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3-AMINO-2-PHENYLTHIETANES AS POTENTIAL MAO INHIBITORS

by

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ABSTRACT

3-Amino-2-phenylthietane derivatives were considered as a useful tool to elucidate the mechanism of inhibition of MAO by tranylcypromine-type inhibitors. The synthesis of 3-amino-2-phenylthietanes appeared worthwhile from the synthetic point of view since no successful preparation has been reported for this type of compound.

It was considered that the reaction between suitable 1, 3-dihalogeno alkanes with alkali sulfide would be the most effective for the synthesis of 3-amino-2-phenylthietane derivatives. Phenylserinol was prepared by reducing phenylserine ethylester using NaBH_4 . Treatment of phenylserinol with thionyl chloride gave 1-phenyl-1-chloro-2-aminopropane-3-ol. Further chlorination of the 3-hydroxyl group was not successful.

Attempts were performed to synthesize 3-amino-2-phenylthietane via 1-phenyl-1-thiocyanato-2-aminopropane-3-ol intermediate. 1-Phenyl-1-thiosulfuryl-2-aminopropane-3-ol was obtained by treating 1-phenyl-1-chloro-2-aminopropane-3-ol with thiosulfate. 1-Phenyl-1-thiocyanato-2-aminopropane-3-ol was not obtained from the reaction of 1-phenyl-1-thiosulfuryl-2-aminopropane-3-ol with sodium cyanide, but 2-amino-4-hydroxymethyl-5-phenyl-2-thiazoline was isolated. Hydrolysis of 1-phenyl-1-thiosulfuryl-2-aminopropane-3-ol gave 1-phenyl-1-mercapto-2-aminopropane-3-ol.

The unsuccessful attempt to prepare 1-phenyl-1,3-dichloro-2-aminopropane appeared due to the electronic character of the primary amino group. Supporting this assumption, 1-phenyl-1,3-dichloro-2-benzoylamino-2-propanol was synthesized from N-benzoylphenylserinol. When an ethanol solution of 1-phenyl-1,3-dichloro-2-benzoylamino-2-propanol was treated with sodium sulfide, 2-phenyl-4-benzylidene-2-oxazoline was isolated instead of 3-N-benzoylamino-2-phenylthietane, indicating the ease of the elimination reaction compared to ring formation. The same result was observed when 1-phenyl-1,3-dibromo-2-benzoylamino-2-propanol synthesized from cinnamyl alcohol was used. The reduction of the amide group of 1-phenyl-1,3-dibromo-2-benzoylamino-2-propanol using diborane was not successful.

N,N-Dimethylphenylserinol was prepared for the purpose of synthesizing 3-N,N-dimethylamino-2-phenylthietane via the intermediate of 1-phenyl-1-thiocyanato-2-N,N-dimethylamino-2-propanol. Synthesis of 1-phenyl-1-chloro-2-N,N-dimethylamino-2-propanol was not successful. 1-p-Nitrophenyl-1,3-dichloro-2-N,N-dimethylamino-2-propanol prepared from p-nitrophenylserinol was treated with sodium sulfide. Isolation of the product as a hydrochloride salt indicated the formation of bis (1-p-nitrophenyl-2-N,N-dimethylamino-3-chloropropane) sulfide hydrochloride.

3-Hydroxy-2-phenylthietane prepared from 3-chloropropenyl benzene was reacted with benzylsulfonylchloride or benzylsulfonylchloride and sodium azide. All attempts using

column chromatography to isolate products resulted in the identification of starting materials, revealing that the sulfonate or the azide might not be formed by the reaction probably because of the resistance of the hydroxyl group of 3-hydroxy-2-phenylthietane to the alkylation.

Discussions on the determination of the synthesized compounds using ir, nmr, uv, and gc-mass spectrometry are included. Recent concepts of the active sites of MAO and mechanisms of inhibition of MAO were reviewed.

Signature of Supervisor

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LIST OF ABBREVIATIONS

b _p	-	boiling point
DCC	-	dicyclohexylcarbodiimide
Diglyme	-	diethyleneglycol dimethyl ether
DMF	-	dimethylformamide
DMSO	-	dimethyl sulfoxide
EtOH	-	ethanol
MeOH	-	methanol
FAD	-	flavin adenine dinucleotide
FMN	-	flavin mononucleotide
gc	-	gas (liquid) chromatography
HMPT	-	hexamethylphosphoric triamide
I ₅₀	-	inhibitor concentration for 50% inhibition of the enzyme activity
ir	-	infrared (spectroscopy)
K _m	-	Michaelis constant
MAO	-	monoamine oxidase
mp	-	melting point
nmr	-	nuclear magnetic resonance (spectroscopy)
SAR	-	structure-activity relationship
THF	-	tetrahydrofuran
tlc	-	thin layer chromatography
uv	-	ultraviolet (spectroscopy)

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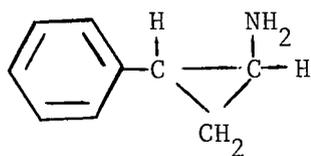
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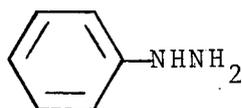
INTRODUCTION

1. General description of the mechanism of action of tranylcypromine-type inhibitors.

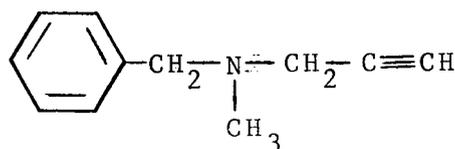
Tranylcypromine (1), because of its relatively rigid and simple structure and unique geometry, has been extensively studied as a model compound to elucidate the mechanism of inhibition of MAO. It is now known that MAO is a flavoprotein and that two other important inhibitors, phenylhydrazine (2) and pargyline (3) elicit their inhibitory action on MAO by interaction with the flavin moiety of the enzyme. Most of



1



2



3

the SAR studies of tranylcypromine derivatives as MAO inhibitors were published before 1965. The relationship of tranylcypromine with active sites of MAO has not been dealt with the same detail as have recent studies of phenylhydrazine and pargyline. Only a broad outline of the interaction has been described. Therefore, it appears worthwhile to generalize recent concepts of the active sites of MAO and its mechanism of inhibition emphasizing the flavin moiety of the receptor

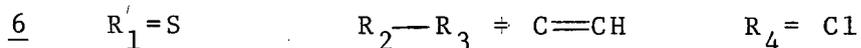
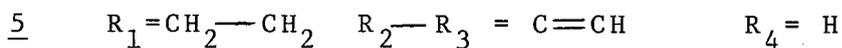
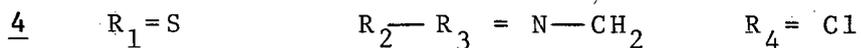
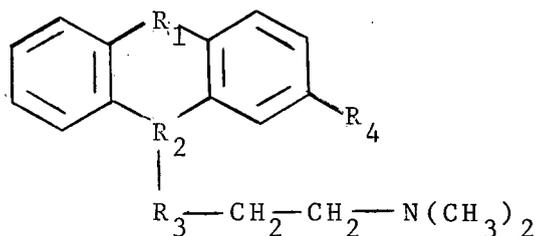
and to establish the right direction for studies of tranylcy-
promine-type inhibitors.

One of the important methods to estimate whether any inhibitors directly combine with active site, or whether they complex with the enzyme at, possibly, allosteric sites and thereby lead to inhibition of binding of substrates is based on kinetic studies using Lineweaver-Burk plots. Maass and Nimmo (1) reported a non-competitive inhibition of rat brain MAO by tranylcypromine with respect to substrate, serotonin. According to Belleau and Moran (2) using kynuramine as the substrate, the mechanism of MAO inhibition by tranylcypromine was clearly of the competitive type. Zeller and Sarkar (3) observed that when tyramine and tranylcy-
promine were added simultaneously to the enzyme preparation, the degree of inhibition was decreased with increasing substrate concentrations. On the other hand, no effect on inhibition was observed when tyramine was added 15-30 minutes after inhibitors. Tranylcypromine is difficult to remove by dialysis from MAO (4). However, 40 per cent reversal of inhibition was shown by dialysis against substrate (5). A long duration of action of tranylcypromine similar to that of a non-competitive inhibitor is due to its high binding affinity for an enzyme. Although a report was published that inhibition by tranylcypromine can be reversed readily by the competitive substrate, 4-phenylbutylamine (3), this evidence was refuted by later work (7). At present, most of the evidence

points to the fact that tranylcypromine is a competitive inhibitor, having high affinity binding and thus elicits its action by direct interference of the binding of substrate at the active sites.

It was postulated by Belleau and Moran (2) that the chemical role of the cyclopropane ring could consist in promoting charge-transfer complex formation through its sp^2 -like electrons with the flavin cofactor. Burger (8) also suggested that it should be possible to draw a picture of tight chemical binding of tranylcypromine to protein-bound riboflavin. When limiting amounts of varying mixtures of pargyline, phenylhydrazine, and tranylcypromine were incubated with the enzyme, the nature of the inhibition observed was additive (5). Benzylamine treatment protected MAO from inhibition by these inhibitors, implying that these inhibitors act independently, but at the same site, i.e. the catalytic site of the enzyme. The puzzling fact, however, is that pargyline and phenylhydrazine reduce flavin while tranylcypromine does not. Although flavin reduction by benzylamine (9) is an attractive fact which might demonstrate the catalytic mechanism of MAO, evidence providing confirmation of the participation of the flavin moiety in the oxidation of substrate has not been published. The reduction of flavin by inhibitors is monitored by the increase in absorbance at 412 nm. The elaboration of better methods to monitor the interactions of drugs or substrates with flavin might reveal some forms of interactions between them which have not yet been detected.

Possible interaction of tranylcypromine with flavin was favored by the analogy that tricyclic psychoactive drugs (chlorpromazine 4, amitriptyline 5, and chlorprothixène 6) inhibit MAO and those having a double bond between the ring moiety and the aliphatic side chain were the most effective inhibitors of type B MAO (10). It has been shown by Karreman et al. (11)



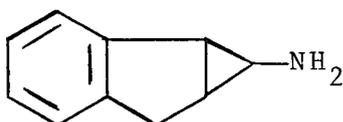
and Yagi (12) that chlorpromazine forms charge-transfer complexes with riboflavin and FAD, respectively. Molecular orbital calculations have indicated that chlorpromazine is an extremely good electron donor (13). These data suggest that it may be electron donating properties of the tricyclic moieties of these drugs which influence their ability to inhibit flavoproteins such as MAO. Lineweaver-Burk plots showed mixed (amitriptyline) or competitive type (chlorprothixene) inhibition.

Pure beef plasma MAO was inhibited by tranylcypromine (14).

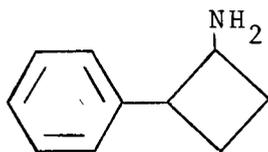
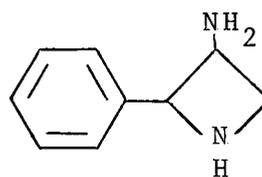
This inhibition is not related to the flavin moiety since beef plasma MAO is a diamine oxidase enzyme which is copper-pyridoxal dependent. It has also been reported that pargyline showed inhibition of beef plasma MAO (15).

Three hypotheses have been published on the binding mode of tranlycypromine to MAO. These hypotheses can be reconciled and complemented each other since they emphasize different points of structure requirement for MAO inhibitors.

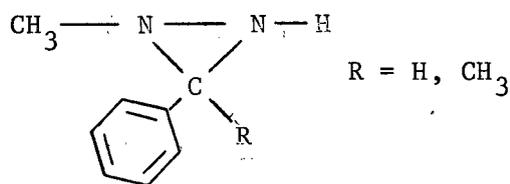
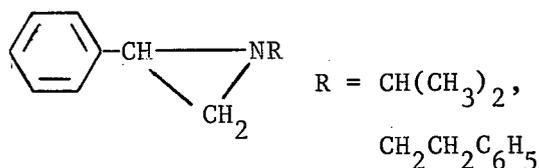
Zirkle et al. (16) postulated that three structural requirements, a cyclopropane ring, an amino group attached directly to the cyclopropane ring, and a 2-substituent containing aromatic moiety are necessary for potent in vivo MAO inhibitory activity. Emphasizing the possible stereochemical factors that may be involved in the binding process, they suggested that in the enzyme-inhibitor complex the tranlycypromine derivatives do not assume a conformation in which the phenyl and amino groups are nearly coplanar but one in which these groups lie in distinctly different planes. The good activity of MAO inhibition of the rigidly built 1-amino-cycloprop(a)indane(7) supports this suggestion since in this derivative the benzene ring can barely attach to the same enzyme surface as the amino group.



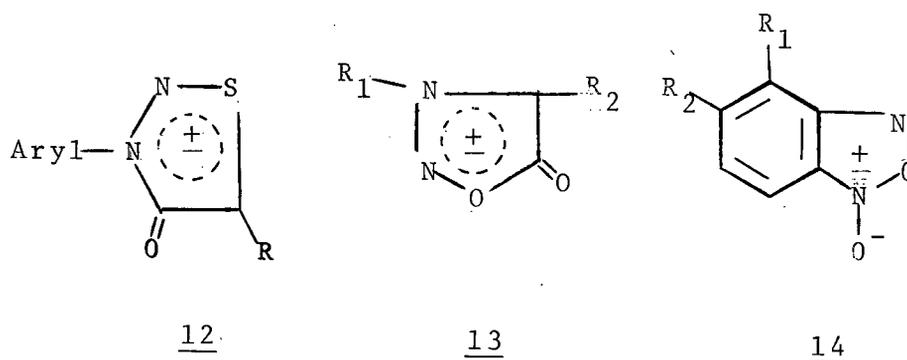
On the basis of isotope effects observed in the MAO-catalyzed oxidation of deuterium-labeled kynuramine, Belleau and Moran (17) concluded that in the oxidation transition state the carbon atoms of the amine substrate acquire double bond character and thereby approach the trigonal state. The high affinity of tranylcypromine for the enzyme could thus be due to the fact that in ground state this amine resembles, electronically and sterically, the transition state of the amine substrate during the oxidation process. This hypothesis suggests that substrates and inhibitors bind to the same active sites. Their idea, however, that the N-C₁-C₂ atoms of the cyclopropylamine are essentially coplanar in the enzyme-inhibitor complex seems unlikely as criticized by Zirkle et al. (16), who emphasized the importance of stereochemical factors for the binding of MAO inhibitors to the receptor site(s). To investigate the importance of the electronic properties of a cyclopropane ring to the binding of inhibitors to the enzyme and to explain that the poor inhibitory action of 2-phenylcyclobutylamine (8) is due to its electronic properties rather than steric factors, 3-amino-2-phenylazetidine (9) was synthesized (18). 3-Amino-2-phenylazetidine has a unique structure which can maintain the electron density of the ring with similar steric properties to those of 2-phenylcyclobutylamine. The fact that 3-amino-2-phenylazetidine was 62 percent as active as iproniazid by in vitro testing could be used as evidence which supports Belleau and Moran's theory.

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Paget and Davis (19) reported MAO inhibition activity of phenyldiaziridines (10), which implies that a free amino group is not necessary for MAO inhibition. The synthesis of phenylaziridines (11) by Wells et al (20) helps confirm

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this evidence. These compounds are unique in that the amine nitrogen is an integral part of the ring system. Similar compounds having mesoionic structures were synthesized by Wiseman and Cameron (21,22). They suggested that the π electron system of the anhydrothiadiazolium compounds (12) and N-arylsydnonones (13) mimics that of the cyclopropyl ring by binding to a π area on the enzyme.



Benzooxadiazoles such as substituted furoxanobenzofuroxan (14) showed in vitro inhibition of MAO (23). This evidence may further support the theory that a high electron conjugation system as well as an aryl group are requirements for effective MAO inhibition in cyclopropylamines and structurally similar compounds.

2. A consideration of MAO and its inhibitors

Amine oxidases could be classified into three groups, MAO, diamine oxidase, and diamine oxidase-related MAO. MAO contains flavin as a prosthetic group. Diamine oxidase and diamine oxidase-related MAO are probably copper-pyridoxal phosphate proteins. These differences in cofactor requirements explain the fact that diamine oxidase and diamine oxidase-related MAO accept only primary amines, whereas MAO oxidizes secondary and tertiary amines as well as primary amines (24). A recent review article by Youdim (25) defined MAO as the enzyme which is responsible for the oxidative deamination of such amines as adrenaline, noradrenaline, isopropylamine, 3,4-dihydroxyphenylethylamine, tyramine, and

tryptamine. MAO (monoamine: O_2 oxidoreductase (deaminating) EC 1,4,3,4) is the name given by the Enzyme Commission of the International Union of Biochemistry.

A. Active sites of MAO

(1) Metal Ions

The presence of metal ion at active sites is derived from the observation that chelating agents inhibit mitochondrial MAO (26). Galay and Valcourt (27) even proposed that the amino group of tranlycypromine participates in an MAO-Cu⁺²-(tranlycypromine)₂ complex which leads to an inhibition of MAO. Their postulation was challenged by the fact that trans-2-phenylcyclopropylcarbinol, which is also able to form a complex with Cu ion, showed a 400- and 1500-fold decrease in MAO inhibitory activity from that of tranlycypromine with human and beef mitochondrial MAO (28). With the availability of highly purified preparations of the enzyme, metal contents were determined. Nara et al. (29) published the presence of 0.07 % copper in preparations of mitochondrial MAO from bovine liver. Youdim and Sourkes (30) reported 0.03 % of copper and 0.12 % of iron in highly purified mitochondrial MAO preparations from rat liver. According to Orelan (31), copper, manganese, and molybdenum were found in negligible amounts but the content of iron was 0.5-2 moles per mole of flavin in pig liver mitochondrial MAO.

Treatment of the preparations with a strong iron chelator, 1,10-phenanthroline did not decrease the enzyme activity, which

implies that iron does not play a part in the catalytic function of the enzyme. From experiments designed to prove the relationship of chelating agents and their inhibition of MAO, Severina and Shermetevskaya (32,33) reported that MAO inhibitory action of 8-hydroxyquinoline is not due to its chelate formation with metal ions but to its ability to bind to a hydrophobic and a polar region in the active site of mitochondrial MAO.

However, support for the role of iron in full functional activity of MAO has been published from studies of iron deficiency in rats. Symes et al. (34) reported that copper deficiency in rats does not affect enzyme activity but significantly lower activity was observed with iron deficient rats. Iron deficiency also leads to a large decrease in the rate at which the animals metabolize C^{14} pentylamine to $^{14}CO_2$. Youdim et al. proposed that iron may be necessary at some stage in the biosynthesis of the apoenzyme. Recent studies on platelet MAO from iron-deficient subjects indicate that this may indeed be so (34). Although the K_m of platelet MAO from iron deficient subjects is similar to the K_m of the enzyme from normal subjects using the substrates dopamine, serotonin, and kynuramine, the maximum velocity is significantly reduced. Evidence that iron-deficient platelet MAO is much more sensitive to heat inactivation and binds significantly less C^{14} deprenil per mg. platelet protein than platelets from normal subjects can be explained in terms of implicating iron in the biosynthesis of MAO protein. Youdim (36) has published a review article on metals and rat liver mitochondrial MAO.

(2) Hydrophobic and Polar region

The presence of a hydrophobic region at the active center of MAO is based on the fact that aliphatic monoamines must have a minimum chain length in order to have significant affinity for MAO. Short chain aliphatic diamines are not oxidized by MAO. It is only the long chain aliphatic diamines that are oxidized by MAO (37).

McEwen et al (56) performed kinetic studies using MAO of human liver mitochondria with substrate analogs and suggested that an electrophilic binding site occupies a definite position adjacent to the hydrophobic region of the enzyme active site as shown by the fact that β -naphthol, but not α -naphthol is a potent competitive inhibitor of the enzyme. Some evidence was proposed that tyramine binds to the nucleophilic polar region and that electrophilic polar region in the immediate vicinity of some hydrophobic region is essential for the binding of serotonin (33,35).

(3) Sulfhydryl group

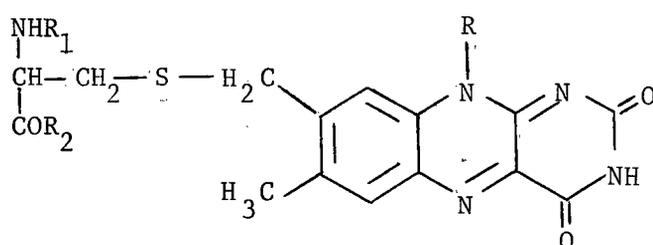
Early assumptions of the importance of a sulfhydryl group stemmed from the fact that alkylating agents which react with sulfhydryl groups cause a decrease in enzymatic activity (39). Erwin and Hellerman (40) published evidence that sulfhydryl groups might be directly involved in catalysis based on the proportionality between the observed activity of beef kidney MAO and measured sulfhydryl group content. Contrary findings were published by Gomes et al. (41) that sulfhydryl

groups do not play a catalytic role but probably only a structural role. It is well known that protein sulfhydryl groups play a role in stabilizing tertiary structure through hydrogen bonding and hydrophobic interaction. Even sulfhydryl groups which are not present in the catalytic site react with alkylating agents to affect conformational stability and cause a decrease in enzyme activity (42). Beef liver mitochondrial MAO contains seven sulfhydryl groups per 100,000 grams of MAO (41). Seven sulfhydryl groups were also reported by Erwin and Hellerman for beef kidney MAO (40). When MAO and methylmercuric chloride are reacted, all seven sulfhydryl groups are titrated, whereas, when harmaline or benzylamine are added before the methylmercuric chloride, only five sulfhydryl groups are titrated. It was postulated therefore that two sulfhydryl groups are near the active site of MAO which is present in a hydrophobic region and that the other five sulfhydryl groups are presumably on the surface of the enzyme playing a role in conformational stability (43). The roles of two sulfhydryl groups near the active site have not been explained.

Treatment of highly purified MAO with oxidizing agents not only decreased the rate of deamination of monoamines by MAO but also induced the ability to catalyze deamination of histamine. This treatment also caused a reversible decrease in the content of sulfhydryl groups (38). These facts may suggest that oxidizing agents affect sulfhydryl groups which result in the conformational change relating to the hydrophobic region and induce new activity of deaminating diamines.

(4) Flavin moiety

Before 1965 when MAO could not be isolated in a purified form, an indirect method was used to demonstrate the presence of flavin. Studies of riboflavin-deficient rats by Hawkins and Sourkes (44) showed that there was a decrease in hepatic MAO activity arising from the deficiency. After that, the presence of flavin was confirmed by absorption spectrum data, fluorescence data and evidence from thin layer chromatography of the purified enzymes isolated from beef liver (45), bovine kidney (40), and pig brain (47). Trichloroacetic acid treatment of the enzyme does not release the flavin moiety and substantial amounts were released only when the enzyme was treated with proteolytic enzyme. It was suggested, therefore, that flavin may be covalently bound to the enzyme. In 1971 the structure of the flavin peptide from MAO was determined (48,49,50) and authenticated through synthesis (51).

15

R = rest of FAD in native enzyme or rest of FMN in pure peptide

R₁ = serylglycylglycine

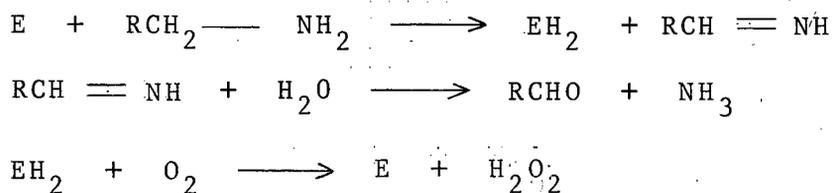
R₂ = tyrosine

It was shown that pure flavin pentapeptide isolated from hepatic MAO contains 1 mole each of serine and tyrosine,

2 moles of glycine, and a cysteine which is covalently linked to C-8 of riboflavin (15). Tipton (52) reported that the enzyme isolated from pig brain contains, in contrast, flavin in a non-covalent linkage. Salach et al. (53) followed his procedures, but confident conclusion on the non-covalently bound flavin could not be made since all samples of the brain enzyme contained some acid-extractable flavin.

Any confirming evidence of the participation of flavin in the catalytic action of MAO have not been published. The only evidence of flavin participation in the oxidation of monoamines was from the study using C¹⁴ labeled benzylamine. One mole of benzaldehyde was produced per mole of FAD in the enzyme. Spectral changes which denote reduction of flavin were observed, but no semiquinone has yet been detected. The existence of semiquinone was indirectly shown by the procedure of Massey and Palmer (9). A plausible mechanistic hypothesis for the reduction of the flavin molecule by a substrate such as benzylamine was proposed (54). This hypothesis described covalent bonding formation of substrate with flavin molecule, reduction of flavin, and formation of imine which is hydrolyzed to the corresponding aldehyde and ammonia. This hypothesis, however, was based on very little experimental data.

Mechanisms explaining the oxidation of amines by MAO propose that oxidation of amine occurs via a dehydrogenation step to yield a schiff base. This idea is based on the very firm evidence that aldehyde and ammonia, in the case of a primary amine, are products of the enzyme reaction.



This does not give a satisfactory description of the molecular mechanism in terms of a flavin moiety or any other catalytic site although it seems real that flavin plays a role in that function.

If tertiary amines are substrates for MAO, the formation of a schiff base seems unlikely since such amines do not have a hydrogen atom attached to the nitrogen. Previous attempts to explain this anomaly seem unsatisfactory, either invoking a protonated substate (6) or postulating hydride ion abstraction (46) from the α -carbon atom. Williams (55) hypothesized the presence of a lysine residue at the active center of MAO and proposed a plausible dehydrogenation mechanism applicable to primary, secondary, and tertiary amines. This report, however, did not show how an α -proton is abstracted and any involvement with flavin. The presence of a polar region whether it is lysine or not seems real.

B. Relationships of flavoprotein with pargyline and hydrazine type inhibitors.

(1) Pargyline type inhibitors

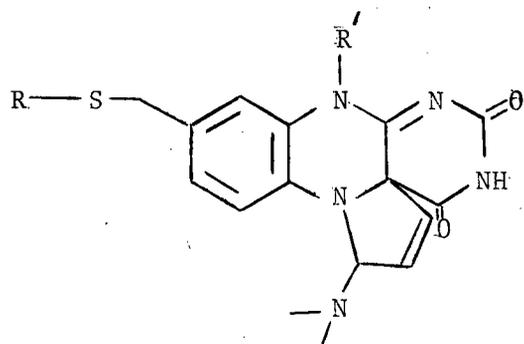
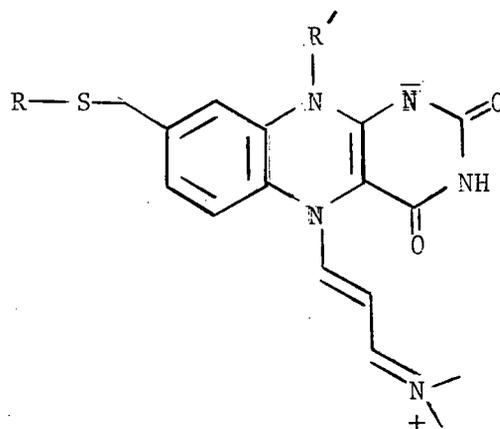
According to Hemmerich (59), the overlap between flavin and substrate π -orbitals within the catalytically active

complex can hardly be the mode of the flavin substrate contact since for efficient π -overlap a rather large area of contact is needed, and this requires less steric restrictions than obviously exist. Sigma character was expected for flavin-substrate contact at the two acceptor sites, C(4a) and N(5). In 1972 a covalent cycloaddition product of flavoquinone and an acetylenic enzyme inhibitor was prepared and elucidated by ir and nmr spectroscopy. The addition of 2-propynylamine occurred to the C(4a)=N(5) azomethine grouping of oxidized enzyme (58). The same procedure of using a flavoquinone model system was applied to pargyline and it was found that a covalent complex which shows disappearance of peaks representing the quinonoid structure was formed and that the triple bond was replaced by an olefinic group which was a part of an enamine system (60).

MAO from beef liver was purified. Addition of pargyline to this purified MAO in the absence of light induced the appearance of a 410 nm peak with disappearance of the 460 nm peak which denotes reduction of the flavine moiety. Several important facts were observed (60). Optical changes at 410 nm closely paralleled the degree of inhibition. The number of titratable sulfhydryl groups did not change after inactivation of the enzyme. Purified MAO does not respond by displaying the 410 nm peak when it is treated with substrate or with tranylcypromine and iproniazid. This implies that the mechanism of catalysis and inhibition of MAO by tranylcypromine or

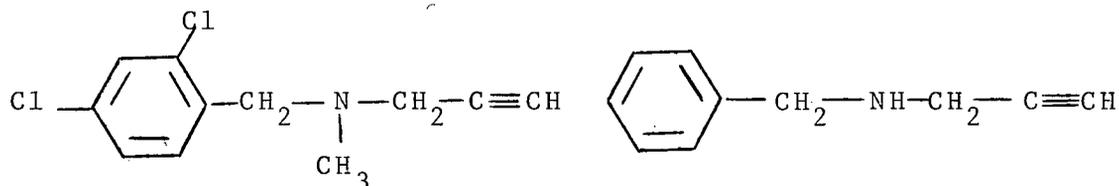
iproniazid seems to be quite different from that of acetylenic amines. By using MAO of bovine kidney, identical results were reported (61).

Spectroscopical data that showed loss of long wavelength absorption (450-500nm) and development of a new band at 410 nm was also observed by experiments using 3-dimethylamino-1-propyne and bovine liver MAO (62). Instead of C(4a)=N(5) adduct formation N(5) adduct formation, was proposed. This result is different from the observation when lactate 2-monooxygenase is treated with the appropriate acetylenic substrate analog. In this case, the inactivator becomes attached to both N-5 and C-4a of the flavin as is the pattern of flavoquinone and 2-propynyl amine interaction (16). The mechanism by which adduct formation occurs at N-5 (17) is not known.

1617

Adduct formation with the flavin of liver MAO at position 5 was also reported in the case of deprenil which is a selective inhibitor of type B MAO (63).

Williams and Lawson (64) observed that a compound such as N-(2,4-dichlorobenzyl)-N-methylpropargylamine (18) is a much better inhibitor than its non-halogenated analog, pargyline and that the latter is more effective than its desmethyl derivative, N-benzylpropargylamine (19).

1819

Differences in the partition coefficients among pargyline derivatives showed a close relationship to the effectiveness of inhibition of mitochondrial MAO as measured by I_{50} values. This implies that the ease of penetration through a lipid barrier attached to the enzyme is an important factor determining the inhibition by pargyline derivatives.

Using C^{14} labelled pargyline and clorgyline it was shown that *in vitro*, these substances fail to bind to proteins other than MAO, and that a number of other inhibitors such as iproniazid and tranlycypromine prevent pargyline from binding to this enzyme (65). The precise mode of irreversible inhibition of plasma MAO by pargyline is not known. It is assumed that the enzyme mediated - double bond migration precedes the actual irreversible inhibition so that the unreactive acetylene is first converted into the highly reactive allene (15). Therefore, before attacking the flavin moiety or unknown group of plasma MAO, electron migration to the allene is a pre-

with formation of the corresponding diazene (21) and this diazene is responsible for the inhibition of MAO by forming an adduct with FAD. However, in the case of phenylethylhydrazine, phenylethylidene hydrazine was isolated, which may result from rearrangement of the diazene or perhaps from a different oxidation route.

C. Multiple forms of MAO and their selective inhibitors.

Initial evidence on the presence of multiple forms of MAO was derived from the fact that characteristic bands of multiple forms were obtained by polyacrylamide gel electrophoresis of purified solubilized enzyme. The same pattern was observed from tissues of specific origin regardless of the methods of solubilization employed although the number of such bands detected is variable depending on the tissue and species used. Initial work done by Youdim et al. (69) showed 5 bands of MAO isolated from rat liver. MAO-1, MAO-2, and MAO-3 were more sensitive to inhibition by clorgyline than MAO-4 and MAO-5 (70). Bands, MAO-4 and MAO-5 contain lower phospholipid than MAO 1-3 (71). However, all forms of rat liver mitochondrial MAO have the same absorption spectra characteristic of the flavin moiety and have similar molecular weight (72,73).

Objection to the concept of multiple forms of MAO was that bands on the gel electrophoresis might be artifacts from the solubilization of MAO since MAO is bound to the outer mitochondrial layer so tightly that drastic conditions have to be employed to solubilize and isolate the enzyme.

It was shown that bands on the gel electrophoresis are due to the varying phospholipid content and that a homogenous band was observed after treatment of the enzyme(s) by a chaotropic agent (74). Houslay and Tipton also (74) suggested that the degree of inhibition by clorgyline and the double sigmoid curve obtained by clorgyline depend solely on the associated phospholipid membraneous material. Removal of phospholipid material by chaotropic agents results in the disappearance of substrate-selective inhibition and the double sigmoid curve. Two sigmoidal curves were usually employed to explain multiple forms of MAO. The first curve designates inhibition by type A MAO, and the second by type B MAO.

It is now generally admitted that this difference in the phospholipid content of MAO is not due to an artifact in the process of solubilization but constitutes important characteristics of MAO in vitro and in vivo. MAO exists in the cell strongly bound to different amounts of phospholipid. Thus, this association may in turn account for observed differences in substrate and inhibitor specificities and also explain conformational differences between the multiple forms of MAO. Heat treatment influences the activities of MAO in the extent of oxidation of substrate and inhibition by inhibitors (75). A plausible explanation would be that the conformation of MAO in the specific environment of lipoprotein could be affected by heat treatment and thus show different enzymatic activity. It was also reported that thermostability of MAO preparations

was dependent on the presence of phospholipid (76).

MAO B which contains high phospholipid is more sensitive to heat than MAO A. The efficacy of pargyline derivatives in inhibiting MAO is to some extent related to lipophilic character (64). This apparent relationship between lipophilicity and inhibitory potency of pargyline derivatives suggest the importance of the lipid environment of MAO.

Yang and Neff (77) reported the existence of two types of MAO in vivo by using selective inhibitors clorgyline and pargyline. Youdim et al. (78) administered clorgyline or deprenil to two different groups of rats in an attempt to demonstrate the in vivo existence of type A and type B enzymes. Analysis of urine samples, however, showed inconclusive results.

Type A MAO selectively deaminates serotonin and nor-epinephrine and is inhibited by harmine and clorgyline. Type B MAO selectively deaminates benzylamine and phenethylamine and is inhibited by pargyline and deprenil. Tyramine, dopamine, and tryptamine are common substrates for both types and inhibitors such as tranylcypramine and phenylethylhydrazine inhibit both types to a similar extent. Serotonin, nor-epinephrine, and clorgyline which interact with MAO A have more polar aromatic rings than benzylamine, phenethylamine, and deprenil which interact with type B MAO. In general, adding a polar hydroxyl group to phenethylamine (tyramine) or removing one from serotonin (tryptamine) produces a common substrate. The enzyme formed with the lower phospholipid

content, type A appears to be more sensitive to inhibition by clorgyline since penetration through lipid associated with MAO may be a factor in the sensitivity of clorgyline towards the multiple forms of the enzyme (77).

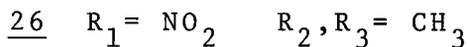
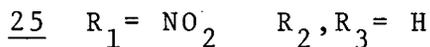
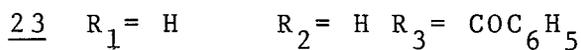
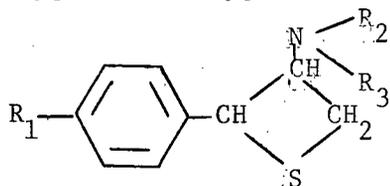
Some evidence was reported that mitochondria are probably not homogenous. The multiple forms of solubilized MAO, therefore, may result from different preparations of mitochondria (79). However, it was found that there is no obvious correlation between heterogeneity of mitochondrial MAO and the electrophoretically separable multiple forms of enzyme (80).

Multiplicity of MAO is not universal. MAO from sources of pig brain, monkey small intestine, and human platelets are homogenous. For example, MAO from human platelets consists of only type B MAO. Human platelet MAO studies should not be used to indirectly evaluate MAO levels in the brain. Peripheral sympathetic nerves mainly show type A MAO and antihypertensive action is produced by blocking MAO in peripheral neurons. It is also generally recognized that the blockade of MAO metabolism of transmitter amines such as dopamine, norepinephrine, and serotonin in brain leads to the alleviation of depression. Type A MAO is related to these substrates. Therefore, it seems that type A MAO is the primary consideration for both antidepressant therapy and antihypertensive treatment. Thus in order to design antihypertensive drugs, the drug structure should provide limited penetration into the brain and accumulate in sympathetic neurons. One attempt to achieve this selective action has been

reported (81). It is also emphasized that depression is related to the deficiency of specific biogenic amines at specific sites of the brain. This was illustrated by post-mortem studies of patients who had been treated with MAO inhibitors (82). Different MAO inhibitory patterns were observed at different sites of the brain. For example, MAO of the pineal body was the most sensitive to inhibition by clorgyline which is a type A MAO inhibitor. Conclusive data for these studies, however, is yet to be obtained since such specimens are difficult to obtain.

3. Thietane derivatives as potential MAO inhibitors.

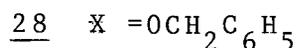
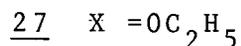
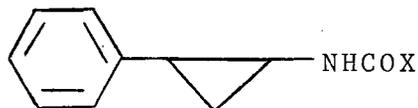
It has been considered in this research project that 3-amino-2-phenylthietane derivatives (22 - 26) could be a useful tool to elucidate the mechanism of inhibition of MAO by tranlylcypromine-type derivatives.



Relative to tranylcypromine, 2-phenylcyclobutylamine is only 1/1000 times as active by in vitro testing. This difference in activity is presumably due to the loss of electronic delocalization and geometrical factors. Contribution of geometrical factors seems to be minimal since 3-amino-2-phenylazetidene (18) and 2-benzyl-3-dimethyl aminothietane (83) showed MAO-inhibitory activity. Although above successful examples may give an evidence on the importance of electronic property of cyclopentane ring for the tranylcypromine derivatives, synthesis of 3-amino-2-phenyl thietane derivatives could provide a confirming proof of Belleau and Moran's hypothesis (17). Sulfur is known to participate in conjugation and thus may enhance electron density of the ring so that attachment to the active sites of MAO could be strengthened, resulting in strong inhibitory activity. Besides, special attention has been drawn from the fact that azetidene has a similar conformation to the thietanes shown by unpublished X-ray work (84). 3-Amino-2-phenyl thietane 1,1-dioxide derivatives synthesized (85) proved to be poor inhibitors of MAO. Some correlation could be drawn from the fact that chloropromazine sulfoxide does not inhibit MAO (10). Electron abstraction from sulfoxide is more difficult and this might lead to the lack of activity of this compound, or steric factors may come into play.

Mono- and di-substitution of the amino group of tranylcypromine with methyl decreases activity only slightly.

N-Carbethoxy (27) and N-Carbobenzoxy (28) compounds also show a fair degree of activity (16).



2-Carbobenzoxy derivative gave twice the in vivo activity as tranylcypromine. It was postulated that the activity of the acyl derivative is due to their hydrolysis in vivo to the parent amine. In this regard, synthesis of compound 23 was considered to be useful.

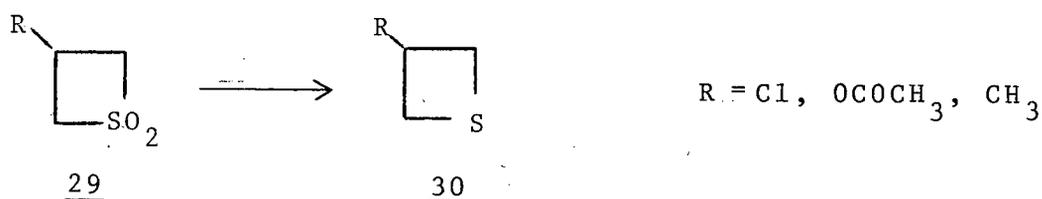
The synthesis of 3-amino-2-phenylthietane derivatives appeared worthwhile from the synthetic point of view. No successful preparation has been reported. Wells and Abbott (85) attempted to reduce 3-dimethylamino-2-phenylthietane 1,1-dioxide and 3-morpholino-2-phenylthietane 1,1-dioxide with LiAlH_4 , only isolating unidentified material resulting from ring cleavage. Modification of a hydroxyl group of 2-phenylthietanol en route to azide formation and reduction to the amino group was not successful (83).

4. Synthetic routes to thietanes.

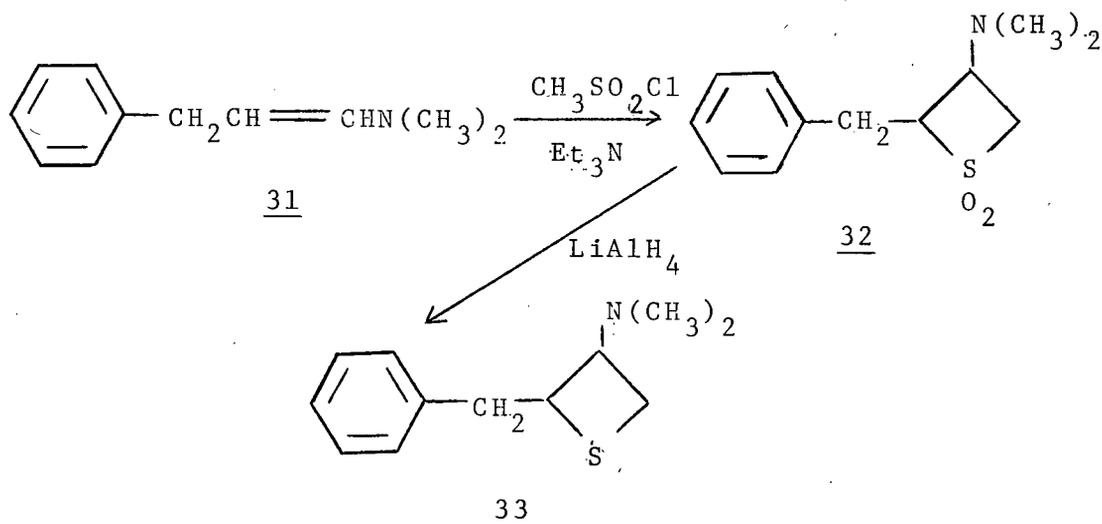
The purpose of this section is not to give a comprehensive description of synthetic routes to thietanes but to explain why the reaction of 1,3-dihaloalkanes with alkali sulfides is the most prospective synthetic route to 3-amino-2-phenylthietane derivatives. Major synthetic routes, therefore, are briefly mentioned. Several review articles

have been published on thietane chemistry (102, 103, 104, 105).

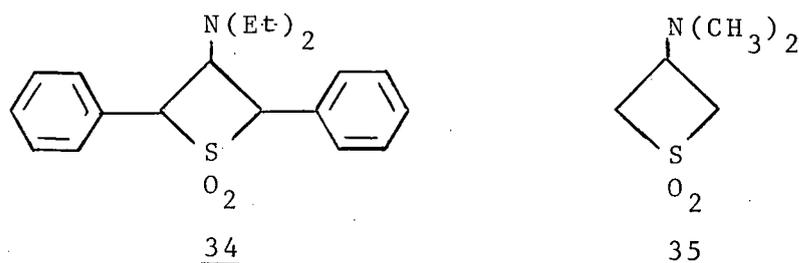
Reduction of thietane 1,1-dioxide results in thietane. Treatment of 29 with LiAlH_4 gave 30 (86). The applicability of this method is favored by the fact that thietane 1,1-dioxide



is relatively more stable than thietane, and modifications of oxide derivatives are more easily accomplished. Moreover, cycloaddition of enamines with sulfene provides a convenient entry to substituted thietane 1,1-dioxides which can be reduced to thietanes having structures necessary for study as potential MAO inhibitors. For example, 33 was synthesized by reducing 32 prepared by reacting an acetonitrile solution

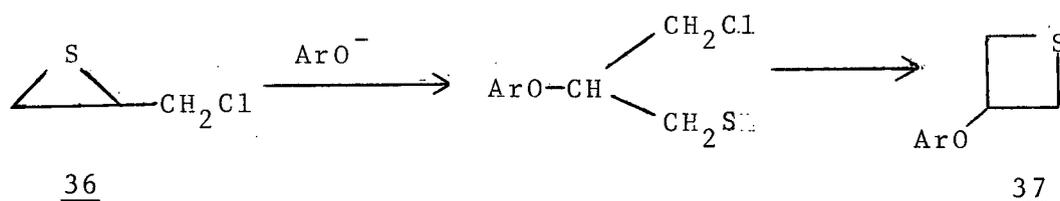


of 31 and triethylamine with methane sulfonylchloride at 0-5° (83). Limitations of the reduction of thietane 1,1-dioxides to thietanes were observed in the case of 2-phenyl substituted derivatives. LiAlH_4 reduction of 34 was attempted but offered a complex mixture of products from which only diethylamine was identified (87). Reduction of 35 with



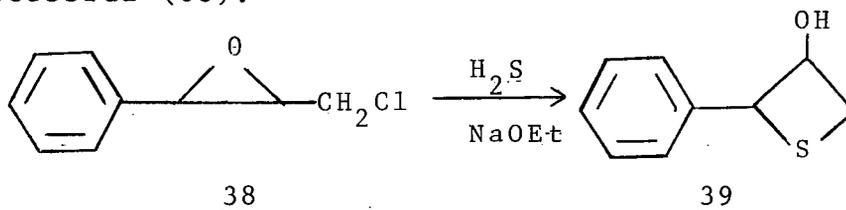
LiAlH_4 , however, is readily accomplished to give 3-(N,N-dimethylamino) thietane (88). Wells and Abbott (85) suggested that the α proton on 2-phenyl substituted thietane 1,1-dioxides may be too acidic for hydride reduction of the sulfone. Base catalysed ring opening of the 2-phenyl substituted thietane 1,1-dioxides was demonstrated.

By reacting chloromethylthiirane (36) with either alkali or alkali phenoxides thietane (37) was formed (89). Dittmer and Christy (90) prepared 3-thietanol by the exposure

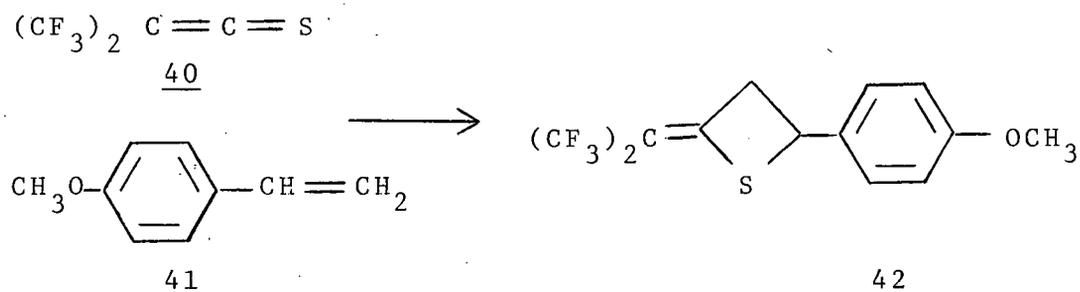


of 3-chloropropylene oxide-1,2 to hydrogen sulfide and barium hydroxide. 3-Hydroxy-2-phenylthietane (39) was prepared by

treating the oxide (38) with hydrogen sulfide (83). Attempts to modify the hydroxyl group to an amino group proved unsuccessful (83).

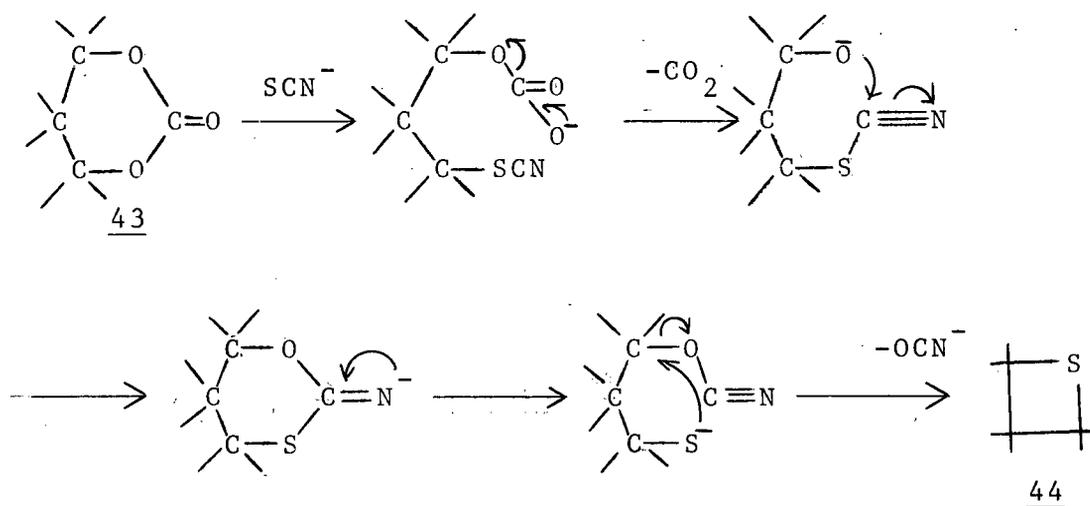


Direct cycloaddition of thioketene with certain olefins, gave thietanes (91). For example, bis(trifluoromethyl)



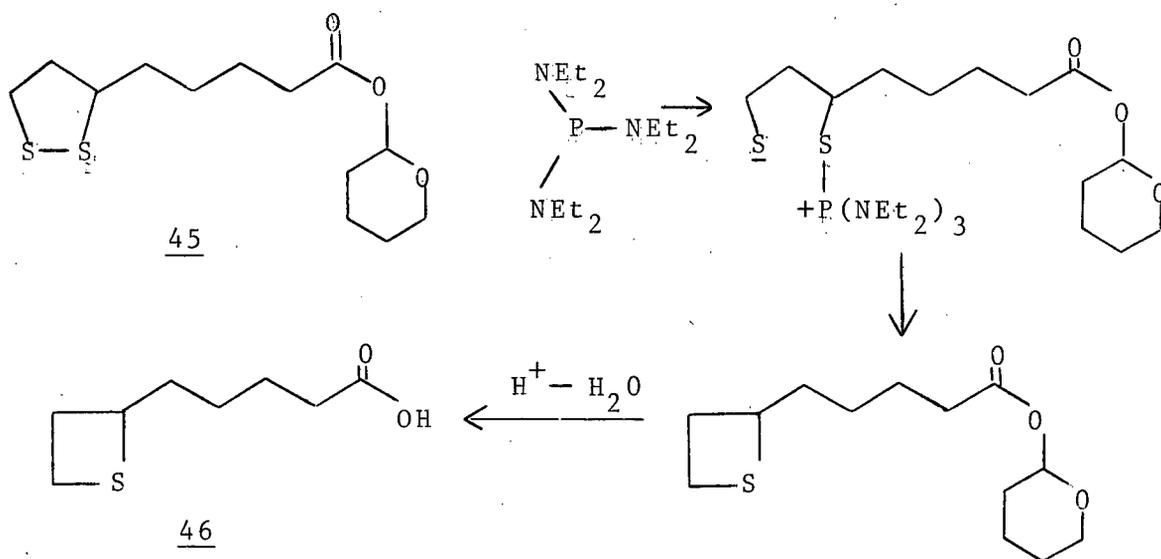
thioketene 40 reacted with p-methoxystyrene 41 to give the thietane 42. The applicability of this reaction to the synthesis of 3-amino-2-phenylthietane derivatives seems limited.

Thietane 44 was obtained by heating the cyclic carbonate of the 1,3-diol 43 with alkali thiocyanate (92). The high

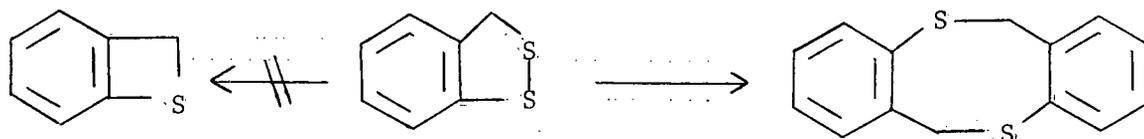


stereospecificity supports the postulated mechanism of successive S_N2 displacements (93). The 1,3-dioxane-2-ones were prepared readily from the corresponding 1,3-diols by ester exchange with ethyl carbonate. The advantage of this method compared to the reaction of 1,3-dibromide with sodium sulfide is the greater convenience in converting 1,3-diols into carbonate ester rather than 1,3-dibromides. This process may have application to the preparation of 2-phenyl-3-aminothietane derivatives.

1,2-Dithiolanes undergo facile desulfurization with tris(diethylamino)phosphine to give thietanes. By this method, the tetrahydropyranyl ester of α -lipoic acid (45) afforded (after hydrolysis) thietane 2-valeric acid (46) (94).

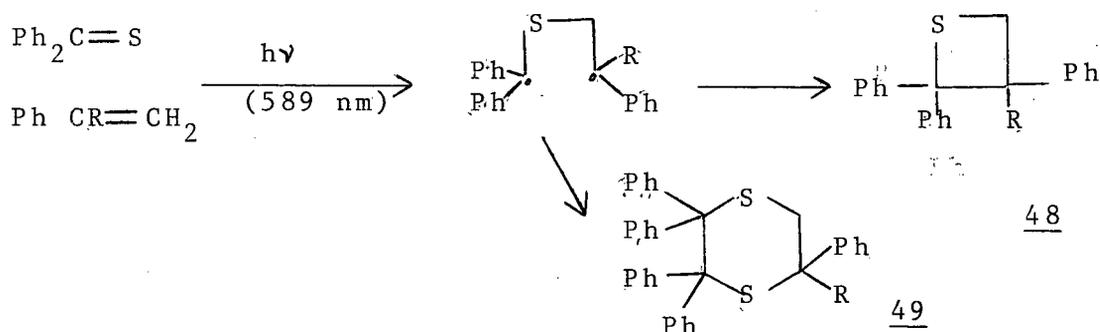


An attempted preparation of benzothiete (47) by this method failed.

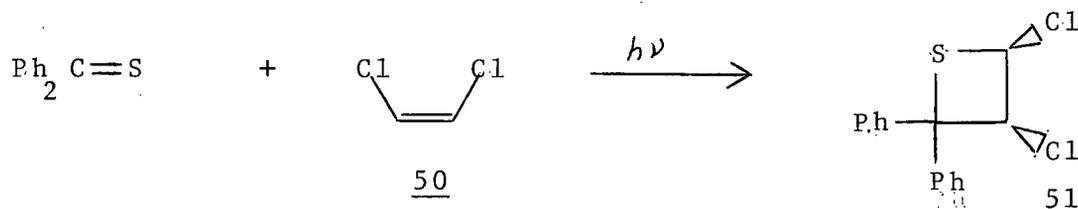


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Photocycloaddition of thiocarbonyls with alkenes gives thietanes (48) and 1,4-dithians (49) (95). The (n, π^*) thiocarbonyl excited state reacts with electron rich alkenes to give

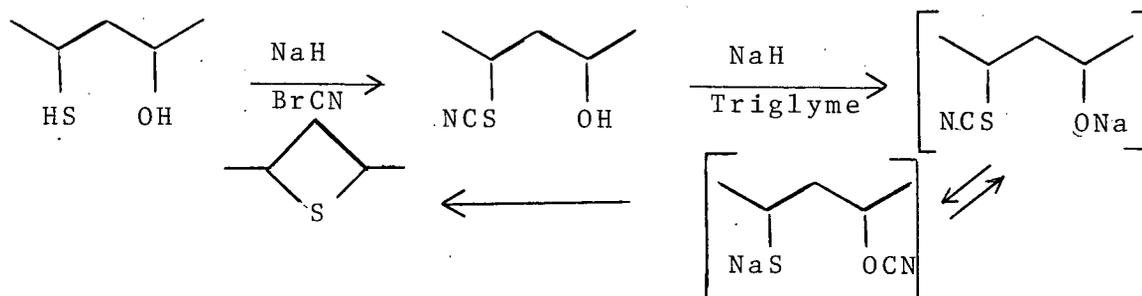


both products and the ratio depends on steric factors and on the concentration of thioketone. A higher energy state of thiobenzophenone reacts with electron deficient alkenes such as dichloroethylene (50) to give a thietane (51), stereospecifically (96).

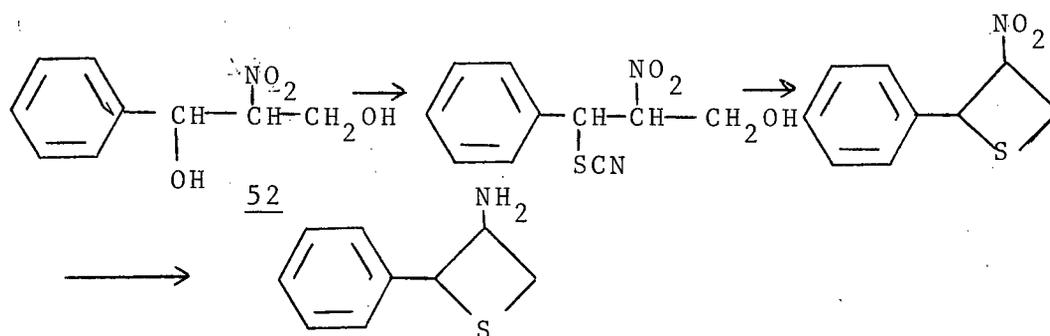


Thietanes are formed by intramolecular cyclization reactions from thiocyanate with sodium hydride, but in this case, both cis- and trans-products are formed. Thiocyanate is prepared from the reaction of cyanogen bromide on thiol or

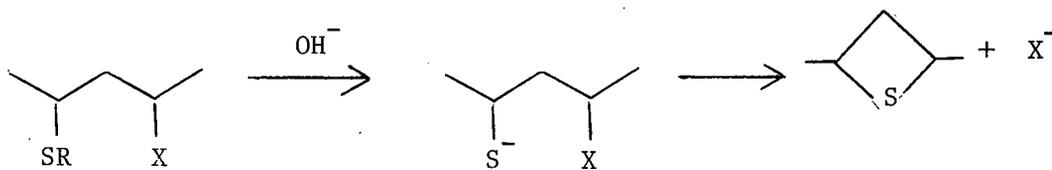
from nucleophilic reaction of potassium thiocyanate on halogen.



Trost et al. (97) prepared cis- and trans-2,4-dimethylthietane and 2,2,4-trimethylthietane from thiocyanate and sodium hydride. Limitations of this reaction for the synthesis of 3-aminosubstituted thietanes are due to the fact that the primary amino group may react with either cyanogen bromide or sodium hydride and that formation of a thiazoline may be possible by reaction between the primary amino and the thiocyanate group. Using this approach, the following sequences of reaction might be applied to the synthesis of 3-amino-2-phenylthietane derivatives. Controulis et al. (100) have reported the synthesis of 2-nitro-1,3-propanediol (52).



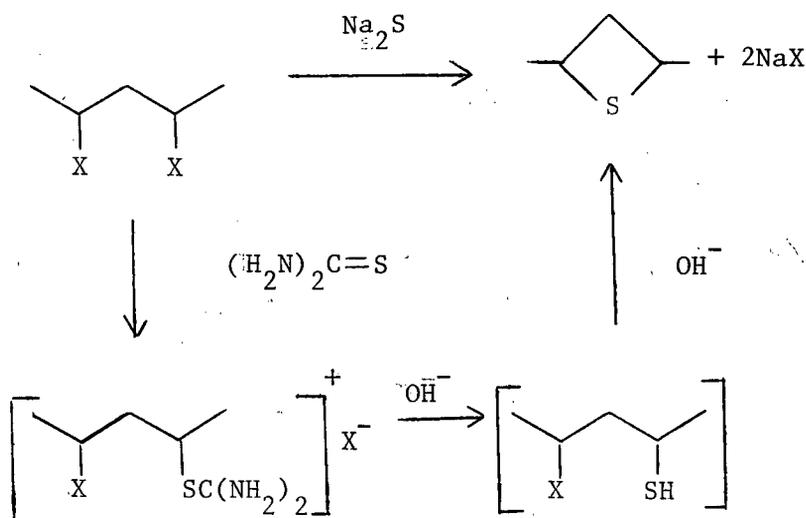
One of the common methods of preparation of thietanes is to react 3-halogenated thiolacetate, thiol, or thiocyanate (53) with alkali.



53 R = COCH₃, H, CN

By this method, 3-hydroxythietane was prepared from 2-hydroxy-3-chloro-propanthiol (101).

The earliest and so far the most general method for the synthesis of thietanes comprises the reaction of 1,3-dihaloalkanes with alkali sulfides or thiourea followed by alkaline cleavage of the thiuronium salt (54).

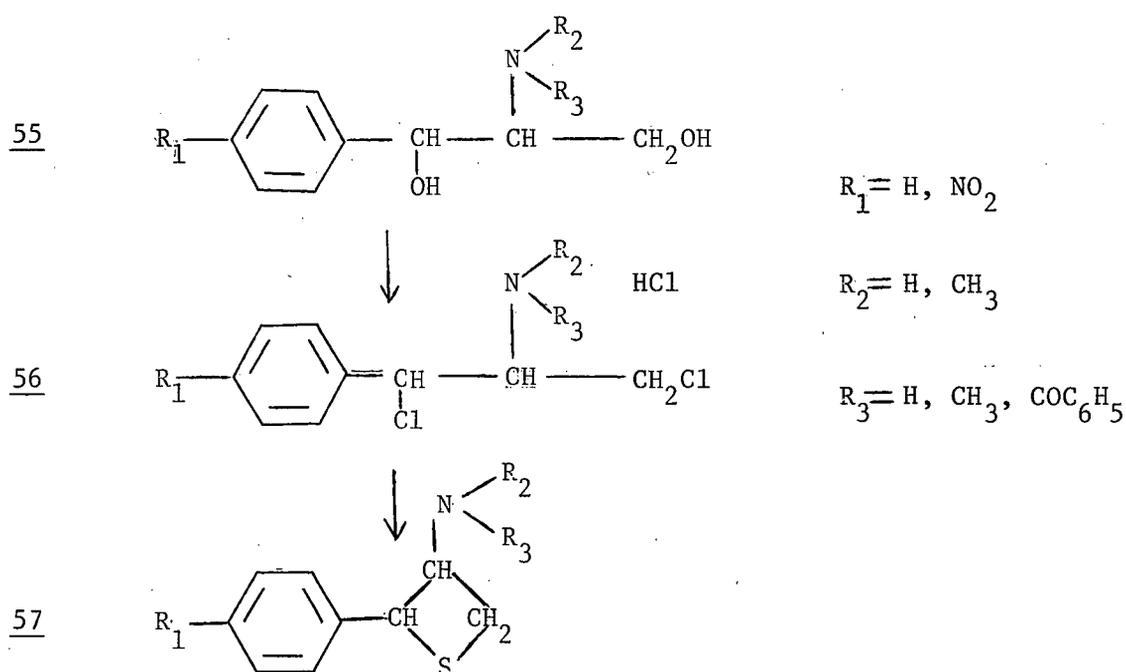


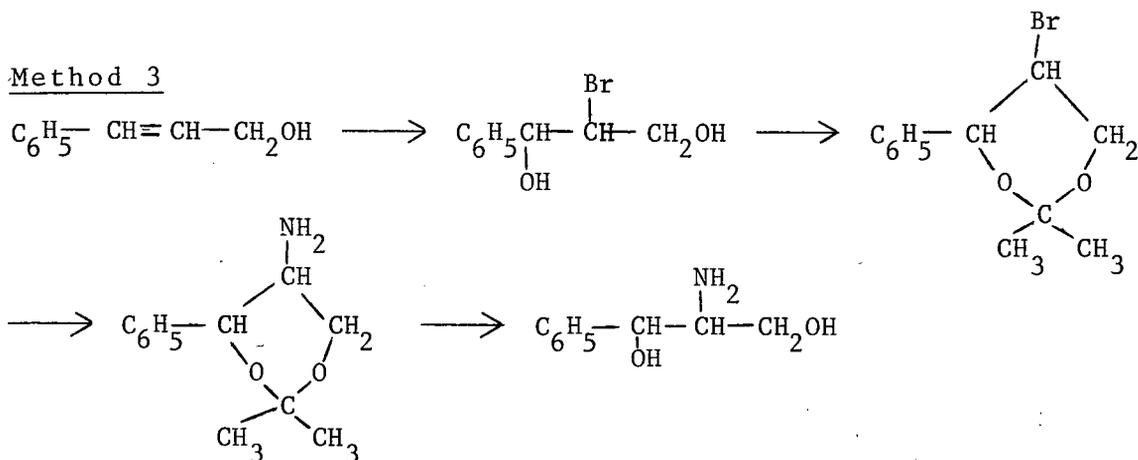
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DISCUSSION OF THE CHEMISTRY

It was considered that the reaction between suitable 1, 3-dihaloalkanes (56) and alkali sulfide would be the most effective for synthesis of 3-amino-2-phenylthietane derivatives (57). Ring formation at the last step might overcome the possible instability problem of thietanes, which is usually encountered when attempting modification of the thietane structure. In addition, since the most favorable route i.e. reduction of thietane 1,1-dioxides from cycloaddition reactions failed to give thietanes especially in the case of 2-phenyl derivatives, it appeared desirable to adopt the most common and classical method for the synthesis of 3-amino-2-phenylthietane derivatives (Scheme 1).

Scheme 1. Proposed Synthetic routes to 3-Amino-2-phenylthietanes (57).



Method 3

Methods 2-3 show parts of the route representing an economical synthesis of chloramphenicol. The hydroxyl groups of phenylserinol are protected by acetylation and the triacetyl derivative is nitrated with fuming nitric acid to give 1-(p-nitrophenyl)-1,3-diacetyl-2-acetylaminopropane. Acid hydrolysis, optical purification, and reaction with methylchloroacetate give chloramphenicol. Method 1 was followed with some modification in the reduction step for the synthesis of phenylserinol used in this project. Although method 3 could be a convenient route to phenylserinol, the ease of acquiring reagents and references was considered in favor of method 1.

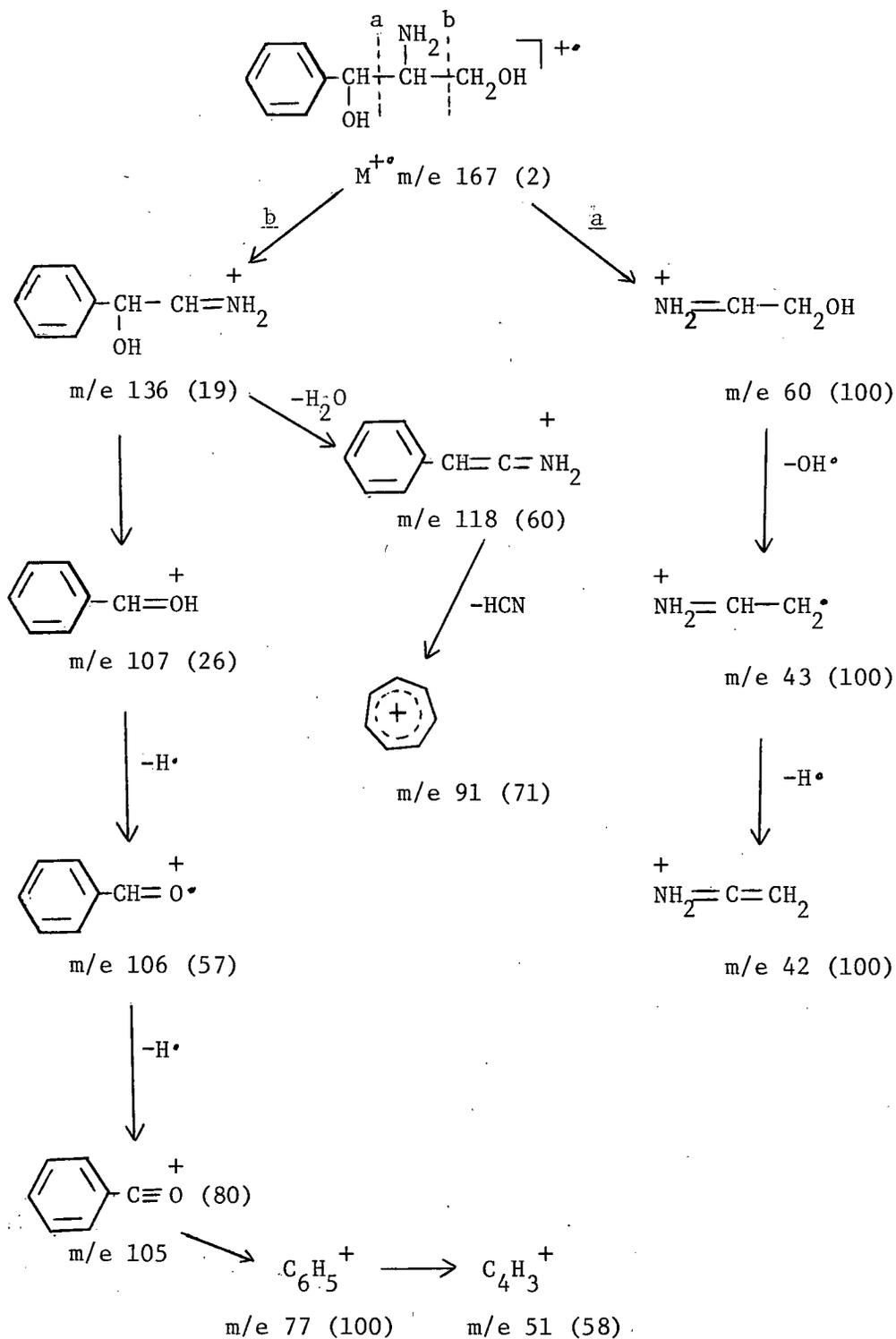
The main product from the condensation of benzaldehyde and glycine under alkaline condition is ordinarily threo-phenylserine. However, some erythro-compound is also formed (106). Shaw and Fox (107) isolated each of the diastereomers from the condensation mixture by using selective recrystallization or by selective precipitation of the stable addition compound of the erythro form with dioxane. They also reported that the ratio of each diastereomer is dependent on the condensation time and thus found that a 24 hours reaction time results exclusively in the threo form. Thus, following the

procedure of Shaw and Fox, threo-phenylserine was prepared.

The original work by Shaw and Fox utilized LiAlH_4 to reduce phenylserine ethylester. In this experiment, NaBH_4 was used for the reduction process. Synthesis of optically-active α -aminoalcohols by the reduction of α -amino acid esters with NaBH_4 was published by Seki et al. (110). They found that the reduction is accomplished in high yield with more than four moles of NaBH_4 to one mole of ester in a 50 % ethanol solvent after stirring at $0-10^\circ$ for 2 days. Application of this process to phenylserine ethylester or its hydrochloride salt showed that continuous extraction was necessary to obtain a high yield but it does ensure easier handling compared to using LiAlH_4 .

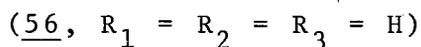
Since threo-phenylserinol is a key intermediate in this research project, several methods were used to confirm its structure. Melting points of threo-phenylserinol and its oxalic and benzoic acid salts were identical with the reported values (111,112). Suzuki and Shino (113) reported a single absorption in the region of $950-1000 \text{ cm}^{-1}$ in the threo-compound and $900-950 \text{ cm}^{-1}$ in the erythro compound possibly due to the C-H bond of the asymmetric carbon atom. Their published ir spectrum in the region of $850-1100 \text{ cm}^{-1}$ was identical with synthesized threo-phenylserinol. An nmr spectrum was not obtained, but Koya and Yamada (114) reported 5.16τ for threo- and 4.86τ for the erythro-benzylic proton of phenylserinol using acetic acid as solvent. The mass spectrum of threo-

Scheme 2. Proposed Fragmentation Pattern of threo-Phenylserinol (58) in the Mass Spectrum

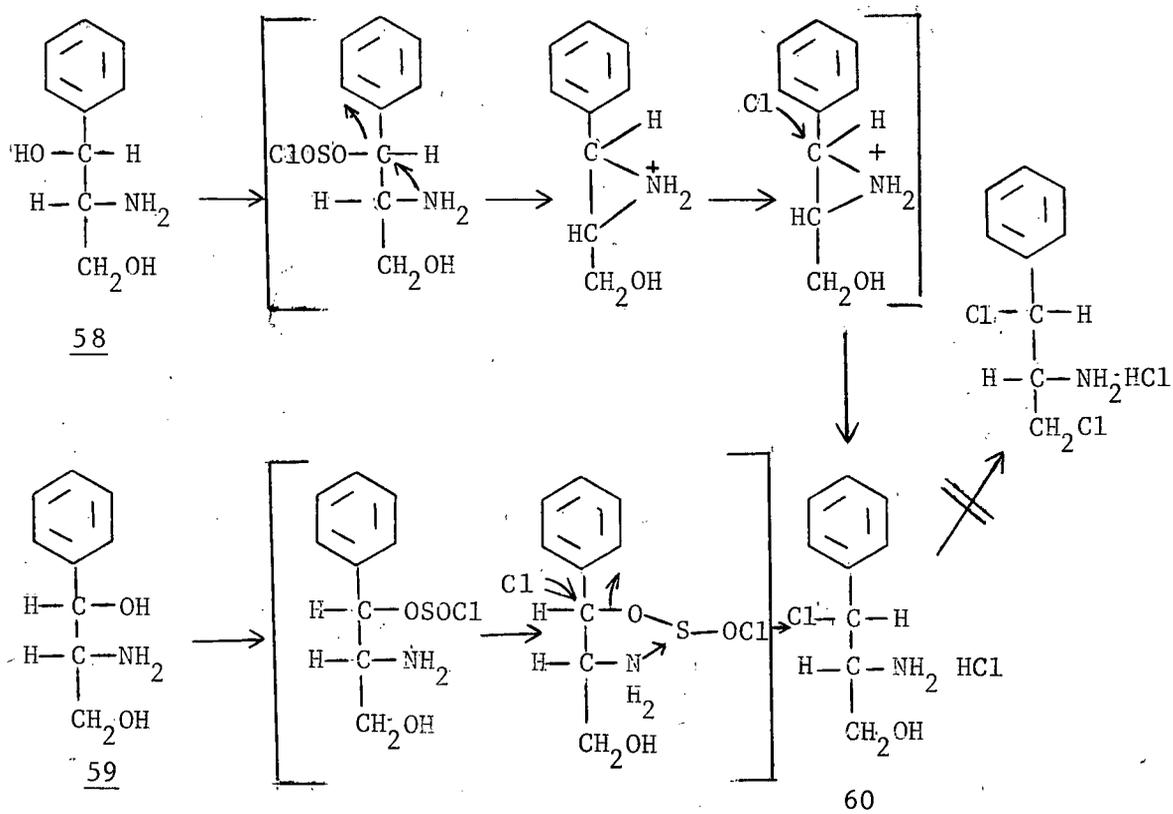


phenylserinol was studied. The molecular ion was observed and a fragmentation pattern consistent with the peaks observed is presented in scheme 2.

B. Threo-1-phenyl-1,3-dichloro-2-aminopropane



According to Ikuma (115), both the threo-(58) and erythro-phenylserinol (59) give rise to threo-1-phenyl-1-chloro-2-aminopropane-3-ol(60) when treated with thionyl chloride. This reaction has been studied extensively by the fact that inversion of the erythro compound to threo form could be applied in the synthesis of chloramphenicol which requires a threo form. The following mechanism was suggested to explain the Walden Inversion (115). Participation of the amino group in the substitution of the hydroxyl group by

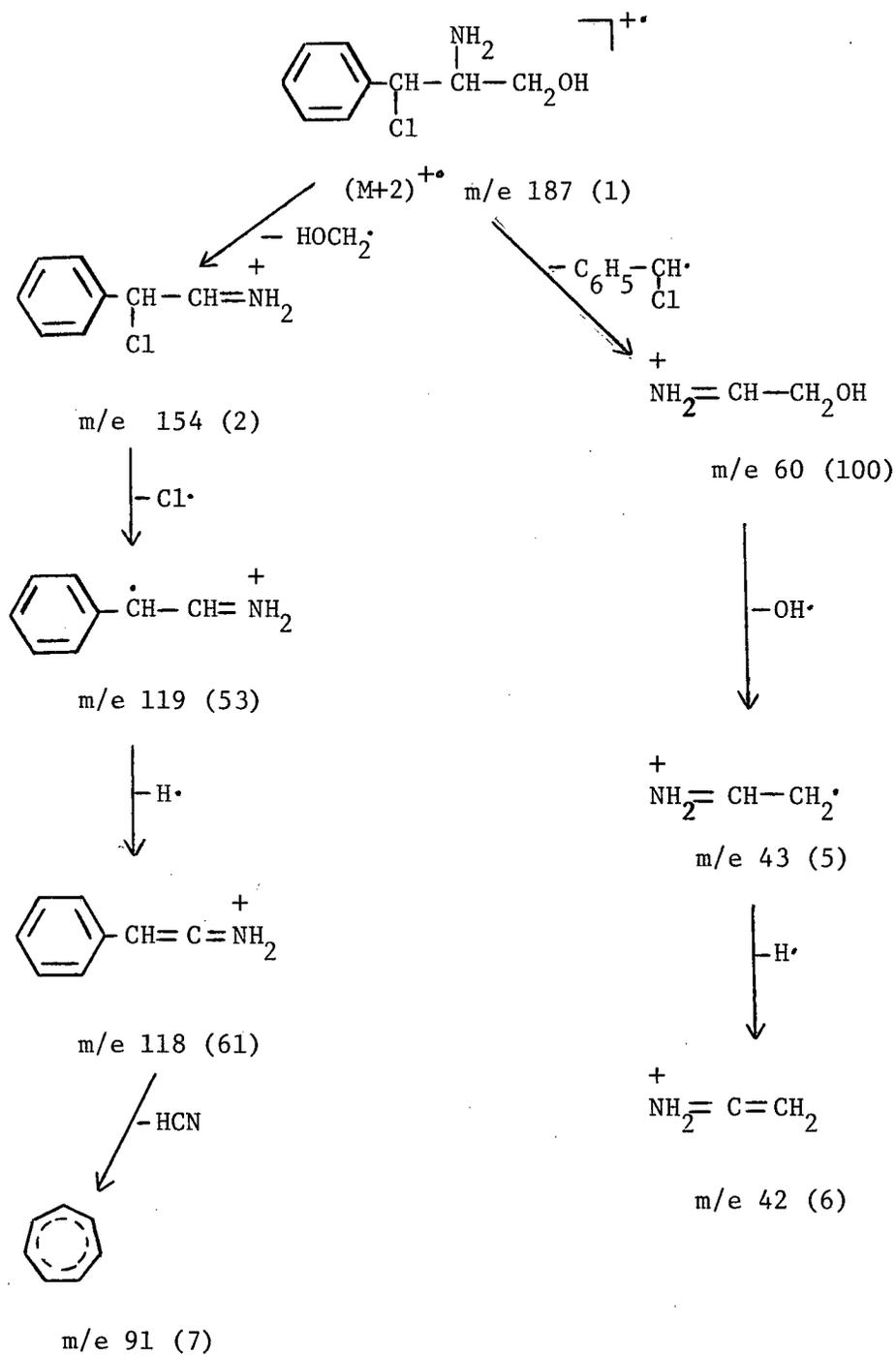


chlorine when treated with thionyl chloride was well known.

Threo-1-phenyl-1-chloro-2-aminopropane-3-ol (60) was synthesized by treating phenylserinol hydrochloride with thionyl chloride. A major difference in the ir spectrum of the product was observed in the range of $1200-1000\text{ cm}^{-1}$. In case of phenylserinol, two strong absorptions were assigned to the secondary alcohol at 1070 cm^{-1} and primary alcohol at 1040 cm^{-1} . The chlorination product showed primary alcohol absorption at 1050 cm^{-1} . However, the fact that reference data assigned to primary and secondary alcohol are $1075-1010\text{ cm}^{-1}$ and $1120-1100\text{ cm}^{-1}$ respectively (116) and that structure determination performed in 1950's might be based on friable data prompted confirmation of this structure by mass spectrometry. The mass spectrum clearly complied with the C-1 chloro compound as shown in Scheme 3. Fragmentation at $m/e\ 60$ and $m/e\ 154$ implied the presence of primary alcohol and C-1 chloro substitution.

Threo-phenylserinol hydrochloride was treated with an excess amount of thionyl chloride in dry chloroform for the purpose of obtaining threo-1-phenyl-1,3-dichloro-3-amino-propane (56, $R_1 = R_2 = R_3 = H$). Only monochloro compound (60) was isolated. The treatment of 60 with thionyl chloride under rigorous conditions led to isolation of the starting material. A possible reason for the resistance of the primary alcohol group to chlorination by thionyl chloride is not known but may result from some participation of the neighbouring amino group.

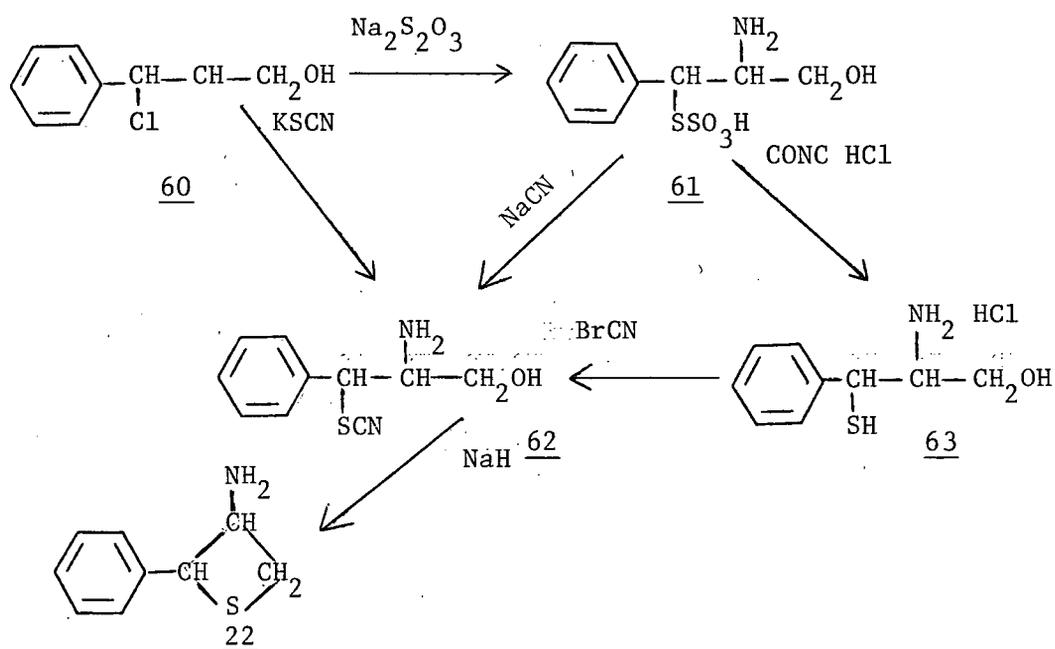
Scheme 3. Proposed Fragmentation Pattern of 1-Phenyl-1-chloro-2-aminopropane-3-ol (60) in the Mass Spectrum.



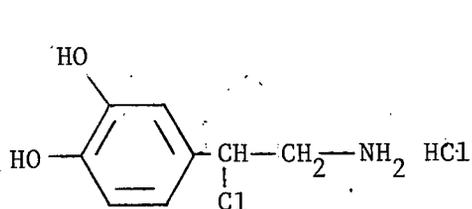
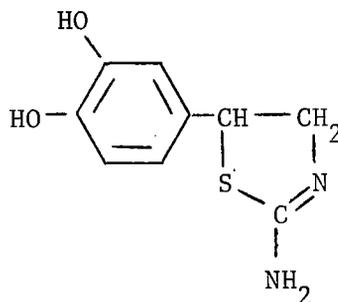
2. Synthetic approach to 3-amino-2-phenylthietane via a thiocyanate intermediate.

This failure to prepare threo-1-phenyl-1,3-dichloro-2-aminopropane led to a new synthetic scheme using threo-1-phenyl-1-chloro-2-aminopropane-3-ol.

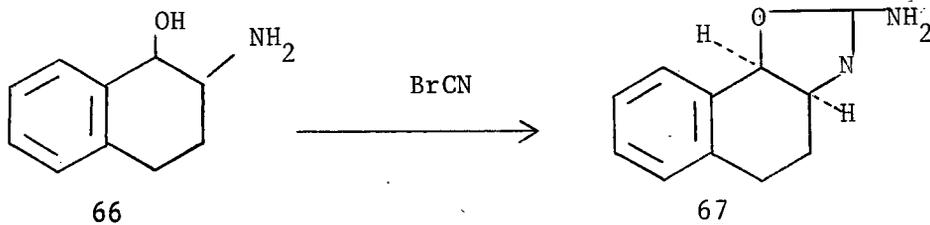
Scheme 4. Proposed synthetic route to thietanes via a thiocyanate intermediate



This scheme, however, contains several problems. Reaction of a thiocyanate group with a neighbouring amino group is well documented as shown by the synthesis of thiazoline or thiazole derivatives (117). Rachlin and Enemark (118) observed that 3-chloro-(3,4-dihydroxy phenyl)ethylamine hydrochloride (**64**) reacts with potassium thiocyanate to form the thiazoline (**65**).

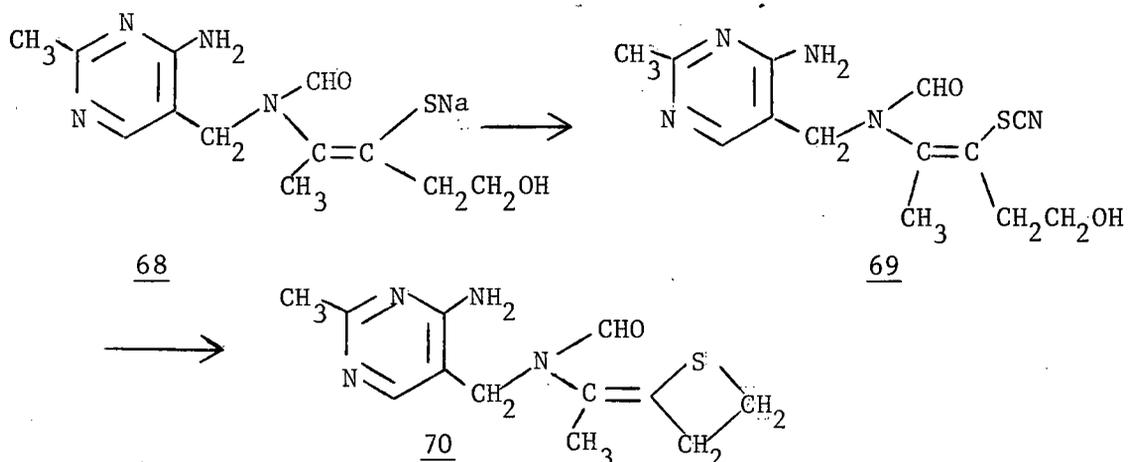
6465

Sodium hydride is a useful reagent to convert an amine to its sodio derivative. Therefore, the amino, as well as the hydroxyl group may react with sodium hydride under the reaction conditions causing formation of side products. Conversion of the thiol group to a thiocyanate group using cyanogen bromide may also involve reaction of the cyanogen bromide with the amino group.

6667

An example of this possible side reaction is illustrated by the reaction of cyanogen bromide with the 1,2-amino alcohol (66) to form the tricyclic product 67 (119).

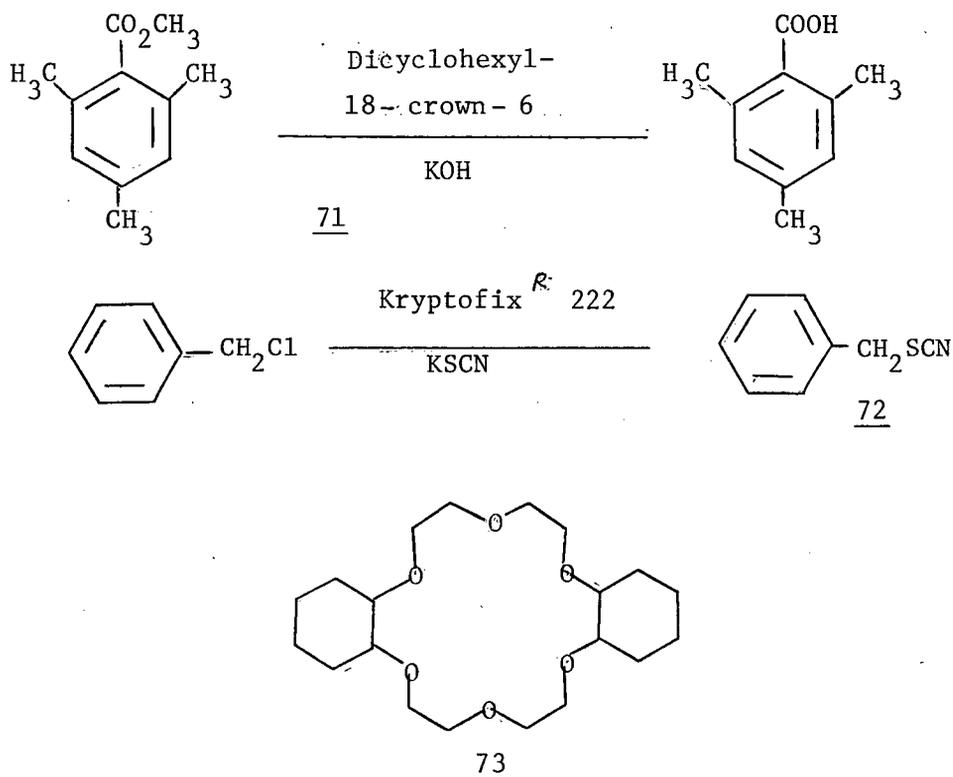
In spite of the above weak points, it was strongly proposed that the product (22) could be synthesized via Scheme 4 through controlling the reaction conditions. The assumption was that the reaction of thiocyanate with amino group may be avoided by reacting at low temperature. For example, the reaction of cyanogen bromide with the sodium salt of the thiol-type thiamine (68) at ice-cooling temperatures afforded the



cyanothiamine (**69**) (98). Dissolving the cyanothiamine in H_2O followed by treatment of alkali gave the thietane (**70**) (99).

A. 2-Amino-4-hydroxy methyl-5-phenyl-2-thiazoline (**74**)

Thiocyanate anion is a strong nucleophile, but usually substitution of chlorine by potassium thiocyanate requires refluxing temperatures (120). To ensure that the reaction would proceed at low temperature, dicyclohexyl-18-crown-6 (**73**) was used. These polyether complexes of sodium, potassium, and related cations by neutral molecules lead to solubilization of the salt in aprotic solvent and increasing dissociation of the ion pairs provides highly reactive, unsolvated anions (121). The hydrolysis of sterically hindered esters (**71**) is greatly accelerated in the presence of the appropriate polyether (122). The reaction of benzylchloride with potassium thiocyanate in the presence of Kryptofix^R 222 in chloroform for 6 days at room temperature gives an 80 % yield of benzylthiocyanate (**72**).



The potassium thiocyanate complex of dicyclohexyl-18-crown-6 was prepared by the method of Pederson (123). Monochloro compound (60) dissolved in methanol was treated with polyether-potassium thiocyanate complex at room temperature. However, attempts to separate reaction products from the polyether complex were not successful. While polyether efficiently activates the anionic function in aprotic solvent, 60 was only soluble in protic solvents. Polyether (73) is a mixture of 2 stereoisomers and is soluble in both protic and aprotic solvents. Therefore, separation is a problem unless the product is precipitated out or can be distilled. It was not possible to confirm the formation of any thiocyanate product by ir spectroscopy of the reaction mixture.

Another route to synthesize thiocyanate compounds instead of direct reaction with potassium thiocyanate is by using organic thiosulfate (Bunte salt). As shown in Scheme 4, the Bunte salt (61) reacts with alkali cyanide forming the thiocyanate (62) at room temperature. The reaction is usually completed in half an hour (124). Treatment of 60 with sodium thiosulfate gave 1-phenyl-1-thiosulfuryl-2-aminopropane-3-ol(61). The ir spectrum showed strong absorption at 1200 and 1230 cm^{-1} indicating the $-\text{SO}_2-$ group. Presence of a strong band at 640 cm^{-1} further proved absorption by the $-\text{SO}_2\text{O}-$ group. It is evident that a strong band at 640 cm^{-1} could be used specifically to differentiate $-\text{SO}_2\text{Cl}$ from $-\text{SO}_2\text{OH}$ of its hydrolyzed product as shown by the example of benzyisulfonic acid and benzyisulfonylchloride. Identification by mass spectrometry was not successful because of its high melting point.

The Bunte salt (61) was dissolved in water by adding sodium carbonate and stirred at room temperature with an equimolar amount of sodium cyanide. Product precipitated out which appeared to be a thiazoline on the basis of a strong band at 1640 cm^{-1} of the ir spectrum (Fig.1). In thiazoline, a band near 1640 cm^{-1} has been signed as the $\text{C}=\text{N}$ stretching vibration in the absence of external conjugation (125). The formation of thiazoline (74) was further confirmed by mass spectrometry. The mass spectrum reported for

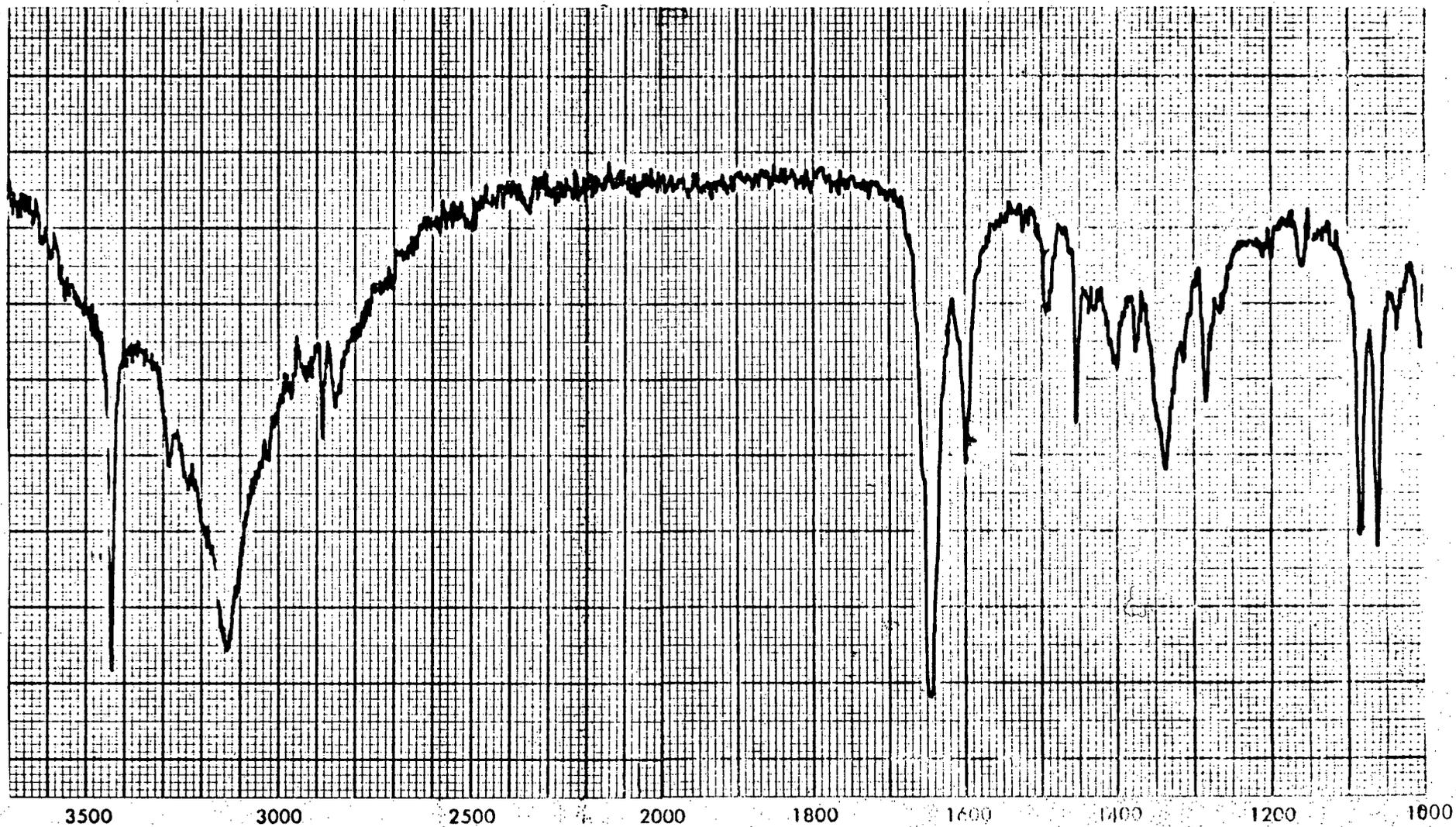
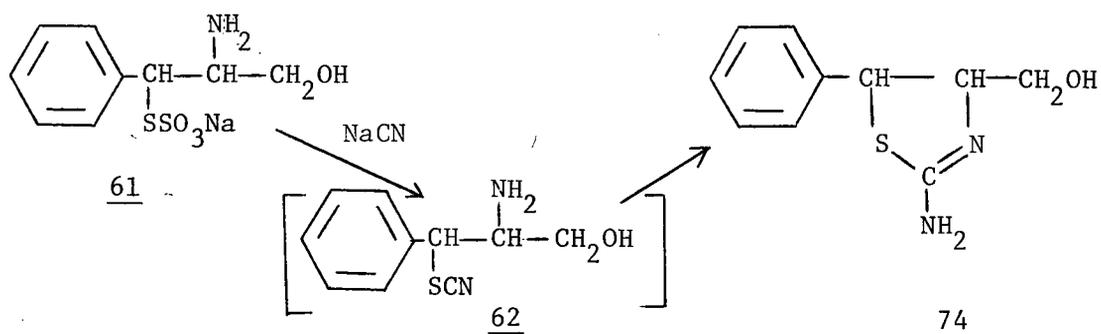
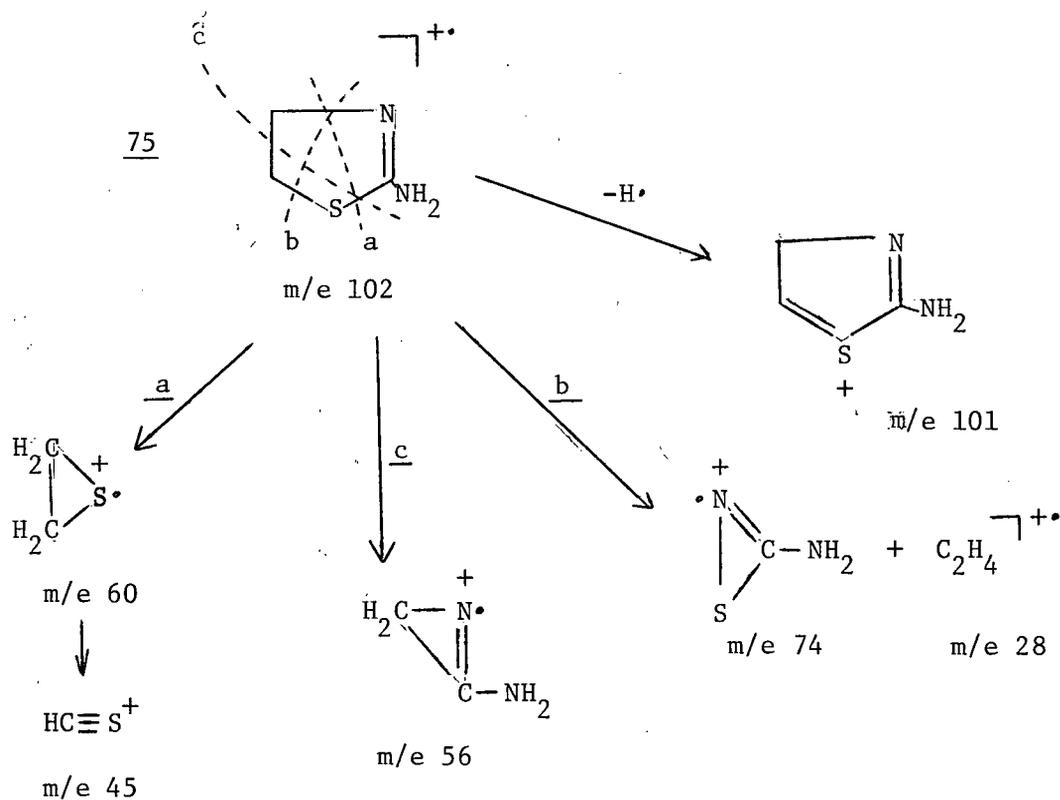


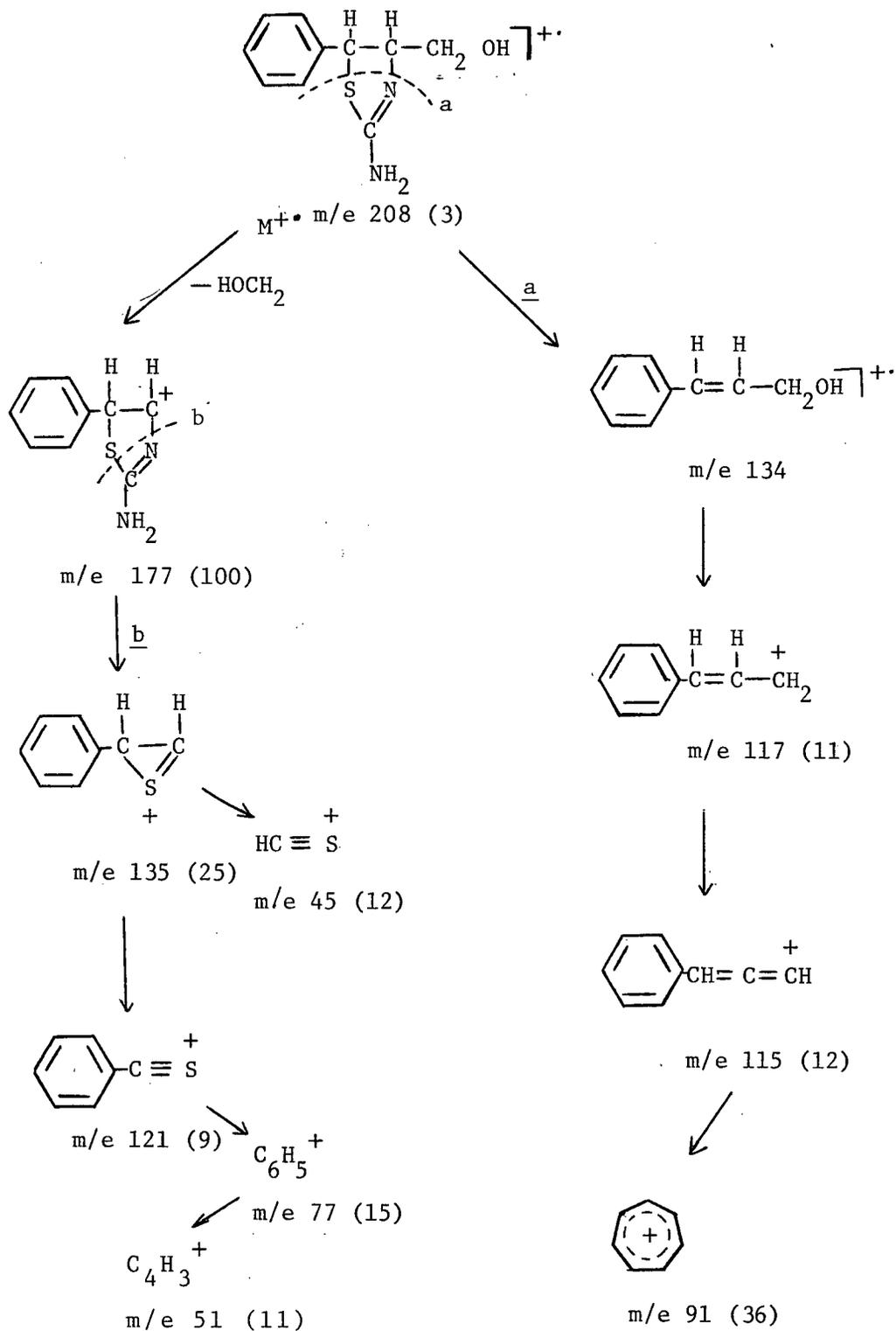
Fig. 1 Ir spectrum of 2-amino-4-hydroxy-methyl-5-phenyl-2-thiazoline (74).



2-aminothiazoline (75) shows three fissions across the ring as described below (126). Synthesized thiazoline (74) gave the molecular ion and also fragmented by a and b fission.



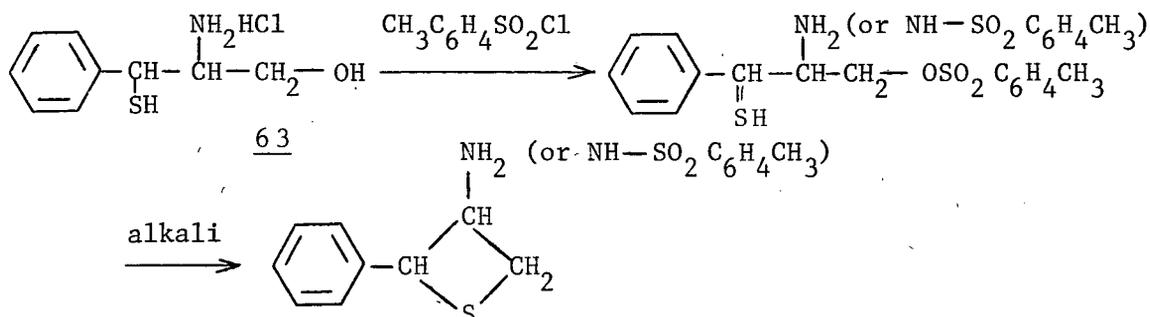
Scheme 5. Proposed Fragmentation Pattern of 2-Amino-4-hydroxymethyl-5-phenyl-2-thiazoline (74)



The facile formation of thiazoline (74) even at room temperature indicates the ease of reaction of the thiocyanate group with the neighbouring amino group in this case and consequently this approach to the thietanes proved disappointing.

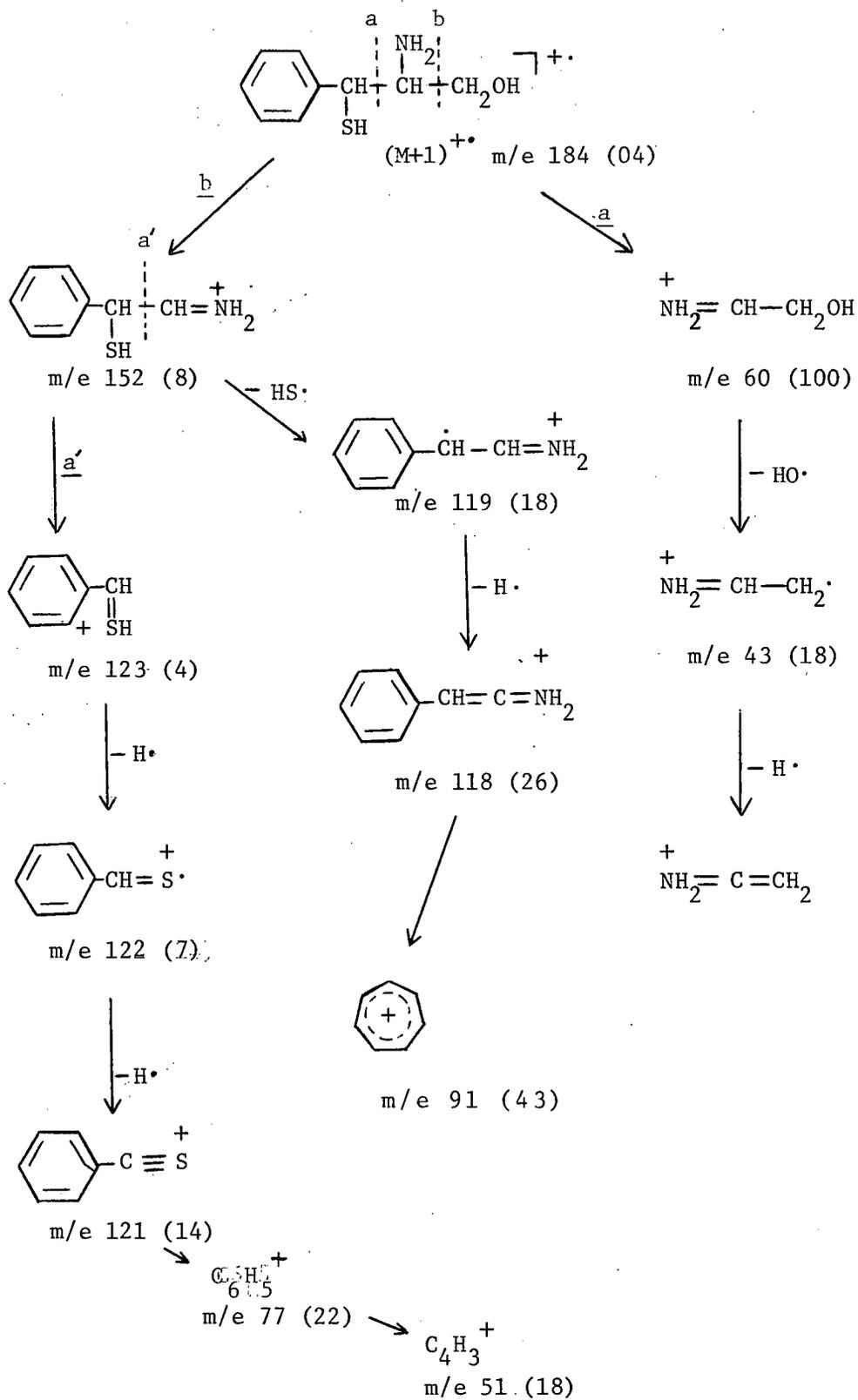
B. 1-Phenyl-1-mercapto-2-aminopropane-3-ol hydrochloride (63).

An alternative approach using the compounds in Scheme 4 was investigated in a preliminary fashion. This stemmed from the fact that 1-mercapto derivatives may be of interest for the synthesis and testing of chloramphenicol derivatives and adrenergic compounds. One possible modification of the

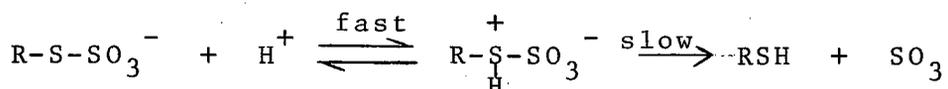


1-mercapto compound 63 to thietanes could not be ruled out as shown above. The reactivity of tosylchloride might provide selective tosylation of the primary hydroxyl group. Tosylamide may be cleaved after formation of the thietane by alkaline conditions or by reductive cleavage. At least, tosyl substituted thietane would be worthwhile to test for pharmacological activity as a MAO inhibitor. However, considering the time used for this research, it was determined to restrict this part of the work to the synthesis of the 1-mercapto compound

Scheme 6. Proposed Fragmentation Pattern of 1-Phenyl-1-mercapto-2-aminopropane-3-ol (63) in the Mass Spectrum.



itself. Acid-catalyzed hydrolysis of S-alkyl and S-aryl thiosulfate is a useful method of preparing thiols (127). Hydrolysis of Bunte salt are known A-1 processes. The hydrolysis is usually performed in situ without isolation



using sulfuric or hydrochloric acid.

Concentrated hydrochloric acid was used to prepare 63 from the Bunte salt (61). The ir spectrum showed a typical band at 2520 cm^{-1} indicating the mercapto group (Fig. 2).

A molecular ion was observed in the mass spectrum. Fragmentation patterns for 63 which account for observed peaks are shown in Scheme 6.

3. Synthetic approach to 3-benzoylamino-2-phenylthietane (23).

The approach proposed for the synthesis of 3-benzoylamino-2-phenylthietane (23) considered as a potential MAO inhibitor in this research project is outlined in Scheme 7.

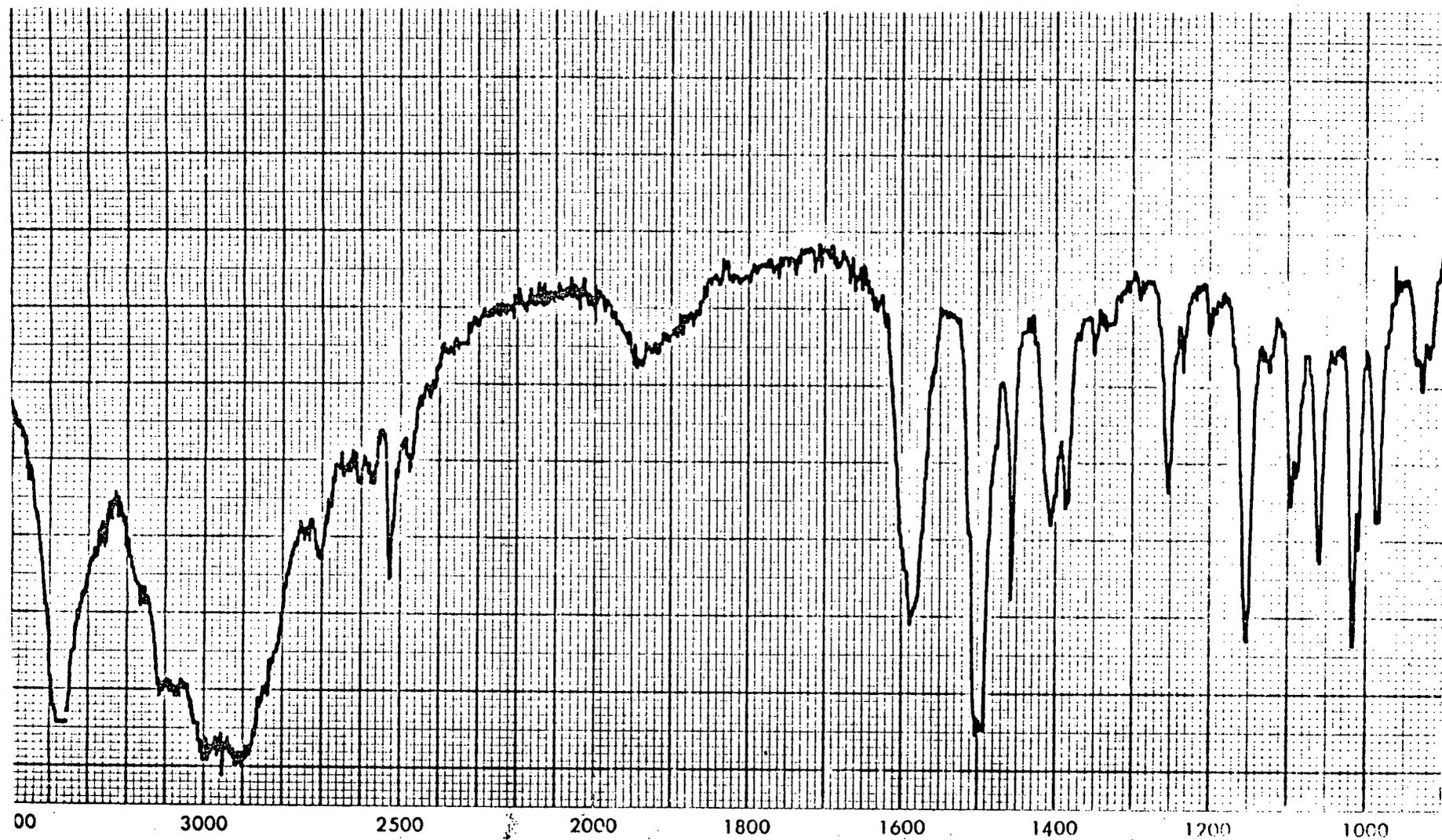
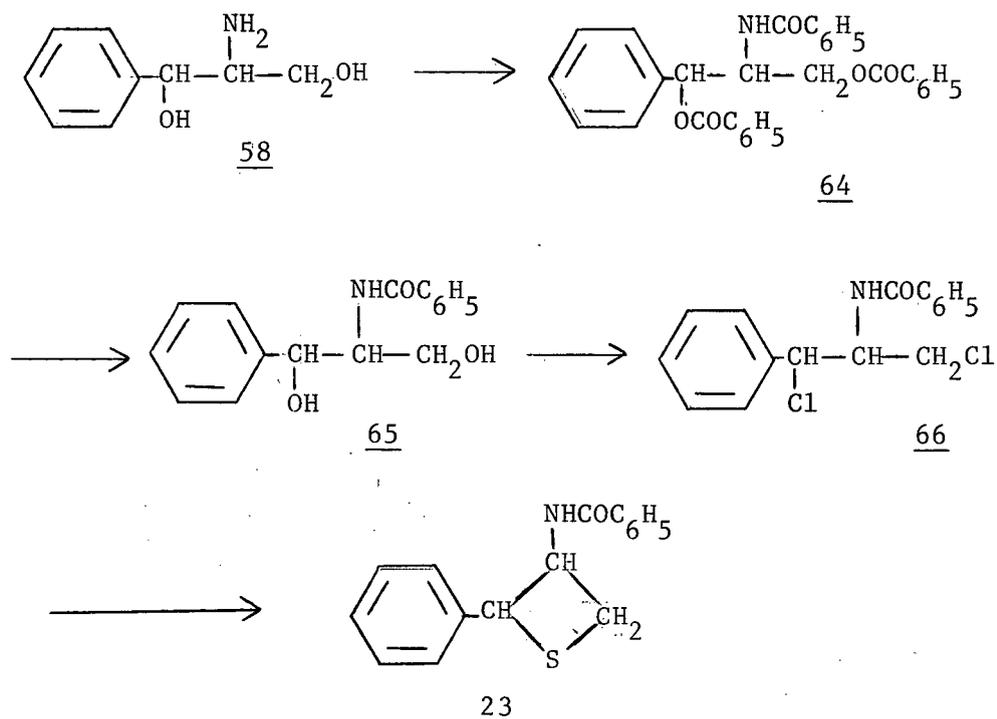


Fig. 2 Ir spectrum of 1-Phenyl-1-mercapto-2-aminopropane-3-ol (63).

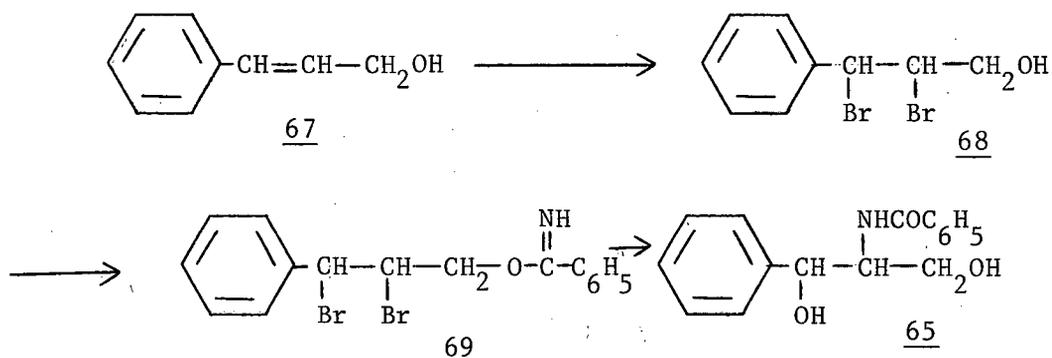
Scheme 7. Proposed synthetic route to
3-benzoylamino-2-phenylthietane (23).



Although 1-phenyl-2-aminopropane-1,3-diol (58) failed to give 1-phenyl-1,3-dichloro-2-aminopropane (56, $R_1=R_2=R_3=H$), the synthesis of 66 from 65 appeared possible. The unsuccessful attempt to prepare 1-phenyl-1,3-dichloro-2-aminopropane appeared due to the electronic character of the primary amino group. A decrease of electron density as in the amino function of the amide compound (65) might allow chlorination of the primary alcohol group.

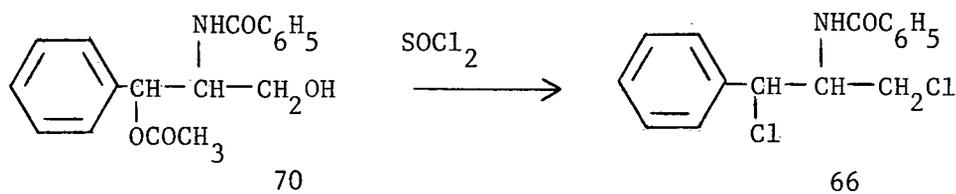
A. 1-Phenyl-1,3-dichloro-2-benzoylamino propane (66).

Several methods for the synthesis of N-benzoylphenylserinol (64) have been published. The direct Schotten-Baumann reaction does not guarantee selective benzylation of the amino group. Therefore, a possible route was to use the tribenzoyl compound (64) and to hydrolyze it by using sodium hydroxide (128). Another procedure is to start from cinnamyl alcohol as shown below (128).



In this research project, N-benzoylphenylserinol (65) was prepared by selective hydrolysis of the tribenzoyl compound. The tribenzoyl compound was prepared by the Schotten-Baumann reaction using an excess amount of benzoyl chloride. The ir spectrum of synthesized N-benzoylphenylserinol showed amide bands but no ketone band thus implying the success of selective hydrolysis. N-benzoylphenylserinol was refluxed with thionyl chloride and work up gave crystals which showed a slight ketone band and no hydroxyl bands in the range of $1200 - 1000 \text{ cm}^{-1}$ in the ir spectrum. Benzene was an efficient recrystallization solvent to remove the contaminating ketone compound. 1-Phenyl-1,3-dichloro-2-benzoylamino propane (66) showed a mp of 148-150.

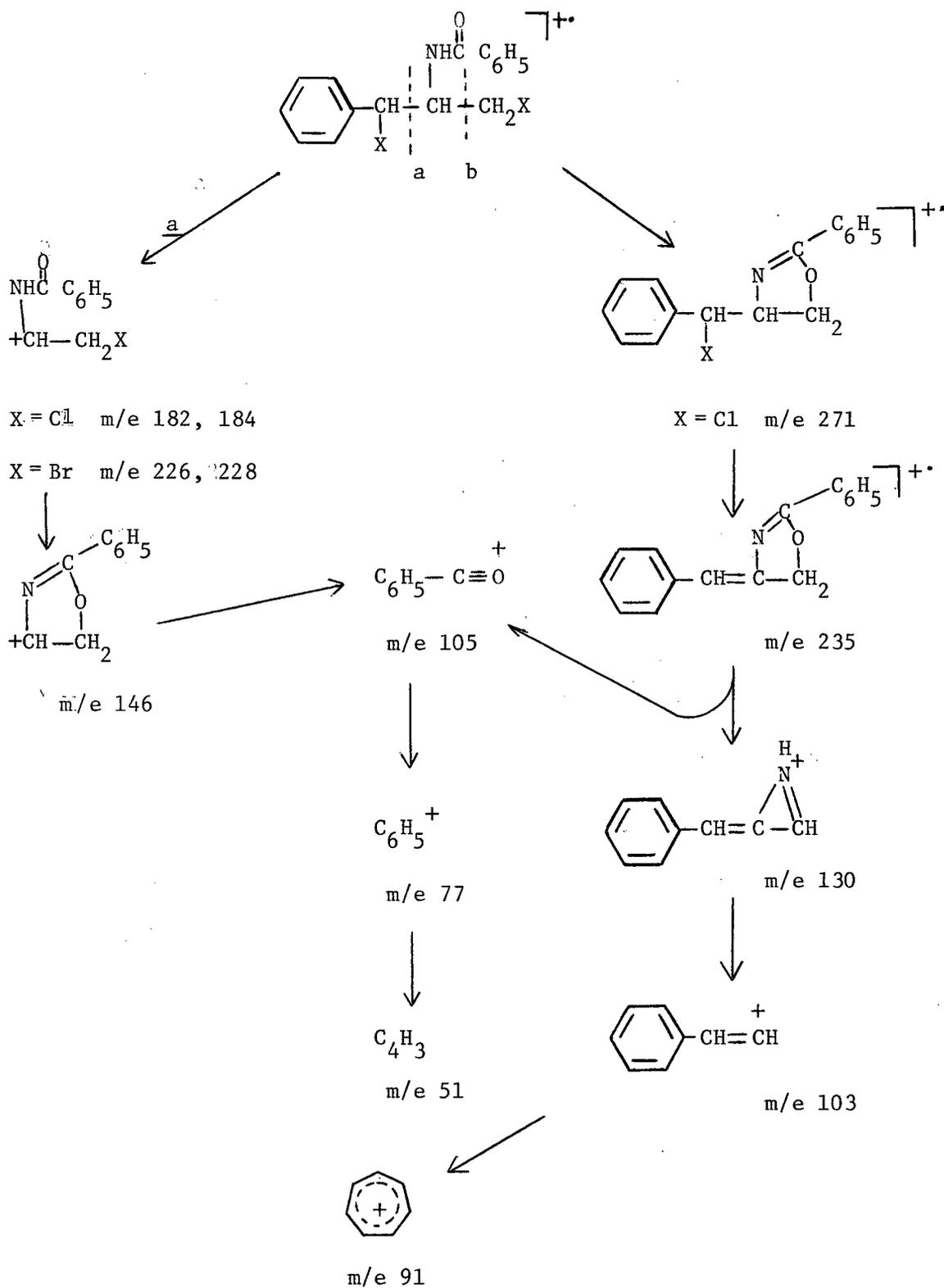
A report has been published on the synthesis of 66 from 70 by treating with thionyl chloride (129). A mp of 131-132



was reported. No spectroscopic data was mentioned. This difference in melting point of synthesized compound from the reported one prompted confirmation of the structure of 66 by using spectroscopic data and elemental analysis. Two amide bands appear in the ir spectrum. Hydroxyl bands are no longer present. In the nmr spectrum, two ortho-phenyl protons to the carbonyl group have signals in the 7.50-7.73 δ region. The remaining eight phenyl protons appeared at 7.60-7.37 δ as a multiplet. A doublet appeared at 5.32 δ is due to the methine proton. Methylene protons attached to chlorine were shown at 3.50 δ as a multiplet. This multiplet nature seems due to the coupling not only with the neighbouring methine but also with phenyl protons. The broad bands centered at 6.40 δ were assigned to the proton in the amide group.

Mass data was collected for 66 and compared with the starting material, N-benzoylphenylserinol (65). The fragmentation of N-benzoylphenylserinol is shown in Scheme 8. The base peak at m/e 164 corresponds to the m/e 60 fragment of phenylserinol. A peak at m/e 240 was observed with high

Scheme 9. Proposed Fragmentation Pattern of 1-Phenyl-1,3-dihalo-2-N-benzoylaminopropane in the Mass Spectrum.

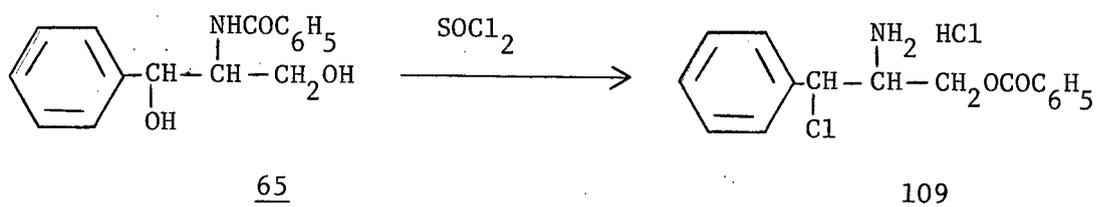


intensity by b fission. As shown in the mass spectra for 66 in Scheme 9, m/e 271 and 235 showed the rearrangement of N-benzoyldichloro compound (66) to the oxazoline structure. Fragmentations by b fission were not observed. Fragmentations by a fission showed ratios of natural isotopic abundances at m/e 182 and 184 for the chloro compound 66 and at m/e 226 and 228 for the bromo compound 72.

Elemental analysis supported these spectroscopic data.

B. 1-Phenyl-1,3-dibromo-2-benzoylaminopropane (72).

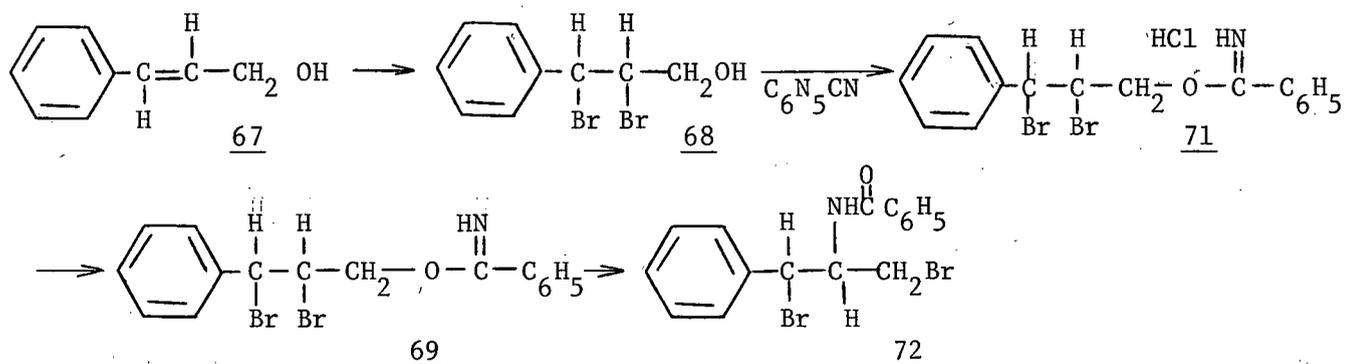
The ring closure reaction to thietane was initially performed using the N-benzoyl-dichloro compound (66). As research progressed, several problems were encountered concerning the preparation of 66. Rearrangement to the ester (109) caused a low yield. The rearrangement of 65 to 109 has been well described (130).



Moreover, preparation of 66 starting from glycine and benzaldehyde was considered a time consuming process. Therefore, 1-phenyl-1,3-dibromo-2-benzoylaminopropane (72) was synthesized to substitute for the dichloro compound.

The synthesis of 72 starting from cinnamyl alcohol (67) has been reported in the patent literature (131,132).

The cinnamyl alcohol, mp 30-33, has been assigned the trans



configuration. Assuming that halogens, as is generally recognized, add preferentially to olefinic double bonds in a trans fashion (133), the dibromide (68) may be assigned the erythro configuration. A dry ether solution of 68 and benzonitrile upon saturation with dry hydrogen chloride and standing in the cold gave 71 which was then converted to its base by treatment with sodium carbonate. The yield was dependent upon anhydrous conditions of the reaction mixture in the condensation step. Compound 69 was carefully dried before use. Refluxing 69 dissolved in dry toluene gave an initial precipitate, the ir spectrum of which was identical to the hydrobromide of 69 reported by Taguche et al (130). Further refluxing and evaporation of the solvent under reduced pressure resulted in precipitation of the N-benzoyl dibromo compound (72). The ir and nmr spectra of 72 were identical to those of the N-benzoyl dichloro compound (66). The mass spectrum also showed the same pattern of fragmentation as that of the N-benzoyldichloro compound (Scheme 9). A high intensity

peak at m/e 235 was similarly indicative of formation of an oxazoline.

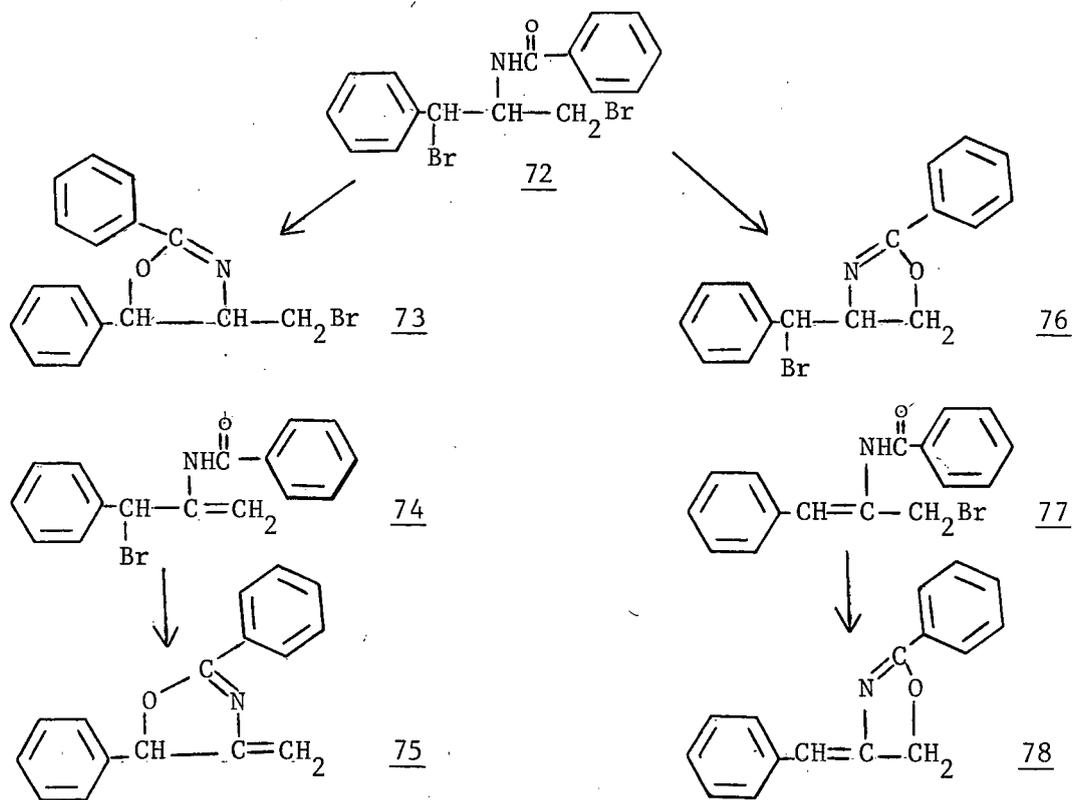
C. 2-Phenyl-4-benzylidene-2-oxazoline (78)

When an ethanol solution of 1-phenyl-1,3-dichloro-2-benzoylamino-propane (66) (or 1-phenyl-1,3-dibromo-2-benzoylamino-propane (72)) was treated with sodium sulfide, the solution turned to a yellow color. After refluxing for 2 hours and distilling the solvent, the residue was dissolved in water and extracted with chloroform. A viscous residue was obtained after removing the chloroform. TLC of this residue on silica gel plates showed 4 spots with R_f 0, 0.2, 0.5, and 0.7. The major spot was at R_f 0.7. Preparative column chromatography using chloroform as eluant was successful in isolating each of the components. Components of R_f 0, 0.2, and 0.5 showed amide bands in their ir spectra. Amide bands were not present for the major component (Fig. 4). Since components with R_f 0.2 and 0.5 were isolated in very small amounts, further attempts to determine their structures were not undertaken.

The main effort was concentrated on determining the structure of the major component at R_f 0.7. Absence of amide bands in their spectrum did not support formation of a thietane. Extensive purification of the solid from hexane using a dry ice-acetone bath elevated the melting point from 60-80° to 90-93° and showed no significant changes in the ir pattern. The yellow coloration denotes high conjugation of this compound.

Several possible reactions leading to the absence of amide and a high degree of conjugation were examined and are illustrated in Scheme 10.

Scheme 10. Proposed products from the side reactions of dibromocompound (72) with sodium sulfide.



The first clue to the solution of this problem was obtained by the results of elemental analysis. The analytical data was consistent with either structures 75 or 78. If the major component is really 75 or 78, it is not an effective tool to selectively identify this compound. The identification of C = N absorption in conjugated cyclic systems is rendered

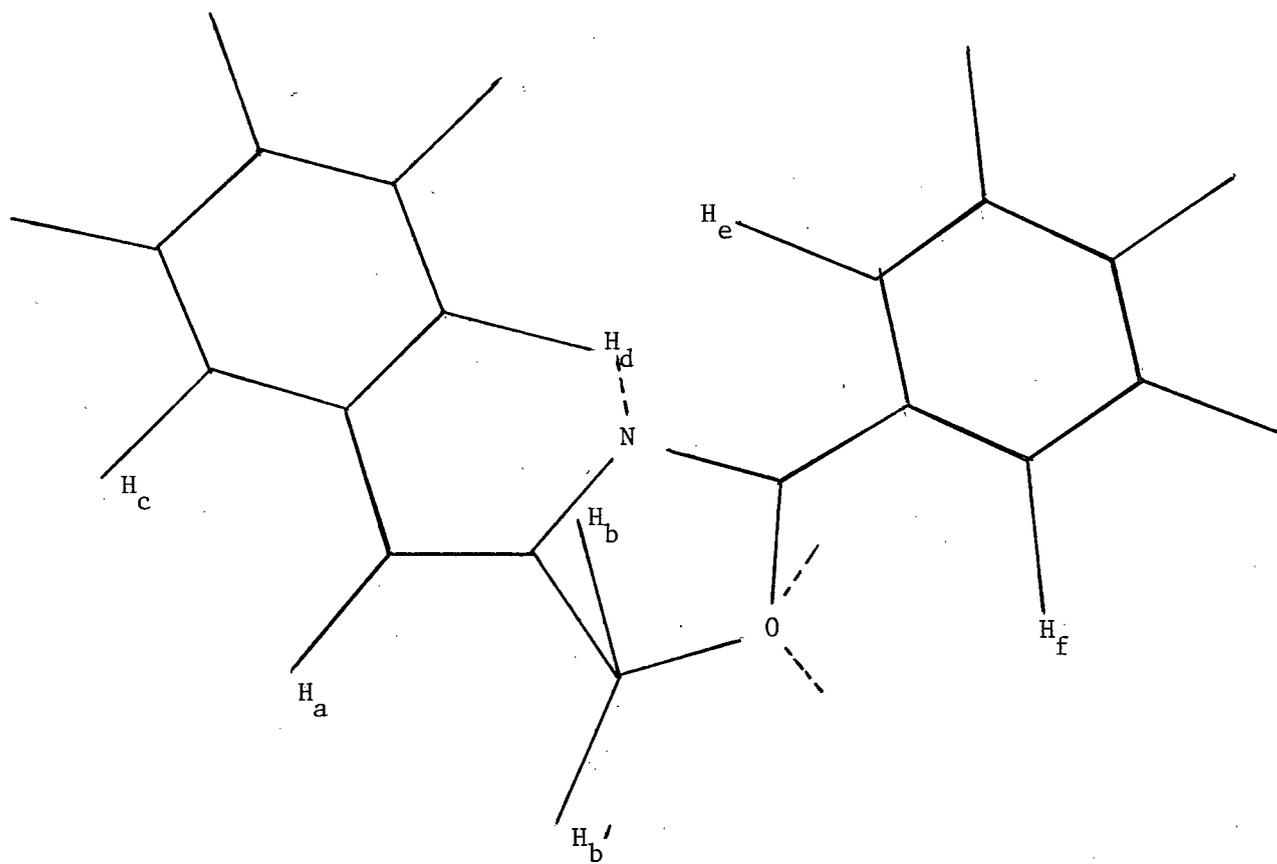


Fig. 3 Molecular structure of 2-Phenyl-4-benzylidene-2-oxazoline (78).

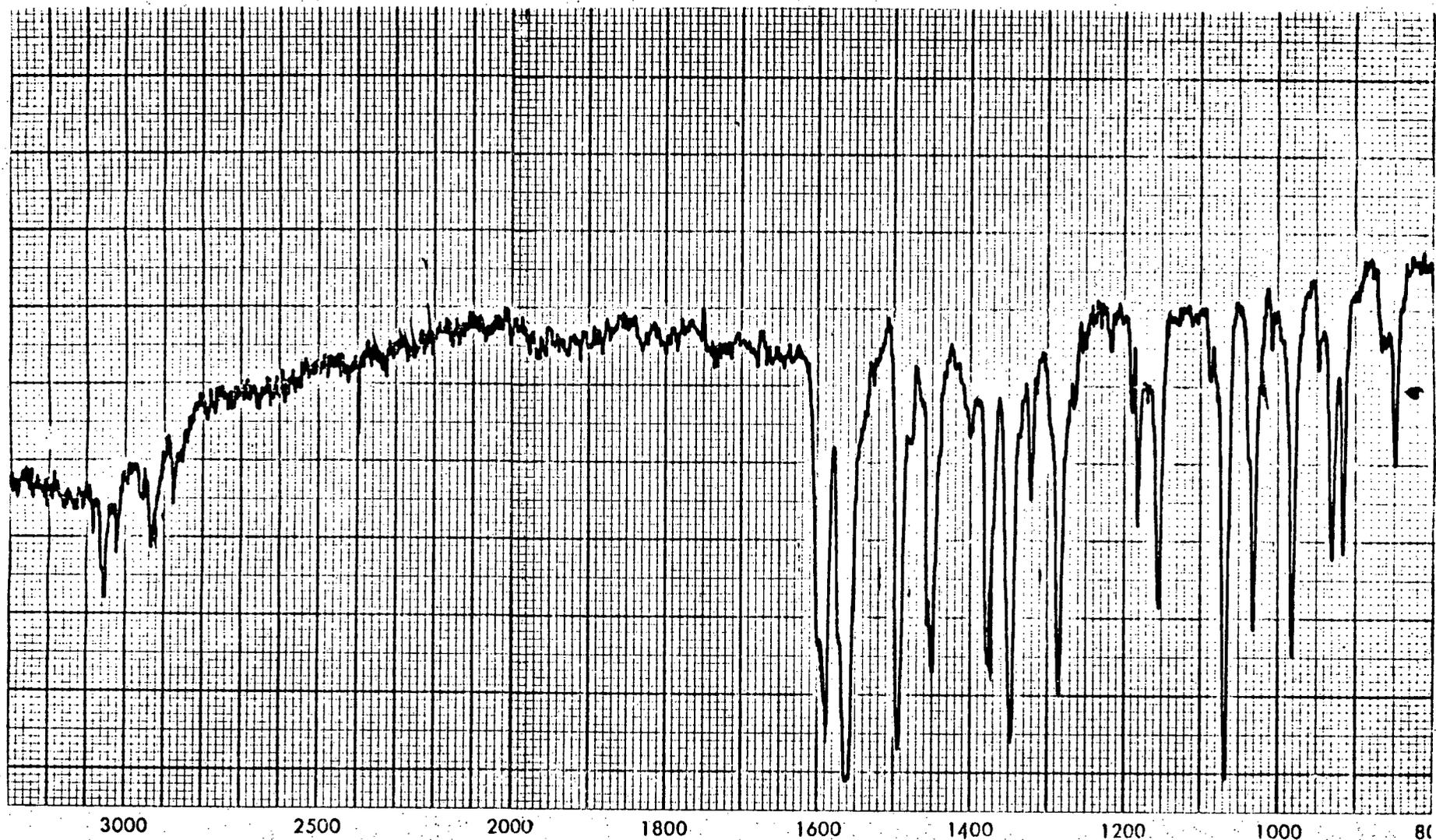


Fig. 4 Ir spectrum of 2-Phenyl-4-benzylidene-2-oxazoline (78).

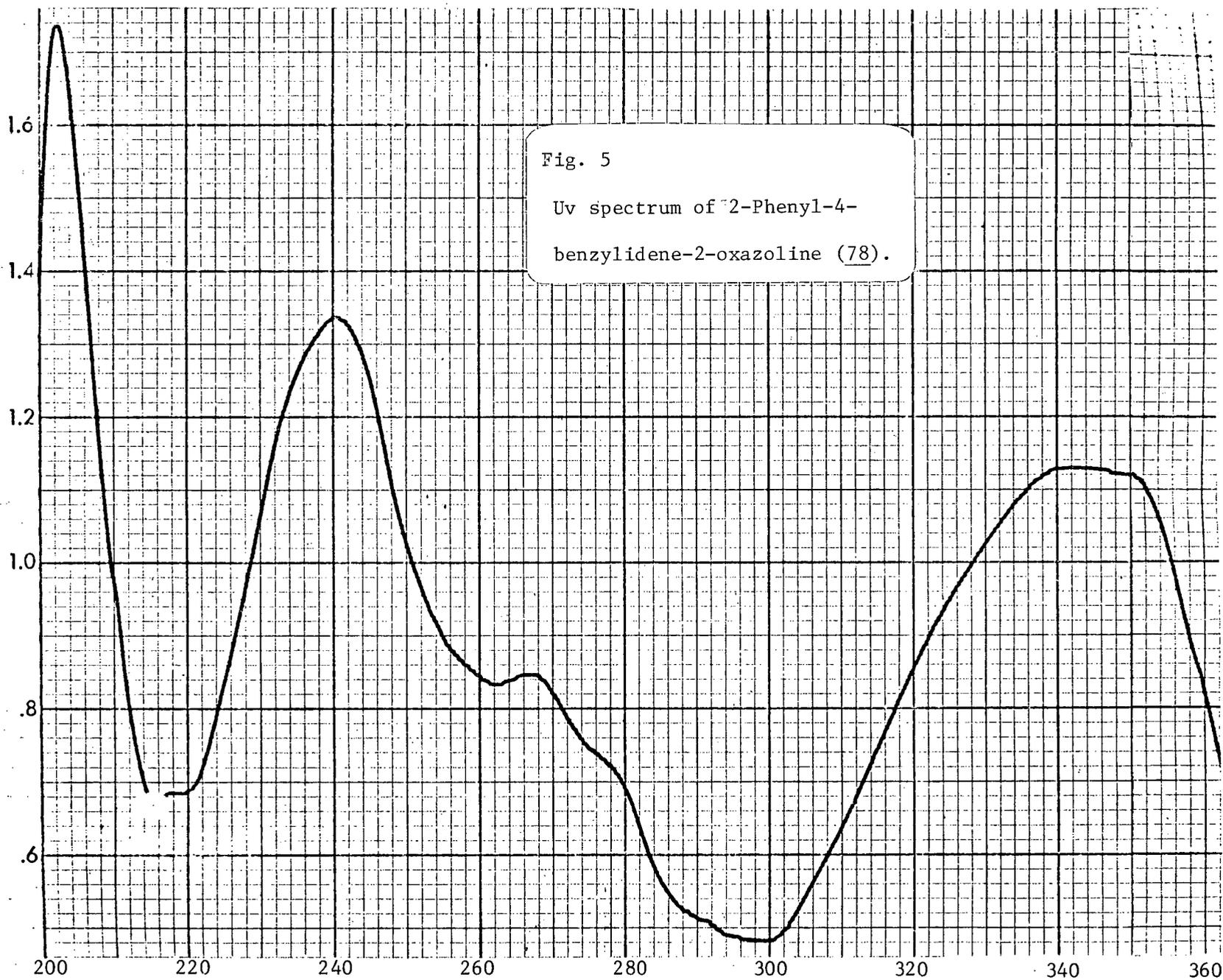
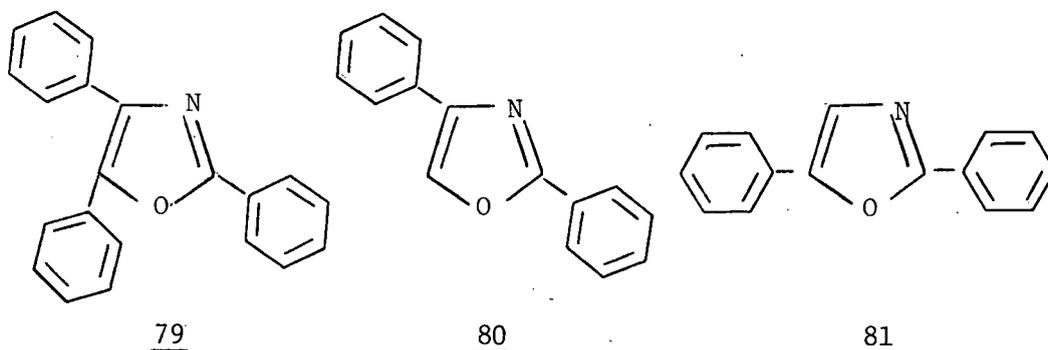


Fig. 5
Uv spectrum of 2-Phenyl-4-
benzylidene-2-oxazoline (78).

difficult by the interaction with other double bonds.

Specific assignments of C = N frequency have not been possible in tetrazoles, benzthiazoles, and thiazoles. The absorption bands found in the $1650-1500\text{ cm}^{-1}$ region in such compounds can only be associated with the entire ring system (116).

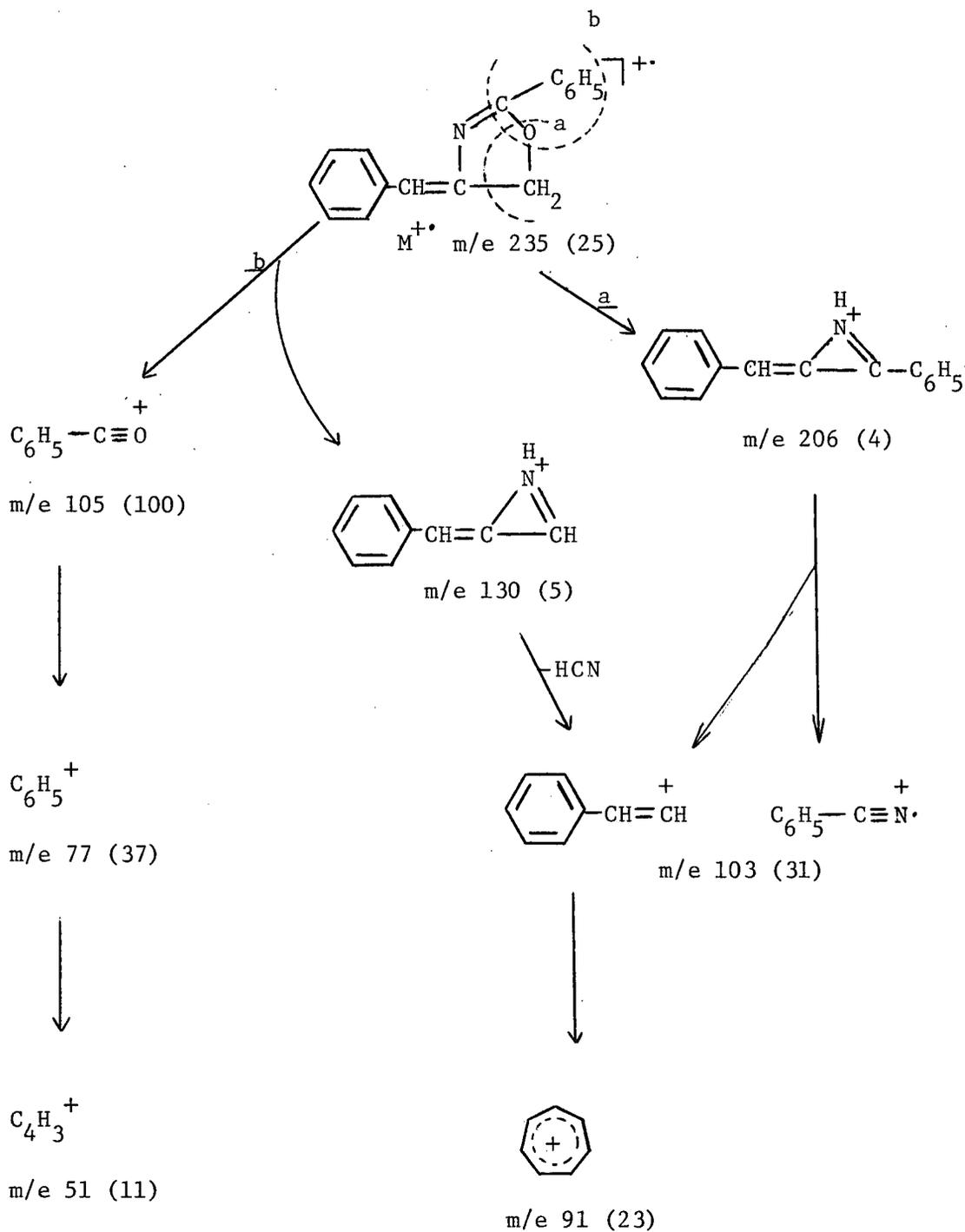
The uv absorption of the major component showed three absorption maxima at 201 nm ($\epsilon 2.4 \times 10^4$), 214 ($\epsilon 1.9 \times 10^4$), and 344 ($\epsilon 1.6 \times 10^4$) (Fig.5). Ethanol was used as a solvent. Absorption at 344 nm indicated the presence of extensive conjugated double bonds. According to the absorption data on oxazole derivatives (134), highly conjugated 2,4,5-triphenyloxazole (79) showed absorption at 306 nm, whereas 2,4-diphenyloxazole (80) and 2,5-diphenyloxazole (81) showed absorption at 280 and 275 nm respectively.



Considering these oxazole examples and the fact that compound 78 is more extensively conjugated than isomer 75, the uv data was considered to favor structure 78.

Mass spectrum data showed a and b fission of the ring (Scheme 11). Molecular ion was observed at m/e 235. Base peak was m/e 105.

Scheme 11. Proposed Fragmentation Pattern of 2-Phenyl-4-benzylidene-2-oxazoline (78) in the Mass Spectrum.



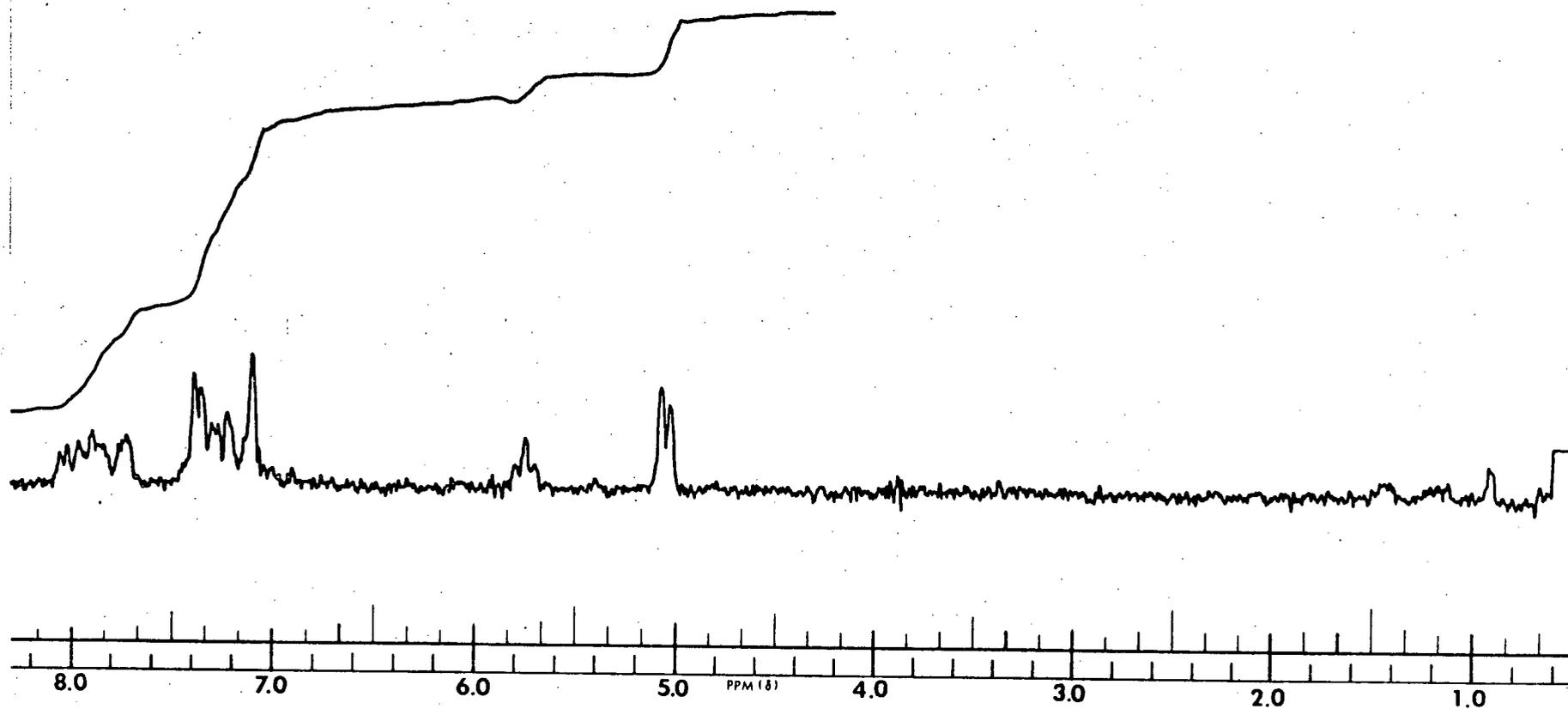
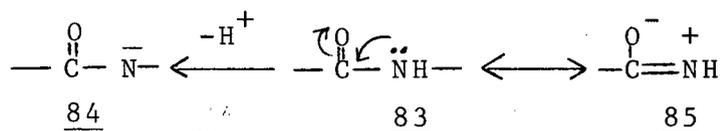


Fig. 6 Nmr spectrum of 2-Phenyl-4-benzylidene-2-oxazoline (78).

The molecular structure for 78 with the configuration shown in Fig. 3 was constructed to fit the observed nmr data (Fig.6). The proton a is equidistant to the equivalent protons B of the ring. The peaks observed were a doublet at $5.05\delta(H_a)$ and a triplet at $5.73\delta(H_b)$ with the long range coupling constant being 3 Hz. The low field bands for the aromatic protons are not as easily explained but were given the following interpretation. After subtracting the contribution of solvent ($CHCl_3$) from the band at $7.10-7.40\delta$, the band centered at 7.20δ represents 6 protons while the band centered at 7.80δ represents 4 protons. The lower field band at 7.8δ was assigned to the c,d,e, and f protons, the deshielding of these ortho aromatic protons occurring because of the paramagnetic influence of nitrogen and oxygen atoms in the ring.

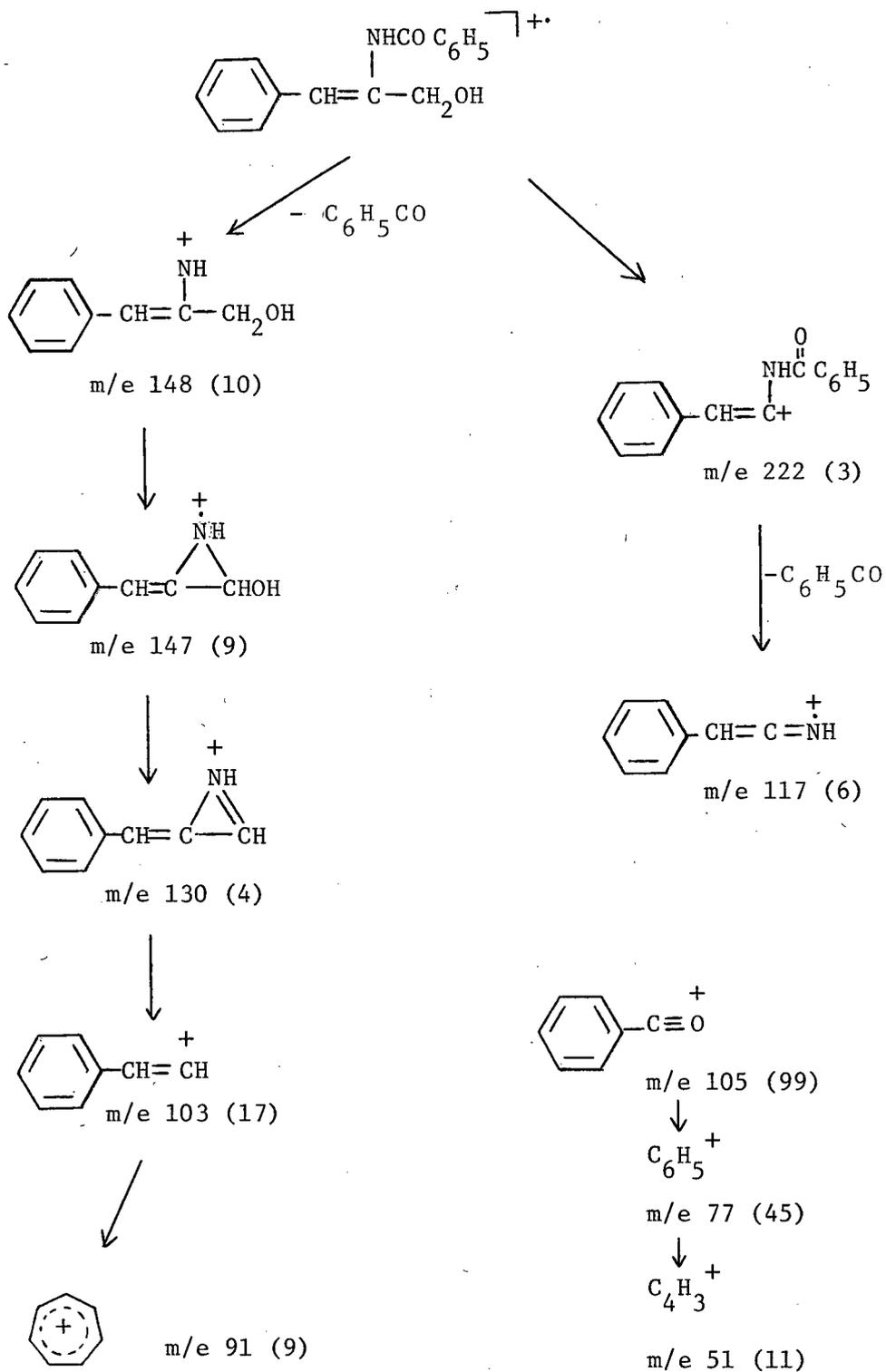
In addition to the major compound 78, the compound with $R_f=O$ was isolated as a small amount of solid. Amide bands (amide I, 1650 cm^{-1} , amide II, 1540 cm^{-1}), $-CH=$ (1420 cm^{-1}), and primary OH (1050 cm^{-1}) were observed in the ir spectrum. A proposed structure 82 was supported by mass spectral data in which such ions as m/e 148 and m/e 222 were observed (Scheme 12).

The formation and isolation of the oxazoline 78 in this work is not without precedent. Amides (83) enter into reactions especially displacement reactions, because of their nucleophilic

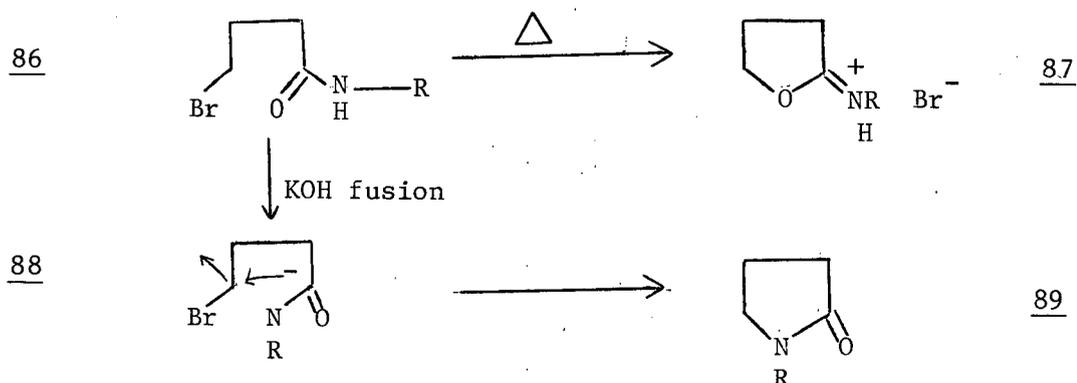


character. Displacement by amide groups can occur either through the intermediate 85 or under strongly basic conditions, through the amide anion 84 (135). This is illustrated by the following set of reactions. Under strongly

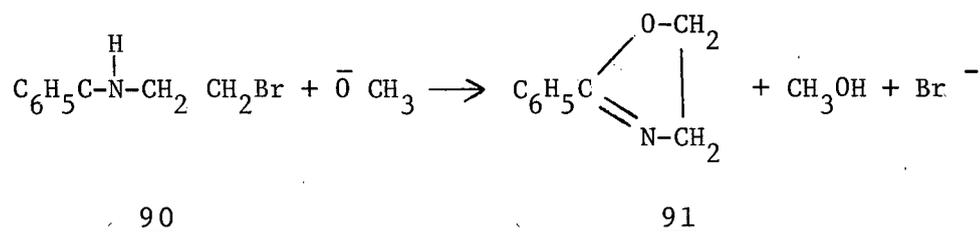
Scheme 12. Proposed Fragmentation Pattern of 1-Phenyl-2-benzoylamino-1-propene-ol (82) in the Mass Spectrum.



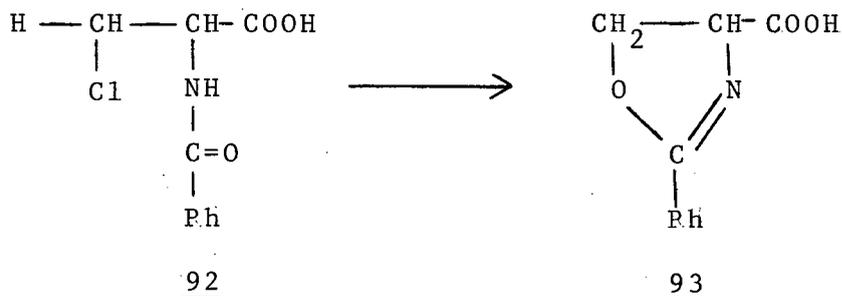
alkaline conditions the γ -bromobutylamine (86) forms the pyrrolidone 89 via the amide anion. Heating or ethanolysis



of 86 gives the iminovalerolactone hydrobromide (87) via the intermediate 85. The formation of the oxazoline 91 by molecular substitution from the reaction of N-2-bromoethylbenzamide (90) with methoxide ion has been published (137). A similar reaction is illustrated by the conversion of α -benzoylamino- β -



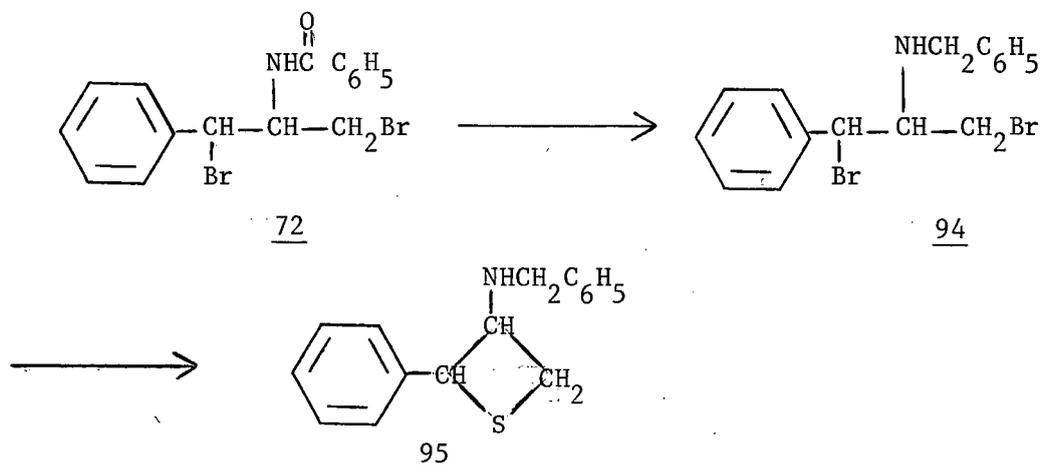
chloropropionic acid (92) to 2-phenyl-4-carboxy oxazoline (93) in approximately 50 % yield in sodium bicarbonate solution (138).



It appears therefore that in this work the reaction of the 1,3-dibromobenzamido compound (72) with the mildly alkaline sodium sulfide favors formation of the oxazoline 78 via an intermolecular substitution reaction. The preferential formation of the structural isomer 78 and the isolation of the unsaturated compound 82 would indicate that elimination of the 1-bromo group occurs prior to ring formation. One can not rule out a thietane structure as a possible intermediate to the oxazoline (78), but the absence of appreciable amounts of any organic sulfur compound in the reaction products makes this unlikely.

(4) 3-Benzylamino-2-phenylthietane (95)

The reduction of the amide carbonyl group of 72 was attempted to remove the possibility of oxazoline formation due to the amide group. The end product would then be the benzylaminothietane 95. A number of methods have been published



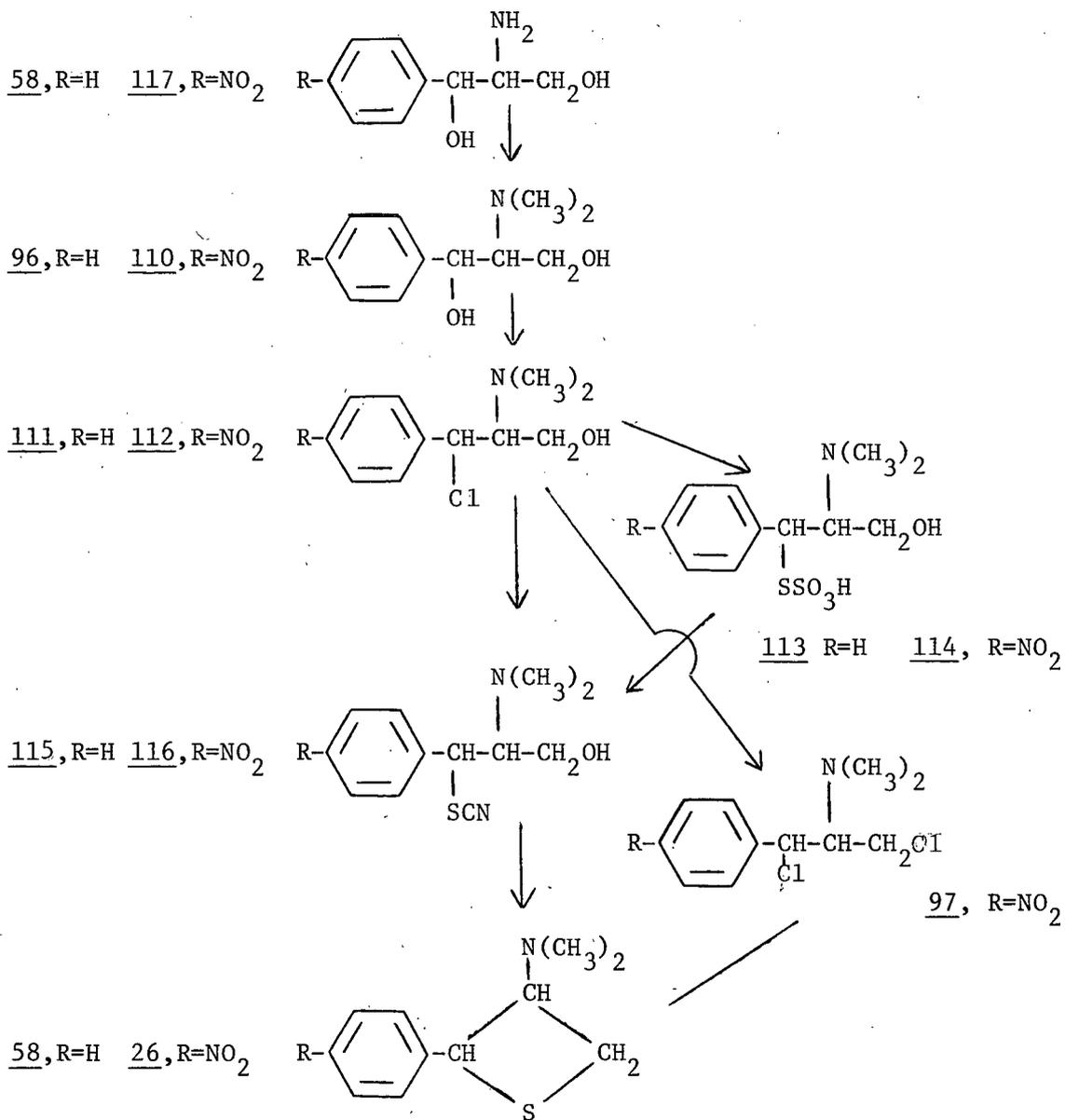
on the reduction of the amide functional group. Methods using sodium acyloxyborohydride (139) and sodium borohydride (140) are examples. Alkaline conditions and any reducing agents causing hydrogenolysis of the carbon-halogen bonds, however, could not be applied in this procedure. Diborane has been successfully utilized for the reduction of halogen-substituted amide derivatives to the corresponding halogen-substituted amines (141,142,143,144).

Diborane was generated externally by the method of Zweifel and Brown (145). After reaction, excess diborane and diborane adduct were destroyed by adding absolute ethanol. Hydrogen chloride solution was avoided to prevent the addition of any possible water which might cause hydrolysis or rearrangement. Dry hydrogen chloride gas was used since it was felt that the reduction product **94** should be isolated as the hydrochloride salt to avoid possible formation of an aziridinium compound. Work up gave a residue. The ir showed a strong ketone band which might have resulted from rearrangement of the starting material under the acidic conditions. The end result implied that amide **72** is reluctant to reduction under the conditions employed. Further attempts at the reduction of **72** were not performed.

4. Synthetic approach to 3-N,N-dimethylamino-2-phenylthietane (24) and 3-N,N-dimethylamino-2-p-nitrophenylthietane (26).

A further consideration of Scheme 4 suggested that thietane synthesis may be possible by this route if the amino group of phenylserinol was replaced by a dimethylamino group. This stemmed from the fact that the formation of thiazoline which was encountered in the case of primary amine would be avoided by using a tertiary amine group (Scheme 13). Reductive alkylation with formaldehyde and formic acid derivatives (Clarke-Eschweiler method) has proved to be a useful method for the preparation of methylated amines. According to a report (147) which described the application of the Clarke-Eschweiler method to the synthesis of N,N-dimethylephedrine, formaldehyde, formic acid, and sodium formate (1:1:1) gave high yields. The marked reduction of carbonyl side product by the addition of sodium formate was considered to presumably occur through enhancement of the reduction step of the methylation sequence (148).

Scheme 13: Proposed synthetic scheme to 3-N,N-dimethylamino-2-phenylthietane (24) and 3-N,N-dimethylamino-2-p-nitrophenylthietane (26).



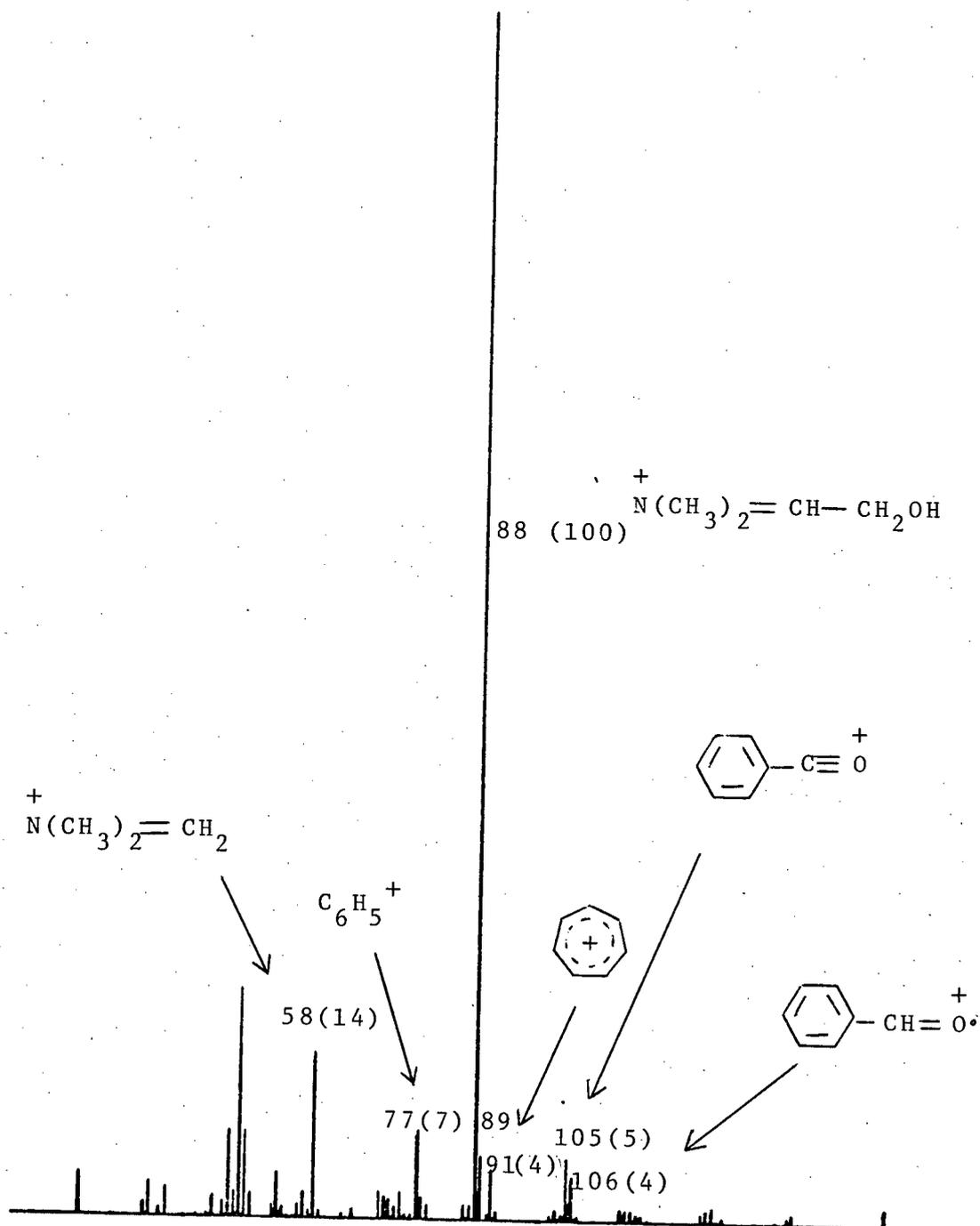
A. N,N-Dimethylphenylserinol (96).

N,N-dimethylphenylserinol was prepared using the Clarke-Eschweiler method. Sodium formate was not required to achieve a high yield. N,N-dimethylphenylserinol was easily soluble in chloroform, whereas phenylserinol was not. The nmr spectrum clearly showed dimethyl protons at 2.5δ . The benzylic proton appeared at 4.37δ indicative of the threo configuration. As already mentioned (114), threo phenylserinol showed the benzylic proton at 4.86δ , the erythro at 5.14δ . Similarly, the value 4.67δ was assigned to the benzylic proton of threo-2-amino-1-phenyl-1-propanol while the erythro compound showed the benzylic proton at 5.20δ . In the mass spectrum of N,N-dimethylphenylserinol (Fig.7), the molecular ion (m/e 195) was present and the base peak at m/e 88 was attributed to the fragment $(\text{CH}_3)_2\overset{+}{\text{N}}=\text{CH}-\text{CH}_2\text{OH}$. A second large peak occurred at m/e 58 $(\text{CH}_3)_2\overset{+}{\text{N}}=\text{CH}_2$ which is diagnostic for dimethylamino alcohols (149). Otherwise, the spectrum was very similar to that for phenylserinol.

B. Synthetic approach to 1-phenyl-1-chloro-2-dimethylamino-propane-3-ol(110).

The hydrochloride salt of 96 was treated with thionyl chloride in order to obtain the C-1 monochloro compound (112). Unidentifiable gummy material was isolated. It was considered that the gummy material may be due to existing impurities resulting from oxidation of the amino group by thionyl chloride.

Fig. 7 Mass Spectrum of N,N-Dimethylphenylserinol (96).



Hence, another chlorination method was used. Tertiary alcohols such as t-butyl alcohol easily react with concentrated hydrochloric acid to give chloro products. Secondary alcohols such as α -phenylethylalcohol give α -chloro ethylbenzene with aqueous hydrochloric acid (150). Rachlin and Enemark (118) prepared 1-(3,4-dihydroxyphenyl)-1-chloro ethylamine by passing dry hydrogen chloride into the suspension of norepinephrine in dry dioxane. They found that this method gave a rather pure product compared to that prepared by thionyl chloride. When N,N-dimethylphenylserinol (96) was treated with concentrated hydrochloric acid or dry hydrogen chloride gas in dry dioxane or dry ether, the result was the same gummy material. Further attempts at purification of this material for identification were unsuccessful. Reactions with potassium thiocyanate or sodium thiosulfate using the gummy material resulted in unidentifiable products.

C. 1-p-Nitrophenyl-1,3-dichloro-2-N,N-dimethylaminopropane (97).

Because of the tedious and difficult process of preparing the dimethylamino phenylserinol (58), attention was turned to p-nitrophenylserinol (117) as a starting material. p-Nitrophenylserinol is an intermediate in chloramphenicol synthesis and was obtained from a pharmaceutical firm. The D(-) threo form was assigned to the p-nitrophenylserinol from melting point and ir spectrum data. Melting points of D(-) and L(+) threo forms are 164° , whereas those of DL-threo and

DL-erythro are $141.5-142.5^{\circ}$ and $107-9^{\circ}$ respectively (112,151). This is a case where the racemic compound has a crystal structure quite different from those of the pure enantiomers and therefore differs in melting point and solubility. p-Nitro-N,N-dimethylphenylserinol (110) was prepared by the same method as for N,N-dimethylphenylserinol (96). Elemental analysis showed consistent values with theory. In the spectrum of 110, a doublet for the benzylic proton at 4.5δ indicated the threo form. The two hydroxyl protons centered at 3.1δ disappeared upon adding D_2O . Two phenyl protons ortho to the nitro group appeared at 8.07δ , while the two meta phenyl protons appeared at 7.47δ . Six protons at 2.5δ were assigned to N-methyl protons. Integration showed partial overlap of the methine proton with N-dimethyl protons. The mass data was in agreement with the required structure; m/e 88 $((CH_3)_2\overset{+}{N}=CH-CH_2OH)$ was the base peak, m/e 58 $((CH_3)_2\overset{+}{N}=CH_2)$ was next most intensive, m/e 209 $(NO_2C_6H_4CH(OH)-CH=N(CH_3)_2)$ was observed as was m/e 181 $(NO_2C_6H_4\overset{+}{C}H(OH)CH=NH_2)$ as shown in the case of p-nitrophenylserinol.

In the case of chlorination of threo-D(-)-p-nitro-N,N-dimethylphenylserinol, possible effects on the optical purity by thionyl chloride was considered. This consideration is based on the fact that partial racemization would lead to difficulty in separation and identification of the compound. A method using $DMF-SOCl_2$ to obtain optically pure products was published (152,153,154). p-Nitro-N,N-dimethylphenylserinol

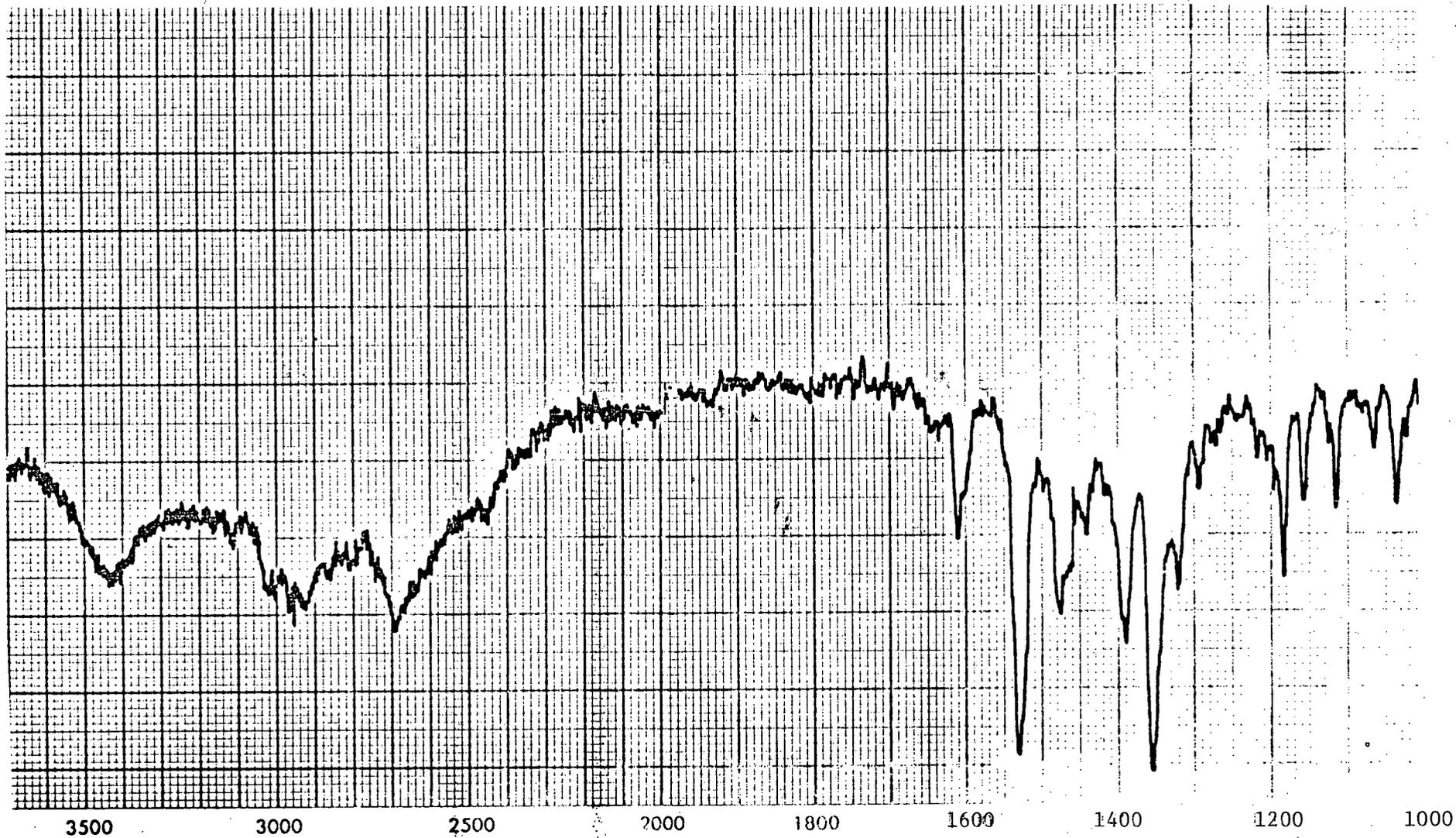
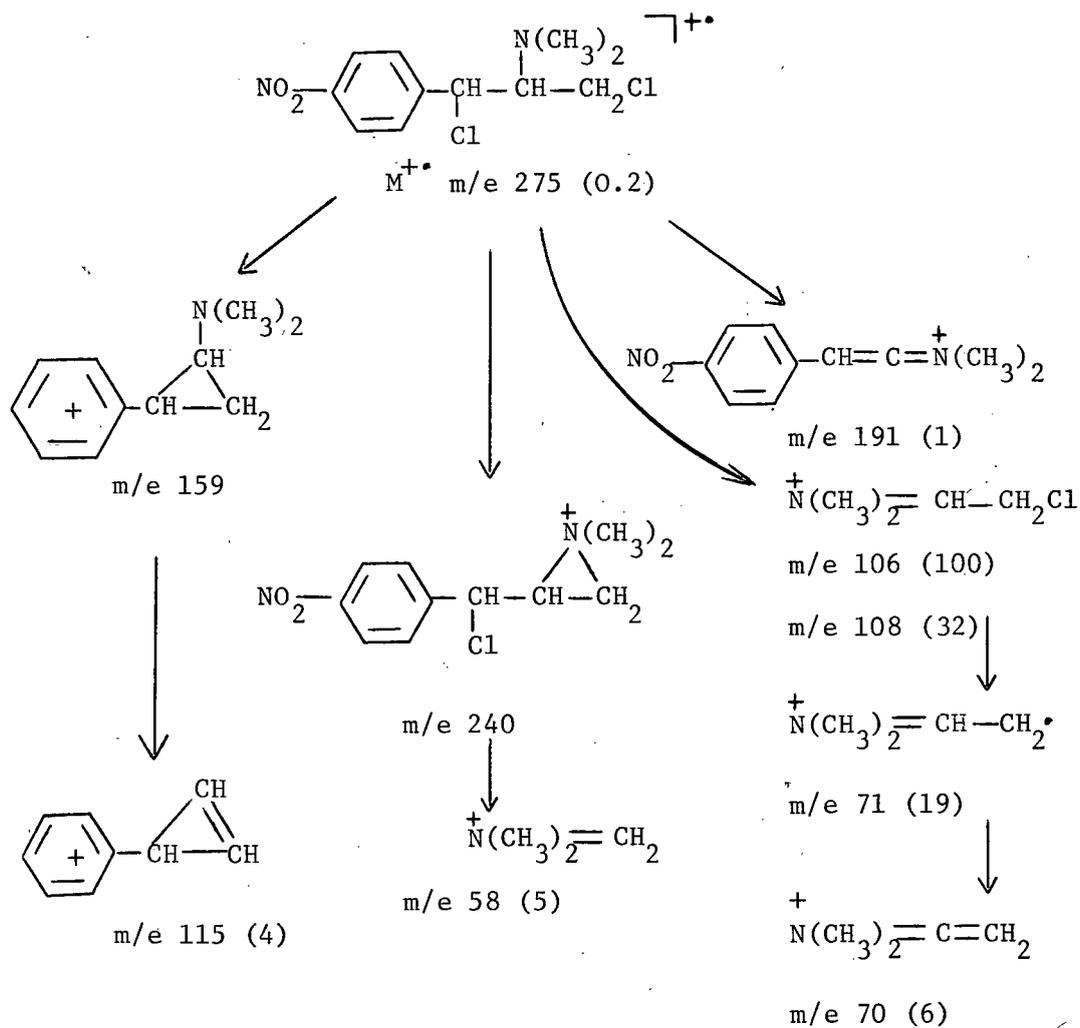


Fig. 8 Ir spectrum of 1-p-Nitrophenyl-1,3-dichloro-2-N,N-dimethylaminopropane (97).

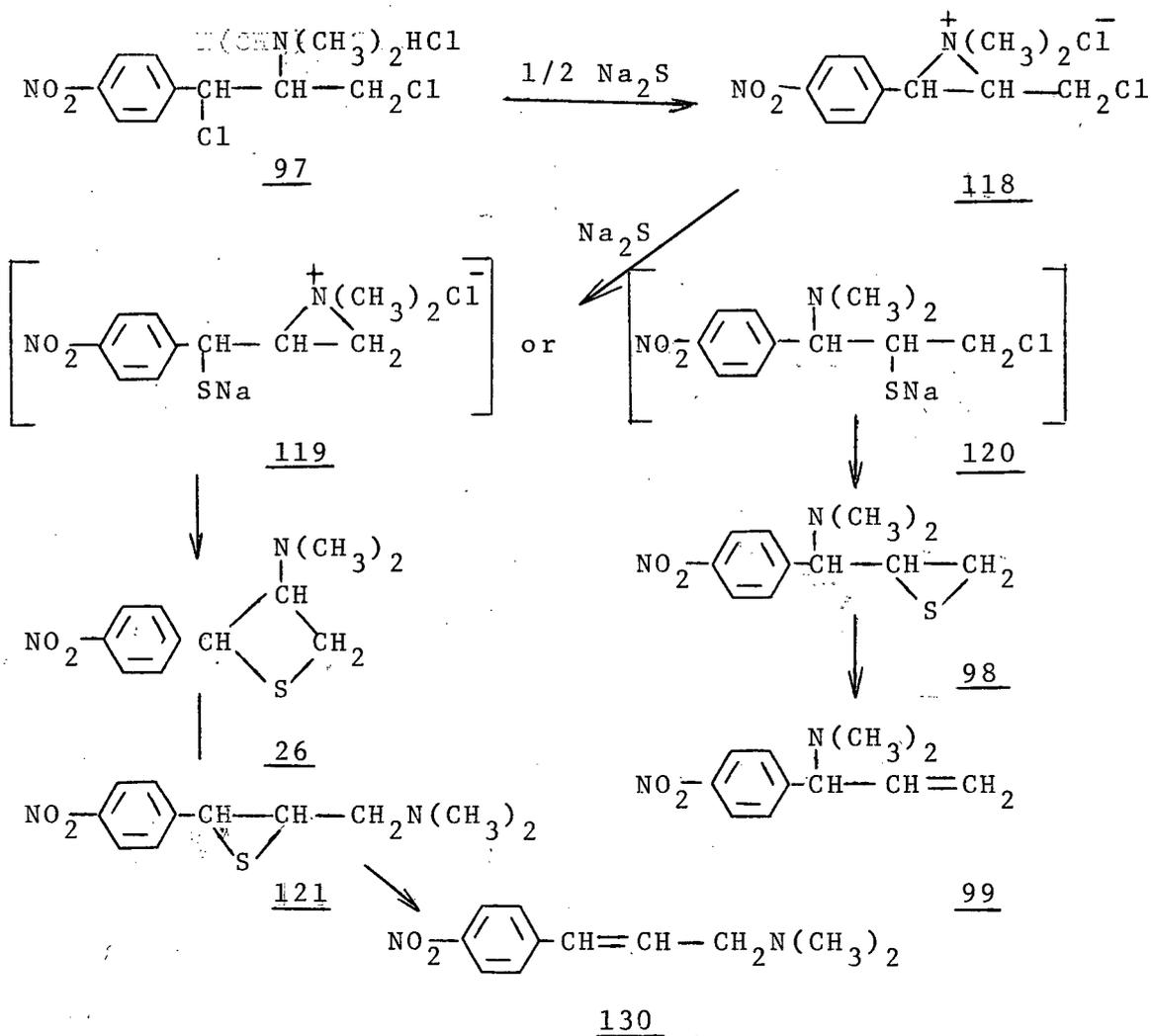
Scheme 13. Proposed Fragmentation Pattern of 1-p-Nitrophenyl-1,3-dichloro-2-N,N-dimethylamino propane (97) in the Mass Spectrum.



(110) was treated with an excess amount of DMF-SOCl₂ reagent and heated for one hour. Work up gave a crystalline product. Chlorination using thionyl chloride was also performed to find out any differences in the products formed or the separation problems encountered. It was found that the ir spectra of the two products isolated from each chlorination reaction were superimposable with each other. Therefore, further preparations of 1-p-nitrophenyl-1,3-dichloro-2-N,N-dimethylaminopropane were made using thionyl chloride. Extensive purification was required to identify the structure. Elemental analysis was performed. Mass spectrum data were collected. Fragmentation patterns of the molecule showed clearly the 1,3-dichloro structure. This is based on the mass numbers such as m/e 106, 108 (N(CH₃)₂-CH-CH₂Cl) and m/e 191 (NO₂C₆H₄-CH=C=N(CH₃)₂) as shown in Scheme 13. Molecular ion was observed at m/e 275.

D. Reactions of 1-p-nitrophenyl-1,3-dichloro-2-N,N-dimethylaminopropane (97) with sodium sulfide.

The 1,3-dichloro compound (97) was treated with sodium sulfide. It was assumed that the reaction of 1,3-dichloro compound (97) and sodium sulfide would lead to the following reaction sequences. Aziridinium salt formation would give two nucleophilic attacking positions at C-1 and C-2 of 118 resulting in the possible end products, 26, 121 or 98. Under alkaline conditions, 98 and 121 would probably form 99 and 130 respectively.



To 1 mol of 1,3-dichloro compound, 2.25 mol (50 % excess) of sodium sulfide was added. After refluxing the reaction mixture for 1 hour, the solution was filtered to give a filter cake which was triturated with H₂O. A brown colored, chloroform soluble compound was obtained. The same compound was obtained from the reaction at room temperature for 3 hours. Melting point was broad (60-110). Attempts to purify the product by recrystallization were not successful. A CHCl₃ solution of the compound was treated with dry HCl gas saturated CHCl₃ to obtain a hydrochloride salt. Dark black-colored material resistant to further purification was precipitated out.

Purification by forming picrate salt was performed. Although picrate could be isolated and recrystallized, the melting point was not consistent, ranging 75-110^o depending upon the depth of coloration. Separation by column chromatography was not successful. Alkali-fusion tests revealed the presence of sulfur.

The nmr (Fig.9) showed a multiplet pattern and a decrease in the ratio of dimethylamino protons to phenyl protons. The ratio was around 4 : 4 while in the case of both the starting material, 97 and the thietane, 26, the ratio is 6 : 4. Possible elimination of the dimethylamino group during the reaction was further supported by the presence of protons at 6.40 δ . An olefinic proton is usually assigned at this range. To confirm this finding, gc-mass spectrometry was performed. The major fractions were observed at retention times, 8.9 (A) and 11.3 minutes (B). The compound A contained the dimethylamino group as indicated by strong m/e 58 fragment. Fragment 58 was not present in the mass spectrum of compound B. Major fragmentation for A agrees with a proposed fragmentation pattern for 2-p-nitrophenyl-3-N,N-dimethylamino-thietane (Scheme 14). However, since mass data alone would not give an absolute determination of the structure, further attempts at the synthesis with the elaboration of reaction conditions to obtain a compound in purified form still remained.

A rational explanation of the fragmentation pattern of B was not successful. To elucidate whether this elimination of the dimethylamino group is due to simple base-catalyzed

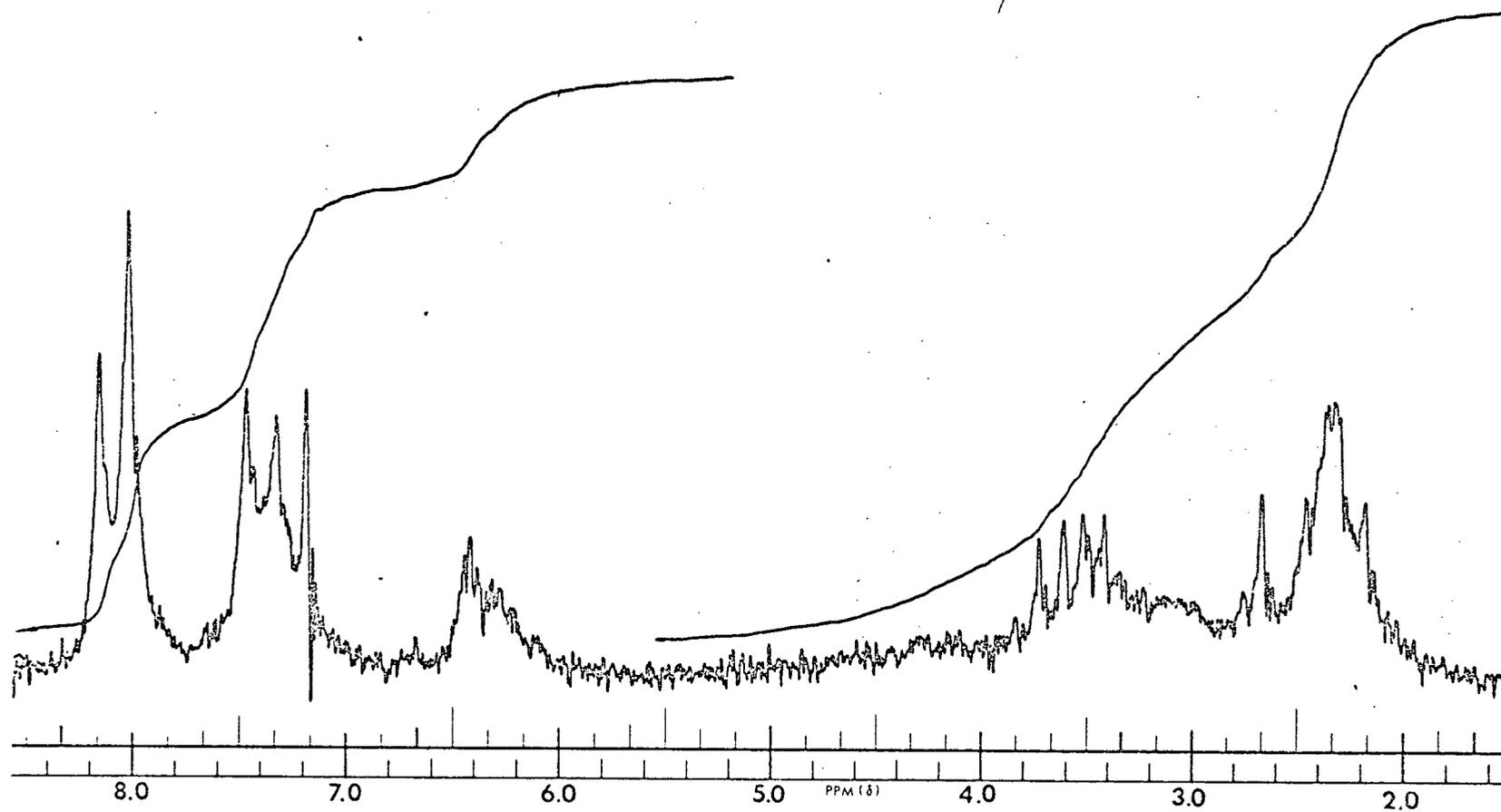
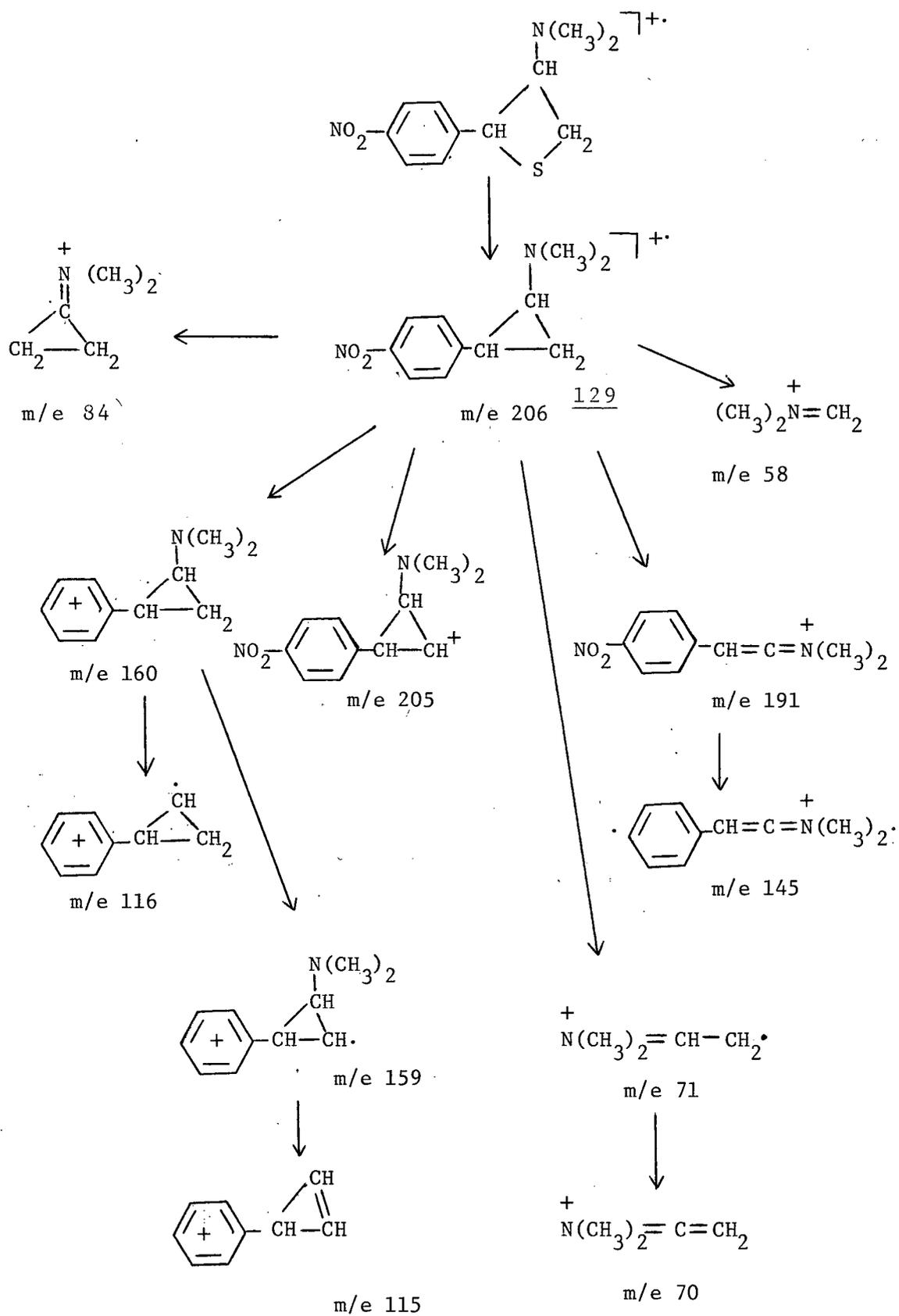


Fig. 9 Nmr spectrum of the products from the reaction of 1-p-nitrophenyl-1,3-dichloro-2-N,N-dimethylaminopropane (97, 1 mol) with sodium sulfide (2.25 mol).

Scheme 14. Proposed Fragmentation Pattern of 3-N,N-dimethylamino-2-p-nitrophenylthietane (26) in the Mass Spectrum.



reaction or a sodium sulfide-participation reaction, the 1,3-dichloro compound was treated with NaOH. No precipitate was formed except NaCl, which implies that sodium sulfide plays a role in this elimination of the dimethylamino group. Further experiments to explain this elimination reaction were not performed.

A filtered solution of the reaction mixture was evaporated and extracted with chloroform. A dark residue was obtained after distilling off the solvent. Gc-mass spectrometry showed at least 6 compounds. The largest gc peak, retention time 9.3 minutes showed similar mass fragmentation to those of compound A. This could be explained by the fact that some portion of compound A is soluble in ethanol and was retained in the reaction solvent. Attempts to isolate each compound were not performed.

An earlier assumption made was that the side products resulting from the elimination of the dimethylamine group may be due to the alkaline condition of the reaction mixture and probably from the excess amount of sodium sulfide present. To determine the effects of the concentration of sodium sulfide, a reaction was performed using 1 mol of sodium sulfide to 1 mol of dichloro compound (97). A solid was precipitated out when the reaction mixture was at neutral pH. Trituration of the solid with water gave a CHCl_3 -soluble yellow compound. Purification by recrystallization was not successful. An alkali-fusion test showed that sulfur was positive, which implied that the

precipitate resulted from Na_2S -participation in the reaction. This fact was further backed up by the observation that the reaction of 1 mol of dichloro compound with 2 mol of NaOH gave only a precipitate of NaCl.

The nmr spectrum (Fig.10) of the yellow material showed dimethyl protons at 2.37δ , 2 phenyl protons ortho to nitro group at 8.10δ , 2 phenyl protons meta to nitro group at 7.33δ , and 4 protons at $3.00-3.63\delta$.

The yellow compound was dissolved in ether and dry HCl gas was introduced. A white crystal was formed. After filtration, the filter cake was thoroughly washed with ether and recrystallized from EtOH-ether. The hydrochloride salt was so hygroscopic that a definite melting point was not obtained. However, drying at 50 at 0.1 mm for 5 hours gave a crystal showing a definite melting point.

Gc-mass spectrometry was performed on both the base and hydrochloride salt. The base contained at least 3 compounds. A major peak occurred at 9.3 minutes of retention time by gc and showed the same fragmentation pattern as that proposed in Scheme 14. The hydrochloride salt was relatively pure and gave the same fragmentation pattern and gc retention time as those obtained for the major gc peak of the free base.

The elemental analysis of the hydrochloride salt showed that the ratio of carbon, hydrogen, nitrogen, and sulfur is 22 : 32 : 4 : 1. This ratio strongly suggested the formation of a dimer. A rational explanation for the formation of the dimer was attempted.(Scheme 15).

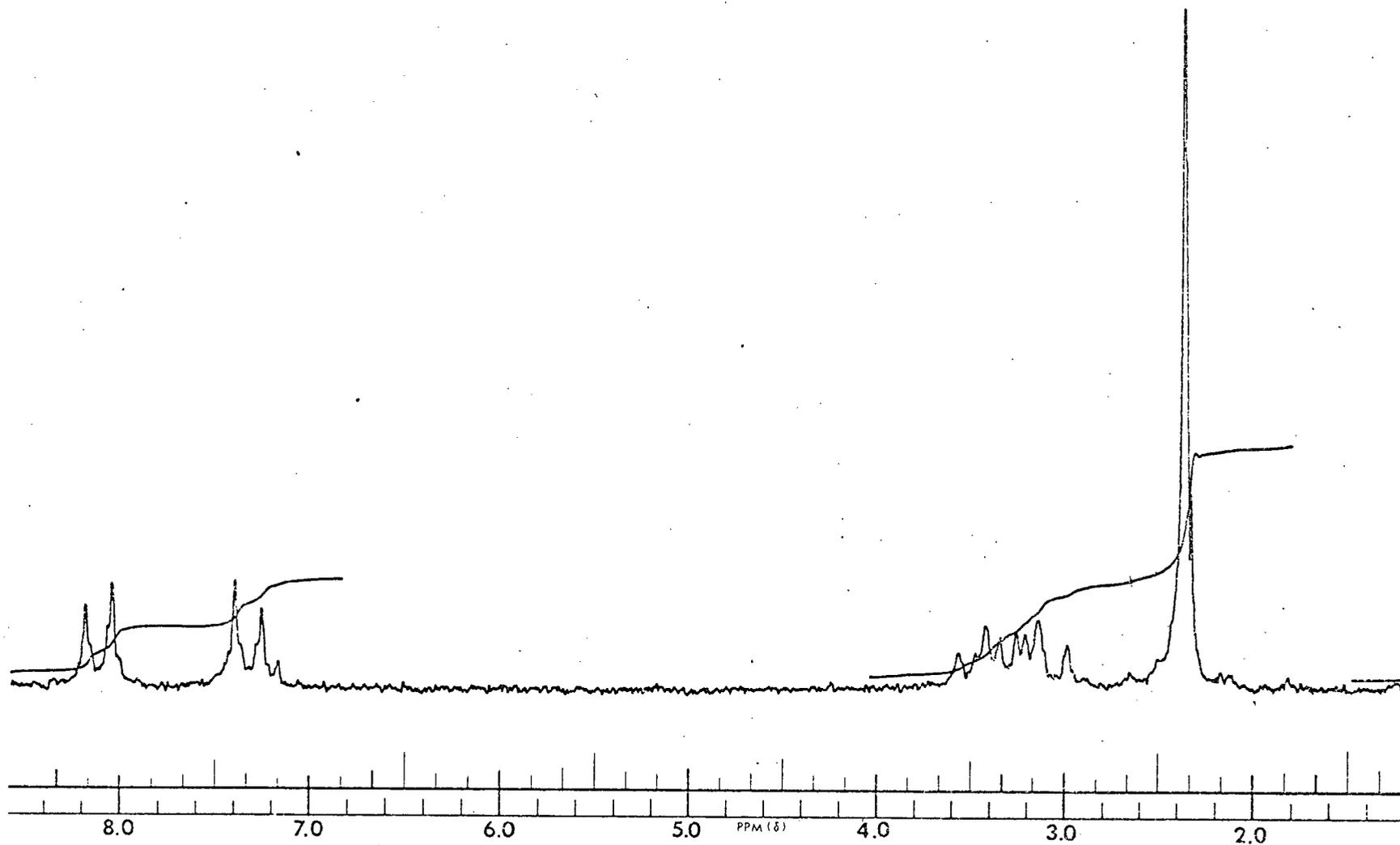
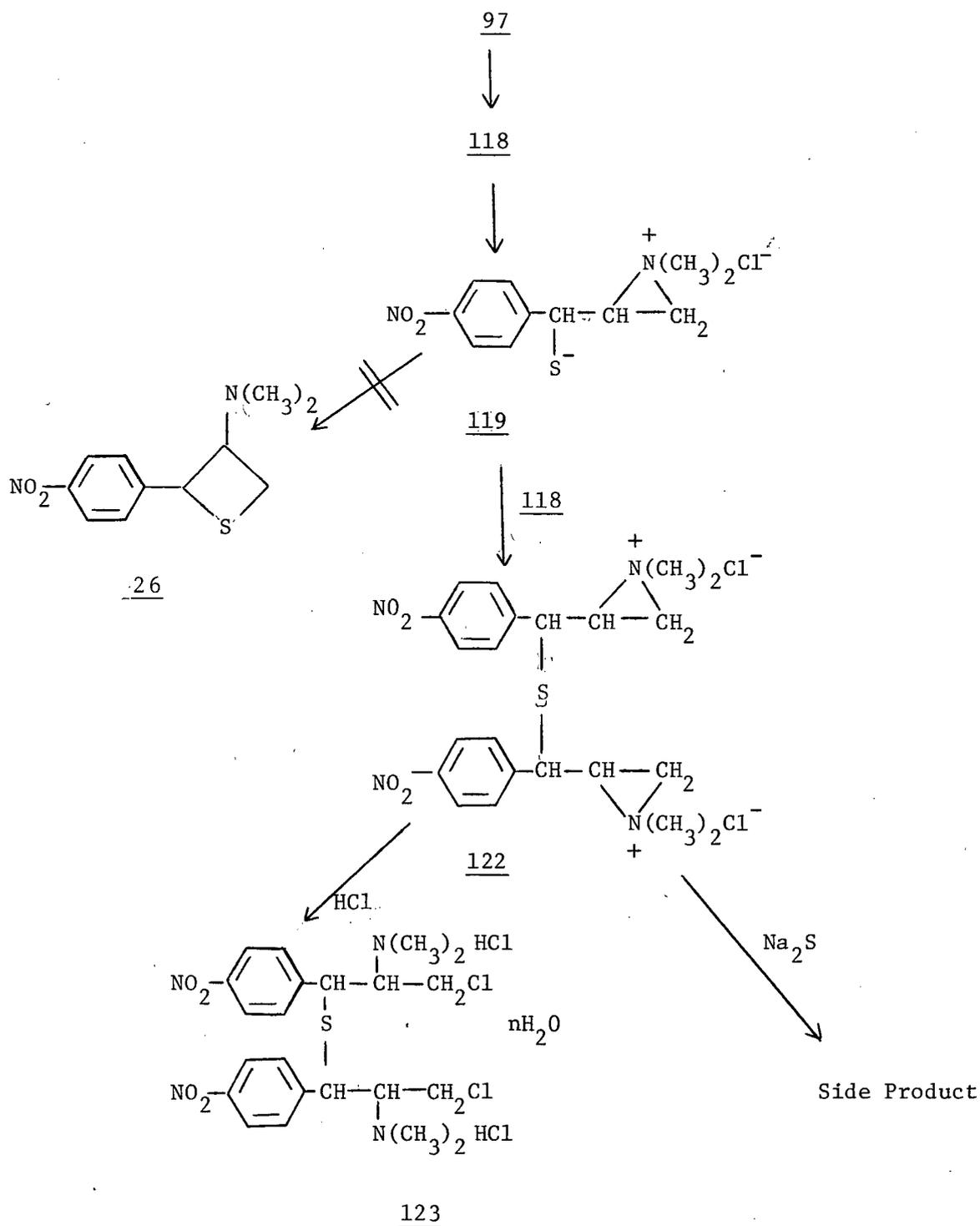


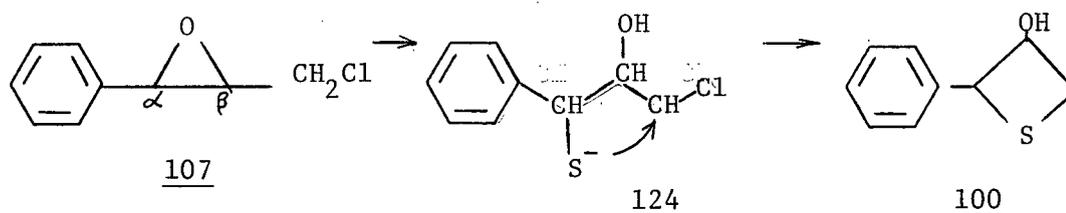
Fig. 10 Nmr spectrum of bis (1-p-nitrophenyl-2-N,N-dimethylamino-3-chloropropane) sulfide (122).

Scheme 15. Proposed Mechanism for the Reaction of 1-p-Nitrophenyl-1,3-dichloro-2-N,N-dimethylamino-propane with Sodium Sulfide.



Evidence supporting structure 122 as the base and structure 123 as the hydrochloride salt was collected. The assignment of the protons of the base was consistent with the nmr spectrum as shown in Fig. 10. The mass fragmentation pattern of 122 and 123 would be the same as the one proposed in Scheme 14 since 122 and 123 would give 129 as a initial fragmentation product. This result implies that the compound A from treatment of 97 with an excess amount of sodium sulfide is the same compound as the base (122) as a comparison of gc retention time shows. The mass spectrum of the hydrochloride salt obtained by direct probe showed fragmentations at m/e 106 and 108 with the intensity ratio, 3 : 1 (Cl isotope ratio), which implied the presence of $N(CH_3)_2=CH-CH_2Cl$ resulting from structure 123. The data from the elemental analysis was direct evidence supporting the structure 123.

Formation of 118 from 97 could be easily explained by the ease of nucleophilic attack at C-1 carbon because of the p-nitro function on the phenyl group. As shown in a report



(83), exclusive formation of 100 is due to the favorable attack of sulfhydryl ion at the α -carbon of 107. By analogy, sulfhydryl anion would favor attack at the C-1 carbon of 118 to give 119 rather than 120 or 121. Besides this, the p-

nitrophenyl group could also contribute to the exclusive formation of 119 by favoring nucleophilic attack at the benzylic carbon atom. One can use similar argument to support the formation of the dimer (122). The formation of dimer indicated that nucleophilic attack of the sulfhydryl anion of 119 on a second molecule of 118 is highly favored over the intramolecular cyclization reaction to form the thietane. To determine any effect of the concentration of 118 relative to sodium sulfide, 97 was added to an excess amount of sodium sulfide. A yellow colored-material isolated was the same compound as obtained when sodium sulfide was added dropwise to a solution of 97.

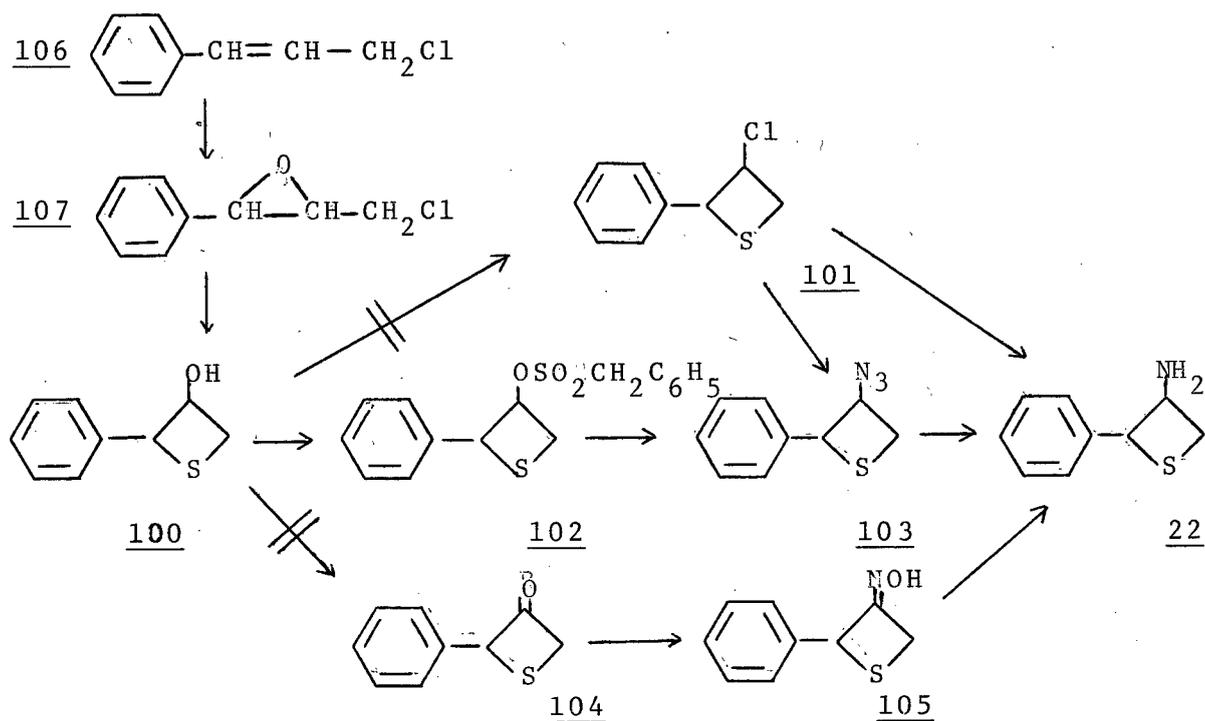
These results suggest that the reaction of sodium sulfide with 1,3-dichloro compound would not be an effective method for the synthesis of 3-amino-2-phenylthietane derivatives.

The reaction of sodium sulfide with 1,3-dichloro compounds which do not contain 2-amino group has been successfully applied to synthesize the intermediates for lipoic acid (155, 156) and the 3-chloromethyl-3-hydroxymethylthietane (157).

5. Synthetic approach to 3-amino-2-phenylthietane (22) from 3-hydroxy-2-phenylthietane (100).

Modification of a hydroxyl group of 3-hydroxy-2-phenylthietane to synthesize 3-amino-2-phenylthietane as shown in Scheme 16 was published (83). The attempts at chlorination or oxidation of the hydroxyl group of 100 were not successful.

Scheme 16. Proposed synthetic routes of 3-amino-2-phenylthietane (22)



Some evidence was given which suggested a successful synthesis of benzenesulfonate (102) and azide (103) but these structures were not confirmed. A plan was made to isolate the benzenesulfonate (102) and azide (103) which would give confirming evidence of a successful synthesis of these compounds. Oxidation of a hydroxyl group of 100 was also performed using a newly established method (162).

Thietane (100) was synthesized from 107 with a modification of the preparation method for the epoxide 107. Instead of monoperphthalic acid, *m*-chloroperbenzoic acid was used which resulted in a better yield of 107. The ir and melting point of

100 were consistent with the reported values (83). Assignments of phenyl protons, methine protons, and methylene protons were the same as those reported (83). A hydroxy proton appeared at 2.98 δ which was exchanged with D₂O.

Modification to the chloro compound (101) was not attempted. No newly established methods for this reaction have been published in the last 2 years. It is certain that direct amination of 101 to 22 would not be favorable because of the propensity for side reactions such as β -elimination and ring fissions (159).

Almost all attempts to oxidize 100 to 104 were made by Haya (83). Oppenauer oxidation, Moffatt oxidation, and other methods using hydrogen abstractors were included in his attempts. Recently, several reports have been published on the oxidation of primary or secondary alcohols. However, most of them describe slight modifications of the Moffatt oxidation. Rao and Filler (160) described the process of using a solution of sodium dichromate and sulfuric acid in DMSO to oxidize primary and secondary alcohols in high yield. It was found that in those oxidations DMSO acts as a solvent and not as a reactant. Omura et al. (161) proposed a DMSO-trifluoroacetic anhydride as a new reagent for oxidation of alcohols. Albright (162) found that cyanuric chloride with DMSO in hexamethylphosphoramide at -20^o oxidize primary and

secondary alcohols in high yield. By applying Moffatt oxidation with DMSO and DCC in the presence of a sulfuric acid (163) or with DMSO acetic anhydride (164), Haya only isolated dark residues which do not show ketone bands in the ir spectrum. In this experiment, application of the method of Albright did not give a positive identification for ketone formation.

The reaction of 100 with benzylsulfonylchloride was performed. Benzylsulfonylchloride which was prepared from benzylchloride using a known method (165) was used. The ir spectrum of the crude product obtained by work up showed 1185 and 1365 cm^{-1} bands as mentioned by Haya. Contrary to his findings that the residue was not soluble in common solvents, the residue was found to be soluble in chloroform. Since the ir spectrum did not appear to give confirmation of formation of a sulfonate ester in the reaction mixture, purification of the residue using column chromatography was performed. Some question was raised as to the stability of the possible sulfonate ester product (102) while on the column. However, column chromatographic techniques for the purification of sulfonates synthesized for use as leaving groups have been widely used (166,167,168). The reaction mixture product did not appear to be unstable.

Tlc showed 4 spots at R_f s A (0), B (0.1), C (0.25), and D (0.8). The reaction mixture was partitioned between chloroform and water. The chloroform layer after reducing in volume was added to a column of silica gel and eluted using the same

solvents as used for tlc. The major component was D while B and C were isolated as gummy materials. B was similar to unreacted 3-hydroxy-2-phenylthietane by ir and R_f values but determination of C was unsuccessful. A was a precipitate having a melting point over 200° and was assumed to be a salt. Absence of a band at 1370 cm^{-1} in the ir spectrum ruled out the possibility of a sulfonate. D was positively identified as unreacted benzylsulfonylchloride by tlc, ir, and melting point. This result strongly suggests that the reaction did not proceed under the conditions used to form the sulfonate (102) although some precipitate of triethylamine hydrochloride was formed.

To confirm this finding, the residue from the reaction of 3-hydroxyphenylthietane and benzylsulfonylchloride was directly treated with sodium azide in hexamethylphosphoramide. Work up gave a residue, which showed three spots by tlc. The residue gave a strong azide band at 2110 cm^{-1} in the ir spectrum. This band, however, would not necessarily be an indication of the formation of 3-azido-2-phenylthietane (103) since even small contamination with an azide impurity could cause a strong band in the ir spectrum. Although azides are unstable and potentially hazardous (169), the isolation of azide products has been described. Reckendork (170) isolated azide components having an amino sugar structure by column chromatography using alumina. Alumina was also used to isolate cholesteryl azide (171) and silica gel chromatography was applied

to isolate an azide compound of a cephalosporin intermediate (172). The reaction mixture from the reaction of cholesteryl 3 β -p-toluenesulfonate with azide ion was separated by chromatographic techniques using florisil (173). Therefore, it appeared worthy to isolate the azide to obtain positive evidence of the reaction. The residue was dissolved in a small amount of chloroform and fractionated on a florisil column using n-hexane. One major compound A with R_f 0.8 by tlc was isolated. Elution of the column with ether gave two fractions, B of R_f 0.4-0.7 (tailing) and C showing a baseline spot by tlc. Elution with methanol gave D which showed a baseline spot by tlc. Initially an azide band was observed in the ir spectrum of A, which disappeared after recrystallization. A was benzylsulfonylchloride. B and C were isolated as unidentified small amounts of dark residues. The ir spectrum of D showed bands at 650 cm^{-1} and 3390 cm^{-1} indicative of a sulfonic acid but confirming identification was not successful.

Haya reported that the hydroxyl group of 100 was resistant to alkylation using methods such as triethyloxonium tetrafluoroborate, Na-EtBr, and p-toluenesulfonylchloride. Two experimental results performed also revealed that the sulfonate (102) might not be formed by the reaction of 3-hydroxy-2-phenylthietane with benzylsulfonylchloride. A suggestion could be made that the use of appropriate selective leaving groups and reaction conditions would be necessary to confirm these findings.

Since unsuccessful formation of sulfonate (102) or azide (103) appeared clear, further reduction of the reaction mixture was not performed. It is well known that azides can be reduced to amines by reductive methods such as catalytic hydrogenation (174), LiAlH_4 (169), and sodium borohydride (175). It would be of interest to use ammonium sulfide for the reduction of azido compounds of the thietane ring since this reagent is widely used in recent semisynthetic penicillin (176) and cephalosporin (172) chemistry.

ANALYTICAL METHODS

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

A Beckman IR-10 Infrared Spectrophotometer was used to record all infrared spectra.

60 MHz nmr spectra were determined at the Department of Chemistry, U.B.C., using a Varian T-60 NMR Spectrometer.

100 MHz nmr spectra were determined at the Fisheries Research Laboratory, Vancouver, Canada, using Varian HA-100 NMR Spectrometer. Peak multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), b (broad), and m (multiplet).

Ultraviolet spectra were obtained using Beckman Model 25 Spectrophotometer.

Mass spectra and gc/mass spectral data were obtained using a Varian MAT-111 mass spectrometer. The ionizing voltage was 80 ev unless specified.

Microanalyses were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium, 5251 Elbach Über Engelskirchen, Firtz-Pregle-Strasse 14-16, West Germany.

EXPERIMENTAL

1. Synthesis of threo-phenylserine ethylester (108)

The methods reported by Shaw and Fox (106,107) were adopted with minor modification. A solution of glycine (30 g, 0.4 mol) and NaOH (24.0 g, 0.6 mol) in 100 ml of H₂O was chilled to 15°. With cooling maintained at 15° on a water bath, and with rapid stirring, benzaldehyde (84.9 g, 0.8 mol) was added all at once. The emulsified reaction mixture changed to paste but further stirring gave dissolution. After 30 minutes, the reaction mixture became a light syrup which turned into a precipitate, followed by rapid and complete solidification. After 24 hours at room temperature, the condensation cake was fragmented and concentrated HCl (50.0 ml, ca. 0.6 mol) was added dropwise during 30 minutes with cooling on a water bath at 15°. Mechanical stirring was continued for one hour after addition of acid. The filter cakes obtained after acidification were thoroughly mixed with boiling EtOH (3x200 ml) and the resulting slurry was filtered each time. Alcohol washed product was recrystallized from H₂O and dried to give threo-phenylserine monohydrate (44.6 g, 56 %). mp 192-193° (lit. (158), 193-194°).

A vigorous stream of dry HCl gas was passed through a suspension of threo-phenylserine monohydrate (40 g, 0.2 mol) in absolute EtOH (250 ml). The solution was accompanied by evolution of sufficient heat to promote gentle refluxing.

The solution was concentrated to 100 ml. Addition of ether (300 ml.) and overnight storage in the cold gave threo-phenylserine ethylester hydrochloride (39.5 g, 80 %). mp 137-140° (lit. (106), 140°).

Dry ammonia was passed through a suspension of threo-phenylserine ethylester hydrochloride (35 g, 0.14 mol) in ether (500 ml) for 15 minutes. The granular ammonium chloride was filtered and washed with warm ether. Evaporation of the filtrate gave threo-phenylserine ethylester (27.8 g, 95 %). mp 79-80° (lit. (106), 82-83°) ir (KBr) 1740 cm^{-1} (carbonyl), 1040 (sec. OH), 1580 (NH_2).

2. Synthesis of threo-phenylserinol (58).

To an ice-cold solution of NaBH_4 (37.8 g, 1 mol) in 70 % EtOH (200 ml) was added dropwise a solution of phenylserine ethylester (35.5 g, 0.17 mol) in 70 % EtOH (100 ml). The mixture was stirred with ice cooling for 3 days. The extent of reaction was monitored by tlc (silica gel, iodine chamber, EtOH). R_f s of ester and phenylserinol were on 0.8 and 0.3 respectively. The reaction mixture was filtered and concentrated to a volume of 20 ml. The precipitate that deposited was filtered off and the filtrate was extracted with ether (300 ml) utilizing a continuous extraction apparatus. Drying the ether on anhydrous Na_2SO_4 and stripping off the solvent gave crystals (20.4 g, 71.8 %). mp 86-89 on recrystallization from ether-cyclohexane (lit. (106), 86-87). ir (KBr)

1070 cm^{-1} , 1040 (-OH), 1580 (primary amine), no carbonyl; mass spectrum M^+ m/e 167(2), m/e 42 (100), m/e 60 (100), m/e 77 (100), m/e 105 (80), m/e 118 (19), m/e 136 (60).

Treatment of a solution of phenylserinol (560 mg) in MeOH (5 ml) with oxalic acid (215 mg) in MeOH (5 ml) gave, after washing with water (1 ml), the oxalate (450 mg), mp 222-223 (lit. (111) 215^o). Phenylserinol (370 mg) in absolute EtOH (1 ml) was treated with benzoic acid (270 mg) dissolved in absolute EtOH (1 ml). Phenylserinol benzoate (300 mg) was collected. mp 159-161^o (lit. (112), 162-163^o).

3. Synthesis of threo-1-phenyl-1-chloro-2-aminopropane - 3-ol hydrochloride (60).

Dry HCl was passed through the solution of threo-phenylserinol (3 g, 0.018 mol) dissolved in absolute EtOH (15 ml). After distilling the EtOH off, the viscous residue was suspended in dry CHCl_3 (30 ml), followed by adding freshly distilled SOCl_2 (2.5 g, 0.02 mol). The mixture was stirred overnight at room temperature. The solution was evaporated in vacuo at room temperature to give a solid. The solid was dissolved in absolute MeOH and to this solution dry ether was added to give a solid (mp 174-176^o). Purified product (1.95 g, 49 %) was obtained on second recrystallization from MeOH-ether. mp 193-194 (lit. (115), 192-193^o); ir (KBr) 1050 cm^{-1} (-OH); mass spectrum (20 ev) $(M+2)^+$ m/e 187(1), m/e 60 (100), m/e 118 (61), m/e 119 (53).

4. Attempted synthesis of 1-phenyl-1,3-dichloro-2-aminopropane.

HCl (56, $R_1=R_2=R_3=H$)

To 1-phenyl-1-chloro-2-aminopropane-3-ol (0.22 g, 0.001 mol) in dry $CHCl_3$ (10 ml) was added freshly distilled $SOCl_2$ (2 g, 0.017 mol). Refluxing on a water bath for 2 hours and distillation of the solvent gave a solid. The solid was dissolved in MeOH. Addition of ether gave crystals. Mp ($193-195^\circ$) and the ir spectrum showed unreacted starting material.

This unreacted material with added $SOCl_2$ (10 g) was refluxed on a water bath for 2 hours. Distillation of $SOCl_2$ under reduced pressure gave a solid. The solid was redissolved in MeOH. Crystals obtained by adding ether showed starting material identified by its ir and mp.

5. Attempted synthesis of 1-phenyl-1-thiocyanato-2-aminopropane-3-ol (62).

A solution of KSCN (393 mg, 0.00405 mol) and dicyclohexyl-18-crown-6 (1.49 g, 0.0004 mol) in MeOH (30 ml) was mixed with 1-phenyl-1-chloro-2-aminopropane-3-ol hydrochloride (444 mg, 0.002 mol) in MeOH (10 ml). Stirring at room temperature for 4 hours and distillation of the solvent gave a viscous liquid. The residue was dissolved in H_2O (10 ml) and extracted with $CHCl_3$ (2 x 100 ml) and thereafter with ethylacetate (2 x 100 ml). Tlc (silica gel, iodine chamber, ethylacetate) of the residues from $CHCl_3$ and ethylacetate showed the same pattern having more than 3 spots. The ir spectrum of ethylacetate and $CHCl_3$ ex-

tractions showed strong polyether (1100 cm^{-1}) and thiocyanate (2090 cm^{-1}) absorptions. Attempts to find a developing solvent for tlc which would give clear separation of the spots were performed using ethylacetate, CHCl_3 , EtOH, CHCl_3 -EtOH, hexane, and EtOH-hexane only to result in severe tailing or incomplete separation.

6. Synthesis of 1-phenyl-1-thiosulfuryl-2-aminopropane-3-ol (61, Bunté salt)

$\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ (1.935 g, 0.078 mol) dissolved in H_2O (15 ml) was added to the solution of 1-chloro compound (60) (1.68 g, 0.075 mol) in EtOH (45 ml). The mixture was refluxed for 5 hours on a water bath. After reducing the volume to 3 ml under reduced pressure, precipitated solid was filtered to give a Bunté salt (900 mg, 45.7 %). mp $246\text{--}249^\circ$; ir (KBr) 1200 cm^{-1} , 1230, 640 (SO_3H).

7. Attempted synthesis of 1-phenyl-1-thiocyanato-2-aminopropane-3-ol (62) via the Bunté salt (Synthesis of 2-amino-4-hydroxy-methyl-5-phenyl-2-thiazoline 74).

Bunté salt 61 (263 mg, 0.001 mol) was dissolved in Na_2CO_3 solution (53 mg, 0.0005 mol) in H_2O (10 ml). A solution of NaCN (49 mg, 0.001 mol) in H_2O (2 ml) was added at room temperature. A precipitate was observed after stirring for one hour. After stirring for one additional hour, white solid was obtained by suction filtration. Recrystallization from

H₂O gave a thiazoline 74 (100 mg, 48.0 %) mp 152-153.5°; ir (KBr) 1640 cm⁻¹ (C=N); mass spectrum M⁺ m/e 208 (3), m/e 177 (100), m/e 91 (36), m/e 135 (25), m/e 45 (12), m/e 115 (12).

8. Synthesis of 1-phenyl-1-mercapto-2-aminopropane-3-ol hydrochloride (63).

Bunté salt 61 (300 mg, 0.0014 mol) with concentrated HCl (5 ml) was stirred at 50-60° for 1.5 hours. The mixture changed to a clear solution. Stirring overnight at room temperature gave a white precipitate. The solid was recrystallized from MeOH-ether. Yield 120 mg (48.1 %). mp 180-182°; ir (KBr) 2520 cm⁻¹ (-SH); mass spectrum (M+1)⁺ m/e 184 (0.4), m/e 60 (100), m/e 42 (78), m/e 91 (43), m/e 118 (26), m/e 77 (22), m/e 51 (18).

9. Synthesis of threo-N-benzoyl phenylserinol (65).

To threo-phenylserinol (1.67 g, 0.01 mol) dissolved in 10 % NaOH (30 ml) was added benzoyl chloride (5.62 g, 0.04 mol) all at once. The mixture was shaken vigorously for 30 min. to give a solid. The solid was filtered and recrystallized from MeOH to give tribenzoylphenylserinol (4.17 g, 87 %). mp 193° (lit. (128), 194-195°). ir (KBr) 1640 cm⁻¹, 1530 (amide), 3360 (NH), 1720 (carbonyl). A solution of tri-benzoylphenylserinol (2.4 g, 0.005 mol) and NaOH (0.4 g, 0.01 mol) in MeOH (200 ml) was refluxed for an hour. A clear

solution was observed. A solid was obtained after concentration of the reaction mixture in vacuo. The solid was filtered, washed with saturated NaHCO_3 , and then H_2O , and dried (mp 153-156°). Recrystallization from ethylacetate gave colorless needles. Yield 1.0 g (74 %). mp 162° (lit. (128), 163-164°); ir (KBr) 1630 cm^{-1} , 1530 (amide), no carbonyl; mass spectrum m/e 105 (100), m/e 147 (100), m/e 164 (100), m/e 106 (95), m/e 240 (45), m/e 222 (45), m/e 223 (27).

10. Synthesis of 1-phenyl-1,3-dichloro-2-benzoylaminopropane (66).

Threo-N-benzoylphenylserinol (2.71 g, 0.01 mol) with freshly distilled SOCl_2 (59.5 g, 0.5 mol) was heated on the water bath for 1.5 hours. After evaporating SOCl_2 under reduced pressure, the resulting residue was treated with dry ether to obtain a solid (2.89 g). Purified product was obtained on recrystallization from benzene (1.75 g, 56.8 %). mp 148-150°; ir (KBr) 3330 cm^{-1} (NH), 1640, 1530 (amide), no carbonyl; nmr (CDCl_3) 7.50-7.73 δ (m, 2, protons ortho to carbonyl group), 7.60-7.37 (m, 8, phenyl protons), 6.40 (b, 1, -NH-CO-), 5.32 (d, 1, $\text{C}_6\text{H}_5\text{-CHCl-}$), 4.43-5.00 (m, 1, $\text{C}_6\text{H}_5\text{-CH-CH-}$), 3.50 (m, 2, $\text{-CH}_2\text{Cl}$); mass spectrum m/e 105 (100), m/e 130 (100), m/e 146 (32), m/e 182 (30), m/e 235 (31).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{NCl}_2\text{O}$: C, 62.33; H, 4.91; Cl, 23.02; mol. wt., 308.05.

Found: C, 62.21; H, 4.89; Cl, 23.20.

11. Synthesis of 1-phenyl-1,3-dibromo-2-benzoylaminopropane (72).

A general procedure for this synthesis was taken from the literature (130,131,132). To a solution of trans-cinnamyl alcohol (10 g, 0.075 mol) in CCl_4 (100 ml), bromine (13.1 g, 0.082 mol) in CCl_4 (10 ml) was added with stirring at -5° for 35 minutes. The CCl_4 solution was washed with 10 % NaHSO_3 (15 ml), saturated NaHCO_3 (30 and 30 ml) and finally with H_2O (50 ml). The CCl_4 solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo until a solid appeared. Standing at -5° for 24 hours gave crystals, which were recrystallized from petroleum ether (30 to 60) to give colorless needles of erythro-3-phenyl-2,3-dibromopropanol (15 g, 68.2 %). mp $72-73^\circ$ (lit. (130), $73-74^\circ$).

A solution of dibromopropanol (10 g, 0.034 mol) and benzonitrile (3.5 g, 0.034 mol) in dry ether (10 ml) was saturated with dry HCl gas at 0° . A solid precipitated after standing in the cold for 7 days. The solid was collected and washed with dry ether to give erythro-3-phenyl-2,3-dibromopropyl benzimino ether HCl (5.2 g, 35.3 %). mp $147-150^\circ$ (lit. (130), $148-150^\circ$); ir (KBr) 3450 cm^{-1} , 1640 ($=\text{NH}\cdot\text{HCl}$).

Benzimino ether HCl (5 g, 0.0115 mol) was ground with 10 % Na_2CO_3 solution (25 ml) in a mortar for 20 minutes and the solid was collected, washed with water and dried. Recrystallization from acetone gave colorless erythro-3-phenyl-2,3-

dibromopropyl benzimino ether (3.85 g, 84.1%). mp 133-135° (lit. (130), 133.5-135°). ir (KBr) 3340 cm^{-1} , 1640 ($=\text{NH}$).

A solution of base (3.5 g, 0.0088 mol) in toluene (35 ml, dried on CaH_2 and distilled) was refluxed on an oil bath. A solid was formed after 30 minutes which then went into solution. After refluxing for 1.5 hours, the solution was concentrated in vacuo to give a solid which was recrystallized from ethylacetate. Yield 1.4 g (40%, lit. (130), 13%). mp 132-134° (lit. (130), 132-134°); ir (KBr) 1650 cm^{-1} , 1530 (amide), 3320 (NH); nmr (CDCl_3) 7.6 - 7.86 δ (m, 2, protons ortho to carbonyl group), 7.13-7.57 (m, 8, phenylprotons), 6.50 (b, 1, $-\text{NH}-\text{CO}-$), 5.38 (d, 1, $\text{C}_6\text{H}_5-\text{CH}-\text{Cl}-$), 4.63-5.0 (m, 1, $\text{C}_6\text{H}_5-\text{CH}-\text{CH}-$) 3.5 (m, 2, $-\text{CH}_2\text{Cl}$); mass spectrum m/e 105 (76), m/e 77 (29), m/e 146 (20), m/e 103 (20), m/e 235 (15), m/e 82 (14).

12. Attempted synthesis of 3-benzoylamino-2-phenylthietane (23) (Synthesis of 2-phenyl-4-benzylidene-2-oxazoline, 78).

To the dibromo compound (72) (397 mg, 0.001 mol) in EtOH (10 ml), $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ (360 mg, 0.0015 mol) in EtOH (10 ml) was added at room temperature over 30 minutes. The mixture was refluxed for 1.5 hours on a water bath. Precipitated NaBr was filtered and distilling off the solvent at reduced pressure gave a residue. After adding H_2O (10 ml), the mixture was extracted with CHCl_3 (3 x 100 ml). Drying over anhydrous Na_2SO_4 and distillation of CHCl_3 gave a yellow viscous material.

Tlc (silica gel, iodine chamber, CHCl_3 : cyclohexane 1:1) showed four spots at R_f baseline (A), 0.2 (B), 0.5 (C), and 0.7 (D).

Above viscous material was dissolved in ether (20 ml). A small amount of ether-insoluble crystals was collected and identified as 1-phenyl-2-benzoylamino-1-propene-3-ol (82). mp 162-167^o; tlc R_f 0; ir (KBr) 1050 cm^{-1} (primary OH), 1540, 1650 (amide), 1420 ($-\text{CH}=\text{}$); mass spectrum m/e 105 (99), m/e 77 (45), m/e 103 (17), m/e 51 (11), m/e 148 (10), m/e 235 (2).

After filtering 1-phenyl-2-benzoylamino-1-propene - 3-ol, the ether solution was concentrated to 2 ml and fractionated on a column using silica gel and CHCl_3 for elution. Fractions showing R_f 0.7 was isolated. Partition on the column was monitored by its yellow band. Distillation of CHCl_3 gave a yellow crystal of oxazoline (120 mg, 50.6 %). Recrystallization from hexane on dry ice-acetone gave needle-like yellow crystals. mp 92-94^o; uv max (EtOH) 210 (ϵ 24,000), 241 (ϵ 19,000), 344 (ϵ 16,000); nmr (CDCl_3) 7.67-8.10 δ (m, 4, 4 phenylprotons), 7.10-7.40 (m, 6, 6 phenylprotons), 5.73 (t, 1, $\text{C}_6\text{H}_5\text{CH}=\text{}$), 5.05 (d, 2, $-\text{CH}_2-\text{O}$); mass spectrum M^+ m/e 235 (25), m/e 105 (100), m/e 77 (37), m/e 103 (31), m/e 91 (23).

Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{NO}$: C, 81.67; H, 5.57; N, 5.80; mol. wt., 235.11.

Found: C, 81.56; H, 5.65; N, 5.81.

B and C were obtained as viscous liquids having amide bands at 1540 and 1650 cm^{-1} in the ir spectrum. Oxazoline 78 was similarly obtained from 1-phenyl-1,3-dichloro-2-benzoylaminopropane. mp. 90-93°. The ir of the product was superimposable with that from the 1,3-dibromo compound reaction.

13. Attempted synthesis of 1-phenyl-1,3-dibromo-2-benzylaminopropane (94).

Diborane prepared by the method of Zweifel and Brown (145) from NaBH_4 (284 mg, 0.0075 mol) and borontrifluoride etherate (1.42 g, 0.01 mol) was passed in a stream of nitrogen during 1.5 hours through a stirred solution of the 1,3-dibromo compound (72) (397 mg, 0.001 mol) in dry THF (20 ml, distilled from LiAlH_4) at 0°. After refluxing for 2 hours, the reaction mixture was mixed cautiously with absolute EtOH (10 ml). Evolving H_2 gas was observed. A stream of dry HCl gas was passed through the solution. It was then evaporated to dryness under reduced pressure to give a viscous residue. The ir spectrum showed a carbonyl band at 1720 cm^{-1} . H_2O (10 ml) was added to the viscous residue and a small amount of solid was precipitated out. The ir spectrum of this solid showed an amide band (1640 cm^{-1} , and 1520) and was identical to that of the starting material. The aqueous layer was extracted with CHCl_3 . After pooling the CHCl_3 , addition of ether gave a solid which soon changed to a gummy material. The ir spectrum showed a carbonyl band at 1730 cm^{-1} .

14. Synthesis of 1-phenyl-2-N,N-dimethylaminopropane-1,3-diol(96).

Freshly distilled formic acid (85 %, 2.5 g, 0.046 mol) and formaldehyde (37 %, 5 g, 0.062 mol) were added to phenylserinol (2 g, 0.012 mol). The mixture was refluxed on a water bath for 20 hours. The reaction mixture was made alkaline to litmus using 50 % NaOH and extracted with ether (3 x 100 ml). After drying on anhydrous Na_2SO_4 , distillation of the solvent gave dimethylphenylserinol (1.85 g, 79 %). Recrystallization from hexane gave needlelike crystals. mp 64-66; ir (KBr) disappearance of NH_2 (1580 cm^{-1}); nmr (CDCl_3) 7.3 δ (s, 5, phenyl protons), 4.37 (d, 1, $\text{C}_6\text{H}_5 \text{CHOH}$), 3.43 (t, 2, $-\text{CH}_2\text{OH}$), 2.97-3.33 (b, 2, hydroxy-CH₂), 2.50-2.85 (m, 7, $-\text{CH}(\text{NCH}_3)_2 -\text{CH}_2$); mass spectrum M^+ m/e 195 (0.2), m/e 88 (100), m/e 58 (21), m/e 105 (7), m/e 77(12).

Anal. Calcd. for $\text{C}_{11}\text{H}_{17}\text{NO}_2$: C, 67.64; H, 8.78; N, 7.18; mol wt., 195.15

Found: C, 67.69; H, 8.85; N, 7.01.

15. Attempted synthesis of 1-phenyl-1-chloro-2-N,N-dimethylaminopropane-3-ol (111).

Dimethylphenylserinol (1.95 g, 0.01 mol) was dissolved in CHCl_3 (50 ml) and dry HCl gas was passed through for 5 minutes. Distillation of the solvent gave a precipitate, which was recrystallized from EtOH-ether to give pure dimethylphenylserinol hydrochloride (2.0 g, 86.6 %) mp 154-

156°. To dimethylphenylserinol hydrochloride (1.16 g, 0.0053 mol) in CHCl_3 (20 ml), freshly distilled SOCl_2 (0.89 g, 0.0075 mol) in CHCl_3 (10 ml) was added dropwise with cooling in an ice bath during a period of 20 minutes. The mixture was stirred for 24 hours at room temperature. Solvent was removed under vacuum resulting in a brown viscous residue. Addition of ether gave a solid which was identical with unreacted hydrochloride as identified by the ir spectrum.

The same procedure was followed except the mixture was refluxed for 2 hours instead of stirring at room temperature for 24 hours. The resulting viscous residue dissolved in EtOH (30 ml) with $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ (1.24 g, 0.005 mol) in H_2O (5 ml) was refluxed on a water bath for 5 hours. While distilling the solvent off, a small amount of solid was precipitated out. Mp (280) and ir ($1230, 640 \text{ cm}^{-1}$) indicated unreacted $\text{Na}_2\text{S}_2\text{O}_3$. Stripping the solvent gave a viscous residue. Absolute EtOH (10 ml) was added to isolate a solid, which was identified as NaCl. The EtOH solution was distilled to give a residue; ir (neat) $1230, 640 \text{ cm}^{-1}$. Positive identification of a Bunte salt was not successful.

Dimethylphenylserinol (2.0 g) was dissolved in dry ether (100 ml). Dry HCl gas was passed into the suspension of isolated dimethylphenylserinol hydrochloride for 5 hours. The mixture was filtered. The filter cake and a solid isolated from the filtrate after evaporating the solvent showed the same mp and ir spectrum as that for dimethyl-

phenylserinol hydrochloride. Dimethylphenylserinol (700 mg) was dissolved in dry dioxane (15 ml, dried on CaH_2 and distilled). Dry HCl gas was passed through the clear solution for 2 hours. Distillation of dioxane under reduced pressure gave a viscous brown residue. Positive identification of 111 was not successful.

16. Synthesis of N,N-dimethyl-p-nitrophenylserinol (110).

D(-)-threo-p-nitrophenylserinol (6.36 g, 0.03 mol) with 37 % formaldehyde (12.5 g, 0.154 mol) and 85 % formic acid (7.5 g, 0.139 mol) was stirred at 80-100° for 13 hours. After making alkaline to litmus using 50 % NaOH, the mixture was extracted with ether (3 x 150 ml). Drying on anhydrous Na_2SO_4 and distillation of the solvent gave a brown solid. Recrystallization from ether-hexane gave a white crystal (5.24 g, 72.18 %). mp 90-92°; ir (KBr) 1530 cm^{-1} , 1360 ($-\text{NO}_2$), disappearance of NH_2 (1580); nmr (CDCl_3) 8.07 δ (d, 2, ortho to nitro group), 7.47 (d, 2, meta to nitro group), 4.50 (d, 1, $\text{NO}_2\text{C}_6\text{H}_5\text{CHOH-}$), 3.52 (d, 2, $-\text{CH}_2\text{OH}$), 3.10 (b, 2, hydroxyl OH , disappeared on addition of D_2O), 2.33-2.66 (m, 7, $-\text{CHN}(\text{CH}_3)_2$); mass spectrum m/e 88 (100), m/e 58 (64), m/e 209 (6), m/e 163 (6).

Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_4$: C, 54.96; H, 6.72; N, 11.67; mol. wt., 240.15.

Found: C, 55.09; H, 6.71; N, 11.54.

17. Attempted synthesis of 1-p-nitrophenyl-1-chloro-2-N,N-dimethylaminopropane-3-ol hydrochloride (112).

To p-nitro-N,N-dimethylphenylserinol (2.4 g) in dry ether (100 ml), HCl gas-saturated ether (200 ml) was added to obtain a solid. Filtration and washing with ether gave a white HCl salt. This salt (mp 116-123^o) was hygroscopic and changed to a yellow color on standing. Freshly distilled SOCl₂ (262 mg, 0.0022 mol) in dry CHCl₃ (10 ml) was added to HCl salt (553 mg, 0.002 mol) in dry CHCl₃ (20 ml). The mixture was refluxed for 2 hours. Distillation of the solvent gave a brown solid. Recrystallization from EtOH-ether showed p-nitro-N,N-dimethylphenylserinol.HCl which was identified by superimposable ir spectrum.

18. Synthesis of 1-p-nitrophenyl-1,3-dichloro-2-N,N-dimethylaminopropane hydrochloride (97).

N,N-dimethyl-p-nitrophenylserinol HCl (5.43 g, 0.02 mol) with freshly distilled thionyl chloride (50 ml) was heated at 70-80^o for 1.5 hours. Distillation of the thionyl chloride under reduced pressure gave a viscous residue. After dissolving the residue by adding EtOH (20 ml), ether (150 ml) was added to obtain a precipitate. Recrystallization from EtOH-ether gave a dichloro compound (4.73 g, 75.4 %). mp 161-163^o; ir (KBr) 3420 cm⁻¹ (tertiary amine), 1530, 1350 (-NO₂), no strong absorption at 1200-1000; mass spectrum m/e 106 (100),

m/e 108 (32), m/e 71 (19), m/e 70 (6), m/e 58 (5).

Anal. Calcd. for $C_{11}H_{15}N_2O_2Cl_3$: C, 42.10; H, 4.82; Cl, 33.93; mol. wt. 313.52.

Found: C, 42.10; H, 4.84; Cl, 33.81.

19. Attempted synthesis of 2-p-nitrophenyl-3-N,N-dimethylaminothietane (26) (Synthesis of bis (1-p-nitrophenyl-2-N,N-dimethylamino-3-chloropropane) sulfide HCl, 123).

1) Reaction using excess amount of $Na_2S \cdot 9H_2O$.

$Na_2S \cdot 9H_2O$ (4.032 g, 0.0168 mol) dissolved in EtOH (50 ml) was added dropwise to the solution of 1-p-nitrophenyl-1,3-dichloro-2-N,N-dimethylaminopropane HCl (2.34 g, 0.0075 mol) in EtOH (30 ml) during 10 minutes at room temperature. Stirring was continued for 2 hours after addition of sodium sulfide at room temperature. The filter cake obtained after filtering the reaction mixture was triturated with H_2O to dissolve precipitated NaCl. Brown-colored crystals (1.22 g) were obtained. mp 60-110°; ir (KBr) 1520 cm^{-1} , 1350 ($-NO_2$); gc-mass spectrum (3 % OV-17 column, injector temperature 170°, column temperature 80-300°, programming 20°/min.) Compound A ; retention time 8.9 minutes, m/e 70 (100), m/e 58 (55), m/e 206 (37), m/e 84 (30), m/e 115 (26). Compound B ; retention time 11.3 minutes, m/e 116 (74), m/e 115 (22), m/e 162 (14), m/e 227 (13), m/e 77 (11).

- 2) Reaction using equimolar concentration of $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ (Synthesis of bis (1-p-nitrophenyl-2-N,N-dimethylamino-3-chloropropane) sulfide $\text{HCl}\cdot\text{H}_2\text{O}$, 123).

$\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ (1.441 g, 0.0066 mol) dissolved in EtOH (30 ml) was added to the solution of 1-p-nitrophenyl-1,3-dichloro-2-N,N-dimethylaminopropane HCl (1.881 g, 0.0066 mol) in EtOH (50 ml). The mixture was stirred for 3 hours at room temperature. The precipitated yellow crystals were filtered and triturated with H_2O . Yield 660 mg. mp. 115-135; alkali-fusion test sulfur, positive; nmr (CDCl_3) 8.10 δ (d, 2, phenyl protons ortho to nitro group), 7.33 (d, 2, phenyl protons meta to nitro group), 2.37 (s, 6, dimethyl protons), 3.00-3.63 (m, 4, $(\text{NO}_2\text{C}_6\text{H}_5\text{CHCHN}(\text{CH}_3)_2\text{CH}_2\text{Cl})_2\text{S}$; gc-mass spectrum (3 % OV-17 column, injector temperature 170°, column temperature 80-275°, programming 20°/min.) retention time 9.3 minutes, m/e 70 (61), m/e 58 (44), m/e 115 (19), m/e 84 (14), m/e 206 (12).

The free base (600 mg) was dissolved in ether (200 ml). A white crystal was obtained by passing HCl gas through the ether solution. Yield 560 mg (overall yield 15.4 %); mp 148 (dec.) (recrystallization from EtOH-ether and drying at 50°/0.1 mm for 5 hours); alkali-fusion test sulfur, positive; gc-mass spectrum (3 % OV-17 column, injector temperature 170°, column temperature 80-275°, programming 20°/min.) retention time 9.3 minutes, m/e 70 (77), m/e 58 (55), m/e 84 (21), m/e 206 (18), m/e 115 (18).

Anal. Calcd. for $\text{C}_{22}\text{H}_{32}\text{N}_4\text{O}_5\text{SCl}_4$: C, 43.55; H, 5.32; N, 9.24; S, 5.29; mol. wt. 606.20.

Found: C, 43.89; H, 5.24; N, 9.06; S, 4.98.

20. Synthesis of 3-chloro-1-phenylpropylene oxide-1,2(107).

Freshly distilled 3-chloropropenylbenzene (68-69°/0.1 mm, 15.2 g, 0.1 mol) was added to 300 ml of a chloroform solution of 85 % m-chloroperbenzoic acid (25.8 g, 0.12 mol). The solution was kept at 0° for 24 hours with frequent shaking. A precipitate (m-chlorobenzoic acid) was formed during this time. To the reaction mixture, 10 % Na₂SO₃ was added to destroy excess peracid until a test with starch-iodine paper was negative. The reaction mixture was filtered into a 1000 ml separatory funnel and washed with saturated NaHCO₃ (150 ml) until the washing solution remained basic. The CHCl₃ layer after washing with H₂O was dried over anhydrous Na₂SO₄ in the cold for 24 hours. The solvent was removed using a flash evaporator. The resulting yellow oil (15.4 g) was distilled under reduced pressure utilizing a vigreux condenser to give 14.1 g (84 %) of a colorless liquid. bp 74-75°/0.03 mm (lit. (83) 67/0.3 mm); ir (neat) 890, 940 cm⁻¹ (epoxide ring).

21. Synthesis of *o*-toluenesulfonylchloride

The preparation of *o*-toluenesulfonylchloride was carried out according to a known procedure (165). 75.6 g (0.6 mol) of benzylchloride was used to obtain 103 g (90.3 %) of *o*-toluenesulfonylchloride. mp 89-91° (lit. (165), 88-91°).

22. Synthesis of 3-hydroxy-2-phenylthietane (100).

The method described by Haya (83) was used. 14.89 g (68 %) of 3-hydroxy-2-phenylthietane was obtained from 22.3 g (0.132 mol) of 3-chloro-1-phenylpropylene oxide-1,2. mp 54-55° (lit. (83), 565-575); ir (KBr) 1065, 3220, 3310 cm^{-1} (-OH); nmr (CDCl_3) 2.95 δ (s, 1, OH, disappeared on addition of D_2O), 3.10 (d, 2, SCH_2), 4.60 (m, 2, ArCHCH_2OH), 7.33 (m, 5, phenyl protons)

23. Attempted synthesis of 3-azido-2-phenylthietane (103).

This experiment was performed following known procedures (83). 3-Hydroxy-2-phenylthietane (4.6 g, 0.027 mol) was used to prepare 3-benzylsulfonyl-2-phenylthietane. THF was distilled over LiAlH_4 . Et_3N was distilled and dried over KOH. Half of the residue was used for determination of 3-benzylsulfonyl-2-phenylthietane. The attempted synthesis of 3-azido-2-phenylthietane was carried out using another half residue.

Half of the residue was dissolved in CHCl_3 and fractionated on column of silica gel (60-200 mesh, Davison Chemical). CHCl_3 was used as eluent. As shown by preliminary tlc (silica gel, iodine chamber, pet. ether: CHCl_3 1:1) separation of 4 compounds was achieved. R_f values of the compounds were: A baseline spot, B 0.1, C 0.25, D 0.8. B and C were isolated as gummy materials. B showed the same R_f values as 3-hydroxy-2-phenylthietane. D showed a high melting point

(over 200°) and strong absorption at 3400 cm^{-1} in the infrared spectrum. D; mp $84-86^{\circ}$ (89° on recrystallization from pet. ether-benzene), ir (KBr) $1175, 1370\text{ cm}^{-1}$ (SO_2); nmr (CDCl_3) 4.83δ (s, 2, ArCH_2), 7.43 (m, 5, Ar).

Half of the residue was dissolved in freshly distilled HMPT (25 ml, $83^{\circ}/0.9\text{ mm}$). NaN_3 (1.5 g, 0.023 mol) was added and the suspension was stirred on a cold water bath under N_2 atmosphere for 15 hours. The solution was added to 50 ml of H_2O and extracted with ether (3 x 50 ml). After drying with anhydrous Na_2SO_4 , the ether extract was concentrated under vacuum. The residue showed a strong azide (2110 cm^{-1}) band in the infrared spectrum. The residue was dissolved in a small amount of CHCl_3 and fractionated on a column of Florisil (60-100 mesh, Fisher Scientific Company). Elution with n-hexane gave Fraction A (R_f 0.8, silica gel, iodine chamber, hexane : CHCl_3 3:1). Elution with ether gave two fractions (B; R_f 0.4-0.7, tailing C; baseline spot). Elution with MeOH gave fraction D which showed also baseline spot. A; mp $87-88.5^{\circ}$ (on recrystallization from ether), ir (KBr) no azide band (azide band was observed before recrystallization), $1175, 1370\text{ cm}^{-1}$ (SO_2). B and C were isolated as small amount of dark residues having strong band at 2110 cm^{-1} . Tlc of the fraction D showed a mixture of the several materials. After dissolving in MeOH, ether was added resulting in precipitation of a crystal, which showed strong band at 650 and 3390 cm^{-1} as well as at 2210 cm^{-1} .

24. Attempted synthesis of 2-phenyl-3-thietanone (104).

A solution of 3-hydroxy-2-phenylthietane (1.32 g, 0.008 mol) in freshly distilled HMPT (15 ml) and DMSO (6 ml) was cooled to -20° and cyanuric chloride (2.95 g, 0.016 mol) was added. After 5 hours at -20° , triethylamine (3.23 g, 0.032 mol) was added and the mixture was allowed to stand at room temperature for 10 minutes. The mixture was poured into ice-water (30 ml) and extracted with CHCl_3 (3 x 150 ml). After drying over anhydrous Na_2SO_4 , CHCl_3 was distilled. Tlc (silicagel, iodine chamber, methanol) showed 2 spots at R_f 0.8 and baseline. The residue was dissolved in a small amount of CHCl_3 and fractionated on a silica gel column. Elution with CHCl_3 gave a yellow oil which showed a spot at R_f 0.8 by tlc. That yellow oil changed to dark brown color. Elution with methanol gave a viscous residue which showed the baseline spot by tlc. Ir of the material showed absorption at 1650 cm^{-1} .

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