{22}H_{23}NO_6S_2$: C, 57.3; H, 5.0; N, 3.0 %).

ν_{max} 1700, 1525, 1340

Tosylate (11)

To the alcohol (2 g) dissolved in a minimum of dry pyridine, was added a small excess of tosyl chloride (1.36 g) also in a minimum of pyridine. After being allowed to stand overnight (18 hours) in a stoppered flask, during which time large crystals of pyridine hydrochloride separated out, the reaction was poured on ice water. The oil which was immediately formed soon solidified and was extracted from the

aqueous phase in chloroform. The chloroform layer was washed succesively with dilute HCl, H_2O, $NaHCO_3$, H_2O and dried (anhyd. $MgSO_4$) The dried chloroform solution was concentrated in vacuo leaving an oily residue (which still smelled slightly of pyridine). On addition of methanol (20 ml) the oil solidified. The solid thus formed was recrystallised from methanol to give the tosylate m.p. 167 - 168°. The mother liquors were concentrated to give a second crop providing a total of 2.28 g of product, which was one spot on the T.L.C. (Found: C, 56.4; H, 4.6; N, 3.3. Calcd for $C_{21}H_{21}NO_6S_2$: C, 56.4; H, 4.7 ; N, 3.1 %).

ν max : 1705, 1525, 1345

Ethoxide treatment of tosylate (10)

Tosylate (o.25 g) was heated with ethanol (5 ml) containing a catalytic amount of ethoxide (from 2-3 mg Na), under reflux conditions for $2\frac{1}{2}$ hours. Thereafter, the reaction was allowed to cool and to stand for a further 12 hours when it was poured into water (15 ml), acidified (6NHCl) and the aqueous phase extracted with chloroform. The chloroform layer was dried (anhyd Mg SO_4) and concentrated in vacuo to a yellow oil whose infrared spectrum was exactly similar to that of the starting tosylate.

Ethoxide treatment of tosylate (11)

Tosylate (0.2 g) was heated with ethoxide employing conditions

similar to the last experiment. After work-up, 0.16 g of the starting tosylate was recovered.

Further ethoxide treatment of tosylate (11)

The tosylate (0.1 g) was covered with an ethanolic solution (5 ml) of sodium ethoxide (from 10 mg Na). The reaction mixture was stirred at room temperature for 4 hours, after which time little reaction appeared to have occurred since much of the solid remained undissolved. This solid (80 mg) was recovered, shown to consist of starting material, and returned to the reaction vessel. The reaction was then warmed with stirring (at about 60°C) for 16 hours, when the reaction solution had become clear and red-orange in colour. Water (3 ml) was added to the cooled solution and the whole was acidified (dil. HCl) and extracted with ether. The yellow ether layer was separated off, washed with water, brine, again with water, dried (ahlyd. Mg SO_4) and concentrated in vacuo to a yellow oil, which on crystallisation from ethanol produced colourless needles (0.015 g) of a T.L.C. pure product. The mother liquors were shown (by T.L.C.) to contain largely the same material. An analytical sample was prepared giving the product m.p. 126 - 127° (from ethanol). (Found: C, 59.9; H, 6.0; N, 4.2. $C_{16}H_{19}NO_4S$ requires: C, 59.8; H, 6.0; N, 4.4 %).

ν Max 1520, 1340

λ max 329; 235 (10,000; 11,000)

Brosylate of (1)

To the alcohol (0.3 g) in dry pyridine was added a similar solution of brosyl chloride in the usual manner. The reaction mixture was set aside for 8 hours. It was then poured into ice water and the brosylate which separated was dissolved in chloroform and this solution well washed with water to remove pyridine. The chloroform layer was dried ($MgSO_4$) and worked up in the usual manner to give the brosylate m.p. 180 decomp. (from methanol) (Found: C, 48.1; H, 3.7; N, 2.8. $C_{21}H_{20}NO_6S_2Br$ requires: C, 47.9; H, 3.8; N, 2.7 %).

ν max 1700, 1525, 1345

Section 3

2,4-trimethylene-2,4-dimethyl-3,5-di-oxo-7-nitro-benzo[b]thiepane

Alcohol (1) (0.25 g) was dissolved in a minimum of acetone and Jones reagent was added dropwise with swirling. The chromate ester precipitated out of solution. Addition was continued until the liquid became orange in colour. The reaction was allowed to stand for a few minutes and then methanol was added slowly until the orange colouration was completely dispelled. Iced water (3 volumes) was poured on the reaction and the product separated out as a whitish solid (0.22 g). It was recrystallised yielding the diketone m.p. 140 - 141° (from benzene/petrol). (Found: C, 58.8; H, 5.2; N, 4.7. $C_{15}H_{15}NO_4S$ requires: C, 59.0; H, 4.95; N, 4.6 %).

ν max 1720, 1695, 1520, 1350

λ max 255 (ε7500) 331 (ε4,300)

Diketone (17)

Alcohol (2) (0.25 g) was dissolved in a minimum of acetone and Jones reagent added as before until an orange colour developed. After a few minutes this colour was dissipated by the addition of methanol. The product was precipitated out by addition of iced water, collected and crystallised for analysis giving the diketone 129.5 - 130.5 (from ethanol). (Found: C, 57.85; H, 4.55; N, 4.5. $C_{14}H_{13}NO_4S$ requires: C, 57.7; H, 4.5; N, 4.8 %).

ν max 1700, 1690, 1530, 1350

λ max 261 (ε7900) 329 (ε4500)

Methoxide treatment of diketone (16)

The diketone (0.05g) was suspended in methanolic sodium methoxide (2 ml from 5 mg Na). Almost immediately, a red tinge appeared in the supernatant liquid. The diketone dissolved as the temperature was raised and after a reflux of $\frac{1}{2}$ hour, the bright red solution was allowed to cool. Water (1 volume) was added and the resultant alkaline medium was acidified (6 NHCl). The light-coloured precipitate formed was filtered off and recrystallised to give colourless needles (0.015 g) m.p. 110° (from ethanol). (Found: C, 57.3; H, 5.7; N, 4.0. Calc'd. for $C_{16}H_{19}NO_5S$: C, 57.0; H, 5.7; N, 4.15 %).

ν max 1715, 1690, 1520, 1340

λ max 341; 256 (ε 11,250 ; 7,300).

Methoxide treatment of diketone (17)

The diketone (0.25 g) was heated with methanolic sodium methoxide (5 ml from 8 mg Na). After 10 minutes the red reaction solution was allowed to cool. Water (10 ml) was added and the aqueous phase acidified (6NHCl), and extracted with chloroform. The chloroform layer was separated off, washed thoroughly with water, dried and concentrated in vacuo. The resultant yellow residue was crystallised from methanol as colourless needles (0.196 g) m.p. 143 - 144°. (Found: C, 55.6; H, 5.3; N, 4.2. $C_{15}H_{17}NO_5S$ requires: C, 55.7; H, 5.3; N, 4.3 %).

ν max 1715, 1695, 1515, 1340

λ max 254 (ε5900) 339 (ε8950).

Ethoxide treatment of diketone (17)

Diketone (0.105 g) was treated as before replacing methanol by ethanol. After work up, the product was obtained as colourless needles m.p. 146 - 147° (from ethanol). (Found: C, 56.8; H, 5.6; N, 3.9. $C_{16}H_{19}NO_5S$ requires: C, 57.0; H, 5.7; N, 4.15 %).

ν max 1710, 1700, 1515. 1345

Alcohol (24)

Alcohol (24) was prepared by stirring the reagent in 2-methylcyclopentanone. It was recrystallised affording the product m.p. 180° (from benzene/petrol).

ν max 3450, 1720, 1520, 1350.

It was characterised as its tosylate, which was obtained by the standard method, m.p. 191° decomp. (from benzene/petrol). (Found: C, 55.2; H , 4.4; N, 3.0. $C_{20}H_{19}NO_6S_2$ requires: C, 55.4; H, 4.4; N, 3.2 %)

ν max 1740, 1525, 1350

Diketone (25)

Alcohol (24) (0.2 g) was dissolved in a minimum of acetone and Jones reagent added dropwise until an orage colour developed. After a short time the orange colour was dispelled by the addition of methanol in the usual way, and then a 3 volumes excess of iced water was added. The product precipitated and was filtered off (197 mgs). A sample was prepared for analysis by recrystallisation from benzene-petrol (m.p. 173°). (Found: C, 56.4; H, 4.0; N, 4.9;. $C_{13}H_{11}NO_4S$ requires: C, 56.3; H, 4.0; N, 5.05 %).

ν max 1740, 1675, 1520, 1345

Methoxide treatment of diketone (25)

Diketone (0.2 g) was covered with methanol (5 ml) containing a catalytic amount of sodium, and heated under reflux. A red colour quickly developed in the solution and after 10 minutes, heating was stopped. Water was added (approx. 2 volumes) and the aqueous solution was acidified (1 drop 6NHCl). The yellow solid which precipitated was recrystallised from aqueous methanol to give T.L.C. pure material which showed carbonyl absorption at 1720 cm^{-1}. (110 mg). A sample was recrystallised for analysis yielding colourless needles m.p. 89 - 90° (from methanol). (Found: C, 54.4; H, 4.8; N, 4.4. $C_{14}H_{15}NO_5S$ requires: C, 54.4; H, 4.9; N, 4.5 %).

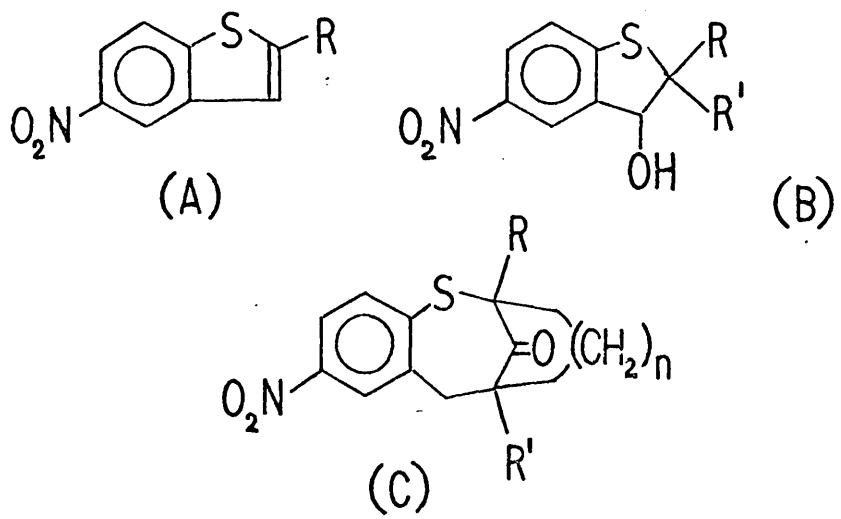
ν_{max} 1720, 1520, 1350

N. M. R. T A B L E 2

benzothiepane aldol (1)	s (3H) 9.00τ; s (3H) 8.60τ; signal ca. 7.55τ (disappears with D_2O); diffuse s (1H) (sharpens with D_2O).
" aldol (2)	s (3H) 8.58τ; s, 6.93τ (disappears with D_2O); d (1H) centre 2.19τ, J = 7 c/s; broad peak (1H) ca. 4.82τ.
" aldol (3)	Poor integration; s, 8.95τ; t, centre 8.75τ J, = 7 c/s; s, 7.9τ (disappears with D_2O); quartet, centre 5.79τ, J = 7 c/s.
aldehyde (4)	d(3H) centre 8.98τ J = 6 c/s; t (3H) centre 8.80τ, J = 7 c/s; quartet (2H) centre 5.80τ. J = 7 c/s; s (1H) - 0.48τ.
tosylate (10)	s (3H) 8.98τ; s (3H) 8.60τ; s(3H) 7.70τ .
tosylate (11)	s (3H) 8.60τ; s (3H) 7.65τ.
diketone (16)	s (3H) 8.81τ; s (3H) 8.44τ .
diketone (17)	s (3H) 8.41τ .
base cleavage products	
(X)	d (3H) centre 8.99τ; s (3H) 8.49τ; s (3H) 6.04τ .
(Y)	s (3H) 8.49τ; s(3H) 6.02τ .
(Z)	t (3H) centre 8.55τ, J = 7 c/s; s (3H) 8.50τ; quartet (2H) centre 5.54τ, J = 7 c/s

Conclusions

By reaction of the reagent with ketones, thianaphthenes of the form (A) have been synthesised, where R may be alkyl, acyl or aryl. Interesting examples were encountered where R = carboxylic acid residue. The method could probably be adapted to obtain the de-nitro, parent benzothiophene, system, and would as such provide a fairly general route to 2-substituted benzothiophenes.



2,3-Dihydro-compounds of the general formula (B), and which can be intermediate in the formation of (A) have been isolated and identified. Moreover, for selected ketones similar reaction conditions have provided a facile route to 2,3,4,5-tetrahydrobenzothiepins, which, for cyclic ketones, were part of a novel tricyclic system (C).

Only compounds with n = 2 or 3 have been described but it seems that the synthesis of compounds having n = 4,5, etc., should be feasible by this method.

The structure of one aldol of this tricyclic system (for n = 3) has been determined and should provide a good basis for interpretation of reactions of the system.

Finally some reactions of the system in base have been described and the products therefrom characterised by spectroscopic methods.

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SUMMARY

2-Formyl-4-nitrobenzenesulphenyl chloride has been synthesised and its reactions with ketones examined. A practical route to a range of 2-substituted, 5-nitro-benzo [b] thiophenes and certain 2, 3-dihydro aldols of the same system has been described.

By reaction of the sulphenyl chloride with isopropyl methyl ketone the 2, 3, 4, 5-tetrahydro benzo [b] thiepin system was formed. Extension of the latter reaction to include selected cyclic ketones permitted the synthesis of novel tricyclic analogues and the crystal structure of one member of the latter group has been unambiguously determined by the X-ray method. Some aspects of the behaviour of these tricyclic compounds, in basic environment, have been described.