THIETANE 1,1-DIOXIDE DERIVATIVES AS POTENTIAL
ANALGETICS OF THE METHADONE TYPE

by

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Date May 8, 1972
DEDICATION

To my parents.
Thietane 1,1-dioxide derivatives were synthesized as potential narcotic analgetics of the methadone type. Thietane 1,1-dioxides are conformationally more restricted than methadone and thus may be useful in elucidating the pharmacophoric conformation of methadone and related analgetics.

The reaction of \( \beta \)-dimethylaminostyrene with phenylmethanesulfonyl chloride in the presence of triethylamine gave a mixture of cis- and trans-2,4-diphenyl-3-dimethylaminothietane 1,1-dioxide and the acyclic isomer, benzyl 1-phenyl-2-dimethylaminoethenyl sulfone. Of the two cyclic isomers, the trans isomer was less stable and decomposed when heated in ethanol. The nature of the decomposition products indicated that the cyclization reaction was reversible. That the trans isomer formed to a greater extent than the more stable cis isomer suggested that thietane 1,1-dioxide ring formation was subject to steric approach control. No apparent correlation was observed between solvent polarity and the amount of acyclic isomer formed. trans-2,4-Diphenyl-3-dimethylaminothietane 1,1-dioxide could be isomerized to the cis and acyclic isomers in the presence of triethylamine and triethylamine hydrochloride.

In the reaction between \( \beta \)-dimethylaminostyrene and p-chlorophenylmethanesulfonyl chloride in the presence of triethylamine, evidence was obtained that only two cyclic isomers were formed. This indicated that the configuration of the enamine was maintained during cyclization. Reaction of the enamine with the sulfene derived from p-nitrophenylmethanesulfonyl bromide afforded cis-2-(4-nitrophenyl)-3-dimethylamino-4-phenylthietane 1,1-dioxide and benzyl 1-(4-nitrophenyl)-2-dimethylaminoethenyl
Submitting the 3-dimethylaminothietane 1,1-dioxides to the Cope elimination reaction gave the corresponding thiete 1,1-dioxides. Examination of the isomeric thiete 1,1-dioxides obtained from cis- and trans-2-(4-chlorophenyl)-3-dimethylamino-4-phenylthietane 1,1-dioxide provided evidence supporting the configurational assignment of the cis and trans isomers. With the p-nitro-substituted thietane 1,1-dioxide, only one elimination product was isolated, which was identified as 2-(4-nitrophenyl)-4-phenylthiete 1,1-dioxide.

Thermolysis of 2,4-diphenylthiete 1,1-dioxide, 2-(4-chlorophenyl)-4-phenylthiete 1,1-dioxide and 2-phenyl-4-(4-chlorophenyl)-thiete 1,1-dioxide gave chalcone, benzylidene p-chloroacetophenone and p-chlorobenzylidene acetophenone, respectively. Refluxing 2,4-diphenylthiete 1,1-dioxide in aqueous THF afforded 1,3-diphenylpropene-3-sulfonic acid. These results supported the proposal that thiete 1,1-dioxides undergo ring opening on heating to give sulfene intermediates. From the decomposition of 2,4-diphenylthiete 1,1-dioxide in refluxing ethanol, a ketonic sulfone was isolated and characterized as bis(1,3-diphenyl-3-oxopropyl) sulfone.

Michael addition of hydrogen cyanide to the thiete 1,1-dioxides followed by reduction to the primary amines and dimethylation gave the potential analgetics, 2,4-diphenyl-3-dimethylaminomethylthietane 1,1-dioxide, 2-(4-chlorophenyl)-3-dimethylaminomethyl-4-phenylthietane 1,1-dioxide and 2-(4-nitrophenyl)-3-dimethylaminomethyl-4-phenylthietane 1,1-dioxide. The fourth compound, 2,4-diphenyl-3-(1-dimethylaminoethyl)-thietane 1,1-dioxide, was prepared by addition of nitroethane to 2,4-diphenylthiete 1,1-dioxide followed by reduction and dimethylation. Configurational and conformational assignments for the four compounds were based on nmr evidence.
The mouse hot plate, mouse phenylquinone writhing and electrically stimulated guinea-pig ileum methods were used to measure analgetic activity. When tested by one or more of these methods, none of the four compounds showed significant activity.

Signatures of Examiners

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INTRODUCTION

The diphenylpropylamine class of narcotic analgetics, the first members of which were synthesized in Germany during World War II, has been extensively reviewed (1,2). The prototype and clinically most useful member of the group is methadone (6-dimethylamino-4,4-diphenyl-3-heptanone, 1). Methadone was the first synthetic analgetic which possessed only one asymmetric centre and was readily resolved into its enantiomeric forms. Analgetic testing of the enantiomers revealed that the (-)-isomer was approximately twice as potent as the racemate, whereas the (+)-isomer was virtually inactive. Subsequent investigation of the optical isomers of other diphenylpropylamines, including the sulfone analogue of methadone 2,
as well as members of other classes of synthetic analgetics possessing an asymmetric centre common to that of 1, indicated that the analgetic activity and morphine-like side effects resided predominantly in one isomer of each enantiomeric pair. As well, it was originally found that the active enantiomers were all configurationally related to R-(-)-alanine. These observations provided stereochemical evidence for the existence of an analgetic receptor (3).

It was proposed by Beckett and Casy that the analgetic receptor was a rigid entity whose topography was complementary to one of the surfaces of the conformationally immobile morphine molecule (3). A particular arrangement of three binding sites on the receptor was considered to account for the observed stereoselectivity. An effort was made to show how members of all important classes of narcotic analgetics could present similar structural features at these binding sites (4). In the case of methadone, evidence was obtained for a preferred conformation which was thought to facilitate association with the receptor (5). The preferred conformation apparently arose from an interaction between the lone pair electrons of the nitrogen atom and the electropositive carbon of the carbonyl moiety. Since a similar intramolecular interaction was possible in 2, it was assumed that the sulfone analogue possessed a preferred conformation similar to that of 1 (5).

As research progressed in the analgetic field, certain observations were made which could not be readily rationalized in terms of the Beckett and Casy receptor hypothesis. Perhaps the most significant of these, as pointed out by Portoghese (6), was the discovery that the more active enantiomers of synthetic analgetics possessing an asymmetric centre common to that of 1 were not all configurationally related. For example,
the configuration of the active antipode of 3, a member of the basic anilide class of narcotic analgetics, was found to be related to S-(+)- rather than to R-(-)-alanine (7). Portoghese proposed that such an inversion in receptor stereoselectivity could be explained in terms of there being more than one mode of binding of analgetics at the receptor. It was also suggested that the receptor was flexible rather than rigid, which would allow for the accommodation of a greater variety of structurally dissimilar, yet potent, narcotic analgetics (6).

Casy has investigated the preferred conformations of compounds 1 and 3 and found them to be significantly different (8,9). In support of Portoghese's concept he has proposed that if it is assumed that these preferred conformations are the same as those adopted by the analgetics at the receptor site, then it is probable that the mode of binding of 1 to the receptor differs markedly from that of 3. Again, it was felt that differing binding modes could account for the inversion of stereoselectivity shown by the receptor for the enantiomers of 1 and 3 (9,10).

Recently, Portoghese has further elaborated the concept of differing binding modes to rationalize the inversions in stereoselectivity seen when the more active isomers of methadone (1), the methadols (4a) and the methadol acetates (4b) are compared (11). It had been known for some time that, like the active enantiomer of 1, the more active diastereoisomers of
4b possessed the (R) configuration at C-6, whereas the more active isomers of 4a had a (6S) configuration. In an effort to explain these observations, the absolute configuration of the isomers of 4a and 4b at C-3 were determined. Correlation of the analgetic activities with the absolute configurations at C-3 for the four diastereoisomers of 4a revealed that the stereochemistry of this centre had a greater influence on activity than that at C-6 and that the two more active isomers both possessed the (S) configuration at C-3 and opposite configurations at C-6. With the methadol acetate diastereoisomers (4b), the reverse was true. The two more active isomers of 4b possessed the (R) configuration at C-6 and opposite stereochemistry at C-3. Portoghese has rationalized these results by assuming that there are several donor and acceptor hydrogen bonding dipoles situated in different locations on the receptor. In the case of methadone and the methadol acetates, interaction of the carbonyl groups of these molecules with donor hydrogen bonding dipoles gives rise to a mode of binding such that the configuration at C-6 is important--the (R) configuration allowing a more effective interaction with the receptor than the (S). With the
methadols, however, interaction of the alcohol group with an acceptor dipole on the receptor leads to a binding mode in which the C-3 asymmetric centre is orientated in a receptor environment that is sterically demanding, the isomers with the (S) configuration at this centre being more readily accommodated than the two with the (R) configuration. In addition to the nature of its hydrogen bonding group, the conformation of an analgetic molecule would determine with which particular receptor dipole hydrogen bonding occurred. Thus, methadone and the methadol acetates are not necessarily interacting with the same donor dipole (11).

It has been proposed that methadone exists in a preferred conformation when dissolved in aqueous solution (5, 8, 11). There is a difficulty, however, in applying this preferred conformation to stereostructure-activity relationship studies because, as has been pointed out (12), the preferred conformation of a drug molecule in solution is not necessarily the conformation of the molecule when bound to its receptor (pharmacophoric conformation). The reason for this is that mutual interactions between the drug molecule and receptor may quite possibly perturb the solution conformation (12). Thus, stereostructure-activity relationship studies employing methadone must contain a certain element of ambiguity which results from the assumption (as made by Casy (9)) that the preferred conformation resembles that adopted by the analgetic at the receptor site. It is possible that the use of conformationally restricted and rigid analogues of methadone may provide an answer to this problem. The concept of employing conformationally constrained derivatives of flexible pharmacological agents in such situations has been reviewed (12).

A few examples of conformationally restricted methadone analogues have appeared in the literature (13). Constraintment of \( 1 \) has involved
either bridging the aromatic rings, as in 5, or cyclizing the propionyl and basic groups to form a piperidine ring, as in 6. In general, such compounds have possessed a low order of analgetic activity or have been inactive (13).

The sulfone analogue of methadone 2 has been found to be as active as methadone and to possess the same enantiomeric potency ratio (1,3). Also, the proposal has been made that 2 interacts with the analgetic receptor in a preferred conformation similar to that of 1 (5). It was considered, therefore, that as an initial approach to constrained derivatives of diphenylpropylamine-type analgetics, the investigation of four-membered cyclic sulfone (thietane 1,1-dioxide) analogues of 2 would be of interest. A derivative of 2 incorporating the thietane 1,1-dioxide ring (7) would be conformationally much more restricted than 2 itself. Perhaps the most desirable of the thietane 1,1-dioxide analogues was 8, which is formally derived
from 2 by joining C-2 to C-5. Attempts to synthesize 8, however, have been unsuccessful (14).

As an alternative to 8, it was proposed that compounds of the type 9 be prepared and tested for analgetic activity. Although not as suitable as 8 because of the repositioning of one of the aromatic groups on the heterocyclic ring (from C-1 to C-4), the synthesis of 9 was considered to be worthwhile in view of the suggestion that only one of the phenyl substituents of diphenylpropylamine-type analgetics is involved in association at the receptor (2,3). By retaining the second phenyl ring in 9, it was hoped that some semblance of the solubility characteristics of 2 would be maintained. Although 9 lacked a methyl substituent α to the dimethylamino group, it was felt that this compound may still possess analgetic activity since the methadone analogue without the methyl substituent (normethadone) is known to be fairly active (2). The synthesis of the derivative of 9 possessing the α-methyl group was undertaken with the anticipation of observing augmented activity. Derivatives of 9 having para-substituents on one of the aromatic rings were also sought, as there was the possibility that such substituents might affect the activity of 9 as a result of an influence
on distribution and drug-receptor interactions.

The work described in this thesis was undertaken as part of a project to explore thietane 1,1-dioxide derivatives and similar novel heterocycles for various types of pharmacological activity. Such compounds may serve as useful pharmacological tools for expanding the knowledge of drug-receptor interactions.

The synthesis of thietane 1,1-dioxides and the chemical manipulation of compounds containing the thietane 1,1-dioxide ring are relatively new areas, a ready synthesis of the heterocycle having become available only as late as 1962. In the process of devising and effecting the synthesis of the compounds described herein, it was deemed appropriate and beneficial to explore, where possible, the intricacies of thietane 1,1-dioxide chemistry in order to provide a broader base for the synthesis of other thietane 1,1-dioxide compounds of potential pharmacological interest.

A limited number of thietane 1,1-dioxides have been investigated for various types of biological activity. In all cases they represented the initial cycloadducts from the reaction of enamines with sulfenes and thus possessed a tertiary amino group attached directly to C-3 of the heterocycle. Compounds of the type 10 (NRR' = dimethylamino, pyrrolidino, etc.)
were prepared as potential monoamine oxidase inhibitors. A significant level of inhibitory activity was not observed (15). A series of spiro-5-norbornene-2,2'-thietane 1',1'-dioxides (11, NRR' = pyrrolidino, piperidino, etc.) is the subject of a patent. Members of the series are apparently claimed for use as bacteriostatics, bactericides and veterinary sedatives (16). Screening a number of compounds based on structure 12 (R = methyl, benzyl, etc.) revealed no significant antibacterial, antiviral, hypotensive or antiinflammatory activity (17).
THIETANE 1,1-DIOXIDE CHEMISTRY

The synthesis of 3-aminothietane 1,1-dioxides by the interaction of aliphatic sulfonyl chlorides with enamines in the presence of triethylamine was first reported independently by two groups in 1962 (18,19). For example, addition of phenylmethanesulfonyl chloride (13) to a solution of the pyrrolidine enamine of isobutyraldehyde (14) and triethylamine gave 2,2-dimethyl-3-pyrrolidino-4-phenylthietane 1,1-dioxide (15) in 70 per cent yield (19). Later in the same year a similar reaction was reported in which addition of methanesulfonyl chloride to a solution of ketene diethylacetal (16) and triethylamine afforded 3,3-diethoxythietane 1,1-dioxide (17) in good yield (20). It was soon discovered that the cycloaddition occurred only with strongly nucleophilic olefins (20,21,22). Besides enamines and ketene
acetals, ketene O,N- and N,N-acetals (23,24) and ynamines (25,26) were subsequently found to yield four-membered cyclic sulfones.

The aliphatic sulfonyl chlorides that are used for the synthesis of thietane 1,1-dioxides are those which possess a hydrogen atom α to the sulfonyl group. It was postulated that formation of the heterocycle involved initial dehydrochlorination of the sulfonyl chloride by triethylamine to give a sulfene 18, which then underwent cycloaddition to the enamine or ketene acetal (19,20,21,27). The existence of sulfene intermediates

$$\text{R} \quad \text{CH} \quad \text{SO}_2\text{Cl} \quad + \quad (\text{Et})_3\text{N} \quad \rightarrow \quad \left[ \text{R} \quad \text{C} \quad \text{SO}_2 \right] \quad + \quad (\text{Et})_3\text{N}.\text{HCl}$$

was eventually demonstrated by the alcoholysis of aliphatic sulfonyl chlorides with deuterated alcohols in the presence of triethylamine, which gave monodeuterated but no polydeuterated sulfonate esters (28,29,30,31). These experiments were followed by the isolation of mesylfulfene (19) as its stable trimethylamine adduct 20. The reactions of 20 were the same as those brought about by treating mesylmethanesulfonyl chloride with triethylamine (22).
Recently, the first direct observation of free sulfene was made by obtaining its infrared spectrum at -196° (32).

The possibility that formation of 3-aminothietane 1,1-dioxides involved reaction of the enamine with the sulfonyl chloride directly, rather than with a sulfene intermediate, has been ruled out (22,27).

It is not known with certainty whether the cycloaddition of sulfenes with enamines is a concerted reaction (path a) or a two-step addition (path b) involving a zwitterionic intermediate 21. However, a two-step mechanism is apparently generally favored (22,33,34) and the intermediacy of a zwitterion has been invoked by various workers (35,36,37,38,39,40).

In support of path b, it has been pointed out that such a mechanism is preferable on the basis of the Woodward-Hoffmann selection rules (41), and that it provides a better explanation of the single orientation (dialkylamino group on C-3 as in 22) and of the fact that only strongly nucleophilic olefins are attacked by sulfenes (22). Also, the intermediate 21 allows for the formation of substitution product 23 by prototropy (path c) (34).
The reactions of phenylsulfene with 1-morpholinocyclohexene and 1-morpholinocyclopentene to give the corresponding thietane 1,1-dioxides, 24 and 25, were considered to be two-step processes involving dipolar intermediates (37). When cycloadduct 24 was crystallized from ethanol, N-benzylsulfonyl morpholine (26) was obtained. Refluxing 25 in ethanol afforded first the substitution product 27 and then the ketone 28. It was felt that these reactions established the reversibility of both stages of the reaction between sulfenes and enamines (37).
The isolation of an enamino sulfone 32 as well as cyclic product 33 in the reaction between phenylsulfene (30) and 1,3-bis(dimethylamino)-propene (29) has been attributed to the intermediacy of zwitterion 31.

It was postulated that the phenyl ring in 31 stabilized the α-sulfonyl carbanion component of the zwitterion to an extent sufficient to permit

\[
\begin{align*}
29 & \quad + \quad \begin{array}{c}
\text{phenylsulfene} \\
\text{1,3-bis(dimethylamino)-propene}
\end{array} \\
\rightarrow & \quad \begin{array}{c}
\text{cyclic product} \\
\text{enamino sulfone}
\end{array}
\end{align*}
\]
cleavage (path a) as a mechanistic alternative to cycloaddition (path b). Further, it was proposed that such results strongly suggested that sulfene-enamine interactions were nonconcerted, at least in those cases where phenylsulfene (30) was involved (35).

Recently, in the reaction of sulfene (35) with the optically active enamine 34 prepared from (R)-(-)-2-methylpyrrolidine and propionaldehyde, it was observed that the cycloadduct 38 was formed to a greater extent than its diastereoisomer 39 (42). Paquette has proposed that this is the
consequence of the rate-determining transition state for thietane 1,1-dioxide ring formation being more product-like than reactant-like (product development control). He has formulated a transition state model in which the enamine and sulfene double bonds are orthogonally orientated with respect to each other. Transition state complex 36 was considered to be preferred, even though 35 approached from the more sterically hindered surface of the enamine 34, since it produced directly a cycloadduct 38 relatively free of non-bonded interactions. The corresponding complex 37 in which 35 approached 34 from the least hindered side was less favored, since the diastereoisomer 39 obtained directly possessed a serious methyl-methyl compression (as indicated) (42).

In 1967 Paquette suggested that the thietane 1,1-dioxide ring, like thietane itself, was puckered, as in 40 (35). He reasoned that introduction of two oxygens on the sulfur atom of thietane could be expected to result in the generation of severe non-bonded interactions which the oxidized species could best alleviate by maintaining the puckered conformation. Support for this assumption was first obtained from the observation that trans-2,4-diphenylthietane 1,1-dioxide (41), upon treatment with sodium methoxide in methanol, gave the cis-isomer 40 to the extent of 96 per cent (35, 43).
Presumably, the cis-isomer was the more stable of the two because it possessed the phenyl groups in pseudoequatorial positions on the puckered heterocyclic ring (43). On the basis of the equilibrium result, it has been proposed that 40 exists almost exclusively in the conformation depicted (43).

In certain instances, application of the Karplus correlation (44a) has provided evidence for a puckered thietane 1,1-dioxide ring. The vicinal coupling constant (10.0 Hz) observed for the ring protons of the sulfone heterocycle in 42 was readily rationalized in terms of a folded thietane 1,1-dioxide ring on which the pyrrolidino and phenyl groups occupied trans pseudoequatorial positions and the two protons in question possessed a dihedral angle of approximately 180° (45). In a similar manner, a puckered conformation was assigned to 43 to explain the vicinal coupling constant of 9.3 Hz. The alternate possibility, a planar thietane 1,1-dioxide ring in which the dihedral angle was 0°, was considered unlikely because it required eclipsing of the bulky piperidino and carbethoxy groups (46). To obtain further evidence for the trans pseudoequatorial disposition of the piperidino and carbethoxy substituents in 43, the compound was exposed to sodium methoxide in methanol. After prolonged treatment, no
epimerization was apparent (46).

*\[ O \]

Investigations of the angle of pucker (\( \Theta \) in 44) have been carried out for a few thietane 1,1-dioxides. On the basis of nmr data and certain assumptions, \( \Theta \) for 40 has been approximated to be 35° (43). Calculations based on dipole moment measurements gave a value of 15° for \( \Theta \) in compound 45 (47), and an angle of pucker of 25.1° has been obtained for 46 by X-ray crystallography (48). It is possible that the nature of the substituents on the thietane ring has an effect on the degree of puckering (49). Several other instances where a puckered conformation for thietane 1,1-dioxides has been alluded to are found in the recent literature (50,51,52,53,54).

The synthesis of thietane 1,1-dioxides by the cycloaddition of sulfenes to electron-rich olefins has been extensively reviewed (22,33,55, 56,57,58). Opitz's review (22) is especially informative. In the following, some recent preparations of thietane 1,1-dioxides by this method will
be briefly considered, as well as several thietane 1,1-dioxide rearrangement reactions. Because of their synthetic utility, a brief discussion of thiete 1,1-dioxides (the $\alpha,\beta$-unsaturated analogues of thietane 1,1-dioxides) is also warranted.

Treatment of the pyrrolidine enamine 47 with sulfene generated in situ in cold tetrahydrofuran gave the thietane 1,1-dioxide 48 in 58% yield (59). Compound 48 allowed for the preparation of a thiete 1,1-dioxide fused $\alpha,\beta$ to naphthalene.

When the cycloadduct 49 from the addition of sulfene to N,N,N',N'-tetramethyl-1-butene-1,3-diamine was resubmitted to the original reaction conditions under which it was formed, 50 was obtained. It was proposed that under the reaction conditions, protonation of the $\alpha$-dimethylaminoethyl
substituent at C-2 of 49 created an electron-deficient centre which permitted a facile ring cleavage with the ejection of dimethylamine (35,60).

Reaction of the disulfonyl chloride 51 with ketene diethylacetal (16) in the presence of excess triethylamine afforded the monocycloadduct 52 rather than a bithietane tetroxide (61). Compound 52 was apparently

$$\text{SO}_2\text{Cl}_{\text{CH}_3\text{CH}_2\text{SO}_2\text{Cl}} + \text{2 CH}_2 = \text{C(OEt)}_2 \xrightarrow{\text{3(Et)}_3\text{N}} \text{THF, 0°}$$

identical to the thietane 1,1-dioxide prepared from 16 and allyl sulfonyl chloride (21).

Interestingly, whereas reaction of phenylsulfene with 1-morpholino-cyclohexene gave the expected cycloadduct 24, the cycloaddition with 1-pyrrolidinocyclohexene under the same conditions yielded the substitution product 53 (37).
Rapid column chromatography of the crude material obtained by reacting the dienamine 54 with sulfene gave, amongst other products, a low yield of the unstable thietane 1,1-dioxide 55 (38). Upon standing in chloroform solution at room temperature, 55 was cleanly converted to 56 by cleavage of the bond common to both rings. A mechanism was suggested for this transformation (38).

As part of an investigation into the possibility of preparing a stable sulfene, sulfonyl chloride 57 was reacted with 1-isobutenylpiperidine (58) in the presence of triethylamine to give the cycloadduct 43 in good yield.
yield (46). When the reaction was run under similar conditions using 1-butenylpiperidine (59) rather than 58, the substitution product 60 was obtained in 86% yield. No attempt was made to rationalize this difference in reactivity between 58 and 59 (46).

The simplest 3-dialkylaminothietane 1,1-dioxide 62 has been prepared directly in 86% yield by the cycloaddition of N,N-dimethylvinylamine (61) to sulfene (62). Enamine 61 was synthesized by dehydrohalogenation
of N,N-dimethyl-N-β-chloroethylamine and was found to be stable below -20° (62).

Addition of methanesulfonyl chloride to a diethyl ether solution of 1,3,3-trimethyl-2-methyleneindoline (63) and triethylamine afforded a 2:1 mixture of the cycloadduct 64 and the substitution product 65 in about 50% yield (36). Prolonged exposure of 64 in diethyl ether to excess triethylamine and one molar equivalent of triethylamine hydrochloride did not generate 65, nor did treating 65 in the same manner yield 64. On this basis, it was concluded that 64 and 65 were formed independently in the reaction of 63 with sulfene, probably from a common intermediate zwitterion. Derivatives of 63 in which the N-methyl group was replaced with other alkyl and aralkyl groups have also been successfully cycloadded to sulfene (17).

The reaction of methanedisulfonyl chloride (66) with ketene diethylacetal (16) and triethylamine gave a crystalline substance which has
been formulated as the spiro bithietane tetroxide 67. It was proposed that
the formation of 67 proceeded through the intermediacy of disulfene
\((O_2S = C = SO_2)\) (39). When 67 was dissolved in cold ethanol and allowed
to stand at -10 to -50°, a ring cleavage and proton transfer occurred to
give 68, quantitatively. This transformation was considered to be due to

\[
\text{ClSO}_2\text{CH}_2\text{SO}_2\text{Cl} + 2 \text{ CH}_2\text{C} = \text{OC}_2\text{H}_5) \rightarrow \frac{2 (\text{Et})_3\text{N}}{\text{benzene, -5°}}
\]

\[
\text{66} \quad \text{16}
\]

\[
\begin{array}{c}
\text{EtO} \quad \text{OEt} \\
\text{S} \quad \text{S} \\
\text{O}_2 \quad \text{EtO} \quad \text{OEt}
\end{array}
\rightarrow
\begin{array}{c}
\text{EtO} \quad \text{OEt} \\
\text{SO}_2\text{CH} = \text{C} \quad \text{OEt}
\end{array}
\]

\[
\text{67} \quad \text{68}
\]

strain inherent in 67 (39).

Addition of the morpholine enamine of acetophenone (69) to sulfene
gave 70 in 46% yield (63). This reaction is of interest because it has been

\[
\begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\]

\[
\text{69}
\]

noted that \(\alpha\)-substitution of the enamine tends to favor the formation of
substitution product rather than cycloadduct (22). Hydrolysis of 70 in
aqueous base yielded the substitution product 71. The para-chloro analogue

\[
\begin{align*}
\text{70} & \quad \text{NaOH/H}_2\text{O} \\
\text{MeOH} & \quad \Delta, 2 \text{ hr}
\end{align*}
\]

of 70 was converted to the corresponding thiete 1,1-dioxide and then reduced with sodium borohydride to give 72. A contrast in susceptibility to base-induced hydrolysis was observed between 70 and 72. Warming 72 with sodium deuteroxide in deuterium oxide and dioxane, rather than resulting in ring cleavage, gave the \( \alpha \)-tetradeuterated sulfone, 73, in 88% yield (63).

\[
\begin{align*}
\text{72} & \quad \text{NaOD/D}_2\text{O} \\
dioxane & \quad 40-50^\circ, 24 \text{ hr}
\end{align*}
\]

\[
\begin{align*}
\text{73}
\end{align*}
\]

A novel thietane 1,1-dioxide synthesis was performed by refluxing a benzene solution of 1-chloroethanesulfinic acid (74) with excess enamine 14 in the presence of triethylamine. The cycloadduct 75 was obtained in 16% yield. It was proposed that the required intermediate, methylsulfene, was generated from 74 by a process that was the formal reverse of that whereby the same intermediate was derived from ethanesulfonyl chloride (64).
Reaction of the $\beta$-cyano-substituted ketene aminal \textit{76} with methanesulfonyl chloride and triethylamine under conditions (22) conducive to the formation of mesylsulfene \textit{19} gave the substitution product \textit{77} rather than the expected cycloadduct \textit{65}. Such a result was perhaps predictable in view of the report that only the substitution product \textit{79} was obtained from the reaction of ketene aminal \textit{78} with phenylsulfene \textit{30}. This was attributed, in part, to steric crowding at the vinylic carbon atom bearing the
gem-diethylamino groups which prevented ring closure of the presumed zwit-terionic intermediate (66).

When the product 80 from the cycloaddition of ketene diethylacetal to phenylsulfene was treated with concentrated hydrochloric acid, the enolic derivative 81 and the thiete 1,1-dioxide 82 were formed (67). An unsuccessful attempt to convert 80 to 81 had previously been reported (68).

Addition of the highly reactive sulfonyl chloride 83 to a dioxane
solution of 84 and triethylamine at 15° gave a 30% yield of cycloadduct 85 (40). When the reaction was repeated using 1-morpholinocyclopentene (86) in place of 84, the substitution product 90 was obtained in 20% yield. The presumption was made that the sulfene 87 derived from 83 could add to 86 to give either the zwitterion 88 or the thietane 1,1-dioxide 89. Ring cleavage in 89 or a prototropic shift in 88 would then yield 90. Although

![Chemical structures](image)

earlier work (69) indicated that the former pathway may have been involved, it was considered that the half-life of 88 might be sufficiently long, owing to resonance stabilization of the negative charge, to permit the latter mechanism (40).
Treatment of cis-2,4-diphenylthietane 1,1-dioxide (40) with tert-butoxy magnesium bromide in diethyl ether at 35° afforded the cyclic sulfonic ester 91 in 70% yield, stereospecifically. In a similar manner, the trans-isomer 41 gave a 41% yield of 92 (72). Heating either 40 or 41 with ethyl magnesium bromide in diethyl ether - benzene yielded trans-1,2-diphenyl-cyclopropanesulfonic acid (93) to the extent of 75 per cent (70). Mechanisms have been proposed for both types of rearrangement (71).
Exposure of 2-methylene-1,3-dioxolane (94) to chloromethanesulfonyl chloride (95) and triethylamine in tetrahydrofuran solution at room temperature gave 96 in 67.5% yield (54). The presence of an \( \alpha \)-chloroketal function

\[
\begin{align*}
\text{CH}_2=\text{C} & \quad \text{ClCH}_2\text{SO}_2\text{Cl} \\
& \quad \text{(Et)}_3\text{N} \\
\quad \text{THF} \\
\end{align*}
\]

\[94\quad 95\quad 96\]

\[230-250^\circ\]

\[\text{CH}_3\text{C} - \text{O} - \text{CH}_2\text{CH}_2\text{Cl} + \text{SO}_2\]

\[97\]

in 96 apparently facilitated its thermal conversion to 2-chloroethyl acetate (97) in high yield. A possible mechanism for this rearrangement was presented (54).

Other reports dealing with the thermal decomposition of thietane 1,1-dioxides have appeared in the recent literature. Thermal desulfonylation of thietane 1,1-dioxide itself (7) at 960\(^\circ\) gave a mixture of propene and cyclopropane, quantitatively (67). When 2,2-dimethyl-3-thietanone 1,1-dioxide (98) was thermolyzed at 940\(^\circ\), formation of isobutylene occurred to the extent of 96.5% by loss of carbon monoxide and sulfur dioxide. It was

\[
\begin{align*}
\text{S} & \quad -\text{SO}_2 \\
\quad \text{7} \\
\end{align*}
\]
postulated that extrusion of one of the oxides followed by coupling gave a three-membered ring from which the second oxide was lost to give the alkene

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH} \\
\text{CH}_3 & \quad \text{S} \\
\text{SO}_2 & \quad \text{CH}_3 \quad \text{C} \equiv \text{CH}_2
\end{align*}
\]

\(98\)

(67). Thermolysis of the 3-hydroxy analogue of 7 gave a complex mixture of products, the formation of most of which has been rationalized in terms of desulfonylation, reverse cycloaddition and dehydration (67). Heating thietane 1,1-dioxide 99 at 230° yielded a mixture of cis- and trans-1-phenyl-2-benzoylcyclopropane (100). Similar results were obtained when 99

\[
\begin{align*}
\text{phenyl} & \quad \text{C} \equiv \text{O} \\
\text{H} & \quad \text{H} \\
\text{SO}_2 & \quad \text{H} \\
\text{100}\end{align*}
\]

101

102
was photolyzed in dilute cyclohexane solution (72). Other pyrolyses of thietane 1,1-dioxides which afforded cyclopropane derivatives have been recorded in the literature (43,51). Lastly, thermal decomposition of \textsuperscript{101} gave the pyrazole \textsuperscript{102} in 52% yield. A mechanism for this transformation has been proposed (73).

The preparation of thiete 1,1-dioxides has been briefly reviewed (57) and an inclusive list of references pertaining to the subject has been compiled to early 1968 (45).

The most common approach to thiete 1,1-dioxides is through the corresponding 3-dialkylaminothietane 1,1-dioxides by the Hofmann (45,62,74) or Cope (45,50,59,63) elimination procedures. Recently, application of the former method to \textsuperscript{62} gave unsubstituted thiete 1,1-dioxide (\textsuperscript{103}) in good yield (62).

3-Dialkylaminothiete 1,1-dioxides are obtained directly from the cycloaddition of ketene 0,N-acetals to sulfenes as a consequence of spontaneous elimination of an alcohol from the initial adduct. For example, reaction of ketene 0,N-acetal \textsuperscript{104} with methanesulfonyl chloride in the presence of triethylamine gave 3-dimethylamino-4,4-dimethylthiete 1,1-dioxide (\textsuperscript{105}) in 69% yield (23). Similarly, the initial cycloadducts from ketene N,N-acetals and sulfenes undergo spontaneous elimination of a dialkylamine.
to give 3-dialkylaminothiete 1,1-dioxides (24,43).

\[
\begin{align*}
\text{CH}_3 & \quad \text{C} & \quad \text{C} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{C} & \quad \text{OEt} & \quad \text{N(CH}_3)_2 & \quad \text{CH}_3 \text{SO}_2 \text{Cl} & \quad \text{(Et)}_3 \text{N} \\
\text{benzene} & \quad \text{EtOH} & \quad \text{EtO} & \quad \text{N(CH}_3)_2 & \quad \text{CH}_3 \\
\text{S} & \quad \text{O}_2
\end{align*}
\]

Another route to 3-dialkylaminothiete 1,1-dioxides that has received considerable attention recently is the cycloaddition of ynamines to sulfenes (25,26,37,50,75). For instance, reaction of 1-diethylamino-2-phenylacetylene (106) with phenylmethanesulfonyl chloride (13) in the presence of triethylamine afforded 107 in 90% yield (37). The cycloaddition has been postulated to occur through a dipolar intermediate (26).

\[
\begin{align*}
\text{C} & \quad \text{C} & \quad \text{N} & \quad \text{Et} & \quad \text{Et} \\
\text{CH}_3 \text{SO}_2 \text{Cl} & \quad \text{(Et)}_3 \text{N} \\
\text{Et}_2 \text{O}, 0^\circ
\end{align*}
\]
Thiete 1,1-dioxides unsubstituted at C-3 are useful for synthesizing thietane 1,1-dioxide derivatives as a result of their propensity to undergo Michael addition with various nucleophiles (15,52,76,77) and to behave as dienophiles in the Diels-Alder reaction (52,77,78,79,80,81). Refluxing an absolute ethanol solution of thiete 1,1-dioxide (103) with thiophenol (108) and triethylamine gave the Michael adduct 109 in 92.5% yield (77). Condensation of 4,4-dimethylthiete 1,1-dioxide (110) with 1,4-diphenyl-2,3-benzofuran (111) in refluxing xylene afforded the Diels-Alder product 112 in good yield (79). Recently, thiete 1,1-dioxide has been shown to undergo 1,2-cycloaddition with enamines to give 2-thiabicyclo [2.2.0]hexane derivatives (82) and 1,3-cycloaddition with diazo alkanes to yield pyrazolines (73).

Reduction of thiete 1,1-dioxides unsubstituted at C-3 to give the
corresponding thietane 1,1-dioxides is apparently generally successful by either catalytic hydrogenation using palladium on charcoal catalyst (52,63, 67,83,84) or by means of sodium borohydride (50,63,77). A diethyl ether solution of 113 hydrogenated over 10% palladium on charcoal gave 114 in greater than 90% yield. At a lower hydrogen pressure and with a shorter hydrogenation time, the exocyclic double bond was selectively reduced (83). Reduction of thiete 1,1-dioxides with lithium aluminum hydride generally results in ring cleavage (63,77,79), although a few exceptions are known (79,85). An attempt to reduce the double bond of certain 3-diethylamino-thiete 1,1-dioxides with sodium borohydride was unsuccessful (50).

Ring cleavage occurs when thiete 1,1-dioxides are treated with aqueous base (15,45,63,68,76,77). For example, heating 2-phenylthiete 1,1-dioxide (115) in a mixture of aqueous sodium hydroxide and methanol gave benzyl methyl sulfone (116) (15). The base-catalyzed reaction has been likened to a reverse aldol condensation (77).

Thermal rearrangements of certain thiete 1,1-dioxides have
recently been investigated (67,86,87). When thiete 1,1-dioxide 117 was heated at 400° in the presence of 9,10-dihydroanthracene, a cyclic sulfinic ester 118 was obtained in good yield. A mechanism accounting for this transformation has been proposed (87).

Acid hydrolysis of 3-dialkylaminothiete 1,1-dioxides affords the corresponding 3-thietanone 1,1-dioxides (22,23,25,26). Stirring 119 in aqueous solution with an acidic ion exchange resin gave 120 in 74% yield. The ketonic sulfone 120 possessed an acidity comparable to that of carboxylic acids (23). Similarly, exposure of 121 to concentrated hydrochloric acid yielded the hydrolysis product 122, quantitatively (26).
$\text{Et}_2\text{N} \xrightarrow{\text{conc. HCl}} \text{Et}_2\text{N}$

121

$\text{CH}_3\text{S}^\text{O}_2\text{C}_6\text{H}_4\text{OH}$

122
DISCUSSION OF THE CHEMISTRY

The thietane 1,1-dioxide derivatives investigated as potential analgetics were 9, 123, 124, and 125. Synthesis of these compounds was approached through the corresponding 3-dimethylaminothietane 1,1-dioxides 126, 127, and 128. The general synthetic pathway employed is outlined in Scheme I using the preparation of 9 as an example. Replacement of phenyl-

\[ \text{N(CH}_3)_2 \]  
\[ \text{CH} \rightarrow R_2 \]  
\[ \text{S} \]  
\[ \text{R}_1 \]  
\[ \text{O}_2 \]  

\[ 9, \ R_1 = R_2 = H \]  
\[ 123, \ R_1 = H; \ R_2 = \text{CH}_3 \]  
\[ 124, \ R_1 = \text{Cl}; \ R_2 = H \]  
\[ 125, \ R_1 = \text{NO}_2; \ R_2 = H \]  

methanesulfonyl chloride (13) with p-chlorophenylmethanesulfonyl chloride (129) or p-nitrophenylmethanesulfonyl bromide (130) allowed for the synthesis of 124 and 125, respectively. A similar scheme in which hydrogen cyanide was replaced by nitroethane was used to prepare compound 123.

The following discussion also deals with, *inter alia*, configurational and conformational aspects, as well as the relative stabilities, of the cycloaducts from the reaction of \( \theta \)-dimethylaminostyrene with phenylsulfene. Data from a brief study of the effect of reaction solvent on this cyclization reaction are considered. The preferential formation of the
SCHEME 1. Synthetic Pathway for 2,4-Diphenyl-3-dimethylaminomethylthietane 1,1-dioxide (9).

\[
\text{Ph-CH=CH-N(CH}_3\text{)}_2 + \text{Ph-CH}_2\text{SO}_2\text{Cl} \xrightarrow{\text{Et}_3\text{N}} \text{131} \xrightarrow{\text{CH}_3\text{CO}_2\text{H}} \text{13} \xrightarrow{\text{HCO}_2\text{H/HCHO}} \text{9}
\]

\[
\text{N(CH}_3\text{)}_2 \xrightarrow{\text{H}_2\text{B}_6\text{H}_6} \text{178} \xrightarrow{\text{CH}_2\text{NH}_2} \text{152} \xrightarrow{\text{HCN}} \text{126}
\]
less stable thietane 1,1-dioxide isomer in the three solvents investigated is interpreted in terms of a recently proposed transition state model for thietane 1,1-dioxide ring formation. Results from the cyclization of \( \beta \)-dimethylaminostyrene with \( p \)-chloro- and \( p \)-nitrophenylsulfene are dealt with in light of the information obtained from the reaction of this enamine with phenylsulfene. Utilization of the 3-dimethylaminothietane 1,1-dioxides to prepare the corresponding thiete 1,1-dioxides is discussed with reference to possible mechanistic dichotomy. The thiete 1,1-dioxides proved to be interesting in respect to their susceptibility to thermal rearrangement.

\( \beta \)-Dimethylaminostyrene (131) is a known compound (15,88). The nmr spectrum (CDCl\(_3\)) of 131 indicated that it existed exclusively in one form at room temperature and showed the vinyl protons as doublets at \( \delta \) 6.73 and 5.13 with \( J = 14 \) Hz. On the basis of the magnitude of this coupling constant, 131 was assigned a trans-configuration. The same assignment has been made by Caserio and co-workers (88). A trans-configuration was also indicated by the presence of a band at 935 cm\(^{-1}\) in the ir spectrum. The nmr spectrum (neat, \(-10^\circ\)) of a sample of 131 which had been stored at \( 0^\circ \) for four months showed only the trans-isomer. Other acyclic enamines that can be isolated in one configuration are known (74,90). For example, the enamine 205 derived from propionaldehyde and methyl-\( \alpha \)-phenethylamine was
apparently obtained only in the trans-form \( J = 13.2 \text{ Hz} \) \((74)\).

Phenylmethanesulfonyl chloride \((13)\) and \(p\)-chlorophenylmethanesulfonyl chloride \((129)\) are known compounds and their synthesis is described in the Experimental for the sake of completeness. Interestingly, upon chlorinolysis of the sodium thiosulfate salt derived from \(p\)-nitrobenzyl bromide, only \(p\)-nitrophenoxyphenylmethanesulfonyl bromide \((130)\) and no sulfonyl chloride was isolated. Similar results have been reported and are attributed to the presence of sodium bromide in the reaction mixture \((91)\). Initially, consideration was also given to the preparation of \(p\)-methoxyphenylmethanesulfonyl chloride. However, two unsuccessful attempts
to prepare this compound are recorded in the literature (21, 91) and, therefore, the matter was not further pursued.

The reaction of 3-dimethylaminostyrene (131) with phenylmethanesulfonyl chloride (13) in the presence of triethylamine has been found (14, 15) to give two cyclic isomers, cis- and trans-2,4-diphenyl-3-dimethylaminothietane 1,1-dioxide (126a and b)*. During the course of the present investigation a third isomer, benzyl 1-phenyl-2-dimethylaminoethenyl sulfone (132), was isolated and characterized. The three isomers could be separated by careful fractional crystallization of the crude product from hexane-methyl ethyl ketone. The configurational and conformational assignments for 126a and 126b were based on their nmr spectra. A determination of the relative stabilities of the two cyclic isomers supported these assignments.

Nmr Determination of the Configuration and Conformation of cis- and trans-2,4-Diphenyl-3-dimethylaminothietane-1,1-dioxide

In the nmr spectrum of 126a the benzylic protons, \( H_a \) and \( H_b \), appeared as a sharp doublet at \( \delta 5.28 \) and were coupled to the remaining ring proton, \( H_c \), which was seen as a triplet at \( \delta 3.68 \), \( J_{ac} = J_{bc} = 9 \) Hz. A six-proton singlet at \( \delta 2.10 \) was attributed to the dimethylamino group. The equivalency of the benzylic protons indicated that the phenyl groups in 126a were attached in a cis-configuration on the thietane 1,1-dioxide ring. The magnitude of the vicinal coupling constant was explicable in terms of a puckered conformation in which all three ring substituents occupied pseudo-

* The designations cis and trans refer to the configurations of the aromatic rings with respect to the plane of the heterocyclic ring.
equatorial positions and the dihedral angle between each benzylic proton and \( H_c \) approached 180°.

In the 60 MHz spectrum of \( 126b \), \( H_a \) and \( H_b \) appeared as a diffuse triplet at \( \delta 5.43 \) and \( H_c \) was seen as a triplet at \( \delta 3.68 \). The protons of the dimethylamino group were revealed as a singlet at \( \delta 1.93 \). The 100 MHz spectrum of \( 126b \) showed \( H_a \) as a doublet at \( \delta 5.494 \), \( H_b \) as a doublet at \( \delta 5.304 \) and \( H_c \) as a sharp triplet at \( \delta 3.648 \), with \( J_{ac} = J_{bc} = 9.4 \) Hz. The doublets were further split as a consequence of transannular coupling, \( J_{ab} = 1 \) Hz. The nonequivalency of protons \( H_a \) and \( H_b \) suggested a trans-configuration for the phenyl groups on the heterocyclic ring. This assignment was supported by the upfield shift of the N-methyl protons in \( 126b \) when compared to the corresponding protons in \( 126a \). Such a shift was attributable to diamagnetic shielding of the N-methyl groups in \( 126b \) by the phenyl group cis to the dimethylamino substituent. A deshielding effect by this phenyl group explained the downfield shift of \( H_a (\delta 5.49) \) in \( 126b \) compared to \( H_a \) and \( H_b (\delta 5.28) \) in \( 126a \). A confident assignment of a puckered conformation to \( 126b \) on the basis of its nmr spectrum was not possible because of the equivalency of the vicinal coupling constants, \( J_{ac} \) and \( J_{bc} \). A puckered conformation for \( 126b \) predicted \( J_{ac} > J_{bc} \). It has been noted (92) that vicinal coupling constants for ring protons on thietane derivatives can, on occasion, be

![Diagram](image-url)
difficult to interpret in a nonambiguous fashion. A situation similar to 
that of 126b in which cis and trans vicinal coupling constants are identi-
cal has been reported (51) for 2,2,4-trimethylthietane 1,1-dioxide (133) 
(J_{ab} = J_{ac} = 9.4 Hz).

The absence of transannular coupling in 126a and its presence 
in 126b has a precedent in the recent literature (43) with the thietane 1-
oxides 134a and b. For 134a, in which the phenyl groups are cis, no trans-
annular coupling was observed, whereas for 134b, in which the phenyls are 
trans, J_{ab} was found to be 1.12 Hz. As with 126b, H_a in 134b was shifted 

![Diagram of 134a and 134b]

to lower field than H_a and H_b in its cis counterpart 134a, presumably as 
a result of the deshielding effect of the pseudoaxial phenyl group in 
134b. The puckered nature of the thietane 1-oxide ring in 134a and 134b 
has been established on the basis of equilibrium, nmr and X-ray crystal-
lography evidence (43).

Before leaving this discussion of the nmr spectra of 126a and 
b, it should be pointed out that 135, the 3-diethylamino analogue of 126a, 
has recently been prepared and its nmr spectrum interpreted (50). 135 was 
synthesized by the reaction of β-diethylaminostyrene with phenylmethanesul-
fonyl chloride in the presence of triethylamine and was the only isomer isolated. The nmr spectrum of 135 showed equivalent benzylic protons coupled to the proton at C-3, \( J = 9.0 \) Hz. This was interpreted in terms of a dihedral angle of 12° with all three protons on the same side of the puckered four-membered ring. No explanation was given for eliminating a more likely dihedral angle of approximately 180°. The assignment by these workers required that all three substituents be on the same side of the thietane 1,1-dioxide ring with either the diethylamino group or the two phenyl rings orientated pseudoaxially. The latter case seems very unlikely since severe 1,3-diaxial non-bonded interactions would ensue. With the diethylamino group pseudoaxial, severe non-bonded interactions are also expected to occur as a consequence of the axially projected oxygen of the sulfonyl group. On this basis, inter alia, it seems that the original configurational assignment for 135 is incorrect and that 135 more likely possesses a configuration analogous to that of 126a.

Examination of the Relative Stabilities of cis- and trans-2,4-Diphenyl-3-dimethylaminothietane 1,1-dioxide

Dodson found that treatment of trans-2,4-diphenylthietane 1,1-dioxide (41) with sodium methoxide in methanol gave the cis-isomer 40 almost quantitatively and interpreted this result as evidence for the puckered
nature of the thietane 1,1-dioxide ring. Of the two isomers, cis-2,4-
diphenylthietane 1,1-dioxide was more stable because both phenyl groups
presumably occupied pseudoequatorial positions on the folded heterocycle
(43). By analogy, isomerization of 126b to 126a would have allowed a more
confident assignment of a puckered conformation to the two isomers.

The conditions used for the equilibration of 126b were consider­
ably milder than those reported by Dodson (43). A sample of crude product
which was found by nmr analysis to be essentially pure in the three isomers
126a (19%), 126b (74%) and 132 (7%) was dissolved in a 2:1 mixture of acetoneitrile and chloroform along with an equimolar amount of triethylamine hydrochloride. Two drops of triethylamine was added and the solution was allowed to sit at room temperature until the 1630 cm\(^{-1}\) ir band of isomer 132 ceased to increase in intensity (3 days, with the greatest increase during the first day). Nmr analysis of the isomerized product (89% recovery) indicated that 92% of the material was accounted for by the three original isomers, of which 64% was 126a, 8% 126b and 28% 132. Thus, equilibration increased the percentages of 126a and 132 in the mixture by approximately 45% and 21%, respectively, at the expense of 126b, which decreased from 74% to 8%. Presumably, equilibration occurred via the \(\alpha\)-sulfonyl carbanion 136, which subsequently underwent either reprotonation with epimerization to give the configurationally more stable isomer 126a or ring cleavage and reprotonation to give the acyclic isomer 132.

There are several reports in the literature of base-catalyzed ring opening of 3-dialkylaminothietane 1,1-dioxides (15,36,63). Rather than triethylamine, however, these cleavage reactions involved the use of alkali hydroxides in refluxing aqueous methanol or ethanol. For example, Nagarajan and Mehta have reported that whereas thietane 1,1-dioxide 64 was
recovered unchanged after exposure to triethylamine in diethyl ether solution for four days, it was converted to the corresponding acyclic isomer to the extent of 22% on being refluxed in an aqueous ethanol solution of potassium hydroxide for six hours (36).

The possibility of an acyclic isomer arising by ring opening of the cycloadduct initially formed in the reaction of a sulfene with an enamine has been opposed by Paquette (35). He has claimed that such a reaction is mechanistically unprecedented, at least with triethylamine as base. The transformation of 126b to 132, however, indicates that ring cleavage can indeed occur, particularly if the initial cycloadduct is sterically unfavorable. Presumably, relief of ring strain as well as the resultant decrease in non-bonded interactions would provide the driving force for the conversion of 126b to 132. The difference in susceptibility of 126b and 64 to base-catalyzed ring opening is perhaps attributable to the acidifying effect of the pseudoaxial phenyl group in 126b on the \( \alpha \)-proton.

Upon crystallization from hexane - ethanol of a sample of crude product from the cyclization of 131 and 13, only 35% was recovered as a crystalline solid. Nmr analysis of this solid and the oil obtained by evaporation of the mother liquor revealed that approximately 95% of 126a initially present in the crude material was accounted for, whereas all but 18% of the trans-isomer 126b had decomposed. An apparent product of this decomposition, dimethylammonium phenylmethanesulfonate (137) was subsequently isolated from the evaporated mother liquor. These results prompted further study of the relative stability of 126a and b.

After refluxing a sample of pure 126a in ethanol 100 for one hour, nmr analysis of the recovered solid showed that 81% remained unchanged. Repeating the procedure with a sample of pure 126b gave a yellow, mobile oil which possessed an odor similar to that of \( \beta \)-dimethylaminosty-
rene. From the nmr spectrum of the oil it was observed that all of the trans-isomer had decomposed and that approximately 57% of the material consisted of 131 (28%), 126a (11%) and ethyl phenylmethanesulfonate (138) (61%). Another sample of pure 126b was refluxed in ethanol 95 for 12 hours. Nmr analysis of the water soluble fraction isolated from the decomposition products showed that 67% of the trans-isomer had been converted to dimethylammonium phenylmethanesulfonate (137). Finally, gas chromatography of a freshly prepared ethanol 95 solution of 126b with the injection port and column temperatures at 280° and 140°, respectively, gave peaks having retention times identical to those of phenylacetaldehyde (139), β-dimethylaminostyrene (131) and ethyl phenylmethanesulfonate (138).

On the basis of the equilibration experiment and the results from refluxing 126a and 126b in ethanol, it was concluded that 126a was definitely more stable than 126b. Furthermore, the results obtained for 126b strongly suggested that the formation of the trans-isomer was a reversible process in that phenylsulfene (30) and β-dimethylaminostyrene (131) could be regenerated by heating 126b in ethanol (Scheme II). Observations with certain other thietane 1,1-dioxides have indicated that the cycloaddition reaction between enamines and sulfenes is a completely reversible process (37). The phenylsulfene thus formed would be trapped either by ethanol to give the ester 138 or by water present in the ethanol to give phenylmethanesulfonic acid (140). The presence of the latter could aid in the hydrolysis of the enamine 131 to liberate dimethylamine (141) which in turn would lead to the formation of the salt 137. The relatively high yield (67%) of 137 obtained from the 12-hour reflux was perhaps due to hydrolysis of the ester 138. The means by which some of the trans-
SCHEME II. Decomposition of **trans**-2,4-Diphenyl-3-dimethylaminothietane 1,1-dioxide (126b) in Ethanol.

\[
\begin{align*}
\text{EtOH} & \quad \Delta \\
\end{align*}
\]

126b → 126a

\[
\begin{align*}
\text{H}_2\text{O} & \\
\end{align*}
\]

131 → NH(CH\(_3\))\(_2\) + 139

\[
\begin{align*}
\text{EtOH} & \\
\end{align*}
\]

30 → 140

\[
\begin{align*}
\text{NH(CH}_3\text{)}\text{_2} & \\
\end{align*}
\]

137

138
isomer 126b isomerized to the cis-form 126a was presumably through either zwitterion 142 or the anion 136.

\[
126b \rightarrow \left[ \begin{array}{c}
\text{CH} - CH = N(CH}_3)_2 \\
\text{SO}_2 - \text{CH} - \text{C} \\
\end{array} \right] \rightarrow 126a
\]

142

Although no acyclic isomer 132 was observed in the decomposition products from either the 1-hour or the 12-hour reflux of 126b in ethanol, it cannot be ruled out that 132 did form but in such an amount as to be undetectable at the concentrations used in the nmr analysis.

**Benzyl 1-Phenyl-2-dimethylaminoethenyl Sulfone**

After most of 126a and b had been removed by fractional crystallization of the crude product from the cyclization reaction of 131 and phenylmethanesulfonyl chloride, benzyl 1-phenyl-2-dimethylaminoethenyl sulfone (132) was isolated as a crystalline solid. That 132 was an acyclic adduct was revealed by the presence of a strong enamine band at 1630 cm\(^{-1}\) in the ir spectrum. The uv spectrum showed a maximum at 253 nm (ε 15,800) which agreed with uv data reported for similar compounds (15,35). Further proof for the structure of 132 was obtained from the nmr spectrum in which the vinyl, benzyl and dimethylamino protons appeared as singlets at δ 7.00, 4.05 and 2.60, respectively. These data compared well with those given (35) for an analogous compound 143 in which the vinyl proton appeared as a singlet at δ 7.22 and the dimethylamino protons as a singlet at δ 2.59.
The configuration of 132 was not discernible from the spectroscopic data. However, a recent report (70) on the configurational preference of α-benzylsulfonyl stilbene has provided a basis for assigning a configuration to 132. Refluxing α-benzylsulfonyl-trans-stilbene (144) in ethanolic sodium hydroxide resulted in an almost quantitative conversion to the cis-isomer 145 (70). Considering this evidence, together with the fact that enamino sulfones such as 132 possess an intrinsic ability to isomerize to the more stable isomer (93), suggested that a trans-configuration for 132 was plausible.
Effect of Reaction Solvent on Isomer Proportions

Fortuitously, the chemical shifts for the N-methyl protons of 131 (52.70), 132 (52.60), 126a (52.10) and 126b (51.93) were adequately separated, which permitted determination by nmr analysis of the proportions of 126a, 126b and 132 in crude products from the reaction of phenyl-sulfene with θ-dimethylaminostyrene (Figure 1). Since a fair amount of 2,4-diphenyl-3-dimethylaminothietane 1,1-dioxide (126a and b) was required for preparation of the corresponding thiete 1,1-dioxide, the opportunity was presented for investigating the effect of reaction solvents on the proportions of 126a, 126b and 132 formed. Such a study may have provided further insight into the mechanism of the cycloaddition of sulfenes to enamines.

The three solvents studied were diethyl ether - tetrahydrofuran, acetonitrile and chloroform. Reactions were run under identical conditions, except where noted, and involved the addition of a solution of phenylmethanesulfonyl chloride (13) over a period of one hour to a cooled solution of θ-dimethylaminostyrene (131) and an equivalent molar amount of triethylamine. At the end of the 15-hour reaction period, the solvent was removed by evaporation in vacuo with the aid of a lukewarm water-bath and the resulting residue was redissolved in chloroform and extracted with water to remove the triethylamine hydrochloride. Evaporation of the dried organic layer gave the crude product as a pale yellow solid. It was on this material that the nmr analysis was performed. The effect of water upon the isomer composition was also studied with aqueous acetonitrile as solvent. The data obtained from these reactions are presented in Table I. When the cycloadditions run in diethyl ether - tetrahydrofuran and acetonitrile were
Figure 1. Nmr spectrum of the crude product from the cycloaddition (in CH₃CN) of β-dimethylamino-styrene to phenylsulfene dissolved in CDCl₃.
### TABLE I

**Effect of Reaction Solvent on the Ratio of Isomers from the Cycloaddition of θ-Dimethylaminostyrene to Phenylsulfene**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>A</th>
<th>B</th>
<th>126a</th>
<th>126b</th>
<th>132</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et₂O-THF</td>
<td>96.7</td>
<td>96</td>
<td>15</td>
<td>82</td>
<td>3</td>
</tr>
<tr>
<td>CHCl₃</td>
<td>99.1</td>
<td>100</td>
<td>19</td>
<td>74</td>
<td>7</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>98.6</td>
<td>99</td>
<td>35</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>CH₃CN-H₂O*</td>
<td>90.7</td>
<td>84</td>
<td>36</td>
<td>47</td>
<td>17</td>
</tr>
</tbody>
</table>

A. % yield based on the weight of crude product isolated.

B. % of A accounted for by 126a, 126b and 132. Calculated from the nmr spectra by comparison of the sum of the integrals for the dimethylamino signals of 126a, 126b and 132 with the integral for the aromatic protons.

C. °L calculated by taking the sum of the integrals for the three dimethylamino peaks as 100%.

* reaction scaled down by a factor of two (0.0340 mole); 0.5 ml (0.03 mole) of distilled water added just prior to initiating the addition of sulfonyl chloride.
repeated, essentially identical results were realized.

It is uncertain whether the cycloaddition of enamines to sulfenes is a two-step process involving a zwitterionic intermediate or a concerted reaction (22). The suggestion has been made that if a two-step mechanism were operative, then one might expect an increase in the amount of substitution product relative to cycloadduct upon using reaction solvents of higher polarity (22). This reasoning is based on the premise that in more polar solvents the lifetime of the zwitterionic intermediate would be increased and thus there would be a greater possibility of a prototropic shift (or protonation followed by deprotonation) occurring to give the substitution product. However, there are apparently no examples reported in the literature for enamine-sulfene reactions in which the polarity of the reaction solvent has had a distinct influence on the amount of acyclic isomer formed. Inspection of Table I, disregarding the cycloaddition run in the presence of water, reveals that the reaction between 131 and phenylsulfene is not an exception. There is no apparent correlation between the yield of benzyl 1-phenyl-2-dimethylaminoethenyl sulfone (132) and solvent polarity.

Interestingly, in all three solvents more of the less stable trans-isomer 126b was formed than cis-isomer 126a. In comparing the ratios of 126a and 126b, however, there appears to be a definite increase in the proportion of the more stable cycloadduct 126a in the most polar solvent, acetonitrile. A possible explanation for this increase can be made if it is assumed that phenylsulfene and 131 approach each other in such a manner as to give a zwitterionic intermediate which subsequently undergoes either direct ring closure to give 126b or bond rotation followed by ring closure
to give 126a. If this is the case, then one might expect that the longer lifetime of the zwitterion in acetonitrile as compared to that in the two less polar solvents would be reflected by a greater incidence of bond rotation and consequently by an increase in the amount of the cis-isomer 126a. This explanation is supported to some extent by the results obtained from the reaction run in acetonitrile with water present. The significant increase in the amount of substitution product 132 in this reaction (17%) compared to that obtained from the reaction without water (5%) may be indicative of trapping of the presumed zwitterion by the presence of a ready proton source. However, further evidence from reactions run in other polar and non-polar aprotic solvents is necessary before this matter can be more seriously considered.

Definitive interpretation of the data in Table I was complicated by the fact that the trans-isomer 126b is unstable and susceptible both to epimerization and to ring cleavage. It has been pointed out that cycloaddition and subsequent ring opening could be mistaken for direct formation of substitution products in the reaction of enamines with sulfenes (22). A further complication was the varying solubility of the cycloadducts (126a and b) and the triethylamine hydrochloride in the three solvents. In diethyl ether - tetrahydrofuran most of the product precipitated from solution and the precipitation of triethylamine hydrochloride was almost quantitative. Chloroform represented the other extreme, all of the product and triethylamine salt remaining in solution. In the case of acetonitrile, much of the salt appeared to precipitate, whereas most of the product remained dissolved.

If spontaneous ring cleavage of 126b were the source of the sub-
stitution product 132, then the amount of 132 formed would be time-depen-
dent. Thus, examination of the crude product after reaction periods shorter
than 15 hours should reveal a lower yield of the acyclic isomer. Prelim-
inary investigation indicated that a period much shorter than 15 hours was
sufficient to complete the reaction between 131 and 13. Unfortunately,
other conditions besides reaction time were altered in these experiments
and, therefore, the results in terms of the amount of 132 formed were not
comparable.

It is also possible that the addition time of the phenylmethanesulfonyl chloride (13) to the solution of 131 and triethylamine is impor-
tant. In those cycloadditions in which 13 is added over a period of one
hour, triethylamine not yet consumed by reaction with 13 may catalyze ring
opening of trans-isomer 126b already formed.

Interpretation of the Preferential Formation of the Less Stable Isomer,
trans-2,4-Diphenyl-3-dimethylaminothietane 1,1-dioxide

In proposing his transition state model for the reaction of en-
amines with sulfoxides, Paquette has implied that product development con-
trol is operative (42). The generality of product development control in
thietane 1,1-dioxide ring formations would appear to be debatable, how-
ever, in light of the results listed in Table I for the reaction of 8-
dimethylaminostyrene (131) with phenylsulfene (30). In all three solvents,
the thermodynamically less stable cycloadduct 126b was formed to a greater
extent than the more stable isomer 126a. Thus, this reaction apparently
preferred to proceed through a transition state that was more reactant-
like than product-like (steric approach control). In terms of steric
approach control, the suggested orthogonal relationship between the enamine and the sulfene in the transition state \((42)\), can be used to accommodate the preferred formation of \(126b\). On steric grounds, it can be reasonably argued that the reactive complex \(147\) will form in preference to \(146\), since
molecular models indicate that there is a serious non-bonded interaction engendered between the enamine dimethylamino group and the sulfene phenyl ring as 131 and 30 approach to form 146 which is not present in the formation of 147.

**Reaction of 9-Dimethylaminostyrene with p-Chlorophenylmethanesulfonyl Chloride and p-Nitrophenylmethanesulfonyl Bromide**

The reaction of 9-dimethylaminostyrene (131) with p-chlorophenylmethanesulfonyl chloride (129) in the presence of triethylamine was similar to the reaction of 131 with the unsubstituted sulfonyl chloride 13 in that two cyclic isomers, 127a and b, were isolated. Spectroscopic evidence was obtained for the presence of an acyclic isomer analogous to 132. That the reaction proceeded with precipitation of 127b as a white, crystalline solid, while 127a remained dissolved in the reaction solvent along with the acyclic material, greatly facilitated separation of the two cyclic isomers. The presence of characteristic sulfone bands and the absence of enamine absorption in the ir spectra of recrystallized 127a and crude 127b indicated that both were cycloadducts. Unlike 127a, which could be recrystallized readily, 127b was quite unstable and decomposed when dissolution was attempted in hot solvent. By analogy to 126a and b in regard to relative
stability, 127a was assigned a cis-configuration for the aromatic groups on the heterocyclic ring, whereas 127b was considered to possess a trans-arrangement. Like the unsubstituted trans-isomer 126b, 127b was formed preferentially. With chloroform as the reaction solvent, a 91% yield of the three isomers was obtained, of which 70% was 127b, 20% 127a and 10% the uncharacterized acyclic isomer. With acetonitrile as solvent, of the total crude product isolated (97%), 59% was 127b, 40% 127a and 1% acyclic isomer. As the two reactions were run under dissimilar conditions, it is not known at this time if there is any significance in the different proportionate yields of the three isomers obtained in the two reactions. The fact that the trans-isomer 127b precipitates from the reaction solvent may make this a useful reaction for mechanistic investigations. That only two cyclic isomers were observed was in agreement with information in the literature to the effect that the configuration of trans-enamines is maintained in the sulfene cycloadducts (42,74,90). It followed, therefore, that the p-chloro-substituted phenyl ring in 127b was cis to the dimethylamino group. A more convincing chemical argument for this assignment is reserved to a later discussion of the thiete 1,1-dioxides derived from 127a and 127b.

In the nmr spectrum (CDCl₃) of 127a the protons at C-2 and C-4 appeared as a doublet of doublets, one centred at δ 5.25 (benzylic proton) and the other at δ 5.22 (p-chlorobenzylic proton). The assignment of chemical shifts to these two protons was made on the basis of the report (94) that the benzylic proton of 2-(4-chlorophenyl)-thietane appears at higher field (287.5 Hz) than the corresponding proton in 2-phenylthietane (291 Hz). The benzylic protons in 127a were equally coupled to the proton at C-3, which appeared as a triplet at 3.57 (J = 9 Hz). The protons of the
dimethylamino group were observed as a singlet at $\delta 2.08$, a chemical shift almost identical to that for the same protons in cis-2,4-diphenyl-3-dimethylaminothietane 1,1-dioxide (126a) ($\delta 2.10$). The low solubility of 127b in common nmr solvents prevented a suitable spectrum from being obtained. However, the HCl salt of 127b was found to be sufficiently soluble in DMSO-d$_6$. The spectrum of the salt showed the benzylic protons as well separated doublets, one at $\delta 6.69$ and the other at $\delta 6.15$. Both were equally coupled to the C-3 proton, which appeared as a triplet at $\delta 4.93$ ($J = 10$ Hz). A singlet at $\delta 2.39$ was attributed to the protons of the dimethylamino group. In the DMSO-d$_6$ spectrum of the HCl salt of 127a, the benzylic protons appeared as a broad doublet at $\delta 6.47$ coupled to a one-proton triplet at $\delta 5.27$ ($J = 9$ Hz). The protons of the dimethylamino group were seen as a singlet at $\delta 2.66$. As with the nmr spectra of 126a and b, the differences in the spectra of the HCl salts of 127a and b were rationalized in terms of the configurational disposition of the aromatic groups with respect to the heterocyclic ring. The upfield shift of the protons of the dimethylamino group of 127b HCl relative to the signal for the same protons in 127a HCl was attributed to the shielding effect of the p-chlorophenyl ring cis to the dimethylamino group in 127b. Taking the puckered nature of the thietane 1,1-dioxide ring into account, the downfield shift of one of the benzylic protons relative to the other in 127b HCl was thought to be due, in part, to deshielding of this proton by the pseudoaxial p-chlorophenyl ring. The characteristic chemical shifts for the protons of the dimethylamino group in the hydrochloride salts of 127a and 127b allowed quantitative determination of these isomers in mixtures.

The ir spectrum of an oily residue isolated by washing crude
with diethyl ether and evaporating the washings, showed a strong band at 1625 cm$^{-1}$, which was indicative of an enamine. The nmr spectrum of the oil showed the presence of 127a as well as signals at $\delta$ 7.31 (doublet, aromatic protons, $>9$), 6.98 (singlet, vinylic proton, 1), 3.97 (singlet, benzylic protons, 2), and 2.60 (singlet, dimethylamino protons, 6) which were attributable to an acyclic isomer analogous to 132. This material was not isolated or further characterized.

It was subsequently found, as in the case of 126a and 126b, that a good yield of the p-chloro-substituted cycloadduct could be obtained after a reaction period shorter than the generally employed 15 hours. For example, a reaction run in acetonitrile using 0.20 mole of each reactant (131, 129 and (Et)$_3$N) was worked up 3 hours following addition of 129 to give a 97% yield of crude product, of which 40% was 127a, 59% 127b and 1% acyclic isomer. It should be mentioned that the nmr spectrum (CDCl$_3$) of the crude 127a fraction revealed a relatively weak singlet at $\delta$ 1.91 which was tentatively assigned to the protons of the dimethylamino group of a residual amount (3%) of 127b. This chemical shift was very similar to that for the same protons in 126b ($\delta$ 1.93).

The reaction of 131 with p-nitrophenylmethanesulfonyl bromide (130) in the presence of triethylamine with chloroform as solvent differed from the reactions of 131 with 13 and 129 in that only one cyclic isomer 128 was obtained, rather than two. In addition, the corresponding acyclic isomer 148 was isolated and characterized. A reaction time of 3 hours following the addition of the sulfonyl bromide was found to be adequate. Removal of the triethylamine hydrochloride by-product by aqueous extraction followed by evaporation of the organic solvent gave a reddish-black oil.
which yielded the crude product 128 as a crystalline precipitate upon
dilution with a mixture of benzene and diethyl ether. Evaporation of the
filtrate and treatment of the resulting oil with diethyl ether gave a
solid from which pure 148 was isolated by fractional crystallization. In
a typical reaction, an 87% yield of crude product was realized, of which
85% was 128 and 15% was 148 as determined by nmr analysis. A pure sample
of 128 was obtained by crystallization from hexane - methyl ethyl ketone.
During crystallization, much decomposition occurred and it became apparent
that 128 was unstable to dissolution in hot solvent. That 128 was a cyclo-
adduct was revealed by its ir spectrum, which showed strong sulfone bands
but no absorption attributable to an enamine. Besides signals expected

![Diagram of 128 and 148]

for an unsubstituted and a p-nitro-substituted phenyl ring, the nmr spec-
trum (CDCl₃) displayed a sharp doublet at δ 5.36 (benzylic protons, 2) J =
9 Hz, a triplet at δ 3.70 (proton on C-3, 1) J = 9 Hz, and a singlet at
δ 2.14 (N-methyl protons, 6). By comparing the chemical shift of the last
signal (δ 2.14) with the corresponding absorption in 126a (δ 2.10) and 127a
(δ 2.08), 128 was tentatively assigned a cis-configuration for the aromatic
groups. If 128 possessed a trans-configuration, presumably the dimethyl-
amino protons would have then been shielded by the aromatic ring cis to
the dimethylamino group, and thus shifted to higher field as in 126b and 127b. The equivalent nature of the benzylic protons was unexpected since they are formally nonequivalent as a consequence of the p-nitro substituent on one of the aromatic rings. Perhaps a solvent other than CDCl₃ would have revealed a difference in chemical shifts. Since no evidence of a third type of dimethylamino group was present in the nmr spectra of any of the crude products obtained from the reaction of 131 with the sulfene derived from 130, the assignment of a cis-configuration to 128 seemed reasonable. The decreased stability of the p-chloro-substituted trans-isomer 127b compared to the unsubstituted trans-isomer 126b suggested that the presence of the electron-withdrawing chlorine atom had a deleterious effect on the structural integrity of 127b. Thus, a further decrease in stability would have been expected for the trans-form of 128 because of the greater electron-withdrawing capacity of the nitro group compared to the chlorine atom. Perhaps the trans-isomer was formed in the reaction of 131 with 130, but because of the enhanced acidity of the p-nitrobenzylic proton, it underwent rapid epimerization and ring cleavage in the presence of triethylamine to give 128 and 148.

Compound 148 was obtained as bright yellow needles upon crystallization from n-butanol. That it was an acyclic isomer was evident from the ir spectrum, which showed a strong enamine band at 1625 cm⁻¹ and sulfone bands at 1297 and 1135 cm⁻¹. Comparison of the asymmetrical stretching frequency of the sulfone group in 128 with that in 148 showed that a definite shift to lower frequency had occurred with the latter (Δν = 33 cm⁻¹). A similar shift (Δν = 44 cm⁻¹) was observed when 126a was compared with 132. Comparing the values stated in the literature (15) for 149 and the corresponding acyclic isomer 150 gave Δν = 40 cm⁻¹. This decrease in
frequency seen for the acyclic isomers is probably attributable to conjugation of the sulfonyl moiety with the enamine double bond. The nmr spectrum of 148 showed similarities to that of 132. In addition to signals

\[
\begin{align*}
&\text{N(CH}_3\text{)}_2 \\
&\text{S} \\
&\text{O}_2
\end{align*}
\]

assigned to the unsubstituted and \( p \)-nitro-substituted phenyl rings, it revealed a singlet at \( \delta 7.11 \) (vinyl proton, 1), a singlet at \( \delta 4.13 \) (benzyl protons, 2) and a singlet at \( \delta 2.67 \) (N-methyl protons, 6). The bright yellow colour of 148 suggested that the \( p \)-nitro substituent was on the phenyl ring which was conjugated with the enamine double bond and not on the aromatic ring of the benzylsulfonyl group. This assignment was in agreement with the uv spectrum (\( \text{CH}_3\text{CN} \)), which showed maxima at 250 and 271 nm, \( \epsilon 18,700 \) and 19,700, respectively. The uv spectrum (\( \text{CH}_3\text{OH} \)) of \( p \)-nitrostyrene has been reported to have a maximum at 303 nm, \( \epsilon 14,500 \) (95). Presumably, steric effects as well as the nature of the substituents on the double bond would account for the shift of \( \lambda_{\text{max}} \) from 303 to 271 nm. As indicated previously, acyclic isomer 132 possessed a maximum in the uv (\( \text{CH}_3\text{CN} \)) at 253 nm, \( \epsilon 15,800 \). A trans-relationship of the dimethylamino and \( \alpha \)-benzylsulfonfyl groups was assigned to 148 for the same reasons that 132 was considered to possess this configuration. Because of the position of the \( p \)-nitrophenyl ring in 148, this isomer must have arisen by ring cleavage of a cyclic intermediate 151. Cleavage of bond a in 151 would give
148, whereas cleavage of bond b would give the corresponding acyclic iso­
mer, which was not observed. Possibly, abstraction of the more acidic β-

\[
graphical\text{structure: 151}
\]

nitrobenzylic proton initiates the cleavage to give 148. When a sample of pure cyclic isomer \(\text{128}\) was dissolved in acetonitrile and allowed to sit at room temperature, it decomposed, causing the solution to turn a bright orange. Nmr analysis of the residue obtained by evaporating the solvent after 43 hours showed that 87% of the material was accounted for, of which 24% was \(\text{128}\) and 76% \(\text{148}\). The tertiary amino group of \(\text{128}\) may be sufficiently basic to cause proton abstraction at room temperature.

A series of thietane 1,1-dioxides prepared by reacting ketene diethylacetal with the sul芬es derived from \(\text{13, 129}\) and \(p\)-nitrophenylmethanesulfonyl chloride has been reported (21). A similar trend was observed when the chemical shifts of the benzyl protons of these adducts were compared to those of \(\text{126a, 127a}\) and \(\text{128}\) (Table II).
TABLE II

Comparison of the Chemical Shifts of the Benzylic Protons of the 3-Dimethylaminothietane 1,1-dioxides with Those Reported for Related 3,3-Diethoxythietane 1,1-dioxides

<table>
<thead>
<tr>
<th>X</th>
<th>(\delta(H_d)) *</th>
<th>(\delta(H_a)) CDC1 (_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>5.37</td>
<td>5.28</td>
</tr>
<tr>
<td>Cl</td>
<td>5.35</td>
<td>5.22</td>
</tr>
<tr>
<td>NO(_2)</td>
<td>5.55</td>
<td>5.36</td>
</tr>
</tbody>
</table>

* Presumably the same solvent was used for all three compounds. Values are taken from reference 21.
Synthesis of Thiete 1,1-dioxides

The synthesis of 2,4-diphenylthiete 1,1-dioxide (152) had been previously accomplished (14) and has recently been reported in the literature (50). For the sake of completeness and since more experimental details became available as a result of the present investigation, the preparation of 152 was included in the Experimental. Treatment of 126a or a mixture of 126a and b with 40% peracetic acid at 0° gave 152 directly, without heating. The crude product was obtained in good yield and found to be relatively free of contaminants by ir and nmr spectroscopy. Other syntheses of thiete 1,1-dioxides by amine oxide elimination have been reported (45,59), which proceeded spontaneously at room temperature without isolation of the N-oxide intermediate. These examples, as well as the formation of 152, probably fit into that category of the amine oxide elimination reaction that has been described as a reversed Michael addition (96,97). The melting point reported (50) for 152, 133-134° (CHCl₃), was low compared to that obtained in the present work, 137-138° (hexane-benzene). This discrepancy was probably the result of the difficulties encountered in recrystallizing the product. Decomposition occurred when 152 was heated in solution. Of several solvents systems investigated, minimum decomposition appeared to occur in hexane-benzene. Whereas an inconclusive elemental analysis has been recorded (50) for the carbon content of 152, satisfactory carbon and hydrogen analyses (±0.4% of theoretical) were obtained for 152 prepared in this laboratory (14). The ir spectrum of 152 showed the absence of the dimethylamino group and a weak band at 1622 cm⁻¹ which was attributed to an olefin double bond conjugated with a phenyl ring (98a). The asymmetrical stretching band of the sulfonyl
group appeared at 1303 cm\(^{-1}\) as compared to 1320 cm\(^{-1}\) in the starting material. This shift to lower frequency was thought to be due to conjugation, as observed with the enamino sulfones, 132 and 148. A maximum occurred in the uv spectrum (CH\(_3\)CN) at 255 nm (ε19,600). A comparable spectrum (EtOH) has been reported for 115, \(\lambda_{\text{max}}\) 253 nm (ε14,000) (15). Besides the

![Diagram 152

10 aromatic protons, the nmr spectrum (CDCl\(_3\)) of 152 showed a doublet at \(\delta 7.03\) (olefinic proton, 1) \(J = 2\) Hz, and a doublet at \(\delta 5.92\) (benzylic proton, 1) \(J = 2\) Hz. The two heterocyclic ring protons were readily assigned by referring to the nmr spectrum (CDCl\(_3\)) of 115, in which the olefinic proton was reported to appear as a triplet at \(\delta 7.0\), \(J = 2\) Hz, and the methylene protons as a doublet at \(\delta 4.54\), \(J = 2\) Hz (15). On this basis, the nmr spectral data given for 152 in the literature (50) are apparently incorrect in that the assignments for the olefinic and benzylic protons were reversed.

Treatment of cis-2-(4-chlorophenyl)-4-phenyl-3-dimethylaminothietane 1,1-dioxide (127a) as a slurry in glacial acetic acid with 40% peracetic acid at 0° gave a mixture of two thiete 1,1-dioxide isomers, 153a and b, with 153a as the major component. The two isomers were separated by fractional crystallization from ethanol 95. The ir spectra of 153a and b showed distinct similarities to each other and to that of the unsubstituted isomer 152. In the nmr spectrum (CDCl\(_3\)) of 153a, the olefinic proton appeared as a doublet at \(\delta 7.02\), \(J = 2\) Hz, and the benzylic
proton as a doublet at δ 5.91, J = 2 Hz. The corresponding protons in the spectrum (CDCl₃) of 153b appeared at δ 6.98 and 5.85, respectively, with J = 2 Hz. That the p-chlorobenzylic proton of 153b appeared at higher field than the benzylic proton of 153a was in accord with the nmr spectrum (CDCl₃) of 127a. The difference between the chemical shifts for each of the two types of ring protons in the two isomers were sufficiently large in the 100 MHz spectrum that integration of these protons could be used to determine the proportions of 153a and b in mixtures. The assignment of the double bond positions in 153a and b was supported by comparison of the uv spectra. In the spectrum of 153a, maxima were apparent at 262 and 294 nm (ε₂₆₂ 26,300, ε₂₉₄ 1,400) whereas in that of 153b, maxima were seen at 230 and 256 nm (ε₂₃₀ 20,300, ε₂₅₆ 22,600). The maximum at longer wavelength in the spectrum of 153b was reminiscent of that observed for the unsubstituted isomer 152, 255 nm (ε₁₉,600). The bathochromic shift observed in the spectrum of 153a when compared to that of 153b was attributed
to the p-chlorophenyl group being conjugated with the double bond in 153a and not conjugated in 153b. In support of this assignment was the observation that 153a was formed in preference to 153b. Assuming that the cis-configuration previously assigned to 127a was correct, then in terms of geometry, the two benzylic protons would show an equal probability of being abstracted in an elimination reaction regardless of whether or not the abstraction process was intermolecular or intramolecular (96). However, when the presumed relative acidities of the two protons are considered, as well as the predicted relative stabilities of the two products (153a and b), then it seems reasonable that the formation of 153a should be favored over that of 153b. A reaction which more clearly showed that 153a was the preferred product was run by adding 40% peracetic acid to a dilute solution of 127a in tetrahydrofuran at room temperature. A 97% yield of crude product was obtained, which was found by nmr analysis to consist of 65% 153a and 35% 153b. Further chemical evidence supporting the assignment of the double bond positions in 153a and 153b will be presented later in the discussion when the thermolysis of the thiete 1,1-dioxides is considered.

The amine oxide elimination reaction was also carried out using 127b, which had tentatively been assigned a trans-configuration with the p-chlorophenyl group cis to the dimethylamino group. It had been hoped that this reaction would confirm the assignment, since in this configuration only the benzylic proton of the unsubstituted phenyl group was cis to the dimethylamino group and thus, according to the postulated intramolecular mechanism for amine oxide elimination (96), thiete 1,1-dioxide isomer 153b should be obtained preferentially. However, when the reaction was run by adding 40% peracetic acid to a slurry of 127b in glacial acetic at 0°, the crude product (89%) was found to consist of 95% 153a and 5%
These results indicated that if the intramolecular elimination mechanism were operative, then the configuration assigned to 127b was probably incorrect. However, when the reaction was repeated by adding peracetic acid to a dilute solution of 127b in tetrahydrofuran at room temperature, the result was in agreement with that predicted by the intramolecular mechanism for the assigned trans-configuration. The crude product (85%) was found by nmr analysis to consist of 82% 153b and 18% 153a. The results from the two reactions suggested that in dilute THF solution the elimination occurred by the proposed intramolecular mechanism (96), whereas in glacial acetic acid an intermolecular process (E2) effectively competed with the intramolecular mechanism. An intermolecular mechanism which gave 153a preferentially from the amine oxide derivative of 127b may be ration-
alized by assuming that in glacial acetic acid the amine oxide intermediate exists in equilibrium with its protonated form 154. Elimination then could be accomplished by nucleophilic attack by an acetate anion on the least sterically hindered hydrogen \( \theta \) to the N,N-dimethylhydroxylamine leaving group. Consideration of the puckered conformation of 154 indicated that the p-chlorobenzylic proton, which occupied a pseudoequatorial position, was much less hindered than the pseudoaxial benzylic proton and, therefore, would be the most likely candidate for removal by a nucleophile. As well, the p-chlorobenzylic proton more closely approximated the ideal trans-diaxial configuration for leaving groups than did the pseudoaxial benzylic proton.

Because of the instability of 128 to recrystallization, crude material containing approximately 12% acyclic isomer 148 was used in the preparation of the corresponding thiete 1,1-dioxide 155. The reaction was run in the same manner as for the synthesis of 152. However, the elimination was found to be relatively rapid and, therefore, a shorter reaction period was required. Nmr analysis of the crude product (96%, based on the calculated amount of 128 in the starting material) indicated that it was free of contaminants and that it consisted of a single isomer (155). The crude material was readily crystallized from ethanol 95 to give 155 as pale
yellow plates. The ir spectrum showed, besides characteristic nitro group absorption, distinct similarities to that of 152. In addition to the 9 aromatic protons, the nmr spectrum (DMSO-d$_6$) displayed doublets at $\delta$ 8.18 and 6.49 ($J = 2$ Hz), which were attributed to the olefinic and benzylic protons, respectively. The chemical shifts for the corresponding protons in the spectrum (CDCl$_3$) of 152 were $\delta$ 7.03 and 5.92. Disregarding possible effects due to a difference in solvent, the greater downfield shift seen for the olefinic proton ($\Delta \delta = -1.15$) compared to that of the benzylic proton ($\Delta \delta = -0.57$) in going from 152 to 155 suggested that the electron-withdrawing p-nitrophenyl group was conjugated with the double bond in 155.

Comparison of the uv spectra (CH$_3$CN) of 152 ($\lambda_{max}$ 255 nm) and 155 ($\lambda_{max}$ 288 nm) revealed a bathochromic shift, which supported this assignment. Presumably, the enhanced acidity of the p-nitrobenzylic proton compared to that of the benzylic proton in 128, together with the expected greater stability of isomer 155 compared to the isomer in which the unsubstituted phenyl group was conjugated with the double bond, predisposed 128 to yield only 155 upon amine oxide elimination.

Base-catalyzed isomerizations of the thiete 1,1-dioxides 153a, 153b and 155 might be useful since such experiments may provide more evidence for the position of the double bond in these compounds. Base-catalyzed isomerizations of thiete 1,1-dioxides are known (52,59,76). For example, treatment of 156 with potassium hydroxide in tetrahydrofuran at
room temperature gave a 90% yield of the endocyclic isomer (157) (76). It was postulated that formation of the more stable allylic carbanion was involved in the isomerization (76).

Thermolysis of Thiete 1,1-dioxides

King and co-workers have recently reported that thermolysis of thiete 1,1-dioxide (103) at 615° under high vacuum gave rise to a cyclic sulfinic acid ester (sultine) 158 in 70% yield. When 103 was thermolyzed at 950°, acrolein (159) was obtained in 85% yield. They have interpreted these results in terms of an electrocyclic ring opening of 103 to give vinylsulfene (160). This species, depending on the temperature, then underwent intramolecular rearrangement to give 158 or the intermediate 161. Loss of sulfur monoxide (desulfinylation) by 161 gave the α,β-unsaturated
carbonyl compound 159. Evidence supporting this mechanism was obtained by trapping the proposed intermediate 160 by heating a solution of 103 in benzene at 220° with an excess of phenol, which gave the predicted sulfonate ester 162 in 15% yield (67, 86). When 115, the phenyl analogue of 103,

\[
\begin{align*}
103 & \xrightarrow{\Delta} \begin{array}{c}
\text{[}
\begin{array}{c}
\text{SO}_2
\end{array}
\end{array} \\
160
\end{align*}
\]

was thermolyzed at 455° a mixture of sultine 163 and \(\alpha,\beta\)-unsaturated ketone 164 was obtained (67). When the thermolysis was carried out at 950°, the

\[
\begin{align*}
\text{115} & \xrightarrow{455^\circ} \text{163} + \ \text{164}
\end{align*}
\]

yield of 164 was 85% (86).

Considering the structural resemblance, similar results might be expected from the thermolysis of 152. It had been observed that at the melting point of 152 a vigorous evolution of gas bubbles occurred. The ir spectrum of the residue remaining after the evolution of gas had subsided was almost identical to that of trans-chalcone (165a). It was sub-
sequently found by glc that a sample of 152 heated at 166° for 3 minutes gave 165a to the extent of 92%. A second, minor peak was present in the chromatogram, which was tentatively identified as cis-chalcone (165b). It is known (99) that exposure of a solution of 165a to sunlight readily gives rise to 165b. Glc of a CHCl₃ solution of 165a before and after exposure to sunlight revealed that a second component was obtained, presumably 165b. The retention time of this component was identical to that of the minor constituent in the thermolysate obtained from 152. Probably no significance can be attached to the observation that mainly the trans-isomer 165a was formed in the thermolysis of 152, since it is known that chalcone is susceptible to thermal isomerization (99). Although the absence of peaks other than the two attributed to 165a and b in the chromatogram of the thermolysate, as well as the high yield of 165a obtained, suggested that a sultine was not present, its formation cannot be ruled
out at the present time.

The thermolysis of thiete 1,1-dioxides to give the corresponding \( \alpha, \beta \)-unsaturated carbonyl compounds was of special significance when the \( p \)-chlorophenyl isomers 153a and b were considered. If the assigned structures were correct, then according to the mechanism proposed by King and co-workers for the thermal conversion of thiete 1,1-dioxide to acrolein (67,86), thermolysis of 153a should have given benzylidene \( p \)-chloroacetophenone (166), whereas thermolysis of 153b should have yielded \( p \)-chlorobenzylidene acetophenone (167). Indeed, these were the observed results.

\[
\begin{align*}
\text{Cl} & \quad \text{H} \\
\text{S} & \quad \text{O}_2 \\
\begin{array}{c}
\text{153a} \\
\text{Cl} \\
\end{array} & \quad \text{H} \\
\text{S} & \quad \text{O}_2 \\
\begin{array}{c}
\text{153b} \\
\text{Cl} \\
\end{array} & \quad \text{Cl} \\
\end{align*}
\]

\[
\text{O} \quad \text{C} \quad \text{CH} \quad \text{CH} \\
\begin{array}{c}
\text{166} \\
\text{Cl} \\
\end{array} & \quad \text{Cl} \\
\text{CH} \quad \text{CH} \quad \text{C} \\
\begin{array}{c}
\text{167} \\
\text{Cl} \\
\end{array}
\]

Heating a sample of pure 153a at 164\( ^\circ \) for 3 minutes gave an 80% yield of 166 and no 167, as determined by glc. In the same manner, pure 153b gave an 85% yield of 167 with no 166 observed. The ir spectra of the thermolysates from 153a and 153b were almost identical to those of authentic samples of 166 and 167, respectively.

A similar thermolysis performed on the \( p \)-nitrophenyl isomer 155 gave a product possessing strong bands in the ir at 1663, 1592 and 1212
cm\(^{-1}\), which were indicative of an \(\alpha,\beta\)-unsaturated ketone. One major peak was observed when the thermolysate was analyzed by glc. However, an authentic sample of the predicted benzylidene \(p\)-nitroacetophenone (168) was not prepared for reference.

According to the proposed mechanism whereby thiete 1,1-dioxides may yield \(\alpha,\beta\)-unsaturated carbonyl compounds (67,86), transformation of 152 to 165a presumably involved loss of sulfur monoxide from the sulfene intermediate 169. The successful trapping of the analogous intermediate 160 derived from thiete 1,1-dioxide (103) prompted a similar attempt utilizing 152. It was anticipated that formation of 169 in the presence of
water would be detected by isolation of the corresponding sulfonic acid 170. That sulfenes readily react with water to yield sulfonic acids is known (22). The reaction was carried out by refluxing a sample of 152 in a mixture of tetrahydrofuran and water (4:1). During the reflux, the odor of hydrogen sulfide was apparent. This observation may be significant with respect to the proposed desulfinylation of sulfenes to give carbonyl compounds (67,86), since it has been shown (in the gas phase) that sulfur monoxide (SO) is extremely reactive and disproportionates to give disulfur monoxide (S₂O), which in the presence of water decomposes to form hydrogen sulfide (100). Work-up of the refluxed reaction gave a water soluble, acidic solid 170 in 71% crude yield and 7% 165a. A ketonic sulfone 171 in 11% crude yield was also isolated. The nature of 171 will be considered separately. The acidic material 170 displayed characteristic sulfonic acid bands in the ir and formed a crystalline salt with dimethylamine.

Besides a multiplet attributable to 10 aromatic protons, the nmr spectrum (DMSO-d₆) showed a doublet at δ 6.61 (α-styryl proton, 1) J = 7 Hz, a singlet at δ 6.56 which was superimposed on the upfield signal of the doublet (benzylic proton, 1) and a doublet at δ 4.57 (β-styryl proton, 1) J = 7 Hz. Apparently, the benzylic proton was orientated in such a manner with respect to the β-styryl proton that no coupling between the two protons was observable at 60 MHz. The magnitude of the coupling between the styryl protons was indicative of a cis-configuration. Maxima in the uv spectrum (CH₃CN) occurred at 253 (ε 21,600), 282.5 (shoulder) (ε 2,740) and 292 nm (ε 1,450).

A definite similarity was observed between this spectrum and that reported (101) for 172, the carboxylic analogue of the structure proposed for 170, which showed maxima (EtOH) at 252 (ε 22,490), 283.5 (ε 2,080) and 292.5 nm.
(≤ 1,320). The configuration of 172 was not specified (101). The nmr

\[
\begin{array}{c}
\text{H} \\
\text{CH} \equiv \text{CH} \quad \text{CH} \\
\text{CO}_2\text{H}
\end{array}
\]

172

spectrum (CDCl\textsubscript{3}) of the dimethylamine salt of 170 was interesting in that it revealed coupling between the benzylic and α-styryl protons (\(J = 2\) Hz) as well as a decrease in the coupling between the styryl protons (\(J = 5.5\) Hz). The uv spectrum (H\textsubscript{2}O) of this material was almost identical to that of the free acid. On one occasion a sample of 170 being stored in a desiccator decomposed to give an oil. Washing the oil with water caused a solid to separate which possessed strong absorption in the ir at 1358, 1190 and 1168 cm\textsuperscript{-1}, characteristic of a sulfonic acid ester. Although the matter was not further pursued, the proposed structure of 170 is such that intramolecular sulfonation to give a γ-sultone 173 may be possible (102).

\[
\begin{array}{c}
\text{H} \\
\text{CH} \equiv \text{CH} \quad \text{CH} \\
\text{SO}_3\text{H}
\end{array} \quad ? \quad \begin{array}{c}
\text{H} \\
\text{O} \quad \text{S} \\
\text{O}_2
\end{array}
\]

170 173

The compound 173 is known and has been reported to show sulfonic ester bands at 1344 and 1172 cm\textsuperscript{-1} in the ir (53).

\textbf{Bis(1,3-diphenyl-3-oxopropyl) Sulfone}

As previously mentioned, crystallization of 152 from hot solvents
caused some decomposition. This was especially noticeable when the solvent was ethanol. Examination of the evaporated mother liquor from a crystallization in ethanol revealed the presence of trans-chalcone (165a) and a white solid which was subsequently identified as bis(1,3-diphenyl-3-oxopropyl) sulfone (171). To determine the extent to which 152 was converted to 171, a sample of the thiete 1,1-dioxide was refluxed in ethanol 95 for 2 hours. The yield of crude 171 was 17%. Crystallization from hexane - methyl ethyl ketone gave short, white needles, m.p. 184 - 185°. Besides sulfone absorptions at 1307 and 1138 cm\(^{-1}\), ir bands indicating the presence of a benzoyl group occurred at 1683 and 1241 cm\(^{-1}\). The nmr spectrum (Figure 2) showed a multiplet at \(\delta 7.93 - 7.67\) (protons ortho to carbonyl groups, 4) and a second multiplet at \(\delta 7.53 - 7.23\) (protons meta and para to carbonyl groups, 6, and phenyl protons, 10). An ABX pattern was present, with the centre of the X quartet at \(\delta 4.70\) (equivalent benzylic protons, 2) and the unsymmetrical AB octet at \(\delta 4.20 - 3.39\) (two equivalent pairs of nonequivalent methylene protons, 4). From the 100 MHz spectrum, the chemical shift of protons A was calculated (44b) to be \(\delta 3.717\) (\(J_{AX} = 2.8\) Hz) and that of protons B to be \(\delta 3.925\) (\(J_{BX} = 10.2\) Hz) with \(J_{AB} = 17.5\) Hz. A maximum occurred in the uv spectrum (CH\(_3\)OH) at 244 nm (\(\varepsilon 25,000\)) which was compatible with a molecule containing two benzoyl groups. For
Figure 2. NMR spectrum of bis(1,3-diphenyl-1-oxopropyl) sulfone dissolved in CDCl₃.
example, the spectrum (EtOH) of acetophenone displays a maximum at 240 nm (ε 13,000) (98b).

If crystallizations of 171 from ethanol or hexane - methyl ethyl ketone were allowed to sit for several days, a second crystalline substance 174 was obtained as colourless, transparent plates, m.p. 196 - 197°. The ir spectrum (KBr) of 174 was quite similar but not identical to that of 171, whereas the nmr spectra were superimposable. The structure proposed for 171 possesses two asymmetric centres and, therefore, presents the possibility of meso- and dl-diastereoisomeric forms. That 171 and 174 were either diastereoisomers or merely polymorphs cannot be stated with certainty at the present time. Instances of meso- and dl-diastereoisomers possessing identical nmr spectra have been reported (61).

At its melting point, 171 decomposed with the vigorous evolution of a gas. Glc analysis of the residue remaining after heating a sample of 171 at 200° for 2 minutes revealed a 4:1 mixture of trans- and cis-chalcone (165a and b). The ir and nmr spectra of the thermolysate were

\[
\begin{align*}
171 & \xrightarrow{- SO_2} 2 \quad \left[ \begin{array}{c}
\text{O} \\
\text{C} - \text{CH}_2 - \text{CH} - \\
\end{array} \right] \\
175 \\
\end{align*}
\]

\[
\begin{align*}
171 & \xrightarrow{- H_2} 2 \quad \left[ \begin{array}{c}
\text{O} \\
\text{C} - \text{CH} = \text{CH} - \\
\end{array} \right] \\
165a, b \\
\end{align*}
\]

very similar to those of 165a. These results were readily rationalized in terms of structure 171. Thermal desulfonylation (103) of 171 would be expected to yield a radical intermediate 175 which, upon loss of a hydro-
gen atom, would give the \( \alpha,\beta \)-unsaturated ketones 165a and b.

The synthetic approach to 171 involved the addition of \( \beta \)-mercapto-\( \beta \)-phenylpropioiophenone (176) (104) to trans-chalcone (165a) under free radical generating conditions to give bis(1,3-diphenyl-3-oxo-propyl) sulfide (177). Reactions of a similar nature are known (105). The

\[
\begin{align*}
\text{165a} & \quad + \quad \begin{array}{c}
\text{CCH} \\
\text{SH}
\end{array} \\
\text{176} & \quad \overset{(C_6H_5CO_2)_2}{\longrightarrow}
\end{align*}
\]

sulfide 177 was obtained as an oil, which was not purified but was oxidized directly to give the corresponding sulfone. The crystallized product, m.p. 184 - 185°, was found to have ir, uv and nmr spectra identical to those of 171. A mixture melting point with 171 was not depressed. Like 171, the synthesized material decomposed at its melting point to give chalcone. Similarly, a second crystalline form, m.p. 196 - 197°, was obtained from the crystallizations of the crude product which possessed an ir spectrum that was identical to that of 174.

Compound 171 is formally derived from two molecules of 2,4-diphenylthiethene 1,1-dioxide (152) by the loss of one molecule of sulfur
monoxide and the addition of one molecule of water. Since chalcone was produced along with 171 in the decomposition of 152 in hot ethanol, and since 171 was obtained in low yield, it is tempting to invoke the α,β-unsaturated ketone in the formation of 171. However, in the absence of additional experiments, further speculation as to the origin of 171 is unwarranted.

It should be noted that a cursory examination of the residues obtained upon evaporation of the mother liquors from the crystallizations in ethanol 95 of the substituted thiete 1,1-dioxides 153a, 153b and 155 did not reveal species analogous to 171.

**Synthesis of 3-Cyanothietane 1,1-dioxides**

The addition of hydrogen cyanide to the double bond of thiete 1,1-dioxides has apparently not been previously reported. Treatment of a chloroform-ethanol solution of 152 with hydrogen cyanide in the pres-
ence of potassium cyanide gave the addition product 178 as a fine precipitate in 77% yield. Evaporation of the filtrate yielded an intractable black tar. The precipitate was poorly soluble in common organic solvents. Crystallization from n-butanol gave white, feather-like crystals, m.p. 236 - 237°C. The adduct was stable at the temperature of boiling n-butanol (118°C) and did not appear to decompose at its melting point. In the ir spectrum, characteristic nitrile absorption occurred at 2245 cm⁻¹. Besides a 10 proton multiplet, the nmr spectrum (DMSO-d₆) showed a doublet at δ6.34 (benzylic protons, 2) J = 10.5 Hz, and a triplet at δ4.77 (proton at C-3, 1) J = 10.5 Hz. The equivalency of the benzylic protons and the magnitude of the vicinal coupling constant indicated a cis-configuration for the phenyl groups on the heterocyclic ring. Considering the relative stabilities already noted for cis- and trans-2,4-diphenyl-3-dimethylaminothietane 1,1-dioxide (126a and b), such a result was not unexpected. The course of the reaction may be rationalized by assuming that the cyanide ion attacks from the least hindered side of 152, i.e., the side opposite the phenyl group at C-4, to generate the intermediate carbanion 179, which may possess planar (sp²) geometry at the carbanionic carbon (52). Such a species could then undergo protonation to give preferentially the more stable cis-isomer 178. Even if some trans-isomer were initially formed, epimerization to 178 could presumably occur under the basic conditions (KCN) of the reaction. No reaction was observed in the absence of potassium cyanide.

When the reaction was repeated using a mixture of the p-chloro-substituted isomers, 153a and b, a 56% yield of the addition product 180 was obtained and 14% of the starting material was recovered. Unlike 178,
180 was reasonably soluble in common organic solvents and was readily crystallized from ethanol 95 to give fine, white needles, m.p. 199 - 200°. Nitrile absorption in the ir spectrum occurred at 2280 cm\(^{-1}\). That the product possessed a cis-configuration was indicated by the nmr spectrum (DMSO-\(d_6\)), which showed the benzylic protons as a doublet at 6 6.39 (\(J = 11\) Hz) and the proton on C-3 as a triplet at 6 4.76 (\(J = 11\) Hz).

\[
\text{C} = \text{N}
\]

\[
180, X = \text{Cl}
\]

\[
181, X = \text{NO}_2
\]

With the p-nitro-substituted isomer 155 the chloroform - ethanol solvent mixture was replaced by THF because of the insufficient solubility of 155 in chloroform. Addition of potassium cyanide caused the solution to turn a dark orange. The colour was perhaps attributable to the carbanion species analogous to 179, in which the p-nitro group would tend to stabilize the negative charge. Unlike the reactions with 152 and 153a - b, the addition product 181 did not precipitate from solution. The residue obtained by evaporating the reaction solvent was washed with ethanol 95 to give 181 as a pale yellow solid in 67% crude yield. The product obtained by column chromatography of the evaporated washings raised the yield to 75%. Crystallization from hexane - chloroform yielded pure 181 in two polymorphic forms, one as fine, white needles (m.p. 164 - 165°) and the other as thick, pale yellow needles (m.p. 152 - 153°). The ir spectra
(KBr) of the two forms were essentially identical and showed nitrile absorption at 2275 cm$^{-1}$. The nmr spectra (DMSO-$d_6$) were superimposable and, in addition to the 9 aromatic protons, revealed a pair of partially overlapped doublets, one at $\delta$ 6.56 ($p$-nitrobenzylic proton, 1) $J = 10.5$ Hz, and the other at $\delta$ 6.48 (benzylic proton, 1) $J = 10.5$ Hz, and a triplet at $\delta$ 4.92 (proton on C-3, 1) $J = 10.5$ Hz. By analogy to 178 and 180, 181 was assigned a cis-configuration for the aromatic groups on the heterocyclic ring.

That the two crystalline forms of 181 were actually polymorphs was supported by the observation that recrystallization of either the high or low melting form gave a mixture of the two crystal types upon cooling.

The residue obtained from the ethanol washings of crude 181 was subjected to column chromatography. Fractionation of this material was prompted by the appearance in its ir spectrum of a medium intensity band at approximately 2220 cm$^{-1}$, which was indicative of a conjugated nitrile, particularly of the cinnamonitrile-type (106). The fraction possessing the characteristic band was obtained as a yellow solid. It became apparent from the behavior of this substance on crystallization that it was a mixture of two components 182a and b which were subsequently separated. The ir spectra of 182a and b were similar and showed nitro group and conjugated nitrile absorption. Sulfone bands were absent. On the basis of the ir data alone, it appeared that 182a and b were base-catalyzed elimination products derived from 181. The presence of the cyano group in 181 would be expected to enhance the acidity of the proton at C-3 and thus promote $\beta$-elimination of the sulfonyl group on exposure to base (107). A possible mechanism for this elimination, assuming it to be a stepwise process, is outlined in Scheme III using structure 183. Abstraction of
SCHEME III

183 → \(-\text{H}^+\) → 184

185 → \(-\text{SO}_2\) → 187

186 → \(-\text{SO}_2\) → 188

187 + \(\text{H}^+\) → 189

188 + \(\text{H}^+\) → 190
the C-3 proton in 183 would give carbanion 184, which could presumably undergo ring opening to give either 185 or 186 or both, depending on the nature of substituents A and B. Loss of SO₂ (103, 107) from 185 and 186 would then give the corresponding allylic carbanions 187 and 188. Protonation by solvent would yield the respective unsaturated nitriles, 189 and 190, each of which may exist as a pair of geometric isomers. Considering 182a and b to be isomers of either 189 or 190 where A = NO₂ and B = H, gave C₁₆H₁₂N₂O₂ as their molecular formula. The elemental analysis results for both compounds agreed satisfactorily with the proposed formula. It can perhaps be argued that because of the inductive effect of the p-nitro substituent, carbanion 188 (A = NO₂, B = H) would be preferred over the alternate resonance form 187. Thus, 182a and b might be the geometric isomers 191a and b. To some extent, the nmr spectra of 182a and b supported such an assignment and indicated that the structure of 182a was perhaps as shown in 191a and that of 182b was as shown in 191b. The non-aromatic protons of 182a were seen as a singlet at 5.7.08 (olefinic proton, 1) and as a singlet at 5.3.83 (benzylic protons, 2), whereas those of 182b appeared as a singlet at 5.3.93 (benzylic protons, 2). Apparently, the olefinic proton in 182b was shifted downfield relative to that in 182a and was hidden under the aromatic envelope. As well, the signal for the benzylic protons of 182b was shifted downfield compared to that of 182a.
Such downfield shifts could be rationalized in terms of structures 191a and 191b. In 191b the olefinic proton is adjacent to the cyano group and the benzylic protons are proximate to the unsubstituted phenyl ring. As a consequence, these protons are subject to a greater degree of deshielding than are the corresponding protons in 191a, which are further removed from the cyano and phenyl substituents. A maximum occurred in the uv spectrum (CH$_3$CN) of 182a at 278 nm (€26,700). In the spectrum (CH$_3$CN) of 182b the maximum was seen at 269 nm (€39,000). The uv spectrum (EtOH) of compound 192 has been reported (106) to show a maximum at 275 nm (€18,620).

That 182a possessed a lower molar absorptivity than 182b may be the result of the former isomer having the cinnamionitrile chromophore in a cis-configuration as in 191a, whereas the latter isomer possesses this entity in a trans-configuration as in 191b. Presumably, the molar absorptivity of 182b was approximately twice that of 192 because of the contribution made by the p-nitrophenyl group in 182b. Obviously, in the absence of suitable reference compounds, the structures assigned to 182a and b are equivocal.

Evidence that 181 itself, rather than a decomposition product of 155, was the source of 182a and b was obtained by treating a tetrahydrofuran - ethanol solution of 181 with aqueous sodium hydroxide at room temperature. A transient magenta colour was observed during the addition of the base, which was perhaps due to a carbanion species such as 188 (A = NO$_2$, B = H). Nmr analysis of the crude product revealed a 2.4:1 mixture
of \(182a\) and \(b\), respectively. A similar ratio was indicated by glc.

That conjugated nitriles analogous to \(182a\) and \(b\) were not detected in the syntheses of the 3-cyanothietane 1,1-dioxide derivatives \(178\) and \(180\) was perhaps due to the fact that under the conditions of the addition reaction both \(178\) and \(180\), unlike \(181\), precipitated from solution. Since \(181\) remained dissolved, it was susceptible to proton abstraction. It was also possible that the \(p\)-nitro substituent of \(181\) has an activating effect with regard to \(\beta\)-elimination of the sulfonyl group. Unfortunately, solutions of \(178\) and \(180\) were not subjected to base treatment. If a conjugated nitrile analogous to \(182a\) and \(b\) could be generated from \(178\), it may prove to be a very useful reference compound for assigning structures to \(182a\) and \(b\).

Reduction of 3-Cyanothietane 1,1-dioxides

Although W-2 Raney nickel is generally employed in the catalytic reduction of nitriles to primary amines (108,109), the ability of this catalyst to cause desulfuration of sulfones (110) made its use in the present instance undesirable. A potential substitute appeared to be sponge nickel catalyst, which had been reported (109) to catalyze the hydrogenation of nitriles under unusually mild conditions (room temperature, 40 - 55 p.s.i. hydrogen pressure). There was the possibility that under such conditions desulfuration would not be a serious problem.

The hydrogenation of \(178\) was carried out in the presence of a large excess of ammonia in order to suppress secondary amine formation (108,109). The product, 2,4-diphenyl-3-aminomethylthietane 1,1-dioxide (193), was obtained as a white solid in 41% crude yield. In the ir spec-
trum of 193, characteristic primary amine bands were present at 3425 and 3365 cm$^{-1}$, and strong sulfone absorption was apparent. The nmr spectrum was in agreement with the proposed structure. In view of the susceptibility of the p-nitro analogue of 178 to base-catalyzed $\beta$-elimination, the relatively low yield of primary amine 193 was perhaps attributable to loss of 178 by desulfonylation in the presence of ammonia. Products resulting from such a process may have gone undetected during the work-up of the hydrogenation.

$\text{HCHO}/\text{HCO}_2\text{H}$

90 - 100°

$\text{H}_2\text{N(CH}_3\text{)}_2$

9, $X = H$

124, $X = Cl$

125, $X = NO_2$
In an attempt to improve the yield of 193, reduction of 178 by diborane was investigated. It has been reported that nitriles are rapidly reduced by this agent, whereas the sulfonyl group is not affected (111). Reaction of 178 with diborane in tetrahydrofuran at room temperature gave 193 in 50% crude yield. In addition to the primary amine, a white solid was isolated which was tentatively identified as a borane derivative of 193.

Diborane reduction of 2-(4-chlorophenyl)-3-cyano-4-phenylthietane 1,1-dioxide (180) gave a 75% crude yield of the corresponding primary amine 194. The low melting product showed a broad, weak band in the N-H stretching region and strong sulfone absorption. The nmr spectrum was in accordance with the proposed structure.

The diborane procedure appeared to be the method of choice for converting 2-(4-nitrophenyl)-3-cyano-4-phenylthietane 1,1-dioxide (181) to the primary amine 195 since the nitro group is inert to diborane under conditions that allow nitrile reduction (111). The material obtained following treatment of 181 with diborane was grossly purified by column chromatography, which gave 195 as a pale yellow oil in 66% yield. Both the ir and nmr spectra of this oil agreed with the proposed structure. An elemental analysis was not obtained for 195.

**Dimethylation of 3-Aminomethylthietane 1,1-dioxides**

The primary amines, 193, 194 and 195, were converted to the corresponding dimethylated derivatives 2, 124 and 125 by the Eschweiler-Clarke procedure (112), which involved warming the amines in a mixture of formaldehyde and formic acid. That the reaction proceeded readily in all three cases was evidenced by the vigorous evolution of a gas, presumably carbon
dioxide (112). The crude products were obtained in good yields and were found to be reasonably pure by nmr analysis. Satisfactory elemental analyses were obtained for 9 and 124. Attempts to prepare suitable derivatives of 125 for elemental analysis were unsuccessful and, therefore, the assignment of structure to this compound rests on spectroscopic data only.

In Table III are summarized the pertinent chemical shift data for the 3-dimethylaminothietane 1,1-dioxides, 126a, 127a and 128. The chemical shift data for the corresponding 3-dimethylaminomethyl homologues are entered in Table IV. Comparison of the chemical shifts of the heterocyclic ring protons in Table III with those in Table IV shows a definite upfield shift for these protons in going from the 3-dimethylamino to the 3-dimethylaminomethyl compounds, the shift being greater for the C-3 proton than for the protons at C-2 and C-4. Such an effect was to be expected as a consequence of the replacement of nitrogen at C-3 for the less electronegative methylene carbon (113).

Of special interest were the chemical shifts for the methylene protons listed in Table IV. As previously mentioned, chemical and nmr evidence indicated that the configuration of 2,4-diphenyl-3-cyanothietane 1,1-dioxide (178) was such that the aromatic groups were cis to each other and trans to the cyano substituent. Although, on the basis of the same chemical evidence, the p-substituted 3-cyano derivatives 180 and 181 were assumed to possess the same configuration as 178, the nmr evidence was not as explicit for these compounds as for 178 because of the formally non-equivalent nature of their benzylic protons. The data in Table IV, however, appear to confirm that 178, 180 and 181 all possessed the same configuration. The nmr spectrum of 9, like that of the corresponding 3-cyano compound 178, indicated a cis-configuration for the phenyl groups.
TABLE III

Chemical Shift Values of the 3-Dimethylaminothiostane 1,1-dioxides

\[
\begin{align*}
\text{Compound} & \quad X & \quad \delta H_a & \quad \delta H_b & \quad \delta H_c & \quad \delta N(CH_3)_2 \\
126a & \quad \text{H} & 5.28 & 5.28 & 3.68 & 2.10 \\
127a & \quad \text{Cl} & 5.22 & 5.25 & 3.57 & 2.08 \\
128 & \quad \text{NO}_2 & 5.36 & 5.36 & 3.70 & 2.14
\end{align*}
\]
**TABLE IV**

*Chemical Shift Values of the 3-Dimethylaminomethylthietane 1,1-dioxides*

![Chemical Shift Diagram](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>X</th>
<th>$\delta H_a$</th>
<th>$\delta H_b$</th>
<th>$\delta H_c$</th>
<th>$\delta N(CH_3)_2$</th>
<th>$\delta CH_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>H</td>
<td>5.13</td>
<td>5.13</td>
<td>3.10</td>
<td>2.06</td>
<td>2.62</td>
</tr>
<tr>
<td>124</td>
<td>Cl</td>
<td>5.09</td>
<td>5.13</td>
<td>3.06</td>
<td>2.06</td>
<td>2.60</td>
</tr>
<tr>
<td>125</td>
<td>NO$_2$</td>
<td>5.23</td>
<td>5.17</td>
<td>3.13</td>
<td>2.10</td>
<td>2.64</td>
</tr>
</tbody>
</table>
similarity of the chemical shifts of the methylene protons of 124 and 125 to that of these protons in 9 was strong evidence that the configurations of all three 3-dimethylaminomethyl compounds were the same. An alternate arrangement for 124 or 125 in which one of the aromatic rings was cis to the dimethylaminomethyl group would be expected to significantly shift the methylene absorption from the position observed in the spectrum of 9. The chemical manipulations whereby the 3-cyano compounds 178, 180 and 181 were converted to the 3-dimethylaminomethyl derivatives were such that epimerization at any of the carbons of the heterocyclic ring was unlikely. Therefore, it followed that the configurations of 180 and 181 were probably identical to that of 178.

Synthesis of 2,4-Diphenyl-3-carboxythietane 1,1-dioxide and 2,4-Diphenyl-3-acetylthietane 1,1-dioxide

Initially, the synthesis of 2,4-diphenyl-3-(1-dimethylaminoethyl)thietane 1,1-dioxide (123) was attempted through the 3-cyano derivative 178. 2,4-Diphenyl-3-carboxythietane 1,1-dioxide (196) and 2,4-diphenyl-3-acetylthietane 1,1-dioxide (197) were intermediates in that approach.

2,4-Diphenyl-3-carboxythietane 1,1-dioxide (196) was prepared by refluxing 178 in a mixture of dimethyl sulfoxide and 50 per cent aqueous sulfuric acid. The dimethylsulfoxide allowed for the formation of a homogeneous mixture at reflux temperature. Work-up of the hydrolysate gave the crude carboxylic acid as an off-white solid in high yield. In the ir spectrum of 196, the presence of the carboxyl group was evidenced by an O - H stretching band at 3270 cm⁻¹ and a strong carbonyl band at 1730 cm⁻¹. The integrity of the thietane 1,1-dioxide ring was revealed by the appearance of the C-2 and C-4 protons as a doublet at δ 5.90 (J = 10 Hz) in the
nmr spectrum. The acid was readily soluble in 5 per cent sodium hydroxide and caused the evolution of a gas, presumably carbon dioxide, when added as a DMSO solution to 5 per cent sodium bicarbonate. Apparently, the only 3-carboxythietane 1,1-dioxide that has been reported in the literature is the parent compound, 198 (114). However, 198 was synthesized (115) by a route quite different from that employed in the preparation of 196. The infrared spectrum published (114) for 198 showed distinct similarities to that of the 2,4-diphenyl derivative.

Refluxing 196 in thionyl chloride gave the corresponding acid chloride 199 as a cream-coloured solid, quantitatively. The acid chloride was used shortly after preparation without purification. A sample of 199 left sitting in the open for several days reverted to the carboxylic acid 196.

Treatment of 199 with an organocadmium reagent prepared from
methylmagnesium bromide and anhydrous cadmium chloride (116) gave 2,4-diphenyl-3-acetylthietane 1,1-dioxide (197) as a white solid in 68% crude yield. In addition, the carboxylic acid 196 was recovered to the extent of 23%. The infrared spectrum of 197 showed a strong ketone carbonyl band at 1715 cm⁻¹ as well as sulfone absorption. That 197 possessed the same configuration as the 3-cyano compound 178 was interpreted from the equivalency of the benzylic protons and the magnitude of the vicinal coupling constant in its nmr spectrum. The isolation of the carboxylic acid 196 indicated that not all of the acid chloride 199 underwent methylation. This was perhaps due either to too short a reaction period (8 hours) or to loss of organocadmium reagent by metallation of 3-acetyl product already formed (116). Treatment of 197 with hydroxylamine gave the corresponding oxime 200 in good yield.

Synthesis of 2,4-Diphenyl-3-(1-dimethylaminoethyl)-thietane 1,1-dioxide

While the work with 196 and 197 was in progress, a more efficient route to 123 was sought. An approach utilizing the nitroethane adduct of 2,4-diphenylthietane 1,1-dioxide (152) appeared to be quite attractive and was attempted. The base-catalyzed addition of nitroalkanes to vinyl sulfones has been known for some time (117). However, the reaction has apparently not previously been applied to thiete 1,1-dioxides. Treatment of a solution of 152 dissolved in a mixture of nitroethane and ethanol 95 with a nitroethane - ethanol 95 solution of potassium hydroxide at room temperature yielded 2,4-diphenyl-3-(1-nitroethyl)-thietane 1,1-dioxide (201) as a white solid. Crystallization of the adduct from hexane - benzene gave fine, white needles in 74 per cent yield. The ir spectrum showed
strong nitro group absorption at 1554 and 1324 cm\(^{-1}\). The asymmetrical stretching band of the sulfonyl group was coincidental with the latter nitro group absorption and the symmetrical stretching band appeared at 1147 cm\(^{-1}\). In the nmr spectrum the benzylic protons (arbitrarily designated d and e) appeared as a triplet which was attributed to two overlapping doublets, one at 5.33 (benzylic proton e, 1) \(J_{eb} = 10\) Hz, and the other at 5.14 (benzylic proton d, 1) \(J_{db} = 11\) Hz. A multiplet was apparent at 4.83 (proton c, 1) \(J_{cb} = 8\) Hz, \(J_{ca} = 7\) Hz, a multiplet centred at 3.50 (remaining ring proton b, 1) \(J_{be} = 10\) Hz, \(J_{bd} = 11\) Hz, \(J_{bc} = 8\) Hz, and a doublet at 1.33 (methyl protons a, 3) \(J_{ac} = 7\) Hz. The upfield signal of the doublet at 5.14 overlapped the lowest field signal of the multiplet at 4.83. It was considered that the carbanion derived from nitroethane would most likely attack 152 in the same manner as proposed for the cyanide ion, i.e., from the least hindered side, to give a thietane 1,1-dioxide adduct in which the phenyl groups were cis to each other and trans to the substituent at C-3. The nonequivalency of \(H_d\) and \(H_e\) was attributable to the introduction of an asymmetric centre by the \(\alpha\)-nitroethyl group at C-3 rather than to a trans-configuration for the phenyl groups. In view of the larger steric bulk of the \(\alpha\)-nitroethyl group compared to that of the cyano group, a trans-configuration of phenyls in 201 seemed even
less likely than such a configuration in the 3-cyano derivative 178, which was obtained only in the cis-arrangement. A molecular model* indicated that with the thietane 1,1-dioxide ring of 201 in a puckered conformation, non-bonded interactions were possible between the pseudoaxial protons at C-2 and C-4 and the oxygens of the α-nitroethyl group. Presumably, such interactions may have been great enough to restrict rotation about the α-nitroethyl - C-3 bond and thus contribute to the nonequivalency of the benzylic protons. Unfortunately, the effect of elevated temperatures on the nmr spectrum of 201 was not investigated. However, some evidence which at least supported the proposal that the phenyl groups were cis to each other and trans to the nitroethyl substituent at C-3 was eventually obtained and will be presented shortly. A sample of 201 which had been re-crystallized several times from hexane - benzene was submitted for elemental analysis and found to have a carbon content 3.2% greater than that calculated on the basis of its molecular formula. It was subsequently found by nmr and glc analysis that 201 co-crystallized with benzene and that the resulting crystals contained one molecule of benzene for every two molecules of 201. Although it was then most desirable to find a substitute for benzene which would give crystals free of solvent, insufficient product was on hand by the time the anomaly was resolved to permit such an undertaking. The elemental analysis results for all elements present in 201 were satisfactory when compared to the values calculated on the basis of the one-to-two composition of the crystals.

Hydrogenation of a solution of 201 dissolved in tetrahydrofuran

and ethanol 100 in the presence of sponge nickel catalyst under mild conditions gave a mixture of primary amine 202 and oxime 200. The two components were readily separated by dissolving the mixture in chloroform and extracting 202 with 4N hydrochloric acid. Work-up of the extract gave crude 202 (60%) as a cream-coloured solid. Only one spot was observed upon tlc analysis. The ir spectrum revealed N-H stretching absorption, strong sulfone bands and the absence of nitro group absorption. In the nmr spectrum were seen a pair of overlapped doublets, one at δ 5.26 (benzylic proton, 1) \( J = 10 \text{ Hz} \), and the other at δ 5.16 (remaining benzylic proton, 1) \( J = 10 \text{ Hz} \), a diffuse multiplet, δ 3.50 - 2.65 (proton on C-3 and proton \( \alpha \) to amino group, 2), a singlet at δ 1.22 (protons on N, 2), and a doublet at δ 0.87 (methyl protons, 3) \( J = 6.5 \text{ Hz} \). The primary amine was dimethylated without further purification.

Evaporation of the chloroform layer following the extraction of
202 gave a beige-coloured solid (36%), which was found by tlc to consist almost entirely of one component possessing the same R_f value as the oxime 200 derived from 2,4-diphenyl-3-acetylthietane 1,1-dioxide (197). The ir and nmr spectra of the crystallized solid were identical to those of 200.

Presumably, the oxime was an intermediate in the pathway whereby 201 was reduced to 202. The initial product in the hydrogenation of a nitroalkane is known to be the corresponding nitrosoalkane, which rearranges to give an oxime if the nitroso group is attached to a primary or secondary carbon atom (118). Oximes, in turn, yield primary amines upon catalytic reduction (108). Thus, it seemed reasonable that 200 should be formed during the hydrogenation of 201, presumably by rearrangement of the nitroso species 203. The nmr spectrum of 200 showed that the protons on C-2 and C-4 possessed identical chemical shifts and were equally coupled to the proton on C-3 (J = 10 Hz). Thus, like the 3-acetyl compound 197 and its nitrile
precursor 178, 200 was considered to possess a configuration in which the phenyl substituents were cis to each other and trans to the group at C-3. Isolation of 200 in the catalytic reduction of 201 was, therefore, important because it provided evidence that 201 and 202 also possessed such a configuration, even though it was not discernible from their nmr spectra. Of course, such a conclusion was dependent on the assumption that no epimerization occurred during the hydrogenation. That the benzylic protons were equivalent in 200 but not in 201 and 202 was attributable to the fact that the substituent on C-3 in 200, unlike the corresponding substituents in 201 and 202, did not possess an asymmetric centre. As a consequence, even if rotation about the bond joining the oximino group to C-3 in 200 were restricted, symmetry with respect to the benzylic protons would still be attained. However, restricted rotation about this bond in 201 and 202 would render the protons on C-2 and C-4 nonequivalent.

Dimethylation of 202 using the Eschweiler-Clarke procedure (112) gave the tertiary amine 123 as a fairly pure, pale beige-coloured solid (79%). Crystallization from hexane - ethanol afforded fine, white needles. The ir spectrum revealed the presence of a dimethylamino group and strong sulfonyl absorption. As with the primary amine 202, the benzylic protons of 123 were nonequivalent in the nmr spectrum and appeared as a rough quartet, which was attributed to a pair of doublets, one at δ 5.26 (benzylic
proton, 1) $J = 9$ Hz, and the other at $\delta 5.07$ (remaining benzylic proton, 
1) $J = 9$ Hz. Shoulders were apparent on each of the signals of the quartet.

With the success of the nitroethane route to 123, the alternate, 
multi-stepped approach utilizing 2,4-diphenyl-3-acetylthietane 1,1-dioxide 
(197) was examined only in a preliminary fashion. It has been shown (119) 
that oximes are hydroborated to hydroxylamines. More recently, however, 
it has been found that treatment of ketoxime acetates with diborane gives 
amines (120,121). It was, therefore, of interest to see if such a proce­
dure could be applied to 2,4-diphenyl-3-acetylthietane 1,1-dioxide oxime 
(200). Reaction of 200 with acetyl chloride gave an oil which, according 
to its ir spectrum, appeared to be the desired acetate 204. The ester was 
not purified but was dissolved in dry tetrahydrofuran and treated with an

\[
\begin{align*}
200 \underset{\text{CH}_3\text{COCl}}\xrightarrow{\text{THF}} \text{O} & \quad \text{CH}_3 \quad \text{O} \\
& \quad \text{C} \quad \text{N} \\
& \quad \text{H} \quad \text{H} \\
& \quad \text{S} \quad \text{O}_2 \\
& \quad \text{204} \\
1. \text{B}_2\text{H}_2 & \quad 2. \text{H}_2\text{O},\Delta \\
& \quad 3. \text{HCHO/} \text{HCO}_2\text{H},\Delta \\
& \quad \text{123}
\end{align*}
\]

excess of diborane at room temperature. The crude product from the reduc­
tion was reacted directly with a mixture of formaldehyde and formic acid. 
Work-up gave a pale yellow solid (14%), the ir spectrum of which was super­
imposable with that of 123. Failure to reflux the product from the dibor­
rane reduction with mineral acid may have been the cause for the low yield 
of 123 (121).
ANALYTICAL METHODS

Melting points were determined using a Thomas-Hoover Capillary Melting Point Apparatus. All melting points and boiling points are reported uncorrected.

Ultraviolet spectra were obtained using a Bausch and Lomb Model 505 recording spectrophotometer. Solvents are specified.

A Beckman IR-10 infrared spectrophotometer was used to record the infrared spectra.

The nmr spectroscopy was performed by Miss Phyllis Watson of the Department of Chemistry, U.B.C., using a Varian A-60, T-60 or XL-100 spectrometer. The concentration of solutions was ca. 10% and tetramethylsilane served as the internal standard. Solvents are specified. Peak multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet).

Gas-liquid chromatography (glc) was carried out using a Micro-Tek gas chromatograph Model MT-200 equipped with a flame ionization detector. Hydrogen and air flows (per flame) were 60 and 283 ml/min, respectively. The carrier gas was nitrogen and the flow rate is specified. Column characteristics and the temperatures of the injection port, oven, and detector are specified. Peak areas were measured by means of a Disc Integrator Model 222.

Microanalyses were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium, 5251 Elbach über Engelskirchen, Fritz-Pregl-Strasse 14-16, West Germany.
EXPERIMENTAL

1. **Synthesis of β-Dimethylaminostyrene (131).**

   The preparation of β-dimethylaminostyrene was carried out according to a known procedure (15,55). Anhydrous potassium carbonate was employed as the drying agent. Vacuum distillation of the crude product gave a pale yellow liquid with a characteristic odor, bp 63-65° at 0.3 mm (lit. (88) 75-78°, 1 mm); nmr (CDCl₃) δ 7.30-6.90 (m, 5, phenyl protons), 6.73 (d, 1, J = 14 Hz; α-styryl proton), 5.13 (d, 1, J = 14 Hz, β-styryl proton) and 2.70 (s, 6, N-methyl protons) (lit. (88) δ 7.1, 6.65, 5.11, 2.63; J = 13.9 Hz). A 100 MHz spectrum (neat, -10°) of a sample of 131 which had been stored at 0° for 4 months indicated the presence of only one isomer and showed a multiplet at δ 7.24-6.76, a doublet at 6.49 (J = 14 Hz), a doublet at 4.99 (J = 14 Hz) and a singlet at 2.32. At no time was the sample allowed to warm above 0° before obtaining the -10° spectrum. Spectra run at -40° and +35° showed no change in isomeric purity from that observed at -10°. Analysis of a sample of fresh distillate dissolved in acetone by glc on a 6 ft x 5/32 in (i.d.) stainless steel column packed with 5% SE-30 on Chromport (70-80 mesh) with the injection port, oven, and detector at 255, 150 and 243°, respectively, and the nitrogen flow at 54 ml/min gave one peak, retention time 2.5 min.

   The average yield of distilled product from 14 reactions using 60 g (0.5 mole) of phenylacetaldehyde, 45 g (1.0 mole) of dimethylamine and 70 g (0.5 mole) of anhydrous potassium carbonate was 61 g (83%).

2. **Synthesis of Phenylmethanesulfonyl Chloride (13).**

   The procedure was taken from a patent (122). A more detailed description of the patented procedure has appeared in the literature (91).
To a 1000 ml three-necked flask fitted with a mechanical stirrer and a reflux condenser were added 75.6 g (0.60 mole) of benzyl chloride (Fisher Scientific, rea.), 148.8 g (0.60 mole) of sodium thiosulfate pentahydrate (Fisher Scientific, A.C.S.), 150 ml of methanol and 150 ml of distilled water. The mixture was heated under reflux, with stirring, for 4 hours to obtain a homogeneous solution. The condenser was then attached to a still head and approximately 140 ml of solvent was distilled off. After the translucent liquid remaining in the flask had cooled to room temperature, 375 ml of glacial acetic acid was added. The condenser was removed and the flask was equipped with a gas inlet and outlet and a thermometer. The inlet tube was positioned below the solution surface. After cooling to 5° in an ice-water bath, chlorine was passed in at such a rate that the reaction temperature remained at approximately 5°. The reaction was exothermic and required efficient stirring and careful regulation of the gas flow. White precipitate appeared almost immediately and after 3 hours a thick suspension was present. Chlorination was stopped when the suspension became light green and chlorine gas began to collect in the air space above the reaction. The mixture was diluted with 300 ml of distilled water and stirred for several minutes. Suction filtration with water washing, followed by drying in a desiccator overnight, gave 90.3 g (79%) of white solid mp 87-92°. Crystallization from pet. ether (80-100°) - benzene yielded 87.6 g (77%) of white needles, mp 89-92° (lit. (123) 91-92°, from benzene). The ir spectrum (KBr) was identical to that of the crude material and showed strong sulfone bands at 1370 and 1165 cm⁻¹. If crystallization solutions were brown, charcoal treatment was necessary in order to prevent the crystals from being discoloured. Phenylmethanesulfonyl chloride showed a tendency to sublime when warmed under vacuum.

The procedure used was similar to that described for the preparation of 13. A mixture of 148.8 g (0.60 mole) sodium thiosulfate pentahydrate, 96.6 g (0.60 mole) p-chlorobenzyl chloride (Eastman, prac.), 70 ml methanol and 70 ml distilled water was heated at reflux for 30 min. During this time a homogeneous system was momentarily obtained, which rapidly gave rise to a copious white precipitate. Upon cooling to room temperature, 900 ml of glacial acetic acid was added and then the mixture was cooled to 5° and chlorinated. When the suspension became pale green, the chlorination was stopped and the contents of the flask were diluted with 1200 ml of cold, distilled water. The solid was collected by suction filtration and washed with water. After drying, the white material weighed 120.4 g (89%), mp 89-91°. Crystallization from hexane - benzene gave 129 as white needles, mp 92-93° (lit. (69) 93-94°). The ir spectrum (KBr) was identical to that of the crude material and showed the pattern characteristic of a para-substituted phenyl group in the region between 2000 and 1650 cm⁻¹. Strong sulfone bands appeared at 1350 and 1140 cm⁻¹.


In the manner described for the preparation of 13 and 129, 115.3 g (0.53 mole) of p-nitrobenzyl bromide (Aldrich), 227.0 g (0.92 mole) of sodium thiosulfate pentahydrate, 229 ml of methanol and 229 ml of distilled water were heated at reflux for 35 min to give a homogeneous solution. After distilling off approximately 220 ml of solvent, the remaining material was allowed to cool to room temperature and then 572 ml of glacial acetic acid was added. The mixture was cooled to 5° and chlorinated in a manner previously described (experiment 2). During the chlorination,
an orange-brown colour, presumably due to bromine, was noticeable around the chlorine inlet. When this colour was no longer produced, the reaction began to turn green. Work-up with 3 l. of water yielded a pale yellow, amorphous solid, mp 102-108°, after drying in a desiccator under vacuum. Crystallization from hexane - benzene gave 108.8 g (73%) of \(130\) as pale yellow needles, mp 109-110° with decomposition; ir (KBr) 3120, 3090, 3015, 2965 (C-H stretching), 1528 (nitro group), 1360 (nitro group and sulfone), 1163 cm\(^{-1}\) (sulfone).

When the synthesis was carried out using \(p\)-nitrobenzyl chloride, rather than the bromide, the crystallized product (\(p\)-nitrophenylmethanesulfonyl chloride) had a mp of 91-92° (lit. (124) 92-93°); ir (KBr) 3120, 3090, 3000, 2928, 2875 (C-H stretching), 1525, 1358 (nitro group), 1374, 1171 cm\(^{-1}\) (sulfone).

Crystallization from hexane - CHCl\(_3\) of the salt ((Et)\(_3\)N • HBr) isolated from the treatment of \(130\) with triethylamine, gave white needles, mp 247-249° (lit. (125) 248°, from CHCl\(_3\)). A pale yellow precipitate, characteristic of bromide salts, was obtained when an aqueous solution of this salt was treated with 5% AgNO\(_3\) solution.

5. Synthesis of cis- and trans-2,4-Diphenyl-3-dimethylaminothietane 1,1-dioxide (126a and b).

trans-2,4-Diphenyl-3-dimethylaminothietane 1,1-dioxide (126b) is a known compound (15,55). The cis-isomer 126a was subsequently isolated (14). The procedure described below was adopted from reference 55.

A dry, 250 ml three-necked flask was fitted with a mechanical stirrer, a dropping funnel, a gas inlet and a drying tube. The gas inlet was connected to a source of dry nitrogen in order to provide an an-
hydrous atmosphere throughout the reaction. To the flask was added 100 ml of sodium-dried diethyl ether followed by 10.00 g (0.0679 mole) of freshly distilled \( \delta \)-dimethylaminostyrene (131) and 6.87 g (0.0679 mole) of dry triethylamine. The pale yellow solution was stirred and cooled in an ice-water bath. Phenylmethanesulfonyl chloride (13), 12.95 g (0.0679 mole), dissolved in 63 ml of dry THF was diluted with 63 ml of dry diethyl ether and added dropwise over a period of 1 hour with efficient stirring. A white precipitate ((Et)\(_3\)N • HCl) appeared immediately. After the addition of 13 was complete, the reaction was stirred for 15 hours at ice-water temperature. The solvent was then removed by evaporation under vacuum to give a pale yellow solid. A lukewarm water bath was used to aid the evaporation. The solid was dissolved in 100 ml of CHCl\(_3\) and extracted with two 200 ml portions and one 100 ml portion of distilled water to remove the (Et)\(_3\)N • HCl. After drying over anhydrous Na\(_2\)SO\(_4\), the yellow CHCl\(_3\) solution was evaporated under reduced pressure to give 19.80 g (96.7%) of yellow solid. Analysis by nmr (CDCl\(_3\)) indicated that 96% (19 g) of this solid was accounted for by three isomers. Of the 19 g, 82% was trans-2,4-diphenyl-3-dimethylaminothietane 1,1-dioxide (126b), 15% was the cis-isomer 126a and approximately 3% was benzyl 1-phenyl-2-dimethylaminoethenyl sulfone (132) (see experiment 6). Fractional crystallization of the crude product from hexane - methyl ethyl ketone gave 126b as white, fluffy needles. After two recrystallizations the mp was 114.5-115.5° with decomposition (lit. (15) 109°, from hexane - ethanol); the ir spectrum (KBr) showed absorption bands in the C-H stretching region that were indicative of the N-CH\(_3\) group. Strong sulfone bands appeared at 1320 and 1160 cm\(^{-1}\). Other strong bands were seen at 1460 and 695 cm\(^{-1}\). A medium intensity absorption which could be used to differentiate between 126a and 126b
occurred at 760 cm\(^{-1}\). The nmr spectrum (CDCl\(_3\)) agreed with that already reported (15): \(\delta 7.68-7.22\) (m, 10, phenyl protons), 5.43 (t (diffuse), 2, protons at C-2 and C-4), 3.68 (t, 1, \(J = 9\) Hz, proton at C-3) and 1.93 (s, 6, N-methyl protons). The triplet at \(\delta 5.43\) was resolved by 100 MHz nmr as two 1 proton doublets, one centred at \(\delta 5.304\) (\(J = 9.4\) Hz) and the other at \(5.494\) (\(J = 9.4\) Hz); the proton at C-3 appeared as a sharp triplet, \(J = 9.4\) Hz. Each peak of the two doublets was split, indicating transannular coupling between the C-2 and C-4 protons with \(J\) approximately 1 Hz.

Repeating the reaction with dry CH\(_2\)CN as the reaction solvent gave 20.19 g (98.6%) of crude product. Analysis by nmr (CDCl\(_3\)) showed that 99% (20 g) of the crude material was accounted for by the three isomers, 126a, 126b and 132. Of this, 60% was the trans-isomer 126b, 35% was 126a and approximately 5% was 132, the acyclic isomer. The cis-isomer 126a was isolated by fractional crystallization from hexane - ethanol 100.

Three recrystallizations from hexane - methyl ethyl ketone gave transparent plates, mp 137.0-138.0\(^\circ\) with decomposition. The ir spectrum (KBr) was similar in overall appearance to that of 126b. Strong bands were present at 1320, 1133 and 692 cm\(^{-1}\). However, unlike that of 126b, there was no absorption band at 760 cm\(^{-1}\); nmr (CDCl\(_3\)) \(\delta 7.70-7.23\) (m, 10, phenyl protons), 5.28 (d, 2, \(J = 9\) Hz, protons at C-2 and C-4), 3.68 (t, 1, \(J = 9\) Hz, proton at C-3) and 2.10 (s, 6, N-methyl protons).

**Anal.** Calcd. for C\(_{17}\)H\(_{19}\)NO\(_2\)S: C, 67.74; H, 6.35; N, 4.65; mol. wt., 301.41. Found: C, 67.91; H, 6.46; N, 4.64.

When the reaction was repeated using dry CHCl\(_3\) (ethanol stabilizer removed by treatment with conc. H\(_2\)SO\(_4\)) as the reaction solvent, essentially all of the crude product was accounted for by the isomers, 126a,
126b and 132, according to the nmr spectrum. From the spectrum, 74% of the product was determined to be 126b, 19% 126a and 7% 132.

6. Benzy1 1-Phenyl-2-dimethylaminoethyl sulfone (132).

As mentioned in experiment 5, the crude product from the cycloaddition reaction carried out in CH₃CN was crystallized from hexane-ethanol 100. Cooling the mother liquor from this crystallization in a dry ice box caused an off-white solid to precipitate. The ir spectrum of the solid indicated that it was a mixture of 126a and 132. Upon evaporation of the filtrate under vacuum, a viscous, brown oil was obtained. The oil was heated with hexane on a steam bath and dissolved with a minimum amount of ethanol 100. Cooling the solution in a refrigerator overnight gave colourless crystals. After collecting the crystals, the filtrate was evaporated and the resulting oil was allowed to sit for two weeks. During this time crystals appeared in the oil. The ir spectra of the two batches of crystals (1 g, 5%) showed that they were both benzy1 1-phenyl-2-dimethylaminoethyl sulfone (132). Crystallization from hexane-methyl ethyl ketone gave transparent plates, mp 130-131°; ir (KBr) 1630 (enamine), 1276, 1125 cm⁻¹ (sulfone); nmr (CDCl₃) δ 7.41 (d, 10, phenyl protons), 7.00 (s, 1, vinylic proton), 4.05 (s, 2, benzylic protons) and 2.60 (s, 6, N-methyl protons); uv max (CH₃CN) 253 nm (ε 15,800).

Anal. Calcd. for C₁₇H₁₉NO₂S: C, 67.74; H, 6.35; N, 4.65; mol. wt., 301.41. Found: C, 67.78; H, 6.34; N, 4.76.

Attempts to reduce the double bond of 132 by treatment with formic acid (126) or by hydrogenation over 10% palladium on charcoal in THF solution (35) were unsuccessful.
7. **Decomposition of cis- and trans-2,4-Diphenyl-3-dimethylaminothietane 1,1-dioxide (126a and b) under Recrystallization Conditions**

Nmr analysis of a mixture of crude products from several cycloaddition reactions indicated that it was 91% pure in the three isomers, 126a, 126b and 132. Of this 91%, 55% was 126b, 40% 126a and 5% 132.

Crystallization of 60 g of the material from hexane - ethanol 100 gave 21 g (35%) of white crystals, mp 124-138° with decomposition. The ir spectrum revealed a mixture of 126a and b. From the nmr spectrum (CDCl₃) the composition was found to be 84% 126a and 16% 126b with no observable impurity present. Upon cooling the mother liquor in a refrigerator overnight, 3.4 g (6%) of white solid precipitated. The solid was found to be a mixture of 126a and 132 by ir analysis. Evaporation of the filtrate under vacuum gave a light brown, viscous oil with a characteristic, unpleasant odor. The nmr spectrum (CDCl₃) of the oil revealed a complex mixture of compounds. By comparison with the nmr spectra of authentic samples, five of the components were identified as β-dimethylaminostyrene (131), benzyl 1-phenyl-2-dimethylaminoethenyl sulfone (132), cis- and trans-2,4-diphenyl-3-dimethylaminothietane 1,1-dioxide (126a and b) and ethyl phenylmethanesulfonate (138). The five compounds accounted for approximately 75% of the total material in the oil. Of this 75%, 26% was 131, 17% 132, 13% 126a, 7% 126b and 37% 138. Thus, a total of 95% of 126a in the 60 g of crude product survived the crystallization from hexane - ethanol 100 (does not include the cis-isomer that was forced out of the original mother liquor by cooling in a refrigerator). However, only a total of 18% of 126b remained after the crystallization. The amount of 132 appeared to increase from 3 g in the crude product to approximately 4.6 g in the oil from the mother liquor. (As well, there was an undeter-
mined amount of 132 in the precipitate referred to above.) Upon sitting
for one week at room temperature, the oil thickened and took on a crystal-
line appearance. This material was dissolved in 100 ml of CHCl₃ and ex-
tracted with a 100 ml and a 50 ml portion of distilled water. Evaporation
of the pooled aqueous extracts under vacuum gave a viscous yellow oil which
crystallized on sitting. Three crystallizations from acetone gave 2 g of
white needles, mp 116-118°. The ir spectrum (KBr) of the crystallized
material was superimposable with that of dimethylammonium phenylmethane-
sulfonate (137). A mixture melting point with an authentic sample of 137
was not depressed. Evaporation in vacuo of the CHCl₃ layer dried over an-
hydrous Na₂SO₄ afforded a viscous brown oil. Upon allowing the oil to sit
for a week, a crystalline solid formed which was collected and identified
as benzyl 1-phenyl-2-dimethylaminoethenyl sulfone (132).

8. Decomposition of trans-2,4-Diphenyl-3-dimethylaminothietane 1,1-dioxide
(126b) in Ethanol.

In a 100 ml boiling flask fitted with a reflux condenser were
placed 233 mg of pure trans-2,4-diphenyl-3-dimethylaminothietane 1,1-diox-
ide (126b) and 50 ml of ethanol 100. After heating for several minutes
a solution was obtained, which was heated at reflux for 1 hour. Evapora-
tion of the solvent under vacuum gave 276 mg of yellow, mobile oil which
had an odor similar to that of β-dimethylaminostyrene (131). In the ir
spectrum (neat) of the oil a strong band at 1640 cm⁻¹ supported the pres-
ence of 131. Strong bands appeared at 1350, 1170 and 920 cm⁻¹, which in-
dicated the presence of a sulfonic acid ester. In the nmr spectrum (CDCl₃)
signals attributable to 131, cis-2,4-diphenyl-3-dimethylaminothietane 1,
1-dioxide (126a) and ethyl phenylmethanesulfonate (138) were present. No
absorptions due to the starting material 126b were observed. According to the nmr spectrum, the three compounds 131, 126a and 138 accounted for approximately 57% of the oil. Of this 57%, 28% was 131, 11% 126a and 61% 138. A major peak at δ 2.28 in the spectrum was unassigned. The oil was dissolved in 20 ml of CHCl₃ and extracted quantitatively with three 20 ml portions of distilled water. Evaporation of the pooled aqueous extracts under high vacuum gave 102 mg of gummy solid. The ir spectrum (neat) of this material was similar but not identical to that of dimethylammonium phenylmethanesulfonate (137). After drying over anhydrous MgSO₄, the CHCl₃ layer was evaporated under reduced pressure to give a yellowish-orange oil which no longer had the odor of 131. A strong band at 1640 cm⁻¹ was absent in the ir spectrum (neat). Strong bands occurred at 1350, 1170 and 920 cm⁻¹, indicating that 138 was present. In the nmr spectrum (CDCI₃), a doublet at δ 5.27 (2 protons) and a singlet at δ 2.10 (6 protons) indicated the presence of cis-2,4-diphenyl-3-dimethylaminothietane 1,1-dioxide (126a). The presence of the sulfonate ester 138 was evident from a singlet at δ 7.40 (5 protons), a singlet at 4.33 (2 protons), a quartet at 4.10 (2 protons) and a triplet at 1.27 (3 protons). The two compounds accounted for approximately 51% of the oil. Of this 51%, 21% was 126a and 79% 138.

A solution of 467 mg (0.00155 mole) of pure 126b in 100 ml of ethanol 95 was refluxed for 12 hours. Evaporation of the solvent under vacuum gave a viscous, pale yellow oil with an aldehydic odor. The oil was dissolved in 30 ml of CHCl₃ and extracted with three 20 ml portions of distilled water. Upon evaporation of the pooled aqueous extracts in vacuo, 300 mg of white, gummy solid was obtained. From the nmr spectrum (CDCI₃), this material was determined to be 75% dimethylammonium phenylmethanesulfonate (137) (225 mg, 0.00104 mole). Addition of D₂O to the nmr
sample caused the diffuse band at δ 8.35-7.72 (protons on N, 2) to disappear and the triplet at δ 2.25 (N-methyl protons, 6) to collapse to a singlet. On the basis of the calculated amount of 137, 67% of 126b was converted to the salt.

The presence of β-dimethylaminostyrene (131) and ethyl phenyl-methanesulfonate (138) as decomposition products of trans-2,4-diphenyl-3-dimethylaminothietane 1,1-dioxide (126b) in hot ethanol was confirmed by glc. A sample of pure 126b, freshly dissolved in ethanol 95, was analyzed on the column described in experiment 1 with the injection port, oven, and detector at 280, 140 and 250°, respectively, and the nitrogen flow at 55 ml/min. Four peaks excluding that of the solvent were observed. The first peak, retention time 1.4 min, corresponded to phenylacetaldehyde; the second, 4.4 min, to 131; and the third, 7.8 min, to 138. The fourth peak, 10.9 min, was not identified. When a sample of dimethylammonium phenyl-methanesulfonate (137) dissolved in ethanol 95 was applied to the column, no peak was observed.

9. Decomposition of cis-2,4-Diphenyl-3-dimethylaminothietane 1,1-dioxide (126a) in Ethanol.

Pure cis-2,4-diphenyl-3-dimethylaminothietane 1,1-dioxide (126a) (229 mg) was treated in the same manner as described in experiment 8 for the 1 hour reflux of 126b in ethanol 100. Evaporation of the solvent in vacuo gave a pale yellow solid. The ir spectrum (KBr) of the solid was identical to that of 126a except for weak bands at 1640, 1400 and 920 cm⁻¹. The nmr spectrum (CDCl₃) indicated that the solid was 81% 126a. The most intense impurity signal occurred at δ 2.76, which suggested the presence of β-dimethylaminostyrene (131). Weak signals attributable to ethyl
phenylmethanesulfonate (138) were also present.

10. **Isomerization of trans-2,4-Diphenyl-3-dimethylaminothietane 1,1-dioxide (126b).**

Crude product from a cycloaddition reaction run in CHCl₃ was used (experiment 5). The nmr spectrum of this material indicated that it was essentially pure in the three isomers, 126a (19%), 126b (74%) and 132 (7%).

In a 100 ml reaction flask fitted with a mechanical stirrer and a drying tube were placed 3.01 g (0.010 mole) of crude product, 1.38 g (0.010 mole) of triethylamine HCl, 20 ml of dry CH₃CN and 10 ml of dry CHCl₃. Stirring the mixture at room temperature gave a pale yellow solution to which 2 drops of dry triethylamine was added. The isomerization was followed by removing samples at intervals and observing the change in the intensity of the band at 1630 cm⁻¹ (enamine band of 132). Sodium chloride cells, 0.1 mm in thickness, were used and samples were analyzed directly; 2:1 CH₃CN - CHCl₃ served as the reference. A new tare line was placed on the reaction flask after each sample was removed so that loss of solvent by evaporation could be adjusted for using 2:1 CH₃CN - CHCl₃ mixture. The greatest increase in intensity of the band at 1630 cm⁻¹ occurred during the first day. After 3 days, the band intensity ceased to change. The solution was stirred for another day and then was evaporated under vacuum to give a pale brown semi-solid. This was dissolved in 20 ml of CHCl₃ and extracted with three 20 ml portions of distilled water. After drying over anhydrous Na₂SO₄, the CHCl₃ layer was evaporated in vacuo to yield 2.69 g (89%) of yellow solid. Approximately 0.1 g (3%) of the starting material was lost as a result of the sampling procedure.
From the nmr spectrum (CDCl₃), 92% of the material was calculated to consist of the three isomers and of the 92%, 64% was 126a, 8% 126b and 28% 132. Evaporation of the pooled aqueous extracts under vacuum gave a yellow semi-solid. Upon washing with a small amount of acetone, 1.21 g (88%) of white needles separated. Infrared analysis showed this material to be triethylamine HCl. Again, approximately 0.05 g (3%) had been lost due to sampling. Evaporation of the acetone washings gave 0.24 g of viscous yellow liquid. The ir spectrum (neat) indicated a mixture of triethylamine HCl and a sulfonic acid derivative (strong bands at 1200 and 1050 cm⁻¹).

11. Preliminary Examination of the Effects of Water, Addition Time and Reaction Temperature on the Synthesis of cis- and trans-2,4-Diphenyl-3-dimethylaminothietane 1,1-dioxide (126a and b).

Under the conditions described in experiment 5, 6.48 g (0.0340 mole) of phenylmethanesulfonyl chloride (13) dissolved in 42.5 ml of dry CH₃CN was added to a solution of 5.00 g (0.0340 mole) of π-dimethylamino-styrene (131) and 3.44 g (0.0340 mole) of dry triethylamine in 34 ml of CH₃CN over a period of 15 min. Just before the addition of 13 was started, 0.5 ml (0.03 mole) of distilled water was added to the enamine solution. Upon work-up, 9.29 g (90.7%) of crude, solid product was obtained. The ir spectrum (KBr) of this material indicated a mixture of cis- and trans-2,4-diphenyl-3-dimethylaminothietane 1,1-dioxide (126a and b) and benzyl 1-phenyl-2-dimethylaminoethenyl sulfone (132). From the nmr spectrum (CDCl₃), 84% of the product was calculated to consist of 126a, 126b and 132. Of the 84%, 36% was 126a, 47% 126b and 17% 132. When the reaction was repeated using 2.0 ml of water, the nmr spectrum of the isolated product indicated that 79% was accounted for by the three isomers. Of the
79%, 42% was 126a, 34% 126b and 24% 132.

Phenylmethanesulfonyl chloride (13), 6.48 g (0.0340 mole), in 42.5 ml of dry CH$_3$CN was reacted with a solution of 5.00 g (0.0340 mole) of 131 and 3.44 g (0.0340 mole) of triethylamine in 34 ml of dry CH$_3$CN under the conditions described in experiment 5, except that the solution of 13 was poured directly into the enamine solution. After stirring for 1 hr, the reaction was worked up to give 8.83 g (86%) of pale yellow solid. From the nmr spectrum, the crude product was calculated to be 99% pure in the three isomers. Of this 99%, 36% was 126a, 57% 126b and 7% 132.

Phenylmethanesulfonyl chloride (13), 3.24 g (0.0170 mole), in 21 ml of dry CH$_3$CN was reacted with a solution of 2.50 g (0.0170 mole) of 131 and 1.72 g (0.0170 mole) of triethylamine in 17 ml of dry CH$_3$CN under the conditions described in experiment 5, except that the reaction was run at room temperature and the solution of 13 was poured directly into the enamine solution. The temperature in the flask rose rapidly from 26 to 41°. After 15 min, the temperature had returned to 26° and the reaction was worked up to give 4.60 g (90%) of pale yellow solid. The nmr spectrum of the crude product indicated that it was 95% pure in the three isomers. Of this 95%, 32% was 126a, 65% 126b and 3% 132.

12. **Synthesis of Dimethylammonium Phenylmethanesulfonate (137).**

In a 250 ml boiling flask fitted with a reflux condenser were placed 2.0 g (0.011 mole) of phenylmethanesulfonyl chloride (13) and 150 ml of distilled water. After refluxing for about 10 min, a homogeneous solution was obtained. The solution was refluxed for another 20 min and then was allowed to cool to room temperature. Evaporation of the water under reduced pressure gave a viscous, pale yellow oil. The ir spectrum
(neat) showed strong bands at 1205 and 1055 cm$^{-1}$, which were indicative of a sulfonic acid. The oil was dissolved in 30 ml of distilled water and dimethylamine gas was bubbled into the solution for about 30 sec. Evaporation in vacuo gave a viscous, pale yellow oil which solidified when washed with acetone. Three crystallizations from hexane - acetone gave 1.2 g (50%) of 137 as transparent, flat needles, mp 116-118°; ir (KBr) 3180 - 2820, 2475 (ammonium band), 1210, 1052 cm$^{-1}$ (sulfonic acid); nmr (CDCl$_3$) $\delta$ 8.37-7.72 (broad peak, 2, protons on N), 7.52-7.20 (m, 5, phenyl protons), 4.05 (s, 2, benzylic protons) and 2.26 (t, 6, $\ J = 5.5.$ Hz, N-methyl protons). In the nmr spectrum, the peak intensities of the triplet were in the ratio of 1:2:1. After adding D$_2$O, the broad peak at $\delta$8.37-7.72 disappeared and the triplet at $\delta$2.26 collapsed to a singlet.

Anal. Calcd. for C$_9$H$_{15}$NO$_3$S: C, 49.75; H, 6.96; N, 6.45; mol. wt., 217.28. Found: C, 49.68; H, 7.38; N, 6.39.

13. **Synthesis of Ethyl Phenylmethanesulfonate (138).**

In a dry 250 ml three-necked flask fitted with a dropping funnel and a reflux condenser and protected from atmospheric moisture by a drying tube were placed 100 ml of ethanol 100 and 5.06 g (0.050 mole) of dry triethylamine. The solution was heated to reflux and 9.53 g (0.050 mole) of phenylmethanesulfonyl chloride (13) dissolved in 30 ml of dry CH$_3$CN was added dropwise over a period of 1 hour. After the addition of 13 was complete, the reaction was refluxed for another 2 hrs and allowed to cool to room temperature. Evaporation of the solvent under vacuum gave a yellow oil containing white crystalline masses. The mixture was dissolved in 50 ml of CHCl$_3$ and extracted with three 50 ml portions of distilled water. The CHCl$_3$ layer was dried over anhydrous MgSO$_4$ and evaporated in vacuo to
give 4.29 g (50%) of pale yellow, mobile oil. The oil was distilled twice using a short-path vacuum distillation apparatus to give ethyl phenylmethanesulfonate (138), bp 87° at 0.02 mm; ir (neat) 3070, 3040, 2989, 2940 (C-H stretching), 1350, 1170, 920 (sulfonic acid ester), 1605, 1500, 1457, 695 cm⁻¹ (phenyl); nmr (CDCl₃), δ 7.34 (s, 5, phenyl protons), 4.32 (s, 2, benzylic protons), 4.11 (q, 2, J = 7 Hz, methylene protons) and 1.25 (t, 3, J = 7 Hz, methyl protons).


Approximately 1 g of 138 was heated on a steam bath with 50 ml of 4 N HCl for 2 hours to obtain a homogeneous solution. The solution was evaporated under high vacuum to give a colourless semi-solid. This material was dissolved in 10 ml of distilled water and treated with dimethylamine gas. Evaporation of the solution in vacuo yielded an oil which solidified upon standing. Crystallization from hexane - acetone gave transparent needles, mp 116-117.5°. The ir spectrum (KBr) was superimposable with that of dimethylammonium phenylmethanesulfonate (137). A mixture melting point with an authentic sample of 137 was not depressed.


A. Acetonitrile as Reaction Solvent. The procedure was identical to that described in experiment 5, except for modifications in the work-up. p-Chlorophenylmethanesulfonyl chloride (129), 16.88 g (0.0750 mole), in 141 ml of dry CH₃CN was reacted with 11.04 g (0.0750 mole) of freshly distilled p-dimethylaminostyrene (131) and 7.59 g (0.0750 mole) of dry triethylamine in 112 ml of dry CH₃CN. Much white precipitate
formed, which was collected by suction filtration, washed with a small
amount of CH$_3$CN and air dried. Evaporation under reduced pressure of the
combined pale yellow filtrate and washings gave a yellow solid.

The white precipitate was magnetically stirred with 200 ml of
distilled water to dissolve the triethylamine HCl, suction filtered, and
dried in a desiccator under vacuum to give 13.55 g (53.8%) of white,
crystalline powder (127b). Attempts to crystallize 127b were unsuccessful
because of extensive decomposition. The compound was not soluble to an
extent of 10% in CHCl$_3$, benzene or DMSO at room temperature. A sample of
127b was purified by washing several times with CHCl$_3$. When placed in a
150° bath, this material decomposed at 154° (heating rate was approximately
1° per min). The ir spectrum (KBr) showed bands in the C-H stretching
region at 3080, 3060, 3005, 2980, 2895, 2855 and 2805 cm$^{-1}$. The latter
two bands were more intense than the one at 2980 cm$^{-1}$. Sulfone bands
appeared at 1323 and 1164 cm$^{-1}$. A strong doublet occurred at 523 cm$^{-1}$. The
HCl salt of 127b was prepared by dissolving 1.0 g in 100 ml of CHCl$_3$ and
treating the solution with dry HCl gas. Removal of the solvent in vacuo
gave a white solid, mp 130-131° with decomposition. The salt decomposed
when an attempt was made to crystallize it from acetone; ir (KBr) 2700 -
2300 cm$^{-1}$ (ammonium band); nmr (DMSO-d$_6$) $\delta$ 9.2-8.7 (band, 1, proton on N),
8.07-7.80 (m, 2, protons ortho to Cl), 7.80-7.26 (m, 7, remaining aromatic
protons), 6.69 (d, 1, $\delta$ = 10 Hz, benzylic proton), 6.15 (d, 1, $\delta$ = 10 Hz,
p-chlorobenzylic proton), 4.93 (t, 1, $\delta$ = 10 Hz, proton at C-3), and 2.39
(s, 6, N-methyl protons). Isomer 127b was submitted for analysis as the
CHCl$_3$-washed, crude product.

Anal. Calcd. for C$_{17}$H$_{18}$ClNO$_2$S: C, 60.80; H, 5.40; N, 4.17; mol. wt.,
335.85. Found: C, 60.63; H, 5.20; N, 4.18.
The yellow solid obtained from the work-up of the cyclization reaction was dissolved in 100 ml of CHCl₃ and extracted with four 50 ml portions of distilled water. Evaporation of the pooled aqueous extracts followed by drying of the residue in a desiccator under vacuum gave 9.78 g (95%) of solid, the ir spectrum of which was superimposable with that of triethylamine hydrochloride. The CHCl₃ layer was dried over anhydrous Na₂SO₄ and then evaporated under vacuum to give 11.27 g (44.7%) of yellow solid (127a). A weak band at 1625 cm⁻¹ in the ir spectrum (KBr) of the crude material indicated that some acyclic isomer may also have been present (approximately 5%). Crystallization from hexane - ethanol 100 gave 127a as white needles, mp 145-146° with decomposition. The ir spectrum (KBr) of 127a was quite similar to that of 127b. In the C-H stretching region the band positions were identical; however, the absorption at 2980 cm⁻¹ was more intense than that at 2855 and 2805 cm⁻¹. The band due to asymmetrical stretching of the sulfonyl moiety was 10 cm⁻¹ higher than that of 127b. A single sharp band appeared at 510 cm⁻¹, rather than the doublet seen at 523 cm⁻¹ for 127b; nmr (CDCl₃) δ 7.63-7.26 (m, 9, aromatic protons), 5.25 (d, 1, J = 9 Hz, benzylic proton), 5.22 (d, 1, J = 9 Hz, p-chlorobenzylic proton), 3.57 (t, 1, J = 9 Hz, proton at C-3), and 2.08 (s, 6, N-methyl protons).

Anal. Calcd. for C₁₇H₁₈ClNO₂S: C, 60.80; H, 5.40; N, 4.17; mol. wt., 335.85. Found: C, 60.88; H, 5.34; N, 4.20.

Treatment of an anhydrous diethyl ether solution of pure 127a with dry HCl gas gave a white solid, mp 166-167° with decomposition; ir (KBr) 2700 - 2200 cm⁻¹ (ammonium band); nmr (DMSO-d₆) δ 7.87-7.33 (m, 9, aromatic protons), 6.47 (d (broad), 2, J = 9 Hz, protons at C-2 and C-3), 5.27 (t, 1, J = 9 Hz, proton at C-3), and 2.66 (s, 6, N-methyl protons).
In a modified procedure, 45.00 g (0.20 mole) of 129 dissolved in 392 ml of dry CH$_3$CN was added to a cooled solution of 29.45 g (0.20 mole) of 131 and 20.24 g (0.20 mole) of triethylamine in 270 ml of CH$_3$CN over a period of 23 min with vigorous stirring. The reaction was exothermic and caused the temperature of the reaction mixture to rise from 0 to 8°C. Three hours following addition of the sulfonyl chloride, the reaction was worked up to give 37.68 g (56%) of 127b and 27.74 g (41%) of crude 127a. In the IR spectrum (KBr) of the latter, a weak band appeared at 1625 cm$^{-1}$ due to the presence of acyclic material. The NMR spectrum (CDCl$_3$) of the crude 127a fraction showed singlets at 2.60, 2.08 and 1.91, which were attributed to the acyclic isomer, 127a and 127b, respectively. These three components were calculated to account for essentially all of the crude material and of this, 3% was the acyclic isomer, 93% 127a and 3% 127b. Thus, of the total 65.42 g (97%) of product isolated, 59% was 127b, 40% 127a and 1% acyclic isomer.

B. Chloroform as Reaction Solvent. Using a procedure similar to that described for the reaction run in CH$_3$CN, 4.50 g (0.020 mole) of 129 in 38 ml of dry, ethanol-free CHCl$_3$ was added to 2.94 g (0.020 mole) of 131 and 2.02 g (0.020 mole) of triethylamine in 30 ml of CHCl$_3$. After stirring for 8 hours, the reaction was suction filtered to give 3.79 g (56%) of 127b, which was identified by its IR spectrum. Evaporation of the pale yellow filtrate in vacuo afforded a solid which was redissolved in 25 ml of CHCl$_3$ and extracted with four 10 ml portions of distilled water. After drying over anhydrous Na$_2$SO$_4$, the CHCl$_3$ solution was evaporated under reduced pressure to give a gummy, yellow solid. Washing with anhydrous diethyl ether gave a pale yellow solid (0.82 g, 12%), which was found to be a mixture of 127a and 127b by IR analysis. In order to determine
the proportions of the two isomers, the mixture was treated with HCl gas to form the corresponding salts as described above for 127b. From the integrals of the N-methyl proton signals in the nmr spectrum (DMSO-d$_6$) the mixture was found to consist of 65% (0.53 g) 127b and 35% (0.29 g) 127a. Evaporation of the filtrate pooled with the ether washings yielded another gummy solid from which 0.30 g (4%) of 127a was isolated by washing with anhydrous ether. The nmr spectrum (CDCl$_3$) of the yellow viscous oil (1.47 g) obtained by evaporating the ether washings showed the presence of two major components, one being 127a and the other, presumably, one of the possible p-chloro-substituted analogues of benzyl 1-phenyl-2-dimethylaminoethenyl sulfone (132). The spectrum of the acyclic isomer consisted of a doublet at 6.7.71 (aromatic protons) and singlets at 6.6.98 (vinyllic proton, 1), 3.97 (benzyllic protons, 2), and 2.60 (N-methyl protons, 6). The integral for the 9 aromatic protons was greater than expected on the basis of the integral for the N-methyl protons because of other minor components in the oil absorbing in the same region. Cycloadduct 127a and the acyclic isomer were calculated to account for 83% (1.22 g) of the oil. Of this 83%, 50% (0.61 g) was 127a and 50% (0.61 g) was the acyclic material. Thus, 91% of the theoretical yield of product was accounted for by 127a, 127b and the acyclic material. Of this 91%, 20% was 127a, 70% 127b and 10% the acyclic adduct. This latter substance was not isolated or further characterized.

15. Synthesis of 2-(4-Nitrophenyl)-3-dimethylamino-4-phenylthietane 1,1-dioxide (128).

The procedure described in experiment 5 was used with several modifications. p-Nitrophenylmethanesulfonyl bromide (130), 21.4 g (0.076
mole), was mixed with 250 ml of dry, ethanol-free CHCl₃ in a stoppered conical flask until most of the solid had dissolved. The slurry was then transferred to a dropping funnel with the aid of 50 ml of CHCl₃ and added dropwise over a period of 2 hrs to a cooled solution of 12.7 g (0.087 mole) of 131 and 8.8 g (0.087 mole) of dry triethylamine in 128 ml of CHCl₃. The reaction mixture rapidly turned bright orange. When the addition of 130 was complete, the solution was stirred for another 3 hours and was then reduced to approximately 100 ml in volume by evaporation in vacuo. A lukewarm water bath was used to aid the evaporation. The reddish-orange solution that remained was extracted with one 200 ml portion and two 100 ml portions of distilled water, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure to give a reddish-black oil. The oil was dissolved in 30 ml of benzene and the resulting solution was diluted with 450 ml of diethyl ether to give a pale orange solution from which a cream-coloured, crystalline solid rapidly precipitated. After sitting overnight, the solid was collected by suction filtration and washed with ether. Upon drying, the material weighed 21.2 g (80.6%). Evaporation of the filtrate, pooled with the ether washings, gave a reddish-black oil which yielded 1.7 g (6.5%) of greenish-yellow solid when treated with ether. The ir spectra (KBr) of the two solids indicated that they were mixtures of the desired cyclic product 128 and acyclic material 148. From the nmr spectra (CDCl₃), using the integrals of the N-methyl proton signals as a basis for calculation, the composition of the first solid was determined to be 89% 128 and 11% 148 and that of the second solid, 36% 128 and 61% 148. Thus, of the total yield of 22.9 g (87.1%) of crude product, 85% was 128 and 15% 148. Crystallization of the first solid from hexane - methyl ethyl ketone gave 128 as pale yellow prisms, mp 130-131° with decomposition; ir (KBr)
1524, 1354 (NO₂ group), 1336, 1324, 1160, 1138 cm⁻¹ (sulfone); nmr (CDCl₃) δ8.47-8.20 (m, 2, protons ortho to nitro group), 7.87-7.60 (m, 2, protons meta to nitro group), 7.60-7.33 (m, 5, phenyl protons), 5.36 (d, 2, J = 9 Hz, protons at C-2 and C-4), 3.70 (t, 1, J = 9 Hz, proton at C-3), and 2.14 (s, 6, N-methyl protons). Recrystallization did not change the melting point and decomposition was apparent.


Although the analysis was inconclusive for carbon, the analysis for the thiete 1,1-dioxide analogue derived from 128 was satisfactory (see experiment 20).

A 100 mg sample of crystallized 128 was dissolved in 5 ml of CH₃CN at room temperature. After sitting for 2 hours the solution had turned a bright orange. Evaporation in vacuo of a portion of the solution after 22 hours gave an orange solid. From the ir spectrum (KBr) of this material it was apparent that a fair amount of 128 had rearranged to the acyclic isomer 148. After 43 hours, the remainder of the solution was evaporated under reduced pressure to give an orange oil. Nmr analysis (CDCl₃) indicated that 87% of the oil was accounted for by the isomers 128 and 148. Of the 87%, 24% was starting material (128) and 76% was the acyclic isomer 148.

16. Benzyl 1-(4-Nitrophenyl)-2-dimethylaminoethenyl Sulfone (148).

Crystallization of the second solid isolated in experiment 15 from hexane - ethanol gave 148 as yellow, granular crystals. Upon recrystallization from n-butanol, bright yellow, flat needles were obtained, mp 165.5-166.5°; ir (KBr) 1625 (enamine), 1530, 1355 (nitro group), 1297, 1135,
132

1115 cm\(^{-1}\) (sulfone); nmr (CDCl\(_3\)) \(\delta\) 8.30-8.03 (m, 2, protons ortho to nitro group), 7.60-7.30 (m, 7, protons meta to nitro group and phenyl protons), 7.11 (s, 1, vinylic proton), 4.13 (s, 2, benzylic protons), and 2.67 (s, 6, N-methyl protons); uv max (CH\(_3\)CN) 250 (\(\varepsilon 18,700\)) and 271 nm (\(\varepsilon 19,700\)).

Anal. Calcd. for C\(_{17}\)H\(_{18}\)N\(_2\)O\(_4\): C, 58.95; H, 5.24; N, 8.09; mol. wt., 346.40. Found: C, 58.99; H, 5.09; N, 8.22

17. **Synthesis of 2,4-Diphenylthiete 1,1-dioxide (152).**

In a 100 ml reaction flask equipped with a mechanical stirrer and a dropping funnel were placed 14.5 g (0.048 mole) of cis-2,4-diphenyl-3-dimethylaminothietane 1,1-dioxide (126a) and 14.5 ml of glacial acetic acid. The stirred mixture was cooled in an ice-water bath and 43.5 ml of 40\% peracetic acid (FMC Corporation) was added dropwise over a period of 45 min. When most of the peracetic acid had been added, a pale yellow solution was obtained. After several hours the solution became translucent and then progressively more opaque as the product (152) precipitated. The reaction was run for 17 hours at ice bath temperature. The contents of the flask were transferred to a 1 litre conical flask, cooled in an ice bath and then neutralized with a saturated, aqueous solution of Na\(_2\)CO\(_3\). The mixture was extracted with 200, 100 and 50 ml portions of CHCl\(_3\). The pooled CHCl\(_3\) extracts were washed with 370 ml of 10\% HCl followed by 300 ml of distilled water. After drying over anhydrous MgSO\(_4\), the yellow solution was evaporated under vacuum with the aid of a lukewarm water bath to give 10.5 g (85\%) of beige-coloured crude product. The ir and nmr spectra of this material were identical to those of the crystallized product. Crystallization from hexane - benzene yielded 9.3 g (76\%) of 152 as white, fluffy needles, mp 137-138\(^{\circ}\) with decomposition (lit. (50) 133-134\(^{\circ}\), from
CHCl₃); ir (KBr) 3082, 3050 (sh) (C-H stretching), 1622 (double bond conjugated with phenyl group), 1303, 1150 cm⁻¹ (sulfone); uv max (CH₃CN) 255 nm (ε 19,600) (lit. (50) EtOH, 257 nm (ε 17,400)); nmr (CDCl₃) δ 7.77-7.27 (m, 10, phenyl protons), 7.03 (d, 1, J = 2 Hz, proton at C-3), and 5.92 (d, 1, J = 2 Hz, proton at C-4).

Recrystallization of 152 using ethanol resulted in decomposition and formation of trans-chalcone (165a) and bis(1,3-diphenyl-3-oxopropyl) sulfone (171) (experiment 21).

18. Synthesis of 2-(4-Chlorophenyl)-4-phenylthiete 1,1-dioxide (153a) and 2-Phenyl-4-(4-chlorophenyl)-thiete 1,1-dioxide (153b).

The procedure used was similar to that described in experiment 17. To a stirred mixture of 27.0 g (0.080 mole) of 127b and 27.0 ml of glacial acetic acid cooled in an ice bath was added 81.0 ml of 40% peracetic acid over a period of 30 min. After stirring for 18 hours, the opaque, cream-coloured reaction mixture was worked up to give a yellow solid. Crystallization from ethanol 95 gave 13.7 g (59%) of 153a as white needles, mp 128-129⁰ with decomposition; ir (KBr) 3095, 3080, 2970 (C-H stretching), 1621 (olefinic double bond conjugated with aromatic group), 1302, 1160 cm⁻¹ (sulfone); uv max (CH₃CN) 262 (ε 26,300) and 294 nm (sh) (ε 1,400); nmr (CDCl₃) δ 7.67-7.25 (m, 9, aromatic protons), 7.02 (d, 1, J = 2 Hz, proton at C-3) and 5.91 (d, 1, J = 2 Hz, benzylic proton).

Anal. Calcd. for C₁₅H₁₁ClO₂S: C, 61.96; H, 3.81; Cl, 12.19; mol. wt., 290.77. Found: C, 61.93; H, 4.25; Cl, 12.31.

In the same manner, 35.4 g (0.105 mole) of 127a mixed with 35 ml of glacial acetic acid was reacted with 106 ml of peracetic acid. When approximately one-half of the peracid had been added, a pale yellow solu-
tion was obtained which persisted throughout the reaction period. After stirring for 18 hours, the reaction was worked up to give a yellow solid. Crystallization from ethanol 95 gave 13.2 g (43.2%) of white crystals, mp 117-119°. Infrared analysis of this material indicated the presence of 153a and another component (153b). Evaporation of the mother liquor under reduced pressure and crystallization of the residue from ethanol 95 gave 4.1 g (13.4%) of white crystals which appeared to be about a 50:50 mixture of 153a and 153b, according to the ir spectrum. Repeated recrystallizations of this latter solid from ethanol 95 eventually gave pure 153b as white, shiny flakes, mp 130-131° with decomposition; ir (KBr) 3095, 3060, 2965 (C-H stretching), 1622 (olefinic double bond conjugated with aromatic group), 1310, 1160 cm⁻¹ (sulfone); uv max (CH₃CN) 230 (ε 20,300), 256 (ε 22,600) and 290 nm (sh) (ε 800); nmr (CDCl₃) δ 7.70-7.08 (m, 9, aromatic protons), 6.98 (d, 1, J = 2 Hz, proton at C-3) and 5.85 (d, 1, J = 2 Hz, p-chlorobenzylic proton).

Anal. Calcd. for C₁₅H₁₁ClO₂S: C, 61.96; H, 3.81; Cl, 12.19; mol. wt., 290.77. Found: C, 61.72; H, 4.12; Cl, 12.10.

A mixture melting point of 153a and b was depressed to 117-119°.

19. Investigation of the Effect of Starting Material Configuration on the Isomer Ratio of the Product in the Synthesis of 2-(4-Chlorophenyl)-4-phenylthietane 1,1-dioxide (153a) and 2-Phenyl-4-(4-chlorophenyl)-thietane 1,1-dioxide (153b).

After reacting 1.90 g (0.0057 mole) of trans-2-(4-chlorophenyl)-3-dimethylamino-4-phenylthietane 1,1-dioxide (127b) in 2.0 ml of glacial acetic acid with 6.0 ml of 40% peracetic acid at ice-water temperature for 20 hours (experiment 18), the reaction was worked up by adding 20 ml of
distilled water - ethanol 95 (1:1) followed by 10 ml of water, and subsequently collecting the solid by suction filtration. The product was washed with more water and then dried in a desiccator under vacuum. Upon adding the washings to the filtrate, a second precipitate formed which was collected by suction filtration, washed and dried. The first solid, 1.24 g (75.6%) was found to be 153a by ir and nmr analysis. The second solid, 0.22 g (13.4%) was a mixture of 153a and b, according to the ir spectrum. From the appearance of the one-proton doublets in the nmr spectrum, the proportions of 153a and b in the mixture were estimated to be 2:1, respectively. Thus, of the 89% of the theoretical amount of product isolated, approximately 95% was 153a and 5% was 153b.

In a 100 ml reaction flask fitted with a mechanical stirrer and a thermometer were placed 0.50 g (0.0015 mole) of 127b and 45 ml of THF. Stirring gave an almost saturated, colourless solution to which 3.0 ml of 40% peracetic acid was added dropwise over a period of 2 min from a pipette. When most of the peracid had been added, the reaction temperature gradually rose from an initial 27 to 28°. The temperature was maintained at 27±1° by cooling the flask in an ice-water bath when necessary. The reaction was monitored by uv analysis. At various times 0.5 ml aliquots were removed from the solution, diluted to 1 litre with ethanol 95 and the absorption determined at 260 nm. Formation of product was essentially complete after 2.5 hours. After running for 5 hours, the volume of the reaction solution was reduced to about 10 ml by evaporation under reduced pressure. Upon adding 40 ml of distilled water a white solid precipitated. The mixture was carefully neutralized with a saturated, aqueous solution of Na₂CO₃ and the solid was collected by suction filtration, washed with water and dried in a desiccator. Neither addition of the washings to the filtrate nor fur-
ther dilution with water caused more precipitate to form. After drying, the white crude product weighed 0.35 g, making the yield 85% when the amount removed by sampling was taken into consideration. The ir spectrum (KBr) of this material indicated that it was free of 127b and that it consisted mainly of 153b, with a small proportion of 153a. In the 100 MHz spectrum (CDCl₃) the absorption due to the vinylic proton of 153b appeared as a doublet at 5.6.980 and that due to the p-chlorobenzylidene proton as a doublet at 5.858 (J = 2 Hz). The corresponding absorptions for 153a were at 6.7.017 and 5.904 (J = 2 Hz). From the doublet integrals, the product was found to consist of 82% 153b and 18% 153a. Thermolysis of a 30.0 mg sample of the product at 166° for 3 min and determination of the amounts of p-chlorobenzylidene acetophenone (167) and benzylidene p-chloroacetophenone (166) in the thermolysate by glc gave the composition as 85% 153b and 15% 153a (see experiment 26).

An identical reaction in THF was run using 0.50 g (0.0015 mole) of 127a. Upon adding the first few drops of peracid, the temperature of the reaction rose rapidly to 30°. Briefly cooling the flask in an ice-water bath returned the temperature to 27°. Uv analysis indicated that the reaction was essentially complete within the first 30 min following the addition of the peracid. Work-up, after running for 5 hours, gave 0.40 g (97%) of white solid. The ir spectrum (KBr) of this material showed the presence of both thiete 1,1-dioxide isomers with no evidence of 127a. From the 100 MHz spectrum (CDCl₃) the composition was determined to be 35% 153b and 65% 153a. The thermolysis procedure gave the composition as 36% 153b and 64% 153a.

20. Synthesis of 2-(4-Nitrophenyl)-4-phenylthiete 1,1-dioxide (155).
The procedure described in experiment 17 was used. However, preliminary experiments indicated that the elimination reaction with 128 was relatively rapid and, therefore, a shorter reaction period was required. Because of the instability of 128 to crystallization, crude material containing approximately 12% 148 as impurity was employed. To a cooled, stirred suspension of 20.3 g of starting material in 20 ml of glacial acetic acid was added 61 ml of 40% peracetic acid over a period of 1 hour. After stirring for another hour, the cream-coloured mixture was neutralized with a saturated aqueous solution of Na₂CO₃ and extracted with one 250 ml portion and two 150 ml portions of CHCl₃. The pooled CHCl₃ extracts were washed with 150 ml of 10% NaCl solution, dried over anhydrous Na₂SO₄ and then evaporated under reduced pressure to give 15.0 g (96%, based on the calculated amount of 128 present in the starting material) of cream-coloured solid, mp 139-142° with decomposition. The ir and nmr spectra of the crude product were identical to those of the purified material. Crystallization from ethanol 95 gave 155 as pale yellow, thin plates, mp 147-148° with decomposition; ir (KBr) 3075, 2955, 2860 (C-H stretching), 1615 (olefinic double bond conjugated with aromatic group), 1520, 1320 (nitro group), 1300, 1155 cm⁻¹ (sulfone); nmr (DMSO-d₆) 8.57-8.30 (m, 2, protons ortho to nitro group), 8.18 (d, 1, J = 2 Hz, proton at C-3), 8.07-7.83 (m, 2, protons meta to nitro group), 7.50 (s, 5, phenyl protons), and 6.49 (d, 1, J = 2 Hz, benzylic proton); uv max (CH₃CN) 288 nm (ε 19,000).

Anal. Calcd. for C₁₅H₁₁NO₄S: C, 59.79; H, 3.68; N, 4.65; mol. wt., 301.32. Found: C, 59.83; H, 3.75; N, 4.79.

A sample of 155 was thermolyzed using the same conditions as described for the thermolysis of 152 in experiment 24. The thermolysate,
a dark brown solid, was dissolved in CHCl₃ and analyzed by glc using the same column and conditions as in experiment 23, except with the oven at 240° and the nitrogen flow at 80 ml/min. Only one major peak was observed in the chromatogram, retention time 4.0 min. The ir spectrum (KBr) of the thermolysate showed strong bands at 1663, 1592 and 1212 cm⁻¹, which supported the presence of an α,β-unsaturated, aromatic ketone. Strong nitro group bands were present at 1517 and 1338 cm⁻¹.

21. Decomposition of 2,4-Diphenylthiete 1,1-dioxide (152) in Ethanol.

**Bis(1,3-diphenyl-3-oxopropyl) Sulfone (171) and trans-Chalcone (165a).**

In a 500 ml boiling flask fitted with a reflux condenser were placed 2.56 g (0.010 mole) of crystalline 2,4-diphenylthiete 1,1-dioxide (152) and 250 ml of ethanol 95. Upon warming the mixture, a solution was obtained which was heated at reflux for 2 hours. Evaporation of the solvent under reduced pressure gave a viscous, yellow oil with a characteristic odor. The oil was mixed with 20 ml of ethanol 95 and heated to reflux temperature on a steam bath and then allowed to cool. Upon cooling, a white precipitate formed. The solid was collected by suction filtration, washed with ethanol 95 and air dried. The filtrate, pooled with the washings, was evaporated in vacuo and the resulting oil was heated with ethanol 95 to give additional precipitate. Repeating the process two more times gave a total of 0.41 g (0.00084 mole, 17%) of 171. The ir spectrum of this crude material was identical to that of the crystallized compound. Crystallization from hexane - methyl ethyl ketone gave bis(1,3-diphenyl-3-oxopropyl) sulfone (171) as short, white needles, mp 184-185° with decomposition; ir (KBr) 3065, 3040, 2925 (C-H stretching), 1683, 1241 (benzoyl group), 1600, 1582, 1452, 765, 715, 702 (mono-substi-
tuted phenyl), 1307, 1138 cm\(^{-1}\) (sulfone); nmr (CDCl\(_3\)) \(\delta\) 7.93-7.67 (m, 4, protons ortho to carbonyl), 7.53-7.23 (m, 16, meta, para, and phenyl protons), 4.70 (q, X portion of ABX pattern, 2, benzylic protons) and 4.20-3.39 (m, AB portion of ABX pattern, 4, methylene protons). From the 100 MHz nmr spectrum of 171, the chemical shift of protons A was calculated (44b) to be \(\delta 3.717\) (\(J_{AX}\) = 2.8 Hz) and that of protons B to be 3.925 (\(J_{BX}\) = 10.2 Hz) with \(J_{AB}\) = 17.5 Hz. The uv spectrum (CH\(_3\)OH) showed a maximum at 244 nm (\(\varepsilon 25,000\)) (contribution of two benzoyl groups).

Anal. Calcd. for C\(_{30}\)H\(_{26}\)O\(_8\): C, 74.66; H, 5.43; O, 13.26; S, 6.64; mol. wt., 482.60. Found: C, 74.21; H, 5.66; O, 13.62; S, 7.00.

Crystallizations of crude 171 gave a second crystalline substance 174 as colourless, transparent plates, mp 196-197\(^\circ\) with decomposition. The ir spectra (KBr) of 171 and 174 were similar, the main difference being that the high frequency sulfone band in the spectrum of 174 was split with one peak at 1310 cm\(^{-1}\) and the other at 1292 cm\(^{-1}\). The nmr spectra (CDCl\(_3\)) were superimposable. Substance 174 was more slowly soluble in CHCl\(_3\) and ethanol 95 than was 171.

Evaporation of the final filtrate from the isolation of 171 gave a brownish-yellow oil. In the ir spectrum (neat) strong bands occurred at 1665 and 1600 cm\(^{-1}\), which suggested the presence of an \(\alpha,\beta\)-unsaturated ketone. Vacuum distillation of the oil using a short-path apparatus gave 0.2 g (10\%) of yellow distillate (165a), bp 120-130\(^\circ\) at 0.1 mm (lit. (127) 208\(^\circ\) at 25 mm). The distillate solidified soon after collection. A black, nondistillable tar remained in the distilling flask. Crystallization of the yellow solid from pet. ether (bp 60-80\(^\circ\)) afforded pale yellow prisms, mp 54-55\(^\circ\) (lit. (127) 57-58\(^\circ\)). Except for minor differences in some band splittings, the ir spectrum (KBr) was superimposable.
with that of an authentic sample of trans-chalcone (165a) (128). The nmr spectrum (CDCl₃) appeared to be identical to a published spectrum (129) except for minor impurity signals at δ 3.50, 1.77 and 0.97. The uv spectrum (hexane) showed two maxima, one at 226 nm (logε 4.06) and the other at 298 nm (logε 4.36) (lit. (130) 226 (logε 4.08) and 299 nm (logε 4.38)). When an acetone solution of the crystallized material was analyzed by glc on the same column as described in experiment 1, with the injection port, oven, and detector at 282, 193 and 253°, respectively, and the nitrogen flow at 80 ml/min, one peak was observed with a retention time (5.1 min) identical to that of an authentic sample of 165a.

22. **Synthesis of Bis(1,3-diphenyl-3-oxopropyl) Sulfone (171).**

β-Mercapto-β-phenylpropiophenone (176) was prepared using a method adopted from the literature (104). A solution of 16.0 g (0.077 mole) of trans-chalcone (165a) (128) and 8.0 g (0.079 mole) of dry triethylamine in 480 ml of dry CHCl₃ was cooled in a dry ice-acetone bath and then placed in a 1 litre bomb of a Parr Pressure Reaction Apparatus No. 4511 (fume hood). Immediately, 80 ml of liquid H₂S (previously collected using a dry ice-acetone bath) was added and the bomb was sealed. The apparatus was heated at 40° for 21 hours and allowed to cool to room temperature over a period of 12.5 hours. The pressure was returned to atmospheric by venting the excess H₂S into an aqueous alkali solution. The contents of the bomb were then transferred to a separatory funnel with the aid of a small amount of CHCl₃ and extracted with two 500 ml portions of dilute HCl followed by two 500 ml portions of distilled water. After drying the orange-brown CHCl₃ solution over anhydrous Na₂SO₄, it was evaporated in vacuo to give a light brown oil, which rapidly reverted to
an off-white, crystalline solid upon sitting (18.0 g, 97%). Crystallization from ethanol 100 gave 176 as silvery-white plates, mp 102-105° (lit. (104) 102-103°). The ir spectrum (KBr) was identical to that of the crude material and showed a strong carbonyl band at 1675 cm⁻¹ and a weak S-H stretching band at 2585 cm⁻¹. 176 darkened on exposure to light.

A mixture of 2.08 g (0.010 mole) of 165a and 2.42 g (0.010 mole) of 176 was triturated to form a fine powder, which was placed in a 100 ml boiling flask. After mixing in 20 mg of benzoyl peroxide (Fisher Scientific, rea.) with a spatula, the flask was stoppered and heated on a steam bath. Within 10 min, a yellow homogeneous liquid was obtained, from which a solid began to separate after 2 hours. After 3 hours, the reaction mixture appeared as a yellow, solid mass. Heating was discontinued after 6 hours and the flask was allowed to cool to room temperature. Washing the product with anhydrous diethyl ether gave a white solid and a yellow supernatant. The solid (1.86 g) was suction filtered, washed further with ether and allowed to dry. The ir spectrum (KBr) of the solid showed an hydroxyl band at 3440 cm⁻¹ and a fairly strong absorption at 1640 cm⁻¹. It was apparent from this spectrum that the solid was not the desired sulfide and it was not further investigated.

Evaporation of the filtrate pooled with the ether washings gave a yellow oil (2.67 g). Analysis of the oil by tlc, using microscope slides coated with silica gel G, benzene as the developing solvent and charring as the visualization method, indicated the presence of one main component, presumably bis(1,3-diphenyl-3-oxopropyl)sulfide (177), as well as relatively small amounts of 165a and 176. In the ir spectrum (neat), no definite absorption due to S-H stretching was observed; a strong band at 1680 cm⁻¹ was attributed to 177, while a shoulder at 1665 cm⁻¹ was appar-
ently due to 165a. The oil was dissolved in 10 ml of CHCl₃ and trans­ferred to a 50 ml reaction flask fitted with a mechanical stirrer. Glacial acetic acid, 10 ml, was added and the resulting yellow solution was cooled in an ice-water bath. Peracetic acid (40%), 4.6 ml, was then added drop­wise over a period of 5 min with stirring. After 20 hours, evaporation of the solution under reduced pressure to remove the CHCl₃ caused the product (171) to precipitate as a white solid. The solid was collected by suction filtration, washed with diethyl ether and dried. The filtrate and ether washings were pooled and mixed with CHCl₃ and water. The organic layer was separated, dried over anhydrous Na₂SO₄ and evaporated to give a pale yellow oil, which on warming with ethanol 95 afforded additional solid product. The total weight of product was 1.70 g (60% yield, based on taking the crude sulfide 177 to be pure). Crystallization from hexane­methyl ethyl ketone gave short white needles, mp 184-185° with decomposi­tion. The ir spectrum (KBr) was superimposable with that of the ketonic sulfone 171 isolated from the decomposition of 2,4-diphenylthiete 1,1-dioxide (152) in refluxing ethanol. The nmr and uv spectra were also identical to those of 171. A mixture melting point with 171 was not de­pressed. As with the crystallization of crude 171, a second substance was obtained as transparent plates from the crystallization of the crude product. The ir spectrum of the transparent plates was identical to that of 174.

23. Decomposition of 2,4-Diphenylthiete 1,1-dioxide (152) in Aqueous Tetrahydrofuran, 1,3-Diphenylpropene-3-sulfonic Acid (170).

A solution of 2.56 g (0.01 mole) of thiete 1,1-dioxide 152 in a mixture of 40 ml of THF and 10 ml of distilled water was refluxed for
41 hours. The temperature of the boiling solution was 66°. After refluxing for 12 hours, the odor of \( \text{H}_2\text{S} \) was noticeable at the open end of the condenser. A piece of filter paper wetted with aqueous \( \text{Pb(OAc)}_2 \) solution was darkened when exposed to these fumes. Evaporation of the solvent under vacuum gave a viscous, yellow oil. The oil was dissolved in 20 ml of \( \text{CHCl}_3 \) and extracted with a 20 ml portion and two 10 ml portions of distilled water. The pooled, pale brown, aqueous extracts had a pH of 1 when tested with indicator paper. The \( \text{Pb(OAc)}_2 \) test for \( \text{H}_2\text{S} \) was negative. Evaporation of the extracts under high vacuum gave a yellow oil which crystallized upon sitting. After storing in a desiccator overnight, the solid (170) weighed 1.95 g (71%). Crystallization from hexane - \( \text{CHCl}_3 \) gave 1.0 g (37%) of 1,3-diphenylpropene-3-sulfonic acid (170) as fine, off-white needles, mp 97-102° with decomposition; ir (KBr) 3700-2400, 1225, 1050 (sulfonic acid), 1600, 1500, 1460, 761, 705 cm\(^{-1}\) (mono-substituted phenyl); nmr (DMSO-d\(_6\)) \( \delta \) 7.64-7.10 (m, 10, phenyl protons), 6.61 (d, 1, \( J = 7 \) Hz, \( \alpha \)-styryl proton), 6.56 (s, superimposed on upfield signal of doublet at 6.61, 1, benzylic proton), and 4.57 (d, 1, \( J = 7 \) Hz, \( \beta \)-styryl proton); uv max (\( \text{H}_2\text{O} \)) 253 (\( \varepsilon \)21,600), 282.5 (sh) (\( \varepsilon \)2.740) and 292 nm (\( \varepsilon \)1,450). The sulfonic acid was unstable and decomposed when stored for 1 week in a desiccator in the dark, at room temperature, to give a water-insoluble solid. The ir spectrum (KBr) of the decomposition material showed the absence of sulfonic acid bands. Strong absorptions occurred at 1358, 1190 and 1168 cm\(^{-1}\), which suggested the presence of a sulfonic acid ester.

The dimethylamine salt of 170 was prepared and found to be relatively stable. Crystallization of this salt from hexane - benzene gave short, white needles, mp 169-170°; ir (KBr) 3040, 2800, 2950, 2480 (ammonium band), 1250, 1225, 1160, 1027 cm\(^{-1}\) (sulfonic acid salt). The
nmr spectrum (CDCl₃) showed a complex multiplet at δ 7.91-7.10 (phenyl protons, 10, and protons on N, 2) an unsymmetrical triplet which was attributed to a doublet at 6.70 (α-styryl proton (c), 1, Jᶜᵃ = 5.5 Hz), the upfield signal of which was superimposed on the upfield signal of a doublet at 6.67 (benzylic proton (b), 1, Jᵇᵃ = 2 Hz), a quartet at 4.77 (β-styryl proton (a), 1, Jᵃᵇ = 2 Hz, Jᵃᶜ = 5.5 Hz), and a singlet at 2.24 (N-methyl protons, 6). Upon addition of D₂O the integral for the multiplet at δ 7.91-7.10 decreased and a diffuse band appeared with its centre at about 4.4. The dimethylamine salt of 170 was submitted for analysis. Anal. Calcd. for C₁₇H₂₁N₂O₃S: C, 63.92; H, 6.63; mol. wt., 319.42. Found: C, 63.93; H, 6.53.

The CHCl₃ layer from the aqueous extraction of the sulfonic acid 170 was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give 1.11 g of translucent, brown oil. Infrared analysis (neat) indicated the presence of bis(1,3-diphenyl-3-oxopropyl) sulfone (171) and trans-chalcone (165a). Approximately 20 ml of hexane was added to the oil and the mixture was heated on a steam bath to extract 165a. After repeating the extraction a second time, a yellowish-brown, viscous syrup remained. The syrup was warmed with a small amount of ethanol 95 and 0.27 g (11%) of 171 was recovered upon cooling. The hexane extracts were analyzed by glc and the total amount of 165a was determined to be 0.15 g (7%). The analysis was carried out using a 6 ft x 5/32 in (i.d.) silanized glass column packed with 6.4 g of 3% QF-1 on Gas-Chrom Q (100-120 mesh) with the injection port, oven, and detector at 240, 170 and 270°, respectively, and the nitrogen flow at 67 ml/min. Under the described conditions, 165a had a retention time of 6.3 min. A straight-line calibration curve was obtained by chromatographing hexane solutions of 165a of known concentra-
tion (0.1, 0.3, and 0.5%) and plotting the observed peak area against concentra-

Approximately 90% of the thiete 1,1-dioxide \(152\) refluxed in aqueous THF was accounted for by the decomposition products \(165a\), \(170\) and \(171\).

**24. Thermolysis of 2,4-Diphenylthiete 1,1-dioxide (152) and Bis(1,3-diphenyl-3-oxopropyl) Sulfone (171).**

A stoppered 8 x 70 mm test tube containing 30.0 mg (0.000117 mole) of pure \(152\) was placed in a 166° oil bath for 3.0 min. During the first min the solid melted and a gas was rapidly evolved from the melt. After 2 min the evolution had almost ceased. Upon cooling, the brownish-yellow residue was dissolved in sufficient CHCl\(_3\) to give 10 ml of pale yellow solution. The solution was analyzed for trans-chalcone (165a) by glc using the same column and conditions as described in experiment 23. By reference to a calibration curve, the total amount of \(165a\) (retention time 6.3 min) in the solution was determined to be 22 mg (92%). A second peak was present in the chromatogram at 3.2 min, which was attributed to cis-chalcone (165b) (see below). The area of this latter peak was about 2% that of the peak at 6.3 min. The ir spectrum (neat) of a residue obtained from a similar thermolysis closely resembled the spectrum (KBr) of 165a.

The thermolysis of \(171\) was investigated qualitatively. A stoppered 8 x 70 mm test tube containing a sample of \(171\) was placed in a 160° oil bath, which was then rapidly heated to 200° by means of a Bunsen flame. At the mp of the sample, there was a vigorous evolution of gas. After heating at 200° for 2 min, the evolution ceased and the tube was removed.
from the bath. Upon removing the stopper, a harsh odor was noticeable. The thermolysate was a viscous, golden-yellow syrup. The ir and nmr spectra of this material were very similar to those of 165a. Analysis by glc of a CHCl₃ solution of the thermolysate using the same column and conditions as mentioned in experiment 23 gave two peaks. The first, at 3.2 min, was attributed to cis-chalcone (165b) and the second, at 6.3 min, corresponded to trans-chalcone (165a). The area of the peak at 3.2 min was 23% that of the peak at 6.3 min.

Isomerization in solution of trans-chalcone to the cis-isomer upon exposure to sunlight is a known process (99). When a freshly-prepared 0.2% CHCl₃ solution of trans-chalcone (mp 57-58°) was analyzed by glc, using the same column and conditions as in experiment 23, only one peak, retention time 6.3 min, was observed. After sitting in a Pyrex container in the open (fluorescent lighting) for 3 hours, a second peak, retention time 3.2 min, was apparent. After placing the container in direct sunlight for 1 hour, the area of the peak at 3.2 min increased and that at 6.3 min decreased, such that the ratio of the two areas was approximately 1:1. Upon removing the flask from direct sunlight, the peak at 3.2 min decreased and that at 6.3 min increased. On the basis of these observations, the peak at 3.2 min was attributed to cis-chalcone (165b). Evaporation of a CHCl₃ solution in which the cis to trans ratio was found to be 1.2:1 by glc gave an orange-yellow liquid. This agreed with the literature observation that a mixture of cis-chalcone, mp 45-46°, with the trans-isomer liquified at room temperature (99). The ir spectrum (neat) was quite similar to the spectrum (KBr) of 165a. Differences in the intensities of some bands as well as differences in some band splittings between the two spectra may have been due to the difference in sampling
technique, as well as to the difference in isomer constitution.

25. Synthesis of trans-p-Chlorobenzylidene Acetophenone (167) and trans-
Benzylidene p-Chloroacetophenone (166).

trans-p-Chlorobenzylidene acetophenone (167) was prepared using a procedure taken from the literature (137). To a 500 ml three-necked flask fitted with a mechanical stirrer and a thermometer were added 240 ml of ethanol 95, 20.08 g (0.142 mole) of p-chlorobenzaldehyde (Eastman, prac.) and 17.16 g (0.143 mole) of acetophenone (Fisher Scientific, rea.). The mixture was stirred to give a colourless solution and then 24 ml of 10% aqueous NaOH solution was added with vigorous stirring. The solution immediately turned yellow and its temperature began to rise. The temperature was maintained at 24-25° by immersing the flask in an ice-water bath when necessary. Approximately 3 minutes after adding the base the solution became translucent and then much solid rapidly precipitated. The mixture was allowed to sit for 15 min and then the solid was collected by suction filtration, washed with 1 litre of distilled water followed by 100 ml of ice-cold ethanol 100 and air dried. The weight of the pale yellow, amorphous solid after drying was 26.12 g (75%). Crystallization from hexane-ethanol 95 gave 167 as pale yellow needles, mp 112-113.5° (lit. (137) 114.5°, from ethanol 95).

Using a similar procedure, 15.05 g (0.142 mole) of benzaldehyde was reacted with 22.11 g (0.143 mole) of p-chloroacetophenone (Eastman, white label) in 240 ml of ethanol 95 in the presence of 24 ml of 10% aqueous NaOH. About 2 min after adding the base, solid began to precipitate, at a slower rate, however, than with the synthesis of 167. One hour after adding the base, the solid was collected by suction filtration and washed
with water followed by cold ethanol. Drying in a desiccator yielded 22.64 g (65%) of pale yellow solid. Crystallization from hexane – ethanol 100 gave 166 as pale yellow, feather-like crystals, mp 96.5-98° (lit. (89) 94-96°).

Gas-liquid chromatography of freshly prepared 0.05, 0.10, 0.20 and 0.30% solutions of trans-p-chlorobenzylidene acetophenone (167) in CHCl₃, each containing 0.10% benzil as internal standard, using the same column and conditions as described in experiment 23, except with the oven at 200°, gave one peak for 167, retention time 3.9 min, and one peak for benzil at 1.5 min. Plotting the ratio of the height of the 167 peak to that of the benzil peak against the concentration of 167 gave a straight-line calibration curve. In a similar manner, a straight-line curve was obtained for trans-benzylidene p-chloroacetophenone (166), retention time 3.6 min.

After allowing CHCl₃ solutions of 167 and 166 to sit in the open in Pyrex containers for about a week, a second peak, retention time 2.2 min, was observed in the chromatogram of the 167 solution and a second, retention time 1.9 min, in that of the 166 solution. By analogy to similar observations made with trans-chalcone (165a) (experiment 24), the two new peaks were assumed to be due to cis-p-chlorobenzylidene acetophenone and cis-benzylidene p-chloroacetophenone, respectively.

26. Thermolysis of 2-(4-Chlorophenyl)-4-phenylthiete 1,1-dioxide (153a) and 2-Phenyl-4-(4-chlorophenyl)-thiete 1,1-dioxide (153b).

A stoppered 8 x 70 mm test tube containing 30.0 mg (0.000103 mole) of pure 153b was placed in a 164° oil bath for 3 min. During the first min, the solid melted and a vigorous evolution of gas from the melt
commenced. Production of gas bubbles ceased after about 2 min. Soon after removing the test tube from the bath, the liquid residue reverted to an orange solid. A harsh odor was noticeable upon removal of the stopper. When cool, the solid was dissolved in sufficient CHCl$_3$ along with 1 ml of 1% benzil solution to give 10 ml of final solution. Immediate glc of this solution using the column and conditions referred to in experiment 25 gave three peaks, the retention times of which corresponded to those of trans-p-chlorobenzylidene acetophenone (167), presumed cis-p-chlorobenzylidene acetophenone (see experiment 25) and benzil. The area of the cis-isomer peak was approximately 1% that of the 167 peak. From a calibration curve (experiment 25) the concentration of 167 was determined to be 0.21%, indicating that 85% of the starting material 153b had been converted to this compound. The ir spectrum (KBr) of the solid product obtained in a similar thermolysis of 153b showed only minor discrepancies from that of an authentic sample of 167.

An identical thermolysis was carried out on 153a. Besides the peak due to the internal standard, two other peaks were present in the chromatogram, one attributable to 166 and the other to the presumed cis-benzylidene p-chloroacetophenone (see experiment 25). The area of the latter peak was approximately 1% that of the former. From a calibration curve (experiment 25) the CHCl$_3$ solution was found to contain 0.20% 166, which meant that 80% of the thiote 1,1-dioxide 153a had been converted to 166. The ir spectrum (KBr) of a sample of solid thermolysate was almost identical to that of authentic 166.

27. Synthesis of 2,4-Diphenyl-3-cyanothieteane 1,1-dioxide (178).

The ethanolic solution of hydrogen cyanide required for this procedure was prepared by mixing 80 ml of liquified HCN (131a) with 2
The synthesis of \( \text{178} \) was carried out in a fume hood. In a 2 litre three-necked flask fitted with a mechanical stirrer were placed 10.0 g (0.039 mole) of crystalline 2,4-diphenylthiete 1,1-dioxide (152) and 250 ml of reagent CHCl₃. The mixture was stirred to give a solution and then 500 ml of ethanol 100 was gradually added, followed by 250 ml of ethanolic HCN solution. The reaction was initiated by adding 575 mg of dry, finely powdered KCN, which caused the solution to turn a bright yellow colour. The flask was stoppered and stirred at a moderate rate for 18 hours, during which time a solid precipitated. The solid was collected by suction filtration and washed with a small amount of ethanol 95. Evaporation of the filtrate pooled with the ethanol washings gave an intractable, black tar. The crude product was stirred in 400 ml of distilled water for several minutes and then suction filtered. Upon drying overnight, the pale yellow powder weighed 8.57 g (77.6\%) and had a mp of 235-237°. The ir spectrum of the powder was identical to that of the crystallized material. Crystallization from n-butyl alcohol gave \( \text{178} \) as heavy, white crystals with a feather-like appearance, which when washed with ethanol 100 and dried had a mp of 236-237°; ir (KBr) 3070, 2960 (C-H stretching), 2245 (nitrile), 1338, 1178, 1138 cm⁻¹ (sulfone); nmr (DMSO-d₆) 6 7.81-7.33 (m, 10, phenyl protons), 6.34 (d, 2, \( J = 10.5 \) Hz, protons at C-2 and C-4), and 4.77 (t, 1, \( J = 10.5 \) Hz, proton at C-3).

**Anal.** Calcd. for \( \text{C}_{16}\text{H}_{13}\text{NO}_2\text{S} \): C, 67.82; H, 4.63; N, 4.94; mol. wt., 283.35. Found: C, 67.80; H, 4.73; N, 4.84.

Washing of the crude product with water was necessary in order to remove an inorganic side-product. Evaporation of the aqueous washings gave a brown solid. The ir spectrum (KBr) of this material (K₂SO₄?) was
quite similar to that of \( \text{Na}_2\text{SO}_4 \). Treatment of an acidified aqueous solution of the inorganic substance with \( \text{Ba(NO}_3\text{)}_2 \) solution caused a white solid to separate, which suggested the presence of the sulfate anion.

Crude thiete 1,1-dioxide 152 could be used in this reaction without affecting the yield of 178.

28. Synthesis of 2-(4-Chlorophenyl)-3-cyano-4-phenylthietane 1,1-dioxide (180).

The reaction procedure was identical to that described in experiment 27. The starting material was a mixture of 2-(4-chlorophenyl)-4-phenylthiete 1,1-dioxide (153a) and 2-phenyl-4-(4-chlorophenyl)-thiete 1,1-dioxide (153b). After reacting 15.00 g (0.0516 mole) of isomer mixture overnight, a precipitate was present, which was collected by suction filtration and washed with a small amount of ethanol 100. Upon drying, the white crystalline solid (180) weighed 6.80 g (42.0%) and had a mp of 198-199\(^\circ\). Evaporation in vacuo of the yellow filtrate pooled with the ethanol washings yielded a yellow solid. Fractional crystallization of this material from ethanol 100 afforded 2.26 g (14.0%) additional product and 2.07 g (13.8%) of crystalline starting material. Crystallization from ethanol 95 gave 180 as white, fine needles, mp 199-200\(^\circ\); ir (KBr) 3070, 2968, 2940 (C-H stretching), 2280 (nitrile), 1333, 1180, 1148 cm\(^{-1}\) (sulfone); nmr (DMSO-d\(_6\)) \( \delta \) 7.89-7.43 (m, 9, aromatic protons), 6.39 (d, 2, \( J = 11 \) Hz, protons at C-2 and C-4), and 4.76 (t, 1, \( J = 11 \) Hz, proton at C-3).

Anal. Calcd. for \( \text{C}_{16}\text{H}_{12}\text{ClNO}_2\text{S} \): C, 60.47; H, 3.81; Cl, 11.16; mol. wt., 317.79. Found: C, 60.26; H, 3.82; Cl, 11.18.
29. Synthesis of 2-(4-Nitrophenyl)-3-cyano-4-phenylthietane 1,1-dioxide (181).

The procedure used was similar to that described in experiment 27 and was carried out in a fume hood. A mixture of 10.26 g (0.0341 mole) of 155 and 308 ml of THF in a stoppered 1 litre conical flask was magnetically stirred to give a pale yellow solution. To the solution was added 256 ml of 1 M ethanolic HCN followed by 590 mg of powdered KCN. Within a few minutes the reaction turned a translucent, orange-brown. After stirring for 5 hours, the solvent was removed by evaporation under reduced pressure to give an orange-brown oil. Upon mixing the oil with 30 ml of ethanol 100, a pale yellow solid separated, which was collected by suction filtration and washed with a small amount of ethanol. Evaporation of the filtrate pooled with the washings gave an orange-brown syrup. Repeating the treatment with ethanol yielded more solid. After washing with 400 ml of distilled water and drying in a desiccator, the pooled solids (181) weighed 7.52 g (67%). Approximately 0.9 g more product was obtained when the oil for the evaporation of the last filtrate was subjected to column chromatography (see experiment 30). Thus, the total yield of crude product was about 75%. The ir spectrum of this material was almost identical to that of the purified compound. Crystallization from hexane - CHCl₃ gave 181 as fine, white needles, mp 164-165°; ir (KBr) 3100, 2975 (C-H stretching), 2275 (nitrile), 1530, 1353 (nitro group), 1334, 1177, 1145 cm⁻¹ (sulfone); nmr (DMSO-d₆) δ 8.57-8.28 (m, 2, protons ortho to nitro group), 8.15-7.91 (m, 2, protons meta to nitro group), 7.88-7.40 (m, 5, phenyl protons), 6.56 (d, 1, J = 10.5 Hz, p-nitrobenzyllic proton), 6.48 (d, 1, J = 10.5 Hz, benzylic proton), 4.92 (t, 1, J = 10.5 Hz, proton at
C-3). A second polymorphic form of 181 was obtained as pale yellow needles in the form of rosettes, mp 152-153°. Usually, the higher melting form came out of solution first, followed by the lower melting form. In one instance, when a mixture of the two forms was left sitting in supernatant at room temperature for several days, the fine white needles gradually disappeared as more of the lower melting form appeared. The ir spectra (KBr) of the two polymorphs were essentially identical and the nmr spectra (DMSO-d6) were superimposable. Compound 181 was submitted for analysis as the low melting polymorph.

**Anal.** Calcd. for C16H12N2O4S: C, 58.53; H, 3.68; N, 8.53; mol. wt., 328.34. Found: C, 58.65; H, 3.75; N, 8.58.

30. **Isolation of Two Unsaturated Nitriles (182a and b).**

Evaporation of the final filtrate from the work-up of the reaction in experiment 29 gave 4.5 g of orange-brown oil. The oil was mixed with 20 ml of benzene, briefly heated on a steam bath, and then suction filtered to remove a reddish-brown insoluble solid. The solid was found to be almost completely water soluble. Evaporation of the benzene filtrate under reduced pressure gave 3.1 g of straw-coloured, viscous oil. This was added to 1.8 g of oil isolated in the same way from a reaction run in an identical manner to that described in experiment 29, but on a smaller scale. The pooled oils were dissolved in 10 ml of benzene and applied to the top of a 2.5 x 60 cm column prepared using 93 g of activated silica gel (60-200 mesh, Davison Chemicals). The column was developed with benzene and four fractions were eluted. Evaporation of the benzene from the first fraction gave 2.6 g of yellow solid. The second fraction yielded 0.1 g of orange-yellow solid, which was not characterized. As the third fraction was eluted, a white crystalline solid appeared in the eluate, the
ir spectrum (KBr) of which was superimposable with that of 2-(4-nitrophenyl)-3-cyano-4-phenylthietane 1,1-dioxide (181). A total of 1.4 g of pure 181 was obtained by evaporation of the supernatant. Fraction four, 0.5 g, appeared to be a mixture of 181 and other unidentified substances, according to its ir spectrum. Crystallization of fraction one from hexane - benzene gave a mixture of pale yellow needles and plates, mp 88-100°. The two crystal forms were separated by hand. Recrystallization of the portion that was mainly plates, from hexane - benzene gave 182a as pale yellow plates, mp 100-101°; ir (KBr) 2220 (medium intensity, \( \alpha, \beta \) -unsaturated nitrile), 1626 (olefinic double bond conjugated with aromatic ring), 1520, 1348 cm\(^{-1}\) (nitro group); nmr (CDCl\(_3\)) \( \delta \) 8.37-8.07 (m, 2, protons ortho to nitro group), 7.87-7.63 (m, 2, ortho protons of phenyl ring, presumably), 7.63-7.27 (m, 5, protons meta to nitro group and remaining protons on phenyl ring), 7.08 (s, 1, vinylic proton), and 3.83 (s, 2, benzylic protons); uv max (CH\(_3\)CN), 278 nm (\( \varepsilon \) 26,700).

Anal. Calcd. for C\(_{16}\)H\(_{12}\)N\(_2\)O\(_2\): C, 72.72; H, 4.58; mol. wt., 264.28.

Found: C, 72.58; H, 4.66.

Recrystallization of the portion that consisted mainly of needles gave 182b as pale yellow needles in the form of rosettes, mp 132-133°; ir (KBr) 2225 (medium intensity, \( \alpha, \beta \) -unsaturated nitrile), 1625 (olefinic double bond conjugated with aromatic group), 1516, 1348 cm\(^{-1}\) (nitro group); nmr (CDCl\(_3\)) \( \delta \) 8.36-8.09 (m, 2, protons ortho to nitro group), 7.61-7.28 (m, 8, protons meta to nitro group, phenyl protons and vinylic proton), and 3.93 (s, 2, benzylic protons); uv max (CH\(_3\)CN) 269 nm (\( \varepsilon \) 39,000).

Anal. Calcd. for C\(_{16}\)H\(_{12}\)N\(_2\)O\(_2\): C, 72.72; H, 4.58; mol. wt., 264.28.

Found: C, 72.53; H, 4.48.
31. Treatment of 2-(4-Nitrophenyl)-3-cyano-4-phenylthietane 1,1-dioxide (181) with Base.

A stirred solution of 0.33 g (0.001 mole) of 181 in 10 ml of THF was diluted with 50 ml of ethanol 95 and then treated with 2 ml of aqueous 1 N NaOH, which was added dropwise from a pipette. Initially, each drop of base caused the solution to turn a magenta colour and sufficient time was allowed between drops for most of the colour to disappear. When approximately 1.75 ml of base had been added, the colour was no longer produced and the reaction remained a translucent brown. After stirring for 30 min following the addition of the base, 2 ml of glacial acetic acid was added and the solution was evaporated under reduced pressure to give an orange solid. The solid was dissolved in 10 ml of CHCl₃ and extracted with four 10 ml portions of distilled water. After drying over anhydrous Na₂SO₄, the CHCl₃ layer was evaporated in vacuo to give 0.26 g of orange solid. The ir spectrum (KBr) of this material was quite similar to that of 182a. No sulfone absorption was evident. The nmr spectrum (CDCl₃) showed a mixture of 182a and b and indicated that these two compounds accounted for about 90% of the crude product. By comparison of the integrals of the benzylic protons, the ratio of 182a to 182b was found to be 2.4:1. Signals due to impurities were present at δ 4.31, 2.40 and 1.25. Analysis of CHCl₃ solutions of pure 182a and 182b by glc using the 3% QF-1 column described in experiment 23 with the oven, injection port and detector at 210, 243 and 270°, respectively, and the nitrogen flow at 67 ml/min gave one peak for 182a, retention time 14.3 min, and one peak for 182b, retention time 13.1 min. Analysis of a CHCl₃ solution of the crude product under the same conditions gave two main peaks, the retention times of which were identical to those of 182a and 182b.
On the basis of peak area, the ratio of $182a$ to $182b$ was 2.2:1. A third peak with an area 5% that of $182a$ was also present, retention time 20.0 min.

32. Synthesis of 2,4-Diphenyl-3-aminomethylthietane 1,1-dioxide (193).

2,4-Diphenyl-3-aminomethylthietane 1,1-dioxide (193) was prepared from 2,4-diphenyl-3-cyanothietane 1,1-dioxide (178) by either catalytic hydrogenation or hydroboration.

For the hydrogenation procedure, a Parr Pressure Reaction Apparatus No. 4511 with a 1 litre bomb was used. In the glass liner of the bomb were placed 5.0 g (0.018 mole) of finely powdered 178 and a solution prepared by bubbling dry ammonia into 550 ml of dioxane until there was 1 g of NH$_3$ per 100 ml of solvent. The dioxane had been previously purified by refluxing with sodium for 12 hours and then distilling. Five teaspoonsful of sponge nickel catalyst (W.R. Grace & Co., No. 986) were suction filtered, washed with a small amount of dioxane and added to the mixture. The catalyst was not allowed to dry at any time. The mixture was then sealed in the pressure apparatus. After flushing the bomb two times with hydrogen, a pressure of 50 psi was applied and the reaction was stirred for 21 hours. The catalyst was removed by suction filtration, washed with dioxane and rapidly covered with water (caution: the catalyst is highly pyrophoric if allowed to dry after exposure to hydrogen). Evaporation of the filtrate pooled with the washings, under vacuum, gave a pale green, viscous oil. Upon adding a small amount of hexane - ethanol (50:50) and scratching with a glass rod, 2.1 g (41%) of white solid (193) separated. Crystallization from water - ethanol 95 gave large transparent prisms, mp 110-113° (after drying under vacuum at 60° for 2 days); ir
(KBr) 3425, 3365 (N-H stretching of 1° amine), 1310, 1165, 1150 cm⁻¹
(sulfone); nmr (CDCl₃) δ 7.61-7.23 (m, 10, phenyl protons), 5.21 (d, 2, J = 10 Hz, protons at C-2 and C-4), 3.38-2.80 (m, 3, proton at C-3 and methylene protons), and 1.60-1.15 (band, 2, protons on N).

Anal. Calcd. for C₁₆H₁₇NO₃S: C, 66.87; H, 5.96; O, 11.13; S, 11.16; mol. wt., 287.38. Found: C, 67.03; H, 6.32; O, 11.32; S, 11.33.

The picrate of 193 was prepared and crystallized from n-butyl alcohol to give bright yellow needles, mp 263° with decomposition.

For the hydroboration procedure, a solution of diborane in THF, approximately 0.3 M, was prepared using a method from the literature (111, 132).

A 500 ml three-necked flask fitted with a mechanical stirrer, a dropping funnel and a reflux condenser protected with a drying tube was flushed with dry nitrogen and flame dried. Upon cooling, 14.15 g (0.050 mole) of finely powdered 178 and 125 ml of dry THF were placed in the flask and the stirrer was activated. The dropping funnel was charged with 250 ml of diborane solution (about 0.08 mole of B₂H₆), which was added dropwise over a period of 1.5 hours. Three hours after the addition was completed, a colourless solution was obtained. After stirring for 13 hours, sufficient ethanol 100 was added, in portions, to decompose the excess diborane and the solution was heated at reflux for 1 hour. Upon reducing the volume to about 100 ml by evaporation under reduced pressure, the solution was diluted with 200 ml of anhydrous diethyl ether and cooled in an ice-water bath. Treatment with anhydrous HCl caused a white solid to precipitate, which was collected by suction filtration, washed with diethyl ether and stored in a desiccator. Addition of the ether washings to the filtrate caused more white solid to separate, which was collected and
treated in the same manner. After repeating this process two more times, a total of 11.0 g of crude 193 was obtained as the HCl salt. When the solid was shaken with 200 ml of distilled water in a separatory funnel, not all the material dissolved. Sufficient 18 N NaOH was added to give a pH of 12 and the mixture was extracted with two 100 ml portions and one 50 ml portion of CHCl₃. The pooled CHCl₃ extracts were an opaque white and upon suction filtering gave 1.1 g of white solid and a transparent filtrate. After drying with anhydrous Na₂SO₄, the filtrate was evaporated in vacuo to give 7.20 g (50%) of 193. The white solid filtered from the CHCl₃ extract had a mp of 239-241° with decomposition. In the IR spectrum (KBr) of the solid no N-H stretching absorption was observed. Bands at 2510 and 1460 cm⁻¹ were attributed to B-H and B-N stretching, respectively (133a). A sample of the presumed aminoborane complex was refluxed for 10 min in dioxane with a few drops of conc. HCl. The residue obtained by evaporation of the solvent was dissolved in water, basified with 5% NaOH, and extracted with CHCl₃. Evaporation of the dried extract gave a light brown, viscous oil. The IR spectrum (neat) of this oil was quite similar to that of 193 and showed N-H stretching absorption but no bands attributable to a borane adduct.

33. Synthesis of 2-(4-Chlorophenyl)-3-aminomethyl-4-phenylthietane 1,1-dioxide (194).

The procedure was similar to the diborane reduction described in experiment 32, with several modifications. To a stirred mixture of 12.9 g (0.041 mole) of 180 and 101 ml of dry THF was added 203 ml of 0.3 M diborane in THF solution, dropwise, over a period of 30 min. After stirring for 22 hours, a solution was present to which 129 ml of ethanol
100 was added, in portions, to decompose the excess diborane. After heating at reflux for 1 hour, the solution was allowed to cool and was treated with anhydrous HCl gas until it turned a slight yellow colour. Evaporation in vacuo gave a pale yellow syrup which was dissolved in 100 ml of distilled water. During the dissolution step an insoluble white solid separated, which was collected by suction filtration and dried. The ir spectrum of this material, 0.9 g, corresponded neither to that of 180 nor to that of the desired product. The combined filtrate and water washings from the solid were placed in a separatory funnel, basified with 5 ml of 18 N NaOH and extracted with two 100 ml portions and one 50 ml portion of CHCl₃. The pooled CHCl₃ extracts were washed with two 100 ml portions of 10% NaCl solution and then dried over anhydrous Na₂SO₄. Evaporation under reduced pressure gave a white oil which solidified when placed under vacuum in a desiccator for 6 hours. The white solid (194) weighed 9.8 g (75%) and had a mp of 39-45°; ir (KBr) 3500-3300 (N-H stretching), 1320, 1150 cm⁻¹ (sulfone); nmr (CDCl₃) δ 7.60-7.30 (m, 9, aromatic protons), 5.23 (d, 1, J = 10 Hz, benzylic proton), 5.20 (d, 1, J = 10 Hz, p-chlorobenzylic proton), 3.33-2.80 (m, 3, proton at C-3 and methylene protons), and 1.18 (s, 2, protons on N). The picrate of 194 was prepared by briefly warming a solution of 0.76 g of the crude primary amine in 5 ml of ethanol 95 with 5 ml of a saturated, ethanolic solution of picric acid. The resulting yellow precipitate was crystallized from 10% aqueous acetic acid to give small, feather-like yellow crystals, mp 249-250° with decomposition. Compound 194 was submitted for analysis as the picrate.

Anal. Calcd. for C₂₂H₁₉Cl₁N₉O₉S: C, 47.96; H, 3.48; N, 10.17; mol. wt., 550.93. Found: C, 48.31; H, 3.36; N, 10.03.
34. **Synthesis of 2,4-Diphenyl-3-dimethylaminomethylthietane 1,1-dioxide (9).**

In a 50 ml round-bottom flask fitted with a reflux condenser were placed 1.77 g (0.0062 mole) of finely powdered 193, 3.2 g (0.06 mole) of 90.7% formic acid and 2.9 ml (0.04 mole) of 37% formaldehyde solution. A boiling stone was added and the mixture was heated at 90 ± 5° in an oil bath (134). Within 3 minutes a vigorous evolution of gas began and a pale yellow solution was rapidly obtained. After heating for 18 hours, the flask was removed from the bath and allowed to cool to room temperature. The solution was mixed with 6.5 ml of 4 N HCl and evaporated under vacuum to give a pale yellow, viscous oil. The oil was dissolved in 60 ml of distilled water and the resulting turbid solution was transferred to a separatory funnel, basified with 2 ml of 18 N NaOH and extracted with three 20 ml portions of CHCl₃. The CHCl₃ extracts were pooled, washed with two 20 ml portions of distilled water and dried over anhydrous Na₂SO₄. Evaporation of the CHCl₃ under reduced pressure gave 1.67 g (86%) of pale yellow solid (9). The IR spectrum of this solid was identical to that of the crystallized material. Crystallization from hexane - ethanol 100 with charcoal treatment gave fine, white needles, mp 123-124°; IR (KBr) 3085, 3060, 3005, 2970, 2880, 2840, 2810, 2790 (C-H stretching), 1315, 1154 cm⁻¹ (sulfone); NMR (CDCl₃) 6 7.63-7.27 (m, 10, phenyl protons), 5.13 (d, 2, J = 10 Hz, protons at C-2 and C-4), 3.45-2.83 (m, 1, proton at C-3), 2.62 (d, 2, J = 6 Hz, methylene protons), and 2.06 (s, 6, N-methyl protons).

**Anal.** Calcd. for C₁₈H₂₁NO₂S: C, 68.54; H, 6.71; N, 4.44; mol. wt., 315.44. Found: C, 68.74; H, 6.65; N, 4.58.

The HCl salt of 9 was prepared from pure free base and isolated as a pale cream-coloured solid. Attempts to crystallize the salt were
unsuccessful. Upon sitting in the open, the derivative liquified.

35. **Synthesis of 2-(4-Chlorophenyl)-3-dimethylaminomethyl-4-phenylthietane 1,1-dioxide (124).**

The procedure was similar to that described in experiment 34. To a 250 ml round-bottom flask fitted with a condenser were added 9.0 g (0.028 mole) of crude 194, 40 ml of 90.7% formic acid and 36 ml of 37% formaldehyde solution. Several boiling chips were added and the flask was placed in an oil bath heated at 93 ± 1°. Within a few minutes a solution was obtained and a vigorous evolution of gas commenced. After heating for 19 hours, the flask was allowed to cool to room temperature and 80 ml of 4 N HCl was added. Evaporation in vacuo gave a viscous, yellow syrup, which was dissolved in 240 ml of distilled water, basified with 25 ml of 18 N NaOH and extracted with two 100 ml portions and one 50 ml portion of CHCl₃. The pooled CHCl₃ extracts were washed with 100 ml of 10% NaCl solution, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure to give 9.6 g (98%) of pale yellow solid. The ir spectrum of the crude product was identical to that of the purified material. Several crystallizations from hexane - ethanol 100 with charcoal treatment gave 124 as short, white needles, mp 124-125°; ir (KBr) 3050, 2950, 2870, 2835, 2785 (C-H stretching), 1325, 1155 cm⁻¹ (sulfone); nmr (CDCl₃) δ 7.48 (s, 9, aromatic protons), 5.13 (d, 1, J = 10 Hz, benzylic proton), 5.09 (d, 1, J = 10 Hz, p-chlorobenzylic proton), 3.39-2.75 (m, 1, proton at C-3), 2.60 (d, 2, J = 6 Hz, methylene protons), and 2.06 (s, 6, N-methyl protons).

**Anal.** Calcd. for C₁₈H₂₀ClNO₂S: C, 61.79; H, 5.76; N, 4.00; mol. wt., 349.88. Found: C, 61.64; H, 5.81; N, 3.91.
36. Synthesis of 2-(4-Nitrophenyl)-3-dimethylaminomethyl-4-phenylthietane 1,1-dioxide (125).

Using a procedure similar to that described in experiment 32, 9.0 g (0.027 mole) of 181, dissolved in 73 ml of dry THF, was reacted with 146 ml of 0.3 M diborane in THF for 21 hours at room temperature. After adding 90 ml of ethanol 100 in portions to decompose the excess diborane, the pale yellow solution was refluxed for 30 min and then evaporated in vacuo to give a yellow, viscous oil. When the oil was dissolved in CHCl₃, a white solid (0.4 g) separated which was removed by suction filtration. Evaporation of the filtrate under reduced pressure gave a yellow syrup which was redissolved in 20 ml of CHCl₃ - ethanol 100 (9:1) and chromatographed in two equal portions on 60 x 2.5 cm silica gel columns (60-200 mesh, 94 g per column), using CHCl₃ - ethanol 100 (9:1) as the developing solvent. Two main fractions were obtained from each column. The second fractions were pooled and evaporated under vacuum to give 5.9 g (66%) of pale yellow, viscous oil, which did not solidify when triturated with various solvents. The oil appeared to be the desired reduction product 2-(4-nitrophenyl)-3-aminomethyl-4-phenylthietane 1,1-dioxide (195), according to spectroscopic evidence; ir (neat) 3400, 3340 (N-H stretching), 1515, 1350 (nitro group), 1310, 1150 cm⁻¹ (sulfone); nmr (CDCl₃) δ 8.41-8.13 (m, 2, protons ortho to nitro group), 7.85-7.55 (m, 2, protons meta to nitro group), 7.55-7.32 (m, 5, phenyl protons), 5.37 (d, 1, J = 10 Hz, p-nitrobenzylic proton), 5.31 (d, 1, J = 10 Hz, benzylic proton), 3.41-2.88 (m, 3, proton at C-3 and methylene protons), and 1.20 (s, 2, protons on N). Minor impurity signals were observed in the nmr spectrum at δ 1.07 and 0.98.

The dimethylation reaction was carried out as described in experiment 34. A mixture of 4.8 g (0.015 mole) of crude primary amine 195, 23
ml of 90.7% formic acid and 20 ml of 37% formaldehyde solution was heated at 93 ± 1° for 11 hours. Addition of 44 ml of 4 N HCl followed by evaporation in vacuo gave a reddish-orange, transparent syrup. The syrup was dissolved in 50 ml of distilled water, basified with 3 ml of 18 N NaOH and extracted with three 50 ml portions of CHCl₃. The pooled CHCl₃ extracts were washed with 100 ml of 10% NaCl solution, dried over anhydrous Na₂SO₄ and then evaporated under reduced pressure to give 3.5 g of straw-coloured syrup (125). The syrup was dissolved in 150 ml of anhydrous diethyl ether, treated with HCl gas, and the resulting white precipitate was collected by suction filtration in a dry nitrogen atmosphere. An attempt to crystallize the salt from anhydrous diethyl ether - absolute ethanol was unsuccessful. A solution of the salt in 50 ml of distilled water was neutralized with a saturated aqueous solution of Na₂CO₃, which caused the formation of a copious white precipitate. The solid was collected by suction filtration, washed with distilled water and placed in a desiccator. Within an hour, the solid darkened and reverted to a straw-coloured syrup. While sitting for two weeks in a desiccator, the syrup solidified to give 125 as a glass, mp 39-43°; ir (KBr) 3105, 3085, 3048, 2990, 2960, 2880, 2840, 2795 (C-H stretching), 1520, 1350 (nitro group), 1320, 1155 cm⁻¹ (sulfone); nmr (CDCl₃) δ 8.44-8.19 (m, 2, protons ortho to nitro group), 7.87-7.58 (m, 2, protons meta to nitro group), 7.50 (s, 5, phenyl protons), 5.23 (d, 1, J = 10 Hz, p-nitrobenzyl proton), 5.17 (d, 1, J = 10 Hz, benzylic proton), 3.35-2.83 (m, 1, proton at C-3), 2.64 (d, 2, J = 6 Hz, methylene protons), and 2.10 (s, 6, N-methyl protons). Only minor extraneous signals occurred at δ 2.25 and 1.92 in the nmr spectrum. The picric acid derivative of 125 was obtained as a yellow, amorphous solid. However, attempts to crystallize the picrate were unsuccessful.
37. **Synthesis of 2,4-Diphenyl-3-carboxythietane 1,1-dioxide (196).**

In a 200 ml round-bottom flask fitted with a reflux condenser were placed 10.00 g (0.0353 mole) of 2,4-diphenyl-3-cyanothietane 1,1-dioxide (178) and 70 ml of DMSO. A boiling stone was added and the mixture was heated to give a solution. To the solution was added 50 ml of 50% H$_2$SO$_4$ and the resulting mixture was heated at reflux. After one hour, a transparent, beige-coloured solution was obtained, which was refluxed for another 2 hours and then was allowed to cool to room temperature. While cooling, the solution became translucent and a white solid began to separate. The reaction mixture was poured onto 200 g of crushed ice with stirring to give an off-white, fluffy solid. This was further diluted with about 500 ml of distilled water and the solid was collected by suction filtration, washed with water and dried in a desiccator overnight. Crystallization from 1,2-dichloroethane gave 9.45 g (89%) of 196 as white, fluffy needles, mp 223-224°; ir (KBr) 3270 (carboxyl OH), 1730 (carboxyl carbonyl), 1305, 1172, 1130 cm$^{-1}$ (sulfone); nmr (DMSO-d$_6$) $\delta$ 7.83-7.33 (m, 10, phenyl protons), 5.90 (d, 2, $J = 10$ Hz, protons at C-2 and C-4), and 4.15 (t, 1, $J = 10$ Hz, proton at C-3).

**Anal.** Calcd. for C$_{16}$H$_{14}$S$_2$O$_4$: C, 63.56; H, 4.67; S, 10.60; mol. wt., 302.35. Found: C, 63.40; H, 4.79; S, 10.54.

38. **Synthesis of 2,4-Diphenyl-3-acetylthietane 1,1-dioxide (197).**

In a dry, 1 litre round-bottom flask fitted with a condenser which was protected from atmospheric moisture by a drying tube were placed 40.00 g (0.132 mole) of 196 and 400 ml of freshly distilled thionyl chloride (BDH, rea.). The mixture was heated to reflux temperature. After refluxing for 1.5 hours, a pale orange solution was obtained. The react-
tion was refluxed for a total of 5 hours and allowed to cool to room temperature. Evaporation of the excess thionyl chloride under reduced pressure in a fume hood gave a cream-coloured solid (199), mp 140-141°; ir (KBr) 1780, 1740 (sh) (acid chloride carbonyl), 1333, 1180, 1137 cm\(^{-1}\) (sulfone). The reaction was readily followed by observing the decrease in intensity of the carboxylic acid bands at 3270 and 1730 cm\(^{-1}\) and the concomitant increase in intensity of the acid chloride band at 1780 cm\(^{-1}\) in the infrared spectra of samples removed at intervals. The acid chloride was stored in a desiccator under vacuum until needed. A sample of 199 left sitting in the open for several days reverted to the carboxylic acid 196.

The following procedure was adopted from the literature (131b). A 250 ml three-necked flask fitted with a mechanical stirrer, dropping funnel, gas inlet and a Friedrich condenser and protected from atmospheric moisture with a drying tube was flushed with dry nitrogen and flame dried. A dry nitrogen atmosphere was provided throughout the reaction. Upon cooling, 4.01 g (0.165 mole) of Mg turnings (previously washed with anhydrous ether and oven dried) was placed in the flask, followed by 40 ml of dry THF and a small piece of iodine. A solution of bromomethane (Eastman, prac.), 20.00 g (0.211 mole), in 80 ml of dry THF was placed in the dropping funnel and approximately 10 ml was drained into the flask with stirring. The flask was gently warmed using a lukewarm water bath. Once the reaction began, the bath was removed and the remainder of the solution was added at such a rate as to maintain a moderate reflux. After cooling to room temperature, the flask containing the dark, almost black Grignard reagent was cooled in an ice-water bath. Anhydrous CdCl\(_2\), 15.13 g (0.0825 mole), was added in portions over a period of 5 min with effi-
cient stirring to give a gray suspension. The bath was removed and the reaction was heated to reflux temperature, which caused the mixture to turn black. After refluxing for 1 hour, a Gilman test (131b) was performed on a sample from the reaction and found to be negative. The flask was allowed to cool to room temperature and then cooled in an ice-water bath. The crude acid chloride 199, 43 g (0.13 mole), was dissolved in 140 ml of dry THF and the yellow solution was placed in the dropping funnel and drained into the flask over a period of 3 min with vigorous stirring. When the addition was completed, the bath was removed and the reaction was stirred at room temperature for 8 hours. Approximately 180 ml of THF was evaporated off under reduced pressure and 200 ml of CHCl₃ was slowly added. The gray mixture was poured, with stirring, onto a mixture of 200 g of crushed ice and 100 ml of dilute H₂SO₄. The resulting mixture was transferred to a separatory funnel, the yellow CHCl₃ layer was drained off and the colourless aqueous layer was extracted with 100 and 50 ml portions of CHCl₃. The combined CHCl₃ extracts were dried over anhydrous MgSO₄ and evaporated in vacuo to give a viscous, beige syrup. Infrared analysis (neat) indicated the presence of the carboxylic acid 196 and a compound with strong carbonyl absorption at 1715 cm⁻¹. The syrup was dissolved in 150 ml of CHCl₃ and 196 was removed by extracting with two 100 ml portions of 10% NaOH solution. Acidification of the pooled basic extracts gave a 22.5% recovery of the carboxylic acid. The CHCl₃ layer was washed with two 100 ml portions of distilled water, dried over anhydrous MgSO₄, and then evaporated under reduced pressure to afford a pale yellow, viscous syrup. Upon adding a few drops of absolute methanol to the syrup and scratching the mixture with a glass rod, a white solid (197), 27.03 g (68.4%), was obtained. Two crystallizations from distilled water - ethanol
95 with charcoal treatment gave was white, feather-like crystals, mp 124-125°. A third crystallization from hexane - ethanol 100 gave shiny white leaflets, mp 125-126°; ir (KBr) 1715, 1364 (methyl ketone), 1330, 1172, 1140 cm⁻¹ (sulfone); nmr (CDCl₃) δ 7.64-7.32 (m, 10, phenyl protons), 5.50 (d, 2, J = 10 Hz, protons at C-2 and C-4), 3.90 (t, 1, J = 10 Hz, proton at C-3), and 2.03 (s, 3, methyl protons).
Anal. Calcd. for C₁₇H₁₆O₃S: C, 67.98; H, 5.37; S, 10.67; mol. wt., 300.37. Found: C, 68.15; H, 5.33; S, 10.64.

The oxime derivative 200 of 2,4-diphenyl-3-acetylthietane 1,1-dioxide was prepared using a method from the literature (135). Crystallization from distilled water - ethanol 95 gave 200 as small white needles, mp 181-186° with decomposition; ir (KBr) 3440 (O-H stretching), 1315, 1170, 1135 cm⁻¹ (sulfone); nmr (DMSO-d₆) δ 7.80-7.36 (m, 10, phenyl protons), 5.81 (d, 2, J = 10 Hz, protons at C-2 and C-4), 4.08 (t, 1, J = 10 Hz, proton at C-3), and 1.68 (s, 3, methyl protons).

39. Synthesis of 2,4-Diphenyl-3-(1-nitroethyl)-thietane 1,1-dioxide (201).

The basic solution referred to in this procedure was prepared by dissolving 1.0 g of KOH in 10 ml of ethanol 95 and adding 5 ml of nitroethane (M.C. & B., prac.). The solution (approx. 1.2 N) was magnetically stirred for 15 min, during which time it became a pale yellow.

In a 500 ml conical flask were placed 4.50 g (0.0176 mole) of 2,4-diphenylthietane 1,1-dioxide (152) and 90 ml of nitroethane. The mixture was stirred magnetically to give a solution, which was then diluted with 90 ml of ethanol 95. Upon adding 9.0 ml of basic solution, the reaction turned a bright yellow. The solution was stirred for 7 hours, during which time it became somewhat turbid. The addition of 9.0 ml of glacial
acetic acid caused the mixture to turn almost colourless. Removal of the solvent under reduced pressure gave a white solid, which was triturated with distilled water, suction filtered and dried in a desiccator. Crystalization from hexane - benzene gave 4.79 g (73.5%) of 201 as fine, white needles, mp 181-182°; ir (KBr) 1554 (nitro group), 1324 (nitro group and sulfone), 1147 cm⁻¹ (sulfone). The nmr spectrum (CDCl₃) showed a doublet at δ 7.48 (phenyl protons, 10), a triplet attributed to two overlapping doublets, one at δ 5.33 (benzylic proton e, 1, Jₑₑ = 10 Hz) and the other at δ 5.14 (benzylic proton d, 1, Jₑᵈ = 11 Hz), a multiplet centred at δ 4.83 (proton c, α to nitro group, 1, Jᶜᶜ = 8 Hz, Jᶜᵃ = 7 Hz), a multiplet centred at δ 3.50 (remaining ring proton b, 1, Jᵇₑ = 10 Hz, Jᵇᵈ = 11 Hz, Jᵇᶜ = 8 Hz), and a doublet at δ 1.33 (methyl protons a, 3, Jᵃᵃ = 7 Hz). The high field signal of the doublet at δ 5.14 overlapped the low field signal of the multiplet at δ 4.83. A singlet at δ 7.38 with an integral equivalent to 3 protons was attributed to benzene. The magnitude of the integral suggested that crystallization of the product from hexane - benzene occurred with the inclusion of one molecule of benzene for every two molecules of 201 in the crystal lattice. Analysis by glc of a solution, prepared by dissolving 20.0 mg of crystals in 1.20 ml of anhydrous DMSO, on a 6 ft x 5/32 in (i.d.) silanized glass column packed with 3% OV-225 on Gas-Chrom Q (100-120 mesh) with the injection port, oven and detector at 250, 35 and 272°, respectively, and the nitrogen flow at 32 ml/min, gave one peak with a retention time of 3.4 min, identical to that obtained for benzene when chromatographed under the same conditions. The calculated concentration of benzene in the solution was 1.76 mg/ml, if the effect of solute volume on solution volume was ignored (calculation based on a 1 to 2 complex between benzene and 201). The area of the peak obtained by injecting 1 µl
of a reference solution containing 1.76 mg/ml of benzene in DMSO was identical to that obtained by applying an equal volume of the sample solution. The retention time of hexane under the described conditions was 1.2 min. The solvent, DMSO, did not come off the column under these conditions. The product 201 was submitted for analysis as the benzene-containing crystals.

**Anal.** Calcd. for \( (C_{17}H_{17}NO_4S)_2 \cdot C_6H_{12} \): C, 64.85; H, 5.44; N, 3.78; O, 17.28; S, 8.65; mol. wt., 740.89. Found: C, 65.04; H, 5.31; N, 3.96; O, 17.33; S, 8.62.

Scaling the reaction up by a factor of 3 or using crude 152 did not affect the percentage yield of 201 significantly.

40. **Synthesis of 2,4-Diphenyl-3-(1-dimethylaminoethyl)-thietane 1,1-dioxide (123).**

Method A. Reduction of 2,4-diphenyl-3-(1-nitroethyl)-thietane 1,1-dioxide (201) to the corresponding primary amine 202 and subsequent dimethylation.

A solution prepared by dissolving 4.00 g (0.0121 mole) of 201 in 30 ml of THF and diluting with 50 ml of ethanol 100 was placed in the bottle of a Parr hydrogenator. To the solution was added 8 g of sponge nickel catalyst (W.R. Grace & Co., No. 986), which had been previously suction filtered and washed with ethanol 100. The bottle was attached to the hydrogenator reservoir and the system was purged 5 times with hydrogen. With the hydrogen pressure at 52 psi, the shaker was activated and the hydrogenation was carried out for 7 hours. The catalyst was then cautiously removed by gravity filtration, washed with THF and placed under water. At no time was the catalyst allowed to go dry, as it was highly pyrophoric. The pale yellow filtrate was combined with the THF washings.
and evaporated under reduced pressure to give a viscous, pale yellow syrup. Analysis by tlc using microscope slides coated with silica gel G, benzene-ethanol 100 (9:1) as developing solvent and charring as the visualization method, indicated the presence of two major components and the absence of 201. The syrup was dissolved in 20 ml of CHCl₃ and extracted with two 20 ml portions of 4 N HCl followed by one 20 ml portion of distilled water. The pooled aqueous extracts were evaporated in vacuo to give an almost colourless, viscous oil. The oil was dissolved in 20 ml of distilled water, 3 ml of 18 N NaOH was added and the resulting white precipitate was extracted with two 20 ml portions and one 10 ml portion of CHCl₃. The pooled CHCl₃ extracts were washed with 10% NaCl solution, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give 2.19 g (60%) of 2,4-diphenyl-3-(1-aminoethyl)-thietane 1,1-dioxide (202) as a pale yellow solid, mp 145-147°; ir (KBr) 3440-3360 (N-H stretching), 1310, 1145 cm⁻¹ (sulfone); nmr (CDCl₃) δ 7.67-7.30 (m, 10, phenyl protons), 5.26 (d, 1, J = 10 Hz, benzylic proton), 5.16 (d, 1, J = 10 Hz, remaining benzylic proton), 3.50-2.65 (m, 2, proton at C-3 and proton ∝ to NH₂ group), 1.22 (s, 2, protons on N), and 0.87 (d, 3, J = 6.5 Hz, methyl protons). The primary amine was not submitted for elemental analysis.

The CHCl₃ layer from the acid extraction was washed with distilled water, dried over anhydrous Na₂SO₄ and then evaporated under reduced pressure to give a beige solid (1.36 g, 36%). This was the second main component observed by the tlc analysis of the crude hydrogenation product. The ir and nmr spectra of the crystallized solid (water-ethanol 95) were superimposable with those of 2,4-diphenyl-3-acetylthietane 1,1-dioxide oxime (200).

The primary amine 202 was dimethylated using a procedure similar
to that described in experiment 34. Crude 202, 2.2 g (0.007 mole), was mixed with 6.6 ml of 90.7% formic acid and 6.0 ml of 37% formaldehyde solution and heated at 93 ± 1° for 3 hours. After cooling to room temperature, 20 ml of 4 N HCl was added and the solution was evaporated in vacuo to give a viscous syrup. The syrup was redissolved in 10 ml of distilled water, 3 ml of 18 N NaOH was added, and the resulting precipitate was extracted with two 20 ml portions and one 10 ml portion of CHCl₃. The pooled CHCl₃ extracts were washed with 50 ml of 10% NaCl solution, dried over anhydrous Na₂SO₄ and then evaporated under reduced pressure to give 1.9 g (79%) of pale beige solid (123). The ir spectrum of this solid was identical to that of the crystallized material. Crystallization from hexane-ethanol 100 with charcoal treatment gave 123 as white needles, mp 145-146°; ir (KBr) 3075, 3045, 2980, 2950, 2880 (C-H stretching), 1310, 1150 cm⁻¹ (sulfone); nmr (CDCl₃) 6 7.70-7.31 (m, 10, phenyl protons), 5.26 (d (with shoulder absorption), 1, J = 9 Hz, benzylic proton), 5.07 (d (with shoulder absorption), 1, J = 9 Hz, remaining benzylic proton), 3.25-2.67 (m, 2, proton at C-3 and proton α to N(CH₃)₂ group), 1.97 (s, 6, N-methyl protons) and 0.75 (d, 3, J = 6 Hz, methyl protons).


Method B. Reduction of 2,4-diphenyl-3-acetylthietane 1,1-dioxide oxime (200) as its acetate ester to the corresponding primary amine 202 and subsequent dimethylation.

The acetate ester of 200 was synthesized using a method adopted from the literature (136). In a stoppered 250 ml conical flask were placed 2.24 g (0.0071 mole) of crystalline 200 and 25 ml of dry THF. After stirring the mixture magnetically to obtain a colourless solution, the flask
was placed in an ice-water bath and allowed to cool. Then 2.0 ml of acetyl chloride was added and the reaction was stirred for 1.5 hours. Evaporation of the solvent under reduced pressure gave a liquid residue, which was dissolved in 100 ml of diethyl ether, washed with 200 ml of 3% NaHCO₃ solution and dried over anhydrous Na₂SO₄. Evaporation of the ether gave 2.35 g (94%) of pale yellow, viscous oil (204). When a sample of the oil was mixed with hexane and rubbed with a glass rod on a watchglass, a white solid separated, mp 55-65°; ir (KBr) 1762 (ester carbonyl), 1325, 1175, 1137 (sulfone), 1206 cm⁻¹ (ester band). Attempts to crystallize the crude ester from various solvents were unsuccessful. Therefore, 204 was used in the hydroboration step (120) without purification. In a dry 50 ml reaction flask fitted with a mechanical stirrer, a dropping funnel, a nitrogen inlet and a reflux condenser protected from atmospheric moisture by a drying tube were placed 1.2 g (0.003 mole) of 204 and 20 ml of dry THF. The mixture was stirred to give a pale yellow solution. The dropping funnel was then charged with 25 ml of 0.3 M diborane solution (experiment 32), which was added dropwise over a period of 20 min. The first few drops of diborane solution decolourized the ester solution. After the addition was complete, the reaction was stirred for 16 hours. A dry nitrogen atmosphere was provided throughout this time. Upon adding 6 ml of distilled water dropwise to decompose the excess diborane, the colourless solution was gently refluxed for one hour. Removal of the solvent in vacuo gave a white solid. Although not isolated, part of this solid was considered to consist of 2,4-diphenyl-3-(1-aminoethyl)-thietane 1,1-dioxide (202). The crude product was treated with 5 ml of 90.7% formic acid and 4.5 ml of 37% formaldehyde solution as described above for the preparation of 123. Work-up gave 0.16 g (14%) of light yellow solid (123). The crude
material was crystallized from hexane - ethanol 100 to afford 123 as white
needles, mp 144-145°. The ir spectrum (KBr) was superimposable with that
of the material obtained by Method A.
To complete the objectives of this investigation, compounds 9, 123, 124 and 125 were tested for analgetic activity. Three test procedures were employed: (A) the mouse hot plate method as described by Janssen and Jageneau (138); (B) the phenylquinone writhing method in mice as outlined by Blumberg, et al. (139); and (C) the electrically stimulated guinea-pig ileum method as described by Cox and Weinstock (140). The use of procedure C is based on the ability of narcotic analgetics to depress the electrically induced contractions of the guinea-pig ileum.

Procedure C was modified somewhat from that outlined by Cox and Weinstock (140). The arrangement for electrical stimulation of the ileum was more similar to that originally described by Paton (141). The glass tubing to which the lower end of the gut was tied was of such a length that its open end protruded approximately 1 cm above the bath surface. Gut movements were recorded by attaching the polyethylene tubing covering the ileum electrode to a microdisplacement myograph transducer (E & M Instrument Co.) which was connected to a type PMP-4A Physiograph (E & M Instrument Co.). After applying a tension of 2 g, the length of the ileum strip was approximately 4 cm. The tissue was stimulated by single shocks with a pulse width of 0.5 milliseconds, delivered every 10 seconds from a Grass S8 stimulator. The voltage was adjusted initially to give a maximal response. The volume of the organ bath was 15 ml and compounds were added in a volume of 0.1 ml. The contact time for test and reference compounds was 3 minutes and the interval between additions of agents to the bath was 25 - 30 minutes.

Only 2,4-diphenyl-3-dimethylaminomethylthietane 1,1-dioxide (9)
was tested by all three methods. The known relative insensitivity of the hot plate method (142) and the fact that compound 9 was found to be inactive by this assay procedure prompted the adoption of the phenylquinone writhing method (method B). The limited supply of 2,4-diphenyl-3-(1-dimethylaminoethyl)-thietane 1,1-dioxide (123) allowed for testing of this compound by method B only. 2-(4-Chlorophenyl)-3-dimethylaminomethyl-4-phenylthietane 1,1-dioxide (124) and 2-(4-nitrophenyl)-3-dimethylaminomethyl-4-phenylthietane 1,1-dioxide (125) were examined by the sensitive isolated tissue procedure, C.

For testing purposes, the hydrochloride salts of 9, 123, 124 and 125 were prepared by treating anhydrous diethyl ether solutions of the purified bases with hydrogen chloride gas and then collecting the white precipitates by suction filtration. The salts were stored in a desiccator until needed. During storage, the hydrochloride salt of 125 changed to a yellow oil and was used in this form. Other drugs employed were morphine sulfate (British Drug Houses), methadone hydrochloride (Pitman-Moore, 10 mg/ml injection USP, with 1.5% benzylalcohol) and phenylquinone (phenyl-p-benzoquinone, Eastman).

With the exception of phenylquinone, all solutions were prepared using distilled water. The 0.02% phenylquinone solution (140) was prepared daily by dissolving 20 mg of the compound in 5 ml of ethanol 100 and diluting to a volume of 100 ml with distilled water. The solution was kept at 37° in order to prevent precipitation of the writhing agent. Saline solution was 0.9% sodium chloride in distilled water. In procedure A, the injection volume for all compounds was 0.1 ml/10 g body weight. The same volume was used in procedure B, except for the writhing agent, the dose of which was 0.25 ml/20 g.
The mice used in procedures A and B were male, Swiss albinos (SPF-derived) weighing 20 - 30 g. In procedure C, male and female guinea-pigs (Hartly strain) weighing 350 - 500 g were employed. All animals were obtained from the Animal Unit, Faculty of Medicine, University of B.C. The guinea-pigs were starved for 24 hours before sacrifice.

When tested by method A, compound 9 showed no analgetic activity at dose levels of 300 mg/kg or less. No Straub-tail was observed. The compound appeared to induce a hyperexcitable state in the mice, especially at higher doses. At 600 mg/kg, 9 produced a convulsant seizure which terminated in death. By test procedure A, all mice receiving methadone hydrochloride or morphine sulfate in a dose of 15 mg/kg showed a positive response ten minutes after injection.

Using the phenylquinone writhing method (method B), the effect of 9 at dose levels of 25, 50, 75 and 100 mg/kg (as the free base) was examined. Five mice were used at each dose level. From the resulting data, the ED50 and 95% confidence limits were determined by the method of Litchfield and Wilcoxon (143) to be 54.0 (68.4 - 42.7) mg/kg. An ED50 given in the literature (144) for methadone hydrochloride, obtained by the phenylquinone writhing method, was 0.78 (0.57 - 1.09) mg/kg. Conversion to a value for methadone free base gave 0.70 (0.51 - 0.97) mg/kg. Observations with methadone hydrochloride in the mice used in the present investigation indicated that such an ED50 was reasonable. From a comparison of ED50 values, compound 9 appeared to be approximately 1/80 as potent as methadone.

Testing of compound 123 by method B revealed that it was fairly toxic. Analgetic activity was not observed below 50 mg/kg, a dose which caused convulsions.
In method C, methadone hydrochloride was found to depress the electrically induced contractions of the ileum by 50% at a concentration of 0.08 nmole/ml. At concentrations somewhat greater than 800 times this, 9, 124 and 125 caused no observable depression.

That the thietane 1,1-dioxides 9, 123, 124 and 125 lacked significant analgetic activity is perhaps attributable to their cis-2,4-diaryl structure. The phenyl ring at C-4 cis to the aromatic group at C-2 may be interfering with effective binding of these compounds at the analgetic receptor. On this basis, an investigation of 2-phenyl-3-dimethylaminomethylthietane 1,1-dioxide and other derivatives not possessing an aromatic substituent at C-4 may be worthwhile.

It has been suggested that a close approach of the basic group and oxygenated function in diphenylpropylamine-type analgetics such as methadone and its sulfone analogue is necessary for high activity (5). If this is correct, then the apparent pseudoequatorial disposition of the basic side chain in 9, 123, 124 and 125, which tends to preclude intimate interaction of the tertiary amino group with the sulfonyl moiety, may also account for the absence of significant activity shown by these compounds. In regard to this point, thietane 1,1-dioxide derivatives possessing the basic side chain cis to the sulfonyl group, which would facilitate a more ready interaction between the two groups, are perhaps worth investigating.
BIBLIOGRAPHY


